Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Organocatalytic Multicomponent Synthesis of Enantioenriched Polycyclic 1,2,3,4-Tetrahydropyridines: Key Substrate Selection Enabling Regio- and Stereoselectivities

Yohan Dudognon, Haiying Du, Jean Rodriguez, Xavier Bugaut, Thierry Constantieux

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1. GENERAL CONSIDERATIONS:

General Procedures. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Macherey-Nagel) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and to anisaldehyde (2.5 mL of *p*-anisaldehyde, 3 mL of concentrated H_2SO_4 and 1.5 mL of AcOH in 100 mL of EtOH) followed by heating. Flash column chromatography was performed using silica gel (35–70 μm, 60 Å, Acros).

Starting Materials. Unless specified, commercial reagents and solvents were used as received.

- β-Ketoamides were prepared according to known literature procedure.[1]
- (*E*)-Cinnamaldehyde was distilled just prior to use.
- Catalysts were purchased from Sigma-Aldrich.
- CH_2Cl_2 were dried using a M-Braun SPS-800 system.

Instrumentation.

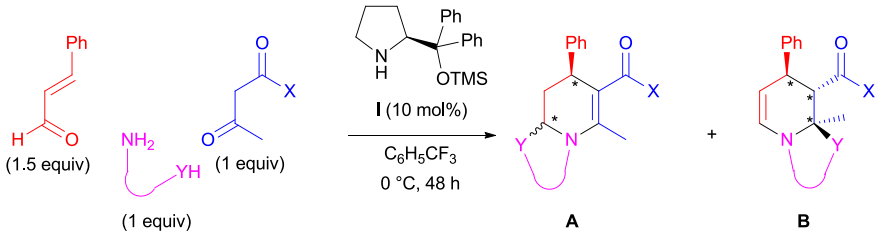
- Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Bruker AV 400 spectrometer. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ($CHCl_3$)). Data are reported as follows: chemical shift (multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sept = septuplet, m = multiplet), coupling constant(s) (Hz), integration).
- Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with Bruker AV 300 or AV 400 spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ 77.16 ($CHCl_3$)). Data are reported as follows: chemical shift (CH_n where n is the number of hydrogen atoms linked to the carbon atom).
- HPLC analyses for the determination of enantiomeric excesses were performed on a Merck-Hitachi system equipped with Chiralpak AD-H, Chiralcel OD-3, Chiralcel IF, Lux-Cellulose-4, Chiralpak IA, Chiralpak AZ-H, and Lux-Cellulose-2.
- Optical Rotations were recorded on a Anton Paar MCP 200 Polarimeter at 589 nm and 25 °C and specific rotations are reported as follows: specific rotation (concentration in grams/100 mL of solution, solvent).
- High resolution mass spectra (HRMS) were recorded on a Waters Synapt G2 HDMS apparatus using a positive electrospray (ESI) ionization source.

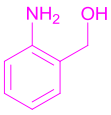
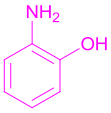
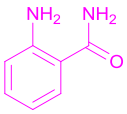
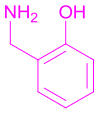
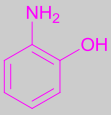
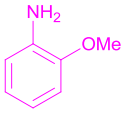
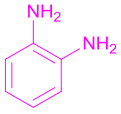
[1] H. Du, J. Rodriguez, X. Bugaut and T. Constantieux, *Chem. Eur. J.*, 2014, **20**, 8458-8466.

2. Optimization of Reaction Conditions:

2.1 Selection of the functionalized amine and β-dicarbonyl compound

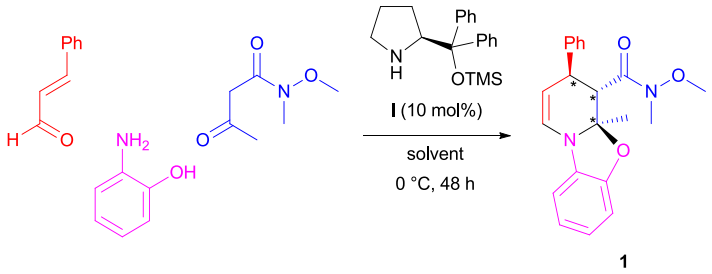
Our initial screening aimed at determining which substrates (functionalized amine and β-dicarbonyl compound) would be suitable to selectively deliver product **B**.



Entry	X	Functionalized amine	**A**; **B** (yield, *dr*, *ee*)
1	O*t*-Bu		complex mixture
2	O*t*-Bu		only **A** (27%, 1.3:1 *dr*, 88% *ee*)
3	O*t*-Bu		**A** (12%, 1.5:1 *dr*, n.d.*ee*); **B** (25%, >20:1 *dr*, 94% *ee*)
4	O*t*-Bu		complex mixture
5	O*t*-Bu		only **A** (76%, 1.8:1 *dr*, 94% *ee*)
6	N(Me)OMe		only **B (19%, >20:1 *dr*, n.d. *ee*)**
7	N(Me)OMe		complex mixture
8	N(Me)OMe		complex mixture

2.2 Solvents and ratio between the reactants

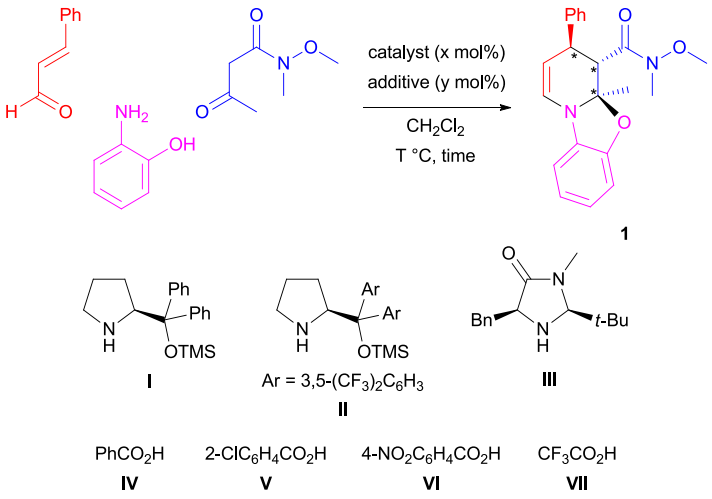
Having found suitable substrates for the selective formation of the 1,2,3,4-tetrahydropyridine regioisomers, we aimed to improve the yield. Changing for CH_2Cl_2 as the solvent was beneficial but modifications of the ratio between the reactants to fight the competing formation of the imine were useless.



Entry	Solvent	β-dicarbonyl/enal/ aminophenol	yield, *dr*, *ee*
1	$C_6H_5CF_3$	1:1.5:1	19%, >20:1 *dr*, n.d. *ee*
2	CH_2Cl_2	1:1.5:1	28%, >20:1 *dr*, 93% *ee*
3	CH_2Cl_2	1:1.5:1.5	23%, >20:1 *dr*, n.d. *ee*
4	CH_2Cl_2	1:3:3	30%, >20:1 *dr*, n.d. *ee*

2.3 Catalysts, additives, temperature and reaction time

To improve the yield of product, different aminocatalysts and additives (acids and water) were evaluated, showing that a combination of catalyst **I** (20 mol%) and BzOH (40 mol%) was the best one. Reaction temperature and time were also optimized. To finish with, a two-fold excess of β-ketoamide had no noticeable impact on the reaction outcome.



Entry	Catalyst (x mol%)	Additive (y mol%)	Temperature	Time	yield, *dr*, *ee*
1	**I** (10 mol%)	none	0 °C	48 h	28%, >20:1 *dr*, 93% *ee*
2	**I** (10 mol%)	**IV** (20 mol%)	0 °C	24 h	32%, >20:1 *dr*, 95% *ee*
3	**I** (20 mol%)	**IV** (40 mol%)	0 °C	24 h	36%, >20:1 *dr*, n.d. *ee*
4	**I** (20 mol%)	**IV** (40 mol%)	0 °C	96 h	52%, >20:1 *dr*, 95% *ee*
5	**I** (20 mol%)	**IV** (100 mol%)	0 °C	96 h	52%, >20:1 *dr*, n.d. *ee*
6	**I** (20 mol%)	**IV** (40 mol%)	10 °C	24 h	36%, >20:1 *dr*, 94% *ee*
7	**I** (20 mol%)	**IV** (40 mol%)	25 °C	48 h	51%, >20:1 *dr*, 91% *ee*
8	**I** (20 mol%)	**IV** (40 mol%)	10 °C	60 h	60%, >20:1 *dr*, 94% *ee*
9	**II** (20 mol%)	**IV** (40 mol%)	10 °C	24 h	23%, >20:1 *dr*, n.d. *ee*
10	**III** (20 mol%)	**IV** (40 mol%)	10 °C	24 h	6%, >20:1 *dr*, n.d. *ee*
11	**I** (20 mol%)	**V** (40 mol%)	10 °C	24 h	28%, >20:1 *dr*, n.d. *ee*
12	**I** (20 mol%)	**VI** (40 mol%)	10 °C	60 h	37%, >20:1 *dr*, n.d. *ee*
13	**I** (20 mol%)	**V** (40 mol%)	10 °C	60 h	12%, >20:1 *dr*, n.d. *ee*
14	**I** (20 mol%)	**IV** (40 mol%) +water (0.1 mL)	10 °C	60 h	44%, >20:1 *dr*, 93% *ee*
15[a]	**I** (20 mol%)	**IV** (40 mol%)	10 °C	60 h	55%, >20:1 *dr*, 92% *ee*

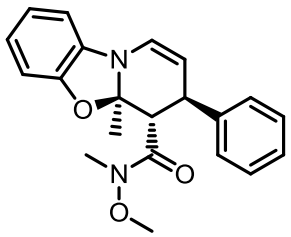
[a]Two equivalent of β-ketoamide were used.

3. GENERAL PROCEDURE, SYNTHESIS AND CHARACTERIZATION OF PRODUCTS:

3.1 General procedure for the three-component reactions:

β-ketoamides (0.2 mmol, 1 equiv), cinnamaldehyde derivatives (0.3 mmol, 1.5 equiv), aminophenol substrates (0.2 mmol, 1equiv) and benzoic acid (0.08 mmol, 0.4 equiv) were dissolved in 2 mL of dry dichloromethane under argon and placed at 10 °C. Then, the Hayashi-Jørgensen catalyst (0.04 mmol, 0.2 equiv) was added to the mixture. After 60 h, around ten drops of NH_4Cl were added to the reaction mixture to deactivate the catalyst. The organic phase was then separated and concentrated under vacuum. The diastereomeric ratio of the crude product was determined by ^1H NMR. Purification over silica gel (dichloromethane/ethyl acetate 100:0.5 (unless specified otherwise)) directly yielded the corresponding three-component product.

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-phenyl-4,4*a*-dihydro-3*H*-benzo [4,5]oxazolo [3,2-*a*]pyridine-4-carboxamide 1

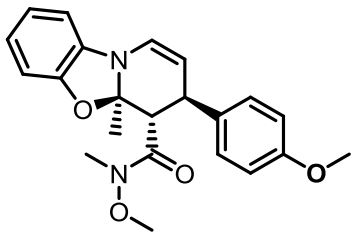


60% yield, dr > 20:1, 94% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), *(2E)*-cinnamaldehyde (39.7 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **1** was isolated as an orange solid (42.0 mg, 0.120 mmol, 60% yield, 94% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.35 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40 – 7.28 (m, 5H), 6.97 – 6.92 (m, 1H), 6.84 – 6.69 (m, 4H), 5.05 (dd, *J* = 7.6, 1.9 Hz, 1H), 4.12 (d, *J* = 11.5 Hz, 1H), 3.76 (d, *J* = 11.5 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 1.87 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.3 (C), 149.5 (C), 142.0 (C), 134.7 (C), 128.5 (2 CH), 128.2 (2 CH), 127.2 (CH), 123.9 (CH), 121.5 (CH), 119.9 (CH), 108.5 (CH), 107.3 (CH), 106.7 (CH), 100.7 (C), 61.1 (CH_3), 48.8 (CH), 43.2 (CH), 32.1 (CH_3), 20.9 (CH_3).
HRMS (ESI) calc´d for $[C_{21}H_{22}N_2O_3+H]^+$: 351.1703, found: 351.1703.
HPLC Chiralpak AZ-H, Heptane/Isopropanol 90:10, 1 mL/min, λ = 254 nm, τ_{minor} = 7.53 min τ_{major} = 8.36 min.
$[\alpha]_D^{20}$ = 151 (c 0.100, $CHCl_3$).
m.p. = 72-73 °C.

(3*R*,4*S*,4*aR*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*,4*a*-dimethyl-4,4*a*-dihydro-3*H*-benzo [4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 2

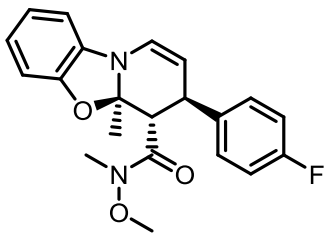


41% yield, dr > 20:1, 82% ee

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), trans-4-methoxycinnamaldehyde (48.7 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product**2** was isolated as an orange oil (31.0 mg, 0.081 mmol, 41% yield, 82% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.35 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.16 (d, *J* = 8.6 Hz, 2H), 6.83 (td, *J* = 7.4, 2.2 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.71 – 6.63 (m, 3H), 6.60 (dd, *J* = 7.7, 1.9 Hz, 1H), 4.90 (dd, *J* = 7.6, 1.7 Hz, 1H), 3.96 (d, *J* = 11.7 Hz, 1H), 3.76 (s, 3H), 3.61 (d, *J* = 11.5 Hz, 1H), 3.29 (s, 3H), 3.02 (s, 3H), 1.74 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.3 (C), 158.6 (C), 149.4 (C), 134.6 (C), 133.8 (C), 129.1 (2 CH), 123.6 (CH), 121.3 (CH), 119.8 (CH), 113.7 (2 CH), 108.4 (CH), 107.6(CH), 106.6 (CH), 100.6 (C), 61.1 (CH_3), 55.2 (CH_3), 48.8 (CH), 42.3 (CH), 32.0 (CH_3), 20.9 (CH_3).
HRMS (ESI) calc´d for $[C_{22}H_{24}N_2O_4+H]^+$: 381.1809, found: 381.1808.
HPLC Chiralpak AD-H, Heptane/Isopropanol 90:10, 1 mL/min, λ = 254 nm, τ_{minor} = 6.32 min τ_{major} = 8.27 min.
$[\alpha]_D^{25}$ = 33.9 (c 0.065, $CHCl_3$).

(3*R*,4*S*,4*aR*)-3-(4-fluorophenyl)-*N*-methoxy-*N*,4*a*-dimethyl-4,4*a*-dihydro-3*H*-benzo[4,5] oxazolo[3,2-*a*]pyridine-4-carboxamide 3



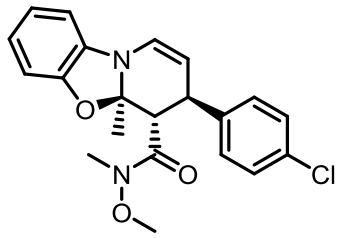
45% yield, dr > 20:1, 86% ee

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-fluorophenyl)prop-2-enal (45.0 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200

mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **3** was isolated as an orange oil (33.0 mg, 0.090 mmol, 45% yield, 86% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.43 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.93 (t, *J* = 8.7 Hz, 2H), 6.83 (td, *J* = 7.3, 1.7 Hz, 1H), 6.72 – 6.60 (m, 4H), 4.88 (dd, *J* = 7.6, 1.8 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.60 (d, *J* = 11.6 Hz, 1H), 3.32 (s, 3H), 3.01 (s, 3H), 1.74 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.2 (C), 162.0 (d, $^{1}J_{CF}$ = 245.0 Hz, CF), 149.5 (C), 137.6 (d, $^{4}J_{CF}$ = 3.1 Hz, C). 134.5 (C), 129.8 (d, $^{3}J_{CF}$= 8.1 Hz, 2 CH),124.0 (CH), 121.5 (CH), 120.1 (CH), 115.4 (d, $^{2}J_{CF}$= 21.3 Hz, 2 CH), 108.6 (CH), 106.9 (CH), 106.8 (CH), 100.6 (C), 61.1 (CH_3), 48.9 (CH), 42.5 (CH), 32.1 (CH_3), 20.9 (CH_3).
HRMS (ESI) calc´d for $[C_{21}H_{21}N_2O_3F+H]^+$: 369.1609, found: 369.1606.
HPLC Chiralpak IF, Heptane/Isopropanol 95:5, 1 mL/min, λ = 254 nm, τ_{minor} = 6.63 min τ_{major} = 7.37 min.
$[\alpha]_D^{25}$ = 186 (c 0.115, $CHCl_3$).

(3*R*,4*S*,4*aR*)-3-(4-chlorophenyl)-*N*-methoxy-*N*,4*a*-dimethyl-4,4*a*-dihydro-3*H*-benzo[4,5] oxazolo[3,2-*a*]pyridine-4-carboxamide 4



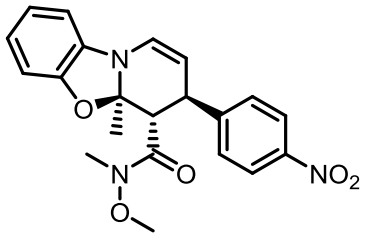
48% yield, dr > 20:1, 90% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-chlorophenyl)prop-2-enal (50.0 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **4**was isolated as a brown oil (37.0 mg, 0.096 mmol, 48% yield, 90% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.45 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.21 – 7.15 (m, 4H), 6.83 (td, *J* = 7.4, 1.4 Hz, 1H), 6.74 – 6.60 (m, 4H), 4.86 (dd, *J* = 7.6, 1.5 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.61 (d, *J* = 11.6 Hz, 1H), 3.34 (s, 3H), 3.02 (s, 3H), 1.73 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.9 (C), 149.3 (C), 140.5 (C), 134.3 (C), 132.7 (C), 129.5 (2 CH), 128.5 (2 CH), 124.1 (CH), 121.4 (CH), 120.0 (CH), 108.5 (CH), 106.7 (CH), 106.4 (CH), 100.4 (C), 61.1 (CH_3), 48.5 (CH), 42.5 (CH), 32.1 (CH_3), 20.8 (CH_3).
HRMS (ESI)calc´d for $[C_{21}H_{21}ClN_2O_3+H]^+$: 430.1164, found: 430.1163.

HPLC Chiralpak AZ-H, Heptane/Isopropanol 90:10, 1 mL/min, λ = 254 nm, τ_{minor} = 6.23 min τ_{major} = 7.29 min.
$[\alpha]_D^{25}$ = 56.0 (c 0.220, $CHCl_3$).

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo [4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 5

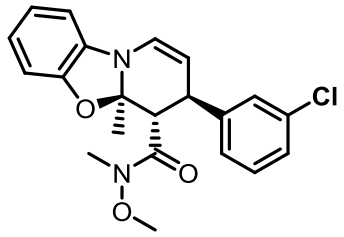


50% yield, dr > 20:1, 94% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **5** was isolated as an orange solid (39.5 mg, 0.100 mmol, 50% yield, 94% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.37 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 8.13 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.72 (m, 4H), 4.88 (d, *J* = 7.6 Hz, 1H), 4.16 (d, *J* = 11.6 Hz, 1H), 3.67 (d, *J* = 11.7 Hz, 1H), 3.41 (s, 3H), 3.02 (s, 3H), 1.76 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.5 (C), 150.0 (C), 149.2 (C), 147.2 (C), 134.1 (C), 129.1 (2 CH), 124.7 (CH), 123.6 (2 CH), 121.6 (CH), 120.3 (CH), 108.6 (CH), 106.9 (CH), 104.9 (CH), 100.2 (C), 61.1 (CH_3), 48.3 (CH), 43.0 (CH), 32.1 (CH_3), 20.8 (CH_3).
HRMS (ESI) calc´d for $[C_{21}H_{21}N_3O_5+H]^+$: 396.1554, found: 396.1552.
HPLC Chiralpak AD-H, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 7.42 min τ_{major} = 12.00 min.
$[\alpha]_D^{25}$ = 137 (c 0.080, $CHCl_3$).
m.p. = 74-75 ^oC.

(3*R*,4*S*,4*aR*)-3-(3-chlorophenyl)-*N*-methoxy-*N*,4*a*-dimethyl-4,4*a*-dihydro-3*H*-benzo [4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 6

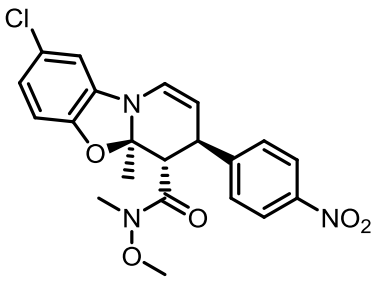


49% yield, dr > 20:1, 94% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(3-chlorophenyl)prop-2-enal (50.0 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **6** was isolated as an orange oil (38.0 mg, 0.099 mmol, 49% yield, 94% *ee*, dr > 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.35 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.20 – 7.11 (m, 3H), 6.83 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.72 – 6.61 (m, 4H), 4.88 (dd, *J* = 7.6, 1.8 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.62 (d, *J* = 11.6 Hz, 1H), 3.33 (s, 3H), 3.03 (s, 3H), 1.74 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C), 149.4 (C), 144.2 (C), 134.4 (C), 134.3 (C), 129.7 (CH), 128.1 (CH), 127.4 (CH), 126.6 (CH), 124.3 (CH), 121.6 (CH), 120.1 (CH), 108.6 (CH), 106.8 (CH), 106.2 (CH), 100.5 (C), 612.2 (CH_3), 48.6 (CH), 42.9 (CH), 32.2 (CH_3), 20.9 (CH_3).
HRMS (ESI) calc´d for $[C_{21}H_{21}N_2O_3Cl+H]^+$: 385.1313, found: 385.1313.
HPLC Chiralpak ID, Heptane/Ethanol 95:5, 1 mL/min, λ = 254 nm, τ_{minor} = 6.34 min τ_{major} = 7.38 min.
$[\alpha]_D^{20}$ = 124 (c 0.100, $CHCl_3$).

(3*R*,4*S*,4*aR*)-8-chloro-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 7



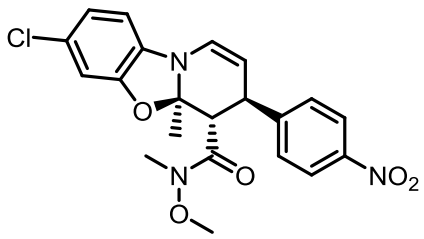
43% yield, dr > 20:1, 90% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-

nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 2-amino-4-chlorophenol (28.7 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **7** was isolated as an orange solid (37.0 mg, 0.086 mmol, 43% yield, 90% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.29 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.69 – 6.54 (m, 4H), 4.92 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.13 (d, *J* = 11.7 Hz, 1H), 3.63 (d, *J* = 11.7 Hz, 1H), 3.35 (s, 3H), 3.00 (s, 3H), 1.74 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.1 (C), 149.5 (C), 148.0 (C), 147.2 (C), 135.2 (C), 129.1 (2 CH), 126.6 (C), 124.2 (CH), 123.7 (2 CH), 119.6 (CH), 108.9 (CH), 107.4 (CH), 106.3 (CH), 101.3 (C), 61.1 (CH_3), 48.3 (CH), 43.0 (CH), 32.1 (CH_3), 20.7 (CH_3).
HRMS (ESI) calc´d for $[C_{21}H_{20}N_3O_5Cl+Na]^+$: 452.0984, found: 452.0984.
HPLC Chiralcel OD-3, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 6.87 min τ_{major} = 13.51 min.
$[\alpha]_D^{25}$ = 218 (c 0.095, $CHCl_3$).
m.p. = 85-87 °C.

(3*R*,4*S*,4*aR*)-7-chloro-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 8



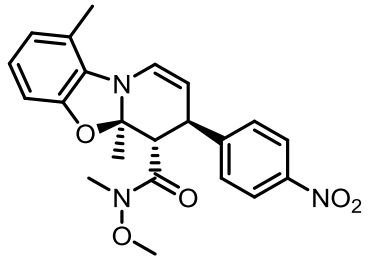
41% yield, dr > 20:1, 92% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 2-amino-5-chlorophenol (28.7 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **8** was isolated as an orange solid (35.0 mg, 0.081 mmol, 41% yield, 92% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.28 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 – 8.02 (m, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 6.82 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.63 (dd, *J* = 7.7, 2.0 Hz, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 4.89 (dd, *J* = 7.7, 1.9 Hz, 1H), 4.12 (d, *J* = 11.8 Hz, 1H), 3.62 (d, *J* = 11.7 Hz, 1H), 3.37 (s, 3H), 3.00 (s, 3H), 1.73 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.2 (C), 150.0 (C), 149.6 (C), 147.2 (C), 133.0 (C), 129.1 (2 CH), 124.8 (C), 124.4 (CH), 123.7 (2 CH), 121.3 (CH), 109.5 (CH), 107.0 (CH), 105.6 (CH), 101.4 (C), 61.2 (CH_3), 48.3 (CH), 42.9 (CH), 32.1 (CH_3), 20.8 (CH_3).

HRMS (ESI) calc´d for $[C_{21}H_{20}N_3O_5Cl+H]^+$: 430.1164, found: 430.1163.
HPLC Chiralpak AD-H, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 5.87 min τ_{major} = 10.16 min.
$[\alpha]_D^{25}$ = 63.7 (c 0.110, $CHCl_3$).
m.p. = 77-79 °C.

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*,9-trimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo[4,5] oxazolo[3,2-*a*]pyridine-4-carboxamide 9

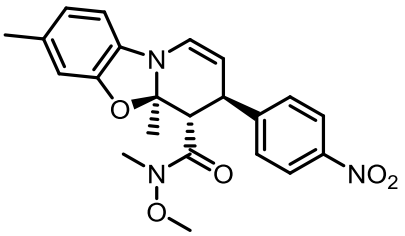


45% yield, dr > 20:1, 90% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 2-amino-3-methylphenol (24.6 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **9** was isolated as an orange solid (36.0 mg, 0.088 mmol, 45% yield, 90% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.29 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.11 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.99 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.68 – 6.60 (m, 2H), 6.56 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.77 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.10 (d, *J* = 11.8 Hz, 1H), 3.69 (d, *J* = 11.8 Hz, 1H), 3.40 (s, 3H), 3.00 (s, 3H), 2.42 (s, 3H), 1.73 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.7 (C), 150.2 (C), 149.2 (C), 147.1 (C), 131.6 (C), 129.1 (2 CH), 126.3 (CH), 124.6 (CH), 123.6 (2 CH), 120.4 (CH), 119.0 (C), 106.6 (CH), 104.2 (CH), 99.6 (C), 61.2 (CH_3), 48.6 (CH_3), 42.6 (CH), 32.1 (CH), 20.6 (CH_3), 18.7 (CH_3).
HRMS (ESI) calc´d for $[C_{22}H_{23}N_3O_5+H]^+$: 410.1710, found: 410.1711.
HPLC Lux-Cellulose-4, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 9.35 min τ_{major} = 11.23 min.
$[\alpha]_D^{25}$ = 36.9 (c 0.095, $CHCl_3$).
m.p. = 89-90 °C

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*,7-trimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo[4,5] oxazolo[3,2-*a*]pyridine-4-carboxamide 10

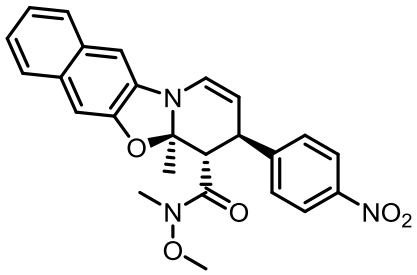


45% yield, dr > 20:1, 92% *ee*

According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 6-amino-*m*-cresol (24.6 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **10** was isolated as an orange solid (36.0 mg, 0.088 mmol, 45% yield, 92% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.28 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) δ 8.17 – 8.00 (m, 2H), 7.49 – 7.38 (m, 2H), 6.68 – 6.63 (m, 2H), 6.57 (d, *J* = 7.7 Hz, 1H), 6.52 (s, 1H), 4.81 (dd, *J* = 7.6, 1.9 Hz, 1H), 4.12 (dd, *J* = 11.5, 2.1 Hz, 1H), 3.62 (d, *J* = 11.6 Hz, 1H), 3.39 (s, 3H), 3.00 (s, 3H), 2.25 (s, 3H), 1.72 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C), 150.3 (C), 149.4 (C), 147.2 (C), 132.0 (C), 130.4 (C), 129.2 (2 CH), 125.1 (CH), 123.7 (2 CH), 121.6 (CH), 109.7 (CH), 106.6 (CH), 104.4 (CH), 100.4 (C), 61.3 (CH_3), 48.4 (CH_3), 43.0 (CH), 32.2 (CH), 21.3 (CH_3), 21.0 (CH_3).
HRMS (ESI) calc´d for $[C_{23}H_{23}N_3O_5+H]^+$: 410.1710, found: 410.1711.
HPLC Chiralpak IF, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 6.57 min τ_{major} = 8.75 min.
$[\alpha]_D^{25}$ = 255 (c 0.090, $CHCl_3$).
m.p. = 73-74 °C.

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-naphtho [2',3':4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 11



55% yield, dr > 20:1, 96% *ee*

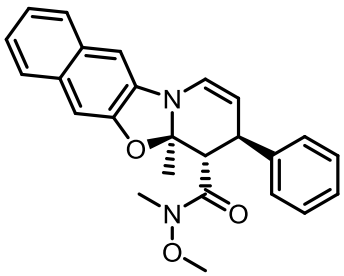
According to the general procedure for the three-component reactions and starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (29.0 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-

nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 3-aminonaphthalen-2-ol (31.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **11** was isolated as an orange solid (49.0 mg, 0.110 mmol, 55% yield, 96% *ee*, dr> 20:1).

2-mmol scale reaction: According to the general procedure for the three-component reactions, a larger amount of (3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H* naphtho[2',3':4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide was prepared starting from *N*-methoxy-*N*-methyl-3-oxobutanamide (290 mg, 2 mmol, 1 equiv), (2*E*)-3-(4-nitrophenyl)prop-2-enal (531 mg, 3 mmol, 1.5 equiv), 3-aminonaphthalen-2-ol (318 mg, 2 mmol, 1 equiv), benzoic acid (98 mg, 0.800 mmol, 0.4 equiv) and the catalyst (130 mg, 0.400 mmol, 0.2 equiv). The product **11** was isolated as an orange solid (472 mg, 1.06 mmol, 53% yield, 94% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.39 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.36 – 7.20 (m, 2H), 6.97 (s, 1H), 6.90 (s, 1H), 6.84 (dd, *J* = 7.6, 1.9 Hz, 1H), 4.98 (dd, *J* = 7.7, 1.9 Hz, 1H), 4.18 (d, *J* = 11.7 Hz, 1H), 3.65 (d, *J* = 11.7 Hz, 1H), 3.38 (s, 3H), 3.03 (s, 3H), 1.79 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.3(C), 149.7 (C), 149.6 (C), 147.2 (C), 134.2 (C), 130.8 (C), 129.9 (C), 129.1 (2 CH), 126.9 (CH), 126.1 (CH), 124.5 (CH), 124.2 (CH), 123.7 (3 CH), 106.4 (CH), 103.8 (CH), 101.5 (CH), 100.3 (C), 61.2 (CH_3), 48.9 (CH), 43.2 (CH), 32.1 (CH_3), 20.7 (CH_3).
HRMS (ESI) calc´d for $[C_{25}H_{23}N_3O_5+H]^+$: 446.1710, found: 446.1709.
HPLC Chiralpak IA, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 7.03 min τ_{major} = 8.01 min.
$[\alpha]_D^{25}$ = 281.6 (c 0.100, $CHCl_3$).
m.p. = 112-113 °C.

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-phenyl-4,4*a*-dihydro-3*H*-naphtho[2',3':4,5] oxazolo[3,2-*a*]pyridine-4-carboxamide 12



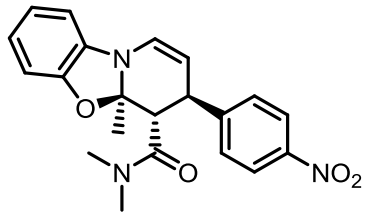
43% yield, dr > 20:1, 94% ee

2-mmol scale reaction: According to the general procedure for the three-component reactions, a larger amount of (3*R*,4*S*,4a*R*)-*N*-methoxy-*N*,4a-dimethyl-3-phenyl-4,4a-dihydro-3*H*-naphtho[2',3':4,5]oxazolo [3,2-a]pyridine-4-carboxamide was prepared starting from *N*-

methoxy-*N*-methyl-3-oxobutanamide (290 mg, 2 mmol, 1 equiv), *(2E)*-cinnamaldehyde (378 µL, 3 mmol, 1.5 equiv), 3-aminonaphthalen-2-ol (318 mg, 2 mmol, 1 equiv), benzoic acid (98 mg, 0.800 mmol, 0.4 equiv) and the catalyst (130 mg, 0.400 mmol, 0.2 equiv). The product **12** was isolated as a yellow oil (344 mg, 0.859 mmol, 43% yield, 94% ee, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.38 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.13 (m, 7H), 6.96 (s, 1H), 6.87 (s, 1H), 6.78 (dd, *J* = 7.7, 1.8 Hz, 1H), 5.07 (dd, *J* = 7.6, 1.8 Hz, 1H), 4.06 (d, *J* = 11.5 Hz, 1H), 3.66 (d, *J* = 11.5 Hz, 1H), 3.24 (s, 3H), 3.04 (s, 3H), 1.81 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 171.0 (C), 150.2 (C), 141.7 (C), 134.8 (C), 131.0 (C), 129.9 (C), 128.5 (2 CH), 128.2 (2 CH), 127.3 (CH), 126.9 (CH), 126.1 (CH), 124.4 (CH), 123.5 (CH), 123.4 (CH), 108.8 (CH), 103.7 (CH), 101.1 (CH), 100.8 (C), 61.1(CH_3), 49.5 (CH), 43.5 (CH), 32.1 (CH_3), 20.8 (CH_3).
HRMS (ESI) calc´d for $[C_{25}H_{24}N_2O_3+H]^+$: 401.1865, found: 401.1866.
HPLC Chiralpak AZ-H, Heptane/Isopropanol 95:5, 1 mL/min, λ = 254 nm, τ_{minor} = 11.36 min τ_{major} = 14.39 min.
$[\alpha]_D^{25}$ = 54.5 (c 0.090, $CHCl_3$).

(3*R*,4*S*,4*aR*)-*N*,*N*,4*a*-trimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 13



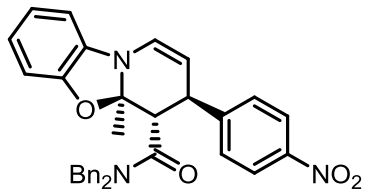
29% yield, dr > 20:1, 92% *ee*

According to the general procedure for the three-component reactions and starting from *N*,*N*-dimethylacetoacetamide (24.0 µL, 0.200 mmol, 1 equiv), (2*E*)-3-(4-nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **13** was isolated as an orange solid (22.0 mg, 0.058 mmol, 29% yield, 92% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.21 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.10 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 6.90 – 6.84 (m, 1H), 6.77 – 6.65 (m, 4H), 4.85 (dd, *J* = 7.6, 1.9 Hz, 1H), 4.26 (d, *J* = 11.3 Hz, 1H), 3.28 (d, *J* = 11.2 Hz, 1H), 2.84 (s, 3H), 2.79 (s, 3H), 1.69 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9 (C), 150.6 (C), 149.1 (C), 147.1 (C), 134.2 (C), 129.1 (2 CH), 124.5 (CH), 123.7 (2 CH), 121.8 (CH), 120.3

(CH), 108.6 (CH), 107.0 (CH), 105.5 (CH), 100.8 (C), 49.7 (CH), 42.9 (CH), 38.0 (CH_3), 36.2 (CH_3), 20.9 (CH_3).
HRMS (ESI) calc´d for $[C_{21}H_{21}N_3O_4+H]^+$: 380.1605, found: 380.1602.
HPLC Chiralpak IA, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 5.58 min τ_{major} = 6.42 min.
$[\alpha]_D^{25}$ = 86.7 (c 0.090, $CHCl_3$).
m.p. = 69-71 °C

(3*R*,4*S*,4*aR*)-*N*,*N*-dibenzyl-4*a*-methyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo[4,5] oxazolo[3,2-*a*]pyridine-4-carboxamide 14



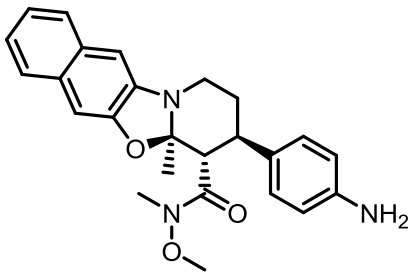
34% yield, dr > 20:1, 92% *ee*

According to the general procedure for the three-component reactions and starting from *N*,*N*-dibenzyl-3-oxobutanamide (56.3 mg, 0.200 mmol, 1 equiv), (2*E*)-3-(4-nitrophenyl)prop-2-enal (53.1 mg, 0.300 mmol, 1.5 equiv), 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv), benzoic acid (9.8 mg, 0.080 mmol, 0.4 equiv) and the catalyst (13.0 mg, 0.040 mmol, 0.2 equiv). The product **14** was isolated as an orange oil (36.0 mg, 0.068 mmol, 34% yield, 92% *ee*, dr > 20:1).

TLC (DCM/EtOAc 97:3) R*f* 0.45 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.29 – 7.25 (m, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.08 – 7.05 (m, 2H), 7.00 (t, *J* = 7.7 Hz, 2H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.73 – 6.65 (m, 3H), 6.60 (d, *J* = 7.7 Hz, 1H), 6.42 (d, *J* = 7.4 Hz, 2H), 4.96 (d, *J* = 15.1 Hz, 1H), 4.86 (dd, *J* = 7.6, 1.8 Hz, 1H), 4.67 (d, *J* = 17.0 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.18 (d, *J* = 17.1 Hz, 1H), 4.03 (d, *J* = 15.1 Hz, 1H), 3.29 (d, *J* = 11.0 Hz, 1H), 1.77 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 169.6 (C), 150.4 (C), 148.8 (C), 147.1 (C), 136.8 (C), 136.1 (C), 134.1 (C), 129.5 (2 CH), 128.6 (4 CH), 127.6 (CH), 127.4 (2 CH), 127.3 (CH), 126.3 (2 CH), 124.5 (CH), 123.7 (2 CH), 121.9 (CH), 120.4 (CH), 108.7 (CH), 107.0 (CH), 105.5 (CH), 100.7 (C), 50.4 (CH_2), 50.3 (CH), 48.8 (CH_2), 42.9 (CH), 21.1 (CH_3).
HRMS (ESI) calc´d for $[C_{33}H_{29}N_3O_4+H]^+$: 532.2231, found: 532.2233.
HPLC Chiralpak IA, Heptane/Isopropanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 6.29 min τ_{major} = 8.81 min.
$[\alpha]_D^{25}$ = 147 (c 0.115, $CHCl_3$).

3.2 Procedures for the post-functionalization of product 11:

(3*R*,4*S*,4*aR*)-3-(4-aminophenyl)-*N*-methoxy-*N*,4*a*-dimethyl-2,3,4,4*a*-tetrahydro-1*H*-naphtho[2',3':4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 15

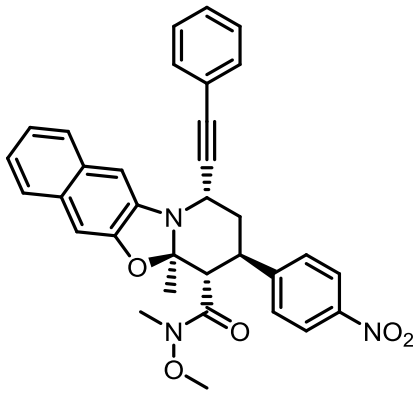


91% yield, dr > 20:1, 94% *ee*

The previously described (3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H* naphtho[2',3':4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide **11** (20 mg, 0.045 mmol, 1 equiv) was dissolved in methanol (2 mL) under an argon atmosphere. Then, Pd/C (4 mg, 0.038 mmol, 20 wt. %) was added to the solution before flushing the reaction mixture with hydrogen. The reaction was stirred at room temperature during 13 h. After filtration on celite and washing with dichloromethane, solvents were removed under vaccum. Purification over silica gel (dichloromethane/ethyl acetate (gradient from 80:20 to 2:1)) directly yielded the corresponding hydrogenated product **15** as a red solid (17 mg, 0.041 mmol, 91 % yield, 94% *ee*, dr> 20:1).

TLC (DCM/EtOAc 100:0.5) R*f* 0.35 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) 7.59 (t, *J* = 6.8 Hz, 2H), 7.19 – 7.34 (m, 2H), 6.96 – 6.87 (m, 3H), 6.65 – 6.57 (m, 3H), 3.88 (dd, *J* = 14.6, 3.0 Hz, 1H), 3.76 (d, *J* = 11.8 Hz, 1H), 3.60 (s, 3H), 3.44 – 3.33 (m, 1H), 3.21 – 3.10 (m, 1H), 2.90 (s, 3H), 1.91 (s, 3H), 1.82 (td, *J* = 13.0, 4.3 Hz, 1H), 1.71 (d, *J* = 12.1 Hz, 1H). The 2 H of the NH_2 group appear as a very broad and flat signal between 4.40 and 2.60 ppm.
^{13}C NMR (101 MHz, $CDCl_3$) 171.8 (C), 149.9 (C), 143.7 (C), 139.0 (C), 133.3 (C), 131.5 (C), 129.4 (C), 128.6 (2 CH), 126.8 (CH), 125.8 (CH), 124.2 (CH), 122.7 (CH), 115.8 (2 CH), 103.8 (CH), 102.2 (C), 99.5 (CH), 61.4 (CH_3), 49.4 (CH), 42.9 (CH), 41.7 (CH_2), 32.1 (CH_3), 30.5 (CH_2), 20.3 (CH_3).
HRMS (ESI) calc´d for $[C_{25}H_{27}N_3O_3+H]^+$: 418.2125, found: 418.2122.
HPLC Lux-Cellulose-4, Heptane/Ethanol 80:20, 1 mL/min, λ = 254 nm, τ_{minor} = 18.99 min τ_{major} = 21.02 min.
$[\alpha]_D^{25}$ = 112 (c 0.095, $CHCl_3$).
m.p. = 126-127°C.

(1*S*,3*R*,4*S*,4a*R*)-*N*-methoxy-*N*,4a-dimethyl-3-(4-nitrophenyl)-1-(phenylethynyl)-2,3,4,4a-tetrahydro-1*H*-naphtho[2',3':4,5]oxazolo[3,2-a]pyridine-4-carboxamide 16



77% yield, dr > 20:1, 90% *ee*

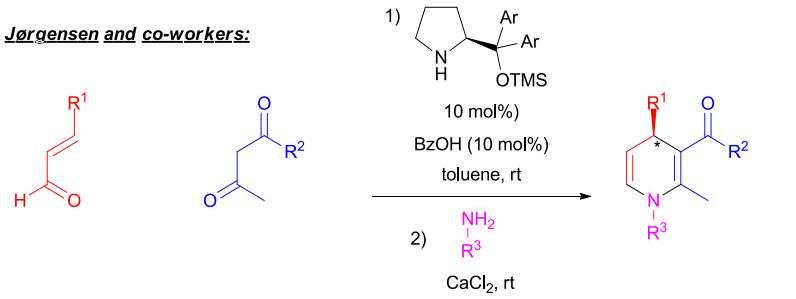
A mixture of (3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H* naphtho[2',3':4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide **11** (20 mg, 0.045 mmol, 1 equiv), potassium phenylacetylenetrifluoroborate (11.2 mg, 0.054 mmol, 1.2 equiv) and scandium triflate (2.2 mg, 0.004 mmol, 0.1 equiv) was dissolved in 2 mL dichloromethane under argon atmosphere. The reaction mixture was stirred at room temperature during 13h. After filtration on celite, the dichloromethane were removed under vaccum. Purification over silica gel (dichloromethane/ethyl acetate (100:0.5)) directly yielded the desired product **16** as pale yellow solid (19 mg, 0.035 mmol, 77 % yield, 90% *ee*, dr> 20:1).

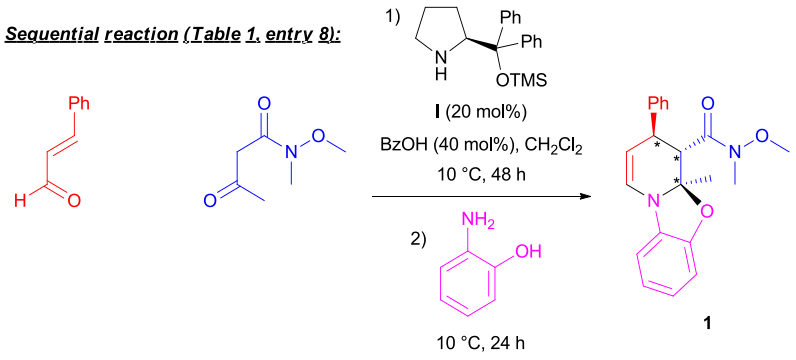
TLC (DCM/EtOAc 100:0.5) R*f* 0.35 (UV, *p*-anisaldehyde).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 – 8.07 (m, 2H), 7.66 – 7.58 (m, 2H), 7.54 – 7.50 (m, 2H), 7.42 – 7.23 (m, 7H), 6.97 (s, 1H), 6.74 (s, 1H), 5.21 (dd, *J* = 5.2 and 1.9 Hz, 1H), 4.02 – 3.89 (m, 2H), 3.74 (s, 3H), 2.91 (s, 3H), 2.17 (s, 3H), 2.22 – 2.06 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.8 (C), 149.4 (C), 148.8 (C), 147.1 (C), 137.8 (C), 131.8 (2 CH), 131.2 (C), 129.7 (C), 129.0 (CH), 128.8 (2 CH), 128.6 (2 CH), 126.9 (CH), 126.1 (CH), 124.5 (CH), 123.9 (2 CH), 123.4 (CH), 122.4 (C), 104.2 (CH), 102.3 (C), 100.3 (CH), 87.2 (C), 85.1 (C), 61.5 (CH_3), 49.2 (CH_3), 45.0 (CH_3), 40.1 (CH), 36.2 (CH_2), 32.2 (CH), 23.2 (CH).
HRMS (ESI) calc´d for $[C_{33}H_{29}N_3O_5+H]^+$: 548.2180, found: 548.2180.
HPLC Lux-Cellulose-2, Heptane/Ethanol 70:30, 1 mL/min, λ = 254 nm, τ_{major} = 8.96 min τ_{minor} = 9.91 min.
$[\alpha]_D^{25}$ = 49.5 (c 0.090, $CHCl_3$).
m.p. = 136-137 °C.

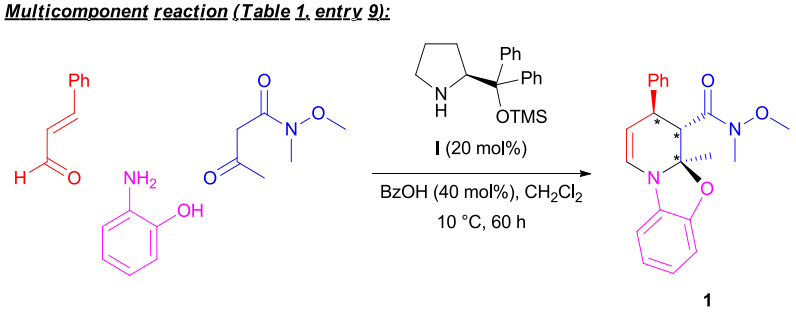
4.DETERMINATION OF RELATIVE CONFIGURATIONS:

4.1 Absolute Configurations of the products of the multicomponent reaction 1-14:

Even though no definitive proof for the absolute configuration could be obtained, it could be tentatively deduced from the previous results by Jørgensen and coworkers.[2] The fact that the sequential reaction (Table 1, entry 9), in which the Michael addition is performed in the absence of the 2-aminophenol, affords the product with the same absolute configuration as the multicomponent reaction (Table 1, entry 8) tends to show that the 2-aminphenol has no direct influence on the enantiodiscriminating step. As a consequence, the absolute configuration of the 1,2,3,4-tetrahydropyridines **1-14** can be attributed with reasonable confidence by comparison with the results obtained by Jørgensen.





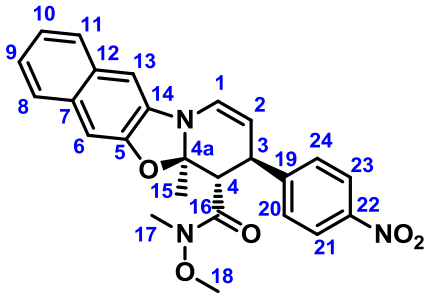


[2] P. T. Franke, R. L. Johansen, S. Bertelsen and K. A. Jørgensen, *Chem. Asian J.*, 2008, **3**, 216-224

4.2 Relative Configurations of the products of the multicomponent reaction 1-14:

The absolute configurations of the products were determined by analogy with related organocatalytic Michael additions.[3] With the use of (*S*)-catalyst, the title multicomponent reaction delivers the product with a (3*R*)-configuration.

The relative configurations of the products were assigned by the analysis of the coupling constants in ^{1}H NMR and NOESY experiments (the study below is given on compound **11**). At first, all the signals of the protons and carbon atoms were attributed thanks to 2D NMR studies (COSY, HMQC, HMBC). These 2D NMR spectra are presented at the end of this discussion on the relative configuration.



11

Attributions:

The attribution of protons and carbon atoms 3 and 4 can be done thanks to HMQC and HMBC experiments:

- The HMQC spectrum shows that the carbon atom at 43.2 ppm is linked to the proton at 4.18 ppm whereas the carbon atom at 48.9 ppm is linked to the proton at 3.65 ppm (see below)
- In HMBC, we can see interactions between C_3 at 43.2 ppm and H_2 (4.98 ppm), H_1 (6.84 ppm) and H_{20} and H_{24} (7.44 ppm) (see below).
- In HMBC, we can see interactions between C_4 at 48.9 ppm and H_{15} (1.79 ppm) and H_2 (4.98 ppm) (see below).
- There is also an interaction between H_4 at 3.65 ppm and C_{4a} at 110.3 ppm.

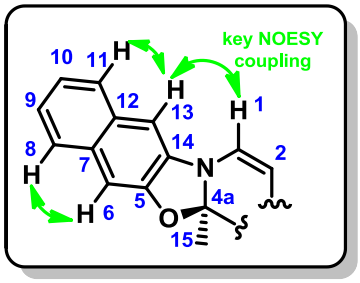
The attribution of protons and carbon atoms 6, 13, 8 and 11 can be done thanks to NOESY and HMBC experiments:

- In the NOESY experiment, H_1 (which can be identified by its NOESY, HMBC and HMQC couplings with H_2 and C_2) only interacts with one proton of the napthyl

[3] P. T. Franke, R. L. Johansen, S. Bertelsenand K. A. Jørgensen, *Chem. Asian J.*, 2008, **3**, 216-224

moeity: it is H_{13} at 6.90 ppm (see below) and we can deduce that H_6 is located just near to H_{13} at 6.97 ppm.

- H_{13} interacts with H_{11} at 7.63 ppm and H_6 interacts with H_8 at 7.58 ppm (see below)



- On the HMBC spectrum, H_{13} at 6.90 ppm interacts with C_{14} at 149.7 ppm, H_6 at 6.97 ppm interacts with C_5 at 134.2 ppm. Moreover, H_{11} at 7.63 ppm interacts with C_{12} at 129.9 ppm, H_8 at 7.58 ppm interacts with C_7 at 130.8 ppm (see below).
- On the other aromatic system, H_2 at 4.98 ppm, H_3 at 4.18 ppm, H_4 at 3.65 ppm and $H_{20,24}$ at 7.44 ppm interact with C_{19} at 149.6 ppm, whereas $H_{21,23}$ at 8.12 ppm and $H_{20,24}$ at 7.44 pm interact with C_{22} at 147.2 ppm (see below).

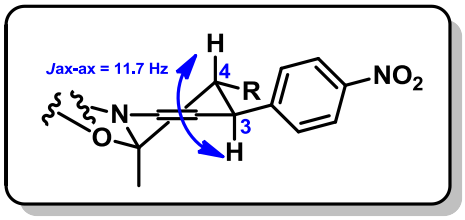
Based on these observations, we can give the following attributions:
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (d, *J* = 8.7 Hz, 2H, H_{21} and H_{23}), 7.63 (d, *J* = 7.9 Hz, 1H, H_{11}), 7.58 (d, *J* = 7.7 Hz, 1H, H_8), 7.44 (d, *J* = 8.6 Hz, 2H, H_{20} and H_{24}), 7.36 – 7.20 (m, 2H, H_9 and H_{10}), 6.97 (s, 1H, H_6), 6.90 (s, 1H, H_{13}), 6.84 (dd, *J* = 7.6, 1.9 Hz, 1H, H_1), 4.98 (dd, *J* = 7.7, 1.9 Hz, 1H, H_2), 4.18 (d, *J* = 11.7 Hz, 1H, H_3), 3.65 (d, *J* = 11.7 Hz, 1H, H_4), 3.38 (s, 3H, H_{18}), 3.03 (s, 3H, H_{17}), 1.79 (s, 3H, H_{15}).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.3 (C_{16}), 149.7 (C_{14}), 149.6 (C_{19}), 147.2 (C_{22}), 134.2 (C_5), 130.8 (C_7), 129.9 (C_{12}), 129.1 (C_{20} and C_{24}), 126.9 (C_8), 126.1 (C_{11}), 124.5 (C_{10}), 124.2 (C_1), 123.7 (C_9, C_{21} and C_{23}), 106.4 (C_2), 103.8 (C_6), 101.5 (C_{13}), 100.3 (C_{4a}), 61.2 (C_{18}), 48.9 (C_4), 43.2 (C_3), 32.1 (C_{17}), 20.7 (C_{15}).

Relative configurations:

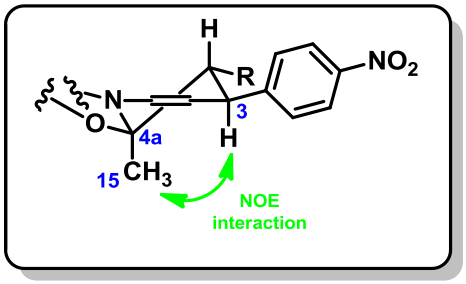
On the schemes of the tetrahydropyridine ring presented below, the Weinreb amide is noted R and the two alkenyl protons are omitted for clarity . By application of Karplus equation:

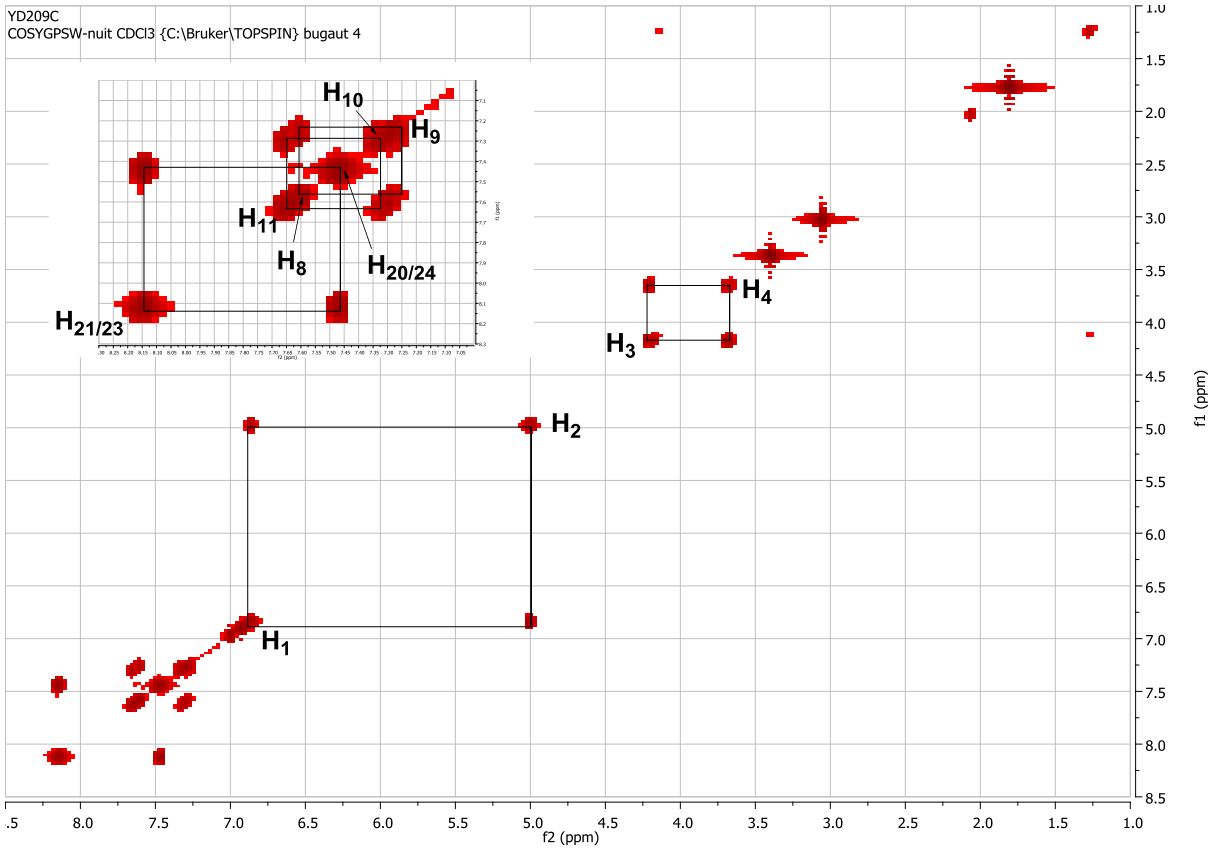
- The $^2J_{gem}$ between two geminal protons will have values between 11 and 14 Hz.
- The $^3J_{ax\text{-}ax}$ between two axial protons on adjacent carbons will have values between 11 and 14 Hz.
- The $^3J_{ax\text{-}eq}$ and $^3J_{eq\text{-}eq}$ between two protons on adjacent carbons that are not both in axial positions will have values between 2 and 7 Hz.

Relative configuration at C_4: In the ^{1}H NMR spectrum, the coupling constants of 11.7 Hz between H_3 and H_4 clearly indicates that those protons are in a *trans*-diaxial relationship, allowing determining the relative configuration at carbon C_4.

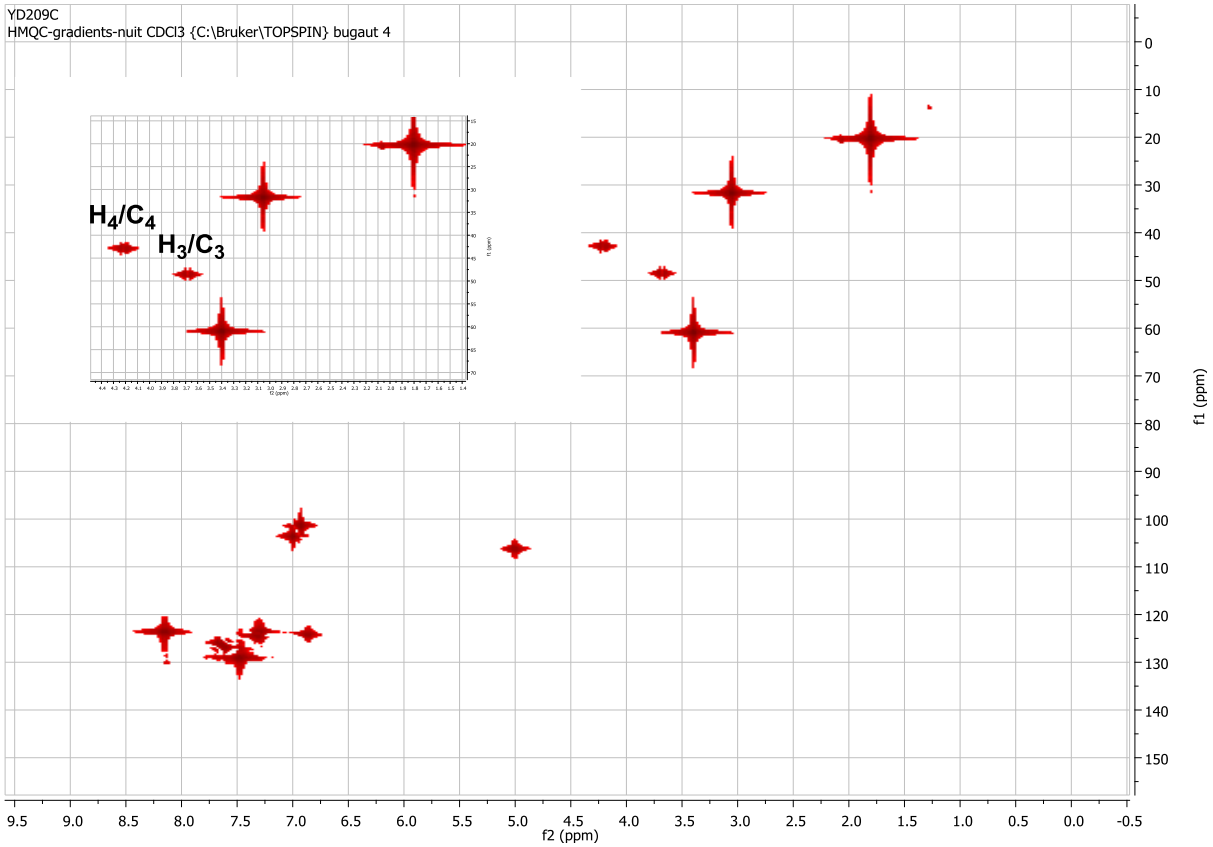


Relative configuration at C_{4a}: The NOE interaction between the 3 H_{15} of the methyl group and H_3 confirms that both groups are located in close proximity, on the same side on the polycyclic ring system, allowing the determination of the relative configuration at C_{4a}.





COSY


YD209C
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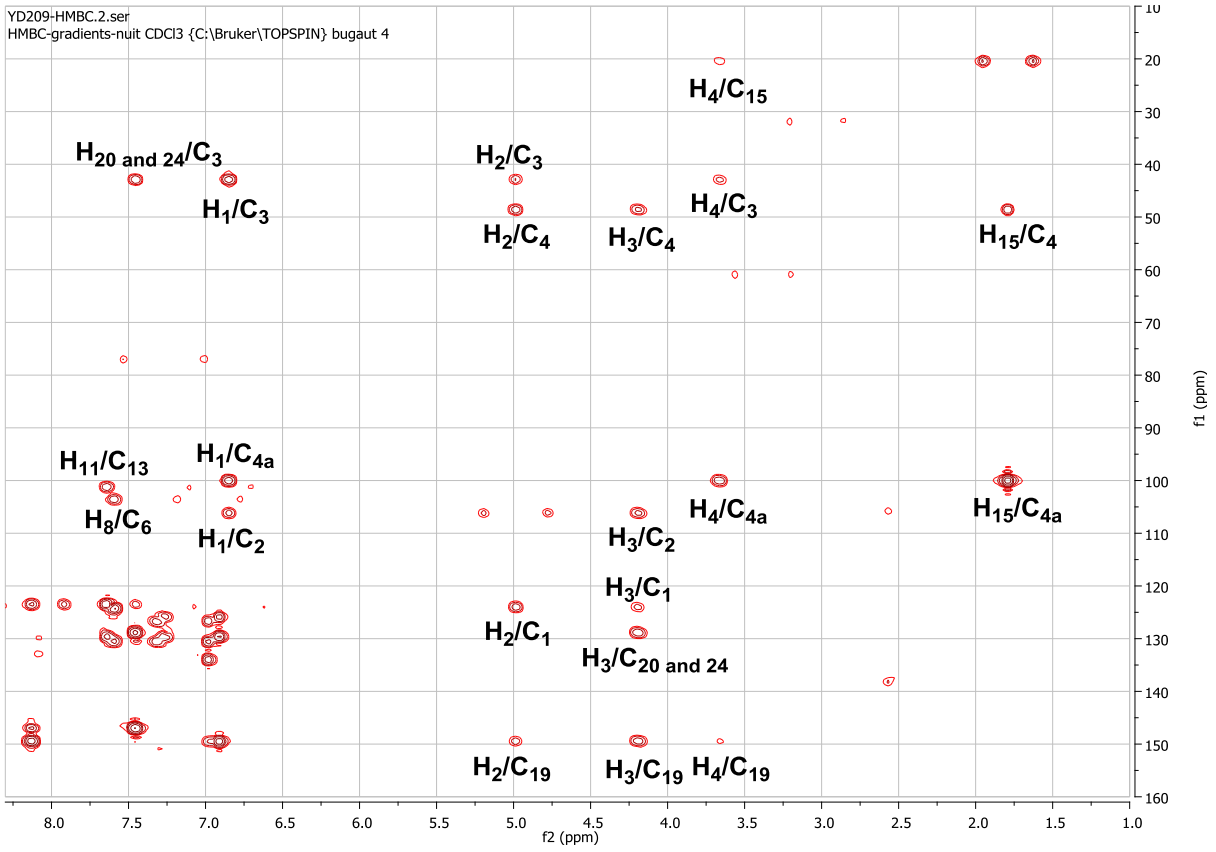
H4/C4
H3/C3
f2 (ppm)
f1 (ppm)

HMQC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HMBC-gradients-nuit CDCl3 {C:\Bruker\TOPSPIN} bugaut 4
H20 and 24/C3
H1/C3
H2/C3
H2/C4
H3/C4
H4/C15
H4/C3
H15/C4
H11/C13
H1/C4a
H8/C6
H1/C2
H4/C4a
H15/C4a
H3/C2
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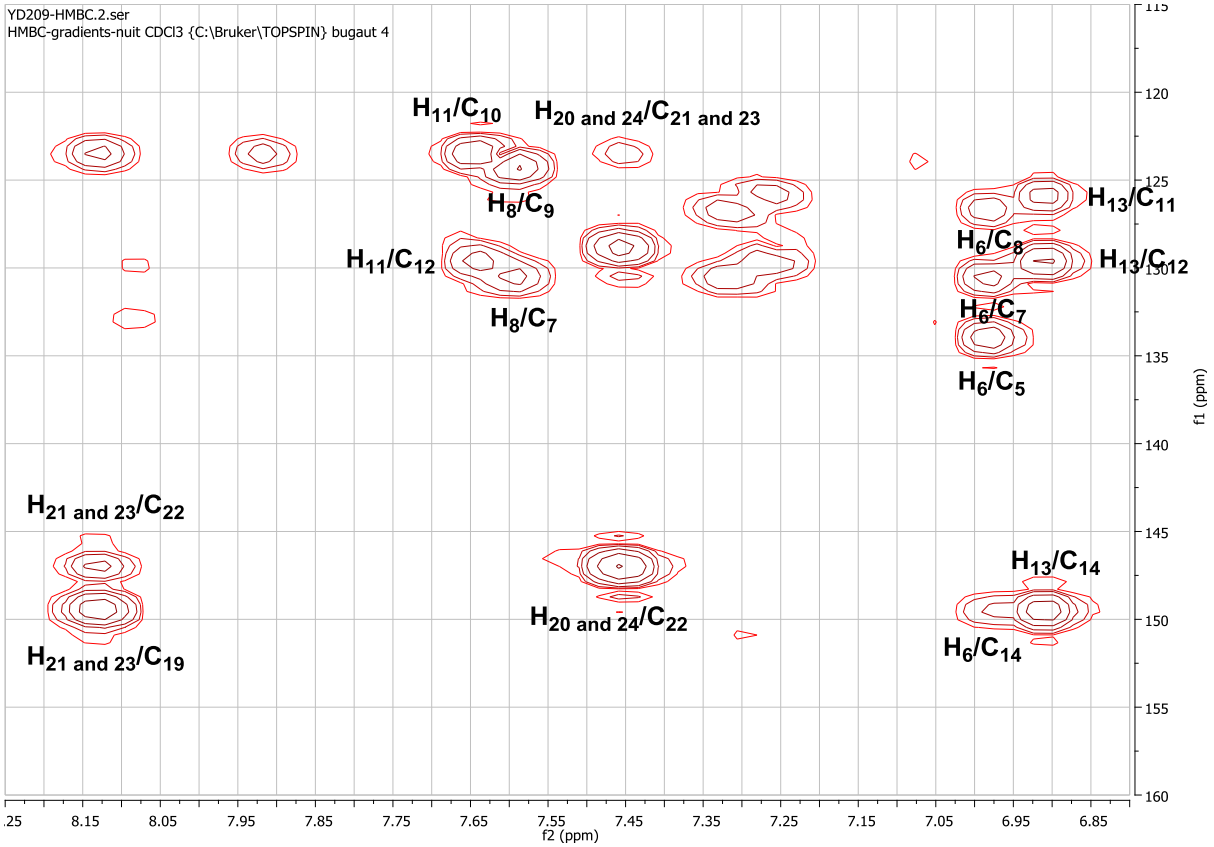
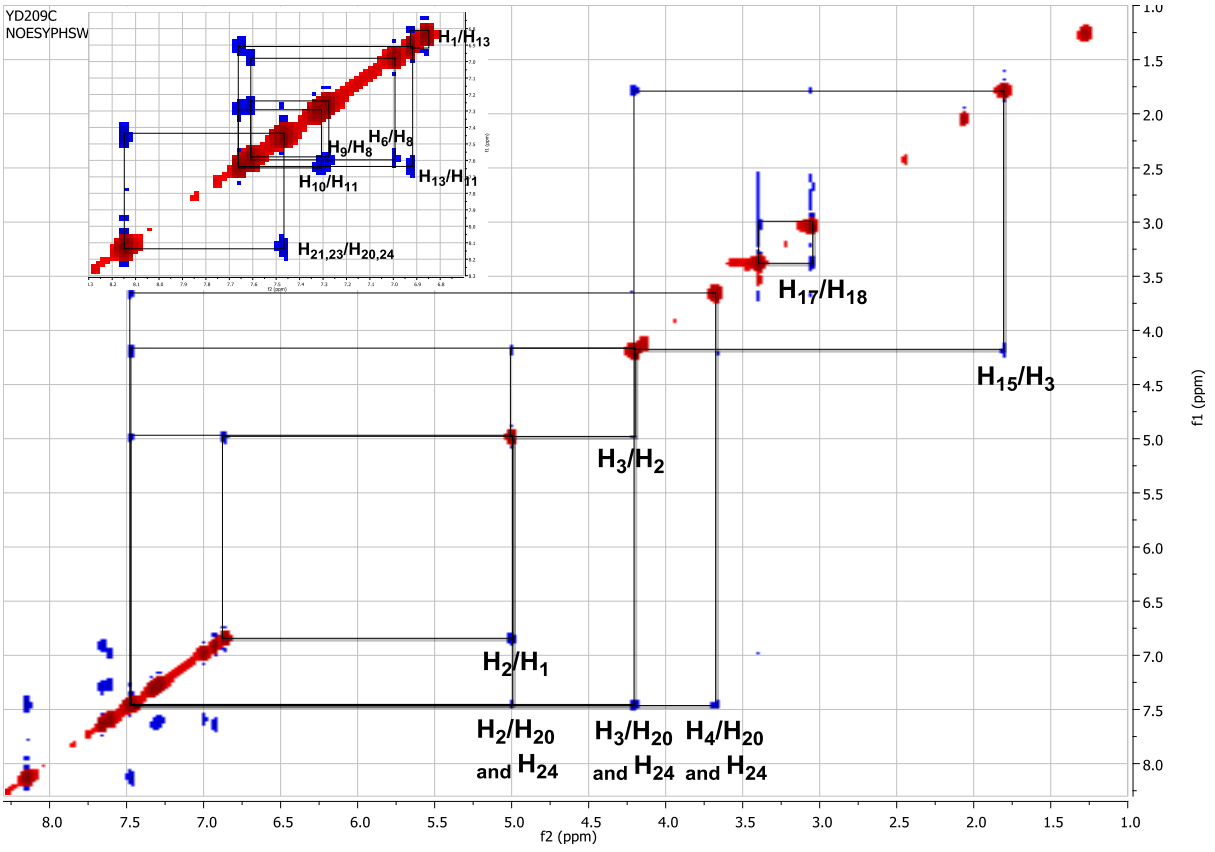
H3/C19
H4/C19
f2 (ppm)
f1 (ppm)

HMBC

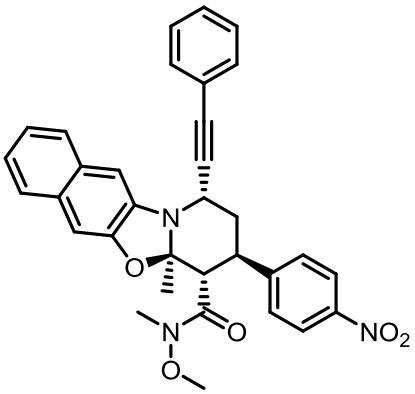


HMBC (zoom)



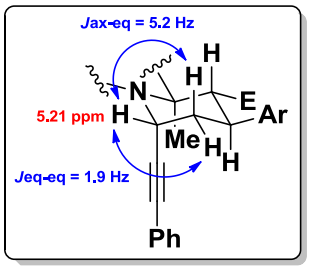
NOESY

4.3 Relative configuration of the product of postfunctionalization 16:

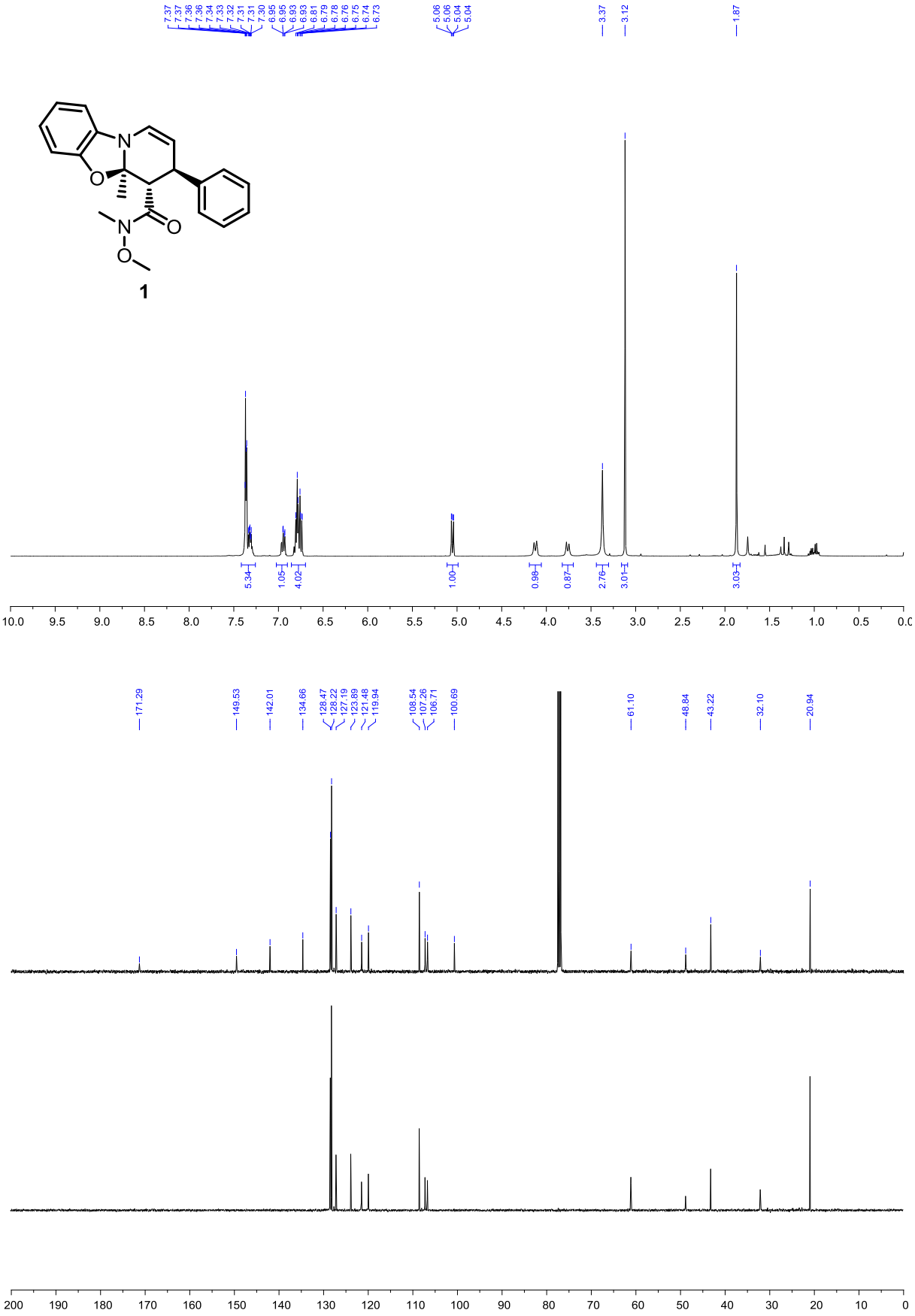


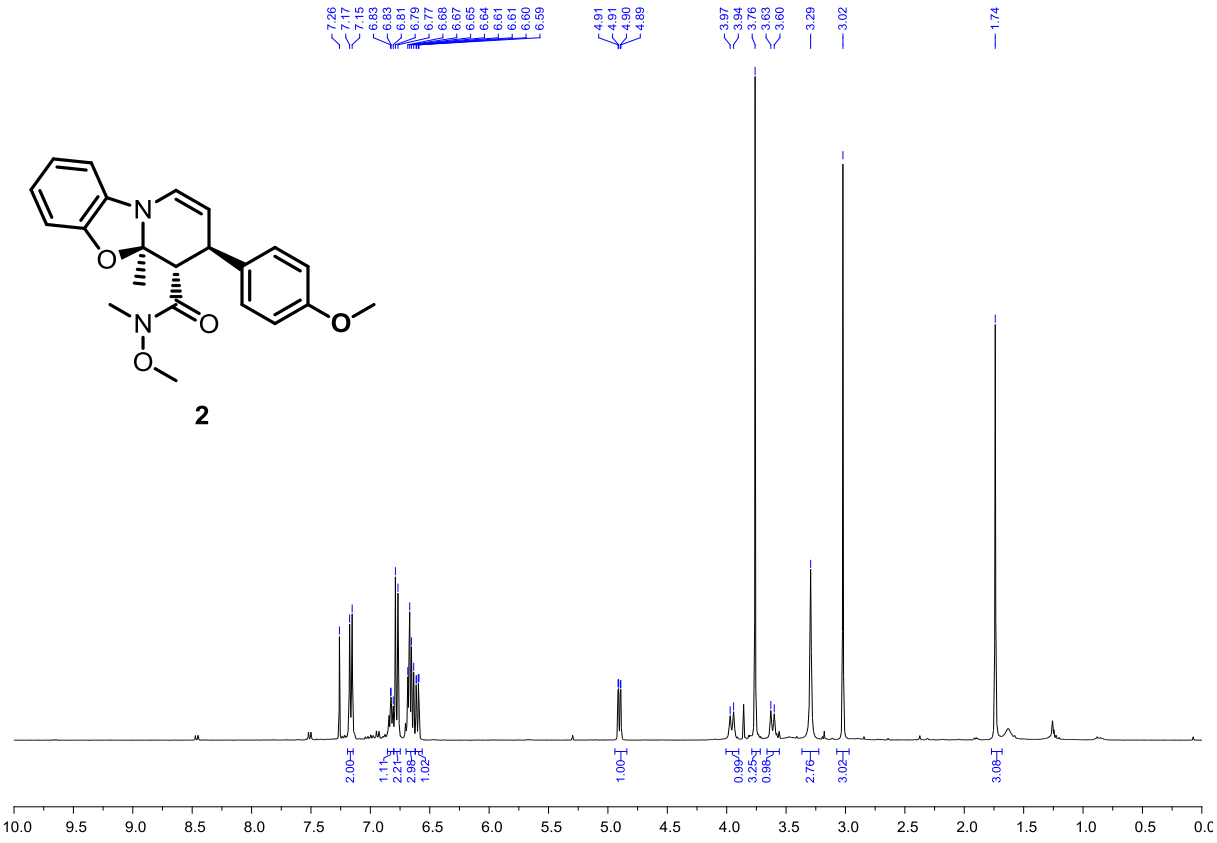
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 – 8.07 (m, 2H), 7.66 – 7.58 (m, 2H), 7.54 – 7.50 (m, 2H), 7.42 – 7.23 (m, 7H), 6.97 (s, 1H), 6.74 (s, 1H), 5.21 (dd, *J* = 5.2 and 1.9 Hz, 1H), 4.02 – 3.89 (m, 2H), 3.74 (s, 3H), 2.91 (s, 3H), 2.17 (s, 3H), 2.22 – 2.06 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 170.8 (C), 149.4 (C), 148.8 (C), 147.1 (C), 137.8 (C), 131.8 (2 CH), 131.2 (C), 129.7 (C), 129.0 (CH), 128.8 (2 CH), 128.6 (2 CH), 126.9 (CH), 126.1 (CH), 124.5 (CH), 123.9 (2 CH), 123.4 (CH), 122.4 (C), 104.2 (CH), 102.3 (C), 100.3 (CH), 87.2 (C), 85.1 (C), 61.5 (CH_3), 49.2 (CH_3), 45.0 (CH_3), 40.1 (CH), 36.2 (CH_2), 32.2 (CH), 23.2 (CH).

For the signal at 5.21 ppm, both coupling constants of 5.2 and 1.9 Hz are in the range of a classic $^{3}J_{ax\text{-}eq}$ and $^{3}J_{eq\text{-}eq}$ interactions, respectively, showing that the alkyne was added in axial position. On the scheme below, the Weinreb amide is noted E and the *para*-nitro aromatic Ar.



5. ^{1}H AND ^{13}C NMR SPECTRA:

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6.83
6.81
6.79
6.77
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6.67
6.65
6.64
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6.61
6.60
6.59
4.91
4.91
4.90
4.89
3.97
3.94
3.76
3.63
3.60
3.29
3.02
1.74
2.00
1.11
2.21
2.86
1.02
1.00
0.99
3.25
0.98
2.76
3.02
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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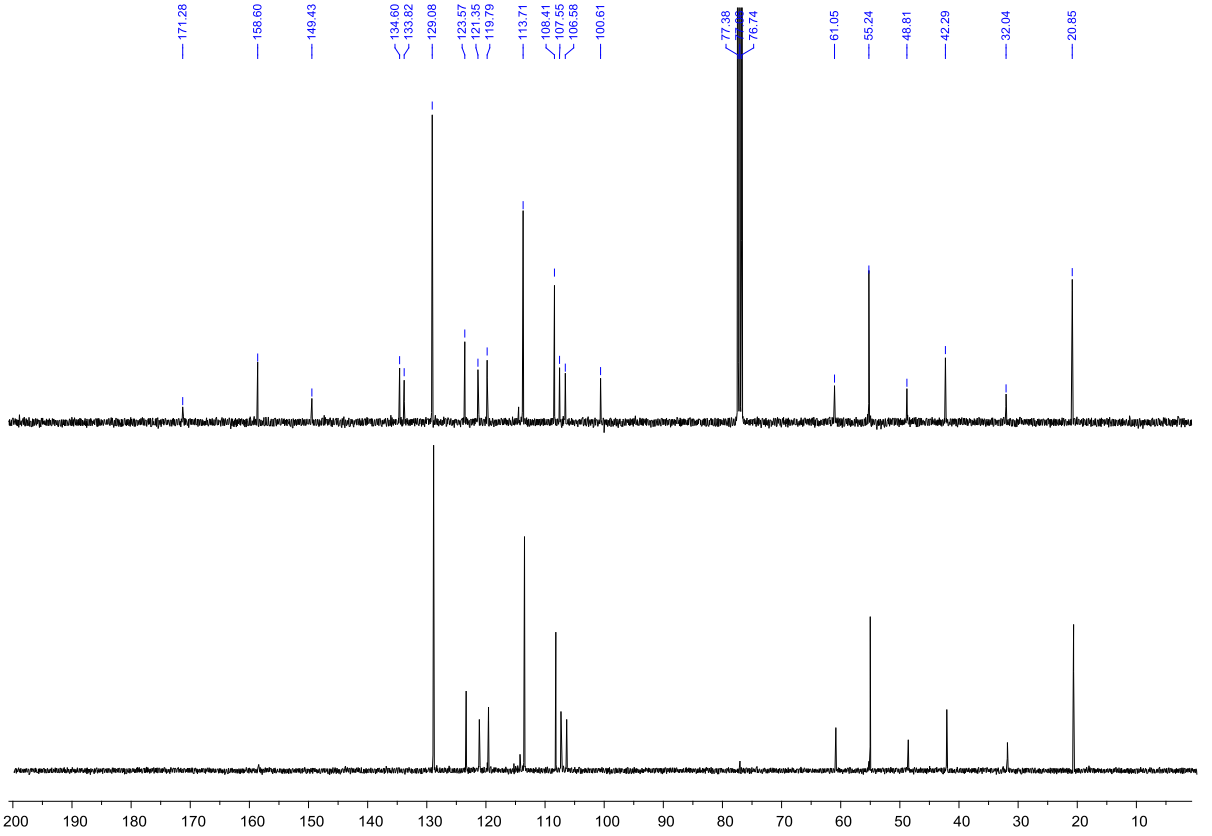
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77.38
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55.24
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42.29
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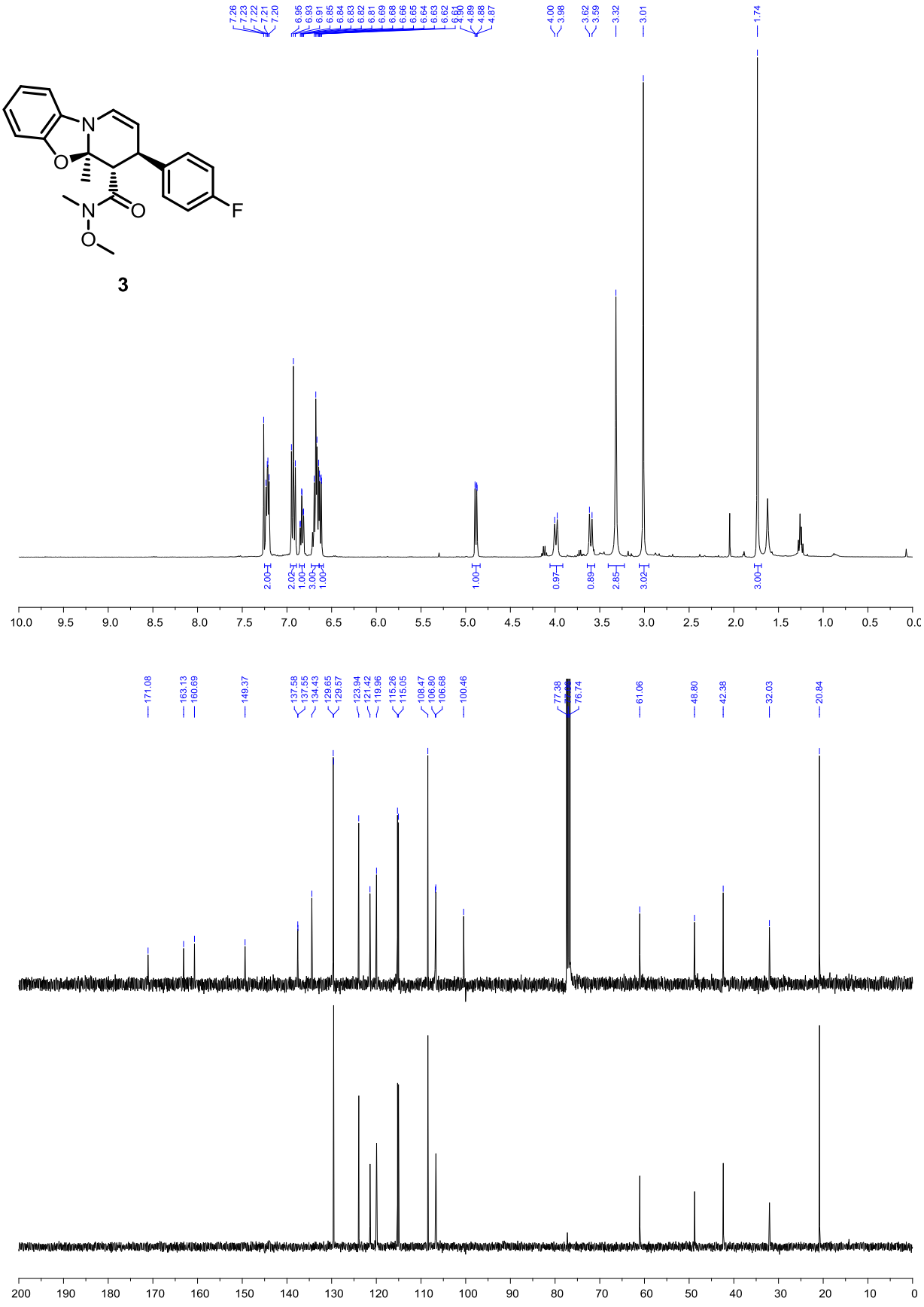
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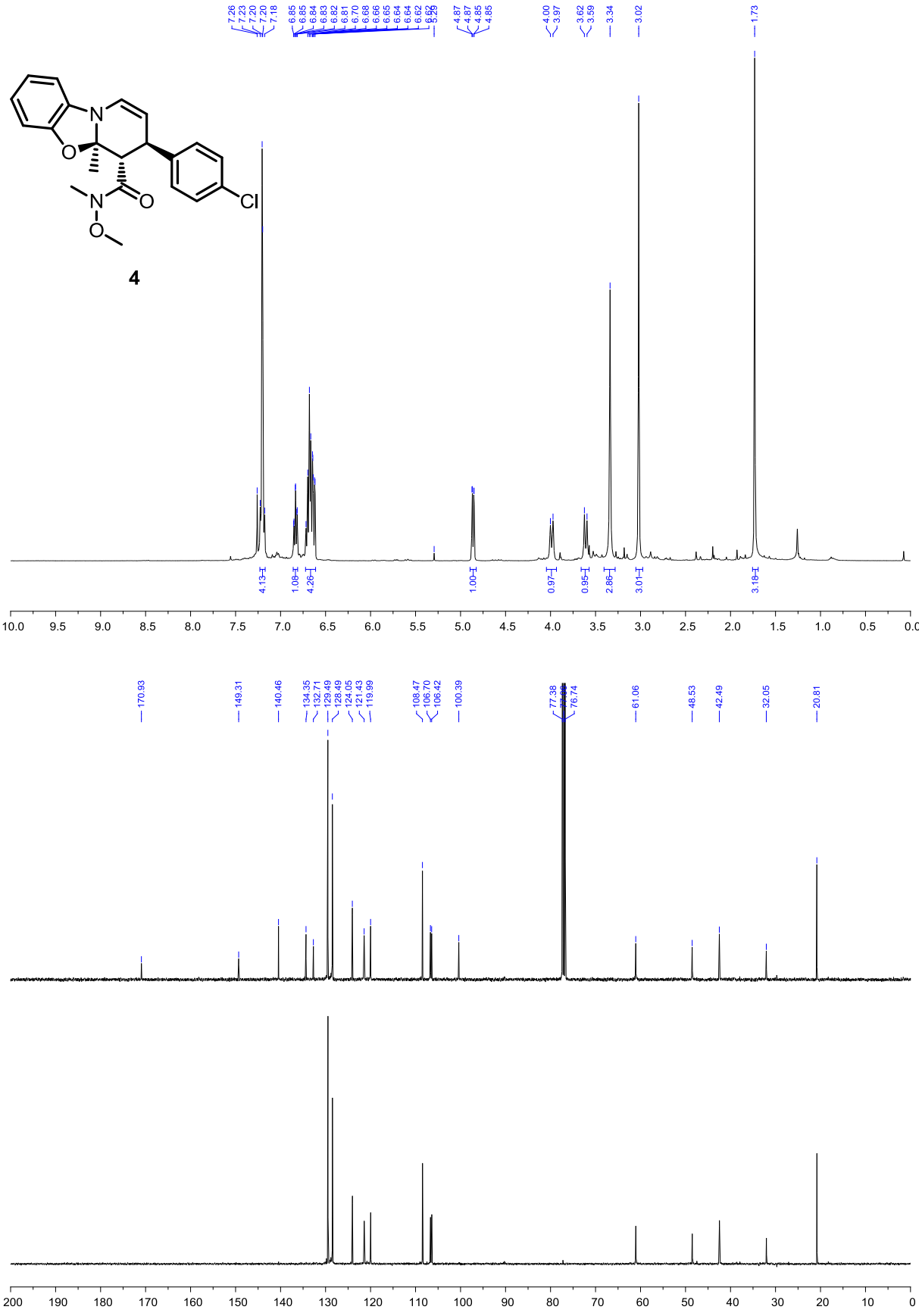
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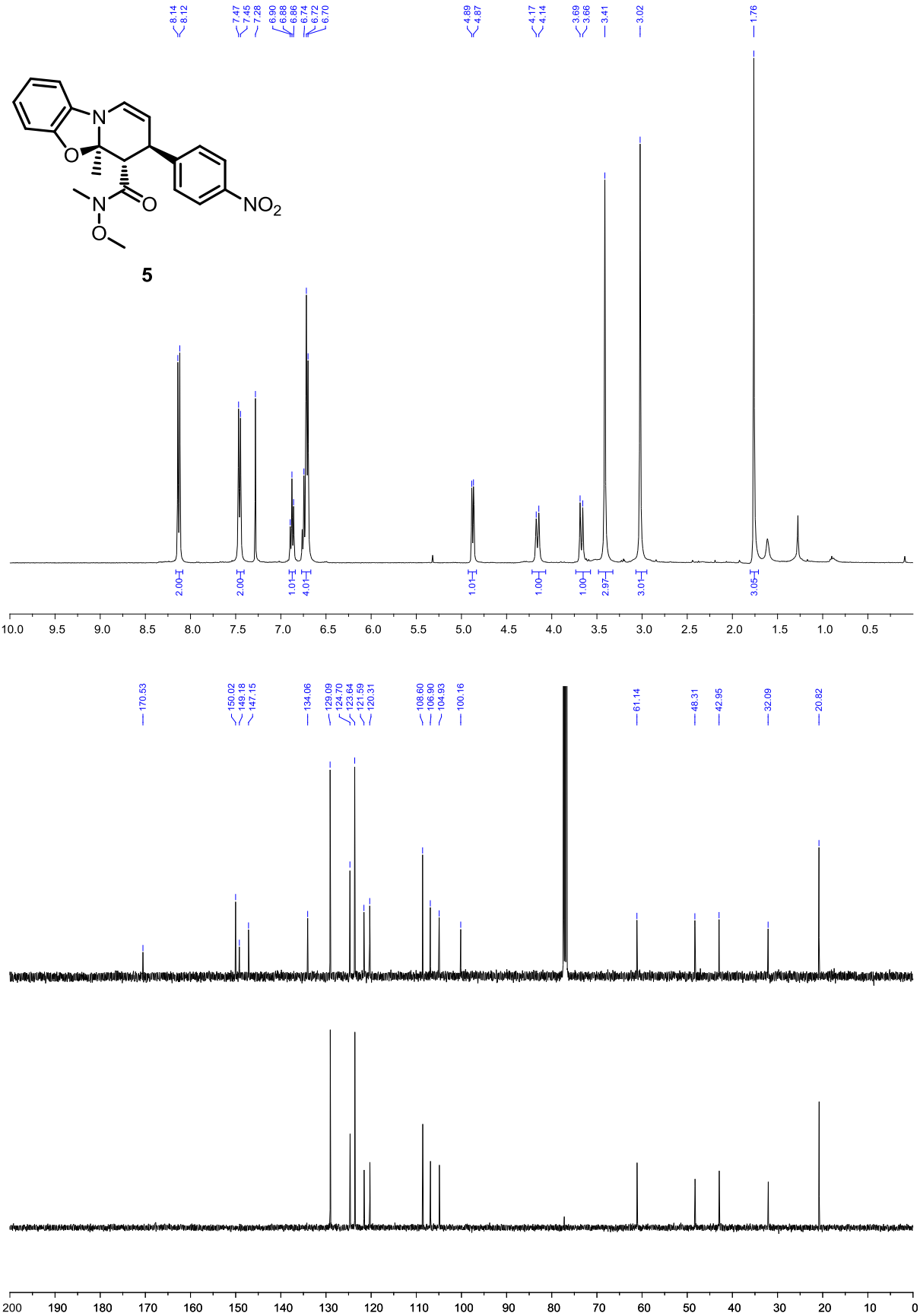
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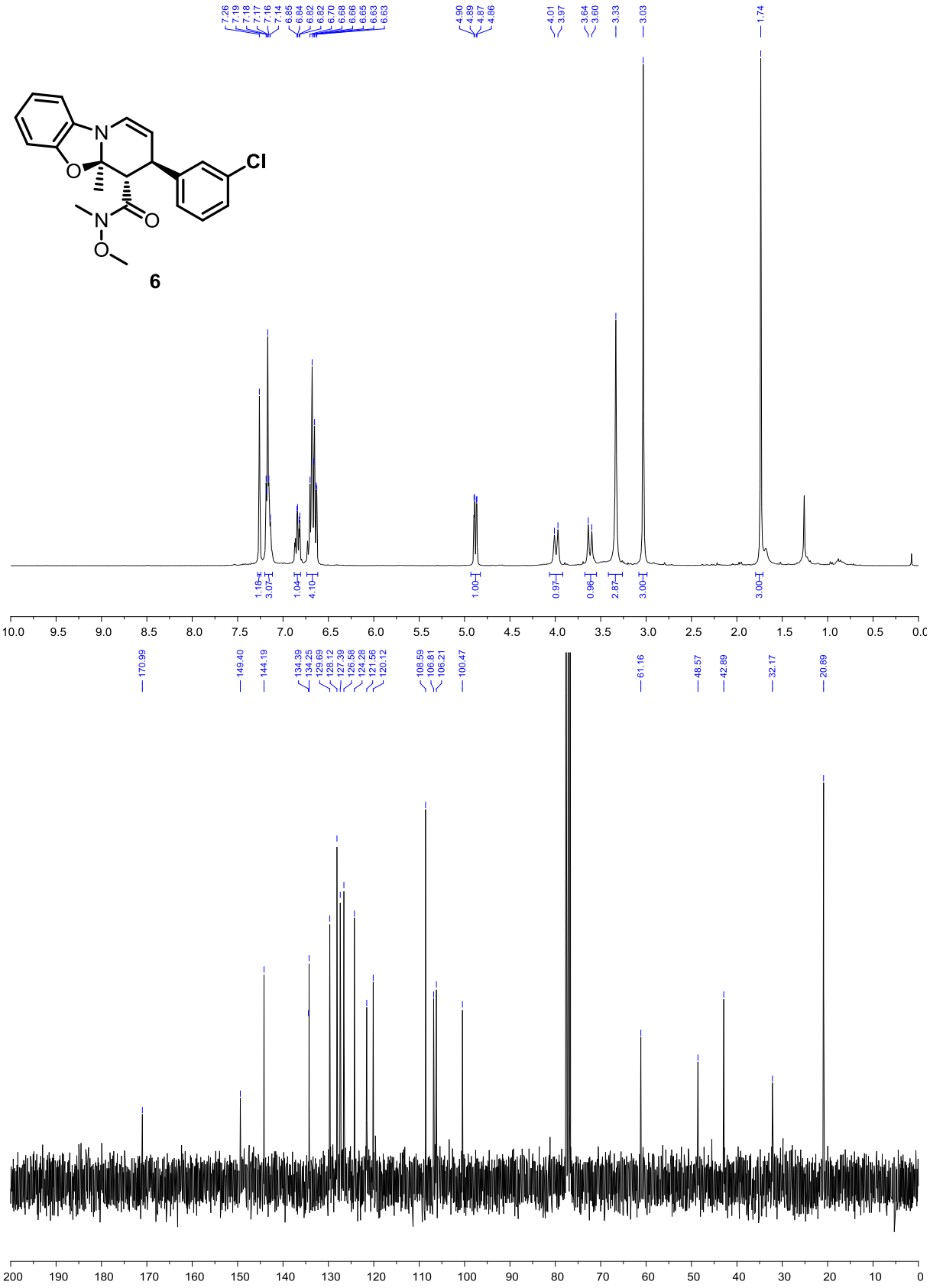
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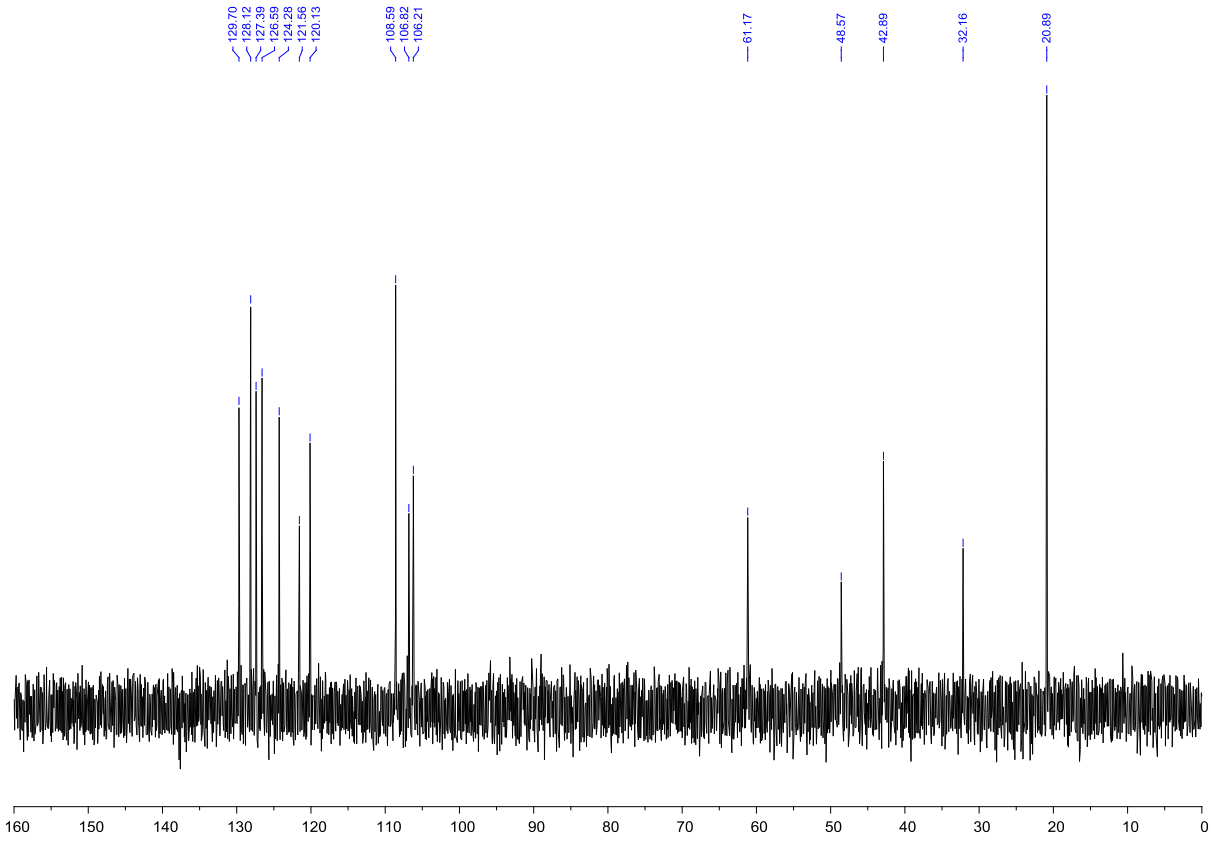
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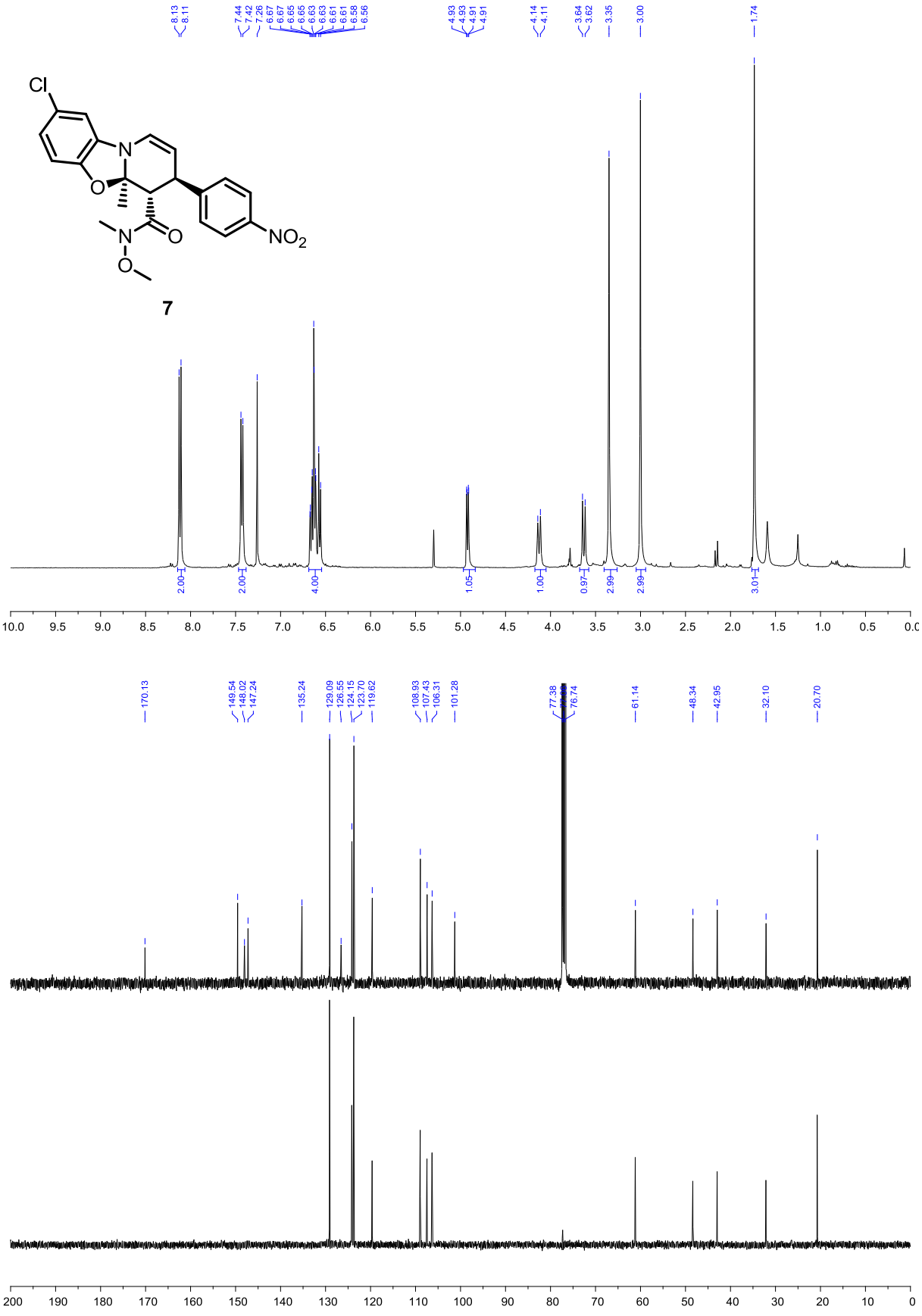
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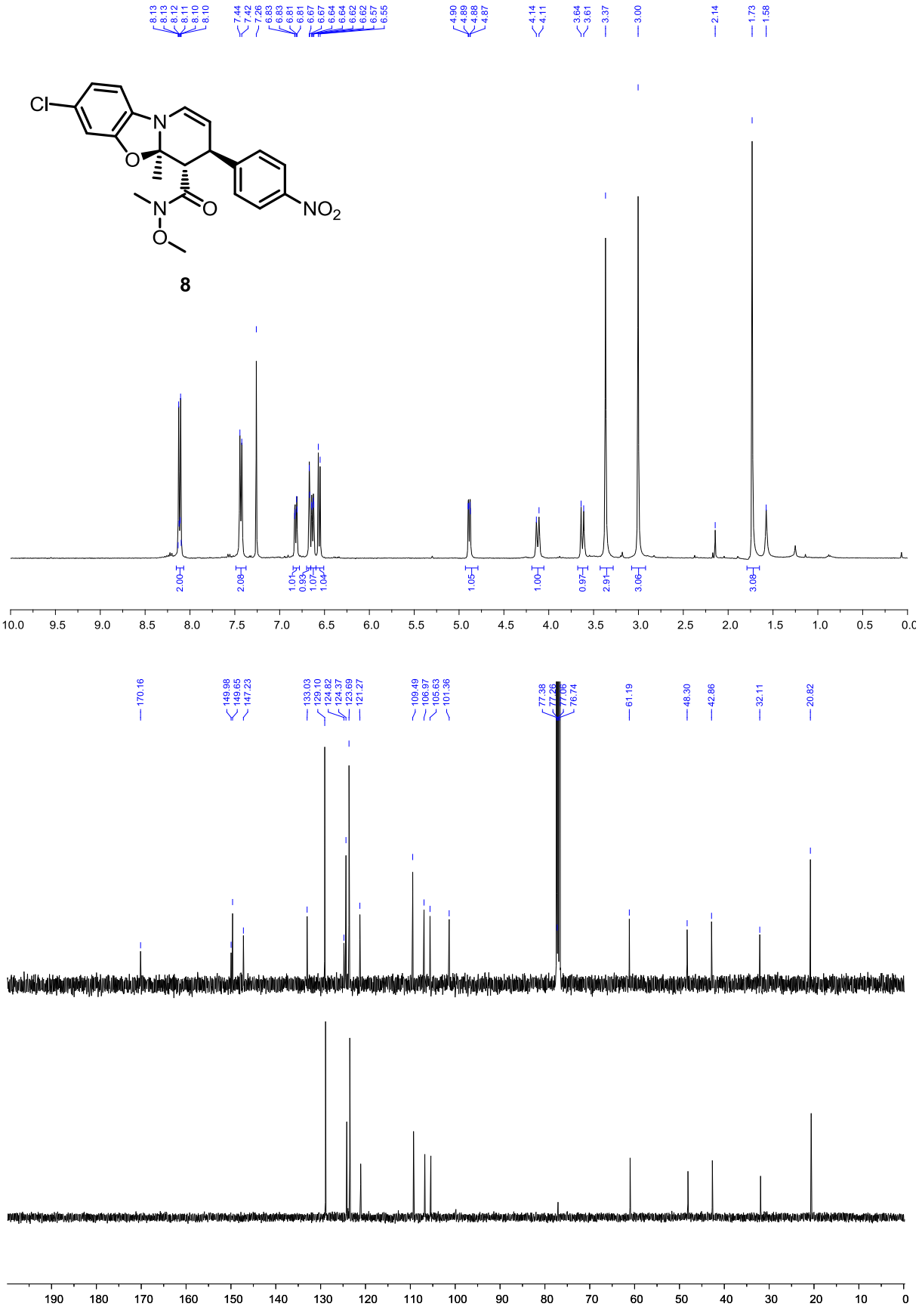
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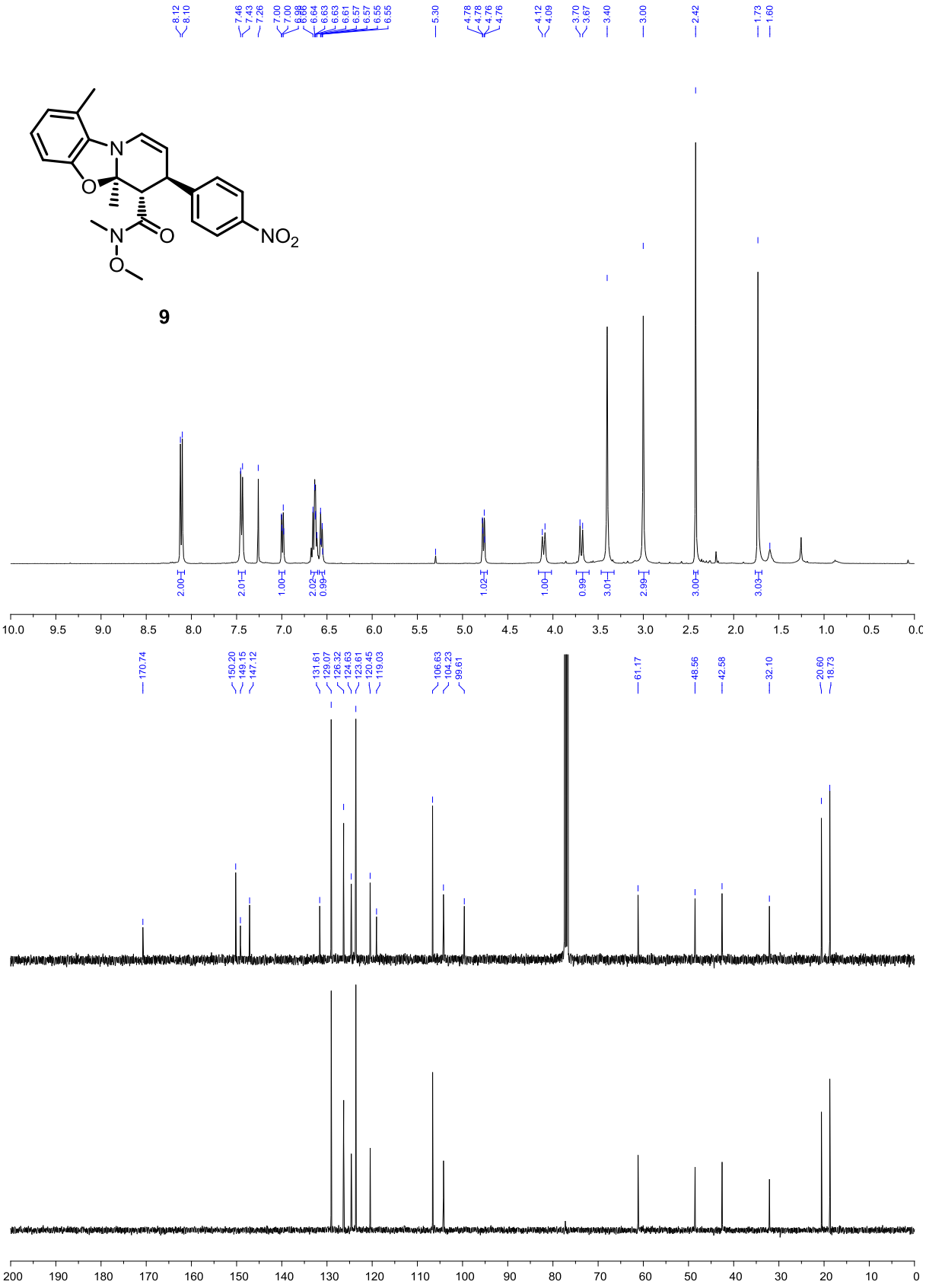
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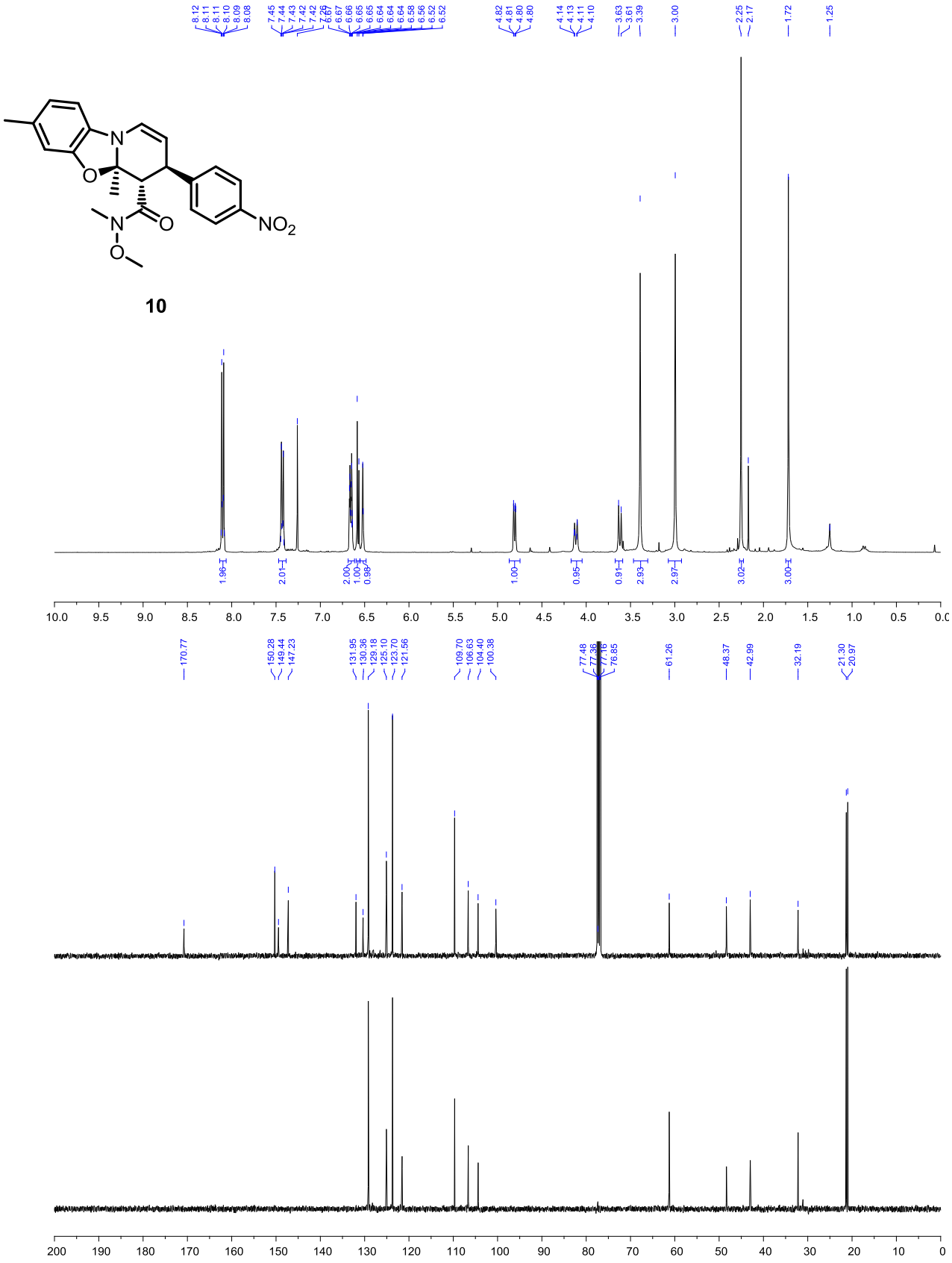
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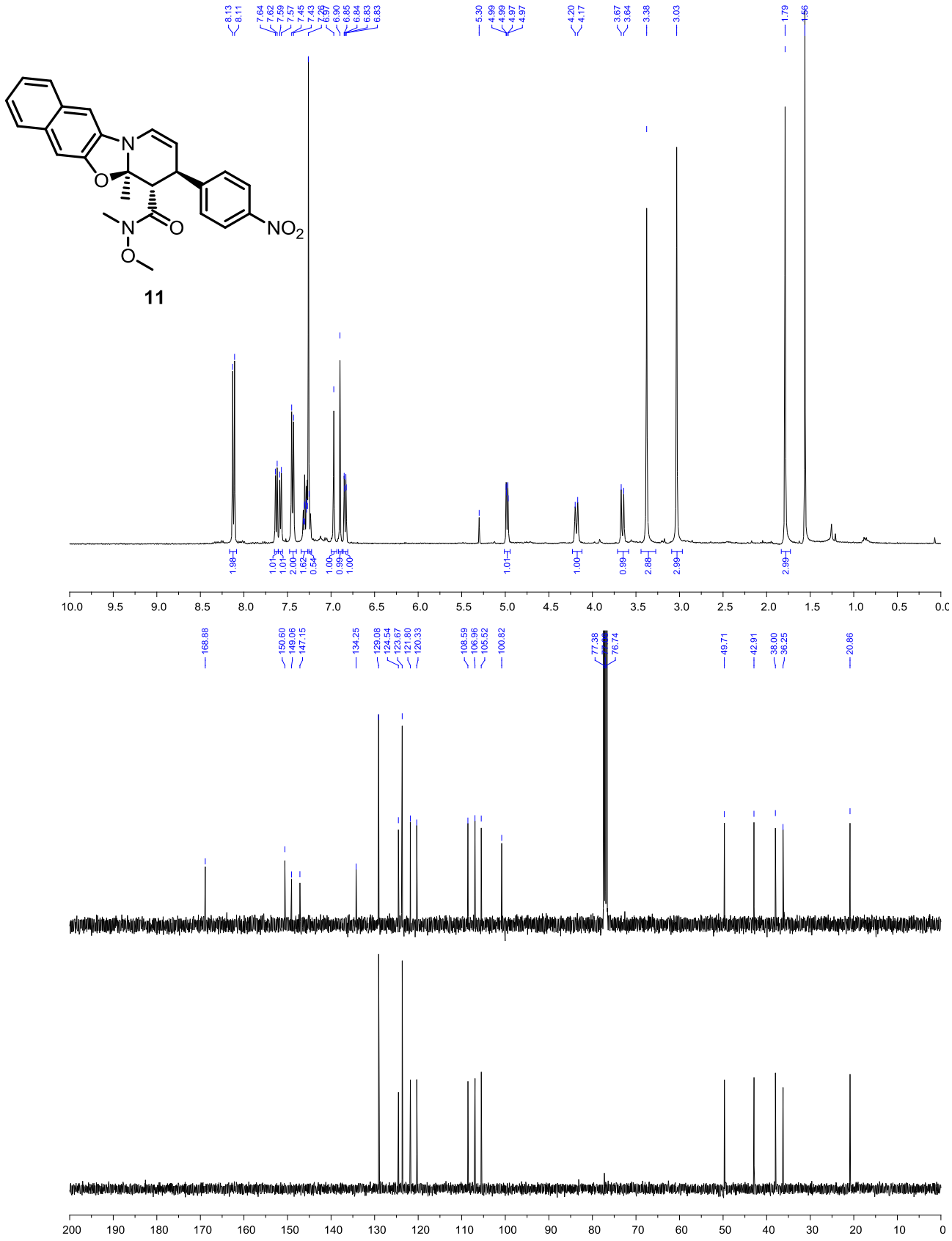
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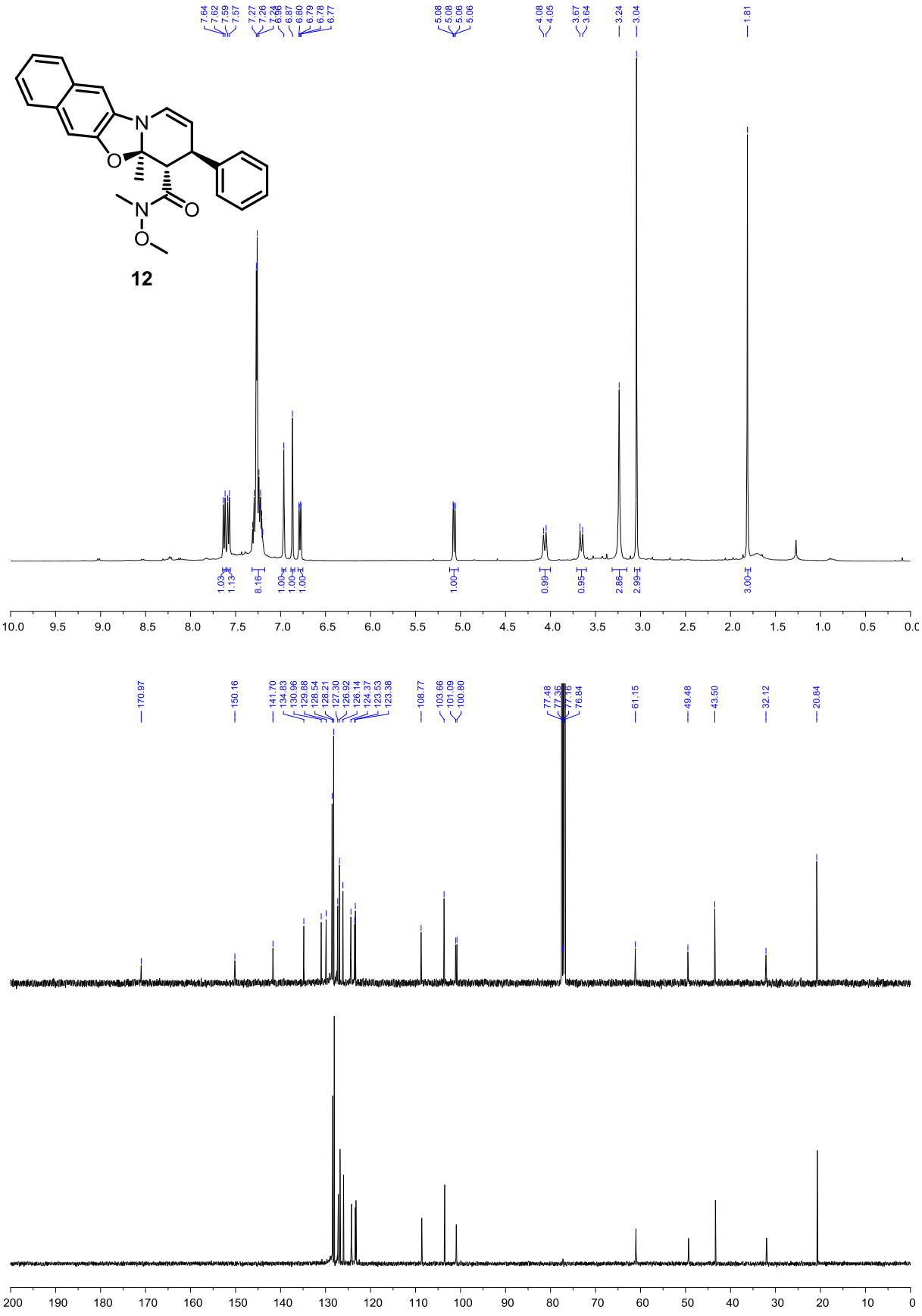
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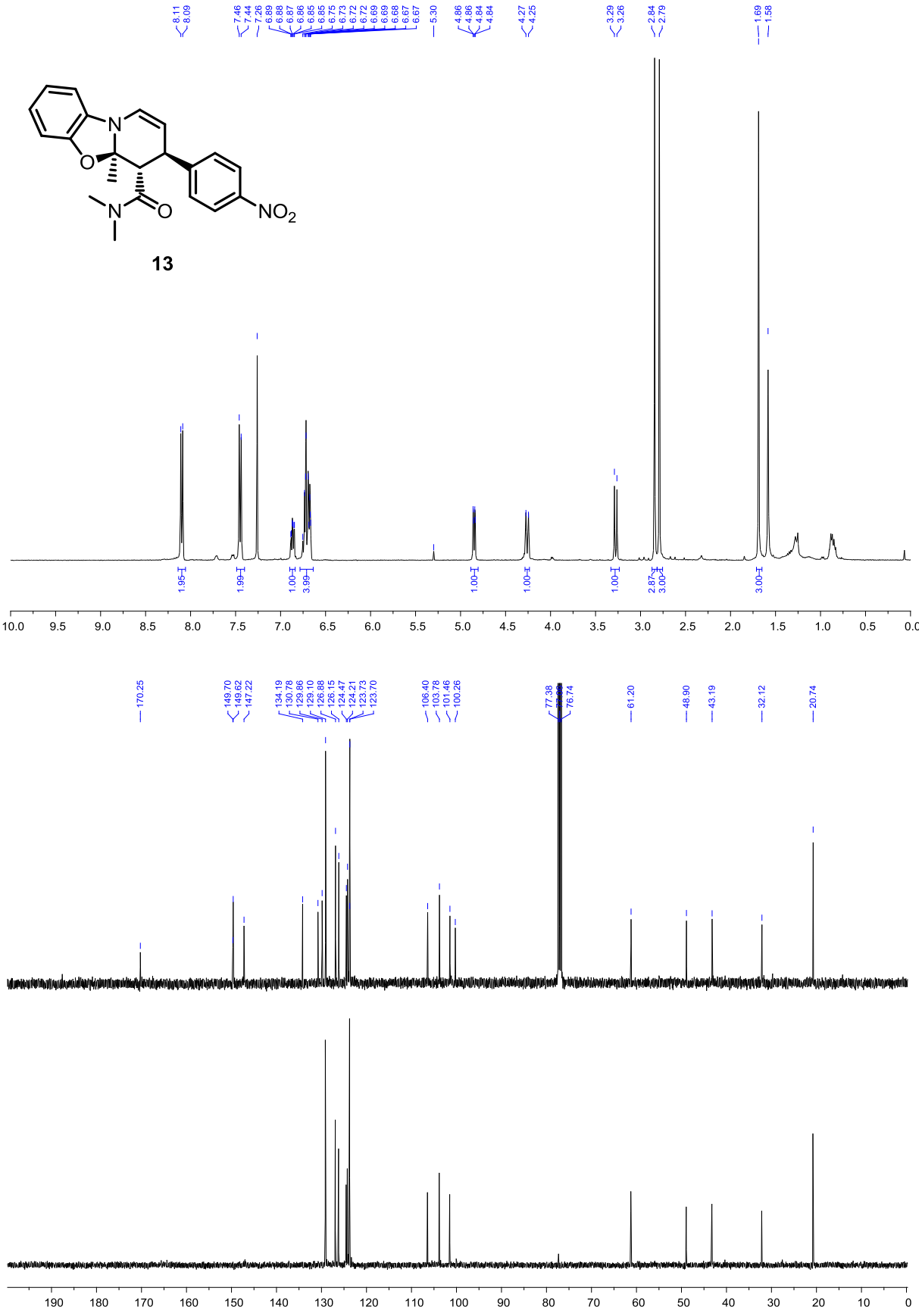
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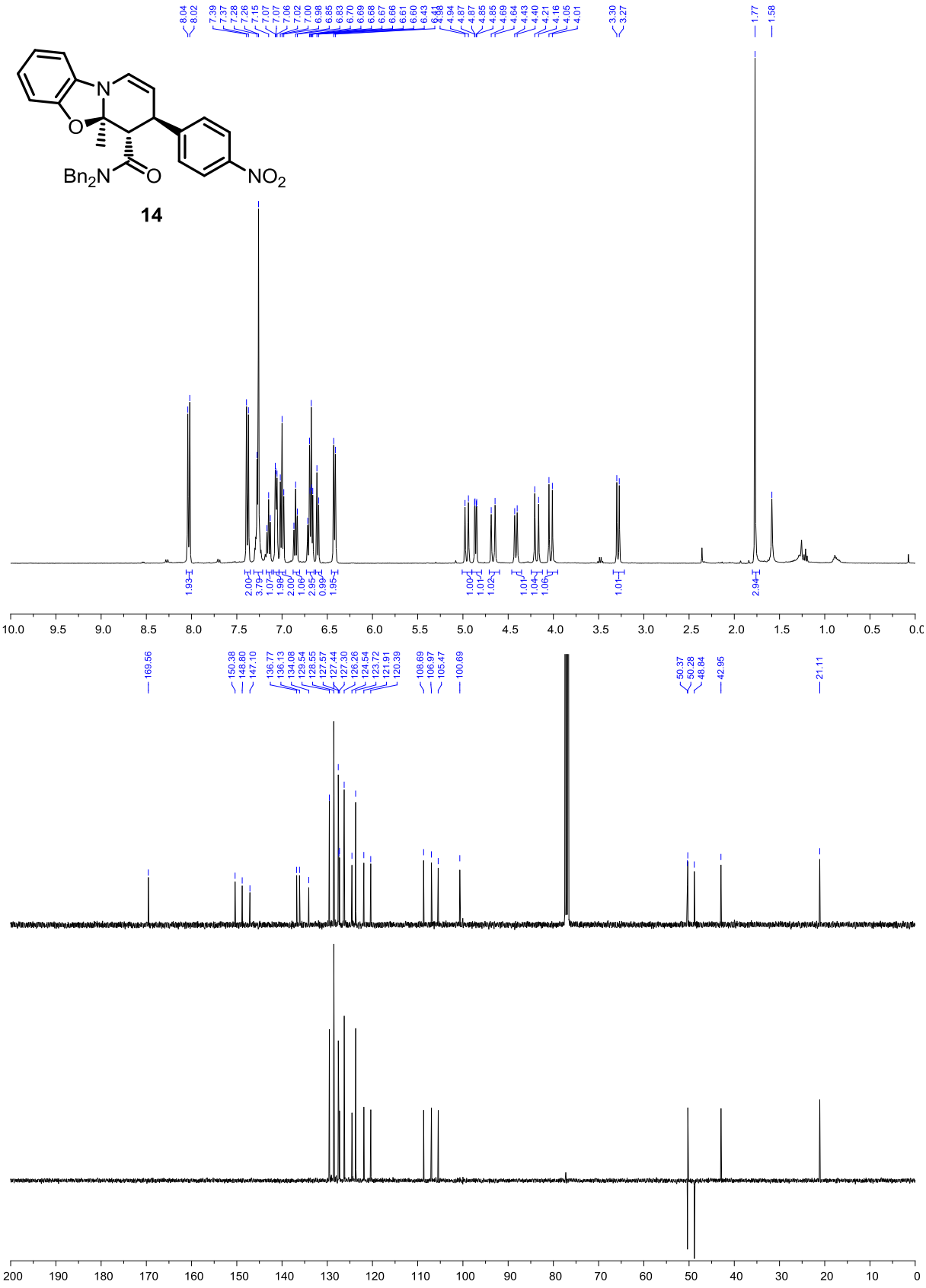
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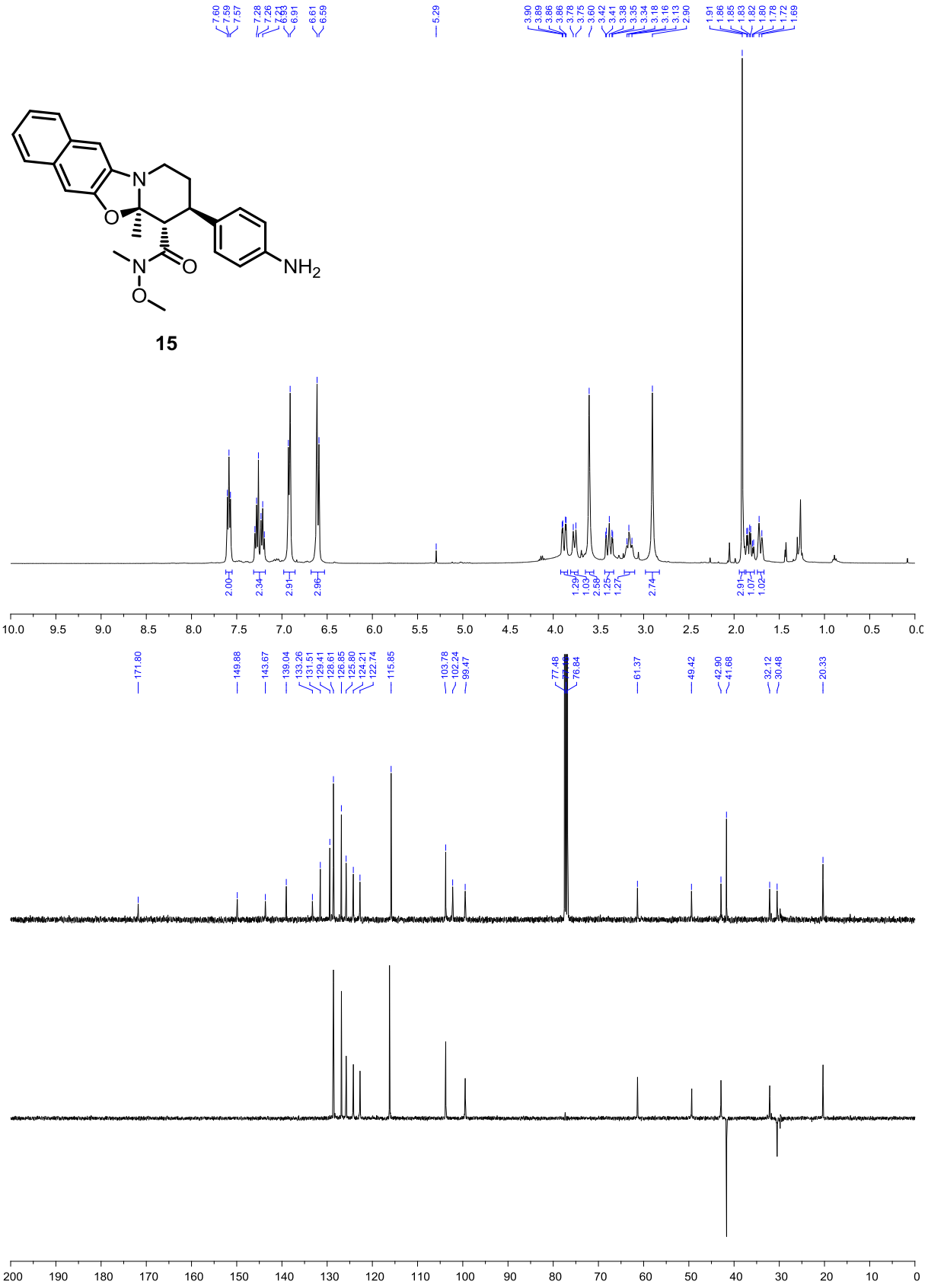
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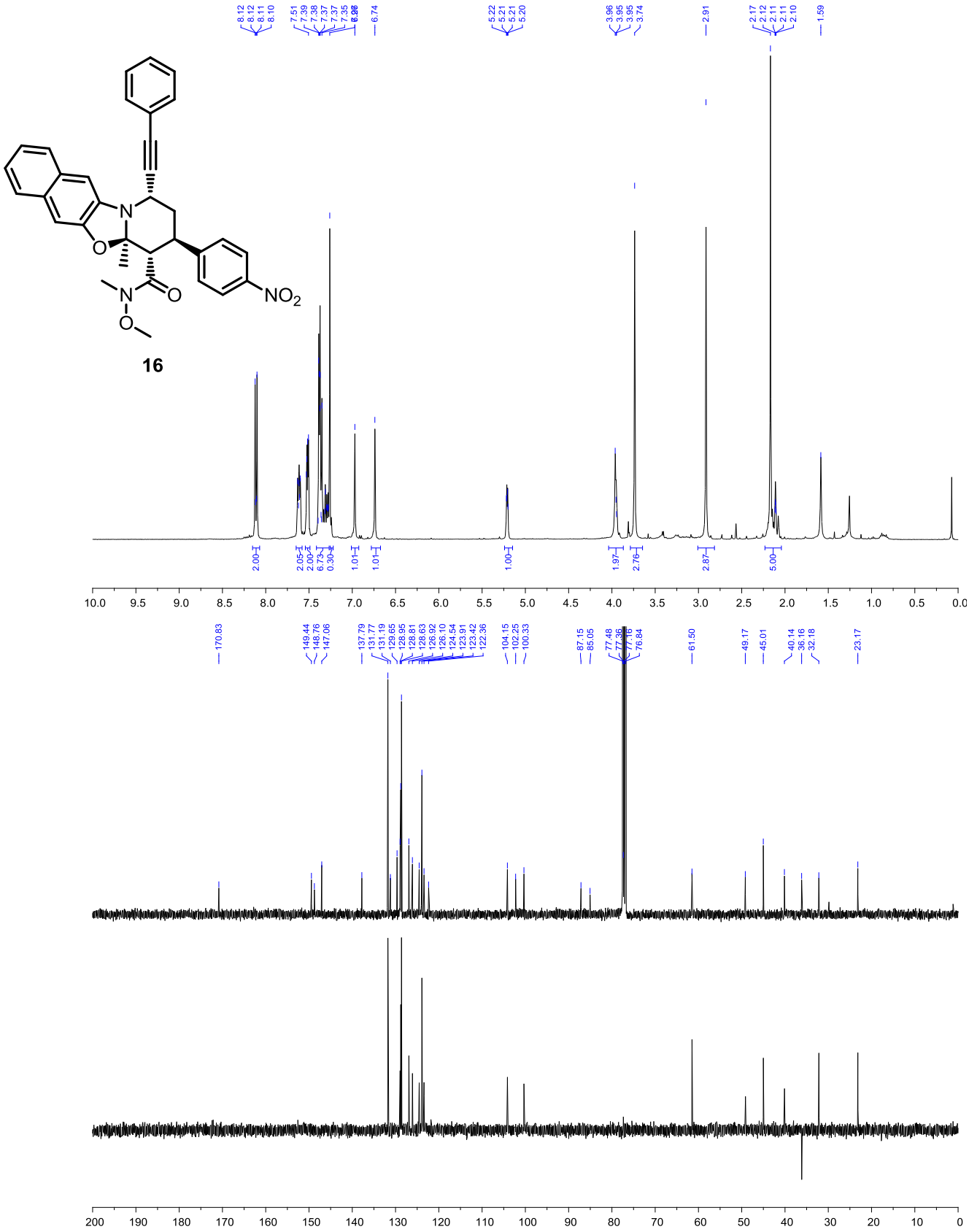
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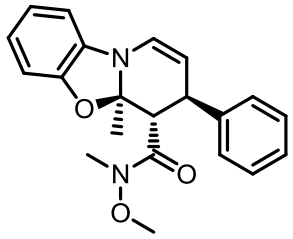
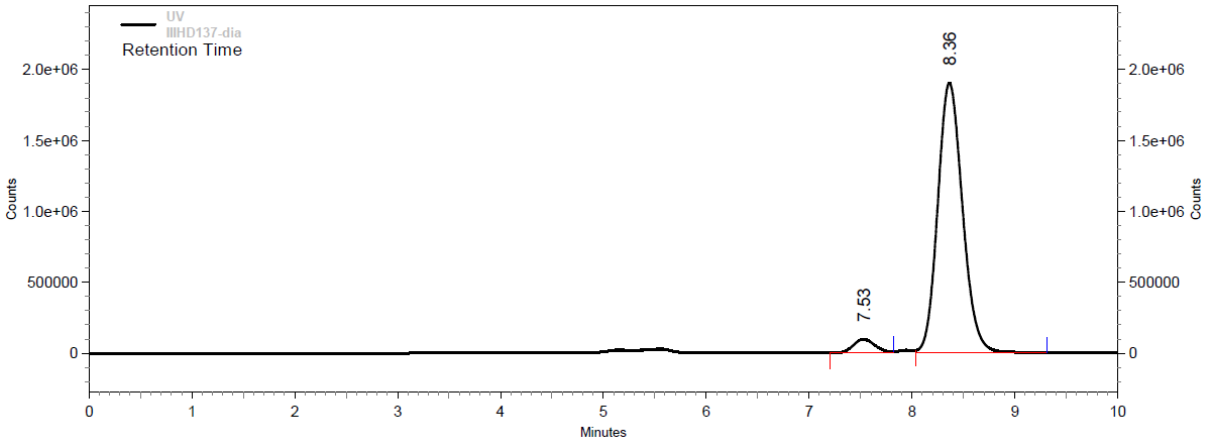
6. HPLC TRACES:



1

Sample : IIIHD137-dia

Method description : Chiralpak AZ-H, Hexane/Isopropanol 90/10, 1 ml/min, UV 254 nm et CD254nm

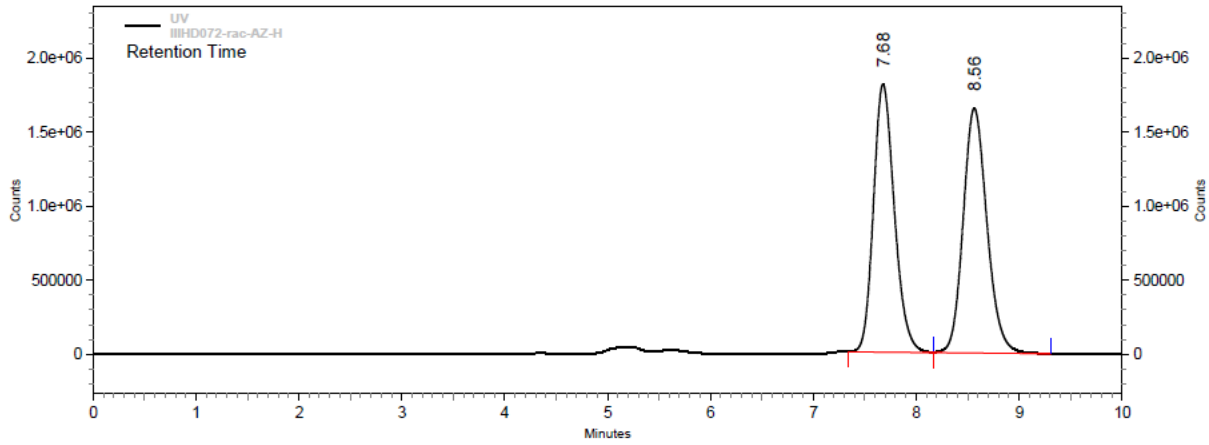


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.53	1429721	4.31	1.51	1.00	0.00
8.36	31720471	95.69	1.79	1.18	1.98

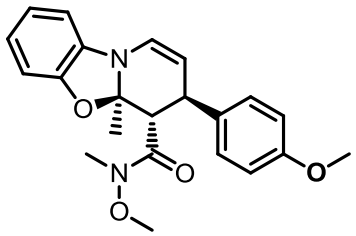
Sample : IIIHD072-rac-AZ-H

Method description : Chiralpak AZ-H, Hexane/Isopropanol 90/10, 1 ml/min, UV 254 nm et CD254nm



UV Results

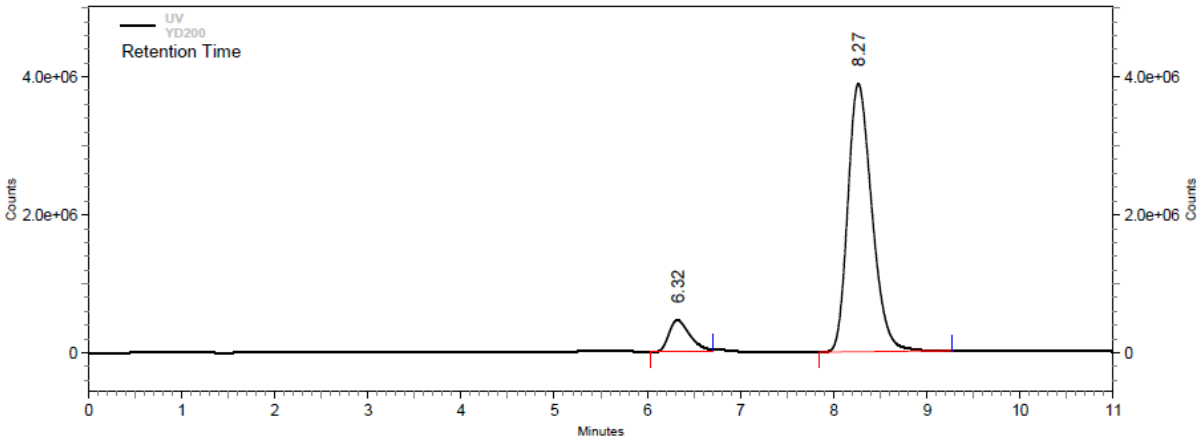
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.68	25595534	49.05	1.56	1.00	0.00
8.56	26590076	50.95	1.85	1.19	2.22



2

Sample : YD200

Method description : Chiralpak AD-H, Heptane/Isopropanol 90/10, 1 ml/min, UV 254 nm et CD254nm

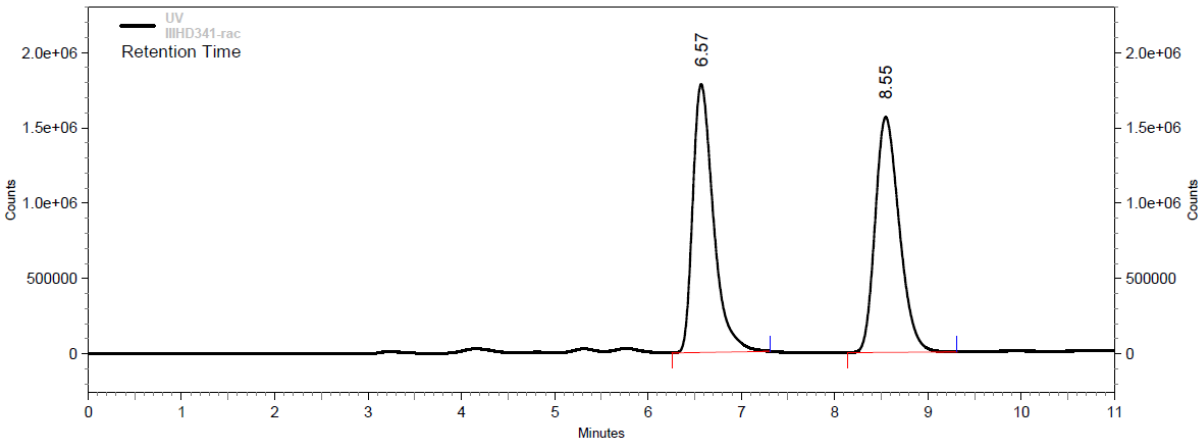


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.32	7289864	9.48	1.11	0.00	0.00
8.27	69591756	90.52	1.76	0.00	4.32

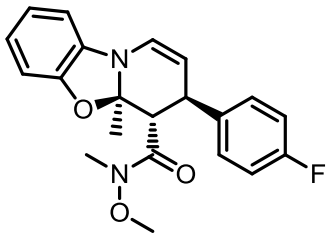
Sample : IIIHD341-rac

Method description : Chiralpak AD-H, Heptane/Isopropanol 90/10, 1 ml/min, UV 254 nm et CD254nm



UV Results

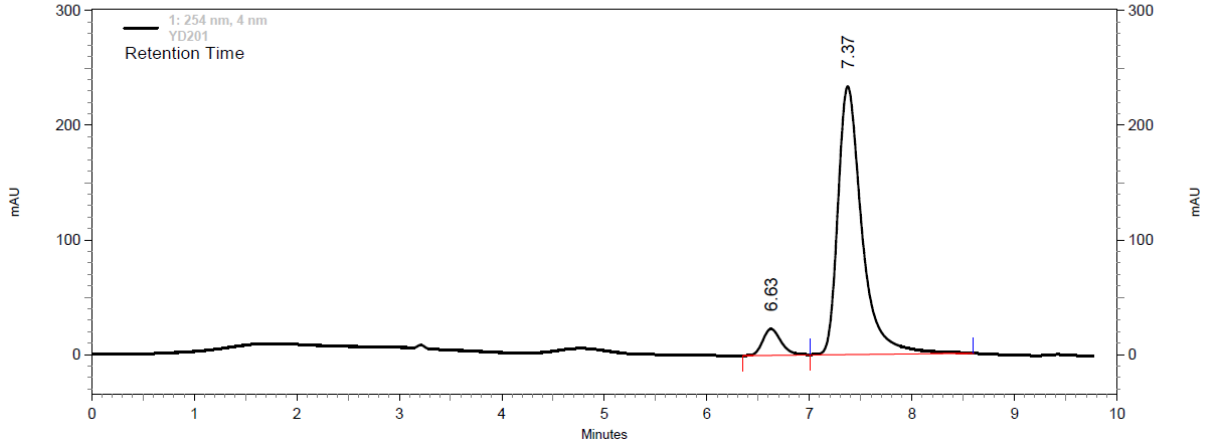
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.57	27458047	49.41	1.19	0.00	0.00
8.55	28109338	50.59	1.85	0.00	4.51



3

Sample : YD201

Method description : Chiralpak IF, Heptane/Isopropanol 95/5, 1 ml/min, DAD + CD254nm

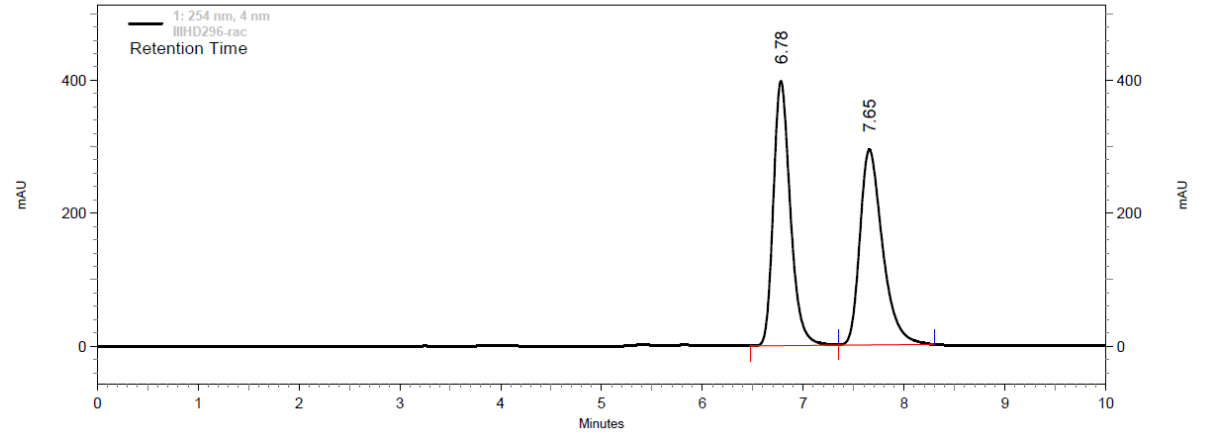


Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.63	1149151	7.01	1.21	1.00	0.00
7.37	15252742	92.99	1.46	1.21	2.05

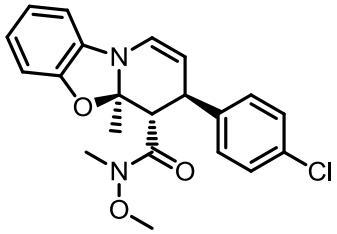
Sample : IIIHD296-rac

Method description : Chiralpak IF, Heptane/Isopropanol 95/5, 1 ml/min, DAD + CD254nm



Results

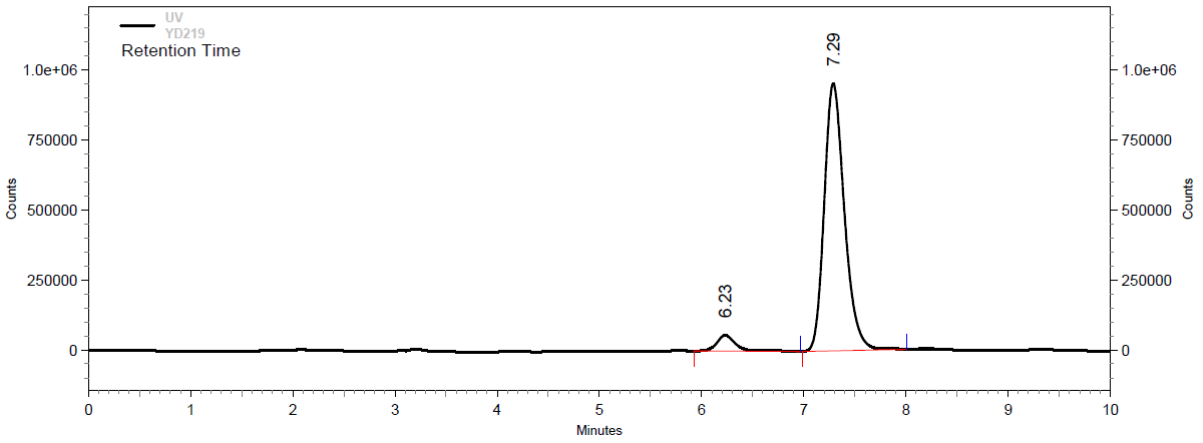
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.78	18645957	50.39	1.26	1.00	0.00
7.65	18356588	49.61	1.55	1.23	2.46



4

Sample : YD219

Method description : Chiralpak AZ-H, Heptane/ethanol 90/10, 1 ml/min, UV 254 nm et CD254nm

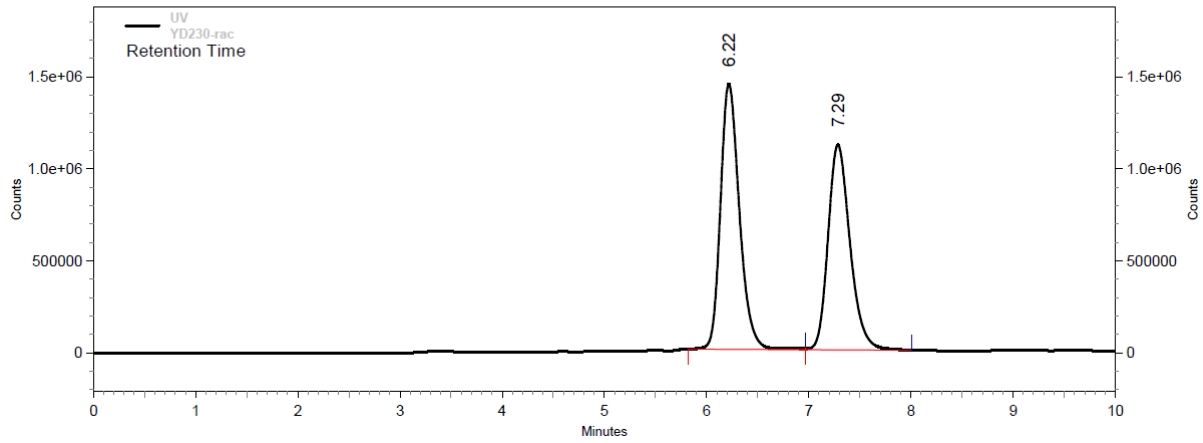


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.23	768439	5.53	1.08	1.00	0.00
7.29	13124214	94.47	1.43	1.33	3.11

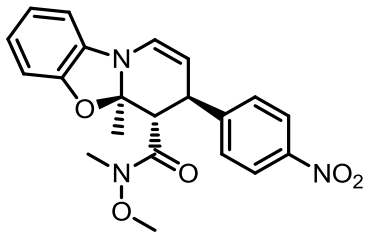
Sample : YD230-rac

Method description : Chiralpak AZ-H, Heptane/ethanol 90/10, 1 ml/min, UV 254 nm et CD254nm



UV Results

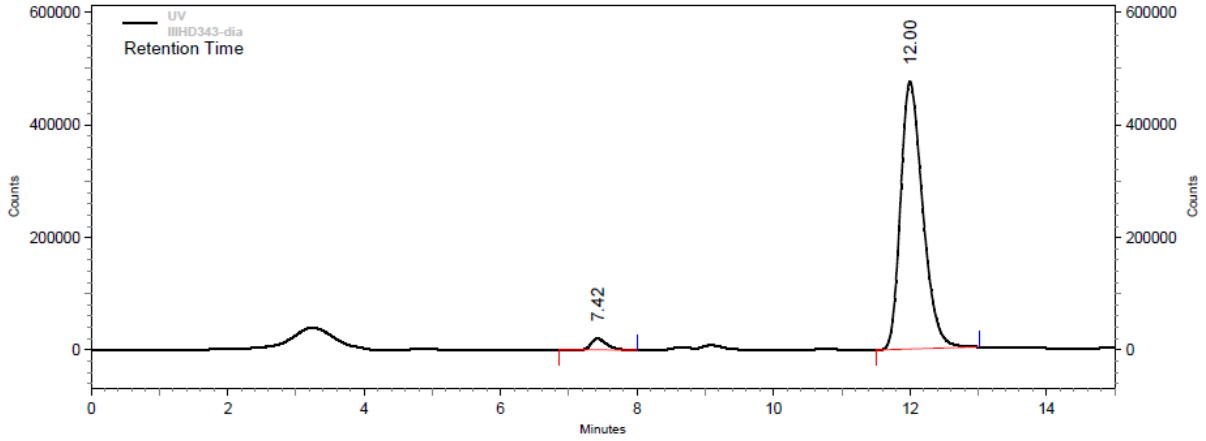
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.22	18619485	52.80	1.07	1.00	0.00
7.29	16644418	47.20	1.43	1.33	2.94



5

Sample : IIIHD343-dia

Method description : Chiralpak AD-H, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et CD254nm

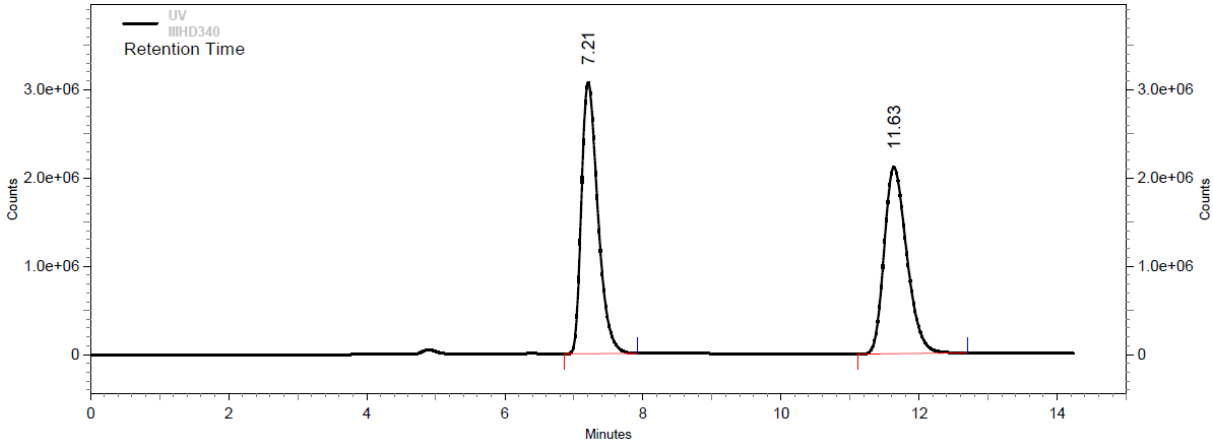


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.42	323863	2.93	1.47	0.00	0.00
12.00	10733675	97.07	3.00	0.00	9.01

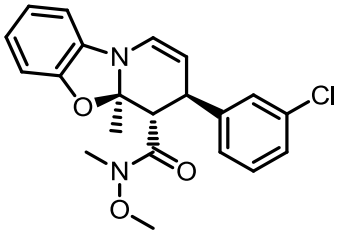
Sample : IIIHD340

Method description : Chiralpak AD-H, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et CD254nm



UV Results

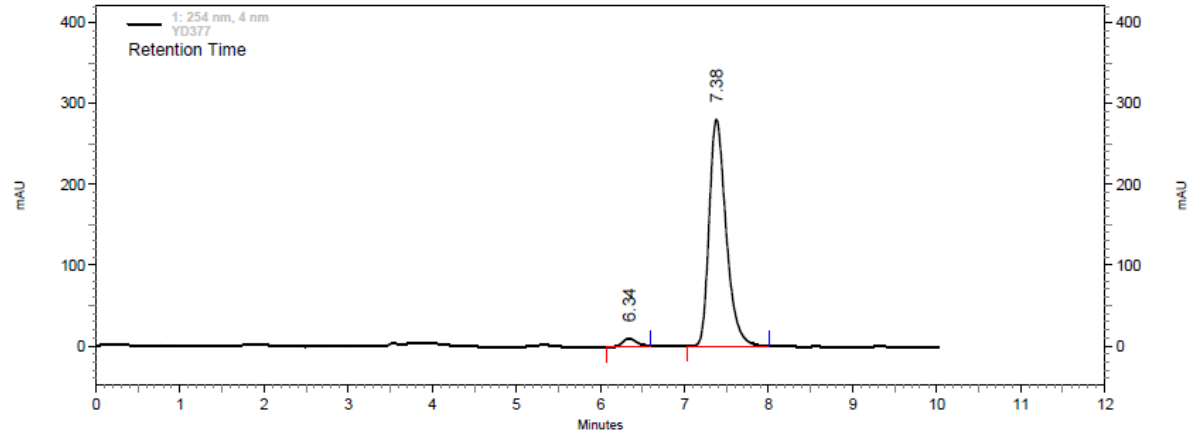
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.21	50702065	51.26	1.40	0.00	0.00
11.63	48217051	48.74	2.88	0.00	8.50



6

Sample : YD377

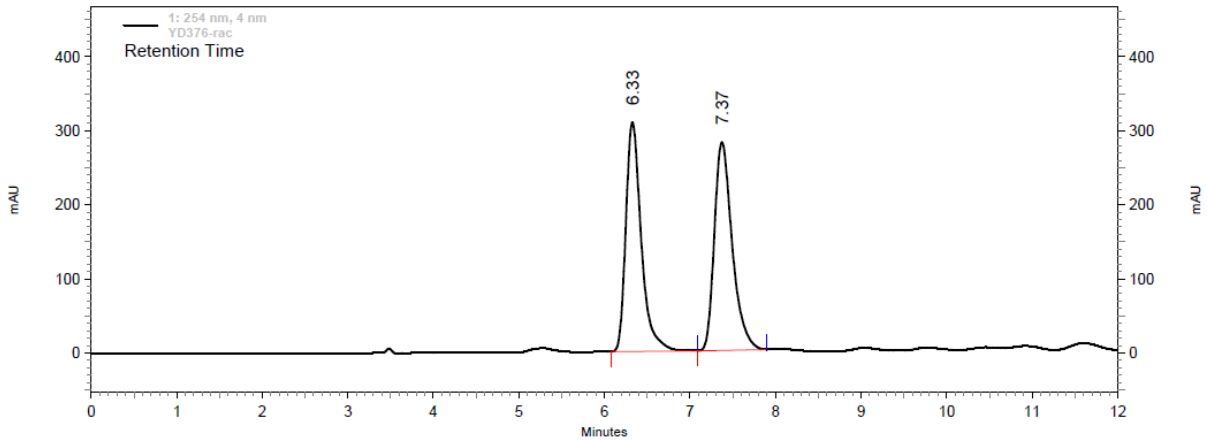
Method description : Chiralpak ID, Heptane/Ethanol 95/5, 1 ml/min, DAD and CD 254nm



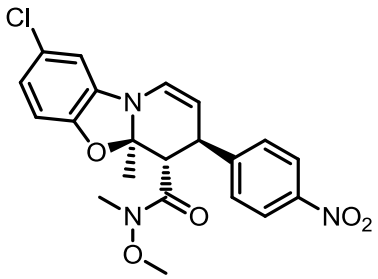
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.34	508786	3.16	1.11	0.00	0.00
7.38	15612443	96.84	1.46	0.00	3.05

Sample : YD376-rac

Method description : Chiralpak ID, Heptane/Ethanol 95/5, 1 ml/min, DAD and CD 254nm



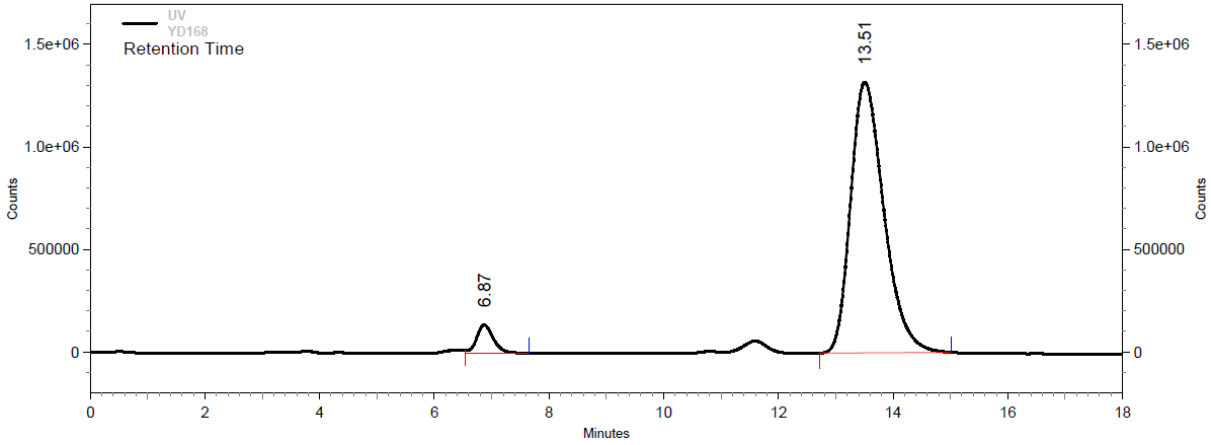
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.33	15521471	48.82	1.11	0.00	0.00
7.37	16269612	51.18	1.46	0.00	3.01



7

Sample : YD168

Method description : Chiralcel OD-3, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et polarimetre

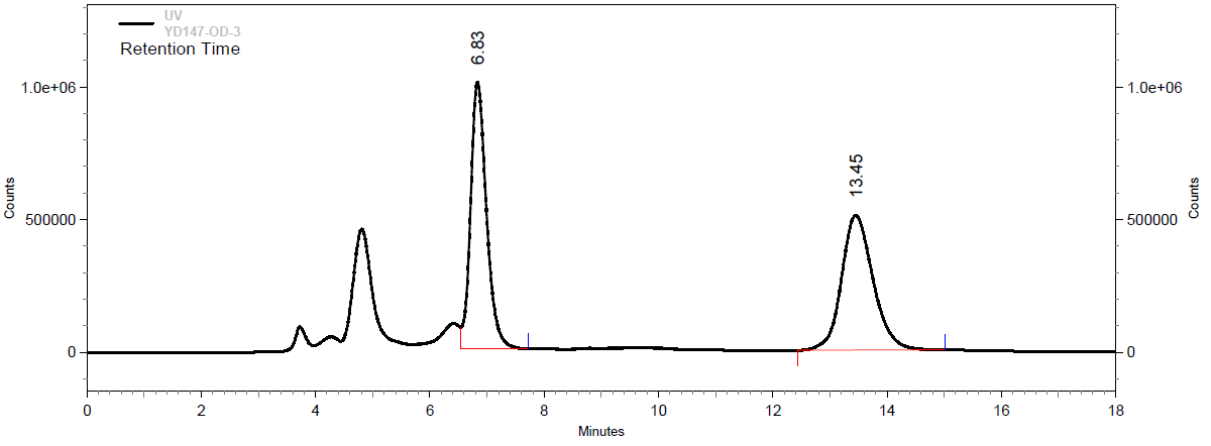


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.87	2788172	4.97	1.29	0.00	0.00
13.51	53296644	95.03	3.50	0.00	8.36

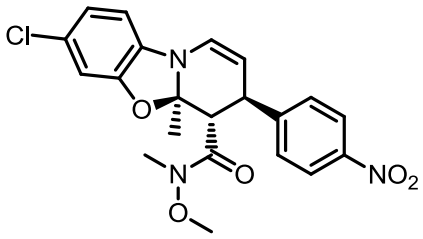
Sample : YD147-OD-3

Method description : Chiralcel OD-3, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et polarimetre



UV Results

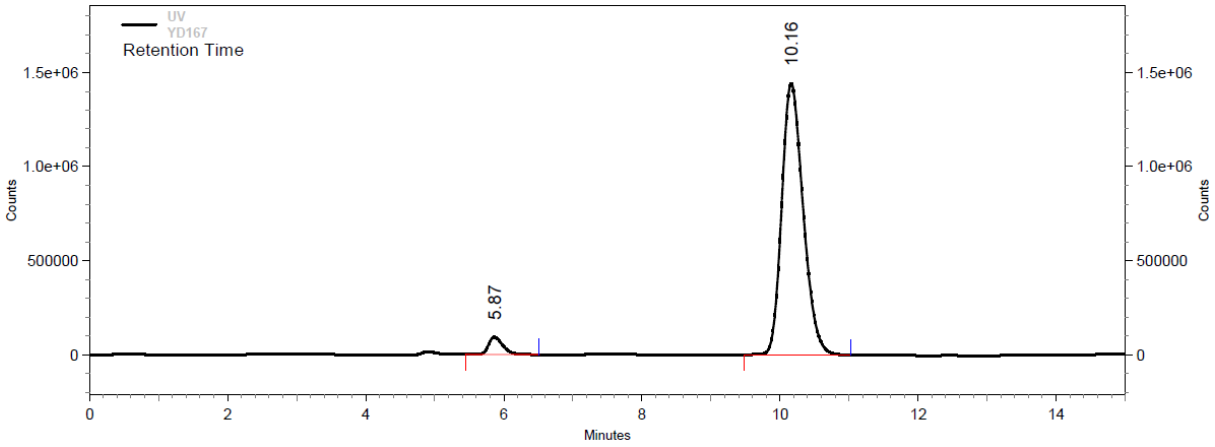
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.83	19426753	49.98	1.28	0.00	0.00
13.45	19445742	50.02	3.48	0.00	8.82



8

Sample : YD167

Method description : Chiralpak AD-H, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et CD254nm

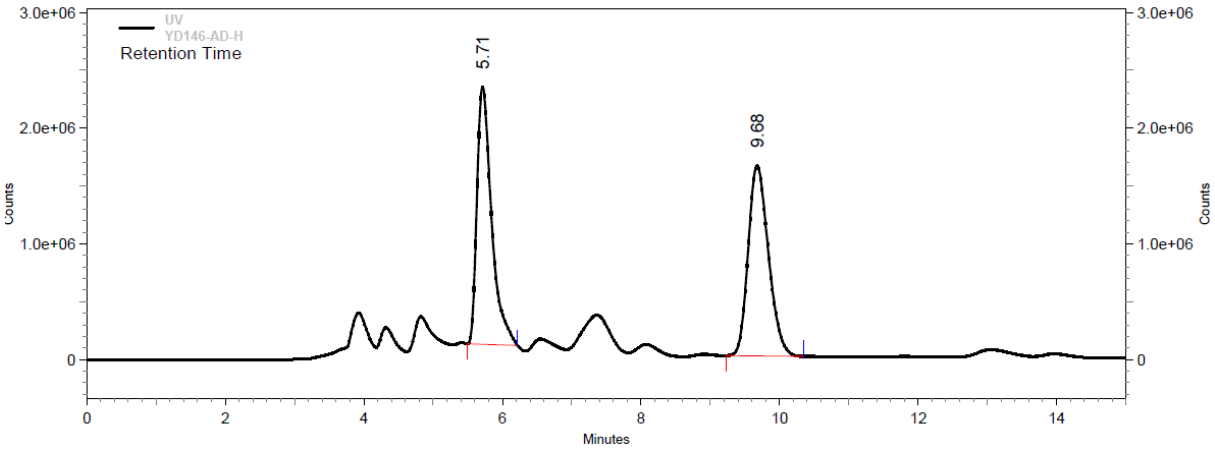


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
5.87	1322019	4.08	0.96	0.00	0.00
10.16	31114321	95.92	2.39	0.00	9.01

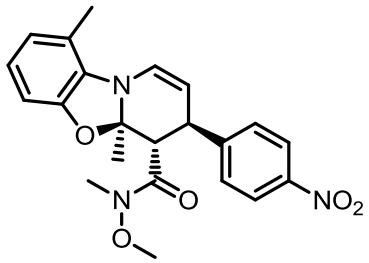
Sample : YD146-AD-H

Method description : Chiralpak AD-H, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et CD254nm



UV Results

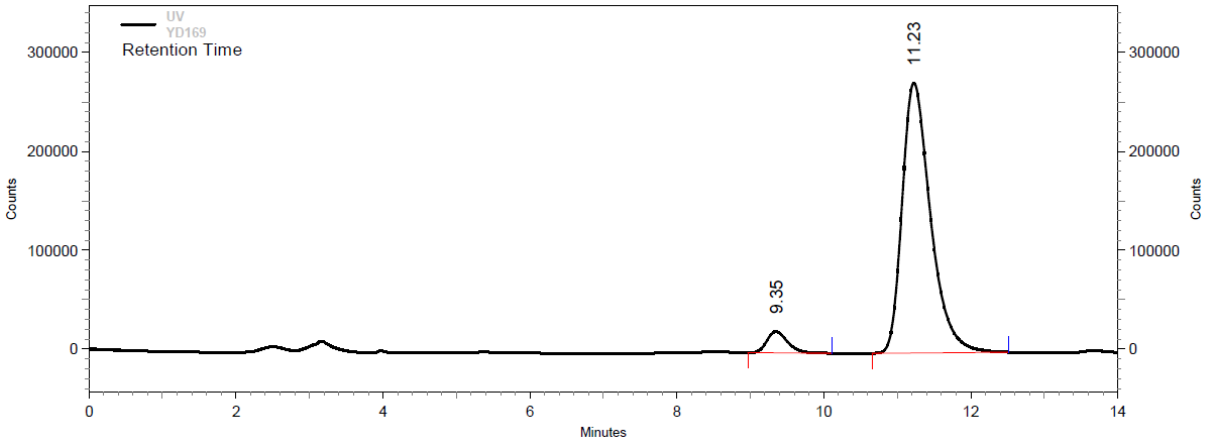
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
5.71	32700319	49.43	0.90	0.00	0.00
9.68	33459187	50.57	2.23	0.00	8.61



9

Sample : YD169

Method description : Lux-Cellulose-4, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et CD254nm

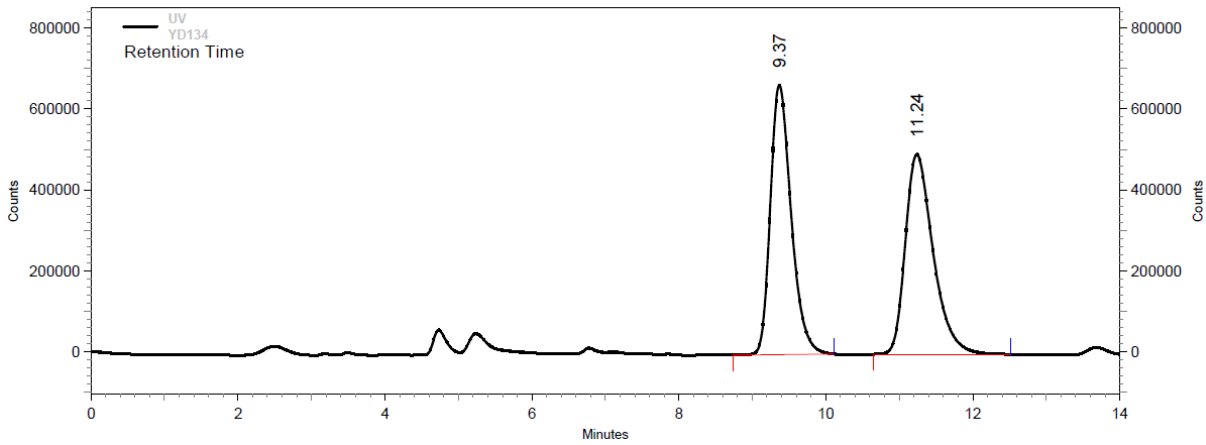


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.35	418129	5.40	2.12	1.00	0.00
11.23	7320720	94.60	2.74	1.30	3.09

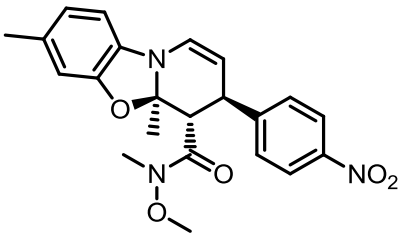
Sample : YD134

Method description : Lux-Cellulose-4, Heptane/Isopropanol 80/20, 1 ml/min, UV 254 nm et CD254nm



UV Results

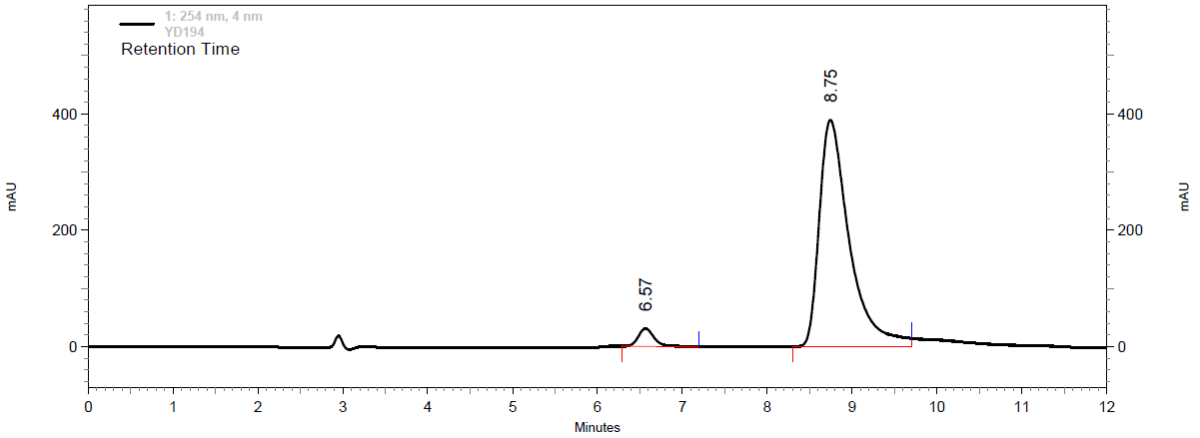
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.37	13107639	50.19	2.12	1.00	0.00
11.24	13008293	49.81	2.75	1.29	3.10



10

Sample : YD194

Method description : Chiralpak IF, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm

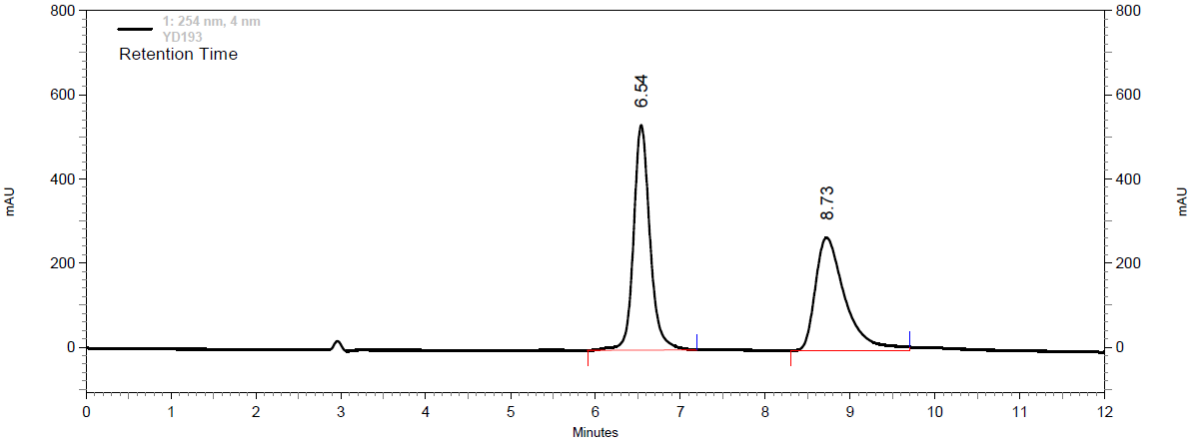


Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.57	1632305	4.08	1.19	0.00	0.00
8.75	38395135	95.92	1.92	0.00	4.62

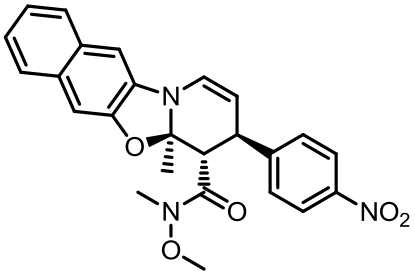
Sample : YD193

Method description : Chiralpak IF, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm



Results

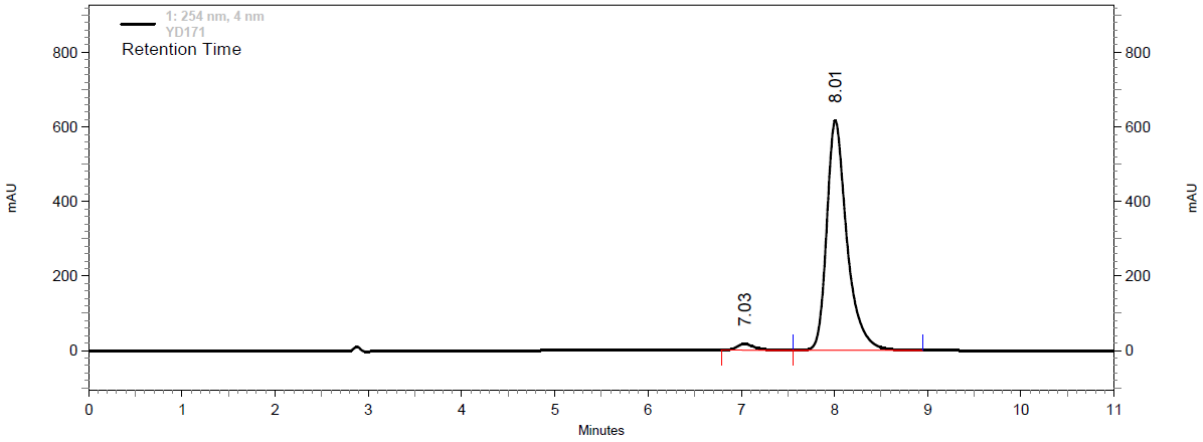
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.54	28751044	52.36	1.18	0.00	0.00
8.73	26161838	47.64	1.91	0.00	4.62



11

Sample : YD171

Method description : Chiralpak IA, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm

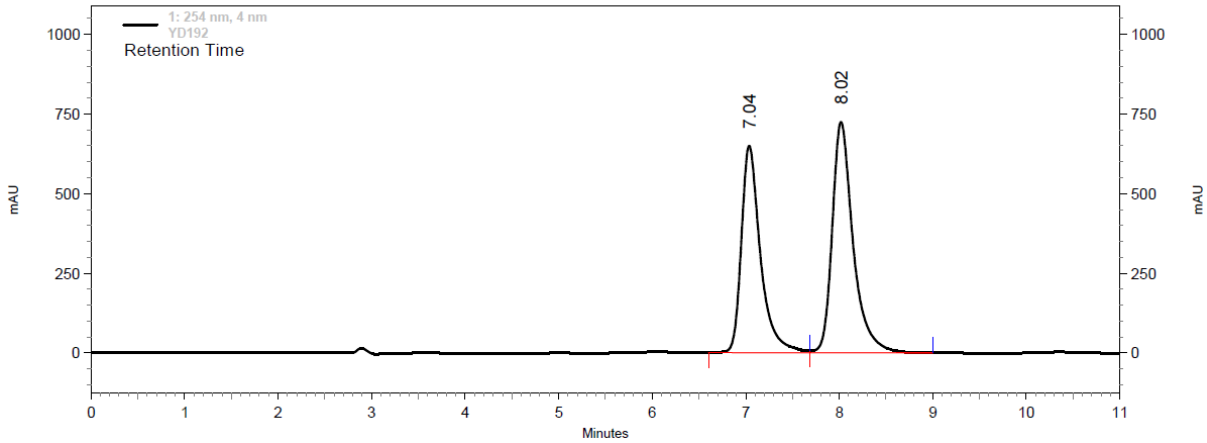


Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.03	865640	2.28	1.34	0.00	0.00
8.01	37178774	97.72	1.67	0.00	2.70

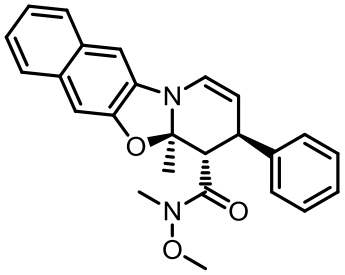
Sample : YD192

Method description : Chiralpak IA, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm



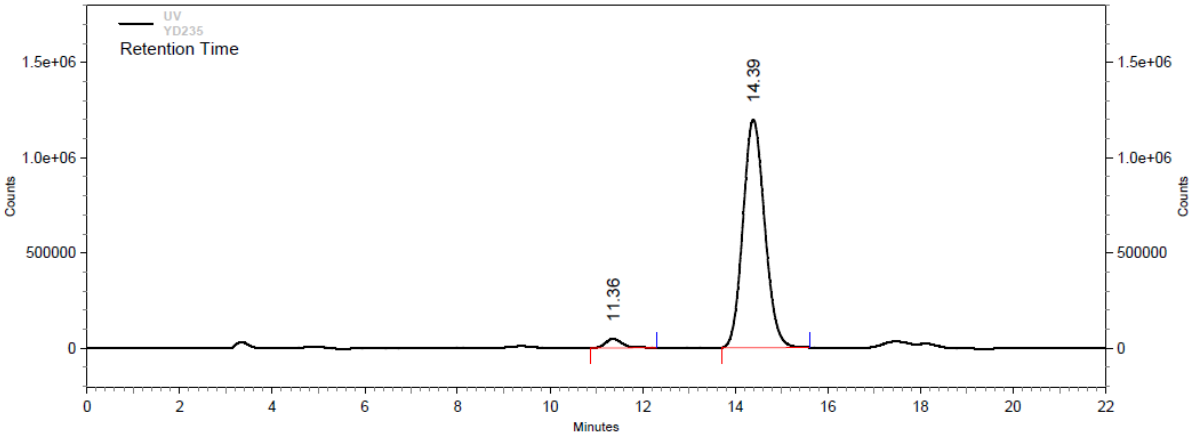
Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
7.04	36926333	45.08	1.35	0.00	0.00
8.02	44994629	54.92	1.67	0.00	2.63



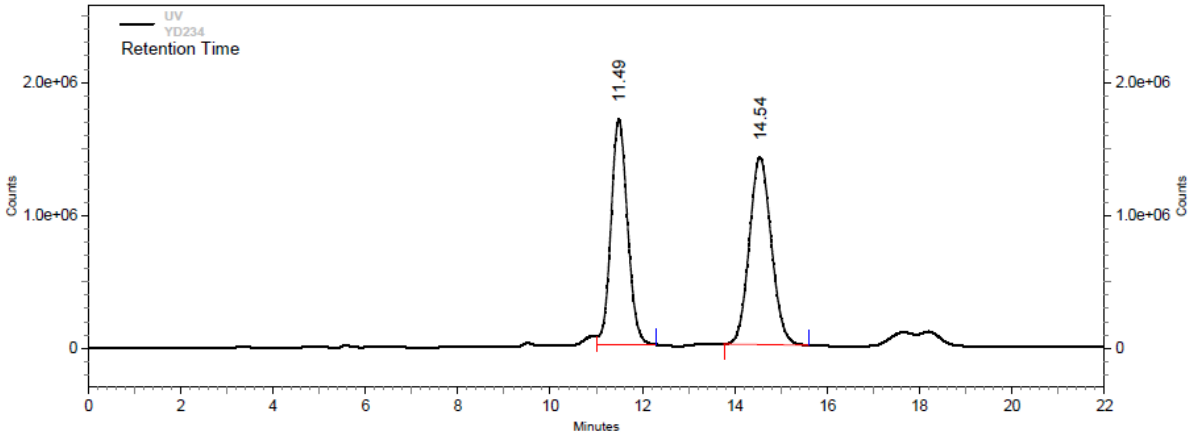
12

Sample : YD235
Method description : Chiralpak AZ-H, Heptane/Isopropanol 95/5, 1 ml/min, UV 254 nm et CD254nm

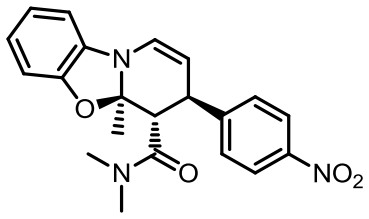


UV Results Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
11.36	1221790	3.04	2.79	0.00	0.00
14.39	39019274	96.96	3.80	0.00	3.97

Sample : YD234
Method description : Chiralpak AZ-H, Heptane/Isopropanol 95/5, 1 ml/min, UV 254 nm et CD254nm



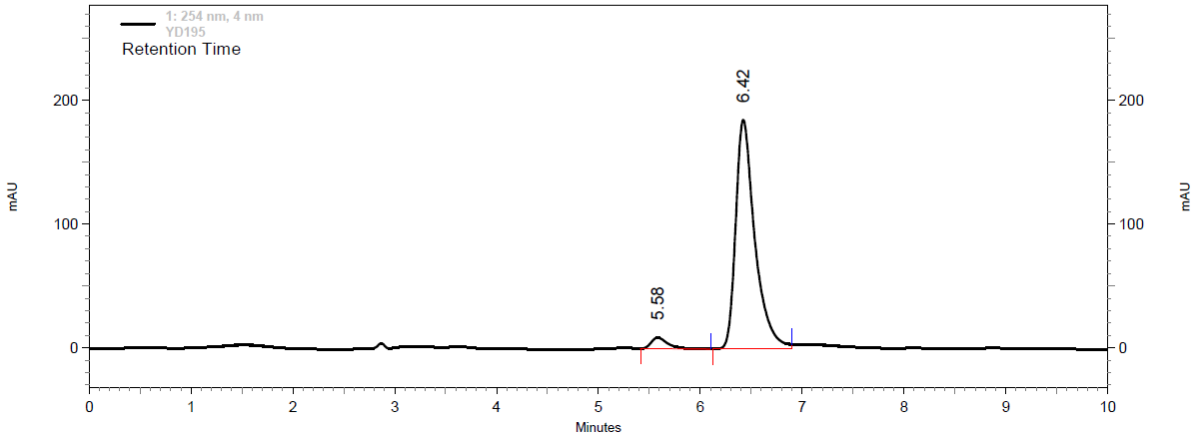
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
11.78	3447808	48.69	0.00	0.00	
14.85	3632647	51.31	0.00	0.00	



13

Sample : YD195

Method description : Chiralpak IA, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm

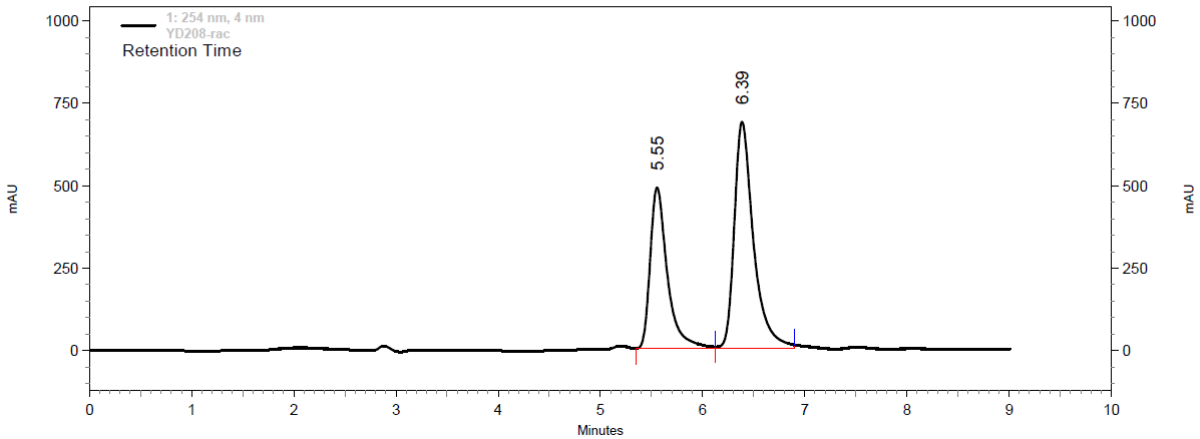


Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
5.58	404406	4.00	0.86	0.00	0.00
6.42	9700608	96.00	1.14	0.00	2.74

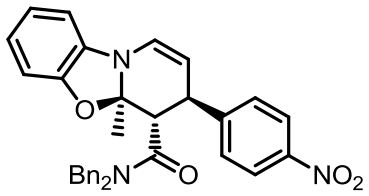
Sample : YD208-rac

Method description : Chiralpak IA, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm



Results

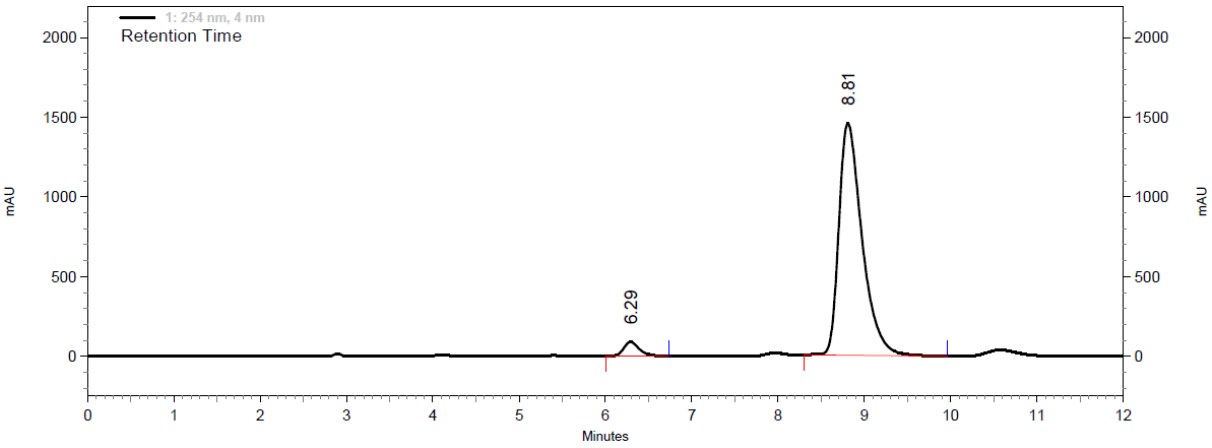
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
5.55	22987213	38.90	0.85	0.00	0.00
6.39	36098398	61.10	1.13	0.00	2.69



14

Sample : YD196

Method description : Chiralpak IA, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm

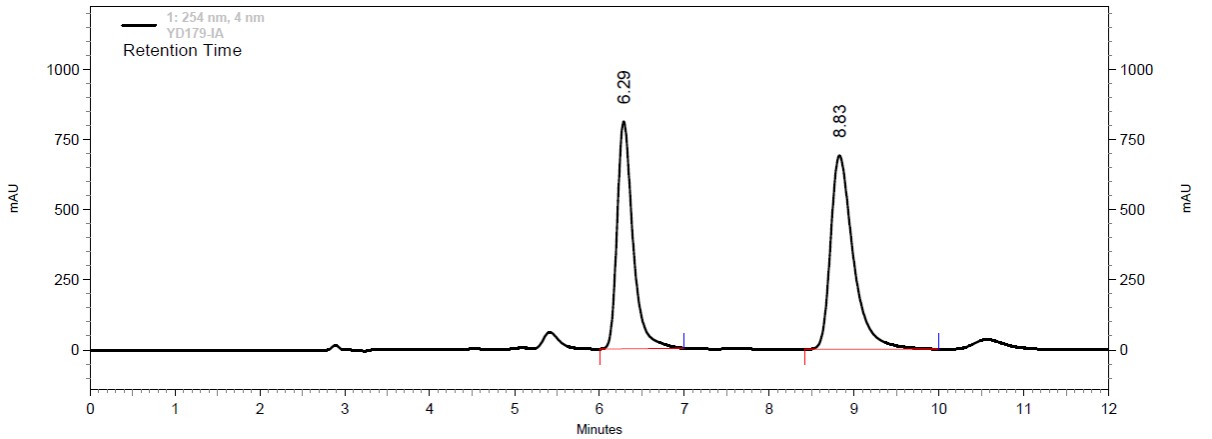


Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.29	4467326	3.95	1.10	0.00	0.00
8.81	108656143	96.05	1.94	0.00	6.22

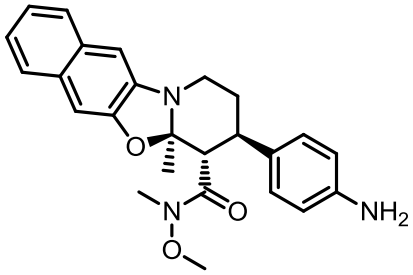
Sample : YD179-IA

Method description : Chiralpak IA, Heptane/Ethanol 80/20, 1 ml/min, DAD and CD254nm



Results

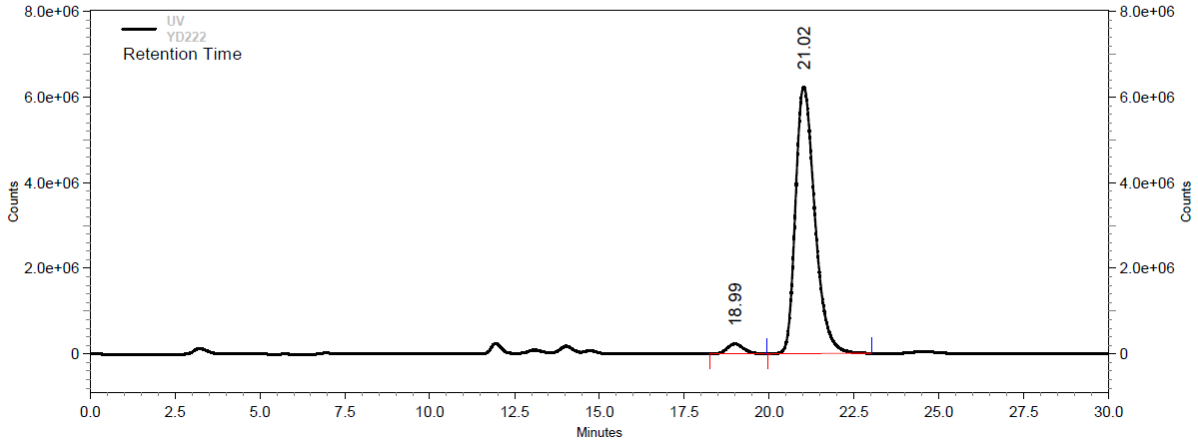
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
6.29	42105236	44.98	1.10	0.00	0.00
8.83	51507250	55.02	1.94	0.00	6.36



15

Sample : YD222

Method description : Lux-Cellulose-4, Heptane/ethanol 80/20, 1 ml/min, UV 254 nm et polarimetre

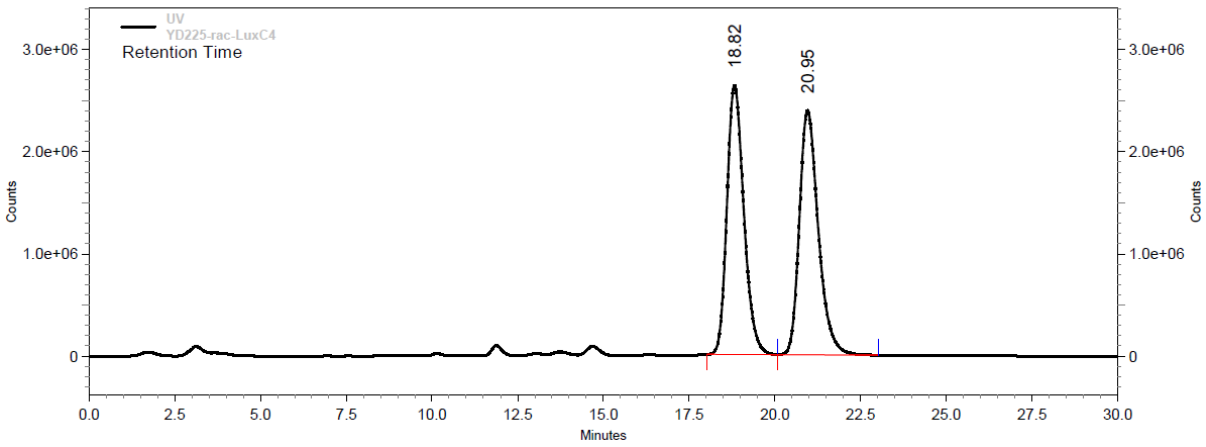


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
18.99	7689178	3.02	5.33	1.00	0.00
21.02	247155788	96.98	6.01	1.13	2.12

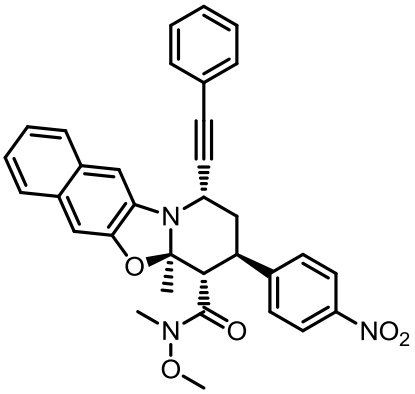
Sample : YD225-rac-LuxC4

Method description : Lux-Cellulose-4, Heptane/ethanol 80/20, 1 ml/min, UV 254 nm et polarimetre



UV Results

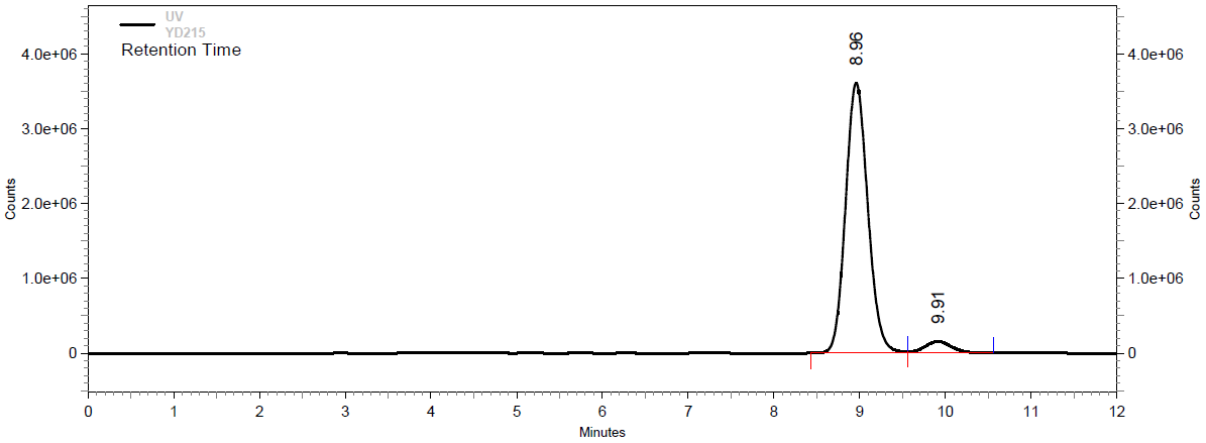
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
18.82	90400327	49.59	5.27	1.00	0.00
20.95	91906403	50.41	5.98	1.13	2.23



16

Sample : YD215

Method description : Lux-Cellulose-2, Heptane/ethanol 70/30, 1 ml/min, UV 254 nm et polarimetre

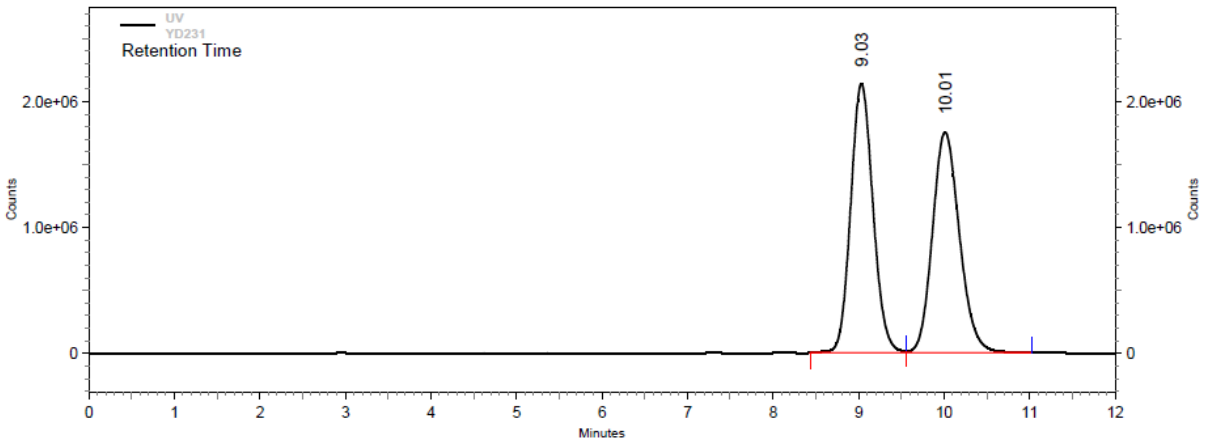


UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
8.96	65169253	95.02	1.99	1.00	0.00
9.91	3418247	4.98	2.30	1.16	1.79

Sample : YD231

Method description : Lux-Cellulose-2, Heptane/ethanol 70/30, 1 ml/min, UV 254 nm et polarimetre



UV Results

Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)
9.03	38846651	50.27	2.01	1.00	0.00
10.01	38435601	49.73	2.34	1.16	1.84