Assymmetric Synthesis of Allocolchicine and a C-Ring Analogue.

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Supporting Information

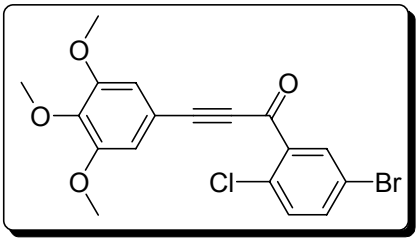
General Methods:

All experiments were carried out under an atmosphere of nitrogen. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ or $(CD_3)_2SO$ solutions using a Bruker AVANCE 300 spectrometer with Me_4Si as an internal standard. High-resolution mass spectra were obtained on a Kratos Concept IIH. Infra-Red analysis was performed with a Bruker EQUINOX 55. HPLC analysis was performed on Waters apparatus using photodiode array detector. HPLC Grade THF, Et_2O, Benzene, Toluene and CH_2Cl_2 are dried and purified via MBraun SP Series solvent purification system. Triethylamine was freshly distilled from NaOH before every use. Dimethylacetamide was degassed with N_2 before every use. Palladium and Copper complexes were stored in a dessicator and were weighed out to air unless otherwise specified. All other reagents and solvents were used without further purification from commercial sources. Unless noted below, all other compounds have been reported in the literature or are commercially available.

Compound **4** was prepared as reported in the literature[1] and exhibited identical spectral data.

Compound **5**[2] and **11**[3] are commercially available or can be prepare as reported in the literature[4] and exhibited identical spectral data.

1-(5-bromo-2-chlorophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (7)[5,6]



To freshly prepared 5-bromo-2-chlorobenzoyl chloride (**5**) (0.546 g, 2.15 mmol) under argon was added the 5-ethynyl-1,2,3-trimethoxybenzene (**4**) (0.275 g, 1.43 mmol), trans-dichlorobis(triphenylphosphine) palladium (II) (10.1 mg, 0.014 mmol) and copper iodide (9.0 mg, 0.047 mmol). THF (7.2 mL) was then added followed by triethylamine (0.181 g, 0.25 mL, 1.79 mmol). The brown solution was stirred at room temperature for 20h after which the solvent was removed by rotary evaporator. DCM and water were added to the brown residue and the organic phase was extracted three times with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated. The brown oil was purified by column chromatography on silica gel using 20% AcOEt/hexane to give solid **7** (0.543 g, 92%).

1H NMR (300 MHz, $CDCl_3$, 293K, TMS): δ 8.14 (1H, d, *J*= 2.4 Hz), 7.59 (1H, dd, *J*= 2.5, 8.6 Hz), 7.37 (1H, d, *J*= 8.7 Hz), 6.89 (2H, s), 3.91 (3H, s), 3.89 (6H,s).

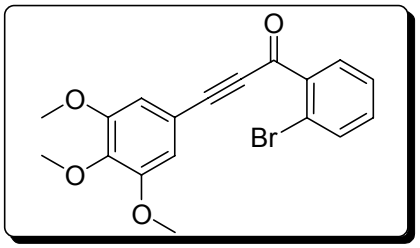
^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 175.2, 153.3, 141.5, 137.4, 136.1, 134.7, 132.9, 132.3, 120.4, 114.2, 110.6, 95.8, 87.6, 61.1, 56.3.

HRMS calculated for $C_{18}H_{14}O_4BrCl$ (M+) 407.9764; Found: 407.9754.

Melting point °C (ether): 114-116

IR: 2947, 2185, 1648, 1503, 1237, 1131, 822, 610.

1-(2-bromophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (12)[5,6]



2-Bromo-benzoyl chloride (**11**) (0.522 g, 2.38 mmol) was added to a solution of the 5-ethynyl-1,2,3-trimethoxybenzene (**4**) (0.305 g, 1.59 mmol), trans-dichlorobis(triphenylphosphine) palladium (II) (10.9 mg, 0.016 mmol) and copper iodide (9.1 mg, 0.048 mmol) in THF (8.0 mL) under argon. Triethylamine (0.181 g, 0.25 mL, 1.79 mmol) was added and the brown solution was stirred at room temperature for 20h. The solvent was then removed by rotary evaporator. DCM and water were added to the brown residue and the organic phase was extracted three times with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated. The brown oil was purified by column chromatography on silica gel using 20% AcOEt/hexane to give solid **12** (0.470 g, 79%).

^{1}H NMR (100 MHz, $CDCl_3$, 293K, TMS): δ 8.05 (1H, dd, *J*= 1.6, 7.6 Hz), 7.70 (1H, d, *J*= 7.8 Hz), 7.47-7.38 (2H, m), 6.89 (2H, s), 3.90 (3H, s), 3.88 (6H, s).

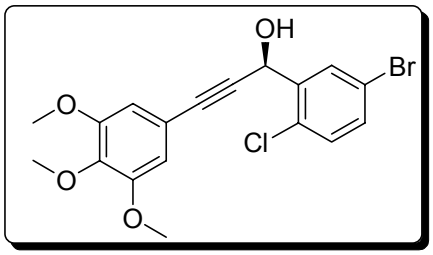
^{13}C NMR (75 MHz, $CDCl_3$, 293K): 177.4, 153.1, 141.1, 137.4, 134.8, 133.2, 127.3, 121.0, 114.4, 110.4, 94.7, 87.4, 60.9, 56.2.

HRMS calculated for $C_{18}H_{15}O_4Br$ (M+) 374.0154; Found: 374.0149.

Melting point °C (ether): 77.5-79.5

IR (ν_{max}/cm^{-1}): 2940, 2188, 1644, 1245, 1129, 1022, 631.

(S)-1-(5-bromo-2-chlorophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (8)[7]



To a flame dried flask fitted with a condenser was added 9-BBN 0.5 M solution in THF (5.9 mL, 2.93 mmol) and (S)-α-pinene (0.439 g, 0.5 mL, 3.22 mmol) under argon. The solution was stirred at reflux for 2.5h after which the solution was cooled to room temperature and a solution of 1-(5-bromo-2-chlorophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (**7**) (0.60 g, 1.46 mmol) in THF was added via cannula. The resulting solution was stirred at room

temperature overnight. A 10% solution of NaOH in water was then added and the mixture was vigorously stirred for 1.5h. THF was removed by rotary evaporator and the aqueous phase was extracted three times with a mixture of EtOAc/Et_2O (1/1). The organic layer was dried over $MgSO_4$, filtered and concentrated. The brown oil was purified by column chromatography on silica gel using 30% AcOEt/hexane to give yellow oil **8** (0.479 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS): δ 7.95 (1H, d, *J*= 2.4 Hz), 7.42 (1H, dd, *J*= 2.3, 9.6 Hz), 7.27 (1H,d, *J*= 8.4 Hz), 6.69 (2H, s), 5.97 (1H, d, *J*= 4.5 Hz), 3.85 (9H, s), 2.66 (1H, bs).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 153.0, 139.8, 139.1, 132.5, 131.5, 131.2, 120.9, 116.9, 108.9, 86.8, 86.0, 61.8, 61.0, 56.1.

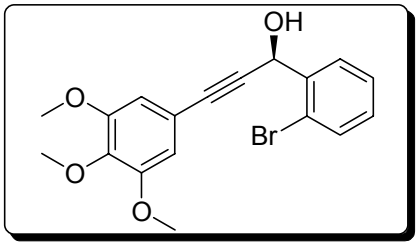
HRMS calculated for $C_{18}H_{16}O_4BrCl$ (M+) 409.9920; Found: 409.9896

HPLC: 97.8% ee; column: chiralcel AS-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (minor) retention time: 25.87 min, 1.1%; (major) retention time: 31.55 min, 98.9%

$[\alpha]_D^{22}$ = -50.5 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 3430, 2938, 2229, 1579, 1237, 1129, 835, 756, 631.

(S)-1-(2-bromophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (13)[7]



To a dry flask fitted with a condenser under argon were added 9-BBN 0.5 M solution in THF (16 mL, 8.00 mmol) and (S)-α-pinene (1.198 g, 1.37 mL, 8.80 mmol). The solution was stirred at reflux for 2.5h after which the solution was cooled to room temperature and a solution of 1-(2-bromophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (**12**) (1.50 g, 4.00 mmol) in THF was added via cannula. The resulting solution was stirred at room temperature for 28h. A saturated solution of $NaHCO_3$ in water followed by a solution of peroxide 30% were added and stirred for 1.5h. The white precipitate was filtered and THF was

removed by rotary evaporator. The aqueous phase was extracted three times with a mixture of EtOAc/Et_2O (1/1). The organic layer was dried over $MgSO_4$, filtered and concentrated. The brown oil was purified by column chromatography on silica gel using 35% AcOEt/hexane to give a yellow solid **13** (1.189 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS): δ 7.83 (1H, d, *J*= 7.8 Hz), 7.56 (1H, d, *J*= 8.1 Hz), 7.37 (1H, t, *J*= 7.5 Hz), 7.19 (1H, t, *J*= 7.5 Hz), 6.68 (2H, s), 6.00 (1H, s), 3.84 (3H, s), 3.81 (6H, s), 3.14 (1H, s).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 152.8, 139.5, 138.8, 132.8, 129.8, 128.5, 127.8, 122.5, 117.2, 108.8, 86.8, 86.3, 64.4, 60.8, 56.0.

HRMS calculated for $C_{18}H_{17}O_4Br$ (M+) 376.0310; Found: 376.0305.

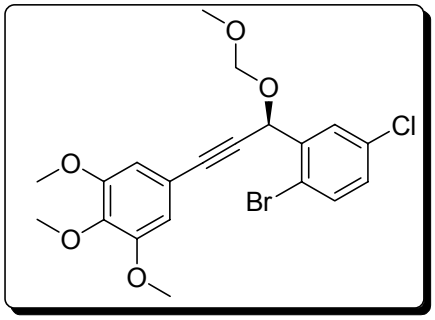
Melting point °C (ether): 97.2-100

HPLC: 98% ee; column: chiralcel AS-H; flow rate: 0.9 mL/min; eluant: 10% iPrOH/hexane: **(**minor) retention time: 30.82 min, 1.0 %; (major) retention time: 34.33 min, 99.0 %.

$[\alpha]_D^{22}$ = +58.0 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 3472, 2938, 2230, 1579, 1237, 1129, 646.

(S)-5-(3-(2-bromo-5-chlorophenyl)-3-(methoxymethoxy)prop-1-ynyl)-1,2,3-trimethoxybenzene (9)



To a solution of **8** (0.961 g, 2.33 mmol) in 12 mL of dry THF was added sodium hydride 60% in mineral oil (0.107 g, 2.68 mmol) at 0°C. The resulting mixture was stirred at room temperature for 1h. Bromo(methoxy)methane (0.356 g, 0.23 mL, 2.57 mmol) was added and the resulting mixture was stirred at 0°C for 15 min before letting the solution warm to room temperature and stir overnight. Water was added slowly and THF was removed under rotary evaporator. The resulting thick oil was extracted twice with ether. The organic layer was dried

over $MgSO_4$, filtered and concentrated. The resulting oil was purified by column chromatography on silica gel using 20% AcOEt/hexane to give white solid **9** (0.996 g, 94%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS): δ 7.94 (1H, d, *J*= 2.4 Hz), 7.43 (1H, dd, *J*= 8.7, 2.4 Hz), 7.27 (1H, d, *J*= 8.4 Hz), 6.70 (2H, s), 5.96 (1H, s), 5.12 (1H, d, *J*= 6.9 Hz), 4.74 (1H, d, *J*= 6.9 Hz), 3.85 (9H, s), 3.47 (3H, s).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 153.4, 139.6, 138.8, 133.0, 132.5, 132.2, 131.4, 121.3, 117.4, 109.6, 109.4, 94.7, 87.9, 84.6, 64.7, 61.4, 56.6, 56.6.

HRMS calculated for $C_{20}H_{20}O_5BrCl$ (M+) 454.0183; Found: 454.0212

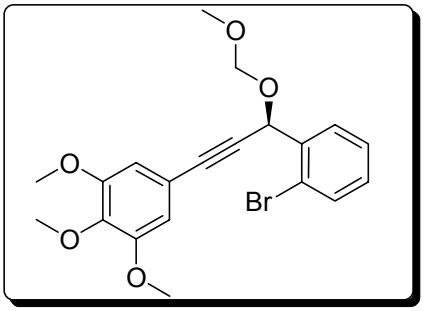
Melting point °C (ether): 56.5-57.4

HPLC: 96.6% ee; column: chiralcel AS-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: **(**major) retention time 9.68 min, 98.3 %; retention time: 10.55 min, 1.7 %.

$[\alpha]_D^{22}$ = -135.4 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 2939, 2221, 1578, 1237, 1129, 1024, 833.

(S)-5-(3-(2-bromophenyl)-3-(methoxymethoxy)prop-1-ynyl)-1,2,3-trimethoxy benzene (14)



To a solution of **13** (1.07 g, 2.84 mmol) in 28 mL of dry THF was added sodium hydride 60% in mineral oil (0.136 g, 3.41 mmol) at 0°C. The resulting mixture was stirred at room temperature for 1h. Bromo(methoxy)methane (0.433 g, 0.28 mL, 3.13 mmol) was added and the resulting mixture was stirred at 0°C for 15 min before letting the solution warm to room temperature and stir overnight. Water was added slowly and THF was removed under rotary evaporator. The resulting thick oil was extracted twice with ether. The organic layer was dried

over $MgSO_4$, filtered and concentrated. The colourless oil was purified by column chromatography on silica gel using 30% AcOEt/hexane to give **14** (1.11 g, 93%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS): δ 7.83 (1H, dd, *J*= 7.8, 1.6 Hz), 7.59 (1H, dd, *J*= 8.0, 0.9 Hz), 7.40 (1H, t, *J*= 7.5 Hz), 7.22 (1H, dt, *J*= 7.7, 1.6 Hz), 6.70 (2H, s), 6.01 (1H, s), 4.94 (2H, dd, *J*= 111, 6.9 Hz), 3.84 (9H, s), 3.48 (3H, s).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 153.0, 139.0, 138.0, 132.9, 130.0, 129.6, 127.9, 123.1, 117.3, 109.0, 94.3, 87.3, 85.1, 67.2, 60.9, 56.2, 56.1.

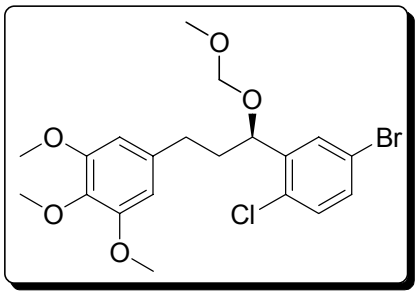
HRMS calculated for $C_{20}H_{21}BrO_5$ (M+): 420.0572**; Found**: 420.0601.

HPLC: 95.4% ee; column: chiralcel AS-H; flow rate: 0.9 mL/min; eluant: 10% iPrOH/hexane: (minor) retention time: 10.23 min, 2.3 %; (major) retention time: 11.03 min, 97.7 %.

$[\alpha]_D^{22}$ = -22.5 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 2940, 2221, 1577, 1504, 1237, 1025, 757, 689.

(R)-5-(3-(5-bromo-2-chlorophenyl)-3-(methoxymethoxy)propyl)-1,2,3-trimethoxy benzene[8] (10)



To a refluxing solution of **9** (0.794 g, 1.75 mmol) and p-toluenesulfonhydrazide (3.91 g, 20.99 mmol) in dimethoxyethane (17 mL) was added a solution of sodium acetate (2.15 g, 26.23 mmol) in water (17 mL) over a 5h period. The solution was refluxed overnight. DME was concentrated under rotary evaporator and Et_2O was added. The organic layer was washed three times with water and then dried over $MgSO_4$, filtered and concentrated. The colourless oil was purified by column chromatography on silica gel using 20% AcOEt/hexane to give **10** (0.76 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS): δ 7.64 (1H, d, *J*= 2.4 Hz), 7.32 (1H, dd, *J*= 8.5, 2.4 Hz), 7.19 (1H, d, *J*= 8.4 Hz), 6.43 (2H, s), 5.04 (1H, t, *J*= 6.2 Hz), 4.58 (2H, dd, *J*= 24.1, 6.8 Hz), 3.85 (6H, s), 3.82 (3H, s), 3.42 (3H, s), 2.86-2.64 (2H, m), 2.05-1.98 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 153.0, 142.1, 137.1, 135.9, 131.4, 131.3, 130.8, 130.5, 120.8, 105.1, 95.1, 73.9, 60.8, 56.0, 55.9, 38.1, 32.3.

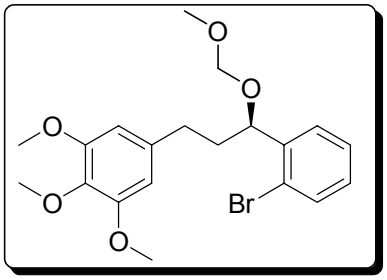
HRMS calculated for $C_{20}H_{25}BrO_5$: (M+) 424.0885; Found: 424.0868.

HPLC: 97% ee; column: chiralcel AS-H; flow rate: 0.8 mL/min; eluant: 2% iPrOH/hexane: (major) retention time: 13.43 min, 98.8 %; (minor) retention time: 15.417 min, 1.2 %.

$[\alpha]_D^{22}$ = 65.4 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 2938, 1590, 1240, 1129, 1025, 816, 667.

(R)-5-(3-(2-bromophenyl)-3-(methoxymethoxy)propyl)-1,2,3-trimethoxy benzene (15)[8]

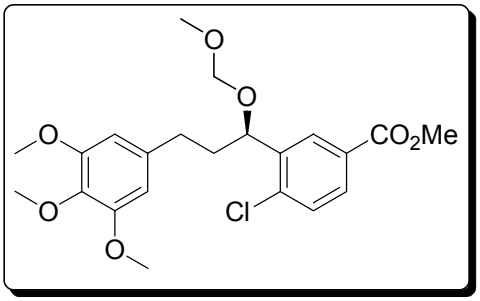


To a refluxing solution of (**14**) (1.025 g, 2.43 mmol) and p-toluene sulfonhydrazide (5.44 g, 29.20 mmol) in dimethoxyethane (25 mL) was added a solution of sodium acetate (2.99 g, 36.50 mmol) in water (25 mL) over a 5h period. The solution was refluxed overnight. DME was concentrated under rotary evaporator and Et_2O was added. The organic layer was washed three times with water and then dried over $MgSO_4$, filtered and concentrated. The colourless oil was purified by column chromatography on silica gel using 25% AcOEt/hexane to give **15** (1.005 g, 97%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS): δ 7.51 (1H, dd, *J*= 8.0, 1.1 Hz), 7.50 (1H, dd, *J*= 7.8, 1.8 Hz), 7.33 (1H, t, *J*= 7.3 Hz), 7.13 (1H, dt, *J*= 7.7, 1.7 Hz), 6.44 (2H, s), 5.07 (1H, t, *J*= 6.3 Hz), 4.57 (2H, dd, *J*= 18.3, 6.9 Hz), 3.85 (6H, s), 3.82 (3H, s), 3.43 (3H, s), 2.87-2.65 (2H, m), 2.06-1.98 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 153.0, 141.4, 137.5, 136.0, 132.7, 128.9, 127.8, 127.7, 122.8, 105.2, 95.0, 76.5, 60.9, 56.0, 56.0, 38.6, 32.6.
HRMS calculated for $C_{20}H_{25}BrO_5$ (M+); 424.0885 Found: 424.0868.
HPLC: 98.4% ee; column: chiralcel AS-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (major) retention time: 13.48 min, 99.2 %; (minor) retention time: 19.12 min, 0.8 %.
$[\alpha]_D^{22}$ = +109.6 (c = 1, CH_2Cl_2)
IR (ν_{max}/cm^{-1}): 2939, 1590, 1463, 1240, 1027, 678.

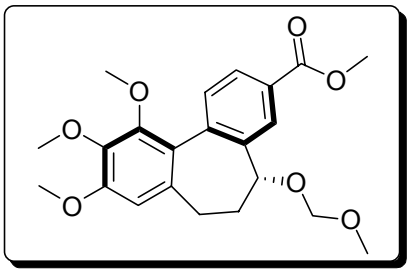
(R)-Methyl 4-chloro-3-(1-(methoxymethoxy)-3-(3,4,5-trimethoxy phenyl) propyl)benzoate (6)[9]



(R)-5-(3-(2-bromophenyl)-3-(methoxymethoxy)propyl)-1,2,3-trimethoxy benzene (**10**) (0.352 g, 0.77 mmol), potassium carbonate (0.318 g, 2.3 mmol) and trans-dichlorobis(triphenylphosphine) palladium (II) (27.0, 0.039 mmol) were placed in a schlenk tube. The tube was purged with carbon monoxide and DMF (3.4 mL) was added. Carbon monoxide was bubbled into the solution for 30 min then methanol was added (0.369 g, 0.47 mL, 11.52 mmol). The solution was bubbled with carbon monoxide for an additional 10 min then the schlenk tube was sealed and the solution was heated at 95°C overnight. The solution was then cooled to room temperature, Et_2O was added and the organic layer was washed 3 times with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The colourless oil was purified by column chromatography on silica gel using 25% AcOEt/hexane to give **6** (0.277 g, 82%).
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ: 8.20 (1H, d, *J*= 2.1 Hz), 7.88 (1H, dd, *J*= 8.3, 2.2 Hz), 7.40 (1H, d, *J*= 8.4 Hz), 6.42 (2H, s), 5.12 (1H, dd, *J*= 7.5, 5.1 Hz), 4.59 (2H, dd, *J*= 29.7, 6.6 Hz), 3.92 (3H, s), 3.85 (6H, s), 3.81 (3H, s), 3.42

(3H, s), 2.89-2.80 (1H, m), 2.70-2.2.62 (1H, m), 2.09-2.04 (2H, m).
^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 166.3, 153.1, 140.5, 137.5, 137.3, 136.0, 129.7, 129.5, 129.1, 129.0, 105.2, 95.2, 74.1, 60.8, 56.1, 56.0, 52.3, 38.3, 32.5.
HRMS calculated for $C_{22}H_{27}ClO_7$ (M+): 438.1445**;** Found**:** 438.1447.
HPLC: 97.4% ee; column: chiralcel AS-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (major) retention time: 10.033 min, 98.7 %; (minor) retention time: 11.38 min, 1.3%
$[\alpha]_D^{22}$ = +76.3 (c = 1, CH_2Cl_2)
IR (v_{max}/cm^{-1}): 2950, 1725, 1590, 1242, 1025, 764.

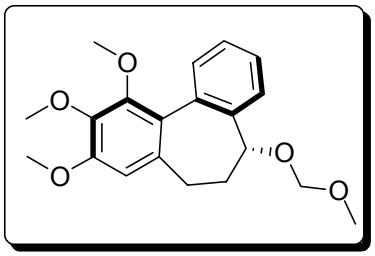
(R)-9,10,11-Trimethoxy-5-methoxymethoxy-6,7-dihydro-5H-dibenzo[a,c] cyclo heptene-3-carboxylic acid methyl ester (16)



(R)-Methyl 4-chloro-3-(1-(methoxymethoxy)-3-(3,4,5-trimethoxyphenyl) propyl)benzoate (**6**) (87 mg, 0.20 mmol), potassium carbonate (57.8 mg, 0.40 mmol) 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (**19**) (7.9 mg, 0.02 mmol) and palladium acetate (4.5 mg, 0.02 mmol) were placed in a flame dried round bottom flask fitted with a condenser. The flask was purged with argon for 10 min and DMA (3.3 mL) was added followed by heating at 145°C overnight. DMA was then removed by short path distillation under vacuum and the residual black precipitate was directly loaded on a silica gel column for chromatography using 20% acetone/hexane to give colourless oil **16** as a 10:1 mixture of atropisomers (58 mg, 73%).
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (Major atropisomer): 8.29 (1H, d, *J*= 1.2 Hz,), 8.01 (1H, dd, *J*= 8.1, 1.8 Hz), 7.54 (1H, d, *J*= 7.8 Hz), 6.60 (1H, s,), 4.71 (1H, d, *J*= 6.9 Hz), 4.57 (1H, d, *J*= 6.6 Hz), 4.51 (1H, dd, *J*= 10.5, 7.2 Hz), 3.95 (3H, s), 3.92 (6H, s), 3.63 (3H, s), 3.36 (3H, s), 2.63-2.39 (2.4H, m, mixture of

atropisomers), 2.29-2.17 (1H, m,), 2.04-2.1.94 (1.1H, m).
(Minor atropisomer): 7.93 (1H, dd, *J*= 1.5 Hz, minor), 7.62 (2H, d, *J*= 8.1 Hz), 6.44 (1H, s), 4.85 (1H, d, *J*= 6.0 Hz,), 4.26-4.13 (2H, m), 3.85 (3H, s), 3.82 (2H, s), 3.59 (3H, s,), 3.20 (3H, s).
^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS) (mixture of atropisomers)**:** 167.3, 153.3, 153.0 (minor), 150.9, 141.0, 139.9, 138.7, 138.3 (minor), 136.1 (minor), 135.5, 132.2 (minor), 130.7 (minor), 129.5 (minor), 130.0, 128.7, 128.5 (minor), 127.6, 127.0 (minor), 124.7, 123.6 (minor), 107.7, 107.4 (minor), 105.2 (minor), 95.4, 95.0 (minor), 74.1, 61.1, 61.0, 60.9 (minor), 60.7 (minor), 56.0, 55.8 (minor), 55.6, 55.2 (minor), 52.1, 39.8, 38.4 (minor), 32.6 (minor), 30.2
HRMS calculated for $C_{22}H_{26}O_7$ (M+): 402.1679; Found: 402.1692.
HPLC: 96.8% ee; column: chiralcel AD-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (minor) retention time: 7.60 min, 1.6 %; (major) retention time: 10.75 min, 98.4 %
$[\alpha]_D^{22}$ = +162.4 (c = 1, CH_2Cl_2)
IR (ν_{max}/cm^{-1}): 2947, 1721, 1598, 1484, 1231, 1149, 1103, 1039, 648.

(R)-1,2,3-Trimethoxy-7-methoxymethoxy-6,7-dihydro-5H-dibenzo[a,c]cyclo heptene (20)



(R)-5-(3-(2-bromophenyl)-3-(methoxymethoxy)propyl)-1,2,3-trimethoxy benzene (**15**) (257mg, 0.60 mmol), potassium carbonate (167 mg, 1.20 mmol) 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (**19**) (23.6 mg, 0.06 mmol) and palladium acetate (13.5 mg, 0.06 mmol) were placed in a flame dried round bottom flask fitted with a condenser. The flask was purged with argon for 10 min and DMA (12.1 mL) was added. The solution was then heated at 145°C overnight. After which the DMA was removed by short path distillation under vacuum. The residual black precipitate was directly loaded on a silica gel column for chromatography using 10% acetone/hexane to give colourless oil **20** as a

15:1 mixture of atropisomers (143 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (major atropisomer): 7.60-7.58 (1H, m), 7.47-7.44 (1H, m), 7.39-7.30 (2H, m), 6.58 (s, 1H), 4.62 (2H, dd, *J*= 29.7, 6.6 Hz), 4.50 (2H, dd, *J*= 10.7, 7.1 Hz), 3.92 (3H, s), 3.91 (3H, s), 3.62 (3H, s), 3.35 (3H, s), 2.60-2.39 (2.2H, m, mixture of atropisomers), 2.34-2.27 (1H, m), 1.99-1.95 (1H, m).

(Minor atropisomer): 7.39 (3H, m), 7.31 (1H, m), 6.44 (1H, s), 4.77 (2H, d, *J*= 6.3 Hz), 4.26 (1H, m), 3.89 (3H, s), 3.57 (3H, s), 3.21 (3H, s), 1.73-1.70 (2H, m).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS) (mixture of atropisomers)**:** 152.7, 150.8, 141, 139.3, 135.5, 133.7, 132.0 (minor), 129.8, 127.1, 126.6 (minor), 126.4, 124.6, 123.1, 107.5, 95.3, 74.4, 61.1, 60.9, 60.6 (minor), 56.0, 55.8 (minor), 55.5, 55.2 (minor), 40.4 (minor), 40.0, 30.3.

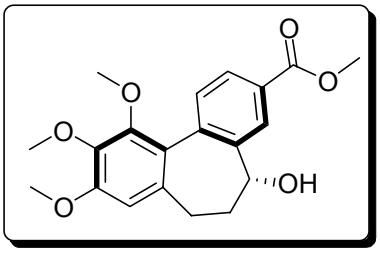
HRMS calculated for $C_{20}H_{24}O_5$ (M+): 344.1624; Found: 344.1641.

HPLC: 98% ee; column:chiralcel AD-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (minor) retention time: 5.43 min, 1.0 %; (major) retention time: 5.82 min 99.0 %

$[\alpha]_D^{22}$ = +132.4 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 2936, 1598, 1483, 1237, 1152, 2034.

(R)-7-Hydroxy-1,2,3-trimethoxy-5,6-dihydro-5H-dibenzo[a,c]cycloheptene - 9-carboxylic acid methyl ester (21)[10]



To a solution of **16** (35 mg, 0.0.09 mmol) in methanol (1.7 mL) was added 0.17 mL of concentrated hydrochloric acid. The resulting solution was refluxed for 1h. Methanol was removed by rotary evaporator, DCM was added and the solution was transferred into a separatory funnel. $NaHCO_3$ was slowly added and the organic layer was extracted three times with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a white solid **21** as a

11:1 mixture of atropisomers (29 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (major atropisomer): 8.36 (1H, d, *J*=1.5 Hz), 8.01 (1H, dd, *J*= 8.1, 1.8 Hz), 7.54 (1H, d, *J*=8.1 Hz), 6.60 (1H, s), 4.65 (1H, dd, *J*= 10.7, 7.4 Hz), 3.95 (3H, s), 3.92 (3.5 H, s, mixture of atropisomers), 3.91 (3H, s), 2.62 (3H, s), 2.67-2.54 (1.2H, m, mixture of atropisomers), 2.49-2.39 (1.2H, m, mixture of atropisomers), 2.33-2.22 (1H, m), 1.98-1.88 (1H, m), 1.77 (1.10H, bs, mixture of atropisomers).

(minor atropisomer): 8.04 (1H, d, *J*= 1.8 Hz), 7.90 (1H, d, *J*= 1.8 Hz), 7.63 (1H, d, *J*= 8.4 Hz), 6.66 (1H, s), 4.86 (1H, d, *J*= 5.7 Hz), 3.85 (2H, s), 3.85 (1H, s), 2.60 (3H, s),

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 167.3, 167.0 (minor), 153.2, 153.1 (minor), 151.1 (minor), 150.9, 142.0, 141.5 (minor), 141.0, 140.0 (minor), 138.0, 137.4 (minor), 136.1 (minor), 135.7, 132.0 (minor), 130.0, 129.4 (minor), 129.1 (minor), 128.7, 128.5 (minor), 127.6, 127.1 (minor), 124.0, 123.6, 107.9 (minor), 107.5, 105.2 (minor), 70.1 (minor), 69.7, 61.2 (minor), 61.1, 61.0, 60.9 (minor), 56.0, 52.2 (minor), 52.1, 42.9 (minor), 41.3, 30.4, 29.7.

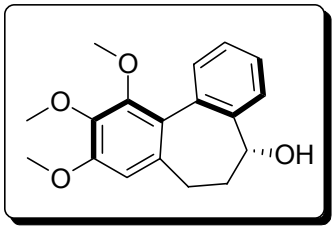
HRMS calculated for $C_{20}H_{22}O_6$ (M+): 358.1416; Found: 358.1404.

HPLC: 97.6 %ee; column: chiralcel AS-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (major) retention time: 18.52 min, 98.8 %; (minor) retention time: 20.03 min, 1.2 %.

$[\alpha]_D^{22}$ = +131.2 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 3481, 3938, 1720, 1292, 1231, 1097.

(R)-7-Hydroxy-1,2,3-trimethoxy-5,6-dihydro-5H-dibenzo[a,c]cycloheptene (22)



To a solution of **20** (109 mg, 0.316 mmol) in methanol (6.3 mL) was added 0.63 mL of concentrated hydrochloric acid. The resulting solution was refluxed for 1h. Methanol was removed by rotary evaporator, DCM was added and the

solution was transferred into a separatory funnel. $NaHCO_3$ was slowly added and the organic layer was extracted three times with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a white solid **22** as a 10:1 mixture of atropisomers (95 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (major atropisomer): 7.65 (1H, dd, *J*= 6.9, 1.5 Hz), 7.45 (1H, dd, *J*= 7.2, 1.8 Hz), 7.40-7.29 (2.3H, m, mixture of atropisomers), 6.59 (1H, s), 4.61 (1H, dd, *J*= 10.7, 7.2 Hz), 3.90 (6.8H, s, mixture of atropisomers), 3.60 (3H, s), 2.57-2.28 (3.8H, m, mixture of atropisomers), 2.09 (1H, bs), 1.94-1.84 (1.3H, s, mixture of atropisomers).

(Minor atropisomer): 7.53 (2H, dd, *J*= 7.5, 1.2 Hz), 7.19 (1H, dd, *J*= 7.4, 1.3 Hz), 6.65 (1H, s), 4.75 (1H, d, *J*= 5.7), 3.83 (2H, s), 3.58 (3H, s), 2.16 (1H, s),

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS) (mixture of atropisomers)**:** 152.7 (minor), 152.6, 151.1 (minor), 150.8, 141.6, 141.2 (minor), 141.2 (minor), 140.9, 136.1 (minor), 135.6, 134.5 (minor), 132.9, 131.6 (minor), 129.7, 127.9 (minor), 127.4 (minor), 127.2, 127.0 (minor), 126.3, 125.5 (minor), 124.5, 122.4, 107.8 (minor), 107.4, 75.2 (minor), 69.9, 61.2 (minor), 61.1, 60.9, 60.8 (minor), 56.0, 55.9 (minor), 43.0 (minor), 41.4, 30.6 (minor), 30.5.

HRMS calculated for $C_{18}H_{20}O_4$ (M+): 300.1362; Found: 300.1369.

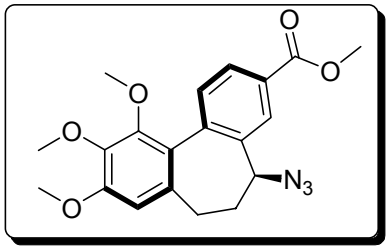
HPLC: 98% ee; column: chiralcel OJ-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (minor) retention time: 12.72 min, 1.0 %; (major) retention time: 20.85 min, 99.0 %.

Melting point °C (ether): 140.6-141.9

$[\alpha]_D^{22}$ = +89.1 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 3439, 2935, 1598, 1453, 1234, 1095, 760.

(S)-7-Deacetamido-7-azidoallocolchicine[10]



To a stirred solution of **21** (25 mg, 0.070 mmol) and triphenylphosphine (36.6 mg, 0.140 mmol) in anhydrous toluene (1.0 mL) under argon was added $Zn(N_3)_2$-2Py[11] (16.0 mg, 0.052 mmol). Diisopropyl azadicarboxylate (28.2 mg, 27 µL, 0.140 mmol) was then added dropwise to the suspension. The suspension was stirred at room temperature overnight. The solvent was then removed by rotary evaporator, the residue was adsorbed onto silica gel for column chromatography using 20 % acetone/hexane which gave colourless oil as a 8:1 mixture of atropisomers (23 mg, 86%). This compound exhibits spectral data that is identical to that reported in the literature.[10].

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (major atropisomer): 8.24 (1H, d, *J* = 0.9 Hz), 8.04 (1H, dd, *J*= 4.8, 0.9 Hz), 7.56 (1H, d, *J*= 4.8 Hz), 6.61 (1H, s), 4.48 (1H, dd, *J*= 6.9, 4.2 Hz), 3.96 (3H, s), 3.93 (3H, s), 3.92 (3.7H, s, mixture of atropisomers), 3.66 (3H, s), 2.65-2.44 (2.6H, m, mixture of atropisomers), 2.33-2.23 (1.2H, m, mixture of atropisomers), 2.07-1.97 (1.2H, m, mixture of atropisomers).

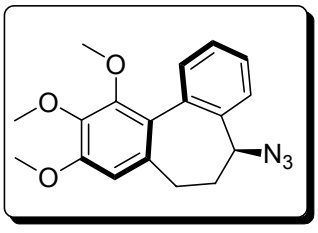
Minor atropisomer: 7.94-7.89 (2H, m), 7.70 (1H, d, *J*= 4.8 Hz), 6.59 (1H, s), 4.84 (1H, d, *J*= 3.9 Hz), 3.95 (3H, s), 3.90 (2H, s), 3.62 (3H, s), 3.45 (2H, s).

HPLC: 93% ee; column: chiralcel AD-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (major) retention time 6.63 min, 96.5%; (minor) retention time: 7.75 min, 3.5%.

$[\alpha]_D^{22}$ = -137.4 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 2936, 2101, 1598, 1455, 1237, 1112.

(S)-7-Azido-1,2,3-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cycloheptene (23)



To a stirred solution of **22** (80 mg, 0.266 mmol) and triphenylphosphine (139.7 mg, 0.533 mmol) in anhydrous toluene (1.6 mL) under argon was added $Zn(N_3)_2$-2Py[11] (61.2 mg, 0.200 mmol). Diisopropyl azadicarboxylate (107.7 mg, 103.2 µL, 0.533) was then added dropwise to the suspension. The suspension

was stirred at room temperature overnight. The solvent was then removed by rotary evaporator, the residue was adsorbed onto silica gel for column chromatography using 10 % acetone/hexane which gave colourless oil **23** as a 5:1 mixture of atropisomers. (65 mg, 76%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (major atropisomer):, 7.59-7.55 (1H, m), 7.49-7.46 (1H, m), 7.42-7.30 (2H, m), 6.60 (1H, s), 4.46 (1H, dd, *J*= 11.3, 6.7 Hz), 3.92 (6H, s,), 3.65 (3H, s), 2.61-2.44 (2.2H, m), 2.36-2.24 (1H, m), 2.04-1.96 (1H, m).

(Minor atropisomer): 7.81 (1H, d, *J*= 6.9 Hz), 7.61 (1H, d, *J*= 7.2 Hz), 7.34-7.30 (2H, m), 6.58 (1H, s), 4.74 (1H, d, *J*= 6.6 Hz), 3.90 (3H, s), 3.90 (2H, s), 3.61 (2H, s), 3.44 (2H, s), 3.08-3.01 (1H, m), 2.81-2.74 (1H, m)

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS) (mixture of atropisomers)**:** 152.9, 152.7 (minor), 152.2 (minor), 150.9, 141.1, 140.7 (minor), 140.4 (minor), 137.1, 136.5 (minor), 135.8 (minor), 134.8, 133.8, 132.3 (minor), 131.8 (minor), 130.1, 129.3 (minor), 128.9 (minor), 128.5(minor), 128.2(minor), 127.5, 126.9, 126.2 (minor), 124.9(minor), 126.5, 107.5, 105.6(minor), 65.2 (minor), 61.1, 61.0, 61.0, 60.6 (minor), 56.0, 55.9 (minor), 39.0, 38.8 (minor), 33.4 (minor), 30.6 (minor), 30.4.

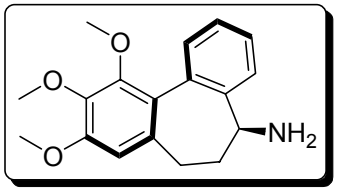
HRMS calculated for $C_{18}H_{19}N_3O_3$ (M+): 325.1426; Found: 325.1435.

HPLC: 96.2 % ee; column: chiralcel AS-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (minor) retention time: 6.55 min, 1.9 %; (major) retention time: 7.38 min, 98.1 %.

$[\alpha]_D^{22}$ = -90.3 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 2936, 2101, 1598, 1454, 1237, 1112.

(S)-7-amino-6,7-dihydro-1,2,3trimethoxy-7H-dibenzo[a,c]cycloheptene [12].



To a stirred solution of **23** (51 mg, 0.157 mmol) in dry THF (1.6 mL) under argon was added a solution of $LiAlH_4$ 1M in THF (0.24 mL, 0.235 mmol). The resulting mixture was stirred at room temperature overnight. 5 ml of water was then added dropwise followed by 5 mL of NaOH 10% followed by 5 mL of water.

Ether was added and the aqueous phase was extracted. HCl 10 % was added to the organic phase and the mixture was stirred for 15 min. It was then extracted twice with ether. The organic layer was discarded and aqueous layer was treated with 10 % aqueous NaOH solution until a pH 12 was reached. The amine was extracted once with DCM and once with ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give a solid as a 15:1 mixture of atropisomers (41 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (major atropisomer)**:**, 7.61 (1H, d, *J*= 7.2 Hz), 7.42 (1H, d, *J*= 7.2 Hz,), 7.40-7.30 (2.3H, m, mixture of atropisomers), 6.59 (1H, s), 3.91 (6H, s), 3.62 (3H, s), 2.52-2.39 (2.2H, m, mixture of atropisomers), 2.34-2.22 (1.2H, m, mixture of atropisomers), 1.87 (2H, bs), 1.79-1.69 (1.1H, m, mixture of atropisomers).

(Minor atropisomer): 7.74-7.70 (1H, m), 7.54-7.52 (2H, m), 6.65 (1H, s), 3.86-3.84 (6H, m), 2.17 (2H, s),

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS): 152.6, 150.8, 142.5 (minor), 140.9, 135.9, 134.3, 131.8 (minor), 130.9 (minor), 129.9, 128.9 (minor), 128.3 (minor), 127.2, 126.7 (minor), 126.1, 124.9, 122.6, 107.8 (minor), 107.3, 68.1(minor), 61.1, 60.9, 60.6 (minor), 56.0, 50.8, 42.6, 31.2, 30.3 (minor), 28.9 (minor).

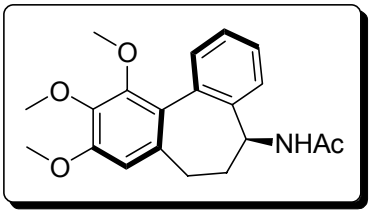
HRMS calculated for $C_{18}H_{21}NO_3$ (M+) 299.1521; Found: 299.1534.

Melting point °C ($CHCl_3$): 91-93.5

$[\alpha]_D^{22}$ = -43.5 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 3318, 2932, 1596, 1453, 1240, 1146, 1103.

(-)-(S)-7-acetamido-6,7-dihydro-1,2,3trimethoxy-7H-dibenzo[a,c] cycloheptene (3)[12.]



To a stirred solution of (S)-7-amino-6,7-dihydro-1,2,3trimethoxy-7H-dibenzo[a,c]cycloheptene (31 mg, 0.104 mmol) and DMAP (3 mg, 0.025 mmol) in DCM (1.0 mL) under argon were added acetic anhydride (12.7 mg, 11.8 µL, 0.124 mmol) and triethylamine (21.0 mg, 28.9 µL, 0.207 mmol). After 36h of

stirring at room temperature the mixture was quenched with water and extracted twice with DCM. The organic layers were combined and washed with 10 % aqueous HCl, dried over $MgSO_4$, filtered and concentrated. The residual solid was purified by column chromatography on silica gel using 40% acetone/hexane to give a white solid **3** as a 5:1 mixture of atropisomers (31.2 mg, 86%). ^{1}H NMR and ^{13}C NMR in $CDCl_3$ for the major atropisomer are identical are identical to that report in the literature[12]. The atropisomer ratio is known to be solvent dependant. We were gratified to find that ^{1}H NMR in $(CD_3)_2SO$ shows only one isomer proving purity product.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) (major atropisomer)**:** 7.52-7.47 (1.5H, m, mixture of atropisomers), 7.34-7.28 (3.4H, m, mixture of atropisomers), 6.57 (1H, s), 5.99 (1H, bs), , 4.88-4.80 (1H, m), 3.93 (3.6H, s), 3.90 (3H, s), 3.51 (3H, s), 2.51-2.37 (3.2H, m, mixture of atropisomers), 2.34-2.28 (1H, m), 2.04 (3H, s), 1.86-1.82 (1H, m).

(Minor atropisomer): 7.38-7.34 (1H, m), 6.67 (1H, s), 6.62 (1H, s), 5.27 (1H, s), 5.18-5.13 (1H, m), 3.94 (3H, s), 3.58 (3H, s), 3.55 (1H, s), 2.18 (3H, s),

^{1}H NMR (300 MHz, $(CD_3)_2SO$, 293K): 8.41 (d, *J*= 8.4 Hz, 1H), 7.34-7.30 (m, 4H), 6.79 (s, 1H), 4.58-4.50 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3), 3.48 (s, 2.6), 3.35 (s, 1.2H), 2.27-1.97 (m, 2.2H), 1.87 (bs, 3.8H).

^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS) (mixture of atropisomers and rotameres)**:** 169.3, 168.0 (minor), 153.0 (minor), 152.7, 151.2, 152.0 (minor), 141.4 (minor), 141.3, 139.1 (minor), 138.9, 138.7 (minor), 135.9, 134.8 (minor), 134.7, 134.4, 134.3 (minor), 134.0 (minor), 131.3, 130.4 (minor), 130.2, 129.0, 127.7 (minor), 127.5 (minor), 127.3 (minor), 127.2, 127.0 (minor), 126.5, 125.8 (minor), 124.9, 124.2 (minor), 122.9 (minor), 122.0, 107.9 (minor), 61.3, 61.2 (minor), 61.1, 60.8 (minor), 60.6 (minor), 56.1, 56.0 (minor), 53.3 (minor), 52.5, 49.2, 41.0 (minor), 40.4 (minor), 39.7, 30.8 (minor), 30.5, 30.4 (minor), 29.7 (minor), 29.3 (minor), 23.3.

HRMS calculated for $C_{20}H_{23}NO_4$ (M+): 341.1627; Found: 341.1628.

HPLC: 96.2% ee; column: chiralcel OD-H; flow rate: 0.8 mL/min; eluant: 10% iPrOH/hexane: (minor) retention time: 11.04 min, 1.9 %; (major) retention time: 13.88 min, 98.1 %.

Melting point °C (ether): 185.2-187.6

$[\alpha]_D^{22}$ = -25.4 (c = 1, CH_2Cl_2)

IR (ν_{max}/cm^{-1}): 3292, 2937, 1650, 1548, 1484, 1237, 1145, 1104.

[1] Lawrence, N.J.; Ghani, F.A.; Hepworth, L.A.; Hadfield, J.A.; McGown, A.T.; Pritchard, R.G.; *Synthesis*, **1999**, *9*, 1656

[2] Commercially available – CAS# 7454-66-7.

[3] Commercially available – CAS# 21900-52-7.

[4] Dubowchik, G. M.; Vrudhula, V. M.; Dasgupta, B.; Ditta, J.; Chen, T.; Sheriff, S.; Sipman, K.; Witmer, M.; Tredup, J.; Vyas, D. M.; Verdoorn, T. A.; Bollini, S.; Vinitsky, A.; *Org. Lett.*, **2001**, *3*, 3987.

[5] Cox, R.J; D J. Ritson, D.J.; Dane, T.A.; Berge, J.; Charmant, J.P.H.; Kantacha, A. ; *Chem. Commun.,* **2005**, *8*, 1037.

[6] (a) Tohda, Y; Sonogashira, K; Hagihara, N.; *Synthesis*, **1977**, *11*, 777. (b)Negishi, E.-I.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J.A.; Stoll, A.T; *Tetrahedron Lett.*, **1983**, *47*, 5181. For recent review see Negishi, E.-I; Anastasia, L.; *Chem Rev.,* **2003**, *103*, 1979.

[7] a) Midland, M.M.; McDowell, D.C.; Hatch, R.L; Tramontano, A.; *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Midland, M.M; Tramontano, A.; kazubski, A; Graham, R.S.; Tsai, D.J.S.; Cardin, D.B.; *Tetrahedron,* **1984,** *40*, 1371.

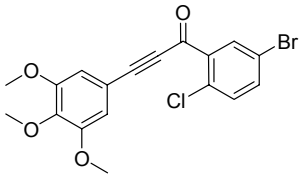
[8] (a) Evans, P.A.; Cui, J.; Gharpure, S.J.; Polosukhin, A.; Zhang, H.-R.; *J. Am. Chem. Soc.,* **2003**, *125*, 14702. (b) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y.: *J. Org. Chem.*, **1997**, *62*, 4665.

[9] Adapted from (a) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A.; *Tetrahedron Lett*. **1993**, *34*, 7595. (b) Back, T. G.; Parvez, M.; Wulff, J. E.; *J. Org. Chem.*, **2003**, *68*, 2223.

[10] Vorogushin, A.V.; Predeus, A.V.; Wulff, W.D.; Hansen, H.J.; *J. Org. Chem.,* **2003**, *68*, 5826

[11] Viaud, M.C.; Rollin, P.; *Synthesis*, **1990**, *1990*, 130.

[12] Boyé, O., Brossi, A.; *Can. J. Chem.*, **1992**, *70*, 1237.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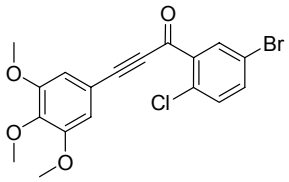
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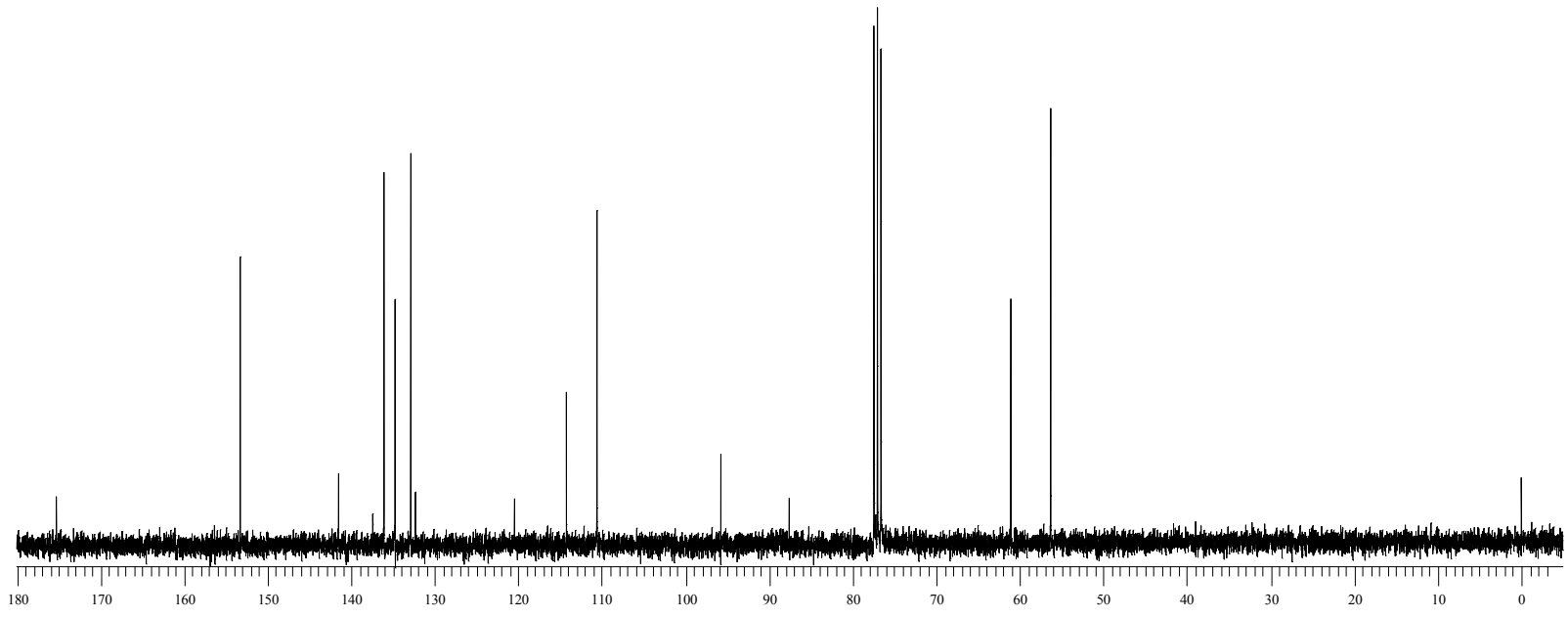
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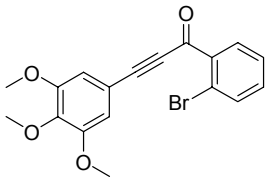
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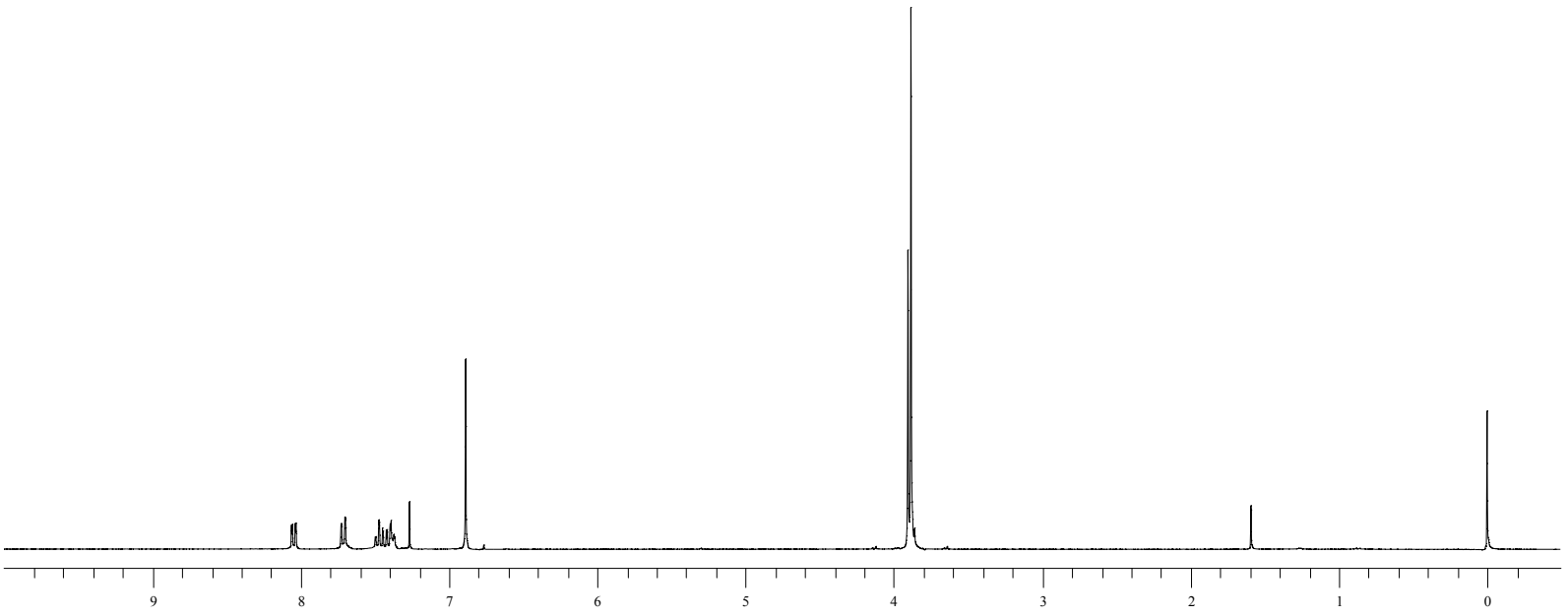
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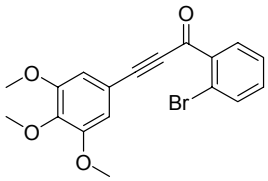
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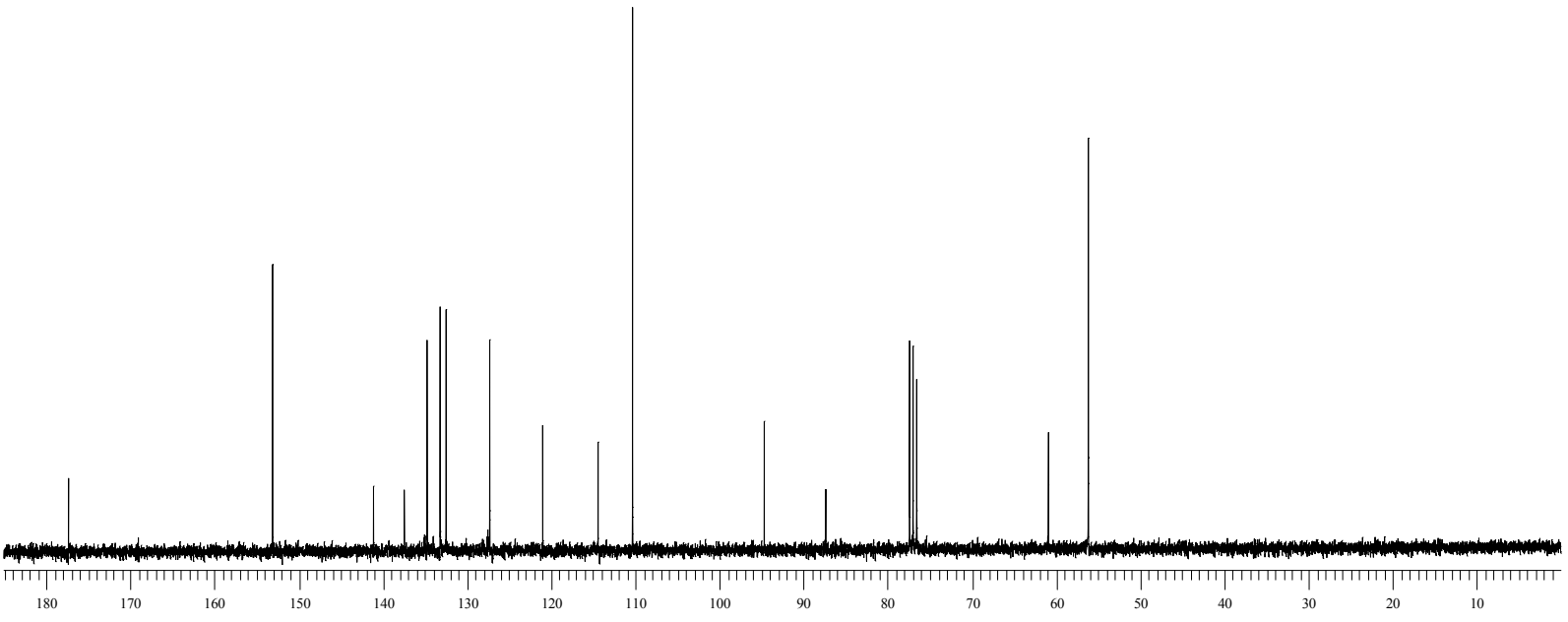
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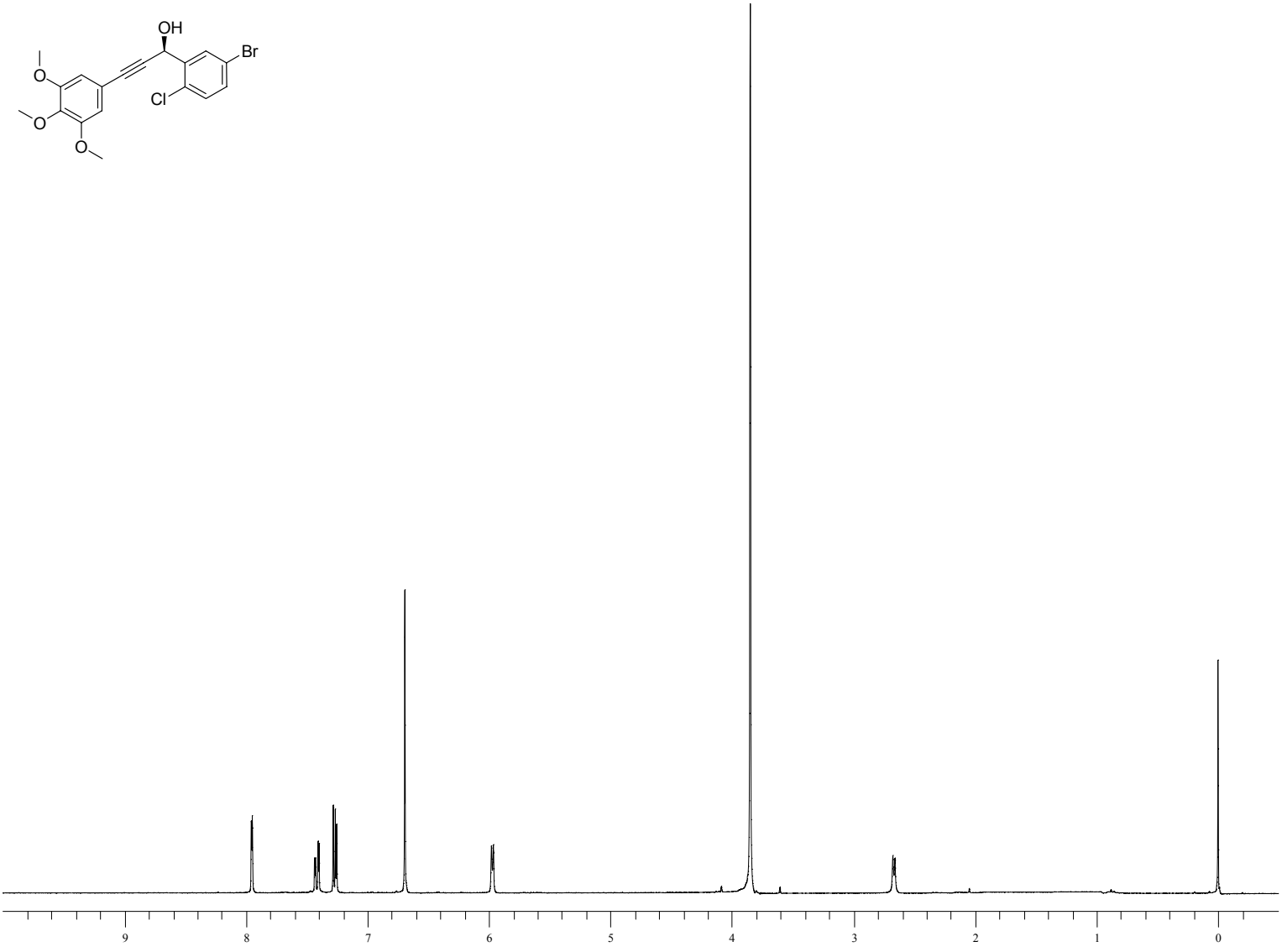
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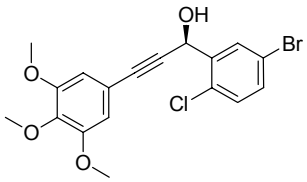
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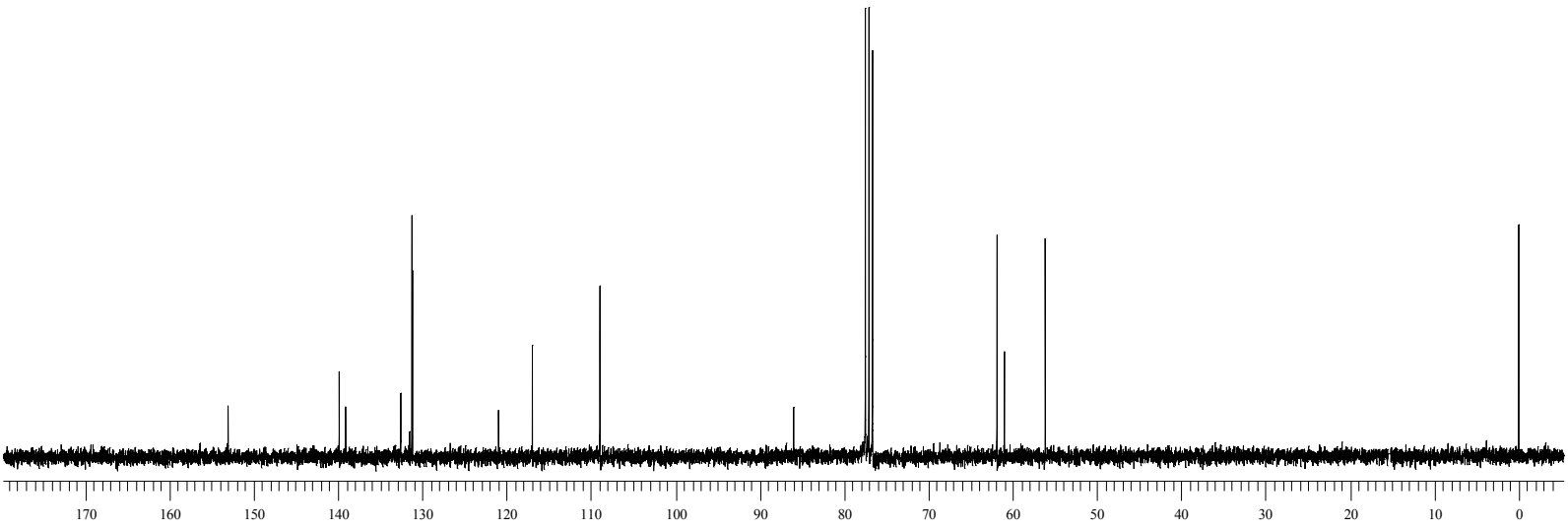
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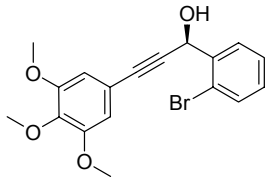
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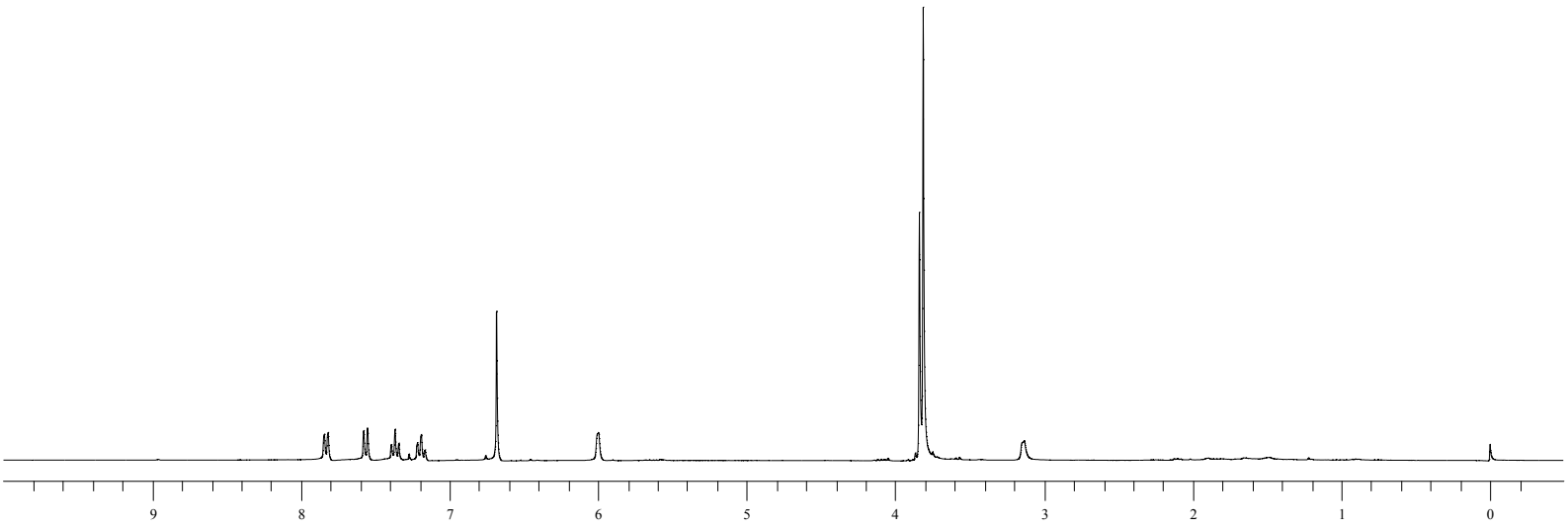
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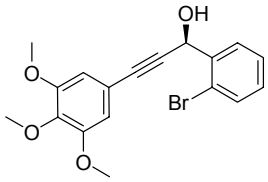
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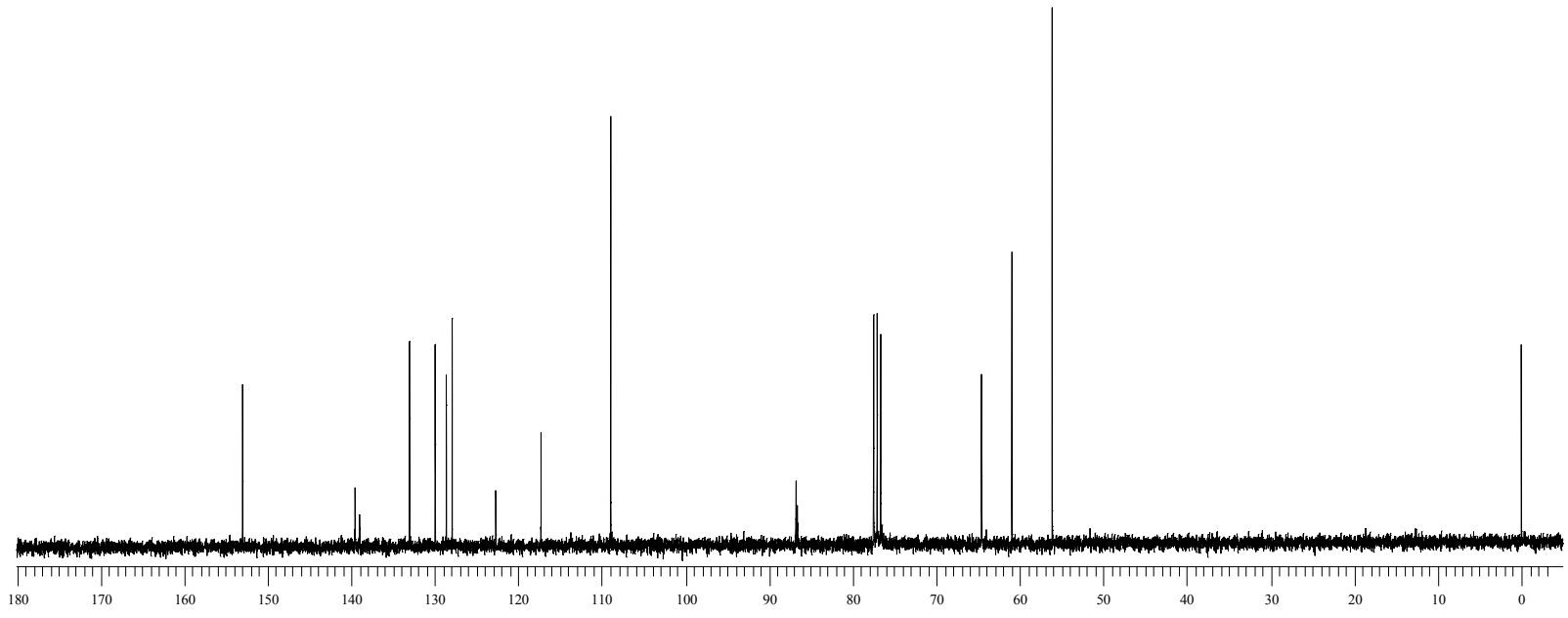
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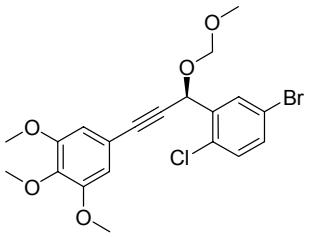
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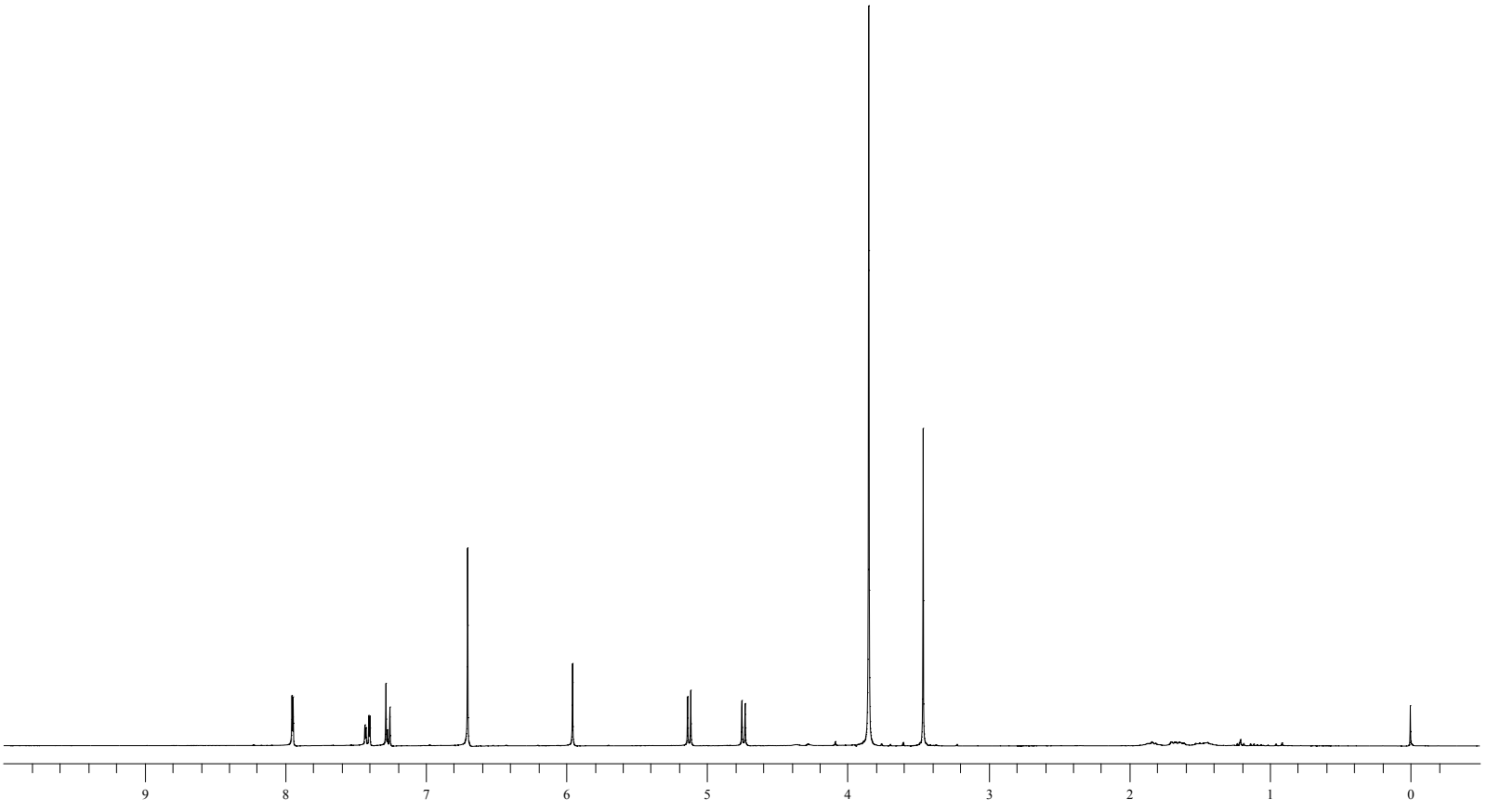
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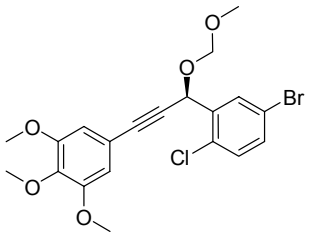
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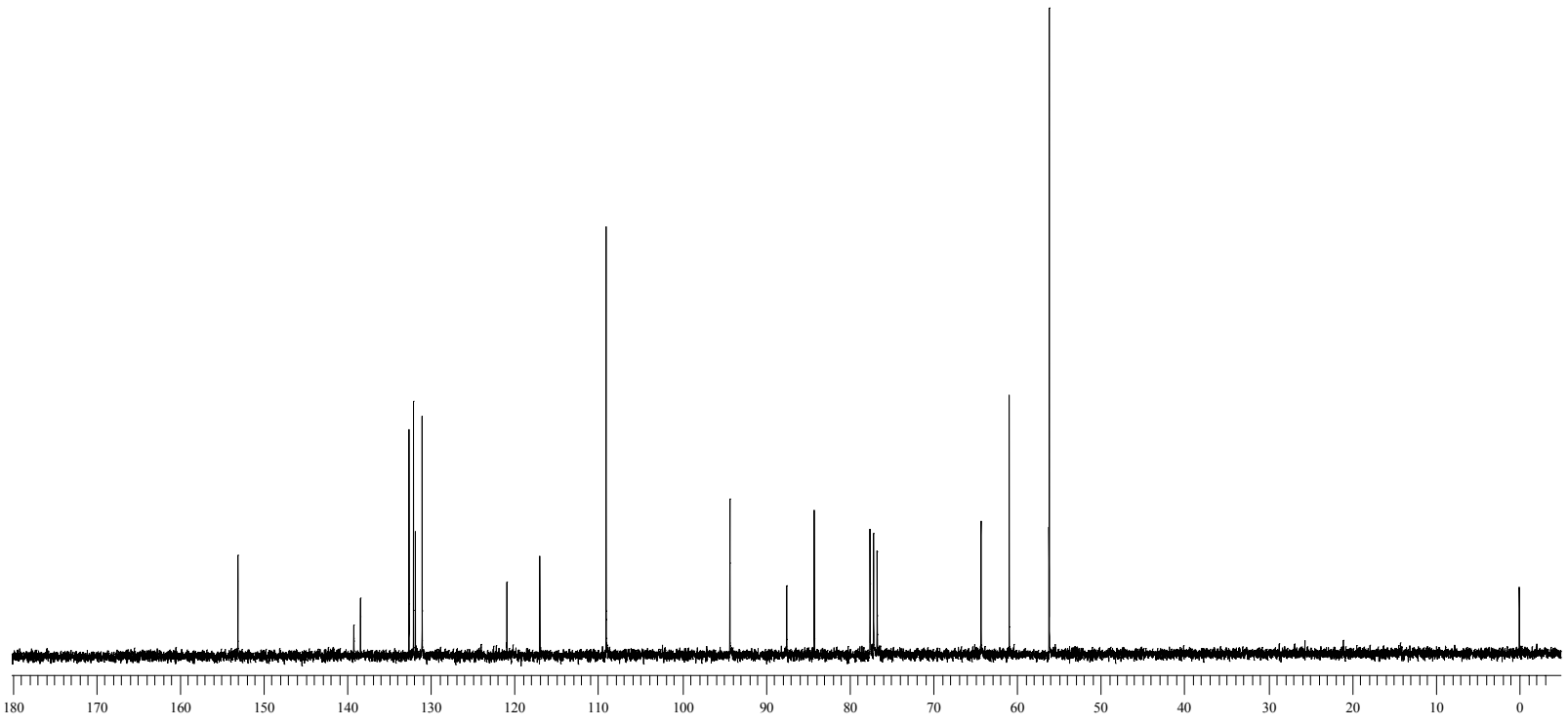
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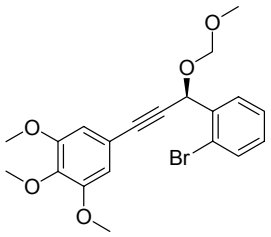
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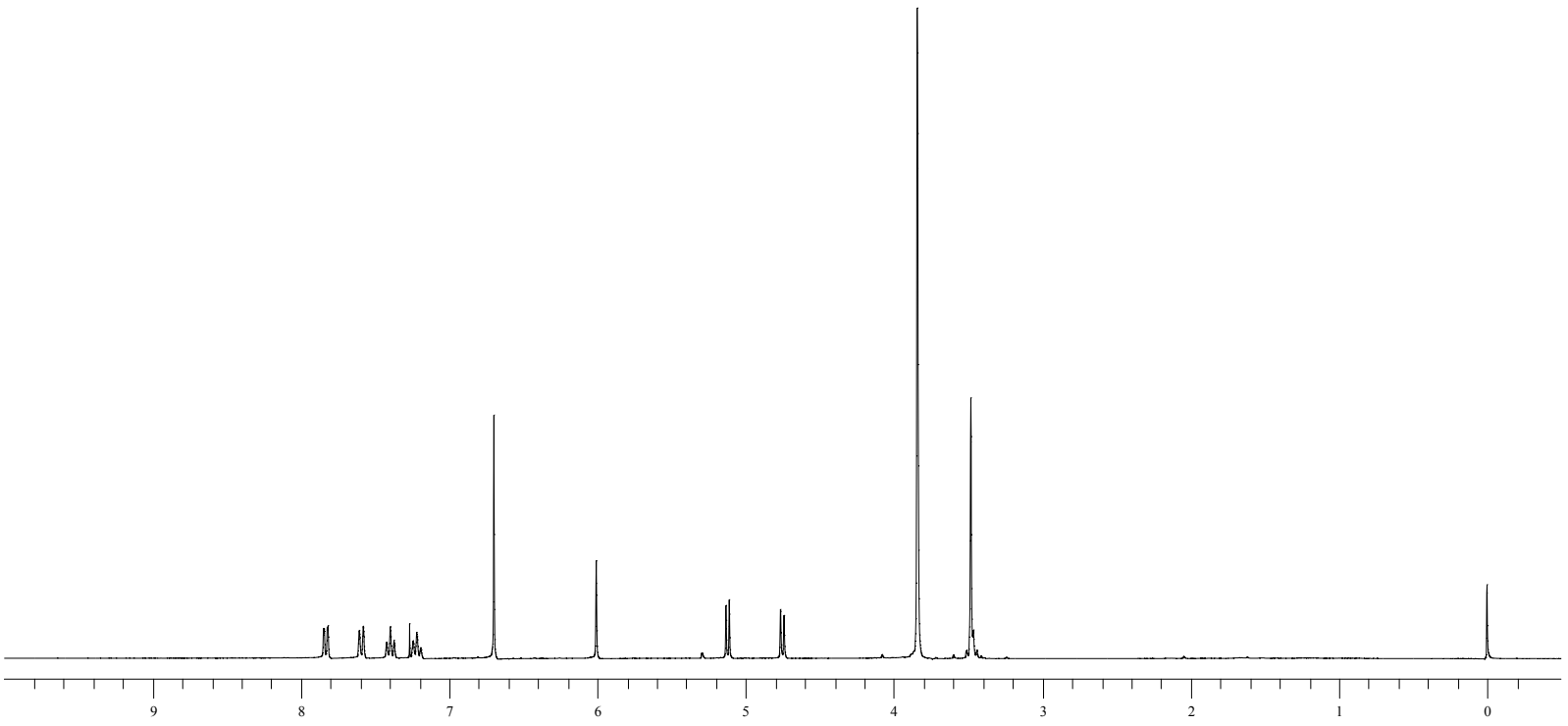
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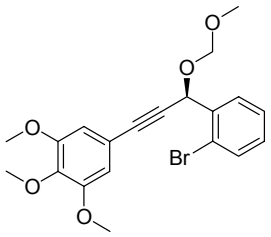
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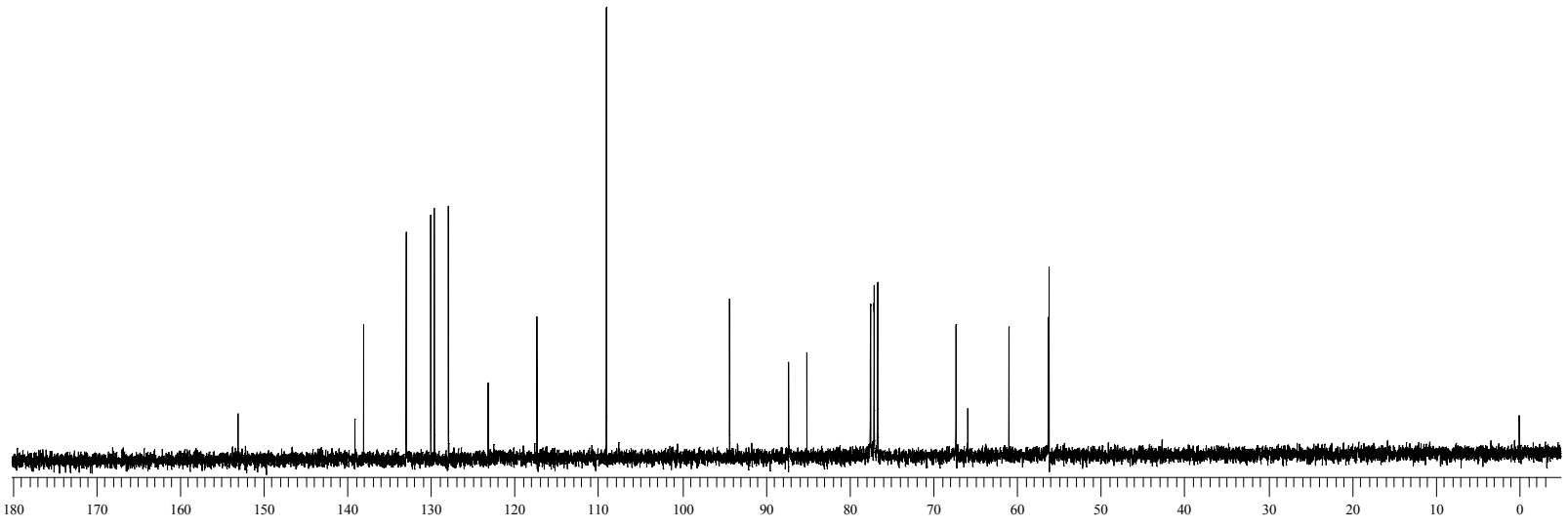
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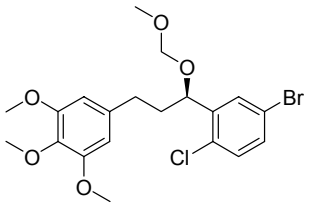
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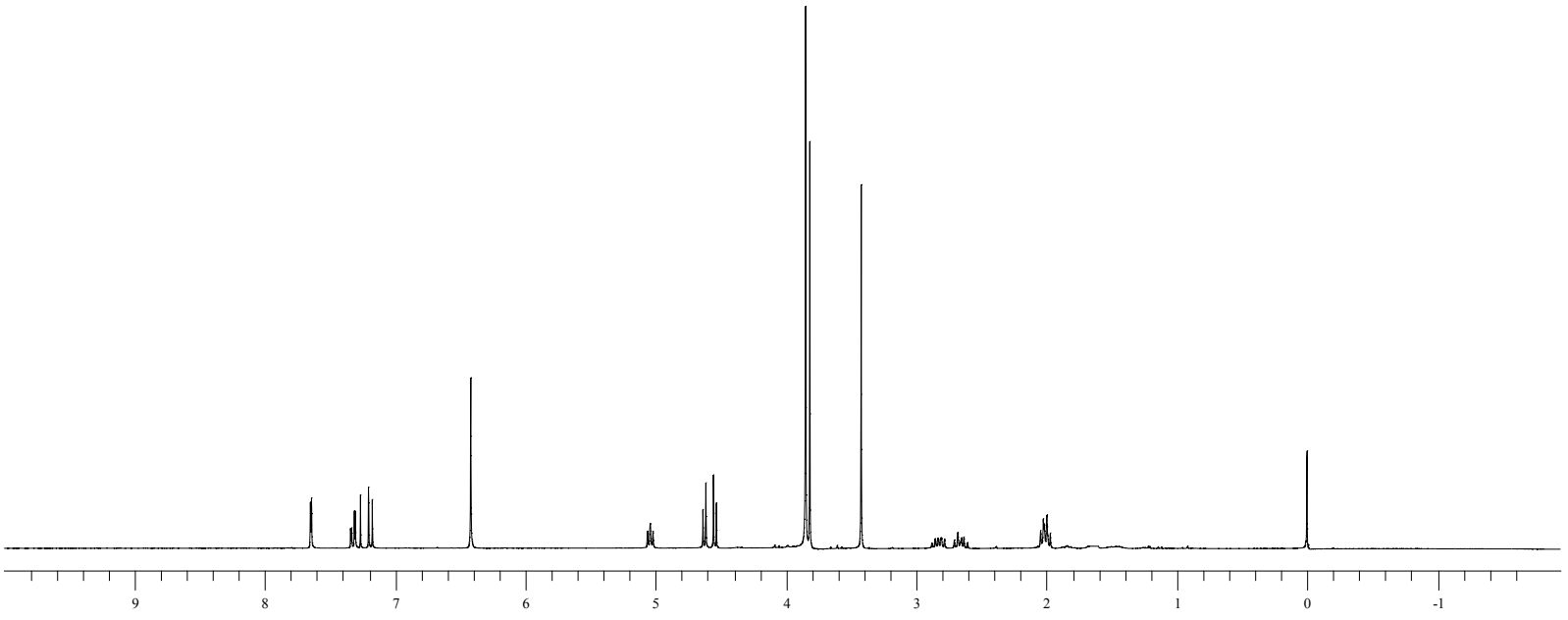
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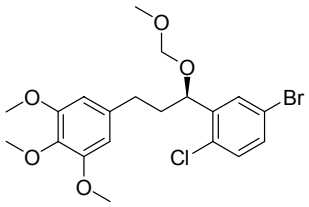
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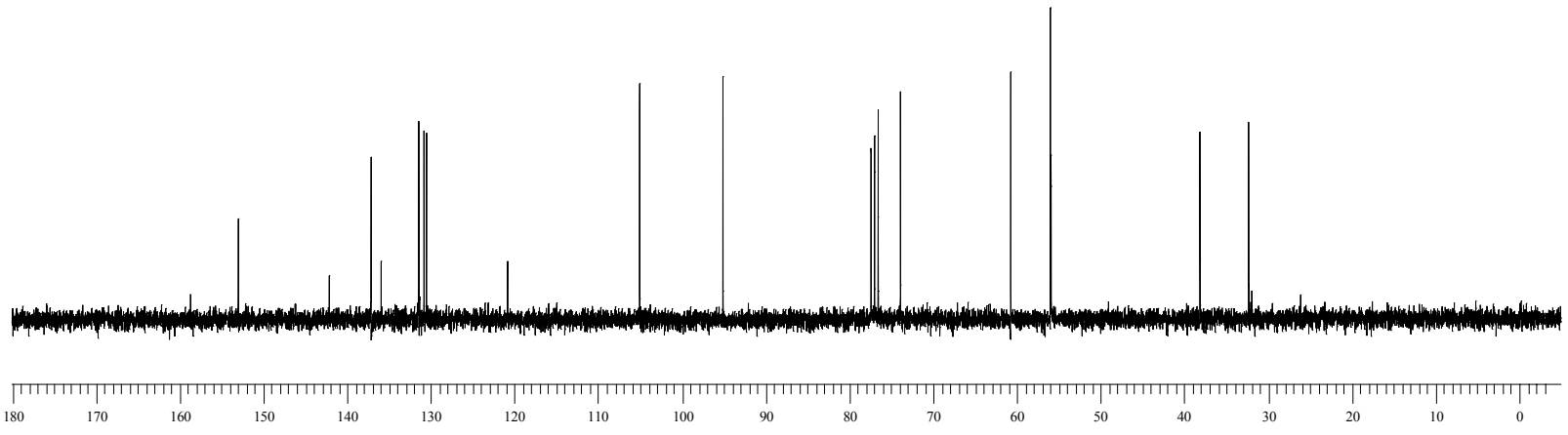
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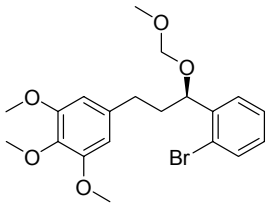
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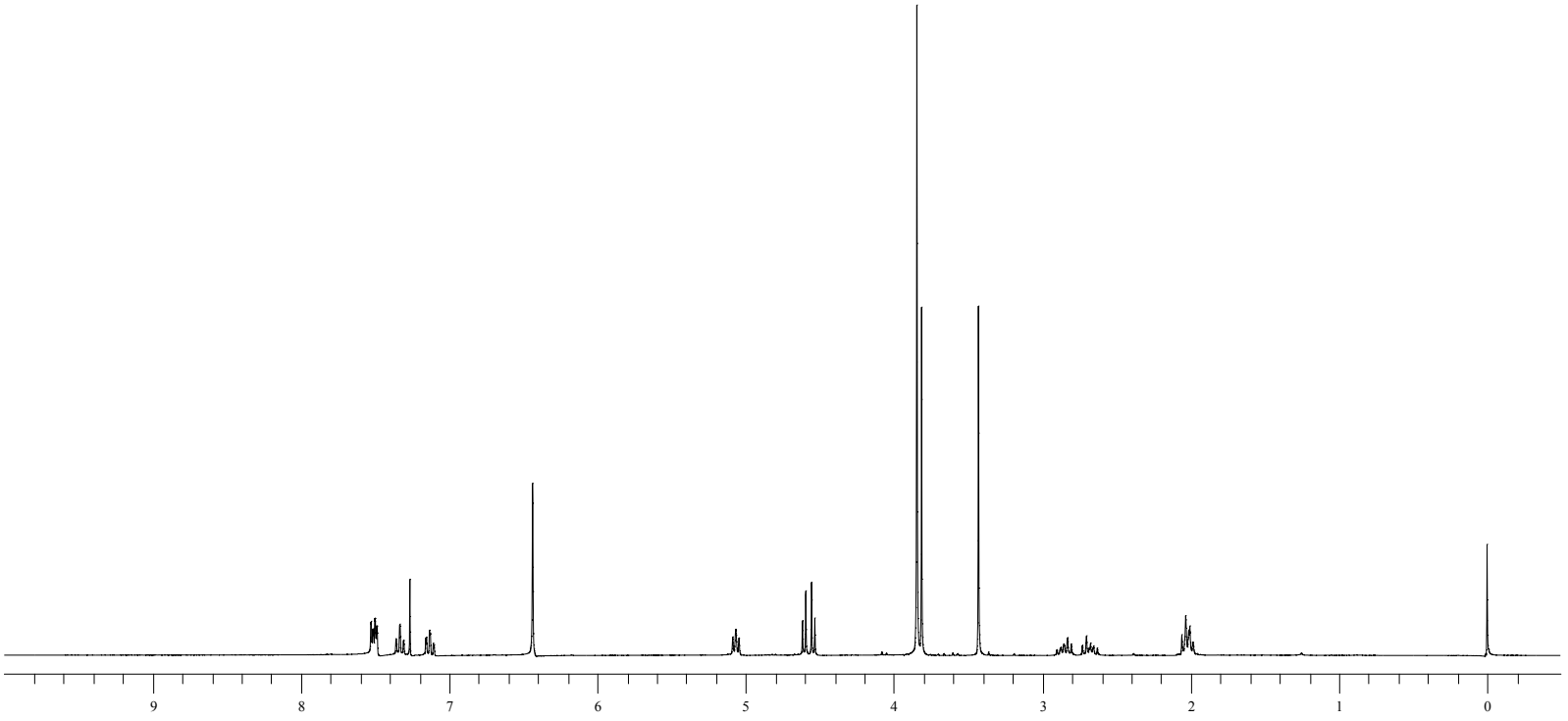
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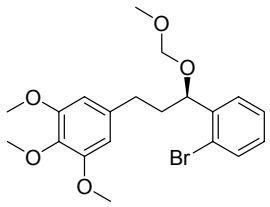
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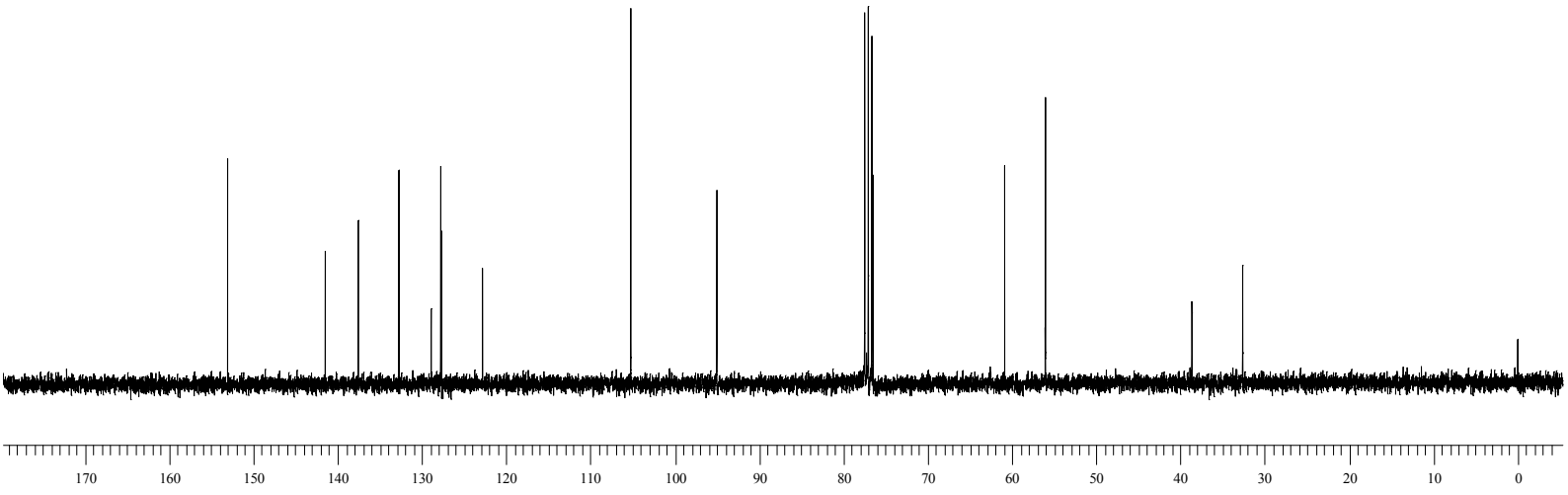
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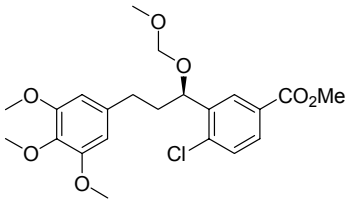
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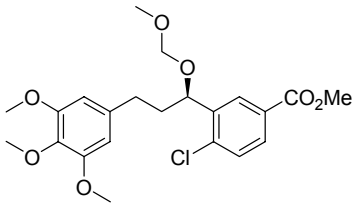
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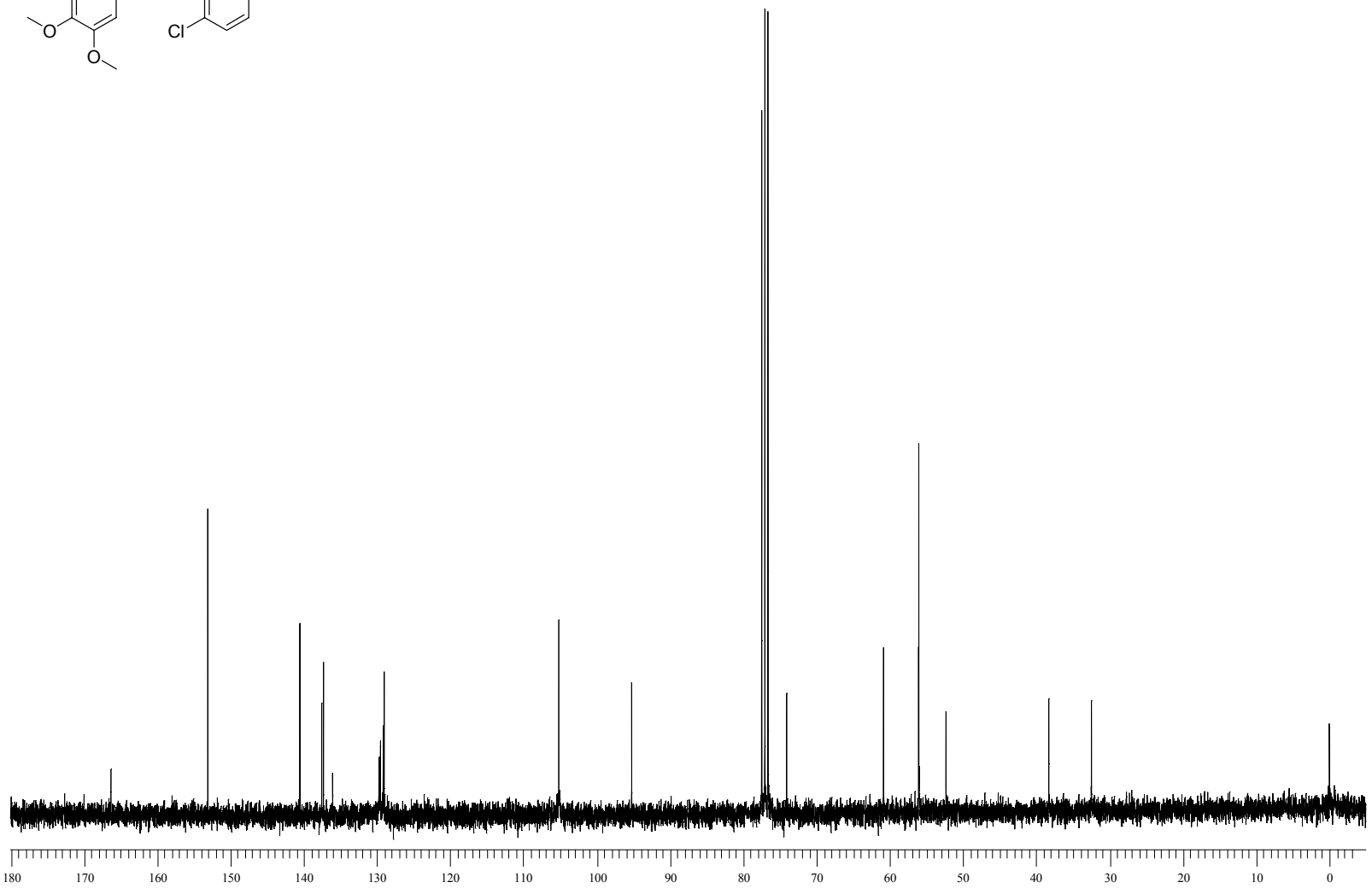
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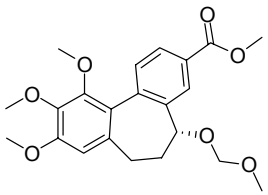
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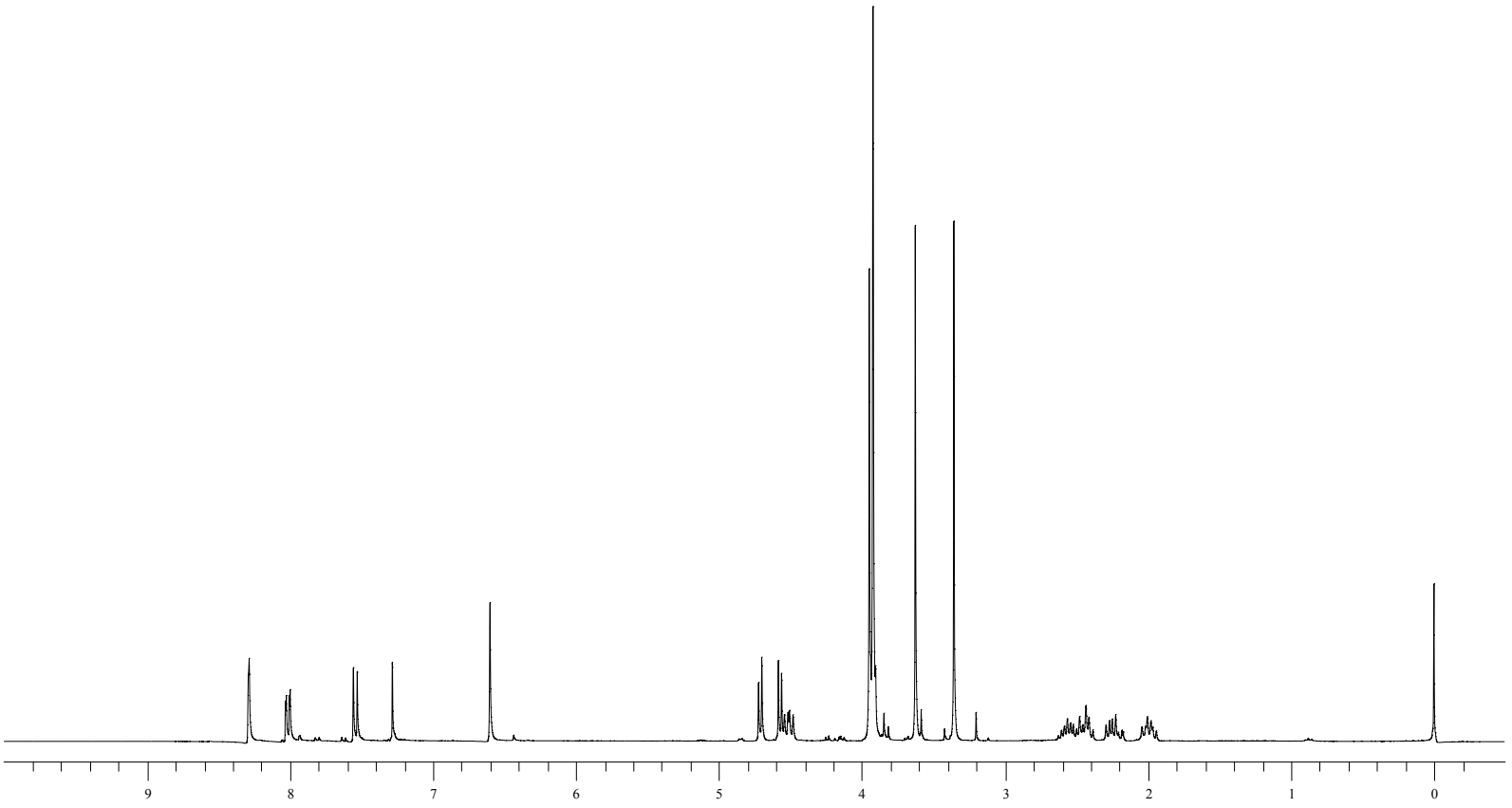
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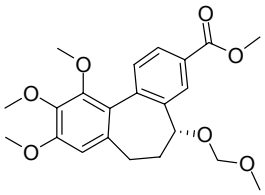

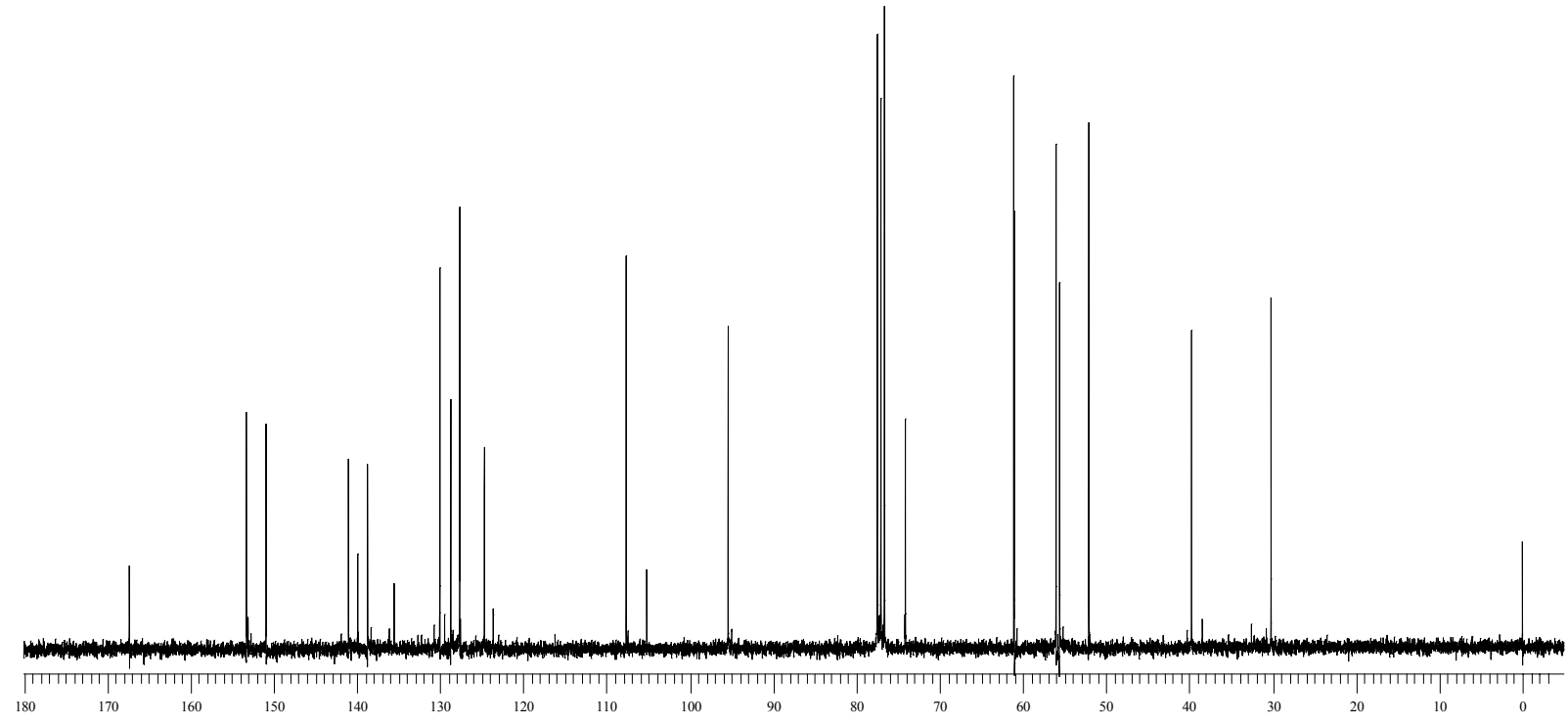
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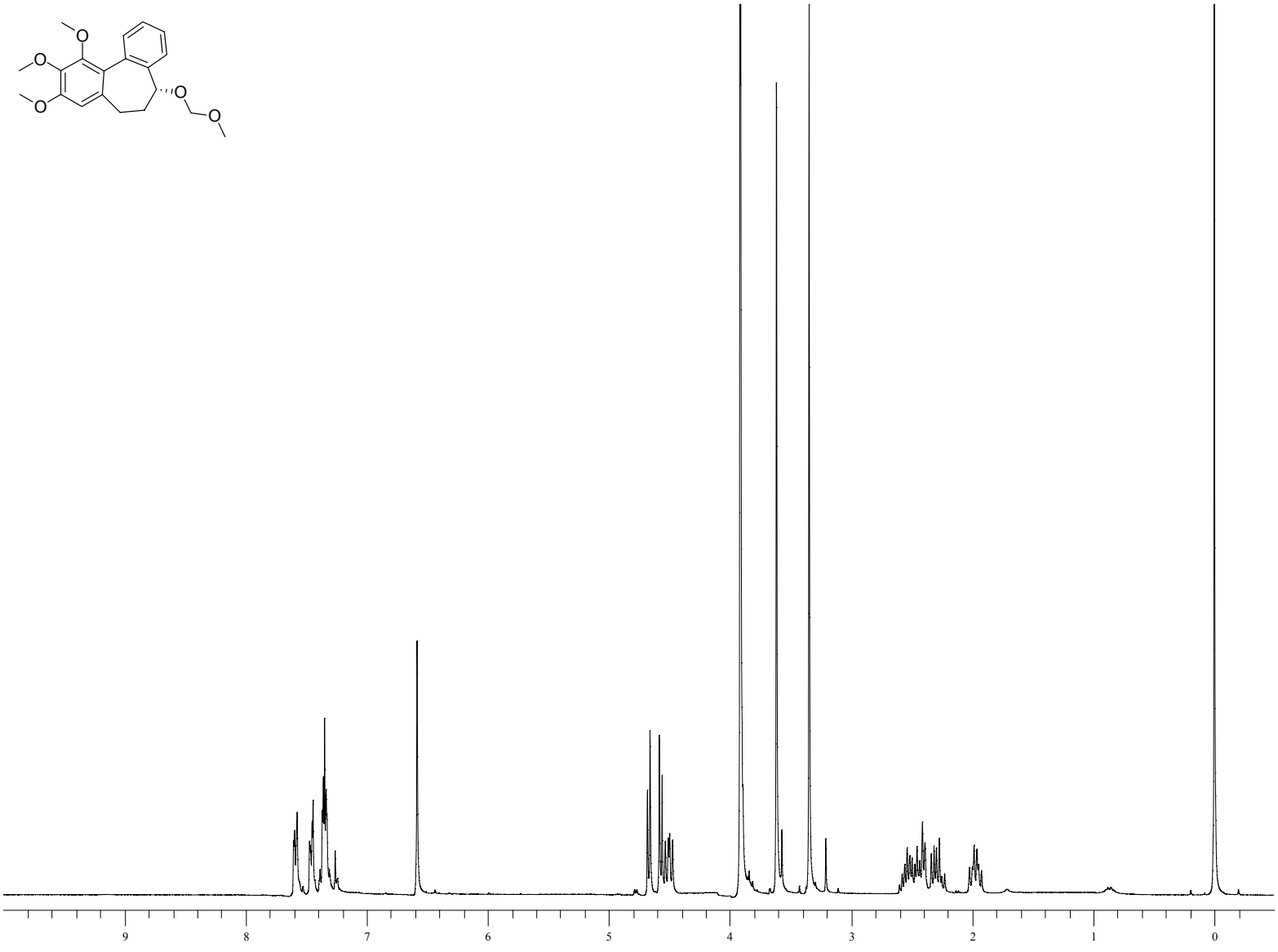
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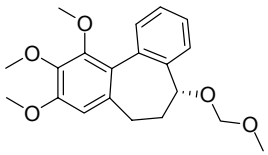

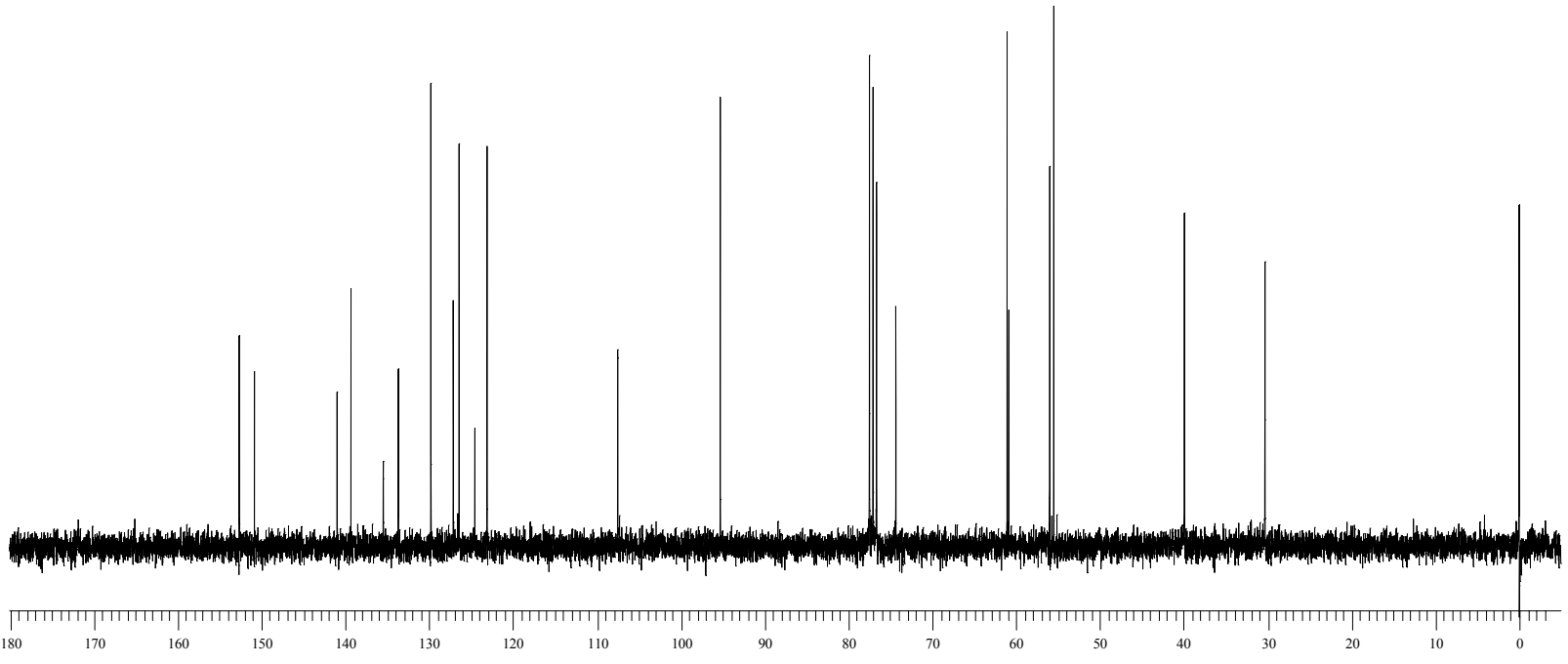
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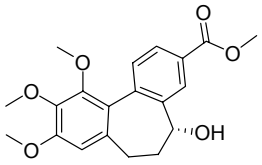
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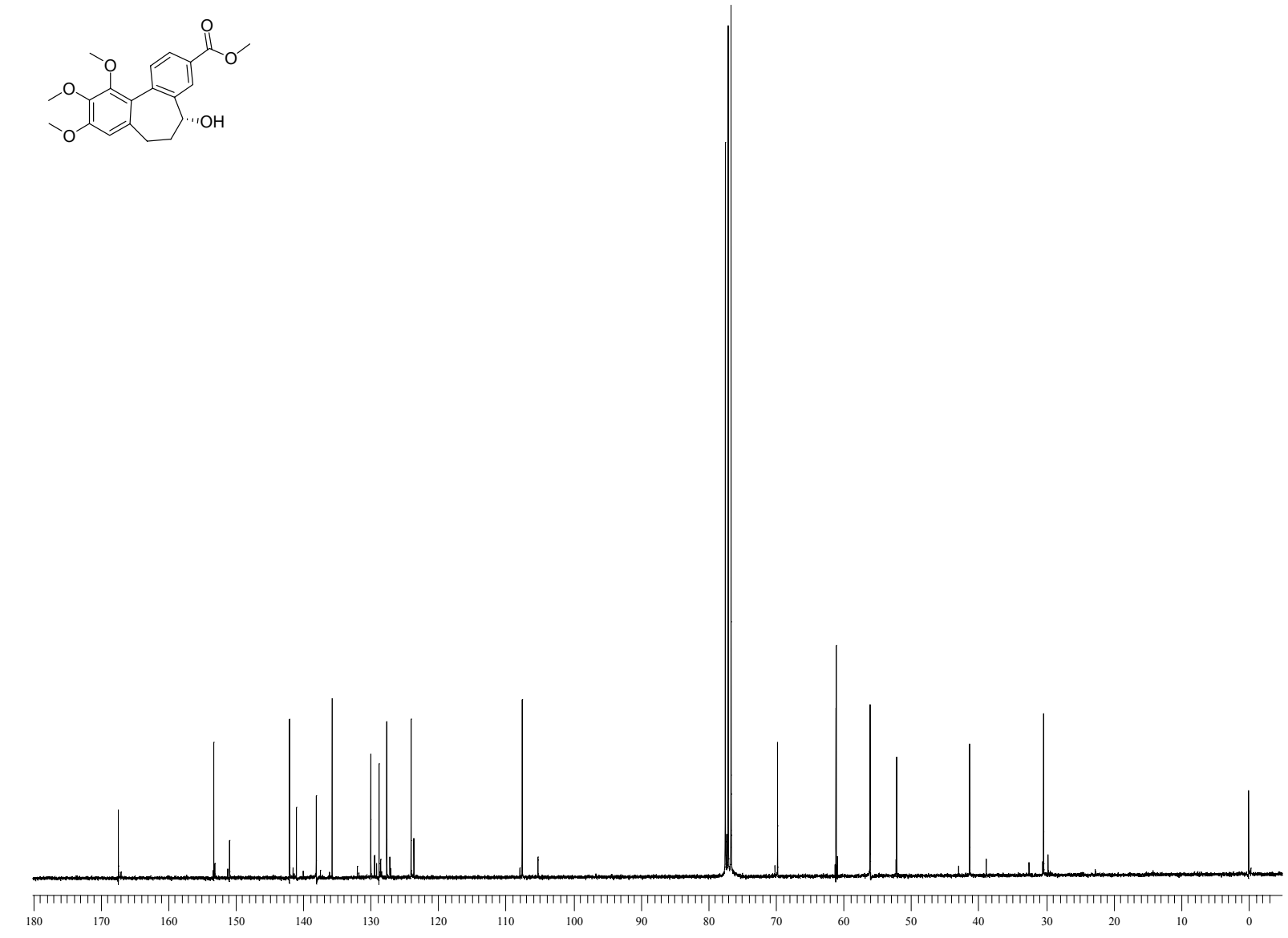
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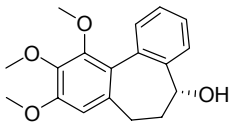
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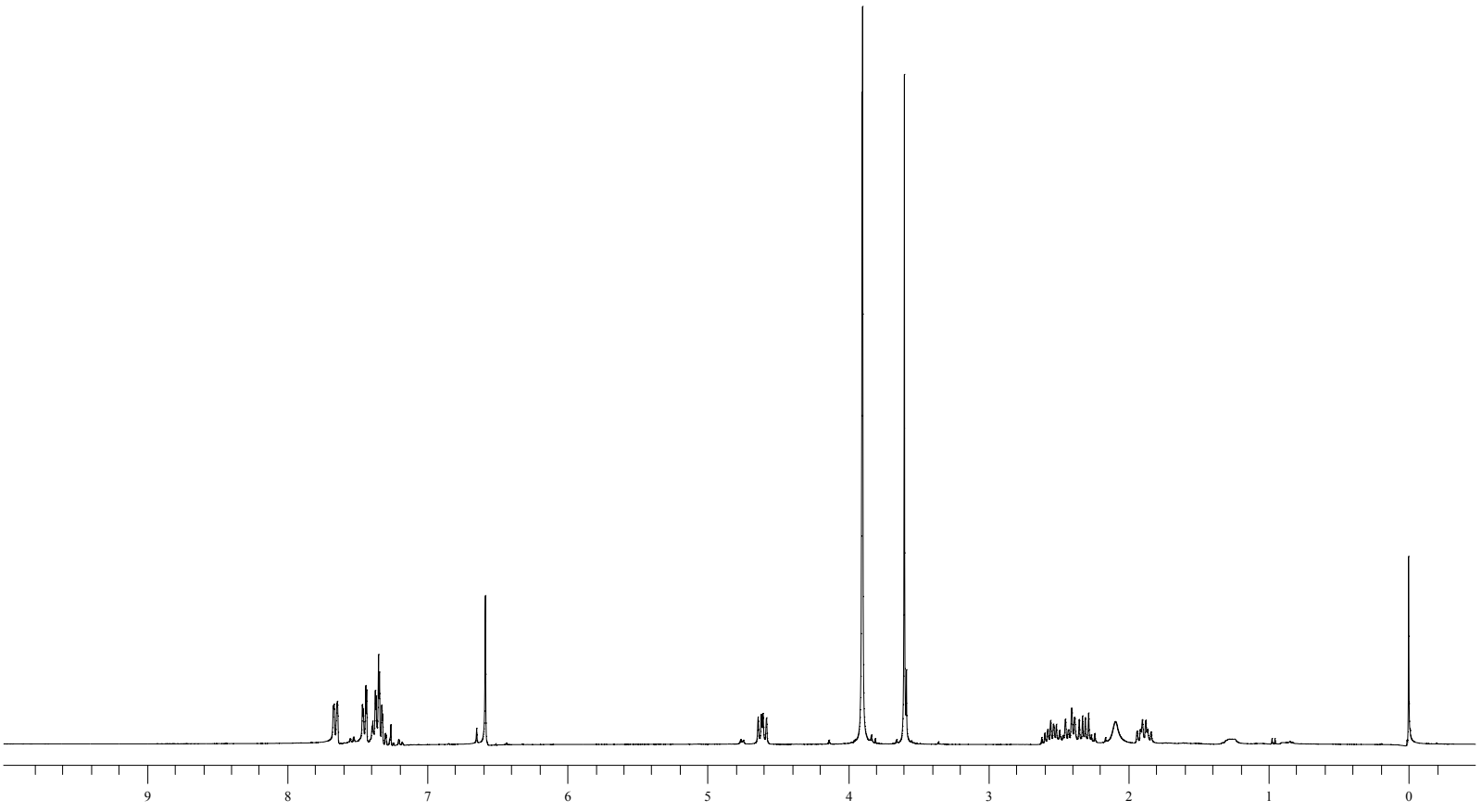
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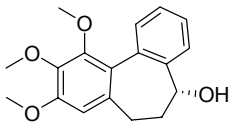
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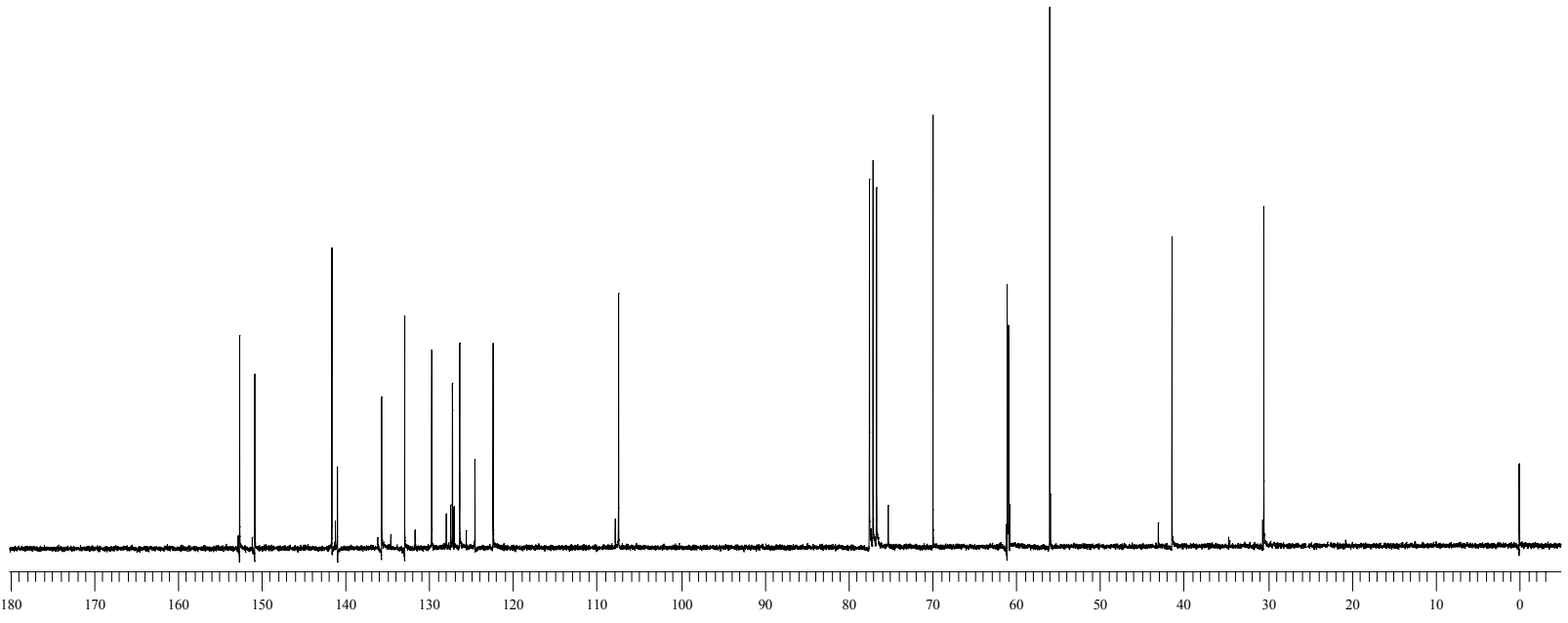
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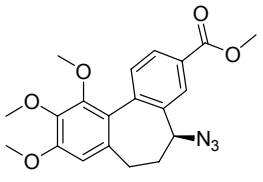
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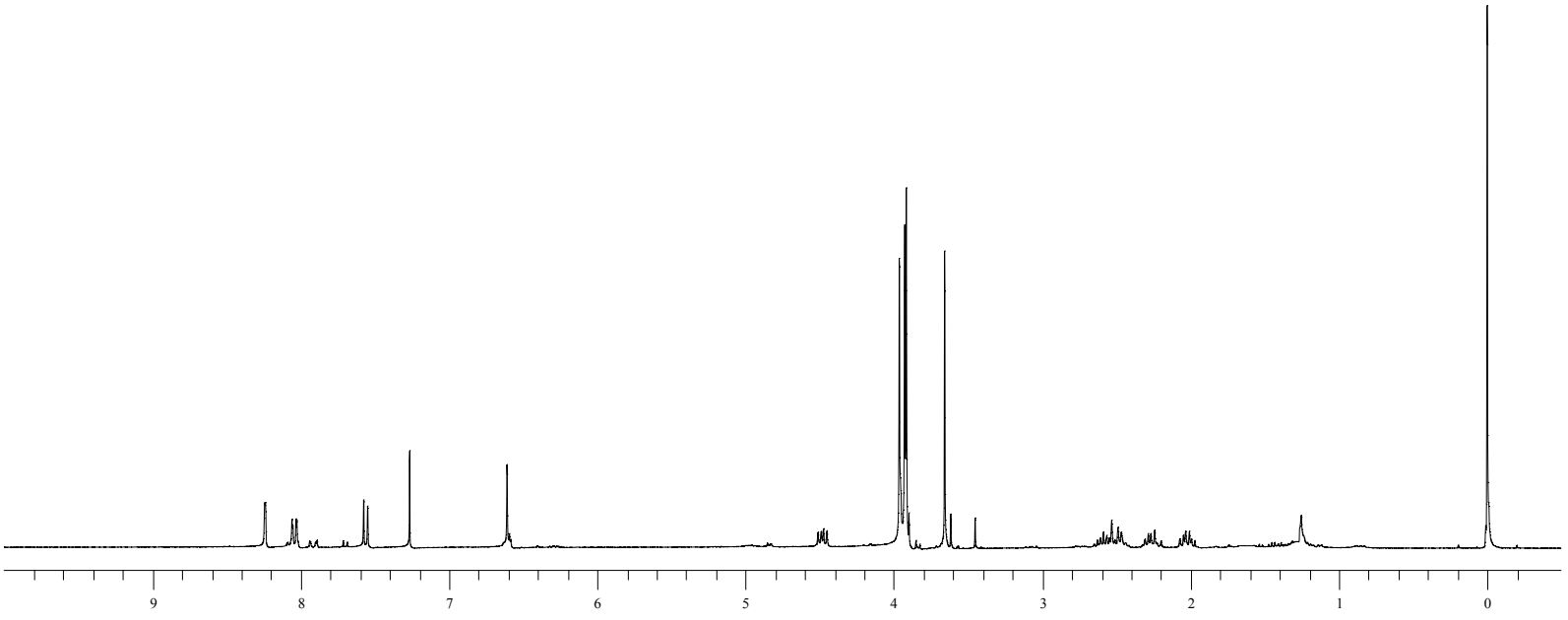
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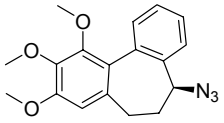
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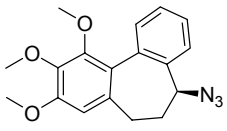
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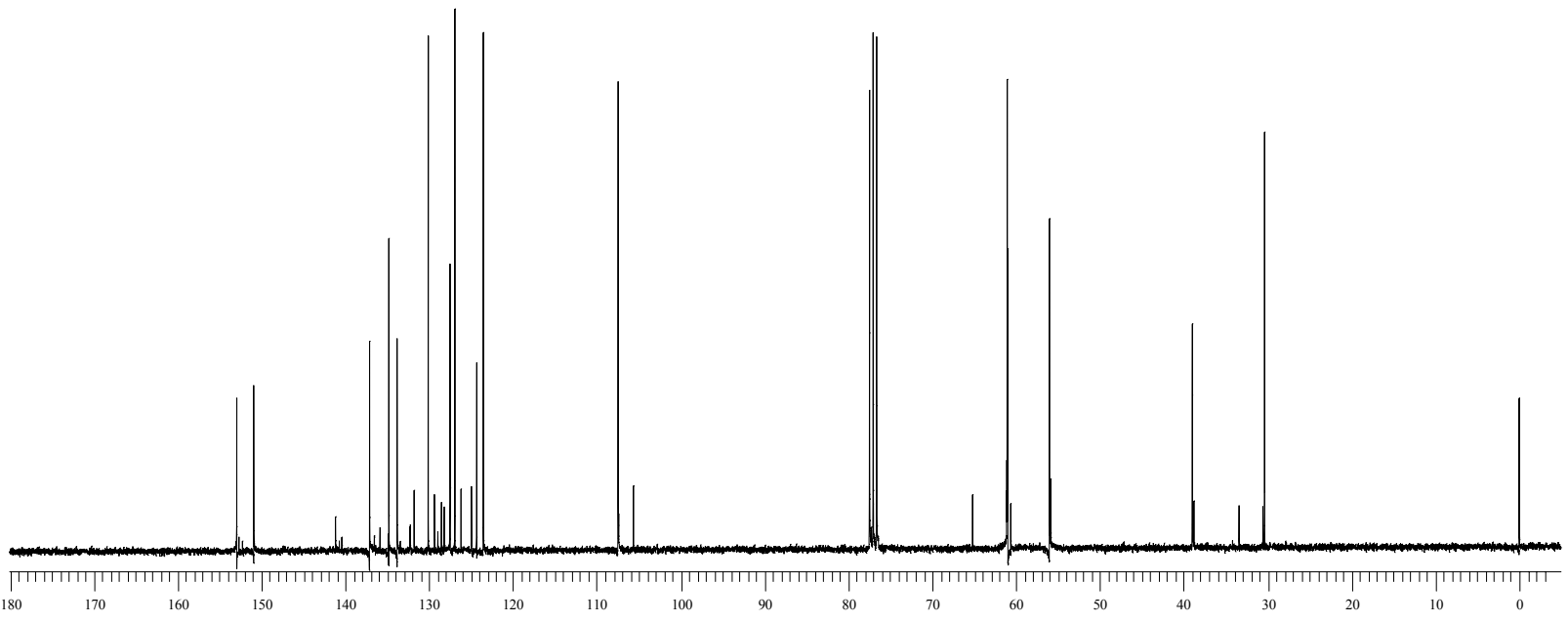
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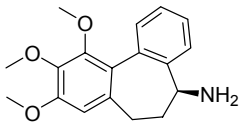
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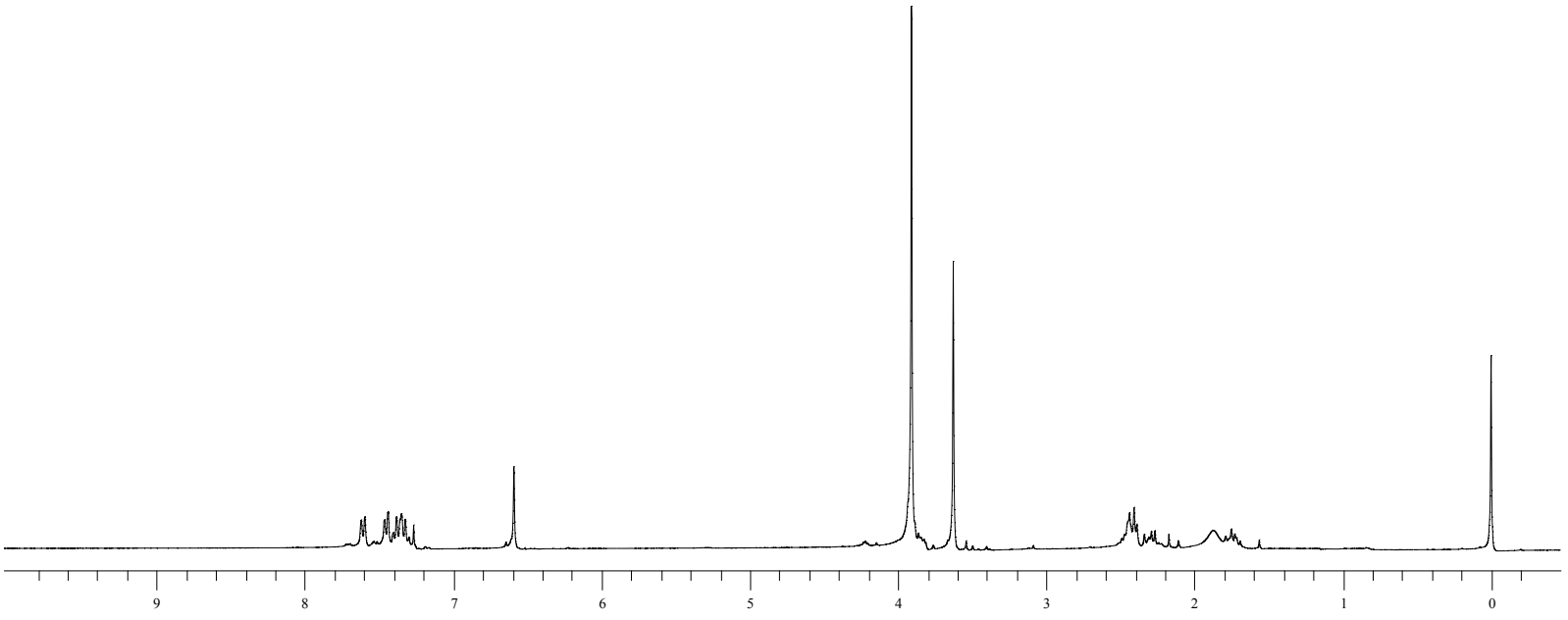
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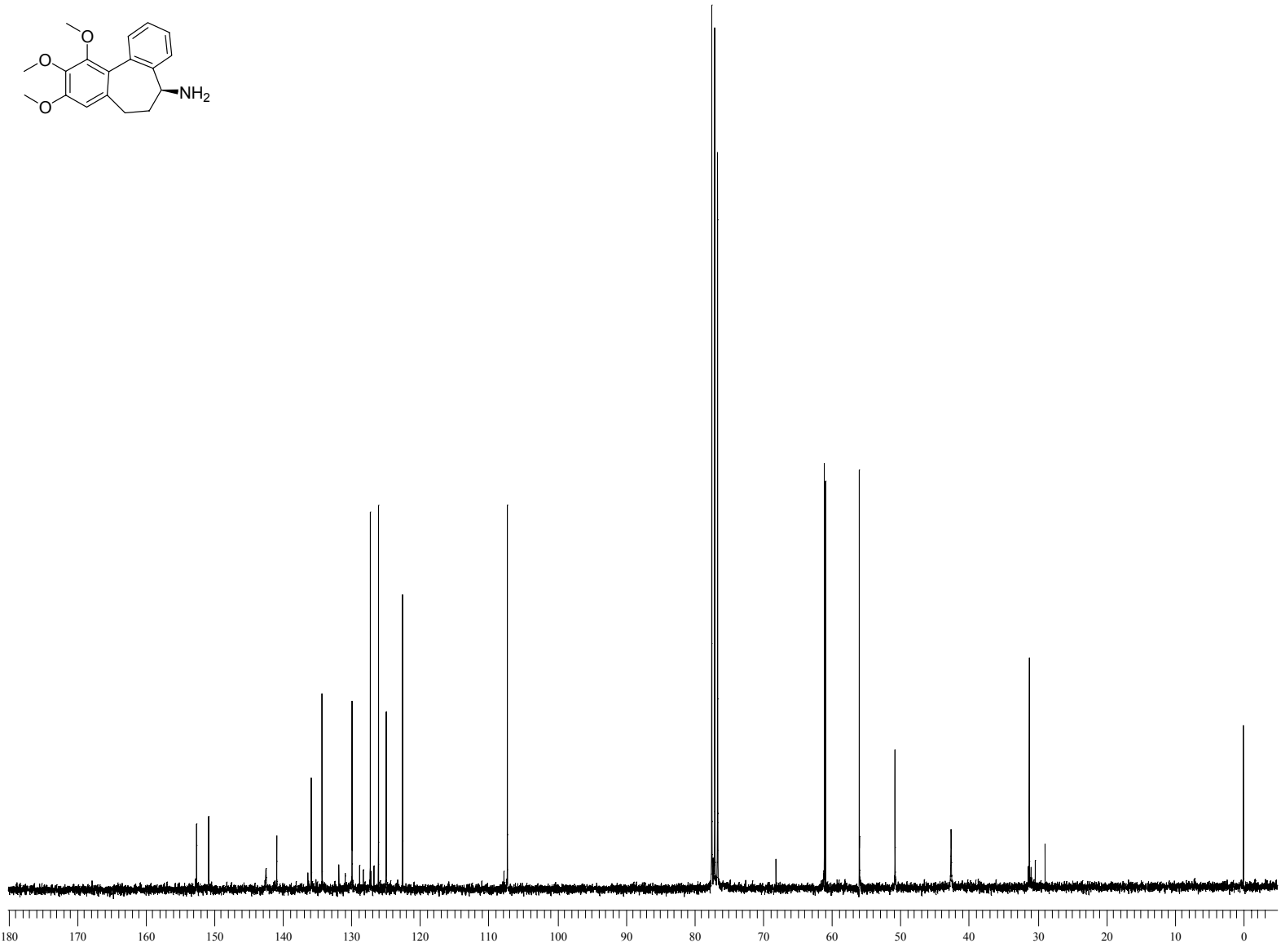
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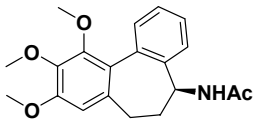
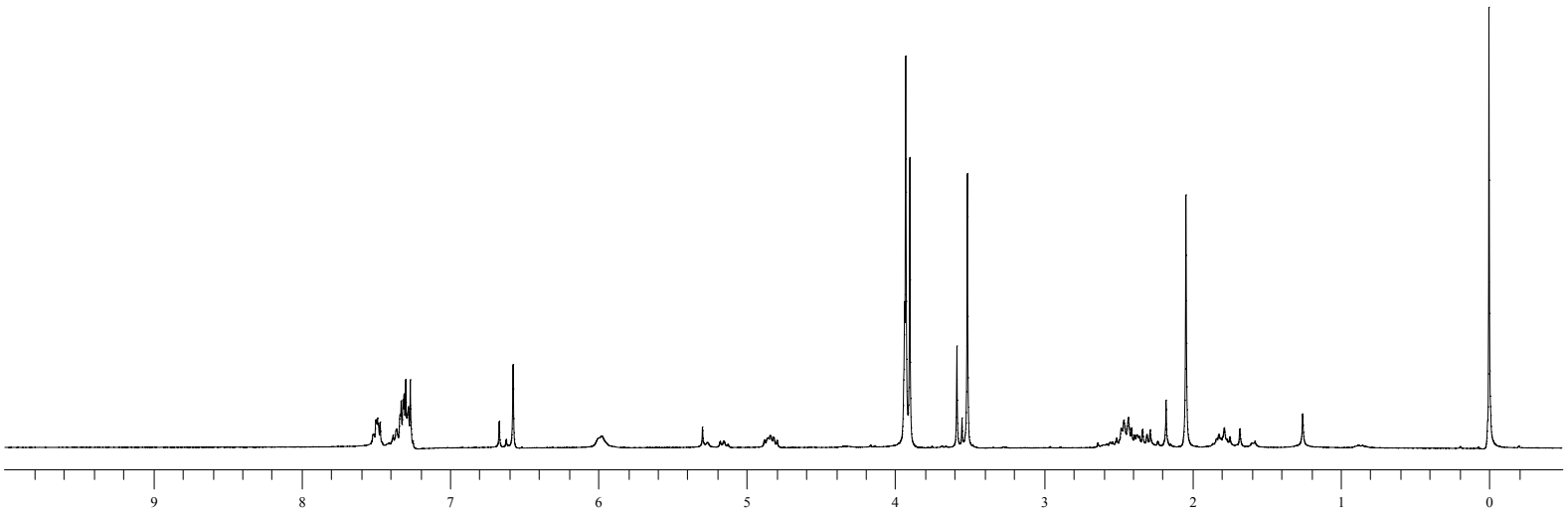
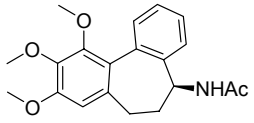
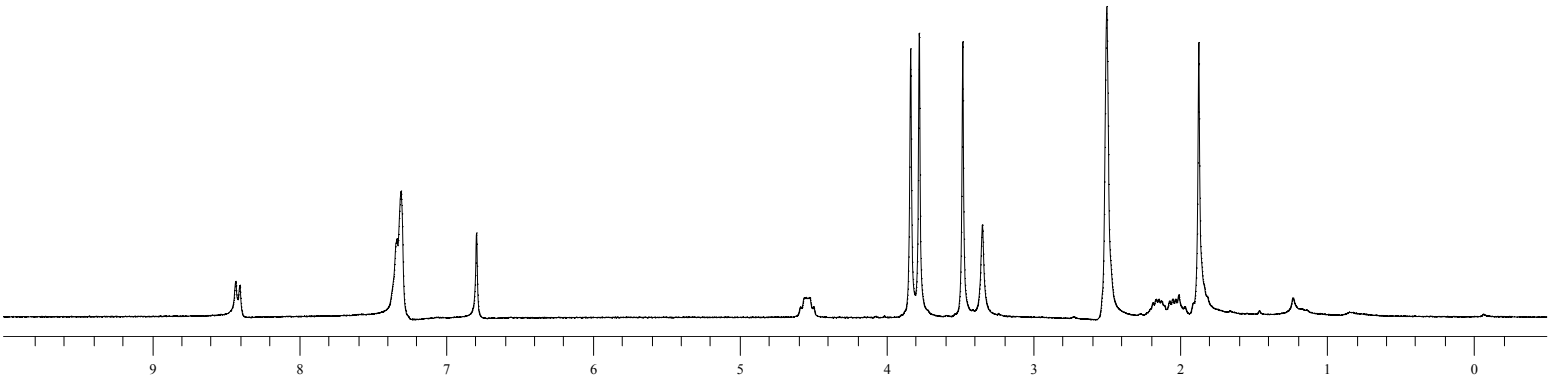


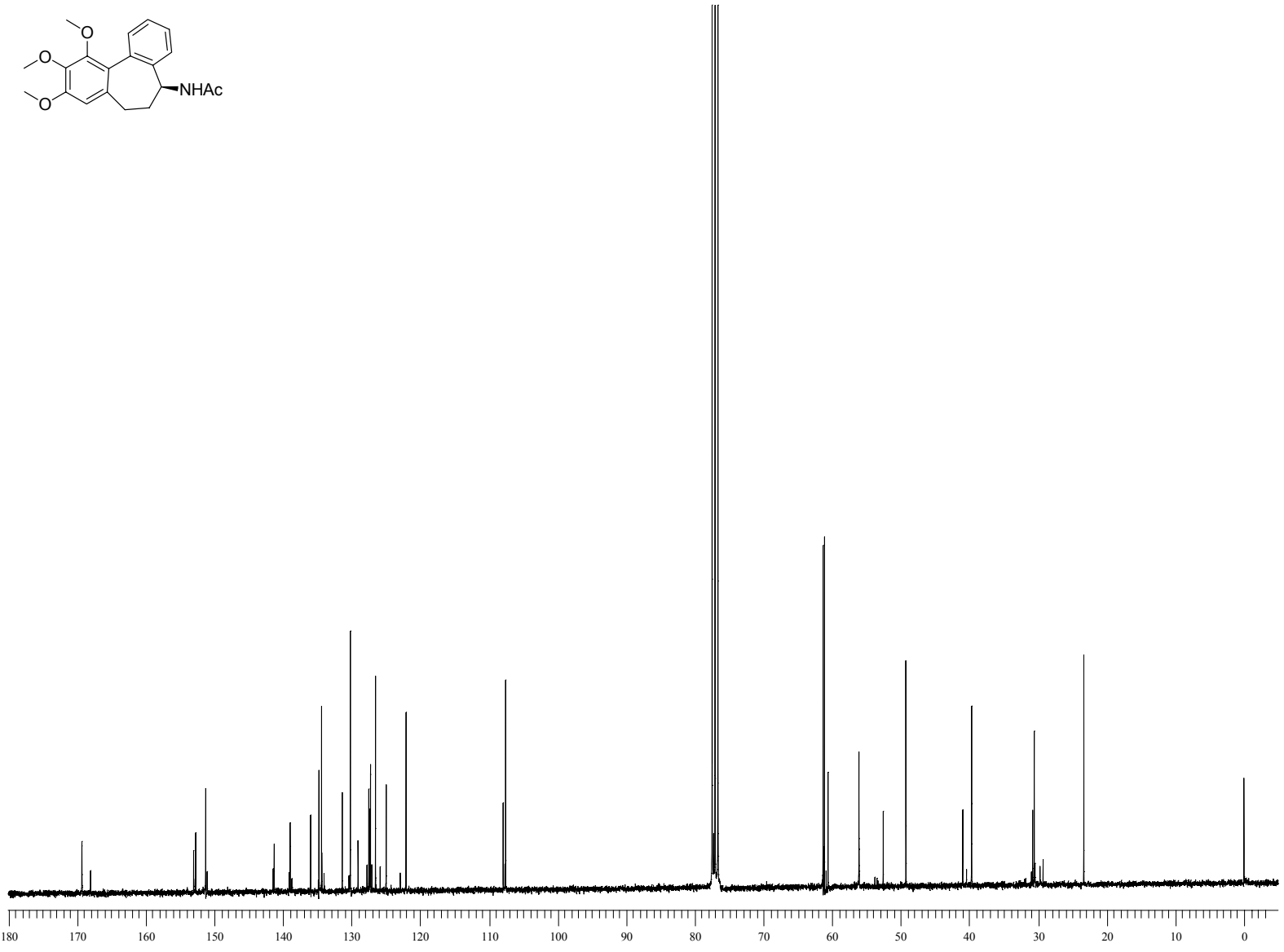
in $CDCl_3$





in $(CD_3)_2SO$

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