Synthetic Method

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Synthesis of Aminocyclobutanes via Iron-Catalyzed [2+2] Cycloaddition. **

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Locking the spatial orientation of a molecule's substituents is essential in order to induce desirable properties such as bioactivity or supramolecular organization. Nitrogen-substituted cyclobutanes in particular combine a small and rigid carbocyclic skeleton with amine-based functional groups which are omnipresent in bioactive compounds.[1] In fact, this scaffold can be found in natural or synthetic biologically active compounds such as Lannotinidine F (**1**), Cyclobut-G (**2**) or rhodopeptin analog **3** (Figure 1).[2] The use of aminocyclobutanes as constrained amino acids has been also studied as their introduction into peptides results in foldamers with interesting properties ranging from cell-penetrating agents to low-molecular-weight gelators.[3]

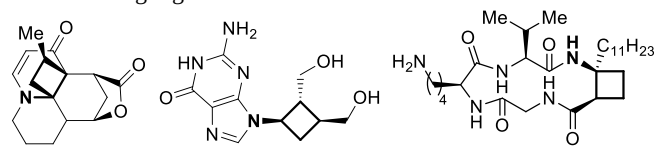
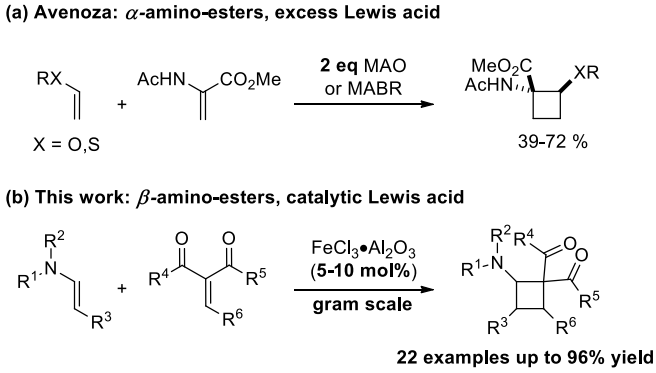


Figure 1. Examples of aminocyclobutanes in natural products and synthetic bioactive compounds.

In addition to their exceptional structural properties, cyclobutanes are also versatile synthetic precursors.[4] Nevertheless, the use of donor-acceptor-substituted cyclobutanes to access formal 1,4-dipoles has been far less exploited than for cyclopropanes in the case of formal 1,3-dipoles.[5] The first report of such a process was described by Saigo in 1991 in a formal [4 + 2] cycloaddition between aminocyclobutanes and carbonyls.[5a] However, the nitrogen atom was lost during the process. All further effort and success were later reported using carbo- and alkoxy- substituted four-membered rings. [5b-f]

The structural and synthetic versatility of aminocyclobutanes makes the development of new methods towards their synthesis particularly attractive. In the past, photochemical and thermal [2+2] cycloadditions have been most often applied to the synthesis of cyclobutanes.[6-8] However, the scope of these transformations was limited, and often harsh conditions or specialized equipment was required. An alternative strategy based on organocatalysis was recently reported, but it remains limited to the specific case of nitrocyclobutanes.[9] Methods involving Lewis acid catalysts were successful for diverse donor-acceptor-substituted cyclobutanes.[10,11] In the specific case of aminocyclobutanes however, there is only a single report by Avenoza and co-workers, who made use of a superstoichiometric amount of an aluminum Lewis acid for the synthesis of α-amino acid derivatives (Scheme 1, (a)).[12] There is consequently a great need for milder catalytic methods giving access to differently substituted aminocyclobutanes.

Herein, we report the first Lewis acid-catalyzed [2+2] cycloaddition between enimides and alkylidene malonates to access β-amino acid cyclobutane derivatives (Scheme 1, (b)). The reaction involves the use of cheap and non-toxic iron trichloride as catalyst and tolerates a wide range of substituents. The method can be used to afford the aminocyclobutanes in gram quantities and the synthetic potential of the obtained products was demonstrated by their transformation into a β-peptide derivative and the first example of catalytic [4+2] cycloaddition of aminocyclobutane proceeding without loss of the precious nitrogen atom.



Scheme 1. Lewis Acid-mediated [2+2] cycloaddition for the synthesis of aminocyclobutanes. MAO: methylaluminoxane, MABR: methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide).

We recently reported that di(alkoxycarbonyl)-substituted cyclopropanes were stable yet still reactive as formal dipoles when substituted by a phthalimide.[13] We wondered if a similar strategy could be also applied in the case of aminocyclobutanes. Consequently, commercially available N-vinyl phthalimide (**4a**) and methylidene malonate **5a** were chosen as partners to attempt the synthesis of aminocyclobutane **6aa** (Table 1). The use of the conditions reported for the synthesis of carbo- or alkoxy-substituted cyclobutanes[5] was not successful in this case (entries 1-3). Nevertheless, when using scandium triflate as catalyst, some traces of product could be detected by ^{1}H NMR (entry 3) and by increasing the reaction temperature a complete conversion could be obtained (entries 4 and 5). In this case, the major product was the desired cyclobutane **6aa**. At higher temperature than 0 °C, degradation of vinylphthalimide (**4a**) as well as product **6aa** was observed. In order to test this system with less reactive substrates, commercially available ethylidene malonate **5b** was used in the presence of scandium triflate at room temperature (entry 6). As no conversion was observed in this case, other Lewis acids were examined for the [2+2] cycloaddition. Indium triflate and iron trichloride supported on alumina[14] were able to catalyze the reaction even if full

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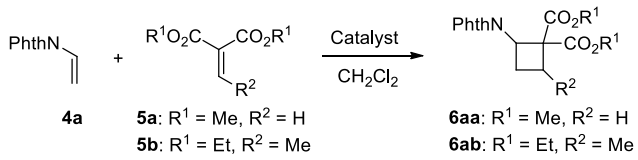
conversion was not reached for indium (entries 7 and 8).[15] Based on these preliminary results, the iron catalyst was selected for the study of the scope of the reaction.

Table 1. Optimization of the [2+2] cycloaddition.



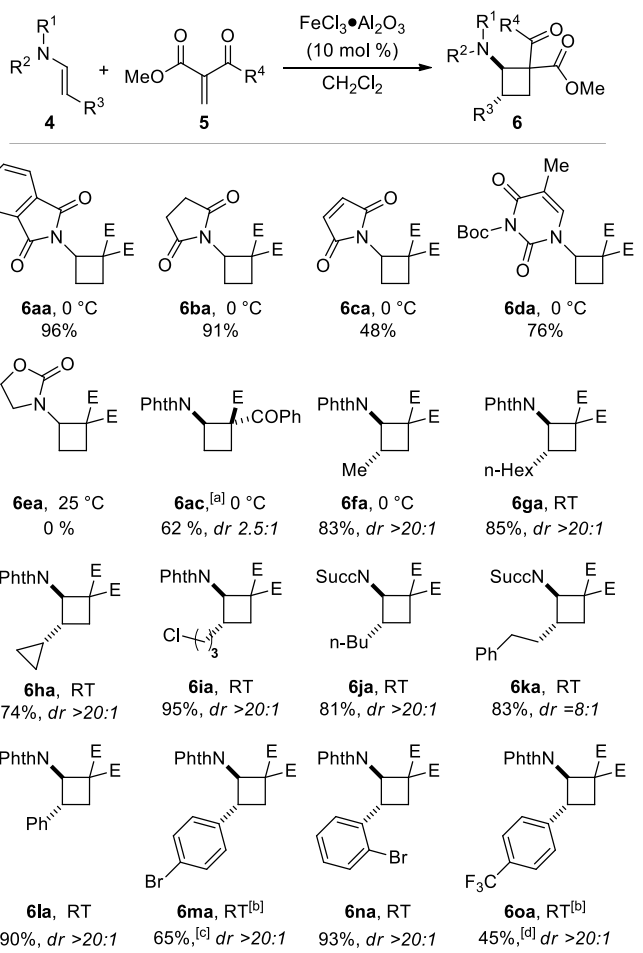
4a **5a**: R^1 = Me, R^2 = H; **5b**: R^1 = Et, R^2 = Me — **6aa**: R^1 = Me, R^2 = H; **6ab**: R^1 = Et, R^2 = Me

Entry	Catalyst (mol %)	t (h)	Malonate	T (°C)	Ratio **6**/**4**[a]
1	$ZnBr_2$ (100)[b]	1	**5a**	-78	0:1
2	$Yb(OTf)_3$ (10)[b]	0.75	**5a**	-78	0:1
3	$Sc(OTf)_3$ (10)[b]	0.75	**5a**	-78	Traces of **6**
4	$Sc(OTf)_3$ (10)[b]	0.75	**5a**	-30	1:2
5	$Sc(OTf)_3$ (10)[b]	0.5	**5a**	0	1:0
6	$Sc(OTf)_3$ (20)[c]	12	**5b**	rt	0:1
7	$In(OTf)_3$ (20)[c]	12	**5b**	rt	1.5:1
8	$FeCl_3$•Al_2O_3 (20)[c]	12	**5b**	rt	1:0

[a] Monitored by ^{1}H NMR. Reaction conditions: See supporting information for details. [b] Following reported procedures.[5] [c] Lewis acid (0.2 eq), dimethyl 2-ethylidenemalonate (**5b**) (1 eq) and 2-vinylisoindoline-1,3-dione (**4a**) (1.2 eq) added dropwise, dichloromethane, 0.1 mM. Phth = Phthaloyl.

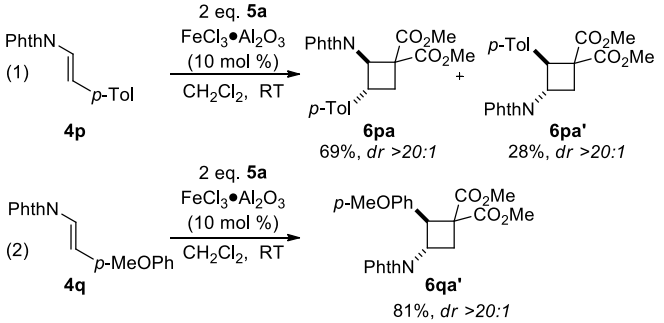
On preparative scale using 10 mol % of catalyst, iron trichloride on alumina was also a good catalyst for the reaction between vinylphthalimide (**4a**) and unsubstituted methylidene malonate **5a** (Scheme 2). Variation of the nitrogen substituent was first examined.[16] Succinimide as well as maleimide were tolerated, giving the cyclobutanes **6ba** and **6ca** in 91% and 48% yield respectively. The reaction also allowed the formation of Boc protected thymine cyclobutane **6da** in 76% yield. The use of a N-vinyl-oxazolidinone failed to deliver product **6ea** due to decomposition of the starting material. Cycloaddition of keto ester substrates was possible, affording cyclobutane **6ac** in 62% yield.

At this point, we turned to the synthesis of multi-substituted aminocyclobutanes. The use of (*E*)-enimides,[17] was examined first. Enimides substituted with a methyl, a hexyl or a cyclopropyl group afforded the corresponding cyclobutanes **6fa**, **6ga** and **6ha** in 74-85% yield. An aliphatic chloro substituent was also compatible with the reaction conditions (product **6ia**). Succinimide substituted cyclobutanes could also be obtained in 81-83% yield (products **6ja** and **6ka**). Importantly, in all the experiments involving (*E*)-enimides except for the formation of cyclobutane **6ka**, only one cyclobutane diastereoisomer could be detected in the crude mixture of the reaction. Aromatic substitution of the enimide was next investigated. The reaction delivered a single diastereoisomer of cyclobutane **6la** bearing a phenyl substituent in 90% yield. Adding a *para*-bromo substituent on the benzene ring slowed down the reaction and no full conversion to cyclobutane **6ma** was observed. However, decreasing the conjugation of the benzene ring with the enimide by moving the bromine atom to the *ortho* position[18] restored the reactivity and product **6na** could be obtained in 93% yield. Finally, in the presence of a trifluoromethyl group, the reaction was slower, but cyclobutane **6oa** could still be obtained in 38% yield (45% based on recovered starting material).



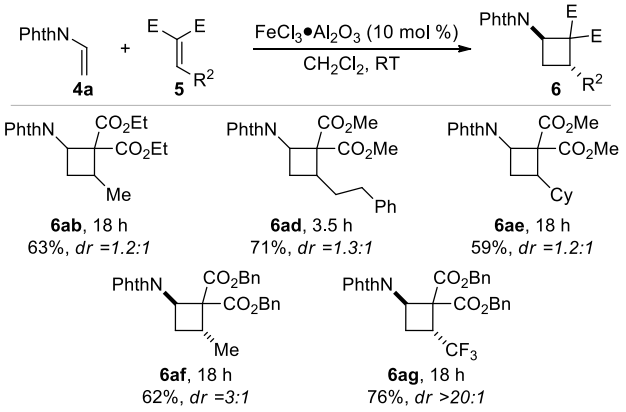
Scheme 2. Scope of the [2+2] cycloaddition with methylidene dicarbonyl compounds. E = CO_2Me. Succ = Succinyl. Reaction conditions: Enimide (0.20 mmol, 1 eq), alkylidene malonate (0.40 mmol, 2 eq), Fe catalyst (1 mmol/g, 20 mg, 0.020 mmol, 0.1 eq) in CH_2Cl_2 (1 mL) for 0.2-5 h. [a] E = CO_2Et. [b] 4 equivalents of methylidene malonate were used. [c] Based on recovered starting material, 50% isolated yield. [d] Based on recovered starting material, 38% isolated yield.

When we switched to electron-rich aromatic rings as substituents, we observed a different regioselectivity (Scheme 3). When tolyl-substituted enimide **4p** was used, a 2.5:1 mixture of "normal" and "inverted" products **6pa** and **6pa'** was obtained (1). *p*-Methoxy benzene-substituted substrate **4q** gave only the "inverted" product **6qa'** (2). This switch in regioselectivity is interesting as it gives access to equally important γ-amino acid cyclobutane derivatives.[19] Additionally, it allowed assigning the relative donating ability of the phthaloyl compared to electron rich aromatic groups in the [2+2] cycloaddition, which may be also useful in the future for the design of other transformations.



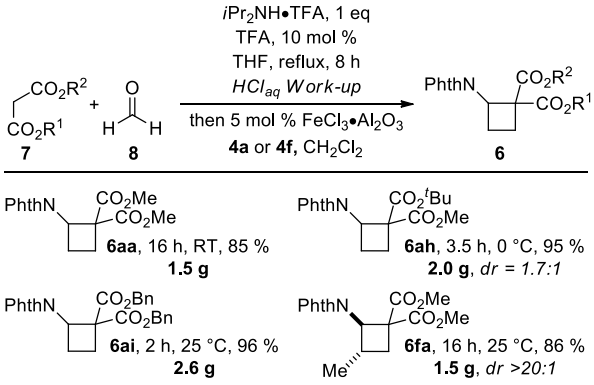
Scheme 3. [2+2] Cycloaddition with enamides substituted with electron-rich benzene rings. Tol = tolyl.

Less reactive substituted alkylidene malonates[20] also afforded cyclobutanes **6ab-e** in 59-71% yields, but usually without diastereoselectivity when using methyl ester substrates (Scheme 4).[21] The use of benzyl substituted alkylidene malonates **5f** allowed the formation of the product **6af** in a better 3:1 diastereomeric ratio and 62% yield. In the case of trifluoromethyl-substituted aminocyclobutane **6ag** only the *trans*-diastereoisomer was obtained in 76% yield. This is an important result, as methods for the synthesis of trifluoromethyl substituted aminocyclobutanes are rare, require numerous steps and usually lack diastereoselectivity.[6b, 22]



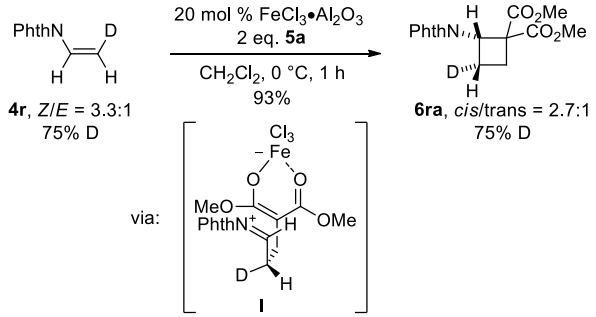
Scheme 4. Scope of the [2+2] cycloaddition with alkylidene malonates. Reaction conditions: Enimide (0.20 mmol, 1 eq), alkylidene malonate (0.40 mmol, 2 eq), Fe catalyst (1 mmol/g, 20 mg, 0.020 mmol, 0.1 eq) in CH_2Cl_2 (1 mL). Cy = cyclohexyl.

Methylidene malonates such as **5a** are very reactive species and start to decompose after a few days even when stored under argon at -20 °C. The access to this building block involves a complex Knoevenagel/Diels-Alder/recrystallization/cracking sequence followed by a base sensitive distillation in paraffin.[23] This difficult access to the methylidene malonates was a serious limitation for the preparative use of our [2+2] cycloaddition methodology. We found that the protocol developed by Connell and co-workers for the methenylation of dicarbonyl compounds[24] could be adapted to the synthesis of the sensitive methylidene malonates (Scheme 5). When the reaction was completed, the crude mixture could be used directly into the cycloaddition reaction. The efficacy of this protocol was demonstrated by accessing cyclobutanes **6aa**, **6ah**, **6ai** and **6fa** within a few hours from commercially available starting materials on a gram scale using 5 mol % catalyst loading.



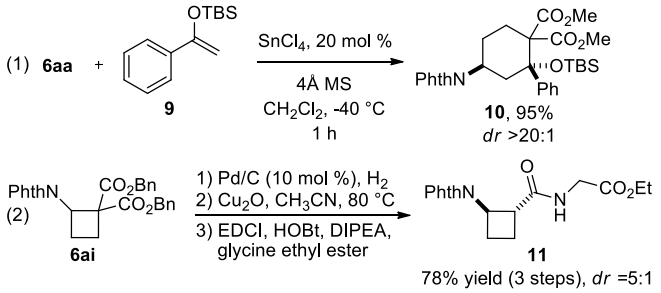
Scheme 5. Gram-scale synthesis of aminocyclobutanes.

In order to better understand the reaction mechanism, it would be important to know if the reaction is stereospecific in relation to the geometry of the enamide or if the observed high *trans*-diastereoselectivity is due only to thermodynamic control. When using (*Z*)-substituted enimides, no conversion was detected, even after prolonged reaction times. The lack of reactivity in the case of the (*Z*) isomer could be tentatively attributed to the loss of conjugation between the nitrogen p orbital and the π system of the olefin due to steric interactions, leading to lower nucleophilicity. To answer the question of stereospecificity, deuterated enimide **4r** was consequently synthesized[25] and submitted to the reaction conditions (Scheme 6). Only a slight loss of stereoinformation was observed during the reaction. This result supported a stepwise mechanism via a zwitterionic intermediate **I**, but also indicated a fast ring-closure, which could compete with single bond rotation.



Scheme 6. Reaction with deuterated enamide **4r** and speculative zwitterionic intermediate **I**.

We finally selected two key transformations to highlight the potential of aminocyclobutanes both as synthetic precursors and as structural units (Scheme 7). First, the tin tetrachloride-catalyzed reaction of aminocyclobutane **6aa** with enol silane **9** afforded one diastereoisomer of aminocyclohexane **10** in 95% yield (1). This is to the best of our knowledge the first report of such a formal [4+2] cycloaddition[26] between an aminocyclobutane and an olefin. Second, conversion of cyclobutane **6ag** to glycine-dipeptide **11** was achieved in three steps with an overall yield of 78% (2).[27]



Scheme 7. [4+2] Formal cycloaddition and synthesis of dipeptide **11**.

In conclusion, we have developed the first Lewis acid-catalyzed [2+2] cycloaddition for the synthesis of β-amino acid cyclobutane derivatives. The reaction gave access to multi-substituted cyclobutanes, including important derivatives for medicinal chemistry, such as nucleoside analogues or trifluoromethylated compounds. A simplified access to highly sensitive methylidene malonates was developed, allowing the gram scale synthesis of aminocyclobutanes. The synthetic potential of the obtained aminocyclobutanes was demonstrated by their transformation into a β-peptide derivative and by the first example of catalytic [4+2] annulation reaction for the synthesis of cyclohexylamines.

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Keywords: Aminocyclobutanes, donor acceptor cyclobutanes, [2+2] cycloaddition, iron catalysis, [4+2] annulation.

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[14] Iron trichloride on alumina was used as it is more stable and easier to handle than the free Lewis acid.

[15] A control experiment confirmed that basic alumina does not catalyze the reaction in absence of iron.

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[21] No reaction was observed when both the enimide and the alkylidene malonate were β-substituted.

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[25] **4r** was synthesized by reduction of the deuterated ynimide with Lindlar catalyst. See supporting information for further details.

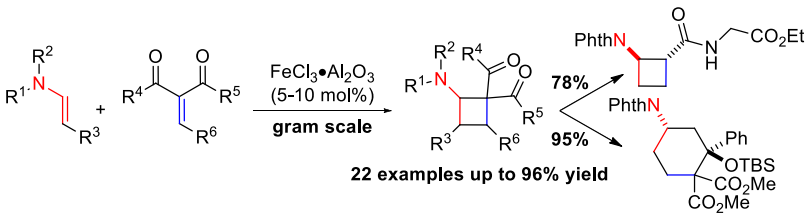
[26] As the reaction between cyclobutane **6aa** and silyl enol ether **9** involve a C-C bond cleavage, the reaction is best described as a "formal cycloaddition" in contrast to the [2+2] cycloaddition process. See also discussion in reference 13c.

[27] Clevage of the phthaloyl group on product **10** occurred smoothly in 87% yield using diaminoethane as reagent. In contrast, cleavage of the pththaloyl group on cyclobutane **11** was not possible in good yield. Alternative synthetic routes to generate the free cyclobutylamines are currently under investigation.

Synthetic Method

Florian de Nanteuil and Jérôme Waser
_____ **Page – Page**

Synthesis of Aminocyclobutanes via Iron-Catalyzed [2+2] Cycloaddition.



Fab Four: A new iron-catalyzed [2+2] cycloaddition for the synthesis of substituted aminocyclobutanes is reported. The reaction proceeds in excellent yield and diastereoselectivity for a broad range of substituents. The products can be obtained on gram scale and can be further converted into β-peptide derivatives in a few steps. Finally, the first example of [4+2] annulation between an aminocyclobutane and an olefin is also reported.

Contents

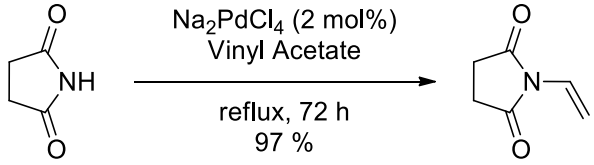
General remarks

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography, technical grade solvents were used. For flash chromatography, for analysis, HPLC grade solvents were used. THF, Et_2O, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H2O content < 7 ppm, Karl-Fischer titration). All chemicals were purchased and used as received unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC plastic plates and visualized with UV light, CAN or p-anisaldehyde stains. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, integration, coupling constant(s) in Hz, interpretation). ^{13}C-NMR spectra were recorded with 1H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.16 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prism and are reported as cm-1 (w = weak, m = medium, s = strong). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. Iron-Alumina complex was synthesized following the procedure of Tietze.[1] Diatereomeric mixtures have been assigned by 2D NMR experiments including COSY/ROESY/HSQC/HMBC. COmmercialy available N-Vinyl Phthalimide [3485-84-5], N-Vinyl-2-pyrrolidone [88-12-0] and Diethyl Ethylidenemalonate [1462-12-0] were used.

[1] Organic Syntheses, Vol. 71, p. 167 (1993); Coll. Vol. 9, p.310 (1998).

1. Synthesis of enimides

1-Vinylpyrrolidine-2,5-dione (4b)

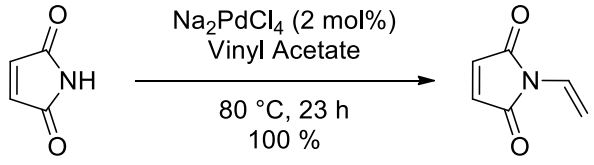


12 **4b**

Following a modified procedure,[2] to a stirred solution of pyrrolidine-2,5-dione (**12**) (1.00 g, 10.1 mmol, 1.00 eq) in vinyl acetate (25.0 mL, 270 mmol, 26.8 eq) was added Na_2PdCl_4 (59.0 mg, 0.202 mmol, 0.02 eq). The mixture was heated under reflux for 72 h. The crude was purified by Biotage (SNAP Cartridge KP-Sil 50 g, 7:3 Hexane/AcOEt) to obtain 1-vinylpyrrolidine-2,5-dione (**4b**) as a yellow solid (1.22 g, 9.78 mmol, 97 % yield).

R_f 0.17 (*Hexane*/*Ethyl acetate* 8/2).
Mp 47.6-48.9 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, 1 H, *J* = 16.4, 9.9 Hz, =*CH*), 6.08 (d, 1 H, *J* = 16.4 Hz, =*CH*), 5.06 (d, 1 H, *J* = 9.9 Hz, =*CH*), 2.72 (s, 4 H, *CH_2*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 124.3, 106.6, 27.8.
IR 2946 (w), 1707 (s), 1382 (s), 1307 (m), 1222 (s), 1113 (s), 974 (m), 906 (m), 821 (w).
HRMS (ESI) calcd for $C_6H_7NO_2^+$ $[M+H]^+$ 126.0555; found 126.0549.

1-Vinyl-*1H*-pyrrole-2,5-dione (4c)



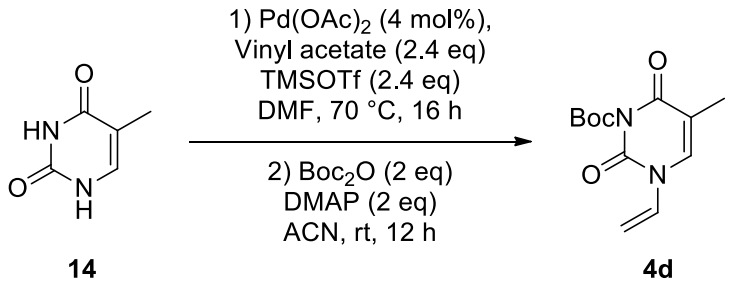
13 **4c**

1H-Pyrrole-2,5-dione (**13**) (1.30 g, 13.4 mmol, 1 eq), palladium(II) chloride (237 mg, 1.34 mmol, 0.1 eq), lithium chloride (57.0 mg, 1.34 mmol, 0.1 eq) and vinyl acetate (33.2 mL, 359 mmol) were added in a sealed tube under nitrogen. The mixture was heated at 80 °C for 23 h. The reaction was diluted with dichloromethane and 20 g of silica were added. The crude was concentrated under reduced pressure, and purified by Biotage (SNAP Cartridge KP-Sil 50 g, 7:3 Hexane/AcOEt) to afford 1-vinyl-1H-pyrrole-2,5-dione (**4c**) (1.74 g, 14.1 mmol, 100 % yield) as a yellow oil.

R_f 0.54 (*Hexane*/*Ethyl acetate* 7/3).
MP 66.2-69.7 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 2 H, *CH-C=O*), 6.67 (dd, 1 H, *J* = 16.4, 9.8 Hz, *CH-N*), 5.87 (d, 1 H, *J* = 16.3 Hz, =*CH_2*), 4.94 (d, 1 H, *J* = 9.8 Hz, =*CH_2*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 134.5, 123.1, 103.4.
IR 3087 (w), 1716 (s), 1641 (w), 1415 (m), 1384 (s).
HRMS (APPI) calcd for $C_6H_5NO_2^+$ $[M^+]$ 123.0320; found 123.0323.

tert-Butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(*6H*)-carboxylate (4d)

[2] Baret, N.; Dulcere, J.-P.; Rodriguez, J.; Pons, J.-M.; Faure, R. *Eur. J. Org. Chem.* **2000**, *2000*, 1507.



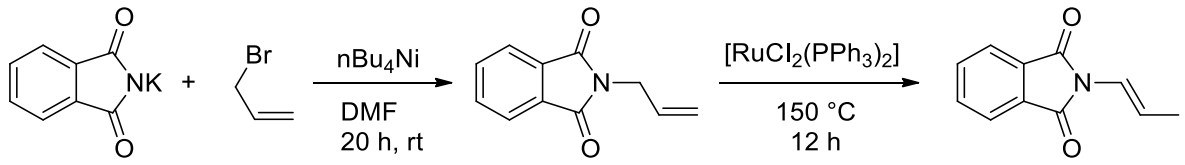
In a sealed vial were added palladium acetate (36.0 mg, 0.160 mmol, 0.04 eq), vinyl acetate (881 µl, 9.52 mmol, 2.4 eq), 5-methylpyrimidine-2,4(*1H*,*3H*)-dione (**14**) (500 mg, 3.96 mmol, 1eq), TMSOTf (1.72 mL, 9.52 mmol, 2.4 eq) and DMF (10.0 mL). The reaction was stirred for 16 hours at 70 °C, then water (25 mL) was added. The reaction was extracted three times with ethyl acetate (30 mL). Then, the organic layers were combined and washed three times with water (30 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with hexane/ethyl acetate/NEt_3 (7/3/0.01) to obtain 5-methyl-1-vinylpyrimidine-2,4(*1H*,*3H*)-dione (**15**) (269 mg, 1.77 mmol, 45% yield) as a colorless solid.

R_f 0.5 (*Hexane*/*Ethyl acetate* 1/1).
Mp 208.0-209.1°C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1 H, NH), 7.34 (s, 1 H, C=C-H), 7.21 (dd, 1 H, *J* = 16.0, 9.1 Hz, -CH=C *vinyl*), 5.07 (dd, 1 H, *J* = 16.0, 2.1 Hz, C=CH_2 *vinyl, trans*), 4.91 (dd, 1 H,*J* = 9.1, 2.1 Hz, C=CH_2 *vinyl, cis*), 1.99 (s, 3 H, Me).
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 149.3, 134.5, 129.6, 112.1, 100.5, 12.6.
IR 3180 (w), 3062 (w), 2827 (w), 1645 (s).
HRMS (ESI) calcd for $C_7H_9N_2O_2^+$ $[M+H]^+$ 153.0659; found 153.0653.

In an oven dried flask, 5-methyl-1-vinylpyrimidine-2,4(*1H*,*3H*)-dione (**15**) (920 mg, 6.05 mmol, 1 eq), di-*tert*-butyl dicarbonate (2.64 g, 12.1 mmol, 2 eq) and dimethylaminopyridine (1.48 g, 12.1 mmol, 2 eq) were stirred in acetonitrile (25.0 mL) for 12 h. Silica was added to the reaction and the solvent was evaporated. The dry residue was loaded on a silica chromatography column and eluted with hexane/ethyl acetate/1% NEt_3 (95:5 to 80:20) to provide *tert*-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(*6H*)-carboxylate (**4d**) (1.15 g, 4.56 mmol, 75% yield) as a colorless solid.

R_f 0.2 (*Hexane*/*Ethyl acetate* 9:1).
Mp 109.9-111.2 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1 H, C=C-H), 7.15 (dd, 1 H, *J* = 16.0, 9.1 Hz, -CH=C *vinyl*), 5.09 (dd, 1 H, *J* = 16.0, 2.2 Hz, C=CH_2 *vinyl, trans*), 4.94 (dd, 1 H, *J* = 9.1, 2.2 Hz, C=CH_2 *vinyl, cis*), 1.99 (s, 3 H), 1.60 (s, 9 H, Me).
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 147.6, 147.5, 134.0, 129.6, 111.8, 101.3, 87.1, 27.5, 12.7.
IR 2982 (w), 2937 (w), 1778 (s), 1721 (s), 1672 (s).
HRMS (ESI) calcd for $C_{12}H_{16}N_2O_4Na^+$ $[M+Na]^+$ 275.1002; found 275.1008.

(*E*)-2-(Prop-1-en-1-yl)isoindoline-1,3-dione (4f)

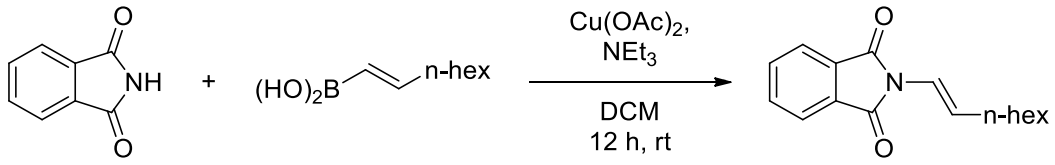


16 **17** **18** **4f**

Following a modified procedure,[3] allyl bromide (**17**) (2.6 mL, 30 mmol, 1.1 eq) was added dropwise at room temperature to a suspension of potassium phthalimide (**16**) (5.0 g, 27 mmol, 1 eq) and Bu_4NI (0.50 g, 1.4 mmol, 0.05 eq) in DMF (10 mL). The mixture was stirred for 20 hours at room temperature, and then H_2O (20 mL) was added. The precipitate was isolated by filtration, dried, and recrystallized from isopropanol to give 2-allylisoindoline-1,3-dione (**18**) (3.4 g, 18 mmol, 68% yield).
2-Allylisoindoline-1,3-dione 18 (2.0 g, 11 mmol, 1 eq) was added in a sealed tube under nitrogen atmosphere to $[RuCl_2(PPh_3)_2]$ (0.10 g, 0.11 mmol, 0.01 eq). The solids were heated at 150 °C during 12 hours and the reaction was cooled down to room temperature. The black mixture was dissolved in toluene and filtered on a celite pad. The solvents were evaporated and the brown orange solid was recrystallized in ethanol.(20 mL) of (*E*)-2-(prop-1-en-1-yl)isoindoline-1,3-dione (**4f**) (1.15 g, 6.10 mmol, 58% yield) as a yellow solid were collected from the first recrystallization.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 2 H, *J* = 5.2, 3.1 Hz, Phth), 7.72 (dd, 2 H, *J* = 5.2, 3.0 Hz, Phth), 6.64-6.54 (m, 2 H, CH=CH), 1.85 (d, 3 H, *J* = 5.1 Hz, CH_3).
HRMS (ESI) calcd for $C_{11}H_{10}NO_2^+$ $[M+H]^+$ 188.0706; found 188.0713.

^{1}H NMR data match literature report.[3]

(*E*)-2-(Oct-1-en-1-yl)isoindoline-1,3-dione (4g)



19 **20** **4g**

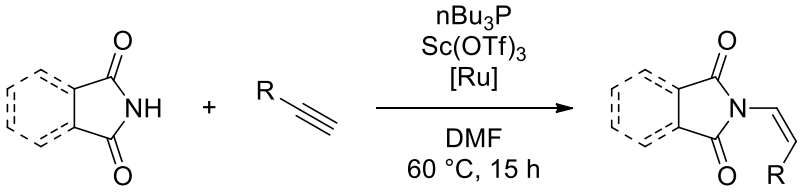
Following a modified procedure,[4] phthalimide (**19**) (200 mg, 1.36 mmol, 1 eq), copper(II)acetate monohydrate (300 mg, 1.50 mmol, 1.1 eq), dichloromethane (2 mL) and triethylamine (379 µL, 2.72 mmol, 2 eq) were added under air in a flask. Subsequently, (*E*)-oct-1-en-1-ylboronic acid (**20**) (212 mg, 1.36 mmol, 1 eq) was added as a solid. The reaction was stirred for 12 hours. Volatiles were removed under reduced pressure and the crude was directly purified by Biotage (SNAP cartridge KP-SIL 25 g, 95:5 to 4:6 Hexane/Ethyl acetate) to give (*E*)-2-(oct-1-en-1-yl)isoindoline-1,3-dione (**4g**) (127 mg, 0.490 mmol, 36% yield) as a pale yellow oil.

Rf 0.6 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2 H, Phth), 7.77-7.69 (m, 2 H, Phth), 6.61-6.57 (m, 2 H, CH=CH), 2.21-2.13 (m, 2 H, CH_2), 1.51-1.41 (m, 2 H, CH_2), 1.39-1.24 (m, 6 H, CH_2), 0.89 (t, 3 H, *J* = 7.0 Hz, CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 134.3, 131.8, 123.5, 123.1, 117.5, 31.7, 31.2, 29.4, 28.9, 22.7, 14.1.
IR 2956 (w), 2929 (w), 2858 (w), 1779 (w), 1719 (s), 1387 (s).

[3] Stojanovic, A.; Renaud, P.; Schenk, K. *Helv. Chim. Acta*, **2004**, *81*, 268.
[4]. Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927

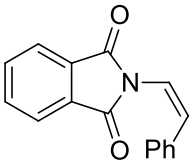
HRMS (ESI) calcd for $C_{16}H_{20}NO_2^+$ $[M+H]^+$ 258.1489; found 258.1499.

1.1. General procedure for the synthesis of (Z)-enimides



Following a modified procedure,[5] in the glovebox, bis-(2-methylallyl)cycloocta-1,5-diene ruthenium (12.8 mg, 0.0400 mmol, 0.02 eq), scandium triflate (39.4 mg, 0.0800 mmol, 0.04 eq) and imide (2.00 mmol, 1 eq) were added in a microwave vial. The vial was sealed with a Teflon septum and subsequently, tri-*n*-butylphosphine (30.0 µL, 0.120 mmol, 0.06 eq), alkyne (4.00 mmol, 2 eq) and freshly distilled DMF (6 mL) were added. The solution was stirred at 60 °C for 15 h and then poured into an aqueous sodium bicarbonate solution (20 mL). The mixture was extracted twice with ethyl acetate (20 mL). The organic fractions were collected, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by Biotage (SNAP cartridge KP-SIL 25 g, 95:5 to 4:6 Hexane/Ethyl acetate).

(*Z*)-2-Styrylisoindoline-1,3-dione ((*Z*)-4l)

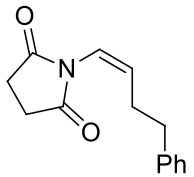


Phthalimide (294 mg, 2.00 mmol, 1 eq) and 1-hexyne (439 µl, 4.00 mmol, 2 eq) were combined to afford (Z)-2-styrylisoindoline-1,3-dione ((*Z*)-**4l**) (65 mg, 0.26 mmol, 13 % yield) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2 H, Phth), 7.79-7.72 (m, 2 H, Phth), 7.28-7.22 (m, 5 H, ArH), 6.71 (d, 1 H, *J* = 9.1 Hz, CH=CH), 6.34 (d, 1 H, *J* = 9.1 Hz, CH=CH).
HRMS (ESI) calcd for $C_{16}H_{12}NO_2^+$ $[M+H]^+$ 250.0863; found 250.0851.

^{1}H NMR Data match literature report.[5]

(*Z*)-1-(4-Phenylbut-1-en-1-yl)pyrrolidine-2,5-dione ((*Z*)-4k)



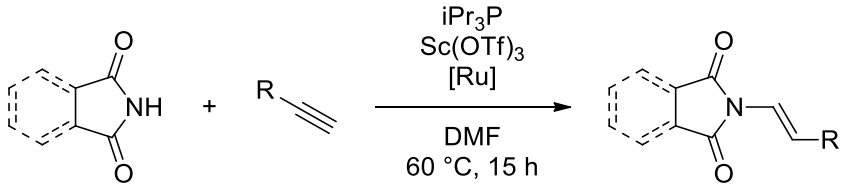
Succinimide (198 mg, 2.00 mmol, 1 eq) and but-3-yn-1-ylbenzene (562 µL, 4.00 mmol, 2 eq) were combined to afford (*Z*)-1-(4-phenylbut-1-en-1-yl)pyrrolidine-2,5-dione ((Z)-**4k**) (400 mg, 1.75 mmol, 87 % yield) as a brown light solid.

[5] Gooßen, L. J.; Blanchot, M.; Brinkmann, C.; Gooßen, K.; Karch, R.; Rivas-Nass, A. *J. Org. Chem.* **2006**, *71*, 9506.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2 H, ArH), 7.22-7.16 (m, 3 H , ArH), 5.92 (d, 1 H, *J* = 8.6 Hz , CH=CH), 5.76 (m, 1 H , CH=CH), 2.80-2.67 (m, 6 H , CH_2), 2.28 (m, 2 H , CH_2).
HRMS (ESI) calcd for $C_{14}H_{16}NO_2^+$ $[M+H]^+$ 230.1176; found 230.1175.

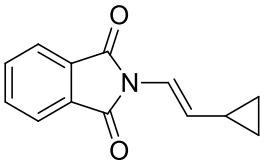
^{1}H NMR data match literature report.[5]

1.2. General procedure for the synthesis of (*E*)-enimides.



Following a modified procedure,[5] bis-(2-methylallyl)cycloocta-1,5-diene ruthenium (31.9 mg, 0.100 mmol, 0.05 eq), scandium triflate (39.4 mg, 0.0800 mmol, 0.04 eq) and imide (2.00 mmol, 1 eq) were added to a microwave vial in the glovebox. The vial was sealed with a Teflon septum and triisopropylphosphine (57.0 µL, 0.300 mmol, 0.15 eq), alkyne (4.00 mmol, 2 eq) and freshly distilled DMF (6 mL) were added. The solution was stirred at 60 °C for 15 h and then poured into an aqueous sodium bicarbonate solution (20 mL). The mixture was extracted twice with ethyl acetate (20 mL). The organic fractions were collected, washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by Biotage (SNAP cartridge KP-SIL 25 g, 95:5 to 4:6 Hexane/Ethyl acetate).

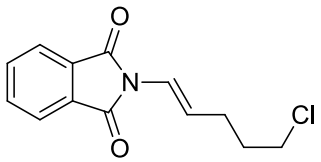
(*E*)-2-(2-Cyclopropylvinyl)isoindoline-1,3-dione (4h)



Phthalimide (294 mg, 2.00 mmol, 1 eq) and ethynylcyclopropane (339 µL, 4.00 mmol, 2 eq) were combined to afford (*E*)-2-(2-cyclopropylvinyl)isoindoline-1,3-dione (**4h**) (159 mg, 0.750 mmol, 37 % yield) as a yellow solid.

Mp 92.2-94.3 °C.
Rf 0.27 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.81 (m, 2 H, Phth), 7.76-7.68 (m, 2 H, Phth), 6.70 (d, 1 H, *J* = 14.6 Hz, N-CH=), 6.20 (dd, 1 H, *J* = 14.6, 9.0 Hz, =CH-C), 1.48 (m, 1 H, CH cyclopropane), 0.87-0.75 (m, 2 H, CH_2 cyclopropane), 0.56-0.48 (m, 2 H, CH_2 cyclopropane).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 134.2, 131.7, 126.6, 123.4, 115.7, 12.7, 6.9.
IR 3080 (w), 3016 (w), 1773 (w), 1772 (w), 1713 (s), 1612 (w), 1468 (w), 1393 (s), 1308 (w), 1207 (w), 1098 (w).
HRMS (ESI) calcd for $C_{13}H_{12}NO_2^+$ $[M+H]^+$ 214.0863; found 214.0854.

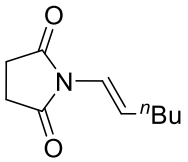
(*E*)-2-(5-Chloropent-1-en-1-yl)isoindoline-1,3-dione (4i)



Phthalimide (294 mg, 2.00 mmol, 1 eq) and 5-chloropent-1-yne (427 µL, 4.00 mmol, 2 eq) were combined to afford (*E*)-2-(5-chloropent-1-en-1-yl)isoindoline-1,3-dione (**4i)** (77 mg, 0.31 mmol, 15 % yield) as a yellow solid.

Mp 78.8-81.2 °C.
Rf 0.35 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.5, 3.1 Hz, 2H, Phth), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H, Phth), 6.68 (dt, *J* = 14.6, 1.2 Hz, 1H, N-CH=), 6.56 (dt, *J* = 14.6, 7.2 Hz, 1H, =CH-C), 3.59 (dd, *J* = 6.5 Hz, 6.5 Hz, 2H, CH_2), 2.39 – 2.30 (m, 2H, CH_2), 1.96 (dt, *J* = 7.9, 6.5 Hz, 2H, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 134.4, 131.6, 123.5, 120.4, 118.7, 44.2, 32.1, 28.23.
IR 2958 (w), 2847 (w), 1780 (w), 1714 (s), 1613 (w), 1436 (w), 1384 (s), 1266 (m), 1113 (w).
HRMS (ESI) calcd for $C_{13}ClH_{13}NO_2^+$ $[M+H]^+$ 250.0629; found 250.0633.

(*E*)-1-(Hex-1-en-1-yl)pyrrolidine-2,5-dione (4j)

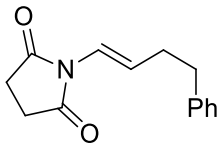


Succinimide (198 mg, 2.00 mmol, 1 eq) and hex-1-yne (463 µL, 4.00 mmol, 2 eq) were combined to afford (*E*)-1-(hex-1-en-1-yl)pyrrolidine-2,5-dione (**4j**) (242 mg,1.34 mmol, 67 % yield) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61-6.55 (m, 1 H, CH=CH), 6.45-6.40 (m, 1 H, CH=CH), 2.72 (s, 4 H , CH_2), 2.11 (qd, 2 H, *J* = 7.2, 1.1 Hz , CH_2), 1.46-1.27 (m, 4 H , CH_2), 0.89 (t, 3 H, *J* = 7.2 Hz , CH_3).
HRMS (ESI) calcd for $C_{10}H_{16}NO_2^+$ $[M+H]^+$ 182.1176; found 182.1177.

^{1}H NMR data match literature report.[5]

(*E*)-1-(4-Phenylbut-1-en-1-yl)pyrrolidine-2,5-dione (4k)



Succinimide (198 mg, 2.00 mmol, 1 eq) and but-3-yn-1-ylbenzene (562 µL, 4.00 mmol, 2 eq) were combined to afford (*E*)-1-(4-phenylbut-1-en-1-yl)pyrrolidine-2,5-dione (**4k**) (209 mg, 0.910 mmol, 46 % yield) as a brown light solid.

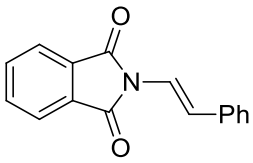
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2 H, ArH), 7.25-7.19 (m, 3 H, ArH), 6.75-6.63 (m, 1 H , CH=CH), 6.50 (d, 1 H, *J* = 14.9 Hz , CH=CH), 2.82-2.72 (m, 6 H , CH_2), 2.51-2.43 (m, 2 H , CH_2).
HRMS (ESI) calcd for $C_{14}H_{16}NO_2^+$ $[M+H]^+$ 230.1176; found 230.1175.

Data match literature report.[5]

1.3. General procedure for the synthesis of (*E)*-styrylphthalimide:

Following a reported procedure,[6] a mixture of aryl halide (4.00 mmol, 1 eq), N-vinylphthalimide (693 mg, 4.00 mmol, 1 eq), Cy_2NMe (1.17 g, 6.00 mmol, 1.5 eq), TBAB (1.29 g, 4.00 mmol, 1 eq) and palladium acetate (1.00 mg, 4.00 µmol, 0.001 eq) in DMF (8 mL) was heated at 120 °C (oil bath temperature) in a pressure tube after 5 cycles of vacuum/N_2. When full conversion was observed by TLC, the yellow solution was poured into toluene (40 mL) and rinsed with toluene (10 mL). This solution was filtered through a pad of celite and concentrated under vacuum. To the yellow oil was added ethanol (20 mL). The product precipitated and was recovered by filtration after rinsing with ethanol.

(*E*)-2-Styrylisoindoline-1,3-dione (4l)

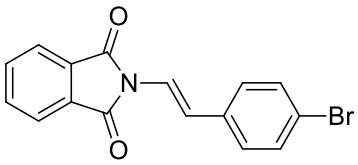


Phenyl iodide (816 mg, 4.00 mmol, 1 eq) was used and stirred 1h30 at 120 °C. (*E*)-2-styrylisoindoline-1,3-dione (**4l**) (700 mg, 2.77 mmol, 69% yield) was obtained as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.77 (dd, 2 H, *J* = 5.4, 3.1 Hz, Phth), 7.66 (d, 1 H, *J* = 15.2 Hz, CH=CH), 7.51-7.45 (m, 2 H, ArH), 7.40-7.32 (m, 3 H, ArH), 7.30-7.24 (m, 1 H, CH=CH).
HRMS (ESI) calcd for $C_{16}H_{12}NO_2^+$ $[M+H]^+$ 250.0863; found 250.0858.

Data match literature report.[7]

(*E*)-2-(4-Bromostyryl)isoindoline-1,3-dione (4m)



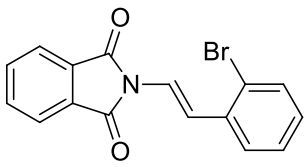
1-Bromo-4-iodobenzene (1.13 g, 4.00 mmol, 1 eq) was used and stirred 3h30 at 120 °C. (*E*)-2-(4-bromostyryl)isoindoline-1,3-dione (**4m**) (330 mg, 1.00 mmol, 25% yield) was obtained as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.88 (m, 2 H, Phth), 7.81-7.75 (m, 2 H, Phth), 7.60-7.54 (m, 1 H, CH=CH), 7.50-7.45 (m, 2 H, ArH), 7.38-7.31 (m, 3 H, ArH + CH=CH).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 135.0, 134.6, 131.8, 131.6, 127.7, 123.7, 121.4, 118.9, 118.1.

[6] Alacid, E.; Nájera, C. *Adv. Synth. Catal*. **2008**, *350*, 1316.
[7] Susanto, W.; Chu, C.-Y.; Ang, W. J.; Chou, T.-C.; Lo, L.-C.; Lam, Y. *J. Org. Chem*. **2012**, *77*, 2729.

Data match literature report, with a slight shift in the carbon spectra for the area 127.7-121.4.[8]

(*E*)-2-(2-Bromostyryl)isoindoline-1,3-dione (4n)

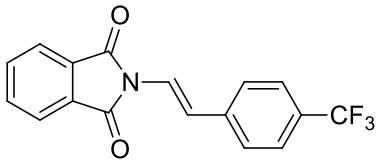


1-Bromo-2-iodobenzene (1.13 g, 4.00 mmol, 1 eq) was used and stirred 3h30 at 120 °C. (*E*)-2-(2-bromostyryl)isoindoline-1,3-dione (**4n**) (320 mg, 0.981 mmol, 24% yield) was obtained as a yellow powder after column chromatography Hexane:dichloromethane 95/5 to 1/1.

Mp 193.2-194.6 °C.
Rf 0.58 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 1 H, *J* = 15.0 Hz, CH=), 7.88-7.96 (m, 2 H, Phth), 7.74-7.82 (m, 2 H, Phth), 7.55-7.63 (m, 2 H, Ar), 7.27-7.36 (m, 2 H, Ar + CH=), 7.10-7.17 (m, 1 H, Ar).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 136.3, 134.7, 133.1, 131.7, 128.9, 127.7, 126.4, 124.1, 123.8, 119.6, 119.4.
IR 1724 (s), 1645 (w), 1383 (s), 1100 (w), 1086 (w), 950 (w).
HRMS (ESI) calcd for $C_{16}{}^{79}BrH_{11}NO_2^+$ $[M+H]^+$ 327.9968; found 327.9960.

Data does not match literature report.[6]

(*E*)-2-(4-(Trifluoromethyl)styryl)isoindoline-1,3-dione (4o)

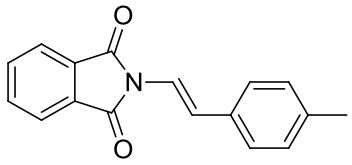


1-Iodo-4-(trifluoromethyl)benzene (1.08 g, 4.00 mmol, 1 eq) was used and stirred 1h30 at 120 °C. (*E*)-2-(4-(trifluoromethyl)styryl)isoindoline-1,3-dione (**4o**) (679 mg, 2.14 mmol, 54% yield) was obtained as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.90 (m, 2 H, Phth), 7.83-7.76 (m, 2 H, Phth), 7.70 (d, 1 H, *J* = 15.2 Hz, CH_2), 7.63-7.54 (m, 4 H, ArH), 7.45 (d, 1 H, *J* = 15.2 Hz, CH=CH).
HRMS (ESI) calcd for $C_{17}F_3H_{11}NO_2^+$ $[M+H]^+$ 318.0736; found 318.0724.

Data match literature report.[7]

(*E*)-2-(4-Methylstyryl)isoindoline-1,3-dione (4p)



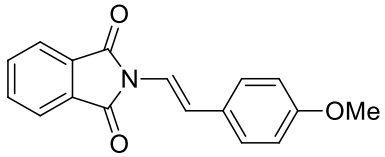
[8] Pawluć, P.; Franczyk, A.; Walkowiak, J.; Hreczycho, G.; Kubicki, M.; Marciniec, B.; *Tetrahedron*, **2012,** *68,* 3545.

1-Iodo-4-methylbenzene (872 mg, 4.00 mmol, 1 eq) was used and stirred 3h30 at 120 °C. (*E*)-2-(4-methylstyryl)isoindoline-1,3-dione (**4p**) (728 mg, 2.77 mmol, 69% yield) was obtained as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.88 (m, 2 H, Phth), 7.79-7.73 (m, 2 H, Phth), 7.63 (d, 1 H, *J* = 15.2 Hz, CH=CH), 7.38 (d, 2 H, *J* = 8.1 Hz, ArH), 7.32 (d, 1 H, *J*= 15.2 Hz, CH=CH), 7.17 (d, 2 H, *J* = 7.9 Hz, ArH), 2.36 (s, 3 H, CH_3).
HRMS (ESI) calcd for $C_{17}H_{14}NO_2^+$ $[M+H]^+$ 264.1019; found 264.1022.

Data match literature report.[7]

(*E*)-2-(4-Methoxystyryl)isoindoline-1,3-dione (4q)



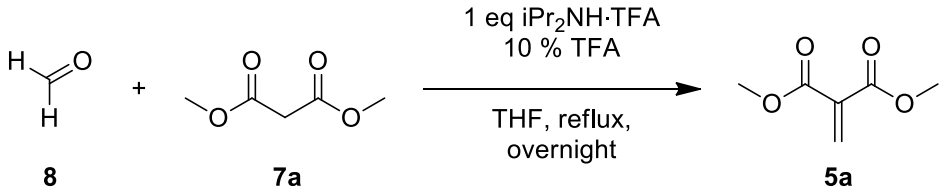
1-Iodo-4-methoxybenzene (936 mg, 4.00 mmol, 1 eq) was used and stirred 1h30 at 120 °C. (*E*)-2-(4-methoxystyryl)isoindoline-1,3-dione (**4q**) (780 mg, 2.79 mmol, 69% yield) was obtained as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.75 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 7.60 (d, 1 H, *J* = 15.2 Hz, CH=CH), 7.42 (d, 2 H, *J* = 8.6 Hz, ArH), 7.26-7.22 (m, 1 H, the doublet was covered by $CDCl_3$ peak, CH=CH), 6.90 (d, 2 H, *J* = 8.8 Hz, ArH), 3.83 (s, 3 H, CH_3).
HRMS (ESI) calcd for $C_{17}H_{14}NO_3^+$ $[M+H]^+$ 280.0968; found 280.0966.

Data match literature report.[7]

2. Synthesis of methylene malonates

Dimethyl 2-methylenemalonate (5a)

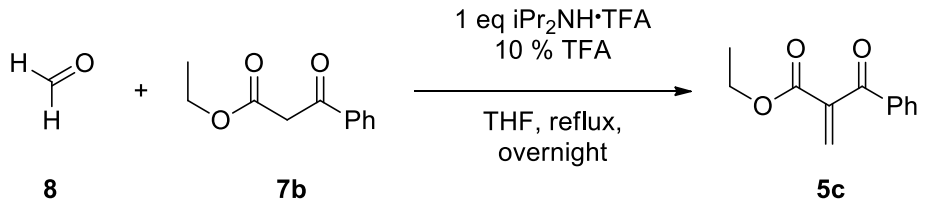


8 **7a** **5a**

Following a modified procedure,[9] dry THF (200 mL), dimethyl malonate (**7a**) (18.3 g, 139 mmol, 1eq), diisopropylamine 2,2,2-trifluoroacetate (29.9 g, 139 mmol, 1 eq), paraformaldehyde (8.35 g, 278 mmol, 2 eq) and trifluoroacetic acid (1.07 mL, 13.9 mmol, 0.1 eq) were added to a 500 mL round bottom flask. A condenser was added and the suspension was stirred to reflux for two hours. Paraformaldehyde (8.35 g, 278 mmol, 2 eq) was added and the reflux was restarted for 6 hours. The reaction was cooled to room temperature and THF was removed under reduced pressure (300 to 50 mbar at 45°C). The crude mixture was dissolved in diethyl ether (75 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1 M HCl (50 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a colorless oil (30 g). The crude oil was purified by distillation (all the glassware needed for distillation had been washed with 2 M HCl, rinsed with methanol and dried in the oven at 110 °C prior to use). Dimethyl 2-methylenemalonate (**5a**) (13.6 g, 94.0 mmol, 68% yield) was collected as a colorless oil between 45 °C at 1.5 mbar and 50 °C at 1 mbar. The product was stored under nitrogen in a freezer and can be kept 2-3 weeks without major degradation. In case of degradation, a short path distillation was enough to obtain pure material.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 2 H), 4.57 (s, 6 H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.38, 135.36, 134.14, 52.59.
IR 1792 (w), 1736 (s), 1440 (m), 1340 (m), 1244 (s), 1128 (s).
HRMS (ESI) calcd for $C_6H_9O_4^+$ $[M+H]^+$ 145.0495; found 145.0502.

Ethyl 2-benzoylacrylate (5c)



8 **7b** **5c**

Following a modified procedure,[9] dry THF (20 mL), ethyl 3-oxo-3-phenylpropanoate (**7b**) (2.50 g, 13.0 mmol, 1 eq), diisopropylamine 2,2,2-trifluoroacetate (2.80 g, 13.0 mmol, 1 eq), paraformaldehyde (780 mg, 27.0 mmol, 2eq) and trifluoroacetic acid (0.100 mL, 1.30 mmol, 0.1 eq) were added to a 50 mL round bottom flask. A condenser was added and the suspension was stirred to reflux for two hours. Paraformaldehyde (780 mg, 27.0 mmol, 2 eq) was added and the reflux was restarted for 6 hours. The reaction was cooled to room temperature and THF was removed under reduced pressure. The crude was dissolved in diethyl ether (20 mL) and filtered through cotton in a

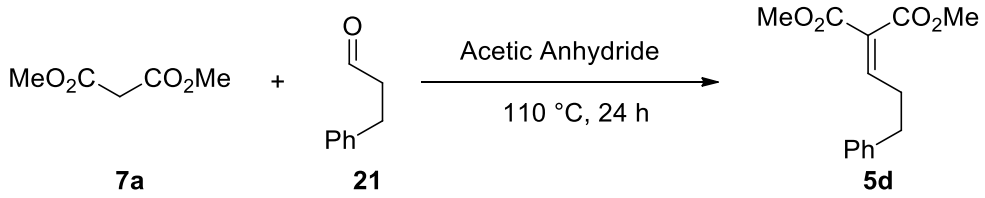
[9] Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun*. **2010,** *46*, 1715.

separatory funnel. The organic layer was washed twice with 1 M HCl (20 mL). The aqueous layers were combined and extracted with diethyl ether (20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a yellow oil. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording ethyl 2-benzoylacrylate (**5c**) (1.75 g, 8.57 mmol, 66 % yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.4, 1.4 Hz, 2H, ArH), 7.65-7.56 (m, 1H, ArH), 7.51-7.42 (m, 2H, ArH), 6.70 (d, *J* = 0.8 Hz, 1H, C=CH_2), 6.07 (d, *J* = 0.8 Hz, 1H, C=CH_2), 4.23 (q, *J* = 7.1 Hz, 2H, CH_2), 1.20 (t, *J* = 7.2 Hz, 3H, CH_3).
HRMS (ESI) calcd for $C_{12}H_{13}O_3^+$ $[M+H]^+$ 205.0859; found 205.0867.

Data match literature report.[10]

Dimethyl 2-(3-phenylpropylidene)malonate (5d)



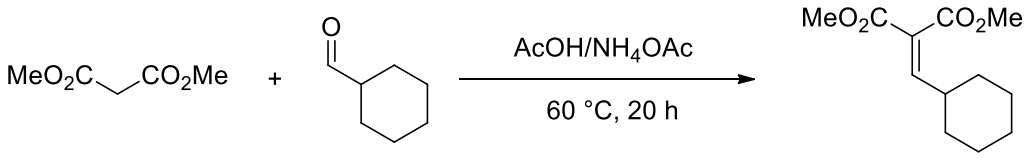
7a **21** **5d**

Following a modified reported procedure,[11] dimethyl malonate (**7a**) (661 mg, 5.00 mmol, 1 eq), acetic anhydride (708 µL, 7.50 mmol, 1.5 eq) and 3-phenylpropanal (**21**) (1.33 mL, 10.0 mmol, 2 eq) were added in a microwave vial. The vial was sealed and the reaction was stirred 24 hours at 110 °C. Evaporation of the acetic anhydride on the rotary evaporator and high vacuum afforded an oil that was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 98:2 Hexane/Ethyl acetate to 95:5 Hexane/Ethyl acetate). Dimethyl 2-(3-phenylpropylidene)malonate (**5d**) (690 mg, 2.78 mmol, 56 % yield) was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H, ArH), 7.24 – 7.16 (m, 3H, ArH), 7.07 (dd, *J* = 7.7, 7.7 Hz, 1H, C=CH), 3.81 – 3.75 (m, 6H, OCH_3), 2.80 (dd, *J* = 8.7, 6.7 Hz, 2H, CH_2), 2.63 (dd, *J* = 7.6, 7.6 Hz, 2H, CH_2).
HRMS (ESI) calcd for $C_{14}H_{16}NaO_4^+$ $[M+Na]^+$ 271.0941; found 271.0933.

Data match literature report.[12]

Dimethyl 2-(cyclohexylmethylene)malonate (5e)



7a **22** **5e**

Dimethyl malonate (**7a**) (2.14 g, 16.2 mmol, 1 eq), AcOH (30 mL), cyclohexanecarbaldehyde (**22**) (2.00 g, 17.8 mmol, 1 eq) and ammonium acetate (1.37 g, 17.8 mmol, 1.1 eq) were added to a 50 mL

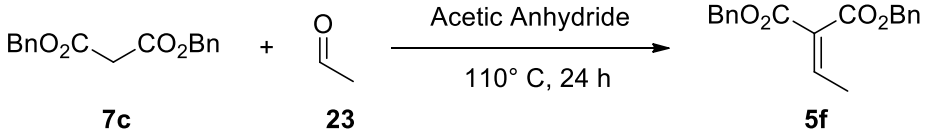
[10] De Fusco, C.; Fuoco, T.; Croce, G.; Lattanzi, A. *Org. Lett.* **2012**, *14*, 4078.
[11] Jabin I.; Revial G.; Monnier-Benoit N.; Netchitailo P. *J. Org. Chem.* **2001**, *66*, 256.
[12] Nickerson, D. M.; Mattson. A. E. *Chem. Eur. J.* **2012**, *18*, 8310.

round bottom flask. A condenser was added and the suspension was stirred at 60 °C for 20 hours. The reaction was poured in brine (25 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed three times with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, Hexane/Ethyl Acetate 95:5) affording dimethyl 2-(cyclohexylmethylene)malonate (**5e**) (2.80 g, 12.4 mmol, 76 % yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 10.4 Hz, 1H, C=CH), 3.83 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.37 (dtt, *J* = 14.1, 6.6, 3.5 Hz, 1H, CH), 1.79 – 1.61 (m, 5H, CH_2), 1.36 – 1.08 (m, 5H, CH_2).
HRMS (ESI) calcd for $C_{12}H_{19}O_4^+$ $[M+H]^+$ 227.1278; found 227.1280.

Data match literature report.[13]

Dibenzyl 2-ethylidenemalonate (5f)

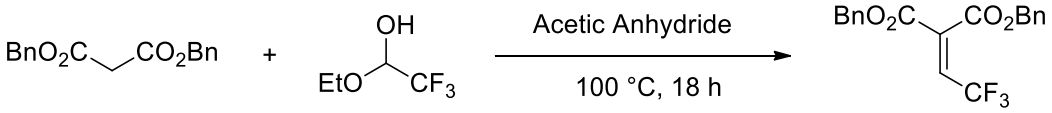


7c **23** **5f**

Following a modified reported procedure,[11] dibenzyl malonate (**7c**) (2.00 g, 7.03 mmol, 1 eq), acetic anhydride (1.08 g, 10.6 mmol, 1.5 eq) and acetaldehyde (**23**) (1.55 g, 35.2 mmol, 5 eq) were added in a microwave vial. The vial was sealed and the reaction was stirred 24 hours at 85 °C. Evaporation of the acetic anhydride on the rotary evaporator and high vacuum afforded an oil that was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:2 to 7:3 Hexane/Ethyl acetate). Dibenzyl 2-ethylidenemalonate (**5f**) (1.10 g, 3.54 mmol, 50 % yield + some traces of malonate left) was obtained as a colorless oil.

R_f 0.6 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 10H, ArH), 7.18 (q, *J* = 7.3 Hz, 1H, =CH), 5.28 (s, 2H, CH_2Ar), 5.22 (s, 2H, CH_2Ar), 1.96 (d, *J* = 7.3 Hz, 3H, Me).
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.07, 163.64, 146.33, 135.53, 135.37, 129.05, 128.57, 128.52, 128.42, 128.30, 128.21, 128.04, 67.04, 66.85, 15.66.
IR 3066 (w), 3035 (w), 2954 (w), 1731 (s), 1499 (w), 1262 (s), 1216 (s), 1138 (m), 1050 (m), 1003 (w), 744 (m).
HRMS (ESI) calcd for $C_{19}H_{19}O_4^+$ $[M+H]^+$ 311.1278; found 311.1281.

Dibenzyl 2-(2,2,2-trifluoroethylidene)malonate (5g)



7c **24** **5g**

Dibenzyl malonate (**7c**) (300 mg, 1.06 mmol, 1 eq), acetic anhydride (500 µL, 5.28 mmol, 5 eq) and 1-ethoxy-2,2,2-trifluoroethan-1-ol (**24**) (368 µL, 3.17 mmol, 3 eq) were added in a microwave vial. The vial was sealed and the reaction was stirred 18 hours at 100 °C. After going back to room temperature the reaction was transferred into a separatory funnel and sat.$NaHCO_3$ (15 mL) and diethyl ether (20

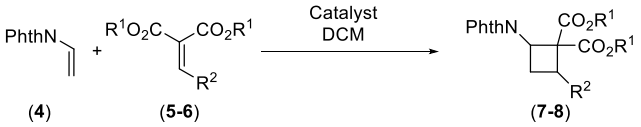
[13] Nickerson, D. M.; Mattson. A. E. *Chem. Eur. J.* **2012**, *18*, 8310.

mL) were added. The layers were separated and the organic layer was dried over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure and the obtained oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 98:2 to 95:5 Hexane/Ethyl acetate). Dibenzyl 2-(2,2,2-trifluoroethylidene)malonate (**5g**) (162 mg, 0.401 mmol, 90 % yield, 90% pure by NMR) was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 10H, ArH), 6.73 (q, *J* = 7.5 Hz, 1H, C=CH), 5.21 (s, 2H, CH_2), 5.18 (s, 2H, CH_2).
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3.
Data match literature report.[14]

[14] L. Wen, Q. Shen, L. Lu, *Org. Lett.* **2010**, *12*, 4655.

3. Screening of Lewis acids



(**4**) (**5-6**) (**7-8**)

Entry	Cat.(mol %)	t (h)	R	T°C	Conversion[a]
1	$ZnBr_2$ (100)	1	R^1=Me, R^2=H (**5/7**)	-78	0
2	$Yb(OTf)_3$ (10)	0.75	R^1=Me, R^2=H (**5/7**)	-78	0
3	$Sc(OTf)_3$ (10)	0.75	R^1=Me, R^2=H (**5/7**)	-78	traces
4	$Sc(OTf)_3$ (10)	0.75	R^1=Me, R^2=H (**5/7**)	-30	35
5	$Sc(OTf)_3$ (10)	0.5	R^1=Me, R^2=H (**5/7**)	0	100
6	$Sc(OTf)_3$ (20)	12	R^1=Et, R^2=Me (**6/8**)	rt	0
7	$In(OTf)_3$ (20)	12	R^1=Et, R^2=Me (**6/8**)	rt	60
8	$FeCl_3.Al_2O_3$ (20)	12	R^1=Et, R^2=Me (**6/8**)	rt	100

Reaction with $ZnBR_2$:

The reaction vessel was washed with aq HCl, rinsed with MeOH and dried in the oven.

Following a modified procedure[15], $ZnBr_2$ (247 mg, 1.10 mmol, 1.6 eq) was added in a flask and dichloromethane (1.5 mL) was added. Vinyl phthalimide (228 mg, 1.30 mmol, 1.9 eq) was dissolved in a second flask and dichloromethane (1.5 mL) was added. Dimethyl 2-methylenemalonate (100 mg, 0.694 mmol, 1eq) was added in a third flask and dissolved in dichloromethane (1.5 mL).

The flask containing the $ZnBr_2$ solution was cooled down to -130 °C with heptane/liq N_2. The dimethyl 2-methylenemalonate solution and the vinyl phthalimide solution were then slowly cannulated to the reaction mixture. The solvents were solid under these conditions.

The flask was warmed to -78 °C. When the solution became liquid again, the reaction was stirred for 1 hour at -78 °C. Pyridine (0.4 mL) in dichloromethane (1 mL) cooled to -78 °C was added to give an orange solution whichwas warmed to room temperature. A saturated Rochelle salt solution was added and the layers were separated. The organic layer was dried over $MgSO_4$ and evaporated. The crude mixture was analyzed by ^{1}H NMR and only vinyl phthalimide was observed.

Reaction with $Yb(OTf)_3$, $Sc(OTf)_3$ and diethyl 2-ethylidenemalonate (**5b**):

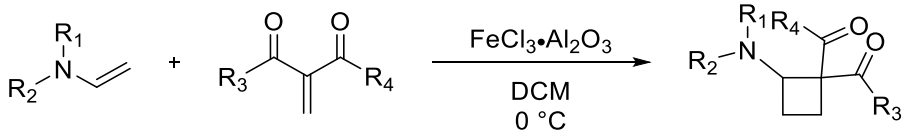
The Lewis acid (0.014 mmol, 0.1 eq) was weighted in the glovebox and dry dichloromethane (200 µL) was added. The reaction was cooled at the indicated temperature. Diethyl 2-ethylidenemalonate (20.0 mg, 0.139 mmol, 1 eq) and 2-vinylisoindoline-1,3-dione (18.5 mg, 0.167 mmol, 1.2 eq) were dissolved in dry dichloromethane (800 µL) and the resulting solution was added dropwise via syringe pump for the indicated time. After the addition was complete, the reaction was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was analyzed by ^{1}H NMR.

Reaction with $In(OTf)_3$, $Sc(OTf)_3$ and $FeCl_3.Al_2O_3$ and dimethyl 2-ethylidenemalonate:

The Lewis acid (0.012 mmol, 0.2 eq) was weighted in the glovebox and dry dichloromethane (0.20 mL) was added. Dimethyl 2-ethylidenemalonate (13 mg, 0.087 mmol, 1 eq) and 2-vinylisoindoline-1,3-dione (10 mg, 0.058 mmol, 1 eq) were dissolved in dry dichloromethane (0.80 mL) and added dropwise. After stirring for the indicated time, the reaction was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was analyzed by ^{1}H NMR.

[15] A. T. Parsons, J. S. Johnson, *J. Am. Chem. Soc*. **2009**, *131*, 14202

4. Synthesis of cyclobutanes



4.1. General procedure **A** for the synthesis of cyclobutanes

In the glovebox, iron trichloride supported on alumina (1.00 mmol/g, 20.0 mg, 0.0200 mmol, 0.1 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (200 µL) was added and the yellow suspension was cooled to 0 °C. The methylene malonate (0.400 mmol, 2 eq) and vinyl amide (0.200 mmol, 1 eq) were dissolved in dry dichloromethane (800 µL). The solution was then added dropwise to the iron trichloride. The reaction was stirred at 0 °C or room temperature and the conversion was followed by TLC (Hexane/Ethyl Acetate 7:3). When full conversion of the vinyl compound was observed, the reaction was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography using the indicated solvents.

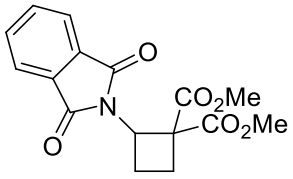
4.2. General procedure **B** for the synthesis of cyclobutanes

In the glovebox, iron trichloride supported on alumina (1.00 mmol/g, 20.0 mg, 0.0200 mmol, 0.1 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and took out of the glovebox. Dry dichloromethane (200 µL) was added. The methylene malonate (0.40 mmol, 2 eq) and vinyl amide (0.200 mmol, 1 eq) were dissolved in dry dichloromethane (800 µL). The solution was then added dropwise to the iron trichloride. The reaction was stirred at room temperature and the conversion was followed by TLC (Hexane/Ethyl Acetate 7:3). When full conversion of the vinyl compound was observed, the reaction was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography as indicated.

4.3. General procedure **C** for the synthesis of cyclobutanes

In the glovebox, iron trichloride supported on alumina (1.00 mmol/g, 20.0 mg, 0.0200 mmol, 0.1 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and took out of the glovebox. Dry dichloromethane (200 µL) was added and the vinyl amide (0.200 mmol, 1 eq) was dissolved in dry dichloromethane (500 µL) and added to the iron trichloride. The methylene malonate (0.400 mmol, 2 eq or 0.800 mmol, 4 eq) was dissolved in dry dichloromethane (300 µL) and added dropwise over 2 hours. When the addition was finished, the reaction was stirred at room temperature until TLC indicated that no more starting material was present. The reaction was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography.

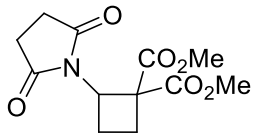
Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6aa)



Using general procedure **A**, 2-vinylisoindoline-1,3-dione (34.6 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 20 minutes at 0 °C. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 5:5 Hexane/Ethyl acetate) affording cyclobutane **6aa** (61.1 mg, 0.190 mmol, 96 % yield) as a colorless solid.

R_f 0.45 (*Hexane*/*Ethyl acetate* 1/1).
Mp 124.1-126.3 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 2 H, Phth), 7.80 (m, 2 H, Phth), 5.17 (t, 1 H, *J* = 10.9 Hz, N-C-H), 3.16 (s, 3 H, CO_2CH_3), 2.98 (s, 3 H, CO_2CH_3), 2.58 (m, 1 H, CH_2), 2.25 (m, 1 H, CH_2), 1.48 (m, 1 H, CH_2), 1.33 (dt, 1 H, *J* = 13.6, 10.4 Hz, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.7, 168.3, 134.3, 131.9, 123.5, 59.0, 53.2, 53.0, 47.9, 24.7, 21.9.
IR 2956 (w), 2848 (w), 1782 (w), 1781 (w), 1741 (s), 1721 (s), 1437 (w), 1378 (m), 1266 (m).
HRMS (ESI) calcd for $C_{16}H_{16}NO_6^+$ $[M+H]^+$ 318.0972; found 318.0978.

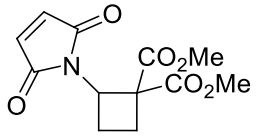
Dimethyl 2-(2,5-dioxopyrrolidin-1-yl)cyclobutane-1,1-dicarboxylate (6ba)



Using general procedure **A**, 1-vinylpyrrolidine-2,5-dione (25.0 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 30 minutes at 0 °C. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ba** (48.8 mg, 0.180 mmol, 91 % yield) as a colorless oil.

R_f 0.35 (*Hexane*/*Ethyl acetate* 6/4).
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (dd, 1 H, *J* = 9.2, 9.2 Hz, N-C-H), 3.74 (s, 3 H, CO_2CH_3), 3.70 (s, 3 H, CO_2CH_3), 3.18-3.03 (m, 1 H, CH_2), 2.98-2.86 (m, 1 H, CH_2), 2.77-2.55 (m, 4 H, Succinimide), 2.26-2.11 (m, 2 H, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 170.5, 168.6, 57.7, 53.1, 52.9, 48.2, 28.0, 24.8, 20.7.
IR 2956 (w), 2848 (w), 1778 (w), 1736 (s), 1706 (s), 1436 (m), 1378 (s), 1262 (s), 1198 (m), 1116 (s).
HRMS (ESI) calcd for $C_{12}H_{15}NNaO_6^+$ $[M+Na]^+$ 292.0792; found 292.0799.

Dimethyl 2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)cyclobutane-1,1-dicarboxylate (6ca)

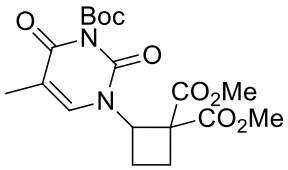


Using general procedure **A**, 1-vinyl-*1H*-pyrrole-2,5-dione (24.6 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 60 minutes at 0 °C. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutanes **6ca** (28.2 mg, 0.100 mmol, 48 % yield) as a colorless oil.

R_f 0.19 (*Hexane*/*Ethyl acetate* 7/3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 2 H, Maleimide), 5.27 (dd, 1 H, *J* = 9.4, 9.4 Hz, N-C-H), 3.74 (s, 3 H, CO_2CH_3), 3.67 (s, 3 H, CO_2CH_3), 3.14 (m, 1 H, CH_2), 2.88 (m, 1 H, CH_2), 2.25 (m, 1 H, CH_2), 2.13 (m, 1 H, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.4, 168.5, 134.2, 58.8, 53.1, 53.0, 47.5, 24.3, 21.7.
IR 2958 (w), 1736 (s), 1709 (s), 1437 (w), 1405 (w), 1379 (m), 1265 (s), 1107 (m).
HRMS (ESI) calcd for $C_{12}H_{13}NNaO_6^+$ $[M+Na]^+$ 290.0635; found 290.0629.

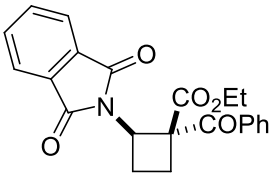
Dimethyl 2-(3-(tert-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)cyclobutane-1,1-dicarboxylate (6da)



Using general procedure **A**, (tert-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(*6H*)-carboxylate (50.5 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 3 hours at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6da** (60.0 mg, 0.150 mmol, 76 % yield) as a colorless oil.

R_f 0.18 (*Hexane*/*Ethyl acetate* 6/4).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1 H, C=CH), 5.22 (dd, 1 H, *J* = 9.5, 9.5 Hz, N-C-H), 3.76 (s, 3 H, CO_2CH_3), 3.69 (s, 3 H, CO_2CH_3), 2.96-2.84 (m, 1 H, CH_2), 2.81-2.72 (m, 1 H, CH_2), 2.38-2.27 (m, 1 H, CH_2), 2.18-2.07 (m, 1 H, CH_2), 1.92 (s, 3 H, Me), 1.59 (s, 9 H, Boc).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.5, 161.3, 149.1, 147.8, 138.0, 110.0, 86.7, 59.1, 56.2, 53.2, 53.1, 27.5, 23.6, 22.9, 12.5.
IR 2984 (w), 2957 (w), 1784 (m), 1734 (s), 1713 (m), 1667 (s), 1437 (m), 1371 (m), 1263 (s), 1238 (s), 1147 (s), 1108 (m).
HRMS (ESI) calcd for $C_{18}H_{25}N_2O_8^+$ $[M+H]^+$ 397.1605; found 397.1605.

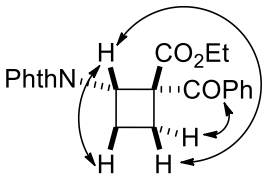
Ethyl 1-benzoyl-2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1-carboxylate (6ac)



Using general procedure **A**, 2-vinylisoindoline-1,3-dione (34.6 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (82.0 mg, 0.400 mmol) were stirred for 4 hours at 0 °C. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ac** (46.8 mg, 0.120 mmol, 62 % yield, 2.5:1 dr determined by integration of the peaks at 3.31-3.23 (*maj*), and 3.04-2.93(min) in the crude ^{1}H NMR) as a colorless oil.

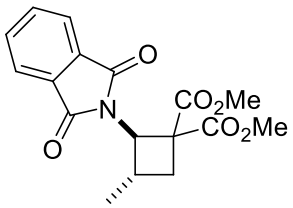
R_f 0.35 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) on a 3(*maj*.):1(*min*.) mixture δ 7.91-7.82 (m, 12 H, Phth and Ar *maj*.), 7.75-7.68 (m, 6 H, Phth *maj*.), 7.64-7.56 (m, 6 H, Phth and Ar *min*.), 7.56-7.50 (m, 4 H, Ar *maj*.), 7.44-7.39 (m, 6 H, Ar *maj*.), 7.20-7.10 (m, 3 H, Ar *min*.), 5.85-5.80 (m, 1 H, N-C-H *min*.), 5.76 (dd, 3

H, *J* = 9.5, 9.5 Hz, N-C-H *maj*.), 4.19 (qd, 2 H, *J* = 7.1, 1.4 Hz, COOEt *min*.), 4.00-3.85 (m, 6 H, COOEt *maj*.), 3.51-3.37 (m, 4 H, CH_2 *maj*. and *min*.), 3.31-3.23 (m, 3 H, CH_2 *maj*.), 3.04-2.93 (m, 1 H, CH_2 *min*.), 2.56-2.44 (m, 1 H, CH_2 *min*.), 2.33-2.23 (m, 4 H, CH_2 *maj*. and *min*.), 2.22-2.14 (m, 3 H, CH_2 *maj*.), 1.11 (t, 3 H, *J* = 7.1 Hz, COOEt *min*.), 0.77 (t, 10 H, *J*= 7.2 Hz, COOEt *maj*.).
^{13}C NMR (101 MHz, $CDCl_3$) *maj.* δ 193.5, 169.1, 168.2, 134.2, 133.9, 133.5, 131.8, 129.0, 128.7, 123.4, 65.6, 62.1, 46.9, 25.3, 22.0, 13.5
^{13}C NMR (101 MHz, $CDCl_3$) *min.* δ 192.7, 171.7, 167.9, 135.4, 133.9, 132.6, 131.3, 128.5, 128.2, 123.0, 62.2, 62.0, 48.2, 25.5, 21.8, 13.9.
IR 1780 (w), 1734 (s), 1719 (s), 1436 (w), 1377 (s), 1263 (s), 1200 (w).
HRMS (ESI) calcd for $C_{22}H_{20}NO_5^+$ $[M+H]^+$ 378.1336; found 378.1338.
Stereochemistry was assigned by 2D ROESY NMR experiment.



ROESY for minor

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)-3-methylcyclobutane-1,1-dicarboxylate (6fa)

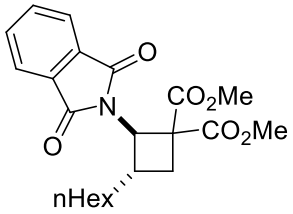


Using general procedure **A**, (*E*)-2-(prop-1-en-1-yl)isoindoline-1,3-dione (37.4 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 20 minutes at 0 °C. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6fa** (55.2 mg 0.170 mmol, 83 % yield) as a colorless solid. The product was recrystallized in ethanol.[16]

R_f 0.26 (*Hexane*/*Ethyl acetate* 7/3).
Mp 112.1-114.3 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2 H, Phth), 7.72 (m, 2 H, Phth), 4.96 (d, 1 H, *J* = 10.3 Hz, N-C-H), 3.71 (m, 4 H, CO_2CH_3 and C-H-CH_3), 3.60 (s, 3 H, CO_2CH_3), 3.00 (dd, 1H, *J* = 10.9, 9.3 Hz, CH_2), 1.74 (dd, 1 H, *J* = 11.5, 9.5 Hz, CH_2), 1.16 (d, 3 H, *J* = 6.6 Hz, CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 168.6, 168.3, 134.2, 131.8, 123.4, 56.3, 54.9, 53.0, 52.9, 32.1, 29.9, 19.3.
IR 3006 (w), 2955 (w), 2869 (w), 1780 (w), 1735 (s), 1716 (s), 1437 (w), 1379 (s), 1261 (s).
HRMS (ESI) calcd for $C_{17}H_{18}NO_6^+$ $[M+H]^+$ 332.1129; found 332.1124.

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)-3-hexylcyclobutane-1,1-dicarboxylate (6ga)

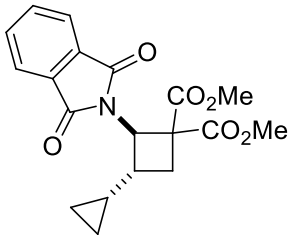
[16] The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 933180.



Using general procedure **A**, (*E*)-2-(oct-1-en-1-yl)isoindoline-1,3-dione (51.5 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 60 minutes at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ga** (68.2 mg, 0.170 mmol, 85 % yield) as a colorless oil.

R_f 0.3 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.80 (m, 2 H, Phth), 7.74-7.69 (m, 2 H, Phth), 5.03 (d, 1 H, *J* = 10.2 Hz, N-C-H), 3.73 (s, 3 H, CO_2CH_3), 3.54-3.65 (m, 4 H, CO_2CH_3 + CH_2 cyclobutane), 2.99 (ddd, 1 H, *J* = 11.4, 9.3, 0.5 Hz, CH_2 cyclobutane), 1.73 (dd, 1 H, *J* = 11.5, 9.3 Hz, CH_2 cyclobutane), 1.60-1.40 (m, 2 H, CH_2 hexyl), 1.25-1.10 (m, 8 H, CH_2 hexyl), 0.84-0.74 (m, 3 H, CH_3 hexyl).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 168.6, 168.2, 134.2, 131.7, 123.4, 56.1, 53.6, 53.0, 53.0, 34.8, 34.7, 31.7, 30.7, 29.1, 26.6, 22.5, 14.0.
IR 2955 (w), 2925 (w), 2855 (w), 1781 (w), 1738 (s), 1716 (s).
HRMS (ESI) calcd for $C_{22}H_{28}NO_6^+$ $[M+H]^+$ 402.1911; found 402.1914.

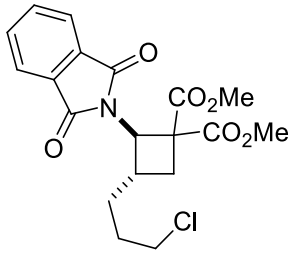
Dimethyl -3-cyclopropyl-2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6ha)



Using general procedure **B**, (*E*)-2-(2-Cyclopropylvinyl)isoindoline-1,3-dione (42.6 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 60 minutes at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ha** (53.1 mg, 0.150 mmol, 74 % yield) as a colorless oil.

R_f 0.20 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H, Phth), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H, Phth), 5.10 (d, *J* = 10.4 Hz, 1H, N-C-H), 3.75 (s, 3H, CO_2CH_3), 3.59 (s, 3H, CO_2CH_3), 3.36-3.20 (m, 1H, CH_2 cyclobutane), 2.92 (dd, *J* = 11.3, 9.4 Hz, 1H, CH_2 cyclobutane), 1.83 (dd, *J* = 11.5, 9.6 Hz, 1H, CH_2 cyclobutane), 0.85 (qt, *J* = 8.1, 4.9 Hz, 1H, CH cyclopropane), 0.55-0.27 (m, 2H, CH_2 cyclopropane), 0.23-0.04 (m, 2H, CH_2 cyclopropane).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 168.7, 168.4, 134.3, 131.9, 123.5, 56.0, 53.1, 53.1, 53.0, 38.4, 29.8, 13.6, 2.7, 2.6.
IR 3081 (w), 3005 (w), 2957 (w), 1779 (w), 1737 (s), 1715 (s), 1436 (m), 1377 (s), 1265 (s), 1199 (m), 1144 (m), 1049 (w).
HRMS (ESI) calcd for $C_{19}H_{20}NO_6^+$ $[M+H]^+$ 358.1285; found 358.1283.

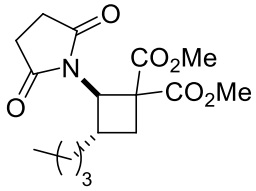
Dimethyl 3-(3-chloropropyl)-2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6ia)



Using general procedure **B**, (*E*)-2-(5-chloropent-1-en-1-yl)isoindoline-1,3-dione (49.9 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 60 minutes at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ia** (75.1 mg, 0.190 mmol, 95 % yield) as a colorless oil.

R_f 0.25 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2 H, Phth), 7.78-7.69 (m, 2 H, Phth), 5.06 (d, 1 H, *J* = 10.1 Hz, N-C-H), 3.75 (s, 3 H, CO_2CH_3), 3.71-3.57 (m, 4 H, CO_2CH_3 + Ar-C-H), 3.52-3.43 (m, 2 H, CH_2-Cl), 3.03 (dd, 1 H, *J* = 11.3, 9.5 Hz, CH_2 cyclobutane), 1.78 (dd, 1 H, *J* = 11.5, 9.3 Hz, CH_2 cyclobutane), 1.74-1.65 (m, 4 H, CH_2 alkyl chain).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.4, 168.2, 134.3, 131.7, 123.4, 56.0, 53.5, 53.1, 53.0, 44.6, 34.1, 33.0, 30.6, 29.8.
IR 2954 (w), 1781 (w), 1736 (s), 1714 (s), 1436 (w), 1378 (s), 1263 (s), 1262 (s), 1200 (m), 1072 (m).
HRMS (ESI) calcd for $C_{19}ClH_{21}NO_6^+$ $[M+H]^+$ 394.1052; found 394.1053.

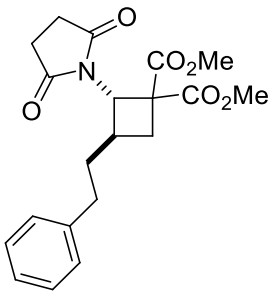
Dimethyl -3-butyl-2-(2,5-dioxopyrrolidin-1-yl)cyclobutane-1,1-dicarboxylate (6ja)



Using general procedure **B**, (*E*)-1-(hex-1-en-1-yl)pyrrolidine-2,5-dione (36.2 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 60 minutes at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ja** (52.4 mg, 0.160 mmol, 81 % yield) as a colorless oil.

R_f 0.34 (*Hexane*/*Ethyl acetate* 1/1).
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (d, *J* = 9.9 Hz, 1H, N-C-H), 3.73 (s, 3H, CO_2CH_3), 3.70 (s, 3H, CO_2CH_3), 3.51 (m, 1H, CH_2 cyclobutane), 2.96 (dd, *J* = 11.7, 9.2 Hz, 1H, CH_2 cyclobutane), 2.75-2.58 (m, 4H, CH_2 succinimide), 1.72 (dd, *J* = 11.6, 9.1 Hz, 1H, CH_2 cyclobutane), 1.52-1.37 (m, 2H, CH_2 butyl), 1.24 (m, 2H, CH_2 butyl), 1.20 – 1.10 (m, 2H, CH_2 butyl), 0.84 (t, *J* = 7.1 Hz, 3H, CH_3 butyl).
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 170.5, 168.6, 55.1, 54.0, 53.1, 53.0, 34.5, 33.5, 30.8, 28.7, 28.0, 22.5, 14.0.
IR 2957 (w), 2956 (w), 2856 (w), 1784 (w), 1736 (s), 1707 (s), 1436 (m), 1375 (m), 1262 (s), 1181 (m), 1132 (s), 1041 (w).
HRMS (ESI) calcd for $C_{16}H_{23}NNaO_6^+$ $[M+Na]^+$ 348.1418; found 348.1411.

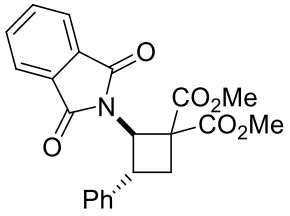
Dimethyl 2-(2,5-dioxopyrrolidin-1-yl)-3-phenethylcyclobutane-1,1-dicarboxylate (6ka)



Using general procedure **B**, (*E*)-1-(4-phenylbut-1-en-1-yl)pyrrolidine-2,5-dione (45.9 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 60 minutes at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ka** (61.7 mg, 0.170 mmol, 83 % yield, 8:1 dr determined by integration of the peaks at 4.90 (*maj*), and 5.09 (*min*) in the crude ^{1}H NMR) as a colorless oil.

R$_f$ 0.20 (*Hexane*/*Ethyl acetate* 1/1).
^{1}H NMR (400 MHz, $CDCl_3$) on a 8(*maj*.):1(*min*.) mixture δ 7.27-7.22 (m, 18H, Ar *maj* + Ar *min* with chloroform peak), 7.19-7.05 (m, 26H, Ar *maj* + Ar *min*), 6.86-6.80 (m, 1H, Ar *min*), 5.09 (d, *J* = 10.5 Hz, 1H, N-C-H *min*), 4.90 (d, *J* = 9.8 Hz, 8H, N-C-H *maj*), 3.72 (m, 30H, CO_2CH_3 *maj* + CO_2CH_3 *min*), 3.68 (s, 24H, CO_2CH_3 *maj*), 3.59 (dtd, *J* = 16.8, 9.4, 7.3 Hz, 8H, CH_2 cyclobutane *maj*), 3.46 (dd, *J* = 11.0, 4.3 Hz, 1H, CH_2 cyclobutane *min*), 2.95 (dd, *J* = 11.4, 9.6 Hz, 8H, CH_2 cyclobutane *maj*), 2.67-2.45 (m, 52H, CH_2 succinimide *maj* + CH_2 succinimide *min* + CH_2 chain *maj*), 2.95 (dd, *J* = 11.4, 9.6 Hz, 1H, CH_2 cyclobutane *min*), 2.13-1.99 (m, 2H, CH_2 chain *min*), 1.85 (ddq, *J* = 17.0, 8.7, 6.8 Hz, 18H CH_2 chain *maj* + CH_2 chain *min*), 1.73 (dd, *J* = 11.7, 9.1 Hz, 8H, CH_2 cyclobutane *maj*), 1.54 (td, *J* = 12.9, 4.5 Hz, 1H, CH_2 cyclobutane *min*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 170.3, 168.4, 141.3, 128.3, 128.1, 125.9, 55.0, 54.0, 53.0, 52.9, 36.2, 33.3, 33.1, 30.7, 27.8. Only major isomer.
IR 2955 (w), 1784 (w), 1783 (w), 1739 (s), 1708 (s), 1673 (w), 1438 (w), 1437 (w), 1384 (m), 1374 (m), 1315 (w), 1267 (s), 1197 (w), 1151 (m), 1150 (m).
HRMS (ESI) calcd for $C_{20}H_{23}NNaO_6^+$ $[M+Na]^+$ 396.1418; found 396.1427.

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)-3-phenylcyclobutane-1,1-dicarboxylate (6la)

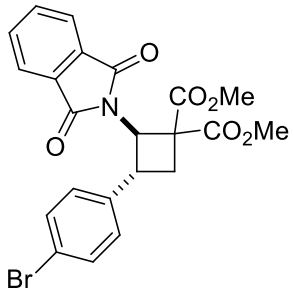


Using general procedure **C**, (*E*)-2-styrylisoindoline-1,3-dione (49.9 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 1 hour at room temperature after the end of the slow addition. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6la** (70.6 mg, 0.179 mmol, 90 % yield) as a colorless oil.

R$_f$ 0.28 (*Hexane*/*Ethyl acetate* 7/3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, 2 H, *J* = 3.7, 2.1 Hz, Phth), 7.55 (dd, 2 H, *J* = 3.8, 2.1 Hz, Phth), 7.29-7.24 (m, 4 H, Ph), 7.23-7.19 (m, 1 H, Ph), 5.52 (dd, 1 H, *J* = 7.4, 0.4 Hz, N-C-H), 4.86-4.96 (m, 1 H, *H*-C-Ph), 3.76 (s, 3 H, CO_2CH_3), 3.65 (s, 3 H, CO_2CH_3), 3.25 (ddd, 1 H, *J* = 7.7, 6.5, 0.4 Hz, CH_2), 2.21 (dd, 1 H, *J* = 7.8, 6.9 Hz, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 157.4, 157.2, 134.0, 128.8, 126.6, 124.1, 122.9, 122.5, 119.7, 63.1, 61.4, 60.7, 60.7, 48.4, 42.9.
IR 2199 (w), 1833 (m), 1790 (w), 1155 (s), 1127 (s), 940 (m), 890 (s), 842 (s).
HRMS (ESI) calcd for $C_{22}H_{20}NO_6^+$ $[M+H]^+$ 394.1285; found 394.1271.

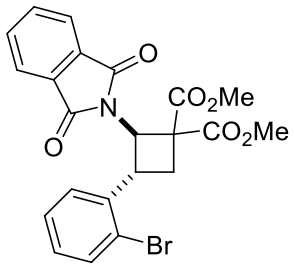
Dimethyl-3-(4-bromophenyl)-2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6ma)



Using general procedure **C**, (*E*)-2-(4-bromostyryl)isoindoline-1,3-dione (65.6 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (115 mg, 0.800 mmol) were stirred for 3 hours at room temperature after the end of the slow addition. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ma** (47.0 mg, 0.100 mmol, 50 % yield) as a colorless oil as well as of (*E*)-2-(4-bromostyryl)isoindoline-1,3-dione (15.4 mg, 0.0469 mmol, 23%, 65% yield of **6ma** b.r.s.m.).

R_f 0.26 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2H, Phth), 7.76-7.70 (m, 2H, Phth), 7.45-7.40 (m, 2H, Ar), 7.18-7.13 (m, 2H, Ar), 5.47 (dd, *J* = 10.9, 0.7 Hz, 1H, N-C-H), 4.88 (q, *J* = 10.1 Hz, 1H, Ar-C-H), 3.78 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 3.26 (ddd, *J* = 11.6, 9.5, 0.8 Hz, 1H, CH_2), 2.19 (dd, *J* = 11.5, 10.0 Hz, 1H, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.3, 168.2, 139.5, 134.3, 131.8, 131.6, 128.6, 123.5, 121.1, 55.9, 53.9, 53.20, 53.15, 38.0, 31.8.
IR 2955 (w), 1782 (w), 1738 (s), 1721 (s), 1492 (w), 1437 (w), 1378 (s), 1267 (m), 1201 (m), 1049 (w).
HRMS (ESI) calcd for $C_{22}{}^{79}BrH_{19}NO_6^+$ $[M+H]^+$ 472.0390; found 472.0385.

Dimethyl -3-(2-bromophenyl)-2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6na)

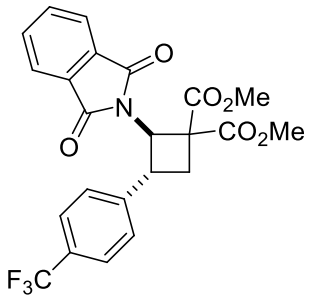


Using general procedure **C**, (*E*)-2-(2-bromostyryl)isoindoline-1,3-dione (65.6 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 5 minutes at room temperature

after the end of the slow addition. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6na** (87.4 mg, 0.185 mmol, 93 % yield) as a colorless oil.

R_f 0.32 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.79 (m, 2H, Phth), 7.77-7.66 (m, 2H, Phth), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar), 7.38 (ddd, *J* = 7.9, 1.6, 0.6 Hz, 1H, Ar), 7.32-7.27 (m, 1H, Ar), 7.08 (dddd, *J* = 7.9, 7.3, 1.7, 0.5 Hz, 1H, Ar), 5.74 (dd, *J* = 10.8, 0.8 Hz, 1H, N-C-H), 5.21-5.06 (m, 1H, Ar-C-H), 3.77 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 3.53 (ddd, *J* = 11.7, 9.6, 0.9 Hz, 1H, CH_2), 2.06 (dd, *J* = 11.6, 9.7 Hz, 1H, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 168.3, 168.2, 139.9, 134.4, 133.1, 131.7, 128.7, 127.9, 127.3, 124.0, 123.6, 55.9, 53.30, 53.28, 51.5, 38.8, 31.9.
IR 3062 (w), 2955 (w), 2848 (w), 1783 (w), 1738 (s), 1722 (s), 1471 (w), 1437 (m), 1379 (s), 1267 (s).
HRMS (ESI) calcd for $C_{22}{}^{79}BrH_{19}NO_6^+$ $[M+H]^+$ 472.0390; found 472.0405.

Dimethyl -2-(1,3-dioxoisoindolin-2-yl)-3-(4-(trifluoromethyl)phenyl)cyclobutane-1,1-dicarboxylate (6oa)

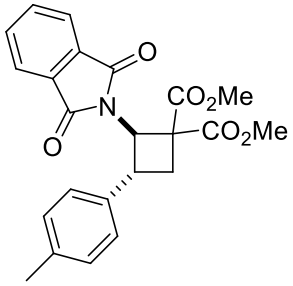


Using general procedure **C**, (*E*)-2-(4-(trifluoromethyl)styryl)isoindoline-1,3-dione (63.5 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (115 mg, 0.800 mmol) were stirred for 5 minutes at room temperature after the end of the slow addition. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6oa** (35.0 mg, 0.0760 mmol, 38 % yield, with a polymeric impurity) as a colorless oil as well as (*E*)-2-(4-(trifluoromethyl)styryl)isoindoline-1,3-dione (10.3 mg, 0.0324 mmol, 16% yield, 45% yield of **6oa** b.r.s.m.).

R_f 0.25 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H, Phth), 7.56 (d, *J* = 8.1 Hz, 2H, Ar), 7.39 (d, *J* = 8.0 Hz, 2H, Ar), 5.53 (d, *J* = 10.8 Hz, 1H, N-C-H), 4.99 (q, *J* = 10.1 Hz, 1H, Ar-C-H), 3.79 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.37 – 3.21 (m, 1H, CH_2 cyclobutane), 2.25 (dd, *J* = 11.6, 10.0 Hz, 1H, CH_2 cyclobutane).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.1, 168.0, 144.5, 134.3, 131.5, 129.5 (q, *J* = 32.4 Hz), 127.0, 125.7 (q, *J* = 3.3 Hz), 124.1 (q, *J* = 272.2 Hz), 123.5, 55.8, 53.6, 53.14, 53.08, 38.1, 31.5.
IR 2957 (w), 1782 (w), 1737 (s), 1720 (s), 1620 (w), 1438 (w), 1378 (s), 1266 (s), 1200 (m), 1164 (s), 1124 (s), 1049 (m).
HRMS (ESI) calcd for $C_{23}H_{18}F_3NNaO_6^+$ $[M+Na]^+$ 484.0978; found 484.0996.

Dimethyl-2-(1,3-dioxoisoindolin-2-yl)-3-(p-tolyl)cyclobutane-1,1-dicarboxylate (6pa) and dimethyl-3-(1,3-dioxoisoindolin-2-yl)-2-(p-tolyl)cyclobutane-1,1-dicarboxylate (6pa')

Using general procedure **A**, (*E*)-2-(4-methylstyryl)isoindoline-1,3-dione (52.7 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 2h30 at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6pa** (56.1 mg, 0.140 mmol, 69 % yield) as a colorless oil and cyclobutane **6pa'** (22.5 mg, 0.0600 mmol, 28 % yield) as a colorless oil. The structure of **6pa** was confirmed by 2D-NMR experiments. The structure of **6pa'** was assigned in analogy with the one of product **6qa'**.



6pa

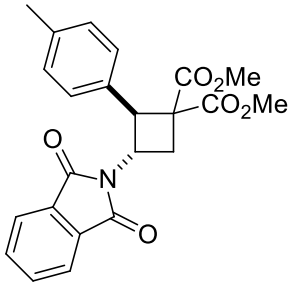
R_f 0.27 (*Hexane*/*Ethyl acetate* 7/3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.78 (m, 2H, Phth), 7.74-7.67 (m, 2H, Phth), 7.22-7.16 (m, 2H, Ar), 7.15-7.07 (m, 2H, Ar), 5.51 (dd, *J* = 10.9, 0.8 Hz, 1H, N-C-H), 4.88 (dd, *J* = 10.1, 10.1, Hz, 1H, Ar-C-H), 3.78 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 3.25 (ddd, *J* = 11.5, 9.5, 0.9 Hz, 1H, CH_2 cyclobutane), 2.30 (s, 3H, CH_3), 2.20 (dd, *J* = 11.5, 10.1 Hz, 1H, CH_2 cyclobutane).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.5, 168.2, 137.5, 136.9, 134.2, 131.7, 129.4, 126.8, 123.4, 55.9, 54.1, 53.11, 53.08, 38.2, 32.1, 21.1.

IR 3023 (w), 2955 (w), 1781 (w), 1736 (s), 1718 (s), 1518 (w), 1437 (w), 1378 (s), 1265 (s), 1199 (m), 1048 (m), 881 (w).

HRMS (ESI) calcd for $C_{23}H_{21}NNaO_6^+$ $[M+Na]^+$ 430.1261; found 430.1257.



6pa'

R_f 0.32 (*Hexane*/*Ethyl acetate* 7/3).

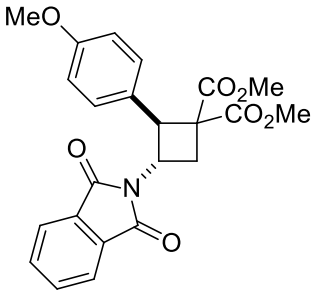
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85- 7.77 (m, 2H, Phth), 7.74- 7.66 (m, 2H, Phth), 7.32- 7.27 (m, 2H, Ar), 7.13-7.07 (m, 2H, Ar), 5.44 (dt, *J* = 10.2, 9.1 Hz, 1H, N-C-H), 5.18 (d, *J* = 10.3 Hz, 1H, Ar-C-H), 3.87 (s, 3H, CO_2CH_3), 3.35 (s, 3H, CO_2CH_3), 3.29 (dd, *J* = 11.4, 9.2 Hz, 1H, CH_2 cyclobutane), 3.00 (ddd, *J* = 11.4, 9.0, 0.8 Hz, 1H, CH_2 cyclobutane), 2.28 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 169.5, 168.3, 137.1, 134.2, 133.0, 131.7, 129.0, 127.4, 123.3, 54.4, 52.9, 52.3, 49.6, 42.2, 30.8, 21.1.

IR 2954 (w), 2926 (w), 2863 (w), 1776 (w), 1734 (s), 1716 (s), 1437 (w), 1384 (m), 1277 (m), 1203 (m), 1128 (m).

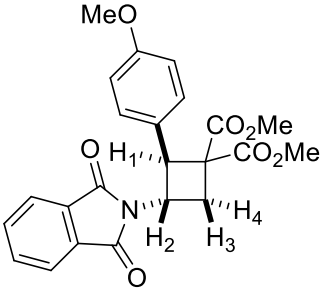
HRMS (ESI) calcd for $C_{23}H_{22}NO_6^+$ $[M+H]^+$ 408.1442; found 408.1451.

Dimethyl-3-(1,3-dioxoisoindolin-2-yl)-2-(4-methoxyphenyl)cyclobutane-1,1-dicarboxylate (6qa')

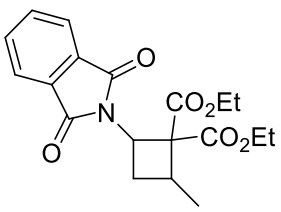


Using general procedure **A**, (*E*)-2-(4-methoxystyryl)isoindoline-1,3-dione (55.9 mg, 0.200 mmol) and dimethyl 2-methylenemalonate (57.7 mg, 0.400 mmol) were stirred for 60 minutes at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6qa'** (69.0 mg, 0.160 mmol, 81 % yield) as a colorless oil.

R_f 0.15 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.78 (m, 2 H, Phth), 7.73-7.67 (m, 2 H, Phth), 7.36-7.30 (m, 2 H, Ar), 6.87-6.80 (m, 2 H, Ar), 5.46-5.38 (m, 1 H, Ar-C-H), 5.15 (d, 1 H, *J* = 10.3 Hz, N-C-H), 3.87 (s, 3 H, CO_2CH_3), 3.76 (s, 3 H, Ar-OMe), 3.36 (s, 3 H, CO_2CH_3), 3.28 (dd, 1 H, *J* = 11.3, 9.2 Hz, CH_2), 2.99 (dd, 1 H, *J* = 11.3, 8.9 Hz, CH_2).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 169.5, 168.3, 159.0, 134.2, 131.7, 128.8, 128.1, 123.4, 113.8, 55.2, 54.4, 52.9, 52.4, 49.4, 42.4, 30.6.
IR 3030 (w), 2955 (w), 1782 (w), 1739 (s), 1721 (s), 1378 (s), 1267 (s).
HRMS (ESI) calcd for $C_{23}H_{22}NO_7^+$ $[M+H]^+$ 424.1391; found 424.1387.
Stereochemistry was assigned by 2D ROESY NMR experiment.



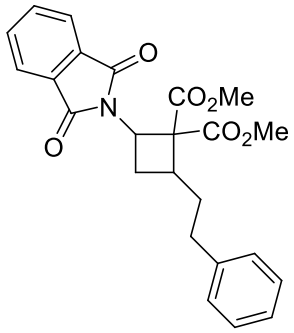
Diethyl 2-(1,3-dioxoisoindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (6ab)



Using general procedure **B**, 2-vinylisoindoline-1,3-dione (34.6 mg, 0.200 mmol) and diethyl 2-ethylidenemalonate (74.5 mg, 0.400 mmol) were stirred for 18 h at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ab** (45.2 mg, 0.130 mmol, 63 % yield, 1.2:1 dr determined by integration of the peaks at 4.91 (*maj*), and 5.58 (*min*) in the crude ^{1}H NMR) as a colorless oil.

R_f 0.25 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) on a 1.6(*maj*.):1(*min*.) mixture δ 7.84-7.79 (m, 5.2 H, Phth *maj* + *min*), 7.72-7.67 (m, 5.2H, Phth *maj* + *min*), 5.58 (ddd, *J* = 10.0, 8.3, 1.2 Hz, 1H, N-C-H *min*), 4.91 (dd, *J* = 10.9, 8.7 Hz, 1.6H, N-C-H *maj*), 4.27-4.18 (m, 5.2H, CO_2CH_2 *maj* + *min*), 4.17- 3.91 (m, 5.2H, CO_2CH_2 *maj* + *min*), 3.65-3.54 (m, 1H, CH cyclobutane *min*), 3.27-3.12 (m, 2.6H, CH_2 cyclobutane *maj* + *min*), 2.78 (ddq, *J* = 10.7, 8.1, 7.0 Hz, 1.6H, CH cyclobutane *maj*), 2.46 (dt, *J* = 10.8, 8.5 Hz, 1.6H, CH_2 cyclobutane *maj*), 1.98 (ddd, *J* = 11.7, 10.0, 5.4 Hz, 1H, CH_2 cyclobutane *min*), 1.32 (d, *J* = 7.0 Hz, 4.6H, CH_3 maj), 1.28-1.21 (m, 7.8H, $CO_2CH_2C\underline{H}_3$ *maj* + *min*), 1.14 (d, *J* = 7.3 Hz, 3H, CH_3 min), 1.05 (t, *J* = 7.1 Hz, 4.6H, $CO_2CH_2C\underline{H}_3$ *maj*), 0.90 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$ *min*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 168.5, 168.4, 168.3, 168.1, 167.5, 134.1, 134.0, 132.0, 131.8, 123.3, 123.2, 62.4, 62.0, 61.7[17], 61.6, 60.9, 47.5, 45.1, 33.8, 31.1, 29.6, 28.7, 16.5, 16.2, 14.2, 14.0, 13.9, 13.6.
IR 2929 (w), 2851 (w), 1780 (w), 1732 (s), 1713 (s), 1614 (w), 1468 (w), 1377 (s), 1256 (s), 1213 (m), 1072 (m).
HRMS (ESI) calcd for $C_{19}H_{21}NNaO_6^+$ $[M+Na]^+$ 382.1261; found 382.1248.

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)-4-phenethylcyclobutane-1,1-dicarboxylate (6ad)



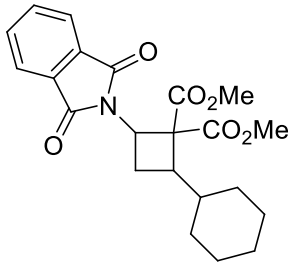
Using general procedure **B**, 2-vinylisoindoline-1,3-dione (34.6 mg, 0.200 mmol) and dimethyl 2-(3-phenylpropylidene)malonate (99.0 mg, 0.400 mmol) were stirred for 3h30 at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ad** (60.0 mg, 0.140 mmol, 71 % yield, 1.3:1 dr determined by integration of the peaks at 4.93 (*maj*), and 5.58 (*min*) in the crude ^{1}H NMR) as a colorless oil.

R_f 0.43 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) on a 1.5(*maj*.):1(*min*.) mixture δ 7.87-7.79 (m, 5H, Phth *maj* + Phth *min*), 7.75-7.67 (m, 5H, Phth *maj* + Phth *min*), 7.32-7.25 (m, 5H, Ar *maj* + Ar *min* with chloroform peak), 7.19 (dd, *J* = 7.5, 4.9 Hz, 7.5H, Ar *maj* + Ar *min*), 5.58 (ddd, *J* = 10.2, 7.7, 1.1 Hz, 1H, N-C-H *min*), 4.93 (dd, *J* = 11.1, 8.6 Hz, 1.5H, N-C-H *maj*), 3.78 (s, 4.5H, CO_2CH_3 *maj*), 3.74 (s, 3H, CO_2CH_3 *min*), 3.60 (s, 4.5H, CO_2CH_3 *maj*), 3.54 (s, 3H, CO_2CH_3 *min*), 3.21 (q, *J* = 10.9 Hz, 1.5H, CH_2 cyclobutane *maj*), 3.09 (ddd, *J* = 12.0, 10.1, 7.8 Hz, 1H, CH_2 cyclobutane *min*), 2.75-2.54 (m, 7.5H, 1xCH_2 cyclobutane *maj*, 2xCH_2 chain *maj*, 1xCH_2 cyclobutane *min*, 2xCH_2 chain *min*), 2.45 (dt, *J* = 10.6, 8.2 Hz, 1.5H, CH_2 cyclobutane *maj*), 2.24-2.06 (m, 2.5H, CH_2 chain *maj*+ CH_2 cyclobutane *min*), 2.01-1.89 (m, 1.5H, CH_2 chain *maj*), 1.89-1.80 (m, 1H, CH_2 chain *min*), 1.76-1.63 (m, 1H, CH_2 chain *min*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.0, 168.9, 168.3, 168.0, 167.9, 141.7, 141.6, 134.2, 134.0, 131.9, 131.7,128.45, 128.44, 128.40, 126.0, 125.9, 123.4, 123.2, 62.1, 61.5, 52.9, 52.8, 52.7, 52.2, 47.7, 45.4, 38.6, 36.6, 33.5, 33.4, 33.1, 32.9, 28.5, 27.3.[18]

[17] Two peaks under this signal as determined by HMBC.

IR 3028 (w), 2953 (w), 1780 (w), 1737 (s), 1715 (s), 1605 (w), 1496 (w), 1455 (w), 1436 (w), 1379 (s), 1262 (m), 1199 (m), 1159 (w).
HRMS (ESI) calcd for $C_{24}H_{23}NNaO_6^+$ $[M+Na]^+$ 444.1418; found 444.1418.

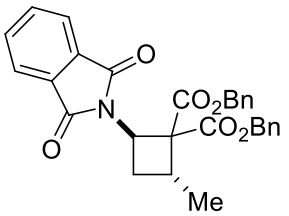
Dimethyl 2-cyclohexyl-4-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6ae)



Using general procedure **B**, 2-vinylisoindoline-1,3-dione (34.6 mg, 0.200 mmol) and dimethyl 2-(cyclohexylmethylene)malonate (91.0 mg, 0.400 mmol) were stirred for 18 h at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ae** (47.0 mg, 0.120 mmol, 59 % yield, 1.2:1 dr determined by integration of the peaks at 4.96 (*min*), and 5.38 (*maj*) in the crude ^{1}H NMR) as a colorless oil.

R_f 0.30 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) on a 1.2(*maj*.):1(*min*.) mixture δ 7.87-7.79 (m, 4.4H, Phth *maj* + *min*), 7.75-7.68 (m, 4.4H, Phth *maj* + *min*), 5.38 (ddd, *J* = 10.5, 5.1, 1.1 Hz, 1.2H, N-C-H *maj*), 4.93 (dd, *J* = 11.4, 8.0 Hz, 1H, N-C-H *min*), 3.79-3.76 (m, 6.6H, CO_2CH_3 *maj* + *min*), 3.59 (s, 3H, CO_2CH_3 *min*), 3.56-3.48 (m, 4.8H, CO_2CH_3 *maj* + CH cyclobutane *maj*), 3.22 (td, *J* = 11.1, 9.9 Hz, 1H, CH_2 cyclobutane *min*), 2.72 (ddd, *J* = 12.4, 10.4, 5.1 Hz, 1.2H, CH_2 cyclobutane *maj*), 2.45-2.27 (m, 3.2H, CH_2 cyclobutane *maj* + *min* + CH cyclobutane *min*), 1.97-1.58 (m, 12.6H, CH cyclohexyl *maj* + *min*), 1.40-0.98 (m, 8H, CH_2 cyclohexyl *maj* + *min*), 0.96-0.73 (m, 3.6H, CH_2 cyclohexyl *maj*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 170.3, 170.2, 169.8, 168.5, 168.2, 134.3, 134.1, 132.0, 131.9, 123.5, 123.4, 62.5, 61.1, 53.0, 52.8, 52.6, 52.2, 48.0, 46.1, 45.2, 44.0, 39.5, 39.4, 31.4, 31.3, 30.0, 29.9, 29.6, 27.4, 26.7, 26.5, 26.1, 26.0, 25.9, 25.8.
IR 2923 (w), 2851 (w), 1780 (w), 1732 (s), 1732 (s), 1714 (s), 1613 (w), 1436 (w), 1376 (s), 1265 (s), 1204 (m), 1157 (w), 1061 (m).
HRMS (ESI) calcd for $C_{22}H_{25}NNaO_6^+$ $[M+Na]^+$ 422.1574; found 422.1590.

Dibenzyl -2-(1,3-dioxoisoindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate 6af

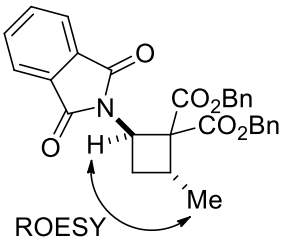


Using general procedure **B**, 2-vinylisoindoline-1,3-dione (34.6 mg, 0.200 mmol) and dibenzyl 2-ethylidenemalonate (124 mg, 0.400 mmol) were stirred for 18 h at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6

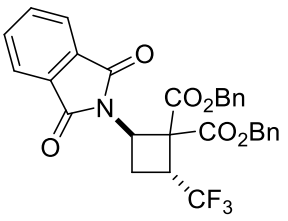
[18] A peak is not resolved in the 128.45-128.40 massif.

Hexane/Ethyl acetate) affording cyclobutane **6af** (60.5 mg, 0.125 mmol, 62 % yield, 3:1 dr determined by integration of the peaks at 3.64 (*maj*), and 2.49 (*min*) in the crude ^{1}H NMR) as a colorless oil.

R$_f$ 0.22 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) on a 2 (*maj*):1(*min*) diatereomeric mixture δ 7.77 – 7.68 (m, 6H, Phth), 7.65 (ddd, *J* = 5.8, 3.2, 1.9 Hz, 6H, Phth), 7.34 – 7.27 (m, 15H, Ar), 7.19 – 7.06 (m, 6H, Ar), 7.06 – 6.98 (m, 6H, Ar), 6.97 – 6.90 (m, 3H, Ar), 5.62 (ddd, *J* = 9.8, 8.4, 1.2 Hz, 2H, N-C-H *maj*), 5.27 – 5.12 (m, 6H, CH_2-Ar *maj* + *min*), 5.06 – 4.88 (m, 7H, N-C-H *min*, CH_2-Ar *maj* + *min*), 3.64 (dddd, *J* = 10.1, 7.4, 5.2, 1.3 Hz, 2H, CH-Me cyclobutane *maj*), 3.28 – 3.13 (m, 3H, CH_2 cyclobutane *maj*+ *min*), 2.86 – 2.74 (m, 1H, CH-Me cyclobutane *min*), 2.49 (dt, *J* = 10.7, 8.3 Hz, 1H, CH_2 cyclobutane *min*), 1.99 (ddd, *J* = 11.6, 9.9, 5.3 Hz, 2H, CH_2 cyclobutane *maj*), 1.32 (d, *J* = 7.0 Hz, 3H, Me cyclobutane *min*), 1.08 (d, *J* = 7.4 Hz, 6H, Me cyclobutane *maj*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 168.3, 168.1, 168.1, 168.0, 167.2, 135.5, 135.2, 134.9, 134.8, 133.9, 133.8, 131.8, 131.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 126.0, 123.3, 123.2, 67.5, 67.4, 67.3, 67.0, 62.4, 62.1, 47.5, 45.1, 34.2, 31.3, 29.8, 28.8, 16.4, 16.2.
IR 2470 (w), 2447 (w), 2386 (w), 1453 (w), 1418 (s), 1407 (s), 1199 (w), 1138 (s), 1045 (m), 1008 (m), 956 (w).
HRMS (ESI) calcd for $C_{29}H_{26}NO_6^+$ $[M+H]^+$ 484.1755; found 484.1756.



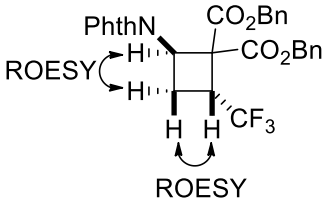
Dibenzyl-2-(1,3-dioxoisoindolin-2-yl)-4-(trifluoromethyl)cyclobutane-1,1-dicarboxylate (6ag)



Using general procedure **B**, 2-vinylisoindoline-1,3-dione (34.6 mg, 0.200 mmol) and dibenzyl 2-(2,2,2-trifluoroethylidene)malonate (146 mg, 0.400 mmol) were stirred for 18 h at room temperature. The crude oil was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ag** (82.2 mg, 0.153 mmol, 76 % yield) as a colorless oil.

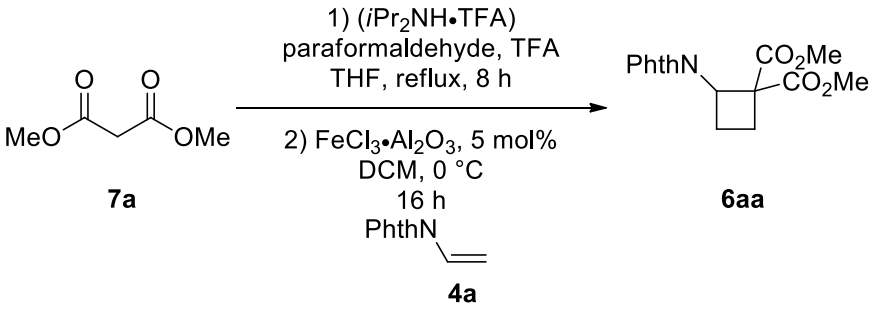
R$_f$ 0.18 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 4H, Phth), 7.33 – 7.26 (m, 5H, Ar), 7.11 – 7.05 (m, 1H, Ar), 7.02 – 6.97 (m, 2H, Ar), 6.92 – 6.88 (m, 2H, Ar), 5.87 – 5.67 (m, 1H, N-C-H), 5.30 – 5.01 (m, 2H, CH_2Ar), 5.00 – 4.77 (m, 2H, CH_2Ar), 4.47 – 4.26 (m, 1H, CH_2 cyclobutane), 3.23 (ddd, *J* = 12.8, 10.8, 7.7 Hz, 1H, CH_2 cyclobutane), 2.60 (ddd, *J* = 12.7, 10.4, 6.5 Hz, 1H, CH_2 cyclobutane).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 166.2, 165.9, 134.6, 134.3, 134.1, 131.3, 128.5, 128.5, 128.5, 128.3, 128.29, 128.26, 125.6 (q, *J* = 278 Hz), 123.6, 68.4, 68.3, 59.3, 45.3, 39.6 (q, *J* = 31.4 Hz), 22.6.
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3.
IR 3035 (w), 2963 (w), 1781 (m), 1741 (s), 1736 (s), 1456 (w), 1380 (s), 1276 (s), 1142 (s), 1088 (m).

HRMS (ESI) calcd for $C_{29}H_{22}F_3NNaO_6^+$ [M+Na]$^+$ 560.1291; found 560.1277.
Stereochemistry was assigned by 2D ROESY NMR experiment.



5. Sequential synthesis of aminocyclobutanes

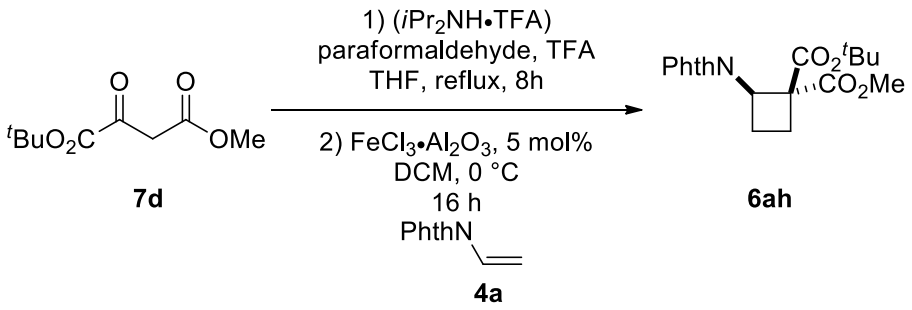
Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6aa)



Dimethyl malonate (**7a**) (1.32 mL, 11.6 mmol, 2 eq), diisopropylamine 2,2,2-trifluoroacetate (2.49 g, 11.6 mmol, 2 eq), paraformaldehyde (0.695 mg, 23.1 mmol, 4 eq) and trifluoroacetic acid (89.0 µL, 1.16 mmol, 0.2 eq) were added to tetrahydrofuran (20 mL). A condenser was added and the suspension was stirred at reflux for two hours. Paraformaldehyde (0.695 mg, 23.1 mmol, 4 eq) was added and the reflux was continued for 6 hours. The reaction was cooled to room temperature and the tetrahydrofuran was removed under reduced pressure (300 to 50 mbar at 45°C). The crude was dissolved in diethyl ether (25 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1 M HCl (25 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give dimethyl crude 2-methylenemalonate as colorless oil.

The iron catalyst (289 mg, 0.289 mmol, 0.05 eq) was weighted in an oven-dry flask in a glovebox. The flask was closed with a silicon septum, taken out of the glovebox and put under positive pressure of nitrogen and dichloromethane (5 mL) was added. 2-vinylisoindoline-1,3-dione (**4a**) (1.00 g, 5.77 mmol, 1 eq) was dissolved in dichloromethane (5 mL)and added to the yellow suspension. Finally, the crude dimethyl 2-methylenemalonate was dissolved in dichloromethane (5 mL) and added to the reaction in one portion. The reaction was stirred at room temperature for 16 h and then filtered over a basic alumina plug, eluting with ethyl acetate. The solvents were evaporated and the brown solid was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6aa** (1.55 g, 4.89 mmol, 85 % yield) as a colorless solid.

1-(Tert-butyl) 1-methyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6ah)



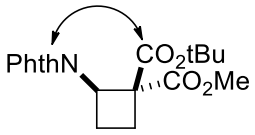
Tert-butyl methyl malonate (**7d**) (1.95 mL, 11.6 mmol, 2 eq), diisopropylamine 2,2,2-trifluoroacetate (2.49 g, 11.6 mmol, 2 eq), paraformaldehyde (0.695 mg, 23.1 mmol, 4 eq) and trifluoroacetic acid (89.0 µL, 1.16 mmol, 0.2 eq) were added to tetrahydrofuran (20 mL). A condenser was added and the suspension was stirred at reflux for two hours. Paraformaldehyde (0.695 mg, 23.1 mmol, 4 eq) was

added and the reflux was continued for 6 hours. The reaction mixture was cooled to room temperature and the tetrahydrofuran was removed under reduced pressure. The crude product was dissolved in diethyl ether (25 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1 M HCl (25 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude methylenemalonate (2.9 g) as colorless oil.

The iron catalyst (289 mg, 0.289 mmol, 0.05 eq) was weighted in an oven-dry flask in a glovebox. The flask was closed with a silicon septum, taken out of the glovebox and put under a positive pressure of nitrogen. Dichloromethane (5 mL) was added. The reaction was cooled to 0 °C and 2-vinylisoindoline-1,3-dione (**4a**) (1.00 g, 5.77 mmol, 1 eq) was dissolved in dichloromethane (5 mL) and added to the yellow suspension dropwise. Finally, the crude methylenemalonate was dissolved in dichloromethane (5 mL) and added to the reaction mixture dropwise. The reaction mixture was stirred at 0 °C for 3h30 and then filtered over a basic alumina plug, eluting with ethyl acetate. The solvents were evaporated and the brown solid was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutanes **6ah** (1.97 g, 5.48 mmol, 95 % yield, 1.7:1 dr determined by integration of the peaks at 2.45-2.33 (*maj*), and 2.31-2.21 (*min*) in the crude ^{1}H NMR) as a colorless oil.

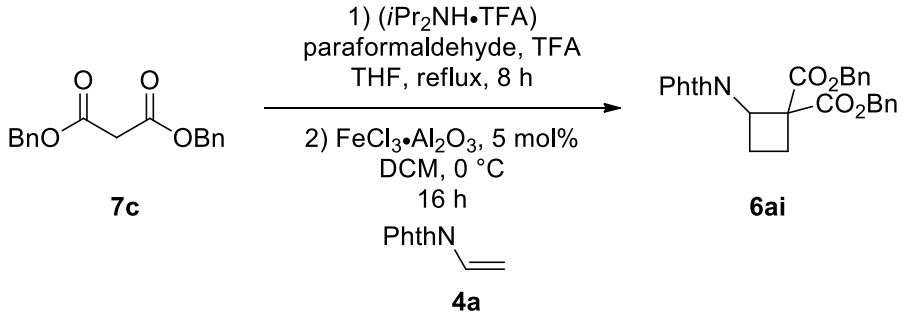
R_f 0.22 (*Hexane*/*Ethyl acetate* 7/3).
1H NMR (400 MHz, $CDCl_3$) on a 1.5 (*maj*):1(*min*) diatereomeric mixture δ 7.95 – 7.78 (m, 5H, Phth), 7.78 – 7.64 (m, 5H, Phth), 5.58 – 5.26 (m, 2.5H, N-C-H *major* + *minor*), 3.75 (s, 4.5H, OMe *major*), 3.57 (s, 3H, OMe *minor*), 3.36 – 3.10 (m, 2.5H, CH_2 cyclobutane *major* + *minor*), 3.08 – 2.83 (m, 2.5H, CH_2 cyclobutane *major* + *minor*), 2.45-2.33 (m, 1.5H, CH_2 cyclobutane *major*), 2.31-2.21 (m, 1 H, CH_2 cyclobutane *minor*) 2.20-2.10 (m, 2.5 H, CH_2 cyclobutane *major* + *minor*), 1.44 (s, 9H, *tBu minor*), 1.16 (s, 13.5H, tBu *major*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 169.0, 169.0, 168.3, 168.2, 167.2, 134.3, 134.2, 132.1, 131.9, 123.4, 123.4, 82.5, 82.2, 60.1, 59.5, 53.0, 52.8, 47.7, 47.6, 27.9, 27.5, 24.8, 24.3, 21.7, 21.3.
IR 2979 (w), 1732 (s), 1717 (s), 1372 (s), 1266 (s), 1129 (m).
HRMS (ESI) calcd for $C_{19}H_{22}NO_6^+$ $[M+H]^+$ 360.1442; found 360.1437.

Stereochemistry was assigned by 2D ROESY NMR experiment.



ROESY: major

Dibenzyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (6ai)

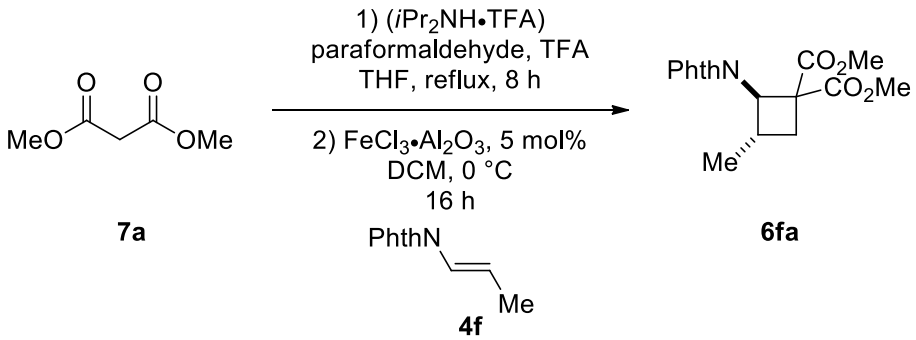


Dibenzyl malonate (**7c**) (2.89 mL, 11.6 mmol, 2 eq), diisopropylamine 2,2,2-trifluoroacetate (2.49 g, 11.6 mmol, 2 eq), paraformaldehyde (0.695 mg, 23.1 mmol, 4 eq) and trifluoroacetic acid (89.0 µL, 1.16 mmol, 0.2 eq) were added to tetrahydrofuran (20 mL). A condenser was added and the suspension was stirred at reflux for two hours. Paraformaldehyde (0.695 mg, 23.1 mmol, 4 eq) was added and the reflux was continued for 6 hours. The reaction was cooled to room temperature and the tetrahydrofuran was removed under reduced pressure. The crude was retaken in diethyl ether (25 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1M HCl (25 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give dibenzyl 2-methylenemalonate crude as colorless oil.

The iron catalyst (289 mg, 0.289 mmol, 0.05 eq) was weighted in an oven-dry flask in a glovebox. The flask was closed with a silicon septum, taken out of the glovebox and put under a positive pressure of nitrogen. Dichloromethane (5 mL) was added. The reaction was cooled to 0 °C and 2-vinylisoindoline-1,3-dione (**4a**) (1.00 g, 5.77 mmol, 1 eq) was dissolved in dichloromethane (5 mL) and added to the yellow suspension dropwise. Finally, the crude dibenzyl 2-methylenemalonate was dissolved in dichloromethane (5 mL) and added to the reaction mixture dropwise. The reaction mixture was stirred at room temperature for 2 hours and then filtered over a basic alumina plug, eluting with ethyl acetate. The solvents were evaporated and the brown solid was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6ai** (2.60 g, 5.54 mmol, 96 % yield) as a colorless oil that solidify upon storage at 4°C.

R_f 0.45 (*Hexane*/*Ethyl acetate* 6/4).
Mp 132.1-133.8 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H, Phth), 7.68 – 7.61 (m, 2H, Phth), 7.34 – 7.26 (m, 5H, Ar), 7.14 – 7.07 (m, 1H, Ar), 7.06 – 7.00 (m, 2H, Ar), 6.97 – 6.91 (m, 2H, Ar), 5.50 (td, *J* = 9.5, 0.9 Hz, 1H, N-C-H), 5.17 (q, *J* = 12.3 Hz, 2H, CH_2Bn), 5.02 – 4.87 (m, 2H, CH_2Bn), 3.34 – 3.16 (m, 1H, CH_2 cyclobutane), 3.02 (dddd, *J* = 11.7, 10.5, 3.8, 1.0 Hz, 1H, CH_2 cyclobutane), 2.32 (dtd, *J* = 11.2, 9.1, 3.7 Hz, 1H, CH_2 cyclobutane), 2.18 (dt, *J* = 11.6, 8.8 Hz, 1H, CH_2 cyclobutane).
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.1, 167.9, 135.3, 134.7, 134.0, 131.6, 128.5, 128.3, 128.2, 128.1, 128.1, 126.0, 123.3, 67.7, 67.5, 59.2, 47.6, 24.4, 21.8.
IR IR 3034 (w), 2360 (w), 2339 (w), 1780 (w), 1738 (s), 1721 (s), 1379 (s), 1378 (s), 1261 (m), 1260 (m).
HRMS (ESI) calcd for $C_{28}H_{24}NO_6^+$ $[M+H]^+$ 470.1598; found 470.1607.

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)-3-methylcyclobutane-1,1-dicarboxylate (6fa)



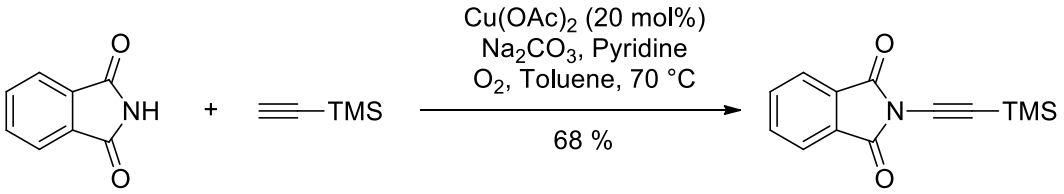
Dimethyl malonate (**7a**) (1.22 mL, 10.7 mmol, 2 eq), diisopropylamine 2,2,2-trifluoroacetate (2.30 g, 10.7 mmol, 2 eq), paraformaldehyde (0.640 mg, 21.4 mmol, 4 eq) and trifluoroacetic acid (82.0 µl,

1.07 mmol, 0.2 eq) were added to tetrahydrofuran (20 mL). A condenser was added and the suspension was stirred at reflux for two hours. Paraformaldehyde (0.640 mg, 21.4 mmol) was added and the reflux was continued for 6 hours. The reaction was cooled to room temperature and the tetrahydrofuran was removed under reduced pressure. The crude was dissolved in diethyl ether (25 mL) and filtered through cotton in a separatory funnel. The organic layer was washed twice with 1M HCl (25 mL). The aqueous layers were combined and extracted with diethyl ether (25 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give dimethyl 2-methylenemalonate crude as colorless oil.

The iron catalyst (267 mg, 0.267 mmol, 0.05 eq) was weighted in an oven-dry flask in a glovebox. The flask was closed with a silicon septum, taken out of the glovebox and put under a positive pressure of nitrogen. Dichloromethane (5 mL) was added. The reaction was cooled to 0 °C and (*E*)-2-(prop-1-en-1-yl)isoindoline-1,3-dione (**4f**) (1.00 g, 5.34 mmol, 1 eq) was dissolved in dichloromethane (5 mL) and added to the yellow suspension dropwise. Finally, the crude dimethyl 2-methylenemalonate was dissolved in dichloromethane (5 mL) and added to the reaction mixture dropwise. The reaction mixture was stirred at room temperature for 4 hours and then filtered over a basic alumina plug, eluting with ethyl acetate. The solvents were evaporated and the brown solid was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 50 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording cyclobutane **6fa** (1.53 g, 4.62 mmol, 86 % yield) as a colorless solid.

6. Synthesis of labeled reagents.

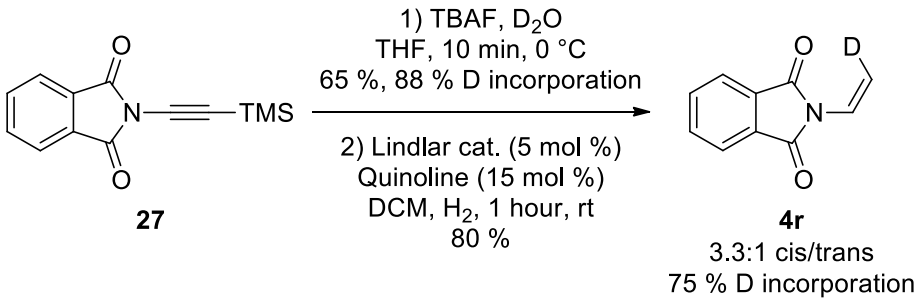
2-((Trimethylsilyl)ethynyl)isoindoline-1,3-dione (27)



Following a reported procedure,[19] copper acetate (0.617 g, 3.40 mmol, 0.2 eq), phthalimide (**25**) (12.5 g, 85.0 mmol, 5 eq), sodium carbonate (3.60 g, 34.0 mmol, 2 eq) and 4Å molecular sieves (10.0 g) were combined in a 1 L three neck round bottom flask equipped with a large magnetic stirring bar. A solution of pyridine (2.75 mL, 34.0 mmol, 2 eq) in dry toluene (150 mL) was added to the reaction flask. The mixture was stirred vigorously and the reaction atmosphere was flushed using oxygen from a balloon. Finally a large balloon of oxygen was connected to the flask and the reaction was stirred in a preheated oil bath at 70 °C. After two hours of stirring at 70 °C, a solution of ethynyltrimethylsilane (**26**) (2.42 mL, 17.0 mmol, 1 eq) in dry toluene (20 mL) was added to the flask in two hours using syringe pump. After the end of addition, the reaction was stirred for 15 additional hours at 70 °C. The reaction mixture was filtered warm through a glass frit and the filtrate was concentrated under reduced pressure. The residue was suspended in diethyl ether (50 mL) and washed with sat. NH_4Cl (50 mL) The layers were separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give an off-white solid. Purification of the crude solid by column chromatography (SiO_2, hexane/ethyl acetate, 95:5 to 80:20,) afforded 2-((trimethylsilyl)ethynyl)isoindoline-1,3-dione (**27**) (2.80 g, 11.5 mmol, 68%) as a white fluffy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 0.29 (s, 9H).
Data match literature report.[19]

(*Z*)-2-(Vinyl-2-d)isoindoline-1,3-dione (4r)



2-((Trimethylsilyl)ethynyl)isoindoline-1,3-dione (**27**) (300 mg, 1.23 mmol, 1 eq) was dissolved in thetrahydrofuran (1 mL), then D_2O (0.5 mL) was added and the reaction was stirred at 0 °C for 5 minutes. TBAF (1 M in thetrahydrofuran, 1.48 mL, 1.48 mmol, 1.2 eq) was added in another flask containing tetrahydrofuran (2 mL) and D_2O (0.5 mL). The TBAF solution was then added dropwise to the ynimide solution. After 10 minutes at 0 °C (some ice has formed during the process), ethyl acetate (10 mL) was added, followed by sat. NH_4Cl (10 mL). The layers were stirred vigorously and the

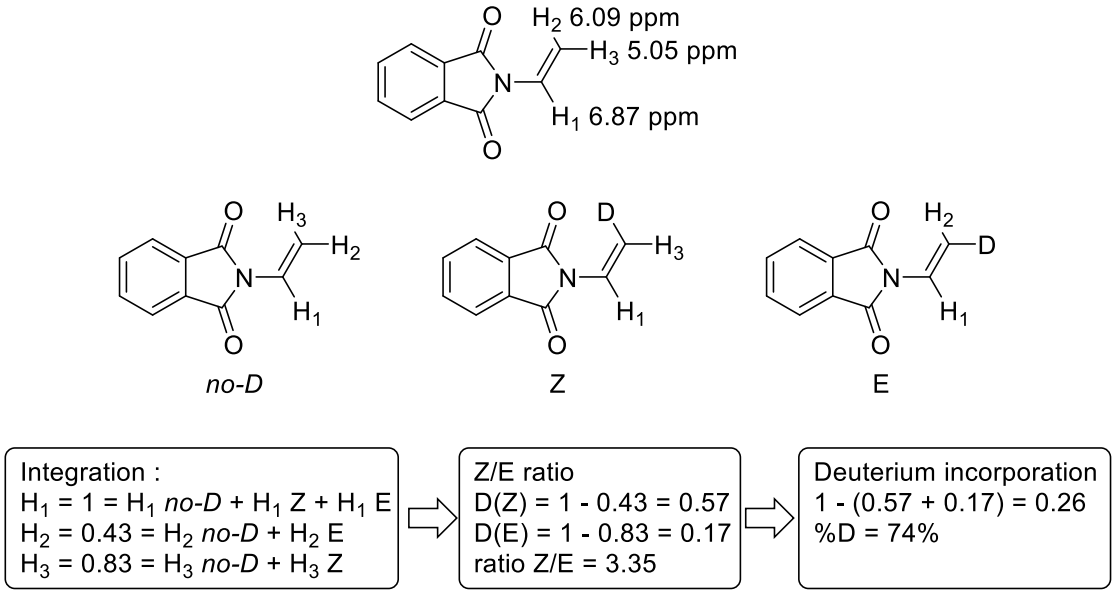
[19] Alford, J. S.; Davies H. M. L. *Org. Lett.*, **2012**, *14* , 6020

organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give an orange solid. The crude product was purified by column chromatography (SiO_2, 7:3, hexane/ethyl acetate) affording deuterated ynamide (138 mg, 0.802 mmol, 65 %, 88 % deuterium incorporation determined by the integrations of the peak at 7.88-7.79 and 3.34) as colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.88 (m, 16H), 7.88 – 7.79 (m, 16H), 3.34 (s, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 135.4, 131.0, 124.5, 67.9.[20]

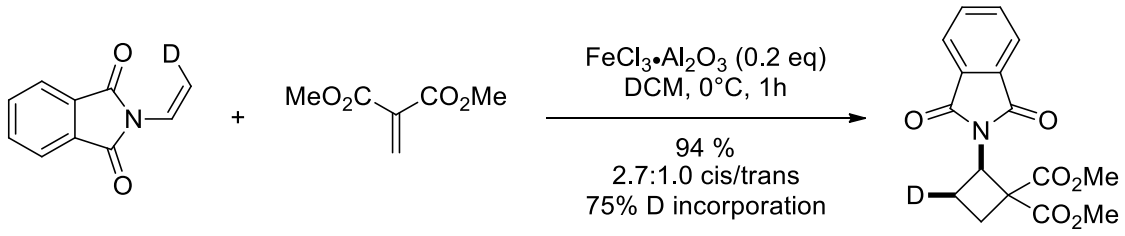
Lindlar catalyst (25 mg, 0.012 mmol, 0.05 eq) and quinoline (5.0, 0.039 mmol, 0.16 eq) were added in dichloromethane (1.0 mL) in a flask under nitrogen atmosphere. The mixture was stirred for 5 minutes and 2-(ethynyl-d)isoindoline-1,3-dione (40 mg, 0.23 mmol, 1 eq) was added as a solution in dichloromethane (0.5 mL). The reaction atmosphere was flushed with hydrogen and a hydrogen balloon was connected to the flask. The reaction was stirred for one hour at room temperature and then filtered on a celite pad, eluting with dichloromethane. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording (*Z*)-2-(vinyl-2-d)isoindoline-1,3-dione (**4r**) (32.5 mg, 0.190 mmol, 80 % yield with 20% of the saturated compound, 3.3:1 Z/E ratio and 75% deuterium incorporation) as a colorless solid.

R_f 0.60 (*Hexane*/*Ethyl acetate* 7/3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.63 (m, 4.7H, Phth), 6.97 – 6.77 (m, 1H, H_1 *no-D* + *Z* + *E*), 6.09 (dd, *J* = 16.4, 5.2 Hz, 0.43H, H_2 *no-D* + *E*), 5.05 (dd, *J* = 9.9, 5.4 Hz, 0.83H, H_3 *no-D* + *Z*), 3.81 – 3.68 (m, 0.35H, CH_2 saturated), 1.35 – 1.19 (m, 0.50H, CH_3 saturated).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 134.6, 131.8, 124.0, 124.0, 123.8, 104.7, 104.4, 104.2.
IR 1776 (w), 1724 (s), 1617 (w), 1468 (w), 1383 (s).
HRMS (ESI) calcd for $C_{10}H_7[^2H]NO_2^+$ $[M+H]^+$ 175.0611; found 175.0620.
Determination of deuterium incorporation and Z/E ratio:



Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate-3-d (6ra)

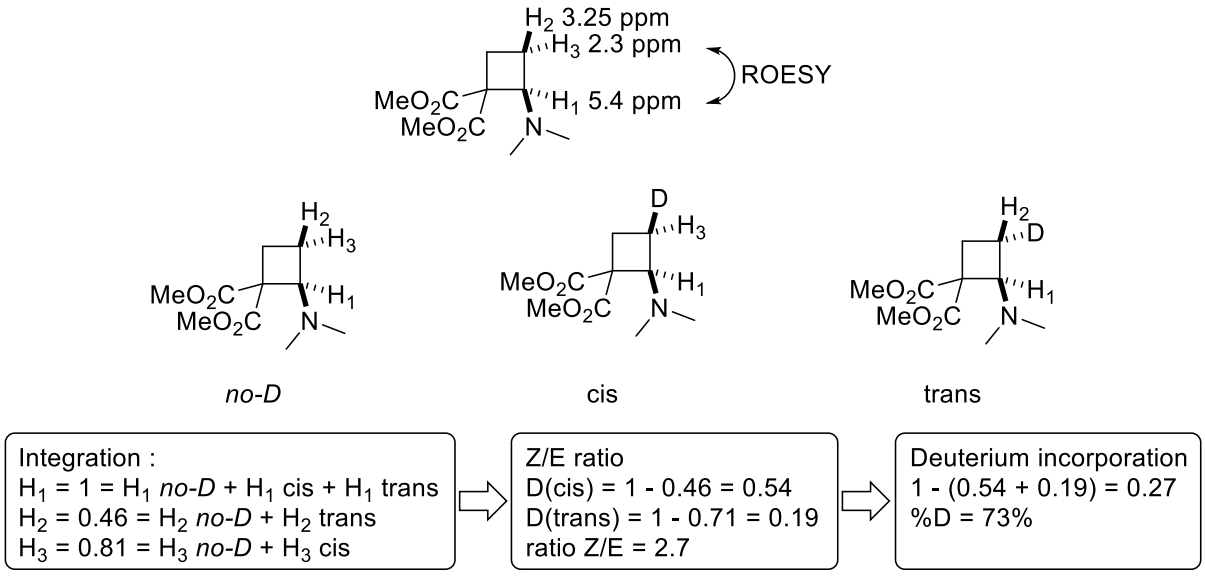
[20] The deuterated carbon was not resolved.



4r **5a** **6ra**

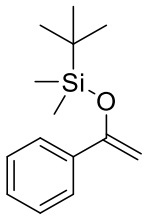
In the glovebox, Iron trichloride supported on alumina (1.00 mmol/g, 11.0 mg, 0.011 mmol, 0.1 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (200 µL) was added and the yellow suspension was cooled to 0 °C. Dimethyl 2-methylenemalonate (**5a**) (16.4 mg, 0.114 mmol, 2 eq) and (*Z*)-2-(vinyl-2-D)isoindoline-1,3-dione (**4r**) (12.4 mg, 0.0570 mmol, 1 eq) were dissolved in dry dichloromethane (800 µL) . The solution was then added dropwise to the iron trichloride solution. The reaction was stirred at 0 °C for 1 hour. The reaction mixture was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 10 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording dimethyl (2R,3R)-2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate-3-d (**6ra**) (17.0 mg, 0.0530 mmol, 94 % yield, 2.7:1.0 diastereomeric ratio and 75% deuterium incorporation determined by the same method than previously, integrating the peaks at 5.51 – 5.39 (no-D + cis + trans) 3.32 – 3.15 (trans + no-D) and 2.36 – 2.23 (cis + no-D)) as a colorless solid. The relative stereochemistry was determined by ROESY experiments.

R_f 0.45 (*Hexane*/*Ethyl acetate* 1/1).
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 – 7.77 (m, 2H, Phth), 7.75 – 7.64 (m, 2H, Phth), 5.51 – 5.39 (m, 1H, H_1 *cis* + *trans* + *no-D*), 3.75 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.32 – 3.15 (m, 0.46H, H_2 *trans* + *no-D*), 3.05 – 2.85 (m, 1H, CH_2 cyclobutane), 2.36 – 2.23 (m, 0.83H, H_3 *cis* + *no-D*), 2.23 – 2.09 (m, 1H, CH_2 cyclobutane).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 168.5, 168.1, 134.1, 131.7, 123.3, 58.74, 58.69, 53.0, 52.8, 47.6, 47.50, 47.48, 24.4, 24.3, 21.7, 21.6, 21.4, 21.2.
IR 2959 (w), 2923 (w), 2852 (w), 1779 (w), 1738 (s), 1715 (s), 1436 (w), 1377 (s), 1263 (s).
HRMS (ESI) calcd for $C_{16}H_{15}[^2H]NO_6^+$ $[M+H]^+$ 319.1034; found 319.1025.
Determination of deuterium incorporation and cis/trans ratio:



7. Formal [4+2]

Tert-butyldimethyl((1-phenylvinyl)oxy)silane (28)



Acetophenone (580 mg, 4.82 mmol, 1 eq) in anhydrous THF (5 mL) is added in an oven-dried flask sealed with a septum and under N_2 atmosphere. The solution is cooled down to -78 °C and a 2 M solution of NaHMDS (2.94 mL, 5.88 mmol, 1.22 eq) is added dropwise. The cold bath is removed and the pale yellow solution is stirred for 1 hour at room temperature. The reaction is cooled again at -78 °C and tert-butylchlorodimethylsilane (871 mg, 5.78 mmol, 1.2 eq) is added dropwise. The reaction is stirred at room temperature for 5 hours after what the solvent is directly removed under reduced pressure. The resulting orange oil is purified by column chromatography on triethylamine-deactivated silica (100 % Hexane). Tert-butyldimethyl((1-phenylvinyl)oxy)silane (**28**) (960 mg, 4.10 mmol, 85% yield) is obtained as a colorless oil which can be re-purified by short path distillation in case of degradation with time.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.60 (m, 2 H, Ar), 7.39-7.29 (m, 3 H, Ar), 4.89 (d, 1 H, *J* = 1.7 Hz, C=CH_2), 4.42 (d, 1 H, *J* = 1.7 Hz, C=CH_2), 1.00 (s, 9 H, $Si(CH_3)_2C(CH_3)_3$), 0.21 (s, 6 H, $Si(CH_3)_2C(CH_3)_3$).
^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 137.8, 128.2, 128.1, 125.3, 90.9, 25.9, 18.4, -4.6.

Data match literature report.[21]

Dimethyl -2-((tert-butyldimethylsilyl)oxy)-4-(1,3-dioxoisoindolin-2-yl)-2-phenylcyclohexane-1,1-dicarboxylate (10)

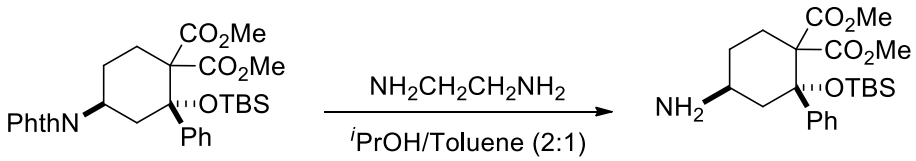
[21] J.-F. Zhao, B.-H. Tan, T.-P. Loh *Chem. Sci.* **2011**, *2*, 349.

6aa **28** **10**

4Å MS pellets (ca 20 mg) were added in an oven dried 5 mL round bottom flask. The flask was closed with a silicon septum and three cycles of vacuum/N_2 were performed. Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (**6aa**) (63.5 mg, 0.200 mmol, 1 eq) and *tert*-butyldimethyl((1-phenylvinyl)oxy)silane (**28**) (70.4 mg, 0.300 mmol, 1.5 eq) were dissolved in dichloromethane (2 mL) and added to the reaction flask. The solution was cooled to -40 °C using an acetonitrile/N_2 bath. A solution of tin tetrachloride (0.43 mol/L, 93.0 µL, 0.0400 mmol, 0.2 eq,) was added dropwise and the reaction was stirred for 1 hour at -40 °C. The reaction was then quenched by adding triethylamine (0.1 mL) and the solvent was removed under reduced pressure. The reaction was purified by column chromatography on Biotage (SNAP cartridge KP-SIL 25 g, 95:5 to 4:6 Hexane/Ethyl acetate) affording aminocyclohexane **10** (105 mg, 5.48 mmol, 95 % yield) as a colorless solid.

R_f 0.61 (*Hexane*/*Ethyl acetate* 6/4).
Mp 188.8-190.0 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H, Phth), 7.72 (dd, *J* = 5.4, 3.1 Hz, 2H, Phth), 7.44 – 7.38 (m, 2H, Ar), 7.26 – 7.21 (m, 3H, Ar), 4.86 (tt, *J* = 12.5, 4.7 Hz, 1H, N-C-H), 3.96 (dd, *J* = 13.6, 12.6 Hz, 1H, CH_2 cyclohexane), 3.66 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.91 (td, *J* = 14.2, 3.7 Hz, 1H, CH_2 cyclohexane), 2.31 (dt, *J* = 13.8, 3.5 Hz, 1H, CH_2 cyclohexane), 2.23 – 2.01 (m, 2H, CH_2 cyclohexane), 1.88 – 1.74 (m, 1H, CH_2 cyclohexane), 1.06 (s, 9H, Si-*t*Bu), 0.14 (s, 3H, Si-Me), -0.55 (s, 3H, Si-Me).
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.9, 168.4, 143.0, 134.1, 132.1, 128.8, 127.8, 126.5, 123.3, 79.7, 64.6, 52.3, 52.0, 46.6, 36.7, 29.4, 26.4, 25.3, 19.3, -1.3, -2.5.
IR 2953 (w), 2890 (w), 2856 (w), 2361 (w), 2339 (w), 1735 (s), 1714 (s), 1373 (m), 1274 (m), 1245 (m), 1039 (m), 1038 (m).
HRMS (ESI) calcd for $C_{30}H_{37}NNaO_7Si^+$ $[M+Na]^+$ 574.2231; found 574.2228.

Dimethyl-4-amino-2-((tert-butyldimethylsilyl)oxy)-2-phenylcyclohexane-1,1-dicarboxylate (10')



10 **10'**

Dimethyl 2-((tert-butyldimethylsilyl)oxy)-4-(1,3-dioxoisoindolin-2-yl)-2-phenylcyclohexane-1,1-dicarboxylate (**10a**) (50 mg, 0.091 mmol, 1 eq) in isopropanol (1.0 mL) and toluene (0.5 mL) was added in an oven dried 5 mL round bottom flask followed by diaminoethane (27.2 mg, 0.45 mmol, 5 eq). The vial was sealed and the solution was heated to 80 °C for 16 hour. The solvent was removed under reduced pressure and the crude was purified by column chromatography (SiO_2, 9:1 DCM/Methanol) affording dimethyl 4-amino-2-((tert-butyldimethylsilyl)oxy)-2-phenylcyclohexane-1,1-dicarboxylate **10'** (33 mg, 0.079 mmol, 87 % yield, > 95% pure) as a colorless oil.

R_f 0.20 (*DCM*/*Methanol*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H, Ar), 7.25 – 7.22 (m, 3H, Ar), 3.60 (s, 3H, COOMe), 3.55 (s, 3H, COOMe), 3.23 (ddt, *J* = 11.7, 8.7, 4.2 Hz, 1H, N-CH), 2.81 – 2.61 (m, 2H, CH_2), 2.24 – 2.06 (m, 2H, CH_2), 1.99 – 1.85 (m, 1H, CH_2), 1.43 – 1.22 (br, 7H, NH_2 and H_2O),[22] 1.02 – 0.84 (m, 10H, Si-^{t}Bu and CH_2), 0.05 (s, 3H, SiMe), -0.60 (s, 3H, SiMe).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.9, 143.2, 128.6, 127.4, 126.1, 79.5, 64.4, 51.8, 51.5, 46.0, 44.6, 32.5, 29.4, 26.0, 18.9, -1.4, -3.1.

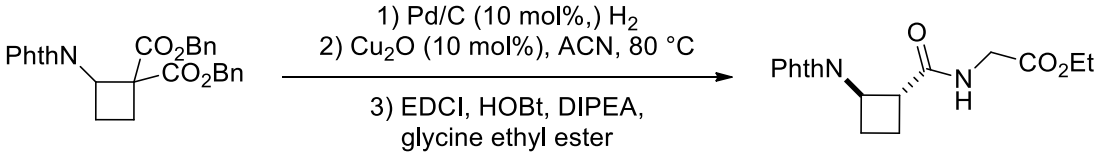
IR 3056 (w), 2953 (w), 2888 (w), 2860 (w), 1732 (m), 1447 (w), 1436 (w), 1266 (s), 1155 (w), 1136 (w), 1044 (m), 1031 (m).

HRMS (ESI) calcd for $C_{22}H_{36}NO_5Si^+$ $[M+H]^+$ 422.2357; found 422.2353.

[22] NH_2 peak over-integrated due to water in $CDCl_3$

8. Synthesis of dipeptide **11**

Ethyl (-2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1-carbonyl)glycinate (11)



6ai **11**

78 % yield (3 steps), 5:1 *dr*

Under nitrogen, dibenzyl 2-(1,3-dioxoisoindolin-2-yl)cyclobutane-1,1-dicarboxylate (**6ai**) (1.00 g, 2.13 mmol, 1 eq) was dissolved in technical ethanol (15 mL). Palladium on charcoal 5% (0.453 g, 0.213 mmol, 0.1 eq) was added and the reaction atmosphere was purged with hydrogen. The reaction was stirred at room temperature for 5 hours. Celite (ca 5 g) was added to the reaction and the suspension was filtered through a pad of celite. The cake was rinsed abundantly with hot ethanol. The solvents were removed on a rotary evaporator and the solid crude diacid was directly used for the next step.

In a glovebox, copper (I) oxide (30.5 mg, 0.213 mmol, 0.1 eq) was added in a vial which was closed with a silicon septum and removed from the glovebox. The crude diacid was quickly added as a solid, the vial was sealed and three cycles of vacuum/N_2 were performed. Dry acetonitrile (2 mL) was added and the reaction was stirred in an oil bath at 80 °C for 3 hours when no more starting material was detected by NMR. The reaction was cooled to room temperature and poured into a separatory funnel. 1 M HCl (15 mL) and ethyl acetate (15 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified on column chromatography (SiO_2, DCM/MeOH/AcOH, 98:2:0.01 to 90:10:0.01) affording 2-(1,3-dioxoisoindolin-2-yl)cyclobutanecarboxylic acid (447 mg, 1.83 mmol, 86% on two steps, 5:1 dr determined by integration of the peaks at 5.02 (*maj*), and 4.91 (*min*) in the crude ^{1}H NMR) as a colorless oil.

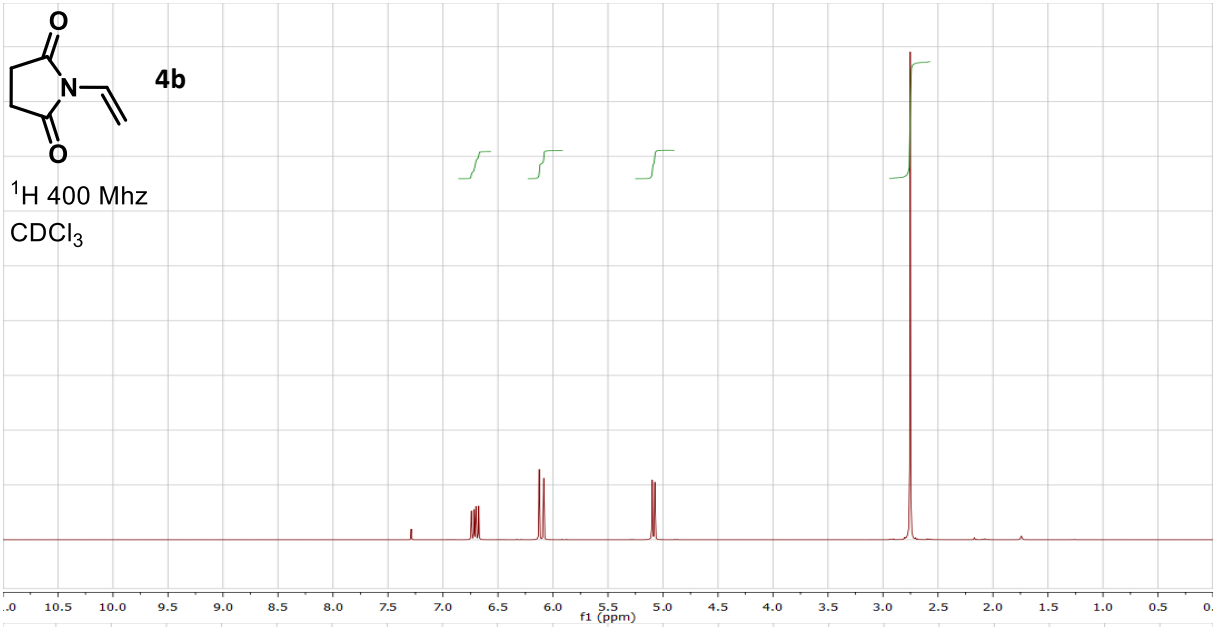
Mp 103.8-105.9 °C.
R_f 0.23 (DCM/MeOH/AcOH 90:10:0.01).
^{1}H NMR (400 MHz, $CDCl_3$) on a 5 (*maj*):1(*min*) diatereomeric mixture δ 7.81 (m, 12H, Phth), 7.71 (m, 12H, Phth), 5.02 (q, *J* = 9.1 Hz, 5H, N-C-H, *major*), 4.91 (q, *J* = 9.2 Hz, 1H, N-C-H, *minor*), 4.12 (q, *J* = 9.4 Hz, 1H, CH_2 cyclobutane, *minor*), 3.65 – 3.54 (m, 5H, CH_2 cyclobutane, *major*), 3.21 – 3.08 (m, 5H, CH_2 cyclobutane, *major*), 2.79 (m, 1H, CH_2 cyclobutane, *minor*), 2.64 (m, 5H, CH_2 cyclobutane, *major*), 2.42 (m, 5H, CH_2 cyclobutane, *major*), 2.31 – 1.97 (m, 8H, CH_2 cyclobutane, *major* + *minor*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2, 177.2, 168.5, 168.2, 134.1, 134.0, 131.8, 131.7, 123.34, 123.29, 46.3, 45.5, 43.2, 42.5, 24.6, 24.0, 19.7, 18.9.

2-(1,3-Dioxoisoindolin-2-yl)cyclobutanecarboxylic acid (200 mg, 0.816 mmol, 1 eq), N-ethyl-N-isopropylpropan-2-amine (316 mg, 2.45 mmol, 3 eq) and HOBT (187 mg, 1.22 mmol, 1.5 eq), were added in a flask, dichloromethane (2 mL) was added and the reaction was cooled to 0 °C. Then, 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride (235 mg, 1.22 mmol, 1.5 eq) and finally ethyl 2-aminoacetate hydrochloride (114 mg, 0.816 mmol, 1 eq) were added and

the reaction was warmed to room temperature and stirred for 24 hours. The reaction was then concentrated to dryness and purified on column chromatography (SiO_2, DCM/MeOH/AcOH, 98:2:0.01 to 90:10:0.01) affording ethyl 2-(2-(1,3-dioxoisoindolin-2-yl)cyclobutanecarboxamido)acetate (**11**) (244 mg, 0.740 mmol, 91%, 5:1 dr determined by integration of the peaks at 3.33-3.14 (*maj*), and 4.26-4.13 (*min*) in the isolated product ^{1}H NMR) as a colorless oil.

R_f 0.35 (*DCM*/*MeOH/AcOH 9*/1/0.01).
^{1}H NMR (400 MHz, $CDCl_3$) on a 5 (*maj*):1(*min*) diatereomeric mixture δ 7.88 – 7.75 (m, 12H, Phth *major*+ *minor*), 7.74 – 7.62 (m, 12H, Phth *major*+ *minor*), 6.24 (s, 1H, NH *minor*), 5.97 (s, 5H, NH, *major*), 5.01 – 4.83 (m, 6H, N-C-H *major*+ *minor*), 4.26 – 4.13 (m, 2H, CH_2 O-CH_2 *minor*), 4.11 – 3.96 (m, 13H, 2H O-CH_2 *major* + 2H CH_2 glycine *minor* + 1H CH_2 cyclobutane *minor*), 3.95 – 3.79 (m, 10H, CH_2 glycine *major*), 3.66 – 3.49 (m, 5H, CH_2 cyclobutane *major*), 3.33 – 3.14 (m, 5H, CH_2 cyclobutane *major*), 2.80 – 2.57 (m, 6H, CH_2 cyclobutane *major* + *minor*), 2.57 – 2.44 (m, 5H, CH_2 cyclobutane *major*), 2.30 – 2.02 (m, 8H, 1H CH_2 cyclobutane *major* + 2H CH_2 cyclobutane *minor*), 1.26 (t, *J* = 7.2 Hz, 3H, CH_3 *minor*), 1.19 (t, *J* = 7.1 Hz, 15H, CH_3 *major*).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.3, 169.8, 169.6, 168.6, 168.3, 134.1, 133.7, 132.0, 131.7, 123.2, 123.1, 61.4, 61.2, 46.9, 46.8, 44.5, 44.0, 41.3, 41.3, 24.3, 24.0, 20.6, 19.0, 14.03, 13.98.
IR 3595 (w), 3377 (w), 2987 (w), 1777 (w), 1748 (w), 1713 (s), 1662 (w), 1538 (w), 1381 (s), 1201 (m), 1027 (w).
HRMS (ESI) calcd for $C_{17}H_{19}N_2O_5^+$ $[M+H]^+$ 331.1288; found 331.1290.

9. Spectra of new compounds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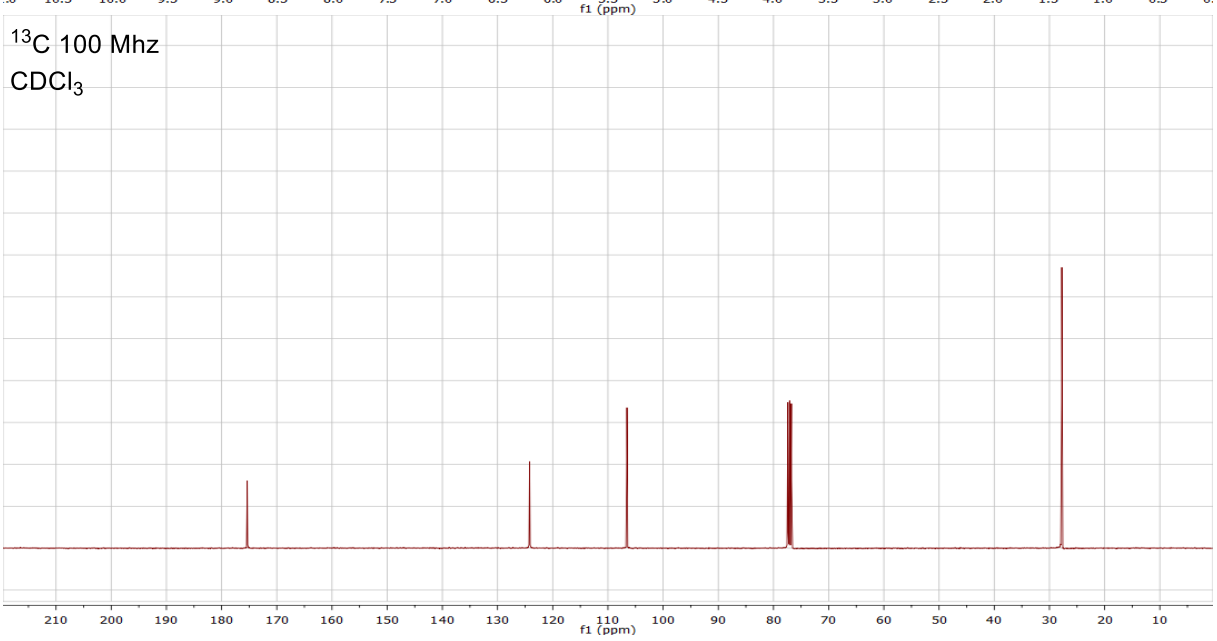
f1 (ppm)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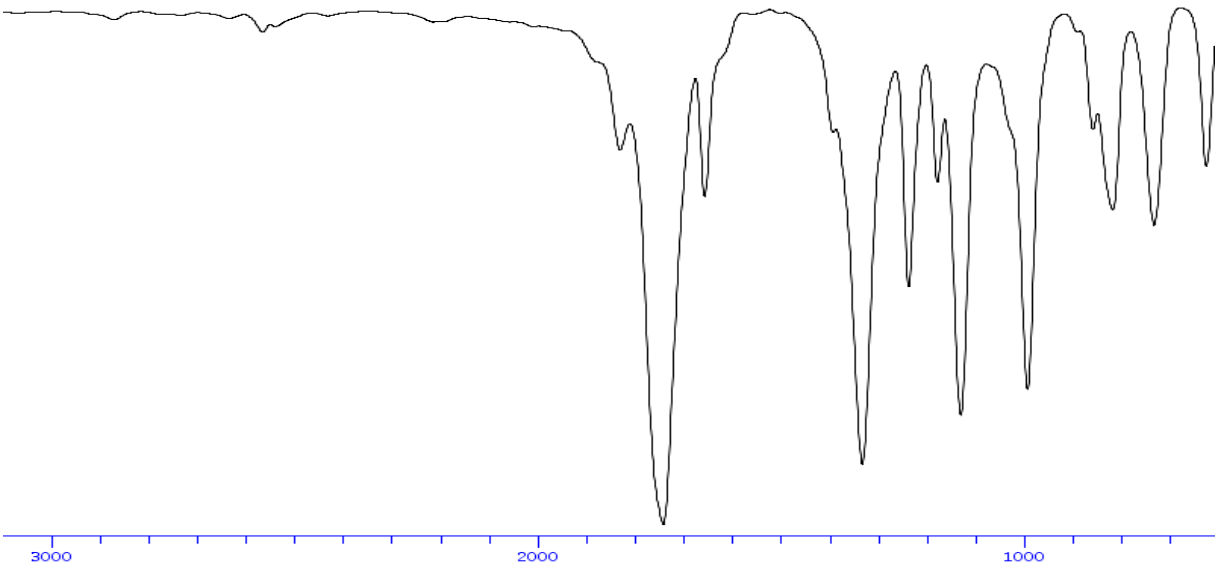
f1 (ppm)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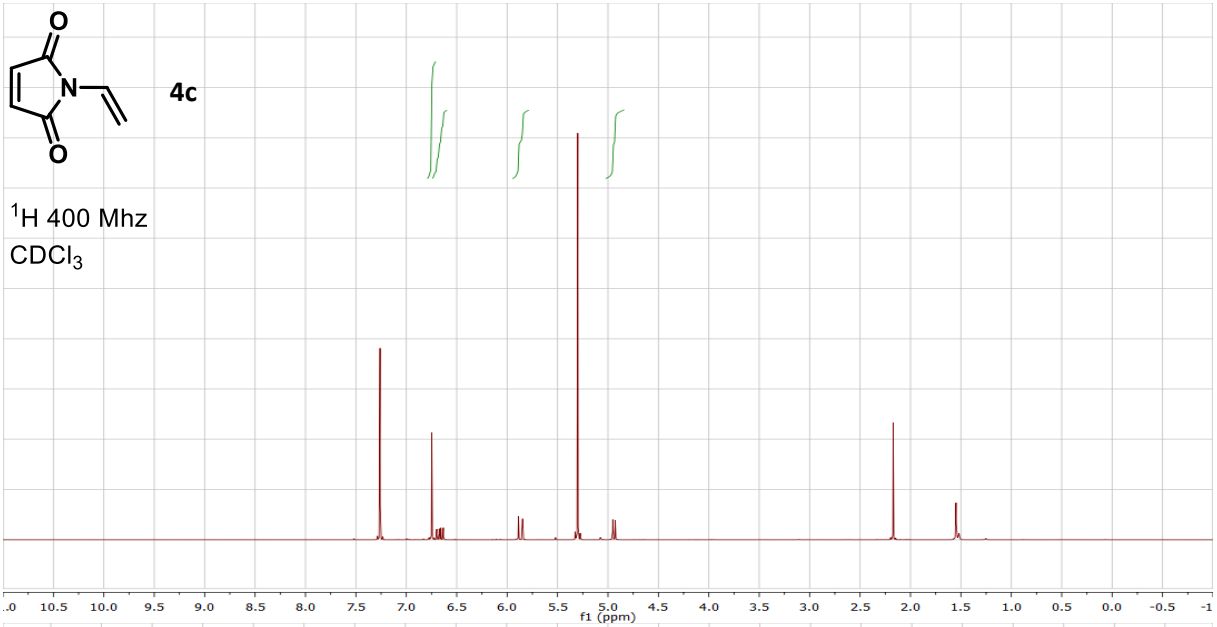
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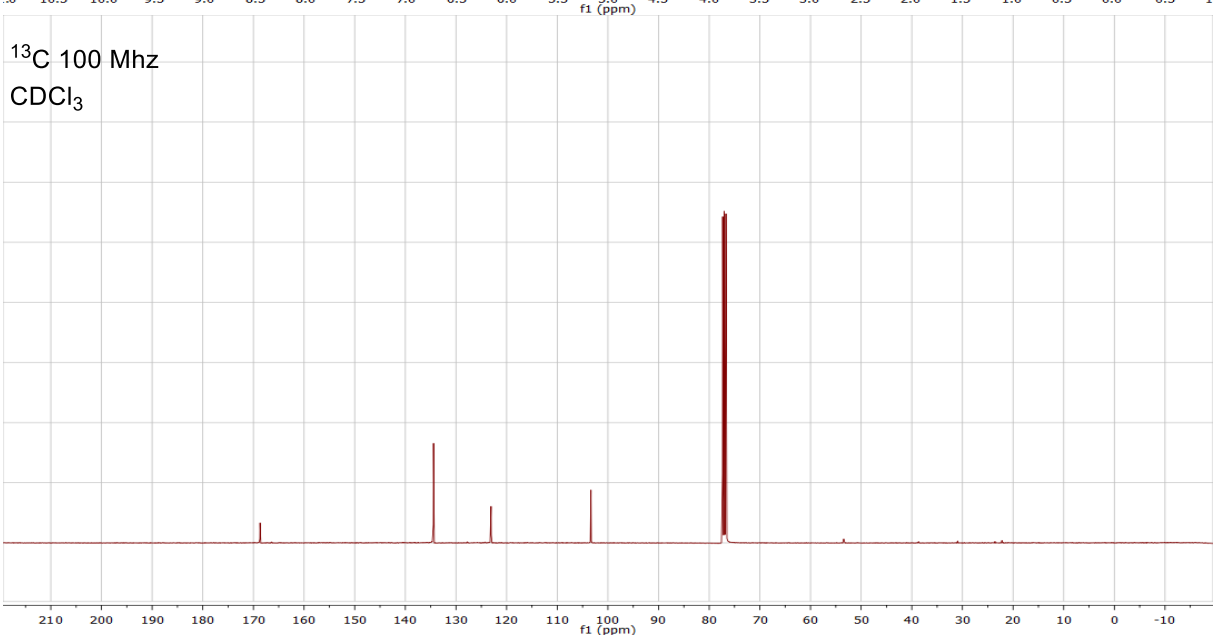
CDCl3
f1 (ppm)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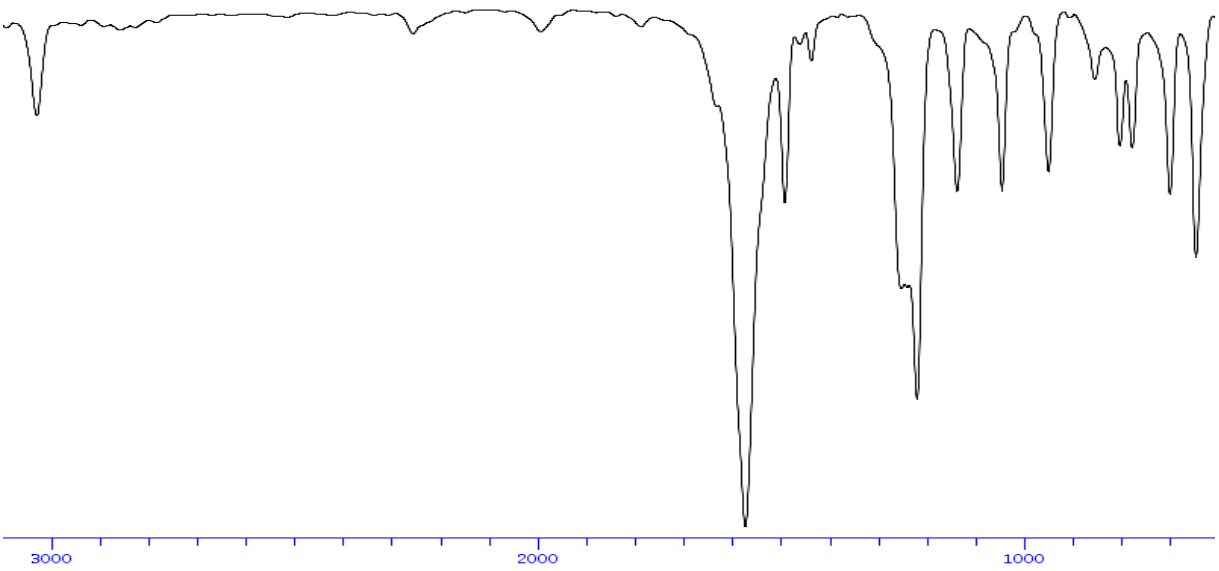
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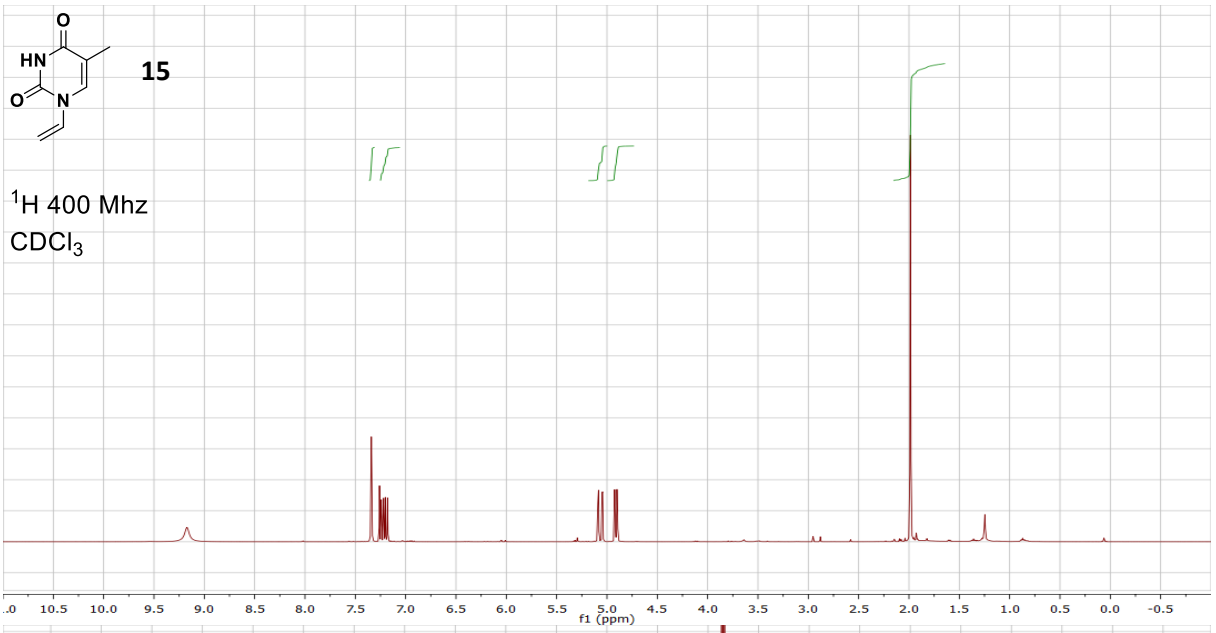
15
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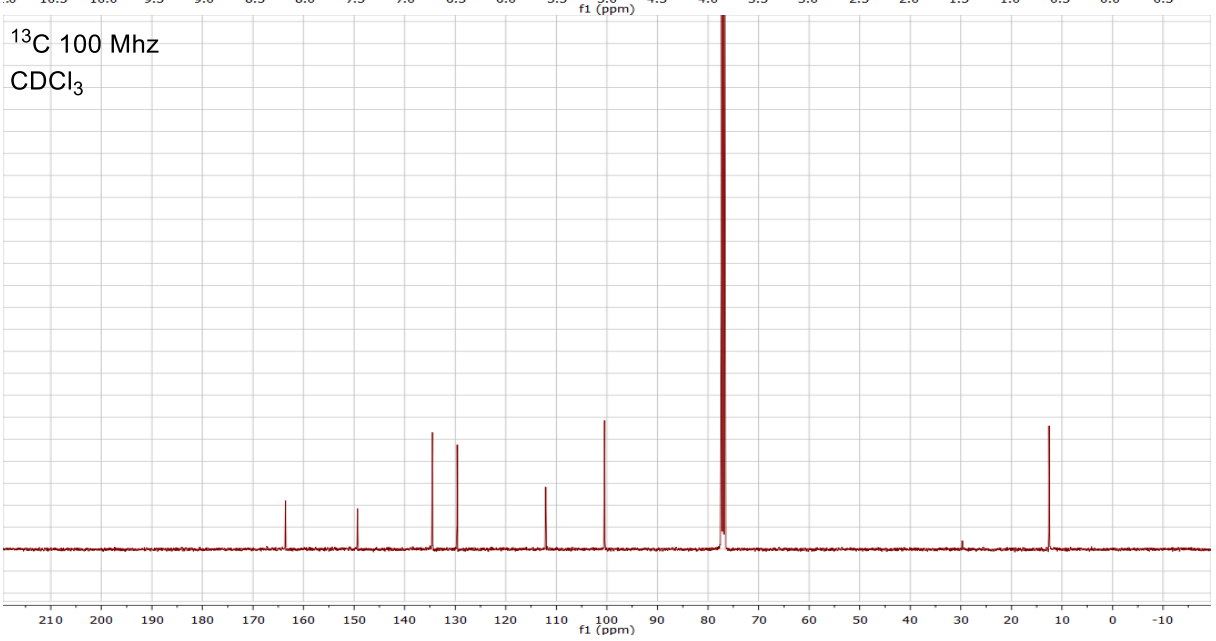
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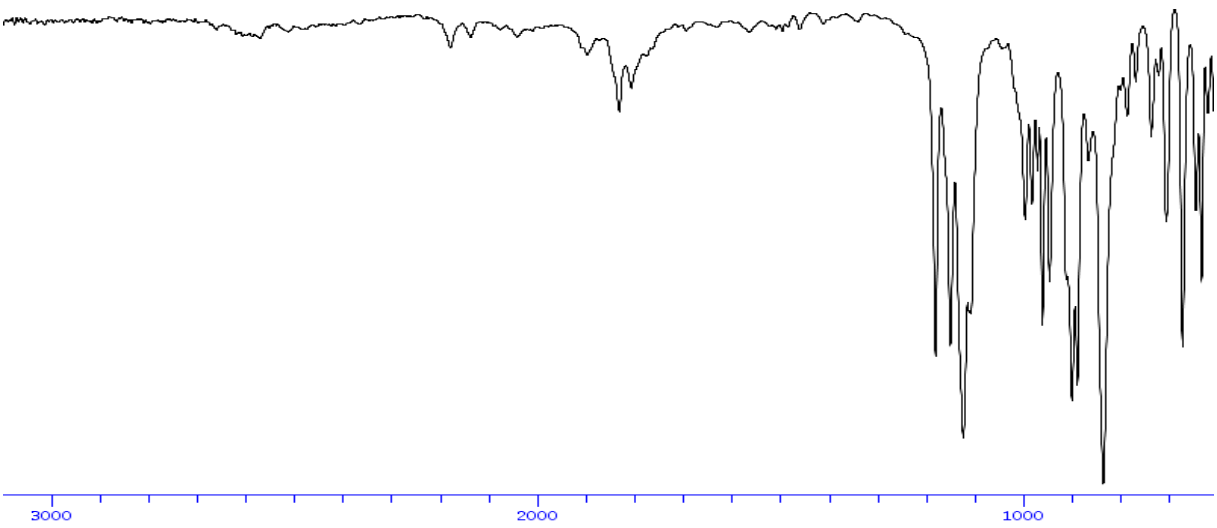
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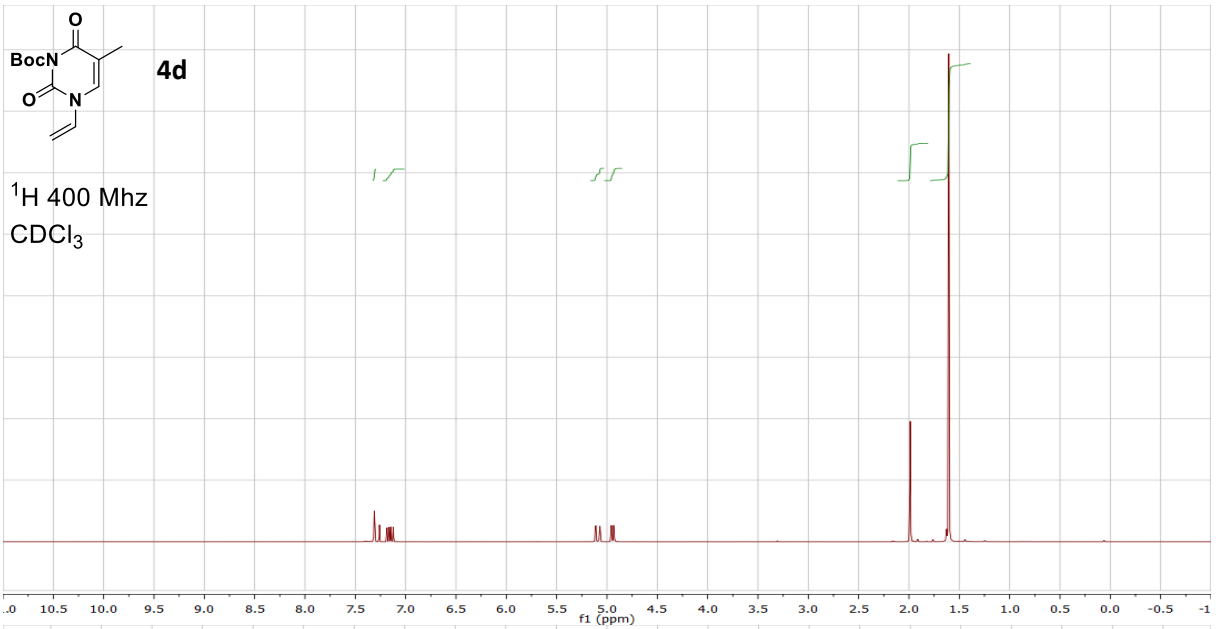
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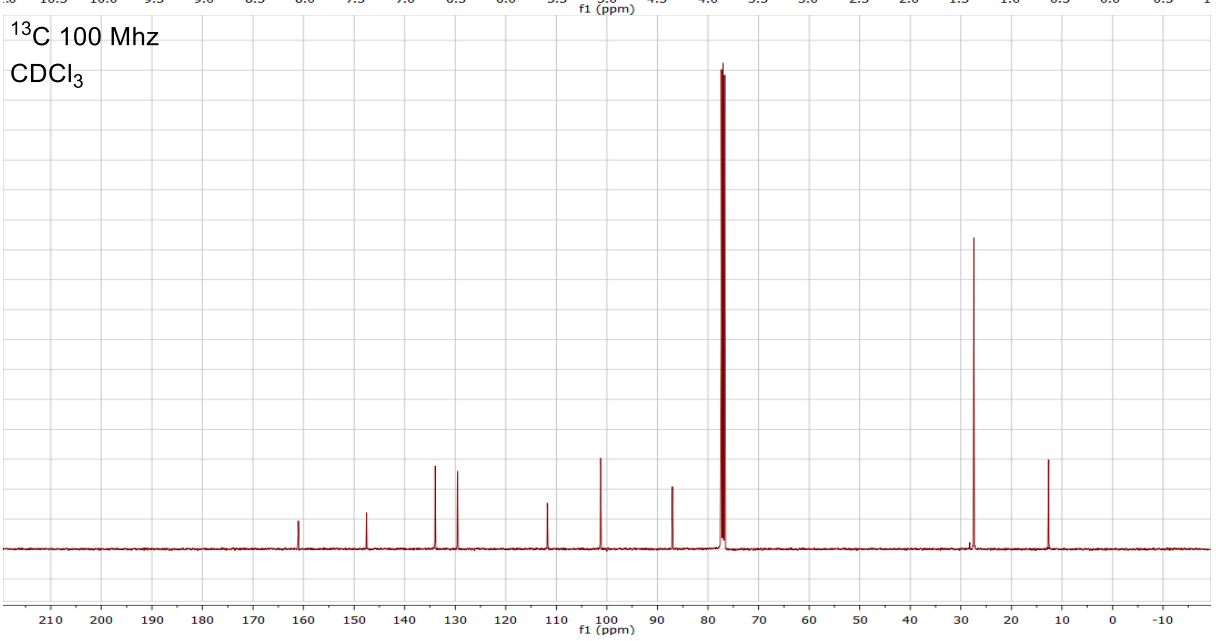
f1 (ppm)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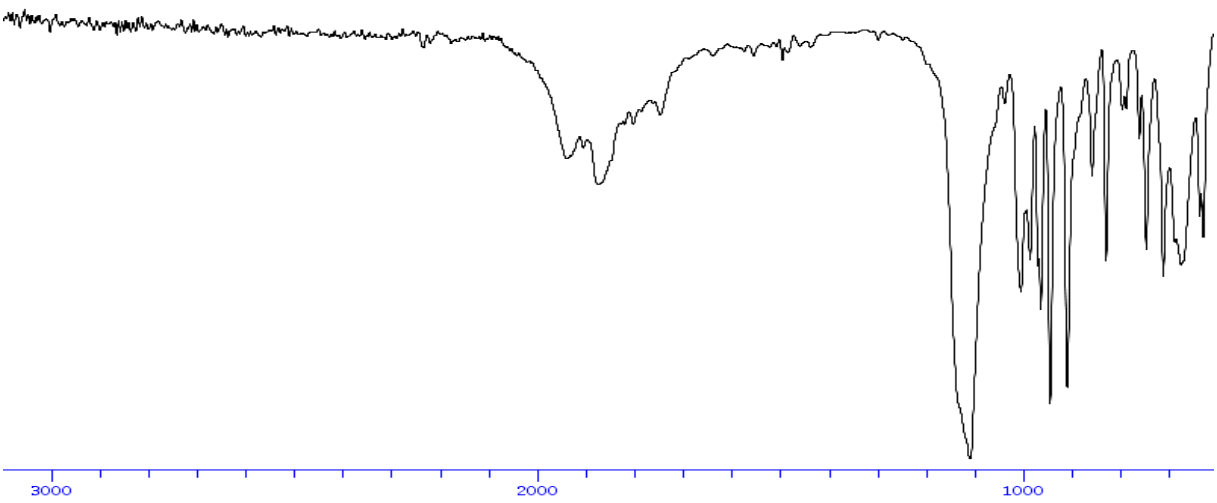
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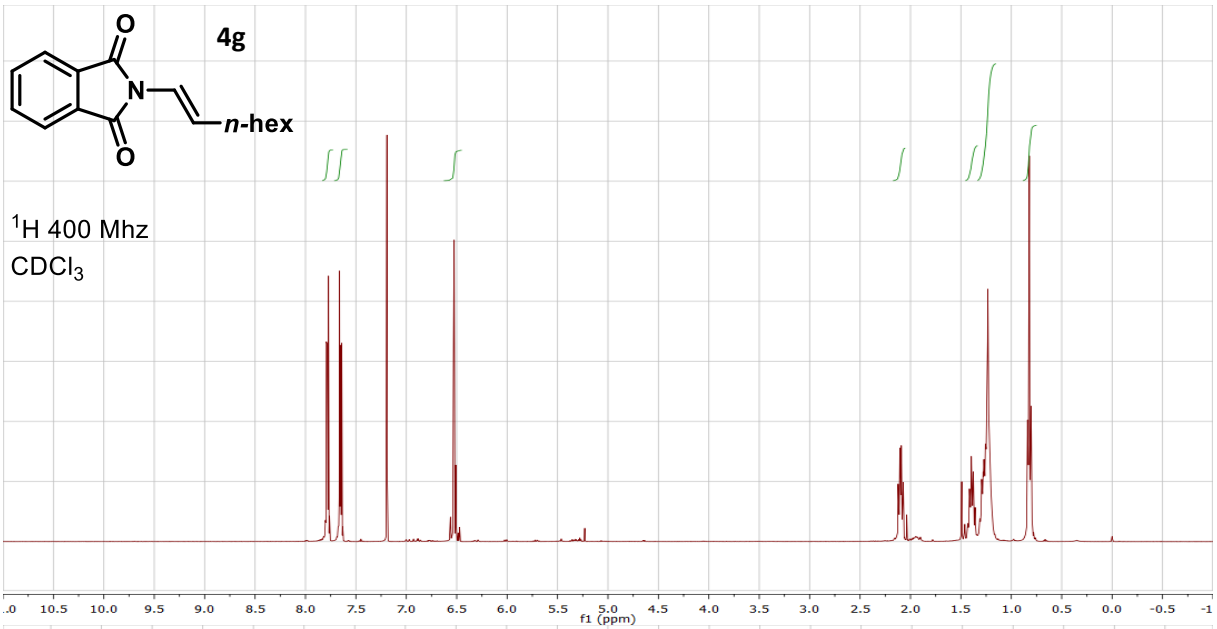
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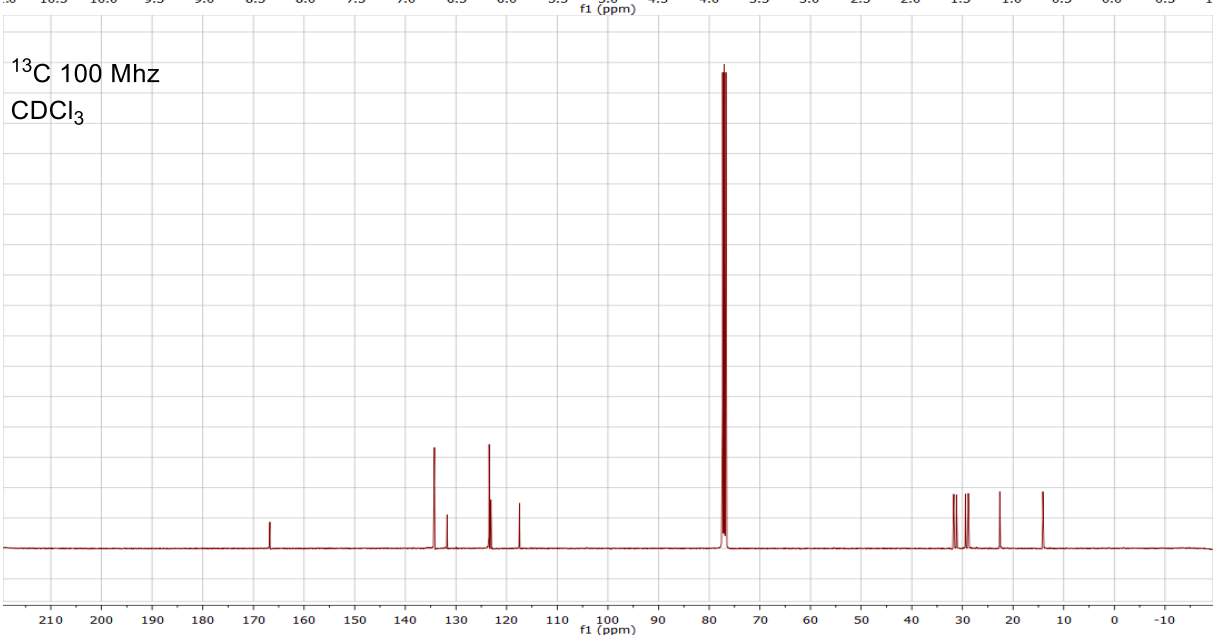
f1 (ppm)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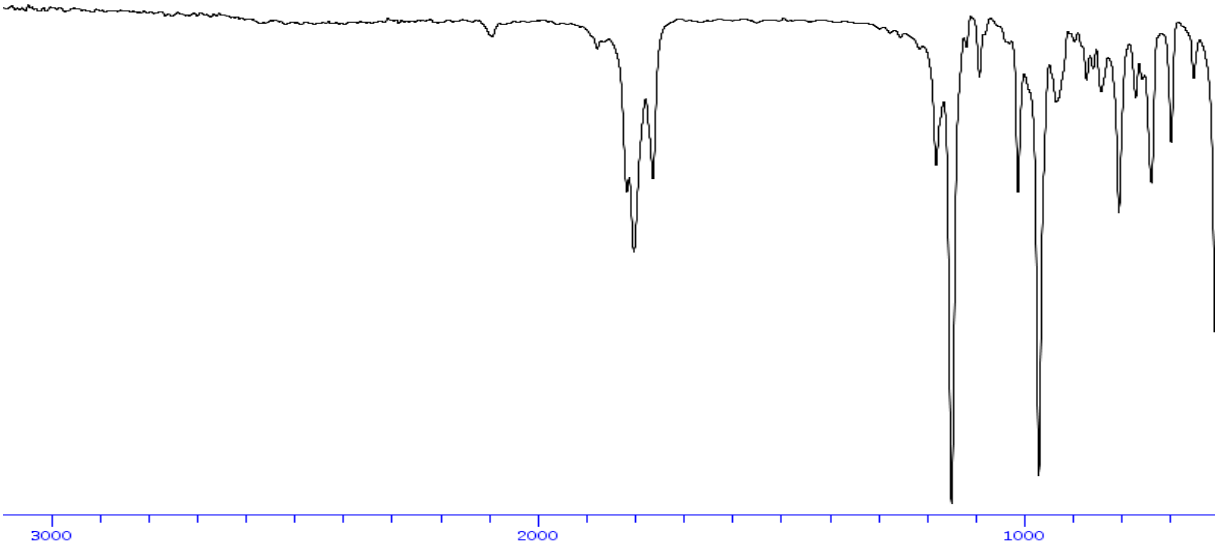
f1 (ppm)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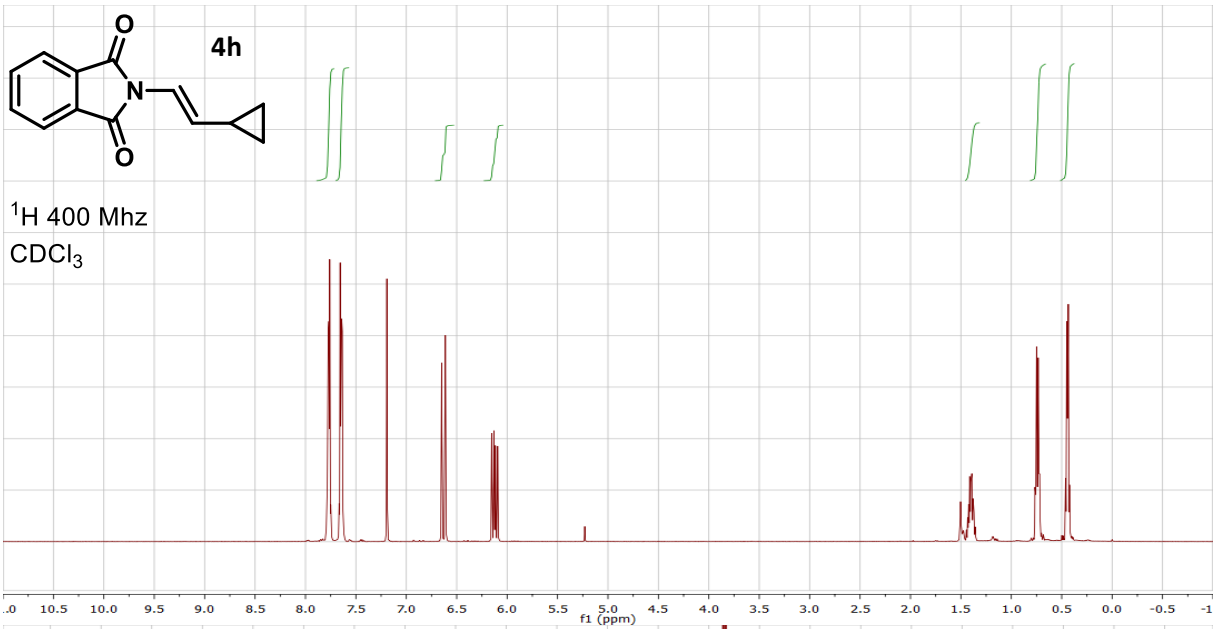
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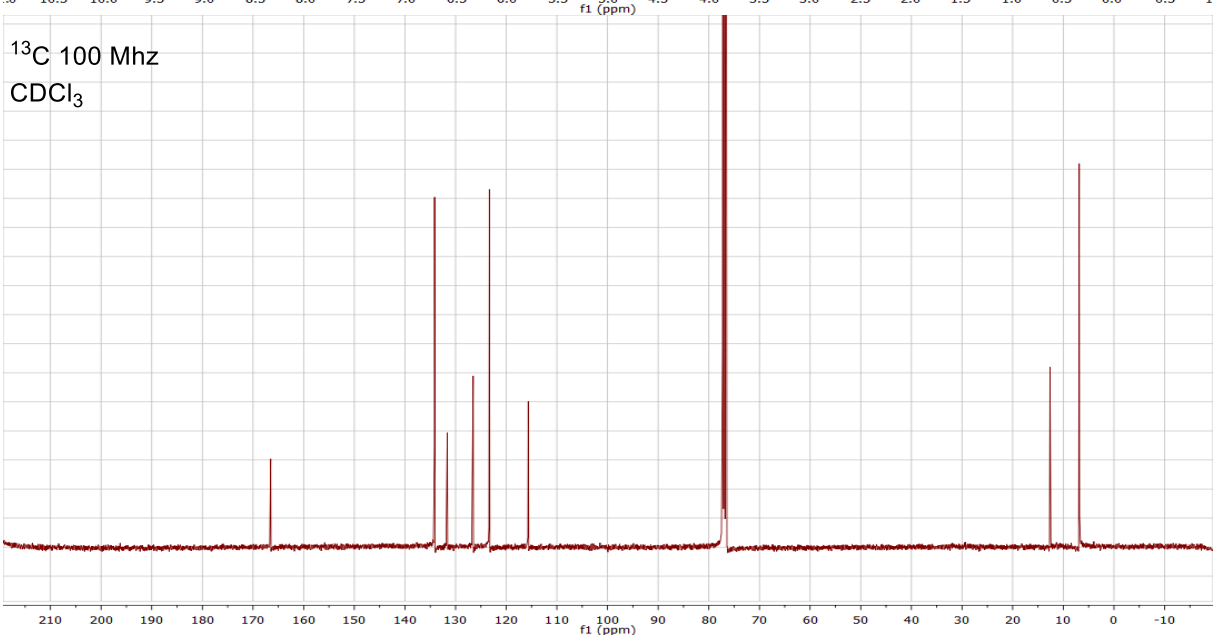
f1 (ppm)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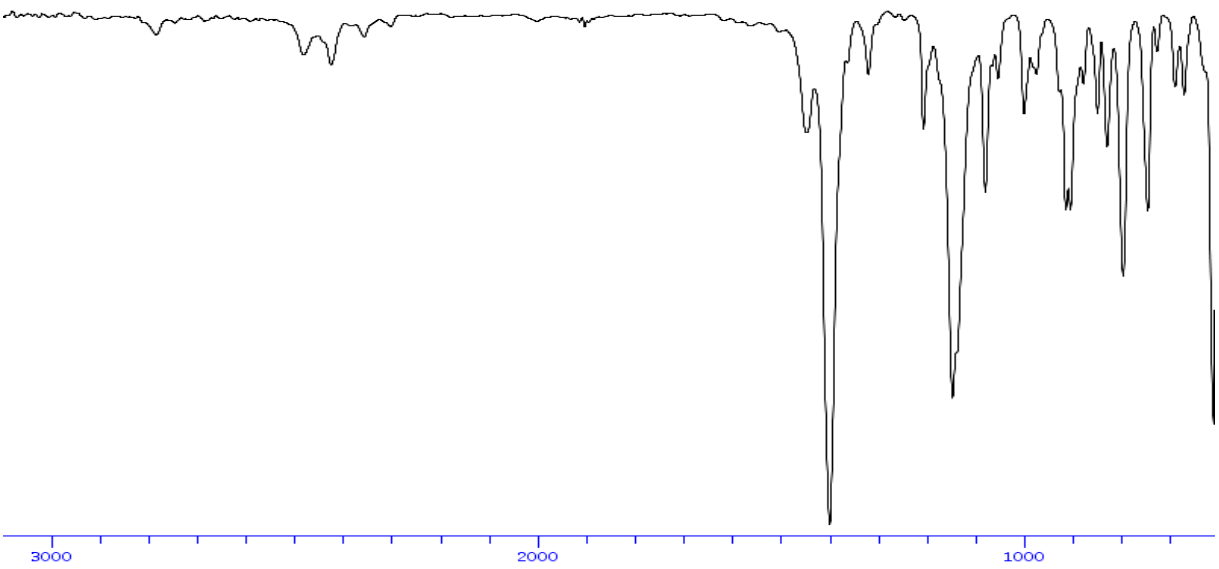
f1 (ppm)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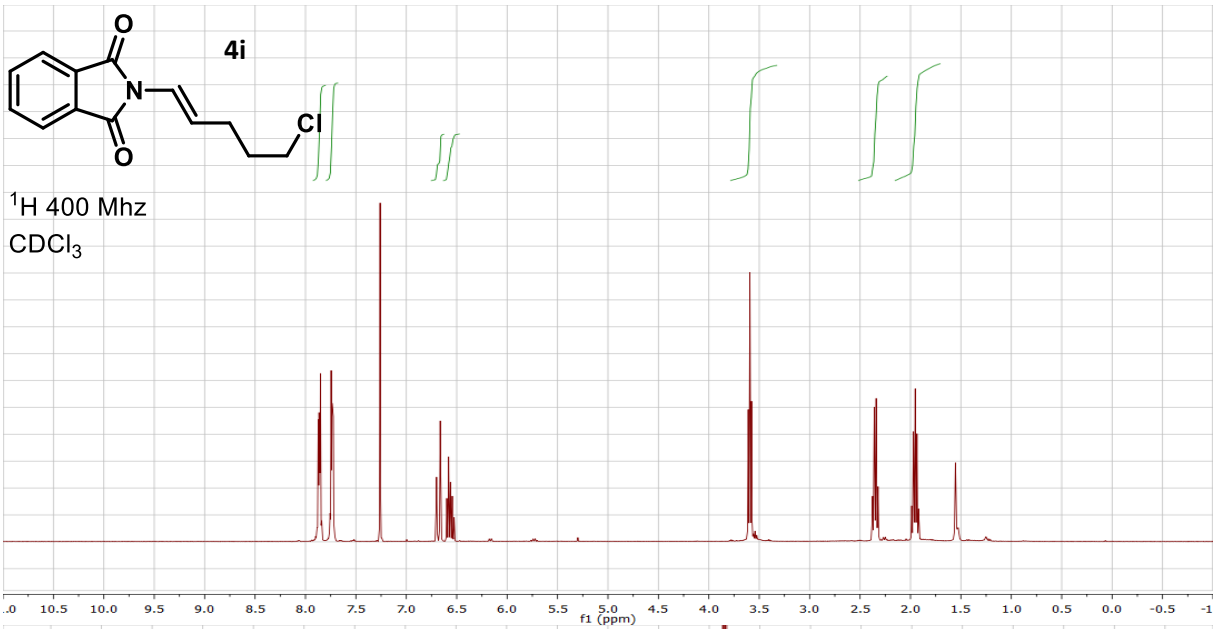
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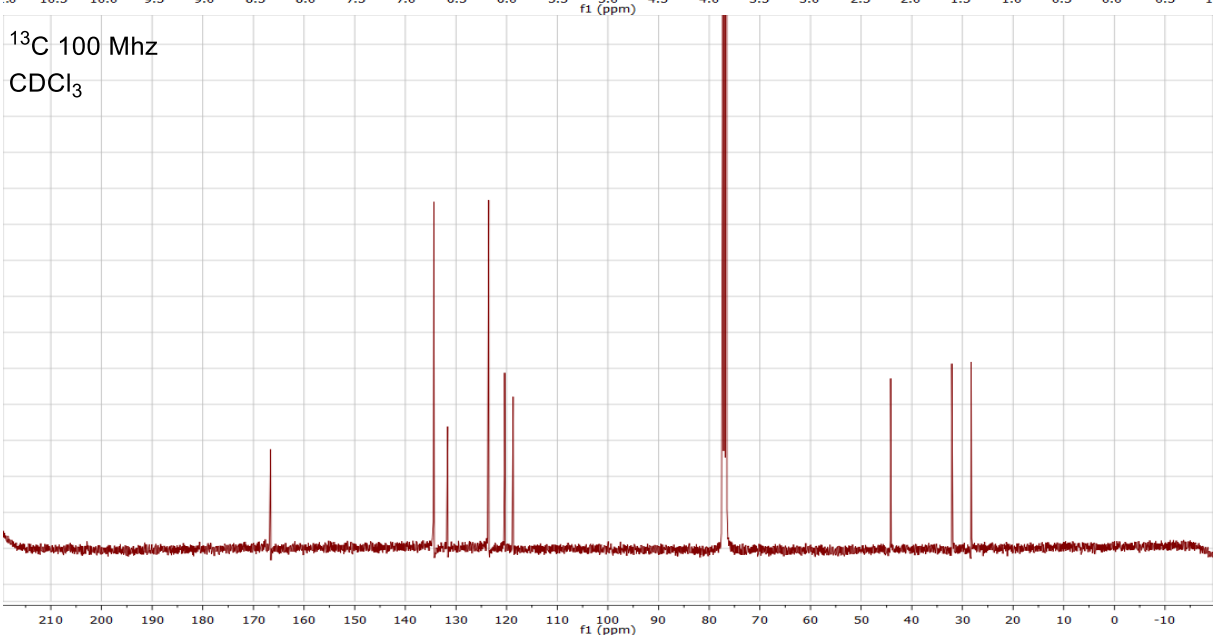
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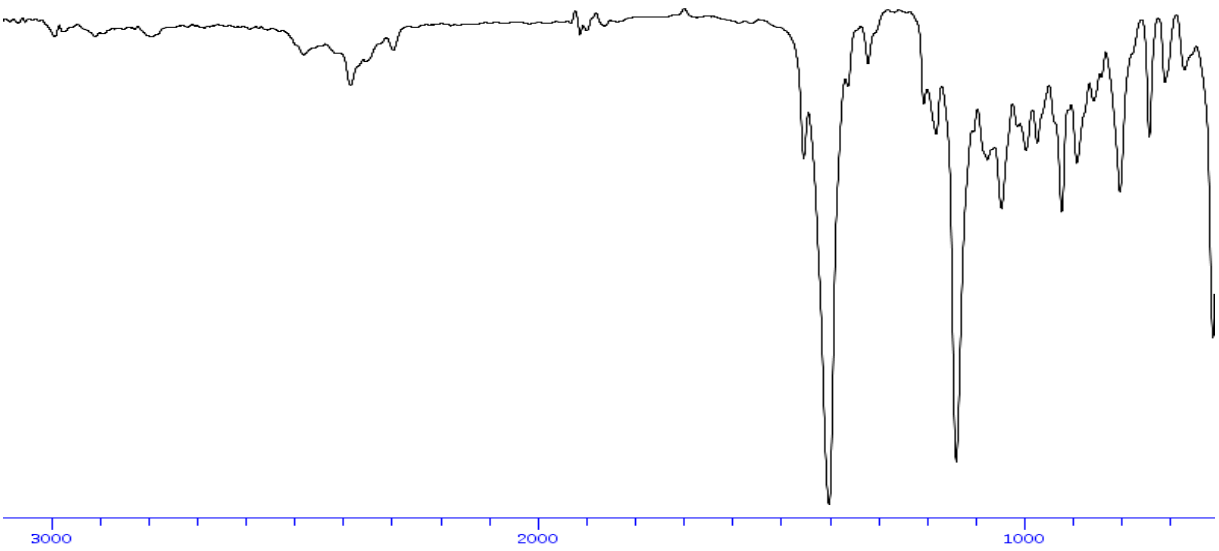
f1 (ppm)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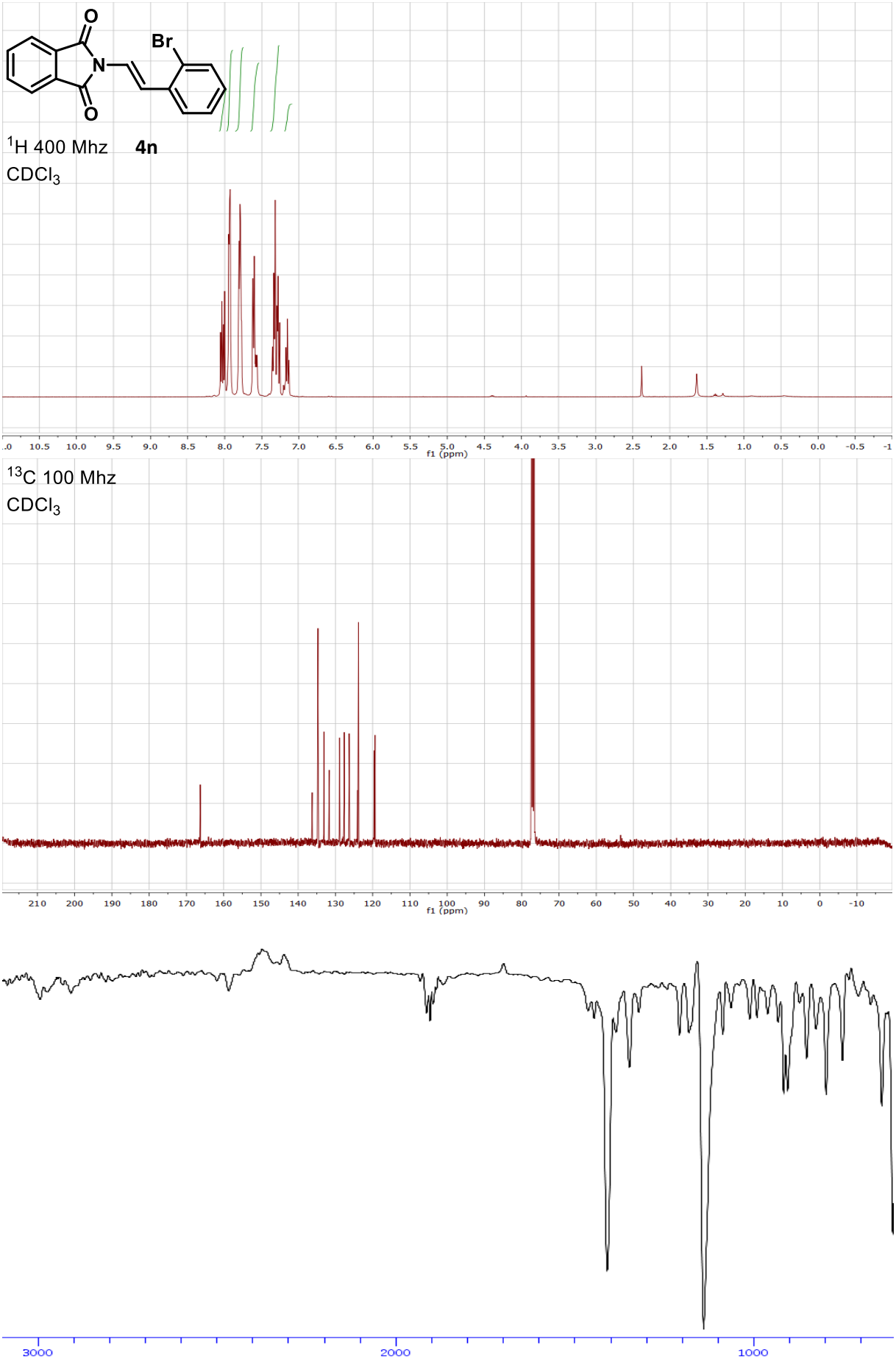
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N
O
Br
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CDCl3
f1 (ppm)
13C 100 Mhz
CDCl3
f1 (ppm)
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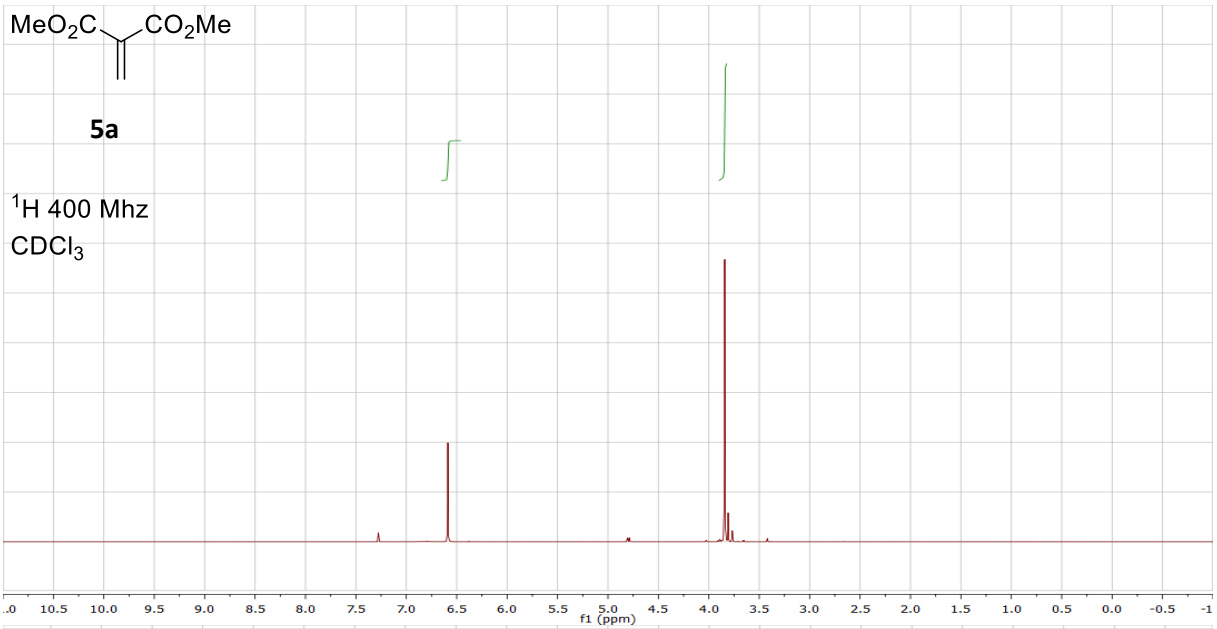
2000
1000


MeO2C
CO2Me
5a
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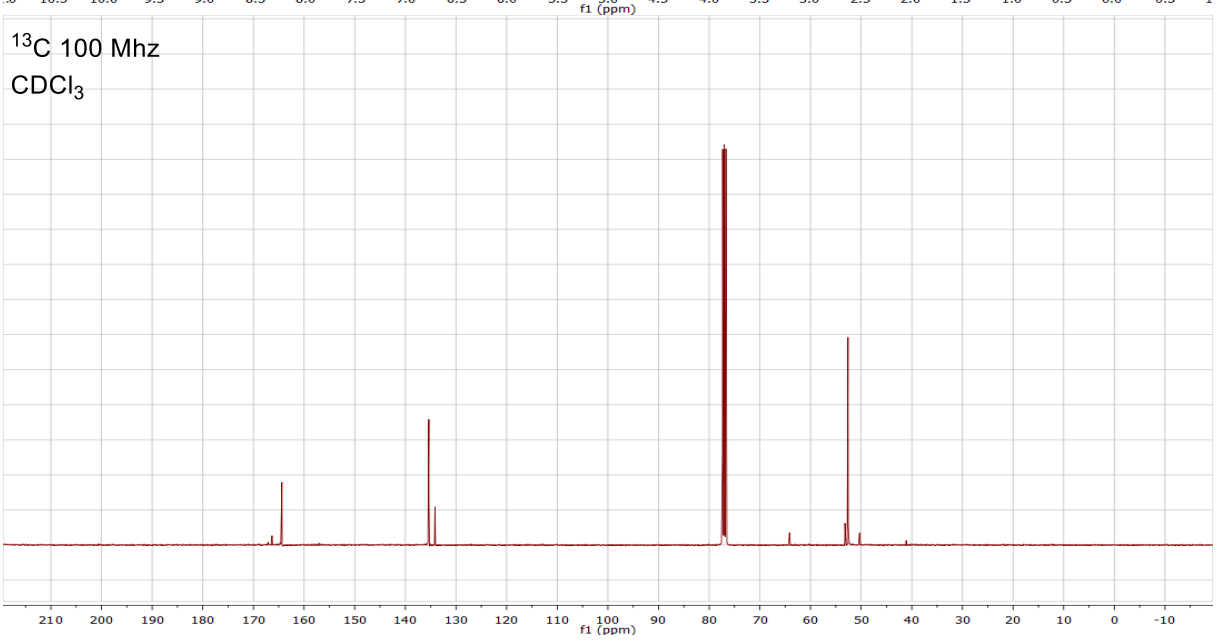
CDCl3
f1 (ppm)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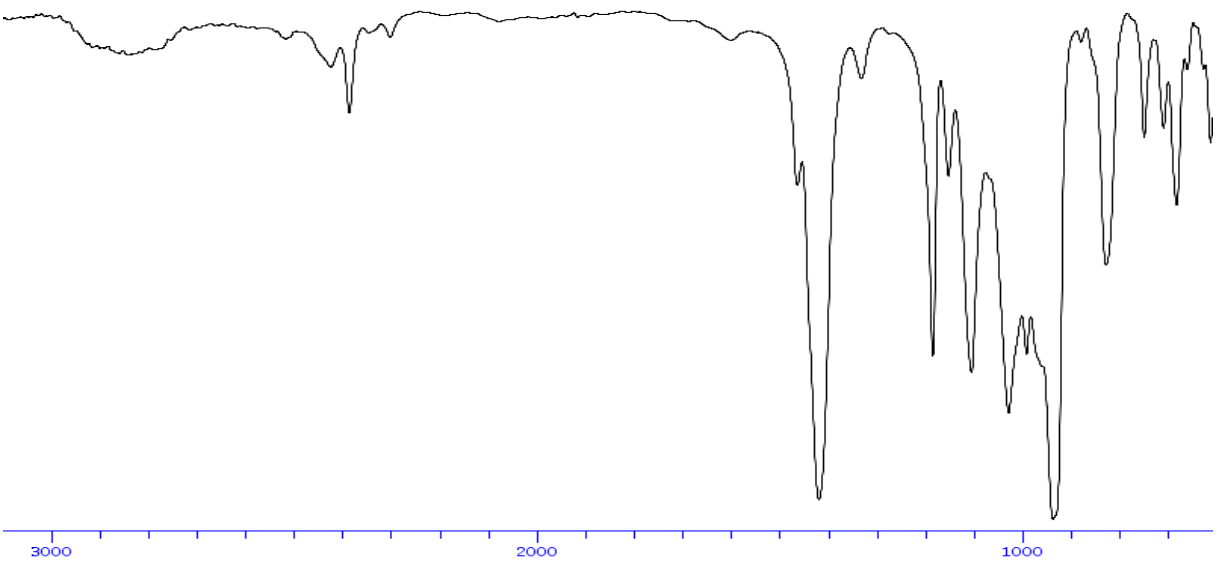
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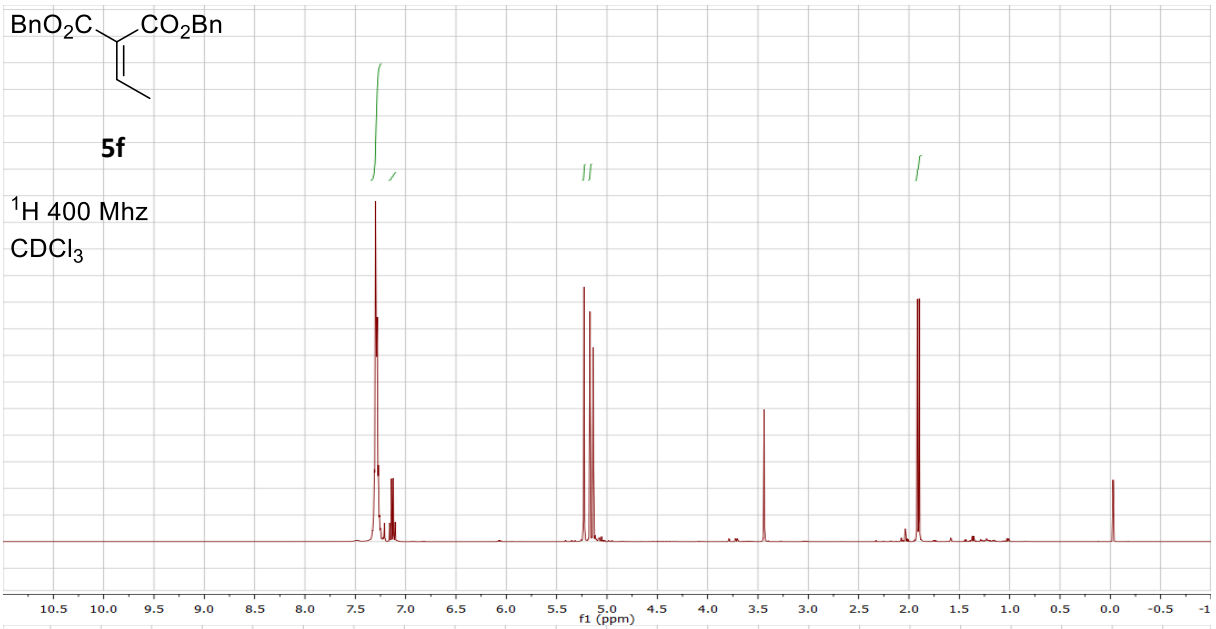
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CO2Bn
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CDCl3
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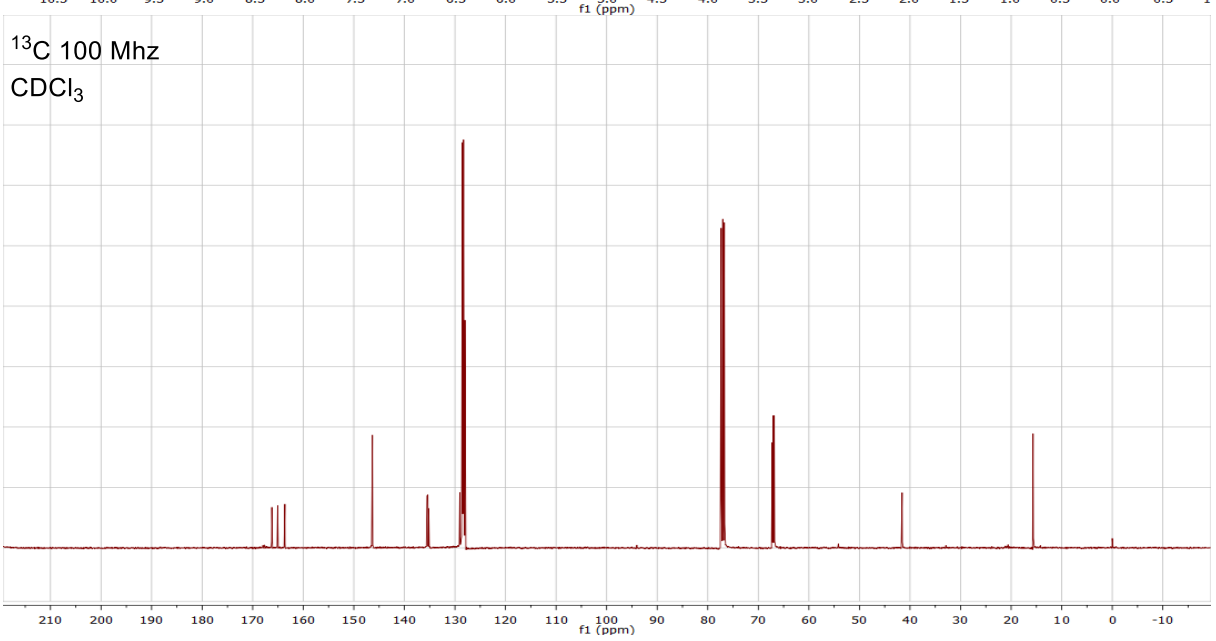
f1 (ppm)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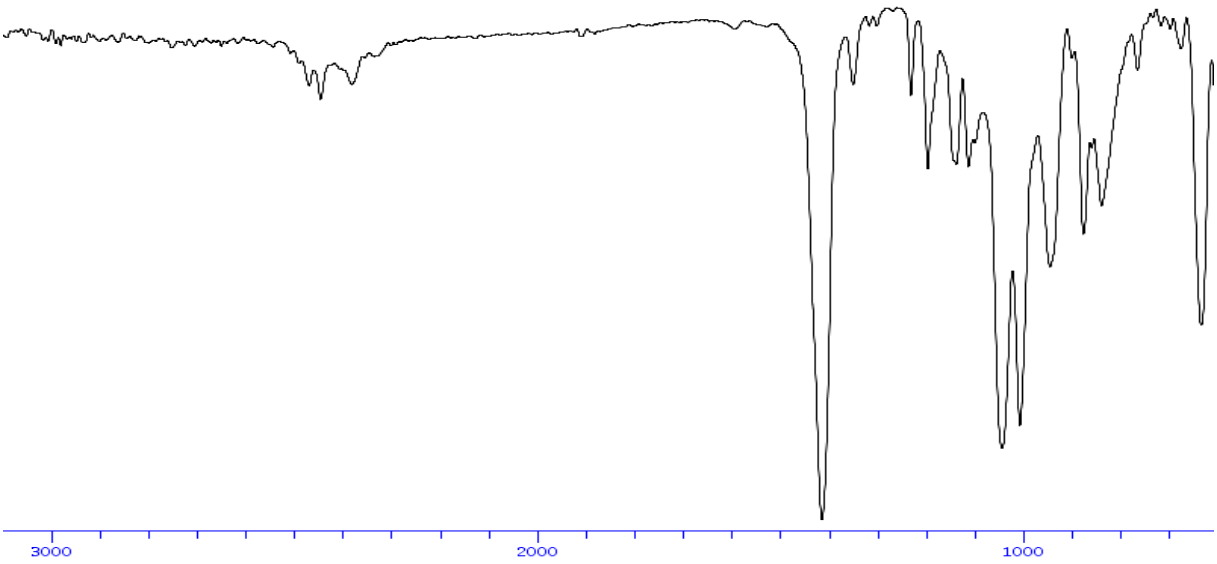
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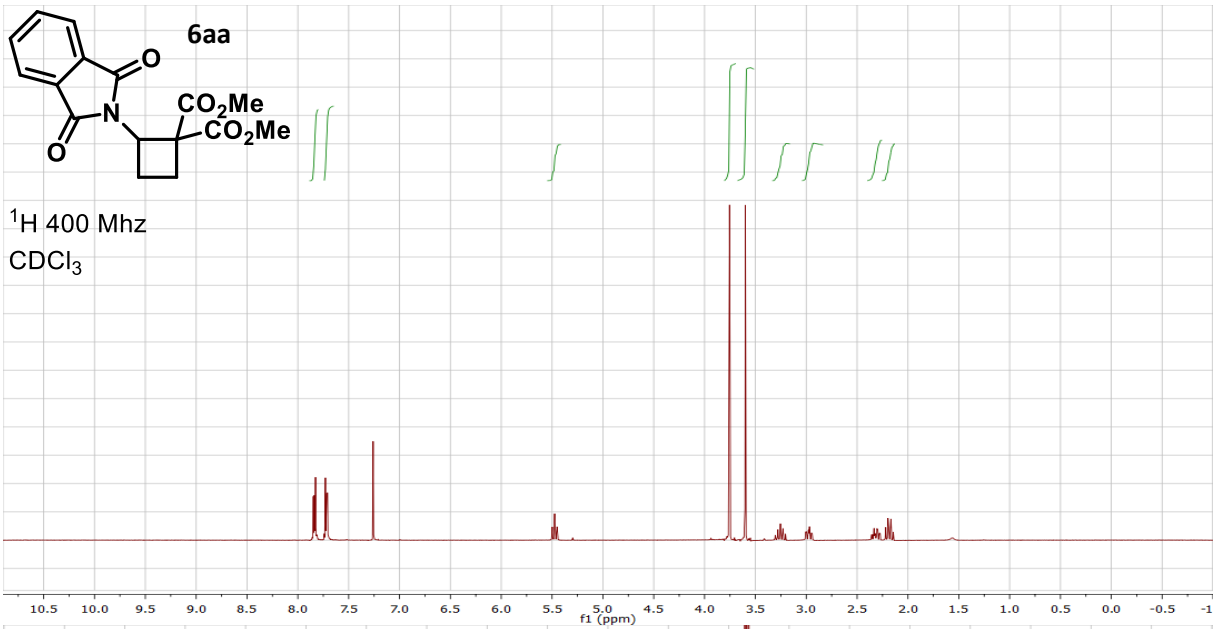
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N
O
CO2Me
CO2Me
1H 400 Mhz
CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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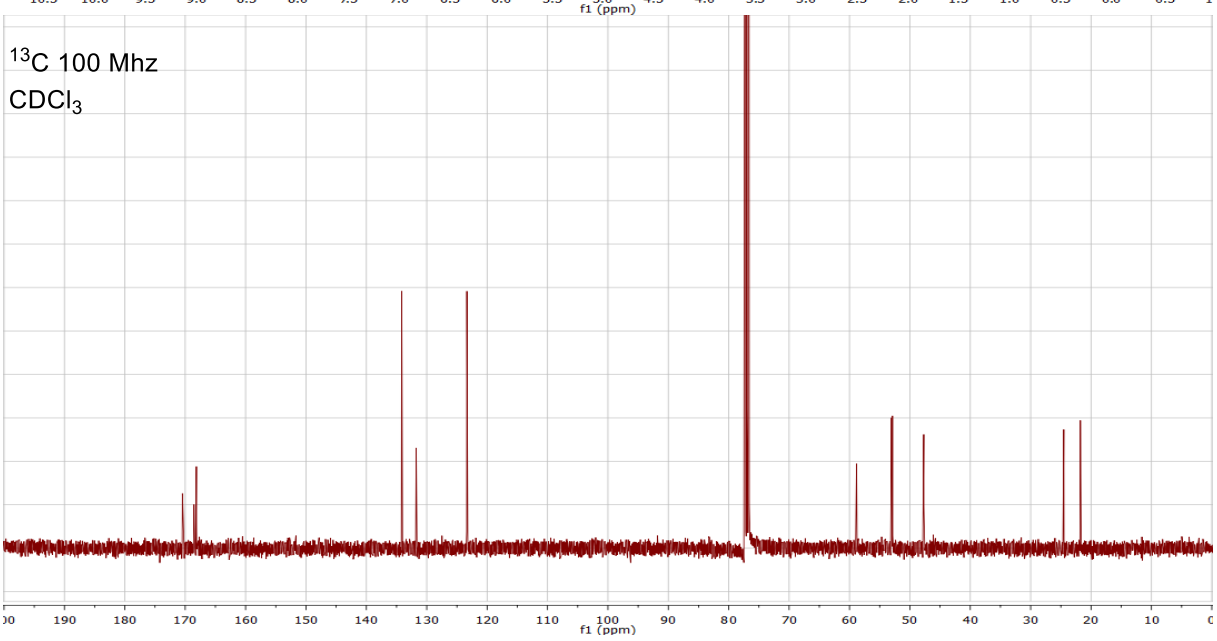
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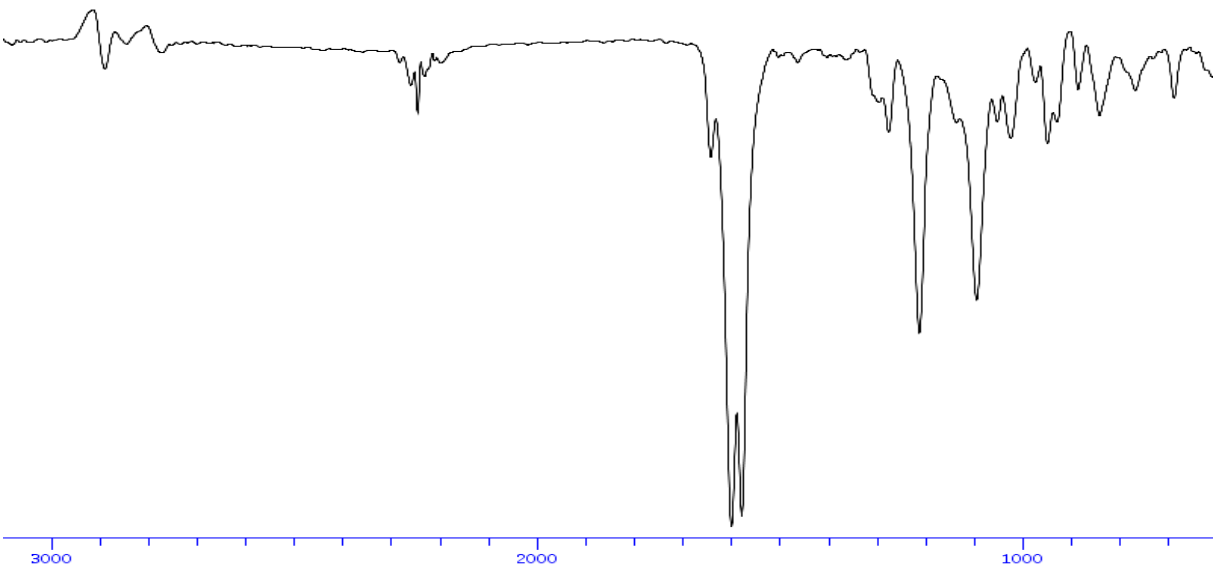
f1 (ppm)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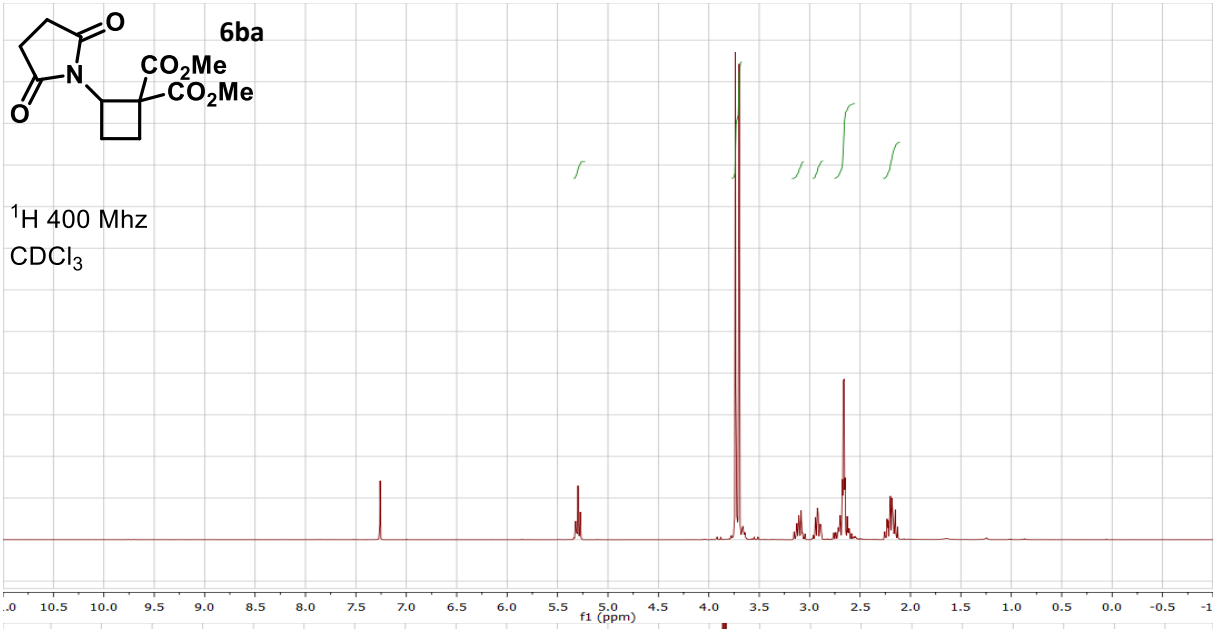
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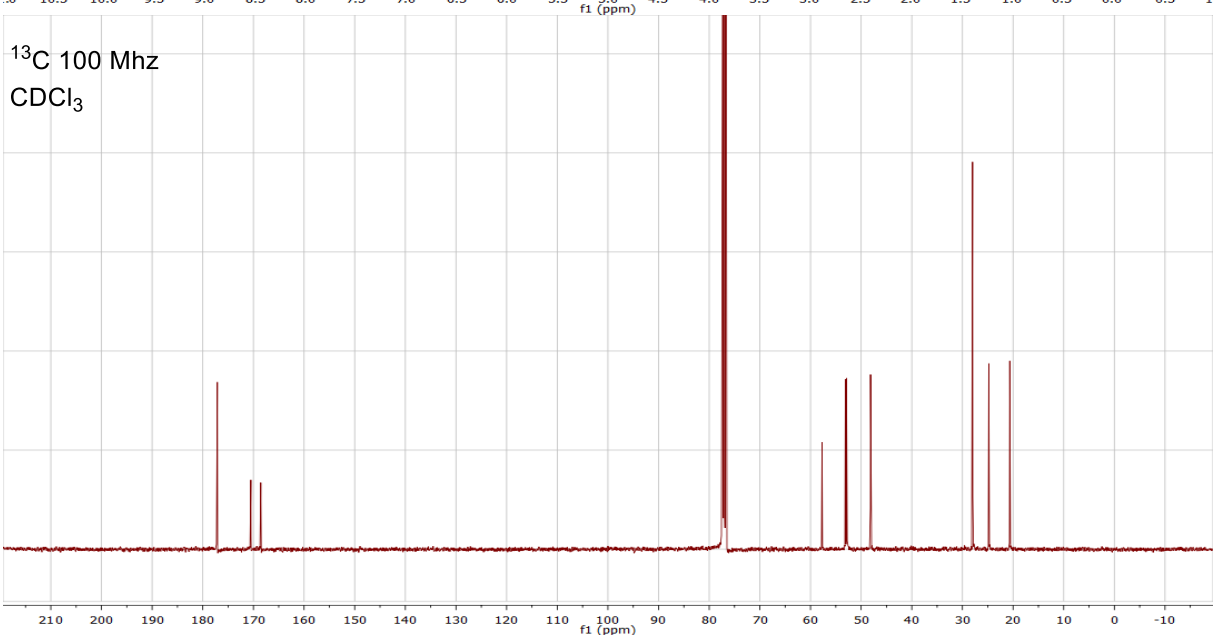
f1 (ppm)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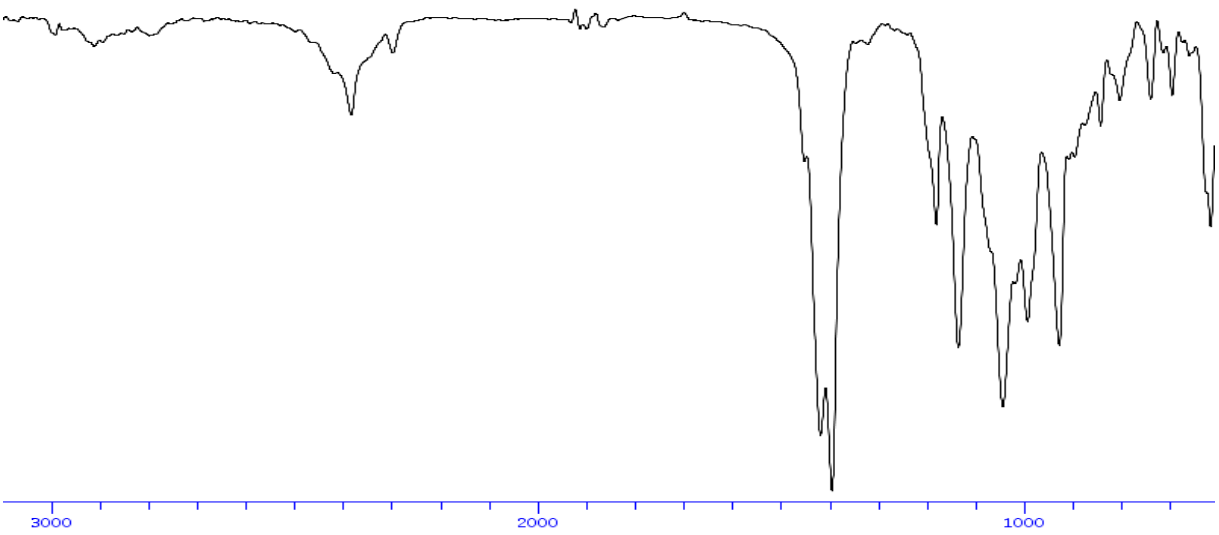
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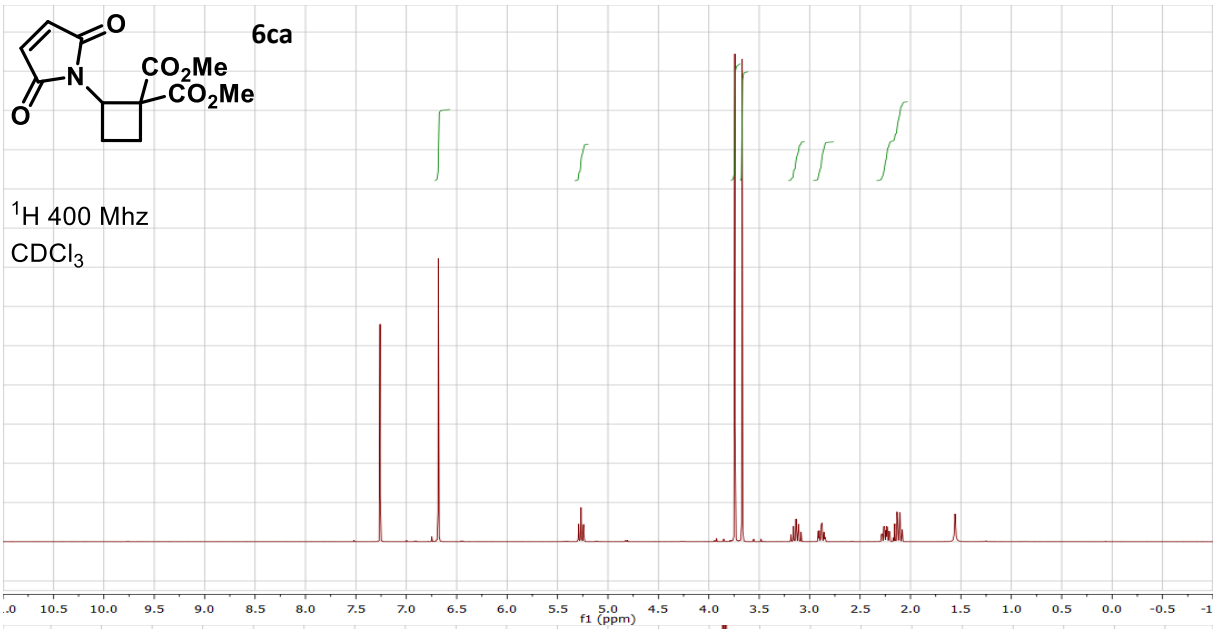
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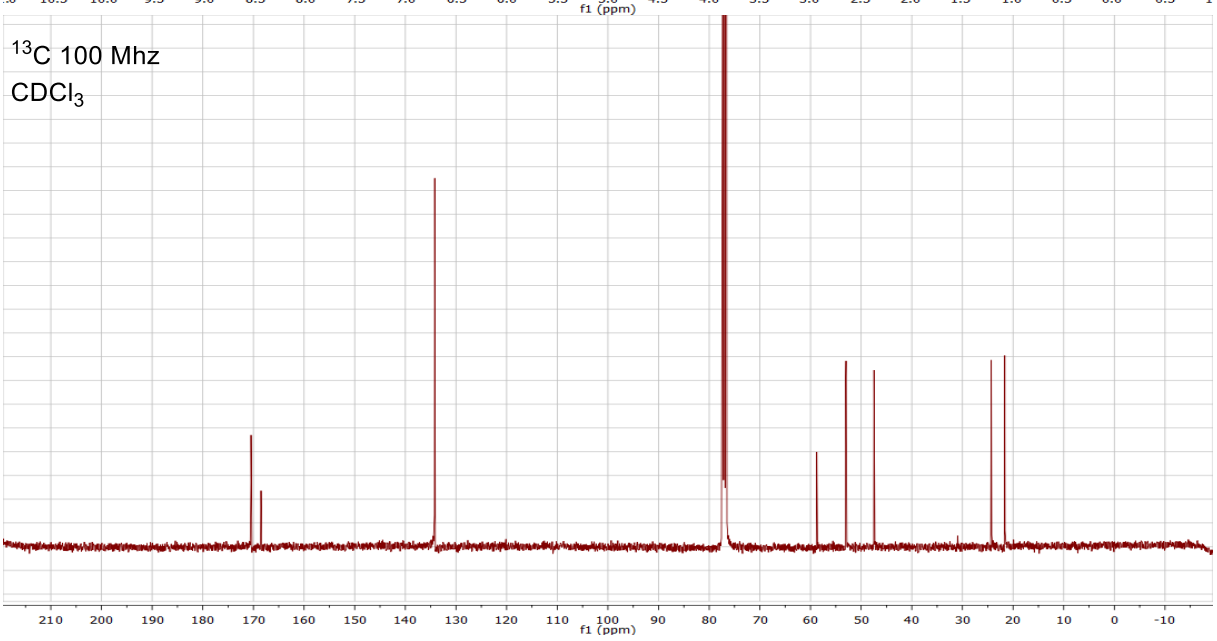
f1 (ppm)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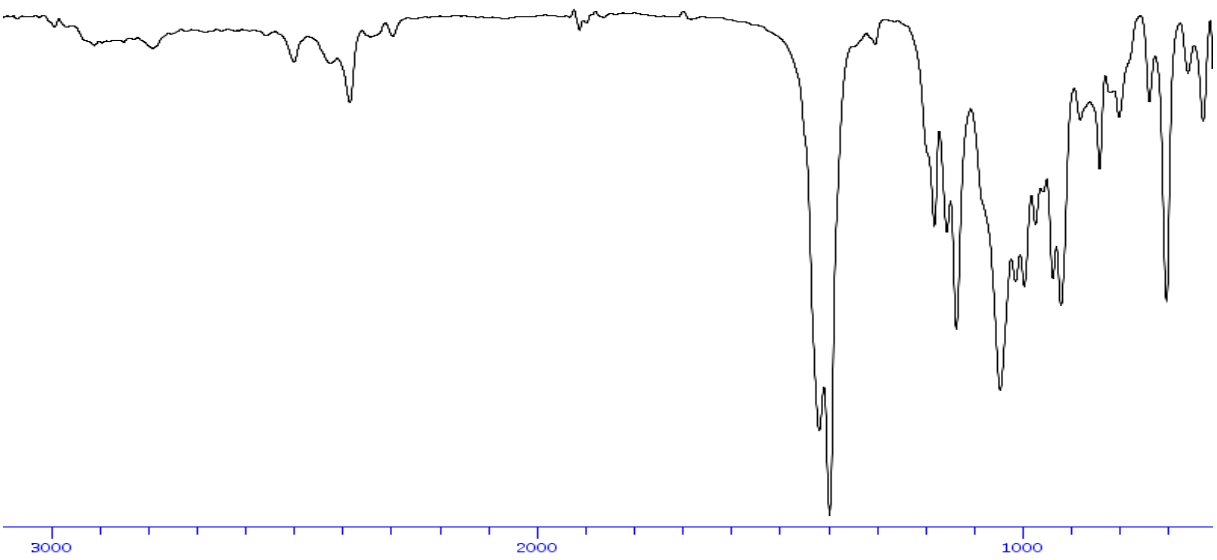
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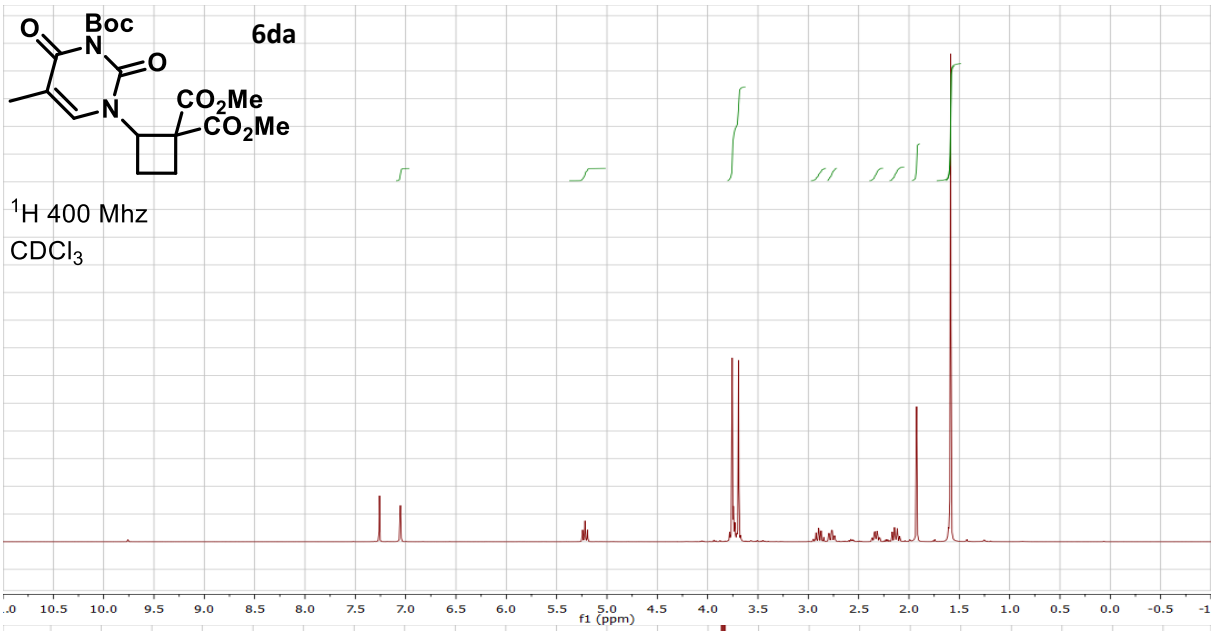
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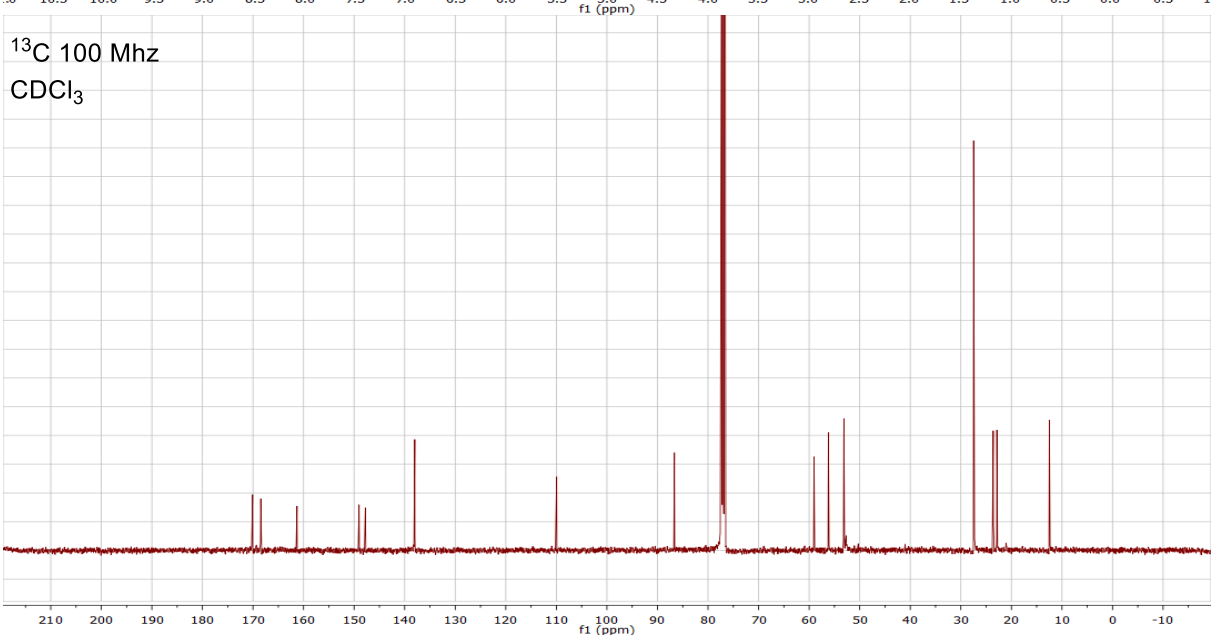
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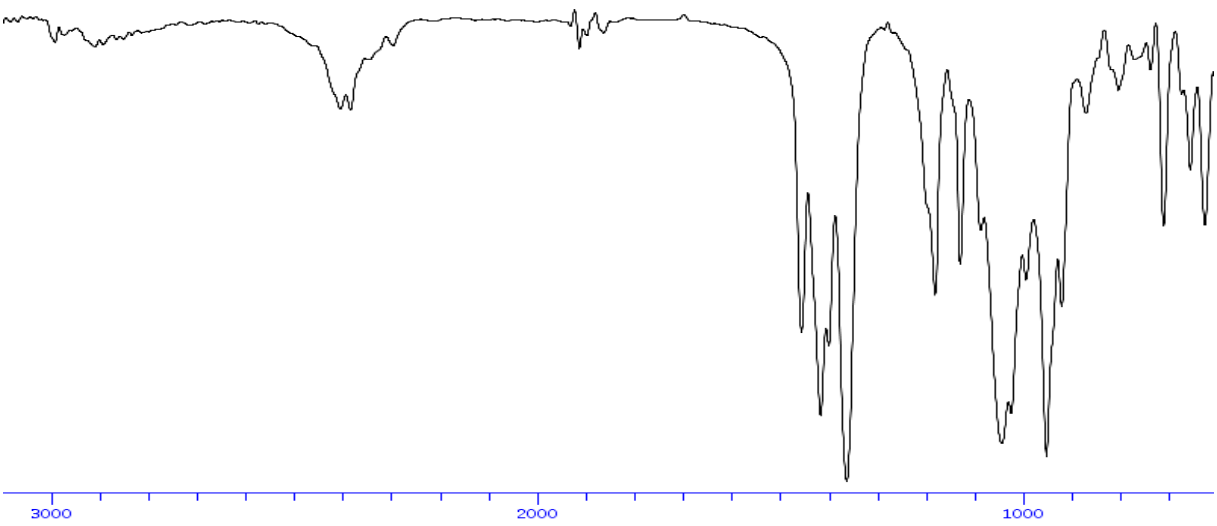
$CDCl_3$
f1 (ppm)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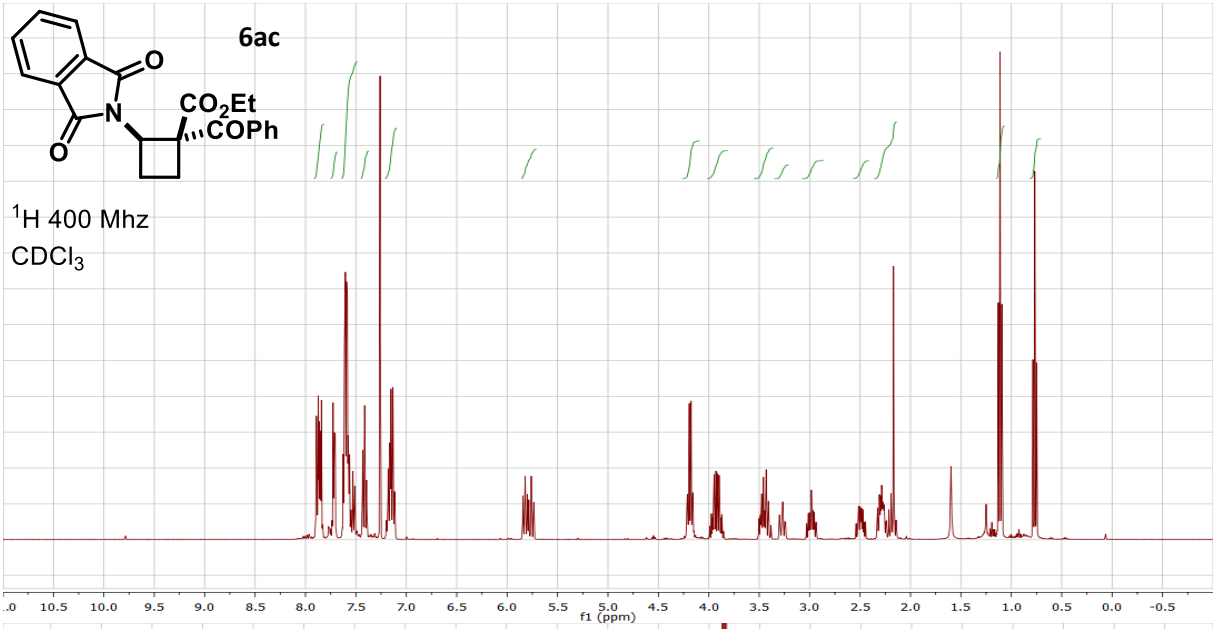
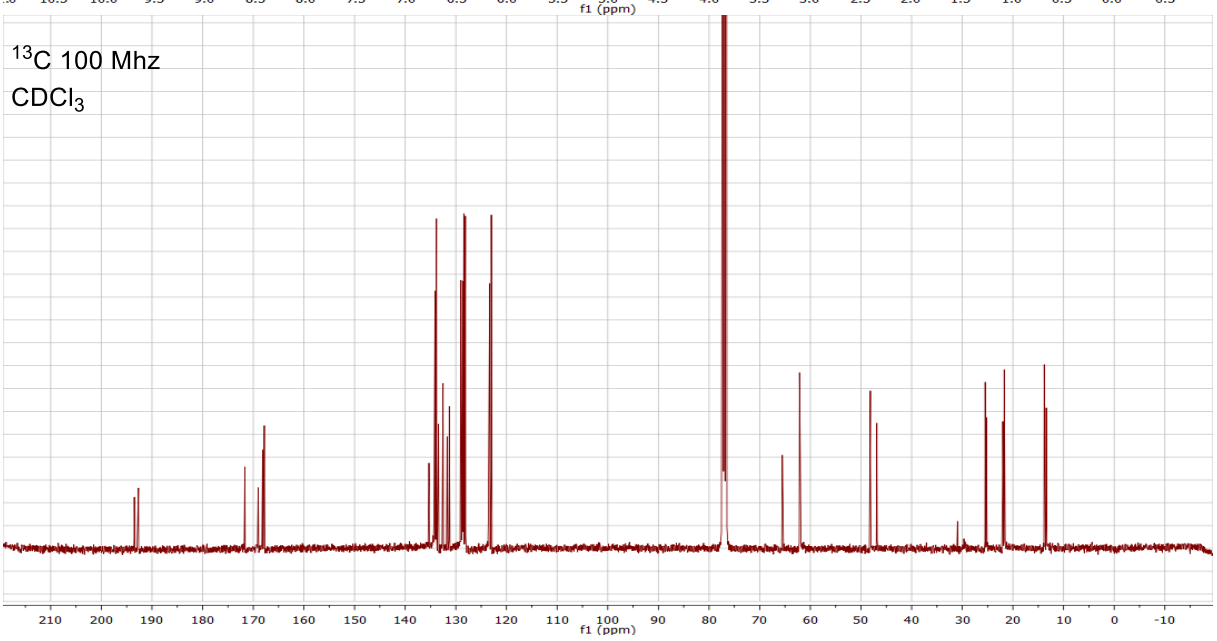
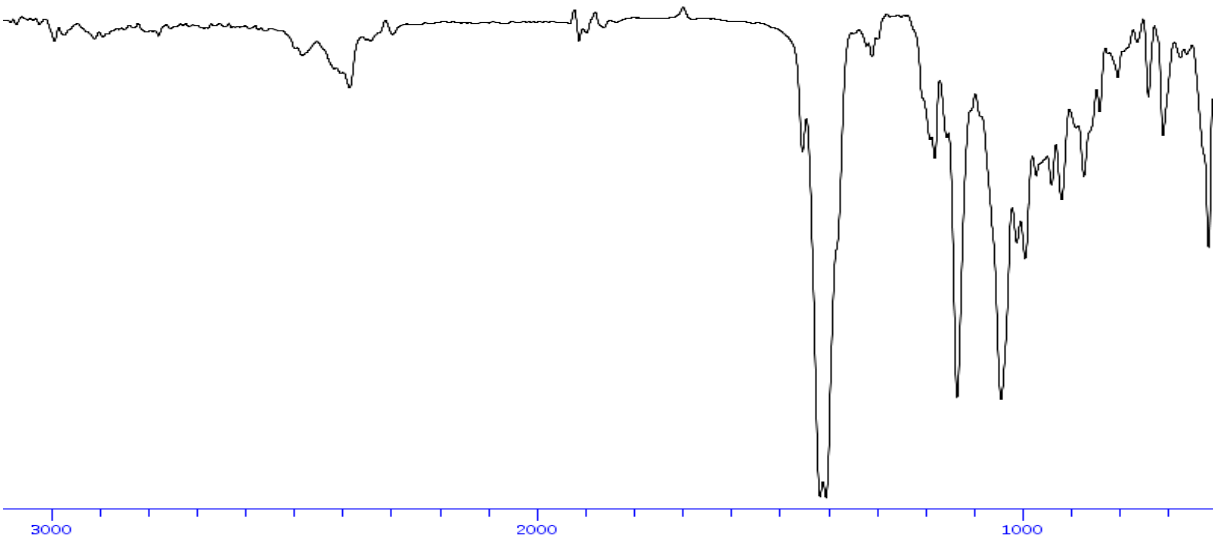
2000
1000


6ac
CO2Et
COPh
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)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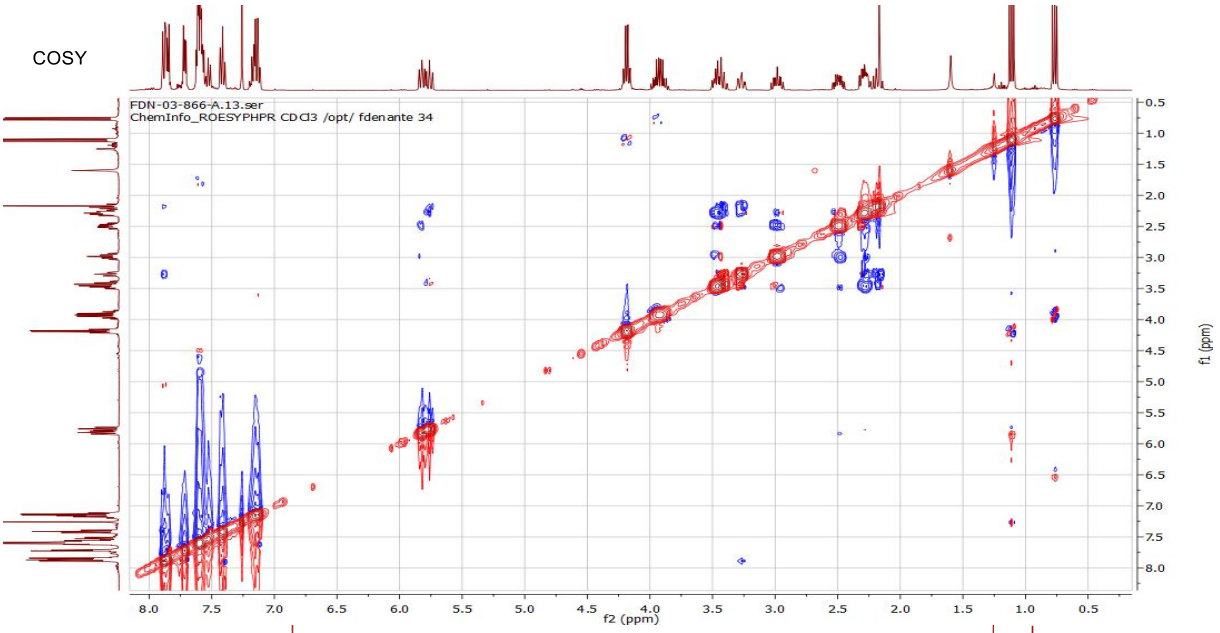
1000

COSY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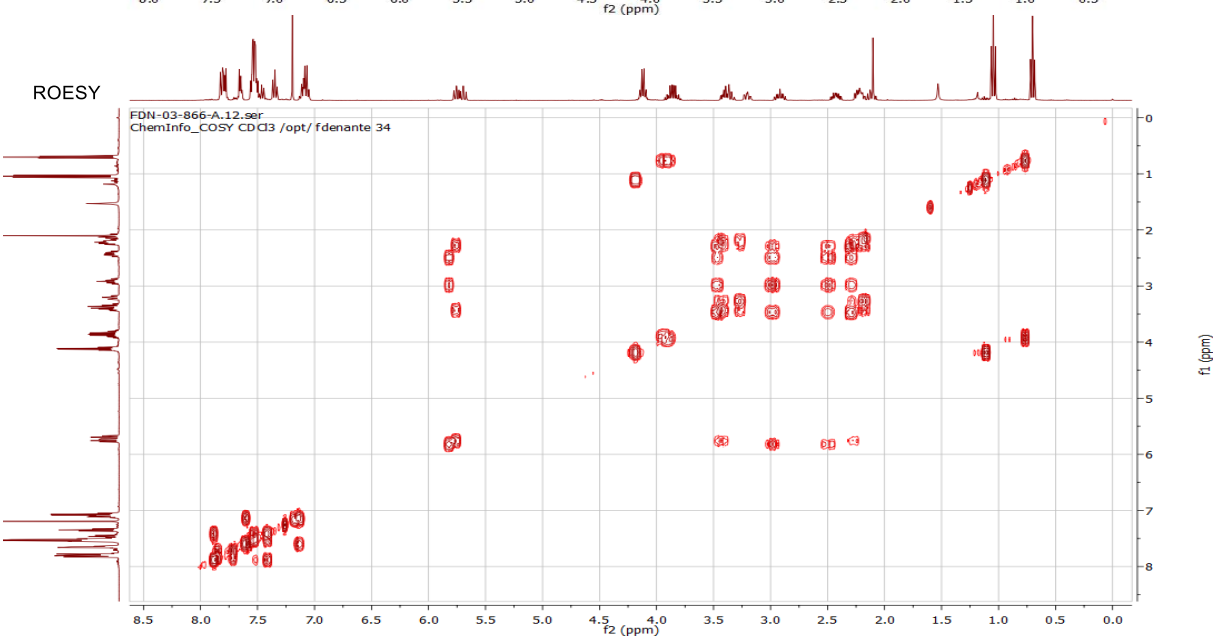
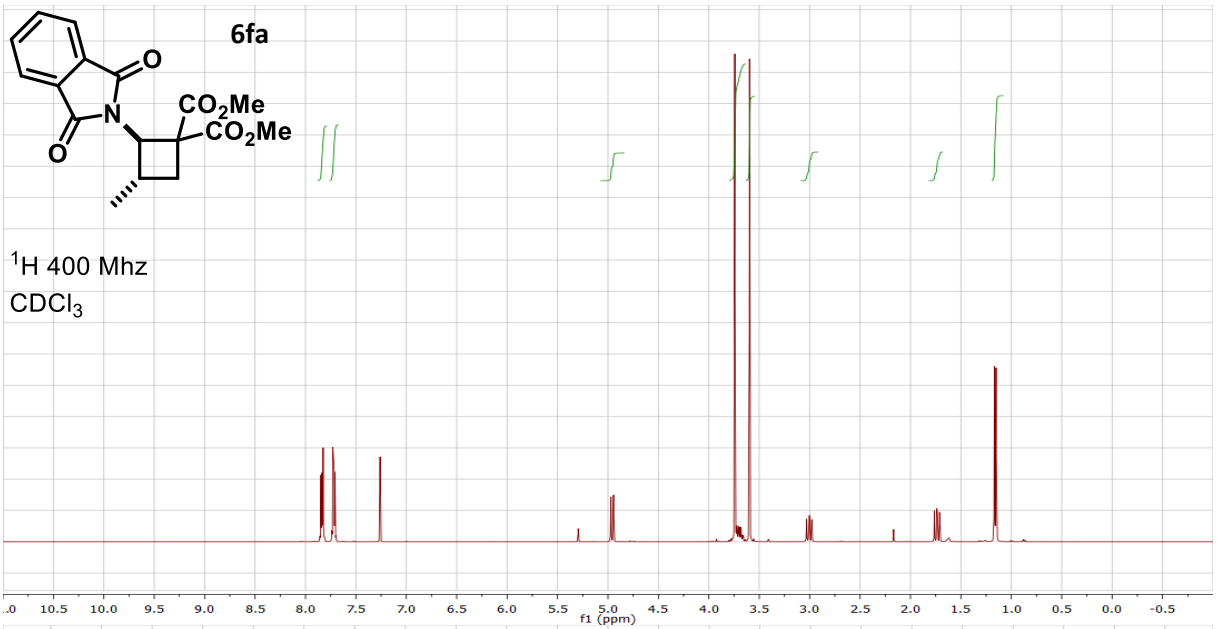
ChemInfo_ROESYPHPR CDCl3 /opt/ fdenante 34
f2 (ppm)
f1 (ppm)

ROESY


FDN-03-866-A.12.ser
ChemInfo_COSY CDCl3 /opt/ fdenante 34
f2 (ppm)
f1 (ppm)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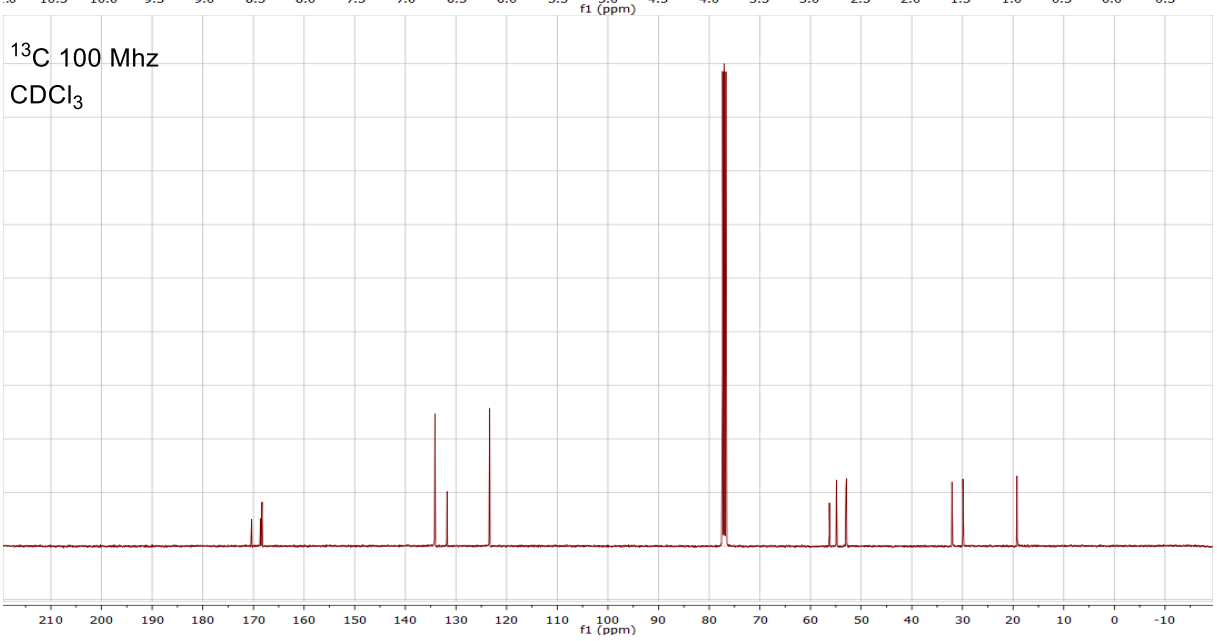
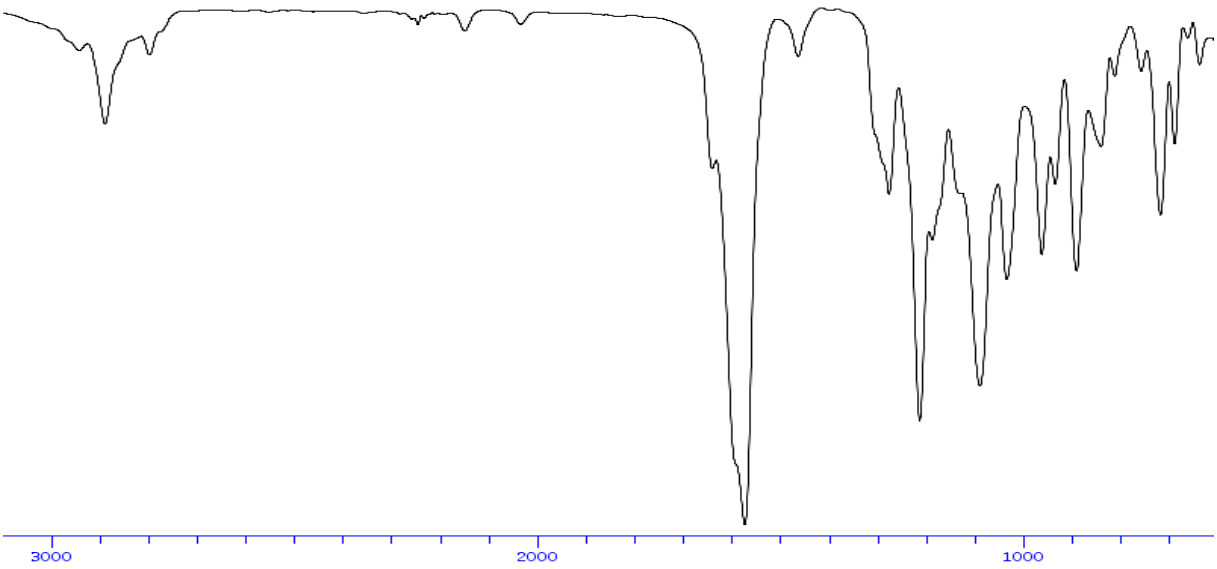
O
N
O
CO2Me
CO2Me
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)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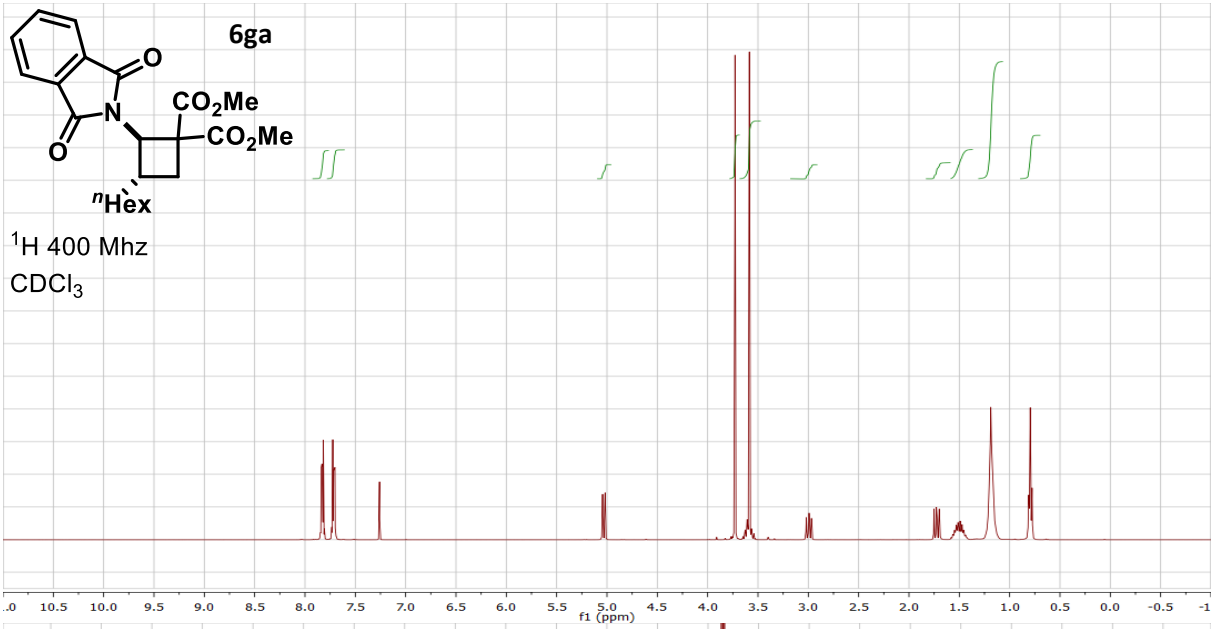
6ga
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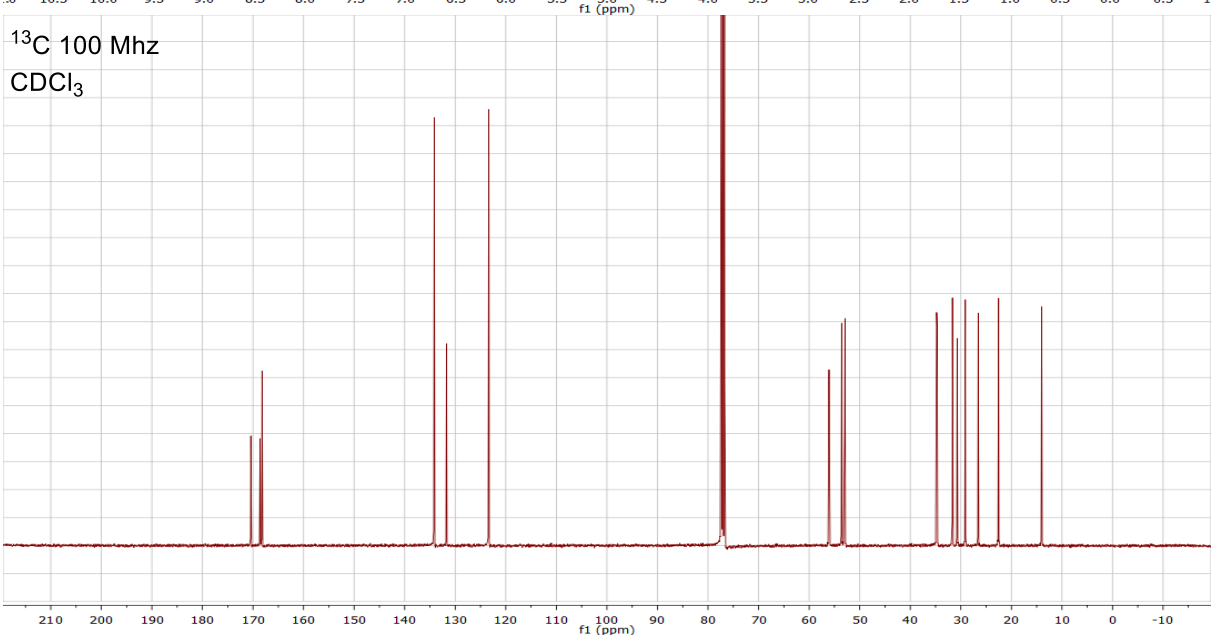
O
N
CO2Me
CO2Me
nHex
1H 400 Mhz
CDCl3
f1 (ppm)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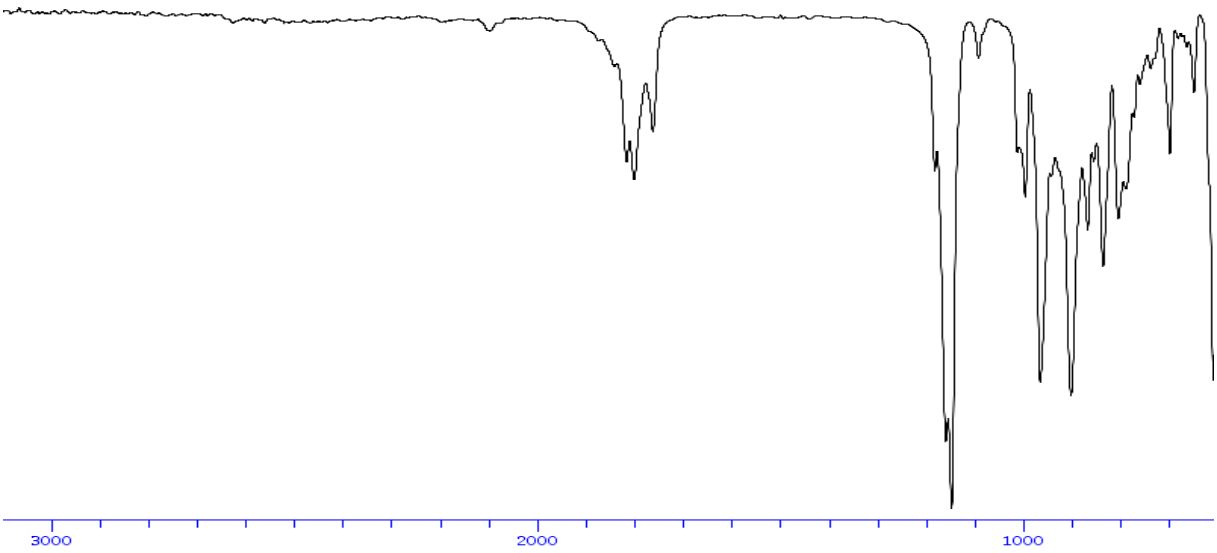
CDCl3
f1 (ppm)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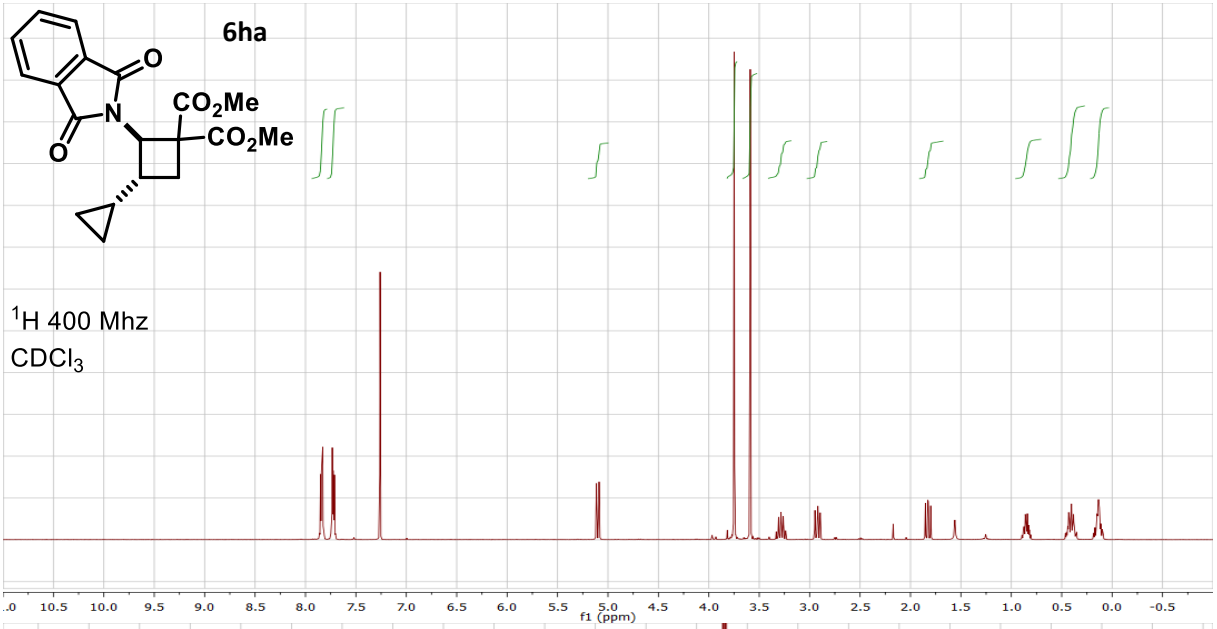
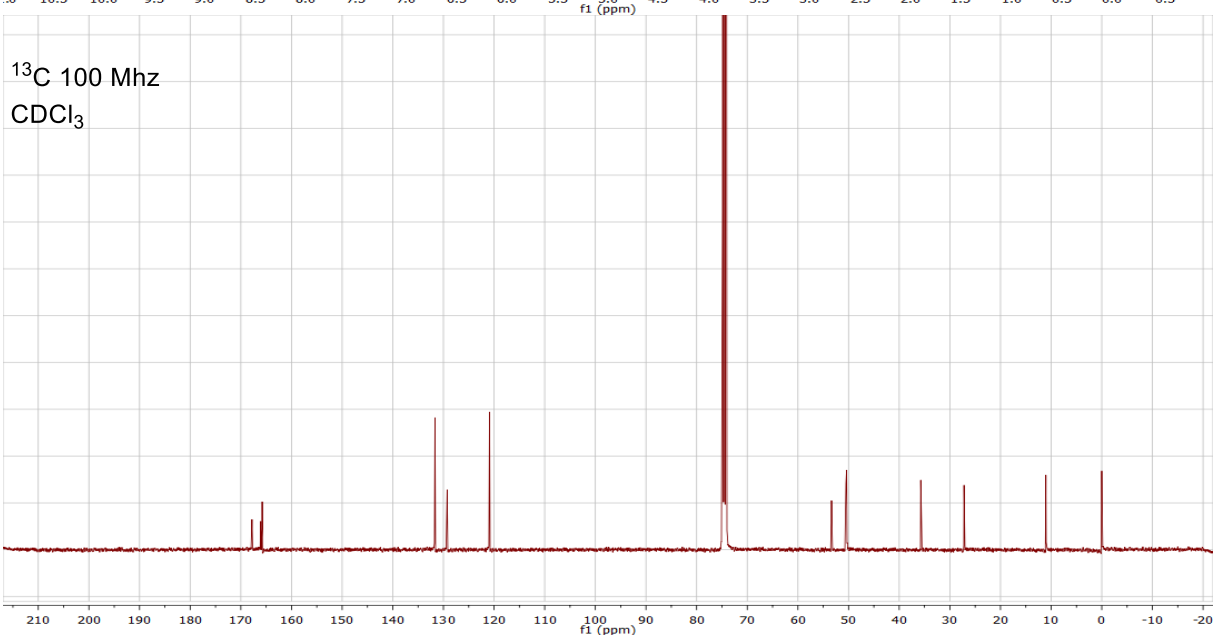
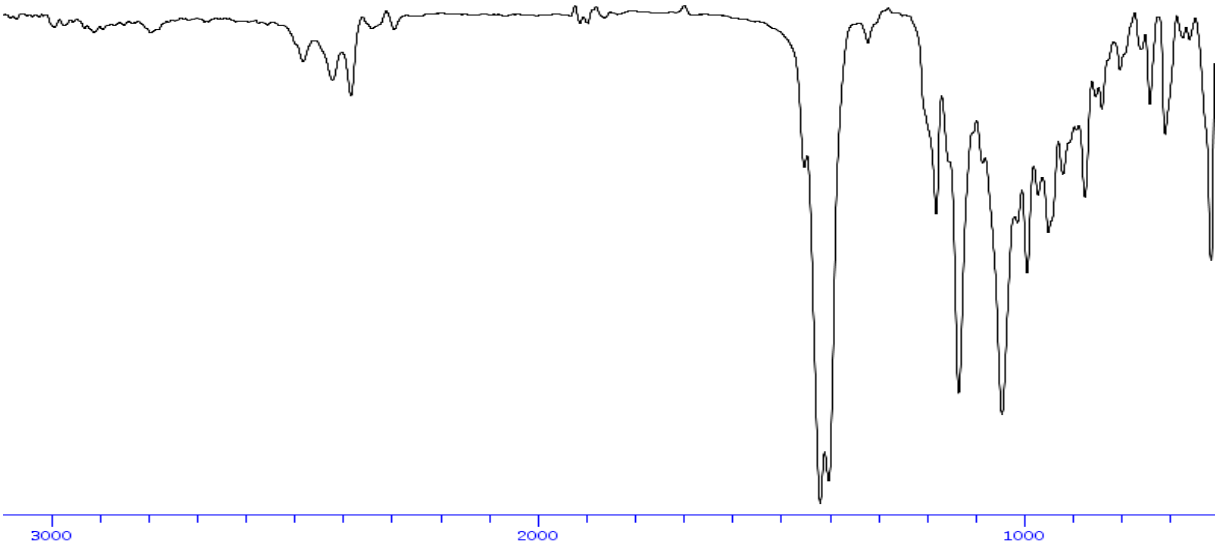

6ha
O
N
O
CO2Me
CO2Me
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)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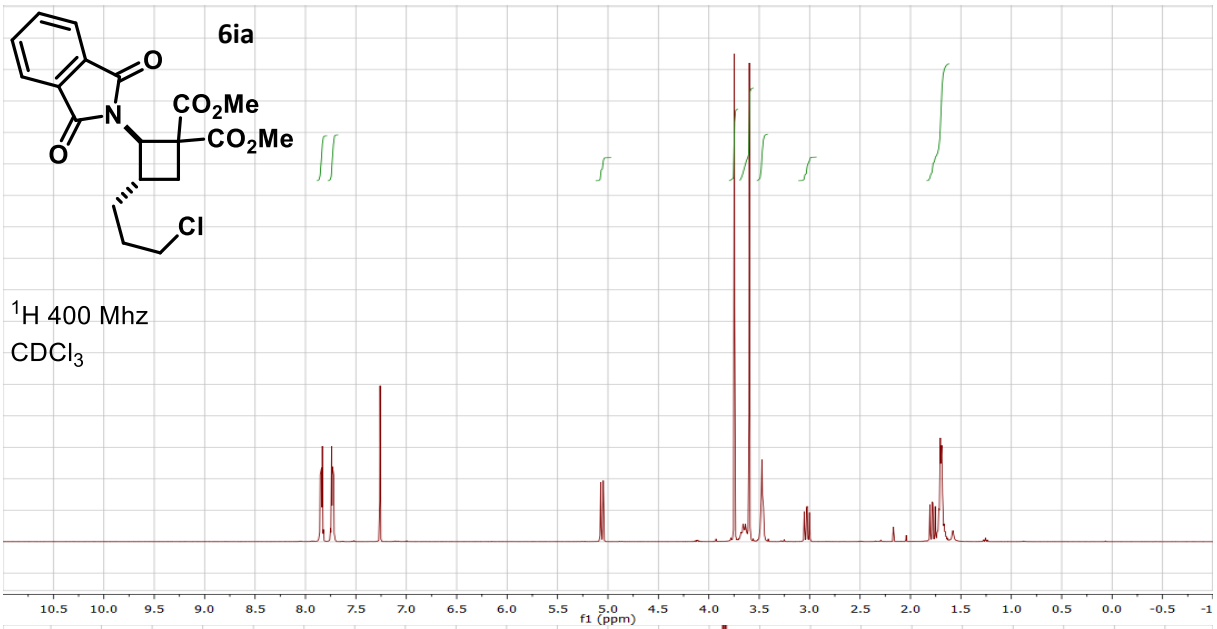
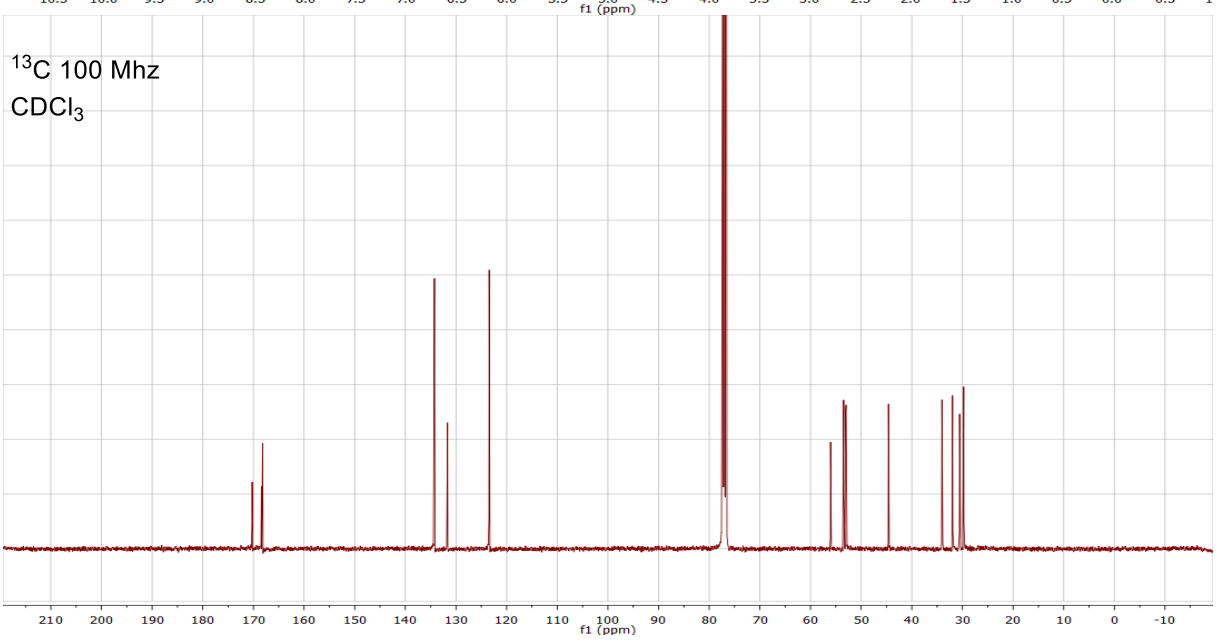
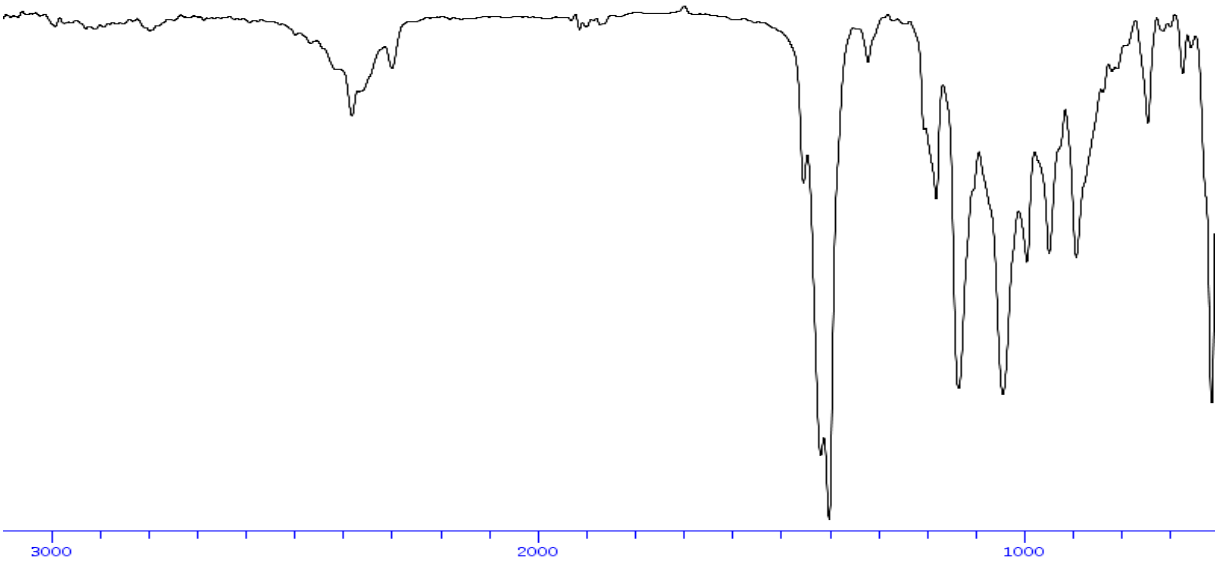
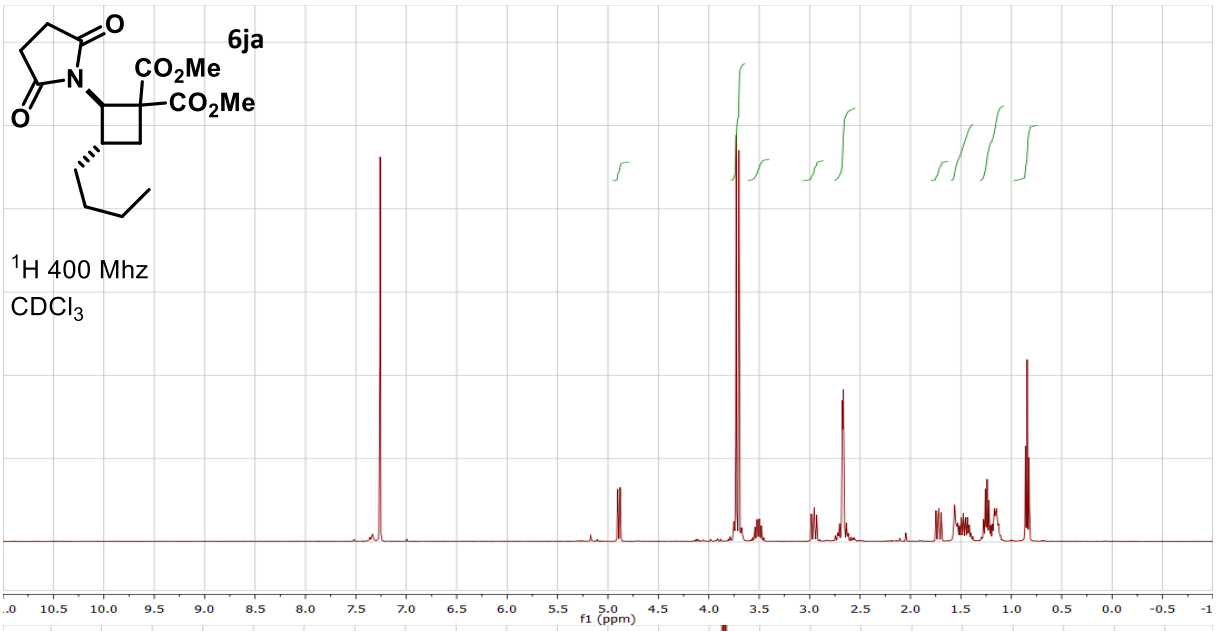
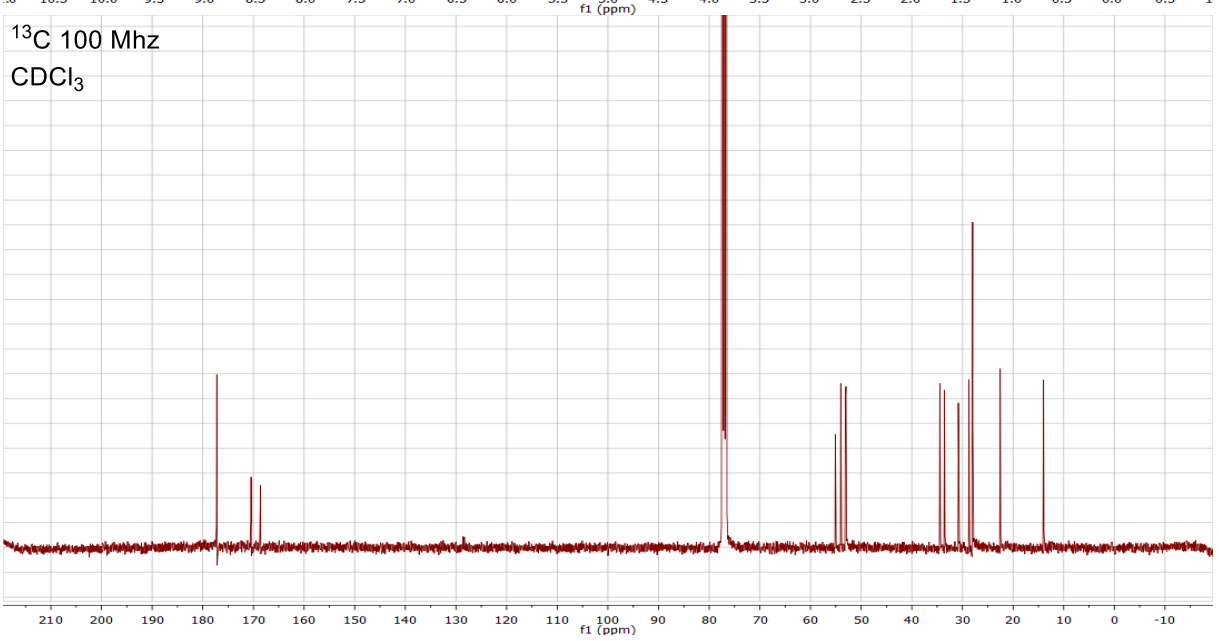
2000
1000

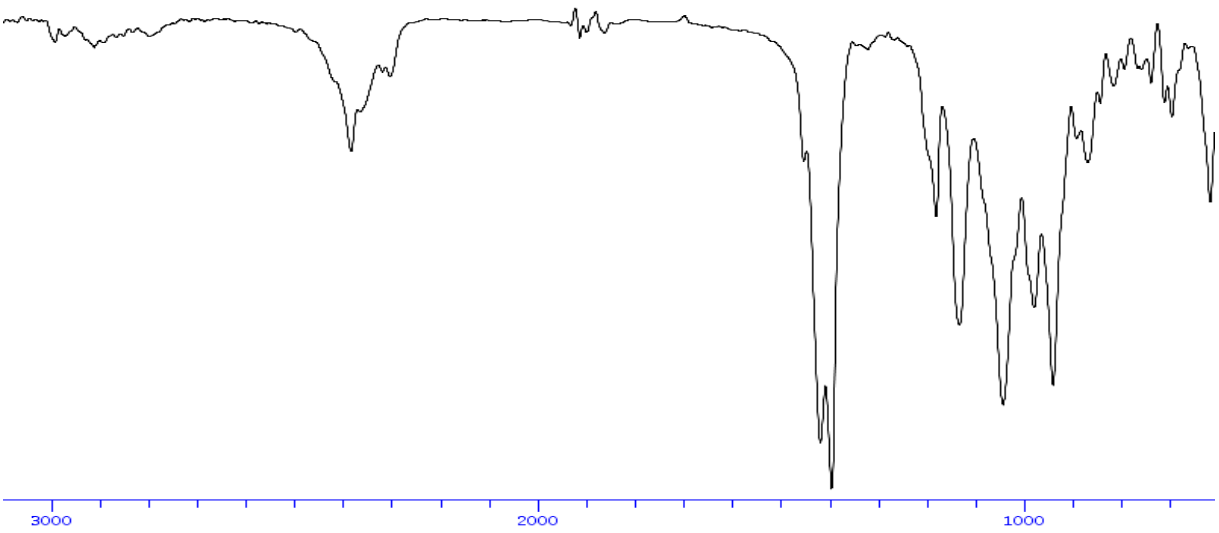

6ia
O
N
O
CO2Me
CO2Me
Cl
1H 400 Mhz
CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


13C 100 Mhz
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)


3000
2000
1000


6ja
CO_2Me
CO_2Me
^1H 400 Mhz
$CDCl_3$
f1 (ppm)


^{13}C 100 Mhz
$CDCl_3$
f1 (ppm)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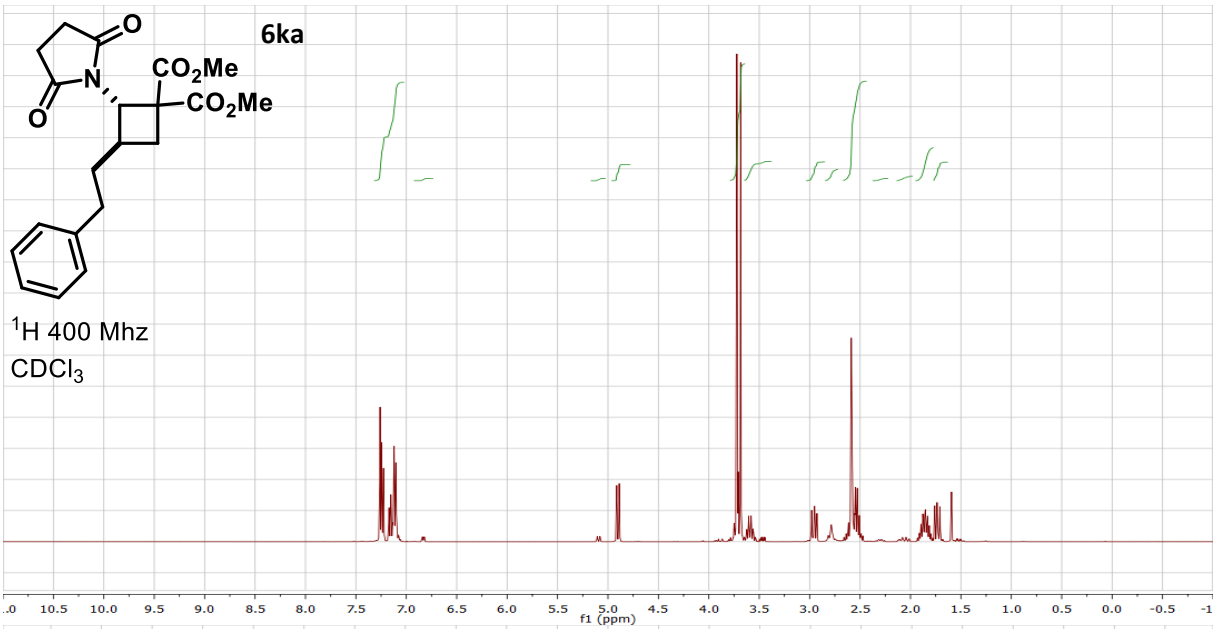
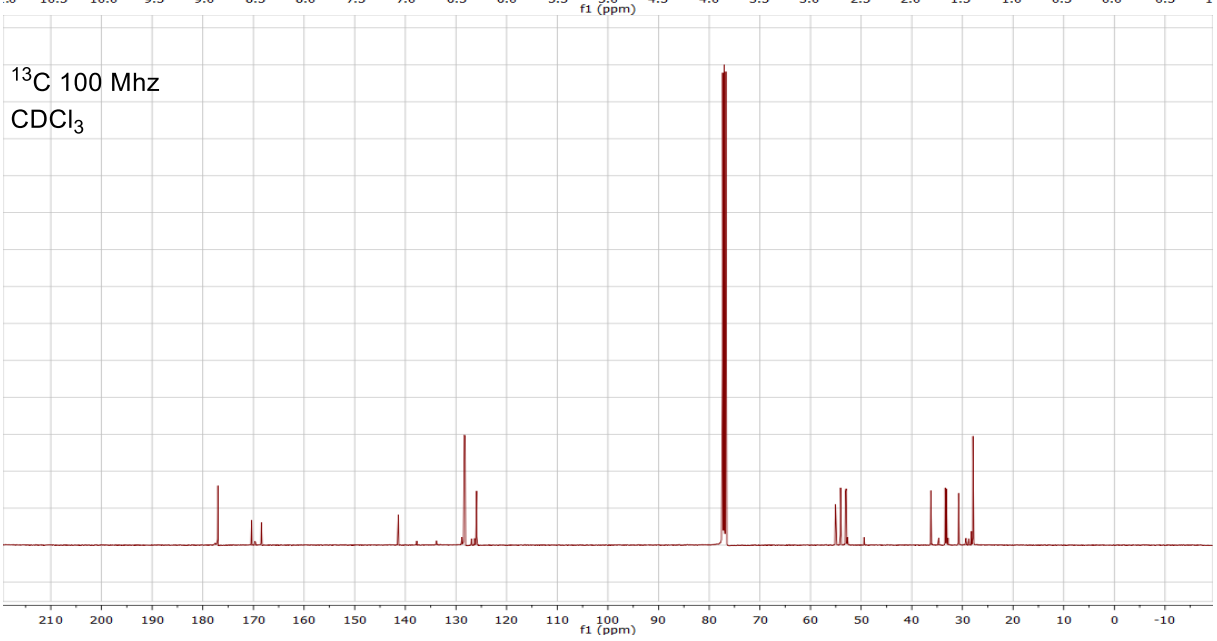
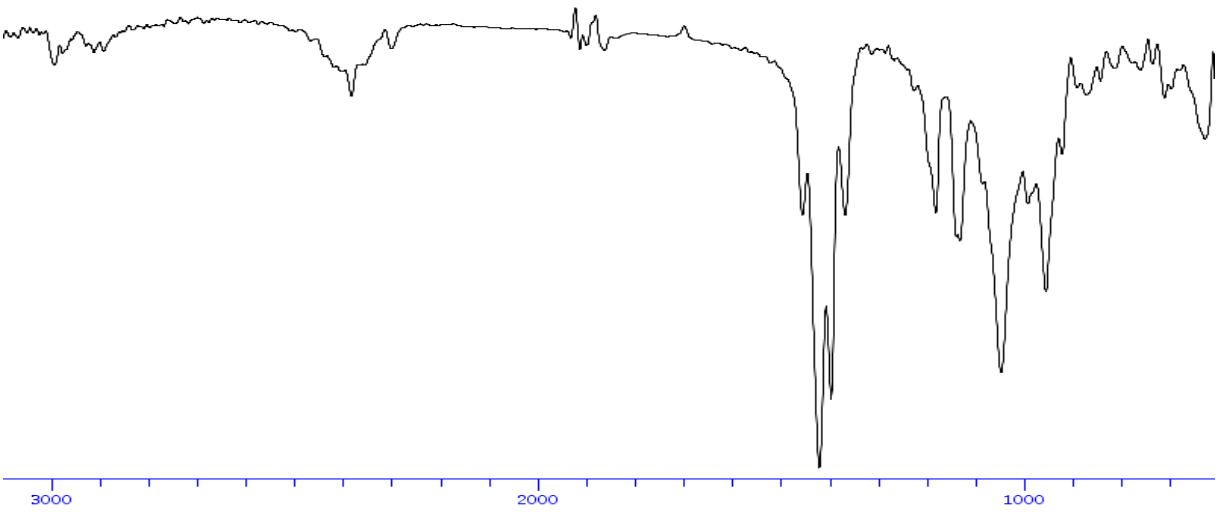
1000


6ka
CO_2Me
CO_2Me
N
O
O
^1H 400 Mhz
$CDCl_3$
f1 (ppm)


^{13}C 100 Mhz
$CDCl_3$
f1 (ppm)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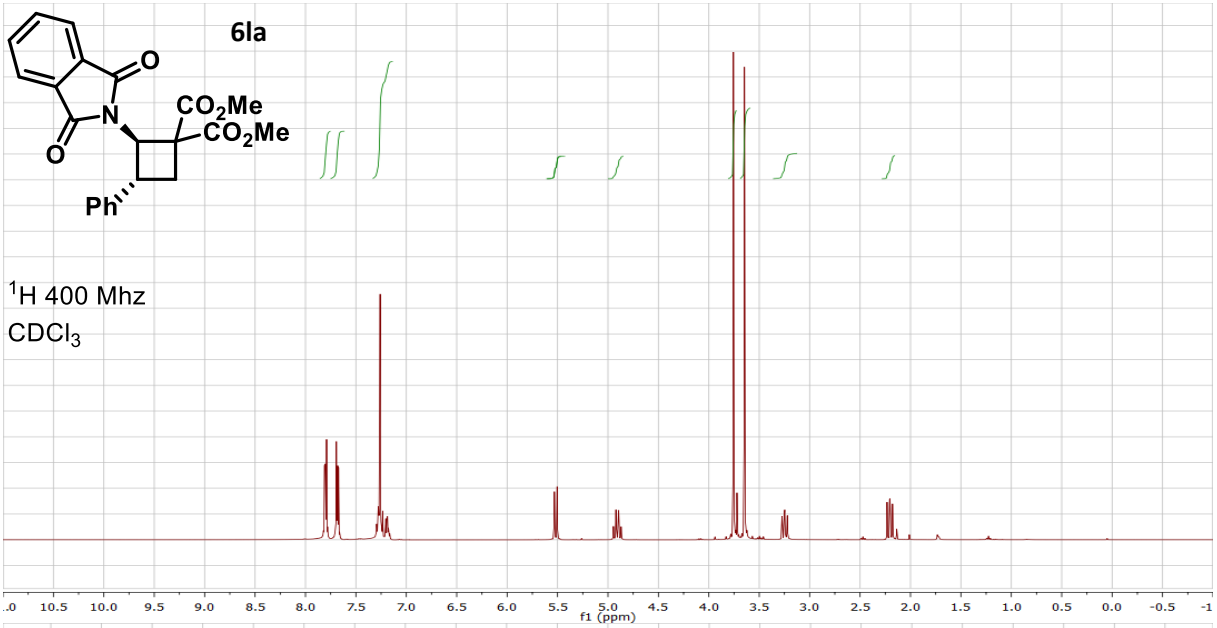
2000
1000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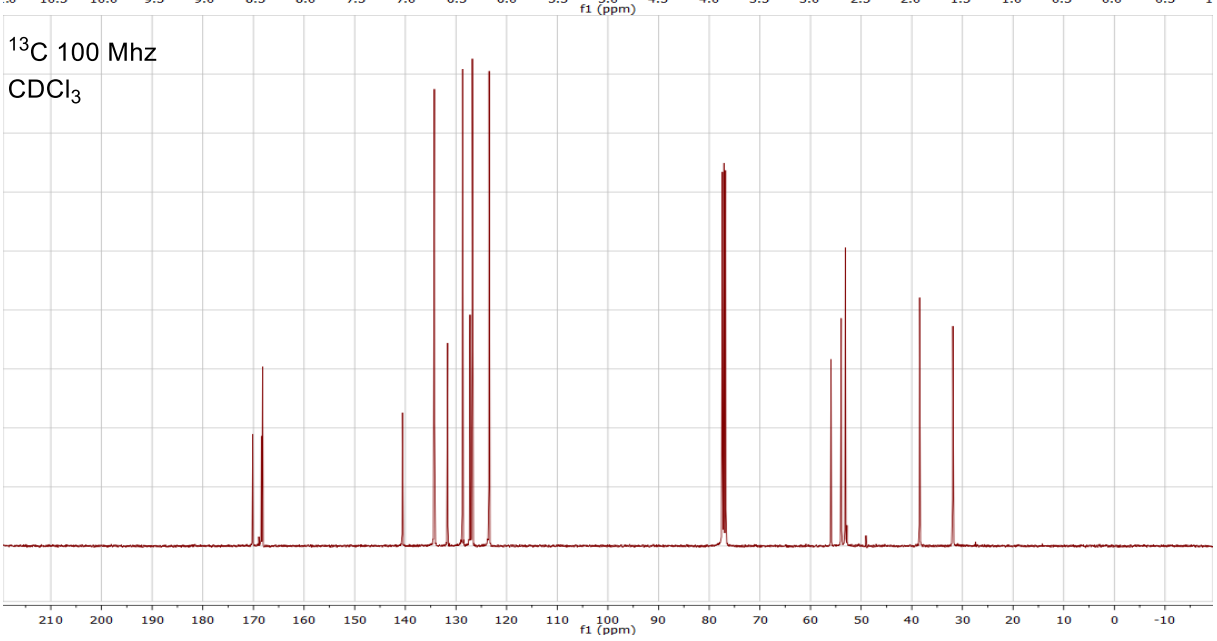
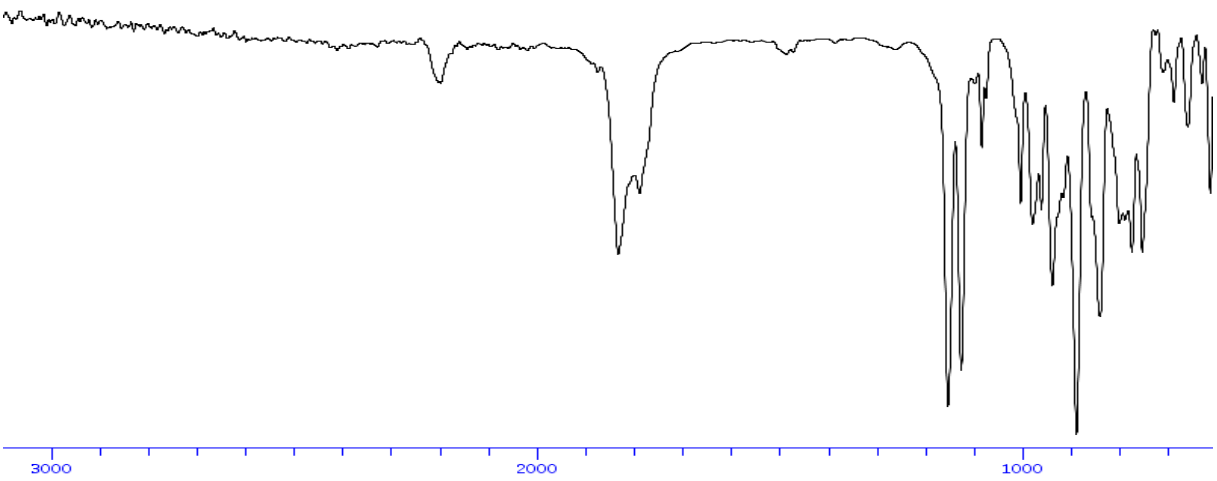
O
N
O
CO2Me
CO2Me
Ph
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)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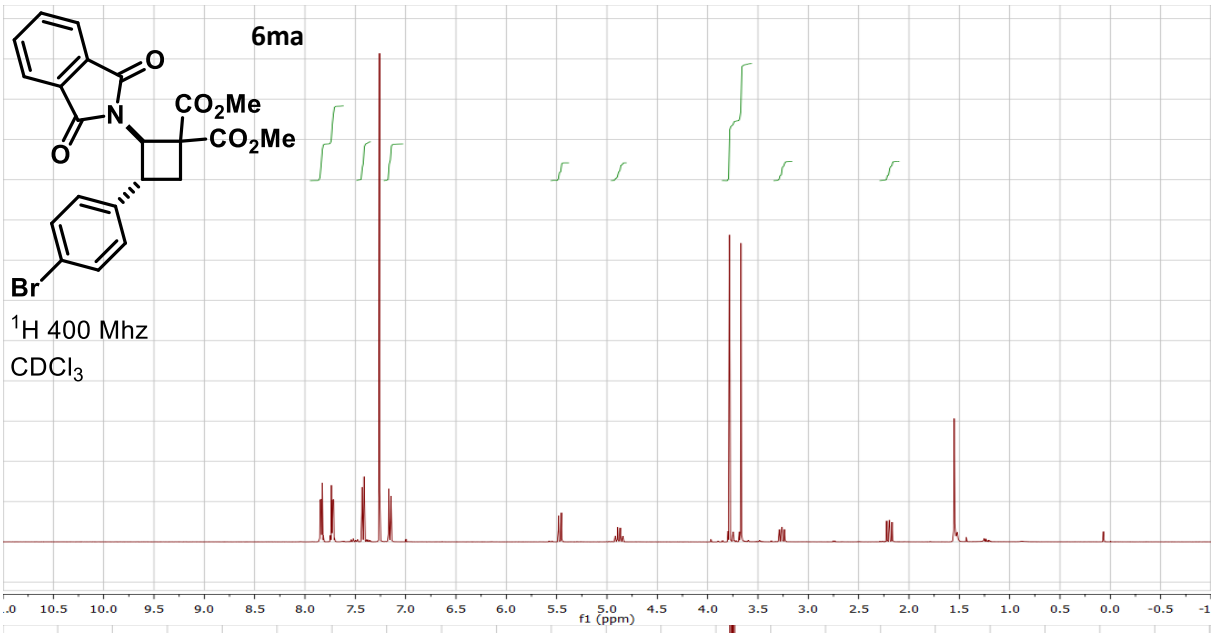
2000
1000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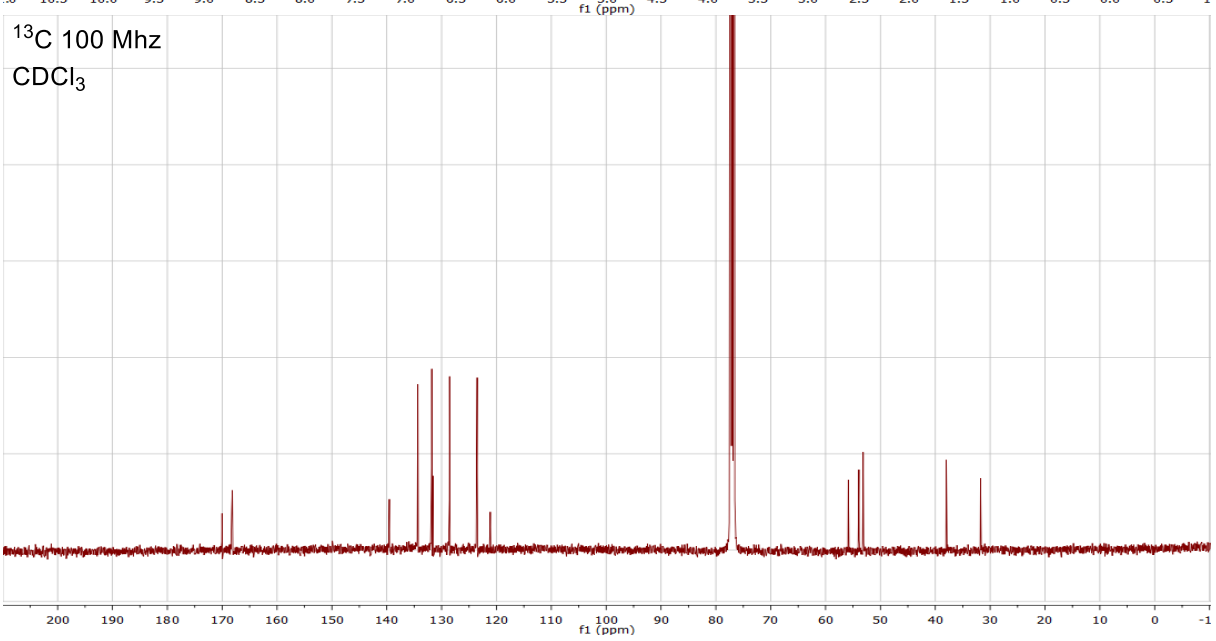
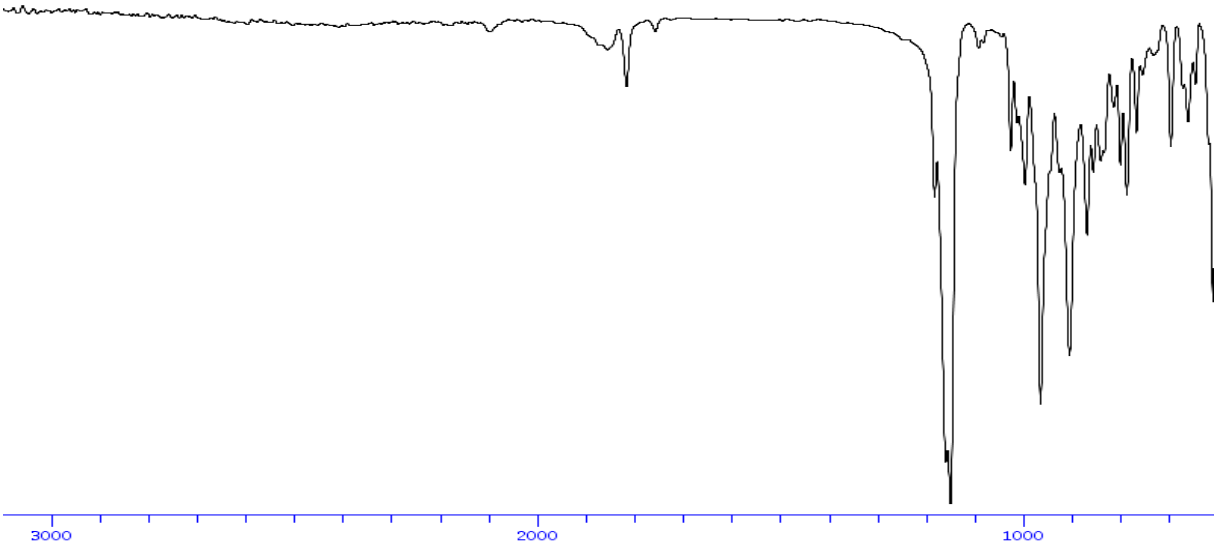
O
N
O
CO2Me
CO2Me
Br
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)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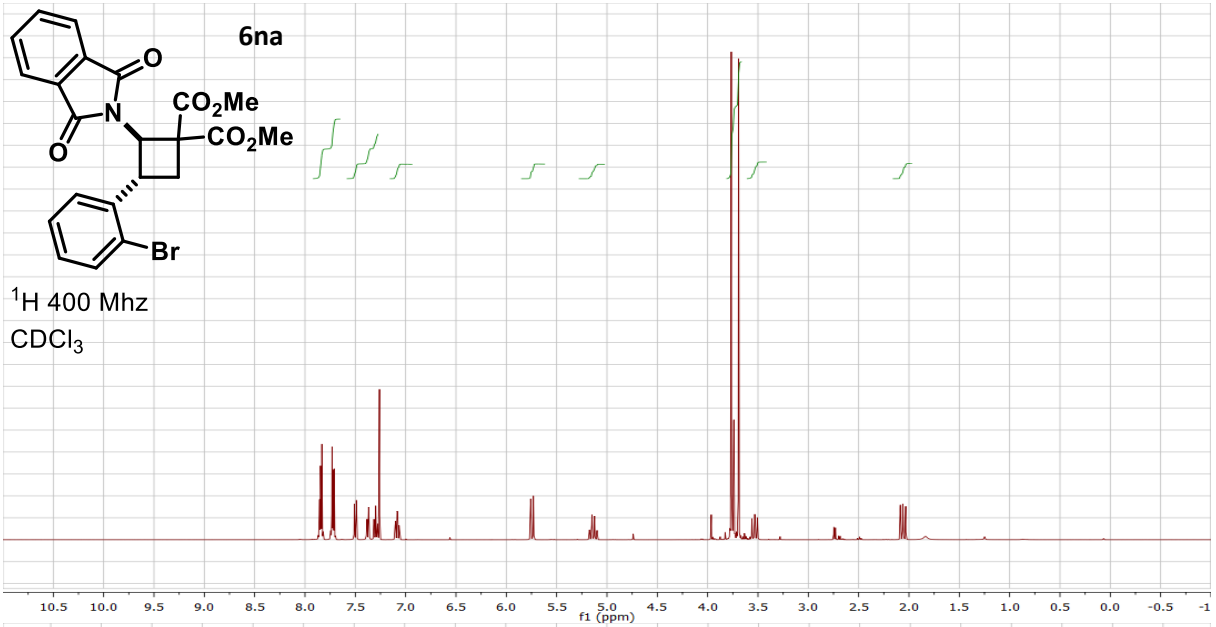
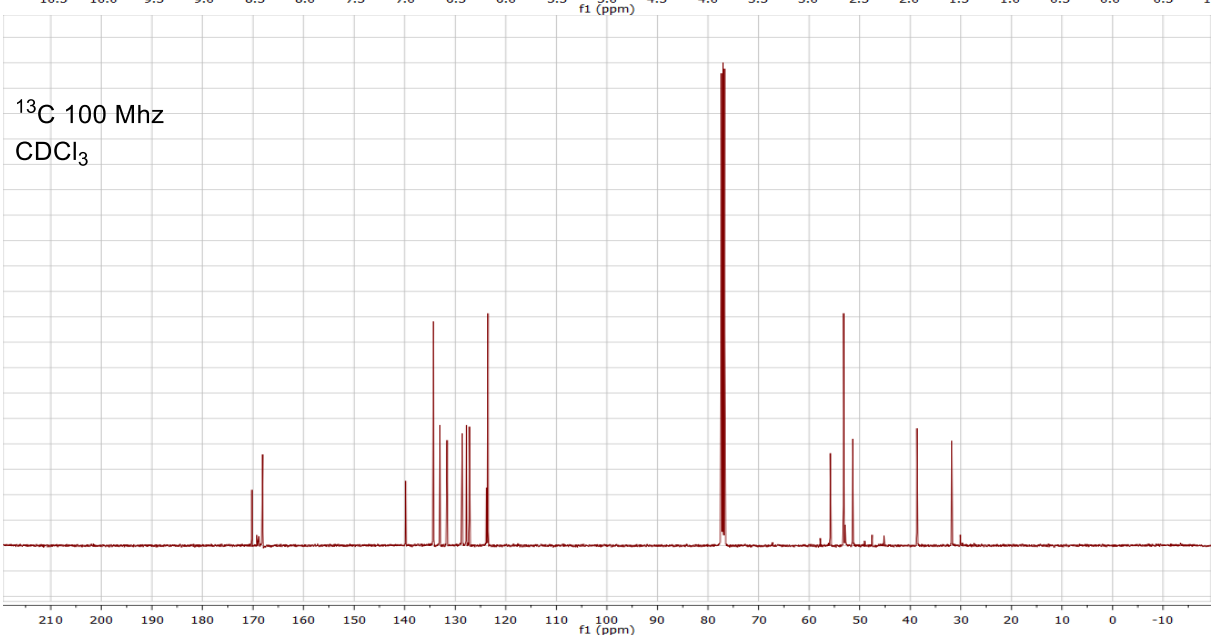
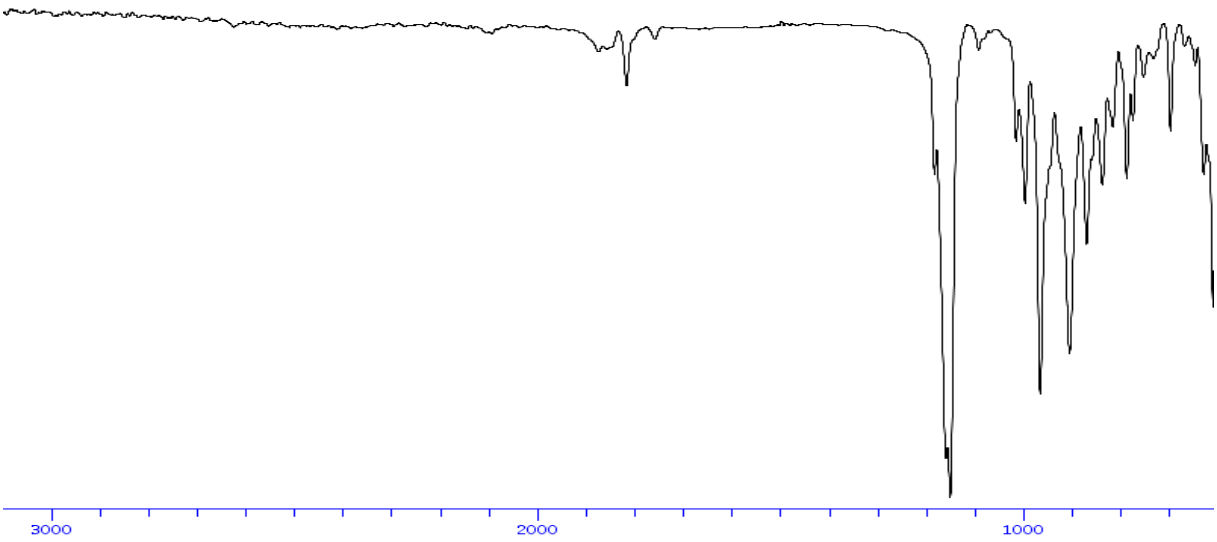
2000
1000


6na
O
N
O
CO2Me
CO2Me
Br
1H 400 Mhz
CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


13C 100 Mhz
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)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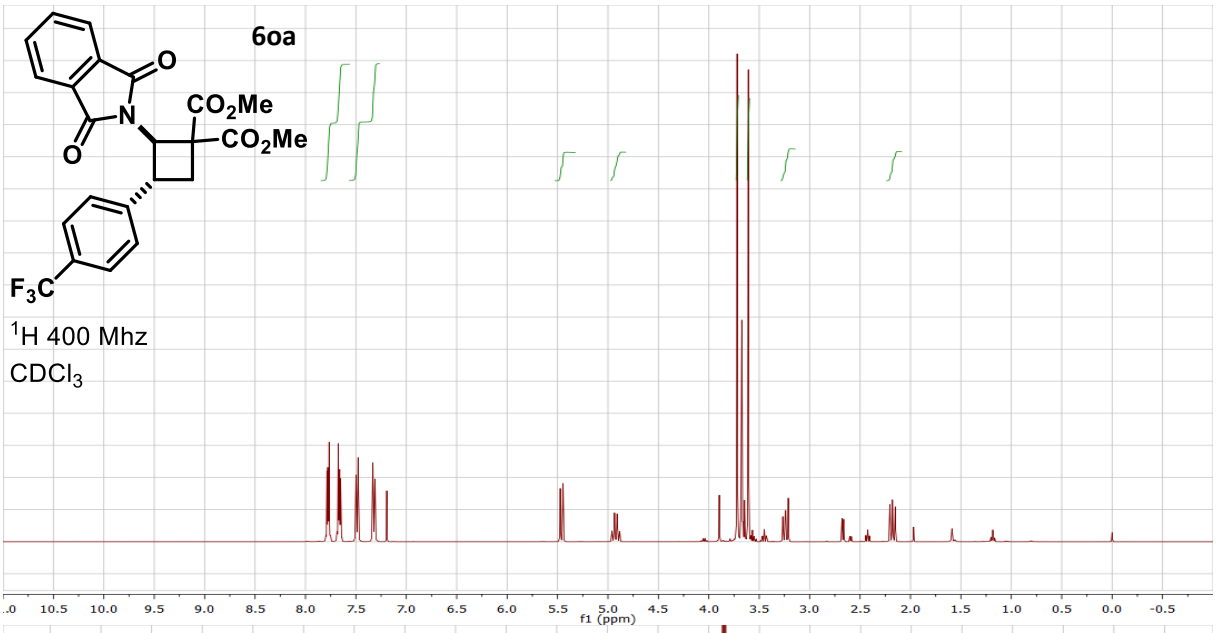
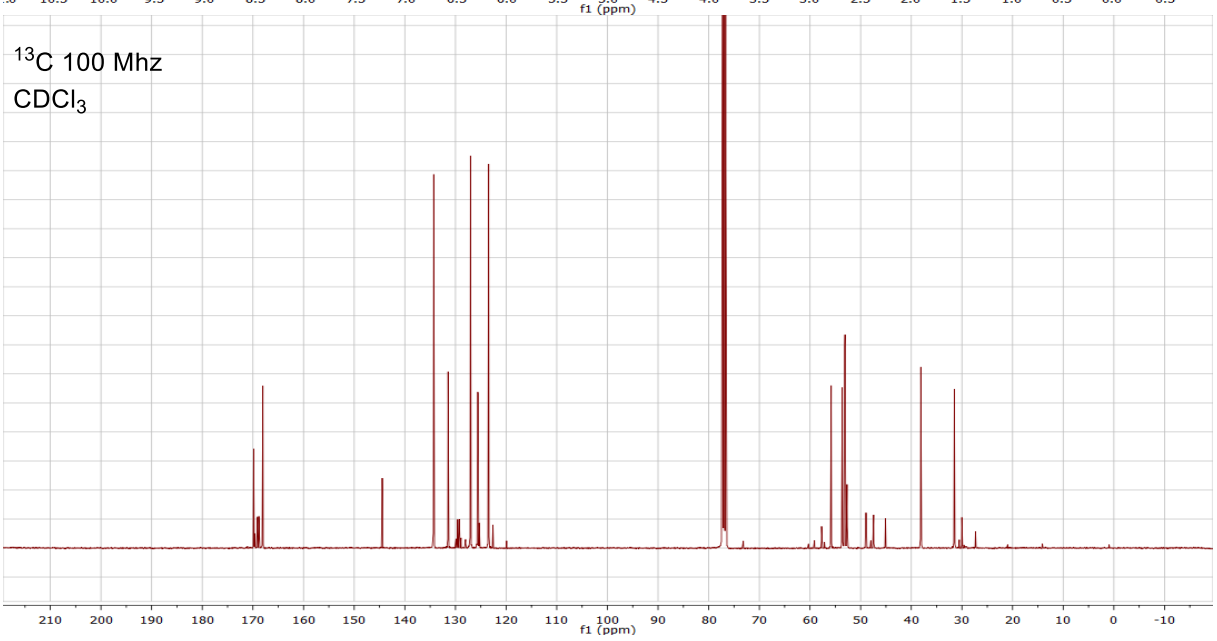
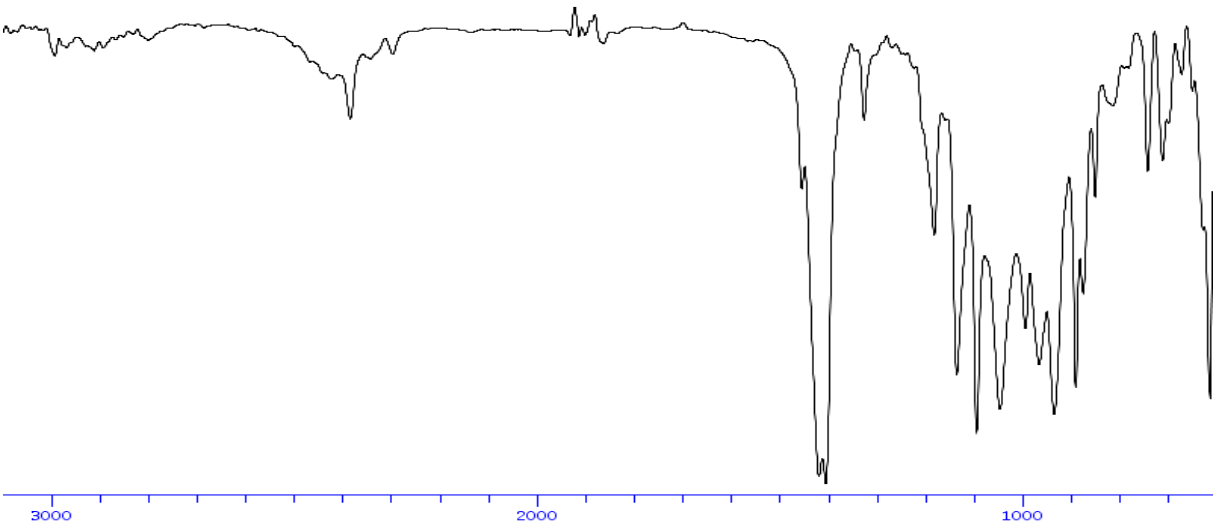
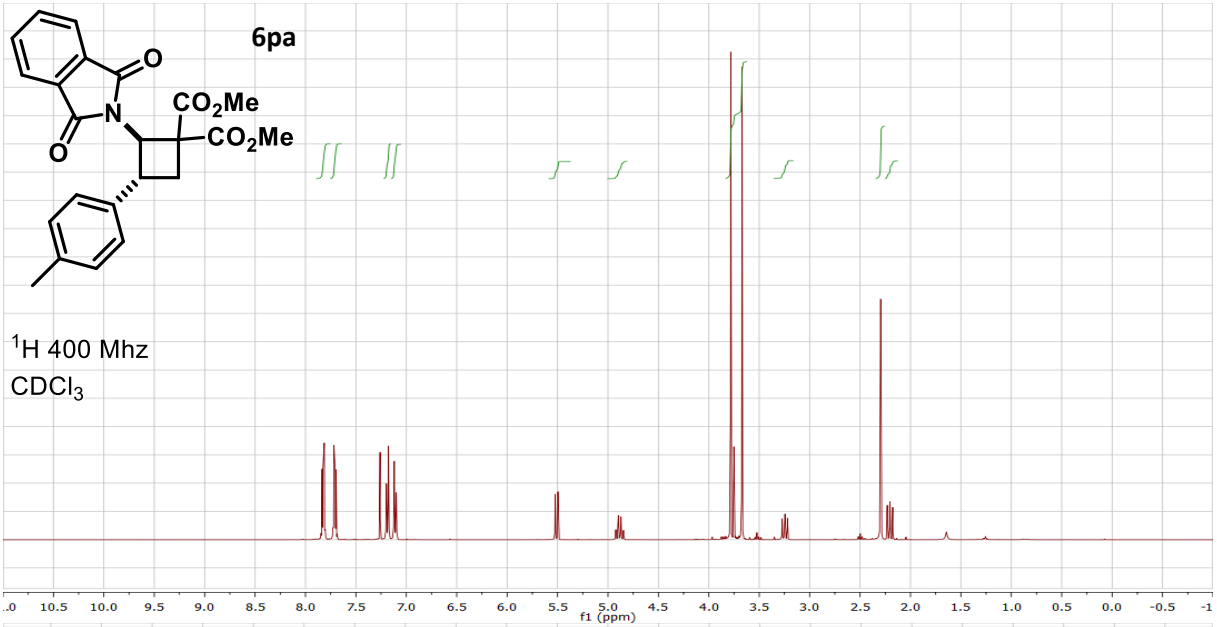
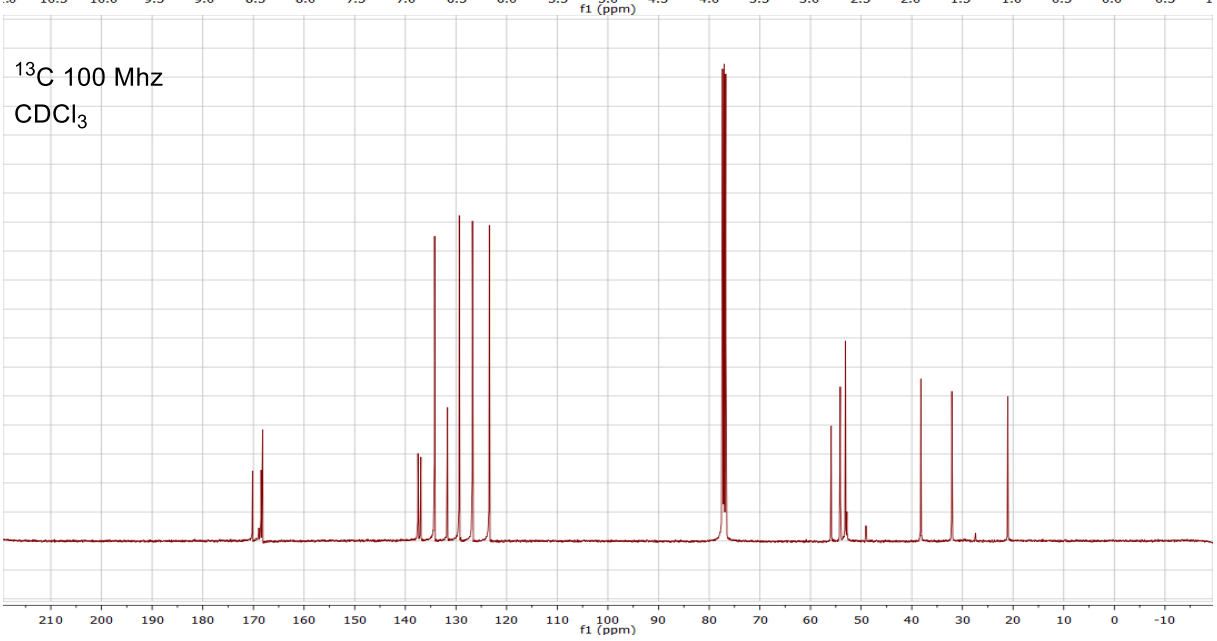
2000
1000

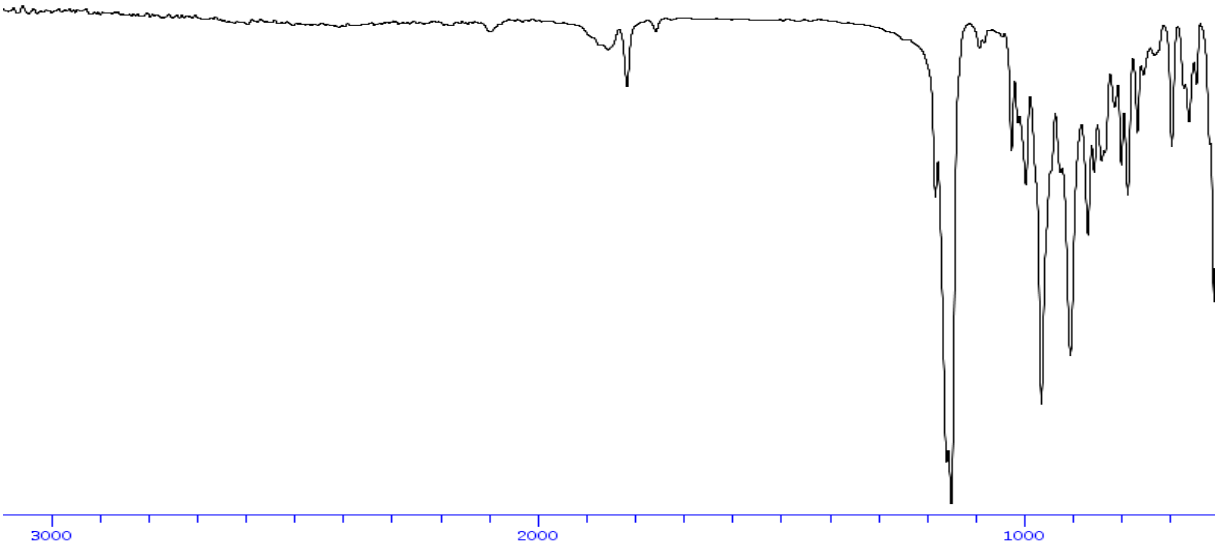

6oa
O
N
O
CO2Me
CO2Me
F3C
1H 400 Mhz
CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


13C 100 Mhz
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)


3000
2000
1000


6pa
O
N
O
CO2Me
CO2Me
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)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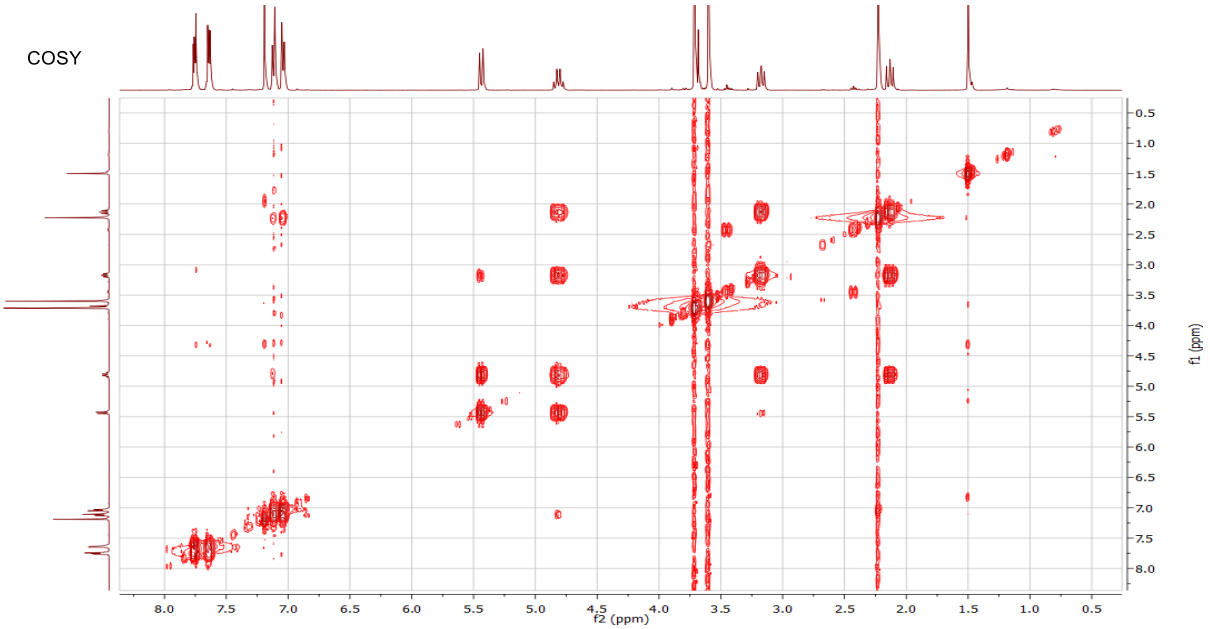
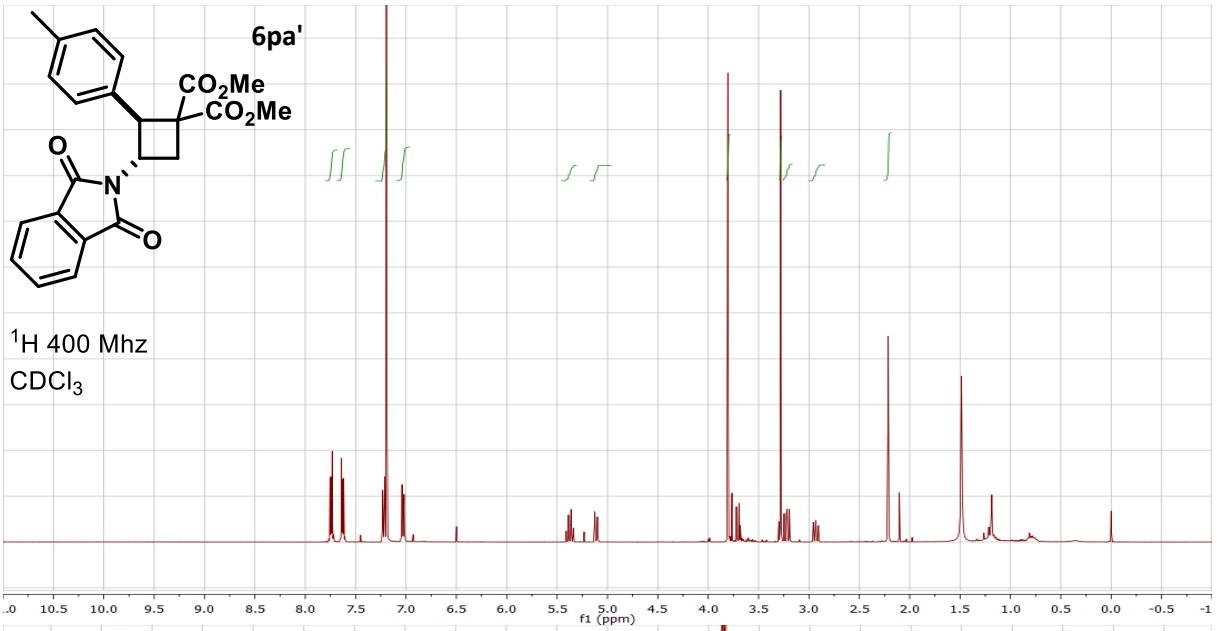
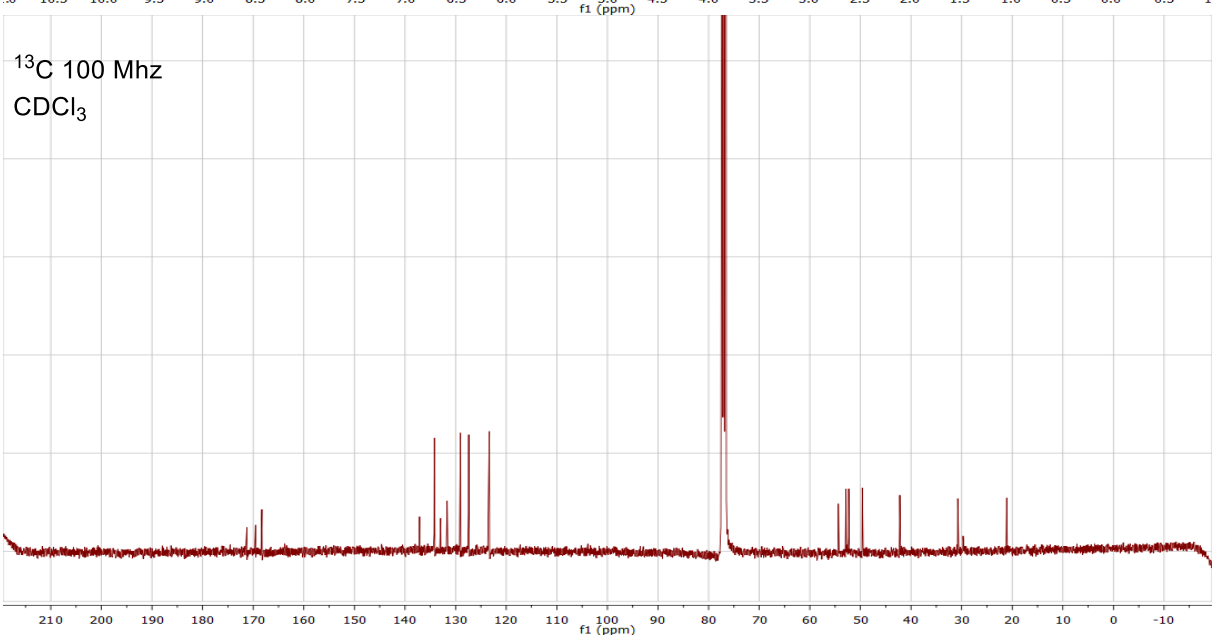
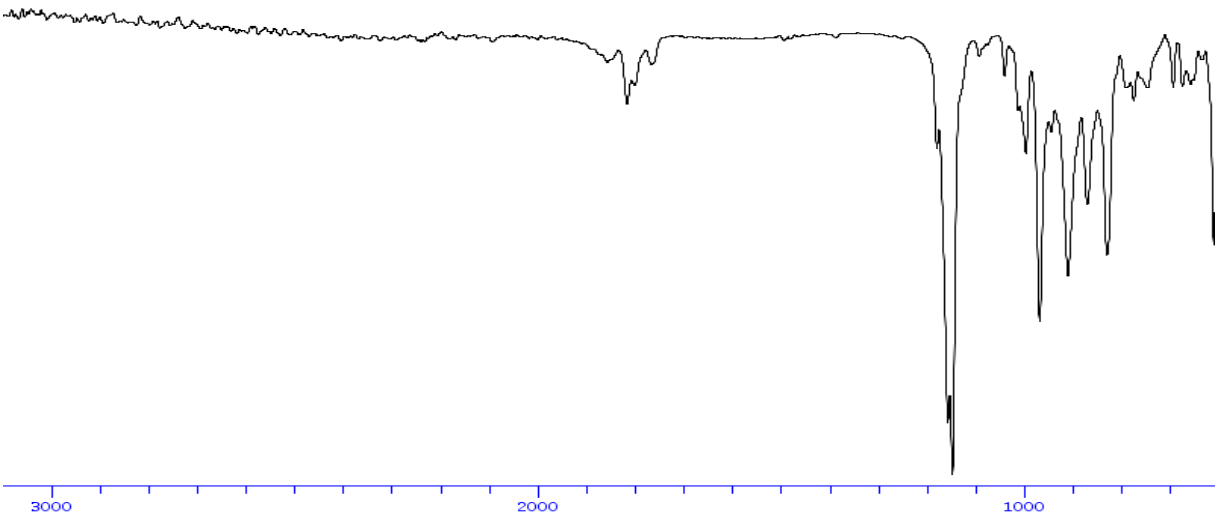
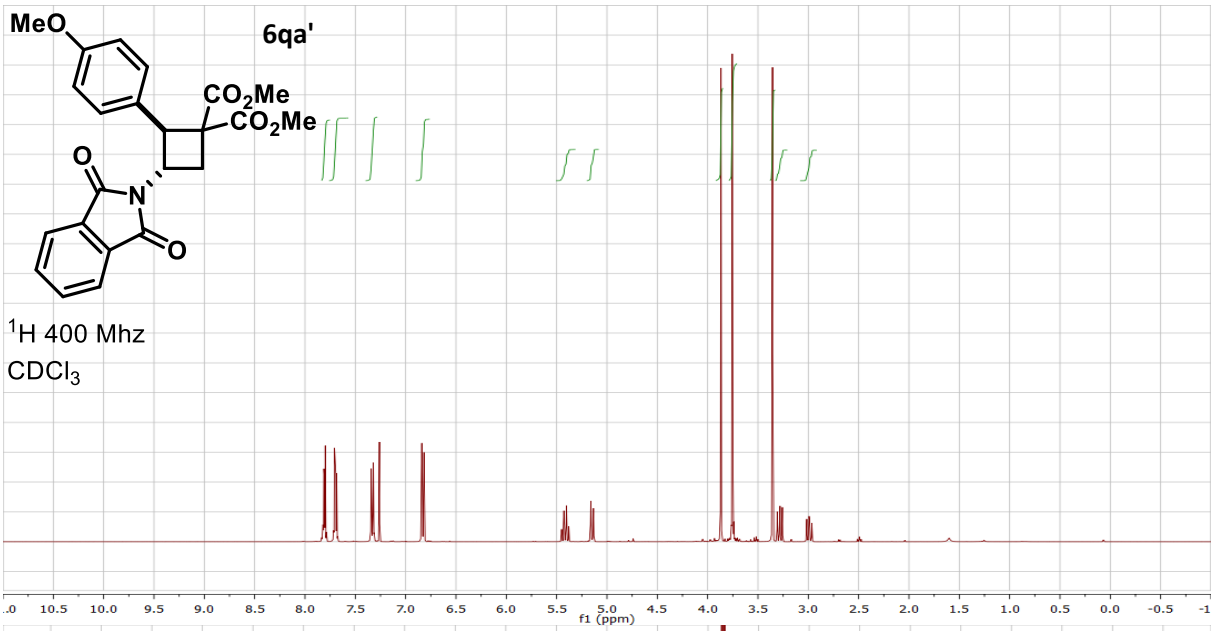
2000
1000

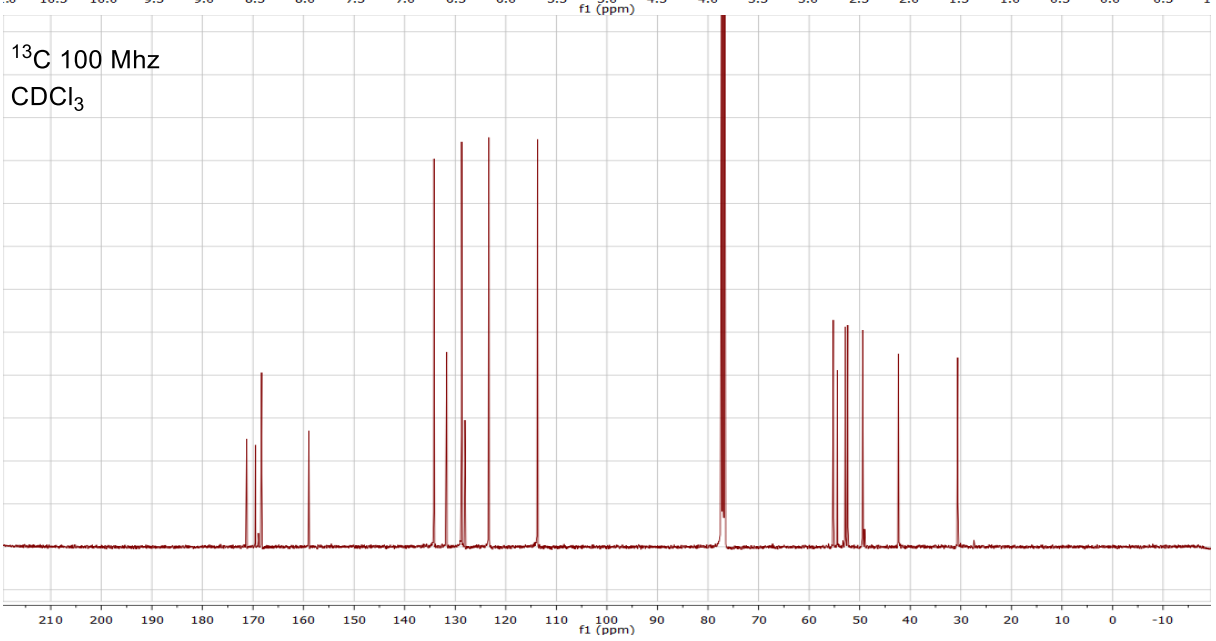

COSY
f2 (ppm)
f1 (ppm)

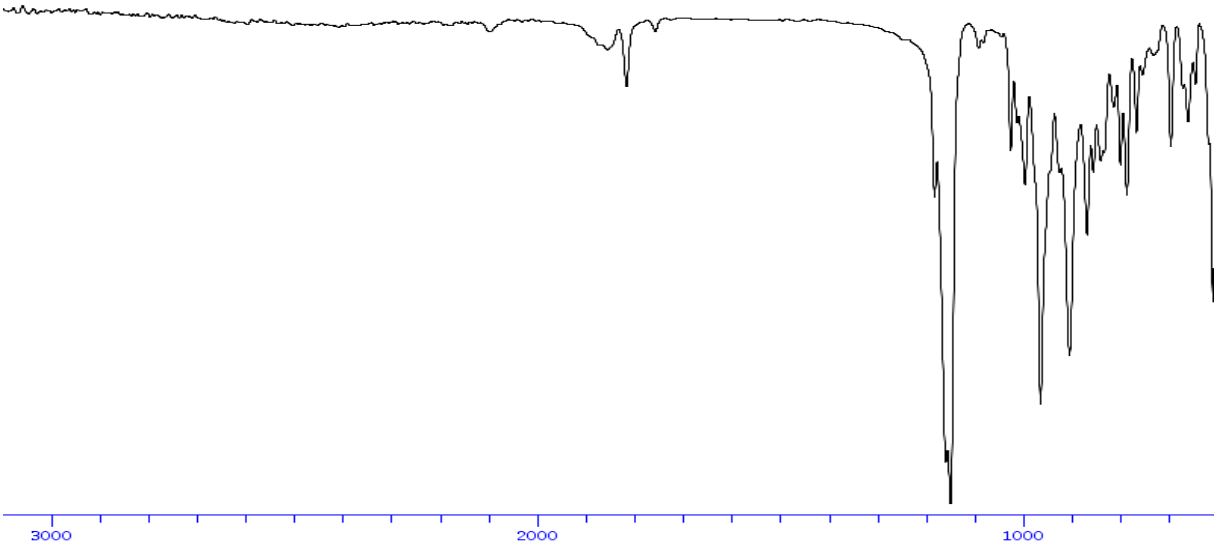

6pa'
CO2Me
CO2Me
O
N
O
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)

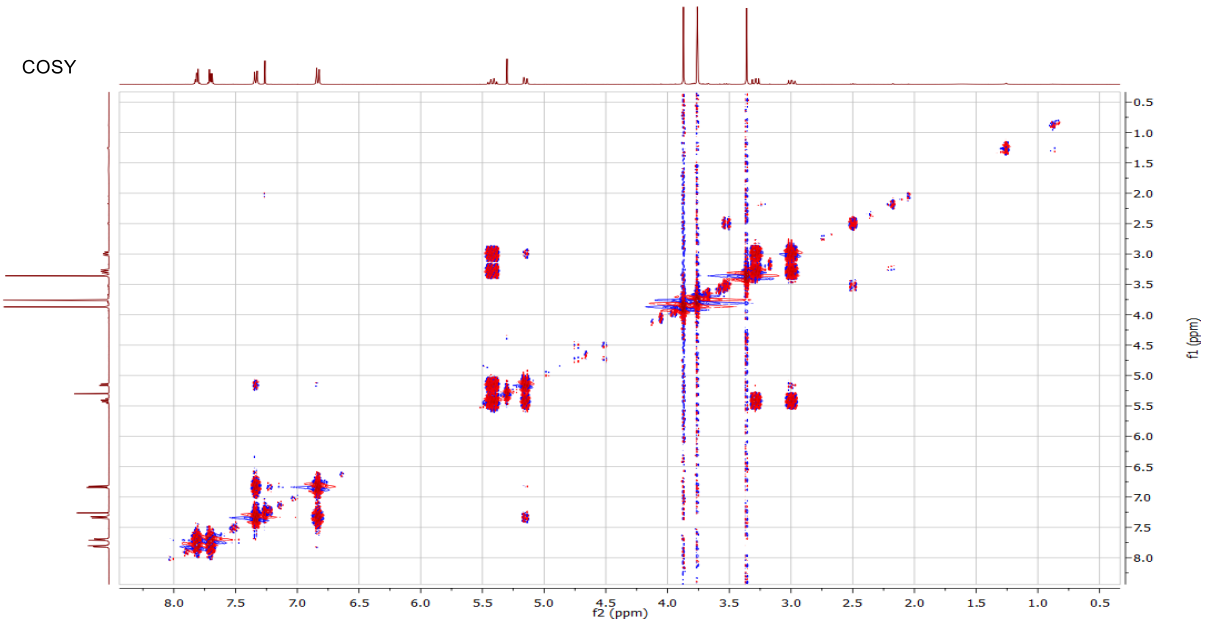

3000
2000
1000


MeO
6qa'
CO2Me
CO2Me
O
N
O
1H 400 Mhz
CDCl3
f1 (ppm)

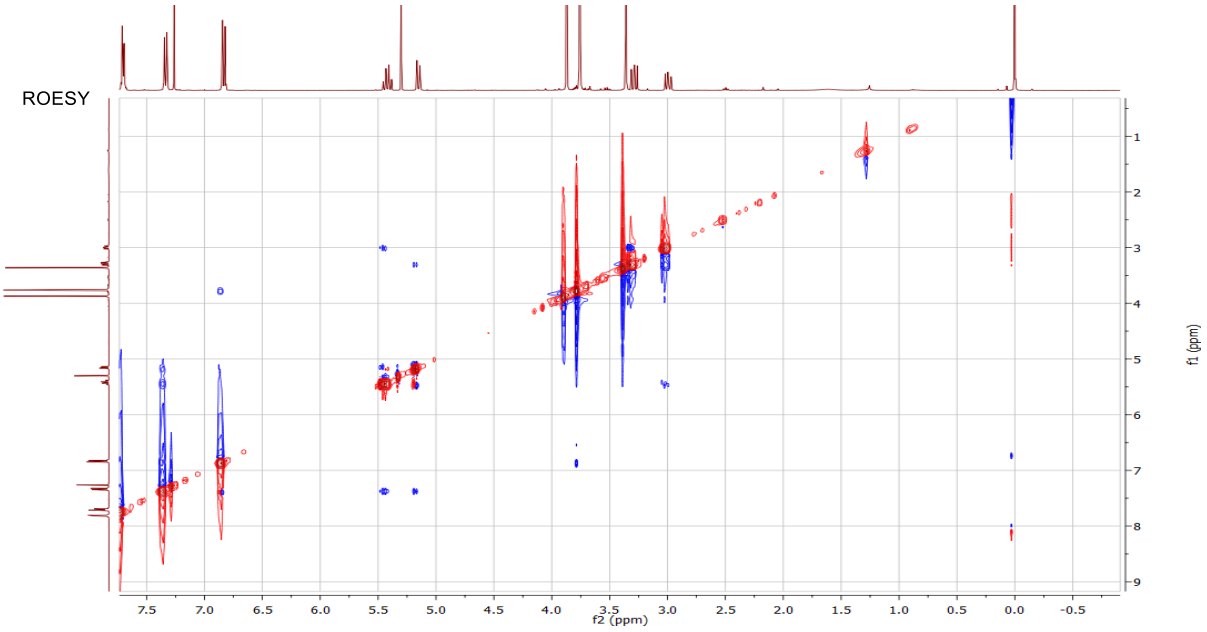

13C 100 Mhz
CDCl3
f1 (ppm)

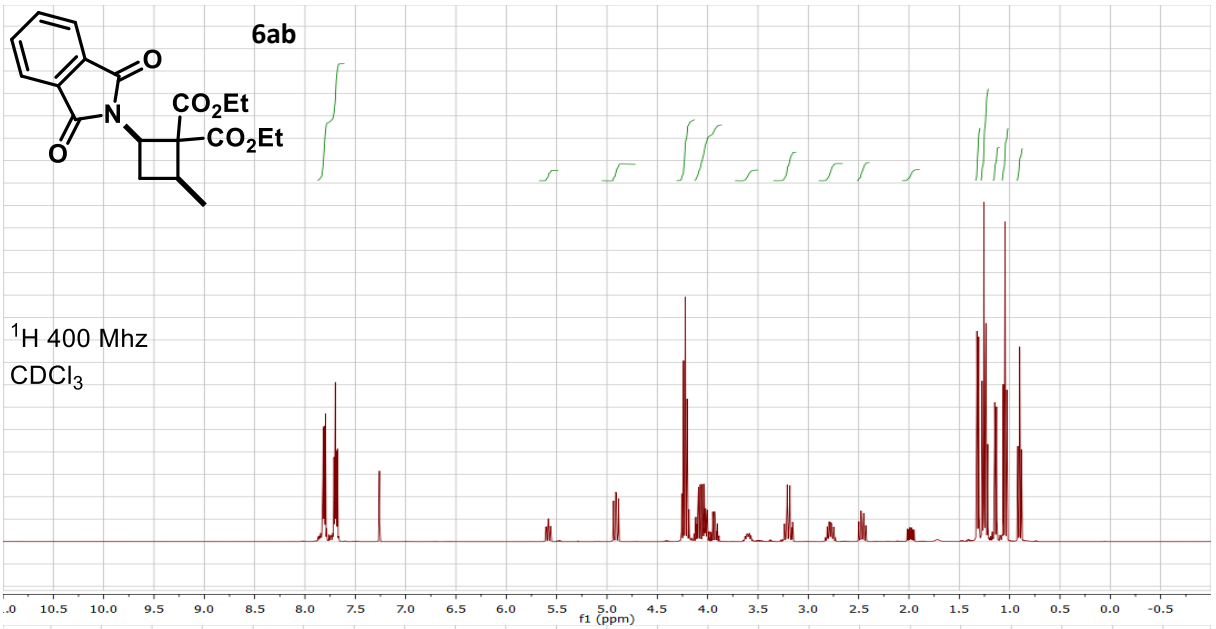

3000
2000
1000

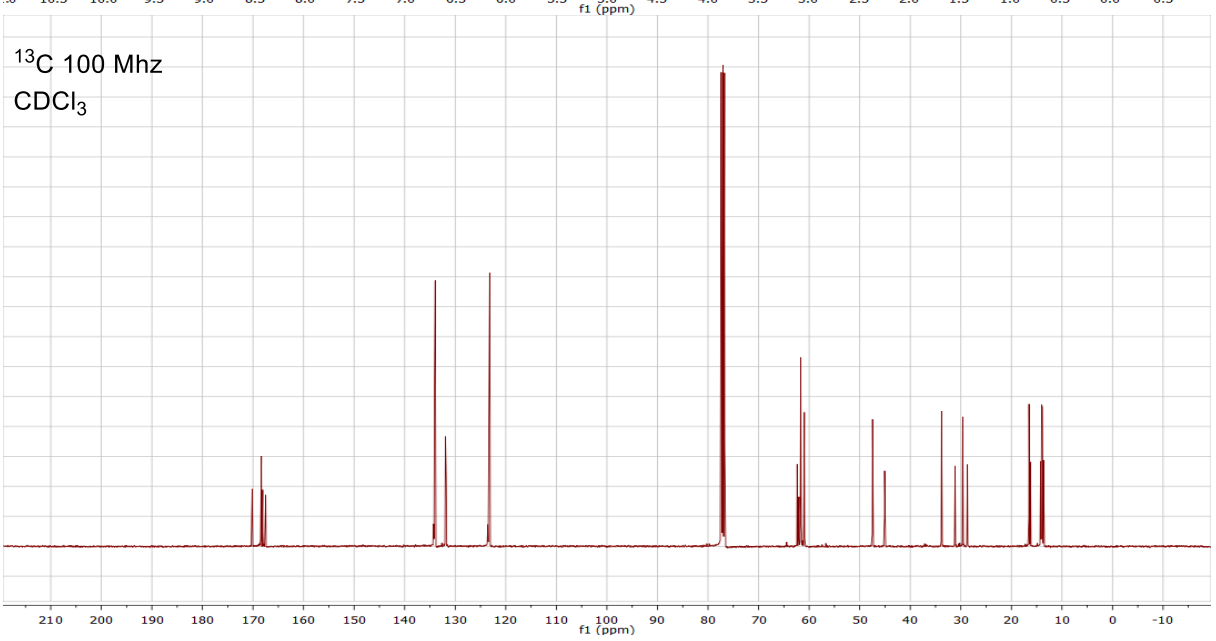
COSY

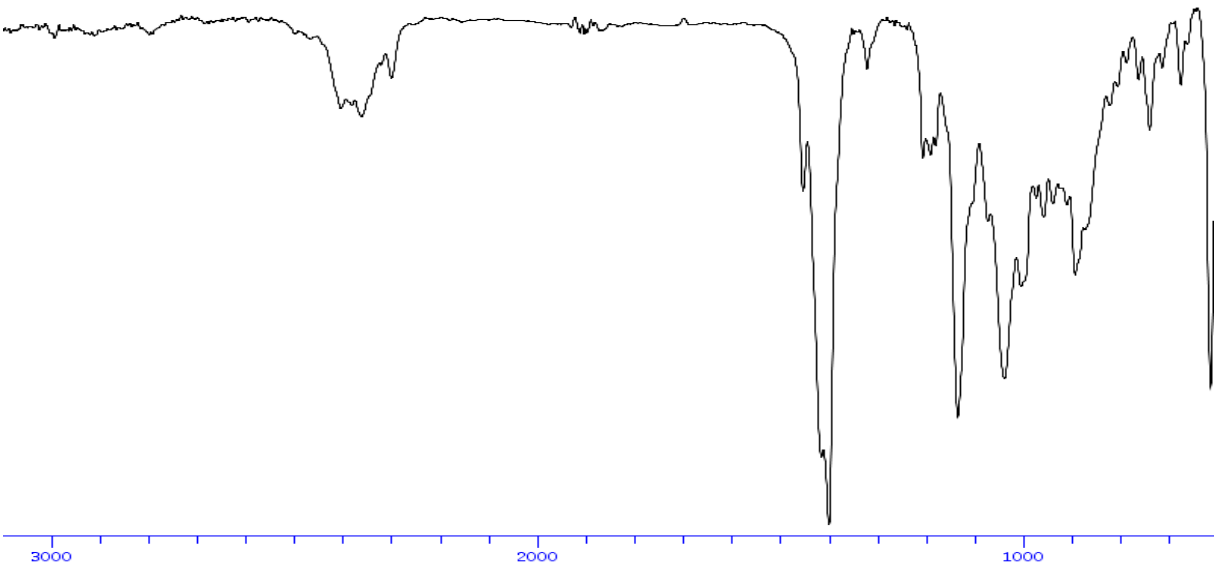


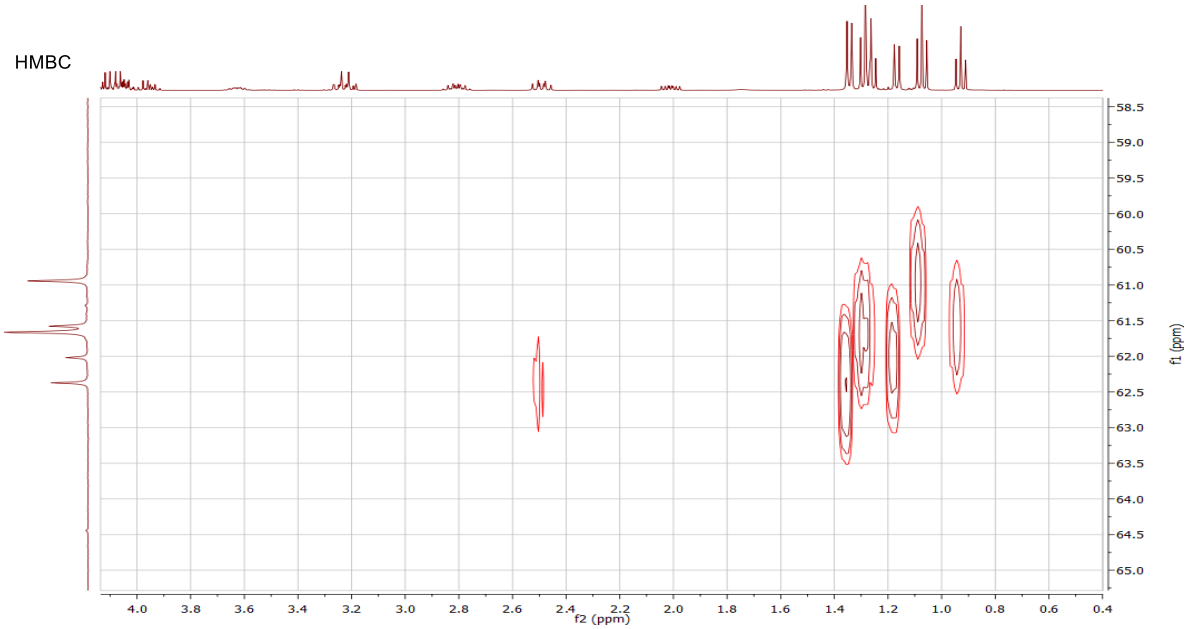
ROESY

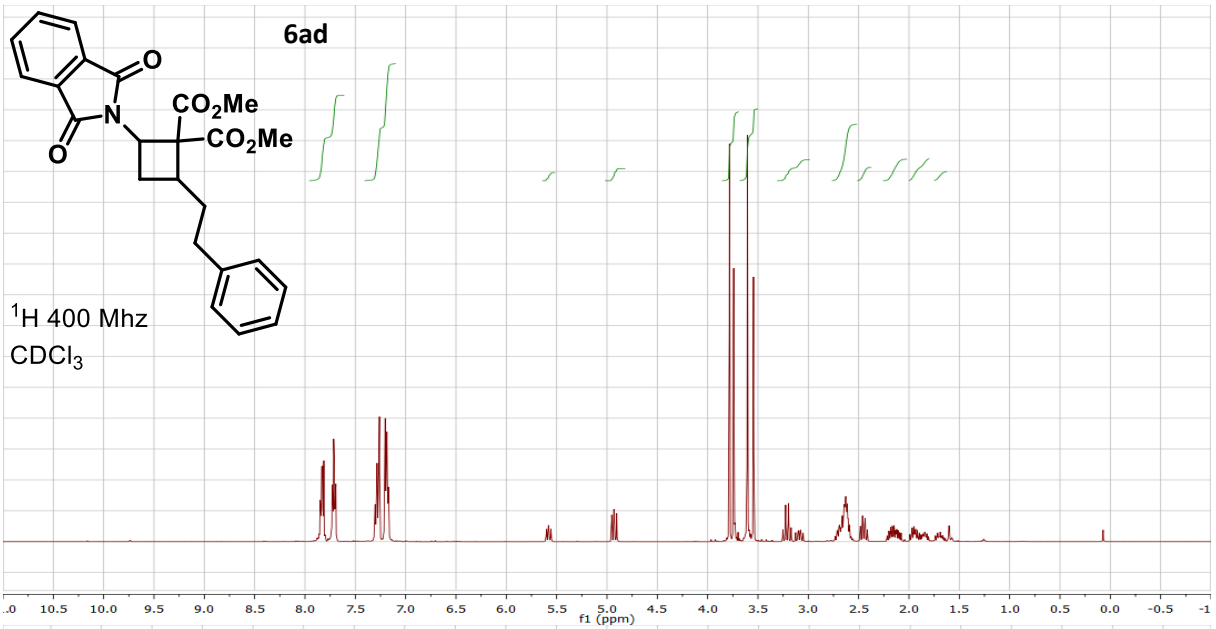


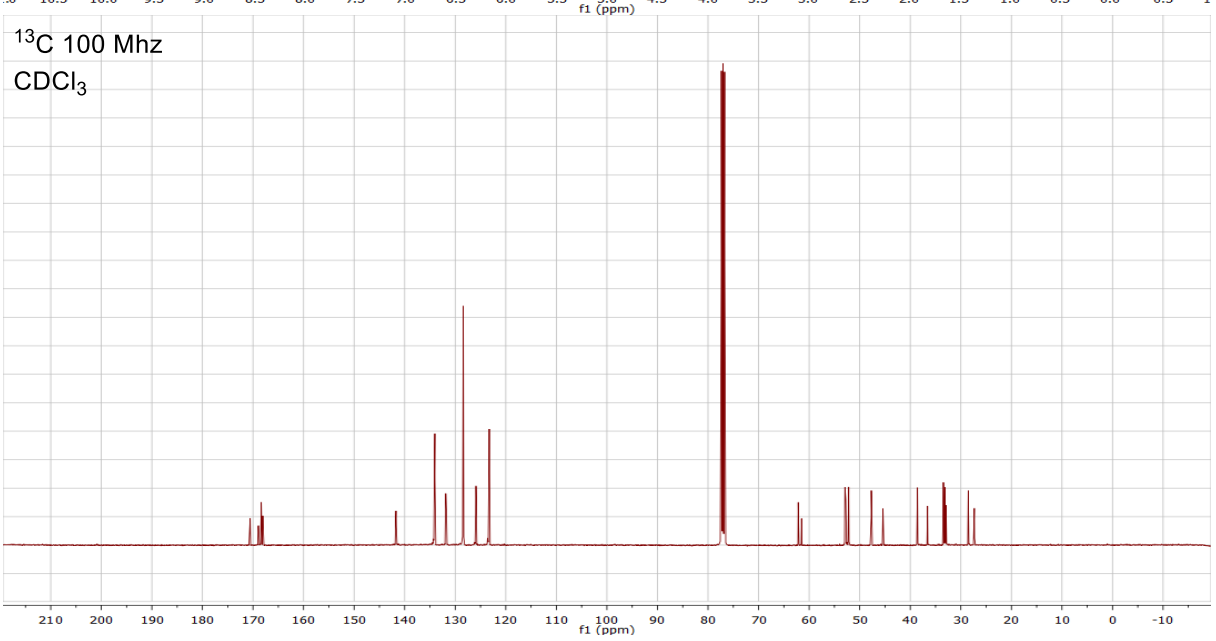

6ab
O
O
N
CO2Et
CO2Et
1H 400 Mhz
CDCl3
f1 (ppm)

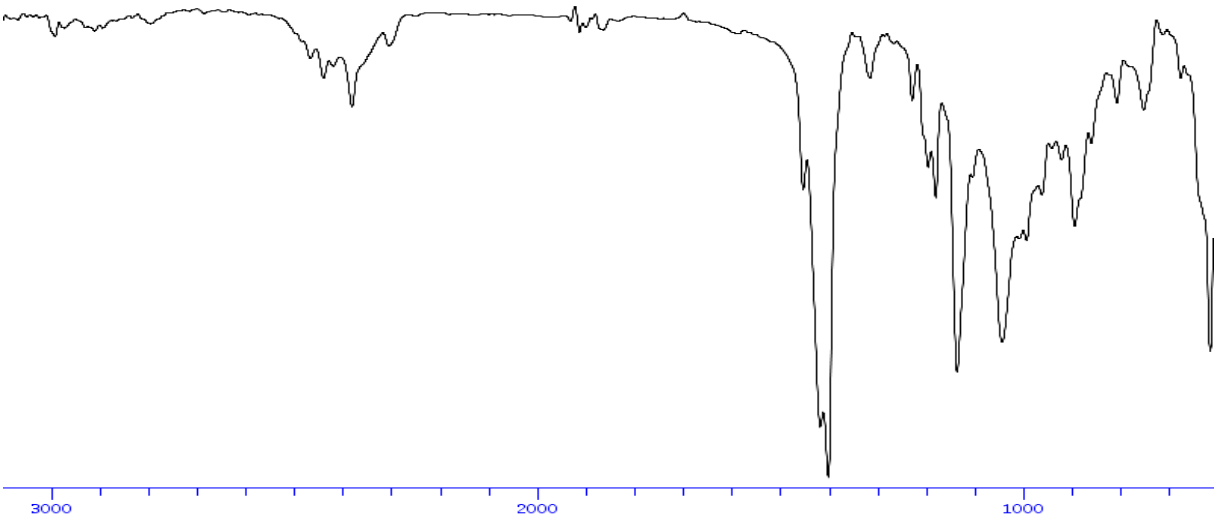

13C 100 Mhz
CDCl3
f1 (ppm)

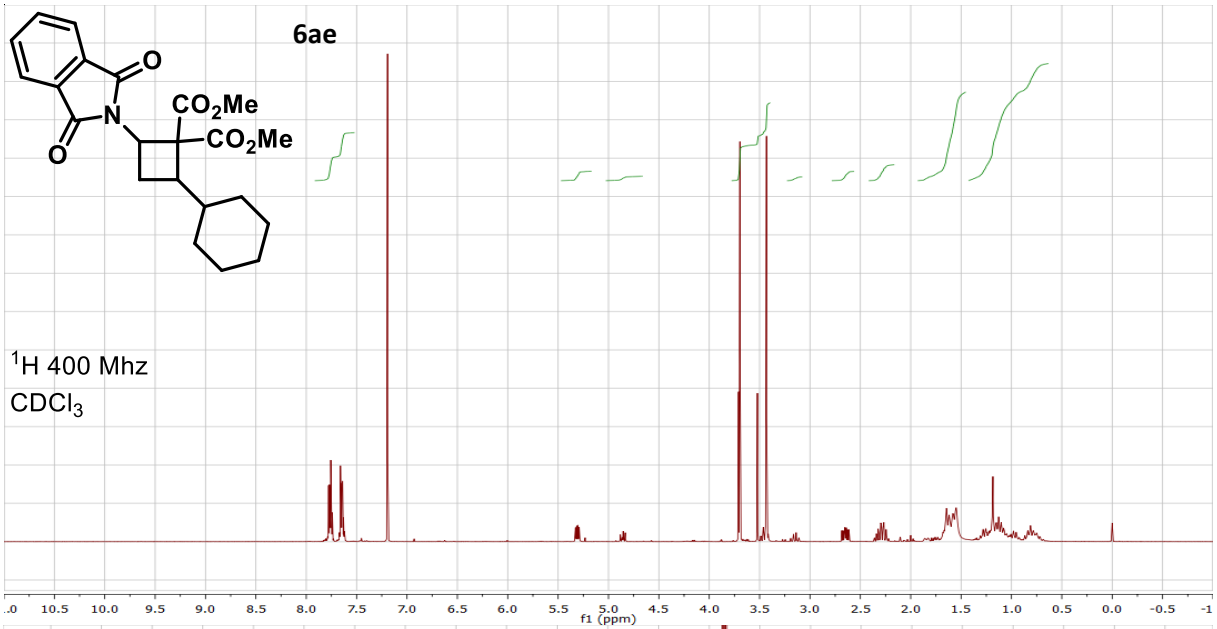

3000
2000
1000

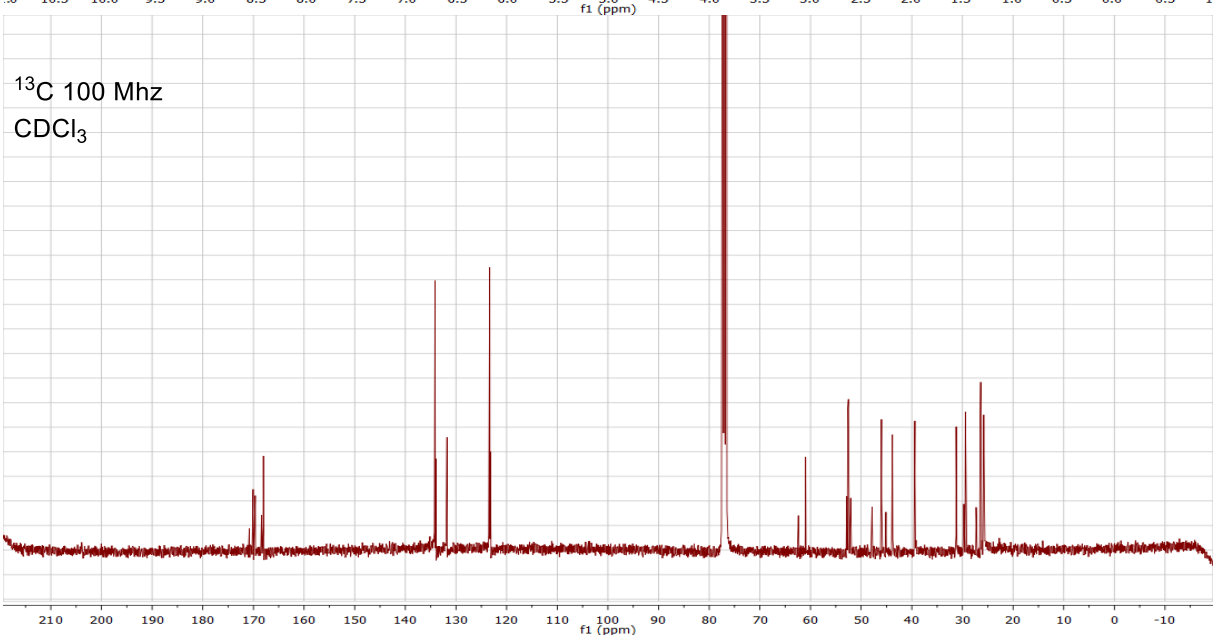

HMBC
58.5
59.0
59.5
60.0
60.5
61.0
61.5
62.0
62.5
63.0
63.5
64.0
64.5
65.0
f1 (ppm)
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
f2 (ppm)

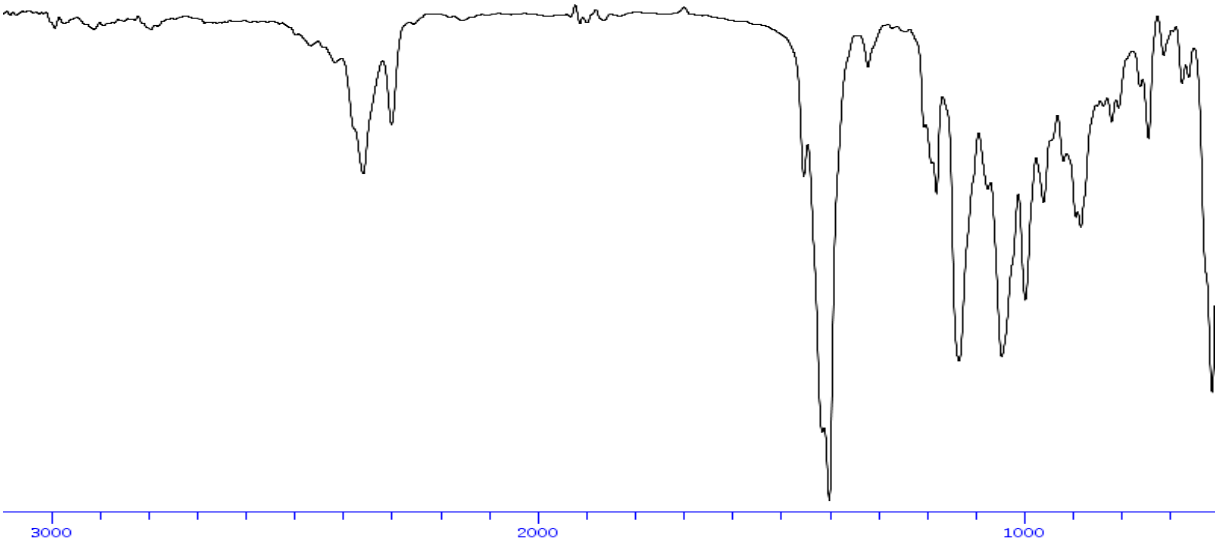

6ad
O
O
N
CO_2Me
CO_2Me
^1H 400 Mhz
$CDCl_3$
f1 (ppm)

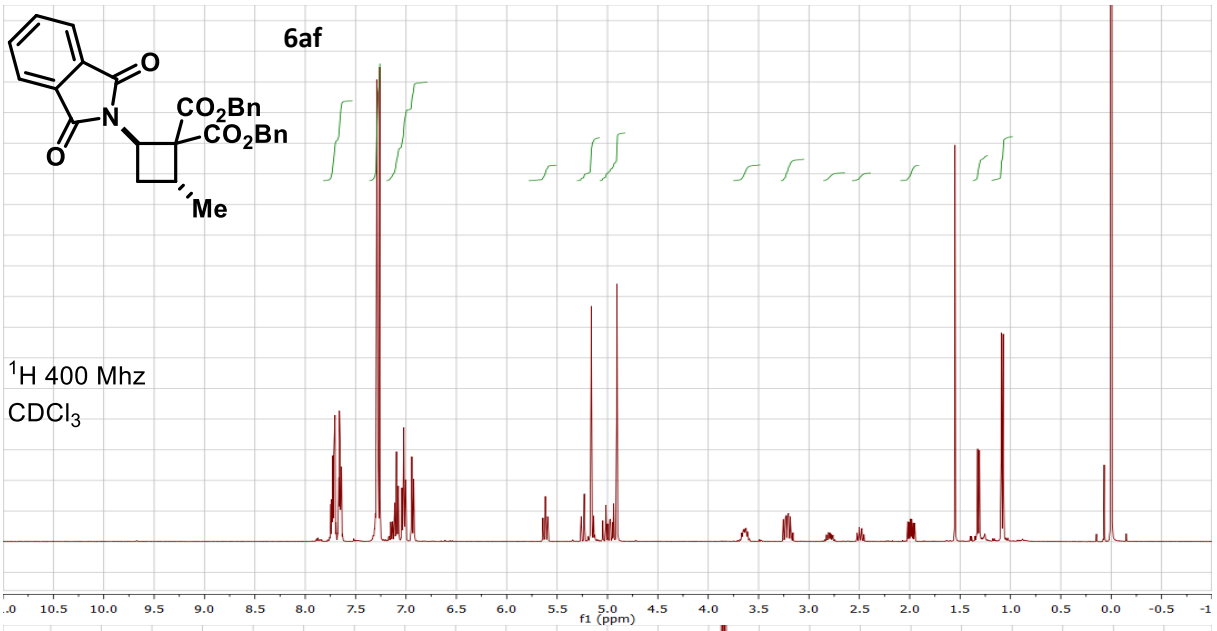

^{13}C 100 Mhz
$CDCl_3$
f1 (ppm)

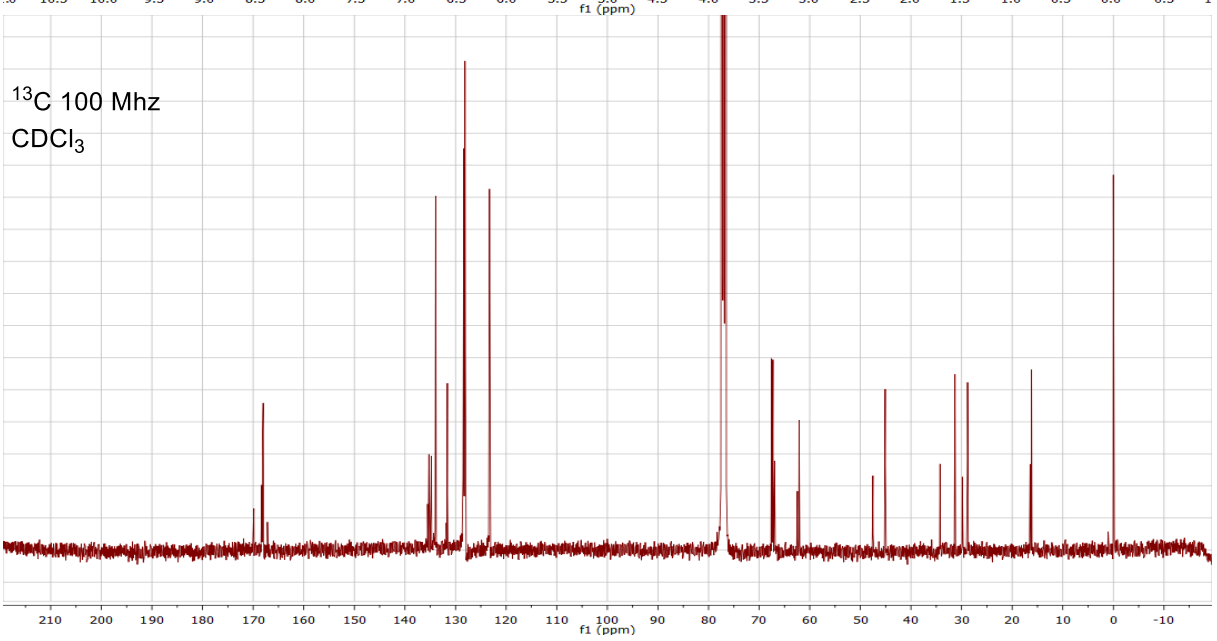

3000
2000
1000

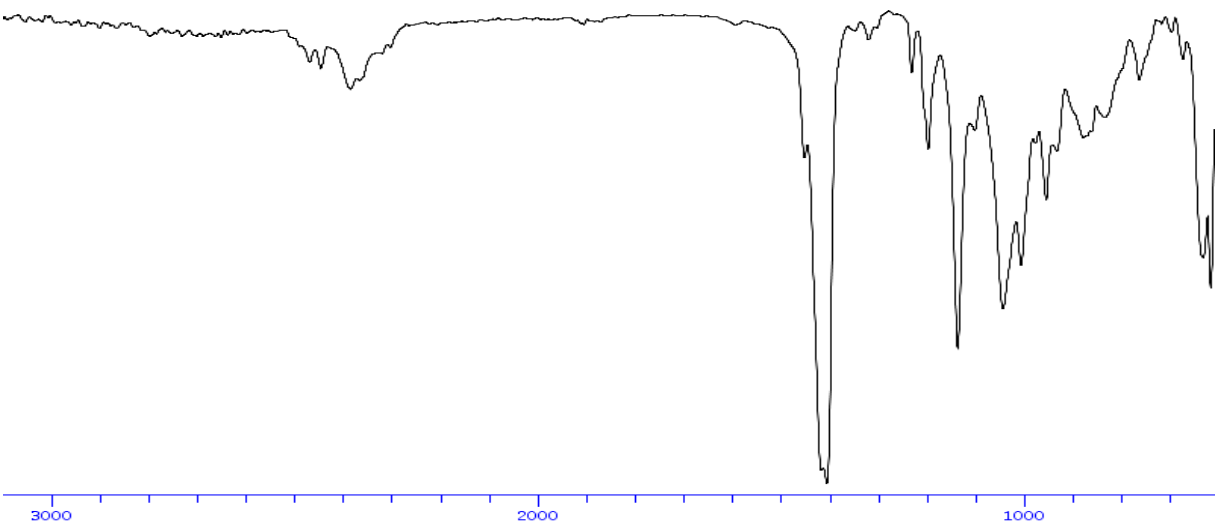

6ae
O
N
O
CO2Me
CO2Me
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)

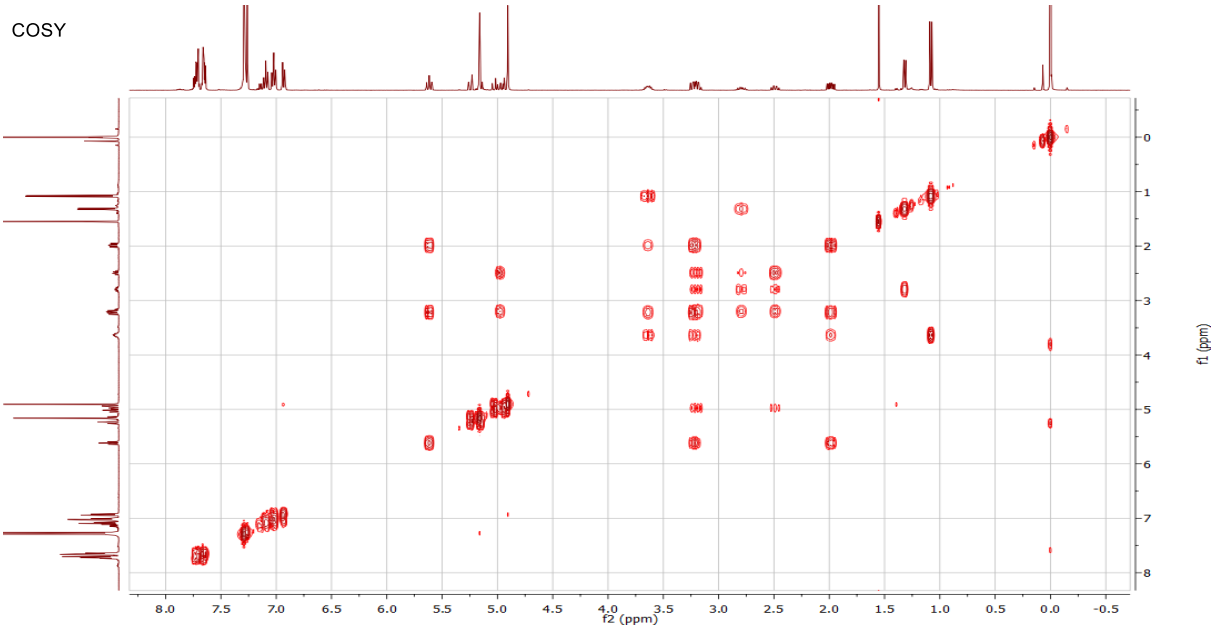

3000
2000
1000


6af
O
N
O
CO2Bn
CO2Bn
Me
1H 400 Mhz
CDCl3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

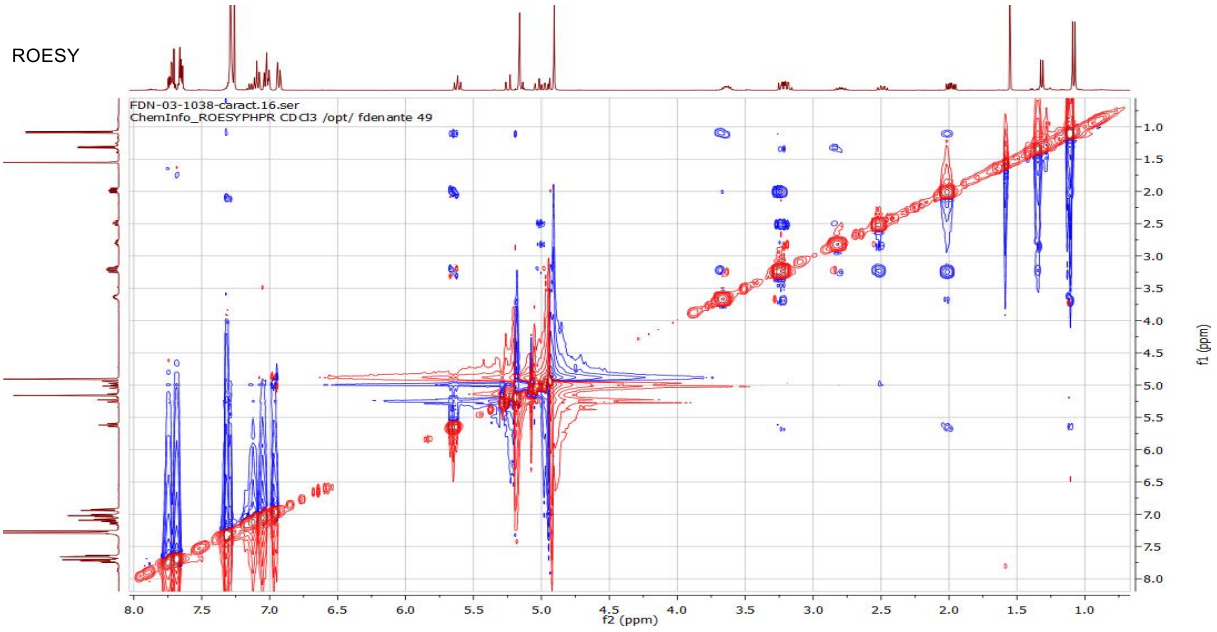

13C 100 Mhz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

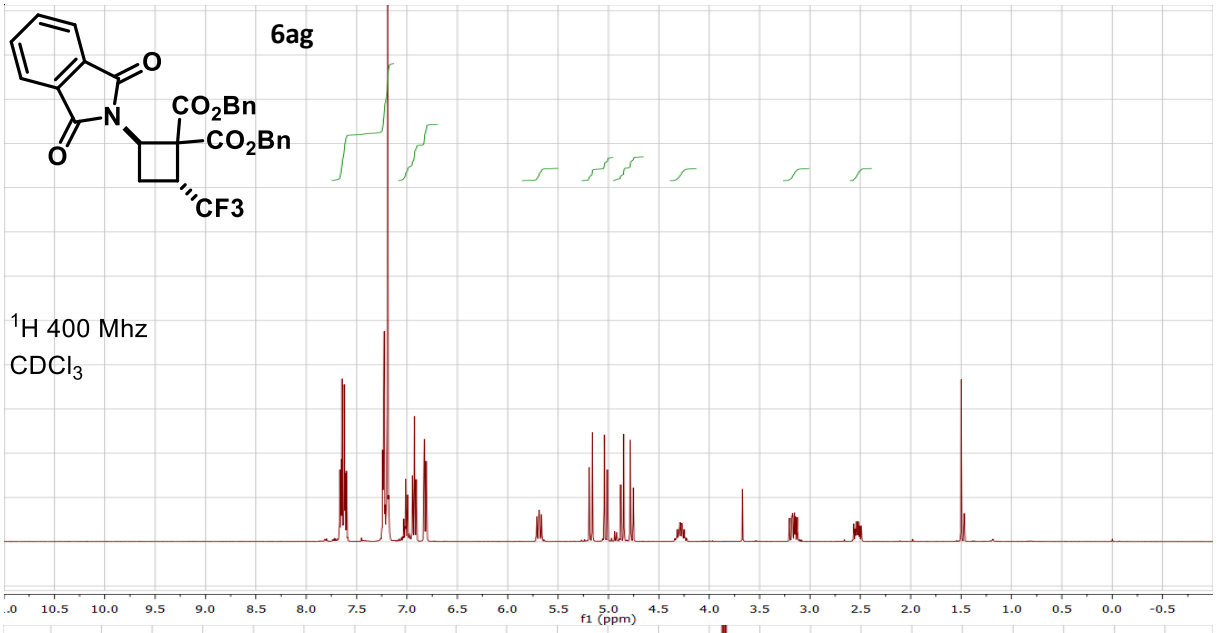

3000
2000
1000

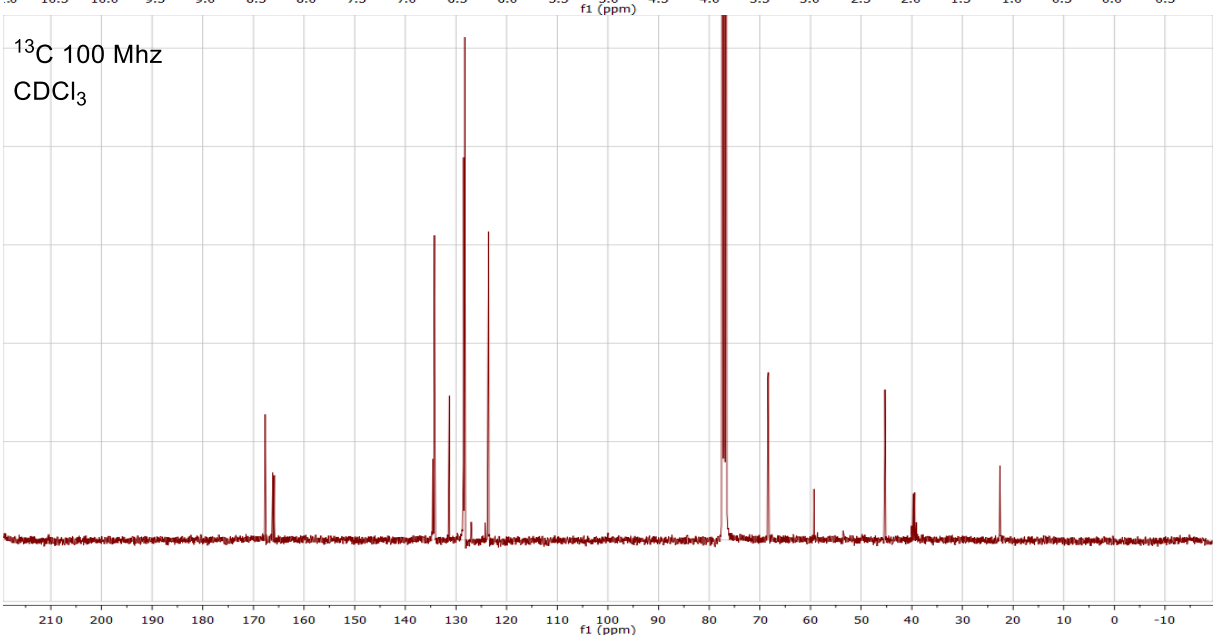
COSY

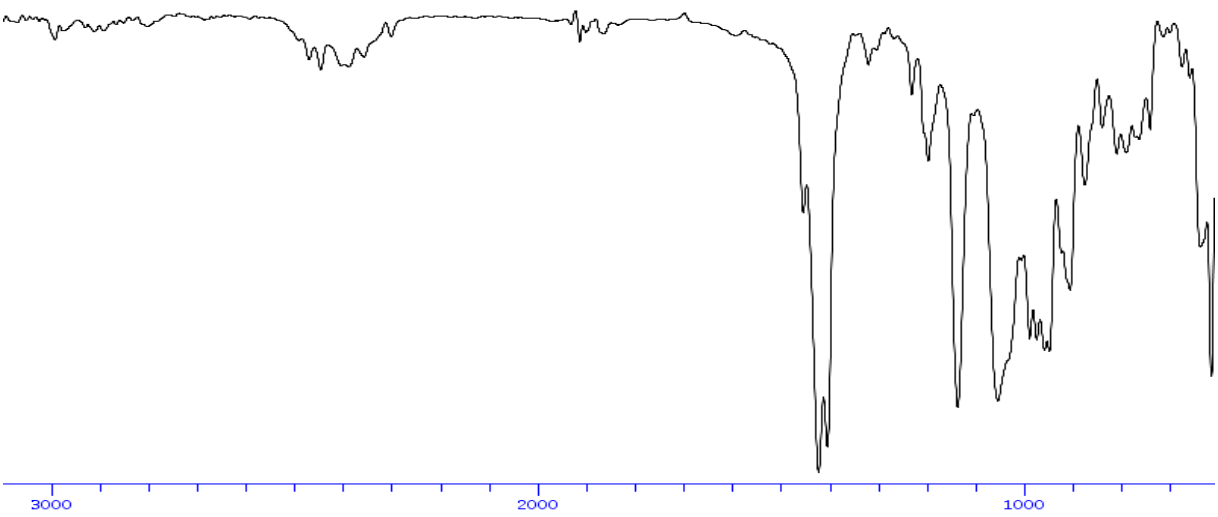

f2 (ppm)
f1 (ppm)

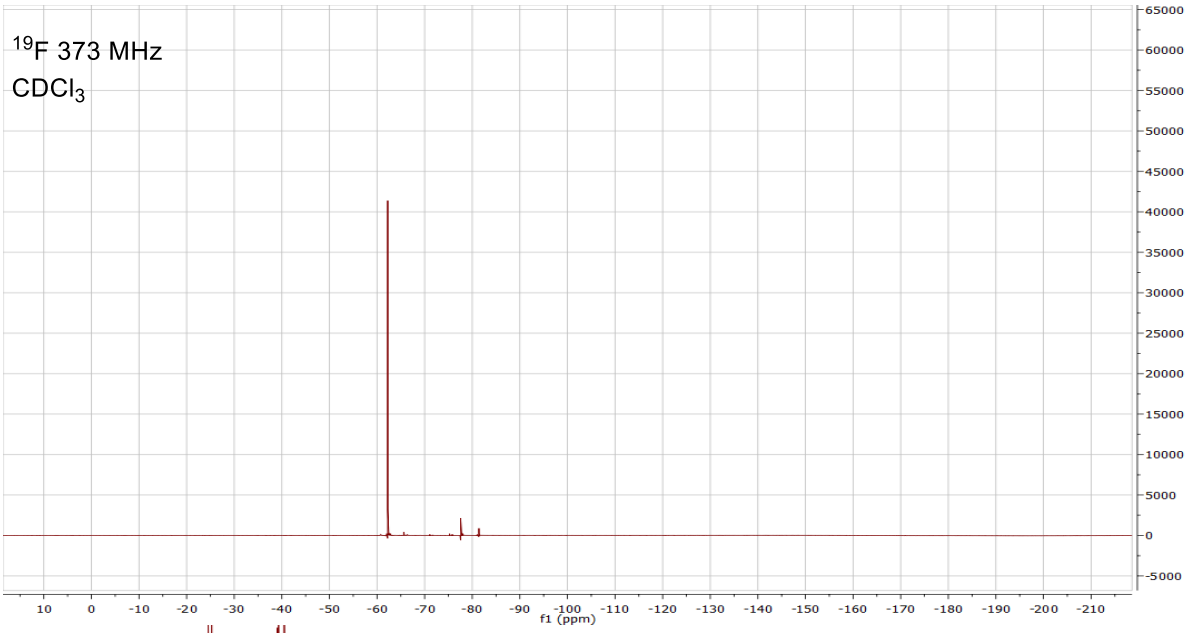
ROESY

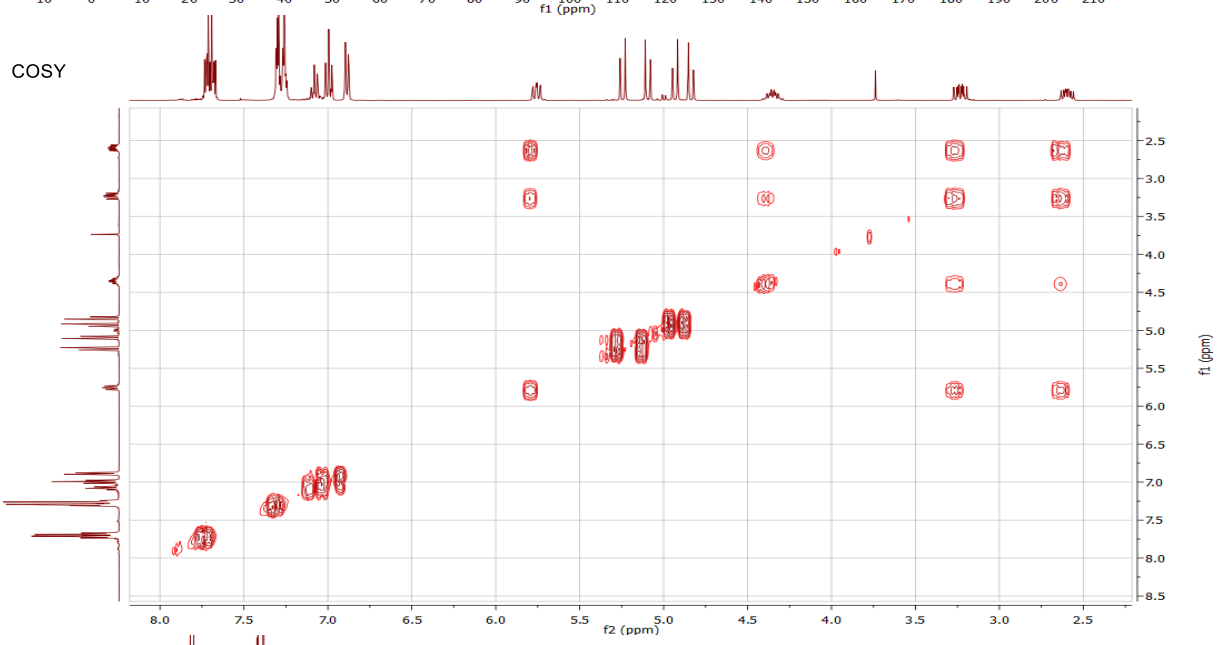

FDN-03-1038-caract.16.ser
ChemInfo_ROESYPHPR CDCl3 /opt/ fdenante 49
f2 (ppm)
f1 (ppm)

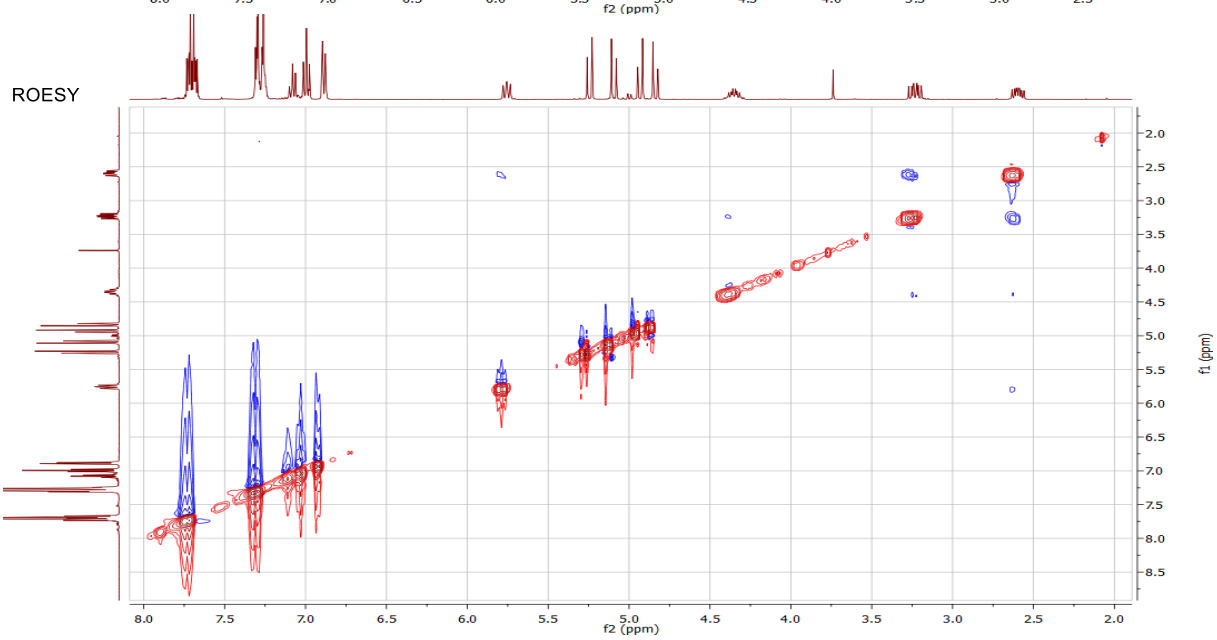

6ag
O
O
N
CO2Bn
CO2Bn
CF3
1H 400 Mhz
CDCl3
f1 (ppm)

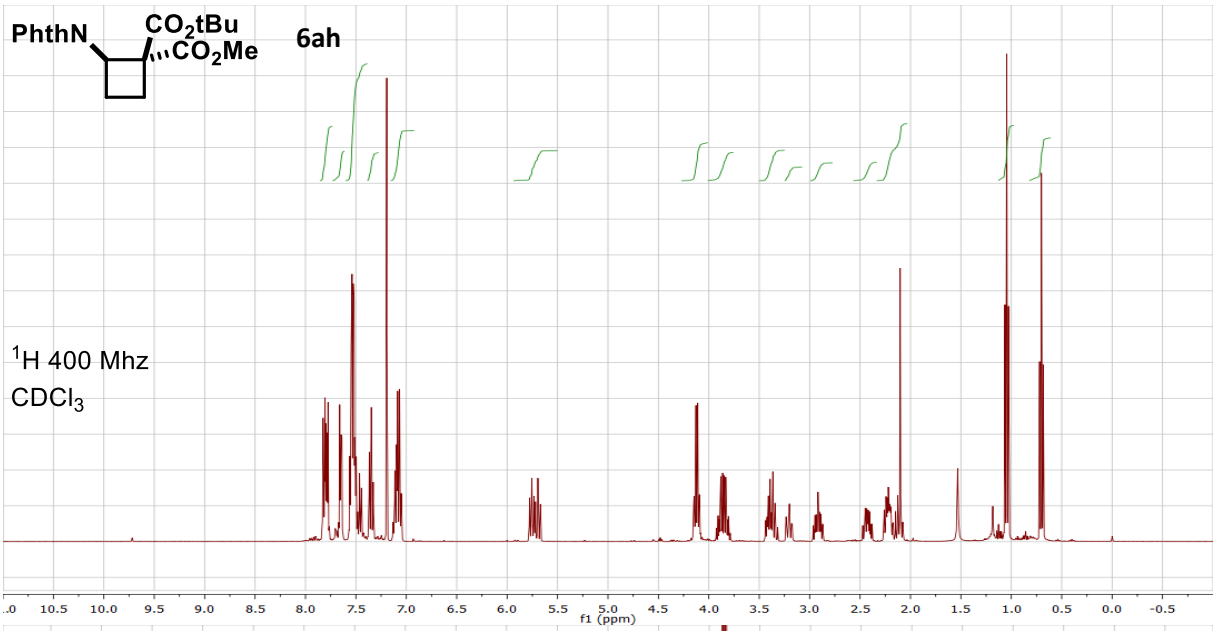

13C 100 Mhz
CDCl3
f1 (ppm)

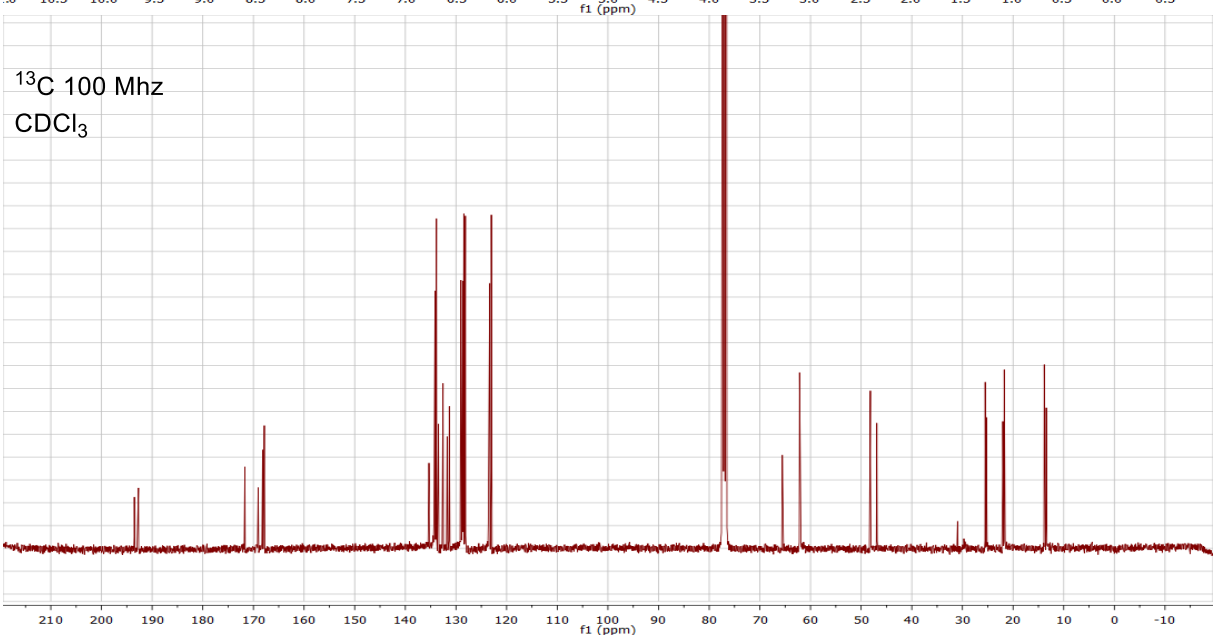

3000
2000
1000

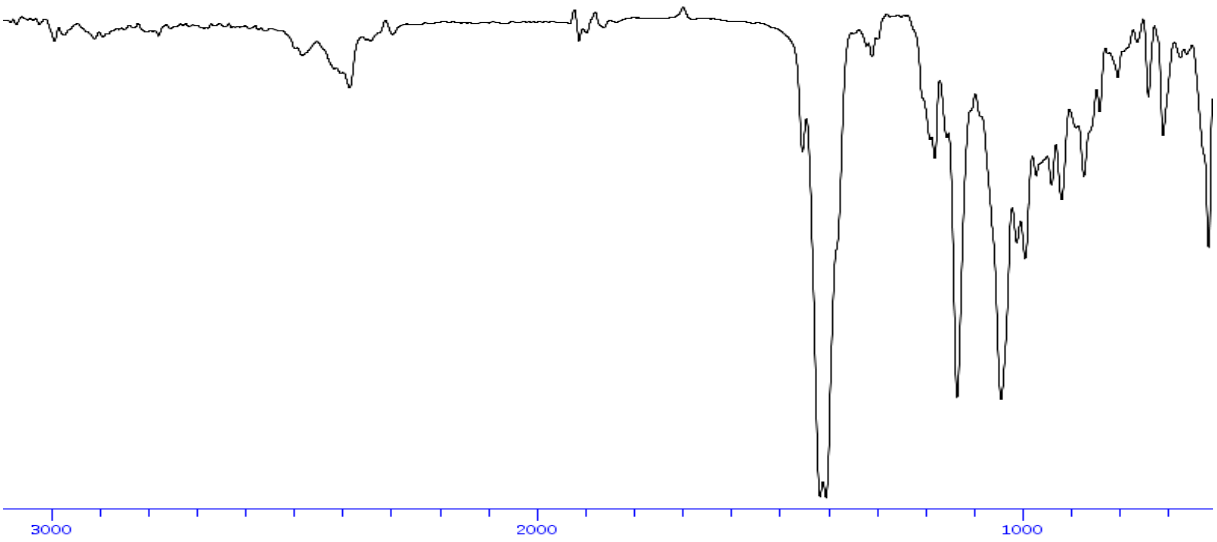

^{19}F 373 MHz
$CDCl_3$
f1 (ppm)

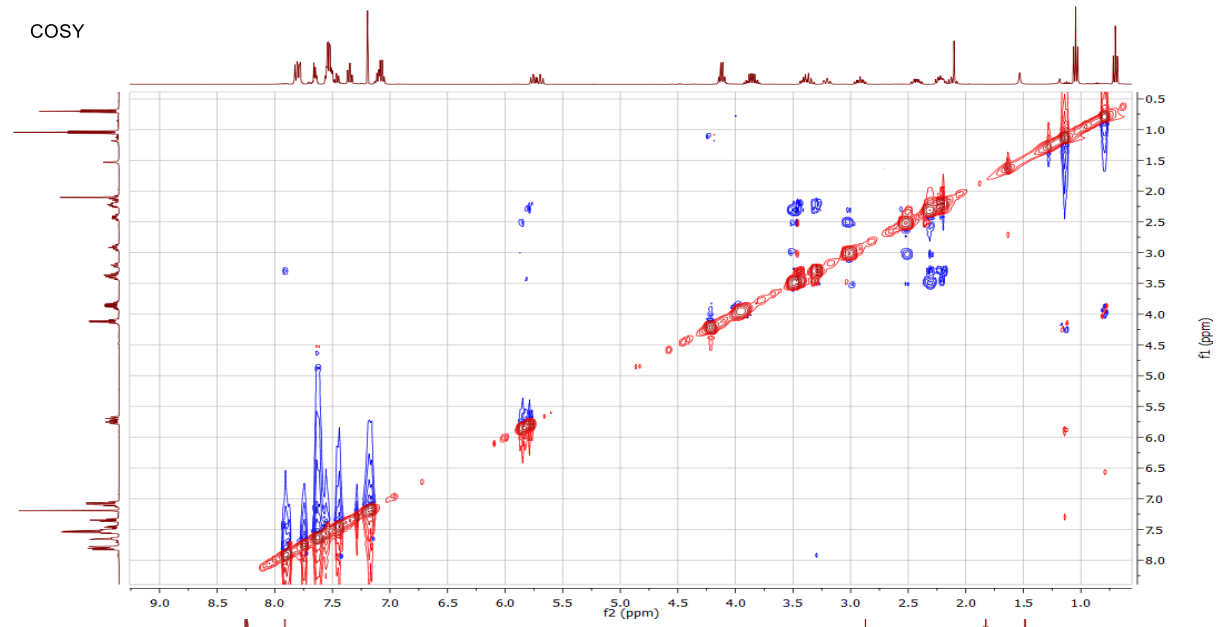

COSY
f2 (ppm)
f1 (ppm)

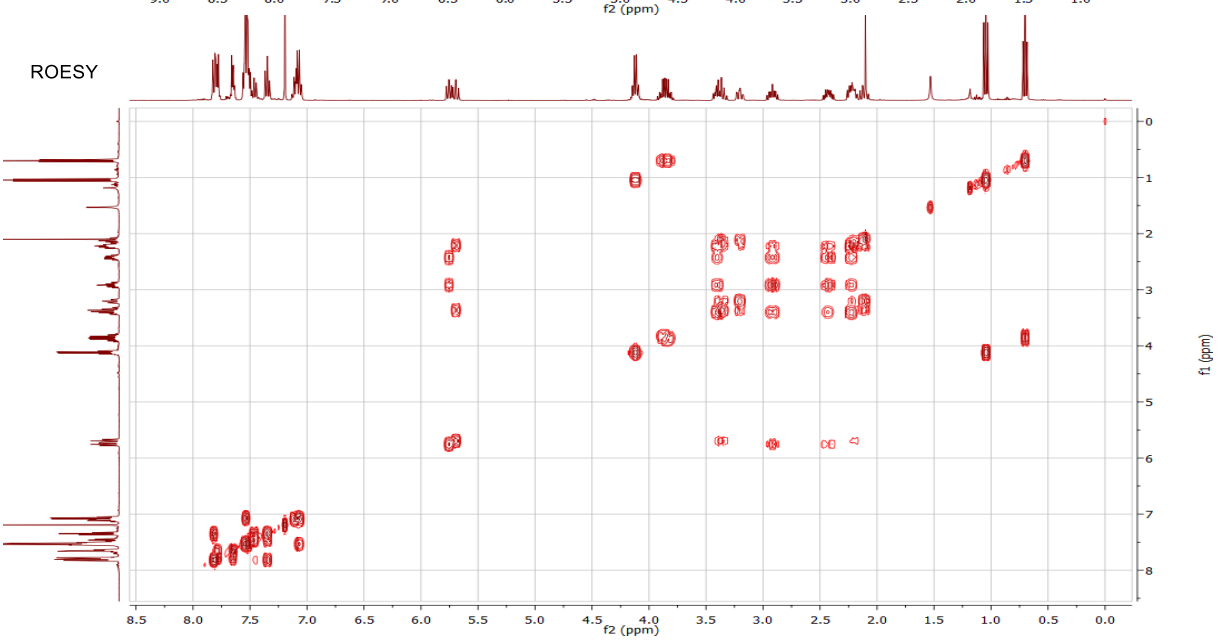

ROESY
f2 (ppm)
f1 (ppm)

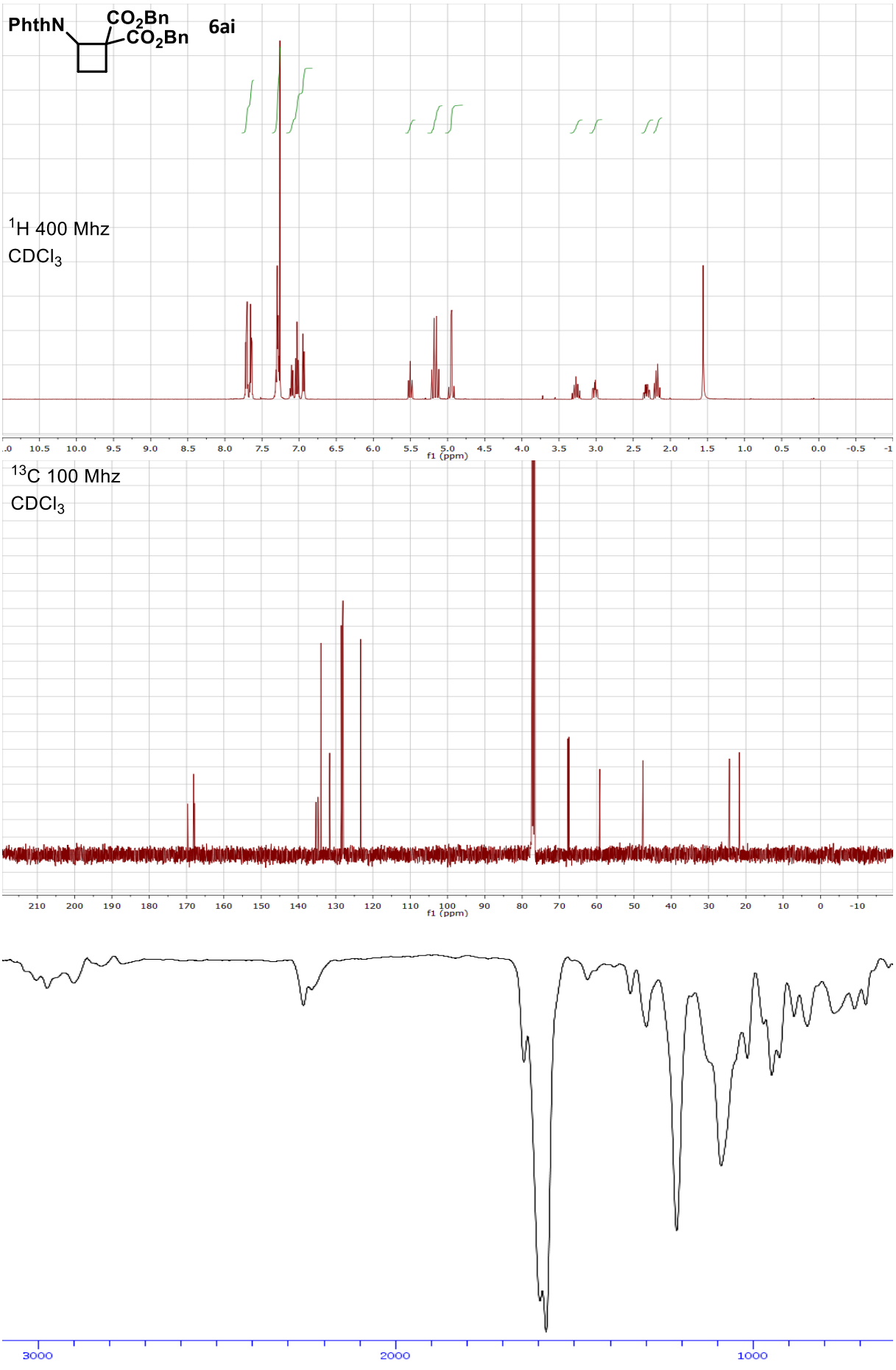

PhthN
CO2tBu
CO2Me
6ah
1H 400 Mhz
CDCl3
f1 (ppm)

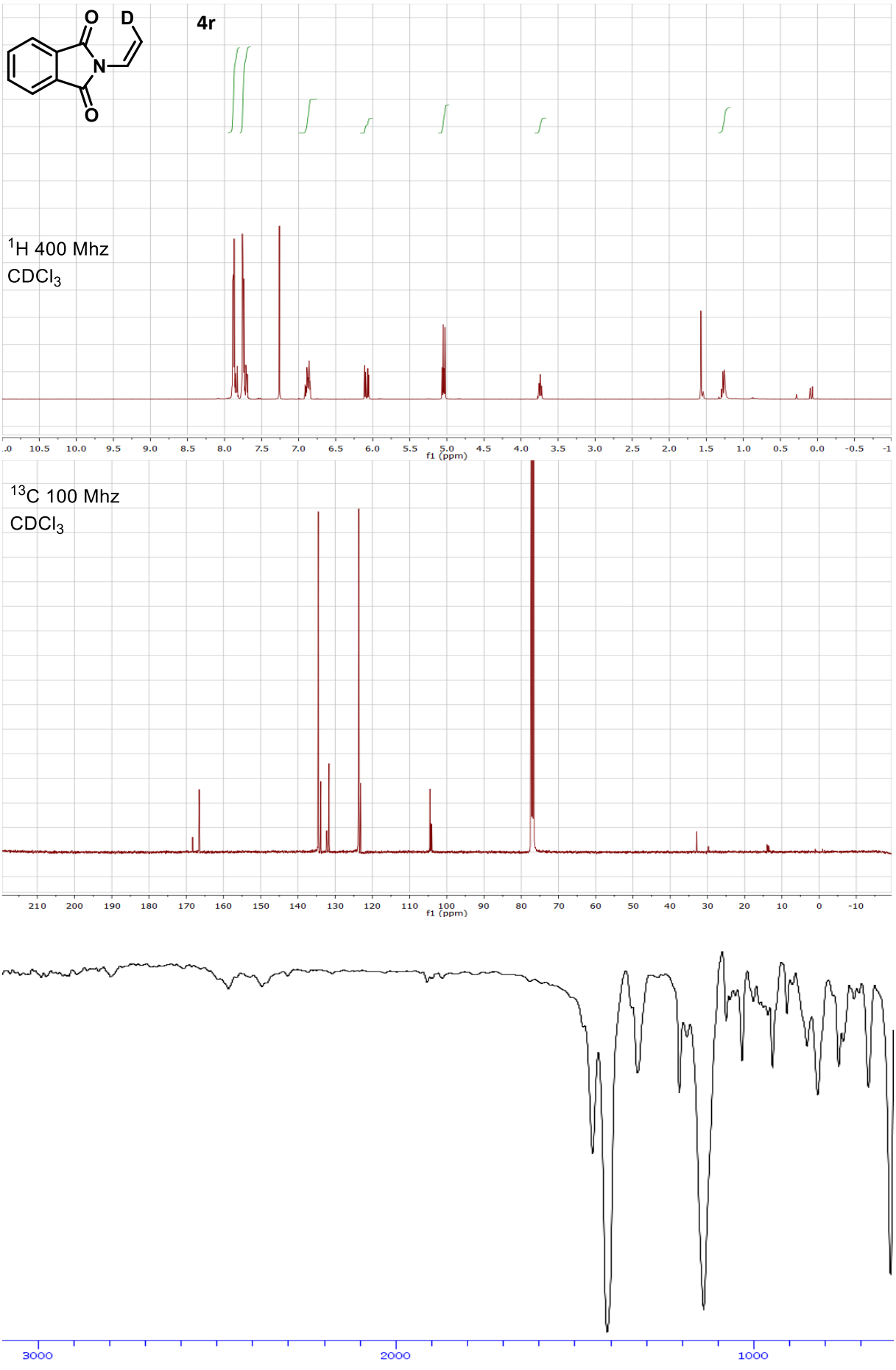

13C 100 Mhz
CDCl3
f1 (ppm)

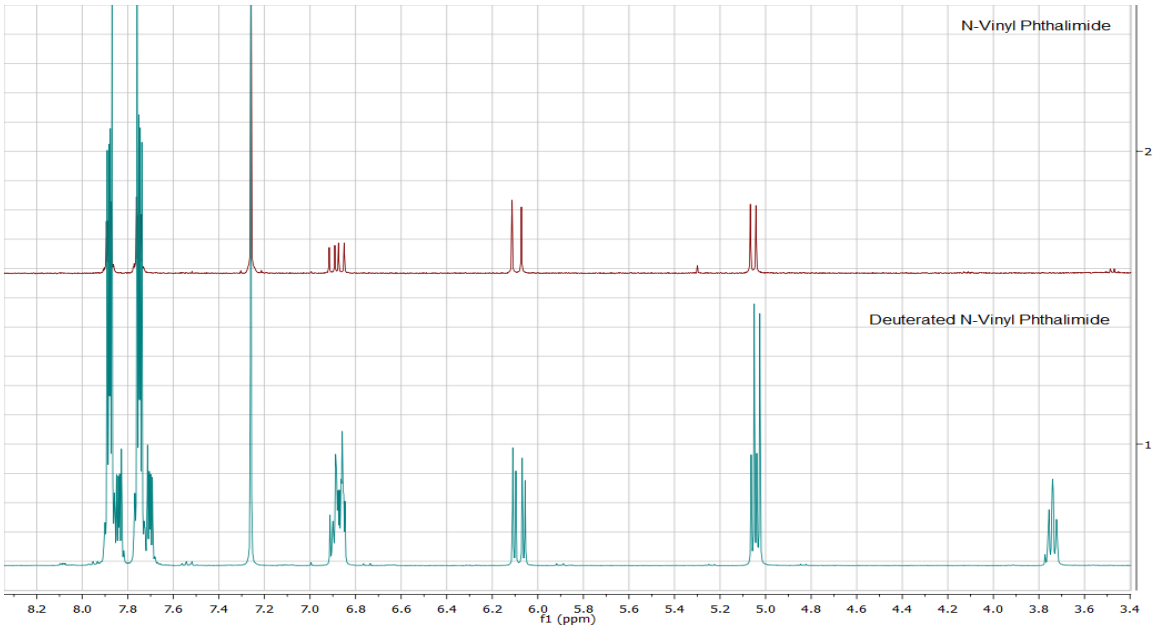

3000
2000
1000

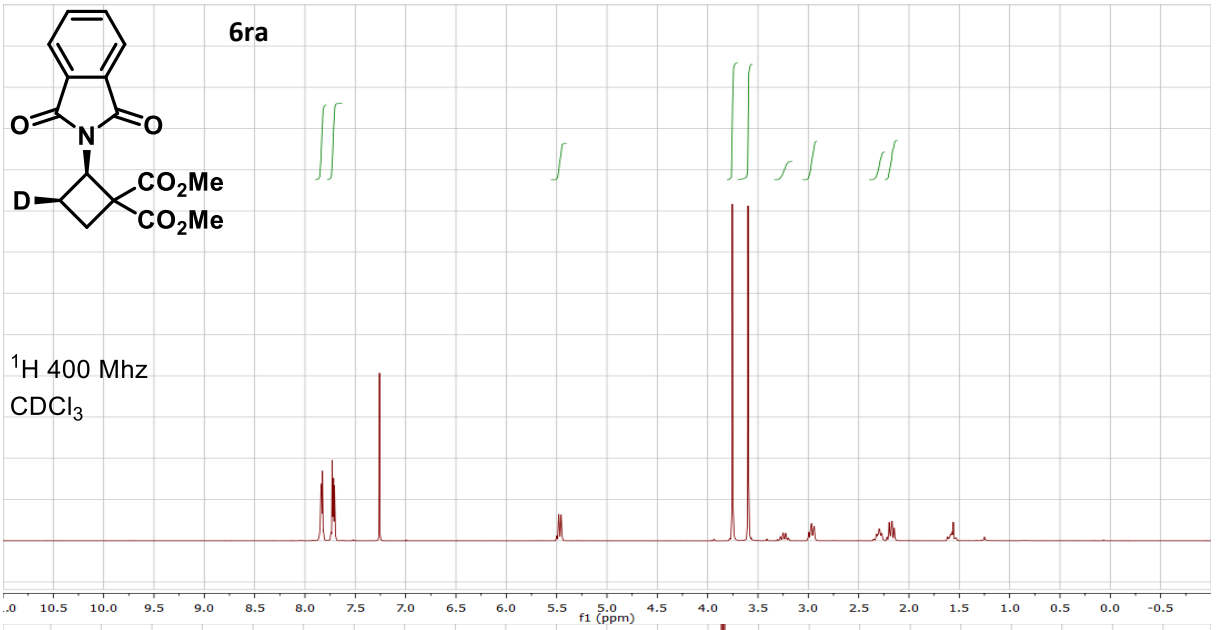

COSY
f2 (ppm)
f1 (ppm)

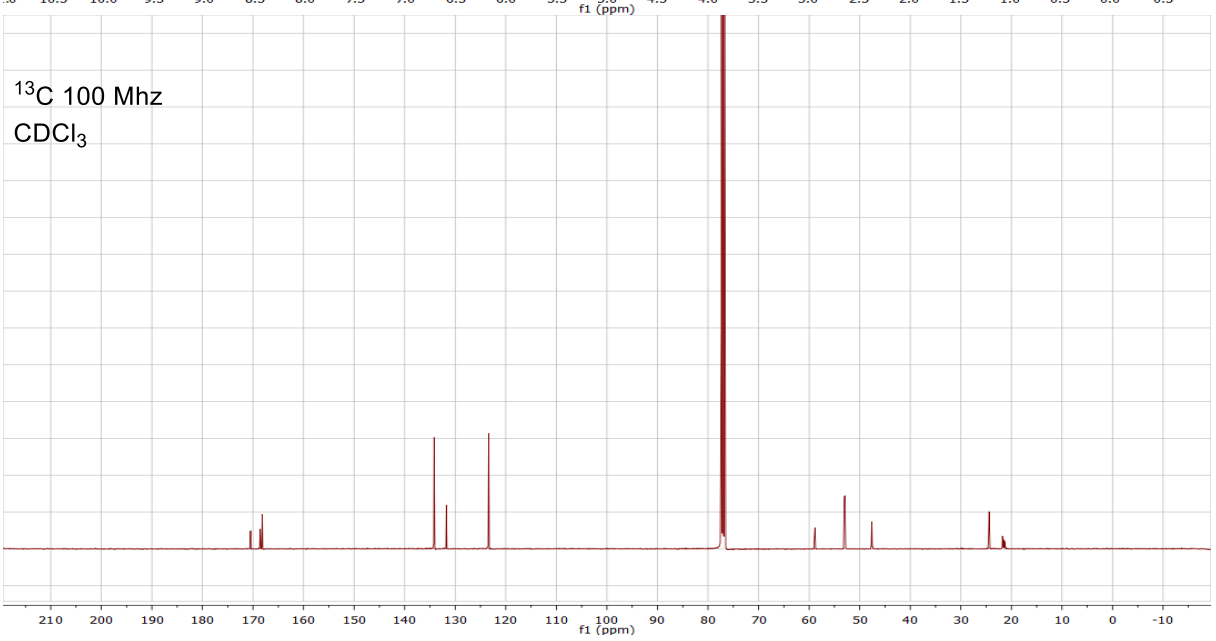

ROESY
f2 (ppm)
f1 (ppm)

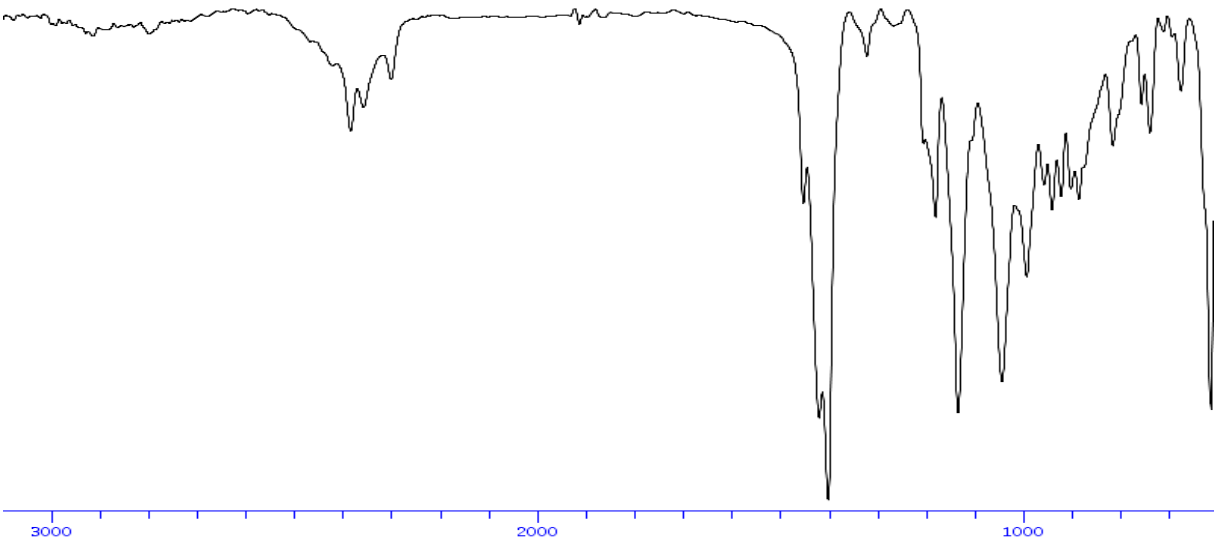

PhthN
CO2Bn
CO2Bn
6ai
1H 400 Mhz
CDCl3
f1 (ppm)
13C 100 Mhz
CDCl3
f1 (ppm)
3000
2000
1000

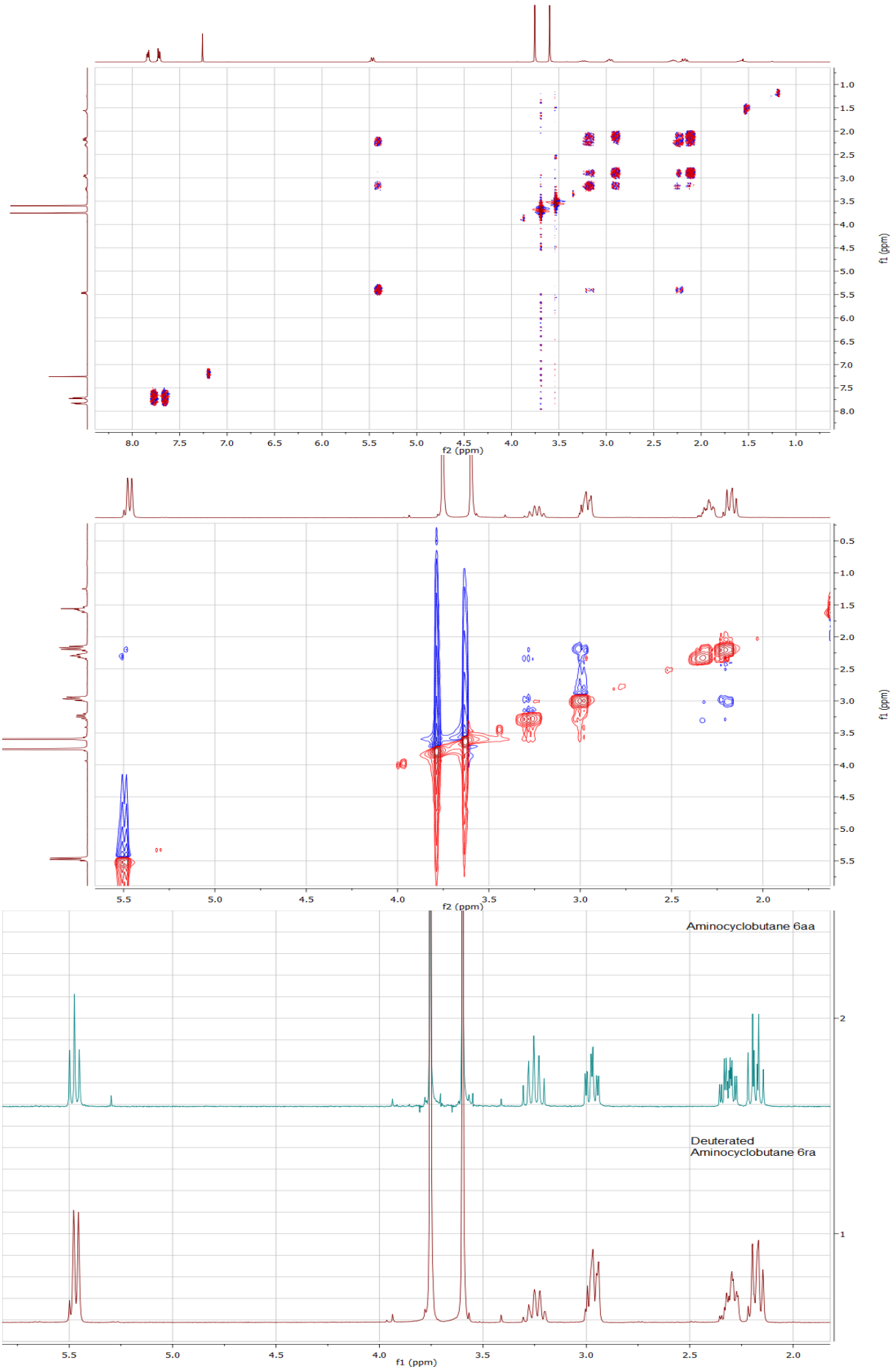

4r
O
D
N
O
1H 400 Mhz
CDCl3
f1 (ppm)
13C 100 Mhz
CDCl3
f1 (ppm)
3000
2000
1000

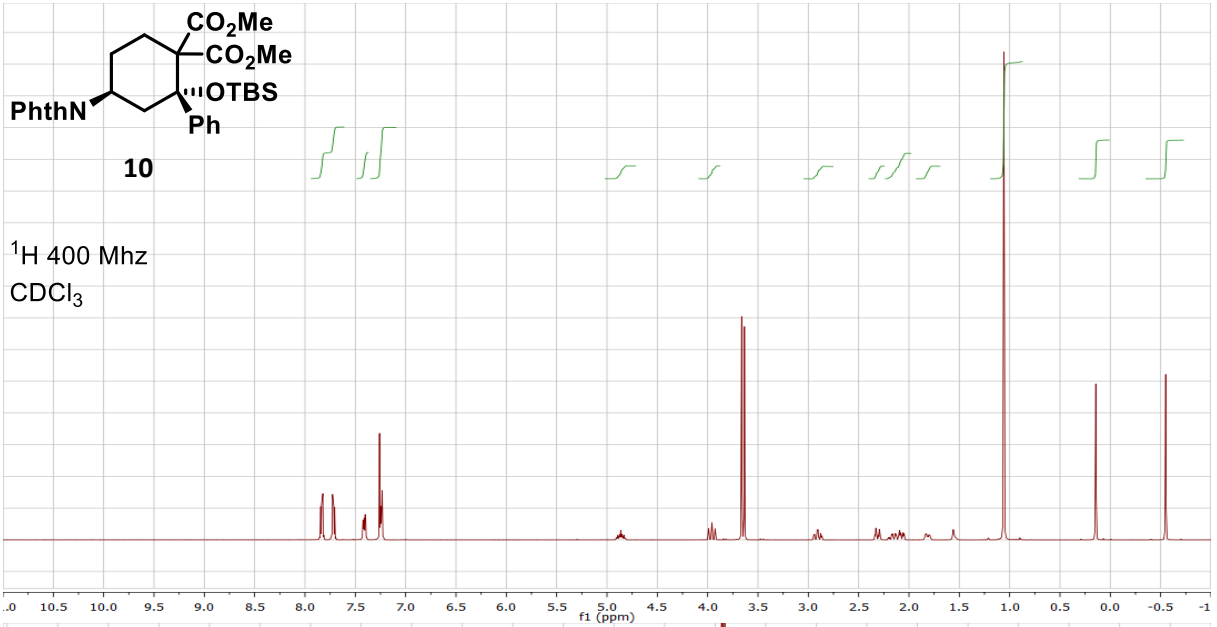

N-Vinyl Phthalimide
Deuterated N-Vinyl Phthalimide
2
1
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4
f1 (ppm)

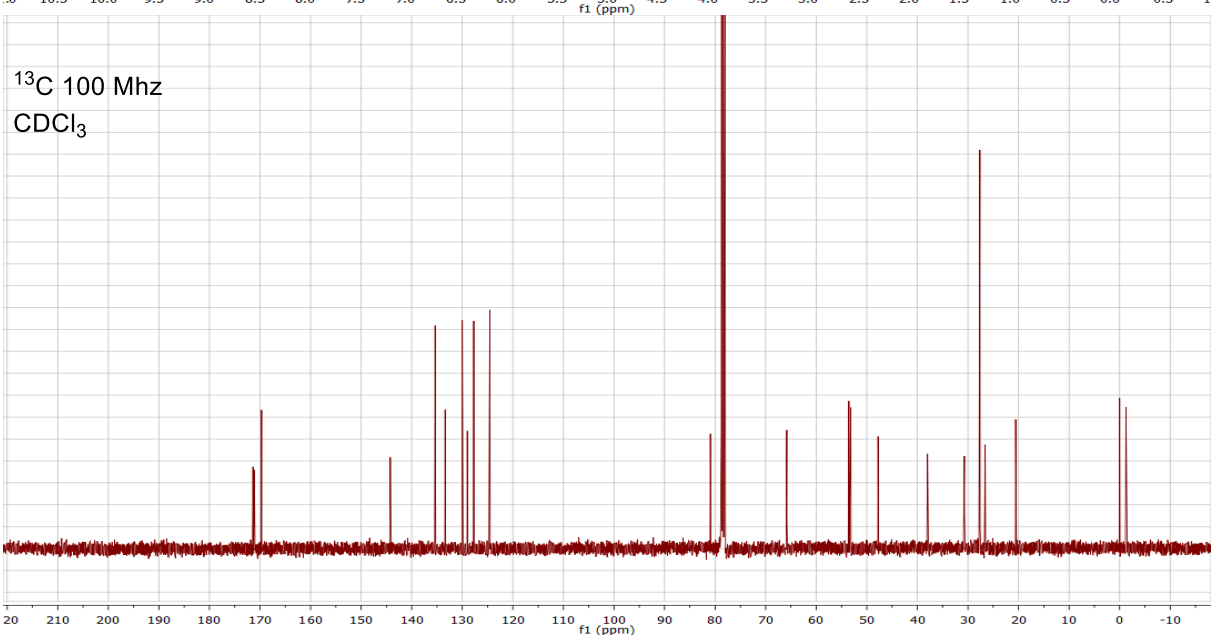

6ra
O
N
O
D
CO2Me
CO2Me
1H 400 Mhz
CDCl3
f1 (ppm)

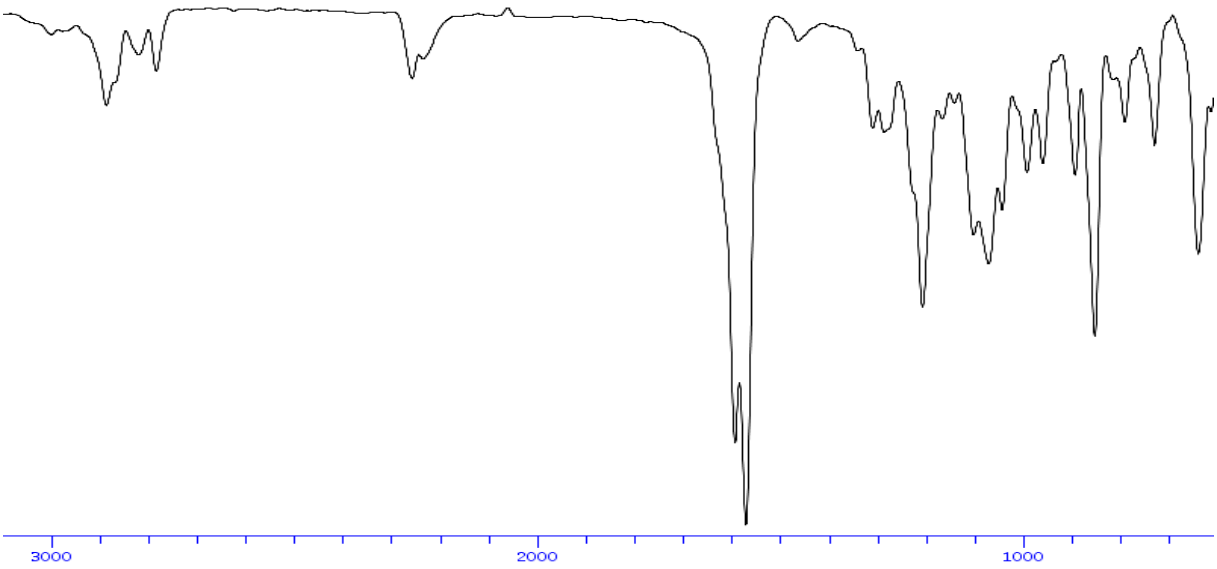

13C 100 Mhz
CDCl3
f1 (ppm)

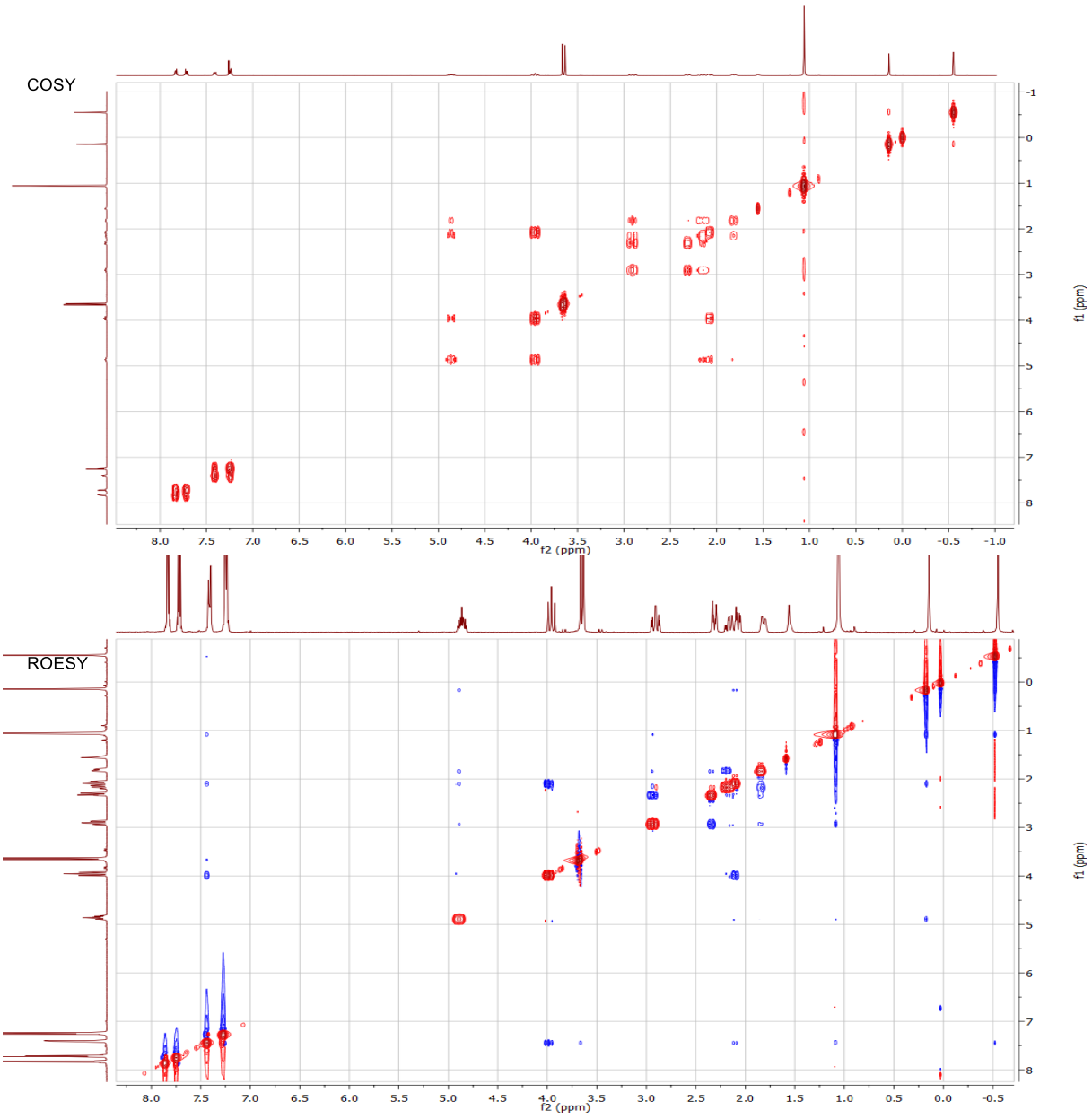

3000
2000
1000

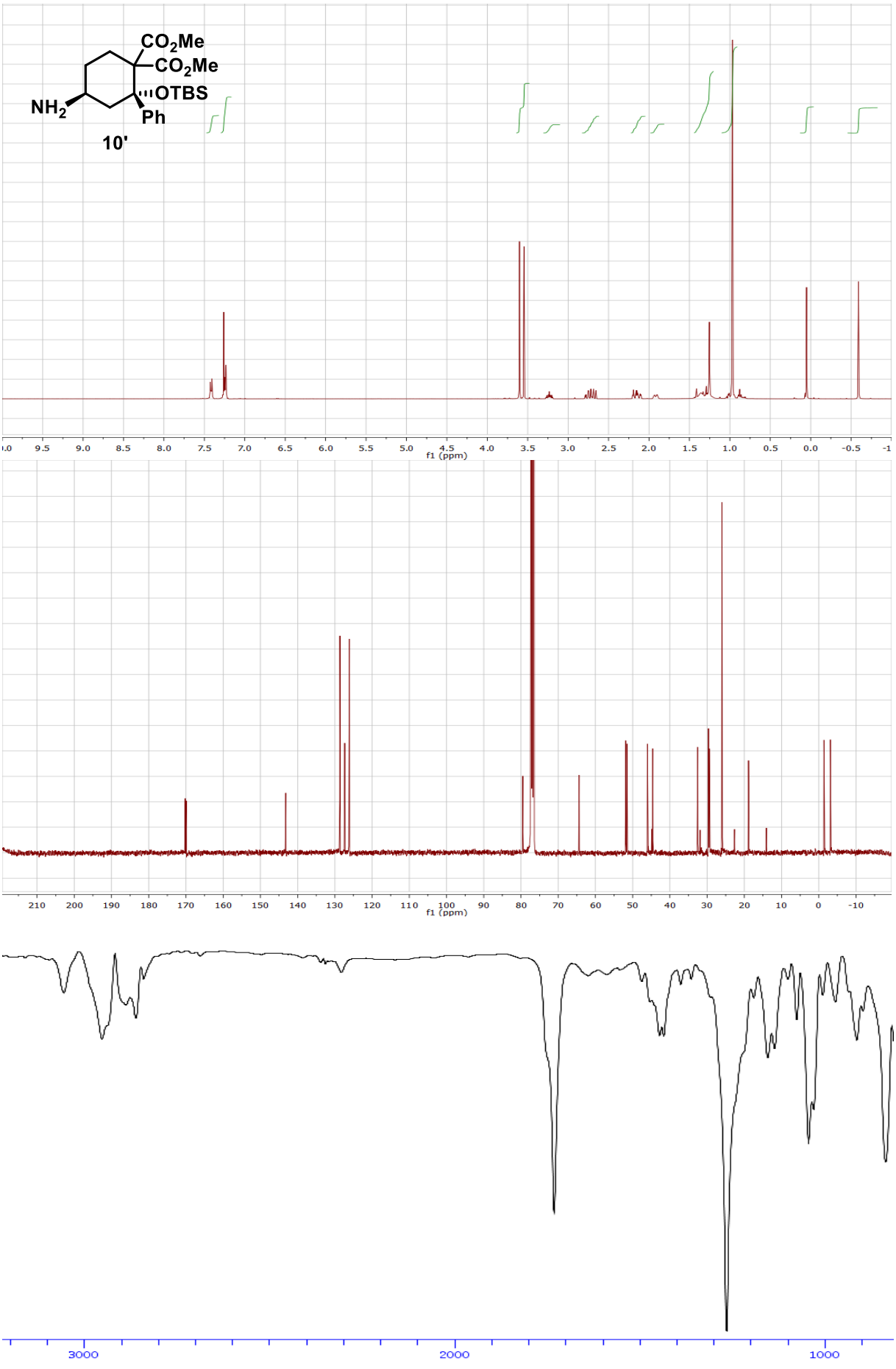

f2 (ppm)
f1 (ppm)
f2 (ppm)
f1 (ppm)
Aminocyclobutane 6aa
Deuterated
Aminocyclobutane 6ra
f1 (ppm)

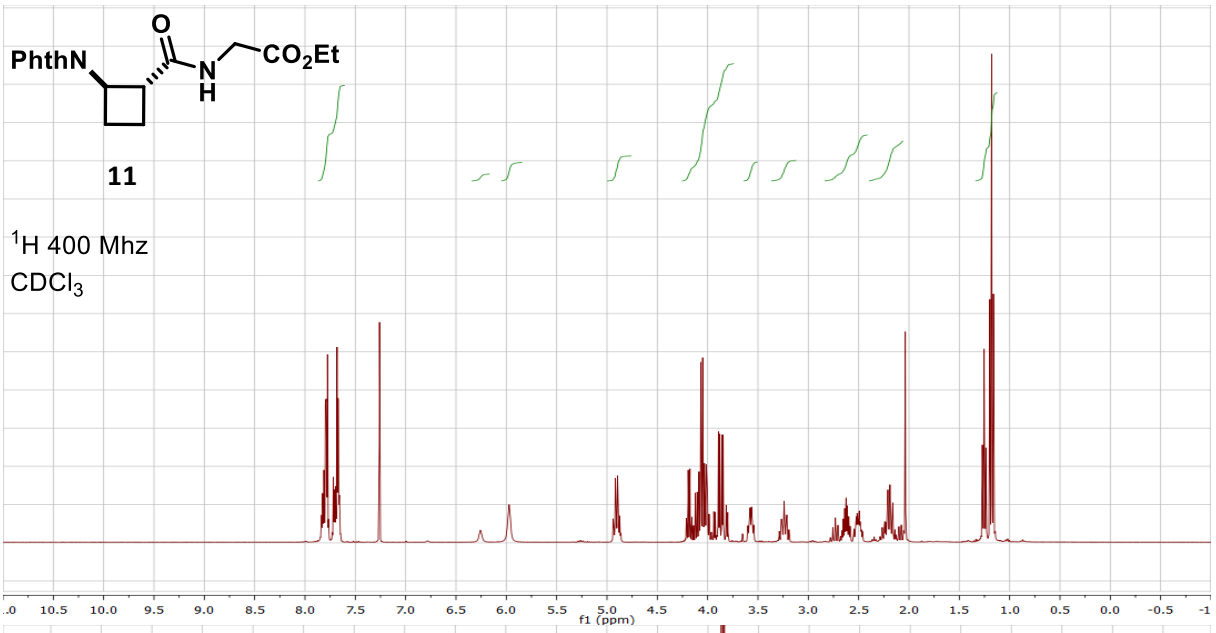

CO2Me
CO2Me
OTBS
PhthN
Ph
10
1H 400 Mhz
CDCl3
f1 (ppm)

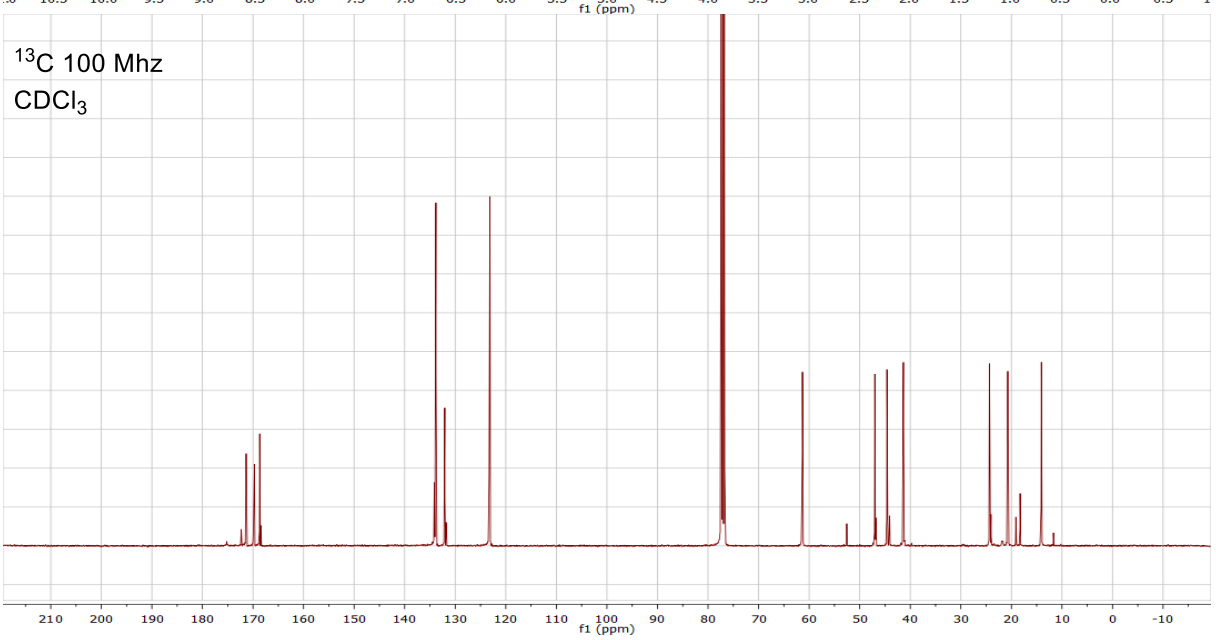

13C 100 Mhz
CDCl3
f1 (ppm)

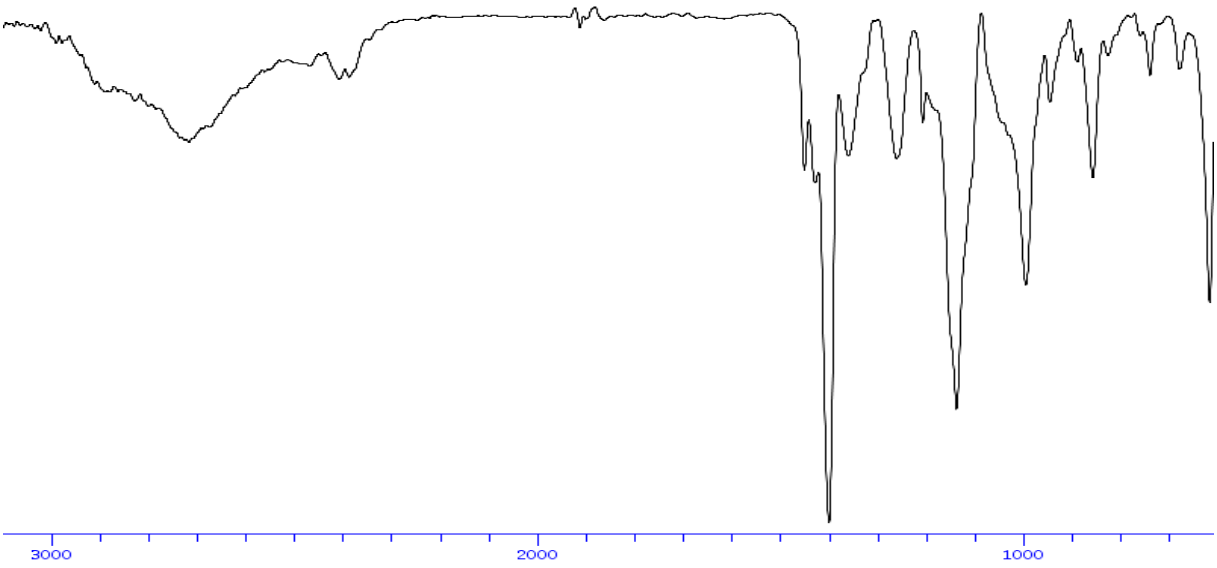

3000
2000
1000

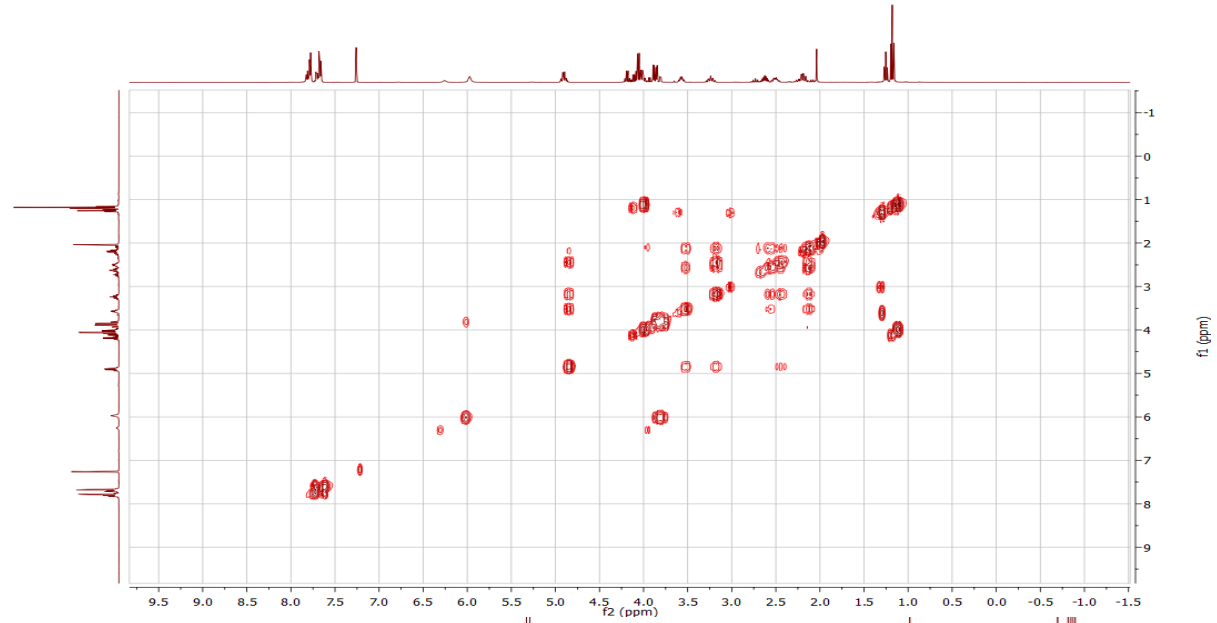

COSY
f2 (ppm)
f1 (ppm)
ROESY
f2 (ppm)
f1 (ppm)

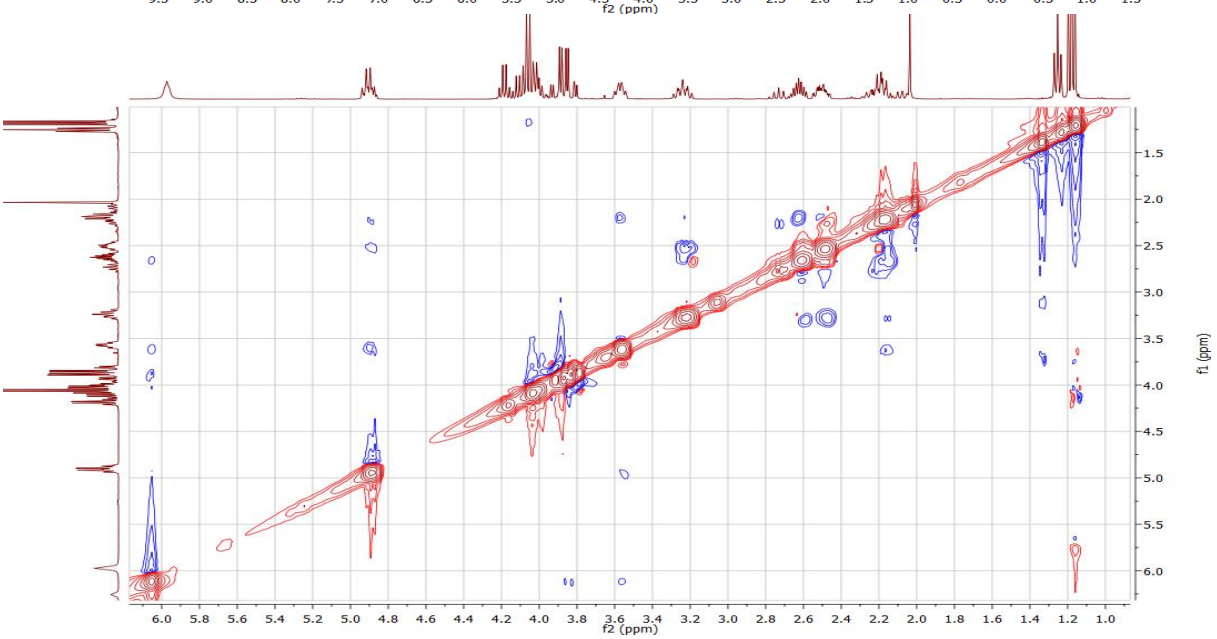

CO2Me
CO2Me
OTBS
NH2
Ph
10'
f1 (ppm)
f1 (ppm)
3000
2000
1000


PhthN
O
N
H
CO2Et
11
1H 400 Mhz
CDCl3
f1 (ppm)


13C 100 Mhz
CDCl3
f1 (ppm)


3000
2000
1000


f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)