

Supporting Information

[4+2] Annulations of Aminocyclobutanes.

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(89 pages)

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1. General Methods

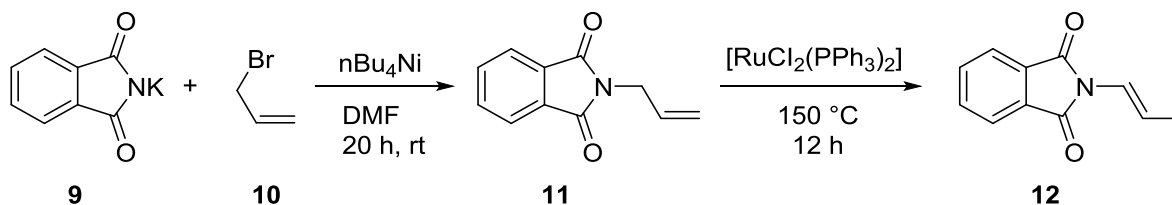
All reactions were carried out in oven- or flame- dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography, distilled technical grade solvents were used. THF, Et₂O, toluene, hexane and CH₂Cl₂ were dried by passage over activated alumina under nitrogen 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 or aluminium plates and visualized with UV light, permanganate CAN or p-anisaldehyde stains. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ¹H-NMR spectra were recorded at room temperature on a Bruker DPX-400 400 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm or DMSO signal at 2.50 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). ¹³C-NMR spectra were recorded with 1H-decoupling on a Bruker DPX-400 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm or DMSO signal at 39.5 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 Diastereoisomeric mixtures have been assigned by 2D NMR experiments including COSY/ROESY/HSQC/HMBC. Commercially available N-Vinyl Phthalimide [3485-84-5], N-Vinyl-2-pyrrolidone [88-12-0], Diethyl Ethylidenemalonate [1462-12-0], Benzaldehyde [100-52-7], 4-Chlorobenzaldehyde [104-88-1], 4-Methoxybenzaldehyde [123-11-5], 2-Methoxybenzaldehyde [135-02-4], and *trans*-Cinnamaldehyde [14371-10-9] were used.

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

2. Synthesis of starting materials

2.1 Synthesis of Enamides and Alkylidene Malonates

(*E*)-2-(Prop-1-en-1-yl)isoindoline-1,3-dione (**12**)



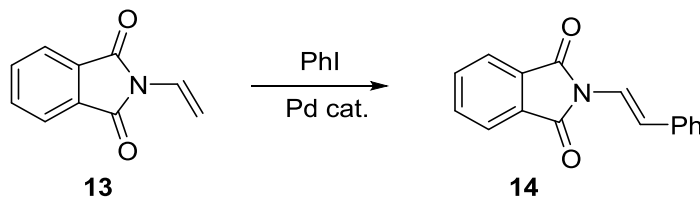
Following a modified procedure,² allyl bromide (**10**) (2.6 mL, 30 mmol, 1.1 eq) was added dropwise at room temperature to a suspension of potassium phthalimide (**9**) (5.0 g, 27 mmol, 1 eq) and Bu_4NI (0.50 g, 1.4 mmol, 0.05 eq) in DMF (10 mL). The mixture was stirred for 20 h at room temperature, 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 (**11**) (3.4 g, 18 mmol, 68% yield).

2-Allylisoindoline-1,3-dione (**11**) (2.0 g, 11 mmol, 1 eq) was added in a sealed tube under nitrogen atmosphere to $[\text{RuCl}_2(\text{PPh}_3)_2]$ (0.10 g, 0.11 mmol, 0.01 eq). The solids were heated at $150\text{ }^\circ\text{C}$ during 12 h 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). (*E*)-2-(prop-1-en-1-yl)isoindoline-1,3-dione (**12**) (1.15 g, 6.10 mmol, 58% yield) was collected as a yellow solid from the first recrystallization.

¹H 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, $\text{CH}=\text{CH}$), 1.85 (d, 3 H, $J = 5.1$ Hz, CH_3).

¹H NMR data match literature report.²

(*E*)-2-Styrylisoindoline-1,3-dione (**14**)



Following a reported procedure,³ a mixture of phenyl iodide (816 mg, 4.00 mmol, 1 eq), N-vinylphthalimide (**13**) (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 $120\text{ }^\circ\text{C}$ (oil bath temperature) in a pressure tube after 5 cycles of vacuum/ N_2 . After 1.5 h, 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 precipitated solid was recovered by filtration and rinsed with ethanol. (*E*)-2-styrylisoindoline-1,3-dione (**14**) (700 mg, 2.77 mmol, 69% yield) was obtained as a yellow powder.

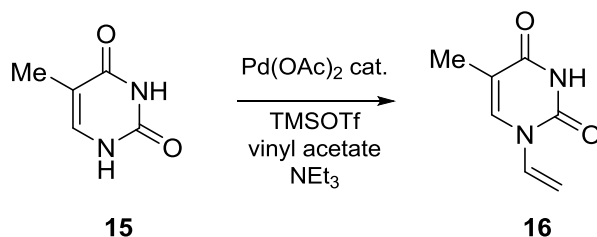
¹H NMR (400 MHz, CDCl_3) δ 7.91 (dd, 2 H, $J = 5.5, 3.1$ Hz, Phth), 7.77 (dd, 2 H, $J = 5.4, 3.1$ Hz, Phth), 7.66 (d, 1 H, $J = 15.2$ Hz, $\text{CH}=\text{CH}$), 7.51-7.45 (m, 2 H, ArH), 7.40-7.32 (m, 3 H, ArH), 7.30-7.24 (m, 1 H, $\text{CH}=\text{CH}$).

Data match literature report.³

² Stojanovic, A.; Renaud, P.; Schenk, K. *Helv. Chim. Acta*, **2004**, *81*, 268.

³ Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2008**, *350*, 1316.

1-Vinylthymine (16).



Following the described procedure of Racine et al.⁴, thymine (**15**) (0.50 g, 3.9 mmol, 1.0 eq), diacetoxypalladium (0.036 g, 0.16 mmol, 0.04 eq) were suspended in DMF (10 mL) in a flame-dried sealed microwave vial under nitrogen atmosphere. Vinyl acetate (0.82 g, 9.5 mmol, and 2.4 eq), triethylamine (1.3 mL, 9.5 mmol, 2.4 eq) and TMSOTf (1.7 mL, 9.5 mmol, and 2.4 eq) were added to the reaction mixture and stirred at 70 °C for 24 hours. The reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography, eluting with a mixture of ethyl acetate/ pentane (7:3). The pure 1-vinylthymine (**16**) (0.44 g, 2.8 mmol, 73% yield) was obtained as white solid.

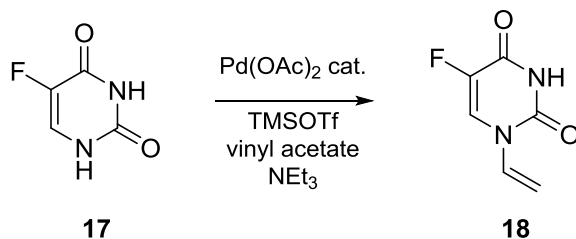
R_f 0.32 (3:7 Pentane/Ethyl acetate).

¹H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1 H, NH), 7.34 (d, *J* = 1.3 Hz, 1 H, thymine C=C-H), 7.20 (dd, *J* = 16.0, 9.1 Hz, 1 H, vinyl-CH), 5.07 (dd, *J* = 16.0, 2.2 Hz, 1 H, vinyl-CH₂), 4.92 (dd, *J* = 9.1, 2.2 Hz, 1 H, vinyl-CH₂), 1.99 (d, *J* = 1.3 Hz, 3 H, thymine-CH₃).

¹³C NMR (101 MHz, Chloroform-*d*) δ 163.4, 149.2, 134.6, 129.7, 112.2, 100.7, 12.7.

NMR values correspond to the literature.⁴

1-Vinylfluorouracil (18)



Following the described procedure of Racine et al.,⁴ fluorouracil (**17**) (0.52 g, 3.9 mmol, 1.0 eq) and diacetoxypalladium (0.036 g, 0.16 mmol, 0.04 eq) were suspended in DMF (10 mL) in a flame-dried sealed microwave vial under nitrogen atmosphere. Vinyl acetate (0.82 g, 9.5 mmol, 2.4 eq), triethylamine (1.3 mL, 9.5 mmol, 2.4 eq) and TMSOTf (1.7 mL, 9.5 mmol, 2.4 eq) were added to the reaction mixture and stirred at 70°C for 24 hours. The reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography, eluting with a mixture of ethyl acetate/ pentane (5:5). The pure 1-vinylfluorouracil (**18**) (0.31 g, 2.0 mmol, 50% yield) was obtained as white solid.

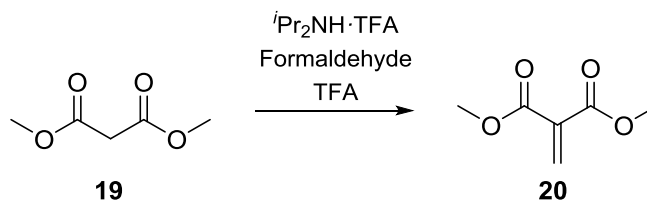
R_f 0.35 (6:4 Pentane/Ethyl acetate).

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.01 (s, 1H, N H), 8.43 (d, *J* = 7.1 Hz, 1 H, F-uracil C=C-H), 7.07 (ddd, *J* = 16.0, 9.2, 1.9 Hz, 1 H, vinyl-CH), 5.36 (dd, *J* = 15.9, 2.0 Hz, 1 H, vinyl-CH₂), 4.88 (dd, *J* = 9.2, 2.0 Hz, 1 H, vinyl-CH₂).

⁴ Racine, S.; de Nanteuil, F.; Serrano, E.; Waser, J. *Angew. Chem. Int. Ed.* **2014**, 53, 8484–8487.

¹H NMR values are in accordance with the spectra performed in chloroform in the literature.⁴

Dimethyl 2-methylenemalonate (**20**)



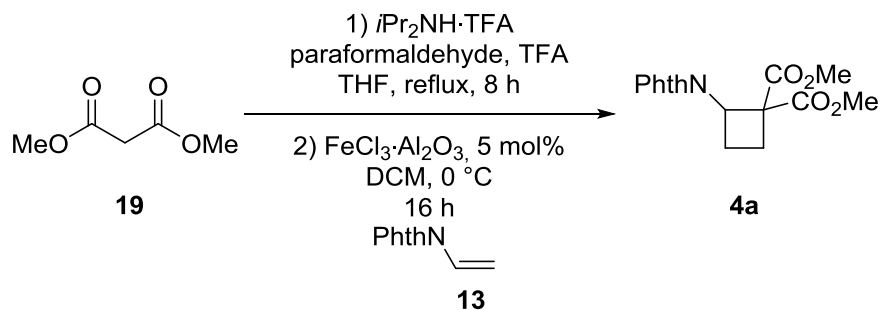
Following the described procedure of De Nanteuil et al.,⁵ paraformaldehyde (2.7 g, 90 mmol, 2.0 eq) and diisopropylamine 2,2,2-trifluoroacetate (9.7 g, 45 mmol, 1.0 eq) were added in a flame dried 250 mL round flask with a condenser. Then, tetrahydrofuran (65 mL), dimethyl malonate (**19**) (5.1 mL, 45 mmol, 1.0 eq) and trifluoroacetic acid (0.35 mL, 4.5 mmol, 0.1 eq) were added into the flask under nitrogen atmosphere and the suspension was stirred to reflux for 2 hours. Paraformaldehyde (2.7 g, 90 mmol, 2.0 eq) was added to the reaction mixture and the reflux was restarted for 12 hours. The reaction mixture was cooled to room temperature and THF was removed under reduced pressure. The crude product was dissolved in diethyl ether (25 mL) and filtrated trough cotton. The organic layer was washed two times with 1 M HCl (25 mL), the aqueous layers were combined and washed three times with diethyl ether (50 mL). The combined organic layers were dry over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude mixture containing **20** was obtained as colorless oil (2.5 g).

¹H NMR (400 MHz, Chloroform-*d*) δ 6.58 (s, 2 H, CH₂), 3.83 (s, 6 H, ester CH₃).

¹H NMR values correspond to the literature.⁵

2.2 Synthesis of Cyclobutanes

Dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**)



Following a reported procedure,⁵ dimethyl malonate (**19**) (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 2 h. Paraformaldehyde (0.695 mg, 23.1 mmol, 4 eq) was added and the reflux was continued for 6 h. 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 2-methylenemalonate crude (**20**) as colorless oil.

⁵ De Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed.* **2013**, 52, 9009–9013.

The iron trichloride supported on alumina (1.00 mmol/g, 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-vinylisindoline-1,3-dione (**13**) (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 (**20**) 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 **4a** (1.55 g, 4.89 mmol, 85% yield) as a colorless solid.

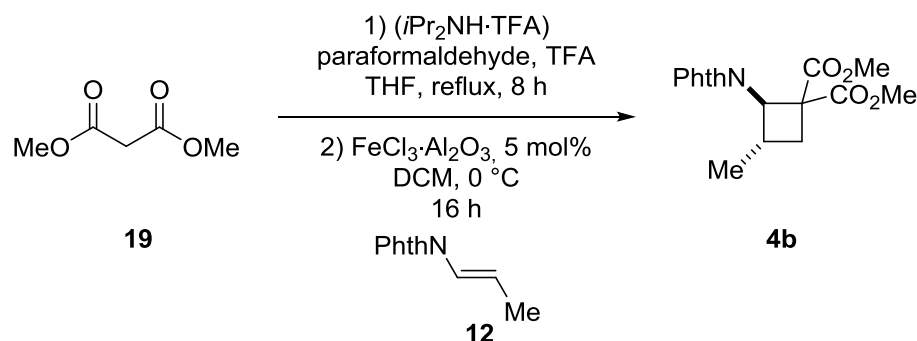
R_f 0.45 (1:1 Hexane/Ethyl acetate).

¹H NMR (400 MHz, CDCl₃) 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, CO₂CH₃), 2.98 (s, 3 H, CO₂CH₃), 2.58 (m, 1 H, CH₂), 2.25 (m, 1 H, CH₂), 1.48 (m, 1 H, CH₂), 1.33 (dt, 1 H, *J* = 13.6, 10.4 Hz, CH₂).

¹³C NMR (101 MHz, CDCl₃) 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.

Data match literature report.⁵

Dimethyl 2-(1,3-dioxoisindolin-2-yl)-3-methylcyclobutane-1,1-dicarboxylate (**4b**)



Following a reported procedure,⁵ dimethyl malonate (**19**) (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 2 h. Paraformaldehyde (0.640 mg, 21.4 mmol) was added and the reflux was continued for 6 h. 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 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 Na₂SO₄, filtered and concentrated under reduced pressure to give dimethyl 2-methylenemalonate crude as colorless oil.

The iron trichloride supported on alumina (1.00 mmol/g, 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)isindoline-1,3-dione (**12**) (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 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 **4b** (1.53 g, 4.62 mmol, 86% yield) as a colorless solid.

R_f 0.26 (7:3 Hexane/Ethyl acetate).

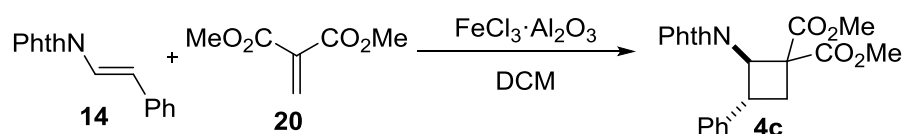
Mp 112.1-114.3 °C.

¹H NMR (400 MHz, CDCl₃) 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, CO₂CH₃ and C-H-CH₃), 3.60 (s, 3 H, CO₂CH₃), 3.00 (dd, 1H, *J* = 10.9, 9.3 Hz, CH₂), 1.74 (dd, 1 H, *J* = 11.5, 9.5 Hz, CH₂), 1.16 (d, 3 H, *J* = 6.6 Hz, CH₃).

¹³C NMR (101 MHz, CDCl₃) 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.

Data match literature report.⁵

Dimethyl 2-(1,3-dioxoisindolin-2-yl)-3-phenylcyclobutane-1,1-dicarboxylate (4c**)**



Following a slightly modified procedure,⁵ in the glovebox, iron trichloride supported on alumina (1.00 mmol/g, 282 mg, 0.282 mmol, 0.05 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (5 mL) was added and (*E*)-2-styrylisindoline-1,3-dione (**14**) (1.41 g, 5.64 mmol, 1 eq) was dissolved in dry dichloromethane (5 mL) and added to the iron trichloride. Dimethyl 2-methylenemalonate (**20**) (1.63 g, 11.3 mmol, 2 eq) was dissolved in dry dichloromethane (5 mL) and added dropwise over 2 h. When the addition was finished, the reaction was stirred for 4 h at room temperature. Then, dimethyl 2-methylenemalonate (406 mg, 2.82 mmol, 0.5 eq) was dissolved in dry dichloromethane (2 mL) and added in one portion. The reaction was stirred at reflux for 2 h, and then filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography (SiO₂, 9:1 to 7:3 Pentane/Ethyl Acetate) affording cyclobutane **4c** (1.74 g, 4.42 mmol, 78% yield) as a colorless oil.

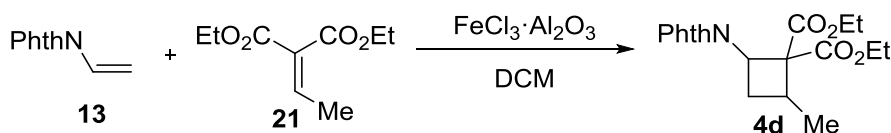
R_f 0.28 (7:3 Hexane/Ethyl acetate).

¹H NMR (400 MHz, CDCl₃) 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, CO₂CH₃), 3.65 (s, 3 H, CO₂CH₃), 3.25 (ddd, 1 H, *J* = 7.7, 6.5, 0.4 Hz, CH₂), 2.21 (dd, 1 H, *J* = 7.8, 6.9 Hz, CH₂).

¹³C NMR (101 MHz, CDCl₃) 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.

Data match literature report.⁵

Diethyl 2-(1,3-dioxoisindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (4d**)**



Following a slightly modified procedure,⁵ in the glovebox, iron trichloride supported on alumina (1.00 mmol/g, 289 mg, 0.289 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 (3 mL) was added. Diethyl 2-

ethylidenemalonate (**21**) (1.07 g, 5.77 mmol, 2 eq) and 2-vinylisoindoline-1,3-dione (**13**) (500 mg, 2.89 mmol, 1 eq) were dissolved in dry dichloromethane (4 mL). The solution was then added dropwise to the iron trichloride. The reaction was stirred at 40 °C for 16 h. Then 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 (SiO₂, 8:2 Pentane/Ethyl Acetate), affording cyclobutane **4d** (806 mg, 2.24 mmol, 78 % yield, 1.1:1 dr determined by integration of the peaks at 5.58 (*maj*) and 4.91 (*min*) in the crude ¹H NMR, as a pale yellow oil.

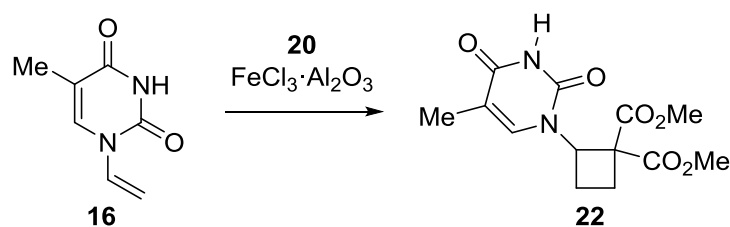
R_f 0.25 (7:3 Hexane/Ethyl acetate).

¹H NMR (400 MHz, CDCl₃) on a 1.1(*maj*):1(*min*) mixture δ 7.84-7.79 (m, 3.8 H, Phth *maj* + *min*), 7.72-7.67 (m, 3.8 H, Phth *maj* + *min*), 5.58 (ddd, *J* = 10.0, 8.3, 1.2 Hz, 1 H, N-C-H *min*), 4.91 (dd, *J* = 10.9, 8.7 Hz, 0.9 H, N-C-H *min*), 4.27-4.18 (m, 3.8 H, CO₂CH₂ *maj* + *min*), 4.17- 3.91 (m, 3.8 H, CO₂CH₂ *maj* + *min*), 3.65-3.54 (m, 1 H, CH cyclobutane *maj*), 3.27-3.12 (m, 1.9 H, CH₂ cyclobutane *maj* + *min*), 2.78 (ddq, *J* = 10.7, 8.1, 7.0 Hz, 0.9 H, CH cyclobutane *min*), 2.46 (dt, *J* = 10.8, 8.5 Hz, 0.9 H, CH₂ cyclobutane *min*), 1.98 (ddd, *J* = 11.7, 10.0, 5.4 Hz, 1 H, CH₂ cyclobutane *maj*), 1.32 (d, *J* = 7.0 Hz, 2.7 H, CH₃ *min*), 1.28-1.21 (m, 5.7 H, CO₂CH₂CH₃ *maj* + *min*), 1.14 (d, *J* = 7.3 Hz, 3 H, CH₃ *maj*), 1.05 (t, *J* = 7.1 Hz, 2.7 H, CO₂CH₂CH₃ *min*), 0.90 (t, *J* = 7.1 Hz, 3 H, CO₂CH₂CH₃ *maj*).

¹³C NMR (101 MHz, CDCl₃) 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, 61.7,⁶ 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.

Data match literature report.⁵

Dimethyl 2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (**22**)



Following an adapted described procedure of De Nanteuil et al.,⁵ 5-methyl-1-vinylpyrimidine-2,4(1H,3H)-dione (**16**) (0.43 g, 2.9 mmol, 1.0 eq) and iron trichloride supported on alumina (1.0 mmol/g, 0.57 g, 0.57 mmol, 0.2 eq) were added in a flame dried microwave vial under nitrogen atmosphere. Then, dry dichloromethane (7 mL) and a solution of crude freshly prepared dimethyl 2-methylenemalonate (**20**) (0.82 g, 5.7 mmol, 2.0 eq) in dichloromethane (3 mL) were added into the vial and the reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was filtrated over a pad of alumina eluting with ethyl acetate (25 mL) and concentrated under reduced pressure. The crude mixture was purified via column chromatography, eluting with a mixture of ethyl acetate/ pentane (6:4 to 9:1). The pure product **22** (0.36 g, 1.2 mmol, 43% yield) was obtained as a white solid.

R_f 0.21 (2 :8 Pentane/Ethyl acetate).

Mp 180.4- 182.1 °C.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 1 H, NH), 7.05 (d, *J* = 1.3 Hz, 1 H, thymine C=C-H), 5.33 (t, *J* = 9.2 Hz, 1 H, cyclobutane-CH), 3.77 (s, 3 H, ester CH₃), 3.69 (s, 3 H, ester CH₃), 2.79 – 2.67 (m, 2 H, cyclobutane-CH₂), 2.35 (q, *J* = 8.5 Hz, 1 H, cyclobutane-CH₂), 2.27 – 2.16 (m, 1 H, cyclobutane-CH₂), 1.93 (d, *J* = 1.2 Hz, 3 H, thymine-CH₃).

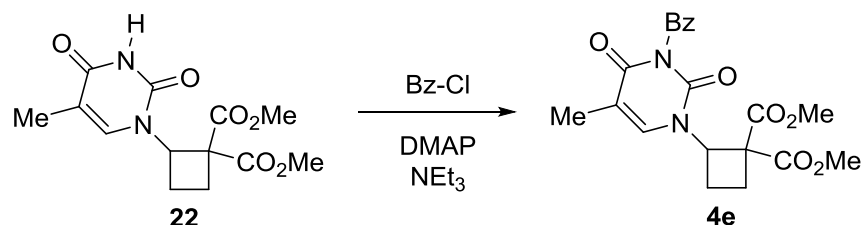
⁶ Two peaks under this signal as determined by HMBC.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.0, 168.8, 163.9, 151.0, 137.7, 110.3, 59.1, 55.0, 53.2, 53.1, 23.7, 22.8, 12.5.

IR 3190 (w), 3034 (w), 2958 (w), 2361 (m), 1733 (s), 1690 (s), 1439 (w), 1278 (m), 1113 (w), 915 (w), 735 (w).

HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{NaO}_6^+ [\text{M}+\text{Na}]^+$ 319.0901, found 319.0904.

Dimethyl 2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (4e).



Following an adapted described procedure of Racine et al.,⁴ in a flame dried microwave vial under nitrogen atmosphere, cyclobutane **22** (0.32 g, 1.1 mmol, 1.0 eq) and dimethyl-4-aminopyridine (0.13 g, 1.1 mmol, 1.0 eq) were dissolved in dry dichloromethane (10 mL). Then, triethylamine (0.60 mL, 4.3 mmol, 4.0 eq) was added and the solution was cooled to 0 °C. Benzoyl chloride (0.38 mL, 3.2 mmol, 3.0 eq) was added dropwise and the reaction mixture was stirred at room temperature for 14 hours. A saturated solution of NaHCO_3 (8 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with 1 M HCl (2 x 40 mL) and with water (30 mL), dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with a mixture of pentane/ ethyl acetate (4:6 to 2:8). The pure product **4e** (0.37 g, 0.93 mmol, 86% yield) was obtained as colorless foam.

R_f 0.32 (4:6 Pentane/Ethyl acetate).

Mp 153.8-155.4°C.

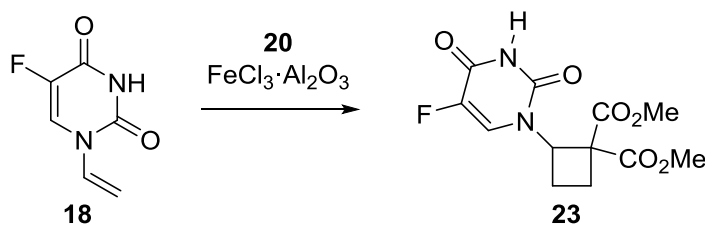
^1H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.90 (m, 2 H, Ar-H), 7.65 – 7.59 (m, 1 H, Ar-H), 7.50 – 7.44 (m, 2 H, Ar-H), 7.16 (d, J = 1.2 Hz, 1 H, thymine C=C-H), 5.17 (t, J = 9.5 Hz, 1 H, cyclobutane-CH), 3.69 (s, 3 H, ester CH_3), 3.66 (s, 3 H, ester CH_3), 2.94 – 2.82 (m, 1 H, cyclobutane- CH_2), 2.74 (td, J = 11.0, 3.1 Hz, 1 H, cyclobutane- CH_2), 2.35 (dtd, J = 11.6, 8.8, 3.1 Hz, 1 H, cyclobutane- CH_2), 2.18 (dt, J = 11.7, 8.9 Hz, 1 H, cyclobutane- CH_2), 1.95 (d, J = 1.2 Hz, 3 H, thymine- CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2, 168.9, 168.7, 162.8, 150.1, 138.7, 135.0, 131.6, 130.7, 129.1, 110.4, 58.8, 56.9, 53.3, 53.2, 23.9, 22.7, 12.6.

IR 3006 (w), 2959 (w), 2358 (w), 2257 (w), 1737 (s), 1702 (m), 1655 (s), 1438 (m), 1266 (s), 1107 (m), 984 (w), 914 (w), 733 (s).

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{NaO}_7^+ [\text{M}+\text{Na}]^+$ 423.1163; found 423.1168.

Dimethyl 2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (23)



Following an adapted described procedure of De Nanteuil et al.,⁵ 5-fluoro-1-vinylpyrimidine-2,4(1H,3H)-dione (**18**) (0.60 g, 3.8 mmol, 1.0 eq) and iron trichloride supported on alumina (1.0 mmol/g, 0.77 g, 0.77 mmol, 0.2 eq) were added in a flame dried microwave vial under nitrogen atmosphere. Then, dry dichloromethane (8 mL) and a solution of crude freshly prepared dimethyl 2-methylenemalonate (**20**) (2.2 g, 15 mmol, 4.0 eq) in dichloromethane (2 mL) were added into the vial and the reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was filtrated over a pad of alumina eluting with ethyl acetate (50 mL) and concentrated under reduced pressure. The crude mixture was purified via column chromatography, eluting with a mixture of ethyl acetate/ pentane (5:5 to 2:8). The pure product **23** (0.78 g, 2.6 mmol, 67% yield) was obtained as a colorless oil.

R_f 0.28 (4:6 Pentane/Ethyl acetate).

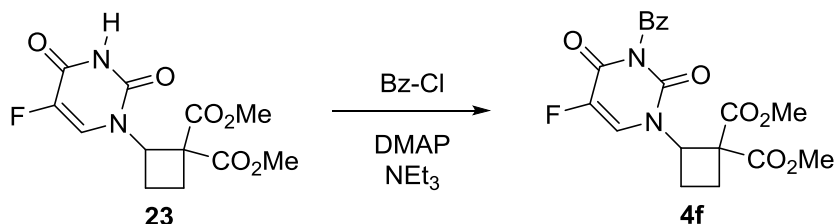
¹H NMR (400 MHz, Chloroform-*d*) δ 9.54 (s, 1 H, NH), 7.36 (d, *J* = 6.1 Hz, 1 H, F-uracil C=C-H), 5.28 (t, *J* = 9.0 Hz, 1 H, cyclobutane-CH), 3.78 (s, 3 H, ester CH₃), 3.73 (s, 3 H, ester CH₃), 2.68 – 2.61 (m, 2 H, cyclobutane-CH₂), 2.41 – 2.32 (m, 1 H, cyclobutane-CH₂), 2.32 – 2.25 (m, 1 H, cyclobutane-CH₂).

¹³C NMR (101 MHz, Chloroform-*d*) δ 169.7, 168.8, 156.8 (d, *J* = 26.7 Hz), 149.7, 140.2 (d, *J* = 237.5 Hz), 126.3 (d, *J* = 33.7 Hz), 59.0, 55.2, 53.3, 53.3, 23.7, 23.0.

IR 3211 (w), 3085 (w), 2960 (w), 2362 (w), 2336 (w), 1726 (s), 1439 (w), 1361 (w), 1273 (m), 1110 (w), 915 (w), 735 (m).

HRMS (ESI) calcd for C₁₂H₁₃FN₂NaO₆⁺ [M+Na]⁺ 323.0650; found 323.0654.

Dimethyl 2-(3-benzoyl-5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (4f**)**



Following an adapted described procedure of Racine et al.,⁴ in a flame dried microwave vial under nitrogen atmosphere, **23** (0.70 g, 2.3 mmol, 1.0 eq) and dimethyl-4-aminopyridine (0.28 g, 2.3 mmol, 1.0 eq) were dissolved in dry dichloromethane (12 mL). Triethylamine (1.3 mL, 9.3 mmol, 4.0 eq) was added and the solution was cooled to 0°C. Then, benzoyl chloride (0.81 mL, 6.9 mmol, 3.0 eq) was added dropwise and the reaction mixture was stirred at room temperature for 16 hours. A saturated solution of NaHCO₃ (8 mL) was added to the reaction mixture and the layer were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with 1 M HCl (2 x 40 mL) and with water (30 mL), dried over MgSO₄ and concentrated under reduced pressure. The pure product **4f** (0.61 g, 1.5 mmol, 65%) was obtained as colorless foam.

R_f 0.55 (4:6 Pentane/Ethyl acetate).

Mp 60.9- 62.5°C.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.89 (m, 2 H, Ar-H), 7.66 – 7.59 (m, 1 H, Ar-H), 7.50 – 7.43 (m, 3 H, Ar-H and F-uracil C=C-H), 5.12 (t, *J* = 9.4 Hz, 1 H, cyclobutane-CH), 3.69 (s, 3 H, ester CH₃), 3.64 (s, 3 H, ester CH₃), 2.73 (q, *J* = 10.0 Hz, 1 H, cyclobutane-CH₂), 2.66 – 2.58 (m, 1 H, cyclobutane-CH₂), 2.33 (dtd, *J* = 10.6, 8.4, 2.4 Hz, 1 H, cyclobutane-CH₂), 2.23 (dt, *J* = 11.6, 8.9 Hz, 1 H, cyclobutane-CH₂).

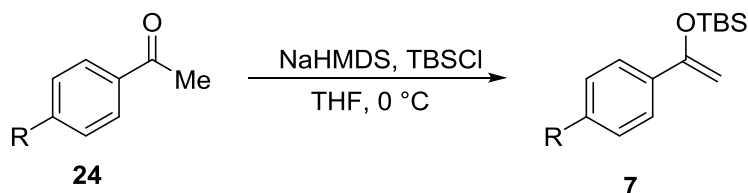
¹³C NMR (101 MHz, Chloroform-*d*) δ 169.8, 168.7, 167.1, 156.3 (d, *J* = 27.1 Hz), 148.6, 139.8 (d, *J* = 239.4 Hz), 135.5, 131.0, 130.9, 129.3, 127.1 (d, *J* = 33.6 Hz), 58.7, 56.8, 53.4, 53.3, 23.9, 22.8.

IR 3090 (w), 3009 (w), 2958 (w), 2361 (w), 2262 (w), 1723 (s), 1668 (s), 1598 (w), 1445 (m), 1357 (w), 1266 (s), 1106 (m), 982 (w), 912 (m), 851 (w), 732 (s).

HRMS (ESI) calcd for $C_{19}H_{17}N_2FNaO_7^+$ $[M+Na]^+$ 427.0917; found 427.0920.

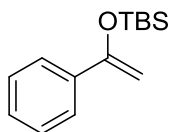
2.3 Synthesis of Enol Ethers

General procedure for the synthesis of TBS enol ethers (GP1)



Ketone **24** (1 eq) is dissolved in dry THF (20 mL) under nitrogen atmosphere and cooled down to 0 °C. NaHMDS (1.2 eq, 1.9 M in THF) is added dropwise. The orange solution is stirred at room temperature for 1 hour and then cooled to 0 °C. The chlorosilane (1.2 eq) is dissolved in THF (3 mL) and added dropwise. The reaction is stirred at room temperature for 2 hours and then concentrated under reduced pressure. The crude oil is filtered through a silica plug, eluting with 250 mL hexanes, concentrated under reduced pressure and purified by bulb to bulb distillation.

Tert-butyldimethyl((1-phenylvinyl)oxy)silane (**7a**)



Acetophenone (**24a**) (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 (**7a**) (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.

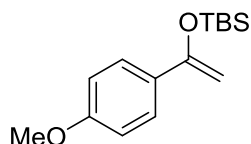
1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.60 (m, 2 H, Ar), 7.39-7.29 (m, 3 H, Ar), 4.89 (d, 1 H, J = 1.7 Hz, $C=CH_2$), 4.42 (d, 1 H, J = 1.7 Hz, $C=CH_2$), 1.00 (s, 9 H, $Si(CH_3)_2C(CH_3)_3$), 0.21 (s, 6 H, $Si(CH_3)_2C(CH_3)_3$).

^{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.⁷

Tert-butyl(1-(4-methoxyphenyl)vinyl)oxydimethylsilane (**7b**)

⁷ J.-F. Zhao, B.-H. Tan, T.-P. Loh *Chem. Sci.* **2011**, 2, 349.



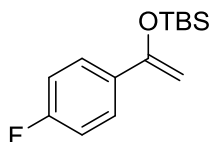
Following GP1, 1-(4-methoxyphenyl)ethanone (**24b**) (2.0 g, 13 mmol, 1 eq), NaHMDS (8.4 mL, 16 mmol, 1.2 eq and *tert*-butylchlorodimethylsilane (2.4 g, 16 mmol, 1.2 eq) were reacted. *Tert*-butyl(1-(4-methoxyphenyl)vinyl)oxy)dimethylsilane (**7b**) (2.5 g, 9.5 mmol, 71%) was obtained as a colorless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54 (d, *J* = 8.9 Hz, 2 H, Ar), 6.93 (d, *J* = 8.9 Hz, 2 H, Ar), 4.89 (d, *J* = 1.8 Hz, 1 H, CH₂ vinyl), 4.32 (d, *J* = 1.8 Hz, 1 H, CH₂ vinyl), 3.77 (s, 3 H, OMe), 0.98 (s, 9 H, OTBS), 0.20 (s, 6 H, OTBS).

¹³C NMR (101 MHz, DMSO) δ 159.4, 154.7, 129.5, 126.2, 113.5, 89.4, 55.1, 25.7, 18.0, -4.7.

NMR data of **7b** corresponded to the reported spectra.⁸

***Tert*-butyl(1-(4-fluorophenyl)vinyl)oxy)dimethylsilane (7c)**



Following GP1, 1-(4-fluorophenyl)ethanone (**24c**) (2.0 g, 15 mmol, 1 eq), NaHMDS (9.1 mL, 17 mmol, 1.2 eq and *tert*-butylchlorodimethylsilane (2.6 g, 17 mmol, 1.2 eq) were reacted. *Tert*-butyl(1-(4-fluorophenyl)vinyl)oxy)dimethylsilane (**7c**) (0.80 g, 3.2 mmol, 22%) was obtained as a colorless oil.

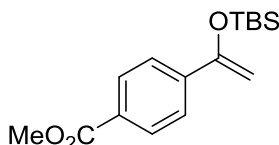
¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (dd, *J* = 9.0, 5.5 Hz, 2 H, Ar), 7.21 (t, *J* = 8.9 Hz, 2 H, Ar), 5.00 (d, *J* = 2.1 Hz, 1 H, CH₂ vinyl), 4.43 (d, *J* = 2.0 Hz, 1 H, CH₂ vinyl), 0.98 (d, *J* = 0.8 Hz, 9 H, OTBS), 0.21 (d, *J* = 0.9 Hz, 6 H, OTBS).

¹³C NMR (101 MHz, DMSO) δ 162.1 (d, *J* = 245.5 Hz), 153.9, 133.5 (d, *J* = 3.2 Hz), 126.9 (d, *J* = 8.4 Hz), 115.1 (d, *J* = 21.6 Hz), 91.1, 25.6, 17.9, -4.8.

IR 2891 (w), 2866 (w), 2821 (w), 2788 (w), 1564 (w), 1470 (w), 1456 (m), 1456 (m), 1351 (m), 1311 (w), 1144 (s), 1144 (s), 1122 (s), 1085 (m), 1060 (s), 1060 (s), 823 (s).

HRMS (ESI) calcd for C₁₄FH₂₁KOSi⁺ [M+K]⁺ 291.0977; found 291.1180.

Methyl 4-(1-(*tert*-butyldimethylsilyl)oxy)vinyl)benzoate (7d)



Following GP1, methyl 4-acetylbenzoate (**24d**) (1.0 g, 5.6 mmol, 1 eq), NaHMDS (3.5 mL, 6.7 mmol, 1.2 eq and *tert*-butylchlorodimethylsilane (1.0 g, 6.7 mmol, 1.2 eq) were reacted. Methyl 4-(1-(*tert*-butyldimethylsilyl)oxy)vinyl)benzoate (**7d**) (0.50 g, 1.7 mmol, 31%) was obtained as a colorless oil.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 – 7.86 (m, 2 H, Ar), 7.86 – 7.68 (m, 2 H, Ar), 5.20 (d, *J* = 2.2 Hz, 1 H, CH₂ vinyl), 4.59 (d, *J* = 2.2 Hz, 1 H, CH₂ vinyl), 3.86 (s, 3 H, OMe), 0.98 (s, 9 H, OTBS), 0.22 (s, 6 H, OTBS).

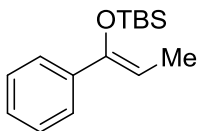
⁸ Ventura, D. L.; Li, Z.; Coleman, M. G.; Davies, H. M. L. *Tetrahedron* **2009**, 65, 3052.

^{13}C NMR (101 MHz, DMSO) δ 165.8, 153.9, 141.4, 129.2, 125.0, 93.8, 52.1, 30.7, 25.6, 18.0, -4.8.

IR 2888 (w), 2866 (w), 2821 (w), 2820 (w), 2787 (w), 1583 (s), 1464 (w), 1146 (m), 1106 (s), 937 (m), 926 (m), 828 (m).

HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{25}\text{O}_3\text{Si}^+$ $[\text{M}+\text{H}]^+$ 293.1567; found 293.1560.

(Z)-Tert-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (7e)



Following GP1, propiophenone (**24e**) (1.0 g, 7.5 mmol, 1 eq), NaHMDS (4.7 mL, 8.9 mmol, 1.2 eq) and *tert*-butylchlorodimethylsilane (1.3 g, 8.9 mmol, 1.2 eq) were reacted. (Z)-Tert-butyldimethyl((1-phenylprop-1-en-1-yl)oxy)silane (**7e**) (0.51 g, 2.0 mmol, 27%) was obtained as a colorless oil, which was used directly in the [4+2] annulation step.

3. Optimization of the [4+2] Annulation

Optimization procedure for SnCl_4 and TiCl_4 :

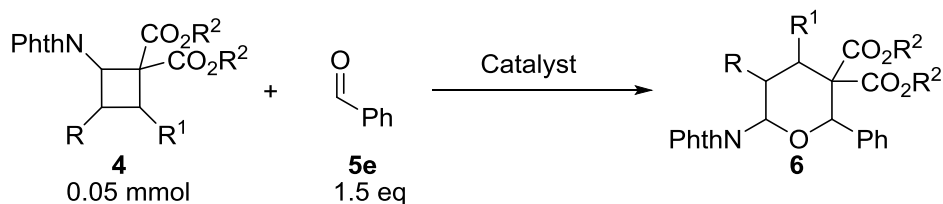
Preparation of the SnCl_4 solution: in an oven dried flask, under nitrogen atmosphere, SnCl_4 (0.22 g, 0.10 mL, 0.86 mmol) were added to dry dichloromethane (1.9 mL) to make a 0.43 M solution.

Preparation of the TiCl_4 solution: in an oven dried flask, under nitrogen atmosphere, TiCl_4 (0.17 g, 0.10 mL, 0.91 mmol) were added to dry dichloromethane (1.9 mL) to make a 0.46 M solution.

The cyclobutane **4** (0.050 mmol, 1 eq) was dissolved in dry dichloromethane (1.0 mL), and added in an oven dried microwave vial under nitrogen atmosphere. The aldehyde **5a** (0.075 mmol, 1.5 eq) was then dissolved in dry dichloromethane (0.50 mL) and added. The Lewis acid solution was then added dropwise to the reaction mixture. The reaction was quenched with triethylamine (0.10 mL), and concentrated under vacuum. The crude mixture was then dissolved in CDCl_3 and analyzed by ^1H NMR.

Optimization procedure for other Lewis acids:

In the glovebox, the Lewis acid was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (0.50 mL) was added. The cyclobutane **4** (0.050 mmol, 1 eq) was dissolved in dry dichloromethane (0.50 mL) and added. The aldehyde **5a** (0.075 mmol, 1.5 eq) was then dissolved in dry dichloromethane (0.50 mL) and added. The reaction was then filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude mixture was then dissolved in CDCl_3 and analyzed by ^1H NMR.



Entry	Catalyst (mol%)	Time	T	Solvent	Conversion ^a	dr ^b	R, R ¹ , R ²
1	FeCl ₃ ·Al ₂ O ₃ (20 mol%)	40 min	rt	DCM	>95% ^c	2:1	H, H, Me
2	SnCl ₄ (20 mol%)	2.5 h	rt	DCM	>95% ^c	6:1	H, H, Me
3	Hf(OTf) ₄ (20 mol%)	2.5 h	rt	DCM	>95% ^c	9:1	H, H, Me
4	Yb(OTf) ₃ (20 mol%)	2.5 h	rt	DCM	<5% ^d	-	H, H, Me
5	Sn(OTf) ₂ (20 mol%)	2.5 h	rt	DCM	<5%	-	H, H, Me
6	Cu(OTf) ₂ (20 mol%)	2.5 h	rt	DCM	<5%	-	H, H, Me
7	AuCl (20 mol%)	2.5 h	rt	DCM	<5%	-	H, H, Me
8	AuCl ₃ (20 mol%)	2.5 h	rt	DCM	>95% ^e	-	H, H, Me
9	TiCl ₄ (20 mol%)	2.5 h	rt	DCM	88% ^c	5:1	H, H, Me
10	In(OTf) ₃ (20 mol%)	2.5 h	rt	DCM	>95%	9:1	H, H, Me
11	Sc(OTf) ₃ (20 mol%)	2.5 h	rt	DCM	>95%	13:1	H, H, Me
12	Sc(OTf) ₃ (20 mol%)	7 h	reflux	DCM	<5% ^d	-	Me, H, Me
13	In(OTf) ₃ (20 mol%)	18 h	reflux	DCM	34%	4.5:1 :1	Me, H, Me
14	FeCl ₃ (100 mol%)	18 h	rt	DCM	>95%	6:1:1 f	Me, H, Me
15	SnCl ₄ (20 mol%)	2.5 h	rt	DCM	<5% ^d	-	Me, H, Me
16	SnCl ₄ (100 mol%)	2.5 h	-40 °C	DCM	>95% ^e	-	Me, H, Me
17	FeCl ₃ ·SiO ₂ (100 mol%)	18 h	rt	DCM	>95% ^c	-	Me, H, Me
18	FeBr ₃ (100 mol%)	18 h	rt	DCM	>95% ^c	-	Me, H, Me
19	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	2.5 h	rt	ACN	<5% ^d	-	Me, H, Me
20	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	2.5 h	rt	MeOH	<5% ^d	-	Me, H, Me
21	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	2.5 h	rt	DMF	<5% ^d	-	Me, H, Me
22	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	2.5 h	rt	THF	<5% ^d	-	Me, H, Me
23	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	18 h	rt	Toluene	76% ^c	-	Me, H, Me
24	FeCl ₃ ·Al ₂ O ₃ (100 mol%) ^g	5 h	rt	DCM	>95% ^e	-	Me, H, Me
25	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	5 h	rt	DCM	>95%	5:1	Me, H, Me
26	InOTf ₃ (20 mol%)	5 h	reflux	DCM	77%	5:1	H, Me, Et
27	AlCl ₃ (20 mol%)	24 h	reflux	DCM	45% ^c	4:1	H, Me, Et

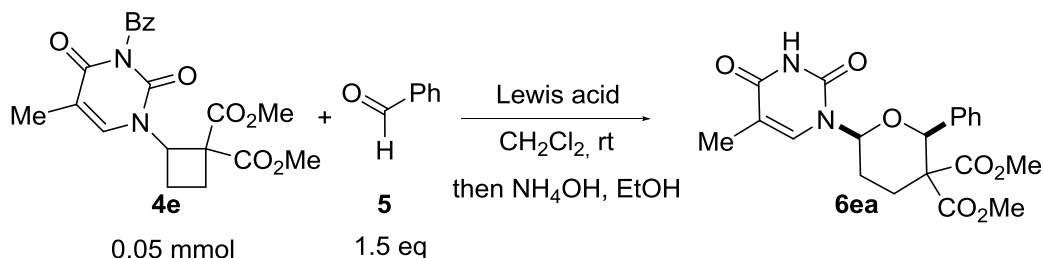
28	TfOH (20 mol%)	18 h	reflux	DCM	61% ^c	1.7:1	H,Me, Et
29	FeCl ₃ ·Al ₂ O ₃ (20 mol%)	30 h	reflux	DCM	89% ^c	3:1	H,Me, Et
30	FeCl ₃ ·Al ₂ O ₃ (20 mol%)	1 h	reflux	DCE	>95% ^e	-	H,Me, Et
31	FeCl ₃ ·Al ₂ O ₃ (20 mol%) ^h	2.5 h	rt	DCM	86% ^c	3:1	H,Me, Et
32	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	2.5 h	rt	DCM	>95% ^c	1.2:1	H,Me, Et
33	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	18 h	-30 °C	DCM	<5% ^d	-	H,Me, Et
34	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	20 h	-20 °C	DCM	>95%	4:1	H,Me, Et
35	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	2 h	0 °C	DCM	>95%	4:1	H,Me, Et
36	FeCl ₃ ·Al ₂ O ₃ (50 mol%)	5.5 h	0 °C	DCM	90%	4:1	H,Me, Et
37	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	18 h	rt	DCM	>95%	5:1	Ph, H, Me
38	ScOTf ₃ (20 mol%)	4 h	rt	DCM	<5% ^d	-	Ph, H, Me
39	YbOTf ₃ (20 mol%)	4 h	rt	DCM	<5% ^d	-	Ph, H, Me
40	SnCl ₄ (100 mol%)	4 h	rt	DCM	<5% ^d	-	Ph, H, Me
41	FeCl ₃ (100 mol%)	18 h	rt	DCM	>95% ^c	-	Ph, H, Me
42	FeBr ₃ (100 mol%)	18 h	rt	DCM	>95% ^c	-	Ph, H, Me

^aEstimated by ¹H NMR of the crude mixture based on the ratio of product to starting material;

^bDetermined by ¹H NMR of the crude; ^cComplex mixture of products was observed in the ¹H NMR of the crude; ^dNo product detected; ^eDegradation; ^fNot reproducible; ^gOpen flask; ^h3 equivalents of aldehyde.

Optimization procedure for cyclobutane **4e** and **4f**

The Lewis acid was added in a flame dried microwave vial and under nitrogen atmosphere. Then, dry dichloromethane and benzaldehyde (**5a**) (7.7 μL, 0.076 mmol, 1.5 eq) were added into the flask. A solution of cyclobutane **4** (20 mg, 0.050 mmol, 1.0 eq) in dry dichloromethane was added dropwise to the reaction mixture. The reaction mixture was filtrated on a pad of silica eluting with ethyl acetate (10 mL) and concentrated under reduce pressure. The crude product was dissolved in ethanol (1.8 mL) and ammonium hydroxide solution (0.6 mL, 60 eq, 25 %) was added. The resulting solution was stirred for 16 hours and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography eluting with a mixture of ethyl acetate/ pentane (5:5 to 9:1).



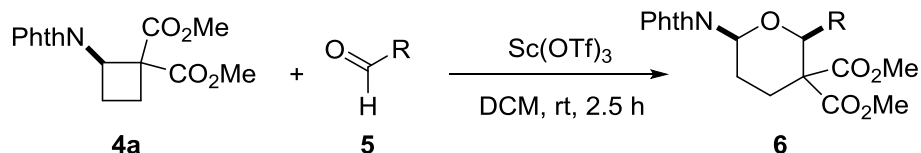
Entry	Catalyst (mol%)	Time	Conversion ^a	Yield ^b
1	Hf(OTf) ₄ (20 mol%)	14 h	> 95 %	51%
2	FeCl ₃ ·Al ₂ O ₃ (20 mol%)	14 h	> 95 %	59%
3	Hf(OTf) ₄ (20 mol%)	30 min	> 95 %	76%
4	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	30 min	> 95 %	62%
5	Hf(OTf) ₄ (20 mol%)	15 min	> 95 %	84%
6	FeCl ₃ ·Al ₂ O ₃ (100 mol%)	15 min	> 95 %	70%
7	Hf(OTf) ₄ (10 mol%)	15 min	> 95 %	87%

^aEstimated by ¹H NMR of the crude mixture based on the ratio of product to starting material, ^b ¹H NMR yield (traces of benzamide originated from the protecting group)

4. Scope of the [4+2] Annulation

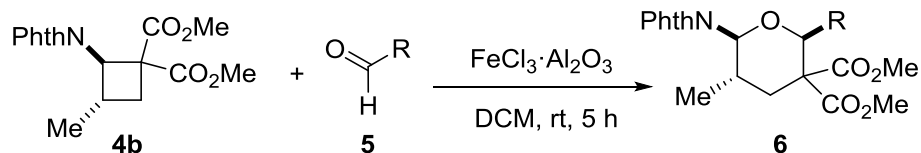
4.1 General Procedures

General Procedure for the [4+2] annulation reaction of dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**). (GP2)



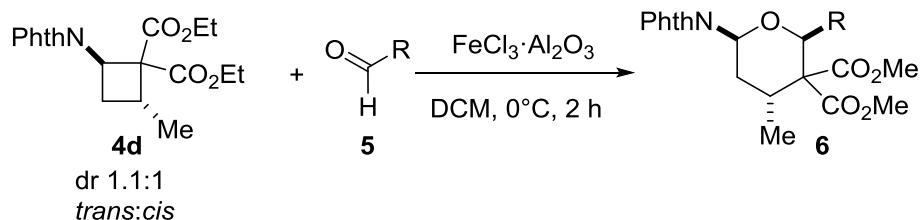
In a glovebox, scandium triflate (19.7 mg, 0.0400 mmol, 0.2 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (2 mL) was added. The cyclobutane **4a** (0.200 mmol, 1 eq) was dissolved in dry dichloromethane (2 mL) and added. The aldehyde **5** (0.300 mmol, 1.5 eq) was then dissolved in dry dichloromethane (2 mL) and added. The reaction was stirred at room temperature for 2.5 h, and then filtered over a pad of basic alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography using the indicated solvents.

General Procedure for the [4+2] annulation reaction of dimethyl 2-(1,3-dioxoisindolin-2-yl)-3-methylcyclobutane-1,1-dicarboxylate (**4b**). (GP3)



In a glovebox, iron trichloride supported on alumina (1.00 mmol/g, 200 mg, 0.200 mmol, 1 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (2 mL) was added. The cyclobutane **4b** (0.200 mmol, 1 eq) was dissolved in dry dichloromethane (2 mL) and added. The aldehyde **5** (0.300 mmol, 1.5 eq) was then dissolved in dry dichloromethane (2 mL) and added. The reaction was stirred at room temperature for 5 h, and then filtered over a pad of basic alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography using the indicated solvents.

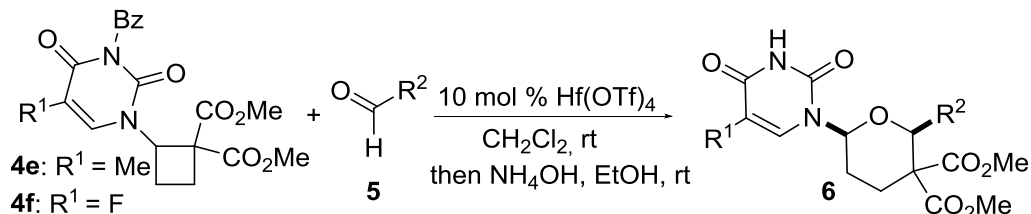
General Procedure for the [4+2] annulation reaction of diethyl 2-(1,3-dioxoisindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (**4d**). (GP4)



In a glovebox, iron trichloride supported on alumina (1.00 mmol/g, 200 mg, 0.200 mmol, 1 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (2 mL) was added. The vial was cooled down at 0 °C with an ice/water bath. The cyclobutane **4d** (0.200 mmol, 1 eq) was dissolved in dry dichloromethane (2 mL) and added dropwise.

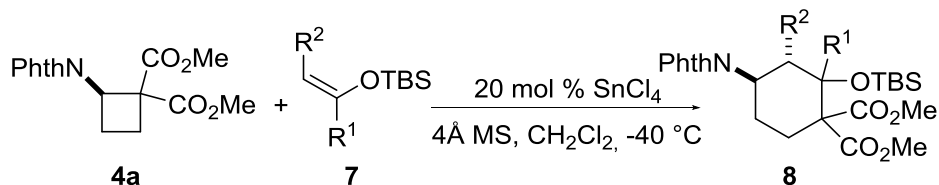
The aldehyde **5** (0.300 mmol, 1.5 eq) was then dissolved in dry dichloromethane (2 mL) and added dropwise. The reaction was stirred at 0 °C for 2 h, and then filtered over a pad of basic alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography using the indicated solvents.

General Procedure for the [4+2] annulation for the synthesis of nucleoside analogues (GP5)



$\text{Hf}(\text{OTf})_4$ (21 mg, 0.030 mmol, 0.1 eq) was added in a flame dried 25 mL flask and under nitrogen atmosphere. Then, dry dichloromethane (4.5 mL) and aldehyde **5** (0.45 mmol, 1.5 eq) were added into the flask. A solution of cyclobutane **4** (0.30 mmol, 1.0 eq) in dry dichloromethane (1.5 mL) was added dropwise to the reaction mixture and stirred at room temperature for 15 minutes. The reaction mixture was filtrated on a pad of silica eluting with a mixture of ethyl acetate/ pentane (8:2) and concentrated under reduce pressure. The crude product was dissolved in ethanol (6 mL) and ammonium hydroxide solution (1.8 mL, 60 eq, 25 %) was added. The resulting solution was stirred for 16 hours. The solvent was removed under reduced pressure and the crude product was dissolved in ethyl acetate (25 mL) and extracted with water (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluting with a mixture of ethyl acetate/ pentane (5:5 to 9:1). The product was recrystallized in ethanol (2 mL).

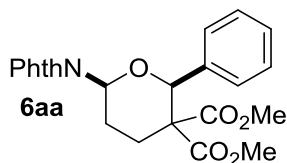
General Procedure for the [4+2] annulation with enol ethers (GP6)



4 Å 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. Aminocyclobutane **4a** (0.200 mmol, 1 eq) and silyl enol ether **7** (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 at -40 °C until full conversion was observed by NMR. 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 the aminocyclohexanes.

4.2 Scope of the [4+2] annulation

Dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6aa**)



Following the general procedure **GP2**, dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and benzaldehyde (**5a**) (31.8 mg, 0.300 mmol, 1.5 eq) were stirred at room temperature for 2.5 h. The crude oil was purified by column chromatography (SiO₂, 8:2 Pentane/Ethyl Acetate) affording dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6aa**) (78.0 mg, 0.184 mmol, 92% yield) as a white solid.

dr 16:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 5.82 and 5.67.

The major *cis* diastereoisomer was characterized. A strong correlation between the signals at 5.67 and 5.21 was observed. In addition, a large coupling constant ($J = 11.6$ Hz) of the signal at 5.67 suggests that this proton is in axial position in anti-periplanar relationship with one proton of the neighboring CH₂.

1 mmol scale reaction :

In a glovebox, scandium triflate (24.6 mg, 0.0500 mmol, 0.05 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (4 mL) was added. The cyclobutane **4a** (317 mg, 1 mmol, 1 eq) was dissolved in dry dichloromethane (3 mL) and added. The benzaldehyde (**5a**) (159 mg, 1.50 mmol, 1.5 eq) was then dissolved in dry dichloromethane (3 mL) and added. The reaction was stirred at room temperature for 5 h, and then was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography (SiO₂, 8:2 Pentane/Ethyl Acetate) affording dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6aa**) (342 mg, 0.808 mmol, 81% yield) as a white solid.

dr 13:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 5.82 and 5.67.

R_f 0.25 (7:3 Pentane/Ethyl Acetate).

Mp 167-170 °C.

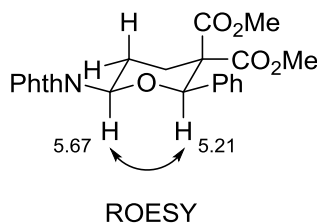
¹H NMR (400 MHz, CDCl₃)⁹ δ 7.87 (dd, $J = 5.5, 3.1$ Hz, 2 H, Phth), 7.73 (dd, $J = 5.5, 3.0$ Hz, 2 H, Phth), 7.40 – 7.36 (m, 2 H, Ph), 7.27 – 7.20 (m, 3 H, Ph), 5.67 (dd, $J = 11.6, 3.0$ Hz, 1 H, N-C(*H*)-O), 5.21 (s, 1 H, O-C(*H*)-Ph), 3.68 (s, 3 H, OCH₃), 3.63 (s, 3 H, OCH₃), 3.35 – 3.21 (m, 1 H, CH₂), 2.79 (ddd, $J = 13.7, 4.4, 3.1$ Hz, 1 H, CH₂), 2.29 (ddd, $J = 13.6, 13.6, 4.3$ Hz, 1 H, CH₂), 1.78 (dddd, $J = 13.5, 4.3, 3.0, 3.0$ Hz, 1 H, CH₂).

¹³C NMR (101 MHz, CDCl₃) δ 170.9, 168.6, 167.0, 138.3, 134.3, 131.8, 127.8, 127.4, 127.3, 123.6, 82.2, 79.3, 58.1, 52.6, 51.9, 32.3, 23.8.

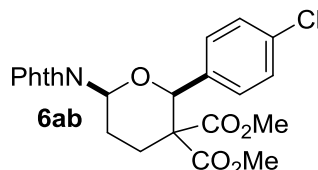
IR 2953 (w), 1781 (w), 1722 (s), 1450 (w), 1440 (w), 1375 (m), 1262 (m), 1209 (w), 1082 (m), 1050 (m), 1012 (w).

HRMS (ESI) calcd for C₂₃H₂₁NNaO₇⁺ [M+Na]⁺ 446.1216; found 446.1213.

⁹ Small amount of other compound (less than 5%) observed by ¹H NMR (probably other diastereoisomer).



Dimethyl 2-(4-chlorophenyl)-6-(1,3-dioxoisindolin-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (6ab)



Following the general procedure **GP2**, dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and 4-chlorobenzaldehyde (**5b**) (42.2 mg, 0.300 mmol, 1.5 eq) were stirred at room temperature for 2.5 h. The crude oil was purified by column chromatography (SiO₂, 8:2 Pentane/Ethyl Acetate) affording dimethyl 2-(4-chlorophenyl)-6-(1,3-dioxoisindolin-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (**6ab**) (69.0 mg, 0.151 mmol, 75% yield) as a white solid.

dr 17:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 5.86 and 5.6.

The major diastereoisomer is the *cis*, in analogy with the ¹H NMR spectrum of **6aa**.

R_f 0.33 (7:3 Pentane/Ethyl Acetate).

Mp 169-176 °C.

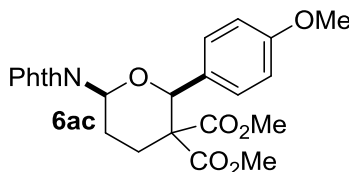
¹H NMR (400 MHz, CDCl₃)⁹ only *maj* diastereoisomer characterized δ 7.87 (dd, *J* = 5.5, 3.0 Hz, 2 H, Phth), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2 H, Phth), 7.34 – 7.28 (m, 2 H, Ph), 7.23 – 7.18 (m, 2 H, Ph), 5.66 (dd, *J* = 11.7, 3.0 Hz, 1 H, N-C(*H*)-O), 5.16 (s, 1 H, O-C(*H*)-Ph), 3.68 (s, 3 H, OCH₃), 3.65 (s, 3 H, OCH₃), 3.27 (dddd, *J* = 13.5, 13.5, 11.6, 4.4 Hz, 1H), 2.78 (ddd, *J* = 13.7, 4.3, 2.9 Hz, 1 H), 2.27 (ddd, *J* = 13.6, 13.6, 4.3 Hz, 1 H), 1.78 (dddd, *J* = 13.5, 4.3, 3.0, 3.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) only *maj* diastereoisomer characterized δ 170.8, 168.3, 167.0, 136.8, 134.4, 133.5, 131.7, 128.9, 127.4, 123.7, 81.6, 79.3, 58.0, 52.7, 52.0, 32.2, 23.7.

IR 2953 (w), 1782 (w), 1724 (s), 1439 (w), 1375 (s), 1344 (w), 1262 (m), 1210 (m), 1075 (m), 1052 (m), 1014 (w).

HRMS (ESI) calcd for C₂₃H₂₀ClNNaO₇⁺ [M+Na]⁺ 480.0820; found 480.0820.

Dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-(4-methoxyphenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (6ac)



Following the general procedure **GP2**, dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and 4-methoxybenzaldehyde (**5c**) (40.8 mg, 0.300 mmol, 1.5 eq) were stirred at room temperature for 2.5 h. The crude oil was purified by column chromatography

(SiO₂, 8:2 to 6:4 Pentane/Ethyl Acetate) affording dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-(4-methoxyphenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (**6ac**) (74.6 mg, 0.165 mmol, 82% yield) as a white solid.

dr 6:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 5.79 and 5.65.

The major diastereoisomer is the *cis*, in analogy with the ¹H NMR spectrum of **6aa**.

R_f 0.22 (7:3 Pentane/Ethyl Acetate).

Mp 154–161 °C.

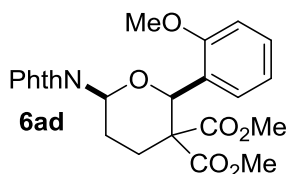
¹H NMR (400 MHz, CDCl₃)⁹ on a 6(*maj*):1(*min*) mixture δ 7.89 – 7.77 (m, 2.3 H, Phth *maj* + *min*), 7.75 – 7.65 (m, 2.3 H, Phth *maj* + *min*), 7.37 – 7.33 (m, 0.3 H, Ph *min*), 7.33 – 7.27 (m, 2 H, Ph *maj*), 6.86 – 6.80 (m, 0.3 H, Ph *min*), 6.80 – 6.73 (m, 2 H, Ph *min*), 6.08 (s, 0.15 H, O-C(*H*)-Ph *min*), 5.79 (dd, *J* = 10.4, 5.3 Hz, 0.15 H, N-C(*H*)-O *min*), 5.65 (dd, *J* = 11.7, 3.0 Hz, 1 H, N-C(*H*)-O *maj*), 5.13 (s, 1 H, O-C(*H*)-Ph *maj*), 3.87 (s, 0.45 H, OCH₃ *min*), 3.76 (s, 0.45 H, OCH₃ *min*), 3.74 (s, 3 H, OCH₃ *maj*), 3.67 (s, 3 H, OCH₃ *maj*), 3.66 (s, 3 H, OCH₃ *maj*), 3.40 (s, 0.45 H, OCH₃ *min*), 3.28 (m, 1 H, CH₂ *maj*), 2.85 – 2.69 (m, 1.15 H, CH₂ *maj* + *min*), 2.69 – 2.58 (m, 0.3 H, CH₂ *min*), 2.26 (ddd, *J* = 13.6, 13.6, 4.3 Hz, 1 H, CH₂ *maj*), 1.97 – 1.88 (m, 0.15 H, CH₂ *min*), 1.81 – 1.72 (m, 1 H, CH₂ *maj*).¹⁰

¹³C NMR (101 MHz, CDCl₃) only *maj* diastereoisomer characterized δ 170.9, 168.6, 167.0, 159.1, 134.3, 131.8, 130.4, 128.7, 123.6, 112.6, 82.0, 79.3, 58.1, 55.1, 52.6, 52.0, 32.2, 23.8.

IR 2954 (w), 1782 (w), 1725 (s), 1615 (w), 1515 (w), 1462 (w), 1440 (w), 1376 (m), 1347 (w), 1253 (m), 1210 (w), 1076 (m), 1045 (m).

HRMS (ESI) calcd for C₂₄H₂₃NNaO₈⁺ [M+Na]⁺ 476.1316; found 476.1319.

Dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-(2-methoxyphenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (6ad**)**



Following the general procedure **GP2**, dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and 2-methoxybenzaldehyde (**5d**) (40.8 mg, 0.300 mmol, 1.5 eq) were stirred at room temperature for 2.5 h. The crude oil was purified by column chromatography (SiO₂, 65:35 Pentane/Ethyl Acetate) affording dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-(2-methoxyphenyl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (**6ad**) (82.8 mg, 0.183 mmol, 91% yield) as a white solid.

dr 8.5:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 6.37 and 5.25.

The major diastereoisomer is the *cis*, in analogy with the ¹H NMR spectrum of **6aa**.

R_f 0.18 (7:3 Pentane/Ethyl Acetate).

Mp 87–97 °C.

¹H NMR (400 MHz, CDCl₃)⁹ only *maj* diastereoisomer characterized δ 7.90 – 7.81 (m, 2 H, Phth), 7.81 – 7.66 (m, 2 H, Phth, 1 H, Ph), 7.24 – 7.16 (m, 1 H, Ph), 6.93 (dd, *J* = 7.5 Hz, 1 H, Ph), 6.75 (d, *J* = 8.1 Hz,

¹⁰ Over-integrated due to overlap with water in CDCl₃.

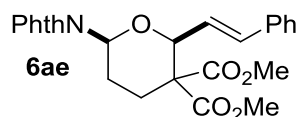
1 H, Ph), 5.64 (dd, $J = 11.5, 3.0$ Hz, 1 H, N-C(*H*)-O), 5.25 (s, 1 H, O-C(*H*)-Ph), 3.76 (s, 3 H, OCH₃), 3.75 (s, 3 H, OCH₃), 3.55 (s, 3 H, OCH₃), 3.03 – 2.85 (m, 1 H, CH₂), 2.72 (ddd, $J = 14.1, 3.8, 3.8$ Hz, 1 H, CH₂), 2.61 – 2.50 (m, 1 H, CH₂), 1.80 (dddd, $J = 13.5, 3.5, 3.5, 3.5$ Hz, 1 H, CH₂).

¹³C NMR (101 MHz, CDCl₃) only *maj* diastereoisomer characterized δ 169.4, 168.9, 167.1, 155.8, 134.3, 131.8, 130.5, 128.8, 126.3, 123.6, 119.9, 108.8, 79.4, 76.4, 57.6, 55.2, 52.3, 52.1, 32.1, 24.2.

IR 2954 (w), 1765 (w), 1724 (s), 1600 (w), 1495 (w), 1464 (w), 1439 (w), 1376 (m), 1293 (w), 1256 (m), 1200 (w), 1111 (w), 1073 (m), 1050 (m).

HRMS (ESI) calcd for C₂₄H₂₃NNaO₈⁺ [M+Na]⁺ 476.1316; found 476.1312.

(*E*)-Dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-styryldihydro-2H-pyran-3,3(4H)-dicarboxylate (6ae)



Following the general procedure **GP2**, dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and cinnamaldehyde (**5e**) (39.6 mg, 0.300 mmol, 1.5 eq) were stirred at room temperature for 2.5 h. The crude oil was purified by column chromatography (SiO₂, 9:1 to 8:2 Pentane/Ethyl Acetate) affording (*E*)-dimethyl 6-(1,3-dioxoisindolin-2-yl)-2-styryldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6ae**) (85.7 mg, 0.191 mmol, 95% yield) as a white solid.

dr 2:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 5.84 and 5.63.

The major diastereoisomer is the *cis*, in analogy with the ¹H NMR spectrum of **6aa**.

R_f 0.3 (7:3 Pentane/Ethyl Acetate).

Mp 88–92 °C.

¹H NMR (400 MHz, CDCl₃)⁹ on a 2(*maj*):1(*min*) mixture δ 7.90 – 7.81 (m, 3 H, Phth *maj* + *min*), 7.79 – 7.68 (m, 3 H, Phth *maj* + *min*), 7.45 – 7.39 (m, 1 H, Ph *min*), 7.38 – 7.31 (m, 3 H, Ph *maj* + *min*), 7.30 – 7.17 (m, 3.5 H, Ph *maj* + *min*),¹¹ 6.85 (dd, $J = 15.8, 1.5$ Hz, 0.5 H, CH vinyl *min*), 6.67 (dd, $J = 16.0, 7.2$ Hz, 1 H, CH vinyl *maj*), 6.54 (d, $J = 16.1$ Hz, 1 H, CH vinyl *maj*), 6.28 (dd, $J = 15.8, 6.4$ Hz, 0.5 H, CH vinyl *min*), 5.84 (dd, $J = 11.2, 3.4$ Hz, 0.5 H, N-C(*H*)-O *min*), 5.63 (dd, $J = 11.8, 3.0$ Hz, 1 H, N-C(*H*)-O *maj*), 5.47 (ddd, $J = 6.4, 1.5, 1.5$ Hz, 0.5 H, O-C(*H*)-vinyl *min*), 4.60 (dd, $J = 7.2, 0.9$ Hz, 1 H, O-C(*H*)-vinyl *maj*), 3.94 (s, 1.5 H, OCH₃ *min*), 3.90 (s, 3 H, OCH₃ *maj*), 3.70 (s, 1.5 H, OCH₃ *min*), 3.67 (s, 3 H, OCH₃ *maj*), 3.08 (dddd, $J = 13.7, 13.7, 11.7, 4.4$ Hz, 1 H, CH₂ *maj*), 2.88 – 2.78 (m, 0.5 H, CH₂ *min*), 2.75 (ddd, $J = 13.6, 4.4, 2.8$ Hz, 1 H, CH₂ *maj*), 2.67 (dddd, $J = 14.3, 3.9, 3.9, 1.6$ Hz, 0.5 H, CH₂ *min*), 2.37 (ddd, $J = 13.9, 13.9, 4.1$ Hz, 0.5 H, CH₂ *min*), 2.23 (ddd, $J = 13.7, 13.7, 4.2$ Hz, 1 H, CH₂ *maj*), 1.82 (dddd, $J = 13.8, 3.9, 3.9, 3.9$ Hz, 0.5 H, CH₂ *min*), 1.75 (dddd, $J = 13.6, 13.6, 4.2, 2.8$ Hz, 1 H, CH₂ *maj*).

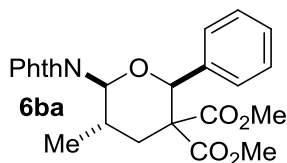
¹³C NMR (101 MHz, CDCl₃) δ 170.4, 169.5, 168.9, 168.8, 167.4, 167.1, 136.5, 136.2, 135.9, 134.4, 134.3, 132.9, 131.8, 131.7, 128.6, 128.4, 128.2, 127.8, 126.8, 126.8, 125.9, 123.6, 123.6, 121.7, 82.8, 79.0, 77.2, 72.9, 58.1, 57.1, 53.3, 53.0, 52.8, 52.6, 31.6, 25.2, 23.8, 23.7.

IR 3027 (w), 2953 (w), 1781 (w), 1724 (s), 1452 (w), 1442 (w), 1376 (m), 1269 (w), 1253 (w), 1209 (w), 1071 (m), 1010 (w).

HRMS (ESI) calcd for C₂₅H₂₃NNaO₇⁺ [M+Na]⁺ 472.1367; found 472.1371.

Dimethyl 6-(1,3-dioxoisindolin-2-yl)-5-methyl-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (6ba)

¹¹ Over-integrated due to overlap with CHCl₃ peak.



Following the general procedure **GP3**, dimethyl 2-(1,3-dioxoisindolin-2-yl)-3-methylcyclobutane-1,1-dicarboxylate (**4b**) (66.3 mg, 0.200 mmol, 1 eq) and benzaldehyde (**5a**) (31.8 mg, 0.300 mmol, 1.5 eq) were stirred at room temperature for 5 h. The crude oil was purified by column chromatography (SiO₂, 8:2 Pentane/Ethyl Acetate) affording dimethyl 6-(1,3-dioxoisindolin-2-yl)-5-methyl-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6ba**) (56.0 mg, 0.128 mmol, 64% yield) as a white solid.

dr 5:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 2.73 and 2.56.

The major diastereoisomer is the *cis-trans*, in analogy with the ¹H NMR spectrum of **6bb**.

R_f 0.36 (7 :3 Pentane/Ethyl Acetate).

Mp 79-86 °C.

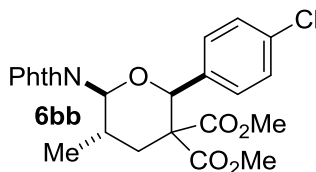
¹**H NMR** (400 MHz, CDCl₃) on a 5(*maj*):1(*min*) mixture δ 7.88 (dd, *J* = 5.4, 3.0 Hz, 2 H, Phth *maj*), 7.82 (dd, *J* = 5.5, 3.1 Hz, 0.4 H, Phth *min*), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2 H, Phth *maj*), 7.71 (dd, *J* = 5.5, 3.1 Hz, 0.4 H, Phth *min*) 7.45 – 7.41 (m, 0.4 H, Ph *min*), 7.40 – 7.35 (m, 2 H, Ph *maj*), 7.34 – 7.18 (m, 3.6 H, Ph *maj* + *min*),¹¹ 6.24 (s, 0.2 H, O-C(*H*)-Ph *min*), 5.33 (d, *J* = 10.5 Hz, 0.2 H, N-C(*H*)-O *min*), 5.26 (d, *J* = 10.6 Hz, 1 H, N-C(*H*)-O *maj*), 5.18 (s, 1 H, O-C(*H*)-Ph *maj*), 3.89 (s, 0.6 H, OCH₃ *min*), 3.68 (s, 3 H, OCH₃ *maj*), 3.62 (s, 3 H, OCH₃ *maj*), 3.47 – 3.34 (m, 1 H, Me-CH *maj*), 3.33 (s, 0.6 H, OCH₃ *min*), 3.09 – 2.96 (m, 0.2 H, Me-CH *min*), 2.72 (dd, *J* = 13.7, 4.2 Hz, 1 H, CH₂ *maj*), 2.55 (dd, *J* = 14.2, 3.6 Hz, 0.2 H, CH₂ *min*), 2.42 (dd, *J* = 14.2, 13.1 Hz, 0.2 H, CH₂ *min*), 1.95 (dd, *J* = 13.7, 12.4 Hz, 1 H, CH₂ *maj*), 0.95 (d, *J* = 8.0 Hz, 0.6 H, CH₃ *min*), 0.93 (d, *J* = 6.8 Hz, 3 H, CH₃ *maj*).

¹³**C NMR** (101 MHz, CDCl₃)¹² δ 170.7, 169.5, 168.7, 167.9, 167.1, 138.2, 137.5, 134.34, 134.30, 131.7, 128.1, 128.0, 127.8, 127.6, 127.4, 127.3, 123.6, 123.5, 84.9, 82.2, 81.0, 77.3, 76.2, 59.9, 59.3, 53.2, 52.6, 52.5, 51.9, 40.5, 34.4, 27.7, 27.0, 16.9, 16.2.

IR 2956 (w), 1774 (w), 1727 (s), 1461 (w), 1439 (w), 1376 (m), 1261 (m), 1214 (w), 1090 (w), 1026 (w).

HRMS (ESI) calcd for C₂₄H₂₃NNaO₇⁺ [M+Na]⁺ 460.1367; found 460.1367.

Dimethyl 2-(4-chlorophenyl)-6-(1,3-dioxoisindolin-2-yl)-5-methyldihydro-2H-pyran-3,3(4H)-dicarboxylate (6bb)



Following the general procedure **GP3**, dimethyl 2-(1,3-dioxoisindolin-2-yl)-3-methylcyclobutane-1,1-dicarboxylate (**4b**) (66.3 mg, 0.200 mmol, 1 eq) and 4-chlorobenzaldehyde (**5b**) (42.2 mg, 0.300 mmol, 1.5 eq) were stirred at room temperature for 5 h. The crude oil was purified by column chromatography (SiO₂, 8:2 Pentane/Ethyl Acetate) affording dimethyl 2-(4-chlorophenyl)-6-(1,3-dioxoisindolin-2-yl)-5-methyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6bb**) (58.0 mg, 0.123 mmol, 62% yield) as a white solid.

dr 5:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 5.35 and 5.25.

The major *cis-trans* diastereoisomer was characterized. Strong correlations between the signals at 5.25 and 5.14, and between 5.25 and 0.92 were observed. In addition, a large coupling constant ($J = 10.6$ Hz) of the signal at 5.25 suggests that this proton is in axial position in anti-periplanar relationship with the proton of the neighboring CH.

R_f 0.38 (7:3 Pentane/Ethyl Acetate).

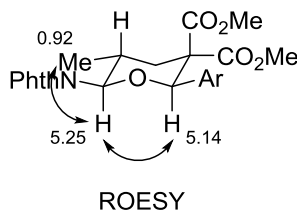
Mp 81-90 °C.

¹H NMR (400 MHz, CDCl₃)⁹ on a 5(*maj*):1(*min*) mixture δ 7.87 (dd, $J = 5.6, 3.2$ Hz, 2 H, Phth *maj*), 7.83 (dd, $J = 5.5, 3.1$ Hz, 0.4 H, Phth *min*), 7.75 (dd, $J = 5.5, 3.1$ Hz, 2 H, Phth *maj*), 7.71 (dd, $J = 5.6, 2.8$ Hz, 0.4 H, Phth *min*), 7.41 – 7.35 (m, 0.4 H, Ph *min*), 7.34 – 7.24 (m, 2.4 H, Ph *maj* + *min*), 7.23 – 7.16 (m, 2 H, Ph *maj*), 6.22 (s, 0.2 H, O-C(*H*)-Ph *min*), 5.35 (d, $J = 10.4$ Hz, 0.2 H, N-C(*H*)-O *min*), 5.25 (d, $J = 10.6$ Hz, 1 H, N-C(*H*)-O *maj*), 5.14 (s, 1 H, O-C(*H*)-Ph *maj*), 3.87 (s, 0.6 H, OCH₃ *min*), 3.68 (s, 3 H, OCH₃ *maj*), 3.64 (s, 3 H, OCH₃ *maj*), 3.44 – 3.35 (m, 1 H, Me-CH *maj*), 3.34 (s, 0.6 H, OCH₃ *min*), 3.05 – 2.94 (m, 0.2 H, Me-CH *min*), 2.71 (dd, $J = 13.7, 4.2$ Hz, 1 H, CH₂ *maj*), 2.50 (dd, $J = 14.2, 3.5$ Hz, 0.2 H, CH₂ *min*), 2.40 (dd, $J = 14.3, 13.1$ Hz, 0.2 H, CH₂ *min*), 1.93 (dd, $J = 13.7, 12.4$ Hz, 1 H, CH₂ *min*), 0.95 (d, $J = 6.6$ Hz, 0.6H, CH₃ *min*), 0.92 (d, $J = 6.6$ Hz, 3 H, CH₃ *maj*).

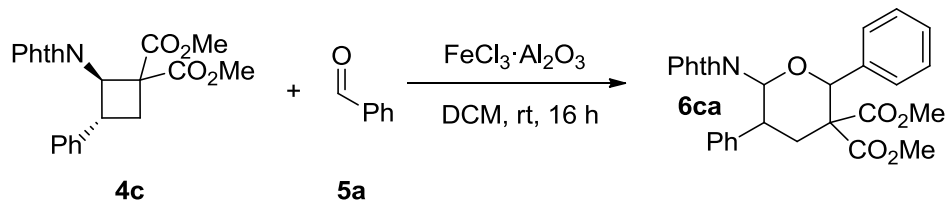
¹³C NMR (101 MHz, CDCl₃)¹² δ 170.7, 170.5, 169.4, 168.4, 167.9, 167.1, 136.7, 136.2, 134.4, 133.8, 133.5, 131.7, 129.0, 128.9, 128.2, 127.4, 123.7, 123.6, 84.8, 81.5, 81.3, 75.4, 60.2, 59.2, 53.2, 52.7, 52.5, 52.0, 40.4, 34.5, 27.6, 26.7, 17.0, 16.2.

IR 2975 (w), 2882, (w), 1780 (w), 1726 (s), 1377 (m), 1263 (m), 1215 (w), 1084 (m), 1021 (w).

HRMS (ESI) calcd for C₂₄H₂₂ClKNO₇⁺ [M+K]⁺ 510.0716; found 510.0715.



Dimethyl 6-(1,3-dioxoisindolin-2-yl)-2,5-diphenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6ca**)



In a glovebox, iron trichloride supported on alumina (1.00 mmol/g, 200 mg, 0.200 mmol, 1 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (2 mL) was added. Dimethyl 2-(1,3-dioxoisindolin-2-yl)-3-phenylcyclobutane-1,1-dicarboxylate (**4c**) (79.0 mg, 0.200 mmol, 1 eq) was dissolved in dry dichloromethane (2 mL) and added. Benzaldehyde (**5a**) (31.8 mg, 0.300 mmol, 1.5 eq) was then dissolved in dry dichloromethane (2 mL) and added. The mixture was stirred at room temperature for 16 h and then filtered over a pad of basic alumina, eluted with ethyl acetate and concentrated under vacuum. The crude oil was purified by column chromatography (SiO₂, 8:2 Pentane/Ethyl Acetate) affording dimethyl 6-(1,3-dioxoisindolin-2-yl)-2,5-

¹² Some peaks are not resolved in the aromatic region.

diphenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6ca**) (53.0 mg, 0.106 mmol, 53% yield) as a white solid.

dr 6:1, diastereoisomeric ratio was calculated in ^1H NMR of the isolated product integrating peaks at 4.70 and 4.25.

R_f 0.16 (8 :2 Pentane/Ethyl Acetate).

Mp 222-228 °C.

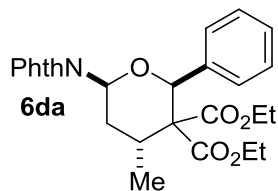
^1H NMR (400 MHz, CDCl_3) on a 5(*maj*):1(*min*) mixture δ 7.94 – 7.57 (m, 4.8 H, Phth *maj* + *min*),¹³ 7.54 – 7.10 (m, 12 H, 2 x Ph *maj* + *min*),¹³ 6.34 (s, 0.2 H, O-C(*H*)-Ph *min*), 5.83 (d, J = 10.8 Hz, 1 H, N-C(*H*)-O *maj*), 5.81 (d, J = 10.4 Hz, 0.2 H, N-C(*H*)-O *min*) 5.42 (s, 1 H, O-C(*H*)-Ph *maj*),¹³ 4.70 (ddd, J = 12.8, 10.9, 4.1 Hz, 1 H, Ph-C(*H*)-CH₂ *maj*), 4.25 (ddd, J = 13.9, 10.8, 3.3 Hz, 0.2 H, Ph-C(*H*)-CH₂ *min*), 3.92 (s, 0.6 H, OCH₃ *min*),¹³ 3.68 (s, 3 H, OCH₃ *maj*),¹³ 3.66 (s, 3 H, OCH₃ *maj*),¹³ 3.34 (s, 0.6 H, OCH₃ *min*),¹³ 2.89 (dd, J = 13.7, 4.2 Hz, 1 H, CH₂ *maj*), 2.75 (dd, J = 14.2, 3.4 Hz, 0.2 H, CH₂ *min*), 2.42 (dd, J = 13.2, 13.2 Hz, 1 H, CH₂ *maj*),¹³ 2.01 – 1.91 (m, 0.6 H, CH₂ *min*).

^{13}C NMR (101 MHz, CDCl_3) only *maj* diastereoisomer characterized δ 170.5, 168.6, 166.9, 139.0, 138.1, 134.2, 128.9, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 123.5, 83.0, 82.3, 59.1, 52.7, 52.0, 40.7, 39.1.

IR 3064 (w), 3034 (w), 2953 (w), 1723 (s), 1438 (w), 1374 (m), 1254 (m), 1216 (m), 1065 (m).

HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{25}\text{KNO}_7^+$ [$\text{M}+\text{K}$]⁺ 538.1268; found 538.1277.

Diethyl 6-(1,3-dioxisoindolin-2-yl)-4-methyl-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (6da)



Following the general procedure **GP4**, diethyl 2-(1,3-dioxisoindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (**4d**) (71.9 mg, 0.200 mmol, 1 eq) and benzaldehyde (**5a**) (31.8 mg, 0.300 mmol, 1.5 eq) were stirred at 0 °C for 2 h. The crude oil was purified by column chromatography (SiO_2 , 8:2 Pentane/Ethyl Acetate) affording diethyl 6-(1,3-dioxisoindolin-2-yl)-4-methyl-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6da**) (58.8 mg, 0.126 mmol, 63% yield, 95% pure) as a white solid.

dr 3:1, diastereoisomeric ratio was calculated in ^1H NMR of the isolated product integrating peaks at 5.82 and 5.71.

The major diastereoisomer is the *cis-trans*, in analogy with the ^1H NMR spectrum of (**6db**)

R_f 0.41 (7:3 Pentane/Ethyl Acetate).

Mp 133-139 °C.

^1H NMR (400 MHz, CDCl_3)¹⁴ on a 3(*maj*):1(*min*) mixture δ 7.85 (ddd, J = 8.4, 5.4, 3.1 Hz, 2.6 H, Phth *maj* + *min*), 7.71 (ddd, J = 8.5, 5.5, 3.1 Hz, 2.6 H, Phth *maj* + *min*), 7.53 – 7.43 (m, 2 H, Ph *maj*), 7.33 (m, 0.6 H, Ph *min*), 7.25 – 7.13 (m, 3.9 H, Ph *maj* + *min*), 5.82 (dd, J = 11.8, 3.0 Hz, 1 H, N-C(*H*)-O *maj*), 5.71 (dd, J = 11.8, 2.9 Hz, 0.3 H, N-C(*H*)-O *min*), 5.48 (s, 1 H, O-C(*H*)-Ph *maj*), 5.17 (s, 0.3 H, O-C(*H*)-Ph *min*), 4.26 – 3.90 (m, 5.2 H, 2 x OCH₂ *maj* + *min*), 3.69 (dddd, J = 10.7, 7.0, 7.0, 7.0 Hz, 1 H, CH₂ *maj*), 3.40 (m, 0.3, CH₂ *min*),¹⁷ 3.06 – 2.94 (m, 1 H, Me-CH *maj*),¹⁷ 2.60 – 2.48 (m, 0.3 H, Me-CH *min*),¹⁷

¹³ Overlapping with signals of impurities (probably other diastereoisomers present in less than 10% each).

¹⁴ 95% pure (other diastereoisomer not characterized and 5% impurity).

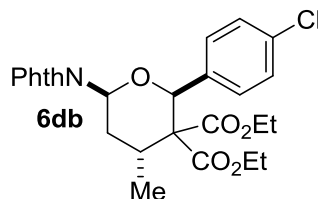
1.75 – 1.63 (m, 0.3 H, CH₂ *min*),^{10,17} 1.56 (ddd, *J* = 13.4, 3.1, 3.1 Hz, 1 H, CH₂ *maj*),¹⁷ 1.26 (d, *J* = 7.2 Hz, 3 H, CH₃ *maj*), 1.25 (d, *J* = 6.8 Hz, 0.9 H, CH₃ *min*), 1.20 (m, 3.9 H, OCH₂CH₃ *maj* + *min*), 1.09 (t, *J* = 7.1 Hz, 0.9 H, OCH₂CH₃ *min*), 0.88 (t, *J* = 7.2 Hz, 3 H, OCH₂CH₃ *maj*).

¹³C NMR (101 MHz, CDCl₃)¹² δ 170.2, 169.5, 168.6, 167.1, 167.0, 166.7, 138.8, 138.5, 134.2, 131.8, 128.2, 127.6, 127.3, 127.2, 127.1, 123.5, 123.5, 83.2, 79.3, 77.2, 76.7, 75.3, 62.9, 61.4, 60.9, 60.7, 60.5, 60.3, 39.2, 32.8, 31.2, 30.5, 17.5, 16.4, 14.0, 13.7, 13.3.

IR 2982 (w), 2983 (w), 2904 (w), 1780 (w), 1723 (s), 1464 (w), 1373 (s), 1287 (w), 1258 (m), 1230 (m), 1201 (m), 1090 (m), 1048 (m), 1033 (m).

HRMS (ESI) calcd for C₂₆H₂₈NO₇⁺ [M+H]⁺ 466.1860; found 466.1852.

Diethyl 2-(4-chlorophenyl)-6-(1,3-dioxoisindolin-2-yl)-4-methyldihydro-2H-pyran-3,3(4H)-dicarboxylate (6db)



Following the general procedure **GP4**, diethyl 2-(1,3-dioxoisindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (**4d**) (71.9 mg, 0.200 mmol, 1 eq) and 4-chlorobenzaldehyde (**5b**) (42.2 mg, 0.300 mmol, 1.5 eq) were stirred at 0 °C for 2 h. The crude oil was purified by column chromatography (SiO₂, 8:2 Pentane/Ethyl Acetate) affording dimethyl 2-(4-chlorophenyl)-6-(1,3-dioxoisindolin-2-yl)-5-methyldihydro-2H-pyran-3,3(4H)-dicarboxylate (**6db**) (81 mg, 0.162 mmol, 81% yield, 90% pure) as a colorless oil.

dr 3:1, diastereoisomeric ratio was calculated in ¹H NMR of the isolated product integrating peaks at 5.80 and 5.69.

The major *cis-trans* diastereoisomer was characterized. Strong correlations between the signals at 5.80 and 5.44, 5.80 and 1.27-1.17, and 5.44 and 1.27-1.17 were observed. This suggests an axial orientation for the three substituents. In addition, a large coupling constant (*J* = 12 Hz) of the signal at 5.80 suggests that this proton is in axial position in anti-periplanar relationship with a proton of the neighboring CH₂.

R_f 0.43 (7:3 Pentane/Ethyl Acetate).

¹H NMR (400 MHz, CDCl₃)¹⁵ on a 3(*maj*):1(*min*) mixture δ 7.92 – 7.77 (m, 2.6 H, Phth *maj* + *min*),¹⁶ 7.77 – 7.65 (m, 2.6 H, Phth *maj* + *min*), 7.48 – 7.38 (m, 2 H, Ph *maj*), 7.31 – 7.23 (m, 0.6 H, Ph *min*),¹¹ 7.23 – 7.13 (m, 2.6 H, Ph *maj* + *min*),¹⁶ 5.80 (dd, *J* = 12.0, 2.8 Hz, 1 H, N-C(*H*)-O *maj*), 5.69 (dd, *J* = 11.8, 2.9 Hz, 0.3 H, N-C(*H*)-O *min*), 5.44 (s, 1 H, O-C(*H*)-Ph *maj*), 5.13 (s, 0.3 H, O-C(*H*)-Ph *min*), 4.28 – 3.89 (m, 5.2 H, 2 x OCH₂ *maj* + *min*), 3.82 – 3.67 (m, 1 H, CH₂ *maj*),^{16,17} 3.43 – 3.30 (m, 0.3 H, CH₂ *min*),¹⁷ 3.04 – 2.91 (m, 1 H, Me-CH *maj*),¹⁷ 2.57 – 2.45 (m, 0.3 H, Me-CH *min*),¹⁷ 1.68 (ddd, *J* = 13.5, 3.6, 3.6 Hz, 0.3 H, CH₂ *min*),¹⁷ 1.55 (ddd, *J* = 13.4, 2.8, 2.8 Hz, 1 H, CH₂ *maj*),¹⁷ 1.27 – 1.17 (m, 7.8 H, 2 x CH₃ *maj* + *min*, 2 x OCH₂CH₃ *maj* + *min*),¹⁶ 1.12 (t, *J* = 7.1 Hz, 0.6 H, OCH₂CH₃ *min*),¹⁶ 0.94 (t, *J* = 7.2 Hz, 3 H, OCH₂CH₃ *maj*).

¹⁵ 90 % pure.

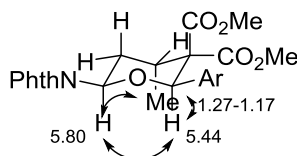
¹⁶ Overlapping with signals of another diastereoisomer present in less than 10% and impurity.

¹⁷ Attributed by HSQC.

^{13}C NMR (101 MHz, CDCl_3)¹⁸ δ 170.2, 169.4, 168.3, 167.1, 167.0, 166.6, 137.4, 137.1, 134.3, 134.3, 133.4, 131.7, 129.7, 128.8, 128.3, 127.8, 127.4, 127.2, 123.6, 82.6, 79.3, 76.5, 75.4, 62.8, 61.5, 61.1, 60.9, 60.7, 60.2, 39.3, 32.8, 31.1, 30.4, 17.6, 16.3, 14.04, 13.98, 13.8, 13.5.

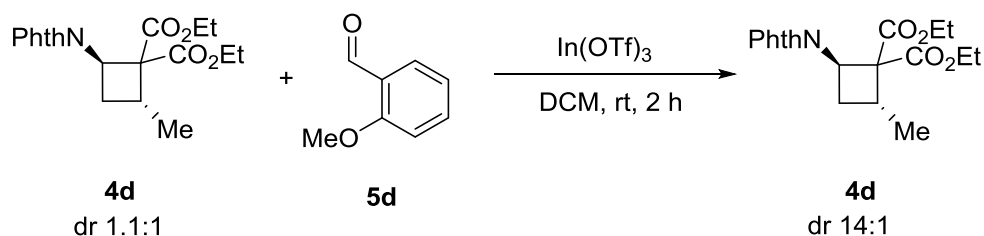
IR 2982 (w), 2983 (w), 2904 (w), 1780 (w), 1723 (s), 1464 (w), 1374 (s), 1287 (w), 1258 (m), 1230 (m), 1201 (m), 1090 (m), 1043 (m), 1033 (m).

HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{26}\text{NO}_7\text{ClNa}^+$ $[\text{M}+\text{Na}]^+$ 522.1290; found 522.1277.



ROESY

Diastereoisomeric resolution of diethyl 2-(1,3-dioxoisindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (**86**)



In a glovebox, indium triflate (22.5 mg, 0.0400 mmol, 0.2 eq) was added to a microwave vial. The vial was sealed with a Teflon septum and taken out of the glovebox. Dry dichloromethane (2 mL) was added. Diethyl 2-(1,3-dioxoisindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (**4d**) (71.9 mg, 0.200 mmol, dr 1.1:1, 1 eq) was dissolved in dry dichloromethane (2 mL) and added. 2-Methoxybenzaldehyde (**5d**) (22.5 mg, 0.300 mmol, 1.5 eq) was then dissolved in dry dichloromethane (2 mL) and added. The reaction was stirred at room temperature for 2 h, and then was filtered over a pad of alumina, eluted with ethyl acetate and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2 , 85:15 Pentane/Ethyl Acetate) affording diethyl 2-(1,3-dioxoisindolin-2-yl)-4-methylcyclobutane-1,1-dicarboxylate (**4d**) (42.4 mg, 0.117 mmol, quantitative yield for the major diastereoisomer) as a pale yellow oil.

dr 14:1, diastereoisomeric ratio was calculated in ^1H NMR of the isolated product integrating peaks at 5.58 and 4.91.

The major *trans* diastereoisomer was characterized. Strong correlations between the signals at 5.58 and 1.98, 5.58 and 1.14, and 1.98 and 1.14 were observed.

R_f 0.44 (6:4 Pentane/Ethyl Acetate).

^1H NMR (400 MHz, CDCl_3) only *maj* diastereoisomer characterized δ 7.82 (dd, $J = 5.4, 3.0$ Hz, 2 H, Phth), 7.70 (dd, $J = 5.5, 3.0$ Hz, 2 H, Phth), 5.58 (ddd, $J = 9.9, 8.3, 1.2$ Hz, 1 H, N-CH), 4.21 (q, $J = 7.1$ Hz, 2 H, OCH_2),¹⁹ 3.97 (m, 2 H, OCH_2),¹⁹ 3.65 – 3.54 (m, 1 H, $\text{CH}_3\text{-CH}$), 3.20 (ddd, $J = 11.7, 10.0, 8.3$ Hz, 1 H, CH_2), 1.98 (ddd, $J = 11.7, 10.0, 5.4$ Hz, 1 H, CH_2), 1.23 (t, $J = 7.1$ Hz, 3 H, OCH_2CH_3), 1.14 (d, $J = 7.3$ Hz, 3 H, CH_3), 0.90 (t, $J = 7.1$ Hz, 3 H, OCH_2CH_3).

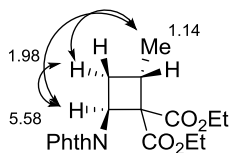
¹⁸ One aromatic carbon not resolved.

¹⁹ Overlapping with signals of the minor diastereoisomer.

^{13}C NMR (101 MHz, CDCl_3) only *major* diastereoisomer characterized δ 168.5, 168.4, 168.1, 134.1, 131.8, 123.3, 62.0, 61.7, 61.6, 45.1, 31.1, 28.7, 16.2, 14.2, 13.6.

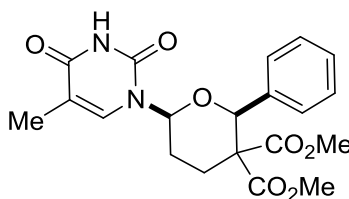
IR 2980 (w), 2943 (w), 2911 (w), 2876 (w), 1779 (w), 1719 (s), 1465 (w), 1376 (s), 1335 (w), 1256 (s), 1216 (m), 1153 (w), 1116 (w), 1091 (w), 1041 (m).

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{NNaO}_6^+$ $[\text{M}+\text{Na}]^+$ 382.1261; found 382.1265.



ROESY

Dimethyl (5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (6ea)



Following the general procedure **GP5**, using benzaldehyde (**5a**) (46 μL , 0.45 mmol, 1.5 eq) cyclobutane **4e** (120 mg, 0.300 mmol, 1.0 eq), a mixture of diastereoisomers (20:1 by integration of methyl esters at 3.52 ppm and 3.49 ppm) **6ea** (102 mg, 0.255 mmol, 85% NMR yield)²⁰ was obtained after column chromatography as a colorless foam. After recrystallization in ethanol, the pure product **6ea** (94 mg, 0.23 mmol, 78% isolated yield) was obtained as a colorless foam and as a mixture of diastereoisomers (> 20:1 by integration of methyl esters at 3.52 ppm and 3.49 ppm).

R_f 0.27 (3:7 Pentane/Ethyl acetate).

Mp 226.2– 227.9 °C.

^1H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.38 (s, 1 H, NH), 7.40 – 7.35 (m, 2 H, Ar-H), 7.34 – 7.27 (m, 4 H, Ar-H and thymine C=C-H), 5.96 (dd, J = 11.1, 2.9 Hz, 1 H, tetrahydropyran-NCH), 5.23 (s, 1 H, tetrahydropyran-CH), 3.68 (s, 3 H, ester CH_3), 3.52 (s, 3 H, ester CH_3), 2.74 – 2.64 (m, 1 H, tetrahydropyran- CH_2), 2.38 (tdd, J = 12.6, 11.0, 4.1 Hz, 1 H, tetrahydropyran- CH_2), 2.25 (td, J = 13.4, 4.1 Hz, 1 H, tetrahydropyran- CH_2), 1.99 (d, J = 1.2 Hz, 3 H, thymine- CH_3), 1.97 – 1.90 (m, 1 H, tetrahydropyran- CH_2).

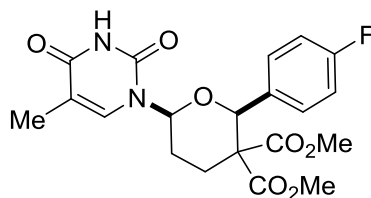
^{13}C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 170.3, 169.2, 163.4, 149.9, 137.5, 135.4, 128.5, 127.7, 127.5, 111.6, 82.3, 82.1, 57.1, 52.8, 52.0, 31.6, 26.6, 12.8.

IR 3191 (w), 3041 (w), 2954 (w), 2361 (w), 1725 (s), 1693 (s), 1461 (w), 1271 (s), 1096 (w), 1043 (w), 915 (w), 735 (m).

HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{NaO}_7^+$ $[\text{M}+\text{Na}]^+$ 425.1319, found 425.1324.

Dimethyl 2-(4-fluorophenyl)-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (6ef).

²⁰ Benzamide as impurity which is not possible to separate by column chromatography.



Following the general procedure **GP5**, using 4-fluorobenzaldehyde (**5f**) (48 μ L, 0.45 mmol, 1.5 eq) cyclobutane **4e** (120 mg, 0.300 mmol, 1.0 eq), a mixture of diastereoisomers (12:1 by integration of methyl esters at 3.54 ppm and 3.49 ppm) **6ef** (99 mg, 0.24 mmol, 79% NMR yield)²⁰ was obtained after column chromatography as a colorless foam. After recrystallization in ethanol, the pure product **6ef** (88 mg, 0.21 mmol, 70% isolated yield) was obtained as a colorless foam and as a mixture of diastereoisomers (12:1 by integration of methyl esters at 3.54 ppm and 3.49 ppm).

R_f 0.30 (3:7 Pentane/Ethyl acetate).

Mp 94.8- 96.9°C.

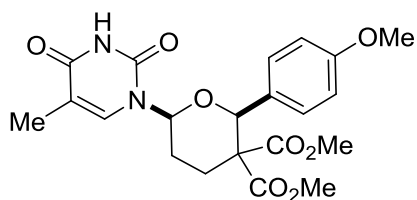
¹H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.06 (s, 1 H, NH), 7.40 – 7.33 (m, 2 H, Ar-H), 7.29 (d, *J* = 1.3 Hz, 1 H, thymine C=C-H), 7.03 – 6.95 (m, 2 H, Ar-H), 5.95 (dd, *J* = 11.3, 2.9 Hz, 1 H, tetrahydropyran-NCH), 5.21 (s, 1 H, tetrahydropyran-CH), 3.69 (s, 3 H, ester CH₃), 3.54 (s, 3 H, ester CH₃), 2.74 – 2.63 (m, 1 H, tetrahydropyran-CH₂), 2.48 – 2.32 (m, 1 H, tetrahydropyran-CH₂), 2.32 – 2.20 (m, 1 H, tetrahydropyran-CH₂), 1.99 (d, *J* = 1.2 Hz, 3 H, thymine-CH₃), 1.93 (dq, *J* = 9.3, 3.3 Hz, 1 H, tetrahydropyran-CH₂).

¹³C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 170.3, 169.1, 163.6, 162.5 (d, *J* = 225.5 Hz), 150.2, 135.2, 133.4 (d, *J* = 3.3 Hz), 129.3 (d, *J* = 8.1 Hz), 114.6 (d, *J* = 21.4 Hz), 111.8, 82.0, 81.6, 57.0, 52.8, 52.1, 31.4, 26.5, 12.8.

IR 3203 (w), 3055 (w), 2961 (w), 2361 (w), 2255 (w), 1724 (s), 1691 (s), 1515 (w), 1464 (w), 1267 (s), 1229 (m), 1100 (m), 1050 (m), 913 (m), 735 (m).

HRMS (ESI) calcd for C²⁰H²¹FN²NaO⁷⁺ [M+Na]⁺ 443.1225; found 443.1224.

Dimethyl 2-(4-methoxyphenyl)-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (6ec).



Following the general procedure **GP5**, using *p*-anisaldehyde (**5c**) (55 μ L, 0.45 mmol, 1.5 eq) cyclobutane **4e** (120 mg, 0.300 mmol, 1.0 eq), a mixture of diastereoisomers (5:1 by integration of methyl esters at 3.55 ppm and 3.49 ppm) **6ec** (115 mg, 0.264 mmol, 88% NMR yield)²⁰ was obtained after column chromatography as a slightly yellow foam. After recrystallization in ethanol, the pure product **6ec** (99 mg, 0.22 mmol, 76% isolated yield) was obtained as a slightly yellow foam and as a mixture of diastereoisomers (7:1 by integration of methyl esters at 3.55 ppm and 3.49 ppm).

R_f 0.26 (3:7 Pentane/Ethyl acetate).

Mp 97.4- 99.5 °C.

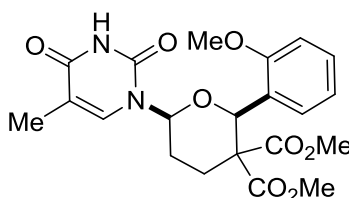
¹H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) 9.03 (s, 1 H, NH), 7.31 (d, *J* = 1.3 Hz, 1 H, thymine C=C-H), 7.30 – 7.27 (m, 2 H, Ar-H), 6.86 – 6.78 (m, 2 H, Ar-H), 5.95 (dd, *J* = 11.1, 2.9 Hz, 1H, tetrahydropyran-NCH), 5.16 (s, 1 H, tetrahydropyran-CH), 3.78 (s, 3 H, O-Me CH₃), 3.67 (s, 3 H, ester CH₃), 3.55 (s, 3 H, ester CH₃), 2.74 – 2.61 (m, 1 H, tetrahydropyran-CH₂), 2.35 (tdd, *J* = 12.6, 11.0, 4.1 Hz, 1 H, tetrahydropyran-CH₂), 2.22 (td, *J* = 13.4, 4.1 Hz, 1 H, tetrahydropyran-CH₂), 1.97 (d, *J* = 1.3 Hz, 3 H, thymine-CH₃), 1.95 – 1.88 (m, 1 H, tetrahydropyran-CH₂).

¹³C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 170.3, 169.3, 163.7, 159.5, 150.2, 135.4, 129.6, 128.8, 113.0, 111.6, 82.0, 82.0, 57.0, 55.3, 52.7, 52.1, 31.4, 26.6, 12.8.

IR 3191 (w), 3049 (w), 2954 (w), 2839 (w), 2360 (w), 2257 (w), 1687 (s), 1517 (w), 1461 (m), 1255 (s), 1109 (m), 1044 (m), 910 (m), 817 (w), 730 (s).

HRMS (ESI) calcd for C₂₁H₂₄N₂NaO₈⁺ [M+Na]⁺ 455.1425; found 455.1428.

Dimethyl 2-(2-methoxyphenyl)-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (6ed):



Following the general procedure **GP5**, using o-anisaldehyde (**5d**) (61 mg, 0.45 mmol, 1.5 eq) cyclobutane **4e** (120 mg, 0.300 mmol, 1.0 eq), a mixture of diastereoisomers (10:1 by integration of methyl esters at 3.54 ppm and 3.40 ppm) **6ed** (108 mg, 0.252 mmol, 84% NMR yield)²⁰ was obtained after column chromatography as a white solid. After recrystallization in ethanol, the pure product **6ed** (98 mg, 0.23 mmol, 76% isolated yield) was obtained as white solid and as a mixture of diastereoisomers (10:1 by integration of methyl esters at 3.54 ppm and 3.40 ppm).

R_f 0.29 (3:7 Pentane/Ethyl acetate).

Mp 193.9- 196.2 °C.

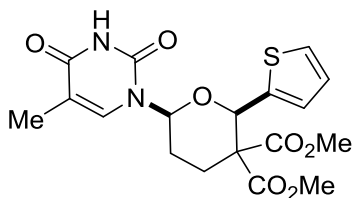
¹H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.05 (s, 1 H, NH), 7.77 (dd, *J* = 7.8, 1.7 Hz, 1 H, Ar-H), 7.39 (d, *J* = 1.4 Hz, 1 H, thymine C=C-H), 7.31 – 7.27 (m, 1 H, Ar-H), 7.01 (td, *J* = 7.6, 1.1 Hz, 1 H, Ar-H), 6.80 (dd, *J* = 8.3, 1.1 Hz, 1 H, Ar-H), 5.92 (dd, *J* = 11.0, 3.0 Hz, 1 H, tetrahydropyran-NCH), 5.29 (s, 1 H, tetrahydropyran-CH), 3.77 (s, 3 H, O-Me CH₃), 3.69 (s, 3 H, ester CH₃), 3.54 (s, 3 H, ester CH₃), 2.63 – 2.55 (m, 2 H, tetrahydropyran-CH₂), 2.05 – 2.01 (m, 1 H, tetrahydropyran-CH₂), 1.99 (d, *J* = 1.3 Hz, 3 H, thymine-CH₃), 1.85 – 1.74 (m, 1 H, tetrahydropyran-CH₂).

¹³C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 169.0, 168.9, 163.8, 156.2, 150.0, 135.7, 129.9, 129.4, 125.6, 120.3, 111.5, 109.4, 82.2, 76.4, 56.9, 55.5, 52.5, 52.3, 31.1, 27.3, 12.9.

IR 3191 (w), 3045 (w), 2955 (w), 2841 (w), 2361 (w), 2338 (w), 2253 (w), 1731 (s), 1690 (s), 1464 (m), 1377 (w), 1259 (s), 1104 (m), 1047 (m), 914 (m), 733 (s).

HRMS (ESI) calcd for C₂₁H₂₄N₂NaO₈⁺ [M+Na]⁺ 455.1425; found 455.1429.

Dimethyl 6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(thiophen-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (6eg):



Following the general procedure **GP5**, using thiophene-2-carbaldehyde (**5g**) (42 μ L, .45 mmol, 1.5 eq) cyclobutane **4e** (120 mg, 0.300 mmol, 1.0 eq), a mixture of diastereoisomers (12:1 by integration of methyl esters at 3.56 ppm and 3.54 ppm) **6eg** (111 mg, 0.270 mmol, 90% NMR yield)²⁰ was obtained after column chromatography as a white foam. After recrystallization in ethanol, the pure product **6eg** (97 mg, 0.24 mmol, 79% isolated yield) was obtained as white foam and as a mixture of diastereoisomers (7:1 by integration of methyl esters at 3.56 ppm and 3.54 ppm).

R_f 0.24 (4:6 Pentane/Ethyl acetate).

Mp 186.4-188.3°C.

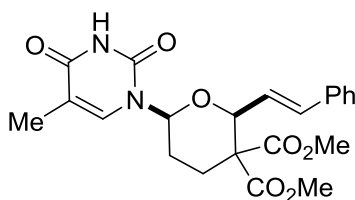
¹H NMR (400 MHz, Chloroform-d, major diastereoisomer) δ 9.74 (s, 1 H, NH), 7.27 (d, J = 1.4 Hz, 1 H, , thymine C=C-H), 7.23 (dd, J = 5.1, 1.2 Hz, 1 H, thiophene-H), 7.04 (dd, J = 3.5, 1.1 Hz, 1 H, thiophene -H), 6.92 (dd, J = 5.1, 3.6 Hz, 1 H, thiophene -H), 5.95 (dd, J = 10.9, 2.8 Hz, 1 H, tetrahydropyran-NCH), 5.48 (d, J = 0.8 Hz, 1 H, tetrahydropyran-CH), 3.71 (s, 3 H, ester CH₃), 3.56 (s, 3 H, ester CH₃), 2.70 – 2.61 (m, 1 H, tetrahydropyran-CH₂), 2.32 – 2.24 (m, 1 H, tetrahydropyran-CH₂), 2.23 – 2.14 (m, 1 H, tetrahydropyran-CH₂), 1.95 (d, J = 1.3 Hz, 3 H, thymine-CH₃), 1.92 (dd, J = 7.9, 2.3 Hz, 1 H, tetrahydropyran-CH₂).

¹³C NMR (101 MHz, Chloroform-d, major diastereoisomer) δ 170.2, 168.9, 163.6, 150.1, 139.8, 135.2, 126.2, 126.2, 125.5, 111.7, 82.1, 79.1, 57.4, 52.9, 52.5, 31.1, 26.5, 12.8.

IR 3195 (w), 3042 (w), 2954 (w), 2832 (w), 2362 (w), 2252 (w), 2252 (w), 1690 (s), 1441 (w), 1375 (w), 1271 (s), 1103 (m), 1050 (w), 913 (m), 734 (m).

HRMS (ESI) calcd for C₁₈H₂₀N₂NaO₇S⁺ [M+Na]⁺ 431.0883; found 431.0879.

(E)-dimethyl 6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-styryldihydro-2H-pyran-3,3(4H)-dicarboxylate (6ee).



Following the general procedure **GP5**, using cinnamaldehyde (**5e**) (57 μ L, .45 mmol, 1.5 eq) cyclobutane **4e** (120 mg, 0.300 mmol, 1.0 eq), a mixture of diastereoisomers (2.5:1 by integration of methyl esters at 3.72 ppm and 3.67 ppm) **6ee** (104 mg, 0.243 mmol, 81% NMR yield)²⁰ was obtained after column chromatography as a yellow foam. After recrystallization in ethanol, the pure product **6ee** (89 mg, 0.21 mmol, 69% isolated yield) was obtained as yellow foam and as a mixture of diastereoisomers (2.5:1 by integration of methyl esters at 3.72 ppm and 3.67 ppm).

R_f 0.37 (3:7 Pentane/Ethyl acetate).

Mp 73.7-75.5 °C.

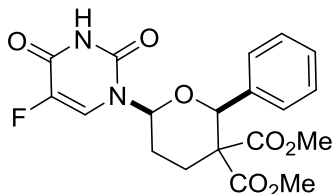
¹H NMR (400 MHz, Chloroform-*d*) δ 9.03 (s, 1H, N H, major diastereoisomer), 8.91 (s, 1 H, NH, minor diastereoisomer), 7.39 – 7.21 (m, 10 H, Ar-H, major and minor diastereoisomers), 7.18 (dd, *J* = 3.4, 2.0 Hz, 2 H, thymine C=C-H, , major and minor diastereoisomers), 6.79 (dd, *J* = 15.7, 1.1 Hz, 1 H, vinyl CH, minor diastereoisomer), 6.61 – 6.49 (m, 2 H, vinyl CH, major diastereoisomer), 6.31 (dd, *J* = 15.7, 8.0 Hz, 1 H, , vinyl CH, minor diastereoisomer), 6.02 (dd, *J* = 11.2, 2.8 Hz, 1 H, tetrahydropyran-NCH, minor diastereoisomer), 5.91 (dd, *J* = 11.0, 3.0 Hz, 1 H, tetrahydropyran-NCH, major diastereoisomer), 5.40 (d, *J* = 8.0 Hz, 1 H, tetrahydropyran-CH, minor diastereoisomer), 4.68 (d, *J* = 5.3 Hz, 1 H, tetrahydropyran-CH, major diastereoisomer), 3.87 (s, 3 H, ester CH₃, minor diastereoisomer), 3.78 (s, 3 H, ester CH₃, major diastereoisomer), 3.71 (s, 3 H, ester CH₃, major diastereoisomer), 3.66 (s, 3 H, ester CH₃, minor diastereoisomer), 2.65 (ddd, *J* = 13.6, 4.2, 2.7 Hz, 1 H, tetrahydropyran-CH₂, major diastereoisomer), 2.58 – 2.35 (m, 2 H, tetrahydropyran-CH₂, minor diastereoisomer), 2.26 – 2.15 (m, 1 H, tetrahydropyran-CH₂, major diastereoisomer), 2.15 – 1.98 (m, 2 H, tetrahydropyran-CH₂, major diastereoisomer and minor diastereoisomer), 1.95 (d, *J* = 1.2 Hz, 3 H, thymine-CH₃, major diastereoisomer), 1.93 (d, *J* = 1.3 Hz, 3 H, thymine-CH₃, minor diastereoisomer), 1.92 – 1.87 (m, 1 H, tetrahydropyran-CH₂, major diastereoisomer), 1.56 – 1.43 (m, 1 H, tetrahydropyran-CH₂, minor diastereoisomer).

¹³C NMR (101 MHz, Chloroform-*d*) δ 170.0, 169.6, 169.0, 168.3, 163.7, 163.7, 150.2, 150.1, 137.8, 136.5, 135.3, 135.3, 132.7, 128.8, 128.8, 128.6, 128.1, 127.1, 126.8, 125.2, 120.4, 111.6, 111.4, 81.8, 81.7, 76.1, 57.0, 56.6, 53.4, 53.2, 53.0, 52.6, 30.7, 27.5, 26.8, 24.1, 12.8.²¹

IR 3730 (w), 2955 (w), 2361 (s), 2336 (s), 1744 (m), 1699 (s), 1666 (m), 1442 (w), 1275 (m), 1099 (w), 976 (w), 914 (w), 736 (m).

HRMS (ESI) calcd for C₂₂H₂₄N₂NaO₇⁺ [M+Na]⁺ 451.1476; found 451.1474.

Dimethyl (5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (6fa)



Following the general procedure **GP5**, using benzaldehyde (**5a**) (46 μL, 0.45 mmol, 1.5 eq) and cyclobutane **4f** (121 mg, 0.300 mmol, 1.0 eq), a mixture of diastereoisomers (13:1 by integration of methyl esters at 3.52 ppm and 3.48 ppm) **6fa** (78 mg, 0.19 mmol, 64% NMR yield)²⁰ was obtained after column chromatography as a white foam. After recrystallization in ethanol, the pure product **6fa** (68 mg, 0.17 mmol, 56% yield) was obtained as white foam and as a mixture of diastereoisomers (>20:1 by integration of methyl esters at 3.52 ppm and 3.48 ppm).

R_f 0.32 (5:5 Pentane/Ethyl acetate).

Mp 80.1- 81.7°C.

¹H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 9.95 (s, 1 H, NH), 7.63 (d, *J* = 5.8 Hz, 1 H, Ar-H), 7.39 – 7.34 (m, 2 H, Ar-H), 7.33 – 7.27 (m, 3 H, Ar-H and F-uracil C=C-H), 6.01 – 5.93 (m, 1 H, tetrahydropyran-NCH), 5.23 (s, 1H, tetrahydropyran-CH), 3.67 (s, 3 H, ester CH₃), 3.52 (s, 3 H, ester CH₃), 2.71 – 2.62 (m, 1 H, tetrahydropyran-CH₂), 2.40 – 2.19 (m, 2 H, tetrahydropyran-CH₂), 2.02 – 1.95 (m, 1 H, tetrahydropyran-CH₂).

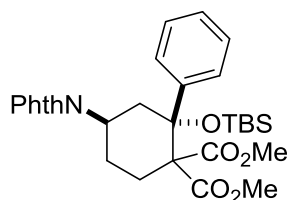
²¹ 3 carbons of the minor diastereoisomer are not resolved.

^{13}C NMR (101 MHz, Chloroform- d , major diastereoisomer) δ 170.1, 169.1, 156.98 (d, J = 26.6 Hz), 148.9, 140.93 (d, J = 238.5 Hz), 137.2, 128.5, 127.7, 127.4, 124.12 (d, J = 33.6 Hz), 82.2, 82.1, 56.9, 52.8, 52.1, 31.2, 26.5.

IR 3204 (w), 3064 (w), 2955 (w), 2361 (m), 2257 (w), 1717 (s), 1457 (w), 1368 (w), 1265 (s), 1103 (m), 1043 (w), 912 (s), 731 (s).

HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{NaO}_7^+$ $[\text{M}+\text{Na}]^+$ 429.1068; found 429.1065.

Dimethyl -2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-phenylcyclohexane-1,1-dicarboxylate (8aa)



Following the general procedure **GP6**, using dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and *tert*-butyldimethyl(1-phenylvinyl)oxy)silane (**7a**) (70.4 mg, 0.300 mmol, 1.5 eq), dimethyl -2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-phenylcyclohexane-1,1-dicarboxylate (**8aa**) (105 mg, 0.190 mmol, 95 % yield) was obtained as a colorless solid.

Mp 188.8-190.0°C.

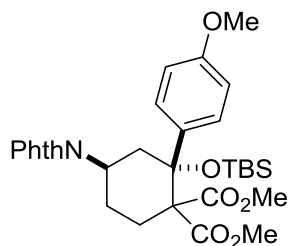
^1H NMR (400 MHz, CDCl_3) δ 7.83 (dd, J = 5.5, 3.0 Hz, 2 H, Phth), 7.72 (dd, J = 5.4, 3.1 Hz, 2 H, Phth), 7.44 – 7.38 (m, 2 H, Ar), 7.26 – 7.21 (m, 3 H, Ar), 4.86 (tt, J = 12.5, 4.7 Hz, 1 H, N-C-H), 3.96 (dd, J = 13.6, 12.6 Hz, 1 H, CH_2), 3.66 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 2.91 (td, J = 14.2, 3.7 Hz, 1 H, CH_2 cyclohexane), 2.31 (dt, J = 13.8, 3.5 Hz, 1 H, CH_2), 2.23 – 2.01 (m, 2 H, CH_2 cyclohexane), 1.88 – 1.74 (m, 1 H, CH_2 cyclohexane), 1.06 (s, 9 H, Si- t Bu), 0.14 (s, 3 H, Si-Me), -0.55 (s, 3 H, 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).

The data for **8aa** matches the reported values.⁵

Dimethyl-2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-(4-methoxyphenyl)cyclohexane-1,1-dicarboxylate (8ab)



Following the general procedure **GP6**, using dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (65.5 mg, 0.200 mmol, 1 eq) and *tert*-butyl(1-(4-methoxyphenyl)vinyl)oxy)dimethylsilane (**7b**) (79.0 mg, 0.300 mmol, 1.5 eq), dimethyl -2-(*tert*-

butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-(4-methoxyphenyl)cyclohexane-1,1-dicarboxylate (**8ab**) (105.2 mg, 0.181 mmol, 90%) was obtained as a colorless solid.

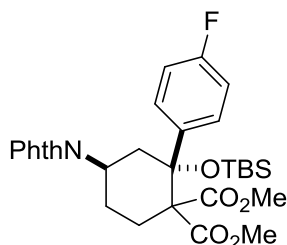
¹H NMR (400 MHz, CDCl₃) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2 H, Ar Phth), 7.71 (dd, *J* = 5.4, 3.1 Hz, 2 H, Ar Phth), 7.34 – 7.29 (m, 2 H, Ar), 6.91 – 6.64 (m, 2 H, Ar), 5.05 – 4.69 (m, 1 H, N-C-H), 3.92 (dd, *J* = 13.5, 12.6 Hz, 1 H, CH₂), 3.79 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 2.89 (td, *J* = 14.2, 3.7 Hz, 1 H, CH₂), 2.30 (dt, *J* = 13.8, 3.5 Hz, 1 H, CH₂), 2.22 – 1.96 (m, 2 H, CH₂), 1.90 – 1.69 (m, 1 H, CH₂), 1.05 (s, 9 H, OTBS), 0.14 (s, 3 H, OTBS), -0.50 (s, 3 H, OTBS).

¹³C NMR (101 MHz, CDCl₃) δ 171.5, 171.2, 169.7, 160.12, 136.5, 135.4, 133.4, 131.2, 124.6, 113.0, 80.7, 65.8, 56.5, 53.6, 53.2, 47.8, 38.2, 30.7, 27.7, 26.6, 20.6, -0.0, -1.1.

IR 2953 (w), 2933 (w), 2856 (w), 1731 (s), 1712 (s), 1612 (w), 1373 (m), 1373 (m), 1254 (m), 1037 (s), 840 (m).

HRMS (ESI) calcd for C₃₁H₄₀NO₈Si⁺ [M+H]⁺ 582.2518; found 582.2500.

Dimethyl-2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-(4-fluorophenyl)cyclohexane-1,1-dicarboxylate (8ac**)**



Following the general procedure **GP6**, using dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and *tert*-butyl(1-(4-fluorophenyl)vinyl)oxydimethylsilane (**7c**) (76.0 mg, 0.300 mmol, 1.5 eq), dimethyl 2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-(4-fluorophenyl)cyclohexane-1,1-dicarboxylate (**8ac**) (113 mg, 0.198 mmol, 99%) was obtained as a colorless solid.

¹H NMR (400 MHz, CDCl₃) δ 7.83 (dd, *J* = 5.5, 3.0 Hz, 2 H, Ar Phth), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2 H, Ar Phth), 7.48 – 7.34 (m, 2 H, Ar), 6.93 (dd, *J* = 9.3, 8.2 Hz, 2 H, Ar), 4.84 (tt, *J* = 12.6, 4.6 Hz, 1 H, N-C-H), 3.97 (dd, *J* = 13.6, 12.6 Hz, 1 H, CH₂), 3.67 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 2.88 (td, *J* = 14.2, 3.7 Hz, 1 H, CH₂), 2.31 (dt, *J* = 13.9, 3.4 Hz, 1 H, CH₂), 2.22 – 1.94 (m, 2 H, CH₂), 1.91 – 1.74 (m, 1 H, CH₂), 1.05 (s, 9 H, OTBS), 0.17 (s, 3 H, OTBS), -0.51 (s, 3 H, OTBS).

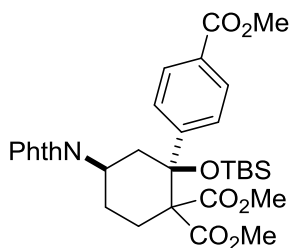
¹³C NMR (101 MHz, CDCl₃) δ 169.8, 169.7, 168.3, 134.0, 132.0, 130.5 (d, *J* = 8.0 Hz), 123.2, 113.1 (d, *J* = 21.1 Hz), 79.2, 64.4, 52.2, 51.8, 46.3, 36.7, 29.2, 26.2, 25.1, 19.1, -1.4, -2.5.²²

IR 2953 (w), 2952 (w), 2857 (w), 2856 (w), 1735 (s), 1715 (s), 1375 (m), 1245 (m), 1244 (m), 1039 (m).

HRMS (ESI) calcd for C₃₀H₃₆FNNaO₇Si⁺ [M+Na]⁺ 592.2137; found 592.2142.

Dimethyl-2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-(4-(methoxycarbonyl)phenyl)cyclohexane-1,1-dicarboxylate (8ad**)**

²² Carbon with fluoride not resolved.



Following the general procedure **GP6**, using dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and methyl 4-(1-(*tert*-butyldimethylsilyl)oxy)vinyl)benzoate (**7d**) (88.0 mg, 0.300 mmol, 1.5 eq). A mixture of two diastereomers of dimethyl -2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-2-(4-methoxycarbonyl)phenyl)cyclohexane-1,1-dicarboxylate (**8ad**) (99.6 mg, 0.163 mmol, 82%) was obtained as a colorless solid.

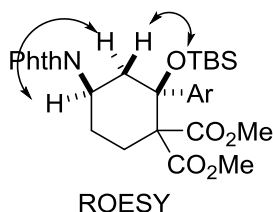
dr = 2:1, Diastereoisomeric ratio was calculated in ^1H crude NMR integrating peaks at 0.17 and 0.12. Analysis of isolated fractions of the chromatography column allowed the characterization of major *cis* diastereomer.

^1H NMR (400 MHz, CDCl_3) δ 7.97 – 7.91 (m, 2 H, Ar), 7.84 (dd, J = 5.4, 3.0 Hz, 2 H, Ar Phth), 7.72 (dd, J = 5.4, 3.0 Hz, 2 H, Ar Phth), 7.55 – 7.48 (m, 2 H, Ar), 4.85 (tt, J = 12.5, 4.7 Hz, 1 H, N-C-H), 3.99 (dd, J = 13.6, 12.6 Hz, 1 H, CH_2), 3.90 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 2.90 (td, J = 14.2, 3.7 Hz, 1 H, CH_2), 2.32 (dt, J = 13.8, 3.4 Hz, 1 H, CH_2), 2.21 – 2.01 (m, 2 H, CH_2), 1.83 (dd, J = 13.1, 3.5 Hz, 1 H, CH_2), 1.05 (s, 9 H, OTBS), 0.17 (s, 3 H, OTBS), -0.56 (s, 3 H, OTBS).

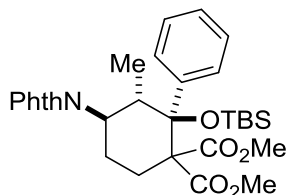
^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 169.6, 168.3, 166.9, 148.1, 134.0, 131.9, 129.2, 128.8, 127.6, 123.2, 79.4, 64.4, 52.2, 52.0, 51.9, 46.2, 36.5, 29.2, 26.2, 25.1, 19.1, -1.4, -2.5.

IR 2955 (w), 2955 (w), 2902 (w), 2902 (w), 2901 (w), 2901 (w), 2860 (w), 1716 (s), 1375 (m), 1375 (m), 1281 (m), 1281 (m), 1246 (w), 1040 (m), 1040 (m).

HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{39}\text{NNaO}_9\text{Si}^+$ $[\text{M}+\text{Na}]^+$ 632.2286; found 632.2282.



Dimethyl-2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-3-methyl-2-phenylcyclohexane-1,1-dicarboxylate (**8ae**)



Following the general procedure **GP6**, using dimethyl 2-(1,3-dioxoisindolin-2-yl)cyclobutane-1,1-dicarboxylate (**4a**) (63.5 mg, 0.200 mmol, 1 eq) and (*Z*)-*tert*-butyldimethyl(1-phenylprop-1-en-1-yl)oxy)silane (**7e**) (74.6 mg, 0.300 mmol, 1.5 eq), a mixture of two diastereomers of dimethyl -2-(*tert*-butyldimethylsilyl)oxy)-4-(1,3-dioxoisindolin-2-yl)-3-methyl-2-phenylcyclohexane-1,1-dicarboxylate (**8ae**) (102 mg, 0.181 mmol, 90%) was obtained as a colorless solid.

dr = 2:1, Diastereoisomeric ratio was calculated in ^1H crude NMR integrating peaks at 4.75 and 4.33. Analysis of isolated fractions of the chromatography column allowed the characterization of each diastereomer.

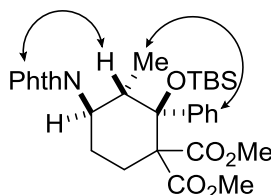
Major *cis*-diastereoisomer

^1H NMR (400 MHz, CDCl_3) δ 7.99 – 7.86 (m, 2 H, Ar Phth), 7.86 – 7.73 (m, 2 H, Ar Phth), 7.70 – 7.59 (m, 2 H, Ar), 7.32 – 7.24 (m, 3 H, Ar), 4.62 (td, $J = 12.0, 4.7$ Hz, 1 H, N-C-H), 4.38 (dq, $J = 11.5, 6.8$ Hz, 1 H, CH-Me), 3.71 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.03 – 2.80 (m, 1 H, CH_2), 2.42 – 2.25 (m, 2 H, CH_2), 1.93 – 1.80 (m, 1 H, CH_2), 1.17 (s, 9 H, OTBS), 0.92 (d, $J = 6.8$ Hz, 3 H, CH_3), 0.42 (s, 3 H, OTBS), 0.00 (s, 3 H, OTBS).

^{13}C NMR²³ (101 MHz, CDCl_3) δ 169.8, 169.7, 168.6, 140.7, 134.1, 132.3, 131.6, 129.7, 127.2, 123.4, 85.5, 65.8, 52.2, 52.2, 51.5, 36.3, 29.4, 26.6, 25.4, 20.4, 13.6, -0.1, -1.6.

IR 2951 (w), 2950 (w), 2857 (w), 1736 (s), 1713 (s), 1372 (m), 1371 (m), 1276 (m), 1240 (m), 1134 (m), 1051 (m), 836 (w).

HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{40}\text{NO}_7\text{Si}^+$ $[\text{M}+\text{H}]^+$ 566.2569; found 566.2563.



ROESY

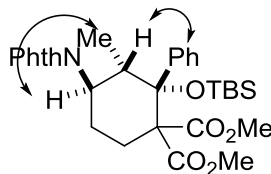
Minor *trans*-diastereoisomer

^1H NMR (400 MHz, CDCl_3) δ 8.11 – 8.01 (m, 2 H, Ar Phth), 7.81 (ddd, $J = 7.7, 1.3, 0.7$ Hz, 1 H, Ar), 7.63 (ddd, $J = 7.0, 1.6, 0.7$ Hz, 1 H, Ar), 7.56 – 7.37 (m, 5 H, Ar + Ar Phth), 4.76 (dd, $J = 9.4, 7.2$ Hz, 1 H, CH-Me), 4.15 (ddd, $J = 12.3, 9.4, 2.9$ Hz, 1 H, N-C-H), 3.87 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 2.88 (td, $J = 14.2, 3.9$ Hz, 1 H, CH_2), 2.42 (dt, $J = 14.2, 3.4$ Hz, 1 H, CH_2), 2.00 (dd, $J = 13.3, 3.3$ Hz, 1 H, CH_2), 1.63 – 1.46 (m, 1 H, CH_2), 1.18 (d, $J = 7.2$ Hz, 3 H, CH_3), 0.94 (s, 9 H, OTBS), -0.03 (s, 3 H, OTBS), -0.34 (s, 3 H, OTBS).

^{13}C NMR the sample was degraded and a mixture of the product and a side product was present (probably the open product as there is a peak at 200 ppm).

IR 2955 (w), 2859 (w), 1740 (m), 1703 (s), 1702 (s), 1329 (w), 1272 (m), 1221 (w), 1093 (m), 1072 (m), 863 (w), 842 (w).

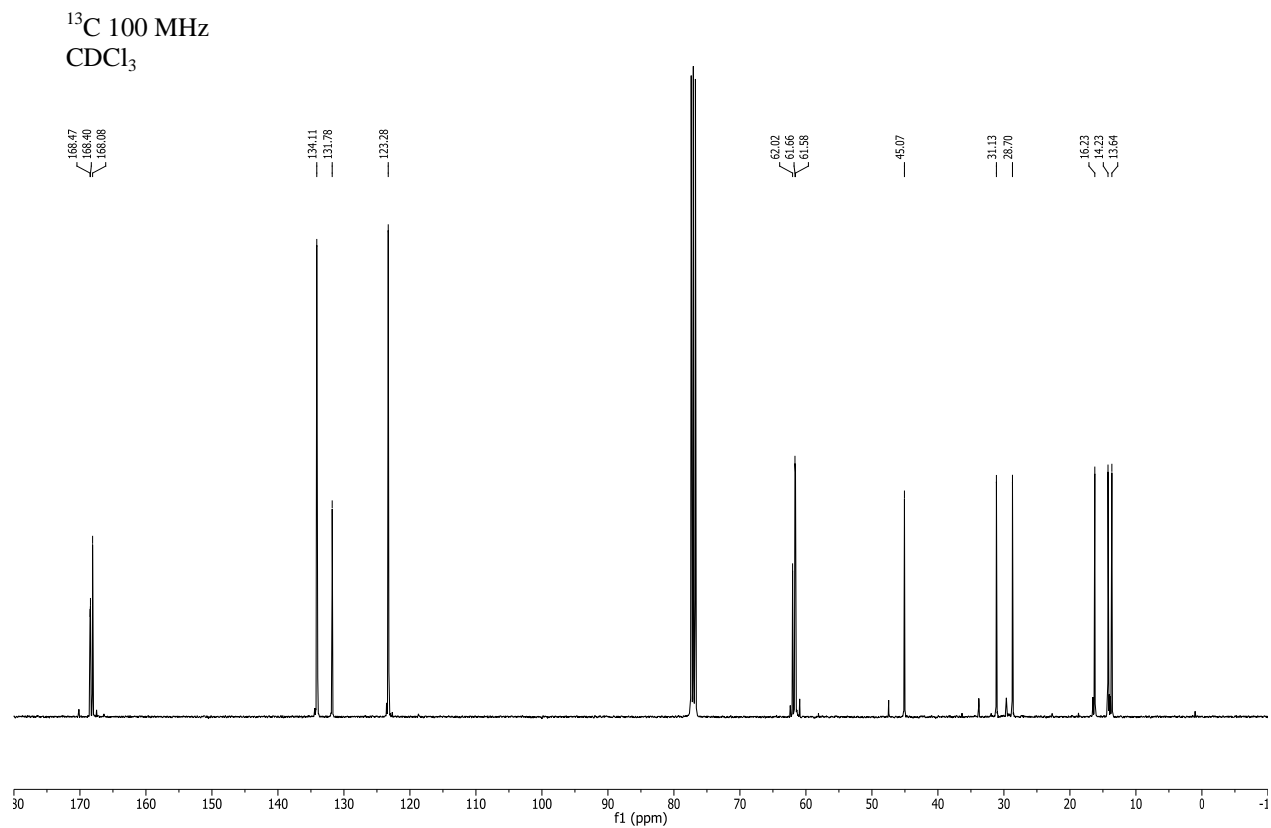
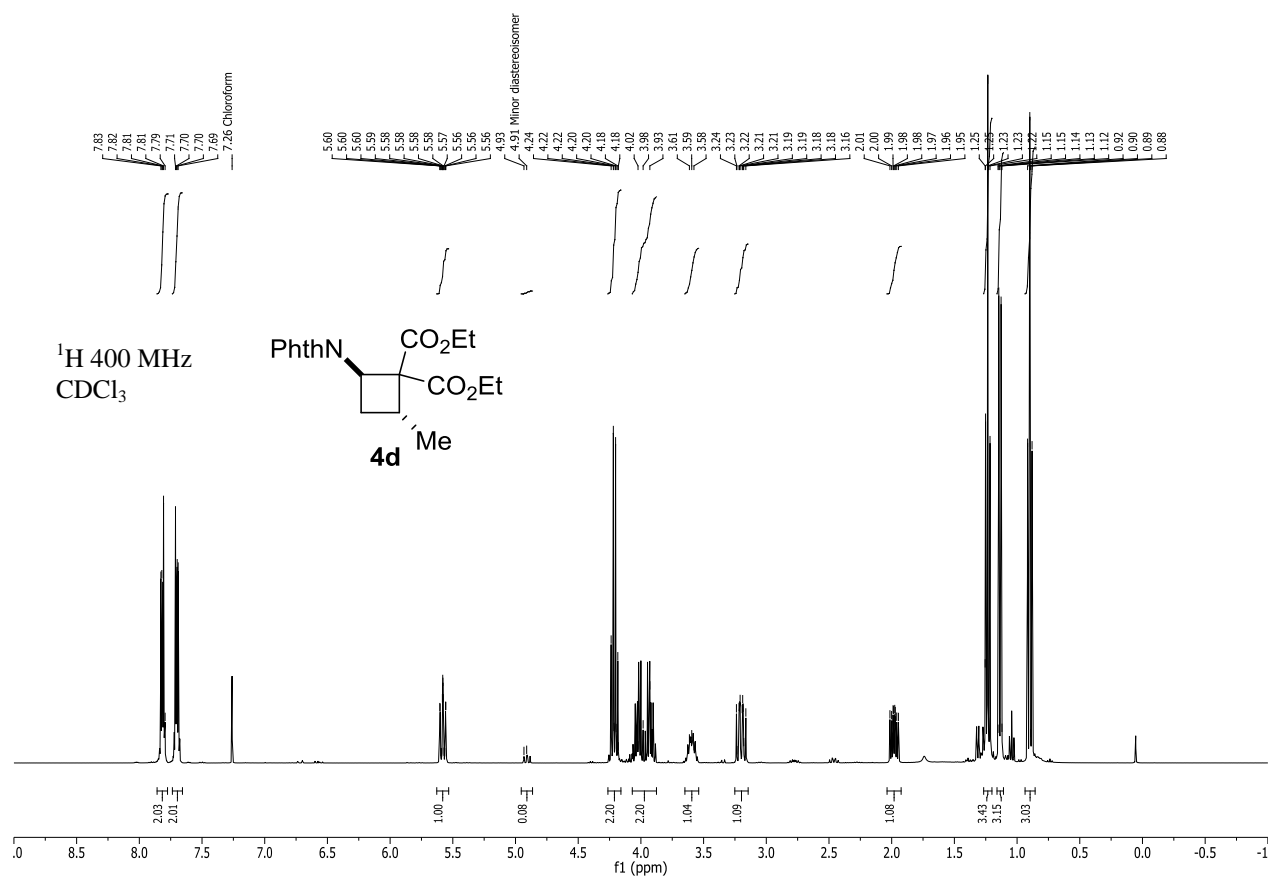
HRMS (ESI). calcd for $\text{C}_{31}\text{H}_{40}\text{NO}_7\text{Si}^+$ $[\text{M}+\text{H}]^+$ 566.2569; found 566.2568.

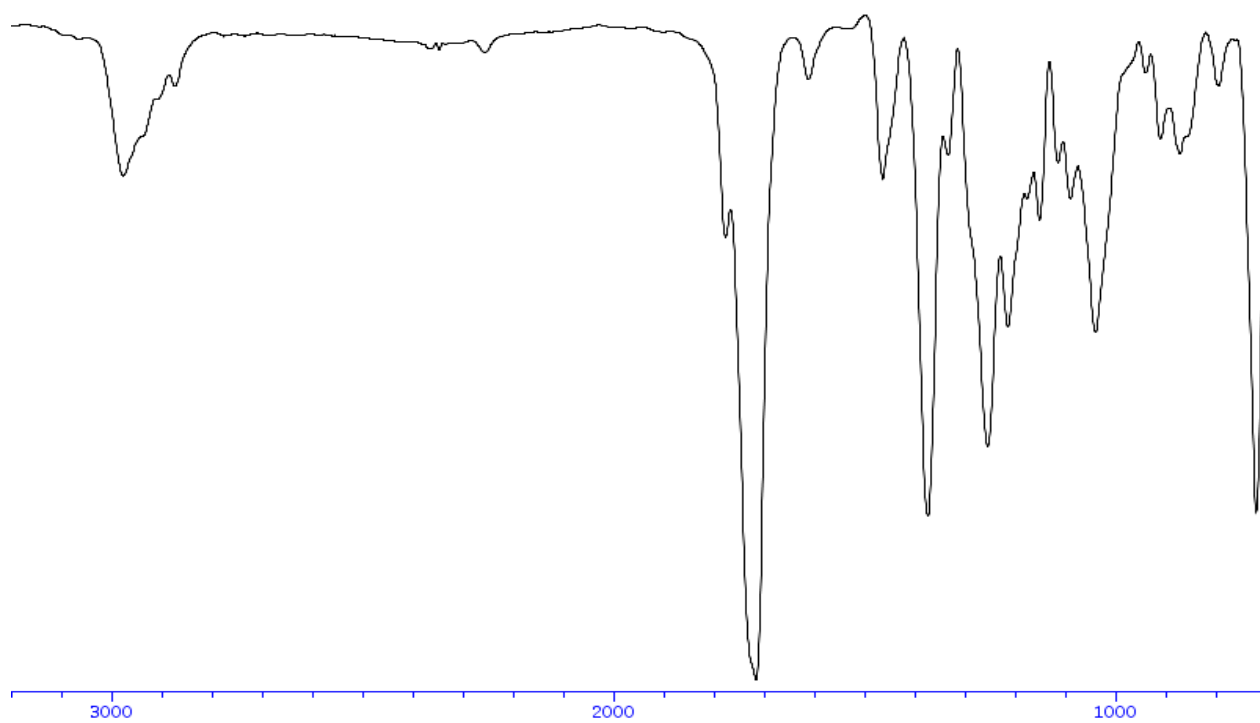


ROESY

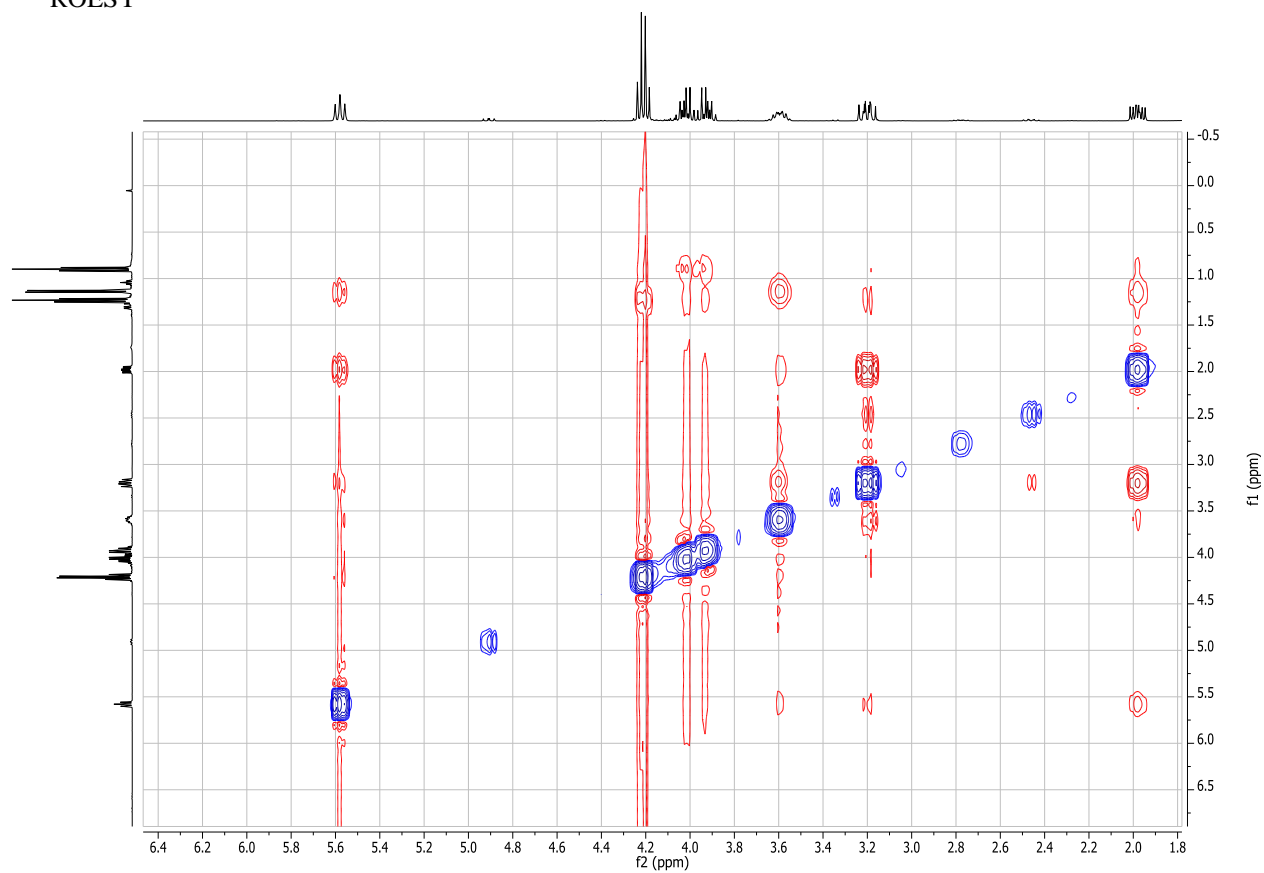
²³ Peaks of impurities are present in the aromatic area.

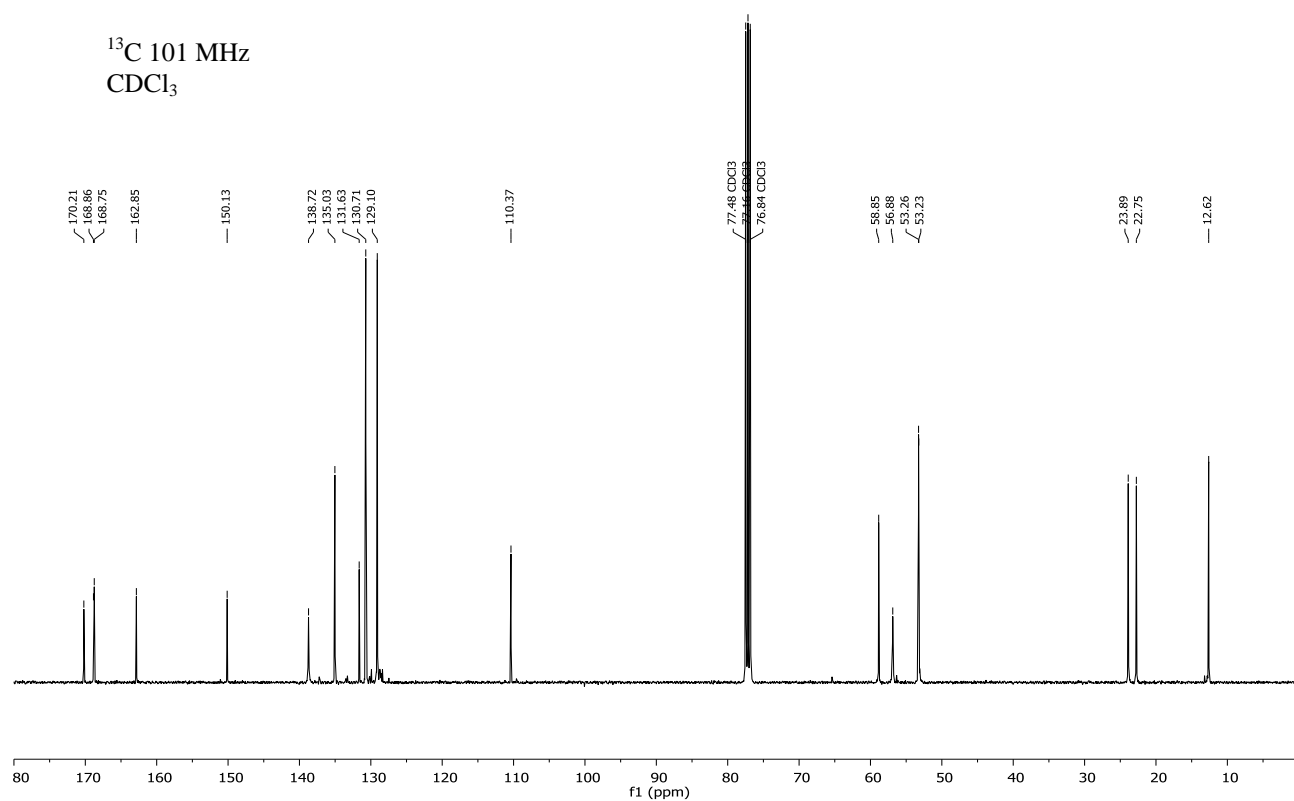
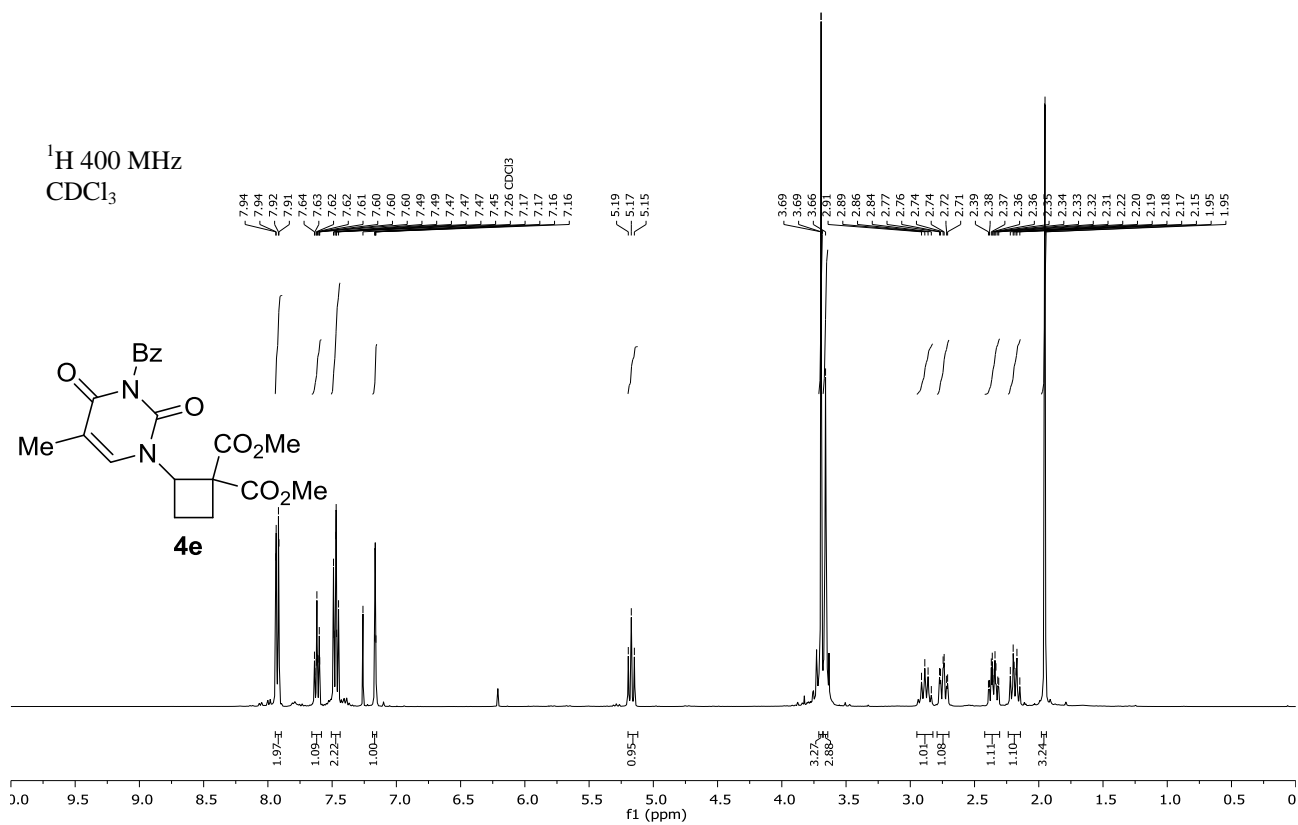
5. Spectra of New Compounds

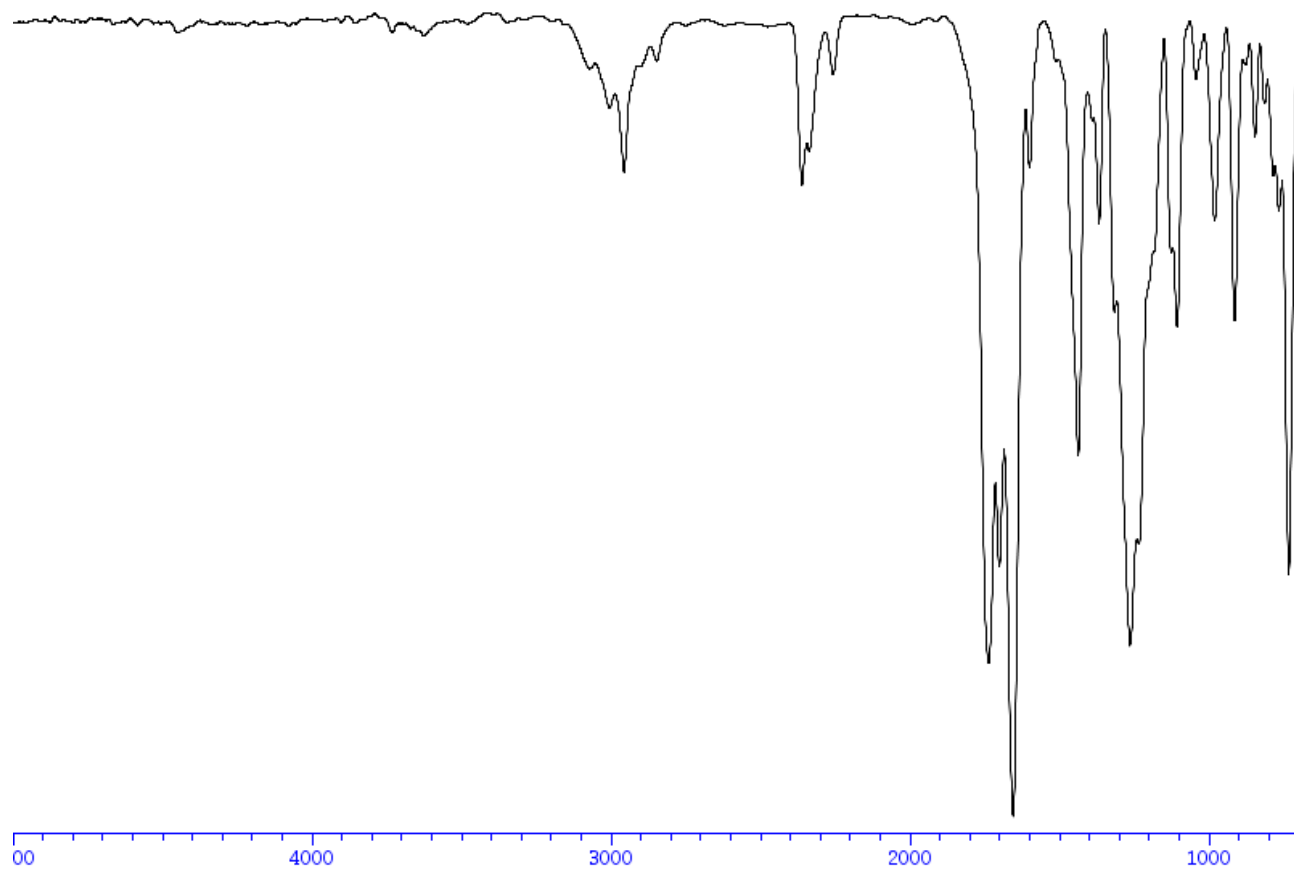


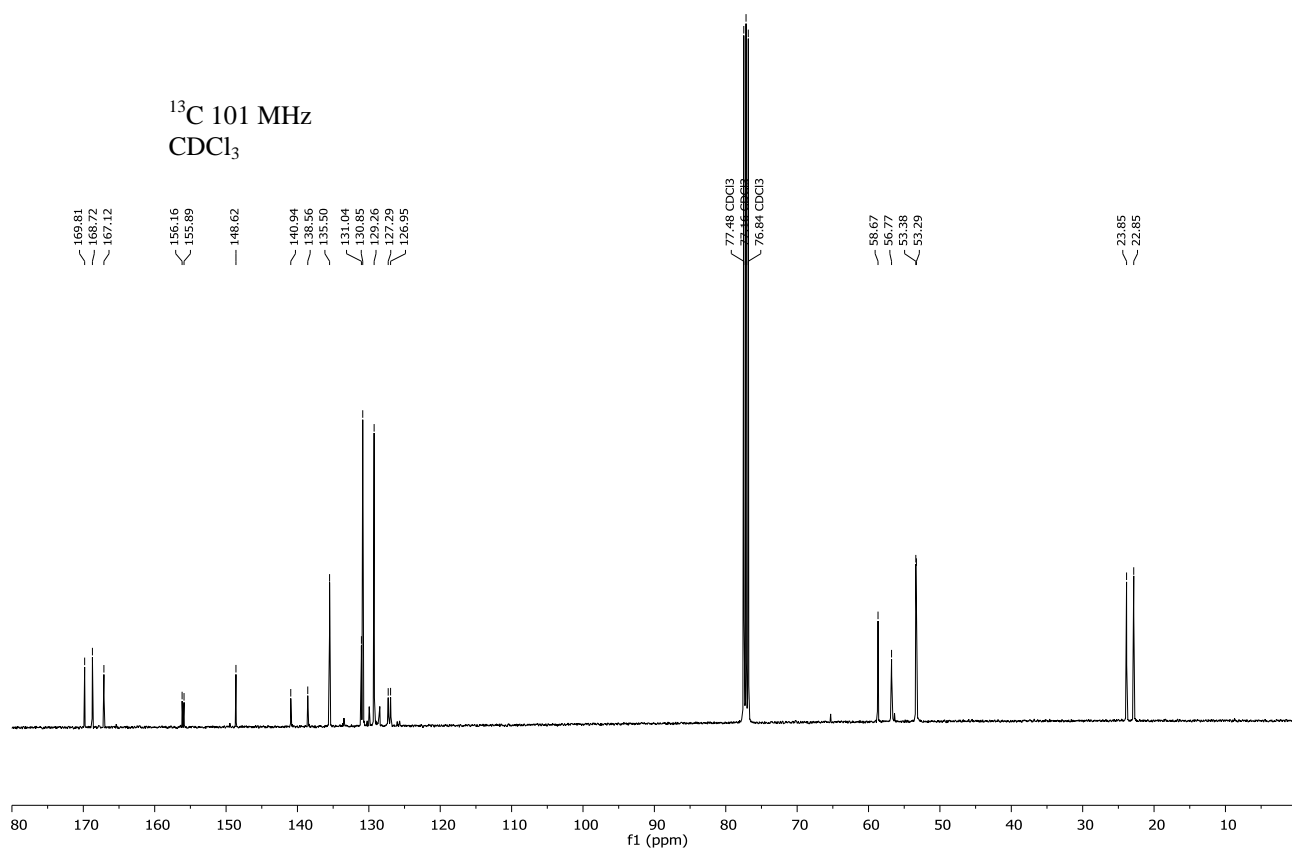
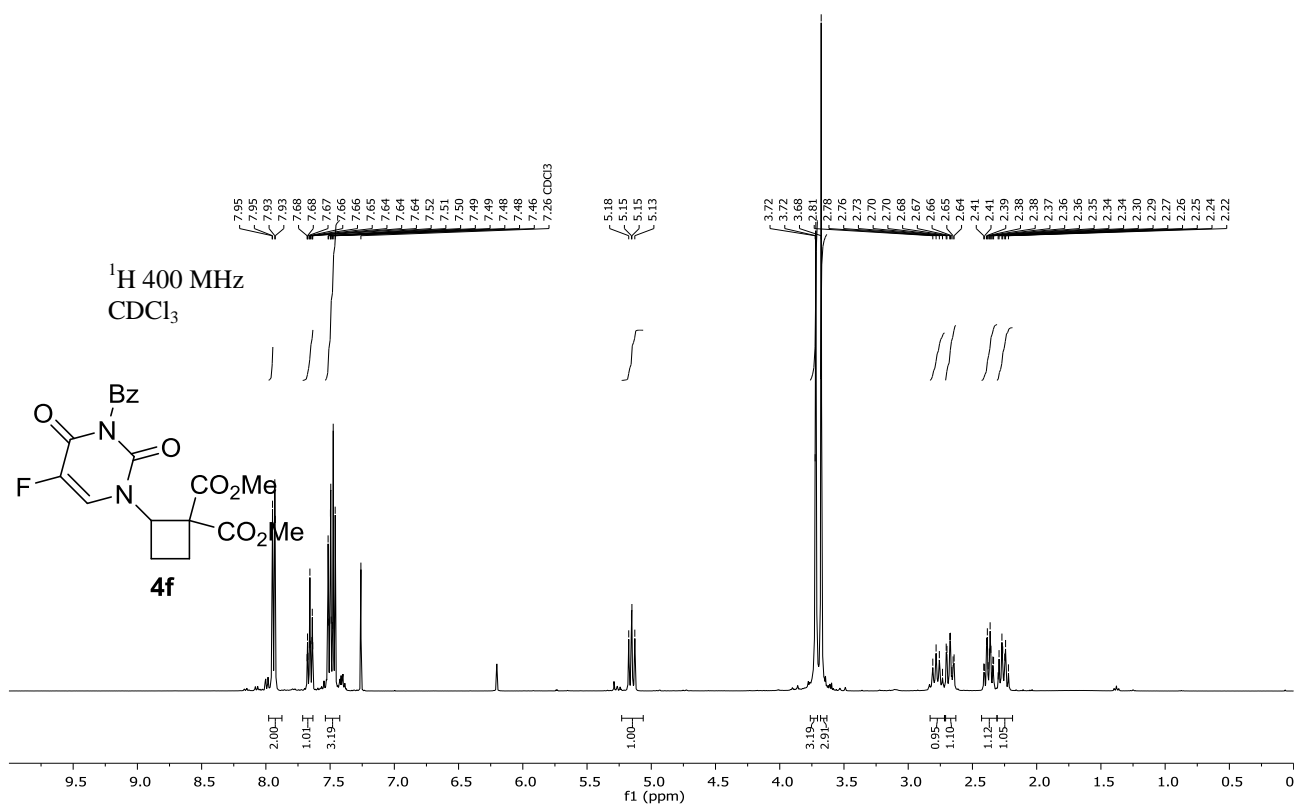


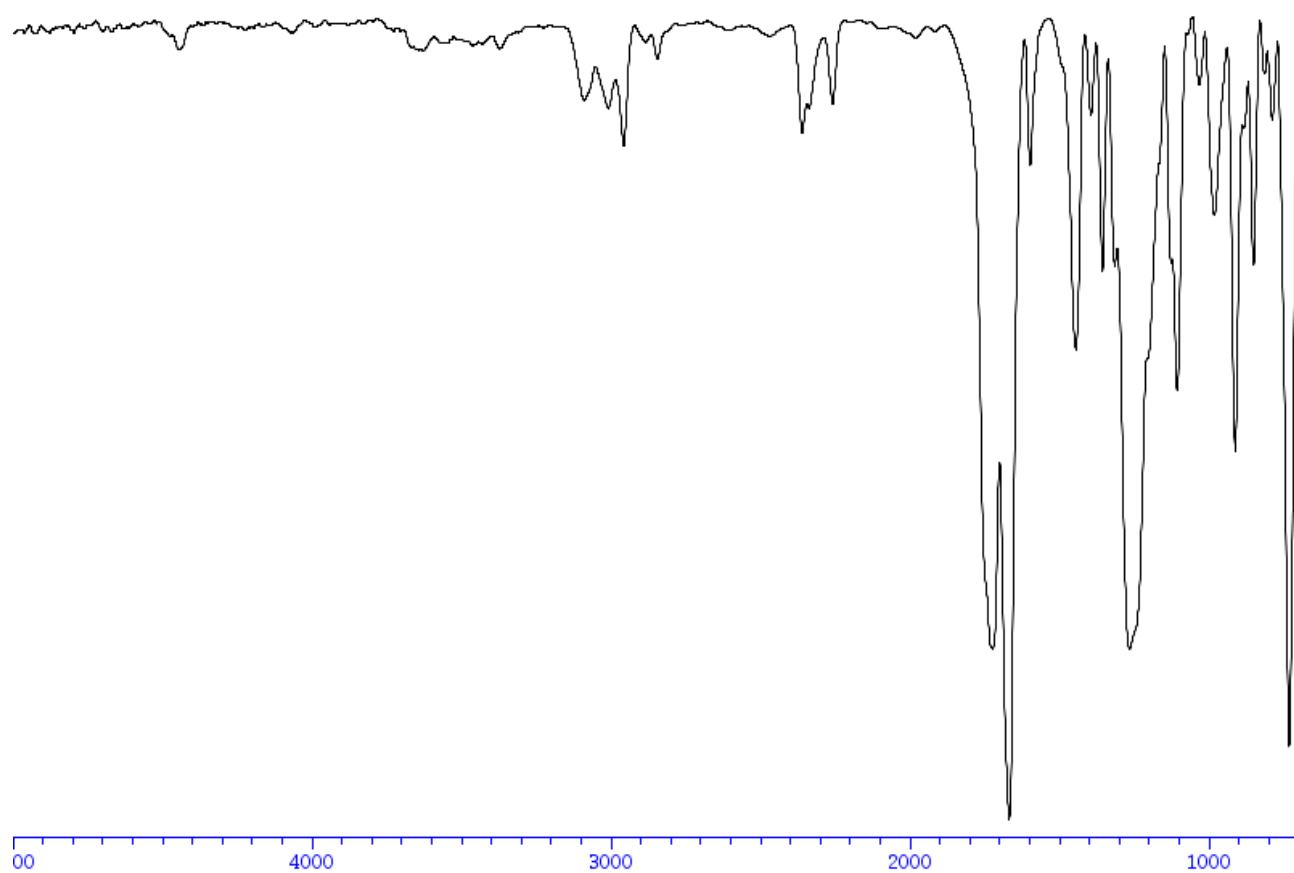
ROESY

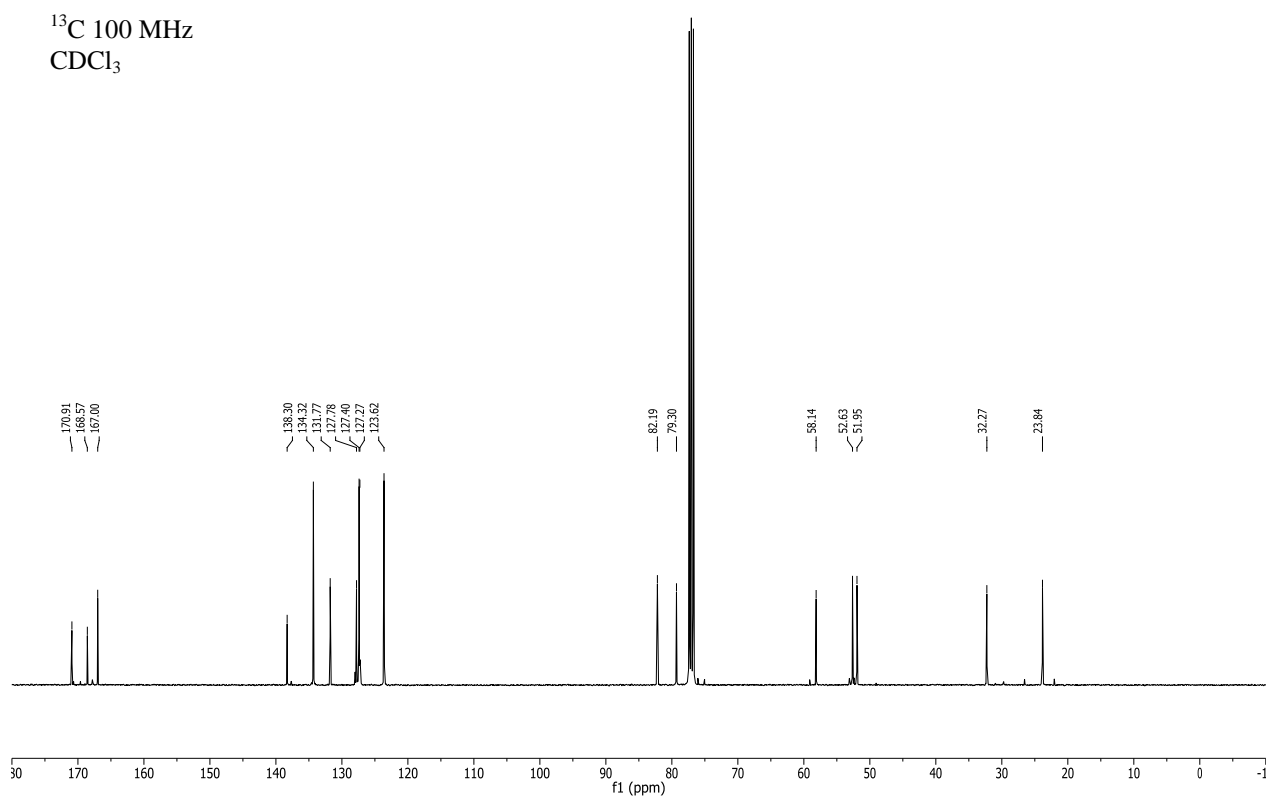
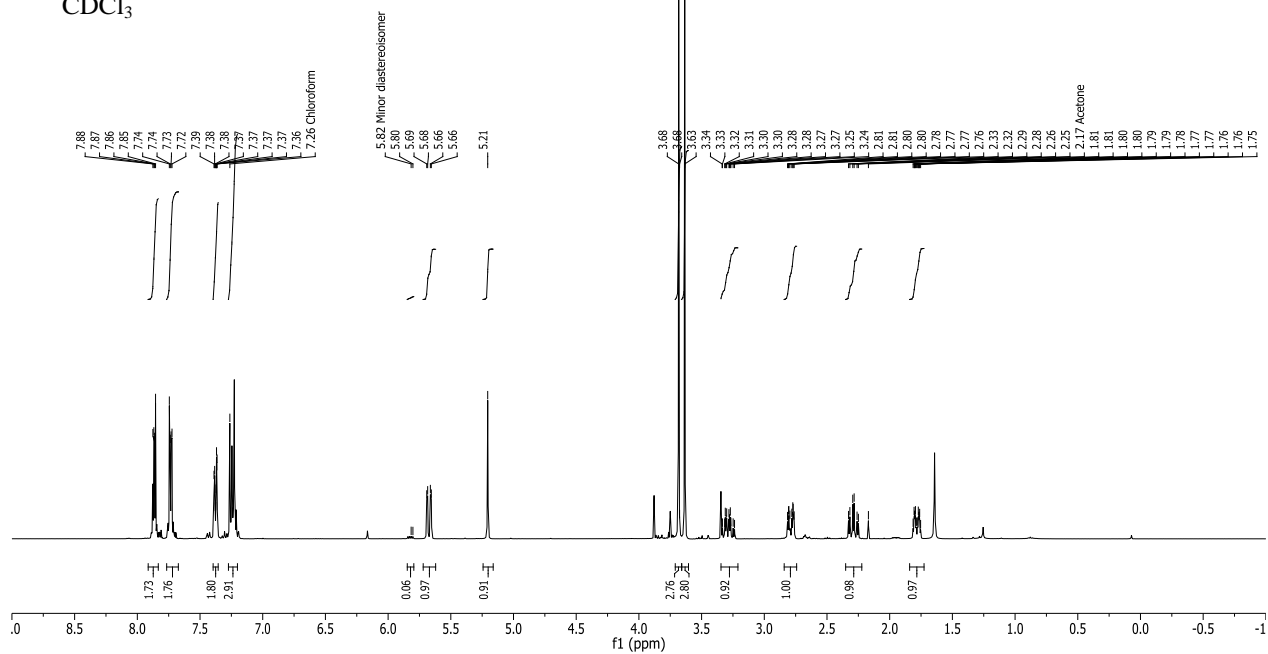
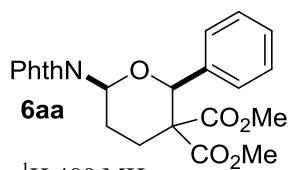


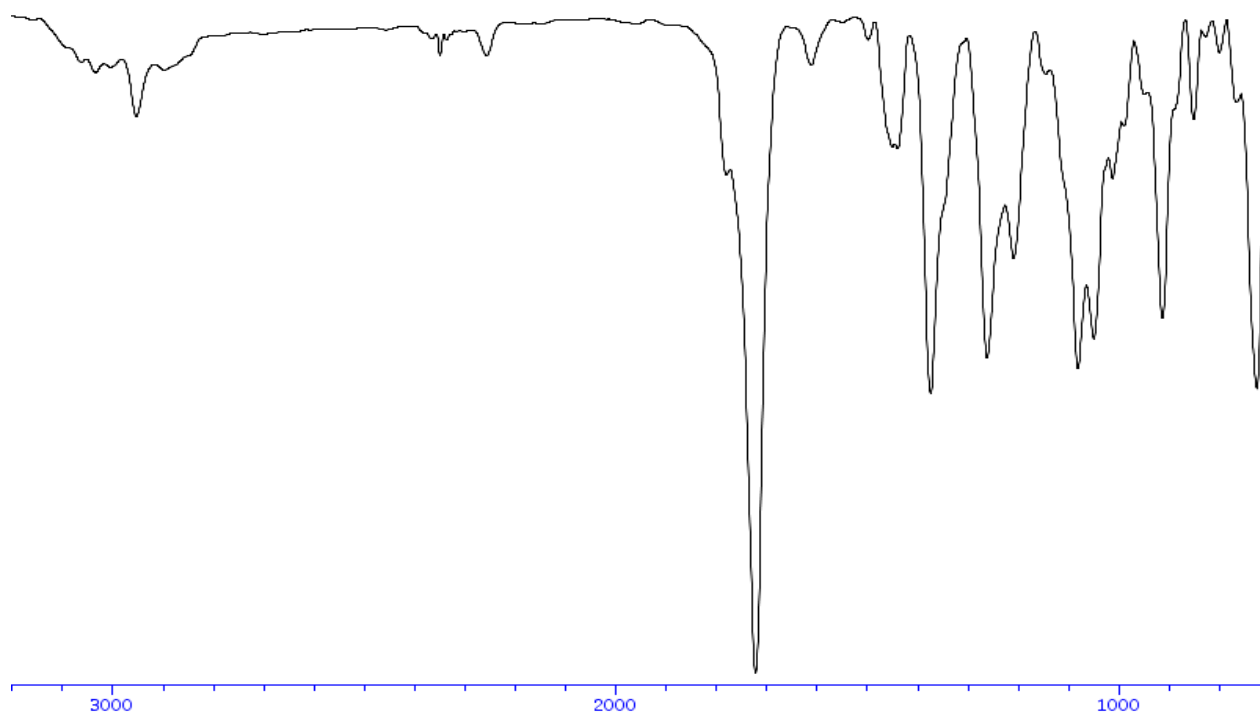




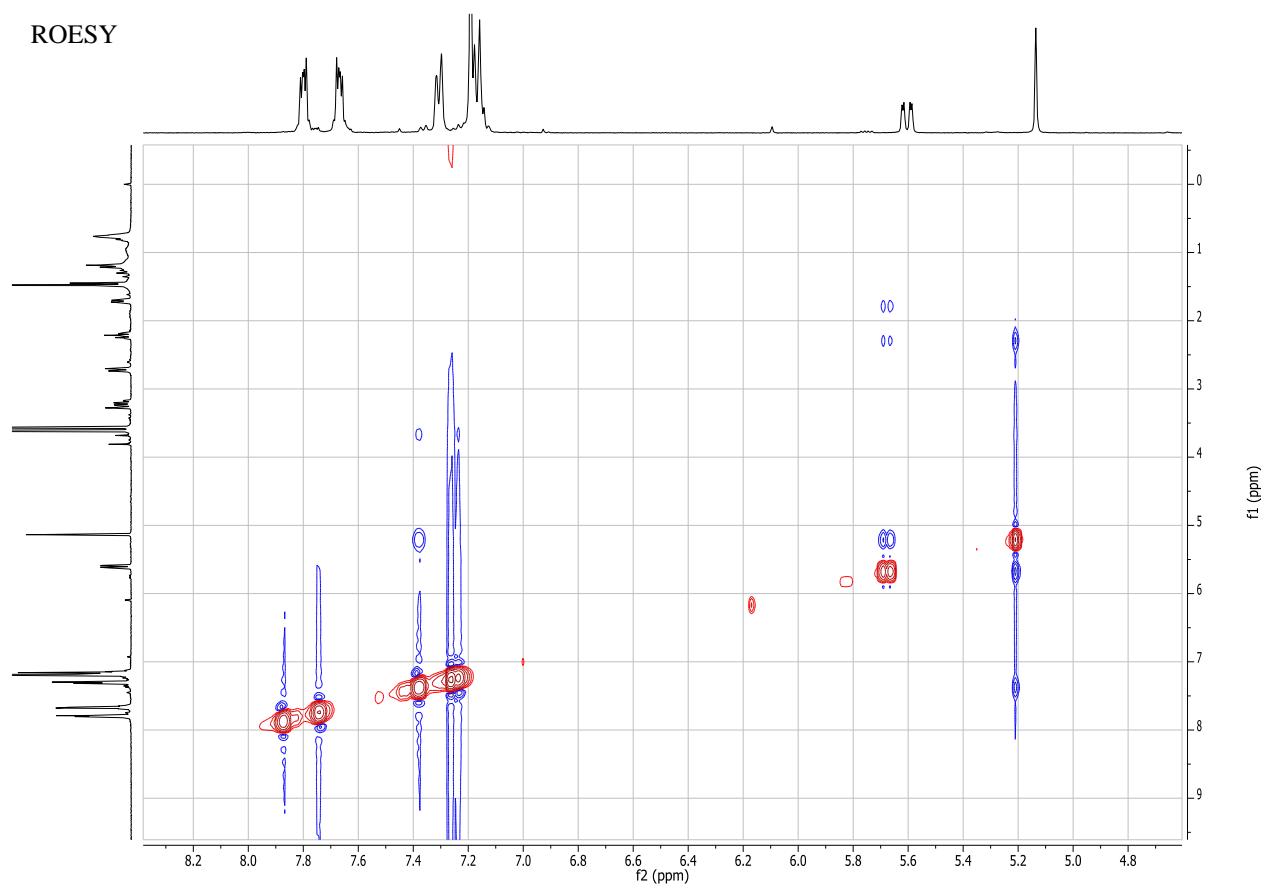


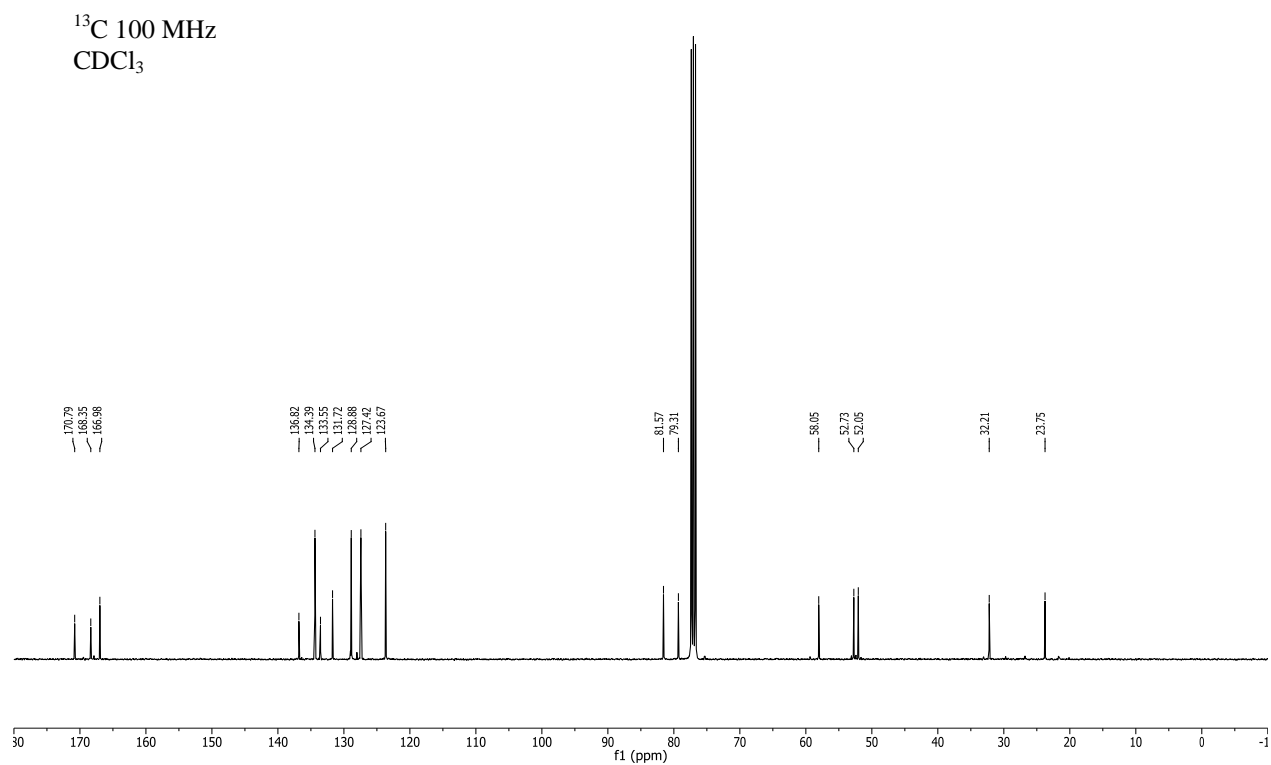
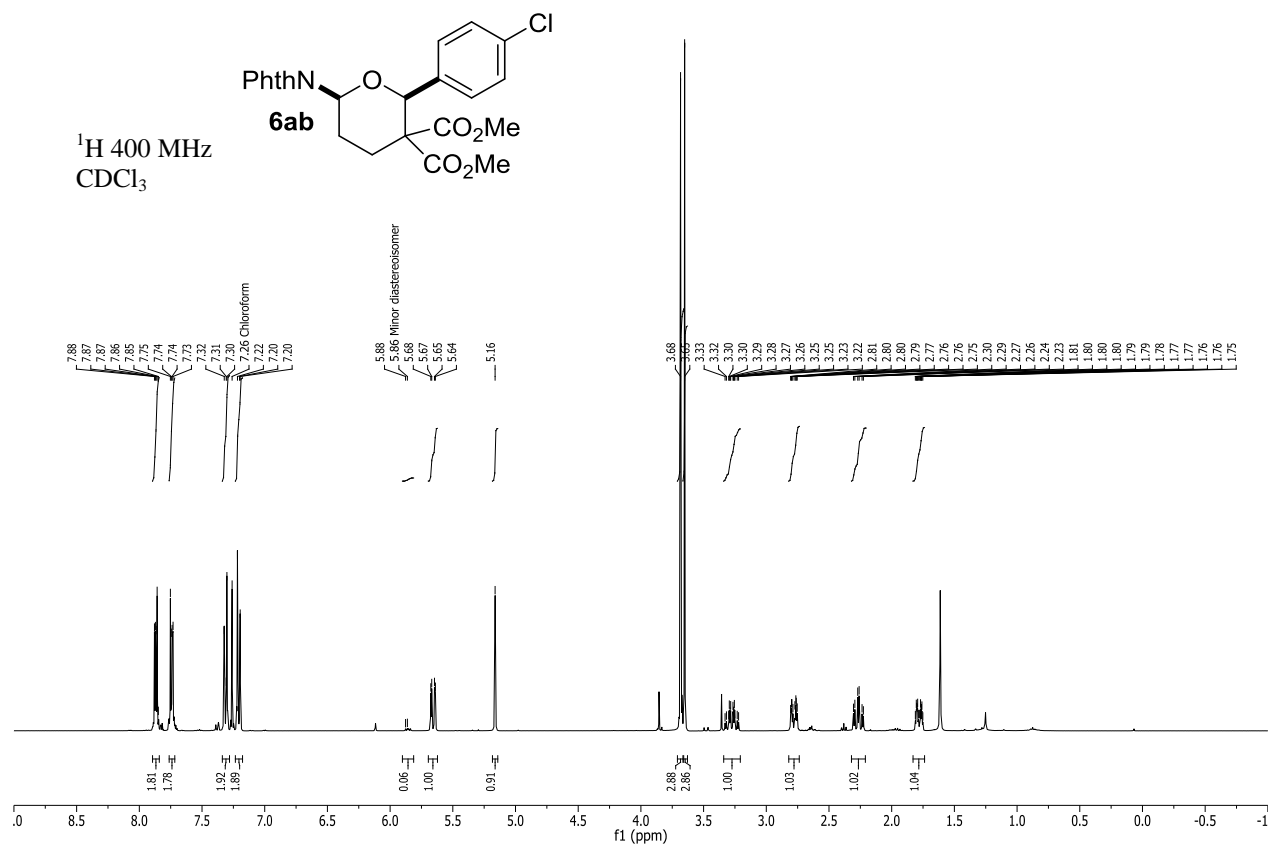


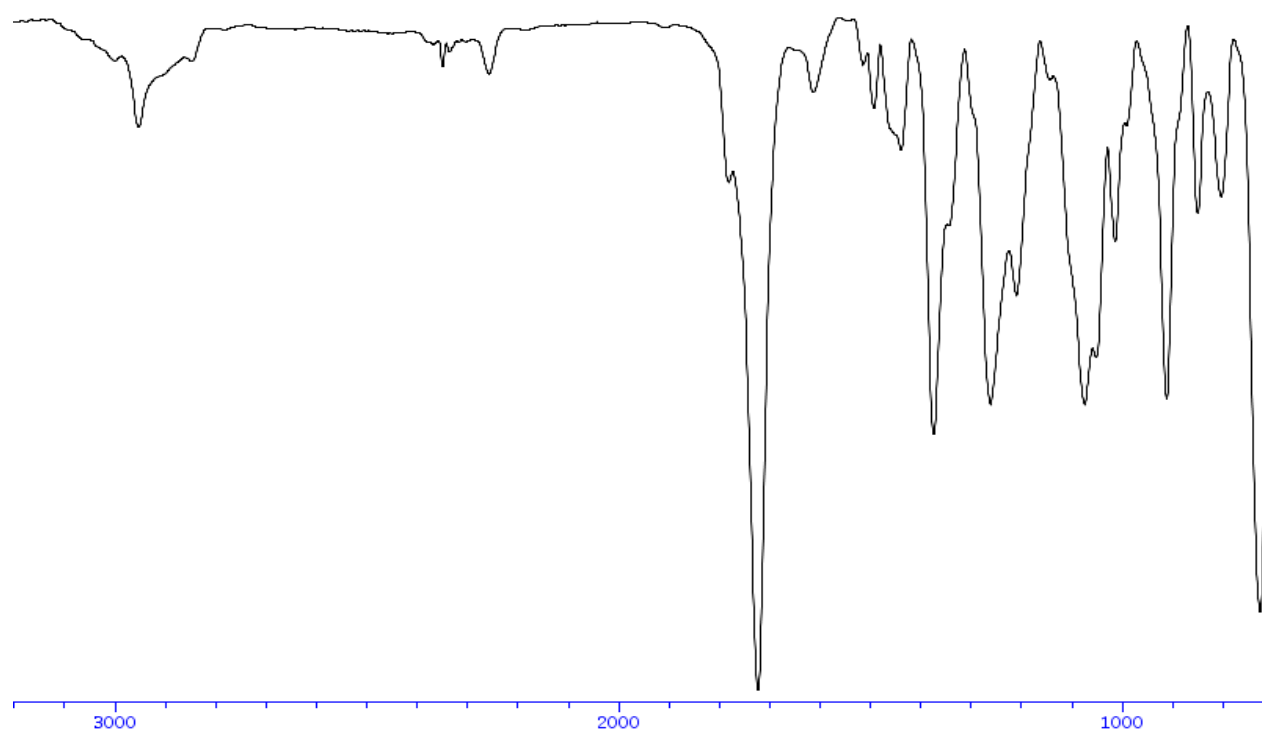


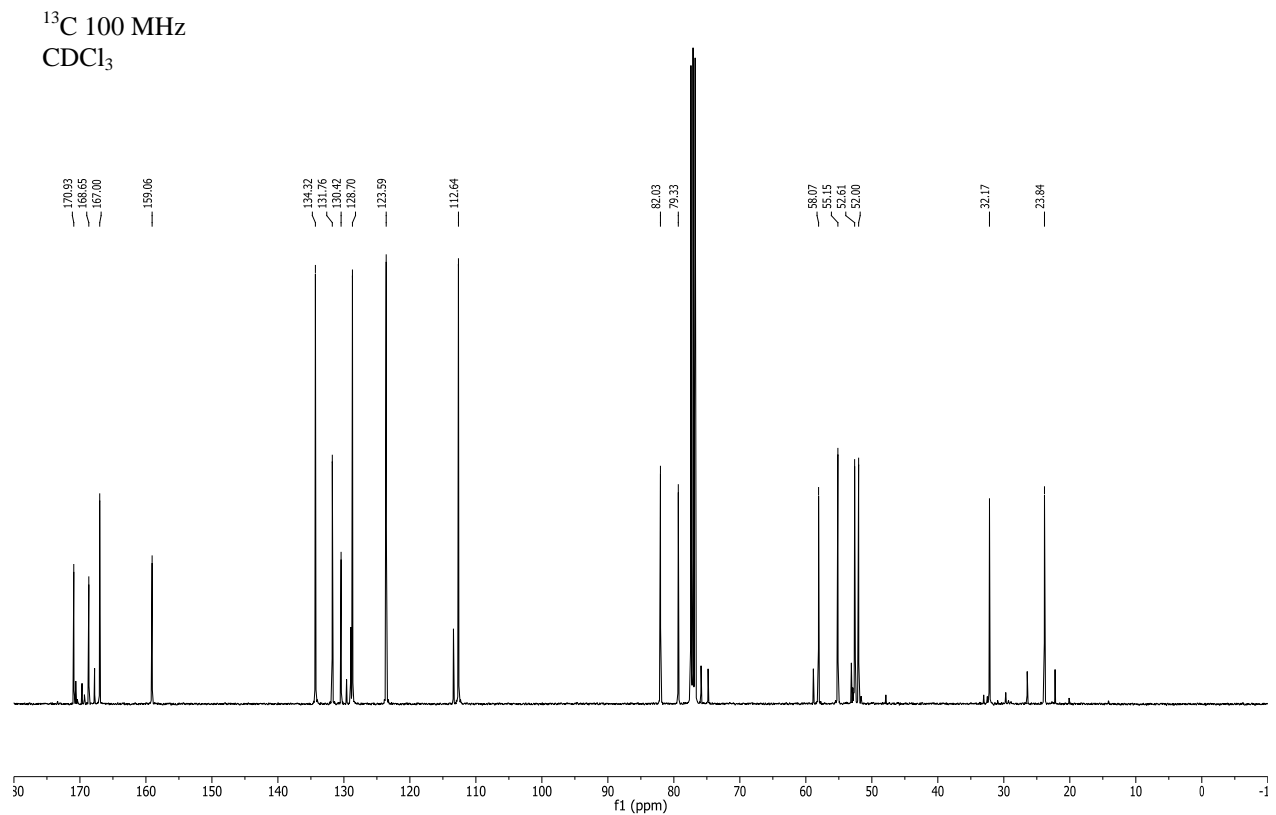
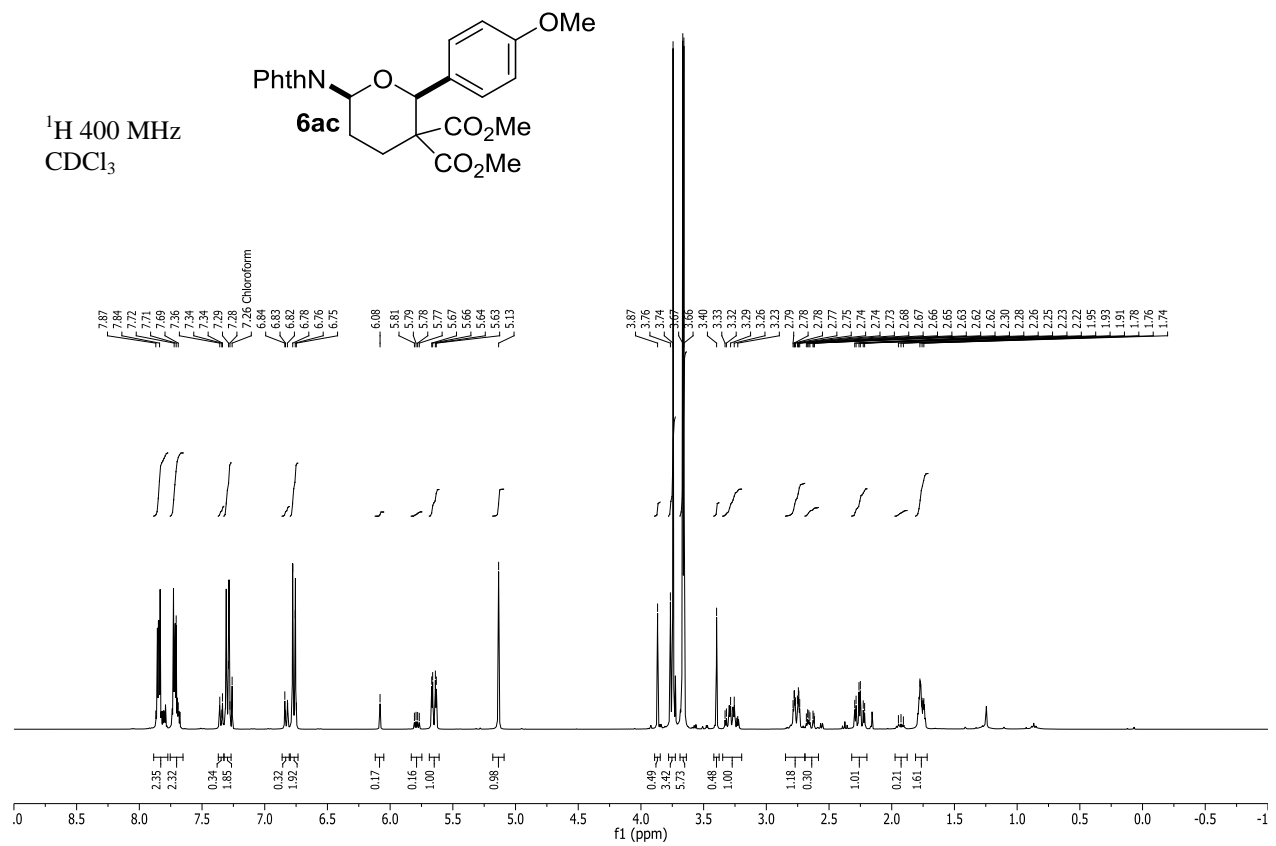


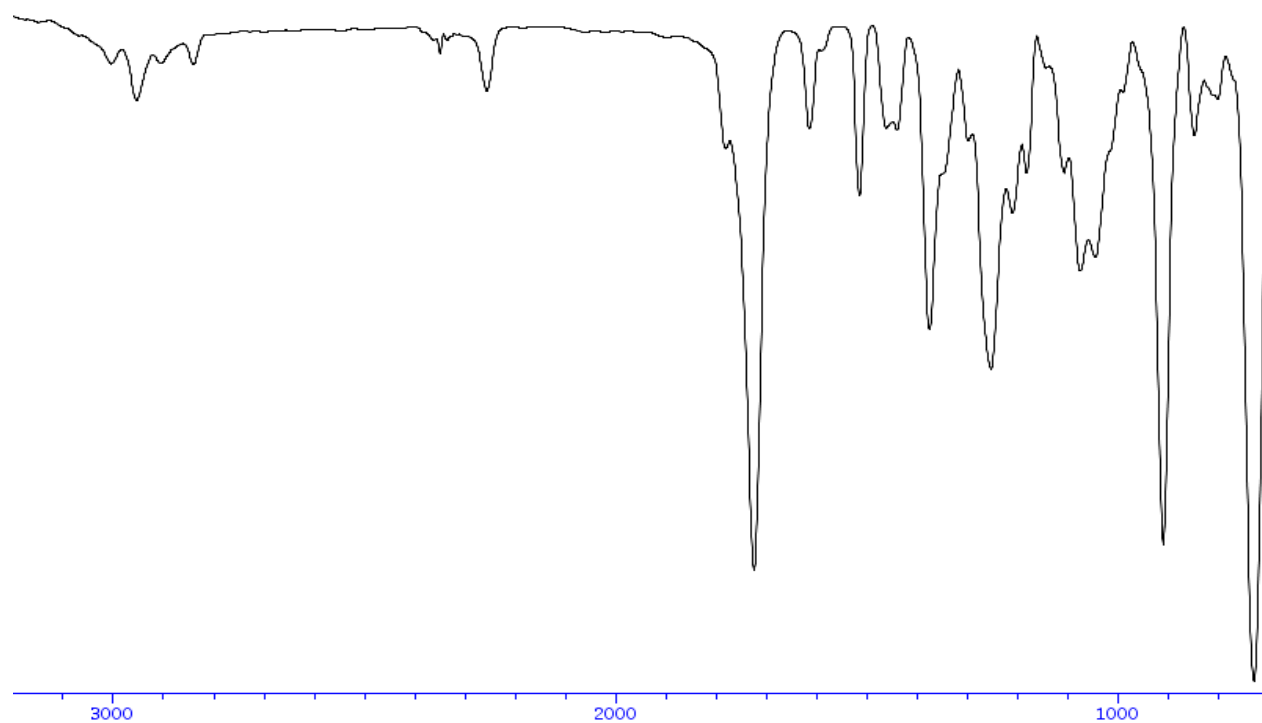
ROESY

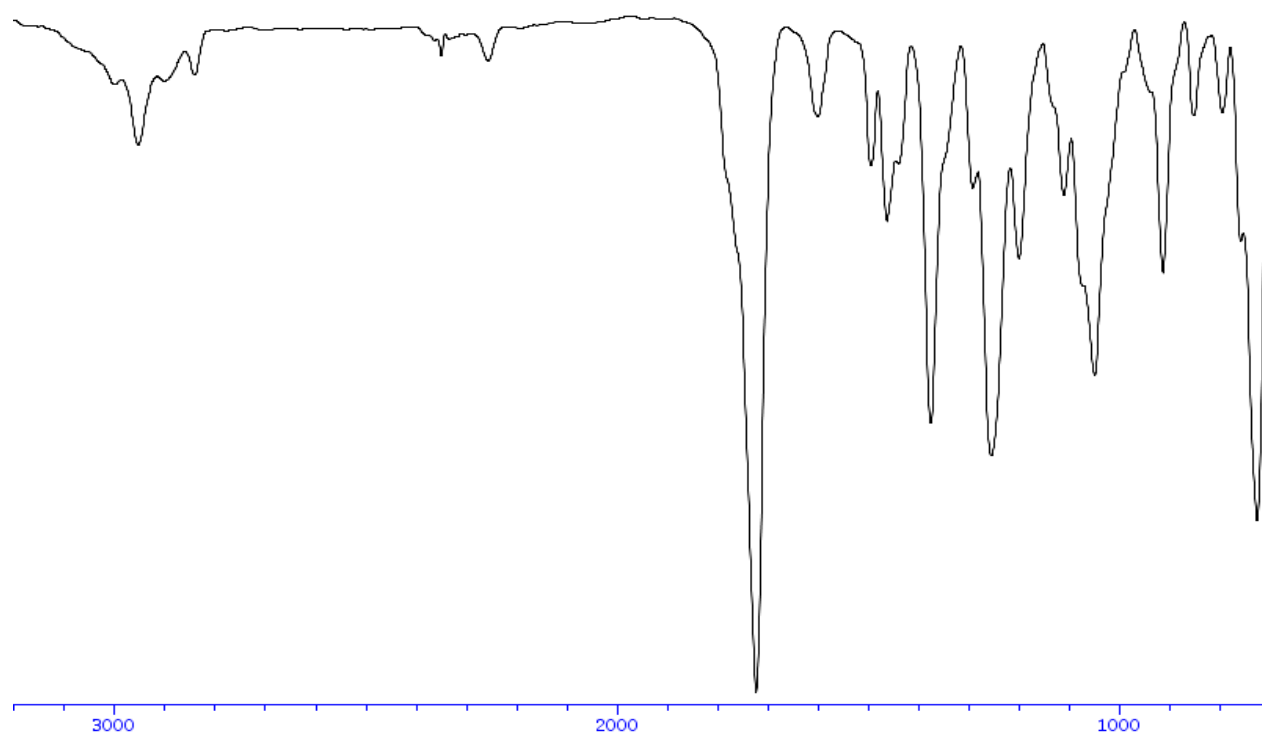


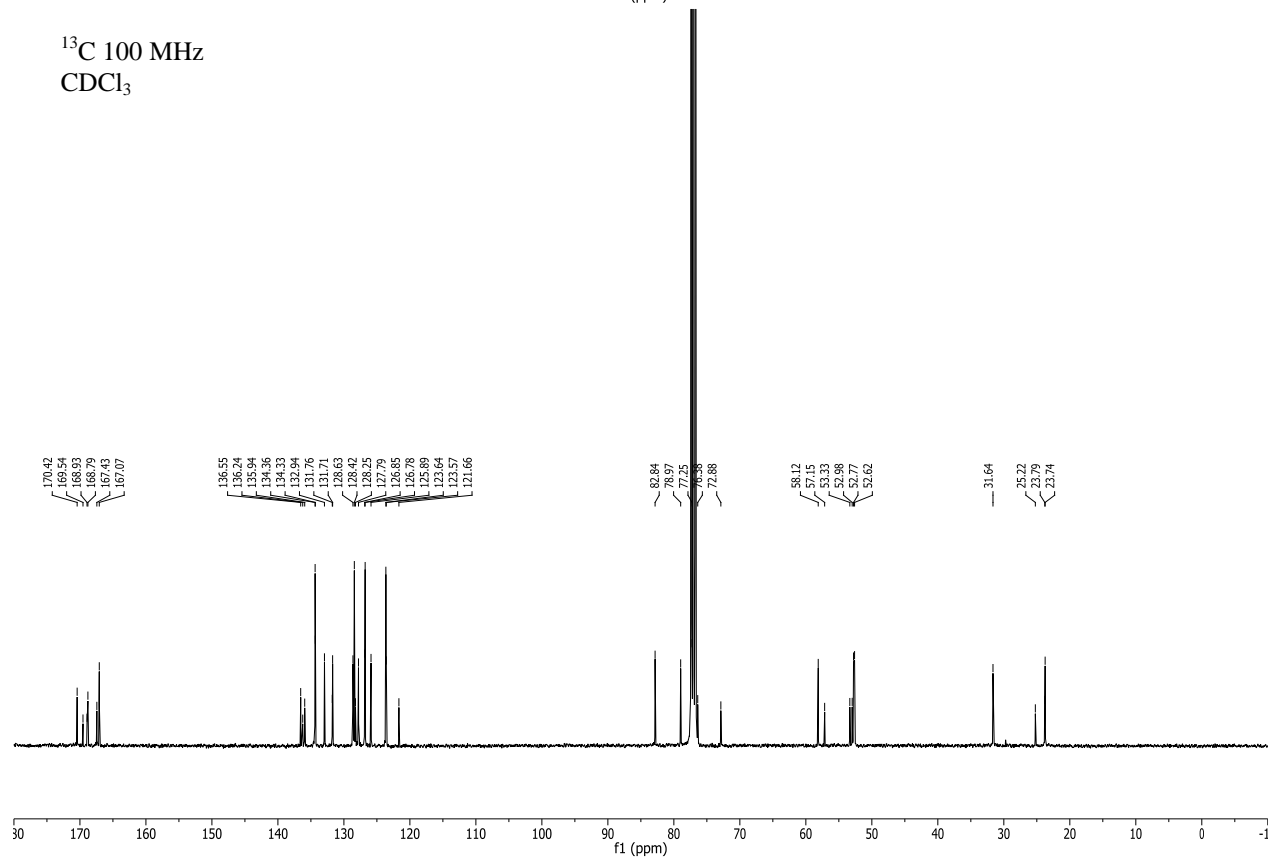
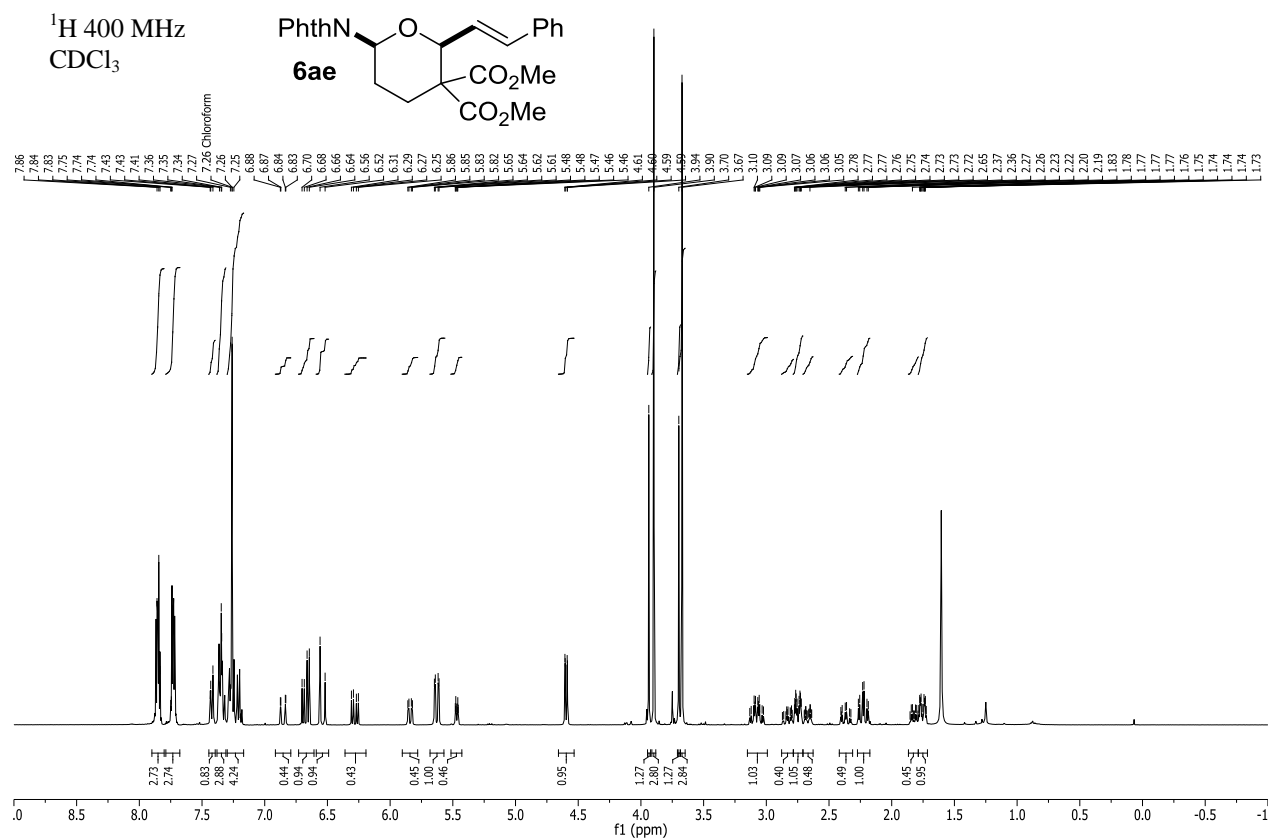


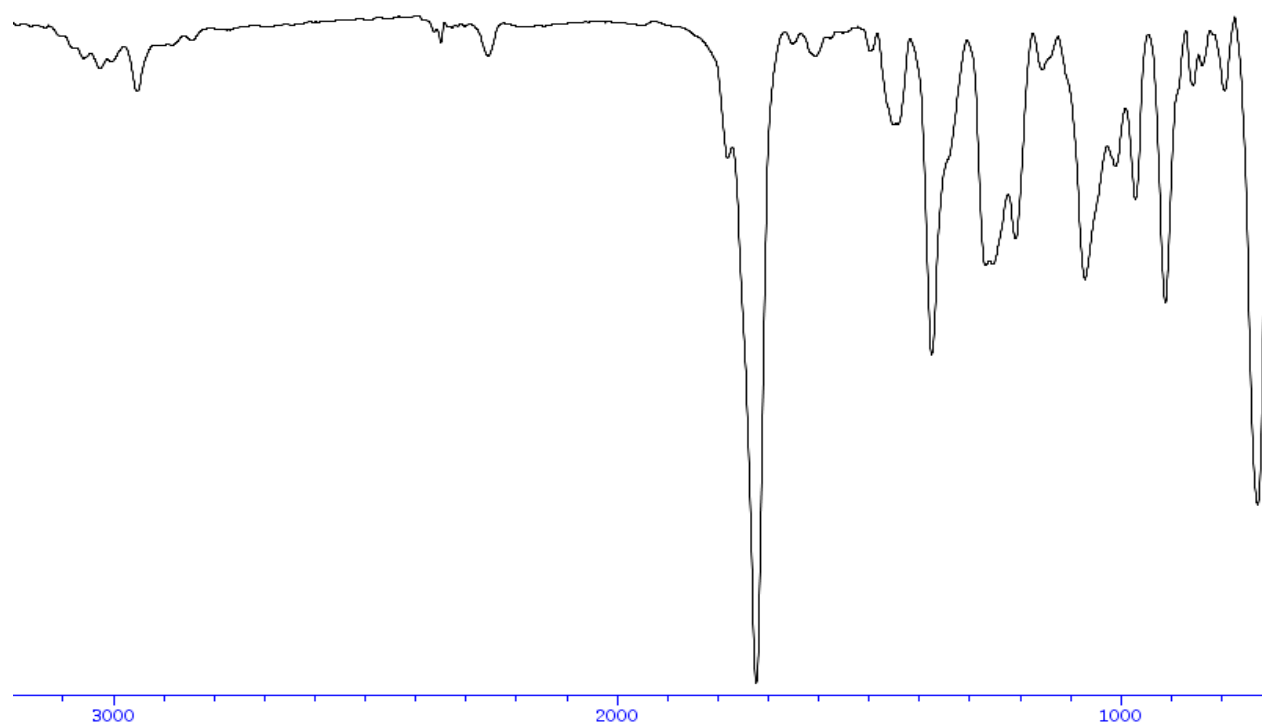


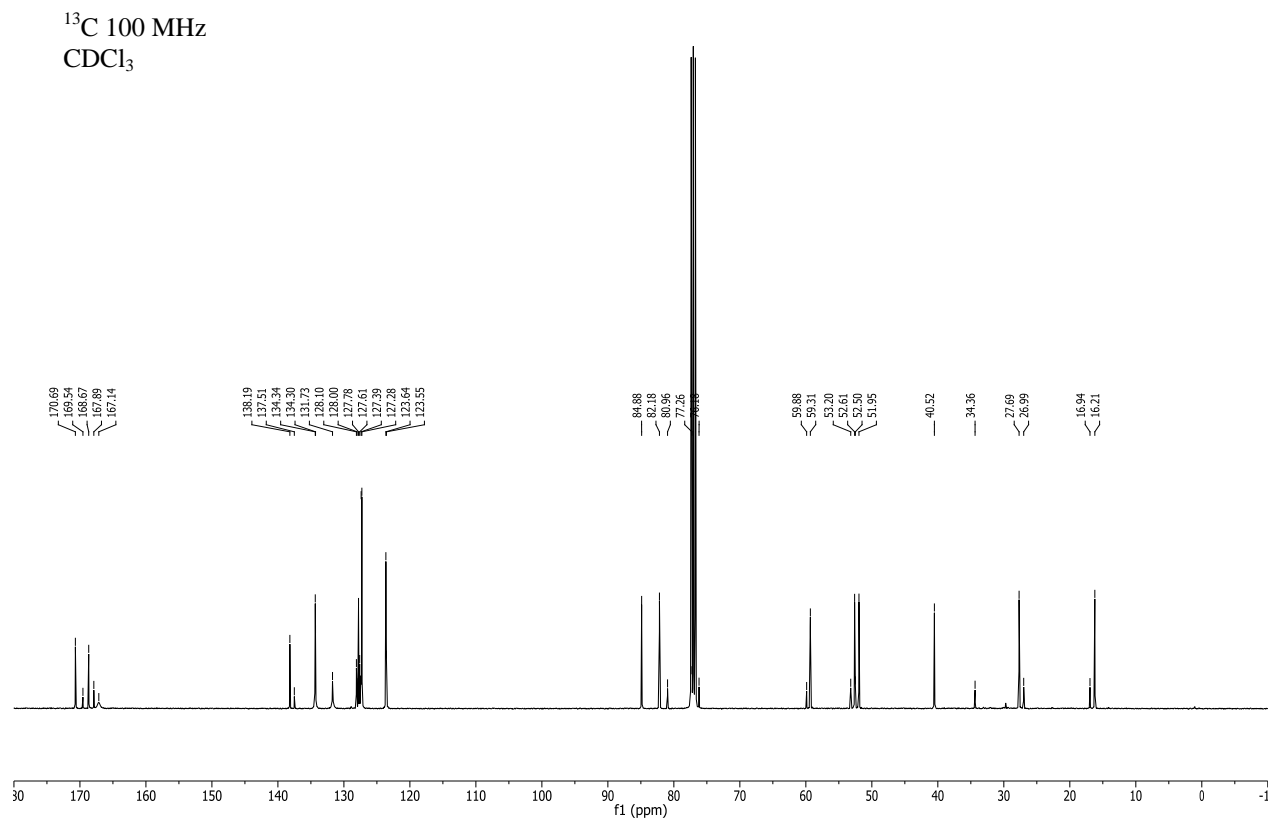
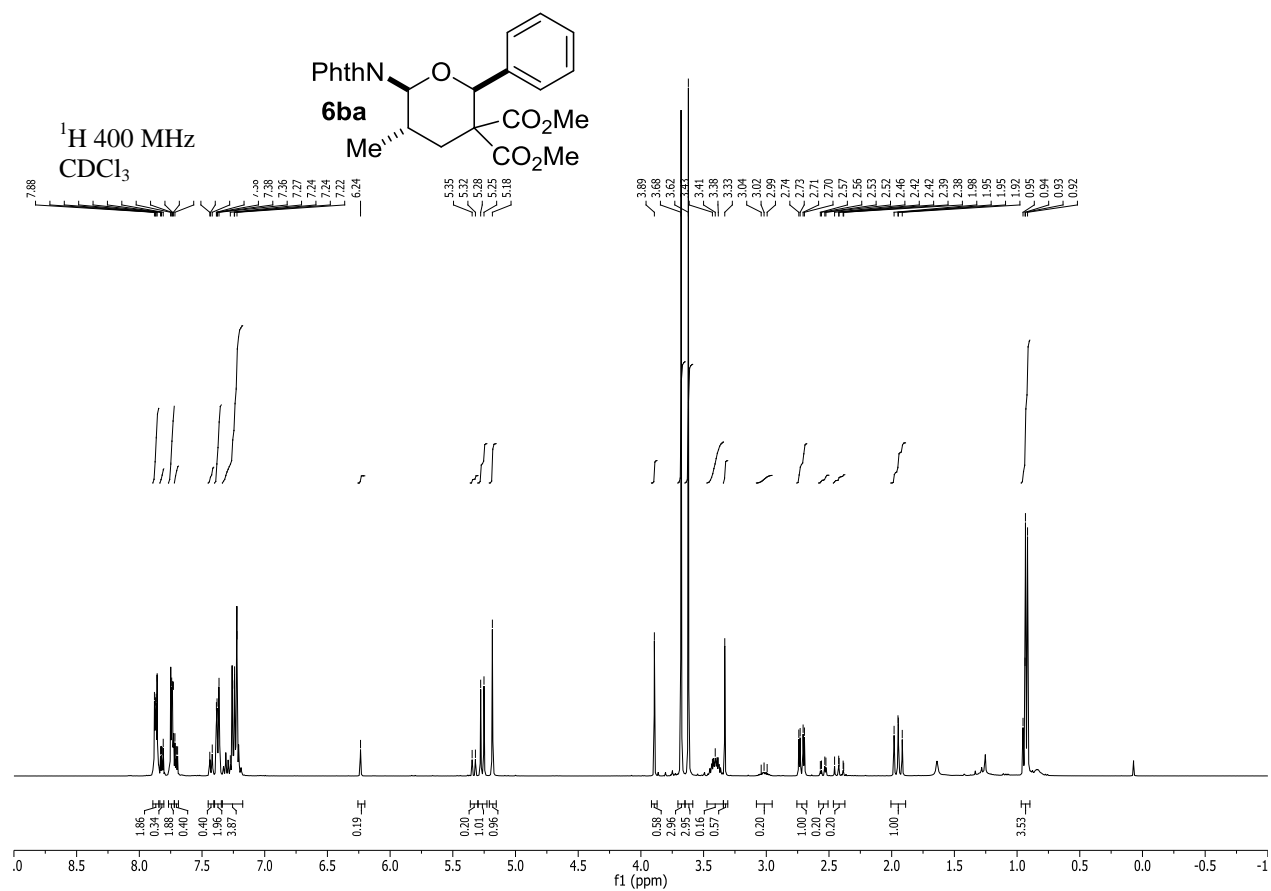


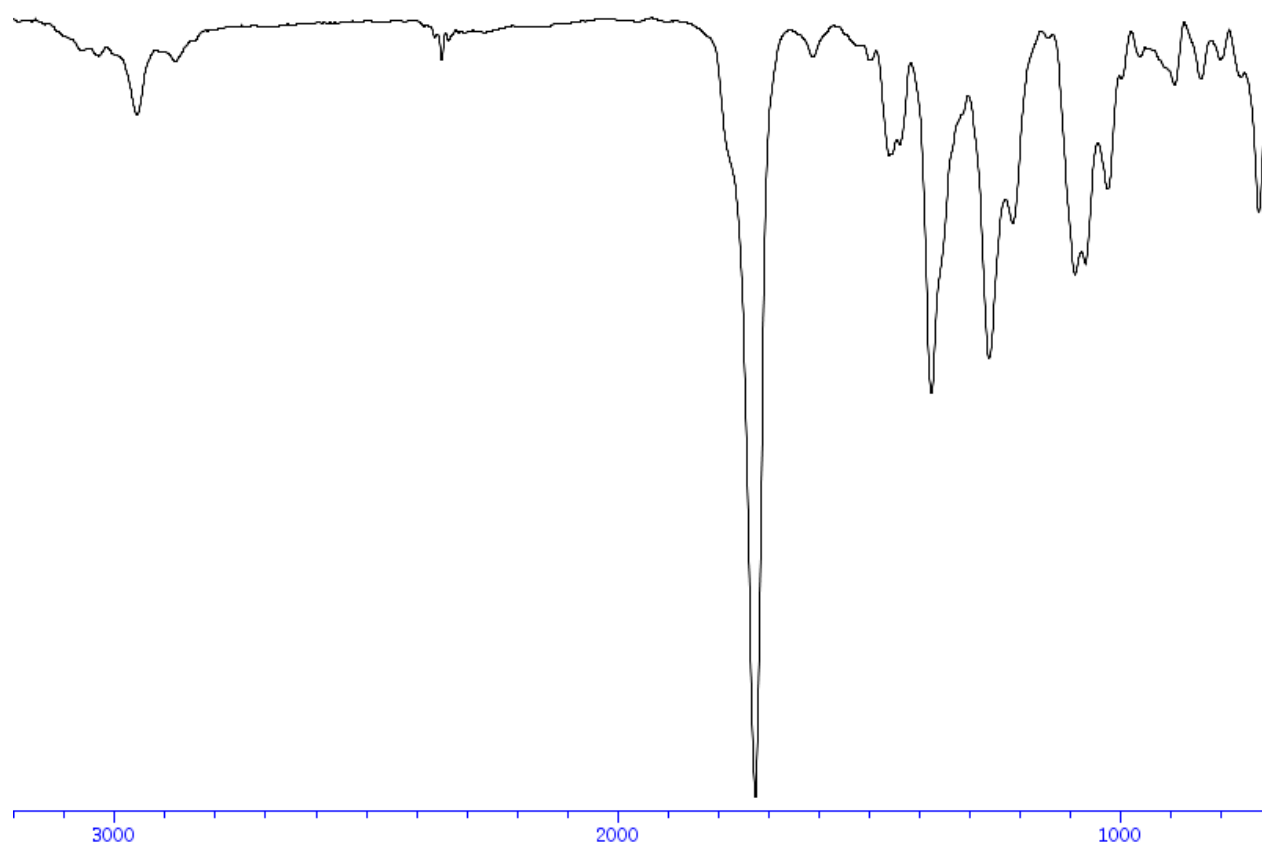


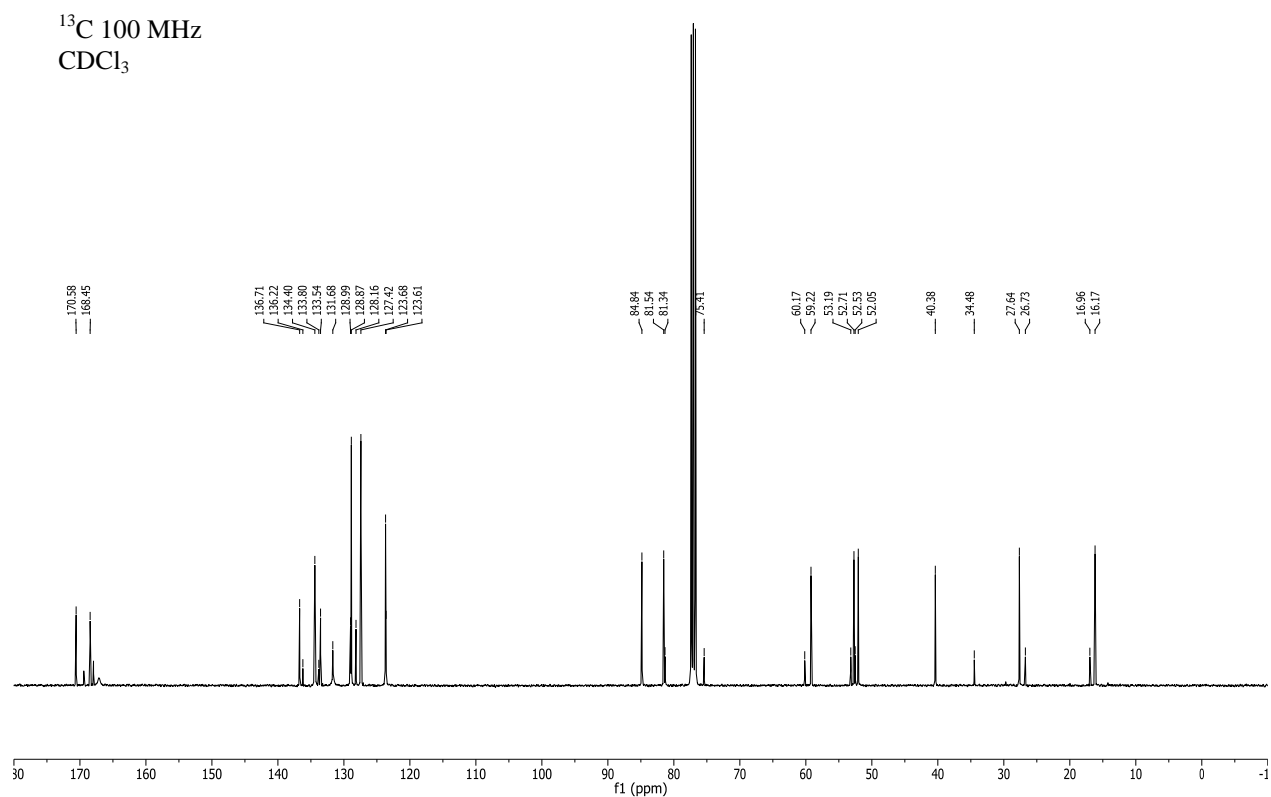
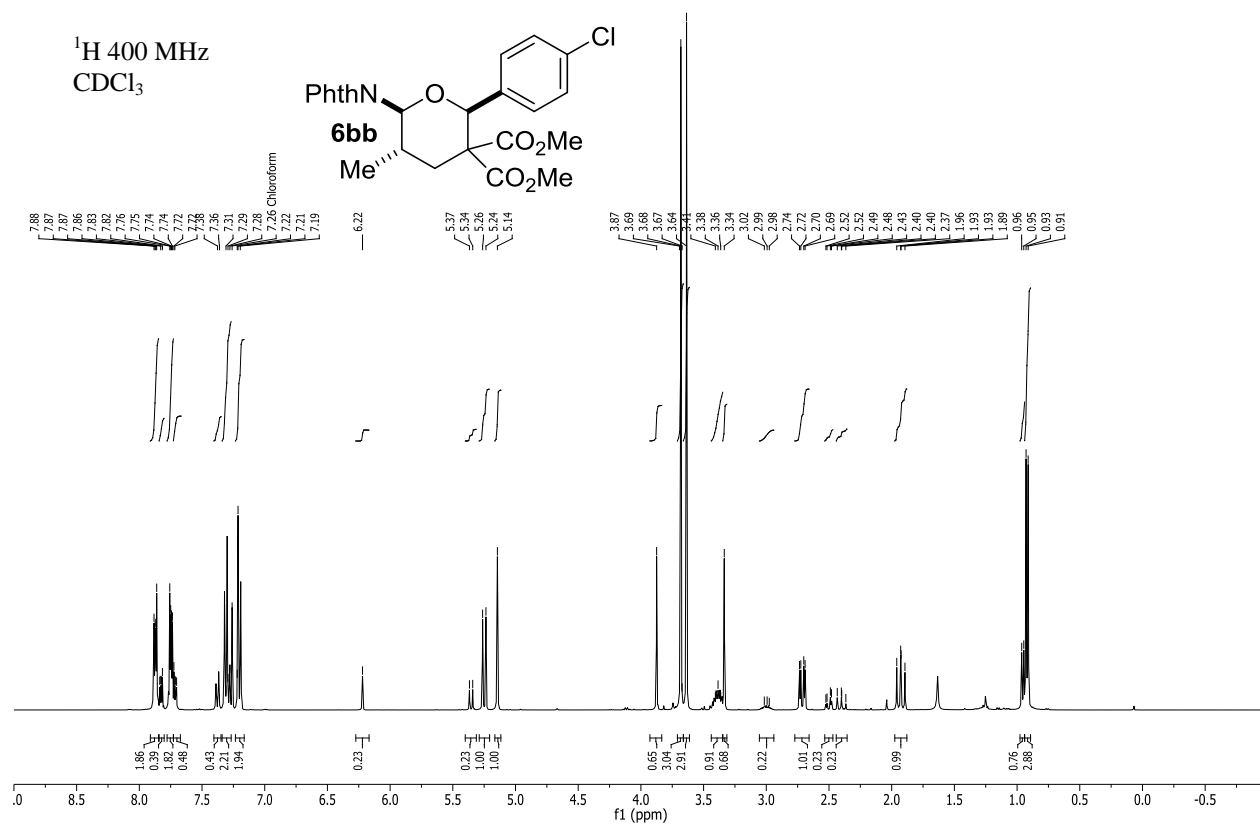


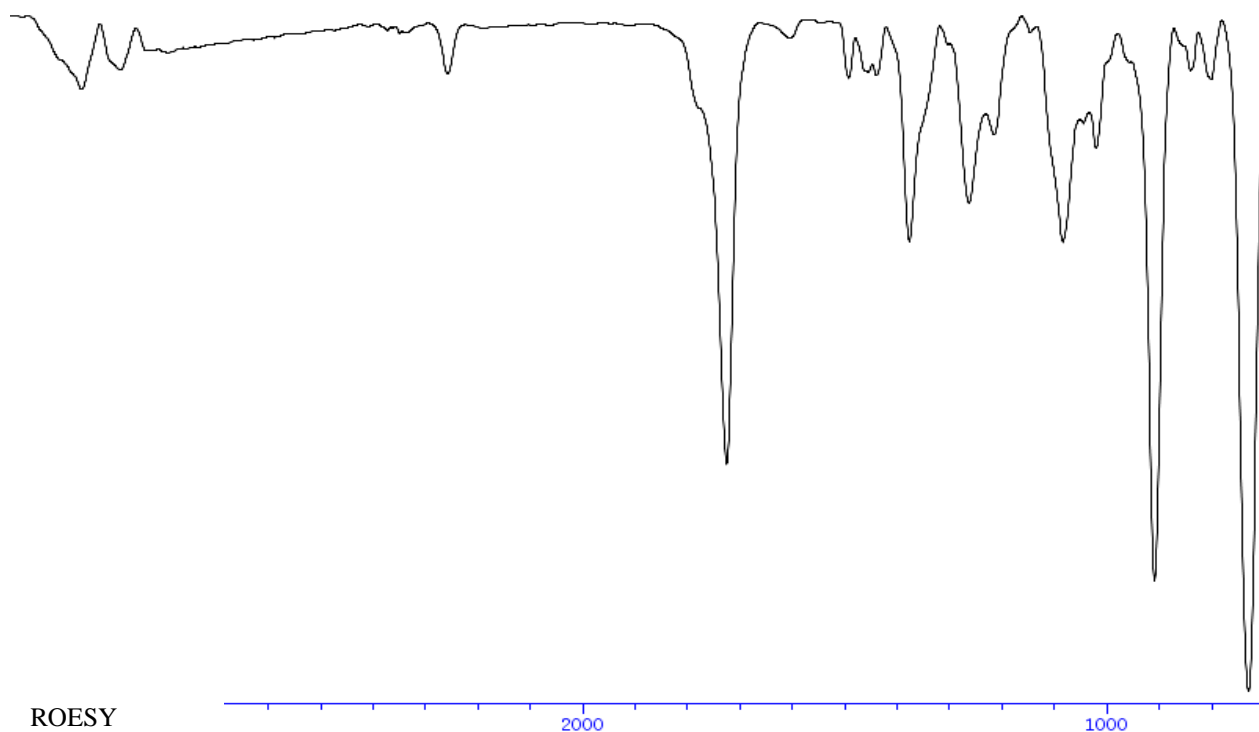




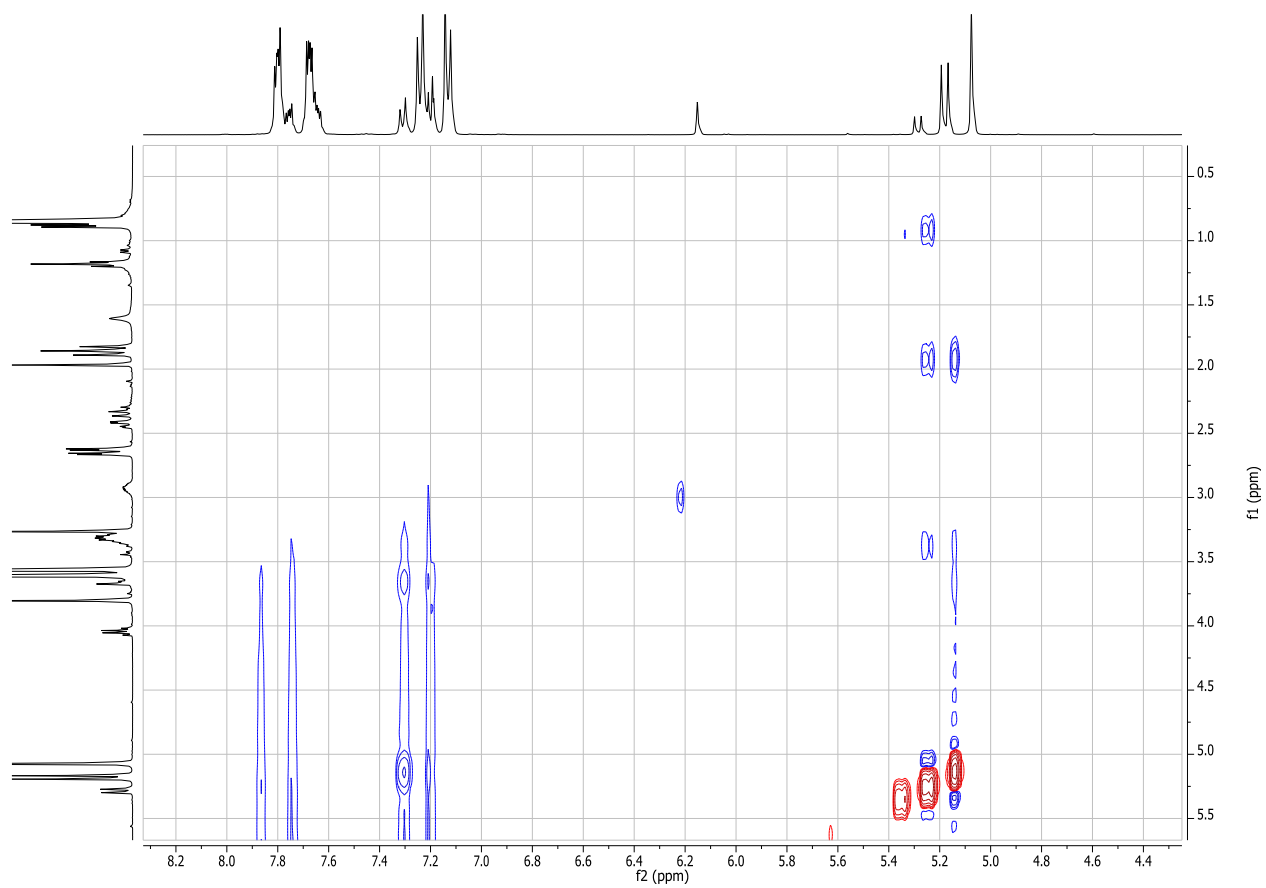


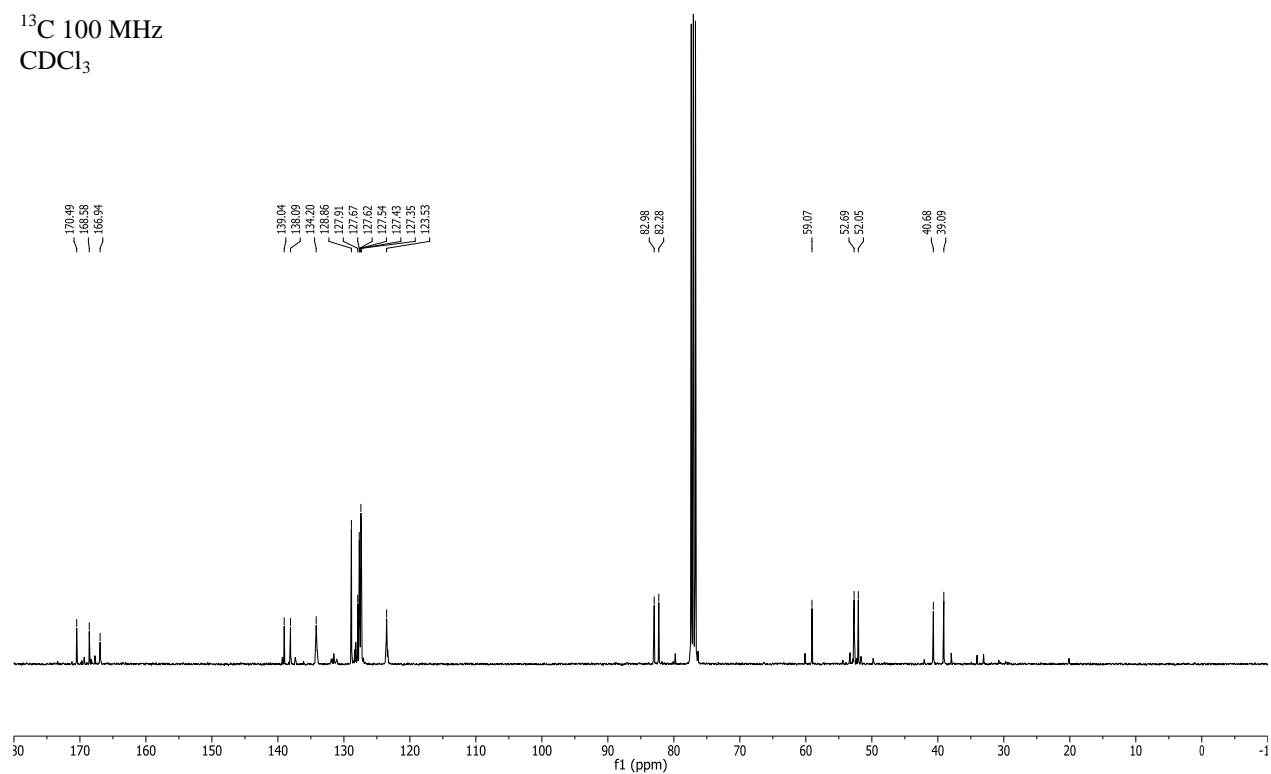
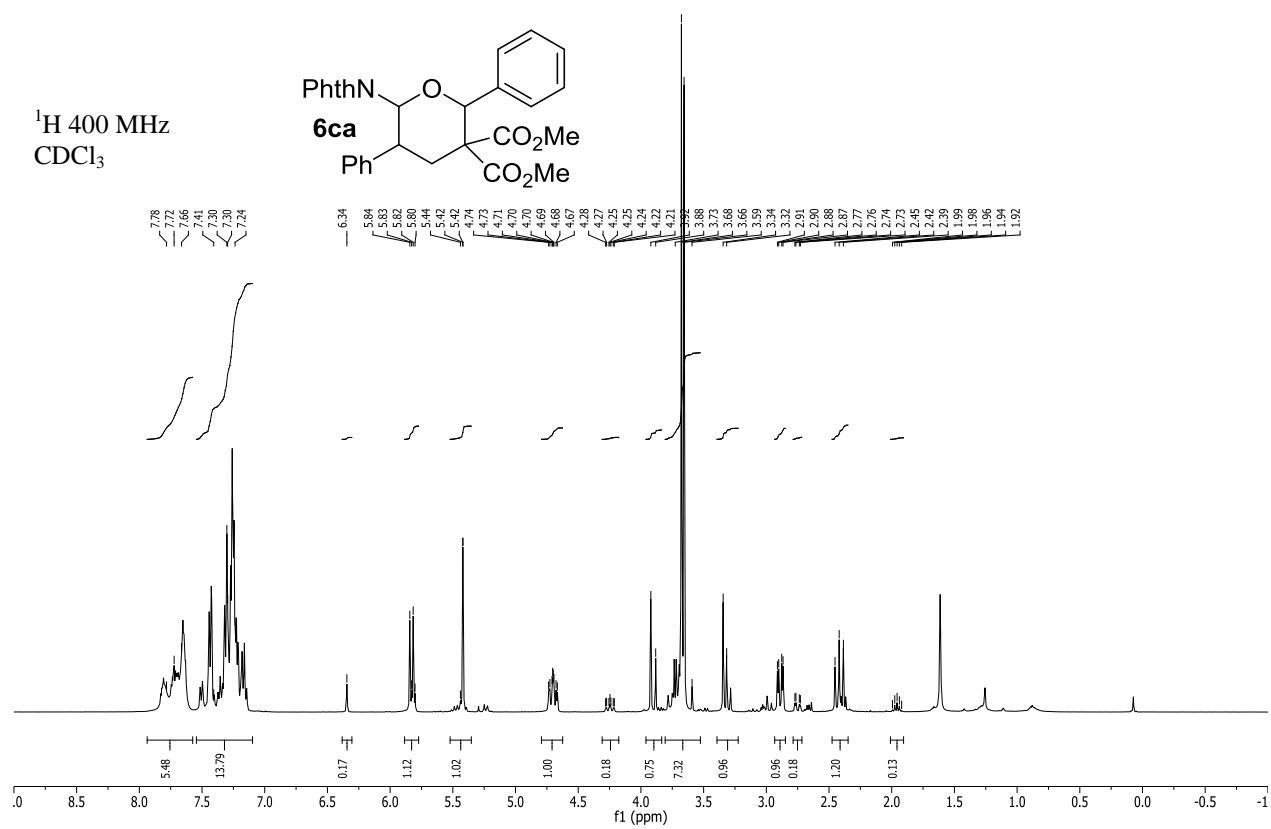


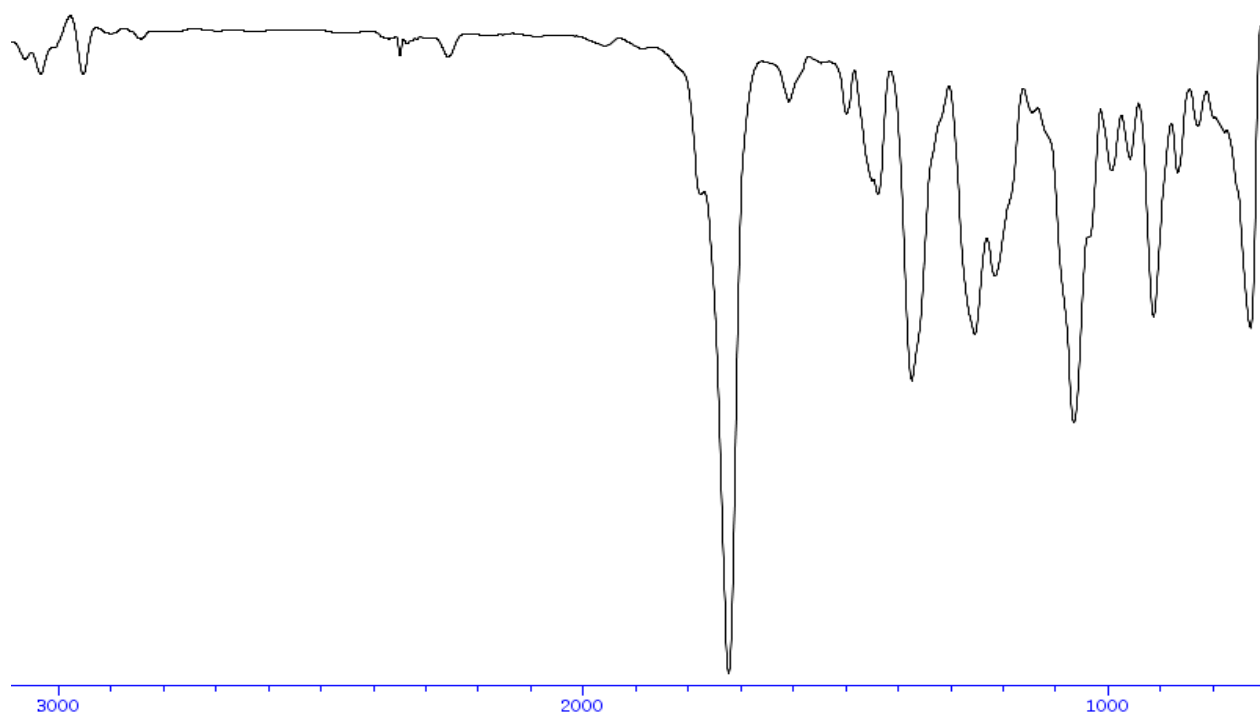


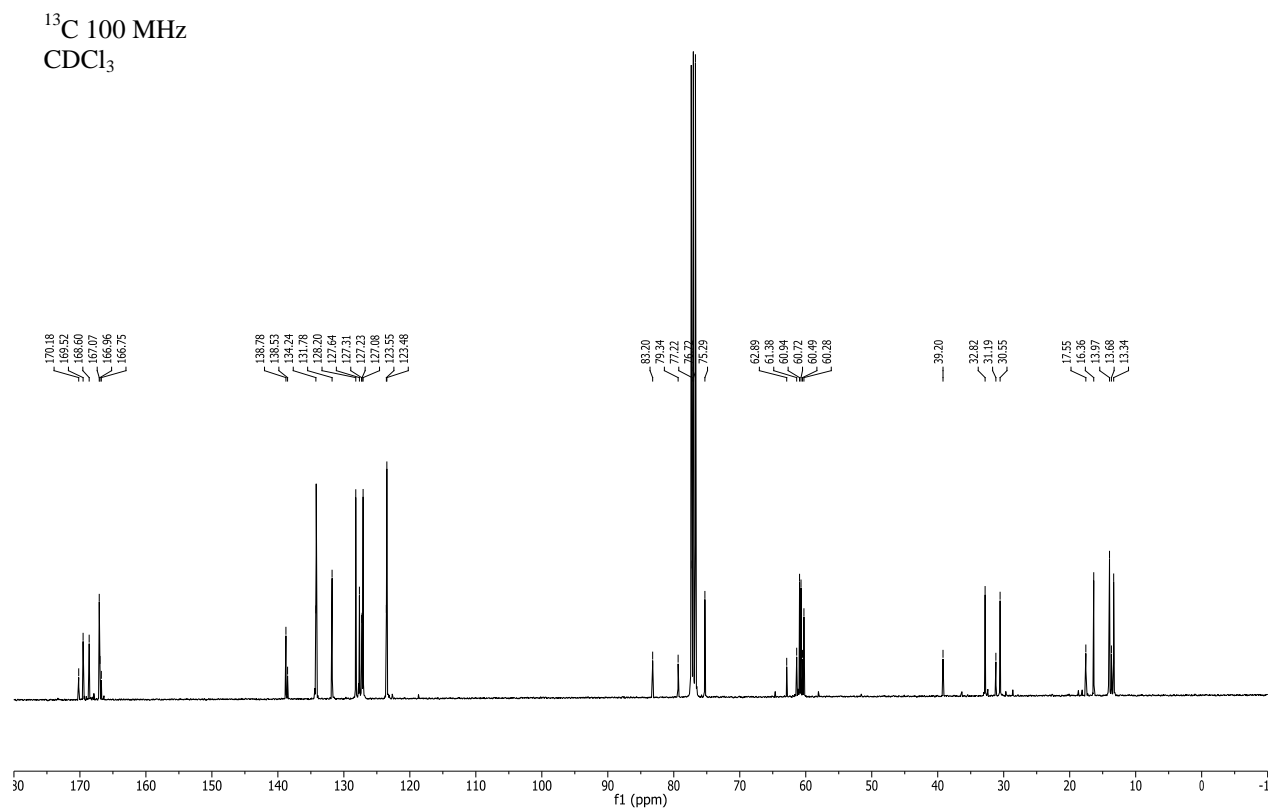
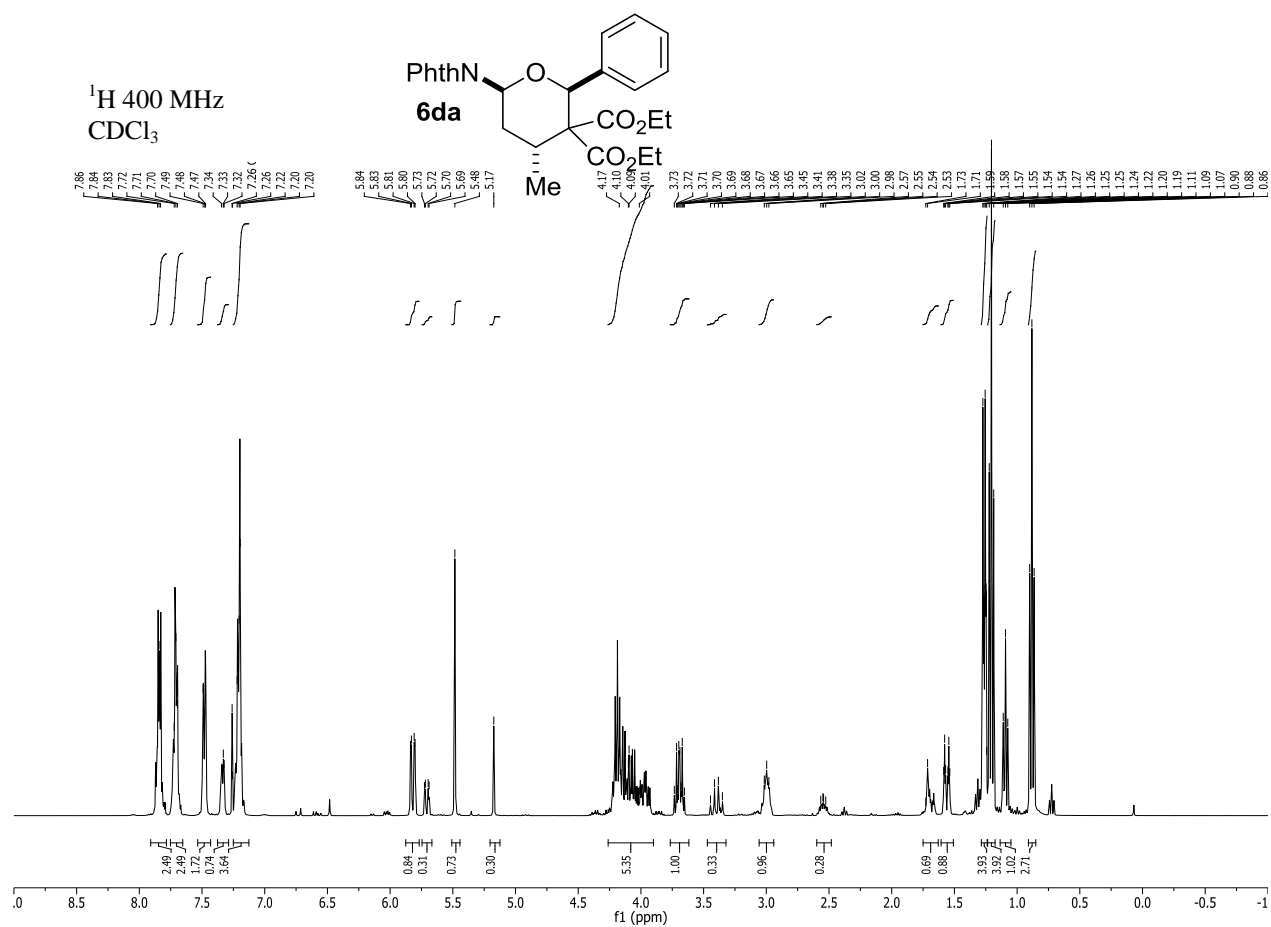


ROESY

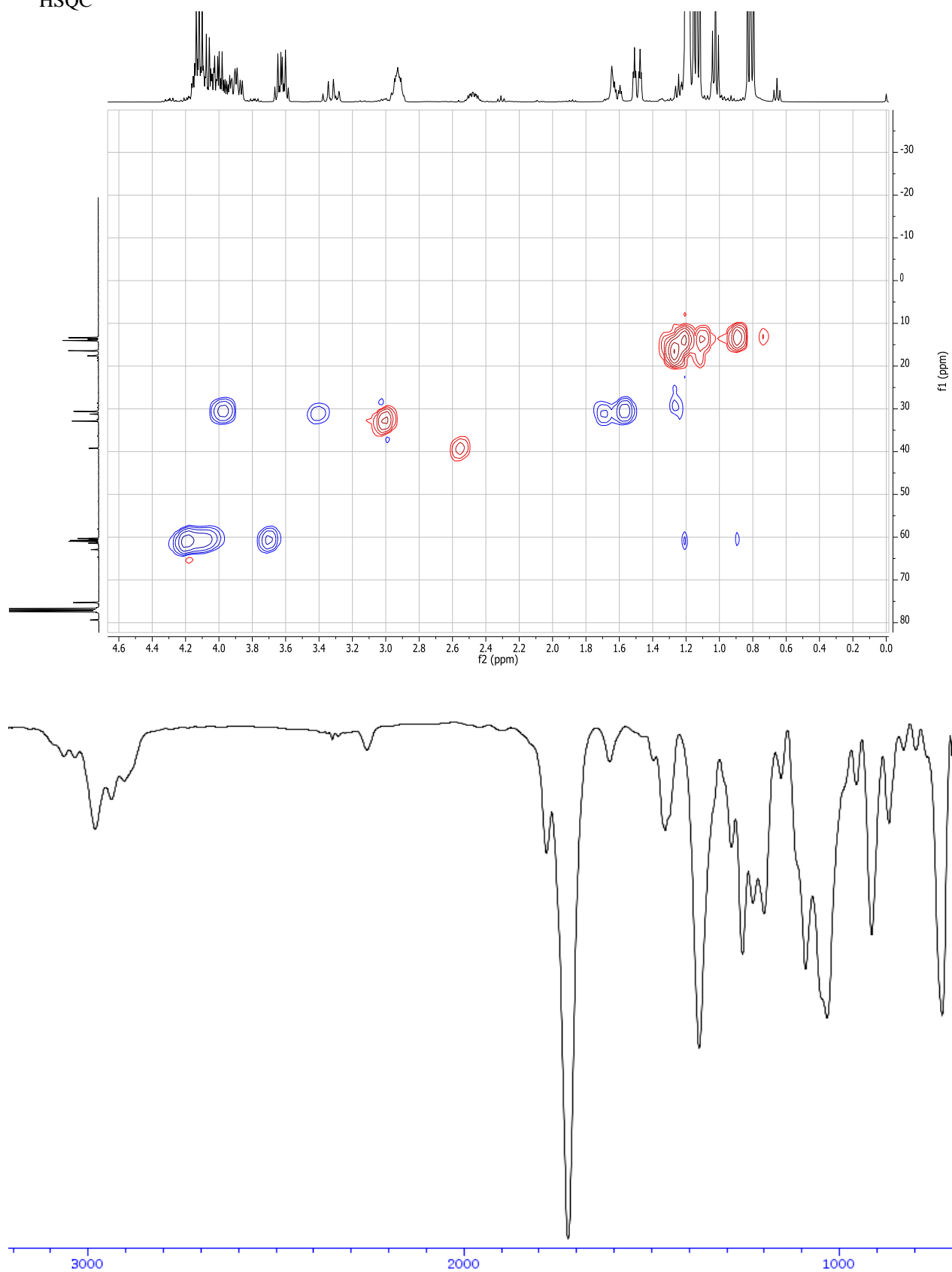


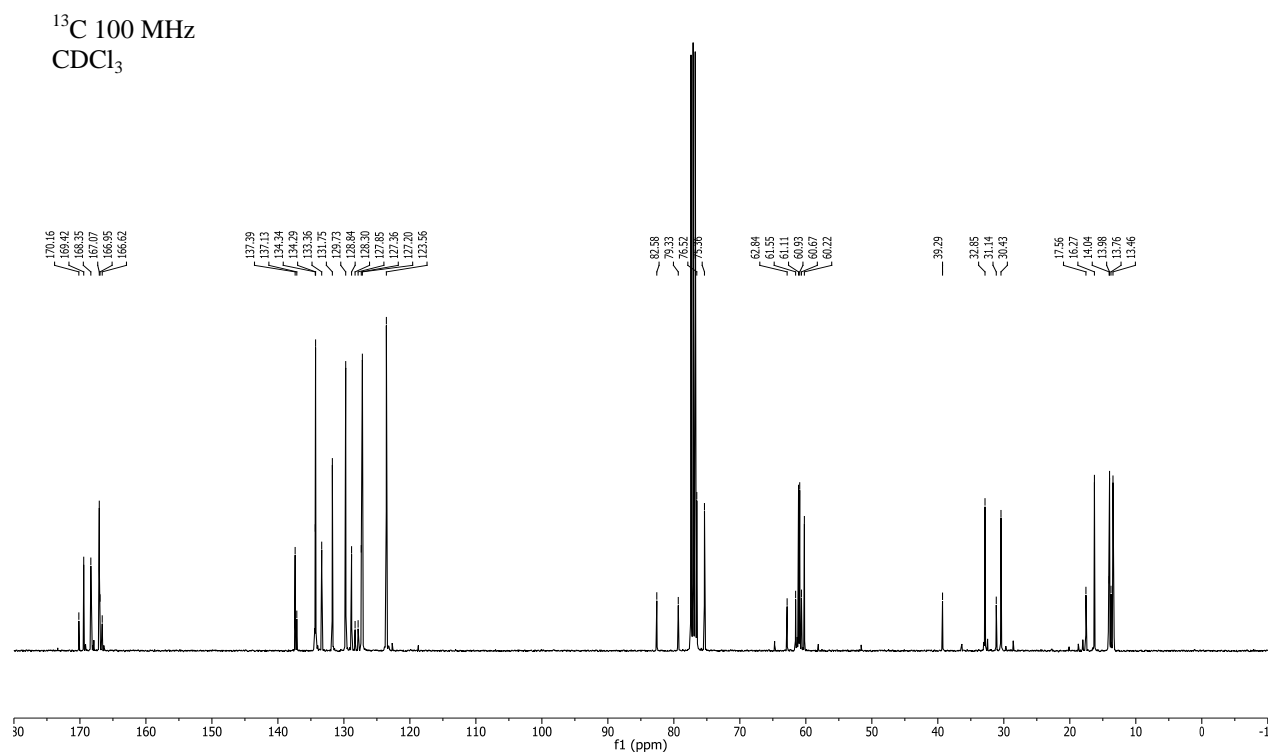
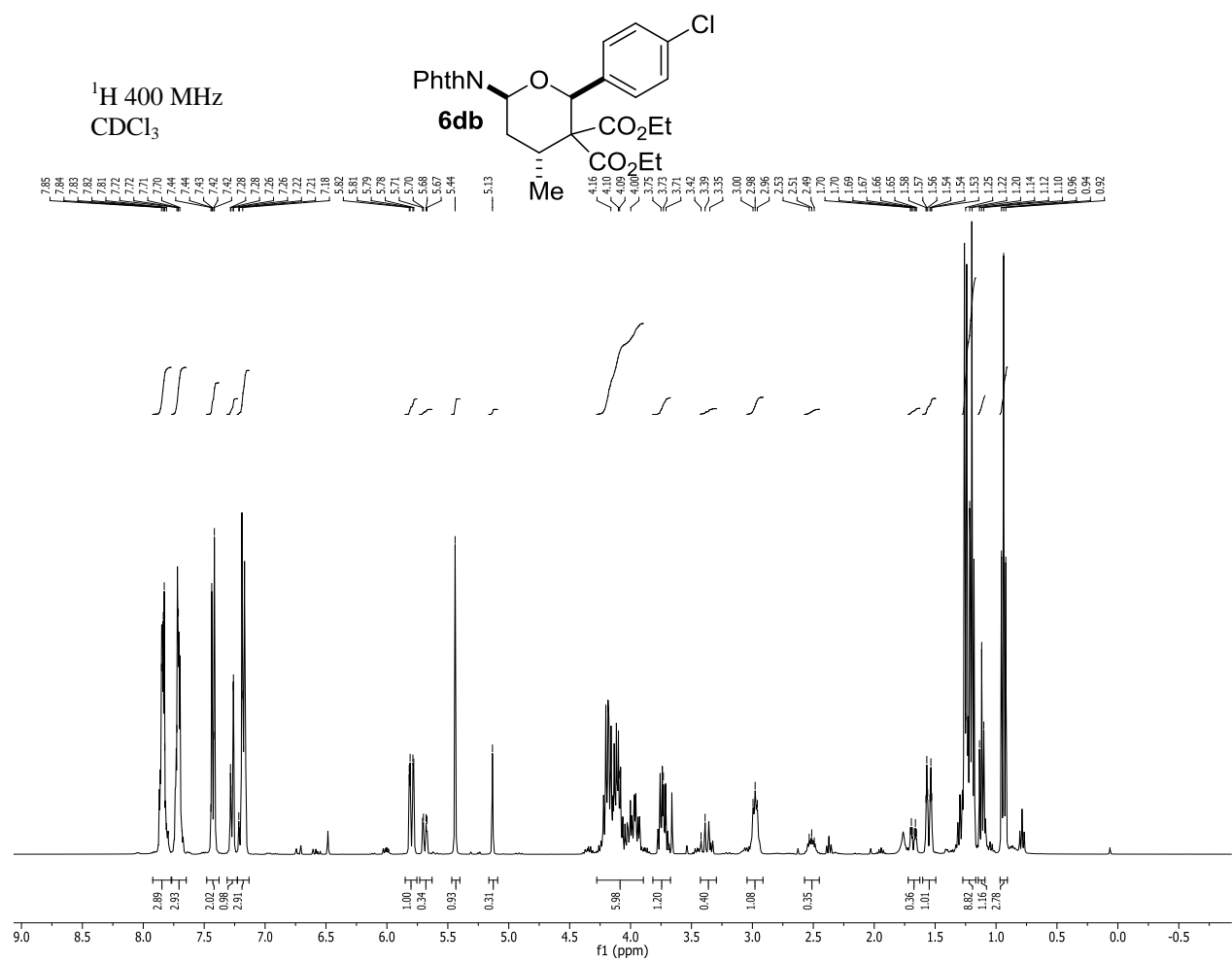




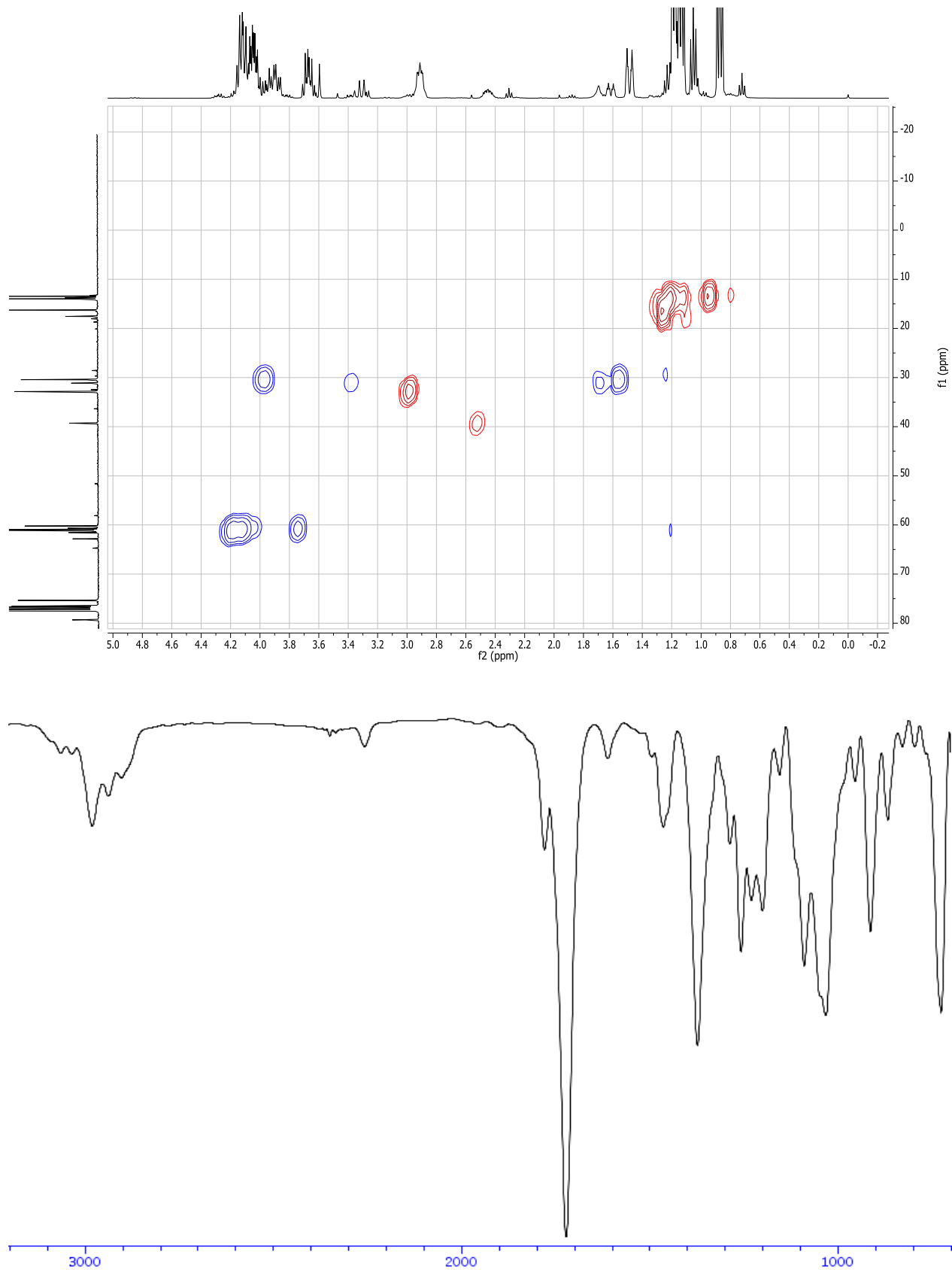


HSQC





HSQC



ROESY

