Electronic Supplementary Information

Enantioselective Total Synthesis of (+)-Methoxystemofoline and (+)-Isomethoxystemofoline

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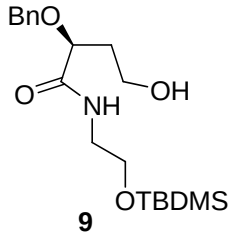
Contents (38 pages):

General Methods. Melting points were uncorrected. Infrared spectra were measured using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were obtained using electrospray ionization and an ICR analyzer (ESI-MS) for high resolution mass spectra (HRMS). Silica gel (300-400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl acetate/hexane. Ether and THF were distilled over sodium benzophenone ketyl under N_2. Dichloromethane was distilled over calcium hydride under N_2.

(*S*)-2-(Benzyloxy)-*N*-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-hydroxybutanamide (9)



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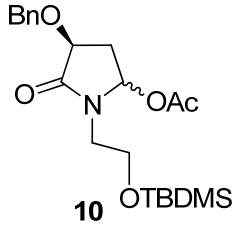
To a cooled solution (0 ºC) of the known (*S*)-α-benzyloxy-γ-lactone[1] **S-8** (9.77 g, 50.9 mmol) in methanol (230 mL) under N_2 was added 2-((*tert*-butyldimethylsilyl)oxy)ethanamine (13.36 g, 76.3 mmol) in methanol (30 mL). The reaction mixture was stirred at room temperature for 3 days. Then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/1) to give hydroxy amide **9** (16.8 g, yield: 90%) as a white solid. M.p. 52-57 °C; $[\alpha]_D^{20}$ –45.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3417, 2952, 2927, 2855, 1661, 1530, 1470, 1454, 1381, 1255, 1094, 836, 777, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 1.95-2.08 (m, 2H), 2.92 (br s, 1H), 3.34-3.47 (m, 2H), 3.65-3.71 (m, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 4.05 (t, *J* = 6.3 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 7.09 (br s, 1H), 7.28-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.4 (2C), 18.2, 25.8 (3C), 35.5, 41.2, 59.6, 61.7, 72.8, 78.7, 128.0 (2C), 128.3, 128.7 (2C), 136.9, 172.7; HRMS calcd for $C_{19}H_{33}NO_4Si$ [M+Na$^+$]: 390.2071; found: 390.2075.

(4*S*)-4-(Benzyloxy)-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-5-oxopyrrolidin-2-yl acetate (10)

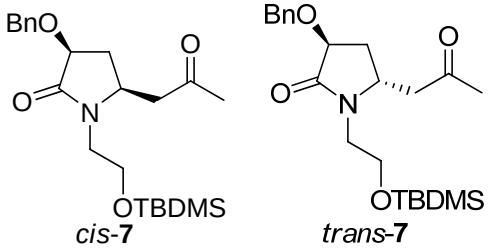


10

To a cooled (0 ºC) suspension of Dess-Martin periodinane (7.94 g, 18.90 mmol) in anhydrous CH_2Cl_2 (50 mL), a solution of hydroxy amide **9** (5.31 g, 14.54 mmol) in CH_2Cl_2 (20 mL) was added. Then reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (30 mL) and a saturated aqueous $Na_2S_2O_3$ (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with MeOH (50 mL), and then silicon gel (2 g) was added. The suspension was refluxed at 75 ºC for 2 h, then silicon gel was filtered and solvent was removed under reduced pressure to give hemiaminal which was used in the next step without purification. The hemiaminal and DMAP (50 mg) was dissolved in CH_2Cl_2 (70 mL) under N_2, and cooled down to 0 ºC. Then Et_3N (6.07 mL, 43.6 mmol) and Ac_2O (3.42 mL, 36.4 mmol) were added successively. After being stirred at room temperature overnight, the reaction was quenched with a saturated aqueous $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/6) to give compound **10** (4.38 g, yield: 73% from **9**) as an inseparable diastereomeric mixture in a ratio of 57 : 43 (^{1}H NMR). Colorless oil. IR (film) ν_{max}: 2953, 2929, 2856, 1716, 1453, 1423, 1362, 1237, 1192, 1102, 1010, 923, 836, 778, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, data read from the diastereoisomeric mixture) $\delta_{\text{major diastereomer}}$: 0.03 (s, 6H), 0.86 (s, 9H), 1.94-2.01 (m,

1H), 2.08 (s, 3H), 2.57-2.69 (m, 1H), 3.60-3.81 (m, 4H), 4.02 (dd, *J* = 3.0, 8.3 Hz, 1H), 4.75 (d, *J* = 12.0 Hz 1H), 4.93 (d, *J* = 12.0 Hz, 1H), 6.21 (dd, *J* = 1.7, 6.4 Hz, 1H), 7.24-7.40 (m, 5H); $\delta_{\text{minor diastereomer}}$: 0.04 (s, 6H), 0.88 (s, 9H), 2.02 (s, 3H), 2.14-2.28 (m, 1H), 2.35 (dd, *J* = 7.8, 14.0 Hz, 1H), 3.10-3.20 (m, 2H), 3.60-3.81 (m, 2H), 4.32 (dd, *J* = 8.2, 8.2 Hz, 1H), 4.77 (d, *J* = 11.9 Hz, 1H), 5.01 (d, *J* = 11.9 Hz, 1H), 6.30 (d, *J* = 5.7 Hz, 1H), 7.24-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$ data read from the diastereoisomeric mixture) $\delta_{\text{major diastereomer}}$: −5.6 (2C), 18.0, 21.0, 25.7 (3C), 33.8, 42.9, 60.5, 72.0, 73.2, 83.1, 127.7, 127.9 (2C), 128.3 (2C), 137.5, 170.3, 172.6; $\delta_{\text{minor diastereomer}}$: −5.5 (2C), 18.0, 21.0, 25.7 (3C), 34.6, 43.2, 60.8, 72.2, 72.9, 83.0, 127.8, 127.9 (2C), 128.3 (2C), 137.5, 170.3, 174.3; HRMS calcd for $C_{21}H_{33}NO_5Si$ [M+Na^+]: 430.2020; found: 430.2023.

(3*S*,5*S*)-3-(Benzyloxy)-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-5-(2-oxopropyl)pyrrolidin-2-one (*cis*-7) and (3*S*,5*R*)-3-(Benzyloxy)-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-5-(2-oxopropyl)pyrrolidin-2-one (*tran*-7)



cis-**7** *trans*-**7**

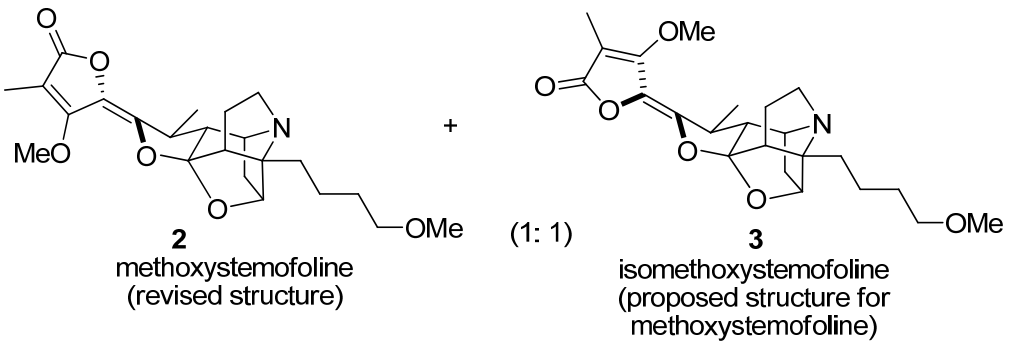
To a cooled solution (−78 ºC) of acetate **10** (8.06 g, 19.8 mmol) in CH_2Cl_2 (200 mL) under N_2 was added dropwise TMSOTf (1.8 mL, 9.9 mmol). After being stirred for 15 min at −78 ºC, trimethyl(prop-1-en-2-yloxy)silane (6.6 mL, 39.6 mmol) was added dropwise into the reaction mixture. After being stirred for 2 h at −78 ºC, the reaction was warmed slowly to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous $NaHCO_3$ (30 mL) at 0-5 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used in the next

step without further purification. The crude partially *O*-desilylation keto-lactam and imidazole (2.69 g, 39.6 mmol) was dissolved in CH_2Cl_2 (90 mL) and cooled down to 0 ºC, then a solution of *t*-butyldimethylsilyl chloride (3.58g, 23.8 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was warmed to room temperature and stirred for 4 h. Then the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL) under an ice-bath. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/4) to give *cis*-**7** (5.61 g, yield: 70% from **10**) and *trans*-**7** (1.52 g, yield: 20% from **10**).

cis-**7**: colorless oil. $[\alpha]_D^{20}$ –49.5 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 2953, 2929, 2857, 1697, 1454, 1421, 1376, 1255, 1098, 1027, 836, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (d, *J* = 2.5 Hz, 6H), 0.85 (s, 9H), 1.61 (td, *J* = 5.0, 13.7 Hz, 1H), 2.12 (s, 3H), 2.53 (td, *J* = 7.6, 13.7 Hz, 1H), 2.61 (dd, *J* = 9.8, 17.7 Hz, 1H), 3.03-3.15 (m, 2H), 3.60-3.77 (m, 3H), 3.97-4.07 (m, 2H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.90 (d, *J* = 11.9 Hz, 1H), 7.23-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.5 (2C), 18.2, 25.8 (3C), 30.7, 33.6, 43.5, 48.1, 52.5, 61.3, 72.0, 75.4, 127.7, 127.9 (2C), 128.4 (2C), 137.9, 172.9, 206.1; HRMS calcd for $C_{22}H_{35}NO_4Si$ [M+Na^+]: 428.2228; found: 428.2229.

trans-**7**: colorless oil. $[\alpha]_D^{20}$ –57.5 (*c* 2.0, $CHCl_3$); IR (film) ν_{max}: 2950, 2928, 2857, 1715, 1459, 1253, 1098, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.95 (ddd, *J* = 3.4, 7.6, 13.5 Hz, 1H), 2.13 (s, 3H), 2.23-2.32 (m, 1H), 2.40 (dd, *J* = 9.6, 17.4 Hz, 1H), 3.00 (dd, *J* = 3.4, 17.4 Hz, 1H), 3.04-3.12 (m, 1H), 3.61 (td, *J* = 4.8, 14.3 Hz, 1H), 3.69-3.80 (m, 2H), 4.12 (t, *J* = 7.6 Hz, 1H), 4.15-4.22 (m, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.93 (d, *J* = 12.0 Hz, 1H), 7.23-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.5, –5.4, 18.2, 25.9 (3C), 30.6, 33.5, 43.6, 47.1, 52.4, 61.4, 71.9, 74.5, 127.7, 127.9 (2C), 128.4 (2C), 137.9, 172.9, 205.7; HRMS calcd for $C_{22}H_{35}NO_4Si$ [M+Na^+]: 428.2228; found: 428.2232.

Methoxystemofoline (2) and isomethoxystemofoline (3)



The mixture of thiocarbonate **25** (10.0 mg, 0.02 mmol) in $P(OMe)_3$ (1.0 mL, 8.5 mmol) was heated to 120 °C in a sealed tube for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (5.0 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the solvents and $P(OMe)_3$ were removed under reduced pressure. The residue was purified by preparative thin layer chromatography (silica gel, CH_2Cl_2/ MeOH = 20: 1) to provide methoxystemofoline (**2**) (2.6 mg, yield: 31%) and isomethoxystemofoline (**3**) (2.5 mg, yield: 30%).

Methoxystemofoline (**2**): colorless oil; $[\alpha]_D^{20}$ +71~85 (*c* 0.1, CH_3OH) {lit.[3] $[\alpha]_D^{21.6}$ +75.6 (*c* 0.037, CH_3OH)}; IR (film) ν_{max}: 2926, 2853, 1745, 1693, 1619, 1454, 1396, 1365, 1239, 1157, 1139, 1121, 1068, 1025, 1000, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.32 (m, 1H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.64-1.50 (m, 5H), 1.75-1.65 (m, 2H), 1.85-1.77 (m, 1H), 1.93-1.86 (m, 1H), 1.96 (d, *J* = 12.2 Hz, 1H), 2.03 (s, 3H), 2.68 (d, *J* = 6.0 Hz, 1H), 3.04-2.95 (m, 1H), 3.22-3.08 (m, 2H), 3.32 (s, 3H), 3.38 (t, *J* = 6.3 Hz, 2H), 3.46 (br s, 1H), 4.10 (s, 3H), 4.27 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ8.7, 16.2, 21.9, 26.7, 30.0, 31.7, 33.1, 36.3, 46.0, 47.5, 50.1, 58.5, 59.4, 60.8, 72.5, 78.7, 82.7, 98.6, 113.6, 128.8, 149.9, 163.3, 170.5; HRMS calcd for $C_{23}H_{31}NO_6$ [M+H^+]: 418.2224; found: 418.2226.

Isomethoxystemofoline (**3**): colorless oil; $[\alpha]_D^{20}$ +220~226 (*c* 0.1, CH_3OH) {lit.[2] $[\alpha]_D^{25}$ +249 (*c* 0.29 CH_3OH)}; IR (film) ν_{max}: 2922, 2851, 1745, 1619, 1458, 1396, 1366, 1140, 1117, 1058, 1007, 988, 966 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35-1.31 (m, 1H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.53-1.45 (m, 1H), 1.64-1.55 (m, 4H), 1.73-1.68 (m, 1H), 1.85-1.78 (m, 2H), 1.92-1.87 (m, 1H), 1.94 (d, *J* = 12.2 Hz, 1H),

2.06 (s, 3H), 2.69 (d, J = 6.0 Hz, 1H), 3.02-2.96 (m, 1H), 3.15-3.05 (m, 2H), 3.32 (s, 3H), 3.37 (t, J = 6.4 Hz, 2H), 3.45 (br s, 1H), 4.13 (s, 3H), 4.26 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ9.3, 18.5, 22.0, 26.8, 30.2, 31.9, 33.5, 34.7, 47.7, 47.8, 50.2, 58.8, 59.0, 61.1, 72.7, 78.7, 83.0, 98.8, 112.9, 128.1, 148.6, 163.0, 169.9; HRMS calcd for $C_{23}H_{31}NO_6$ [M+H$^+$]: 418.2224; found: 418.2225.

Table 1. ^{1}H NMR Data for methoxystemofoline (**2**) and isomethoxystemofoline (**3**)

1H NMR			
Natural product reported by Xu[3] (300 MHz, $CDCl_3$)	Semi-synthetic reported by Pyne[2] (500 MHz, $CDCl_3$)	Our Synthetic compound **2** (400 MHz, $CDCl_3$)	Our Synthetic compound **3** (500 MHz, $CDCl_3$)
	4.26 (br s, 1H)	4.27 (br s, 1H)	4.26 (br s, 1H)
4.15 (s, 3H)	4.13 (s, 3H)	4.10 (s, 3H)	4.13 (s, 3H)
	3.45 (br s, 1H)	3.46 (br s, 1H)	3.45 (br s, 1H)
	3.37 (t, *J* = 6.0 Hz, 2H)	3.38 (t, *J* = 6.3 Hz, 2H)	3.37 (t, *J* = 6.4 Hz, 2H)
3.31 (s, 3H)	3.32 (s, 3H)	3.32 (s, 3H)	3.32 (s, 3H)
	3.15-3.06 (m, 1H)	3.22-3.08 (m, 2H)	3.15-3.05 (m, 2H)
	3.15-3.06 (m, 1H)		
	3.01-2.96 (m, 1H)	3.04-2.95 (m, 1H)	3.02-2.96 (m, 1H)
2.61 (m , 1H)	2.69 (d, *J* = 6.0 Hz, 1H)	2.68 (d, *J* = 6.0 Hz, 1H)	2.69 (d, *J* = 6.0 Hz, 1H)
2.03 (s, 3H)	2.07 (s, 3H)	2.03 (s, 3H)	2.06 (s, 3H)
	1.94 (d, *J* = 11.5 Hz, 1H)	1.96 (d, *J* = 12.2 Hz, 1H)	1.94 (d, *J* = 12.2 Hz, 1H)
	1.91-1.87 (m, 1H)	1.93-1.86 (m, 1H)	1.92-1.87 (m, 1H)
	1.84-1.79 (m, 1H)	1.85-1.77 (m, 1H)	1.85-1.78 (m, 2H)
	1.84-1.79 (m, 1H)		
	1.70 (d, *J* = 12.0 Hz, 1H)	1.75-1.65 (m, 2H)	1.73-1.68 (m, 1H)
	1.56-1.62 (m, 2H)	1.64-1.50 (m, 5H)	1.64-1.55 (m, 4H)
	1.56-1.62 (m, 2H)		1.53-1.45 (m, 1H)
1.44 (d, *J* 6.7 Hz, 3H)	1.37 (d, *J* = 6.0 Hz, 3H)	1.44 (d, *J* = 6.7 Hz, 3H)	1.37 (d, *J* = 6.5 Hz, 3H)
	1.35-1.32 (m, 2H)	1.39-1.32 (m, 1H)	1.35-1.31 (m, 1H)

Table 2. ^{13}C NMR Data for methoxystemofoline (**2**) and isomethoxystemofoline (**3**)

13C NMR			
Natural product reported by Xu[3] (75 MHz, $CDCl_3$)	Semi-synthetic reported by Pyne[2] (125 MHz, $CDCl_3$)	Our Synthetic compound **2** (125 MHz, $CDCl_3$)	Our Synthetic compound **3** (125 MHz, $CDCl_3$)
170.5 (s)	169.8 (C)	170.5	169.9
163.5 (s)	163.0 (C)	163.3	163.0
149.8 (s)	148.6 (C)	149.9	148.6
128.3 (s)	128.0 (C)	128.8	128.1
113.5 (s)	112.8 (C)	113.6	112.9
98.8 (s)	98.7 (C)	98.6	98.8
83.0 (s)	82.9 (C)	82.7	83.0
78.6 (d)	78.7 (CH)	78.7	78.7
72.4 (t)	72.7 (CH_2)	72.5	72.7
61.0 (d)	61.1 (CH)	60.8	61.1
59.4 (q)	59.7 (CH_3)	59.4	59.0
58.4 (q)	58.8 (CH_3)	58.5	58.8
50.1 (d)	50.2 (CH)	50.1	50.2
47.4 (d)	47.8 (CH)	47.5	47.8
46.0 (t)	47.7 (CH_2)	46.0	47.7
36.2 (d)	34.7 (CH)	36.3	34.7
33.0 (t)	33.5 (CH_2)	33.1	33.5
31.5 (t)	31.9 (CH_2)	31.7	31.9
30.0 (t)	30.2 (CH_2)	30.0	30.2
26.5 (t)	26.8 (CH_2)	26.7	26.8
21.9 (t)	22.0 (CH_2)	21.9	22.0
16.2 (q)	18.5 (CH_3)	16.2	18.5
8.7 (q)	9.3 (CH_3)	8.7	9.3

References:

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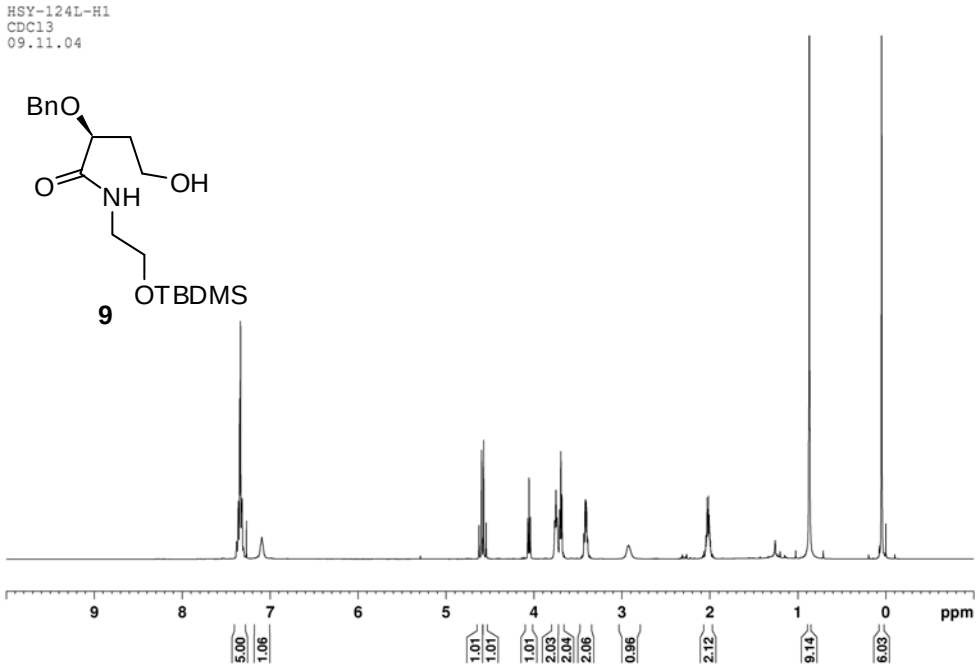
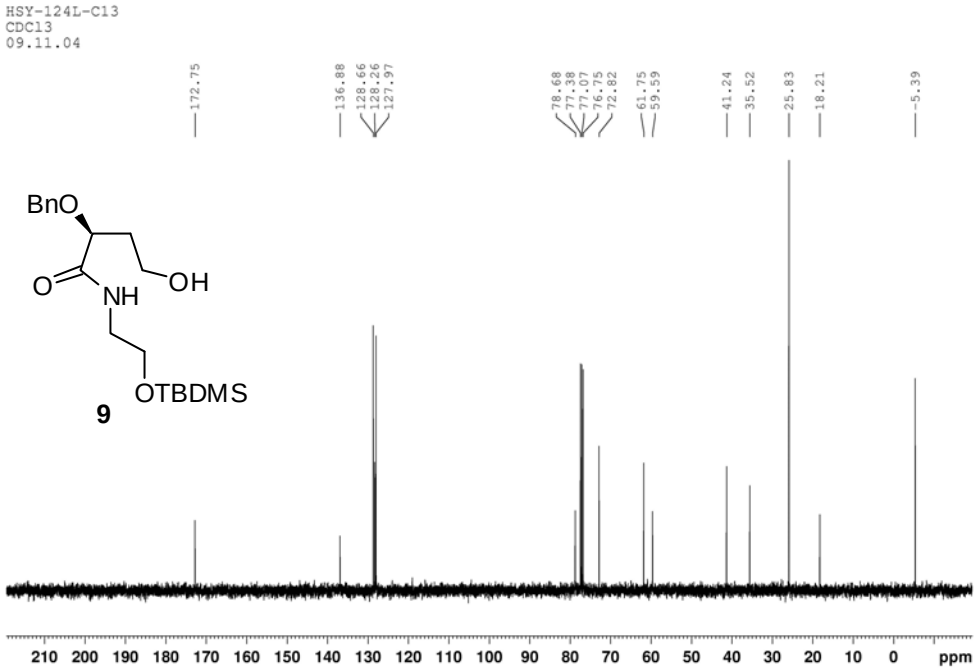
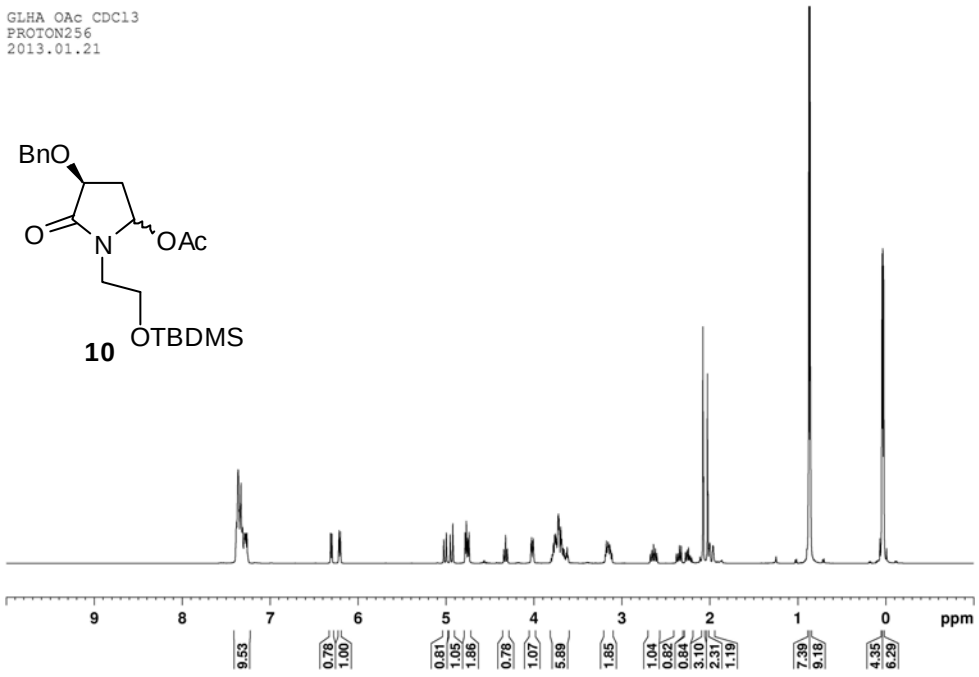
(3) Lin, H. W.; Xu, R. S. *Acta Chim. Sinica* **1991**, *49*, 1034-1037.

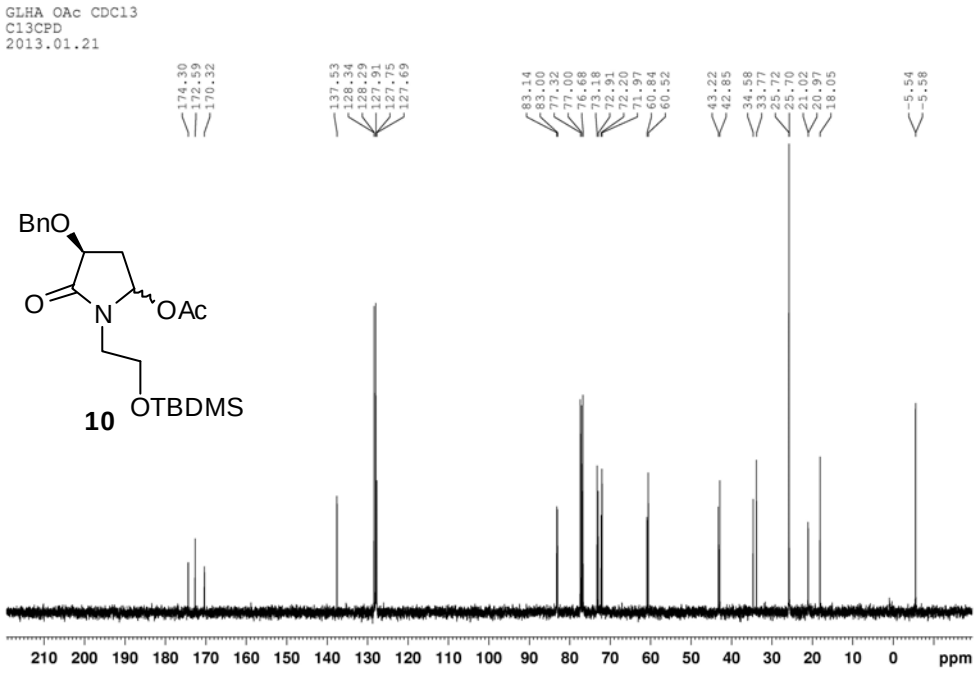
(*S*)-2-(Benzyloxy)-*N*-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-hydroxybutanamide (9)



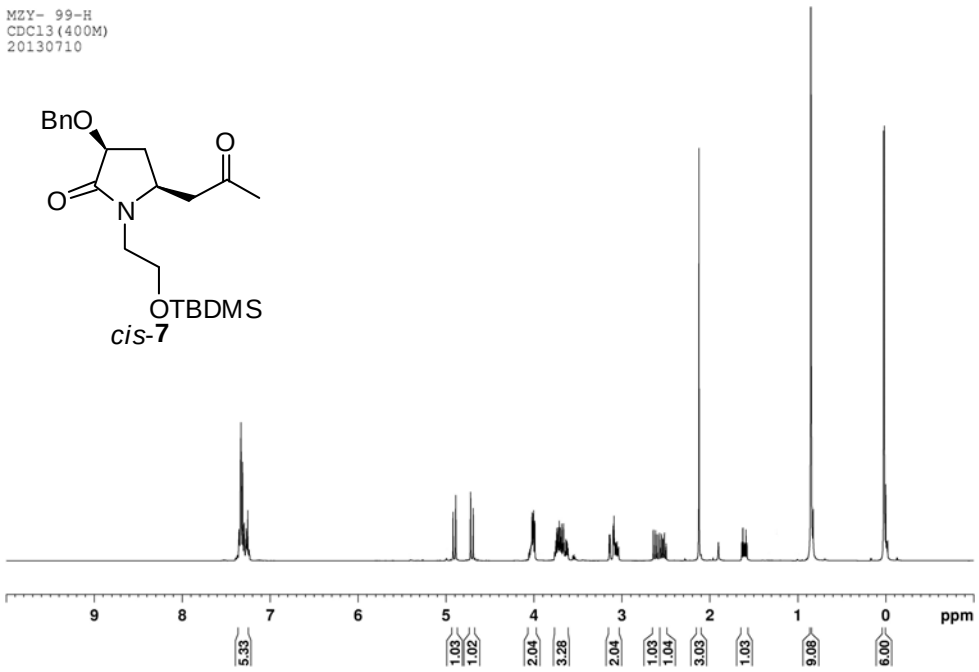


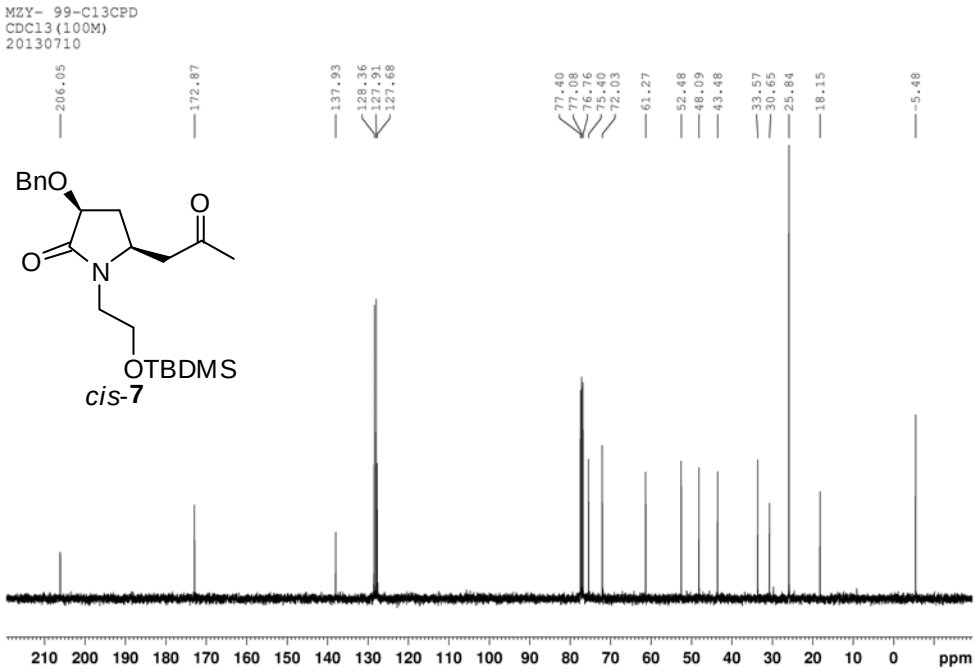
(4*S*)-4-(Benzyloxy)-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-5-oxopyrrolidin-2-yl acetate (10)



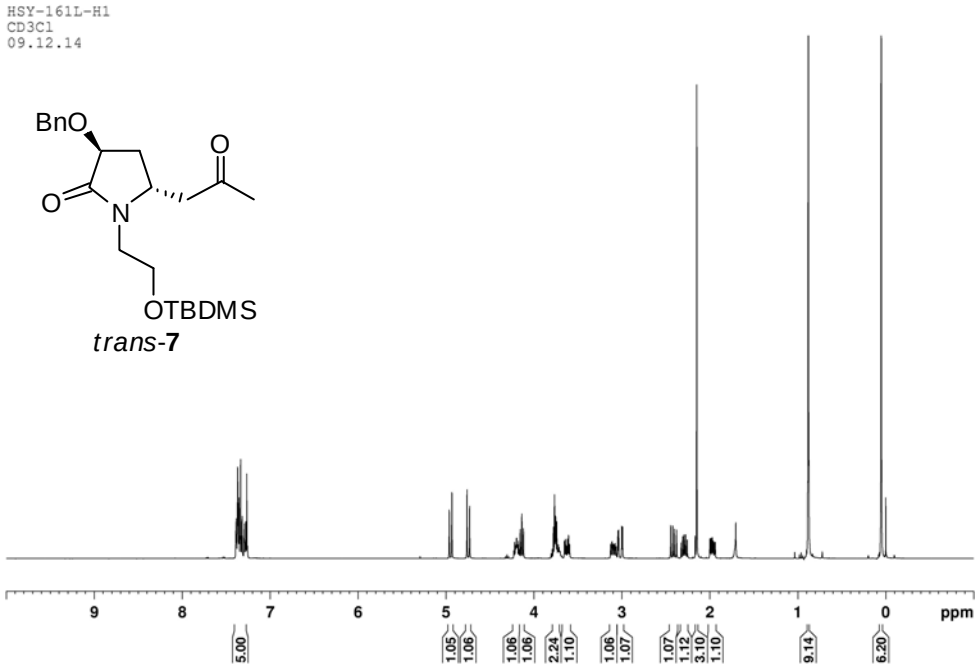


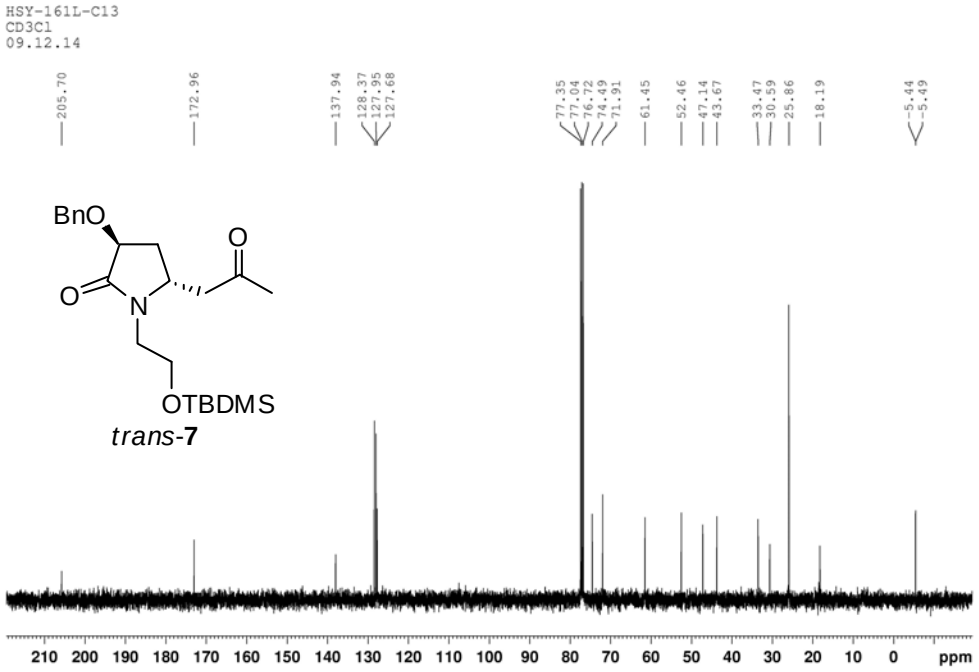
(3*S*,5*S*)-3-(Benzyloxy)-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-5-(2-oxopropyl)pyrrolidin-2-one (*cis*-7)



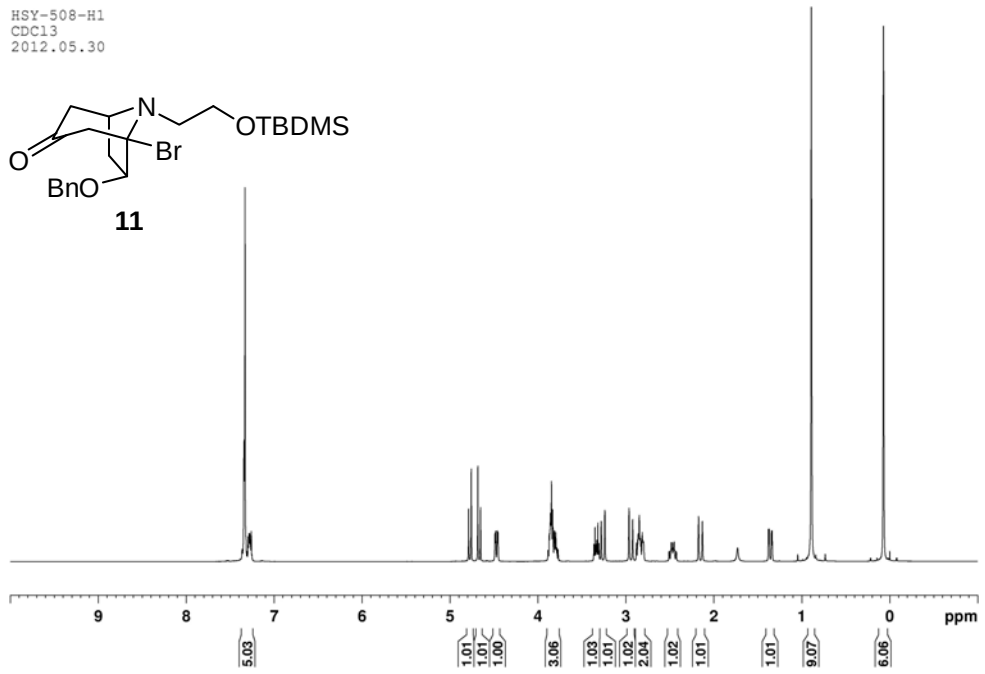


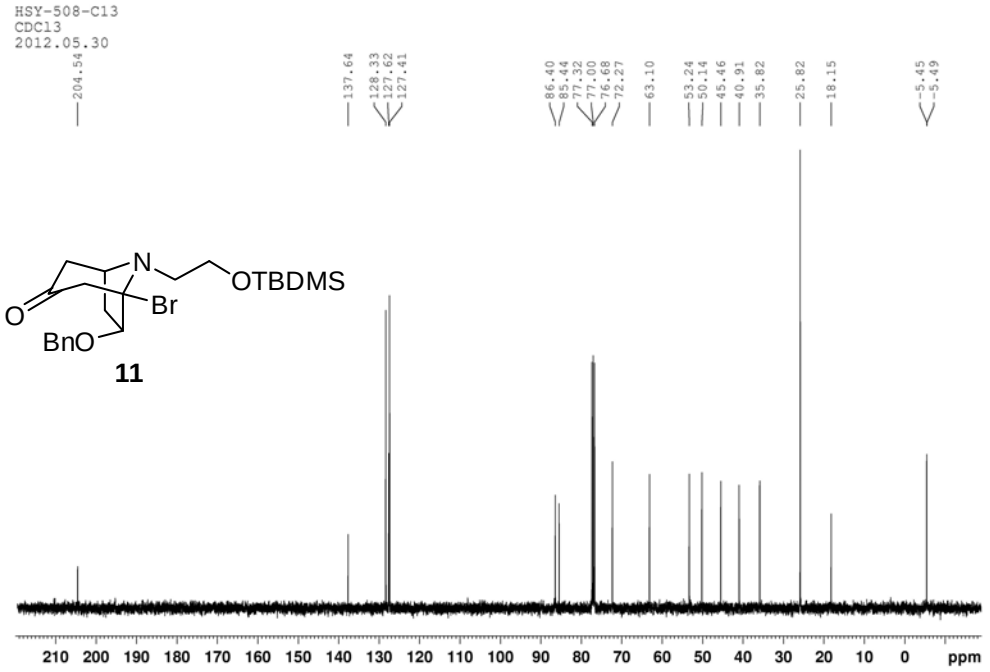
(3*S*,5*R*)-3-(Benzyloxy)-1-[2-(*tert*-butyldimethylsilyloxy)ethyl]-5-(2-oxopropyl)pyrrolidin-2-one (*tran*-7)



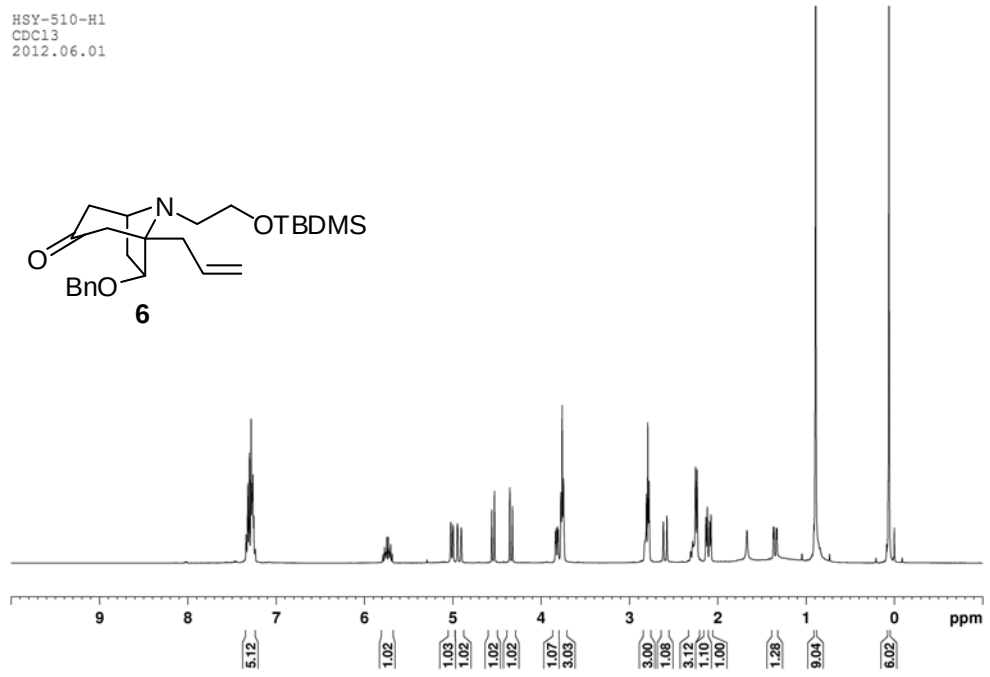


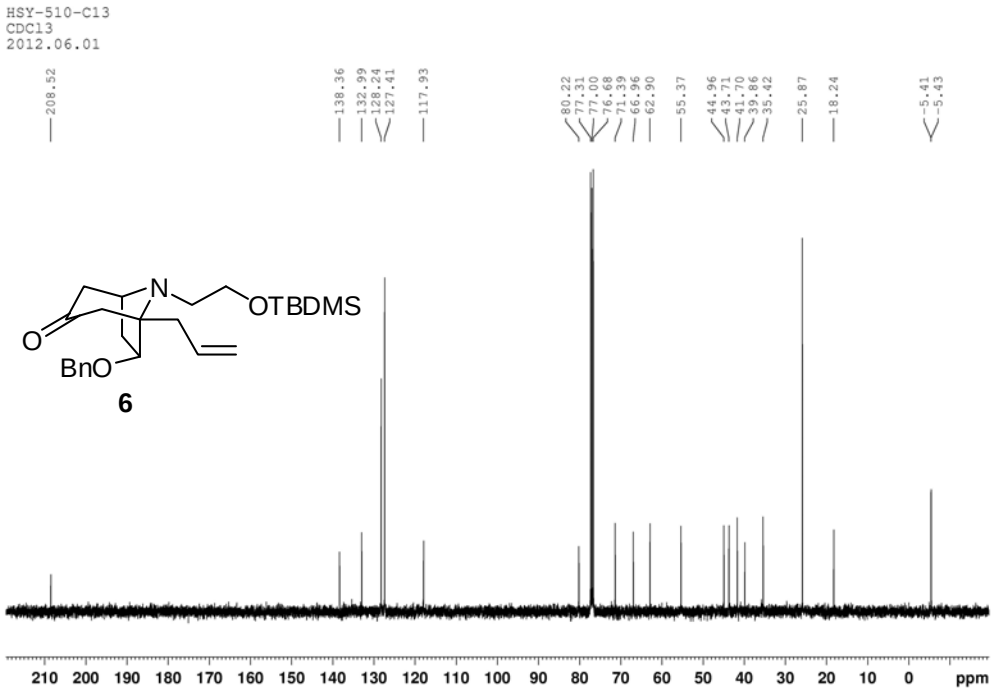
(1*R*,5*S*,7*S*)-7-(Benzyloxy)-1-bromo-8-[2-(*tert*-butyldimethylsilyloxy)ethyl]-8-azabicyclo[3.2.1]octan-3-one (11)





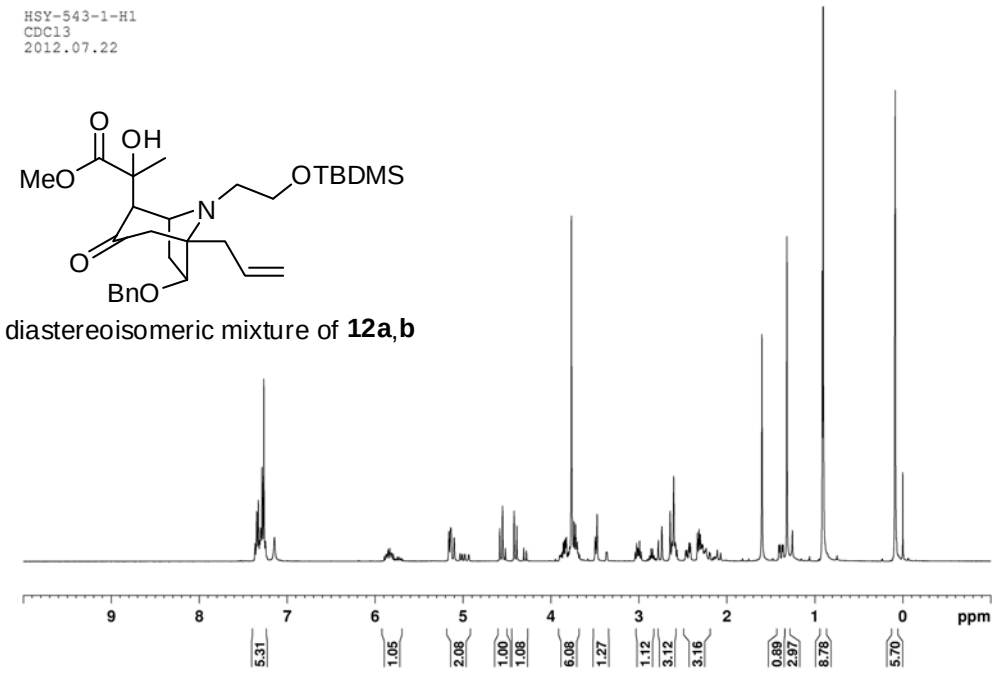
(1*S*,5*S*,7*S*)-1-Allyl-7-(benzyloxy)-8-[2-(*tert*-butyldimethylsilyloxy)ethyl]-8-azabicyclo[3.2.1]octan-3-one (6)

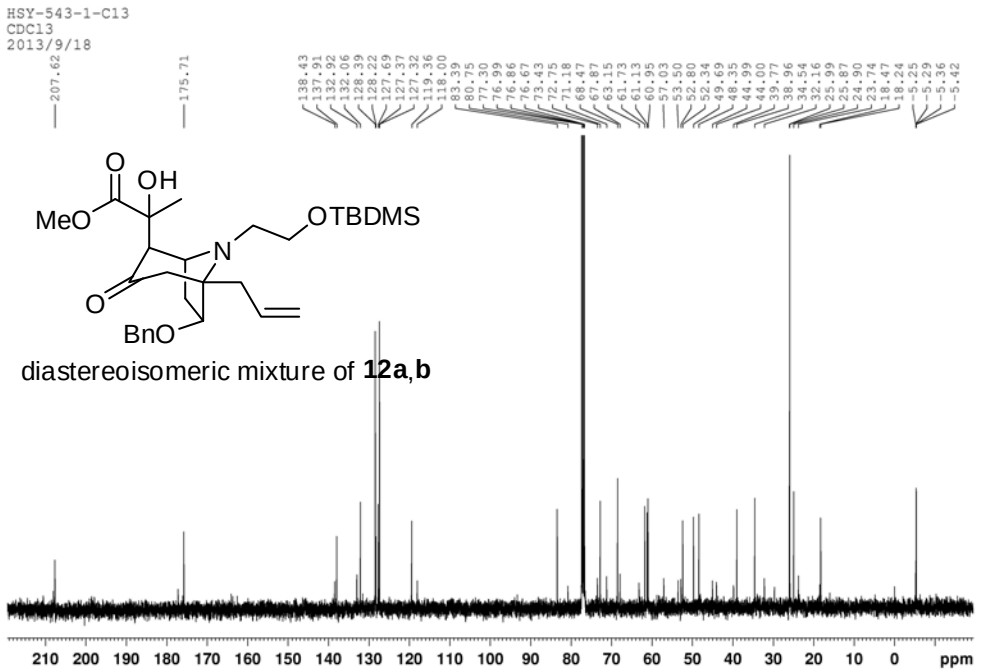


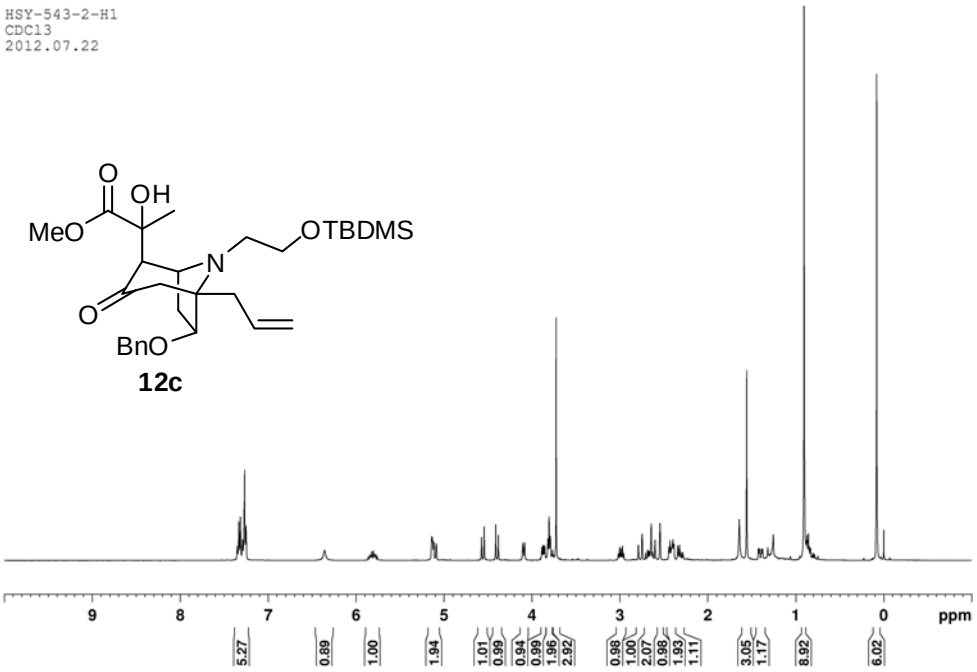


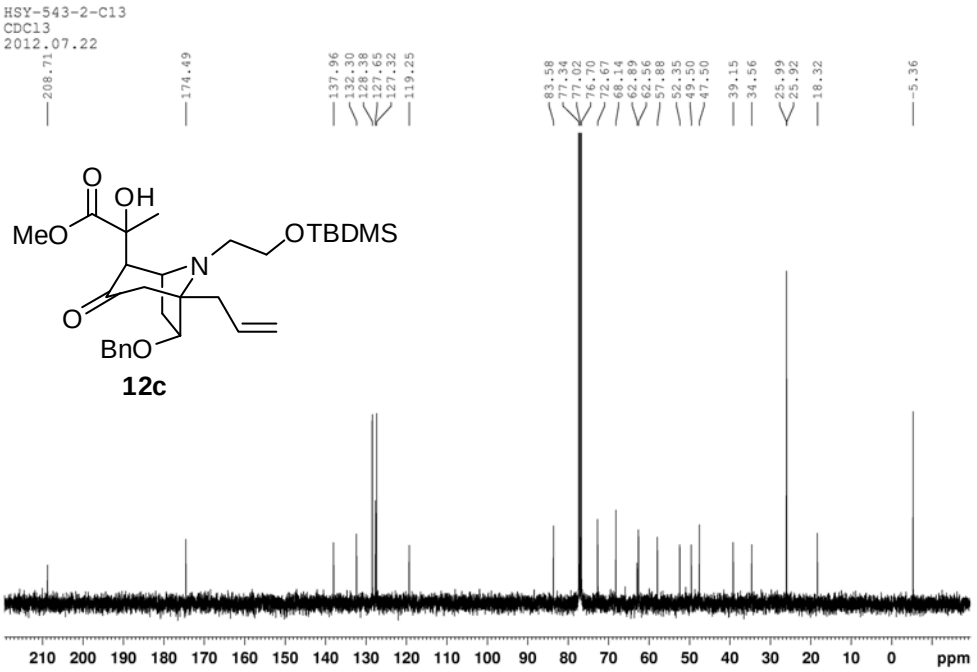
Methyl

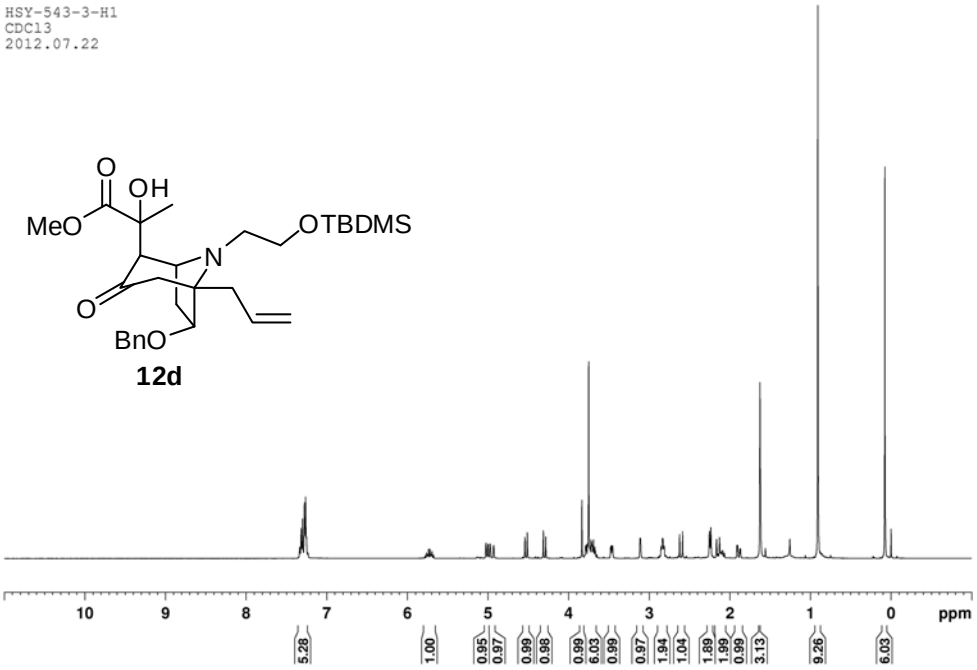
(*R*/*S*)-2-{(1*S*,2*R*/*S*,5*S*,6*S*)-5-allyl-6-(benzyloxy)-8-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-yl}-2-hydroxypropanoate (12)

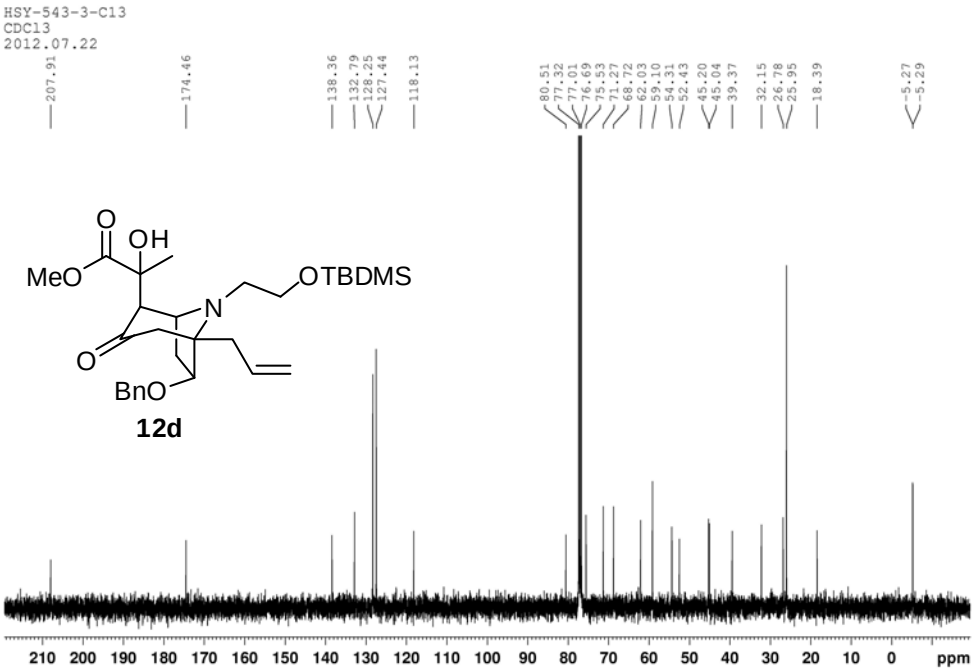





HSY-543-2-H1
CDCl3
2012.07.22
O
OH
MeO
OTBDMS
N
O
BnO
12c
9
8
7
6
5
4
3
2
1
0
ppm
5.27
0.89
1.00
1.94
1.01
0.99
0.94
0.99
1.96
2.92
0.98
1.00
2.07
0.98
1.93
1.11
3.05
1.17
8.92
6.02

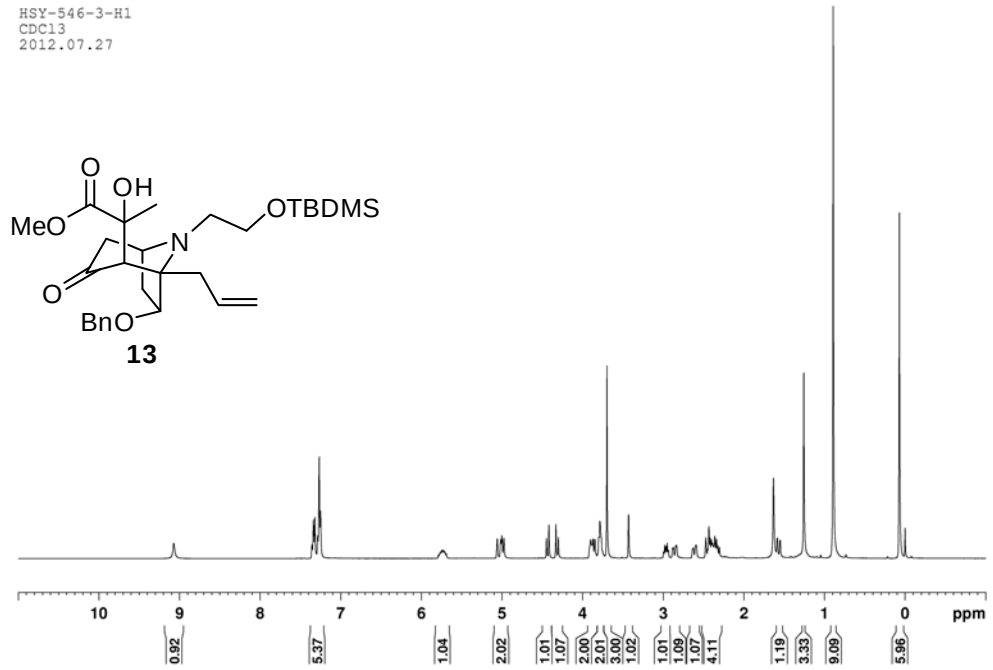

HSY-543-2-C13
CDCl3
2012.07.22
208.71
174.49
137.96
132.30
128.38
127.65
127.32
119.25
83.58
77.34
77.02
76.70
72.67
68.14
62.89
62.56
57.88
52.35
49.50
47.50
39.15
34.56
25.99
25.92
18.32
-5.36
O
OH
MeO
OTBDMS
N
O
BnO
12c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

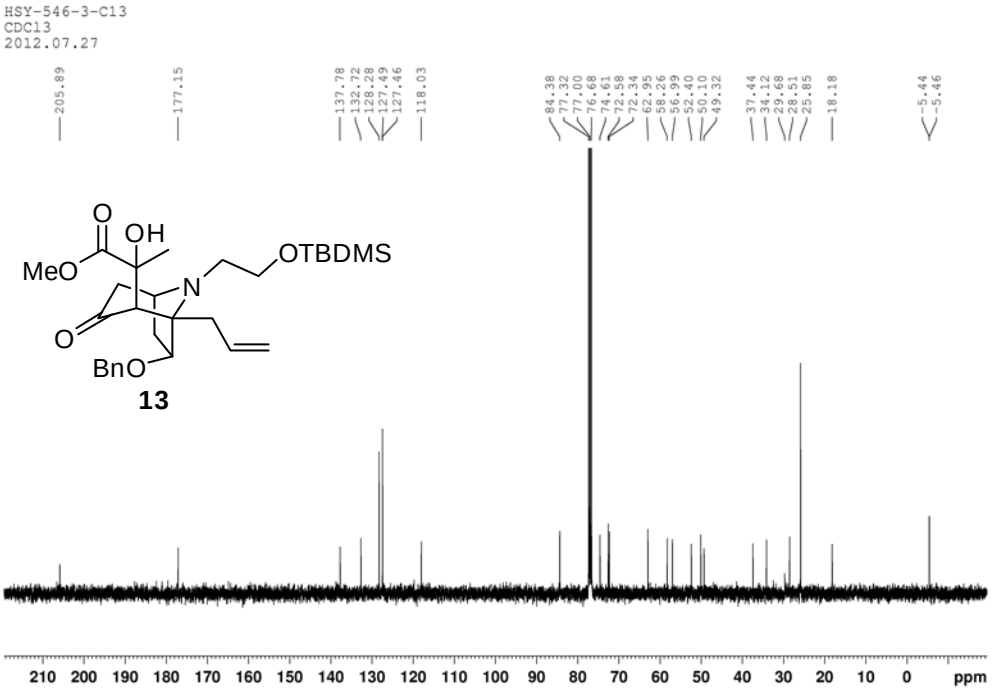

HSY-543-3-H1
CDCl3
2012.07.22
O
OH
MeO
OTBDMS
N
O
BnO
12d
10 9 8 7 6 5 4 3 2 1 0 ppm
5.28 1.00 0.95 0.97 0.99 0.98 0.99 6.03 0.99 0.97 1.94 1.04 1.89 1.99 0.99 3.13 9.26 6.03


HSY-543-3-C13
CDCl3
2012.07.22
207.91
174.46
138.36
132.79
128.25
127.44
118.13
80.51
77.32
77.01
76.69
75.53
71.27
68.72
62.03
59.10
54.31
52.43
45.20
45.04
39.37
32.15
26.78
25.95
18.39
-5.27
-5.29
O
OH
MeO
OTBDMS
N
O
BnO
12d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

Methyl

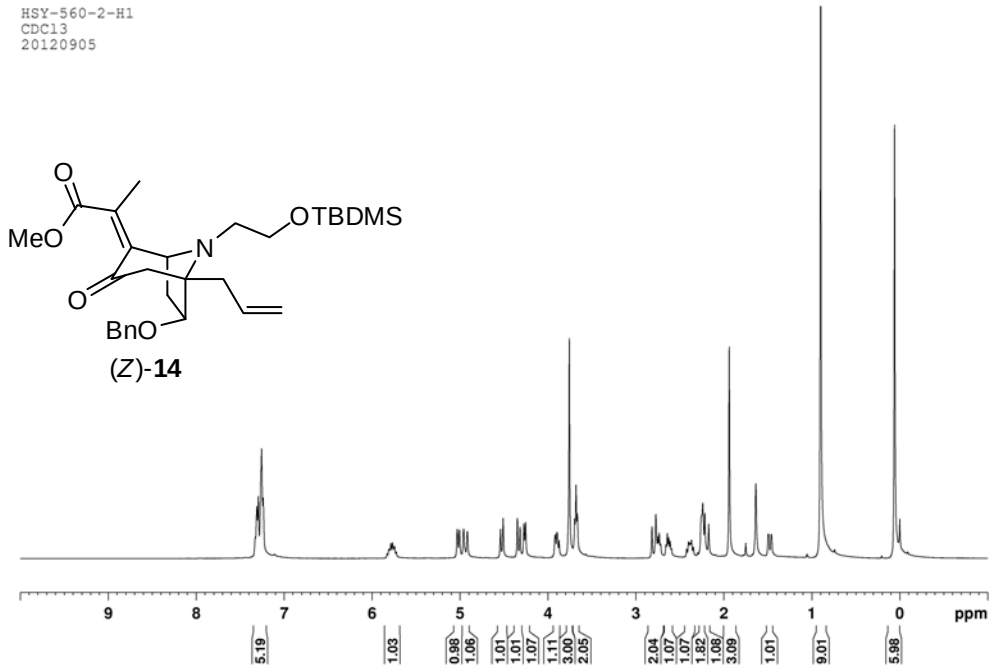
2-{(1*S*,5*S*,7*S*)-1-allyl-7-(benzyloxy)-8-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-yl}-2-hydroxypropanoate (13)

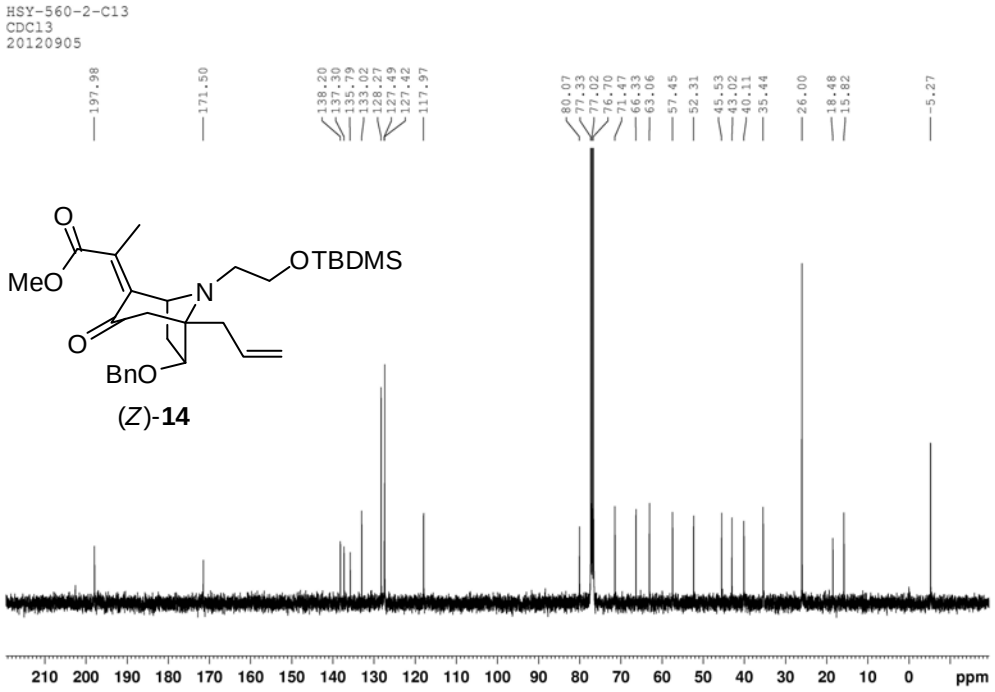




Methyl

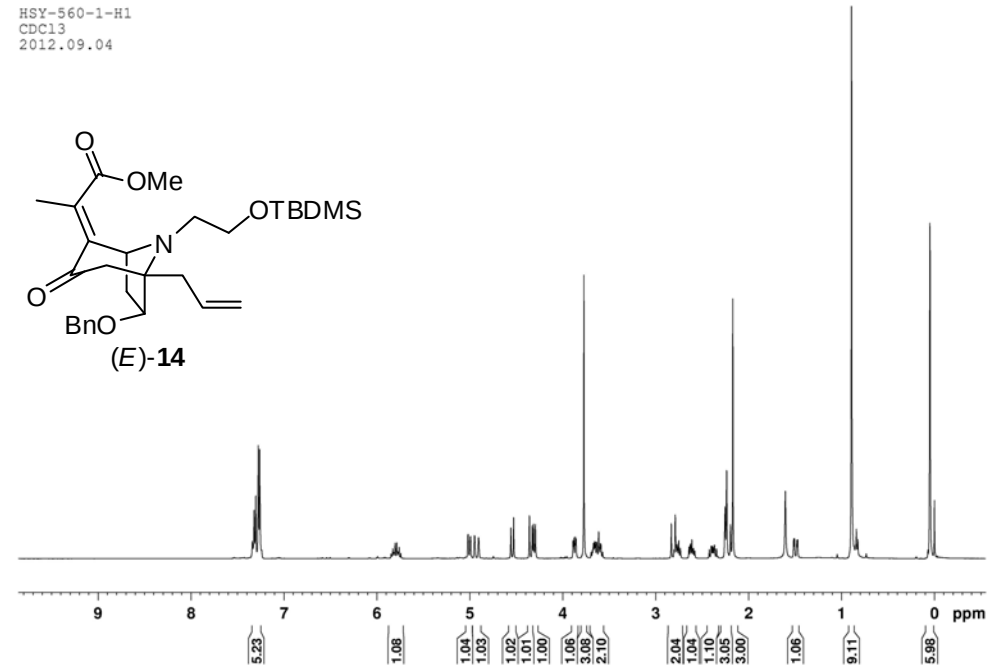
(*Z*)-2-{(1*S*,5*S*,6*S*)-5-allyl-6-(benzyloxy)-8-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate [(*Z*)-14]

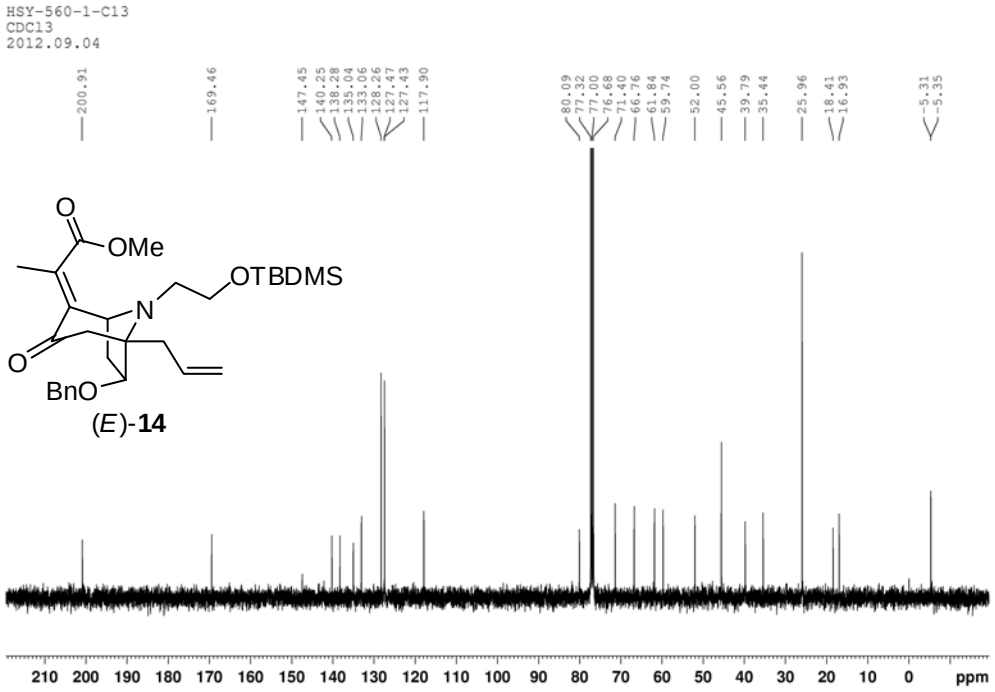




Methyl

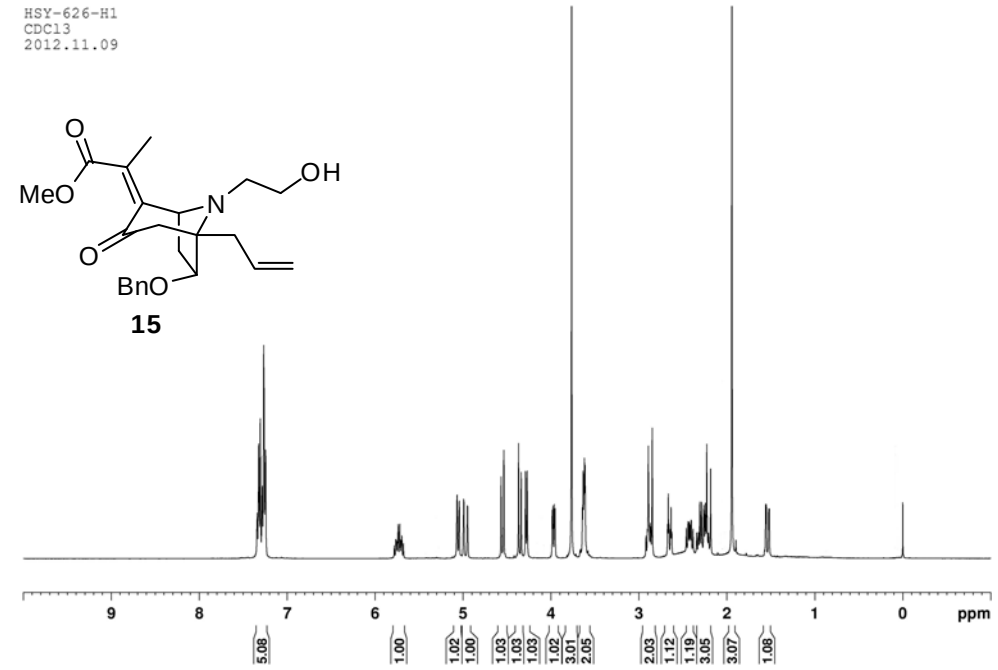
(*E*)-2-{(1*S*,5*S*,6*S*)-5-allyl-6-(benzyloxy)-8-[2-(*tert*-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate [(*E*)-14]

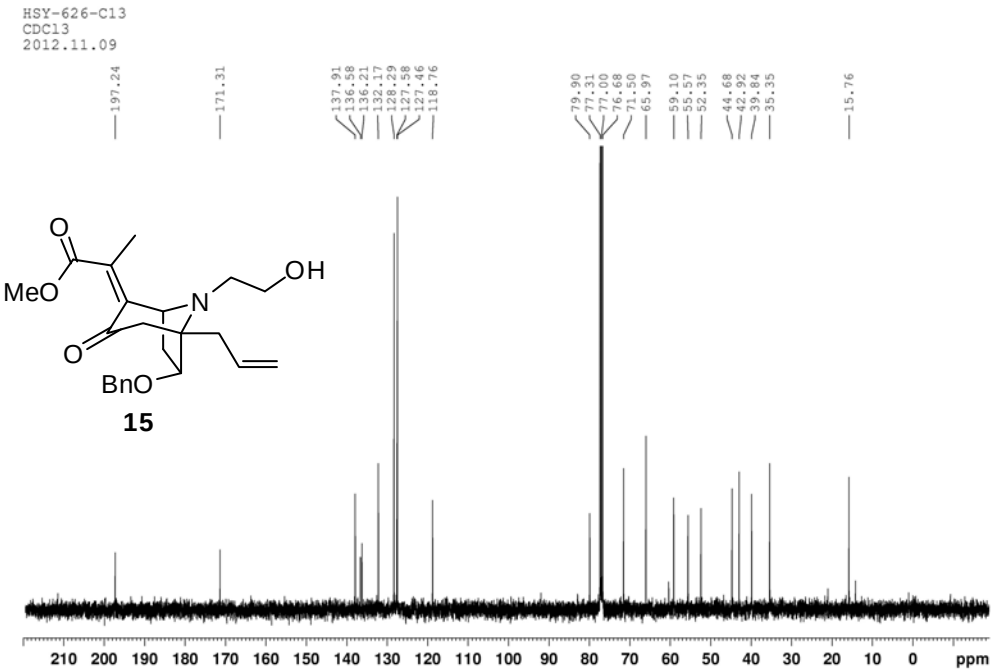




Methyl

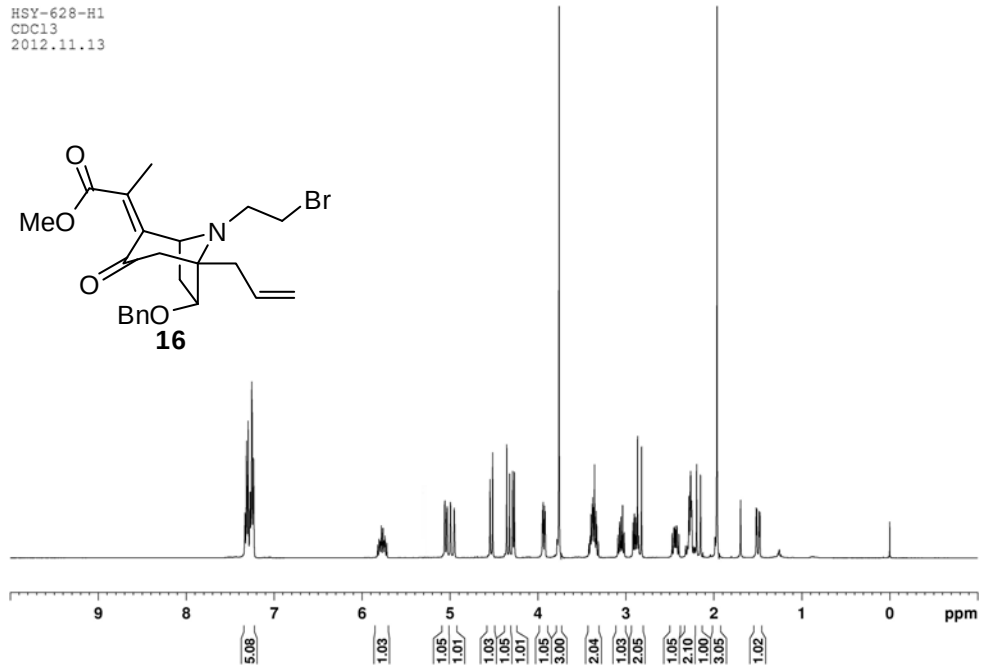
(*Z*)-2-{(1*S*,5*S*,6*S*)-5-allyl-6-(benzyloxy)-8-(2-hydroxyethyl)-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate (15)

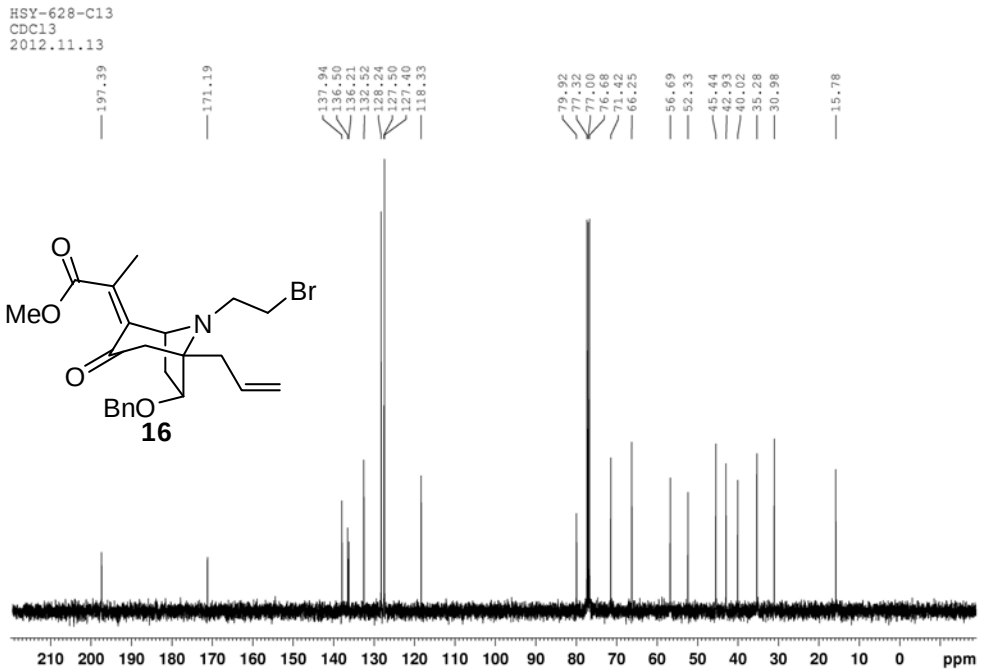




Methyl

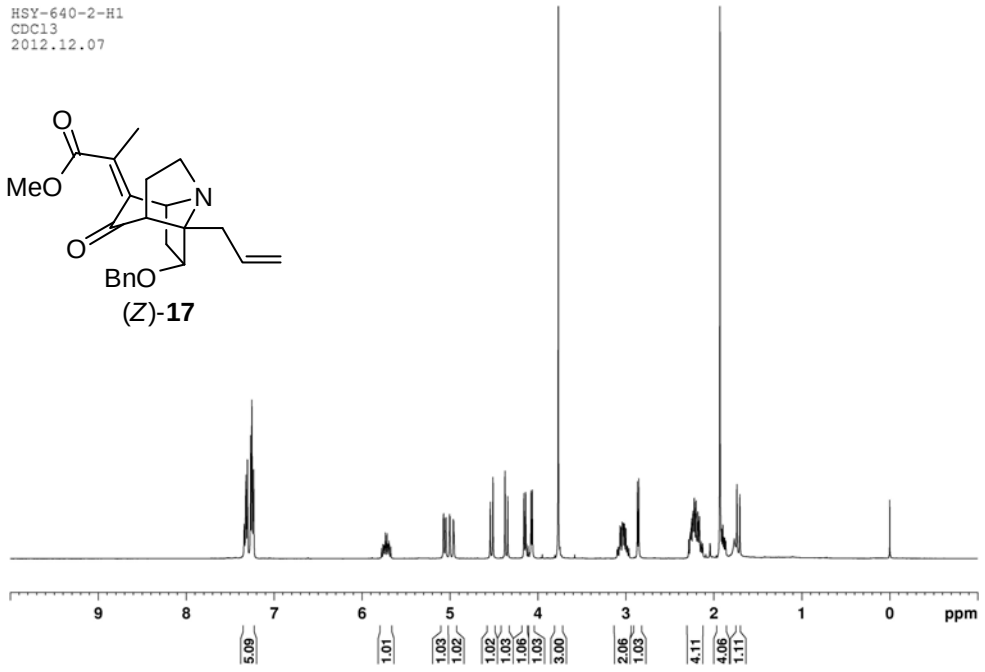
(*Z*)-2-{(1*S*,5*S*,6*S*)-5-allyl-6-(benzyloxy)-8-(2-bromoethyl)-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate (16)

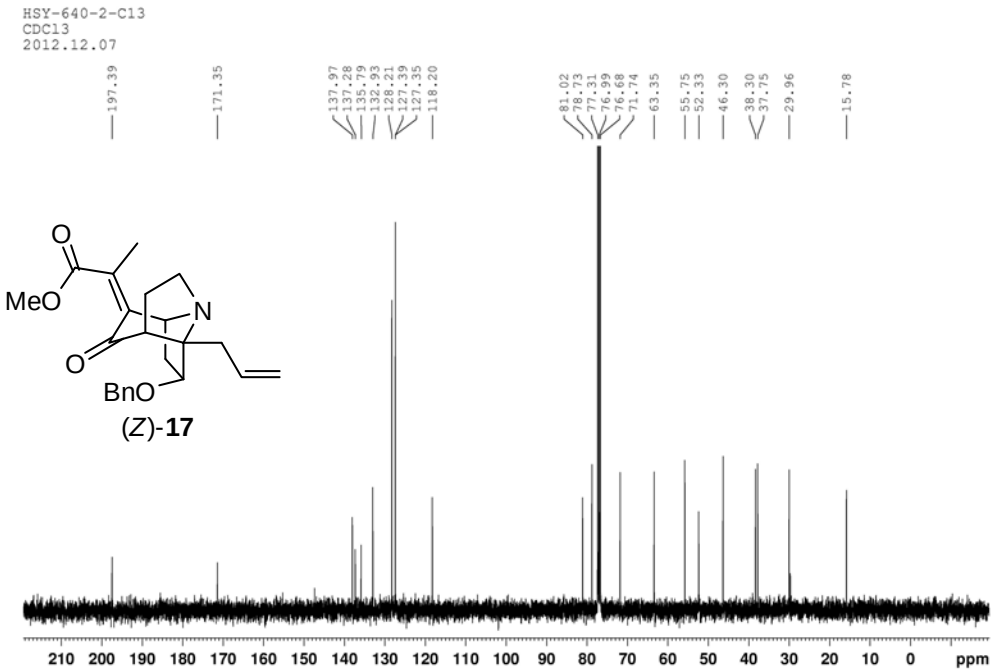




Methyl

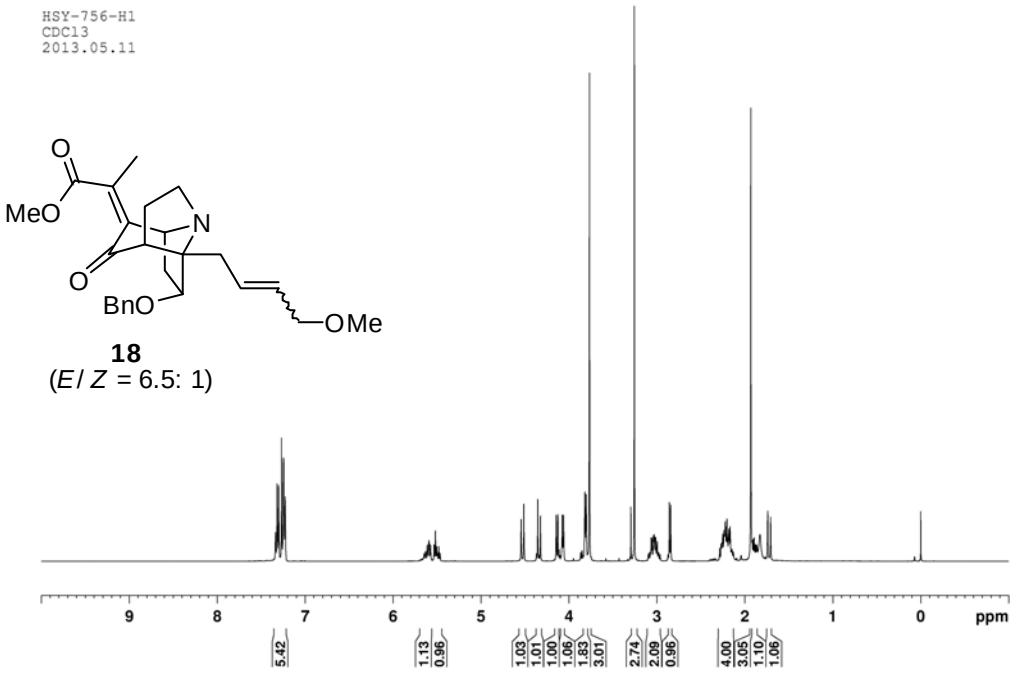
(*Z*)-2-[(1*R*,4*R*,5*S*,7*S*,7a*S*)-7a-allyl-7-(benzyloxy)-9-oxohexahydro-1*H*-1,5-ethanopyrrolizin-8-ylidene]propanoate [(*Z*)-17]

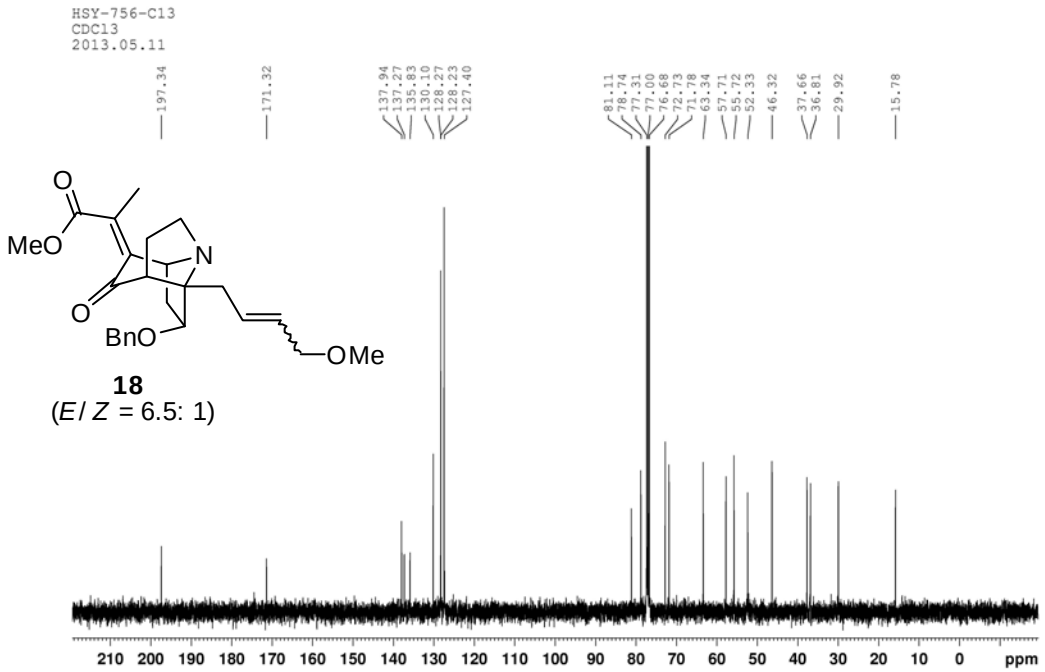




Methyl

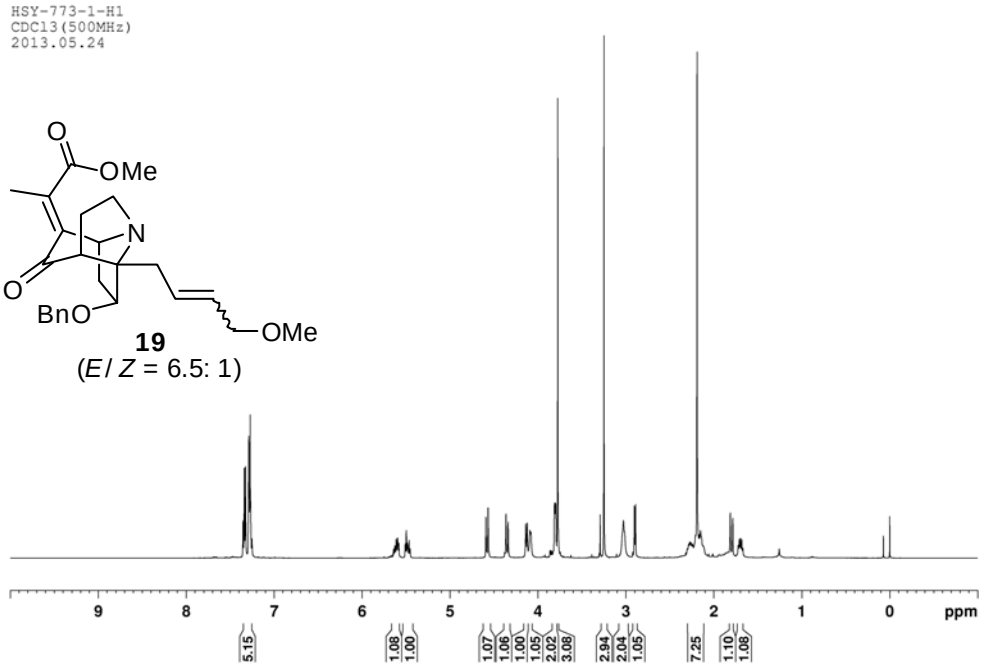
(*Z*)-2-{(1*R*,4*R*,5*S*,7*S*,7a*S*)-7-(benzyloxy)-7a-[(*E*)-4'-methoxybut-2'-en-1-yl]-9-oxoh exahydro-1*H*-1,5-ethanopyrrolizin-8-ylidene}propanoate (18) and 2'(*Z*)-isomer

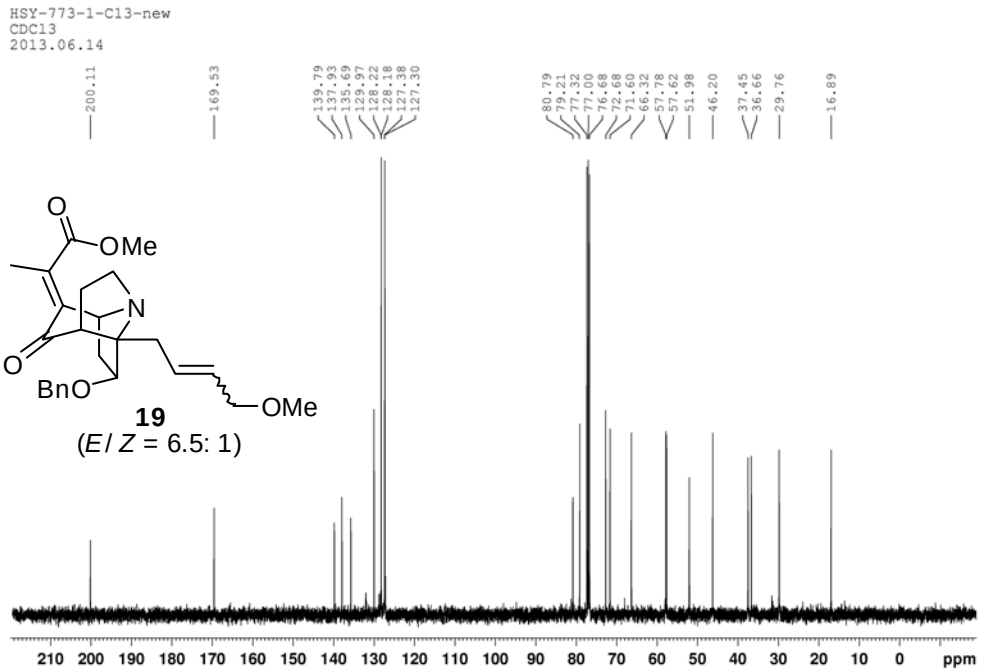




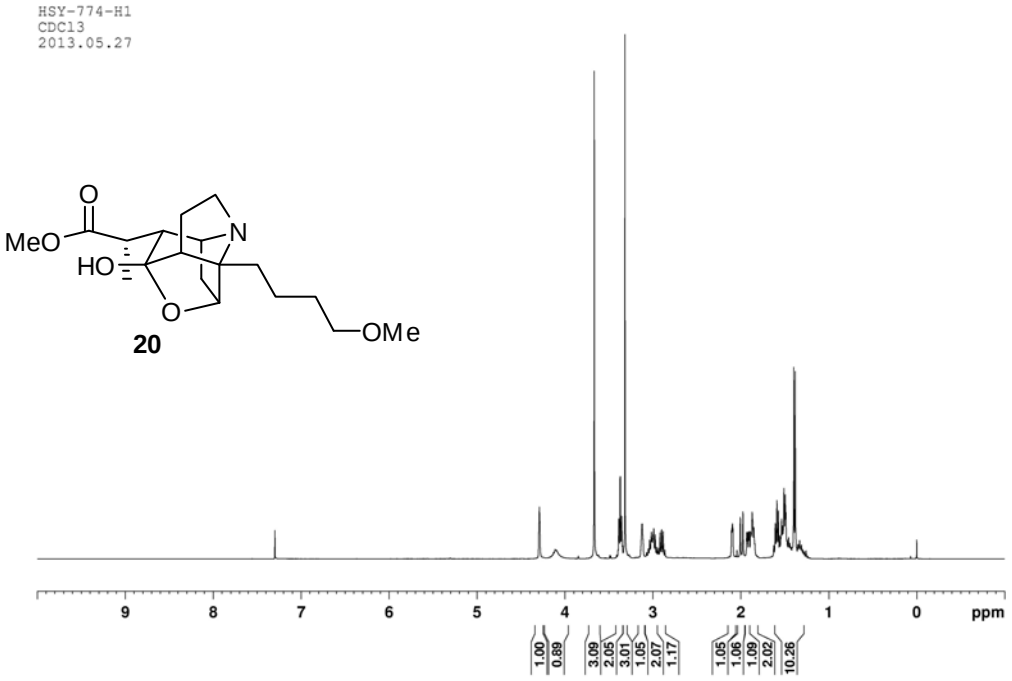
Methyl

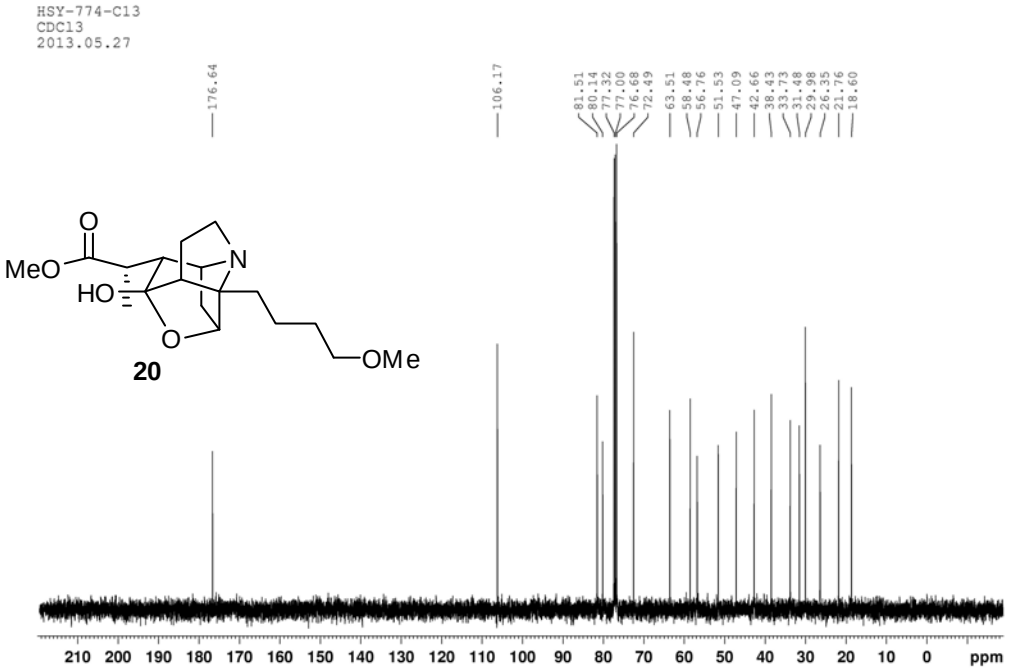
(*E*)-2-{(1*R*,4*R*,5*S*,7*S*,7a*S*)-7-(benzyloxy)-7a-[(*E*)-4'-methoxybut-2'-en-1-yl]-9-oxo hexahydro-1*H*-1,5-ethanopyrrolizin-8-ylidene}propanoate (19) and 2'(*Z*)-isomer



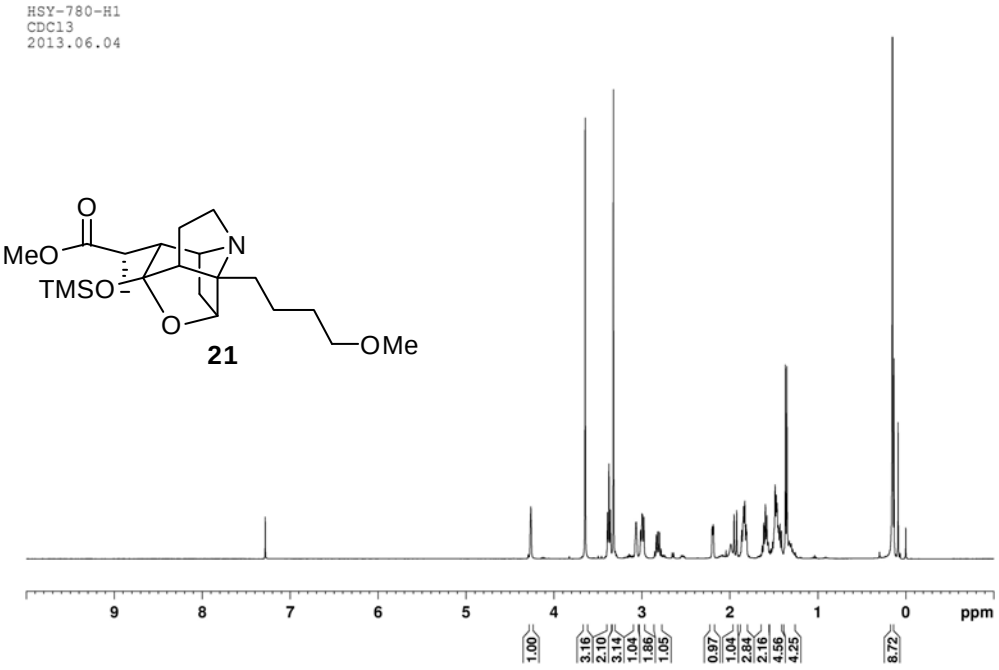


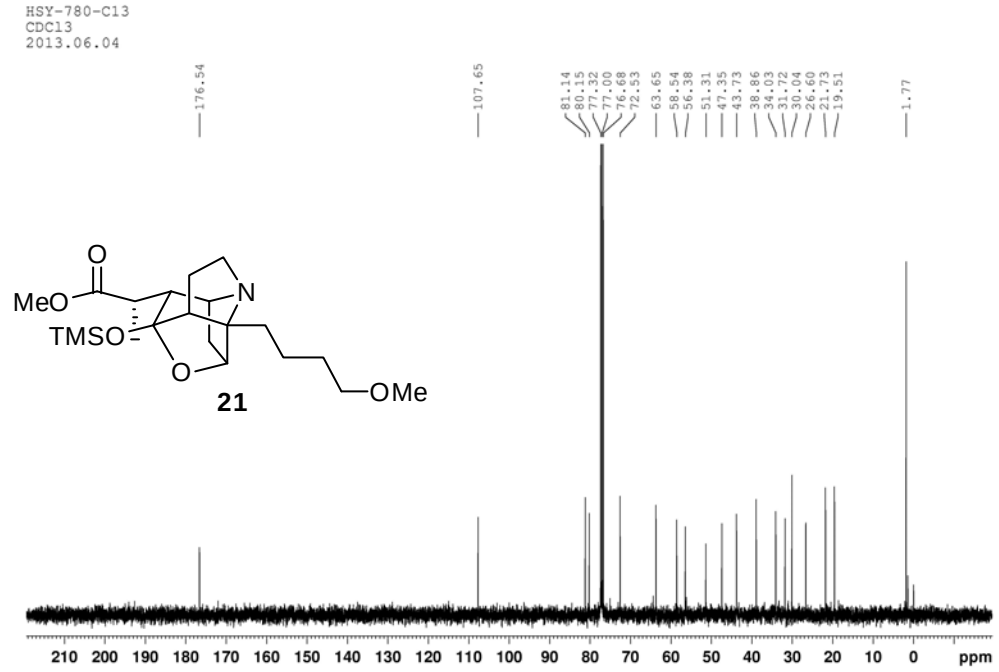
Methyl (*R*)-2-{(2*R*,2a*R*,2a^1*S*,5*R*,6*S*,7a*S*,8*R*)-2-hydroxy-2a^1-(4'-methoxybutyl)octa hydro-2,6-methanofuro[2,3,4-*gh*]pyrrolizin-8-yl}propanoate (20)



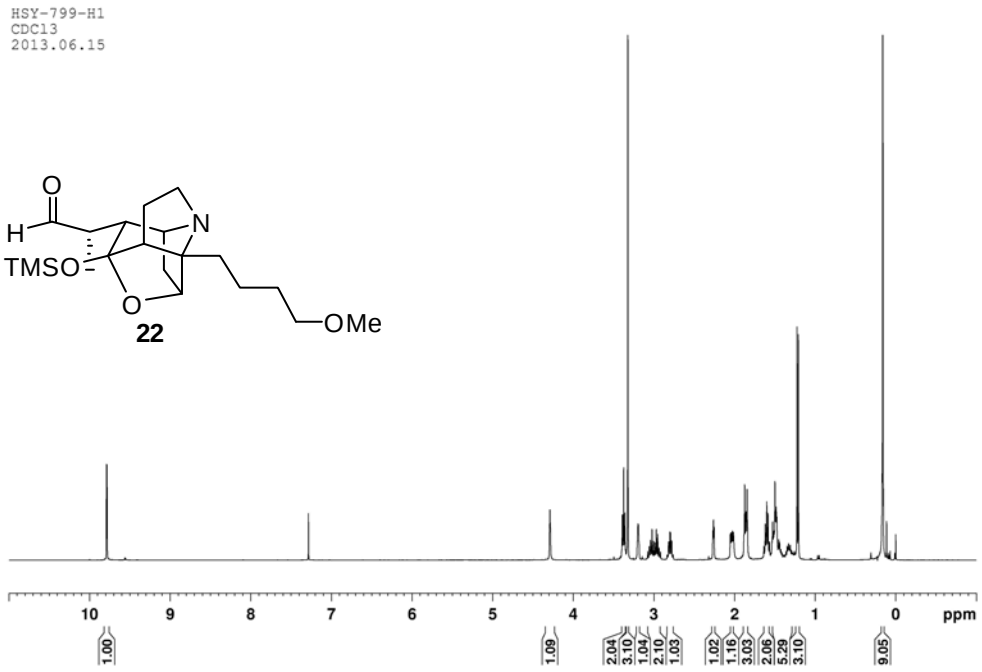


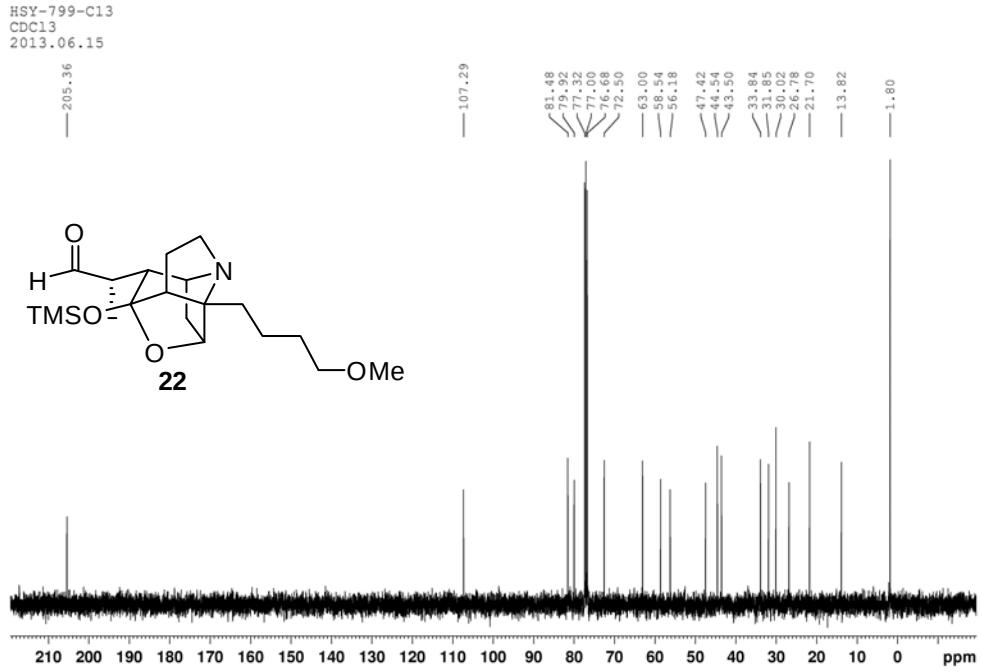
Methyl (*R*)-2-{(2*S*,2a*R*,2a^1*S*,5*R*,6*S*,7a*S*,8*R*)-2a^1-(4'-methoxybutyl)-2-(trimethylsily loxy)octahydro-2,6-methanofuro[2,3,4-*gh*]pyrrolizin-8-yl}propanoate (21)



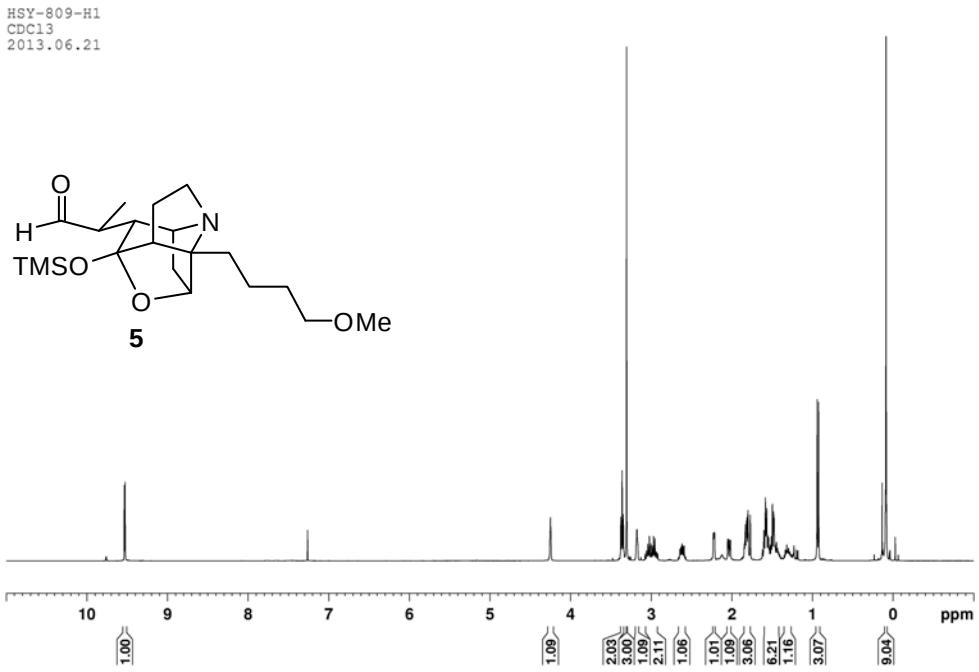


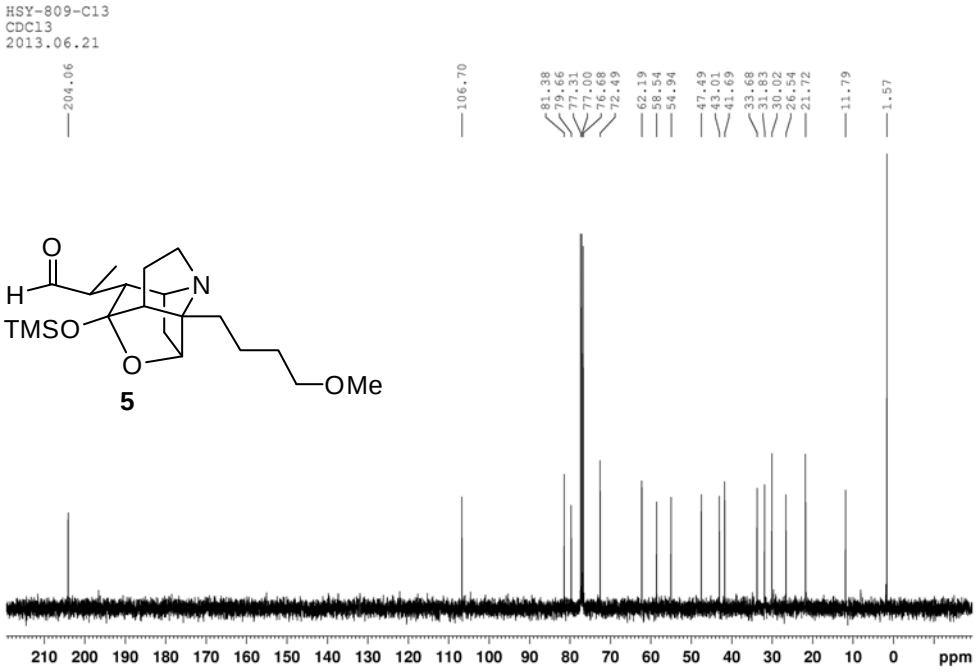
(*R*)-2-{(2*S*,2a*R*,2a^1*S*,5*R*,6*S*,7a*S*,8*R*)-2a^1-(4'-Methoxybutyl)-2-(trimethylsilyloxy)octahydro-2,6-methanofuro[2,3,4-*gh*]pyrrolizin-8-yl}propanal (22)



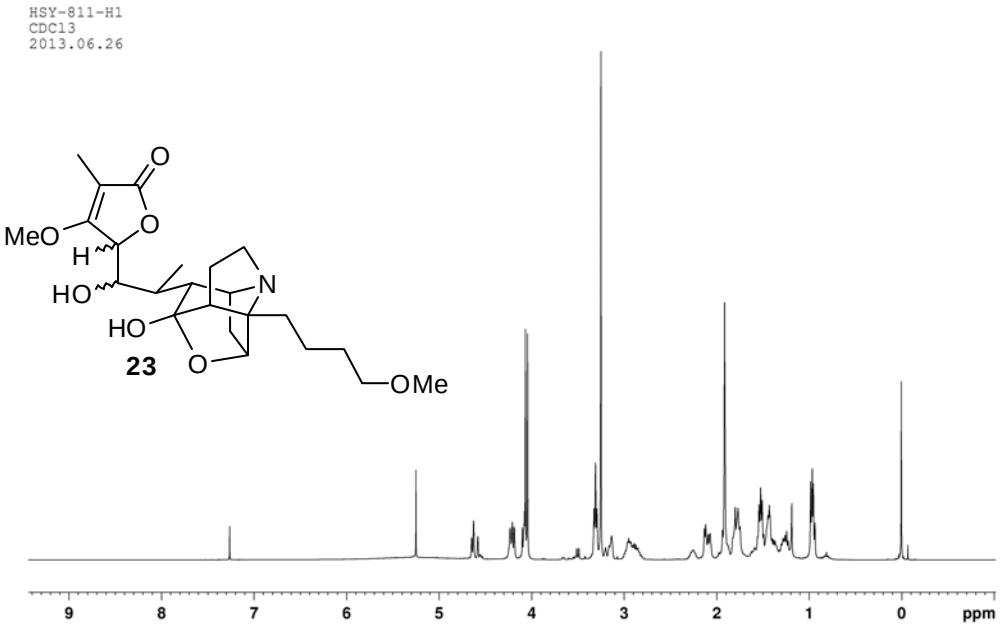


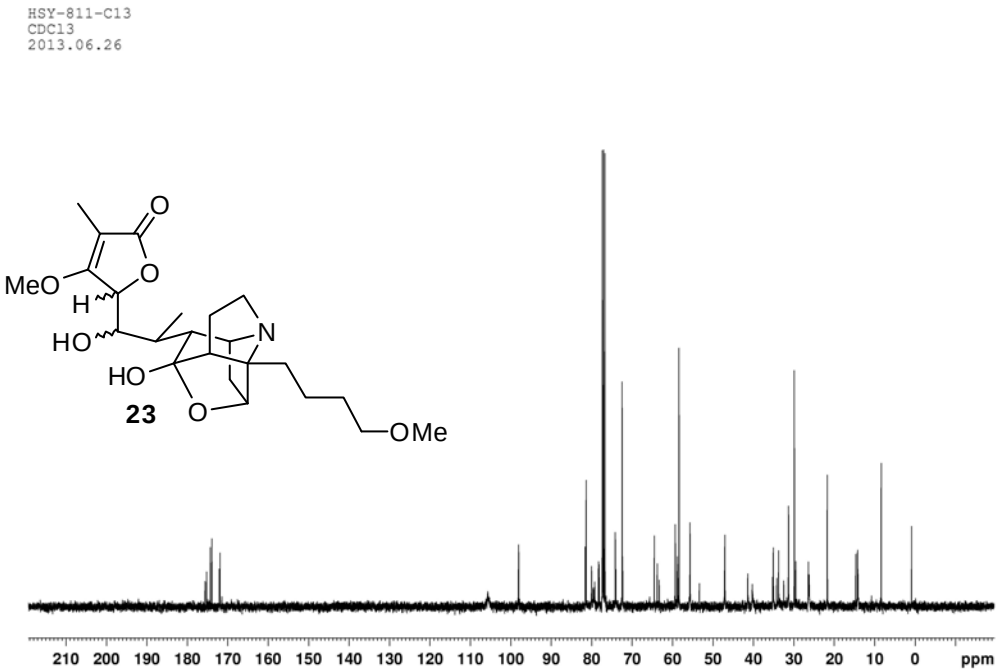
(*S*)-2-{(2*S*,2a*R*,2a^1*S*,5*R*,6*S*,7a*S*,8*R*)-2a^1-(4'-Methoxybutyl)-2-(trimethylsilyloxy)octahydro-2,6-methanofuro[2,3,4-*gh*]pyrrolizin-8-yl}propanal (5)



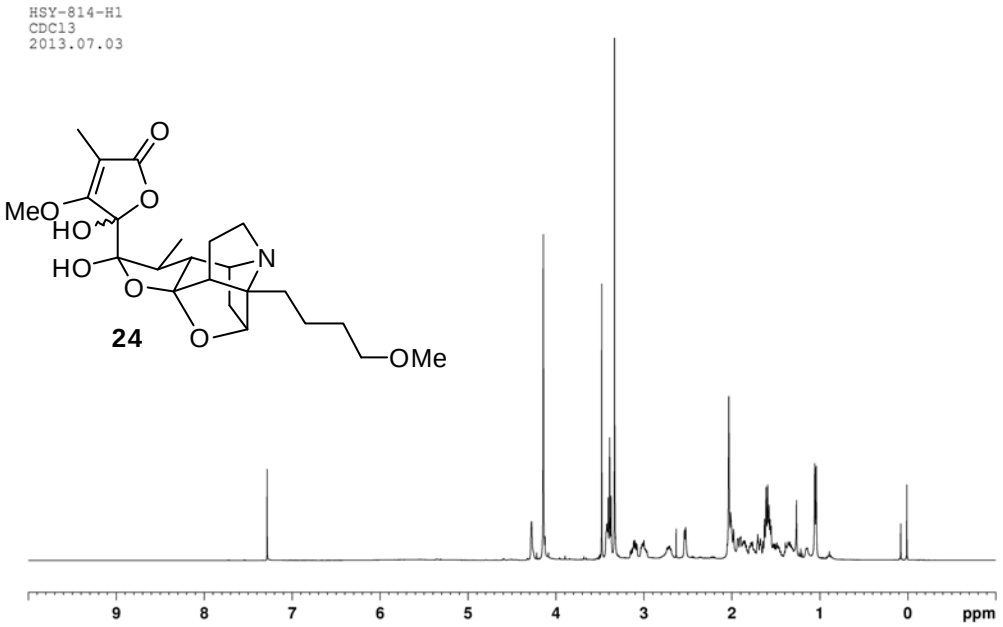


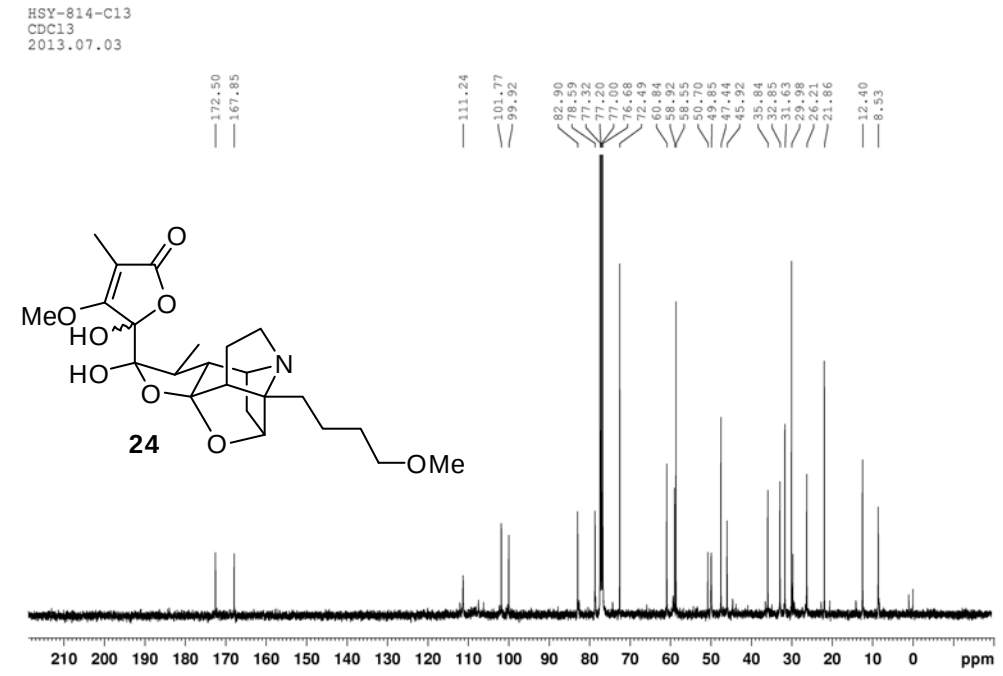
Compound 23


HSY-811-H1
CDCl3
2013.06.26
MeO
H
HO
HO
23
O
N
OMe
9
8
7
6
5
4
3
2
1
0
ppm

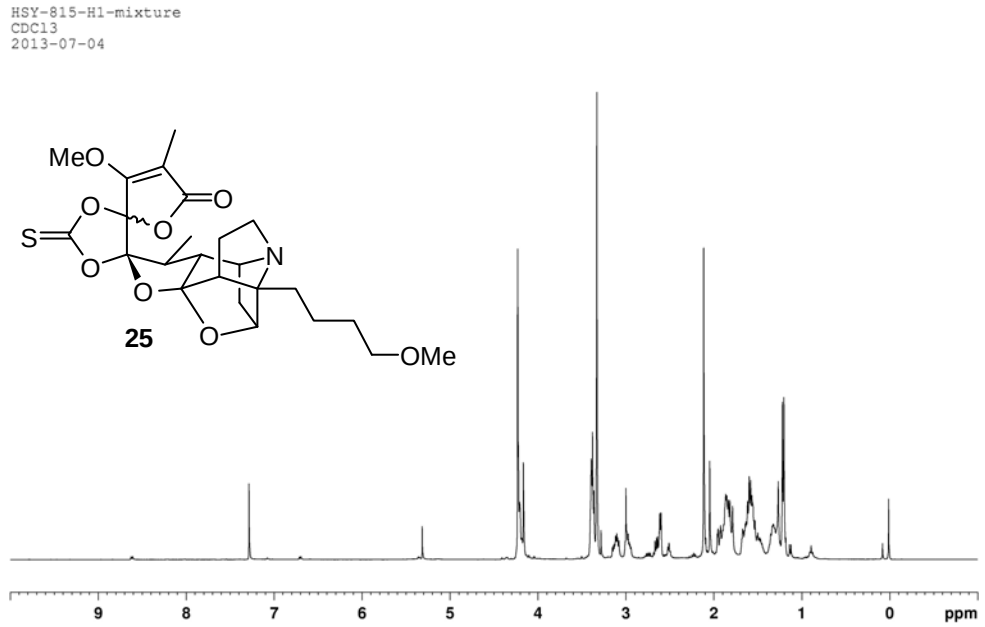

HSY-811-C13
CDCl3
2013.06.26
MeO
H
HO
HO
23
O
N
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

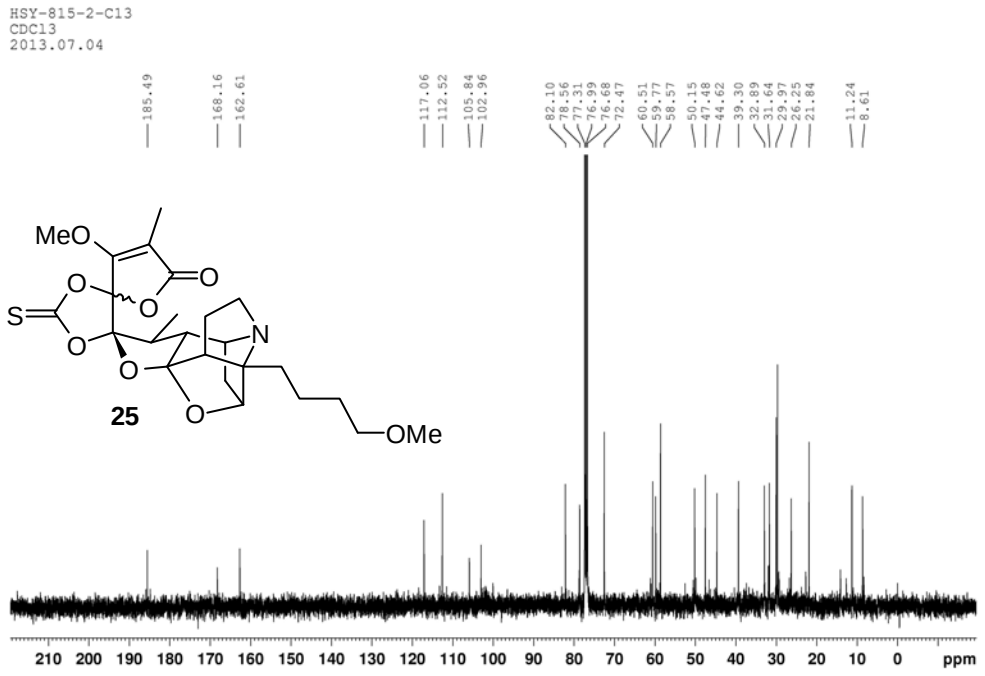
Compound 24


HSY-814-H1
CDCl3
2013.07.03
MeO
HO
HO
O
O
O
O
N
O
OMe
24
9
8
7
6
5
4
3
2
1
0
ppm

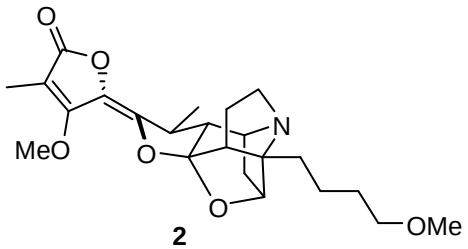

HSY-814-C13
CDCl3
2013.07.03
172.50
167.85
111.24
101.77
99.92
82.90
78.59
77.32
77.20
77.00
76.68
72.49
60.84
58.92
58.55
50.70
49.85
47.44
45.92
35.84
32.85
31.63
29.98
26.21
21.86
12.40
8.53
MeO
HO
HO
O
O
O
O
N
O
OMe
24
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

Compound 25

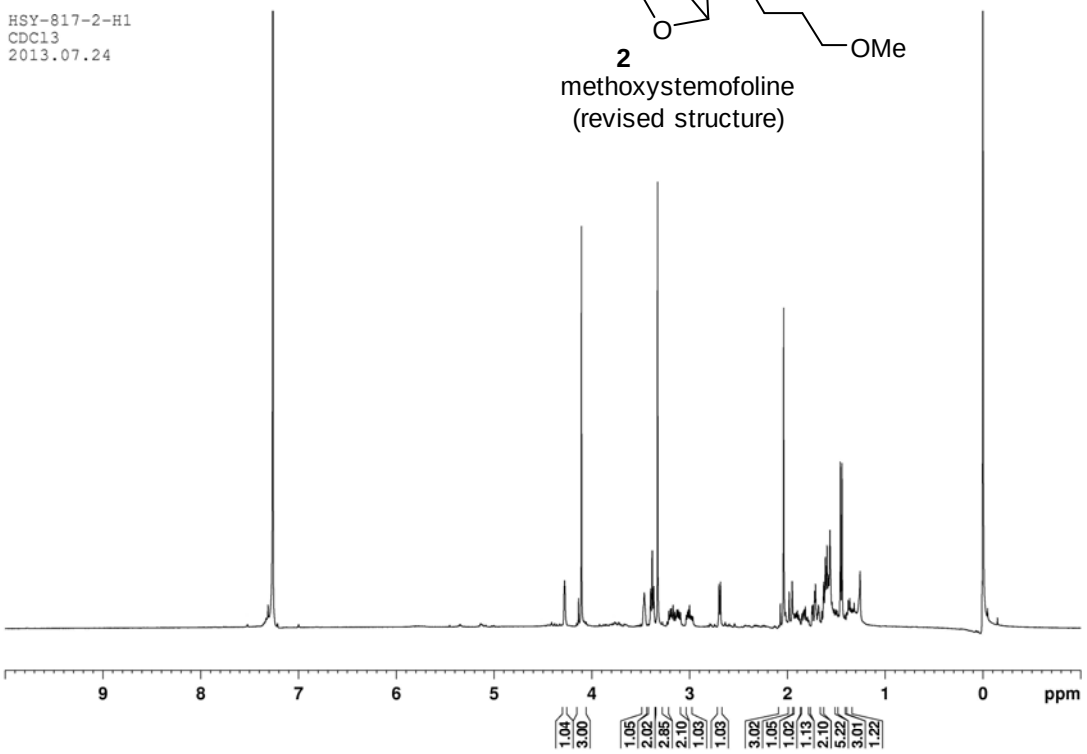

HSY-815-H1-mixture
CDCl3
2013-07-04
MeO
O
O
O
S
O
O
N
O
O
25
OMe
9
8
7
6
5
4
3
2
1
0
ppm

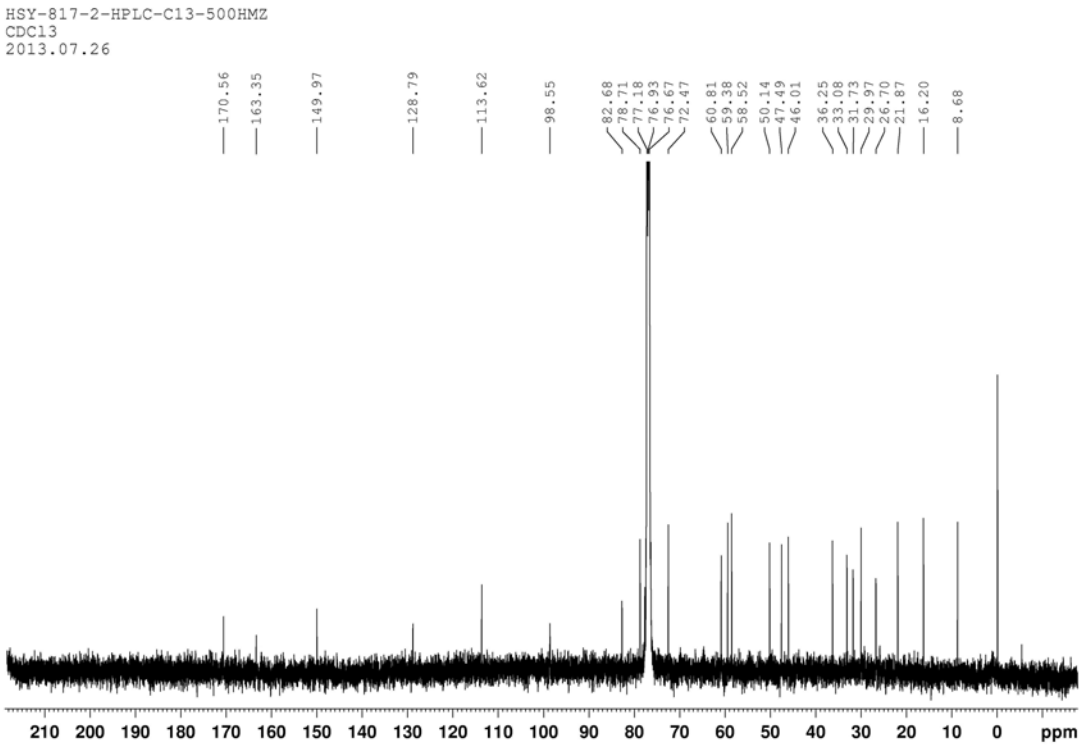

HSY-815-2-C13
CDCl3
2013.07.04
185.49
168.16
162.61
117.06
112.52
105.84
102.96
82.10
78.56
77.31
76.99
76.68
72.47
60.51
59.77
58.57
50.15
47.48
44.62
39.30
32.89
31.64
29.97
26.25
21.84
11.24
8.61
MeO
O
O
O
S
O
O
N
O
O
25
OMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

Methoxystemofoline (2)

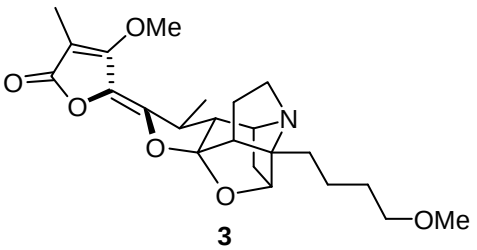


2
methoxystemofoline
(revised structure)

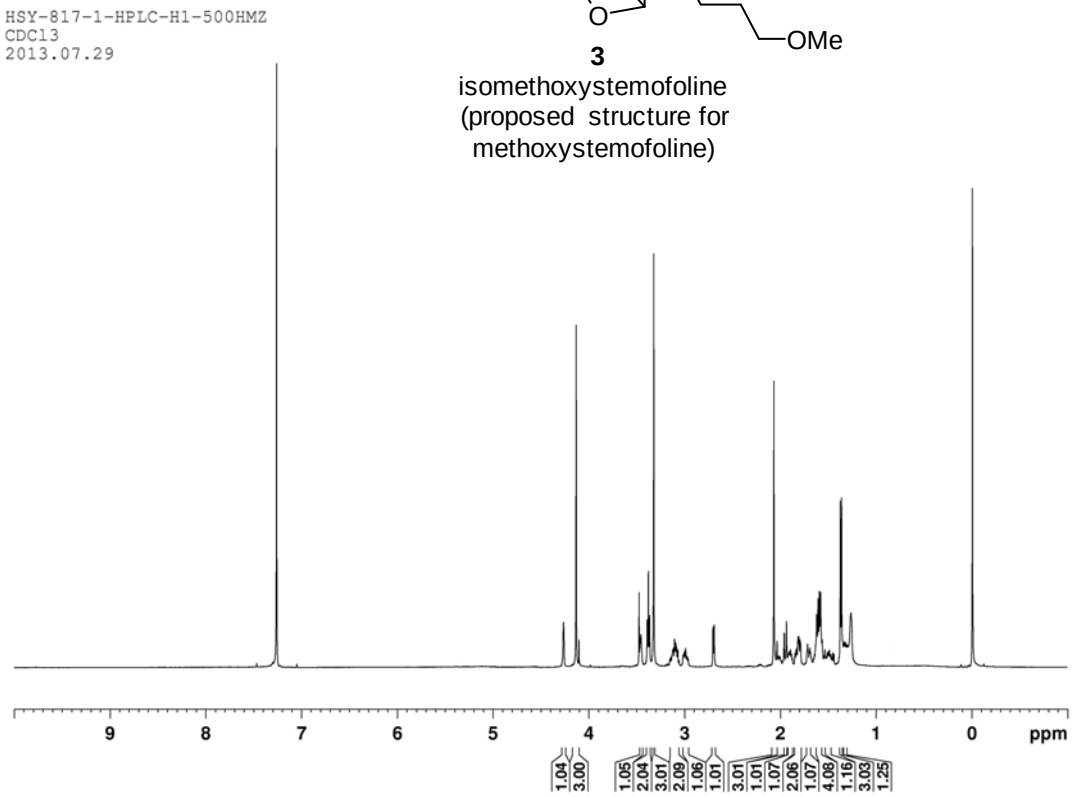


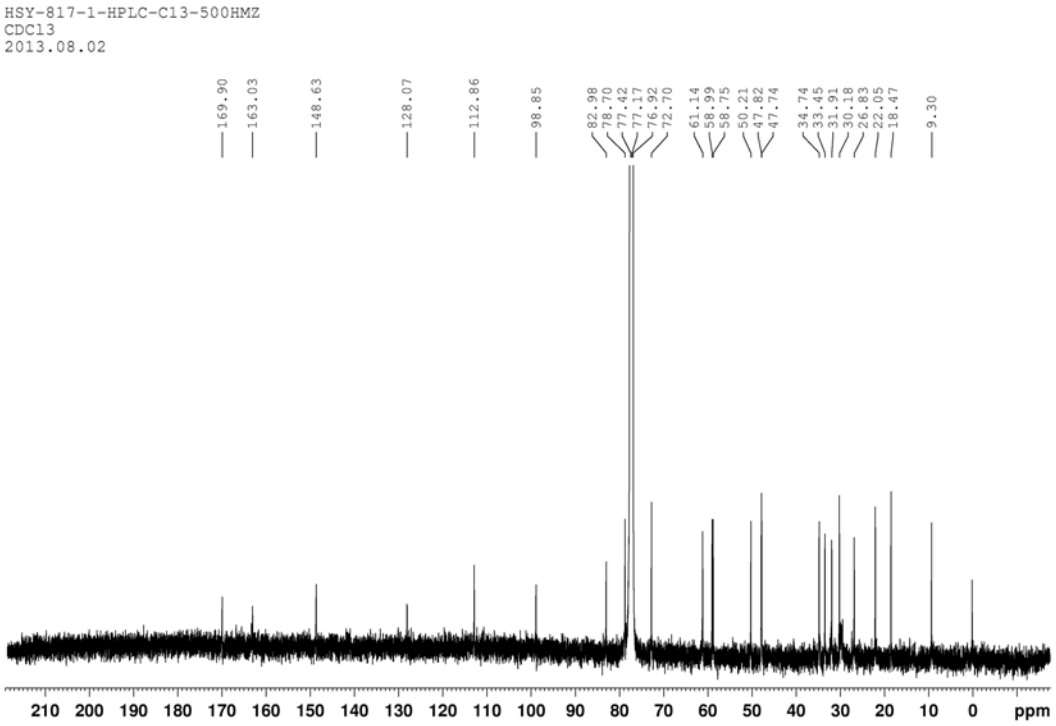


Isomethoxystemofoline (3)



3
isomethoxystemofoline
(proposed structure for
methoxystemofoline)





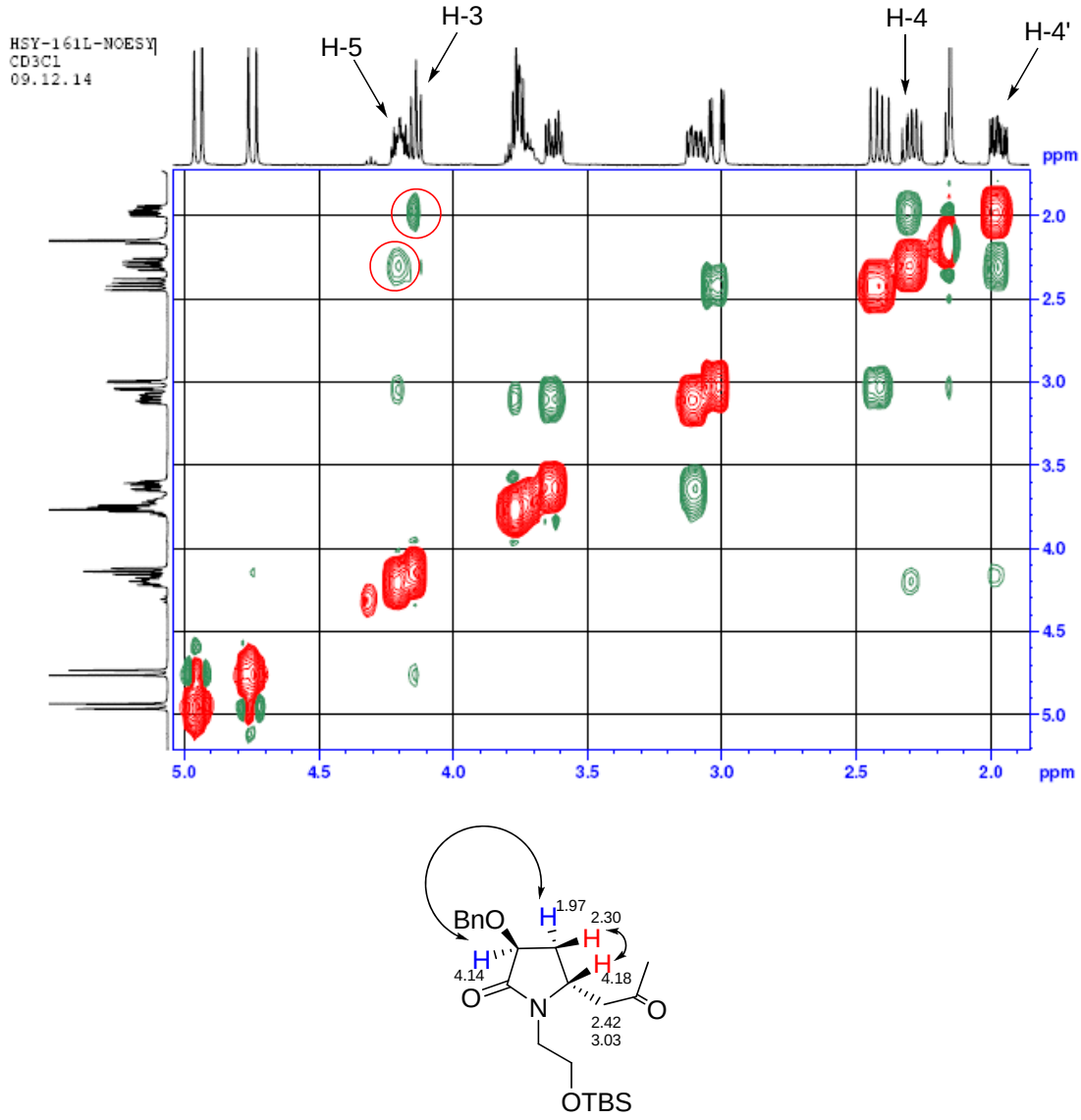


Figure 1. NOESY spectrum and structure of compound *trans*-**7**.

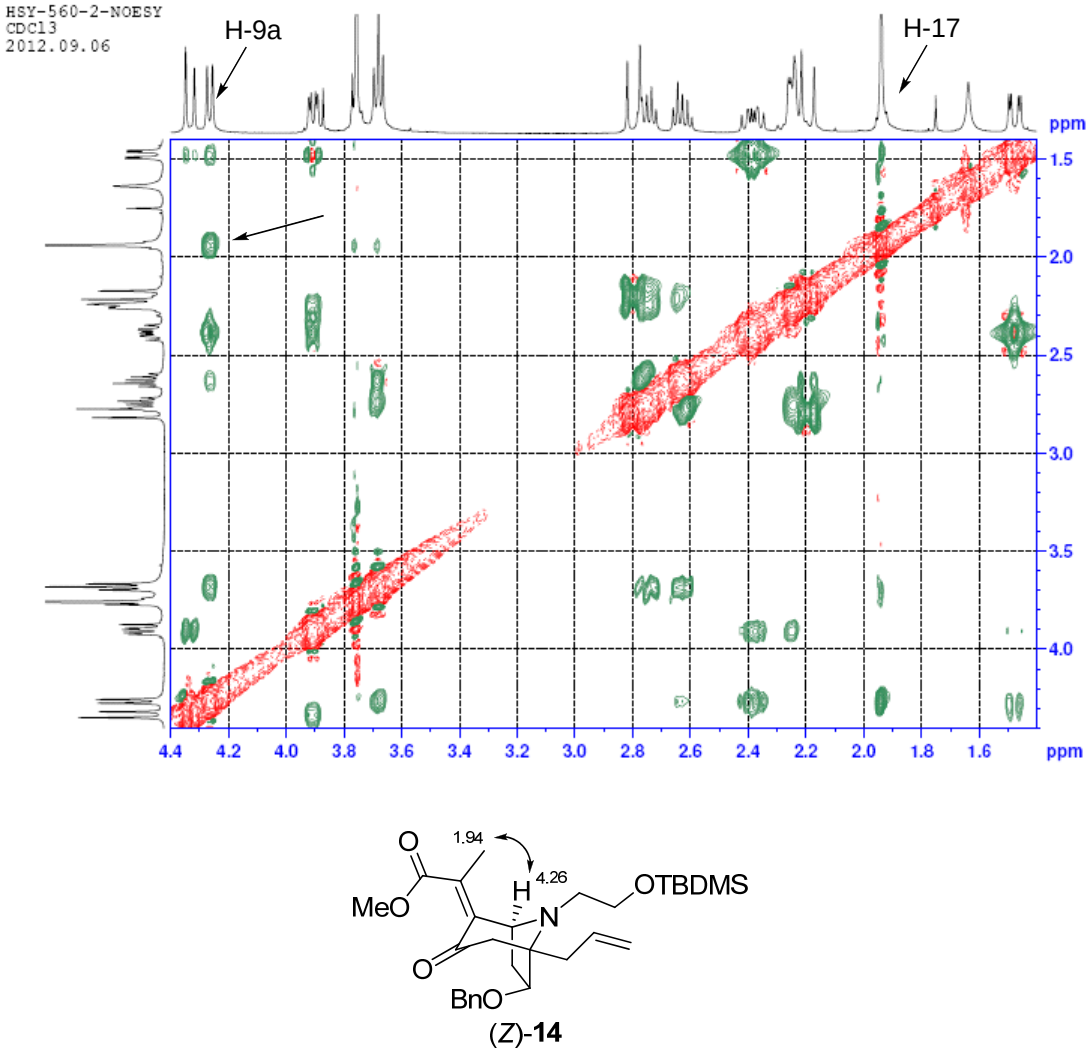


Figure 2. NOESY spectrum and structure of compound (*Z*)-**14**.

X-ray structure of compound **20**