Supporting Information

Identification of the first enantiopure Rac1-Tiam1 Protein-Protein interaction inhibitor and optimized synthesis via phosphine free remote group directed hydroarylation

Alessandro Ruffoni [a*], Nicola Ferri [b], Andrea Pinto [c], Sara Pellegrino [d], Alessandro Contini [d], Francesca Clerici [d*].

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General Experimental Details

Synthesis. All reagents and solvents were obtained from commercial sources.

1 (AR-148), 2, 3, 4, 5 [1] [2] are known compounds and were synthesized according to the literature. Reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60 F254) using UV light as a visualizing agent. Column chromatography was performed on Kieselgel 60 (70−230 mesh ASTM) or Davisil LC 60 A (230−400 mesh) using ethyl acetate/hexane as eluting solvents. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini 200 or Bruker Avance 300 or 500 MHz spectrometers in the solvent indicated. Coupling constants (J) are given in Hertz. The infrared spectra were recorded with a Perkin-Elmer 16 PC FT-IR spectrometer using NaCl disks for liquid samples and tablets of KBr for solid samples. The low resolution mass spectra were recorded in electron impact on a Fisons MD800 spectrometer and electrospray ion trap with Finnigan LCQ ADVANTAGE Thermo spectrometer. Melting points were determined on a Buchi 530 melting point apparatus and are uncorrected. Chiral HPLC analyses were performed with a Jasco PU-980 pump equipped with a UV–vis detector Jasco UV-975 (wavelength: 220 nm) and Phenomenex Lux Amylose-2 column (4.6 × 150 mm, 5 μm). Preparative HPLC was performed with a 1525 Extended Flow Binary HPLC Pump, equipped with a Waters 2489 UV-vis detector and a Phenomenex Lux Amylose-2 column (21.2 × 250 mm) at a flow rate of 15 mL/min. Rotary power determinations were carried out with a Jasco P-1010 spectropolarimeter coupled with a Haake N3-B thermostat.

Experimental Procedures and Characterizations

Ethyl (1S*,2R*,3S*,4S*,5S*)-2-amino-5-(3-aminophenyl)-3-(phenylthio)bicyclo[2.2.1]heptane-2-carboxylate (7) and Ethyl (1R*,2R*,3S*,4R*,6R*)-2-amino-6-(3-aminophenyl)-3-(phenylthio)bicyclo[2.2.1]heptane-2-carboxylate (8)

Compound **5** (1 eq.) was dissolved in dry CH_3CN (0.1M) in a Pyrex tube under nitrogen. $Pd(OAc)_2$ (0.05 eq.), 3-iodoaniline (**6**) (1.1 eq), dry TEA (3.5 eq.) and formic acid (3 eq.) was added under stirring. The tube was sealed with Teflon caps and stirred at 45 °C for 24-48 h. The reaction was monitored by TLC analysis (DCM : MeOH = 1 : 10) and ^{1}H-NMR analysis. Upon consumption of starting material the solvent was removed under reduced pressure and the crude was purified using flash chromatography [Flash chromatography after deactivation of silica gel with a solution of EtOAc : n-hexane = 1 : 5 + 10% of TEA (EtOAc : n-hexane = 1 : 3-3 : 1)] to give a clean mixture of two regioisomers **7** and **8**. Total Yield = 82-88%. (**7**:**8** = 30:70 %). Pure samples of **7** and **8** were successfully separated for

the characterization. Compound **7** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 – 7.00 (m, 6H), 6.63 – 6.45 (m, 3H), 4.32 – 4.04 (m, 2H), 3.57 (bs, 4H, NH_2), 3.12 (d, *J* = 2.9 Hz, 1H), 2.92 (t, *J* = 8.0 Hz, 1H), 2.63 (s, 1H), 2.50 (s, 1H), 2.39(d, *J* = 11.3 Hz, 1H), 2.04(s, 1H), 1.81 (d, *J* = 11.3 Hz, 1H), 1.64 – 1.44 (m, 1H), 1.32 – 1.16 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2 (CO), 147.3, 146.5, 137.2 (Cq arom), 129.7, 129.5, 129.1, 126.4, 117.3, 113.8, 113.0 (CH arom), 69.6 (C2), 65.2 (C3), 61.5 (OCH_2), 51.4, 46.8, 46.4 (C1, C4, C6), 37.7 (C5), 32.9 (C7), 14.2 (CH_3). Mass: (+)ESI-MS (m/z): [M + H+] 383.3; Anal. $C_{22}H_{26}N_2O_2S$ (382.17) were within ± 0.4 % of the theoretical values.

Compound **8** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 – 7.01 (m, 6H), 6.71 – 6.43 (m, 3H), 4.28 – 4.04 (m, 2H), 3.63 (t, *J* = 6.8 Hz, 1H), 3.05 (d, *J* = 2.7 Hz, 1H), 2.66 (s, 1H), 2.65 (bs, 4H, NH_2), 2.42 (s, 1H), 2.33 (d, *J* = 10.7 Hz, 1H), 1.96 (s, 1H), 1.95 – 1.90 (m, 1H), 1.75 (d, J = 10.7 Hz, 1H), 1.29 – 1.22 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5 (CO), 147.1, 146.5, 137.5 (Cq arom), 129.9, 129.6, 129.3, 129.0, 126.3, 117.8, 114.4, 112.7 (CH arom), 69.9 (C2), 64.0 (C3), 61.4 (OCH_2), 52.7, 45.7, 38.5 (C1, C4, C5), 37.1 (C6), 36.4 (C7), 14.2 (CH_3). Mass: (+)ESI-MS (m/z): [M + H+] 383.2; Anal. $C_{22}H_{26}N_2O_2S$ (382.17) were within ± 0.4 % of the theoretical values.

Ethyl (1S*,2R*,3S*,4S*,5S*)-2-amino-5-(3-((4-nitrophenyl)amino)phenyl)-3-(phenylthio)bicyclo[2.2.1]heptane-2-carboxylate (9) and Ethyl (1R*,2R*,3S*,4R*,6R*)-2-amino-6-(3-((4-nitrophenyl)amino)phenyl)-3-(phenylthio)bicyclo[2.2.1]heptane-2-carboxylate (10)

The regioisomeric mixture of **7** and **8** (0.289 mmol, 1 eq, 110mg) was dissolved in 3 mL of dry CH_3CN (0.1 M) in a pyrex tube under nitrogen. Pd(tetrakis) (0.014mmol, 0.05 eq, 16.17mg), 1-iodo-4-nitrobenzene (0.32mmol, 1.1 eq, 79.68 mg) and K_3PO_4 (0.578mmol, 2 eq, 120.92mg) was added under stirring to a mixture. The tube was sealed with Teflon caps and stirred at 70 °C for 40h. The reaction was monitored by TLC analysis (1 : 1 = EtOAc : n-hexane) and ^{1}H-NMR analysis until completion. Solvent was removed under reduced pressure and, after deactivation of silica gel with a solution EtOAc : n-hexane = 1 : 5 + 10% of TEA, the crude was purified using flash chromatography EtOAc : n-hexane = 1 : 4 to give two fractions containing compound **9** and compound **10** in pure form. Total Yield= 90%. Compound **9**: ^{1}H NMR (200 MHz, $CDCl_3$)δ 8.09 (d, *J* = 9.2 Hz, 2H), 7.42 – 7.08 (m, 6H), 7.10 – 6.92 (m, 3H), 6.91 (d, *J* = 9.2 Hz, 2H), 4.36 – 4.01 (m, 2H), 3.12 (d, *J* = 2.8 Hz, 1H), 3.05 (t, *J* = 7.6 Hz, 1H), 2.69 – 2.63 (m, 1H), 2.58 – 2.47 (m, 2H), 2.42 (d, *J* = 9.2 Hz, 1H),

1.96 (s, 2H), 1.80 (d, *J* = 11.9 Hz, 1H), 1.53 (ddd, *J* = 12.7, 6.5, 3.8 Hz, 1H), 1.30 – 1.21 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5 (CO), 150.3, 148.0, 139.8, 139.7, 137.2 (Cq arom), 129.9, 129.6, 129.1, 126.4, 126.3, 123.2, 120.5, 119.4, 113.8 (CH arom), 69.5 (C2), 65.3 (C3), 61.5 (OCH2), 51.5, 46.9, 46.5 (C1, C4, C5), 37.7 (C7), 33.0 (C6), 14.2 (CH_3). Mass: (+)ESI-MS (m/z): [M + H+] 504.1; Anal. $C_{28}H_{29}N_3O_4S$ (503.19) were within ± 0.4 % of the theoretical values.

Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.2 Hz, 2H), 7.39 – 7.23 (m, 5H), 7.24 – 7.15 (m, 1H), 7.08 – 7.00 (m, 3H), 6.91 (d, *J* = 9.2 Hz, 2H), 6.40 (s, 1H), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.14 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.76 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.07 (d, *J* = 2.7 Hz, 1H), 2.68 (s, 1H), 2.46 (d, *J* = 3.9 Hz, 1H), 2.37 (d, *J* = 10.9 Hz, 1H), 2.05 – 1.97 (m, 3H), 1.93 (dq, *J* = 13.2, 4.2 Hz, 1H), 1.73 (d, *J* = 10.9 Hz, 1H), 1.27 – 1.24 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$pedice) δ 174.3 (CO), 150.3, 147.8, 139.7, 139.6, 137.1 (Cq arom), 129.6, 129.6, 129.0, 126.3, 126.2, 123.8, 121.2, 119.3, 113.6 (CH arom), 69.8 (C2), 63.8 (C3), 61.4 (OCH_2), 52.4, 45.6, 38.5 (C1, C4, C6), 37.1 (C7), 36.2 (C5), 14.1 (CH_3). Mass: (+)ESI-MS (m/z): [M +H]+ 504.1; Anal. $C_{28}H_{29}N_3O_4S$ (503.19) were within ± 0.4 % of the theoretical values.

Chiral HPLC resolution of racemate (±)-**10**

Analytical chiral HPLC was performed on (±)-**10** (λ 220 nm, eluent: n-hexane/iPrOH 1:1, flow rate: 1 mL/min); tr (-)-**10**: 6.7 min.; tr (+)-**10**: 8.5 min.

Enantiomerically pure (-)-**10** and (+)-**10** were obtained from racemate (±)-**10** by preparative chiral HPLC (λ 220 nm, eluent: n-hexane/iPrOH 1:1, flow rate: 15 mL/min); tr (-)-**10**: 14.8 min.; tr (+)-**10**: 21.1 min.

(-)-**10**: [α]D20= − 25.2 (c = 0.25, $CHCl_3$).

(+)-**10**: [α]D20= + 25.5 (c = 0.25, $CHCl_3$).

Ethyl (1R,2R,3S,4R,6R)-2-amino-6-(3-((4-aminophenyl)amino)phenyl)-3-(phenylthio)bicyclo[2.2.1]heptane-2-carboxylate and Ethyl (1S,2S,3R,4S,6S)-2-amino-6-(3-((4-aminophenyl)amino)phenyl)-3-(phenylthio)bicyclo[2.2.1]heptane-2-carboxylate

Aqueous solution of HCl (3 M, 1.4ml) was added dropwise under vigorous stirring to a solution of starting materials ((-) or (+)-**10** 0.046 mmol, 1 eq, 25mg) in MeOH (0.05 M) at r.t. then zinc dust (1.41 mmol, 30 eq., 91.4 mg) was added in portion and the mixture was warmed up to 50 °C. The reaction is monitored by TLC analysis (10 : 1 = DCM : MeOH) until completion (8 hours). Upon consumption of starting material the reaction was filtered

under vacuum on a Büchner funnel and the liquid phase was concentrated under reduced pressure. Saturated $NaHCO_3$ was added to the crude mixture until pH 8. The acqueous phase was extracted 3 times in EtOAc and combined organic layers were dried over Na_2SO_4, then evaporated under reduced pressure. The crude was filtered through celite column with a solution 1:200 = MeOH: DCM. Yield 90 % light yellow wax.

Full characterization has been previously reported [1].

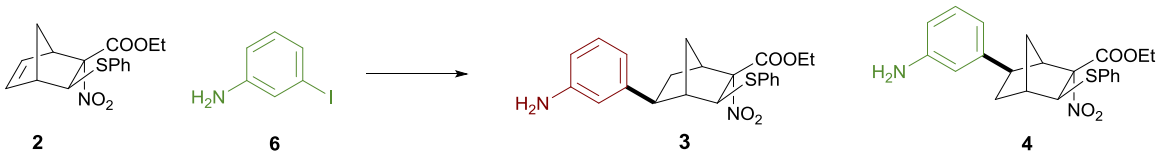
(–)AR-148: [α]D20= − 48.0 (c = 0.25, $CHCl_3$).

(+)AR-148: [α]D20= + 48.6 (c = 0.25, $CHCl_3$).

Cell Culture and G-LISA assay.

Human SMCs (A617 from human femoral artery) were grown in monolayers at 37 °C in a humidified atmosphere of 5% CO_2 in DMEM supplemented with 10% (v/v) FCS, 100 U/mL penicillin, 0.1 mg/mL streptomycin, and nonessential amino acids. The medium was changed every third day. For the experiments cells were seeded at a density of 2 ×105/35 mm Petri dish and incubated with DMEM supplemented with 10% FCS; 24 h later the medium was changed to one containing 0.4% FCS, and the cultures were incubated for 48 h. At this time, the compounds were added to the cultured medium, and after 4 h the intracellular amounts of Rac1−GTP were determined by using the G-LISA assay, as previously described [1]

Reaction condition optimization for Heck Hydroarylation phosphine free protocol



2 6 3 4

Table 1 SI. Conditions tested

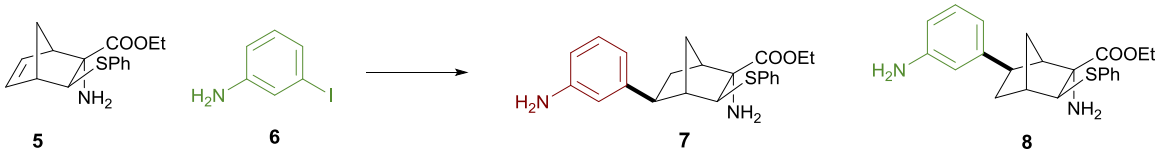
entry	Catalytic system (0.26 mmol **2**) and 3-iodoaniline **6** (0.78 mmol)	solvent	Yield % (**3**+**4**)	**3:4** ratio
1	$Pd(OAc)_2$/R-BINAP/HCOOH, K_2CO_3, reflux, [a]	MeCN 3mL	78	70:30
2	$Pd(OAc)_2$/R-BINAP/HCOOH, TEA, reflux, [a]	MeCN 3mL	65	70:30

3	$Pd(OAc)_2$/BINAP/HCOOH, Cs_2CO_3, reflux, [a]	MeCN 3mL	40	70:30
4	$Pd(OAc)_2$/PPh_3/HCOOH, TEA, reflux, [b]	Toluene 30 mL	28	70:30
5	$Pd(OAc)_2$/PPh_3/TEA, $AgNO_3$; HCOOH, reflux. [c]	MeCN 3mL	15	65:35
6	$Pd(OAc)_2$/PPh_3/TEA, $AgNO_3$; HCOOH (after 24h), reflux, [c]	MeCN 3mL	15	55:45
7	$Pd(OAc)_2$/PPh_3/HCOOH, TEA, reflux, [b]	MeCN 3mL	75	70:30
8	$Pd(OAc)_2$/PPh_3/HCOOH, TEA, 50 °C, [b]	MeCN 3mL	68	70:30
9	$Pd(OAc)_2$/HCOOH, TEA, 50 °C [d]	MeCN 3mL	72	70:30
10	$Pd(OAc)_2$/HCOOH, TEA, 50 °C, (3-iodoaniline 3x0.26 mmol. every 4h), [d]	MeCN 3mL	80	70:30
11	$Pd(OAc)_2$/HCOOH, TEA, 50 °C, (3-iodoaniline 0.38 mmol.)[d]	MeCN 3mL	59	70:30

[a] $Pd(OAc)_2$ 0.01 mmol, BINAP 0.015 mmol, HCOOH 0.8, base 1.0 mmol; 24h [b] $Pd(OAc)_2$ 0.02 mmol, PPh_3 0.04 mmol, TEA 0.9 mmol, HCOOH 0.78 mmol, 24h, [c] $Pd(OAc)_2$ 0.01 mmol, PPh_3 0.03 mmol, HCOOH 0.8 mmol, TEA 0.9 mmol, $AgNO_3$ 0.4 mmol, 24h, [d] $Pd(OAc)_2$ 0.02 mmol, TEA 0.9 mmol, HCOOH 0.78 mmol, 24h.

The ratio **3:4** are referred to isolated compounds and has been estimated as reported in our previous work. [1]

Reaction condition optimization for Heck Hydroarylation on amine substrate



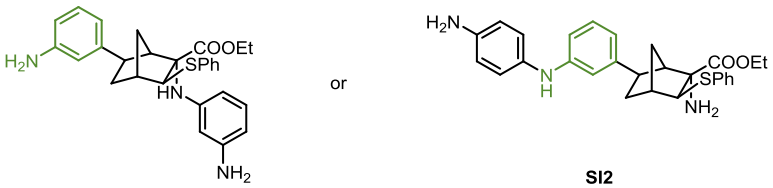
5 6 7 8

Table 2 SI. Conditions tested

entry	Catalytic system(0.26 mmol **5**), and 3-iodoaniline **6** (from 0.26 to 0.78 mmol)	solvent	Yield % (**7**+**8**)	**7**/**8** ratio

1	$Pd(OAc)_2/PPh_3$/HCOOH, TEA , reflux, [a]	MeCN 3mL	30	35:65 [e]
2	$Pd(OAc)_2/PPh_3$/HCOOH, TEA ,45°C, [b]	MeCN 3mL	62	35:65 [e]
3	$Pd(OAc)_2/PPh_3$/HCOOH, TEA , 45°C, [b]	MeCN 3mL	73	35:65 [e]
4	$Pd(OAc)_2/PPh_3$/HCOOH, K_2CO_3, reflux, [b]	MeCN 3mL	10	------
5	$Pd(OAc)_2/PPh_3$/HCOOH, Cs_2CO_3, reflux, [b]	MeCN 3mL	58	32:68 [e]
7	$Pd(OAc)_2$/HCOOH, TEA, 45°C, [a]	MeCN 3mL	70	35:65
8	$Pd(OAc)_2$/HCOOH, TEA, 45°C, [b]	MeCN 3mL	80	35:68
9	$Pd(OAc)_2$/HCOOH, TEA, 45°C, [c]	MeCN 3mL	88	30:70
10	$Pd(OAc)_2$/HCOOH, Cs_2CO_3, reflux, [c]	MeCN 3mL	30	35:65
11	$Pd(OAc)_2$/TEA, HCOOH, $AgNO_3$ (after 24h)[d], 45°C, [c]	MeCN 3mL	--------	------

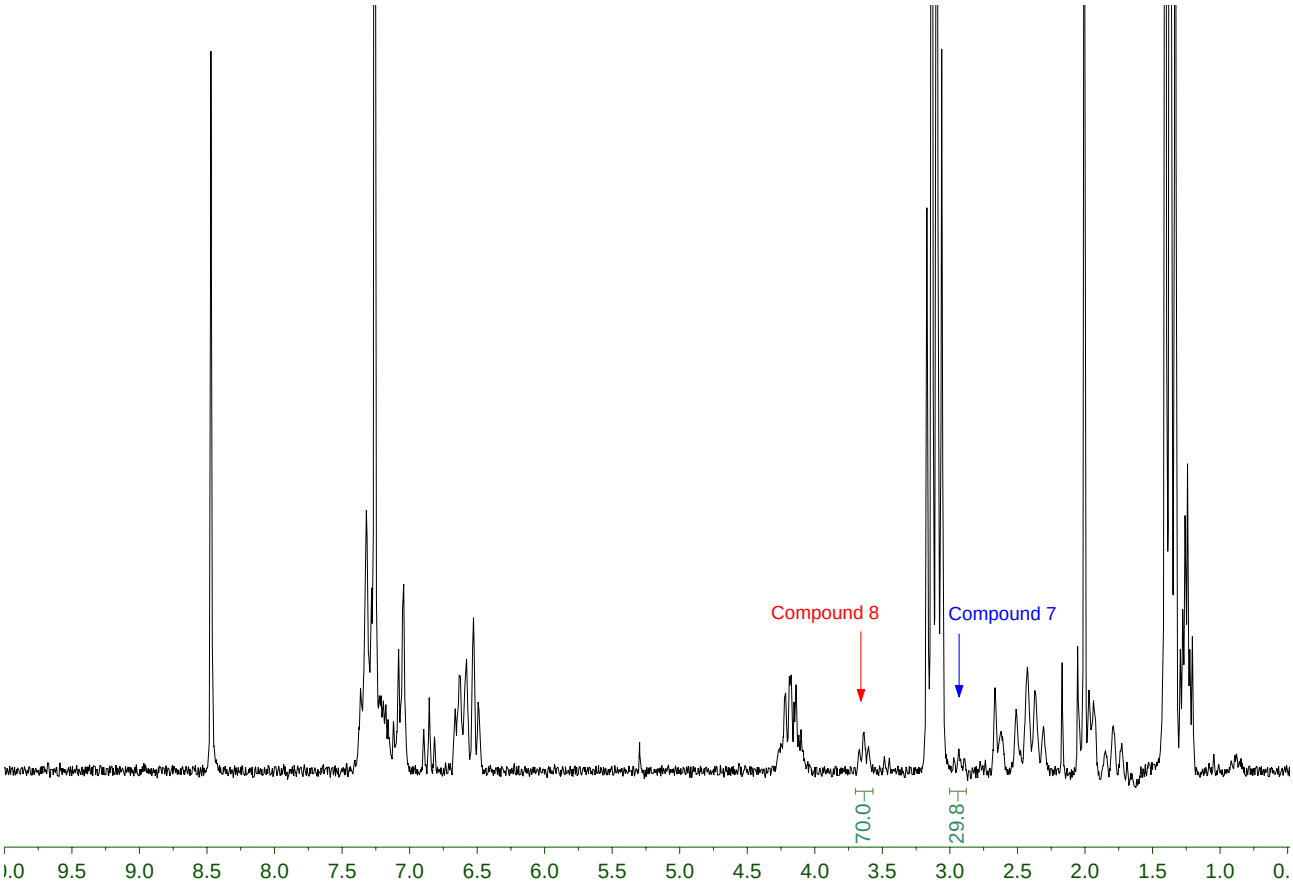
$Pd(OAc)_2$ 0.01 mmol, PPh_3 0.02 mmol, TEA 0.9 mmol, HCOOH 0.78 mmol, [a] 3-iodoaniline **6** (0.78 mmol), [b] 3-iodoaniline **6** (0.26 mmol x 3 every 4h), [c] 3-iodoaniline **6** (0.29 mmol), [d] $AgNO_3$ 0.4 mmol. [e] Crude mass analysis ((+)ESI-MS (m/z)) provided information about the possible formation of compounds :



SI1 **SI2**

The ratios **7:8** reported are referred to isolated compound. Crude ^{1}H-NMR ($CDCl_3$) of the reaction mixture after evaporation of the solvent furnished comparable data.

Figure 1 SI. Crude ^{1}H-NMR ($CDCl_3$) of optimized conditions (**Table 2 SI, entry 9**) Characteristic signals: compound **7** (2.92 (t, *J* = 8.0 Hz, 1H)) compound **8** 3.63 (t, *J* = 6.8 Hz, 1H).



NMR elucidation compounds 7 and 8

NMR analysis of the regioisomeric mixture of **7** and **8** and of the single separated compound was performed. The main difference between the two regioisomers appeared to be the chemical shift of the hydrogens at C3, C5 and C6 and allowed the evaluation of the ratio (compound **7**: H-3, d, 3.09 δ (J = 2.9 Hz); H-5, t, 2.93 δ, (J = 7.7 Hz); compound **8**: H-3, d, 3.05 δ (J = 2.2 Hz); H-5, t, 3.63 δ, (J = 6.9 Hz)). The hypothesized stereo- and regiochemistry of compound **7** and **8** were definitively assigned by NMR analysis of compounds **9** and **10**, confirming our previous considerations.

NMR elucidation compounds SI3 and SI4 for confirmation of exo-selectivity in Heck Hydroarylation

AR-148 obtained from **5** (Paper, Scheme 2) has identical ^{1}H-NMR, ^{13}C-NMR, of that one obtained from **2** through intermediates **3** and **4** with the already reported procedure (Paper, Scheme 1) [1]. Structures of precursors **SI3** and **SI4** have been undoubtedly determined by NOE signals [1]

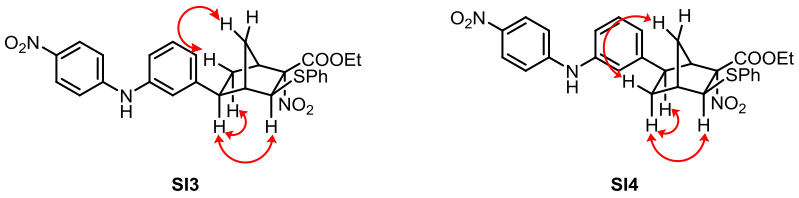


Figure 2 SI. NOE signal observed for structural elucidation

Solvent screening on Phosphine free Heck Hydroarylation

Model reaction for screening of coordinative and non coordinative solvent.

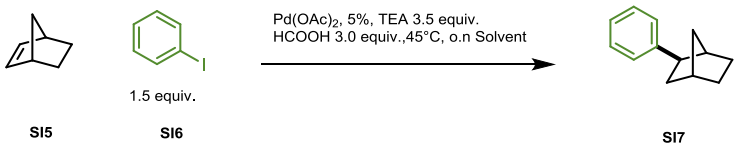
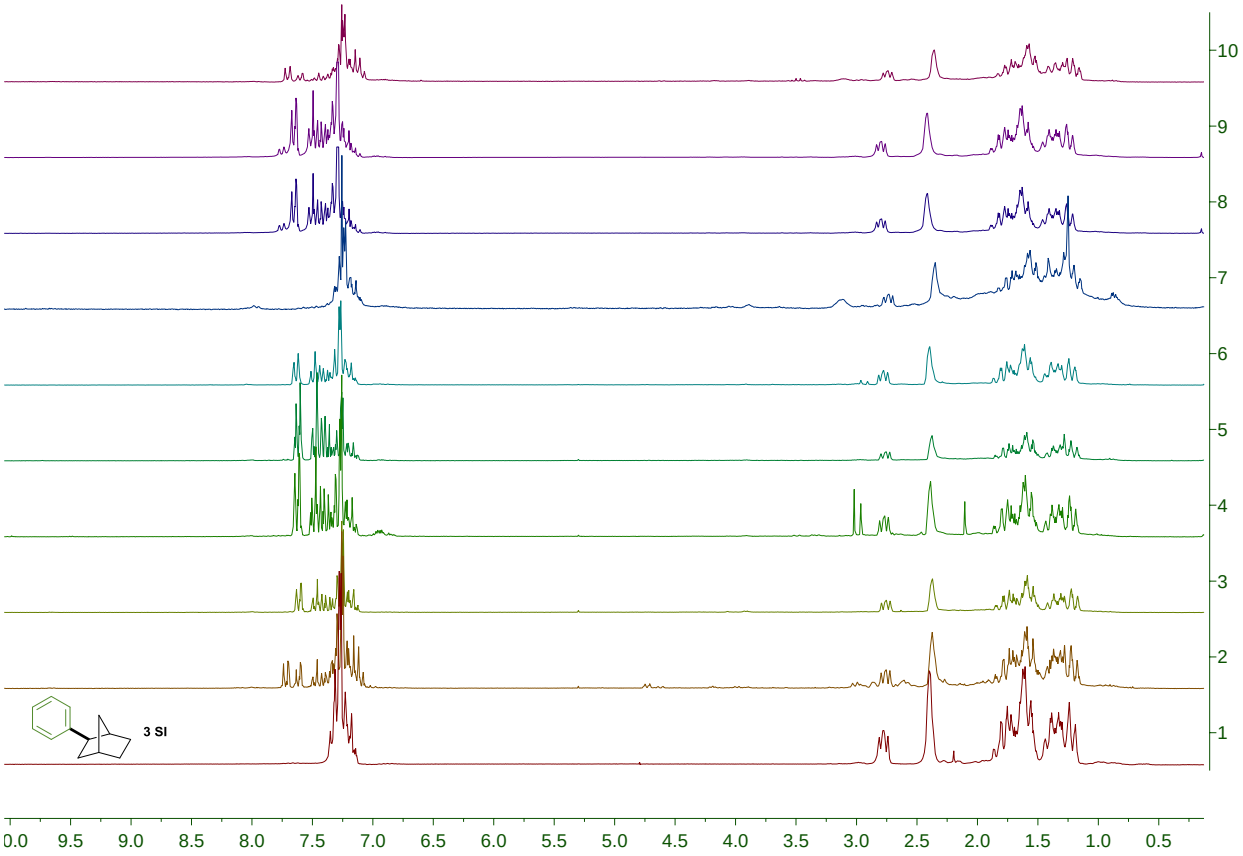


Figure 3 SI. Crude ^{1}H NMR analysis



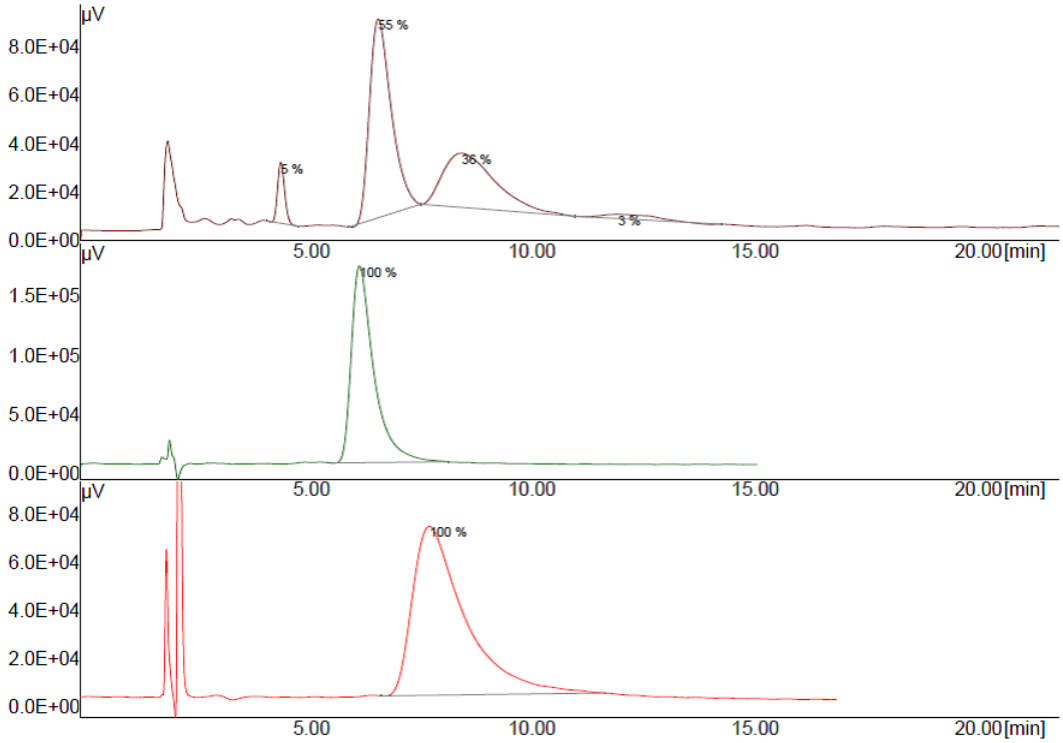
Purified reference compound **SI7** in agreement with literature (*Eur. J. Org. Chem*. **2012**, 16, 3151–3156). 2) DCM, 3) Et_2O, 4) DMSO, 5) DMF, 6) EtOAc 7) MeOH, 8) CH_3CN, 9) THF, 10) DCE.

Chiral HPLC analysis and preparative chiral HPLC separation

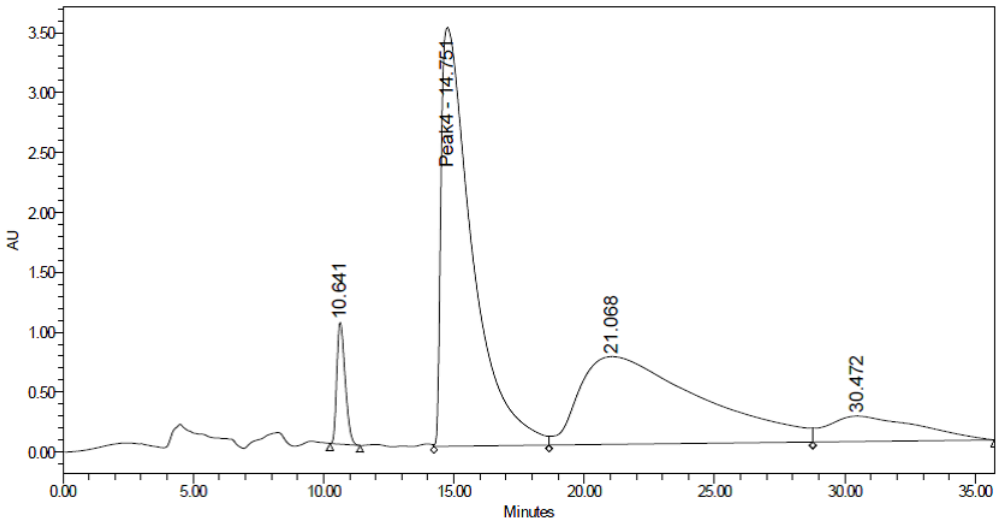
Chiral HPLC analyses were performed with a Jasco PU-980 pump equipped with a UV–vis detector Jasco UV-975 (wavelength: 220 nm) and Phenomenex Lux Amylose-2 column (4.6 × 150 mm, 5 μm). Preparative HPLC was performed with a 1525 Extended Flow Binary HPLC Pump, equipped with a Waters 2489 UV-vis detector and a Phenomenex Lux Amylose-2 column (21.2 × 250 mm) at a flow rate of 15 mL/min. Rotary power determinations were carried out with a Jasco P-1010 spectropolarimeter coupled with a Haake N3-B thermostat.

Analytical chiral HPLC was performed on **(±)10** (λ 220 nm, eluent: *n*-hexane/*i*PrOH 1:1, flow rate: 1 mL/min); t_r **(-)10**: 6.7 min.; t_r **(+)10**: 8.5 min.
Enantiomerically pure **(-)10** and **(+)10** were obtained from **(±)10** by preparative chiral HPLC (λ 220 nm, eluent: *n*-hexane/*i*PrOH 1:1, flow rate: 15 mL/min); t_r **(-)10**: 14.8 min.; t_r **(+)10**: 21.1 min.

(–)10: $[\alpha]_D^{20} = -25.2$ (c = 0.25, $CHCl_3$). HPLC purity>**99**% ee>**99**%
(+)10: $[\alpha]_D^{20} = +25.5$ (c = 0.25, $CHCl_3$). HPLC purity>**99**% ee>**99**%



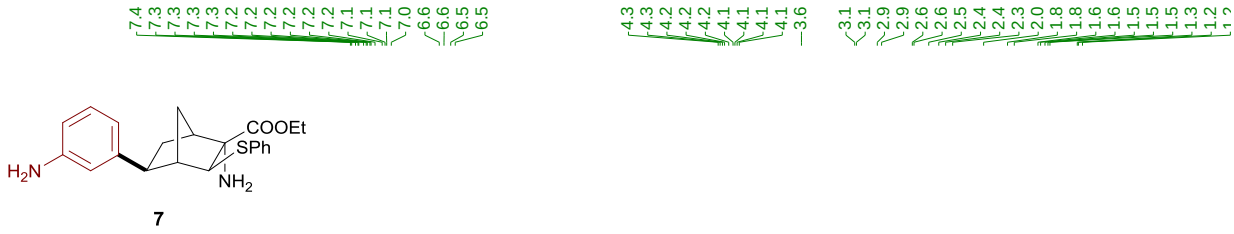
Chromatogram 1. Analytical HPLC chromatogram of the racemate **(±)10** and the pure enantiomers **(-)10** and **(+)10** obtained by preparative HPLC



Chromatogram 2. Preparative HPLC chromatogram of the racemate **(±)10**

^{1}H-NMR, ^{13}C-NMR, Mass data

Compound 7 ^{1}H-NMR, ^{13}C-NMR, Mass data



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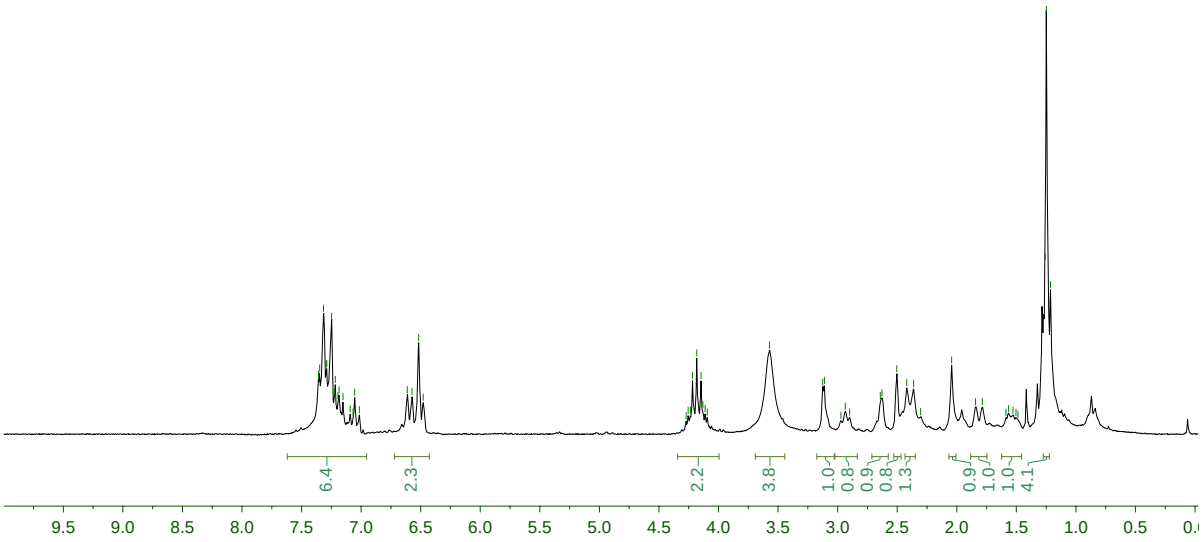

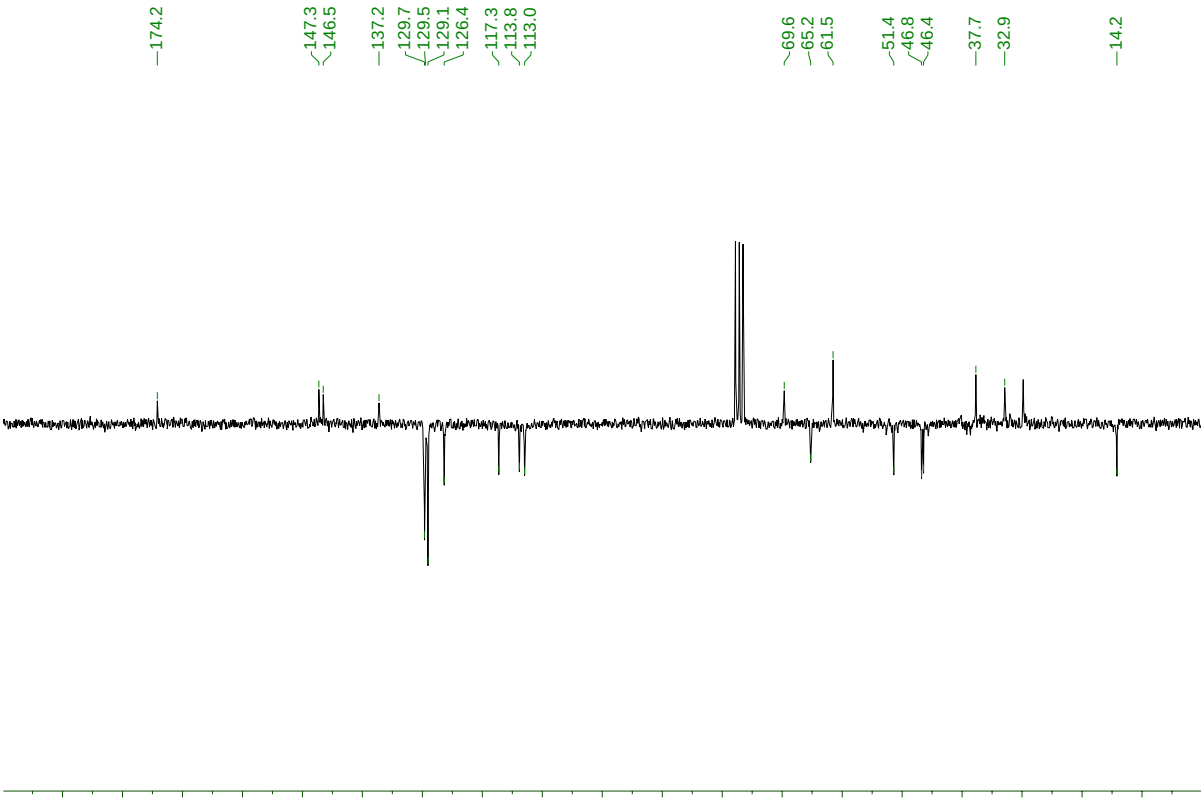

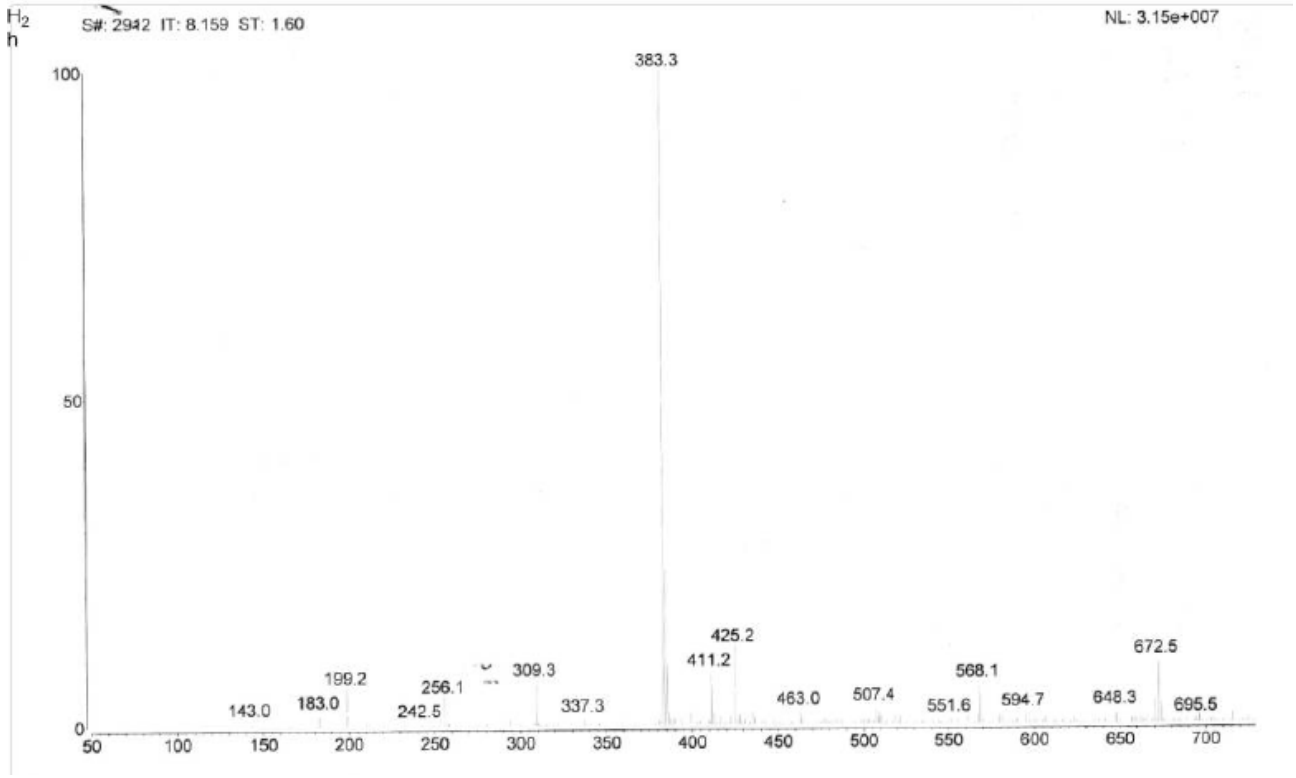
H2
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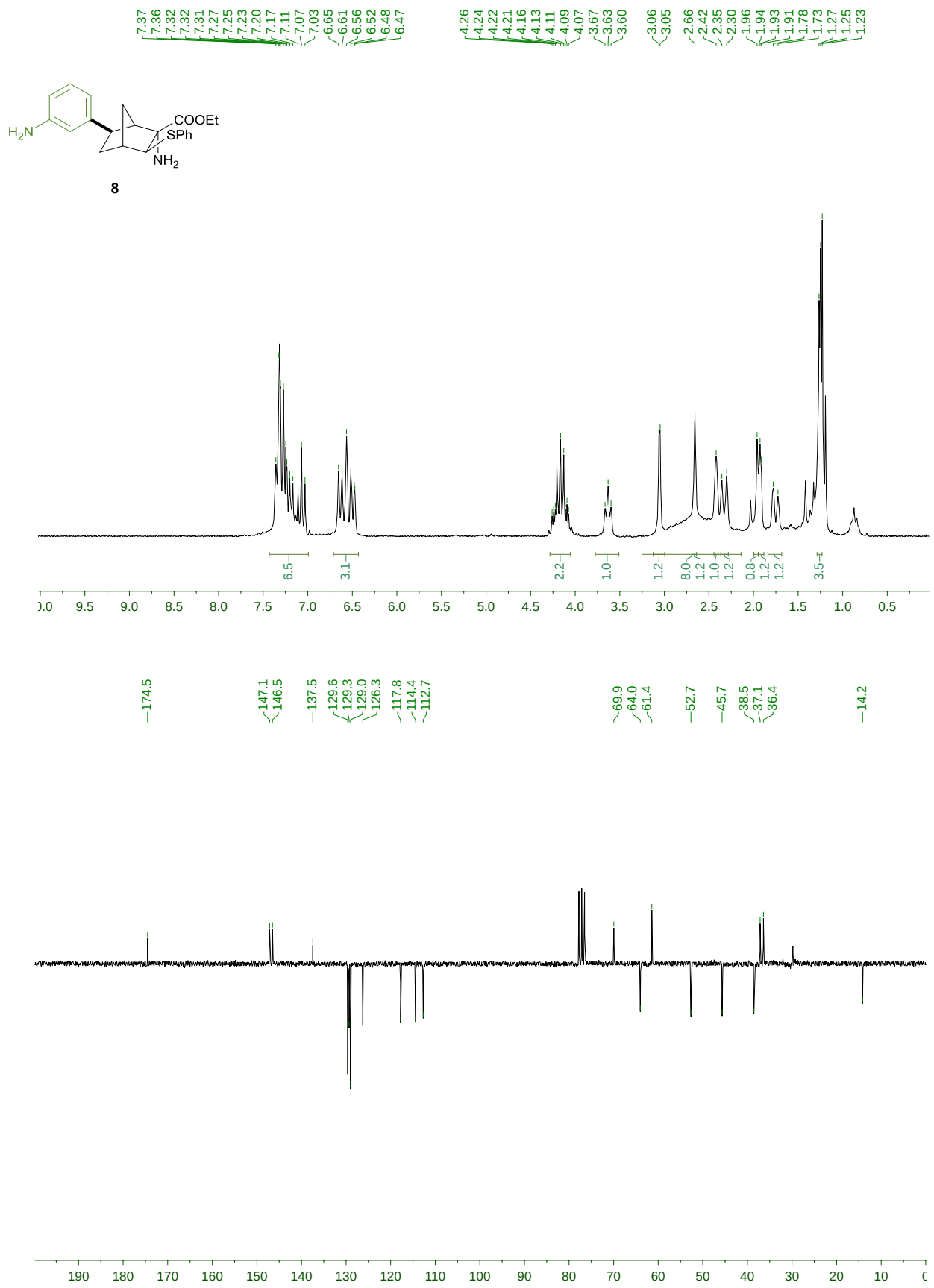
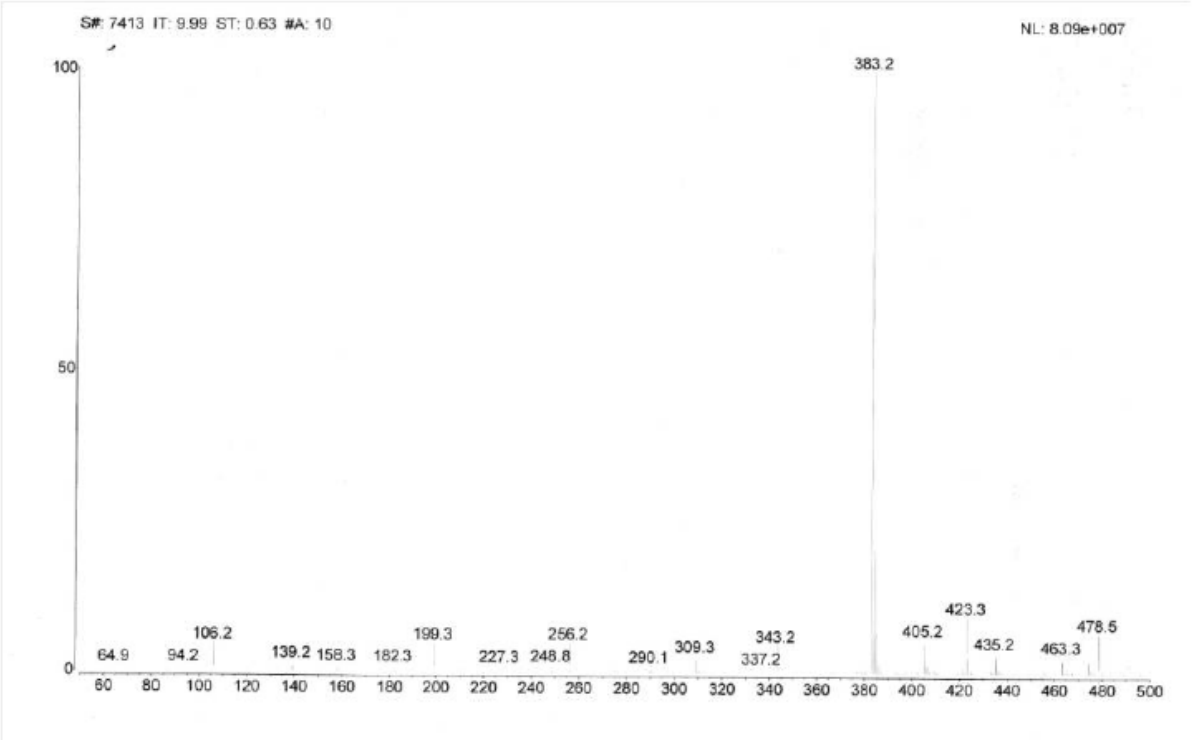
NL: 3.15e+007
100
50
0
383.3
425.2
411.2
672.5
568.1
199.2
309.3
256.1
183.0
143.0
242.5
337.3
463.0
507.4
551.6
594.7
648.3
695.5
50
100
150
200
250
300
350
400
450
500
550
600
650
700

Compound 8 ^{1}H-NMR, ^{13}C-NMR, Mass data

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NL: 8.09e+007
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0
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343.2
405.2
435.2
463.3
64.9
94.2
139.2
158.3
182.3
227.3
248.8
290.1
337.2
60
80
100
120
140
160
180
200
220
240
260
280
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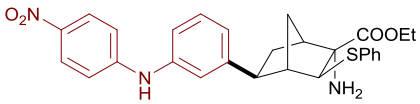
320
340
360
380
400
420
440
460
480
500

Compound 9 ^{1}H-NMR, ^{13}C-NMR, Mass data



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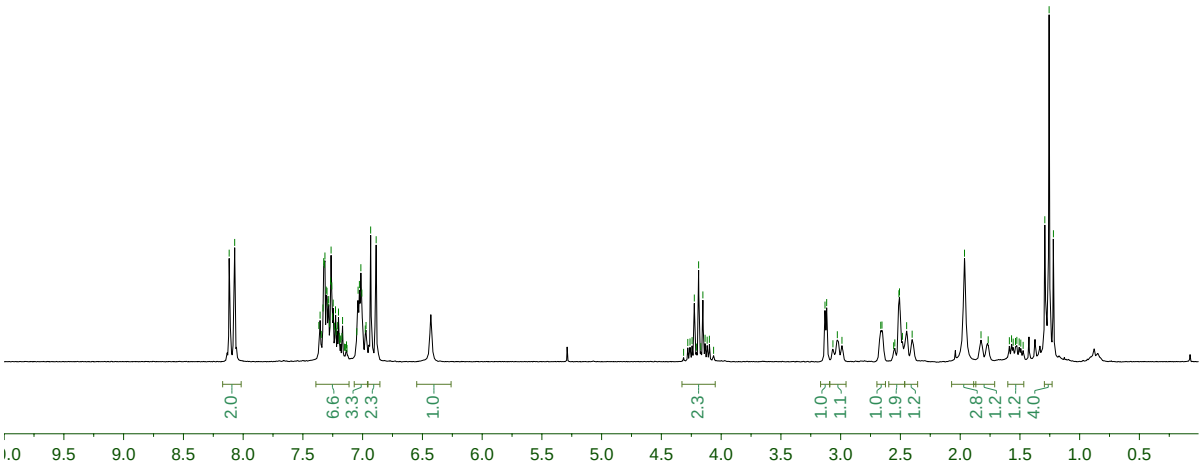

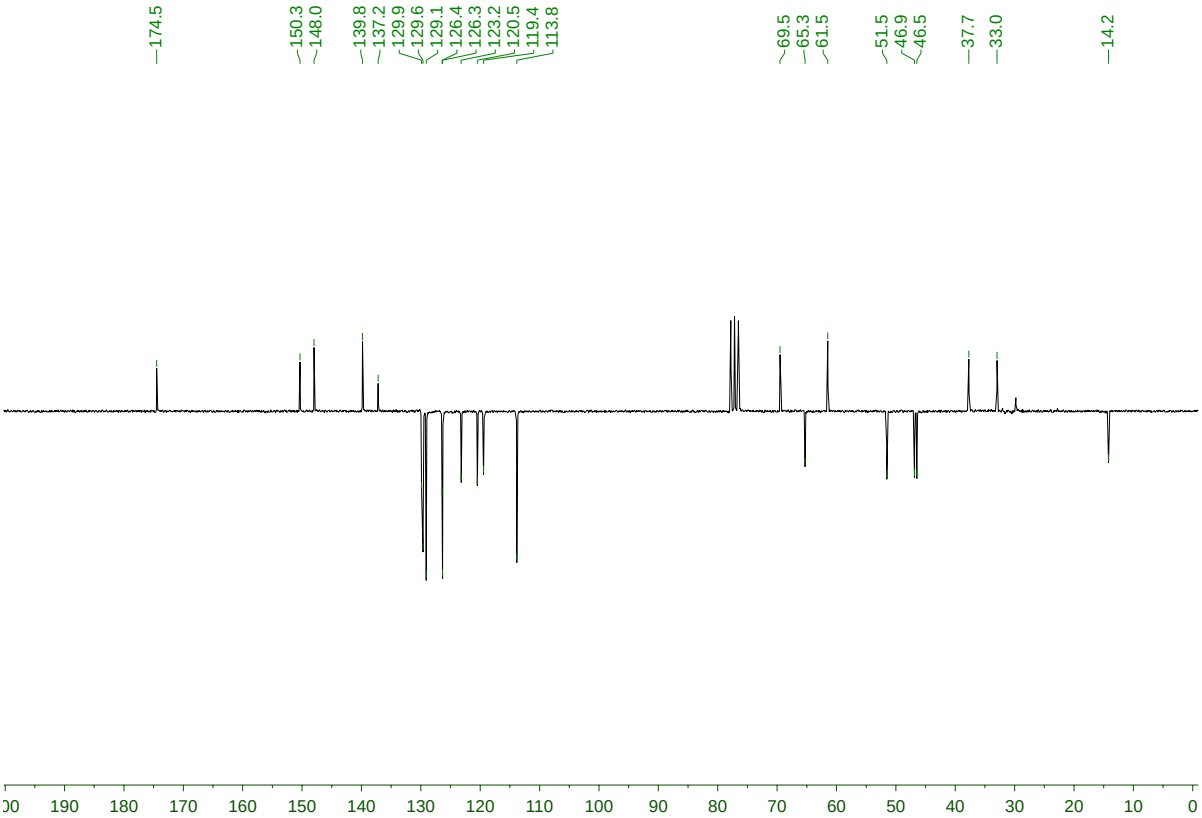

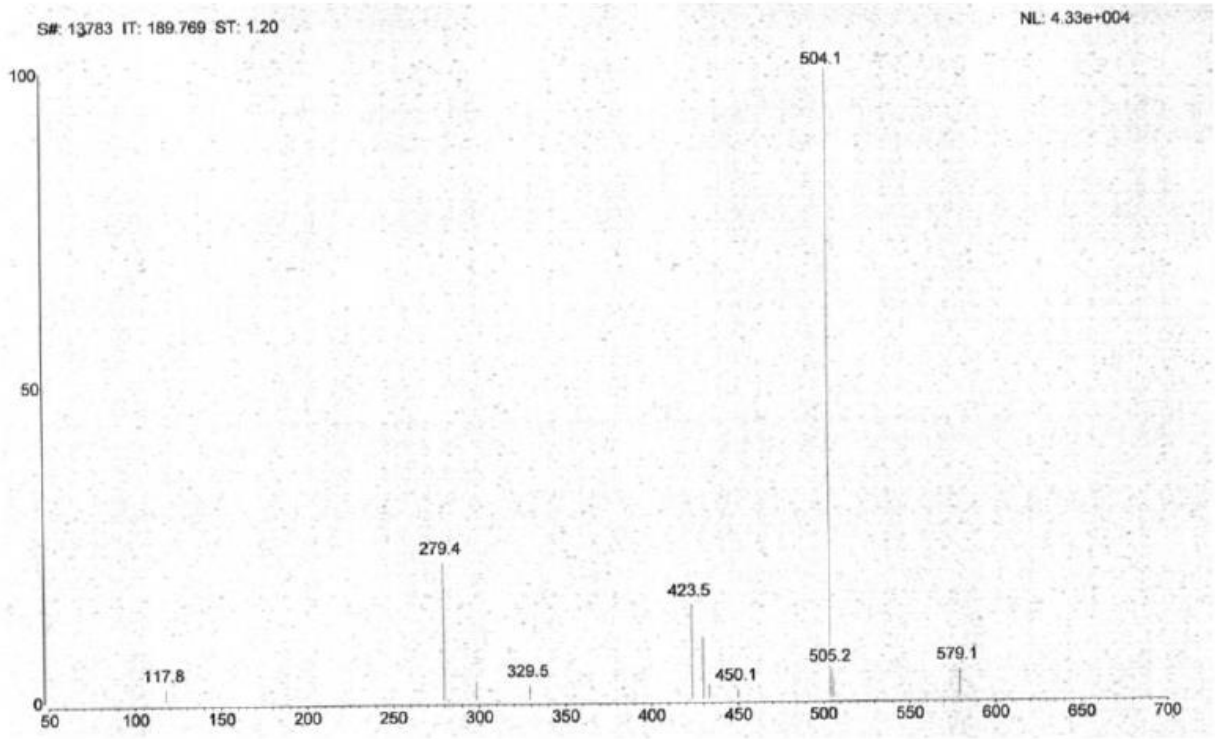
S#: 13783 IT: 189.769 ST: 1.20
NL: 4.33e+004
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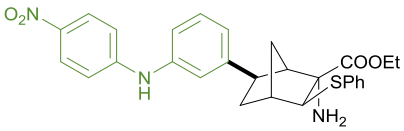
117.8
329.5
450.1
50
100
150
200
250
300
350
400
450
500
550
600
650
700

Compound 10 ^{1}H-NMR, ^{13}C-NMR, Mass data



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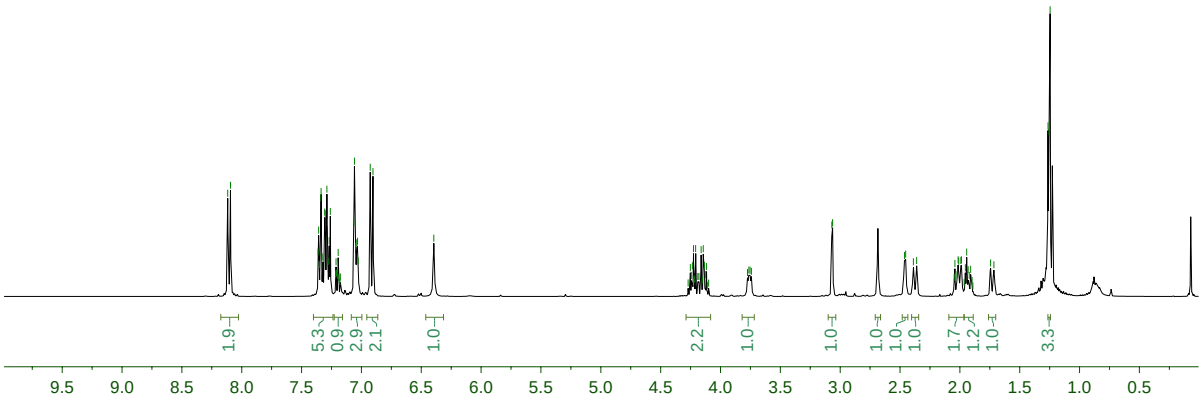

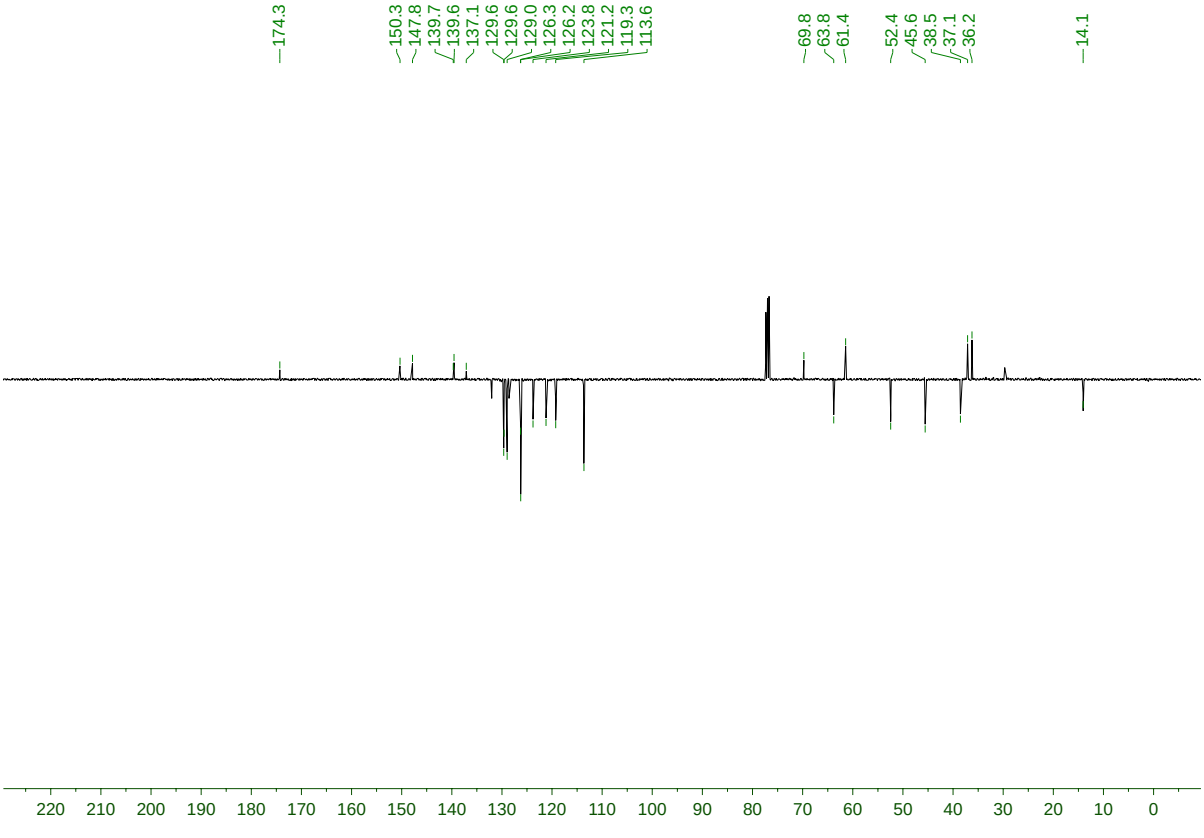

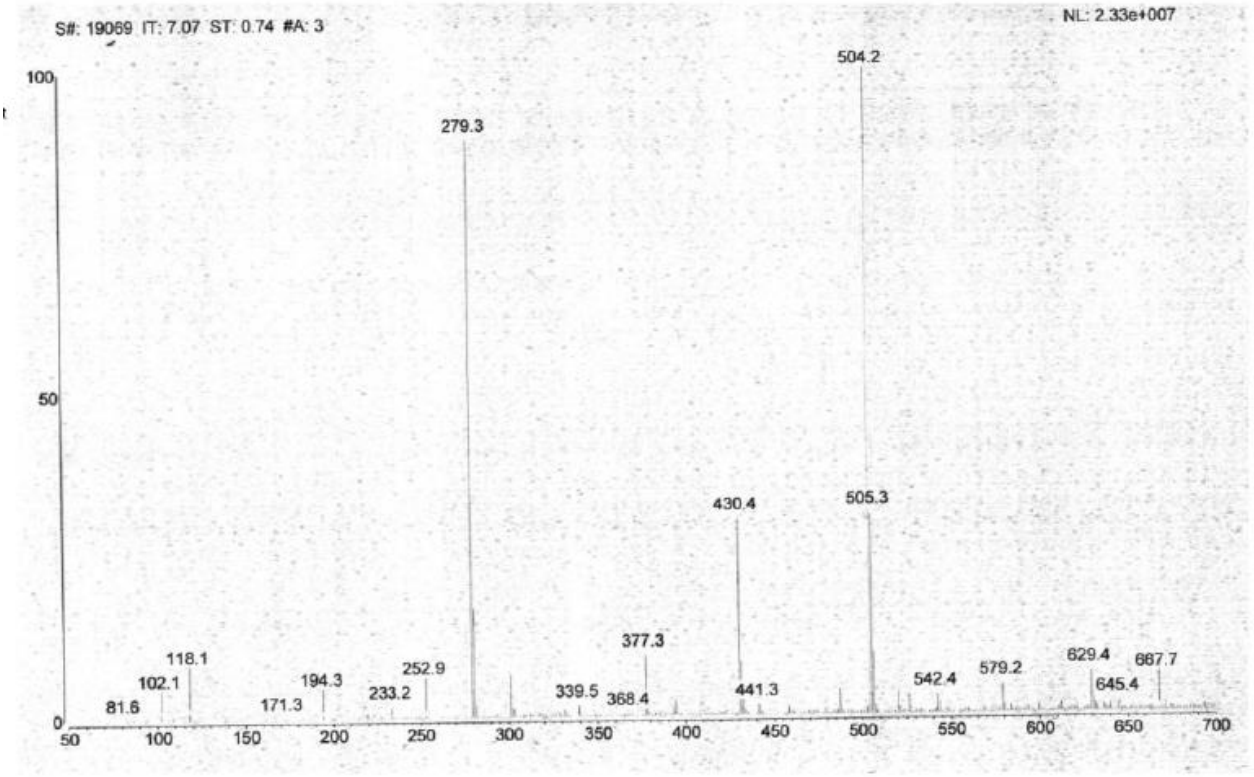

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