Supporting Information

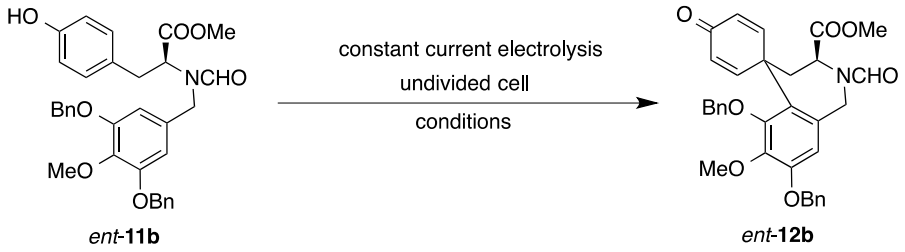
General information

Unless otherwise stated, in all the reactions, standard reagent grade solvents and chemicals from Sigma Aldrich, Alfa Aesar, Acros Organic and FluoroChem were used without further purification. All air sensitive reactions were carried out under argon or nitrogen atmosphere using oven dried glassware. Dry THF were collected from a solvent purification system (SPS) from the company MBRAUN (MB SPS-800). Dry CH_2Cl_2 was distilled over CaH_2. Thin-layer chromatography (TLC) was performed on pre-coated aluminium sheets of Merck silica gel 60 F254 (0.20 mm) and visualized by UV radiation (254 nm). Automated column chromatography was performed on a Biotage Isolera Four. ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker DPX 400 or 500 apparatus and were referenced to the residual proton solvent peak (^{1}H: CDCl3, δ 7.26 ppm) and solvent ^{13}C signal (CDCl3, δ 77.0 ppm). Chemical shifts δ were reported in ppm, multiplicity of the signals was declared as followed: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dt = doublet of triplets, m = multiplet, br = broad; and coupling constants (J) in Hertz. High resolution mass spectrometry (HRMS, m/z) data was acquired at Cardiff University on a Micromass LCT Spectrometer.

In the flow set-ups, the syringe pumps that were used were KR Analytical Ltd Fusion 100 Touch syringe pumps. The electrochemical reactions were carried out in a galvanostatic mode using a GWINSTEK GPR-30H10D. The Ion electrochemical reactor from Vapourtec Ltd was used for the experiments.[1] Electrode materials: Platinum, Glassy Carbon (GC), Graphite, Nickel, Boron doped diamond (BDD). The electrodes (5 x 5 cm) are separated by a 0.5 mm spacer with a channel volume of 0.6 mL and an exposed electrode surface area of 12 cm^2 (each electrode). This is similar to the electrochemical reactor published previously.[2]

Electrochemistry

Batch electrolysis



ent-**11b** *ent*-**12b**

Table S1: Optimization of batch electrolysis conditions

Entry	Anode material	Solvent	T [ºC]	*J* [mA/cm^2]	Q [F]	*ent*-**12b** Yield[a] [%]
1	C	TFE	rt	5	1.6	11
2	Pt	TFE	rt	5	1.6	trace
3	**RVC**	**TEF**	**rt**	**5**	**1.6**	**20**
4	C	MeCN	rt	5	2	8
5	RVC	HFIP	rt	5	1.6	18
6	RVC	MeCN	rt	5	1.6	15
7	RVC	MeCN/CH_2Cl_2	rt	5	1.6	NA
8	RVC	TFE	0	5	2	NA
9	RVC	TFE	40	5	2	15
10	RVC	TFE	rt	10	1.6	18
11	RVC	TFE	rt	5	2	17
12	RVC	TFE	rt	20	1.6	11

Procedure: All experiments were performed in an undivided three neck RBF with an immersed electrode surface of 1 cm^2 (Cathode: Pt). A solution of ent-**11** (0.02 M) with supporting electrolyte *n*Bu_4NClO_4 (0.1 M) in solvent was electrolyzed under the conditions specified in the table. After the reaction, the mixture was concentrated under vacuo. [a] Yields of isolated product by chromatographic purification on silica (CH_3Cl/MeOH = 200:1 then 160:1).

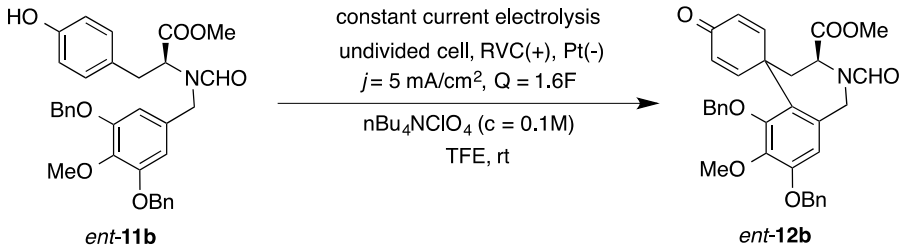


Table S2: Optimization of the concentration and acid additives

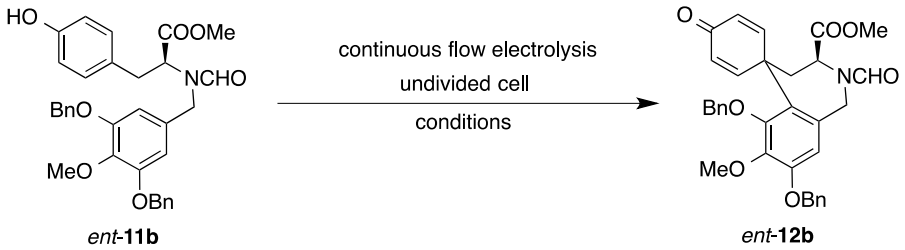
Entry	Concentration [mol/L]	Additive	*ent*-**12b** Yield[a] [%]
1	0.025	-	17
2	0.01	-	22
3	0.01	TFA (1 eq)	36
4	0.01	AcOH (1 eq)	trace
5	0.01	TFA (1.5 eq)	40
6	0.01	TFA (2 eq)	25

Procedure: All experiments were performed in an undivided three neck RBF with an immersed electrode surface of 1 cm^2 (Anode: RVC, Cathode: Pt). A solution of ent-**11** with supporting electrolyte $n$$Bu_4NClO_4$ (0.1 M) and acid additive in TFE was electrolyzed (j = 5 mA/cm^2, Q = 1.6 F). After reaction time the reaction mixture was concentrated under vacuo. [a] Yield of isolated products by chromatographic purification on silica (CH_3Cl/MeOH = 200:1 then 160:1).

Electrolysis in continuous flow

Optimization of the Continuous Flow Electrolysis

All experiments were performed in an undivided cell using a Vapourtec Ion Electrochemical Flow Reactor[1] (reactor volume = 0.6 mL, spacer 0.5 mm, electrodes immersed surface area: A = 12 cm^2). The reaction solution was drawn up into a proper size syringe and promptly connected to the flow system. Syringe pumping was then initiated, and the outlet of the flow system was set to waste for the first 1.2 mL of reaction mixture to allow the flow system to be filled. After this initial priming, the power supply was switched on and the electrolysis commenced at a constant current with the system outlet still set to waste for a further 1.2 mL, then collect the rest reaction mixture into a RBF and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography ($CHCl_3$/MeOH 200:1, then 160:1) to give the pure product.

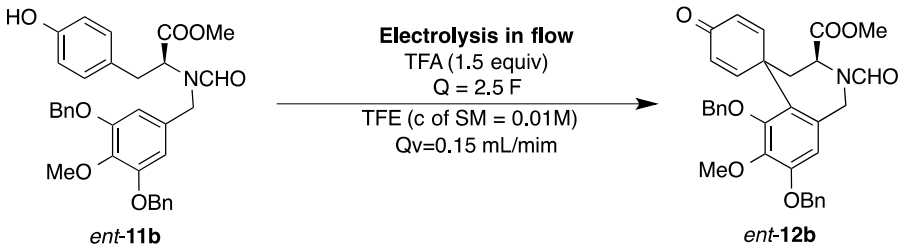


ent-**11b** *ent*-**12b**

Table S3: Initial experiments, reactions performed at rt.

Entry	Electrode materials	Solvent	Flow rate [mL/min]	Concentration [mol/L]	Q [F]	*ent*-**12b** Yield[a] [%]
1	C(+), Ni(–)	TFE	0.1	0.036	1.5/2	30
2	C(+), Ni(–)	TFE	0.15	0.036	1.5	32
3	C(+), Ni(–)	TEF	0.15	0.012	1.5	35
4	C loaded on PTFE(+), Ni(–)	TFE	0.15	0.036	1.5	28
5	C(+), Ni(–)	HFIP	0.15	0.036	1.5	NA

[a] Yield of isolated products by chromatographic purification on silica (CH_3Cl/MeOH = 200:1 then 160:1).



ent-**11b** *ent*-**12b**

Table S4: Electrode screening, reactions performed at rt.

Entry	Electrodes	*ent*-**12b** Yield[a] [%]
1	C(+), stainless steel(–)	43
2	C (+), Pt(–)	32
3	Glassy carbon(+), stainless steel(–)	45
4	Glassy carbon(+), Pt(–)	39
5	BDD(+), stainless steel(–)	NA
6	Panasonic carbon(+), Pt(–)	42
7	Panasonic carbon(+), Pt on Ti(–)	52
8	Panasonic carbon (+), Pt on Nb(-)	53

[a] Yield of isolated products by chromatographic purification on silica (CH_3Cl/MeOH = 200:1 then 160:1).

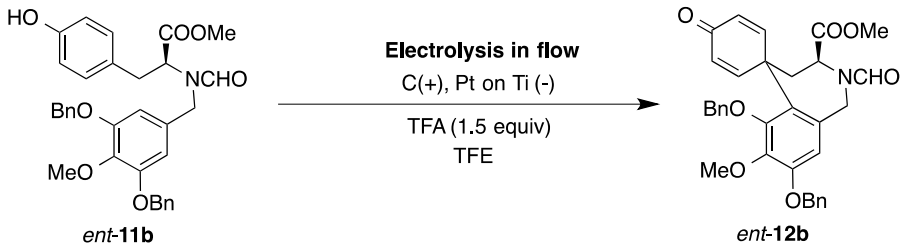


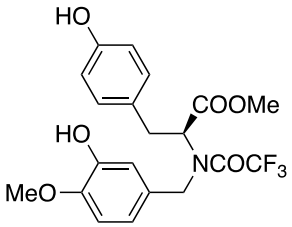
Table S5: Concentration, flow rate, current and supporting electrolyte screening, reactions performed at rt.

Entry	Concentration [mol/L]	Flow rate [mL/min]	Current [mA]	Q [F]	Voltage [V]	Supporting Electrolyte	*ent*-**12b** Yield[a] [%]
1	0.01	0.15	6	2.5	20-22	-	52
2	0.01	0.2	8	2.5	22-24	-	52
3	0.01	0.5	20	2.5	34-36	-	57
4	0.02	0.5	40	2.5	38-40	-	56
5	**0.02**	**0.5**	**32**	**2**	**32-34**	**-**	**55 (80)**[b]
6	0.02	0.5	24	1.5	32-34	-	40 (76)[b]
7	0.02	0.5	32	2	1-2	nBu$_4$NClO$_4$ (0.05M)	0
8	0.02	0.5	32	2	3-4	nBu$_4$NClO$_4$ (0.02M)	trace
9	0.02	0.5	32	2	5-6	nBu$_4$NClO$_4$ (0.005M)	32 (82)[b]
10	0.02	0.5	32	2	5-6	nBu$_4$NBF$_4$ (0.005M)	31 (82)[b]

[a] Yield of isolated products by chromatographic purification on silica (CH_3Cl/MeOH = 200:1 then 160:1). [b] Yield based on recovered starting material.

Experimental Procedures

Methyl *N*-(3-hydroxy-4-methoxybenzyl)-*N*-(2,2,2-trifluoroacetyl)-L-tyrosinate *ent*-4



ent-**4**

Prepared according to reference [3].

$[\alpha]_D^{20}$ = –46.8° (c = 0.111, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.76 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.73 (s, 1H, Ar-H), 6.64 (d, *J* = 2.0 Hz, 1H, Ar-H), 6.57-6.55 (dd, *J* = 8.4, 2.0 Hz, 1H, Ar-H), 4.46 (d, *J* = 15.6 Hz 1H, CH), 3.89-3.85 (4H, -OCH_3 + CH), 3.67 (s, 3H, -OCH_3), 3.50-3.46 (m, 1H, CH), 3.32-3.19 (m, 2H, CH_2) ppm.

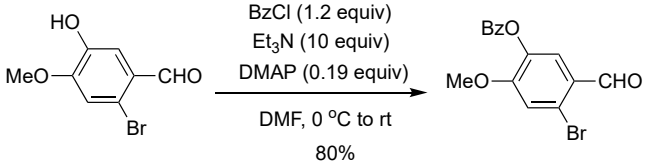
^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 154.9, 146.9, 145.8, 130.5, 129.3, 126.4, 120.9, 115.8, 115.2, 110.6, 61.7, 56.1, 52.9, 52.7, 33.2 ppm.

IR (neat): 3397, 3025, 2989, 2956, 2901, 2845, 1737, 1683, 1614, 1595, 1515, 1442, 1371, 1352, 1273, 1209, 1147, 1065, 1058, 1028, 996, 970, 911, 862, 828, 800, 749, 703, 668, 717, 581, 536 cm^{-1}.

HRMS (ESP): calcd. for $[C_{20}H_{20}F_3NO_6Na]^+ = [M+Na]^+$: 450.1140, found 450.1146

Synthesis of 4-Bromo-2-methoxy-5-((2,2,2-trifluoro-*N*-(4-hydroxyphenethyl)acetamido) methyl)phenyl benzoate 9

4-Bromo-5-formyl-2-methoxyphenyl benzoate S2



S1 **S2**

To a stirred solution of 2-bromoisovanilline **S1** (1.000 g, 4.33 mmol, 1.0 equiv.) in DMF (22 mL) at 0 °C Et_3N (6.0 mL, 43.43 mmol, 10.03 equiv.), BzCl (0.6 mL, 5.20 mmol, 1.2 equiv.) and DMAP (100 mg, 0.82 mmol, 0.19 equiv.) were added. After addition, the reaction mixture was warmed up to rt and stirred for 30 min. The mixture was diluted with EtOAc (50 mL) and washed with cold water (3 x 30 mL). The aqueous layer was extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine and subsequently dried over $MgSO_4$, filtered, and concentrated under vacuum.. The crude residue was purified by SiO_2 flash chromatography (Pet. Ether / EtOAc = 5:1) gave product **S2** (1.157 g, 3.45 mmol, 80%) as a white solid.

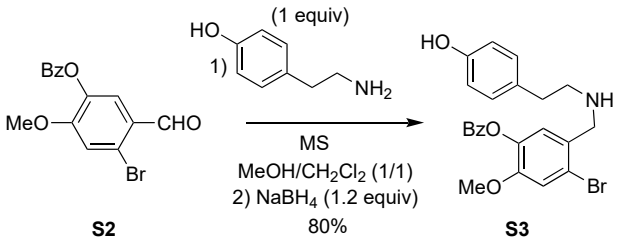
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (s, 1H, CHO), 8.21 – 8.16 (m, 2H, $CH_{arom.}$), 7.76 (s, 1H, $CH_{arom.}$), 7.69 – 7.63 (m, 1H, $CH_{arom.}$), 7.55 – 7.49 (m, 2H, $CH_{arom.}$), 7.22 (s, 1H, $CH_{arom.}$), 3.91 (s, 3H, OCH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.0 (CHO), 164.1 (CO), 156.6, 139.9, 133.9, 130.4, 128.63, 128.57 126.9, 125.7, 123.9, 116.9, 56.6 ppm.

IR (neat): 3109, 3082, 3048, 2984, 2947, 2865, 1733, 1679, 1599, 1498, 1451, 1435, 1395, 1316, 1259, 1234, 1199, 1176, 1139, 1076, 1058, 1015, 984, 921, 860, 704, 678, 648, 553 cm^{-1}.

TOF ESP HRMS: $[M+H]^+$ calcd. for $C_{15}H_{12}O_4{}^{79}Br$ = 334.9919. Found = 334.9917.

4-Bromo-5-(((4-hydroxyphenethyl)amino)methyl)-2-methoxyphenyl benzoate S3



S2 **S3**

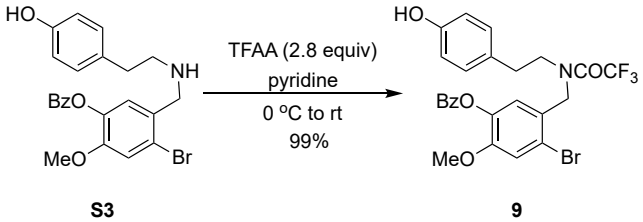
To a rt stirred solution of **S2** (1 g, 2.98 mmol) in $MeOH/CH_2Cl_2$ (1 : 1, 30 mL) was added molecular sieve 4 Å (3.8 g) followed by tyramine (0.41 g, 2.98 mmol, 1 equiv). The resulting mixture was stirred at rt for 16 h. Then the molecular sieve 4 Å was filtered off, MeOH (30 mL) was added to the filtrate. The whole solution was cooled to 0 °C, $NaBH_4$ (0.135 g, 3.58 mmol, 1.2 equiv) was added. The resulting mixture was stirred at rt for 2 h, concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet.Ether/EtOAc 3:1, then 1:3) gave **S3** (1.08 g, 80%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 – 8.15 (m, 2H, $CH_{arom.}$), 7.69 – 7.59 (m, 1H, $CH_{arom.}$), 7.51 (t, J = 7.7, 7.7 Hz, 2H, $CH_{arom.}$), 7.14 (m, 2H, $CH_{arom.}$), 7.02 (m, 2H, $CH_{arom.}$), 6.68 (m, 2H, $CH_{arom.}$), 3.82 (s, 2H, CH_2), 3.78 (d, J = 1.8 Hz, 3H, CH_3), 2.86 (t, J = 6.9 Hz, 2H, CH_2), 2.76 (d, J = 6.9 Hz, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 154.5, 15.9, 139.1, 133.7, 131.1, 130.3, 129.8, 129.0, 128.6, 124.4, 120.6, 116.8, 115.5, 56.2, 52.6, 50.0, 35.0 ppm.

IR (neat): 3270, 3003, 2992, 2952, 2935, 2903, 2857, 2835, 1600, 1510, 1460, 1434, 1381, 1357, 1336, 1252, 1230, 1209, 1163, 1112, 1084, 1036, 1030, 1003, 978, 795, 786, 771, 585, 558, 504 cm^{-1}.

4-Bromo-2-methoxy-5-((2,2,2-trifluoro-*N*-(4-hydroxyphenethyl)acetamido)methyl)phenyl benzoate 9



S3 **9**

To a stirred solution of **S3** (0.5 g, 1.1 mmol, 1 equiv) in pyridine (3.5 mL) at 0 ºC was added TFAA (0.45 mL, 3.09 mmol, 2.8 equiv) dropwise over 8 min. The resulting solution was allowed to warm to rt and stirred for 5 h. EtOAc (20 mL) was added and the mixture was washed with 10% HCl solution (2 x 20 mL). The separated aqueous layers were extracted with EtOAc (20 mL), the combined organic layers were then washed with sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet. Ether/EtOAc 3:1) gave **9** (0.6 g, 99%) as white solid. NMR data show that **9** is a 3 : 2 mixture of rotamers.

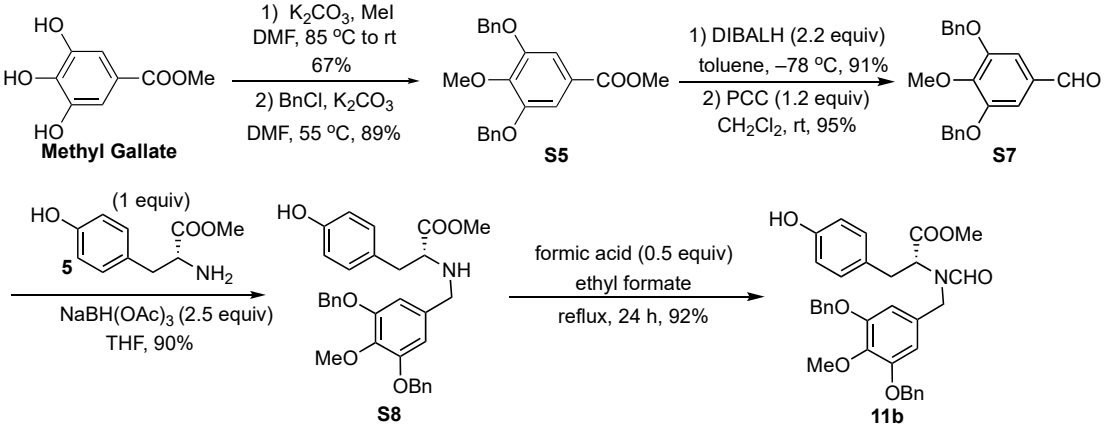
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 – 8.15 (m, 2H, $CH_{arom.}$), 7.69 – 7.59 (m, 1H, $CH_{arom.}$), 7.51 (t, J = 7.8Hz, 2H, $CH_{arom.}$), 7.19 (s, 1H, $CH_{arom.}$), 7.09 and 6.88 (s, 1H, $C\underline{H}_{arom}$), 7.03 (dq, J = 8.1, 3.0 Hz, 2H, $CH_{arom.}$), 6.78 – 6.72 (m, 2H, $CH_{arom.}$), 4.79 and 4.51 (s, 2H, CH_2), 3.81 (s, 3H, CH_3), 3.49 (dt, J = 7.6, 5.3 Hz, 2H, CH_2), 2.90 – 2.79 (m, 2H, CH_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4, 154.6 and 154.5, 151.7 and 151.6, 139.8 and 139.7, 133.8, 130.52, 130.4, 130.0, 129.8, 128.7, 128.64, 128.60 127.1, 126.4, 124.1, 122.3, 120.8, 119.8, 117.0, 116.8, 115.6 and 115.5, 56.3, 48.8, 48.7, 48.6, 34.4, 31.9 ppm.

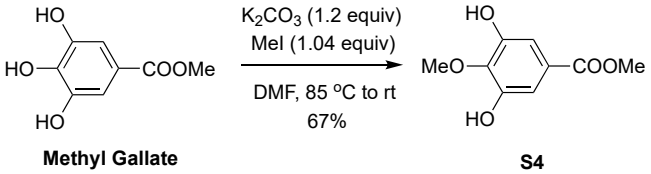
IR (neat): 3392, 3074, 3031, 2974, 2947, 2846, 1738, 1664, 1613, 1600, 1516, 1505, 1463, 1439, 1387, 1355, 1313, 1279, 1265, 1240, 1223, 1193, 1168, 1140, 1081, 1055, 1023, 1002, 922, 801, 635 cm^{-1}.

TOF ESP HRMS: $[C_{25}H_{21}NO_5F_3BrNa]^+ = [M+Na]^+$: 574.0453, found 574.0461

Synthetic Route to substrate 11b



Methyl 3,5-dihydroxy-4-methoxybenzoate S4



To a stirred solution of methyl gallate (50 g, 0.271 mol) in DMF (542 mL) was added K_2CO_3 (44.9 g, 0.325 mol, 1.2 equiv). The resulting mixture was heated to 85 ºC for 1 h and then cooled down to 0 ºC, MeI (17.6 mL, 0.281 mol, 1.04 equiv) was added dropwise and stirred at 0 ºC for 30 min before being warmed up to rt. After stirred at rt for further 20 h, EtOAc (500 mL) was added to the reaction mixture

and then washed with cold water (3 x 300 mL). The combined aqueous layer was extracted with EtOAc (4 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Crude product **S4** (36.2 g, 67%) was obtained as white solid and used directly in the next step. The spectral data agree with literature.[4]

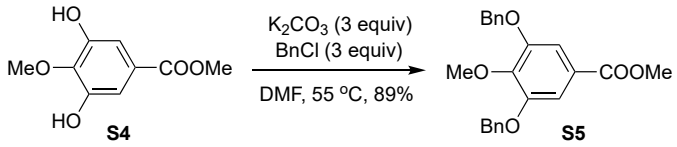
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 2H, Ar), 5.56 (br, s, 2H, OH), 3.96 (s, 3H, OMe), 3.88 (s, 3H, OMe) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 148.6, 138.5, 126.2, 109.8, 61.1, 52.3 ppm.

IR (neat): 3378, 3310, 2999, 2976, 2957, 2844, 1707, 1591, 1507, 1456, 1437, 1377, 1352, 1341, 1283, 1252, 1214, 1156, 1087, 1058, 1001, 982, 915, 867, 844, 791, 769, 757, 715, 638, 620, 569, 545, 520 cm^{-1}.

HRMS (ESP): $[C_9H_{11}O_5]^+ = [M+H]^+$: calc 199.0606, found 199.0607

Methyl 3,5-bis(benzyloxy)-4-methoxybenzoate S5

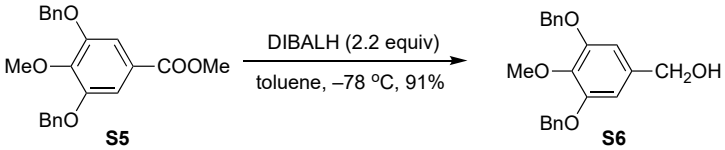


To a stirred solution of **S4** (20 g, 0.101 mol) in DMF (400 mL) was added K_2CO_3 (41.9 g, 0.303 mol, 3 equiv) followed by BnCl (34.9 mL, 0.303 mol, 3 equiv). The reaction was heated to 55 ºC and stirred for 6 h before being cooled down to rt. The reaction mixture was diluted with EtOAc (300 mL) and filtered off through a Büchner funnel, the filtrate was washed with cold water (3 x 300 mL), the combined water layers were extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by recrystallisation from Et_2O with petroleum ether to give ester **S5** (34 g, 89%) as white solid. The spectral data agree with literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 – 7.31 (m, 12H, Ar), 5.17 (s, 4H, C$\underline{H}_2$Ph), 3.94 (s, 3H, OMe), 3.88 (s, 3H, OMe) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 152.2, 143.6, 136.6, 128.6, 128.0, 127.4, 124.9, 109.1, 71.1, 61.0, 52.2 ppm.

(3,5-Bis(benzyloxy)-4-methoxyphenyl)methanol S6



To a stirred solution of **S5** (8 g, 21.1 mmol) in dry toluene (211 mL) at –78 ºC under argon, DIBAL-H (1 M solution in hexane) (46.5 mL, 46.5 mmol, 2.2 equiv) was added dropwise over 20 min. The resulting solution was stirred at –78 ºC for 30 min before being allowed to warm to rt. EtOAc (200 mL) and sat. Rochelle's salt solution (300 mL) were added, the biphasic solution was stirred for 2 h, then transferred to a separating funnel. The separated aqueous layer was extracted with EtOAc (2 x 80 mL).

The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by SiO_2 flash chromatography (Pet. Ether/EtOAc 3:1) gave **25** (6.73 g, 91%) as white solid. The spectral data agree with literature.[5]

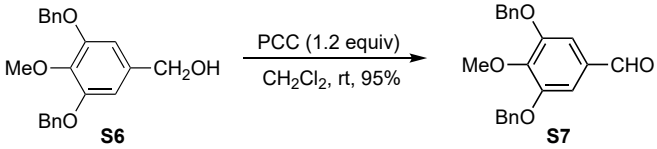
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 – 7.28 (m, 10H, Ph), 6.65 (s, 2H, Ar), 5.14 (s, 4H, C<u>H</u>$_2$Ph), 4.55 (s, 2H, C<u>H</u>$_2$OH), 3.89 (s, 3H, OMe) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.7, 138.8, 137.1, 136.4, 128.5, 127.8, 127.2, 106.4, 71.0, 65.4, 60.9 ppm.

IR (neat): 3515, 3088, 3038, 3009, 2964, 2935, 2887, 2857, 2827, 1592, 1501, 1469, 1457, 1437, 1386, 1372, 1309, 1253, 1228, 1204, 1139, 1104, 1055, 1029, 989, 836, 818, 778, 660, 605 cm^{-1}.

HRMS (ESP): $[C_{22}H_{22}O_4Na]^+ = [M+Na]^+$: calc 373.1416, found 373.1414

3,5-Bis(benzyloxy)-4-methoxybenzaldehyde S7



To a stirred rt solution of alcohol **25** (6.5 g, 18.5 mmol) in CH_2Cl_2 (185 mL) was added PCC (4.8 g, 22.2 mmol, 1.2 equiv). The resulting suspension was stirred at rt for 4 h, then filtered through a pad of Celite. The filtrate was concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet.Ether/EtOAc 8:1 to 4:1) gave **19** (6.1 g, 95%) as white solid. The spectral data agree with literature.[5]

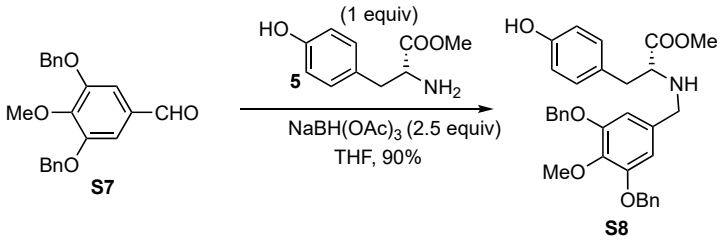
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1H), 7.47-7.34 (m, 10H), 7.18 (s, 2H), 5.19 (s, 4H), 3.98 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.9, 152.9, 145.0, 136.4, 131.5, 128.6, 128.1, 127.3, 109.0, 71.2, 61.0 ppm.

IR (neat): 3089, 3064, 3039, 3011, 2937, 2895, 2827, 2803, 2732, 1689, 1680, 1583, 1500, 1464, 1456, 1436, 1427, 1378, 1322, 1236, 1177, 1141, 1108, 1076, 1029, 991, 909, 697, 652, 588 cm^{-1}.

HRMS (ESP): $[C_{22}H_{21}O_4]^+ = [M+H]^+$: calc 349.1440, found 349.1440.

Methyl (3,5-bis(benzyloxy)-4-methoxybenzyl)-D-tyrosine S8



To a stirred solution of aldehyde **S7** (3 g, 8.61 mmol) and methyl D-tyrosine **5** (1.765 g, 9.04 mmol, 1.05 equiv) in dry THF (57.4 mL) at rt under argon was added $NaBH(OAc)_3$ (4.562 g, 21.525 mmol, 2.5 equiv). The resulting mixture was stirred at rt overnight before being concentrated under vacuum.

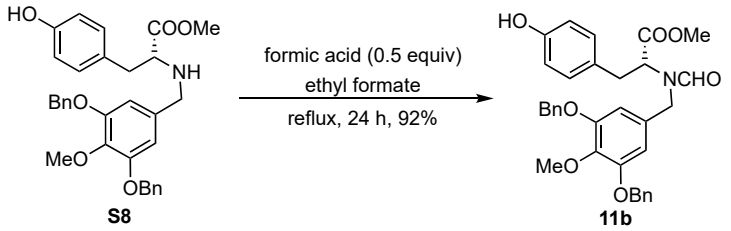
The crude residue was then dissolved in EtOAc (80 mL) and washed with aq. sat. $NaHCO_3$ solution (100 mL). The separated aqueous layer was then extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet. Ether/EtOAc 3:1, then 2:1) gave **S8** (4.1 g, 90%) as colorless foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 – 7.40 (Bn-H, m, 4H), 7.36 (Bn-H, m, 4H), 7.33 – 7.27 (Bn-H, m, 2H), 6.98 – 6.90 (Ar-H, m, 2H), 6.70 – 6.64 (Ar-H, m, 2H), 6.52 (Ar-H, s, 2H), 5.04 (Ph-CH_2, s, 4H), 3.87 (O-CH_3, s, 3H), 3.71 (NH-CH, d, *J* = 13.2 Hz, 1H), 3.66 (COO-CH_3, s, 3H), 3.52 – 3.41 (NH-CH_2, m, 2H), 2.91 – 2.76 (Ar-CH_2, m, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.1, 154.8, 152.4, 138.1, 137.1, 134.9, 130.3, 128.5, 128.4, 127.8, 127.3, 115.4, 107.5, 70.9, 61.7, 60.9, 51.9, 51.8, 38.6 ppm.

IR (neat): 3346, 3284, 3091, 3066, 3031, 2948, 2877, 2831, 1730, 1591, 1516, 1507, 1436, 1374, 1328, 1233, 1203, 1171, 1154, 1101, 1076, 1028, 1001, 908, 824, 779, 735, 696, 551 cm^{-1}.

Methyl *N*-(3,5-bis(benzyloxy)-4-methoxybenzyl)-*N*-formyl-D-tyrosine 11b



S8 **11b**

To a stirred solution of **S8** (6 g, 11.37 mmol) in ethylformate (64 mL) at rt formic acid (0.43 mL, 11.37 mmol, 1 equiv) was added. The resulting mixture was heated to 54 ºC and stirred overnight. Then the mixture was concentrated under vacuum. The residue was dissolved in EtOAc (100 mL) and washed with aq. sat. $NaHCO_3$ solution (120 mL). The separated aqueous layer was then extracted with EtOAc (2 x 60 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet.Ether/EtOAc 2:1, then 3:2) gave **11b** (5.8 g, 92%) as white foam. NMR data show that **11b** is a mixture of 1 : 1 ratio amide rotamers.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 and 8.07 (NCO-H, s, 1H), 7.48 – 7.40 (Bn-H, m, 4H), 7.40 – 7.33 (Bn-H, m, 4H), 7.33 – 7.27 (Bn-H, m, 2H), 6.85 and 6.68 (Ar-H, m, 1H), 6.84 – 6.69 (Ar-H, m, 1H), 6.65 (Ar-H, m, 2H), 6.55 and 6.30 (br s, OH), 6.43 and 6.34 (Ar-H, s, 2H), 5.03 (O-CH_2, s, 4H), 4.52 and 4.02 (N-CH-, dd, *J* = 10.5, 5.4 Hz, 1H), 4.38 and 3.78 (N-CH_2-, d, *J* = 14.8 Hz, 1H), 4.22 (N-CH_2-, dd, *J* = 14.8 Hz, 1H), 3.878 and 3.876 (O-CH_3, s, 3H), 3.64 and 3.55(COO-CH_3, s, 3H), 3.21 and 3.06 (Ar-CH_2, dd, *J* = 14.6, 5.4 Hz, 1H), 3.0 – 2.76 (Ar-CH_2, dd, *J* = 14.5, 10.1 Hz, 1H) ppm.

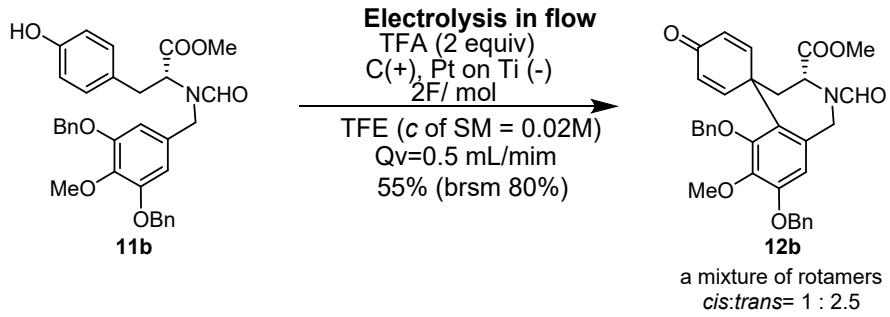
$[\alpha]_D^{20}$ = +76.9° (c = 0.052, MeOH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.6, 170.2, 163.7, 163.5, 155.3, 155.0, 152.6, 152.4, 139.1, 138.8, 137.0, 136.8, 131.3, 130.4, 129.9, 128.6, 128.5, 128.3, 128.0, 127.9, 127.4, 127.3, 126.8, 115.6, 115.4, 108.2, 107.8, 71.0, 70.9, 61.6, 60.9, 57.1, 52.5, 52.4, 51.5, 46.8, 35.6, 33.6 ppm.

IR (neat): 3337, 3065, 3032, 2949, 2878, 2832, 1739, 1653, 1614, 1593, 1516, 1506, 1436, 1372, 1353, 1327, 1267, 1230, 1203, 1172, 1159, 1101, 1077, 1003, 907, 736, 537 cm^{-1}.

TOF ES+ HRMS: $[M+Na]^+$ calcd. for $C_{33}H_{34}NO_7Na$ = 556.2335. Found = 556.2338.

Methyl (*R*)-6,8-bis(benzyloxy)-2-formyl-7-methoxy-4'-oxo-1,2,3,4-tetrahydrospiro[benzo[*c*]azepine-5,1'-cyclohexane]-2',5'-diene-3-carboxylate 12b



The electrolysis was performed in an undivided cell using a Vapourtec Ion Electrochemical Flow Reactor (reactor volume = 0.6 mL, spacer 0.5 mm) with Panasonic carbon as the anode and Pt plated on Ti as the cathode (surface area: A = 12 cm^2). A solution of **11b** (0.5 g, 0.9 mmol) and TFA (0.103 mL, 1.35 mmol, 1.5 equiv) in TFE (45 mL) was pumped into the electrochemical reactor through a syringe pump (0.5 mL/min) applying constant current conditions (I = 32 mA, Q = 2 F). After reaching a steady state (2.4 min, 2 reactor vol.), the solution was collected and concentrated under vacuo. Purification of the crude mixture by SiO_2 flash chromatography ($CHCl_3$/MeOH 200:1, then 160:1) gave **12b** (0.276 g, 55%) as yellowish foam and **11b** (0.156 g, 31%) was recovered as a yellowish foam. The TLC of compound **12b** showed two closely running spots corresponding to the two amide rotamers which were clearly apparent from the NMR spectrum, the ratio of *cis* / *trans* rotamers is 1 : 2.5.

$[\alpha]_D^{20}$ = –35.7° (c = 0.056, MeOH).

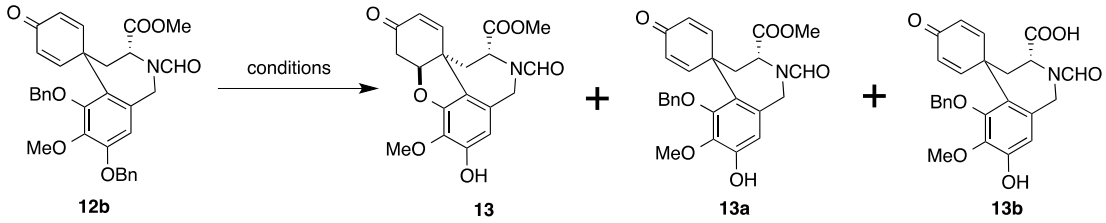
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 and 8.19 (s, 1H), 7.47 – 7.28 (m, 8H), 7.23 – 7.20 (m, 2H), 7.02 and 6.95 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.91 and 6.87 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.72 and 6.57 (s, 1H), 6.26 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.05 and 6.04 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.21 – 4.91 (m, 5H), 4.82 and 4.81 (d, *J* = 10.8 Hz, 1H), 4.44 (d, *J* = 17.0 Hz, 1H), 3.76 and 3.75 (s, 3H), 3.733 and 3.726 (s, 3H), 2.86 (dd, *J* = 15, 13 Hz, 1H), 2.13 – 2.04 (m, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 184.89 and 184.86, 170.76 and 170.75, 162.75 and 162.16, 157.09 and 156.38, 153.50 and 153.08, 151.99 and 151.98, 150.34 and 149.61, 142.53 and 142.14, 136.77 and 136.64, 136.37 and 136.26, 133.21 and 132.97, 129.63 and 129.41, 128.70 and 128.62, 128.37 and 128.34, 128.24 and 128.12, 127.89 and 127.83, 127.67 and 127.66, 127.41 and 127.29, 125.00 and 124.66, 123.60 and 123.16, 110.64 and 109.92, 75.70 and 75.66, 71.01 and 70.74, 60.88 and 60.82, 57.64 and 53.22, 52.97 and 52.71, 49.38 and 46.63, 46.68 and 44.29, 41.11 and 40.72 ppm.

IR (neat): 3062, 3033, 3004, 2954, 2933, 1743, 1658, 1620, 1592, 1572, 1497, 1455, 1413, 1374, 1328, 1209, 1120, 1097, 1071, 1029, 1001, 908, 857, 813, 737, 696, 601, 523 cm^{-1}.

TOF ES+ HRMS: $[M+H]^+$ calcd. for $C_{33}H_{32}NO_7$ = 554.2179. Found = 554.2188.

Optimisation for debenzylation of 12b



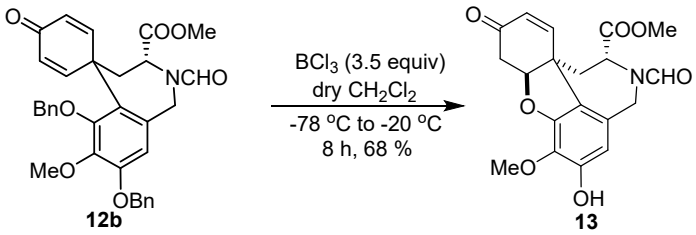
12b **13** **13a** **13b**

Table S6: Investigation of the debenzylation of **12b**

Entry	Reagent	Solvent	Temperature [ºC]	Time [h]	Product(s)
1	CF_3COOH	CH_3SCH_3	rt	24	-
2	CH_3SO_3H	CH_3SCH_3	rt	24	-
3	BCl_3	CH_2Cl_2	–78	1	**13a**
4	BCl_3	CH_2Cl_2	–78	48	**13**, **13a**
5	BCl_3	CH_2Cl_2	–78	168	**13**, **13a**
6	BCl_3	CH_2Cl_2	–78, then –40	24	**13**, **13a**
7	BCl_3	CH_2Cl_2	–78, then –20	1	**13**
8	BCl_3	CH_2Cl_2	–78, then 0	1	**13a**, **13b**

We examined the debenzylation step with Node's procedures,[6] the combination of dimethyl sulfide with strong acid such as trifluoroacetic acid or methanesulfonic acid. This gave very messy results (Table S6, entries 1-2). Only the Lewis acid BCl_3 at –78 ºC conditions gave clean deprotection, but no matter how long the reaction was kept at –78 ºC, we always obtain a mixture of mono deprotection product **13a** with the desired product **13** by uncertain ratio (Table S6, entries 3-5). And it is very difficult to separate these two products. To optimise these conditions, different reaction temperatures were investigated. At temperatures higher than –20 ºC (Table S6, entry 8), the hydrolysis of the ester group was observed. At temperatures lower than –40 ºC (Table S6, entry 6), the reaction is not going to completion. In the end, it worked out that after the mono deprotection performed at –78 ºC, the reaction should be warmed up to –20 ºC and one more equivalent BCl_3 needs to be added to drive the reaction to completion (Table S6, entry 7). The yield was finally improved to 68%.

Methyl (4aS,8aS,10S)-11-formyl-2-hydroxy-3-methoxy-6-oxo-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 13



To a stirred solution of **12b** (2.16 g, 3.9 mmol) in dry CH_2Cl_2 (39 mL) at –78 ºC under argon was added BCl_3 (1 M solution in CH_2Cl_2) (5.85 mL, 5.85 mmol, 1.5 equiv) dropwise over 5 min. The resulting mixture was stirred at –78 ºC around 1 h until the TLC indicated the disappearance of the starting material **12b**. Then the reaction could warm up to –30 ºC and BCl_3 (1 M solution in CH_2Cl_2) (7.8 mL, 7.8 mmol, 2 equiv) was added dropwise over 8 min. The reaction was stirred at –20 ºC for 6 h, then diluted with CH_2Cl_2 (20 mL) and quenched with aq. sat. $NaHCO_3$ solution (40 mL). The biphasic mixture was stirred at rt for 15 min and then transferred to a separating funnel. The separated aqueous layer was then extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography ($CHCl_3$/MeOH 200:1, then 160:1, then 120:1) gave **13** (0.98 g, 68%, dr = 3.3 : 1) as white foam. The diastereoisomer of **13** cannot be removed at this stage, the NMR spectra show a mixture of diastereoisomers.

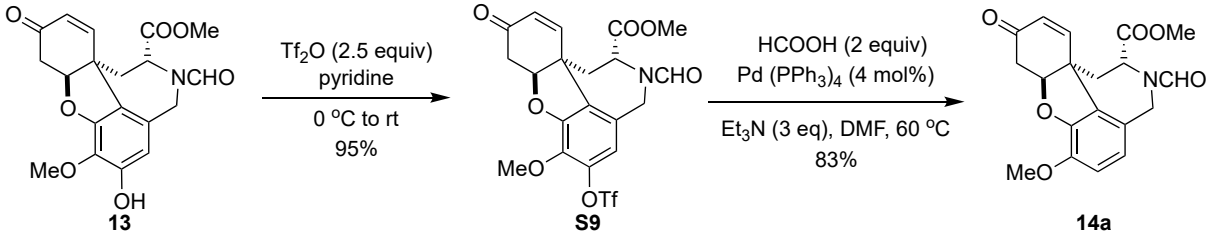
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (CHO, s, 1H), 6.40 (-CH=CH-, dd, *J* = 10.4, 2.3 Hz, 1H), 6.35 (Ar, s, 1H), 6.06 (-CH=CH-, dd, *J* = 10.4, 0.7 Hz, 1H), 5.88 (Ar-OH, s, 1H), 5.24 (brs, 1H), 4.69 (dd, *J* = 5.4, 3.0 Hz, 1H), 4.64 (dd, *J* = 39.3, 17.7 Hz, 2H), 3.92 (s, 3H), 3.76 (s, 3H), 3.10 (ddd, *J* = 17.7, 2.9, 1.0 Hz, 1H), 2.80 (dd, *J* = 17.7, 3.3 Hz, 1H), 2.64 (ddd, *J* = 13.9, 6.1, 0.5 Hz, 1H), 2.40 (dd, *J* = 13.9, 12.9 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 193.9, 170.4, 163.9, 149.1, 144.2, 131.2, 128.7, 122.4, 105.7, 88.2, 60.6, 52.8, 51.9, 47.7, 46.5, 37.0, 35.1 ppm.

IR (neat): 3346, 2954, 1735, 1662, 1600, 1508, 1421, 1394, 1355, 1249, 1197, 1168, 1056, 1026, 1006, 985, 748, 698, 667, 624 cm^{-1}.

TOF ES+ HRMS: $[M+Na]^+$ calcd. for $C_{19}H_{20}NO_7Na$ = 374.1240. Found = 374.1241.

Methyl (4aS,8aS,10S)-11-formyl-3-methoxy-6-oxo-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 14a



To a stirred solution of **13** (2.3 g, 6.16 mmol) in the dry pyridine (41 mL, *c* = 0.15 M) at 0 ºC under argon, Tf_2O (2.59 mL, 15.4 mmol, 2.5 equiv) was added dropwise over 10 min. The resulting solution was stirred at 0 ºC for 1 h and then stirred at rt for 4 h. The reaction was then diluted with CH_2Cl_2 (100 mL) and washed with 10% aq. HCl (2 x 60 mL). The combined acid aqueous layers were extracted with CH_2Cl_2 (60 mL). The combined organic layers were then washed with aq. sat. $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography ($CHCl_3$/MeOH 300:1, then 200:1) gave **S9** (2.96 g, 95%) as yellowish foam.

To a stirred solution of **S9** (2.9 g, 5.74 mmol) and $Pd(PPh_3)_4$ (0.265 g, 0.23 mmol, 0.04 equiv) in dry DMF (38.3 mL) at rt under argon, Et_3N (2.4 mL, 17.22 mmol, 3 equiv) was added followed by HCOOH (0.433 mL, 11.48 mmol, 2 equiv). The resulting mixture was heated to 60 ºC and stirred for 2 h. Then the reaction was cooled to rt and diluted with EtOAc (100 mL) and washed with aq. sat. $NaHCO_3$ (100 mL). The separated aqueous layer was extracted with EtOAc (2 x 60 mL). The combined organic layers were washes with cold H_2O (3 x 80 mL). The combined water layers were then extracted with EtOAc (50 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography ($CHCl_3$/MeOH 300:1, then 200:1, then 150:1) gave **14a** (1.7 g, 83%, dr = 3.3 : 1) as yellowish foam.

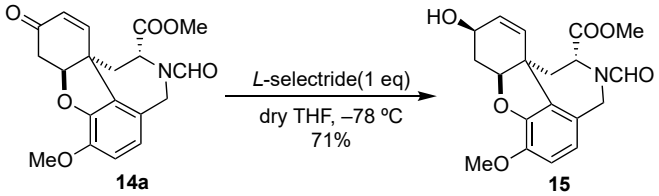
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (CHO, s, 1H), 6.73 (Ar, d, *J* = 8.3 Hz, 1H), 6.71 (Ar, d, *J* = 8.3 Hz, 1H), 6.39 (-CH=CH-, dd, *J* = 10.4, 2.3 Hz, 1H), 6.07 (-CH=CH-,dd, *J* = 10.4, 0.7 Hz, 1H), 5.22 (brs, 1H), 4.70 (m, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.15 (ddd, *J* = 17.9, 2.7, 0.95 Hz, 1H), 2.80 (dd, *J* = 17.9, 3.4 Hz, 1H), 2.64 (ddd, *J* = 13.9, 5.9, 0.6 Hz, 1H), 2.43 (dd, *J* = 13.9, 13.0 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 193.5, 170.3, 163.8, 147.7, 144.5, 143.4, 130.2, 129.2, 126.5, 119.4, 112.8, 87.5, 56.2, 52.8, 52.0, 47.6, 47.1, 36.7, 34.8 ppm.

IR (neat): 3001, 1737, 1666, 1625, 1508, 1435, 1282, 1213, 1193, 1174, 1070, 1002, 979, 798 cm^{-1}.

TOF ES+ HRMS: $[M+H]^+$ calcd. for $C_{19}H_{20}N_1O_6$ = 358.1291. Found = 358.1288.

Methyl (4a*S*,6*R*,8a*S*,10*S*)-11-formyl-6-hydroxy-3-methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 15



To a stirred solution of **14a** (0.14 g, 0.392 mmol) in dry THF (4 mL) at –78 ºC L-selectride (1 M solution in THF) (0.4 mL, 0.4 mmol, 1.02 equiv) was added dropwise over 3 min. The resulting solution was stirred at –78 ºC for 30 min, then quenched by MeOH (1 mL). The reaction solvent was then removed under vacuum. The residue was dissolved in CH_2Cl_2 (10 mL), an sat. aq. solution of Rochelle salt (15 mL) was added and the biphasic mixture was stirred at rt for 20 min. The separated aqueous layer was then extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered

and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet.Ether/EtOAc 1:1, then 1:2) yielded **15** (0.1 g, 71%, dr = 3.3 : 1) as yellowish foam.

$[\alpha]_D^{20}$ = –40.0° (c = 0.05, MeOH).

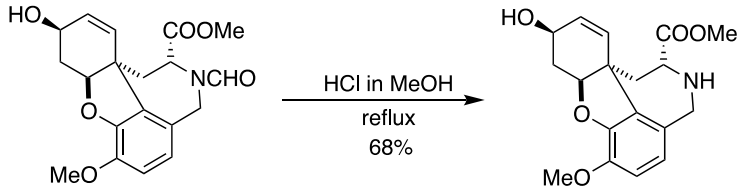
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.07 (ddd, *J* = 10.1, 5.0, 1.1 Hz, 1H), 5.5 (d, *J* = 10.1 Hz, 1H), 5.20 (brs, 1H), 4.68 (d, *J* = 6.1 Hz, 2H), 4.62 (dd, *J* = 3.9, 2.1 Hz, 1H), 4.16 (m, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.70 (m, 1H), 2.39 (m, 1H), 2.25 (dd, *J* = 13.6, 12.9 Hz, 1H), 2.11 (ddd, *J* = 15.8, 5.2, 2.1 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9, 163.8, 146.7, 144.5, 132.5, 130.2, 126.6, 126.3, 119.2, 112.1, 88.4, 61.6, 56.1, 52.7, 46.5, 35.2, 29.5 ppm.

IR (neat): 3057, 2957, 2931, 2878, 2839, 1742, 1669, 1624, 1591, 1507, 1436, 1280, 1220, 1177, 1118, 1071, 1011, 996, 981, 863, 845, 803, 754, 719, 693, 669, 535, 504 cm^{-1}.

TOF ES+ HRMS: $[M+H]^+$ calcd. for $C_{19}H_{22}NO_6$ = 360.1447. Found = 360.1456.

Methyl (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate S10



15 **S10**

Amide **15** (0.28 g, 0.779 mmol) and a 1.25 M HCl solution in MeOH (10 mL) was heated to reflux and stirred for 5 h before being cooling down to rt and concentrated under vacuum. Aq. sat. $NaHCO_3$ (15 mL) was added carefully to the crude residue, then CH_2Cl_2 (15 mL) was added. The biphasic solution was stirred at rt for 20 min. The separated aqueous layer was then extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet.Ether/EtOAc 1:2, then 1:3) gave **S10** (0.176 g, 68%) as a white foam.

$[\alpha]_D^{20}$ = –52.0° (c = 0.05, MeOH).

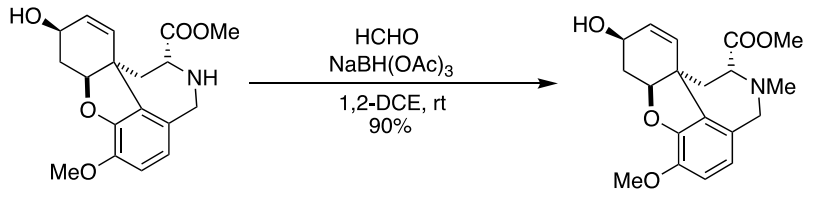
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.69 (dd, *J* = 15.2, 8.23 Hz, 2H), 6.04 (ddd, *J* = 10.1, 4.9, 1.1 Hz, 1H), 5.95 (dt, *J* = 10.1, 1.0 Hz, 1H), 4.60 (p, *J* = 1.5 Hz, 1H), 4.15 (t, *J* = 4.54 Hz, 1H), 4.03 (s, 2H), 3.96 (dd, *J* = 11.9, 1.9 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.69 (ddt, *J* = 15.7, 3.5, 1.5 Hz, 1H), 2.20 (dd, *J* = 13.2, 1.9 Hz, 1H), 2.04 (ddd, *J* = 15.8, 5.1, 2.4 Hz, 1H), 1.78 (dd, *J* = 13.0, 12.0 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.5, 146.2, 144.1, 132.8, 132.2, 128.4, 126.4, 120.5, 111.2, 88.2, 61.9, 59.9, 55.9, 52.3, 52.0, 47.8, 42.5, 29.8 ppm.

IR (neat): 3519, 3296, 3025, 2942, 2917, 2906, 2835, 1734, 1683, 1623, 1589, 1507, 1434, 1366, 1277, 1217, 1206, 1194, 1174, 1136, 1122, 1102, 1054, 1004, 976, 946, 802, 746, 665, 644, 535, 509 cm^{-1}.

TOF ES+ HRMS: $[M+H]^+$ calcd. for $C_{18}H_{22}NO_5$ = 332.1498. Found = 332.1512.

Methyl (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 16



S10 **16**

Amine **S10** (0.1g, 0.3 mmol) was dissolved in 1,2-dichloroethane (1,2-DCE) (6 mL) under argon and 37% aq. formaldehyde (44.9 µL, 0.6 mmol, 2 equiv) was added. The solution was stirred at rt for 15 min before sodium triacetoxyborohydride (0.254 g, 1.2 mmol, 4 equiv) was added. The solution was stirred at rt for 2 h, then diluted with CH_2Cl_2 (10 mL) and stirred with aq. sat. $NaHCO_3$ (15 mL) for 10 min. The separated aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude residue by SiO_2 flash chromatography (Pet.Ether/EtOAc 1:2, then 1:3) gave **16** (92 mg, 90%) as white foam.

$[\alpha]_D^{20} = -76.9°$ (c = 0.052, MeOH).

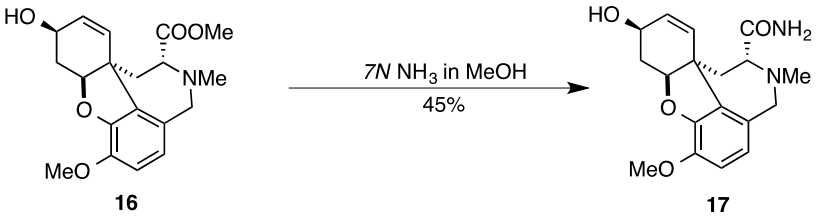
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.68 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.02 (ddd, *J* = 10.2, 5.0, 1.3 Hz, 1H), 5.95 (dt, *J* = 10.1, 1.3 Hz, 1H), 4.65 (p, *J* = 1.9 Hz, 1H), 4.23 (d, *J* = 15.9 Hz, 1H), 4.23 – 4.08 (m, 2H), 3.98 (d, *J* = 15.9 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 2.70 (ddt, *J* = 15.7, 3.5, 1.5 Hz, 1H), 2.37 (m, 1H), 2.24 (s, 3H), 2.20 (dd, *J* = 14.0, 12.5 Hz, 1H), 2.07 (ddd, *J* = 15.8, 5.1, 2.2 Hz, 1H), 1.93 (dd, *J* = 14.0, 2.2 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.7, 145.9, 144.2, 132.0, 128.8, 128.4, 126.1, 122.0, 111.4, 88.4, 63.2, 61.9, 59.7, 55.9, 52.4, 47.3, 34.4, 29.8 ppm.

IR (neat): 3370, 3028, 3003, 2948, 2930, 2874, 2844, 2793, 1728, 1617, 1589, 1507, 1437, 1419, 1374, 1362, 1288, 1249, 1201, 1182, 1169, 1140, 1050, 983, 847, 747, 647, 539 cm^{-1}.

TOF ES+ HRMS: $[M+H]^+$ calcd. For $C_{19}H_{24}NO_5$ = 346.1654. Found = 346.1662.

(4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxamide 17



16 **17**

To the 5 mL round bottom flask which contained the alcohol **16** (0.03 g, 0.087 mmol) and a stirrer bar inside was added NH_3 (7 N in MeOH) (1 mL). The reaction flask was then sealed with septum and parafilm and stirred for 10 days before the reaction solvent was removed under vacuum. The crude mixture was dissolved in EtOAc (5 mL) and washed with aq. sat. $NaHCO_3$ (5 mL). The separated aqueous phase was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried over

$MgSO_4$ and concentrated under vacuum. Purification of the crude residue by prep. TLC ($CHCl_3$/MeOH 20:1) gave **17** (13 mg, 25%) as white solid and **16** (6 mg, 20%) was recovered as white solid.

$[\alpha]^{20}_D$ = –48 (c 0.25, $CHCl_3$)

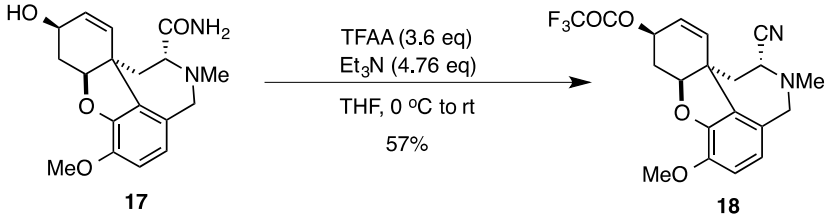
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (brd, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.62 (dd, *J* = 8.2, 0.7 Hz, 1H), 5.99 (ddd, *J* = 10.2, 5.1, 1.3 Hz, 1H), 5.88 (ddd, *J* = 10.2, 1.6, 0.8 Hz, 1H), 5.64 (brd, *J* = 8.6 Hz, 1H), 4.65 (p, *J* = 1.8 Hz, 1H), 4.34 (d, *J* = 15.7 Hz, 1H), 4.19 – 4.08 (m, 1H), 4.02 (dd, *J* = 12.4, 1.8 Hz, 1H), 3.88 (d, *J* = 15.8 Hz, 1H), 3.84 (s, 3H), 2.68 (ddt, *J* = 15.7, 3.5, 1.5 Hz, 1H), 2.38 (dd, *J* = 14.1, 1.9 Hz, 2H), 2.14 (ddd, *J* = 15.8, 5.1, 2.2 Hz, 1H), 2.13 (s, 3H), 1.94 (dd, *J* = 14.2, 12.3 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.8, 146.0, 144.4, 132.1, 128.4, 128.2, 126.0, 122.1, 111.4, 88.5, 64.0, 62.0, 60.1, 55.9, 47.3, 33.7, 29.8, 29.6 ppm.

IR (neat): 3432, 3316, 3028, 2930, 2840, 2364, 1684, 1624, 1507, 1437, 1283, 1223, 1195, 1166, 1143, 1120, 1092, 1048, 1004, 988, 955, 844, 798, 748, 696, 668, 540 cm^{-1}.

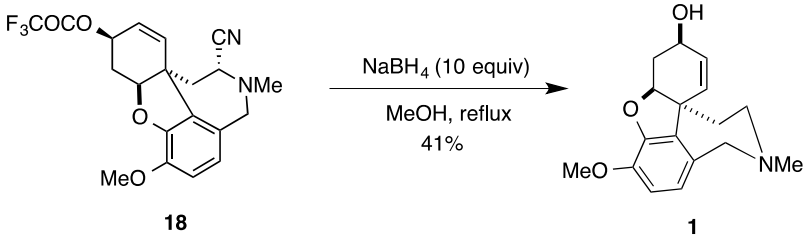
TOF ES+ HRMS: $[M+H]^+$ calcd. For $C_{18}H_{23}N_2O_4$ = 331.1658. Found = 331.1662.

(4a*S*,6*R*,8a*S*,10*S*)-10-cyano-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepin-6-yl 2,2,2-trifluoroacetate 18



To a stirred solution of **17** (10 mg, 0.03 mmol) in the dry THF (1 mL) at 0 ºC under argon TFAA (15 uL, 0.108 mmol, 3.6 equiv) was added followed by Et_3N (20 uL, 0.143 mmol, 4.76 equiv). The resulting solution was then allowed to warm to rt and stirred for 2 h before being concentrated under vacuum. The residue was then dissolved in EtOAc (5 mL) and washed with sat. $NaHCO_3$ solution (10 mL). The separated aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by prep. TLC ($CHCl_3$/MeOH 20:1) gave **18** (7 mg, 57%) as colorless oil.

(–)-Galanthamine 1



To a stirred solution of **18** (7 mg, 0.017 mmol) in dry MeOH (0.5 mL) at 0 ºC $NaBH_4$ (6.47 mg, 0.17 mmol, 10 equiv) was added. The resulting mixture was then heated to reflux and stirred for 2 h (another

30 equiv of $NaBH_4$ were added equally in 3 times in the next 20 h) before cooling down to rt and concentrating under vacuum. The residue was then dissolved in CH_2Cl_2 (10 mL) and washed with aq. sat. $NaHCO_3$ (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by prep. TLC ($CHCl_3$/MeOH 6:1) gave **1** (2 mg, 41%) as a white solid and recovered **18** (3 mg, 43%) as a white solid.

$[\alpha]^{20}_D$ = –50 (c 0.04, EtOH), (lit: $[\alpha]^{20}_D$ = −91.0 (c 1.0, $CHCl_3$, 99% *ee*).[7]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.68 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.06-6.0 (m, 2H), 4.68 – 4.59 (m, 1H), 4.21-4.12 (m, 2H), 3.84 (OCH_3, s, 3H), 3.77 (d, *J* = 15.2 Hz, 1H), 3.35 (t, *J* = 13.6 Hz, 1H), 3.12 (d, *J* = 14.4 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.46 (NCH_3, s, 3H), 2.11 (td, *J* = 13.4, 3.1 Hz, 1H), 2.01 (ddd, *J* = 15.7, 5.0, 2.5 Hz, 1H), 1.65 (d, *J* = 14.2 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.9, 144.5, 132.9, 128.0, 126.4, 122.4, 111.4, 88.7, 62.0, 60.3, 55.9, 53.7, 48.1, 41.4, 33.3, 29.9 ppm.

IR (neat): 3375, 3029, 2923, 2850, 2800, 1623, 1591, 1507, 1437, 1362, 1279, 1229, 1201,1166, 1151, 1125, 1112,1068, 1043, 989, 963, 948, 922, 869, 834, 799,750, 663, 640, 600, 549, 535 cm^{-1}.

TOF ES+ HRMS: $[M+Na]^+$ calcd. for $C_{17}H_{22}NO_5Na$ = 288.1600. Found = 288.1605.

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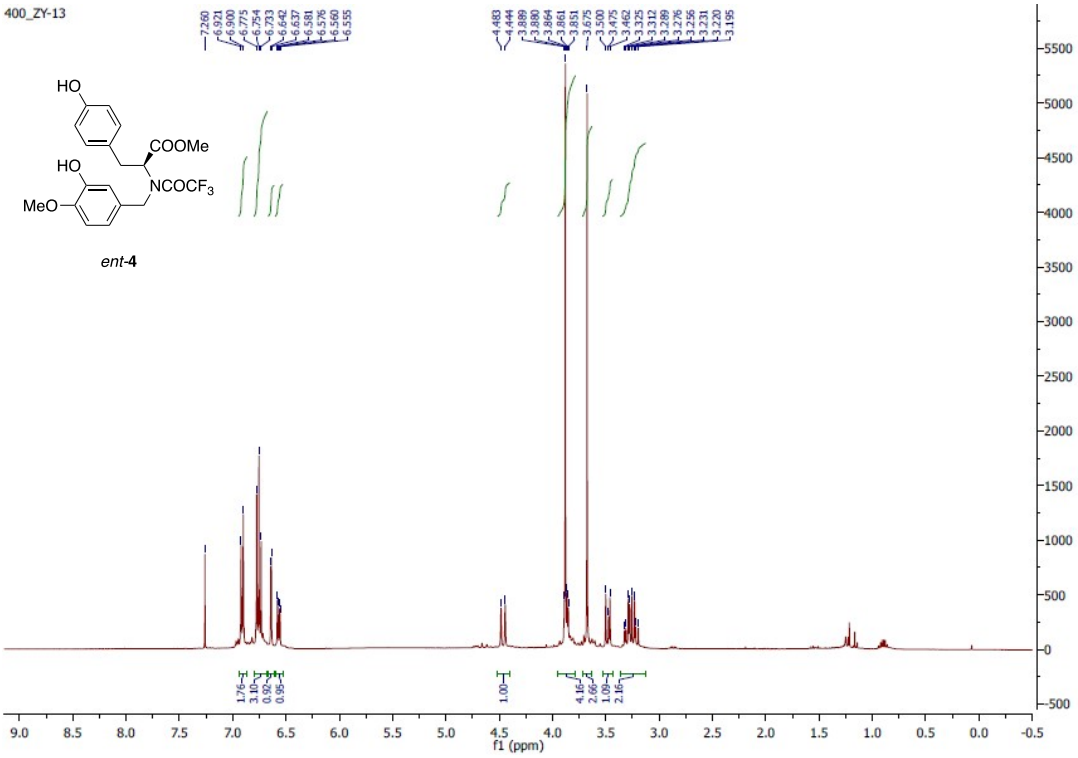
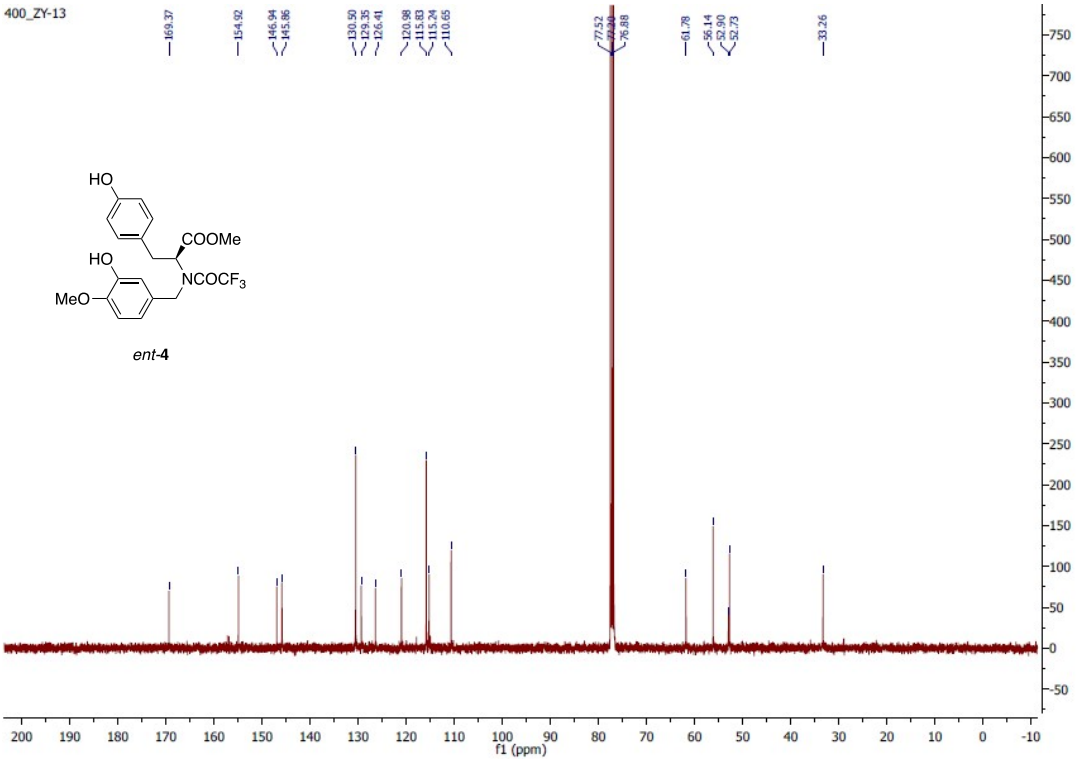
NMR spectra:

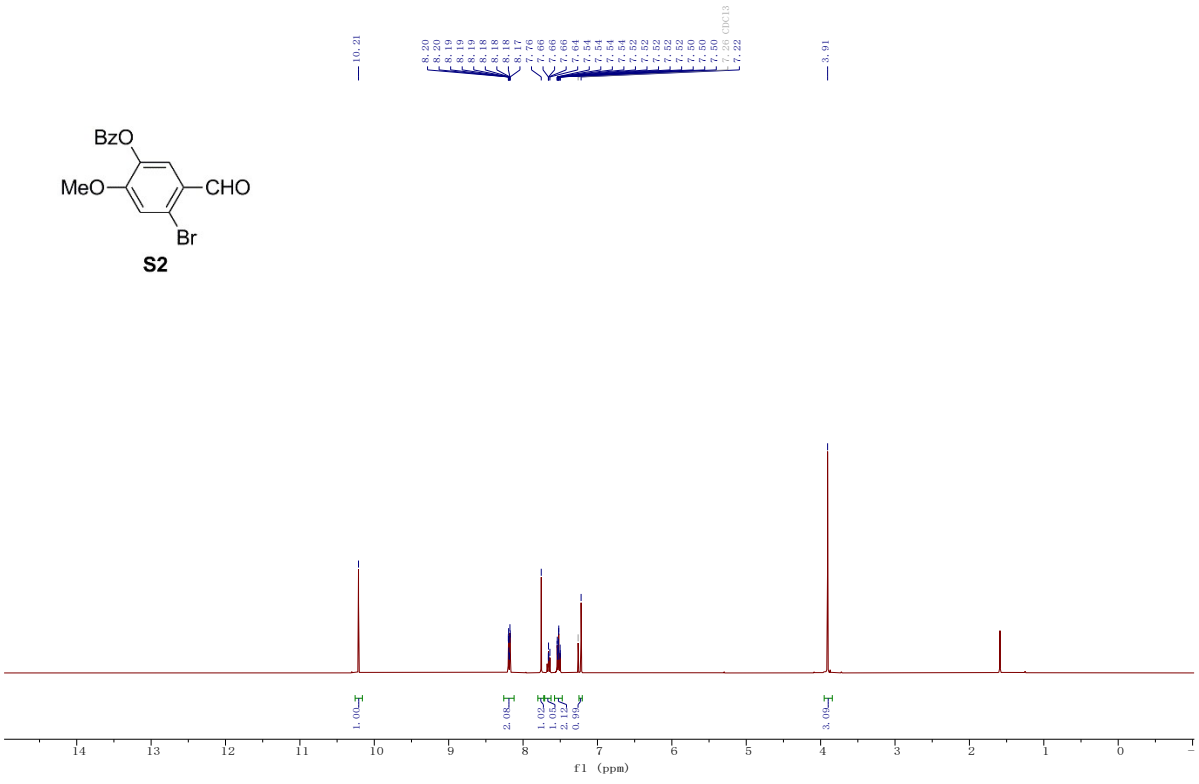
^{1}H NMR (400 Hz, $CDCl_3$): Methyl *N*-(3-hydroxy-4-methoxybenzyl)-*N*-(2,2,2-trifluoroacetyl)-L-tyrosinate *ent*-4



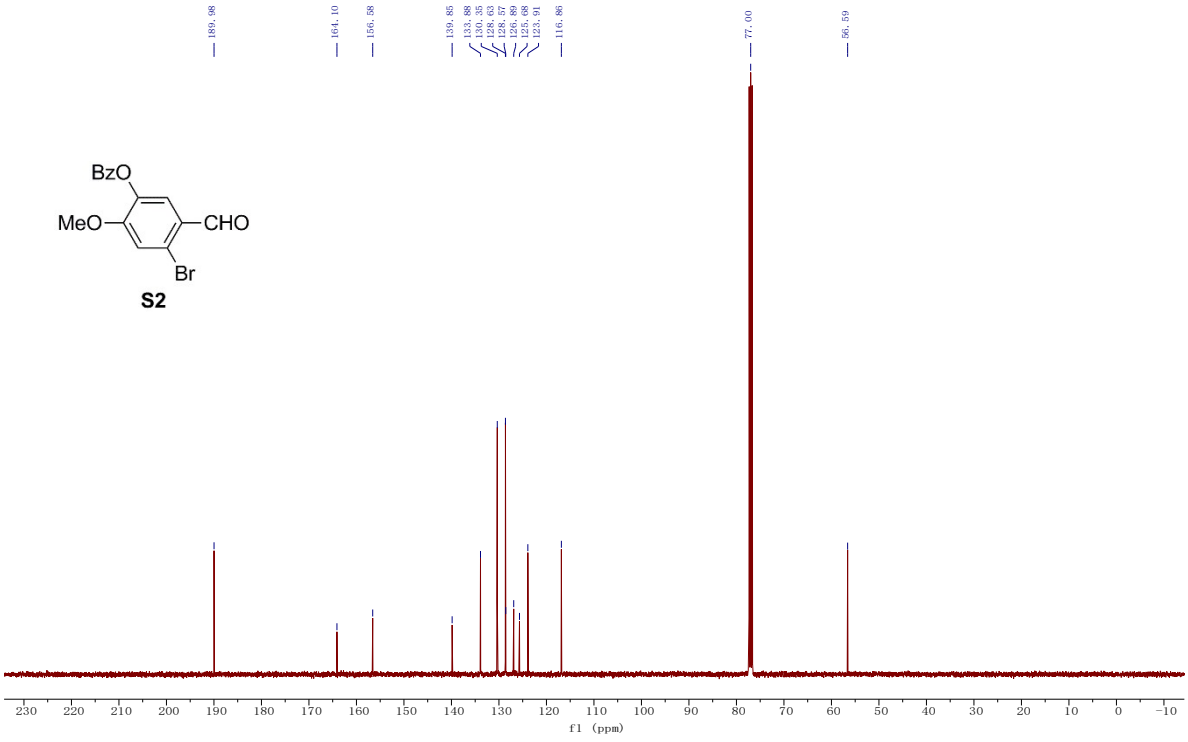
^{13}C NMR (101 Hz, $CDCl_3$): Methyl *N*-(3-hydroxy-4-methoxybenzyl)-*N*-(2,2,2-trifluoroacetyl)-L-tyrosinate *ent*-4



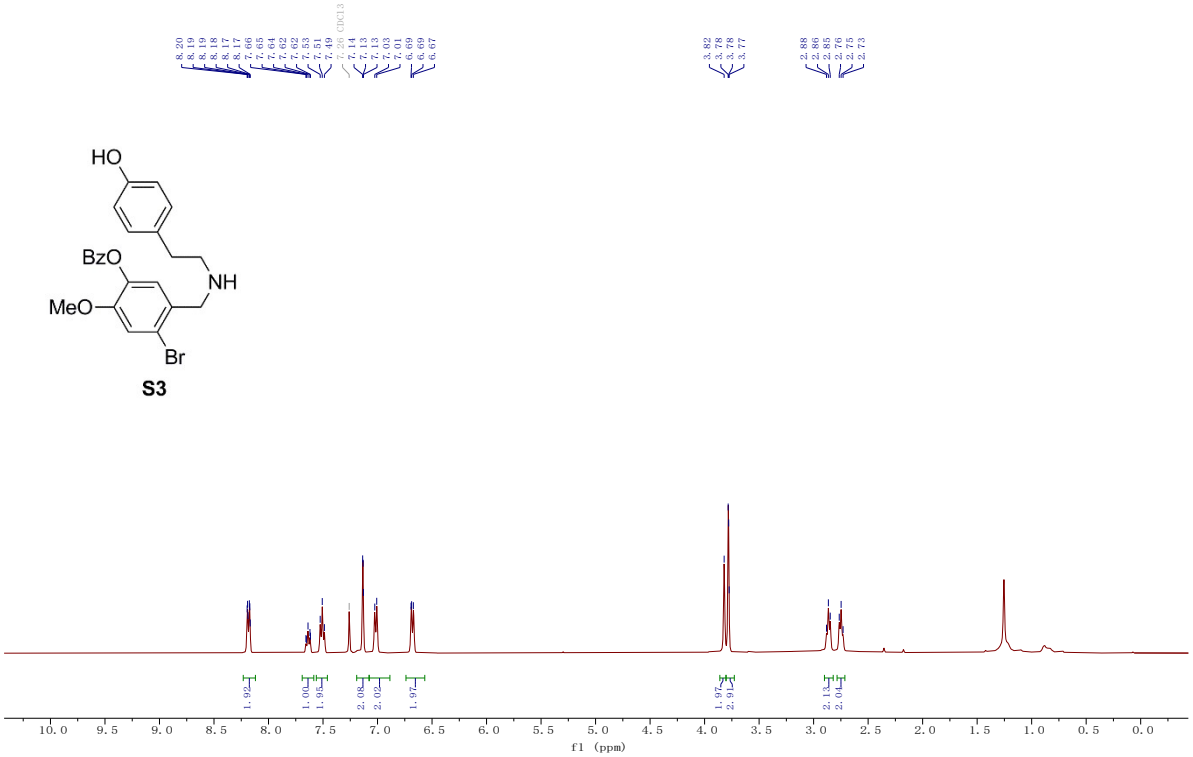
^{1}H NMR (400 Hz, $CDCl_3$): 4-Bromo-5-formyl-2-methoxyphenyl benzoate S2



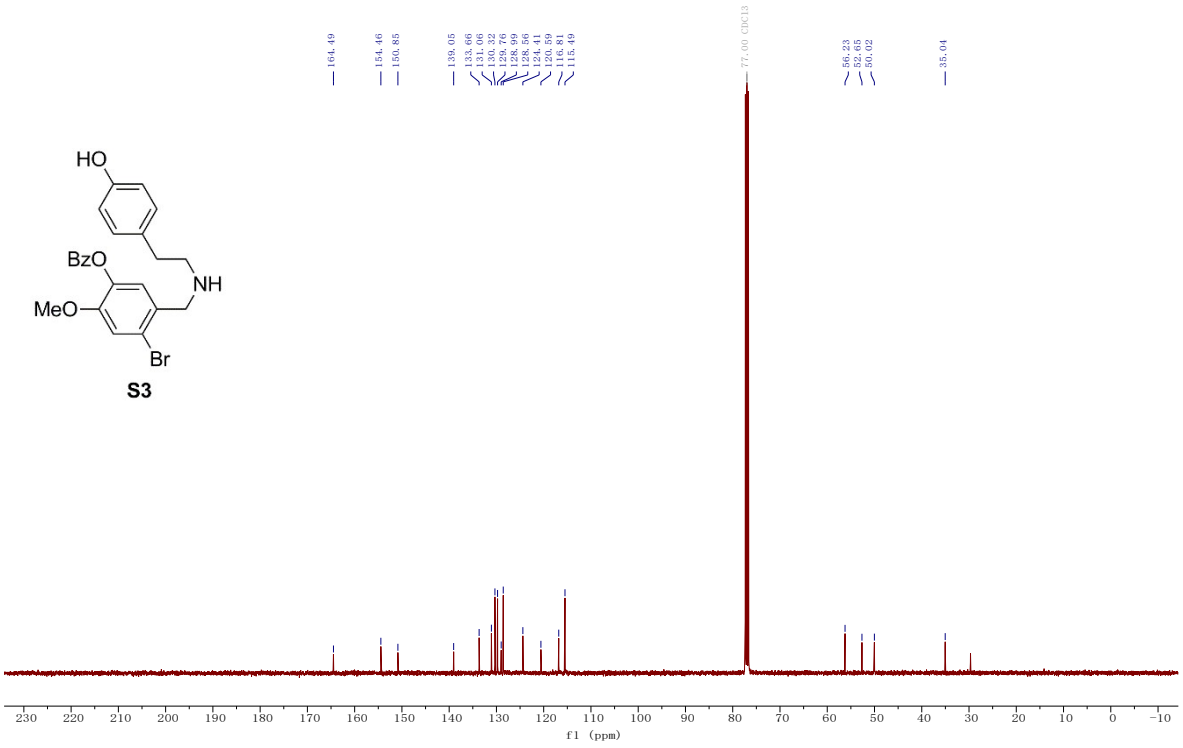
^{13}C NMR (101 Hz, $CDCl_3$): 4-Bromo-5-formyl-2-methoxyphenyl benzoate S2



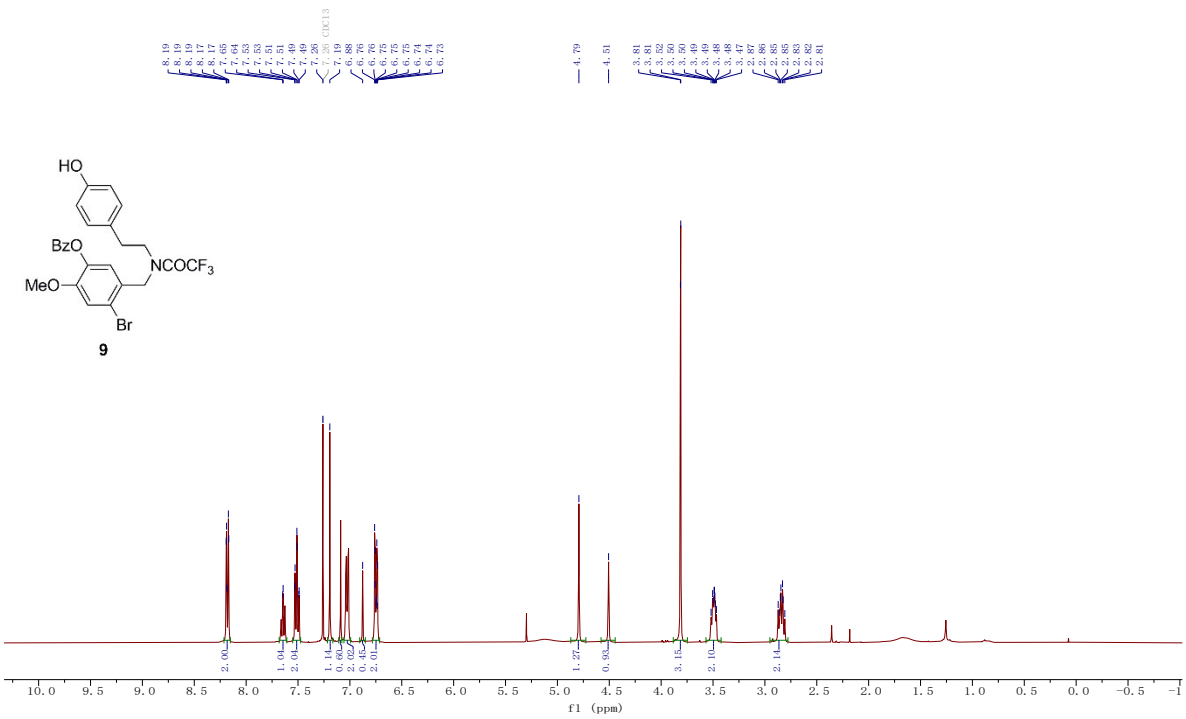
^{1}H NMR (400 Hz, $CDCl_3$): 4-Bromo-5-(((4-hydroxyphenethyl)amino)methyl)-2-methoxyphenyl benzoate S3



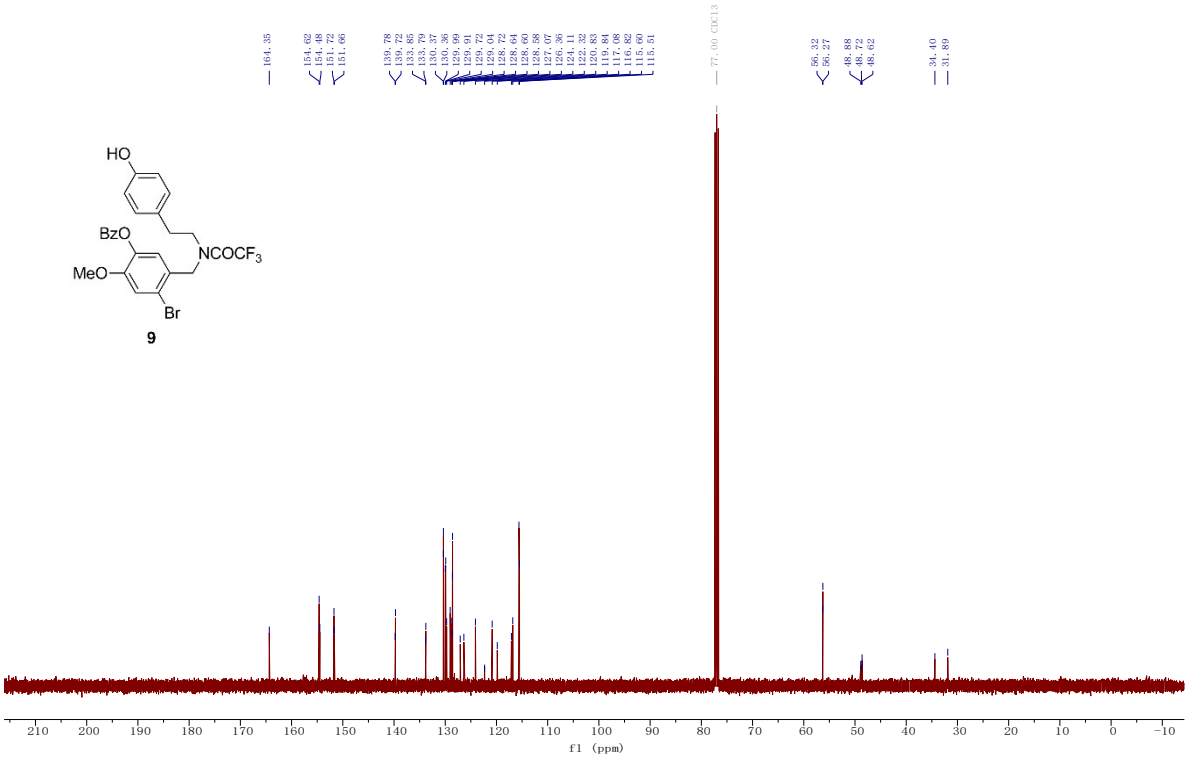
^{13}C NMR (101 Hz, $CDCl_3$): 4-Bromo-5-(((4-hydroxyphenethyl)amino)methyl)-2-methoxyphenyl benzoate S3



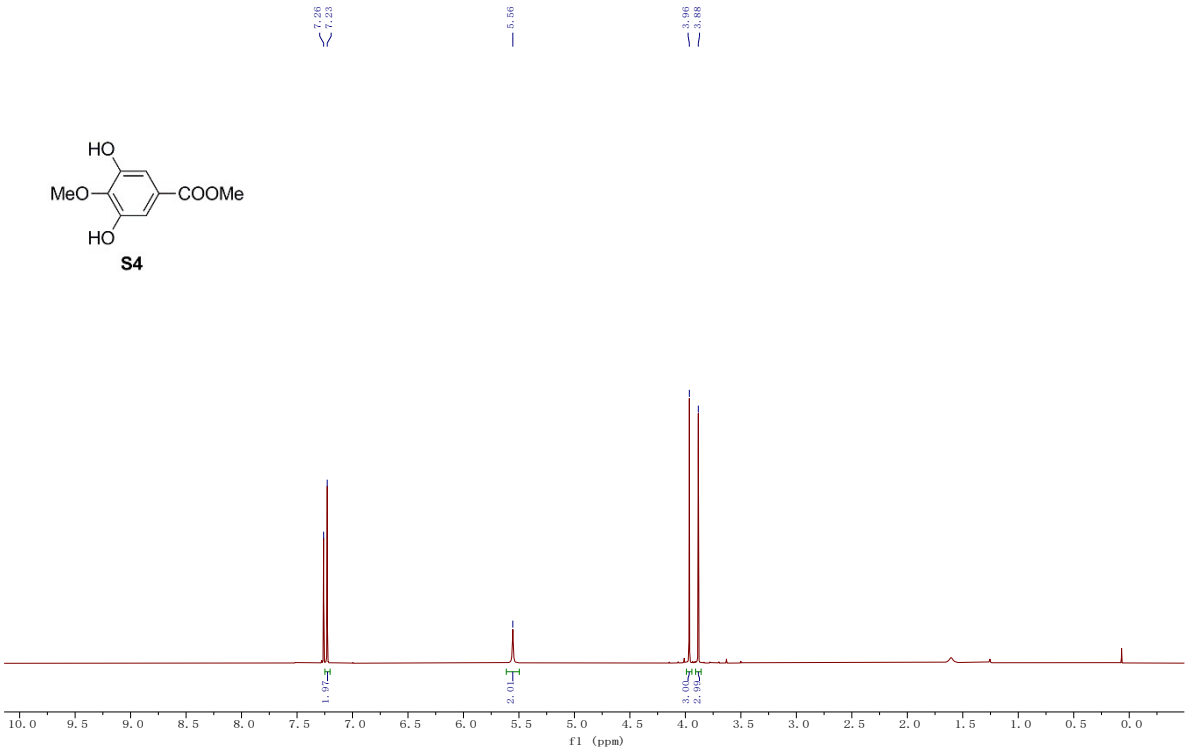
^{1}H NMR (400 Hz, $CDCl_3$): 4-Bromo-2-methoxy-5-((2,2,2-trifluoro-*N*-(4 hydroxyphenethyl)acetamido)methyl)phenyl benzoate 9



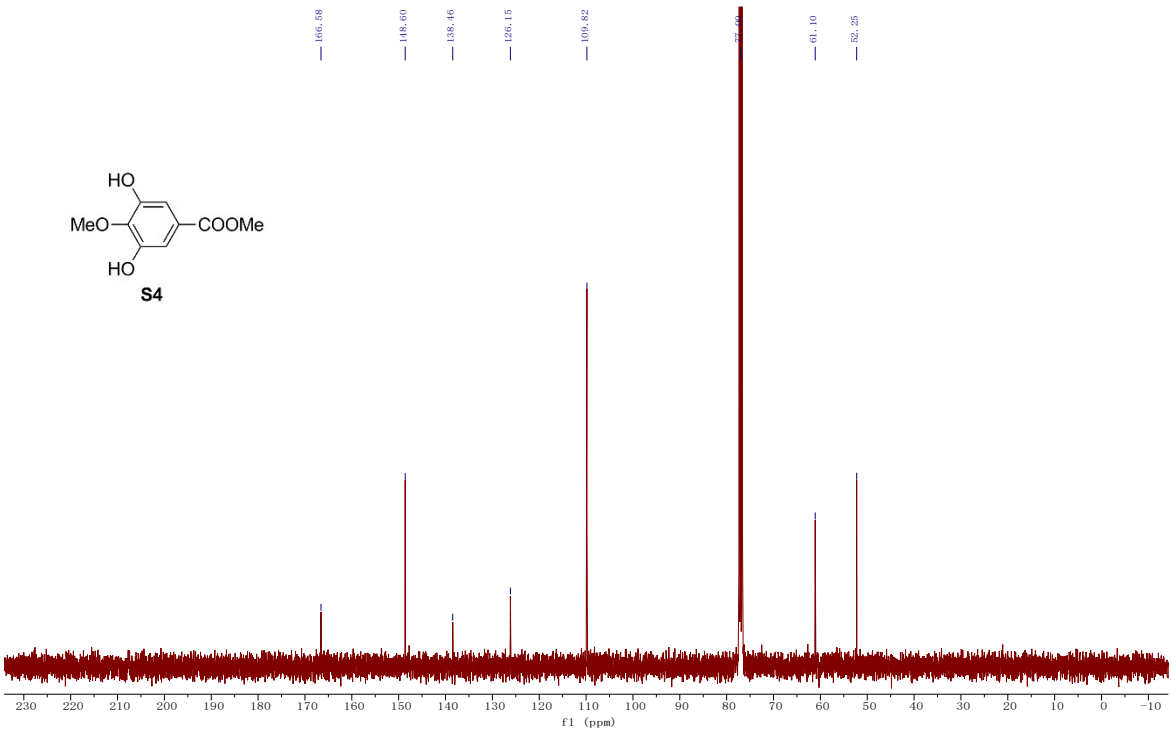
^{13}C NMR (101 Hz, $CDCl_3$): 4-Bromo-2-methoxy-5-((2,2,2-trifluoro-*N*-(4-hydroxyphenethyl)acetamido)methyl)phenyl benzoate 9



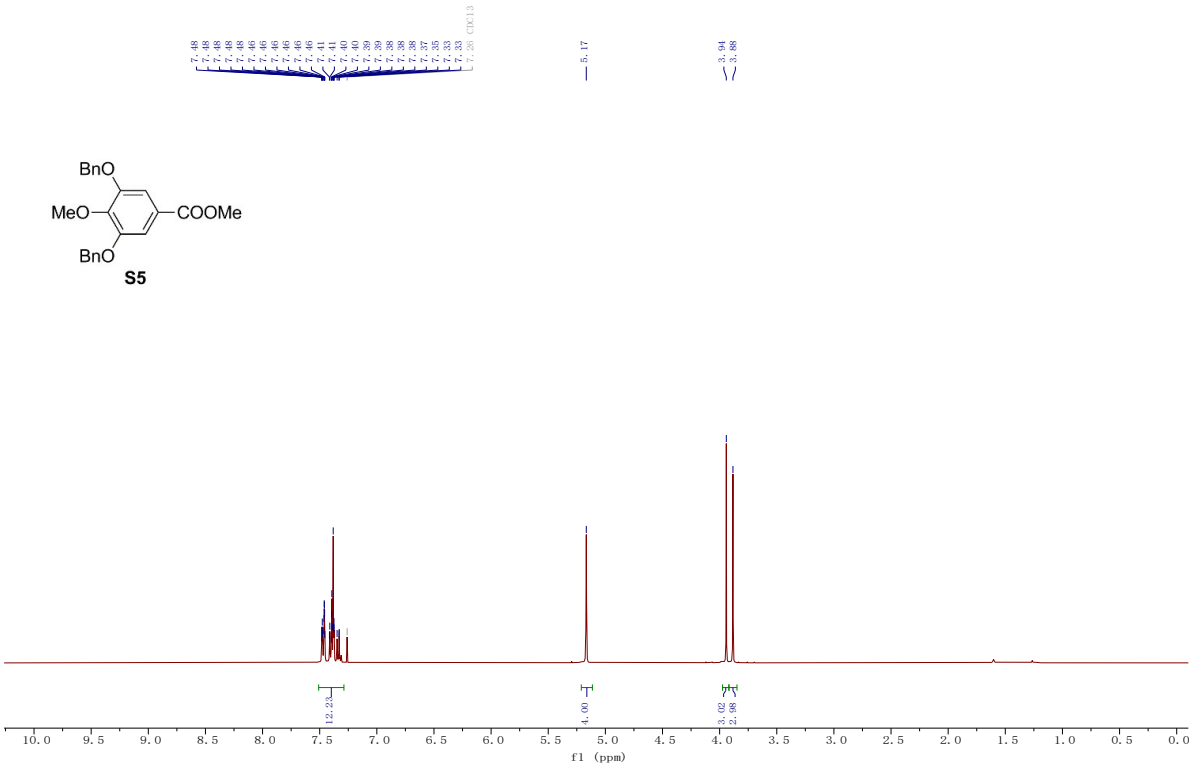
^{1}H NMR (400 Hz, $CDCl_3$): Methyl 3,5-dihydroxy-4-methoxybenzoate S4



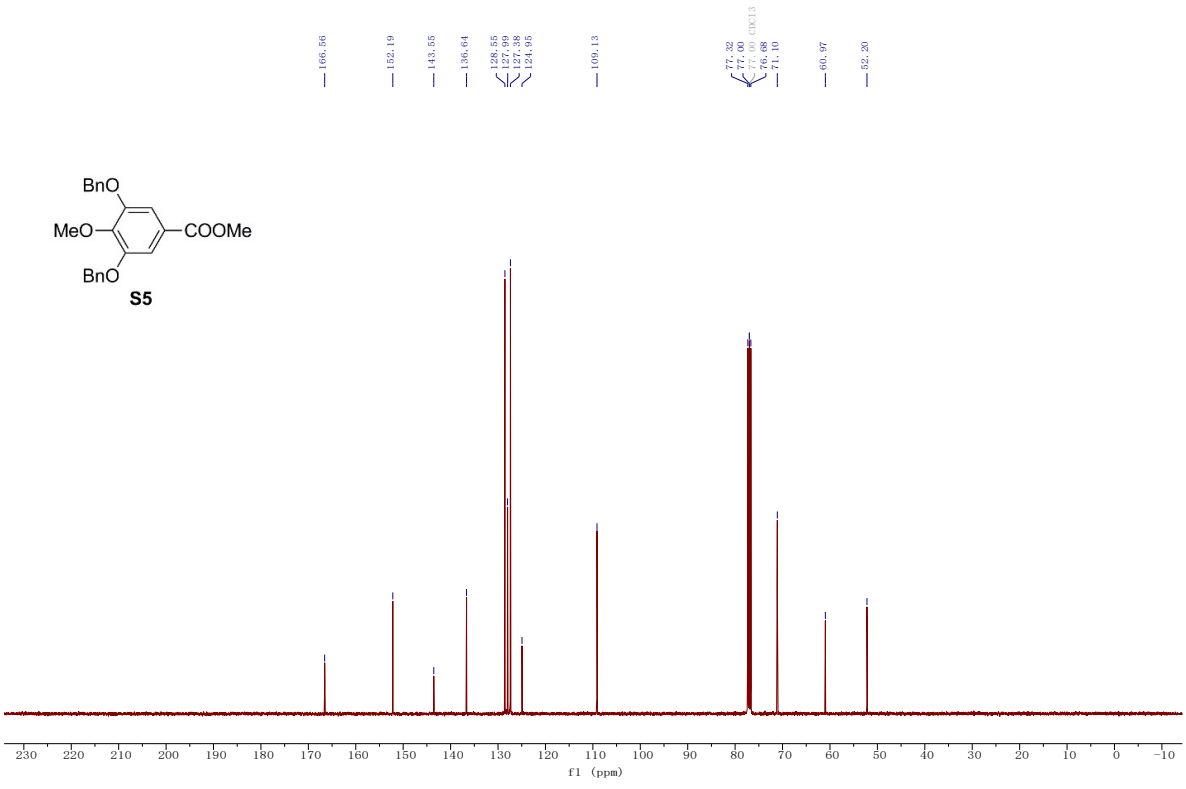
^{13}C NMR (101 Hz, $CDCl_3$): Methyl 3,5-dihydroxy-4-methoxybenzoate S4



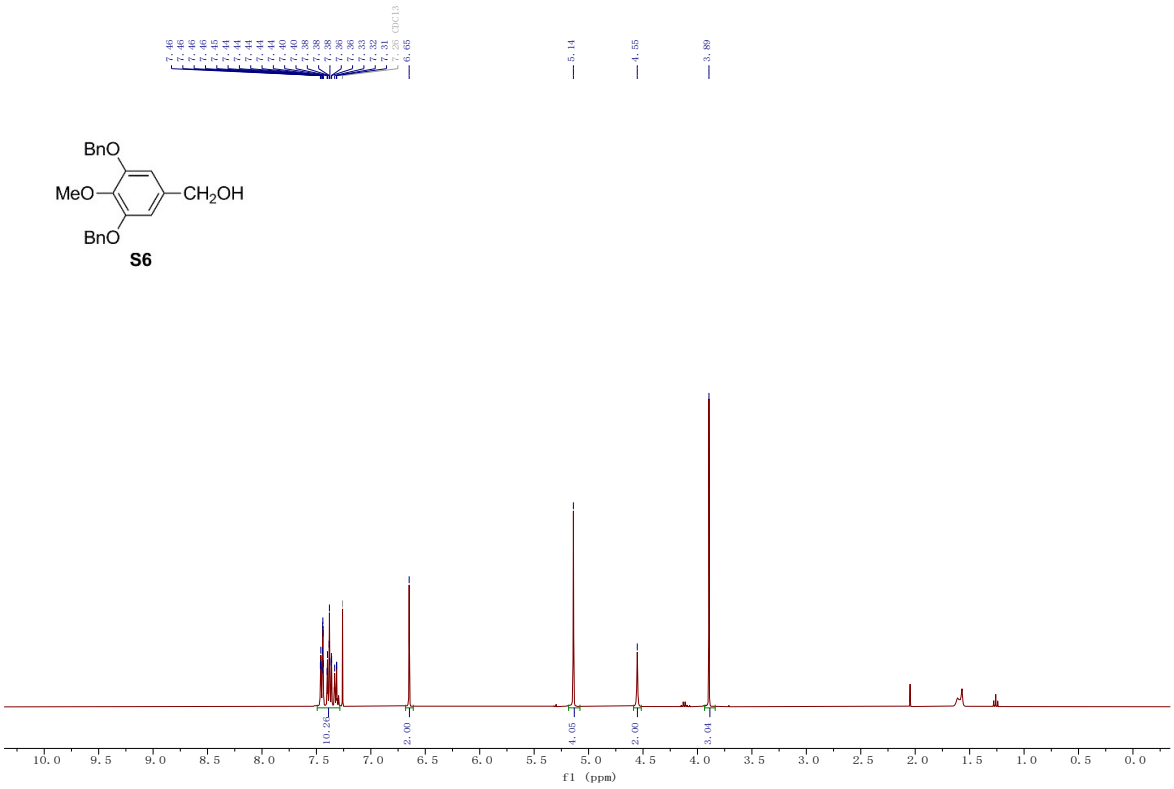
^{1}H NMR (400 Hz, $CDCl_3$): Methyl 3,5-bis(benzyloxy)-4-methoxybenzoate S5



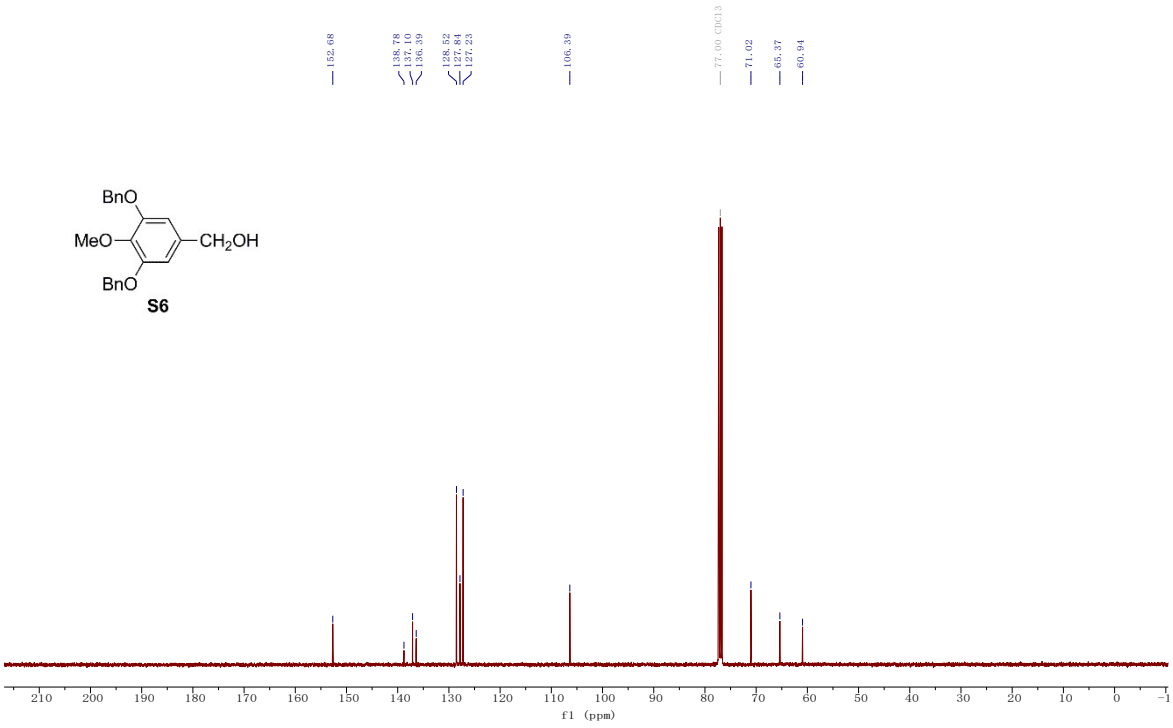
^{13}C NMR (101 Hz, $CDCl_3$): Methyl 3,5-bis(benzyloxy)-4-methoxybenzoate S5



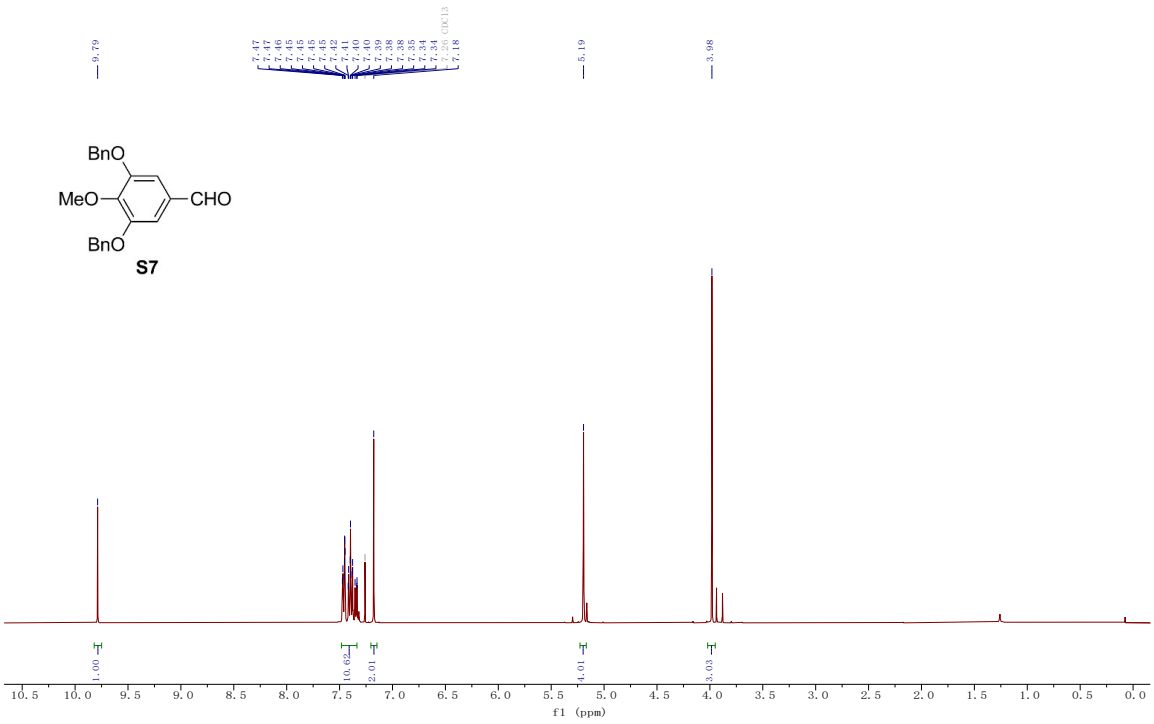
^{1}H NMR (400 Hz, $CDCl_3$): (3,5-Bis(benzyloxy)-4-methoxyphenyl)methanol S6



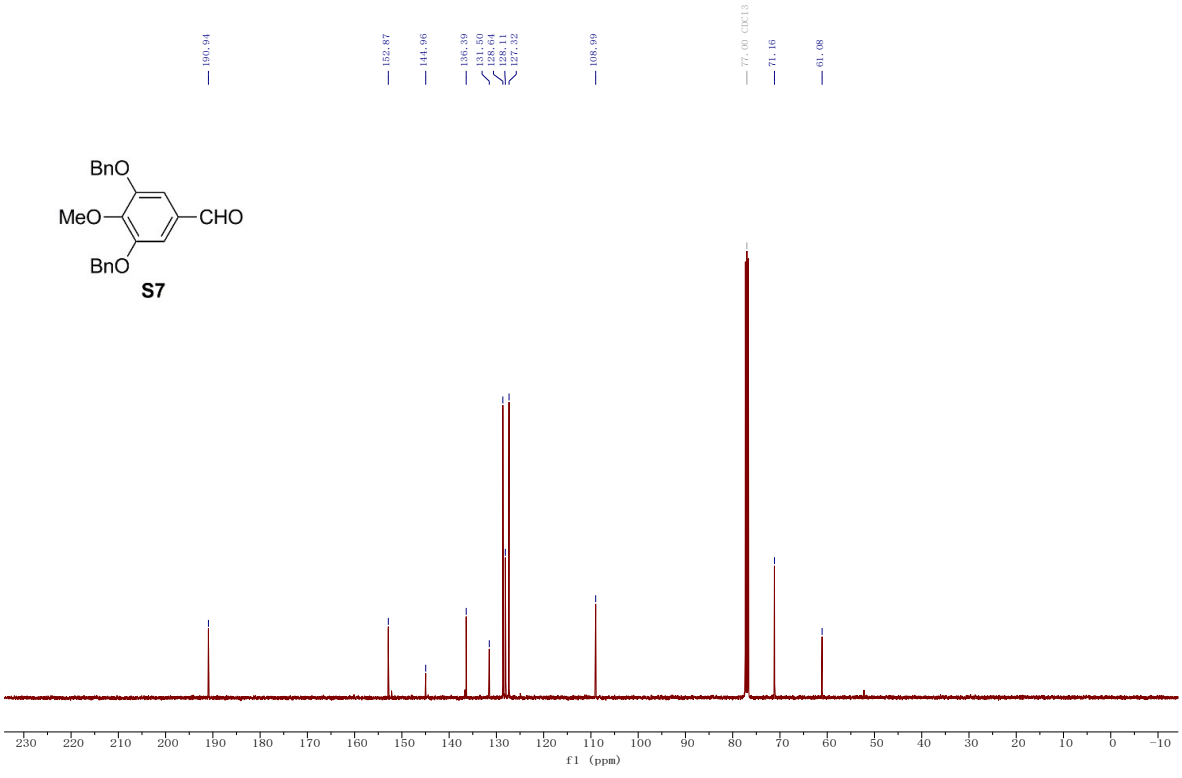
^{13}C NMR (101 Hz, $CDCl_3$): (3,5-Bis(benzyloxy)-4-methoxyphenyl)methanol S6



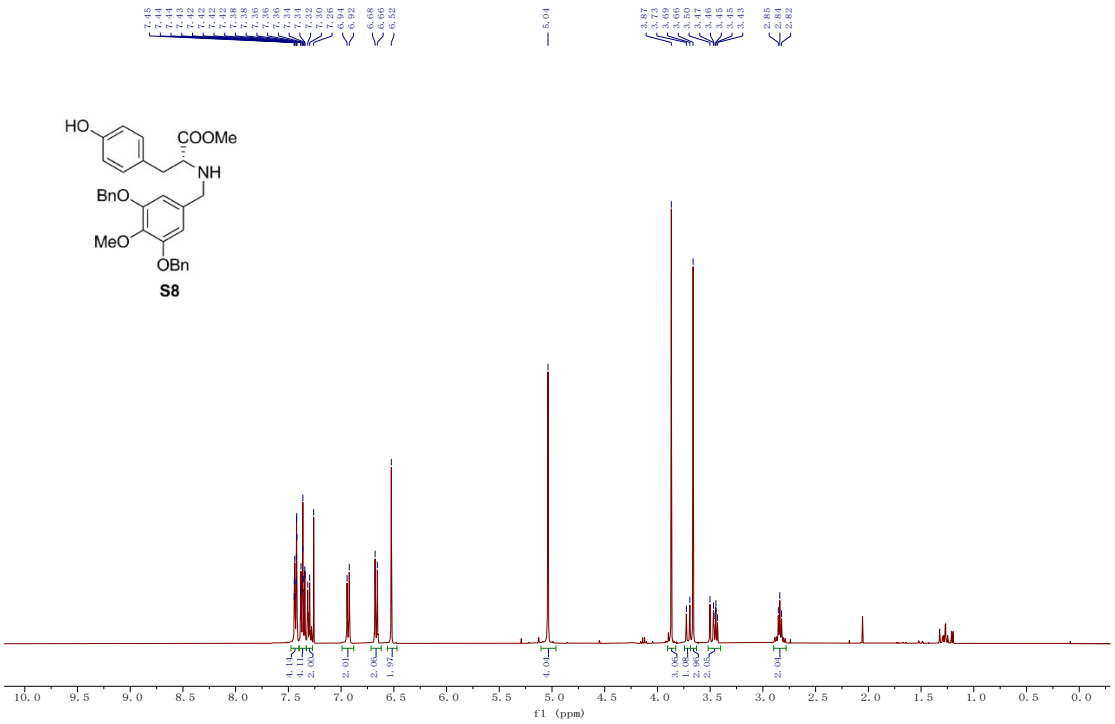
^{1}H NMR (400 Hz, $CDCl_3$): 3,5-Bis(benzyloxy)-4-methoxybenzaldehyde S7



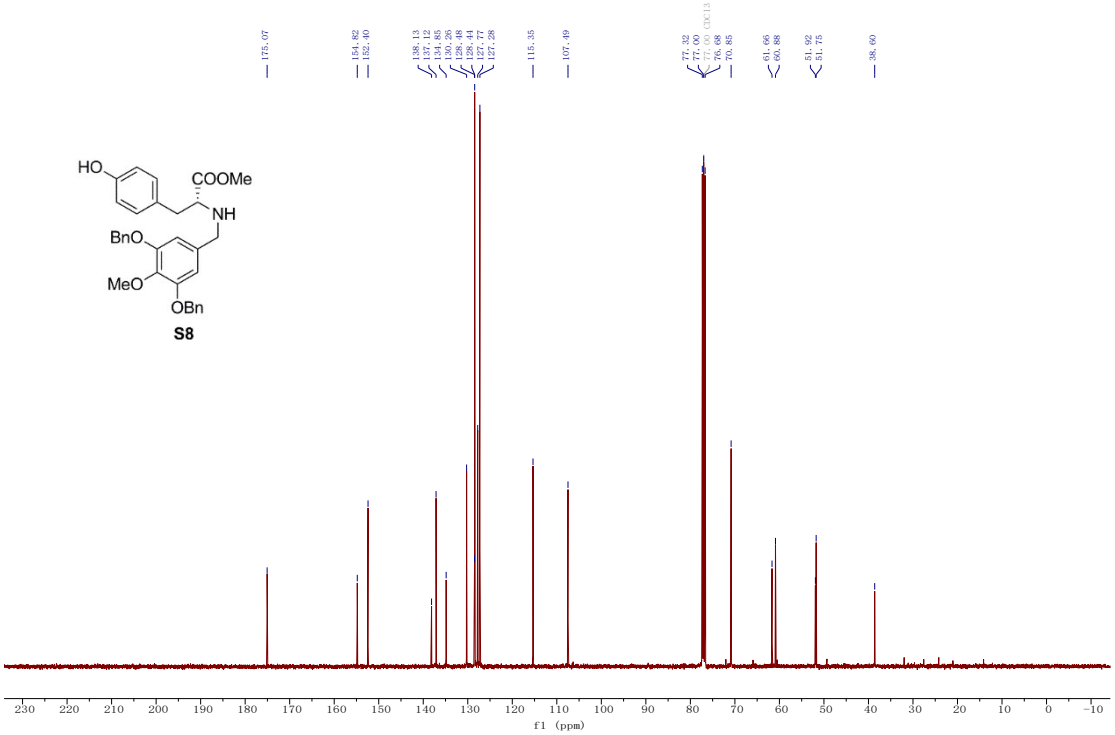
^{13}C NMR (101 Hz, $CDCl_3$): 3,5-Bis(benzyloxy)-4-methoxybenzaldehyde S7



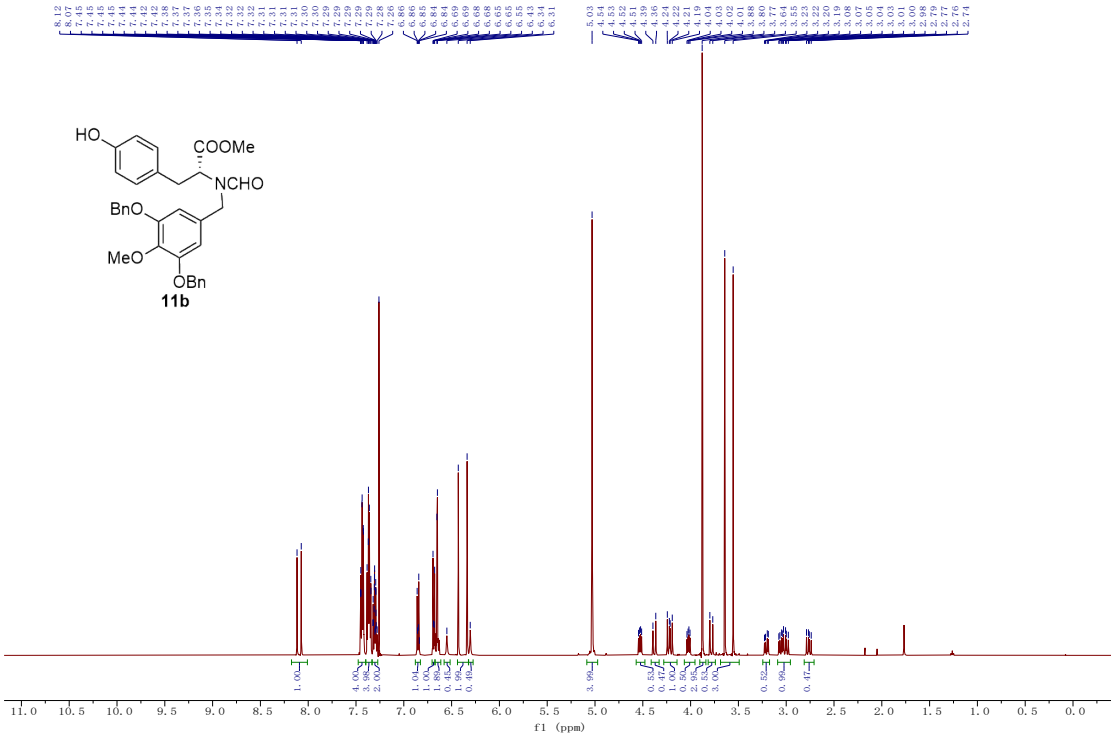
^{1}H NMR (400 Hz, $CDCl_3$): Methyl (3,5-bis(benzyloxy)-4-methoxybenzyl)-D-tyrosine S8



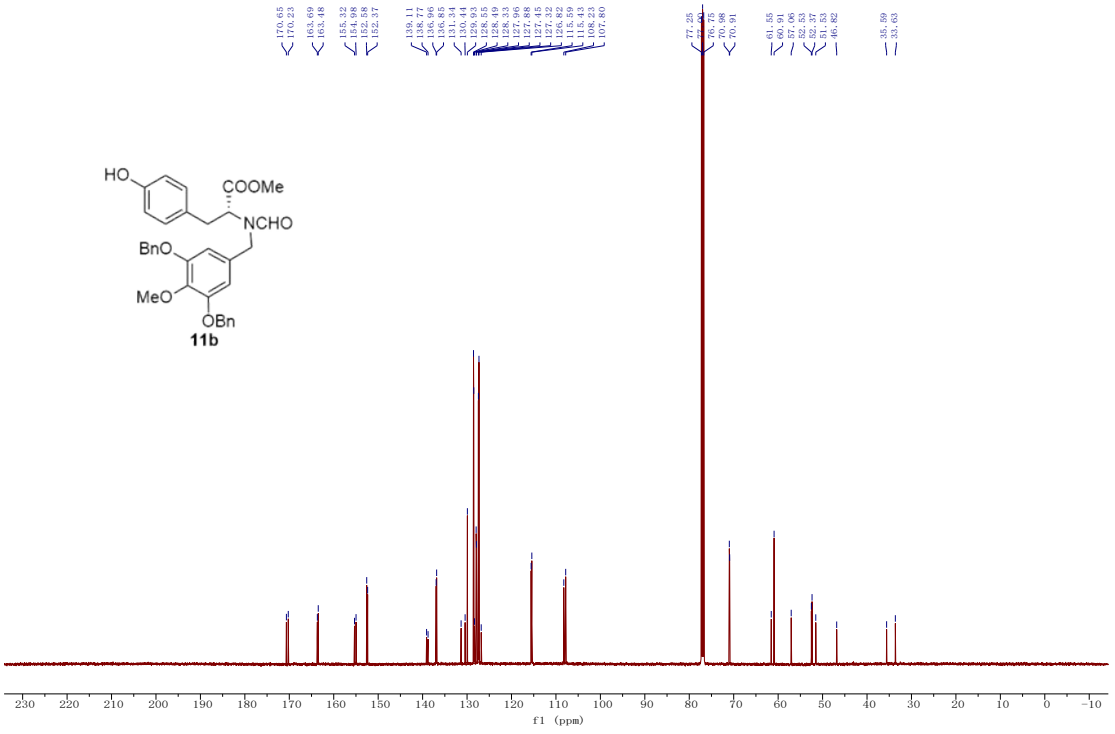
^{13}C NMR (101 Hz, $CDCl_3$): Methyl (3,5-bis(benzyloxy)-4-methoxybenzyl)-D-tyrosine S8



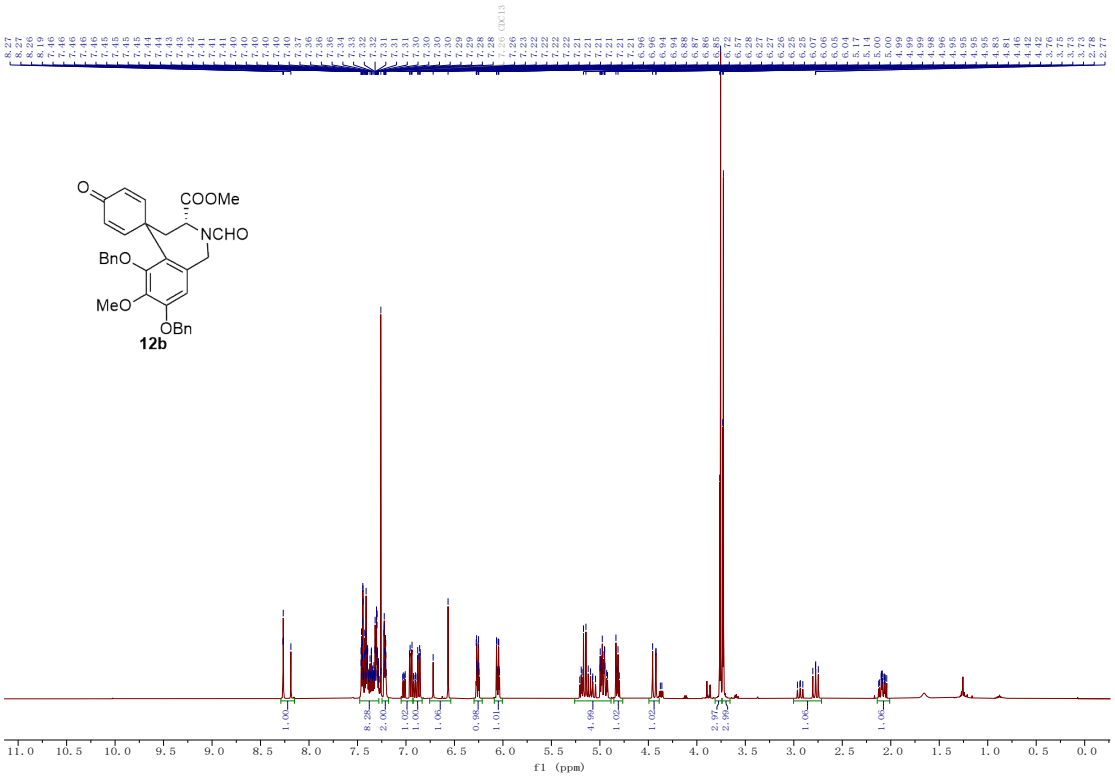
^{1}H NMR (500 Hz, $CDCl_3$): Methyl N-(3,5-bis(benzyloxy)-4-methoxybenzyl)-N-formyl-D-tyrosine 11b



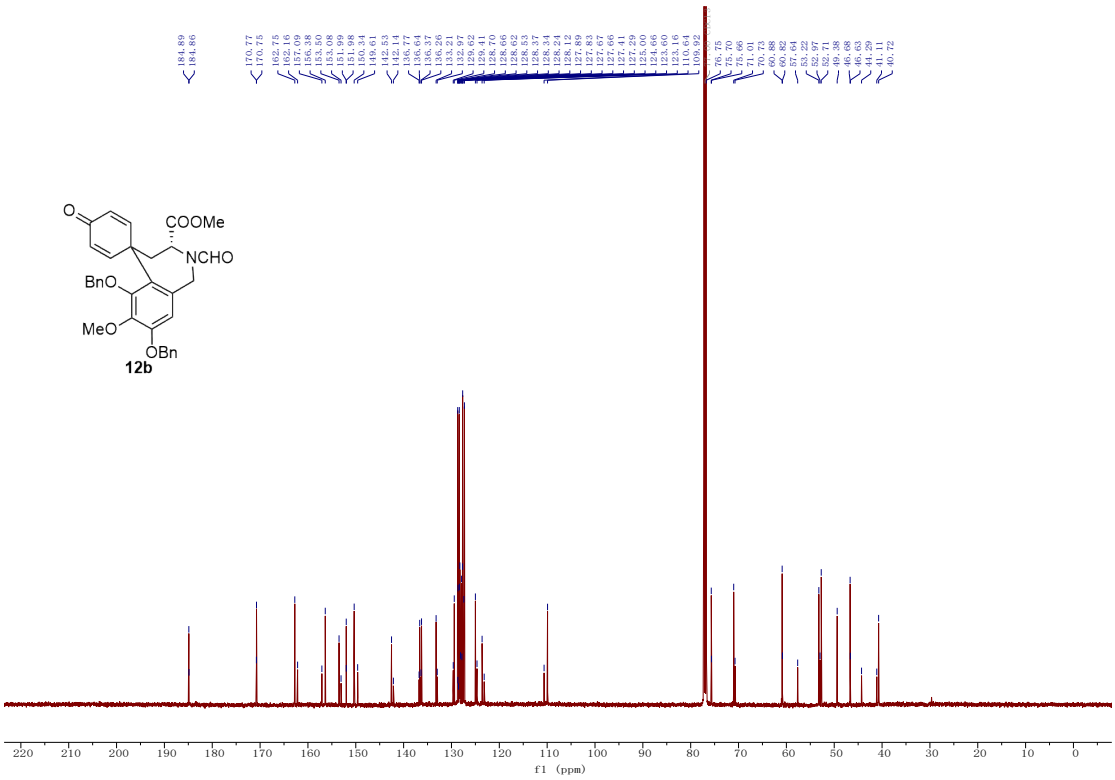
^{13}C NMR (126 Hz, $CDCl_3$): Methyl N-(3,5-bis(benzyloxy)-4-methoxybenzyl)-N-formyl-D-tyrosine 11b



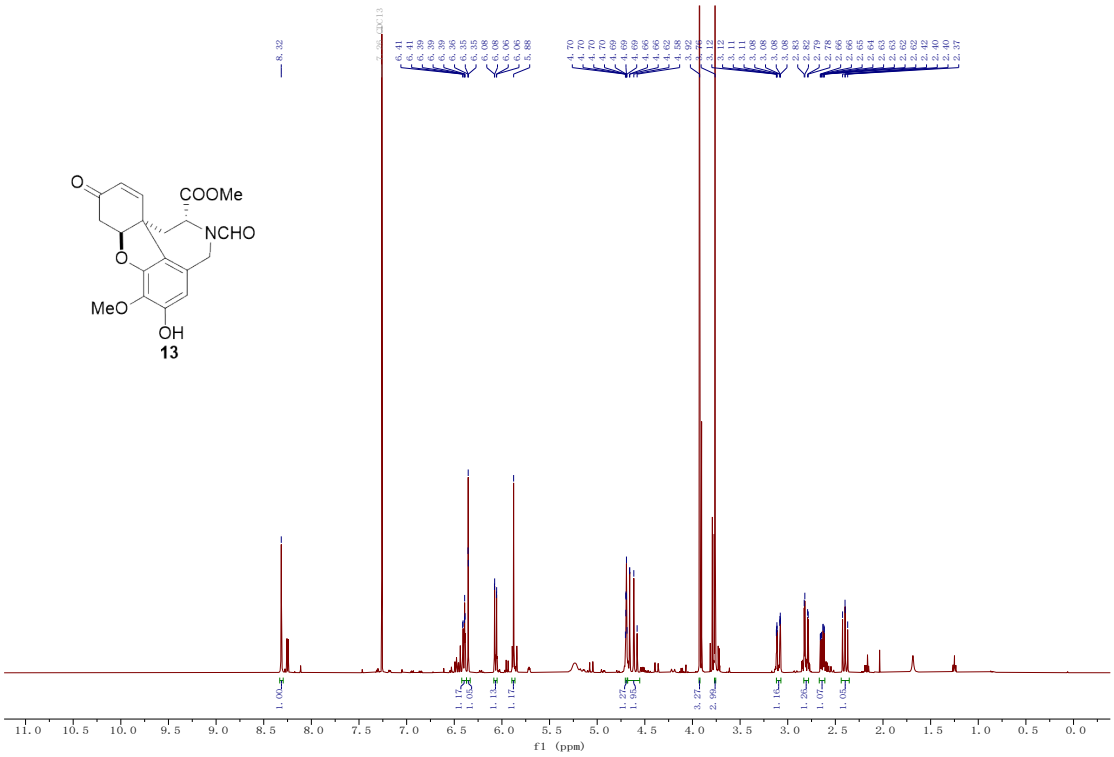
^{1}H NMR (500 Hz, $CDCl_3$): Methyl (*R*)-6,8-bis(benzyloxy)-2-formyl-7-methoxy-4'-oxo-1,2,3,4-tetrahydrospiro[benzo[*c*]azepine-5,1'-cyclohexane]-2',5'-diene-3-carboxylate 12b



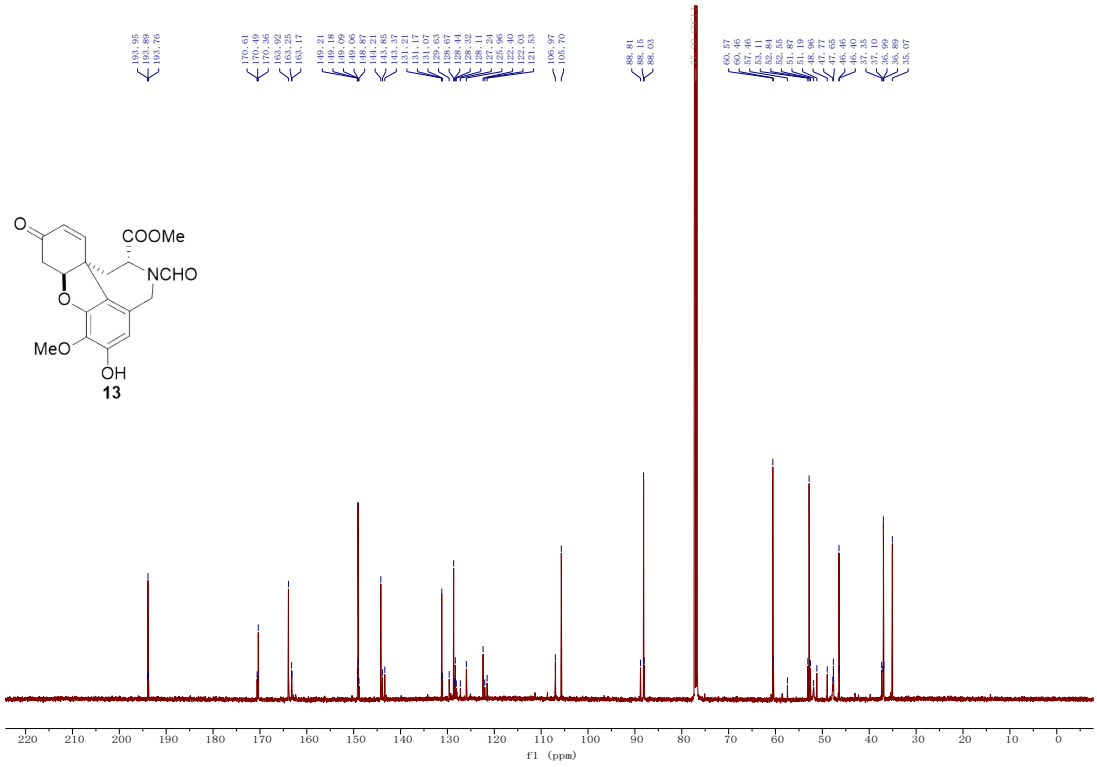
^{13}C NMR (126 Hz, $CDCl_3$): Methyl (*R*)-6,8-bis(benzyloxy)-2-formyl-7-methoxy-4'-oxo-1,2,3,4-tetrahydrospiro[benzo[*c*]azepine-5,1'-cyclohexane]-2',5'-diene-3-carboxylate 12b



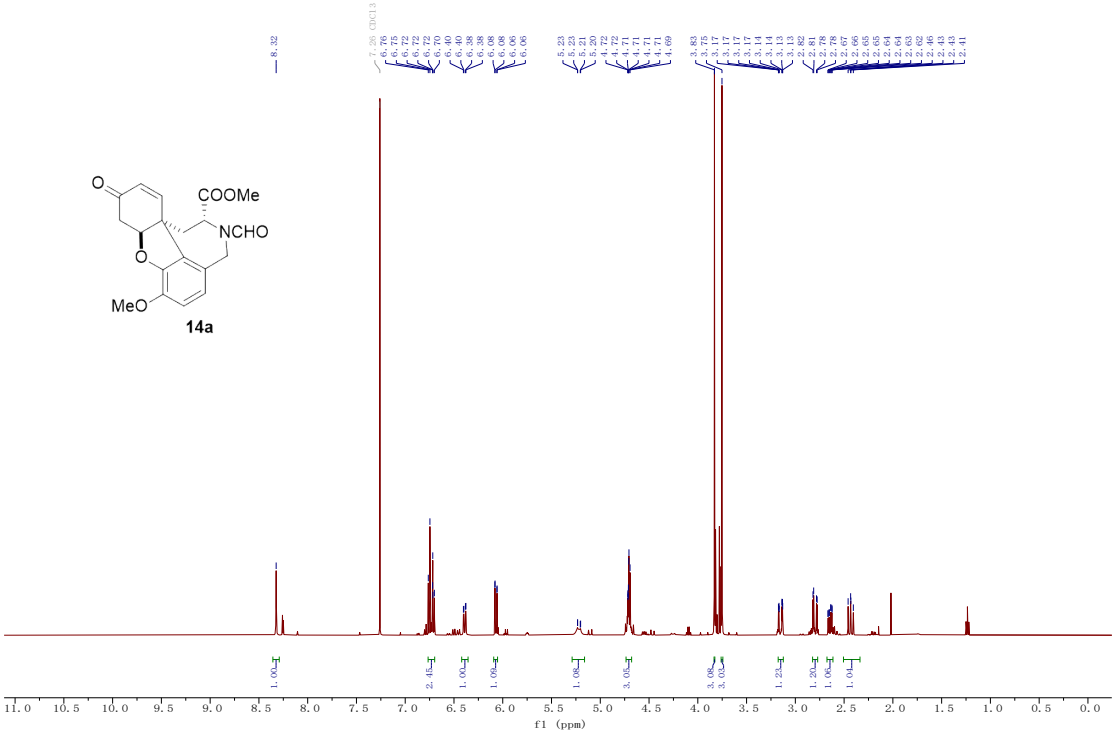
^{1}H NMR (500 Hz, $CDCl_3$): Methyl (4a*S*,8a*S*,10*S*)-11-formyl-2-hydroxy-3-methoxy-6-oxo-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 13



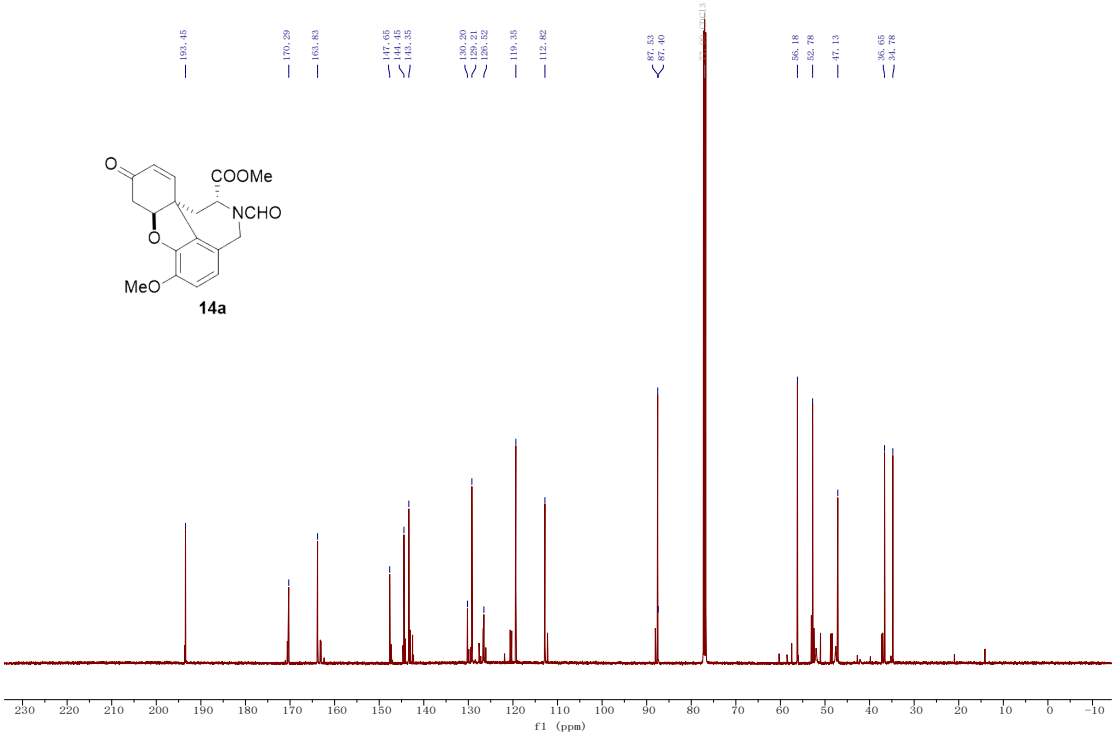
^{13}C NMR (126 Hz, $CDCl_3$): Methyl (4a*S*,8a*S*,10*S*)-11-formyl-2-hydroxy-3-methoxy-6-oxo-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 13



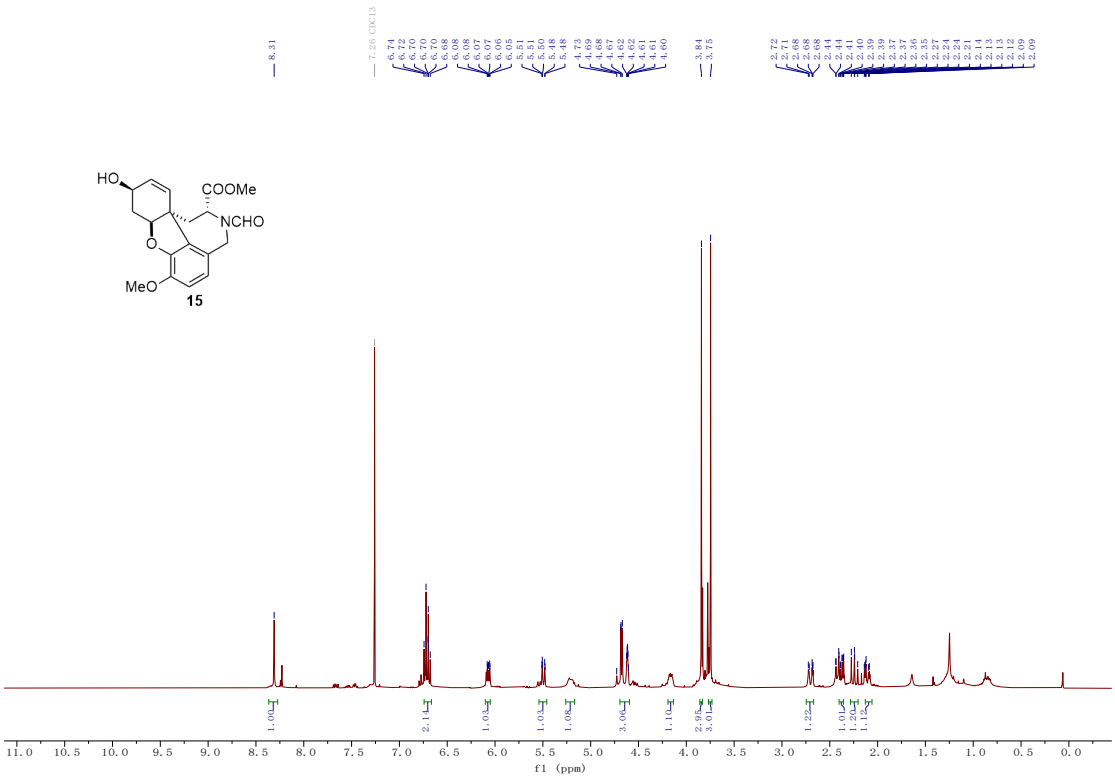
^{1}H NMR (500 Hz, $CDCl_3$): Methyl (4a*S*,8a*S*,10*S*)-11-formyl-3-methoxy-6-oxo-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 14a



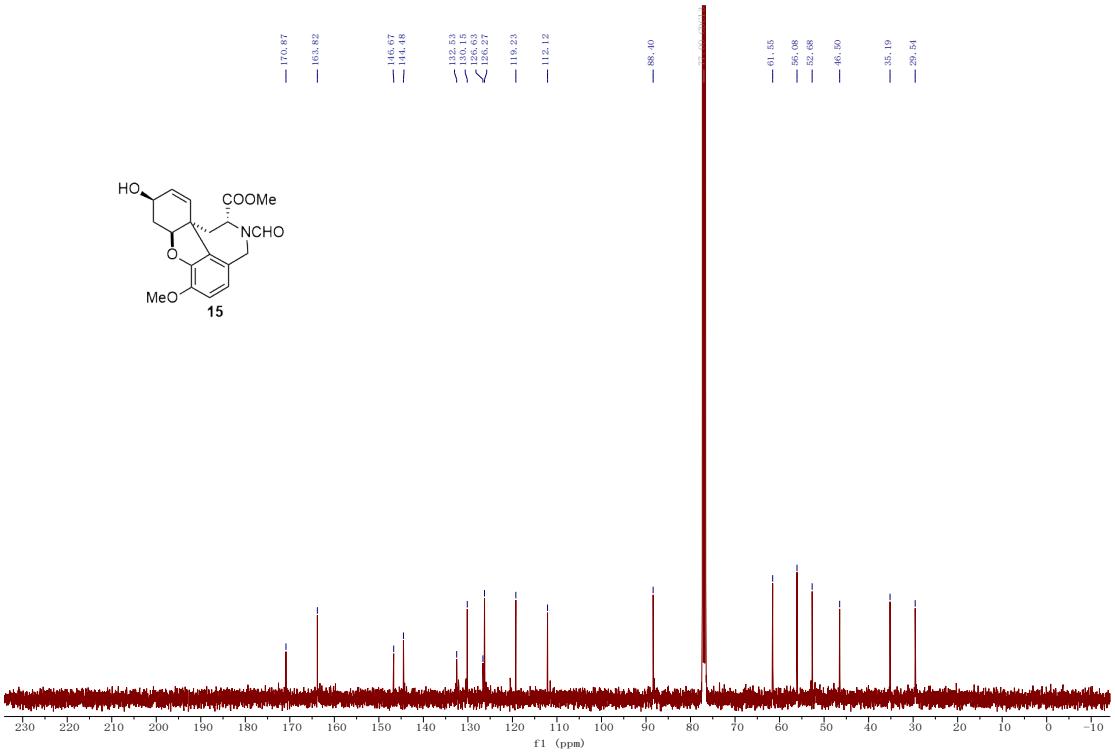
^{13}C NMR (126 Hz, $CDCl_3$): Methyl (4a*S*,8a*S*,10*S*)-11-formyl-3-methoxy-6-oxo-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 14a



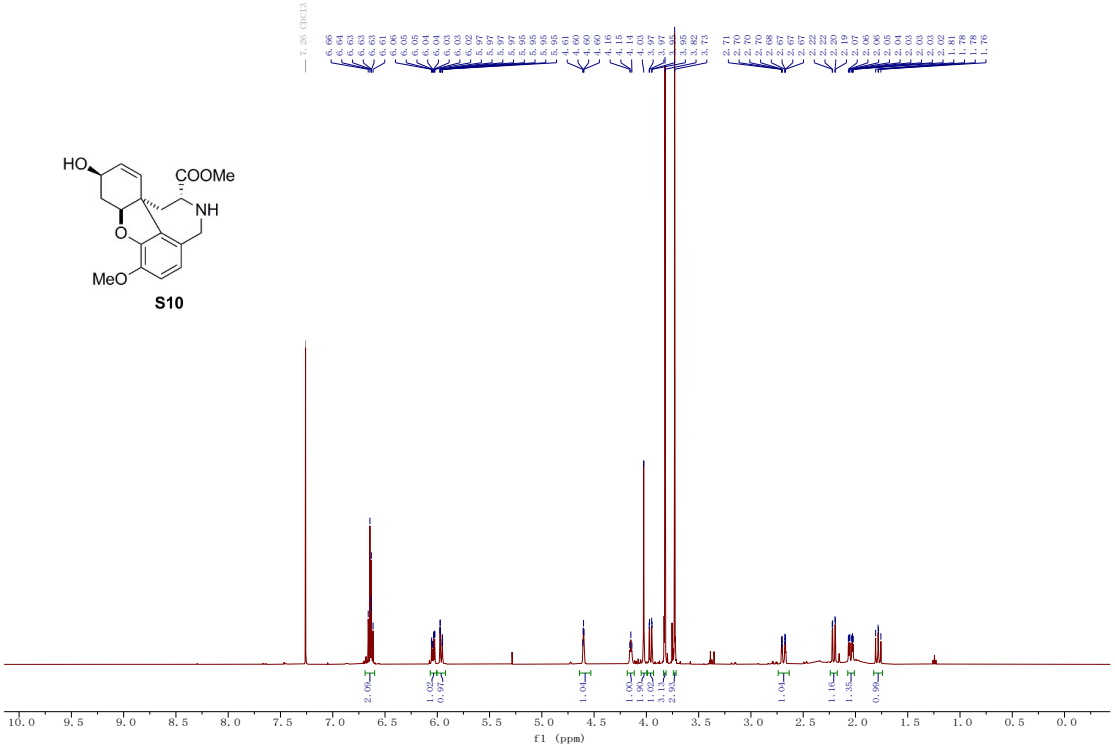
^{1}H NMR (400 Hz, $CDCl_3$): Methyl (4a*S*,6*R*,8a*S*,10*S*)-11-formyl-6-hydroxy-3-methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 15



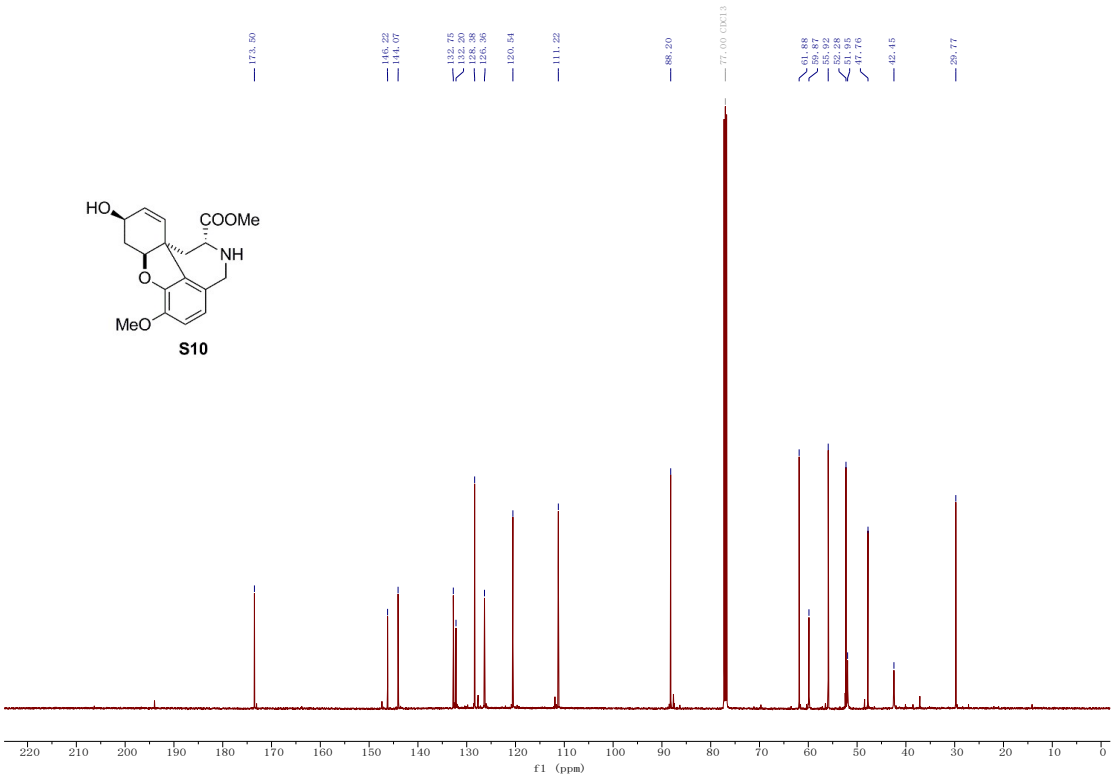
^{13}C NMR (101 Hz, $CDCl_3$): Methyl (4a*S*,6*R*,8a*S*,10*S*)-11-formyl-6-hydroxy-3-methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 15



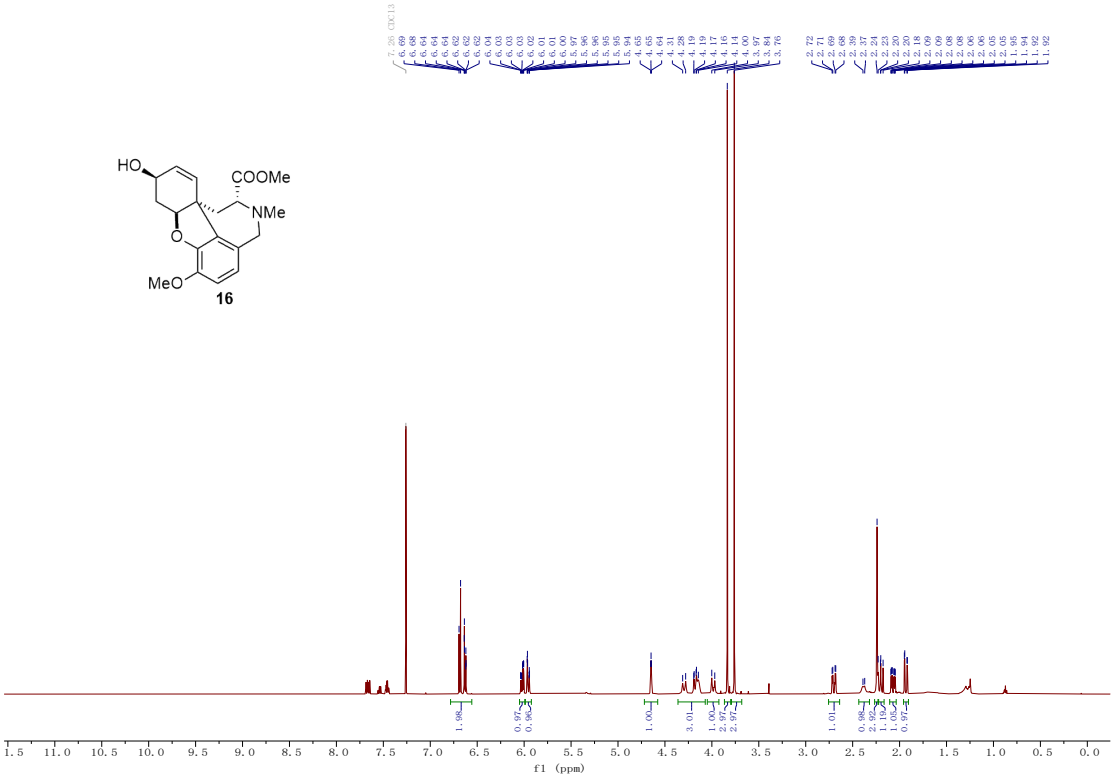
^{1}H NMR (500 Hz, $CDCl_3$): Methyl (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate S10



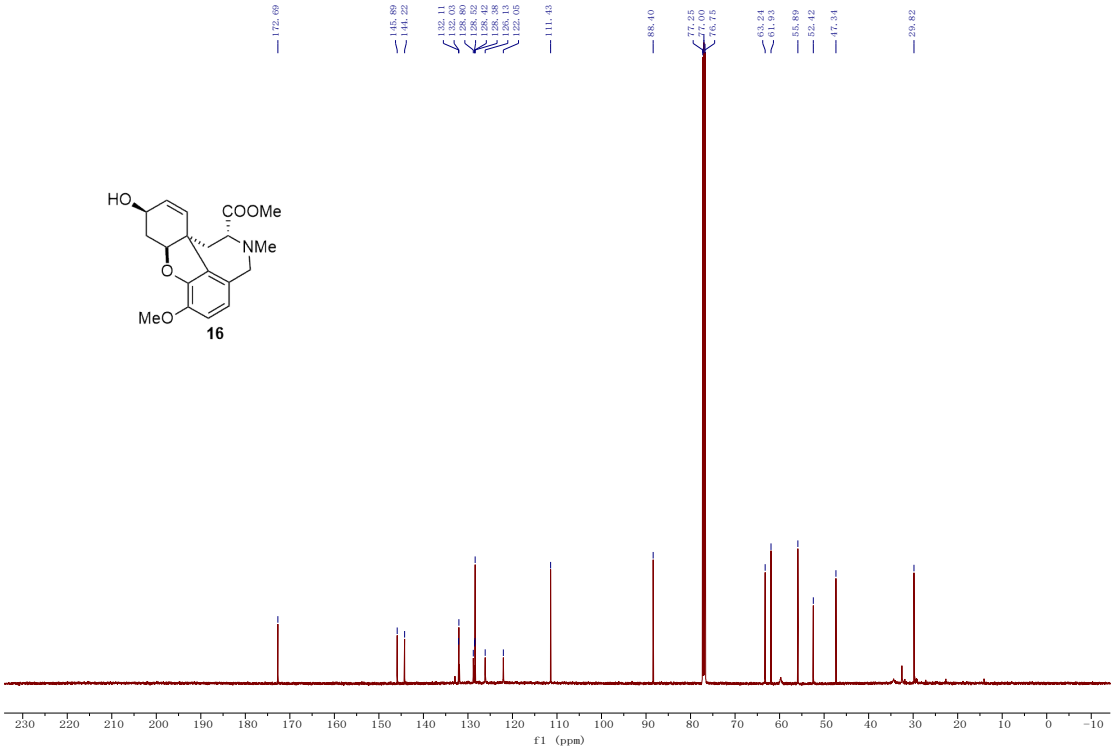
^{13}C NMR (126 Hz, $CDCl_3$): Methyl (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate S10



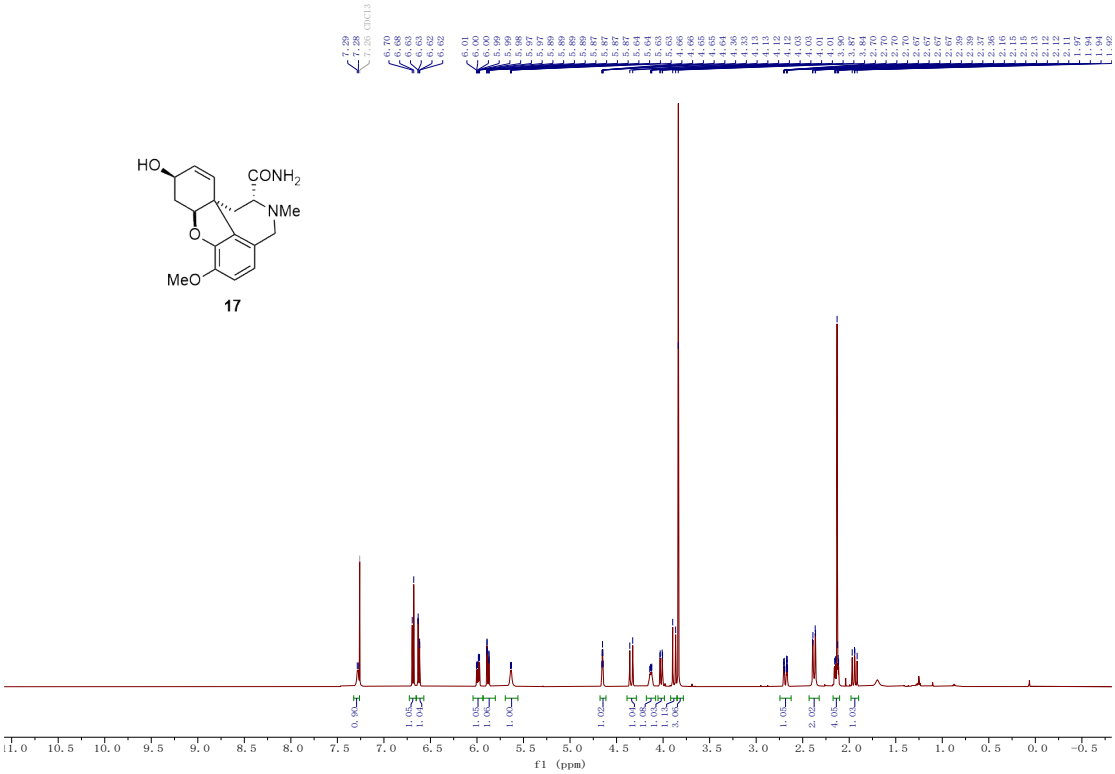
^{1}H NMR (500 Hz, $CDCl_3$): Methyl (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 16



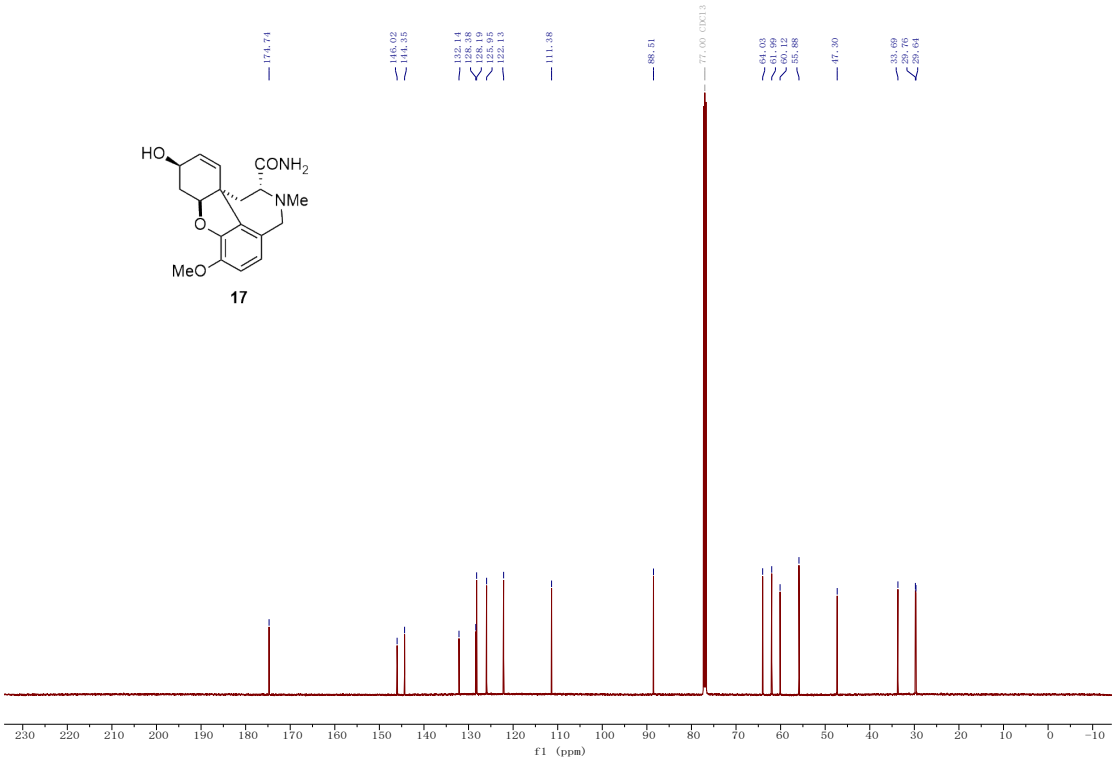
^{13}C NMR (126 Hz, $CDCl_3$): Methyl (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxylate 16



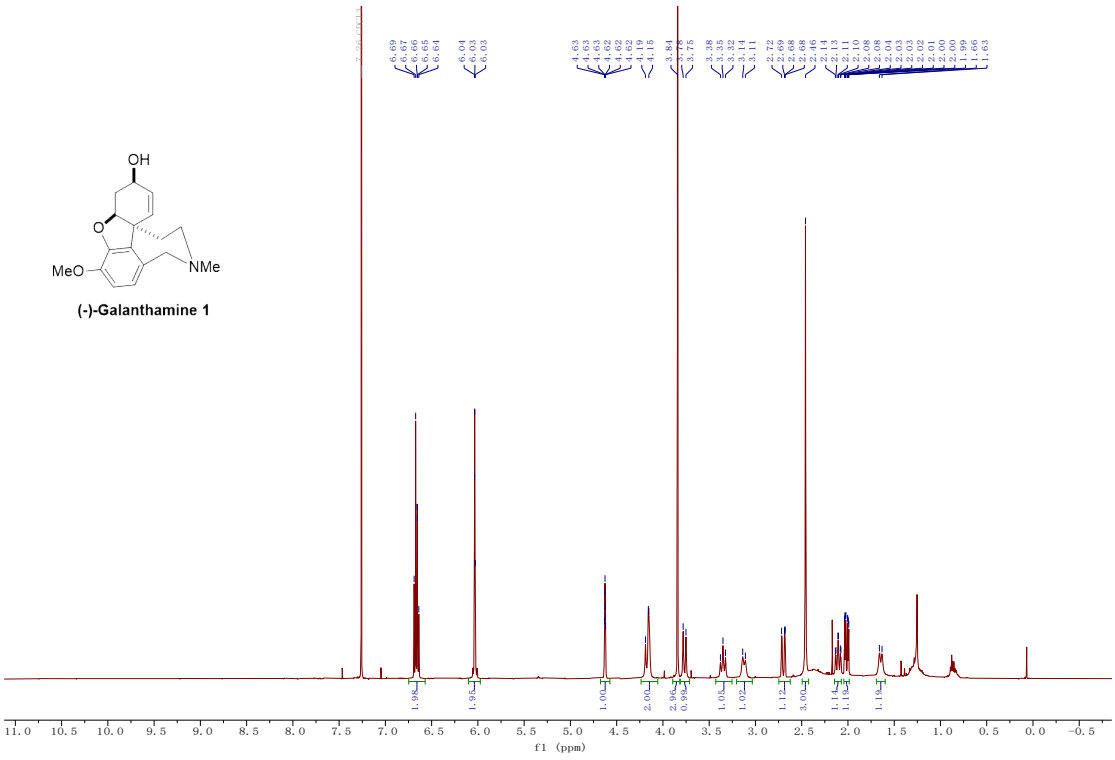
^{1}H NMR (500 Hz, $CDCl_3$): (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxamide 17



^{13}C NMR (126 Hz, $CDCl_3$): (4a*S*,6*R*,8a*S*,10*S*)-6-hydroxy-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6*H*-benzo[2,3]benzofuro[4,3-cd]azepine-10-carboxamide 17



^{1}H NMR (500 Hz, $CDCl_3$): (–)-Galanthamine (1)



^{13}C NMR (126 Hz, $CDCl_3$): (–)-Galanthamine (1)