Supporting Information

Memory of Chirality in Bromoalkyne Carbocyclization: Applications in Asymmetric Total Synthesis of Hasubanan Alkaloids

Shenpeng Tan, Feng Li, Soojun Park, and Sanghee Kim*

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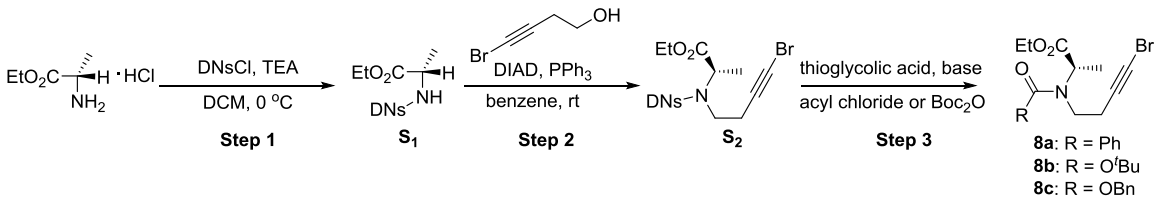
1. Methods and Materials

All of the chemicals were of reagent grade and were used as purchased. All of the reactions were performed under an inert atmosphere consisting of dry nitrogen using distilled dry solvents. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel 60 F-254 TLC plates. The compound spots were visualized using UV light (254 nm). The melting points were measured by using a Buchi B-540 melting point apparatus without correction. Flash column chromatography was carried out on silica gel (230–400 mesh). The optical rotations were measured by using sodium light (D line 589.3 nm), and the values are given as specific optical rotation with exact temperature, concentration (c/(10 mg/mL)) and solvent. ^{1}H NMR (800, 600, 500, or 400 MHz) and ^{13}C NMR (200, 150, 125, or 100 MHz) spectra were referenced to Me_4Si (0 ppm), residual $CHCl_3$ (^{1}H NMR δ = 7.24 ppm, ^{13}C NMR δ = 77.16 ppm). The splitting patterns are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and brs (broad singlet) for the ^{1}H NMR data. The IR spectra were measured on a Fourier Transform Infrared spectrometer. The high-resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB) or quadrupole time-of-flight (Q-TOF). HPLC was performed on an Agilent 1200 series or Agilent 1000 series instrument with a UV detector and CHIRALCEL OD–H column (0.46 × 25 cm).

2. General Procedures

Procedures for the preparation of 8



Step 1: 2,4-Dinitrobenzenesulfonyl chloride (DNsCl) (2.86 g, 10.7 mmol, 1.10 eq) was added to L-alanine ethyl ester hydrochloride (1.50 g, 9.76 mmol) in DCM (40 mL) at 0 °C. Then, TEA (3.00 mL, 21.5 mmol, 2.20 eq) in DCM (20 mL) was slowly added into the mixture with a syringe pump for more than 30 min. After the reaction mass was maintained between 0 ℃–20 ℃ for 5 h, the reaction was quenched with H_2O (30 mL), warmed to room temperature, and extracted with DCM (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The brown residue was purified by flash column chromatography (Hexane:EtOAc = 3:1) to yield **S_1** (2.75 g, 7.91 mmol, 81%) as a yellow oil.

Rf 0.40 (Hexane:EtOAc = 2:1), light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 6.18 (s, 1H), 4.22 (brs, 1H), 4.00–3.94 (m, 2H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3, 149.6, 147.6, 139.4, 132.1, 127.1, 120.7, 61.9, 52.6, 19.2, 13.8.

IR (neat, cm^{-1}): 3326, 3106, 2989, 1733, 1538, 1348, 1172, 1133.

HRMS (FAB): calcd for $C_{11}H_{14}N_3O_8S$ $[M+H]^+$ 348.0502, found 348.0500.

$[\alpha]_D^{20}$ -162.8 (c = 0.5, $CHCl_3$).

Step 2: To a stirred solution of the sulfonamide **S_1** (842 mg, 2.43 mmol), 4-bromo-3-butyn-1-ol[1] (539 mg, 3.64 mmol, 1.50 eq), and PPh_3 (1.27 g, 4.85 mmol, 2.00 eq) in benzene (40 mL), DIAD (1.02 mL, 4.85 mmol, 2.00 eq) in benzene (15 mL) was added dropwise with a syringe pump for more than 15 min at room temperature under an inert atmosphere. After 1 h, the mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 5:1) to yield **S_2** (1.09 g, 2.29 mmol, 94%) as a light yellow oil.

Rf 0.40 (Hexane:EtOAc = 3:1), light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.40 (d, *J* = 2.1 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 4.75 (q, *J* = 7.4 Hz, 1H), 4.11–3.99 (m, 2H), 3.63 (ddd, *J* = 15.5, 10.0, 5.4 Hz, 1H), 3.24 (ddd, *J* = 15.4, 9.9, 5.8 Hz, 1H), 2.73 (qd, *J* = 16.4, 5.3 Hz, 1H), 2.54 (qd, *J* = 16.5, 5.4 Hz, 1H), 1.57 (d, *J* = 7.4 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8, 149.7, 148.1, 137.9, 132.7, 126.0, 119.6, 76.2, 62.0, 56.9, 45.2, 41.4, 22.3, 16.9, 14.0.

IR (neat, cm^{-1}): 3101, 2987, 1736, 1555, 1540, 1353, 1157.

HRMS (FAB) $C_{15}H_{17}BrN_3O_8S$ $[M+H]^+$ 477.9920, found 477.9933.

$[\alpha]_D^{20}$ +27.4 (c = 0.5, $CHCl_3$).

Step 3: For synthesis of benzoyl amide (8a): To a solution of **S₂** (273 mg, 0.57 mmol) and thioglycolic acid (79.6 μL, 1.14 mmol, 2.00 eq) in DCM (10 mL), TEA (241 μL, 1.72 mmol, 3.00 eq) in DCM (4 mL) was added dropwise at room temperature under an inert atmosphere. The reaction was stirred until judged to be complete by TLC analyis. After quenching with sat. $NaHCO_3$ solution (10 mL), the mixture was extracted with DCM (2×15 mL). The crude residue was filtered with a pad of silica and celite to yield pure secondary amine as a light yellow oil. TEA (161 μL, 1.14 mmol, 2.00 eq) and benzoyl chloride (99.7 μL, 0.86 mmol, 1.50 eq) were added to the above secondary amine in DCM (5 mL) at 0 ℃. After 10 min, the reaction was quenched with H_2O (5 mL) and extracted with DCM (2×10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (Hexane:EtOAc = 3:1) to yield **8a** (173 mg, 0.49 mmol, 86%) as a colorless oil.

Rf 0.30 (Hexane:EtOAc = 3:1), colorless oil. Rotamers were observed, and the ratio was 2:3 from ^{1}H NMR.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.39–7.36 (m, 5H), 4.44–4.41 (m, 1H), 4.22–4.15 (m, 2H), 3.75 (s, 0.5H), 3.48–3.43 (m, 0.9H), 3.22 (s, 0.6H), 2.67 (s, 1.1H), 2.39 (s, 0.9H), 1.59 (s, 1.2H), 1.43 (s, 1.8H), 1.25 (s, 3H).

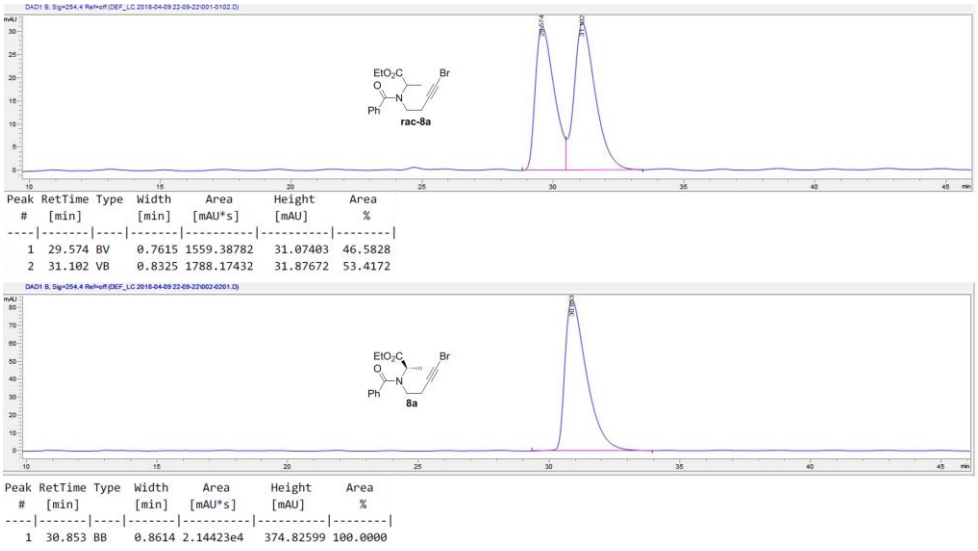
^{13}C NMR (200 MHz, $CDCl_3$) δ = 172.6/171.8, 171.2, 136.0 (2C), 129.8/129.7, 128.6, 126.4 (2C), 77.7/76.4, 61.6/61.3, 57.6/55.0, 47.5/42.5, 40.9/39.8, 20.7/19.2, 16.1/14.9, 14.1.

IR (neat, cm^{-1}): 2984, 2938, 2344, 1736, 1639, 1219, 1075.

HRMS (FAB) calcd for $C_{16}H_{19}BrNO_3$ $[M+H]^+$ 352.0548, found 352.0542.

$[\alpha]_D^{20}$ -64.1 (c = 0.5, $CHCl_3$).

HPLC analysis Chiralpak OD-H (Hexane/*i*PrOH = 95/5, 0.5 mL/min, 254 nm, 25 ℃); 30.9 min; >99% ee.



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1	30.853	BB	0.8614	2.14423e4	374.82599	100.0000

Step 3: For synthesis of Boc amide (8b): To a solution of **S₂** (193 mg, 0.41 mmol) and thioglycolic acid (42.2 μL, 0.62 mmol, 1.50 eq) in DCM (5 mL), DIPEA (141 μL, 0.81 mmol, 2.00 eq) in DCM (2 mL) was added dropwise at room temperature under an inert atmosphere. After the starting material disappeared, DIPEA (141 μL, 0.81 mmol, 2.00 eq) and Boc_2O (133 mg, 0.62 mmol, 1.50 eq) were added to the above complex at room temperature. The reaction mixture was stirred for another 12 h at room temperature before the addition of H_2O (10 mL), and extracted with DCM (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and

concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 10:1) to yield **8b** (127 mg, 0.36 mmol, 90%) as a colorless oil.

Rf 0.50 (Hexane:EtOAc = 5:1), colorless oil. Rotamers were observed, and the ratio was 1:1 from ^{1}H NMR.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 4.45–4.44 (m, 0.5H), 4.14–4.07 (m, 2.5H), 3.48–3.40 (m, 1H), 3.33–3.30 (m, 0.5H), 3.21–3.18 (m, 0.5H), 2.52–2.41 (m, 2H), 1.44–1.38 (m, 12H), 1.25–1.21 (m, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 172.2/172.1, 155.1/154.6, 80.6/80.5, 78.0/77.7, 61.1, 56.5/55.0, 46.1/44.8, 39.5/39.3, 28.3/28.2 (3C), 20.7/20.0, 16.1/15.5, 14.1.

IR (neat, cm^{-1}): 2980, 2939, 1740, 1696, 1367, 1163, 1073, 1035.

HRMS (FAB) calcd for $C_{14}H_{23}BrNO_4$ $[M+H]^+$ 348.0810, found 348.0819.

$[\alpha]_D^{20}$ -22.2 (c = 0.5, $CHCl_3$).

Step 3: For synthesis of Cbz amide 8c: To a solution of **S_2** (500 mg, 1.05 mmol) and thioglycolic acid (146 μL, 2.10 mmol, 2.00 eq) in DCM (15 mL), TEA (441 μL, 3.15 mmol, 3.00 eq) in DCM (5 mL) was added dropwise at room temperature under an inert atmosphere. The reaction was stirred until judged to be complete by TLC analyis. After quenching with sat. $NaHCO_3$ solution (10 mL), the mixture was extracted with DCM (2×20 mL). The crude residue was filtered with a pad of silica and celite to yield pure secondary amine as a light yellow oil. $NaHCO_3$ (176 mg, 2.10 mmol, 2.00 eq) and benzyl chloroformate (149 μL, 1.05 mmol, 1.00 eq) were added to the above secondary amine in H_2O/acetone (1:1, 6 mL) at 0 ℃. After 15 min, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (Hexane:EtOAc = 7:1) to yield **8c** (336 mg, 0.88 mmol, 84%) as a colorless oil.

Rf 0.50 (Hexane:EtOAc = 5:1), colorless oil. Rotamers were observed, and the ratio was 1.2:1 from ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.29 (m, 5H), 5.17–5.06 (m, 2H), 4.52 (q, *J* = 7.3 Hz, 0.55H), 4.32 (q, *J* = 7.1 Hz, 0.45H), 4.13 (q, *J* = 6.9 Hz, 1.1H), 4.08–3.93 (m, 0.9H), 3.56–3.48 (m, 1H), 3.39–3.25 (m, 1H), 2.59–2.39 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 1.6H), 1.12 (t, *J* = 7.0 Hz, 1.4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.93/171.86, 156.0/155.6, 136.5/136.3, 128.6/128.5 (2C), 128.3 (2C), 128.1/127.9, 77.9/77.5, 67.5, 61.3, 56.0/55.8, 46.1/44.8, 40.1/39.8, 20.8/20.0, 16.2/15.6, 14.2/14.1.

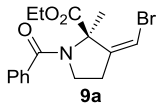
IR (neat, cm^{-1}):, 2984, 2945, 1739, 1702, 1472, 1416, 1369, 1295, 1215, 1184, 1072, 1020.

HRMS (FAB) calcd for $C_{17}H_{21}BrNO_4$ $[M+H]^+$ 382.0654, found 382.0652.

$[\alpha]_D^{20}$ -16.1 (c = 0.5, $CHCl_3$).

MOC reaction procedure

To a solution of haloalkyne substrates (**8a–8c**, 0.10 mmol) in DMF (5 mL, 0.02 M), KO*t*Bu (0.15 mmol, 1.50 eq for **8a and 8c**, 2.00 eq for **8b**) was added at 0 ℃. After 5 min, sat. NH_4Cl (5 mL) and H_2O (5 mL) were added, and the aqueous phase was extracted with EtOAc (4×20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated by high-vacuum evaporation. The residue was purified by flash column chromatography on silica gel to afford analytically pure products **9a–9c**.



9a

Prepared with **8a** according to the general MOC procedure in 78% yield.

Rf 0.30 (Hexane:EtOAc = 3:1), White solid (m.p. = 129–131°C)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.35 (m, 5H), 6.14 (t, *J* = 1.9 Hz, 1H), 4.30–4.20 (m, 2H), 3.66–3.59 (m, 2H), 2.78–2.62 (m, 2H), 1.92 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

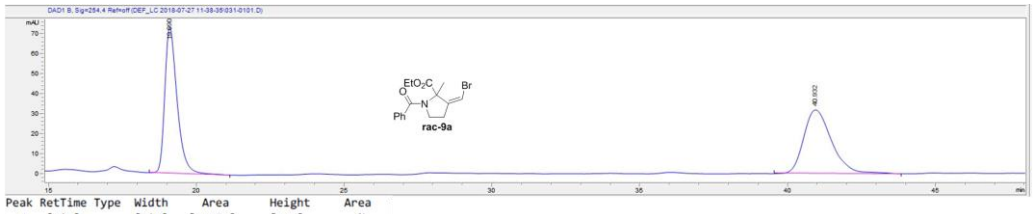
^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.4, 168.8, 145.5, 136.4, 130.0, 128.3 (2C), 126.8 (2C), 98.9, 69.2, 61.4, 48.5, 34.1, 18.7, 14.2.

IR (neat, cm^{-1}): 3062, 2981, 1746, 1632, 1405, 1250, 1023.

HRMS (FAB) calcd for $C_{16}H_{19}BrNO_3$ $[M+H]^+$ 352.0548, found 352.0560.

$[\alpha]_D^{20}$ -118.98 (c = 0.5, CH_2Cl_2).

HPLC analysis Chiralpak OD–H (Hexane/*i*PrOH = 85/15, 0.5 mL/min, 254 nm, 25 ℃); 19.7 (minor), 40.9 (major) min; 93% ee.



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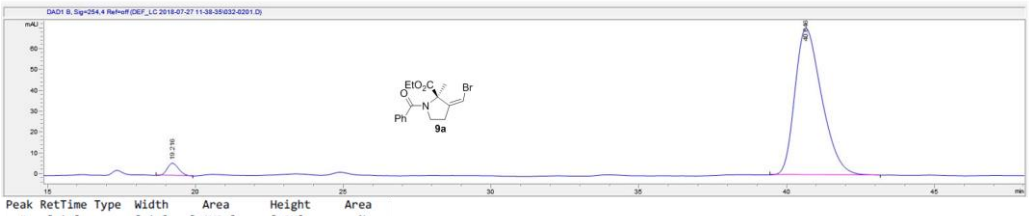

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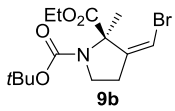
1	19.216	BB	0.4162	163.50136	5.95722	3.5473
2	40.646	BB	0.9468	4445.61426	70.39645	96.4527



9b

Prepared with **8b** according to the general MOC procedure in 81% yield.

Rf 0.40 (Hexane:EtOAc = 5:1), colorless oil. Rotamers were observed, and the ratio was 1:2 from ^{1}H NMR.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.05 (t, *J* = 2.1 Hz, 1H), 4.23–4.10 (m, 2H), 3.60–3.53 (m, 2H), 2.65–2.59 (m, 2H), 1.73 (s, 1H), 1.70 (s, 2H), 1.40 (s, 9H), 1.26–1.24 (m, 3H).

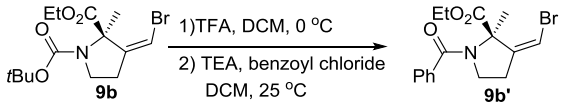
^{13}C NMR (150 MHz, $CDCl_3$) δ = 170.34/170.25, 153.6/153.4, 147.4/146.4, 98.1, 80.8/80.1, 68.4/67.9, 61.4/61.3, 46.2/45.8, 33.0/32.3, 28.3/28.2 (3C), 20.2/19.6, 14.1.

IR (neat, cm^{-1}): 3072, 2979, 2937, 2845, 1751, 1698, 1385, 1367, 1249, 1163, 1114, 1056.

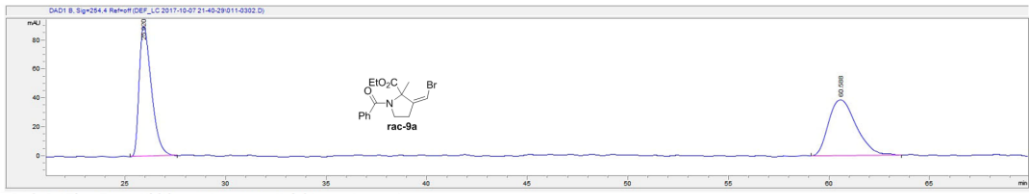
HRMS (FAB) calcd for $C_{14}H_{23}BrNO_4$ $[M+H]^+$ 348.0810, found 348.0810.

$[\alpha]_D^{20}$ -32.96 (c = 0.5, $CHCl_3$).

HPLC analysis Because **9b** can not be fully separated after trying a few chiral columns and conditions, we transform **9b** to **9b'** for HPLC analysis. Chiralpak OD-H (Hexane/*i*PrOH = 90/10, 0.5 mL/min, 254 nm, 25 ℃); 26.0 (minor), 59.4 (major) min; 98% ee.



Trifluoroacetic acid (0.5 mL) was added to a solution of compound **9b** (16.5 mg, 0.047 mmol) in DCM (1.5 mL) and the mixture was stirred at room temperature for 30 min. The mixture was concentrated, dissolved in DCM (20 mL), washed with aq. $NaHCO_3$ and concentrated. The residue was redissolved in DCM (3 mL) and treated with TEA (27 μL, 0.19 mmol, 4.00 eq) and benzoyl chloride (12 μL, 0.095 mmol, 2.00 eq). The mixture was stirred at room temperature for 2 h, and diluted with DCM, and then, the organic phase was washed with water and concentrated. The residue was purified with flash purification by column chromatography on silica gel (Hexane:EtOAc = 3:1) to afford compound **9b'** (14.7 mg, 0.042 mmol, 88%) as a white solid.



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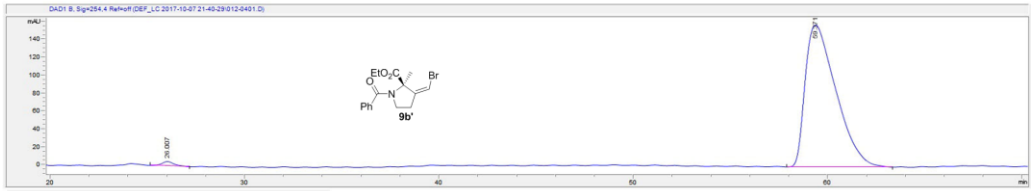
2	60.450	BB	1.3695	3673.61963	39.33695	49.0240



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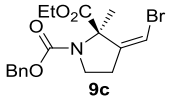
1	26.007	BB	0.6261	219.57074	4.94445	1.2367
2	59.371	BB	1.5759	1.75355e4	159.59450	98.7633



Prepared with **8c** according to the general MOC procedure in 78% yield.

Rf 0.40 (Hexane:EtOAc = 5:1), colorless oil. Rotamers were observed, and the ratio was 1.3:1 from ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.24 (m, 5H), 6.08 (s, 1H), 5.14–5.06 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 1H), 3.95–3.88 (m, 1H), 3.69–3.63 (m, 2H), 2.70–2.63 (m, 2H), 1.74 (d, *J* = 20.4 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 1.7H), 1.06 (t, *J* = 7.0 Hz, 1.3H).

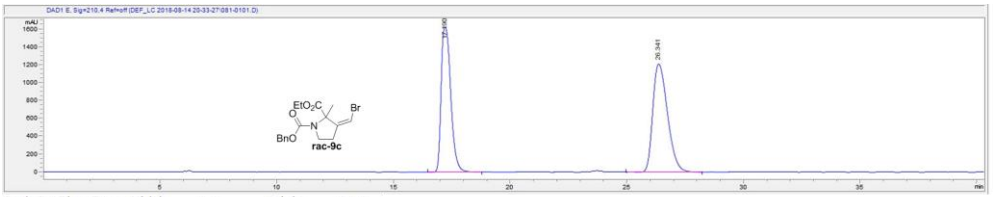
^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4/170.3, 154.3/154.2, 147.3/146.3, 136.8/136.2, 128.7, 128.4, 128.3, 128.2, 128.1, 98.8/98.6, 69.1/68.3, 67.6/67.1, 61.7, 46.6/46.1, 33.1/32.4, 20.5/19.6, 14.2/14.1.

IR (neat, cm^{-1}): 2982, 2939, 2888, 1750, 1701, 1403, 1350, 1251, 1114, 1087, 1055.

HRMS (FAB) calcd for $C_{17}H_{21}BrNO_4$ $[M+H]^+$ 382.0654, found 382.0652.

$[\alpha]_D^{20}$ -21.56 (c = 0.5, $CHCl_3$).

HPLC analysis Chiralpak OD–H (Hexane/*i*PrOH = 90/10, 0.5 mL/min, 210 nm, 25 ℃); 17.4 (minor), 27.1 (major) min; 97% ee.



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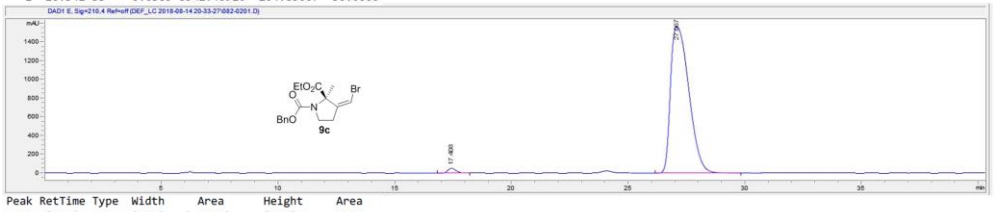
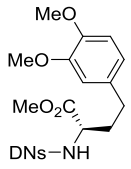
2	26.342	BB	0.6385	8542.48926	204.85007	50.0060



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.408	BB	0.3718	1258.90625	52.11567	1.4580
2	27.067	BB	0.8668	8.50862e4	1558.77185	98.5420

3. Total Synthesis of (–)-Runanine (2)

Methyl (*R*)-4-(3,4-dimethoxyphenyl)-2-((2,4-dinitrophenyl)sulfonamido)butanoate (11)



11

$SOCl_2$ (910 mL, 12.5 mmol, 1.50 eq) was slowly added to a cooled solution of the (*R*)-3,4-dimethoxy-homophenylalanine **10** (2.00 g, 8.36 mmol, 98% ee) in dry methanol (30 mL). The mixture was refluxed for 5 h and left at room temperature under stirring for 2 h. Methanol was then removed and the crude product was washed with toluene three times to give (*R*)-3,4-dimethoxy-homophenylalanine methyl ester hydrochloride as a white solid. 2,4-Dinitrobenzenesulfonyl chloride (2.45 g, 9.20 mmol, 1.10 eq) was added to (*R*)-3,4-dimethoxy-homophenylalanine methyl ester hydrochloride in DCM (50 mL) at 0 °C. Then, TEA (2.58 mL, 18.4 mmol, 2.20 eq) in DCM (20 mL) was added into the mixture slowly with a syringe pump for more than 30 min. After 5 h at 0 ℃ – 20 ℃ under an inert atmosphere, the reaction was quenched with H_2O (30 mL), warmed to room temperature, and extracted with DCM (2×50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The brown residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 2:1) to yield **11** (3.41 g, 6.94 mmol, 83% overall yield) as a light yellow oil.

Rf 0.20 (Hexane:EtOAc = 2:1), light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70 (d, *J* = 2.2 Hz, 1H), 8.46 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.69–6.67 (m, 2H), 6.16 (d, *J* = 9.2 Hz, 1H), 4.45 (td, *J* = 9.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.47 (s, 3H), 2.76–2.63 (m, 2H), 2.21–2.13 (m, 1H), 2.05–1.96 (m, 1H).

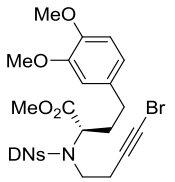
^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.4, 149.7, 148.8, 147.7, 147.5, 139.4, 132.1, 132.0, 127.1, 120.9, 120.3, 111.9, 111.3, 56.2, 55.8, 55.7, 52.6, 34.5, 30.8.

IR (neat, cm^{-1}): 3309, 3102, 2953, 2935, 2837, 1738, 1537, 1513, 1347, 1259, 1234, 1165, 1100, 1025.

HRMS (FAB) calcd for $C_{19}H_{21}N_3O_{10}S$ $[M]^+$ 483.0948, found 483.0946.

$[\alpha]_D^{20}$ +70.36 (c = 0.5, $CHCl_3$).

Methyl (*R*)-2-((*N*-(4-bromobut-3-yn-1-yl)-2,4-dinitrophenyl)sulfonamido)-4-(3,4-dimethoxyphenyl) butanoate (mitsunobu product)



mitsunobu product

PPh_3 (1.18 g, 4.51 mmol, 2.00 eq) and 4-bromo-3-butyn-1-ol (0.50 g, 3.39 mmol, 1.50 eq) were added to a solution of sulfonamide **11** (1.09 g, 2.26 mmol) in benzene (40 mL) at room temperature. DIAD (0.90 mL, 4.51 mmol, 2.00 eq) in benzene (15 mL) was added slowly to the mixture with a syringe pump for more than 20 min under an inert

atmosphere. After 1 h, the mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 3:1) to yield **mitsunobu product** (1.31 g, 2.14 mmol, 95%) as a yellow oil.

Rf 0.30 (Hexane:EtOAc = 2:1), yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.39 (d, *J* = 2.1 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.74–6.71 (m, 2H), 4.61 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.65 (ddd, *J* = 15.5, 10.2, 5.3 Hz, 1H), 3.59 (s, 3H), 3.30 (ddd, *J* = 15.6, 10.1, 5.6 Hz, 1H), 2.84 (ddd, *J* = 16.3, 10.4, 5.6 Hz, 1H), 2.77–2.68 (m, 2H), 2.55 (ddd, *J* = 16.4, 10.4, 5.9 Hz, 1H), 2.41–2.32 (m, 1H), 2.03–1.94 (m, 1H).

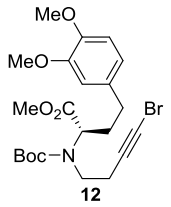
^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8, 149.7, 149.0, 148.1, 147.6, 137.3, 132.8, 132.4, 125.9, 120.3, 119.6, 111.9, 111.4, 76.1, 60.9, 55.91, 55.88, 52.7, 45.7, 41.6, 32.0, 31.8, 22.1.

IR (neat, cm^{-1}): 3101, 2953, 2936, 2837, 1739, 1554, 1537, 1514, 1349, 1257, 1236, 1160, 1137, 1107, 1026.

HRMS (FAB) calcd for $C_{23}H_{24}BrN_3O_{10}S$ $[M]^+$ 613.0366, found 613.0375.

$[\alpha]_D^{20}$ -38.72 (c = 0.5, $CHCl_3$).

Methyl (*R*)-2-((4-bromobut-3-yn-1-yl)(*tert*-butoxycarbonyl)amino)-4-(3,4-dimethoxyphenyl)butanoate (12)



12

DIPEA (506 μL, 2.90 mmol, 2.00 eq) in DCM (5 mL) was added dropwise to a solution of **mitsunobu product** (0.89 g, 1.45 mmol) and thioglycolic acid (156 μL, 2.18 mmol, 1.50 eq) in DCM (25 mL) at room temperature under an inert atmosphere. After the starting material disappered, DIPEA (506 μL, 2.90 mmol, 2.00 eq) and Boc_2O (634 mg, 0.62 mmol, 1.50 eq) were added to the above complex at room temperature. The reaction was stirred until judged to be complete by TLC analysis. The complex was quenched with H_2O (20 mL) and extracted with DCM (3×30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated, the solvent evaporated and the crude residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 10:1) to yield **12** (630 mg, 1.30 mmol, 90%) as a colorless oil.

Rf 0.60 (Hexane:EtOAc = 2:1), colorless oil. Rotamers were observed, and the ratio was 1:1 from ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.79–6.77 (m, 1H), 6.72–6.70 (m, 2H), 4.40 (m, 0.5H), 3.96 (m, 0.5H), 3.85 (s, 3H), 3.83 (s, 3H), 3.68 (s, 3H), 3.58–3.55 (m, 0.5H), 3.42 (m, 0.5H), 3.21–3.14 (m, 1H), 2.60–2.59 (m, 2H), 2.55–2.45 (m, 2H), 2.34–2.27 (m, 1H), 2.06 (brs, 1H), 1.46 (s, 4.5H), 1.38 (s, 4.5H).

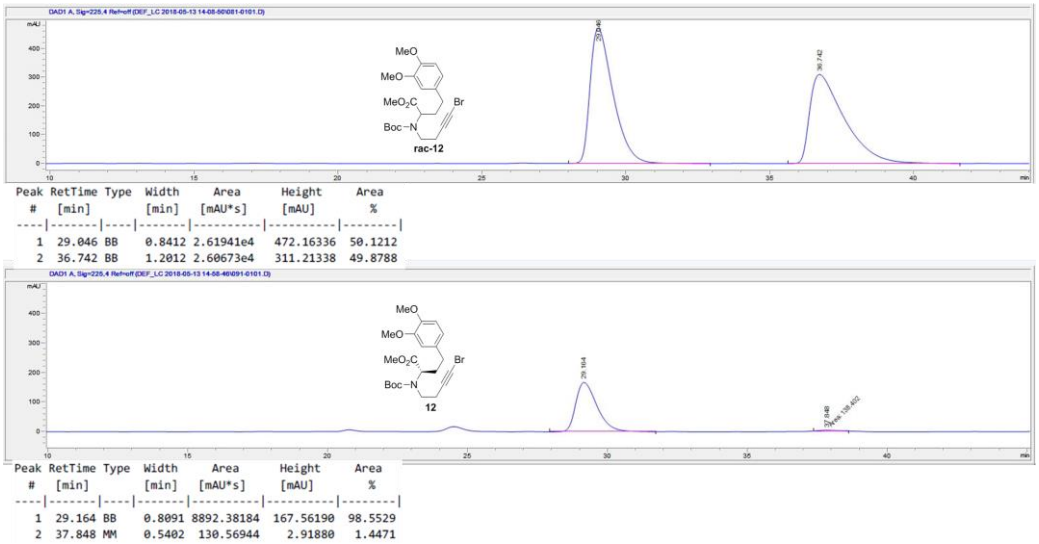
^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2/172.0, 155.4/154.7, 148.9/147.4, 133.5/133.4, 120.2, 111.72/111.66, 111.3, 80.7, 77.8/77.5, 60.1/58.8, 56.1/56.0, 55.9/55.8 (2C), 52.1, 46.9/45.3, 39.6/39.3, 32.2/31.5, 32.1, 28.3/28.2 (3C), 20.4/19.6.

IR (neat, cm^{-1}): 2974, 2952, 2937, 2837, 1741, 1695, 1515, 1254, 1238, 1157, 1029.

HRMS (FAB) calcd for $C_{22}H_{30}BrNO_6$ $[M]^+$ 483.1256, found 483.1245.

$[\alpha]_D^{20}$ +11.12 (c = 0.5, $CHCl_3$).

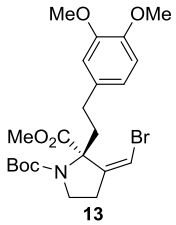
HPLC analysis Chiralpak OD–H (Hexane/*i*PrOH = 95/5, 0.5 mL/min, 225 nm, 25 ℃); 37.8 (minor), 29.2 (major) min; 97% ee.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.046	BB	0.8412	2.61941e4	472.16336	50.1212
2	36.742	BB	1.2012	2.60673e4	311.21338	49.8788

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.164	BB	0.8091	8892.38184	167.56190	98.5529
2	37.848	MM	0.5402	130.56944	2.91880	1.4471

1-(*Tert*-butyl) 2-methyl (*S,Z*)-3-(bromomethylene)-2-(3,4-dimethoxyphenethyl)pyrrolidine-1,2-dicarboxylate (13)



To a solution of compound **12** (500 mg, 1.05 mmol) in DMF (51.5 mL, 0.02 M), KO*t*Bu (234 mg, 2.10 mmol, 2.00 eq) was added in three portions at 0 ℃. After 10 min, The reaction was quenched by the addition of sat. NH_4Cl (25 mL) and concentrated in vacuo. The residue was dissolved in EtOAc (15 mL) and water (15 mL), and extracted with EtOAc (3×20 mL).The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. After purification with flash column chromatography over silica gel (Hexane:EtOAc = 3:1), and compound **13** (397 mg, 0.84 mmol, 79%) was obtained as a colorless oil.

Rf 0.30 (Hexane:EtOAc = 3:1), colorless oil. Rotamers were observed, and the ratio was 1:2 from ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.77–6.75 (m, 1H), 6.70–6.68 (m, 2H), 6.17 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.70 (s, 3H), 3.66–3.60 (m, 2H), 2.90–2.82 (m, 1H), 2.75–2.69 (m, 1.4H), 2.62–2.52 (m, 1.6H), 2.46–2.35 (m, 2H), 1.43–1.41 (m, 9H).

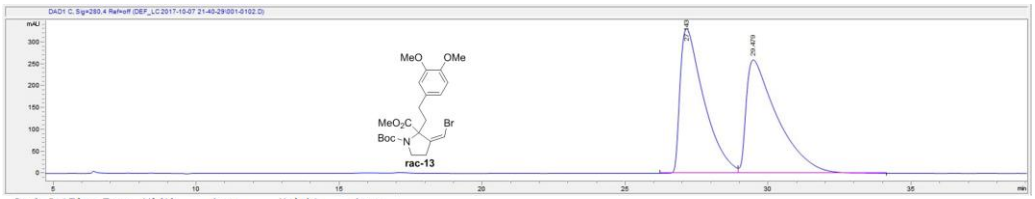
^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.9/170.6, 153.8/153.5, 148.9, 147.3, 145.3/144.4, 134.2, 120.1, 111.7/111.3, 99.1, 81.0/80.3, 71.8/71.3, 55.9, 55.8, 52.3, 46.7/46.5, 34.1/33.8, 33.0/32.6, 30.0, 29.7, 28.3 (3C).

IR (neat, cm^{-1}): 3068, 2975, 2950, 2836, 1750, 1695, 1513, 1454, 1383, 1231, 1158, 1137, 1028.

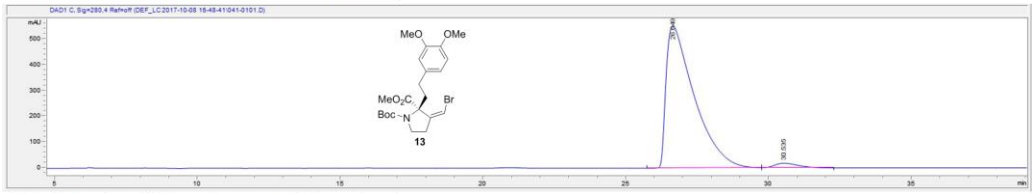
HRMS (FAB) calcd for $C_{22}H_{30}BrNO_6$ $[M]^+$ 483.1256, found 483.1263.

$[\alpha]_D^{20}$ -10.96 (c = 0.5, $CHCl_3$).

HPLC analysis Chiralpak OD–H (Hexane/*i*PrOH = 95/5, 0.5 mL/min, 280 nm, 25 ℃); 30.5 (minor), 26.6 (major) min; 95% ee.

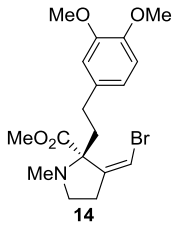


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.143	BV	0.8509	1.92750e4	332.20770	49.4023
2	29.479	VB	1.0625	1.97414e4	260.40576	50.5977



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.649	BB	0.9892	3.79361e4	555.15387	97.4638
2	30.535	BB	0.8576	987.15399	17.40761	2.5362

Methyl (*S,Z*)-3-(bromomethylene)-2-(3,4-dimethoxyphenethyl)-1-methylpyrrolidine-2-carboxylate (14)



To a solution of compound **13** (470 mg, 0.97 mmol) in DCM (6 mL), trifluoroacetic acid (2 mL) was added, and the mixture was stirred at room temperature for 1 h. The mixture was quenched by aq. $NaHCO_3$, extracted by DCM and concentrated in vacuo. The residue was redissolved in methanol (5 mL) and treated with formaldehyde (0.65 mL, 9.73 mmol, 10.0 eq, 37% in H_2O) and sodium cyanoborohydride (557 mg, 2.91 mmol, 3.00 eq). The mixture was stirred at room temperature for 1 h and diluted with DCM (25 mL), and then, the organic phase was washed with water and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 4:1), and compound **14** (0.35 g, 0.88 mmol, 91%) was obtained as a colorless oil.

Rf 0.40 (Hexane:EtOAc = 3:1), colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.77–6.72 (m, 3H), 6.10 (t, *J* = 1.7 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.69 (s, 3H), 3.07–3.02 (m, 1H), 2.88–2.82 (m, 1H), 2.60 (d, *J* = 9.6 Hz, 2H), 2.54–2.46 (m, 2H), 2.34 (dd, *J* = 12.5, 9.2 Hz, 1H), 2.25 (s, 3H), 1.97 (dd *J* = 12.6, 9.8 Hz, 1H).

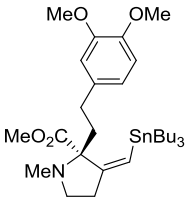
^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 148.7, 147.6, 147.0, 135.3, 120.2, 111.9, 111.1, 98.3, 74.2, 55.9, 55.8, 53.2, 51.3, 34.8, 34.3, 32.2, 29.6.

IR (neat, cm^{-1}): 2946, 2834, 2789, 1728, 1513, 1451, 1258, 1218, 1155, 1029, 1002.

HRMS (FAB) calcd for $C_{18}H_{25}BrNO_4$ $[M+H]^+$ 398.0967, found 398.0970.

$[\alpha]_D^{20}$ -10.34 (c = 0.5, $CHCl_3$).

Methyl (*S,Z*)-2-(3,4-dimethoxyphenethyl)-1-methyl-3-((tributylstannyl)methylene)pyrrolidine-2-carboxylate (15)



15

To a solution of compound **14** (215 mg, 0.54 mmol) in diethyl ether (10 mL), *n*BuLi (0.51 mL, 0.81 mmol, 1.50 eq, 1.6 M in hexane) was added at -78 °C. After stirring for 30 min, tributyltin chloride (435 μL, 1.63 mmol, 3.00 eq) in diethyl ether (3 mL) was added slowly at -78 °C and the mixture was allowed to warm to room temperature for 3 h. The mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 5:1) to yield **15** (223 mg, 0.37 mmol, 68%) as a colorless oil.

Rf 0.20 (Hexane:EtOAc = 10:1), colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.76–6.69 (m, 3H), 5.84 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H), 3.00–2.96 (m, *J* = 7.9 Hz, 1H), 2.89–2.84 (m, 2H), 2.75–2.68 (m, 1H), 2.56 (dd, *J* = 15.5, 6.3 Hz, 1H), 2.39 (td, *J* = 13.3, 5.0 Hz, 1H), 2.25 (s, 3H), 2.14 (td, *J* = 13.3, 3.8 Hz, 1H), 1.99 (td *J* = 13.2, 4.8 Hz, 1H), 1.65–1.59 (m, 1H), 1.46–1.33 (m, 6H), 1.31–1.20 (m, 6H), 0.91–0.77 (m, 15H).

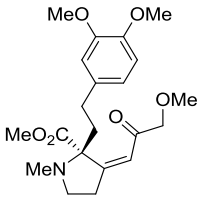
^{13}C NMR (125 MHz, $CDCl_3$) δ = 173.9, 161.0, 148.7, 146.9, 135.6, 120.1, 120.0, 111.8, 111.2, 73.6, 55.9, 55.7, 52.6, 50.9, 37.2, 35.2, 34.4, 29.2, 29.1, 29.0, 28.9, 27.8, 27.6, 27.4, 27.1, 26.8, 17.5, 13.64, 13.58, 10.7.

IR (neat, cm^{-1}): 2954, 2922, 2851, 1725, 1613, 1514, 1462, 1259, 1218, 1156, 1140, 1075, 1032, 1004.

HRMS (FAB) calcd for $C_{30}H_{50}NO_4Sn$ $[M-H]^-$ 608.2762, found 608.2768.

$[\alpha]_D^{20}$ -15.3 (c = 0.5, $CHCl_3$).

Methyl (*S*,*Z*)-2-(3,4-dimethoxyphenethyl)-3-(3-methoxy-2-oxopropylidene)-1-methylpyrrolidine-2-carboxylate (16)



16

To a deoxygenated solution (3 × freeze – pump – thaw) of the vinylstannane compound **15** (170 mg, 0.28 mmol), $PCy_3{\cdot}HBF_4$ (10.3 mg, 0.028 mmol, 0.10 eq), DIPEA (4.90 μL, 0.028 mmol, 0.10 eq), and $Pd_2(dba)_3$ (12.8 mg, 0.014 mmol, 0.05 eq) in toluene (5 mL), methoxyacetyl chloride (32.4 μL, 0.56 mmol, 2.00 eq) was added dropwise. The reaction mixture was heated at 50 °C for 12 h and then cooled and diluted with EtOAc (20 mL). The mixture was washed with 3% aq. NH_4OH (5 mL) and water and then concentrated in vacuo. The residue was purified by flash column chromatography over silica gel (Hexane:EtOAc = 1:1), and compound **16** (80 mg, 0.20 mmol, 74%) was obtained as a yellow oil.

Rf 0.10 (Hexane:EtOAc = 2:1), yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.72 (d, *J* = 7.9 Hz, 1H), 6.64–6.61 (m, 2H), 6.43 (s, 1H), 3.97 (d, *J* = 0.9 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.38 (s, 3H), 3.09–3.04 (m, 1H), 2.79–2.72 (m, 2H), 2.70–2.54 (m, 2H), 2.50–2.43 (m, 1H), 2.29 (s, 3H), 2.24–2.04 (m, 2H).

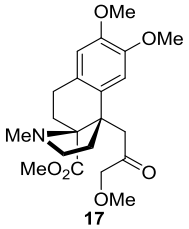
^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.1, 170.4, 165.6, 148.7, 147.0, 135.2, 120.0, 116.8, 111.7, 111.1, 78.0, 74.0, 59.2, 55.9, 55.8, 51.8, 51.0, 35.6, 35.3, 31.2, 29.9.

IR (neat, cm^{-1}): 2946, 2834, 2789, 1735, 1624, 1514, 1452, 1420, 1340, 1260, 1230, 1156, 1141, 1105, 1029.

HRMS (FAB) calcd for $C_{21}H_{30}NO_6$ $[M+H]^+$ 392.2073, found 392.2072.

$[\alpha]_D^{20}$ -12.66 (c = 0.5, $CHCl_3$).

Methyl (3a*S*,9b*S*)-7,8-dimethoxy-9b-(3-methoxy-2-oxopropyl)-3-methyl-1,2,3,4,5,9b-hexahydro-3a*H*-benzo[*e*]indole-3a-carboxylate (17)



17

To a solution of compound **16** (80 mg, 0.20 mmol) in DCM (4 mL), TfOH (90.0 μL, 1.02 mmol, 5.00 eq) was added dropwise at 0 °C. After 10 min, the mixture was quenched with aq. $NaHCO_3$ (5 mL), and then extracted with DCM (20 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 2:1), and compound **17** (66.3 mg, 0.17 mmol, 83%) was obtained as a yellow oil.

Rf 0.10 (Hexane:EtOAc=2:1), yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.74 (s, 1H), 6.49 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 3.57 (q, *J* = 24.1 Hz, 2H), 3.22 (s, 3H), 2.94 (td, *J* = 7.6, 7.5 Hz, 1H), 2.84–2.80 (m, 1H), 2.72–2.66 (m, 1H), 2.70 (d, *J* = 14.2 Hz, 1H), 2.62–2.57 (m, 1H), 2.53 (dd, *J* = 16.3, 3.4 Hz, 1H), 2.46 (d, *J* = 14.2 Hz, 1H), 2.37 (ddd, *J* = 12.4, 8.7, 3.2 Hz, 1H), 2.24 (s, 3H), 2.12 (td, *J* = 13.8, 5.5 Hz, 1H) 2.04 (dd, *J* = 14.6, 3.7 Hz, 1H).

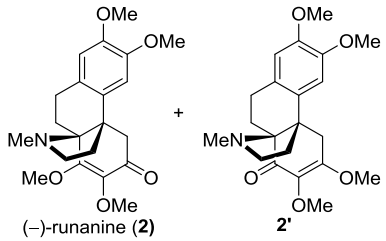
^{13}C NMR (150 MHz, $CDCl_3$) δ = 207.0, 174.2, 147.2, 147.1, 132.3, 127.9, 111.2, 110.8, 78.8, 73.6, 59.0, 56.0, 55.7, 51.4, 51.1, 50.4, 47.5, 37.1, 34.8, 24.8, 23.3.

IR (neat, cm^{-1}): 2939, 2838, 2790, 1719, 1516, 1450, 1357, 1234, 1204, 1134, 1077, 1029, 1016.

HRMS (FAB) calcd for $C_{21}H_{30}NO_6$ $[M+H]^+$ 392.2073, found 392.2071.

$[\alpha]_D^{20}$ +172.12 (c = 0.5, $CHCl_3$).

(–)-runanine (2) and (–)-runanine isomer 2'



To a solution of compound **17** (39 mg, 0.10 mmol) in THF (3 mL), KO*t*Bu (0.15 mL, 0.15 mmol, 1.50 eq, 1.0 M in THF) was added dropwise at 0 °C. After 15 min, the mixture was quenched with sat. NH_4Cl (2 mL) and H_2O (2 mL), and then extracted with DCM and *i*PrOH (2:1, 30 mL) and concentrated in vacuo. The residue was redissolved in MeOH and CH_3CN (1:3, 2 mL) and treated with DIPEA (26.0 μL, 0.15 mmol, 1.50 eq) and (trimethylsilyl)diazomethane (0.25 mL, 0.15 mmol, 1.50 eq, 0.6 M in hexane). The mixture was stirred at room temperature for 12 h, and diluted with DCM (20 mL), and then, the organic phase was washed with water and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 1:2 for **2'**; DCM:MeOH = 20:1 for **2**) to afford the (–)-runanine **(2)** and (–)-runanine isomer **2'** as oil (26.0 mg, 0.07 mmol, 70%, **2:2' = 2**:**1**).

For (–)-runanine **(2):**

Rf 0.10 (Hexane:EtOAc = 1:2), colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.65 (s, 1H), 6.48 (s, 1H), 4.06 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.62 (s, 3H), 2.99 (d, *J* = 15.9 Hz, 1H), 2.83–2.79 (m, 1H), 2.77–2.72 (m, 1H), 2.60 (d, *J* = 16.0 Hz, 1H), 2.55–2.54 (m, 1H), 2.51 (s, 3H), 2.18–2.13 (m, 1H), 2.06–1.94 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 193.8, 165.4, 147.8, 147.1, 138.0, 134.5, 126.9, 111.0, 110.4, 67.2, 60.7, 60.6, 56.1, 55.8, 51.3, 48.5, 47.9, 37.1, 36.2, 25.2, 23.0.

IR (neat, cm^{-1}): 2934, 2849, 2797, 1668, 1603, 1516, 1451, 1334, 1241, 1211, 1145, 1119, 1062, 1051, 1018.

HRMS (FAB) calcd for $C_{21}H_{28}NO_5$ $[M+H]^+$ 374.1967, found 374.1974.

$[\alpha]_D^{25}$ -245 (c = 0.2, $CHCl_3$). Natural[4]: $[\alpha]_D^{18}$-400 (c = 0.8, $CHCl_3$). Synthetic (by Herzon)[5]: $[\alpha]_D^{25}$ -265 (c = 0.2, $CHCl_3$).

For (–)-runanine isomer **2'**:

Rf 0.15 (Hexane:EtOAc = 1:2), colorless oil.

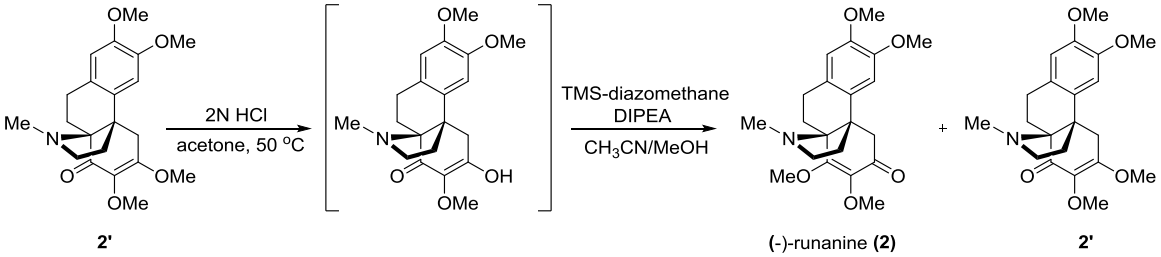
^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.71 (s, 1H), 6.50 (s, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H), 2.96 (d, *J* = 16.9 Hz, 1H), 2.81–2.79 (m, 2H), 2.74–2.68 (m, 1H), 2.70 (d, *J* = 17.5 Hz, 1H), 2.54–2.51 (m, 1H), 2.50 (s, 3H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.98–1.60 (m, 1H), 1.90–1.85 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ = 195.7, 160.1, 147.7, 147.3, 136.1, 134.2, 127.9, 111.4, 110.0, 68.2, 60.7, 58.3, 56.3, 55.8, 51.8, 47.8, 38.1, 37.7, 35.5, 25.4, 21.5.

IR (neat, cm^{-1}): 2930, 2851, 2832, 2793, 1657, 1611, 1513, 1450, 1353, 1337, 1252, 1210, 1144, 1124, 1014.

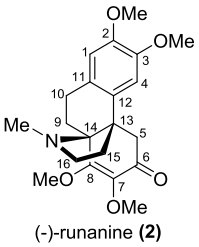
HRMS (FAB) calcd for $C_{21}H_{28}NO_5$ $[M+H]^+$ 374.1967, found 374.1971.

$[\alpha]_D^{20}$ -217.6 (c = 0.5, $CHCl_3$).



A solution of the (-)-runanine isomer **2'** (6.9 mg, 0.018 mmol) in 2N HCl (1 mL) and acetone (1 mL) was heated to 50 °C for 15 h. The mixture was cooled to room temperature, extracted with DCM/*i*PrOH (2:1, 15 mL) and concentrated. The residue was redissolved in MeOH and CH_3CN (1:3, 2 mL) and treated with DIPEA (9.5 μL, 0.054 mmol, 3.00 eq) and (trimethylsilyl)diazomethane (90 μL, 0.054 mmol, 3.00 eq, 0.6 M in hexane). The mixture was stirred at room temperature for 12 h and diluted with DCM (10 mL), and then, the organic phase was washed with water and concentrated. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 1:2 for **2'**; DCM:MeOH = 20:1 for **2**) to afford the (–)-runanine **(2)** and (–)-runanine isomer **2'** (5.5 mg, 0.014 mmol, 80%, **2**:**2' = 2**:**1**).

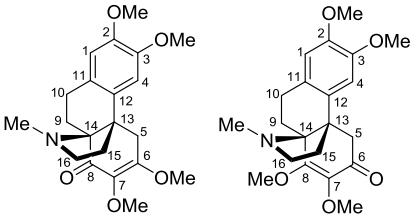
Table S1. Comparison of natural and synthetic (–)-runanine (**2**).



	^{1}H NMR			^{13}C NMR	
position	**[2]Natural (300 MHz, $CDCl_3$)**	**[3]Herzon (500 MHz, $CDCl_3$)**	**Synthetic (500 MHz, $CDCl_3$)**	**[3]Herzon (125MHz, $CDCl_3$)**	**Synthetic (125 MHz, $CDCl_3$)**
1	6.47 (s, 1H)	6.47 (s, 1H)	6.47 (s, 1H)	111.0	111.0
2				147.1	147.1
3				147.8	147.8
4	6.64 (s, 1H)	6.67 (s, 1H)	6.64 (s, 1H)	110.4	110.4
5	3.00 (d, 13.2) 2.60 (d, 13.2)	3.00 (d, 16.0) 2.62 (d, 16.0)	3.00 (d, 15.9) 2.60 (d, 16.0)	48.5	48.5
6				193.8	193.8
7				138.0	138.0
8				165.4	165.4
9	2.8 (m)	2.22-2.15 (m) 1.99-1.93 (m)	2.18-2.13 (m) 2.00-1.94 (m)	23.0	23.0
10	2.8 (m)	2.80-2.71 (m) 2.57-2.52 (m)	2.77-2.71 (m) 2.57-2.51 (m)	25.2	25.2
11				126.9	126.9
12				134.5	134.5
13				47.9	47.9

14				67.2	67.2
15	2.0 (m)	2.22-2.15 (m) 2.08-2.02 (m)	2.18-2.13 (m) 2.06-2.00 (m)	37.1	37.1
16	2.0 (m)	2.86-2.82 (m) 2.80-2.71 (m)	2.83-2.79 (m) 2.77-2.71 (m)	51.2	51.3
C_2OCH_3	3.79 (s)	3.82 (s)	3.79 (s)	55.8	55.8
C_3OCH_3	3.80 (s)	3.84 (s)	3.81 (s)	56.1	56.1
C_7OCH_3	3.61 (s)	3.65 (s)	3.62 (s)	60.7	60.7
C_8OCH_3	4.05 (s)	4.09 (s)	4.06 (s)	60.6	60.6
NCH_3	2.51 (s)	2.53 (s)	2.51 (s)	36.2	36.2

Table S2. Comparison of synthetic (–)-runanine (**2**) and its isomer **2'**.

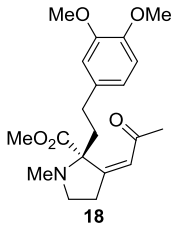


	^{1}H NMR		**^{13}C NMR**	
position	**Isomer (2') (600 MHz, $CDCl_3$)**	**Runanine (2) (500 MHz, $CDCl_3$)**	**Isomer (2') (600 MHz, $CDCl_3$)**	**Runanine (2) (125 MHz, $CDCl_3$)**
1	6.50 (s, 1H)	6.47 (s, 1H)	111.4	111.0
2			147.3	147.1
3			147.7	147.8
4	6.70 (s, 1H)	6.64 (s, 1H)	110.0	110.4
5	2.96 (d, 16.9) 2.70 (d, 16.9)	3.00 (d, 15.9) 2.60 (d, 16.0)	35.5	48.5
6			160.1	193.8
7			136.1	138.0
8			195.7	165.4
9	2.17 (t, 7.6, 2H)	2.18-2.13 (m) 2.00-1.94 (m)	21.5	23.0
10	2.74-2.70 (m) 2.54-2.51 (m)	2.77-2.71 (m) 2.57-2.51 (m)	25.4	25.2
11			127.9	126.9
12			134.2	134.5
13			47.8	47.9
14			68.2	67.2
15	1.98-1.96 (m) 1.90-1.85 (m)	2.18-2.13 (m) 2.06-2.00 (m)	38.1	37.1
16	2.81-2.79 (m, 2H)	2.83-2.79 (m) 2.77-2.71 (m)	51.8	51.3
C_2OCH_3	3.81 (s)	3.79 (s)	55.8	55.8
C_3OCH_3	3.85 (s)	3.81 (s)	56.3	56.1

C_7OCH_3	3.60 (s)	3.62 (s)	60.7	60.7
C_6OCH_3	3.95		58.3	
C_8OCH_3		4.06 (s)		60.6
NCH_3	2.50 (s)	2.51 (s)	37.7	36.2

4. Formal Synthesis of (–)-8-Demthoxyrunanine (4) and (–)-Cepharatine D (21)

Methyl (*S*,*Z*)-2-(3,4-dimethoxyphenethyl)-1-methyl-3-(2-oxopropylidene)pyrrolidine-2-carboxylate (18)



18

To a deoxygenated solution (3 × freeze – pump – thaw) of the vinylstannane compound **15** (76.1 mg, 0.12 mmol), $PCy_3{\cdot}HBF_4$ (4.61 mg, 0.012 mmol, 0.10 eq), DIPEA (2.24 μL, 0.012 mmol, 0.10 eq), and $Pd_2(dba)_3$ (5.71 mg, 0.006 mmol, 0.05 eq) in toluene (5 mL), acetyl chloride (17.8 μL, 0.25 mmol, 2.00 eq) was added dropwise. The reaction mixture was heated at 50 °C for 12 h and then cooled and diluted with EtOAc (20 mL). The mixture was washed with 3% aq. NH_4OH (5 mL) and water and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 1:1), and compound **18** (31.7 mg, 0.087 mmol, 70%) was obtained as a yellow oil.

Rf 0.30 (Hexane:EtOAc = 1:1), yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.73–6.71 (m, 1H), 6.64–6.62 (m, 2H), 6.29 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.07–3.04 (m, 1H), 2.75–2.62 (m, 3H), 2.54–2.52 (m, 1H), 2.42 (td, *J* = 13.0, 5.1 Hz, 1H), 2.28 (s, 3H), 2.19 (td, *J* = 12.8, 5.1 Hz, 1H), 2.13 (s, 3H), 2.06 (td, *J* = 13.0, 3.7 Hz, 1H).

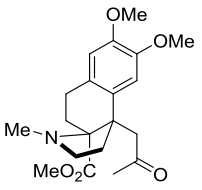
^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.7, 170.6, 163.0, 148.7, 147.0, 135.3, 121.3, 120.0, 111.7, 111.1, 73.7, 55.9, 55.8, 51.8, 50.9, 35.3, 35.2, 31.2, 31.1, 29.9.

IR (neat, cm^{-1}): 2946, 2834, 2788, 1734, 1691, 1626, 1513, 1226, 1155, 1028.

HRMS (FAB) calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$ 362.1967, found 362.1974.

$[\alpha]_D^{20}$ -19.84 (c = 0.5, $CHCl_3$).

Methyl (3a*S*,9b*S*)-7,8-dimethoxy-3-methyl-9b-(2-oxopropyl)-1,2,3,4,5,9b-hexahydro-3a*H*-benzo[*e*]indole-3a-carboxylate (Friedel-Crafts product)



Friedel-Crafts product

To a solution of compound **18** (147 mg, 0.41 mmol) in DCM (5 mL), TfOH (180 μL, 2.03 mmol, 5.00 eq) was added dropwise at 0 °C. After 10 min, the mixture was quenched with aq. $NaHCO_3$ (5 mL), and then extracted with DCM (20 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 2:1), and **Friedel-Crafts product** (124 mg, 0.35 mmol, 85%) was obtained as a colorless oil.

Rf 0.50 (Hexane:EtOAc = 1:1), colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.80 (s, 1H), 6.49 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 2.93 (td, *J* = 7.8, 7.6 Hz, 1H), 2.85–2.74 (m, 2H), 2.72–2.65 (m, 1H), 2.58–2.51 (m, 3H), 2.37 (ddd, *J* = 12.4, 8.7, 3.3 Hz, 1H), 2.23 (s, 3H), 2.12–2.00 (m, 2H), 1.81 (s, 3H).

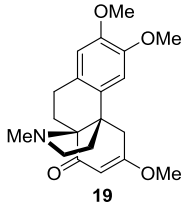
^{13}C NMR (100 MHz, $CDCl_3$) δ = 208.3, 174.2, 147.1, 147.0, 132.7, 127.9, 111.0, 110.9, 73.5, 56.0, 55.6, 52.5, 51.3, 51.1, 50.5, 37.2, 34.8, 32.7, 24.8, 23.3.

IR (neat, cm^{-1}): 2947, 2838, 2789, 1716, 1514, 1449, 1356, 1232, 1204, 1134, 1078, 1014.

HRMS (FAB) calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$ 362.1967, found 362.1962.

$[\alpha]_D^{20}$ +236.46 (c = 0.5, $CHCl_3$).

(4b*S*,8a*S*)-2,3,6-Trimethoxy-11-methyl-9,10-dihydro-8a,4b-(epiminoethano)phenanthren-8(5*H*)-one (19)



19

To a solution of the **Friedel-Crafts product** (39 mg, 0.11 mmol) in THF (3 mL), KO*t*Bu (0.16 mL, 0.16 mmol, 1.50 eq, 1.0 M in THF) was added dropwise at 0 °C. After 15 min, the mixture was quenched with sat. NH_4Cl (2 mL) and H_2O (2 mL), extracted with DCM/*i*PrOH (2:1, 30 mL) and concentrated in vacuo. The residue was redissolved in methanol (3 mL) and treated with $TiCl_4$ (8 drops, 1 M solution in DCM). The mixture was stirred at room temperature for 12 h. After quenching with sat. $NaHCO_3$, the reaction was extracted with DCM (2×10 mL). The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 1:1) to afford compound **19** (30.0 mg, 0.09 mmol, 81%) as a colorless oil.

Rf 0.15 (Hexane:EtOAc = 1:1), colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.71 (s, 1H), 6.50 (s, 1H), 5.33 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 2.95 (d, *J* = 16.5 Hz, 1H), 2.89–2.87 (m, 1H), 2.78 (td, *J* = 9.5, 4.3 Hz, 1H), 2.74–2.69 (m, 1H), 2.69 (d, *J* = 17.4 Hz, 1H), 2.56–2.51 (m, 1H), 2.47 (s, 3H), 2.17–2.07 (m, 3H), 1.80 (ddd, *J* = 13.1, 7.6, 5.3 Hz, 1H).

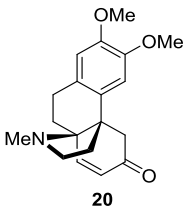
^{13}C NMR (150 MHz, $CDCl_3$) δ = 199.7, 174.9, 147.7, 147.3, 134.1, 128.1, 111.4, 110.1, 101.9, 68.0, 56.3, 55.9, 55.8, 52.0, 49.3, 39.8, 38.3, 35.6, 25.8, 21.0.

IR (neat, cm^{-1}): 2934, 2834, 2793, 1643, 1614, 1513, 1445, 1376, 1253, 1201, 1134, 1014.

HRMS (FAB) calcd for $C_{20}H_{26}NO_4$ $[M+H]^+$ 344.1862, found 344.1858.

$[\alpha]_D^{20}$ -284.36 (c = 0.5, $CHCl_3$).

(4b*S*,8a*R*)-2,3-dimethoxy-11-methyl-9,10-dihydro-8a,4b-(epiminoethano)phenanthren-6(5*H*)-one (20)



20

To a solution of compound **19** (41.4 mg, 0.12 mmol) in DCM (3 mL), diisobutylaluminium hydride (0.30 mL, 0.30 mmol, 2.50 eq, 1 M solution in Hexane) was added dropwise at -78 °C. After 30 min, the mixture was quenched with brine (2 mL), extracted with DCM (2×10 mL) and concentrated in vacuo. The residue was redissolved in diethyl ether (5 mL) and treated with 2N HCl (1 mL) at 0 °C. After 10 min, the reaction was quenched with sat. $NaHCO_3$, and then extracted with EtOAc (2×10 mL). The residue was purified by flash column chromatography on silica gel (Hexane:EtOAc = 1:1) to afford compound **20** (21.7 mg, 0.07 mmol, 58%) as a colorless oil.

Rf 0.20 (Hexane:EtOAc = 1:1), colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.82 (d, *J* = 10.4 Hz, 1H), 6.66 (s, 1H), 6.51 (s, 1H), 6.12 (d, *J* = 10.4 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.95–2.84 (m, 1H), 2.89 (d, *J* = 16.3 Hz, 2H), 2.57–2.53 (m, 1H), 2.54 (td, *J* = 16.4 Hz, 1H), 2.43 (s, 3H), 2.43–2.41 (m, 1H), 2.28–2.22 (m, 1H), 2.04–1.96 (m, 2H), 1.78–1.71 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 198.8, 150.3, 147.9, 147.1, 135.6, 129.9, 126.3, 111.1, 110.5, 63.2, 56.1, 55.8, 51.6, 49.5, 48.3, 36.2, 33.3, 25.1, 24.6.

IR (neat, cm^{-1}): 2929, 2833, 2790, 1678, 1513, 1452, 1255, 1207, 1140, 1067.

HRMS (FAB) calcd for $C_{19}H_{24}NO_3$ $[M+H]^+$ 314.1756, found 314.1757.

$[\alpha]_D^{20}$ -413.96 (c = 0.5, $CHCl_3$).

All data obtained are in full agreement with those by Reisman.[4]

5. Computational Study

Calculation of the nucleophilicity of the oxygen

Theoretical background of Fukui fuction

Local softness is therefore one of the widely used local density functional descriptors to compare reactivity at different sites within one molecule. Local softness is given by

$$s(r) = Sf(r)$$

where S is global softness and $f(r)$ is the Fukui function.[5] The global softness can be approximated as

$$S = 1 / (\mathrm{IP} - \mathrm{EA})$$

where IP and EA are the ionization potential and electron affinity respectively, of the chemical species.

The Fukui function describes the variation of the electronic density ($\rho(r)$) upon changing the number of electrons (N) in the system.[6]

$$f(r) = [\partial\rho(r) / \partial N]_{v(r)}$$

Thus, fukui functions for nucleophilic and electrophilic attack on an atom, k, in an N electron system was introduced by Yang and Mortier[7] as

$$f_k^+ = \rho_k(N + 1) - \rho_k(N) \text{ (nucleophilic attck)}$$

$$f_k^- = \rho_k(N) - \rho_k(N - 1) \text{ (electrophilic attack)}$$

where $\rho_k(N+1)$, ρ_k(N) and $\rho_k(N - 1)$ are the electronic populations on atom k in the $N+1$, N and $N-1$ electron systems. These functions can be condensed to the nuclei by using an atomic charge partitioning scheme, such as Mulliken[8] population analysis. Therefore, the local softness for atom k can be written as

$$s_k^+ = [\rho_k(N + 1) - \rho_k(N)]S$$

$$s_k^- = [\rho_k(N) - \rho_k(N - 1)]S$$

Local softness is used as reactivity index, however not always provide the correct reactivity trends. So new parameres are devised by S. Pal,[9] which is "relative electrophilicity" and "relative nucleophilicity".

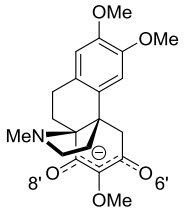
$$\text{Relative electrophilicity} = s_k^+ / s_k^-$$

$$\text{Relative nucleophilicity} = s_k^- / s_k^+$$

This two relative values indicate to the preferable reactive sites in the reaction.

Geometry optimization and energy minimization of 1,3-diketone intermediate

The computational energy minimization of **1,3-diketone intermediate** was performed using the DMol3 program in Material Studio 2018. The Fukui function, ionization potential and electron affinity were also calculated by using DMol3 program.[10] In these calculations, we employed generalized gradient approximation (GGA) in the Perdew-Burke-Ernzerhof (PBE)[11] form as well as a double numerical polarized (DNP) basis sets. To calculate the Fukui function values, a Mulliken partitioning scheme was employed.



1,3-diketone intermediate

Table S3. Cartesian coordinates of the **1,3-diketone intermediate**.

1,3-diketone intermediate

Atom	X	Y	Z	Atom	X	Y	Z
C	-1.44658	-1.30985	-0.48253	C	1.433279	-0.91594	-0.08688
C	-1.0042	-0.09347	0.062277	C	0.773348	1.480819	-0.72642
C	-1.9735	0.852379	0.455541	H	0.422832	1.24684	-1.7429
C	-3.3415	0.61793	0.329819	H	0.208883	2.363804	-0.40501
C	-3.77677	-0.60179	-0.22485	C	2.895483	-0.49081	-0.45639
C	-2.82671	-1.53582	-0.61595	C	3.208537	0.867756	-0.7143
H	-1.63551	1.795087	0.870977	C	2.24346	1.905889	-0.81728
H	-3.18433	-2.47595	-1.03221	O	2.486854	3.115133	-1.03575
O	-5.12216	-0.91423	-0.33146	O	4.53024	1.196394	-1.01706
O	-4.32472	1.504309	0.713482	C	5.412405	1.149206	0.089702
C	-5.83486	-0.18775	-1.33159	H	6.401371	1.444736	-0.28246
H	-5.39688	-0.36365	-2.32476	H	5.100873	1.858464	0.873957
H	-6.86004	-0.56962	-1.31429	H	5.470789	0.136215	0.509364
H	-5.83917	0.886906	-1.11704	C	0.822484	0.631075	1.696426
C	-3.92309	2.733659	1.294743	H	1.504649	1.485261	1.736416
H	-3.31987	3.332633	0.599063	H	-0.07676	0.896576	2.260604
H	-4.84732	3.268172	1.527671	C	1.49789	-0.63133	2.268713
H	-3.35241	2.573667	2.21971	H	2.558551	-0.4278	2.514652
C	-0.47079	-2.38231	-0.91172	H	1.01583	-0.99868	3.18688
H	-0.86804	-2.91367	-1.78847	N	1.370415	-1.63114	1.214813
H	-0.38024	-3.12548	-0.10719	C	2.158334	-2.82871	1.451549
C	0.482507	0.285565	0.206253	H	2.058878	-3.52532	0.614476
C	0.908731	-1.80554	-1.225	H	3.233409	-2.6297	1.584708
H	1.636161	-2.6	-1.42176	H	1.76833	-3.32075	2.356874
H	0.861042	-1.19532	-2.13762	O	3.741705	-1.42287	-0.48647

Table S4. Molecular energy of **1,3-diketone intermediate**.

Compound	Hartree (Ha)[a]	Ionizaion potential (eV)	Electron affinity (eV)	Global softness (eV^{-1})[b]
1,3-diketone intermediate	–1206.446295	2.459881997	–3.544065212	–3.544065212

[a]1Ha = 627.509391 kcal/mol. [b]Global softness = 1 / (Ionization potential – Electron affinity).

Table S5. Molecular property of **1,3-diketone intermediate**.

Atom	Fukui function (−)	Fukui function (+)	Local softness (S−)[a]	Local softness (S+)	Relative nucleophilicity[b]
O-8'	0.151	0.026	0.02515	0.00433	5.81
O-6'	0.148	0.037	0.02465	0.00616	4.00

[a]Local softness = Global softness x Fukui function. [b]Relative nucleophilicity = Local softness (S−) / Local softness (S+).

6. Crystal Structure of 9a

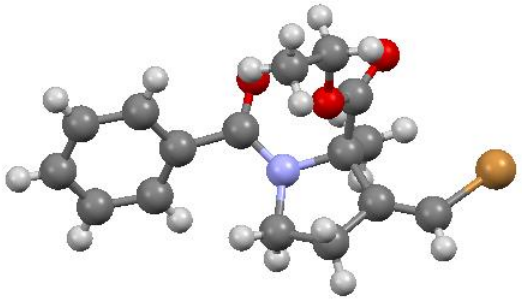


Table S6. Crystal data and structure refinement for **9a**.

Identification code	9a
Empirical formula	$C_{16}H_{18}BrO_3N$
Formula weight	352.23
Temperature/K	293.37(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.27280(10)
b/Å	9.2844(2)
c/Å	24.0663(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1625.04(5)
Z	4
ρ_{calc}g/cm^3	1.4396
μ/mm^{-1}	3.528
F(000)	719.2
Crystal size/mm^3	0.518 × 0.261 × 0.193
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.34 to 147.22
Index ranges	$-9 \le h \le 8$, $-10 \le k \le 11$, $-17 \le l \le 29$
Reflections collected	5835
Independent reflections	3190 [R_{int} = 0.0106, R_{sigma} = 0.0117]
Data/restraints/parameters	3190/0/192
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0272, wR_2 = 0.0715
Final R indexes [all data]	R_1 = 0.0276, wR_2 = 0.0720
Largest diff. peak/hole / e Å^{-3}	0.17/-0.45
Flack parameter	0.023(18)

7. Reference

1. Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365.

2. Zhi-Da, M.; Ge, L.; Guang-Xi, X.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1985**, *24*, 3084.

3. Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8863.

4. Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew.Chem. Int. Ed.* **2011**, *50*, 9447.

5. Yang, W.; Parr, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 6723.

6. Parr, R. G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049.

7. Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.

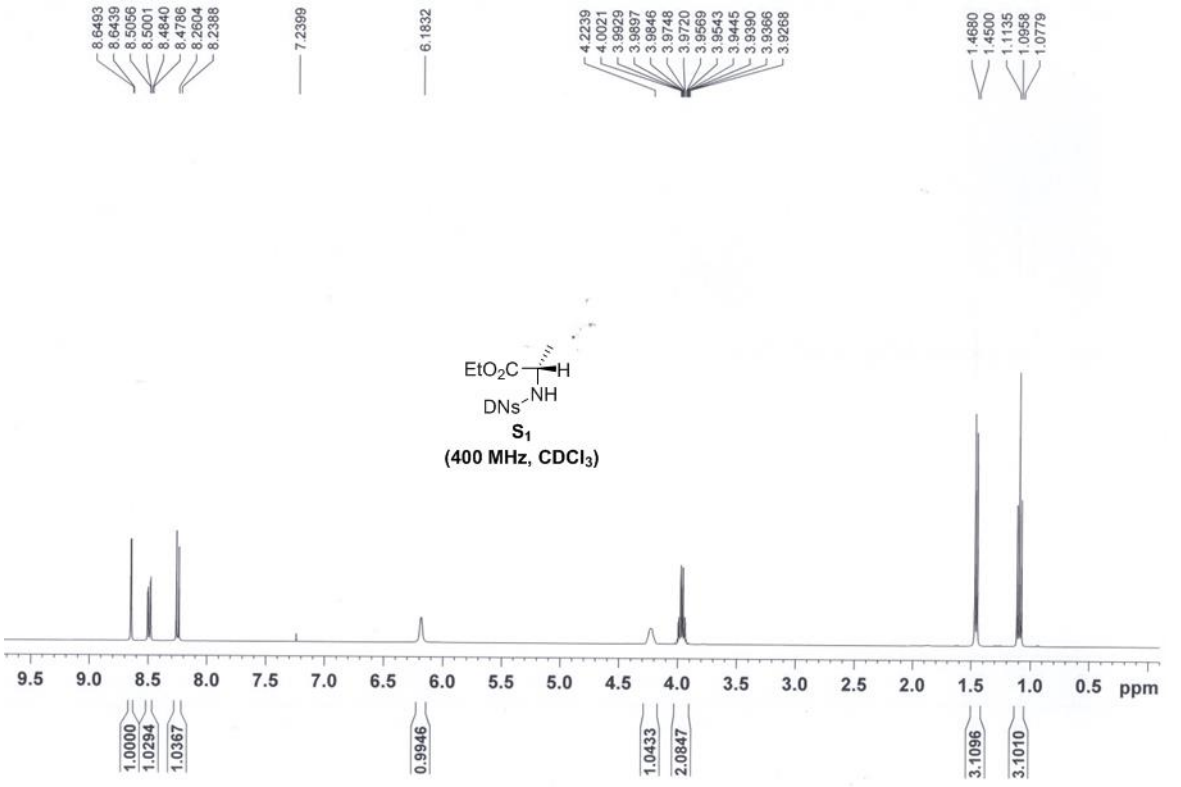
8. Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

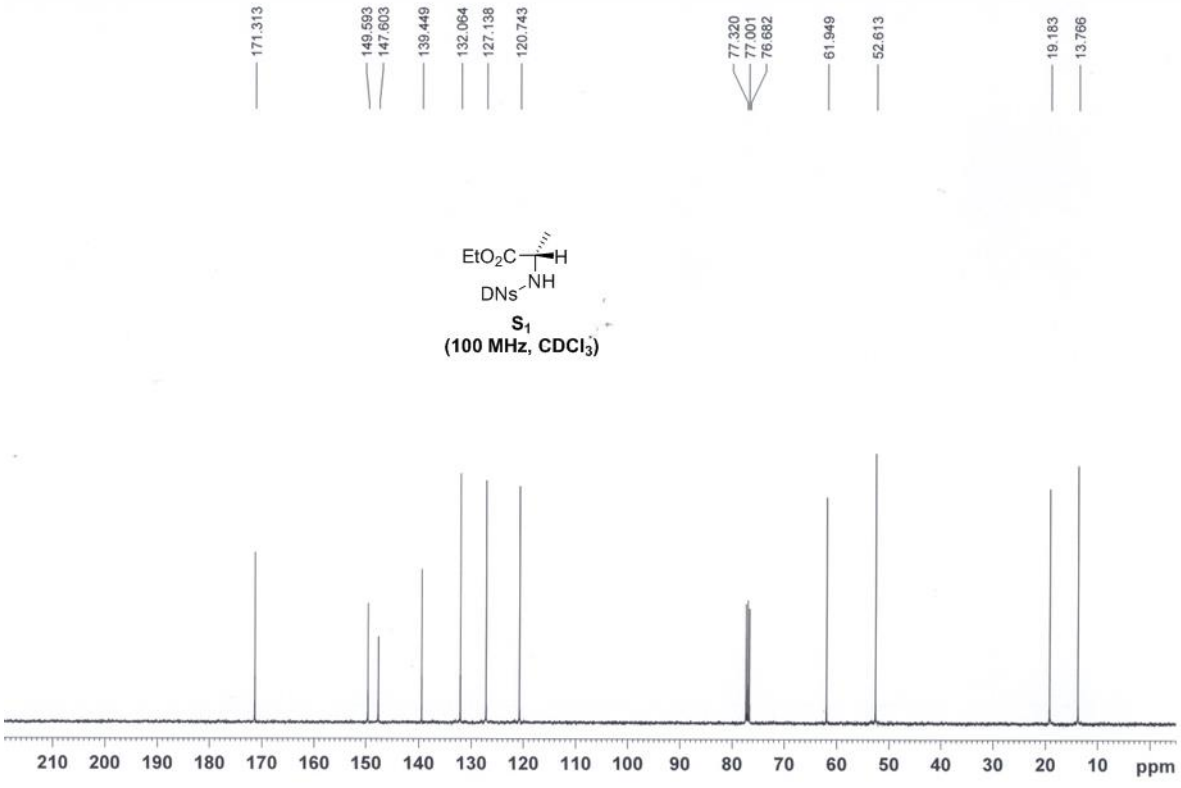
9. Roy, R. K.; Krishnamurti, S.; Geerlings, P.; Pal, S. *J. Phys. Chem.* A **1998**, *102*, 3746.

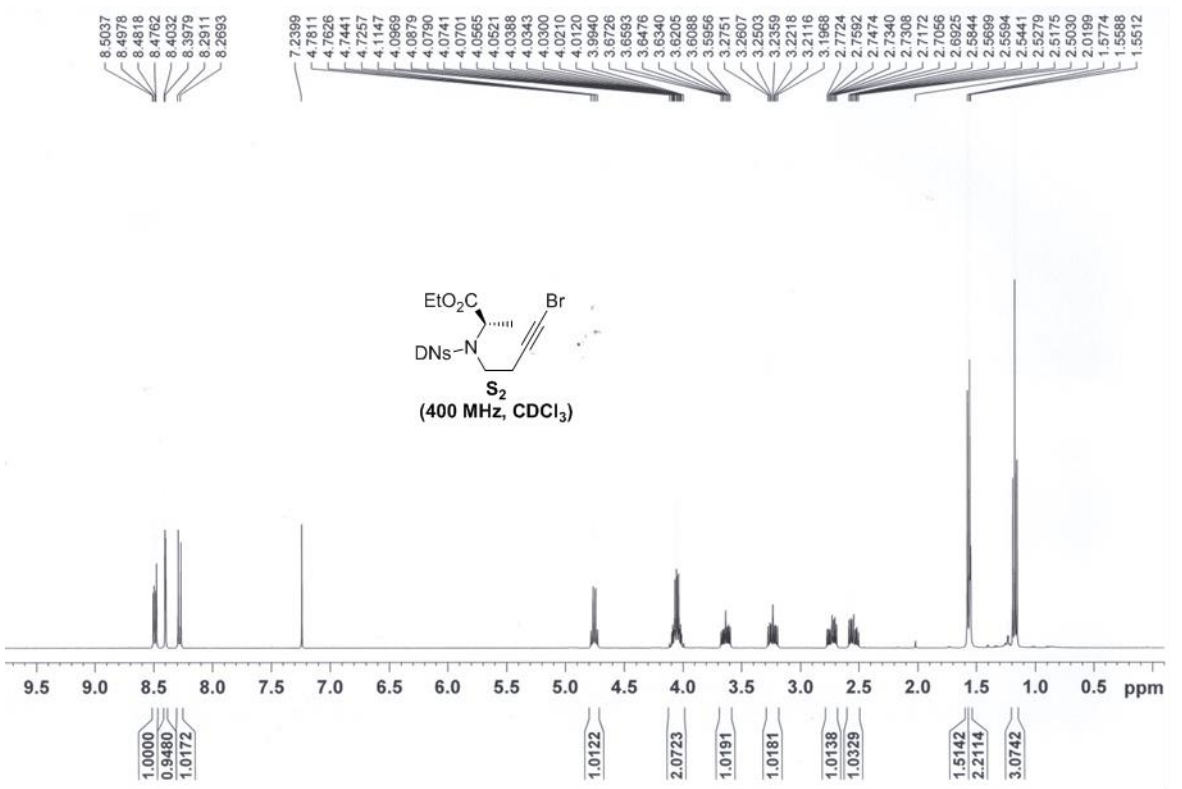
10. (a) Delley, B. *J. Chem. Phys.* **1990**, *92*, 508. (b) Delley, B. *J. Chem. Phys.* **2000**, *113*, 7756.

11. Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.

8. ^{1}H NMR and ^{13}C NMR Spectra



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8.4818
8.4762
8.4032
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8.2911
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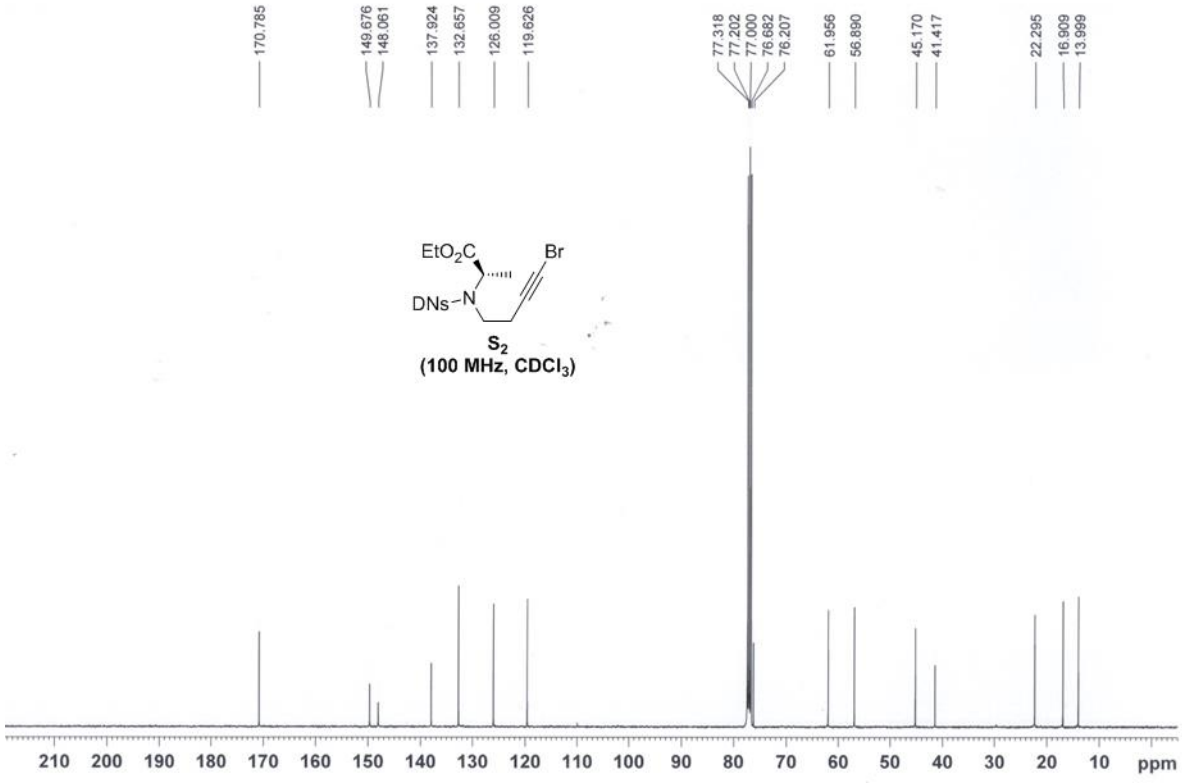
7.2399
4.7811
4.7626
4.7441
4.7257
4.1147
4.0969
4.0879
4.0790
4.0741
4.0701
4.0565
4.0521
4.0388
4.0343
4.0300
4.0210
4.0120
3.9940
3.6726
3.6593
3.6476
3.6340
3.6205
3.6088
3.5956
3.2751
3.2607
3.2503
3.2359
3.2218
3.2116
3.1968
2.7724
2.7592
2.7474
2.7340
2.7308
2.7172
2.7056
2.6925
2.5844
2.5699
2.5594
2.5441
2.5279
2.5175
2.5030
2.0199
1.5774
1.5588
1.5512
EtO2C
Br
DNs–N
S2
(400 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
0.9480
1.0172
1.0122
2.0723
1.0191
1.0181
1.0138
1.0329
1.5142
2.2114
3.0742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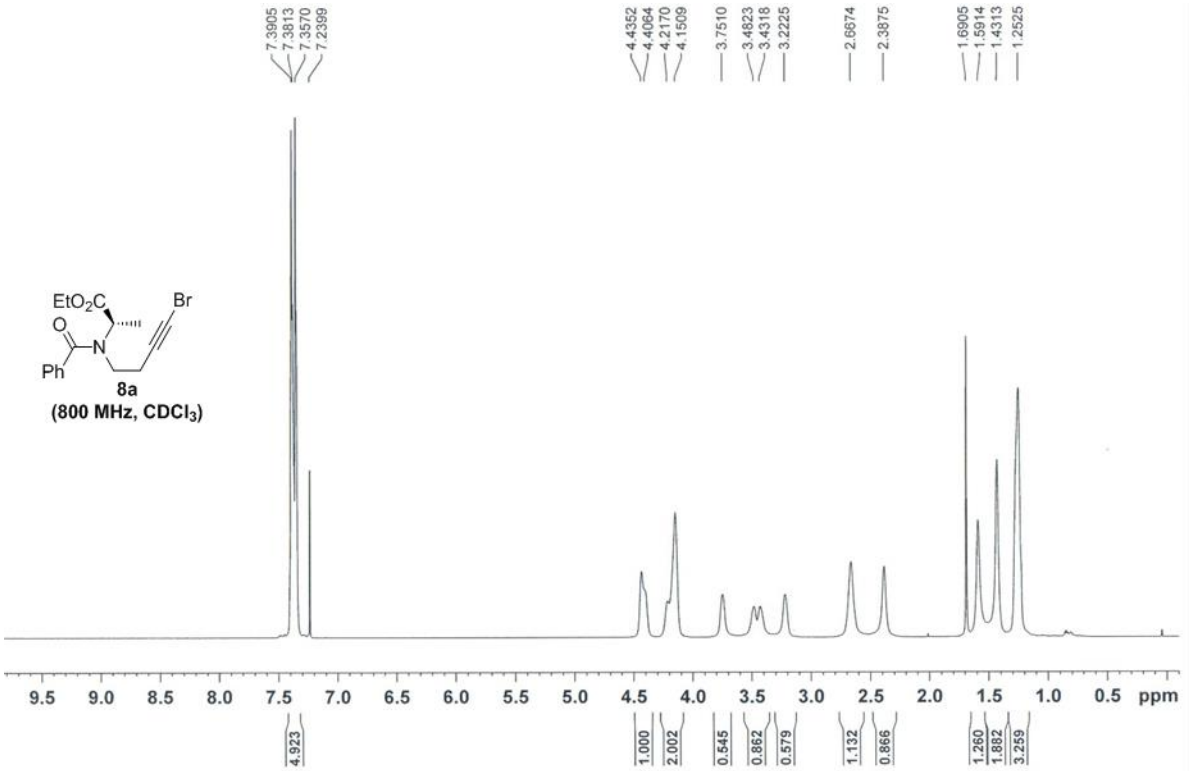
149.676
148.061
137.924
132.657
126.009
119.626
77.318
77.202
77.000
76.682
76.207
61.956
56.890
45.170
41.417
22.295
16.909
13.999
EtO2C
Br
DNs–N
S2
(100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.3813
7.3570
7.2399
4.4352
4.4064
4.2170
4.1509
3.7510
3.4823
3.4318
3.2225
2.6674
2.3875
1.6905
1.5914
1.4313
1.2525
EtO2C
Br
O
N
Ph
8a
(800 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.923
1.000
2.002
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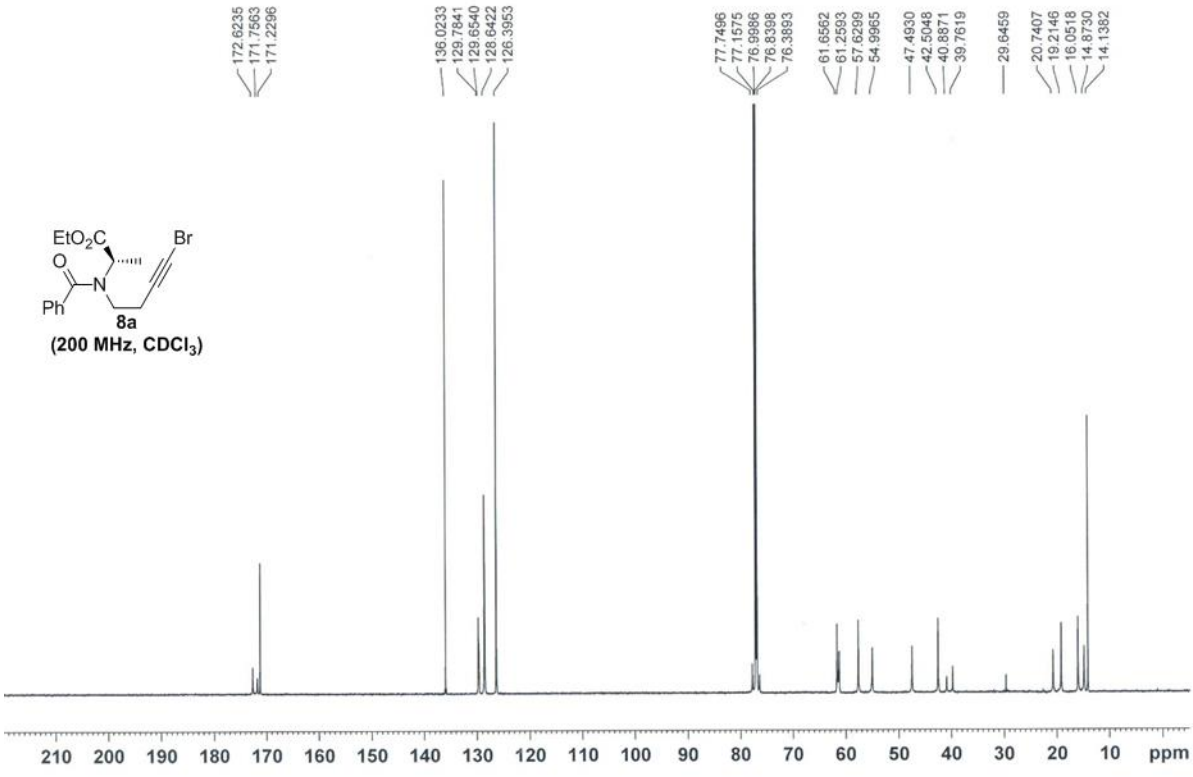
0.579
1.132
0.866
1.260
1.882
3.259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171.2296
136.0233
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128.6422
126.3953
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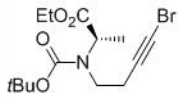
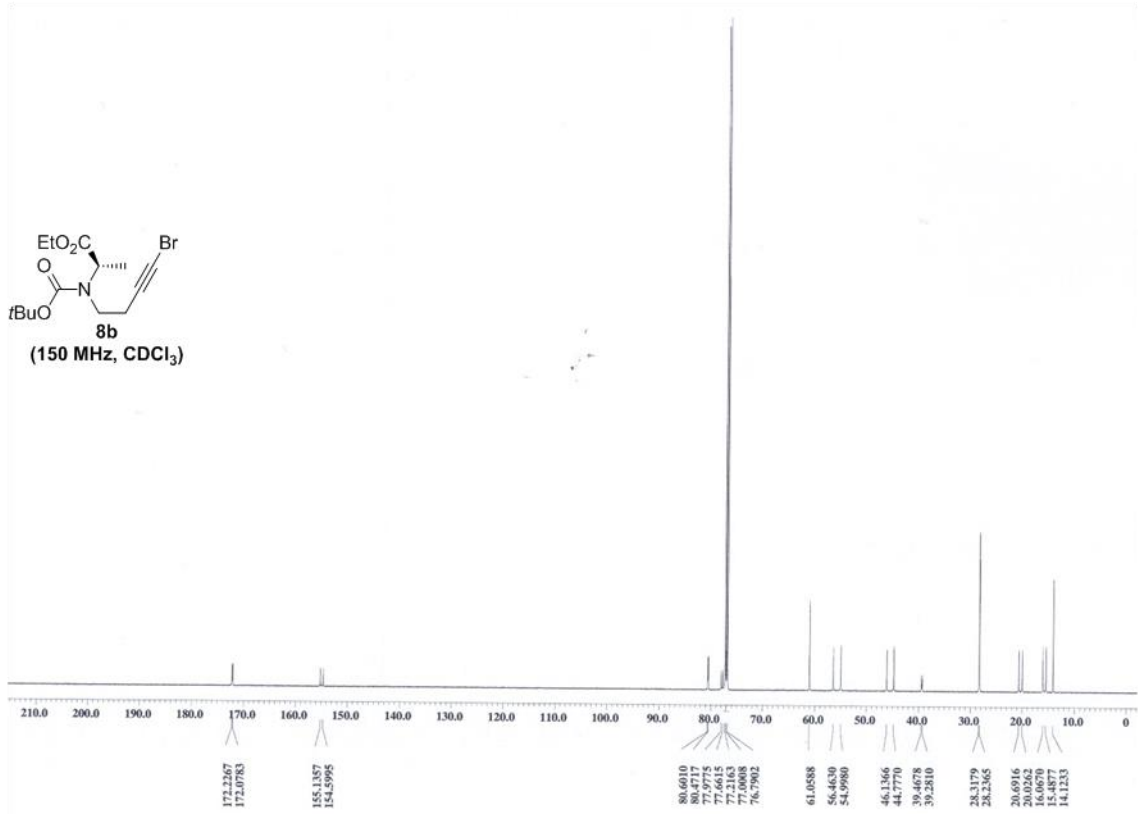
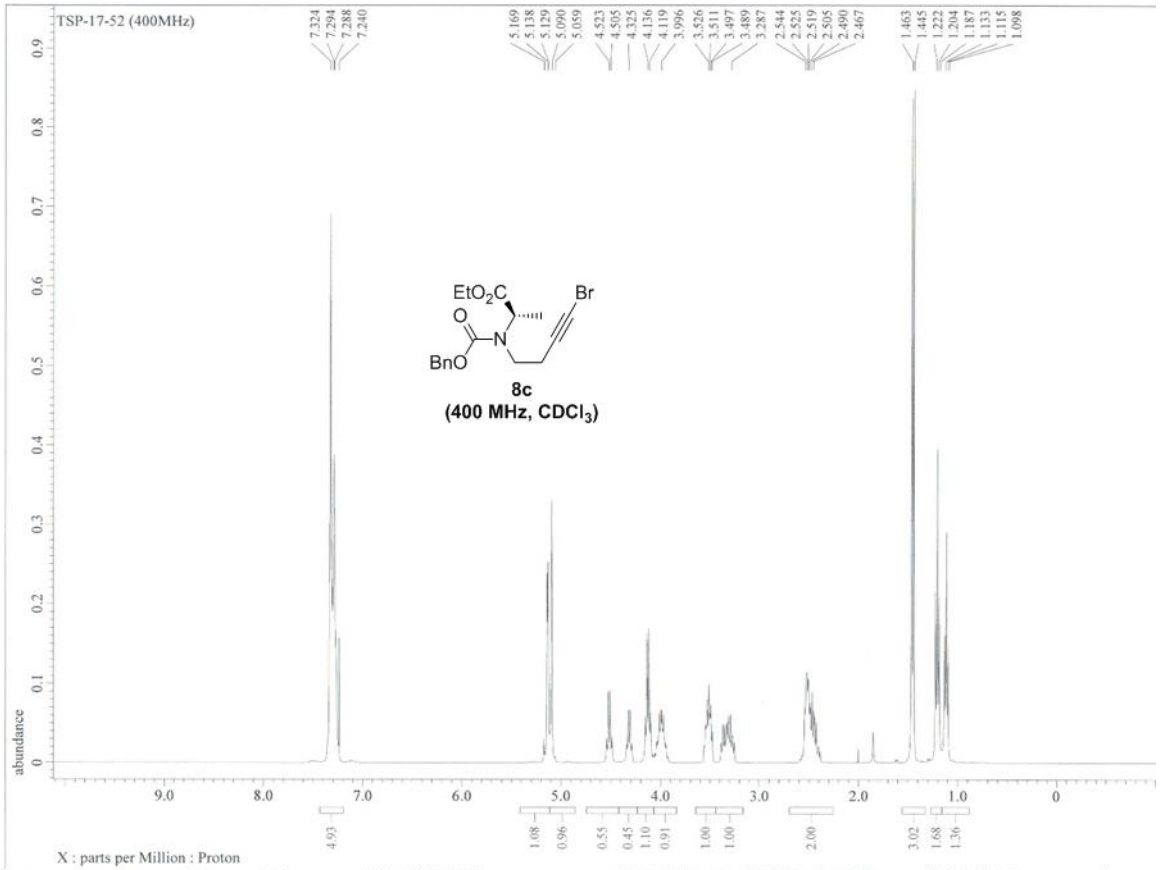
76.8398
76.3893
61.6562
61.2593
57.6299
54.9965
47.4930
42.5048
40.8871
39.7619
29.6459
20.7407
19.2146
16.0518
14.8730
14.1382
EtO2C
Br
O
N
Ph
8a
(200 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

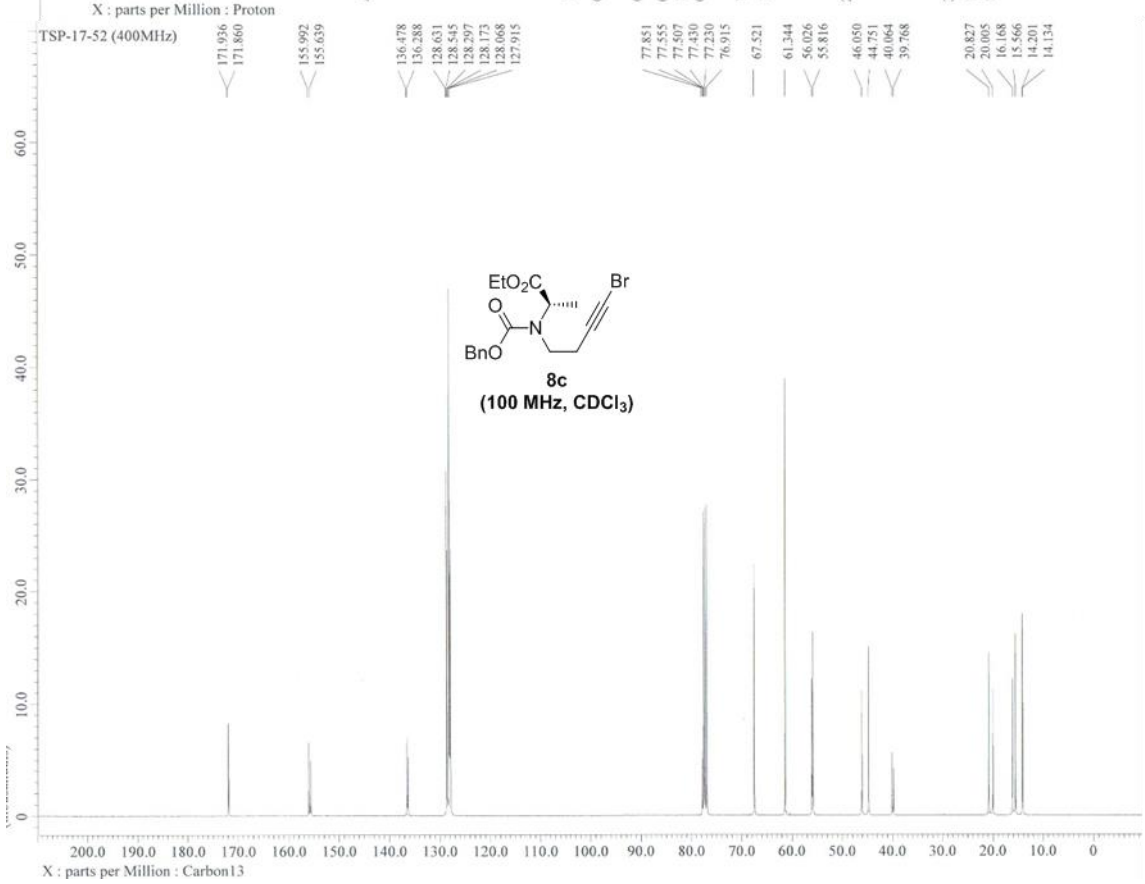


8b
(600 MHz, $CDCl_3$)

8b
(150 MHz, $CDCl_3$)




TSP-17-52 (400MHz)
abundance
X : parts per Million : Proton
8c
(400 MHz, CDCl3)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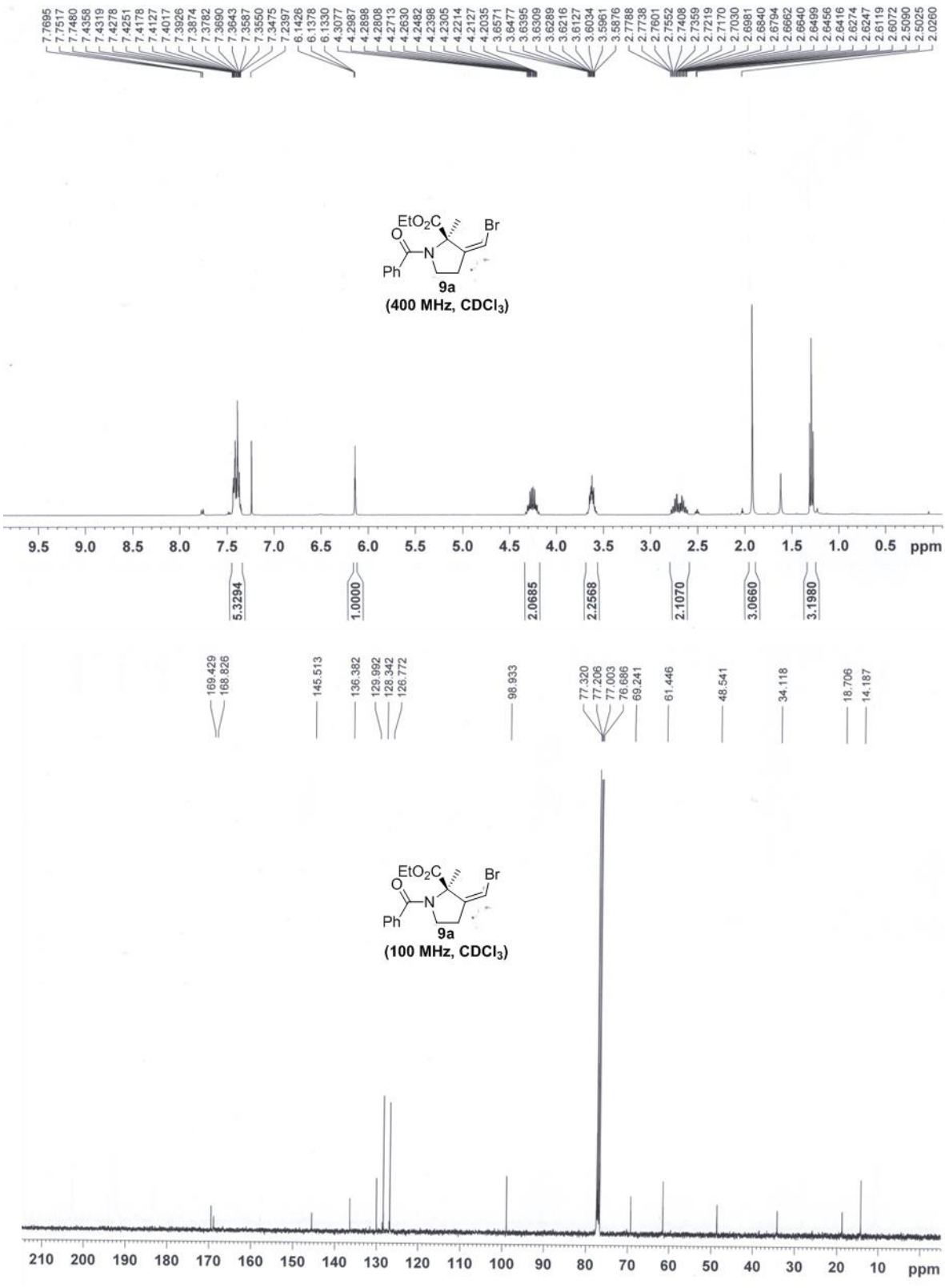
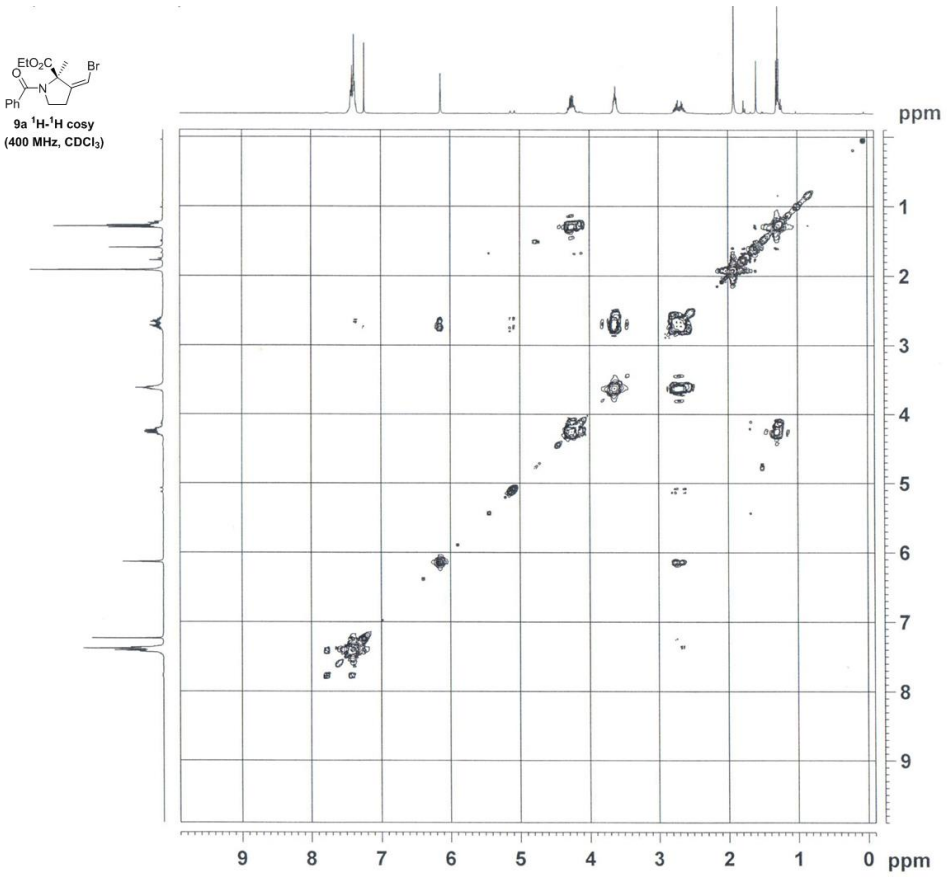
X : parts per Million : Carbon13
8c
(100 MHz, CDCl3)


7.7695 7.7517 7.7480 7.4358 7.4319 7.4278 7.4251 7.4178 7.4127 7.4017 7.3926 7.3874 7.3782 7.3690 7.3643 7.3587 7.3550 7.3475 7.2397 6.1426 6.1378 6.1330 4.3077 4.2987 4.2898 4.2808 4.2713 4.2630 4.2482 4.2398 4.2305 4.2214 4.2127 4.2035 3.6571 3.6477 3.6395 3.6309 3.6289 3.6216 3.6127 3.6034 3.5981 3.5876 2.7788 2.7738 2.7601 2.7552 2.7408 2.7359 2.7219 2.7170 2.7030 2.6981 2.6840 2.6794 2.6662 2.6640 2.6499 2.6456 2.6416 2.6274 2.6247 2.6119 2.6072 2.5090 2.5025 2.0260
EtO2C
O
N
Ph
Br
9a
(400 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.3294 1.0000 2.0685 2.2568 2.1070 3.0660 3.1980
169.429 168.826 145.513 136.382 129.992 128.342 126.772 98.933 77.320 77.206 77.003 76.686 69.241 61.446 48.541 34.118 18.706 14.187
EtO2C
O
N
Ph
Br
9a
(100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



9a ^{1}H-^{1}H cosy
(400 MHz, $CDCl_3$)

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Current Data Parameters
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EXPNO                    11
PROCNO                    1

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Date_              20180412
Time                  11.14
INSTRUM                spect
PROBHD    5 mm Multinucl
PULPROG            cosyqf45
TD                     2048
SOLVENT               CDC13
NS                       12
DS                       16
SWH                5592.841 Hz
FIDRES             2.730880 Hz
AQ                 0.1831412 sec
RG                       256
DW                  89.400 usec
DE                   6.00 usec
TE                   298.0 K
d0                0.00000300 sec
D1                2.00000000 sec
IN0               0.00017880 sec
MCREST            0.00000000 sec
MCWRK             2.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                    11.90 usec
PL1                    5.50 dB
SFO1           400.1320191 MHz

F1 - Acquisition parameters
ND0                       1
TD                      256
SFO1              400.132 MHz
FIDRES          21.847036 Hz
SW                 13.977 ppm
FnMODE                   QF

F2 - Processing parameters
SI                      1024
SF             400.1300162 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
PC                      1.00

F1 - Processing parameters
SI                      1024
MC2                       QF
SF             400.1300161 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
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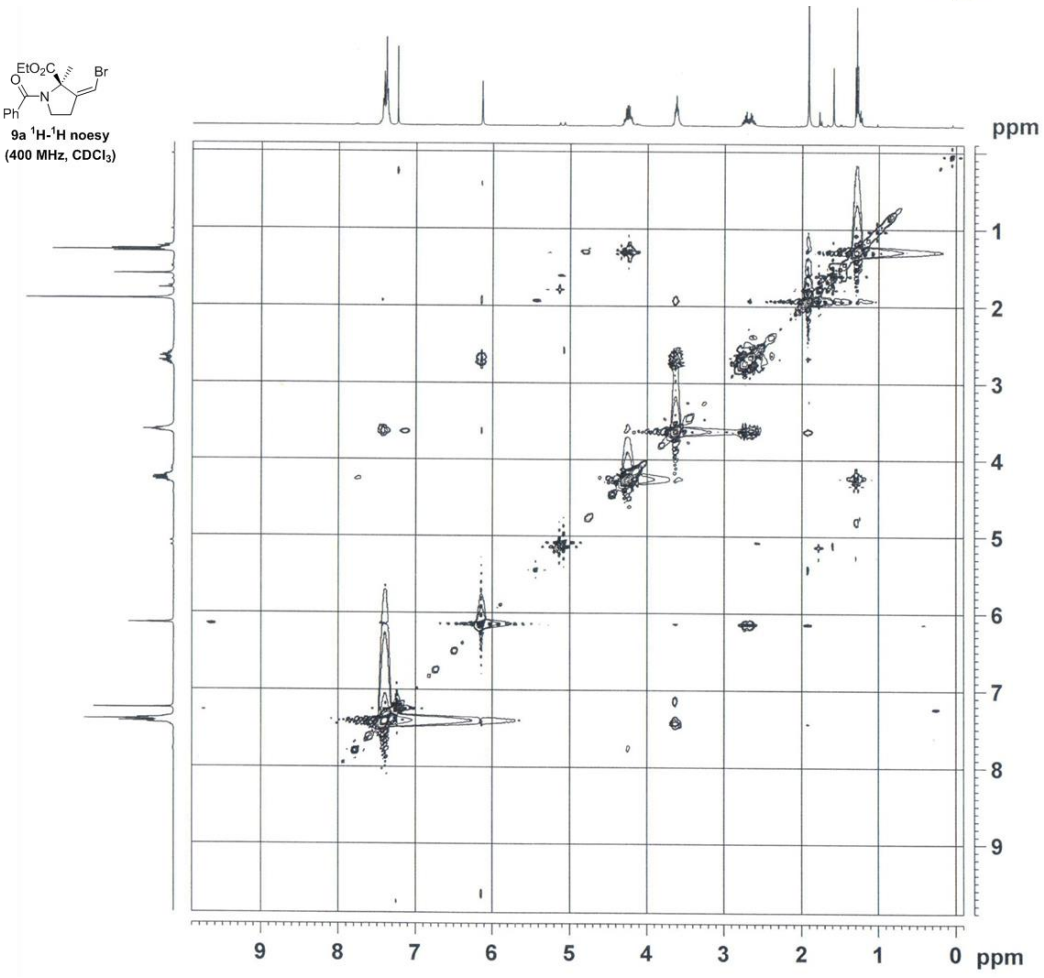

9a ^{1}H-^{1}H noesy
(400 MHz, $CDCl_3$)

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EXPNO                    14
PROCNO                    1

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PROBHD    5 mm Multinucl
PULPROG            noesyph
TD                     2048
SOLVENT               CDC13
NS                       16
DS                       16
SWH                5592.841 Hz
FIDRES             2.730880 Hz
AQ                 0.1831412 sec
RG                     228.1
DW                  89.400 usec
DE                   6.00 usec
TE                   298.0 K
d0                0.00007425 sec
D1                2.00000000 sec
D8                1.00000000 sec
IN0               0.00017880 sec
MCREST            0.00000000 sec
MCWRK             1.00000000 sec
ST1CNT                   128

======== CHANNEL f1 ========
NUC1                      1H
P1                    11.90 usec
PL1                    5.50 dB
SFO1           400.1320191 MHz

F1 - Acquisition parameters
ND0                       1
TD                      256
SFO1              400.132 MHz
FIDRES          21.847036 Hz
SW                 13.977 ppm
FnMODE         States-TPPI

F2 - Processing parameters
SI                      2048
SF             400.1300175 MHz
WDW                     SINE
SSB                        2
LB                      0.00 Hz
GB                         0
PC                      1.00

F1 - Processing parameters
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MC2            States-TPPI
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WDW                     SINE
SSB                        2
LB                      0.00 Hz
GB                         0
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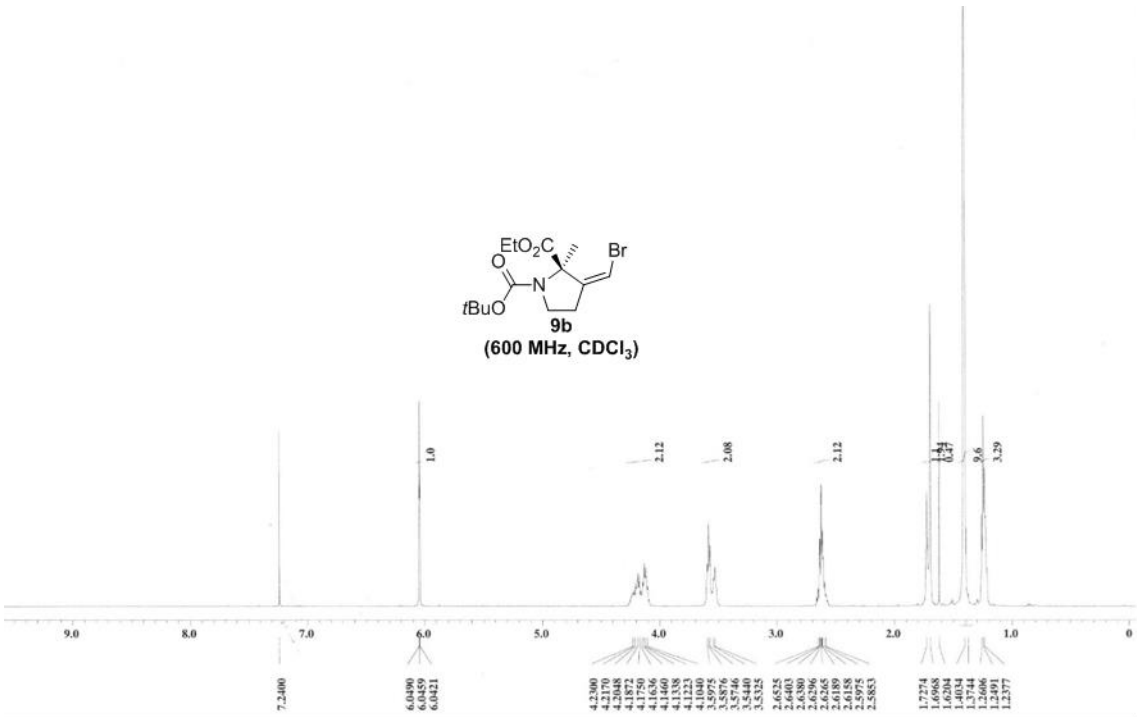
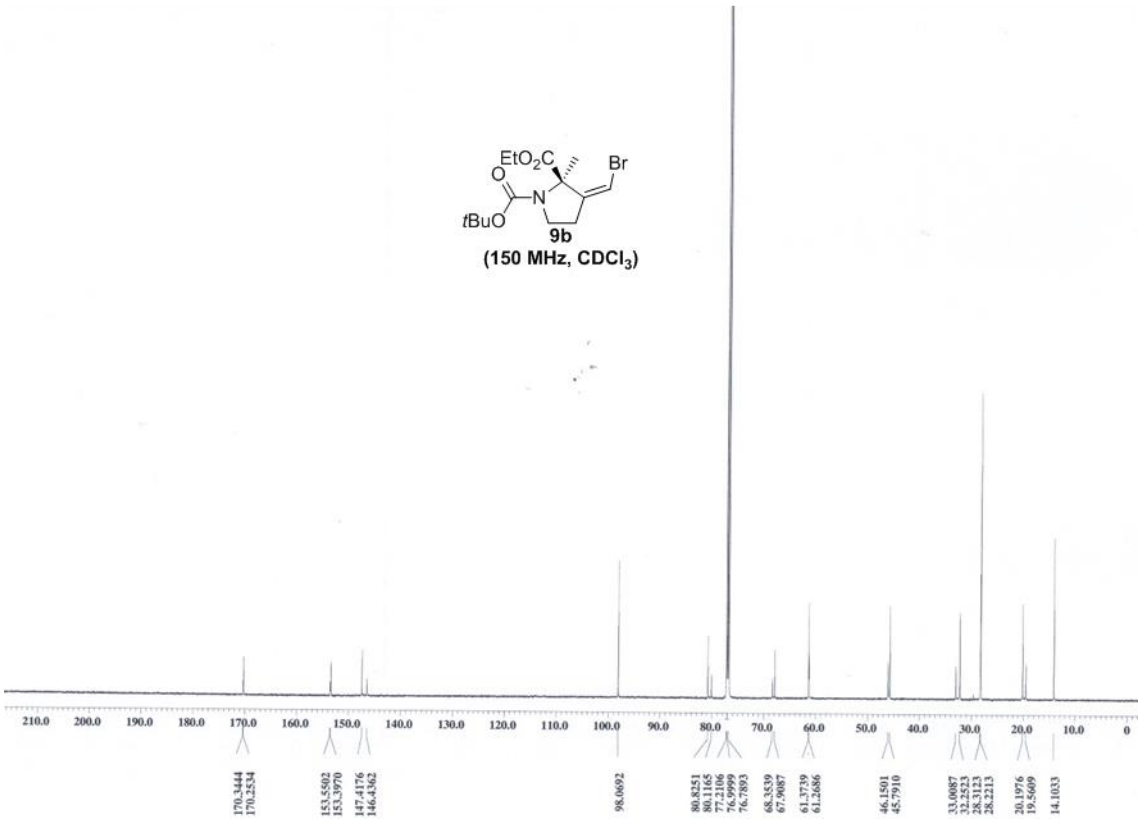

EtO2C
O
N
Br
tBuO
9b
(600 MHz, CDCl3)


EtO2C
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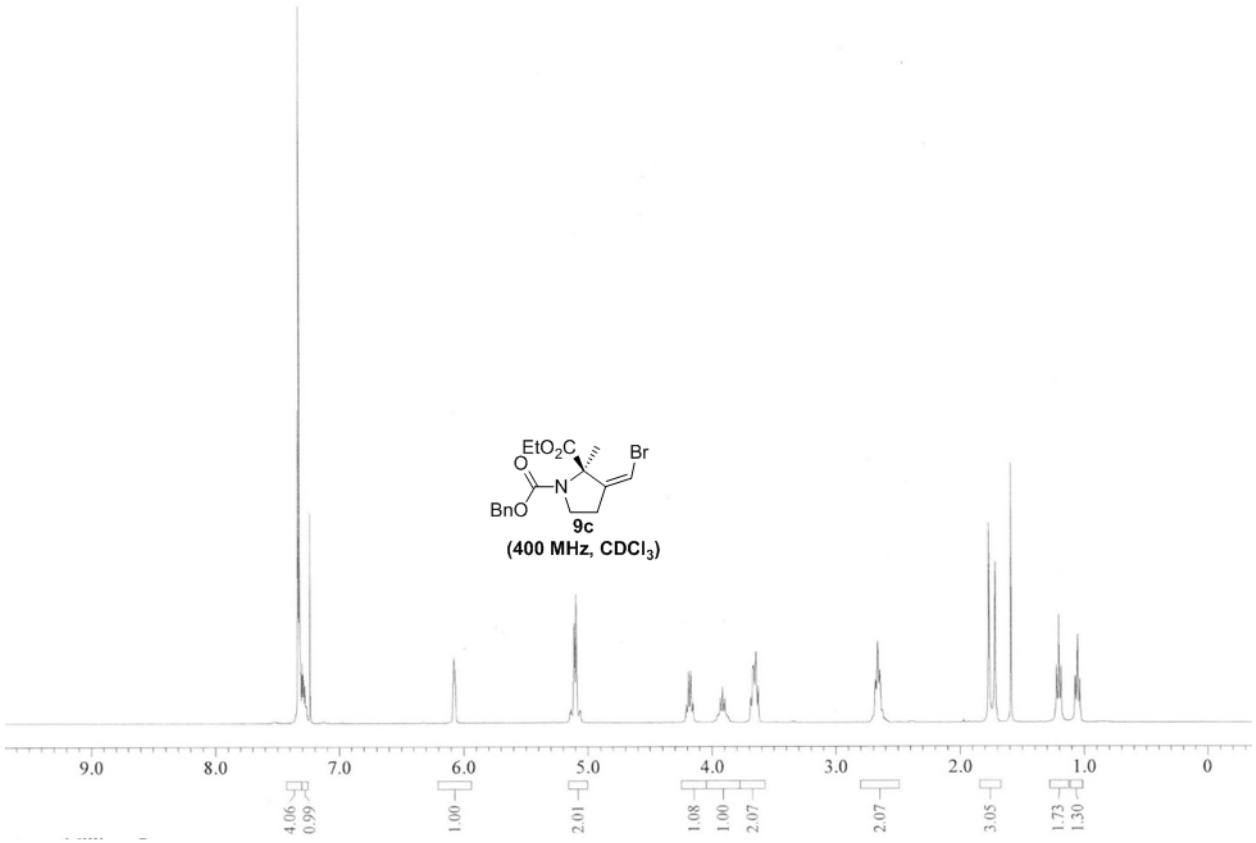
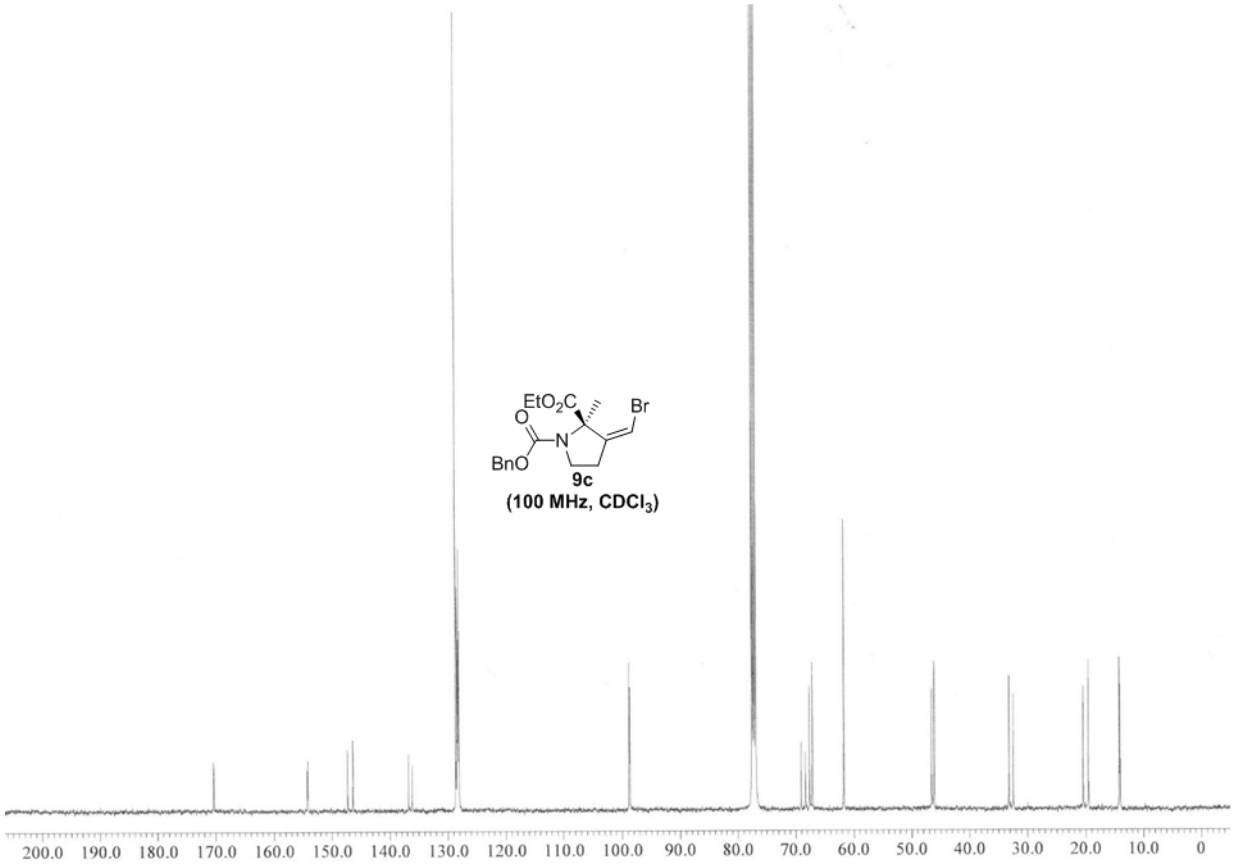
N
Br
tBuO
9b
(150 MHz, CDCl3)


EtO2C
O
N
Br
BnO
9c
(400 MHz, CDCl3)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
4.06
0.99
1.00
2.01
1.08
1.00
2.07
2.07
3.05
1.73
1.30


EtO2C
O
N
Br
BnO
9c
(100 MHz, CDCl3)
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180.0
170.0
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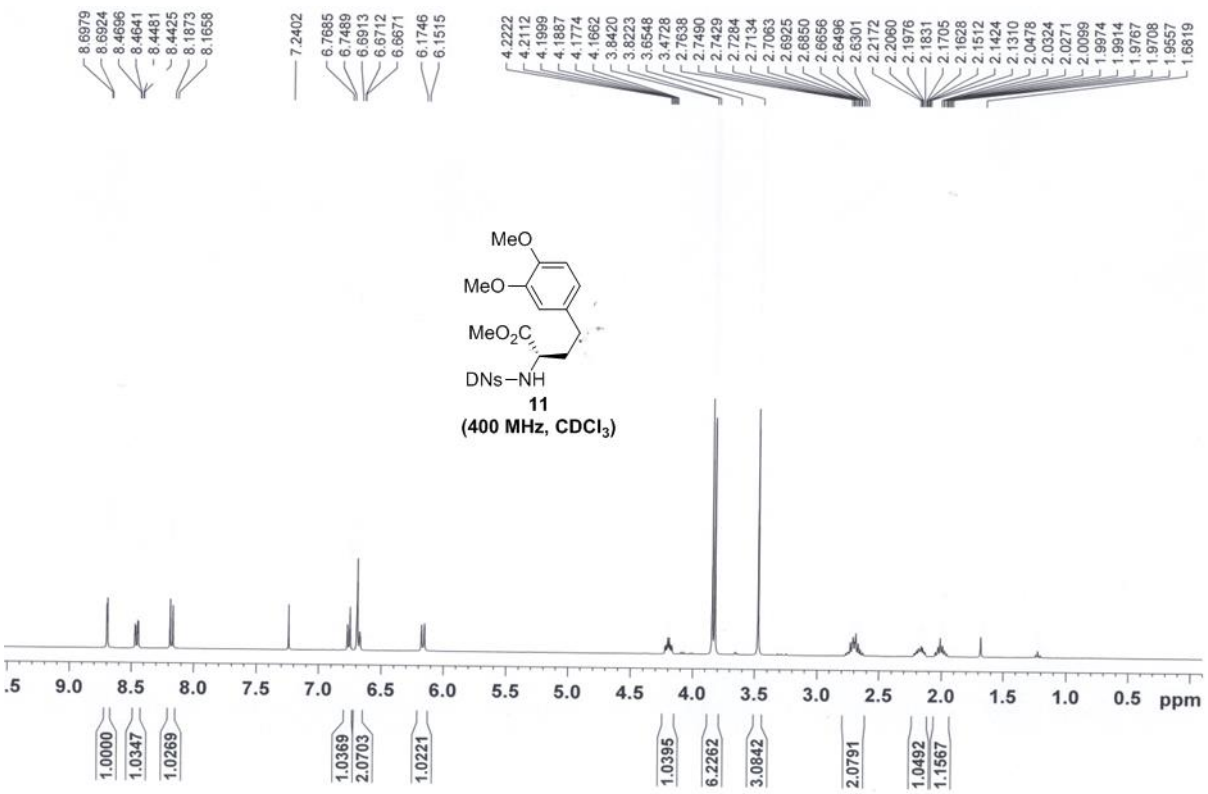
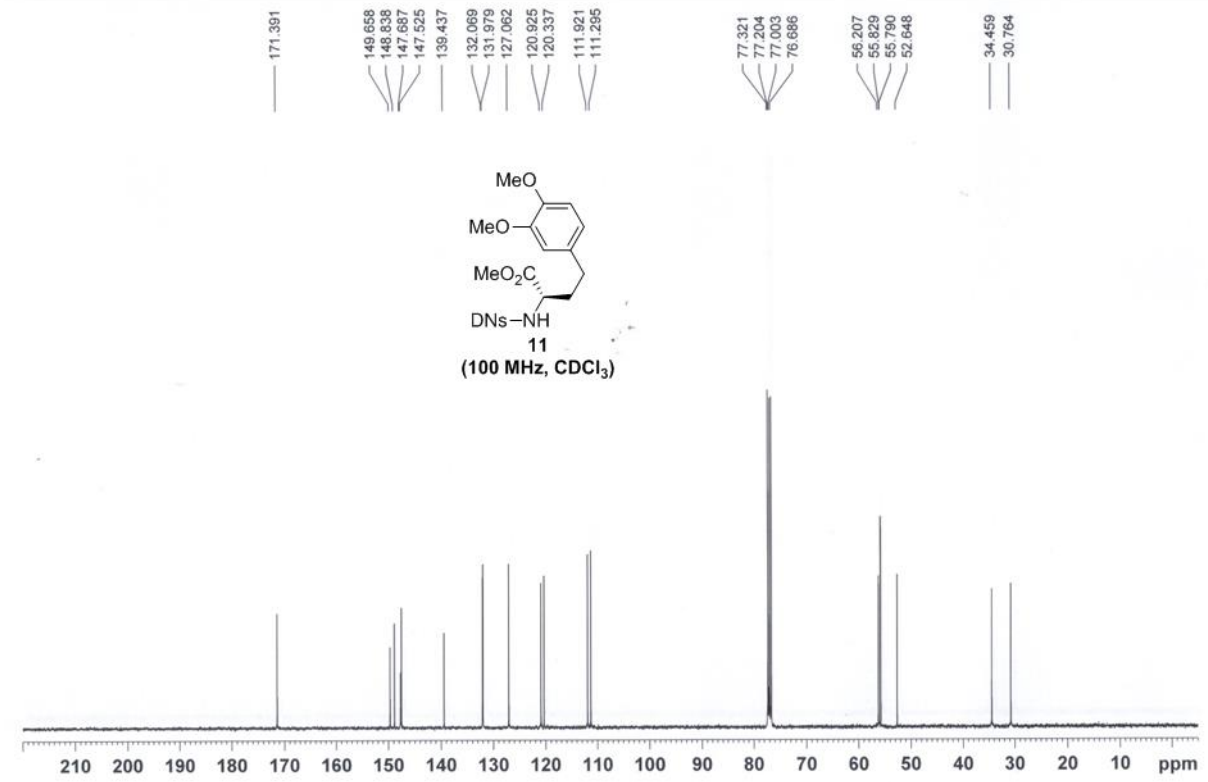
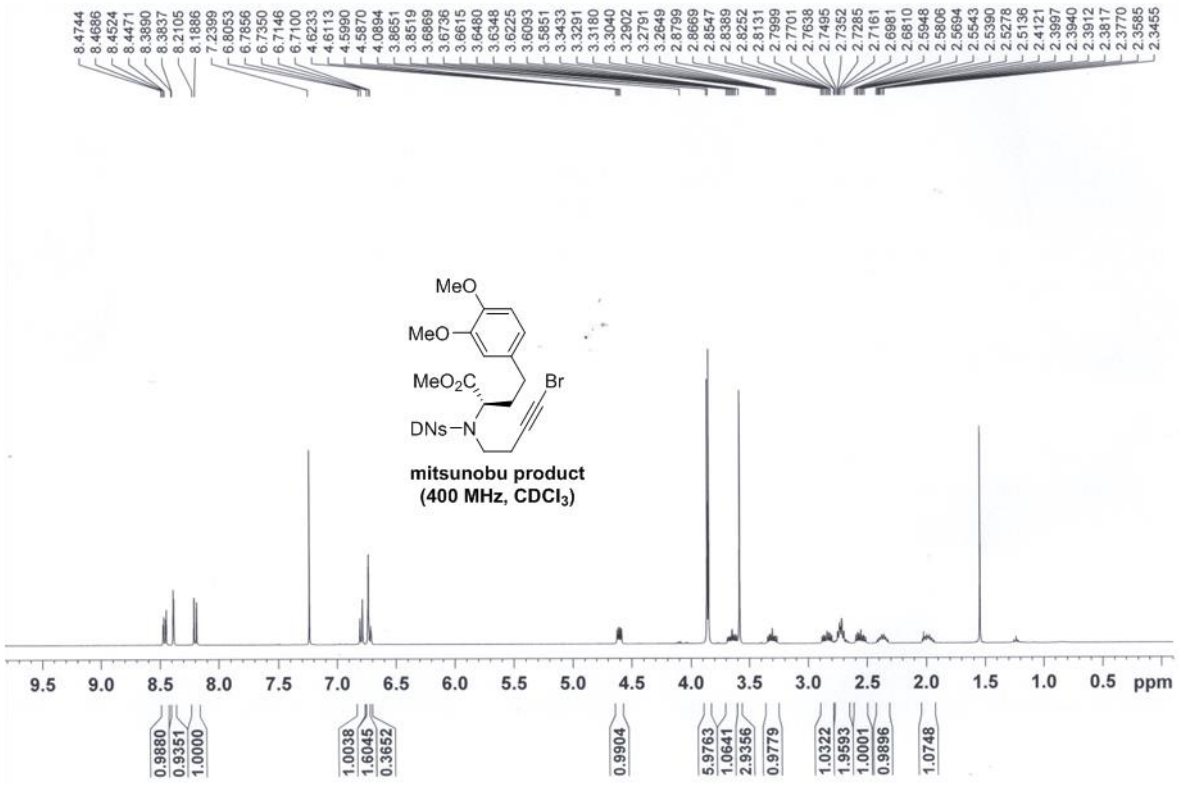
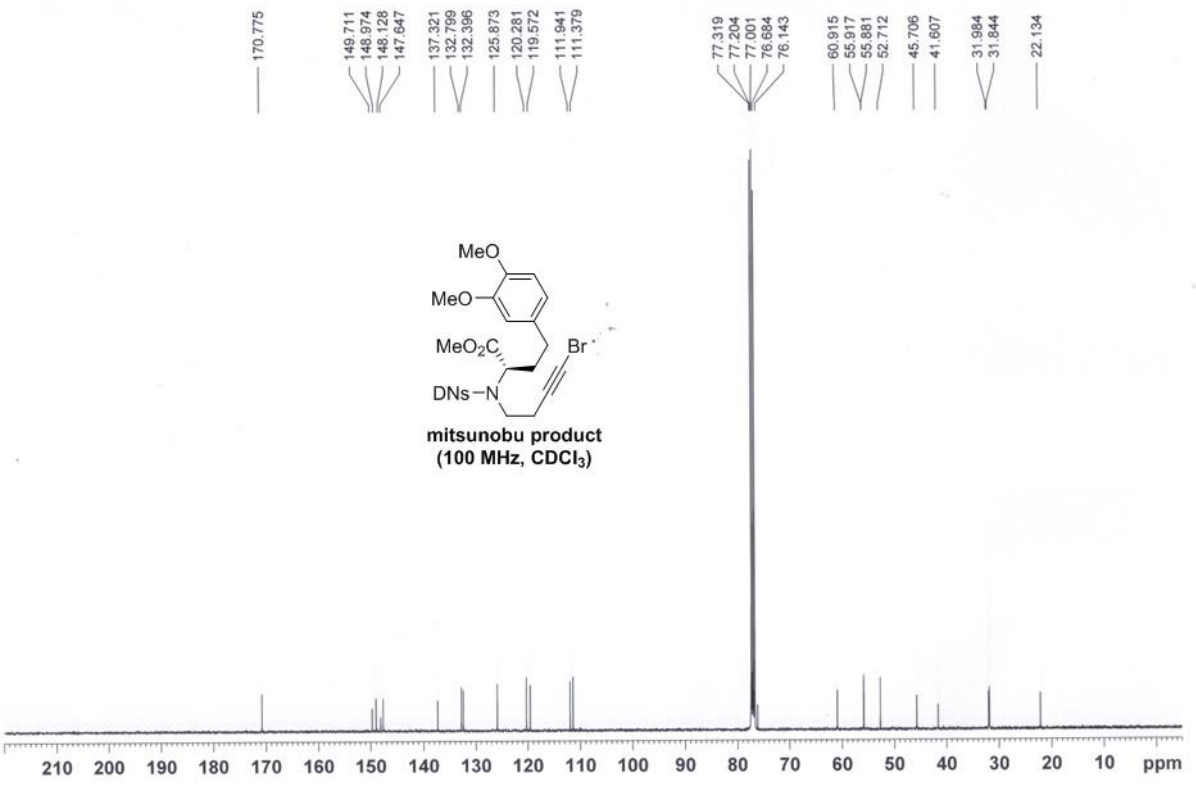
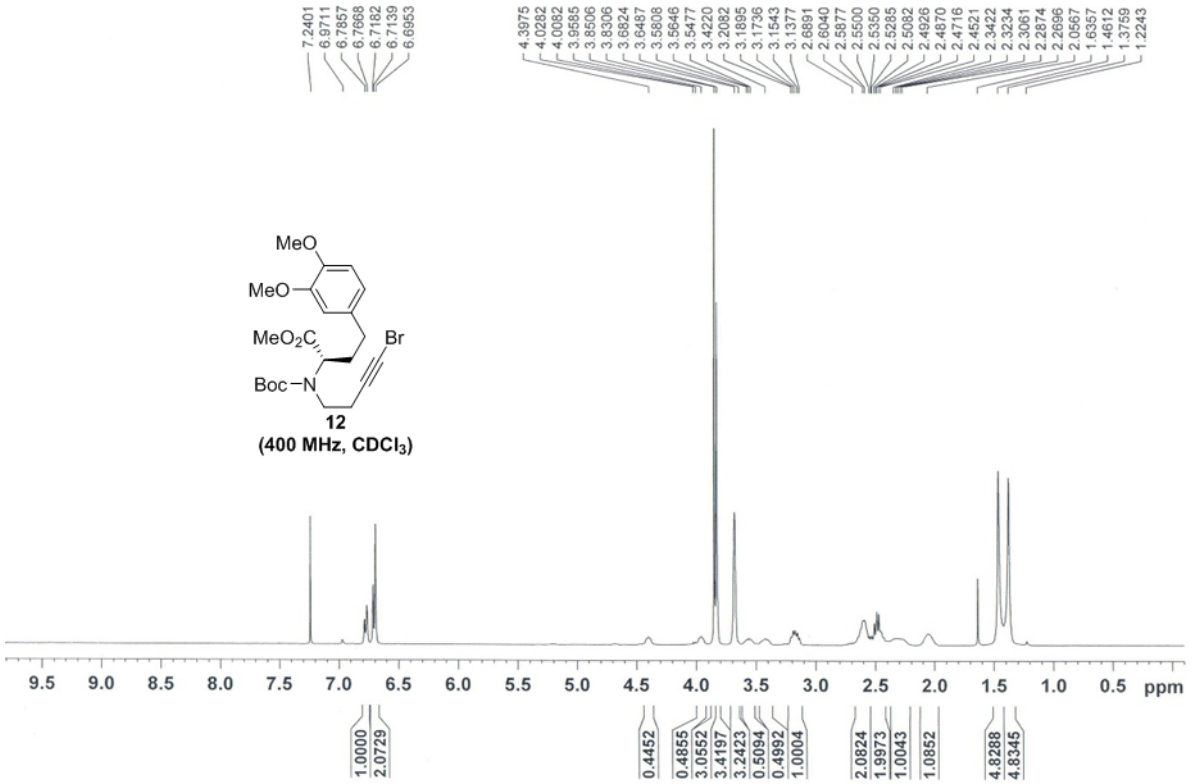
50.0
40.0
30.0
20.0
10.0
0

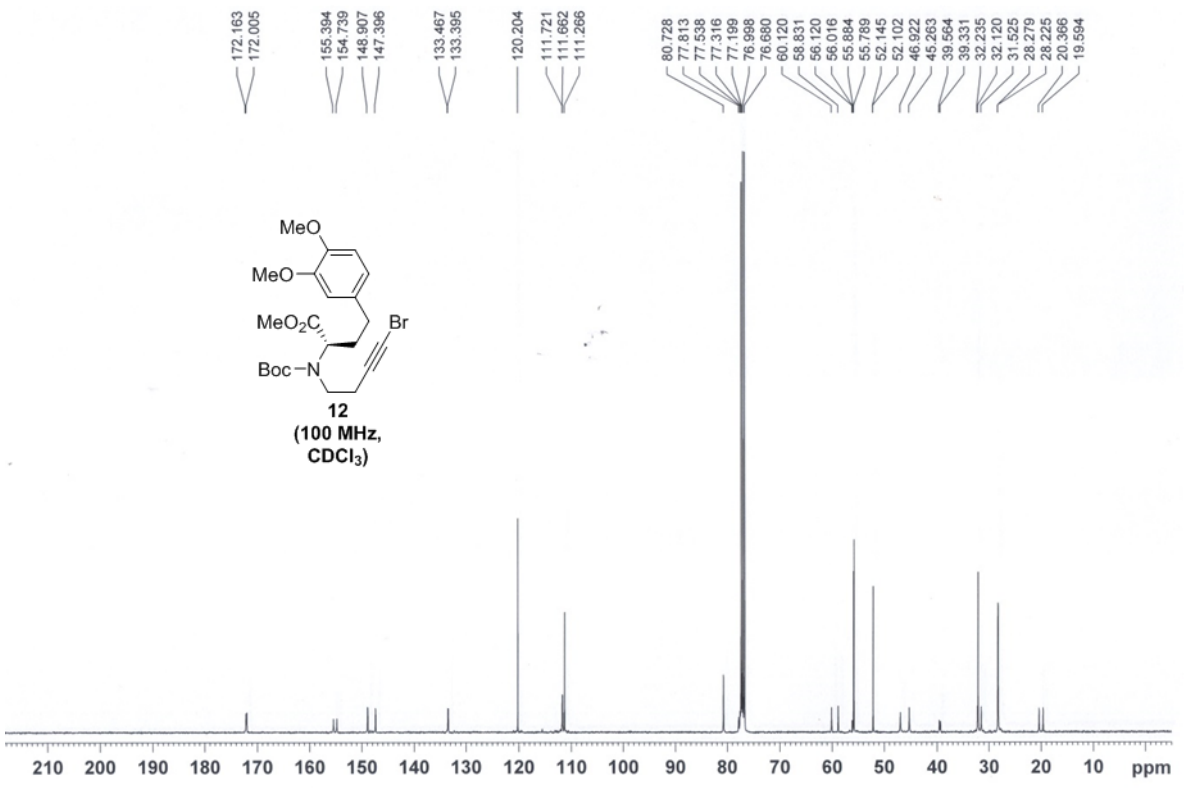

MeO
MeO
MeO2C
DNs–NH
11
(400 MHz, CDCl3)
ppm

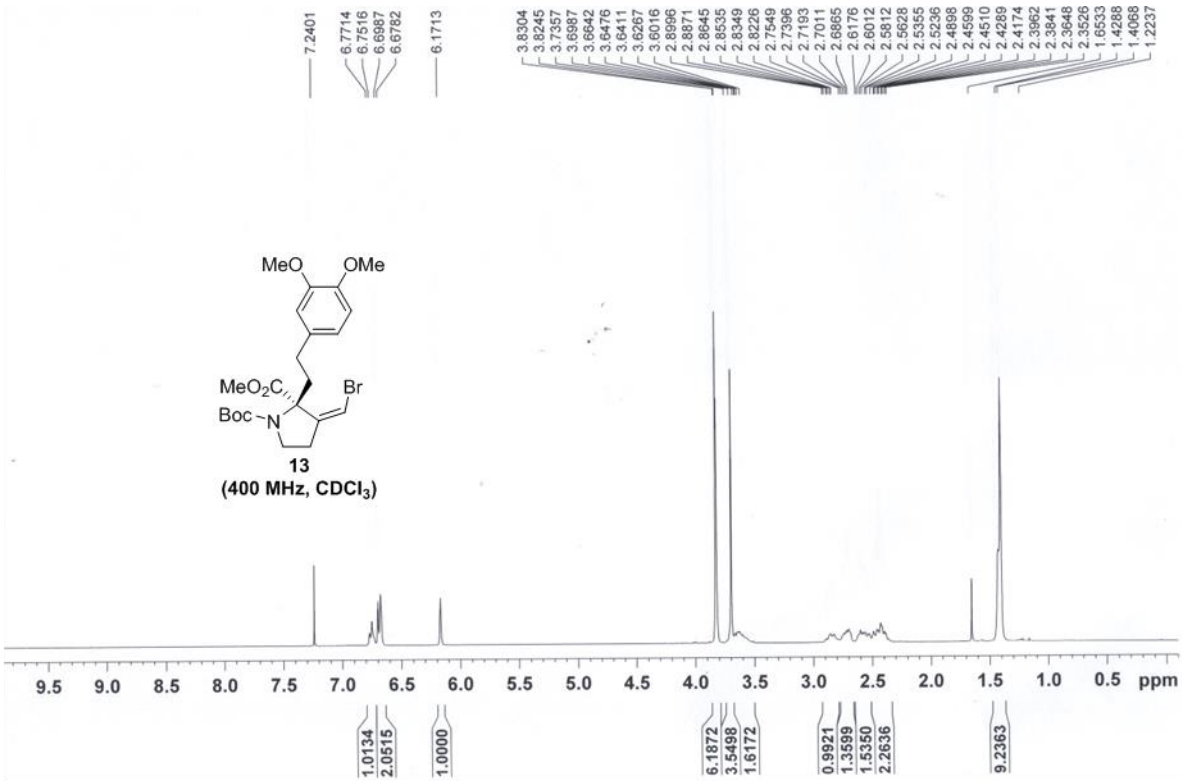

MeO
MeO
MeO2C
DNs–NH
11
(100 MHz, CDCl3)
ppm

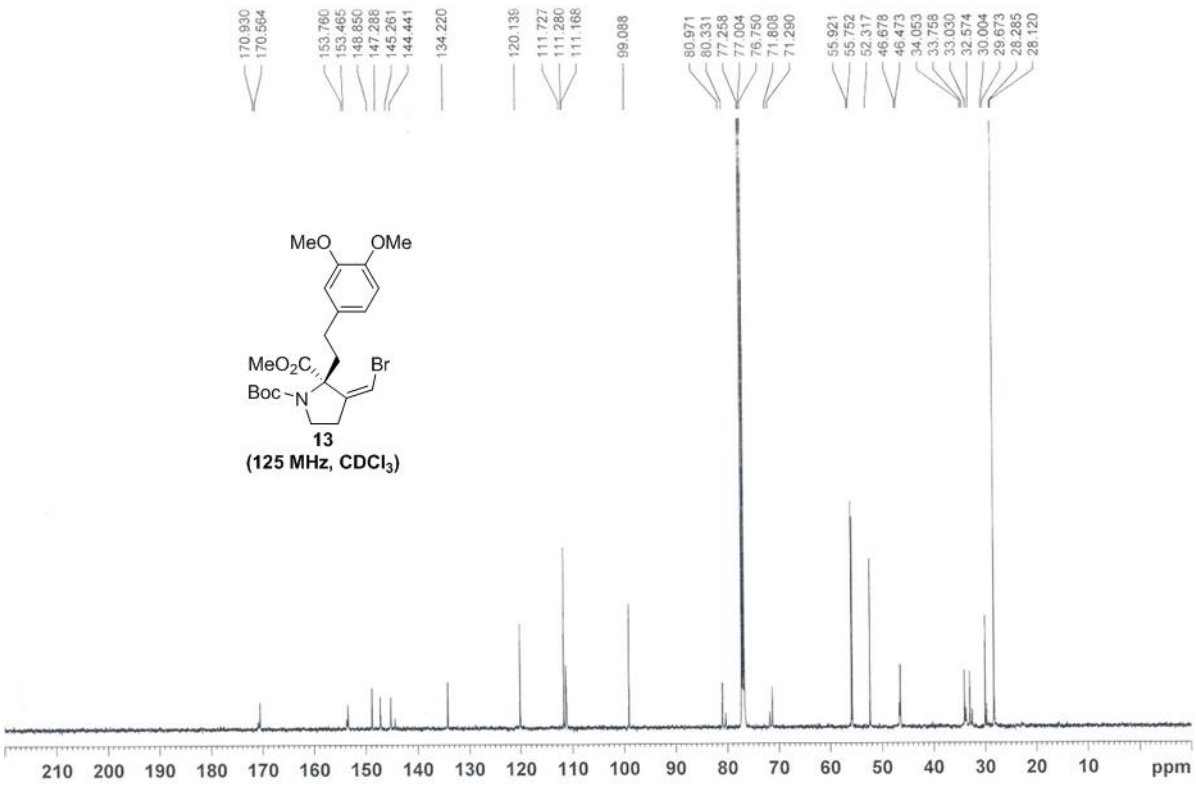

MeO
MeO
MeO2C
Br
DNs–N
mitsunobu product
(400 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

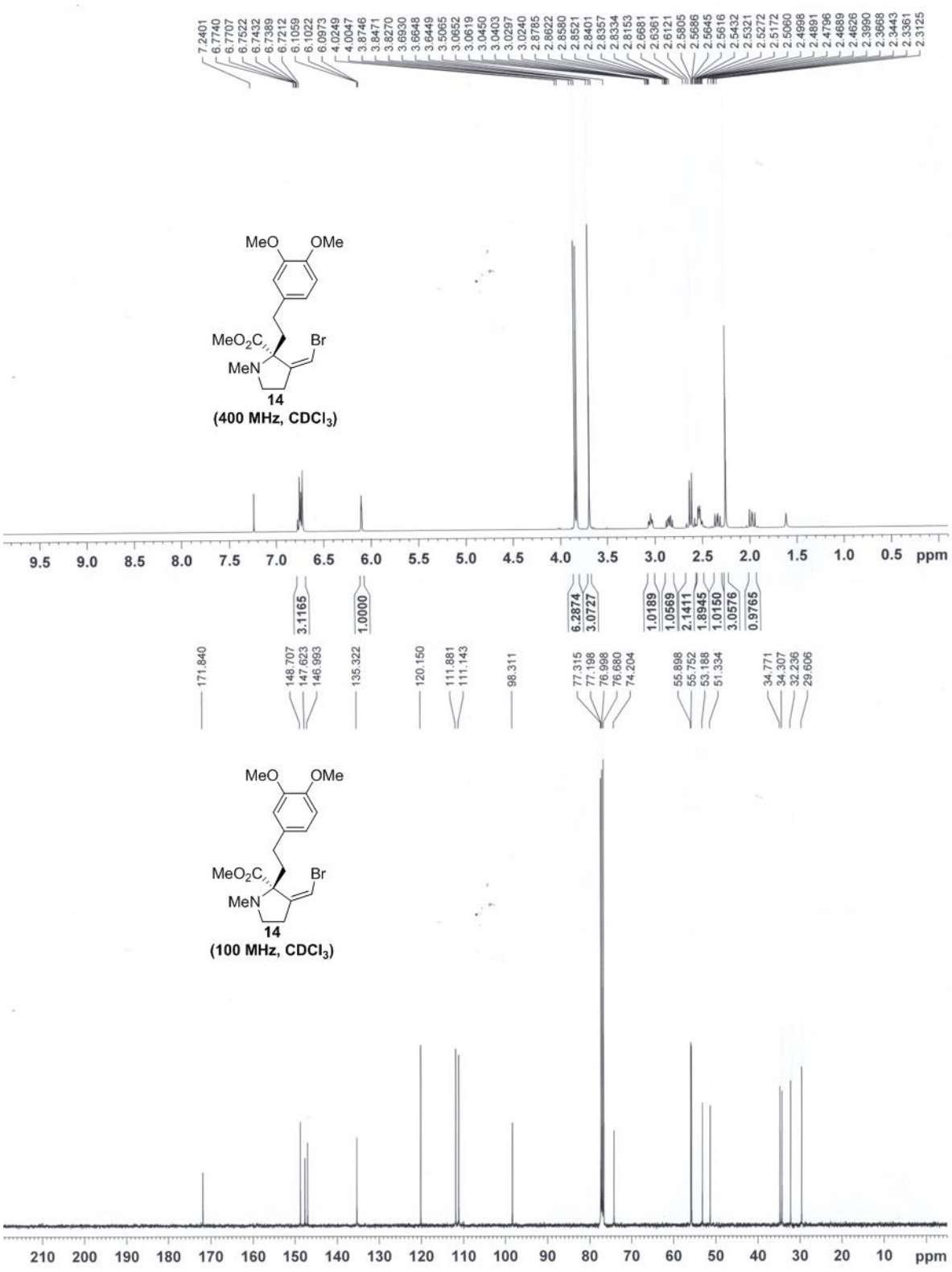

MeO
MeO
MeO2C
Br
DNs–N
mitsunobu product
(100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

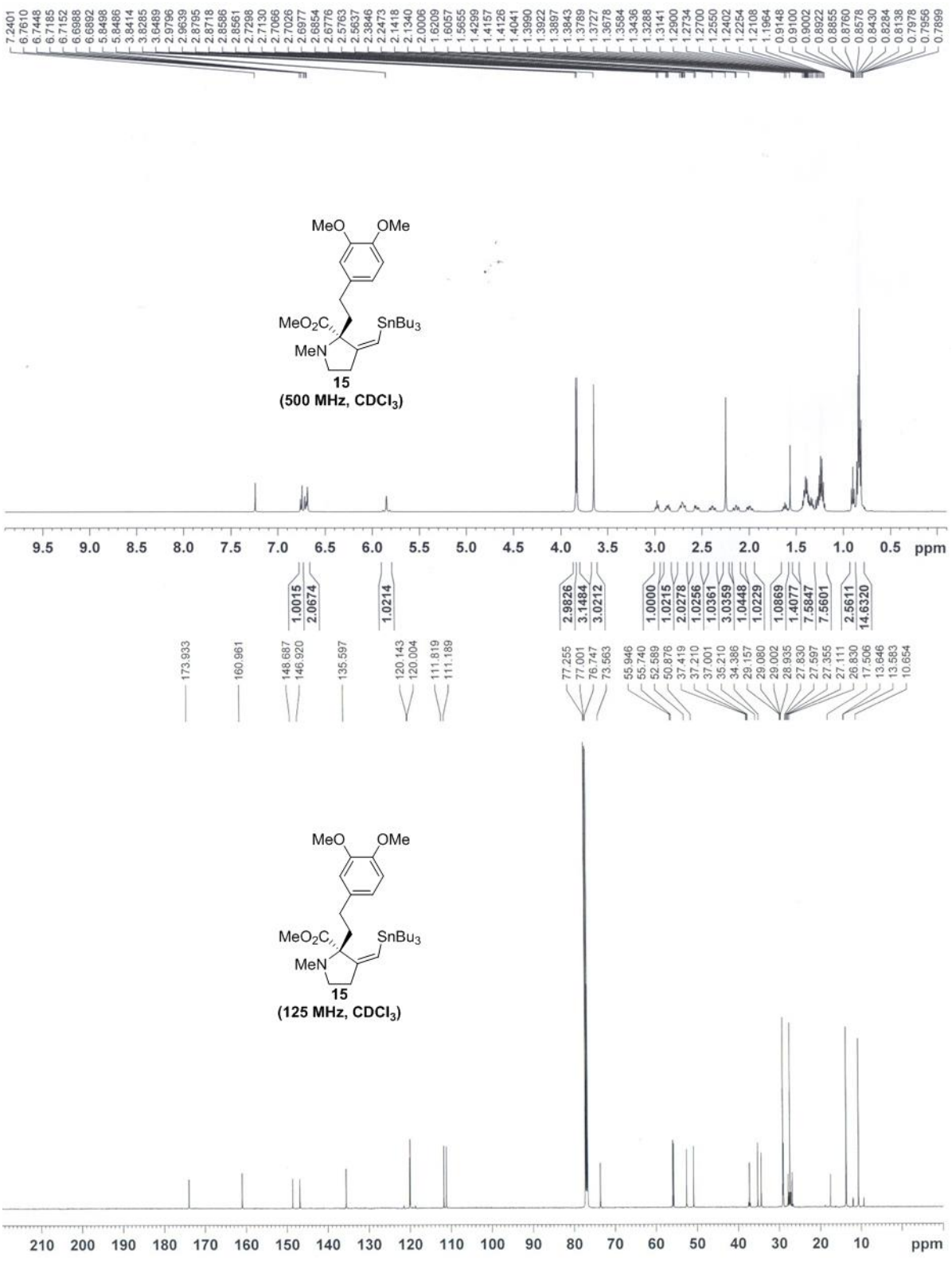

MeO
MeO
MeO2C
Br
Boc–N
12
(400 MHz, CDCl3)
ppm

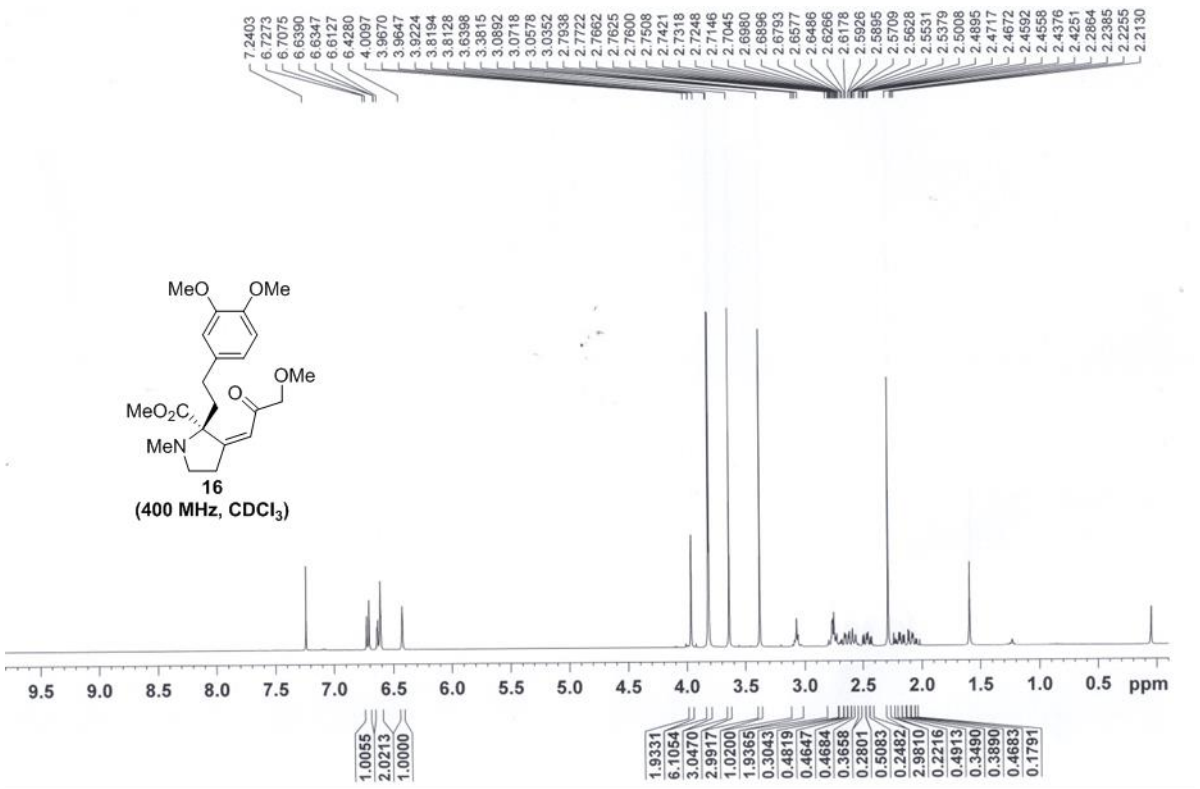

MeO
MeO
MeO2C
Br
Boc–N
12
(100 MHz,
CDCl3)
ppm

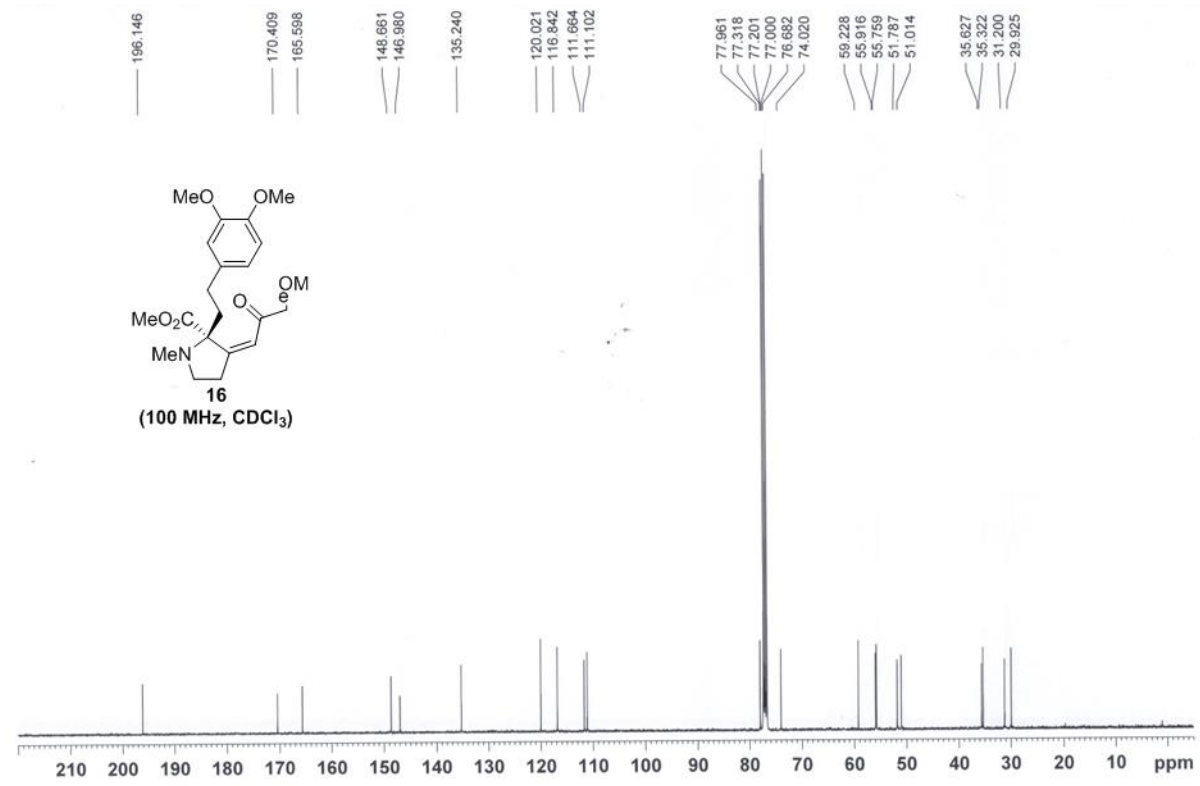

MeO
OMe
MeO2C
Br
Boc
N
13
(400 MHz, CDCl3)
ppm

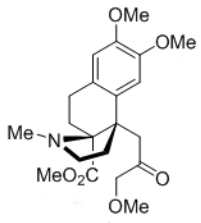

MeO
OMe
MeO2C
Br
Boc
N
13
(125 MHz, CDCl3)
ppm


MeO
OMe
MeO2C
Br
MeN
14
(400 MHz, CDCl3)
14
(100 MHz, CDCl3)

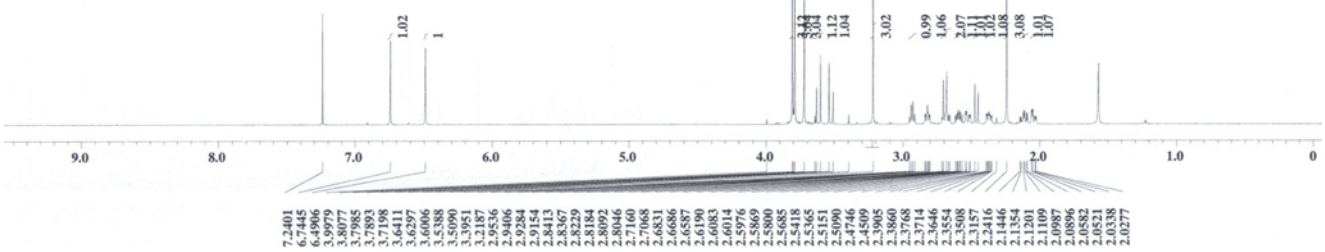

MeO
OMe
MeO2C
SnBu3
MeN
15
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0015 2.0674 1.0214 2.9826 3.1484 3.0212 1.0000 1.0215 2.0278 1.0256 1.0361 3.0359 1.0448 1.0229 1.0869 1.4077 7.5847 7.5601 2.5611 14.6320
173.933 160.961 148.687 146.920 135.597 120.143 120.004 111.819 111.189
77.255 77.001 76.747 73.563 55.946 55.740 52.589 50.876 37.419 37.210 37.001 35.210 34.386 29.157 29.080 29.002 28.935 27.830 27.597 27.355 27.111 26.830 17.506 13.646 13.583 10.654
MeO
OMe
MeO2C
SnBu3
MeN
15
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

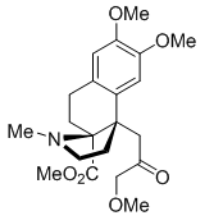

MeO
OMe
OMe
O
MeO2C
MeN
16
(400 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


MeO
OMe
OM
e
O
MeO2C
MeN
16
(100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

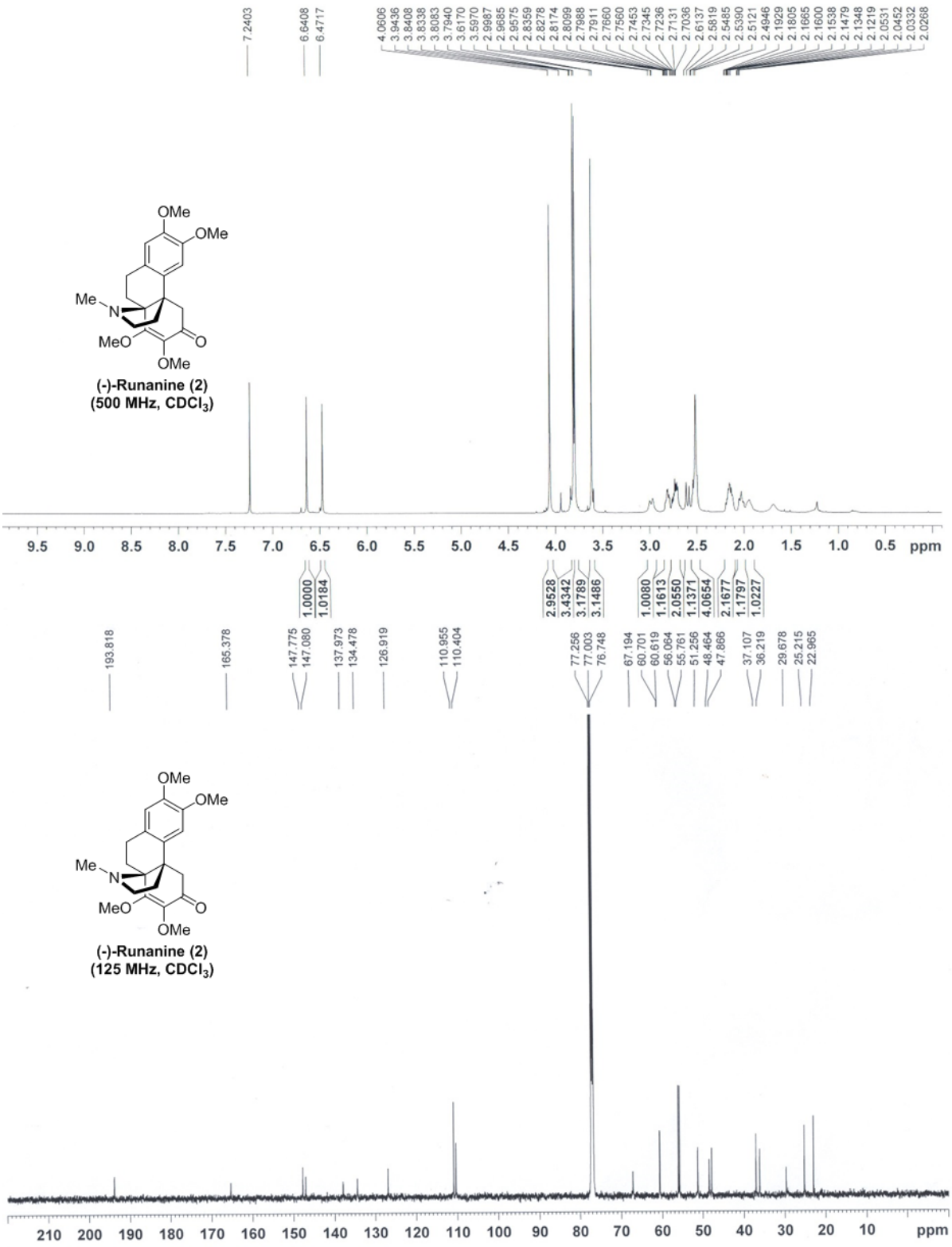


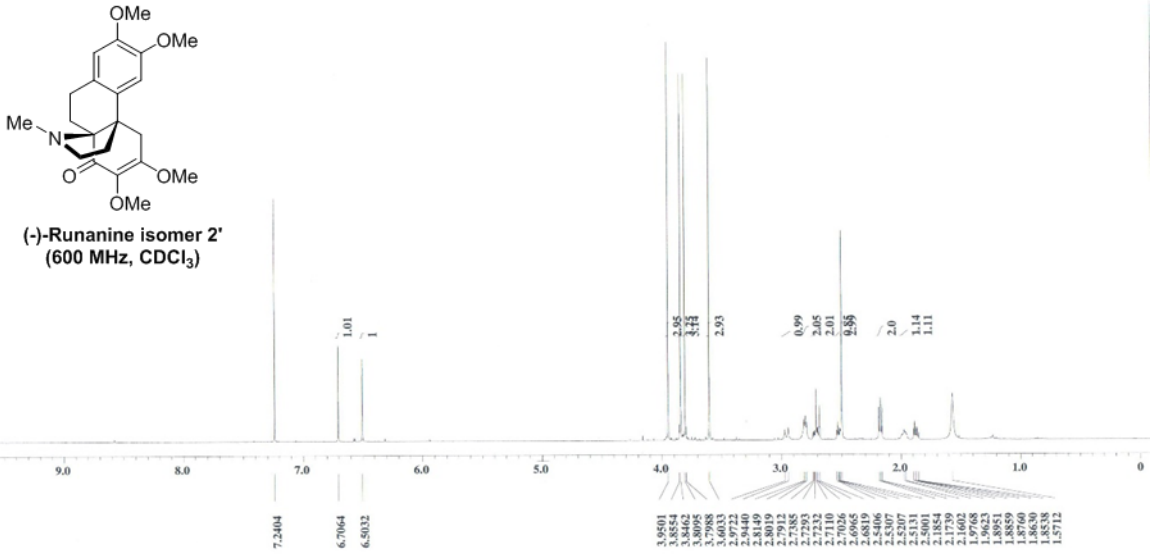
17
(600 MHz, $CDCl_3$)



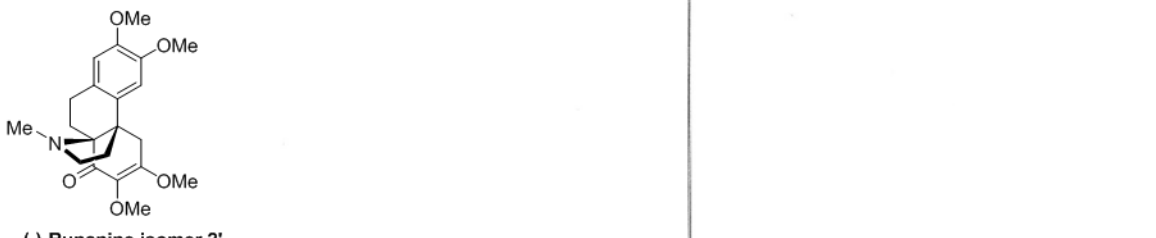


17
(150 MHz, $CDCl_3$)

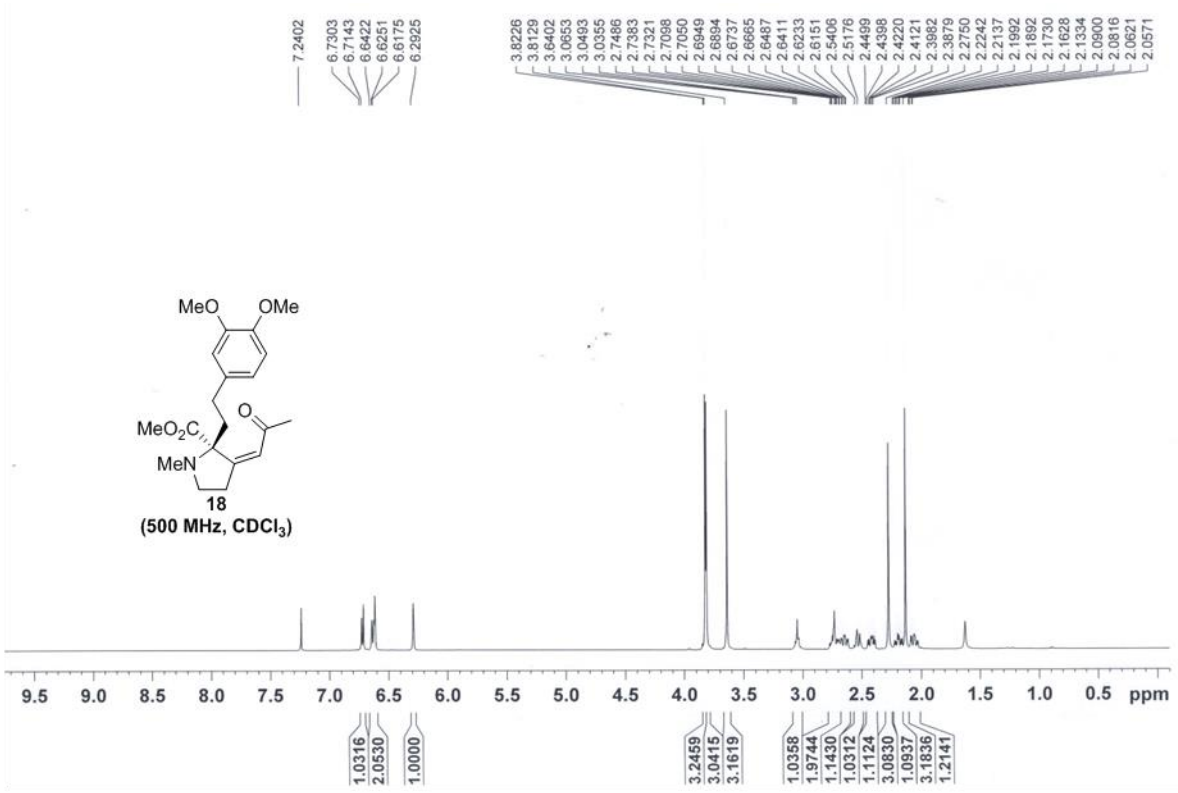

7.2403
6.6408
6.4717
4.0606
3.9436
3.8408
3.8338
3.8083
3.7940
3.6170
3.5970
2.9987
2.9685
2.9575
2.8359
2.8278
2.8174
2.8099
2.7988
2.7911
2.7660
2.7560
2.7453
2.7345
2.7236
2.7131
2.7036
2.6137
2.5819
2.5485
2.5390
2.5121
2.4946
2.1929
2.1805
2.1685
2.1600
2.1538
2.1479
2.1348
2.1219
2.0531
2.0452
2.0332
2.0268
OMe
OMe
Me
N
MeO
O
OMe
(-)-Runanine (2)
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
1.0184
2.9528
3.4342
3.1789
3.1486
1.0080
1.1613
2.0550
1.1371
4.0654
2.1677
1.1797
1.0227
193.818
165.378
147.775
147.080
137.973
134.478
126.919
110.955
110.404
77.256
77.003
76.748
67.194
60.701
60.619
56.064
55.761
51.256
48.464
47.866
37.107
36.219
29.678
25.215
22.965
OMe
OMe
Me
N
MeO
O
OMe
(-)-Runanine (2)
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

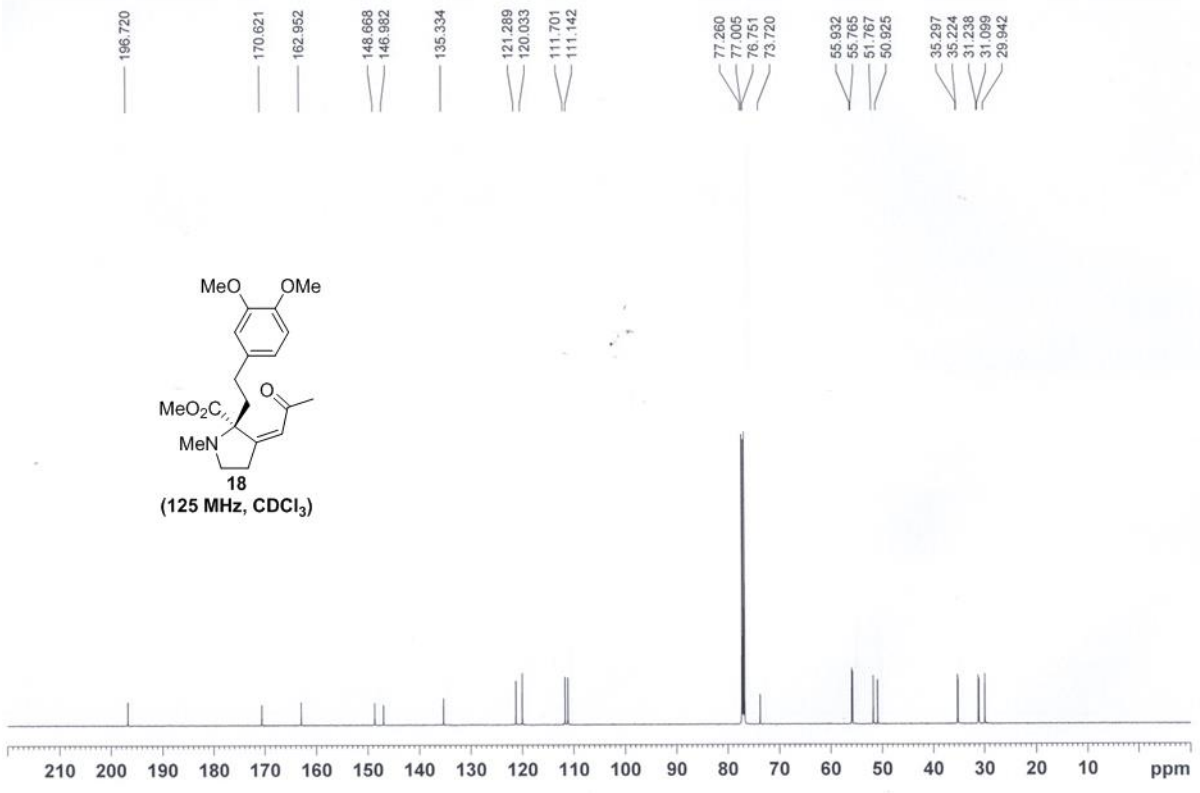


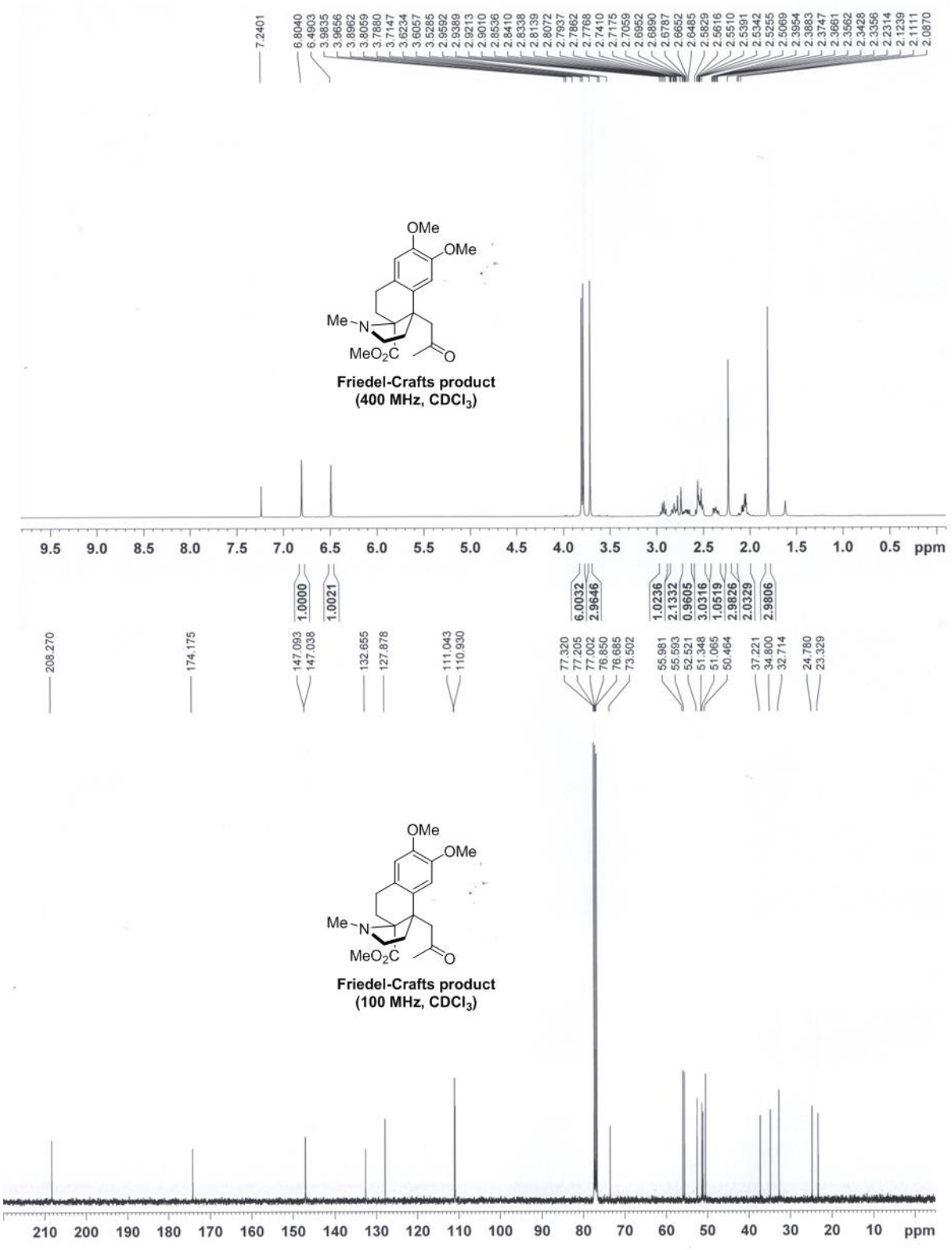
(-)-Runanine isomer 2'
(600 MHz, $CDCl_3$)

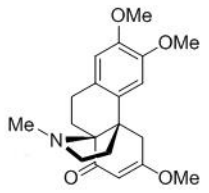


(-)-Runanine isomer 2'
(150 MHz, $CDCl_3$)

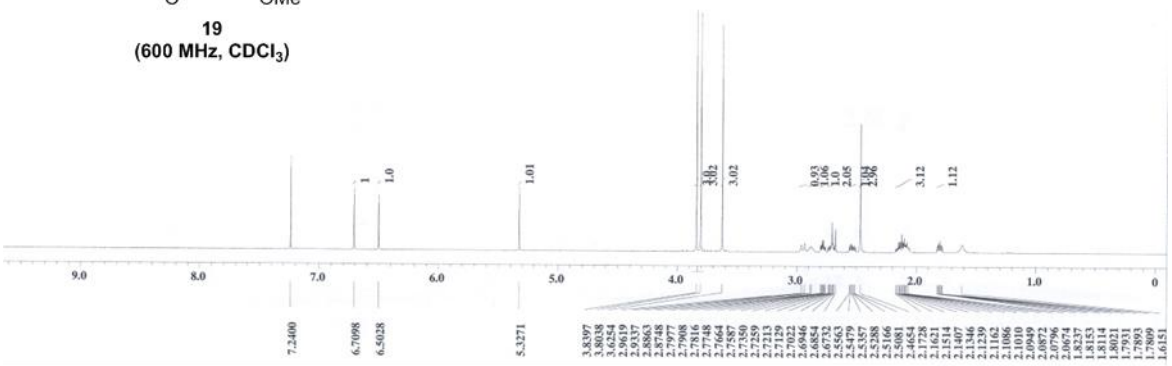

7.2402
6.7303
6.7143
6.6422
6.6251
6.6175
6.2925
3.8226
3.8129
3.6402
3.0653
3.0493
3.0355
2.7486
2.7383
2.7321
2.7098
2.7050
2.6949
2.6894
2.6737
2.6685
2.6487
2.6411
2.6233
2.6151
2.5406
2.5176
2.4499
2.4398
2.4220
2.4121
2.3982
2.3879
2.2750
2.2242
2.2137
2.1992
2.1892
2.1730
2.1628
2.1334
2.0900
2.0816
2.0621
2.0571
MeO
OMe
MeO2C
MeN
O
18
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0316
2.0530
1.0000
3.2459
3.0415
3.1619
1.0358
1.9744
1.1430
1.0312
1.1124
3.0830
1.0937
3.1836
1.2141

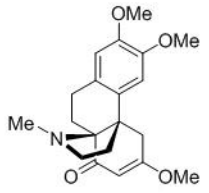

196.720
170.621
162.952
148.668
146.982
135.334
121.289
120.033
111.701
111.142
77.260
77.005
76.751
73.720
55.932
55.765
51.767
50.925
35.297
35.224
31.238
31.099
29.942
MeO
OMe
MeO2C
MeN
O
18
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.2401
6.8040
6.4903
3.9835
3.9656
3.8962
3.8059
3.7880
3.7147
3.6234
3.6057
3.5285
2.9592
2.9389
2.9213
2.9010
2.8536
2.8410
2.8338
2.8139
2.8072
2.7937
2.7862
2.7768
2.7410
2.7175
2.7059
2.6952
2.6890
2.6787
2.6652
2.6485
2.5829
2.5616
2.5510
2.5391
2.5342
2.5255
2.5069
2.3954
2.3883
2.3747
2.3661
2.3562
2.3428
2.3356
2.2314
2.1239
2.1111
2.0870
OMe
OMe
Me
N
MeO2C
O
Friedel-Crafts product
(400 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0000
1.0021
6.0032
2.9646
1.0236
2.1332
0.9605
3.0316
1.0519
2.9826
2.0329
2.9806
208.270
174.175
147.093
147.038
132.655
127.878
111.043
110.930
77.320
77.205
77.002
76.850
76.685
73.502
55.981
55.593
52.521
51.348
51.065
50.464
37.221
34.800
32.714
24.780
23.329
OMe
OMe
Me
N
MeO2C
O
Friedel-Crafts product
(100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

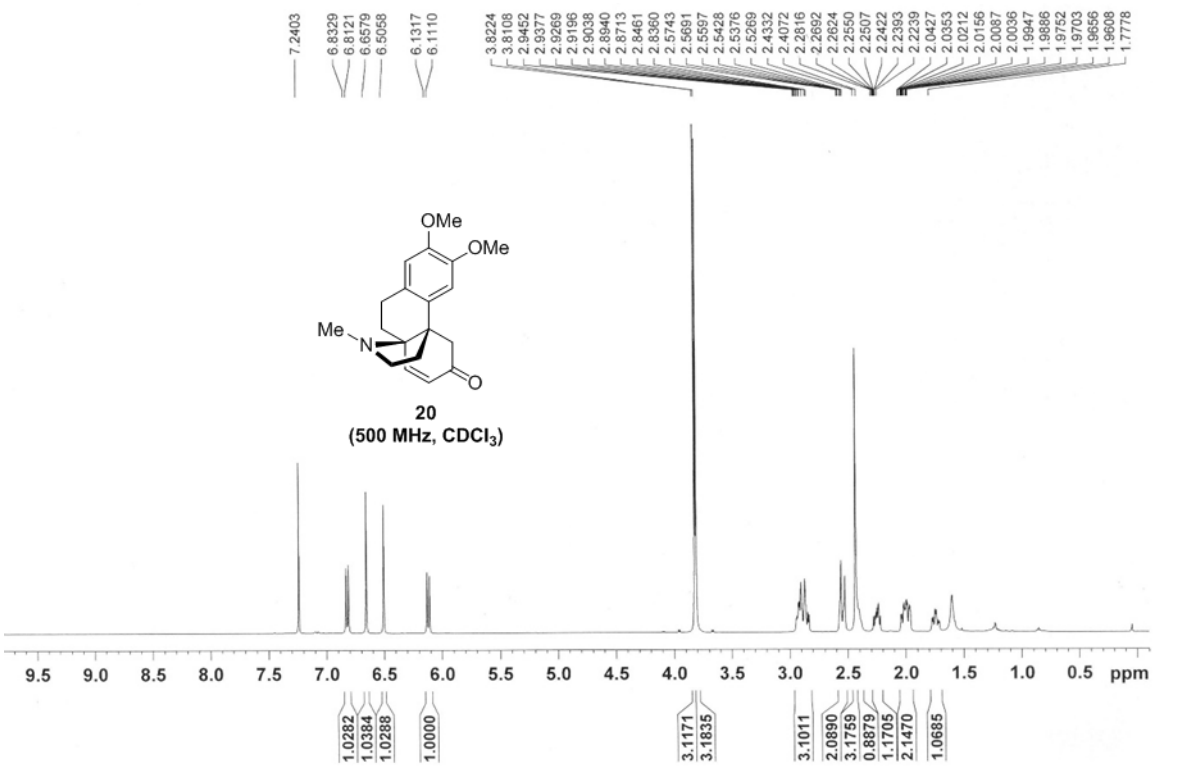


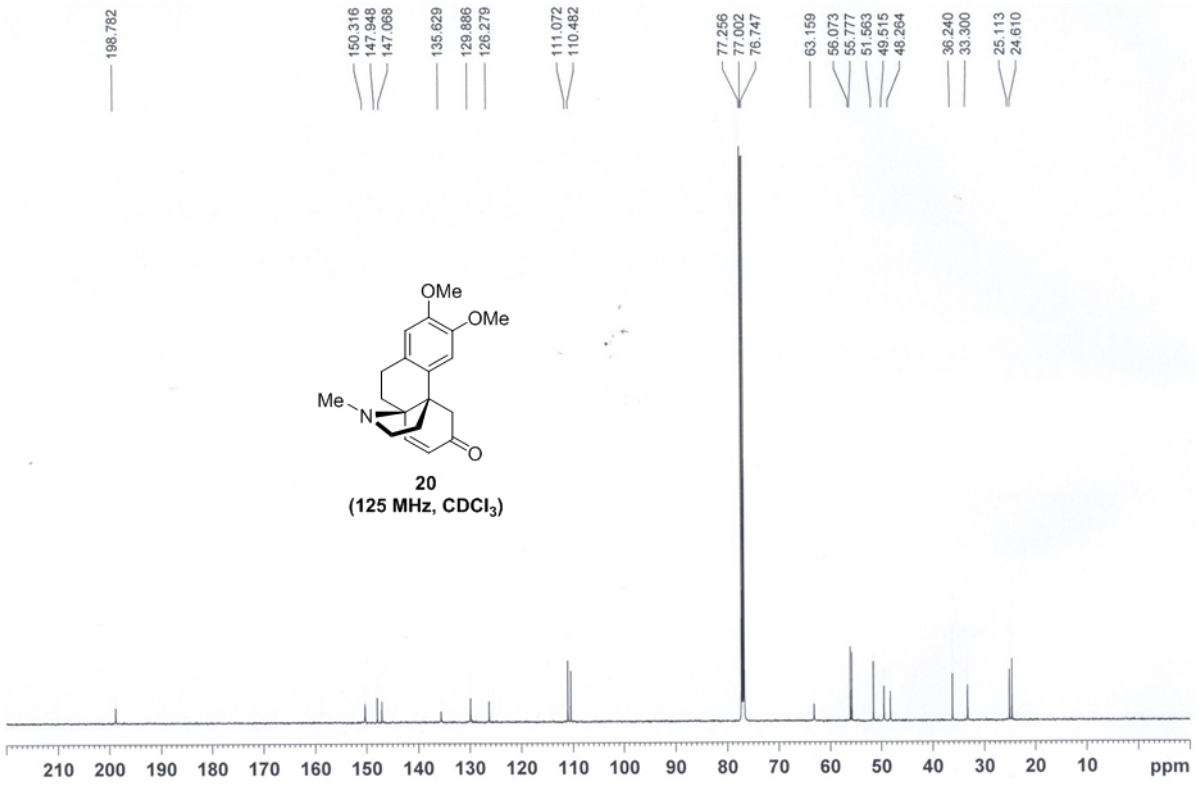
19
(600 MHz, $CDCl_3$)





19
(150 MHz, $CDCl_3$)


7.2403
6.8329
6.8121
6.6579
6.5058
6.1317
6.1110
3.8224
3.8108
2.9452
2.9377
2.9269
2.9196
2.9038
2.8940
2.8713
2.8461
2.8360
2.5743
2.5691
2.5597
2.5428
2.5376
2.5269
2.4332
2.4072
2.2816
2.2692
2.2624
2.2550
2.2507
2.2422
2.2393
2.2239
2.0427
2.0353
2.0212
2.0156
2.0087
2.0036
1.9947
1.9886
1.9752
1.9703
1.9656
1.9608
1.7778
OMe
OMe
Me
N
O
20
(500 MHz, CDCl3)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.0282
1.0384
1.0288
1.0000
3.1171
3.1835
3.1011
2.0890
3.1759
0.8879
1.1705
2.1470
1.0685


198.782
150.316
147.948
147.068
135.629
129.886
126.279
111.072
110.482
77.256
77.002
76.747
63.159
56.073
55.777
51.563
49.515
48.264
36.240
33.300
25.113
24.610
OMe
OMe
Me
N
O
20
(125 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm