# Effective and Diastereoselective Preparation of Dispiro[cyclopent-3′-ene]bisoxindoles via Novel [3 + 2] Annulation of Isoindigos and MBH Carbonates

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## Supporting Information

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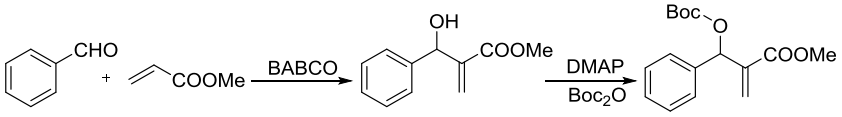
**1. General Information**

Commercial grade solvent was dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance (300 MHz for $^{1}$H NMR, 75 MHz for $^{13}$C NMR) instrument. Data for $^{1}$H NMR are reported as chemical shift (ppm, tetramethylsilane as the internal standard), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet), coupling constant (Hz). Data for $^{13}$C NMR are reported as chemical shift. High resolution mass spectra were obtained with the Q-TOF-Premier mass spectrometer. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with ultraviolet light.

**2. General Procedures for the preparations of Isoindigos 1 and Morita−Baylis−Hillman Carbonates 2**

All isoindigos **1** were synthesized according to our previous report. [1]

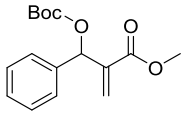
Morita−Baylis−Hillman carbonates **2** were synthesized as reported method: [2]



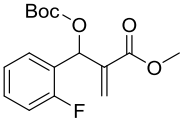

Benzaldehyde (1.06 g, 10 mmol), methyl acrylate (1.72 g, 20 mmol) and DABCO (1.25 g, 10 mmol) were stirred for 3-7 days in a round-bottom flask. The reaction was detected by TLC. When completed, 20 mL water was added, and the aqueous phase was extracted with $CH_2Cl_2$ (20 mL × 2). The combined organic phase was washed with brine and dried over anhydrous $Na_2SO_4$. After removal of solvent, the crude product was further purified by flash column chromatography (petroleum ether : ethyl acetate = 10:1) to obtain the MBH alcohol.

To the solution of MBH alcohol (1 g, 5.4 mmol) and $Boc_2O$ (1.62 g, 5.73 mmol) in 10 mL $CH_2Cl_2$ was added DMAP (0.12 g, 1.04 mmol) in 2 mL $CH_2Cl_2$ dropwise. The mixture was stirred at room temperature for 90 mins and washed with water (20 mL×2). The $CH_2Cl_2$ phase was washed with brine and dried over anhydrous $Na_2SO_4$. After removal of solvent, the crude product was further purified by flash column chromatography (petroleum ether : ethyl acetate = 15:1) to obtain the MBH carbonates **2**.

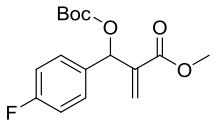
Other MBH carbonates were synthesized with the same procedures.



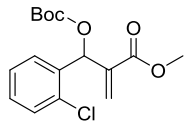

**Methyl 2-((tert-butoxycarbonyloxy)(phenyl)methyl)acrylate (2a).** $^{1}$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.34 (m, 5H), 6.48 (s, 1H), 6.40 (s, 1H), 5.91 (s, 1H), 3.71 (s, 3H), 1.46 (s, 9H)



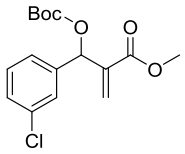

**Methyl 2-((tert-butoxycarbonyloxy)(2-fluorophenyl)methyl)acrylate (2b).** $^{1}$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.32 (m, 2H), 7.08 (m, 1H), 7.05 (m, 1H), 6.77 (s, 1H), 6.46 (s, 1H), 5.86 (d, *J* = 0.6 Hz, 1H), 3.71 (s, 3H), 1.46 (s, 9H)



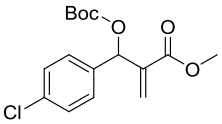
**Methyl 2-((tert-butoxycarbonyloxy)(4-fluorophenyl)methyl)acrylate (2c).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.45–7.31 (m, 2H), 7.09–6.92 (m, 2H), 6.44 (s, 1H), 6.40 (d, *J* = 0.9 Hz, 1H), 5.94 (dd, *J* = 1.5, 0.8 Hz, 1H), 3.70 (s, 3H), 1.45 (s, 9H).



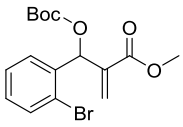
**Methyl 2-((tert-butoxycarbonyloxy)(2-chlorophenyl)methyl)acrylate (2d).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.57–7.32 (m, 2H), 7.32–7.04 (m, 2H), 6.89 (d, *J* = 1.0 Hz, 1H), 6.48 (t, *J* = 0.8 Hz, 1H), 5.66 (dd, *J* = 1.4, 0.7 Hz, 1H), 3.75 (s, 3H), 1.47 (s, 9H).



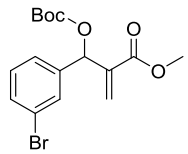
**Methyl 2-((tert-butoxycarbonyloxy)(3-chlorophenyl)methyl)acrylate (2e).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.39 (s, 1H), 7.33–7.20 (m, 3H), 6.43 (dq, *J* = 1.5, 0.9 Hz, 2H), 5.95 (dd, *J* = 1.4, 0.6 Hz, 1H), 3.72 (s, 3H), 1.47 (s, 9H).



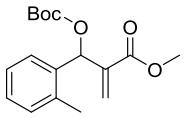
**Methyl 2-((tert-butoxycarbonyloxy)(4-chlorophenyl)methyl)acrylate (2f).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.36–7.29 (m, 4H), 6.42 (d, *J* = 6.2 Hz, 2H), 5.94 (d, *J* = 1.4 Hz, 1H), 3.71 (s, 3H), 1.46 (s, 9H).



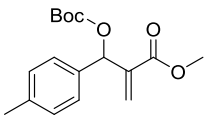
**Methyl 2-((2-bromophenyl) (tert-butoxycarbonyloxy)methyl)acrylate (2g).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.40 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.32 (td, *J* = 7.5, 1.3 Hz, 1H), 7.19 (td, *J* = 7.6, 1.9 Hz, 1H), 6.84 (s, 1H), 6.48 (s, 1H), 5.62 (s, 1H), 3.76 (s, 3H), 1.48 (s, 9H).



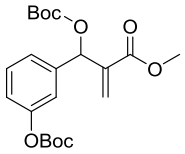
**Methyl 2-((3-bromophenyl) (tert-butoxycarbonyloxy) methyl)acrylate (2h).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.53 (t, *J* = 1.9 Hz, 1H), 7.43 (ddd, *J* = 7.9, 2.0, 1.2 Hz, 1H), 7.34 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.28–7.16 (m, 1H), 6.42 (q, *J* = 1.8, 1.3 Hz, 2H), 5.95 (d, *J* = 1.3 Hz, 1H), 3.72 (s, 3H), 1.46 (s, 9H).



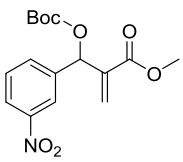
**Methyl 2-((tert-butoxycarbonyloxy)(o-tolyl)methyl)acrylate (2i).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.31 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.19 (dd, *J* = 5.6, 3.2 Hz, 3H), 6.72 (s, 1H), 6.42 (s, 1H), 5.72 (s, 1H), 3.73 (s, 3H), 2.40 (s, 3H), 1.46 (s, 9H).



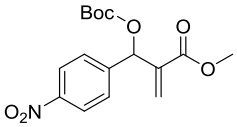
**Methyl 2-((tert-butoxycarbonyloxy)(p-tolyl)methyl)acrylate (2j).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.39–7.22 (m, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.45 (s, 1H), 6.39 (s, 1H), 5.91 (s, 1H), 3.70 (s, 3H), 2.33 (s, 3H), 1.46 (s, 9H).



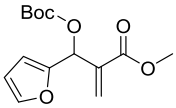
**Methyl 2-((tert-butoxycarbonyloxy)(3-(tert-butoxycarbonyloxy)phenyl)methyl) acrylate (2k).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.34 (t, *J* = 7.8 Hz, 1H), 7.29–7.23 (m, 1H), 7.20 (t, *J* = 1.9 Hz, 1H), 7.13 (ddd, *J* = 8.0, 2.4, 1.2 Hz, 1H), 6.47 (s, 1H), 6.41 (s, 1H), 5.91 (s, 1H), 3.72 (s, 3H), 1.55 (s, 9H), 1.46 (s, 9H).



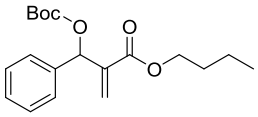
**Methyl 2-((tert-butoxycarbonyloxy)(3-nitrophenyl)methyl)acrylate (2l).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 8.24 (s, 1H), 8.14 (m, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 6.51 (s, 1H), 6.46 (s, 1H), 6.04 (s, 1H), 3.70 (s, 3H), 1.44 (s, 9H).



**Methyl 2-((tert-butoxycarbonyloxy)(4-nitrophenyl)methyl)acrylate (2m).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 8.21 (d, *J* = 6.8 Hz, 2H), 7.60 (d, *J* = 6.8 Hz, 2H), 6.53 (s, 1H), 6.47 (s, 1H), 6.03 (s, 1H), 3.73 (s, 3H), 1.47 (s, 9H)



**Methyl 2-((tert-butoxycarbonyloxy)(furan-2-yl)methyl)acrylate (2n).** $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.39 (dd, *J* = 1.7, 1.0 Hz, 1H), 6.54 (s, 1H), 6.48 (t, *J* = 0.8 Hz, 1H), 6.37–6.28 (m, 2H), 6.06 (dd, *J* = 1.4, 0.7 Hz, 1H), 3.73 (s, 3H), 1.50 (s, 9H).

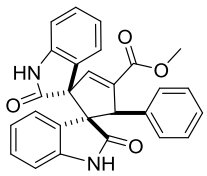


**Butyl 2-((tert-butoxycarbonyloxy)( phenyl)methyl)acrylate (2o)**. $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 7.44–7.29 (m, 5H), 6.48 (s, 1H), 6.41 (s, 1H), 5.89 (s, 1H), 4.10 (td, *J* = 6.6, 4.8 Hz, 2H), 1.63–1.50 (m, 2H), 1.46 (s, 9H), 1.37–1.21 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

**3. Procedure for Gram-Scale [3 + 2] Annulation and the deprotection of [3 + 2] product 3a**

The Gram-Scale [3 + 2] Annulation: 3 mmol **1a** (1.38 g), 3.6 mmol **2a** (1.05 g) and 20 mol% $Bu_3P$ was stirred in 25 mL toluene at room temperature under $N_2$ atmosphere, detected by TLC. After the reaction was completed (about 0.17 h), the crude product was directly purified by silica gel chromatography to give the desired [3 + 2] product **3a** (1.87 g, 98% yield, HPLC 99.5%).

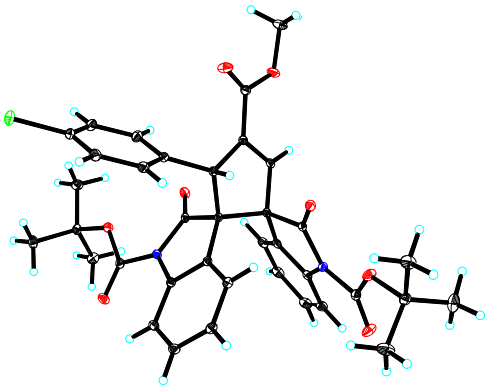
To a solution of **3a** (63.6 mg, 0.1 mmol) in $CH_2Cl_2$ (5 mL) was added $CF_3COOH$ (1.4 mL, 20 mmol) at 0 $^oC$. The reaction mixture was allowed to warm up to room temperature and stirred for 2h. Saturated $Na_2CO_3$ aqueous solution (10 mL) was added to quench the reaction, and the resulting mixture was extracted with $CH_2Cl_2$ (10 mL×3) and the combined organic layer was washed with brine (20 mL) and dried by anhydrous $Na_2SO_4$. After removal of solvent, the crude product was purified by flash column chromatography (PE: EA = 2:1) to afford the product **8** (41.9 mg, 96% yield, HPLC 99.3%).



***Anti*-1'-ethyl-spiro[4.3']oxindole-spiro[5.3'']1''-H-oxindole-cyclopent-2-methoxy carbonyl-3-benzene-1-ene 8:** 96 % yield, white solid, m.p. 218.6-219.3 $^oC$; $^1$H NMR (300 MHz, Chloroform-*d*) $\delta$ 9.88 (s, 1H), 9.19 (s, 1H), 7.27–6.37 (m, 1H), 7.16 (d, *J* = 6 Hz, 1H), 6.66 (m, 6H), 6.47 (m, 3H), 6.36 (m, 1H), 6.31 (m, 1H), 6.07 (m, 1H), 4.98 (d, *J* = 2.5 Hz, 1H), 3.28 (s, 3H); $^{13}$C NMR (75 MHz, Chloroform-*d*) $\delta$ 175.2, 174.0, 163.6, 142.4, 141.7, 141.6, 140.2, 135.5, 128.2, 127.9, 127.8, 126.3, 126.2, 126.0, 125.7, 125.0, 124.1, 121.1, 120.9, 108.8, 108.2, 66.8, 64.3, 56.0, 50.5, 39.5, 39.3, 39.0, 38.7, 38.4. HRMS-ESI (m/z): Calcd for $C_{27}H_{20}N_2O_4$, $(M + H)^+$: 437.14958, found: 437.14978.

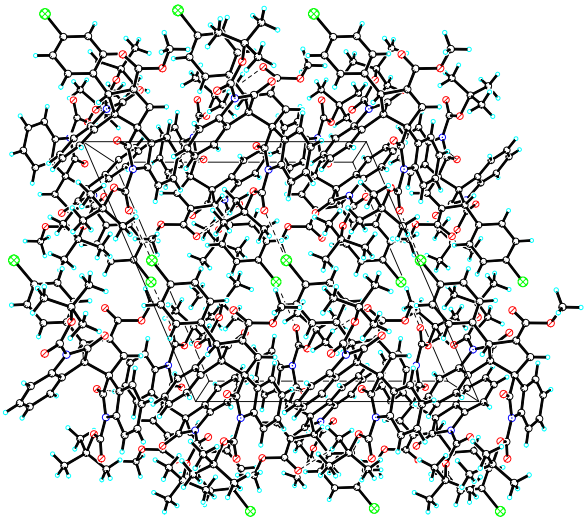
**4. Crystal Information for 3f**

Crystal data for **3f** (CCDC 1550592):



View of a molecule of **3f** with the atom-labelling scheme.

Displacement ellipsoids are drawn at the 30% probability level.



View of the pack drawing of **3f**.

Hydrogen-bonds are shown as dashed lines.

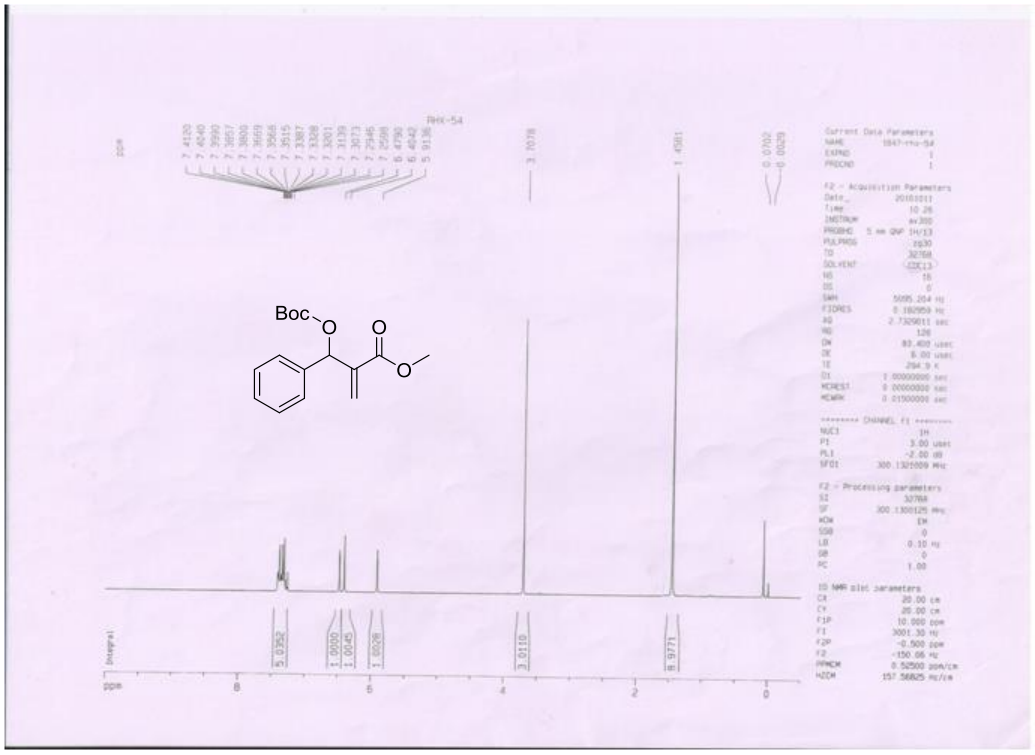
Table 1. Crystal data and structure refinement for mo_wlx_rhx1_0m.

| | |
|---|---|
| Identification code | mo_wlx_rhx1_0m |
| Empirical formula | C37 H35 Cl N2 O8 |
| Formula weight | 671.12 |

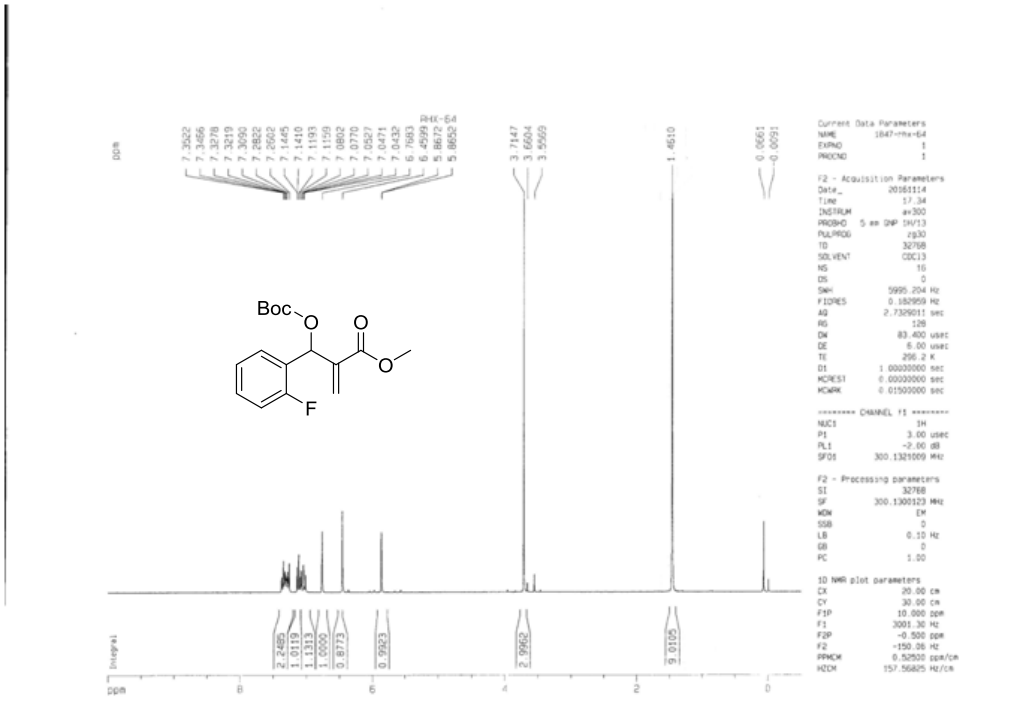
| | |
|---|---|
| Temperature | 100(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions | a = 15.0500(15) Å = 90°. |
| | b = 15.9438(16) Å = 113.382(2)°. |
| | c = 15.0274(15) Å = 90°. |
| Volume | 3309.8(6) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.347 $Mg/m^3$ |
| Absorption coefficient | 0.172 $mm^{-1}$ |
| F(000) | 1408 |
| Crystal size | 1.080 x 0.510 x 0.310 $mm^3$ |
| Theta range for data collection | 1.474 to 31.087°. |
| Index ranges | -21<=h<=20, -21<=k<=22, -21<=l<=21 |
| Reflections collected | 36531 |
| Independent reflections | 9809 [R(int) = 0.0271] |
| Completeness to theta = 25.242° | 99.8 % |
| Absorption correction | Semi-empirical from equivalents |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 9809 / 0 / 440 |
| Goodness-of-fit on $F^2$ | 1.026 |
| Final R indices [I>2sigma(I)] | R1 = 0.0410, wR2 = 0.1064 |
| R indices (all data) | R1 = 0.0506, wR2 = 0.1126 |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 1.296 and -0.507 $e.Å^{-3}$ |

**5. $^{1}$H and $^{13}$C NMR spectra for related reactants and products**

**Reactant 2a**




**Reactant 2b**



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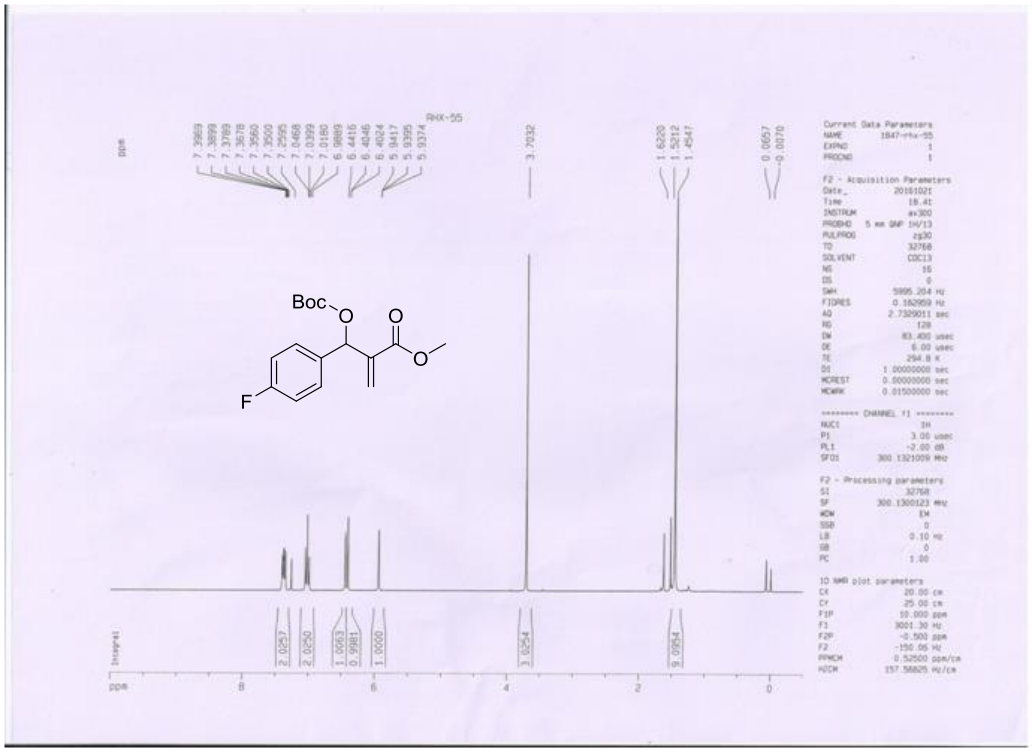
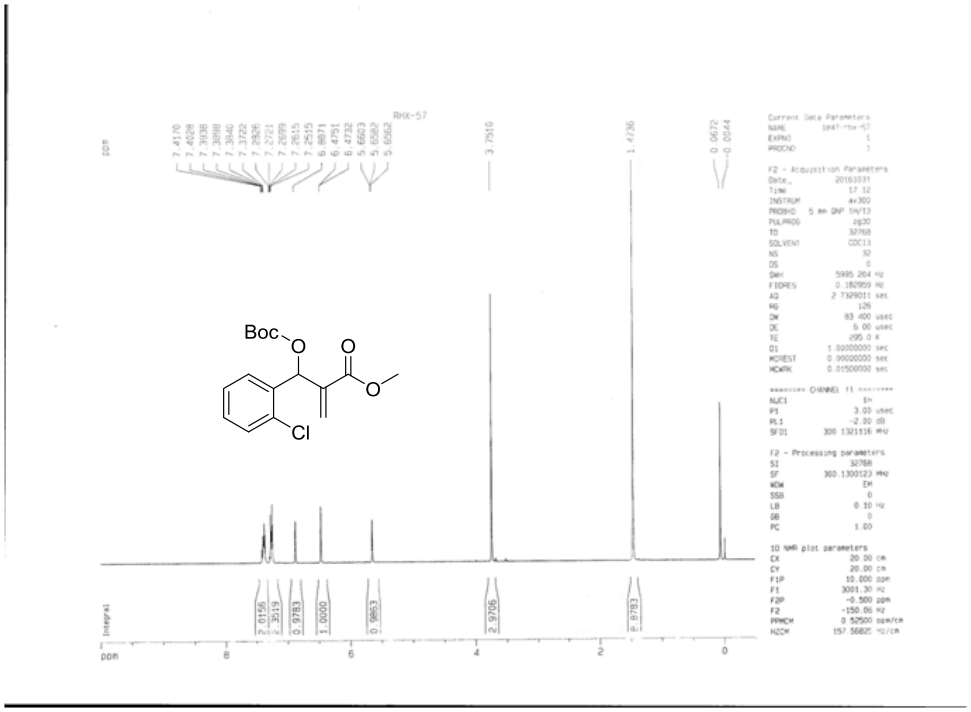
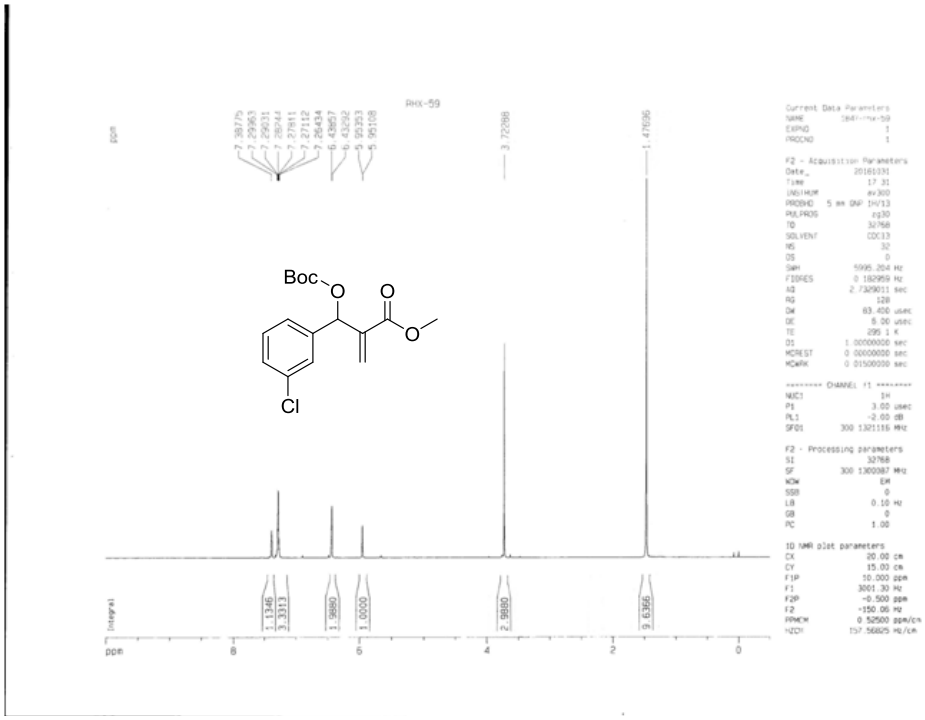


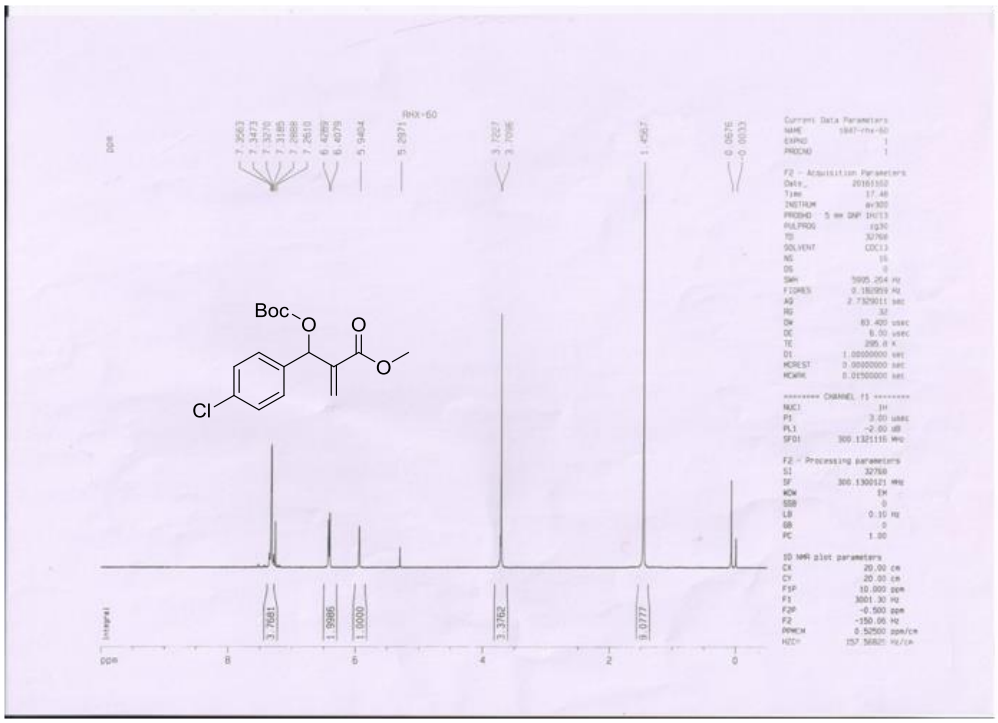

**Reactant 2d**



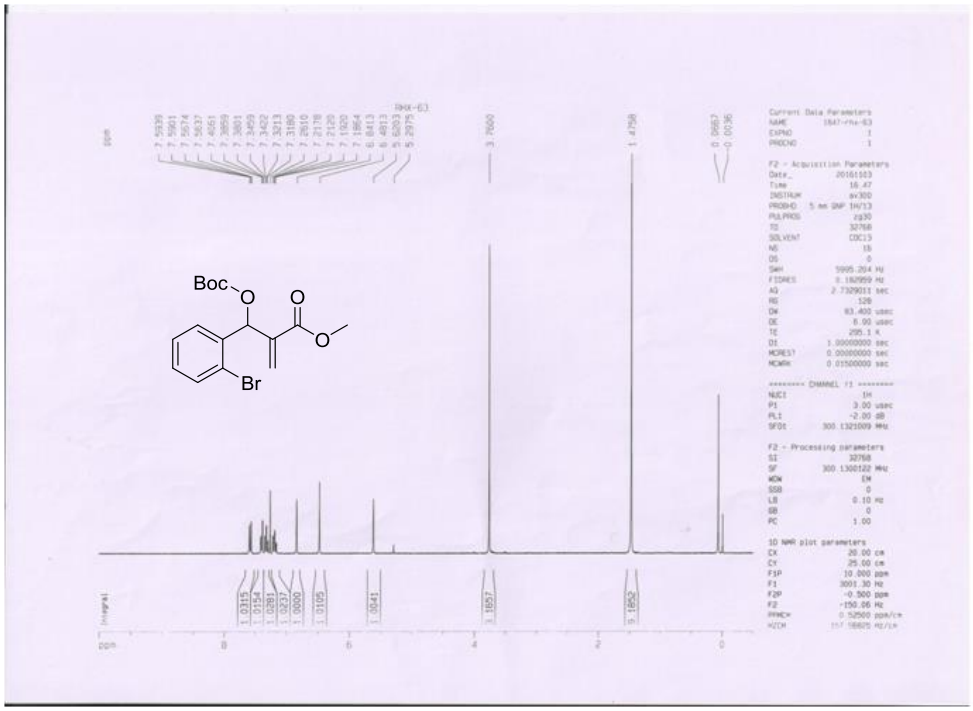
**Reactant 2e**




**Reactant 2f**



**Reactant 2g**

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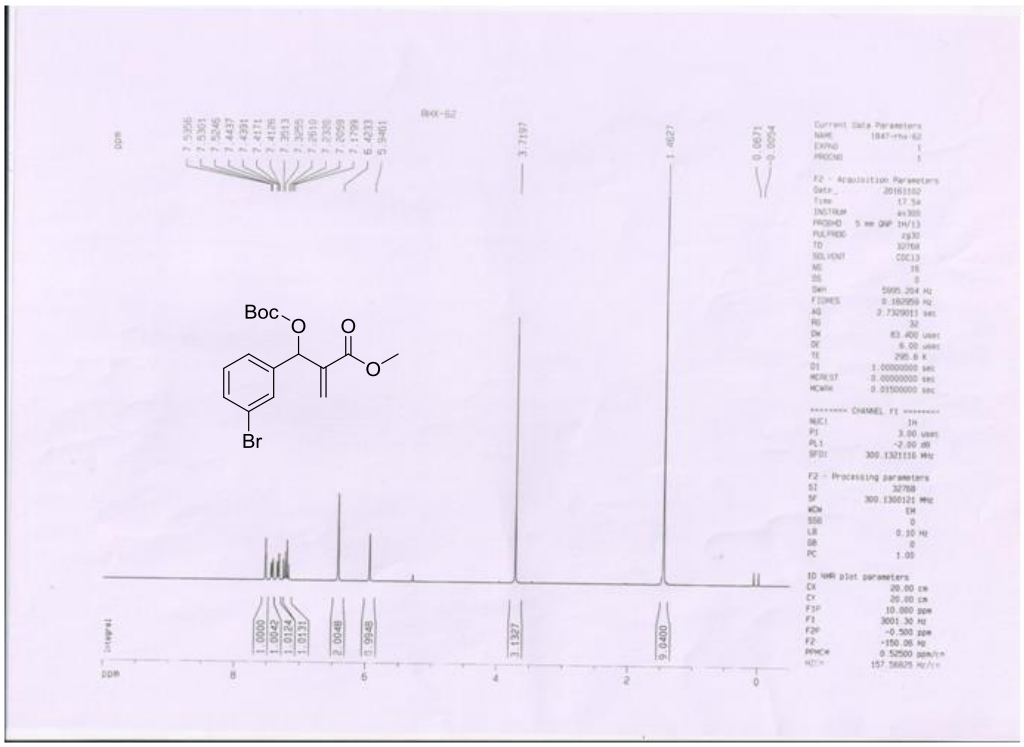
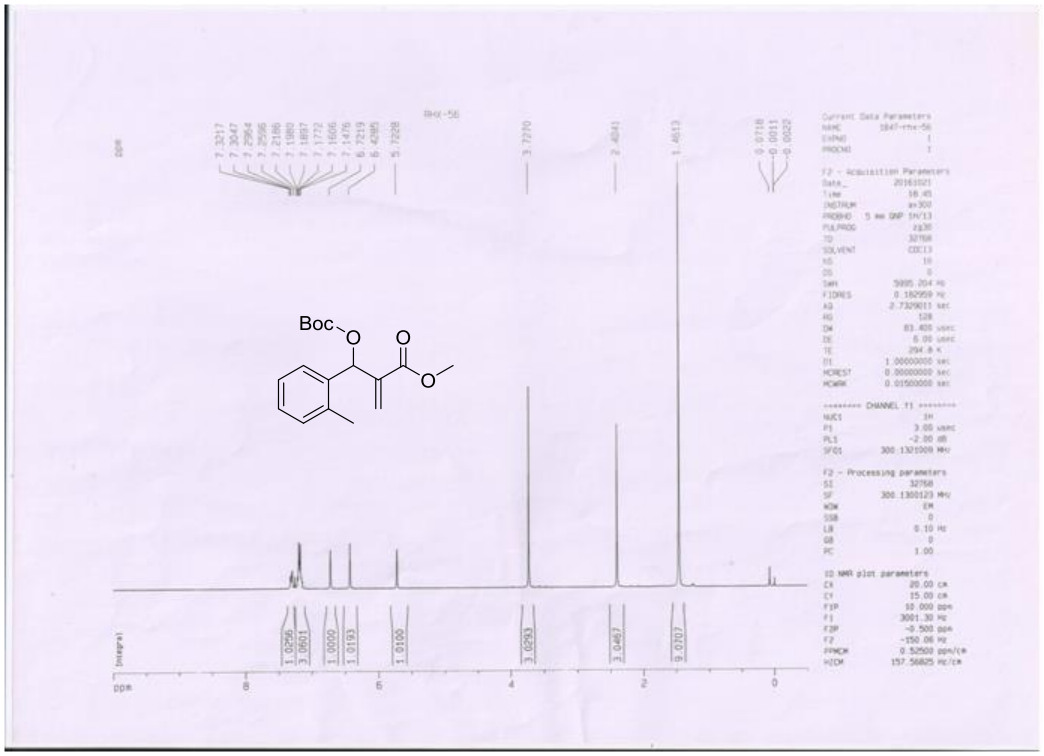
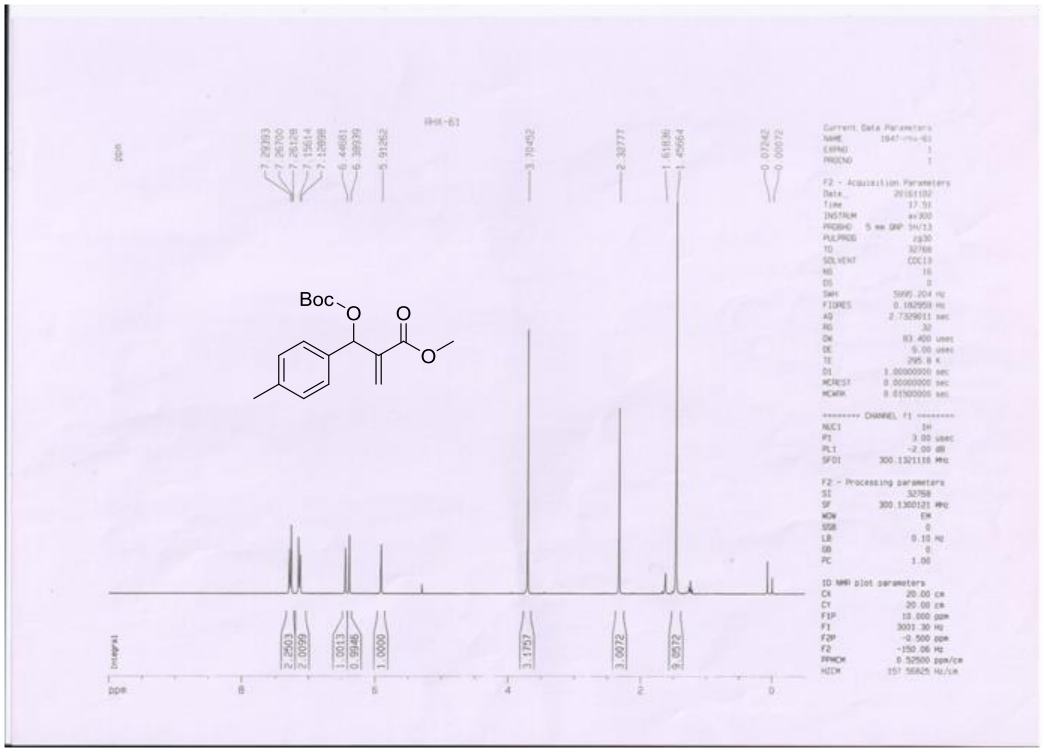


**Reactant 2i**




**Reactant 2j**



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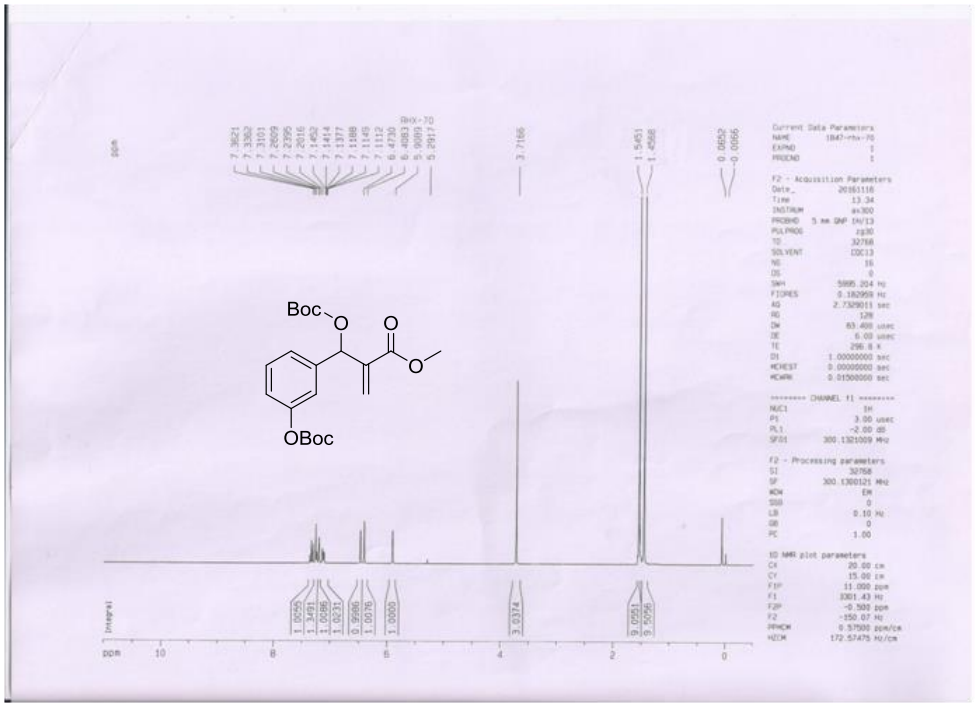


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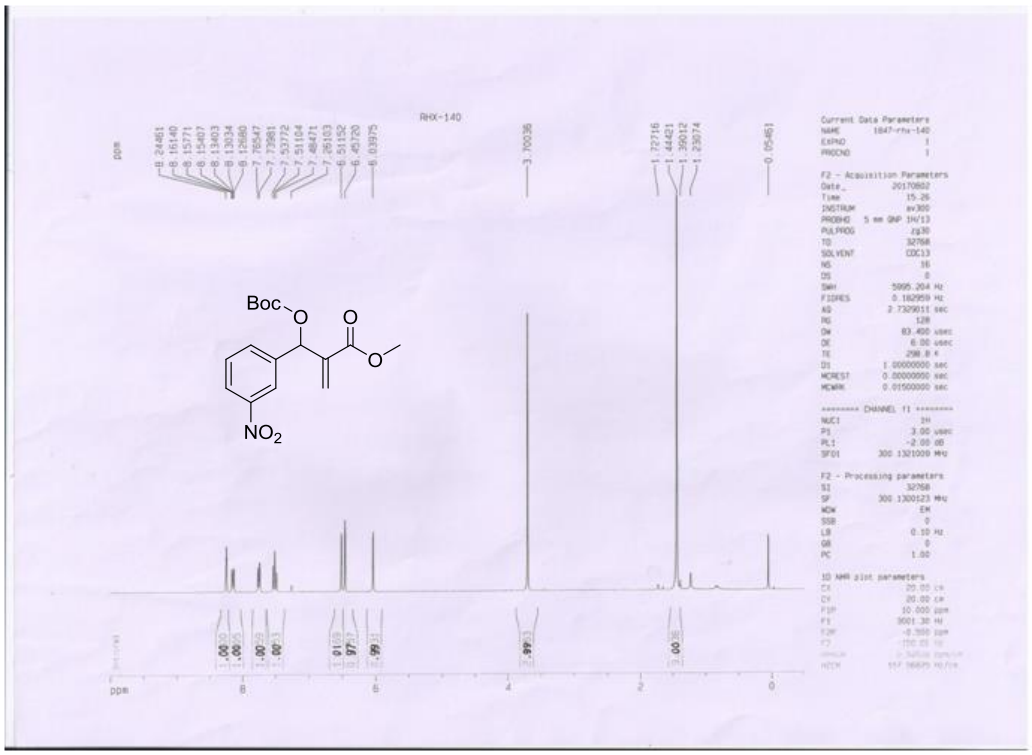
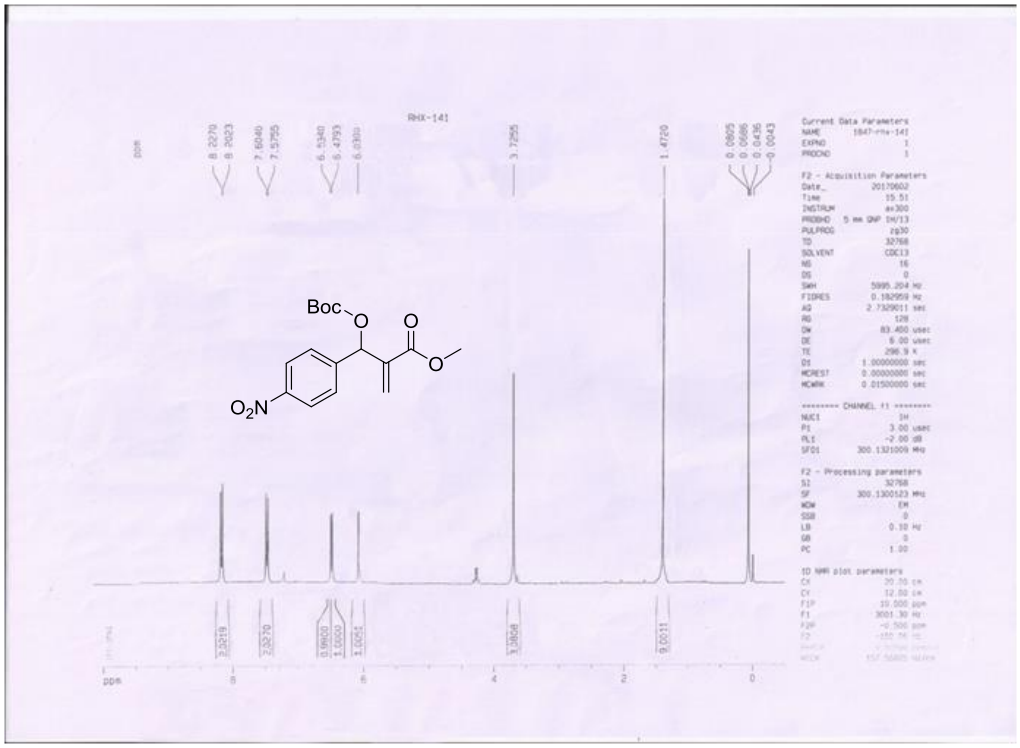
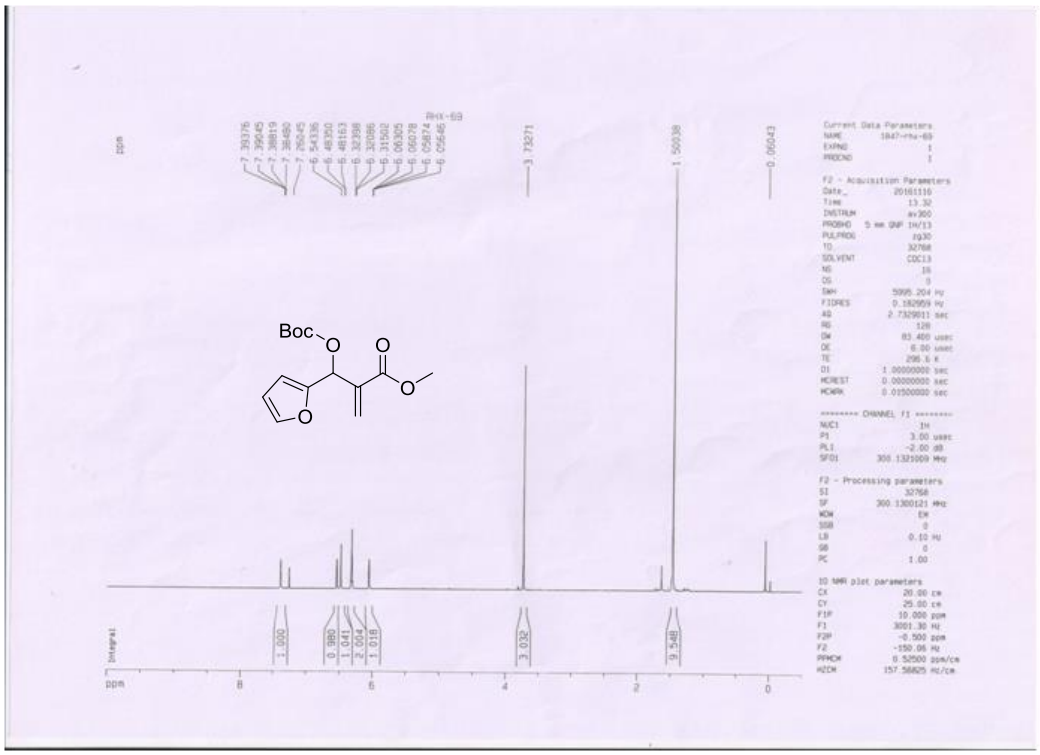


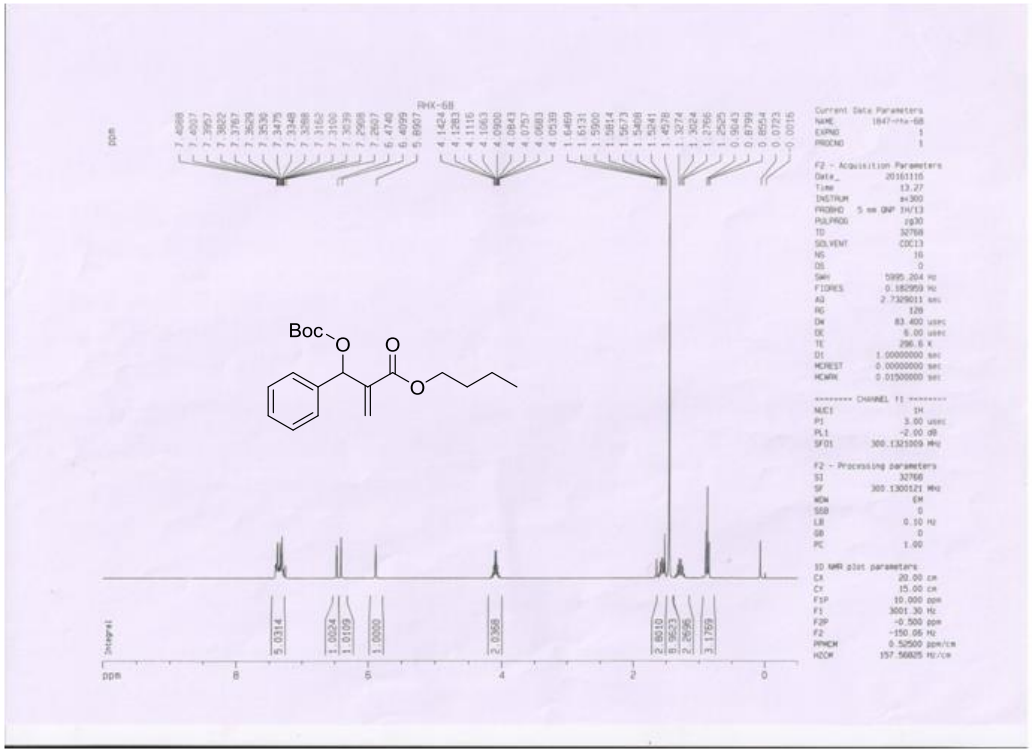
**Reactant 2m**



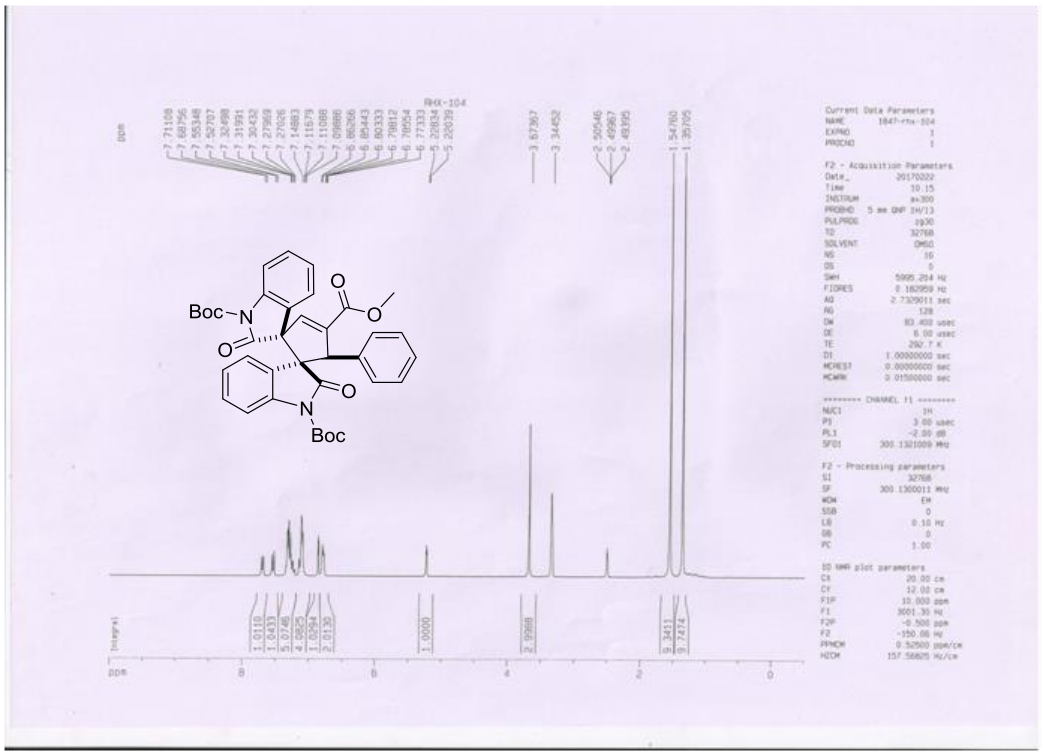

**Reactant 2n**

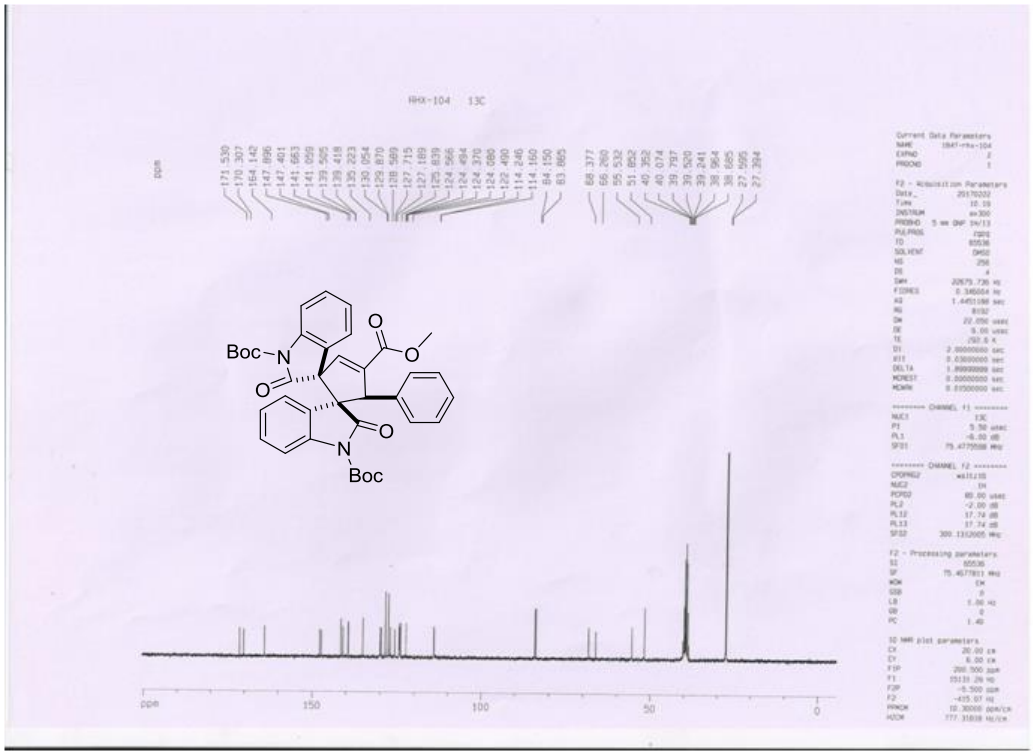


**Reactant 2o**

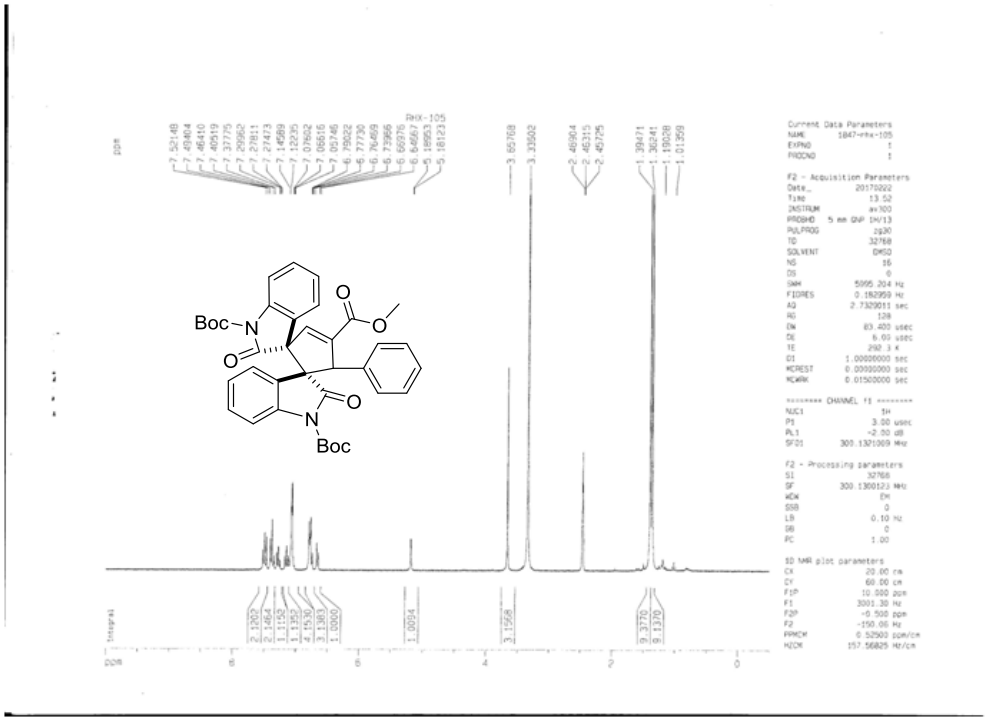


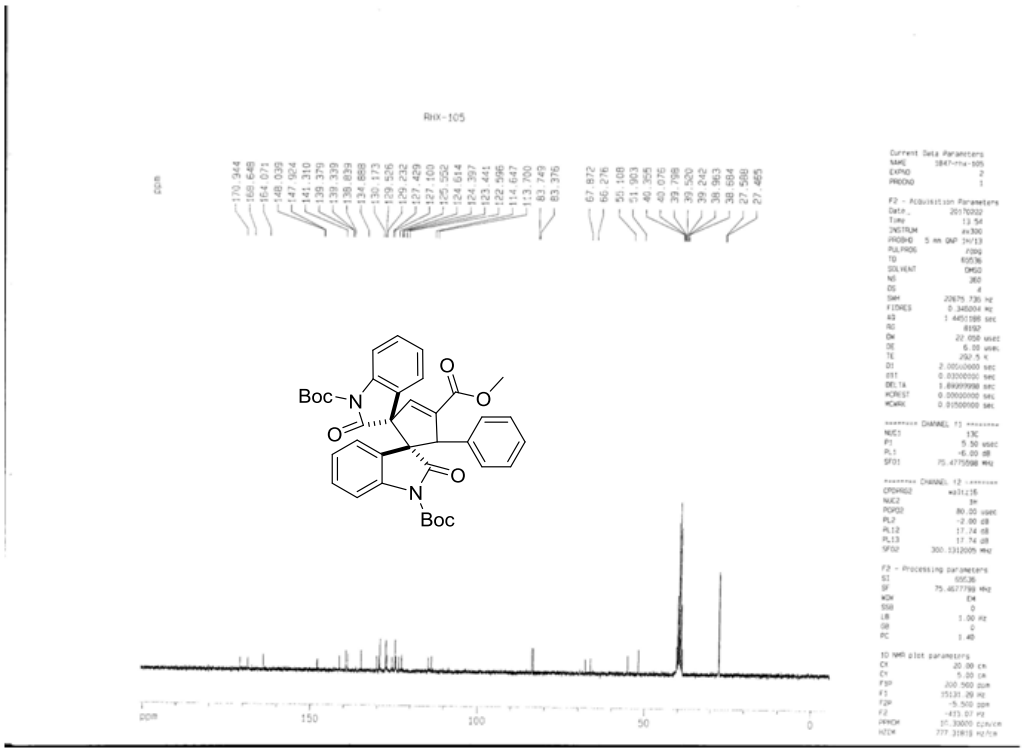

**Product 3a**



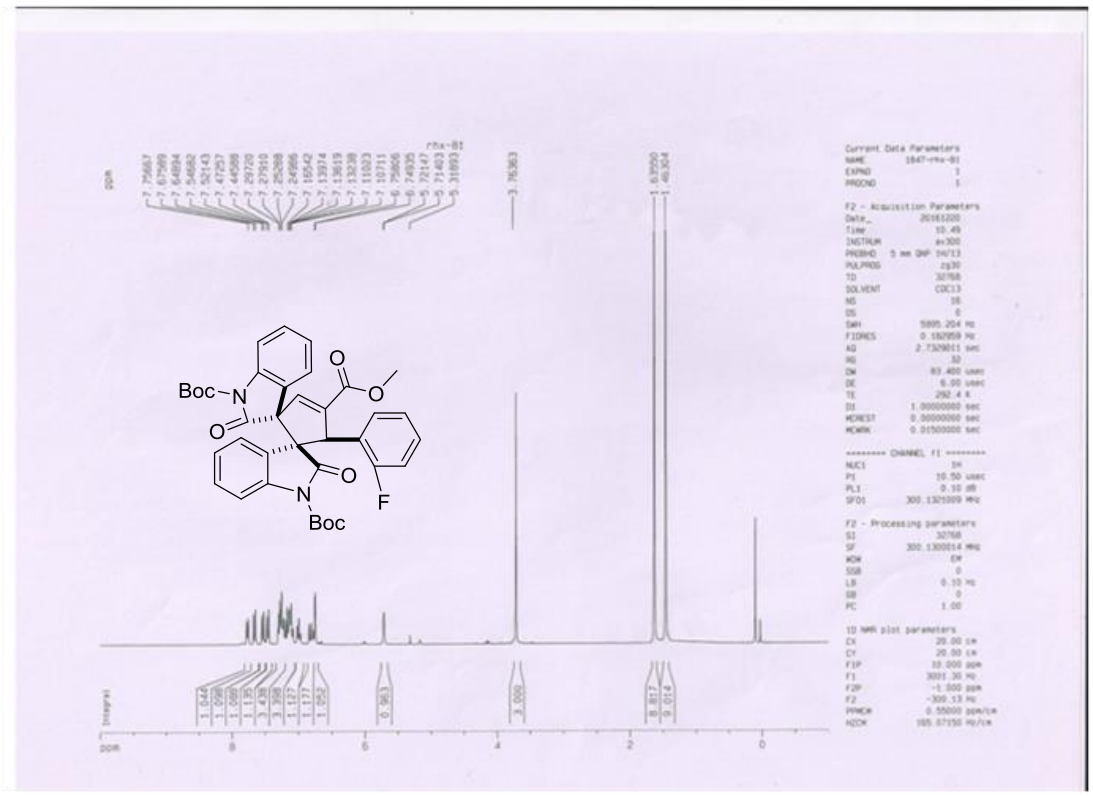


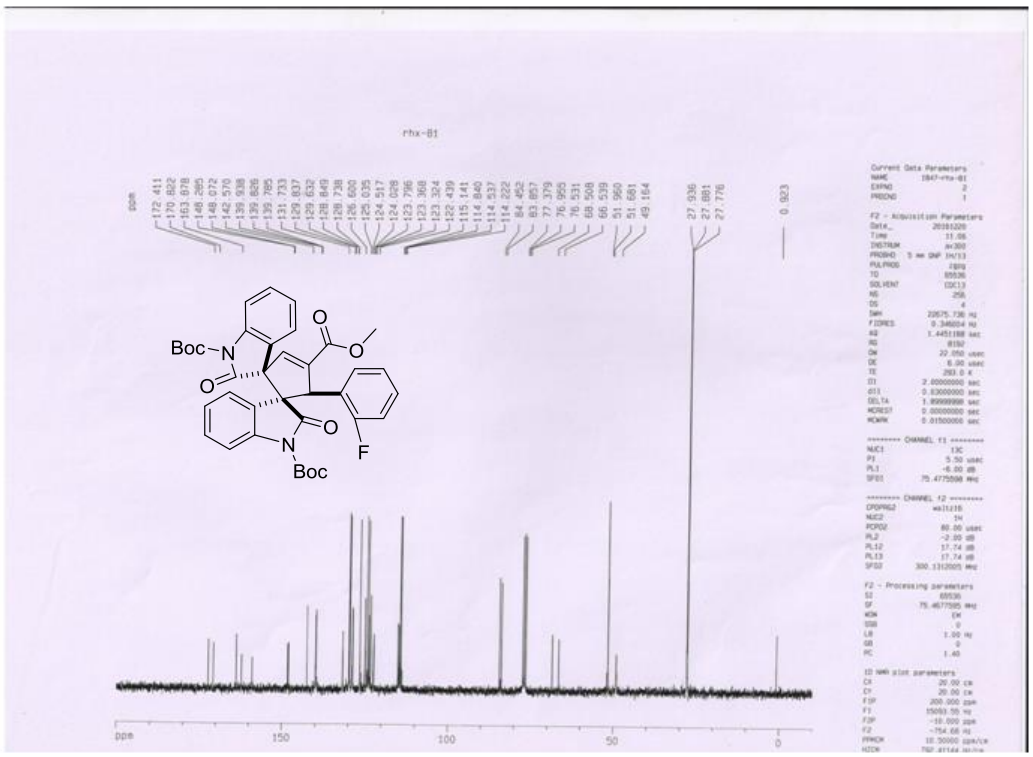

**Product 3a'** (the diastereomer of **3a**)





**Product 3b**



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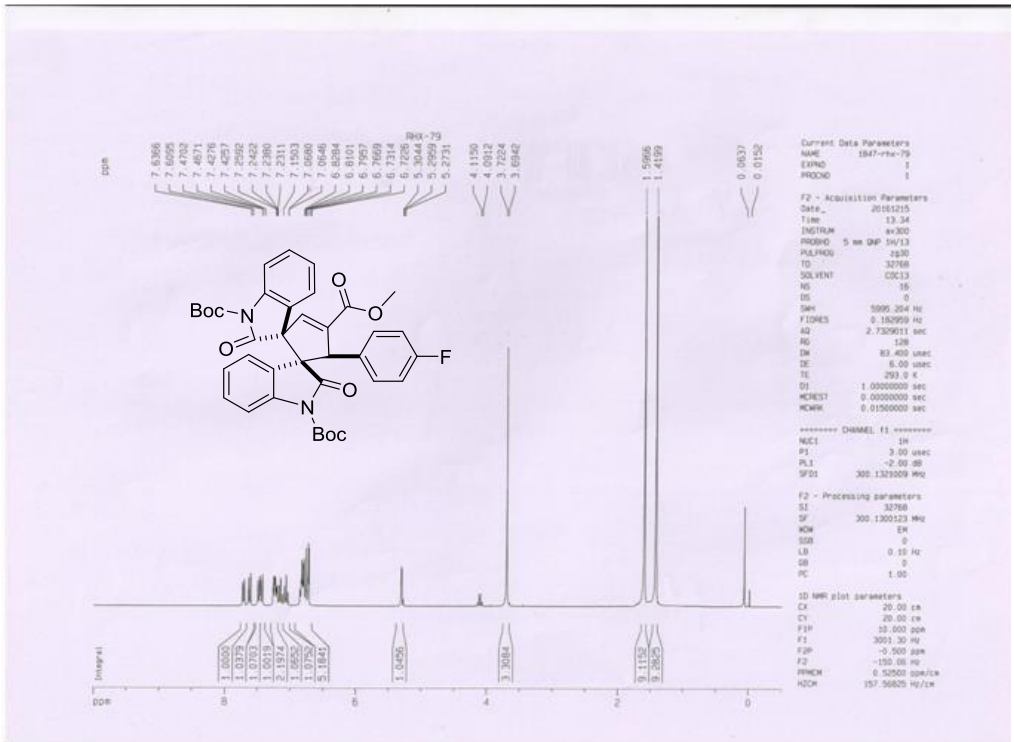

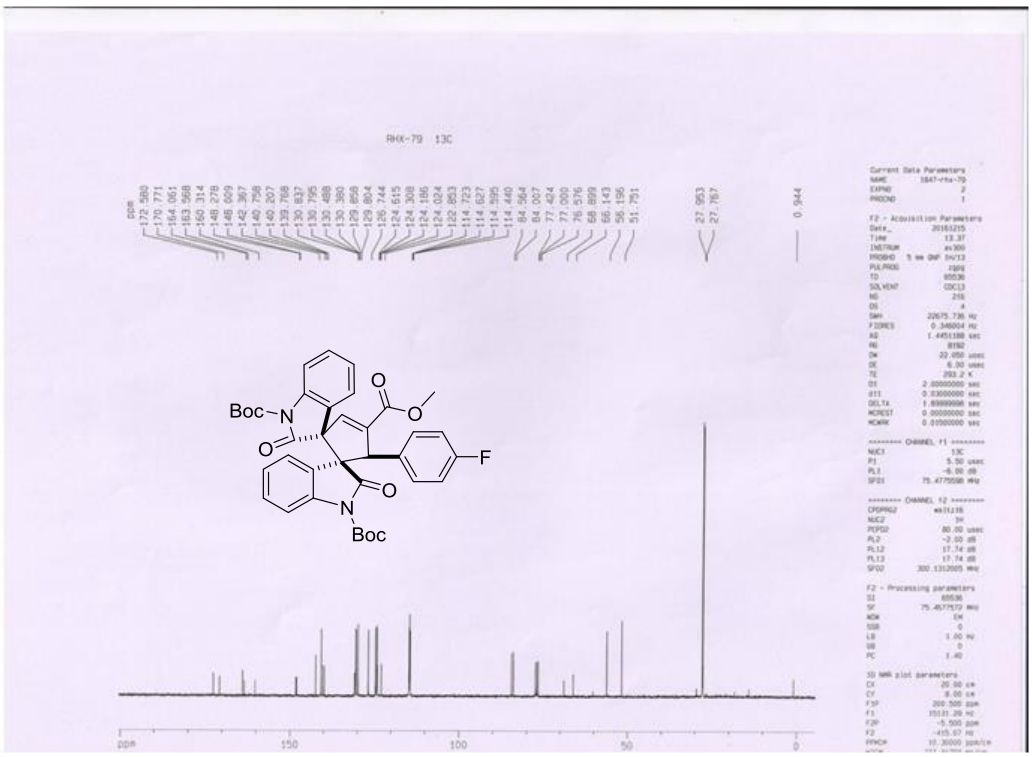


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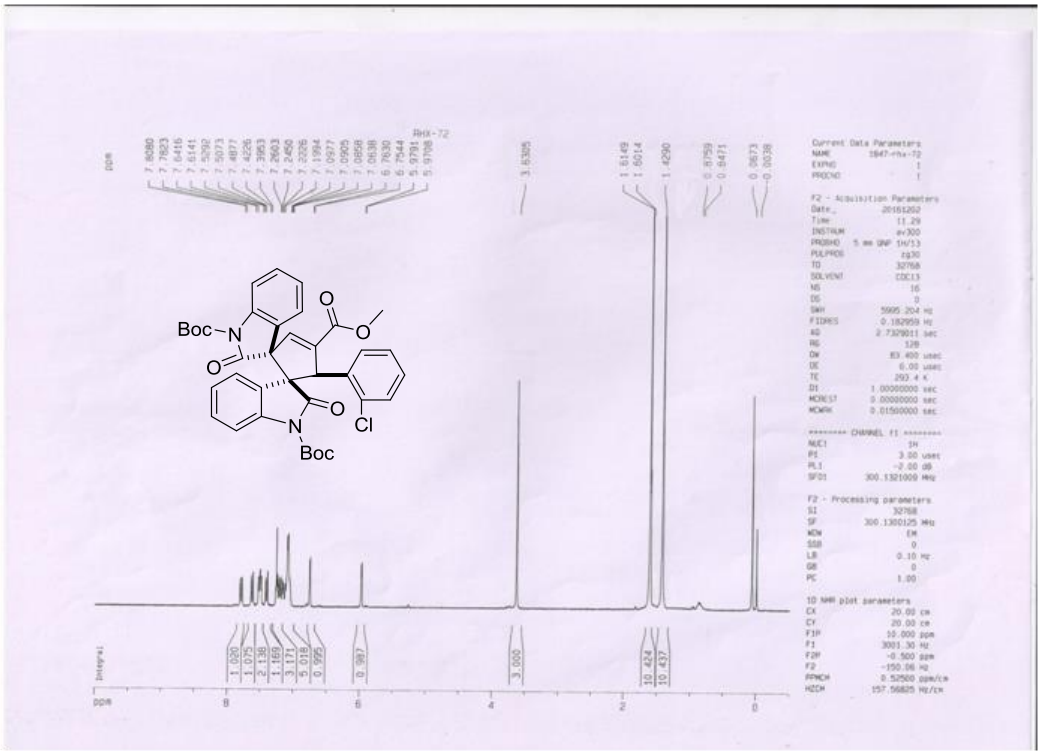

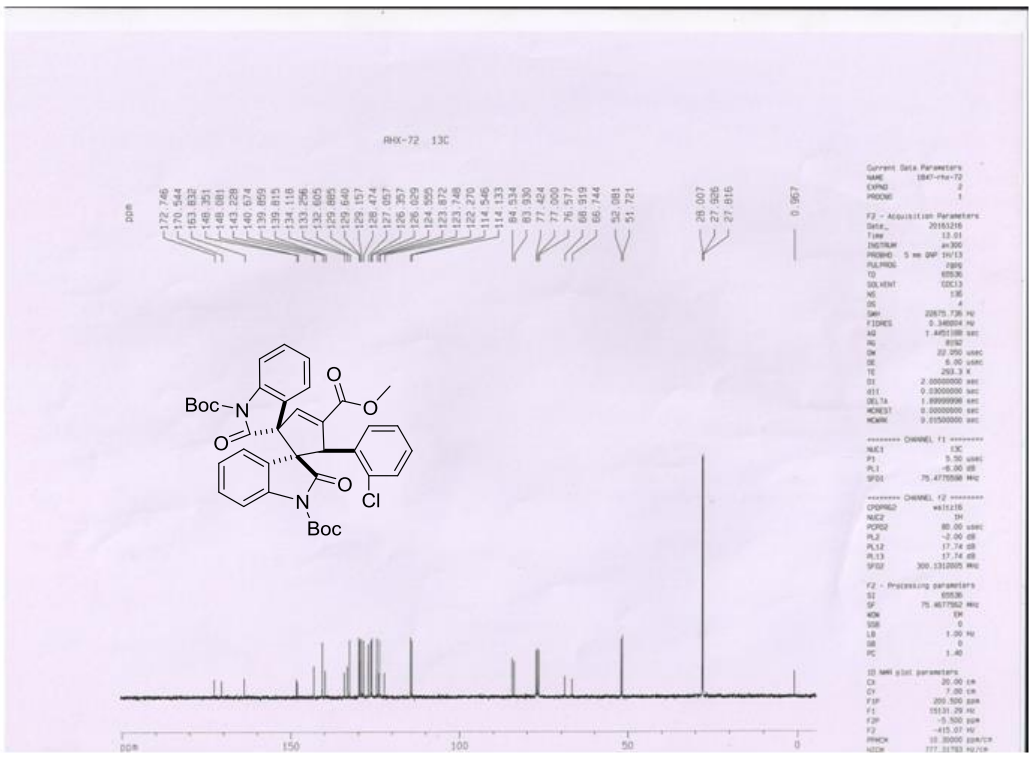


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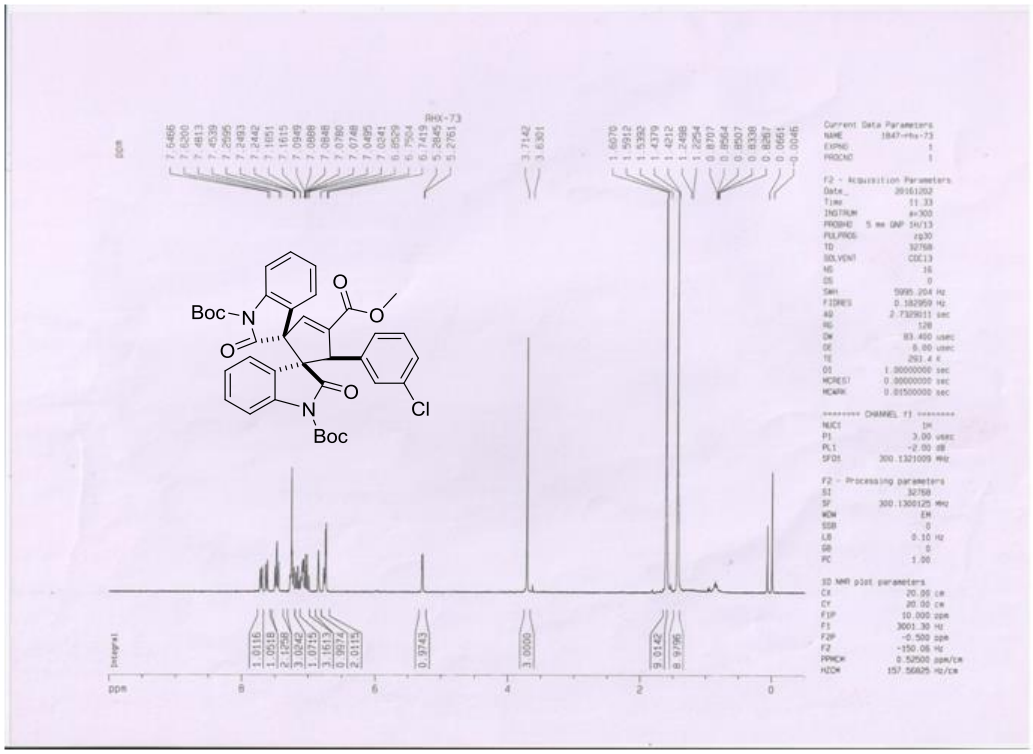

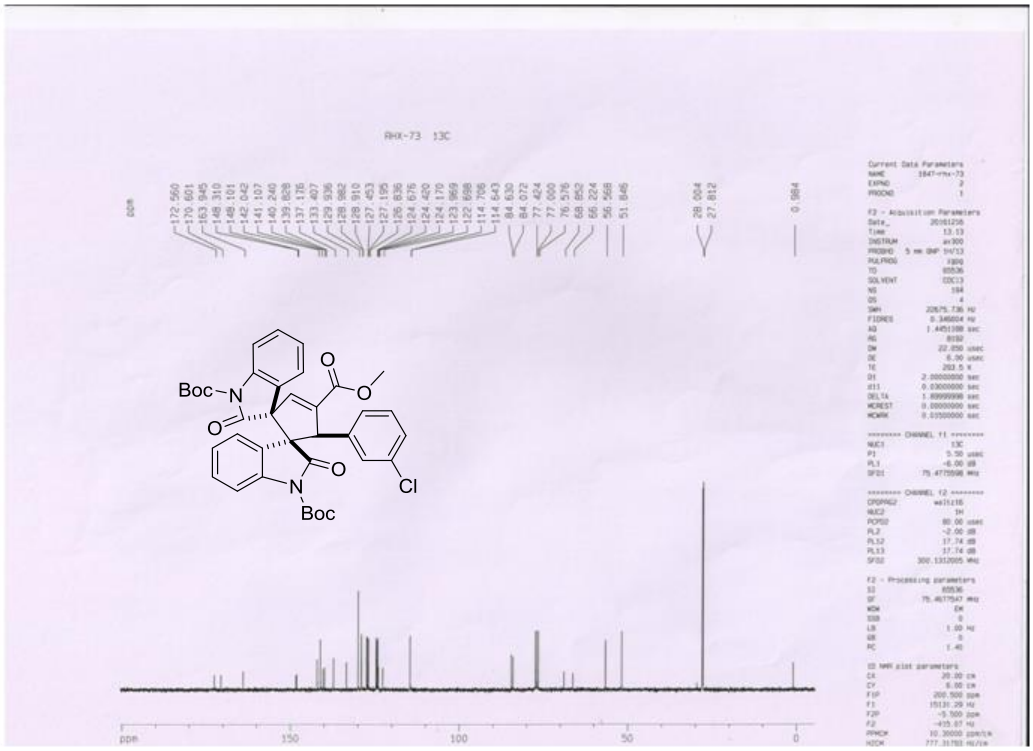


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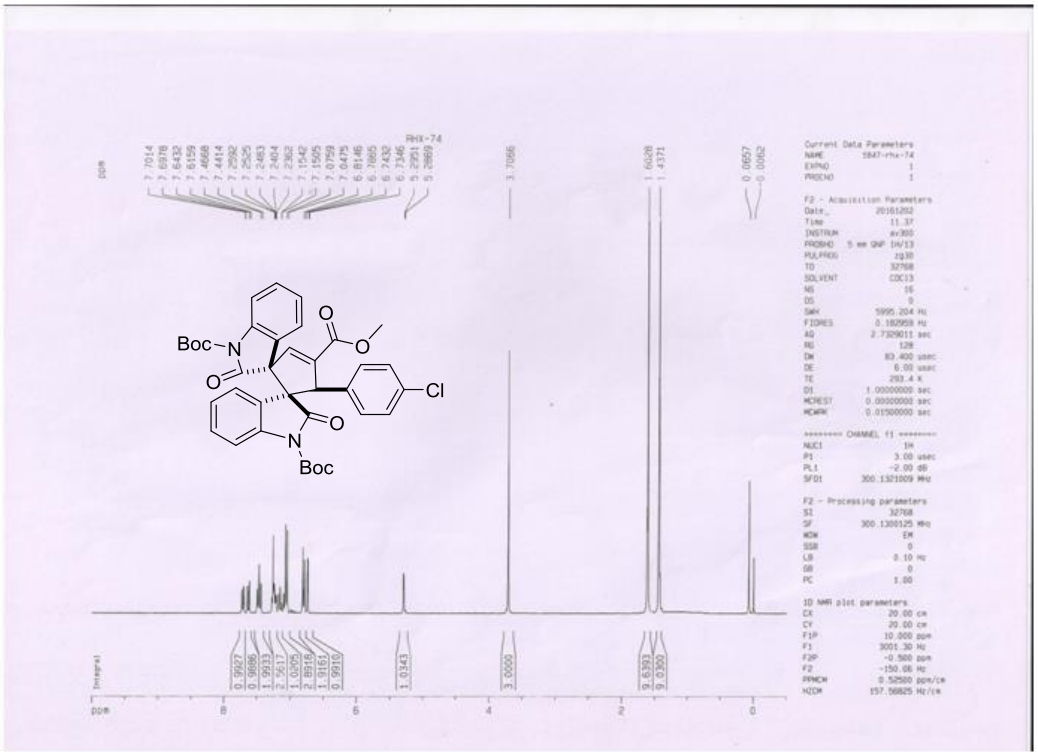

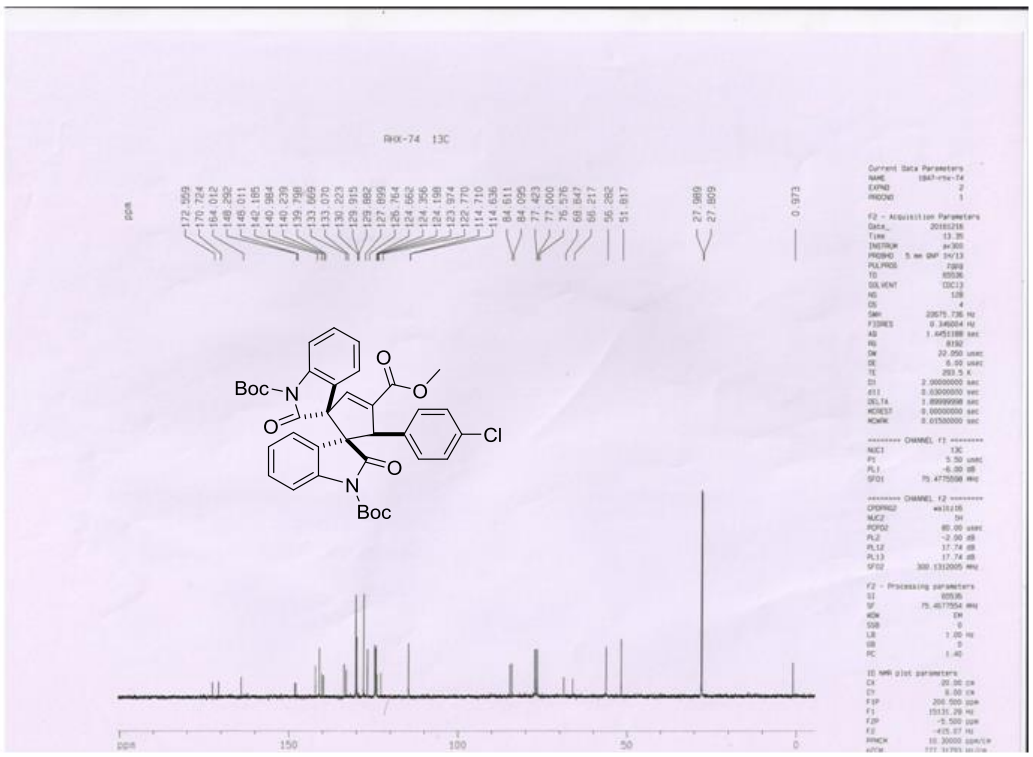


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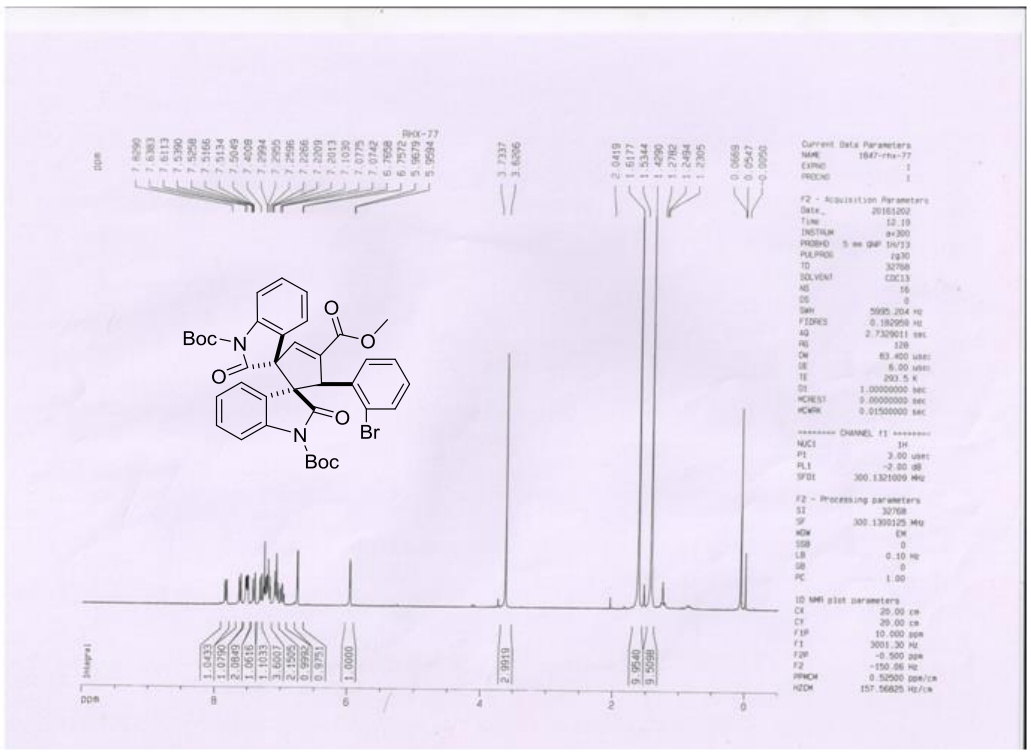

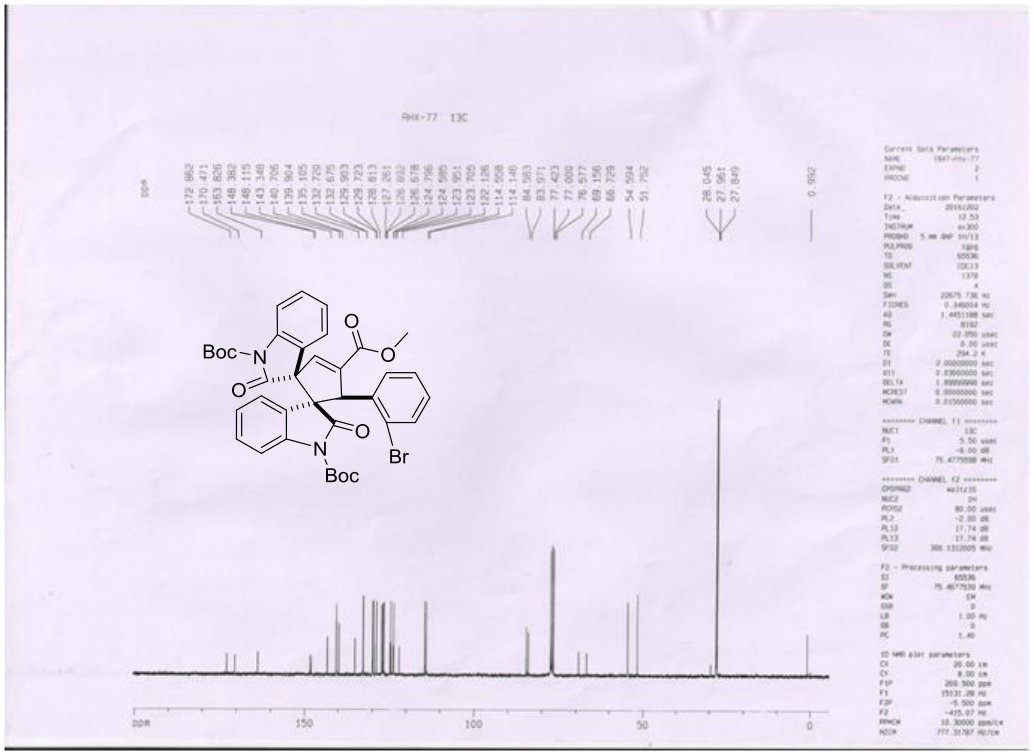


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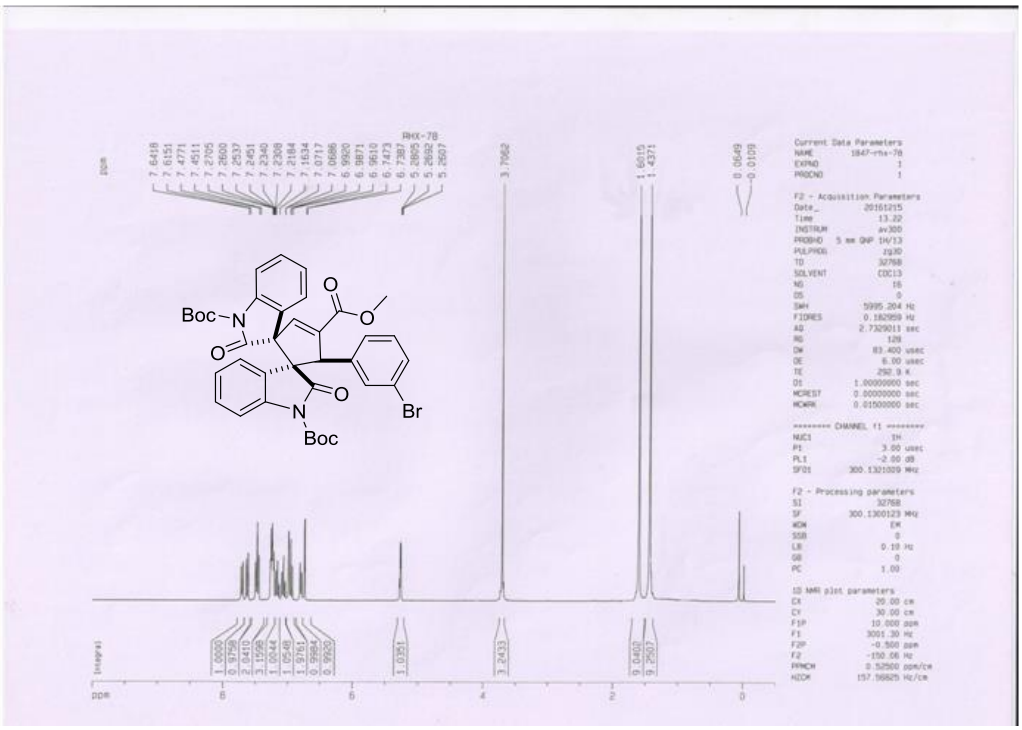
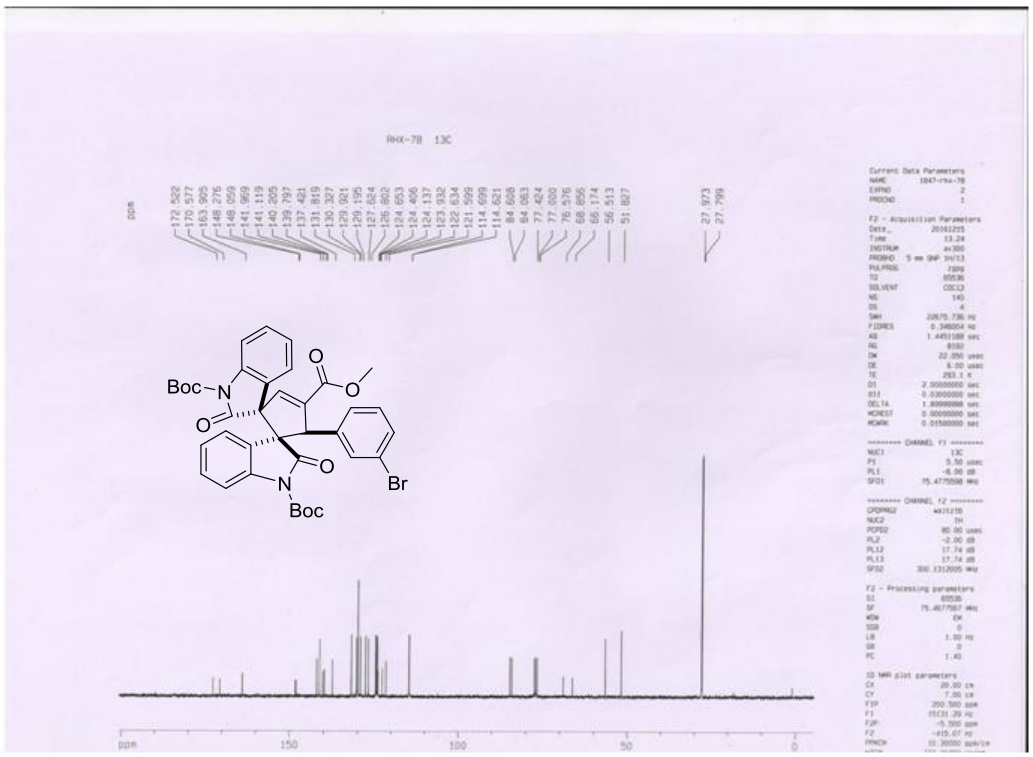
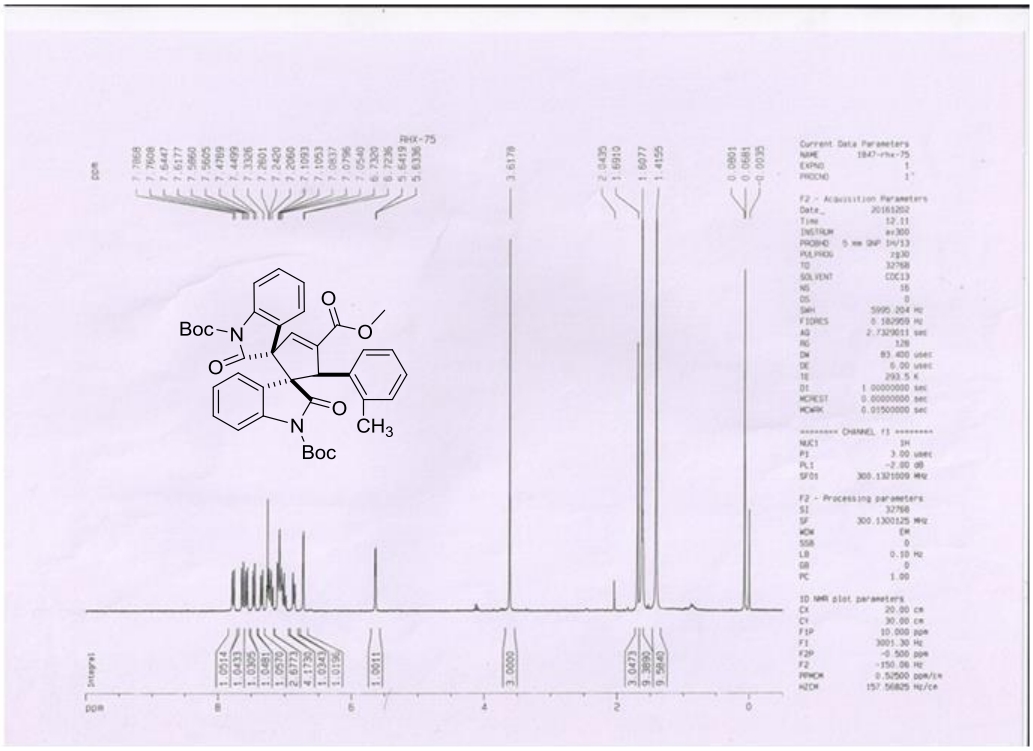
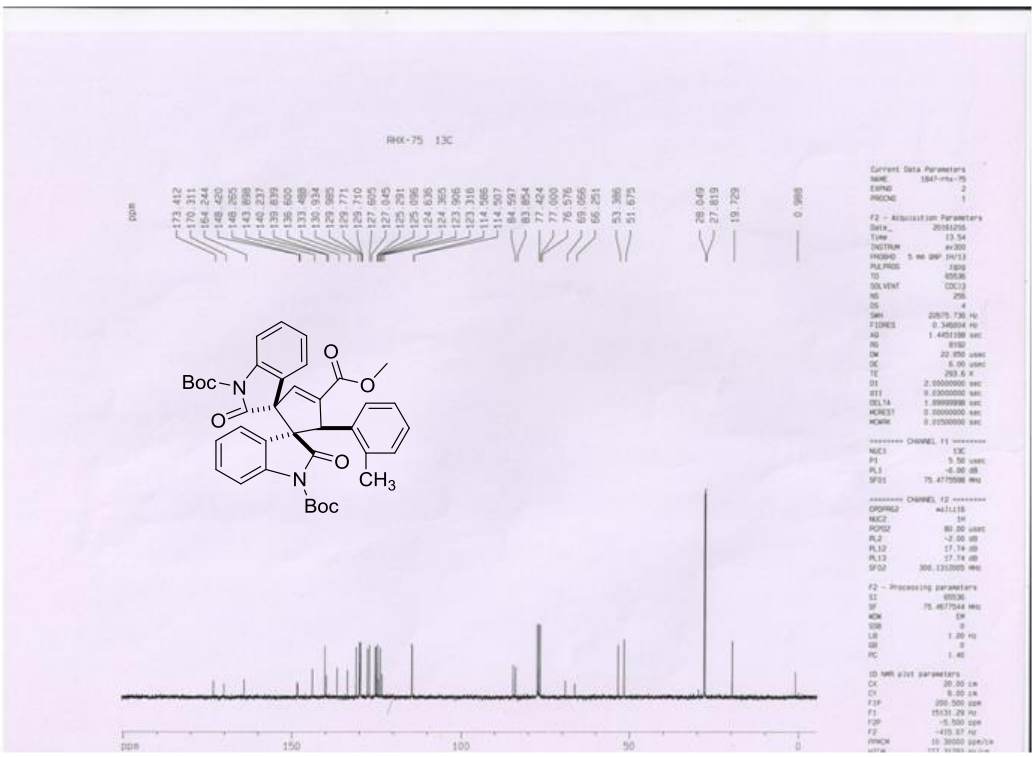



RHX-78 13C
Boc
N
O
O
O
O
N
Boc
Br
ppm
150
100
50
0

**Product 3i**


RHX-75
Boc
N
O
O
O
O
N
Boc
CH3
ppm
8
6
4
2
0
Integral



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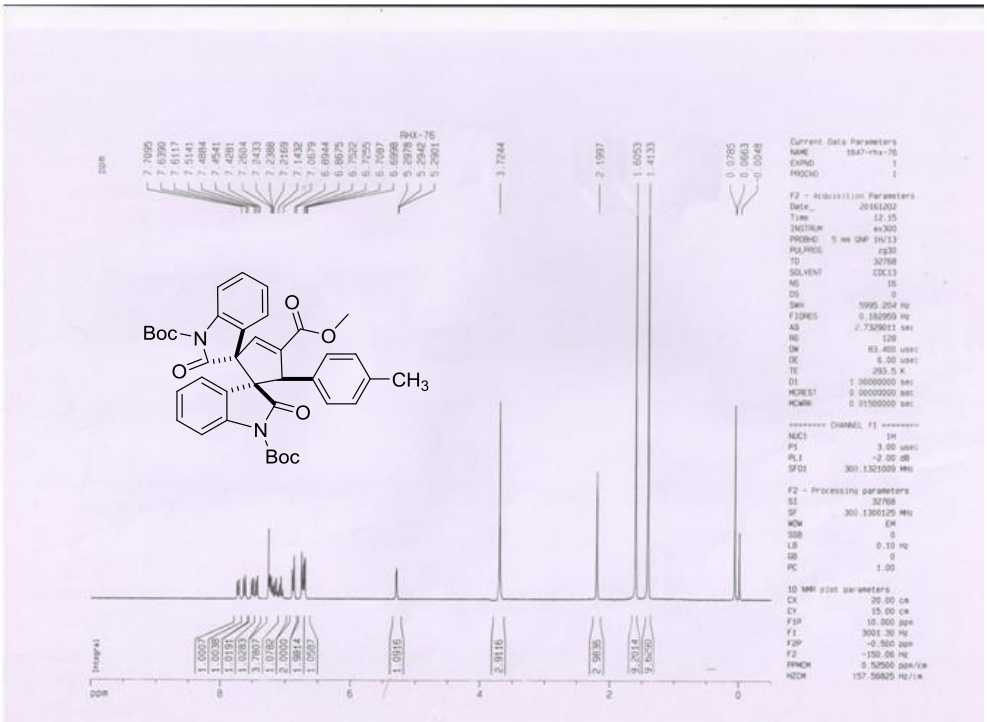
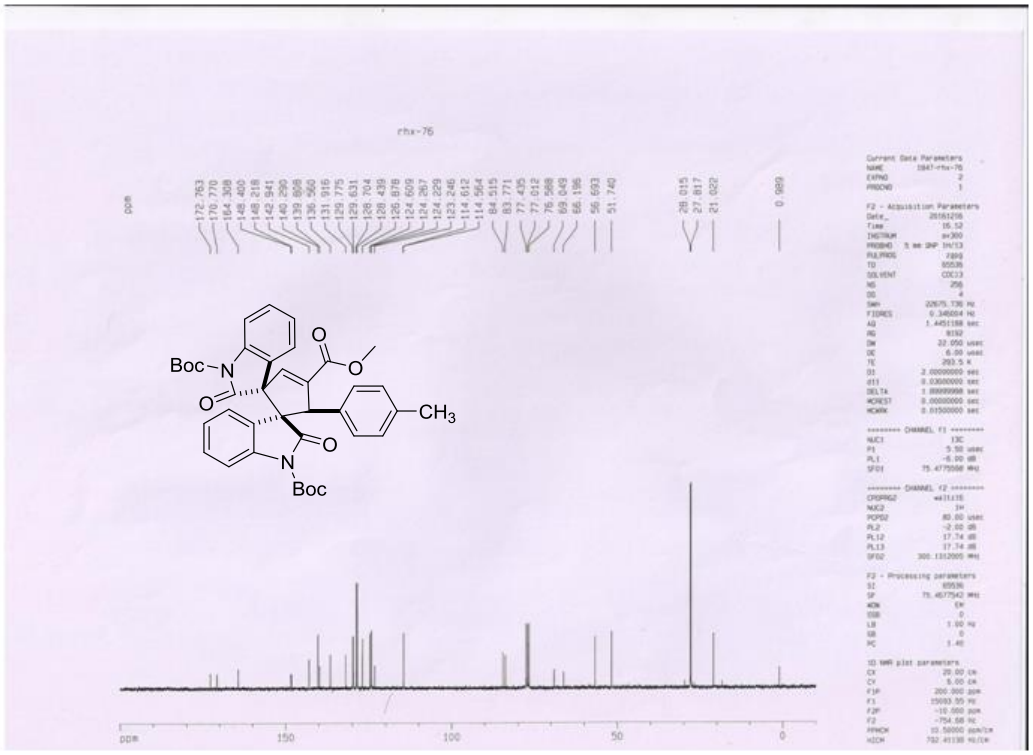
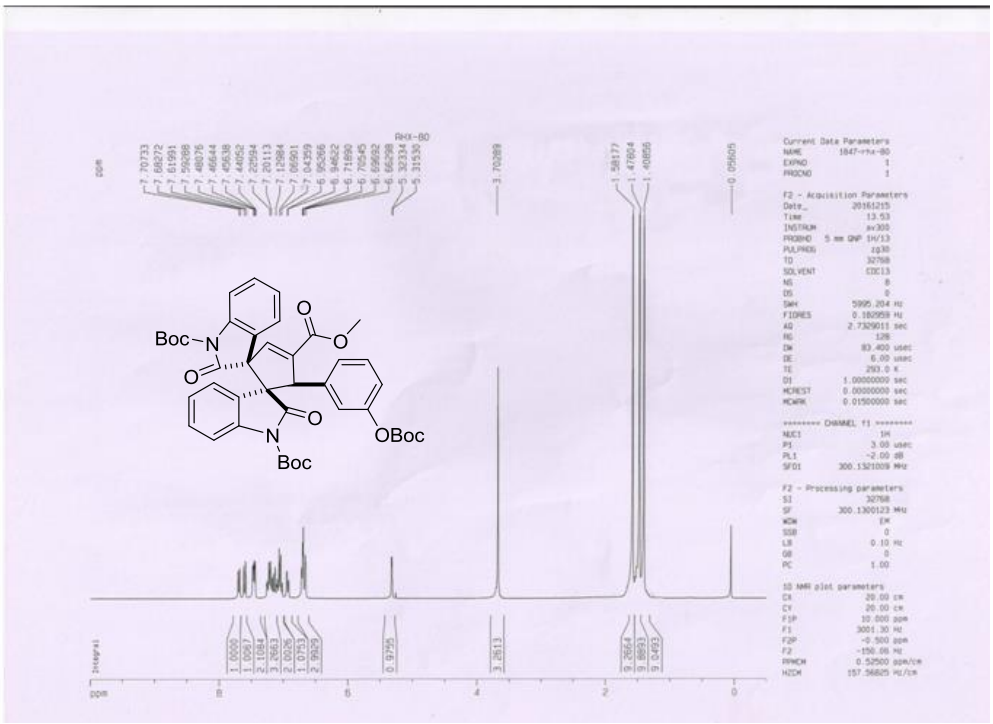
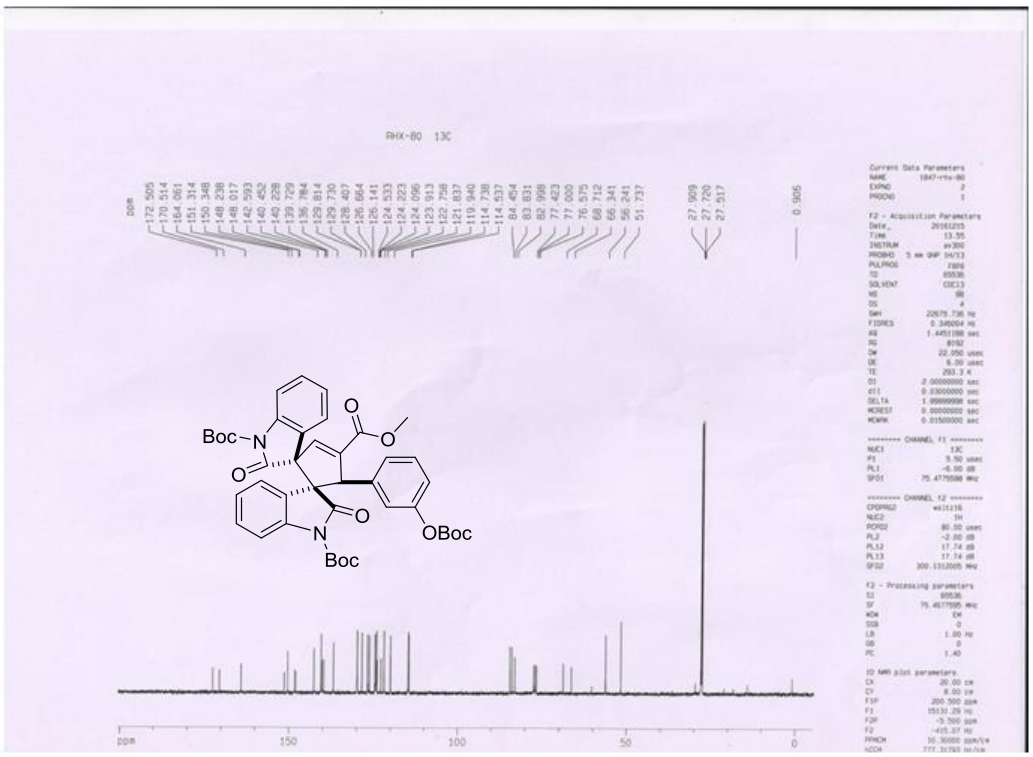


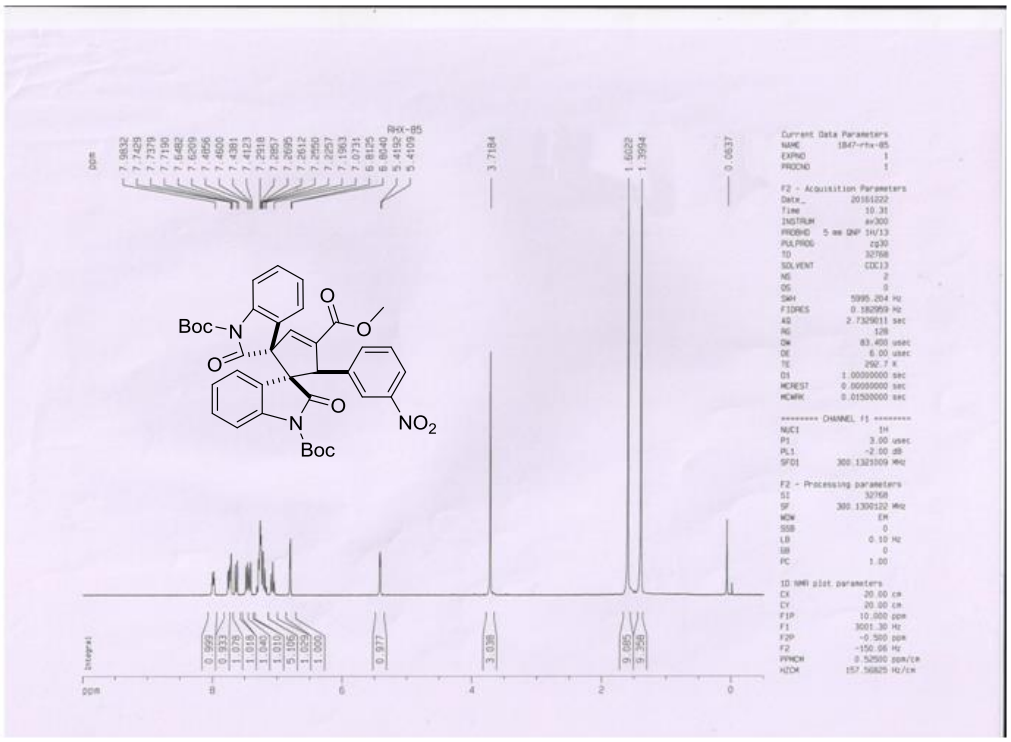


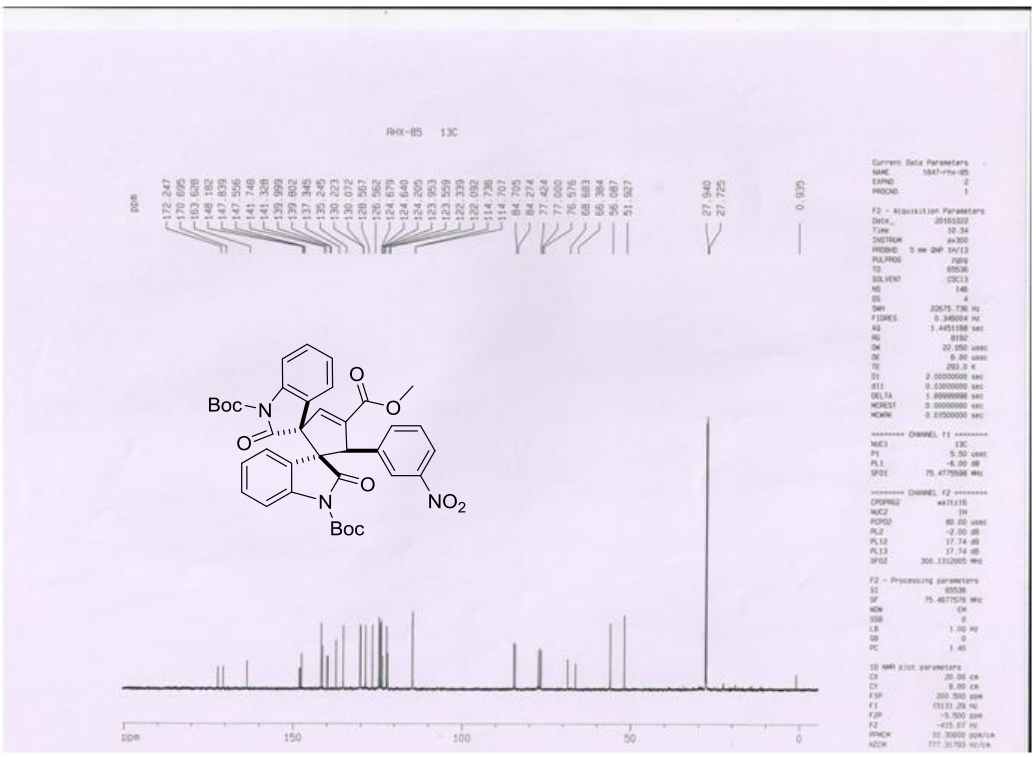
**Product 3k**



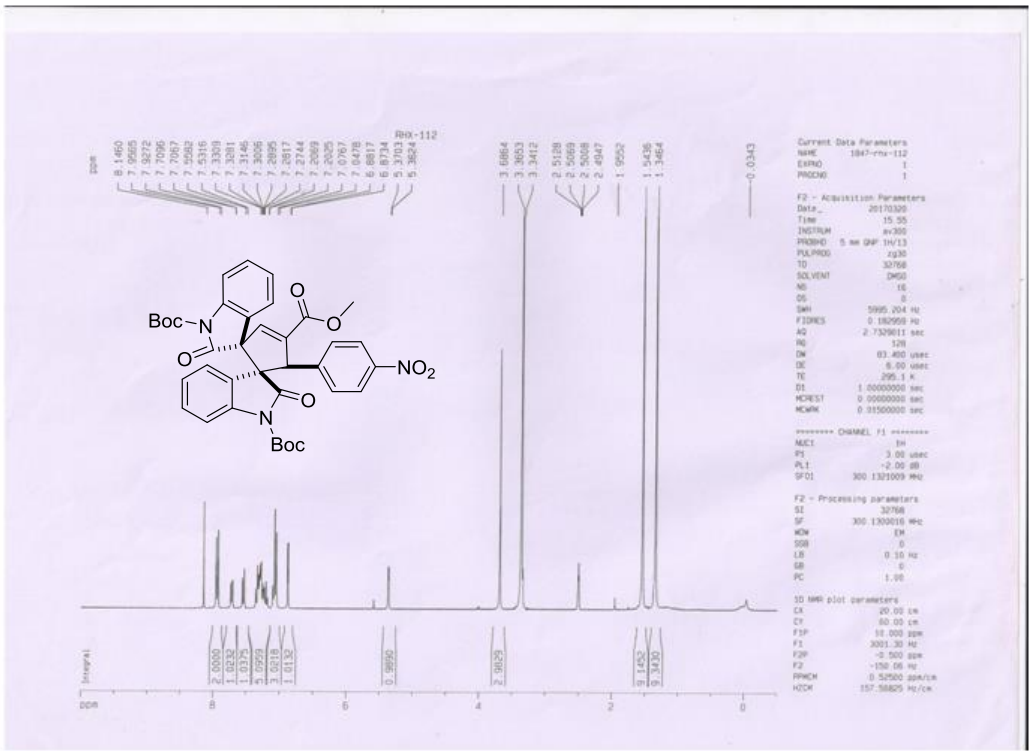

RHX-80 13C
Boc
N
O
O
O
O
N
Boc
OBoc
ppm
150
100
50
0

**Product 3l**


RHX-85
Boc
N
O
O
O
O
N
Boc
NO2
ppm
8
6
4
2
0


RHX-85 13C
Boc
N
O
O
O
O
N
Boc
NO2
ppm
150
100
50
0

**Product 3m**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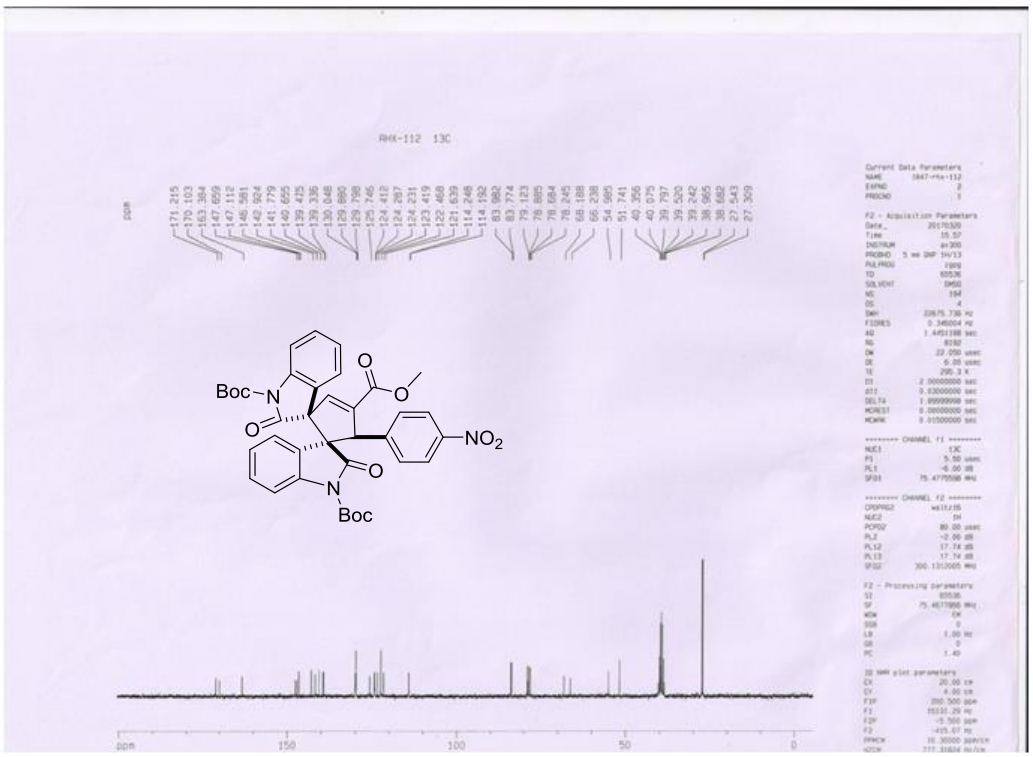
Boc
N
O
O
O
O
N
Boc
NO2
ppm
8
6
4
2
0
Integral

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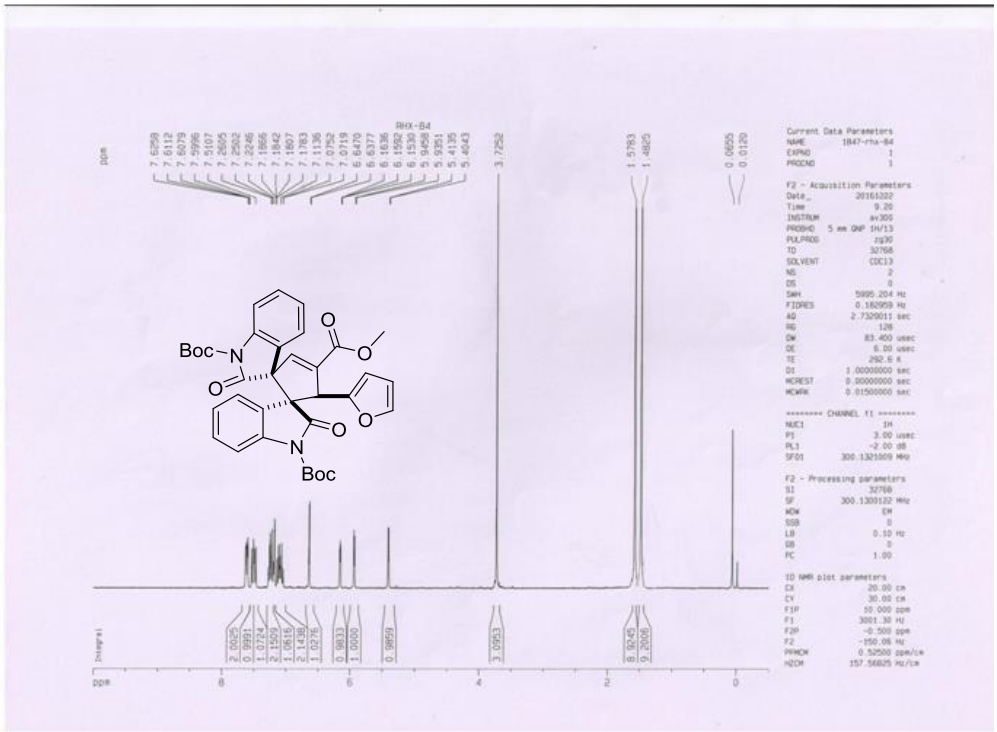

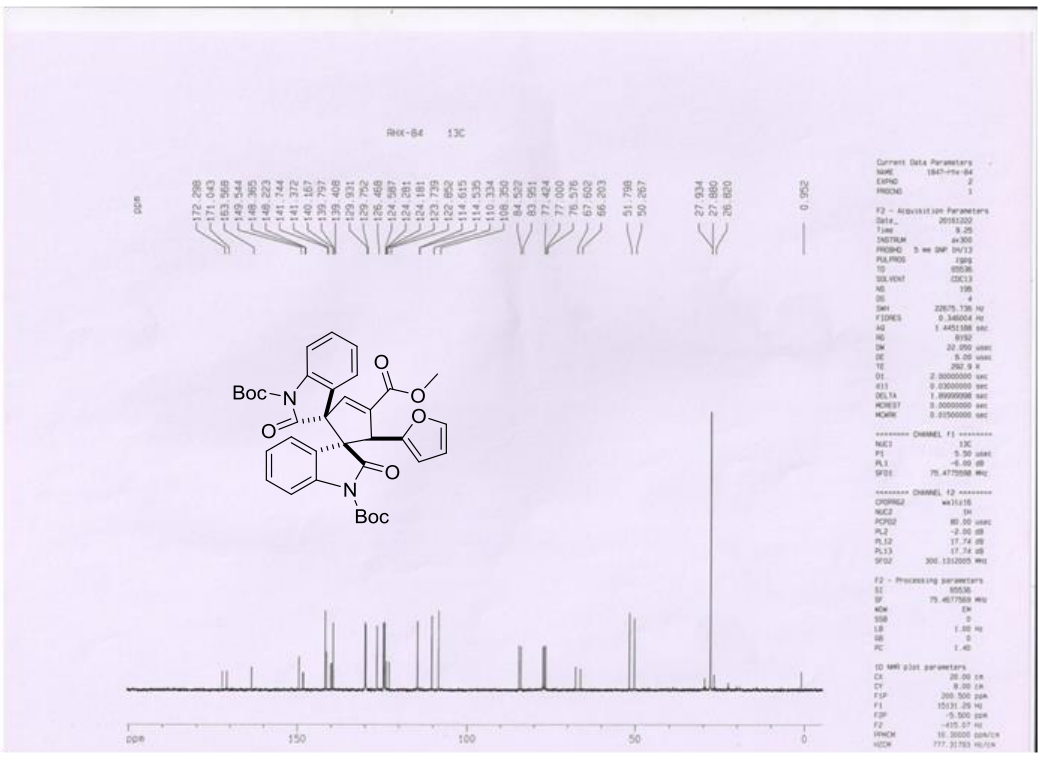
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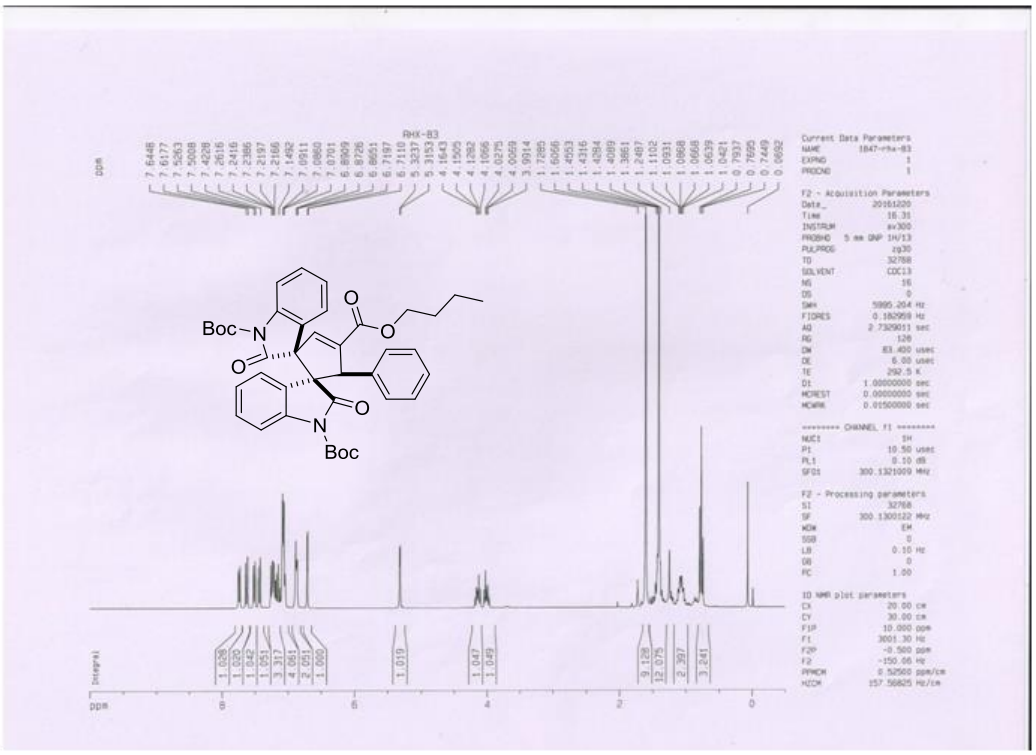
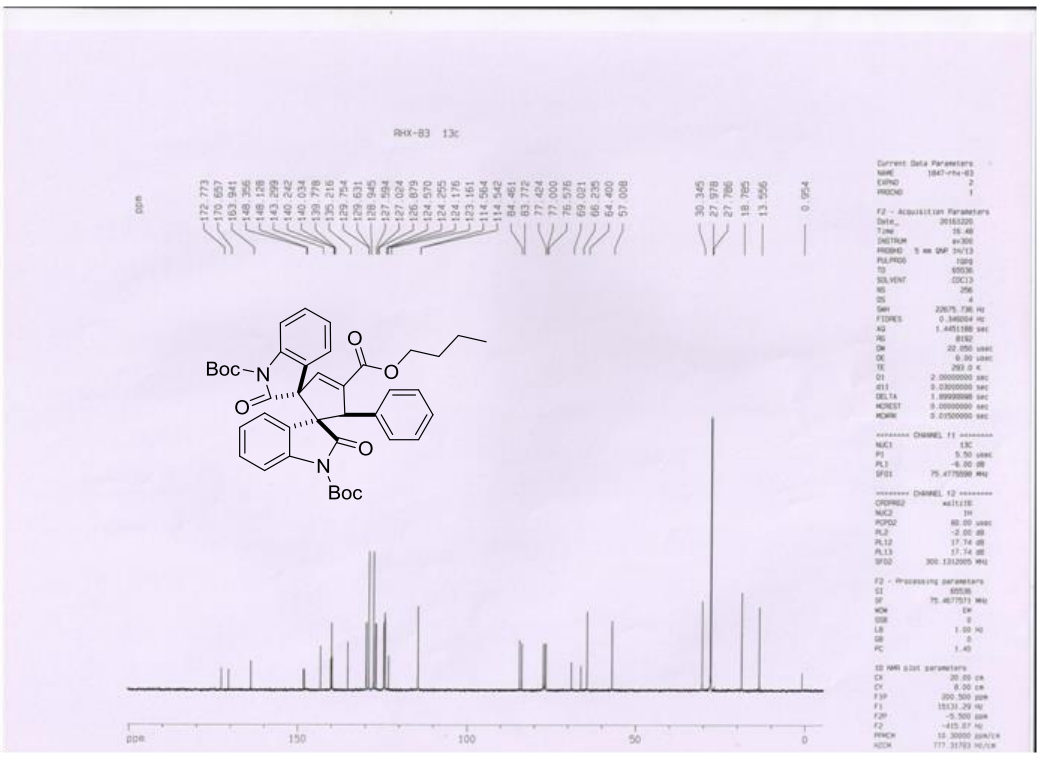
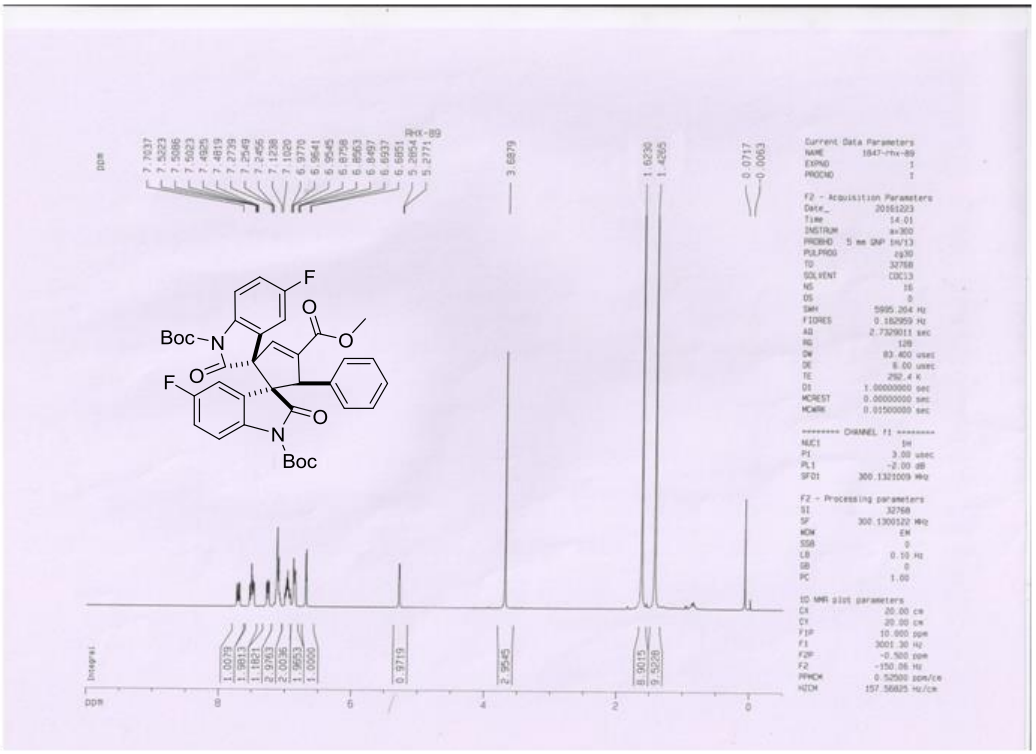
Boc
Boc
O
O
O
O
O
N
N
ppm
150
100
50
0

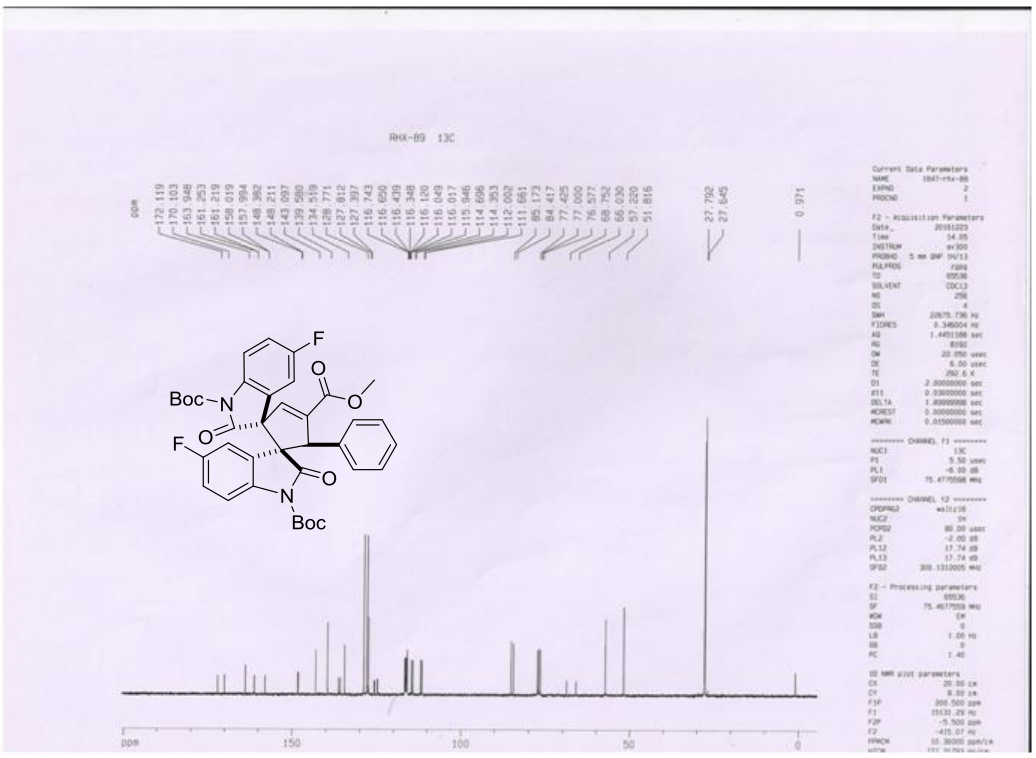
**Product 3o**


RHX-B3
Boc
Boc
O
O
O
O
O
N
N
ppm
8
6
4
2
0
Integral

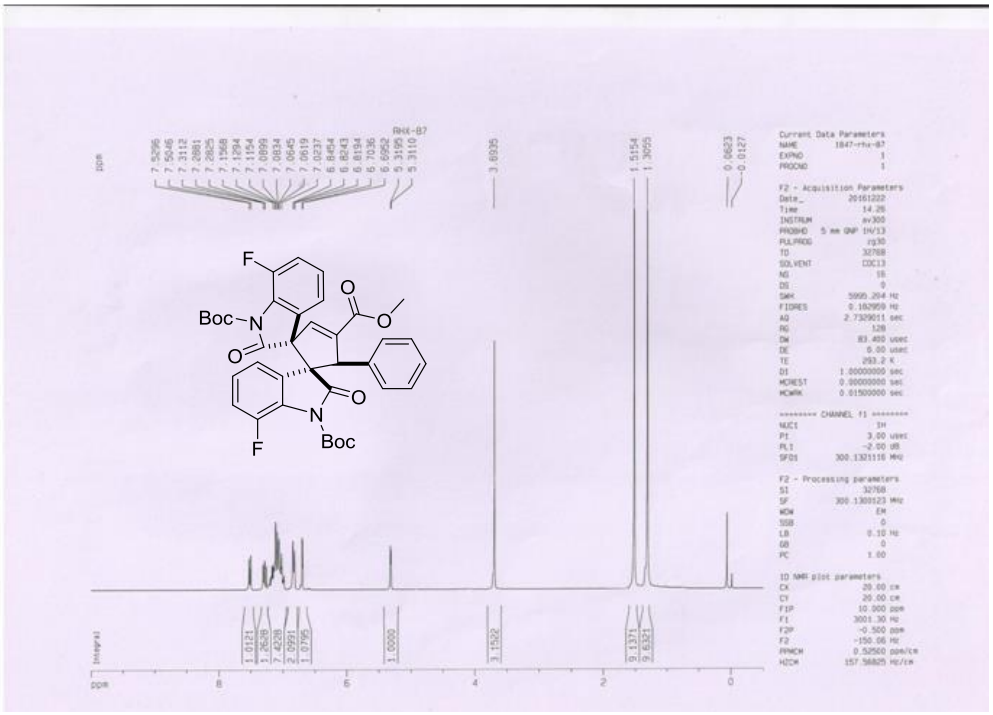


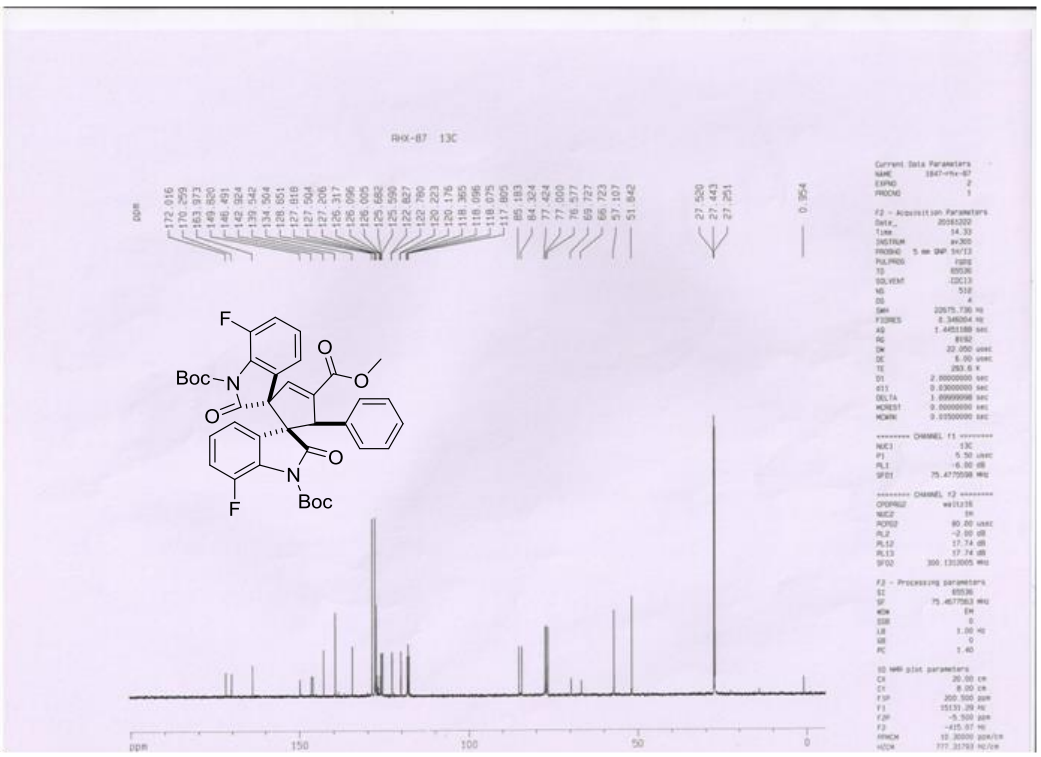
**Product 3p**






**Product 3q**





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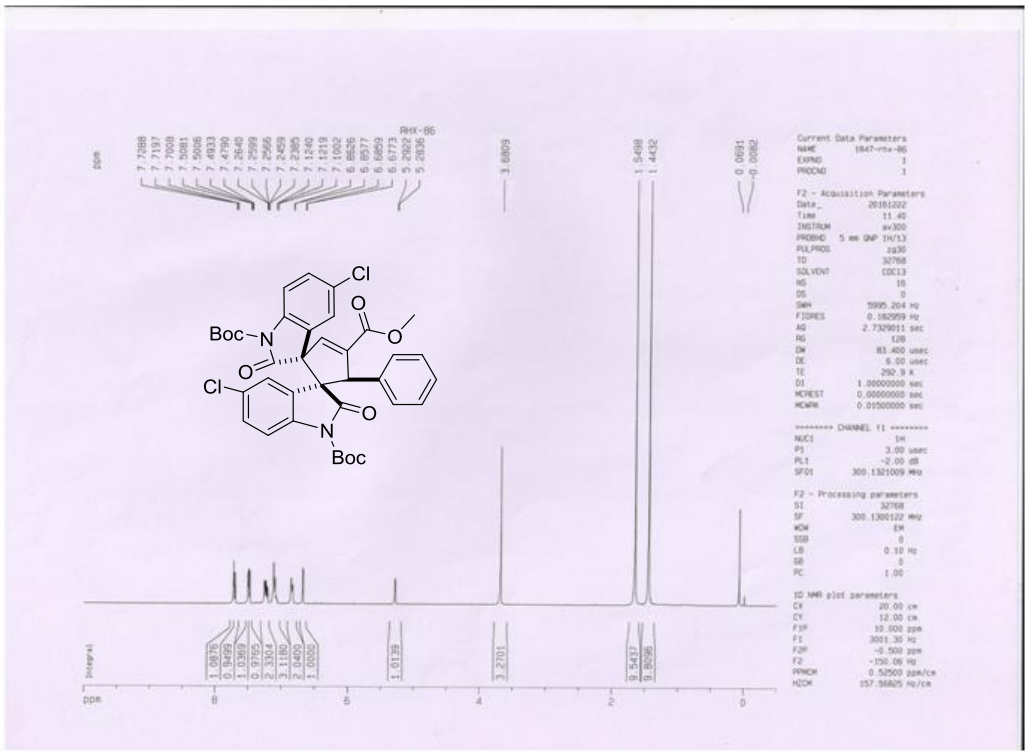
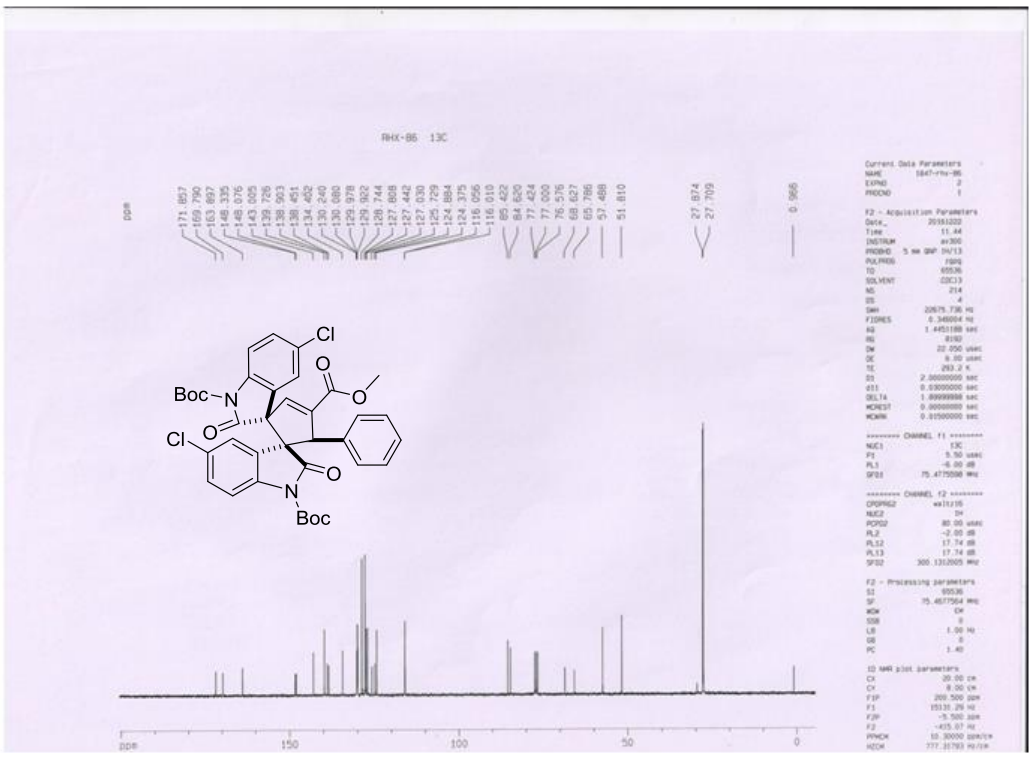
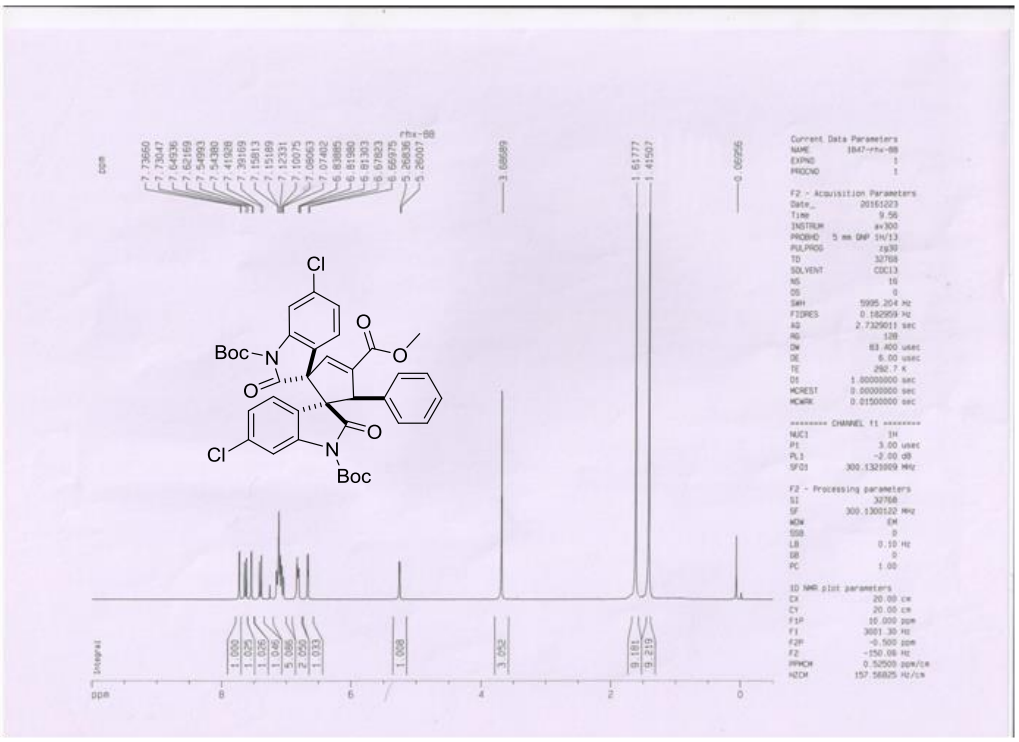
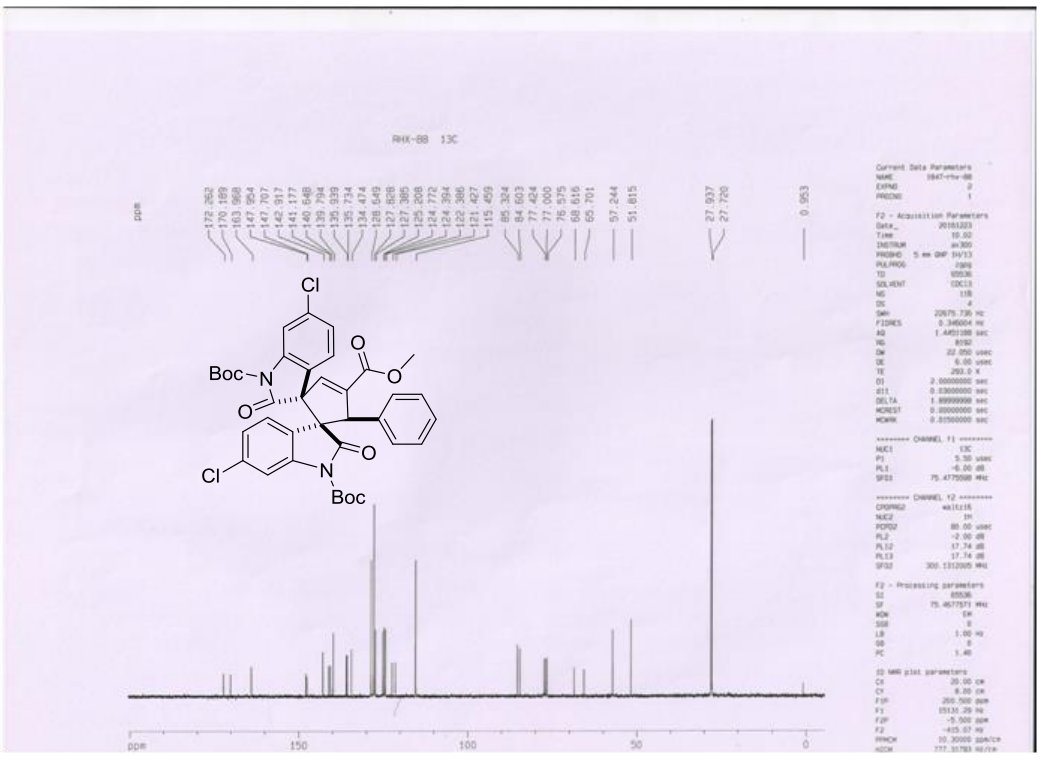


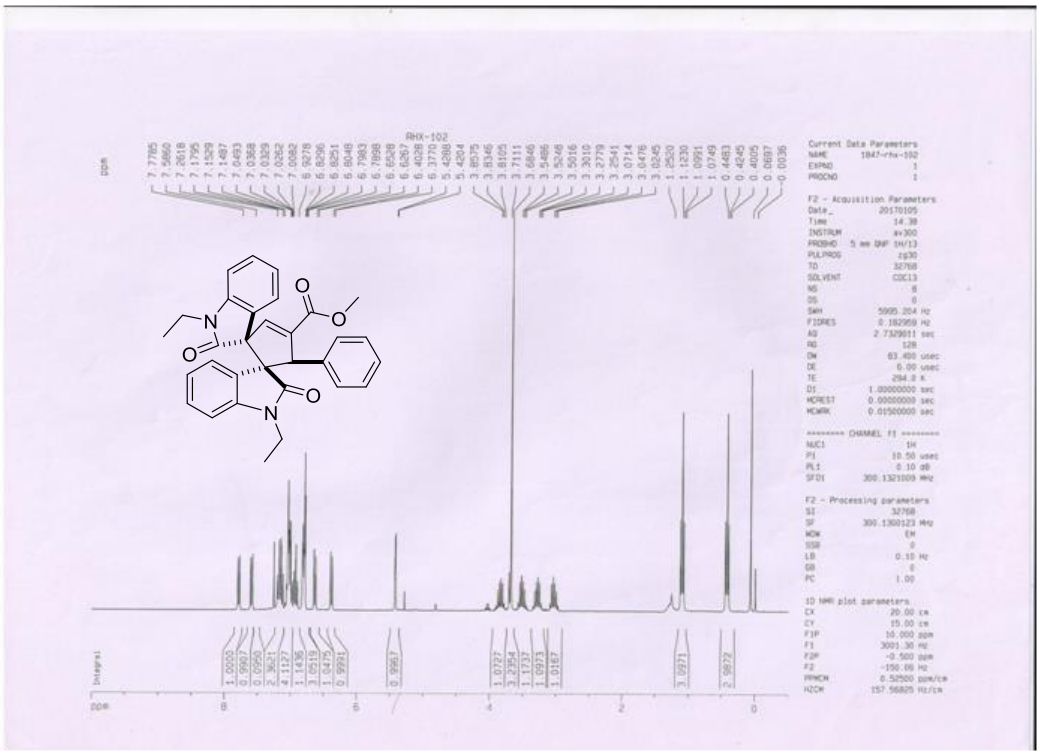


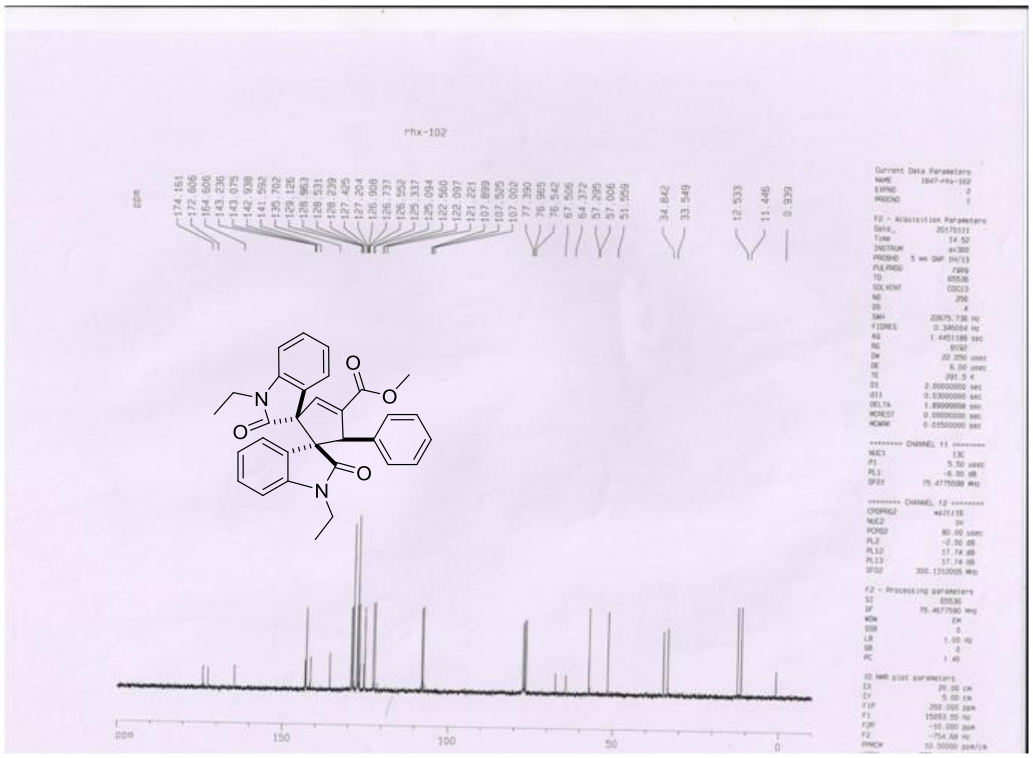
**Product 3s**



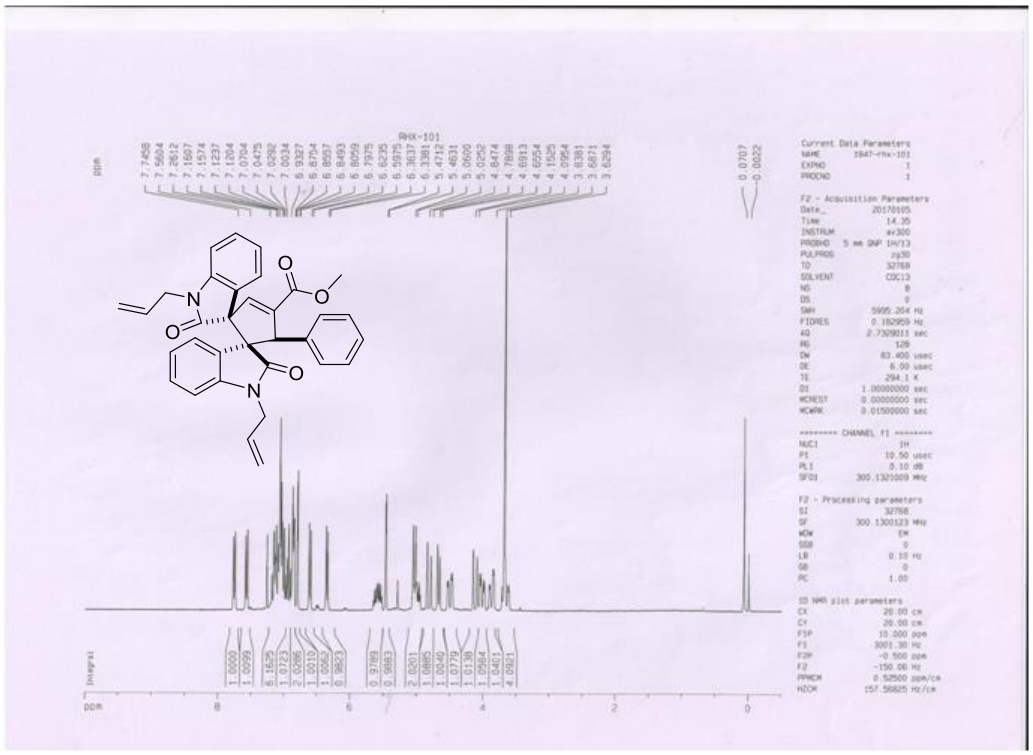


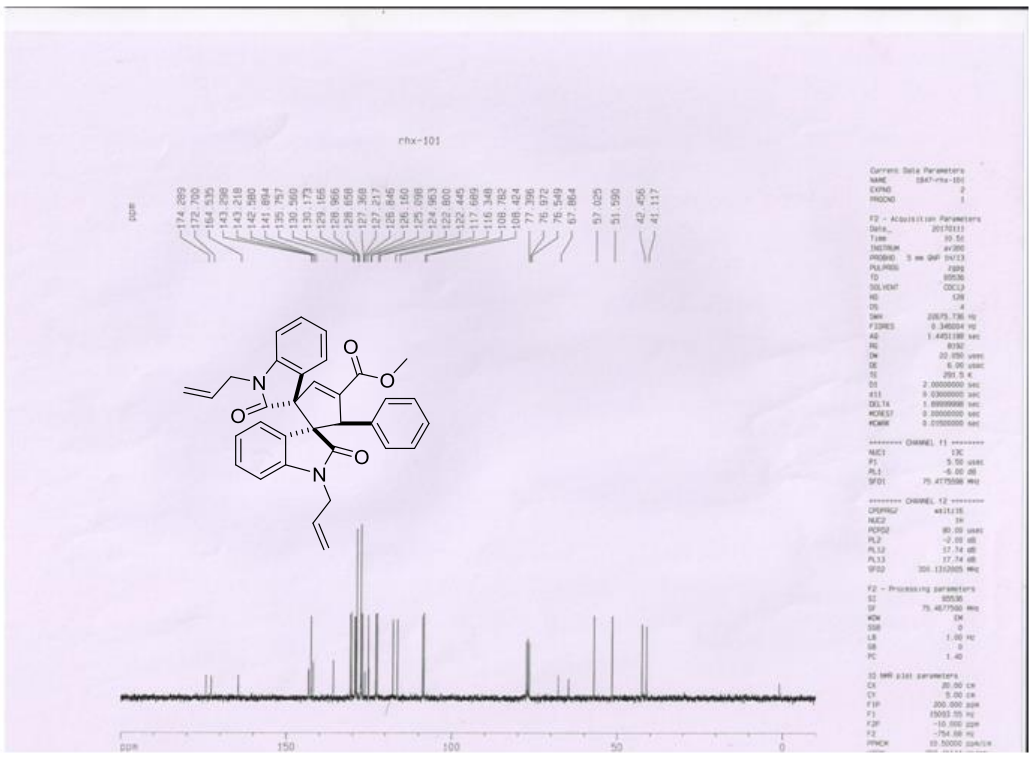
**Product 3t**



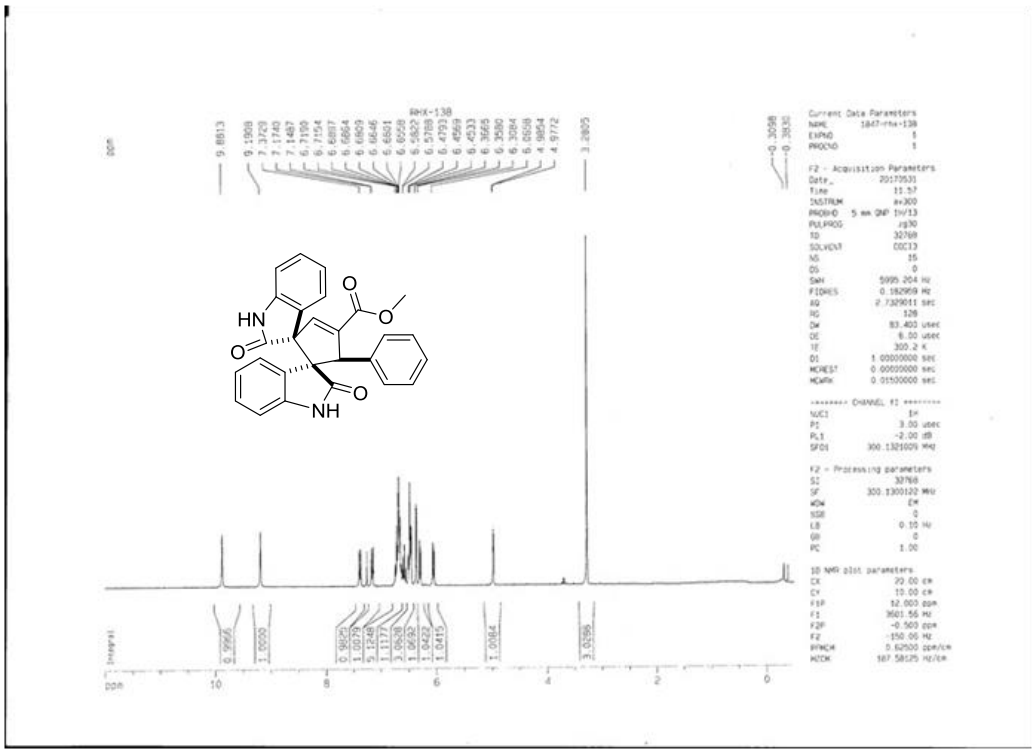


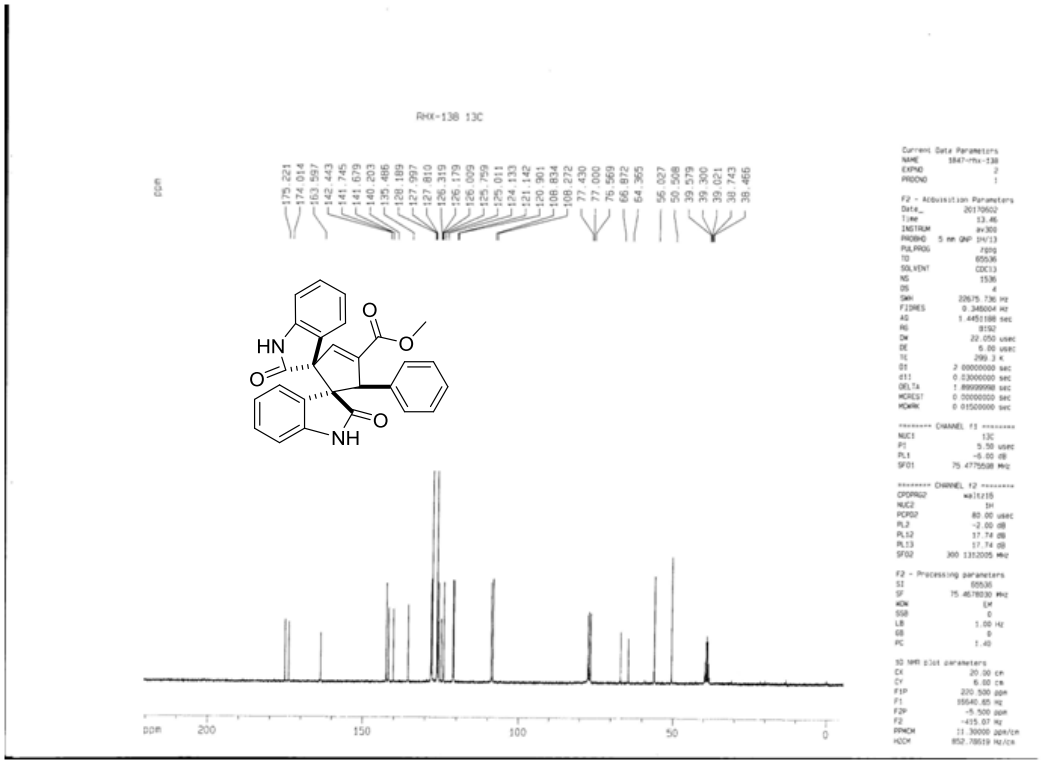
**Product 3w**





**Product 8**






[1] Y.-Y. Gui, J. Yang, L.-W. Qi, X. Wang, F. Tian, X.-N. Li, L. Peng and L.-X. Wang, *Org. Biomol. Chem.*, 2015, **13**, 6371.

[2] J. T. M. Correia, L. V. Acconcia, F. Coelho, *Eur. J. Org. Chem.,* 2016, 1972.