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Supplementary information

Main element chemistry enables gas-cylinder-free hydroformylations

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Supplementary Information

Main element chemistry enables gas cylinder-free hydroformylations

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Supplementary Methods

1. General Experimental Details

All chemicals were used as received without further purification. Unless otherwise stated, all non-aqueous reactions were performed in oven dried apparatus under a nitrogen atmosphere at room temperature. Solvents were dried according to standard procedures and flash chromatography was carried out on silica gel 60 (230-400 mesh). The chemical shifts are reported in ppm relative to solvent residual peak stated ($CDCl_3$ (δ = 7.26/77.2)). The ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 101 MHz, ^{19}F NMR spectra were recorded at 367 MHz on a Bruker 400 spectrometer. NMR spectra are reported as follows (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, sext = sextet, sep = septet, oct = octet, m = multiplet, dd = double doublet, dt = double triplet, ddd = double double doublet; coupling constant(s) in Hz are reported to nearest 0.5 Hz; integration). HRMS spectra were recorded on a LC TOF (ES) apparatus. Melting point were recorded on a Büchi Melting Point B-540 and are uncorrected.

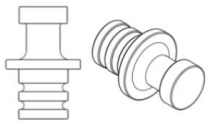
COware®

Two glass vials (Chamber A and B) connected with a glass tube to allow gas-transfer. Total volume = 20.0 mL. Both systems are sealed using a screw cap and a H-cap.

Supplementary Figure 1. COware®

H-caps

PTFE caps sealed with two NBR70, 7.1 × 1.6 mm O-rings for tight fit to the vials of COware®.



Supplementary Figure 2. H-caps

Handling of carbon monoxide

All hydroformylation reactions were performed in a two-chamber system, in which gaseous CO and H_2 was released in one chamber and utilized in a second chamber. The two-chamber system (COware®) is depicted to the above (Supplementary Figure 1) and is composed of two glass vials (Chamber A and B) connected with a glass tube to allow gas-transfer (total volume = 20 mL). The chambers can be sealed with a screw cap and a H-caps equipped with O-rings. CO was released from methyldiphenylsilanecarboxylic acid (silacarboxylic acid **2**), and H_2 are released using diboron **1** in water / THF 9:1 at 30 °C. Precise conditions are given in the general procedures.

Glassware under pressure - Warning!

- Glass equipment should always be examined for damages to its surface, which may weaken its strength.

- One must abide to all laboratory safety procedures and always work behind a shield when working with glass equipment under pressure.

- COware® is pressure tested to 224 psi (15 bar). However, under no circumstances the COware® should be operated above 60 psi (5 bar).

2. Gas Pressure Studies

Supplementary Figure 3. Two-chamber reactor fitted with a manometer (chamber A)

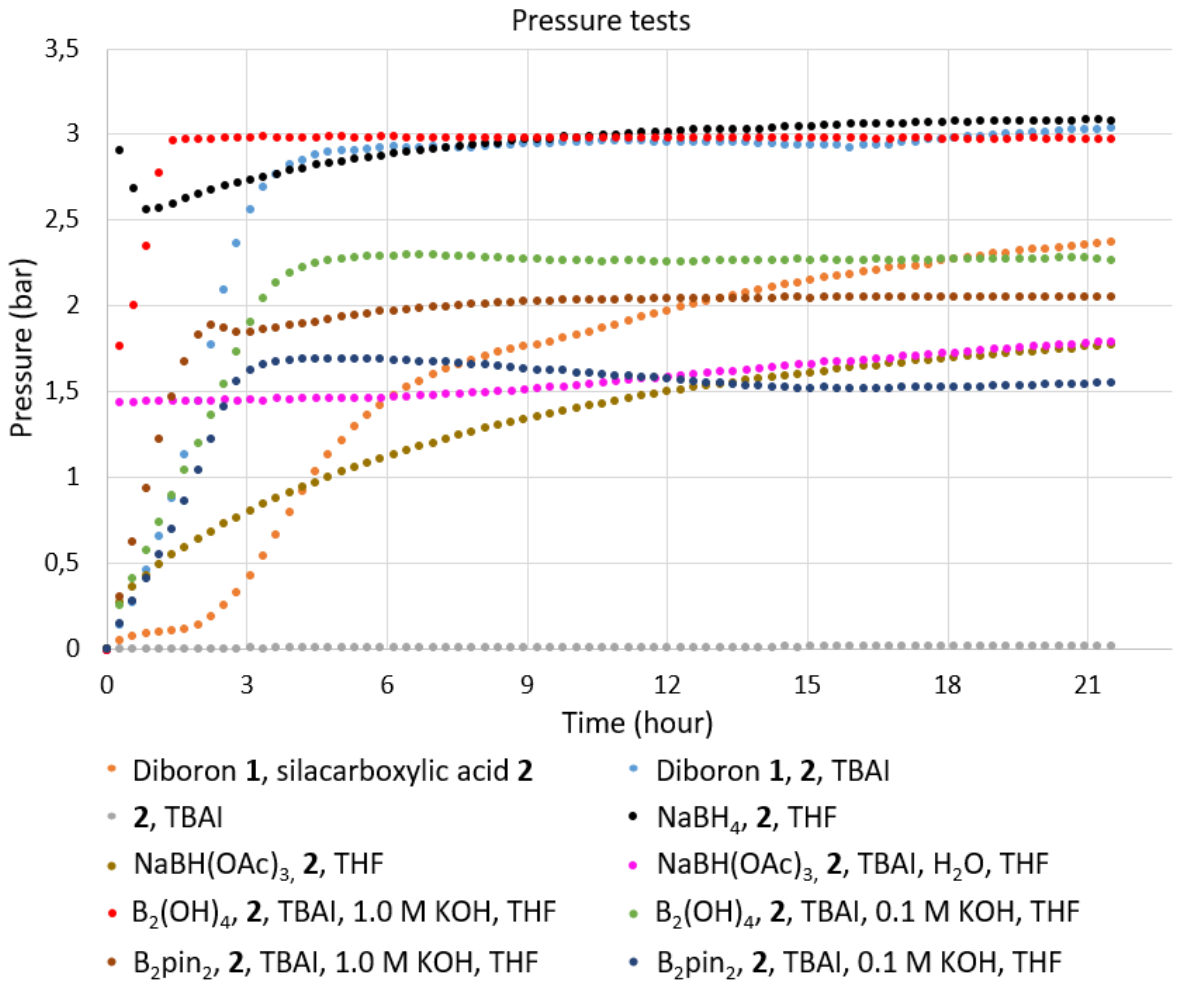
Experiment 1: In an argon-filled glovebox; To chamber A was added THF (1.0 mL) and the chamber was sealed with a manometer equipped with two O-rings (**Supplementary Figure 3**). To the syngas-producing chamber (chamber B) was added diboron **1** (228 mg, 1.0 mmol, 1.0 equiv.) and silacarboxylic acid **2** (242 mg, 1.0 mmol, 1.0 equiv.) followed by H_2O / THF (9:1, 3.0 mL) and the chamber was quickly closed. The reaction was left stirring for 16 hours at 30 °C (heat-block) with the pressure recorder every 5 seconds (**Supplementary Figure 4**).

Experiment 2: Same as for Experiment 1, with addition of and TBAI (15 mg, 0.04 mmol, 4 mol%) to the syngas producing chamber (chamber B, **Supplementary Figure 4**).

Experiment 3: Same as for Experiment 2, with exclusion of diboron **1** (**Supplementary Figure 4**).

Experiment 4: In an argon-filled glovebox; To chamber A was added THF (1.0 mL) and the chamber was sealed with a manometer equipped with two O-rings (**Supplementary Figure 3**). To the syngas-producing chamber (chamber B) was added $NaBH_4$ (38 mg, 1.0 mmol, 1.0 equiv.) and silacarboxylic acid **2** (242 mg, 1.0 mmol, 1.0 equiv.) followed by THF (3.0 mL) and the chamber was quickly closed. The reaction was left stirring for 16 hours at 30 °C (heat-block) with the pressure recorder every 5 seconds (**Supplementary Figure 4**). Note, addition of $NaBH_4$ resulted in an extremely rapid evolution of flammable hydrogen gas.

Experiment 5: In an argon-filled glovebox; To chamber A was added THF (1.0 mL) and the chamber was sealed with a manometer equipped with two O-rings (**Supplementary Figure 3**). To the syngas-producing chamber (chamber B) was added $NaBH(OAc)_3$ (212 mg, 1.0 mmol, 1.0 equiv.) and silacarboxylic acid **2** (242 mg, 1.0 mmol, 1.0 equiv.) followed by THF (3.0 mL) and the chamber was quickly closed. The reaction was left stirring for 16 hours at 30 °C (heat-block) with the pressure recorder every 5 seconds (**Supplementary Figure 4**).



Supplementary Figure 4. Pressure measurements on the gas release studies with diboron **1**, $NaBH_4$, $NaBH(OAc)_3$, $B_2(OH)_2$ and B_2pin_2 with silacarboxylic acid **2**.

Experiment 6: Same as for Experiment 5, with addition of TBAI (15 mg, 0.04 mmol, 4 mol%), and H_2O / THF (9:1, 3.0 mL) to the syngas producing chamber (chamber B, **Supplementary**

Figure 4). Note, addition of $NaBH(OAc)_3$ in presence of water resulted in an extremely rapid evolution of flammable hydrogen gas.

Experiment 7: In an argon-filled glovebox; To chamber A was added THF (1.0 mL) and the chamber was sealed with a manometer equipped with two O-rings (**Supplementary Figure 3**). To the syngas-producing chamber (chamber B) was added $B_2(OH)_4$ (90 mg, 1.0 mmol, 1.0 equiv.), silacarboxylic acid **2** (242 mg, 1.0 mmol, 1.0 equiv.) and TBAI (15 mg, 0.04 mmol, 4 mol%) followed by 1.0 M KOH in H_2O / THF (9:1, 3.0 mL) and the chamber was quickly closed. The reaction was left stirring for 16 hours at 30 °C (heat-block) with the pressure recorder every 5 seconds (**Supplementary Figure 4**).

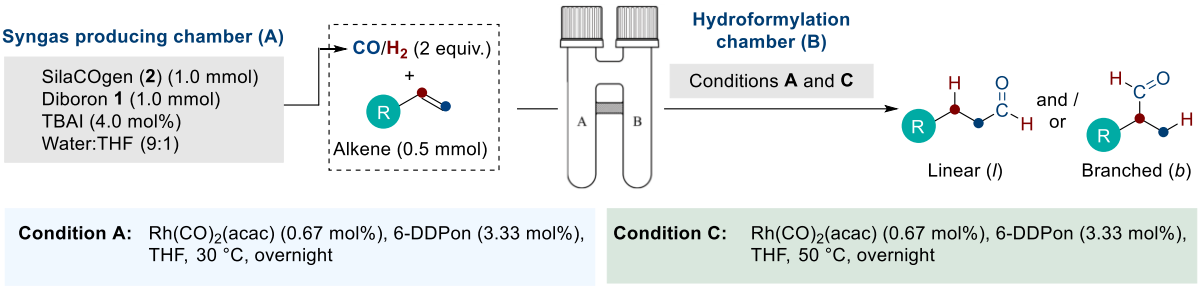
Experiment 8: Same as for experiment 7, with addition of 0.1 M KOH in H_2O / THF (9:1, 3.0 mL) to the syngas producing chamber (chamber B, **Supplementary Figure 4**).

Experiment 9: In an argon-filled glovebox; To chamber A was added THF (1.0 mL) and the chamber was sealed with a manometer equipped with two O-rings (**Supplementary Figure 3**). To the syngas-producing chamber (chamber B) was added B_2Pin_2 (254 mg, 1.0 mmol, 1.0 equiv.), silacarboxylic acid **2** (242 mg, 1.0 mmol, 1.0 equiv.) and TBAI (15 mg, 0.04 mmol, 4 mol%) followed by 1.0 M KOH in H_2O / THF (9:1, 3.0 mL) and the chamber was quickly closed. The reaction was left stirring for 16 hours at 30 °C (heat-block) with the pressure recorder every 5 seconds (**Supplementary Figure 4**).

Experiment 10: Same as for experiment 9, with addition of 0.1 M KOH in H_2O / THF (9:1, 3.0 mL) to the syngas producing chamber (chamber B, **Supplementary Figure 4**).

3. General Experimental Procedures

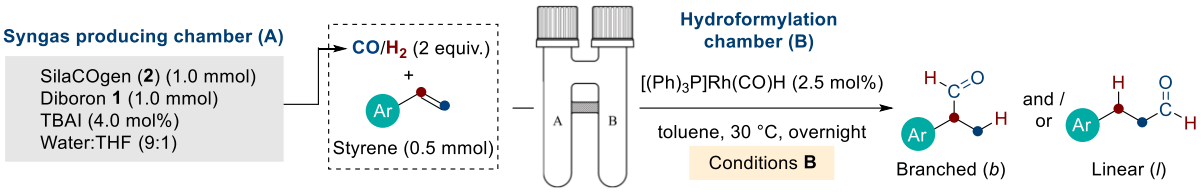
General Procedure 1: General Hydroformylation Conditions (Condition A/Condition C)



Supplementary Figure 5. General hydroformylation of alkenes.

In an argon-filled glovebox was prepared a solution of $Rh(CO)_2(acac)$ (0.67 mol%) and 6-DPPon (3.33 mol%) in THF (0.3 mL / µmol catalyst). In a two-chamber reactor; The syngas-consuming chamber (chamber B) was charged with alkene (1.0 equiv.) while the syngas-producing chamber (chamber A) was charged with diboron **1** (2.0 equiv.), silacarboxylic acid **2** (2.0 equiv.) and tetra-*n*-butylammonium iodide (TBAI) (4.0 mol%). Subsequently, the catalyst solution (2.0 mL / mmol substrate) was added to the alkene and the syngas-consuming chamber (chamber B) sealed with a screw cap fitted with an H-cap. To the syngas-producing chamber (chamber A) was added a mixture of water and THF (9:1 mixture, 3.0 mL / mmol surrogate) and directly sealed with a screw cap fitted with a H-cap. The two-chamber reactor was removed from the glovebox and placed in a heat-block at the stated temperature (30 °C for Condition A, 50 °C for Condition C) and stirred vigorously for the time stated (normally overnight). The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give the crude aldehyde which was either reduced to the corresponding alcohol (General Procedure 3), purified *via* column chromatography or used directly in the next reaction without further purification.

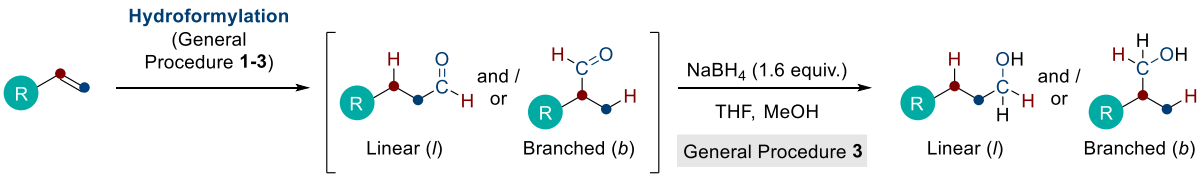
General Procedure 2: Hydroformylation of Styrenes (Condition B)



Supplementary Figure 6. General hydroformylation of styrenes.

Inside an argon-filled glovebox using a two-chamber reactor; The syngas-consuming chamber (chamber B) was charged with alkene (1.0 equiv.) and $RhH(CO)(PPh_3)_3$ (2.5 mol%) while the syngas-producing chamber (chamber A) was charged with diboron **1** (2.0 equiv.), silacarboxylic acid **2** (2.0 equiv.) and TBAI (4.0 mol%). Subsequently, toluene (2.0 mL / mmol substrate) was added to the alkene and the syngas-consuming chamber sealed with a screw cap fitted with an H-cap. To the syngas-producing chamber was added a mixture of water and THF (9:1 mixture, 3.0 mL / mmol surrogate) and directly sealed with a screw cap fitted with a H-cap. The two-chamber reactor was removed from the glovebox and placed in a heat-block at the stated temperature (30 °C) and stirred vigorously for the time stated (normally overnight). The reaction mixture was then filtered through Celite and concentrated *in vacuo* to give the crude aldehyde which was either reduced to the corresponding alcohol (General Procedure 3), purified *via* column chromatography or used directly in the next reaction without further purification.

General Procedure 3: General Reduction of Aldehydes to Alcohols

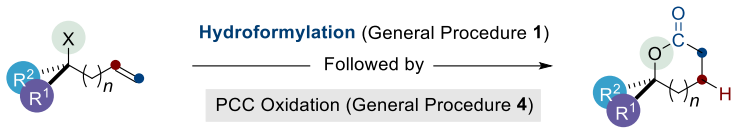


Supplementary Figure 7. General reduction of aldehydes to alcohols.

To a solution of crude aldehyde(s) (1.0 equiv.) in THF (1.0-3.0 mL / mmol substrate) was added $NaBH_4$ (1.6 mmol / mmol substrate) followed by MeOH (8 drops / mmol substrate).

After stirring at room temperature for 1 hour (or until completion as indicated by TLC). The resulting mixture was diluted with CH_2Cl_2 (10 mL / mmol substrate) and quenched by slow addition of water (10 mL / mmol substrate). The organic layer was separated, and the aqueous layer was further extracted two times with CH_2Cl_2 (10 mL / mmol substrate). The combined aqueous layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude alcohol(s) which was purified *via* column chromatography.

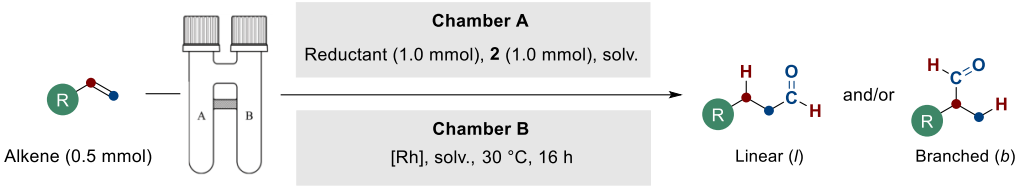
General Procedure 4: General Oxidative Cyclisation Procedure

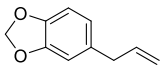
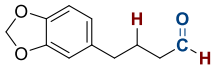
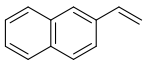
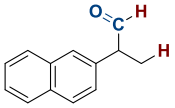


Supplementary Figure 8. General oxidative cyclisation.

After filtration of the hydroformylation reaction through Celite, the resulting mixture was concentrated *in vacuo* and the resulting crude aldehyde residue was re-dissolved in CH_2Cl_2 (8.0 mL / mmol substrate) and crushed activated 4Å molecular sieves (100 mg / mmol substrate) added. To this stirred suspension was added pyridinium chlorochromate (PPC) (3.0 mmol / mmol substrate) followed by further stirring at room temperature overnight. The resulting reaction mixture was diluted with Et_2O (20 mL / mmol substrate) and filtered through Celite. The filtrate was washed with 1.0 M aqueous solution of NaOH (10 mL / mmol substrate) then water (10 mL / mmol substrate). The combined aqueous layers were extracted once with Et_2O (20 mL / mmol substrate) and the combined organic layers dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude lactone was purified *via* column chromatography.

4. Hydroformylation, Comparison of Syngas Surrogates



Entry	Substrate	Chamber A	Chamber B	Product(s) yield[a]
1	 Safrole	Diboron **1**, H_2O:THF (9:1), TBAI (4 mol%)	$Rh(CO)_2(acac)$ (0.67 mol%), 6-DDPon (3.33 mol%), THF	 **5**, 98% (92%[b], *l*:*b* = 10:1)
2	"	$NaBH_4$, THF	"	**5**, 72% + 15% product of alkene reduction
3	"	$NaBH(OAc)_3$, THF	"	**5**, 67% (*l*:*b* = 10:1)
4	"	$NaBH(OAc)_3$, H_2O:THF (9:1), TBAI (4 mol%)	"	**5**, 4% + 70% product of alkene reduction
5	"	$B_2(OH)_4$, 1.0 M KOH:THF (9:1), TBAI (4 mol%)	"	**5**, 90% (*l*:*b* = 5:1)
6	"	$B_2(OH)_4$, 0.1 M KOH:THF (9:1), TBAI (4 mol%)	"	**5**, 94% (*l*:*b* = 9:1)
7	"	B_2pin_2, 1.0 M KOH:THF (9:1), TBAI (4 mol%)	"	**5**, 86% (*l*:*b* = 6:1)
8	"	B_2pin_2, 0.1 M KOH:THF (9:1), TBAI (4 mol%)	"	**5**, 75% (*l*:*b* = 5:1)
9	 2-Vinylnaphthalene	Diboron **1**, H_2O:THF (9:1), TBAI (4 mol%)	$Rh(CO)_2(acac)$ (0.67 mol%), 6-DDPon (3.33 mol%), MeOH	 **6**, 39% (*b*:*l* = 4:1)
10	"	Diboron **1**, H_2O:THF (9:1), TBAI (4 mol%)	$RhH(CO)(PPh_3)_3$ (2.5 mol%), toluene	**6**, 99% (91%[b], *b*:*l* = 4:1)
11	"	B_2pin_2, 1.0 M KOH:THF (9:1), TBAI (4 mol%)	"	**6**, 55% (*b*:*l* = 4:1) + 13% product of alkene reduction
12	"	B_2pin_2, 0.1 M KOH:THF (9:1), TBAI (4 mol%)	"	**6**, 78% (*b*:*l* = 4:1)

Supplementary Table 1. Comparison of the syngas surrogates diboron **1**, $NaBH_4$, $NaBH(OAc)_3$, $B_2(OH)_4$ and B_2pin_2 with the silacarboxylic acid **2** under hydroformylation conditions. [a]Yields obtained by ^1H NMR spectroscopy of crude reaction mixture with internal standard (mesitylene) and are the combined yields of the linear and branched aldehydes. [b]Isolated yield.

Supplementary Table 1, entries 1-8: Following General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and safrole (81 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and either (as stated) diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), $NaBH_4$ (38 mg, 1.0 mmol, 1.0 equiv.), $NaBH(OAc)_3$ (212 mg, 1.0 mmol, 1.0 equiv.), $B_2(OH)_4$ (90 mg, 1.0 mmol, 1.0 equiv.), or B_2Pin_2 (254 mg, 1.0

mmol, 1.0 equiv.), with silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), with or without (as stated) TBAI (17 mg, 0.046 mmol, 4.0 mol%) in either (as stated) THF (0.3 mL) and water (2.7 mL), THF (3.0 mL), 1.0 M aqueous solution of KOH (2.7 mL) and THF (0.3 mL), or 0.1 M aqueous solution of KOH (2.7 mL) and THF (0.3 mL), with a 16 h reaction time at 30 °C. The resulting reaction mixtures were filtered through celite and concentrated *in vacuo* to give crude **5**. Unless otherwise stated the yields were obtained by ^{1}H NMR spectroscopy of the crude reaction mixture with internal standard (mesitylene) and represents the combined yield of the linear and branched aldehydes.

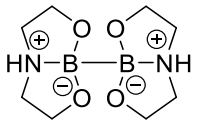
Supplementary Table 1, entry 9: Following General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and 2-vinylnaphthalene (77 mg, 0.50 mmol, 1.0 equiv.) in MeOH (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting reaction mixture was filtered through celite and concentrated *in vacuo* to give crude **6** with the yield obtained by ^{1}H NMR spectroscopy of crude reaction mixture with internal standard (mesitylene) and represents the combined yield of the linear and branched aldehydes.

Supplementary Table 1, entries 10-12: Following General Procedure 2 (Condition B), with $RhH(CO)(PPh_3)_3$ (11 mg, 1.3 µmol, 2.5 mol%) and 2-vinylnaphthalene (77 mg, 0.50 mmol, 1.0 equiv.) in toluene (1.0 mL), and either (as stated) diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), or $B_2(OH)_4$ (90 mg, 1.0 mmol, 1.0 equiv.), with silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), with or without (as stated) TBAI (17 mg, 0.046 mmol, 4.0 mol%) in either (as stated) THF (0.3 mL) and water (2.7 mL), 1.0 M aqueous solution of KOH (2.7 mL) and THF (0.3 mL), or 0.1 M aqueous solution of KOH (2.7 mL) and THF (0.3 mL), with a 16 h reaction time at 30 °C. The resulting reaction mixtures were filtered through celite and

concentrated *in vacuo* to give crude **6**. Unless otherwise stated the yields were obtained by ^{1}H NMR spectroscopy of crude reaction mixture with internal standard (mesitylene) and represents the combined yield of the linear and branched aldehydes.

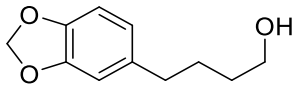
5. Experimental Procedures

2,2'-Bi(1,3,6,2-dioxazaborocane), 1



Diboron **1** was prepared in accordance to what we have previously reported[1]. To a solution of diethanolamine (12.5 g, 119 mmol, 2.0 equiv.), in CH_2Cl_2 (450 mL) was added tetrahydroxydiboron (5.34 g, 59.0 mmol, 1.0 equiv.). After stirring at 30 °C for 6 min, the reaction mixture was filtered and the remaining solid was washed with cold EtOH (50 mL), EtOAc (3 × 50 mL) and pentane (50 mL). The remaining solid were transferred to a flask and dried under vacuum to give diboron **1** (7.80 g, 34.2 mmol, 58%) as a white solid.

4-(Benzo[d][1,3]dioxol-5-yl)butan-1-ol, 5



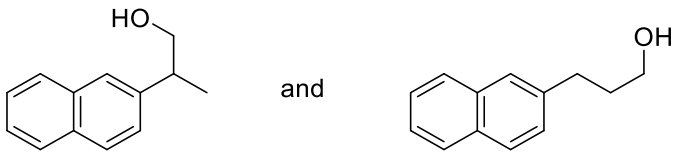
5 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and safrole (81 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* = 10:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.)

and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / EtOAc (25%)) gave **5** (89 mg, 0.46 mmol, 92%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.72 (1H, d, *J* = 8.0 Hz), 6.67 (1H, d, *J* = 1.5 Hz), 6.62 (1H, dd, *J* = 8.0 and 1.5 Hz), 5.90 (2H, s), 3.63 (2H, t, *J* = 6.0 Hz), 2.55 (2H, t, *J* = 7.5 Hz), 1.72 (1H, s), 1.70-1.51 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.5, 145.5, 136.2, 121.1, 108.8, 108.1, 100.7, 62.7, 35.4, 32.2, 27.8.

Spectroscopic data in agreement with that reported by Romeiro *et al*[2].

2-(Naphthalen-2-yl)propan-1-ol and 3-(naphthalen-2-yl)propan-1-ol, 6-branched and 3-(naphthalen-2-yl)propan-1-ol, 6-linear



6-branched **6-linear**

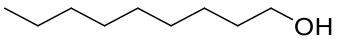
6 was prepared using General Procedure 2 (Condition B), with $RhH(CO)(PPh_3)_3$ (11 mg, 1.3 µmol, 2.5 mol%) and 2-vinylnaphthalene (77 mg, 0.50 mmol, 1.0 equiv.) in toluene (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*b*:*l* = 4:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / EtOAc (20%)) gave **6-branched** and **6-linear** (85 mg, 0.46 mmol, 91%) as an inseparable mixture of regioisomers (*b*:*l* = 4:1).

6-branched (major) and 6-linear (minor): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87-7.74 (3.8H, m), 7.69 (1H, s), 7.64 (0.3H, s), 7.52-7.33 (3.8H, m), 3.83-3.75 (2H, m), 3.70 (0.5H, t, *J* = 6.5

Hz), 3.13 (1H, sext, *J* = 7.0 Hz), 2.88 (0.5H, t, *J* = 7.5 Hz), 2.03-1.88 (0.5H, quin, *J* = 7.0 Hz), 1.38 (3H, dd, *J* = 7.0 and 1.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 141.3, 139.4, 133.8, 133.7, 132.6, 132.1, 128.4, 128.1, 127.7, 127.5, 127.4, 126.5, 126.2, 126.1, 126.0, 125.9, 125.6, 125.3, 68.6, 62.3, 42.7, 34.2, 32.3, 17.7.

Spectroscopic data in agreement with that reported by Cheung *et al* (**6-branched**)[3] and by Liao *et al* (**6-linear**)[4].

Nonan-1-ol, 7

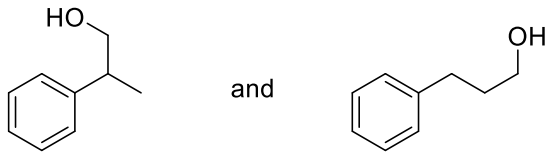


7 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and 1-octene (56 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / Et_2O (10%)) gave **7** (58 mg, 0.40 mmol, 79%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.60 (2H, t, *J* = 6.5 Hz), 1.83 (1H, s), 1.54 (2H, quin, *J* = 6.5 Hz), 1.39-1.06 (12H, m), 0.86 (3H, t, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 63.1, 32.9, 32.0, 29.7, 29.6, 29.4, 25.9, 22.8, 14.2.

Spectroscopic data in agreement with that reported by Kim and Chung.[5]

2-phenylpropan-1-ol and 3-phenylpropan-1-ol, 8-branched and 3-phenylpropan-1-ol, 8-linear



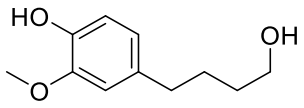
8-branched **8-linear**

8 was prepared using General Procedure 2 (Condition B), with $RhH(CO)(PPh_3)_3$ (11 mg, 1.3 μmol, 2.5 mol%) and styrene (52 mg, 0.50 mmol, 1.0 equiv.) in toluene (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*b*:*1* = 4:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (CH_2Cl_2 / Et_2O (15-20%)) gave **8-branched** and **8-linear** (51 mg, 0.38 mmol, 75%) as an inseparable mixture of regioisomers (*b*:*1* 4:1).

8-branched (major) and 8-linear (linear): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87-7.74 (3.5H, m), 7.69 (1H, s), 7.64 (0.2H, s), 7.52-7.33 (3.5H, m), 3.83-3.75 (2H, m), 3.70 (0.3H, t, *J* = 6.5 Hz), 3.13 (1H, sext, *J* = 7.0 Hz), 2.88 (0.3H, t, *J* = 7.5 Hz), 2.03-1.88 (0.3H, quin, *J* = 7.0 Hz), 1.38 (3H, dd, *J* = 7.0 and 1.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 141.3, 139.4, 133.8, 133.7, 132.6, 132.1, 128.4, 128.1, 127.7, 127.5, 127.4, 126.5, 126.2, 126.1, 126.0, 125.9, 125.6, 125.3, 68.6, 62.3, 42.7, 34.2, 32.3, 17.7.

Spectroscopic data in agreement with that reported by Bettoni *et al* (**8-branched**)[6] and by Szostak *et al* (**8-linear**)[7].

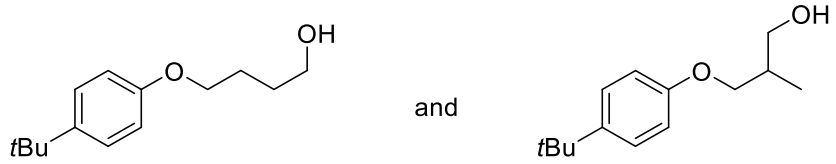
4-(4-Hydroxybutyl)-2-methoxyphenol, 9



9 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and eugenol (82 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (Pentane / EtOAc (30-40%)) gave **9** (75 mg, 0.38 mmol, 76%) as a pale-yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.82 (1H, d, *J* = 8.0 Hz), 6.71-6.63 (2H, m), 3.86 (3H, s), 3.65 (2H, t, *J* = 6.5 Hz), 2.57 (2H, t, *J* = 7.5 Hz), 1.77-1.49 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.5, 143.8, 134.4, 121.0, 114.3, 111.1, 62.9, 56.0, 35.4, 32.4, 27.89; **HRMS** (ESI+) calc. for $C_{11}H_{16}NaO_3$ $[M+Na]^+$ 219.0992, found 219.0989.

4-(4-(*tert*-Butyl) phenoxy) butan-1-ol, 10-linear and 3-(4-(*tert*-butyl) phenoxy)-2-methyl propan-1-ol, 10-branched



10-linear **10-branched**

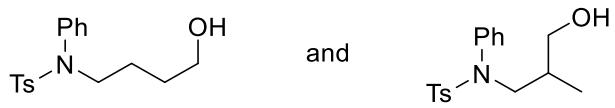
10 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and 1-(allyloxy)-4-(tert-butyl)benzene (85 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00

mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude aldehyde (*l*:*b* = 2.4:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / EtOAc (15%)) gave **10-linear** (66 mg, 0.30 mmol, 59%) and **10-branched** (29 mg, 0.13 mmol, 26%) as a colourless oil.

10-linear: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 (2H, d, *J* = 9.0 Hz), 6.84 (2H, d, *J* = 9.0 Hz), 3.99 (2H, t, *J* = 6.0 Hz), 3.72 (2H, q, *J* = 6.0 Hz), 1.88 (2H, quin, *J* = 6.5 Hz), 1.76 (2H, quin, *J* = 6.5 Hz), 1.57-1.52 (1H, m), 1.30 (9H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.6, 143.4, 126.2, 114.0, 67.7, 62.6, 34.1, 31.5, 29.6, 25.9; **HRMS** (ESI+) calc. for $C_{15}H_{22}O_2$ $[M+H]^+$ 223.1693, found 223.1693.

10-branched: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 (2H, d, *J* = 8.5 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 4.04-3.88 (2H, m), 3.73 (2H, t, *J* = 5.5 Hz), 2.32-2.10 (1H, m), 1.91 (1H, t, *J* = 5.5 Hz), 1.32 (9H, d, *J* = 1.0 Hz), 1.05 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.5, 143.6, 126.2, 114.0, 71.4, 66.4, 35.7, 34.1, 31.5, 13.6; **HRMS** (ESI+) calc. for $C_{15}H_{22}O_2$ $[M+H]^+$ 223.1693, found 223.1691.

***N*-(4-Hydroxybutyl)-4-methyl-*N*-phenylbenzenesulfonamide, 11-linear and *N*-(3-hydroxy-2-methylpropyl)-4-methyl-*N*-phenylbenzenesulfonamide, 11-branched**



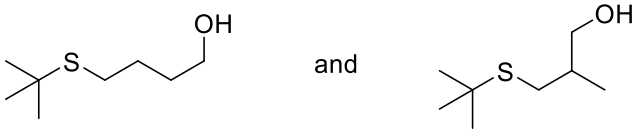
11-linear **11-branched**

11 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and *N*-allyl-4-methyl-*N*-phenylbenzen esulfonamide (144 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1**

(228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude aldehyde (*l*:*b* = 1.3:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (CH_2Cl_2 / Et_2O (20-50%)) gave **11** (144 mg, 0.45 mmol, 90%) as an inseparable mixture of the regioisomers (*l*:*b* 1.3:1).

11-linear (major) and 11-branched (minor): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48-7.42 (3.5H, m), 7.35-7.20 (8.8H, m), 7.11-6.97 (3.5H, m), 3.85-3.75 (0.8H, m), 3.66 (0.8H, dd, *J* = 13.5 and 8.5 Hz), 3.62-3.46 (4.8H, m), 3.29 (0.8H, dd, *J* = 13.5 and 6.0 Hz), 2.41 (2.3H, s), 2.40 (3H, s), 1.71-1.55 (3.8H, m), 1.54-1.44 (2H, m), 0.88 (2.3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.6, 143.4, 139.6, 139.1, 135.3, 135.1, 129.6, 129.5, 129.2, 129.1, 128.9, 128.8, 128.1, 128.0, 127.8, 127.7, 64.1, 62.3, 53.1, 50.3, 34.4, 29.4, 24.7, 21.6, 14.6; **HRMS** (ESI+) calc. for $C_{17}H_{22}NO_3S$ $[M+H]^+$ 320.1315, found 320.1318.

4-(*tert*-Butylthio)butan-1-ol, 12-linear and 3-(*tert*-butylthio)-2-methylpropan-1-ol, 12-branched



12-linear **12-branched**

12 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and allyl(tert-butyl)sulfane (65 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude aldehyde (*l*:*b* = 2.4:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79

mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (CH_2Cl_2 / Et_2O (15-20%)) gave **12-linear** (38 mg, 0.24 mmol, 47%) and **12-branched** (16 mg, 0.097 mmol, 19%) as colourless oils.

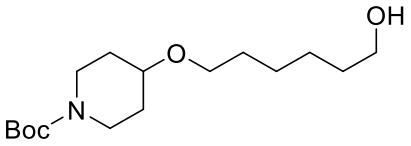
12-linear: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.64 (2H, t, *J* = 6.0 Hz), 2.54 (2H, t, *J* = 7.0 Hz), 1.68 (1H, bs) 1.67-1.60 (4H, m), 1.29 (9H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 62.4, 41.9, 32.2, 31.0, 28.0, 26.1.

Spectroscopic data in agreement with that reported by Aberkane *et al*[8].

12-branced: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.58 (2H, t, *J* = 5.5 Hz), 2.63 (1H, dd, *J* = 12.0 and 6.5 Hz), 2.50 (1H, dd, *J* = 12.0 and 6.5 Hz), 1.90 (1H, oct, *J* = 6.5 Hz), 1.70 (1H, t, *J* = 5.5 Hz), 1.32 (9H, s), 1.01 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 67.7, 42.1, 36.3, 32.4, 31.0, 17.0.

Spectroscopic data in agreement with that reported by Sharma *et al*[9].

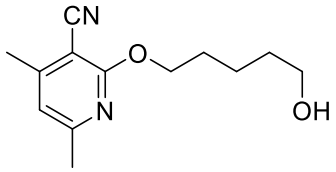
***tert*-Butyl 4-((6-hydroxyhexyl)oxy)piperidine-1-carboxylate, 13**



13 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and tert-butyl 4-(pent-4-en-1-yloxy)piperidine-1-carboxylate (135 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / EtOAc (25-40%)) gave **13** (128 mg, 0.43 mmol, 85%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) [rotameric mixture] δ_H 3.79-3.67 (2H, m), 3.59 (2H, t, *J* = 6.5 Hz), 3.50-3.32 (3H, m), 3.04 (2H, ddd, *J* = 13.0, 9.0 and 3.5 Hz), 2.07 (1H, bs), 1.85-1.73 (2H, m), 1.58-1.44 (6H, m), 1.42 (9H, s), 1.36-1.27 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) [rotameric mixture] δ_C 154.9, 79.4, 74.4, 67.9, 62.7, 41.3, 32.7, 31.1, 30.0, 28.4, 26.0, 25.6; **HRMS** (ESI+) calc. for $C_{16}H_{31}NaNO_4$ $[M+Na]^+$ 324.2145, found 324.2150.

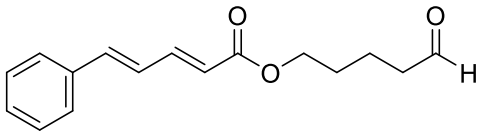
2-((5-Hydroxypentyl)oxy)-4,6-dimethylnicotinonitrile, 14



14 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and 2-(but-3-en-1-yloxy)-4,6-dimethyl nicotinonitrile (101 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (CH_2Cl_2 / EtOAc (10-20%)) gave **14** (97 mg, 0.42 mmol, 83%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.64 (1H, s), 4.37 (2H, t, *J* = 6.5 Hz), 3.64 (2H, t, *J* = 6.5 Hz), 2.40 (6H, s), 1.87-1.77 (2H, m), 1.69-1.59 (2H, m), 1.57-1.46 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.1, 160.7, 154.3, 117.3, 115.1, 93.8, 66.9, 62.7, 32.3, 28.5, 24.5, 22.3, 20.0; **HRMS** (ESI+) calc. for $C_{13}H_{19}N_2O_2$ $[M+H]^+$ 235.1441, found 235.1439.

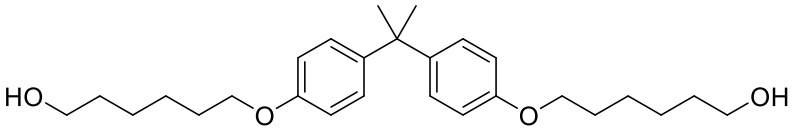
5-Oxopentyl (2*E*,4*E*)-5-phenylpenta-2,4-dienoate, 15



15 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and but-3-en-1-yl (2*E*,4*E*)-5-phenylpenta-2,4-dienoate (114 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was purified *via* column chromatography (pentane / EtOAc (20%)) to give **15** (103 mg, 0.40 mmol, 80%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.82 (1H, t, *J* = 1.5 Hz), 7.56-7.30 (6H, m), 7.02-6.84 (2H, m), 6.01 (1H, d, *J* = 15.5 Hz), 4.31-4.09 (2H, m), 2.60-2.42 (2H, m), 1.84-1.65 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.8, 167.0, 144.8, 140.6, 136.0, 129.1, 128.8, 127.2, 126.2, 121.0, 63.8, 43.4, 28.2, 18.7; **HRMS** (ESI+) calc. for $C_{16}H_{18}NaO_3$ $[M+Na]^+$ 281.1154, found 281.1158.

6,6'-((Propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(hexan-1-ol), 16

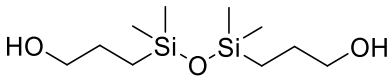


16 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 1.34 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 6.66 mol%) and 4,4'-(propane-2,2-diyl)bis((pent-4-en-1-yloxy)benzene) (91 mg, 0.25 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 4.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 4.0 equiv.), TBAI (17 mg, 0.046 mmol, 16.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a

16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* *>20*:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 3.2 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / EtOAc (60-100%)) gave **16** (60 mg, 0.15 mmol, 60%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.16-7.08 (4H, m), 6.80-6.73 (4H, m), 3.93 (4H, t, *J* = 6.5 Hz), 3.65 (4H, t, *J* = 6.5 Hz), 1.78 (4H, quin, *J* = 6.5 Hz), 1.69 (2H, bs), 1.63 (6H, s), 1.60 (4H, quin, *J* = 7.0 Hz), 1.55-1.38 (8H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.9, 143.0, 127.7, 113.8, 67.7, 62.9, 41.7, 32.7, 31.1, 29.3, 25.9, 25.6; **HRMS** (ESI+) calc. for $C_{27}H_{41}O_4$ $[M+H]^+$ 429.2999, found 429.3001.

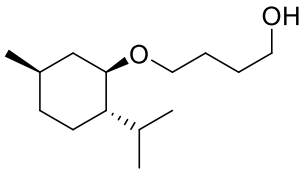
3,3'-(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(propan-1-ol), 17



17 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 1.34 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 6.66 mol%) and 1,1,3,3-tetramethyl-1,3-divinyldisiloxane (47 mg, 0.25 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 4.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 4.0 equiv.), TBAI (17 mg, 0.046 mmol, 16.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* > 20:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 3.2 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / EtOAc (40-60%)) gave **17** (38 mg, 0.15 mmol, 61%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.60 (4H, t, *J* = 6.5 Hz), 1.67 (2H, bs), 1.64-1.54 (4H, m), 0.59-0.47 (4H, m), 0.07 (12H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 65.6, 26.7, 14.2, 0.42; **HRMS** (ESI+) could not be found.

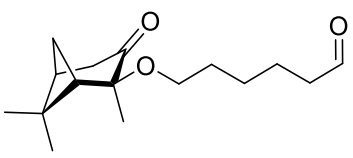
4-(((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)butan-1-ol, 18



18 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and (1*S*,2*R*,4*R*)-2-(allyloxy)-1-isopropyl-4-methylcyclohexane (98 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL) and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* = 4.6:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (pentane / EtOAc (10-20%)) gave **18** (59 mg, 0.26 mmol, 52%) as a colourless oil as well as mixture of the combined geometrical isomers (13 mg, 0.057 mmol, 11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.68-3.55 (3H, m), 3.35-3.28 (1H, m), 3.02 (1H, dt, *J* = 10.5 and 4.0 Hz), 2.76 (1H, bs), 2.16 (1H, dp, *J* = 7.0 and 3.0 Hz), 2.11-2.04 (1H, m), 1.75-1.51 (6H, m), 1.38-1.25 (1H, m), 1.25-1.14 (1H, m), 1.00-0.78 (8H, m), 0.75 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 79.6, 68.5, 62.8, 48.3, 40.5, 34.7, 31.7, 30.5, 27.5, 25.8, 23.5, 22.4, 21.1, 16.4; **HRMS** (ESI+) calc. for $C_{14}H_{29}O_2$ $[M+H]^+$ 229.2162, found 229.2159.

6-(((1*S*,2*S*,5*S*,6*R*)-2,6,5-Trimethyl-3-oxobicyclo[3.1.1]heptan-2-yl)oxy)hexanal, 19

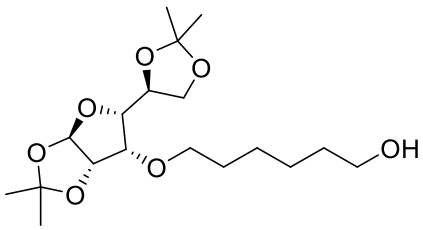


19 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and (1*R*,2*R*,5*R*)-2,6,6-

trimethyl-2-(pent-4-en-1-yloxy)bicyclo[3.1.1]heptan-3-one (118 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was purified *via* column chromatography (pentane / EtOAc (5-10%)) gave **19** (74 mg, 0.28 mmol, 55%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.71 (1H, t, *J* = 1.5.0 Hz), 3.37-3.23 (2H, m), 2.530 (2H, s), 2.37 (2H, dt, *J* = 7.5 and 2.0 Hz), 2.35-2.25 (1H, m), 2.11 (1H, t, *J* = 6.0 Hz), 2.07-1.98 (1H, m), 1.75 (1H, d, *J* = 10.5 Hz), 1.57 (2H, quin, *J* = 7.5 Hz), 1.51-1.39 (2H, m), 1.36-1.26 (5H, m), 1.25 (3H, s), 0.81 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 209.5, 202.6, 80.0, 61.6, 50.0, 43.8, 43.7, 39.1, 38.7, 29.8, 28.1, 27.4, 25.8, 22.6, 21.9, 19.6; **HRMS** (ESI+) calc. for $C_{16}H_{27}O_3$ $[M+H]^+$ 267.1955, found 267.1955.

6-(((3a*R*,5*R*,6*S*,6a*R*)-5-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro [2,3-d][1,3]dioxol-6-yl)oxy)hexan-1-ol, 20



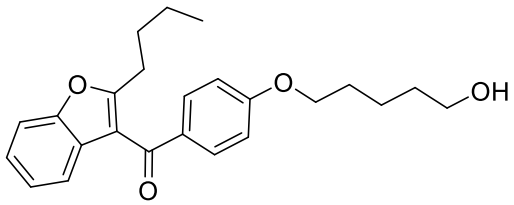
20 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and (3a*R*,5*R*,6*S*,6a*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(pent-4-en-1-yloxy)tetrahydrofuro[2,3-d][1,3]dioxole (164 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 3, with $NaBH_4$

(30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (CH_2Cl_2 / Et_2O (30%)) gave **20** (157 mg, 0.44 mmol, 87%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.87 (1H, d, *J* = 3.5 Hz), 4.53 (1H, d, *J* = 3.5 Hz), 4.30 (1H, q, *J* = 6.0 Hz), 4.15-4.03 (2H, m), 3.99 (1H, dd, *J* = 8.5 and 6.0 Hz), 3.85 (1H, d, *J* = 3.0 Hz), 3.68-3.57 (3H, m), 3.56-3.46 (1H, m), 1.62-1.53 (5H, m), 1.49 (3H, s), 1.42 (3H, s), 1.41-1.36 (4H, m), 1.35 (3H, s), 1.32 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 111.9, 109.1, 105.4, 82.7, 82.3, 81.4, 72.7, 70.7, 67.4, 63.0, 32.8, 29.8, 27.0, 26.9, 26.4, 26.0, 25.6, 25.5.

Spectroscopic data in agreement with that reported by Pejanović *et al*[10].

(2-Butylbenzofuran-3-yl)(4-((5-hydroxypentyl)oxy)phenyl)methanone, 21

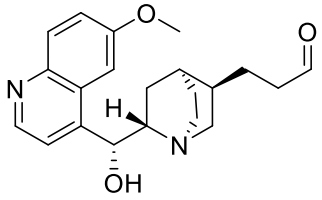


21 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and (4-(but-3-en-1-yloxy)phenyl)(2-butylbenzofuran-3-yl)methanone (174 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL) and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (CH_2Cl_2 / EtOAc (10-20%)) gave **21** (150 mg, 0.39 mmol, 78%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.82 (2H, d, *J* = 9.0 Hz), 7.47 (1H, d, *J* = 8.0 Hz), 7.36 (1H, d, *J* = 8.0 Hz), 7.28-7.22 (1H, m), 7.20-7.14 (1H, m), 6.93 (2H, d, *J* = 9.0 Hz), 4.03 (2H, t, *J* =

6.5 Hz), 3.67 (2H, t, *J* = 6.5 Hz), 2.90 (2H, t, *J* = 7.5 Hz), 2.07 (1H, bs), 1.85 (2H, quin, *J* = 6.5 Hz), 1.75 (2H, quin, *J* = 7.5 Hz), 1.69-1.60 (1H, m), 1.60-1.50 (2H, m), 1.35 (2H, sext, *J* = 7.5 Hz), 0.88 (3H, t, *J* = 7.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 190.7, 164.7, 163.1, 153.6, 131.8, 131.6, 127.2, 124.2, 123.3, 121.2, 116.8, 114.1, 111.0, 68.1, 62.6, 32.4, 30.2, 28.9, 27.8, 22.4, 13.8; **HRMS** (ESI+) calc. for $C_{24}H_{29}O_4$ $[M+H]^+$ 381.2060, found 381.2063.

3-((1S,3R,4S,6S)-6-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)propanal, 22

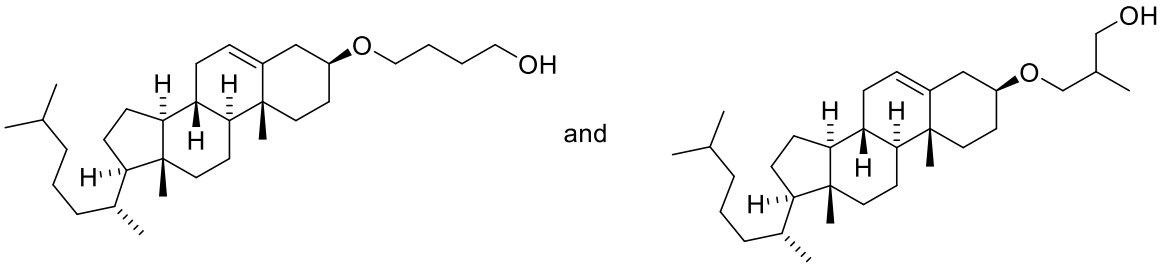


22 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and quinine (162 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >10:1) was purified *via* column chromatography (CH_2Cl_2 / MeOH (10-20%) with NEt_3 (1%)) gave **22** (90 mg, 0.45 mmol, 90%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.72 (1H, d, *J* = 1.5 Hz), 8.75 (1H, d, *J* = 4.5 Hz), 8.01 (1H, d, *J* = 9.0 Hz), 7.55 (1H, d, *J* = 4.5 Hz), 7.35 (1H, dd, *J* = 9.0 and 2.5 Hz), 7.23 (1H, d, *J* = 3.0 Hz), 5.71 (1H, s), 3.91 (3H, s), 3.66-3.52 (1H, m), 3.22-3.12 (2H, m), 2.73 (1H, t, *J* = 11.5 Hz), 2.53-2.33 (3H, m), 1.89-1.74 (4H, m), 1.59 (2H, t, *J* = 6.0 Hz), 1.54-1.26 (3H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.0, 157.8, 147.6, 147.4, 144.4, 131.7, 126.6, 121.5, 118.4, 101.4, 72.0, 59.8, 58.3, 55.7, 43.1, 41.9, 35.1, 28.1, 26.8, 25.7, 21.4.

Spectroscopic data in agreement with that reported by Lambers *et al*[11].

4-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy) butan-1-ol, 23-linear and 33-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methyl heptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a] phenanthren-3-yl)oxy)-2-methylpropan-1-ol, 23-branched



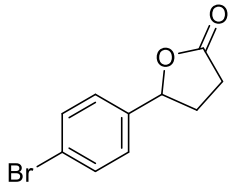
23-linear **23-branched**

23 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and cholesterol (214 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude aldehyde (*l*:*b* = 2.8:1) was then subjected to General Procedure 3, with $NaBH_4$ (30 mg, 0.79 mmol, 1.6 equiv.) and MeOH (4 drops), with a 1 h reaction time. Purification *via* column chromatography (CH_2Cl_2 / EtOAc (10-20%)) gave **23-linear** (119 mg, 0.26 mmol, 52%) and **23-branched** (42 mg, 0.92 mmol, 18%) as colourless solids.

23-linear: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 5.34 (1H, d, *J* = 5.0 Hz), 3.71-3.58 (2H, m), 3.57-3.45 (2H, m), 3.30-3.11 (1H, m), 2.81 (1H, bs), 2.42-2.32 (1H, m), 2.25-2.13 (1H, m), 2.07-1.76 (5H, m), 1.75-1.63 (4H, m), 1.62-0.80 (33H, m), 0.67 (3H, s); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ_C 140.8, 121.7, 79.3, 68.0, 62.8, 56.8, 56.2, 50.2, 42.3, 39.8, 39.5, 39.0, 37.2, 36.9, 36.2, 35.8, 32.0, 31.9, 30.6, 28.3, 28.2, 28.0, 27.5, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9. Spectroscopic data in agreement with that reported by Behera and Madhavan[12].

23-branched: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.34 (1H, d, *J* = 5.0 Hz), 3.68-3.53 (3H, m), 3.45-3.34 (1H, m), 3.27-3.08 (1H, m), 3.21-3.08 (1H, m), 2.93 (1H, bs), 2.41-2.30 (1H, m), 2.24-2.11 (1H, m), 2.11-1.72 (6H, m), 1.70-1.76 (36H, m), 0.68 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.7, 121.7, 79.7, 73.9, 68.6, 56.8, 56.2, 50.2, 42.3, 39.8, 39.5, 39.0, 37.2, 36.9, 36.2, 35.8, 35.6, 32.0, 31.9, 28.3, 28.2, 28.0, 24.3, 23.8, 22.8, 22.5, 21.1, 19.4, 18.7, 13.4, 11.9; **HRMS** (ESI+) calc. for $C_{31}H_{54}NaO_2$ $[M+Na]^+$ 481.4016, found 481.4012.

5-(4-Bromophenyl)dihydrofuran-2(3*H*)-one, 24

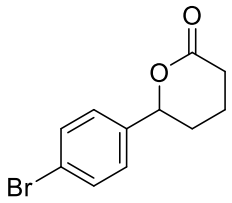


24 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and 1-(4-bromophenyl)prop-2-en-1-ol (107 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 4, with pyridinium chlorocromate (323 mg, 1.5 mmol, 3.0 equiv.), 4Å molecular sieves in CH_2Cl_2. Purification *via* column chromatography (pentane / EtOAc (15-30%) gave **24** (85 mg, 0.36 mmol, 71%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59-7.52 (2H, m), 7.27-7.21 (2H, m), 5.49 (1H, dd, *J* = 8.5 and 6.0 Hz), 2.75-2.64 (3H, m), 2.26-2.09 (1H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.6, 138.5, 131.9, 127.1, 122.4, 80.5, 30.9, 28.9.

Spectroscopic data in agreement with that reported by Xu and Li[13].

5-(4-Bromophenyl)-5-hydroxypentanal, 25

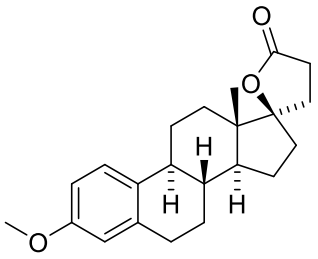


25 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and 1-(4-bromophenyl)but-3-en-1-ol (114 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 4, with pyridinium chlorocromate (323 mg, 1.5 mmol, 3.0 equiv.), 4Å molecular sieves in CH_2Cl_2. Purification *via* column chromatography (pentane / EtOAc (25%) gave **25** (69 mg, 0.27 mmol, 54%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 (2H, d, *J* = 8.5 Hz), 7.21 (2H, d, *J* = 8.5 Hz), 5.29 (1H, dd, *J* = 10.5 and 3.5 Hz), 2.69 (1H, dt, *J* = 18.0 and 6.5 Hz), 2.55 (1H, dt, *J* = 18.0 and 8.0 Hz), 2.14 (1H, dq, *J* = 13.5 and 4.5 Hz), 1.97 (2H, quin, *J* = 8.0 Hz), 1.86-1.73 (1H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.0, 138.8, 131.7, 127.4, 122.2, 80.9, 30.5, 29.4, 18.6.

Spectroscopic data in agreement with that reported by Zhou *et al*[14].

(8*R*,9*S*,13*S*,14*S*,17*R*)-3-methoxy-13-methyl-3',4',6,7,8,9,11,12,13,14,15,16-dodecahydro-5'H-spiro[cyclopenta[a]phenanthrene-17,2'-furan]-5'-one, 26

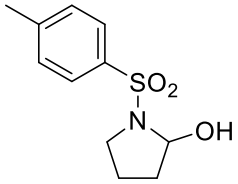


26 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and 8R,9S,13S,14S,17R)-3-methoxy-13-methyl-17-vinyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a] phenanthren-17-ol (156 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was then subjected to General Procedure 4, with pyridinium chlorocromate (323 mg, 1.5 mmol, 3.0 equiv.), 4Å molecular sieves in CH_2Cl_2. Purification *via* column chromatography (CH_2Cl_2/ EtOAc (5%) gave **26** (123 mg, 0.36 mmol, 72%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.20 (1H, d, *J* = 8.5 Hz), 6.72 (1H, dd, *J* = 8.5 and 3.0 Hz), 6.64 (1H, d, *J* = 3.0 Hz), 3.78 (3H, s), 2.93-2.81 (2H, m), 2.67-2.52 (2H, m), 2.51-2.41 (1H, m), 2.39-2.24 (2H, m), 2.19 (1H, dq, *J* = 10.5 and 4.5 Hz), 2.02-1.82 (3H, m), 1.82-1.72 (1H, m), 1.72-1.63 (1H, m), 1.61-1.42 (4H, m), 1.42-1.24 (2H, m), 0.97 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.9, 157.6, 137.9, 132.0, 126.4, 113.9, 111.6, 96.1, 55.3, 48.8, 46.1, 43.6, 39.1, 35.7, 32.0, 31.4, 29.8, 29.5, 27.3, 26.1, 22.7, 14.6.

Spectroscopic data in agreement with that reported by Bull and Steer[15].

1-Tosylpyrrolidin-2-ol, 27

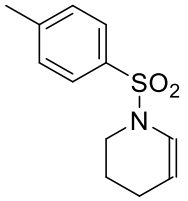


27 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and *N*-allyl-4-methylbenzenesulfonamide (106 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude material (*l*:*b* = 4:1) was purified *via* column chromatography (CH_2Cl_2 / MeOH (3-5%)) to give **27** (93 mg, 0.39 mmol, 77%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (2H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 5.78 (1H, d, *J* = 5.5 Hz), 3.53-3.44 (1H, m), 3.01 (1H, td, *J* = 9.5 and 7.0 Hz), 2.42 (3H, s), 2.08-1.85 (2H, m), 1.75-1.63 (m, 1H), 1.50-1.37 (1H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.5, 135.5, 129.8, 127.4, 89.2, 47.8, 33.7, 23.1, 21.5.

Spectroscopic data in agreement with that reported by Unthank *et al*[16].

1-Tosyl-1,2,3,4-tetrahydropyridine, 28



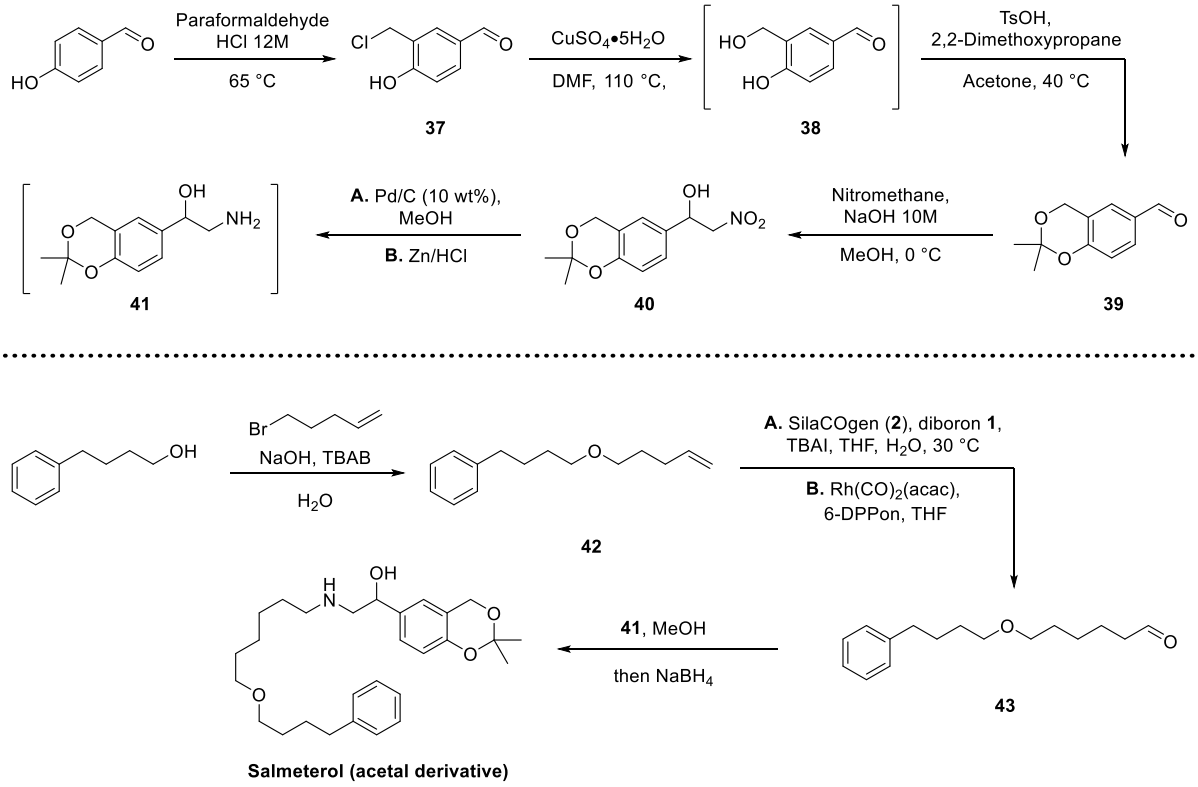
28 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and *N*-(but-3-en-1-yl)-4-methyl benzenesulfonamide (113 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17

mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude material (*l*:*b* >20:1) was purified *via* column chromatography (CH_2Cl_2 / Et_2O (33%)) gave a mixture of **27** and the corresponding hemiaminal. The mixture was dissolved in toluene (25 mL) and heated at reflux for 24 h before being concentrated *in vacuo* to afford **27** (100 mg, 0.42 mmol, 83%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (2H, d, *J* = 7.5 Hz), 7.30 (2H, d, *J* = 7.5 Hz), 6.63 (1H, d, *J* = 8.5 Hz), 5.02-4.92 (1H, m), 3.47-3.30 (2H, m), 2.42 (3H, s), 2.00-1.87 (2H, m), 1.66 (2H, quin, *J* = 6.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.6, 135.3, 129.8, 127.2, 125.2, 108.4, 44.0, 21.7, 21.1, 21.0.

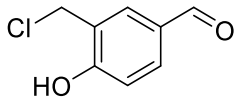
Spectroscopic data in agreement with that reported by Dake *et al*[17].

Preparation of salmeterol (acetal derivative)



Supplementary Figure 9. Preparation of salmeterol (acetal derivative).

3-(Chloromethyl)-4-hydroxybenzaldehyde, 37

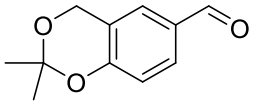


To a flask containing 4-hydroxybenzaldehyde (5.54 g, 45.4 mmol, 1.0 equiv.) and paraformaldehyde (1.51 g, 49.9 mmol, 1.1 equiv.) was added concentrated HCl (46 mL, 12 M, 545 mmol, 12 equiv.). After stirring at 65 °C for 3 h, the resulting suspension was allowed to reach room temperature before being cooled to 0 °C. Crude **37** (6.29 g, 36.9 mmol, 81%) was collected by filtration, washing the filtrate with ice cold water, as a grey solid after drying which was used in the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 11.1 (1H, s), 9.80 (1H, s, C*H*O), 7.91 (1H, d, *J* = 2.0 Hz), 7.76 (1H, dd, *J* = 8.5 and 2.0 Hz), 7.04 (1H, d, *J* = 8.5 Hz), 4.75 (1H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 141.0, 139.9, 130.6, 130.5, 130.3, 129.9, 129.8, 126.5, 109.6, 90.0, 75.5, 69.8, 64.0, 38.7, 28.3, 0.0.

Prepared in accordance with that reported by Buchanan *et al*[18].

2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxine-6-carbaldehyde, 39

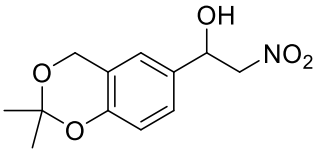


To a solution of **37** (0.85 g, 5.0 mmol, 1.0 equiv.) in DMSO (7.1 mL) and H_2O (3.6 mL) was added $CuSO_4$•$5H_2O$ (1.23 g, 5.0 mmol, 1.0 equiv.). After stirring at 110 °C overnight, the resulting green solution was allowed to reach room temperature before being diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated and the aqueous layer further extracted with EtOAc (2 × 50 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude **38** as yellow oil, which was used in the next reaction without further purification. To a stirred suspension of this

product, 2,2-dimethoxypropane (3.1 mL, 25 mmol, 5.0 equiv.), and Na_2SO_4 (2.6 g, 18.5 mmol, 3.7 equiv.), in acetone (17 mL) was added *p*-TsOH•H_2O(95 mg, 0.5 mmol, 10 mol%). After stirring at 40 °C overnight, the resulting reaction mixture was allowed to reach room temperature before being diluted with EtOAc (50 mL) and quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous layer further extracted with EtOAc (2 × 50 mL), the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in* vacuo to give the crude product which was purified *via* column chromatography (pentane / EtOAc (10%)) to give **39** (406 mg, 2.10 mmol, 42%) as a clear oil.

R_f 0.29 (pentane / EtOAc (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.85 (1H, s), 7.71 (1H, dd, *J* = 8.5 and 2.0 Hz), 7.57-7.53 (1H, m), 6.91 (1H, d, *J* = 8.5 Hz), 4.91 (1H, s), 1.57 (1H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 190.9, 157.0, 130.6, 129.6, 127.0, 119.9, 117.9, 100.9, 60.8, 25.0. Spectroscopic data in agreement with that reported by Gisch *et al*[19].

1-(2,2-Dimethyl-4*H*-benzo[*d*][1,3]dioxin-6-yl)-2-nitroethan-1-ol, 40

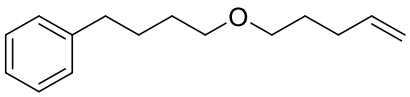


To a solution of **39** (547 mg, 2.85 mmol, 1.0 equiv.) and nitromethane (0.6 mL, 10.5 mmol, 3.7 equiv.) in MeOH (1.0 mL) was added dropwise an aqueous solution of NaOH (0.53 mL, 10.0 M, 5.25 mmol, 1.8 equiv.) at 0 °C. After stirring for 1 h, the resulting suspension was diluted with EtOAc (5 mL) and water (5 mL), the organic layer was separated, and the aqueous layer further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (pentane / EtOAc (10%) → pentane / EtOAc (20%)) to give **40** (541 mg, 2.14 mmol, 75%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.19 (1H, dd, *J* = 8.5 and 2.0 Hz), 7.09-7.01 (1H, m), 6.86 (1H, d, *J* = 8.5 Hz), 5.40 (1H, dt, J = 9.5 and 3.0 Hz), 4.85 (2H, s), 4.61 (1H, dd, *J* = 13.5 and 9.5 Hz), 4.49 (1H, dd, *J* = 13.5 and 3.0 Hz), 2.84 (1H, d, *J* = 3.5 Hz), 1.56 (1H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 151.9, 130.1, 126.0, 122.6, 120.1, 117.8, 100.0, 81.4, 70.8, 60.9, 24.9, 24.8.

Spectroscopic data in agreement with that reported by Guo *et al*[20].

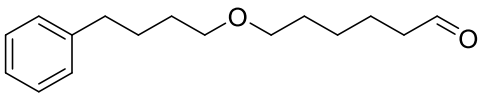
(4-(Pent-4-en-1-yloxy)butyl)benzene, 42



To a stirred solution of NaOH (2.00 g, 50.4 mmol, 7.0 equiv.) in H_2O (4.0 mL, 50 wt%) was added TBAB (464 mg, 1.44 mmol, 20 mol%), 4-phenylbutan-1-ol (1.10 mL, 7.20 mmol, 1.0 equiv,) and 5-bromo-1-pentene (2.60 mL, 21.6 mmol, 3.0 equiv.). After stirring vigorously overnight, the resulting reaction mixture was diluted with water (20 mL) and Et_2O (25 mL), the organic layer separated, and the aqueous layer further extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (pentane / Et_2O (10%)) to give **42** (1.11 g, 5.10 mmol, 71%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33-7.12 (5H, m), 5.88-5.75 (1H, m), 5.08-4.91 (2H, m), 3.41 (4H, app. q, *J* = 6.5 Hz), 2.63 (2H, t, *J* = 7.50 Hz), 2.17-2.05 (2H, m), 1.77-1.54 (6H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 142.6, 138.5, 128.5, 128.4, 125.8, 70.8, 70.3, 35.9, 30.5, 29.5, 29.0, 28.2; **HRMS** (ESI+) calc. for $C_{22}H_{15}NaO$ $[M+Na]^+$ 241.1563, found 241.1565.

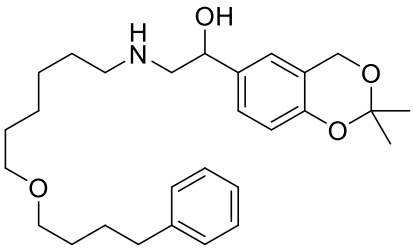
6-(4-Phenylbutoxy)hexanal, 43



6-(4-Phenylbutoxy)hexanal was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **43** (109 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (10%)) gave 6-(4-phenylbutoxy) hexanal (100 mg, 0.40 mmol, 81%) as a clear oil.

R_f 0.18 (petroleum ether / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.76 (1H, t, *J* = 1.5 Hz), 7.35-7.11 (5H, m), 3.51-3.28 (4H, app. q, *J* = 6.5 Hz), 2.63 (2H, t, *J* = 7.50 Hz), 2.43 (2H, dt, *J* = 7.5 and 1.5 Hz), 1.77-1.50 (8H, m), 1.46-1.32 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.8, 142.6, 128.6, 128.4, 125.8, 70.9, 70.7, 44.0, 35.9, 29.7, 29.5, 28.2, 26.0, 22.1; **HRMS** (ESI+) calc. for $C_{16}H_{25}O_2$ $[M+H]^+$ 249.1849, found 249.1854.

Salmeterol (acetal derivative)



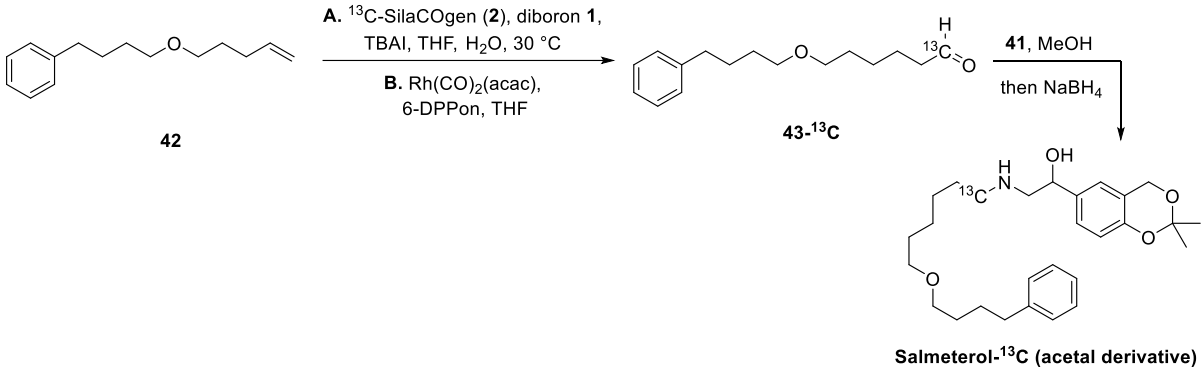
In a two-chamber reactor; The hydrogen consuming chamber was charged with Pd/C (13 mg, 10 wt% Pd, 10 wt%) and **40** (127 mg, 0.50 mmol, 1.0 equiv.) in methanol (2 mL) and sealed with a screw cap fitted with an H-cap. The hydrogen producing chamber was charged with zinc granules (164 mg, 2.50 mmol, 2.5 equiv.) followed by addition of an aqueous solution of HCl (1.9 mL, 4.0 M, 7.5 mmol, 7.5 equiv.) and directly sealed with a screw cap fitted with a H-cap.

After stirring at room temperature overnight, the resulting reaction mixture was filtered through celite and the filtrate concentrated to give crude **41** as a clear oil which was used in the next reaction without further purification. To a stirred solution of **43** (82 mg, 0.33 mmol, 1.0 equiv.) in MeOH (0.6 mL) was added a solution of the crude **41** (104 mg, 0.47 mmol, 1.4 equiv.) in MeOH (0.6 mL) and the resulting mixture stirred overnight before cooling down to 0 °C followed by addition of $NaBH_4$ (28 mg, 0.75 mmol, 2.3 equiv.). After stirring for 1 h, the resulting mixture was diluted with water (5 mL) and EtOAc (5 mL), the organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (4%)) to give salmeterol (acetal derivative) (98 mg, 0.22 mmol, 67%) as a yellow oil.

R_f 0.27 (CH_2Cl_2 / MeOH (4%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30-7.11 (6H, m), 7.02 (1H, s), 6.79 (1H, d, *J* = 8.5 Hz), 4.90 (1H, dd, *J* = 10.0 and 2.0 Hz), 4.84 (2H, s), 3.47-3.33 (4H, m), 2.89-2.66 (4H, m), 2.63 (2H, t, *J* = 7.5 Hz), 1.74-1.46 (14H, m), 1.42-1.31 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 150.9, 142.6, 133.8, 128.6, 128.4, 126.0, 125.8, 122.4, 119.5, 117.2, 99.7, 71.0, 70.9, 68.1, 61.1, 35.8, 29.8, 29.5, 28.2, 27.2, 26.9, 26.3, 25.0, 24.7; **HRMS** (ESI+) not found.

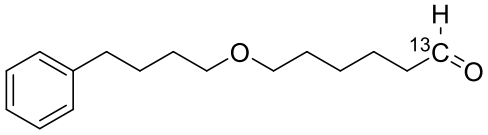
Spectroscopic data in agreement with that reported by Coe *et al*[21].

Preparation of salmeterol-^{13}C (acetal derivative)



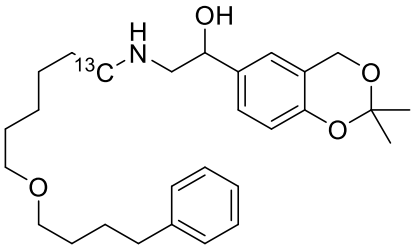
Supplementary Figure 10. Preparation of salmeterol-^{13}C (acetal derivative).

6-(4-phenylbutoxy)hexanal-1-^{13}C, 43-^{13}C



43-^{13}C was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **42** (109 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (10%)) gave **43-^{13}C** (111 mg, 0.45 mmol, 89%) as a clear oil. $\mathbf{R_f}$ 0.18 (petroleum ether / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.76 (1H, dt, J = 170.0 and 1.5 Hz), 7.33-7.14 (5H, m), 3.50-3.31 (4H, app. q, J = 6.5 Hz), 2.64 (2H, t, J = 7.50 Hz), 2.44 (2H, dt, J = 7.5 and 1.5 Hz), 1.75-1.53 (8H, m), 1.45-1.34 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.7 (^{13}C), 142.6, 128.5, 128.4, 125.8, 70.9, 70.7, 44.0 (d, J = 38.5), 35.8, 29.6, 29.5, 28.2, 26.0 (d, J = 3.5 Hz), 22.1 (d, J = 1.0 Hz); **HRMS** (ESI+) calc. for $C_{15}{}^{13}C_1H_{24}NaO_2$ $[M+Na]^+$ 272.1708, found 272.1702.

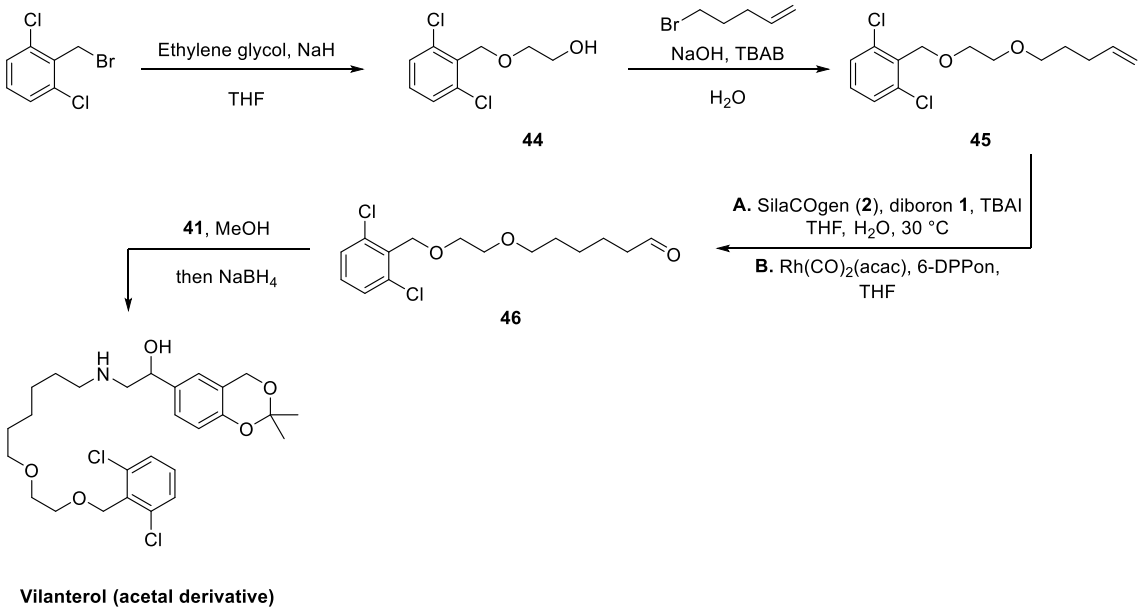
Salmeterol-^{13}C (acetal derivative)



To a stirred solution of **43-^{13}C** (82 mg, 0.33 mmol, 1.0 equiv.) in MeOH (0.6 mL) was added a solution of crude **41** (104 mg, 0.47 mmol, 1.4 equiv.) in MeOH (0.6 mL) and the resulting mixture stirred overnight before cooling down to 0 °C followed by addition of $NaBH_4$ (28 mg, 0.75 mmol, 2.3 equiv.). After stirring for 1 h, the resulting mixture was diluted with water (5 mL) and EtOAc (5 mL), the organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (4%)) to give salmeterol-^{13}C (acetal derivative) (98 mg, 0.22 mmol, 67%) as a yellow oil.

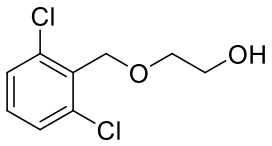
R_f 0.27 (CH_2Cl_2 / MeOH (4%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30-7.24 (2H, m),7.21-7.11 (4H, m), 7.03 (1H, s), 6.79 (1H, d, *J* = 8.5 Hz), 4.91 (1H, dd, *J* = 10.0 and 2.0 Hz), 4.87-4.80 (3H, m), 3.42 (2H, t, *J* = 6.5 Hz), 3.39 (2H, t, *J* = 6.5 Hz), 3.02-2.47 (6H, m), 1.74-1.46 (14H, m), 1.42-1.31 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C150.9, 142.6, 133.7, 128.5, 128.4, 126.0, 125.8, 122.4, 119.5, 117.2, 99.7, 71.0, 70.9, 68.1, 61.1 (^{13}C), 35.8, 29.8, 29.5, 28.2, 27.2, 26.9 (d, *J* = 38.5 Hz), 26.3 (d, *J* = 4.0 Hz), 25.0, 24.7; **HRMS** (ESI+) not found.

Preparation of vilanterol (acetal derivative)



Supplementary Figure 11. Preparation of vilanterol (acetal derivative).

2-((2,6-Dichlorobenzyl)oxy)ethan-1-ol, 44

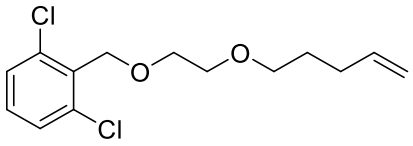


To a stirred suspension of NaH (1.80 g, 60 wt% in mineral oil, 45.0 mmol, 1.2 equiv.) in THF (60 mL) was added ethylene glycol (10.5 mL, 188 mmol, 5.0 equiv.) dropwise at 0 °C, the cooling bath was removed, and the mixture was allowed to reach room temperature. After stirring for 30 min, the resulting mixture was cooled to 0 °C followed by dropwise addition of a solution of 2,6-dichlorobenzyl bromide (9.00 g, 37.5 mmol, 1.0 equiv.) in THF (15 mL). After stirring at reflux overnight, the resulting reaction mixture was allowed to reach room temperature before quenching with a saturated aqueous solution of NH_4Cl (75 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*

to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / Et_2O (20%)) to give **44** (6.96 g, 31.5 mmol, 84%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44-7.10 (3H, m), 5.03-4.61 (2H, s), 3.86-3.71 (2H, m), 3.71-3.55 (2H, m), 2.05 (1H, bs); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 137.0, 133.3, 130.2, 128.6, 71.8, 67.5, 61.9; **HRMS** (ESI+) calc. for $C_9H_{10}Cl_2O_2Na$ $[M+Na]^+$ 242.9956, found 242.9957.

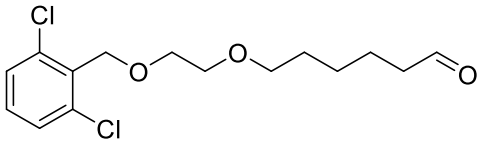
1,3-Dichloro-2-((2-(pent-4-en-1-yloxy)ethoxy)methyl)benzene, 45



To a stirred solution of NaOH (2.00 g, 50.4 mmol, 7.0 equiv.) in H_2O (4.0 mL, 50 wt%) was added TBAB (464 mg, 1.44 mmol, 20 mol%), **44** (1.10 mL, 7.20 mmol, 1.0 equiv,) and 5-bromo-1-pentene (2.60 mL, 21.6 mmol, 3.0 equiv.). After stirring vigorously overnight, the resulting reaction mixture was diluted with water (20 mL) and Et_2O (25 mL), the organic layer separated, and the aqueous layer further extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (pentane / Et_2O (10%)) to give **45** (1.71 g, 5.91 mmol, 82%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32-7.10 (3H, m), 5.85-5.71 (1H, m), 5.03-4.87 (2H, m), 4.89 (2H, s), 3.67 (2H, app. t, J = 5.5 Hz), 3.58 (2H, app. t, J = 5.5 Hz), 3.44 (2H, t, J = 6.50 Hz), 2.13-2.03 (2H, m), 1.71-1.57 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.4, 137.0, 133.5, 129.9, 128.4, 114.7, 70.7, 70.1, 70.0, 67.6, 30.3, 29.0; **HRMS** (ESI+) calc. for $C_{14}H_{18}Cl_2NaO_2$ $[M+Na]^+$ 311.0576, found 311.0577.

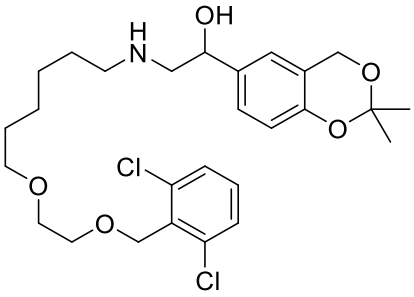
6-(2-((2,6-Dichlorobenzyl)oxy)ethoxy)hexanal, 46



46 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **45** (145 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (20%)) gave **46** (135 mg, 0.42 mmol, 85%) as a clear oil.

R_f 0.29 (petroleum ether / Et_2O (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (1H, t, *J* = 1.5 Hz, *H*1), 7.36-7.12 (3H, m, Ar*H*), 4.82 (2H, s, *H*11), 3.74-3.65 (2H, m, *H*8), 3.65-3.56 (2H, m, *H*9), 3.46 (2H, t, *J* = 6 .5 Hz, *H*6), 2.42 (2H, dt, *J* = 7.5 and 1.5 Hz, *H*2), 1.70-1.52 (4H, m, *H*3 and *H*5), 1.46-1.33 (2H, m, *H*4); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.8, 137.1, 133.6, 130.0, 128.5, 71.2, 70.2, 70.1, 67.7, 44.0, 29.6, 25.9, 22.1; **HRMS** (ESI+) calc. for $C_{15}H_{20}Cl_2NaO_3$ $[M+Na]^+$ 341.0682, found 341.0688.

Vilanterol (acetal derivative)



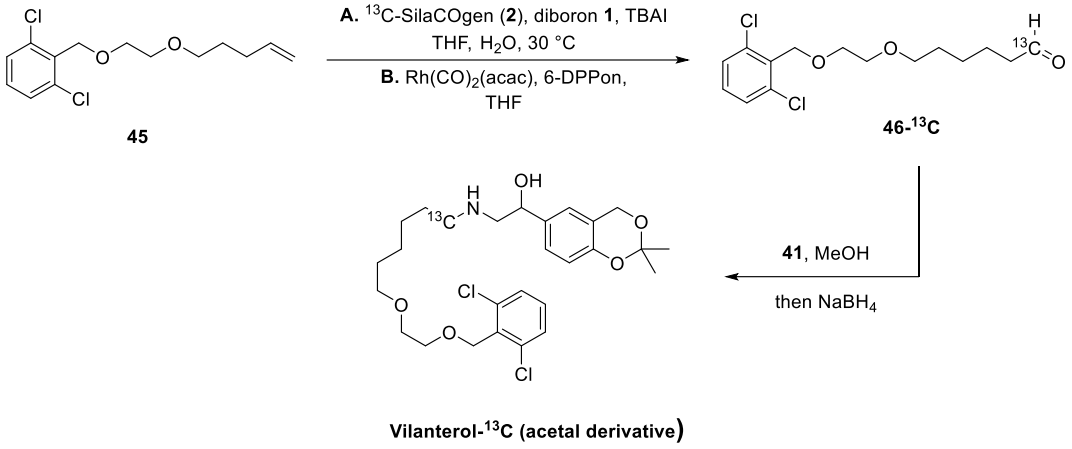
To a stirred solution of **46** (106 mg, 0.33 mmol, 1.0 equiv.) in MeOH (0.6 mL) was added a solution of crude **41** (112 mg, 0.50 mmol, 1.5 equiv.) in MeOH (0.6 mL) and the resulting mixture stirred overnight before cooling down to 0 °C followed by addition of $NaBH_4$ (28 mg,

0.75 mmol, 2.3 equiv.). After stirring for 1 h, the resulting mixture was diluted with water (5 mL) and EtOAc (5 mL), the organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (3%)) to give pro-vilanterol (126 mg, 0.24 mmol, 73%) as a yellow oil.

R_f 0.27 (CH_2Cl_2 / MeOH (3%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33-7.27 (2H, m), 7.20-7.11 (2H, m), 7.02 (1H, s), 6.79 (1H, d, *J* = 8.5 Hz), 4.92 (1H, dd, *J* = 10.0 and 2.0 Hz), 4.83 (4H, s), 3.75-3.65 (2H, m), 3.64-3.56 (2H, m), 3.46 (2H, t, *J* = 6.5 Hz), 2.89-2.60 (4H, m), 1.74-1.46 (10H, m), 1.44-1.29 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) 150.7, 136.9, 133.6, 133.4, 129.9, 128.4, 125.9, 122.3, 119.3, 117.0, 99.5, 71.3, 70.0, 69.9, 68.0, 67.5, 61.0, 29.6, 27.0, 26.6, 26.0, 24.8, 24.6; **HRMS** (ESI+) not found.

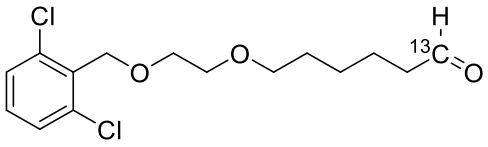
Spectroscopic data in agreement with that reported by Procopiou *et al*[22].

Preparation of vilanterol-^{13}C (acetal derivative)



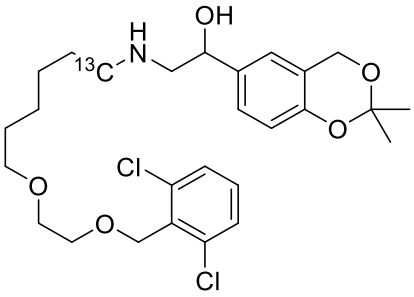
Supplementary Figure 12. Preparation of vilanterol-^{13}C (acetal derivative).

6-(2-((2,6-Dichlorobenzyl)oxy)ethoxy)hexanal-1-^{13}C, 46-^{13}C



46-^{13}C was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **45** (145 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (20%)) gave **46-^{13}C** (146 mg, 0.46 mmol, 91%) as a clear oil. $\mathbf{R_f}$ 0.29 (petroleum ether / Et_2O (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (1H, dt, J = 170.0 and 1.5 Hz), 7.38-7.12 (3H, m), 4.82 (2H, s), 3.73-3.66 (2H, m), 3.63-3.57 (2H, m), 3.46 (2H, t, J = 6 .5 Hz), 2.42 (2H, dt, J = 7.5 and 1.5 Hz), 1.70-1.50 (4H, m), 1.47-1.32 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 202.8 (^{13}C), 137.1, 133.6, 130.0, 128.5, 71.2, 70.2, 70.1, 67.7, 44.0 (d, J = 39.0 Hz), 29.6, 25.9 (d, J = 3.50 Hz), 22.1 (d, J = 1.5 Hz); **HRMS** (ESI+) calc. for $C_{14}{}^{13}C_1H_{20}Cl_2NaO_3$ $[M+Na]^+$ 342.0721, found 342.0712.

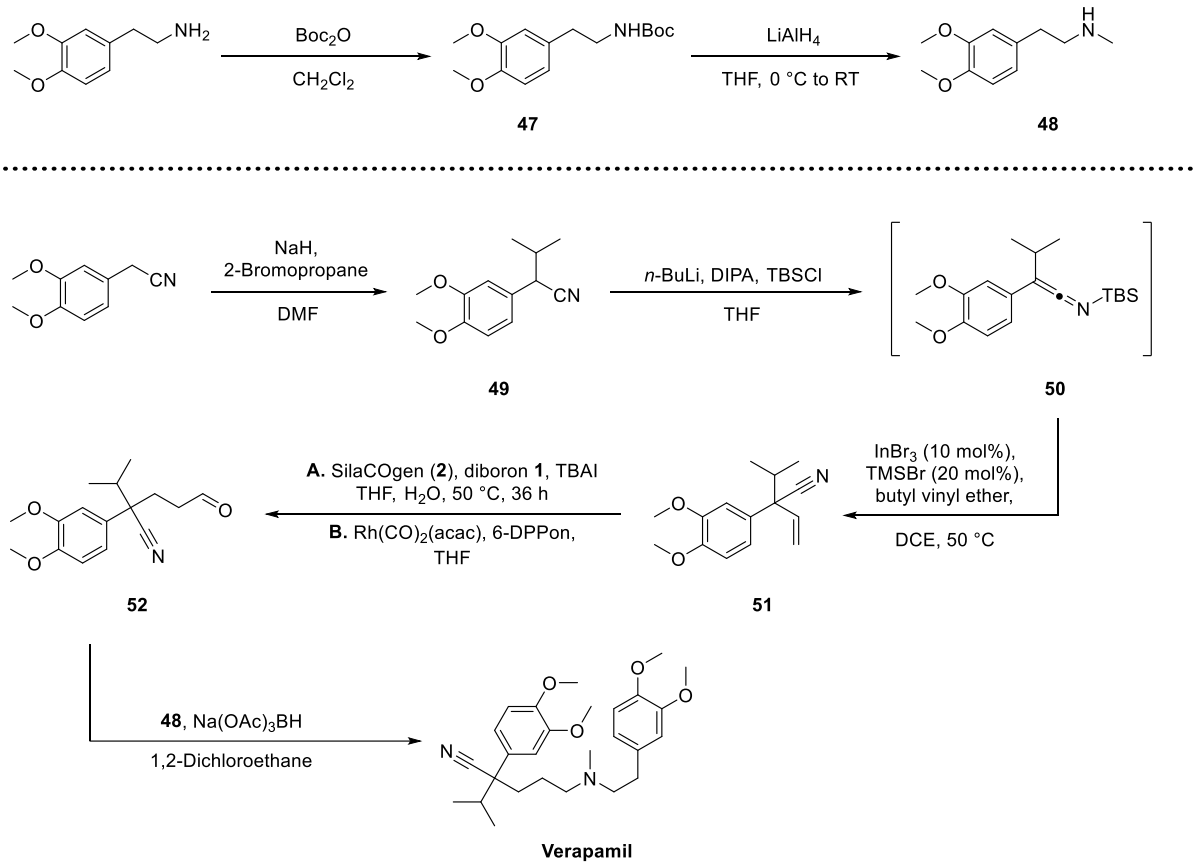
Vilanterol-^{13}C (acetal derivative)



To a stirred solution **46-^{13}C** (106 mg, 0.33 mmol, 1.0 equiv.) in MeOH (0.6 mL) was added a solution of crude **41** (112 mg, 0.50 mmol, 1.5 equiv.) in MeOH (0.6 mL) and the resulting mixture stirred overnight before cooling down to 0 °C followed by addition of $NaBH_4$ (28 mg, 0.75 mmol, 2.3 equiv.). After stirring for 1 h, the resulting mixture was diluted with water (5 mL) and EtOAc (5 mL), the organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (3%)) to give vilanterol-^{13}C (acetal derivative) (104 mg, 0.20 mmol, 60%) as a yellow oil.

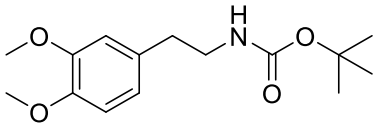
R_f 0.27 (CH_2Cl_2 / MeOH (3%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31-7.26 (2H, m, Ar*H*), 7.18-7.10 (2H, m, Ar*H*), 7.01 (1H, s, Ar*H*), 6.78 (1H, d, *J* = 8.5 Hz, Ar*H*), 4.90 (1H, dd, *J* = 10.0 and 2.0 Hz, *H*14), 4.81 (4H, s, ArC*H*$_2$O and *H*1), 3.72-3.65 (2H, m, *H*4), 3.62-3.56 (2H, m, *H*6), 3.45 (2H, t, *J* = 6.5 Hz, *H*3), 3.01-2.68 (3H, m, *H*11 and *H*13), 2.64-2.44 (1H, m, *H*11'), 1.69-1.44 (10H, m, *H*7, *H*10 and C(C*H*$_3$)$_2$), 1.44-1.29 (4H, m, *H*8 and *H*9); **^{13}C NMR** (101 MHz, $CDCl_3$) 150.9, 137.1, 133.8, 133.6, 130.0, 128.5, 126.1, 122.4, 119.5, 117.1, 99.7, 71.5, 70.2, 70.1, 68.1, 67.7, 61.1 (^{13}C), 29.7, 27.1, 26.8, 26.2 (d, *J* = 4.0 Hz), 25.0, 24.8; **HRMS** (ESI+) not found.

Preparation of verapamil



Supplementary Figure 13. Preparation of verapamil.

tert-Butyl (3,4-dimethoxyphenethyl)carbamate, 47



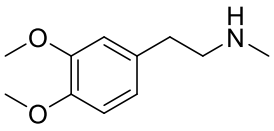
To a solution of 3,4-dimethoxyphenylethylamine (4.20 mL, 24.8 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) was added di-*tert*-butyl dicarbonate (6.30 mL, 27.3 mmol, 1.1 equiv.) dropwise *via* syringe at 0 °C. After stirring at room temperature for 1 h, the resulting reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4,

filtered and concentrated *in vacuo* to give crude **47** (6.92 g, 24.6 mmol 99%) as a yellow solid, which was pure enough to use in subsequent reactions.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.81 (1H, d, J = 8.0 Hz), 6.76-6.68 (2H, m), 4.54 (1H, bs), 3.88 (3H, s), 3.86 (3H, s), 3.43-3.27 (2H, m), 2.74 (2H, t, J = 7.0 Hz), 1.44 (9H, s_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 2156.0, 140.0, 147.7, 131.6, 120.7, 112.0, 111.4, 79.2, 56.0, 55.9, 42.0, 35.8, 28.5.

Spectroscopic data in agreement with that reported by Lin *et al*[23].

2-(3,4-Dimethoxyphenyl)-N-methylethan-1-amine, 48

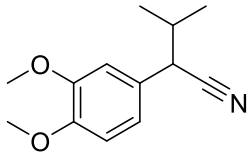


To a stirred suspension of $LiAlH_4$ (809 mg, 21.3 mmol, 1.5 equiv.) in THF (32 mL) at 0 °C was added slowly *via* syringe a solution of **47** (4.00 g, 14.2 mmol, 1.0 equiv.) in THF (15 mL). The cooling bath was removed, and the reaction mixture stirred at reflux for 6 h. After allowing to reach room temperature, the reaction was cooled to 0 °C and quenched by slow addition of water (0.8 mL) followed by addition of an aqueous solution of NaOH (0.8 mL, 15% w/v) and water (2.4 mL). The cooling bath was removed, and the resulting mixture stirred for 15 min, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was re-dissolved in Et_2O (30 mL) and extracted with 1.0 M aqueous solution of HCl (3 × 20 mL). The combined aqueous layers were adjusted to pH > 8 and extracted with Et_2O (3 × 60 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **48** (1.98 g, 10.1 mmol, 71%) as a colourless oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.80 (1H, d, J = 8.0 Hz), 6.77-6.70 (2H, m), 3.88 (3H, s), 3.86 (3H, s), 2.87-2.79 (2H, m), 2.79-2.71 (2H, m), 2.44 (3H, s), 1.23 (1H, bs); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 149.1, 147.6, 132.8, 120.7, 112.2, 111.5, 56.1, 56.0, 53.5, 36.6, 36.0.

Spectroscopic data in agreement with that reported by Theodore and Nelson[24].

2-(3,4-Dimethoxyphenyl)-3-methylbutanenitrile, 49

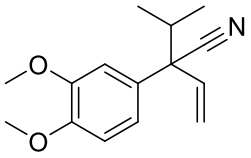


To a stirred suspension of NaH (2.20 g, 60 wt% in mineral oil, 55.0 mmol, 1.1 equiv.) in DMF (70 mL) was added 2-(3,4-dimethoxy)acetonitrile (9.20 g, 52.0 mmol, 1.06 equiv.) dropwise at 0 °C, the cooling bath was removed, and the mixture was allowed to reach room temperature. After stirring for 30 min, the resulting mixture was cooled to 0 °C followed by dropwise addition of a solution of 2-bromopropane (4.60 mL, 49.0 mmol, 1.0 equiv.) in DMF (10 mL). After stirring at room temperature overnight, the resulting reaction mixture was diluted with Et_2O (50 mL) and quenched with a saturated aqueous solution of NH_4Cl (80 mL), the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with water (3 × 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (pentane / EtOAc (10%)) to give **49** (10.5 g, 47.8 mmol, 98%) as a clear oil.

R_f 0.40 (pentane / EtOAc (15%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.87-6.81 (2H, m), 6.78 (1H, s), 3.89 (3H, s), 3.87 (3H, s), 3.59 (1H, d, *J* = 6.5 Hz), 2.17-2.01 (1H, m), 1.04 (6H, d, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 149.2, 148.8, 127.5, 120.3, 120.1, 111.3, 110.9, 56.1, 56.0, 44.8, 33.9, 20.8, 19.0.

Spectroscopic data in agreement with that reported by Chen *et al*[25].

2-(3,4-Dimethoxyphenyl)-2-isopropylbut-3-enenitrile, 51

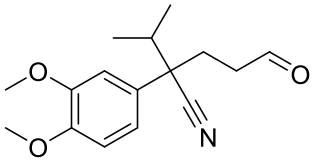


To a solution of DIPA (2.90 mL, 20.5 mmol, 1.0 equiv.) in THF (21 mL) was added a solution of *n*-BuLi (8.40 mL, 2.5 M in hexanes, 20.5 mmol, 1.0 equiv.) dropwise *via* syringe at 0 °C. After stirring at 0 °C for 10 min, the resulting mixture was cooled to –78 °C followed by sequential additions of solutions of **49** (4.50 g, 20.5 mmol, 1.0 equiv.) in THF (15 mL) and TBSCl (3.40 g, 22.6 mmol, 1.1 equiv.) in THF (15 mL). Subsequently, the cooling bath was removed, and the resulting mixture was allowed to reach room temperature. After stirring at the aforementioned temperature for 1 h, the solvent was removed under reduced pressure followed by addition of addition of hexane (50 mL) and the resulting suspension was filtered under nitrogen *via* cannula and concentrated *in vacuo* to give crude **50** (4.35 g) as a yellow oil. To a solution of the freshly prepared crude **50** (4.35 g, ca. 13 mmol, 1.5 equiv.), indium bromide (307 mg, 0.87 mmol, 15 mol%) and TMSBr (0.23 mL, 1.73 mmol, 20 mol%) in 1,2-dichloroethane (17 mL) was added butyl vinyl ether (868 mg, 8.67 mmol, 1.0 equiv.). After stirring at 80 °C for 2 h, the resulting reaction mixture was allowed to reach room temperature before being quenched by addition of 1.0 M aqueous solution of HCl (20 mL). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (pentane / Et_2O (30%)) to give **51** (1.33 g, 5.42 mmol, 63%) as a clear oil.

R_f 0.34 (pentane / Et_2O (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.97 (1H, dd, *J* = 8.5 and 2.5 Hz), 6.93 (1H, d, *J* = 2.5 Hz), 6.86 (1H, d, *J* = 8.5 Hz), 5.95 (1H, dd, *J* = 17.0 and 10.5 Hz), 5.56 (1H, d, *J* = 17.0 Hz), 5.29 (1H, d, *J* = 10.5 Hz), 3.90 (3H, s), 3.88 (3H, s), 2.26 (1H, sep,

J = 6.5 Hz), 1.10 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 149.3, 148.7, 137.0, 131.6, 119.5, 118.5, 116.5, 111.5, 109.7, 56.8, 56.2, 56.1, 37.0, 18.5. Spectroscopic data in agreement with that reported by Nishimoto *et al*[26].

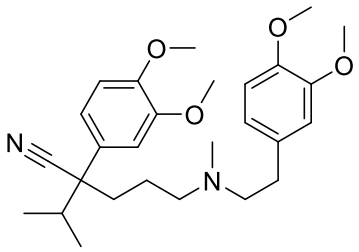
2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-oxopentanenitrile, 52



52 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **51** (123 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 32 h reaction time at 50 °C. Purification *via* column chromatography (pentane / EtOAc (30%)) gave **52** (124 mg, 0.45 mmol, 90%) as a clear oil.

R_f 0.34 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.66 (1H, s), 6.91 (1H, dd, *J* = 8.5 and 2.0 Hz), 6.85 (1H, d, *J* = 8.5 Hz), 6.82 (1H, d, *J* = 2.0 Hz), 3.89 (3H, s), 3.88 (3H, s), 2.70-2.55 (1H, m), 2.51-2.38 (1H, m), 2.25-2.02 (3H, m), 1.21 (3H, d, *J* = 6.5 Hz), 0.81 (3H, d, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 200.4, 149.5, 148.8, 129.8, 120.9, 118.9, 111.5, 109.6, 56.2, 56.1, 52.8, 40.7, 38.1, 30.1, 19.2, 18.7; **HRMS** (ESI+) calc. for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$ 298.1419, found 298.1421.

Verapamil

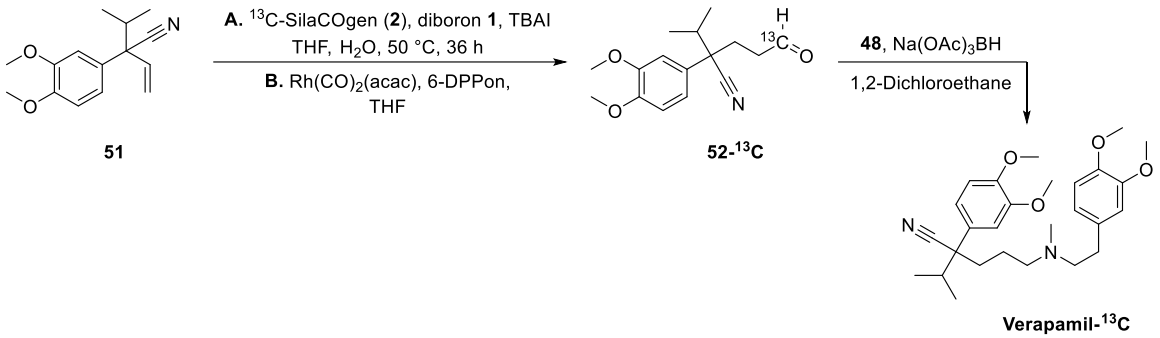


To a solution of **52** (44 mg, 0.16 mmol, 1.0 equiv.) and **48** (31 mg, 0.16 mmol, 1.0 equiv.) in 1,2-dichloroethane (5 mL) was added $NaBH(OAc)_3$ (44 mg, 0.21 mmol, 1.3 equiv.). After stirring at room temperature overnight, the resulting reaction mixture was quenched by addition of 1.0 M aqueous solution of HCl (0.5 mL) and diluted with EtOAc (15 mL) and water (5 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with a 6.0 M aqueous solution of NaOH (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (5%)) to give verapamil (74 mg, 0.16 mmol, 99%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.91 (1H, dd, J = 8.5 and 2.0 Hz), 6.87-6.75 (3H, m), 6.72-6.65 (2H, m), 3.88 (3H, s), 3.87 (3H, s), 3.86 (3H, s), 3.85 (3H, s), 2.76-2.61 (2H, m), 2.61-2.48 (2H, m), 2.48-2.32 (2H, m), 2.21 (3H, s), 2.17-2.01 (2H, m), 1.93-1.80 (1H, m), 1.64-1.49 (1H, m), 1.28-1.09 (4H, m), 0.78 (3H, d, J = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 149.2, 149.0, 148.5, 147.6, 132.9, 130.8, 121.6, 120.7, 118.8, 112.2, 111.5, 111.3, 109.8, 59.5, 56.9, 56.2, 56.1, 56.02, 56.01, 53.5, 41.9, 38.1, 35.7, 33.1, 23.3, 19.1, 18.7; **HRMS** (ESI+) calc. for $C_{27}H_{39}N_2O_4$ $[M+H]^+$ 455.2910, found 455.2919.

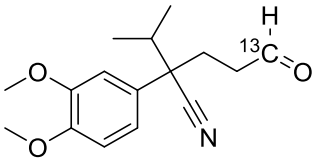
Spectroscopic data in agreement with that reported by Mermerian and Fu[27].

Preparation of verapamil-^{13}C



Supplementary Figure 14. Preparation of verapamil-^{13}C.

2-(3,4-Dimethoxyphenyl)-2-isopropyl-5-oxopentanenitrile-5-^{13}C, 52-^{13}C

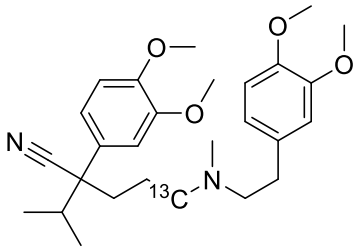


52-^{13}C was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **51** (123 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (20%)) gave **52-^{13}C** (131 mg, 0.47 mmol, 94%) as a clear oil.

R_f 0.34 (petroleum ether / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.66 (1H, d, *J* = 175.0 Hz), 6.91 (1H, dd, *J* = 8.5 and 2.0 Hz), 6.85 (1H, d, *J* = 8.5 Hz), 6.82 (1H, d, *J* = 2.0 Hz), 3.89 (3H, s), 3.88 (3H, s), 2.70-2.55 (1H, m), 2.51-2.38 (1H, m), 2.25-2.02 (3H, m), 1.21 (3H, d, *J* = 6.5 Hz), 0.81 (3H, d, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 200.4 (^{13}C), 149.5, 148.8, 129.7, 120.9, 118.9, 111.4, 109.5, 56.2, 56.1, 52.8 (d, *J* = 4.0 Hz), 40.7 (d, *J* = 38.0 Hz),

38.1, 30.0, 19.1, 18.7; **HRMS** (ESI+) calc. for $C_{15}{}^{13}C_1H_{22}NO_3$ $[M+H]^+$ 277.1633, found 277.1631.

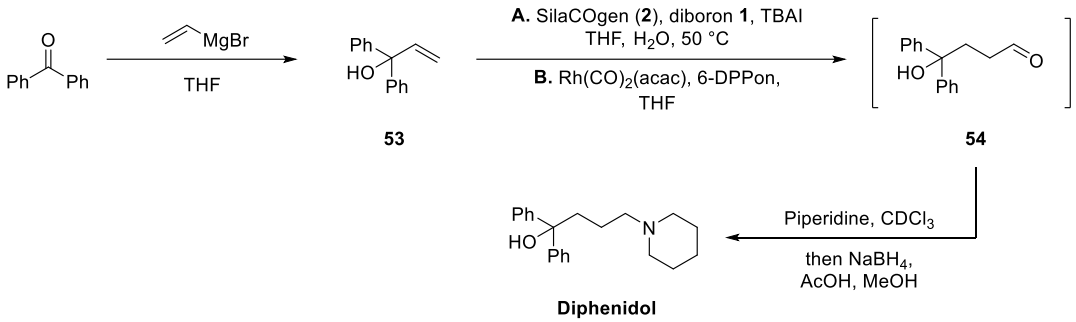
Verapamil-^{13}C



To a solution of **52-^{13}C** (44 mg, 0.16 mmol, 1.0 equiv.) and **48** (31 mg, 0.16 mmol, 1.0 equiv.) in 1,2-dichloroethane (5 mL) was added $NaBH(OAc)_3$ (44 mg, 0.21 mmol, 1.3 equiv.). After stirring at room temperature overnight, the resulting reaction mixture was quenched by addition of 1.0 M aqueous solution of HCl (0.5 mL) and diluted with EtOAc (15 mL) and water (5 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with a 6.0 M aqueous solution of NaOH (3 × 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (5%)) to give verapamil-^{13}C (73 mg, 0.16 mmol, 99%) as a yellow oil.

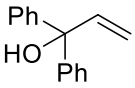
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.91 (1H, dd, *J* = 8.5 and 2.0 Hz), 6.88-6.75 (3H, m), 6.72-6.65 (2H, m), 3.88 (3H, s), 3.87 (3H, s), 3.86 (3H, s), 3.85 (3H, s), 2.82-2.41 (2H, m), 2.64-2.42 (3H, m), 2.41-2.17 (4H, m), 2.17-2.00 (2H, m), 1.96-1.81 (1H, m), 1.64-1.49 (1H, m), 1.28-1.12 (4H, m), 0.78 (3H, d, *J* = 6.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 149.2, 149.0, 148.5, 147.6, 132.8, 7130., 121.6, 120.7, 118.8, 112.2, 111.4, 111.2, 109.7, 59.4, 56.9 (^{13}C), 56.2, 56.1, 56.02, 56.00, 53.5 (d, *J* = 4.5 Hz), 41.9, 38.1, 35.7, 33.0, 23.3, 19.1, 18.8; **HRMS** (ESI+) calc. for $C_{26}{}^{13}C_1H_{39}N_2O_4$ $[M+H]^+$ 456.2944, found 456.2949.

Preparation of diphenidol



Supplementary Figure 15. Preparation of diphenidol.

1,1-Diphenylprop-2-en-1-ol, 53

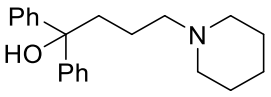


To a solution of benzophenone (1.82 g, 10.0 mmol, 1.0 equiv.) in THF (25 mL) was added a solution of vinylmagnesium bromide (11.0 mL, 1.0 M in THF, 11.0 mmol, 1.1 equiv.) dropwise at 0 °C. After stirring at the aforementioned temperature for 30 minutes, the cooling bath was removed, and the reaction stirred for further 2 h at room temperature before being quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (pentane / Et_2O (5-8%)) to give **53** (1.14 g, 5.42 mmol, 54%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.44-7.40 (4H, m), 7.39-7.33 (4H, m), 7.33-7.25 (3H, m), 6.60-6.49 (1H, m), 5.42-5.35 (1H, m), 5.34-5.32 (1H, m), 2.29 (1H, bs); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.9, 143.6, 128.3, 127.4, 127.0, 114.1, 79.5.

Spectroscopic data in agreement with that reported by Zhang *et al*[28].

Diphenidol

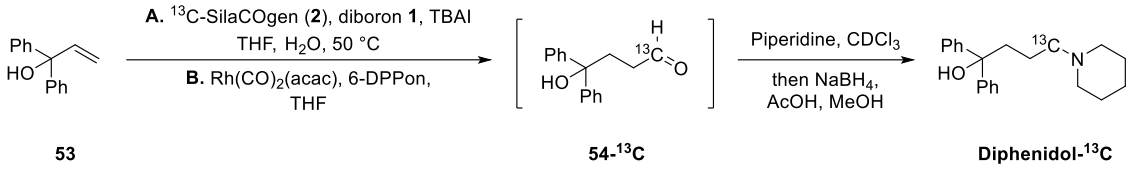


Diphenidol was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **53** (105 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude **54** (98% as determined by ^{1}H NMR of the crude with mesitylene as the internal standard, *l*:*b* >20:1) was concentrated *in vacuo* and re-dissolved in $CDCl_3$ (1.5 mL) followed by addition of piperidine (0.060 mL, 0.61 mmol, 1.2 equiv.). After stirring at room temperature overnight, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaBH_4$ (38 mg, 1.0 mmol, 2.0 equiv.) and a solution of acetic acid in MeOH (1.0 mL, 10 vol%). After stirring at 0 °C for 3 h, the reaction was diluted with EtOAc (20 mL) and quenched by addition of a saturated aqueous solution of $NaHSO_4$ (10 mL), the organic layer was separated and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (pentane / EtOAc (5-10%) with NEt_3 (1%)) to give diphenidol (125 mg, 0.41 mmol, 81%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.82 (1H, br), 7.51 (4H, d, *J* = 7.5 Hz), 7.28 (4H, t, *J* = 7.5 Hz), 7.16 (2H, t, *J* = 7.5 Hz), 2.55-2.42 (2H, m), 2.37-2.28 (2H, m), 2.28-2.21 (4H, m), 1.71-1.50 (6H, m), 1.50-1.33 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 148.8 , 128.0, 126.4, 126.2, 76.6, 60.0, 54.3, 42.9, 25.4, 24.3, 22.0; **HRMS** (ESI+) calc. for $C_{21}H_{28}ON$ $[M+H]^+$ 310.2165, found 310.2180.

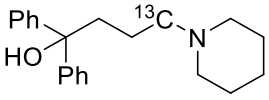
Spectroscopic data in agreement with that reported by Schmidt *et al*[29].

Preparation of diphenidol-^{13}C



Supplementary Figure 16. Preparation of diphenidol-^{13}C.

Diphenidol-^{13}C

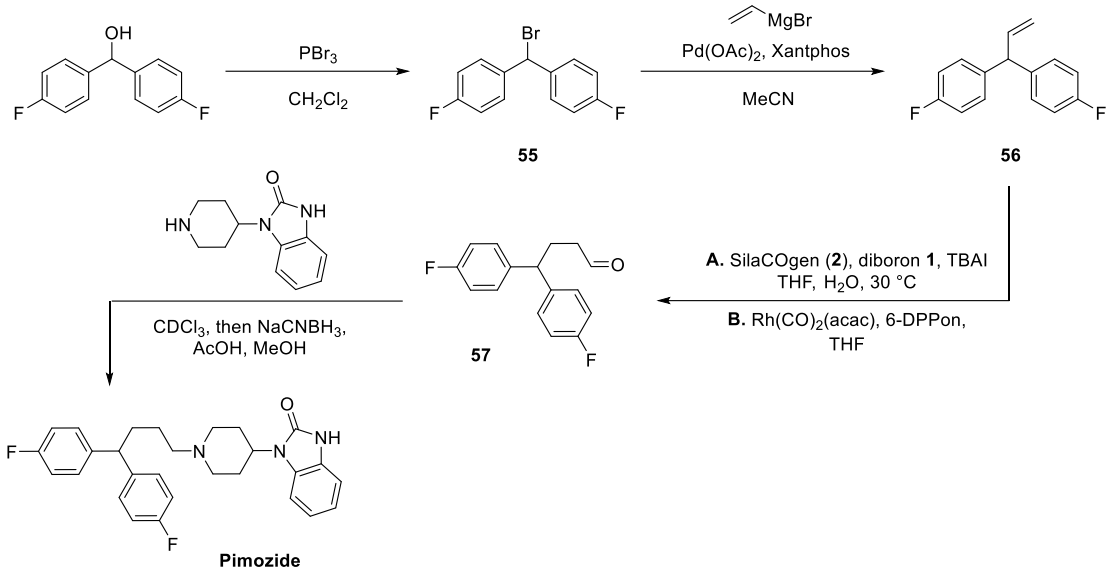


Diphenidol-^{13}C was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **53** (105 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. The resulting crude **54-^{13}C** (67% as determined by ^{1}H NMR of the crude with mesitylene as the internal standard, *l*:*b* >20:1) was concentrated *in vacuo* and re-dissolved in $CDCl_3$ (1.5 mL) followed by addition of piperidine (0.060 mL, 0.61 mmol, 1.2 equiv.). After stirring at room temperature overnight, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaBH_4$ (38 mg, 1.0 mmol, 2.0 equiv.) and a solution of acetic acid in MeOH (1.0 mL, 10 vol%). After stirring at 0 °C for 3 h, the reaction was diluted with EtOAc (20 mL) and quenched by addition of a saturated aqueous solution of $NaHSO_4$ (10 mL), the organic layer was separated and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (pentane / EtOAc (5-10%) with NEt_3 (1%)) to give diphenidol-^{13}C (91 mg, 0.30 mmol, 88%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.89 (1H, br), 7.60-7.55 (4H, m), 7.34 (4H, t, J = 7.5 Hz), 7.25-7.19 (2H, m), 2.59-2.47 (3H, m), 2.43-2.23 (4H, m) 2.23-2.17 (1H, m), 1.75-1.57 (6H,

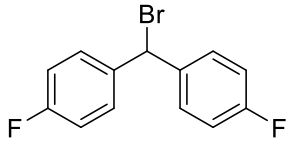
m), 1.56-1.40 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 148.7, 127.9, 126.3, 126.1, 76.5, 59.9 (^{13}C), 54.2, 42.8, 25.4 (d, *J* = 4.0 Hz), 24.2, 21.9 (d, *J* = 37.5 Hz); **HRMS** (ESI+) calc. for $C_{20}{}^{13}C_1H_{28}ON$ $[M+H]^+$ 311.2199, found 311.2205.

Preparation of pimozide



Supplementary Figure 17. Preparation of pimozide.

4,4'-(bromomethylene)bis(fluorobenzene), 55



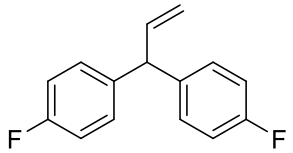
To a solution of bis(4-fluorophenyl)methanol (2.86 g, 13.0 mmol, 1.0 equiv.) in CH_2Cl_2 (40 mL) was added PBr_3 (0.73 mL, 7.70 mmol, 0.60 equiv.) dropwise at 0 °C. After stirring at the aforementioned temperature, the cooling bath was removed, and the reaction stirred for further 30 min at room temperature before cooling again to 0 °C and quenched by addition of ice water (15 mL) and diluted with EtOAc (100 mL). The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ (3 × 20 mL), then brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude was purified *via*

column chromatography (pentane / EtOAc (5-15%)) to give **55** (3.40 g, 12 mmol, 92%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.48-7.40 (4H, m), 7.12-6.99 (4H, m), 6.28 (1H, s).

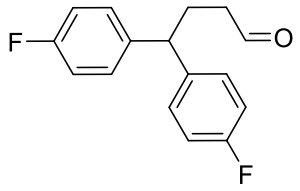
Spectroscopic data in agreement with that reported by Padmanaban *et al*[30].

4,4'-(Prop-2-ene-1,1-diyl)bis(fluorobenzene), 56



To a solution of **55** (3.40 g, 12.0 mmol, 1.0 equiv.) in acetonitrile (120 mL) was added $Pd(OAc)_2$ (81 mg, 0.36 mmol, 3.0 mol%) and xantphos (208 mg, 0.36 mmol, 3.0 mol%). The resulting mixture was then cooled to –10 °C followed by dropwise addition of a solution of vinylmagnesium bromide (18.0 mL, 1.0 M in THF, 18.0 mmol, 1.5 equiv.). After stirring at room temperature overnight, the reaction was quenched by addition of water (10 mL) and the resulting mixture concentrated *in vacuo* followed by addition of EtOAc (20 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (pentane (100%)) to give **56** (827 mg, 3.62 mmol, 30%), as a colourless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.16-7.07 (4H, m), 7.05-6.93 (4H, m), 6.23 (1H, ddd, *J* = 17.0, 10.0 and 7.0 Hz), 5.24 (1H, dt, *J* = 10.0 and 1.5 Hz), 4.95 (1H, dt, *J* = 17.0 and 1.5 Hz), 4.70 (1H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.9, 160.5, 140.4, 138.9, 138.9, 130.1, 130.1, 116.8, 115.5, 115.3, 53.5; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ_F –116.7; **HRMS** (ESI+) not found.

4,4-bis(4-fluorophenyl)butanal, 57

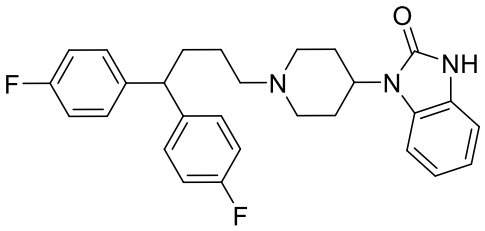


57 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **56** (115 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was purified *via* column chromatography (pentane / Et_2O (10 %)) to give **57** (115 mg, 0.44 mmol, 88%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.74 (1H, d, *J* =1.5 Hz), 7.21-7.12 (4H, m), 7.06-6.90 (4H, m), 3.90 (1H, t, *J* = 8.0Hz), 2.47-2.39 (2H, m), 2.38-2.28 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.5, 162.7, 160.3, 139.6, 139.6, 129.2, 129.1, 115.6, 115.4, 48.8, 42.2, 27.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.4.

Spectroscopic data in agreement with that reported by Tai *et al*[31].

Pimozide



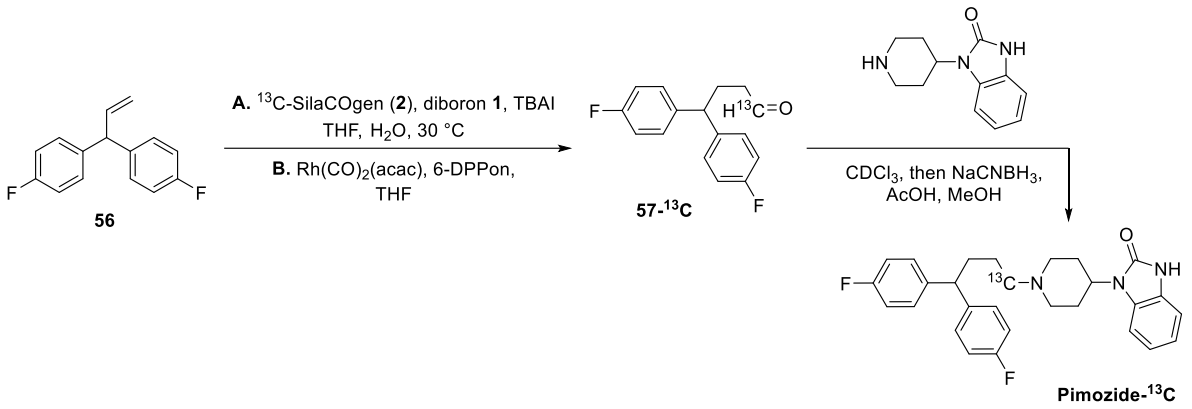
To a solution of **57** (115 mg, 0.44 mmol, 1.0 equiv.) in $CDCl_3$ (1.5 mL) was added 4-(2-keto-1-benzimidazolinyl)piperidine (107 mg, 0.493, 1.1 equiv.). After stirring for 1 h, the reaction was cooled to 0 °C and $NaCNBH_3$ (42 mg, 0.67 mmol, 1.5 equiv.) was added and a solution of AcOH in MeOH (1 mL, 10 vol%). After stirring at room temperature overnight, the resulting

reaction mixture was diluted with CH_2Cl_2 (10 mL) and quenched by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL), the organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (CH_2Cl_2 / MeOH (2.5-5%)) to give pimozide (132 mg, 0.29 mmol, 66%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.79-9.33 (1H, m), 7.22-7.12 (4H, m), 7.13-7.01 (4H, m), 6.98 (4H, m), 4.44-4.23 (1H, m), 3.89 (1H, t, *J* = 8.0 Hz), 3.12-2.92 (2H, m), 2.58-2.32 (4H, m), 2.17-1.91 (4H, m), 1.81 (2H, d, *J* = 10.5 Hz), 1.47 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.6, 160.2, 155.5, 140.5, 129.2, 129.1, 129.0, 128.3, 121.3, 121.1, 115.5, 115.3, 109.9, 58.3, 53.3, 50.8, 49.8, 33.9, 29.2, 25.5; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F –117.0; **HRMS** (ESI+) calc. for $C_{28}H_{30}F_2N_3O$ $[M+H]^+$ 462.2351, found 462.2365.

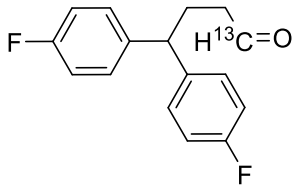
Spectroscopic data in agreement with that reported by Saitot *et al*[32].

Preparation of pimozide-^{13}C



Supplementary Figure 18. Preparation of pimozide-^{13}C.

4,4-bis(4-fluorophenyl)butanal-1-^{13}C, 57-^{13}C

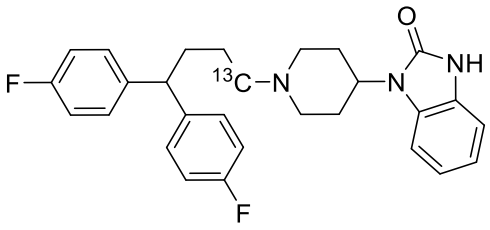


57-^{13}C was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **56** (115 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL). and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), SilaCOgen-^{13}C (**2**) (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude aldehyde (*l*:*b* >20:1) was purified *via* column chromatography (pentane / Et_2O (10 %)) to give **57-^{13}C** (124 mg, 0.48 mmol, 95%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.74 (1H, d, *J* = 172.0), 7.21-7.12 (4H, m), 7.06-6.90 (4H, m), 3.91 (1H, t, *J* = 8.0 Hz), 2.47-2.39 (2H, m), 2.38-2.28 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.6 (^{13}C), 162.8, 160.4, 139.7, 139.6, 129.3, 129.2, 115.7, 115.5, 48.8, 42.3 (d, *J* = 38.5

Hz), 28.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.4; **HRMS** (ESI+) calc. for $C_{15}{}^{13}CH_{15}F_2O$ $[M+H]^+$ 262.1119, found 262.1114.

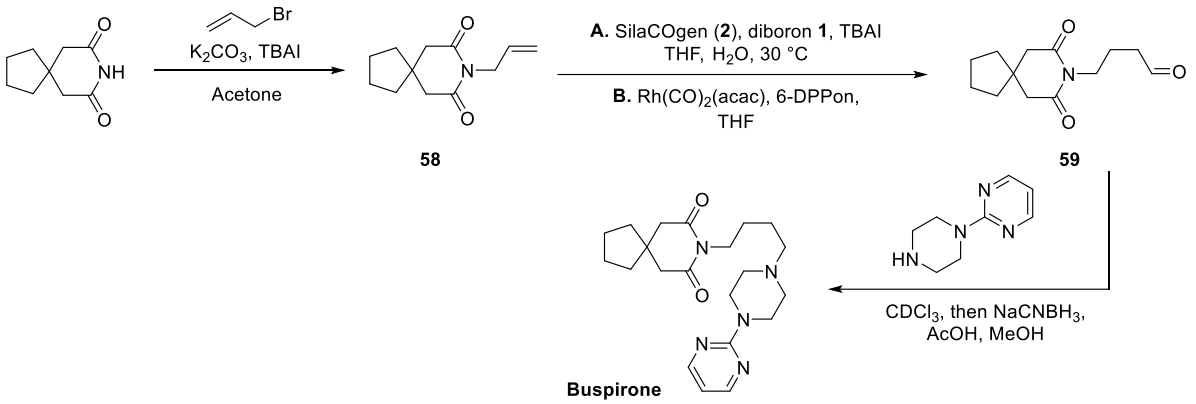
Pimozide-^{13}C



57-^{13}C (124 mg, 0.48 mmol, 1.0 equiv.) was dissolved in $CDCl_3$ (1.5 mL) and 4-(2-keto-1-benzimidazolinyl)piperidine (116 mg, 0.532 mmol, 1.1 equiv.) was added. After stirring for 1 h, the reaction was cooled to 0 °C and $NaCNBH_3$ (45 mg, 0.72 mmol, 1.5 equiv.) was added and a solution of AcOH in MeOH (1 mL, 10 vol%). After stirring at room temperature overnight, the resulting reaction mixture was diluted with CH_2Cl_2 (10 mL) and quenched by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL), the organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (CH_2Cl_2 / MeOH (2.5-5%)) to give pimozide-^{13}C (177 mg, 0.38 mmol, 79%) as a colourless solid.

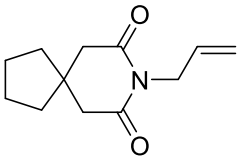
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 10.53-10.21 (1H, m), 7.22-7.14 (4H, m), 7.12-7.01 (4H, m), 7.01-6.93 (4H, m), 4.44-4.25 (1H, m), 3.89 (1H, t, *J* = 8.0 Hz), 3.00 (2H, d, *J* = 10.5 Hz), 2.56 (1H, t, *J* = 7.5 Hz), 2.43 (2H, dq, *J* = 12.5 and 4.0 Hz), 2.25 (1H, t, *J* = 7.5 Hz), 2.14-1.95 (4H, m), 1.80 (2H, d, *J* = 11.5 Hz), 1.53-1.38 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.7, 160.3, 155.1, 140.7, 129.4, 129.3, 129.2, 128.1, 121.3, 121.2, 115.4, 115.2, 115.3 109.9, 58.4 (^{13}C), 53.5, 51.1, 49.9 (d, *J* = 4.5 Hz), 34.0, 29.4 (d, *J* = 4.0 Hz), 25.5 (d, *J* = 38.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F –117.0; **HRMS** (ESI+) calc. for $C_{27}{}^{13}CH_{29}F_2N_3O$ $[M+H]^+$ 463.2385, found 463.2387.

Preparation of buspirone



Supplementary Figure 19. Preparation of buspirone.

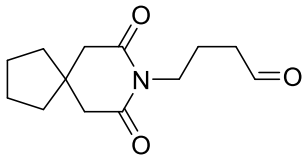
8-allyl-8-azaspiro[4.5]decane-7,9-dione, 58



To a solution of 8-azaspiro[4.5]decane-7,9-dione (1.19 g, 7.11 mmol, 1.0 equiv.) in acetone (15 mL) was added allyl bromide (0.675 mL, 7.8 mmol, 1.1 equiv.), K_2CO_3 (1.96 g, 14.2 mmol, 2.0 equiv.) and TBAI (0.25 g, 0.68 mmol, 9.5 mol%). After stirring for 72 h at room temperature, the reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to give the crude which was purified *via* column chromatography (pentane / EtOAc (10 %)) to give **58** (1.32 g, 6.35 mmol, 89%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.79 (1H, ddt, J = 17.5, 10.5 and 6.0 Hz), 5.21-5.10 (2H, m), 4.37 (2H, dt, J = 6.0 and 1.5 Hz), 2.61 (4H, s), 1.93-1.66 (4H, m), 1.55-1.45 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.9, 132.1, 117.3, 44.8, 41.5, 39.5, 37.6, 24.2; **HRMS** (ESI+) calc. for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.1332, found 208.1332.

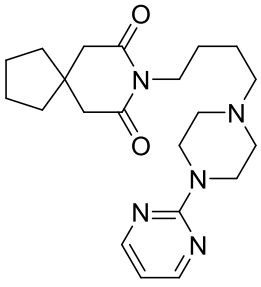
4-(7,9-Dioxo-8-azaspiro[4.5]decan-8-yl)butanal, 59



59 was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **58** (104 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / EtOAc (20-25%)) gave **59** (72 mg, 0.31 mmol, 61%) as a colourless oil which was immediately used in the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.72 (1H, t, *J* = 1.5 Hz), 3.77 (2H, t, *J* = 7.0 Hz), 2.56 (4H, s), 2.43 (2H, dt, *J* = 7.5 and 1.5 Hz), 1.83 (2H, quin, *J* = 7.5 Hz), 1.72-1.64 (4H, m), 1.50-1.42 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.3, 172.4, 44.9, 41.4, 39.5, 38.7, 37.7, 24.3, 20.5; **HRMS** (ESI+) calc. for $C_{13}H_{19}NO_3$ $[M+H]^+$ 238.1438, found 238.1440.

Buspirone



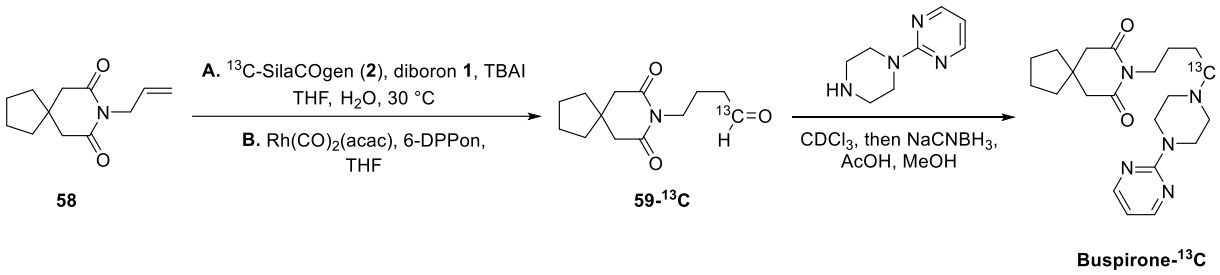
To a solution of **59** (72 mg, 0.31 mmol, 1.0 equiv.) in $CDCl_3$ (1.5 mL) was added 2-(piperazin-1-yl)pyrimidine (54 mg, 0.33 mmol, 1.1 equiv.). After stirring at room temperature overnight, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaCNBH_3$ (42 mg, 0.67 mmol, 2.2 equiv.) and a solution of acetic acid in MeOH (1.0 mL, 10 vol%). After stirring

at room temperature overnight h, the reaction was diluted with CH_2Cl_2 (10 mL) and quenched by addition of a saturated aqueous solution of Na_2CO_3 (10 mL), the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (CH_2Cl_2 / EtOAc (2.5-5%)) to give buspirone (94 mg, 0.24 mmol, 80%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.29 (2H, d, *J* = 4.5 Hz), 6.46 (1H, t, *J* = 4.5 Hz), 3.92-3.69 (6H, m), 2.58 (4H, s), 2.48 (4H, t, *J* = 5.0 Hz), 2.38 (2H, t, *J* = 6.5 Hz), 1.75-1.65 (4H, m), 1.58-1.43 (8H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.3, 161.8, 157.8, 109.9, 58.5, 53.2, 45.0, 43.8, 39.6, 39.5, 37.7, 26.2, 24.4, 24.3; **HRMS** (ESI+) calc. for $C_{21}H_{31}N_5O_2$ $[M+H]^+$ 386.2551, found 386.2565

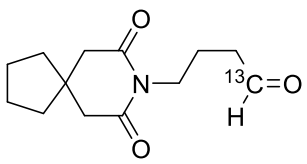
Spectroscopic data in agreement with that reported by Labes *et al*[33].

Preparation of buspirone-^{13}C



Supplementary Figure 20. Preparation of buspirone-^{13}C.

4-(7,9-Dioxo-8-azaspiro[4.5]decan-8-yl)butanal-1-^{13}C, 59-^{13}C

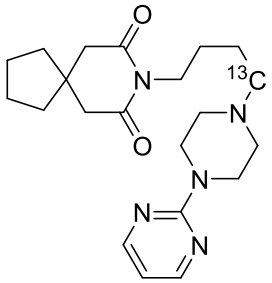


59-^{13}C was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **58** (104 mg, 0.50

mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / EtOAc (20-25%)) gave **59-^{13}C** (84 mg, 0.35 mmol, 70%) as a colourless oil which was immediately used in the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.72 (1H, d, *J* = 172.5 Hz), 3.78 (2H, t, *J* = 7.0 Hz), 2.58 (4H, s), 2.50-2.39 (2H, m), 1.91-1.78 (2H, m), 1.75-1.66 (4H, m), 1.57-1.44 (4H, m); **^{13}C NMR** (101 MHz, CDCl3) δ_C 201.5 (^{13}C), 176.4, 44.9, 41.4 (d, *J* = 38.5 Hz), 39.6, 38.8 (d, *J* = 4.0 Hz), 37.7, 24.3, 20.6; **HRMS** (ESI+) calc. for $C_{12}{}^{13}C_1H_{19}NO_3$ $[M+H]^+$ 239.1471, found 239.1474.

Buspirone-^{13}C

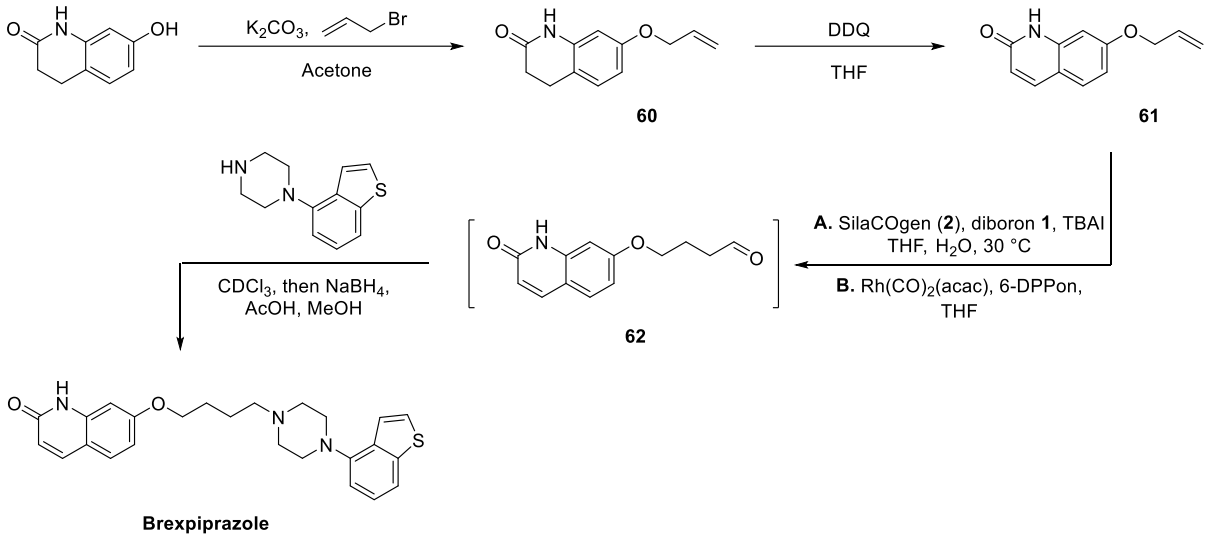


To a solution of **59-^{13}C** (84 mg, 0.35 mmol, 1.0 equiv.) in $CDCl_3$ (1.5 mL) was added 2-(piperazin-1-yl)pyrimidine (87 mg, 0.53 mmol, 1.5 equiv.). After stirring at room temperature for 1h, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaCNBH_3$ (63 mg, 1.0 mmol, 2.9 equiv.) and a solution of acetic acid in MeOH (1.0 mL, 10 vol%). After stirring at room temperature overnight h, the reaction was diluted with CH_2Cl_2 (10 mL) and quenched by addition of a saturated aqueous solution of Na_2CO_3 (10 mL), the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*

to give the crude which was purified *via* column chromatography (CH_2Cl_2 / EtOAc (2.5-5%)) to give buspirone-^{13}C (114 mg, 0.29 mmol, 84%) as a colourless solid.

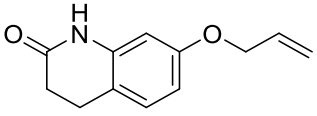
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.30 (2H, d, *J* = 5.0 Hz), 6.47 (1H, t, *J* = 5.0 Hz), 3.88-3.80 (4H, m), 3.77 (2H, t, *J* = 7.0 Hz), 2.62-2.53 (5H, m), 2.53-2.44 (4H, m), 2.28-2.17 (1H, m), 1.76-1.65 (4H, m), 1.57-1.44 (8H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.2, 161.7, 157.7, 109.8, 58.3 (^{13}C), 53.1, 44.9, 43.6, 43.6, 39.5, 39.3 (d, *J* = 4.5 Hz), 37.6, 26.0, 24.2, 24.1 (d, *J* = 38.5 Hz); **HRMS** (ESI+) calc. for $C_{20}{}^{13}C_1H_{32}N_5O$ $[M+H]^+$ 387.2584, found 387.2598.

Preparation of brexpripazole



Supplementary Figure 21. Preparation of brexpiprazole.

7-(Allyloxy)-3,4-dihydroquinolin-2(1*H*)-one, 60

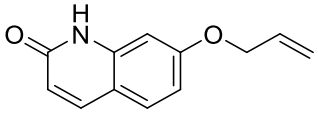


To a solution of 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (2.00 g, 12.3 mmol, 1.0 equiv.) in acetonitrile (20 mL) was added K_2CO_3 (5.09 g, 36.9 mmol, 3.0 equiv.) followed by a dropwise addition of allyl bromide (2.10 mL, 24.4 mmol, 2.0 equiv.). After stirring at 40 °C overnight, the resulting reaction mixture was diluted EtOAc (20 mL) and quenched by addition of water

(20 mL), the organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* column chromatography (pentane / EtOAc (0-40 %)) gave **60** (2.25g 11.1 mmol, 90%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.92 (1H, s), 7.05 (1H, d, *J* = 8.5 Hz), 6.54 (1H, dd, *J* = 8.5 and 1.5 Hz), 6.33 (1H, d, *J* = 2.5 Hz), 6.10-5.96 (1H, m), 5.40 (1H, d, *J* = 17.0 Hz), 5.28 (1H, d, *J* = 10.5), 4.50 (2H, d, *J* = 4.5 Hz), 2.90 (2H, t, *J* = 7.5 Hz), 2.62 (2H, t, *J* = 7.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.0, 158.4, 138.3, 133.2, 128.8, 117.9, 116.1, 109.1, 102.6, 69.2, 31.2, 24.7. **HRMS** (ESI+) calc. for $C_{12}H_{13}NO_2$ $[M+H]^+$ 204.1019, found 204.1021.

7-(Allyloxy)quinolin-2(1*H*)-one, 61

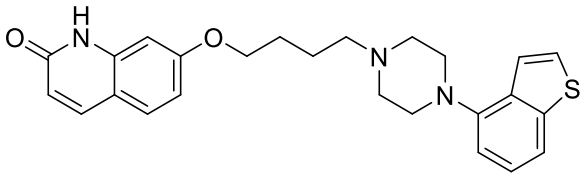


To a solution of **60** (1.16 g, 5.70 mmol, 1.0 equiv.) in THF (100 mL) was added DDQ (4.54 g, 20.0 mmol, 3.5 equiv.). After stirring vigorously at room temperature overnight, the resulting reaction mixture was diluted EtOAc (30 mL) and quenched by addition of water (50 mL), the organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with a 1.0 M aqueous solution of NaOH (5 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was recrystallized from isopropanol to give **61** (686 mg, 3.40 mmol, 60%) as colourless crystals.

M.p. 156-157; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 11.84 (s, 1H), 7.73 (1H, d, *J* = 9.5 Hz), 7.45 (1H, d, *J* = 8.5 Hz), 6.90-6.76 (2H, m), 6.55 (1H, d, *J* = 9.5 Hz), 6.14-6.01 (1H, m), 5.47 (1H, dd, *J* = 17.5 and 1.5 Hz), 5.34 (1H, dd, *J* = 10.5 and 1.5 Hz), 4.64 (2H, d, *J* = 5.5 Hz); **^{13}C**

NMR (101 MHz, CDCl3) δ_C 164.8, 161.0, 140.9, 140.4, 132.6, 129.3, 118.5, 118.4, 114.5, 112.8, 99.5, 69.3; **HRMS** (ESI+) calc. for $C_{12}H_{11}NO_2$ $[M+Na]^+$ 224.0682, found 224.0685

Brexpiprazole

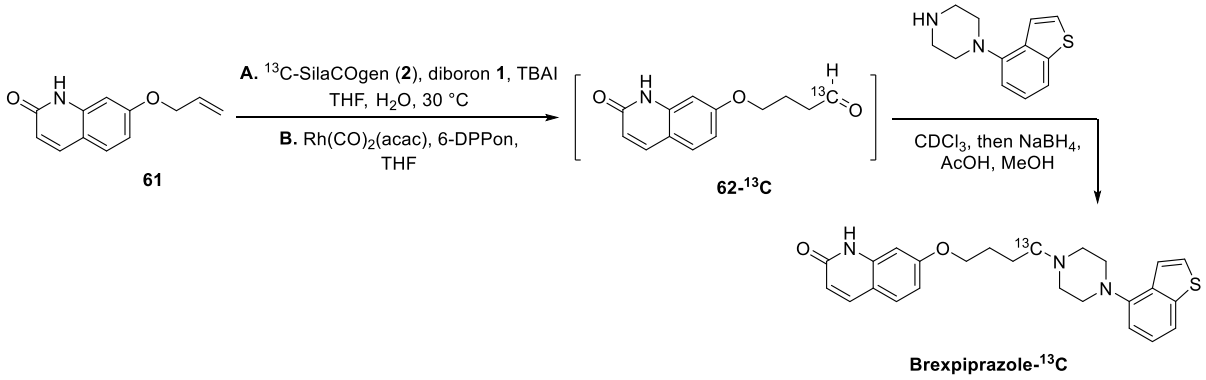


Brexpiprazole was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **61** (101 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude **62** (48% as determined by ^{1}H NMR of the crude with mesitylene as the internal standard, *l*:*b* 1:1) was then filtered through a plug of silica (CH_2Cl_2 / MeOH (10 %)) and concentrated *in vacuo*. This crude aldehyde mixture was dissolved in $CDCl_3$ (1.5 mL) followed by addition of 1-(benzo[b]thiophen-4-yl)piperazine (164 mg, 0.75 mmol, 1.5 equiv.) After stirring at room temperature for 1 h, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaBH_3CN$ (63 mg, 1.0 mmol, 2 equiv.) and a solution of AcOH in MeOH (1 mL, 10 vol%). After stirring at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and quenched by addition of a saturated aqueous solution of Na_2CO_3 (10 mL), the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (EtOAc / EtOH (10-20%)) to give brexpiprazole (80 mg, 0.18 mmol, 37%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 12.87 (1H, m), 7.71 (1H, d, *J* = 9.5 Hz), 7.55 (1H, d, *J* = 8.0 Hz), 7.46-7.36 (3H, m), 7.27 (1H, t, *J* = 8.0 Hz), 6.89 (1H, dd, *J* = 6.0 and 3.5 Hz), 6.82 (1H,

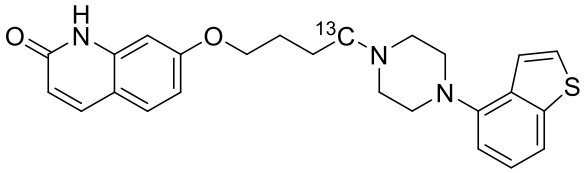
dd, *J* = 8.5 and 2.5 Hz), 6.78 (1H, m), 6.53 (1H, d, *J* = 9.5 Hz), 4.10 (2H, t, *J* = 6.0 Hz), 3.25-3.15 (4H, m), 2.79-2.65 (4H, m), 2.53 (2H, t, *J* = 7.5 Hz), 1.93-1.82 (2H, m), 1.83-1.70 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.4, 161.5, 148.6, 141.2, 141.0, 140.6, 134.1, 129.1, 125.1, 125.0, 122.0, 117.9, 117.0, 114.3, 112.8, 112.2, 99.1, 68.2, 58.4, 53.7, 52.2, 27.3, 23.5. Spectroscopic data in agreement with that reported by Kumar *et al*[34].

Preparation of brexpiprazole-^{13}C



Supplementary Figure 22. Preparation of brexpiprazole-^{13}C.

Brexpiprazole-^{13}C

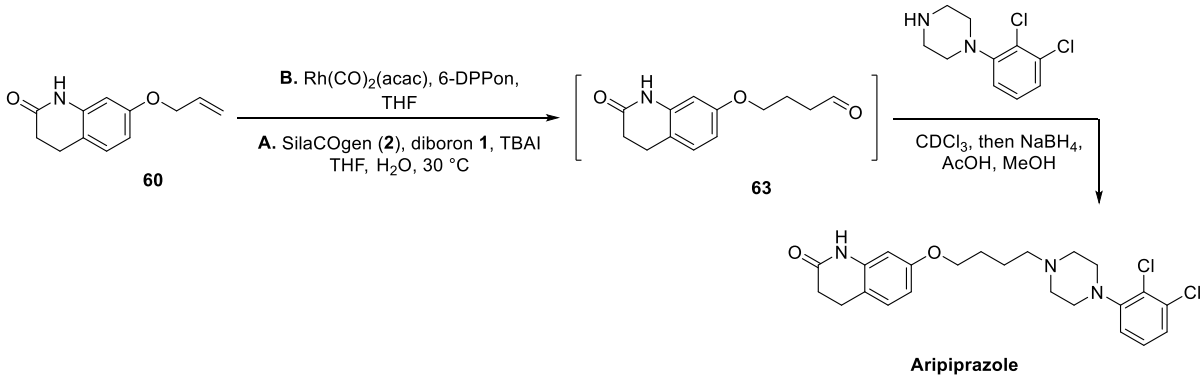


Brexpiprazole-^{13}C was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **61** (101 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude **62-^{13}C** (50% as determined by ^{1}H NMR of the crude with mesitylene as the internal standard, *l*:*b* 1:1) was then filtered through a plug of silica (CH_2Cl_2 / MeOH (10 %)) and

concentrated *in vacuo*. This crude aldehyde mixture was dissolved in $CDCl_3$ (1.5 mL) followed by addition of 1-(benzo[b]thiophen-4-yl)piperazine (164 mg, 0.75 mmol, 1.5 equiv.) After stirring at room temperature for 1 h, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaBH_3CN$ (63 mg, 1.0 mmol, 2 equiv.) and a solution of AcOH in MeOH (1 mL, 10 vol%). After stirring at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and quenched by addition of a saturated aqueous solution of Na_2CO_3 (10 mL), the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude which was purified *via* column chromatography (EtOAc / EtOH (10-20%)) to give brexpiprazole-^{13}C (80 mg, 0.18 mmol, 37%) as a colourless solid.

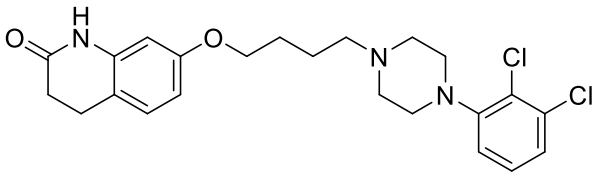
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 12.79 (1H, s), 7.71 (1H, d, *J* = 9.5 Hz), 7.53 (1H, d, *J* = 8.0 Hz), 7.41 (1H, d, *J* = 8.5 Hz), 7.40-7.35 (2H, m), 7.25 (1H, t, *J* = 8.0 Hz), 6.69-6.84 (2H, m), 6.80 (1H, dd, *J* = 8.5 and 2.5 Hz), 6.55 (1H, d, *J* = 9.5 Hz), 4.08 (2H, t, *J* = 6.0 Hz), 3.30-3.15 (4H, m), 2.94-2.67 (5H, m), 2.43 (1H, t, *J* = 7.5 Hz), 1.96-1.69 (4H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.3, 161.4, 148.2, 141.1, 141.0, 140.4, 134.0, 129.0, 125.14, 125.07, 121.8, 117.7, 117.2, 114.3, 112.9, 112.3, 99.0, 68.0 (d, *J* = 4.0 Hz), 63.8, 62.0, 58.0 (^{13}C), 53.3, 51.7 (d, *J* = 4.0 Hz), 27.1, 23.0 (d, *J* = 37.5 Hz); **HRMS** (ESI+) calc. for $C_{24}{}^{13}C_1H_{27}N_3O_2S$ $[M+H]^+$ 435.1930, found 435.1934.

Preparation of Aripiprazole



Supplementary Figure 23. Preparation of aripiprazole.

Aripiprazole



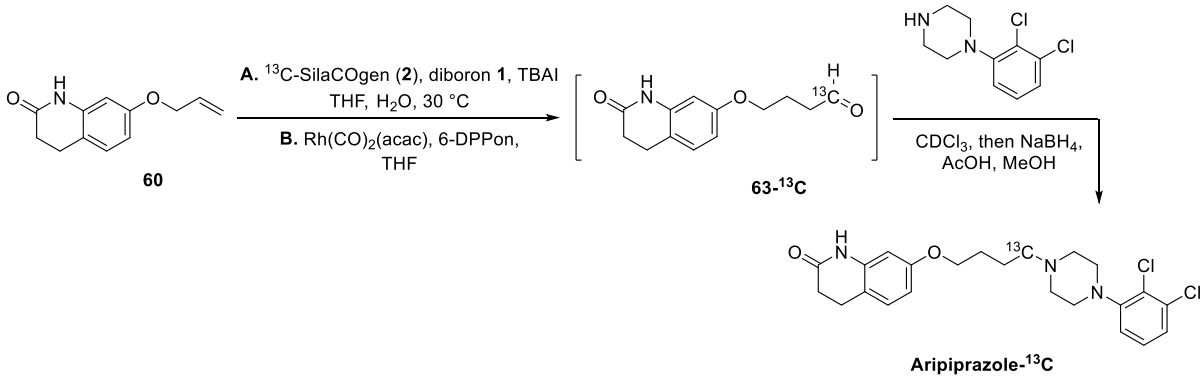
Aripiprazole was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **60** (102 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude **63** (57% as determined by ^{1}H NMR of the crude with mesitylene as the internal standard, *l*:*b* 2:1) was then filtered through a plug of silica (CH_2Cl_2 / MeOH (10 %)) and concentrated *in vacuo*. This crude aldehyde mixture was dissolved in $CDCl_3$ (1.5 mL) followed by addition of 1-(2,3-dichlorophenyl)piperazine (173 mg, 0.75 mmol, 1.5 equiv.) After stirring at room temperature for 1 h, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaCNBH_3$ (63 mg, 1.0 mmol, 2.0 equiv.) and a solution of AcOH in MeOH (1 mL, 10 vol%). After stirring at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and quenched by addition of a saturated aqueous solution of Na_2CO_3 (10 mL), the organic

layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give aripiprazole (59 mg, 0.13 mmol, 26 %) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.05 (1H, s), 7.18-7.08 (2H, m), 7.02 (1H, d, *J* = 8.5 Hz), 6.95 (1H, dd, *J* = 6.5 and 3.0 Hz), 6.51 (1H, dd, *J* = 8.5 and 2.5 Hz), 6.39 (1H, d, *J* = 2.5 Hz), 3.95 (2H, t, *J* = 6.0 Hz), 3.11-3.02 (4H, m), 2.88 (2H, t, *J* = 7.0 Hz), 2.73-2.63 (4H, m), 2.61 (2H, t, *J* = 8.0 Hz), 2.50 (2H, t, *J* = 7.5 Hz), 1.85-1.76 (2H, m), 1.76-1.64 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.4, 158.7, 151.3, 138.3, 134.1, 128.7, 127.5, 124.6, 118.7, 115.7, 108.8, 102.4, 67.9, 58.3, 53.4, 51.3, 31.2, 27.3, 24.6, 23.4.

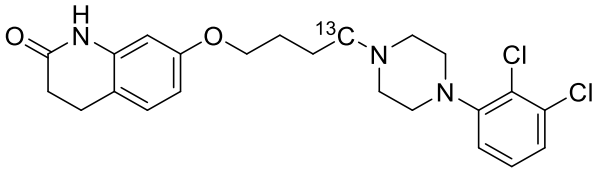
Spectroscopic data in agreement with that reported by Shi *et al*[35].

Preparation of aripiprazole-^{13}C



Supplementary Figure 24. Preparation of aripiprazole-^{13}C.

Aripiprazole-^{13}C

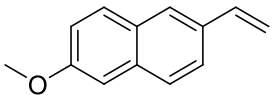


Aripiprazole-^{13}C was prepared using General Procedure 1 (Condition A), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **60** (102 mg,

0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4.0 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. The resulting crude **63-^{13}C** (63% as determined by ^{1}H NMR of the crude with mesitylene as the internal standard, *l*:*b* 2:1) was then filtered through a plug of silica (CH_2Cl_2 / MeOH (10 %)) and concentrated *in vacuo*. This crude aldehyde mixture was dissolved in $CDCl_3$ (1.5 mL) followed by addition of 1-(2,3-dichlorophenyl)piperazine (173 mg, 0.75 mmol, 1.5 equiv.) After stirring at room temperature for 1 h, the resulting reaction mixture was cooled to 0 °C followed by addition of $NaCNBH_3$ (63 mg, 1.0 mmol, 2.0 equiv.) and a solution of AcOH in MeOH (1 mL, 10 vol%). After stirring at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 (15 mL) and quenched by addition of a saturated aqueous solution of Na_2CO_3 (10 mL), the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give aripiprazole-^{13}C (66 mg, 0.15 mmol, 29 %) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.62 (1H, s), 7.18-7.08 (2H, m), 7.05 (1H, d, *J* = 8.5 Hz), 6.96 (1H, dd, *J* = 6.5 and 3.0 Hz), 6.52 (1H, dd, *J* = 8.5 and 2.5 Hz, Ar*H*), 6.29 (1H, d, *J* = 2.5 Hz), 3.96 (2H, t, *J* = 6.0 Hz), 3.11-3.02 (4H, m), 2.89 (2H, dd, *J* = 8.5 and 6.5 Hz), 2.69-2.54 (7H, m), 2.32 (1H, t, *J* = 7.5 Hz), 1.88-1.76 (2H, m), 1.76-1.64 (2H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.3, 158.8, 151.3, 138.3, 134.1, 128.7, 127.6, 124.7, 118.7, 115.8, 108.8, 102.4, 67.9, 58.3(^{13}C), 53.3, 51.3, 31.2, 29.7, 27.3, 24.7, 23.4 (d, *J* = 37.5 Hz); **HRMS** (ESI+) calc. for $^{13}C_1C_{22}H_{27}N_3O_2$ $[M+Na]^+$ 449.1406 found 449.1407.

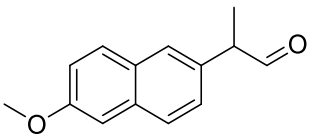
2-Methoxy-6-vinylnaphthalene, 29



To a suspension of methyltriphenylphosphonium bromide (3.57 g, 10.0 mmol, 1.0 equiv.) in THF (10 mL) was added NaH (0.410 g, 60 wt% in mineral oil, 10.2 mmol, 1.02 equiv.). After stirring for 2 h at room temperature, was added a solution of 6-methoxy-2-naphthaldehyde (1.85 g, 10.0 mmol, 1.0 equiv.) in THF (4 mL) dropwise *via* syringe. After stirring at room temperature for 16 h, the resulting mixture was quenched by addition of water (20 mL), the organic layer was separated, and the aqueous layer was further extracted with pentane (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (pentane / Et_2O (10%)) to **29** (1.42 g, 7.70 mmol, 77%) as a colourless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.75-7.58 (5H, m), 7.19-7.10 (2H, m), 6.87 (1H, dd, *J* = 17.5 and 11.0 Hz), 5.84 (1H, dd, *J* = 17.5 and 1.0 Hz), 5.30 (1H, dd, *J* = 11.0 and 1.0 Hz), 3.93 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.8, 137.0, 134.3, 133.0, 129.5, 129.0, 127.0, 126.1, 123.8, 118.9, 113.1, 105.9, 55.3.

Spectroscopic data in agreement with that reported by Gärtner *et al*[36].

2-(6-Methoxynaphthalen-2-yl)propanal, 30



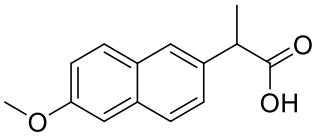
2-(6-Methoxynaphthalen-2-yl)propanal was prepared using General Procedure 2 (Condition B), with $RhH(CO)(PPh_3)_3$ (11.6 mg, 12.5 µmol, 2.5 mol%) and **29** (92 mg, 0.50 mmol, 1.0 equiv.) in toluene (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and

water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (20%)) gave **30** (52 mg, 0.24 mmol, 48%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (1H, d, *J* = 1.0 Hz), 7.75 (1H, d, *J* = 9.0 Hz), 7.72 (1H, d, *J* = 9.0 Hz), 7.60 (1H, s), 7.28 (1H, dd, *J* = 8.5 and 1.5 Hz), 7.19-7.11 (2H, m), 3.92 (3H, s), 3.77 (1H, q, *J* = 7.0 Hz), 1.52 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.3, 158.0, 134.0, 132.9, 129.4, 129.3, 127.8, 127.2, 126.9, 119.5, 105.8, 55.5, 53.1, 14.8.

Spectroscopic data in agreement with that reported by Abrams *et al*[37].

Naproxen



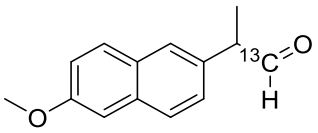
To a solution of **30** (38 mg, 0.18 mmol, 1.0 equiv.) and 2-methyl-2-butene (0.19 mL, 1.8 mmol, 10 equiv.) in *t*-BuOH (1.0 mL) were added aqueous solutions of NaH_2PO_4 (0.45 mL, 0.5 M, 0.90 mmol, 5.0 equiv.) and $NaClO_2$ (0.53 mL, 1.0 M, 0.53 mmol, 3.0 equiv.) sequentially at 0 °C. After stirring vigorously at room temperature for 1 h, the resulting reaction mixture was quenched by addition of 1.0 M aqueous solution of HCl (5.0 mL) and diluted with EtOAc (5.0 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5.0 mL). The combined organic layers were then extracted with a 2.0 M aqueous solution of NaOH (3 × 5.0 mL) before re-acidifying by addition of a 1.0 M aqueous solution of HCl. The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give naproxen (41 mg, 0.18 mmol, 99%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (1H, s, Ar*H*), 7.69 (1H, s, Ar*H*), 7.42 (1H, dd, *J* = 8.5 and 1.0 Hz, Ar*H*), 7.18-7.07 (2H, m, Ar*H*), 3.96-3.83 (4H, m, C*H* and OCH_3), 1.59 (3H, d, *J* = 7.0 Hz, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 180.5, 157.9, 135.0, 134.0, 129.4, 129.1,

127.4, 126.33, 126.29, 119.8, 105.8, 55.5, 45.4, 18.3; **HRMS** (ESI–) calc. for $C_{13}H_{13}O$ [M – $CO_2H]^-$ 185.0972 found 185.0974.

Spectroscopic data in agreement with that reported by Zhang *et al*[38].

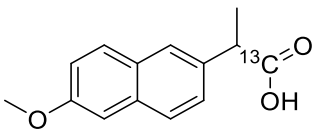
2-(6-Methoxynaphthalen-2-yl)propanal-1-^{13}C, 30-^{13}C



30-^{13}C was prepared using General Procedure 2 (Condition B), with $RhH(CO)(PPh_3)_3$ (11.6 mg, 12.5 µmol, 2.5 mol%) and **29** (92 mg, 0.50 mmol, 1.0 equiv.) in toluene (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C- silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (20%)) gave **30-^{13}C** (59 mg, 0.27 mmol, 54%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (1H, dd, *J* = 174.5 and 1.0 Hz), 7.76 (1H, d, *J* = 9.0 Hz), 7.72 (1H, d, *J* = 9.0 Hz), 7.60 (1H, s), 7.28 (1H, dd, *J* = 8.5 and 1.5 Hz), 7.19-7.11 (2H, m3.93 (3H, s), 3.82-3.71 (1H, q, *J* = 7.0 Hz), 1.53 (3H, dd, *J* = 7.0 and 5.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.3 (^{13}C), 158.0, 134.0, 132.8, 129.3, 129.3, 127.8, 127.2 (d, *J* = 2.5 Hz), 126.9 (d, *J* = 1.5 Hz), 119.5, 105.8, 55.5, 53.1 (d, *J* = 37.5 Hz), 14.8; **HRMS** (ESI+) calc. for $C_{13}{}^{13}C_1H_{15}O_2$ $[M+H]^+$ 216.1100 found 216.1103.

Naproxen-^{13}C

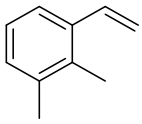


To a solution of **30-^{13}C** (37 mg, 0.17 mmol, 1.0 equiv.) and 2-methyl-2-butene (0.18 mL, 1.7 mmol, 10 equiv.) in *t*-BuOH (1.0 mL) were added aqueous solutions of NaH_2PO_4 (0.4 mL, 0.5

M, 0.85 mmol, 5.0 equiv.) and $NaClO_2$ (0.51 mL, 1.0 M, 0.51 mmol, 3.0 equiv.) sequentially at 0 °C. After stirring vigorously at room temperature for 1 h, the resulting reaction mixture was quenched by addition of 1.0 M aqueous solution of HCl (5.0 mL) and diluted with EtOAc (5.0 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5.0 mL). The combined organic layers were then extracted with a 2.0 M aqueous solution of NaOH (3 × 5.0 mL) before re-acidifying by addition of a 1.0 M aqueous solution of HCl. The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give naproxen-^{13}C (39 mg, 0.17 mmol, 99%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (1H, s, Ar*H*), 7.69 (1H, s, Ar*H*), 7.42 (1H, d, *J* = 8.5 Hz, Ar*H*), 7.18-7.07 (2H, m, Ar*H*), 3.96-3.83 (4H, m, C*H* and OCH_3), 1.59 (3H, dd, *J* = 7.0 and 5.5 Hz, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 180.7 (^{13}C), 157.8, 135.0, 134.0, 129.4, 129.1, 127.4, 126.33 (d, *J* = 1.5 Hz), 126.29 (d, *J* = 2.0 Hz), 119.8, 105.8, 55.5, 45.4 (d, *J* = 54.5 Hz), 18.3; **HRMS** (ESI–) calc. for $C_{13}H_{13}O$ $[M - CO_2H]^-$ 185.0972 found 185.0966.

1,2-Dimethyl-3-vinylbenzene, 31



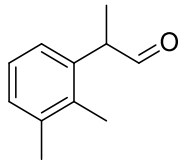
To a suspension of methyltriphenylphosphonium bromide (3.57 g, 10.0 mmol, 1.0 equiv.) in THF (14 mL) was added NaH (0.410 g, 60 wt% in mineral oil, 10.2 mmol, 1.02 equiv.). After stirring for 2 h at room temperature, was added 2,3-dimethylbenzaldehyde (1.52 mL, 11.7 mmol, 1.0 equiv.) dropwise *via* syringe. After stirring at room temperature for 16 h, the resulting mixture was quenched by addition of water (20 mL), the organic layer was separated, and the aqueous layer was further extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude

product which was purified *via* column chromatography (pentane / Et_2O (5%)) to give **31** (727 mg, 5.50 mmol, 55%) as a low boiling colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35-7.29 (1H, m), 7.11-7.07 (2H, m), 7.03 (1H, dd, *J* = 17.5 and 11.0 Hz), 5.58 (1H, dd, *J* = 17.5 and 1.5 Hz), 5.29 (1H, dd, *J* = 11.0 and 1.5 Hz), 2.29 (3H, s), 2.29 (3H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 137.4, 136.7, 135.9, 134.0, 129.3, 125.5, 123.8, 115.5, 20.6, 15.3.

Spectroscopic data in agreement with that reported by Gaspar *et al*[39].

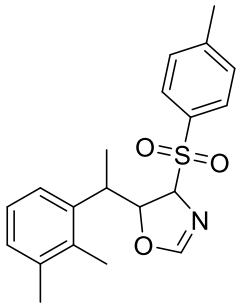
2-(2,3-Dimethylphenyl)propanal, 32



2-(2,3-Dimethylphenyl)propanal was prepared using General Procedure 2 (Condition B), with $RhH(CO)(PPh_3)_3$ (11.6 mg, 12.5 µmol, 2.5 mol%) and **31** (66 mg, 0.50 mmol, 1.0 equiv.) in toluene (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (10%)) gave **31** (45 mg, 0.28 mmol, 55%) as a low boiling colourless oil.

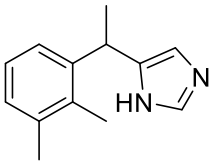
R_f 0.34 (pentane / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.67 (1H, d, *J* = 1.0 Hz), 7.17-7.09 (2H, m), 6.93-6.87 (1H, m), 3.89 (1H, dq, *J* = 7.0 and 1.0 Hz), 2.33 (3H, s,), 2.25 (3H, s), 1.40 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.6, 137.9, 136.5, 135.3, 129.4, 126.2, 125.7, 49.9, 21.1, 15.4, 14.7; **HRMS** (ESI+) mass not found.

5-(1-(2,3-dimethylphenyl)ethyl)-4-tosyl-4,5-dihydrooxazole, 33



To a solution of **32** (89 mg, 0.55 mmol, 1.0 equiv.) and TosMIC (107 mg, 0.55 mmol, 1.0 equiv.) in MeOH (1.8 mL) at 0 °C was added K_2CO_3 (76 mg, 0.55 mmol, 1.0 equiv.). After stirring at the aforementioned temperature for 1 h, the resulting reaction mixture was diluted with EtOAc (5 mL) and quenched by addition of water (5 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was quickly purified *via* column chromatography (pentane / EtOAc (30%)) to give **33** (156 mg, 0.44 mmol, 80%) which was used immediately in the next reaction. $\mathbf{R_f}$ 0.42 (pentane / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz), 7.13-7.07 (3H, m), 7.04 (1H, s), 5.20 (1H, t, *J* = 5.5 Hz), 4.79 (1H, dd, *J* = 5.5 and 1.5 Hz), 3.34-3.24 (1H, m), 2.44 (3H, s), 2.31 (3H, s), 2.23 (3H, s), 1.28 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.9, 145.5, 139.1, 137.3, 134.3, 133.4, 129.9, 129.6, 129.0, 126.0, 124.8, 88.7, 82.8, 39.3, 21.8, 21.3, 15.4, 15.2; **HRMS** (ESI+) mass not obtained.

Medetomidine

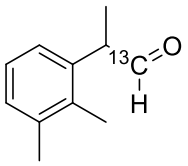


To a pressure tube containing **33** (149 mg, 0.42 mmol, 1.0 equiv.) was added a solution of ammonia (3.0 mL, 7 M in MeOH, 21 mmol, 50 equiv.), the pressure tube was sealed and heated, under stirring, at 100 °C overnight. The resulting mixture was allowed to reach room temperature, then diluted with CH_2Cl_2 (15 mL) and extracted with 1.0 M aqueous solution of HCl (3 × 10 mL). The combined aqueous layers were re-basified by addition of a 2.0 M aqueous solution of NaOH and the resulting aqueous extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give medetomidine (51 mg, 0.25 mmol, 60%) as an orange to red solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 (1H, s), 7.06-6.88 (3H, m), 6.66 (1H, s), 4.35 (1H, q, *J* = 7.0 Hz), 2.26 (3H, s), 2.18 (3H, s), 1.55 (3H, d, *J* = 7.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.4, 141.2, 136.9, 134.8, 134.2, 128.0, 125.7, 124.8, 117.7, 34.2, 21.0, 20.9, 14.8; **HRMS** (ESI+) calc. for $C_{13}H_{17}N_2$ $[M+H]^+$ 201.1386 found 201.1396.

Spectroscopic data in agreement with that reported by Fakhraian *et al*[40].

2-(2,3-Dimethylphenyl)propanal-1-^{13}C, 32-^{13}C

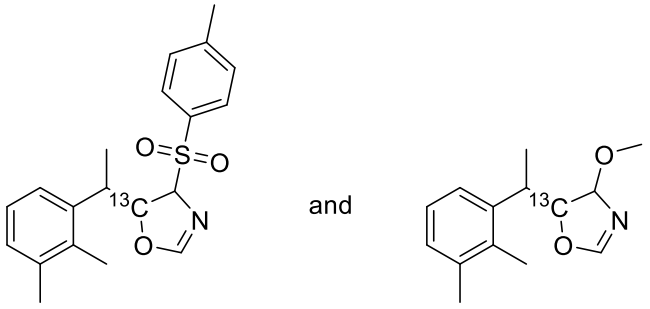


32-^{13}C was prepared using General Procedure 2 (Condition B), with $RhH(CO)(PPh_3)_3$ (11.6 mg, 12.5 µmol, 2.5 mol%) and **31** (66 mg, 0.50 mmol, 1.0 equiv.) in toluene (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C- silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a

16 h reaction time at 30 °C. Purification *via* column chromatography (pentane / Et_2O (10%)) gave **32-^{13}C** (44 mg, 0.27 mmol, 53%) as a low boiling colourless oil.

R_f 0.34 (pentane / Et_2O (10%)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.67 (1H, dd, *J* = 174.0 and 1.0 Hz), 7.17-7.09 (2H, m), 6.93-6.87 (1H, m3.89 (1H, dq, *J* = 7.0 and 1.0 Hz), 2.33 (3H, s), 2.25 (3H, s), 1.40 (3H, dd, *J* = 7.0 and 5.0 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 201.6 (^{13}C), 137.9, 136.5, 135.4, 129.4, 126.2, 125.7 (d, *J* = 2.0 Hz), 49.9 (d, *J* = 38.0 Hz), 21.1, 15.4, 14.7; **HRMS** (ESI+) mass not found.

5-(1-(2,3-dimethylphenyl)ethyl)-4-tosyl-4,5-dihydrooxazole-5-^{13}C, 33-^{13}C-Ts and 5-(1-(2,3-dimethylphenyl)ethyl)-4-methoxy-4,5-dihydrooxazole-5-^{13}C, 33-^{13}C-OMe

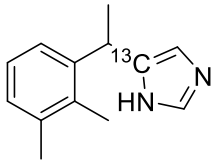


33-^{13}C-Ts **33-^{13}C-OMe**

To a solution of 2-(2,3-dimethylphenyl)propanal-1-^{13}C (85 mg, 0.52 mmol, 1.0 equiv.) and TosMIC (102 mg, 0.52 mmol, 1.0 equiv.) in MeOH (1.7 mL) at 0 °C was added K_2CO_3 (72 mg, 0.52 mmol, 1.0 equiv.). After stirring at the aforementioned temperature for 1 h, the resulting reaction mixture was diluted with EtOAc (5 mL) and quenched by addition of water (5 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was quickly purified *via* column chromatography (pentane / EtOAc (30%)) to give an inseparable mixture (3.7:1) of **33-^{13}C-** and **33-^{13}C-OMe** (145 mg, 0.43 mmol, 84%) which was used immediately in the next reaction.

R_f 0.42 (pentane / EtOAc (30%)); **33-^{13}C-Ts and 33-^{13}C-OMe: ^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.5 Hz), 7.33 (2H, d, *J* = 8.5 Hz), 7.16-7.01 (5.2H, m), 7.04 (1H, s), 5.20 (1H, dt, *J* = 157.0 and 5.5 Hz), 4.79 (1H, dd, *J* = 5.5 and 1.5 Hz), 4.76-4.72 (0.3H, m), 4.42 (0.3H, ddd, *J* = 153.0, 8.0 and 4.0 Hz), 3.34-3.21 (1.9H, m), 3.14-3.04 (0.3H, m), 2.44 (3H, s), 2.31 (3.9H, s), 2.23 (3H, s), 2.21 (0.9H, s), 1.32-1.24 (3.9H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.9, 145.5, 139.1, 137.3, 134.3, 133.4, 129.9, 129.6, 129.0, 126.0, 124.8, 88.7 (d, *J* = 33 Hz), 87.7 (^{13}C (**33-^{13}C-Ts**)) 82.8 (^{13}C (**33-^{13}C-OMe**), 39.3 (d, *J* = 37.5 Hz), 21.8, 21.3, 15.4, 15.2.

Medetomidine-^{13}C

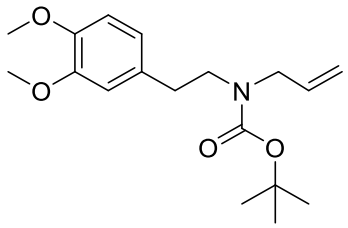


To a pressure tube containing a mixture of **33-^{13}C-** and **33-^{13}C-OMe** (137 mg, 0.38 mmol, 1.0 equiv.) was added a solution of ammonia (2.7 mL, 7 M in MeOH, 19 mmol, 50 equiv.), the pressure tube was sealed and heated, under stirring, at 100 °C overnight. The resulting mixture was allowed to reach room temperature, then diluted with CH_2Cl_2 (15 mL) and extracted with 1.0 M aqueous solution of HCl (3 × 10 mL). The combined aqueous layers were re-basified by addition of a 2.0 M aqueous solution of NaOH and the resulting aqueous extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give medetomidine-^{13}C (51 mg, 0.25 mmol, 60%) as an orange to red solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 (1H, d, *J* = 7.0 Hz), 7.06-6.88 (3H, m), 6.66 (1H, d, *J* = 11.5 Hz), 4.35 (1H, q, *J* = 7.0 Hz), 2.26 (3H, s), 2.18 (3H, s), 1.55 (3H, dd, *J* = 7.0 and 5.5 Hz); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.3, 141.2 (^{13}C), 136.9, 134.8, 134.2, 128.1, 125.7, 124.8,

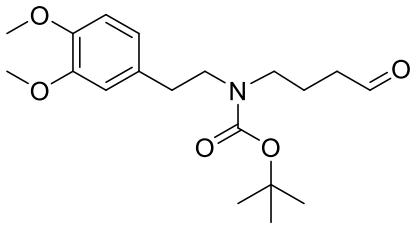
117.7 (d, *J* = 36.5 Hz), 34.2 (d, *J* = 52.5 Hz), 21.0, 20.9, 14.8; **HRMS** (ESI+) calc. for $C_{12}{}^{13}C_1H_{17}N_2$ $[M+H]^+$ 202.1425 found 202.1428.

***tert*-Butyl allyl(3,4-dimethoxyphenethyl)carbamate, 34**



To a solution of *tert*-butyl (3,4-dimethoxyphenethyl)carbamate (1.41 g, 5.00 mmol, 1.0 equiv.) in toluene (17 mL) was added allyl bromide (0.65 mL, 7.50 mmol, 1.5 equiv.), K_2CO_3 (898 mg, 6.50 mmol, 1.3 equiv.), KOH (842 mg, 15.0 mmol, 3.0 equiv.) and TBAB (161 mg, 0.50 mmol, 10 mol%). After stirring at 80 °C for 5 h, the resulting reaction mixture was allowed to reach room temperate before adjusting the pH to 4-5 by addition of aqueous solution of HCl (15 wt%). The organic layer was separated, and the aqueous layer was further extracted with toluene (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (pentane / EtOAc (20%)) to give **34** (1.19 g, 3.71 mmol, 74%) as a yellow oil. $\mathbf{R_f}$ 0.48 (pentane / EtOAc (30%)); **^{1}H NMR** (400 MHz, $CDCl_3$) [rotameric mixture] δ_H 6.78 (1H, d, *J* = 8.0 Hz), 6.75-6.62 (2H, m), 5.83-5.65 (1H, m), 5.18-5.02 (2H, m), 3.85 (3H, s), 3.84 (3H, s), 3.82-3.66 (2H, m), 3.43-3.26 (2H, m), 2.84-2.66 (2H, m), 1.44 (9H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) [rotameric mixture] δ_C 155.5, 149.0, 147.6, 134.4, 132.1, 120.8, 116.5 [rotamer A], 116.0 [rotamer B], 112.2, 111.4, 79.5, 55.0, 55.9, 50.5 [rotamer A], 49.7 [rotamer B], 48.8, 34.8 [rotamer A], 34.3 [rotamer B], 28.5; **HRMS** (ESI+) calc. for $C_{18}H_{27}NNaO_4$ $[M+Na]^+$ 344.1838, found 344.1845.

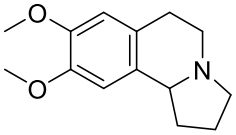
***tert*-Butyl (3,4-dimethoxyphenethyl)(4-oxobutyl)carbamate, 35**



35 was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **34** (161 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), silacarboxylic acid **2** (242 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. Purification *via* column chromatography (pentane / EtOAc (20%)) gave **35** (104 mg, 0.30 mmol, 59%) as a clear oil.

R_f 0.13 (petroleum ether / EtOAc (20%)); **^{1}H NMR** (400 MHz, $CDCl_3$) [rotameric mixture] δ_H 9.74 (1H, s), 6.78 (1H, d, *J* = 8.0 Hz), 6.75-6.61 (2H, m), 3.85 (3H, s), 3.83 (3H, s,), 3.44-3.24 (2H, m), 3.21-3.03 (2H, m), 2.83-2.65 (2H, m), 2.48-2.34 (2H, m), 1.88-1.70 (2H, m), 1.43 (9H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) [rotameric mixture] δ_C 201.8, [rotamer A], 201.5 [rotamer B], 155.6, 149.0, 147.6, 131.8, 120.8, 112.1, 111.4, 79.6, 56.0, 55.9, 49.5 [rotamer A], 49.4 [rotamer B], 46.8 [rotamer A], 46.5 [rotamer B], 41.2, [rotamer A], 41.0 [rotamer B], 34.9 [rotamer A], 34.1 [rotamer B], 28.5, 21.2 [rotamer A], 20.9 [rotamer B]; **HRMS** (ESI+) calc. for $C_{19}H_{29}NNaO_5$ $[M+Na]^+$ 374.1944, found 374.1954.

(±)-Crispine A



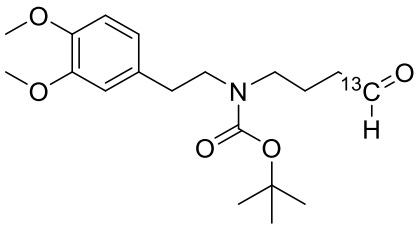
To a solution of *tert*-butyl (3,4-dimethoxyphenethyl)(4-oxobutyl)carbamate (50 mg, 0.14 mmol, 1.0 equiv.) in 1.2-dichloroethane (0.5 mL) was added trifluoroacetic acid (0.21 mL, 2.8

mmol, 20 equiv.) dropwise *via* syringe at 0 °C. After stirring at 80 °C overnight, the resulting reaction mixture was allowed to reach room temperature before being diluted with EtOAc (5 mL) and quenched by addition of a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (10%)) to give (±)-Crispine A (25 mg, 0.11 mmol, 77%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.60 (1H, s), 6.55 (1H, s), 3.83 (6H, s), 3.69 (1H, app t, *J* = 8.0 Hz), 3.22-3.13 (1H, m), 3.12-3.02 (1H, m), 3.02-3.92 (2H, m), 2.86-2.72 (3H, m), 2.43-2.33 (1H, m), 2.00-1.86 (2H, m), 1.83-1.70 (1H, m); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.7, 147.6, 125.8, 111.4, 109.0, 62.6, 56.1, 56.0, 53.2, 48.1, 31.0, 27.5, 22.4; **HRMS** (ESI+) calc. for $C_{14}H_{20}NO_2$ $[M+H]^+$ 234.1494 found 234.1500.

Spectroscopic data in agreement with that reported by Chiou *et al*[41].

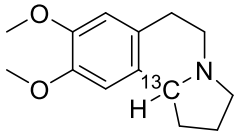
***tert*-Butyl (3,4-dimethoxyphenethyl)(4-oxobutyl-4-^{13}C)carbamate, 35-^{13}C**



35-^{13}C was prepared using General Procedure 1 (Condition C), with $Rh(CO)_2(acac)$ (0.86 mg, 3.35 µmol, 0.67 mol%), 6-DPPon (4.69 mg, 16.8 µmol, 3.33 mol%) and **34** (161 mg, 0.50 mmol, 1.0 equiv.) in THF (1.0 mL), and diboron **1** (228 mg, 1.00 mmol, 2.0 equiv.), ^{13}C-silacarboxylic acid **2** (243 mg, 1.00 mmol, 2.0 equiv.), TBAI (17 mg, 0.046 mmol, 4 mol%) in THF (0.3 mL) and water (2.7 mL), with a 16 h reaction time at 50 °C. Purification *via* column chromatography (pentane / EtOAc (20%)) gave **35-^{13}C** (138 mg, 0.39 mmol, 78%) as a clear oil.

R_f 0.13 (petroleum ether / EtOAc (20%)); **^{1}H NMR** (400 MHz, $CDCl_3$) [rotamaeric mixture] δ_H 9.74 (1H, d, *J* = 172.5 Hz), 6.77 (1H, d, *J* = 8.0 Hz), 6.74-6.59 (2H, m), 3.84 (3H, s), 3.83 (3H, s), 3.42-3.24 (2H, m), 3.21-3.03 (2H, m), 2.84-2.62 (2H, m), 2.48-2.31 (2H, m), 1.87-1.69 (2H, m), 1.42 (9H, s); **^{13}C NMR** (101 MHz, $CDCl_3$) [rotameric mixture] δ_C 201.8 (^{13}C, rotamer A), 201.5 (^{13}C, rotamer B), 155.5 (rotamer A), 155.4 (rotamer B), 148.9, 147.6, 131.8, 120.8, 112.1, 111.4, 79.5, 55.9, 55.8, 49.4 (rotamer A), 49.3 (rotamer B), 41.1 (d, *J* = 38.5 Hz, rotamer A), 40.9 (d, *J* = 38.5 Hz, rotamer B), 34.8 (rotamer A), 34.1 (rotamer B), 28.5, 21.1 (rotamer A), 29.9 (rotamer B); **HRMS** (ESI+) calc. for $C_{18}{}^{13}C_1H_{29}NNaO_5$ $[M+Na]^+$ 375.1977 found 375.1987.

(±)-Crispine A-^{13}C



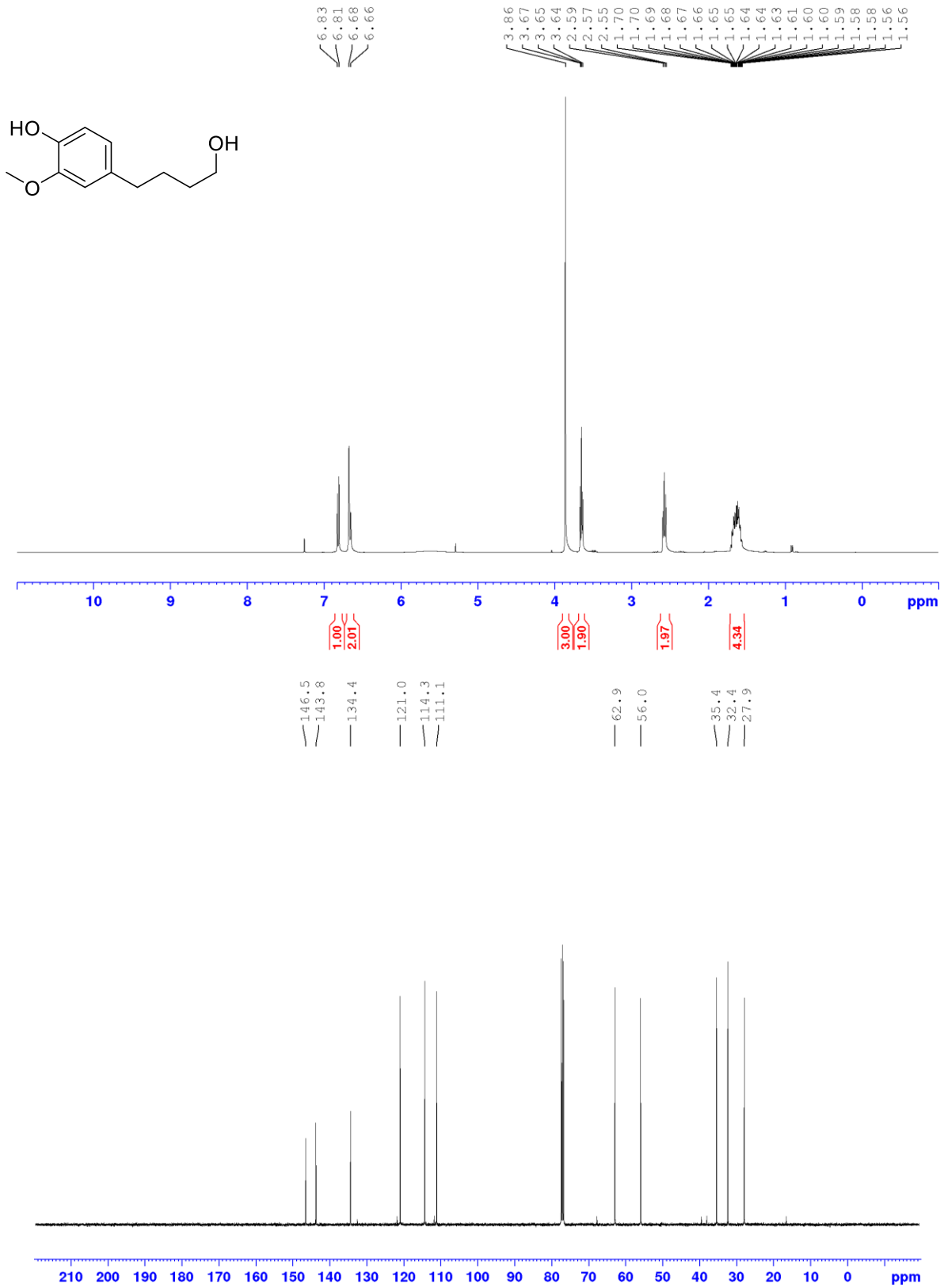
To a solution of **35-^{13}C** (50 mg, 0.14 mmol, 1.0 equiv.) in 1.2-dichloroethane (0.5 mL) was added trifluoroacetic acid (0.21 mL, 2.8 mmol, 20 equiv.) dropwise *via* syringe at 0 °C. After stirring at 80 °C overnight, the resulting reaction mixture was allowed to reach room temperature before being diluted with EtOAc (5 mL) and quenched by addition of a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified *via* column chromatography (CH_2Cl_2 / MeOH (10%)) to give (±)-Crispine A-^{13}C (20 mg, 0.085 mmol, 61%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.60 (1H, s), 6.56 (1H, d, *J* = 4.5 Hz), 6.74-6.59 (2H, m), 3.88-3.77 (6.5H, m), 3.50 (0.5H, t, *J* = 8.0 Hz), 3.23-3.13 (1H, m), 3.12-3.02 (1H, m), 3.02-3.92 (2H, m), 2.86-2.72 (3H, m), 2.43-2.31 (1H, m), 2.03-1.84 (2H, m), 1.83-1.69 (1H, m); **^{13}C**

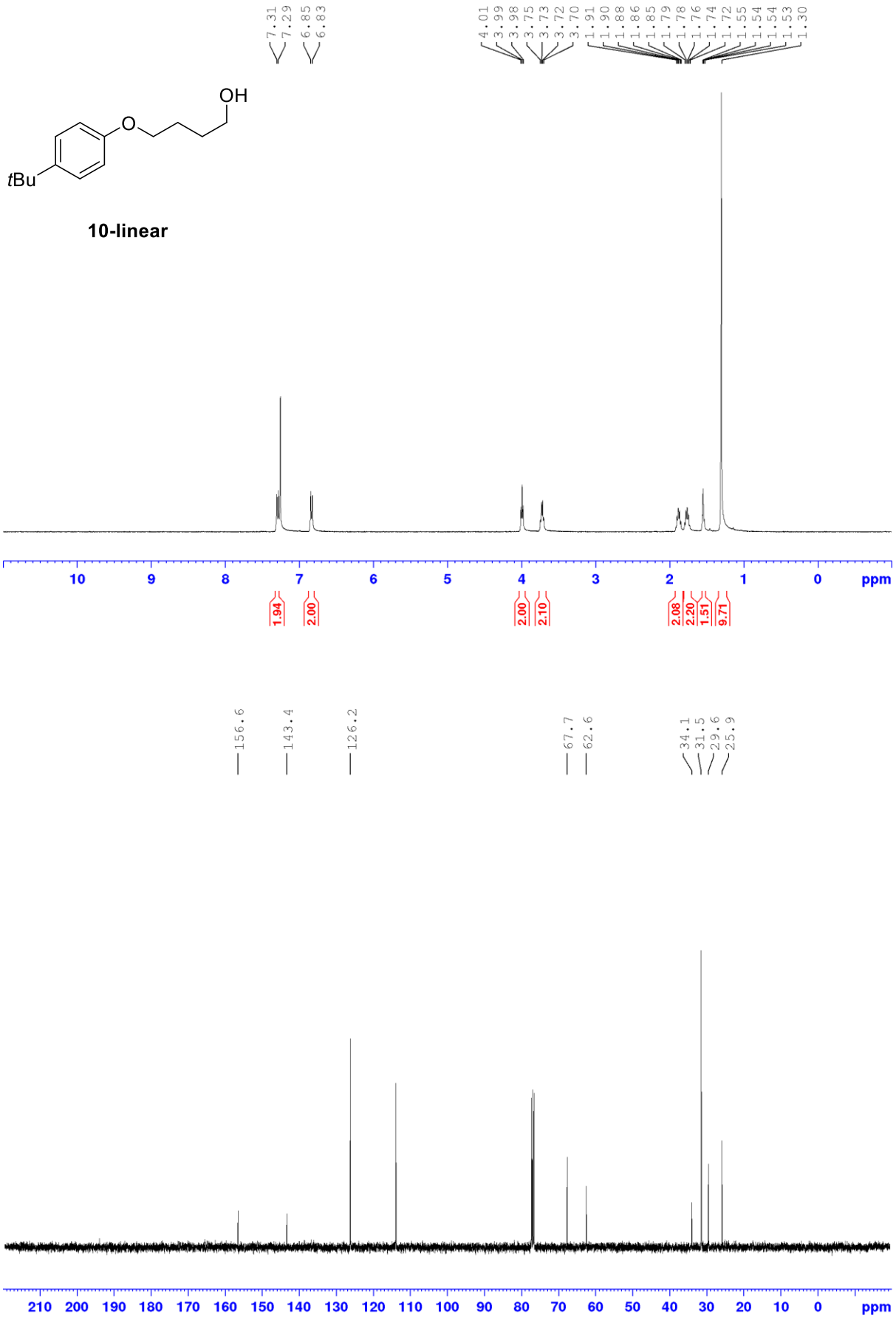
NMR (101 MHz, $CDCl_3$) δ_C 147.7, 147.6 (d, *J* = 5.0 Hz), 129.8 (d, *J* = 48.0 Hz), 125.8, 111.4 (d, 3.0 Hz), 109.0 (d, 4.5 Hz), 62.6 (^{13}C), 56.1, 56.0, 53.2 (d, *J* = 2.5 Hz), 48.2, 31.0 (d, *J* = 35.0 Hz), 27.5, 22.4; **HRMS** (ESI+) calc. for $C_{13}{}^{13}C_1H_{20}NO_2$ $[M+H]^+$ 235.1528 found 235.1532.

NMR Spectra

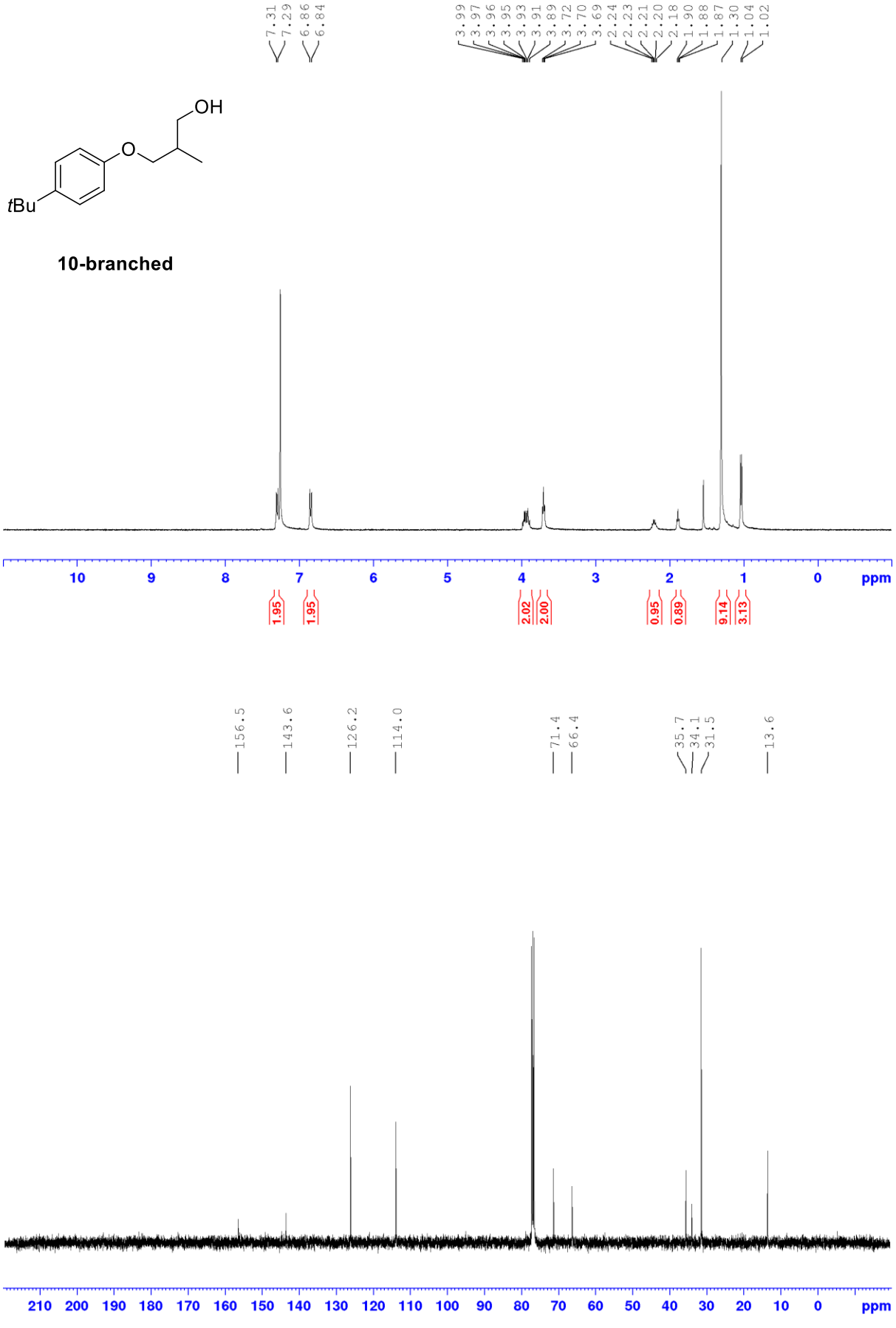
9 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



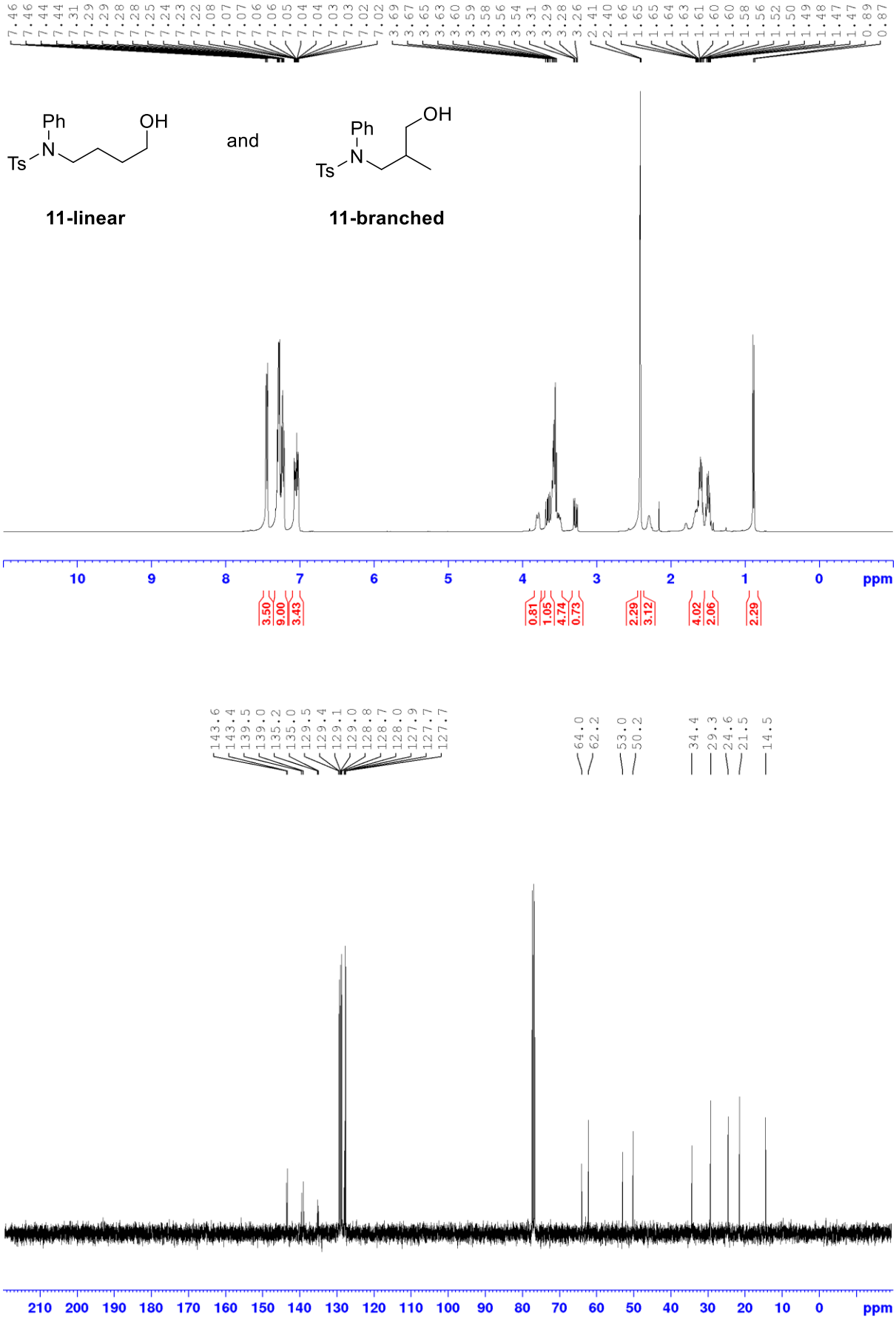
10-linear [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



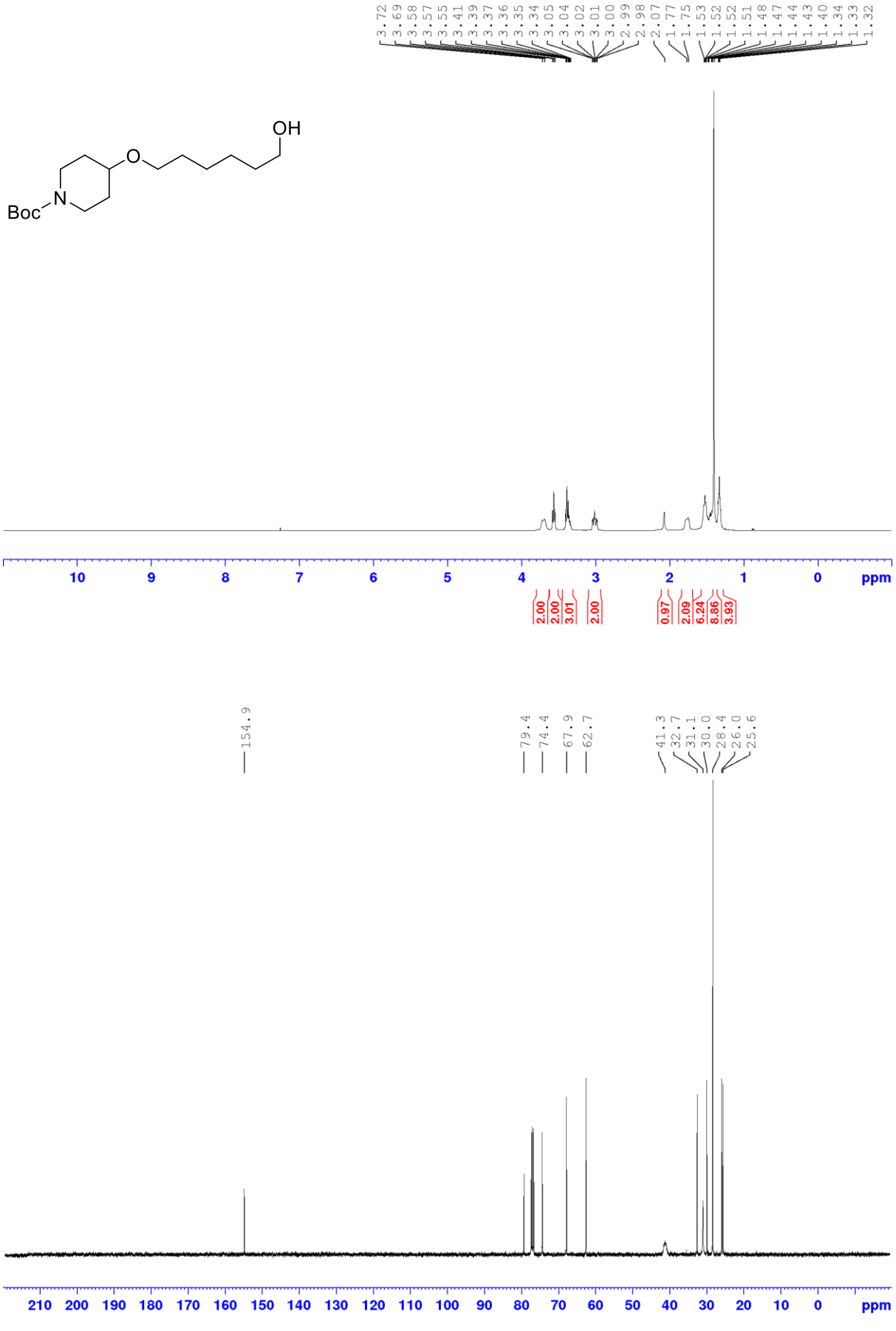
10-branched [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



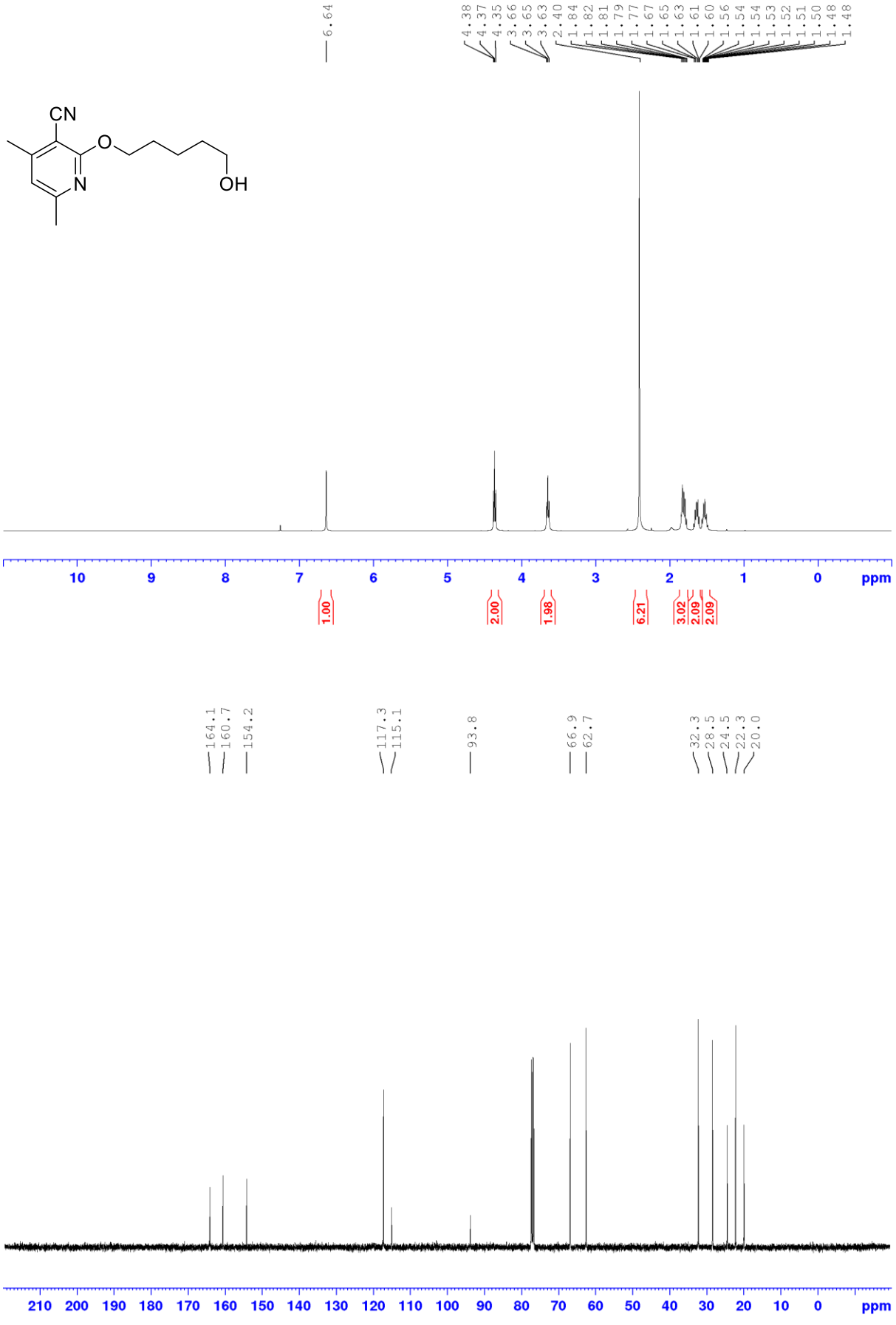
11-branched [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



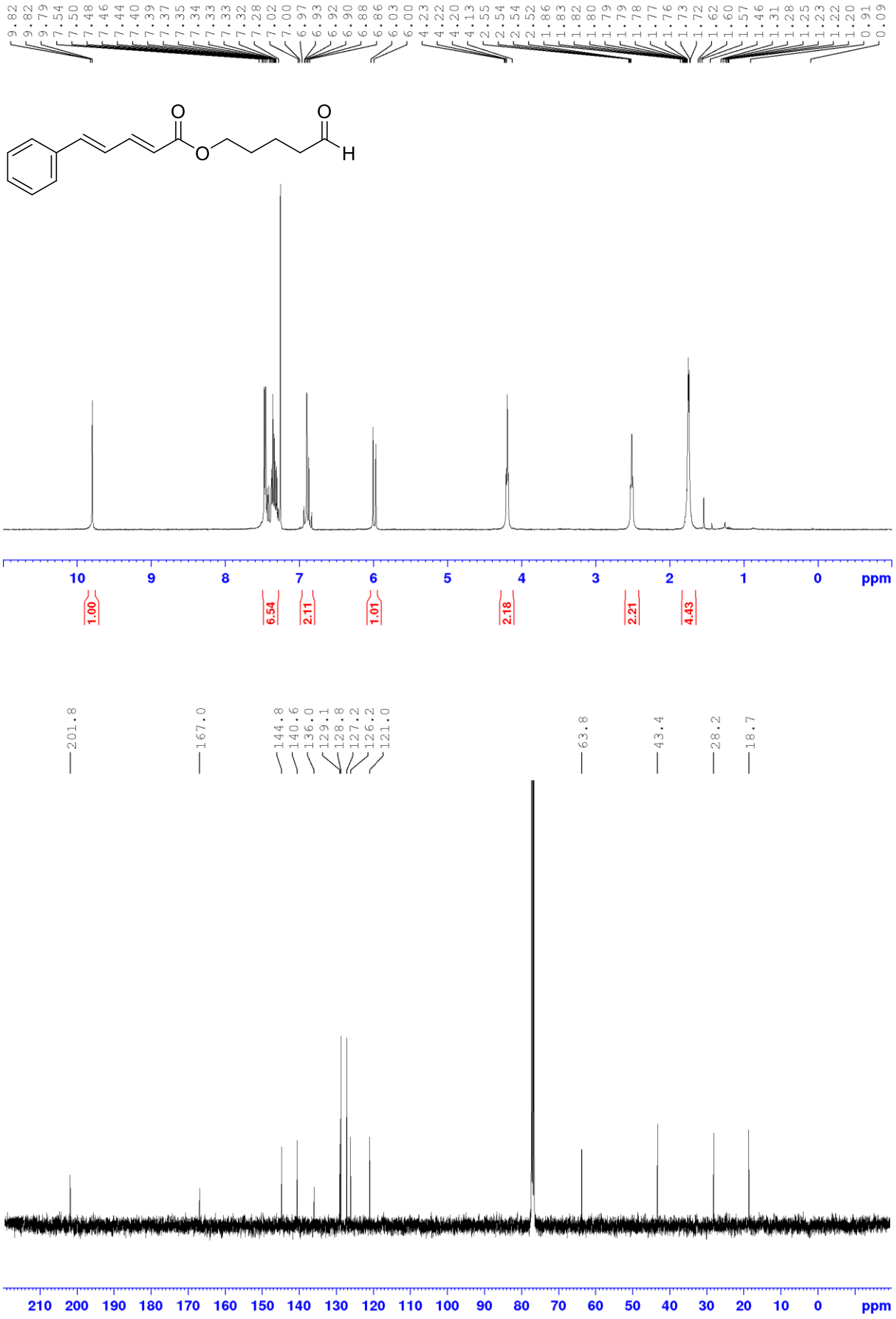
13 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



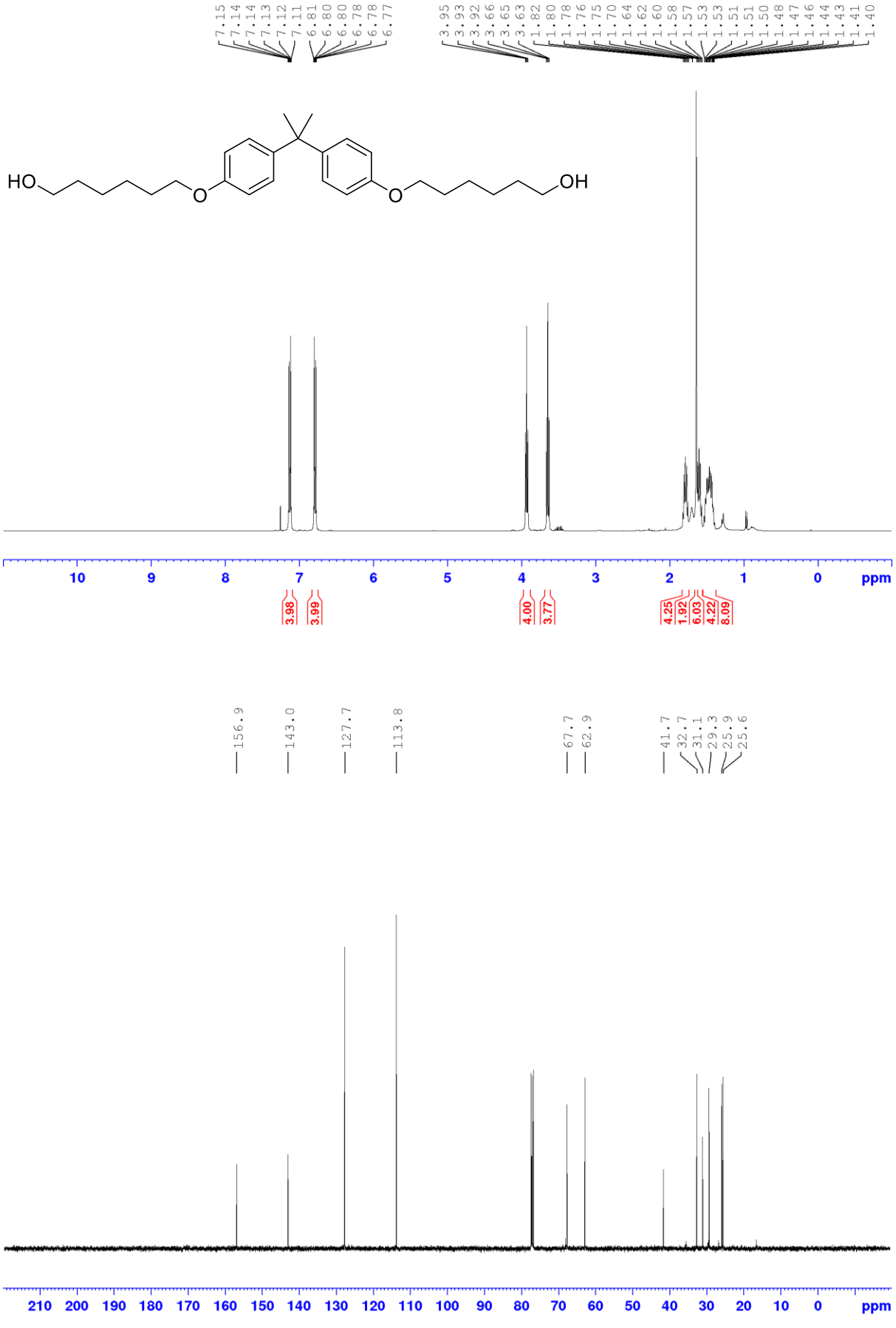
14 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



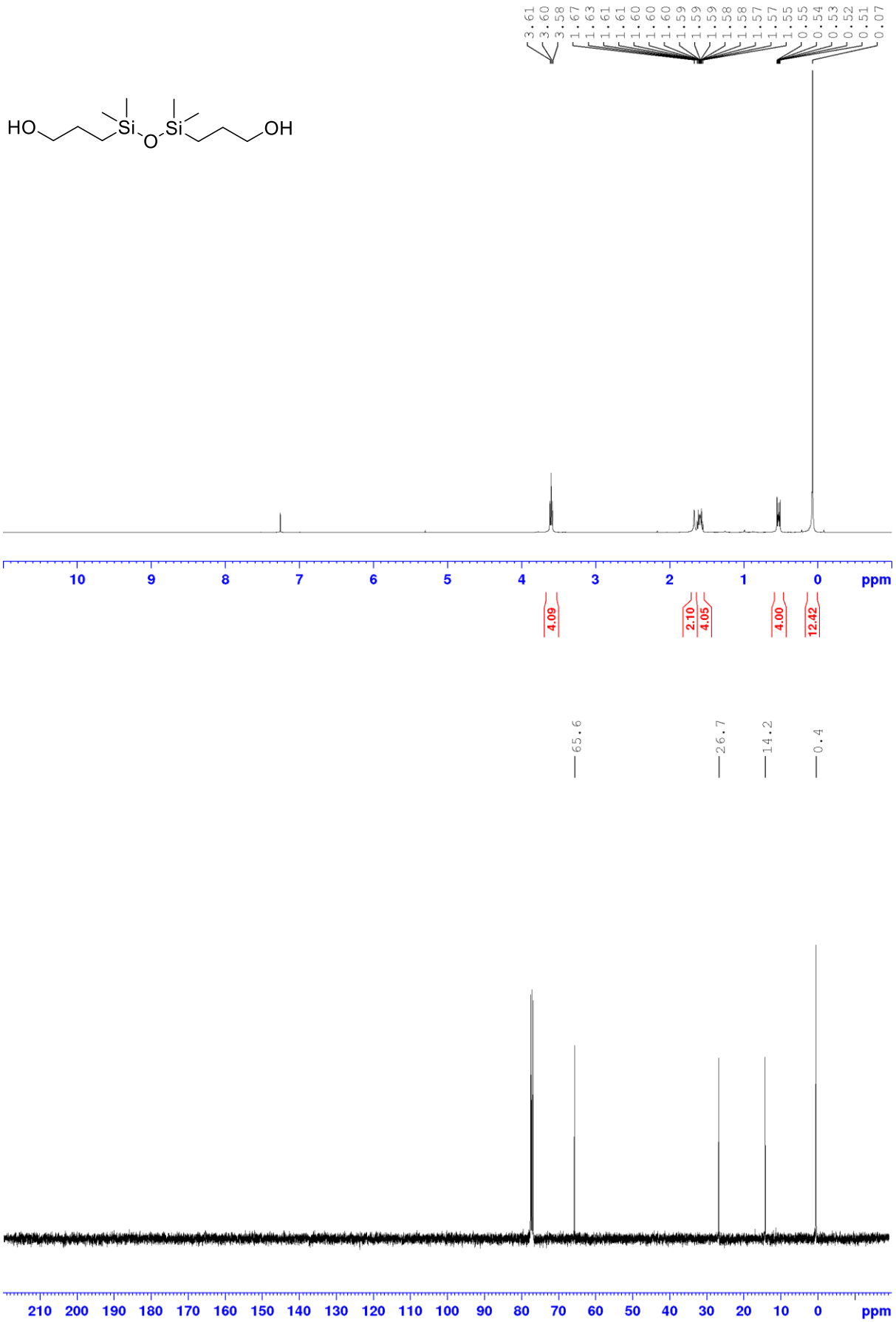
15 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



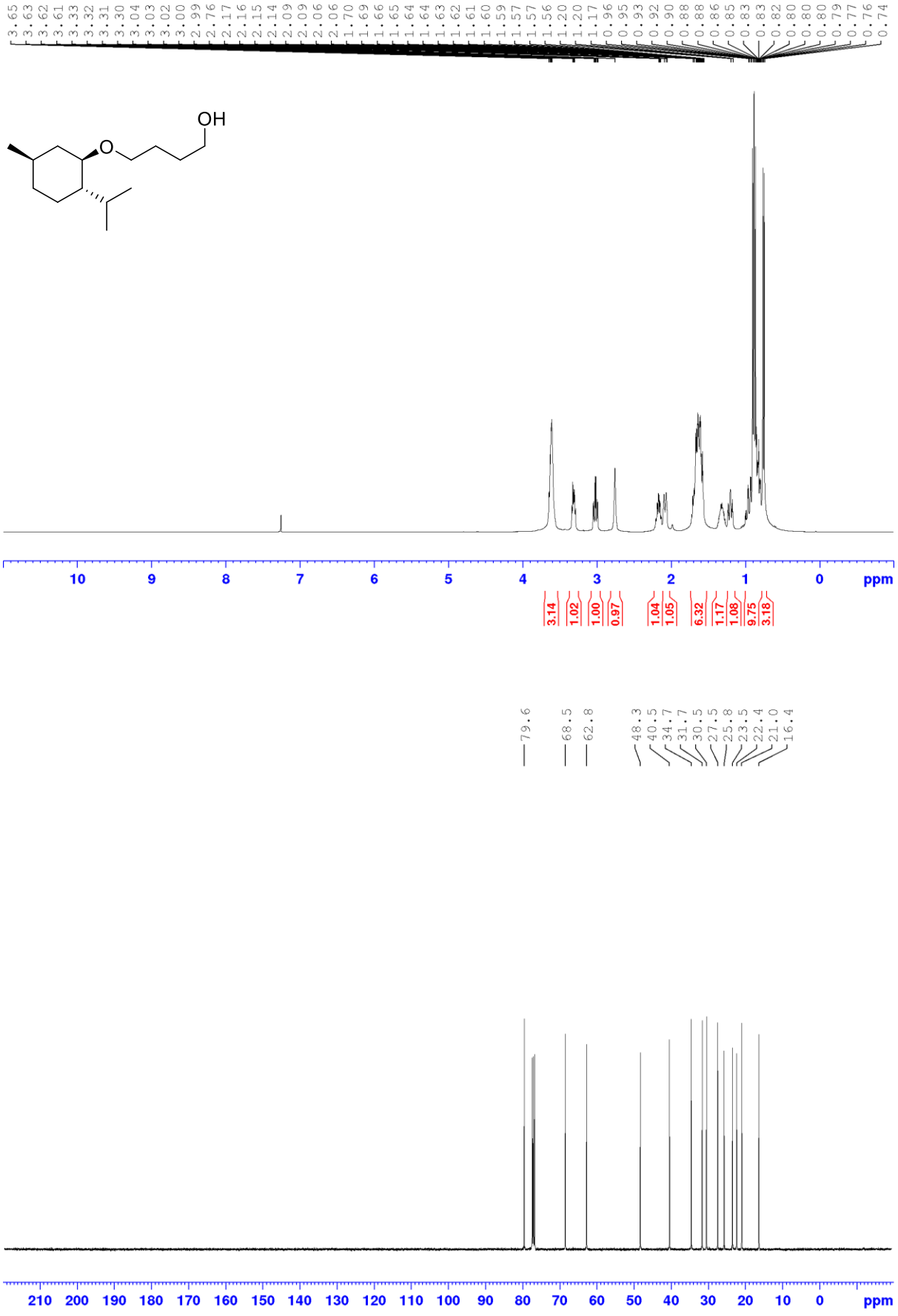
16 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



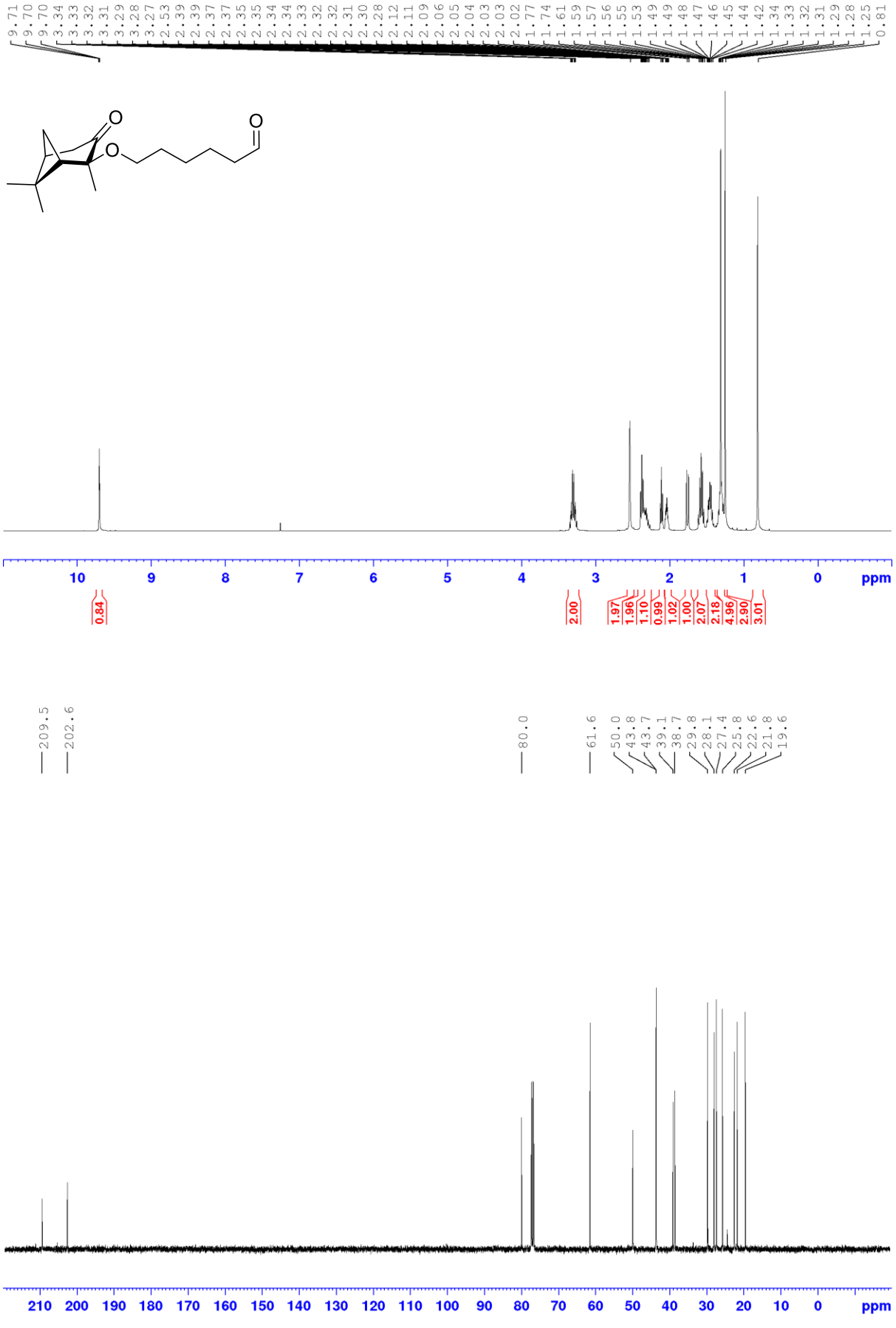
17 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



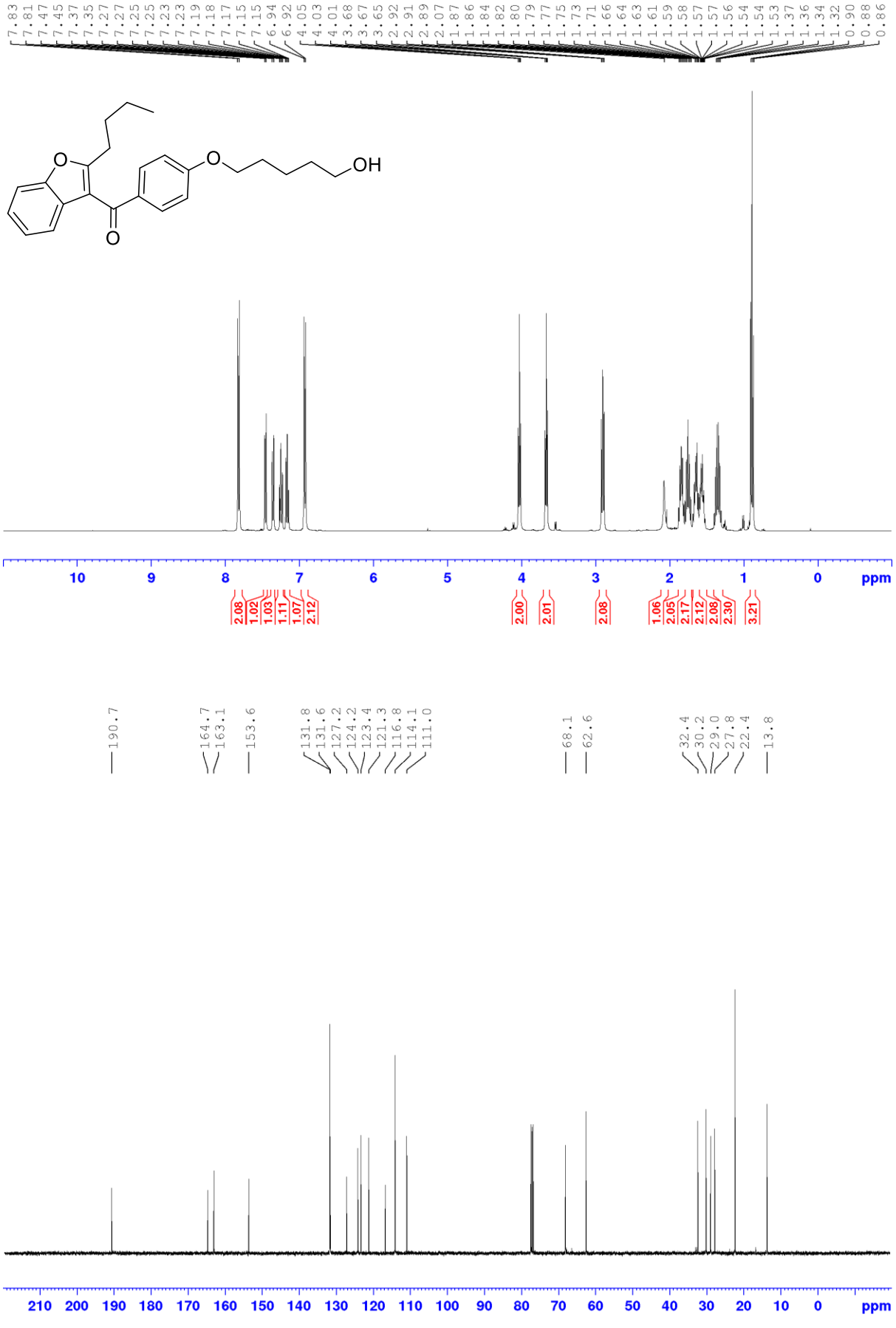
18 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



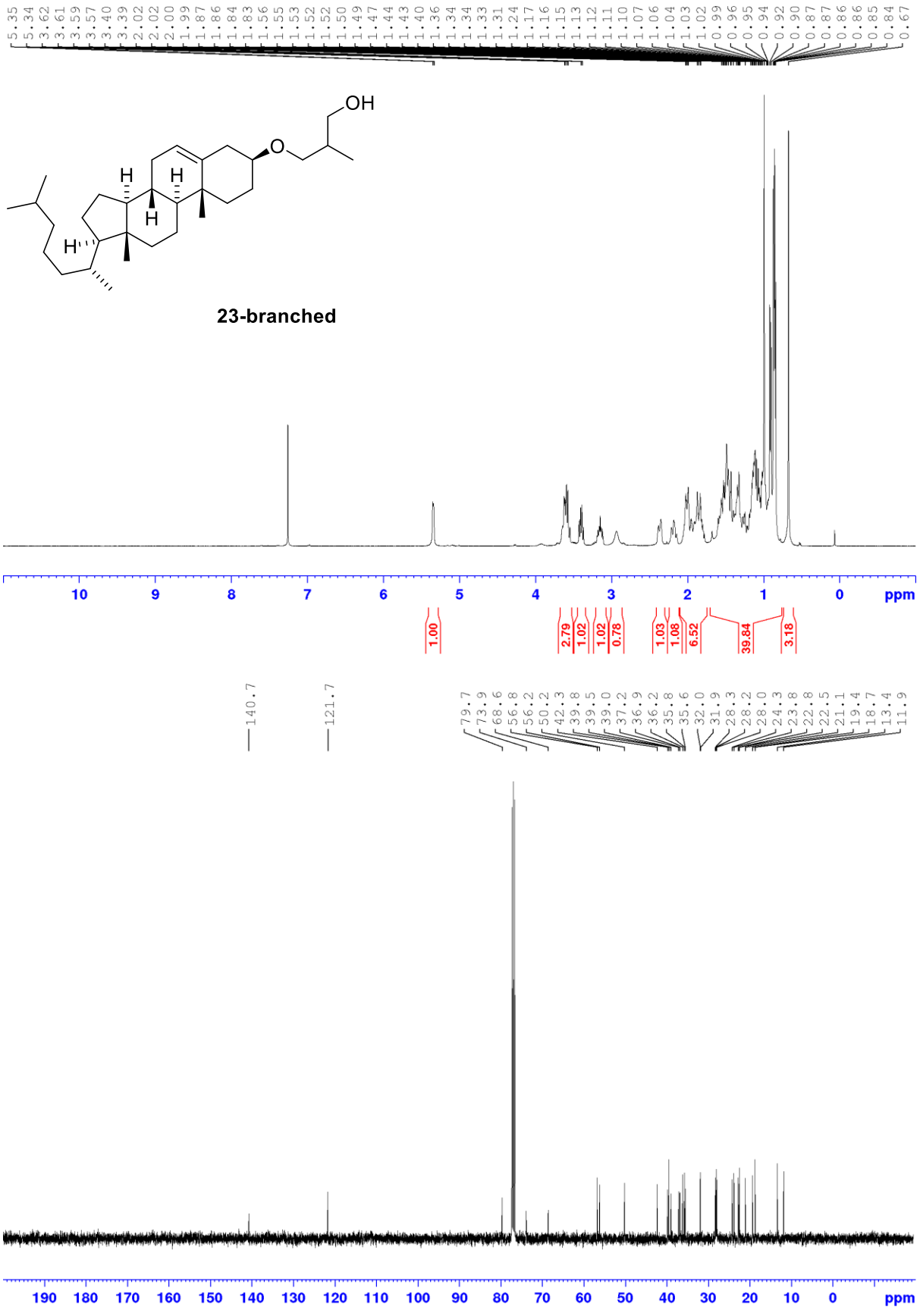
19 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



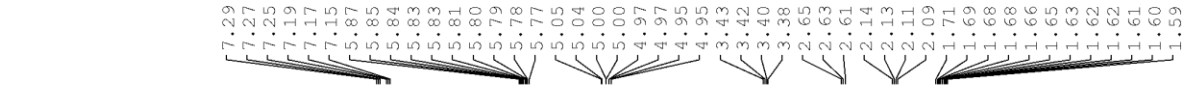
21 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

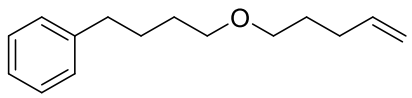


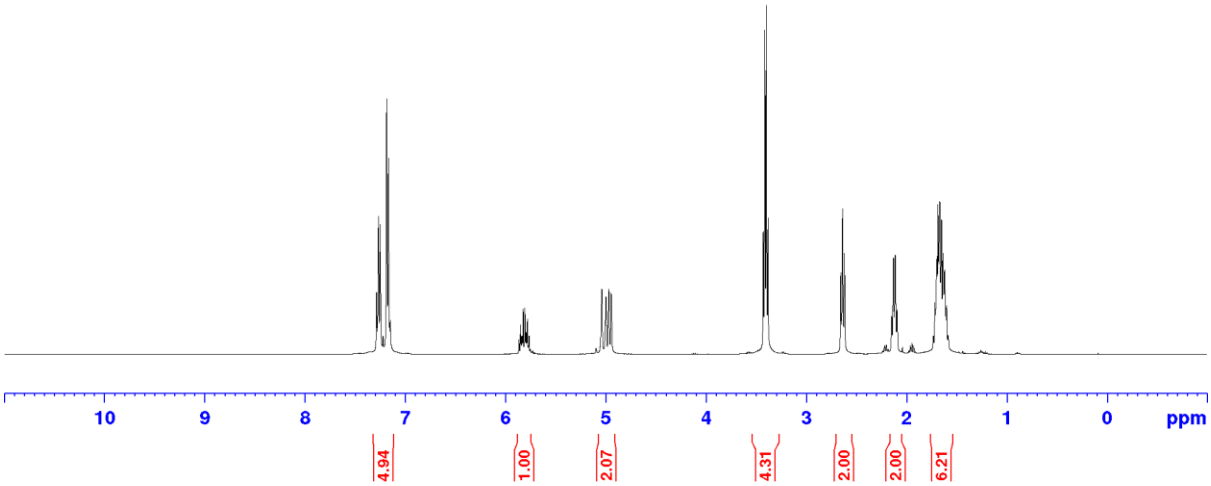
23-branched [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

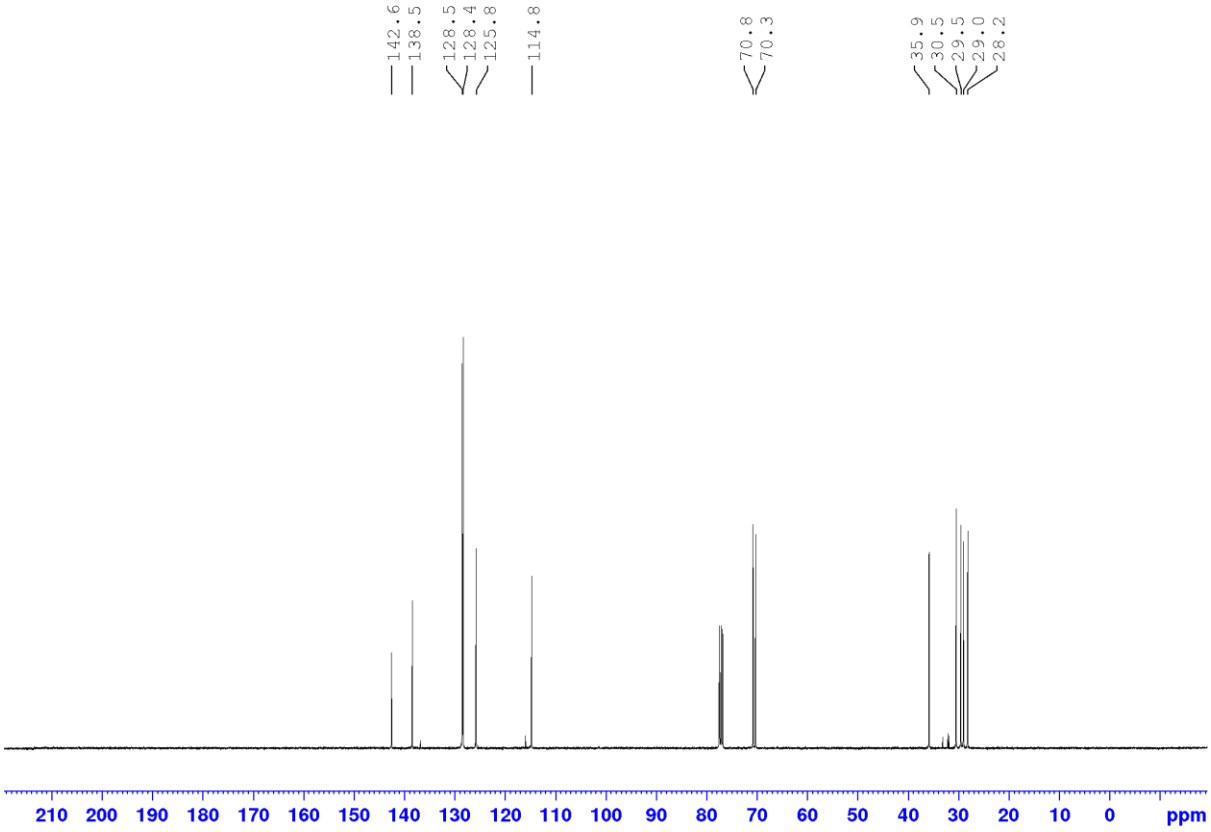


42 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

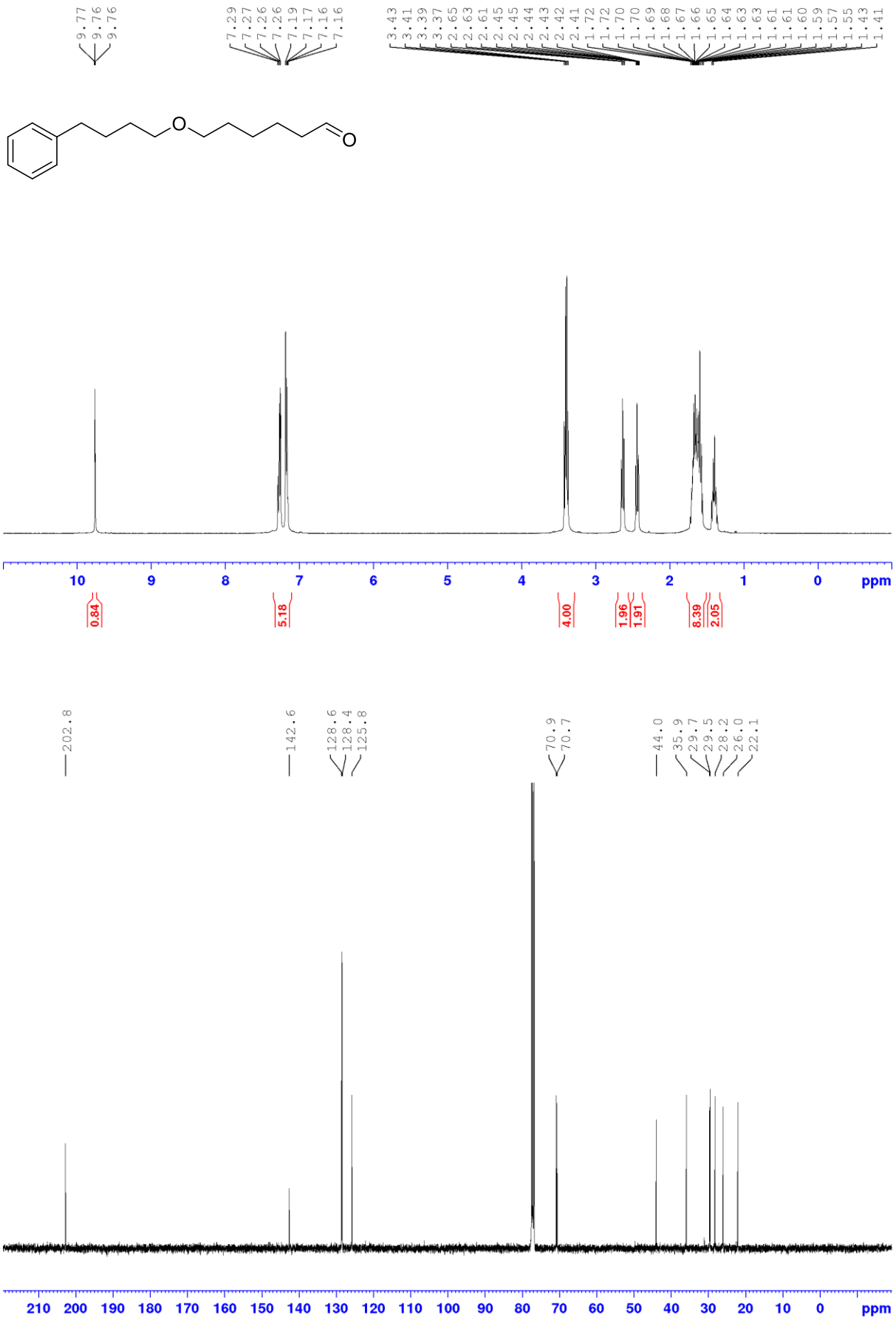




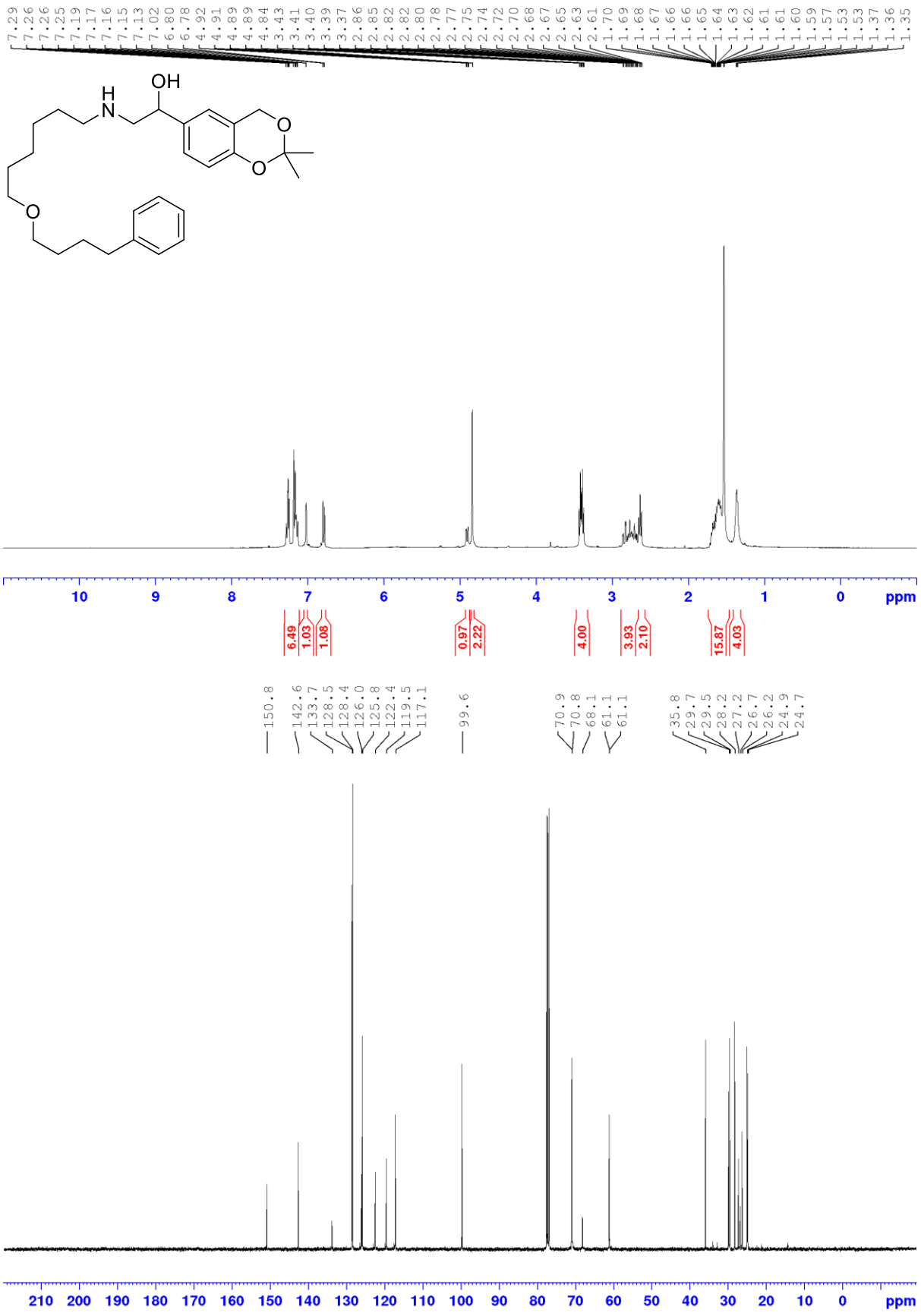




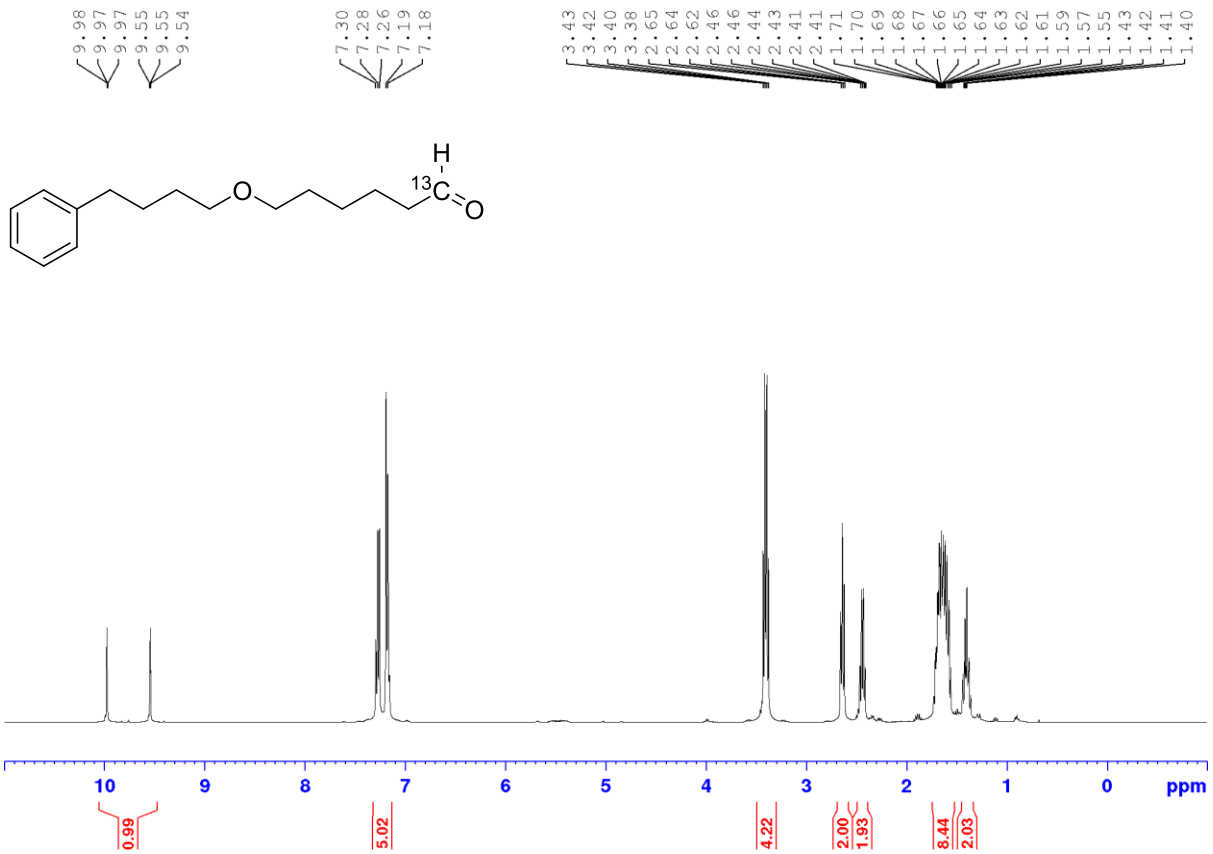
43 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

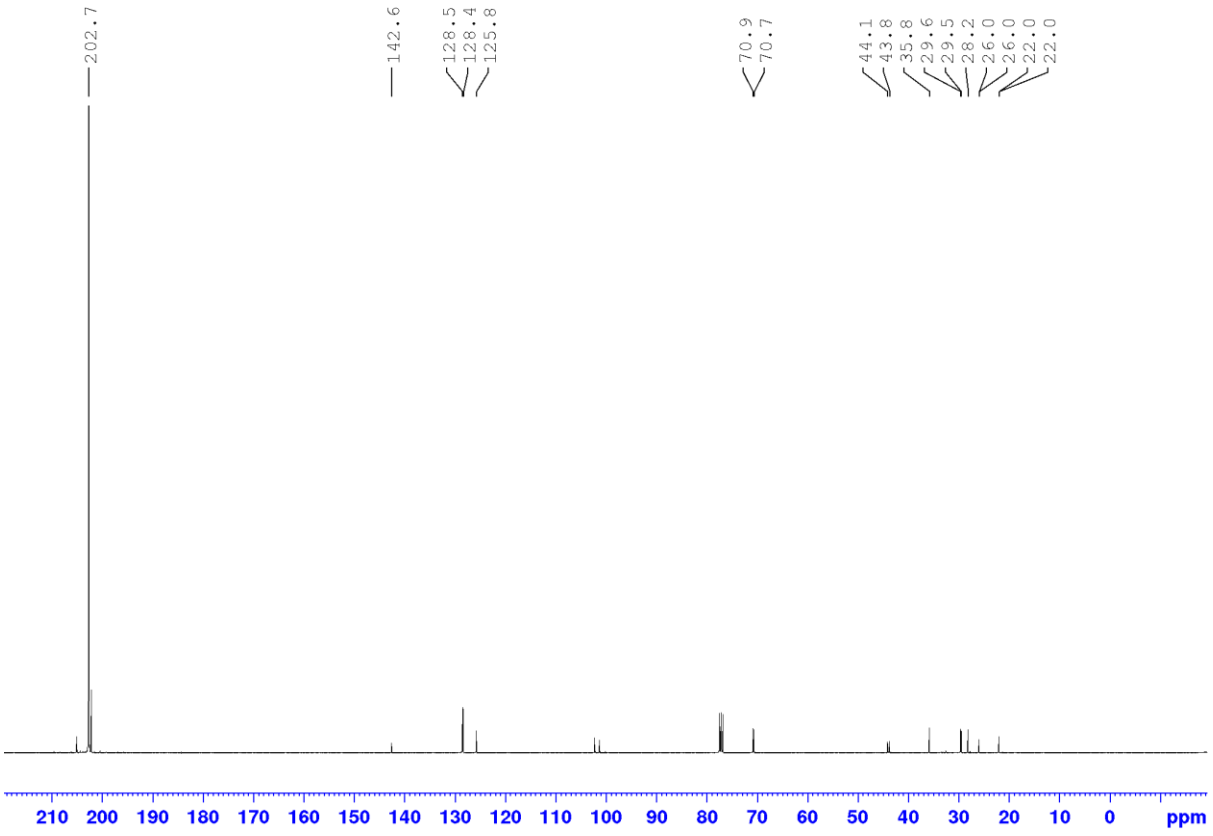


Salmeterol (acetal derivative) [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

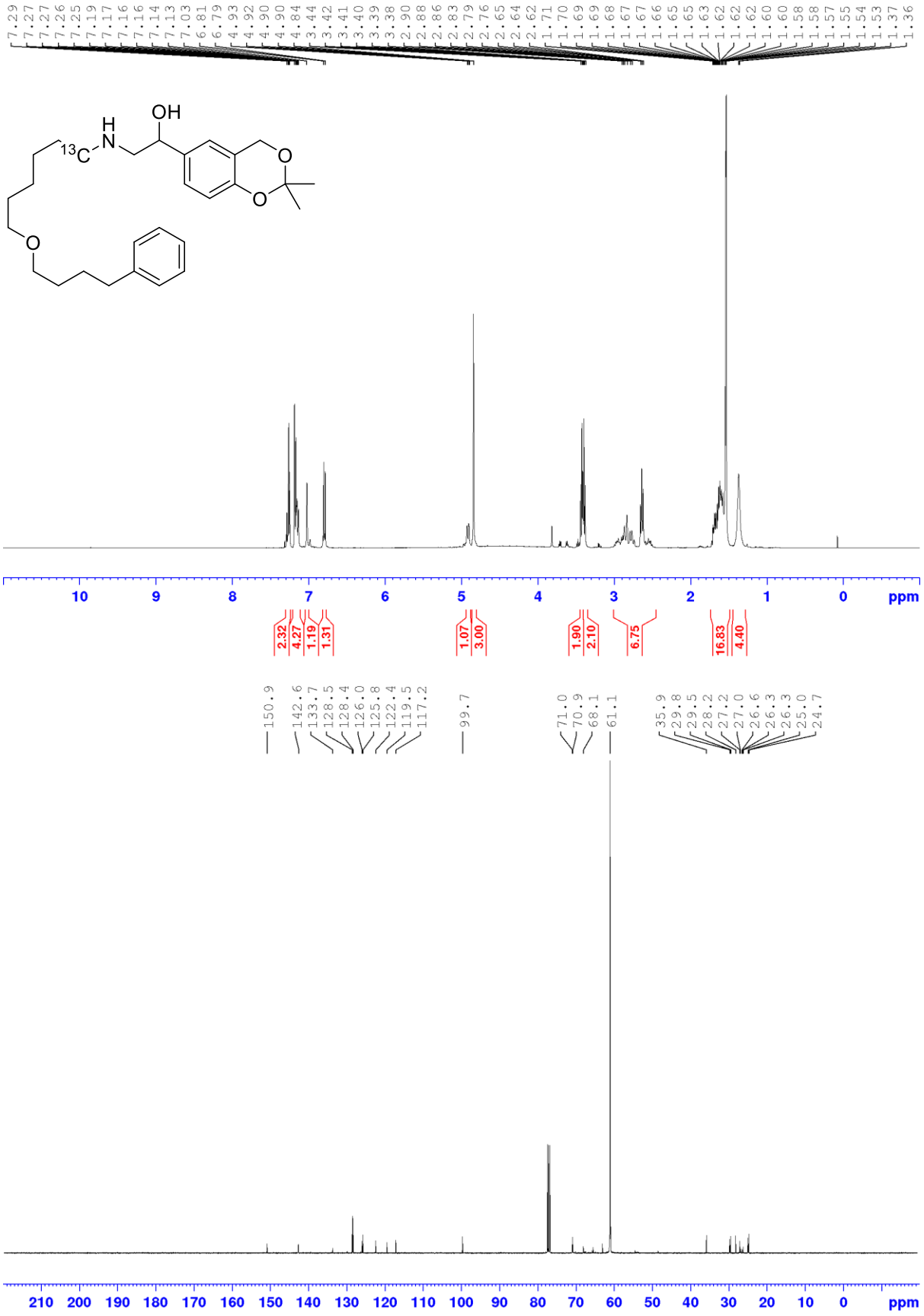


43-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

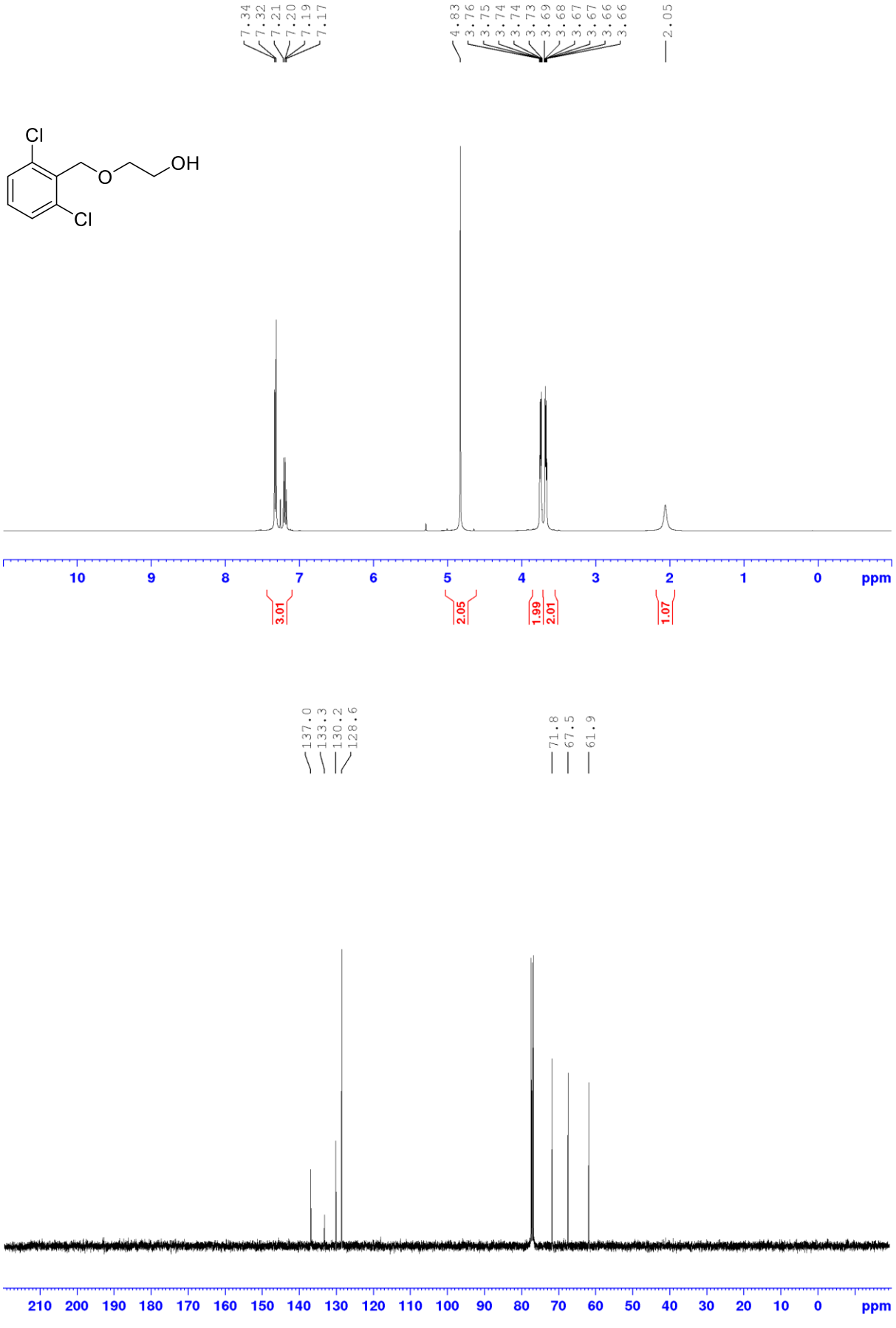




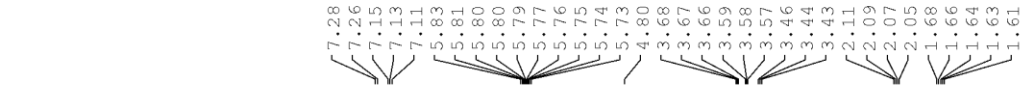
Salmeterol-^{13}C (acetal derivative) [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

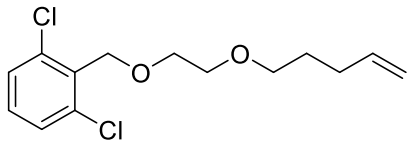


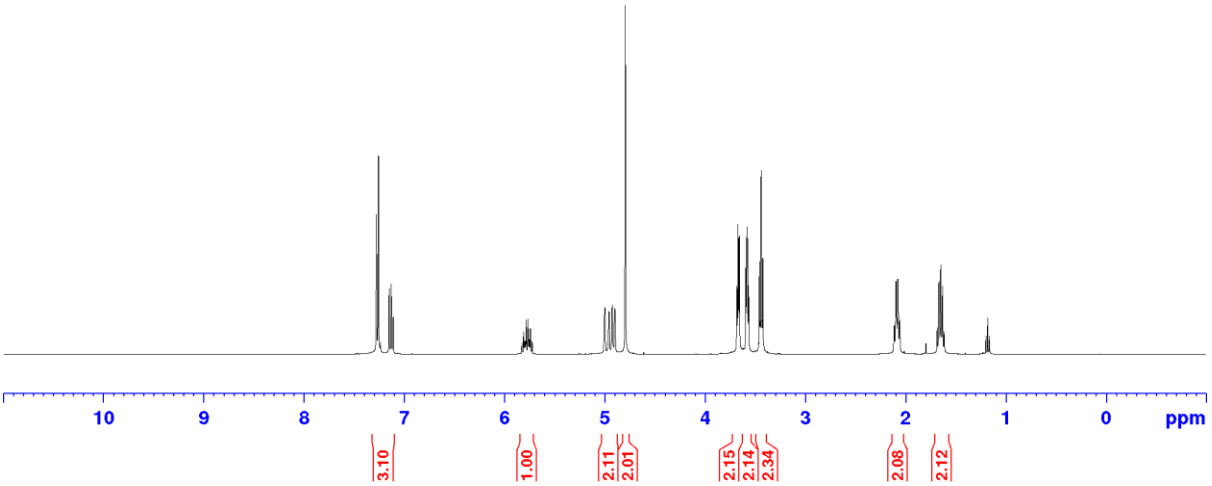
44 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

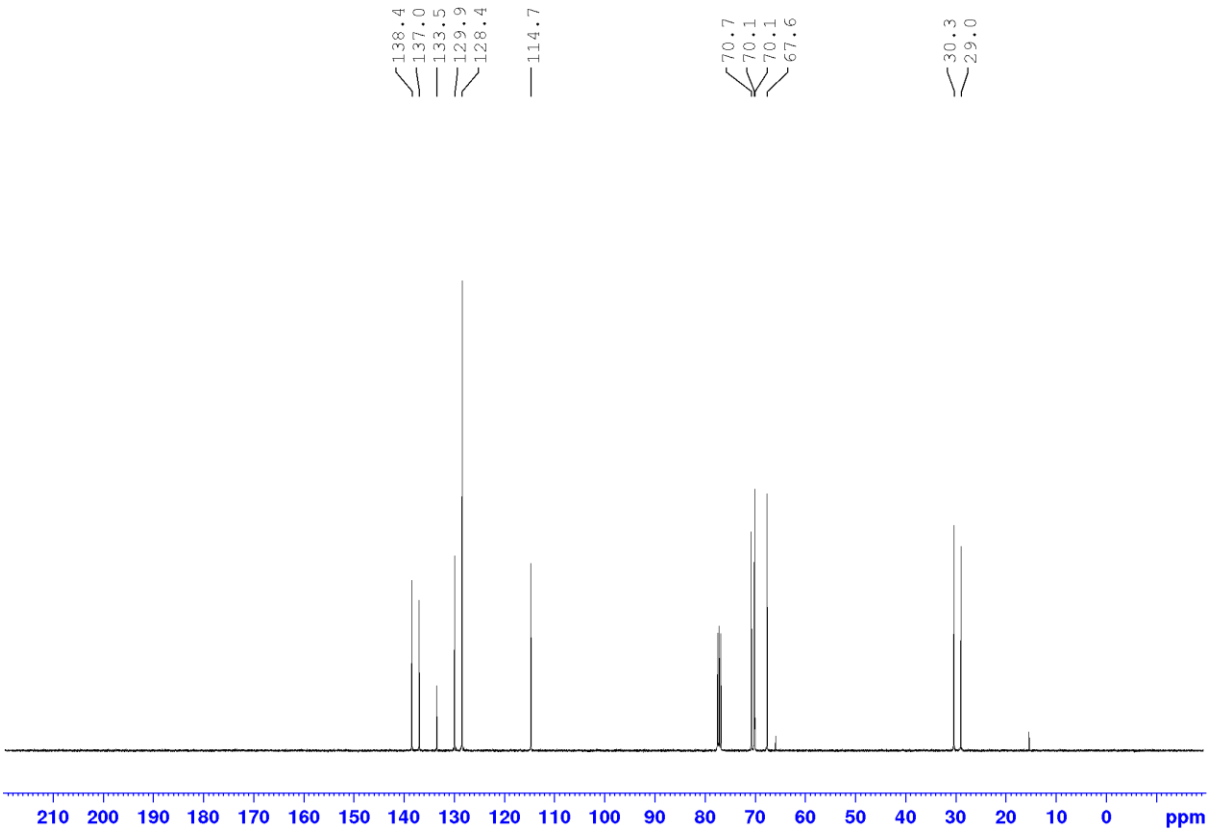


45 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

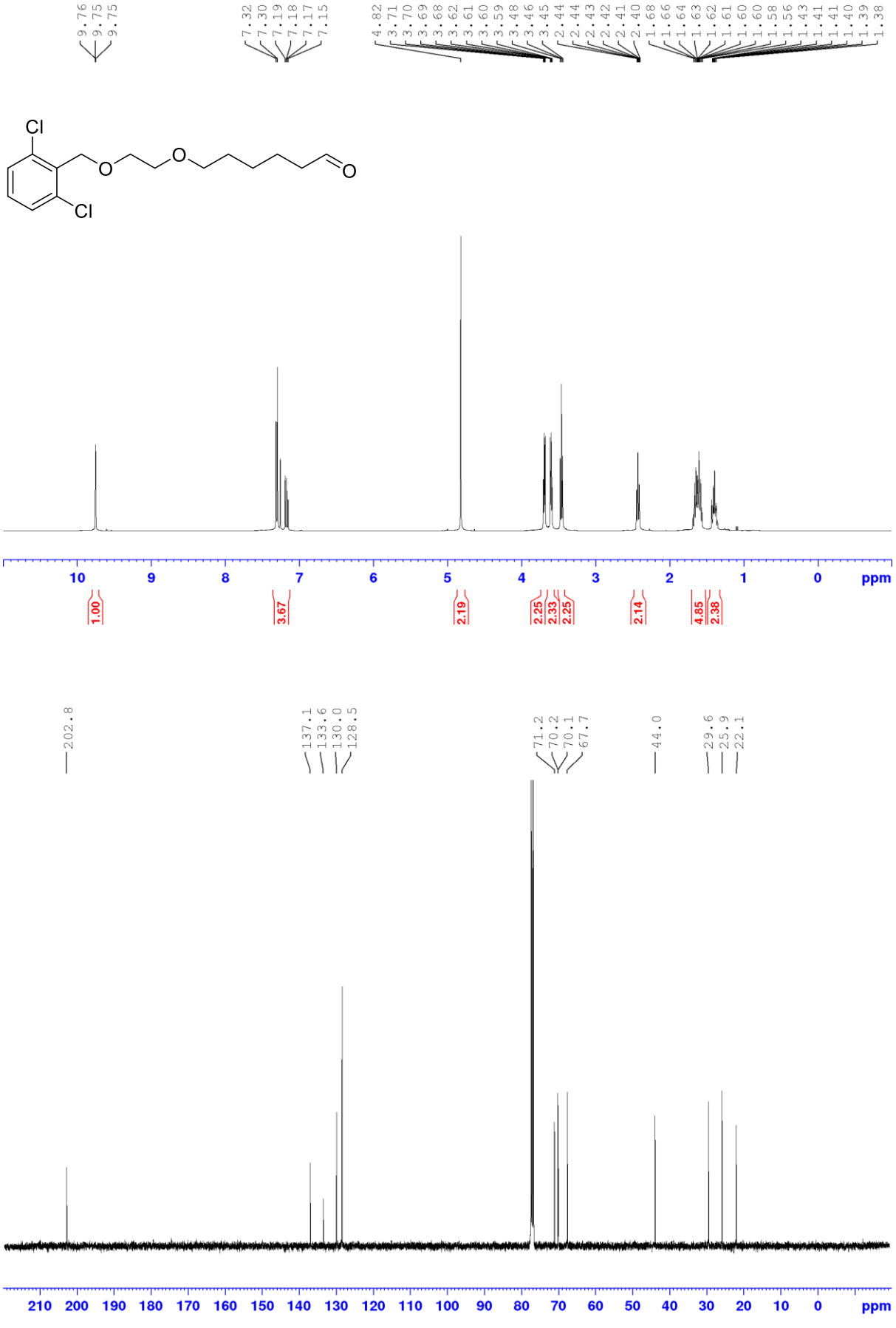




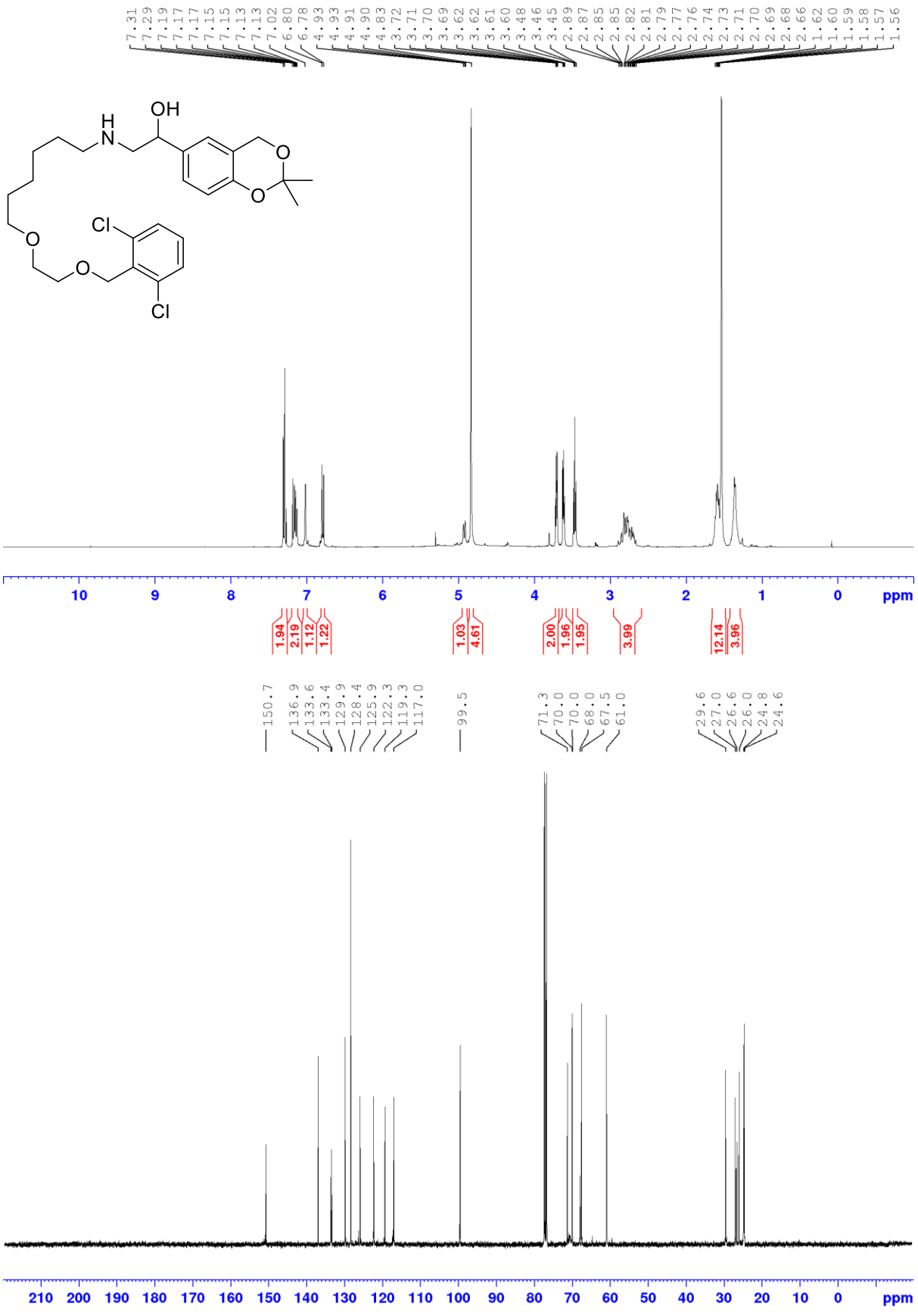




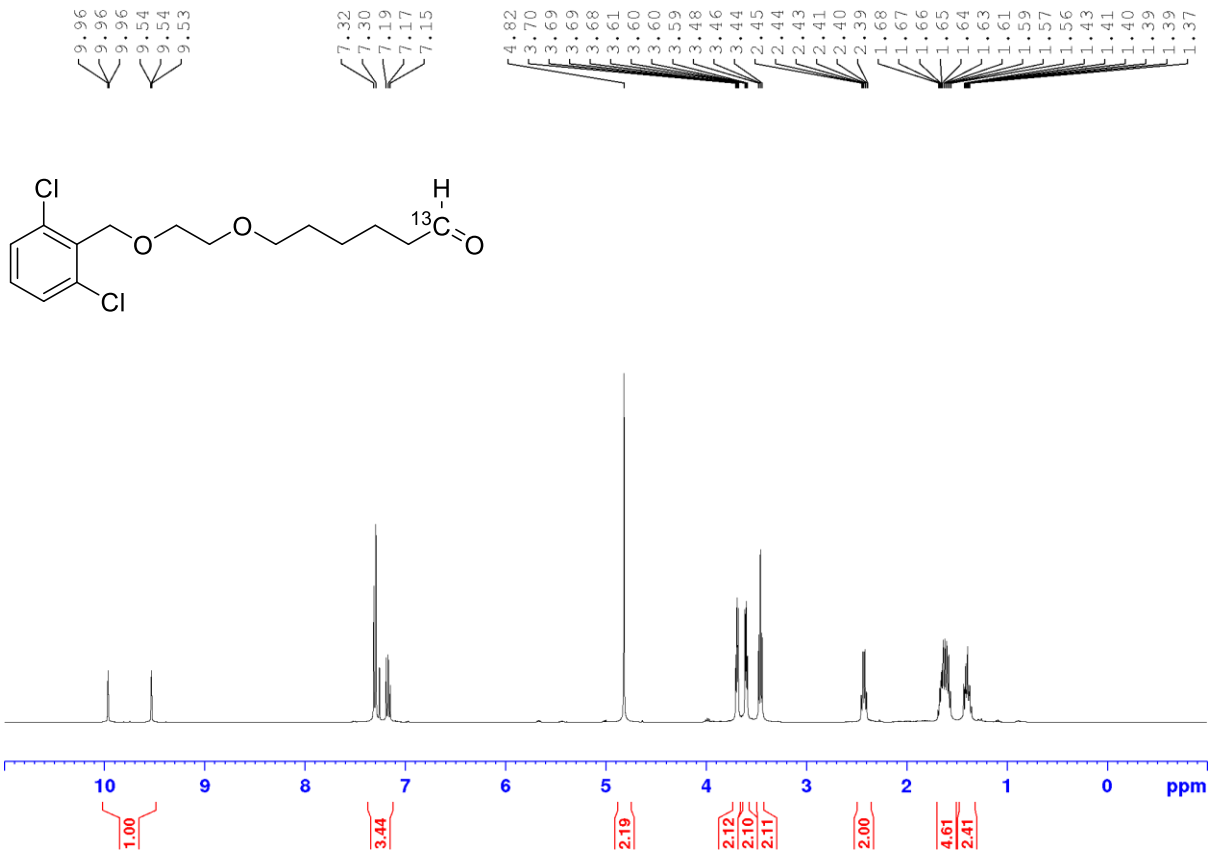
46 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



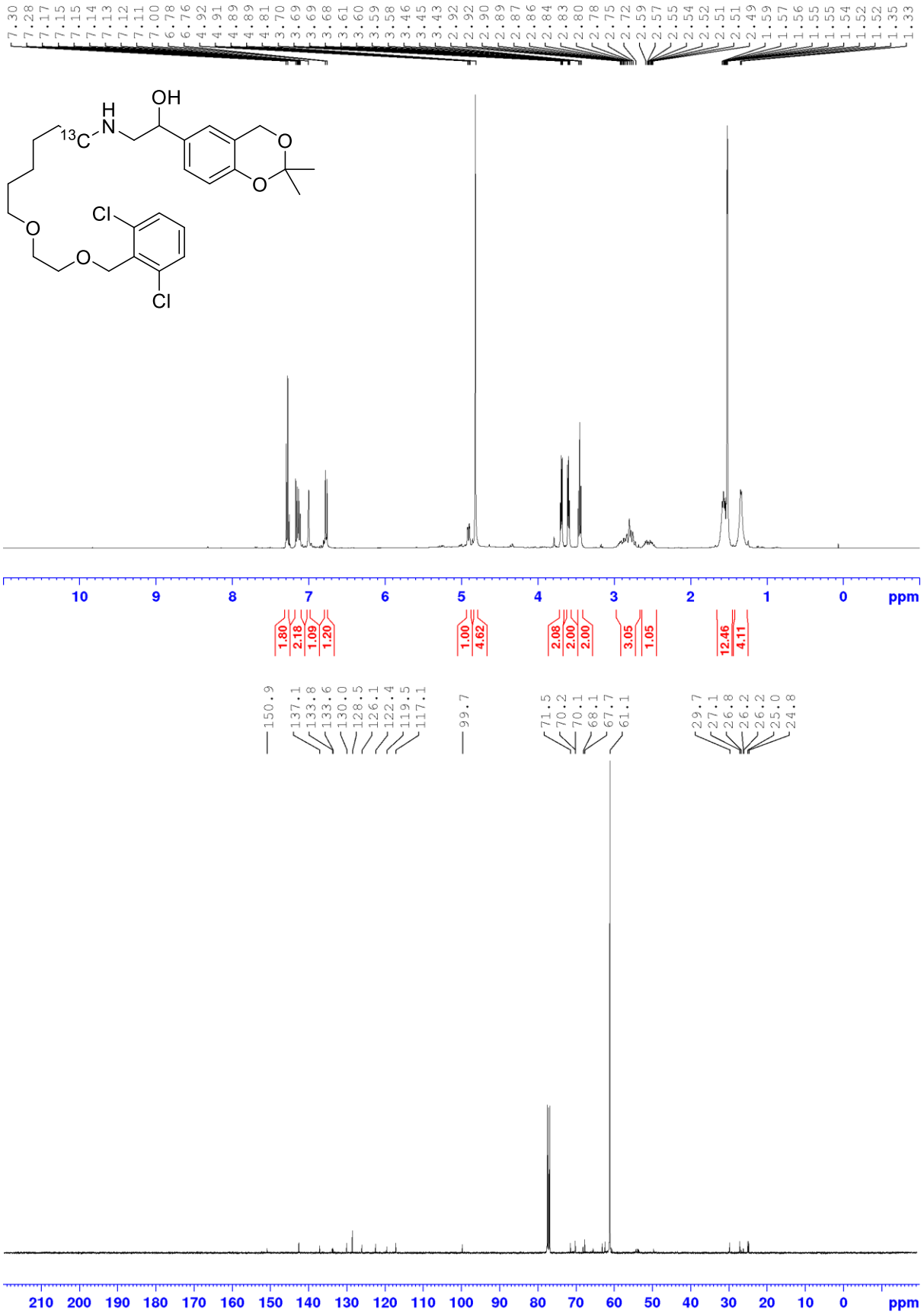
Vilanterol (acetal derivative) [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



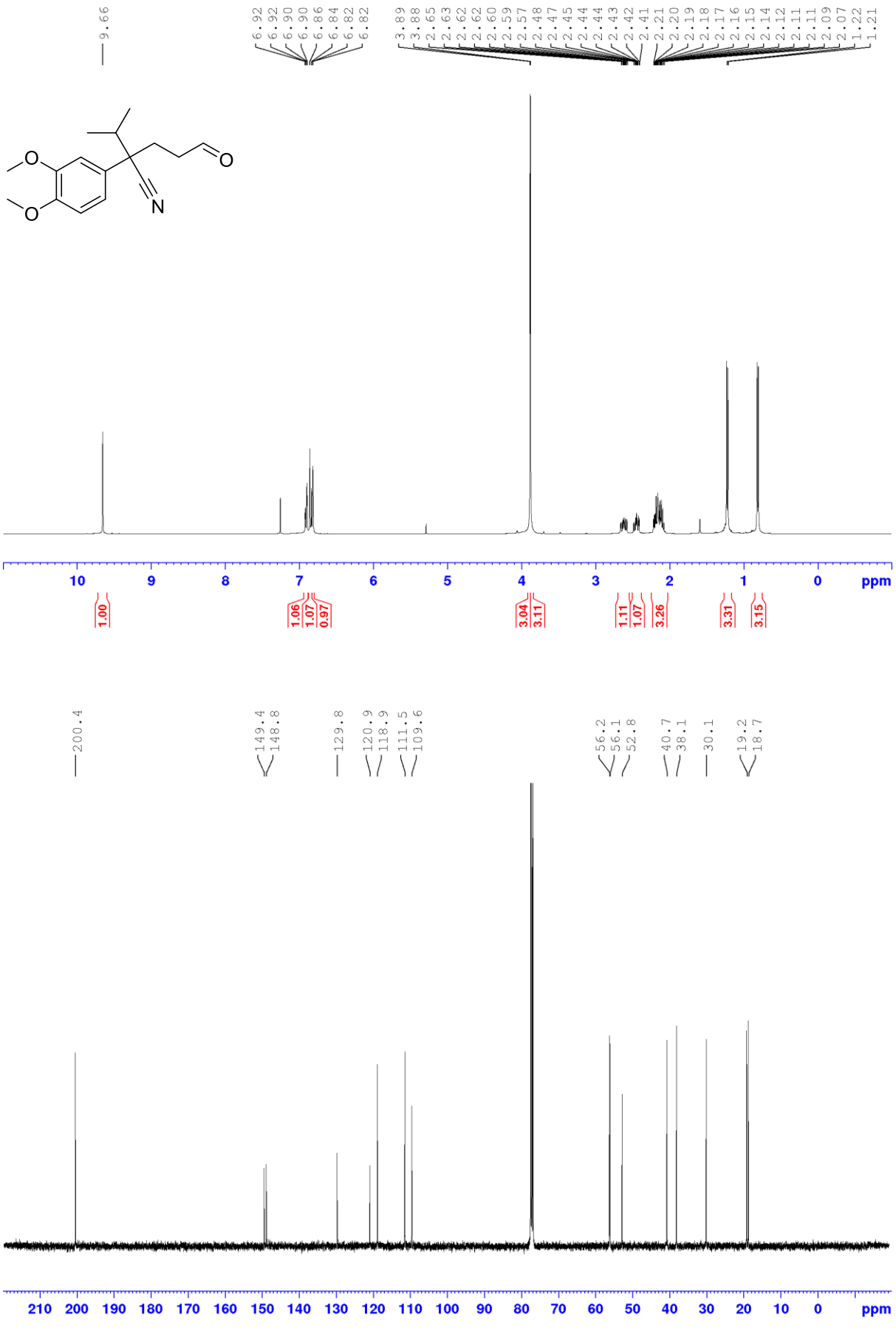
46-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



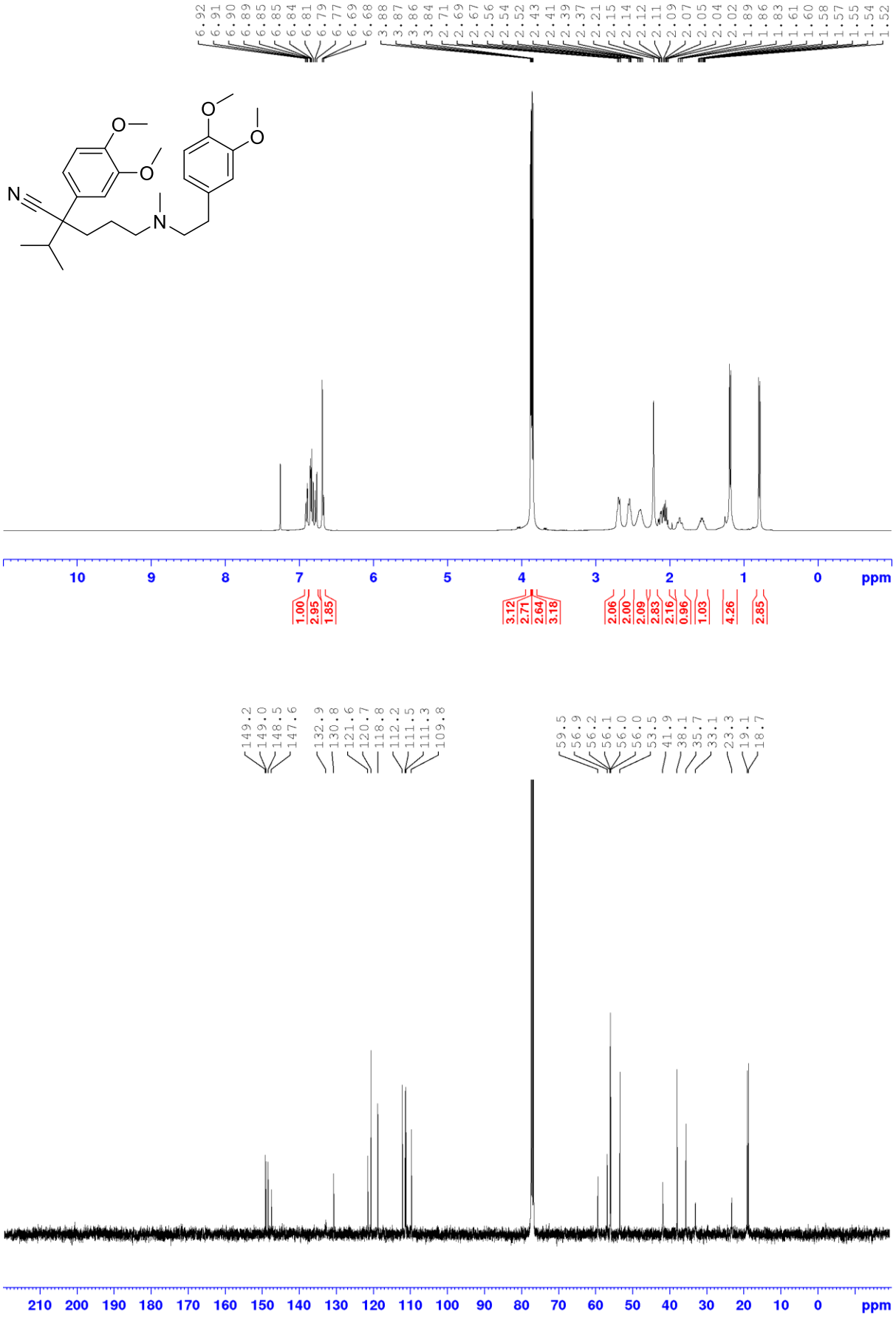
Vilanterol-^{13}C (acetal derivative) [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



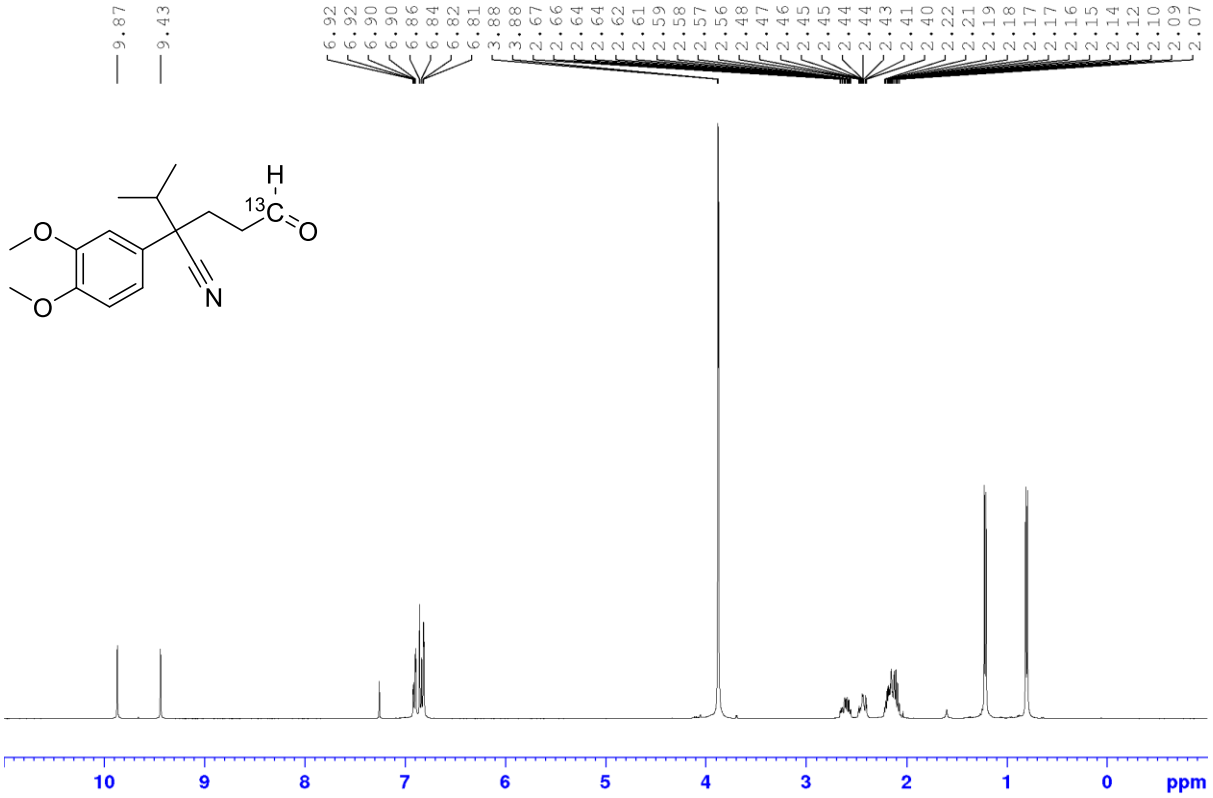
51 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

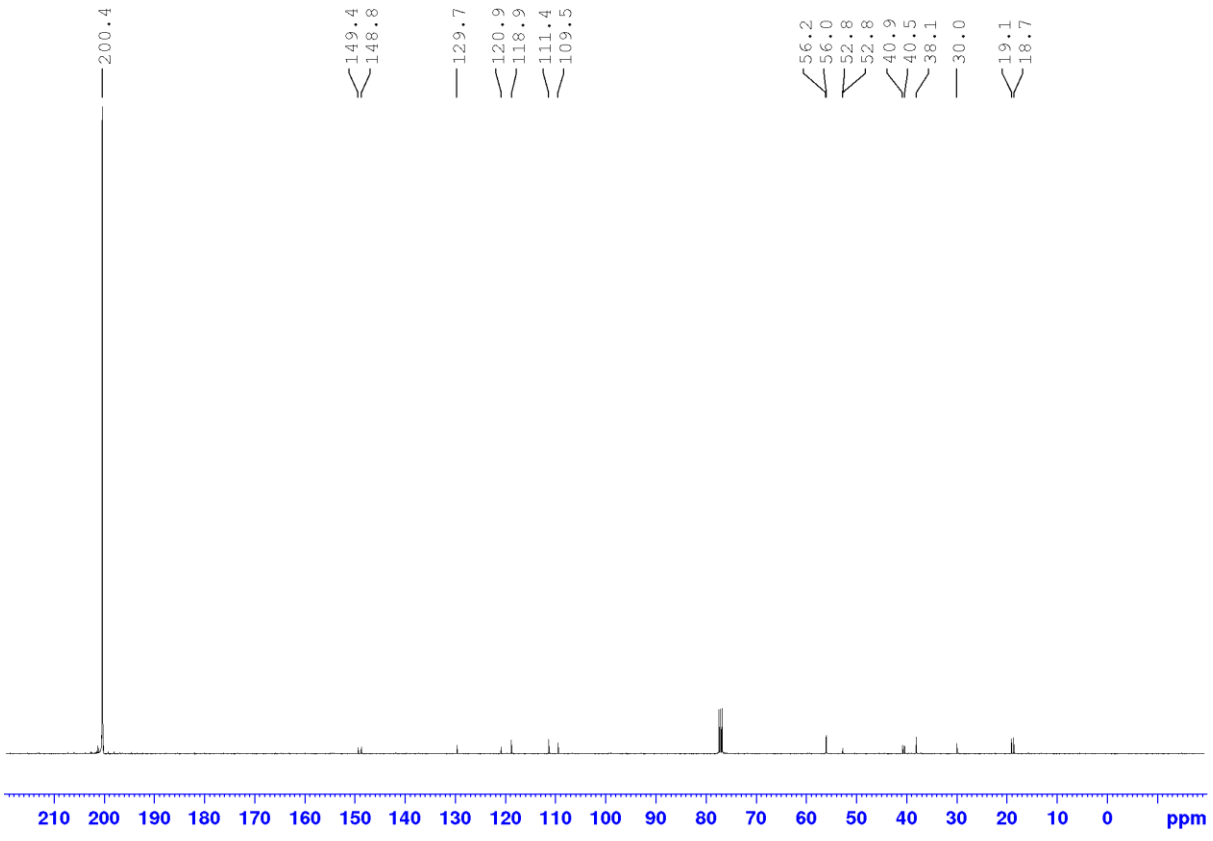


Verapamil [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

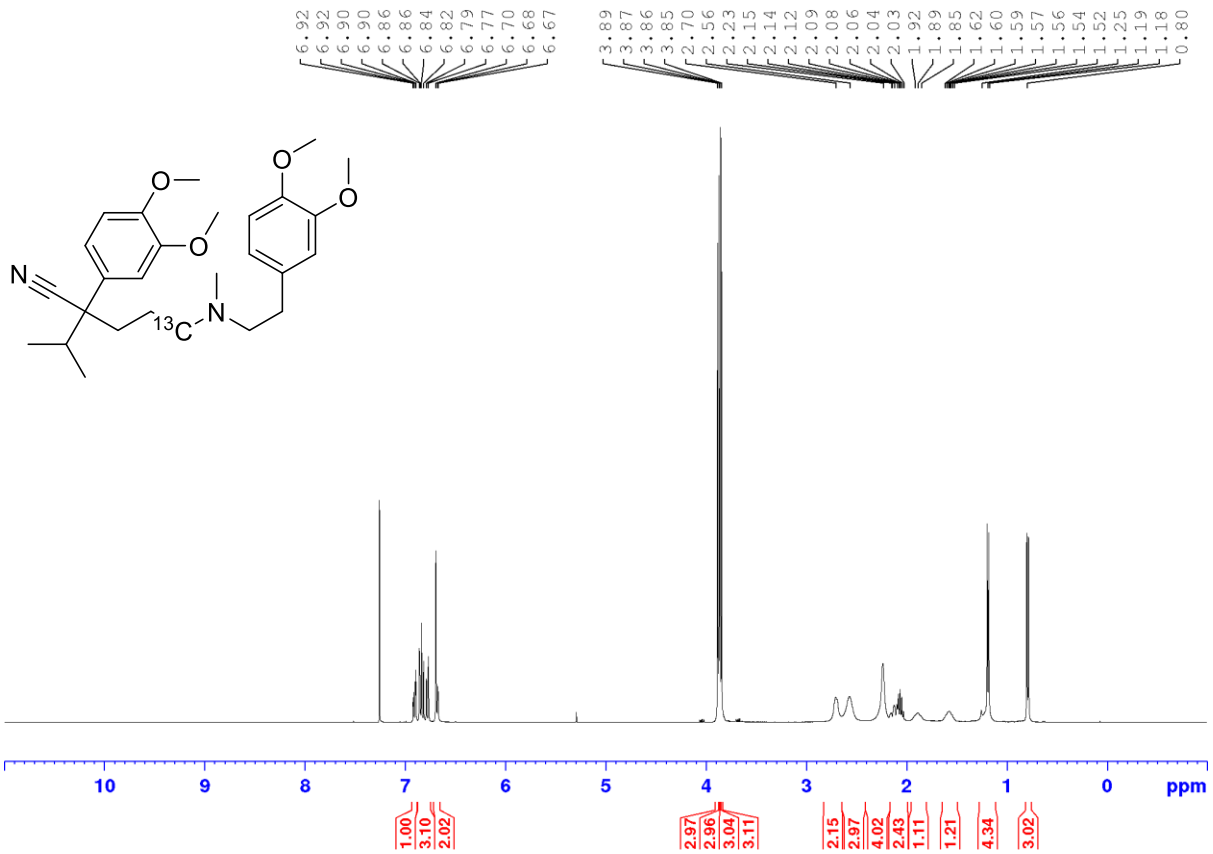


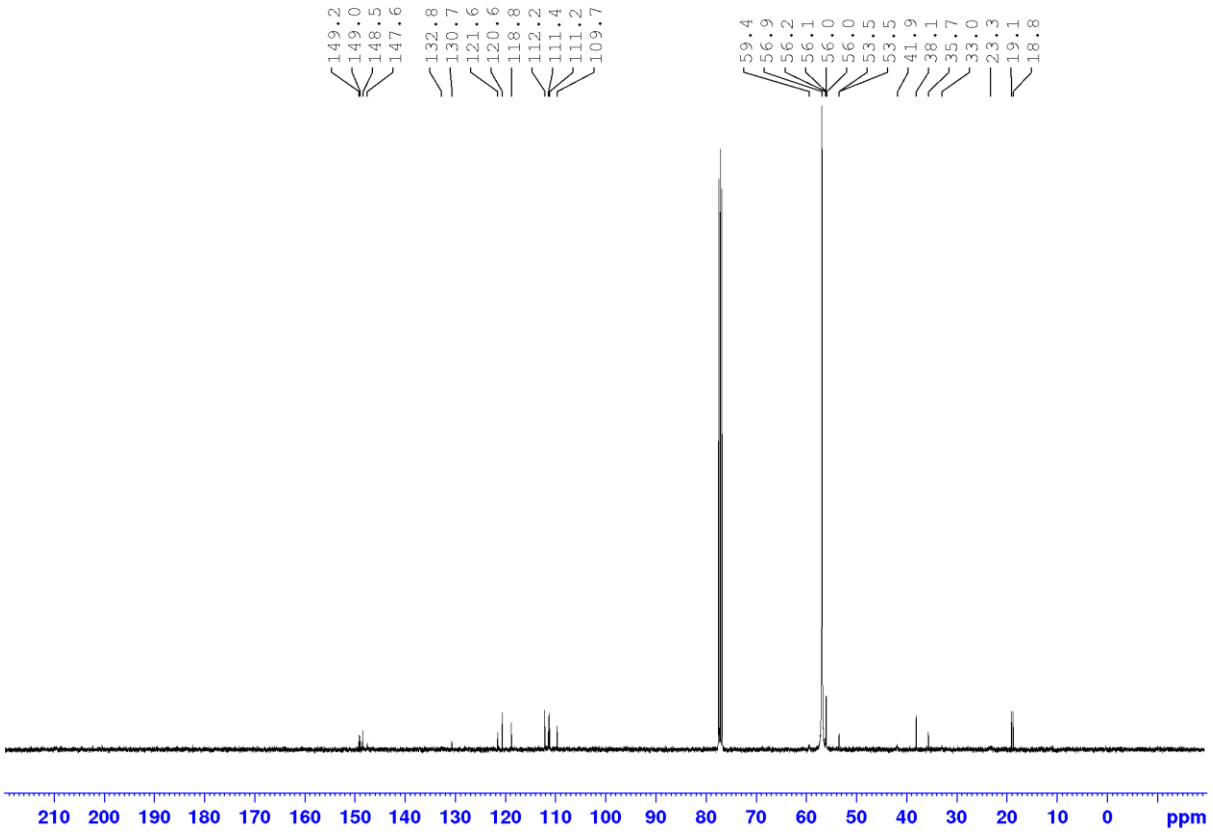
52-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



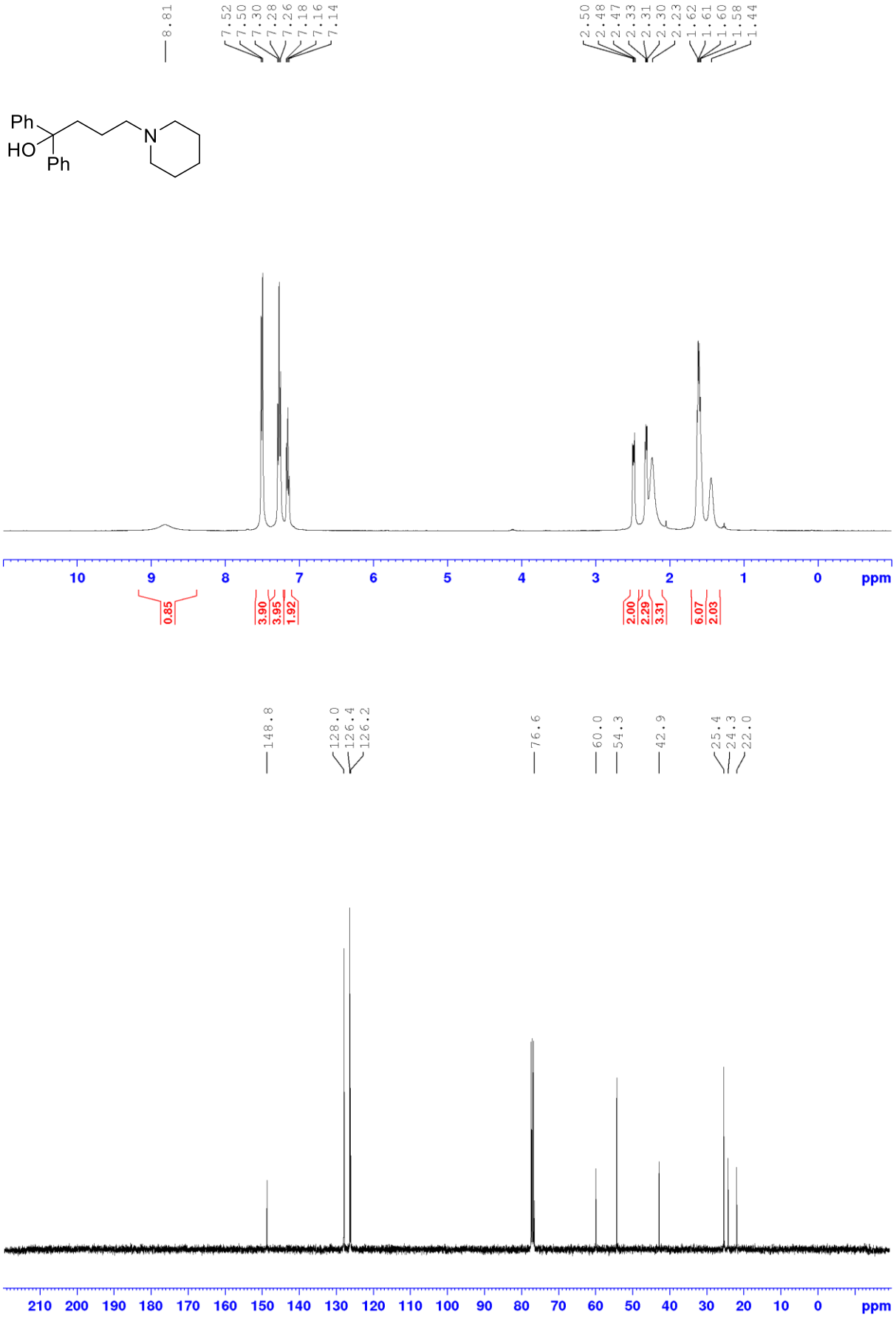


Verapamil-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

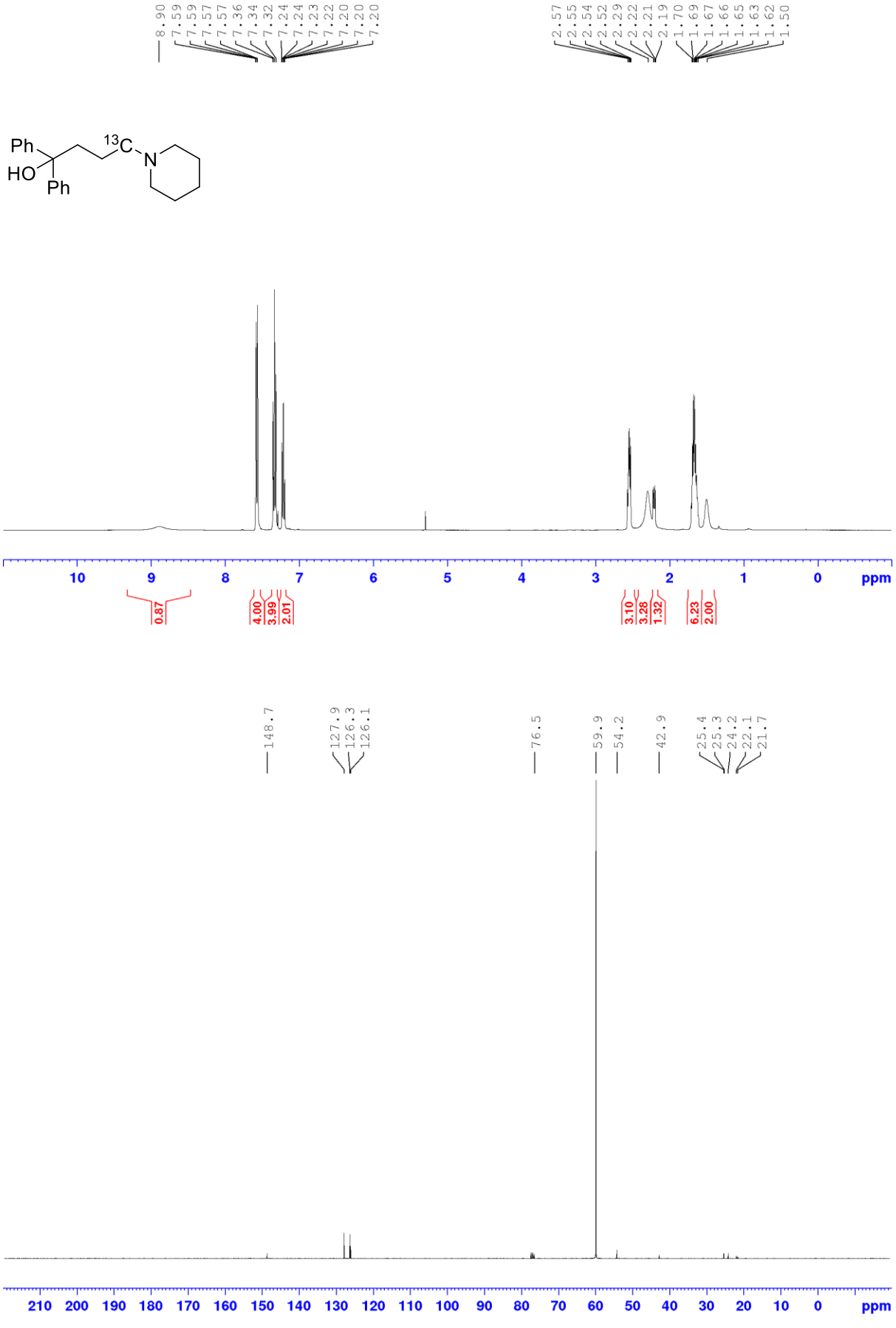




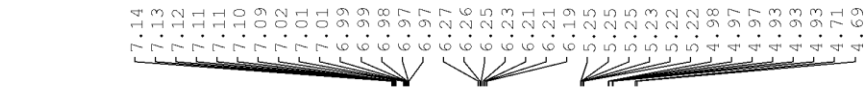
Diphenidol [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz in $CDCl_3$]

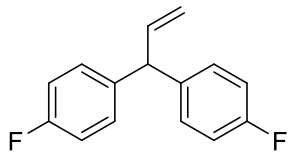


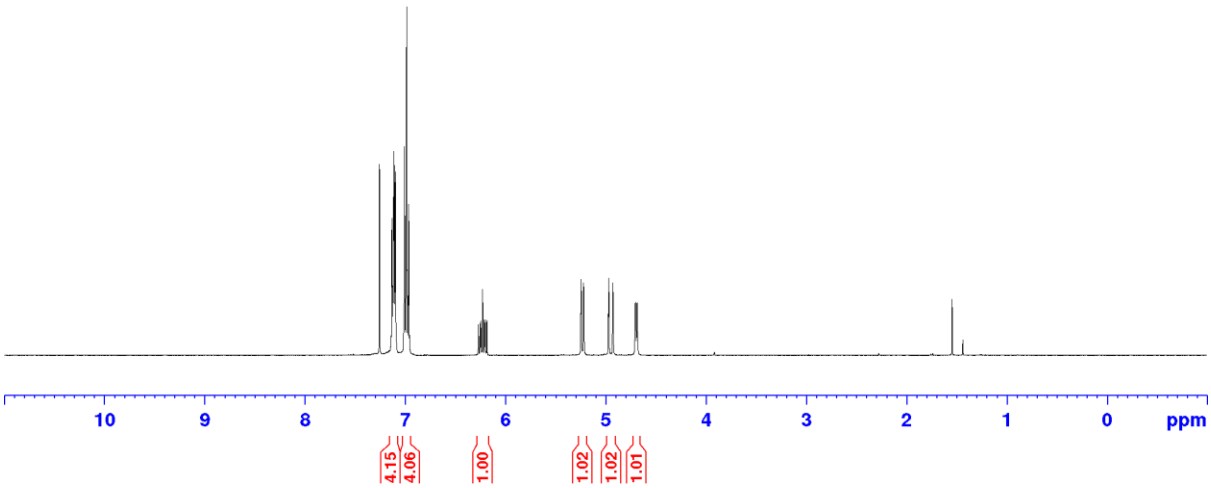
Diphenidol-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

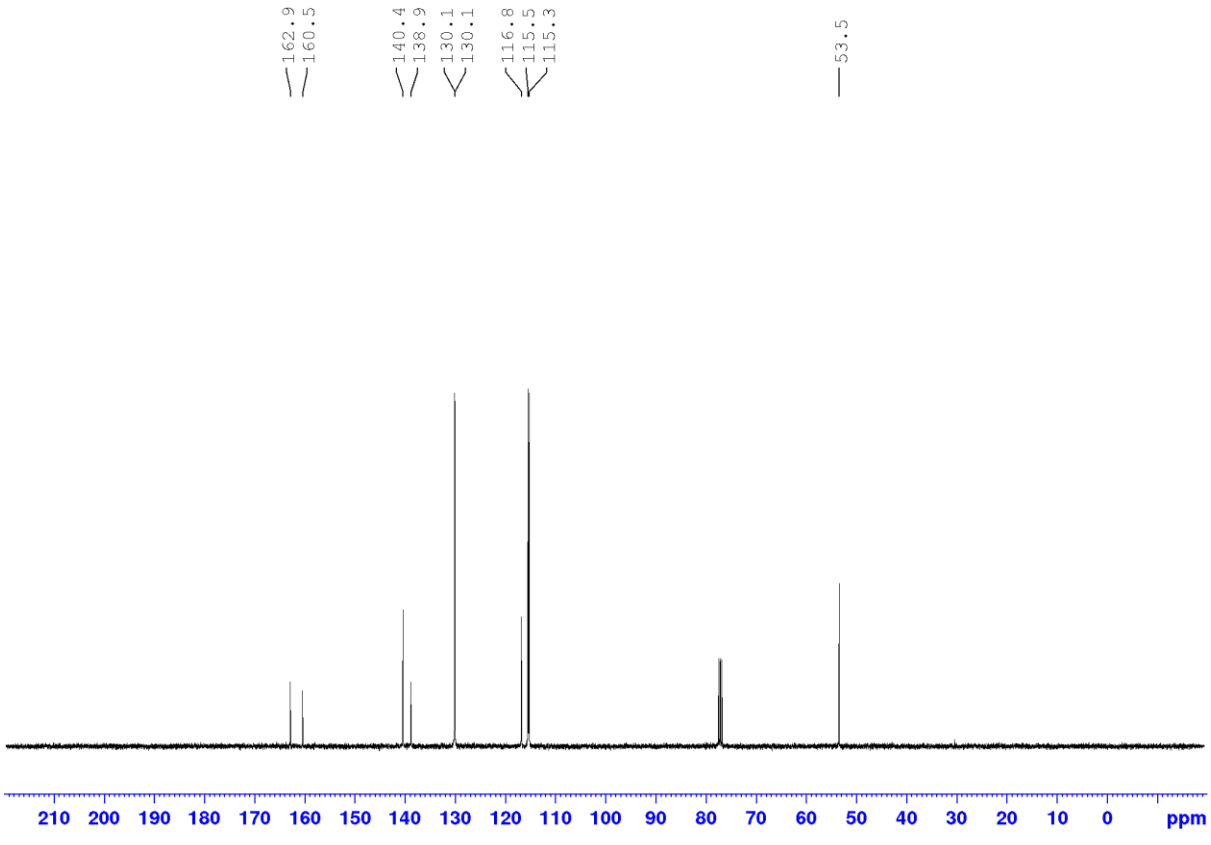


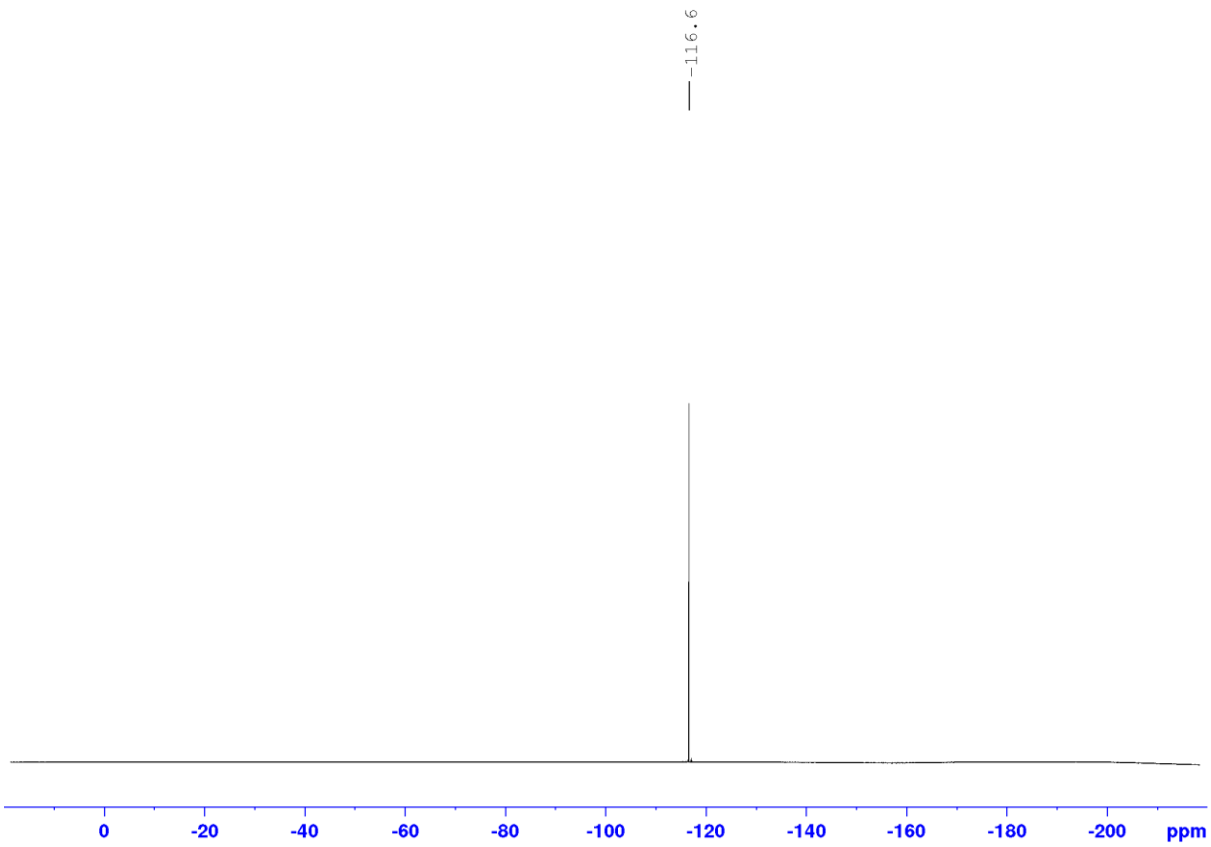
55 [^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F (376 MHz) in $CDCl_3$]



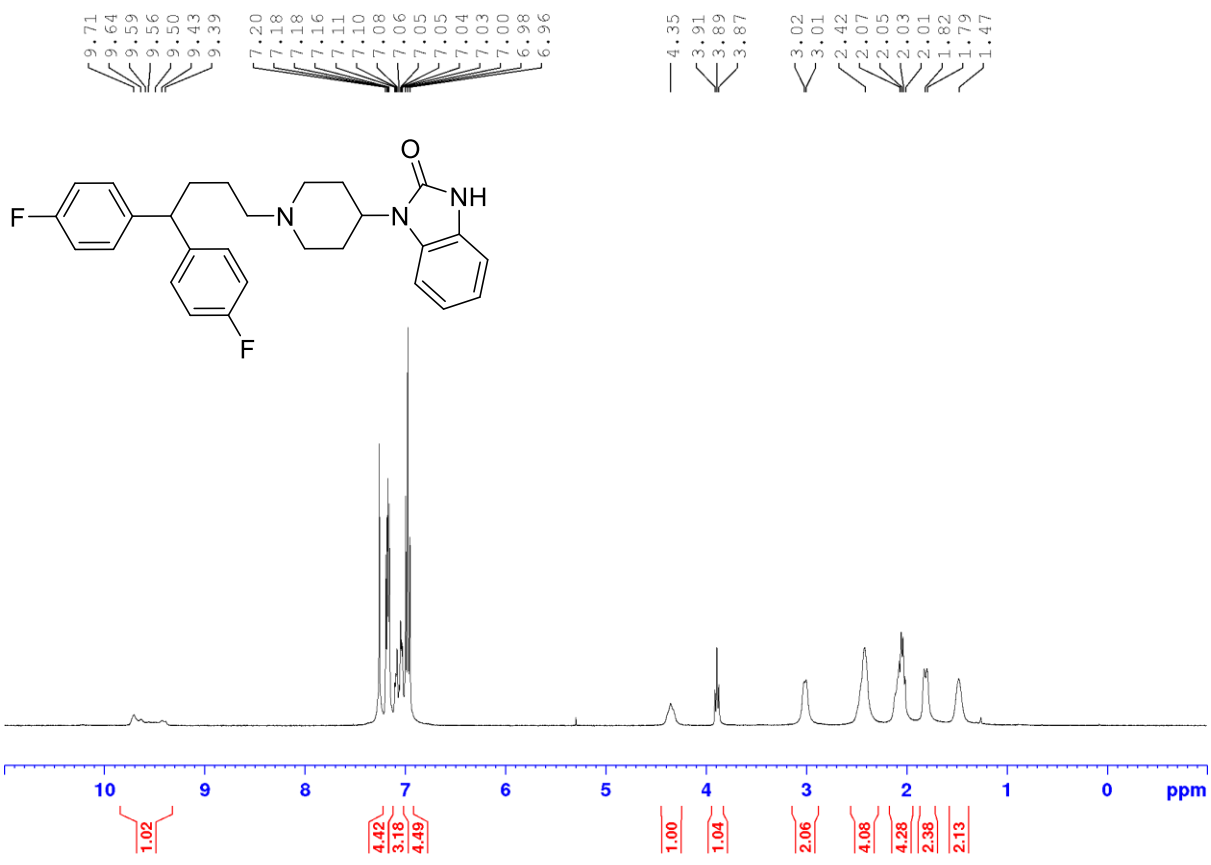


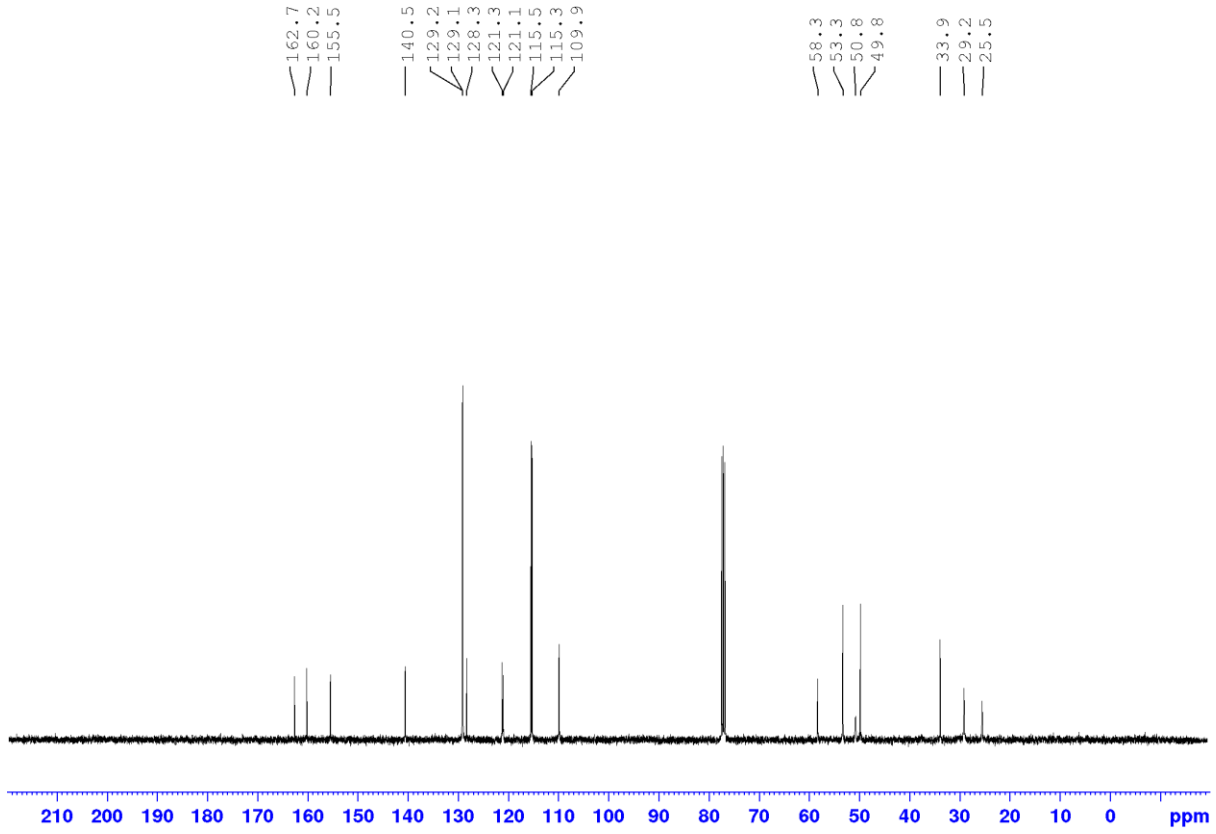






Pimozide [^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F (376 MHz) in $CDCl_3$]




162.7
160.2
155.5
140.5
129.2
129.1
128.3
121.3
121.1
115.5
115.3
109.9
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50.8
49.8
33.9
29.2
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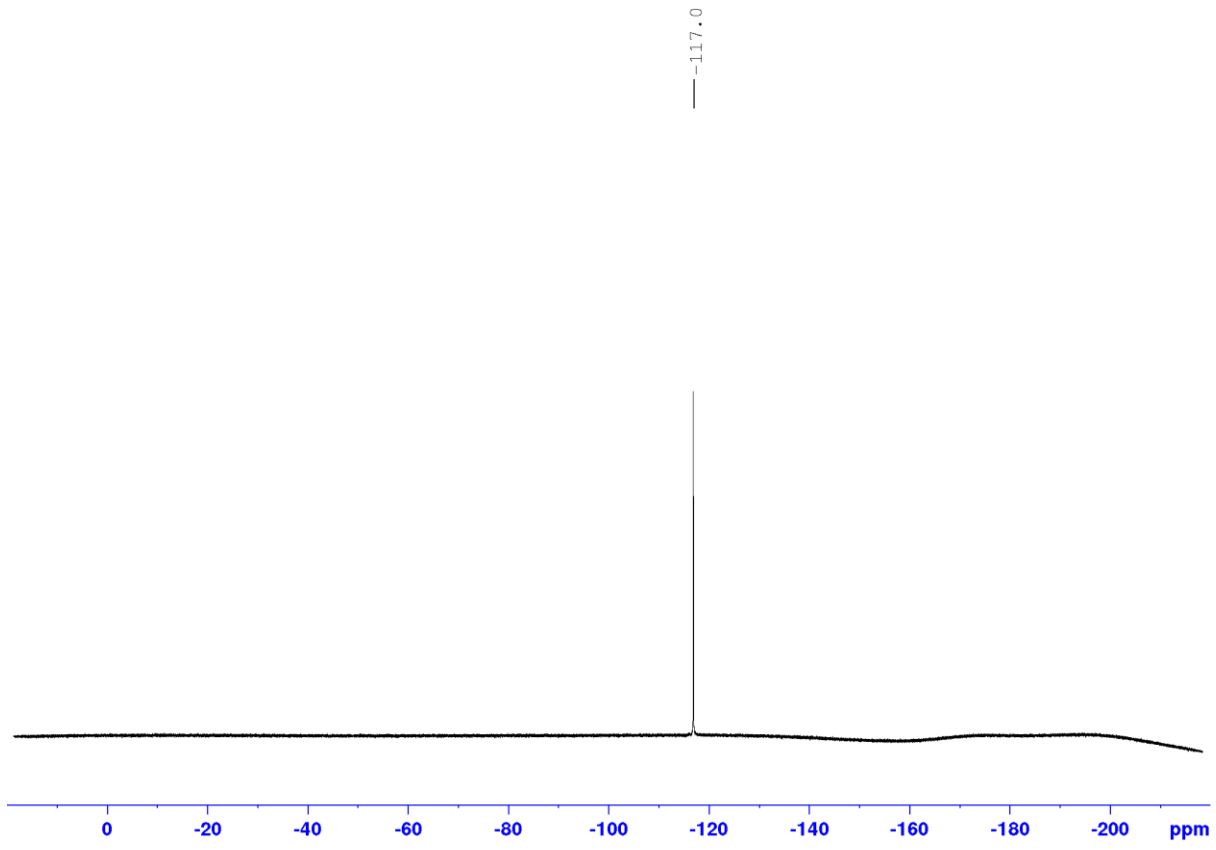
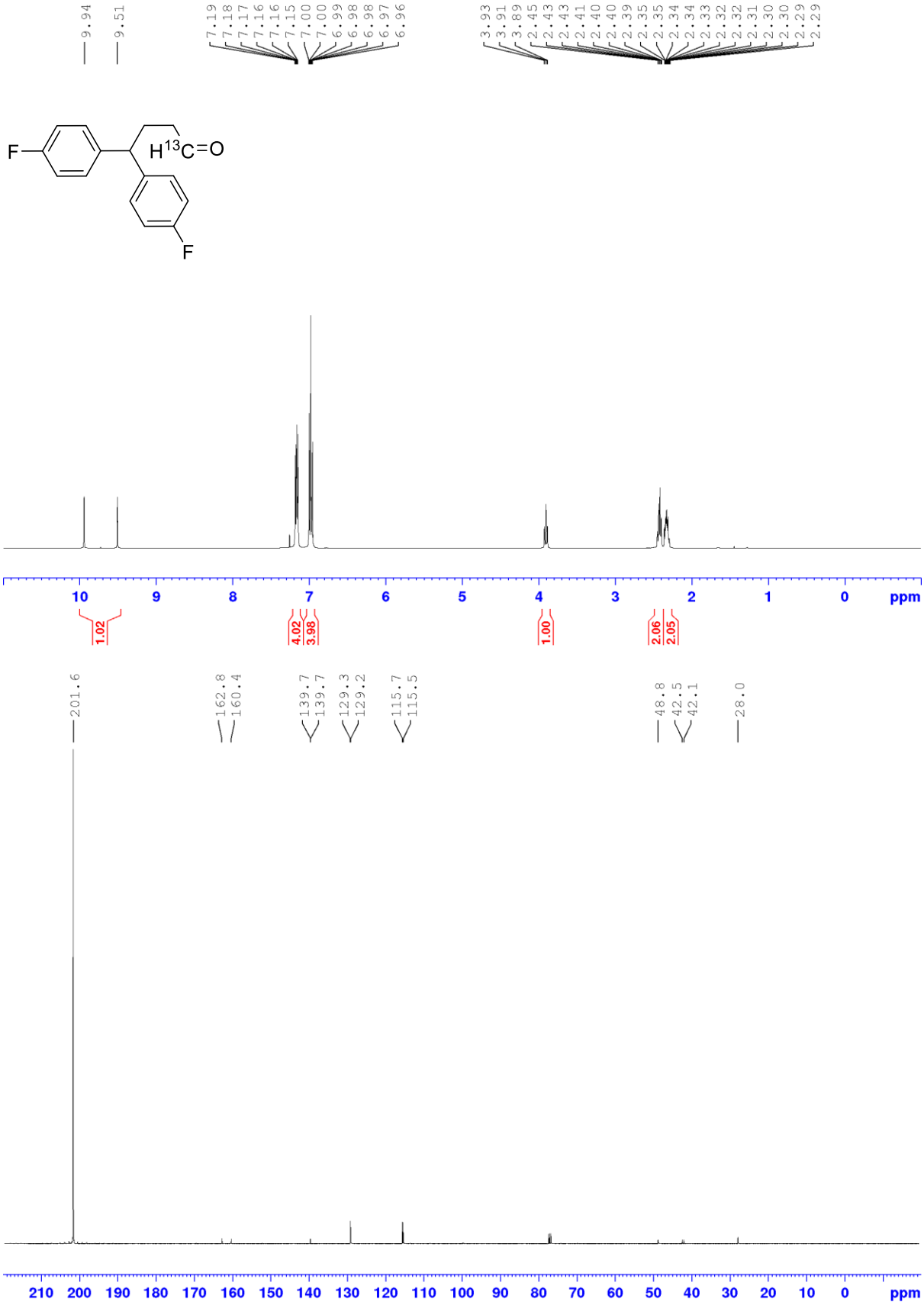
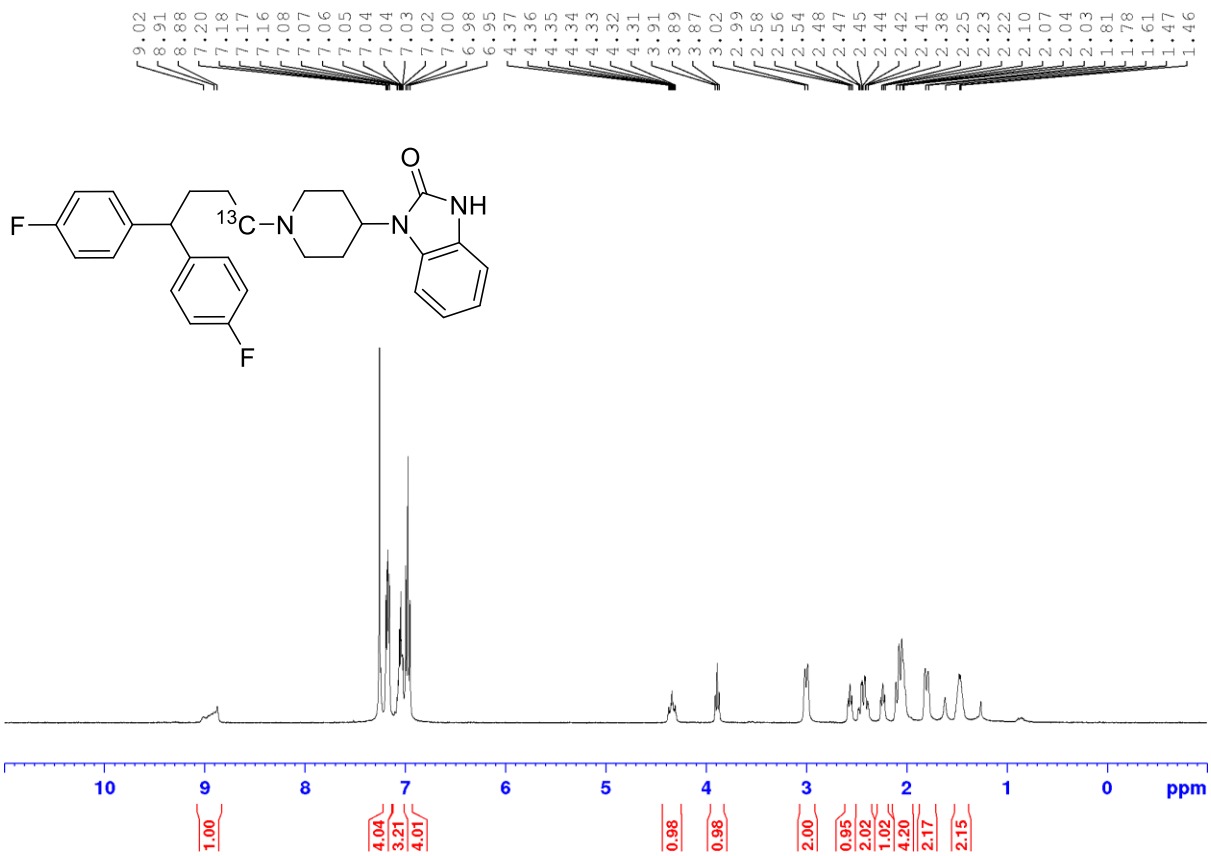
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

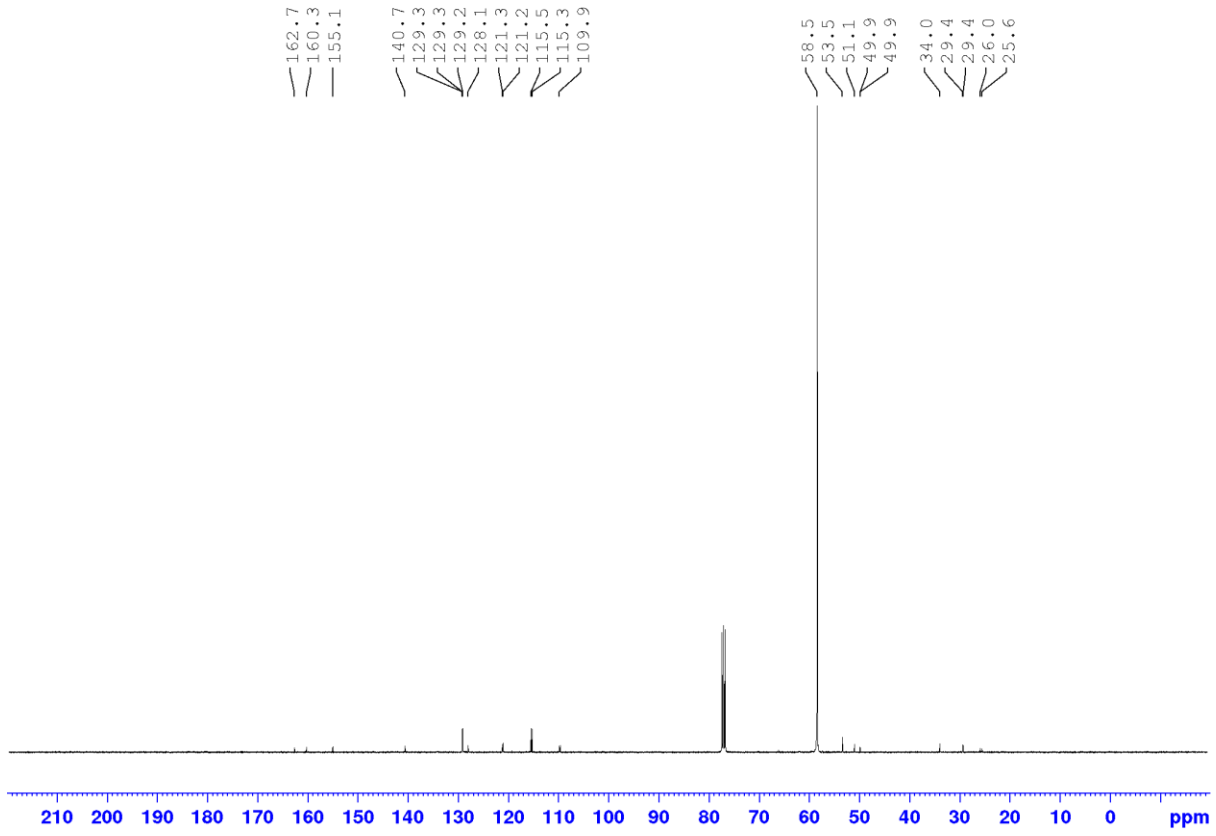

-117.0
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

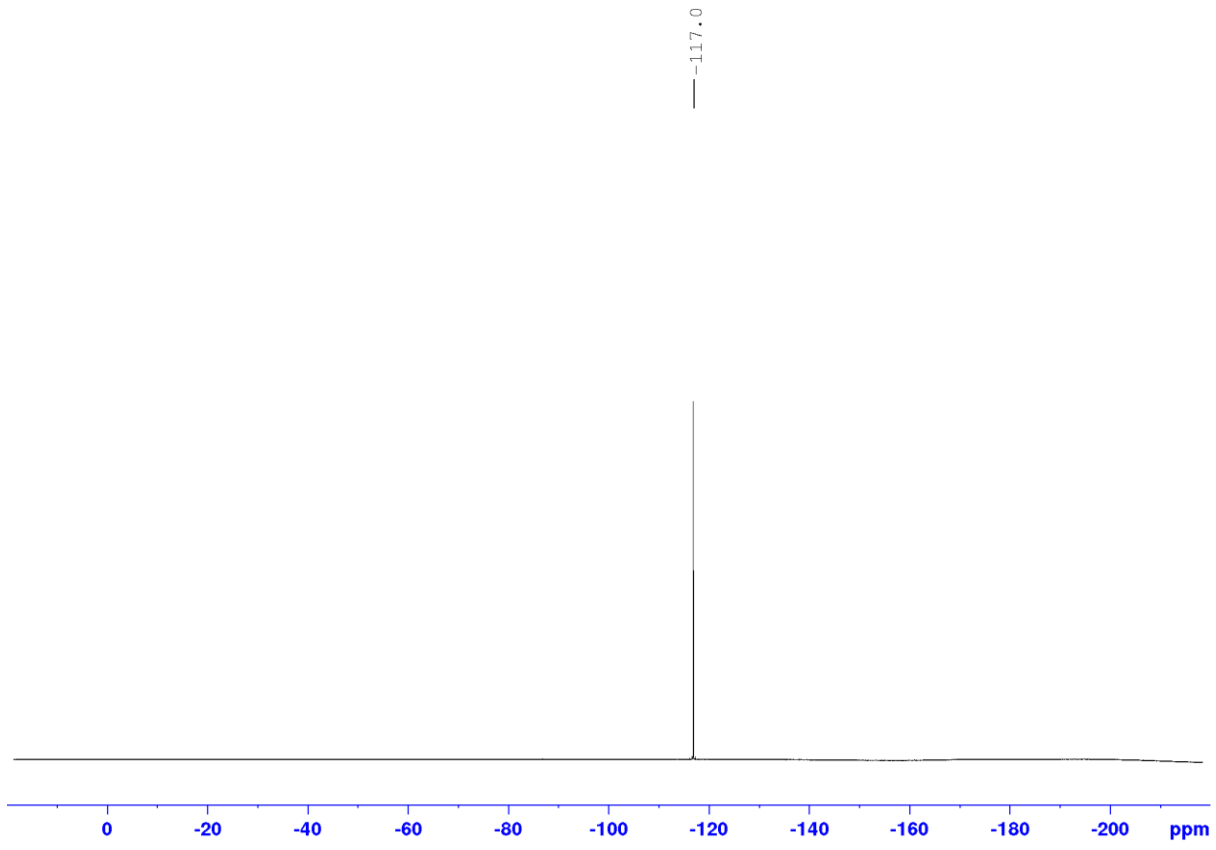
57-^{13}C [^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F (376 MHz) in $CDCl_3$]



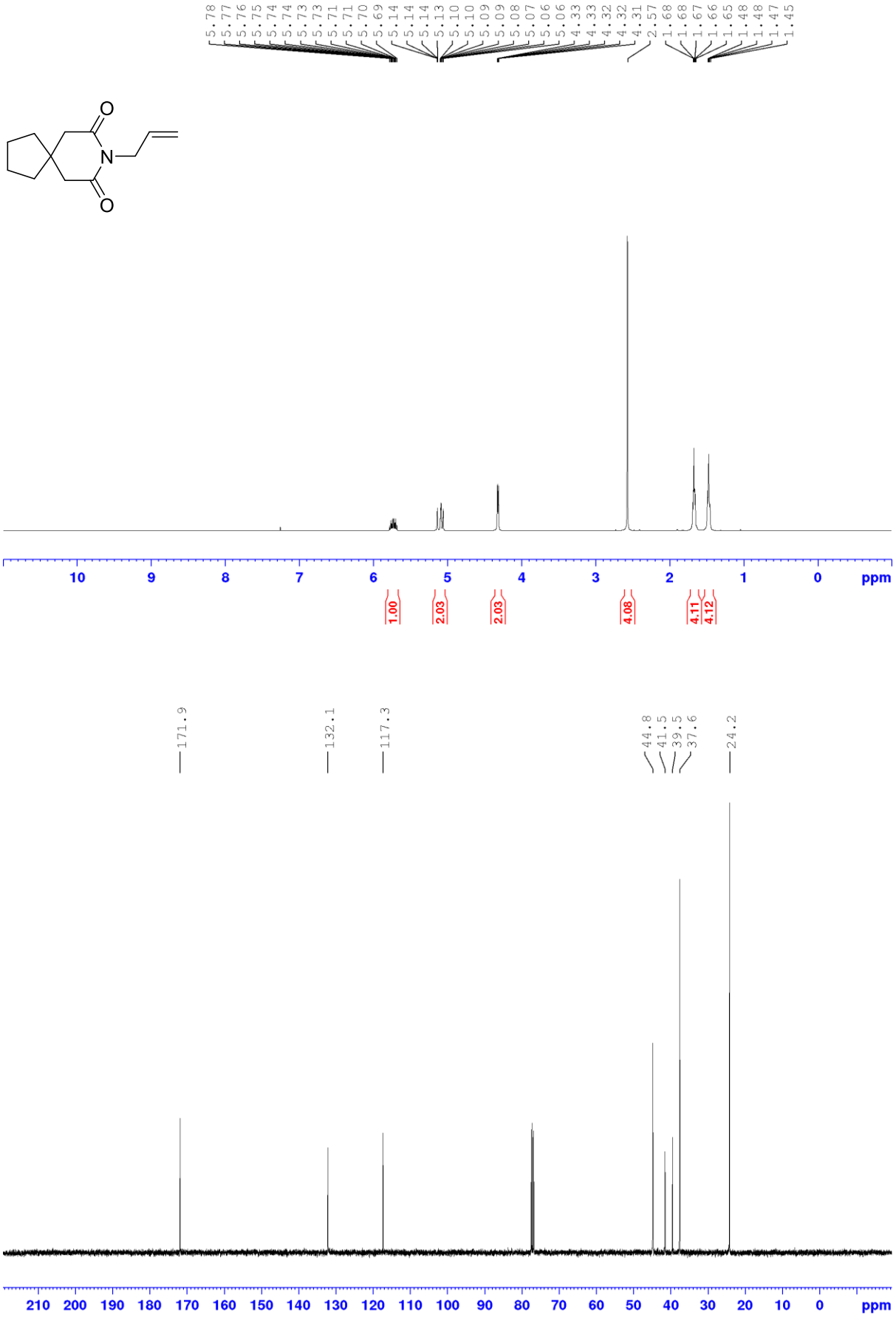
Pimozide-^{13}C [^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz) and ^{19}F (376 MHz) in $CDCl_3$]



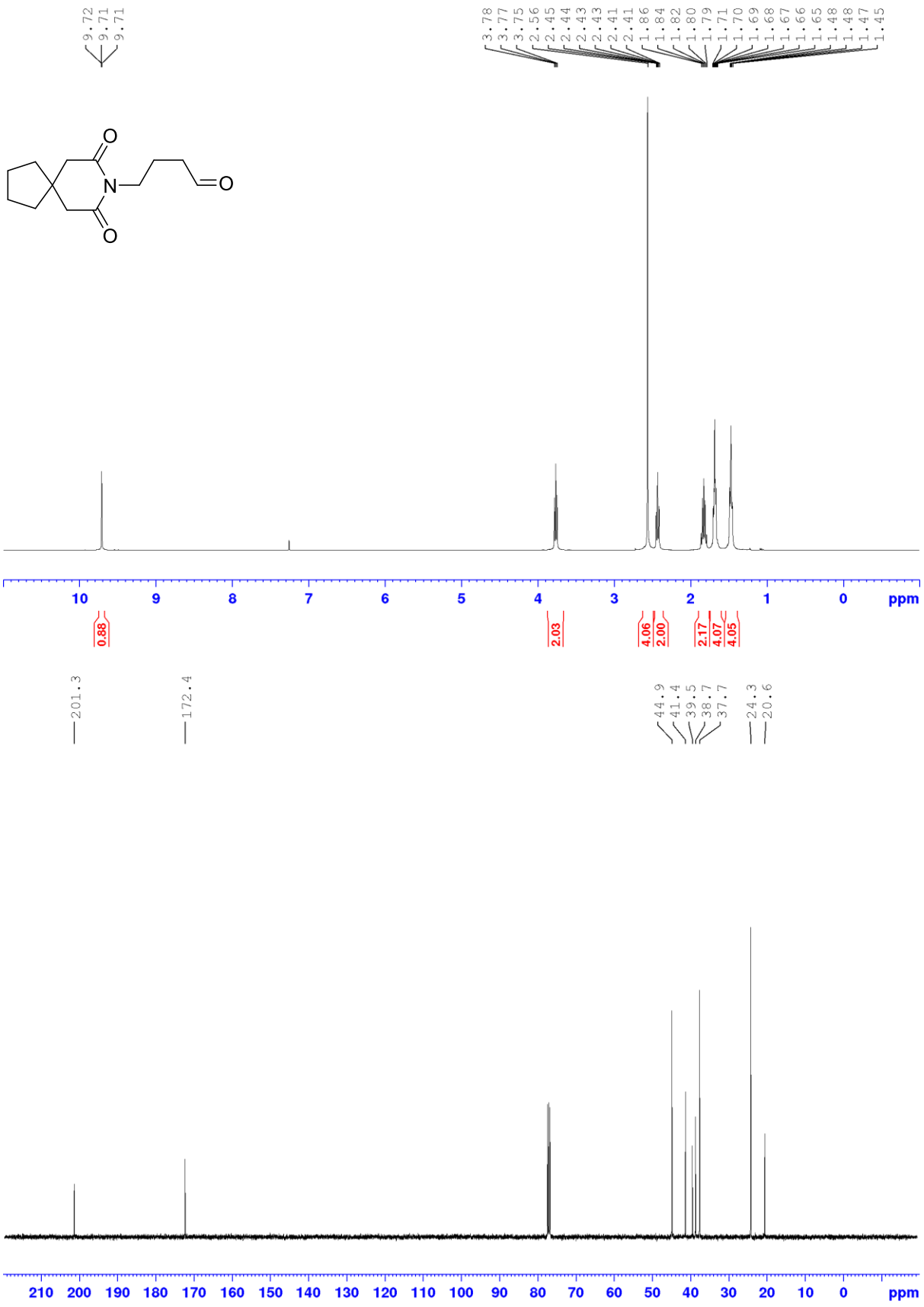

162.7
160.3
155.1
140.7
129.3
129.3
129.2
128.1
121.3
121.2
115.5
115.3
109.9
58.5
53.5
51.1
49.9
49.9
34.0
29.4
29.4
26.0
25.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


-117.0
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm

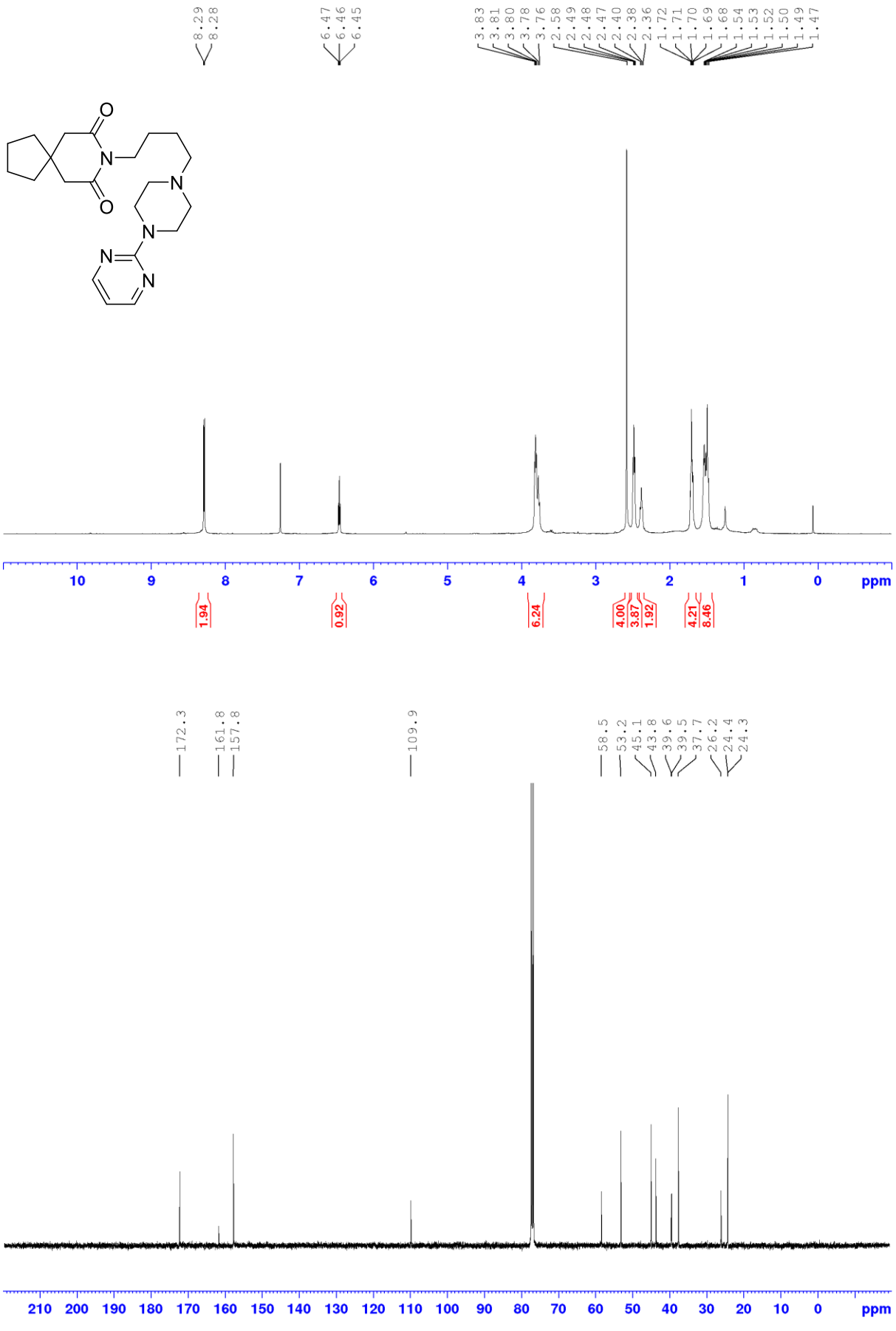
58 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



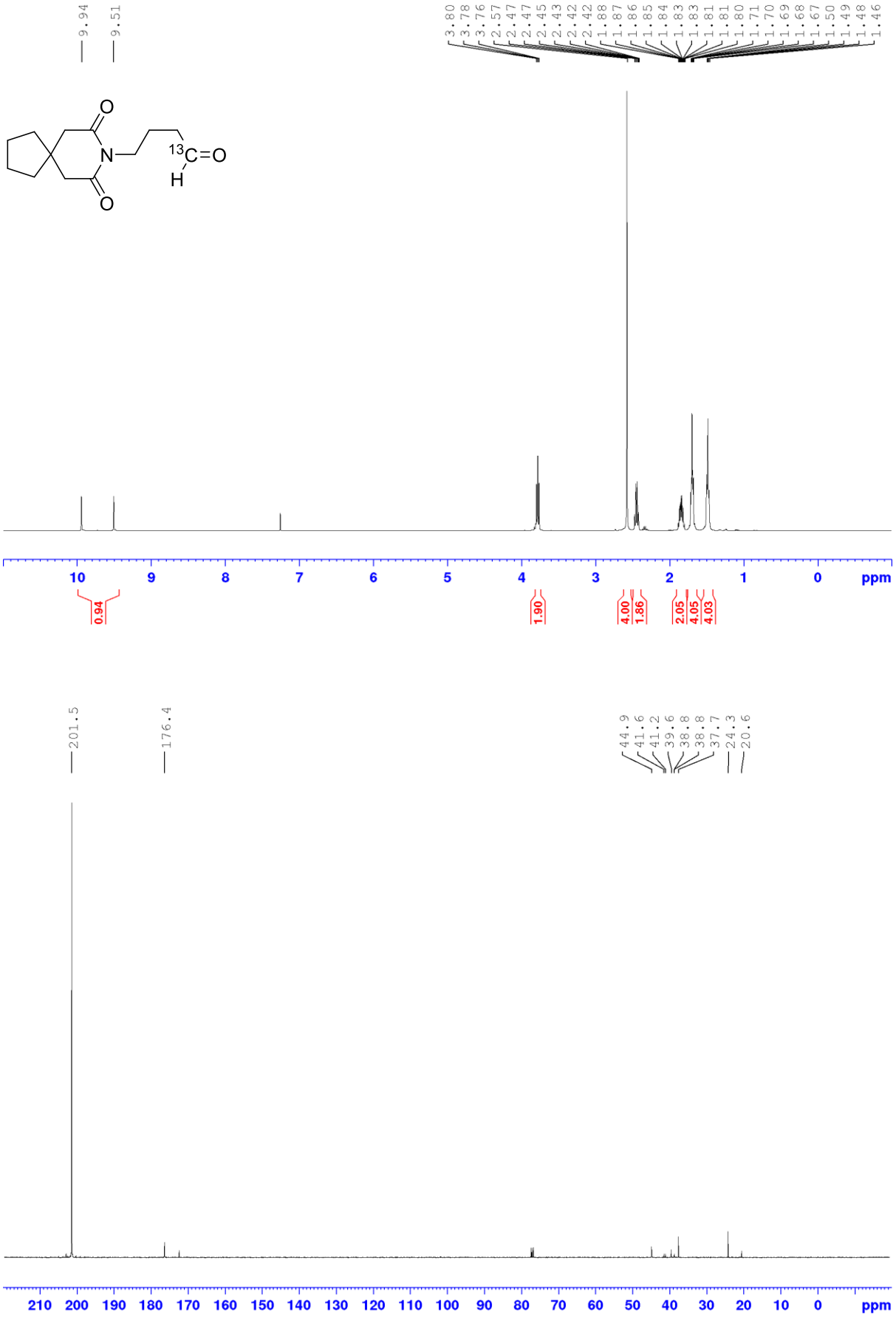
59 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



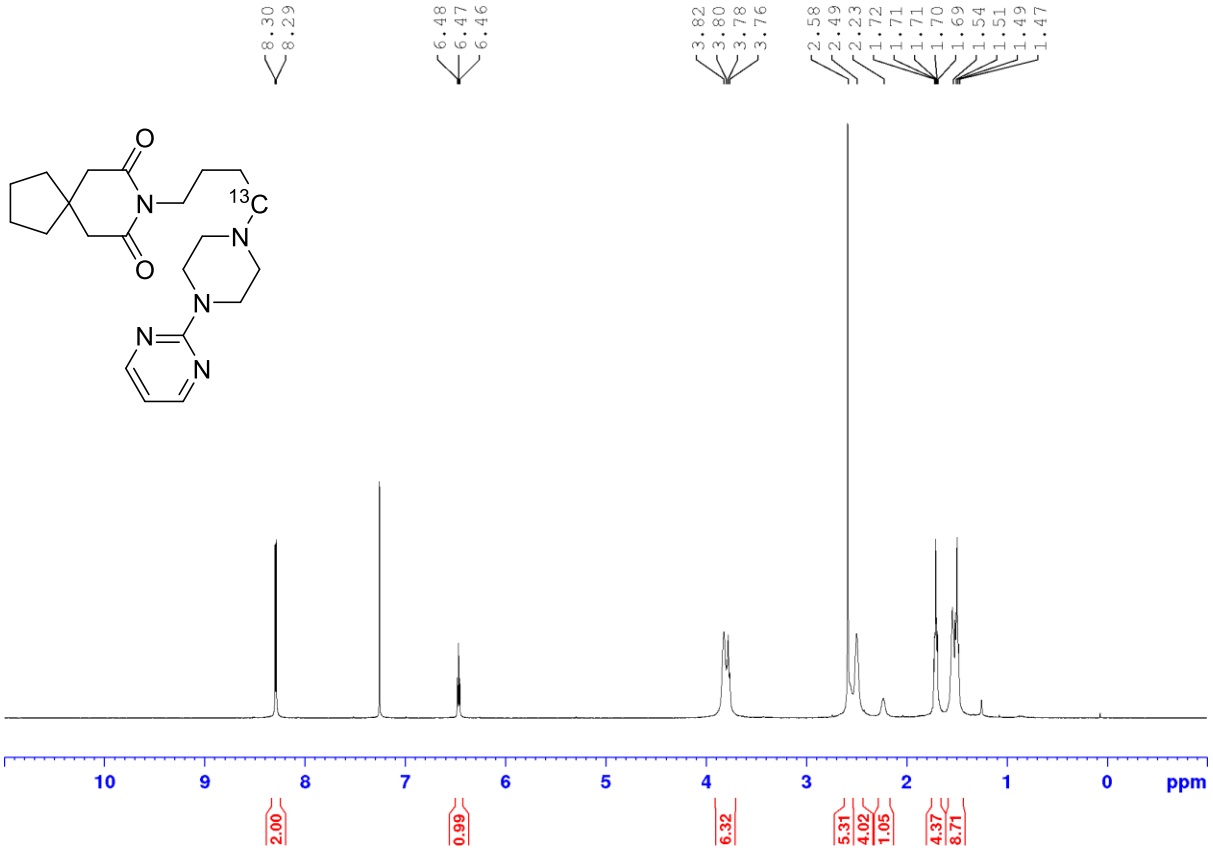
Buspirone [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

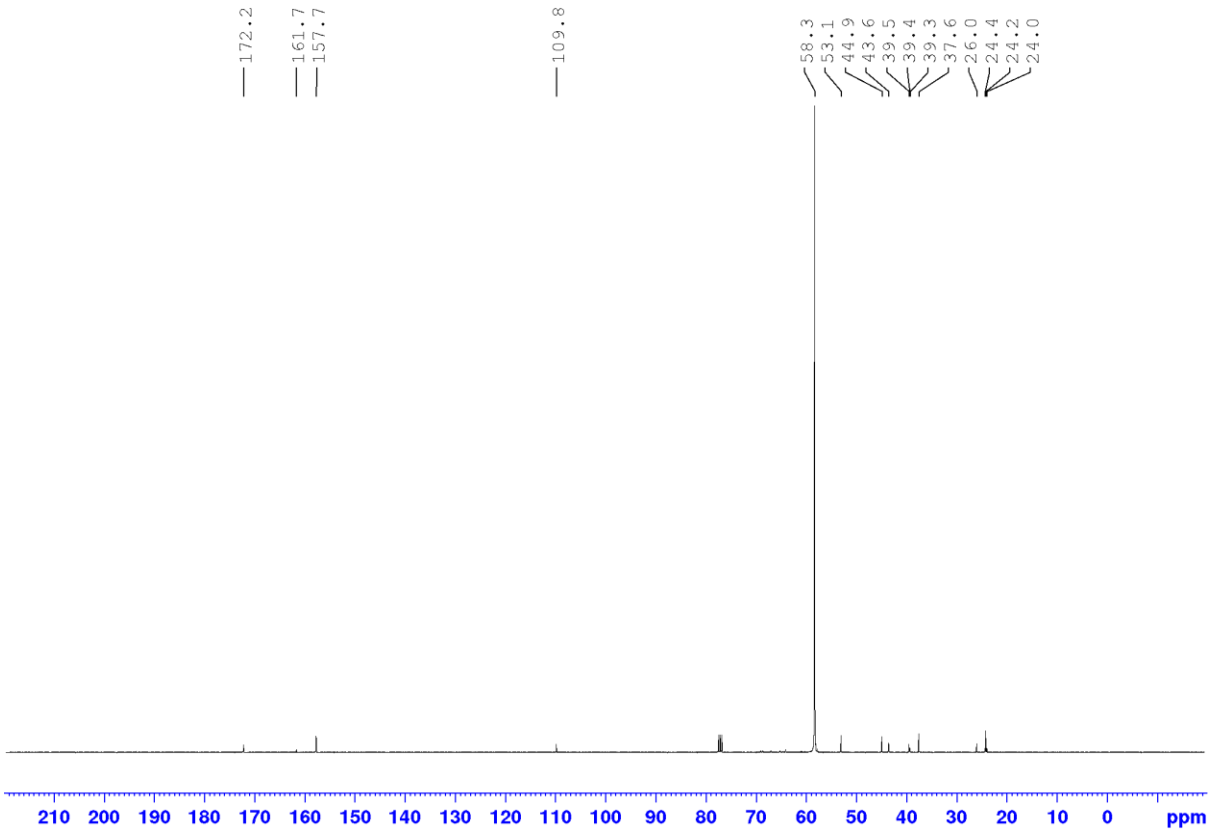


59-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

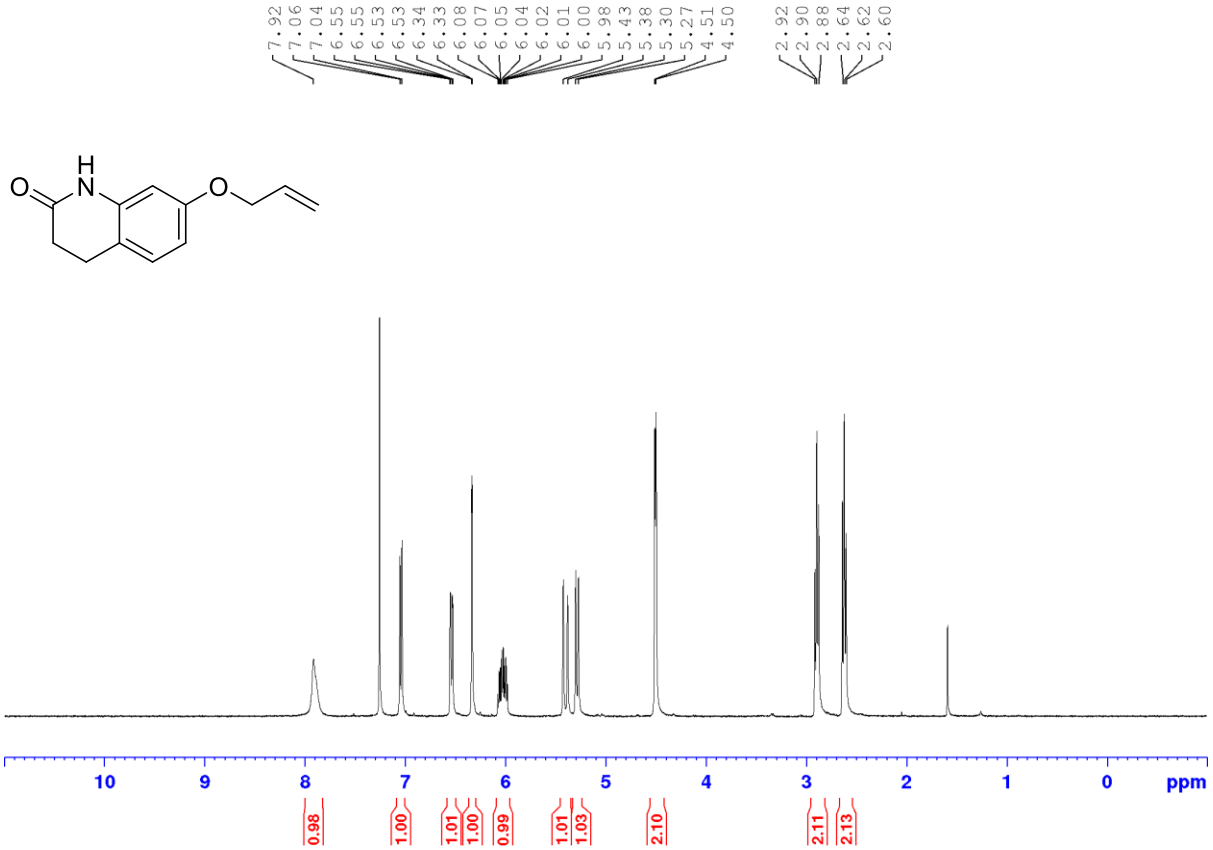


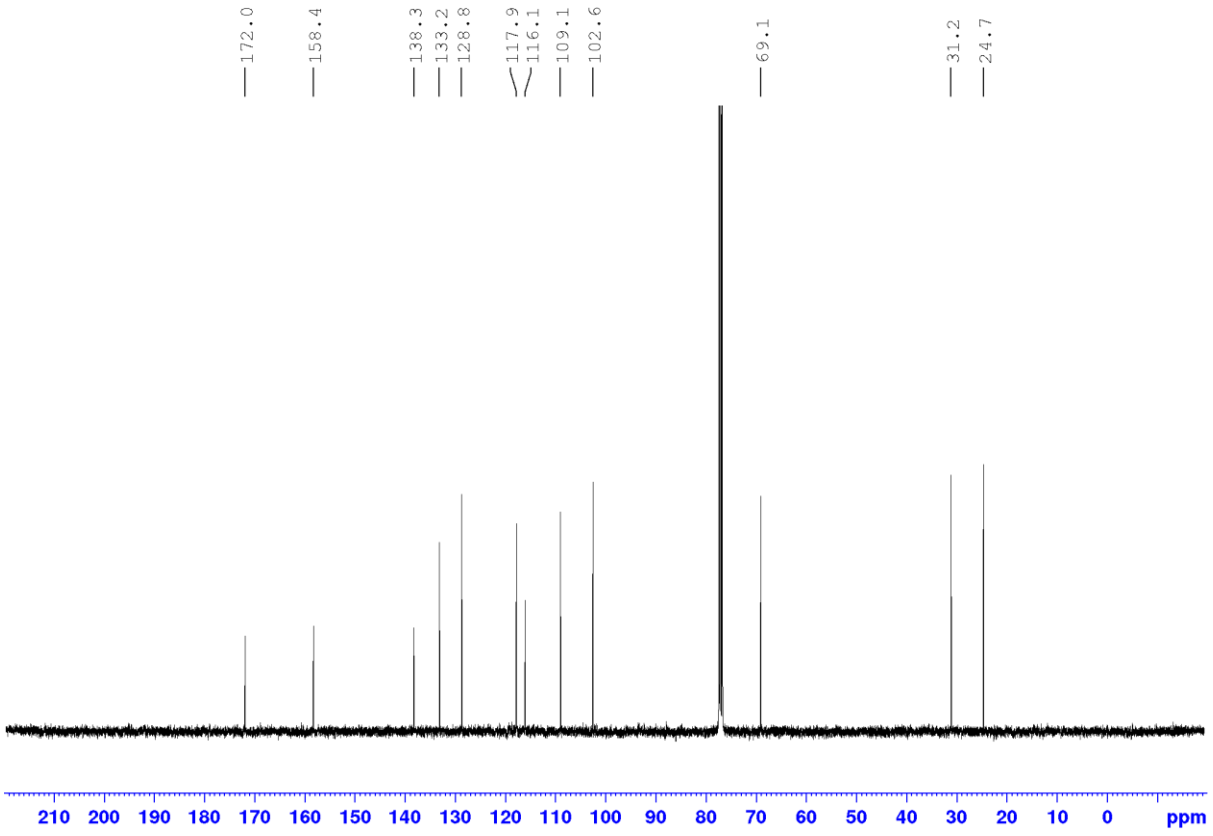
Buspirone-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



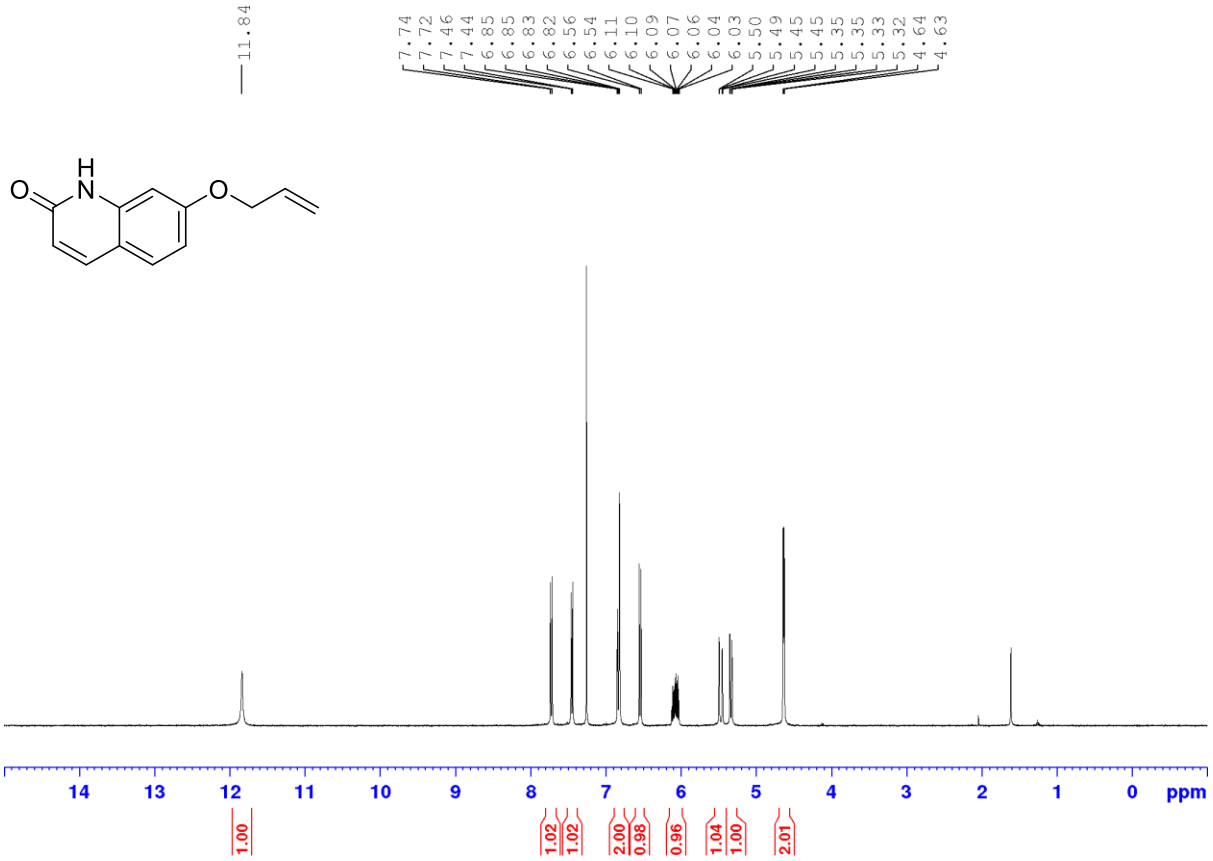


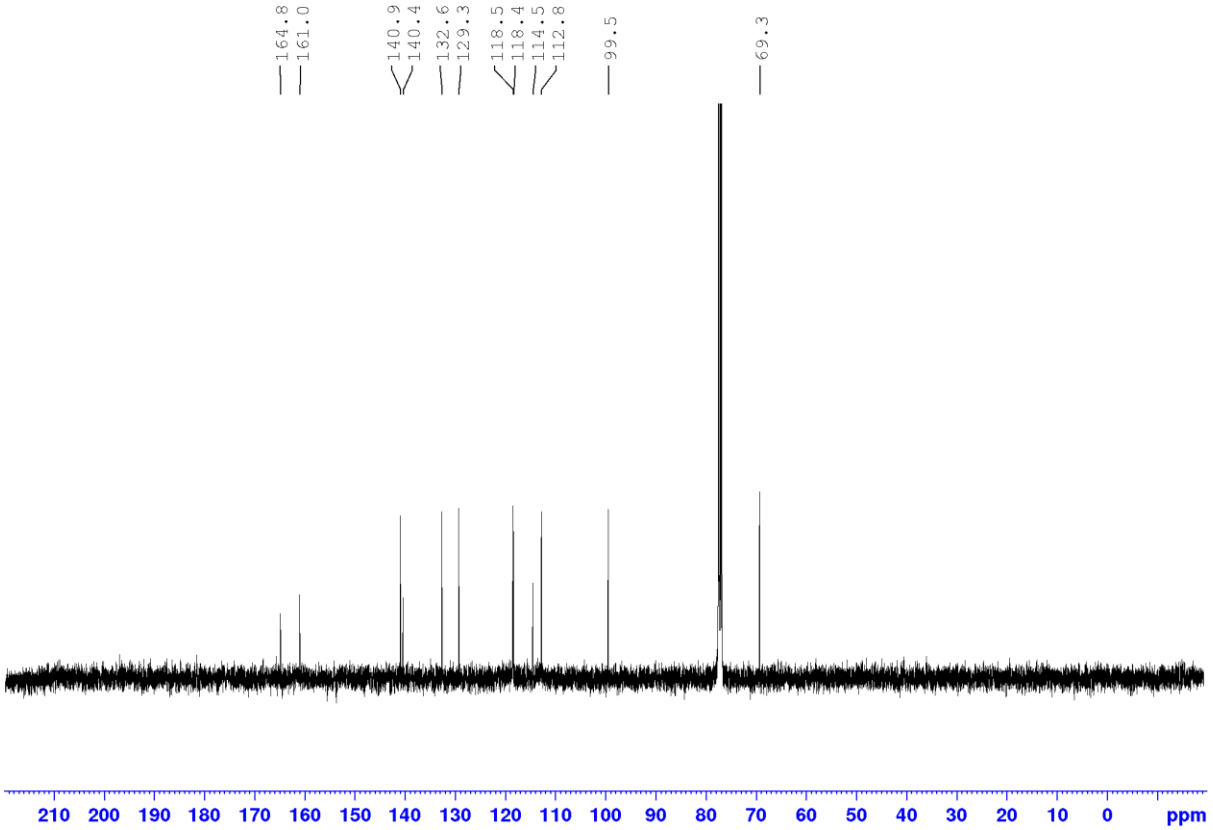
60 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



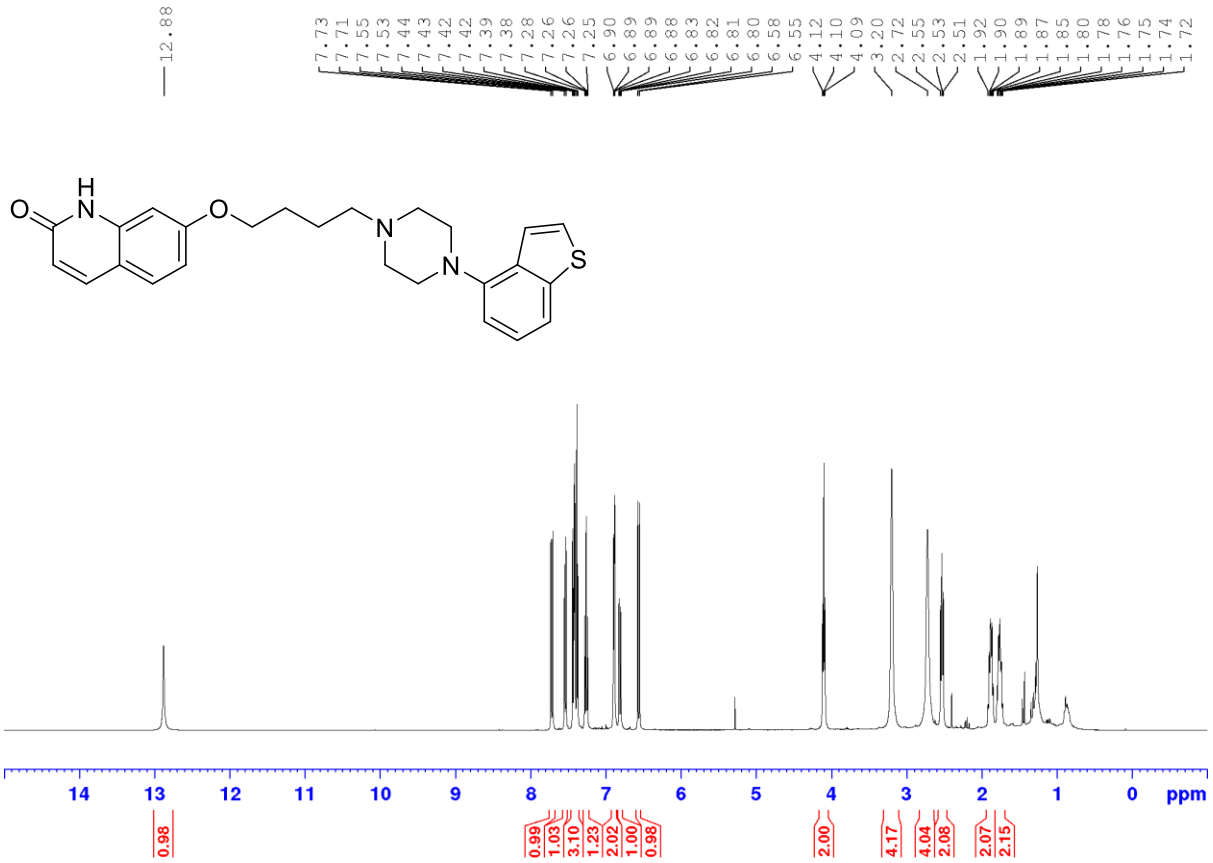


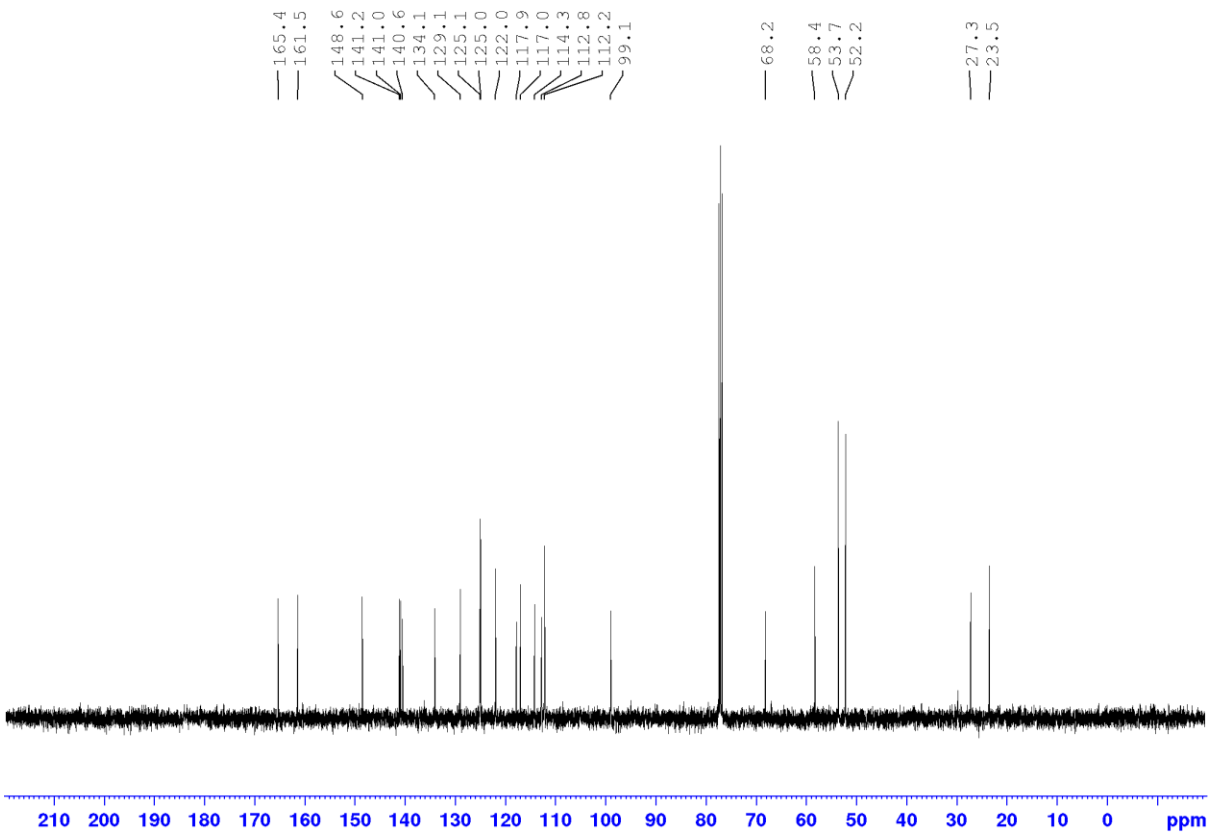
61 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



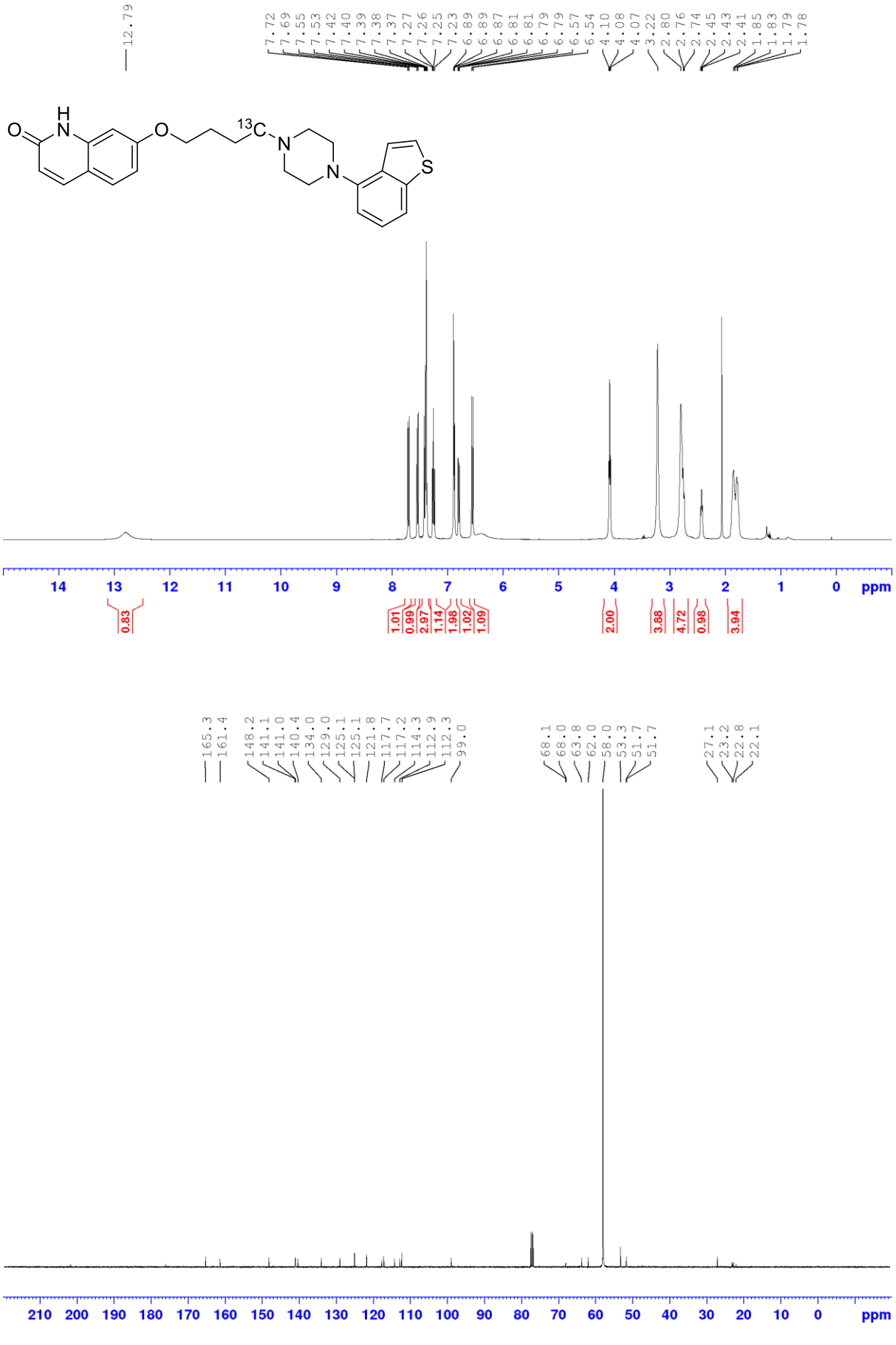


Brexiprazole [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

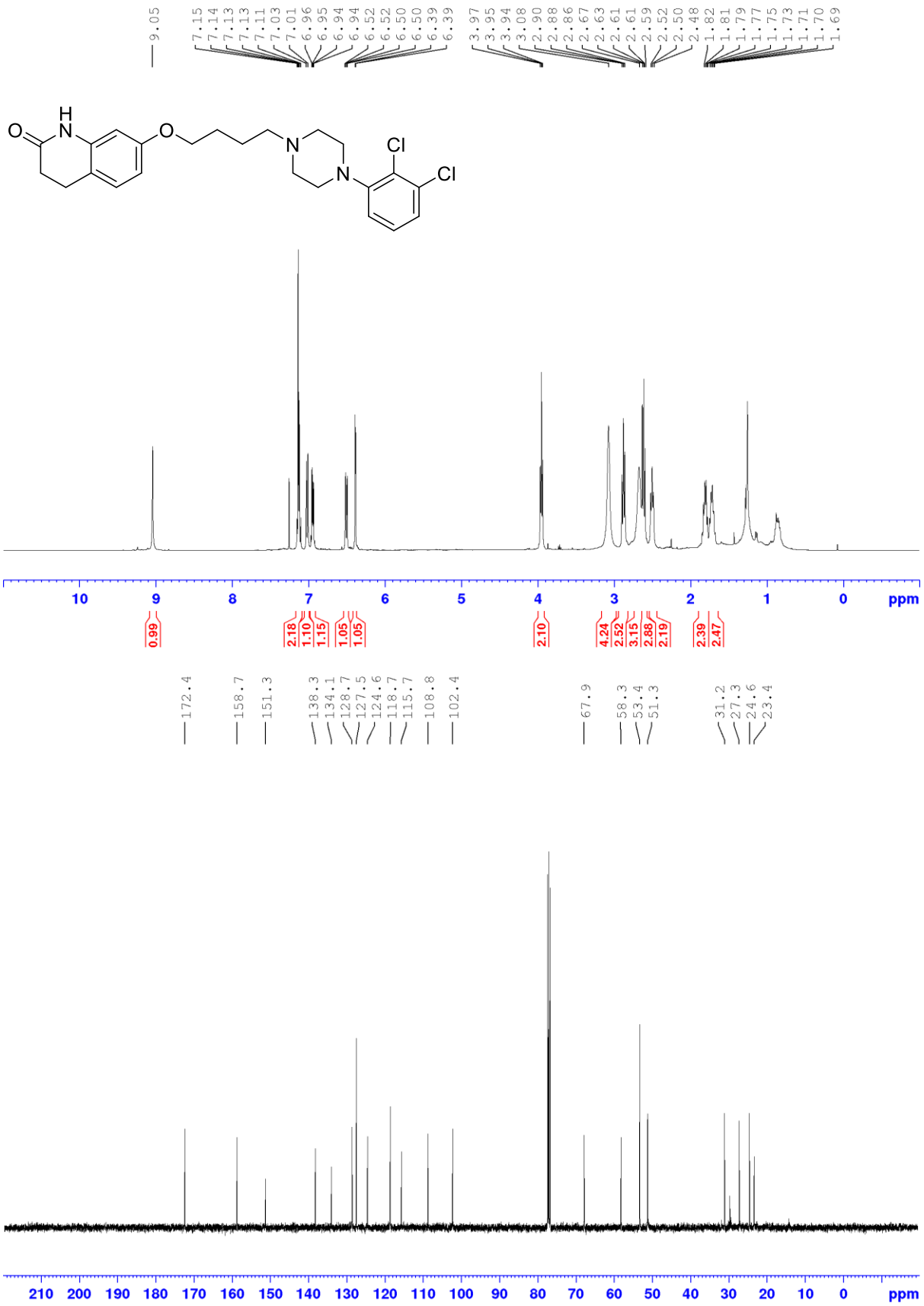




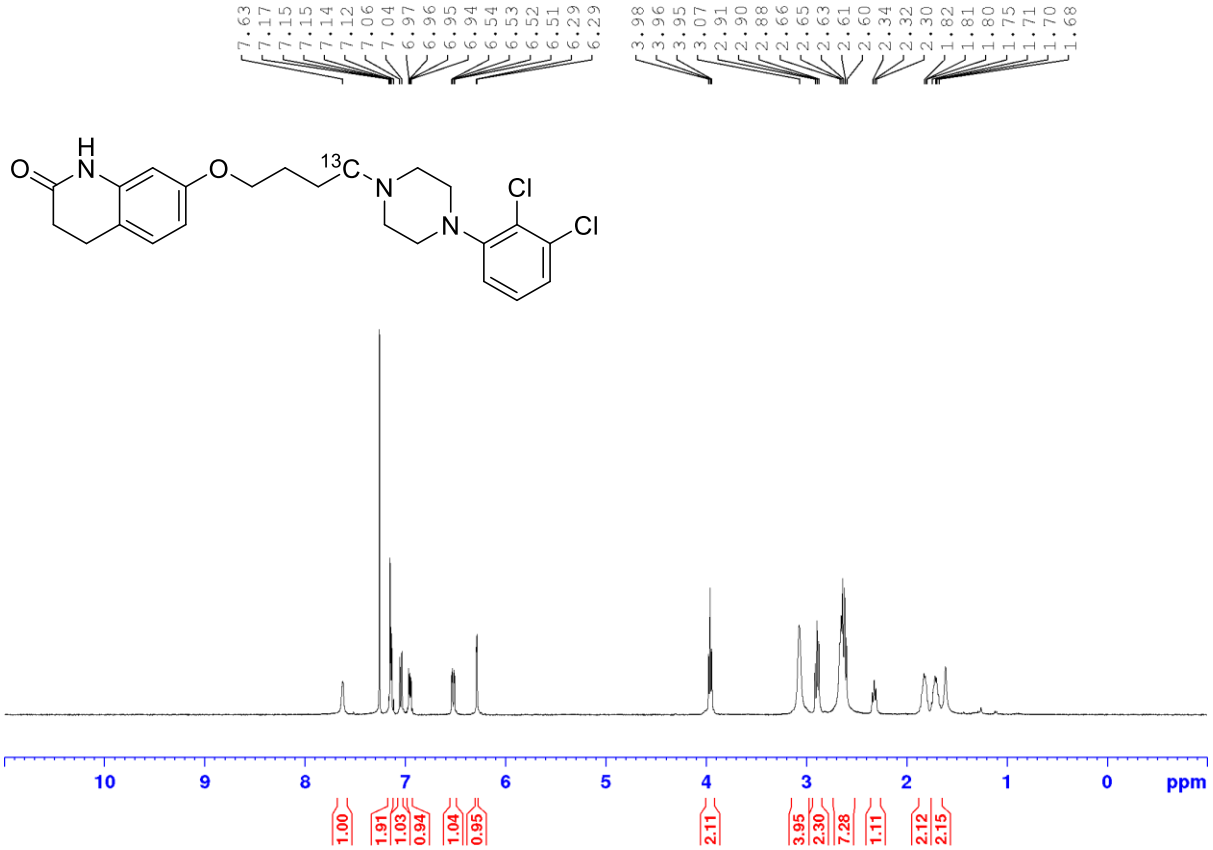
Brexiprazole-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

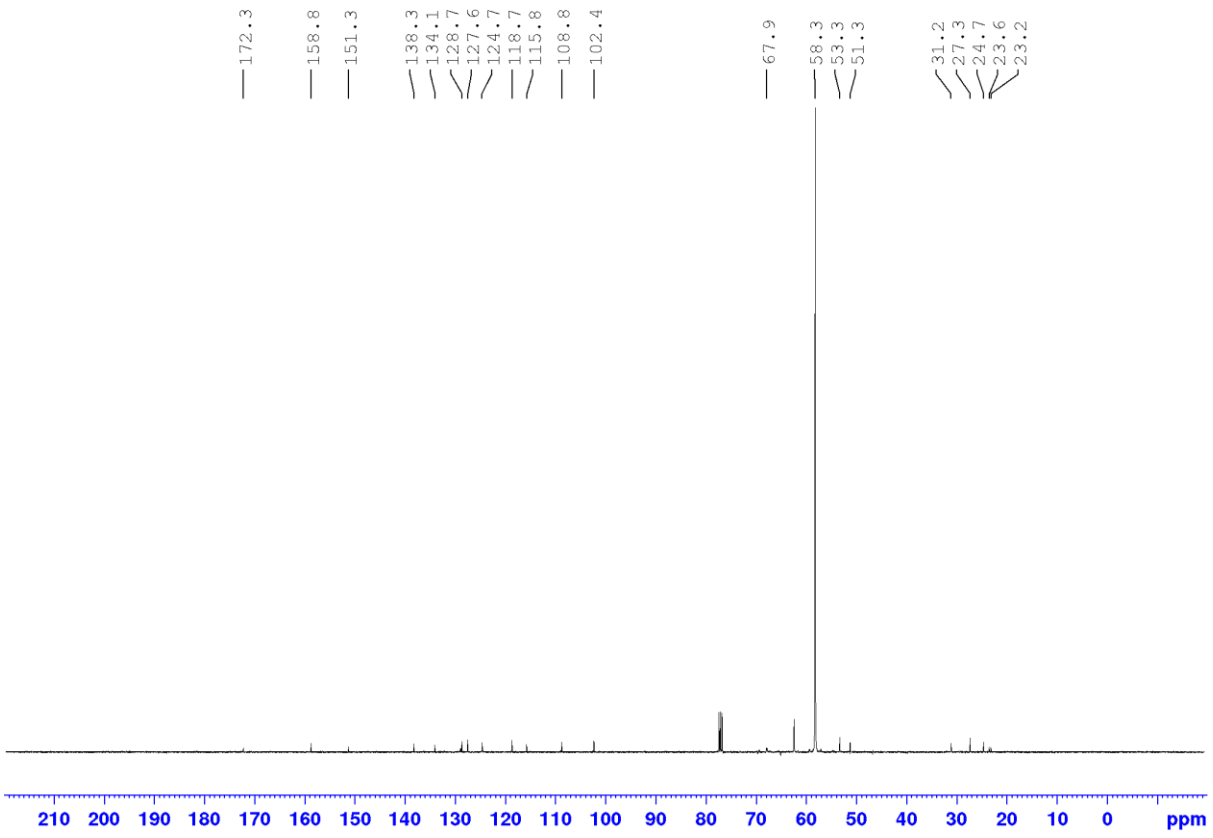


Aripiprazole [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

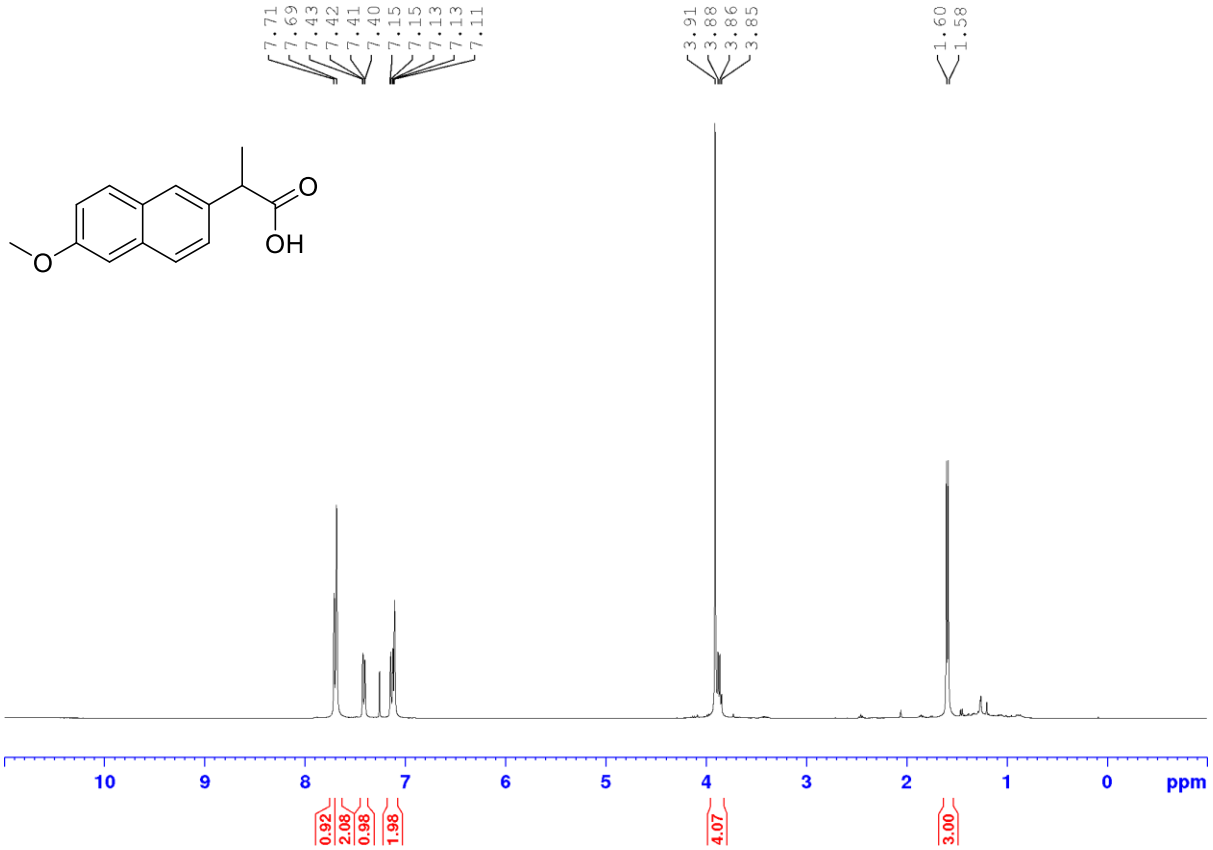


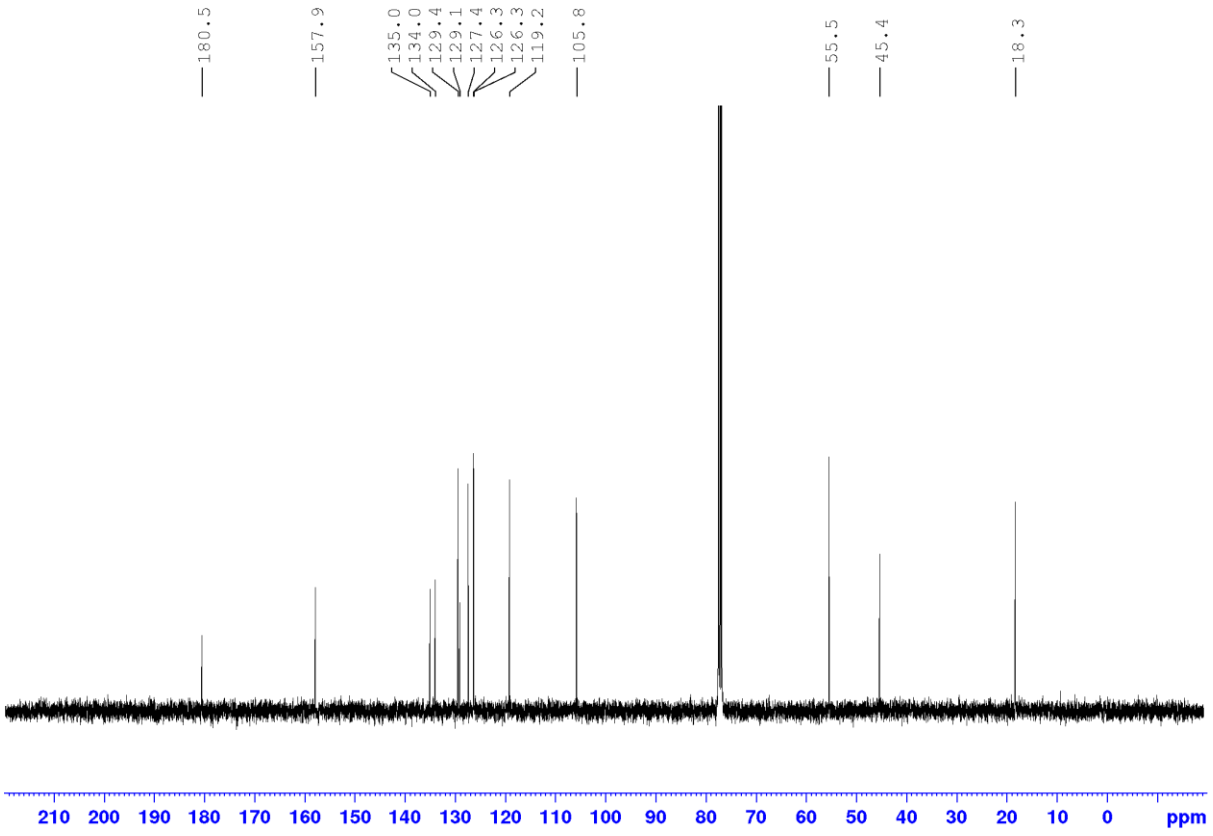
Aripiprazole-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



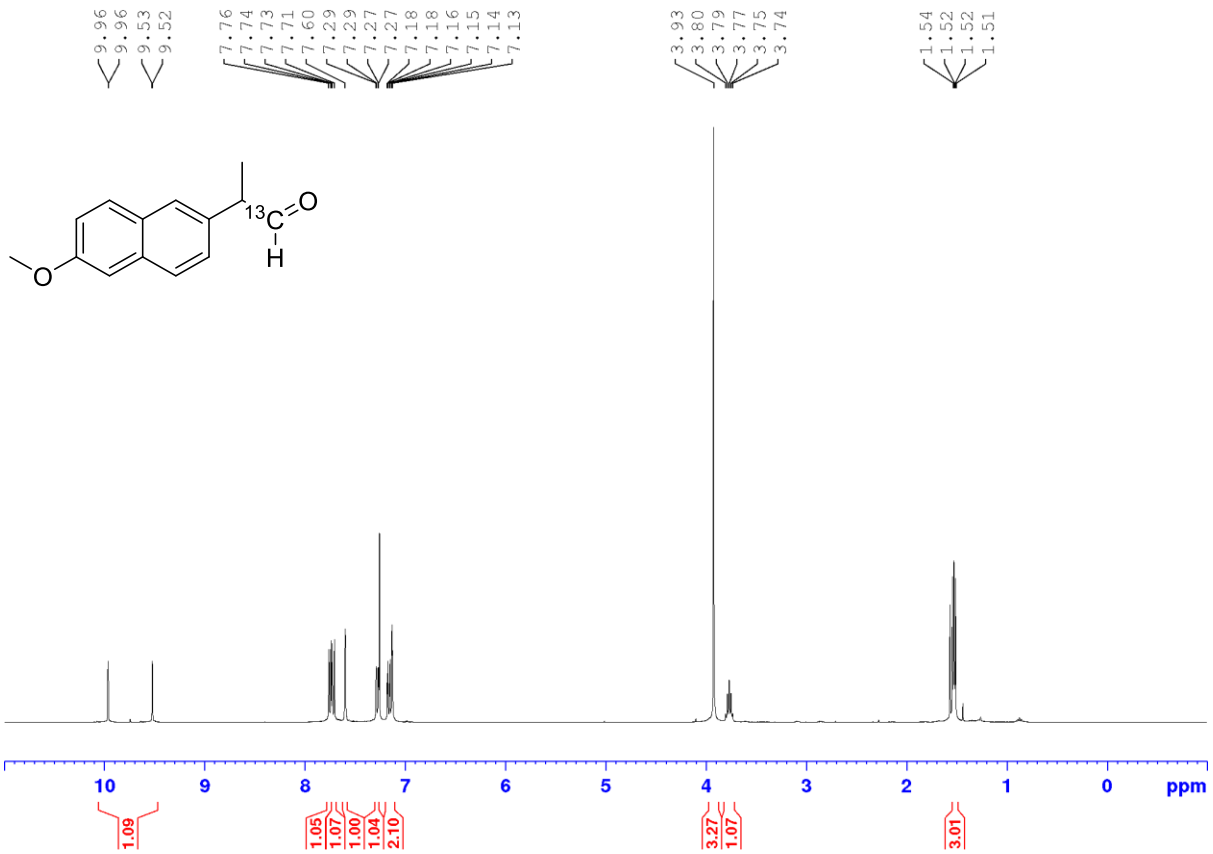


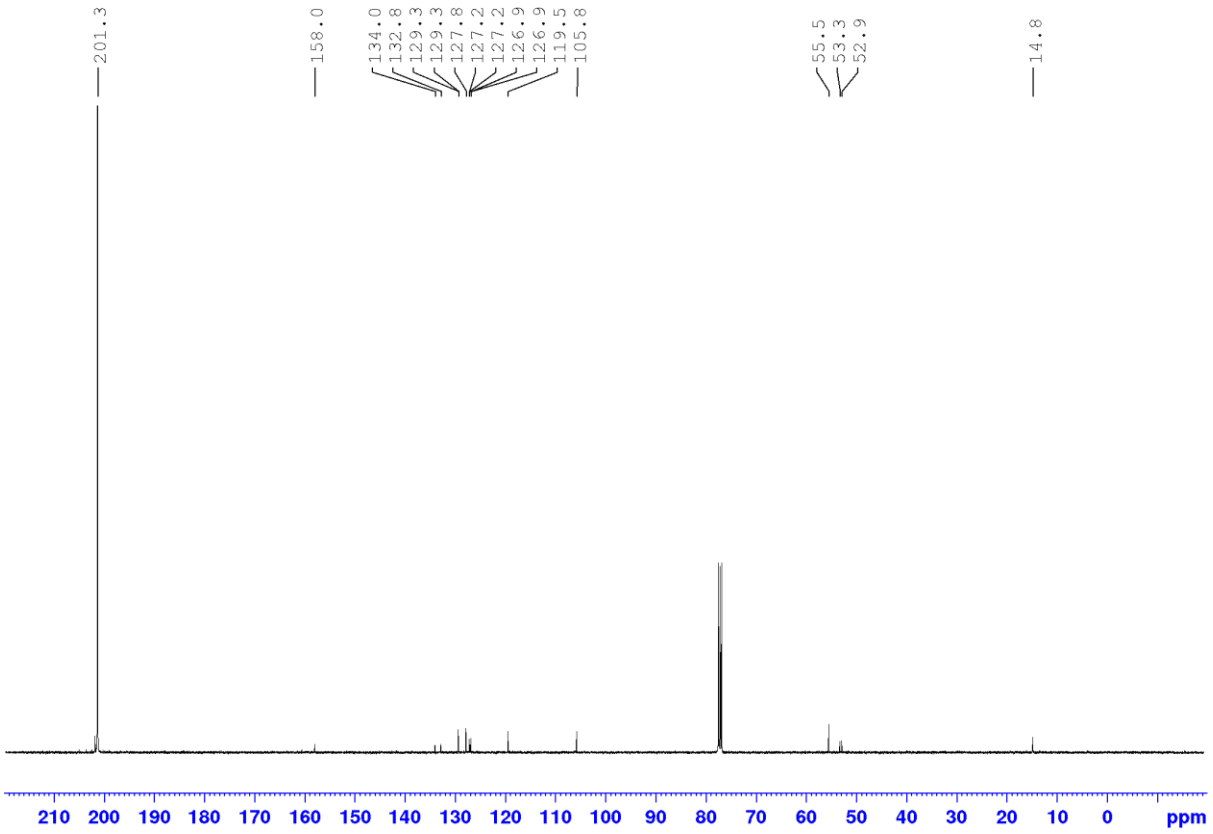
Naproxen [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



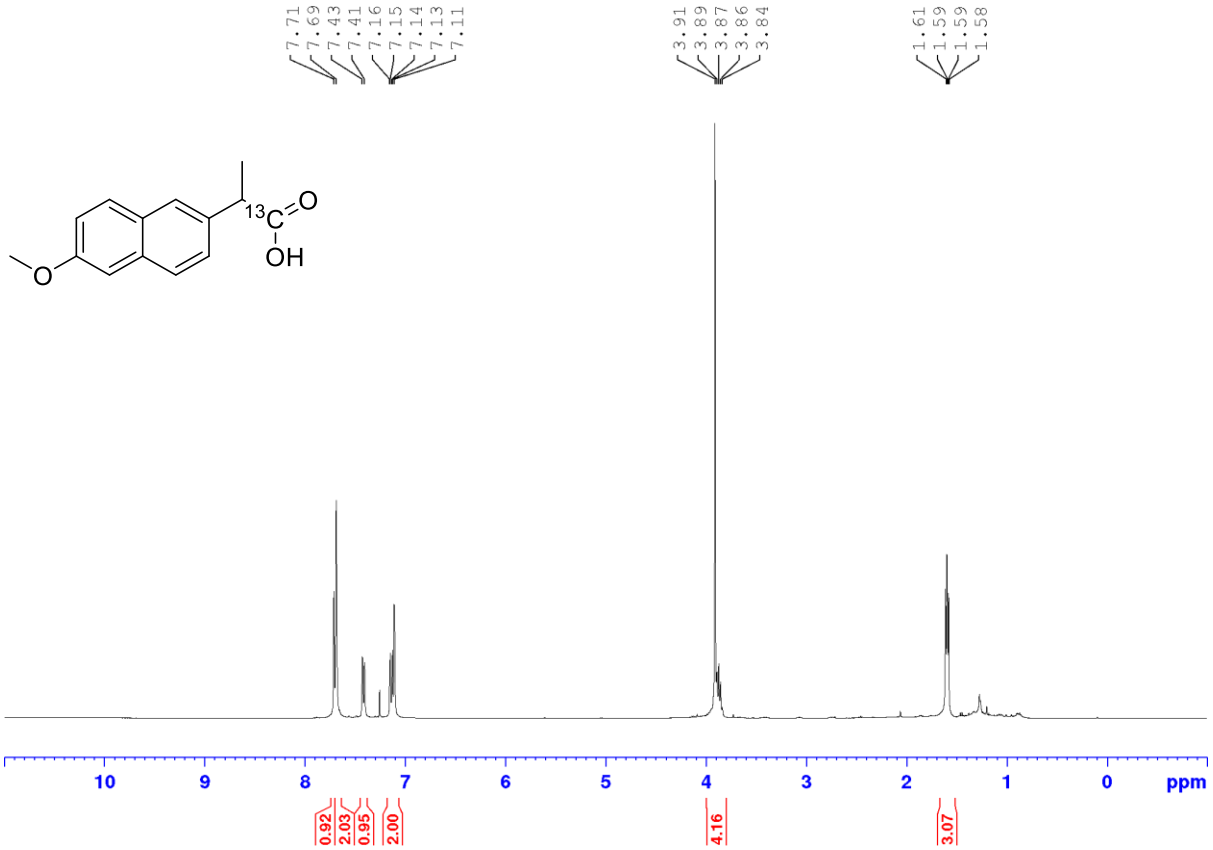


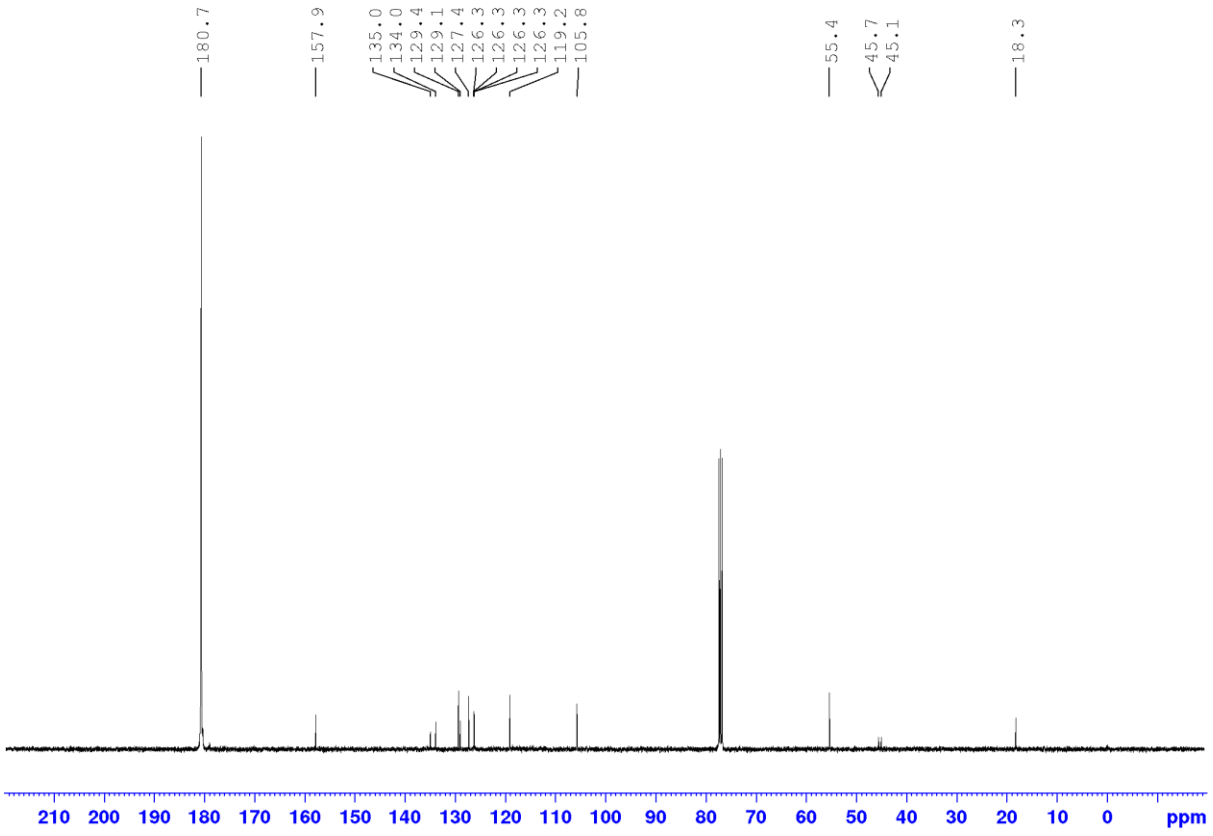
30-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



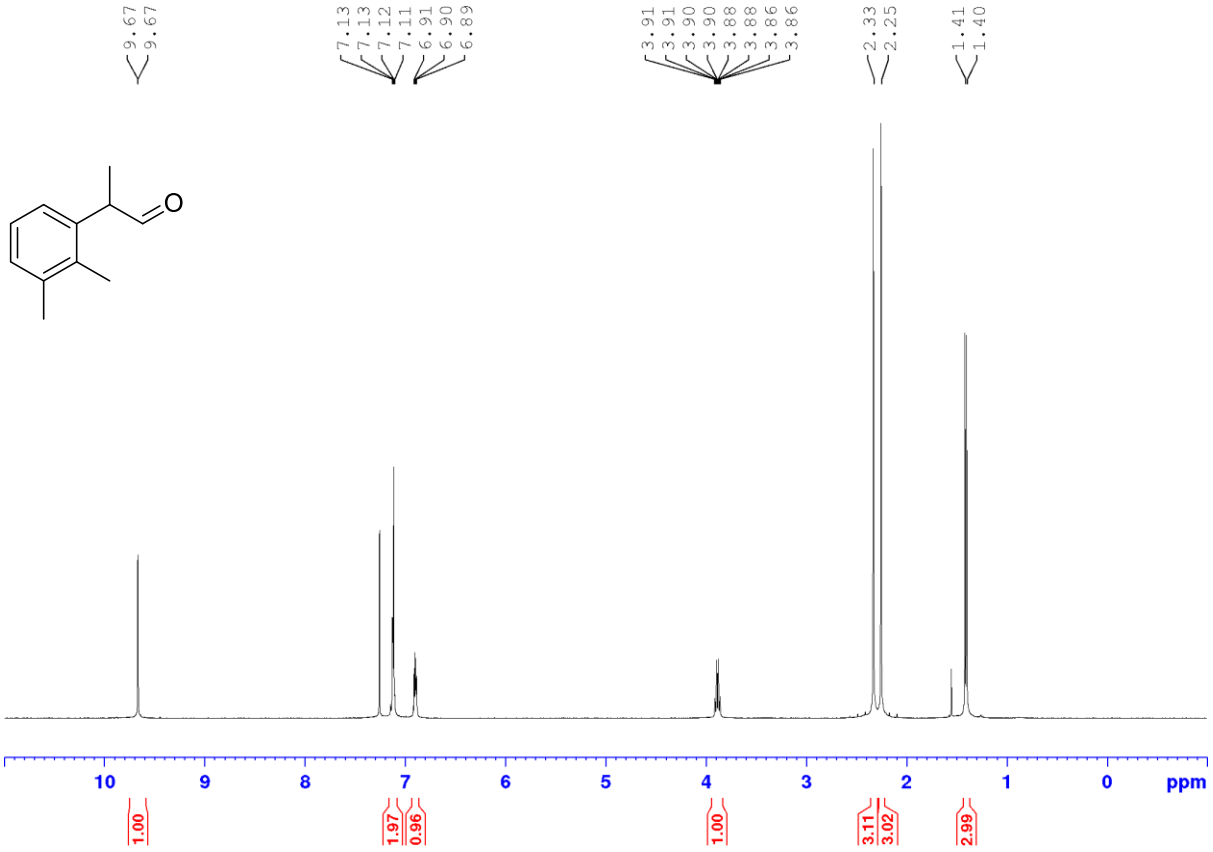


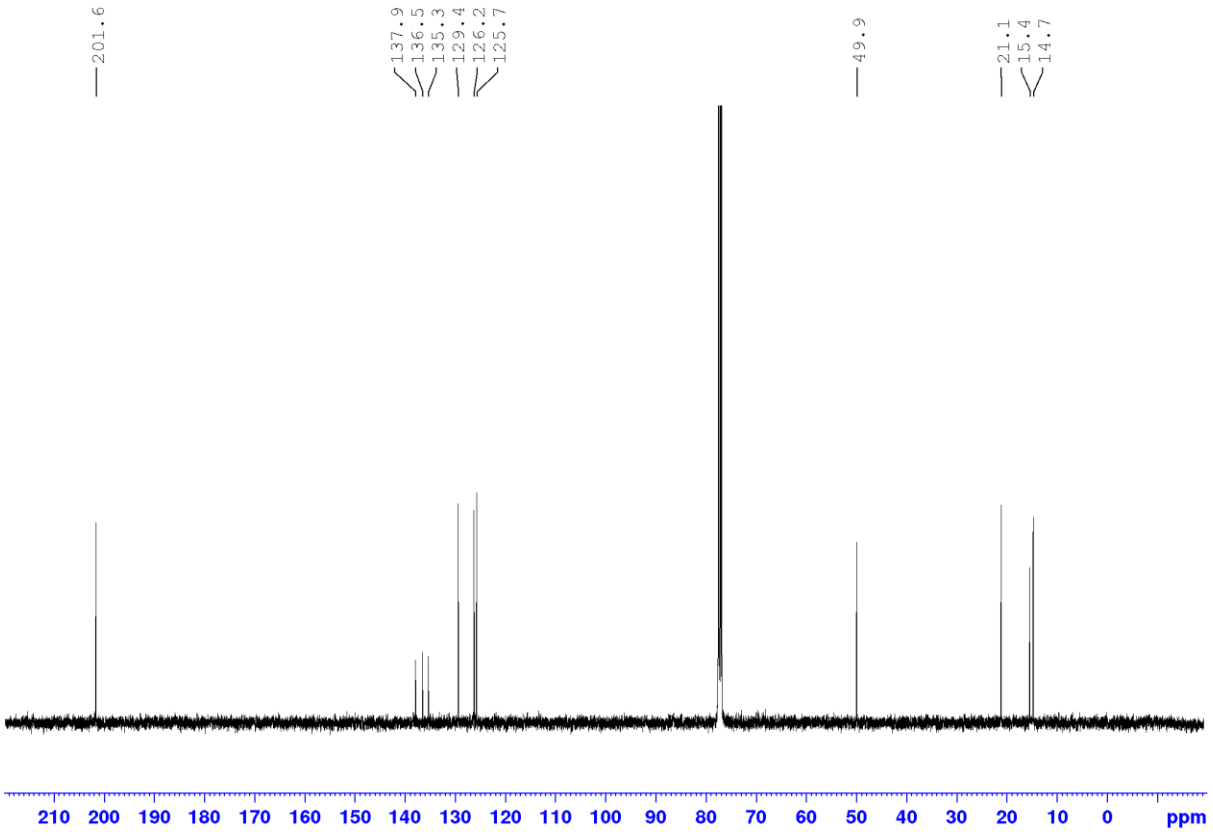
Naproxen-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



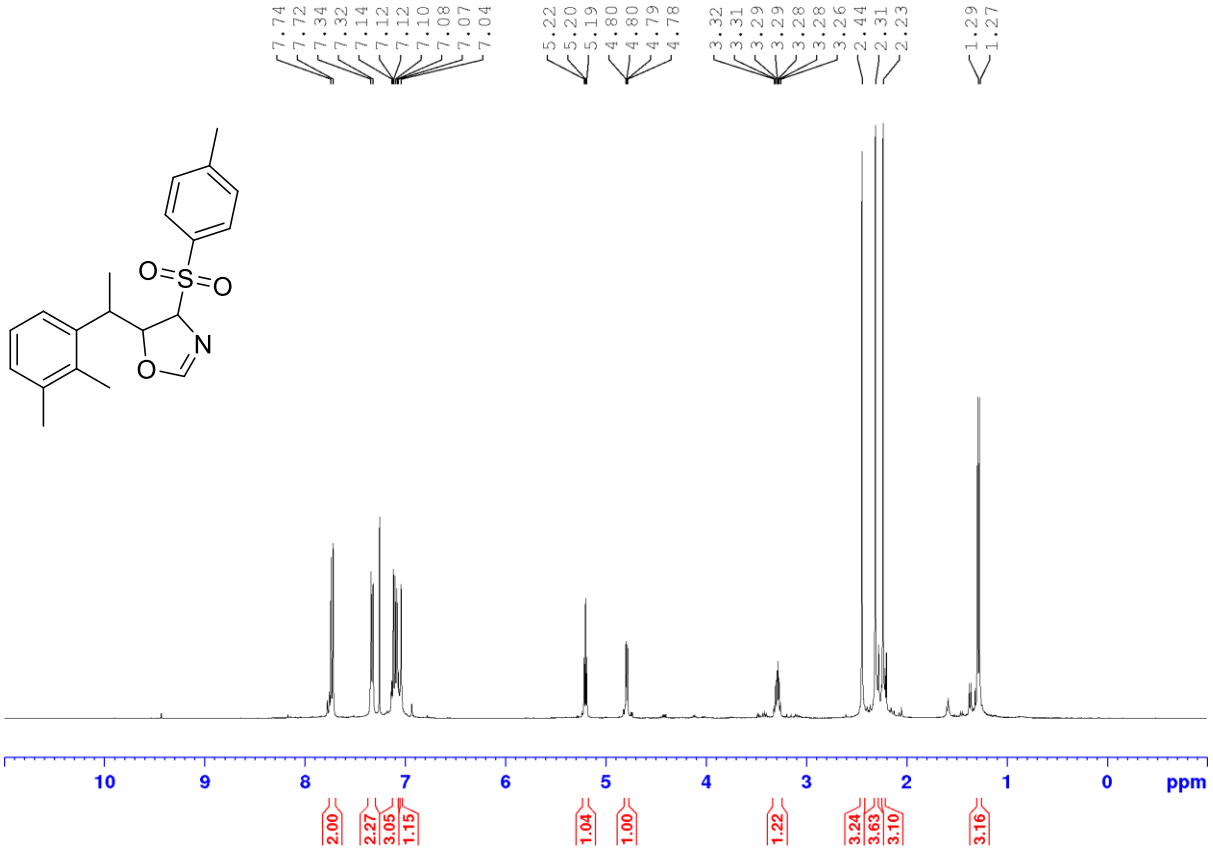


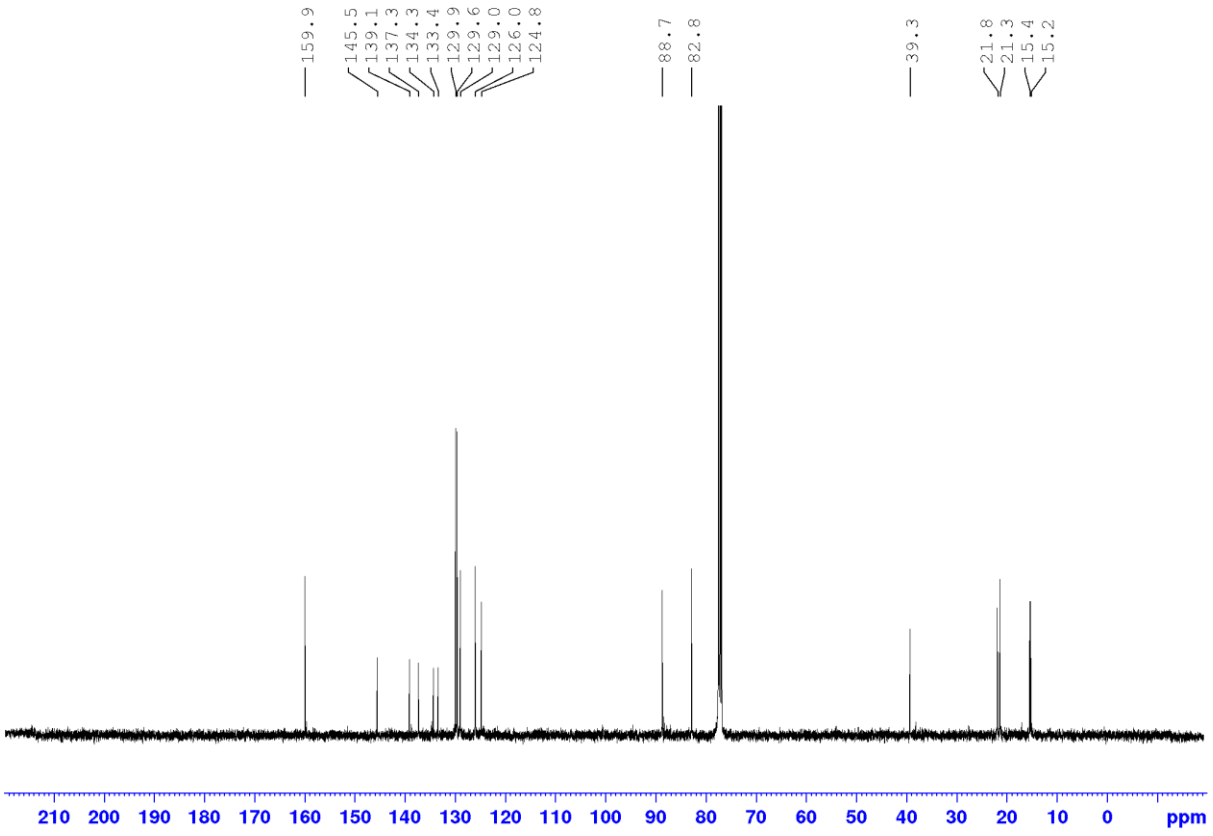
32 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



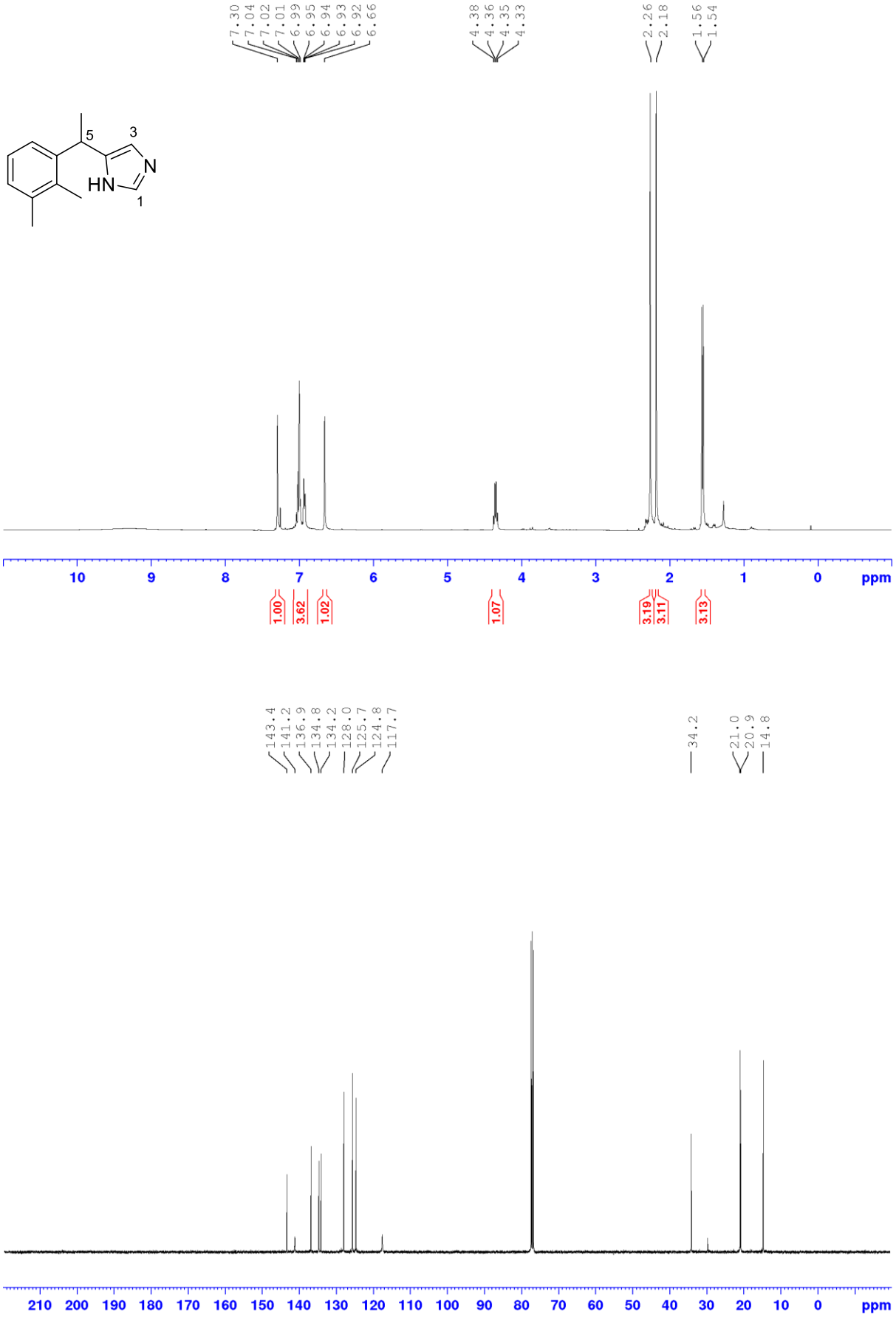


33 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

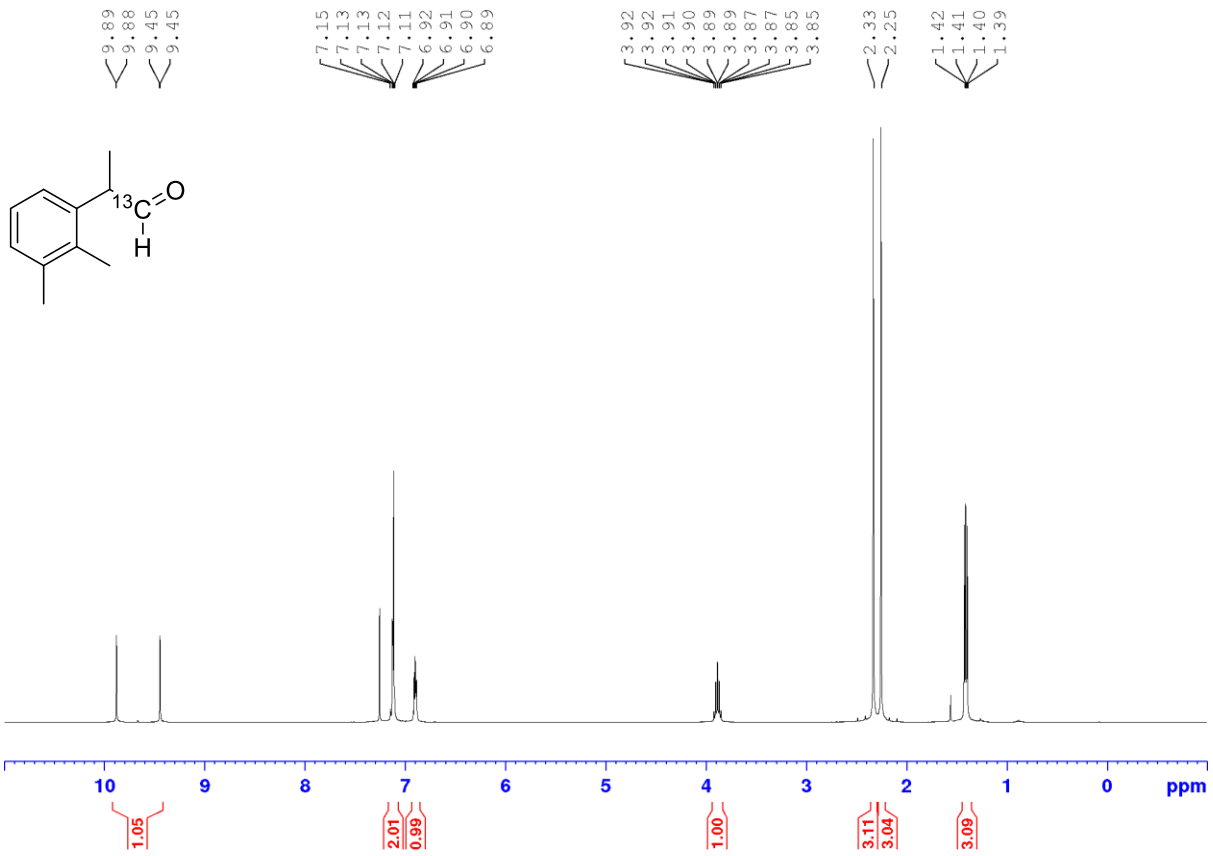


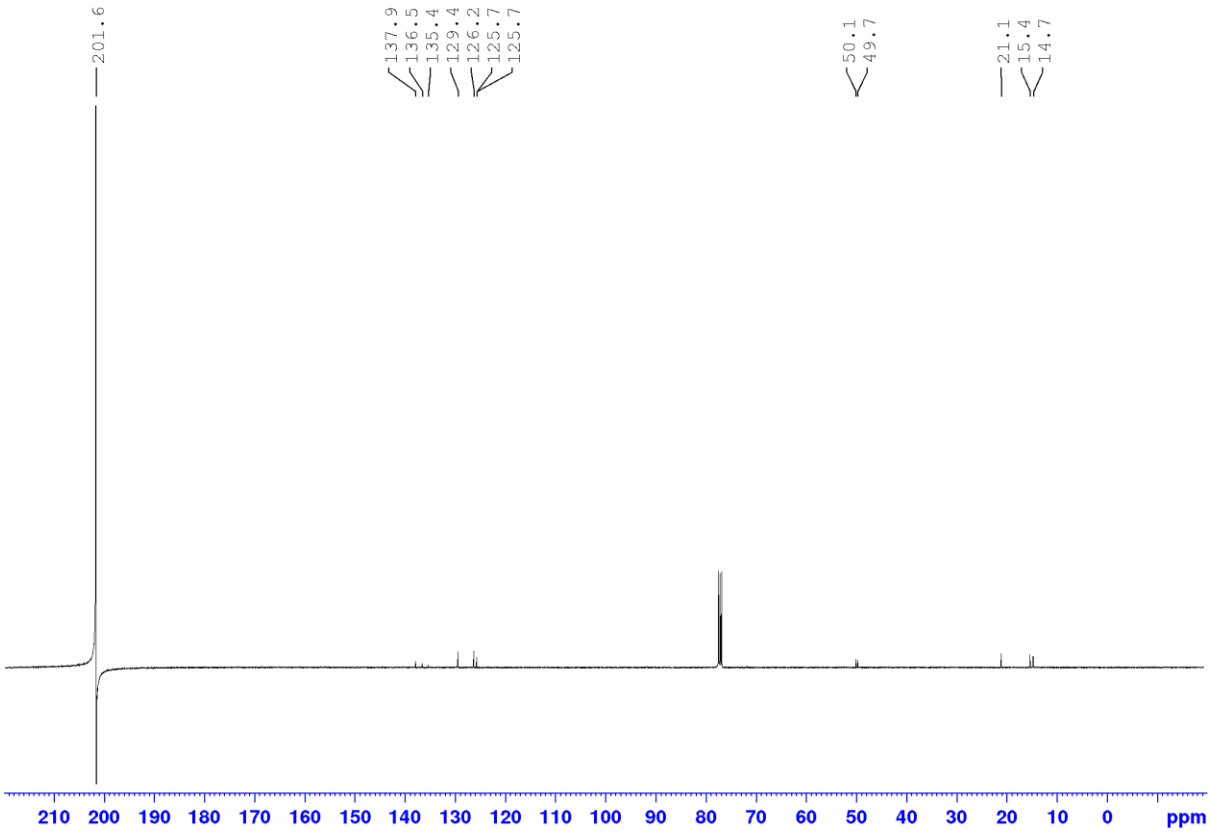


Medetomidine [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

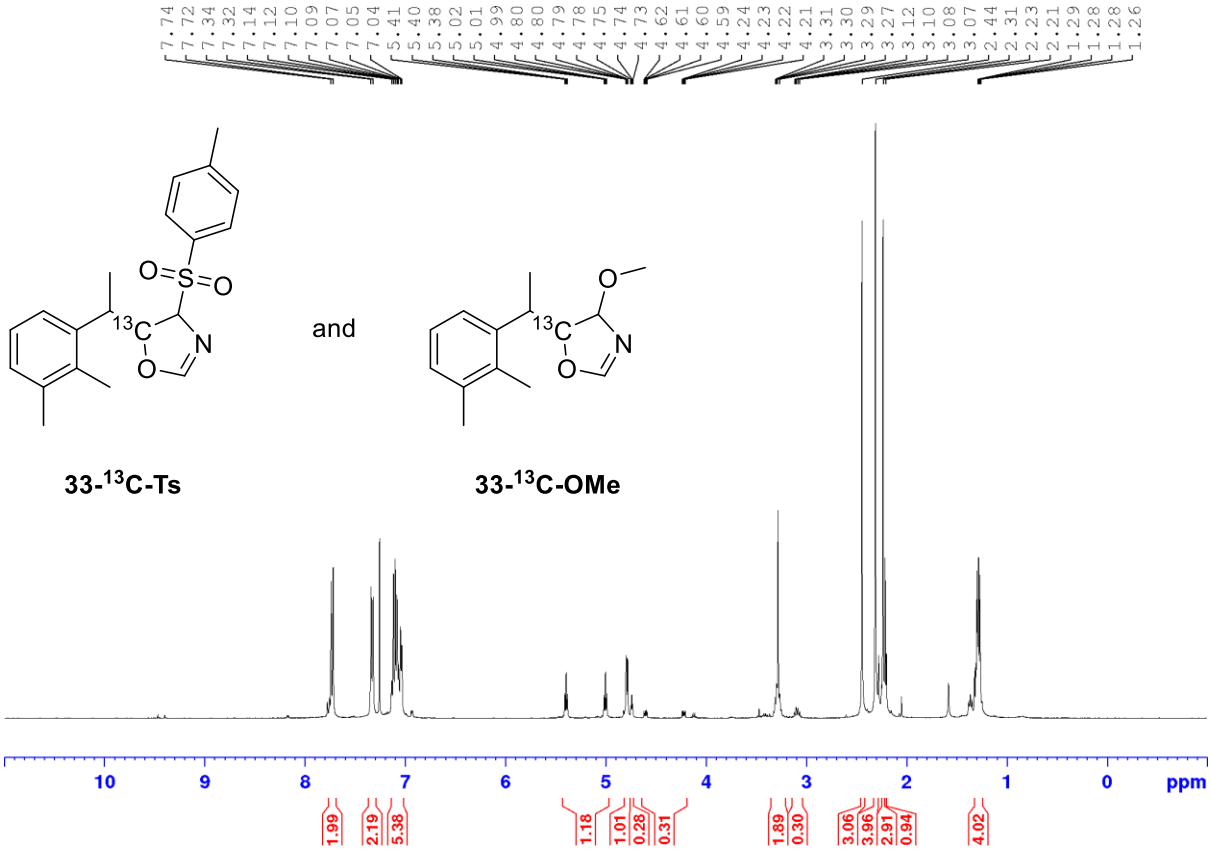


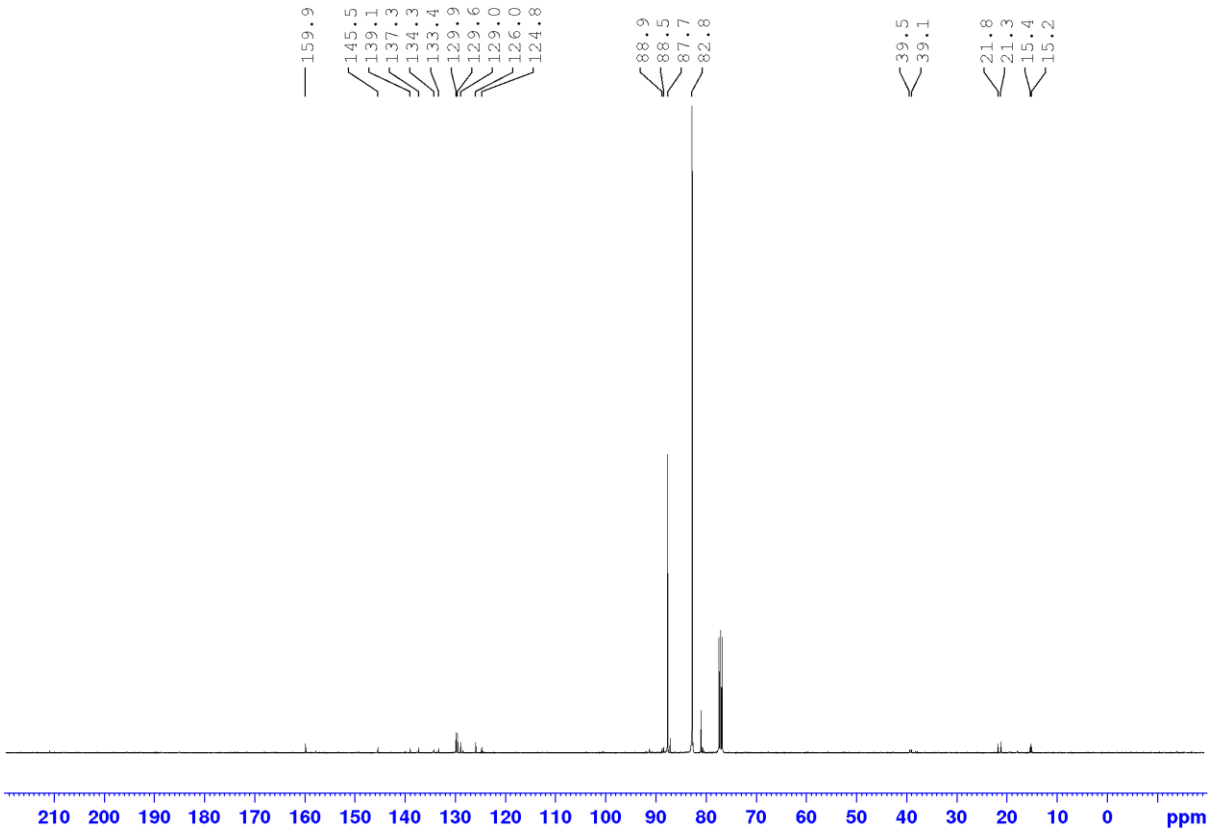
32-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]



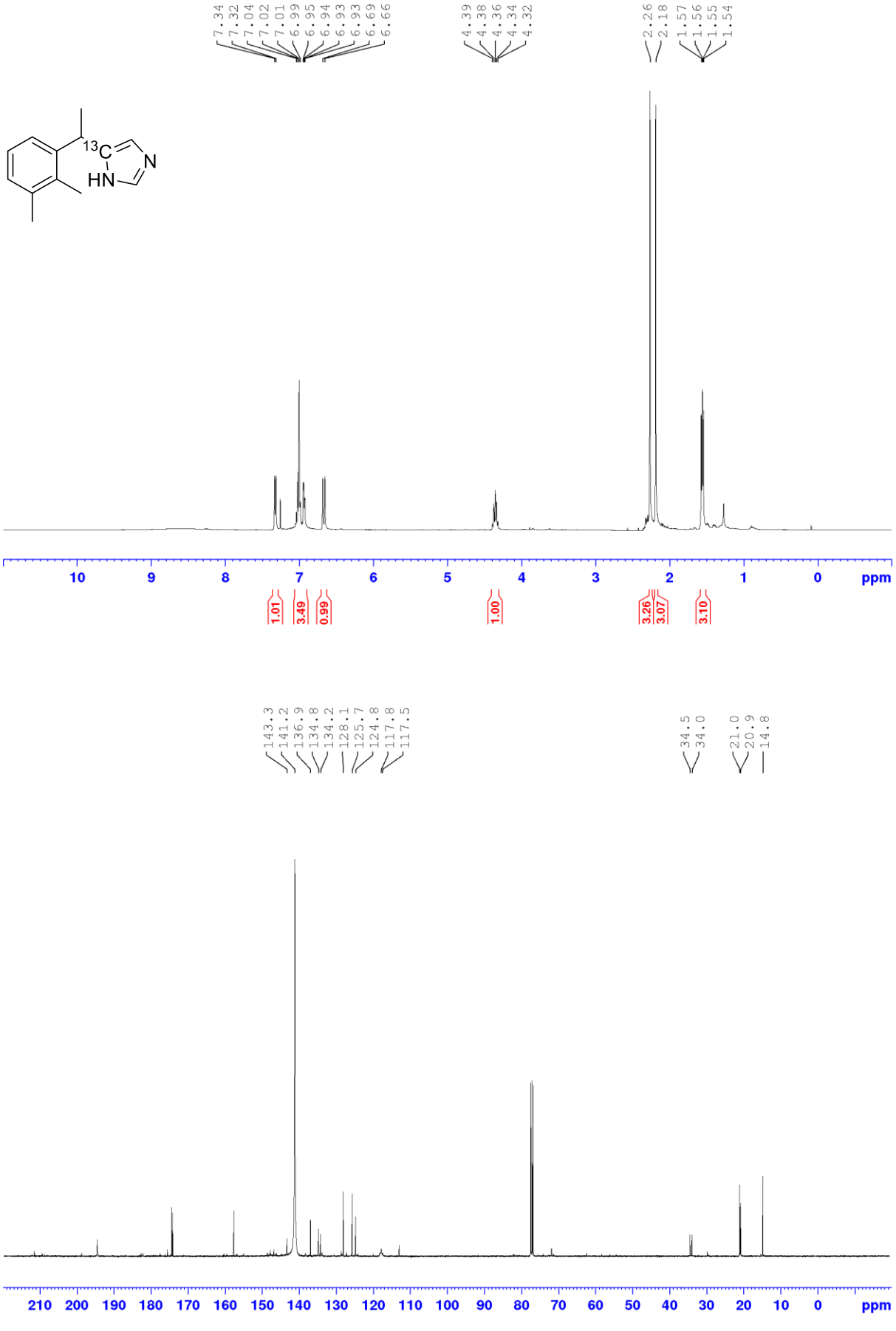


33-^{13}C-Ts and 33-^{13}C-OMe [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

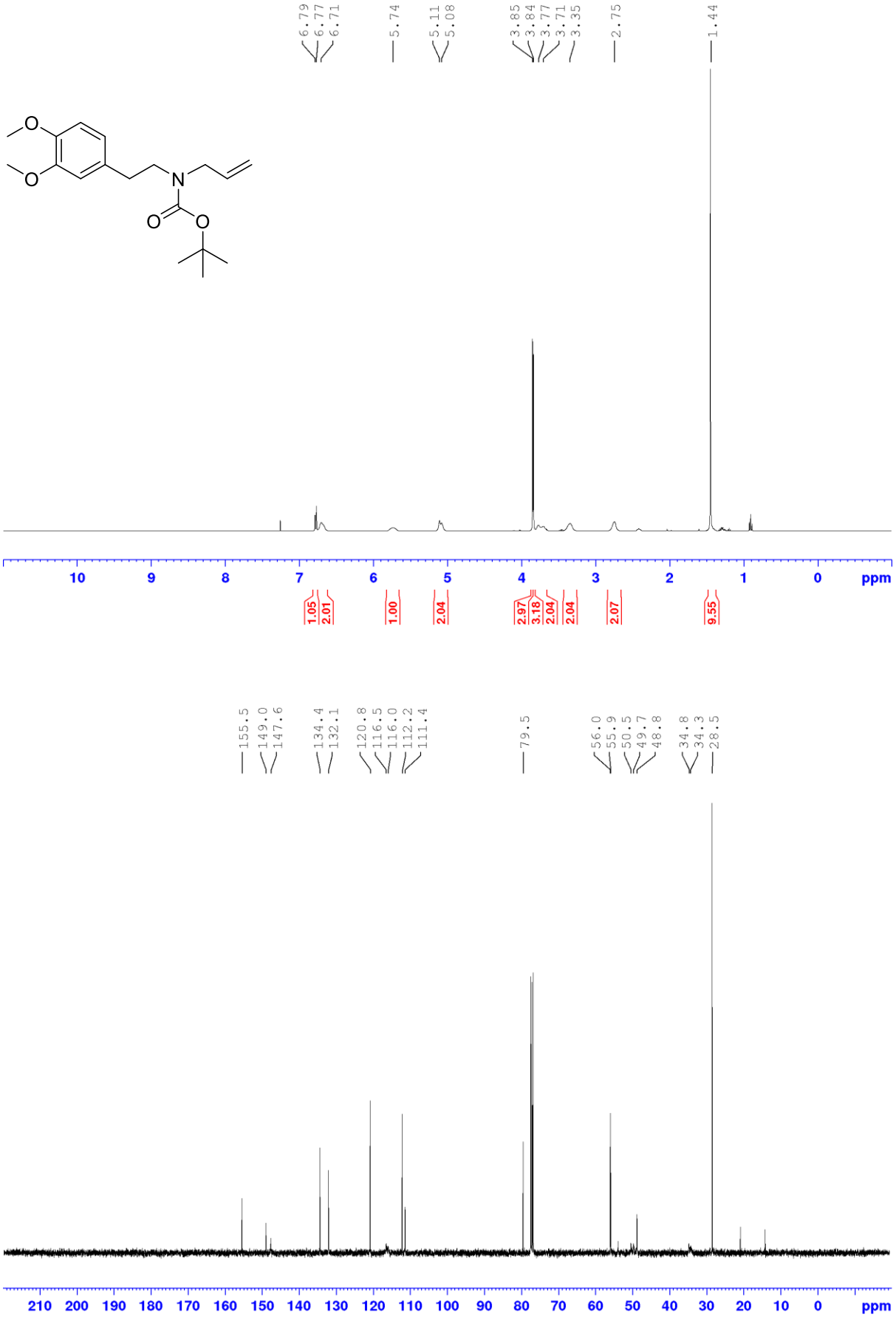




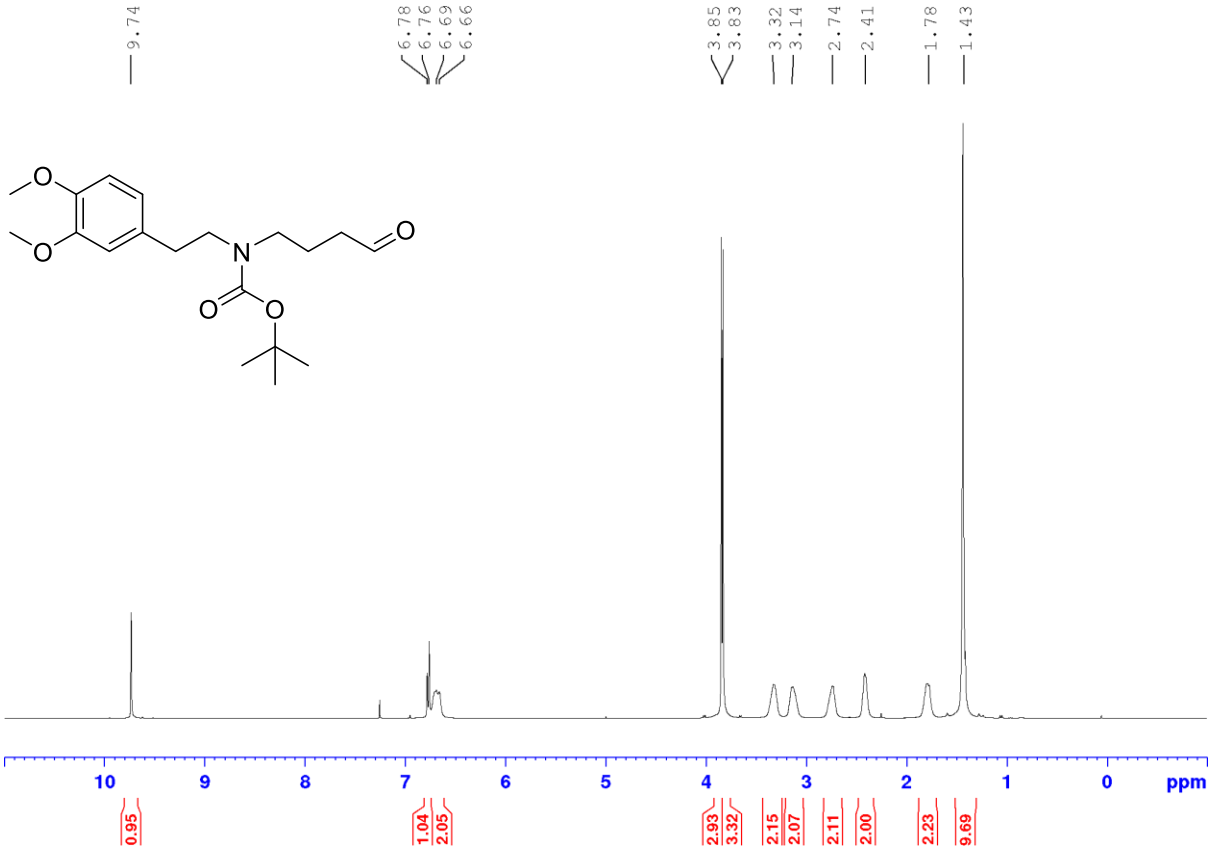
Medetomidine-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

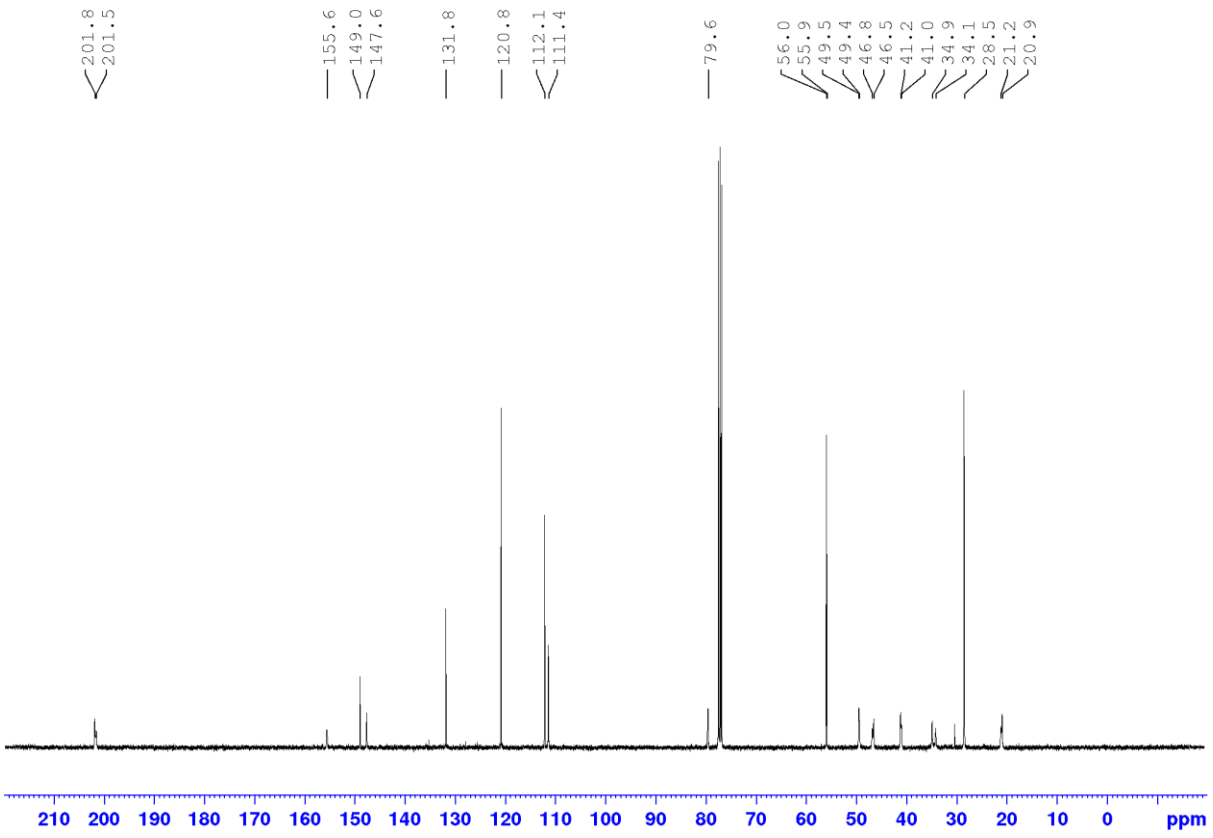


34 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

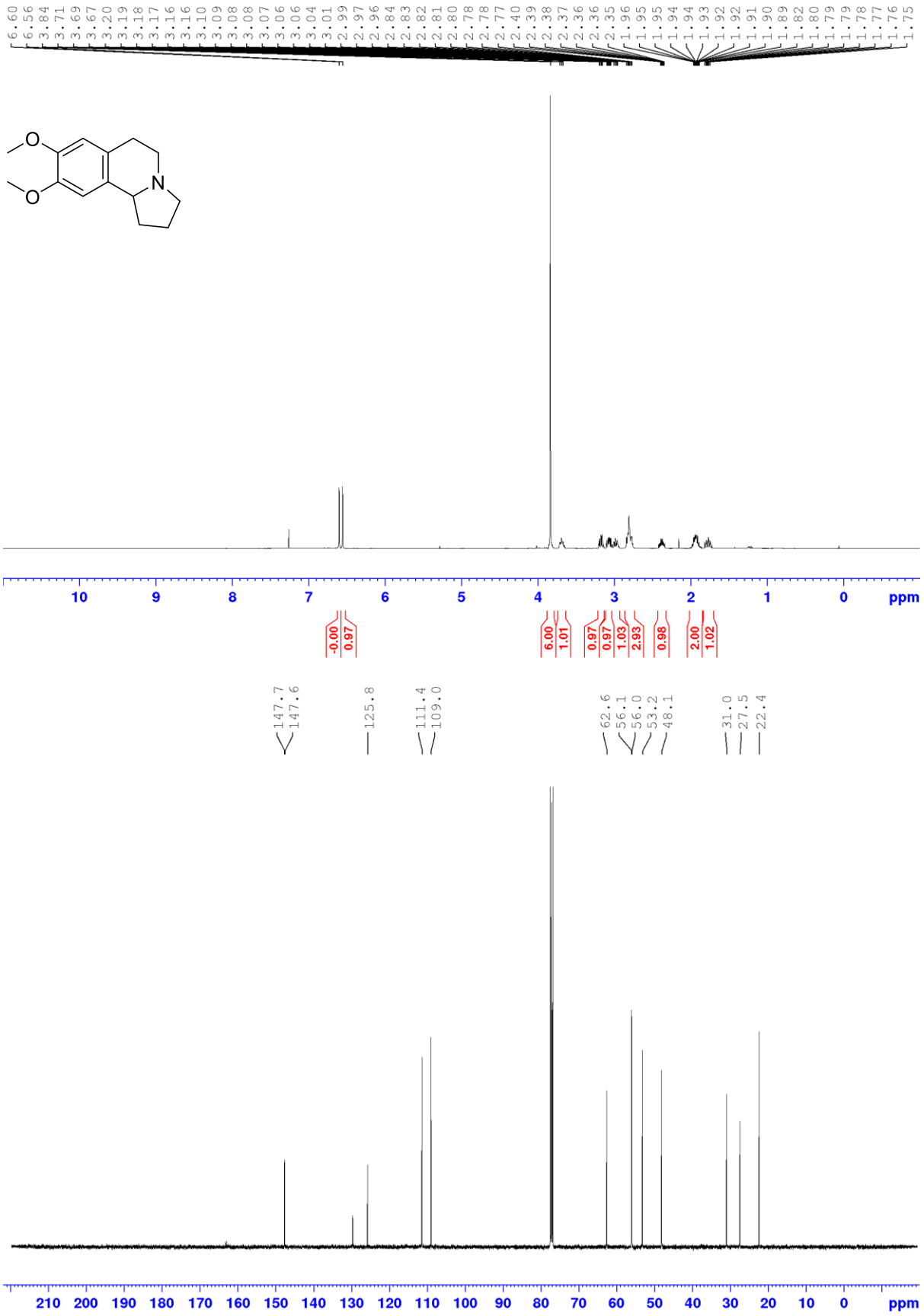


35 [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

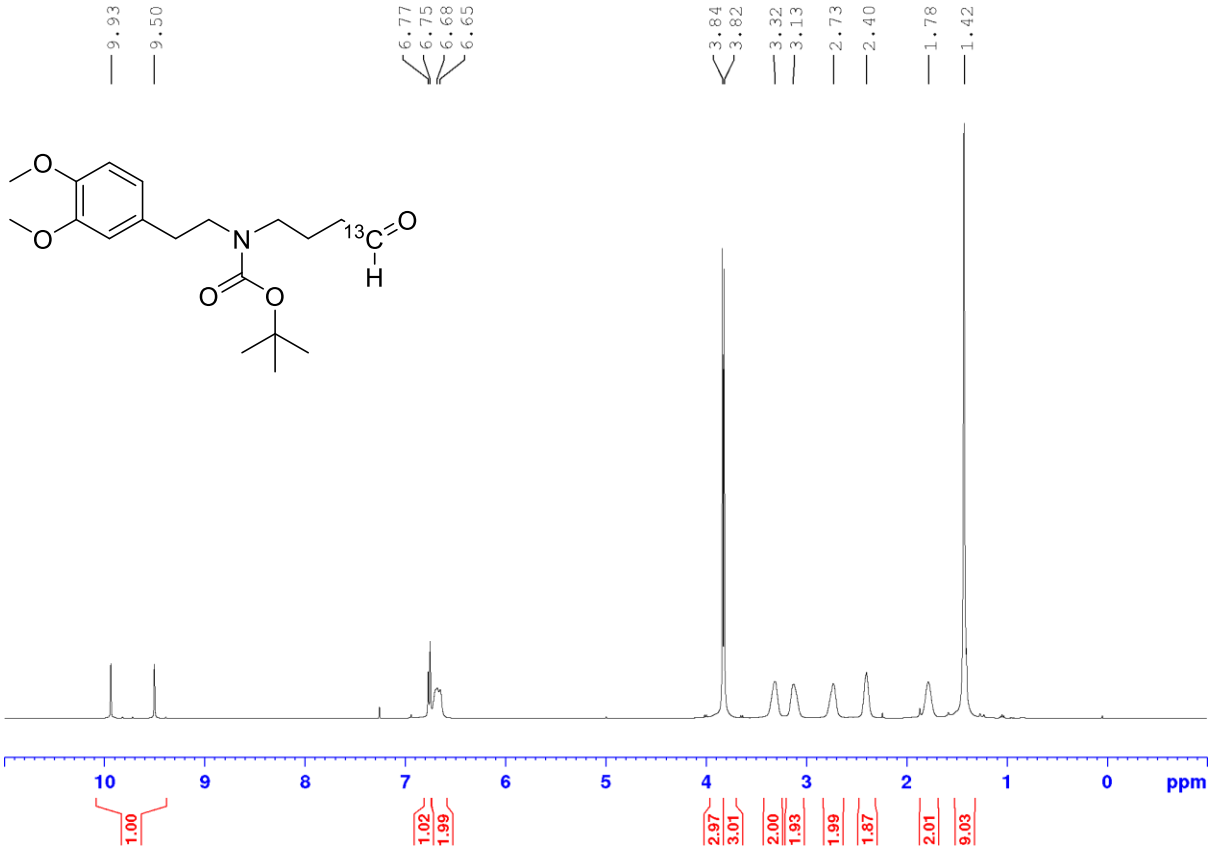


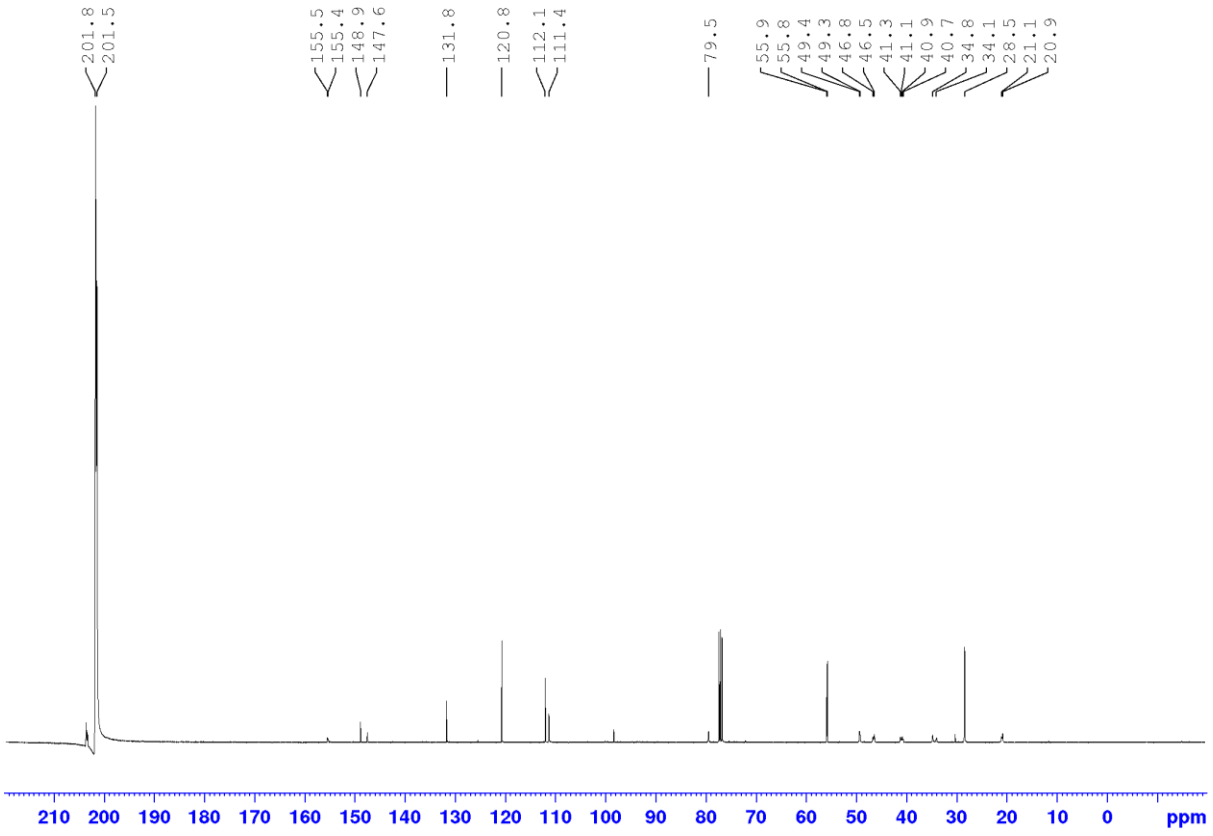


(±)-Crispine A [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]

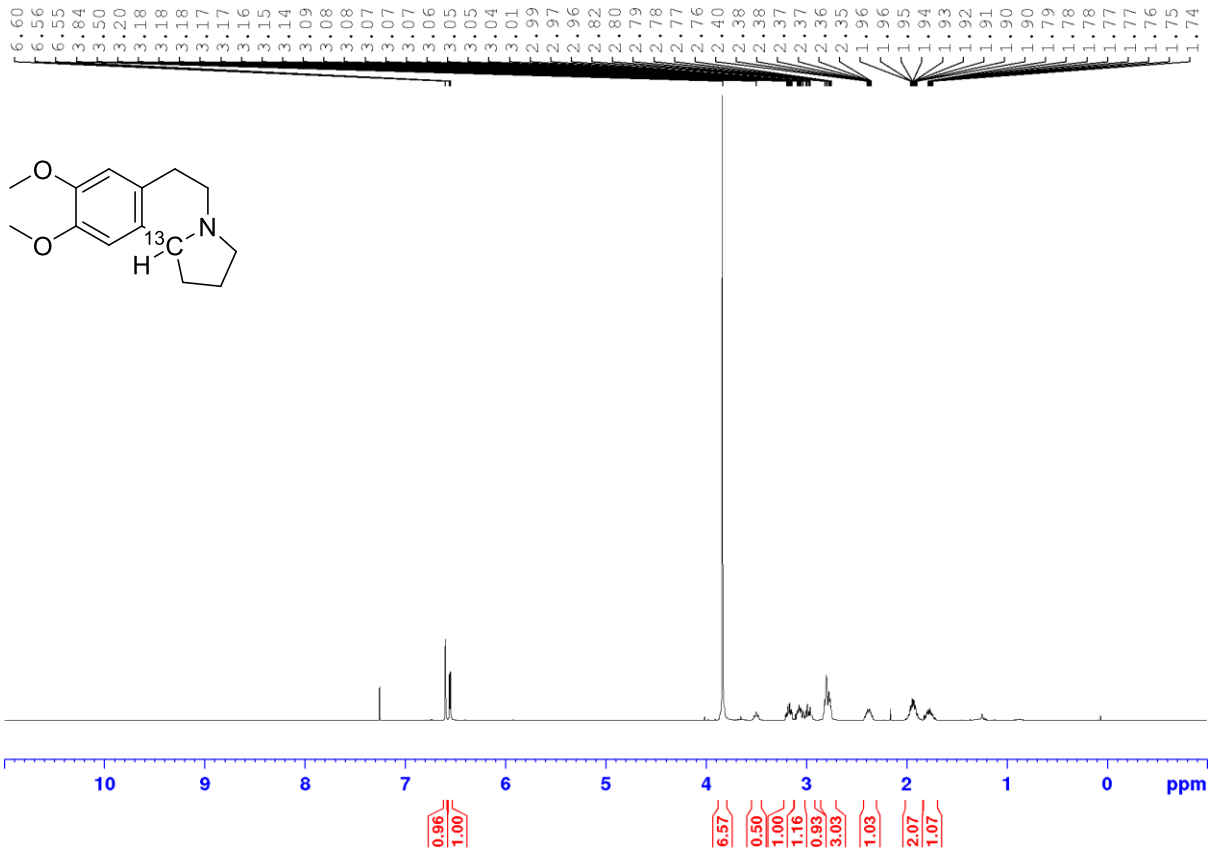


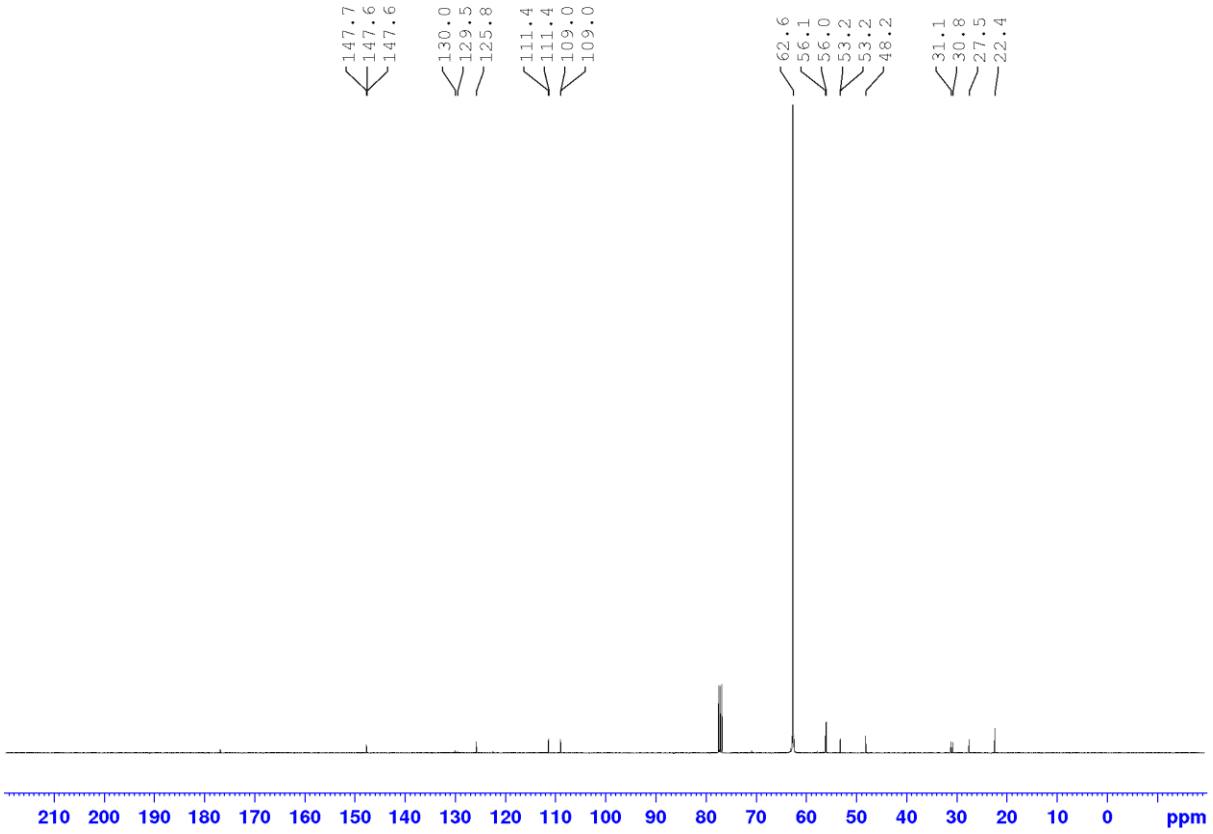
35-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]





(±)-Crispine A-^{13}C [^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) in $CDCl_3$]





Supplementary References

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