Supporting Information

Synthesis of *Aza*-Rocaglates *via* ESIPT-Mediated (3+2) Photocycloaddition

Wenyu Wang, Regina Cencic, Luke Whitesell, Jerry Pelletier, and John A. Porco, Jr.

Department of Chemistry and Center for Molecular Discovery (BU-CMD), Boston University, Boston, Massachusetts 02215, United States

McGill University, Department of Biochemistry and the Rosalind and Morris Goodman Cancer Research Centre Room 810, 3655 Drummond St., Montreal, QC, H3G 1Y6 (Canada)

Whitehead Institute for Biomedical Research (WIBR), Cambridge, Massachusetts 02142, United States

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I. GENERAL INFORMATION

A. Instrumentation and Methods

^{1}H NMR spectra were recorded at 500 MHz at ambient temperature with $CDCl_3$ (Cambridge Isotope Laboratories, Inc.) as solvent. Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (brs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hz. ^{13}C NMR spectra were recorded at 125 MHz at ambient temperature with the same solvents unless otherwise stated. Chemical shifts are reported in parts per million relative to deuterated solvents. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF API-US mass spectrometer. Melting points were recorded on a Mel-Temp apparatus (Laboratory Devices). Analytical LC-MS was performed on a Waters Acquity UPLC (Ultra Performance Liquid Chromatography (Waters MassLynx Version 4.1) with a Binary solvent manager, SQ mass spectrometer, Water 2996 PDA (PhotoDiode Array) detector, and ELSD (Evaporative Light Scattering Detector). An Acquity UPLC BEH C_{18} 1.7 μm column was used for analytical UPLC-MS. The Scilligence ELN electronic laboratory notebook was used for experimental procedure planning.

Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. HPLC grade tetrahydrofuran, methylene chloride, diethyl ether, toluene, acetonitrile, and benzene were purchased from Fisher and VWR and were purified and dried by passing through a PURE SOLV® solvent purification system (Innovative Technology, Inc.). Other ACS grade solvents for chromatography were purchased from Clean Harbors.

Photochemistry experiments were performed using a Rayonet RPR-100 photochemical reator equipped with RPR-3500Å irradiation lamps ($\lambda > 330$ nm, $\lambda_{max} = 350$ nm). For the Hanovia photoflow reactor, a 450 medium pressure mercury lamp housed in quartz immersion well with a Pyrex absorption sleeve ($\lambda > 290$ nm) was used. An A-40 Refrigerated & Heating Circulator was used for Immersion well cooling (Anova Industries Inc.). For the Rayonet photoflow reactor, a Rayonet RPR-100 photobox was used as light source and a Thermo Scientific™ Neslab CC65 Immersion Cooler was using as a cooling system. A benchtop pump with 114DV flip top single channel pumphead (model: 120S) was chosen as the peristaltic pump for the continuous photoflow reactor (Waston Marlow Fluid Technology Group). Microwave experiments were performed using a CEM Discover microwave. All other reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

II. EXPERIMENTAL PROCEDURES

A. Continuous Photoflow Reactor Design

1. Rayonet Continuous Photoflow Reactor

Rayonet continuous photoflow reactor (**Figure SI-1a**) was constructed using PTFE Tubing (1/32"ID x 1/16"OD) (Cole-Parmer Instrument Company) twined around a 500 mL Pyrex graduated cylinder (**Figure SI-1d**). Tubing volume was measure to be 56 mL. The reactor was placed into Rayonet RPR-100 photobox equipped with RPR-3500Å irradiation lamps ($\lambda > 330$ nm, $\lambda_{max} = 350$ nm) (**Figure SI-1c**). The tubing was connected to a peristaltic pump (Benchtop pump with 114DV flip top single channel pumphead, model: 120S, Waston Marlow Fluid Technology Group) using 2 conical adapter assemblies (IDEX Health & Science, P-798) (**Figure SI-1b**). Two needle adapters (IDEX Health & Science, Flangeless Ferrule Tefzel®, P-300X; Flangeless Short Nut, P-335X; Luer Adapters, P-655) were also installed to connect the reaction flask with the peristaltic pump and reaction tubing. A Thermo Scientific™ Neslab CC65 Immersion Cooler was using as cooling system for the photoflow reactor.

Figure SI-1a. Rayonet Continuous Photoflow Reactor Overview

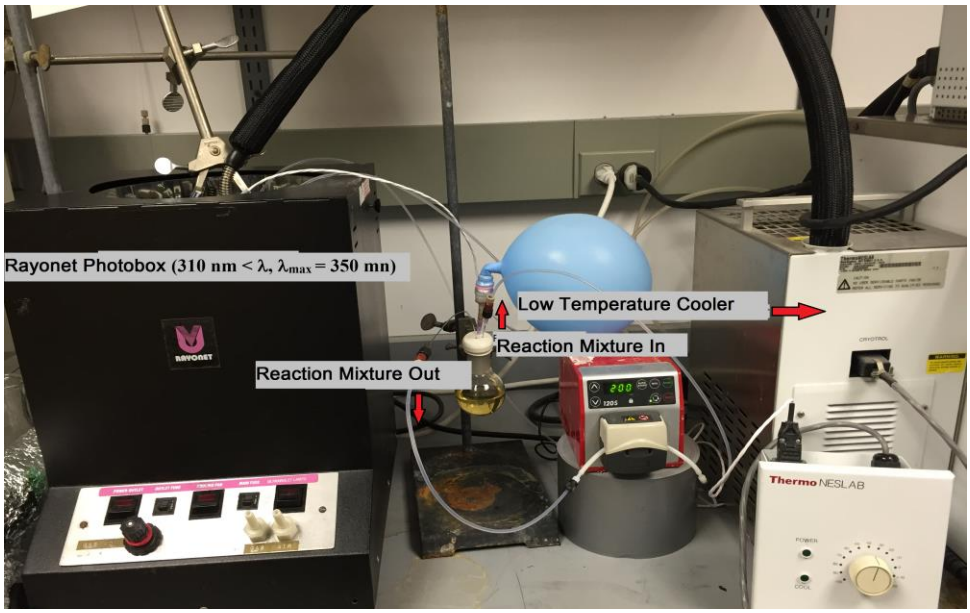


Figure SI-1b. Solvent Pumping System

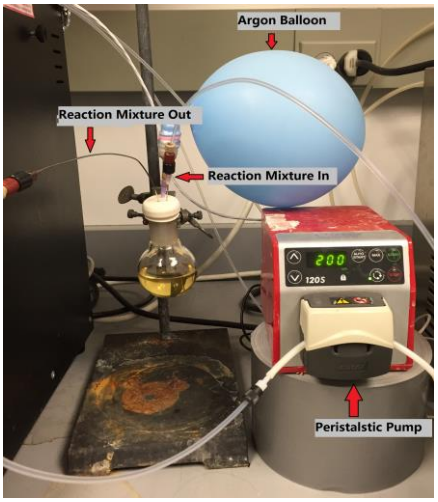


Figure SI-1c. Rayonet Photobox

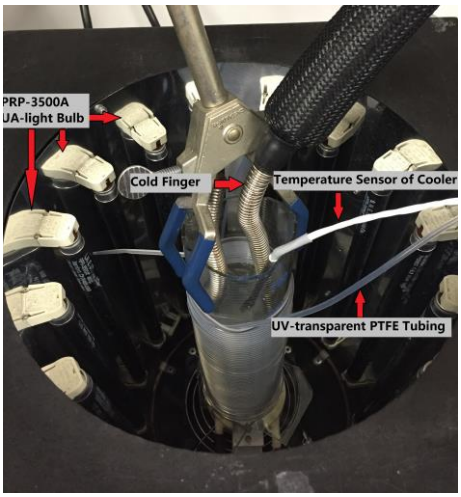
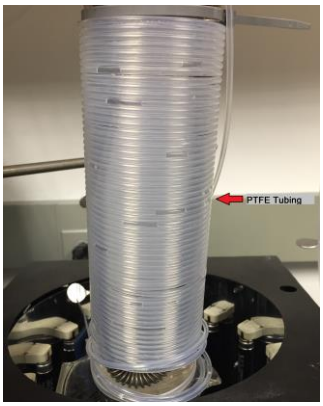


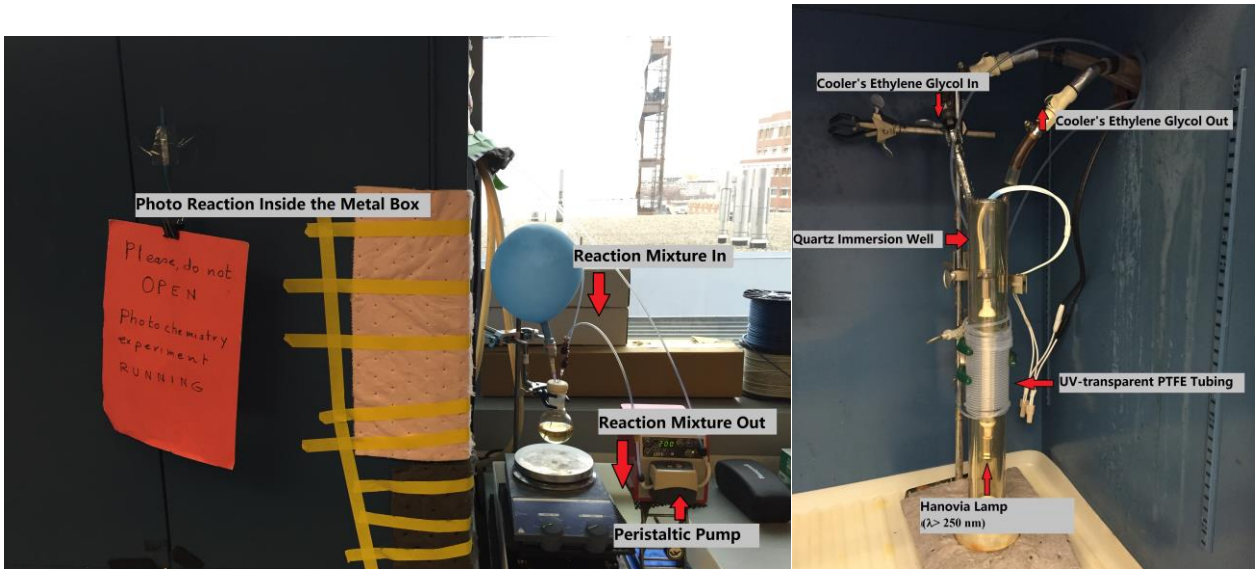
Figure SI-1d. Reactor outside Photobox



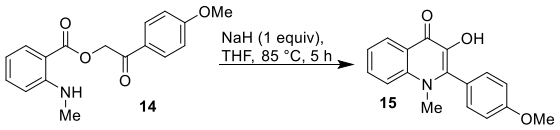
2. Hanovia Continuous Photoflow Reactor

The same PTFE tubing was used to twine around an immersion well (290 mm B quartz immersion well, 7854-27, Ace Glass Inc.) to construct a Hanovia photoflow reactor (tubing volume was measured to be 36 mL). The same parts were used to build the Hanovia photoflow reactor, with the exception that a 450 medium pressure mercury lamp housed in quartz immersion well with a Pyrex absorption sleeve (λ > 290 nm) was used as the light source and an A-40 Refrigerated & Heating Circulator was used for immersion well cooling (Anova Industries Inc.) (**Figure SI-2**).

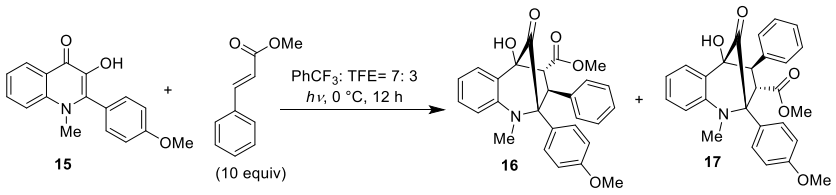
Figure SI-2. Overview of the Hanovia Continuous Photoflow Reactor



B. General Procedures



***N*-Me-3-HQ 15:** A 250 mL flame-dried, round bottom flask was charged with anthranilate **14**[S1] (3.0 g, 10 mmol, 1 equiv) and 130 mL anhydrous THF and the reaction was purged with argon. After NaH (60% dispersion in mineral oil) (0.4 g, 10 mmol, 1 equiv) was added, a water condenser was installed and the solution was heated to 85 °C for 5 h before being cooled to room temperature and immersed in an ice bath. Saturated aqueous ammonium chloride solution was added to work up the reaction until pH < 7 was achieved (250 mL was added). Then CH_2Cl_2 80 mL × 5 was used for extraction, and the combined organic layers were washed with saturated aqusous NaCl solution and dried with anhydrous Na_2SO_4. After concentrated *in vacuo*, 20 mL of cold acetone was added. The white precipitate was filtered and washed with cold acetone. Product **15**[S2] was obtained as a white solid (83% yield).



General procedure for (3+2) photocycloaddition of 1-methyl-2-(4-methoxyphenyl)-3-hydroxyquinolinone 15 with methyl cinnamate using the Rayonet photoreactor: To a Pyrex reaction tube was added substrate **15** (500 mg, 1.78 mmol, 1 equiv), methyl cinnamate (2.88 g, 17.8 mmol, 10 equiv), α, α, α-trifluorotoluene (35 mL), and 2, 2, 2-trifluoroethanol (15 mL). The resulting mixture was first sonicated and then sparged with argon while sonicating for 10 min. The tube was then sealed and chilled to 0 °C. The resulting solution was irradiated using a Rayonet RPR-100 photochemical reactor for 48 h at 0 °C. The reaction mixture was then concentrated and purified *via* column chromatography (EtOAc/hexanes = 1:10 to first remove methyl cinnamate then EtOAc/hexanes = 1:6 to EtOAc/hexanes = 1:4) to elute products. Compound **16** (633 mg, 40%) was obtained as a white solid and compound **17** (127 mg, 8%) was isolated as a colorless oil.

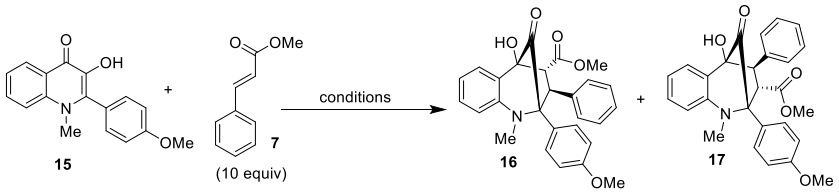
16: R_f = 0.19 (EtOAc / hexanes = 1 : 4); mp 103 - 105°C (CH_2Cl_2); IR (thin film): ν_{max} 3438, 2950, 1708, 1612, 1500, 1209, 1151, 1078, 1010, 815.73, 736 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 7.29 (d, J = 7.5

[S1] P. Hradil, J. Hlavác, K. Lemr, *J. Heterocyclic Chem.***1999**, *36*, 141. [S2] D. A. Yushchenko, M. D. Bilokin, O. V. Pyvovarenko, G. Duportail, Y. Mély, V. G. Pivovarenko, *Tetrahedron Lett*. **2006**, *47*, 905.

Hz, 1H), 7.21 (m, 3H), 7.06 (m, 3H), 6.90 (m, 3H), 6,79 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 7 Hz, 2H), 4.63 (d, J = 7 Hz, 1H), 3.70 (s, 3H), 3.54 (s, 1H), 3.50 (s, 3H), 3.35 (d, J = 7 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 210.2, 170.5, 158.6, 145.6, 141.5, 131.5, 130.8, 129.8, 128.8, 128.4, 126.7, 126.6, 124.3, 120.7, 117.7, 113.0, 80.4, 72.9, 59.9, 55.1, 51.1, 38.8, 29.7; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{27}H_{25}NO_5$ 444.1811, found 444.1809.

17: R_f = 0.27 (EtOAc / hexanes = 1 : 4); IR (thin film): ν_{max} 3507, 3065, 2950, 1738, 1601, 1487, 1255, 1181, 1088, 737, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.42 (d, J = 10 Hz, 1H), 7.30 (m, 3H), 7.22 (m, 1H), 7.03 (d, J = 11.5 Hz, 2H), 6.98 (d, J = 11.5 Hz, 2H), 6.82 (t, J = 10 Hz, 1H), 6.52 (d, J = 10 Hz, 1H), 4.55 (d, J = 7.5 Hz, 1H), 4.10 (d, J = 7.5 Hz, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 2.60 (s, 1H, OH), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 171.4, 159.7, 144.3, 139.5, 129.5, 129.2, 128.9, 128.5, 127.7, 125.8, 122.8, 118.5, 113.8, 111.2, 79.1, 77.2, 73.9, 55.3, 53.8, 53.4, 52.5, 35.7; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{27}H_{25}NO_5$ 444.1811, found 444.1811.

Table SI-1 Condition optimization for (3+2) photocycloaddition of 1-methyl-(4-methoxyphenyl)-3-hydroxyquinolinone with methyl cinnamate.



Entry	Conc. (M)	Solvent	Time (h)	Temp. (°C)	Ratio (**16**: **17**)[a]	Yield (%)
1	0.02	CH_2Cl_2 : MeOH= 1 : 1	24 h	0	1 : 1.4	27
2	0.02	$CHCl_3$: TFE= 4 : 1	24 h	0	3 : 1	39
3	0.02	$CHCl_3$	24 h	0	2 : 1	31
4	0.02	$CHCl_3$: HFIP= 4 : 1	24 h	0	1 : 1.6	34
5	0.02	CH_3CN: $CHCl_3$= 3 : 1	24 h	0	1 : 1	31
6	0.02	$PhCF_3$: TFE= 5 : 1	24 h	0	4.5 : 1	40
7	0.04	$PhCF_3$: TFE= 4 : 1	36 h	0	3 : 1	43
8	0.035	$PhCF_3$: TFE= 7 : 3	48 h	0	5 : 1	40

[a] The isomeric ratio of **16**/**17** was determined by ^{1}H NMR analysis.

General procedure for (3+2) photocycloaddition of 1-methyl-2-aryl-3-hydroxyquinolinone with methyl cinnamate using a continuous photoflow reactor: In a 200 mL flame dried flask, compound **15** (1 g, 3.56 mmol, 1 equiv), methyl cinnamate (8.64 g, 53.25 mmol, 15 equiv), 50 mL α,α,α-trifluorotoluene, and 21 mL 2,2,2-trifluoroethanol were added. After degassing with argon for 10 min in a sonicator, the reaction flask was connected to the continuous flow photochemistry system. After the solvent pump started, nitrogen gas was bubbled into the reaction mixture for another 10 min to further purge the remaining air out of the reaction system. The reaction mixture cooled to 0 °C and was kept circulating and irradiated (Rayonet, λ > 330 nm) at 0 °C for 9 h. After being concentrated *in vacuo*, the reaction mixture was purified by silica gel column chromatography (gradient of EtOAc/hexane 1:10 to remove the methyl cinnamate first, then EtOAc/hexane from 1:6 to 1:4 to obtain the product). Compound **16** (483.5 mg, 46%) was obtained as a white solid. and compound **17** (97 mg, 9%) was isolated as a colorless oil.

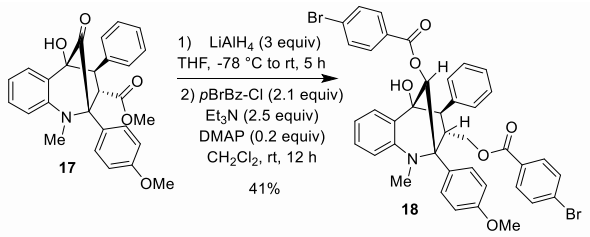
Table SI-2 Selctected Condition Optimization in Continuous Photoflow Reactor

Entry	Conc. (M)	Solvent	Time, Temp.	Reactor	Ratio (**16** : **17**)	Yield (%)
1	0.06	$PhCF_3$: TFE = 7 : 3	14 h, 5 °C[a]	Hanovia[b]	N/A	Decomp.
2	0.06	$PhCF_3$: TFE = 7 : 3	14 h, 0 °C	Rayonet	4 : 1	43%
3	0.04	$PhCF_3$: TFE = 7 : 3	14 h, -20 °C	Hanovia (Pyrex)	3 : 1	19%
4	0.04	$PhCF_3$: TFE = 7 : 3	14 h, -20 °C	Rayonet	4.5 : 1	44%
5	0.035	$CHCl_3$: TFE = 7 : 3	10 h, 0 °C	Rayonet	4 : 1	43%
6	0.035	$PhCF_3$: TFE = 4 : 1	9 h, 0 °C	Rayonet	5 : 1	43%
7	0.035	$PhCF_3$: TFE = 7 : 3	9 h, 0 °C	Rayonet	5 : 1	46%

Note: a. Due to powerful heat release from the Hanovia lamp, in order to maintain a low temperature for the reaction, every 2 h the lamp was turned off to allow the reaction system to recool to - 5 °C. Accordingly, 5 °C is an average temperature for the photoreaction over 14 h.

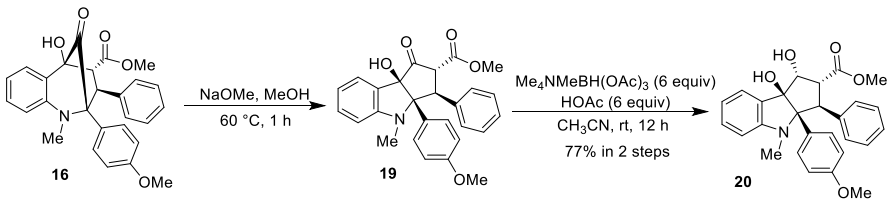
b. Photodegradation of 3-hydroxyquinolinones was observed when the stronger irradiation of the Hanovia lamp system was used.[S3]

[S3] T. Matsuura, T. Takemoto, T. Nakashima, *Tetrahedron* **1973**, *29*, 3337.



***Bis-p*-bromobenzoate 18**: A 50 mL flask was charged with compound **17** (50 mg, 0.11 mmol, 1 equiv) and a stir bar in 20 mL of dry THF. The solution was cooled to -78 °C before $LiAlH_4$ (19.1 mg, 0.56 mmol, 5 equiv) was added. The reaction mixture was warmed to room temperature and stirred overnight before saturated NH_4Cl (20 mL) and potassium sodium tartrate tetrahydrate (20 mL) aqueous solution were added to quench the reaction. 3 × 20 mL of CH_2Cl_2 was used for extraction and the organic layers were combined. After drying the organic layers with anhydrous Na_2SO_4, filtration, and concentration *in vacuo*, the resulting brown oil was used in the next step without further purification. The brown oil was dissolved in 50 mL of dry CH_2Cl_2 and was cooled to 0 °C before 4-bromobenzoyl chloride (52 mg, 0.24 mmol, 2.1 equiv) was added. The reaction mixture was stirred at room temperature for 3 h. Saturated aqueous Na_2CO_3 (20 mL) solution was added to quench the reaction. CH_2Cl_2 (3×20 mL) was used for extraction and the combined organic layers were washed with saturated aqueous NaCl and dried with anhydrous sodium sulfate. After filtration, and concentration *in vacuo*, the crude product was purified *via* SiO_2 gel column chromatography (1:10 EtOAc/hexanes to 1:5 EtOAc/hexanes) to afford compound **18** (41% yield) as a white solid.

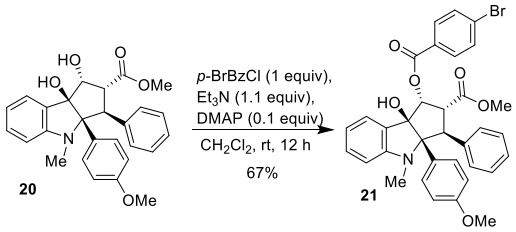
18: R_f = 0.63 (EtOAc / hexanes = 3 : 7); mp 151-152 °C (CH_2Cl_2); IR (thin film): ν_{max} 3062, 2927, 1719, 1590, 1513, 1265, 1102, 1012, 752 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 7.49 (m, 6H), 7.32 (m, 11H), 6.85 (d, J = 8.5 Hz, 2H), 6.76 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 5.70 (s, 1H), 4.78 (dd, J1 = 6 Hz, J2 = 11 Hz), 4.33 (dd, J1 = 8.5 Hz, J2 = 11 Hz), 4.02 (ddd, J1 = 6 Hz, J2 = 8 Hz, J3 = 8.5 Hz), 3.79 (s, 3H), 3.53 (d, J = 8 Hz), 2,79 (s, 3H), 2.16 (s, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 165.6, 165.3, 159.3, 144.5, 139.3, 131.7, 131.4, 131.2, 131.0, 130.1, 130.0, 129.8, 129.3, 129.2, 128.5, 128.4, 128.3, 128.1, 127.7, 122.1, 116.8, 114.1, 109.8, 78.7, 77.4, 69.0, 65.9, 59.1, 55.3, 50.9, 36.9; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{40}H_{33}Br_2NO_6$ 782.0953, found 782.0771.



General procedure for the synthesis of *aza*-rocaglates from *aza*-aglain ketones:

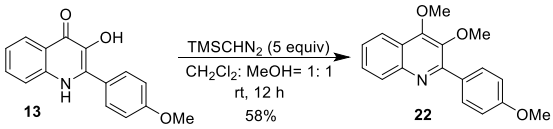
***N*-methyl *aza*-rocaglate 20**: A 100 mL flame dried flask was charged with compound **16** (100 mg, 0.225 mmol, 1 equiv) and a stir bar. Then 20 mL of dry methanol were added to form a pale yellow solution. A sodium methoxide solution prepared from sodium metal (52 mg, 2.25 mmol, 10 equiv) and 10 mL of dry methanol was added to the solution of compound **16** and the resulting mixture was heated to 60 °C for 20 min before being quenched with saturated NH_4Cl aqueous (20 mL). The reaction was diluted and extracted with EtOAc (3 x 10 mL), then washed with saturated aqueous NaCl (20 mL), dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Crude ^{1}H NMR analysis of the crude product **19** ($CDCl_3$, ratio = 2 : 1) showed a mixture of keto and enol tautomers in solution. To a 25 mL flame dried flask was added crude product **19** (85 mg), tetramethylammonium triacetoxyborohydride (356 mg, 1.35 mmol, 6 equiv), acetic acid (65 µL, 1.13 mmol, 6 equiv), and 10 mL of dry acetonitrile. The resulting yellow solution was stirred for 14 h at room temperature before being quenched with sat. NH_4Cl solution (10 mL) and saturated aqueous potassium sodium tartrate tetrahydrate (Rochelle salt) (10 mL) to remove boron compounds by complexation. The mixture was then extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with sat. $NaHCO_3$ (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (gradient of EtOAc/hexane from 1:4 to 1:2) to afford pure *N*-Me-*aza*-rocaglate **20** (77 mg, 77% over 2 steps) as a white solid.

20: R_f = 0.12 (EtOAc / hexanes = 1 : 4); mp 85 - 86°C (CH_2Cl_2); IR (thin film): ν_{max} 3401, 2927, 1711, 1628, 1514, 1254, 1185, 1112, 1036, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.5 Hz, 2H), 7.37 (d, J = 7.5 Hz, 1H), 7.22 (m, 4H), 6.83 (d, J = 9 Hz, 2H), 6.80 (d, J = 7.5 Hz, 1H), 6.60 (d, J = 9 Hz, 2H), 6.31 (d, J = 8 Hz, 1H), 4.77 (dd, J_1 = 9 Hz, J_2 = 10.5 Hz, 1H), 4.51 (d, J = 3 Hz, 1H), 3.89 (d, J = 10.5 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 3H), 3.20 (dd, J_1 = 3 Hz, J_2 = 9 Hz, 1H), 2.61 (bs, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 158.7, 151.2, 140.9, 130.3, 129.6, 129.4, 129.3, 128.2, 127.6, 126.4, 125.1, 117.7, 113.3, 106.0, 90.6, 85.9, 79.6, 55.0, 52.7, 52.6, 51.6, 29.6; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{27}H_{27}NO_5Na$ 468.1787, found 468.1779.



***Para*-bromo benzoate 21**: A 25 mL flame dried flask was charged with compound **20** (52 mg, 0.12 mmol, 1 equiv), 4-bromobenzoyl chloride (27 mg, 0.12 mmol, 1 equiv), triethylamine (18 µL, 0.13 mmol, 1.1 equiv), and CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 12 h before being quenched with sat. Na_2CO_3 solution. The mixture was then extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with sat. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (gradient of EtOAc/hexane from 1:6 to 1:4) to afford compound **21** (48 mg, 67%) as a white solid.

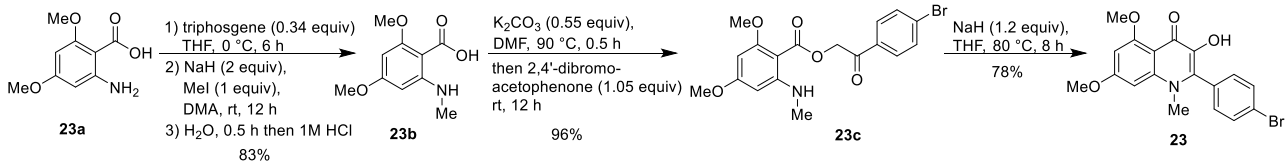
21: R_f = 0.41 (EtOAc / hexanes = 3 : 7); mp 218 - 219 °C (CH_2Cl_2); IR (thin film): ν_{max} 3491, 2952, 2837, 1733, 1161, 1511, 1269, 1121, 1038, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 9 Hz, 2H), 7.45 (d, J = 9 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 7.21 (t, J = 9 Hz, 2H), 7.12 (m, 3H), 6.79 (d, J = 9 Hz, 2H), 6.62 (d, J = 9 Hz, 2H), 6,53 (t, J = 7.5 Hz, 1H), 6.41 (d, J = 7.5 Hz, 1H), 5.95 (d, J = 5.5 Hz, 1H), 4.72 (d, J = 10.5 Hz, 1H), 4.22 (dd, J1 = 5.5 Hz, J2 = 10.5 Hz, 1H), 3.67 (s, 3H), 3.55 (s, 3H), 3.12 (s, 3H), 1.85 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 164.8, 158.6, 150.9, 138.5, 131.5, 131.0, 130.6, 130.4, 129.0, 128.5, 128.2, 128.1, 126.5, 126.2, 125.8, 125.0, 116.7, 113.1, 104.3, 93.0, 85.8, 80.6, 55.0, 54.4, 52.1, 52.0, 30.9; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{34}H_{31}BrNO_6$ 628.1335, found 628.1348.



3,4-Dimethoxyquinoline 22: A flame dried test tube was charged with compound **13** (50 mg, 0.19 mmol, 1 equiv). Anhydrous CH_2Cl_2/ MeOH = 1:1 (5 mL) was added to afford a heterogeneous solution. Then, $TMSCHN_2$ (0.95 mL, 2M ether solution, 5 equiv) was added which led to slow dissolution of compound **13**. The resulting mixture was stirred at room temperature for 12 h before 10 mL of 10% aqueous AcOH solution was added dropwise to quench the reaction. The mixture was then extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with sat. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient of EtOAc/hexane from 1:4 to 1:2) afforded compound **22** (32 mg, 58%) as a colorless oil.

22: R_f = 0.44 (EtOAc / hexanes = 1 : 4); IR (thin film): ν_{max} 2936, 2837, 1607, 1515, 1378, 1252, 1177, 1107, 1045, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 10.5 Hz, 1H), 8.06 (d, J = 10.5 Hz, 1H),

7.99 (d, J = 11 Hz, 2H), 7.62 (t, J = 10.5 Hz, 1H), 7.48 (t, J = 10.5 Hz, 1H), 7.02 (d, J = 11Hz, 2H), 4.24 (s, 3H), 3.88 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 154.1, 145.9, 142.4, 130.8, 130.6, 129.1, 128.5, 125.7, 123.9, 121.6, 113.6, 61.1, 60.8, 55.3; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{18}H_{17}NO_3$ 296.1287, found 296.1287.



General procedure for the synthesis of N-alkyl-3-hydroxyquinolinones from anthranilic acid:

N-methyl dimethoxyanthranilic acid 23b: To a flame dried 250 mL flask, dimethoxyanthranilic acid **23a**[S4] (5.5 g, 27.9 mmol, 1 equiv) and 150 mL of anhydrous THF was added. After the resulting solution was cooled to 0 °C in an ice bath, triphosgene (2.81 g, 9.5 mmol, 0.34 equiv) was added and a precipitate formed immediately. The reaction mixture was warmed to room temperature and stirred overnight before being concentrated *in vacuo*. Then CH_2Cl_2 was added and the remaining solid was separated by filtration. The solid obtained (dimethoxy isatoic anhydride) was washed with cold CH_2Cl_2, dried, and was then redissolved in 150 mL of dry DMA in a 250 mL flask. Then NaH (60 % dispersion in mineral oil) (2.23g, 55.8 mmol, 2 equiv) was added. The mixture was stirred for 10 min at room temperature before MeI (1.74 mL, 27.9 mmol, 1 equiv) was added. The reaction was stirred at room temperature for 10 h before 15 mL of H_2O was added to quench the reaction which was stirred at room temperature for 0.5 h to facilitate hydrolysis of the N-methyl isatoic anhydride to N-methyl anthranilic acid **23b**. Then 1M aqueous HCl was added dropwise to acidify the reaction to pH 6 - 7. The mixture was extracted 3 × 150 mL of CH_2Cl_2, and the combined organic layers were washed by 3 × 150 mL of H_2O to remove the remaining DMA and was then washed with sat. NaCl (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient of EtOAc/hexane from 1:4 to 1:2) afforded N-methyl dimethoxyanthranilic acid **23b** (4.91 g 83%) as a white solid.

23b: R_f = 0.32 (EtOAc / hexanes = 3 : 7); mp 131 - 133 °C (CH_2Cl_2); IR (thin film): ν_{max} 3322, 3202, 2948, 1686, 1620, 1414, 1223, 1154, 1049, 803 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.11 (s, 1H, OH), 8.88 (d, J = 5Hz, 1H, NH), 5.78 (s, 2H), 3.97 (s, 3H), 3.84 (s, 3H), 2.88 (d, J = 5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 164.6, 161.4, 155.9, 92.5, 88.1, 86.8, 56.6, 55.2, 29.8; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{10}H_{13}NO_4$ 211.0845, found 211.0842.

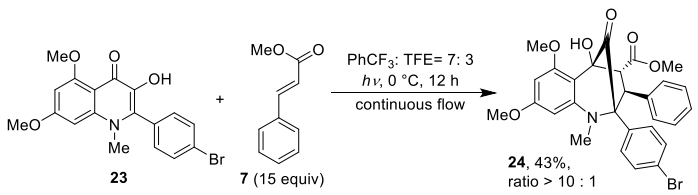
[S4] Hennequin, L. F.; Allen, J.; Breed, J.; Curwen, J.; Fennell, M.; Green, T. P.; van der Brempt, C. L.; Morgentin, R.; Norman, R. A.; Olivier, A.; Otterbein, L.; Ple, P. A.; Warin, N.; Costello, G.; *J. Med. Chem.*, **2006**, *49*, 6465.

***N*-Methyl dimethoxyanthranilate 23c:** A 250 mL flame dried flask was charged with N-methyl dimethoxyanthranilic acid **23b** (4.5 g, 31.3 mmol, 1 equiv), K_2CO_3 (1.62 g, 11.7 mmol, 0.55 equiv), 135 mL dry DMF and a stir bar. The reaction mixture was heated to 90 °C for 0.5 h before being cooled to room temperature. Then 2,4′-dibromoacetophenone (5.92 g, 21.3 mmol, 1 equiv) was added and the reaction mixture was stirred at room temperature overnight and added to ice water. After 5 min, compound **23c** precipitated from the solution. The solid was filtered and dried. (If no precipitate was formed, extraction with CH_2Cl_2 could be used to obtain crude product.) Purification by silica gel column chromatography (gradient of EtOAc/hexane from 1:4 to 1:1) afforded N-methyl dimethoxyanthranilate **23c** (8.33g, 96%) as a white solid. Product recrystallization from MeOH was also found to be effective for purification of **23c**: 150 mL MeOH was added to the crude solid product which was followed by heating to 80 °C for 20 min before being cooled to 0 °C. Filtration and drying of the solid product afforded **23c** 7.5 g (87% yield) product as a white solid.

23c: R_f = 0.36 (EtOAc / hexanes = 3 : 7); mp 126 - 127 °C (CH_2Cl_2); IR (thin film): ν_{max} 3396, 2937, 1698, 1587, 1416, 1261, 1159, 1104, 1009, 807 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 7.40 (d, J = 4 Hz, 1H, NH), 5.80 (d, J = 2 Hz, 1H), 5.76 (d, J = 2 Hz, 1H), 5.43 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.88 (d, J = 4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 167.3, 164.6, 163.0, 154.0, 133.1, 132.1, 129.5, 129.0, 95.4, 87.6, 87.4, 65.9, 56.0, 55.1, 30.1; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{18}H_{19}BrNO_5$ 408.0447, found 408.0445.

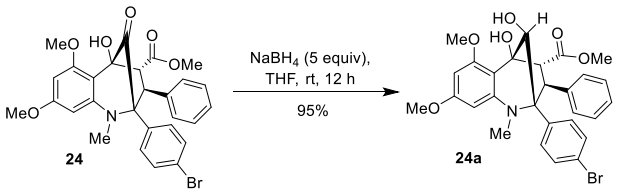
1-Methyl-2-(4-bromophenyl)-3-hydroxydimethoxyquinolinone 23: A 500 mL flame dried flask was charged with N-methyl dimethoxyanthranilate **23b** (2 g, 4.9 mmol, 1 equiv), 250 mL dry THF and a stir bar. Then NaH (60 % dispersion in mineral oil) (0.17 g, 5.9 mmol, 1.2 equiv) was added to the solution at room temperature. The reaction mixture was heated to 80 °C for 8 h and was then cooled to 0 °C using an ice bath. Subsequently, the cold reaction mixture was added slowly at 0 °C to 400 mL of a sat. solution of NH_4Cl solution. Then 1 M aqueous HCl solution was added to acidify the mixture to pH = 6. The mixture was extracted 3 × 200 mL with CH_2Cl_2, the combined organic layers were washed with Sat. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient of EtOAc/hexane from 1:2 to 1:1 to remove byproducts, then acetone/CH_2Cl_2 from 1:2 to 1:1 to elute products) afforded compound **23** (1.5 g, 78%) as a light yellow solid.

23: R_f = 0.41 (CH_2Cl_2 / acetone = 2 : 1); mp 192 - 193 °C (CH_2Cl_2); IR (thin film): ν_{max} 3401, 3268, 2939, 1617, 1581, 1489, 1458, 1301, 1265, 1166, 1092, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 6.35 (s, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 162.9, 162.0, 143.5, 139.7, 132.2, 131.5, 130.8, 130.7, 123.7, 108.8, 93.7, 89.5, 56.3, 55.4, 38.1; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{18}H_{17}BrNO_4$ 390.0341, found 390.0333.



N-Methyl aglain ketone 24: The general procedure for (3+2) photocycloaddition using the continuous photoflow system was used. Compound **23** (800 mg, 2.05 mmol, 1 equiv), methyl cinnamate (4.99 g, 30.8 mmol, 15 equiv), 35 mL of α,α,α-trifluorotoluene, and 15 mL of 2,2,2-trifluoroethanol were used for the reaction. The reaction mixture was purified by silica gel column chromatography (gradient of EtOAc/hexane 1:10 to first remove methyl cinnamate, then EtOAc/hexane from 1:4 to 1:2 to elute the product). Additional impurities were also removed by recrystallization from diethyl ether. Compound **24** (484 mg, 43%) was obtained as a white solid.

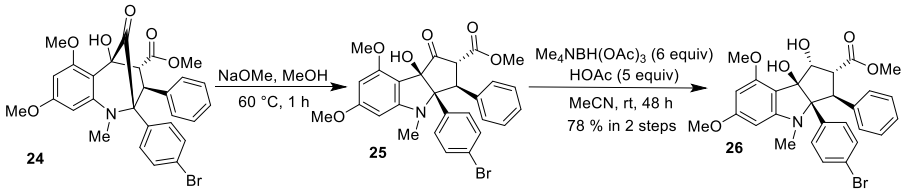
24: R_f = 0.29 (EtOAc / hexanes = 3 : 7); mp 172 - 173 °C (CH_2Cl_2); IR (thin film): ν_{max} 3510, 3032, 2951, 1736, 1609, 1457, 1291, 1209, 1071, 816, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 6.98 (m, 3H), 6.81 (m, 3H), 6.15 (d, J = 2.5 Hz, 1H), 6.12 (d, J = 2.5 Hz, 1H), 5.62 (s, 1H, OH), 4.33 (d, J = 9.5 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.56 (s, 3H), 3.36 (d, J = 9.5 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 170.7, 161.4, 158.0, 148.4, 139.5, 134.0, 131.4, 130.7, 129.5, 128.1, 126.8, 121.4, 111.8, 99.4, 93.7, 82.1, 71.2, 56.0, 55.3, 52.6, 52.0, 41.4; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{28}H_{27}BrNO_6$ 552.1022, found 552.1005.



***N*-Me-*aza*-aglain 24a**: A flame-dried test tube was charged with *aza*-aglain ketone **24** (40 mg, 0.072mmol, 1.0 equiv) and 2.5 mL of dry THF. Then $NaBH_4$ (13.7 mg, 0.36 mmol, 5.0 equiv) was added. The resulting mixture was stirred at room temperature for 12 h before 5 mL of a sat. NH_4Cl aqueous solution was added. The reaction mixture was extracted with 3 × 2 mL of CH_2Cl_2 and the combined organic layers were washed with sat. NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient of EtOAc/hexane from 1:5 to 1:2) afforded compound **24a** (38 mg, 95%) as a white solid.

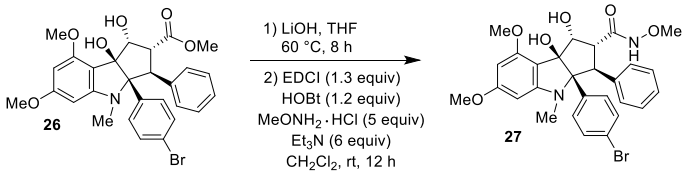
24a: R_f = 0.4 (EtOAc / hexanes = 1 : 1); mp 235-236 °C (CH_2Cl_2); IR (thin film): ν_{max} 3496, 2949, 1735, 1610, 1583, 1456, 1343, 1244, 1207, 1072, 1010, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.19 (d, J = 9 Hz, 2H), 7.12 (d, J = 9 Hz, 2H), 6.98 (m, 3H), 6.73 (m, 2H), 6.15 (d, J = 2.5 Hz, 1H), 6.02 (d, J = 2.5 Hz,

1H), 6.015 (s, 1H, OH), 4.67 (d, J = 5 Hz, 1H), 4.00 (d, J = 9.75 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.56 (s, 3H), 3.06 (d, J = 9.75 Hz, 1H), 2.72 (s, 3H), 2.61 (d, J = 5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 155.9, 154.6, 144.9, 136.8, 132.9, 127.2, 125.8, 123.3, 121.4, 116.3, 99.0, 91.3, 85.6, 75.9, 72.5, 70.2, 66.0, 58.9, 51.8, 50.9, 50.4, 46.9, 36.7; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{28}H_{29}BrNO_6$ 554.1178, found 554.1163.



***N*-Me-Br-*aza*-rocaglate 26**: General procedure to access *aza*-rocaglates from *aza*-aglain ketones was used to synthesize N-Me-Br-*aza*-rocaglate **26**. Compound **26** (157 mg, 78% from **24**) was purified by silica gel column chromatography (gradient of EtOAc/hexane from 1:5 to 1:2) and was obtained as a white solid.

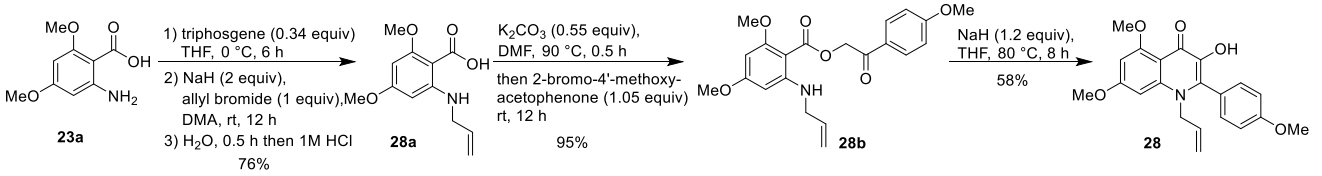
26: R_f =0.36 (EtOAc / hexanes = 1 : 1); mp 217 - 219 °C (CH_2Cl_2); IR (thin film): ν_{max} 3534, 2950, 1712, 1618, 1500, 1252, 1210, 1150, 1079, 736 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 13.5 Hz, 2H), 7.19 (m, 5H), 6.92 (d, J = 9 Hz, 2H), 5.94 (d, J = 2 Hz, 1H), 5.61 (d, J = 2 Hz, 1H), 4.78 (dd, J_1 = 7 Hz, J_2 = 9 Hz, 1H), 4.46 (d, J = 5 Hz, 1H), 3.92 (d, J = 9 Hz, 1H) 3.88 (s, 3H), 3.80 (s, 3H), 3.67 (s, 1H, OH), 3.63 (s, 3H), 3.33 (dd, J_1 = 5 Hz, J_2 = 7 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 163.7, 157.4, 152.9, 140.1, 134.5, 130.7, 130.3, 129.6, 128.2, 126.5, 121.4, 106.1, 91.5, 88.3, 87.0, 86.2, 81.2, 55.7, 55.4, 52.9, 52.7, 51.7, 30.0; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{28}H_{29}BrNO_6$ 554.1178, found 554.1188.



Hydroxamate 27: To a flame-dried test tube was added *N*-Me-Br-*aza*-rocaglate **26** (30.0 mg, 0.05 mmol, 1.0 equiv), LiOH (6.4 mg, 0.27 mmol, 5 equiv), and 2.5 mL of anhydrous THF. The mixture was heated to 65 °C for 12 h. Subsequently, after the reaction was cooled to room temperature, 1 M HCl (5 mL) was added to acidify the solution (pH = 6). After extraction with 3 × 2 mL CH_2Cl_2, the combined organic layers were washed with sat. NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting *aza*-rocaglaic acid was subjected to the next step without further purification. To a flame-dried test tube was added the acid and 2.5 mL of dry CH_2Cl_2, methoxyamine hydrochloride (22.6 mg, 0.27

mmol, 5 equiv), Et_3N (45 μL, 0.32 mmol, 6 equiv), HOBt (8.8 mg, 0.065 mmol, 1.2 equiv), and EDCI (13.5 mg, 0.07 mmol, 1.3 equiv). The resulting mixture was sonicated for 3 min to dissolve the methoxyamine hydrochloride before being stirred at room temperature for 12 h. 1 mL of 1M HCl and 5 mL of sat. NaCl were added to quench the reaction. After being extracted with 3 × 2 mL CH_2Cl_2, the combined organic layers were washed with sat. NaCl (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by preparative thin layer chromatography (EtOAc/ CH_2Cl_2 = 1 : 2 with 5% MeOH) afforded hydoxamate **27** (15.8 mg, 51% over 2 steps) as a white solid.

27: R_f = 0.27 (EtOAc / CH_2Cl_2 = 1 : 1); mp 238 - 239 °C (CH_2Cl_2); IR (thin film): ν_{max} 3372, 2933, 1615, 1500, 1254, 1149, 1076, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H, NH), 7.41 (d, J = 7.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.19 (m, 3H), 6.89 (d, J = 8.5 Hz, 2H), 5.91 (d, J = 1.5 Hz, 1H), 5.60 (d, J = 1.5 Hz, 1H), 4.97 (d, J = 7 Hz, 1H), 4.68 (d, J = 2.5 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.51 (s, 1H, OH), 3.44 (s, 3H), 3.15 (s, 1H, OH), 3.06 (dd, J_1 = 7 Hz, J_2 = 2.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 164.1, 156.5, 153.2, 141.3, 135.3, 130.5, 130.4, 129.7, 128.2, 126.4, 121.4, 105.3, 91.2, 87.6, 86.8, 85.3, 80.9, 64.1, 55.54, 55.49, 52.7, 51.0, 29.4; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{28}H_{30}BrN_2O_6$ 569.1278, found 569.1275.



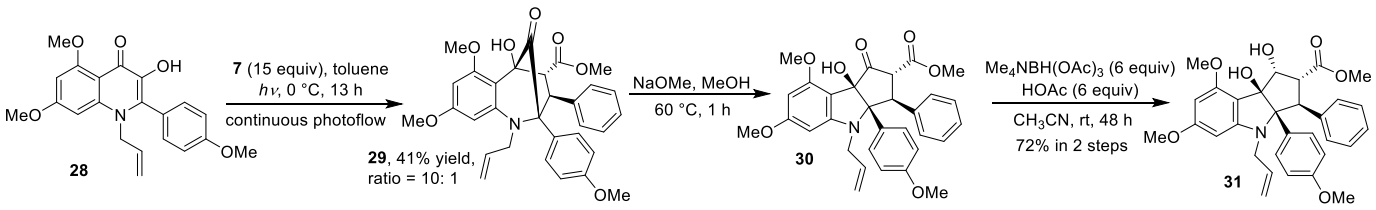
***N*-allyl-3-HQ 28**: Starting from dimethoxyanthranilic acid **23a** (5.5 g, 27.9 mmol, 1 equiv), the general procedure to access *N*-alkyl-3-HQ was utilized for the synthesis of compound **28**. After the crude product was obtained from the allylation protocol, purification by silica gel column chromatography (gradient of EtOAc/hexane from 1:6 to 1:4) afforded *N*-allyl-anthranilic acid **28a** (5.0 g, 76% from **23a**) as a pale yellow oil. *N*-allyl-anthranilate **28b** (7.76 g, 95% from **28a**) was isolated by silica gel column chromatography (gradient of EtOAc/hexane from 1:6 to 1:2) as a white solid. *N*-allyl-3-HQ **28** (1.32 g, 58%) was isolated by silica gel column chromatography (gradient of EtOAc/hexane from 1:2 to remove impurities then CH_2Cl_2 : acetone = 2 : 1 to elute product) as a pale yellow solid from **28b** (2.4 g, 12.5 mmol).

28a: R_f = 0.39 (EtOAc / hexanes = 3 : 7); IR (thin film): ν_{max} 3303, 2947, 2844, 1681, 1614, 1455, 1354, 1220, 1146, 923, 807 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.52 (s, 1H, OH), 9.08 (s, 1H, NH), 5.88 (ddt, J_1 = 17 Hz, J_2 = 10.5 Hz, J_3 = 5.5 Hz, 1H), 5.76 (s, 1H), 5.75 (s, 1H), 5.24 (d, J = 17 Hz, 1H), 5.14 (d, J = 10.5 Hz, 1H), 3.93 (s, 3H), 3.81 (t, J = 5.5 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6,

164.5, 161.3, 154.8, 134.2, 116.1, 92.6, 89.1, 87.0, 56.6, 55.2, 45.5; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{12}H_{15}NO_4$ 237.1001, found 237.997.

28b: R_f = 0.35 (EtOAc / hexanes = 1 : 2); mp 95-96 °C (CH_2Cl_2); IR (thin film): ν_{max} 3370, 2937, 1683, 1602, 1459, 1233, 1155, 1106, 1021, 806 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 9 Hz, 2H), 7.54 (t, J = 5 Hz, 1H, NH), 6.96 (d, J = 9 Hz, 2H), 5.95 (m, 1H), 5.81 (d, J = 2 Hz, 1H), 5.79 (d, J = 2 Hz, 1H), 5.48 (s, 2H), 5.30 (ddd, J_1 = 1.5 Hz, J_2 = 3 Hz, J_3 = 17 Hz, 1H), 5.17 (ddd, J_1 = 1.5 Hz, J_2 = 3 Hz, J_3 = 10.5 Hz, 1H), 3.87 (s, 3H), 3.86 (tdd, J_1 = 5 Hz, J_2 = J_3 = 1.5 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 167.1, 164.2, 164.0, 162.7, 152.4, 134.9, 130.3, 127.4, 116.0, 114.0, 96.5, 88.7, 87.6, 65.8, 56.0, 55.0, 46.0; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{21}H_{24}NO_6$ 386.1604, found 386.1595.

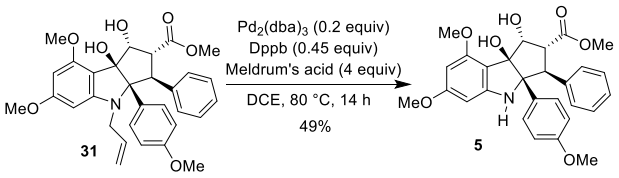
28: R_f = 0.33 (CH_2Cl_2 / acetone = 2 : 1); mp 159-161 °C (CH_2Cl_2); IR (thin film): ν_{max} 3268, 2936, 2839, 1579, 1508, 1239, 1205, 1165, 1033, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 6.37 (d, J = 2 Hz, 1H), 6.33 (d, J = 2 Hz, 1H), 5.82 (m, 1H), 5.26 (d, J = 10.5 Hz, 1H), 4.98 (d, J = 17 Hz, 1H), 4.54 (s, 2H), 3.99 (s, 3H), 3.85 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 162.5, 161.9, 160.3, 142.6, 139.9, 132.2, 132.0, 130.8, 123.8, 117.6, 114.2, 109.0, 93.7, 90.6, 56.3, 55.34, 55.29, 51.5; HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{21}H_{22}NO_5$ 368.1498, found 368.1491.



***N*-allyl-*aza*-rocaglate 31:** The general procedure for (3+2) photocycloaddition using the continuous Rayonet continuous photoflow system was used. Toluene was found to be an optimal solvent for the photoreaction, as the reaction could be completed in 13 h in toluene instead of 36 h in a solvent mixture (TFE / $PhCF_3$ = 3 : 7) used previously. 800 mg of *N*-allyl-3-HQ substrate and 5.3 g of methyl cinnamate was used. We also found that compound **29** could undergo the ketol rearrangement slowly itself, so purification by flash silica gel column chromatography (gradient of EtOAc / hexane 1:10 to first remove methyl cinnamate followed by elution with EtOAc / hexane 1 : 5 to 1 : 4) afforded crude compound **29** (475 mg, 41% combined with **30**) which was subjected to the next step directly. After concentration *in vacuo*, the yellow oil obtained was used for the next step without further purification. Finally, the general

procedure for the synthesis of *aza*-rocaglates from *aza*-aglain ketones was used and *N*-allyl-*aza*-rocaglate **31** (345 mg, 72% over 2 steps) was obtained as a white solid.

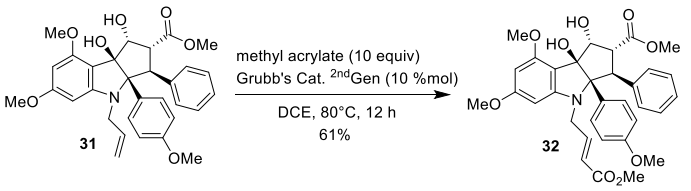
31: R_f = 0.33 (EtOAc / hexanes = 1 : 1); mp 86 - 88 °C (CH_2Cl_2); IR (thin film): ν_{max} 3525, 2951, 1744, 1610, 1512, 1463, 1249, 1151, 1039, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 2H), 7.12 (m, 1H), 6.95 (d, J = 9 Hz, 2H), 6.61 (d, J = 9 Hz, 2H), 5.90 (d, J = 1.75 Hz, 1H), 5.72 (d, J = 1.75, 1H), 5.64 (m, 1H), 5.31 (dd, J_1 = 17.25 Hz, J_2 = 1.25 Hz, 1H), 5.15 (dd, J_1 = 10.25 Hz, J_2 = 1.25 Hz, 1H), 4.77 (m, 1H), 4.60 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.76 (m, 2H), 3.69 (dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 3.23 (d, J = 4 Hz, 1H, OH), 2.98 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 163.5, 158.5, 157.5, 153.1, 139.8, 134.4, 130.5, 129.4, 128.03, 127.98, 126.4, 116.8, 112.6, 104.6, 92.5, 87.7, 87.1, 87.0, 80.2, 55.5, 55.3, 55.0, 54.6, 53.0, 51.8, 48.8. HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{31}H_{34}NO_7$ 532.2342, found 532.2347.



***N*-H-*aza*-rocaglate 5:** In a flame-dried test tube, *N*-allyl-*aza*-rocaglate **31** (20 mg, 0.038 mmol, 1 equiv) and Meldrum's acid (21.7 mg, 0.15 mmol, 4 equiv) was dissolved in DCE (1 mL). To another flame-dried test tube was added $Pd_2(dba)_3$ (6.89 mg, 7.52 μmol, 0.2 equiv) and 1,4- *bis*(diphenyl-phosphino)butane (dppb, 7.22 mg, 0.017 mmol, 0.45 equiv) in DCE (2 mL). The test tube was then evacuated and backfilled with argon for three times and stirred for 0.5 h at room temperature. The two solutions were combined into one test tube by cannulation then sparged with argon for 10 min with sonication. The reaction was heated to 80 °C. After 14 h, the reaction was cooled to room temperature and quenched with saturated Na_2CO_3 aqueous solution (3 mL). Then 5 × 2 mL CH_2Cl_2 was used for extraction, and the combined organic layer was washed with sat. NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (gradient of EtOAc / hexane from 1 : 4 to 1 : 1 to elute the product) afforded *N*-H-*aza*-rocaglate **5** (9.1 mg, 49%) as a colorless oil.

5: R_f = 0.27 (EtOAc / hexanes = 1 : 1); IR (thin film): ν_{max} 3466, 2927, 2849, 1743, 1614, 1515, 1456, 1218, 1202, 1151, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (m, 3H), 6.96 (d, J = 18.5 Hz, 2H), 6.71 (d, J = 18.5 Hz, 2H), 6.69 (m, 2H), 6.09 (d, J = 1.5 Hz, 1H), 6.01 (d, J = 1.5 Hz, 1H), 5.11 (d, J = 7.5 Hz, 1H), 4.72 (bs, 1H, OH), 4.16 (bs, 1H, OH), 4.01 (d, J = 14 Hz, 1H), 3.88 (s, 3H), 3.85 (dd, J_1 = 14 Hz, J_2 = 7.5 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 163.8, 158.4, 157.2, 150.9, 137.4, 129.7, 128.1, 127.89, 127.87, 126.8, 112.8, 108.5, 94.4, 90.9, 89.6,

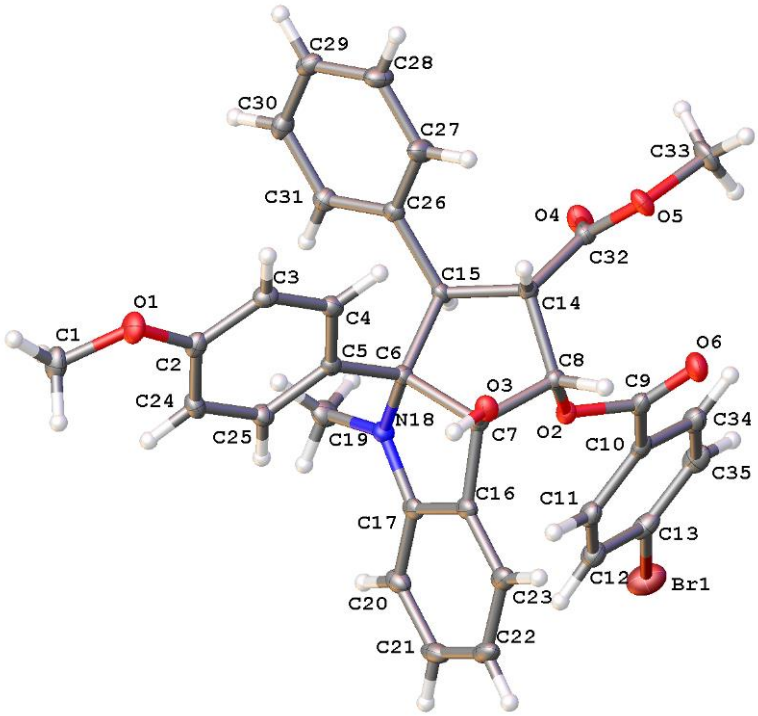
80.9, 80.7, 56.4, 55.6, 55.5, 55.2, 51.7, 51.3. HRMS-ESI (m/z): $[M+H]^+$ calculated for $C_{28}H_{29}NO_7$ 492.2022, found 492.2029.



***Aza*-rocaglate 32:** To a flame-dried test tube was added *N*-allyl-*aza*-rocaglate **31** (35 mg, 0.066 mmol, 1 equiv) and methyl acrylate (60 μL, 0.66 mmol, 10 equiv) in dry DCE (2 mL). The test tube was then evacuated and backfilled with argon three times. Then, in a glove box, 2nd Generation Grubb's Catalyst (5.6 mg, 6.6 μmol, 0.1 equiv) was added to another flame-dried test tube and the former reaction solution was cannulated into the test tube. An additional 1 mL of dry DCE was used to wash the residue and the solutions were combined together by cannulation. The reaction mixture was heated to 80 °C in the dark for 12 h before being cooled to room temperature. Subsequently, 5 mL of brine was added to quench the reaction. After extraction with 3 × 2 mL of CH_2Cl_2, the combined organic layers were washed with sat. NaCl solution (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc / hexanes 3 : 2) afforded compound **32** (23.6 mg, 61%) as a colorless oil.

32: R_f = 0.25 (EtOAc / hexanes = 1 : 1); IR (thin film): ν_{max} 3525, 2951, 1718, 1610, 1513, 1462,1351, 1251, 1152, 1040 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 7.5 Hz, 2H), 7.20 (t, J = 7.5 Hz, 2H), 7.14 (m, 1H), 6.94 (d, J = 9 Hz, 2H), 6.69 (m, 1H), 6.60 (d, J = 9 Hz, 2H), 4.80 (dd, $J_1 = J_2$ = 7 Hz, 1H), 4.51 (d, J = 7 Hz, 1H), 3.865 (s, 3H), 3.864 (m, 1H), 3.78 (s, 3H), 3.73 (m, 1H), 3.672 (s, 3H), 3.665 (s, 3H), 3.65 (s, 3H), 3.57 (d, J = 7 Hz, 1H, OH), 3.55 (dd, $J_1 = J_2$ = 7 Hz, 1H), 3.25 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 166.4, 163.5, 158.7, 157.6, 152.3, 144.3, 139.9, 130.4, 129.4, 128.2, 128.0, 126.5, 121.7, 112.8, 105.5, 91.9, 88.3, 87.3, 86.9, 80.5, 55.6, 55.4, 54.9, 54.3, 52.8, 51.9, 51.4, 46.8. HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{33}H_{35}NO_9Na$ 612.2210, found 612.2214.

III. X-RAY CRYSTALLOGRAPHIC DATA FOR COMPOUND 21



Crystals of compound **21** suitable for X-ray analysis were obtained by slow evaporation from hexanes/CH_2Cl_2. Crystallographic data have been deposited with the Cambridge Cystallograhic Data Centre (CCDC# 1457719). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Computing details

Data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT* (Bruker, 2006); program(s) used to solve structure: SHELXT (Sheldrick, 2015); program(s) used to refine structure: *SHELXL2014*/7 (Sheldrick, 2014); molecular graphics: Olex2 (Dolomanov *et al.*, 2009); software used to prepare material for publication: Olex2 (Dolomanov *et al.*, 2009).[S5-S11]

Crystal data

$C_{34}H_{30}BrNO_6$	$Z = 2$
$M_r = 628.50$	$F(000) = 648$
Triclinic, $P\bar{1}$	$D_x = 1.484$ Mg m^{-3}
$a = 9.979$ (4) Å	Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å
$b = 11.195$ (4) Å	Cell parameters from 9870 reflections
$c = 13.087$ (5) Å	$\theta = 4.1–74.4°$
$\alpha = 77.795$ (15)°	$\mu = 2.40$ mm^{-1}
$\beta = 81.273$ (19)°	$T = 100$ K
$\gamma = 83.202$ (16)°	Block, colorless
$V = 1406.8$ (10) Å^3	0.2 × 0.1 × 0.08 mm

[S5] G. M. Sheldrick, *et al. J. Appl. Cryst.* **2015** *48*, 3-10. [S6] G. M. Sheldrick, *Acta Cryst.* **2008** *A64*, 112-122. [S7] G. M. Sheldrick, *Acta Cryst.* **2015** *C71*, 3-8. [S8] Bruker (2006). *SAINT*. Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA. [S9] Bruker (2006). *APEX2*. Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA. [S10] Bruker (2006). *SADABS*. Bruker Analytical X-ray Instruments Inc., Madison, Wisconsin, USA. [S11] O. V. Dolmanov, *et al. J. Appl. Cryst.* **2009** *42*, 339-341.

Data collection

Bruker D8 Quest diffractometer	5750 independent reflections
Radiation source: Microfocus sealed tube	5262 reflections with $I > 2\sigma(I)$
Bruker MX	$R_{int} = 0.032$
ω and phi scans	$\theta_{max} = 74.8°$, $\theta_{min} = 3.5°$
Absorption correction: multi-scan *SADABS* (Bruker, 2006)	$h = -12 \rightarrow 12$
$T_{min} = 0.658$, $T_{max} = 0.754$	$k = -13 \rightarrow 13$
41363 measured reflections	$l = -16 \rightarrow 16$

Refinement

Refinement on F^2	0 restraints
Least-squares matrix: full	Hydrogen site location: mixed

$R[F^2 > 2\sigma(F^2)] = 0.031$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.074$	$w = 1/[\sigma^2(F_o^2) + (0.0298P)^2 + 1.3237P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.04$	$(\Delta/\sigma)_{max} = 0.001$
5750 reflections	$\Delta\rangle_{max} = 0.62$ e Å^{-3}
373 parameters	$\Delta\rangle_{min} = -0.65$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. CheckCIF Alert and Discussion:

Alert level B PLAT420_ALERT_2_B D—H Without Acceptor O3 – H3. Please Check Discussion: While H3 does not have a strong H-bond acceptor due to packing constraints, there is a close OH-pi inter-action with C22 with the H3 – C22 distance at 2.590 Angstroms.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.54030 (2)	0.85482 (2)	0.98152 (2)	0.03175 (7)
O1	1.48134 (12)	-0.08455 (11)	0.63504 (10)	0.0216 (3)
O2	0.72363 (11)	0.33194 (10)	0.79972 (9)	0.0146 (2)
O3	0.88737 (12)	0.03125 (10)	0.80277 (9)	0.0161 (2)
H3	0.946 (2)	-0.005 (2)	0.8285 (18)	0.024*
O4	0.68413 (12)	0.42167 (11)	0.55496 (10)	0.0219 (3)
O5	0.59996 (12)	0.24241 (10)	0.56141 (9)	0.0181 (2)
O6	0.50480 (12)	0.34615 (12)	0.76999 (10)	0.0226 (3)
C1	1.60845 (17)	-0.06256 (16)	0.66123 (15)	0.0234 (4)
H1A	1.6822	-0.1112	0.6258	0.035*
H1B	1.6086	-0.0862	0.7377	0.035*
H1C	1.6221	0.0248	0.6382	0.035*
C2	1.37016 (16)	-0.00940 (15)	0.66373 (13)	0.0162 (3)
C3	1.25421 (17)	-0.01664 (15)	0.61884 (13)	0.0168 (3)

H3A	1.2559	-0.0730	0.5736	0.020*
C4	1.13694 (17)	0.05761 (15)	0.63969 (12)	0.0154 (3)
H4	1.0585	0.0512	0.6089	0.018*
C5	1.13142 (16)	0.14238 (14)	0.70552 (12)	0.0136 (3)
C6	1.00307 (16)	0.22660 (14)	0.72642 (12)	0.0125 (3)
C7	0.88783 (16)	0.15613 (14)	0.80678 (12)	0.0135 (3)
C8	0.75351 (16)	0.21607 (14)	0.76594 (12)	0.0134 (3)
H8	0.6775	0.1620	0.7913	0.016*
C9	0.59516 (16)	0.38517 (15)	0.80092 (12)	0.0163 (3)
C10	0.58266 (16)	0.49863 (15)	0.84552 (12)	0.0164 (3)
C11	0.66764 (17)	0.51086 (16)	0.91717 (13)	0.0184 (3)
H11	0.7358	0.4470	0.9373	0.022*
C12	0.65263 (18)	0.61627 (16)	0.95913 (14)	0.0203 (3)
H12	0.7083	0.6243	1.0096	0.024*
C13	0.55536 (18)	0.70941 (16)	0.92630 (14)	0.0212 (3)
C14	0.79292 (16)	0.23437 (14)	0.64626 (12)	0.0131 (3)
H14	0.8080	0.1519	0.6264	0.016*
C15	0.93037 (15)	0.29001 (14)	0.62642 (12)	0.0126 (3)
H15	0.9088	0.3782	0.6317	0.015*
C16	0.90733 (16)	0.18310 (15)	0.91093 (13)	0.0156 (3)
C17	0.98491 (16)	0.28404 (15)	0.89096 (13)	0.0155 (3)
N18	1.02820 (14)	0.31863 (12)	0.78541 (10)	0.0145 (3)
C19	1.11368 (18)	0.41758 (16)	0.74101 (14)	0.0203 (3)
H19A	1.1917	0.3882	0.6948	0.031*
H19B	1.1462	0.4459	0.7980	0.031*
H19C	1.0610	0.4856	0.7001	0.031*
C20	1.00652 (17)	0.33636 (16)	0.97423 (13)	0.0197 (3)
H20	1.0559	0.4067	0.9620	0.024*
C21	0.95320 (18)	0.28207 (18)	1.07615 (14)	0.0236 (4)
H21	0.9673	0.3164	1.1337	0.028*
C22	0.88037 (18)	0.17978 (18)	1.09600 (13)	0.0234 (4)
H22	0.8474	0.1436	1.1664	0.028*
C23	0.85548 (17)	0.12981 (16)	1.01162 (13)	0.0194 (3)
H23	0.8040	0.0608	1.0237	0.023*
C24	1.36557 (17)	0.06954 (15)	0.73282 (13)	0.0177 (3)
H24	1.4429	0.0730	0.7661	0.021*
C25	1.24611 (17)	0.14407 (15)	0.75315 (13)	0.0157 (3)
H25	1.2433	0.1976	0.8011	0.019*
C26	1.00617 (10)	0.29006 (10)	0.51484 (6)	0.0137 (3)
C27	0.96738 (10)	0.22014 (10)	0.45010 (8)	0.0210 (3)

H27	0.8951	0.1691	0.4754	0.025*
C28	1.03440 (11)	0.22496 (10)	0.34832 (7)	0.0215 (4)
H28	1.0079	0.1772	0.3041	0.026*
C29	1.14019 (11)	0.29971 (10)	0.31129 (6)	0.0185 (3)
H29	1.1860	0.3030	0.2417	0.022*
C30	1.17898 (9)	0.36963 (9)	0.37603 (8)	0.0186 (3)
H30	1.2513	0.4207	0.3507	0.022*
C31	1.11197 (10)	0.36481 (9)	0.47781 (7)	0.0160 (3)
H31	1.1385	0.4126	0.5221	0.019*
C32	0.68787 (16)	0.31204 (15)	0.58250 (12)	0.0143 (3)
C33	0.48553 (18)	0.30850 (17)	0.51147 (15)	0.0238 (4)
H33A	0.5189	0.3585	0.4435	0.036*
H33B	0.4339	0.3618	0.5570	0.036*
H33C	0.4264	0.2498	0.5002	0.036*
C34	0.48351 (17)	0.59226 (16)	0.81540 (13)	0.0205 (3)
H34	0.4246	0.5829	0.7676	0.025*
C35	0.47017 (19)	0.69944 (16)	0.85492 (14)	0.0229 (4)
H35	0.4040	0.7645	0.8334	0.028*

IV. BIOLOGICAL STUDIES

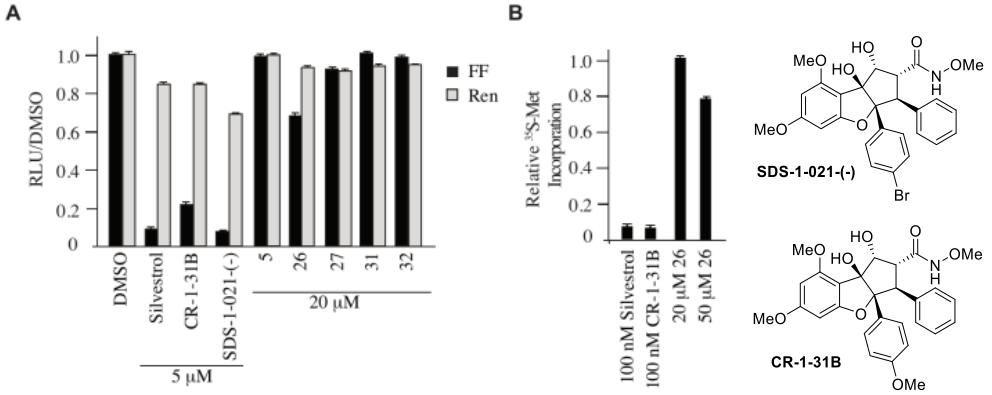


Figure SI-3. a. Effect of *aza*-rocaglates on *in vitro* translation of FF/HCV/Ren. Effect of *aza*-rocaglates on *in vitro* translation of FF/HCV/Ren. Rabbit reticulocyte lysate (RRL) from Promega was programmed with 4 ng/μL of *in vitro* transcribed FF/HCV/Ren mRNA and translations performed according to the manufacturer's instructions. *In vitro* translations were performed in the presence of vehicle (0.5% DMSO) or the indicated concentrations of compound. Firefly (FF) and Renilla (Ren) luciferase activities were measured on a Berthold Lumat LB9507 Luminometer and values normalized against vehicle control, which was set at 1. Results are the average of duplicates with the error of the mean shown. **b.** Assessing translation inhibition activity of **26** on HeLa cells. Cells were treated with the indicated concentrations of compounds for 1 hr, during which time ^{35}S-methionine was present for the last 15 minutes. Protein synthesis was assessed by quantitating the amount of ^{35}S-methionine incorporated in trichloroacetic acid insoluble material. Radioactivity was quantitated by scintillation counting and normalized to total protein levels. Results are the average of duplicates with the error of the mean shown.

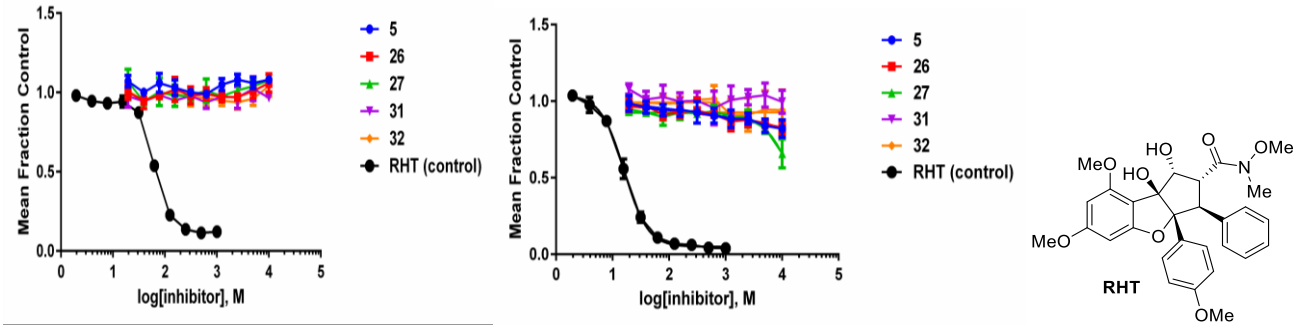


Figure SI-4. Concentration-dependent activity of *aza*-rocaglates in whole cells.

A. Constitutive reporter: Inhibition of translation. Cells expressing firefly luciferase, a labile reporter protein were cultured in 384-well format in compounds as indciated for 24 hours followed by measurement of reporter activity in a microplate luminometer.
B. Cytotoxicity: Inhibition of cell proliferation and survival. After addition of the indicated compounds in 384-well format, cells were cultured for 3 days. Relative viable cell number was determined by reduction of the dye resazurin (Alamar Blue®) using a microplate fluorometer (Tecan). All data are plotted as the mean ratio of treated to control with each determination performed in quadruplicate. Error bars: SD

Methods: Reporter Assay Luciferase reporter cell line was generated by infecting 293T cells (American Type Culture Collection) with a lentiviral vector expressing firefly luciferase from a strong constitutive CMV promoter ("constitutive reporter").To evaluate concentration-dependent inhibition of reporter activity, cells were seeded in white 384-well plates (20,000 cells/40 µl/well). The following day, serial compound dilutions were added to quadruplicate wells and plates incubated at 37 ℃ for 24 hr. Measurement of relative luciferase activity was achieved using Steady-Glo luciferase assay reagent (Promega) per manufacturer's recommendations and an Envision plate luminometer (Perkin-Elmer).

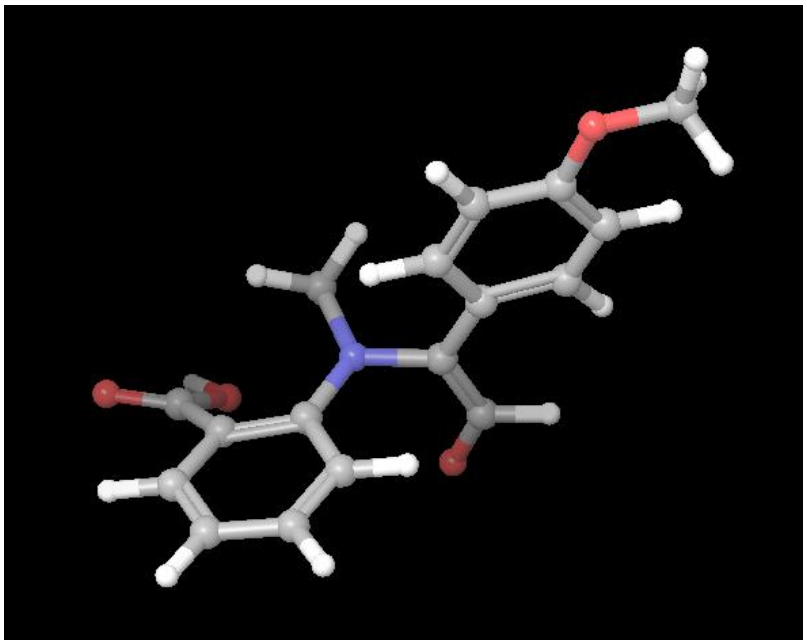
Cytotoxicity Assay Human 293T cancer cells were grown under 5% CO_2 in DMEM supplemented with 10% FBS. Surveillance testing for *Mycoplasma* contamination was performed on a monthly basis and was consistently negative. Compounds were formulated in DMSO and maintained at –80°C in the dark prior to testing. Cells were seeded into 384-well plates (1,000 cells/40 µl/well) and allowed to adhere overnight. Serial dilutions of compounds or DMSO vehicle control (not exceeding 0.1%) were added robotically to quadruplicate wells and plates incubated for an additional 3 days prior to assay of relative viable cell number by reduction of the dye resazurin (Alamar Blue®).

V. COMPUTATIONAL MODEL FOR 14B

Computational Details

The structure of the proposed intermediate **14B** was fully optimized by using Density Functional Theory (DFT) using Schrodinger 2015-3[S12] with the B3LYP functional. All calculations were carried out with the 6-31G**++ basis set[S13] for all atoms. Structures were evaluated by optimized energy values at the same level of theory.

1. Ground State DFT Model (E_{rel} = 0.0 kcal/mol)



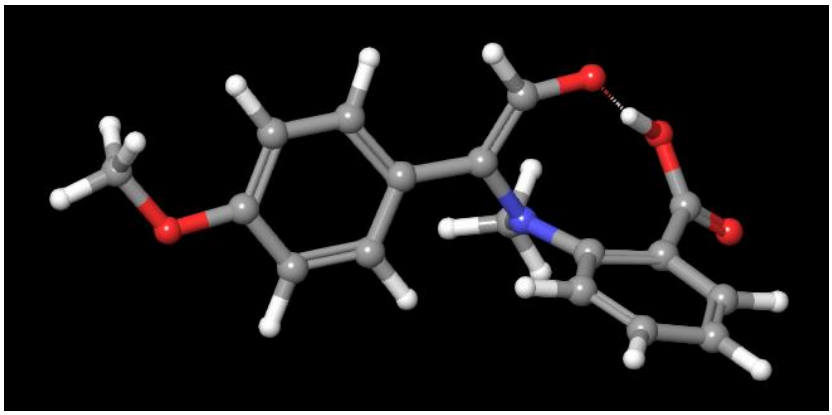
Cartesian coordinates:

C1 0.4178660000000 -1.4739760000000 0.8022600000000
C2 -0.1838240000000 -1.0842160000000 -0.4338880000000
C3 -1.5237290000000 -1.5543660000000 -0.6636720000000
C4 -2.2368150000000 -2.1698110000000 0.3938400000000
C5 -1.6520930000000 -2.4535910000000 1.6142200000000
C6 -0.2922160000000 -2.1249530000000 1.7893990000000
C7 -2.2272820000000 -1.6291210000000 -1.9568470000000
O8 -1.4158090000000 -1.8158290000000 -3.0340600000000
O9 -3.4478550000000 -1.6368180000000 -2.1060470000000
N10 0.5103380000000 -0.2300090000000 -1.2505390000000
C11 1.9403760000000 -0.0622950000000 -1.1318820000000
C12 2.7690550000000 -1.1082000000000 -1.5824240000000
H13 3.8554640000000 -0.9240110000000 -1.4180070000000
C14 -0.1203610000000 0.5599940000000 -2.2979860000000
C15 2.4210870000000 1.1842840000000 -0.5591580000000

[S12] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 1372; [S13] R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724.

C16 3.7522480000000 1.6561760000000 -0.7070480000000
C17 4.2005480000000 2.8452700000000 -0.1265030000000
C18 3.3221460000000 3.6465090000000 0.6116810000000
C19 1.9945070000000 3.2314660000000 0.7538110000000
C20 1.5591100000000 2.0369720000000 0.1874820000000
O21 3.6630670000000 4.8523430000000 1.2172230000000
C22 4.9990490000000 5.2881420000000 1.0947660000000
H23 1.4542270000000 -1.2011320000000 0.9585410000000
H24 -3.2605560000000 -2.4662880000000 0.1884030000000
H25 -2.2151610000000 -2.9514150000000 2.3981430000000
H26 0.2108210000000 -2.3711680000000 2.7220880000000
H27 -2.0136300000000 -1.8929450000000 -3.7953930000000
O28 2.4292380000000 -2.2034660000000 -2.0941740000000
H29 0.3652120000000 1.5405200000000 -2.3188930000000
H30 -0.0191450000000 0.0914370000000 -3.2823620000000
H31 -1.1849350000000 0.7097830000000 -2.0868210000000
H32 4.4570640000000 1.0858130000000 -1.3024340000000
H33 5.2338370000000 3.1401160000000 -0.2801660000000
H34 1.3092620000000 3.8541260000000 1.3233760000000
H35 0.5271280000000 1.7340270000000 0.3366080000000
H36 5.0648150000000 6.2324400000000 1.6415590000000
H37 5.7065200000000 4.5683110000000 1.5329770000000
H38 5.2800000000000 5.4608530000000 0.0449980000000

2. Hydrogen-bond Enolate DFT Model (E_{rel} = 17.3 kcal/mol)

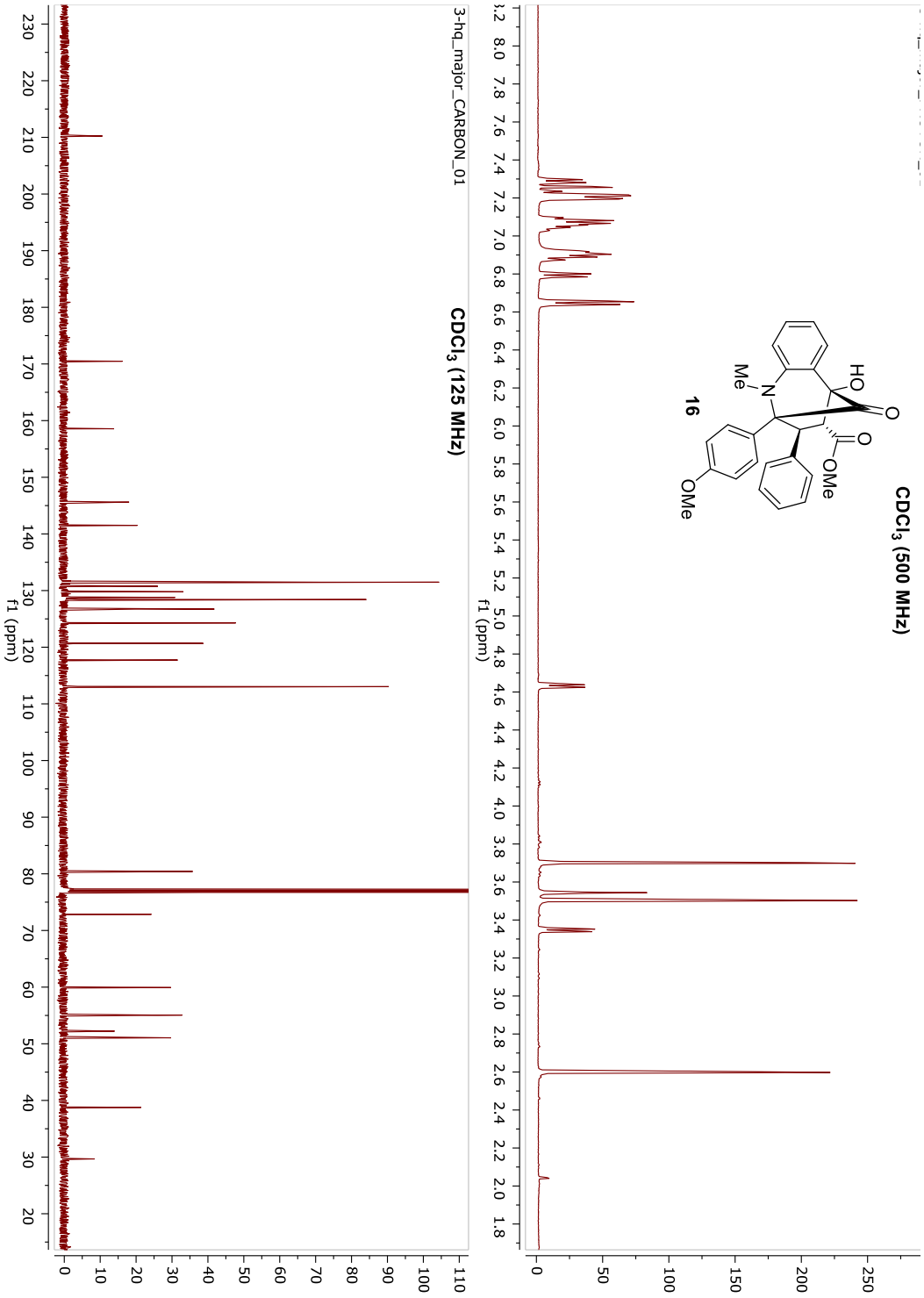


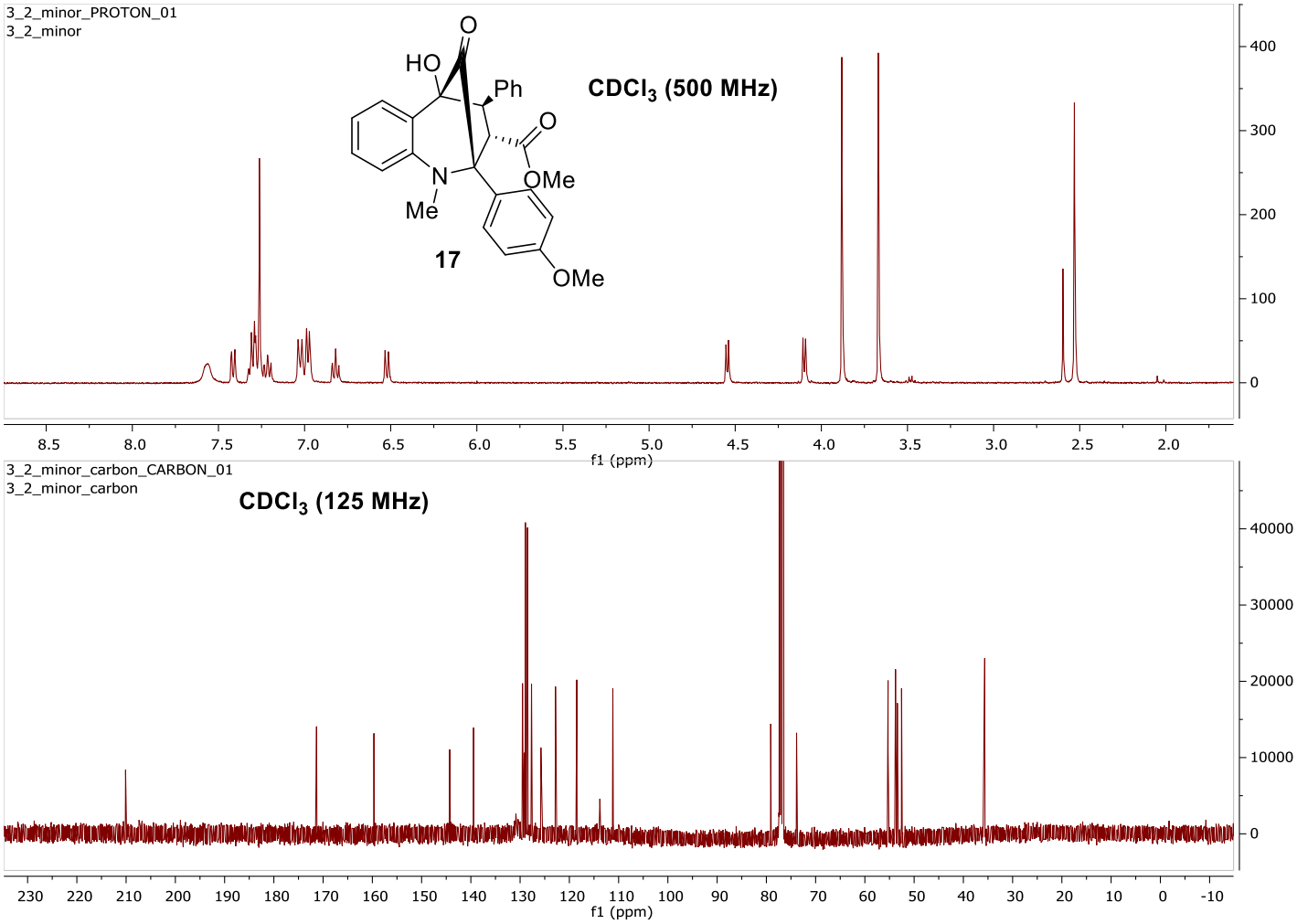
Cartesian coordinates:

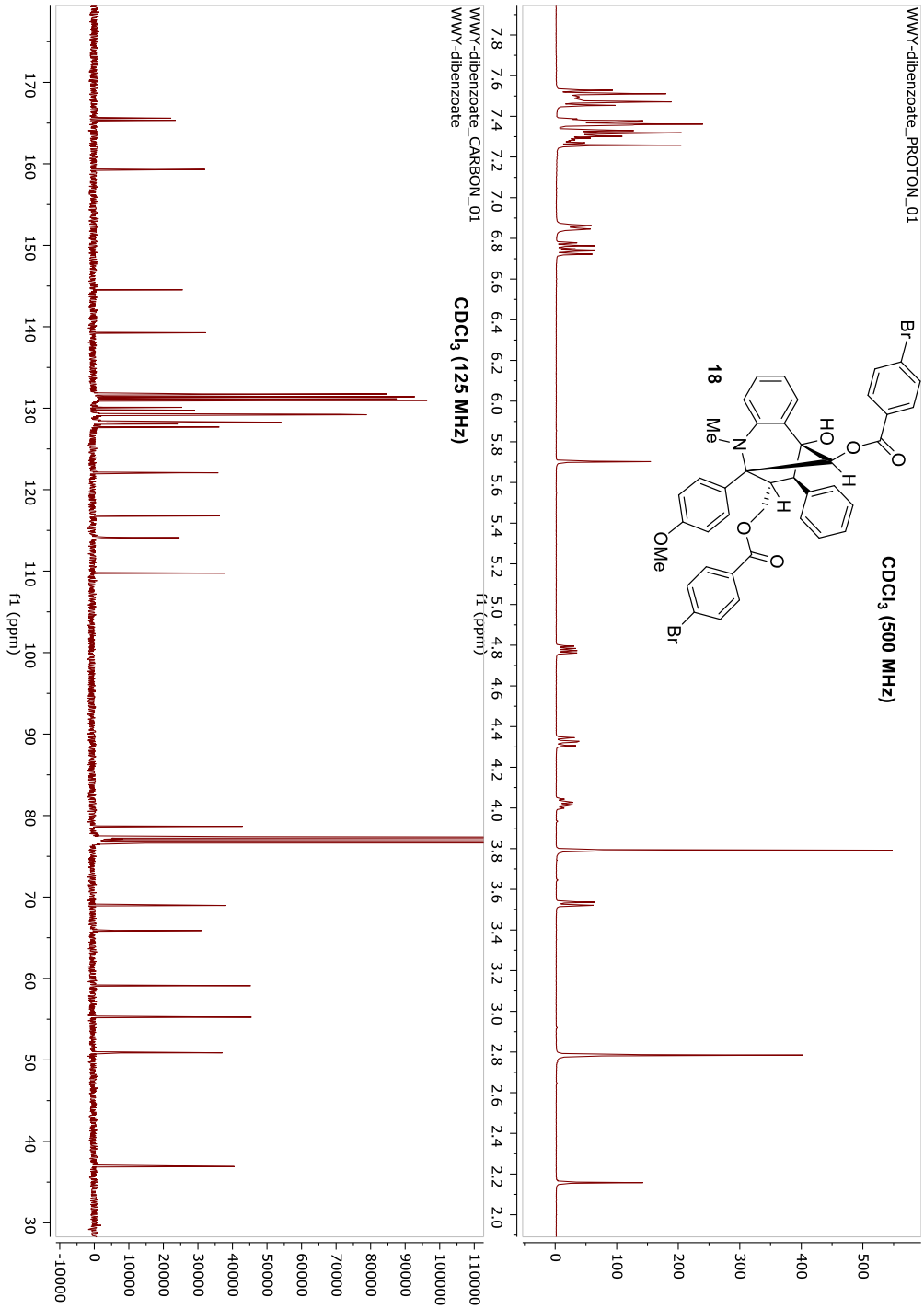
C1	-0.0886100000000	-1.0903500000000	1.1104230000000
C2	-0.4412620000000	-0.9329180000000	-0.2476170000000
C3	-1.4085930000000	-1.8128730000000	-0.7879240000000
C4	-2.0824940000000	-2.7046980000000	0.0620300000000
C5	-1.7508030000000	-2.8225330000000	1.4049730000000
C6	-0.7215740000000	-2.0222080000000	1.9185090000000
C7	-1.6970680000000	-1.9658640000000	-2.2623730000000
O8	-0.6571870000000	-1.9305340000000	-3.0789750000000
O9	-2.8335950000000	-2.1804710000000	-2.6672280000000
N10	0.1527080000000	0.1178320000000	-0.9655070000000

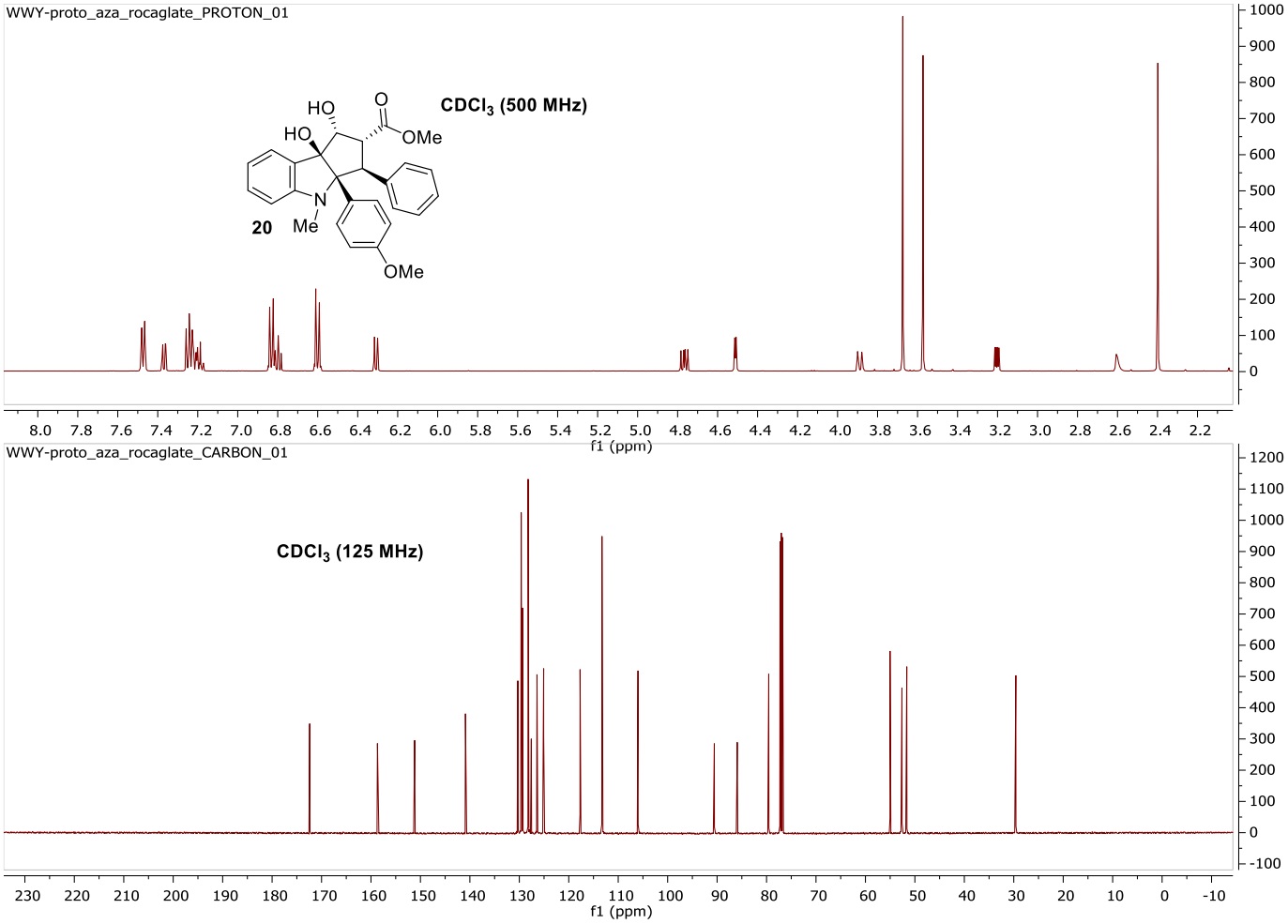
C11	1.5881410000000	0.1648820000000	-1.0384010000000
C12	2.2253270000000	-0.9196220000000	-1.6265470000000
H13	3.3299680000000	-0.9229860000000	-1.5794790000000
C14	-0.5818250000000	0.8442270000000	-1.9941640000000
C15	2.2700330000000	1.3376330000000	-0.5033160000000
C16	3.6135040000000	1.6652680000000	-0.7986770000000
C17	4.2475060000000	2.7859560000000	-0.2618820000000
C18	3.5460590000000	3.6562530000000	0.5771110000000
C19	2.2073890000000	3.3775660000000	0.8681120000000
C20	1.5901880000000	2.2498440000000	0.3432560000000
O21	4.0710730000000	4.8050870000000	1.1488850000000
C22	5.4006450000000	5.1363910000000	0.8239250000000
H23	0.6778790000000	-0.4382240000000	1.5166120000000
H24	-2.8482360000000	-3.3335820000000	-0.3824350000000
H25	-2.2689130000000	-3.5351910000000	2.0416330000000
H26	-0.4331290000000	-2.1067510000000	2.9643190000000
H27	0.2855150000000	-1.8951500000000	-2.6088880000000
O28	1.6823520000000	-1.9393300000000	-2.1759250000000
H29	-0.2622830000000	1.8934930000000	-1.9709480000000
H30	-0.4223890000000	0.4511780000000	-3.0051670000000
H31	-1.6550750000000	0.8093530000000	-1.7787830000000
H32	4.1778750000000	1.0380300000000	-1.4808970000000
H33	5.2819170000000	2.9788680000000	-0.5274360000000
H34	1.6628680000000	4.0601520000000	1.5151910000000
H35	0.5521100000000	2.0448310000000	0.5857590000000
H36	5.6260790000000	6.0686450000000	1.3489620000000
H37	6.1135680000000	4.3641890000000	1.1498630000000
H38	5.5363300000000	5.2942670000000	-0.2565030000000

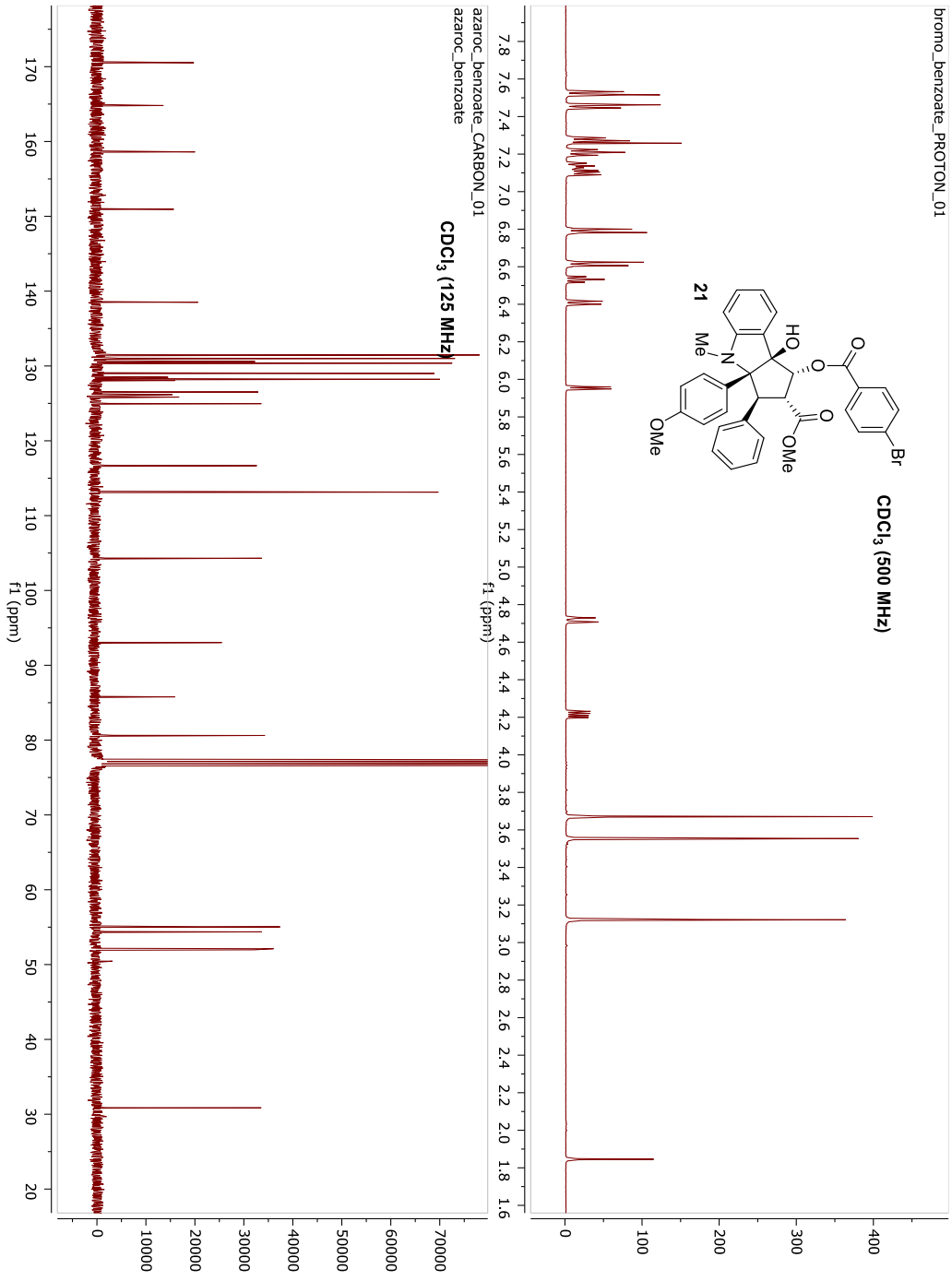
VI. SELECT NMR SPECTRA

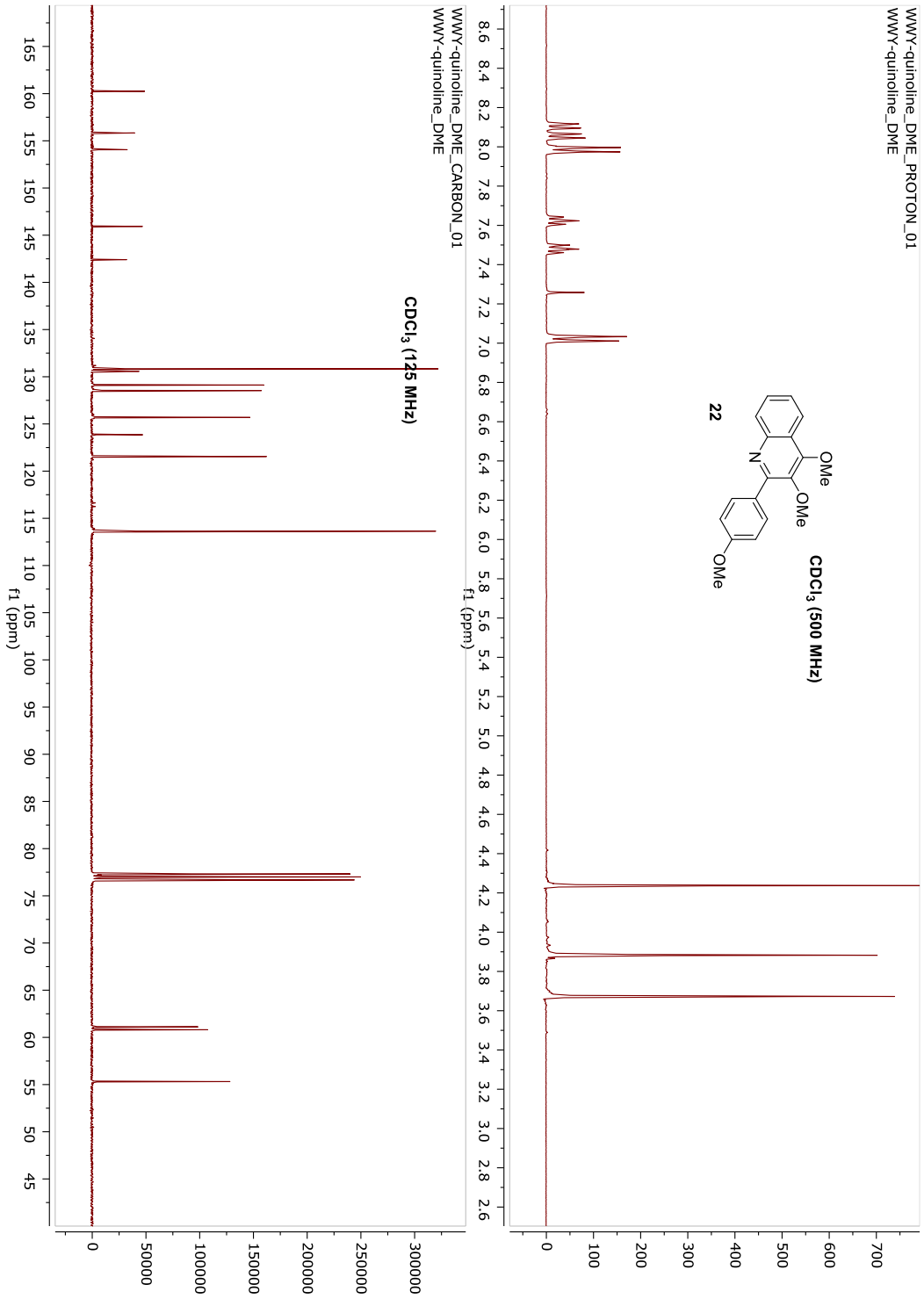


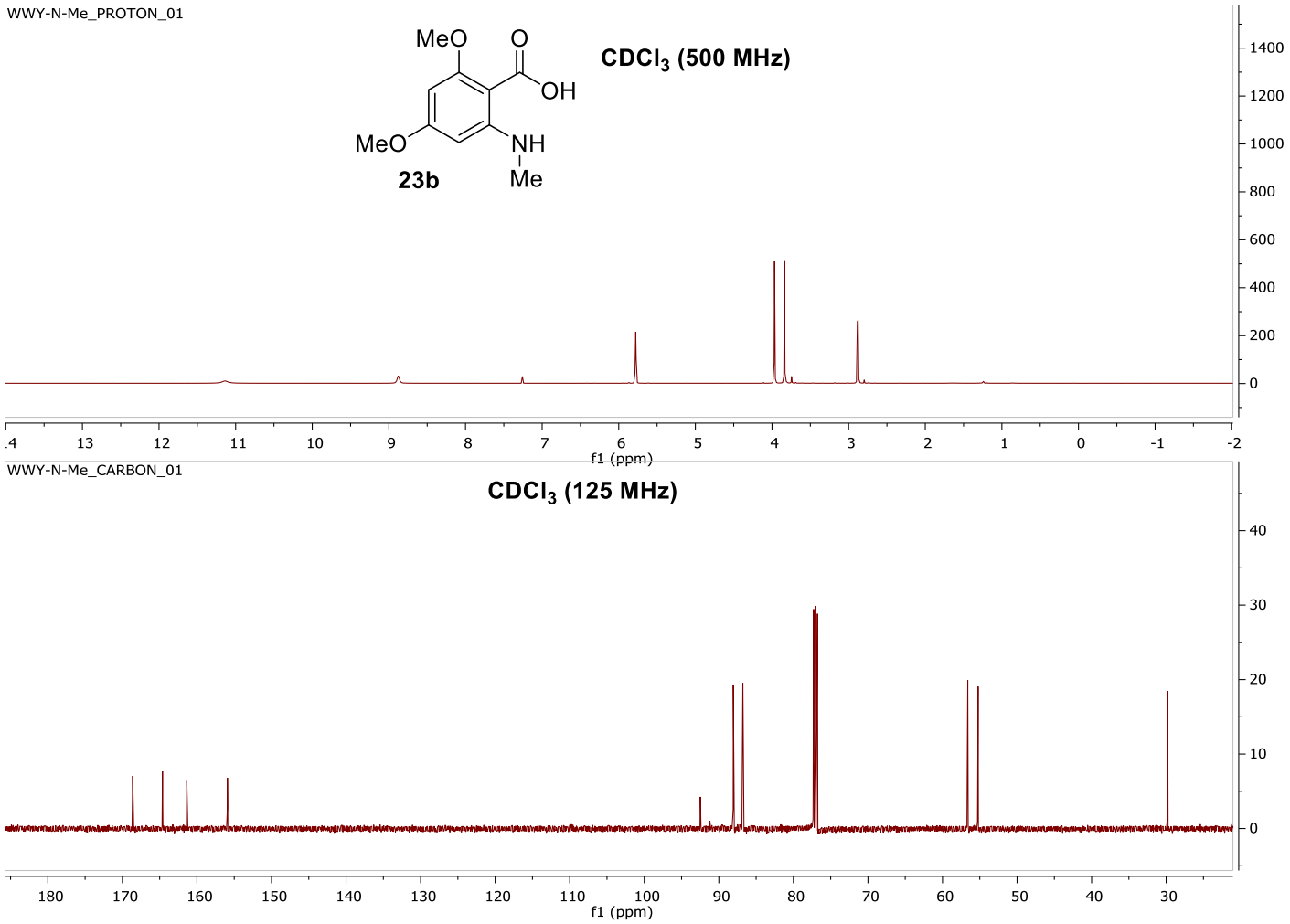

3_2_minor_PROTON_01
3_2_minor
CDCl3 (500 MHz)
17
f1 (ppm)
3_2_minor_carbon_CARBON_01
3_2_minor_carbon
CDCl3 (125 MHz)
f1 (ppm)

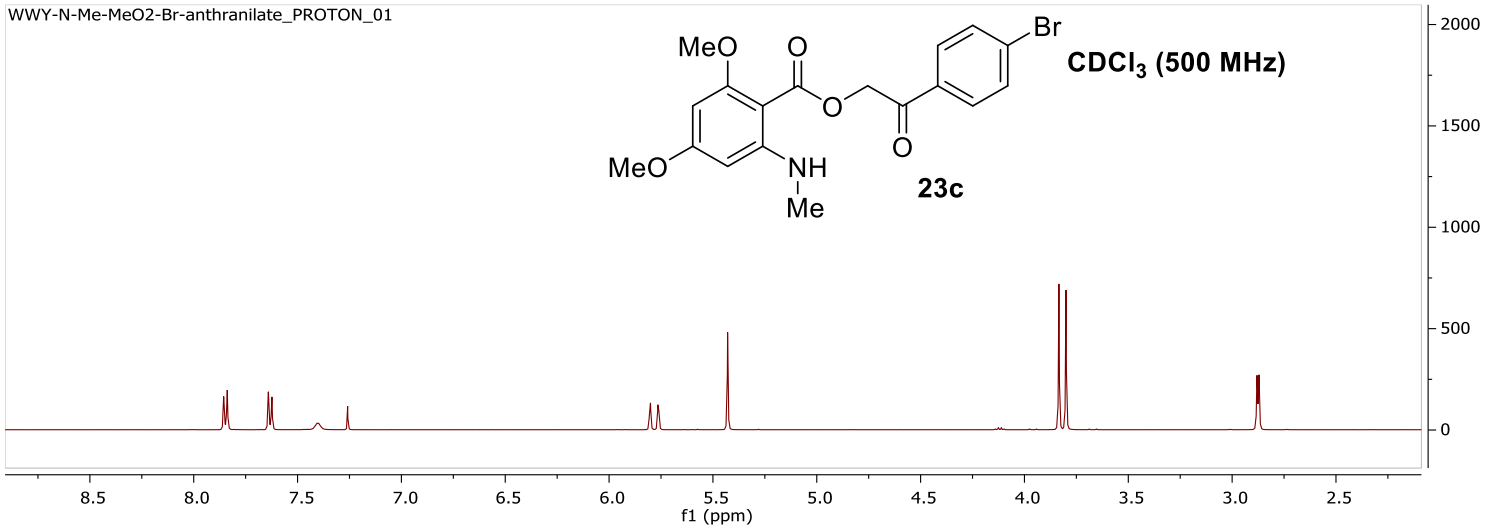

WWY-dibenzoate_PROTON_01
CDCl3 (500 MHz)
18
Br
HO
O
H
Me
N
H
O
OMe
O
Br
WWY-dibenzoate_CARBON_01
WWY-dibenzoate
CDCl3 (125 MHz)
f1 (ppm)

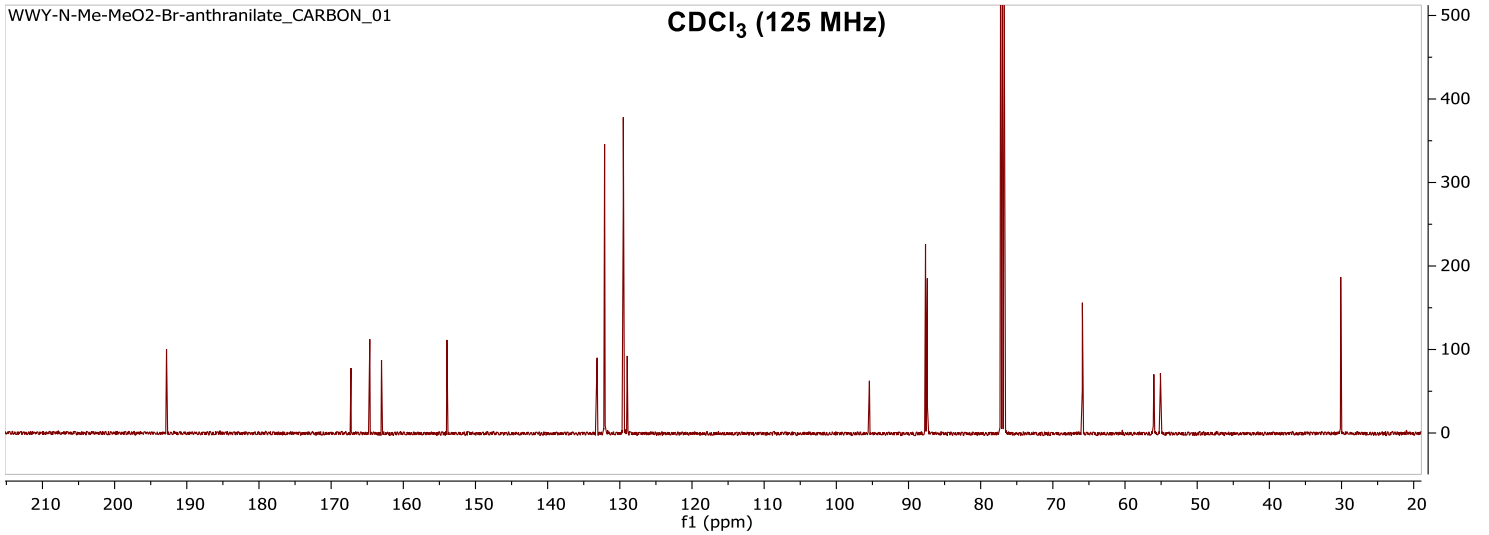

WWY-proto_aza_rocaglate_PROTON_01
CDCl3 (500 MHz)
HO
HO
O
OMe
N
Me
20
OMe
f1 (ppm)
WWY-proto_aza_rocaglate_CARBON_01
CDCl3 (125 MHz)
f1 (ppm)

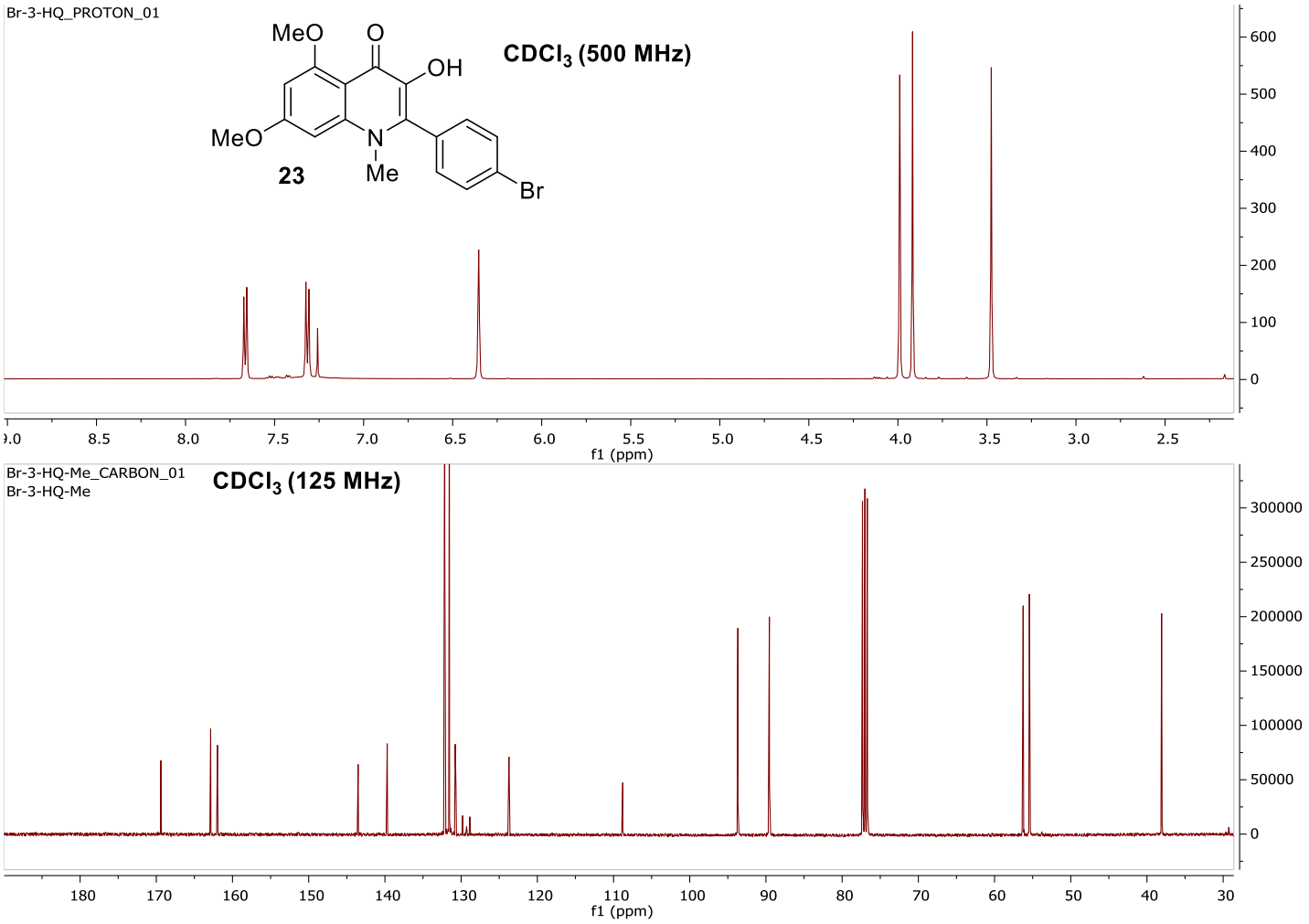

bromo_benzoate_PROTON_01
CDCl3 (500 MHz)
21
azaroc_benzoate_CARBON_01
azaroc_benzoate
CDCl3 (125 MHz)
f1 (ppm)

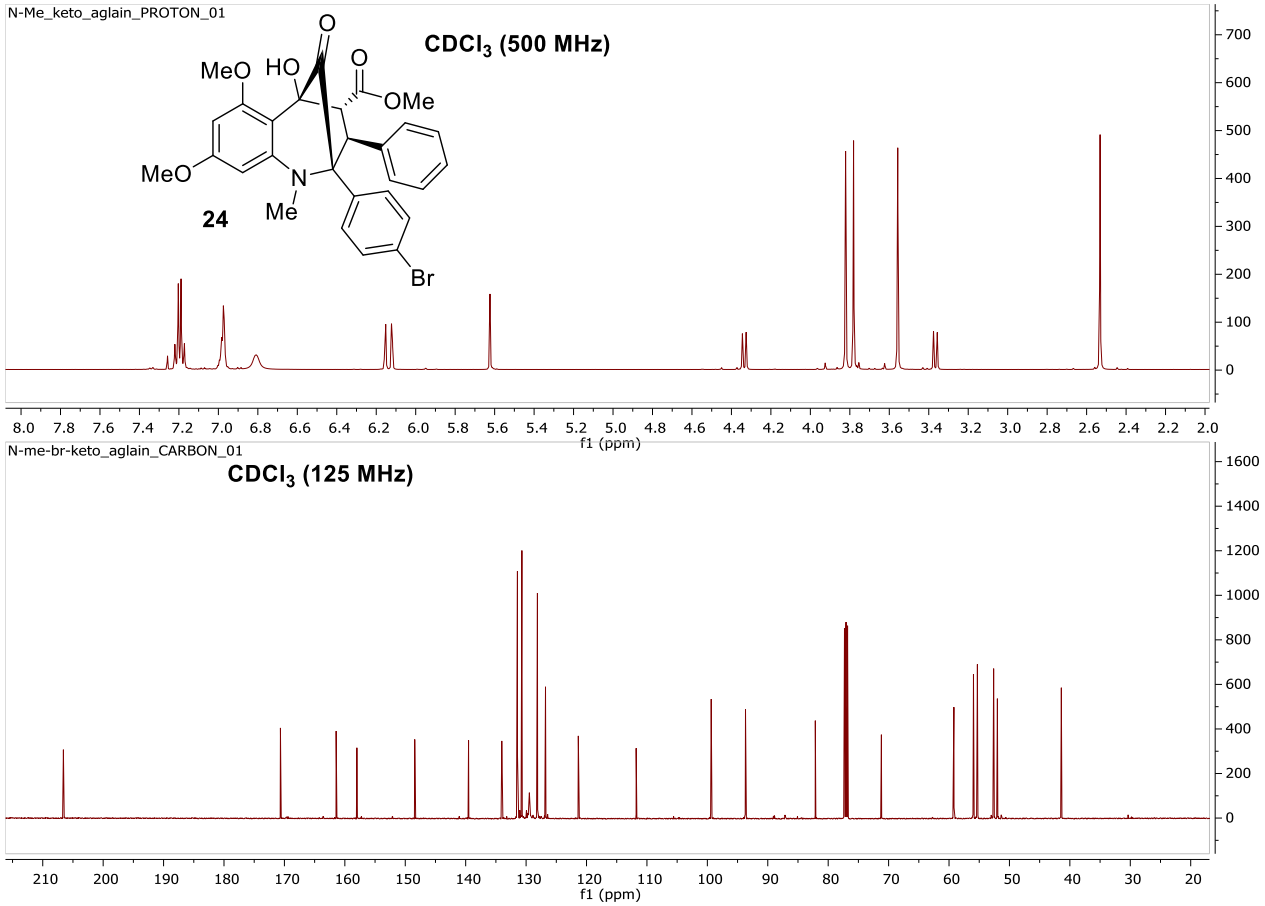

WWY-quinoline_DME_PROTON_01
WWY-quinoline_DME
22
OMe
OMe
OMe
N
CDCl3 (500 MHz)
f1 (ppm)
WWY-quinoline_DME_CARBON_01
WWY-quinoline_DME
CDCl3 (125 MHz)
f1 (ppm)

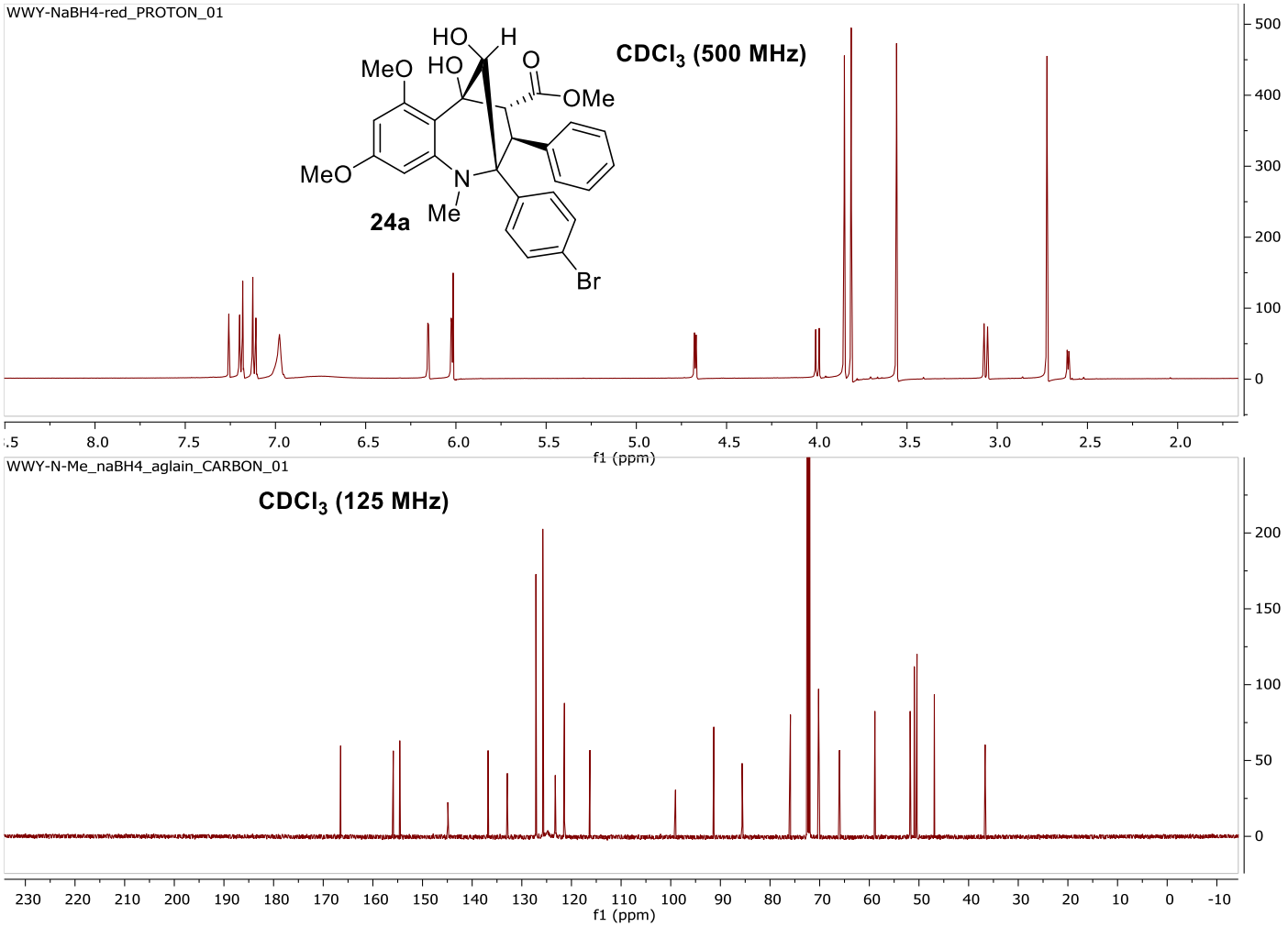

WWY-N-Me_PROTON_01
MeO
O
OH
MeO
NH
Me
23b
CDCl3 (500 MHz)
1400
1200
1000
800
600
400
200
0
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
f1 (ppm)
WWY-N-Me_CARBON_01
CDCl3 (125 MHz)
40
30
20
10
0
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)

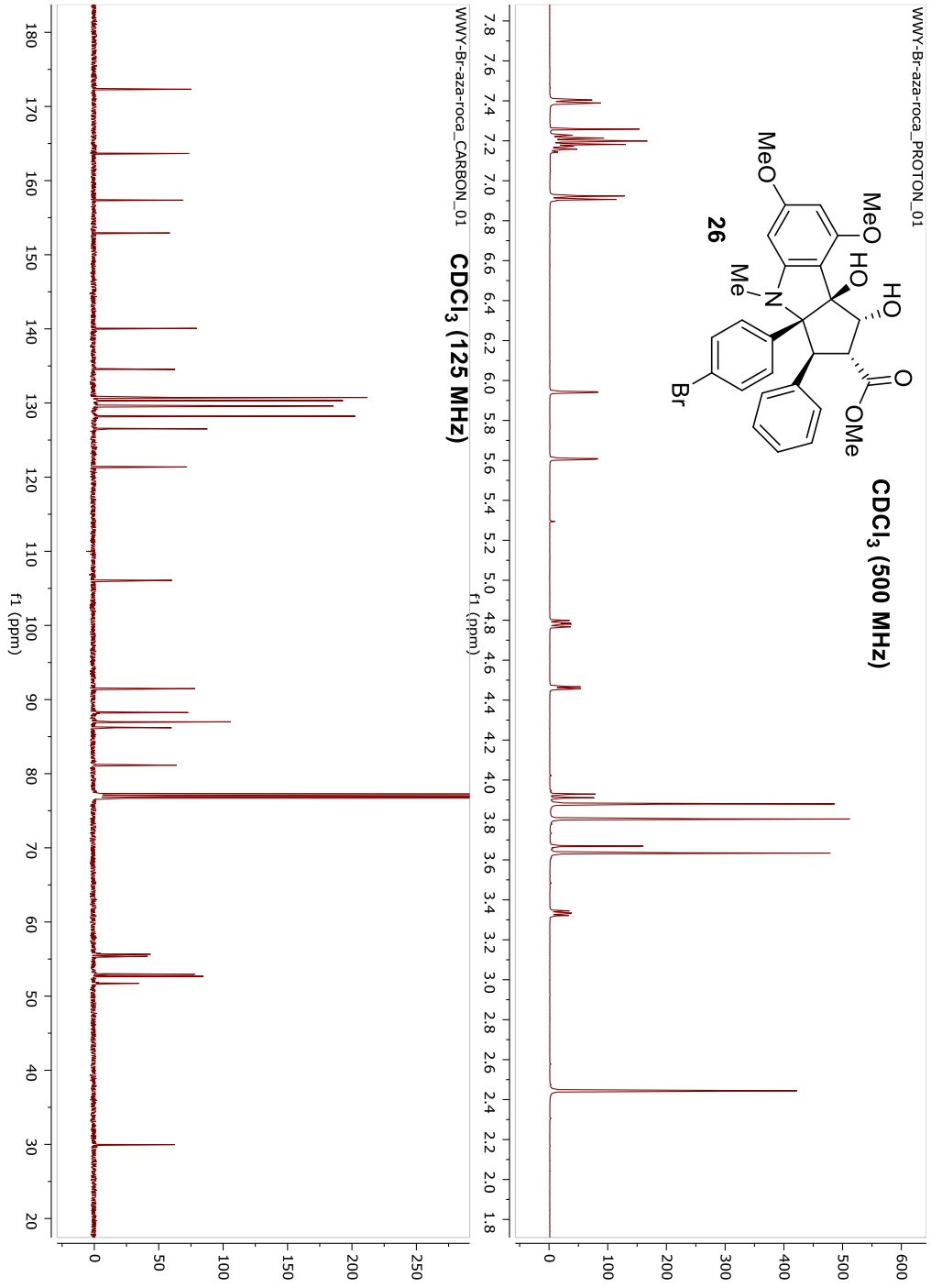

WWY-N-Me-MeO2-Br-anthranilate_PROTON_01
MeO
O
O
O
Br
MeO
NH
Me
23c
CDCl3 (500 MHz)
2000
1500
1000
500
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

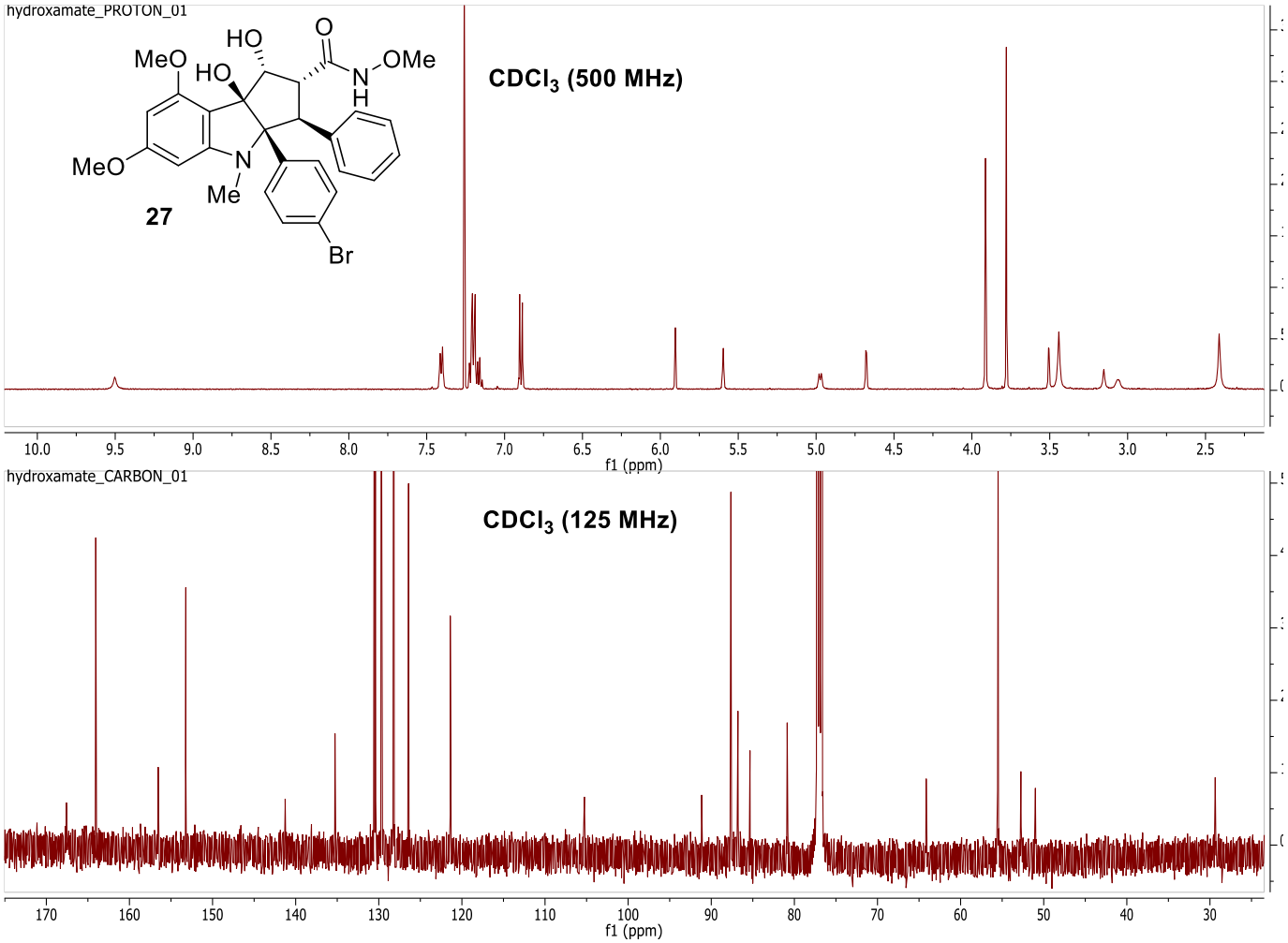

WWY-N-Me-MeO2-Br-anthranilate_CARBON_01
CDCl3 (125 MHz)
500
400
300
200
100
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

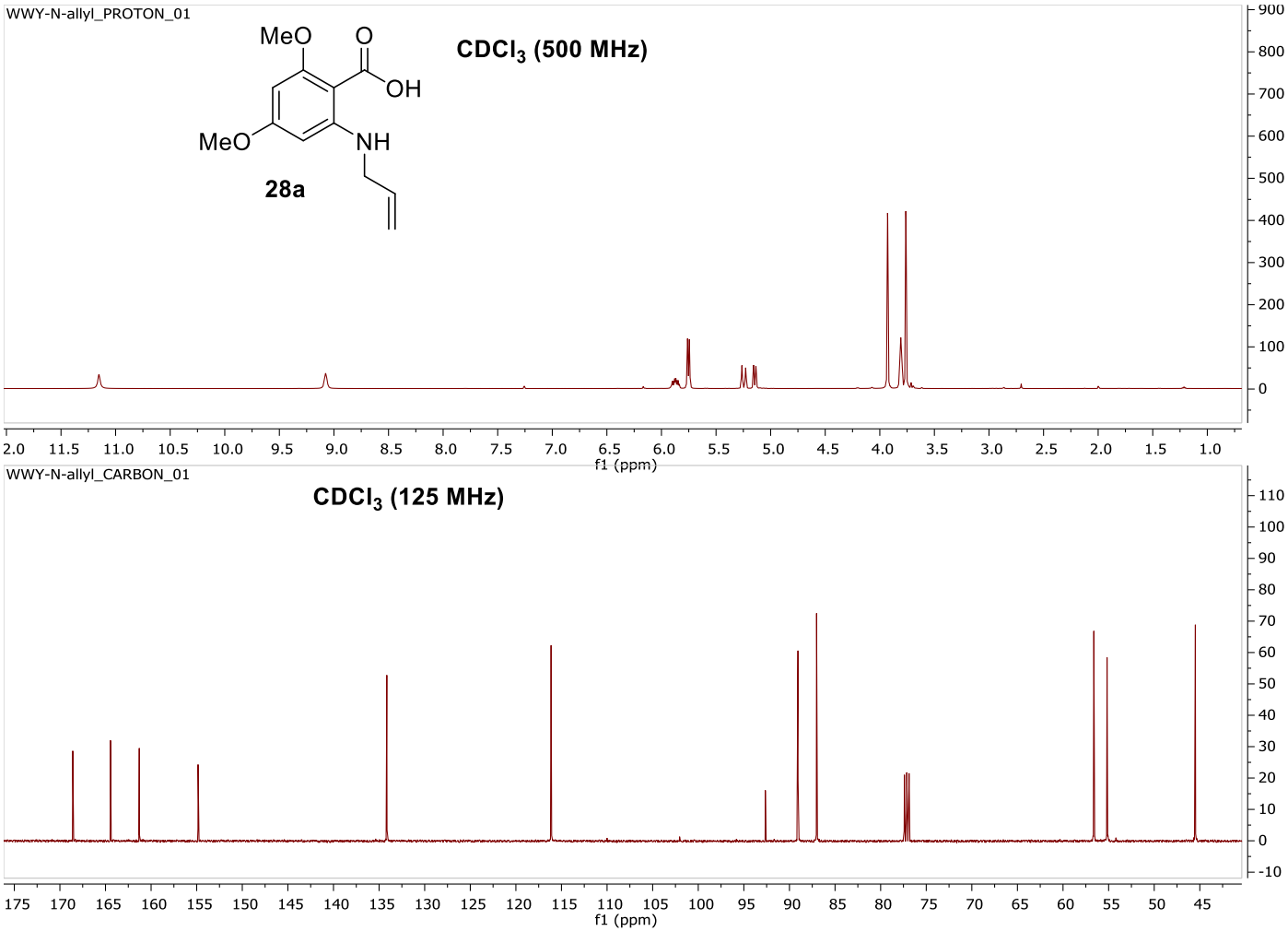

Br-3-HQ_PROTON_01
MeO
O
OH
MeO
N
Me
Br
23
CDCl3 (500 MHz)
f1 (ppm)
Br-3-HQ-Me_CARBON_01
Br-3-HQ-Me
CDCl3 (125 MHz)
f1 (ppm)

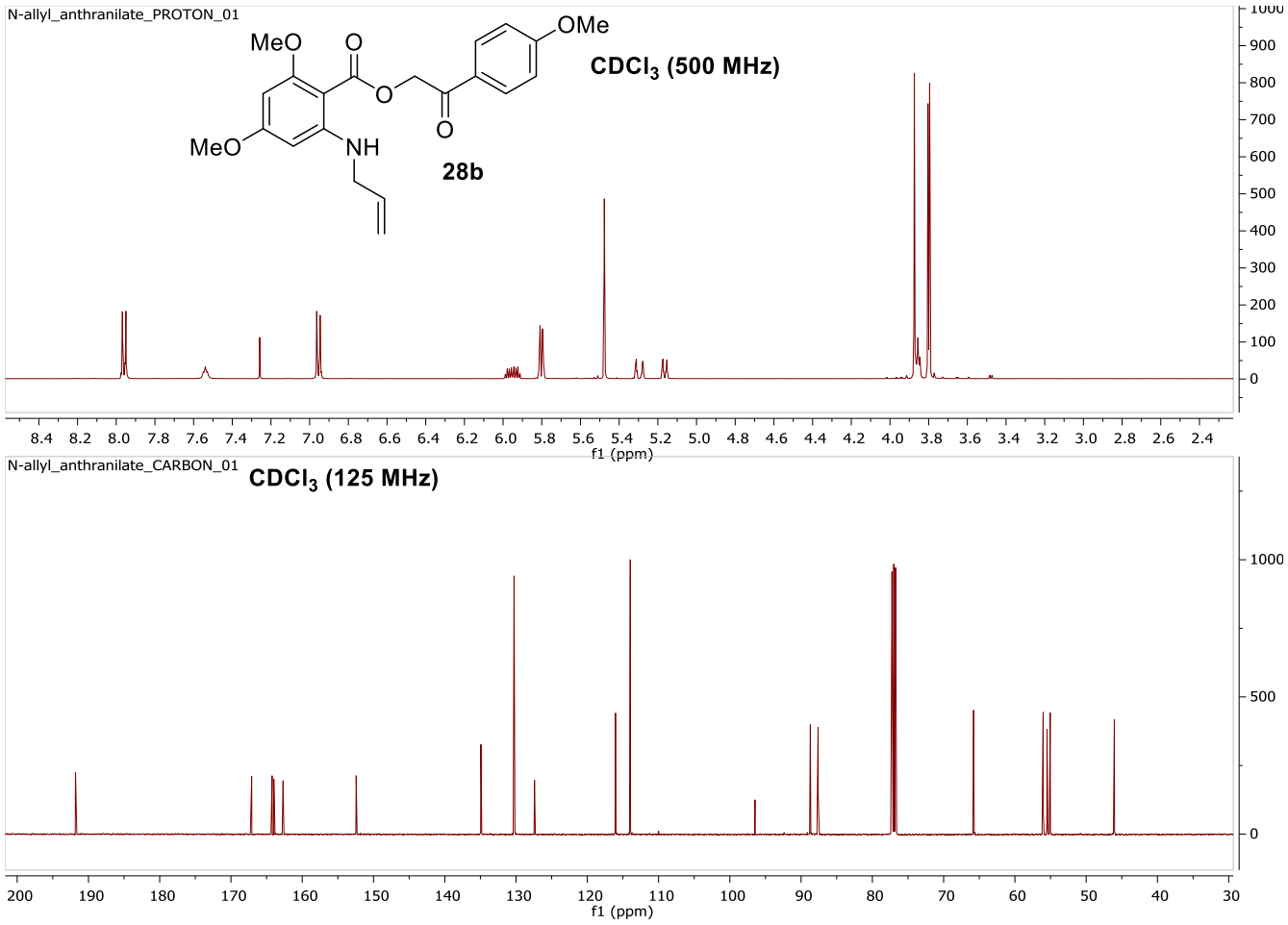

N-Me_keto_aglain_PROTON_01
CDCl3 (500 MHz)
MeO
HO
O
O
OMe
MeO
N
Me
24
Br
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0
f1 (ppm)
700 600 500 400 300 200 100 0
N-me-br-keto_aglain_CARBON_01
CDCl3 (125 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)
1600 1400 1200 1000 800 600 400 200 0

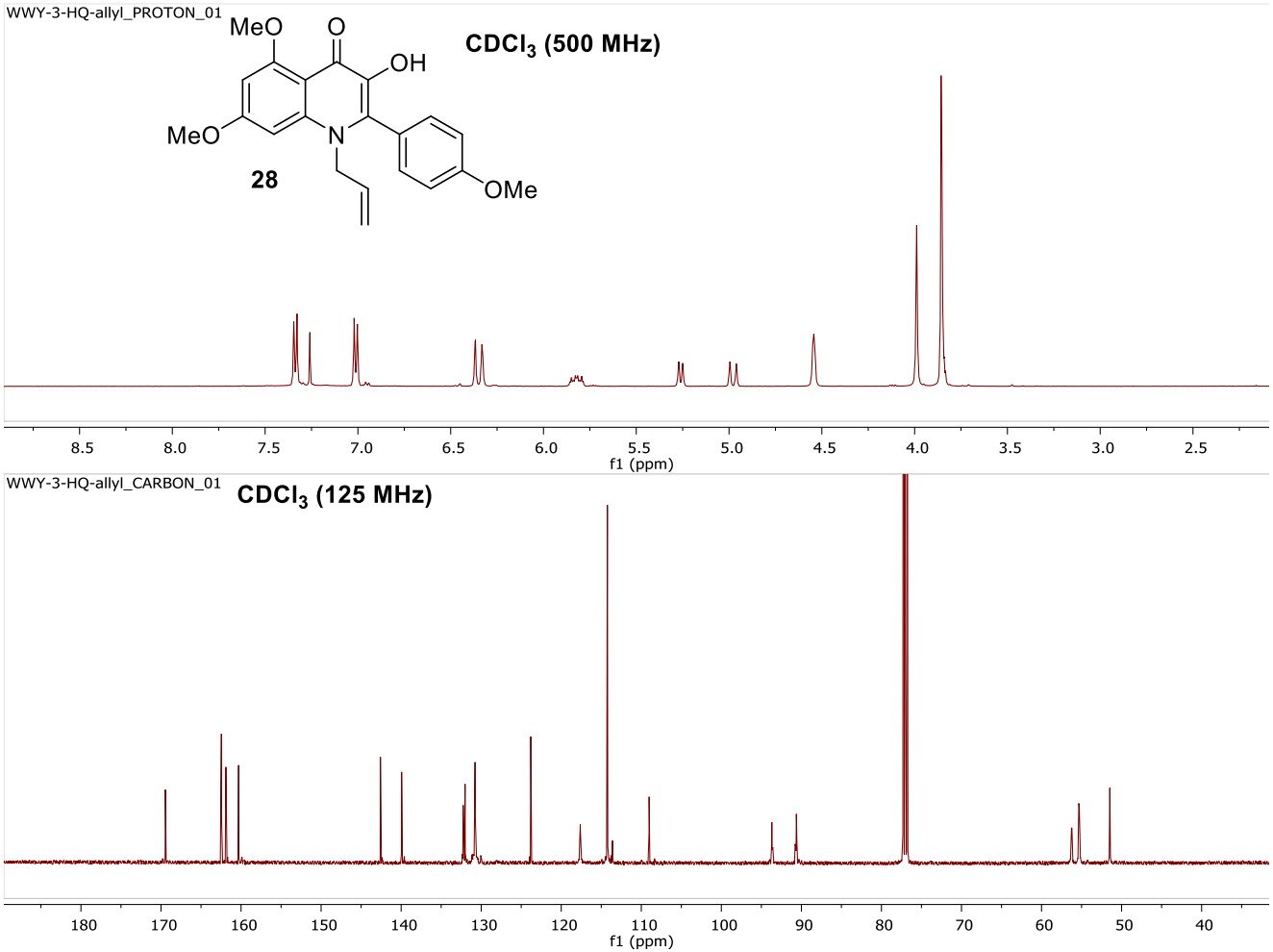

WWY-NaBH4-red_PROTON_01
CDCl3 (500 MHz)
HO
H
MeO
HO
O
OMe
MeO
N
Me
24a
Br
f1 (ppm)
WWY-N-Me_naBH4_aglain_CARBON_01
CDCl3 (125 MHz)
f1 (ppm)

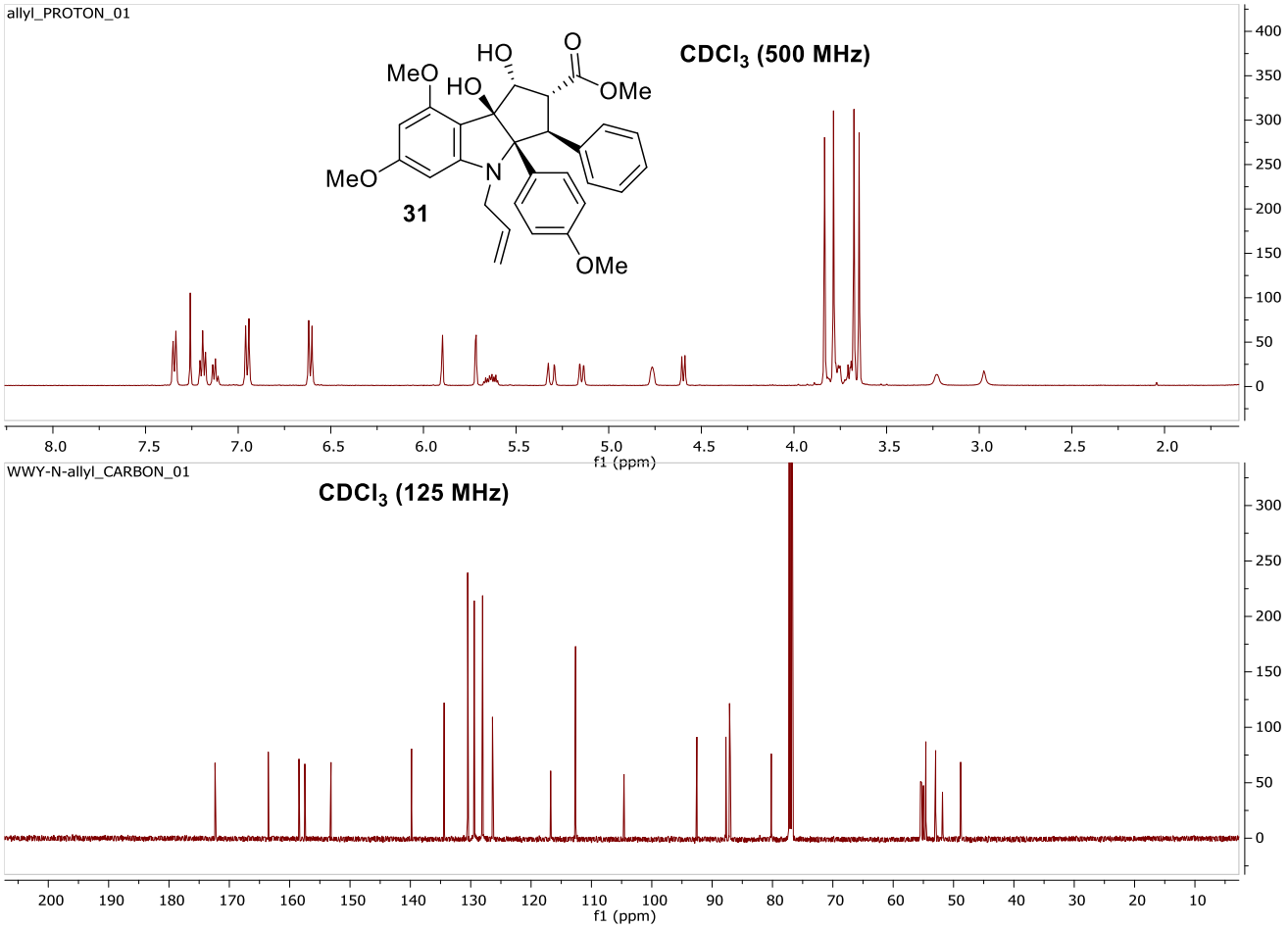

WWY-Br-aza-roca_PROTON_01
CDCl3 (500 MHz)
26
MeO
MeO
HO
HO
Me
N
Br
O
OMe
WWY-Br-aza-roca_CARBON_01
CDCl3 (125 MHz)
f1 (ppm)

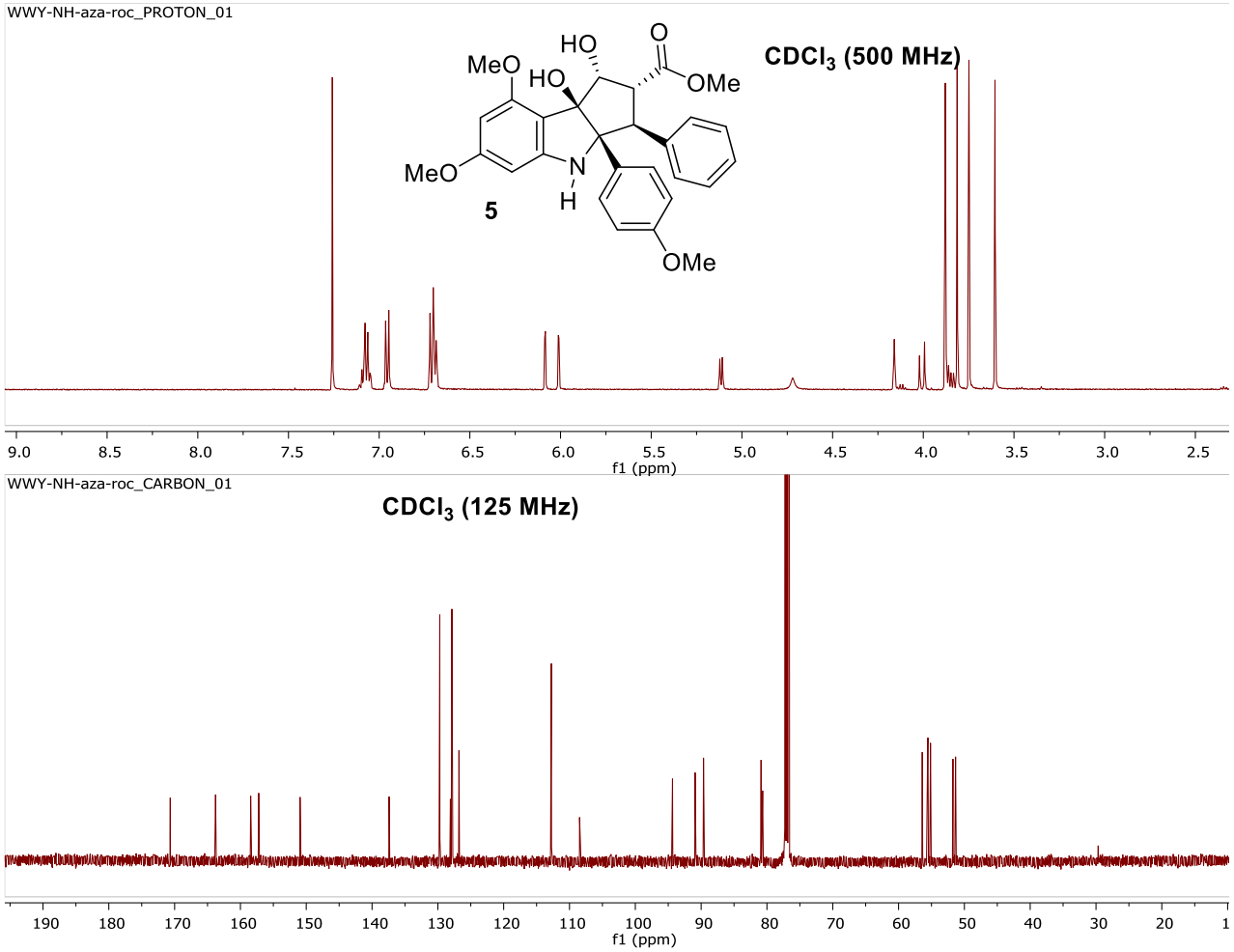

hydroxamate_PROTON_01
HO
O
MeO
HO
N
OMe
H
CDCl3 (500 MHz)
MeO
N
Me
27
Br
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)
hydroxamate_CARBON_01
CDCl3 (125 MHz)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

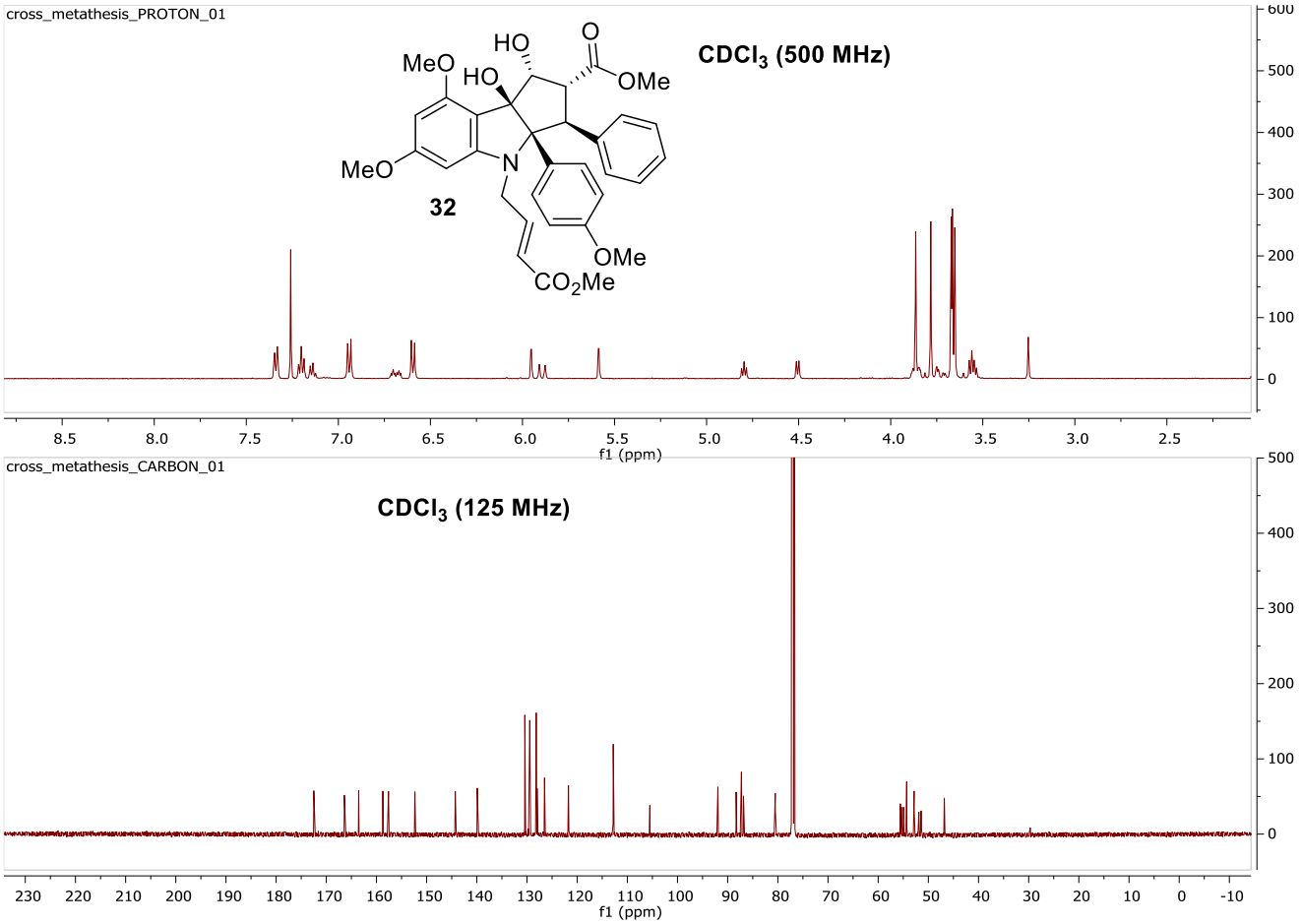

WWY-N-allyl_PROTON_01
MeO
O
OH
MeO
NH
28a
CDCl3 (500 MHz)
f1 (ppm)
WWY-N-allyl_CARBON_01
CDCl3 (125 MHz)
f1 (ppm)


N-allyl_anthranilate_PROTON_01
MeO
O
OMe
O
O
MeO
NH
28b
CDCl3 (500 MHz)
f1 (ppm)
N-allyl_anthranilate_CARBON_01
CDCl3 (125 MHz)
f1 (ppm)


WWY-3-HQ-allyl_PROTON_01
MeO
O
OH
MeO
N
OMe
28
CDCl3 (500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)
WWY-3-HQ-allyl_CARBON_01
CDCl3 (125 MHz)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
f1 (ppm)

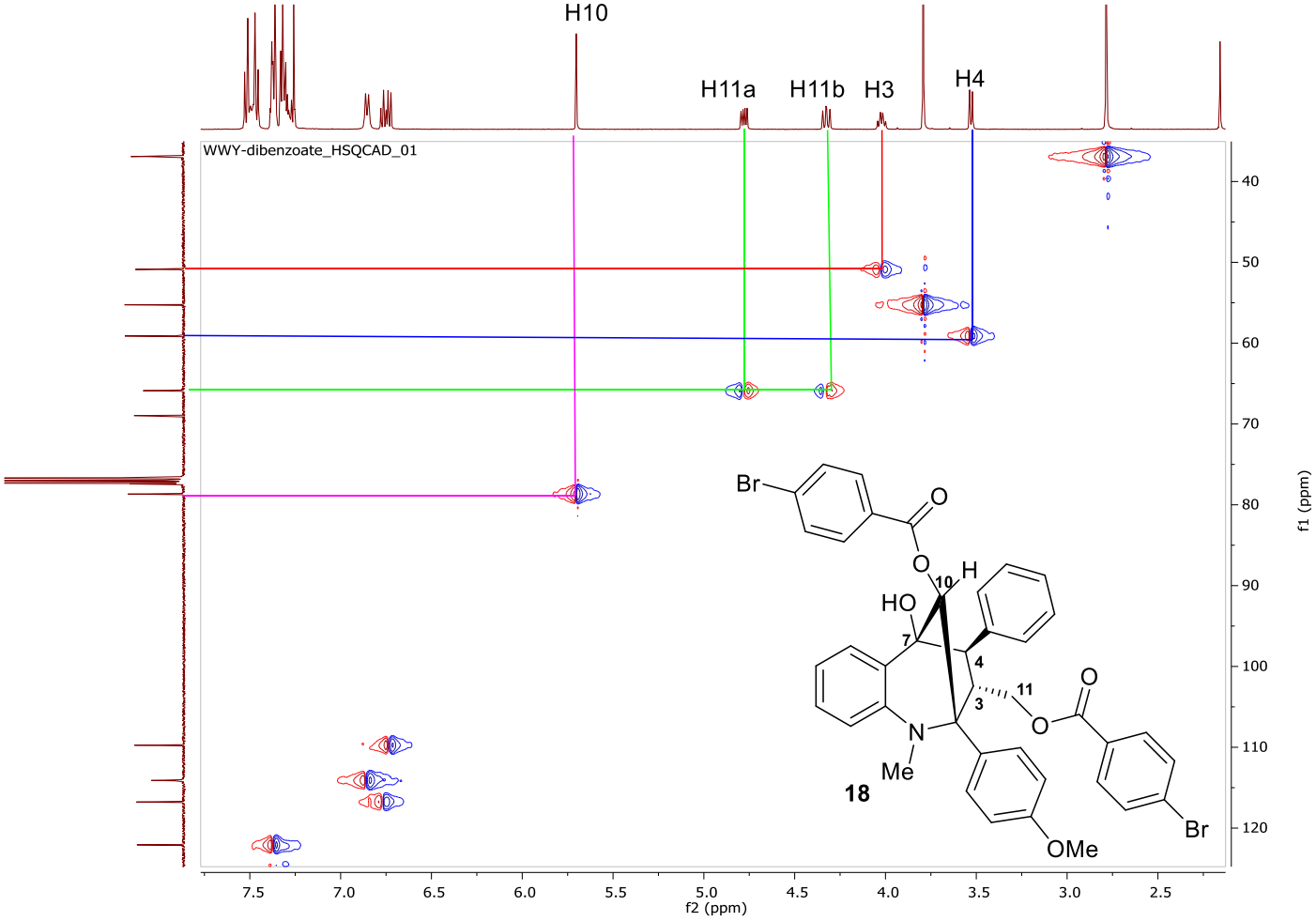

allyl_PROTON_01
HO
O
MeO
HO
OMe
MeO
N
31
OMe
CDCl3 (500 MHz)
f1 (ppm)
WWY-N-allyl_CARBON_01
CDCl3 (125 MHz)
f1 (ppm)

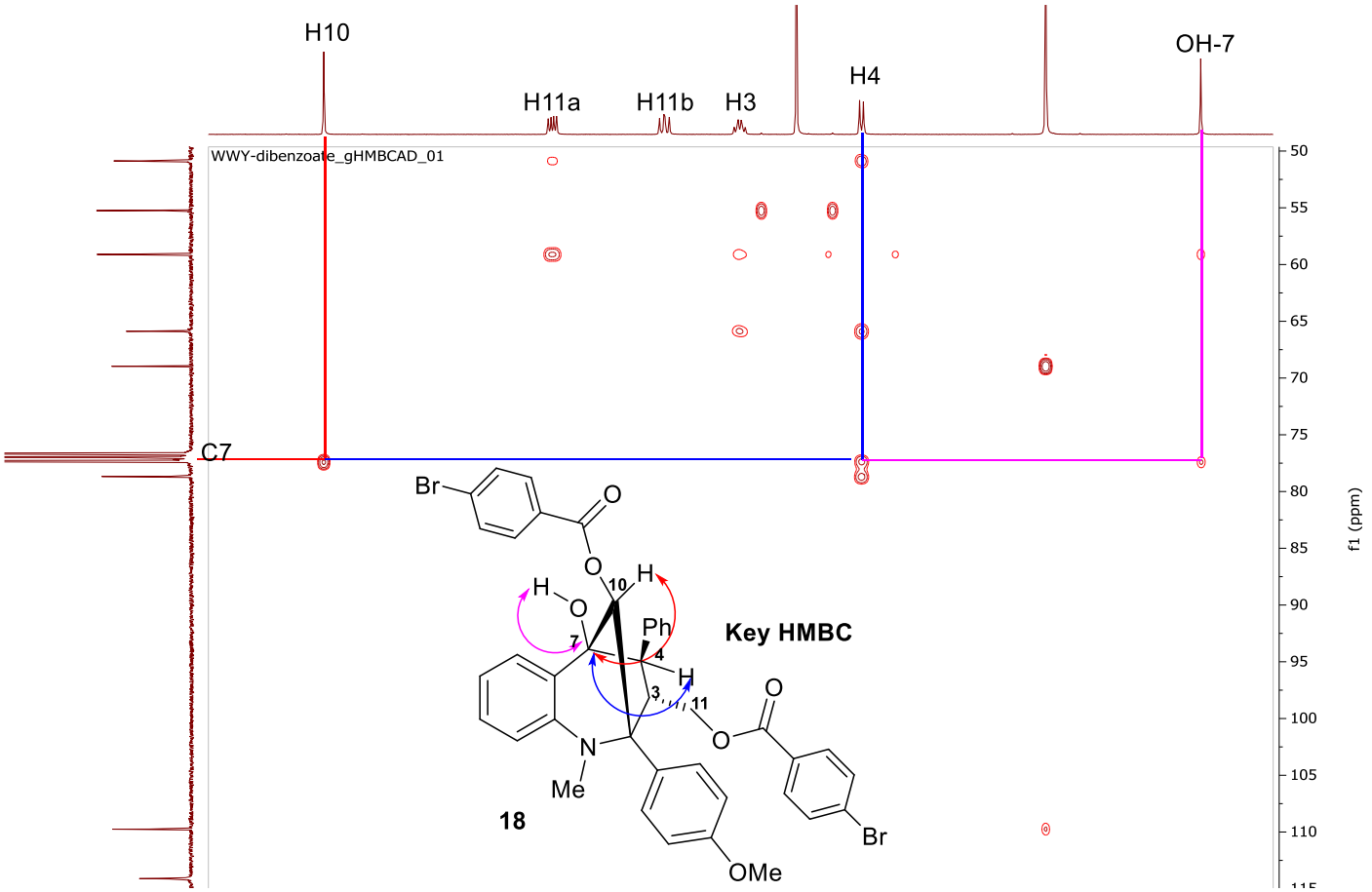

WWY-NH-aza-roc_PROTON_01
HO
O
MeO
HO
OMe
CDCl3 (500 MHz)
MeO
N
H
5
OMe
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)
WWY-NH-aza-roc_CARBON_01
CDCl3 (125 MHz)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
1
f1 (ppm)

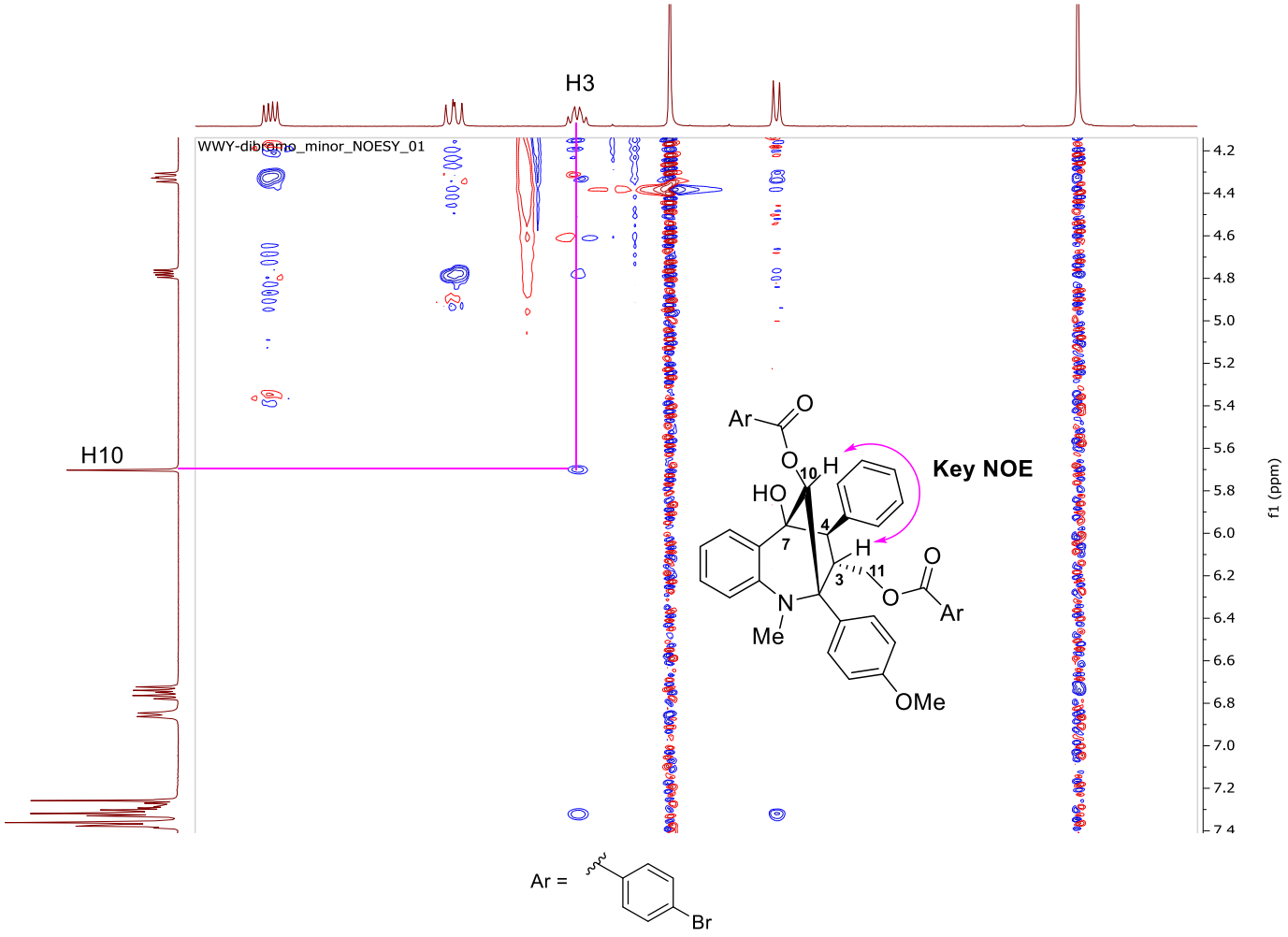

cross_metathesis_PROTON_01
CDCl3 (500 MHz)
HO
O
MeO
HO
OMe
MeO
N
32
OMe
CO2Me
f1 (ppm)
cross_metathesis_CARBON_01
CDCl3 (125 MHz)
f1 (ppm)

2D NMR Spectra

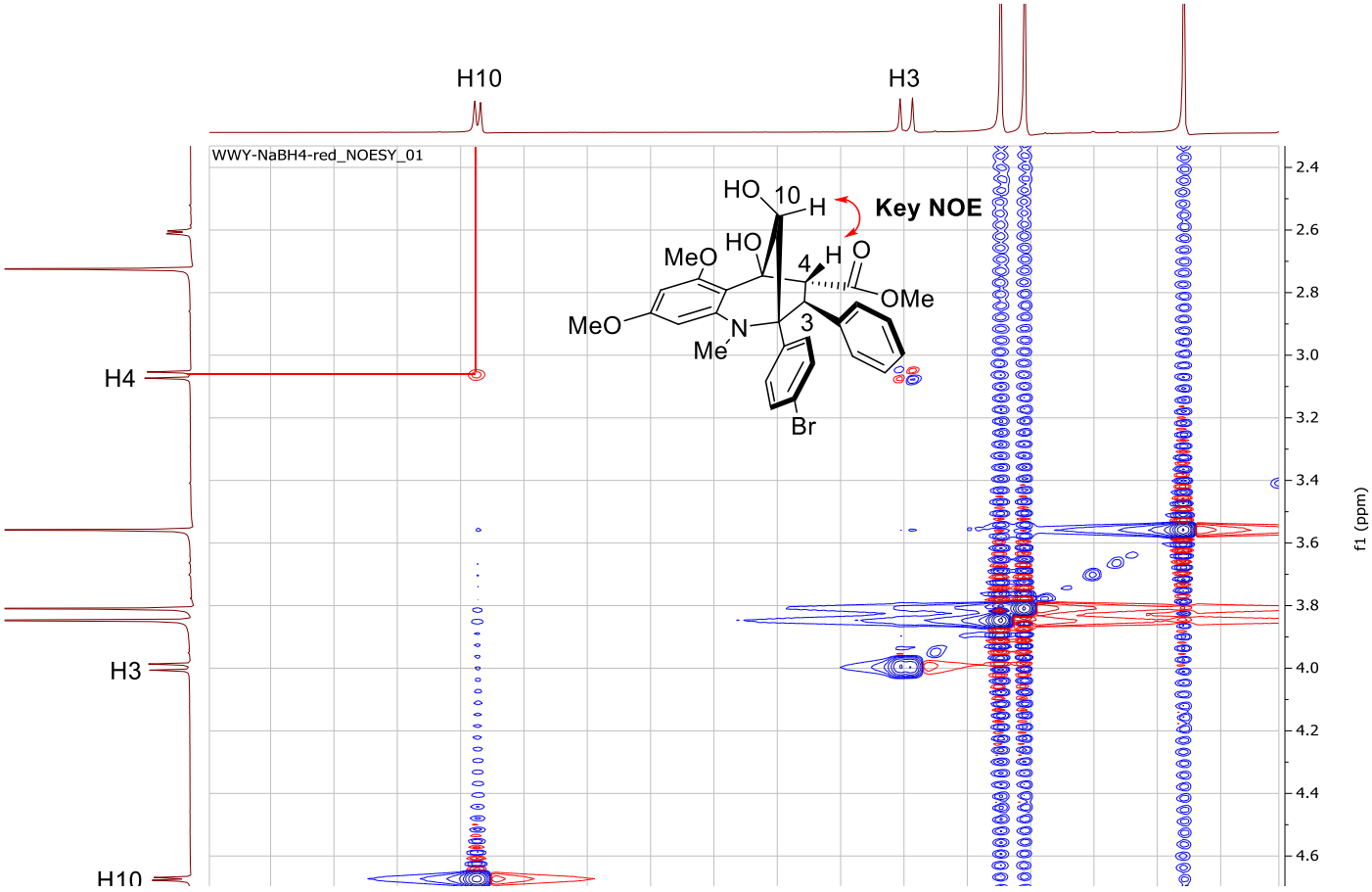
HSQC, HMBC, and NOESY Spectra for Compound **19**



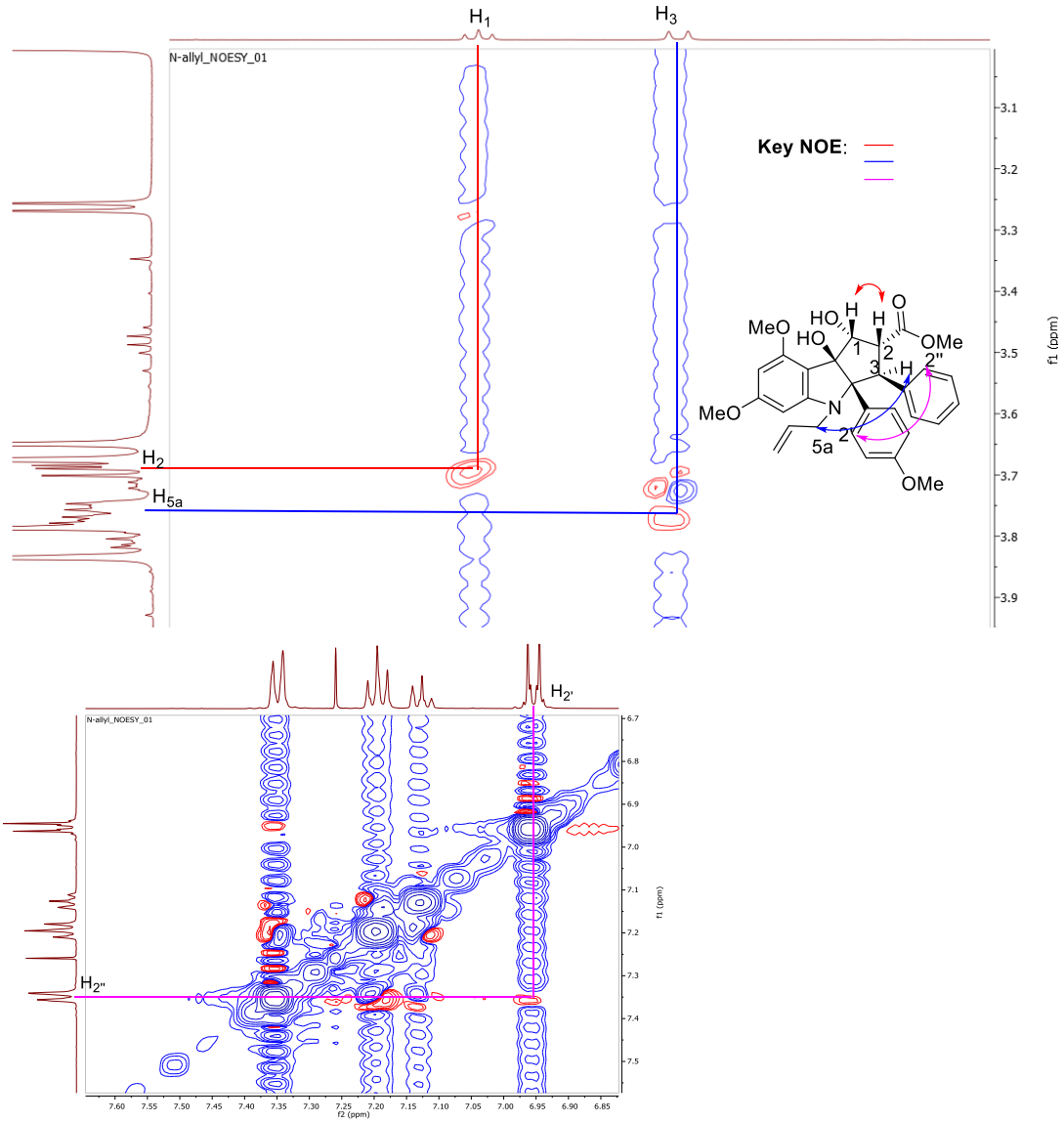

H10
H11a
H11b
H3
H4
OH-7
WWY-dibenzoate_gHMBCAD_01
C7
f1 (ppm)
Br
O
O
H
10
H
O
7
Ph
4
H
3
11
O
O
N
Me
Br
OMe
18
Key HMBC


H3
H10
WWY-dibromo_minor_NOESY_01
f1 (ppm)
Key NOE
Ar
O
HO
H
10
4
7
3
11
N
Me
OMe
Ar =
Br

NOESY Spectrum for Compound **24a**:



NOESY Spectrum for Compound **31**:



DFT Model of Compound **31** (B3LYP_6-31G*).