Electronic Supplementary Material (ESI) for Catalysis Science & Technology.

Supporting Information

Removing the superfluous: a supported squaramide catalyst with a minimalistic linker applied to the enantioselective flow synthesis of pyranonaphthoquinones

Laura Osorio-Planes, Carles Rodríguez-Escrich and Miquel A. Pericàs*

mapericas@iciq.es

Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans, 16, 43007 Tarragona (Spain), The Barcelona Institute of Science and Technology
and
Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona (Spain)

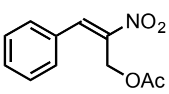
Table of Contents

1. General information

Unless otherwise stated, all commercial reagents were used as received. Flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. Thin layer chromatography was carried out using Merck TLC Silicagel 60 F254 aluminum sheets. Components were visualized by UV light (λ = 254 nm) and stained with *p*-anisaldehyde or phosphomolybdic acid dip. NMR spectra were recorded at 298 K on a Fourier 300 MHz Bruker, a Bruker Avance 400 Ultrashield or a Bruker Avance 500 Ultrashield apparatus. ^{1}H NMR spectroscopy chemical shifts are quoted in ppm relative to tetramethylsilane (TMS). $CDCl_3$ was used as internal standard for ^{13}C NMR spectra. Chemical shifts are given in δ and coupling constants in Hz. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses of the polystyrene supported catalysts were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid (Spain) or at MEDAC Ltd. (Surrey, UK). High performance liquid chromatography (HPLC) was performed on an Agilent Technologies chromatograph (1100 Series), using Chiralpak columns and guard columns. ESI mass spectra were obtained on a Waters LCT Premier Instrument. Specific optical rotation measurements were carried out on a Jasco P-1030 polarimeter. Racemic standard products were prepared using the same general procedures but with 10 mol% of DABCO as catalyst in order to establish HPLC conditions.

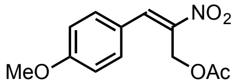
2. Preparation of Morita-Baylis-Hillman acetates 6a-6g

The MBH acetates **6** were prepared according to a procedure described in the literature.[1] In the same reference, **6a** and **6e** are characterized. Spectroscopic data for all the MBH acetates are given below and the corresponding ^{1}H and ^{13}C NMR spectra can be found in Section 9.



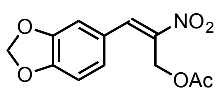
6a

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.51-7.43 (m, 5H), 5.22 (s, 2H), 2.15 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.2, 145.3, 139.9, 131.3, 130.9, 130.0 (×2), 129.2 (×2), 57.8, 20.7.



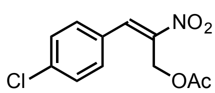
6b

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.48-7.42 (m, 2H), 7.01-6.96 (m, 2H), 5.25 (s, 2H), 3.87 (s, 3H), 2.15 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.4, 162.4, 143.0, 140.0, 132.5 (×2), 123.2, 114.9 (×2), 58.1, 55.5, 20.8.



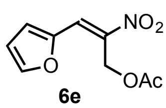
6c

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.03 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.97 (d, *J* = 1.8 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.07 (s, 2H), 5.23 (s, 2H), 2.15 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.4, 150.7, 148.7, 143.5, 140.1, 126.7, 124.8, 109.4, 109.2, 102.0, 58.0, 20.8.



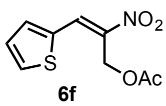
6d

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.49-7.44 (m, 2H), 7.43-7.38 (m, 2H), 5.19 (s, 2H), 2.14 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.2, 145.6, 138.5, 137.7, 131.2 (×2), 129.7 (×2), 139.3, 57.5, 20.7.



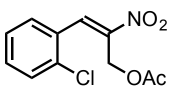
6e

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.01 (d, *J* = 3.5 Hz, 1H), 6.63 (dd, *J* = 3.5, 1.8 Hz, 1H), 5.51 (s, 2H), 2.09 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.5, 148.0, 146.6, 141.3, 125.0, 122.6, 113.4, 57.9, 20.8.



6f

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.73 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.54 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.22 (dd, *J* = 5.1, 3.8 Hz, 1H), 5.40 (s, 2H), 2.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.6, 141.7, 136.7, 134.2, 133.3, 132.6, 128.7, 57.9, 20.6.

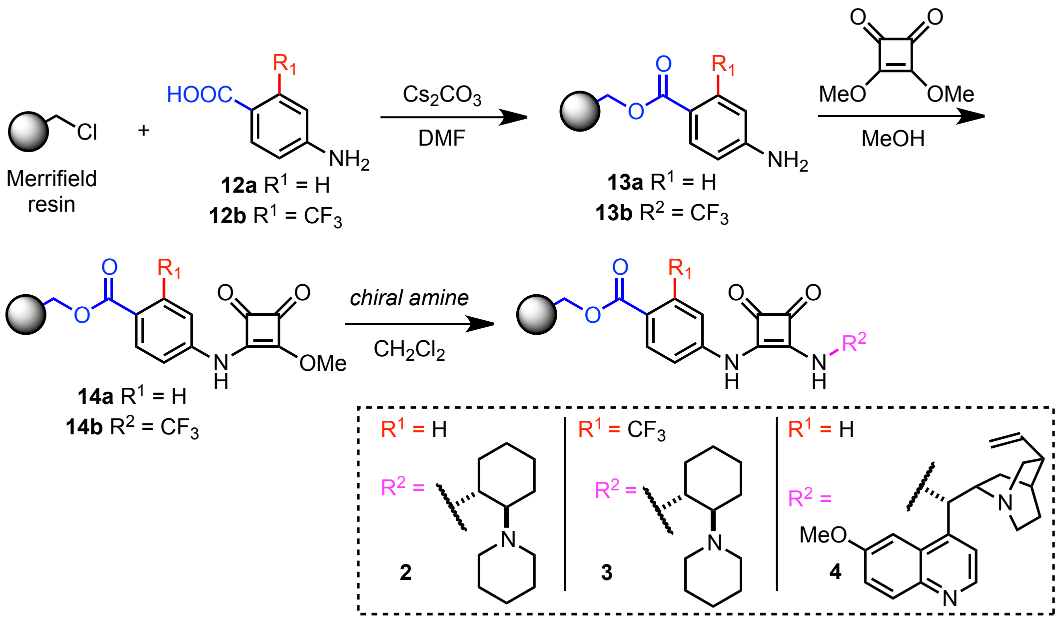


6g

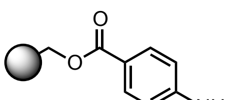
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.51 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.46-7.40 (m, 1H), 7.39-7.35 (m, 2H), 5.11 (s, 2H), 2.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.0, 146.7, 136.7, 135.1, 132.0, 130.2 (×2), 130.0, 127.3, 57.6, 20.6.

3. Preparation of catalytic resins 2-5

General synthetic scheme for the preparation of resins 2-4



Scheme S1



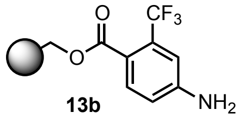
13a

Merrifield resin (Novabiochem, 1% DVB, 0.53 mmol/g of active chlorine, 0.50 g) was charged in a screw cap Schlenk flask and was suspended in 3.3 mL of dry DMF under Ar atmosphere. Then, Cs_2CO_3 (0.13 g, 0.40 mmol) and 4-aminobenzoic acid (0.055 g, 0.40 mmol) were added to the previous suspension and the reaction mixture was shaken at rt for 1 h and at 80 °C for 10 more hours. The resulting resin was allowed to cool down to rt, filtered and washed successively with water (60 mL), water/MeOH 1:1 (60 mL), MeOH/CH_2Cl_2 1:1 (60 mL) and CH_2Cl_2 (60 mL). After drying it overnight under vacuum at 45 °C, 0.50 g of **13a** were isolated.

N elemental analysis (%): 0.72 ± 0.25.

f: 0.51 mmol/g (quantitative anchoring, $\boldsymbol{f_{max}}$: 0.48 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1707 cm^{-1} (carbonyl band).



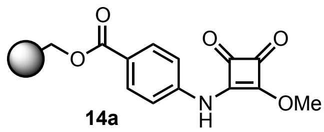
13b

Merrifield resin (Novabiochem, 1% DVB, *f* = 0.53 mmol/g of active chlorine, 0.55 g) was charged in a screw cap Schlenk flask and was suspended in 3.6 mL of dry DMF under Ar atmosphere. Then, Cs_2CO_3 (0.14 g, 0.44 mmol) and 4-amino-2-(trifluoromethyl)benzoic acid (0.090 g, 0.44 mmol) were added to the previous suspension and the reaction mixture was shaken for 1 h at rt and subsequently at 80 °C for 10 more hours. The resulting resin was allowed to cool down to rt, filtered and washed successively with water (60 mL), water/MeOH 1:1 (60 mL), MeOH/CH_2Cl_2 1:1 (60 mL) and CH_2Cl_2 (60 mL). After drying it overnight under vacuum at 45 °C, 0.63 g of **13b** were isolated.

F elemental analysis (%): 2.73 ± 0.25.

f: 0.49 mmol/g (quantitative anchoring, f_{max}: 0.46 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1728 cm^{-1} (carbonyl band).



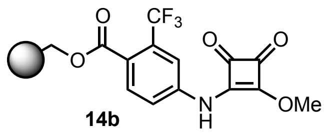
14a

3,4-Dimethoxy-3-cyclobutene-1,2-dione (0.06 g, 0.43 mmol) was added to a suspension of **13a** (0.45 g, 0.23 mmol) in 3.5 mL of MeOH. The reaction mixture was shaken overnight at rt, filtered and washed successively with MeOH (60 mL), MeOH/CH_2Cl_2 1:1 (60 mL) and CH_2Cl_2 (60 mL). After drying it overnight under vacuum at 45 °C, 0.42 g of **14a** were isolated.

N elemental analysis (%): 0.69 ± 0.25.

f: 0.49 mmol/g (quantitative anchoring, f_{max}: 0.45 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1802, 1714 cm^{-1} (carbonyl bands).



14b

3,4-Dimethoxy-3-cyclobutene-1,2-dione (0.08 g, 0.52 mmol) was added to a suspension of **13b** (0.57 g, 0.26 mmol) in 3.6 mL of MeOH. The reaction mixture was shaken overnight at rt, filtered and washed successively with MeOH (60 mL), MeOH/CH_2Cl_2 1:1 (60 mL) and CH_2Cl_2 (60 mL). After drying it overnight under vacuum at 45 °C, 0.49 g of **14b** were isolated.

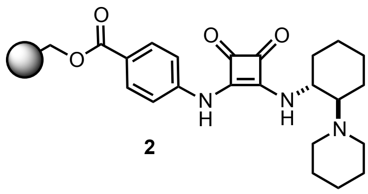
F elemental analysis (%): 2.60 ± 0.25.

f: 0.46 mmol/g (quantitative anchoring, f_{max}: 0.44 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1804, 1733 cm^{-1} (carbonyl bands).

General procedure for the preparation of resins 2-4 from 14a or 14b

Resins **14a** or **14b** (0.15 mmol) were suspended in 2 mL of CH_2Cl_2 and then a solution of the corresponding diamine, either (1*R*,2*R*)-*trans*-2-(1-piperidinyl)cyclohexylamine[2] or *epi*-aminoquinine,[3] in CH_2Cl_2 (0.30 mmol, 0.37 M) was added. The reaction mixture was shaken at rt for 3 days, filtered and washed successively with MeOH (60 mL), MeOH/CH_2Cl_2 1:1 (60 mL) and CH_2Cl_2 (60 mL). Then it was allowed to dry overnight under vacuum at 45 °C.

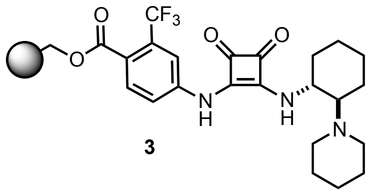


2

N elemental analysis (%): 0.90 ± 0.25.

f: 0.21 mmol/g (51% functionalization, f_{max}: 0.43 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1792, 1708 cm^{-1} (carbonyl bands).

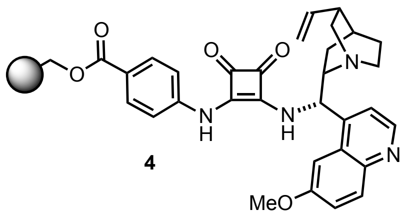


3

N elemental analysis (%): 0.94 ± 0.25.

f: 0.22 mmol/g (52% functionalization, f_{max}: 0.42 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1792, 1727 cm^{-1} (carbonyl bands).



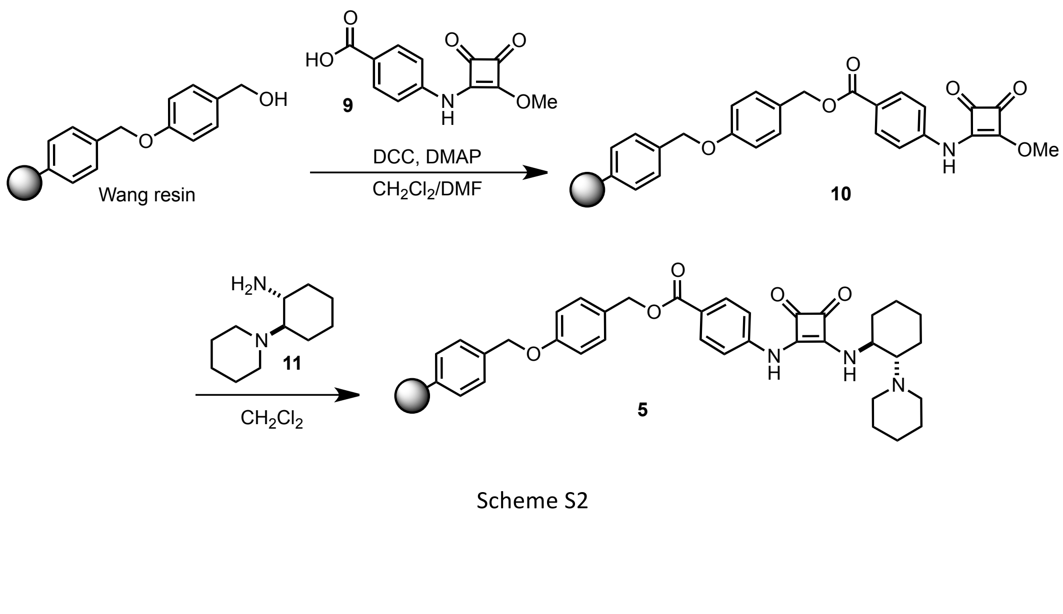
4

N elemental analysis (%): 1.03 ± 0.25

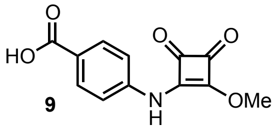
f: 0.24 mmol/g (54% functionalization, f_{max}: 0.44 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1707 cm^{-1} (carbonyl bands).

Synthetic scheme for the preparation of resin 5



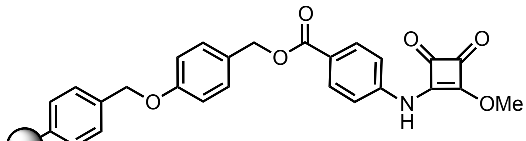
Scheme S2



9

A mixture of 4-aminobenzoic acid (11.6 g, 84.0 mmol) and 3,4-dimethoxy-3-cyclobutene-1,2-dione (12.0 g, 84.0 mmol) was suspended in 184 mL of MeOH and stirred at rt for 3 days. The resulting pale yellow solid was isolated by filtration and used in the next step without any further purification (19.6 g, 79.0 mmol, 94% yield).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 4.41 (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ 188.1, 184.9, 180.0, 169.6, 167.2, 142.45, 131.1 (×2), 126.1, 119.2 (×2), 61.2; **IR** (ATR): ν 3247, 3190, 3098, 2969, 1799, 1709, 1675, 1607, 1569, 1374, 1280 cm^{-1}; **mp**: 282-285 °C; **HRMS** (ESI–): *m/z* calcd. for $C_{12}H_8NO_5$ $[M–H]^-$: 246.0408, found: 246.0404.



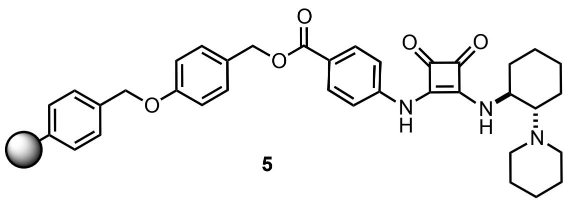
10

The Wang resin (Iris Biotech, f = 1.2 mmol/g, 5 g) and DMAP (0.15 g, 1.2 mmol) were suspended in 40 mL of dry CH_2Cl_2 and a solution of **9** (1.79 g, 7.2 mmol) in 10 mL of dry DMF was added under N_2 atmosphere. The mixture was cooled to 0 °C and a solution of dicyclohexylcarbodiimide (DCC, 1.86 g, 9.0 mmol) in 10 mL of dry DMF was added. It was allowed to slowly reach rt and shaken overnight. Then, the resin was filtered and washed with DMF (100 mL), DMF/H_2O 1:1 (200 mL), H_2O (100 mL), H_2O/MeOH 1:1 (200 mL), MeOH (200 mL), MeOH/CH_2Cl_2 1:1 (200 mL) and CH_2Cl_2 (200 mL) and dried under vacuum at 45 °C. After this, 5.75 g of a deep orange resin were obtained.

N elemental analysis (%): 1.30 ± 0.25.

f: 0.94 mmol/g (quantitative anchoring, $\boldsymbol{f_{max}}$: 0.93 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1802, 1715 cm^{-1} (carbonyl bands).



5

Resin **10** (2.3 g, 2.1 mmol) was swollen in 14 mL of CH_2Cl_2 and (1*R*,2*R*)-*trans*-2-(1-piperidinyl)cyclo-hexylamine[2] (0.78 g, 4.3 mmol), dissolved in 4 mL of CH_2Cl_2, was added. It was shaken at rt for two days. Then, it was filtered and washed with CH_2Cl_2 (150 mL), CH_2Cl_2/MeOH 1:1 (150 mL), MeOH (120 mL), CH_2Cl_2/MeOH 1:1 (120 mL) and CH_2Cl_2 (150 mL) and dried under vacuum at 45 °C. After this, 2.4 g of a yellow resin were obtained.

N elemental analysis (%): 2.45 ± 0.25.

f: 0.58 mmol/g (72% functionalization, $\boldsymbol{f_{max}}$: 0.82 $mmol_{monomer}/g_{resin}$).

IR (ATR): ν 1792, 1710 cm^{-1} (carbonyl bands).

4. General procedure for the synthesis of 8a in batch

PS-squaramide **5** (5.5 mg, 3.2 μmol) was charged in a vial and it was swollen with 0.25 mL of solvent. Subsequently, (*E*)-2-nitro-phenylallyl acetate (**6a**, 14 mg, 0.06 mmol) and hydroxynaphthoquinone (12 mg, 0.07 mmol) were added to the suspension and the reaction mixture was shaken at rt until total consumption of the starting nitroacetate **6a** (TLC monitoring). Then, the resin was filtered and washed with the specific solvent. After this, 0.5 mL of aqueous $NaHCO_3$ (sat) solution were added to the filtrate and the biphasic mixture was stirred for 1 h. The phases were then separated and the aqueous layer was washed with CH_2Cl_2 twice. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated under vacuum to dryness. The crude was finally purified by silica gel column chromatography (cyclohexane/EtOAc 80:20) to give a yellow solid.

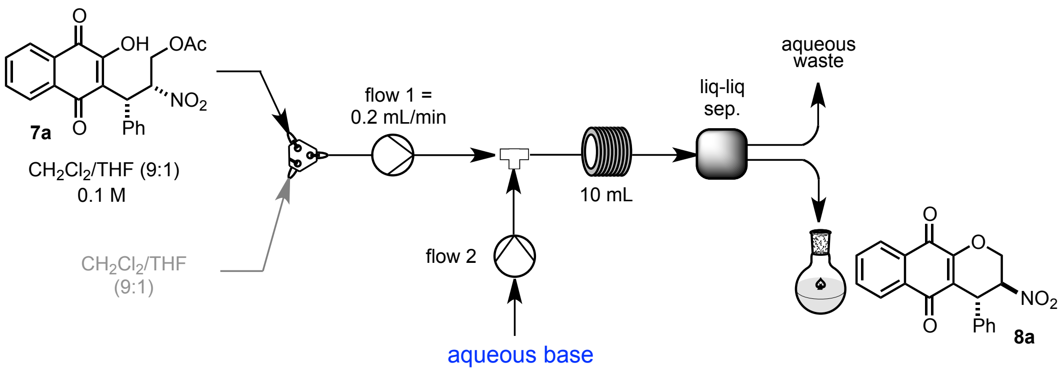
Screening of solvents

Solvent	Reaction time	Yield	dr	ee
CH_2Cl_2	*1 h*	*87%*	*>95:5*	*98%*
$CHCl_3$	1 h	90%	91:9	92%
DCE	1.5 h	73%	>95:5	98%
dioxane	2 h	67%	90:10	90%
toluene	5 h	77%	91:9	82%
THF	3 h	88%	>95:5	96%
EtOAc	3 h	89%	92:8	97%

Table S1

5. Optimization of the cyclization reaction in flow

A solution of Michael adduct **7a** in a 9:1 mixture of CH_2Cl_2/THF (0.1 M, flow 1 = 0.2 mL/min; HPLC pump AZURA P 4.1S from KNAUER) and the solution of aqueous base (flow 2; syringe pump Legato 200 from KDSCIENTIFIC) were mixed in a T-junction (PTFE). The reaction mixture was circulated through the coil (Ø = 0.8 mm, 10 mL, PTFE) at rt. The solution with the starting material was pumped for 2 min. After this time, the 3-position valve was switched to the reservoir of solvent (CH_2Cl_2/THF 9:1; Scheme S3) and it was passed through the system at equal flow rate. The organic phase at the outlet of the liquid-liquid separator was collected and evaporated under reduced pressure. Conversion was determined by ^1H NMR. Subsequently, new conditions were tested utilizing the same procedure (Table S2 and Table 3 main text).



Scheme S3

Screening of basic aqueous solutions for the cyclization reaction

Aqueous base	Flow 2 (mL/min)	Conversion	Notes
$NaHCO_3$	*0.45*	*100%*	–
Na_2CO_3	0.3	100%	A precipitate is formed.
Na_2CO_3/$NaHCO_3$ buffer pH = 9.3	0.3	13%	–
Na_3PO_4 (0.3 M)	0.3	100%	Only deprotonation (aqueous phase), no cyclized product observed.
Tris buffer pH = 8	0.3	50%	–
Na_2HPO_4 (0.35 M)	0.4	80%	–

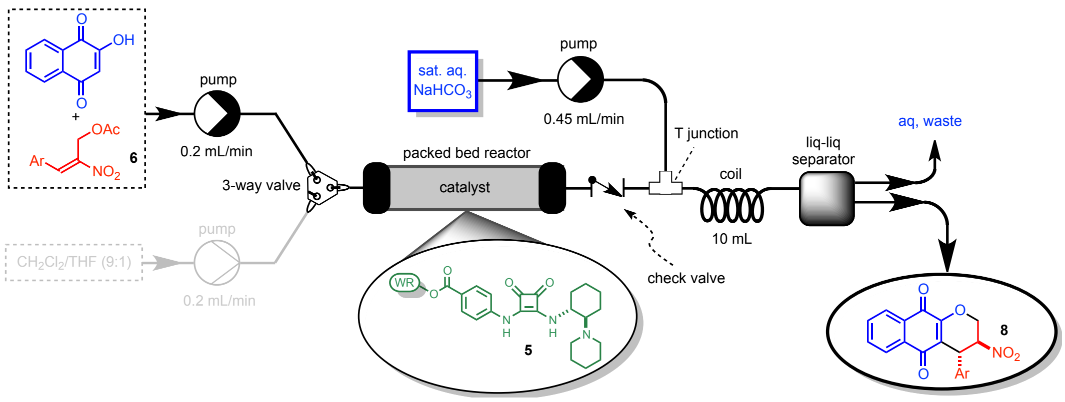
Table S2

6. Preparation of the library of enantioenriched pyranonaphthoquinones in flow (*GP1*)

Catalyst **5** (400 mg, 0.23 mmol) was introduced in a PTFE column (Ø = 3.9 mm diameter) and this was connected to the flow set-up depicted in Scheme S4. Then, the resin was swollen by circulating a mixture of CH_2Cl_2/THF 9:1 (HPLC pump AZURA P 4.1S from KNAUER).

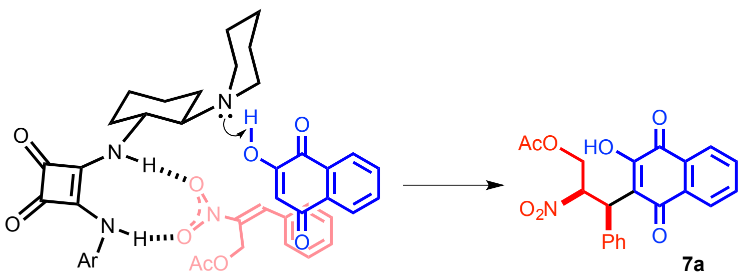
Solutions containing hydroxynaphthoquinone (1.1 mmol, 1.1 equiv.) and the corresponding nitroalkene (1 mmol, 1.0 equiv.) in CH_2Cl_2 (9 mL) and THF (1 mL) were sequentially circulated through the column (0.2 mL/min, syringe pump Legato 200 from KDSCIENTIFIC equipped with a gastight syringe from Hamilton, ca. 50 min for each run). A solution of sat. aq. $NaHCO_3$ was circulated downstream of the column to carry out the cyclization step in a 10-mL coil (0.45 mL/min, syringe pump as above equipped with plastic syringes). At the end, the biphasic mixture was separated with the aid of a liquid-liquid separator.

When each combination of reagents was consumed, the system was rinsed with the solvent mixture for 1 h (0.2 mL/min) to ensure all organic materials were collected before the next combination was introduced in the flow set-up.



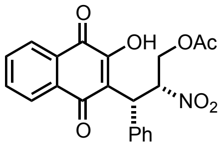
Scheme S4

7. Stereochemical model to account for the observed selectivity



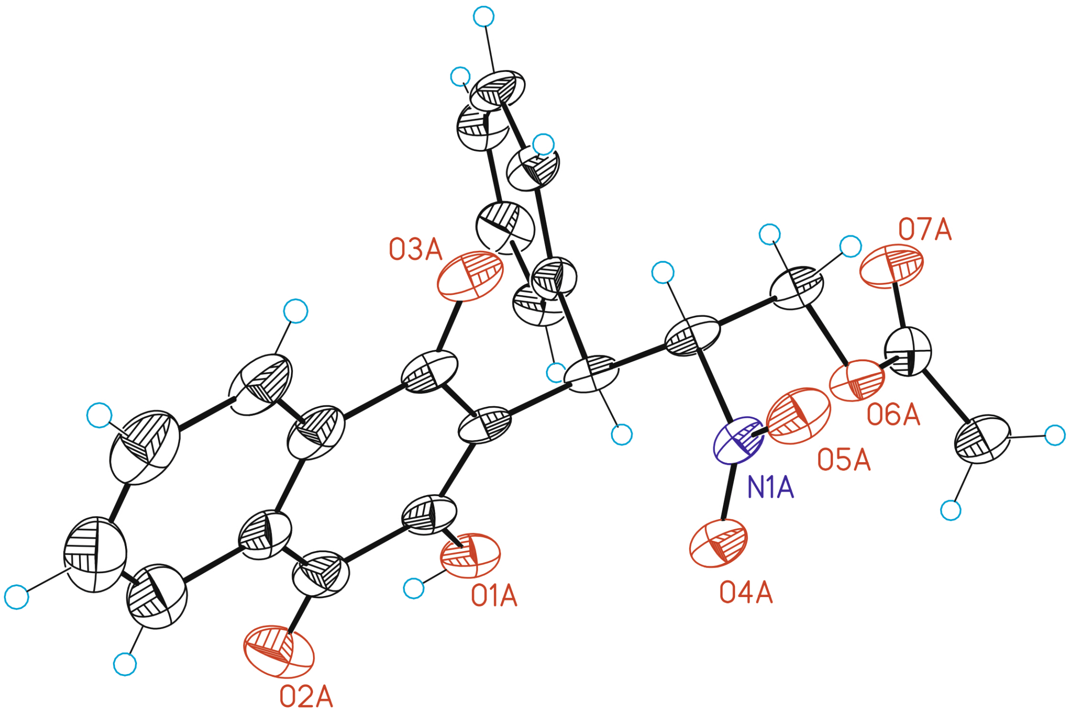
7a

8. Characterization of 7a



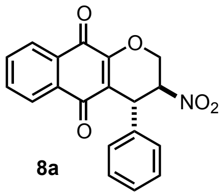
Orange foam; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 7.8, 1.3 Hz, 1H), 8.01 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.90 (br s, 1H), 7.74 (td, *J* = 7.6, 1.3 Hz, 1H), 7.65 (td, *J* = 7.6, 1.3 Hz, 1H), 7.57-7.53 (m, 2H), 7.35-7.30 (m, 2H), 7.29-7.24 (m, 1H), 6.30 (ddd, *J* = 12.0, 8.5, 2.9 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.47 (dd, *J* = 12.3, 2.9 Hz, 1H), 4.30 (dd, *J* = 12.3, 8.5 Hz, 1H), 2.06 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 188.3, 180.9, 170.0, 153.1, 136.1, 135.4, 133.3, 132.5, 129.3 (×2), 128.9 (×2), 128.8, 128.3, 127.2, 126.2, 120.0, 85.8, 63.6, 42.2, 20.5; **$[\alpha]^{25}_{D}$**: +23.4 (*c* 1.12, $CHCl_3$); **HRMS** (ESI+): *m/z* calcd. for $C_{21}H_{17}NNaO_7$ $[M+Na]^+$: 418.0897, found: 418.0904; **IR** (ATR): ν 1750, 1672, 1649, 1594, 1556, 1459, 1370, 1227 cm^{-1}; **HPLC** (Daicel Chiralpak IA column, Hx/CH_2Cl_2/EtOH/TFA 90:5:5:0.1; flow rate 1.0 mL/min, λ = 254 nm): t_R(maj) = 20.0 min; t_R(min) = 32.6 min.

The relative configuration of **7a** was determined by X-ray diffraction:



The corresponding CIF file has been deposed with the CCDC and has reference number 1456999.

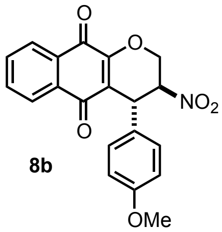
9. Characterization of compounds 8a-8g



8a

Compound **8a** was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene **6a** (0.221 g, 1.0 mmol) according to the General Procedure *GP1*. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 71% yield (0.237 g, 0.71 mmol), 87:13 dr and 98% ee.

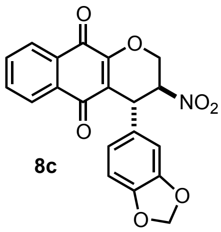
^{1}H and ^{13}C NMR data match with those reported in the literature.[4] **HPLC** (Daicel Chiralpak IC column, hexane/*i*-PrOH (75:25), flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 20.0 min; t_{minor} = 15.5 min.



8b

Compound **8b** was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene **6b** (0.251 g, 1.0 mmol) according to the General Procedure *GP1*. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 83% yield (0.300 g, 0.83 mmol), 85:15 dr and 97% ee.

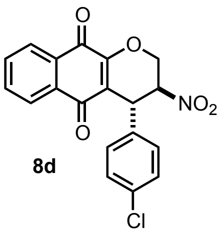
^{1}H and ^{13}C NMR data match with those reported in the literature.[4] **HPLC** (Daicel Chiralpak IA column, hexane/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 51.2 min; t_{minor} = 10.0 min.



8c

Compound **8c** was prepared in flow from hydroxynaphthoquinone (0.163 g, 0.94 mmol) and nitroalkene **6c** (0.225 g, 0.85 mmol) according to the General Procedure *GP1*. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 74% yield (0.239 g, 0.63 mmol), 87:13 dr and 97% ee.

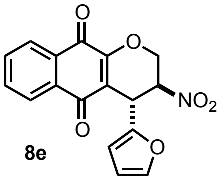
^{1}H and ^{13}C NMR data match with those reported in the literature.[4] **HPLC** (Daicel Chiralpak IA column, hexane/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 52.9 min; t_{minor} = 12.3 min.



8d

Compound **8d** was prepared in flow from hydroxynaphthoquinone (0.176 g, 1.01 mmol) and nitroalkene **6d** (0.235 g, 0.92 mmol) according to the General Procedure *GP1*. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 80% yield (0.273 g, 0.74 mmol), 92:8 dr and 96% ee.

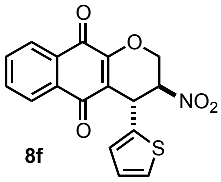
^{1}H and ^{13}C NMR data match with those reported in the literature.[4] **HPLC** (Daicel Chiralpak IA column, hexane/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 46.1 min; t_{minor} = 9.1 min.



8e

Compound **8e** was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene **6e** (0.211 g, 1.0 mmol) according to the General Procedure *GP1*. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 62% yield (0.203 g, 0.62 mmol), 84:16 dr and 97% ee.

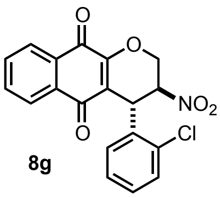
^{1}H and ^{13}C NMR data match with those reported in the literature.[4] **[α]**$^{25}_{D}$: +103 (*c* 1.00, $CHCl_3$); **HPLC** (Daicel Chiralpak IA column, hexane/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 19.5 min; t_{minor} = 8.1 min.



8f

Compound **8f** was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene **6f** (0.227 g, 1.0 mmol) according to the General Procedure *GP1*. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 65% yield (0.223 g, 0.65 mmol), 78:22 dr and 98% ee.

^{1}H and ^{13}C NMR data match with those reported in the literature.[4] **HPLC** (Daicel Chiralpak IA column, hexane/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 31.7 min; t_{minor} = 8.9 min.



8g

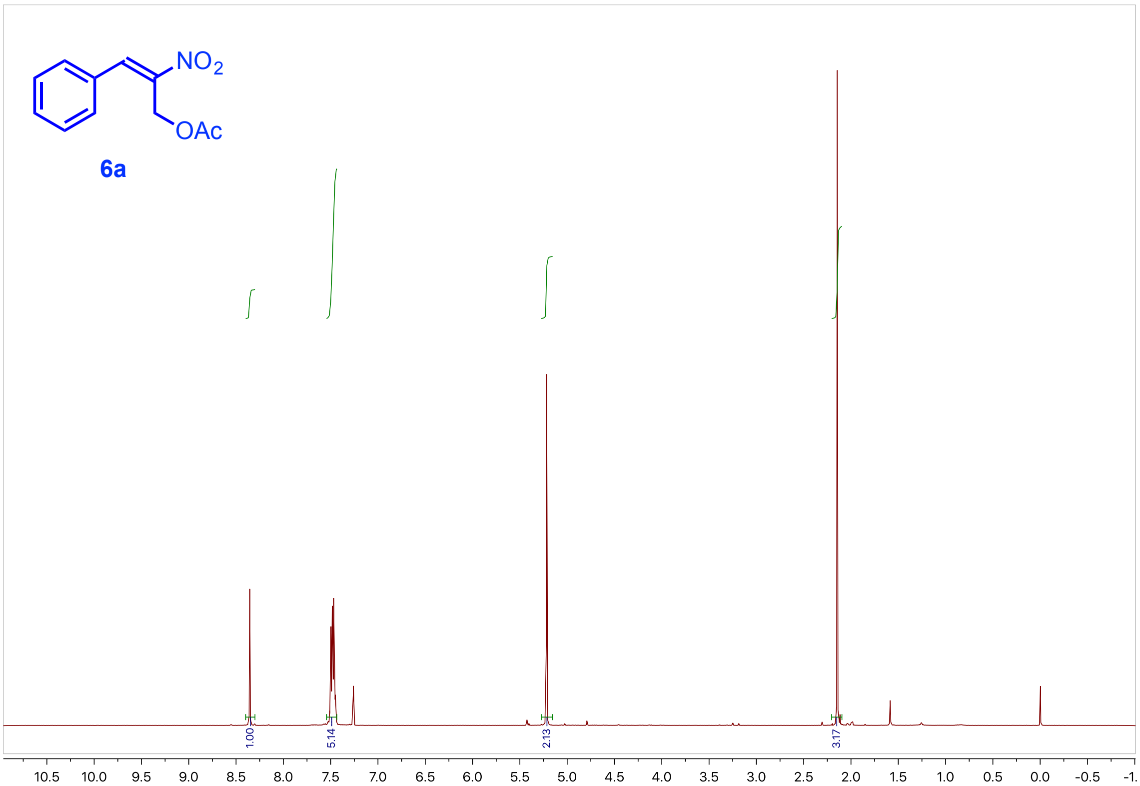
Compound **8g** was prepared in flow from hydroxynaphthoquinone (0.192 g, 1.1 mmol) and nitroalkene **6g** (0.256 g, 1.0 mmol) according to the General Procedure *GP1*. The desired product was obtained after flash chromatography on silica gel (cyclohexane/EtOAc, 90:10 to 70:30) in 81% yield (0.299 g, 0.81 mmol), >99:1 dr and 98% ee.

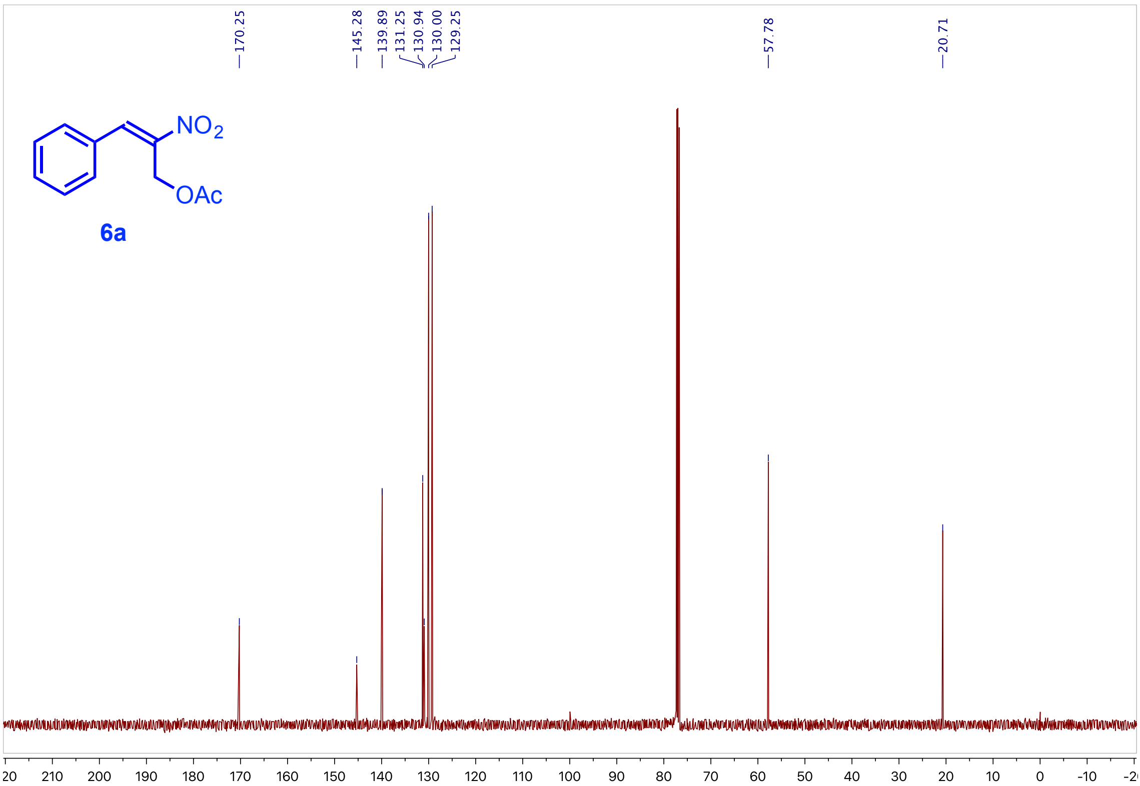
^{1}H and ^{13}C NMR data match with those reported in the literature.[4] **HPLC** (Daicel Chiralpak IA column, hexane/*i*-PrOH (70:30), flow rate 1.0 mL/min, λ = 254 nm): t_{major} = 30.8 min; t_{minor} = 8.8 min.

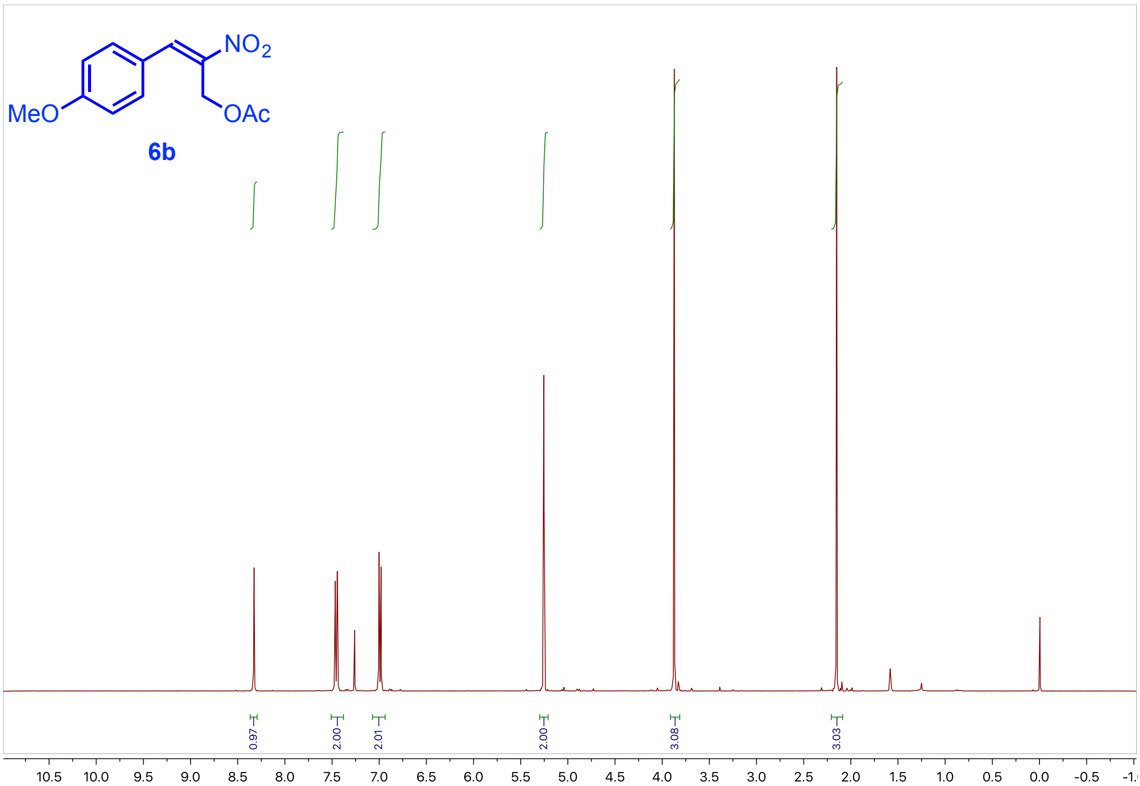
---

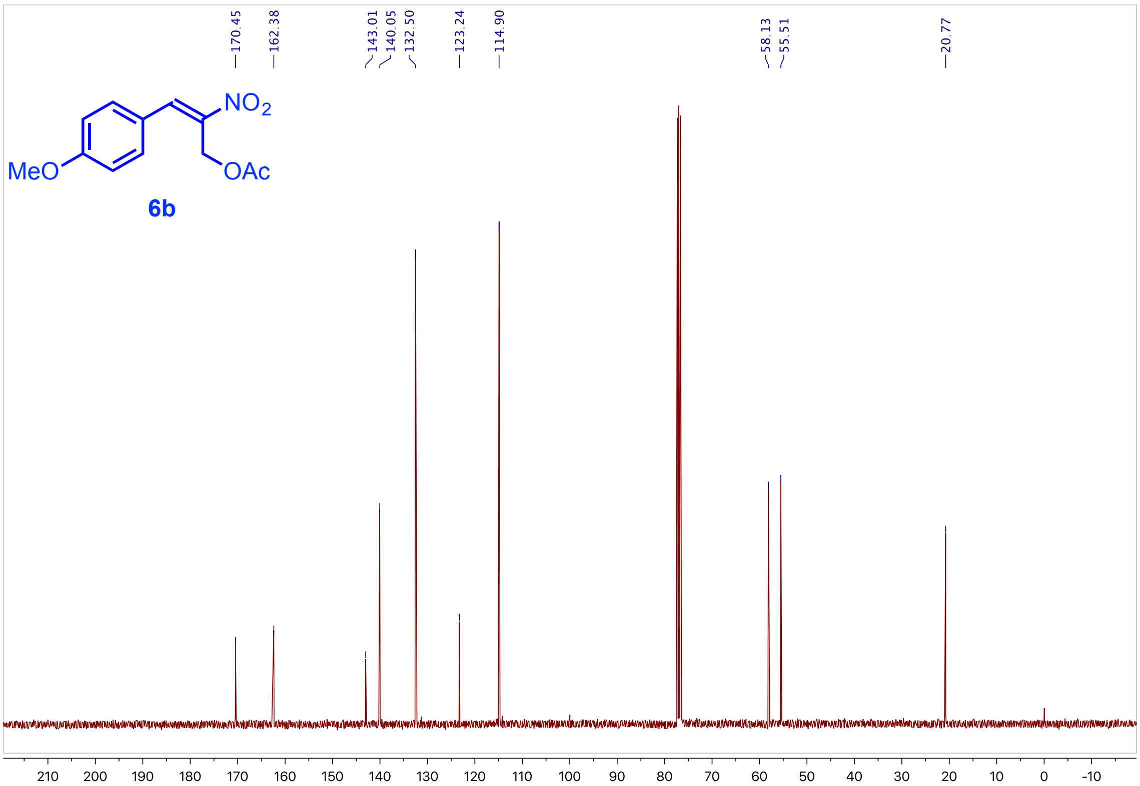
1. C.-L. Cao, Y.-Y. Zhou, J. Zhou, X.-L. Sun, Y. Tang, Y.-X. Li, G.-Y. Li and J. Sun, *Chem. Eur. J.*, 2009, **15**, 11384-11389.
2. Y. Zhu, J. P. Malerich and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2010, **49**, 153-156.
3. C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo and P. Melchiorre, *Nat. Protocols*, 2013, **8**, 325-344.
4. D. K. Nair, R. F. S. Menna-Barreto, E. N. da Silva Junior, S. M. Mobin and I. N. N. Namboothiri, *Chem. Commun.*, 2014, **50**, 6973-6976.

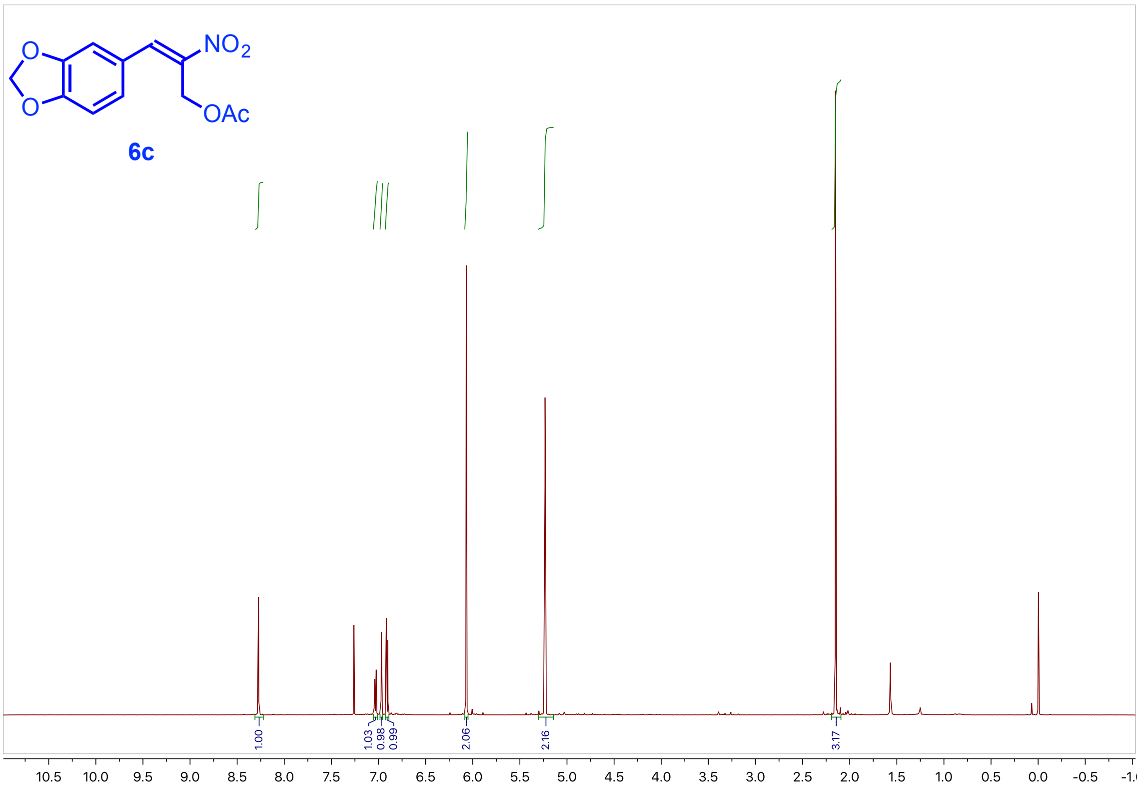
10. ^{1}H and ^{13}C NMR spectra

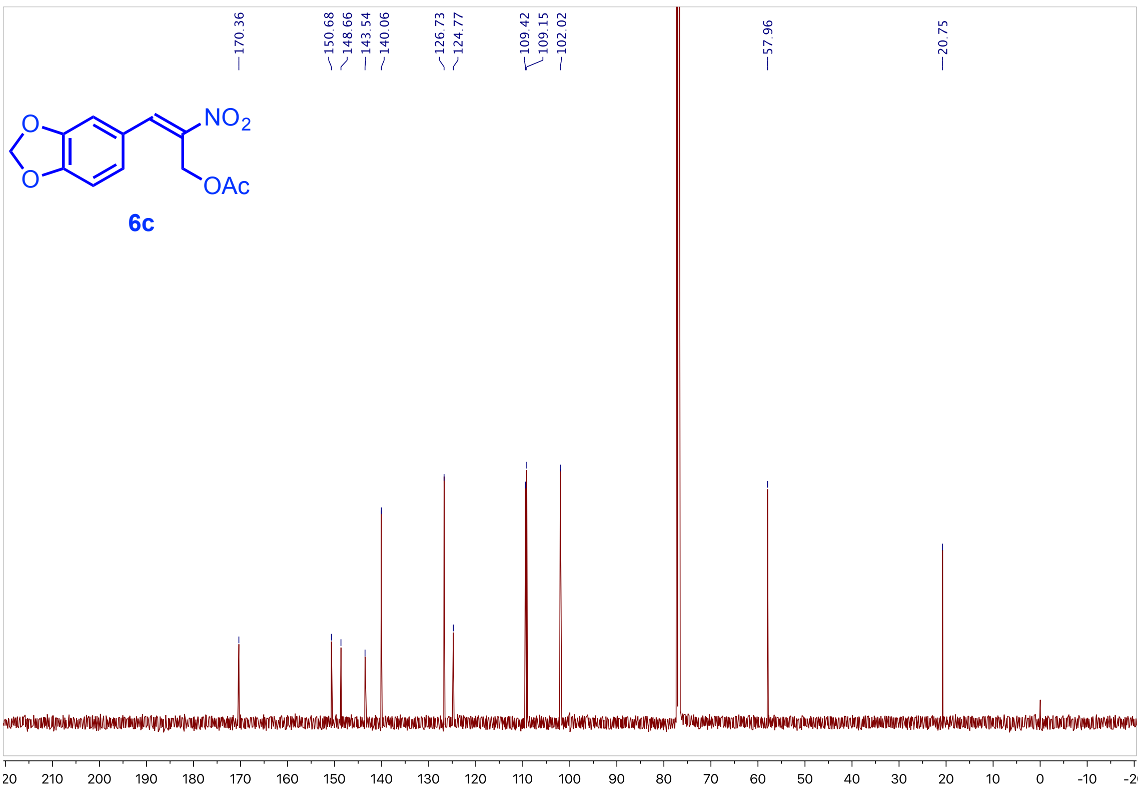


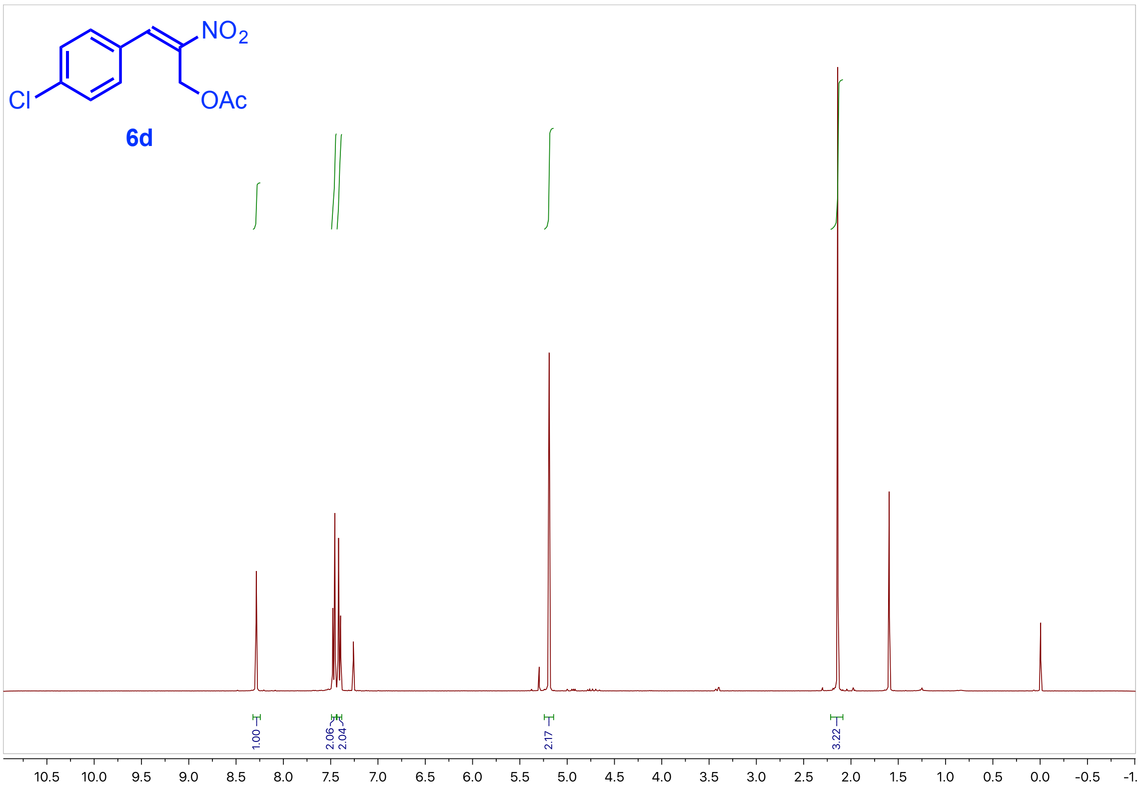


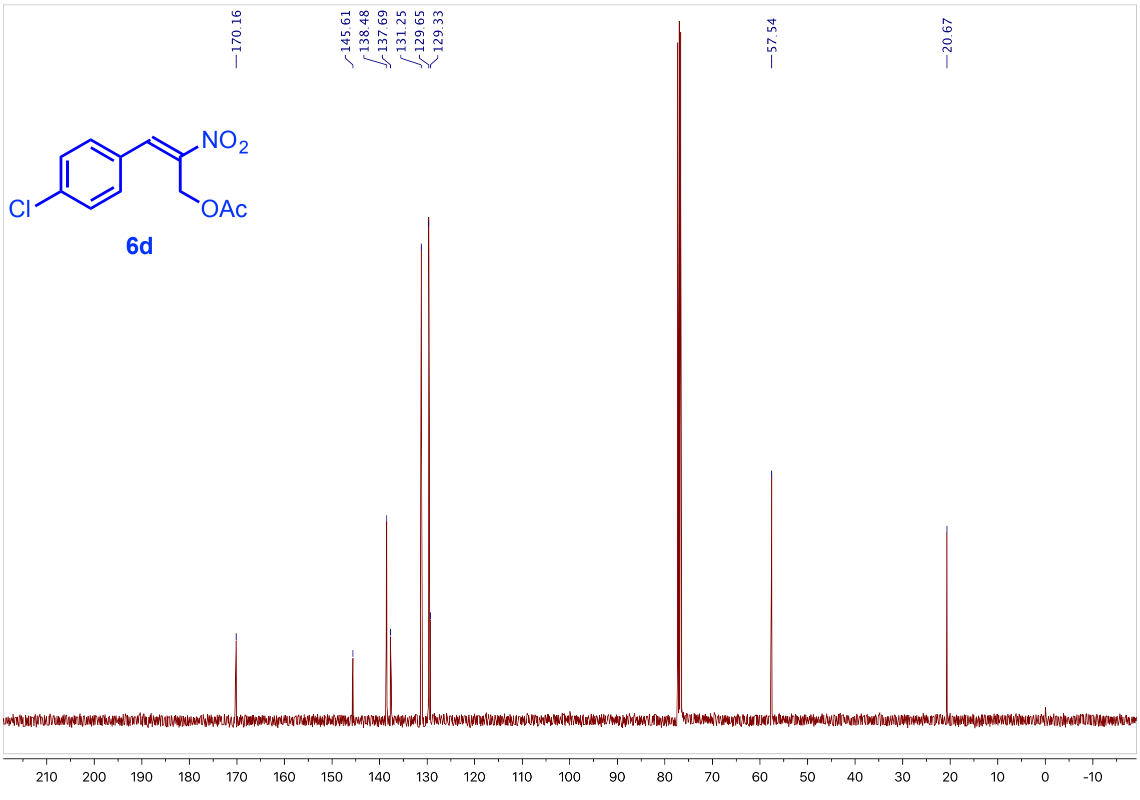

NO2
MeO
OAc
6b
0.97
2.00
2.01
2.00
3.08
3.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

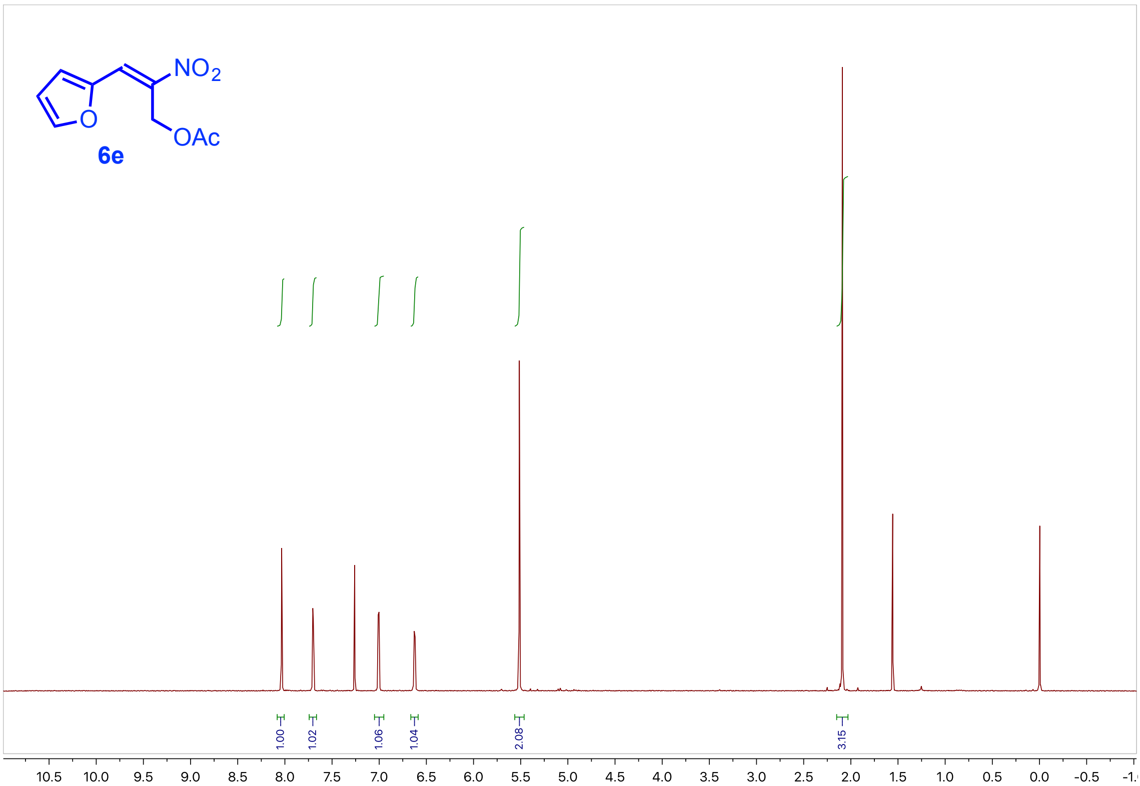

170.45
162.38
143.01
140.05
132.50
123.24
114.90
58.13
55.51
20.77
NO2
MeO
OAc
6b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

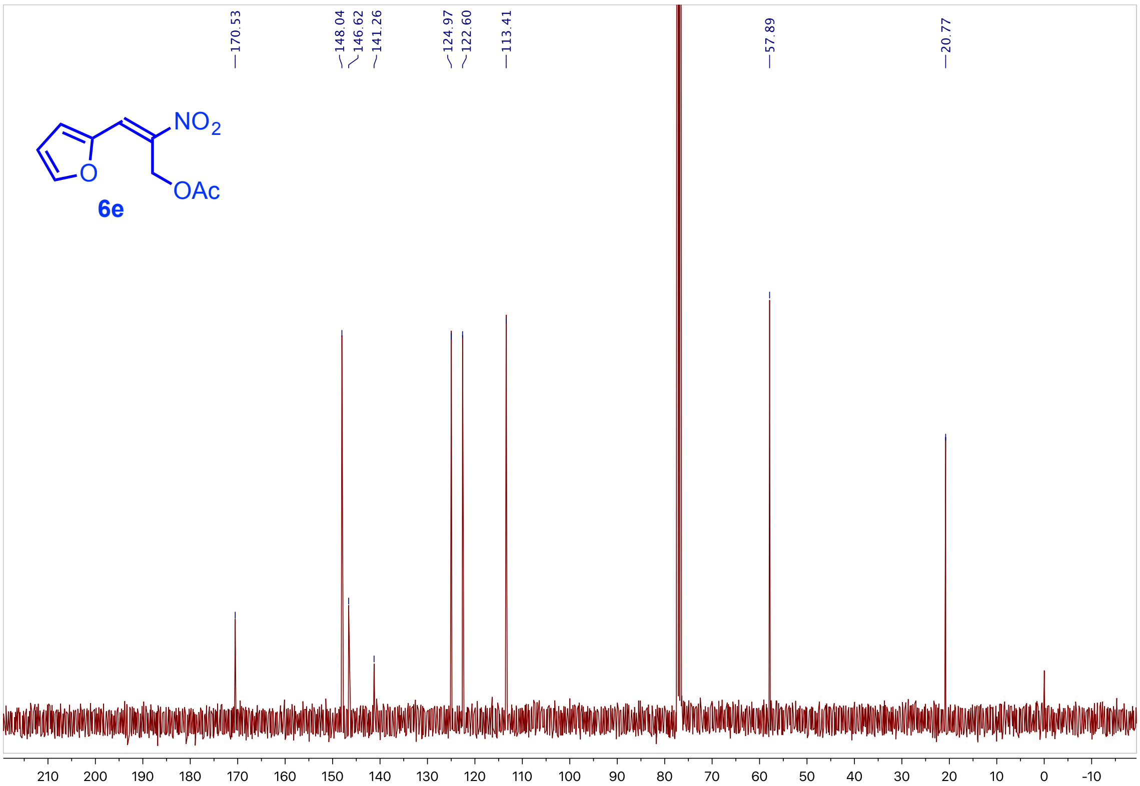

NO2
OAc
6c
1.00
1.03
0.98
0.99
2.06
2.16
3.17
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

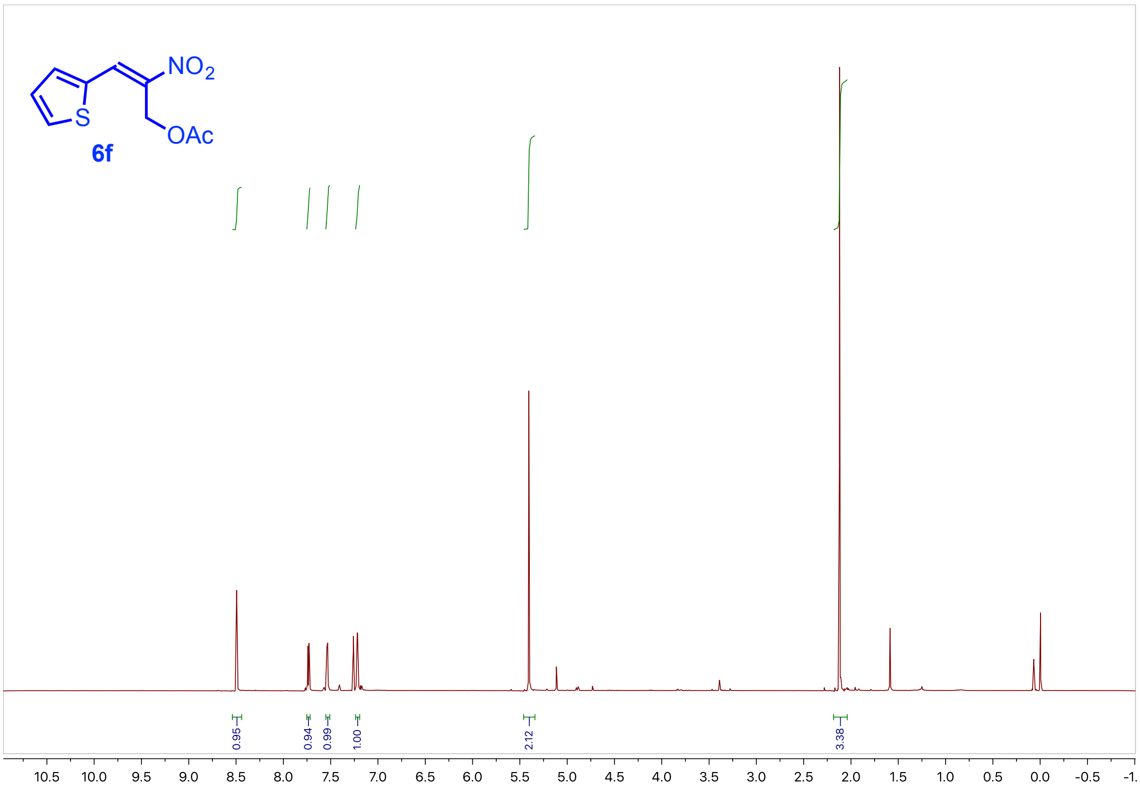

170.36
150.68
148.66
143.54
140.06
126.73
124.77
109.42
109.15
102.02
57.96
20.75
NO2
OAc
6c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

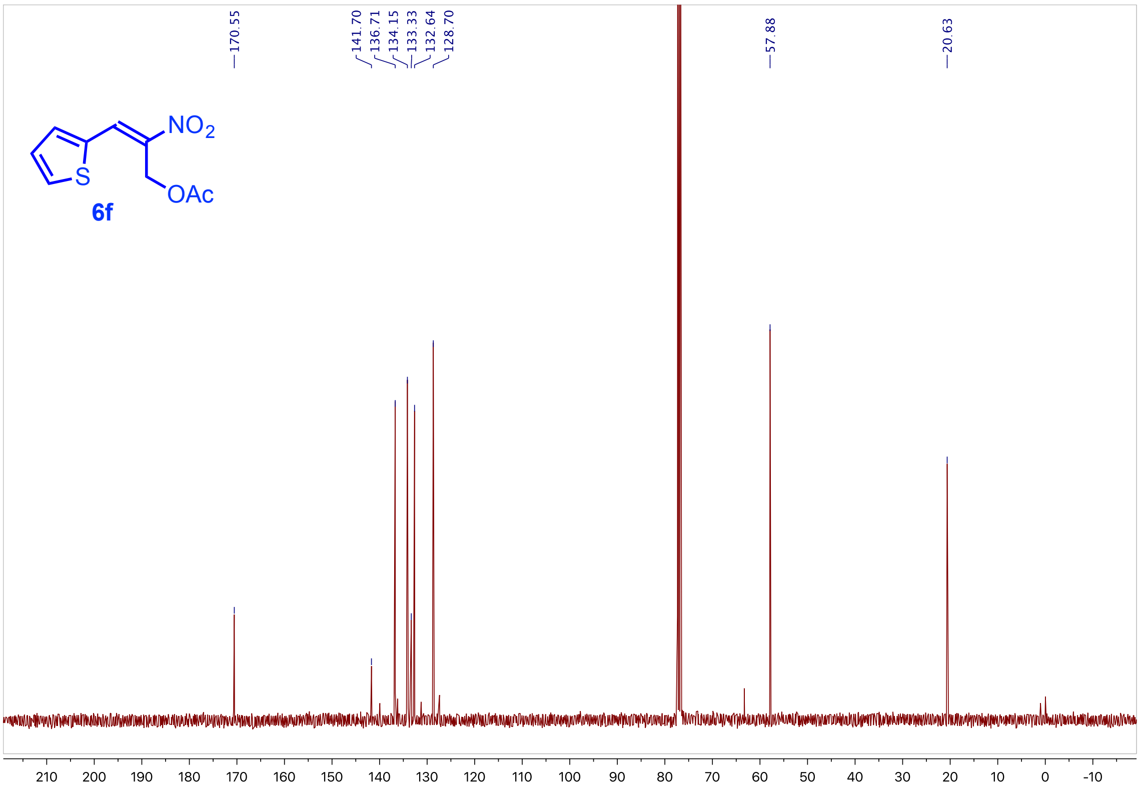

NO2
Cl
OAc
6d
1.00
2.06
2.04
2.17
3.22
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

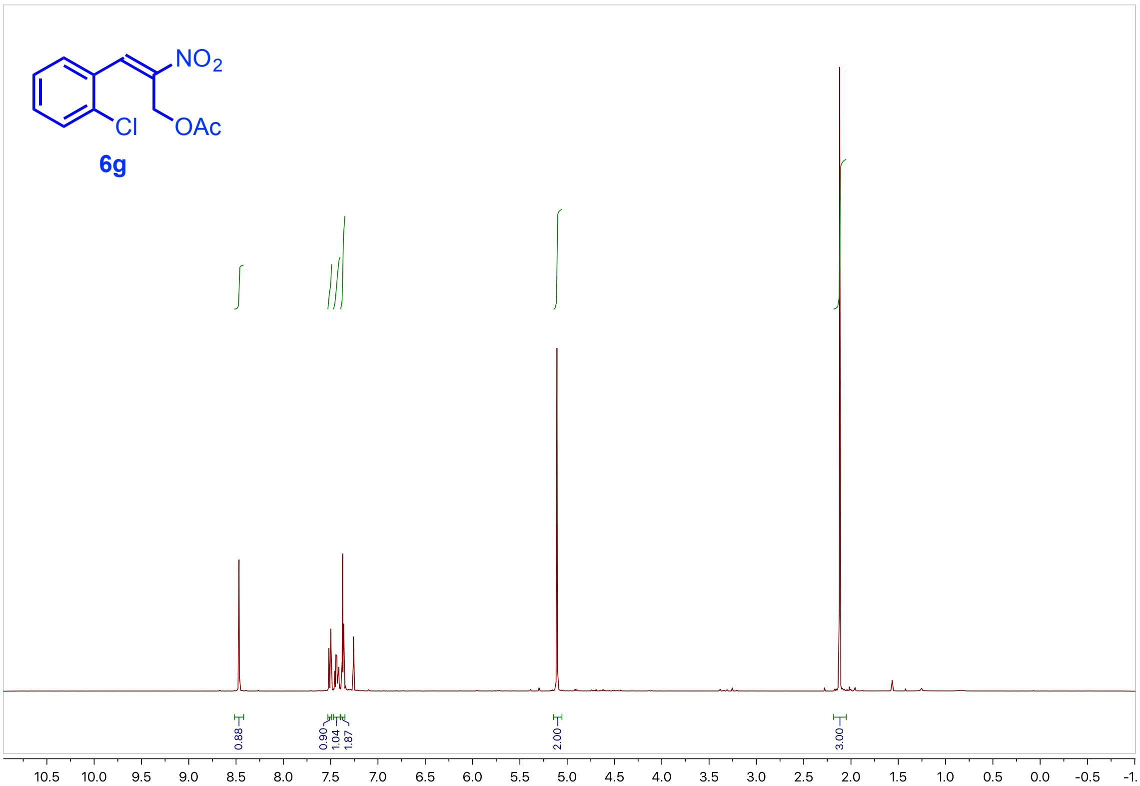

170.16
145.61
138.48
137.69
131.25
129.65
129.33
57.54
20.67
NO2
Cl
OAc
6d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

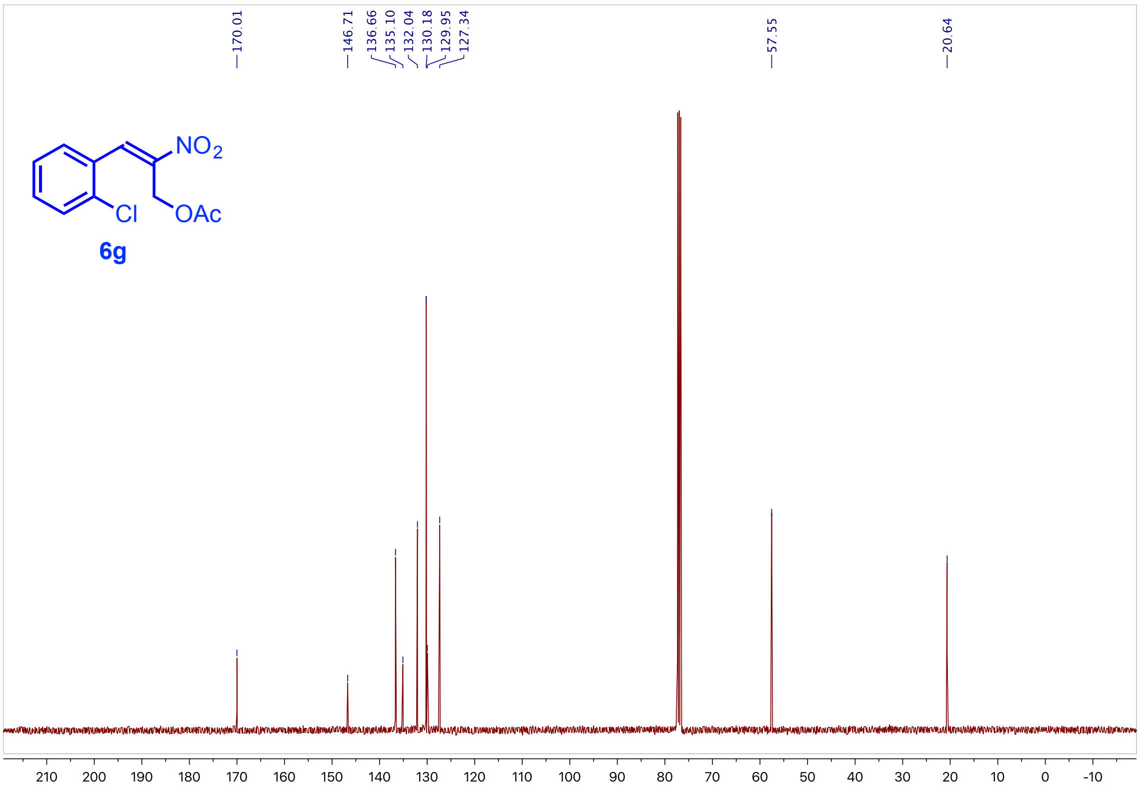

NO2
OAc
6e
1.00
1.02
1.06
1.04
2.08
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

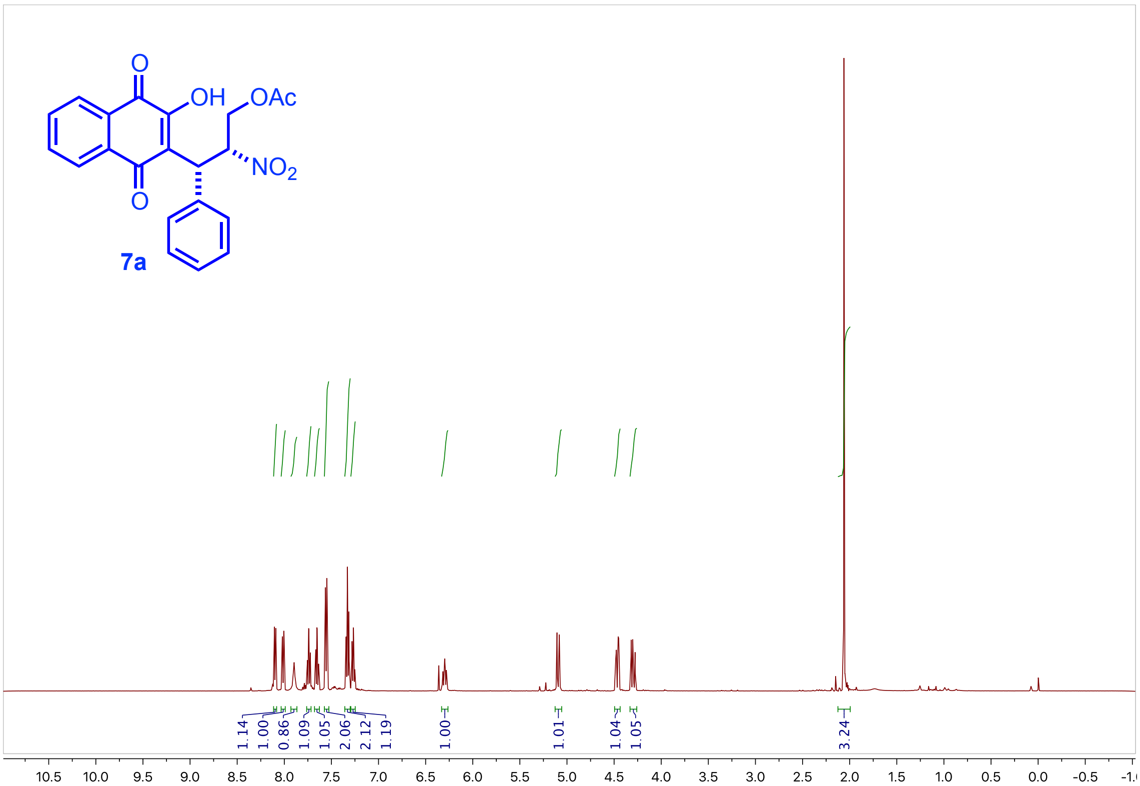

170.53
148.04
146.62
141.26
124.97
122.60
113.41
57.89
20.77
NO2
OAc
6e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

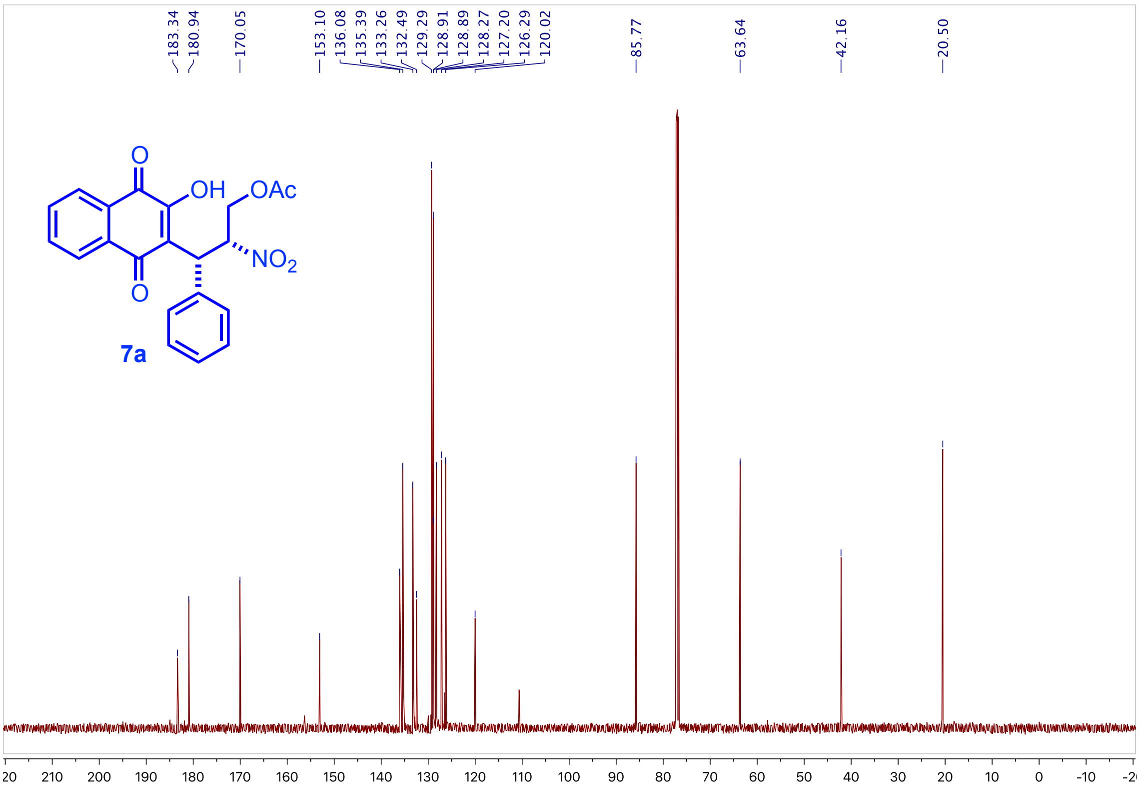


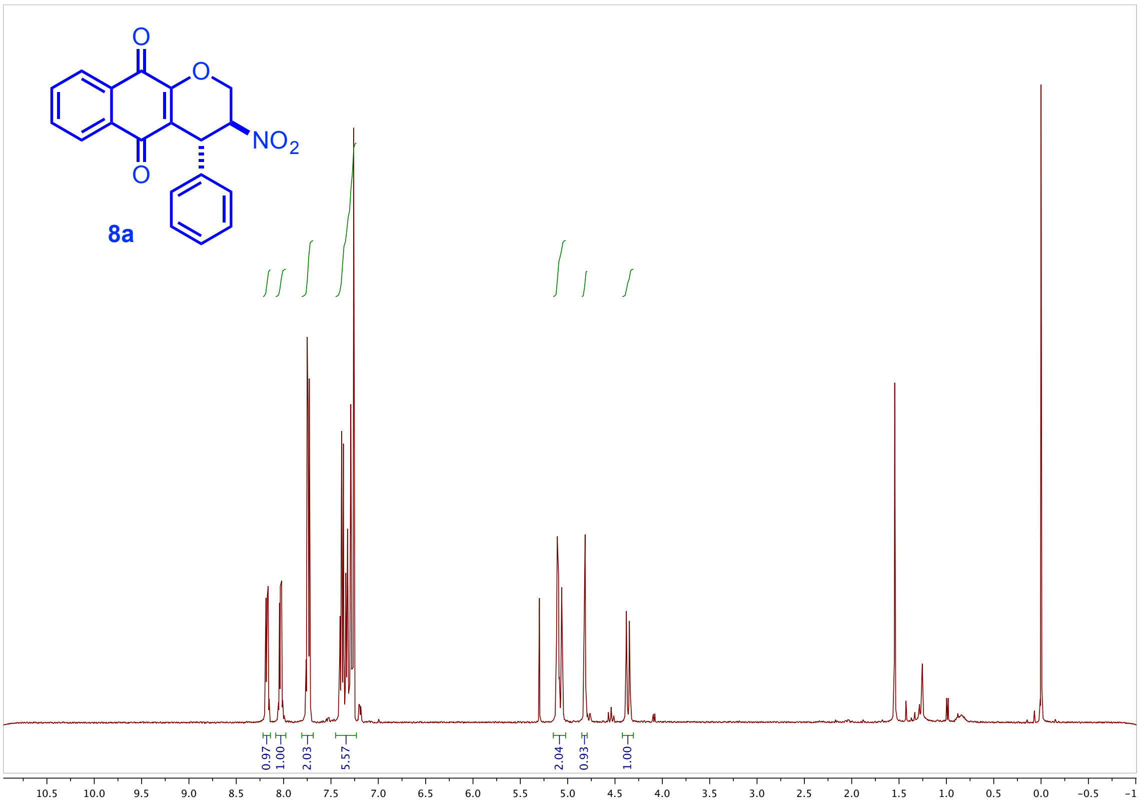


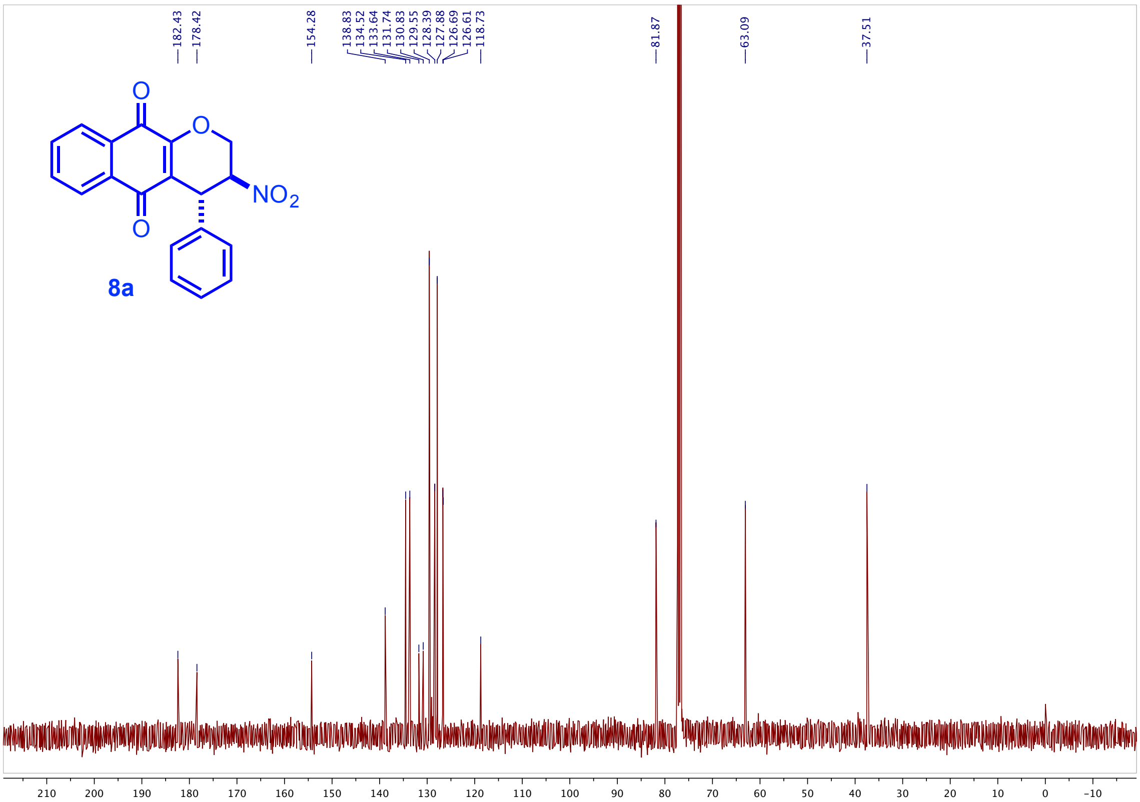

NO2
Cl
OAc
6g
0.88
0.90
1.04
1.87
2.00
3.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

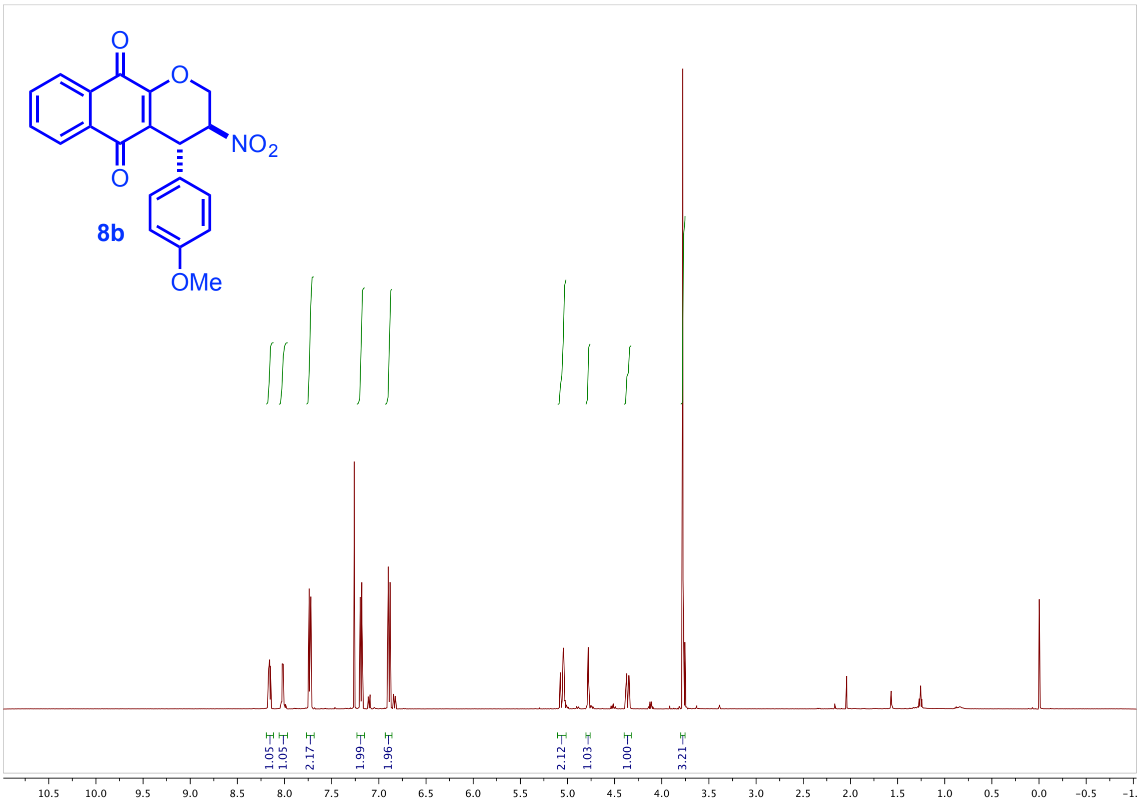

170.01
146.71
136.66
135.10
132.04
130.18
129.95
127.34
57.55
20.64
NO2
Cl
OAc
6g
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

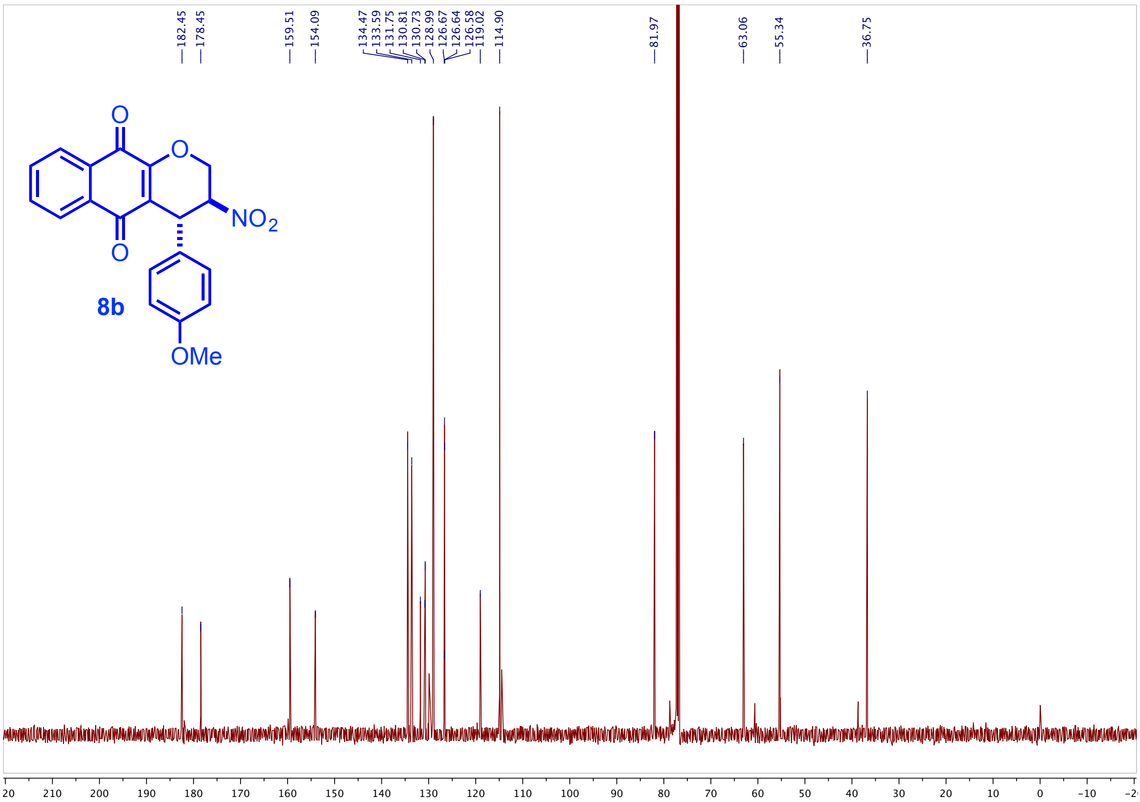

OH
OAc
NO2
O
O
7a
1.14
1.00
0.86
1.09
1.05
2.06
2.12
1.19
1.00
1.01
1.04
1.05
3.24
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

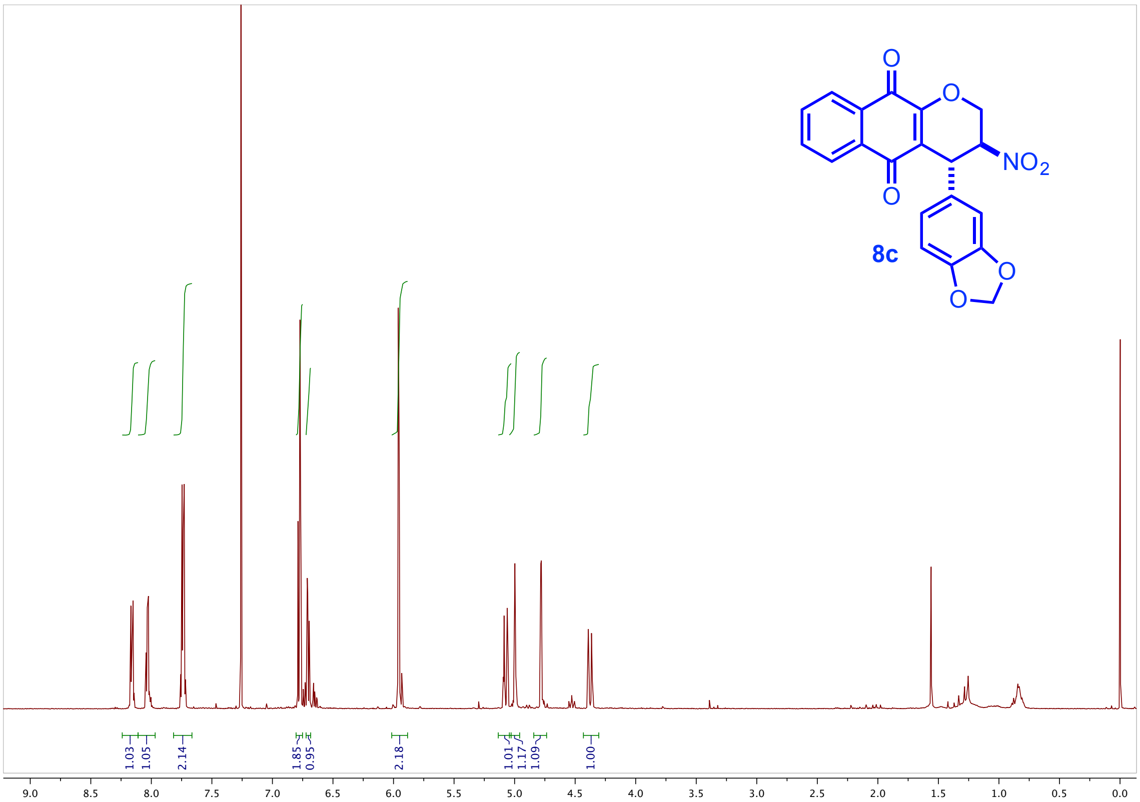

183.34
180.94
170.05
153.10
136.08
135.39
133.26
132.49
129.29
128.91
128.89
128.27
127.20
126.29
120.02
85.77
63.64
42.16
20.50
OH
OAc
NO2
O
O
7a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

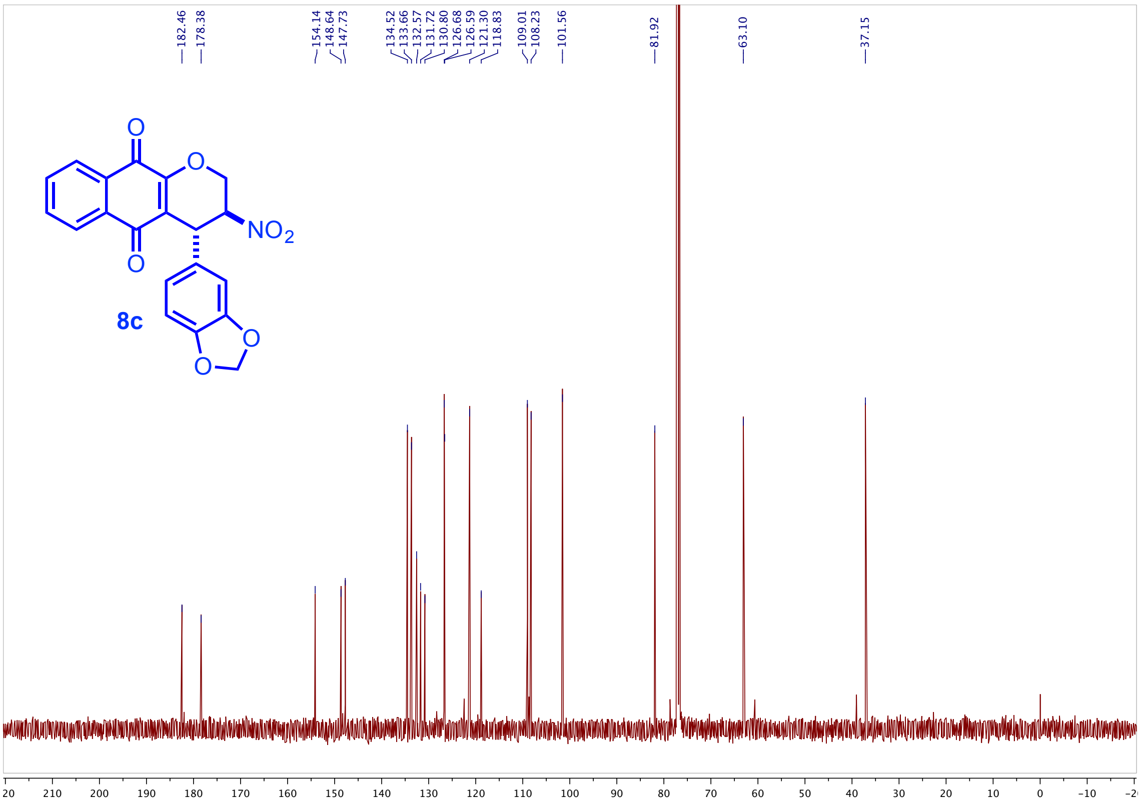

NO2
8a
0.97
1.00
2.03
5.57
2.04
0.93
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

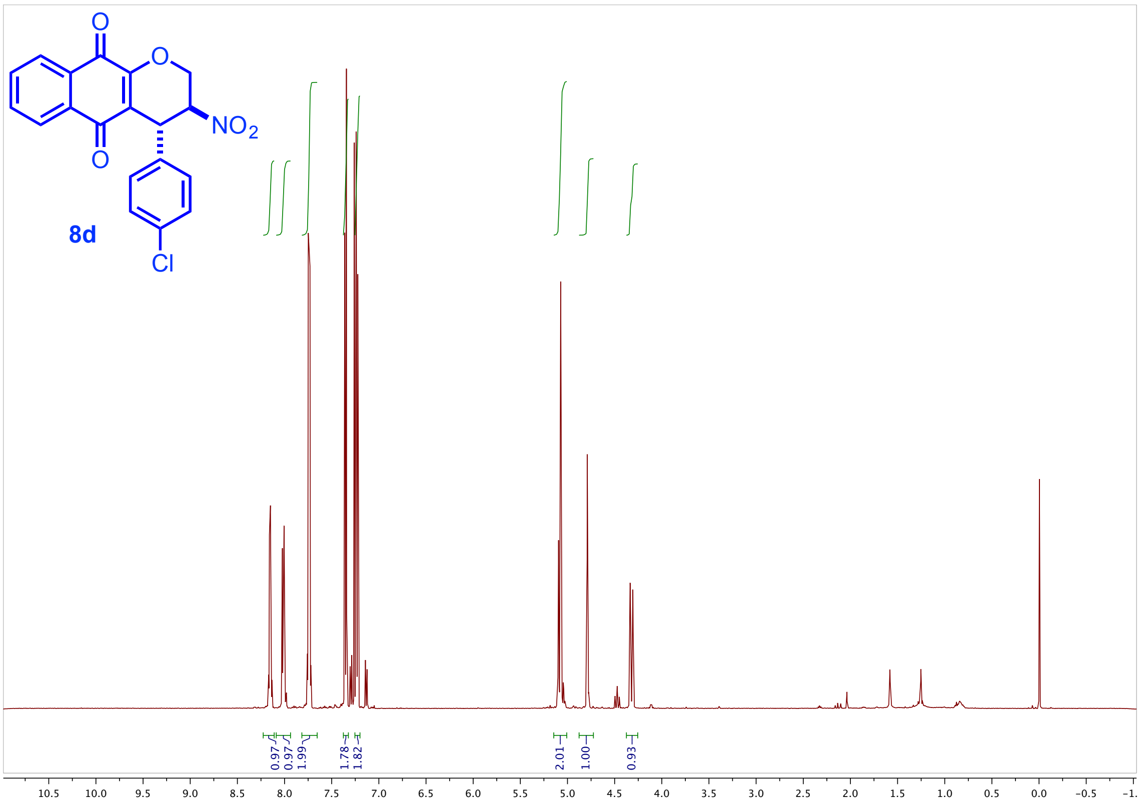

182.43
178.42
154.28
138.83
134.52
133.64
131.74
130.83
129.55
128.39
127.88
126.69
126.61
118.73
81.87
63.09
37.51
NO2
8a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

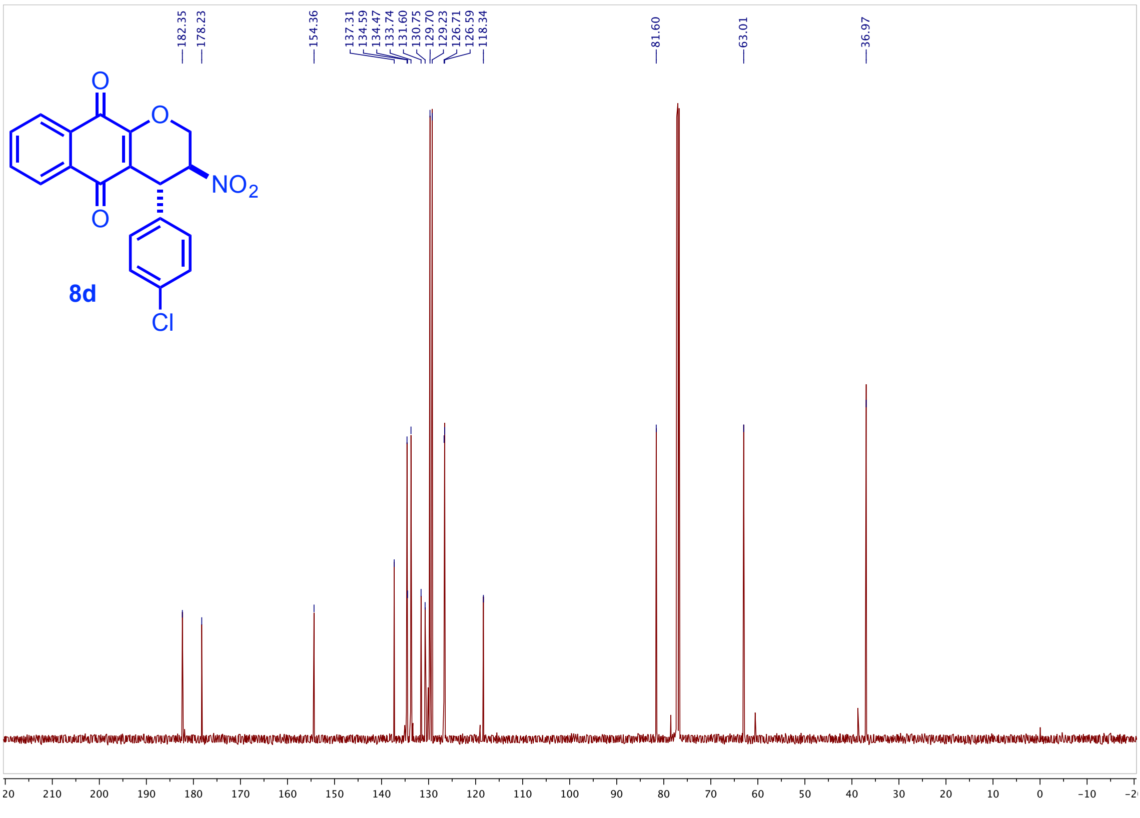

NO2
8b
OMe
1.05
1.05
2.17
1.99
1.96
2.12
1.03
1.00
3.21
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

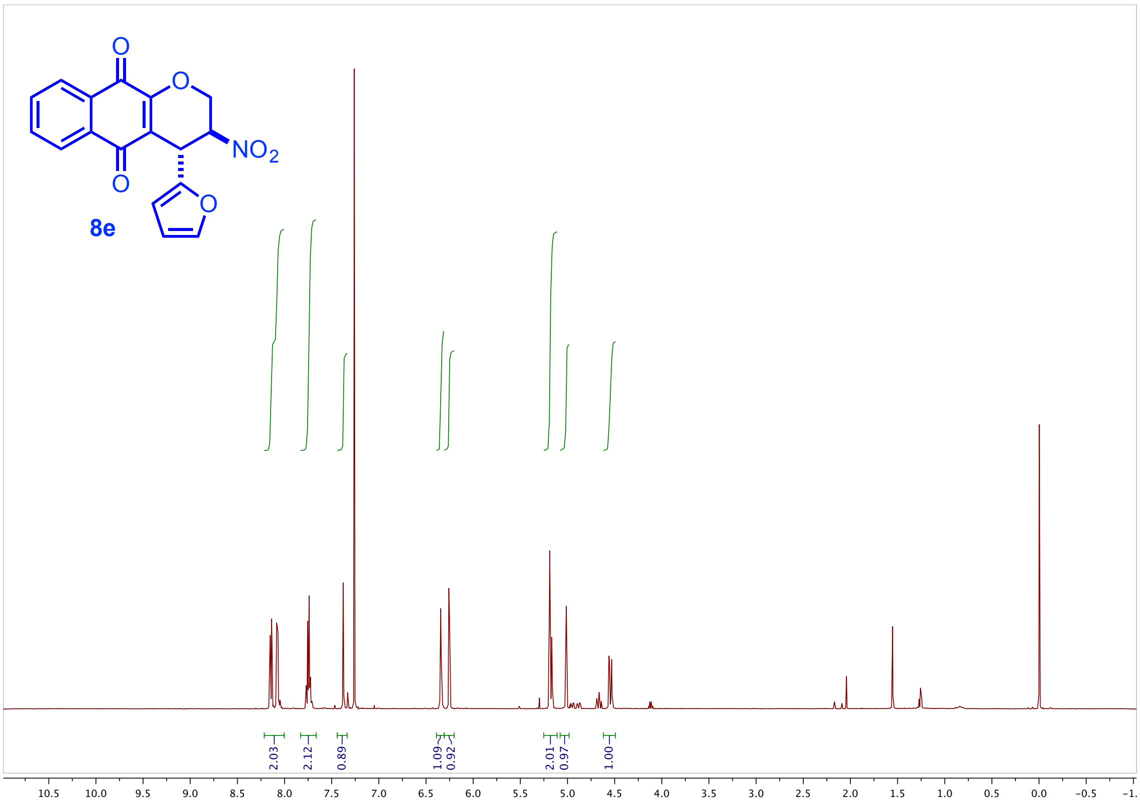

182.45
178.45
159.51
154.09
134.47
133.59
131.75
130.81
130.73
128.99
126.67
126.64
126.58
119.02
114.90
81.97
63.06
55.34
36.75
NO2
8b
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

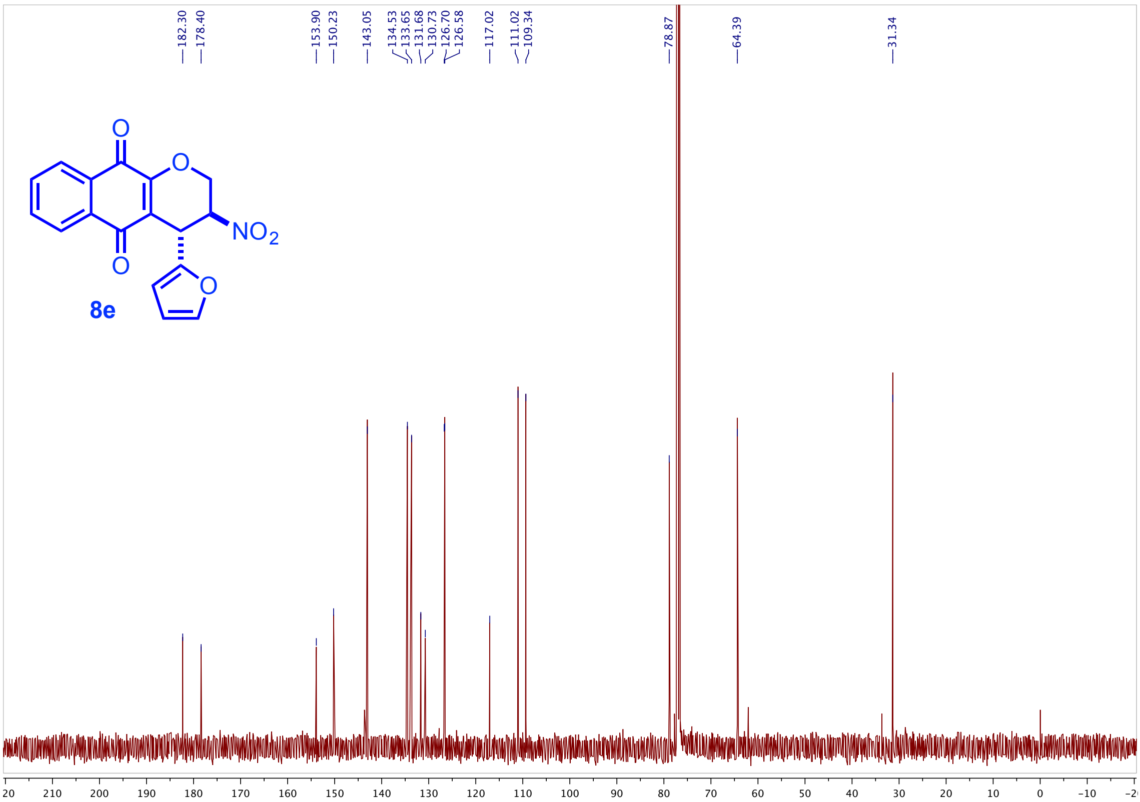

8c
1.03
1.05
2.14
1.85
0.95
2.18
1.01
1.17
1.09
1.00

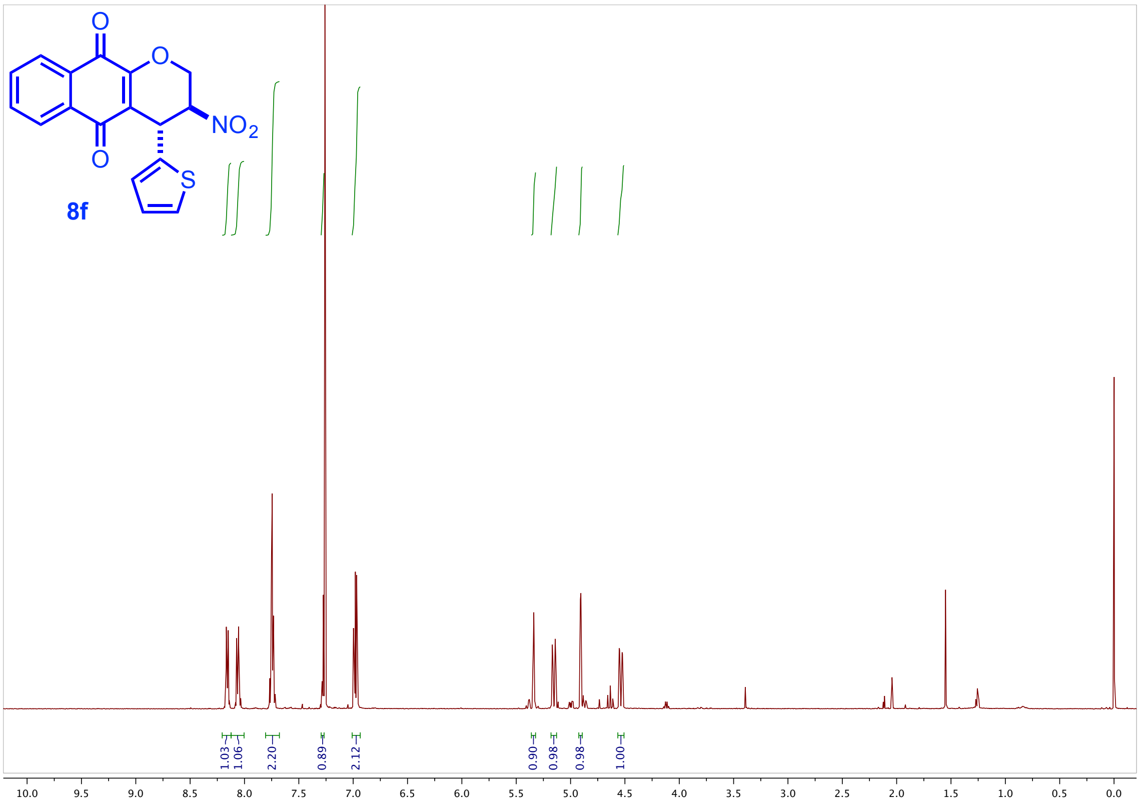

182.46
178.38
154.14
148.64
147.73
134.52
133.66
132.57
131.72
130.80
126.68
126.59
121.30
118.83
109.01
108.23
101.56
81.92
63.10
37.15
8c

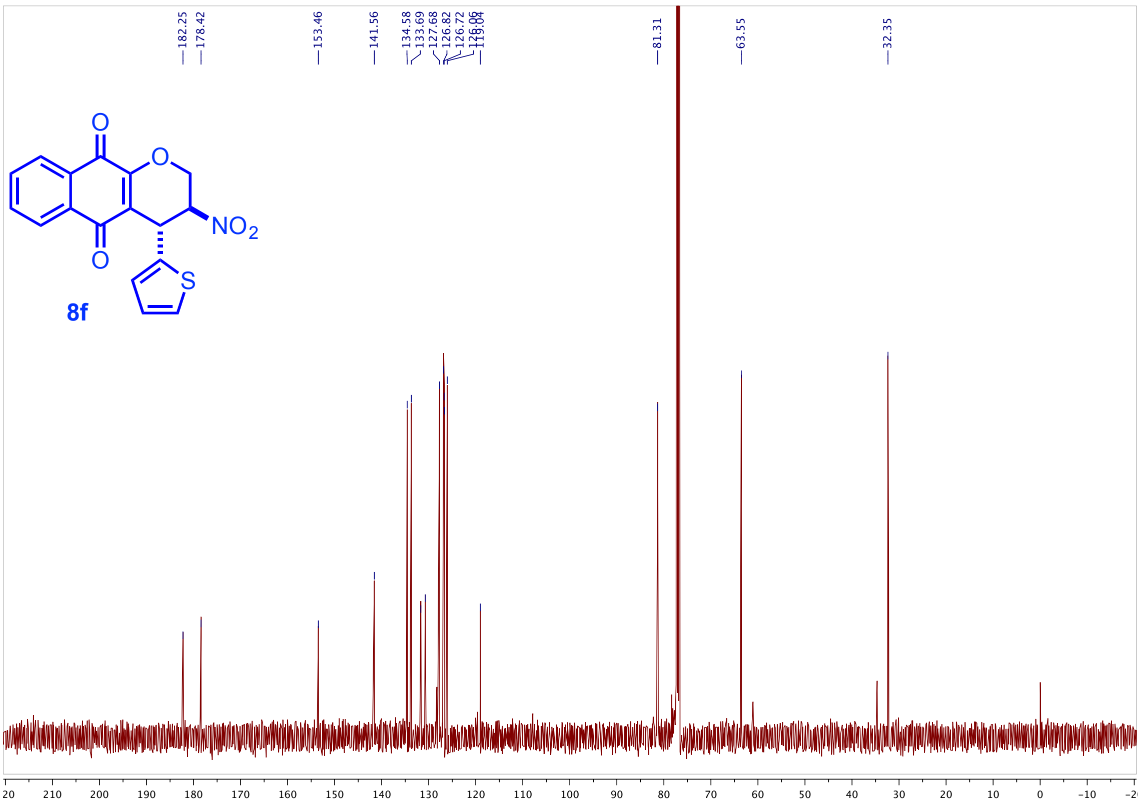

8d
NO2
Cl
0.97
0.97
1.99
1.78
1.82
2.01
1.00
0.93

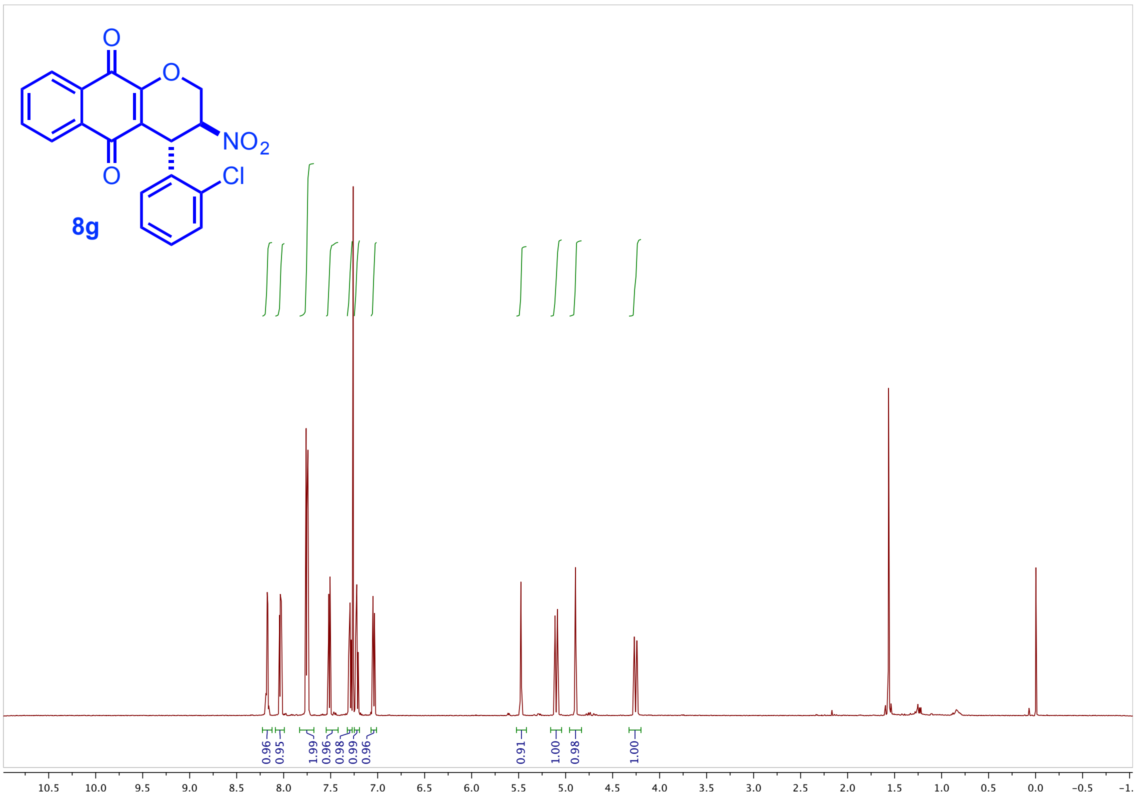

8d
182.35
178.23
154.36
137.31
134.59
134.47
133.74
131.60
130.75
129.70
129.23
126.71
126.59
118.34
81.60
63.01
36.97

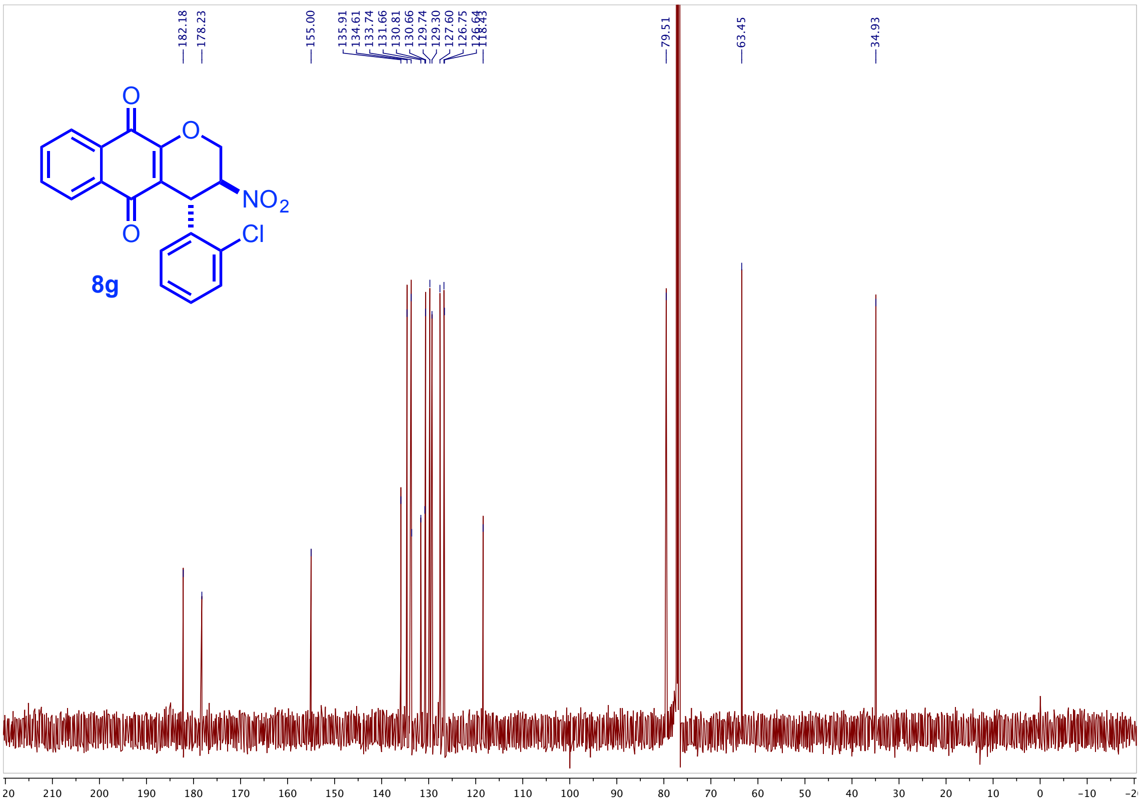

NO2
O
8e
2.03
2.12
0.89
1.09
0.92
2.01
0.97
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


182.30
178.40
153.90
150.23
143.05
134.53
133.65
131.68
130.73
126.70
126.58
117.02
111.02
109.34
78.87
64.39
31.34
NO2
O
8e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

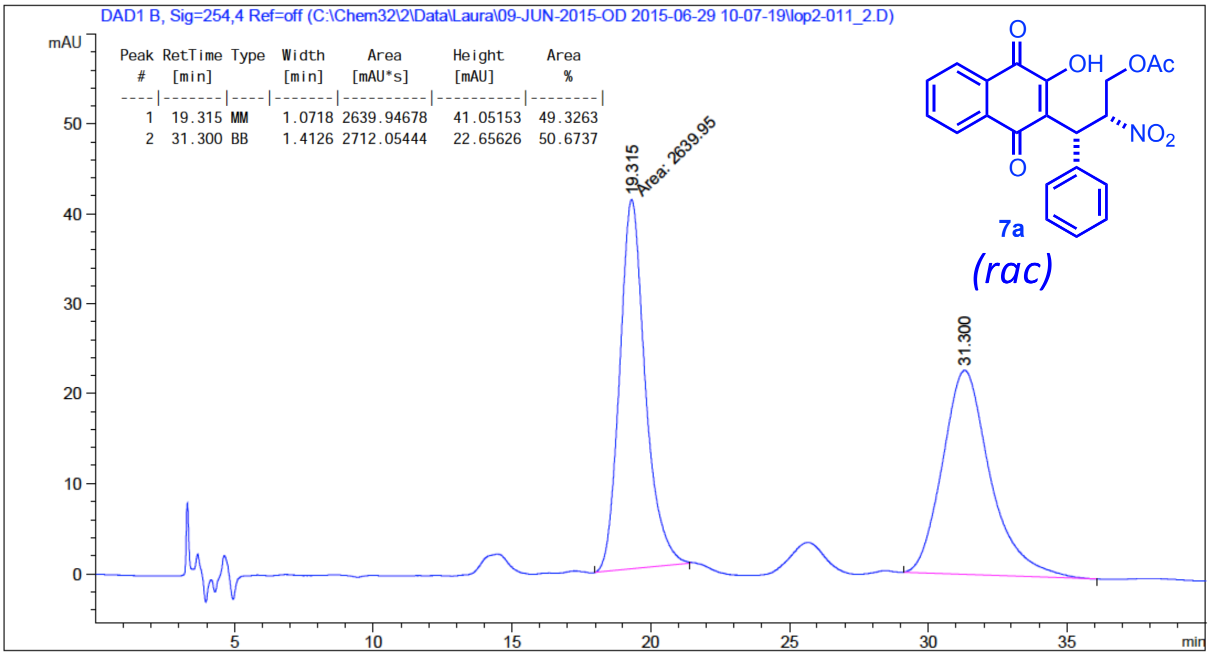

8f
NO2
1.03
1.06
2.20
0.89
2.12
0.90
0.98
0.98
1.00


8f
NO2
182.25
178.42
153.46
141.56
134.58
133.69
127.68
126.82
126.72
119.04
81.31
63.55
32.35

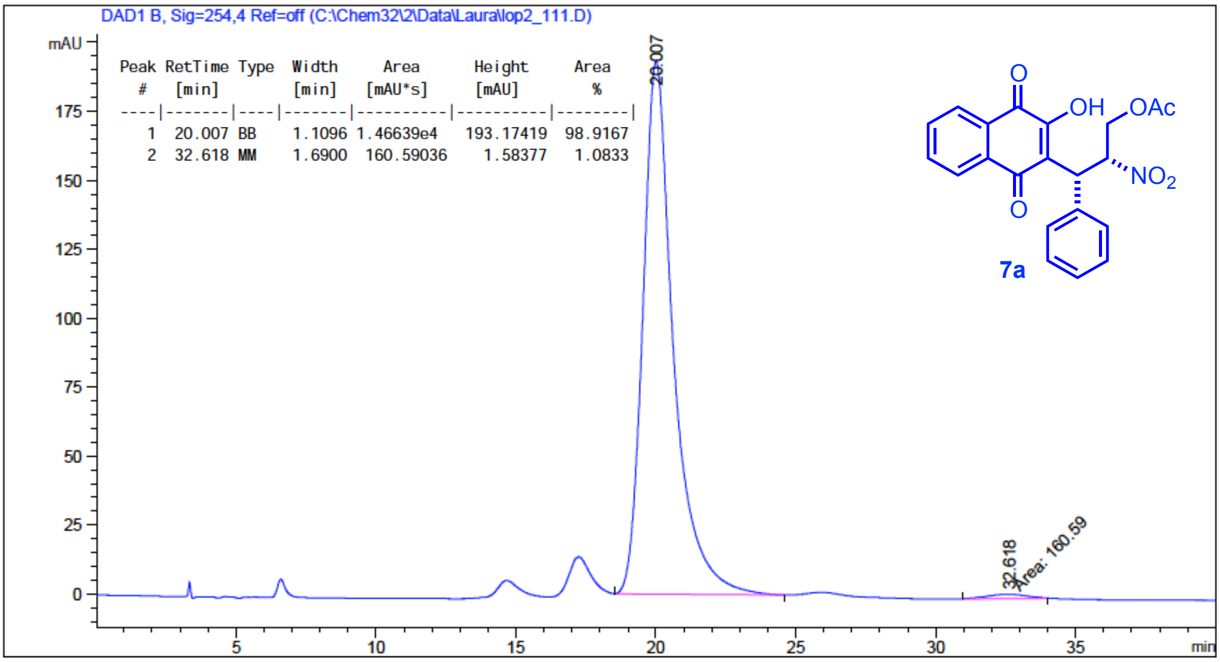




11. HPLC chromatograms



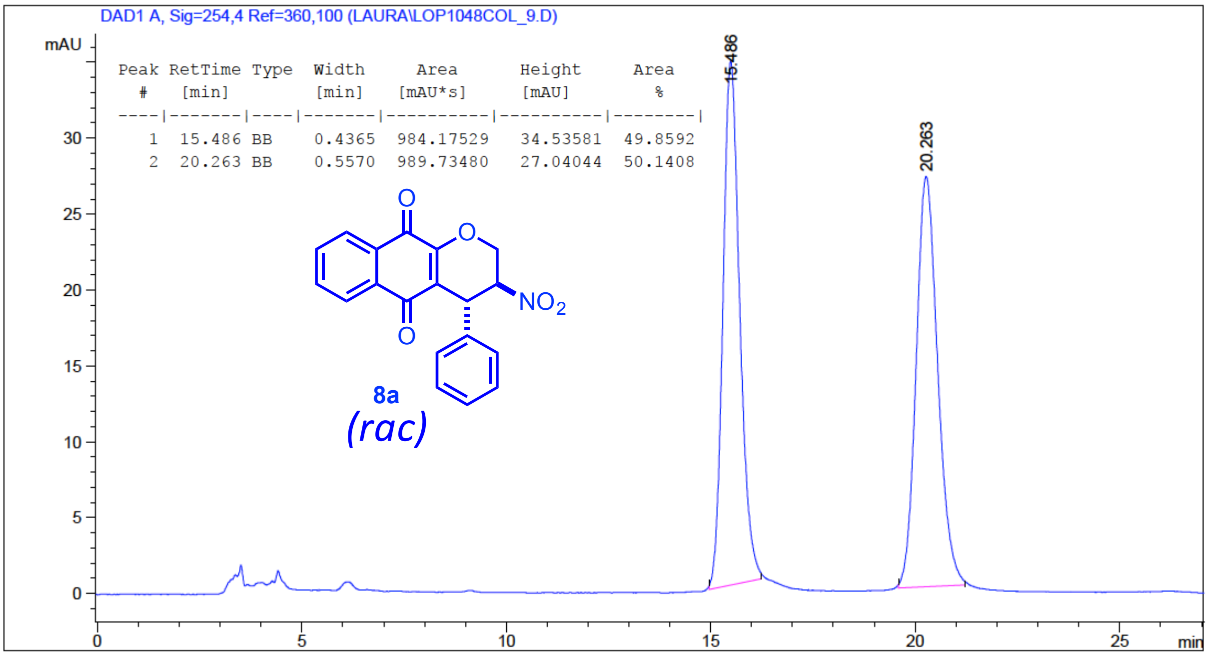
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.315	MM	1.0718	2639.94678	41.05153	49.3263
2	31.300	BB	1.4126	2712.05444	22.65626	50.6737



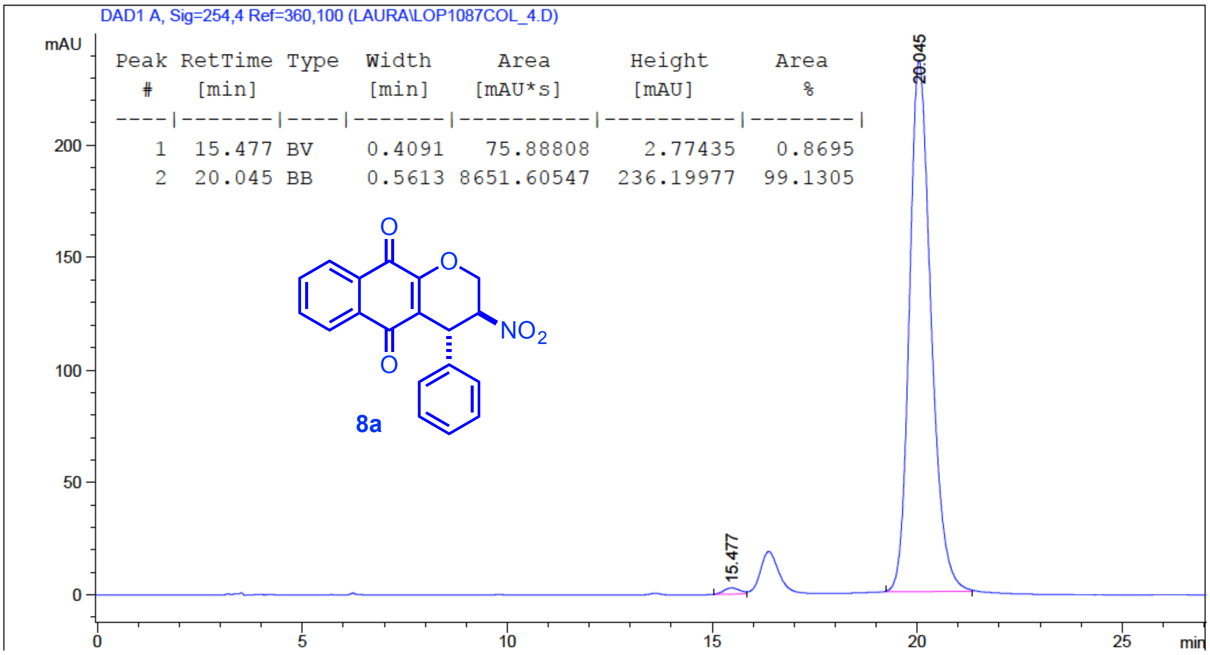
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.007	BB	1.1096	1.46639e4	193.17419	98.9167
2	32.618	MM	1.6900	160.59036	1.58377	1.0833

```
Sample Info      : IC hex/IPA 75/25 1 ml/min 254nm

Additional Info : Peak(s) manually integrated
```



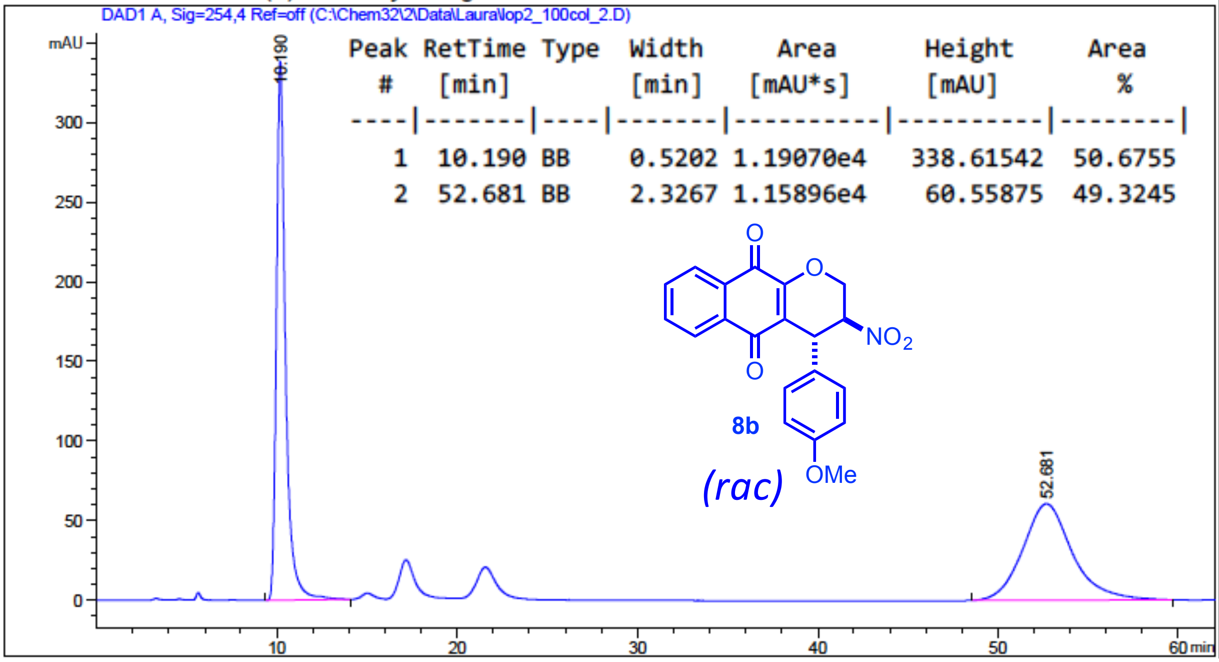
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.486	BB	0.4365	984.17529	34.53581	49.8592
2	20.263	BB	0.5570	989.73480	27.04044	50.1408



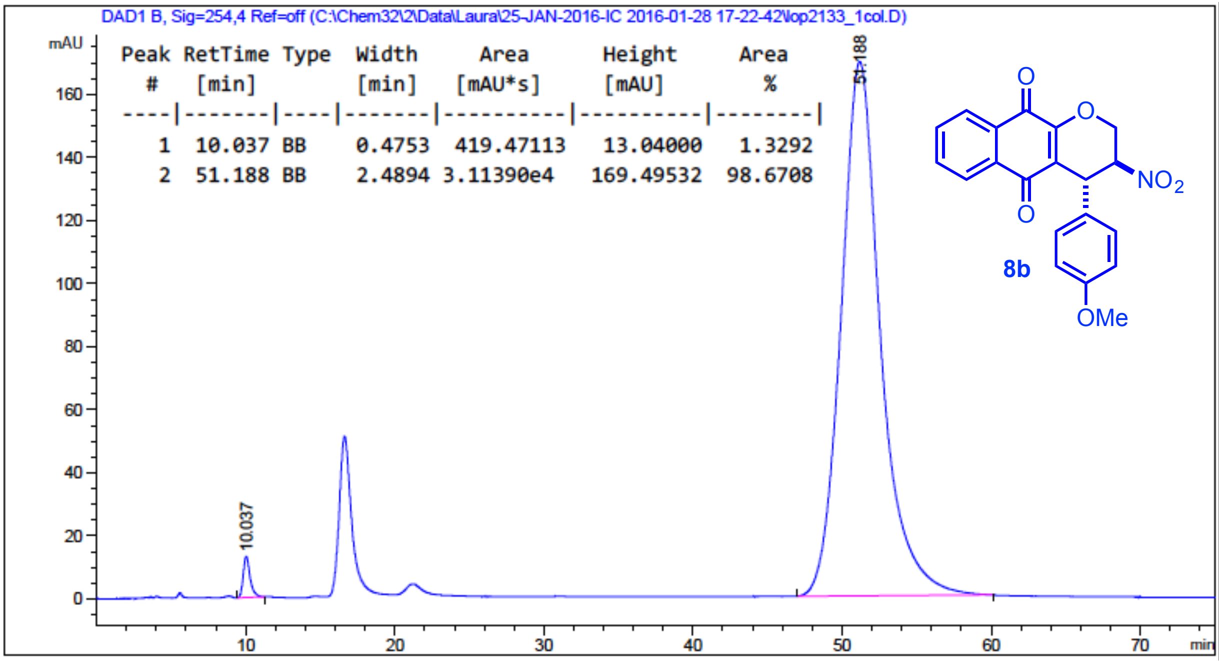
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.477	BV	0.4091	75.88808	2.77435	0.8695
2	20.045	BB	0.5613	8651.60547	236.19977	99.1305

Sample Info : IA hex/IPA 70/30 1 mL/min 230 nm

Additional Info : Peak(s) manually integrated



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.190	BB	0.5202	1.19070e4	338.61542	50.6755
2	52.681	BB	2.3267	1.15896e4	60.55875	49.3245



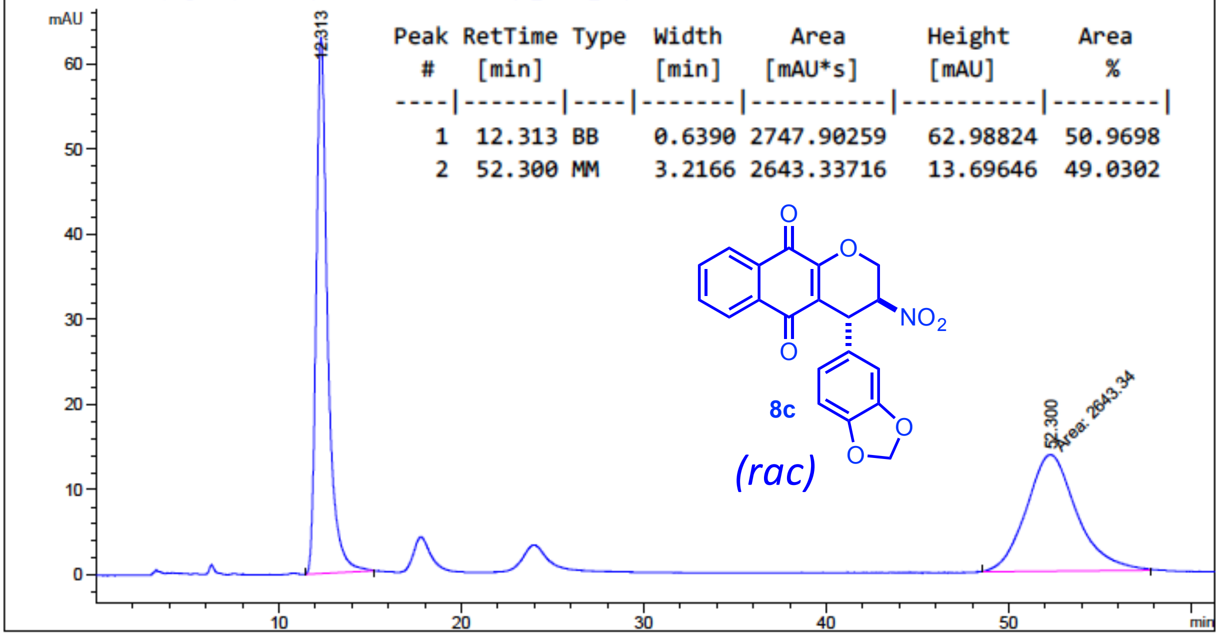
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.037	BB	0.4753	419.47113	13.04000	1.3292
2	51.188	BB	2.4894	3.11390e4	169.49532	98.6708

Sample Info : IA hex/IPA 70/30 1 mL/min 230 nm

Additional Info : Peak(s) manually integrated

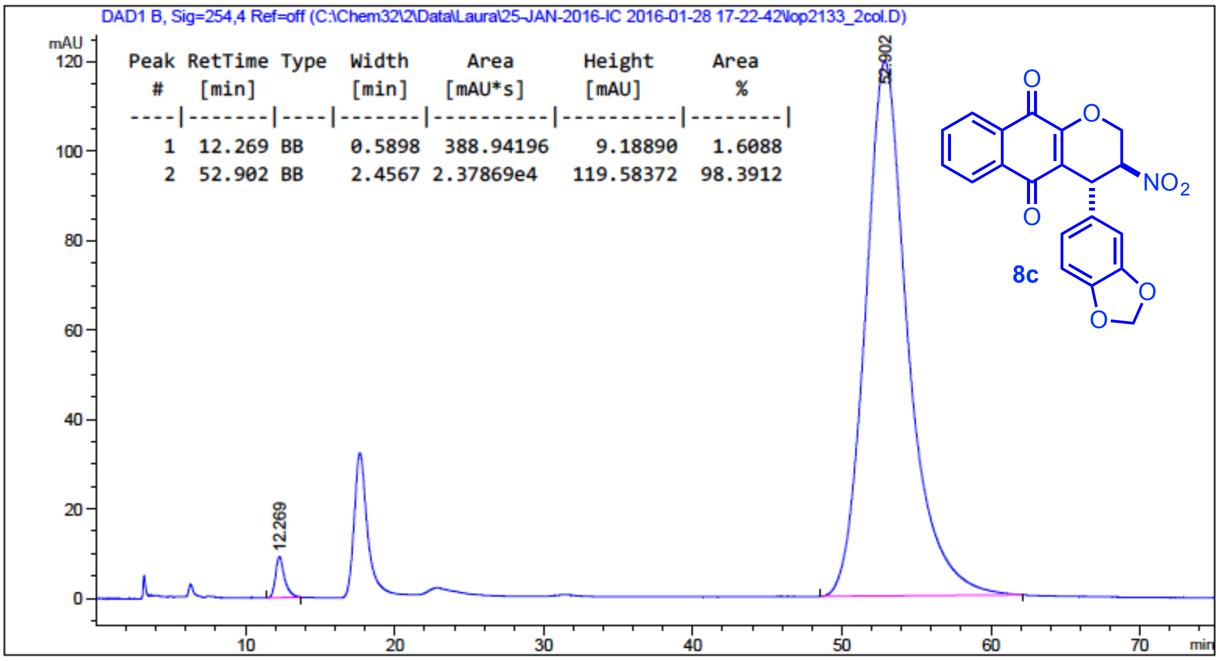
DAD1 A, Sig=254,4 Ref=off (C:\Chem32\2\Data\Laura\lop2_099col_2.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.313	BB	0.6390	2747.90259	62.98824	50.9698
2	52.300	MM	3.2166	2643.33716	13.69646	49.0302



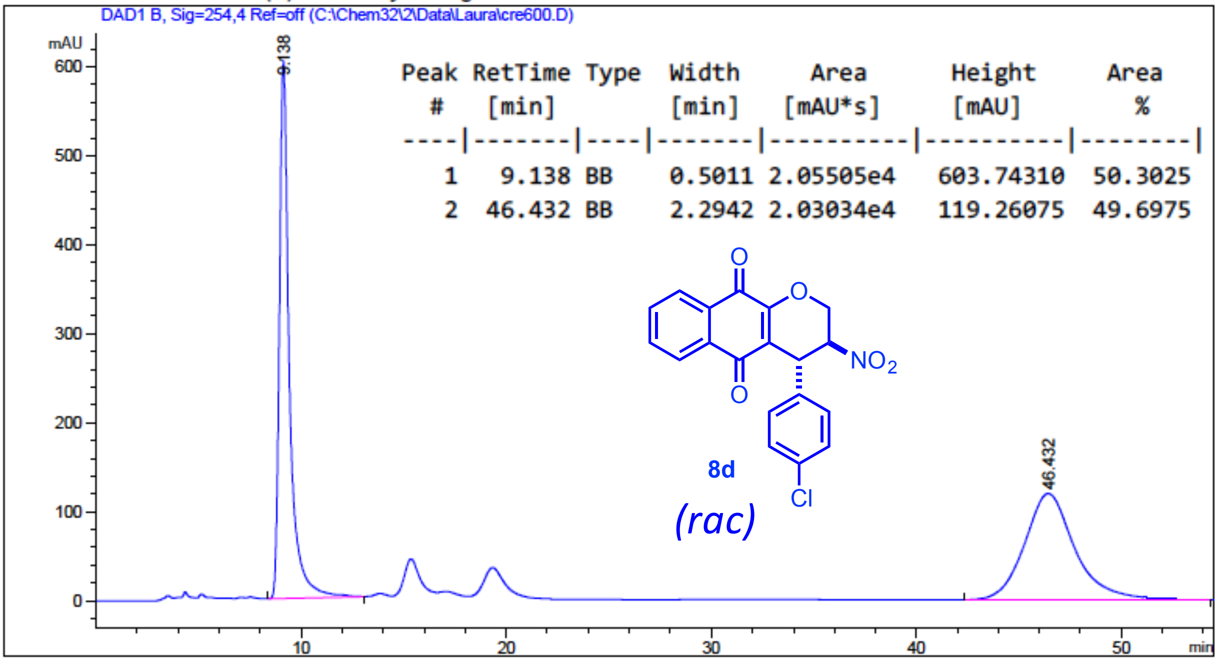
DAD1 B, Sig=254,4 Ref=off (C:\Chem32\2\Data\Laura\25-JAN-2016-IC 2016-01-28 17-22-42\lop2133_2col.D)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.269	BB	0.5898	388.94196	9.18890	1.6088
2	52.902	BB	2.4567	2.37869e4	119.58372	98.3912

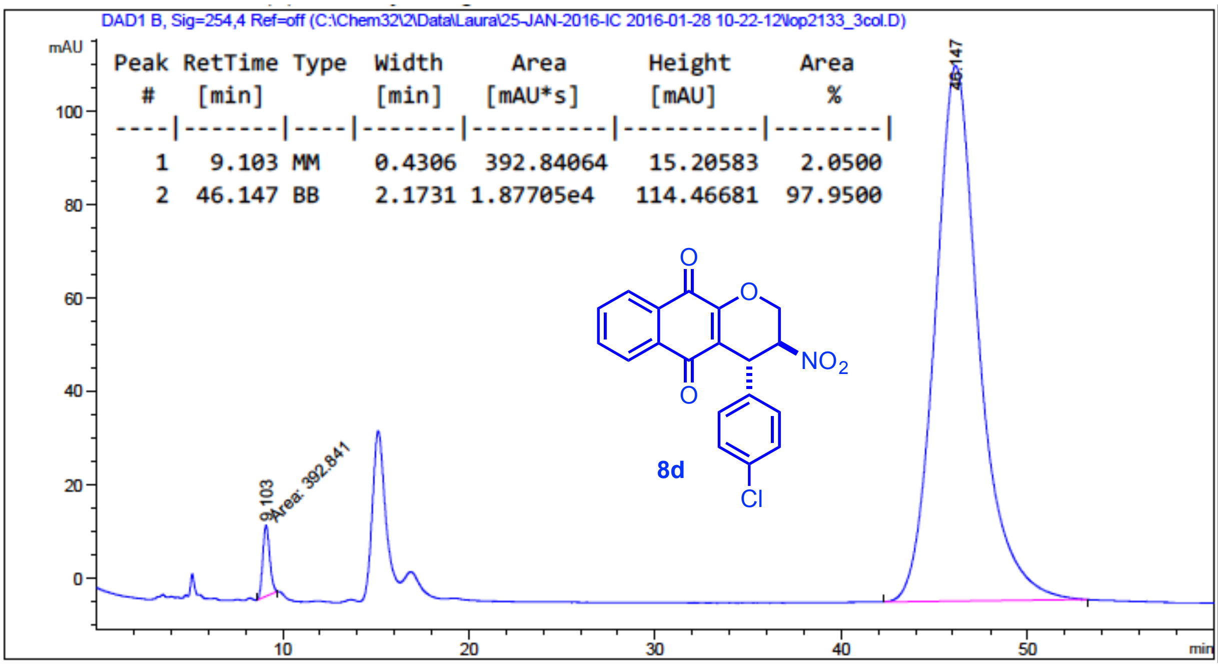


```
Sample Info     : IA   hex/IPA 70/30  1.0 mL/min 230 nm
                  racemic

Additional Info : Peak(s) manually integrated
```



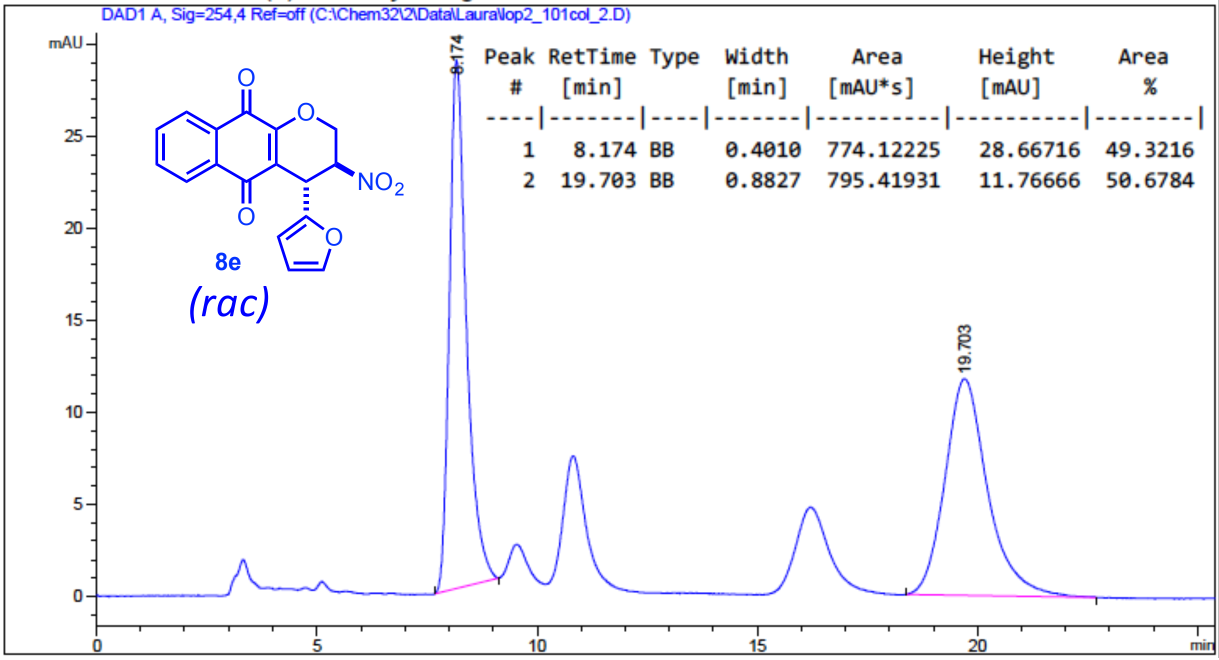
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.138	BB	0.5011	2.05505e4	603.74310	50.3025
2	46.432	BB	2.2942	2.03034e4	119.26075	49.6975



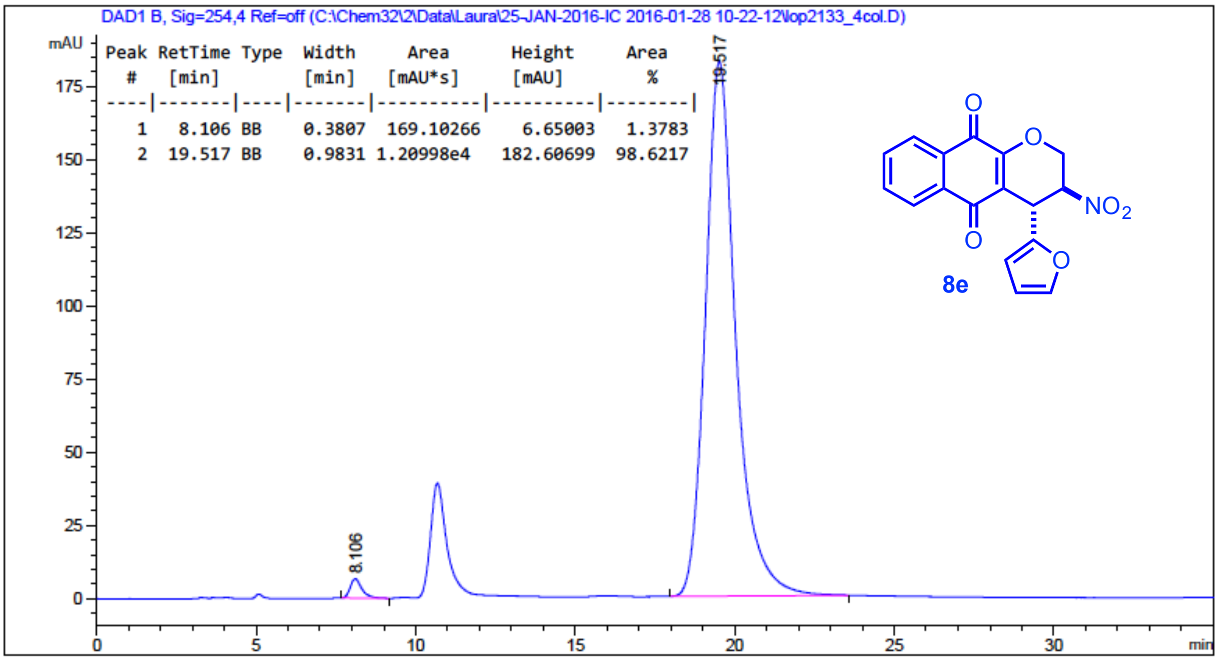
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.103	MM	0.4306	392.84064	15.20583	2.0500
2	46.147	BB	2.1731	1.87705e4	114.46681	97.9500

Sample Info   : IA hex/IPA 70/30 1 mL/min 230 nm

Additional Info : Peak(s) manually integrated



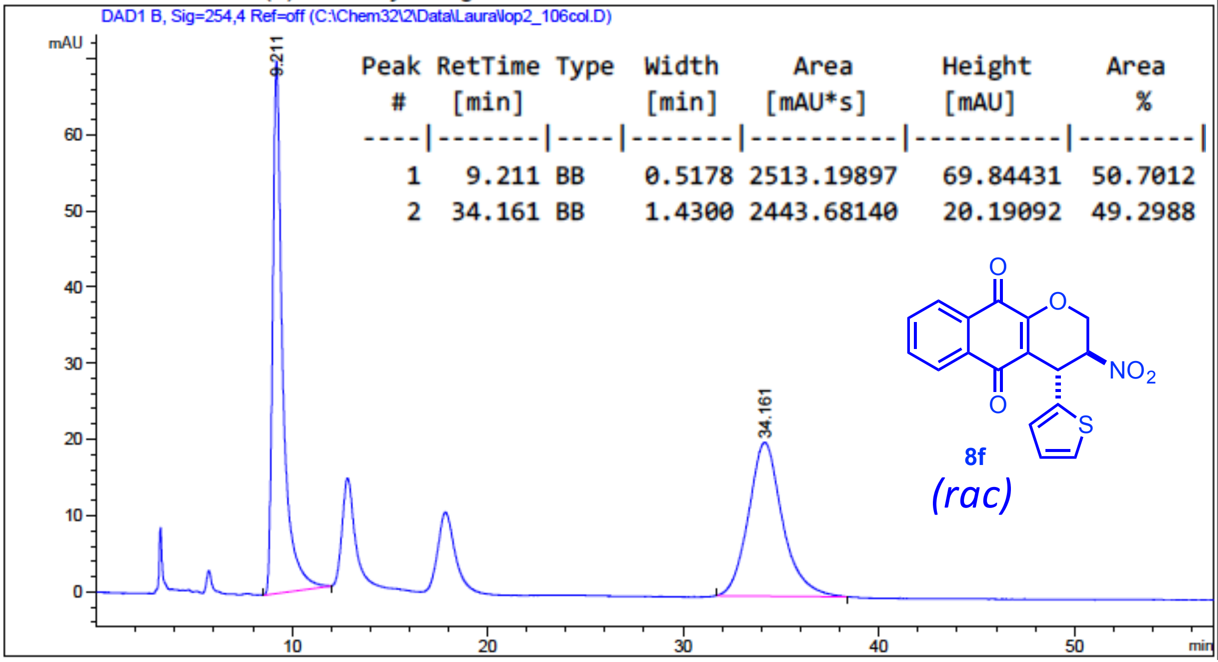
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.174	BB	0.4010	774.12225	28.66716	49.3216
2	19.703	BB	0.8827	795.41931	11.76666	50.6784



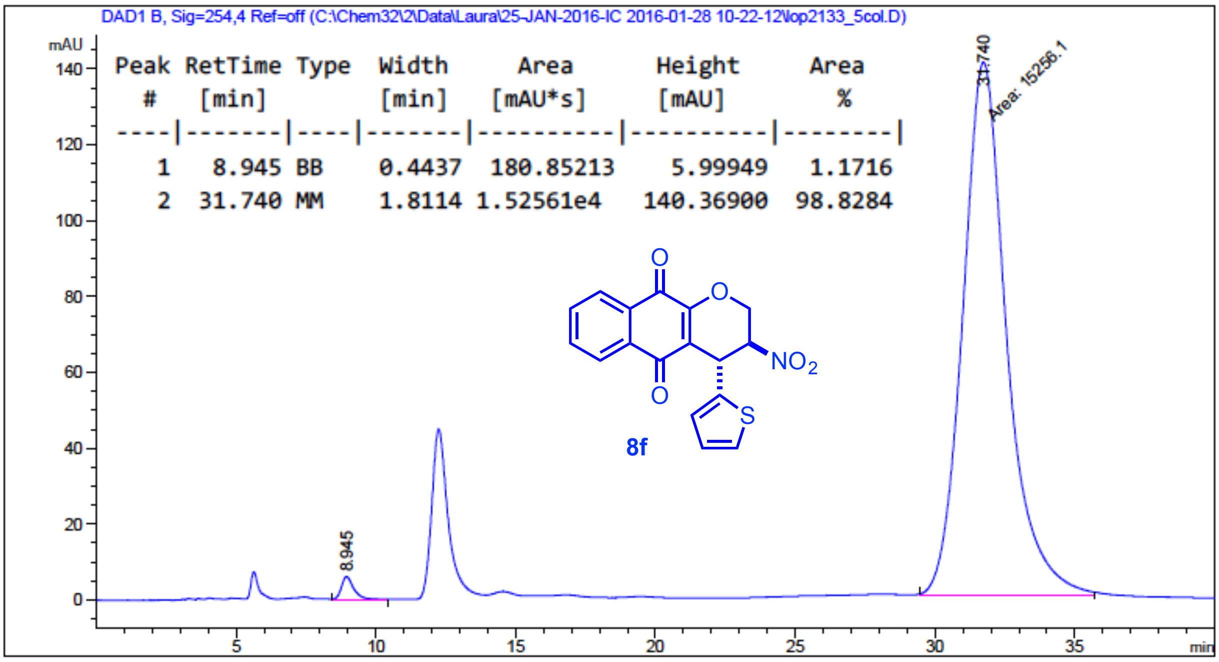
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.106	BB	0.3807	169.10266	6.65003	1.3783
2	19.517	BB	0.9831	1.20998e4	182.60699	98.6217

```
Sample Info      : IA   hex/IPA 70/30 1.0 mL/min 230 nm
                   thienyl racemic

Additional Info : Peak(s) manually integrated
```

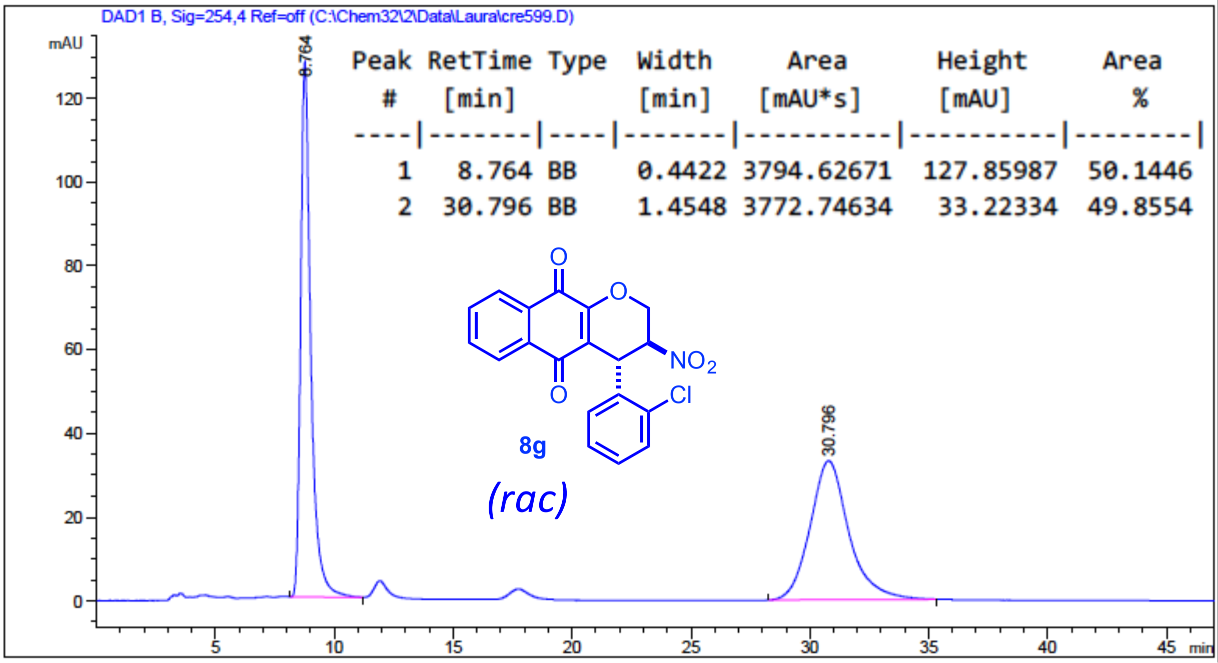


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.211	BB	0.5178	2513.19897	69.84431	50.7012
2	34.161	BB	1.4300	2443.68140	20.19092	49.2988

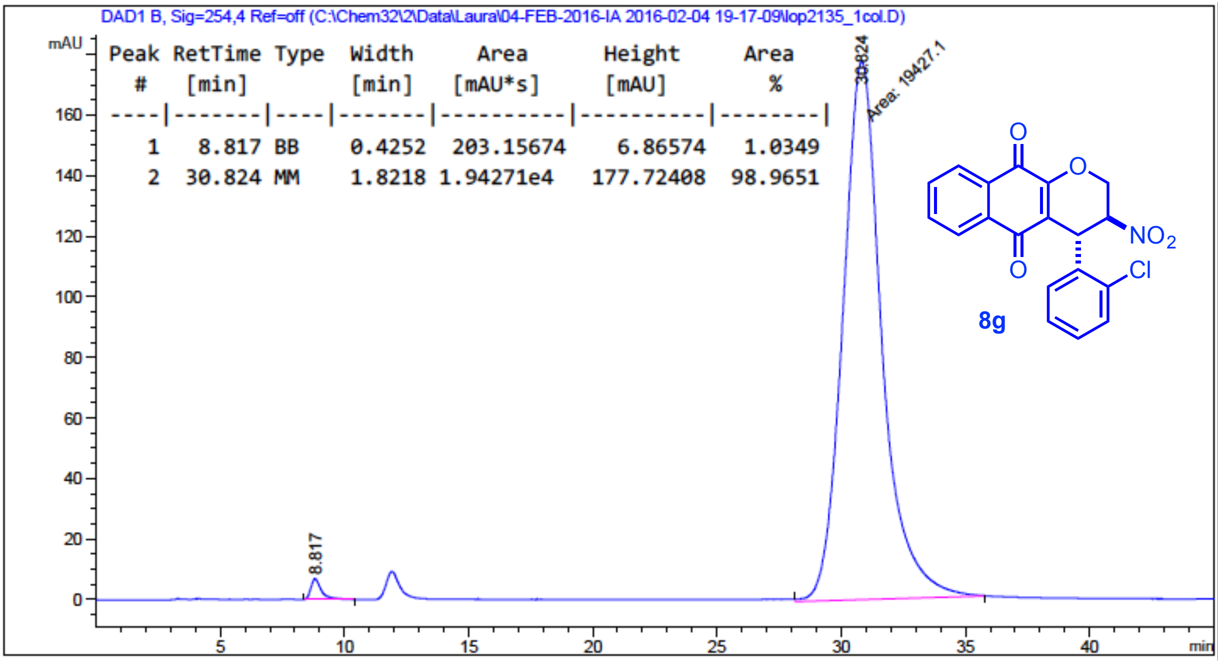


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.945	BB	0.4437	180.85213	5.99949	1.1716
2	31.740	MM	1.8114	1.52561e4	140.36900	98.8284

Sample Info : IA hex/IPA 70/30 1.0 mL/min 230 nm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.764	BB	0.4422	3794.62671	127.85987	50.1446
2	30.796	BB	1.4548	3772.74634	33.22334	49.8554



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.817	BB	0.4252	203.15674	6.86574	1.0349
2	30.824	MM	1.8218	1.94271e4	177.72408	98.9651