

The Direct Catalytic Enantioselective Vinylogous Aldol Reaction of α -Branched Enals with Isatins

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Supporting Information

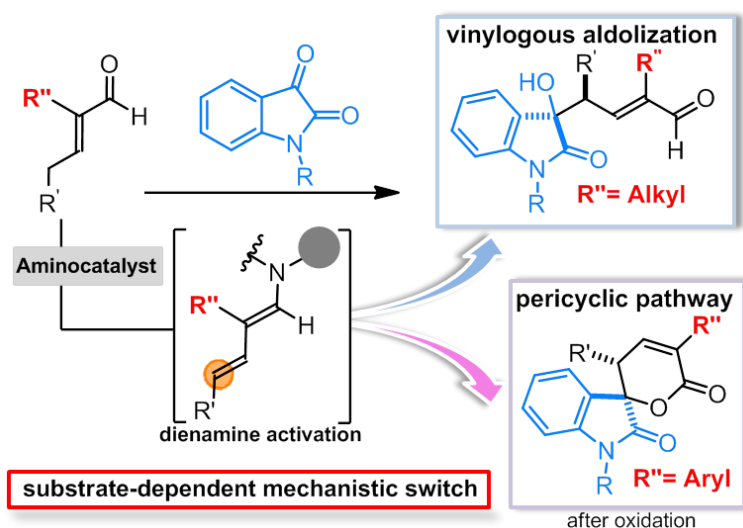


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A. General Information

The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^1H or at 100 MHz and 125 MHz for ^{13}C , respectively. The chemical shifts (δ) for ^1H and ^{13}C are given in ppm relative to residual signals of the solvents (CHCl_3 @ 7.26 ppm ^1H NMR, 77.16 ppm ^{13}C NMR). Coupling constants are given in Hz. When necessary, ^1H and ^{13}C signals were assigned by means of g-COSY, g-HSQC and g-HMBC 2D-NMR sequences. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; bs, broad signal.

High-resolution mass spectra (HRMS) were obtained from the ICIQ High Resolution Mass Spectrometry Unit on Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionization (EI). X-ray data were obtained from the ICIQ X-Ray Unit using a Bruker-Nonius diffractometer equipped with an APPEX 2 4K CCD area detector. Optical rotations are reported as follows: $[\alpha]_{\text{D}}^{25}$ (c in g per 100 mL, solvent).

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General Procedures. All the reactions were set up under air and using freshly distilled solvents, without any precautions to exclude moisture, unless otherwise noted - open air chemistry on the benchtop.

Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (35-70 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permanganate (KMnO_4), and heat as developing agents. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

Determination of Diastereomeric Ratios

The diastereomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture.

Determination of Enantiomeric Purity. HPLC analysis on a chiral stationary phase column was performed on an Agilent 1200-series instrumentation. Daicel Chiralpak AD-H, IA, IB or IC columns and Daicel Chiralcel OD-H with *i*-PrOH/hexane as the eluent were used, as specified in the individual experiment.

HPLC traces were compared to racemic samples prepared by using a racemic mixture of the commercial available chiral amine **C**.

Determination of Yield and Conversion in the Optimization Studies. The conversion of the starting materials and the yield of product in the optimization studies related to the model reaction depicted in Table 1 of the main manuscript were determined by ^1H NMR spectroscopy adding an internal standard in the crude reaction: 2,5-dimethylfuran: δ 2.26 ppm (s, 6H), 5.84 (s, 2H). Since in all instances the conversion of isatin **1a** was equal to the yield of product **3a**, in some cases the yield was determined by integration of the signals of the unreacted isatin **1a** in the ^1H NMR spectra (N-benzyl isatin **1a** NMR signal @ δ 4.92 ppm (s) and product **3a** signal @ 9.34 (s) and 9.21 (s); double checked with the product signals @ 6.42 (d) and 6.16 (d)).

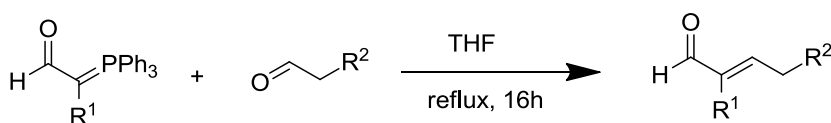
Materials. Commercial grade reagents and solvents were purchased from Sigma Aldrich, Fluka, and Alfa Aesar and used as received, without further purification; otherwise, where necessary, they were purified as

recommended.¹ The cinchona-based primary amine catalysts, 9-amino(9-deoxy)*epi*-quinine **A**² and 6'-hydroxy-9-amino-9-deoxy*epi*quinine **B**,³ were both prepared from commercially available quinine following the literature procedure. Chiral secondary amine catalyst **C** is commercially available (Aldrich or Alfa Aesar); it was purified by flash column chromatography prior to use and stored at 4 °C under argon to avoid undesired desilylation that would affect the catalytic potential of the amine. Catalysts **D**⁴ and **E**⁵ have been synthesized following the procedure reported in the literature.

The N-benzyl protected isatins **1** were easily synthesized from the corresponding, commercially available unprotected isatins, according to the following procedure: a solution of N-H isatin (5 mmol in 40 ml of dry DMF) was slowly added to a suspension of sodium-hydride (1.04 g, 60% dispersion in paraffin liquid, 1.3 equiv) in dry DMF (100ml) at 0 °C over a period of 10 minutes. The mixture was stirred at the same temperature for further 30 minutes. Then benzylbromide (6 mmol, 1.2 equiv) was added dropwise at the same temperature. The mixture was slowly warmed up at room temperature and stirring continued until the reaction was over (complete consumption of the starting N-H isatin, as judge by analytical TLC). The reaction was cooled at 0 °C and quenched with water (750 ml). The suspension was then filtered and the filtrate recrystallized from EtOAc and hexane to give the final product **1**.

Most of the α -branched unsaturated aldehydes **2** are commercially available and were purchased from Aldrich or Alfa Aesar and used as received. Otherwise, they were synthesized according to the following procedure.

Preparation of α -Branched Enals⁶



R¹= Me, Et R²= Et, Bn, Ar, CH₂S-Me, CH₂N-Cbz

A mixture of linear aliphatic aldehyde (1 equiv) and the appropriate triphenylphosphorane (1.5 equiv) was dissolved in THF and refluxed for 16h. The solution was then allowed to reach room temperature; the solvent was removed under reduced pressure and the crude mixture was purified by flash column chromatography (silica gel) to yield the desired product α -branched enals **2** (yield 40-50 %).

Note: For all the α -branched enals **2**, a *E/Z* ratio >95:5 was determined by ¹H NMR analysis. No double bond scrambling was observed neither during the catalytic reaction (checked by analysis of the crude reaction mixture) nor mixing the enal with a catalytic amount of catalyst **C**.

¹ W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.

² S. H. McCooey, S.J. Cannon, *Org. Lett.* **2007**, 9, 599–602.

³ W. Chen, W. Du, Y. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2007**, 46, 7667–7670.

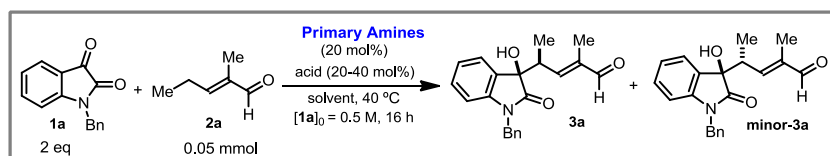
⁴ Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. *Helv. Chim. Acta* **2009**, 92, 1225-1259.

⁵ Ł. Albrecht, G. Dickmeiss, F. Cruz Acosta, C. Rodríguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, 134, 2543–2546.

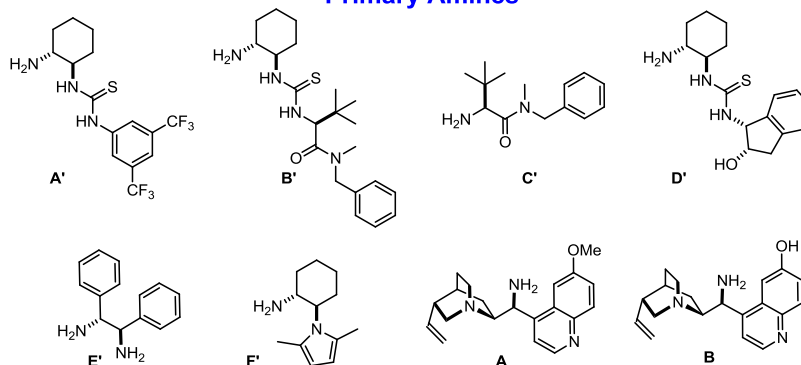
⁶ Adapted from: Gagosz, F. *Org. Lett.* **2005**, 7, 4129-4132

B. Optimization Studies

Table S1. Catalyst Screening - **Primary Amines**



Primary Amines



catalyst	additive	solvent	conv. (%) ^b	dr ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
A'	BA	toluene	28	1.3:1	6	0
B'	BA	toluene	66	1:1.9	20	20
C'	TFA	toluene	55	1:1.2	-	-
D'	BA	toluene	55	1:1	15	23
E'	TFA	toluene	47	1:1	0	0
E'	BA	toluene	n.r.	-	-	-
F'	TFA	toluene	23	1.3:1	55	43
A	TFA	CH ₃ Cl	42	6:1	<5	<5
A	p-TSA	CH ₃ Cl	40	4.5:1	<5	<5
B	TFA	CH ₃ Cl	67	2.8:1	42	65
B	TFA	toluene	74 ^d	2.5:1	40	51
B	TFA	THF	43	3.1:1	46	58

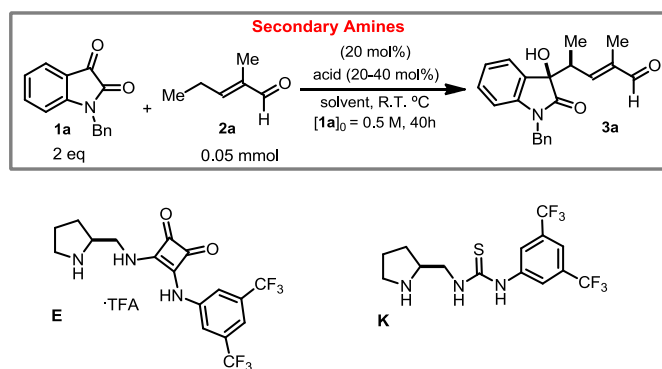
BA: benzoic acid; TFA: trifluoroacetic acid; p-TSA: p-toluensulfonic acid. The absolute configuration of the minor isomer was not univocally determined. ^a Reactions performed at 40 °C on a 0.05 mmol scale using 2 equivalents of (*E*)-2-methylpent-2-enal **2a** with [1a]₀ = 0.5 M, reaction time 16h. ^b Both conversion and diastereomeric ratios (dr) were determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Reaction time 40 h.

Table S2. Catalyst screening - Secondary Amines

Secondary Amines
(20 mol%)
acid (20-40 mol%)
solvent, 40 °C
[1a]₀ = 0.5 M, 16 h

catalyst	additive	solvent	conv. (%) ^b	dr ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
C	BA	toluene	45	1/1	40	20
B	BA	toluene	n.r.	-	-	-
K	BA	EtOH	n.r.	-	-	-
F	BA	toluene	n.r.	-	-	-
G	TFA	toluene	30	1.9:1	5	5
H	HCl	EtOH	n.r.	-	-	-
I	TFA	EtOH	n.r.	-	-	-
J	AcOH _(1eq)	EtOH	n.r.	-	-	-
C	BA	EtOH	>95	1.2:1	75	65
D	BA	EtOH	>95	1.2:1	83	76
D^d	BA	EtOH	>95	1.4:1	89	84

n.r.: no reaction. BA: benzoic acid; TFA: trifluoroacetic acid; p-TSA: p-toluensulfonic acid. ^a Reactions performed at 40 °C on a 0.05 mmol scale using 2 equivalents of (*E*)-2-methylpent-2-enal **2a** with [1a]₀ = 0.5 M, reaction time 16h. ^b Both conversion and diastereomeric ratios (dr) were determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Reaction carried out at 25 °C.

Table S3. Catalyst screening – Bifunctional Secondary Amines

catalyst	additive	solvent	conv. (%) ^b	dr ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
K	none	EtOH	n.r. ^a	-	-	-
E	none	DCM	n.r.	-	-	-
E	DEA ^c	DCM	n.r.	-	-	-
E^f	DEA/H ₂ O ^{c,d,e}	DCM	n.r.	-	-	-
E	none	toluene	n.r.	-	-	-
E	none	EtOH	n.r.	-	-	-

n.r.: no reaction. DCM dichloromethane; DEA N,N-diethylacetamide. ^a Reactions performed at 25 °C on a 0.05 mmol scale using 2 equivalents of (*E*)-2-methylpent-2-enal **2a** with [1a]₀ = 0.5 M, reaction time 16h. ^b Reactions performed at 40 °C. ^c 1 eq (0.05 mmol) of DEA was used. ^d 2.8 eq of water were used. ^e Reactions performed with [1a]₀ = 0.25 M. ^f These reaction conditions (selected for entry 4, Table 1 of the main manuscript) reflect the optimized system as reported in the original papers describing the preparation and the synthesis of catalyst **E**.^{5,7}

Table S4. Solvent screening

solvent	conv. (%) ^b	dr ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
EtOH	>95	1.2	83	76
DCE	10	2.5:1	92	67
dioxane	n.r.	-	-	-
CHCl ₃	n.r.	-	-	-
Et ₂ O	n.r.	-	-	-
THF	n.r.	-	-	-
EtOAc	n.r.	-	-	-
CH ₃ CN	30	3:1	92	77
2,2,2-trifluoroethanol	n.r.	-	-	-
EtOH/CH ₃ CN (1/1)	75	2.2:1	91	79
EtOH/CH₃CN (1/9)	49	2.7:1	92	76

n.r.: no reaction. ^a Reactions performed at 25 °C on a 0.05 mmol scale using 2 equiv. of **2a** with [1a]₀ = 0.5 M, reaction time 16 h. 20 mol% of amine **D** and benzoic acid was used. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis.

⁷ L. Albrecht, F. Cruz Acosta, A. Fraile, A. Albrecht, J. Christensen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2012, **51**, 9088–9092. See also Ref 5 in the S.I.

Table S5. Acidic additive screening

$\text{1a} + \text{2a} \xrightarrow[\text{EtOH/CH}_3\text{CN (9/1), 25 }^\circ\text{C, [1a]}_0 = 0.5 \text{ M, 16 h}]{\text{D (20 mol\%), Additive (20 mol\%)}}$

Acids tested

Binol, N-Boc-PhGly

Additive	Conv. (%) ^b	dr ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
AcOH	45	2.8:1	92	81
CH ₂ Cl-CO ₂ H	44	2.9:1	88	80
2-F-C ₆ H ₄ CO ₂ H	45	2.8:1	88	78
(L)-N-Boc-PhGly	52	3.2:1	83	75
(D)-N-Boc-PhGly	52	3.2:1	83	70
(S)-Binol	38	2:1	91	83
(R)-Binol	47	2.2:1	91	82
Salicylic Acid	50	2.5:1	89	81
2-NO ₂ -C ₆ H ₄ CO ₂ H	60	2.6:1	84	74
p-NO ₂ -Phenol	65	1.6:1	80	60
2,6-F-C ₆ H ₃ CO ₂ H	57	3.1:1	87	77
2,4,6-Me-C ₆ H ₂ CO ₂ H	50	2.7:1	88	73
4-NO ₂ -C ₆ H ₄ CO ₂ H	43	3:1	89	73
2,6-CF₃-C₆H₃CO₂H	59	3.2:1	91	77
3,5- <i>t</i> -butyl-C ₆ H ₃ CO ₂ H	45	2.8:1	90	73
2-Ph-C ₆ H ₄ CO ₂ H	44	2.8:1	90	73
2,6-MeO-C ₆ H ₃ CO ₂ H	60	2.7:1	91	75

^a Reactions performed at 25 °C on a 0.05 mmol scale using 20 mol% of amine **D** and 2 equiv. of (*E*)-2-methylpent-2-enal **2a** with [1a]₀ = 0.5 M, reaction time 16h. ^b Both conversion and diastereomeric ratios (dr) were determined by ¹H NMR analysis of the crude reaction mixture.

Table S6. Amine **D**/2,6-CF₃-C₆H₃CO₂H ratio

$\text{1a} + \text{2a} \xrightarrow[\text{EtOH/CH}_3\text{CN (9/1), 25 }^\circ\text{C, [1a]}_0 = 0.5 \text{ M, 16 h}]{\text{D (20 mol\%), 2,6-CF}_3\text{BA (x mol\%)}}$

x	Conv. (%) ^b	Dr _{3a:4a} ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
40	35	3.2/1	90	77
20	59	3.2/1	91	77
10	48	3.2/1	91	78
0	20	3.3/1	91	76

^a Reactions performed on a 0.05 mmol scale using 20 mol% of amine **D** in combination with different amount of 2,6-bis (trifluoromethyl) benzoic acid. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis.

Table S7. Temperature effect

T (°C)	Conv. (%) ^b	dr ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
40	100	2/1	83	64
30	74	2.7/1	89	70
r.t.	59	3.2/1	91	77
10	<10	3.5/1	n.d.	n.d.

^a Reactions performed on a 0.05 mmol scale using 20 mol% of amine **D** in combination with 20 mol% of 2,6-bis (trifluoromethyl) benzoic acid. ^b Determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis

Table S8. Concentration effect.

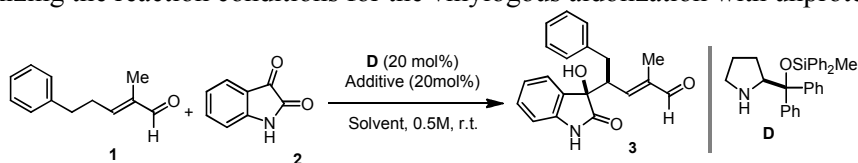
[1a]	Conv. (%) ^b	Dr _{3a:4a} ^b	ee _{3a} (%) ^c	ee _{minor} (%) ^c
2	>95	2.8/1	89	70
2	95 (87) ^d	3.2/1	90	76
1	>95	2.9/1	89	72
0.5	55	3.2/1	91	77
0.25	30	3.3/1	91	79

^a Reactions performed on a 0.05 mmol scale using 2 equivalents of 2-methyl pentenal **1**, reaction time 16h. ^b Yield and d.r. determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis on a chiral stationary phase. ^d 10 mol % of **D** and 10 mol % of acid, reaction time 36 h. Value between brackets refers to the yield of the isolated compound **3a** after chromatography.

Table S9. The importance of different N-protecting groups on the isatin derivatives **1**

PG	R ¹	Conv. (%)	dr	ee ₃ (%)
Bn	CH ₃	49	3.2:1	92
Me	CH ₃	50	2.9:1	91
Boc	CH ₃	<10 ^b	-	-
Cbz	CH ₃	<10 ^b	-	-
H	CH ₂ C ₆ H ₅	43	2:1	84

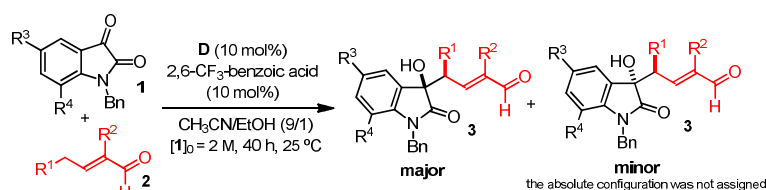
^a Reactions performed on a 0.05 mmol scale using 2 equivalents of **2** with [1]₀ = 0.5 M, reaction time 16h. A combination of catalyst **D** and benzoic acid was used. ^b the formation of the hemiacetal deriving from the attack of ethanol on the isatin derivatives was observed.

Table S10. Optimizing the reaction conditions for the vinylogous aldolization with unprotected N-H isatin.

additive	solvent	conv. (%) ^b	dr ^b	ee 3 (%) ^c	ee _{minor} (%) ^c
BA	DCM	n.r.	-	-	-
BA	CH ₃ CN	41	2.5:1	85	81
BA	EtOH	72	1.1:1	85	80
BA	CH ₃ CN/EtOH (9/1)	43	2:1	84	81
BA	CH ₃ CN/EtOH (1/1)	53	1.6:1	79	60
AcOH	CH ₃ CN	38	2:1	85	81
(L)-N-Boc-PhGly	CH ₃ CN	30	2.8:1	88	80
(D)-N-Boc-PhGly	CH ₃ CN	25	3:1	87	80
2,6-F-C ₆ H ₃ CO ₂ H	CH ₃ CN	35	3.3:1	88	-
2,4,6-Me-C ₆ H ₂ CO ₂ H	CH ₃ CN	46	2.2:1	81	-
4-NO ₂ -C ₆ H ₄ CO ₂ H	CH ₃ CN	14	3.3:1	90	82
2,6-OH-C ₆ H ₃ CO ₂ H	CH ₃ CN	n.r.	-	-	-

n.r.: no reaction. BA: benzoic acid; N-Boc-PhGly: N-Boc phenylglycine, see Table S5 for the structure.

^a Reactions performed at 25 °C on a 0.05 mmol scale using 2 equivalents of enal **2a** with [**1a**]₀ = 0.5 M, reaction time 16h. ^b Both conversion and diastereomeric ratios (dr) were determined by ¹H NMR analysis of the crude reaction mixture. ^c Determined by HPLC analysis on a chiral stationary phase.

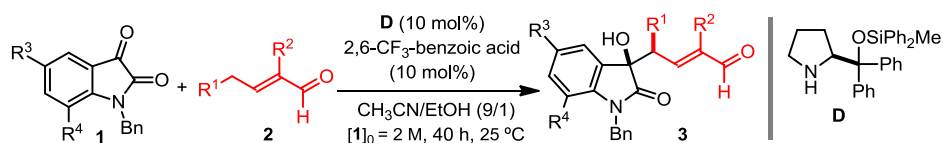
Table S11. Scope of the Direct Vinylogous Aldolization – ee of the minor diastereoisomer

entry	R ¹	R ²	R ³	R ⁴	3	yield (%) ^b	dr ^c	e.e. % ^d major/minor
1	Me	Me	H	H	a	87	3.2:1	90 / 76
2	Bn	Me	H	H	b	68	2.5:1	95 / 77
3	CH ₂ -SMe	Me	H	H	c	89	1.6:1	94 / 70
4	CH ₂ NHCbz	Me	H	H	d	63	3:1	94 / 74
5 ^e	Bn	Bn	H	H	e	65	1.5:1	90 / 78
6 ^e	Et	Et	H	H	f	28 ^f	1.5:1	94 / -
7	Me	Me	Cl	H	g	92	1.7:1	86 / 73
8	Bn	Me	Cl	H	h	69	1.6:1	92 / 78
9	Me	Me	Br	H	i	68	1.9:1	85 / 78
10	Me	Me	Me	H	j	76	3.8:1	92 / 81
11	Me	Me	NO ₂	H	k	87	1.5:1	87 / 75
12	Me	Me	CF ₃ O	H	l	71	2.9:1	89 / 63
13	Me	Me	Me	Me	m	65	3.9:1	91 / 77
14	Me	Me	H	Br	n	88	2.4:1	92 / 71

^a Reactions performed on a 0.2 mmol scale using 2 equiv of **2**. *E/Z* ratio of **2**: >95:5. Only the (*E*)-isomer of the aldol products **3** has been detected. ^b Yield of the isolated product **3** after chromatographic purification on silica gel. ^c Determined by ¹H NMR analysis of the crude mixture.

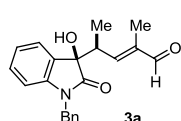
^d Ee values determined by HPLC analysis. ^f Yield of the isolated major diastereomer of **3f**.

C. General Procedure for the Vinylogous Aldol Reaction



All the reactions were carried out in a 9/1 mixture of acetonitrile and ethanol without any precaution for excluding air and moisture (open air chemistry on the benchtop). An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol methyl-diphenylsilyl ether **D** (9.00 mg, 0.02 mmol, 10 mol%) and 2,6-bis(trifluoromethyl)benzoic acid (5.2 mg, 0.02 mmol, 10 mol%). Then the solvent mixture (100 μ L) and the α -branched enal **2** (0.4 mmol) were sequentially added and the resulting solution stirred at ambient temperature for 5 minutes. The reaction was started by the addition of the *N*-benzyl protected isatin derivative **1** (0.2 mmol). The vial was sealed and immersed in a water bath (thermostated at 25 °C) and stirring continued over 40 hours. Then the crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (5 ml). Solvent was removed under reduced pressure and the crude mixture was analyzed by ^1H NMR spectroscopy to determine the diastereomeric ratio. The product **3** was isolated by flash column chromatography using the specified eluent.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (**3a**)

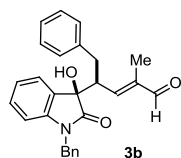


The reaction was carried out according to the general procedure to furnish the crude product as a 3.2:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.42 ppm (d), δ_{minor} 6.21 ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.24 hexane/ethyl acetate 9/1) in 87% yield (white solid). The enantiomeric excess was determined to be 90% for the major diastereoisomer (76% EE for the minor) by HPLC analysis on a Daicel Chiralpak IB column: 95:5 hexane/*i*-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 26.7 min, τ_{minor} = 62.5 min. $[\alpha]_{\text{D}}^{28}$ = +61.0 (c = 0.79, CHCl_3 , d.r. 3.2/1, major 90% ee, minor 76% ee). HRMS calc. for ($\text{C}_{21}\text{H}_{21}\text{NO}_3 + \text{Na}$): 358.1419, found 358.1419.

^1H NMR (400 MHz, CDCl_3): δ 9.33 (s, 1H), 7.39 (d, 1H, J_l = 7.3 Hz, J_2 = 1.1 Hz), 7.35-7.19 (m, 7H, overlap with the signal from the minor diastereoisomer), 7.08 (dt, 1H, J_d = 7.6 Hz, J_t = 0.9 Hz), 6.78 (d, 1H, J = 7.8 Hz, overlap with the signal from the minor diastereoisomer), 6.42 (dq, 1H, J_d = 10.5 Hz, J_q = 1.3 Hz), 5.05 (d, 1H, J = 15.6 Hz, overlap with the signal from the minor diastereoisomer), 4.71 (d, 1H, J = 15.6 Hz), 3.49-3.39 (m, 1H, overlap with the signal from the minor diastereoisomer), 1.74 (d, 3H, J = 1.2 Hz), 1.00 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 195.2, 177.3, 151.7, 142.9, 141.3, 135.5, 130.2, 129.0, 128.3, 128.1, 127.6, 127.5, 124.7, 123.3, 109.7, 78.4, 44.2, 41.5, 14.1, 9.8 ppm.

(*S,E*)-4-((*R*)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-methyl-5-phenylpent-2-enal (**3b**)



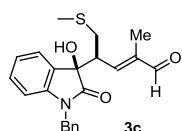
The reaction was carried out following the general procedure to furnish the crude products as a 2.5:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 9.18 ppm (s), δ_{minor} 9.11 ppm (s).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.3 hexane/ethyl acetate 8/2) in 68% yield (white solid). The enantiomeric excess was determined to be 95%

for the major diastereoisomer (77% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 90/10 hexane/i-PrOH, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 22.9$ min, $\tau_{\text{minor}} = 41.0$ min. $[\alpha]_{\text{D}}^{26} = +149.0$ ($c = 1.0$, CHCl_3 , d.r. 2.5/1, $\text{major } 95\%$ ee, $\text{minor } 77\%$ ee). HRMS calc. for $(\text{C}_{27}\text{H}_{25}\text{NO}_3 + \text{Na})$: 434.1732, found 434.1740.

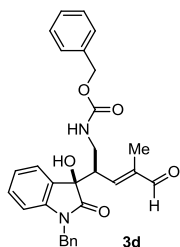
^1H NMR (400 MHz, CDCl_3): δ 9.18 (s, 1H), 7.46 (d, 1H, $J_1 = 7.4$ Hz, $J_2 = 0.9$ Hz), 7.37-6.69 (m, 12H, overlap with the signal from the minor diastereoisomer), 6.81 (d, 1H, $J = 7.7$ Hz), 6.31 (dq, 1H, $J_d = 10.8$ Hz, $J_q = 1.2$ Hz), 5.05 (d, 1H, $J = 15.8$ Hz, overlap with the signal from the minor diastereoisomer), 4.73 (d, 1H, $J = 15.8$ Hz), 3.66 (td, 1H, $J_t = 11.0$ Hz, $J_d = 3.3$ Hz, overlap with the signal from the minor diastereoisomer), 3.08 (dd, 1H, $J_1 = 13.4$ Hz, $J_2 = 11.2$ Hz), 1.26 (d, 3H, $J = 1.3$ Hz, overlap with the signal from the minor diastereoisomer) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 194.8, 177.2, 149.5, 143.2, 142.8, 138.4, 135.4, 130.4, 129.1, 129.0, 128.6, 128.5, 128.0, 127.6, 127.5, 126.6, 124.5, 123.5, 109.9, 78.1, 49.5, 44.2, 35.1, 9.5 ppm

(S,E)-4-((R)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-methyl-5-(methylthio)pent-2-enal (3c)



The reaction was carried out following the general procedure A to furnish the crude products as a 1.6:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.14 ppm (d), δ_{minor} 5.89 ppm (d).

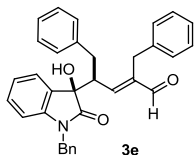
The title compound was isolated as a mixture of diastereoisomers ($R_f = 0.28$ hexane/ethyl acetate 8/2) in 89% yield (colourless solid). The enantiomeric excess was determined to be 95% for the major diastereoisomer (77% ee for the minor) by HPLC analysis on a Daicel Chiralpak IB column: 95:5 hexane/i-PrOH, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 32.0$ min, $\tau_{\text{minor}} = 97.4$ min. $[\alpha]_{\text{D}}^{26} = +103.5$ ($c = 0.68$, CHCl_3 , d.r. 1.6/1, $\text{major } 95\%$ ee, $\text{minor } 77\%$ ee). HRMS calc. for $(\text{C}_{22}\text{H}_{23}\text{NO}_3\text{S} + \text{Na})$: 404.1296, found 404.1286. ^1H NMR (400 MHz, CDCl_3): δ 9.17 (s, 1H), 7.38 (d, 1H, $J = 7.7$ Hz), 7.34-7.15 (m, 5H, overlap with the signal from the minor diastereoisomer), 7.06 (dt, 1H, $J_d = 7.6$ Hz, $J_t = 0.8$ Hz), 6.78 (d, 1H, $J = 7.8$ Hz), 6.14 (dq, 1H, $J_d = 10.9$ Hz, $J_q = 1.4$ Hz), 5.02 (d, 1H, $J = 15.5$ Hz, overlap with the signal from the minor diastereoisomer), 4.70 (d, 1H, $J = 15.5$ Hz), 3.68 (bs, 1H), 3.65-3.55 (m, 1H, overlap with the signal from the minor diastereoisomer), 2.94 (dd, 1H, $J_1 = 13.1$ Hz, $J_2 = 4.6$ Hz), 2.54 (dd, 1H, $J_1 = 13.0$ Hz, $J_2 = 10.0$ Hz), 2.07 (s, 3H), 1.66 (d, 3H, $J = 1.3$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 194.8, 176.7, 148.8, 143.3, 143.3, 142.5, 135.4, 130.4, 129.0, 128.2, 127.4, 124.3, 123.5, 109.7, 77.9, 46.5, 44.2, 33.3, 16.1, 10.1 ppm.



benzyl ((R,E)-2-((R)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-4-methyl-5-oxopent-3-en-1-yl)carbamate (3d). The reaction was carried out following the general procedure to furnish the crude products as a 3.0:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.10 ppm (bd), δ_{minor} 5.91 ppm (bd).

The title compound was isolated as a mixture of diastereoisomers ($R_f = 0.25$ hexane/ethyl acetate 7/3) in 63% yield (white solid). The enantiomeric excess was determined to be 94% for the major diastereoisomer by HPLC analysis on a Daicel Chiralpak IB column: 85/15 hexane/i-PrOH, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 27.4$ min, $\tau_{\text{minor}} = 45.1$ min. $[\alpha]_{\text{D}}^{26} = +55.5$ ($c = 0.90$, CHCl_3 , d.r. 3.0/1, 94% ee $_{\text{major}}$, 74% ee $_{\text{minor}}$). HRMS calc. for $(\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_5 + \text{Na})$: 507.1896, found 507.1911. ^1H NMR (400 MHz, CDCl_3): δ 9.04 (bs, 1H), 7.50-7.13 (m, 14H, overlap with the signal from the minor diastereoisomer), 7.05 (t, 1H, $J_t = 7.4$ Hz), 6.73 (d, 1H, $J = 7.8$ Hz), 6.10 (bd, 1H, $J = 10.0$ Hz), 5.34-5.25 (m, 1H), 5.07-5.03 (m, 1H, overlap with the signal from the minor diastereoisomer), 4.99 (d, 1H, $J = 15.6$ Hz, overlap with the signal from the minor diastereoisomer), 4.66 (d, 1H, $J = 15.6$ Hz), 3.82-3.73 (m, 1H, overlap

with the signal from the minor diastereomer), 3.64-3.47 (m, 2H, overlap with the signal from the minor diastereomer), 1.50 (bs, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 194.7, 176.6, 153.7, 147.2, 143.3, 142.2, 136.4, 135.4, 130.3, 129.4, 129.0, 128.6, 128.2, 127.5, 124.1, 123.6, 109.6, 77.2, 66.9, 47.2, 44.0, 40.0, 9.7 ppm.

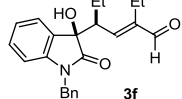


(S,E)-2-benzyl-4-((R)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-5-phenylpent-2-enal (3e). The reaction was carried out following the general procedure (using 20% mol of catalyst loading) to furnish the crude products as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 9.32 ppm (s), δ_{minor} 9.24 ppm (s).

The title compound was isolated as a mixture of diastereoisomers (hexane/ethyl acetate 10/1) in 65% yield (white solid). The enantiomeric excess was determined to be 90% for the major diastereoisomer by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 9.3 min, τ_{minor} = 11.7 min. $[\alpha]_{\text{D}}^{26}$ = +92.5 (c = 0.75, CHCl_3 , d.r. 1.5/1, major 90% ee, minor 76% ee). HRMS calc. for ($\text{C}_{33}\text{H}_{29}\text{NO}_3 + \text{Na}$): 510.2045, found 510.2021.

^1H NMR (400 MHz, CDCl_3): δ 9.32 (bs, 1H), 7.36-6.93 (m, 20H, overlap with the signal from the minor diastereomer), 6.79 (bd, 1H, J = 7.8 Hz, overlap with the signal from the minor diastereomer), 6.76-6.71 (m, 2H), 6.48 (d, 1H, J = 11.0 Hz), 5.00 (d, 1H, J = 15.9 Hz, overlap with the signal from the minor diastereomer), 4.72 (d, 1H, J = 15.9 Hz), 3.72 (td, 1H, J_t = 11.0 Hz, J_d = 3.4 Hz), 3.41 (d, 1H, J = 15.1 Hz), 3.02-2.95 (m, 1H, overlap with the signal from the minor diastereomer), 2.92 (d, 1H, J = 15.0 Hz, signal overlapped with minor isomer), 2.87 (bs, 1H), 2.39 (dd, 1H, J_t = 13.3 Hz, J_2 = 10.7 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 194.1, 177.0, 150.9, 146.0, 142.4, 138.3, 138.1, 135.3, 130.2, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.5, 126.6, 126.0, 124.7, 123.4, 109.8, 77.9, 49.3, 44.1, 35.4, 29.7 ppm.

(S,E)-4-((R)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-2-ethylhex-2-enal (3f)



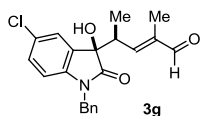
The reaction was carried out following the general procedure (using 20% mol of the catalyst **D**/acid combination) to furnish the crude products as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.22 ppm (d), δ_{minor} 5.87 ppm (d).

The title compound was isolated as a single diastereoisomer (hexane/ethyl acetate 10:1) in 28% yield (white solid). The enantiomeric excess was determined to be 94% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 9.1 min, τ_{minor} = 12.9 min. $[\alpha]_{\text{D}}^{26}$ = +84.5 (c = 1.45, CHCl_3 , 94% ee). HRMS calc. for ($\text{C}_{23}\text{H}_{25}\text{NO}_3 + \text{Na}$): 386.1732, found 386.1739.

^1H NMR (400 MHz, CDCl_3): δ 9.35 (s, 1H), 7.37 (dd, 1H, J_t = 7.4 Hz, J_2 = 1.0 Hz), 7.34-7.22 (m, 6H), 7.07 (td, 1H, J_t = 7.5 Hz, J_d = 1.0 Hz), 6.77 (d, 1H, J = 7.8 Hz), 6.22 (d, 1H, J = 11.0 Hz), 5.01 (d, 1H, J = 15.4 Hz), 4.74 (d, 1H, J = 15.4 Hz), 3.26 (td, 1H, J_t = 11.1 Hz, J_d = 3.0 Hz), 2.96 (bs, 1H), 2.36-2.23 (m, 2H), 1.67-1.58 (m, 1H), 1.20-1.10 (m, 1H), 0.95 (t, 3H, J = 7.5 Hz), 0.76 (t, 3H, J = 7.5 Hz) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 194.9, 177.4, 150.4, 149.3, 142.9, 135.5, 130.2, 129.0, 128.0, 127.6, 124.7, 123.3, 109.8, 78.2, 48.6, 44.2, 21.7, 18.1, 13.4, 12.1 ppm.

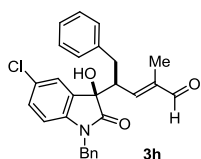
(S,E)-4-((R)-1-benzyl-5-chloro-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (3g)



The reaction was carried out following the general procedure to furnish the crude products as a 1.7:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.39 ppm (d), δ_{minor} 6.17 ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 92% yield (white solid). The enantiomeric excess was determined to be 86% for the major diastereoisomer (73% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 90:10 hexane/i-PrOH, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 15.3 min, τ_{minor} = 22.2 min. $[\alpha]_{\text{D}}^{26}$ = +31.0 (c = 1.15, CHCl_3 , d.r. 1.7/1, major 86% ee, minor 73% ee). HRMS calc. for $(\text{C}_{21}\text{H}_{20}\text{NO}_3\text{Cl}+\text{Na})$: 392.1029, found 392.1038.

^1H NMR (400 MHz, CDCl_3): δ 9.36 (s, 1H), 7.39 (d, 1H, J = 2.1 Hz), 7.37-7.18 (m, 7H, overlap with the signal from the minor diastereomer), 6.72 (d, 1H, J = 8.5 Hz, overlap with the signal from the minor diastereomer), 6.39 (dq, 1H, J_d = 10.2 Hz, J_q = 1.3 Hz), 5.05 (d, 1H, J = 15.7 Hz, overlap with the signal from the minor diastereomer), 4.72 (d, 1H, J = 15.7 Hz), 3.49-3.39 (m, 1H, overlap with the signal from the minor diastereomer), 1.77 (d, 3H, J = 1.3 Hz), 1.05 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 195.0, 176.9, 150.8, 141.6, 141.4, 135.0, 130.1, 129.1, 128.9, 128.3, 127.5, 127.4, 125.2, 110.7, 78.4, 44.3, 41.5, 14.0, 9.9 ppm.

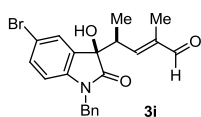


(S,E)-4-((R)-1-benzyl-5-chloro-3-hydroxy-2-oxoindolin-3-yl)-2-methyl-5-phenylpent-2-enal (3h)

The reaction was carried out following the general procedure to furnish the crude products as a 1.6:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.42 ppm (d), δ_{minor} 5.97 ppm (d).

The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 69% yield (white solid). The enantiomeric excess was determined to be 92% for the major diastereoisomer (78% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 52.5/2.5/50 hexane/i-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.9 min, τ_{minor} = 9.2 min. $[\alpha]_{\text{D}}^{26}$ = +80.0 (c = 0.77, CHCl_3 , d.r. 1.6/1, major 92% ee, minor 78% ee). HRMS calc. for $(\text{C}_{27}\text{H}_{24}\text{NO}_3\text{Cl}+\text{Na})$: 468.1342, found 468.1358.

^1H NMR (400 MHz, CDCl_3): δ 9.19 (s, 1H), 7.42 (d, 1H, J = 2.2 Hz), 7.36-7.12 (m, 9H, overlap with the signal from the minor diastereomer), 7.05-7.01 (m, 2H overlap with the signal from the minor diastereomer), 6.71 (d, 1H, J = 8.4 Hz, overlap with the signal from the minor diastereomer), 6.42 (dq, 1H, J_d = 10.9 Hz, J_q = 1.3 Hz), 5.02 (d, 1H, J = 15.4 Hz, overlap with the signal from the minor diastereomer), 4.73 (d, 1H, J = 15.4 Hz), 3.62 (td, 1H, J_t = 10.9 Hz, J_d = 3.6 Hz, overlap with the signal from the minor diastereomer), 3.34 (bs, 1H), 3.07 (dd, 1H, J_1 = 13.6 Hz, J_2 = 3.1 Hz), 2.49 (dd, 1H, J_1 = 13.6 Hz, J_2 = 10.9 Hz), 1.27 (s, 3H, signal overlapped with minor isomer) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 194.6, 176.8, 148.7, 143.5, 141.2, 138.1, 134.9, 130.4, 130.3, 129.2, 129.0, 128.6, 128.3, 127.6, 126.7, 125.0, 110.9, 78.0, 49.5, 44.3, 34.9, 9.5 ppm.

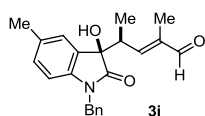


(S,E)-4-((R)-1-benzyl-5-bromo-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (3i)

The reaction was carried out following the general procedure to furnish the crude products as a 1.9:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.36 ppm (d), δ_{minor} 6.19 ppm (d). The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 68% yield (white solid). The enantiomeric excess

was determined to be 85% for the major diastereoisomer (78% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 90:10 hexane/*i*-PrOH, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 8.3$ min, $\tau_{\text{minor}} = 11.5$ min. $[\alpha]_{\text{D}}^{26} = +51.0$ ($c = 1.33$, CHCl_3 , d.r. 1.9/1, $\text{major } 85\%$ ee, $\text{minor } 78\%$ ee). HRMS calc. for ($\text{C}_{21}\text{H}_{20}\text{NO}_3\text{Br}+\text{Na}$): 436.0524, found 436.0533.

^1H NMR (400 MHz, CDCl_3): δ 9.32 (s, 1H), 7.50 (d, 1H, $J = 2.0$ Hz), 7.39-7.23 (m, 7H, overlap with the signal from the minor diastereoisomer), 6.64 (d, 1H, $J = 8.3$ Hz, overlap with the signal from the minor diastereoisomer), 6.36 (dq, 1H, $J_d = 10.4$ Hz, $J_q = 1.4$ Hz), 5.01 (d, 1H, $J = 15.6$ Hz, overlap with the signal from the minor diastereoisomer), 4.67 (d, 1H, $J = 15.6$ Hz), 3.51 (bs, 1H), 3.47-3.36 (m, 1H, overlap with the signal from the minor diastereoisomer), 1.74 (d, 3H, $J = 1.4$ Hz), 1.05 (d, 3H, $J = 6.9$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 195.1, 176.9, 150.9, 141.9, 141.6, 134.9, 132.9, 130.6, 129.1, 128.2, 127.9, 127.5, 116.1, 111.2, 78.4, 44.2, 41.5, 14.1, 9.8 ppm.

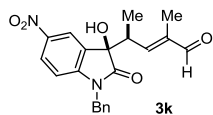


(S,E)-4-((R)-1-benzyl-3-hydroxy-5-methyl-2-oxoindolin-3-yl)-2-methylpent-2-enal (3j). The reaction was carried out following the general procedure to furnish the crude products as a 3.8:1 mixture of diastereoisomers; d.r. determined by integration of ^1H

NMR signal: $\delta_{\text{major}} 6.46$ ppm (d), $\delta_{\text{minor}} 6.22$ ppm (d). The title compound was isolated as a mixture of diastereoisomers ($R_f = 0.30$ hexane/ethyl acetate 8/2) in 76% yield (white solid). The enantiomeric excess was determined to be 95% for the major diastereoisomer (81% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49:2:49 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 7.4$ min, $\tau_{\text{minor}} = 10.3$ min. $[\alpha]_{\text{D}}^{26} = +66.7$ ($c = 1.345$, CHCl_3 , d.r. 3.8/1, $\text{major } 95\%$ ee, $\text{minor } 81\%$ ee). HRMS calc. for ($\text{C}_{22}\text{H}_{23}\text{NO}_3+\text{Na}$): 372.1576, found 372.1586.

^1H NMR (400 MHz, CDCl_3): δ 9.36 (s, 1H), 7.35-7.19 (m, 6H, overlap with the signal from the minor diastereoisomer), 7.06 (bd, 1H, $J = 7.9$ Hz), 6.68 (d, 1H, $J = 7.9$ Hz, overlap with the signal from the minor diastereoisomer), 6.46 (dq, 1H, $J_d = 10.5$ Hz, $J_q = 1.3$ Hz), 5.02 (d, 1H, $J = 15.6$ Hz, overlap with the signal from the minor diastereoisomer), 4.69 (d, 1H, $J = 15.6$ Hz), 3.49-3.41 (m, 2H, overlap with the signal from the minor diastereoisomer), 2.34 (s, 3H), 1.76 (d, 3H, $J = 1.3$ Hz), 1.02 (d, 3H, $J = 6.8$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 195.2, 177.4, 152.1, 141.2, 140.5, 135.6, 132.9, 130.4, 128.9, 128.5, 127.9, 127.6, 127.4, 125.4, 109.5, 78.6, 44.1, 41.5, 21.2, 14.2, 9.8 ppm.

(S,E)-4-((R)-1-benzyl-3-hydroxy-5-nitro-2-oxoindolin-3-yl)-2-methylpent-2-enal (3k)



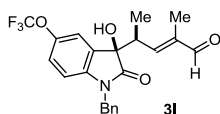
The reaction was carried out following the general procedure to furnish the crude products as a 1.5:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: $\delta_{\text{major}} 6.33$ ppm (d), $\delta_{\text{minor}} 6.15$ ppm (d).

The title compound was isolated as a mixture of diastereoisomers ($R_f = 0.30$ hexane/ethyl acetate 7/3) in 87% yield (white solid). The enantiomeric excess was determined to be 87% for the major diastereoisomer (75% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49:2/49 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 10.7$ min, $\tau_{\text{minor}} = 14.0$ min. $[\alpha]_{\text{D}}^{26} = +80.3$ ($c = 0.80$, CHCl_3 , d.r. 1.5/1, $\text{major } 87\%$ ee, $\text{minor } 75\%$ ee). HRMS calc. for ($\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_5+\text{Na}$): 403.1270, found 403.1270.

^1H NMR (400 MHz, CDCl_3): δ 9.32 (s, 1H), 8.35-8.25 (m, 2H, overlap with the signal from the minor diastereoisomer), 7.39-7.23 (m, 5H), 6.88 (d, 1H, $J = 6.7$ Hz, overlap with the signal from the minor diastereoisomer), 6.33 (dq, 1H, $J_d = 10.4$ Hz, $J_q = 1.4$ Hz), 5.09 (d, 1H, $J = 15.4$ Hz, signal overlapped with minor isomer), 4.78 (d, 1H, $J = 15.4$ Hz), 3.55-3.39 (m, 1H, signal overlap with the signal from the minor diastereoisomer), 3.26 (bs, 1H, overlap with the signal from the minor diastereoisomer), 1.71 (d, 3H, $J = 1.4$ Hz),

1.08 (d, 3H, $J = 6.7$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 195.1, 178.3, 151.2, 141.3, 140.3, 136.9, 136.1, 132.0, 128.7, 127.5, 126.8, 124.6, 123.8, 103.1, 77.4, 44.8, 41.8, 14.0, 9.8 ppm.

(S,E)-4-((R)-1-benzyl-3-hydroxy-2-oxo-5-(trifluoromethoxy)indolin-3-yl)-2-methylpent-2-enal (3l)

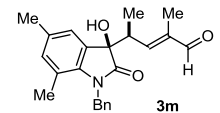


The reaction was carried out following the general procedure to furnish the crude products as a 2.9:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.28 ppm (d), δ_{minor} 6.16 ppm (d).

The title compound was isolated as a mixture of diastereoisomers ($R_f = 0.30$ hexane/ethyl acetate 8/2) in 71% yield (white solid). The enantiomeric excess was determined to be 89% for the major diastereoisomer (63% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49/2/49 hexane/i-PrOH/DCM, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 8.2$ min, $\tau_{\text{minor}} = 10.5$ min. HRMS calc. for ($\text{C}_{22}\text{H}_{20}\text{NO}_4\text{F}_3 + \text{Na}$): 442.1242, found 442.1259.

^1H NMR (400 MHz, CDCl_3): δ 9.28 (s, 1H), 7.36-7.26 (m, 6H, overlap with the signal from the minor diastereoisomer), 7.14-7.10 (m, 1H), 6.76 (d, 1H, $J = 8.4$ Hz, overlap with the signal from the minor diastereoisomer), 6.28 (dq, 1H, $J_d = 10.3$ Hz, $J_q = 1.2$ Hz), 5.06 (d, 1H, $J = 15.6$ Hz, signal overlap with the signal from the minor diastereoisomer), 4.70 (d, 1H, $J = 15.6$ Hz), 3.45-3.37 (m, 1H, signal overlapped with minor isomer), 3.02 (bs, 1H, overlap with the signal from the minor diastereoisomer), 1.70 (d, 3H, $J = 1.2$ Hz), 1.07 (d, 3H, $J = 6.6$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 194.9, 177.1, 150.5, 145.1, 141.6, 141.4, 134.9, 129.2, 128.4, 127.6, 123.3, 118.6, 110.3, 78.3, 44.4, 41.7, 13.9, 9.8 ppm.

(S,E)-4-((R)-1-benzyl-3-hydroxy-5,7-dimethyl-2-oxoindolin-3-yl)-2-methylpent-2-enal (3m)

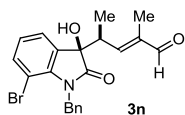


The reaction was carried out following the general procedure to furnish the crude products as a 3.9:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.47 ppm (d), δ_{minor} 6.39 ppm (d) in deuterated toluene.

The title compound was isolated as a mixture of diastereoisomers ($R_f = 0.30$ hexane/ethyl acetate 10/1) in 65% yield (pale-pink solid). The enantiomeric excess was determined to be 91% for the major diastereoisomer (77% for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 48.5:3:48.5 hexane/i-PrOH/DCM, flow rate 1.00 mL/min, $\lambda = 215, 254$ nm: $\tau_{\text{major}} = 6.4$ min, $\tau_{\text{minor}} = 7.7$ min. $[\alpha]_{\text{D}}^{26} = +64.5$ ($c = 1.40$, CHCl_3 , d.r. 3.9/1, $\text{major } 90\% \text{ ee}$, $\text{minor } 77\% \text{ ee}$). HRMS calc. for ($\text{C}_{23}\text{H}_{25}\text{NO}_3 + \text{Na}$): 386.1732, found 386.1751.

^1H NMR (400 MHz, CDCl_3): δ 9.40 (s, 1H), 7.32-7.20 (m, 3H, overlap with the signal from the minor diastereoisomer), 7.17-7.12 (m, 2H, overlap with the signal from the minor diastereoisomer), 7.08 (bs, 1H, signal overlap with the signal from the minor diastereoisomer), 6.81 (bs, 1H), 6.47 (dq, 1H, $J_d = 10.4$ Hz, $J_q = 1.4$ Hz), 5.15 (s, 1H, overlap with the signal from the minor diastereoisomer), 5.10 (s, 1H, overlap with the signal from the minor diastereoisomer), 3.48-3.38 (m, 2H, overlap with the signal from the minor diastereoisomer), 2.28 (s, 3H), 2.21 (s, 3H, overlap with the signal from the minor diastereoisomer), 1.73 (d, 3H, $J = 1.4$ Hz), 1.06 (d, 3H, $J = 6.9$ Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 195.3, 178.5, 152.4, 141.1, 138.5, 137.3, 134.6, 132.9, 129.0, 127.5, 125.9, 123.3, 120.2, 77.6, 45.3, 41.6, 20.9, 18.8, 14.3, 9.8 ppm.

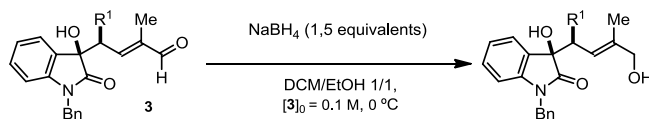
(S,E)-4-((R)-1-benzyl-7-bromo-3-hydroxy-2-oxoindolin-3-yl)-2-methylpent-2-enal (**3n**)



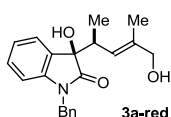
The reaction was carried out following the general procedure to furnish the crude products as a 2.4:1 mixture of diastereoisomers; d.r. determined by integration of ^1H NMR signal: δ_{major} 5.46 ppm (d), δ_{minor} 5.40 ppm (d). The title compound was isolated as a mixture of diastereoisomers (R_f = 0.30 hexane/ethyl acetate 8/2) in 88% yield (white solid). The enantiomeric excess was determined to be 92% for the major diastereoisomer (71% ee for the minor) by HPLC analysis on a Daicel Chiralpak IA column: 49:2:49 hexane/i-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 8.2 min, τ_{minor} = 10.3 min. $[\alpha]_D^{26}$ = +38.6 (c = 1.15, CHCl_3 , d.r. 2.4/1, major 92% ee, minor 71% ee). HRMS calc. for ($\text{C}_{21}\text{H}_{20}\text{NO}_3\text{Br}+\text{Na}$): 436.0524, found 436.0508.

^1H NMR (400 MHz, CDCl_3): δ 9.30 (s, 1 H, overlap with the signal from the minor diastereomer), 7.43 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.2 Hz, overlap with the signal from the minor diastereomer), 7.36 (dd, 1H, J_1 = 7.4 Hz, J_2 = 1.2 Hz), 7.33-7.21 (m, overlap with the signal from the minor diastereomer), 6.97 (dd, 1 H, J_1 = 8.2 Hz, J_2 = 7.3 Hz, signal overlapped with minor isomer), 6.35 (dq, 1H, J_d = 10.6 Hz, J_q = 1.5 Hz, overlap with the signal from the minor diastereomer), 5.46 (d, 1H, J = 16.1 Hz), 5.29 (d, 1H, J = 16.1 Hz, overlap with the signal from the minor diastereomer), 3.45-3.33 (m, 2H, overlap with the signal from the minor diastereomer), 1.69 (d, 3H, J = 1.3 Hz), 1.03 (d, 3H, J = 6.7 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 195.1, 178.3, 151.1, 141.4, 140.3, 136.9, 136.2, 132.0, 127.6, 126.8, 126.5, 124.6, 123.7, 103.1, 77.4, 44.8, 41.8, 14.0, 9.8 ppm.

D. General Procedure for the Reduction of Products **3**

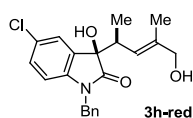


0.1 mmol of adducts **3a**, **3h**, and **3j** were transferred in a vial and dissolved in 1 mL of a DCM/ethanol mixture (1 to 1 v/v) and cooled to 0 °C (ice bath). After the addition of NaBH_4 (1.5 equivalents, added in small portions) the mixture was stirred until the reaction was considered complete by TLC analysis (typically 1-2h). The reaction was then quenched with water and the compound extracted with diethyl ether. The aqueous phase was washed three times with diethyl ether and the combined organic phases dried over sodium sulphate. Solvent was removed under reduced pressure and the crude mixture was purified by chromatography column. Separation of the two diastereoisomers was straightforward, securing access to diastereomerically pure alcohol adducts.



Compound **3a** was reduced to the corresponding alcohol following the general procedure. The crude was purified by flash column chromatography (gradient from hexane/ethyl acetate 7/3 to 1/1, R_f = 0.15 in hexane/ethyl acetate 7/3) to afford compound **3a-red** as a single diastereoisomer in 71% yield (colorless solid, 47% overall yield).

^1H NMR (400 MHz, CDCl_3): δ 7.44-7.39 (m, 1H), 7.36-7.26 (m, 5H), 7.22 (td, 1H, J_t = 7.9 Hz, J_d = 1.3 Hz), 7.05 (td, 1H, J_t = 7.9 Hz, J_d = 1.3 Hz), 6.75 (d, 1H, J = 7.9 Hz), 5.48 (d, 1H, J = 10.3 Hz), 5.07 (d, 1H, J = 15.3 Hz), 4.70 (d, 1H, J = 15.3 Hz), 4.02 (bs, 1H), 3.25-3.17 (m, 1H), 3.03 (bs, 1H), 1.71 (s, 3H), 0.88 (d, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 177.9, 143.1, 139.0, 135.8, 129.6, 129.1, 128.9, 127.9, 127.6, 124.9, 123.8, 122.9, 109.4, 78.9, 68.6, 44.1, 40.2, 15.1, 14.4 ppm.

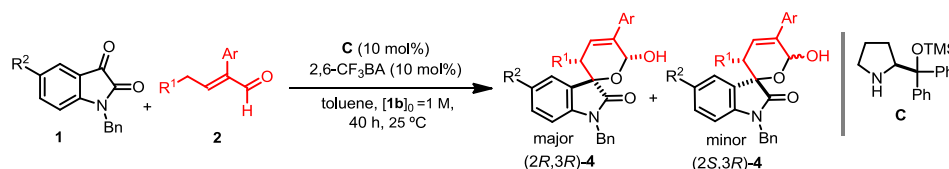


Compound **3h** was reduced to the corresponding alcohol following the general procedure. Chromatographic purification on silica gel (gradient from hexane/ethyl acetate 8:2 to 6:4, $R_f = 0.2$ in hexane/ethyl acetate 7/3) afforded the reduced adduct **3h-red** as single diastereoisomer in 55% yield (colorless solid, 35% overall yield). Since the alcohol was not solid, the major diastereoisomer was then re-oxidized to the aldehyde adduct **3h** in order to get suitable crystals for X-ray crystallographic analysis. Oxidation of the alcohol **3h-red**: compound **3h-red** was transferred in a round bottom flask, then DCM (1.5 ml, 0.05M) and activated MnO_2 (10 equivalents) were added and the stirring continued over a period of 16 hours. The mixture was filtered on celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ethyl acetate 7/3) to give the pure **3h** as single diastereoisomer in a 32% overall yield.



Compound **3j** was reduced to the corresponding alcohol following the general procedure. Chromatographic purification on silica gel (gradient from hexane/ethyl acetate 7/3 to hexane/ethyl acetate 1/1, $R_f = 0.15$ in hexane/ethyl acetate 7/3) to afford compound **3j-red** as single diastereoisomer in 74% yield (colorless solid, 44% overall yield). ^1H NMR (500 MHz, CDCl_3): δ 7.34–7.29 (m, 5H), 7.23–7.20 (m, 1H), 7.02 (d, 1H, $J = 7.7$ Hz), 6.63 (d, 1H, $J = 8.0$ Hz), 5.49 (d, 1H, $J = 10.5$ Hz), 5.05 (d, 1H, $J = 15.8$ Hz), 4.69 (d, 1H, $J = 15.8$ Hz), 4.02 (bs, 1H), 3.23–3.15 (m, 1H), 2.95 (bs, 1H), 2.95 (bs, 1H), 2.31 (s, 3H), 1.72 (s, 3H), 0.88 (d, 3H, $J = 6.8$ Hz) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 177.8, 140.7, 138.9, 135.9, 132.6, 129.8, 129.2, 129.1, 128.9, 127.8, 127.6, 125.6, 124.0, 109.1, 78.9, 68.7, 44.1, 40.2, 21.2, 15.1, 14.4 ppm

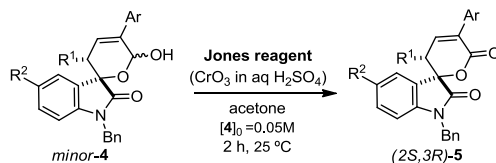
E. General Procedure for the Hetero-Diels-Alder-type Reaction of α -Aryl Substituted Enals



All the reactions were carried out in toluene (synthesis grade, >99%) without any precaution for excluding air and moisture (open air chemistry on the benchtop). An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **C** (6.5 mg, 0.02 mmol, 10 mol%) and 2,6-bis(trifluoromethyl)benzoic acid (5.2 mg, 0.02 mmol, 10 mol%). Then the solvent (200 μL) and the α -branched enal **2** (0.4 mmol) were sequentially added and the resulting solution stirred at ambient temperature for 5 minutes. The reaction was started by the addition of the *N*-benzyl protected isatin derivative **1** (0.2 mmol). The vial was sealed and immersed in a water bath (thermostated at 25 $^\circ\text{C}$) and stirring continued over 40 hours. Then the crude mixture was flushed through a short plug of silica, using dichloromethane/diethyl ether 1:1 as the eluent (5 ml). Solvent was removed under reduced pressure and the crude mixture was analyzed by ^1H NMR spectroscopy to determine the diastereomeric ratio. The two diastereoisomers for product **4** were isolated by flash column chromatography using the specified eluent.

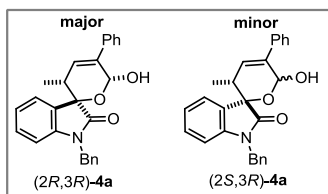
While the major isomers, the spirooxindole lactols (*2R,3R*)-**4** are stable compounds that can be stored after isolation, the minor isomers (the (*2S,3R*)-**4** adducts) are stable on the bench only for 2-3 days. In addition, given the difficulties of determining their enantiomeric excess by HPLC analysis, spirooxindole lactols (*2S,3R*)-**4** were oxidized suddenly after their isolation. The procedure for the oxidation is as follows:

Procedure for the Oxidation of Lactol **4** to Lactones **5**

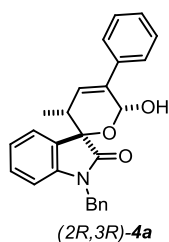


The oxidation of compounds **4** to the corresponding lactones **5** was performed following a slightly modified procedure reported in literature.⁸ 0.1 mmol of compound **4** were placed and dried in a 5 ml vial, followed by the sequential addition of acetone (0.5 mL) and the Jones reagent (dropwise, 0.2 mL). The mixture was stirred at room temperature over 2 hours, then diluted with diethyl ether and quenched with water. The aqueous phase was washed three times with diethyl ether and the combined organic phases dried over sodium sulphate. Solvent was removed under reduced pressure and the crude mixture was purified by chromatography on silica gel (typically with hexane/ethyl acetate 9/1 as the eluent) to afford the pure spirooxindole dihydropyran-2-ones (2*S*,3*R*)-**5**.

Jones reagent was prepared carefully diluting a solution of CrO₃ (5g) in 5 mL of H₂SO₄ with 25 mL of water at 0 °C.

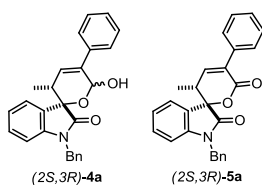


The reaction was carried out following the general procedure to furnish the crude products as a mixture of 2.2:1 diastereoisomers (2*R*,3*R*)-**4a**/(2*S*,3*R*)-**4a**; d.r. determined by integration of ¹H NMR signal: δ_{major} 6.13 ppm (bs), δ_{minor} 6.22 ppm and 6.25 ppm (bs). (2*R*,3*R*)-**4a**/(2*S*,3*R*)-**4a** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl ether 9/1 to 8/2).



The major diastereoisomer (2*R*,3*R*)-**4a** was isolated as single diastereoisomer (*R_f* = 0.3 hexane/diethyl ether 8/2) in 45% yield (white solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.8 min, τ_{minor} = 5.7 min. $[\alpha]_{\text{D}}^{26}$ = -59.0 (*c* = 1.60, CHCl₃, 99% ee). HRMS calc. for (C₂₆H₂₃NO₃+Na): 420.1576, found 420.1571.

¹H NMR (400 MHz, CDCl₃): δ 7.55-7.51 (m, 2H), 7.35-7.30 (m, 3H), 7.28-7.17 (m, 7H), 7.06 (td, 1H, *J_t* = 7.5 Hz, *J_d* = 0.9 Hz), 6.67 (d, 1H, *J* = 7.7 Hz), 6.06-6.04 (m, 1H), 5.85 (d, 1H, *J* = 12.8 Hz), 5.09 (d, 1H, *J* = 12.7 Hz), 5.00 (d, 1H, *J* = 15.5 Hz), 4.65 (d, 1H, *J* = 15.5 Hz), 3.03-2.96 (m, 1H), 0.87 (d, 3H, *J* = 7.5 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 177.9, 142.8, 137.7, 137.2, 135.4, 130.1, 129.7, 129.0, 128.6, 127.9, 127.5, 126.7, 126.6, 124.0, 123.9, 109.5, 92.1, 78.6, 44.3, 36.9, 14.8 ppm.



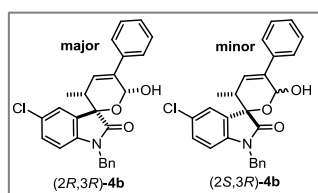
The minor (2*S*,3*R*)-**4a** isomer was isolated as a 1/1 mixture of anomers (*R_f* = 0.20 hexane/ethyl acetate 8/2) in 22% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2*S*,3*R*)-**5a** using Jones reagent following the reported procedure. The corresponding lactone was obtained as a

⁸ A. Füstner, T. Nagano, *J. Am. Chem. Soc.*, **2007**, *129*, 1906-1907

single diastereoisomer and isolated after chromatography column (R_f = 0.3 hexane/diethyl ether 8/2) in 95% yield.

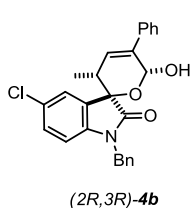
(2*S*,3*R*)-**5a**. The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 50/50 hexane/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.1 min, τ_{minor} = 6.1 min. HRMS calc. for (C₂₆H₂₁NO₃+Na): 418.1419, found 418.1407.

¹H NMR (400 MHz, CDCl₃): δ 7.61-7.55 (m, 2H), 7.48-7.23 (m, 10H), 6.97 (td, 1H, J_t = 7.7 Hz, J_d = 0.9 Hz), 6.84 (d, 1H, J = 7.9 Hz), 5.02 (d, 1H, J = 15.6 Hz), 4.86 (d, 1H, J = 15.6 Hz), 3.66 (qd, 1H, J_q = 7.2 Hz, J_d = 2.4 Hz), 0.98 (d, 3H, J = 7.3 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 172.1, 162.1, 144.9, 143.4, 135.1, 134.8, 132.5, 131.2, 129.1, 128.8, 128.3, 128.3, 128.1, 127.4, 125.1, 125.0, 123.3, 110.3, 84.6, 44.3, 34.6, 14.6 ppm.



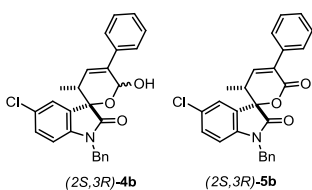
The reaction was carried out following the general procedure to furnish the crude products as a mixture of 2.3:1 diastereoisomers (2*R*,3*R*)-**4b**/(2*S*,3*R*)-**4b**; d.r. determined by integration of ¹H NMR signal: δ_{major} 6.12 ppm (bs), δ_{minor} 6.19 ppm and 6.23 ppm (bs). (2*R*,3*R*)-**4b**/(2*S*,3*R*)-**4b** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl

ether 9/1 to 8/2).



(2*R*,3*R*)-**4b** was isolated as a single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 47% yield (white solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.5 min, τ_{minor} = 6.9 min. $[\alpha]_D^{26}$ = -20.7 (*c* = 1.3, CHCl₃, 99% ee). HRMS calc. for (C₂₆H₂₂NO₃Cl+Na): 454.1186, found 454.1183.

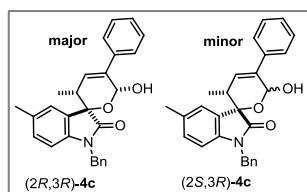
¹H NMR (400 MHz, CDCl₃): δ 7.61-7.57 (m, 2H), 7.42-7.18 (m, 11H), 6.65 (d, 1H, J = 8.5 Hz), 6.12-6.09 (m, 1H), 5.91 (s, 1H), 5.04 (d, 1H, J = 15.8 Hz), 4.69 (d, 1H, J = 15.8 Hz), 3.07-2.99 (m, 1H), 0.94 (d, 3H, J = 7.4 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 177.4, 141.2, 137.4, 137.2, 134.9, 131.4, 130.0, 129.4, 129.1, 128.6, 128.1, 127.9, 127.5, 126.7, 126.3, 124.6, 110.5, 92.1, 44.4, 36.9, 14.7 ppm.



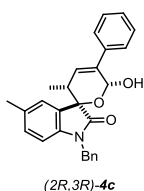
(2*S*,3*R*)-**4b** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 17% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2*S*,3*R*)-**5b** using the Jones reagent following the reported procedure. The corresponding lactone was obtained as a single diastereoisomer and isolated after chromatography column (R_f = 0.3

hexane/diethyl ether 8/2) in 98% yield. (2*S*,3*R*)-**5b**. The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 40/60 hexane/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.3 min, τ_{minor} = 9.3 min. HRMS calc. for (C₂₆H₂₁NO₃+Na): 418.1419, found 418.1407.

¹H NMR (400 MHz, CDCl₃): δ 7.58-7.53 (m, 2H), 7.48-7.40 (m, 3H), 7.38-7.21 (m, 8H), 6.84 (t, 1H, J = 2.8 Hz), 6.70 (d, 1H, J = 8.4 Hz), 4.99 (d, 1H, J = 15.6 Hz), 4.85 (d, 1H, J = 15.6 Hz), 3.65 (qd, 1H, J_q = 7.5 Hz, J_d = 2.9 Hz), 1.00 (d, 3H, J = 7.3 Hz) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 171.7, 161.6, 144.6, 141.8, 134.6, 134.6, 132.6, 131.1, 129.2, 128.9, 128.7, 128.7, 128.3, 128.3, 127.4, 126.6, 125.5, 111.4, 84.3, 44.4, 34.5, 14.5 ppm.



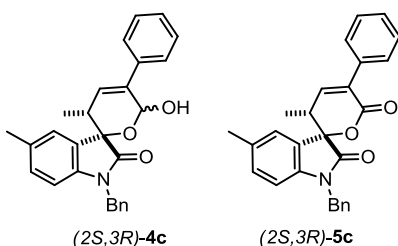
(*2R,3R*)-**4c** and (*2S,3R*)-**4c**. The reaction was carried out following the general procedure, using 20 mol% of the catalyst, to furnish the crude products as a mixture of 3.0:1 diastereoisomers (*2R,3R*)-**4c**/*2S,3R*)-**4c**; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.11 ppm (bs), δ_{minor} 6.19 ppm and 6.22 ppm (bs). (*2R,3R*)-**4c**/*2S,3R*)-**4c** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl ether 9/1 to 8/2) as described below.



(*2R,3R*)-**4c** was isolated as a single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 63% yield (white solid). The enantiomeric excess was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.5 min, τ_{minor} = 5.6 min. $[\alpha]_{\text{D}}^{27}$ = -30.8 (c = 1.25, CHCl_3 , 99% ee). HRMS calc. for ($\text{C}_{27}\text{H}_{25}\text{NO}_3 + \text{Na}$): 434.1732, found 434.1716.

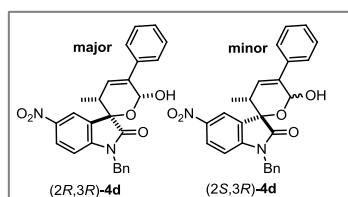
^1H NMR (400 MHz, CDCl_3): δ 7.61-7.56 (m, 2H), 7.42-7.25 (m, 10H), 7.20-7.17 (m, 1H), 7.04 (d, 1H, J = 8.3 Hz), 6.61 (d, 1H, J = 8.2 Hz), 6.11-6.09 (m, 1H), 6.10 (bs, 1H), 5.89 (dq, 1H, J_d = 12.6 Hz, J_q = 1.2 Hz), 5.20 (d, 1H, J = 12.7 Hz), 5.04 (d, 1H, J = 15.6 Hz), 4.70 (d, 1H, J = 15.6 Hz), 4.70 (d, 1H, J = 15.8 Hz), 3.08-2.99 (m, 1H), 2.32 (s, 3H), 0.94 (d, 3H, J = 7.4 Hz) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 177.8, 140.3, 137.7, 137.2, 135.5, 133.7, 130.4, 129.7, 129.0, 128.6, 127.9, 127.8, 127.5, 126.7, 126.7, 124.7, 109.3, 92.2, 78.7, 44.3, 36.9, 21.2, 14.9 ppm.

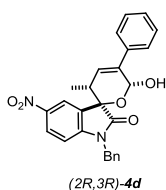


(*2S,3R*)-**4c** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 17% yield (white solid). The title compound was directly oxidized to the corresponding lactone (*2S,3R*)-**5c** using the Jones reagent following the reported procedure. The corresponding lactone **5c** was obtained as a single diastereoisomer and isolated after chromatography column (R_f = 0.3 hexane/ethyl acetate 9/1) in 94% yield.

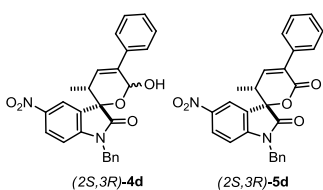
(*2S,3R*)-**5c**. The enantiomeric excess was determined to be 98% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.5 min, τ_{minor} = 5.3 min. $[\alpha]_{\text{D}}^{26}$ = -73.63 (c = 0.4, CHCl_3 , 98% ee). ^1H NMR (400 MHz, CDCl_3): δ 7.60-7.54 (m, 2H), 7.48-7.39 (m, 3H), 7.36-7.22 (m, 5H), 7.18 (bs, 1H), 7.05 (bd, 1H, J = 7.8 Hz), 6.83 (d, 1H, J = 2.6 Hz), 6.65 (d, 1H, J = 8.1 Hz), 4.99 (d, 1H, J = 15.7 Hz), 4.83 (d, 1H, J = 15.7 Hz), 3.65 (qd, 1H, J_q = 7.4 Hz, J_d = 2.7 Hz), 2.63 (s, 3H), 0.98 (d, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 172.1, 162.2, 145.1, 140.9, 135.2, 135.0, 132.9, 132.5, 131.4, 129.1, 128.8, 128.7, 128.4, 128.0, 127.4, 125.8, 125.0, 110.1, 84.8, 44.4, 34.6, 21.3, 14.6 ppm.



(*2R,3R*)-**4d** and (*2S,3R*)-**4d**. The reaction was carried out following the general procedure, using 20 mol % of the catalyst, to furnish the crude products as a mixture of 1.3:1 diastereoisomers (*2R,3R*)-**4d**/*2S,3R*)-**4d**; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.14 ppm (bs), δ_{minor} 6.18 ppm and 6.22 ppm (bs). (*2R,3R*)-**4d**/*2S,3R*)-**4d** were individually isolated by chromatographic purification on silica gel (gradient hexane/ethyl acetate 9/1 to hexane/ethyl acetate 7/3) as described below.

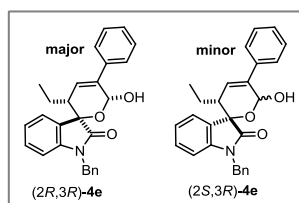


(2R,3R)-**4d** was isolated as mixture of diastereoisomers (18/1) (R_f = 0.3 hexane/diethyl ether 7/3) in 45% yield (white solid). The enantiomeric excess of (2R,3R)-**4d** was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/i-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 6.3 min, τ_{minor} = 9.2 min. $[\alpha]_{\text{D}}^{26}$ = +15.4 (c = 0.85, CHCl_3 , 99% ee). HRMS calc. for ($\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_5+\text{Na}$): 465.1426, found 465.1429. ^1H NMR (400 MHz, CDCl_3): δ 8.27 (d, 1H, J = 2.4 Hz), 8.22 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.3 Hz), 7.60-7.55 (m, 5H), 7.43-7.26 (m, 9H), 6.82 (d, 1H, J = 8.7 Hz), 6.12-6.09 (bs, 1H), 5.93 (d, 1H, J = 12.9 Hz), 5.10 (d, 1H, J = 15.5 Hz), 4.77 (d, 1H, J = 15.5 Hz), 4.73 (d, 1H, J = 12.3 Hz), 3.16-3.07 (m, 1H), 0.93 (d, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 178.0, 148.3, 144.5, 137.3, 137.2, 134.2, 130.8, 129.3, 128.7, 128.5, 128.1, 127.5, 127.1, 126.7, 125.9, 120.1, 109.3, 77.9, 11.6, 36.8, 14.7 ppm.

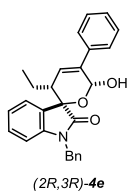


(2S,3R)-**4d** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 17% yield (white solid). The title compound was directly oxidized to the corresponding lactone (2S,3R)-**5d** using the Jones reagent and following the reported procedure. The corresponding lactone was obtained as a single diastereoisomer and isolated after chromatography column (R_f = 0.3 hexane/ethyl acetate 8/2) in 94% yield.

(2S,3R)-**5d**. The enantiomeric excess was determined to be 97% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/i-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 7.3 min, τ_{minor} = 9.3 min. $[\alpha]_{\text{D}}^{27}$ = -122.75 (c = 0.75, CHCl_3 , 97% ee). HRMS calc. for ($\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_5+\text{Na}$): 463.1270, found 463.1266. ^1H NMR (400 MHz, CDCl_3): δ 8.31 (d, 1H, J = 2.3 Hz), 8.24 (dd, 1H, J_1 = 8.6 Hz, J_2 = 2.2 Hz), 7.59-7.54 (m, 2H), 7.50-7.27 (m, 9H), 6.89 (d, 1H, J = 8.8 Hz), 6.86 (d, 1H, J = 2.9 Hz), 5.06 (d, 1H, J = 15.8 Hz), 4.93 (d, 1H, J = 15.8 Hz), 3.67 (qd, 1H, J_q = 7.3 Hz, J_d = 2.0 Hz), 1.03 (d, 3H, J = 7.5 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 172.1, 162.2, 145.1, 140.9, 135.2, 135.0, 132.9, 132.5, 131.4, 129.1, 128.8, 128.7, 128.4, 128.0, 127.4, 125.8, 125.0, 110.1, 84.8, 44.4, 34.6, 21.3, 14.6 ppm.



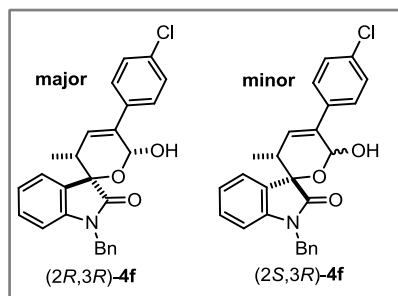
(2R,3R)-**4e** and (2S,3R)-**4e**. The reaction was carried out following the general procedure **B**, using 20 mol % of the catalyst, to furnish the crude products as a mixture of 2.2:1 diastereoisomers (2R,3R)-**4e**/(2S,3R)-**4e**; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.31 ppm (bs), δ_{minor} 6.38 ppm and 6.40 ppm (bs). The reaction conversion was approximately 60% after 72 hours reaction time.



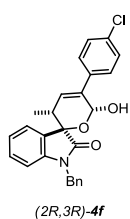
(2R,3R)-**4e** was isolated as a single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 36% yield (white solid). The enantiomeric excess of (2R,3R)-**4e** was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/i-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 4.8 min, τ_{minor} = 5.6 min. $[\alpha]_{\text{D}}^{26}$ = -51.5 (c = 0.65, CHCl_3 , 99% ee). HRMS calc. for ($\text{C}_{27}\text{H}_{25}\text{NO}_3+\text{Na}$): 434.1737, found 434.1716.

^1H NMR (400 MHz, CDCl_3): δ 7.26-7.57 (m, 2H), 7.41-7.36 (m, 3H), 7.36-7.21 (m, 7H), 7.21 (td, 1H, J_1 = 2.8 Hz, J_2 = 0.7 Hz), 6.74 (d, 1H, J = 7.7 Hz), 6.31-6.28 (m, 1H), 5.90 (bd, 1H, J = 11.8 Hz), 5.08 (bd, 1H, J = 11.8 Hz), 5.04 (d, 1H, J = 15.6 Hz), 4.72 (d, 1H, J = 15.6 Hz), 2.80-2.75 (m, 1H), 1.35-1.24 (m, 1H), 1.16-1.06 (m, 1H), 0.92 (t, 1H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 178.1, 142.9, 137.9, 137.4, 135.3,

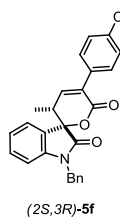
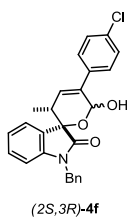
130.1, 129.9, 129.0, 128.6, 127.9, 127.8, 127.5, 126.7, 123.9, 123.9, 109.4, 92.1, 77.9, 44.2, 43.7, 21.5, 11.7 ppm.



(*2R,3R*)-**4f** and (*2S,3R*)-**4f**. The reaction was carried out following the general procedure, using 20 mol% of catalyst, to furnish the crude products as a mixture of 3.2:1 diastereoisomers (*2R,3R*)-**4f**/(*2S,3R*)-**4f**; d.r. determined by integration of ^1H NMR signal: δ_{major} 6.12 ppm (bs), δ_{minor} 6.22 ppm and 6.28 ppm (bs). (*2R,3R*)-**4f**/(*2S,3R*)-**4f** were individually isolated by chromatographic purification on silica gel (gradient from hexane/diethyl ether 9/1 to hexane/ethyl acetate 8/2) as described below.



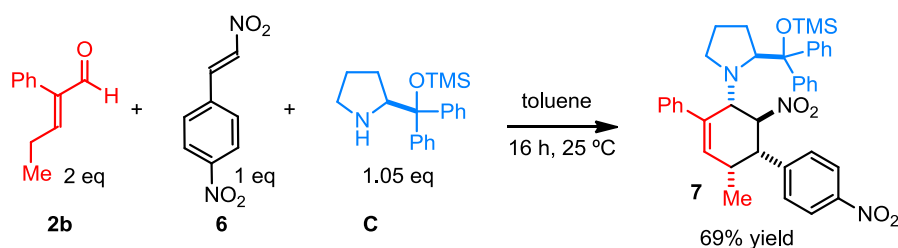
(*2R,3R*)-**4f** was isolated as single diastereoisomer (R_f = 0.3 hexane/diethyl ether 8/2) in 69% yield (white solid). The enantiomeric excess of (*2R,3R*)-**4f** was determined to be 99% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.6 min, τ_{minor} = 8.2 min. $[\alpha]_{\text{D}}^{27}$ = -60.0 (c = 1.05, CHCl_3 , 99% ee). ^1H NMR (400 MHz, CDCl_3): δ 7.58-7.53 (m, 2H), 7.40-7.25 (m, 10H), 7.17-7.12 (m, 1H), 6.77 (d, 1H, J = 7.8 Hz), 6.14-6.11 (bs, 1H), 5.86 (d, 1H, J = 12.8 Hz), 5.20 (d, 1H, J = 12.6 Hz), 5.07 (d, 1H, J = 15.5 Hz), 4.74 (d, 1H, J = 15.5 Hz), 3.10-3.39 (m, 1H), 0.94 (d, 3H, J = 7.3 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 177.9, 142.7, 136.2, 136.1, 135.3, 133.7, 130.2, 129.6, 129.0, 128.7, 128.0, 127.5, 127.0, 124.0, 123.9, 109.5, 91.9, 78.6, 44.3, 36.9, 14.8 ppm.



(*2S,3R*)-**4f** was isolated as a 1/1 mixture of anomers (R_f = 0.20 hexane/ethyl acetate 8/2) in 22% yield (white solid). The title compound was directly oxidized to the corresponding lactone (*2S,3R*)-**5f** using the Jones reagent and following the reported procedure. The corresponding lactone was obtained as a single diastereoisomer and isolated by chromatography column (R_f = 0.3 hexane/ethyl acetate 9/1) in 98% yield.

(*2S,3R*)-**5f**. The enantiomeric excess was determined to be 98% by HPLC analysis on a Daicel Chiralpak IA column: 49.5/1/49.5 hexane/*i*-PrOH/DCM, flow rate 1.00 mL/min, λ = 215, 254 nm: τ_{major} = 5.7 min, τ_{minor} = 7.0 min. HRMS calc. for ($\text{C}_{26}\text{H}_{20}\text{NO}_3\text{Cl} + \text{Na}$): 452.1017, found 452.1029. ^1H NMR (400 MHz, CDCl_3): δ 7.54-7.49 (m, 2H), 7.43-7.38 (m, 2H), 7.37-7.24 (m, 7H), 6.98 (td, 1H, J_f = 7.7 Hz, J_d = 0.7 Hz), 6.84 (d, 1H, J = 2.8 Hz), 6.78 (d, 1H, J = 7.9 Hz), 5.02 (d, 1H, J = 15.6 Hz), 4.85 (d, 1H, J = 15.6 Hz), 3.62 (td, 1H, J_f = 7.4 Hz, J_d = 2.8 Hz), 0.99 (d, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 172.10, 161.9, 145.1, 143.4, 135.1, 135.0, 133.2, 131.5, 131.3, 129.7, 129.1, 128.9, 128.1, 127.4, 125.0, 124.9, 123.4, 110.4, 84.5, 44.4, 34.7, 14.7 ppm.

F. Synthesis of 7

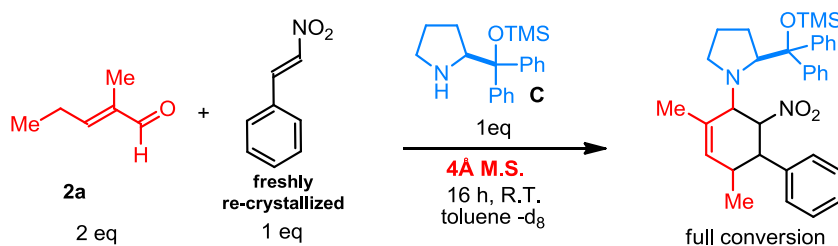


An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **C** (17.0 mg, 0.0525 mmol, 1.05 equivalents) and the α -branched enal **2b** (15.9 μ L, 0.1 mmol, 2 equivalents). Then toluene (100 μ L), was added and the reaction stirred for 5 minutes. Finally the (*E*)-1-nitro-4-(2-nitrovinyl)benzene **6** (9.7 mg, 0.05 mmol, 1 equivalent) was added, the vial closed and stirring continued over 40 hours at 25 °C. After this time the mixture was directly charged on a preparative TLC (20x20cm) and eluted with toluene (R_f = 0.9 in toluene). The silica containing the compound was washed with diethyl ether and DCM and the solvent removed under vacuum to afford the pure product **7** as single diastereoisomer in 69% yield.

Compound **7** was characterized by X-ray crystallographic analysis, see page S36.

As reported in Figure 2c and discussed within the text of the main manuscript, when running the same experiment under the same reaction condition but using the enal **2a** bearing a methyl substituent (that is, mixing 2 equivalents of enal **2a**, 1.05 equivalents of amine **C** and 1 equivalent of nitrostyrene in toluene d_8), the reaction did not proceed at all.

We however found that the cyclic structure of type **7** incorporating the aminocatalyst **C** can form also from the α -methyl substituted enal **2a** when running the same experiment under strictly anhydrous conditions and in the presence of freshly activated molecular sieves (4Å), see Scheme S1.⁹



Scheme S1.

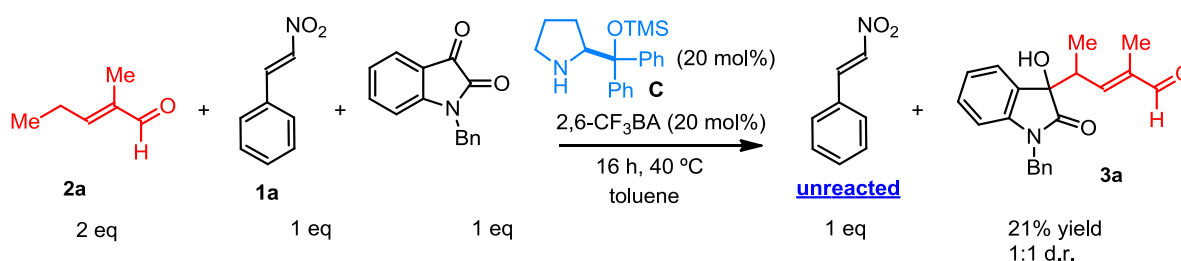
In a Schlenk tube equipped with a Teflon-coated stir bar was charged with 4Å M.S. (50 mg) and the molecular sieves activated by heating under vacuum. Then catalyst **C** (0.05mmol), nitrostyrene (0.05mmol), toluene- d_8 (100 μ L) and enal **2a** (0.1mmol) were sequentially added under argon atmosphere. The mixture was stirred for 16 h at room temperature and then analyzed by ^1H NMR after filtration on 20 μm Teflon HPLC filter under argon. The crude ^1H NMR spectrum revealed complete conversion of the nitrostyrene into the product depicted in the scheme and the unreacted excess of enal **2a**.

⁹ Experiment under strictly anhydrous conditions and using a freshly re-crystallized nitrostyrene

A similar experiment has been performed adding the nitrostyrene to the preformed dienamine of **2a** generated in the presence of freshly activated molecular sieves (4Å) and in toluene *d*₈. In a first attempt, the addition of the nitrostyrene resulted, after 4 hours, in the complete hydrolysis of the dienamine intermediate back to the starting components, the amine **C** and the aldehyde **2a**, without providing any trace of possible products. When repeating the experiment under strictly anhydrous conditions and using a freshly re-crystallized nitrostyrene, we observed the formation of the Diels-Alder-type product of type **7** reported in Scheme S1.

The formation of cyclic adduct requires anhydrous conditions and the presence of freshly activated molecular sieves (4Å), conditions that do not reflect (are very far from) the catalytic reaction system. To provide direct evidence that the dienamine of **2a** can form in the presence of nitrostyrene but under the *actual reaction conditions*, we designed the competitive experiment described in Scheme S2. When adding two different electrophiles, such as the nitrostyrene (1 equiv) and the isatin **2a** (1 equiv), to a mixture of (*E*)-2-methylpent-2-enal **2a** (2 equiv), amine **C** (20 mol%), and the 2,6-bis (trifluoromethyl) benzoic acid (20 mol%) in toluene, only the formation of the aldol product **3a** was observed. The nitrostyrene remained totally unreacted. This indicates that, under the catalytic reaction conditions, the dienamine intermediate generated by the condensation of amine **C** and enal **2a** is formed, with the reaction exclusively channeled through the aldol pathway.

This experiment also indicates that the presence of nitrostyrene does not affect the aldol reaction. Indeed, the aldol process performed in the absence of the nitrostyrene gave very similar results (as detailed in Table 1, entry 3 of the main text).



Scheme S2. Competitive experiment

An ordinary vial equipped with a Teflon-coated stir bar and a plastic screw cap was charged with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **C** (0.01 mmol, 0.2 equivalents), 2,6-bis(trifluoromethyl)benzoic acid (0.01 mmol, 0.2 equivalents) and the α -branched enal **2a** (0.1 mmol, 2 equivalents). Then toluene (200 μ L) was added and the reaction stirred for 5 minutes. Finally the (*E*)-(2-nitrovinyl)benzene (0.05 mmol, 1 equivalent) and the *N*-benzyl protected isatin derivative **1a** (0.05 mmol, 1 equivalent) were added, the vial closed and stirring continued over 16 hours at 25 °C. Then the crude mixture was flushed through a short plug of silica gel using dichloromethane/diethyl ether 1:1 as the eluent (5 ml). Solvent was removed under reduced pressure and the crude mixture was analyzed by ¹H NMR spectroscopy to determine the diastereomeric ratio. The product **3a** was isolated by flash column chromatography using the specified eluent.

G. Conformational Investigations on the Dienamine Intermediates

We focused on the conformational analysis of the covalent dienamine intermediate actively involved in the stereo-defining step. An intimate appreciation of the interactions that allow the aminocatalyst of effectively controlling the molecular topology of the dienamine intermediate may provide fundamental clues to understand and rationalize the origin of the stereoselectivity. We investigated spectroscopically the dienamine intermediate generated by direct condensation of the α -branched enals **2a** and **2b** (bearing a methyl or a phenyl α -branched substituent, respectively) with the catalyst **C**. The formation of the dienamine intermediates were achieved under anhydrous conditions (using Schlenk technique) by mixing an almost equimolar amount of the catalyst **C** (1.05 equivalent) and enals **2** (1 equivalent, 0.15 mmol) in presence of freshly activated molecular sieves (4Å) directly in deuterated solvent ($[2]_0 = 1\text{ M}$). After the complete disappearance of the aldehyde the reaction was filtered through a 0.2 μm PTFE filter directly into the NMR tube. After dilution (till approximately 0.2-0.3M) with the same deuterated solvent (previously anhydridified on activated molecular sieves in pellets) the sample was analyzed by NMR spectroscopy.

The dienamine adduct (**II** in Figure 2 of the main manuscript) has a moderate half-life (less than 1 day) depending on the presence of water in the media.

We first studied the dienamine adduct derived by aldehyde **2b** and catalyst **C** condensation in deuterated chloroform. In this solvent two different conformers (shown in Figure S1) were found in solution with a ratio of 2.7:1.

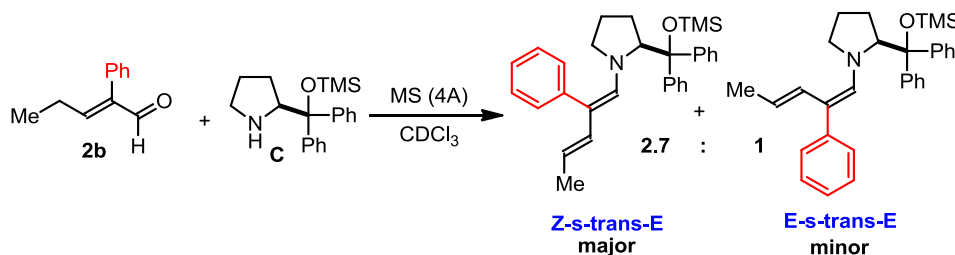


Figure S1. The dienamines from 2-phenyl-pentenal **2b** and catalyst **C**.

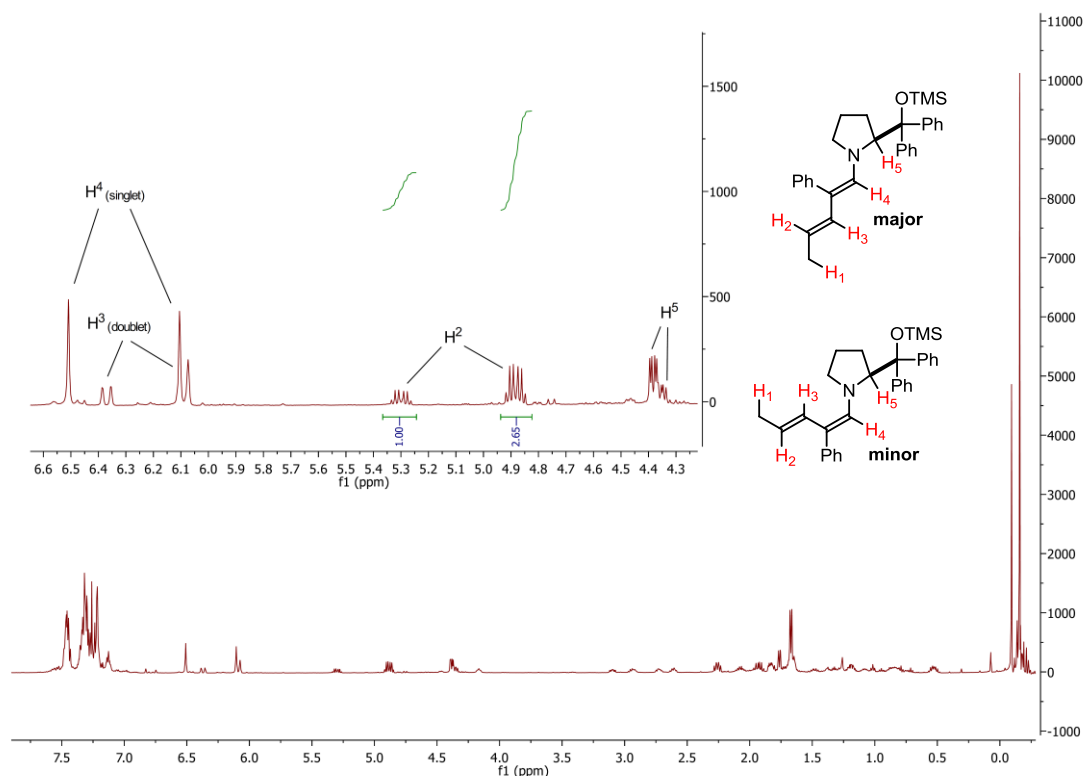


Figure S2. ^1H NMR of the dienamine derived from **2b** and catalyst **C** in CDCl_3 .

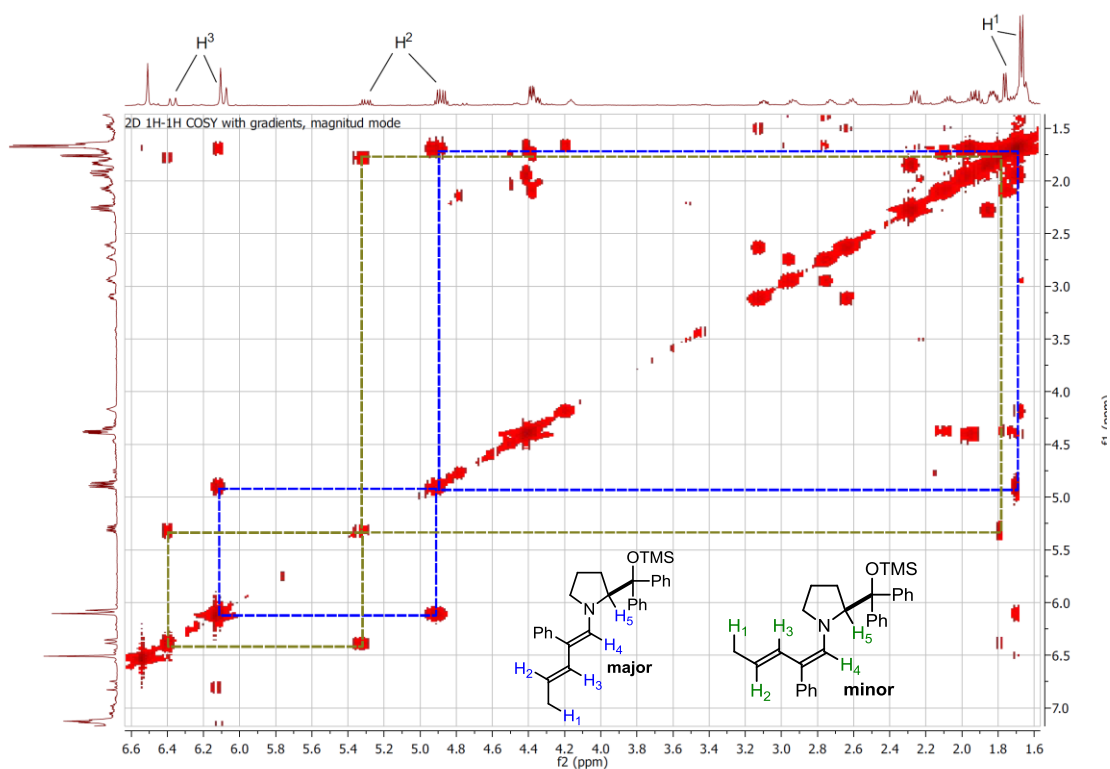


Figure S3. COSY experiment in CDCl_3 .

Comments: H^1 H^2 and H^3 were assigned using COSY experiment. Blue lines refer to the major conformer and green lines to the minor.

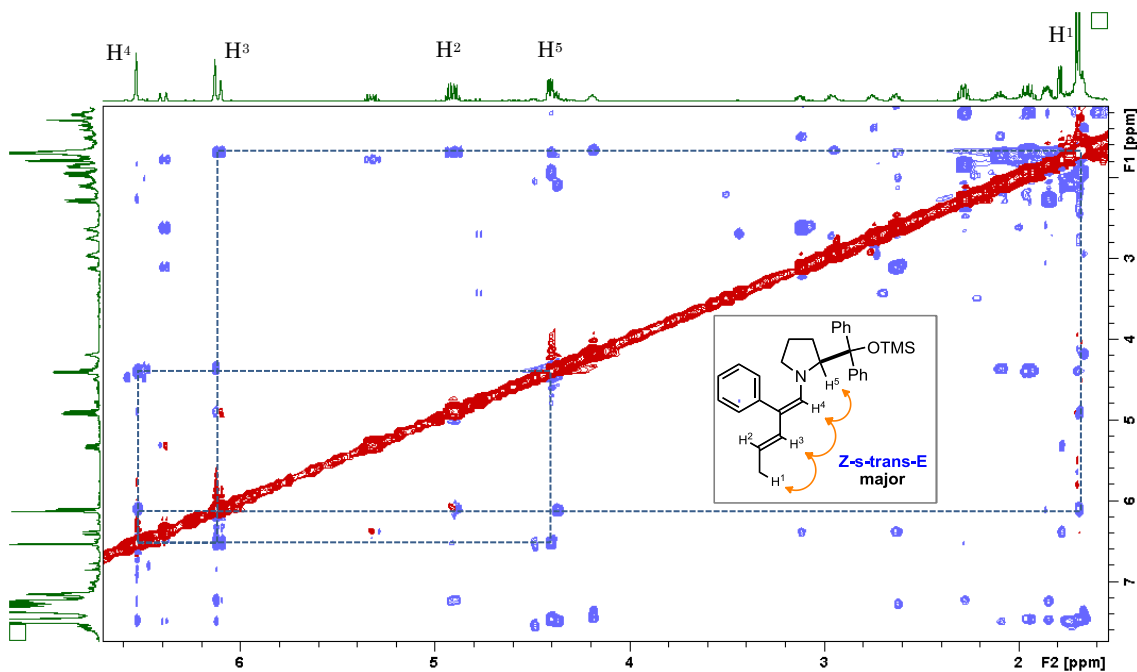


Figure S4. NOESY experiment in CDCl_3 - major conformer.

Comments: the most diagnostic signals of the NOESY experiment are highlighted. Strong nuclear Overhauser effects are shown between $(\text{H}^1) - (\text{H}^3)$, $(\text{H}^3) - (\text{H}^4)$, and $(\text{H}^4) - (\text{H}^5)$, indicating a Z-s-trans-E conformation of the dienamine.

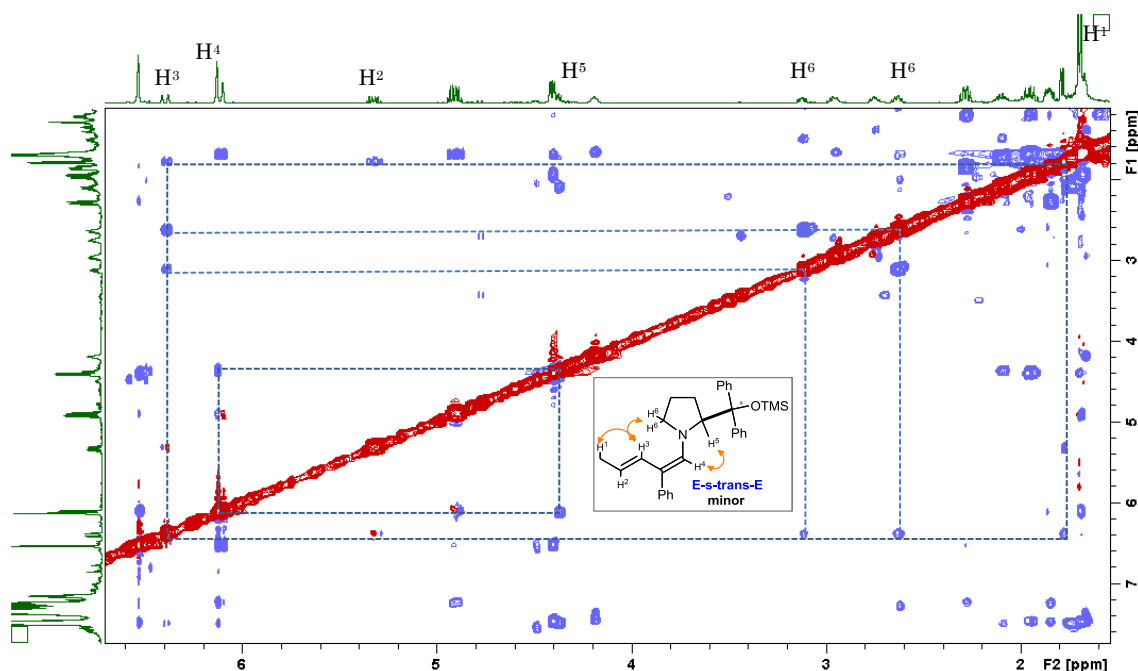


Figure 5S. NOESY experiment in CDCl_3 - minor conformer.

Comments: the most diagnostic signals of the NOESY experiment are highlighted. Strong nuclear Overhauser effects are shown between ($\text{H}^1\text{-H}^3$), ($\text{H}^3\text{-H}^6$), and ($\text{H}^4\text{-H}^5$), indicating a *E-s-trans-E* conformation of the dienamine.

The NOESY experiment in deuterated chloroform revealed that the two conformers of the dienamine are both *s-trans*. However, different geometries of the double bond closer to the nitrogen atom can be inferred. The major isomer has a *Z*-configure double bond, while the minor has an *E*-configuration.

In addition, the second double bond, more distant from the nitrogen atom, is *E*-configured in both of the conformations detectable by spectroscopic analysis. In support of the results obtained in the NOESY analysis, the *J* (15.5 Hz) for protons H^3 and H^2 is identical for both conformers, clearly pointing to a relative *E* geometry.

On the basis of the spectroscopic analysis, we can conclude that the major isomer has a *Z-s-trans-E* conformation, while the minor isomer has an *E-s-trans-E* topology.

These findings are in contrast to the spectroscopic studies by Jørgensen and co-workers¹⁰ carried out on the dienamine obtained by condensation of catalyst **C** with a linear, non-substituted α,β -unsaturated aldehyde (see Figure S6). For this system, two possible conformers were detected in CDCl_3 solution, differing in the geometry of the second double bond, more distant from the nitrogen atom.

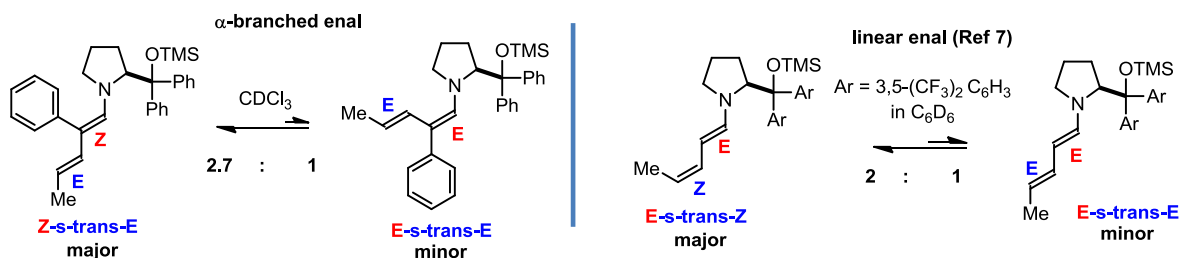


Figure S6. Comparison of the conformational behavior of the dienamines formed by condensation of α -branched and linear enals with catalyst **C.**

¹⁰ S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980.

Remarkably, the detected dienamines from α -branched enal **2b** both show an exclusive *E* geometry at the remote double bond. There thus arises the interesting prospect that the α -branched enals, which are difficult substrates for enamine and iminium ion catalysis, have the structural properties (namely the α -substituent) to bias the dienamine geometry, a necessary requirement for forging a stereogenic centre at the γ position with high fidelity.

We then carried out conformational studies in toluene- d_8 , the reaction medium. In contrast to the experiments carried out in $CDCl_3$, the *Z-s-trans-E* dienamine shows a much higher stability than *E-s-trans-E* in toluene- d_8 . As shown Figure S7, almost only one conformer can be detected (ratio > 16:1).

NOESY (Figure S8), COSY experiments (Figure S9) and *J* analysis confirm that the thermodynamically most stable conformation of the dienamine derived from aldehyde **2b** has a *Z-s-trans-E* geometry, the same observed for the major conformer in $CDCl_3$.

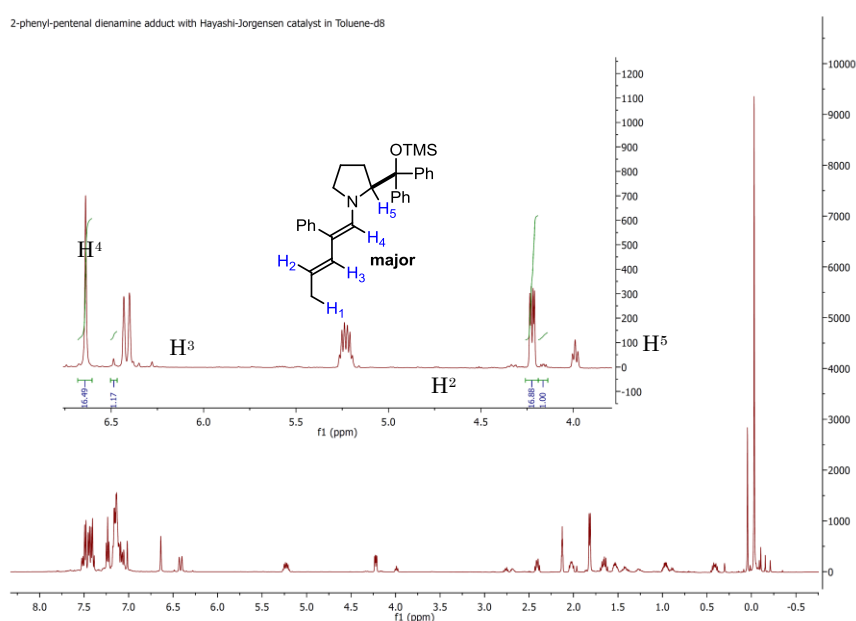


Figure S7. H^1 NMR of the dienamine derived from **2b** and catalyst **C** in toluene- d_8 .

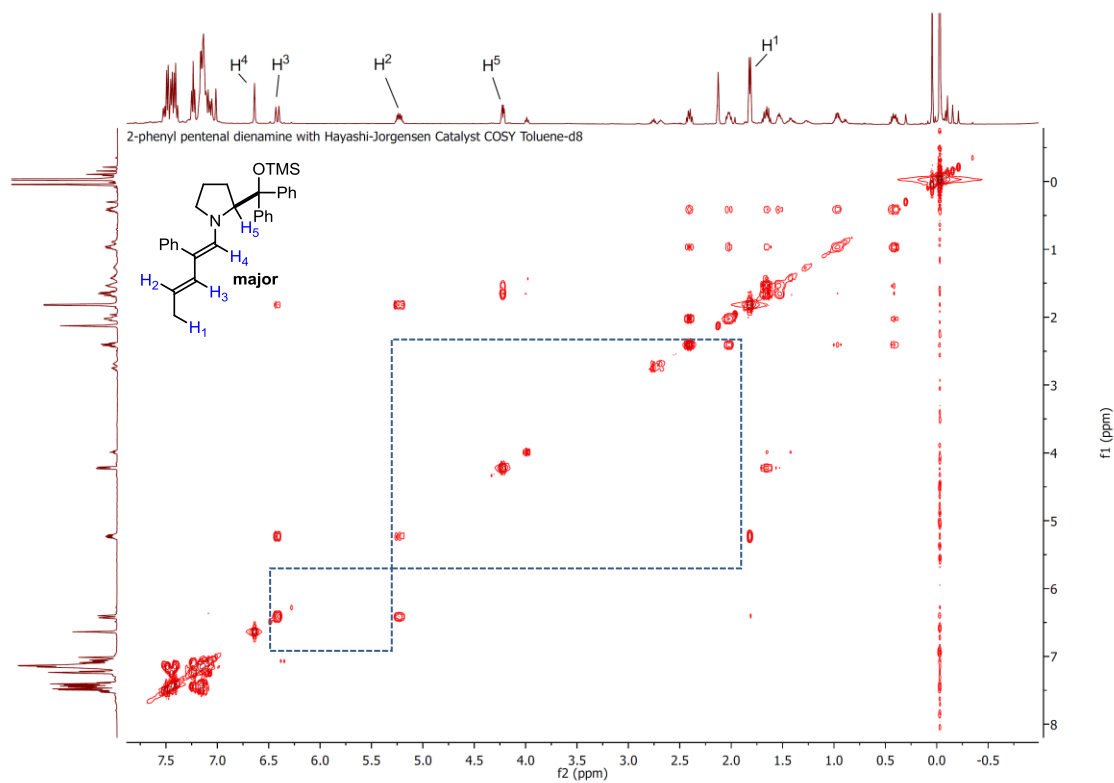


Figure S8. COSY experiment in toluene-d₈.

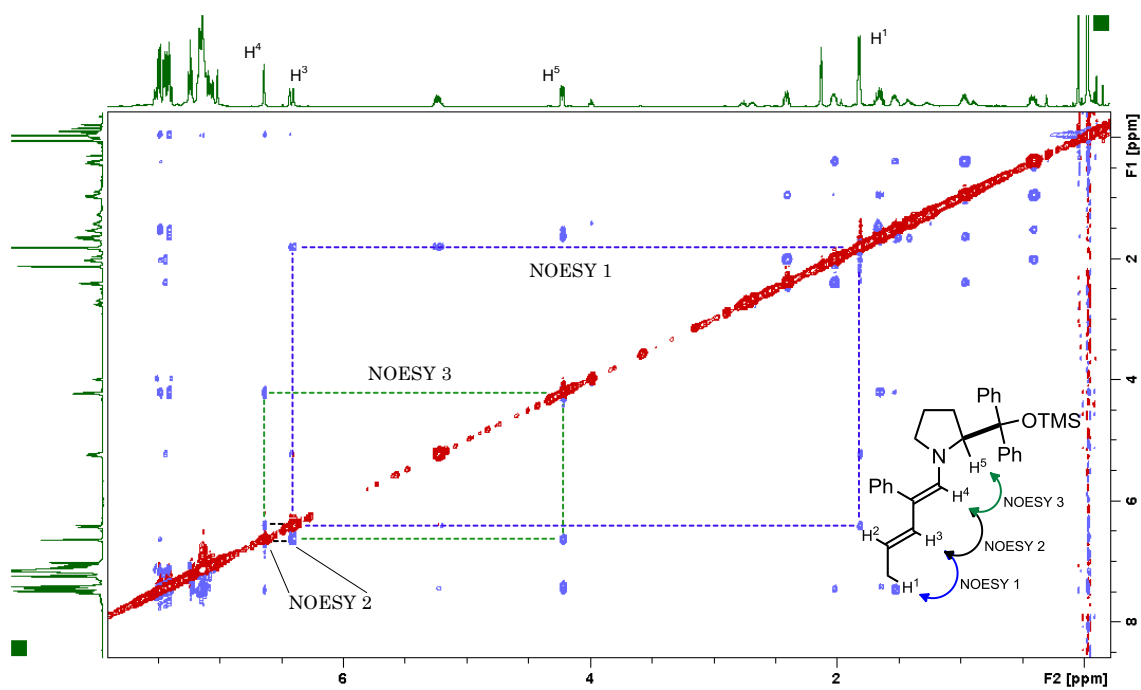


Figure S9. NOESY experiment in toluene-d₈.

We then studied the conformational behavior of the dienamine adduct derived from aldehyde **2a**, bearing a methyl α -substituent, and catalyst **C** condensation in deuterated toluene. The same major conformer observed in the previous case (using enal **2b**) was observed, in this case in a 7:1 ratio with respect to the minor conformer (Figure S10).

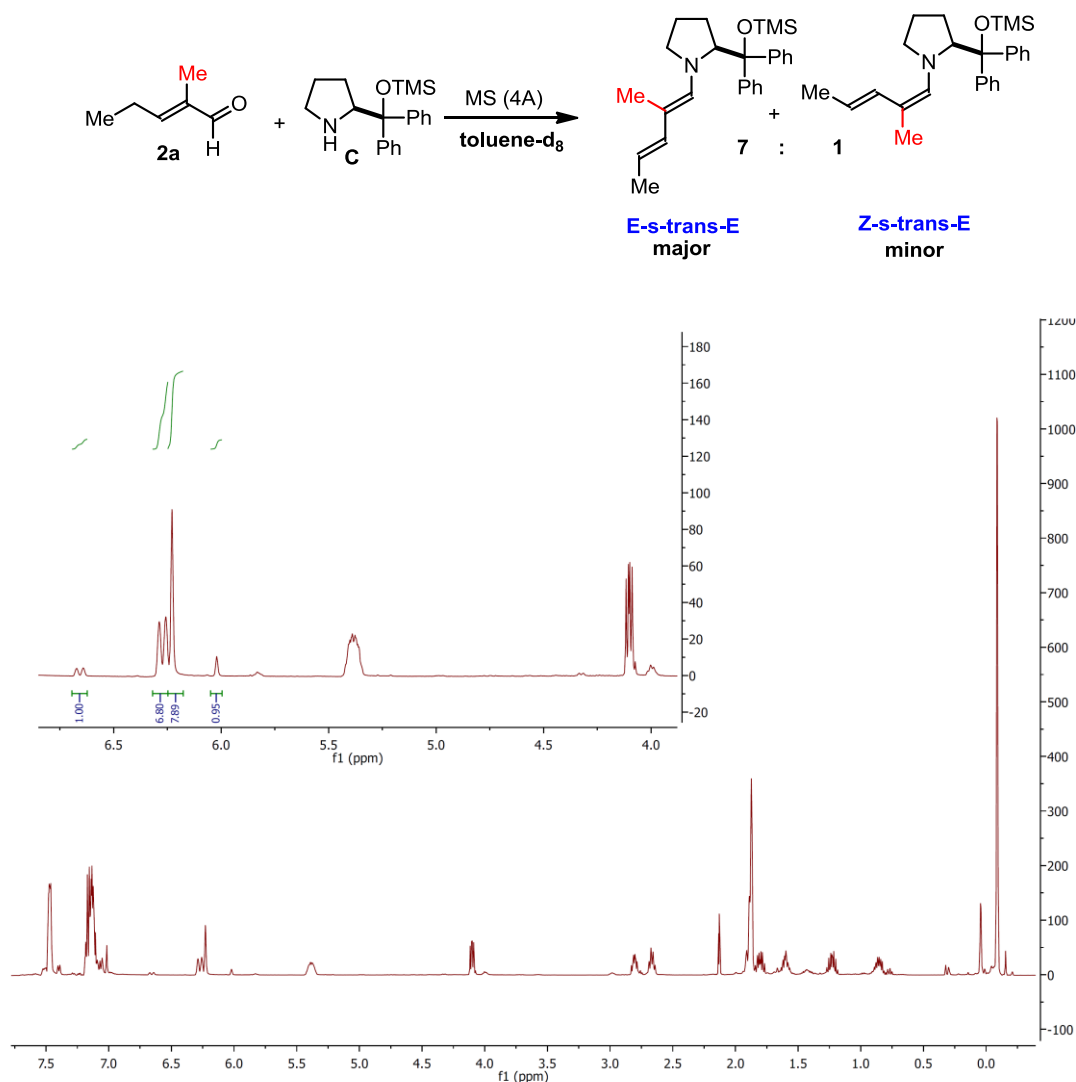


Figure S10. The dienamine from 2-methyl-pentenal **2a** and catalyst **C** in toluene-d_8 : two conformers (7:1 ratio) were detected.

The same sequence of experiments carried out for the dienamine derived from **2b** (Figures S2-9) served to establish that the dienamines derived from **2a** and **2b** ($R_{\text{branched}} = \text{Me}$ and Ph , respectively) have similar ground state thermodynamic stability: we can conclude that the nature of the α -branched substituent did not alter the conformational preference of the dienamine, being the *s-trans* dienamine with the same geometry of the two double bonds the more stable species in both the cases.¹¹

¹¹ It should be noted that different α -branched substituents (Ph vs Me) change the priority for the double bond, thereby switching the nomenclature of the first insaturation. The more stable dienamine derived from enal **2a** ($R = \text{Me}$) has a *E-s-trans-E* configuration, while when $R = \text{Ph}$ the nomenclature change to *Z-s-trans-E*; still the two dienamines show the same structural topology.

H. X-ray Crystallographic Data

Single Crystal X-ray Diffraction Data for compound **3h**

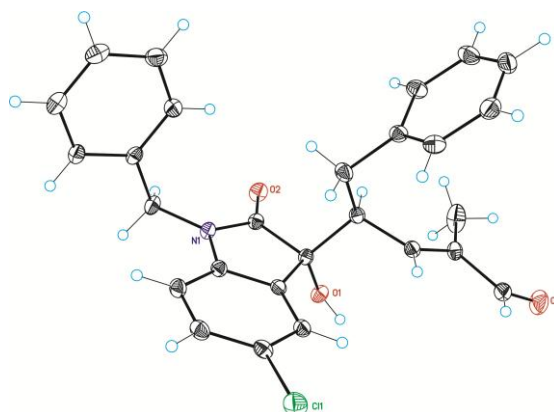
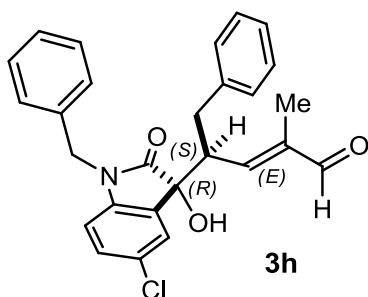
X-ray structure determinations: Crystals of compound **3h** were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature. The measured crystals were unstable under atmosphere conditions; they were prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation.

Data Collection. Measurements were made on a Bruker-Nonius diffractometer equipped with an APEX 2 4K CCD area detector, a FR591 rotating anode with Mo K_{α} radiation, Montel mirrors and a Cryostream Plus low temperature device ($T = 100\text{K}$). Full-sphere data collection was used with ω and φ scans.

Programs used: Data collection Apex2 V2009.11 (Bruker-Nonius 2008), data reduction Saint + Version 7.60A (Bruker AXS 2008) and absorption correction TWINABS V. 2008-1 (2008).

Structure Solution. SIR2008

Structure Refinement. SHELXTL V6.14



Crystal data for **3h** at 100 K: **CCDC 885390**

Empirical formula	C ₂₇ H ₂₄ Cl N O ₃	
Formula weight	445.92	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.784 Å	$\alpha = 90.00^\circ$.
	b = 13.467 Å	$\beta = 90.00^\circ$.
	c = 16.619 Å	$\gamma = 90.00^\circ$.
Volume	2189.7 Å ³	
Z	4	
Density (calculated)	1.353 Mg/m ³	
Absorption coefficient	0.205 mm ⁻¹	
F(000)	936	
Crystal size	0.20 x 0.10 x 0.05 mm ³	
Theta range for data collection	1.95 to 37.20 °.	
Index ranges	-11 ≤ h ≤ 16, -22 ≤ k ≤ 22, -28 ≤ l ≤ 27	
Reflections collected	29424	

Independent reflections	10964 [R(int) = 0.0447]
Completeness to theta =37.20 °	0.982 %
Absorption correction	Empirical
Max. and min. transmission	0.9898 and 0.9602
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	10964 / 0 / 291
Goodness-of-fit on F ²	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0416 , wR2 = 0.1008
R indices (all data)	R1 = 0.0525 , wR2 = 0.1070
Flack parameter	x =0.01(3)
Largest diff. peak and hole	0.409 and -0.263 e.Å ⁻³

Single Crystal X-ray Diffraction Data for compound (2*R*,3*R*)-**4b**

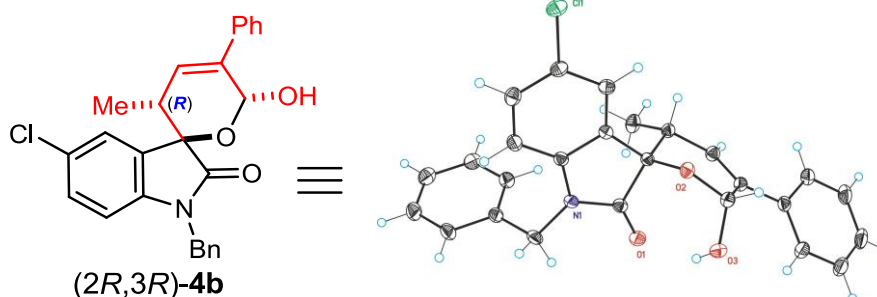
X-ray structure determinations: Crystals of compound (2*R*,3*R*)-**4b** (major diastereomer) were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature. The measured crystals were unstable under atmosphere conditions; they were prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation.

Data Collection. Measurements were made on a Bruker-Nonius diffractometer equipped with an APEX 2 4K CCD area detector, a FR591 rotating anode with MoK α radiation, Montel mirrors and a Cryostream Plus low temperature device (*T* = 100K). Full-sphere data collection was used with ω and φ scans.

Programs used: Data collection Apex2 V2009.11 (Bruker-Nonius 2008), data reduction Saint + Version 7.60A (Bruker AXS 2008) and absorption correction TWINABS V. 2008-1 (2008).

Structure Solution. SIR2008

Structure Refinement. SHELXTL V6.14



Crystal data for (2*R*,3*R*)-**4b** at 100 K: **CCDC 885391**

Empirical formula	C ₂₆ H ₂₂ Cl N O ₃
Formula weight	431.90
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 26.891(4) Å α = 90.00 °.

	$b = 6.5139(9) \text{ \AA}$	$\beta = 117.976(7)^\circ$
	$c = 13.524(2) \text{ \AA}$	$\gamma = 90.00^\circ$
Volume	$2092.1(5) \text{ \AA}^3$	
Z	4	
Density (calculated)	1.371 Mg/m^3	
Absorption coefficient	0.212 mm^{-1}	
F(000)	904	
Crystal size	$0.20 \times 0.05 \times 0.05 \text{ mm}^3$	
Theta range for data collection	$1.70 \text{ to } 34.54^\circ$	
Index ranges	$-40 \leq h \leq 32, -9 \leq k \leq 9, -21 \leq l \leq 21$	
Reflections collected	12374	
Independent reflections	6476 [R(int) = 0.0568]	
Completeness to $\theta = 34.54^\circ$	0.869 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9895 and 0.9589	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6476 / 7 / 292	
Goodness-of-fit on F^2	1.051	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0441, wR2 = 0.1027$	
R indices (all data)	$R1 = 0.0635, wR2 = 0.1092$	
Flack parameter	$x = -0.02(4)$	
Largest diff. peak and hole	$0.374 \text{ and } -0.264 \text{ e.\AA}^{-3}$	

Single Crystal X-ray Diffraction Data for compound (2*S*,3*R*)-**5b**

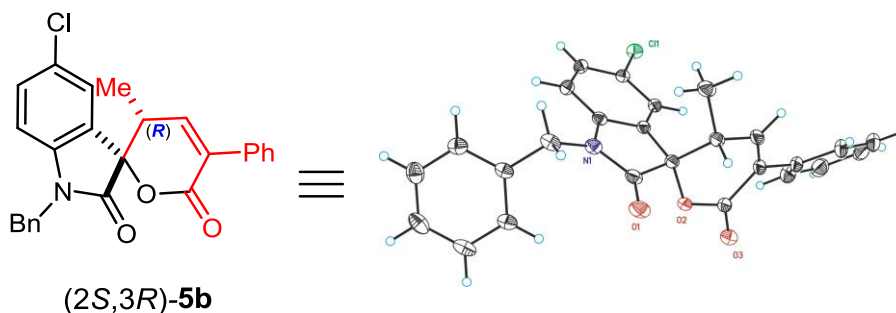
X-ray structure determinations: Crystals of compound (2*S*,3*R*)-**5b** were obtained by slow evaporation of a mixture of hexane/diethyl ether at room temperature. The measured crystals were unstable under atmosphere conditions; they were prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation.

Data Collection. Measurements were made on a Bruker-Nonius diffractometer equipped with an APEX 2 4K CCD area detector, a FR591 rotating anode with $\text{MoK}\alpha$ radiation, Montel mirrors and a Cryostream Plus low temperature device ($T = 100\text{K}$). Full-sphere data collection was used with ω and φ scans.

Programs used: Data collection Apex2 V2009.11 (Bruker-Nonius 2008), data reduction Saint + Version 7.60A (Bruker AXS 2008) and absorption correction TWINABS V. 2008-1 (2008).

Structure Solution. SIR2008

Structure Refinement. SHELXTL V6.14

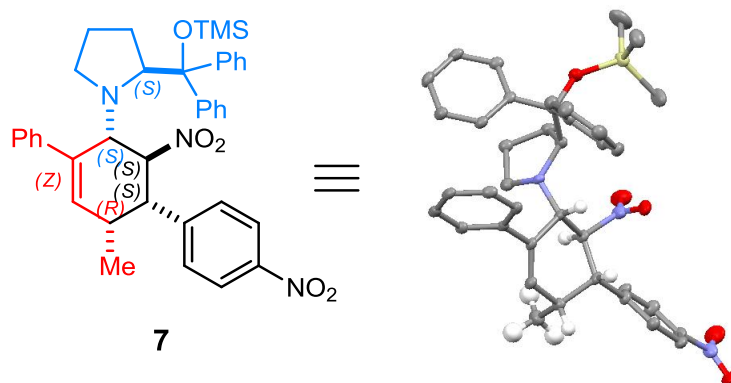


Crystal data for (2*S*,3*R*)-**5b** at 100 K: **CCDC 885392**

Empirical formula	C ₂₆ H ₂₀ Cl N O ₃	
Formula weight	429.88	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.9520(8) Å	α = 90.00 °.
	b = 12.8684(13) Å	β = 90.00 °.
	c = 23.405(3) Å	γ = 90.00 °.
Volume	2093.9(4) Å ³	
Z	4	
Density (calculated)	1.364 Mg/m ³	
Absorption coefficient	0.211 mm ⁻¹	
F(000)	896	
Crystal size	0.20 x 0.20 x 0.20 mm ³	
Theta range for data collection	1.81 to 36.54 °.	
Index ranges	-9 ≤ h ≤ 11, -20 ≤ k ≤ 19, -29 ≤ l ≤ 38	
Reflections collected	16479	
Independent reflections	9299 [R(int) = 0.0215]	
Completeness to theta = 36.54 °	0.932 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9589 and 0.9589	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	9299 / 0 / 281	
Goodness-of-fit on F ²	1.026	
Final R indices [I > 2σ(I)]	R1 = 0.0385, wR2 = 0.0976	
R indices (all data)	R1 = 0.0442, wR2 = 0.1016	
Flack parameter	x = -0.01(4)	
Largest diff. peak and hole	0.477 and -0.233 e.Å ⁻³	

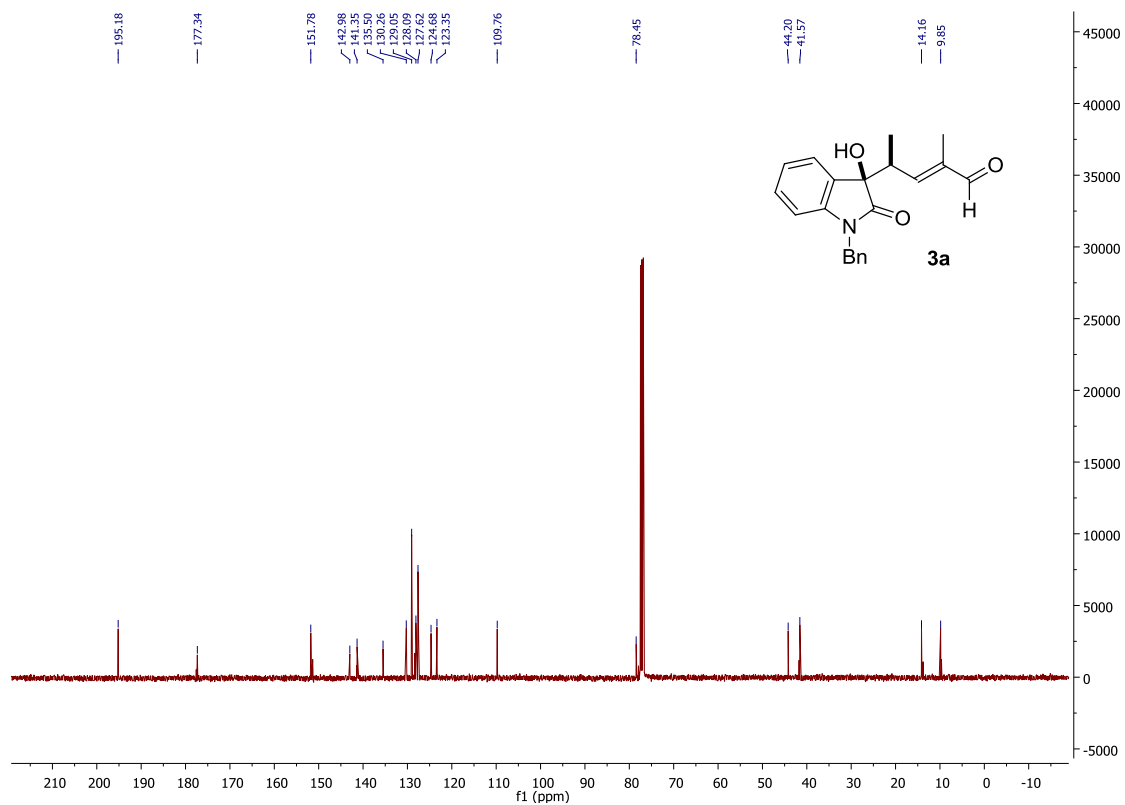
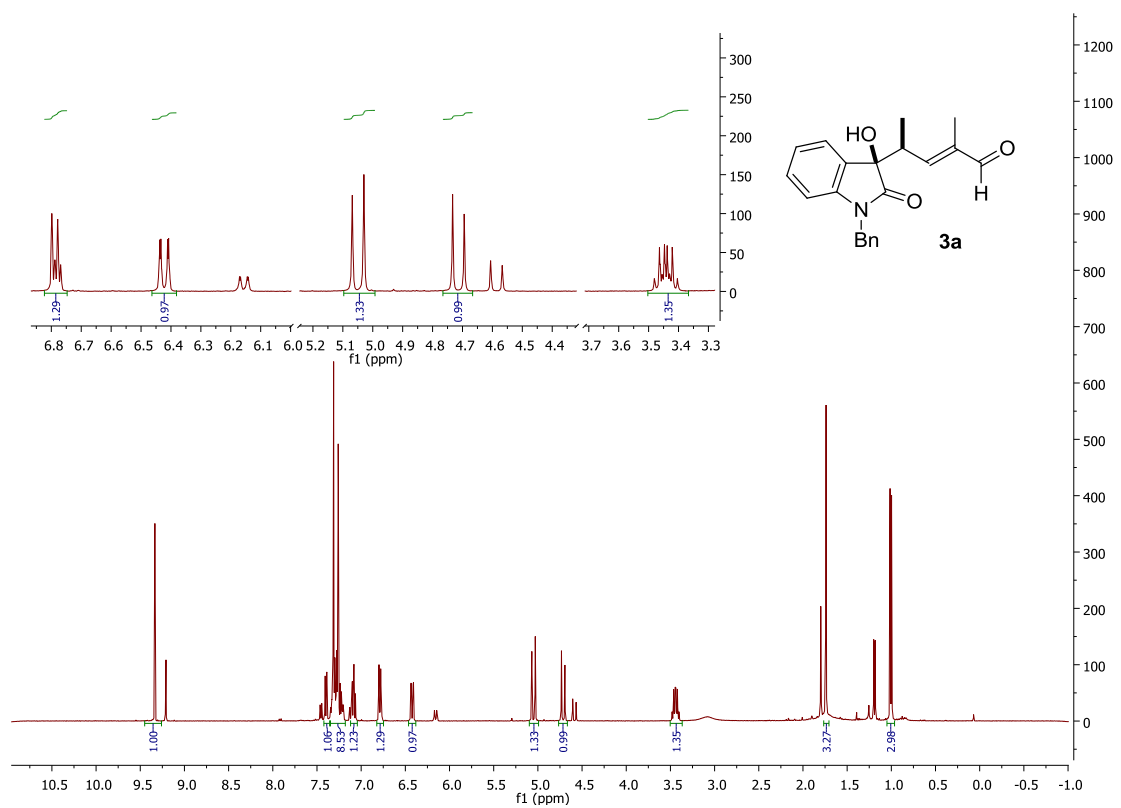
Single Crystal X-ray Diffraction Data for compound **7**

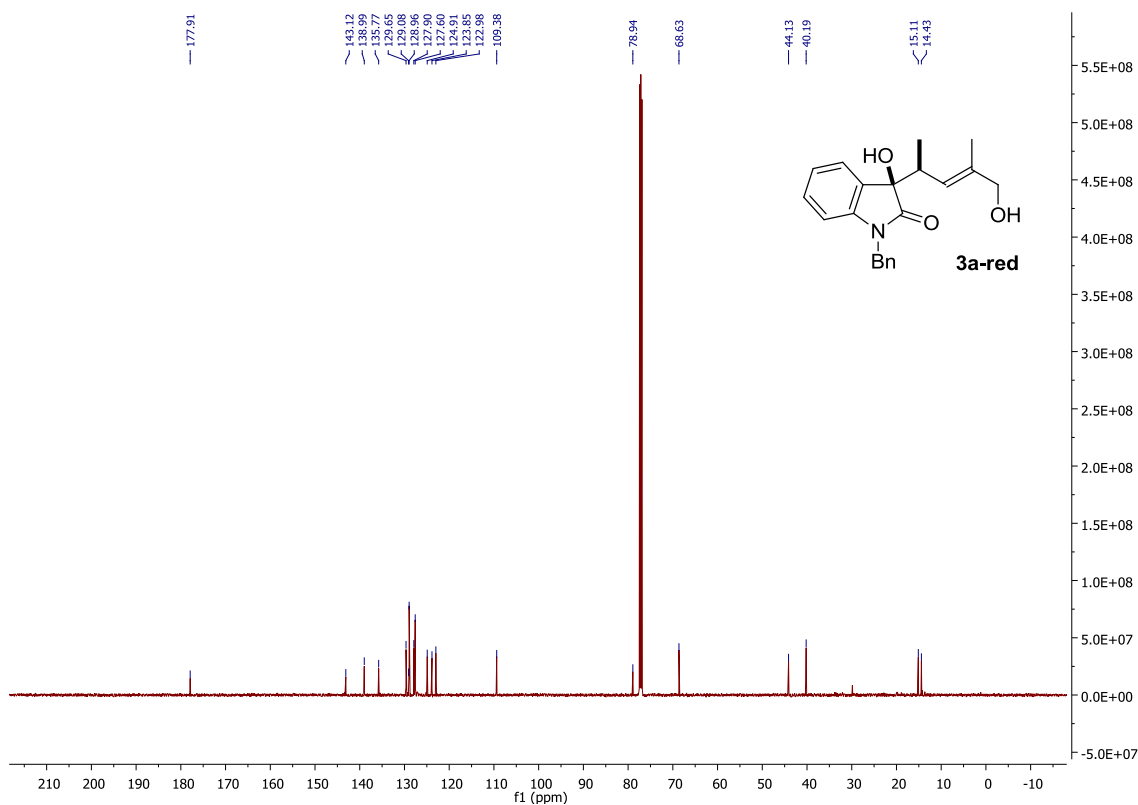
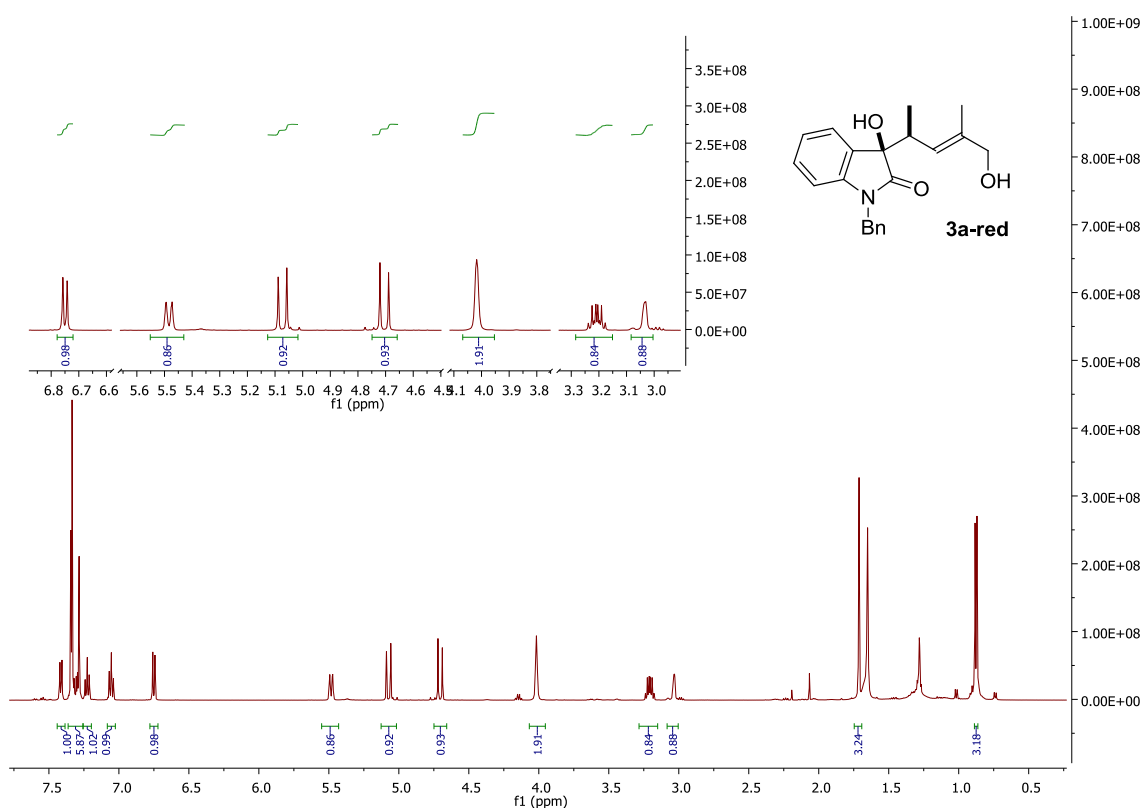
X-ray structure determinations: Crystals of compound **7** were obtained by slow evaporation of hexane at room temperature.

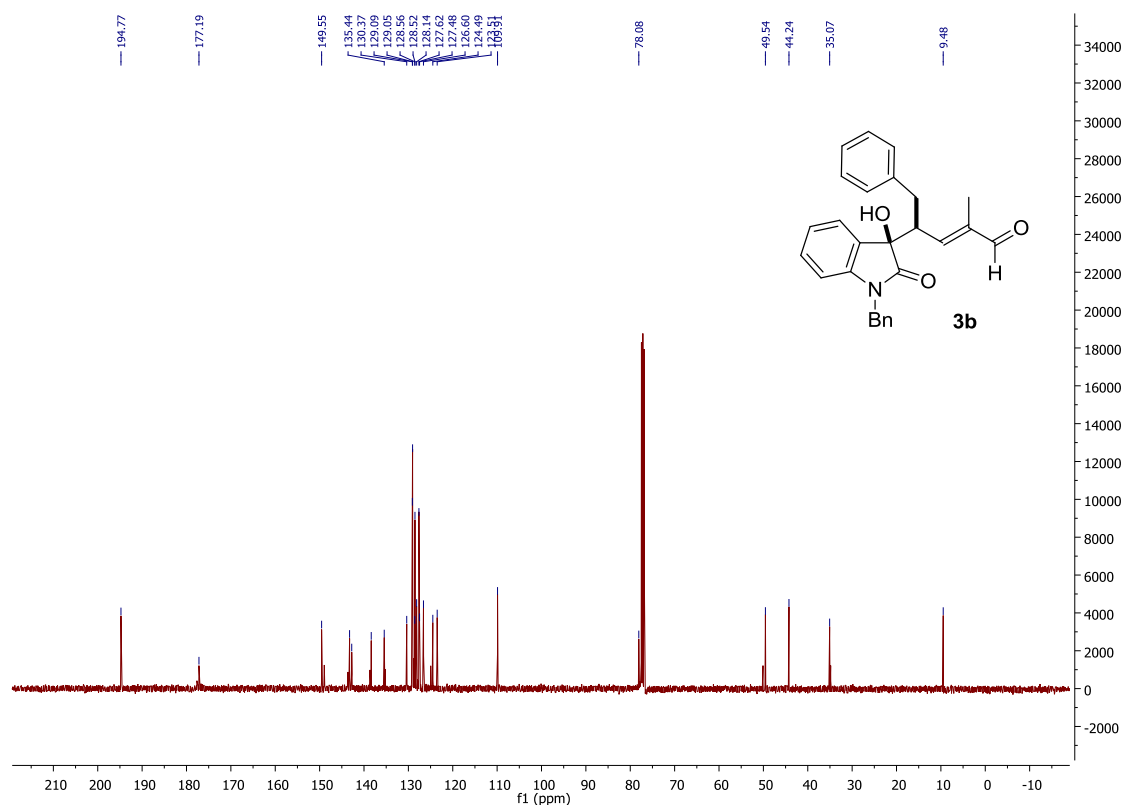
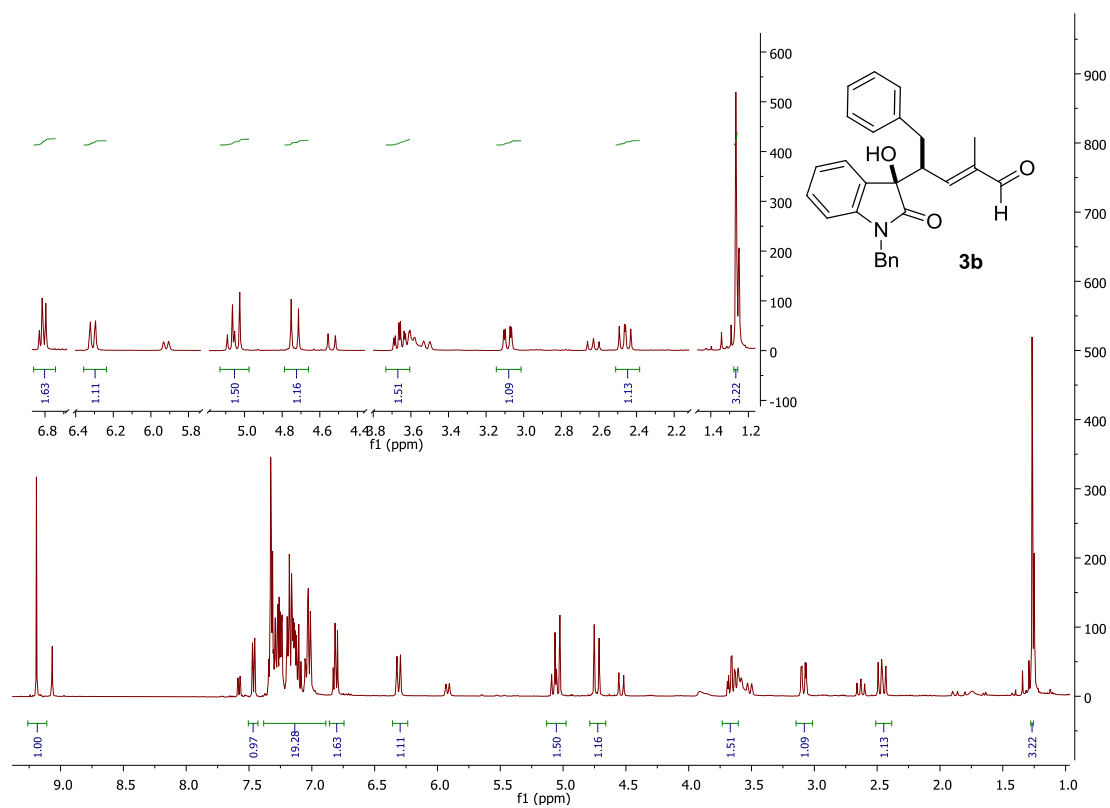


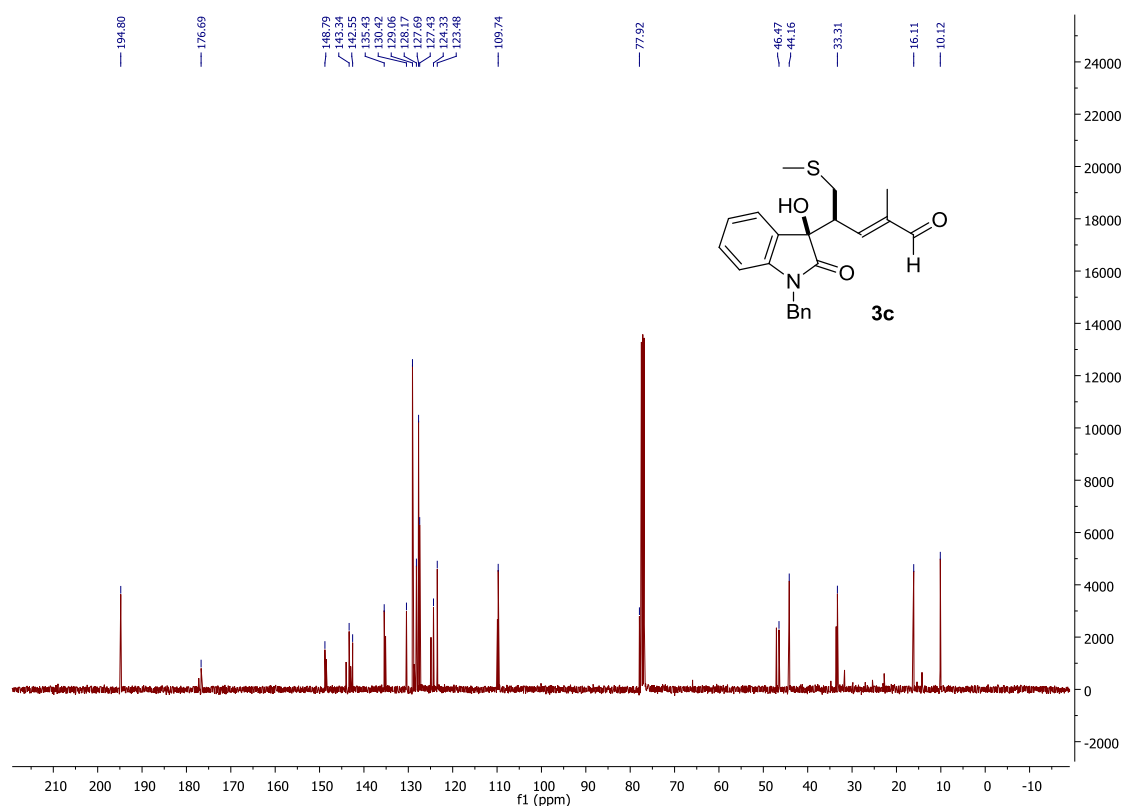
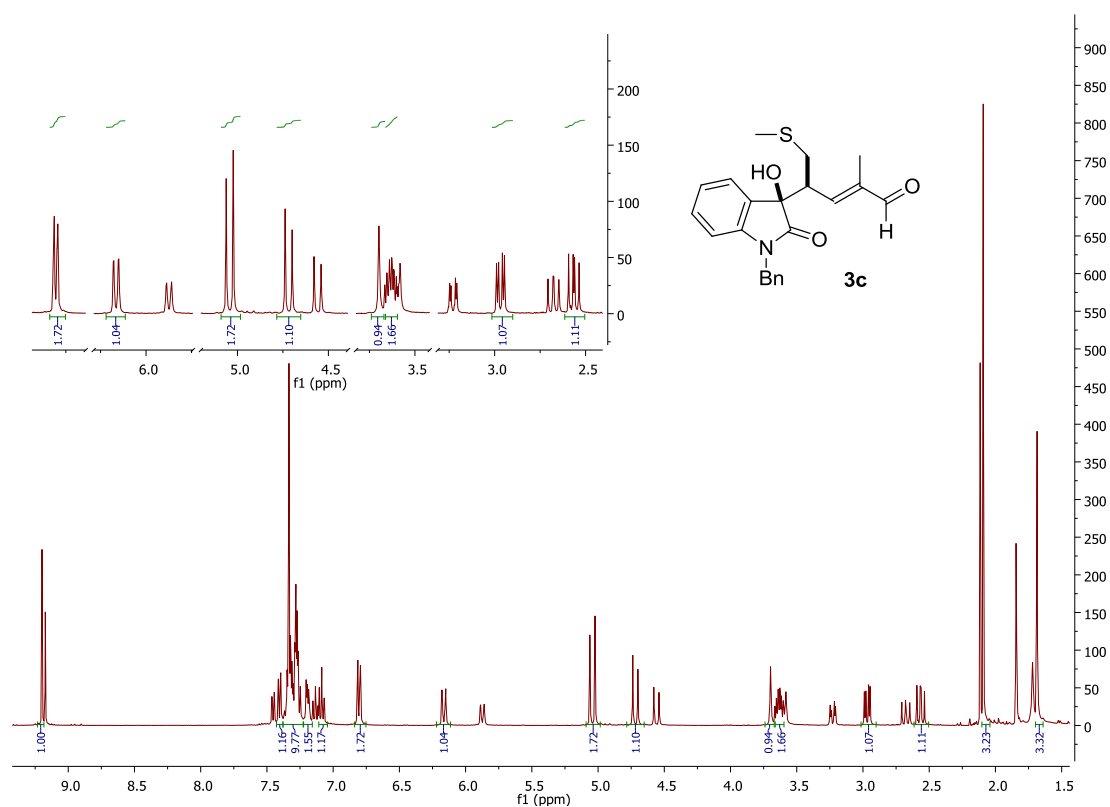
Crystal data for **7** at 100 K: **CCDC 885695**

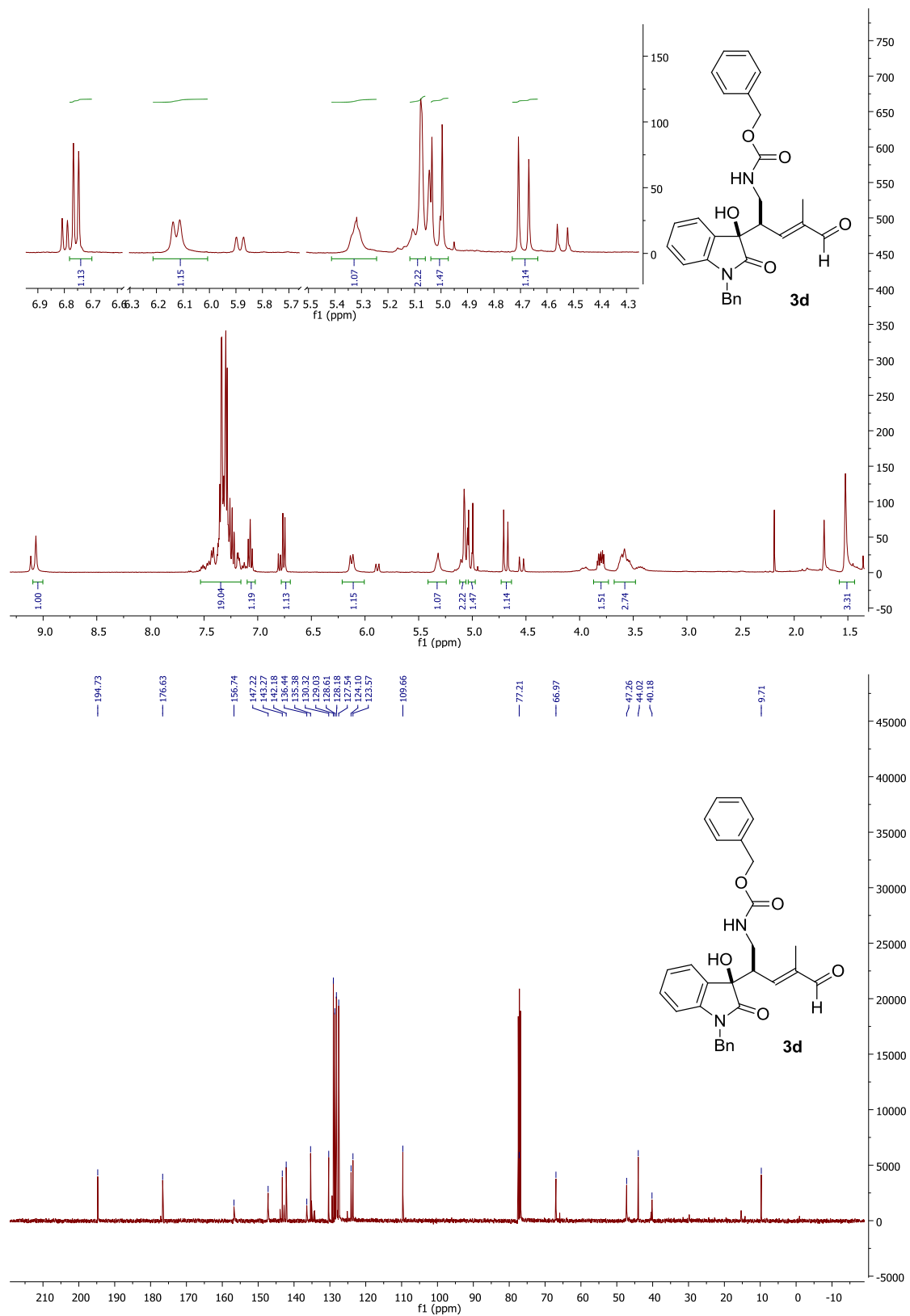
Empirical formula	C ₃₉ H ₄₃ N ₃ O ₅ Si
Formula weight	661.85
Temperature	100(2)K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 10.6855(16) Å α = 90.00 °. b = 9.3798(15) Å β = 99.839(5) °. c = 18.076(3) Å γ = 90.00 °.
Volume	1785.1(5) Å ³
Z	2
Density (calculated)	1.231 Mg/m ³
Absorption coefficient	0.113 mm ⁻¹
F(000)	704
Crystal size	0.30 x 0.15 x 0.01 mm ³
Theta range for data collection	1.14 to 26.26 °.
Index ranges	-13 ≤ h ≤ 10, -9 ≤ k ≤ 11, -21 ≤ l ≤ 22
Reflections collected	15425
Independent reflections	6511 [R(int) = 0.0493]
Completeness to theta = 26.26 °	0.989 %
Absorption correction	Empirical
Max. and min. transmission	0.9989 and 0.9670
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	6511 / 1 / 437
Goodness-of-fit on F ²	1.024
Final R indices [I > 2σ(I)]	R1 = 0.0539, wR2 = 0.1244
R indices (all data)	R1 = 0.0737, wR2 = 0.1394
Flack parameter	x = 0.09(17)
Largest diff. peak and hole	0.500 and -0.325 e.Å ⁻³

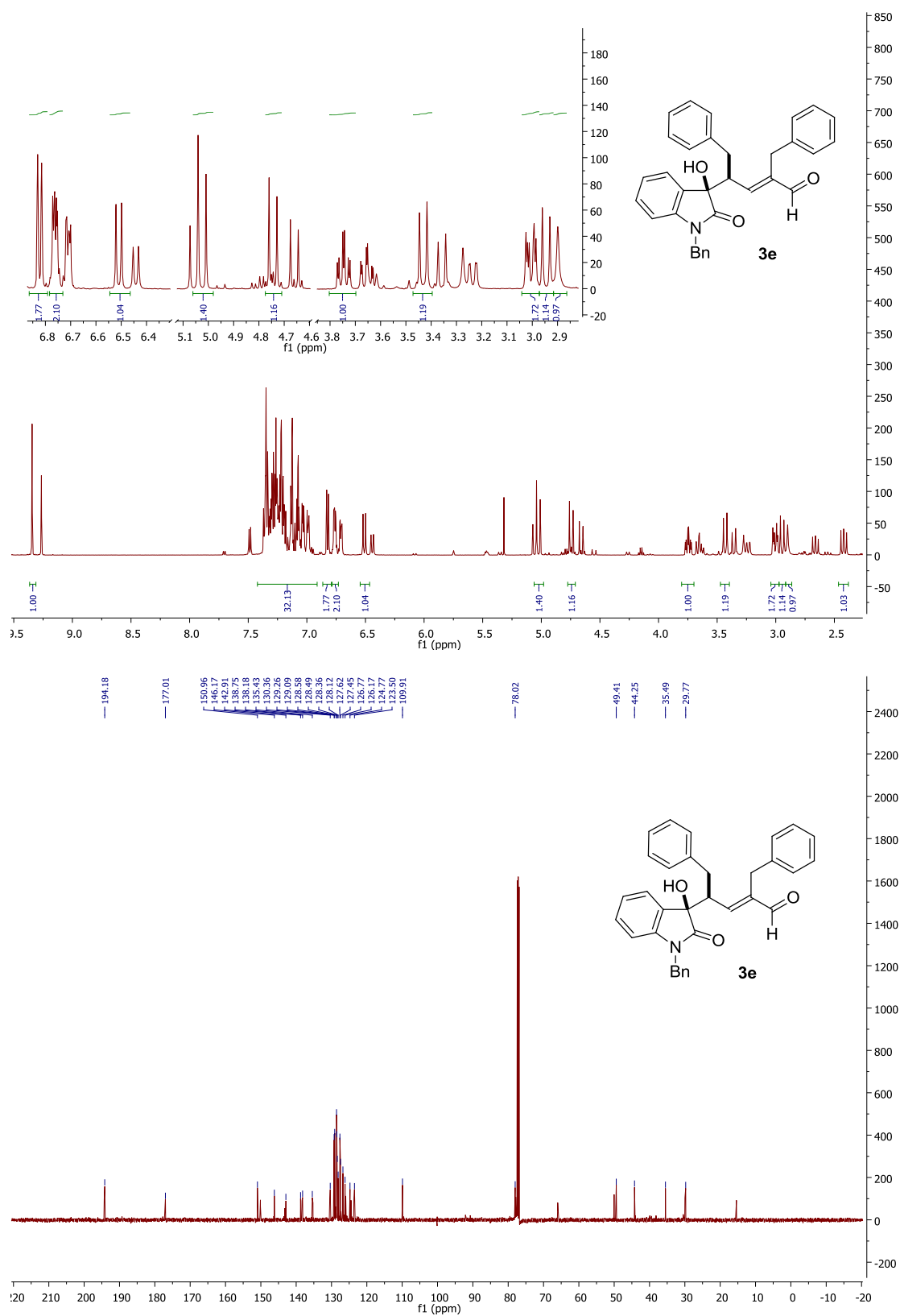


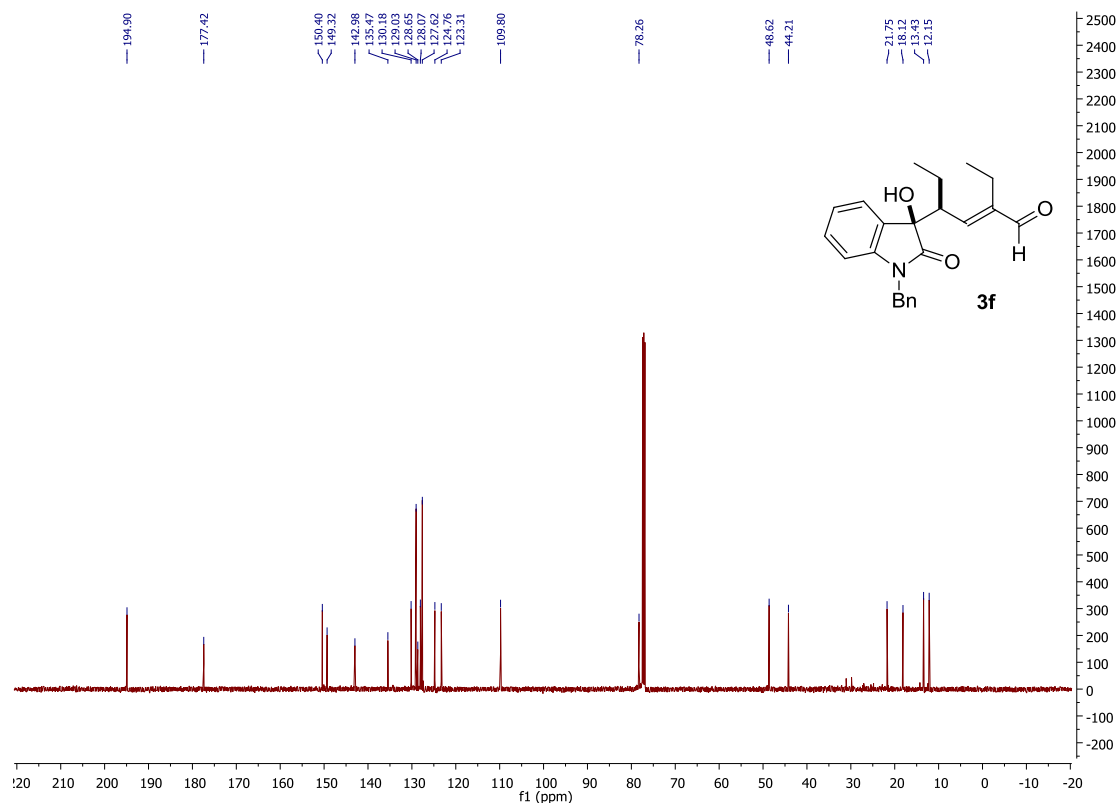
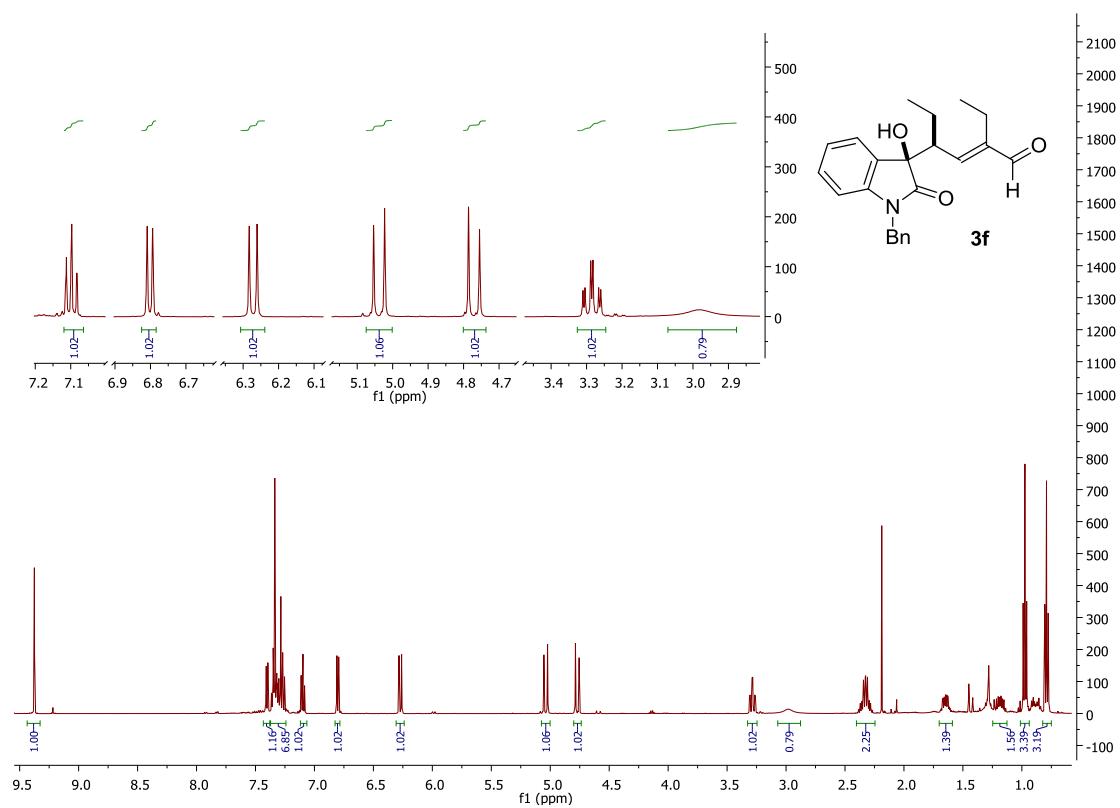


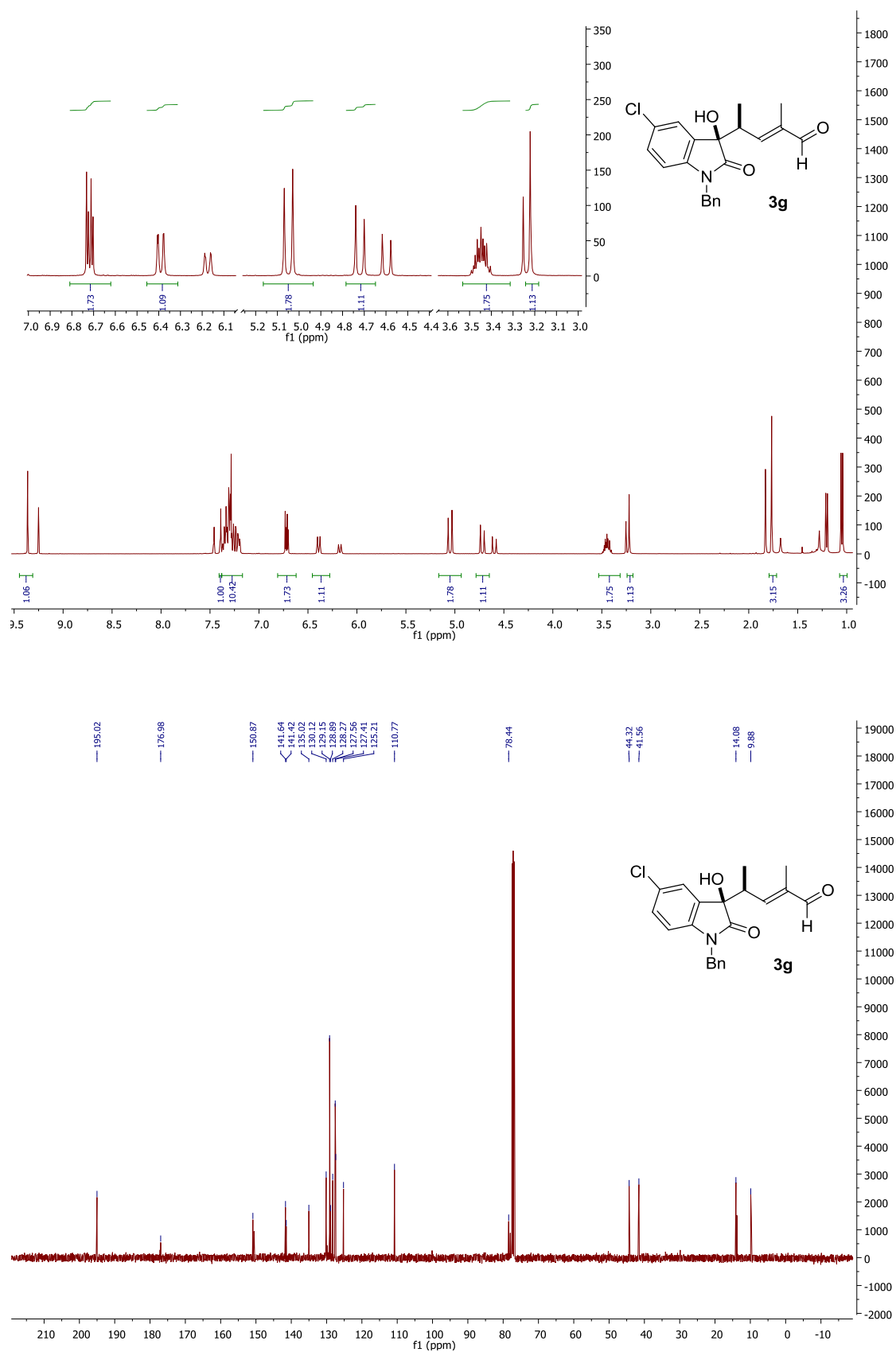


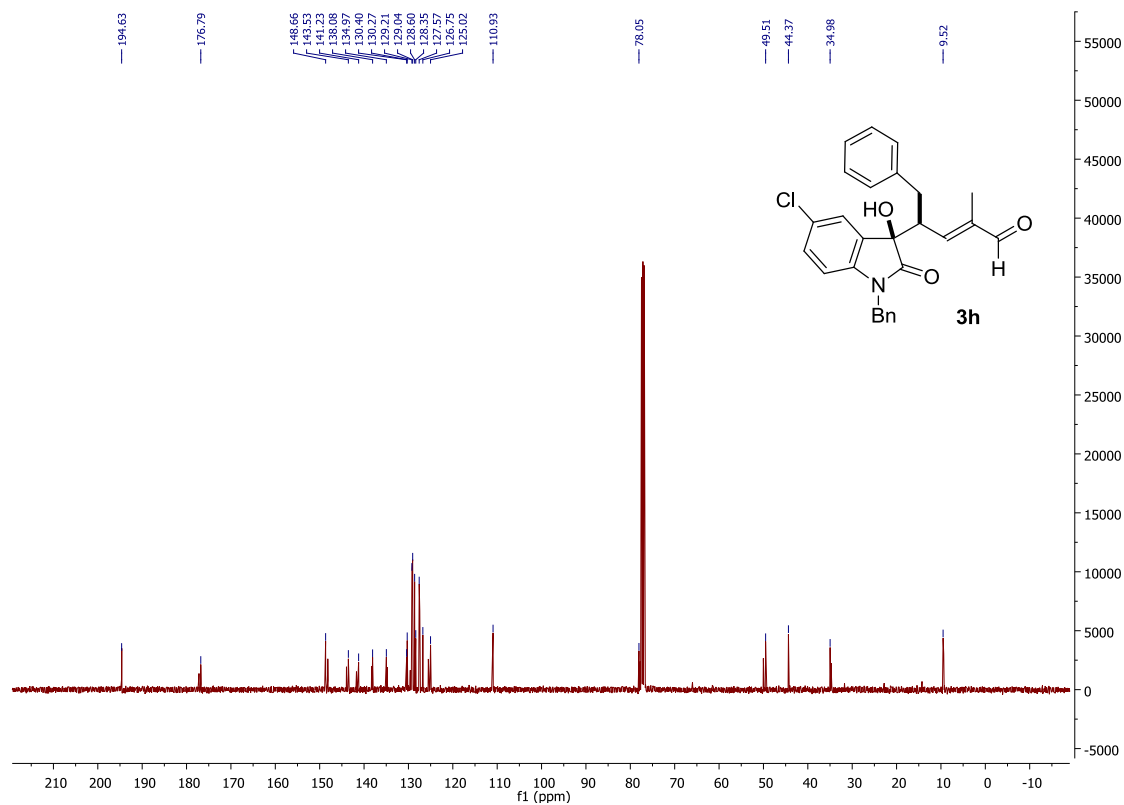
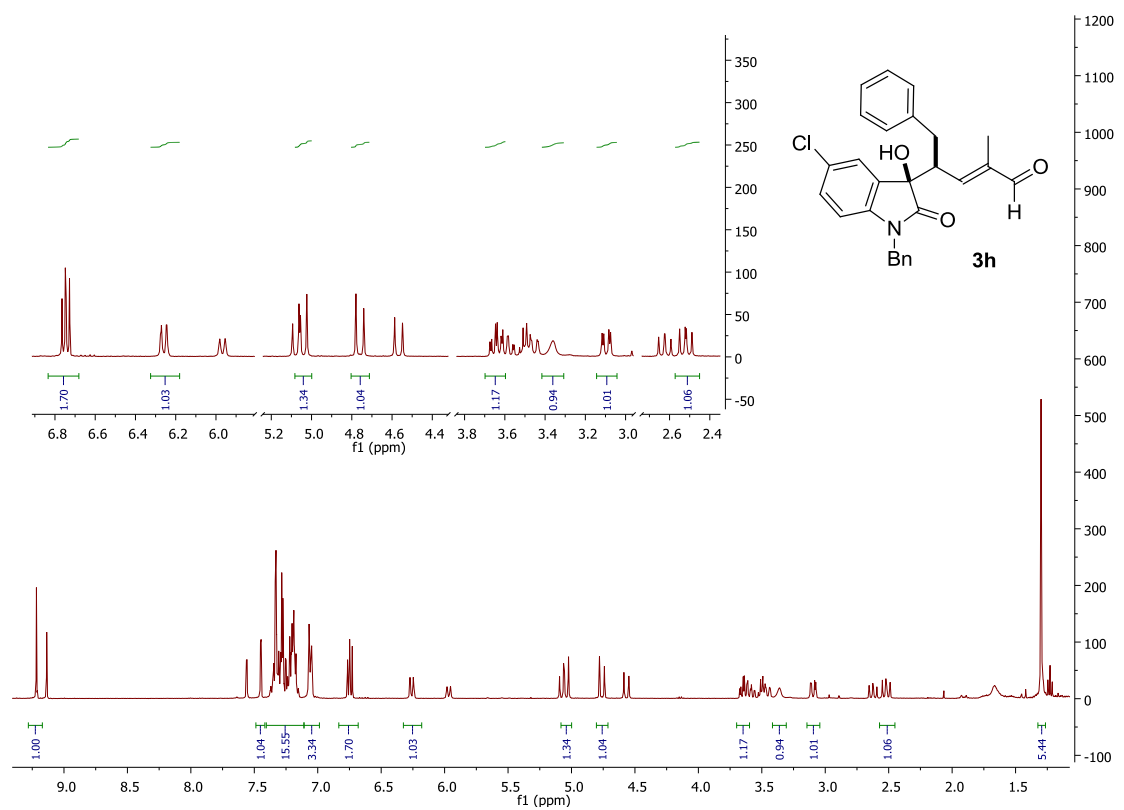


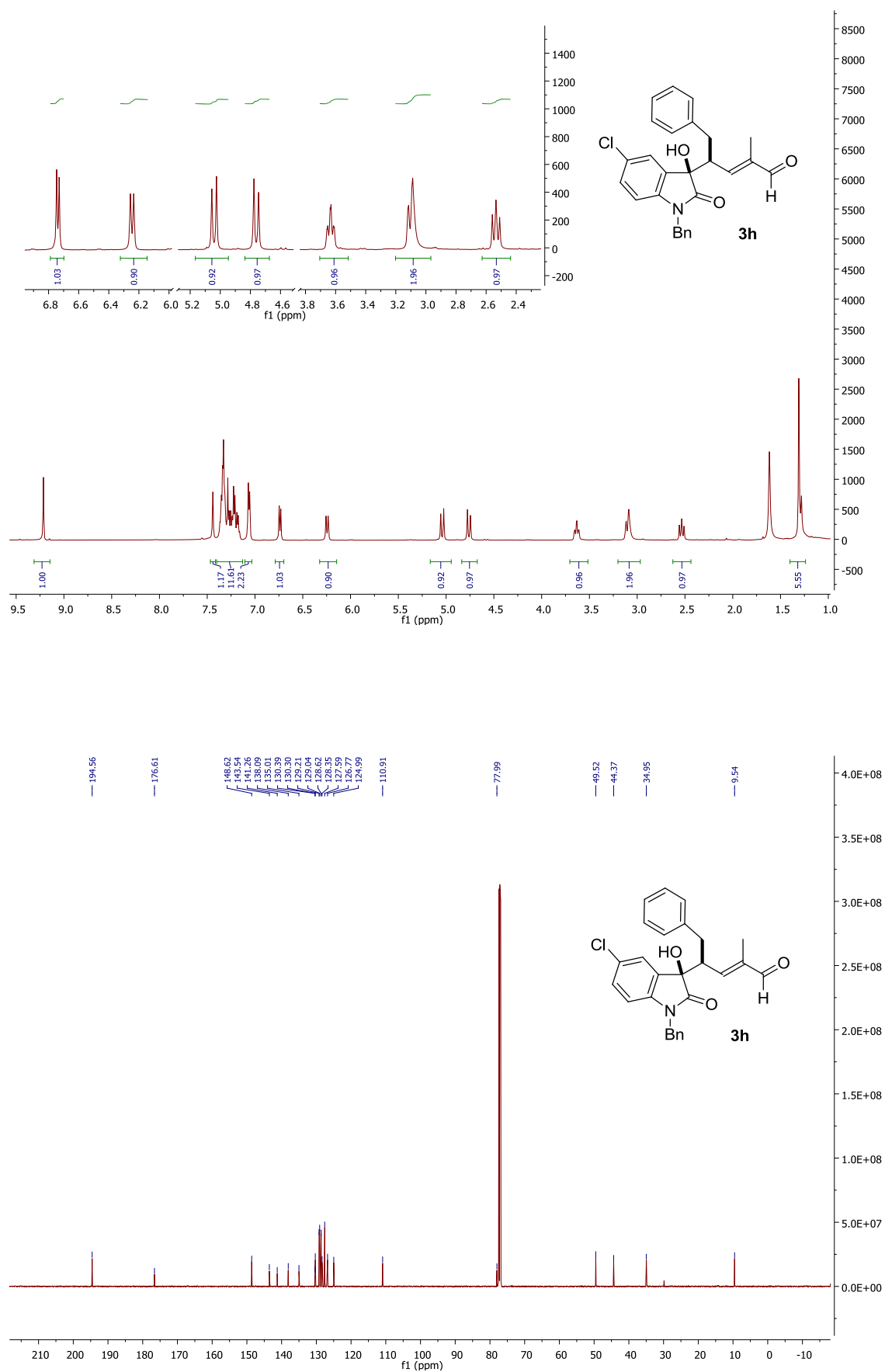


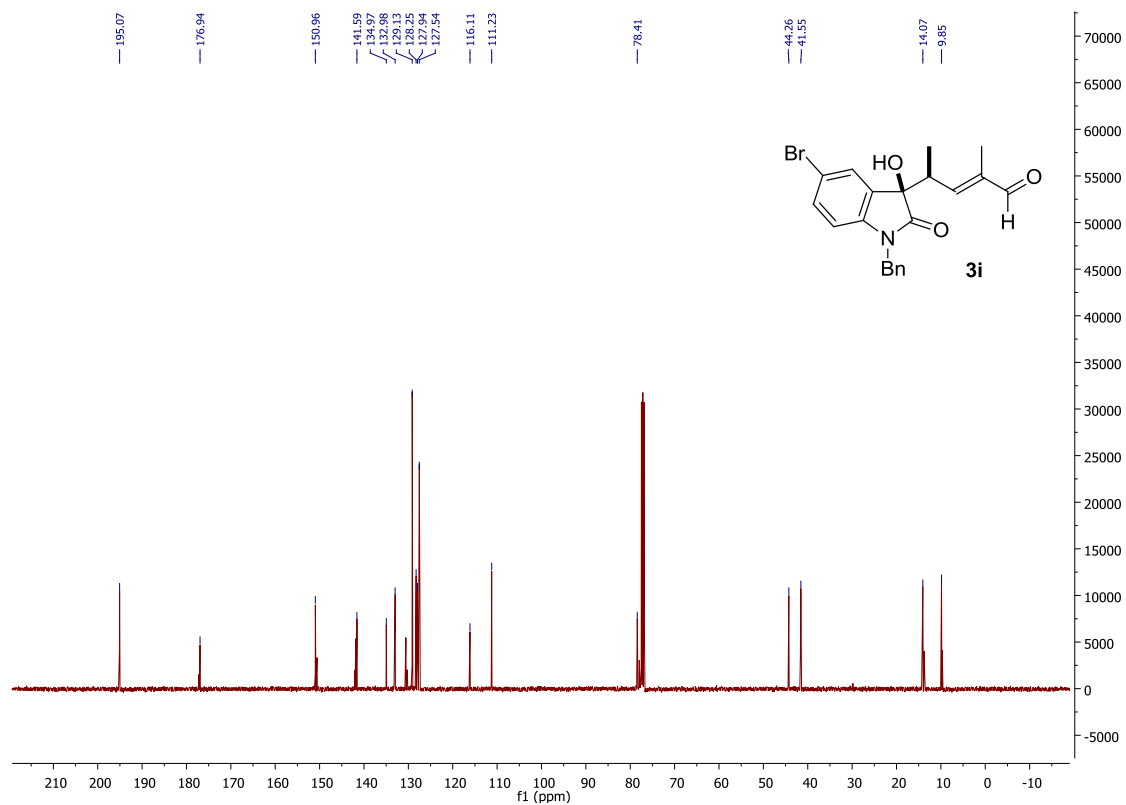
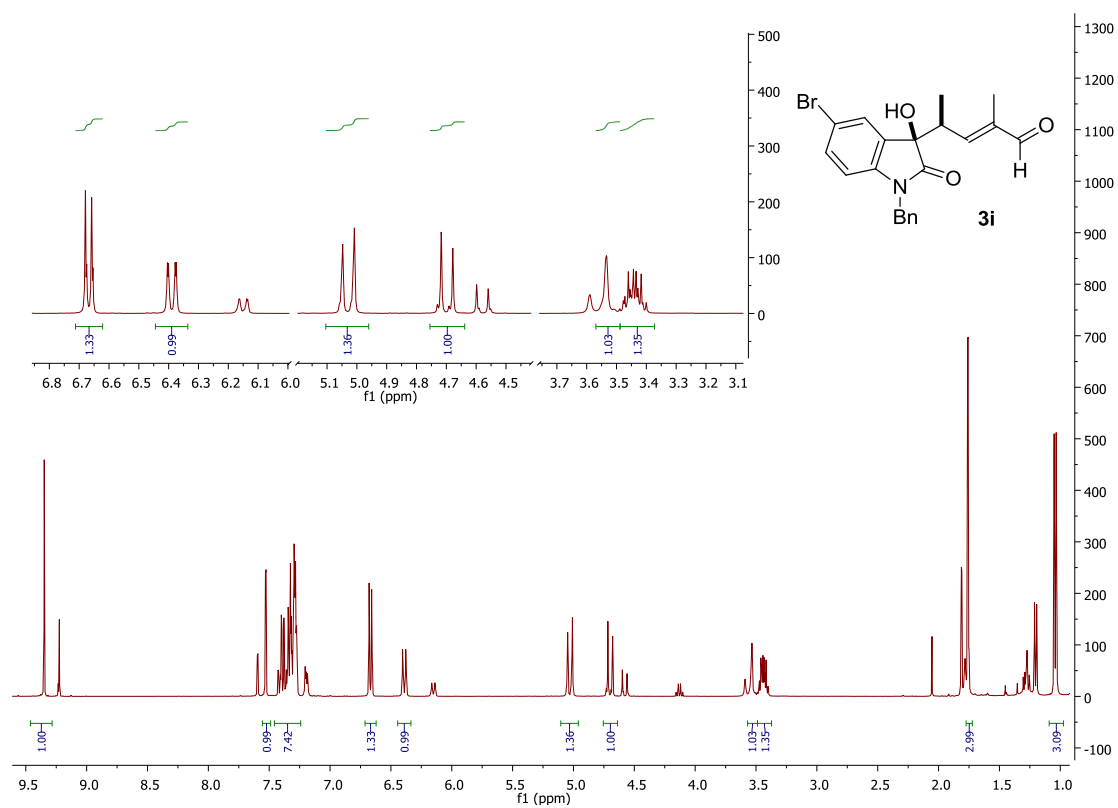


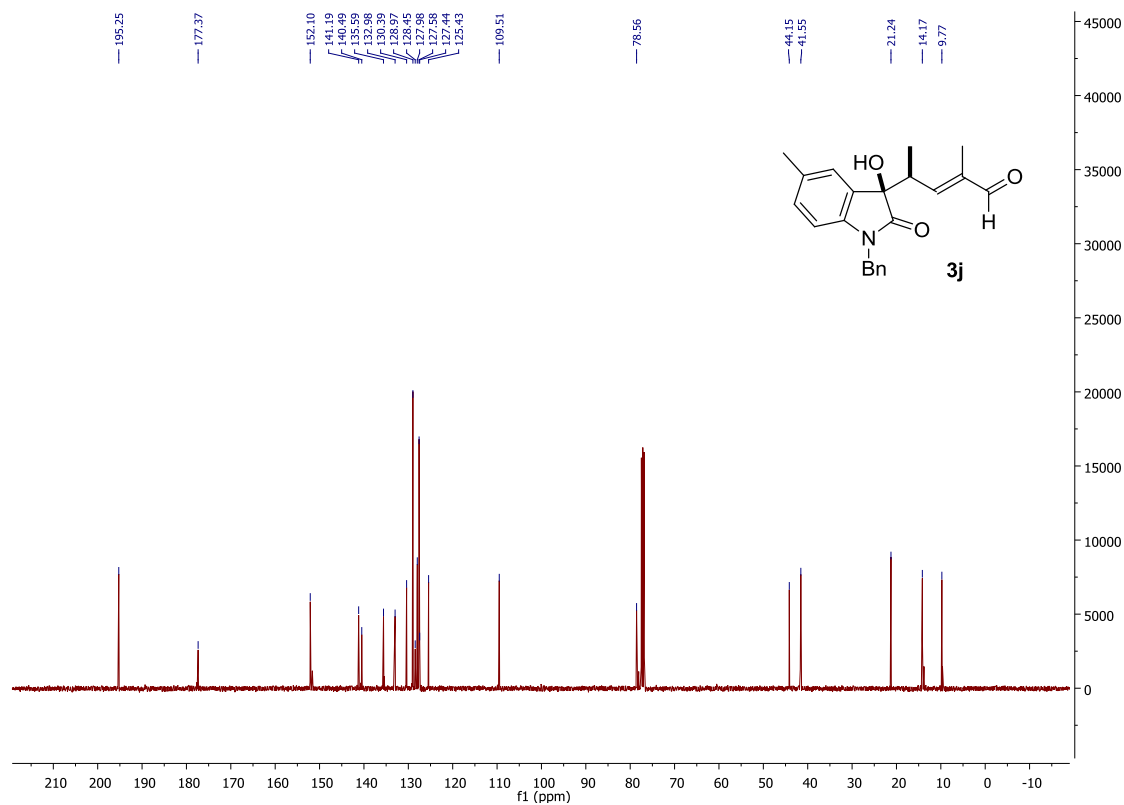
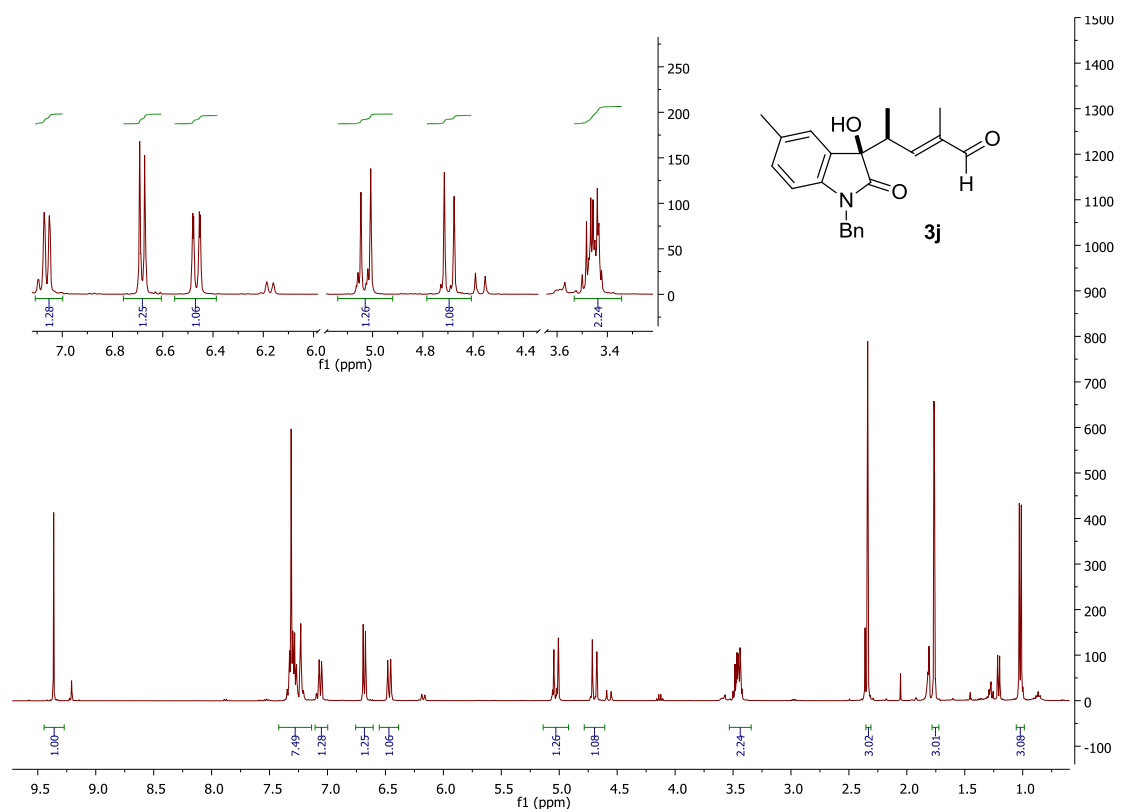


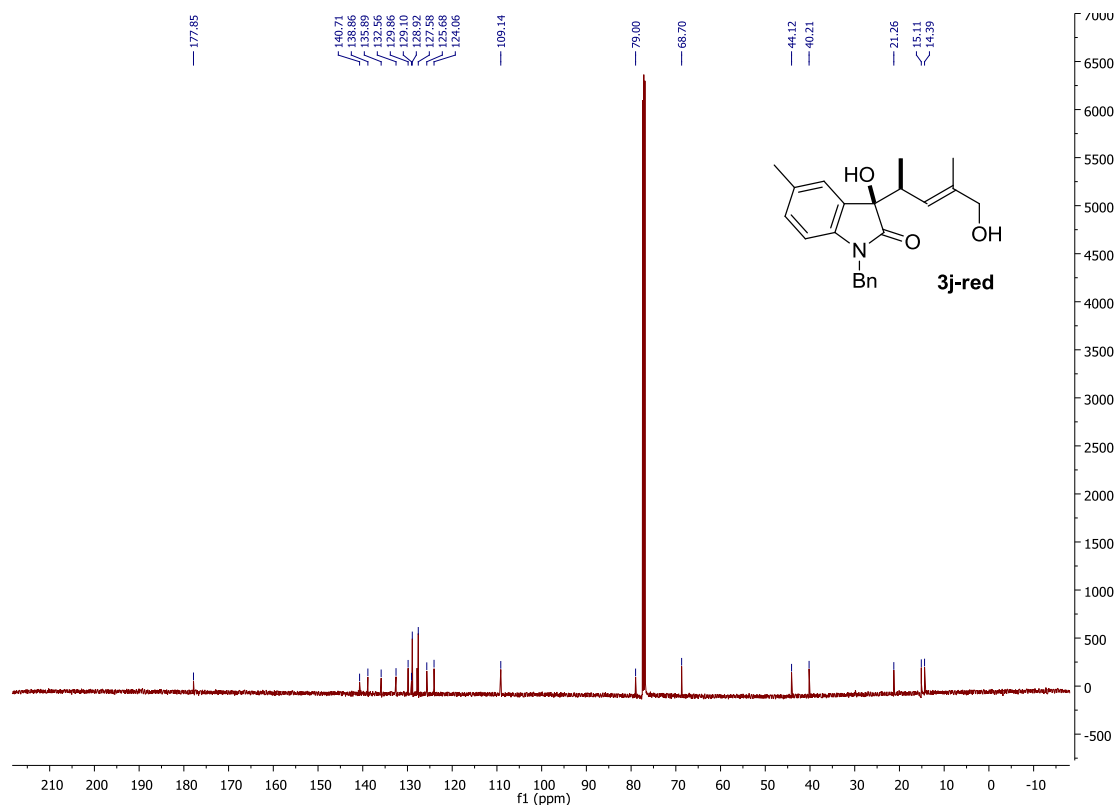
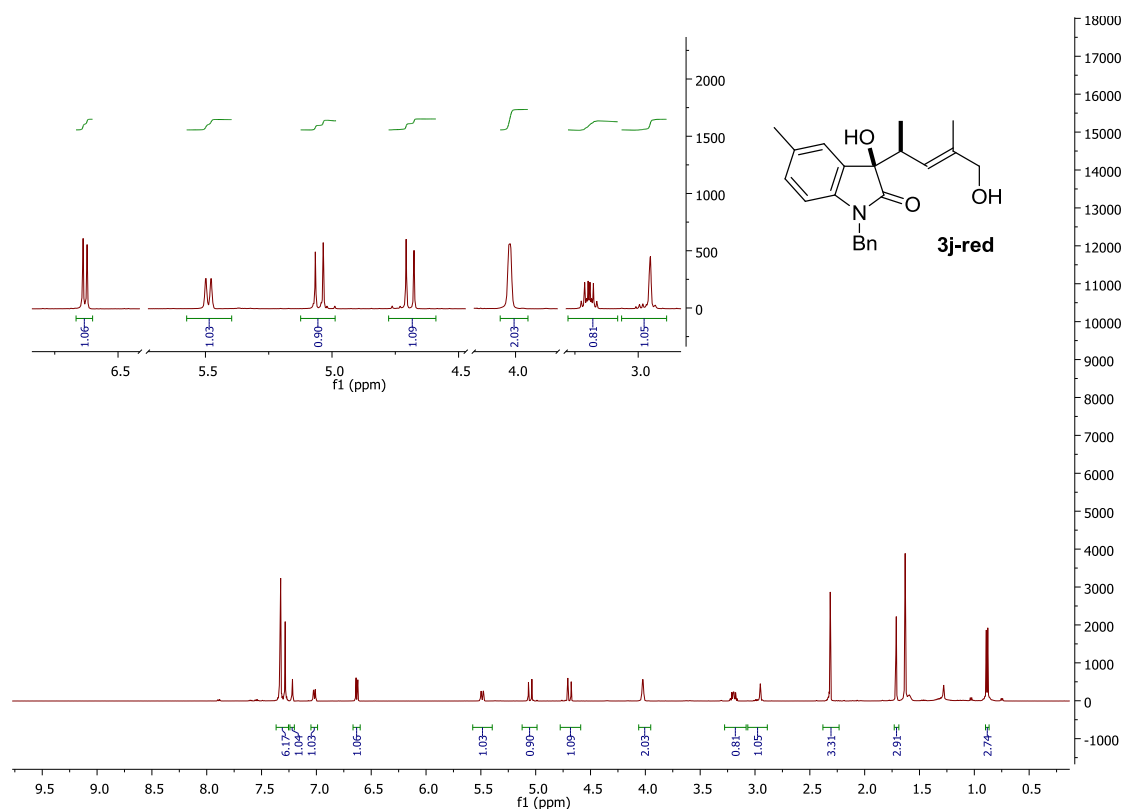


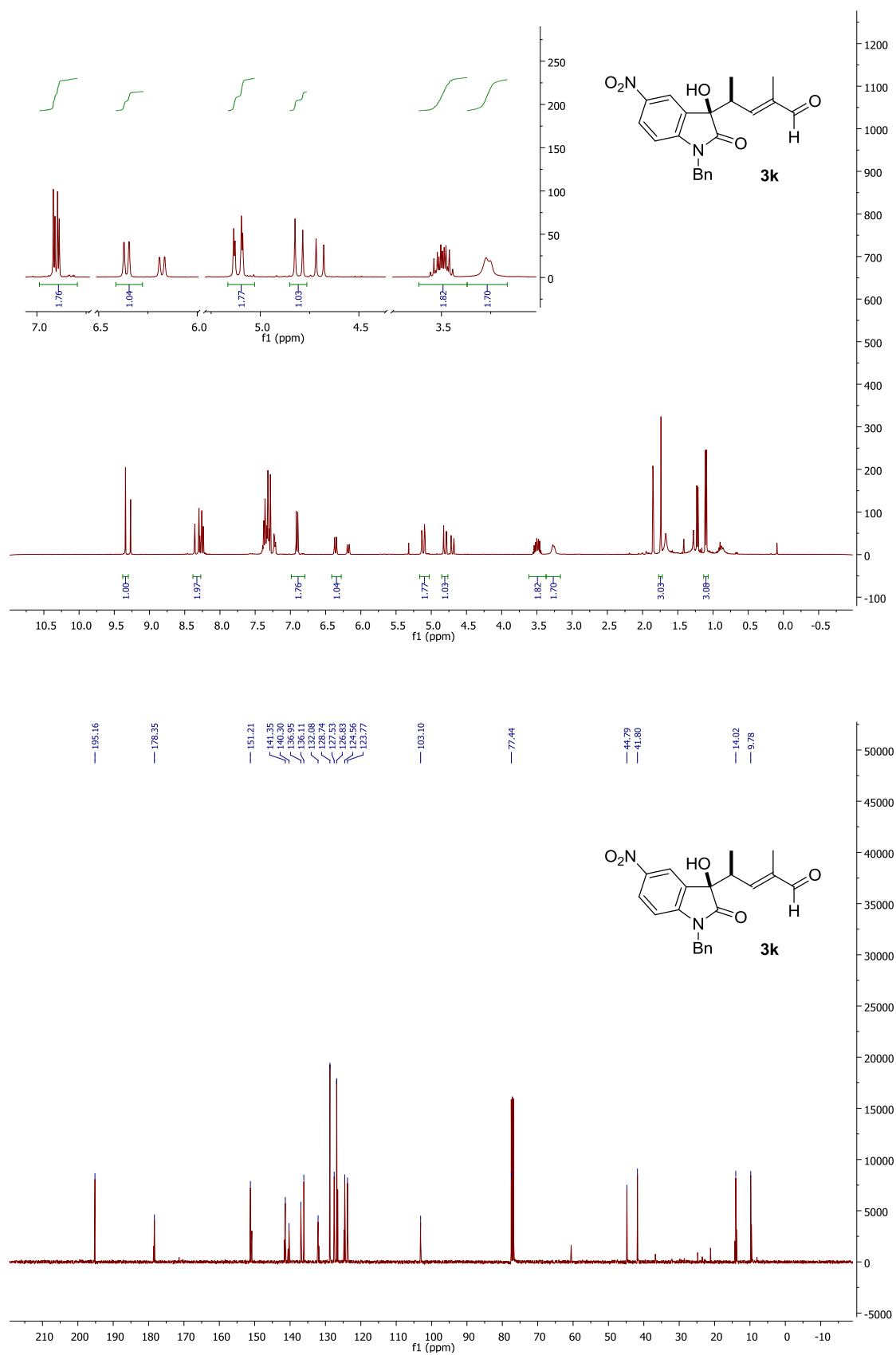


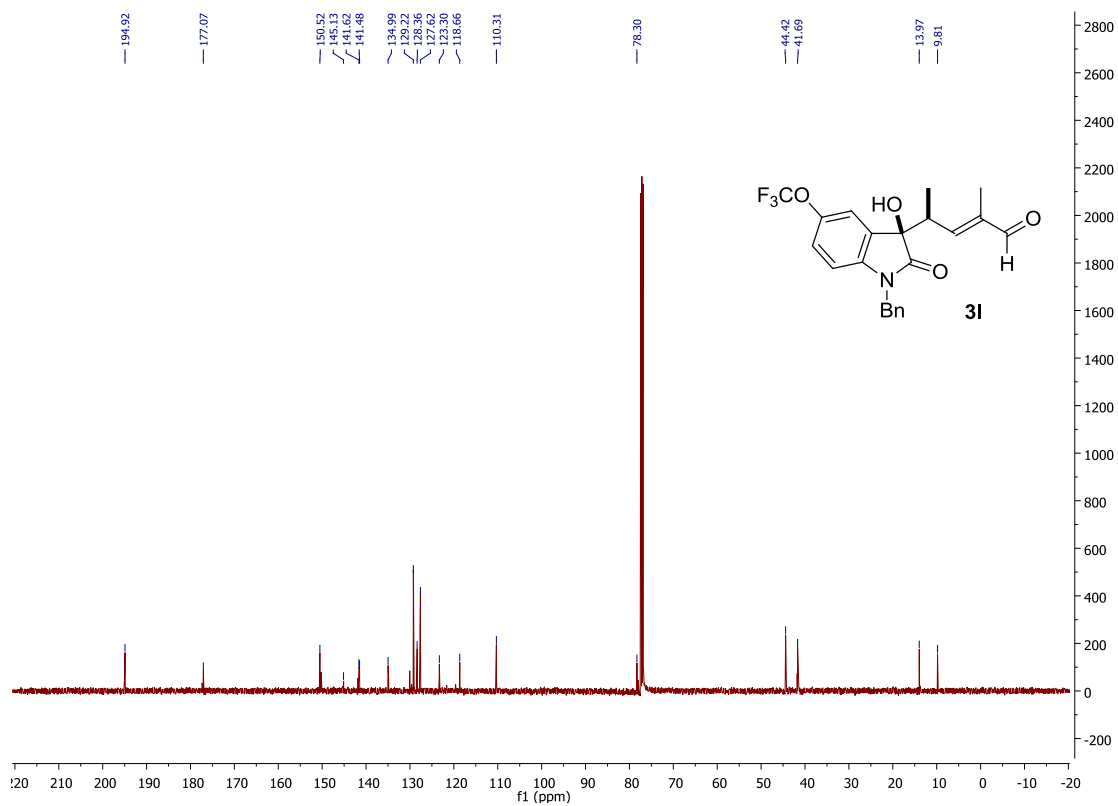
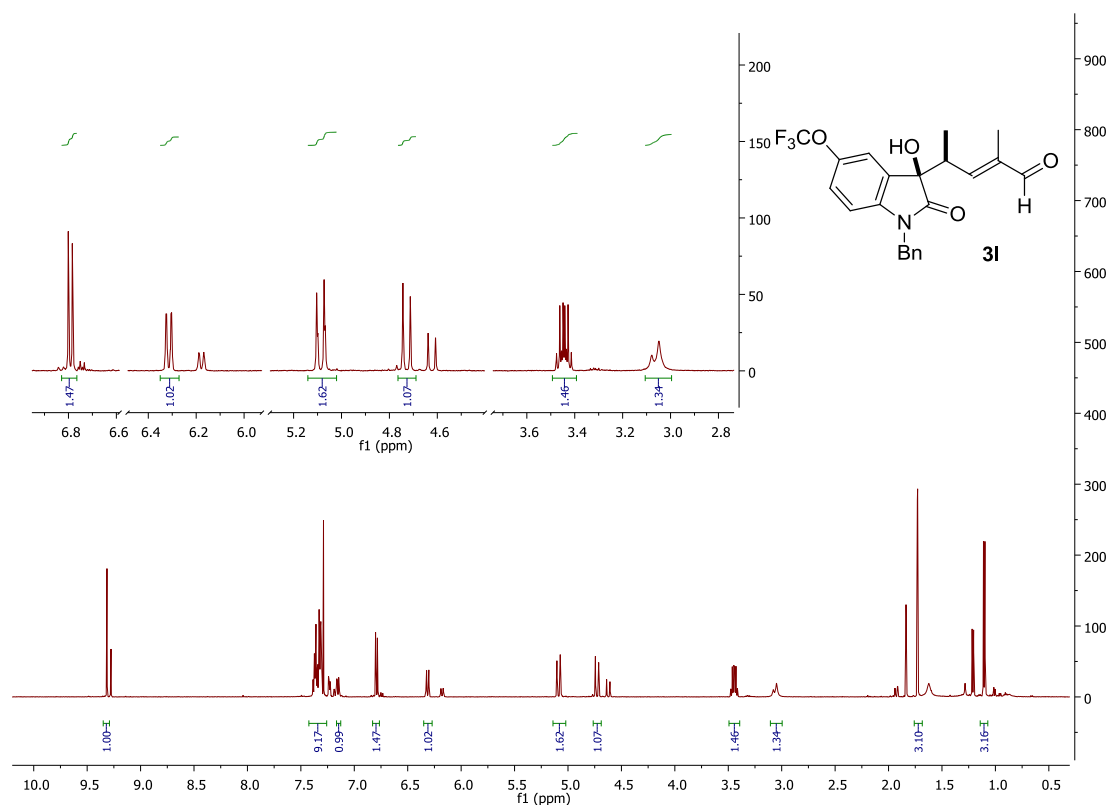


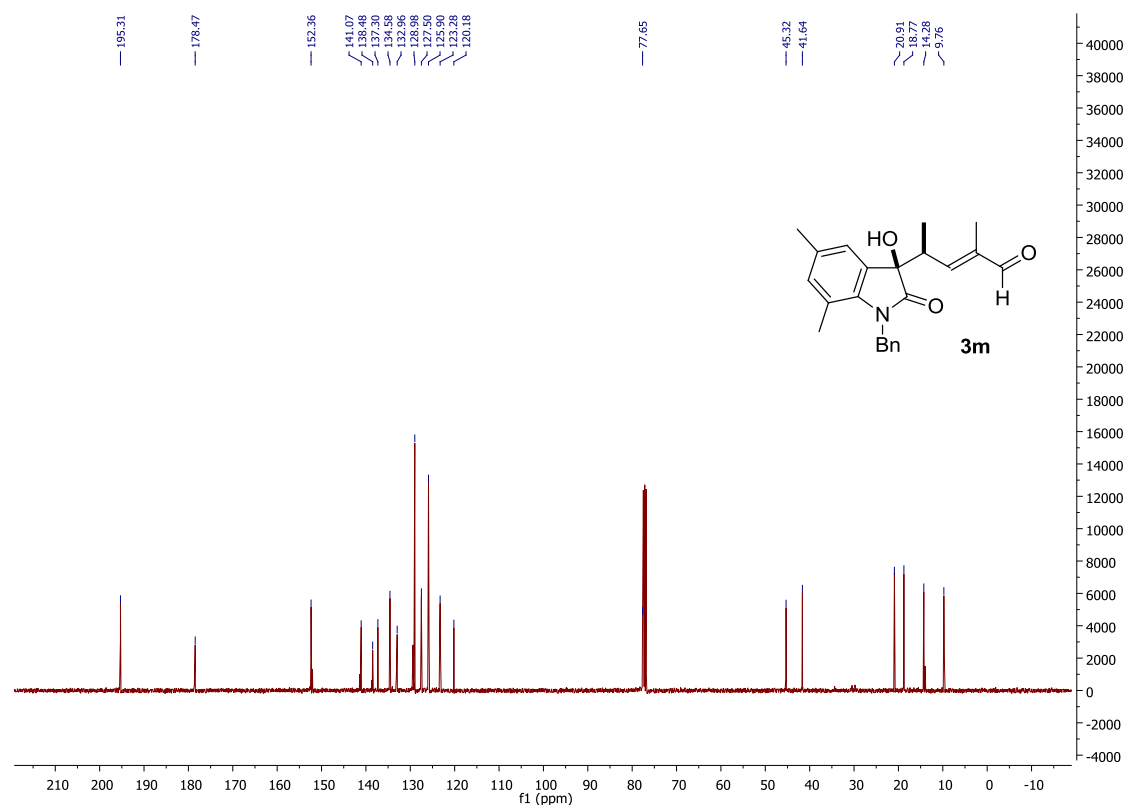
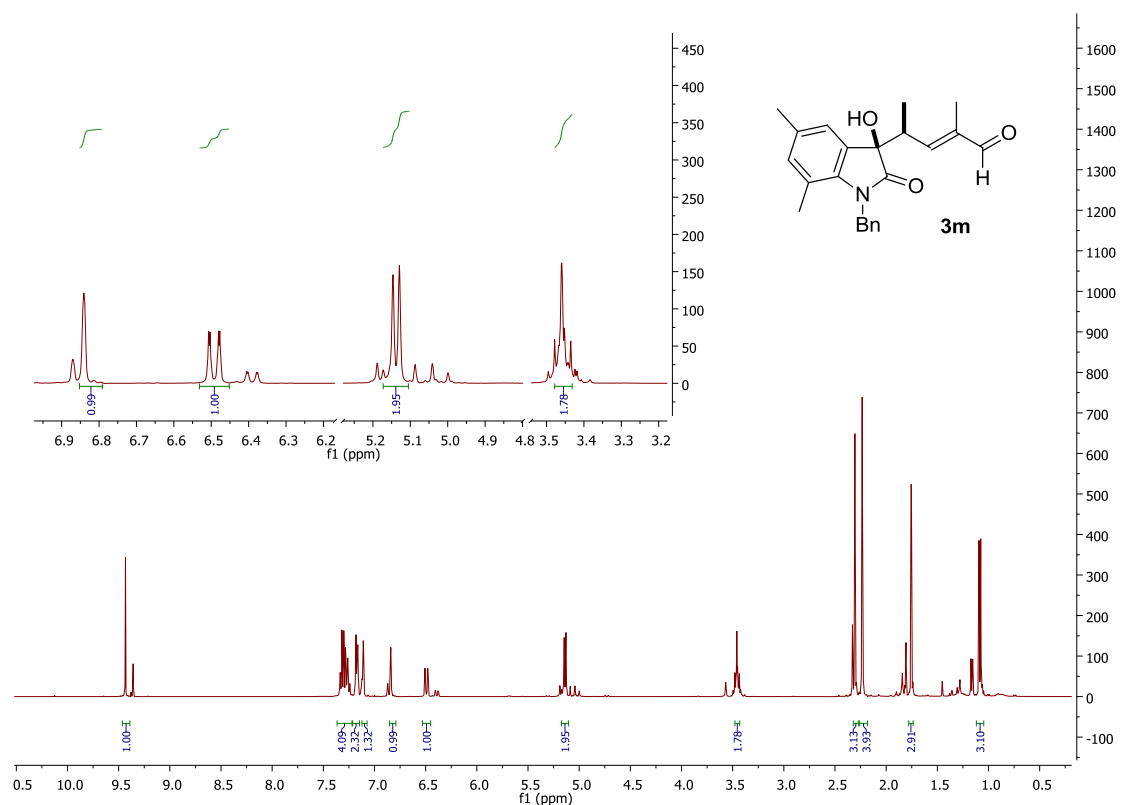


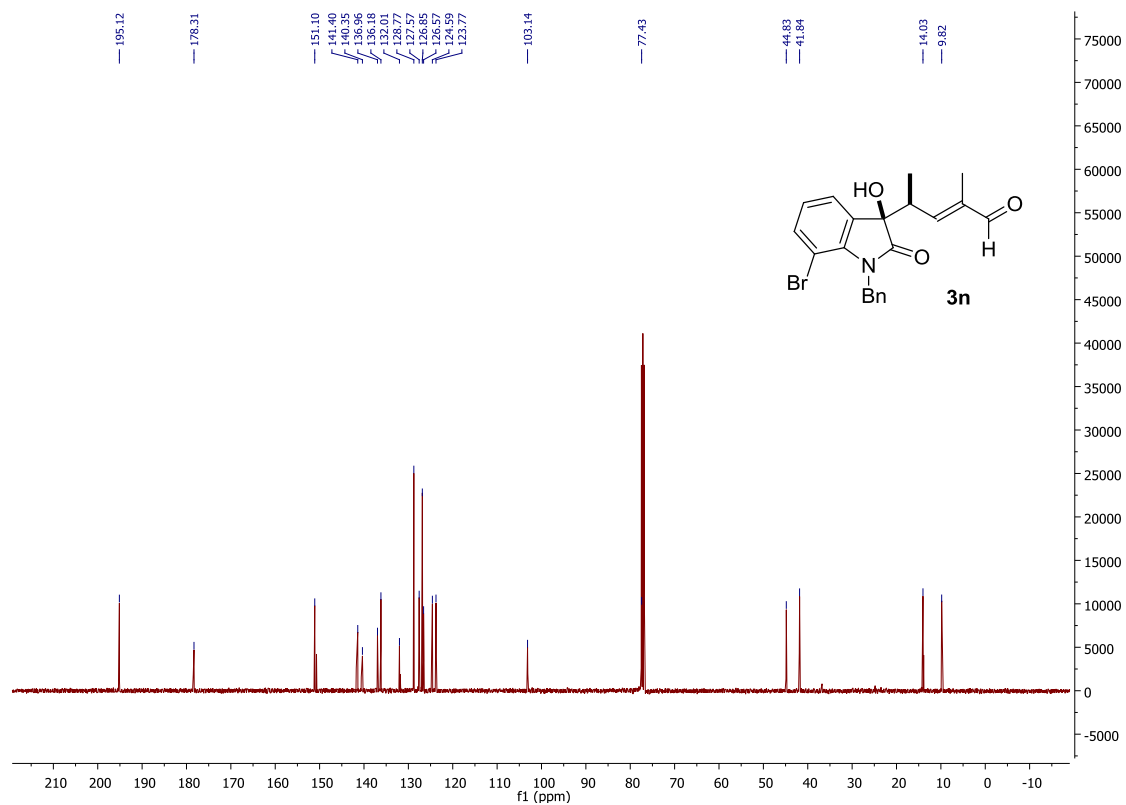
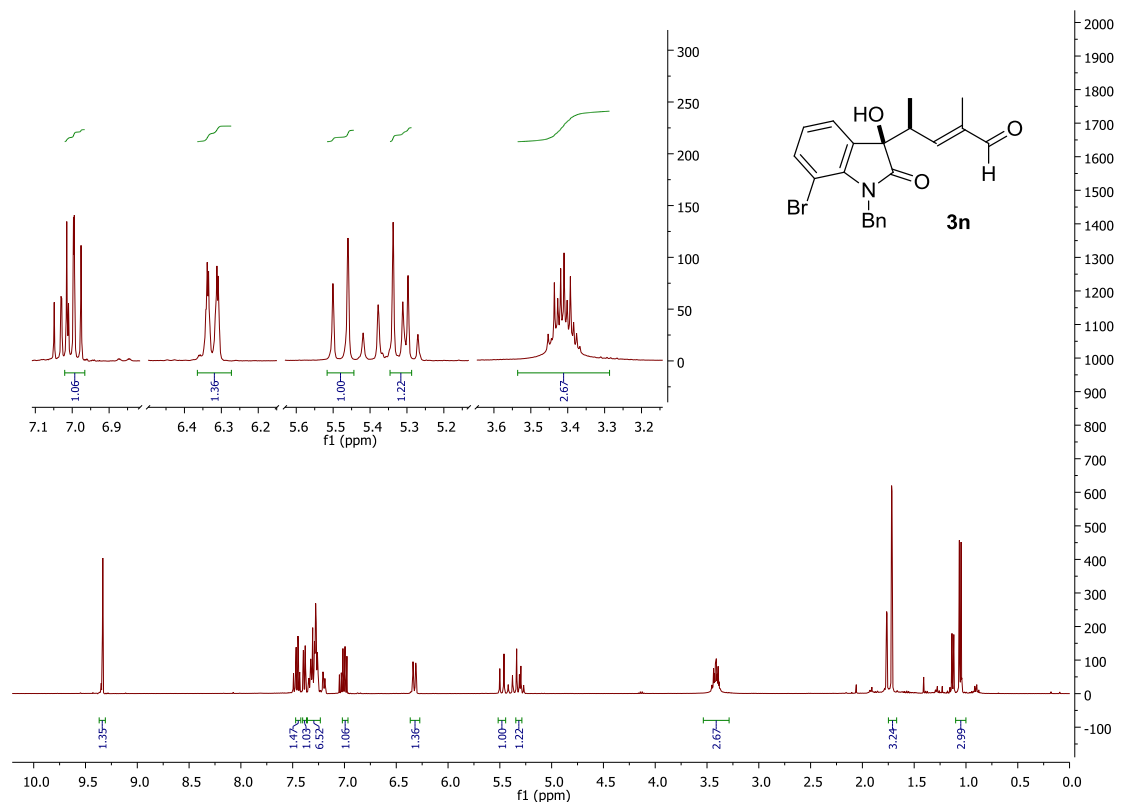


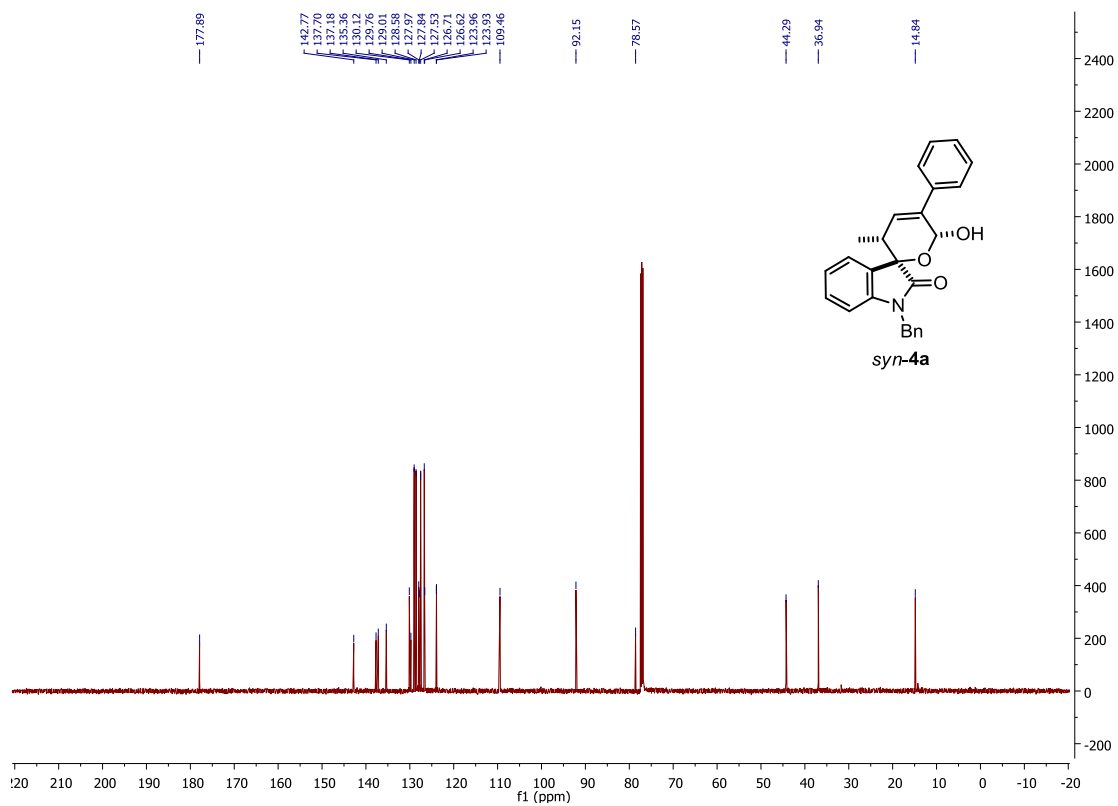
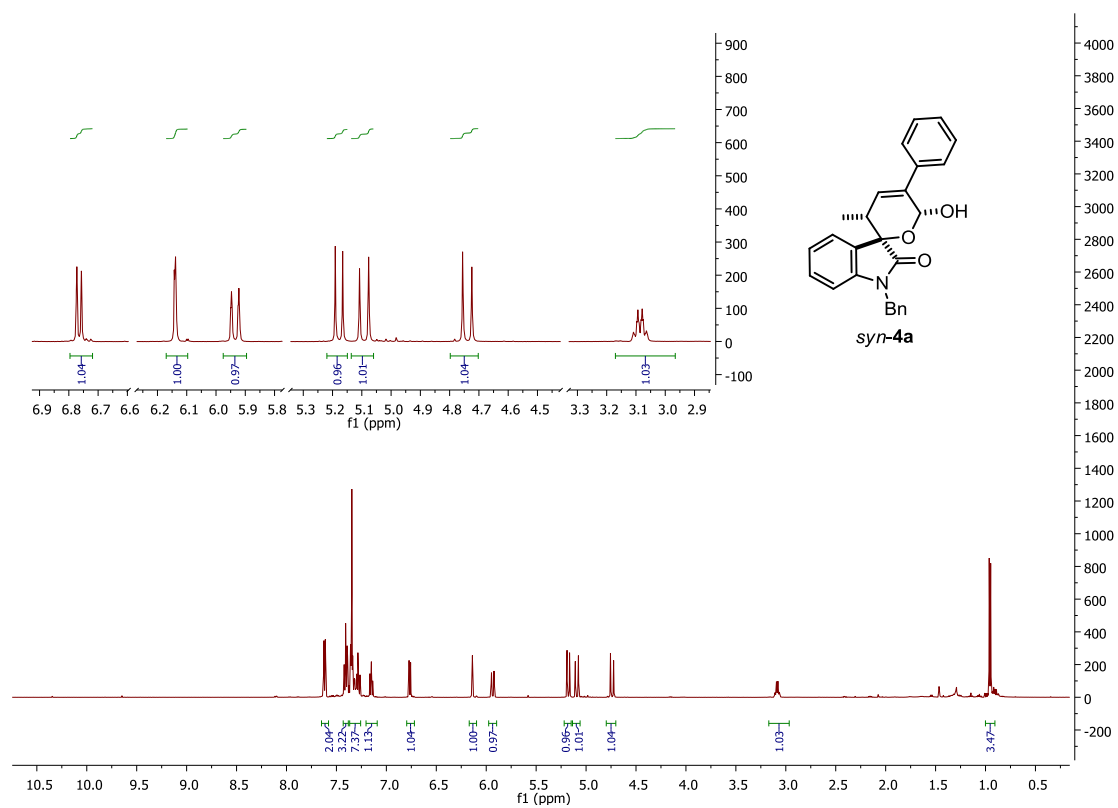


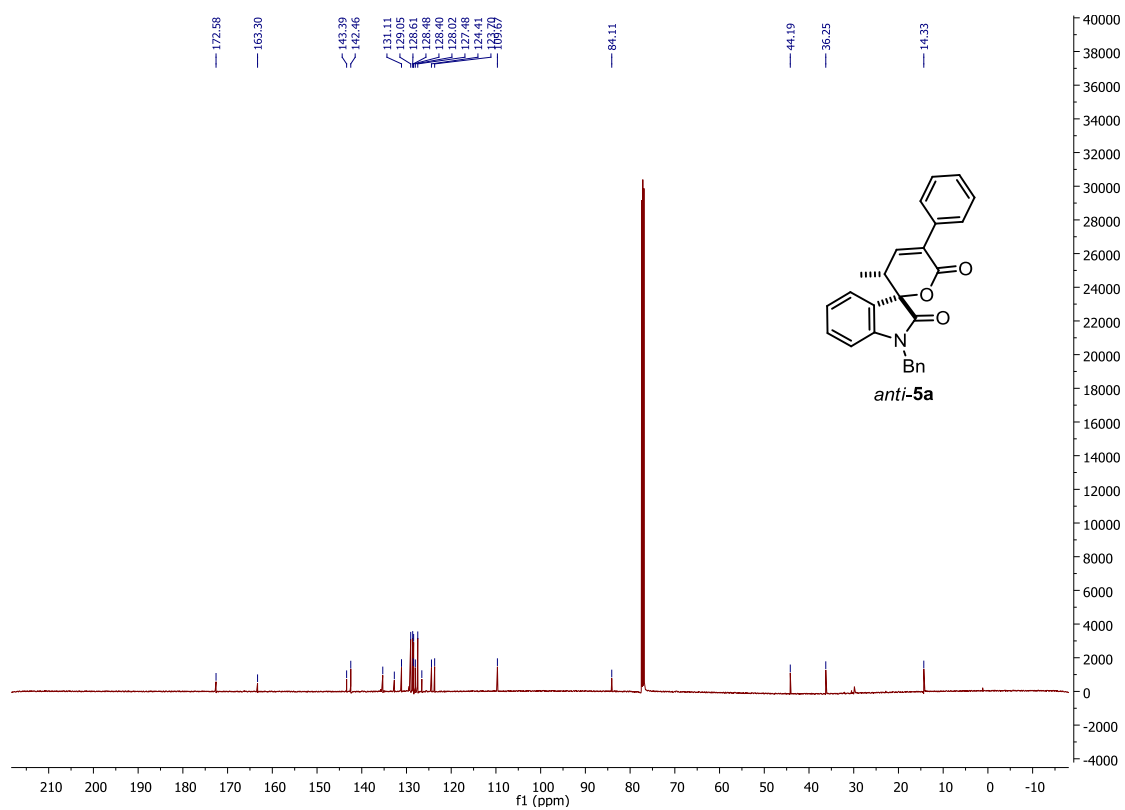
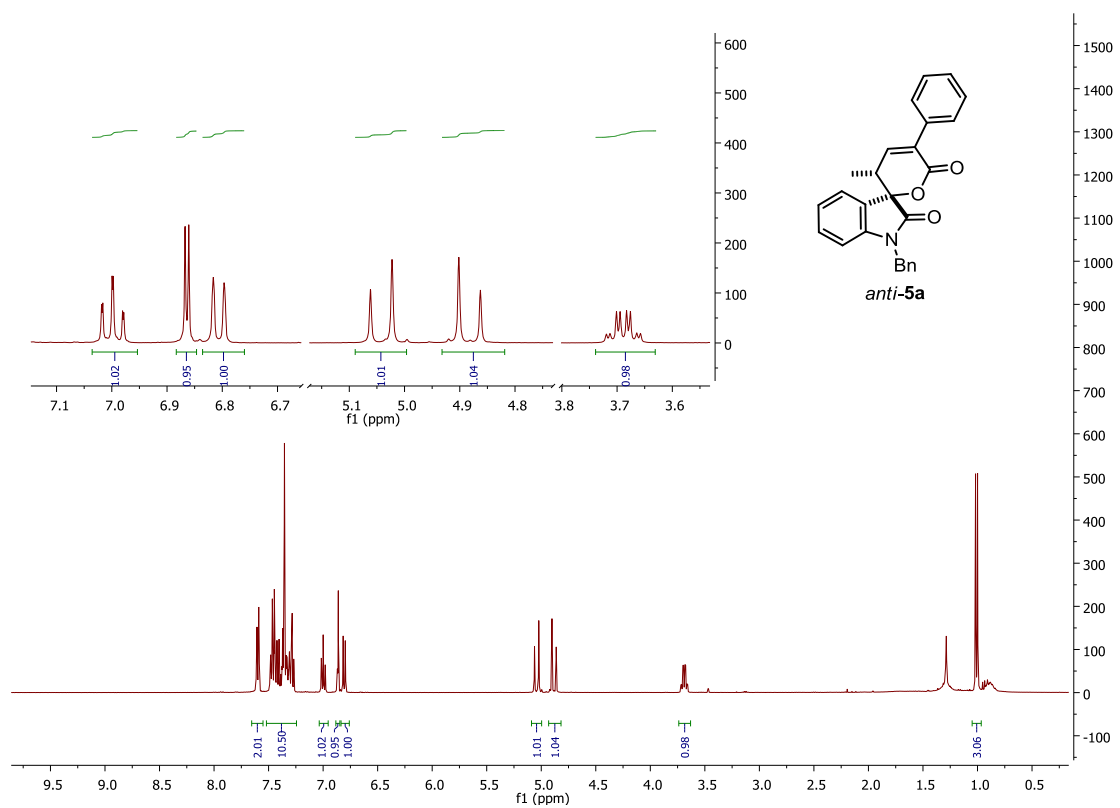


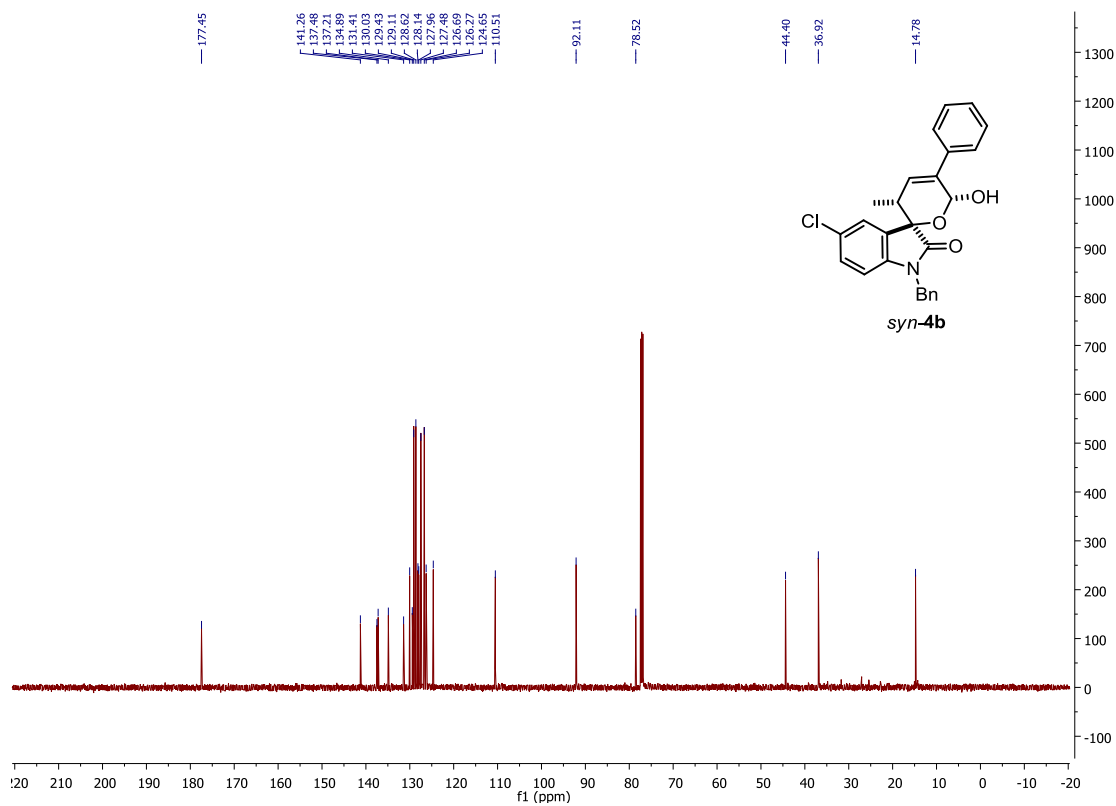
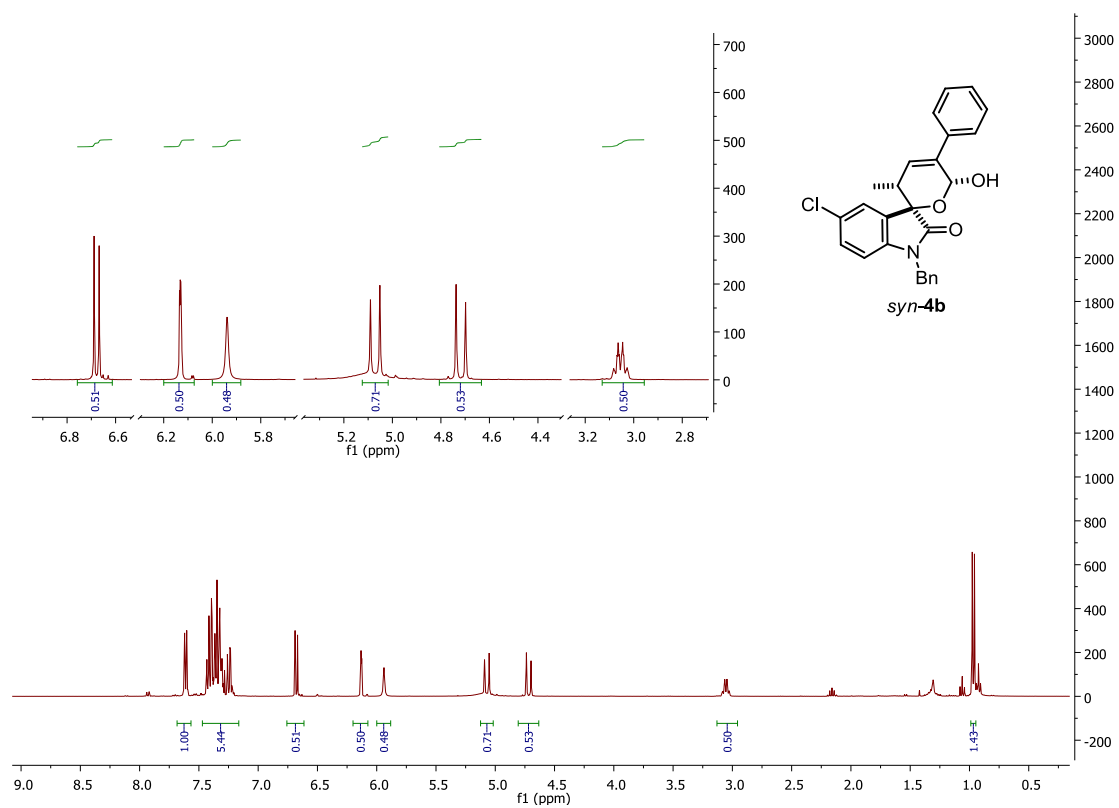


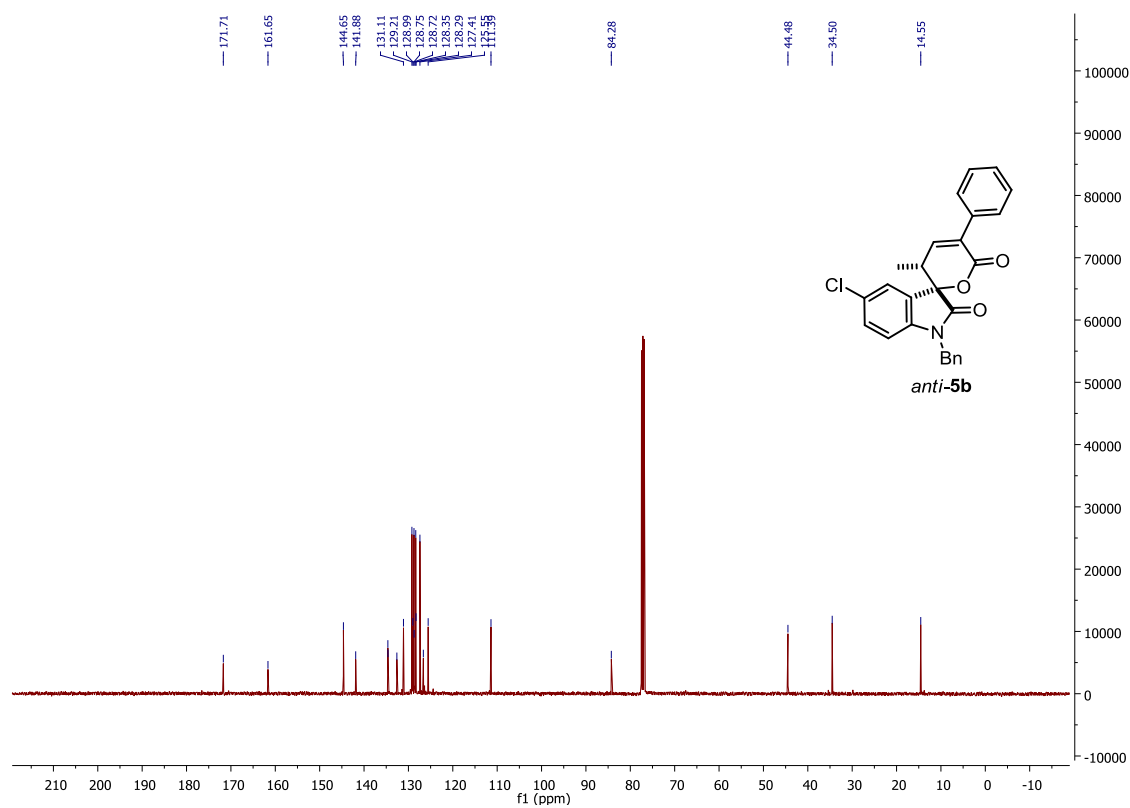
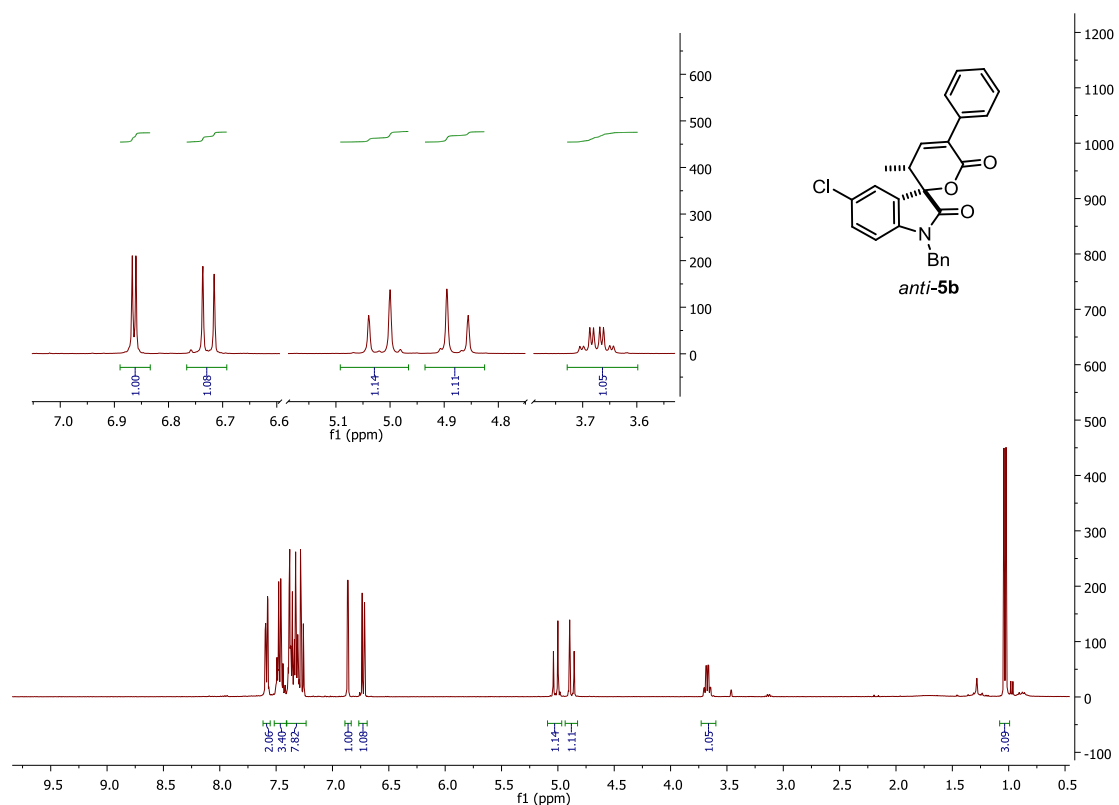


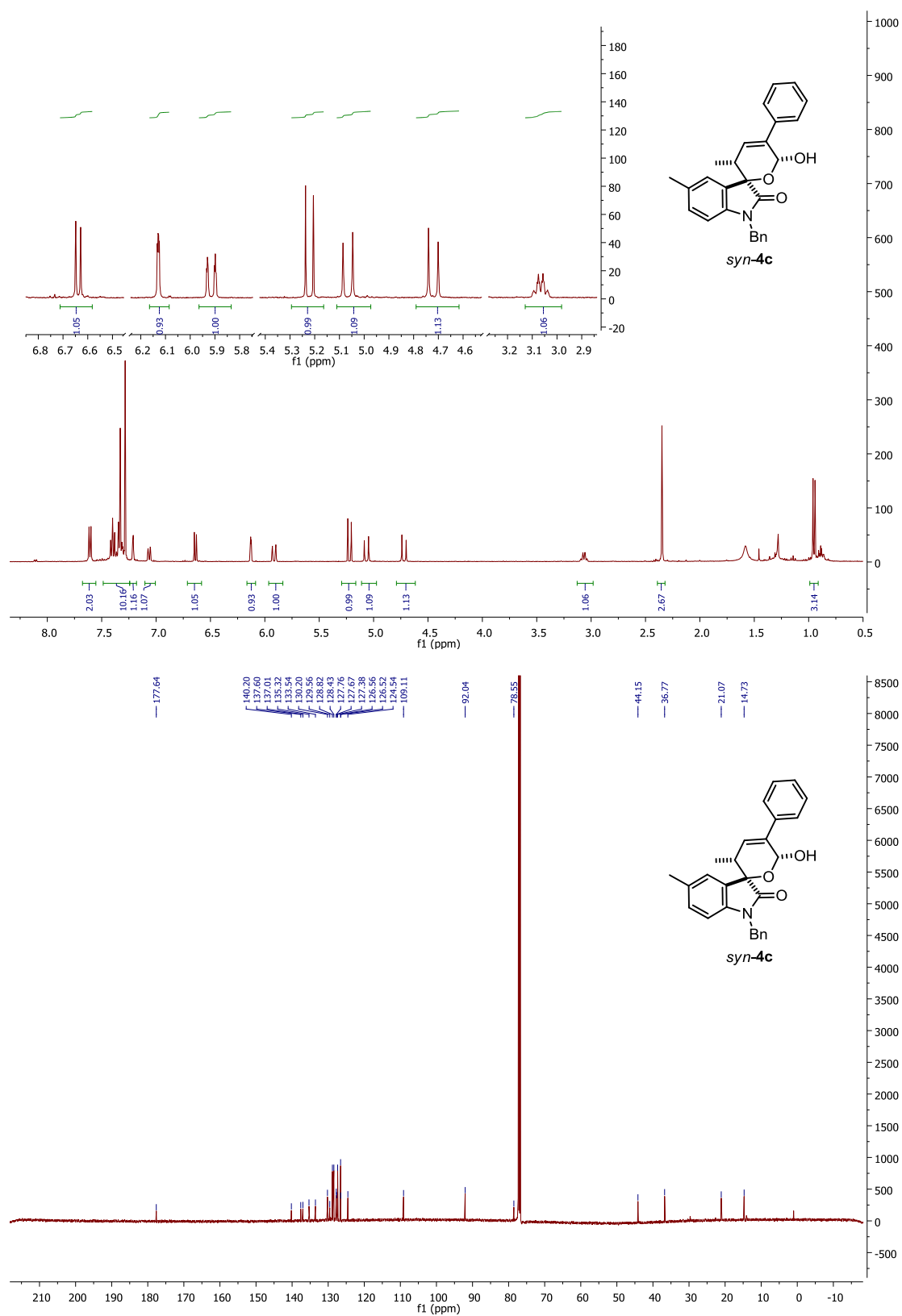


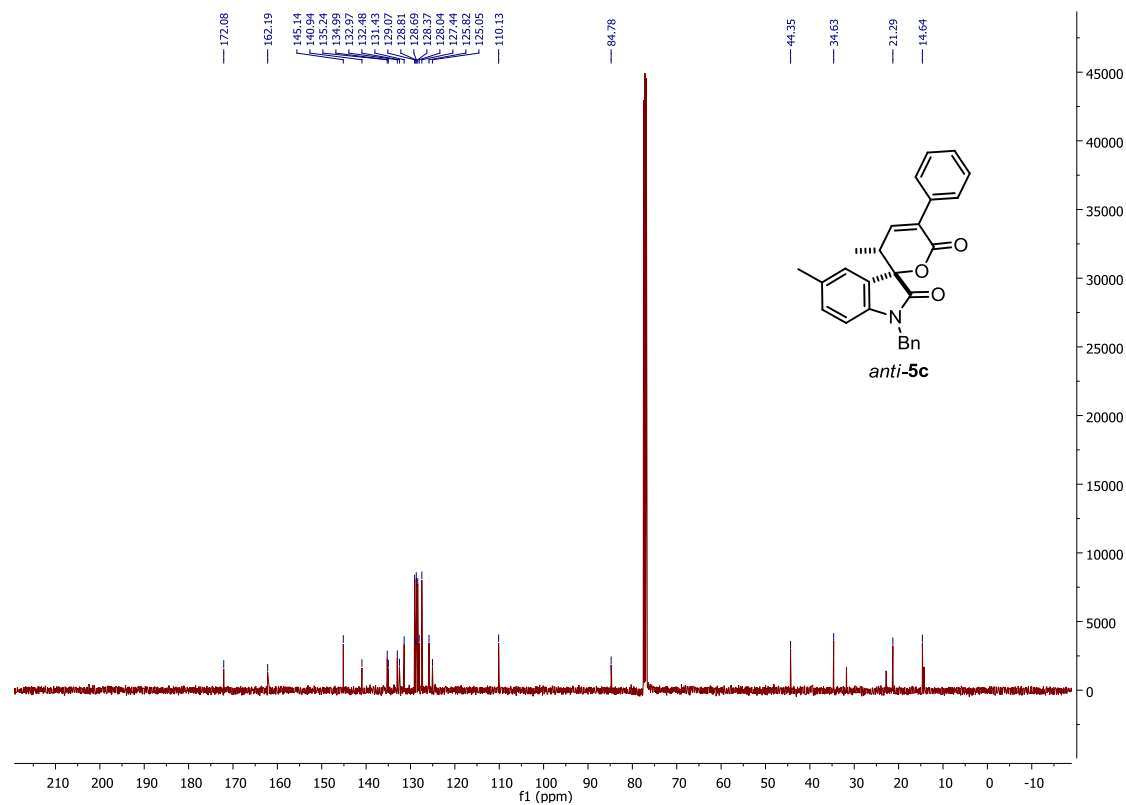
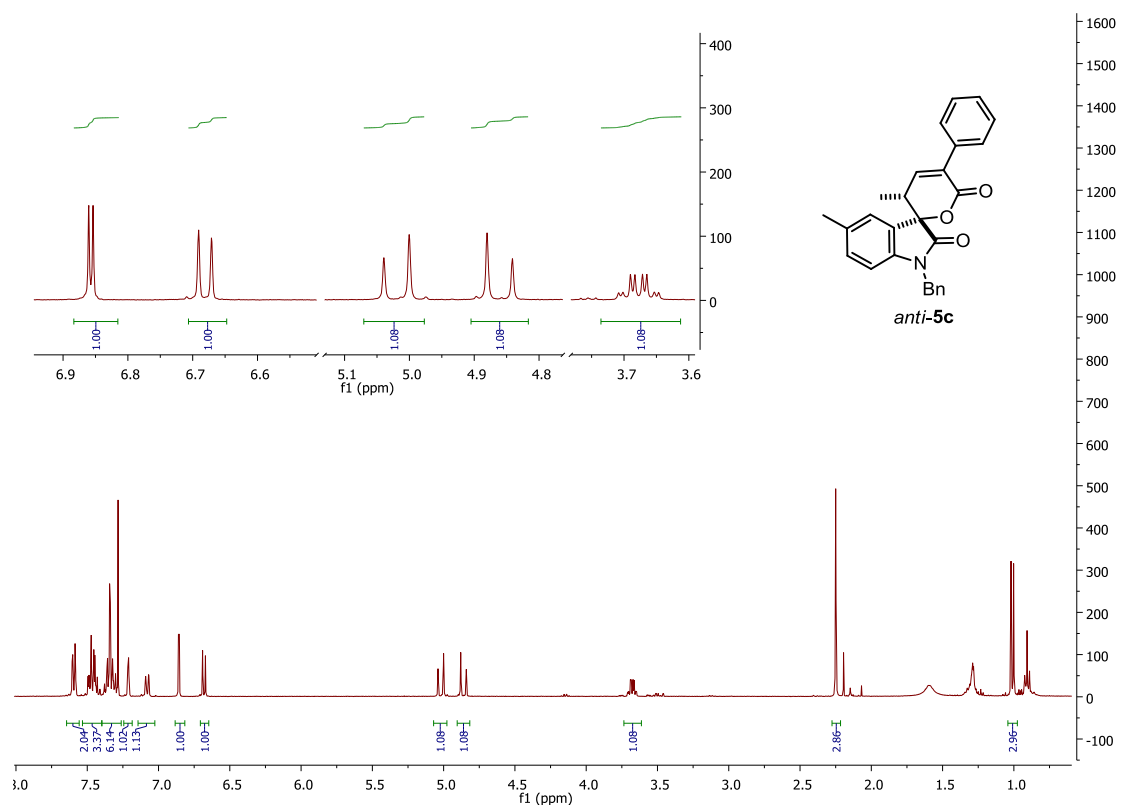


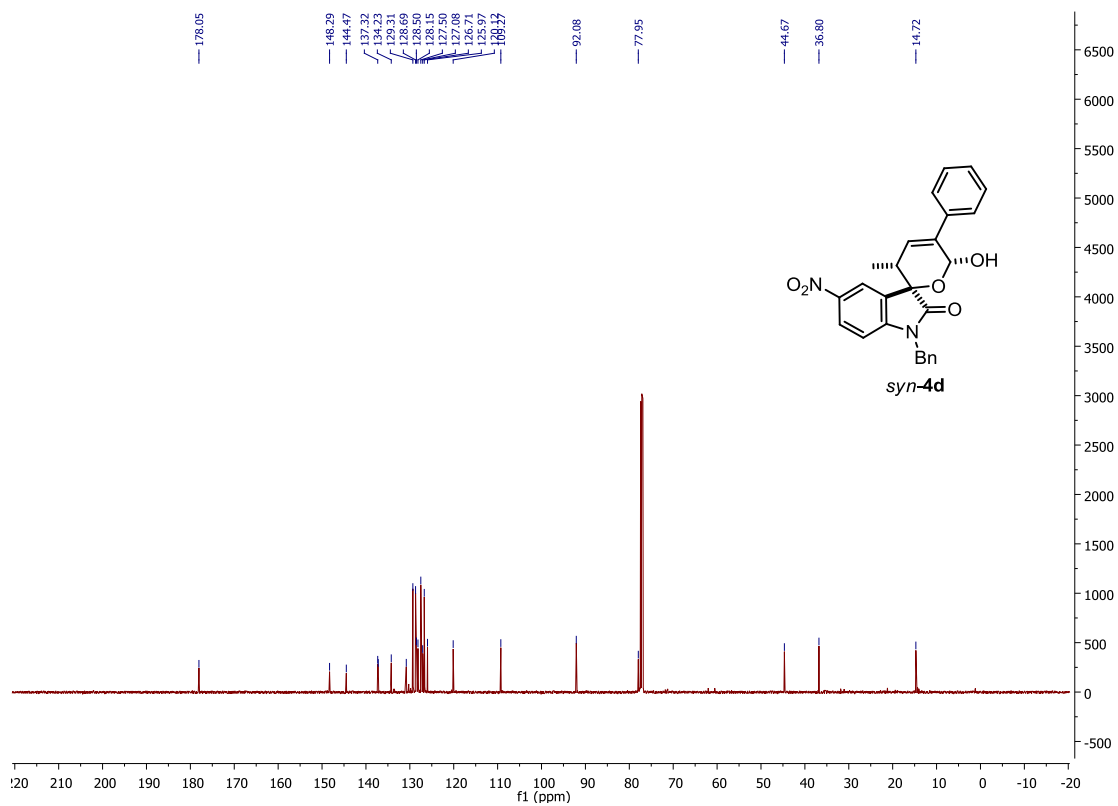
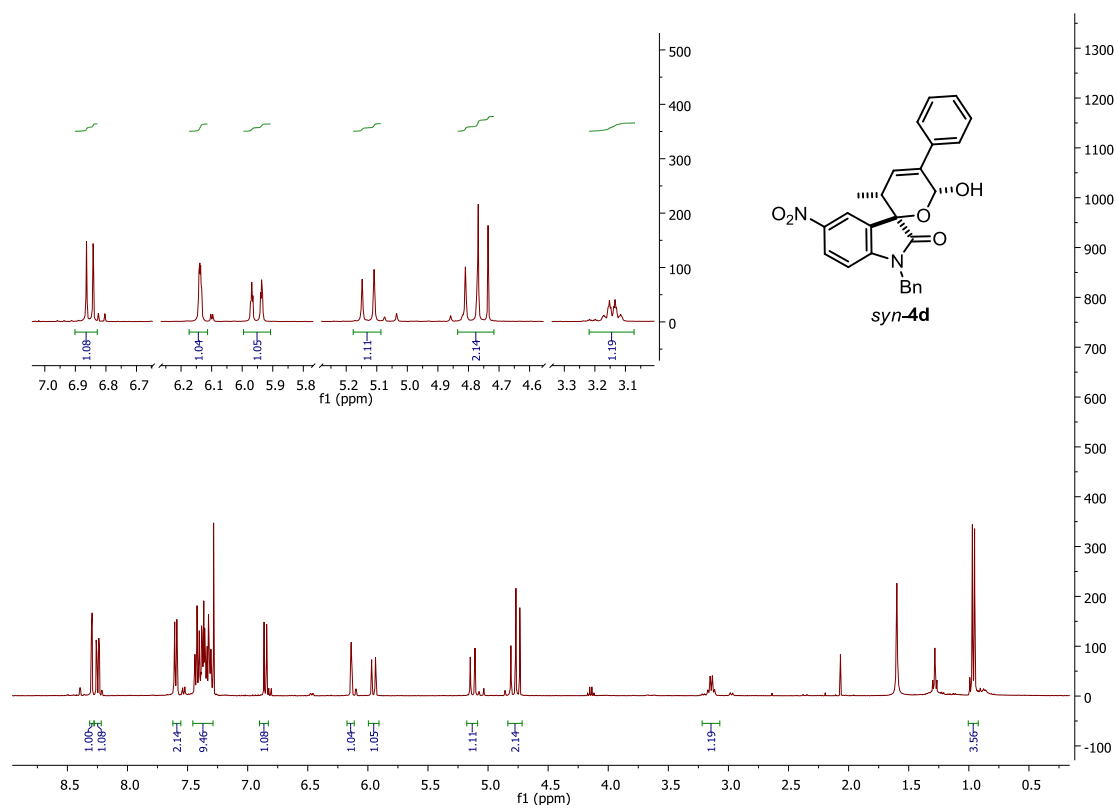


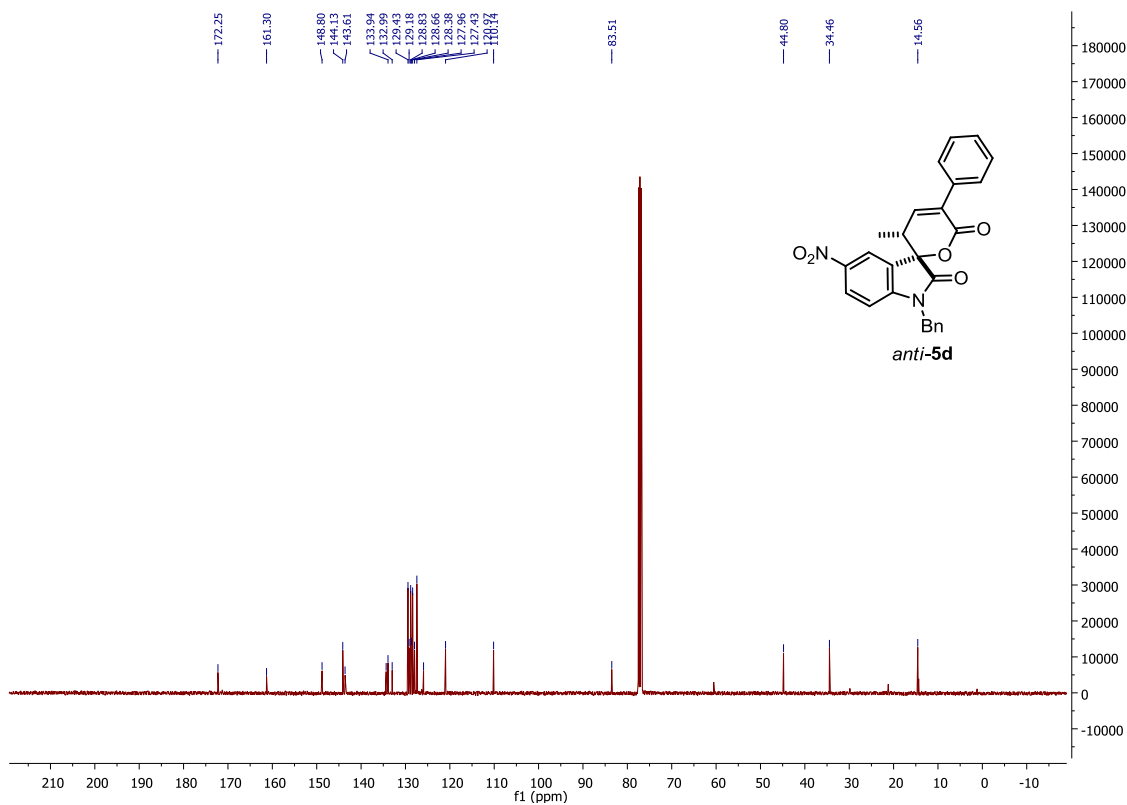
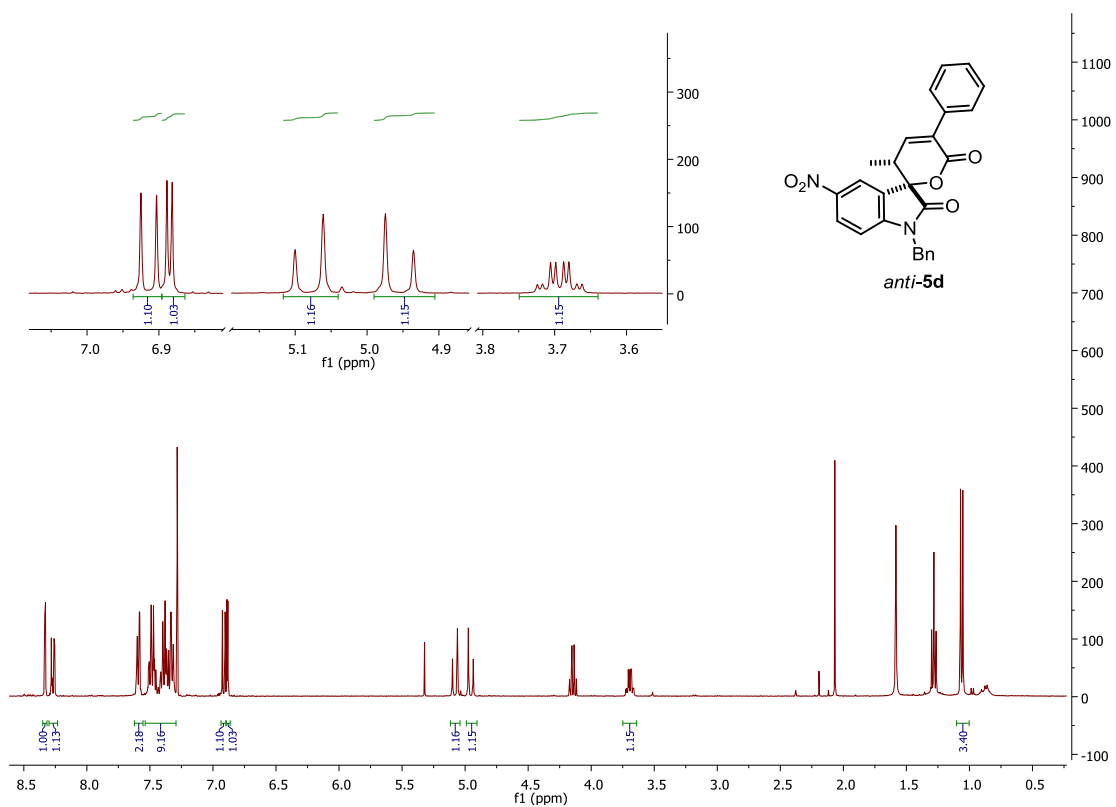


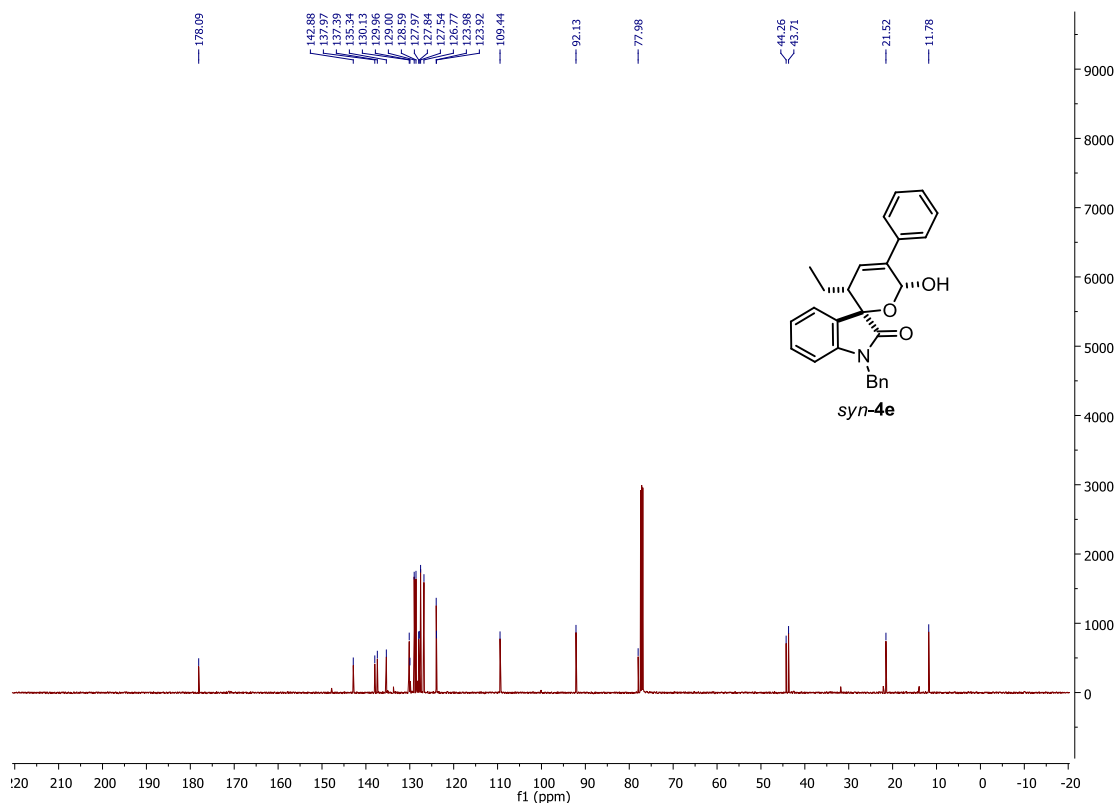
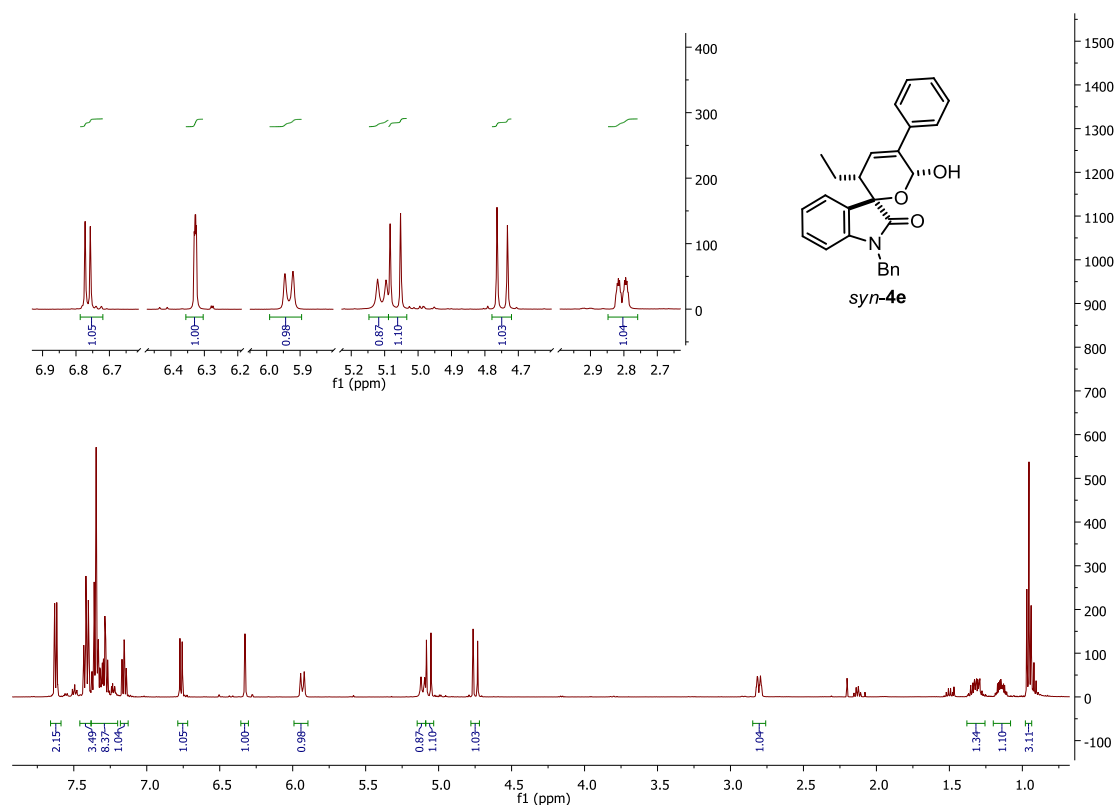


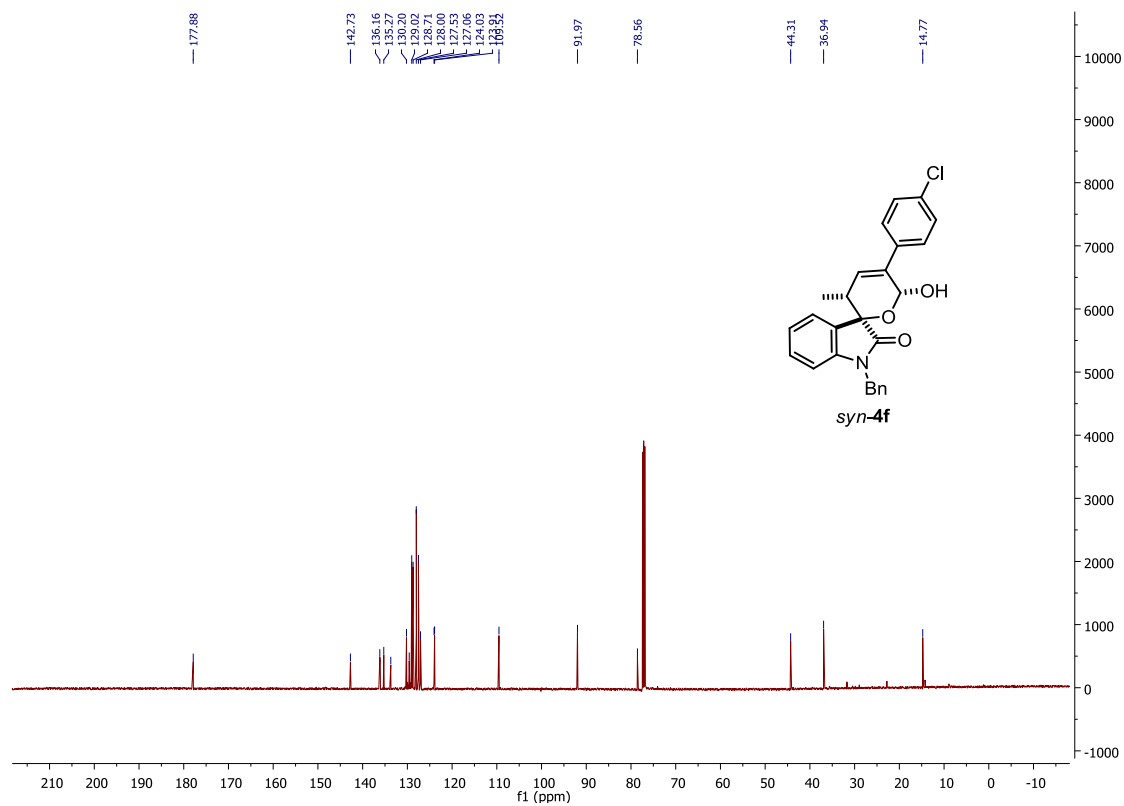
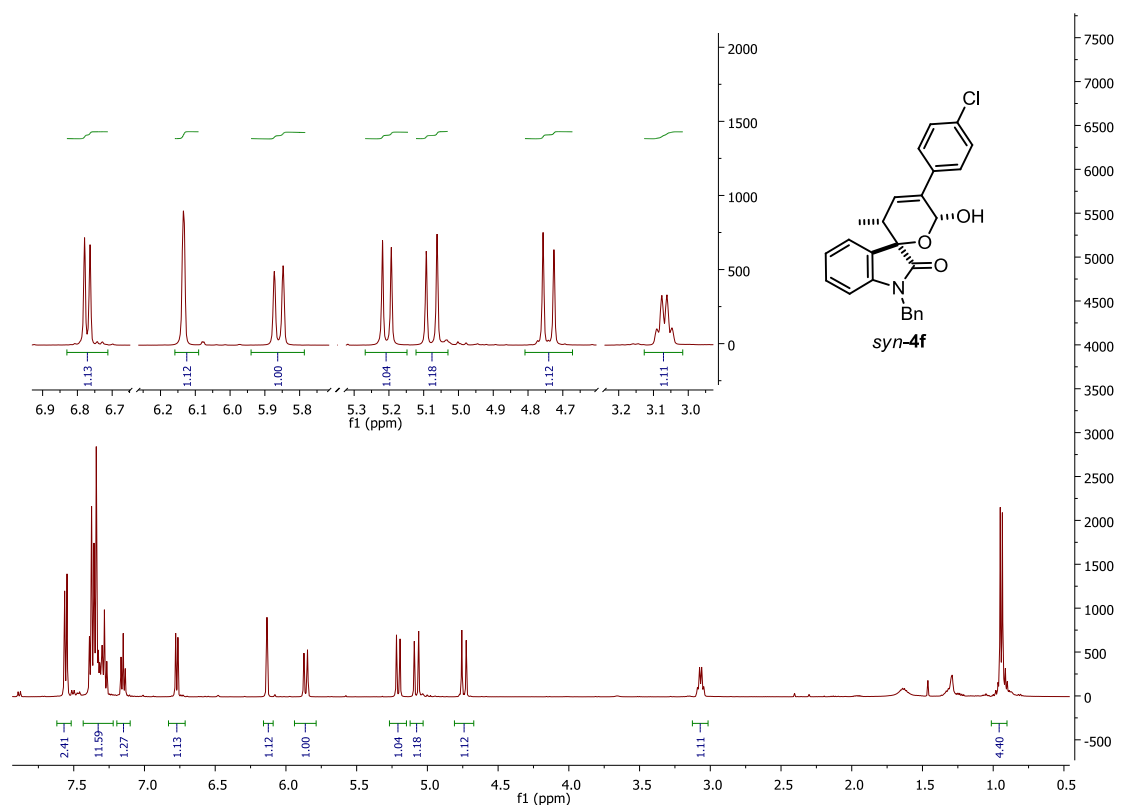


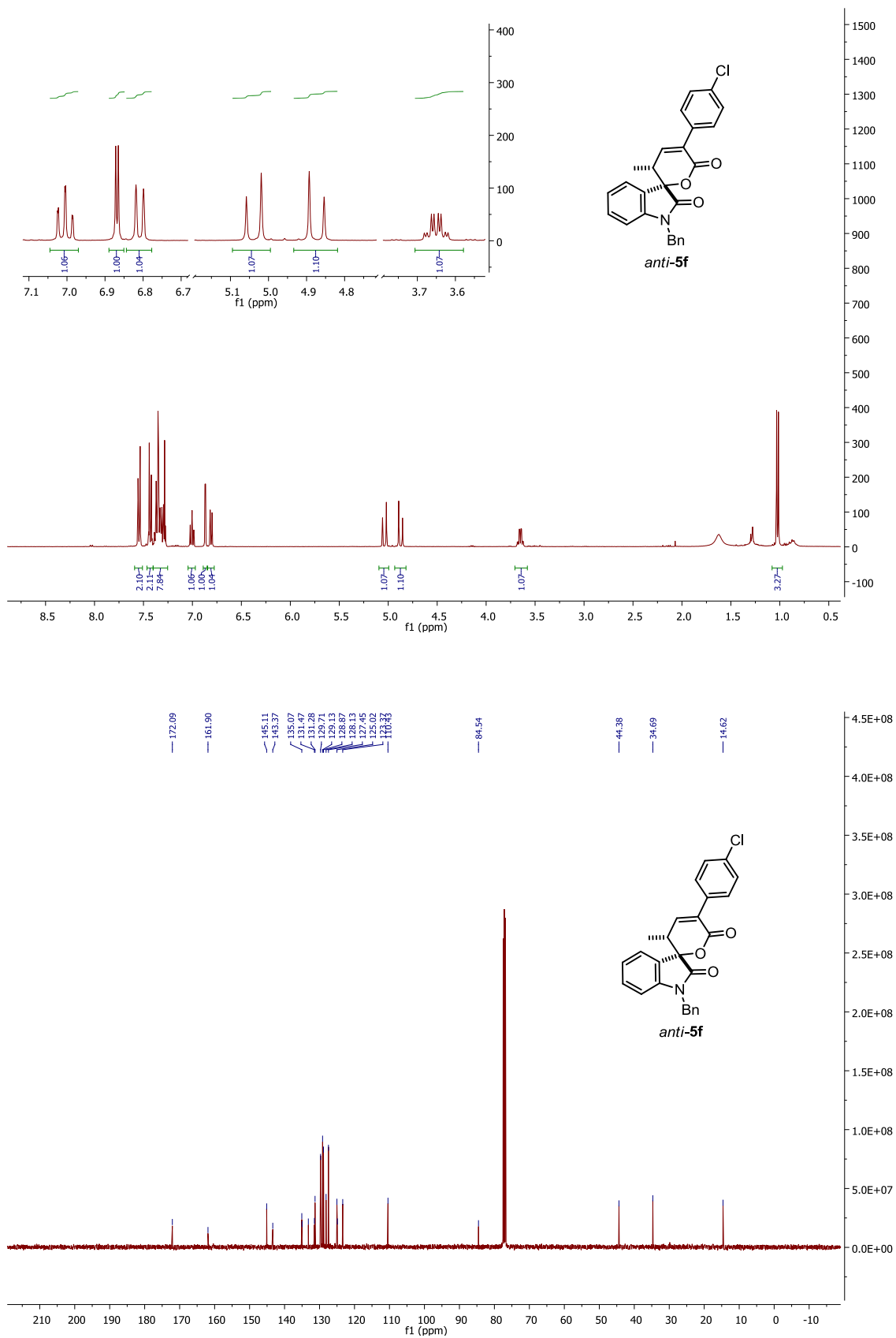


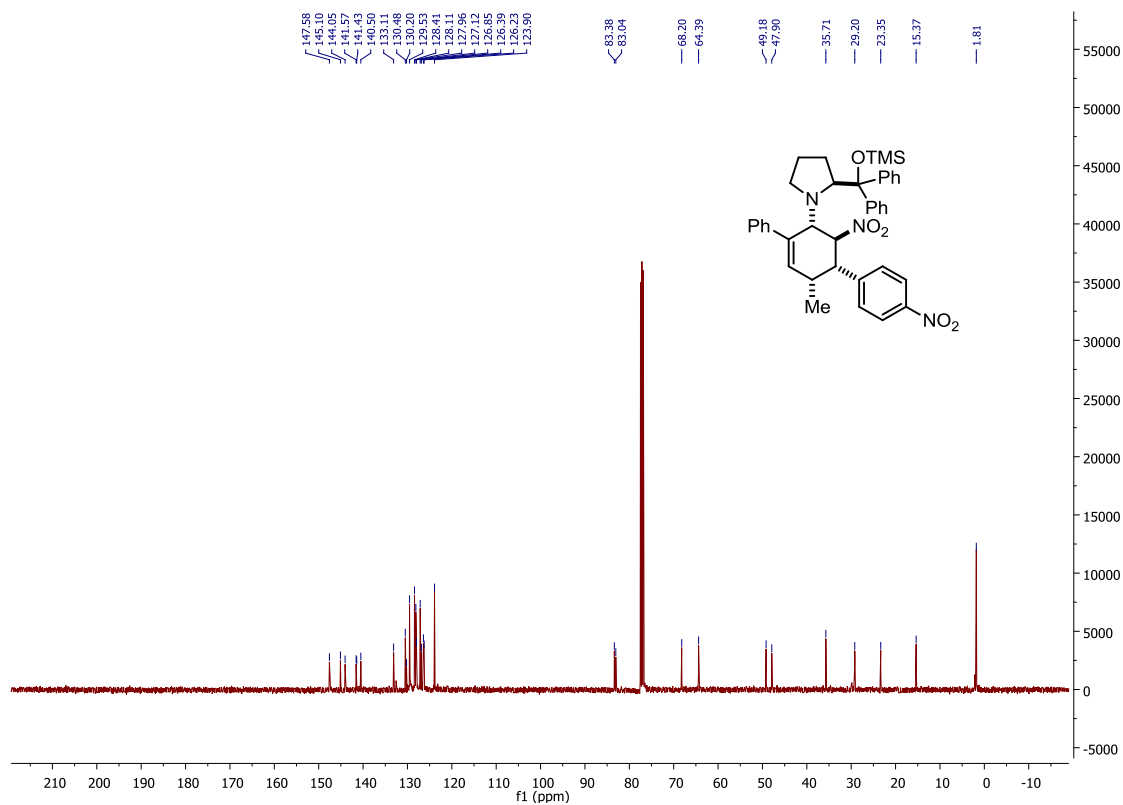
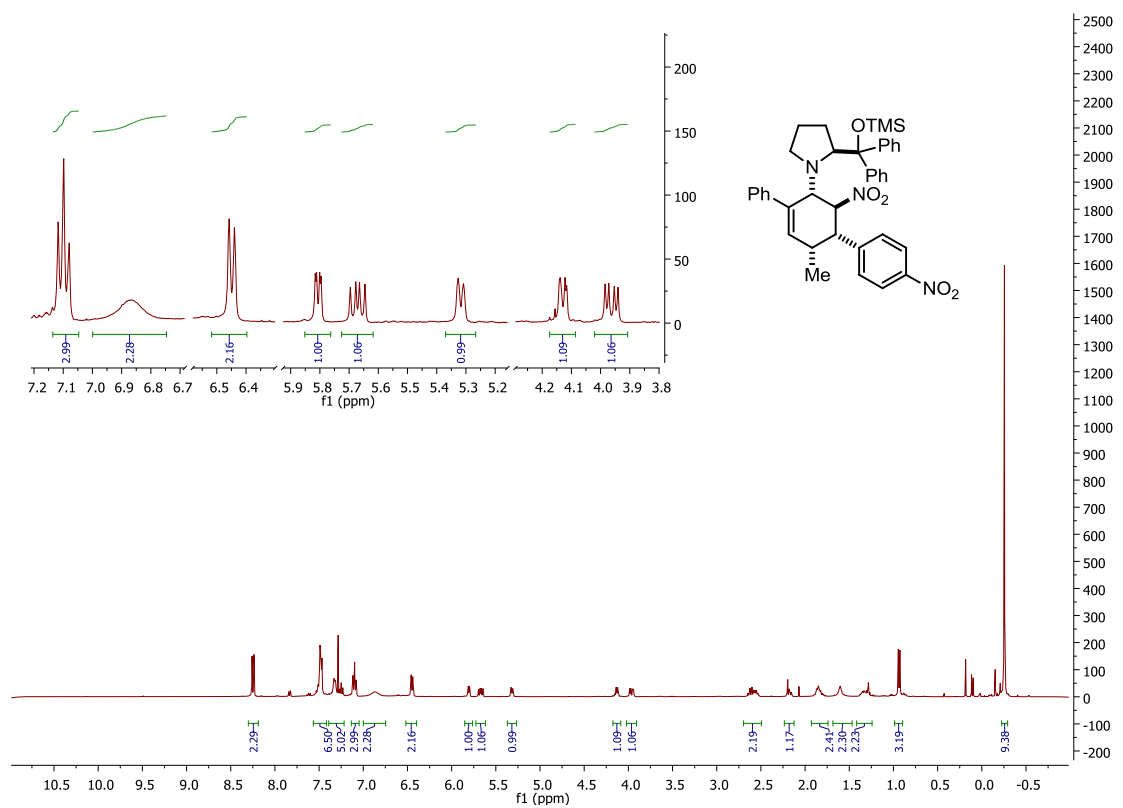


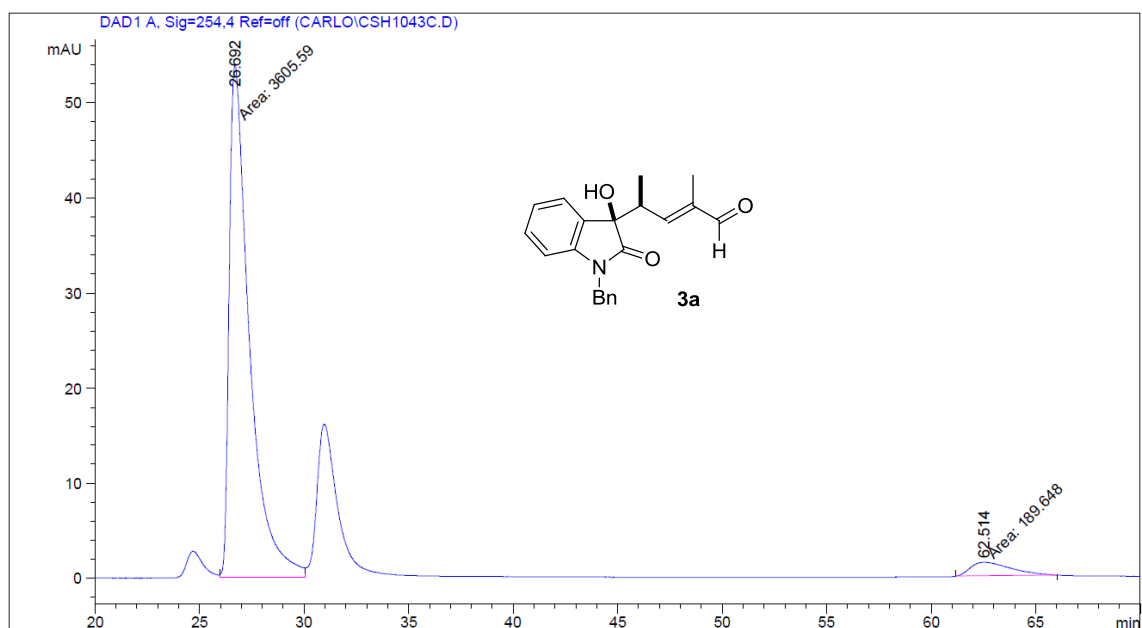
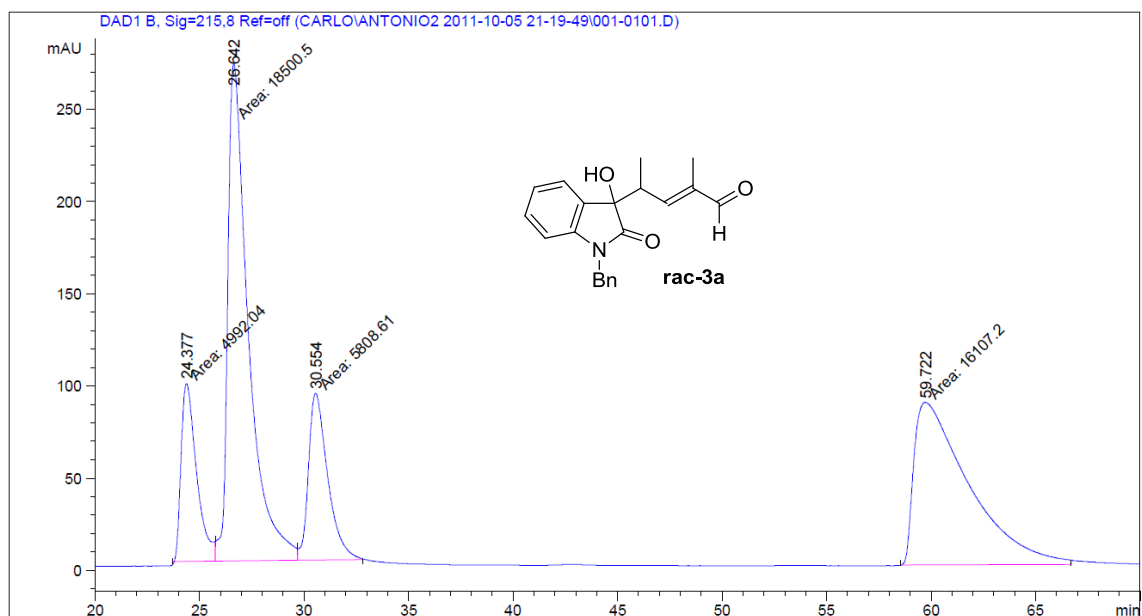


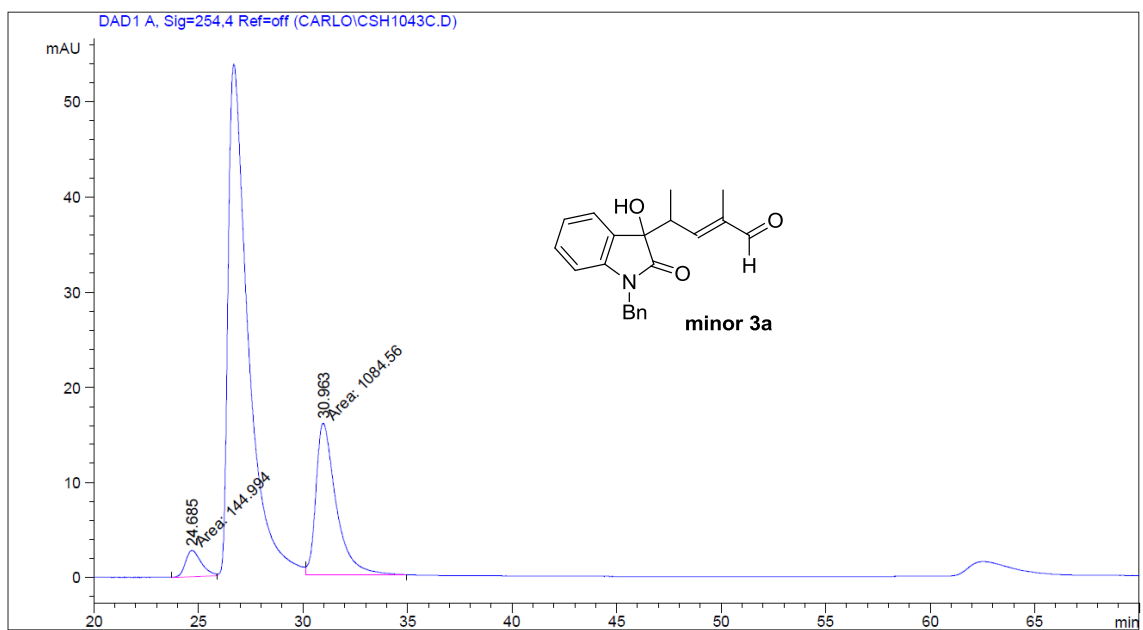




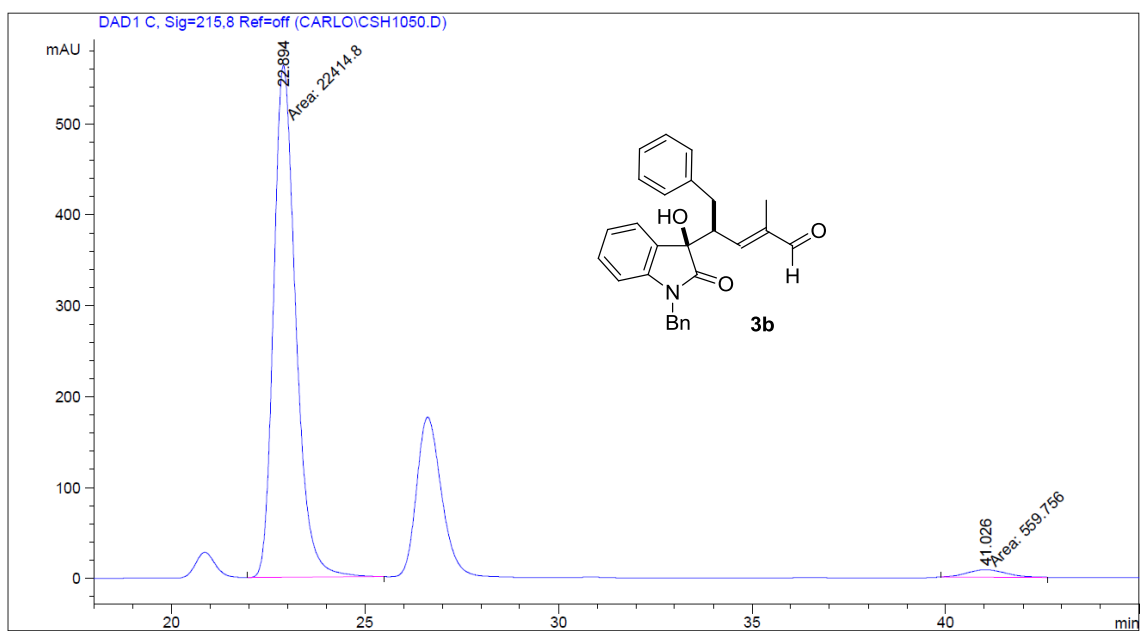
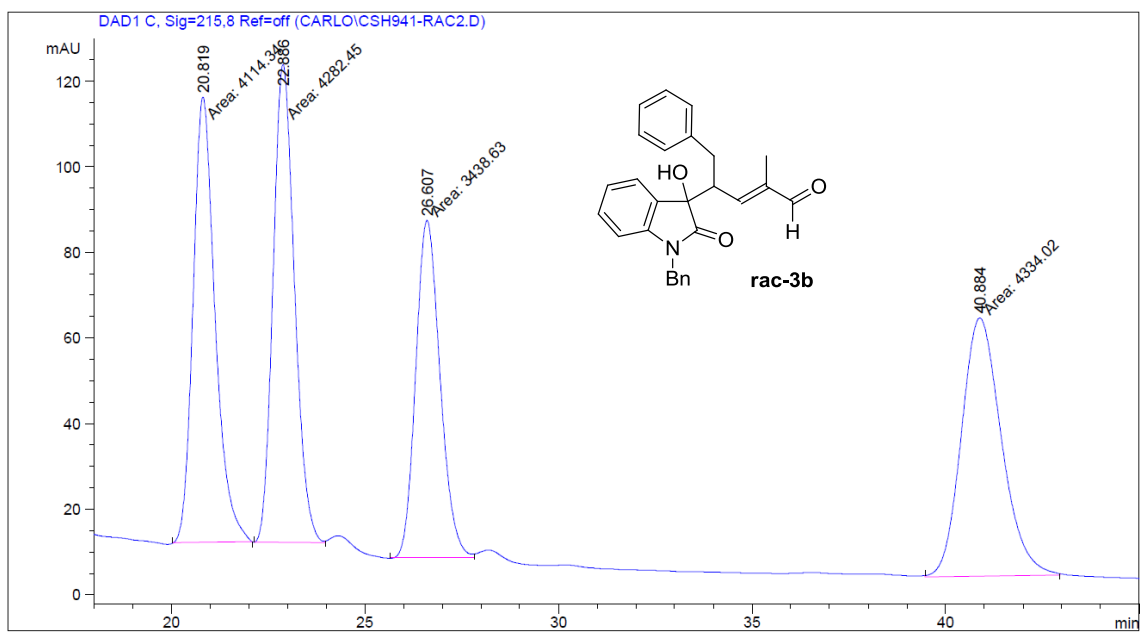


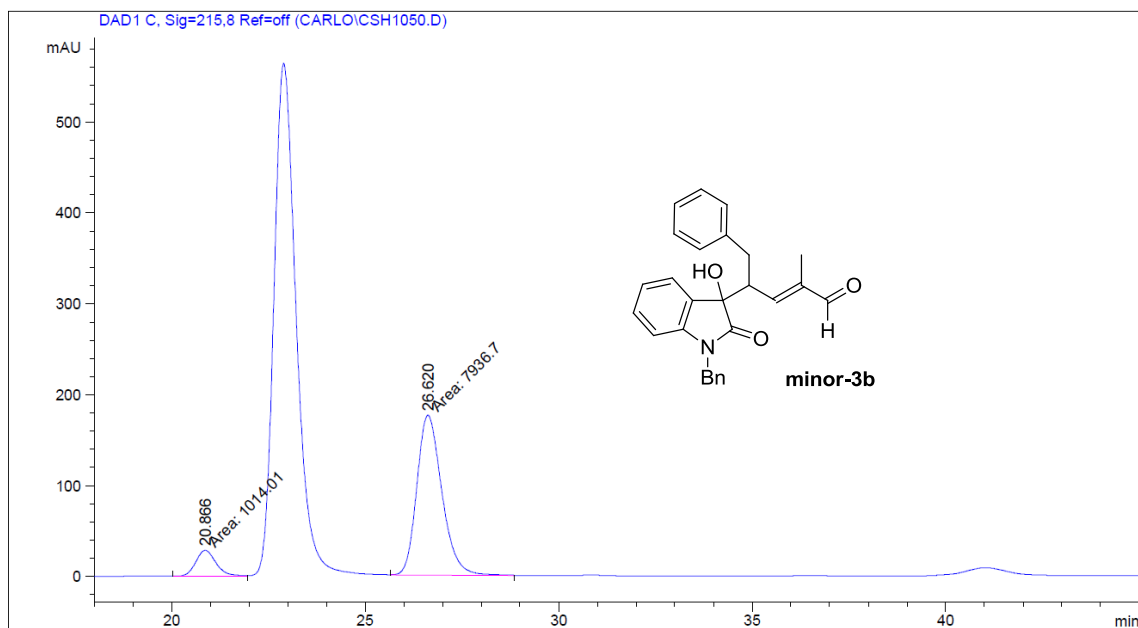




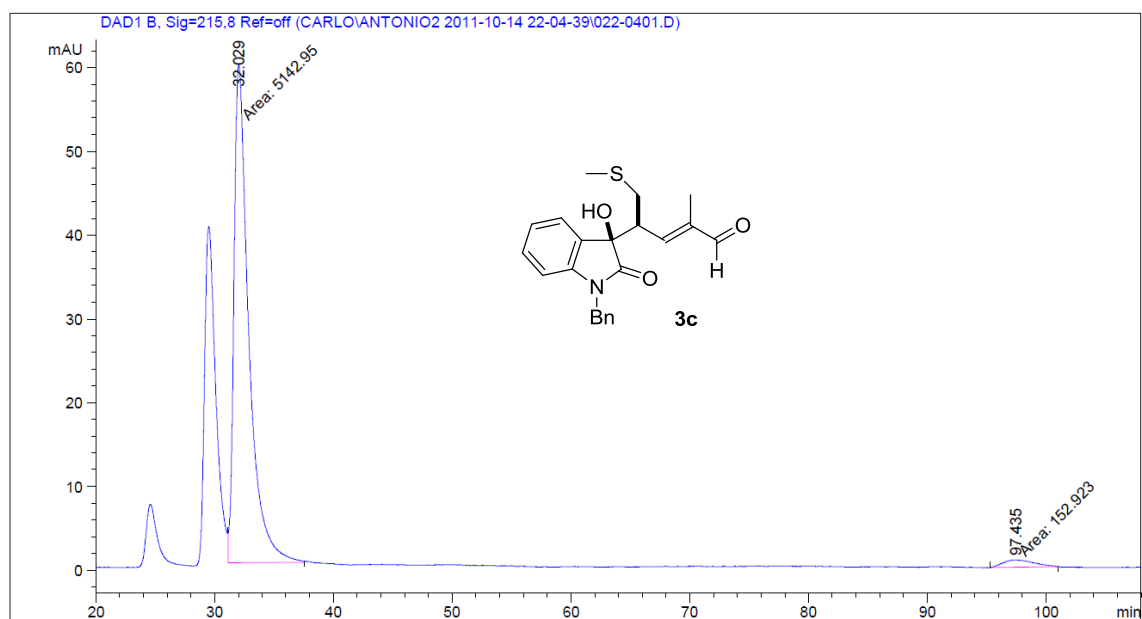
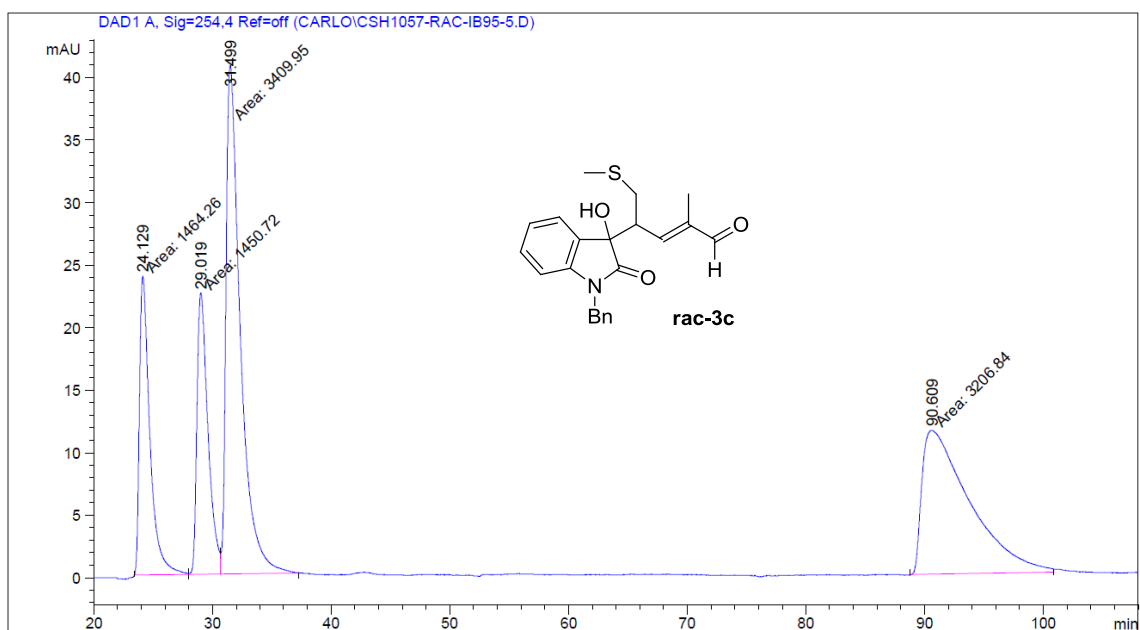


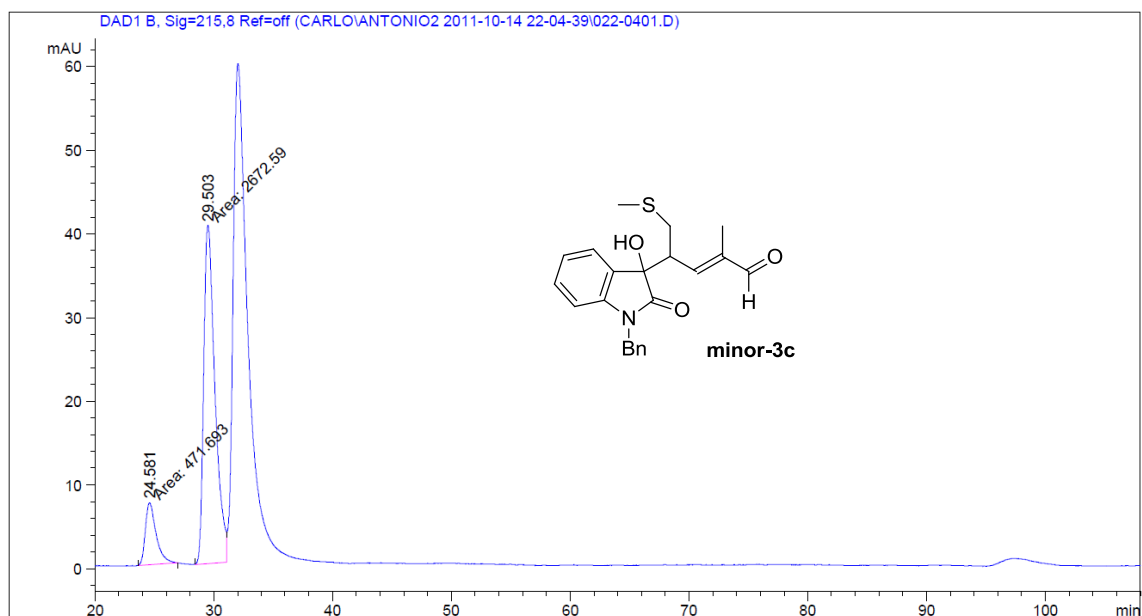
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.685	MM	0.8818	144.99400	2.74063	11.7924
2	30.963	MM	1.1325	1084.55872	15.96165	88.2076



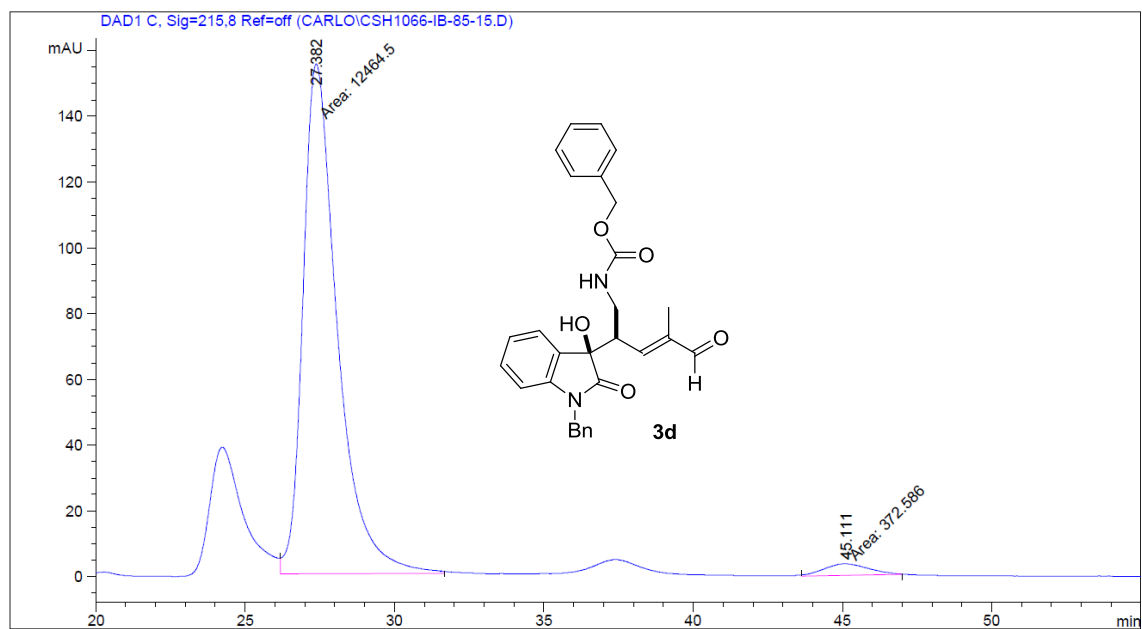
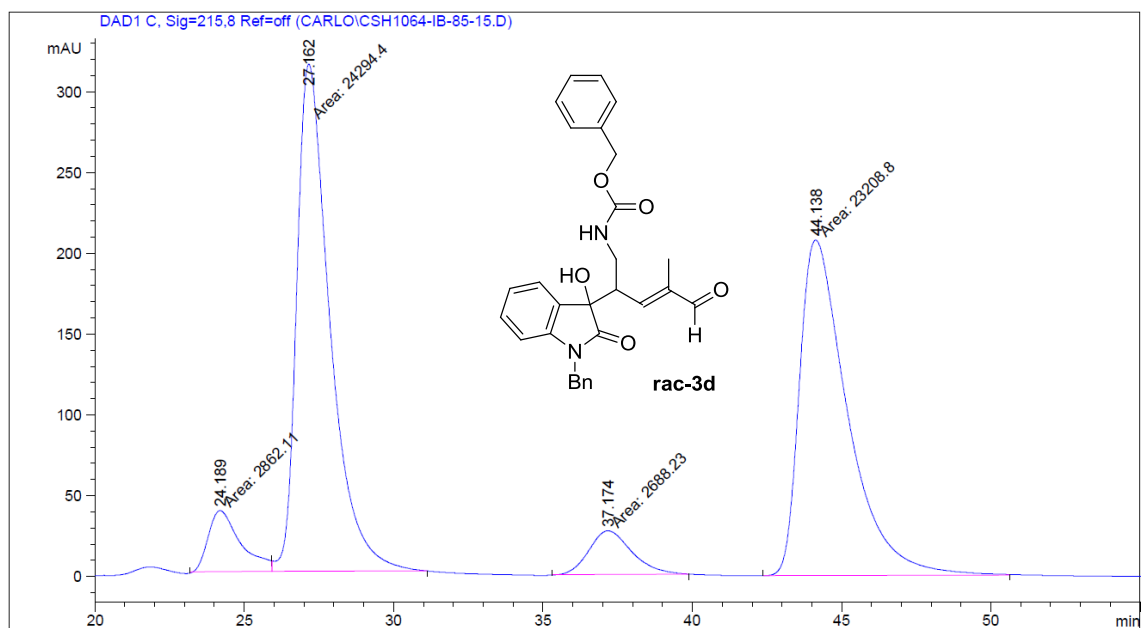


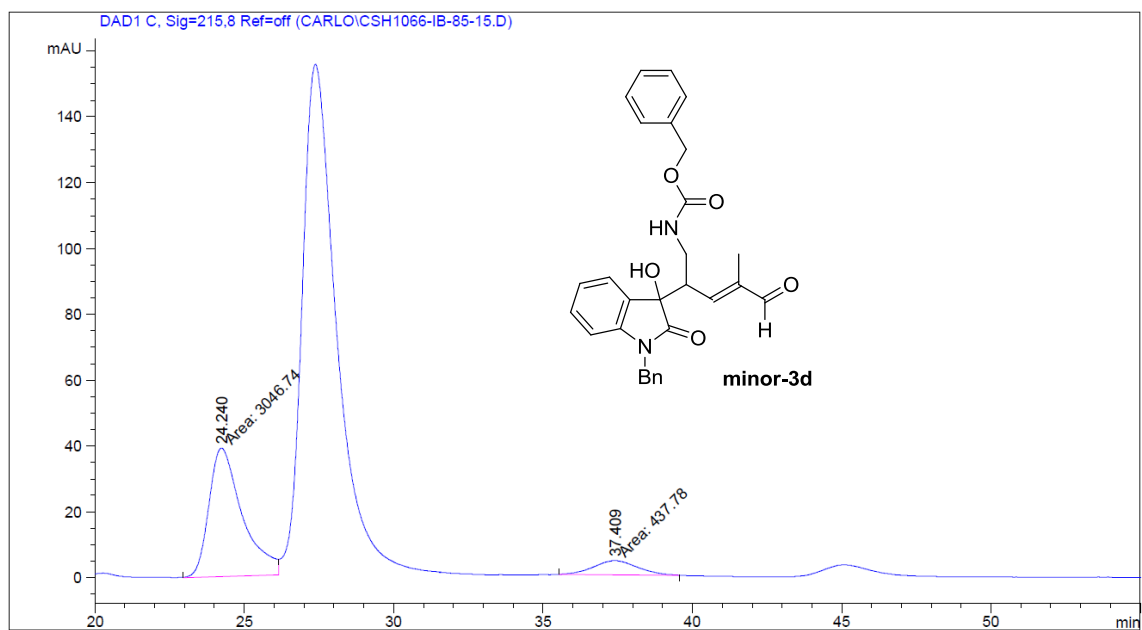
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.866	MM	0.5989	1014.01294	28.21827	11.3288
2	26.620	MM	0.7513	7936.70313	176.06934	88.6712



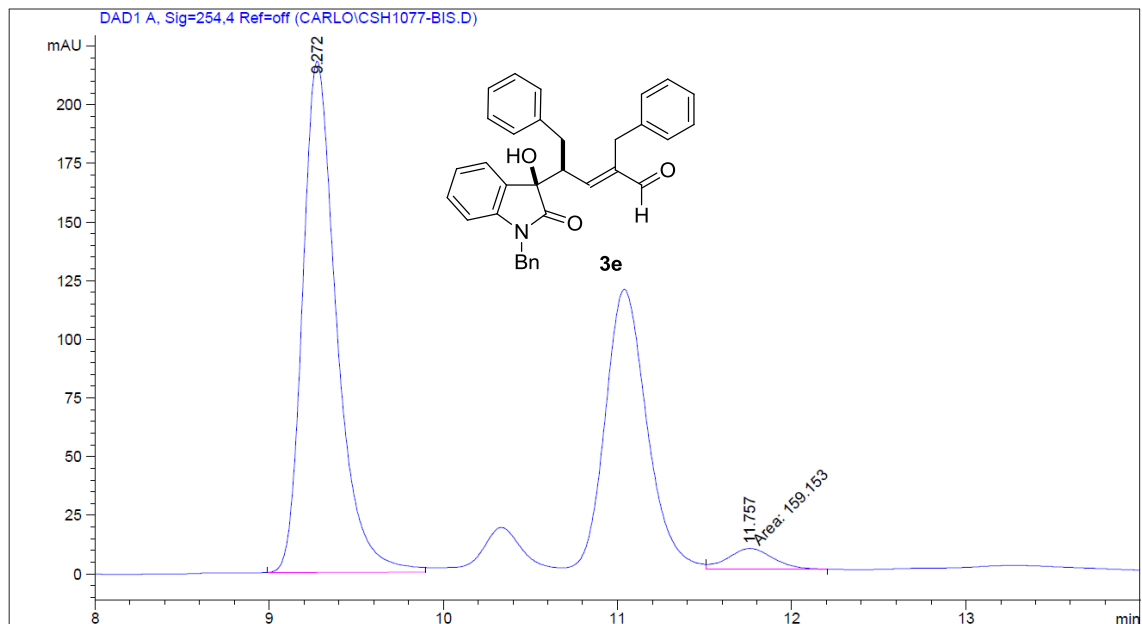
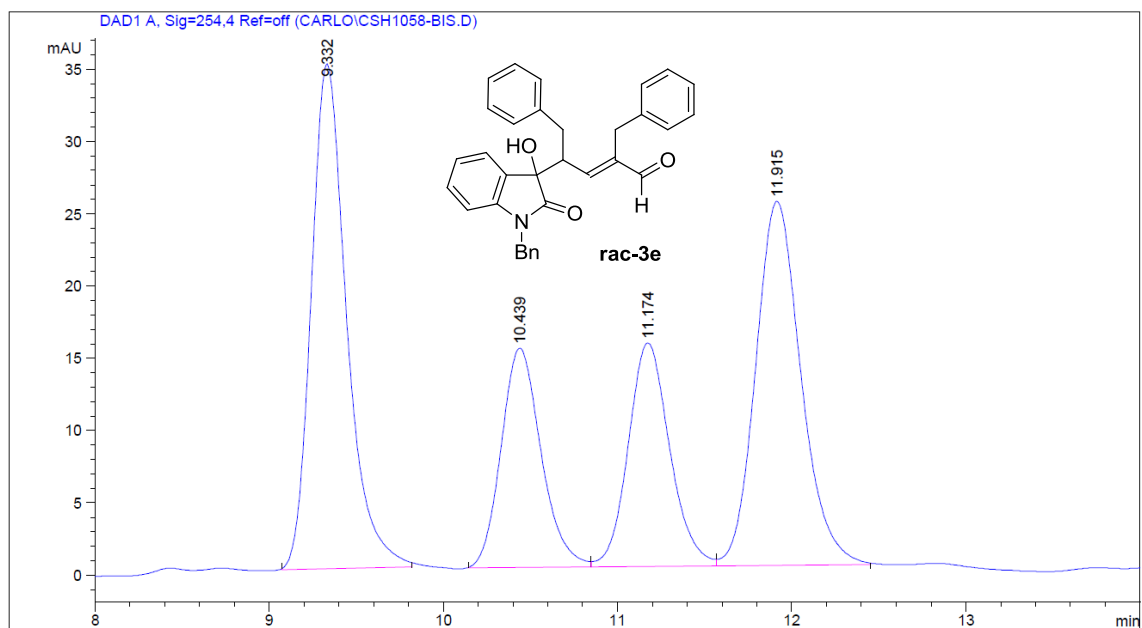


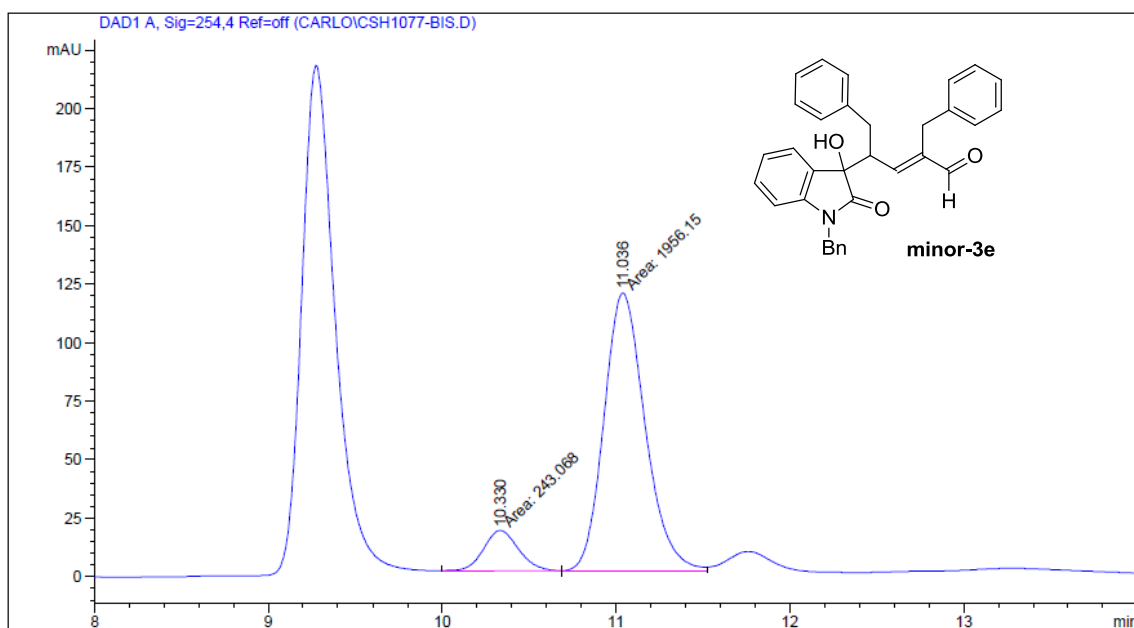
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.581	MM	1.0589	471.69299	7.42394	15.0016
2	29.503	MM	1.1025	2672.59399	40.40058	84.9984



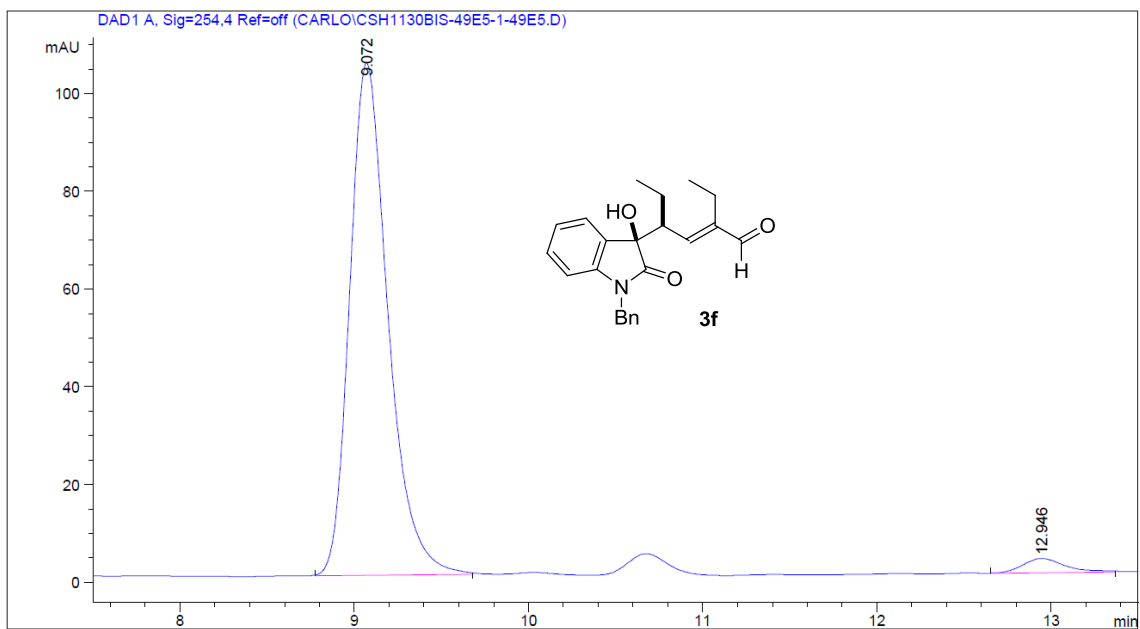
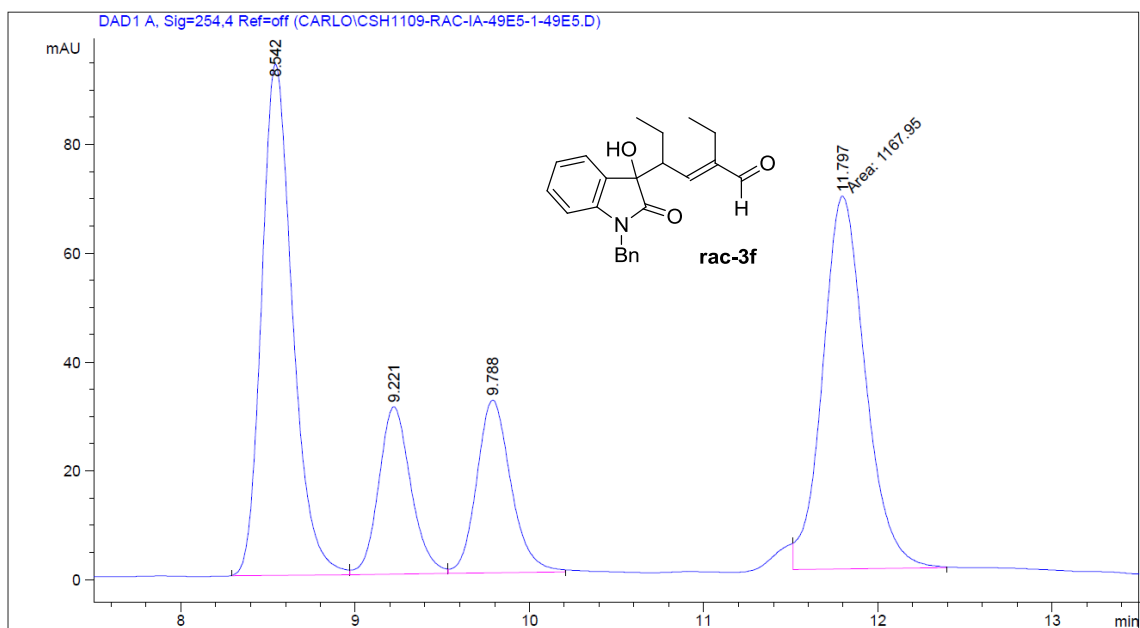


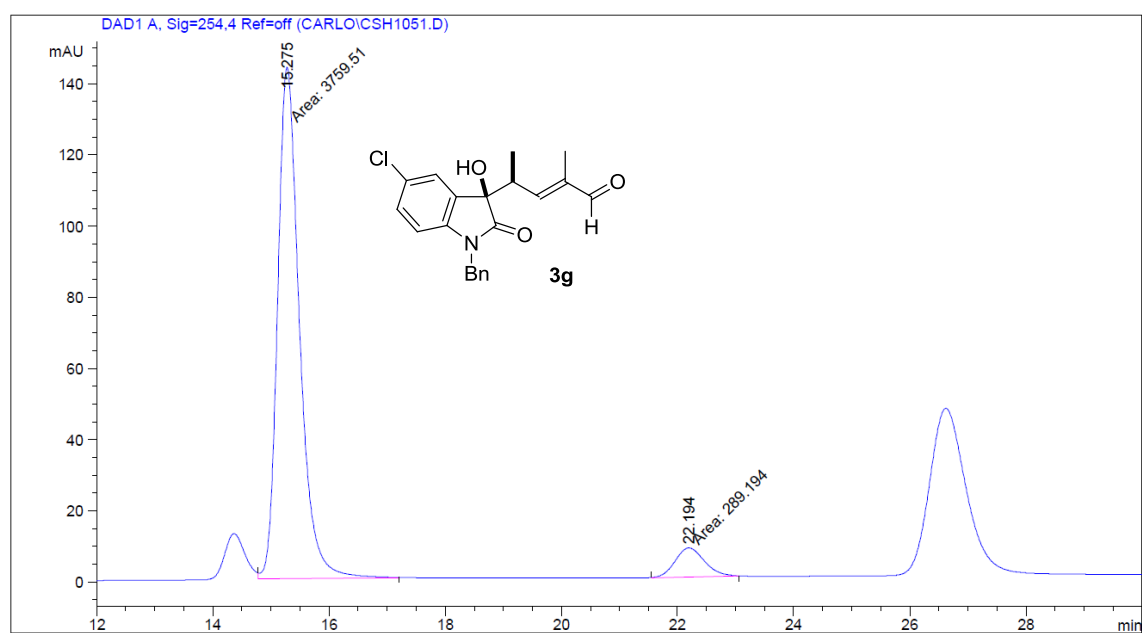
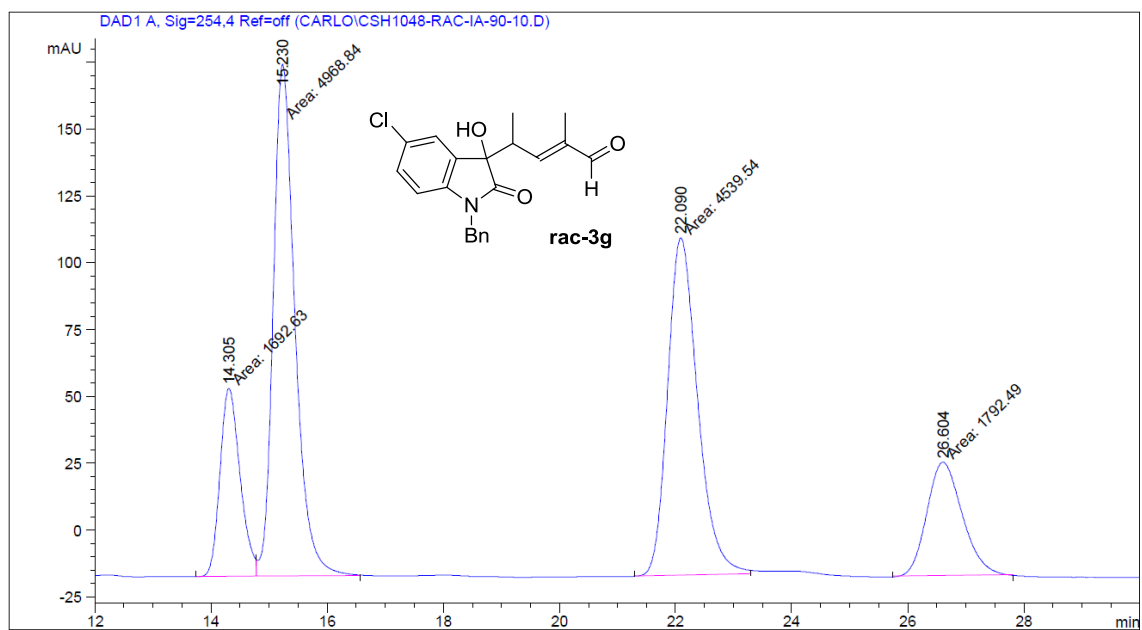
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.240	MM	1.2997	3046.73828	39.07076	87.4364
2	37.409	MM	1.7012	437.78006	4.28898	12.5636

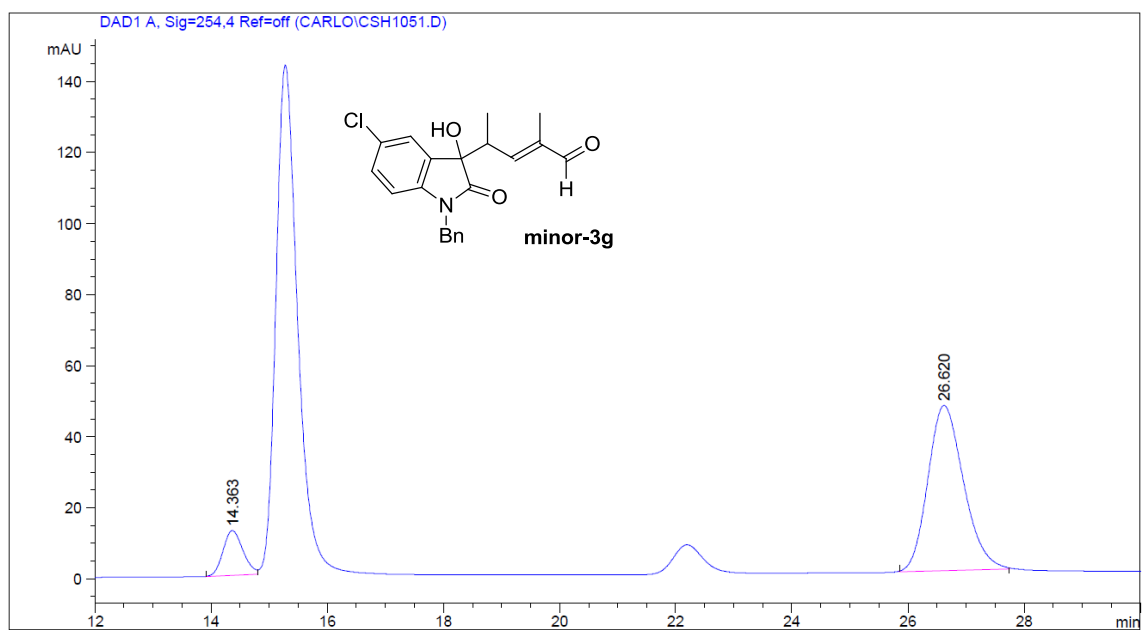




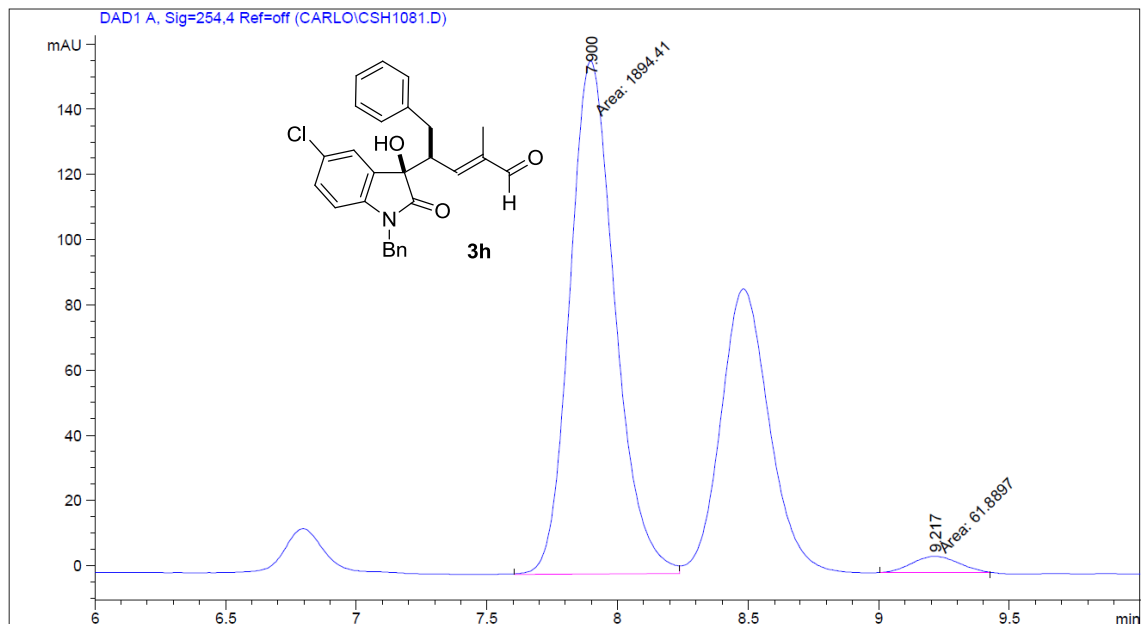
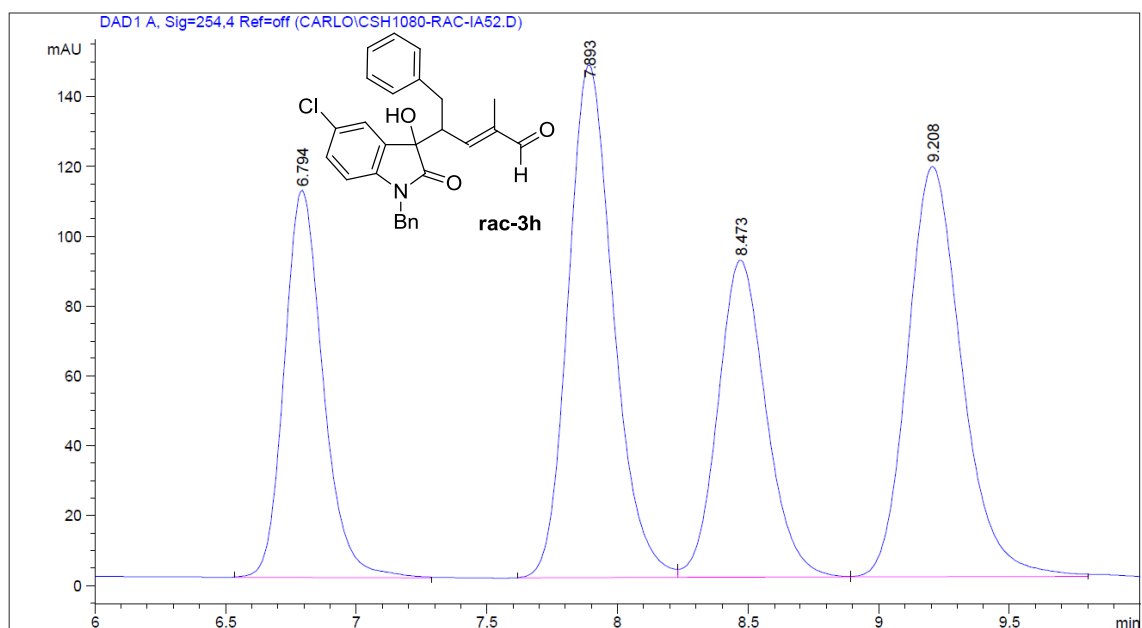
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.330	MF	0.2341	243.06848	17.30475	11.0525
2	11.036	FM	0.2745	1956.15308	118.75937	88.9475

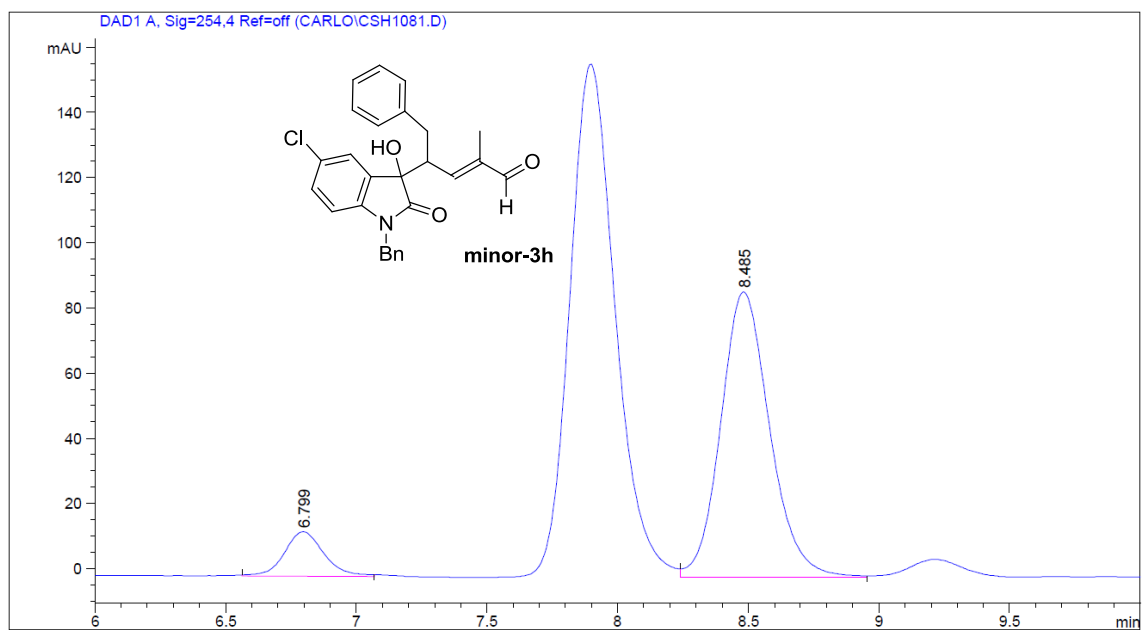




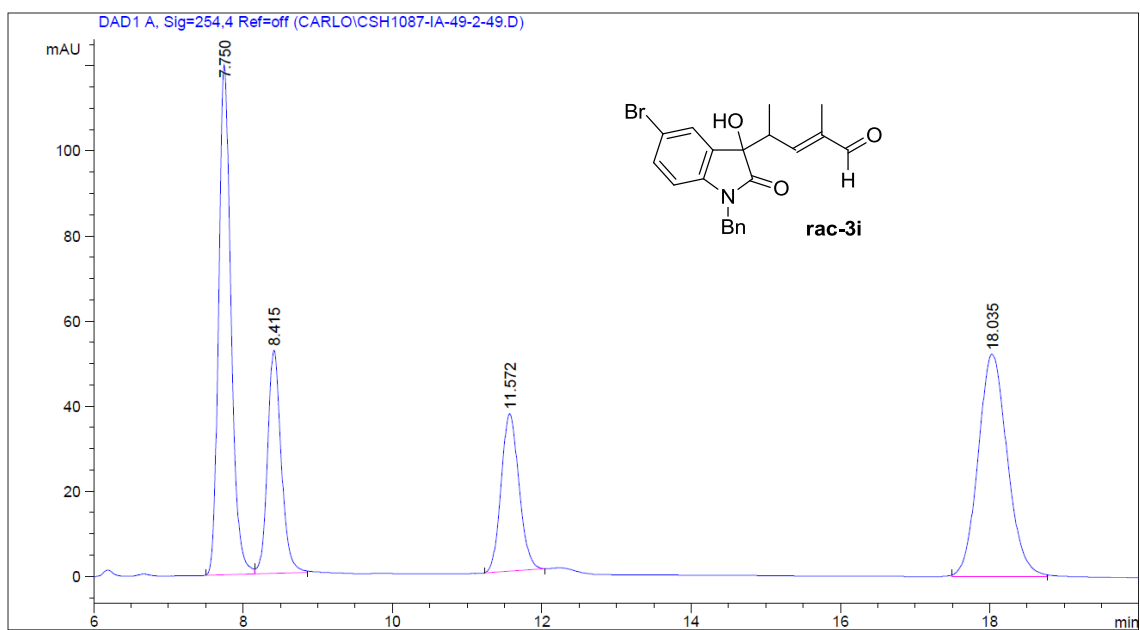


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.363	BV	0.3675	300.28757	12.62275	13.1120
2	26.620	BB	0.6548	1989.87793	46.54338	86.8880

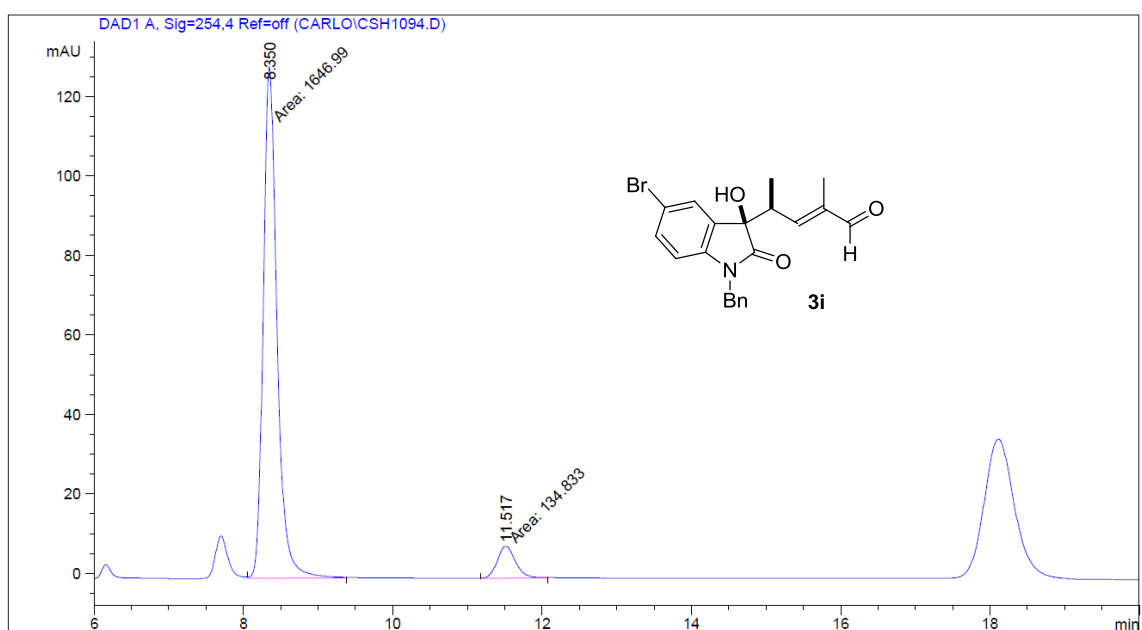




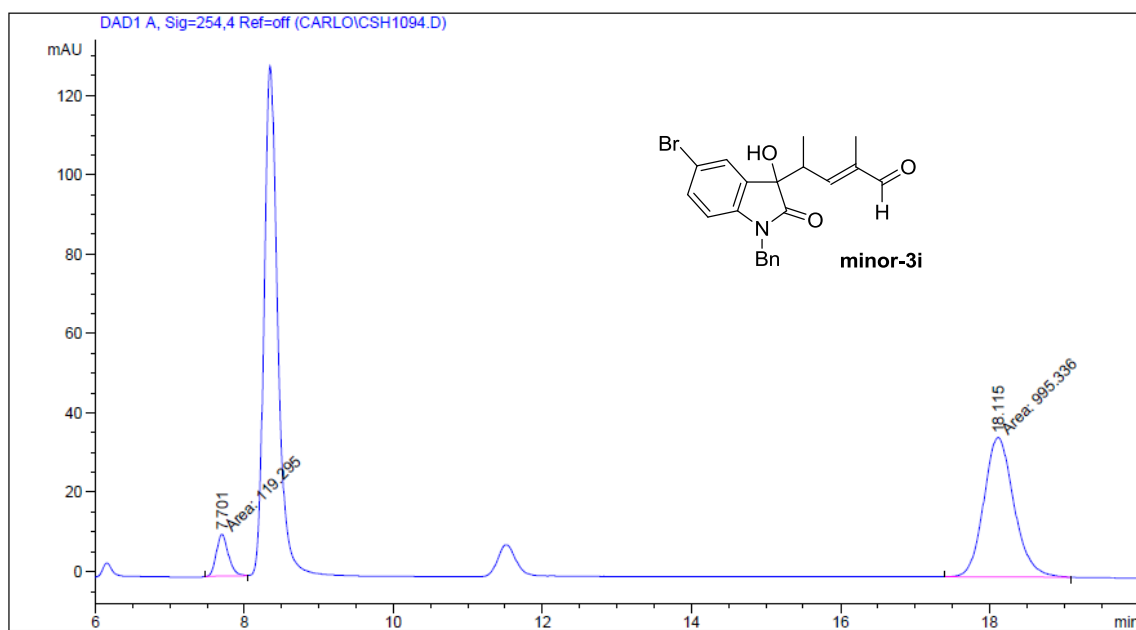
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.799	BB	0.1583	142.68256	13.61268	11.1329
2	8.485	VB	0.1998	1138.95020	87.54805	88.8671



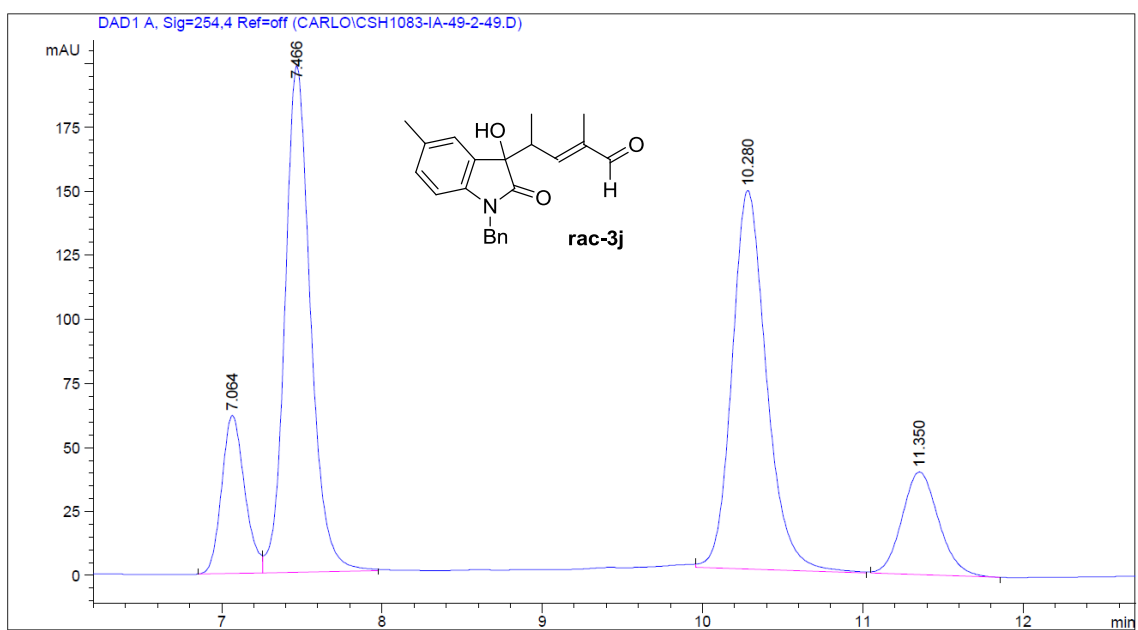
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.750	BV	0.1761	1376.19531	119.70969	33.7870
2	8.415	VB	0.1950	669.62732	52.44112	16.4400
3	11.572	BB	0.2583	615.44397	36.94635	15.1098
4	18.035	BB	0.4178	1411.88379	52.16154	34.6632



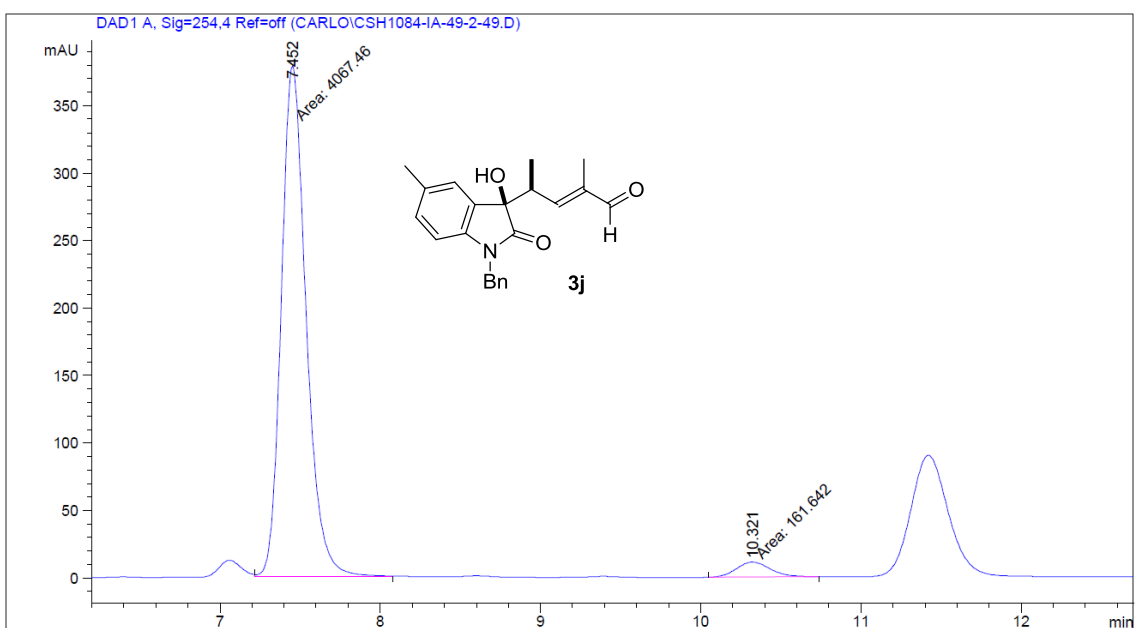
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.350	MM	0.2134	1646.98682	128.65370	92.4328
2	11.517	MM	0.2809	134.83328	7.99874	7.5672



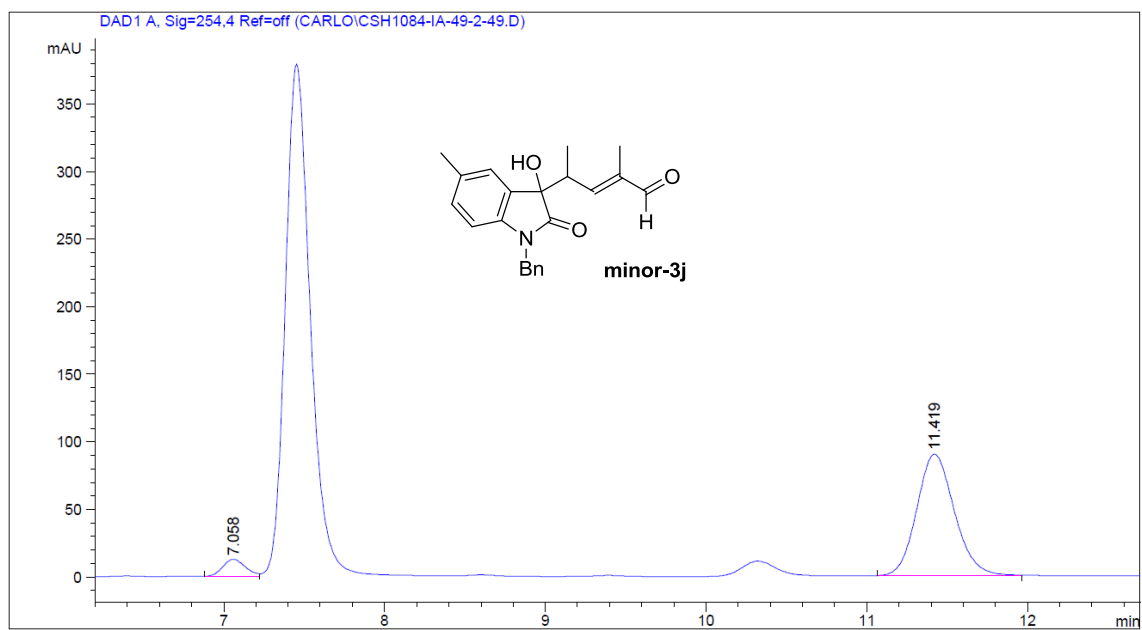
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.701	MM	0.1880	119.29466	10.57328	10.7026
2	18.115	MM	0.4711	995.33588	35.21309	89.2974



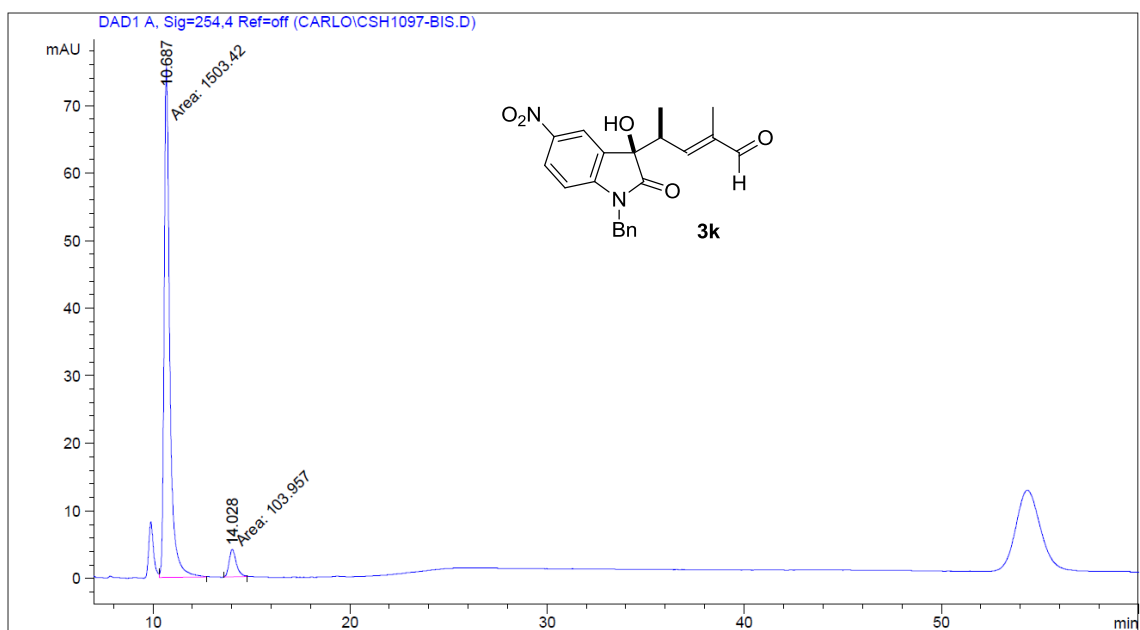
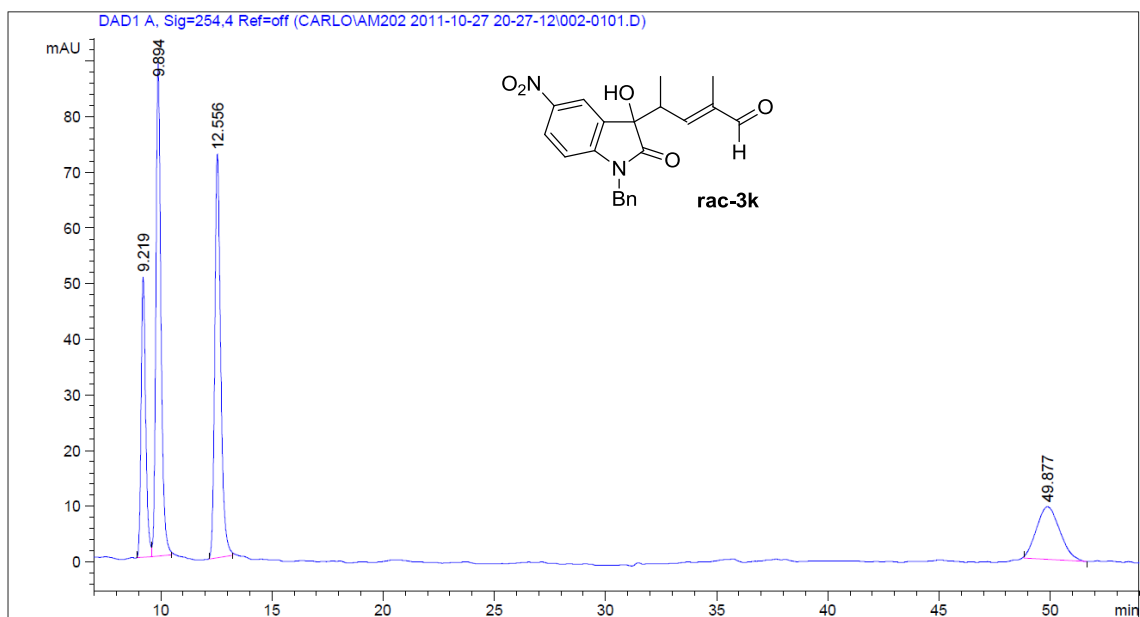
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.064	BV	0.1545	615.89227	61.68438	10.9023
2	7.466	VB	0.1694	2193.22412	197.80807	38.8237
3	10.280	BB	0.2259	2202.62793	147.80676	38.9902
4	11.350	BB	0.2454	637.43884	40.11445	11.2837

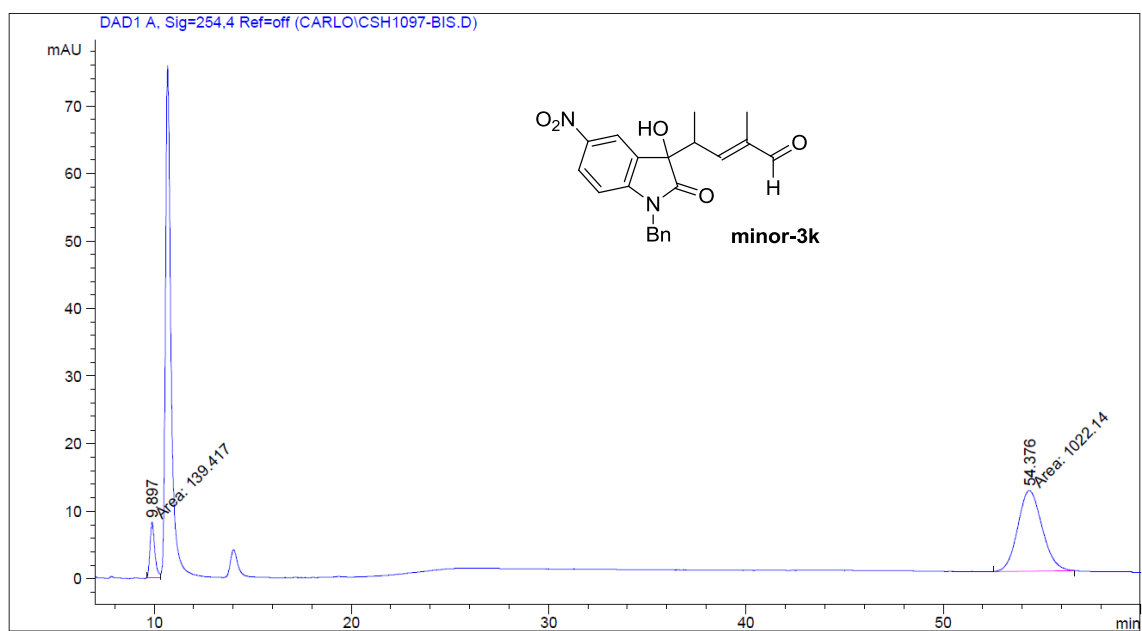


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.452	MM	0.1790	4067.45654	378.66370	96.1779
2	10.321	MM	0.2444	161.64211	11.02412	3.8221

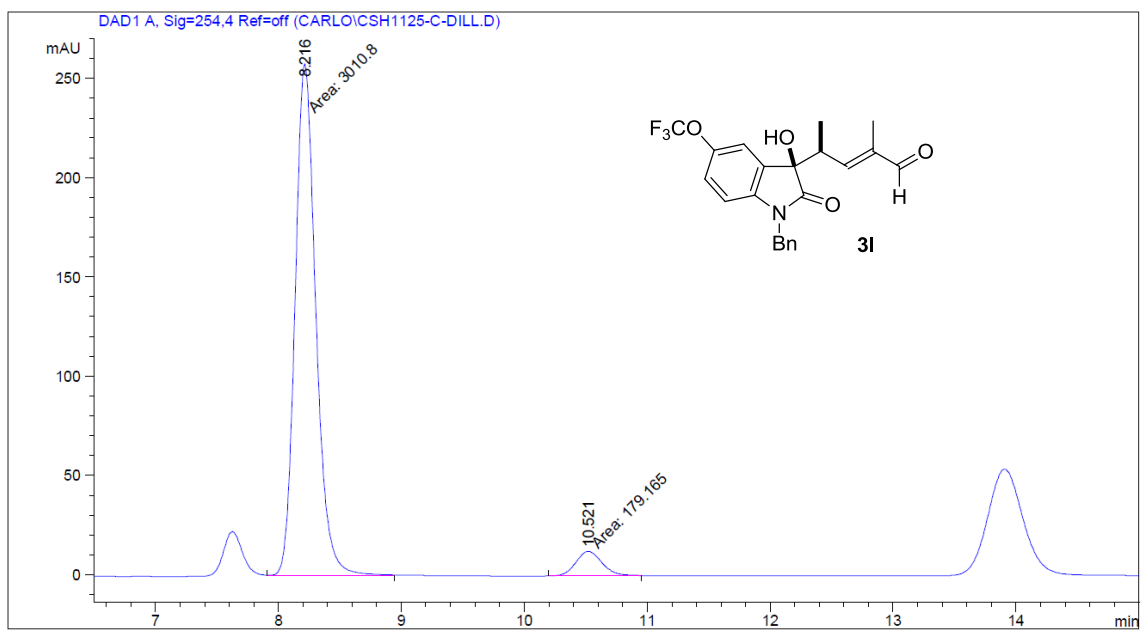
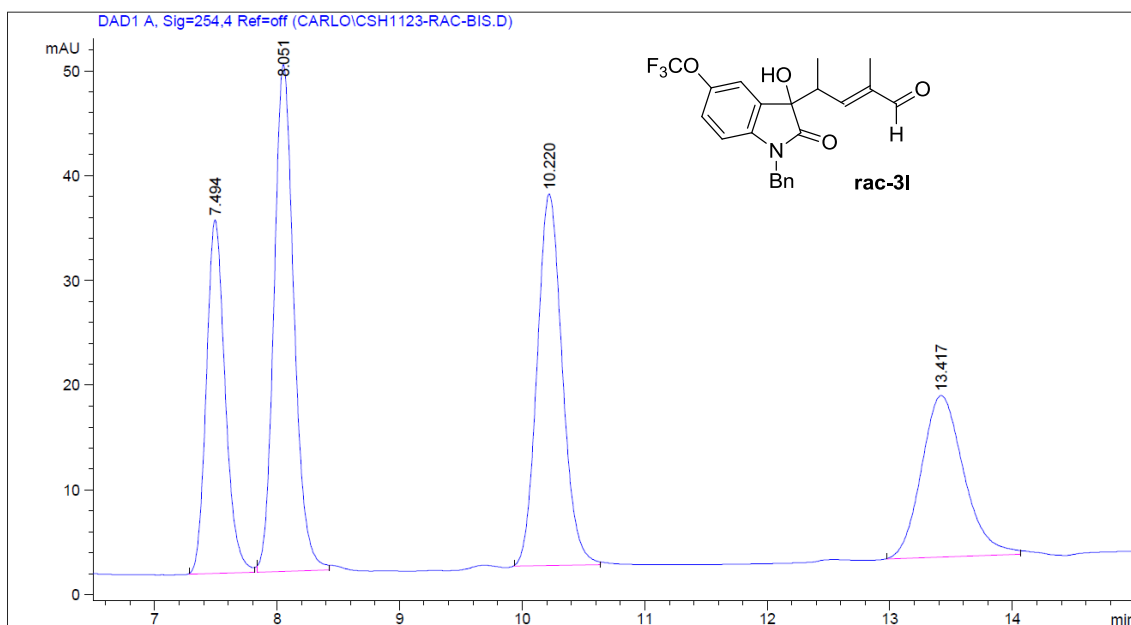


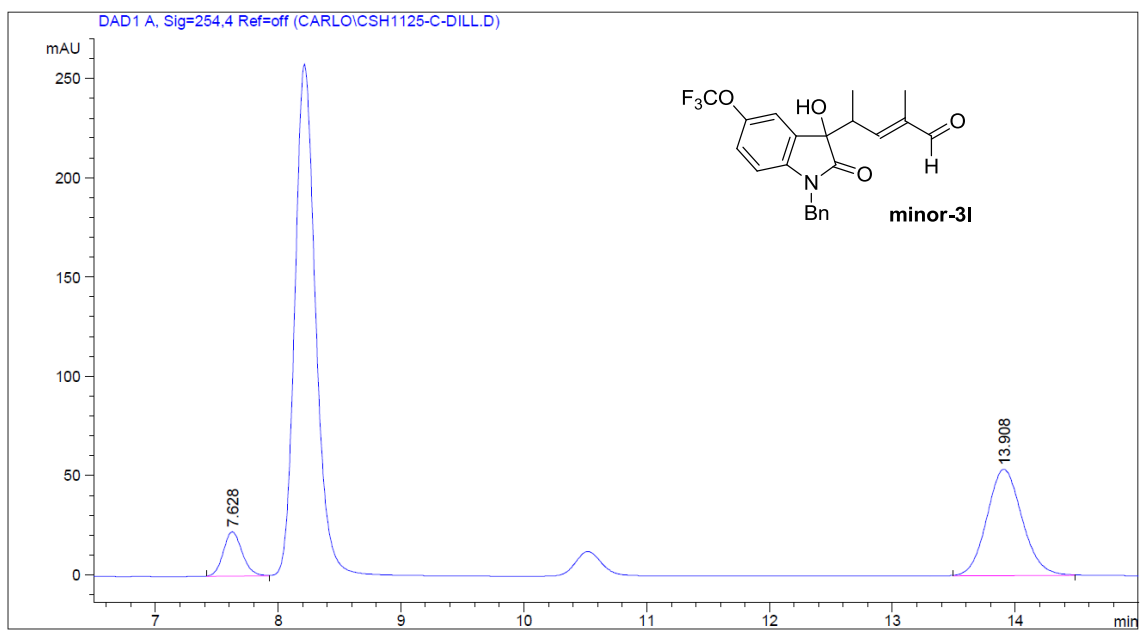
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.058	BV	0.1514	121.21336	12.46582	7.6296
2	11.419	BB	0.2522	1467.51990	90.00616	92.3704



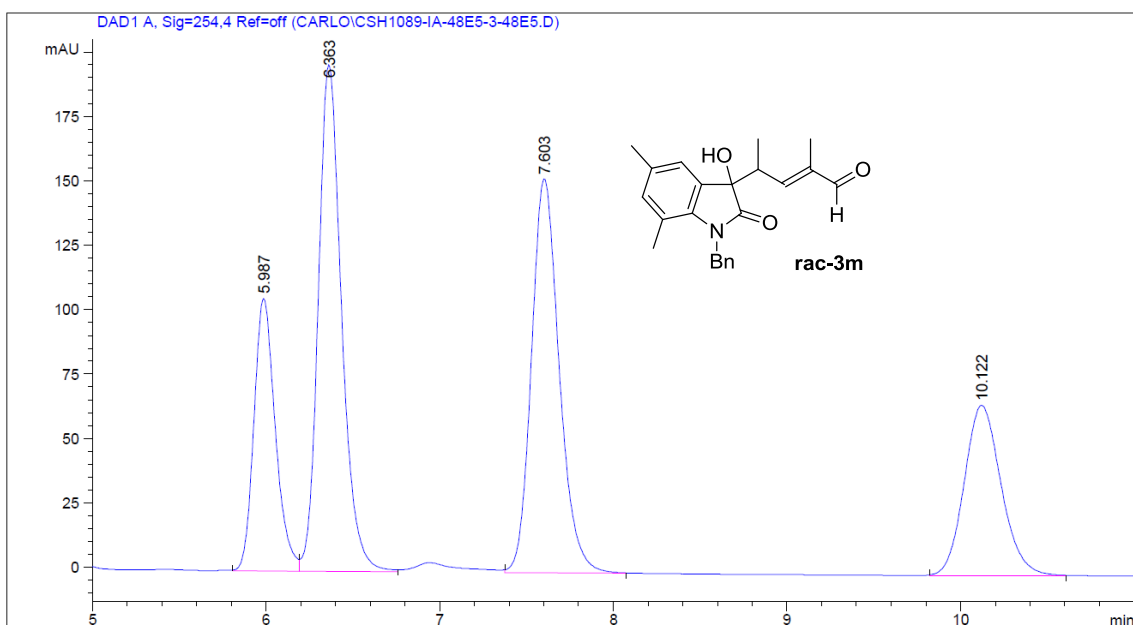


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.897	MM	0.2810	139.41658	8.27007	12.0026
2	54.376	MM	1.4292	1022.13580	11.91970	87.9974

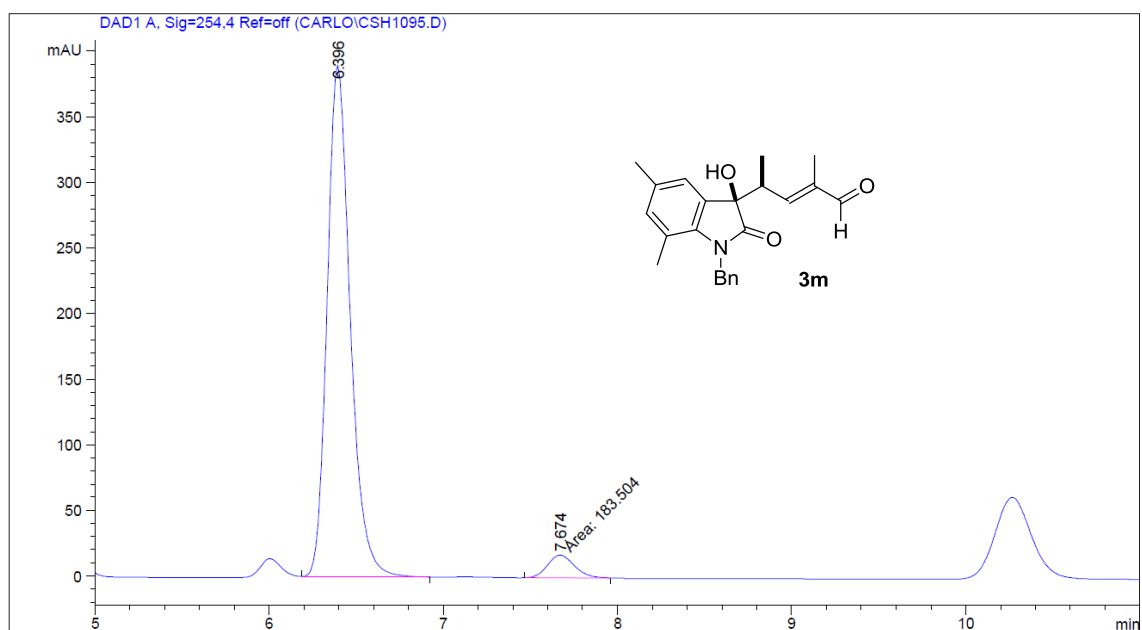




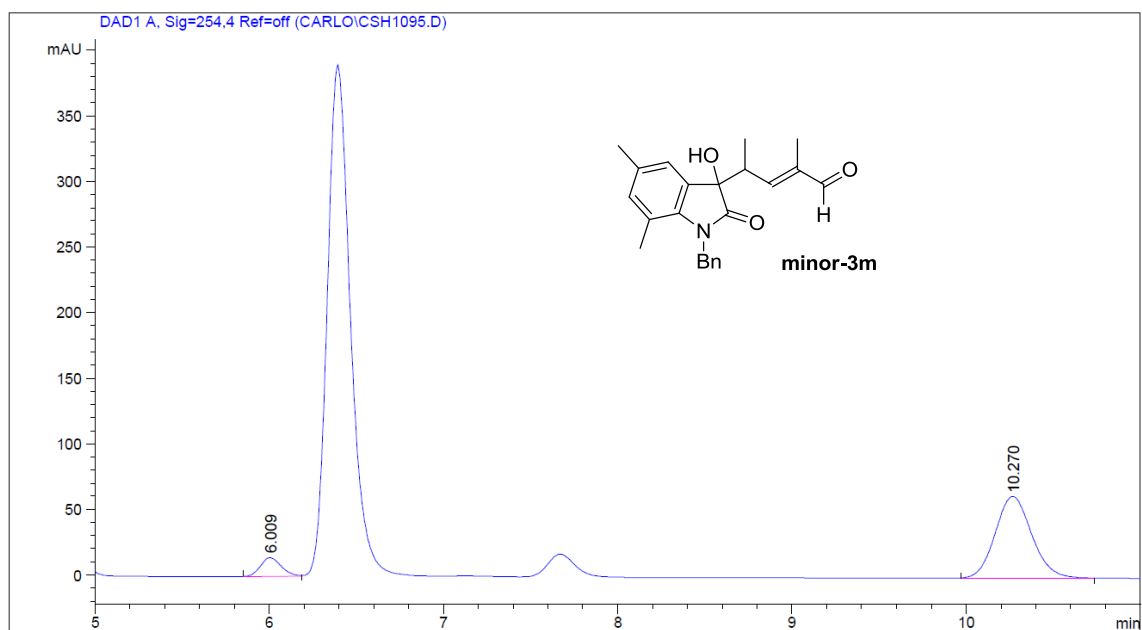
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.628	BB	0.1649	239.97270	22.41173	18.3476
2	13.908	BB	0.3085	1067.95081	53.58628	81.6524



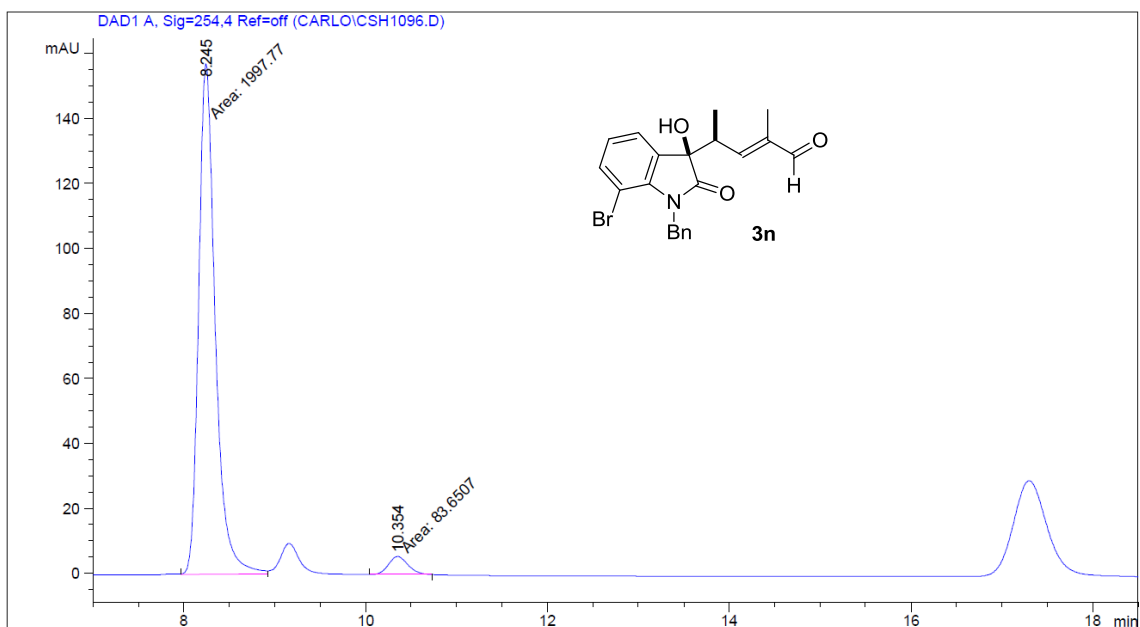
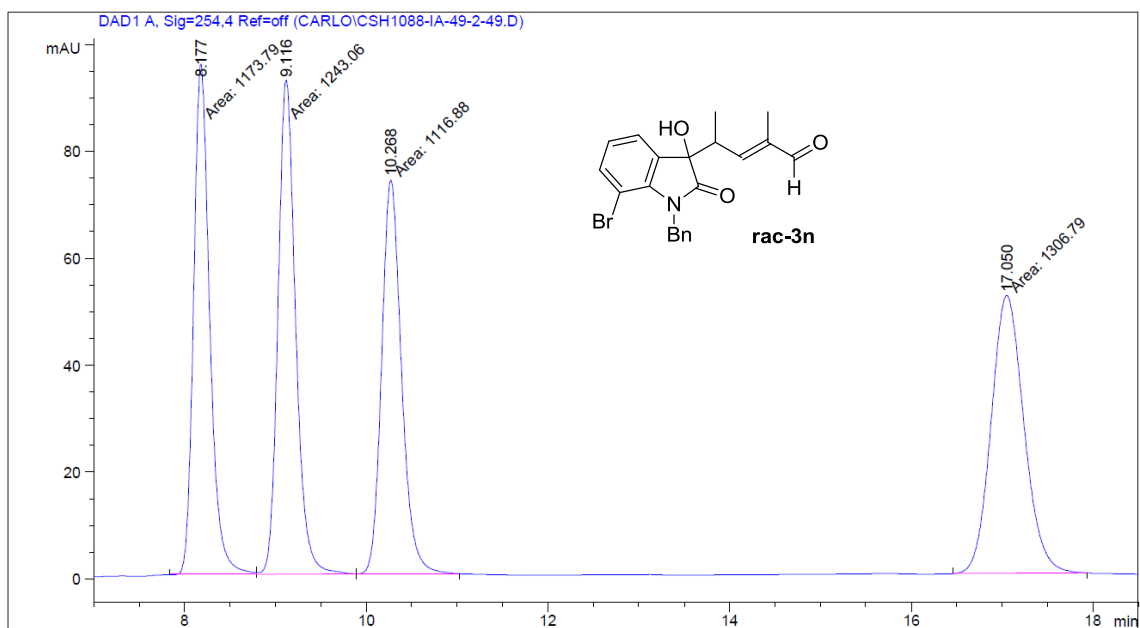
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.987	BV	0.1298	904.70215	105.74374	16.7248
2	6.363	VB	0.1426	1830.04907	196.55920	33.8313
3	7.603	BB	0.1697	1698.77612	152.80586	31.4045
4	10.122	BB	0.2264	975.81372	66.02898	18.0394

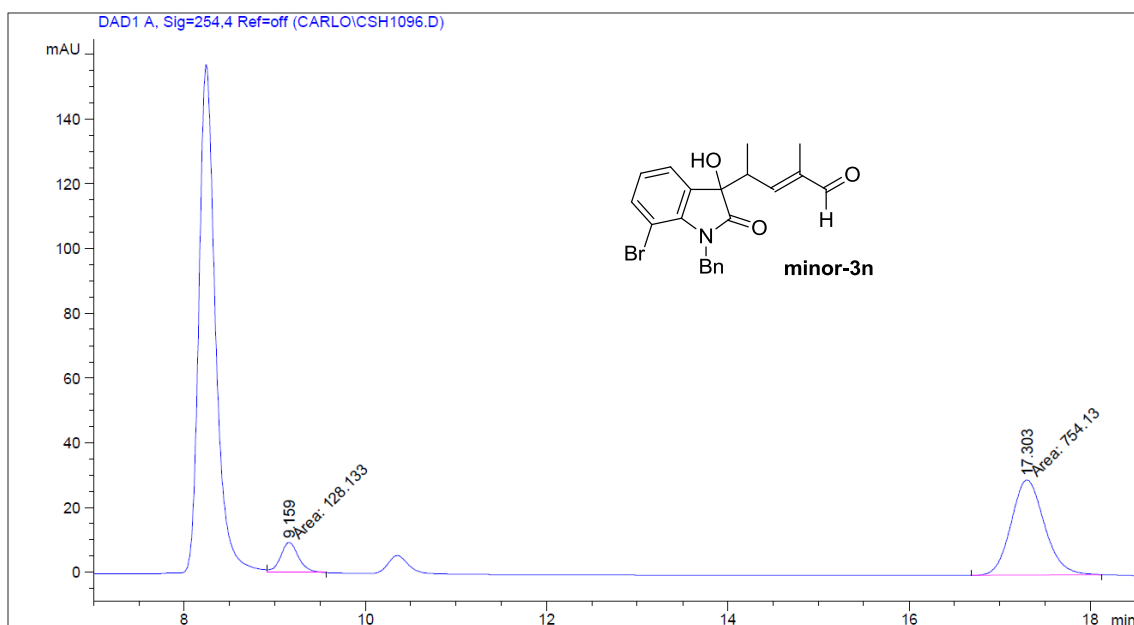


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.396	VB	0.1415	3590.26465	389.66937	95.1374
2	7.674	MM	0.1777	183.50363	17.21000	4.8626

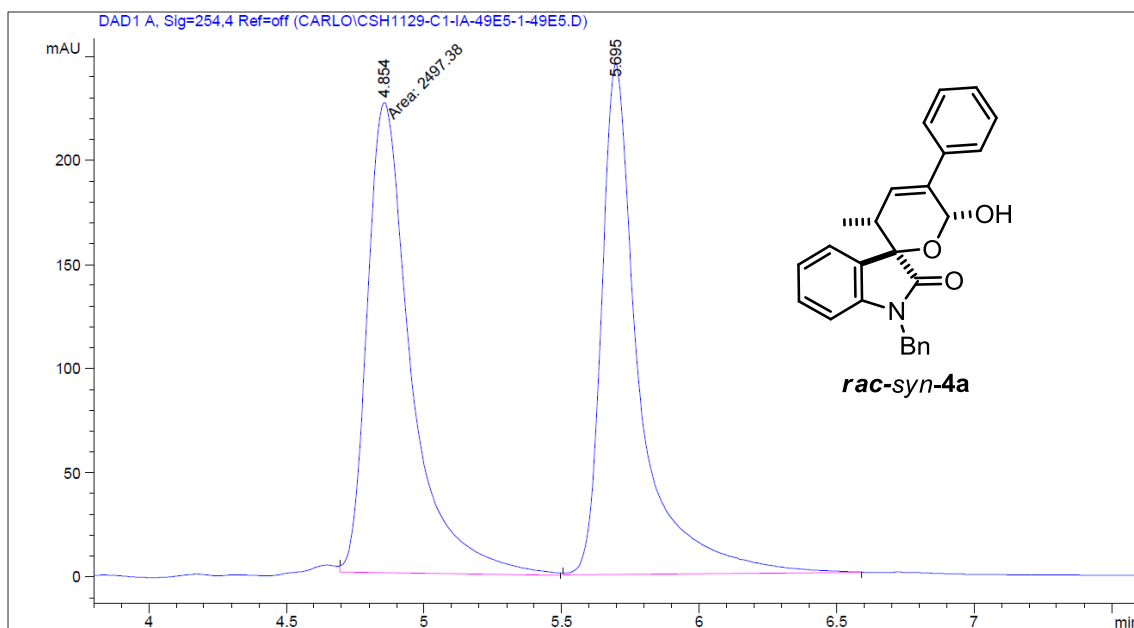


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.009	BV	0.1292	119.53513	14.34897	11.6028
2	10.270	BB	0.2243	910.69336	62.39051	88.3972

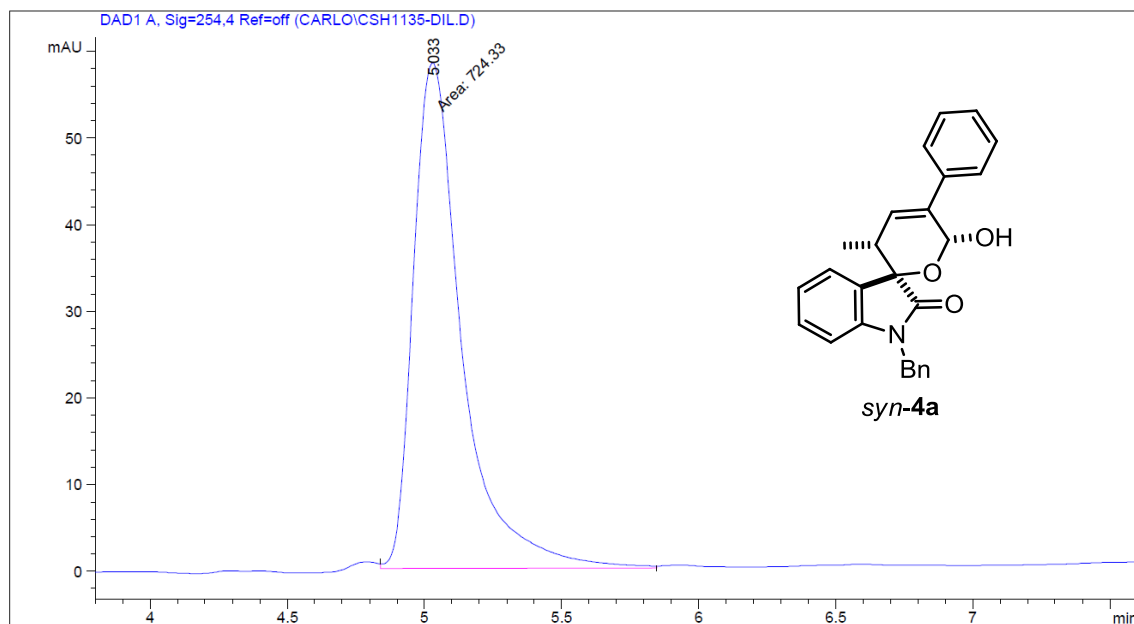




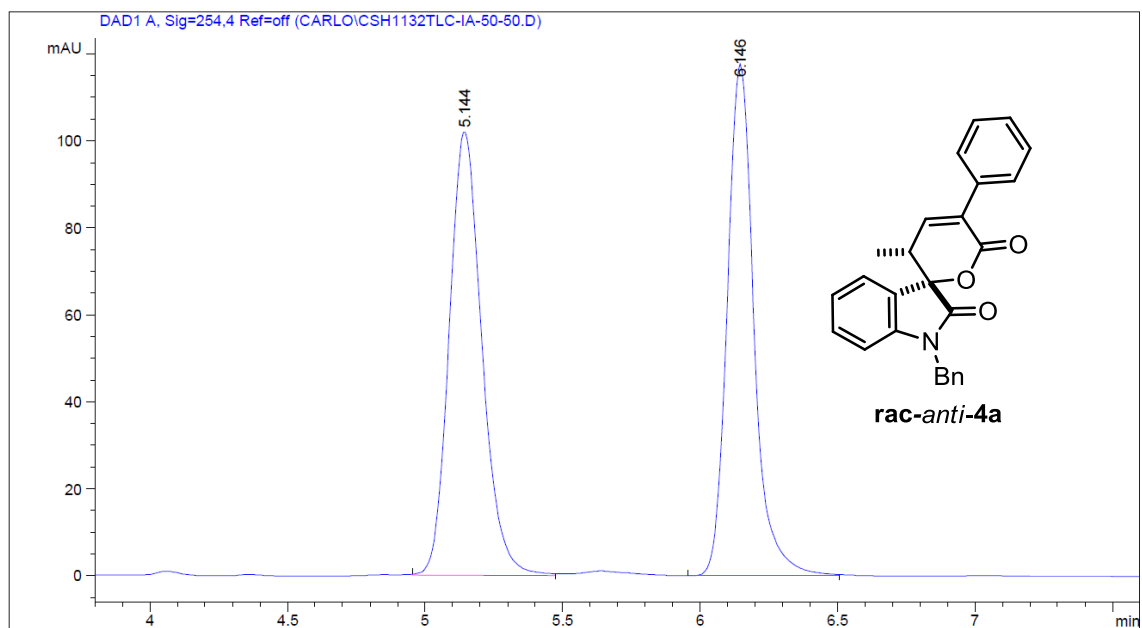
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.159	MM	0.2298	128.13318	9.29414	14.5232
2	17.303	MM	0.4270	754.13013	29.43535	85.4768



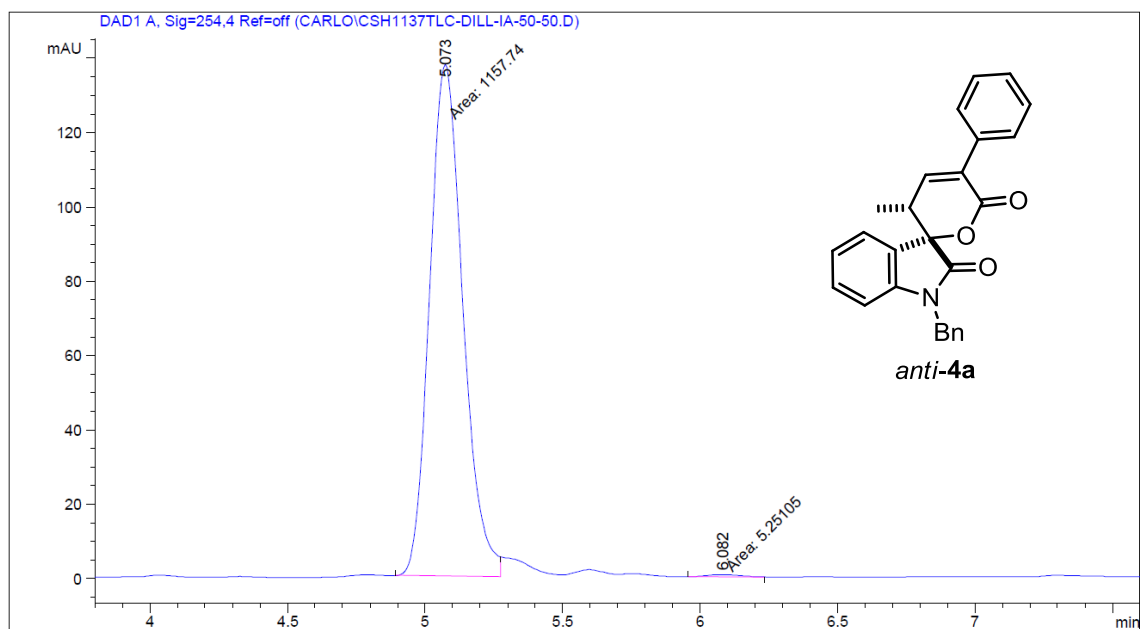
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.854	MM	0.1841	2497.38354	226.04759	51.5663
2	5.695	VB	0.1375	2345.67261	245.32803	48.4337



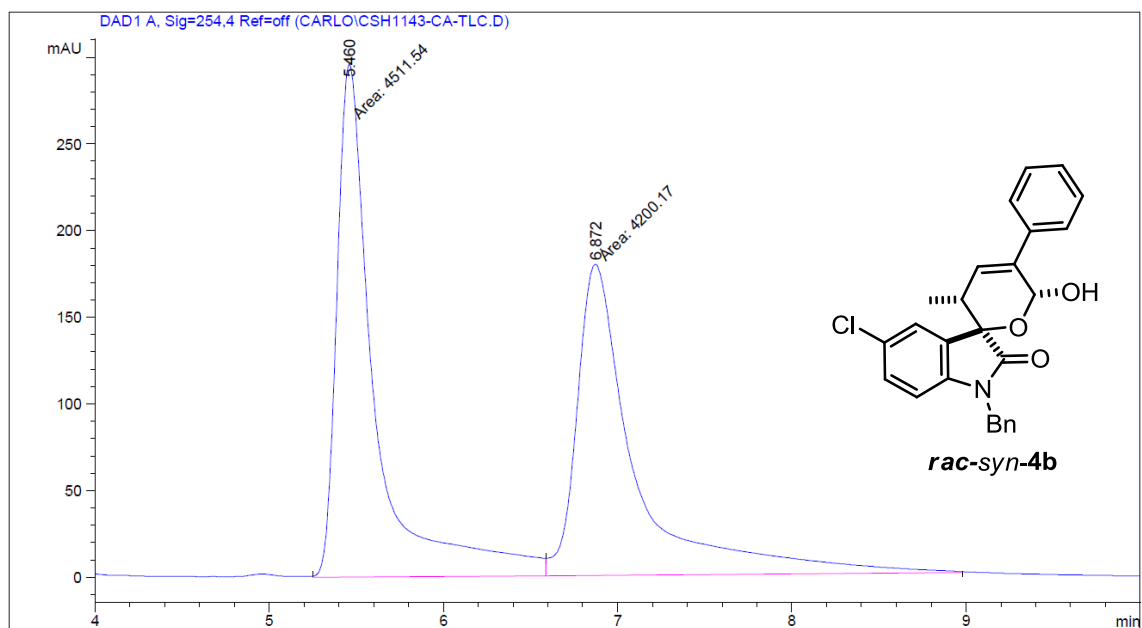
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.033	MM	0.2067	724.32996	58.41415	100.0000



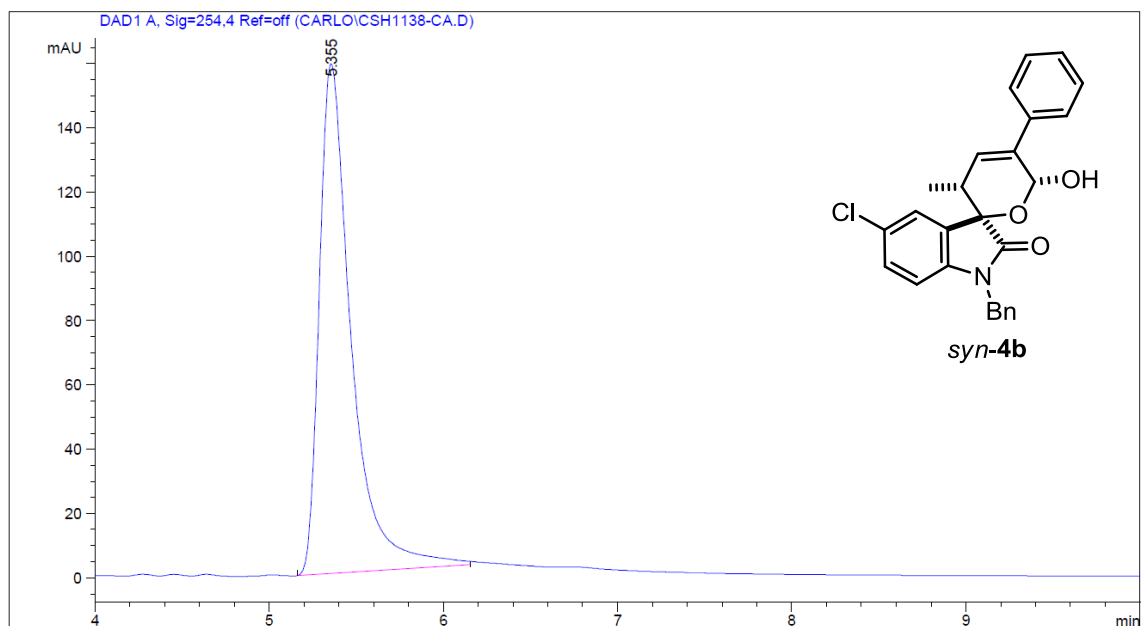
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.144	BB	0.1284	842.88971	102.04626	51.4832
2	6.146	VB	0.1048	794.32196	117.66401	48.5168



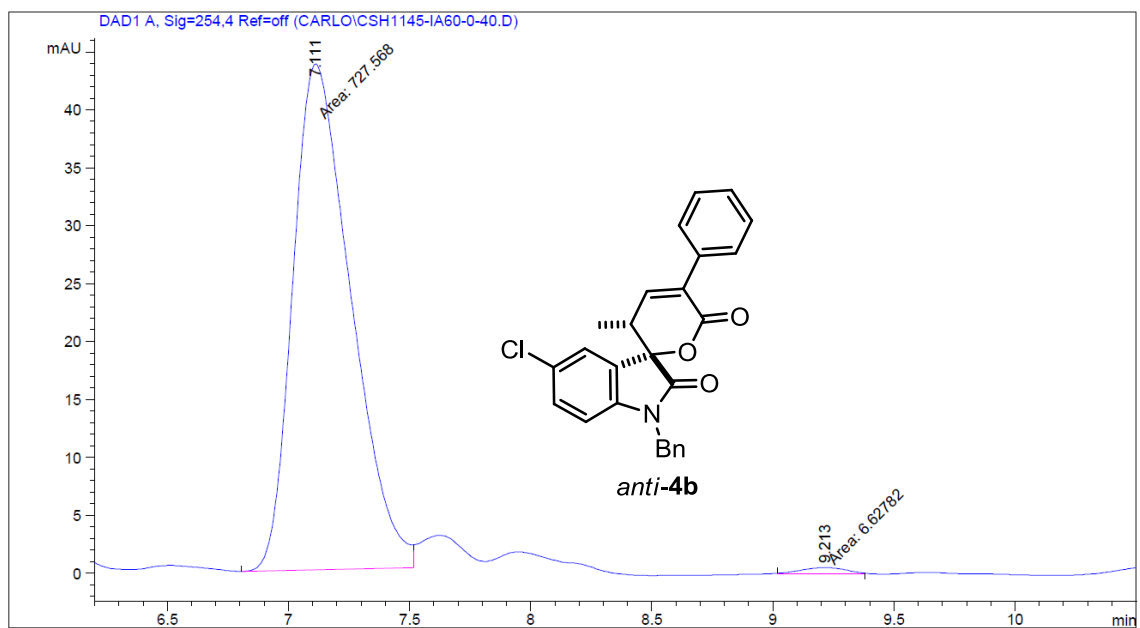
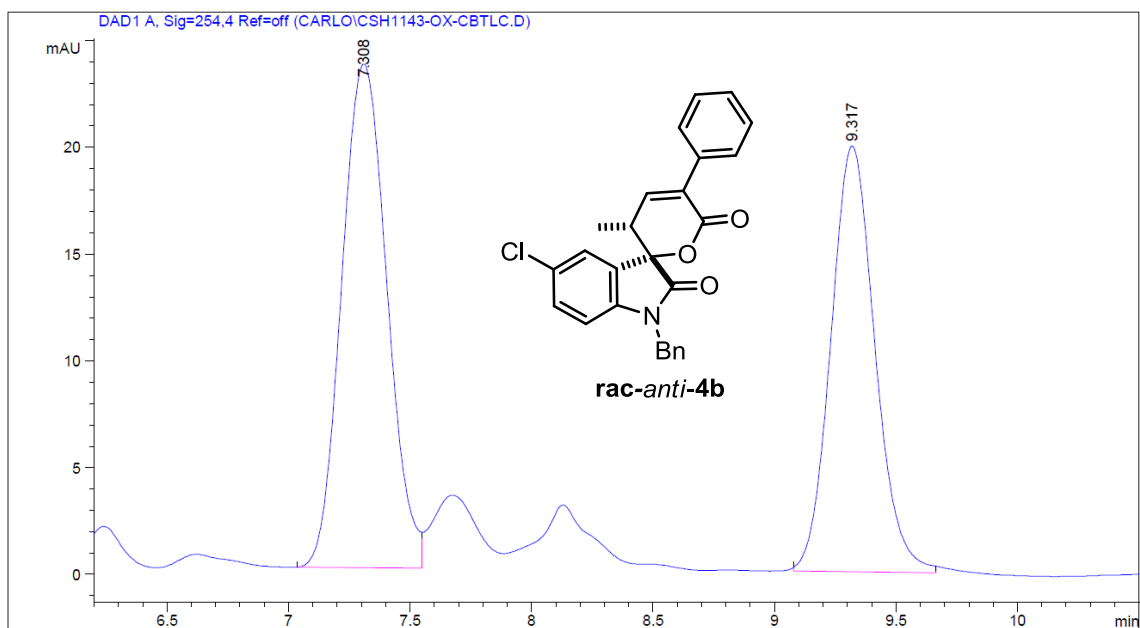
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.073	MM	0.1401	1157.74329	137.72940	99.5485
2	6.082	MM	0.1365	5.25105	6.41304e-1	0.4515

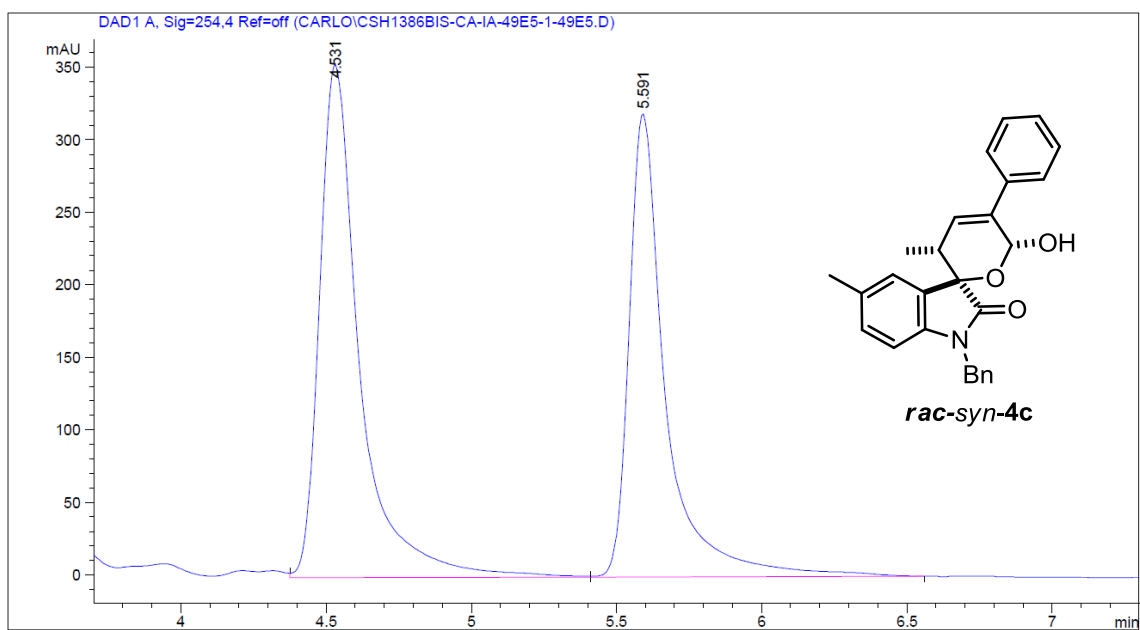


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.460	MF	0.2540	4511.54492	295.98309	51.7871
2	6.872	FM	0.3899	4200.17285	179.52324	48.2129

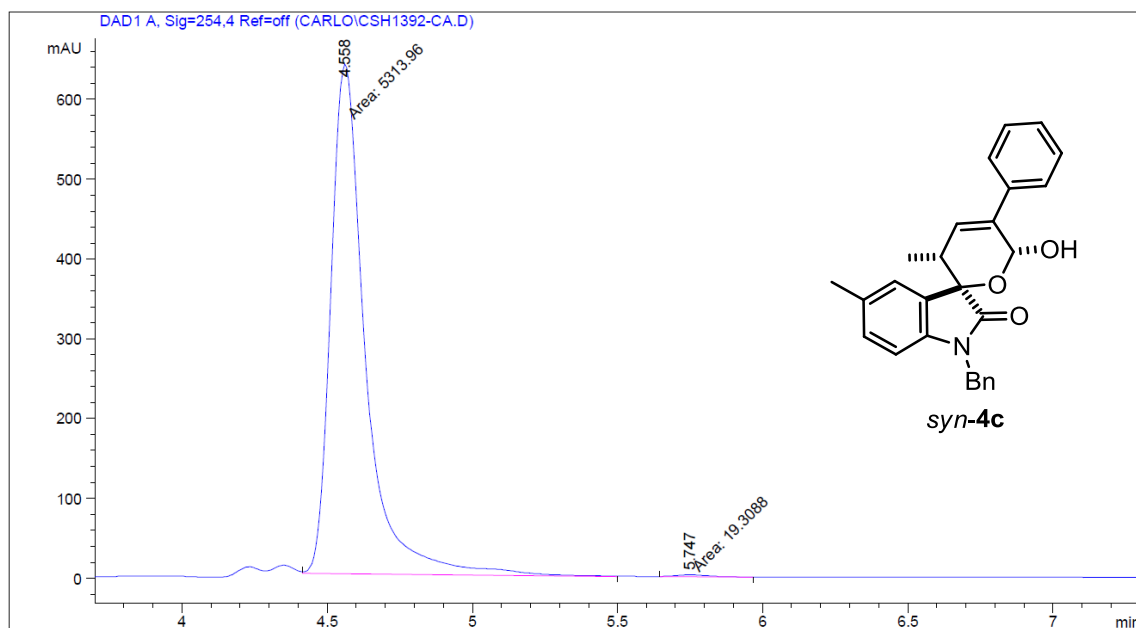


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.355	BB	0.1895	2032.24927	158.55994	100.0000

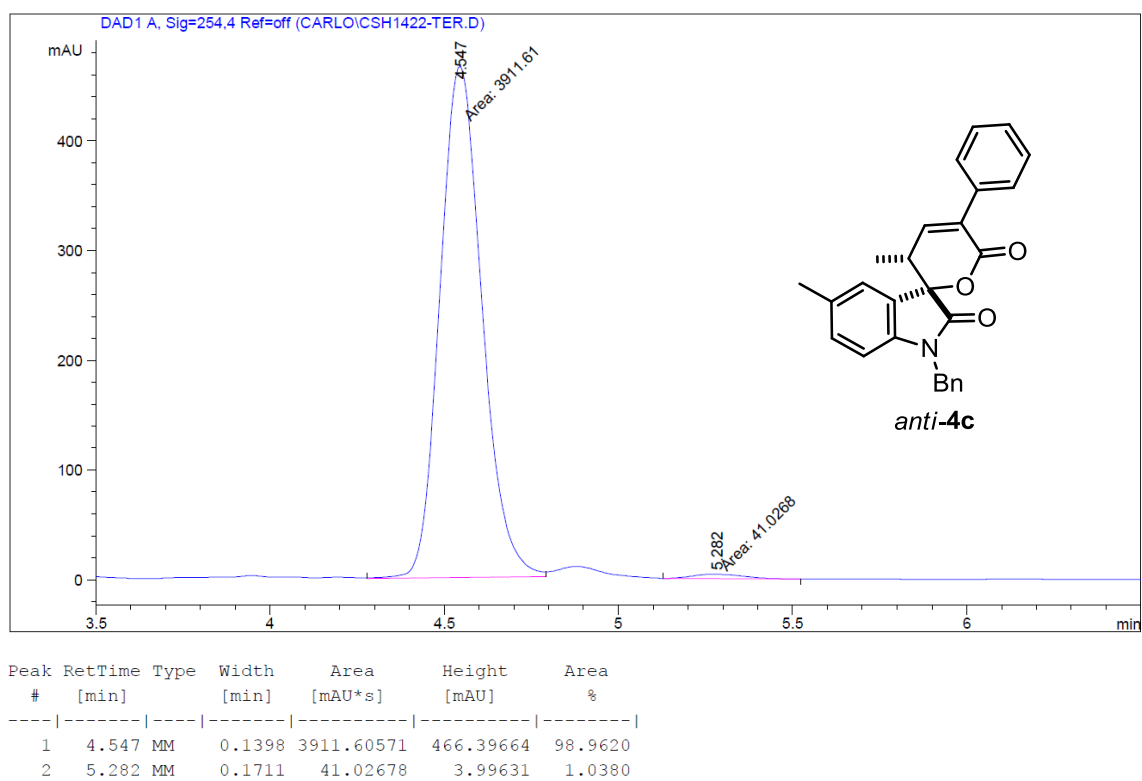
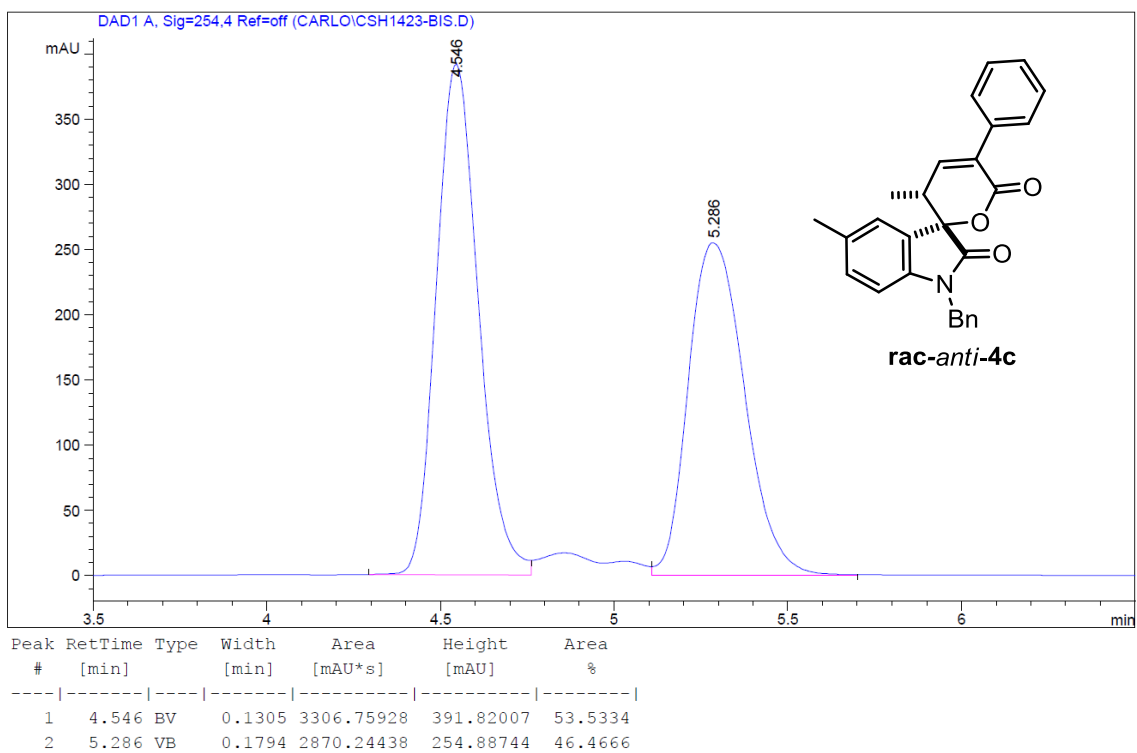


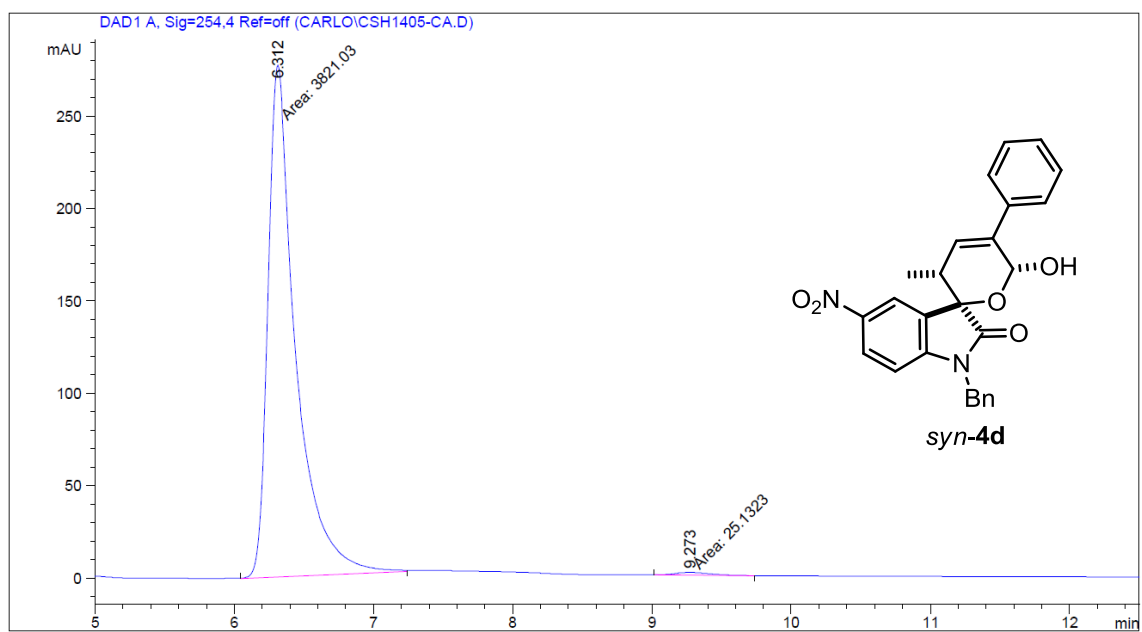
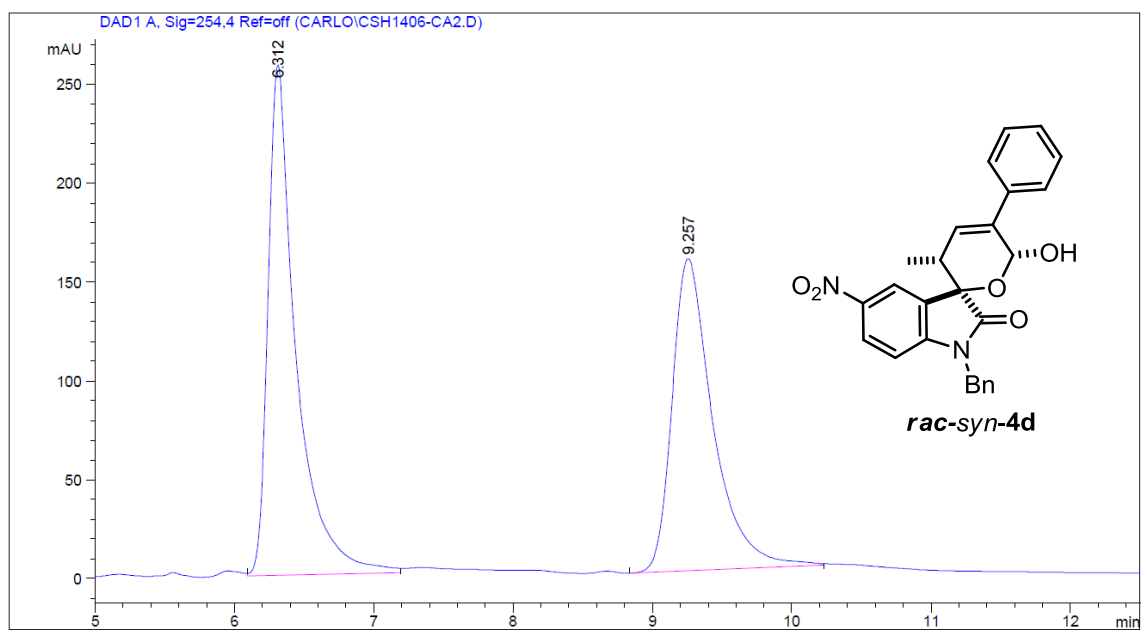


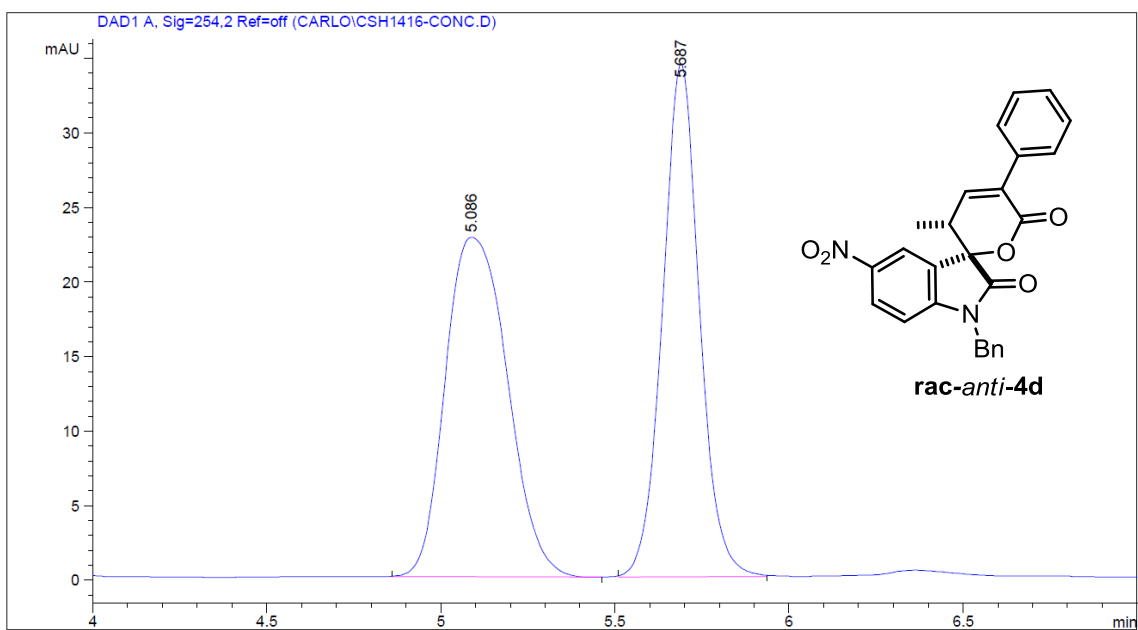
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.531	VV	0.1426	3412.83740	353.76453	54.7567
2	5.591	VB	0.1269	2819.88940	319.57239	45.2433



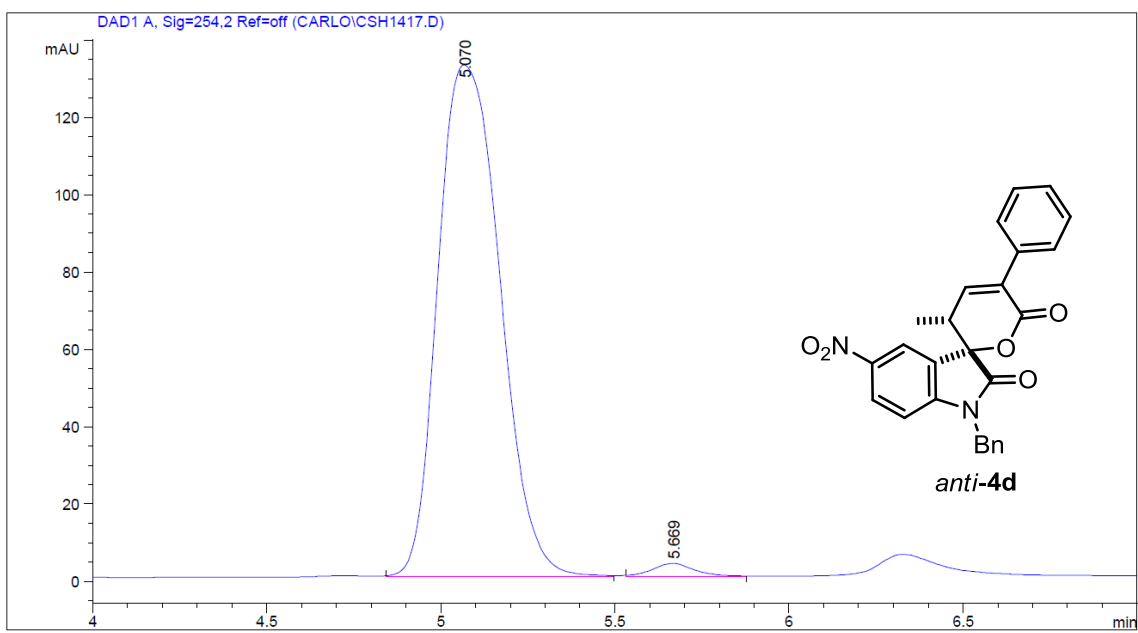
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.558	MM	0.1386	5313.95508	639.13660	99.6380
2	5.747	MM	0.1285	19.30883	2.50364	0.3620



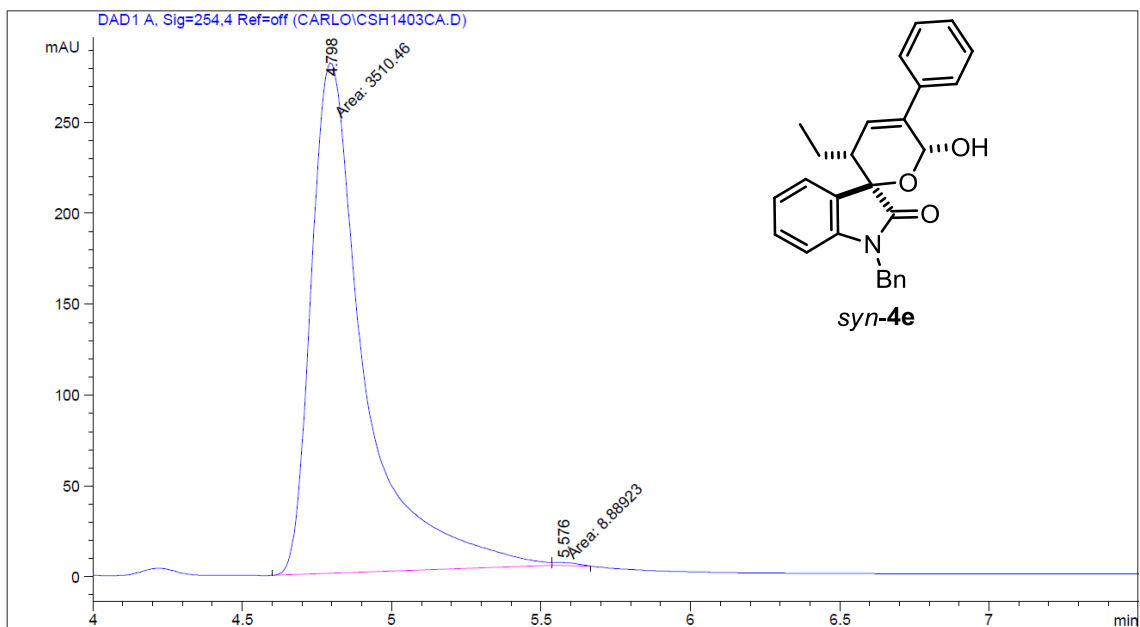
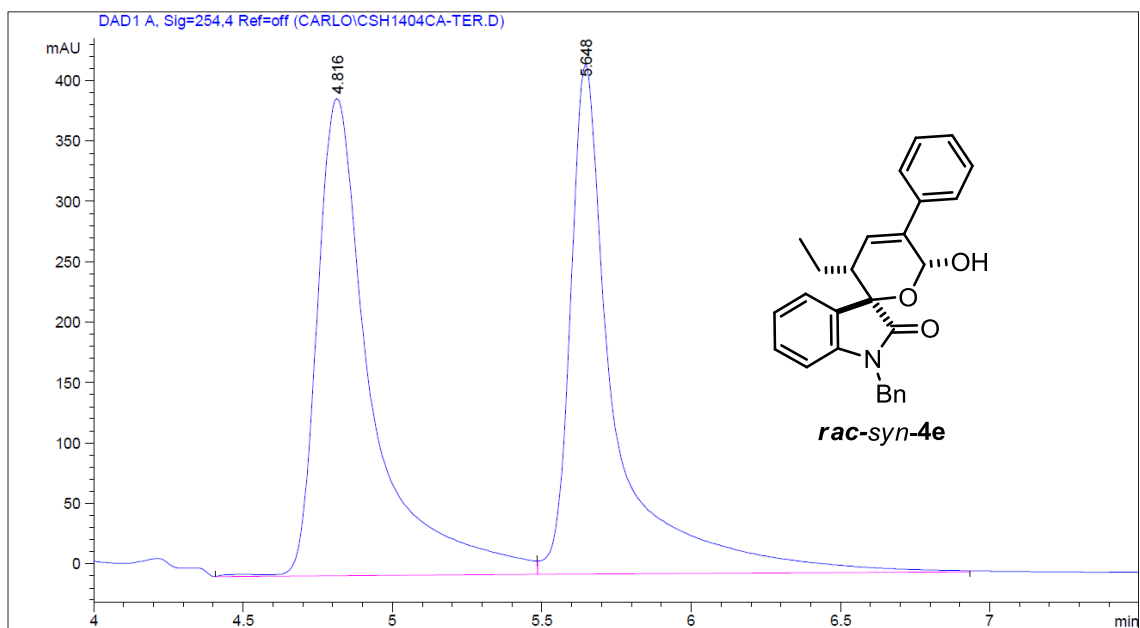


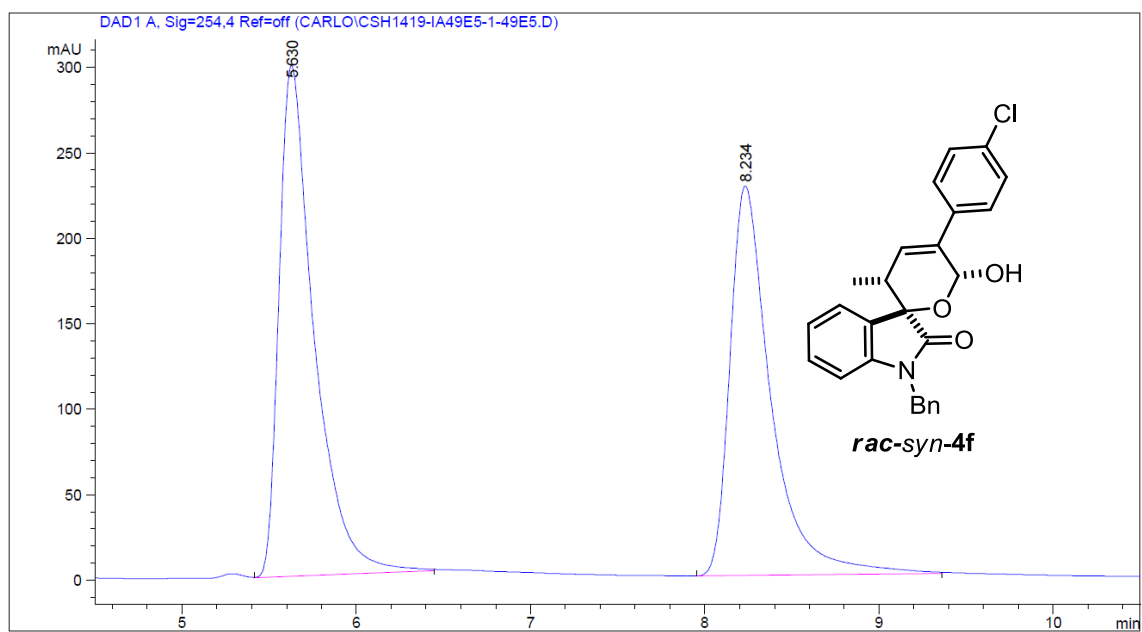


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.086	BB	0.2008	282.90732	22.79844	52.7355
2	5.687	BB	0.1139	253.55757	34.44197	47.2645

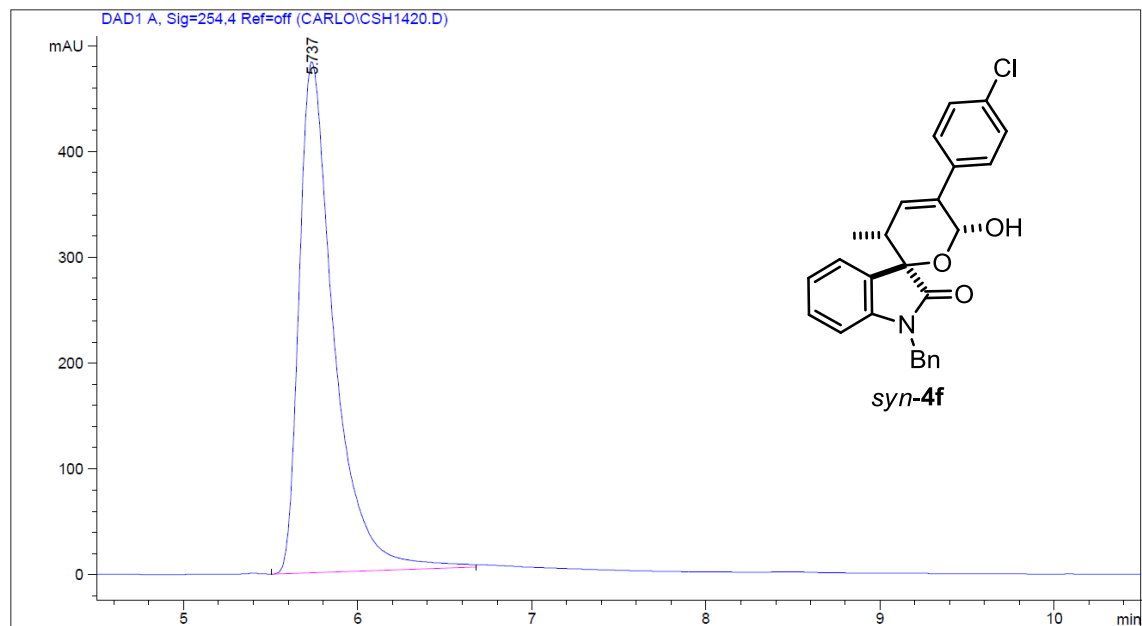


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.070	BB	0.1985	1636.89514	132.17401	98.3714
2	5.669	BB	0.1237	27.10050	3.30509	1.6286





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.630	VB	0.2051	4182.32764	299.09503	52.7277
2	8.234	BB	0.2439	3749.61230	227.98657	47.2723



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.737	VB	0.2071	6750.75342	482.87054	100.0000

