*Supplementary Information*

# Rapid Access to 2-Substituted Bicyclo[1.1.1]pentanes

Olivia L. Garry*, Michael Heilmann*, Jingjia Chen, Yufan Liang, Xiaheng Zhang, Xiaoshen Ma, Charles S. Yeung, David Jonathan Bennett and David W. C. MacMillan[†]

*Merck Center for Catalysis at Princeton University, Princeton, NJ 08544, USA and Department of Discovery Chemistry, Merck & Co., Inc., Boston, MA 02115, USA*

**These authors contributed equally to this work. [†]Corresponding author. Email: dmacmill@princeton.edu*

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## General Information

Commercial reagents were used without further purification unless otherwise indicated. All photocatalysts investigated are commercially available but are also available *via* synthetic procedures from the literature. Supersilanol and adamantylaminosupersilane are commercially available but were prepared according to the literature procedures.[1-2] All organic reaction solvents were purified according to the method of Grubbs.[3] Unless indicated otherwise, filtrations of heterogeneous mixtures were performed using ChemRus 20 mL or 60 mL disposable filters. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator with a water bath. Crude reaction mixtures containing high boiling point solvents were concentrated on a GeneVac HT-4X Centrifugal Vacuum Evaporator Series II machine at 30°C under 1.5 mbar for 2 to 6 hours.

Chromatographic purification of products was accomplished on an automated Combi-flash NextGen $300^{+}$ system or an automate Biotage Isolera Four system using RediSep Rf Gold silica gel columns (20 to 40 microns). Reverse phase chromatography was performed on a Teledyne ISCO ACCQPrep HP150 system using RediSep® Prep HPLC Columns (30 mm x 250 mm C18, 100 Å) with 0.1% formic acid buffered water and acetonitrile solutions. Reverse phase chromatography of acid-sensitive compounds such as Boc-protected heterocycles and amines was performed on the same PrepHPLC system using a Waters XBridge BEH C18 OBD Prep Column (30 mm x 150 mm, 130 Å, 5 μm) with 0.1% ammonium hydroxide buffered water and acetonitrile solutions. Thin-layer chromatography (TLC) was performed on Analtech Uniplate 0.25 mm or Supelco 0.20 mm silica gel F-254 plates. Visualization of the developed chromatography was performed by fluorescence quenching or *via* the use of $KMnO_4$ or iodine stains. Preparative thin-layer chromatography was performed on Analtech 1 mm or Supelco 0.50 mm silica gel F-254 plates.

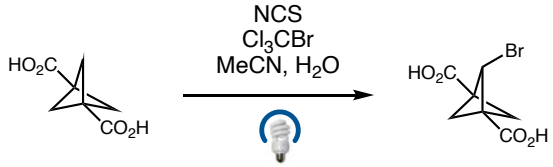
$^{1}H$ NMR spectra were recorded at 400 MHz or 500 MHz, using a BRUKER NanoBay Avance III HD 400 or BRUKER Avance III NMR spectrometer, respectively. $^{13}C$ NMR spectra were recorded at 101 MHz or 126 MHz on a BRUKER NanoBay Avance III HD 400 or BRUKER Avance III NMR spectrometer, respectively. Chemical shifts of $^{1}H$ NMR and $^{13}C$ NMR spectra (measured at 298 K) are given in ppm by using residual solvent signals as references ($CDCl_3$: 7.26 ppm and 77.16 ppm, respectively; DMSO-*d6*: 2.50 ppm and 39.52 ppm, respectively; MeOD: 3.31 ppm and

49.00 ppm, respectively; MeCN-*d3*: 1.94 ppm and 118.26 ppm, respectively; $D_2O$: 4.79 ppm).[4] $^{19}F$ NMR spectra were recorded on a BRUKER NanoBay Avance III HD 300 or BRUKER NanoBay Avance III HD 300, and are reported unreferenced. Coupling constants (J) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), s (sextet), h (septet), m (multiplet), b (broad). Apparent multiplets arising from overlapping signals are marked as virtual multiplets (*virt*). Data for $^{13}C$ NMR are reported in terms of chemical shifts; multiplicity and coupling constants are included only when coupling with $^{19}F$ nuclei.

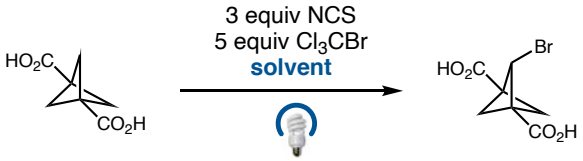
Liquid chromatography (LC) analysis was performed on an Agilent 1200 Infinity or 1290 Infinity II LC system. Chiral purification was performed as detailed below title compound. IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer and are reported in wavenumbers ($cm^{-1}$). High Resolution Mass Spectra (HRMS) were obtained from the Princeton University Mass Spectral Facility.

## Synthesis of 2-Brominated Bicyclo[1.1.1]pentanes

### Optimization of the BCP 2-Bromination

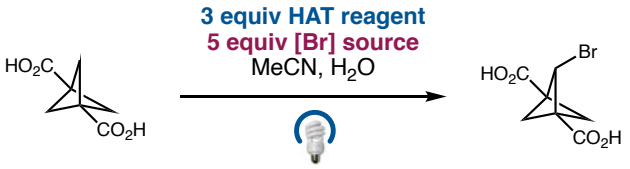



To an oven-dried 8 mL vial equipped with a cross-shaped stir bar was added bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (31.2 mg, 200 µmol) and *N*-chlorosuccinimide (NCS, 80.1 mg, 600 µmol, 3.0 equiv), the vial was evacuated and backfilled with nitrogen three times. Then, MeCN (1 mL) and $H_2O$ (0.1 mL) were added, the mixture was stirred at room temperature for 5 min and then sonicated for 1 min. The now clear solution was degassed by sparging with nitrogen for 5 min before $Cl_3CBr$ (98 µL, 198 mg, 1.00 mmol, 5.0 equiv) was added and the vial was sealed with parafilm. Then, the vial was placed in the Integrated Photoreactor and stirred for 16 hours (450 nm, 100% light intensity, 600 rpm stir rate, 5200 rpm fan rate). The reaction mixture was removed from the light and stirred at room temperature for 5 min. The yield was determined via $^1H$ NMR assay using mesitylene as internal standard.



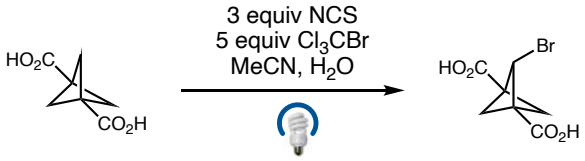

| solvent | yield | solvent | yield |
|---|---|---|---|
| MeCN | 19% | acetone + 10% $H_2O$ | < 5% |
| MeCN + 5% $H_2O$ | 31% | tBuOH + 10% $H_2O$ | 0% |
| **MeCN + 10% $H_2O$** | **35%** | $PhCF_3$ | < 5% |
| MeCN + 20% $H_2O$ | 29% | $PhCF_3$ + 10% $H_2O$ | 26% |
| MeCN + 50% $H_2O$ | 19% | $CCl_4$ | 0% |
| $CD_3CN$ + 10% $H_2O$ | 36% | $CCl_4$ + 10% $H_2O$ | 15% |

**Table S1.** Optimization of solvents for the BCP 2-bromination.



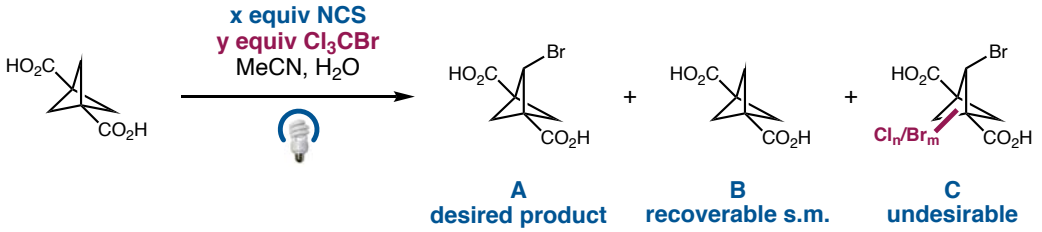

| HAT reagent | yield | [Br] source | yield |
|---|---|---|---|
| **NCS** | **35%** | **$Cl_3CBr$** | **35%** |
| NCP | 32% | $CBr_4$ | 30% |
| N-chlorosaccharin | 32% | NBS | 12% |
| TCCA | 26% | NBP | 12% |
| trichloromelamine | < 5% | N-bromosaccharin | 10% |
| Chloramine-B / T | 0% / 0% | DBDMH | 7% |
| *t*BuOH | 0% | $Bu_4N^+ Br_3^-$ | 0% |
| *t*BuOOH + 2% $Ru(bpy)_3PF_6$ | 0% | bis(collidine)bromonium $PF_6$ | 0% |

**Table S2.** Optimization of HAT reagent and bromine source.



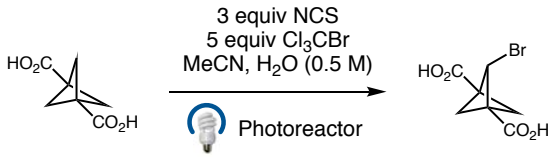

| concentration | yield |
|---|---|
| 0.05 M | 26% |
| 0.1 M | 29% |
| 0.2 M | 35% |
| 0.4 M | 35% |
| **0.5 M** | **35%** |
| 0.6 M | 31% |
| 1.0 M | 30% |

**Table S3.** Optimization of concentration.



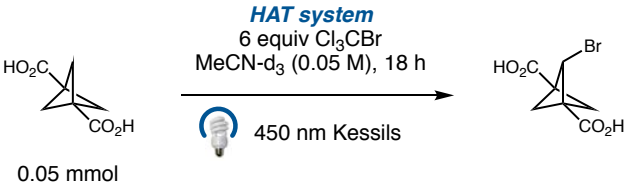

| equiv NCS | equiv $Cl_3CBr$ | yield A | yield B | yield C | yield A (b.r.s.m.) |
|---|---|---|---|---|---|
| 3.0 | 5 | 35% | 22% | 45% | 45% |
| 2.0 | 5 | 34% | 38% | 28% | 55% |
| **1.1** | **5** | **35%** | **57%** | **8%** | **82%** |
| 1.1 | 5 | 35% | 40% | 23% | 58%[a] |
| 1.1 | 5 | 21% | 73% | 6% | 56%[b] |
| 1.1 | 2 | 30% | 56% | 13% | 68% |

**Table S4.** Optimization of HAT reagent and bromine source equivalents. [a] Reaction performed by irradiation at 365 nm. [b] Reaction performed at 80 °C with 1 equiv AIBN without irradiation.




| Change | Yield |
|---|---|
| Standard | 45% |
| No NCS | 0% |
| No $CCl_3Br$ | 0% |
| Kessils | 42% |
| No Light | 10% |

**Table S5.** Control reactions.




| HAT system | Yield |
|---|---|
| NFSI + 2 mol% $Ir(ppy)_3$ | < 5% |
| Selectfluor + 2 mol% $Ir(ppy)_3$ | < 5% |
| Selectfluor + 5 mol% $Cu(bcp)_2PF_6$ | 21% |
| 1 mol% KDT* | 38% |

*using 365 nm photoreactor

**Table S6.** Rejected HAT systems. All yields are $^1$H NMR yields vs. 1,4-difluorobenzene.

Potassium decatungstate was ultimately rejected due to its requirement for deuterated acetonitrile for higher yields, and lack of scaleability compared to NCS conditions.

## Substrate Limitations for BCP 2-Bromination

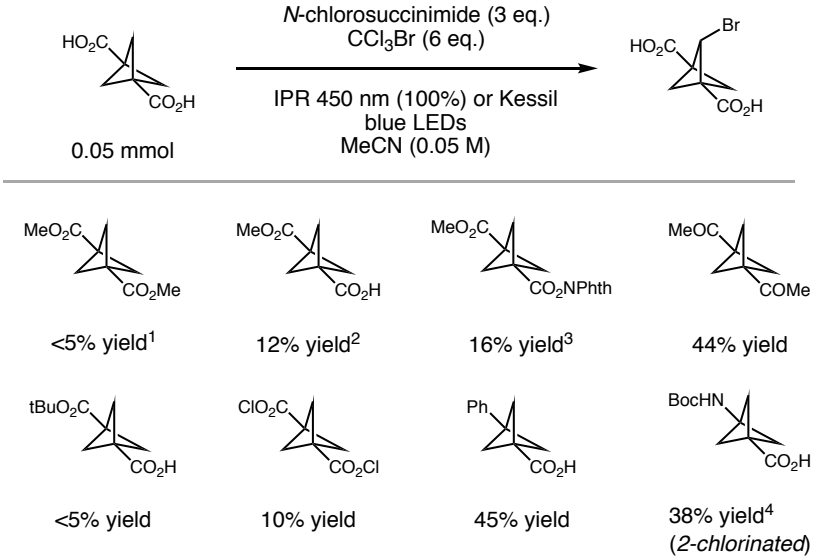



**Table S7.** Additional substrates and limitations of 2-bromination reaction. All yields are $^1$H NMR yields vs. 1,4-difluorobenzene. [1]Major product is ester methyl C–H brominated product. [2]12% yield ester methyl C–H brominated product, 19% yield dibromination products. [3]12% ester methyl C–H brominated product, 8% yield dibromination products. [4]No $CCl_3Br$.

## Absorption Spectrum of Reaction Mixture for BCP 2-Bromination

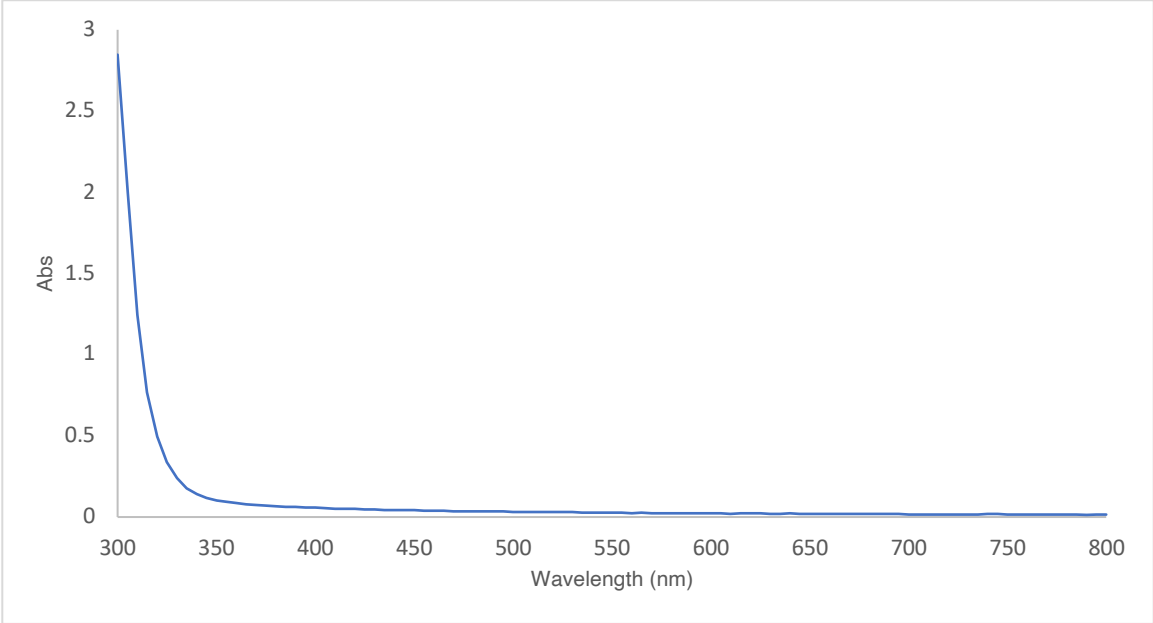
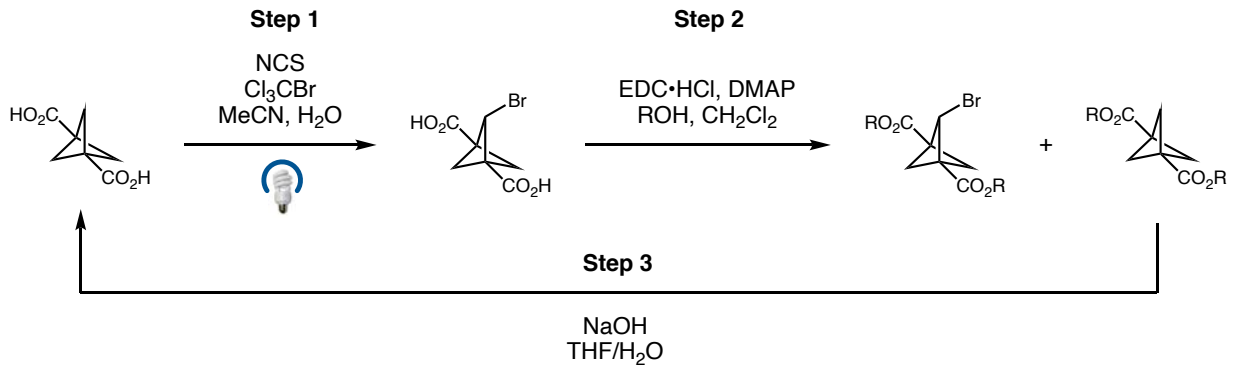



**Figure S1.** Absorption spectrum of reaction mixture for BCP 2-bromination. See general procedure for reaction composition using bicyclo[1.1.1]pentane-1,3-dicarboxylic acid.

The spectral window of the Integrated Photoreactor is 400–500 nm.[5]

**General Procedure for the BCP 2-Bromination (60 mmol scale)**

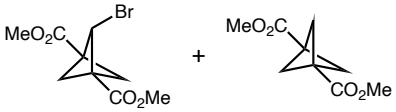



**Step 1)** To a 40 mL vial equipped with a stir bar was added bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (1.56 g, 10.0 mmol) and *N*-chlorosuccinimide (NCS, 1.47 g, 11.0 mmol, 1.1 equiv), the vial was evacuated and backfilled with nitrogen three times. Then, MeCN (20 mL) and $H_2O$ (2 mL) were added, the mixture was stirred at room temperature for 5 min and then sonicated for 1 min. The now clear solution was degassed by sparging with nitrogen for 5 min before $Cl_3CBr$ (4.9 mL, 9.91 g, 50.0 mmol, 5.0 equiv) was added and the vial was sealed with parafilm. Then, the vial was placed in the Integrated Photoreactor and stirred for 16 hours (450 nm, 100% light intensity, 600 rpm stir rate, 5200 rpm fan rate). The reaction mixture was removed from the light and stirred at room temperature for 5 min. The mixture was transferred into a 250 mL round-bottom flask, the solvent was removed, the residue was resuspended in PhMe (≈ 100 mL) and the solvent was removed *in vacuo*, repeated for two times. The resulting residue was dried under high vacuum for 2 h and then directly used for the subsequent step.

**Step 2)** A 250 mL round-bottom flask equipped with a stir bar containing 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylic acid (crude material from the previous step, 10 mmol) was charged with DMAP (4.89 g, 40.0 mmol, 4.0 equiv) and EDC•HCl (11.5 g, 60.0 mmol, 6.0 equiv). Then, $CH_2Cl_2$ (100 mL) was added, followed by the corresponding alcohol ROH (100 mmol, 10.0 equiv) and the resulting dark brown to black solution was stirred at room temperature for 24 h. Saturated $NH_4Cl$ (150 mL) was added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 100 mL) and the combined organic layers were washed with $H_2O$ (200 mL) and saturated $NaHCO_3$ (200 mL), then dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude material was purified *via* flash column chromatography to give the 2-brominated BCP diester and unbrominated BCP diester.

**Step 3)** The isolated unbrominated BCP diester (1.0 mmol) and NaOH (400 mg, 10.0 mmol, 10 euqiv) were added to an 8 mL vial equipped with a cross-shaped stir bar, followed by addition of THF (1 mL) and $H_2O$ (1 mL) and the reaction mixture was stirred at 50 °C for 24 h. The now clear solution was cooled to room temperature, HCl (12 M, 1 mL) was added slowly and the mixture was extracted with EtOAc (4 x 2 mL). The combined organic layers were washed with brine (4 mL), dried ($Mg_2SO_4$) and filtered (Celite). Then, the solvent was removed *in vacuo* to give bicyclo[1.1.1]pentane-1,3-dicarboxylic acid as a free-flowing, white solid.

**Dimethyl Ester**

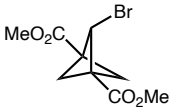



Prepared according to the general procedure on a 60 mmol scale (6 photoreactions on a 10 mmol scale performed in parallel for step 1) with 29.3 g DMAP (240 mmol, 4.0 equiv), 69.0 g EDC•HCl (360 mmol, 6.0 equiv) and 24 mL MeOH (600 mmol, 10.0 equiv) in $CH_2Cl_2$ (300 mL). Purification *via* flash column chromatography (50–100% ($CH_2Cl_2$ + 1% MeCN)/hexane, then rinsing with EtOAc) gave 5.52 g (21.0 mmol, 35% yield) of the desired 2-brominated BCP dimethyl ester as a white solid and 6.47 g (35.1 mmol, 59% yield) of the unbrominated dimethyl ester as a white solid.

The hydrolysis of the unbrominated BCP dimethyl ester was performed on a 1 mmol scale (184 mg BCP dimethyl ester) with according to the general procedure to obtain 156 mg (999 µmol, >99% yield) of the BCP diacid as a white solid. To validate scalability, the hydrolysis was also performed on a 90 mmol scale (16.6 g BCP dimethyl ester) with 36.0 g NaOH (0.90 mol, 10 equiv), THF (90 mL) and $H_2O$ (90 mL) to obtain 14.0 g (89.7 mmol, >99% yield) of the BCP diacid as a white solid.

Based on the recyclable starting material, the desired 2-brominated BCP dimethyl ester was obtained in 85% yield.

**Dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (4)**



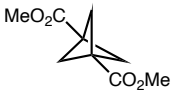

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.55 (d, *J* = 7.5 Hz, 1H), 3.74 (s, 6H), 3.04 (dd, *J* = 9.9, 3.1 Hz, 1H), 2.82 (d, *J* = 2.8 Hz, 1H), 2.43 (dd, *J* = 7.5, 3.1 Hz, 1H), 2.31 (dd, *J* = 10.0, 2.8 Hz, 1H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 166.9, 61.5, 52.4, 50.6, 50.0, 43.1.

**IR (film):** $\nu_{max}(cm^{-1})$ 3019.0, 1725.2, 1438.7, 1300.5, 1252.3, 1209.8, 1192.8, 1142.0, 1104.3, 1052.1, 1011.9, 957.0, 923.2, 913.6, 875.2, 790.4, 774.2, 722.4, 595.4, 463.7, 422.7.

**HRMS (ESI)** m/z calcd. for $C_9H_{11}O_4BrNa$ ($[M+Na]^+$) 284.9738, found 284.9737.

**Dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate (S1)**

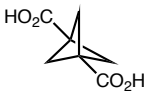



**$^1$H NMR (400 MHz, $CDCl_3$)** δ 3.69 (s, 6H), 2.32 (s, 6H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.9, 53.0, 52.0, 37.7.

The spectroscopic data matched those reported in the literature.[6]

**Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (1)**

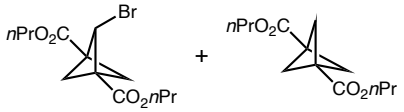



**$^1$H NMR (400 MHz, DMSO-*d6*)** δ 12.52 (s, 2H), 2.15 (s, 6H).

**$^{13}$C NMR (101 MHz, DMSO-*d6*)** δ 170.5, 51.8, 37.1.

The spectroscopic data matched those reported in the literature.[6]

**Di-*n*-propyl Ester (60 mmol scale)**

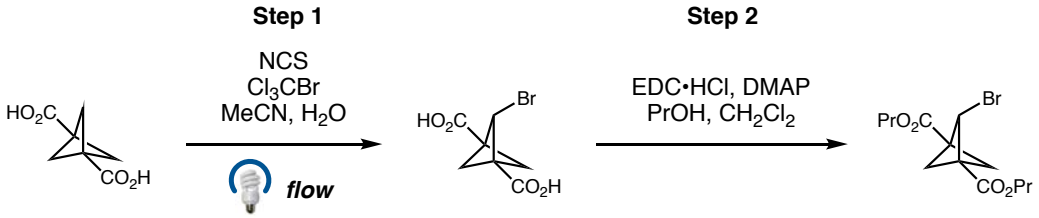



Prepared according to the general procedure on a 60 mmol scale (6 photoreactions on a 10 mmol scale performed in parallel for step 1) with 29.3 g DMAP (240 mmol, 4.0 equiv), 69.0 g EDC•HCl (360 mmol, 6.0 equiv) and 45 mL *n*PrOH (600 mmol, 10.0 equiv) in $CH_2Cl_2$ (300 mL). Purification *via* flash column chromatography (40–100% ($CH_2Cl_2$ + 1% MeCN)/hexane, then rinsing with EtOAc) gave 6.54 g (20.5 mmol, 34% yield) of the desired 2-brominated BCP di-*n*-propyl ester as a colorless oil and 8.16 g (34.0 mmol, 57% yield) of the unbrominated di-*n*-propyl ester as a colorless oil.

The hydrolysis of the unbrominated BCP di-*n*-propyl ester was performed on a 1 mmol scale (240 mg BCP di-*n*-propyl ester) with according to the general procedure to obtain 156 mg (999 µmol, >99% yield) of the BCP diacid as a white solid.

Based on the recyclable starting material, the desired 2-brominated BCP di-*n*-propyl ester was obtained in 79% yield.

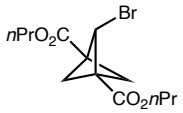
**Di-*n*-propyl Ester (0.16 mol scale)**




**Step 1)** Add bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (25.0 g, 0.16 mol, 1 eq.) in MeCN (800 mL) and $H_2O$ (80 mL) at 25 °C to 1 L three-neck round bottom flask under Ar atmosphere with magnetic stirring. Add *N*-chlorosuccinimide (64.1 g, 0.48 mol, 3 eq.) to the mixture under stirring. Add bromotrichloromethane (190 g, 0.96 mol, 6 eq.) to the mixture under stirring. The reaction was illuminated with blue LED box [460–465 nm (100 W * 5), pump: 4 mL/min; coli: 50 mL*5; retention time: 90 min; pump time: 9 hr, 65 °C (water bath)] – NOTE: Blue LED 460–465 nm (100 W) was from ®Xin xingyan. Following reaction, the reaction mixture was dried with anhydrous $Na_2SO_4$, filtered and concentrated to obtain crude 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylic acid (90 g) which was used in the next step directly.

**Step 2)** *Two reactions in parallel.* Crude 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylic acid (0.08 mol, crude), EDCI (61.2 g, 0.32 mol, 4.0 eq.) in *n*-PrOH (192 g, 3.2 mol, 40 eq.) and DCM (469 mL) at 25 °C in 1 L three-neck round bottom flask under $N_2$ atmosphere with magnetic stirring. Add DMAP (19.5 g, 0.319 mol) to the mixture under stirring. Stir the solution for 16 h at 25–30 °C. Following reaction, the two reactions were combined and quenched with ice-water (300 mL) at 0 °C. The resulting solution was concentrated to remove *n*-PrOH at 45 °C with water pump, and the aqueous later was extracted with DCM (500 mL * 3). The organic phases were combined and adjusted to pH 2–3 with 2 M HCl aq. (150 mL) at 20–25 °C. The aqueous phase was extracted with DCM (200 mL). The organic layer mixture was adjusted to pH = 7 with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with DCM (200 mL) to get the organic layer. The organic layer was dried with anhydrous $Na_2SO_4$. The organic layer was filtered and concentrated in vacuum to give the crude product. The crude product was purified by column chromatography two times, eluting with pet ether/EtOAc = 100/1 to 2/1 to give 2-brominated BCP di-*n*-propyl ester (28.5 g, 0.089 mol, 56% yield) as a yellow oil.

**Di-*n*-propyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (5)**



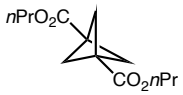

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 4.55 (d, *J* = 7.5 Hz, 1H), 4.09 (td, *J* = 6.7, 2.0 Hz, 4H), 3.02 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.81 (d, *J* = 2.7 Hz, 1H), 2.42 (dd, *J* = 7.5, 3.1 Hz, 1H), 2.30 (dd, *J* = 10.1, 2.8 Hz, 1H), 1.67 (h, *J* = 7.2 Hz, 4H), 0.95 (t, *J* = 7.4 Hz, 6H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 166.7, 66.9, 61.6, 50.5, 49.8, 43.2, 22.0, 10.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2968.5, 1729.8, 1463.4, 1391.7, 1360.4, 1292.4, 1255.8, 1201.3, 1178.7, 1059.2, 1010.0, 930.7, 770.3, 465.8.

**HRMS (ESI)** m/z calcd. for $C_{13}H_{20}O_4Br$ ($[M+H]^+$) 319.0545, found 319.0540.

**Di-*n*-propyl bicyclo[1.1.1]pentane-1,3-dicarboxylate (S2)**



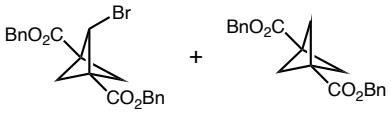

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 4.04 (t, *J* = 6.7 Hz, 4H), 2.31 (s, 6H), 1.65 (h, *J* = 7.2 Hz, 4H), 0.93 (t, *J* = 7.4 Hz, 6H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.7, 66.4, 52.9, 37.8, 22.0, 10.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2969.2, 1727.0, 1463.4, 1391.1, 1340.8, 1284.4, 1203.9, 1172.1, 1141.7, 1059.5, 1027.4, 931.1, 731.4, 458.7.

**HRMS (ESI)** m/z calcd. for $C_{13}H_{21}O_4$ ($[M+H]^+$) 241.1440, found 241.1437.

**Dibenzyl Ester**

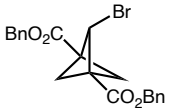



Prepared according to the general procedure on a 10 mmol scale with 10.4 mL BnOH (100 mmol, 10.0 equiv) in $CH_2Cl_2$ (100 mL). Purification *via* flash column chromatography (40–100% ($CH_2Cl_2$ + 1% MeCN)/hexane, then rinsing with EtOAc) gave 1.41 g (3.40 mmol, 34% yield) of the desired 2-brominated BCP dibenzyl ester as a white solid and 1.93 g (5.74 mmol, 57% yield) of the unbrominated dibenzyl ester as a white solid.

The hydrolysis of the unbrominated BCP dimethyl ester was performed on a 1 mmol scale (336 mg BCP dibenzyl ester) with according to the general procedure to obtain 157 mg (1.00 mmol, >99% yield) of the BCP diacid as a white solid.

Based on the recyclable starting material, the desired 2-brominated BCP dibenzyl ester was obtained in 79% yield.

**Dibenzyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (6)**



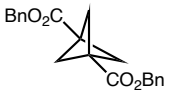

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.30 (m, 10H), 5.17 (s, 4H), 4.59 (d, *J* = 7.5 Hz, 1H), 3.08 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.85 (d, *J* = 2.8 Hz, 1H), 2.46 (dd, *J* = 7.5, 3.1 Hz, 1H), 2.33 (dd, *J* = 10.0, 2.8 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 166.4, 135.4, 128.8, 128.5, 128.2, 67.0, 61.6, 50.7, 50.0, 43.2.

**IR (film):** $\nu_{max}(cm^{-1})$ 1722.9, 1496.6, 1454.4, 1380.8, 1291.8, 1262.2, 1205.9, 1142.4, 1080.6, 1048.6, 1017.3, 1007.9, 967.7, 944.6, 925.0, 905.8, 859.2, 769.0, 751.5, 694.0, 587.3, 572.0, 512.1, 484.3, 467.6, 419.2.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{19}O_4BrNa$ ($[M+Na]^+$) 437.0364, found 437.0362.

**Dibenzyl bicyclo[1.1.1]pentane-1,3-dicarboxylate (S3)**

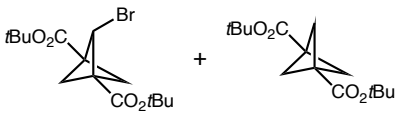



**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.29 (m, 10H), 5.12 (s, 4H), 2.36 (s, 6H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.3, 135.8, 128.7, 128.4, 128.2, 66.5, 53.0, 37.9.

The spectroscopic data matched those reported in the literature.[6]

**Di-*tert*-butyl Ester**




Prepared according to the general procedure on a 20 mmol scale (2 photoreactions on a 10 mmol scale performed in parallel) for step 1.

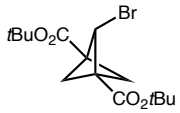
In a 250 mL round-bottom flask equipped with a stir bar, the 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylic acid (crude material from the previous step, 20 mmol) was suspended in $CH_2Cl_2$ (80 mL) and cyclohexane (40 mL) and sonicated for 5 min under nitrogen atmosphere. Then, *tert*-

butyl 2,2,2-trichloroacetimidate (36 mL, 43.7 g, 200 mmol, 10.0 equiv) was added, followed by dropwise addition of $BF_3$•$Et_2O$ (120 µL, 1 mmol, 0.05 equiv). The reaction mixture was stirred vigorously at room temperature for 24 h after which it was cooled to 0 °C and $NaHCO_3$ (16.8 g, 200 mmol, 10 equiv) was added in one portion. After allowing the reaction mixture to warm up to room temperature, the mixture was filtered (Celite), rinsing with $CH_2Cl_2$/cyclohexane (v/v = 1/2), and the solvent was removed *in vacuo*. Purification *via* flash column chromatography (40–100% ($CH_2Cl_2$ + 1% MeCN)/hexane, then rinsing with EtOAc) gave 2.38 g (6.85 mmol, 34% yield) of the desired 2-brominated BCP di-*tert*-butyl ester as a white solid and 3.05 g (11.4 mmol, 57% yield) of the unbrominated di-*tert*-butyl ester as a white solid.

For the hydrolysis of the unbrominated BCP di-*tert*-butyl ester, the diester (268 mg, 1 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and TFA (1.5 mL, 2.28 g, 20 mmol, 20 equiv) was added. The reaction mixture was stirred vigorously for 16 h after which the volatiles were removed *in vacuo*, the residue was resuspended in PhMe (10 mL) and the volatiles were removed *in vacuo* again. After repeating this procedure for two more times, the residue was dried under high vacuum to obtain 155 mg (993 µmol, >99% yield) of the BCP diacid as a white solid.

Based on the recyclable starting material, the desired 2-brominated BCP di-*tert*-butyl ester was obtained in 79% yield.

**Di-*tert*-butyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (7)**



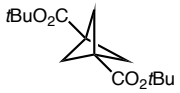

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 4.45 (d, *J* = 7.6 Hz, 1H), 2.91 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.72 (d, *J* = 2.7 Hz, 1H), 2.30 (dd, *J* = 7.5, 3.0 Hz, 1H), 2.20 (dd, *J* = 10.0, 2.7 Hz, 1H), 1.46 (s, 18H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 166.2, 82.1, 62.0, 50.1, 49.4, 43.5, 28.1.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2974.5, 1717.7, 1456.1, 1369.4, 1315.5, 1256.5, 1215.9, 1154.2, 1098.0, 1055.0, 1035.2, 1009.8, 918.3, 840.0, 815.7, 770.4, 739.1, 465.7, 419.9.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{23}O_4BrNa$ ($[M+Na]^+$) 369.0677, found 369.0673.

**Di-*tert*-butyl bicyclo[1.1.1]pentane-1,3-dicarboxylate (S4)**



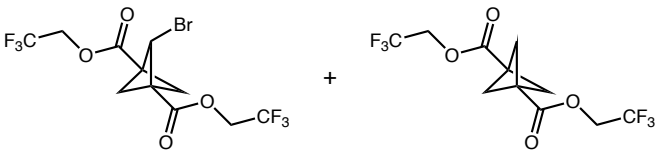

**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 2.20 (s, 6H), 1.44 (s, 18H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.3, 81.0, 52.6, 38.2, 28.1.

**IR (film):** $\nu_{max}(cm^{-1})$ 2989.7, 1719.6, 1475.8, 1459.2, 1395.3, 1368.2, 1305.1, 1260.0, 1216.1, 1145.7, 1114.2, 1042.2, 1017.7, 837.3, 813.7, 733.8, 462.6, 414.4.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{24}O_4Na$ ($[M+Na]^+$) 291.1572, found 291.1568.

**Bis(trifluoroethyl) Ester**

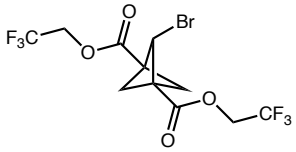



Prepared according to the general procedure on a 10 mmol scale with 7.3 mL trifluoroethanol (100 mmol, 10.0 equiv) in $CH_2Cl_2$ (100 mL). Purification *via* flash column chromatography (20–100% ($CH_2Cl_2$ + 1% MeCN)/hexane, then rinsing with EtOAc) gave 1.39 g (3.48 mmol, 35% yield) of the desired 2-brominated BCP bis(trifluoroethyl) ester as a colorless oil and 1.74 g (5.43 mmol, 54% yield) of the unbrominated bis(trifluoroethyl) ester as a white solid.

The hydrolysis of the unbrominated BCP bis(trifluoroethyl) ester was performed on a 1 mmol scale (320 mg BCP bis(trifluoroethyl) ester) with according to the general procedure to obtain 156 mg (999 μmol, >99% yield) of the BCP diacid as a white solid.

Based on the recyclable starting material, the desired 2-brominated BCP bis(trifluoroethyl) ester was obtained in 76% yield.

**Bis(2,2,2-trifluoroethyl) 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (8)**



**$^{1}$H NMR (500 MHz, $CDCl_3$)** δ 4.55 (d, *J* = 7.5 Hz, 1H), 4.09 (td, *J* = 6.7, 2.0 Hz, 4H), 3.02 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.81 (d, *J* = 2.7 Hz, 1H), 2.42 (dd, *J* = 7.5, 3.1 Hz, 1H), 2.30 (dd, *J* = 10.1, 2.8 Hz, 1H), 1.67 (h, *J* = 7.2 Hz, 4H), 0.95 (t, *J* = 7.4 Hz, 6H).

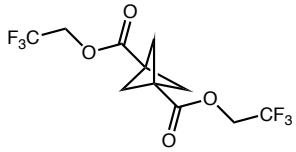
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 164.5, 122.7 (q, *J* = 277.2 Hz), 60.904 (q, J = 37.1 Hz), 60.896, 51.0, 50.4, 42.8.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -73.79 (t, *J* = 8.2 Hz, 6F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 1753.3, 1412.4, 1264.8, 1200.5, 1157.2, 1068.1,977.5, 915.8, 841.6, 771.8, 649.2, 557.8.

**HRMS (ESI)** m/z calcd. for $C_{11}H_8O_4F_6Br$ ($[M–H]^-$) 396.9516, found 396.9519.

**Bis(2,2,2-trifluoroethyl) bicyclo[1.1.1]pentane-1,3-dicarboxylate (S5)**



**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 4.47 (q, *J* = 8.3 Hz, 4H), 2.44 (s, 6H).

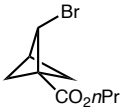
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 167.2, 122.9 (q, *J* = 277.0 Hz), 60.7 (q, *J* = 36.8 Hz), 53.3, 37.5.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -73.84 (t, *J* = 8.4 Hz, 6F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 3033.8, 1750.7, 1444.5, 1415.1, 1306.6, 1288.7, 1254.9, 1207.8, 1169.0, 1065.1, 1052.6, 974.2, 835.6, 775.8, 730.1, 664.8, 583.9, 551.1, 474.3, 457.8.

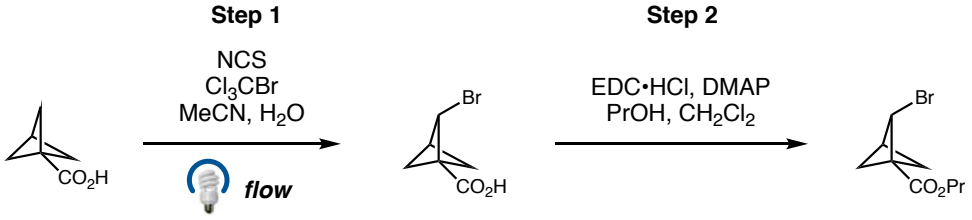
**HRMS (ESI)** m/z calcd. for $C_{11}H_{21}O_4F_6$ ($[M+H]^+$) 321.0561, found 321.0553.

**Monopropyl Ester (5 mmol scale)**




Prepared according to a slightly altered general procedure for step 1 on a 5 mmol scale with bicyclo[1.1.1]pentane-1-carboxylic acid (560 mg, 5.0 mmol), NCS (1.34 g, 10.0 mmol, 2.0 equiv) and $Cl_3CBr$ (3.0 mL, 5.95 g, 30 mmol, 6.0 equiv) in a mixture of MeCN (10 mL) and $H_2O$ (1 mL). Following a slightly altered general procedure for step 2, 2-bromobicyclo[1.1.1]pentane-1-carboxylic acid (crude material from the last step, 5 mmol) was converted with DMAP (611 mg, 5.00 mmol, 1.0 equiv), EDC•HCl (1.92 g, 10.0 mmol, 2.0 equiv) and *n*PrOH (3.7 mL, 3.01 g, 50.0 mmol, 10.0 equiv) in $CH_2Cl_2$ (50 mL). Purification *via* flash column chromatography (20–100% ($CH_2Cl_2$ + 1% MeCN)/hexane) gave 470 mg (2.02 mmol, 40% yield) of the desired 2-brominated BCP *n*-propyl ester as a colorless oil.

**Monopropyl Ester (71.3 mmol scale)**

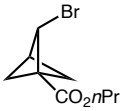



**Step 1)** Four reactions were carried out separately. Add *N*-chlorosuccinimide (19.1 g, 143 mmol, 2 eq.) into a solution of bicyclo[1.1.1]pentane-1-carboxylic acid (8.0 g, 71.3 mmol, 1 eq.) in MeCN (720 mL) at 25 °C (inner temp.) under Ar to 2 L three-neck round bottom flask with magnetic stirring. Add bromotrichloromethane (85 g, 428 mmol, 6 eq.) into the reaction system and stir the mixture at 25 °C (inner temp.) under Ar for 1 minute until homogenous. The reaction was illuminated with blue LED box [460–465 nm (100 W * 5), pump: 2.5 mL/min; coli: 50 mL*5; retention time: 100 min; pump time: 7 hr, 50 °C (water bath)] – NOTE: Blue LED 460–465 nm (100 W) was from ®Xin xingyan. Following reaction, the reaction mixture was concentrated to obtain crude 2-bromobicyclo[1.1.1]pentane-1-carboxylic acid (28 g) which was used in the next step directly. *NOTE: This intermediate BCP carboxylic acid is unstable.*

**Step 2)** Four reactions were carried out separately. Add EDCI (56.2 g, 293 mmol, 2.0 eq.) into solution of DMAP (17.9 g, 147 mmol, 1.0 eq.), crude 2-bromobicyclo[1.1.1]pentane-1-carboxylic

acid (28.0 g, crude) and *n*-PrOH (110 mL, 1.47 mol, 10 eq.) in DCM (700 mL) at 25–30 °C (inner temp.) under $N_2$ atmosphere with magnetic stirring in 2 L three-neck round bottom flask. Stir the solution for 12 h at 25–30 °C under $N_2$ atmosphere. Following reaction, dilute the reaction solution with DCM (300 mL). The DCM layer was washed with ice-water (1 L), the DCM layer was adjusted to pH = 3–4 with HCl (2 M, 20 mL) and $H_2O$ (500 mL) was added. The two layers were separated and the organic later adjusted to pH = 7–8 with saturated $NaHCO_3$ (50 mL). $H_2O$ (500 mL) was added and the two layers separated to get the organic layer. The organic layer was concentrated to get the crude product. The crude product was purified by column chromatography on silica gel (pet ether:ethyl acetate = 10:1-0:1) to give 33.2 g (four reactions combined) of the desired 2-brominated BCP *n*-propyl ester (28% combined yield, 91.5% purity).

**(±)-Propyl (2-bromobicyclo[1.1.1]pentane-1-carboxylate (9)**



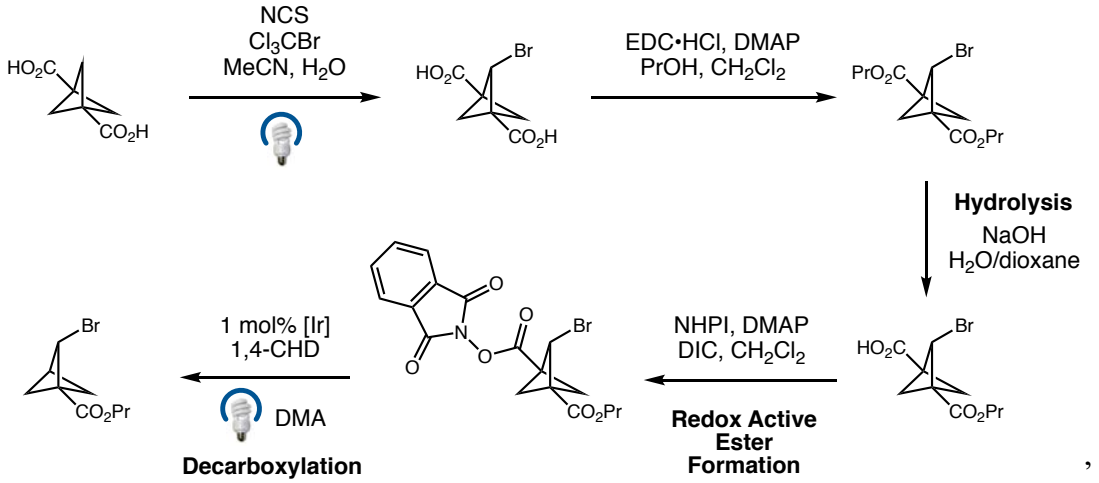

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 4.41 (d, J = 7.7 Hz, 1H), 4.05 (td, J = 6.6, 2.3 Hz, 2H), 2.88 – 2.82 (m, 1H), 2.65 (s, 1H), 2.58 (d, J = 3.0 Hz, 1H), 2.24 – 2.13 (m, 1H), 1.74 – 1.55 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 166.9, 66.5, 62.3, 49.8, 47.3, 35.1, 22.0, 10.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2969.1, 2938.2, 2901.1, 1729.2, 1492.3, 1464.0, 1393.5, 1378.9, 1325.9, 1252.2, 1204.4, 1146.4, 1068.9, 1055.0, 1007.6, 982.0, 956.7, 924.5, 908.3, 885.7, 824.9, 783.6, 755.4, 698.4.

**GC/HRMS (EI)** m/z calcd. For $C_9H_{13}O_2Br$ ($[M+H]^+$) 233.0172, found 233.0190

**Monopropyl Ester (Decarboxylation Route)**



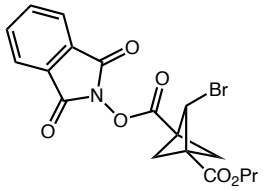

**Hydrolysis)** See compound S9.

**Redox Active Ester Formation)** To a 40 mL vial equipped with a stir bar was added 2-bromo-3-(propoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (1.11 g, 4 mmol, 1 equiv), *N*-hydroxyphthalimide (783 mg, 4.8 mmol, 1.2 equiv), and 4-(dimethylamino)pyridine (DMAP, 97.7 mg, 0.48 mmol, 0.2 equiv). Then, 20 mL DCM was added, followed by *N,N′*-diisopropylcarbodiimide (DIC, 0.75 ml, 4.8 mmol, 1.2 equiv). The vial was capped and allowed to stir at room temperature for 16 h. Next, the reaction mixture was filtered to remove the precipitate, and the filtrate was concentrated *in vacuo*. The crude material was purified using flash chromatography (25–35% ethyl acetate/hexane) and 1.18g (2.8 mmol, 70% yield) of the final product was isolated as a white solid.

**Decarboxylation)** To a 40 mL vial equipped with a stir bar was added 2-bromo-3-(propoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (422.2 mg, 1 mmol, 1 equiv) and photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ (9.14 mg, 0.01 mmol, 1 mol%). Then 20 mL N,N-dimethylacetamide (DMA) was added, followed by the addition of triethylamine ($Et_3N$, 0.28 mL, 2 mmol, 2 equiv) and 1,4-cyclohexadiene (CHD, 0.11 mL, 2 mmol, 2 equiv). Next, the solution was capped and degassed by sparging with nitrogen for 5 min before sealing with parafilm. The reaction was stirred and irradiated using two 34 W blue LED lamps (3 cm away, with cooling fan on top) for 5 hours. The reaction mixture was then removed from the light, cooled to ambient temperature. Next, diethyl ether ($Et_2O$, 40 mL) was added followed by the addtion of $H_2O$ (20

mL). The organic phase was seperated and then washed with $H_2O$ (2 x 20 mL) to remove most of the DMA. Next, the organic phase was dried over $Na_2SO_4$, filtered, and then concentrated in vacuo. The crude material was purified using flash chromatography (10% diethyl ether/hexane) and n-propyl (2-bromobicyclo[1.1.1]pentane-1-carboxylate was isolated in 163.2 mg (0.7 mmol, 70% yield) as a colorless liquid.

**(±)-1-(1,3-dioxoisoindolin-2-yl) 3-propyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (S6)**



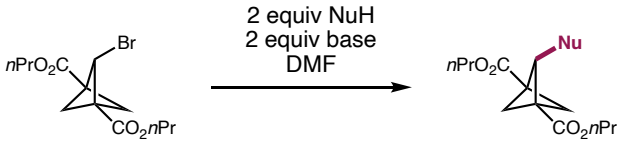

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.73 (d, *J* = 7.5 Hz, 1H), 4.12 (tt, *J* = 6.1, 3.2 Hz, 2H), 3.27 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.06 (d, *J* = 2.9 Hz, 1H), 2.66 (dd, *J* = 7.5, 3.2 Hz, 1H), 2.55 (dd, *J* = 10.0, 2.9 Hz, 1H), 1.70 (h, *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 165.96, 162.42, 161.54, 135.06, 128.94, 124.26, 67.18, 61.34, 51.59, 50.55, 44.12, 40.89, 22.00, 10.43.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2969.0, 1813.1, 1785.7, 1727.9, 1609.3, 1467.0, 1397.9, 1354.2, 1276.5, 1200.3, 1186.9, 1115.4, 1080.5, 1052.6, 1028.7, 1015.2, 988.5, 909.0, 876.6, 825.7, 785.1, 770.0, 695.5, 605.2, 518.3, 475.2.

## Reactivity of 2-Brominated Bicyclo[1.1.1]pentanes Utilizing Conventional Chemistry

To an oven-dried 8 mL vial equipped with a cross-shaped stir bar was added di-*n*-propyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (31.9 mg, 100 µmol) and nucleophile (200 µmol, 2.0 equiv), the vial was evacuated and backfilled with nitrogen three times. Then, DMF (1 mL) was added, followed by base (200 µmol, 2.0 equiv) and the reaction mixture was stirred vigorously at 90 °C for 12 h, after which the reaction mixture was cooled to room temperature and the yield was determined via $^1$H NMR assay using 1,4-difluorobenzene as internal standard.

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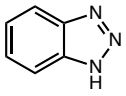
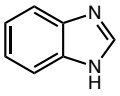
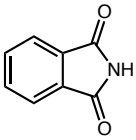
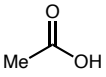
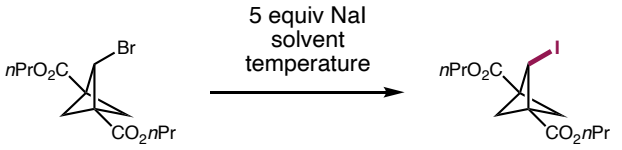
| |  |  |  |  |  |  |
| $Cs_2CO_3$ | 0% yield<br>72% s.m. | 0% yield<br>48% s.m. | 0% yield<br>76% s.m. | 0% yield<br>59% s.m. | 0% yield<br>98% s.m. | 0% yield<br>85% s.m. |
| BTMG | 0% yield<br>90% s.m. | 0% yield<br>76% s.m. | 0% yield<br>85% s.m. | 0% yield<br>83% s.m. | 0% yield<br>97% s.m. | 0% yield<br>90% s.m. |

**Table S8.** Control experiments for S$_N$2 reactivity of BCP 2-bromide.

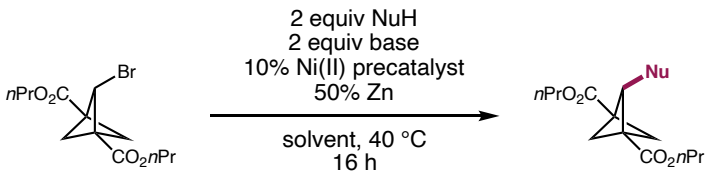



DMF, 100 °C: 0% yield, 98% s.m.

acetone, 50 °C: 0% yield, 96% s.m.

10 mol% CuI, dioxane, 100 °C: 0% yield, 86% s.m.

**Figure S2.** Control experiments for nucleophilic iodination of BCP 2-bromide.



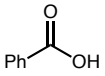
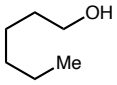
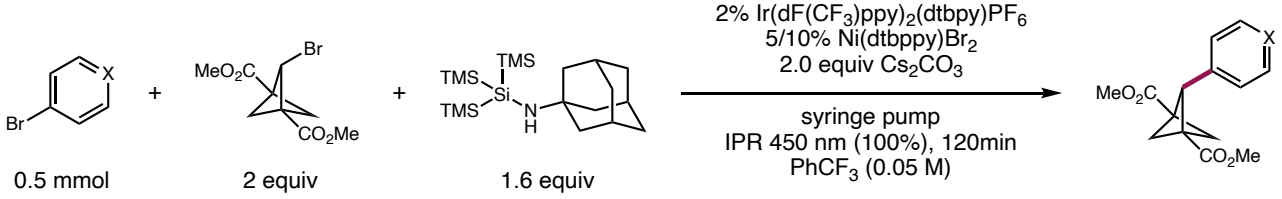

| nucleophile | base | Ni source | solvent | yield | recovered s.m. |
|---|---|---|---|---|---|
|  | $NEt_3$ | $NiBr_2$•DME | DMA | 0% | 98% |
| | DABCO | $NiBr_2$•DME | DMA | 0% | 93% |
|  | $NEt_3$ | Ni(dtbpy)$Br_2$ | DMF | 0% | 88% |
| | quinuclidine | Ni(dtbpy)$Br_2$ | DMF | 0% | 91% |
|  | $NEt_3$ | Ni(dtbpy)$Cl_2$ | MeCN | 0% | 95% |
| | DBU | Ni(dtbpy)$Cl_2$ | MeCN | 0% | 86% |

**Table S9.** Control experiments for reactivity of BCP 2-bromide under cross-coupling conditions.[7]

## Cross-Electrophile Coupling for 2-Arylation of BCP Bromides

### General Procedure for BCP-Arylation




A 40 mL vial equipped with a cross-shaped stir bar was charged with dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (326 mg, 1.00 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (11.2 mg, 10.0 µmol, 0.02 equiv) and $Ni(dtbpy)Br_2$ (12.2 mg, 25.0 µmol, 0.05 equiv). The vial was closed, sealing the cap with parafilm, evacuated and filled with nitrogen three times followed by addition of trifluorotoluene (previously degassed by sparging with nitrogen for 15 min, 10 mL). The mixture is stirred at room temperature for 5 min after which the $Ni(dtbpy)Br_2$ is fully dissolved. The vial is then placed in a water bath with a stir bar positioned above the Integrated Photoreactor and stirred under nitrogen for 2 hours (450 nm, 100% light intensity, 800 rpm stir rate, 5200 rpm fan rate). While stirring and irradiating the reaction mixture, a solution of (hetero)aryl halide (0.50 mmol) and *N*-tris(trimethylsilyl)silyladamantan-1-amine (318 mg, 0.80 mmol, 1.6 equiv) in trifluorotoluene (previously degassed by sparging with nitrogen for 15 min, 5 mL) is added via syringe pump (3 mL/hour, completion of addition after 100 min, followed by irradiation for 20 min without any further addition of (hetero)aryl halide solution). After 2 hours, the reaction mixture was removed from the water bath on top of the Integrated Photoreactor, opened to air and EtOAc (≈ 10 mL) and methanol (300 µL) were added. The reaction mixture was stirred at room temperature for 60 min and then filtered through celite, rinsing with EtOAc. The filtrate was concentrated *in vacuo* and the resulting crude material was purified *via* flash column chromatography to give the 2-arylated BCP compound.

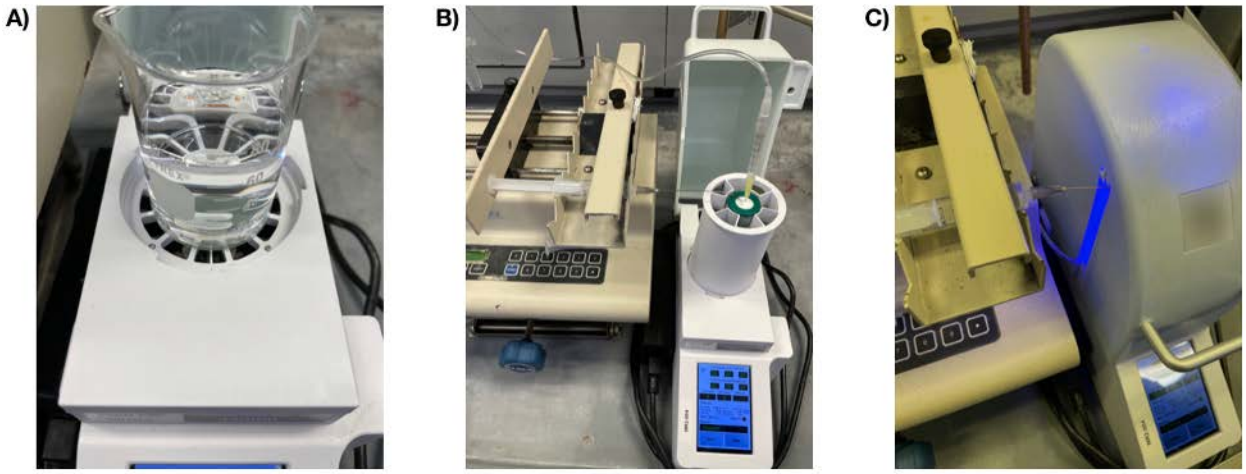



**Figure S3. A)** Setup including a beaker filled with ≈ 70 mL water and a stir bar put directly on top of the LED of the integrated photoreactor. **B)** Reaction vial put into vial holder of the integrated photoreactor, ensuring immersion into the water bath. The syringe containing the (hetero)aryl bromide and silane reagent is put in the syringe pump and ready for slow addition into the reaction mixture. The headspace of the reaction vial is connected to a $N_2$ line as an exhaust for the overpressure resulting from the slow addition. **C)** The lid of the integrated photoreactor is modified with a custom railing to allow for closing. Both the reaction and the slow addition is started.

*Notes:*

- **Reaction setup**: In many cases, running the cross-electrophile coupling by adding all compounds to one vial without utilizing the syringe pump setup has led to appreciable amounts of the desired product, although at significantly reduced yields.
- **Temperature**: Temperature control can be critical for certain substrates with substantial drops in yield at higher temperatures. The temperature of the water bath should therefore be monitored and kept below 40 °C.
- **Solvents**: For polar (hetero)aryl halides insoluble in $PhCF_3$, using a co-solvent in as low amounts as possible for the solution that is added slowly via syringe pump is beneficial. The ideal co-solvent for this was found to be *t*BuOH which was found to be not deleterious to the yield up to 90% *t*BuOH/$PhCF_3$, even in cases that do not necessitate a polar co-solvent. Acetone and acetonitrile were observed suitable in low amounts but slightly deleterious to the yield in higher amounts.
- **Electrophile stoichiometry**: Increasing the BCP bromide equivalents over 2.0 equiv did not lead to improved yields when performing the reaction with the syringe pump setup. Similarly, reducing the BCP bromide equivalents resulted in only marginally reduced yields in the syringe pump setup down to approx. 1.5 equiv for a number of substrates but employing less than 1.5 equiv of the BCP bromide resulted in significantly reduced yields of the cross-coupling

products. When running the reaction in a one-pot setup without slow addition of the BCP bromide, higher equivalencies of the BCP bromide could lead to improved yields but lower than 2.0 equiv led to low yields. For cases in which the BCP might be the more valuable coupling partner, a complete inversion of the stoichiometry (performing the reaction with an excesss of (hetero)aryl halide and the BCP bromide as limiting reagent) may be beneficial; during optimization, we found that similar to slightly diminished yields could be obtained for a number of different substrates when utilizing the syringe pump setup but significantly reduced yields were observed too, particularly for more electron-rich (hetero)aryl halide substrates.

- **Photocatalyst**: $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ was chosen for availability reasons. However, during optimization, the reaction proved to be operational within a large window of photocatalysts that fulfill the requirements of being oxidizing enough to facilitate oxidation of the supersilyl radical precursor and reduction of the Ni catalyst. A non-exhaustive list of photocatalysts employed with similar outcome includes:
    - $Ir(ppy)_2(dtbpy)PF_6$
    - $Ir(ppy)_2(bpy)PF_6$
    - $Ir(F(Me)ppy)_2(dtbpy)PF_6$
    - $Ir(dF(Me)ppy)_2(dtbpy)PF_6$
    - $Ir(dF(Me)ppy)_2(bpy)PF_6$
    - $Ir(dF(F)ppy)_2(dtbpy)PF_6$
    - $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$
    - $Ir(dF(CF_3)ppy)_2(bpy)PF_6$
    - $Ir(dF(CF_3)ppy)_2(4,4'\text{-}dFbpy)PF_6$
    - $Ir(dF(CF_3)ppy)_2(5,5'\text{-}dFbpy)PF_6$
    - 4-CzIPN (necessitates higher catalyst loading)
- **Ni loading**: In many cases, the yield is dependant on nickel loading; broadly, electron-deficient (hetero)aryl halides work best with 5% nickel and yields deteriorate at higher nickel loading, resulting in higher amounts of aryl homocoupling instead. Electron-rich (hetero)aryl halides work best with 10% nickel with sluggish conversion at lower nickel loading.
- **Ni precatalyst**: Instead of using previously synthesized $Ni(dtbpy)Br_2$, the same amount of $NiBr_2$•glyme and dtbpy can be used without an observable drop in yield. However, in this case it is critical that the material is fully dissolved before starting the irradiation and addition of

(hetero)aryl halide and silane. This can be achieved by sonication of the solution containing BCP bromide, cesium carbonate, Ir photocatalyst, and the Ni complex precatalysts for ≈ 10 min.

- **Base**: A range of inorganic bases proved to lead to comparable or slightly diminished yield, furthermore, a range of organic bases could be used to result in a homogeneous reaction mixture for transformations in which this may be desirable. A non-exhaustive list of bases employed with similar or slightly diminished yield includes $K_2CO_3$, $K_3PO_4$, CsOAc, lutidine and BTMG. Bases that led to significantly reduced yields include KOPiv, DBU and TMG. It was possible to run the reaction with both higher and lower base equivalencies (0.2 ... 5.0 equivalents) with limited effect on the product formation, however to facilitate the complete decomposition of the silyl bromide with MeOH after the photochemical step, a base loading slightly superstoichiometric to the supersilyl radical precursor is advised.
- **Silyl radical precursor**: (Adamantylamino)supersilane (Sigma-Aldrich, cat.-no. 915319) was identified as the best silyl radical precursor for this transformation, but supersilanol (Cas no. 7428-60-6) could also be used with slightly diminished yield of the cross-coupling product for a number of different substrates. Other silanes led to either significantly diminished yields or no desired product. Increased supersilyl radical precursor equivalents up to 3.0 equiv did not lead to changes in the reaction outcome but lowering the equivalencies below 1.5 equiv resulted in incomplete conversion for a number of different substrates.
- **Workup**: In some instances, particularly for compounds of which coordination to the nickel complex appear likely, slight modifications of the workup procedure have led to improved yields over the standard workup procedure. Two alternative workup procedures were employed:
  - **Alternate workup procedure A:** After the irradiation is finished, the reaction mixture was removed from the water bath on top of the Integrated Photoreactor, opened to air and $CHCl_3$ (≈ 10 mL) and methanol (300 µL) were added. The reaction mixture was stirred at room temperature for 60 min and then filtered through celite, rinsing with $CHCl_3$. The resulting crude material was purified by sequential flash column chromatography (first wash column: gradient 0–10% MeOH/$CH_2Cl_2$; second column: adequate eluent for target compound isolation).
  - **Alternate workup procedure B:** After the irradiation is finished, the reaction mixture was removed from the water bath on top of the Integrated Photoreactor, opened to air and $CHCl_3$ (≈ 10 mL) and methanol (300 µL) were added. The reaction mixture was stirred at room

temperature for 60 min and then transferred into a separatory funnel. Aqueous $Na_4EDTA$ (0.1 M, 20 mL) was added, the layers were separated and the aqueous layer was extracted with $CHCl_3$ (3 x 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (40 mL), dried ($Mg_2SO_4$) and filtered. After removal of the solvent, the crude material was purified *via* flash column chromatography.

- **Unsuccessful substrates:** Lower yielding substrates are described in the following table:

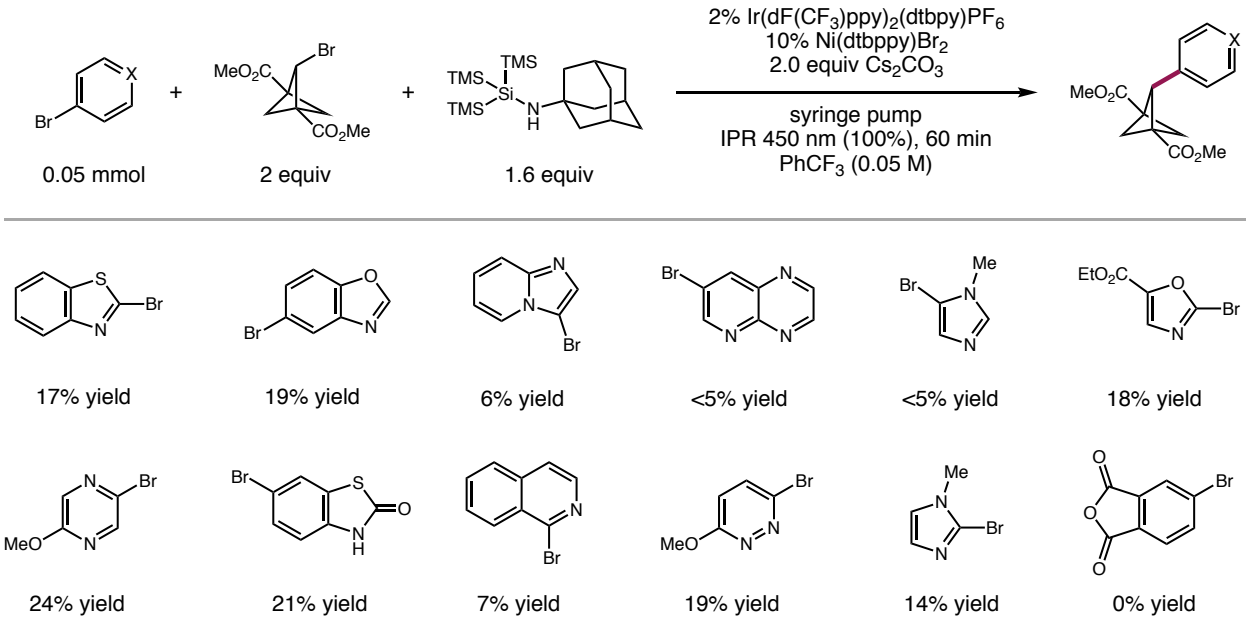
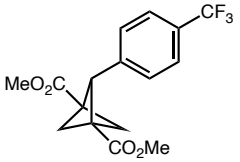



**Table S10.** All yields are $^1H$ NMR yields vs. mesitylene.

**Dimethyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (10)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (3–20% EtOAc/hexane) gave 139 mg (424 μmol, 85% yield) of the desired product as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 4.03 (d, *J* = 6.7 Hz, 1H), 3.74 (s, 6H), 2.67 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.45 – 2.34 (m, 3H).

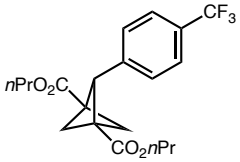
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.2, 140.5 (q, *J* = 1.4 Hz), 129.4 (q, *J* = 32.4 Hz), 129.1, 127.6 – 120.8 (m), 125.3 (q, *J* = 3.7 Hz), 66.6, 52.9, 52.2, 48.3, 41.3.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ - 62.59 (s, 3F).

**IR (film):** $\nu_{max}(cm^{-1})$ 1722.8, 1618.0, 1450.2, 1436.3, 1326.6, 1287.7, 1206.8, 1190.9, 1156.8, 1135.1, 1111.8, 1066.0, 1048.4, 1025.7, 1013.1, 919.1, 879.4, 865.4, 819.0, 804.2, 790.1, 748.0, 671.4, 600.4, 535.2.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{16}O_4F_3$ ($[M+H]^+$) 329.1001, found 329.0994.

**Di-*n*-propyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (11)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of di-*n*-propyl 2-bromobicyclo[1.1.1]pentane-1,3-

dicarboxylate (319.2 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (3–15% EtOAc/hexane) gave 160 mg (415 μmol, 83% yield) of the desired product as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.91 (t, *J* = 6.7 Hz, 4H), 3.83 (d, *J* = 6.7 Hz, 1H), 2.46 (dd, *J* = 10.1, 3.1 Hz, 1H), 2.25 – 2.16 (m, 3H), 1.48 (h, *J* = 7.3 Hz, 4H), 0.74 (t, *J* = 7.4 Hz, 6H).

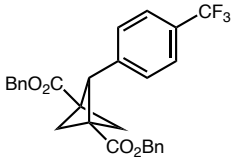
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.9, 140.7, 129.3 (q, *J* = 32.4 Hz), 129.1, 125.2 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 272.0 Hz), 66.8, 66.5, 52.8, 48.2, 41.4, 22.1, 10.5.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -62.57 (s, 3F).

**IR (film):** $\nu_{max}(cm^{-1})$ 2970.4, 1725.2, 1619.2, 1457.0, 1379.0, 1324.5, 1279.5, 1196.6, 1163.4, 1119.5, 1068.5, 1044.0, 1017.5, 933.9, 869.5, 819.0, 773.0, 751.6, 699.1, 673.1, 600.3, 501.5.

**HRMS (ESI)** m/z calcd. for $C_{20}H_{24}O_4F_3$ ($[M+H]^+$) 385.1627, found 385.1621.

**Dibenzyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (12)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dibenzyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (415.3 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (3–15% EtOAc/hexane) gave 196 mg (408 μmol, 83% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 (d, *J* = 8.1 Hz, 2H), 7.39 – 7.31 (m, 10H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.18 (s, 4H), 4.03 (d, *J* = 6.7 Hz, 1H), 2.65 (dd, *J* = 10.2, 3.1 Hz, 1H), 2.46 – 2.43 (m, 2H), 2.41 (dd, *J* = 6.8, 3.1 Hz, 1H).

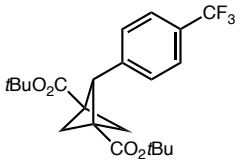
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.5, 140.3, 135.5, 129.3 (q, *J* = 32.4 Hz), 129.1, 128.8, 128.7, 128.5, 125.2 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.0 Hz), 66.9, 66.8, 52.7, 48.2, 41.4.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ - 62.60 (s, 3F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 2936.0, 1715.1, 1618.0, 1494.9, 1455.9, 1414.1, 1377.9, 1327.1, 1279.9, 1198.5, 1155.0, 1119.1, 1069.8, 1042.6, 1016.0, 979.4, 954.6, 916.4, 900.3, 868.8, 817.9, 774.4, 752.7, 699.0, 673.5, 599.3, 585.4, 518.1, 501.4.

**HRMS (ESI)** m/z calcd. for $C_{28}H_{24}O_4F_3$ ($[M+H]^+$) 481.1627, found 481.1621.

**Di-*tert*-butyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (13)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of di-*tert*-butyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (347.2 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (3–10% EtOAc/hexane) gave 173 mg (418 μmol, 84% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 3.91 (d, *J* = 6.6 Hz, 1H), 2.53 (dd, *J* = 9.9, 3.0 Hz, 1H), 2.33 – 2.28 (m, 2H), 2.26 (dd, *J* = 6.8, 3.1 Hz, 1H), 1.47 (s, 18H).

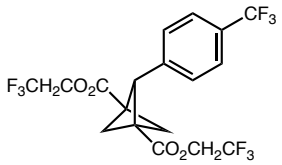
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.5, 141.2 (q, *J* = 1.4 Hz), 129.1, 129.1 (q, *J* = 32.3 Hz), 125.1 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.8 Hz), 81.7, 66.4, 52.5, 47.7, 41.8, 28.2.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ - 62.51 (s, 3F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 2980.4, 1712.0, 1617.9, 1455.6, 1367.7, 1324.9, 1306.7, 1198.4, 1157.2, 1119.9, 1068.9, 1056.0, 1016.7, 896.6, 869.6, 837.9, 817.9, 748.8, 726.0, 699.7, 672.7, 604.2.

**HRMS (ESI)** m/z calcd. for $C_{22}H_{27}O_4F_3Na$ ([M+Na]$^+$) 435.1759, found 435.1758.

**Bis(2,2,2-trifluoroethyl) 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (14)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of di-*tert*-butyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (399.1 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (3–20% EtOAc/hexane) gave 163 mg (351 μmol, 70% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 4.54 (qd, *J* = 8.3, 2.9 Hz, 4H), 4.16 (d, *J* = 6.7 Hz, 1H), 2.80 (dd, *J* = 10.1, 3.3 Hz, 1H), 2.53 (ddd, *J* = 9.9, 4.7, 2.7 Hz, 3H).

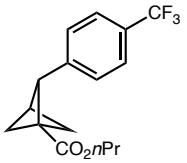
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 166.6, 139.3 (q, *J* = 1.2 Hz), 129.9 (q, *J* = 32.6 Hz), 128.9, 125.6 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.0 Hz), 122.8 (q, *J* = 277.3 Hz), 67.2, 60.7 (q, *J* = 36.9 Hz), 53.0, 48.7, 41.0.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -62.69 (s, 3F), -73.65 (t, *J* = 8.4 Hz, 6F).

**IR (film):** $\nu_{max}$(cm$^{-1}$) 1748.5, 1618.9, 1450.0, 1408.8, 1325.6, 1293.9, 1270.7, 1251.2, 1197.4, 1157.2, 1135.4, 1113.3, 1058.7, 1013.8, 973.6, 887.7, 865.6, 846.3, 833.8, 821.3, 739.9, 673.5, 658.3, 608.25, 556.6, 539.2.

**HRMS (ESI)** m/z calcd. for $C_{20}H_{16}F_9O_6$ ([M+AcO]$^-$) 523.0803, found 523.0806.

**(±)-Propyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1-carboxylate (15)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of propyl 2-bromobicyclo[1.1.1]pentane-1-carboxylate (233 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br₂** in $PhCF_3$. Purification *via* flash column chromatography (10–75% $CH_2Cl_2$/hexane) gave 122 mg (409 μmol, 82% yield) of the desired product as a colorless oil.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.08 (t, *J* = 6.7 Hz, 2H), 3.75 (d, *J* = 6.8 Hz, 1H), 2.81 (s, 1H), 2.35 (dd, *J* = 9.7, 3.0 Hz, 1H), 2.19 (d, *J* = 1.9 Hz, 1H), 2.17 – 2.11 (m, 2H), 1.67 (h, *J* = 7.2 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

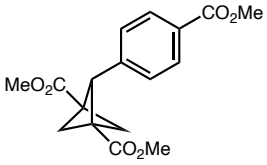
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.3, 142.9 (q, *J* = 1.4 Hz), 129.0, 128.8 (q, *J* = 32.3 Hz), 125.1 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.9 Hz), 66.4, 64.7, 49.9, 47.9, 46.0, 31.1, 22.1, 10.5.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ - 62.43 (s, 3F).

**IR (film):** $\nu_{max}(cm^{-1})$ 2969.5, 2901.3, 1730.4, 1492.2, 1463.4, 1393.4, 1326.2, 1252.4, 1205.3, 1146.7, 1068.9, 1054.9, 1008.6, 956.6, 924.5, 885.6, 824.6, 783.3, 755.3.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{16}O_4F_3$ ($[M+H]^+$) 299.1259, found 299.1255.

**Dimethyl 2-(4-(methoxycarbonyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (16)**




Prepared according to the general procedure slowly adding a solution of methyl 4-bromobenzoate (108 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br₂**

in $PhCF_3$. Purification *via* flash column chromatography (10–100% $CH_2Cl_2$/hexane) gave 129 mg (405 μmol, 81% yield) of the desired product as a white solid.

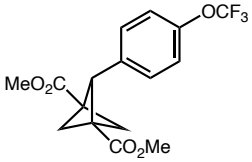
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.01 – 7.96 (m, 2H), 7.37 – 7.33 (m, 2H), 4.04 (d, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 6H), 2.68 (ddd, *J* = 9.2, 3.0, 0.9 Hz, 1H), 2.43 – 2.39 (m, 2H), 2.37 (dd, *J* = 6.7, 3.1 Hz, 1H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.2, 167.0, 141.7, 129.7, 129.0, 128.7, 67.0, 52.9, 52.25, 52.18, 48.2, 41.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 1716.6, 1609.4, 1453.7, 1439.2, 1289.6, 1276.8, 1225.9, 1206.7, 1130.5, 1108.6, 1047.3, 1023.8, 967.2, 920.2, 880.9, 868.3, 818.6, 719.8, 763.1, 745.2, 712.9, 696.3, 545.0.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{19}O_6$ ($[M+H]^+$) 319.1182, found 319.1179.

**Dimethyl 2-(4-(trifluoromethoxy)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (17)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-(trifluoromethoxy)benzene (121 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–30% EtOAc/hexane) gave 128 mg (372 μmol, 74% yield) of the desired product as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.36 – 7.28 (m, 2H), 7.19 – 7.12 (m, 2H), 3.99 (d, *J* = 6.7 Hz, 1H), 3.74 (s, 6H), 2.69 (dd, *J* = 10.1, 3.0 Hz, 1H), 2.42 – 2.36 (m, 3H).

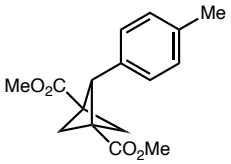
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.3, 148.3 (q, *J* = 1.8 Hz), 135.2, 130.1, 120.9, 120.6 (q, *J* = 257.1 Hz), 66.3, 52.9, 52.2, 48.2, 41.2.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -57.84 (s, 3F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 2954.6, 1729.1, 1511.3, 1436.4, 1286.2, 1255.4, 1199.6, 1154.8, 1050.3, 1019.7, 922.1, 868.0, 787.7, 742.9, 648.8, 509.2.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{16}O_5F_3$ ($[M+H]^+$) 345.0945, found 345.0945.

**Dimethyl 2-(*p*-tolyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (18)**




Prepared according to the general procedure slowly adding a solution of 4-bromotoluene (85.5 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2 $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (3–20% EtOAc/hexane) gave 105 mg (383 μmol, 77% yield) of the desired product as a white solid.

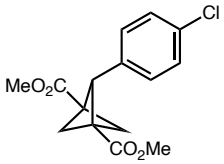
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.16 – 7.09 (m, 4H), 3.99 (d, *J* = 6.7 Hz, 1H), 3.73 (s, 3H), 2.73 (dd, *J* = 9.3, 2.9 Hz, 1H), 2.42 – 2.29 (m, 6H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.6, 136.7, 133.4, 129.1, 128.4, 67.2, 52.8, 52.1, 47.9, 41.1, 21.3.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3008.9, 2953.6, 1719.3, 1514.7, 1433.3, 1371.6, 1287.4, 1230.7, 1203.0, 1187.4, 1158.6, 1133.9, 1046.5, 1025.5, 934.3, 920.0, 877.5, 860.6, 804.6, 788.0, 778.5, 741.4, 546.4, 491.6.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{19}O_4$ ($[M+H]^+$) 275.1283, found 275.1278.

**Dimethyl 2-(4-chlorophenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (19)**




Prepared according to the general procedure slowly adding a solution of 1-bromo-4-chloro-benzene (95.7 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br₂** in $PhCF_3$. Purification *via* flash column chromatography (5–40% EtOAc/hexane) gave 119 mg (404 μmol, 81% yield) of the desired product as a white solid.

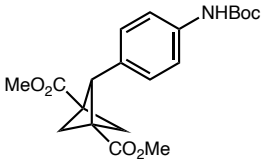
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.30 – 7.26 (m, 2H), 7.24 – 7.20 (m, 2H), 3.97 (d, *J* = 6.7 Hz, 1H), 3.73 (s, 6H), 2.68 (dd, *J* = 10.0, 3.0 Hz, 1H), 2.44 – 2.32 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.3, 134.9, 133.1, 130.0, 128.6, 66.5, 52.8, 52.1, 48.2, 41.2.

**IR (film):** $\nu_{max}(cm^{-1})$ 3011.2, 2953.3, 1720.8, 1489.0, 1434.1, 1327.5, 1287.0, 1224.6, 1202.6, 1134.5, 1092.6, 1045.7, 1024.5, 1012.9, 934.2, 920.3, 878.4, 861.5, 838.2, 808.9, 788.6, 751.4, 721.3, 707.1, 545.4, 495.2.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{16}O_4Cl$ ($[M+H]^+$) 295.0732, found 295.0729.

**Dimethyl 2-(4-((*tert*-butoxycarbonyl)amino)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (20)**




Prepared according to the general procedure slowly adding a solution of *N*-Boc-4-bromoaniline (136 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂**

in $PhCF_3$. Purification *via* flash column chromatography (5–30% EtOAc/hexane) gave 145 mg (386 μmol, 77% yield) of the desired product as a pale yellow oil.

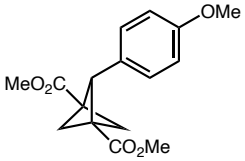
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.27 (m, 2H), 7.20 – 7.16 (m, 2H), 6.43 (bs, 1H), 3.97 (d, $J$ = 6.6 Hz, 1H), 3.72 (s, 6H), 2.71 (dd, $J$ = 10.1, 2.9 Hz, 1H), 2.39 – 2.35 (m, 2H), 2.33 (dd, $J$ = 6.8, 2.9 Hz, 1H), 1.51 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.5, 152.9, 137.3, 131.1, 129.2, 118.6, 80.7, 67.0, 52.8, 52.1, 48.0, 41.2, 28.5.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3354.0, 2978.0, 1717.6, 1615.0, 1592.1, 1524.1, 1435.5, 1409.0, 1392.4, 1367.0, 1317.6, 1286.0, 1229.1, 1202.3, 1153.7, 1050.2, 1017.9, 922.1, 863.7, 834.7, 811.5, 753.7, 736.3, 666.7, 517.3.

**HRMS (ESI)** m/z calcd. for $C_{20}H_{26}NO_6$ ($[M+H]^+$) 376.1760, found 376.1757.

**Dimethyl 2-(4-methoxyphenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (21)**




Prepared according to the general procedure slowly adding a solution of 4-bromoanisole (93.5 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (0–80% $CH_2Cl_2$/hexane) gave 111 mg (382 μmol, 76% yield) of the desired product as a white solid.

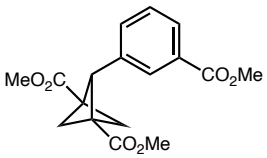
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.23 – 7.12 (m, 2H), 6.93 – 6.78 (m, 2H), 3.98 (d, $J$ = 6.6 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 6H), 2.72 (dd, $J$ = 10.0, 2.9 Hz, 1H), 2.42 – 2.31 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.6, 158.7, 129.7, 128.6, 113.9, 66.9, 55.4, 52.8, 52.0, 48.0, 41.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3006.1, 2954.7, 1722.1, 1611.6, 1579.1, 1511.7, 1461.6, 1438.8, 1357.0, 1286.8, 1251.6, 1230.3, 1198.6, 1181.7, 1111.9, 1090.9, 1055.5, 1033.5, 1023.6, 937.6, 923.7, 859.1, 814.2, 797.5, 783.6, 741.4, 725.9, 601.3, 573.9, 548.9, 520.9, 486.2.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{18}O_5Na$ ($[M+Na]^+$) 313.1052, found 313.1044.

**Dimethyl 2-(3-(methoxycarbonyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (22)**




Prepared according to the general procedure slowly adding a solution of methyl 3-bromobenzoate (108 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (10–100% $CH_2Cl_2$/hexane) gave 110 mg (346 μmol, 69% yield) of the desired product as a white solid.

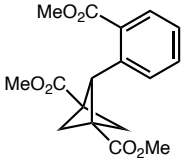
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.97 (t, *J* = 1.9 Hz, 1H), 7.94 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.48 (dt, *J* = 7.6, 1.9 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 4.03 (d, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 6H), 2.68 (dd, *J* = 10.1, 3.0 Hz, 1H), 2.43 – 2.40 (m, 2H), 2.38 (dd, *J* = 6.8, 3.1 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.3, 167.1, 136.8, 133.2, 130.3, 129.9, 128.5, 128.4, 66.8, 52.7, 52.3, 52.2, 48.2, 41.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2952.6, 1720.0, 1586.3, 1434.7, 1370.5, 1339.6, 1282.5, 1200.7, 1154.2, 1109.3, 1085.5, 1050.4, 986.2, 924.7, 822.6, 787.3, 754.1, 740.5, 700.8, 682.2.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{19}O_6$ ($[M+H]^+$) 319.1182, found 319.1178.

**Dimethyl 2-(2-(methoxycarbonyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (23)**




Prepared according to the general procedure slowly adding a solution of methyl 2-bromobenzoate (108 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (10–100% $CH_2Cl_2$/hexane) gave 102 mg (320 μmol, 64% yield) of the desired product as a white solid.

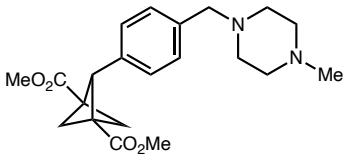
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.04 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.50 (td, *J* = 7.6, 1.5 Hz, 1H), 7.37 (td, *J* = 7.5, 0.9 Hz, 1H), 7.29 (dt, *J* = 7.7, 0.8 Hz, 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 6H), 2.72 (dd, *J* = 9.5, 3.0 Hz, 1H), 2.44 (dd, *J* = 9.5, 2.0 Hz, 1H), 2.29 (d, *J* = 2.0 Hz, 1H), 2.26 (dd, *J* = 6.5, 3.0 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.6, 167.5, 137.4, 132.1, 131.6, 130.5, 129.9, 127.4, 69.0, 52.1, 52.0, 50.4, 48.3, 41.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3000.0, 2947.5, 1723.6, 1572.7, 1489.8, 1435.1, 1285.4, 1255.7, 1196.8, 1184.2, 1147.1, 1136.5, 1107.0, 973.3, 923.9, 825.0, 813.1, 788.8, 813.1, 788.8, 764.6, 738.9, 764.6, 738.9, 725.5, 695.9, 643.4, 555.8, 507.5.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{19}O_6$ ($[M+H]^+$) 319.1182, found 319.1178.

**Dimethyl 2-(4-((4-methylpiperazin-1-yl)methyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (24)**




Prepared according to the general procedure slowly adding a solution of 1-[(4-bromophenyl)methyl]-4-methyl-piperazine (135 mg, 0.50 mmol) and *N*-adamantyl-*N*-

supersilylamine (1.6 equiv) in *t*BuOH/$PhCF_3$ (v/v = 1/3, 5 mL total) *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)$Br_2$** in $PhCF_3$. Purification *via* flash column chromatography (0–20% $MeOH/CH_2Cl_2$ + 2% $NH_4OH$) gave 99.9 mg (268 µmol, 54% yield) of the desired product after complete removal of solvents as a brown sticky solid.

The resulting pure free base was subsequently converted into the dihydrochloride for storage by dissolving the material in chloroform and adding HCl in dioxane (4 M, 2 mL), followed by removal of the volatiles, repeated three times to give 120 mg (268 µmol, quantitative conversion of the free base) of the dihydrochloride as an off-white solid. Analytical data are given for the dihydrochloride.

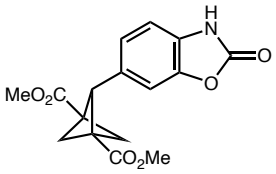
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 13.94 (bs, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 4.24 – 4.10 (m, 4H), 4.03 – 3.89 (m, 3H), 3.75 (s, 6H), 3.48 (d, *J* = 12.3 Hz, 4H), 2.90 (s, 3H), 2.65 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.45 – 2.35 (m, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.1, 139.6, 131.3, 130.1, 125.5, 66.4, 61.0, 52.9, 52.3, 49.8, 48.2, 48.0, 43.2, 41.3.

**IR (film):** $\nu_{max}(cm^{-1})$ 3412.2, 2953.5, 2374.6, 1724.0, 1614.3, 1549.7, 1433.7, 1407.4, 1370.4, 1282.2, 1202.7, 1155.8, 1103.8, 1051.0, 1022.8, 948.3, 913.1, 867.4, 848.9, 815.5, 789.1, 744.3, 662.1, 639.3, 612.5.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{29}N_2O_4$ ($[M+H]^+$) 373.2127, found 373.2122.

**Dimethyl 2-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (25)**




Prepared according to the general procedure slowly adding a solution of 6-bromo-3H-1,3-benzoxazol-2-one (107 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in

*t*BuOH/$PhCF_3$ (v/v = 1/3, 5 mL total) *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂** in $PhCF_3$. Purification *via* flash column chromatography (5–75% EtOAc/hexane) gave 116 mg (366 µmol, 73% yield) of the desired product as a white solid.

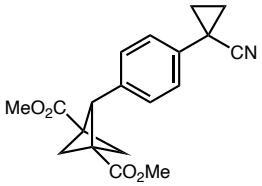
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.19 (s, 1H), 7.20 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.08 (ddd, *J* = 8.1, 1.6, 0.8 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 4.03 (d, *J* = 6.6 Hz, 1H), 3.75 (s, 6H), 2.71 (dd, *J* = 9.6, 2.9 Hz, 1H), 2.42 – 2.35 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.3, 155.9, 144.1, 131.5, 128.4, 124.4, 110.7, 109.8, 66.8, 52.7, 52.2, 48.3, 41.4.

**IR (film):** $\nu_{max}(cm^{-1})$ 3090.5, 3010.8, 1780.9, 1715.7, 1508.5, 1433.9, 1405.2, 1369.1, 1285.9, 1258.5, 1215.2, 1201.3, 1108.1, 1053.0, 1029.6, 970.6, 956.4, 924.5, 891.0, 839.9, 831.9, 811.1, 801.7, 786.3, 747.5, 724.8, 697.9, 610.6, 597.9, 584.0, 538.7, 516.6, 485.0, 475.8, 434.1.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{16}NO_6$ ($[M+H]^+$) 318.0978, found 318.0976.

**Dimethyl 2-(4-(1-cyanocyclopropyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (26)**




Prepared according to the general procedure slowly adding a solution of 1-(4-bromophenyl)cyclopropanecarbonitrile (111 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂** in $PhCF_3$. Purification *via* flash column chromatography (5–40% EtOAc/hexane) gave 117 mg (360 µmol, 72% yield) of the desired product as a white solid.

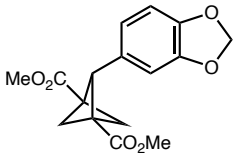
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.30 – 7.20 (m, 4H), 3.98 (d, *J* = 6.7 Hz, 1H), 3.73 (s, 6H), 2.68 (dd, *J* = 9.9, 3.0 Hz, 1H), 2.41 – 2.34 (m, 3H), 1.73 – 1.69 (m, 2H), 1.40 – 1.36 (m, 2H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.3, 136.1, 134.9, 129.2, 125.9, 122.6, 66.7, 52.8, 52.1, 48.2, 41.2, 18.2, 13.7.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3006.0, 2234.2, 1716.7, 1518.9, 1440.5, 1413.5, 1361.1, 1286.6, 1227.3, 1207.9, 1128.3, 1102.8, 1073.6, 1054.1, 1029.3, 1003.2, 949.6, 922.2, 879.6, 860.8, 834.6, 800.9, 788.4, 749.9, 734.6, 711.6, 689.2, 586.1, 570.0, 536.4, 518.3, 502.0, 450.2, 414.0.

**HRMS (ESI)** m/z calcd. for $C_{19}H_{20}NO_4$ ($[M+H]^+$) 326.1392, found 326.1388.

**Dimethyl 2-(benzo[*d*][1,3]dioxol-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (S7)**




Prepared according to the general procedure slowly adding a solution of 5-bromo-1,3-benzodioxole (101 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 112 mg (368 μmol, 74% yield) of the desired product as a white solid.

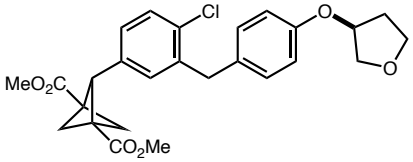
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 6.80 – 6.67 (m, 3H), 5.93 (s, 2H), 3.94 (d, *J* = 6.7 Hz, 1H), 3.73 (s, 6H), 2.73 (dd, *J* = 10.0, 2.9 Hz, 1H), 2.37 – 2.33 (m, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.5, 147.7, 146.7, 130.2, 121.7, 109.1, 108.3, 101.1, 67.0, 52.7, 52.1, 47.9, 41.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2951.9, 1723.9, 1503.1, 1490.0, 1434.7, 1352.1, 1284.1, 1237.5, 1199.8, 1155.2, 1104.6, 1037.1, 931.4, 904.2, 866.3, 829.3, 811.6, 788.4, 744.3, 606.5, 483.2, 428.1.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{17}O_6$ ($[M+H]^+$) 305.1025, found 305.1020.

***rac*-Dimethyl (*S*)-2-(4-chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-bicyclo[1.1.1]pentane-1,3-dicarboxylate (27)**




Prepared according to the general procedure slowly adding a solution of *rac*-(*3R*)-3-[4-[(5-bromo-2-chloro-phenyl)methyl]phenoxy]tetrahydrofuran (184 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2 $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–60% EtOAc/hexane) gave 167 mg (355 μmol, 71% yield) of the desired product as a white solid.

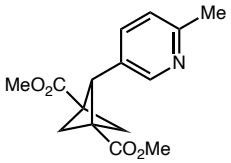
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.30 (d, *J* = 8.2 Hz, 1H), 7.13 – 7.03 (m, 3H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.79 (ddd, *J* = 8.7, 3.0, 2.0 Hz, 2H), 4.89 (ddd, *J* = 5.5, 4.4, 2.3 Hz, 1H), 4.03 – 3.84 (m, 7H), 3.66 (s, 6H), 2.63 (dd, *J* = 10.1, 3.0 Hz, 1H), 2.37 – 2.30 (m, 3H), 2.24 – 2.10 (m, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.2, 156.0, 139.0, 135.2, 133.0, 131.9, 131.1, 130.2, 129.5, 127.8, 115.5, 77.4, 73.3, 67.3, 66.5, 52.7, 52.1, 48.1, 41.1, 38.5, 33.1.

**IR (film):** $\nu_{max}(cm^{-1})$ 2950.2, 1716.2, 1610.3, 1508.3, 1481.0, 1437.2, 1354.1, 1282.1, 1234.9, 1206.6, 1109.9, 1084.5, 1061.0, 1044.5, 1027.2, 923.1, 892.7, 844.4, 830.4, 813.9, 804.1, 786.9, 842.5, 730.9, 691.4, 551.5, 524.1, 484.2, 415.7.

**HRMS (ESI)** m/z calcd. for $C_{26}H_{28}O_6Cl$ ($[M+H]^+$) 471.1574, found 471.1572.

**Dimethyl 2-(6-methylpyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (28)**




Prepared according to the general procedure slowly adding a solution of 5-bromo-2-methyl-pyridine (86.0 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via*

syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂** in $PhCF_3$. Utilizing **alternate workup procedure A**, purification *via* sequential flash column chromatography (wash column: 0–5% $MeOH/CH_2Cl_2$, concentrate fractions, then 5–100% EtOAc/hexane) gave 105 mg (381 μmol, 76% yield) of the desired product as a brown solid.

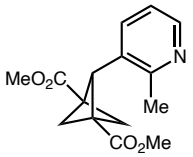
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.42 (d, *J* = 2.1 Hz, 1H), 7.55 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 3.95 (d, *J* = 6.7 Hz, 1H), 3.73 (s, 6H), 2.67 (dd, *J* = 9.5, 3.0 Hz, 1H), 2.55 (s, 3H), 2.43 – 2.38 (m, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.1, 157.1, 149.2, 136.8, 128.9, 122.9, 64.5, 53.0, 52.2, 48.3, 41.0, 24.2.

**IR (film):** $\nu_{max}(cm^{-1})$ 3012.1, 2953.7, 1716.9, 1601.6, 1560.9, 1494.3, 1432.8, 1381.5, 1338.2, 1283.3, 1201.5, 1135.9, 1109.2, 1051.2, 1028.9, 918.6, 872.8, 827.5, 787.4, 729.2, 643.1, 537.2, 479.7, 455.9, 410.9.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{18}NO_4$ ($[M+H]^+$) 276.1236, found 276.1232.

**Dimethyl 2-(2-methylpyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (29)**




Prepared according to the general procedure slowly adding a solution of 3-bromo-2-methyl-pyridine (86.0 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂** in $PhCF_3$. Utilizing **alternate workup procedure A**, purification *via* sequential flash column chromatography (wash column: 0–5% $MeOH/CH_2Cl_2$, concentrate fractions, then 5–100% EtOAc/hexane) gave 106 mg (385 μmol, 77% yield) of the desired product as a pale yellow solid.

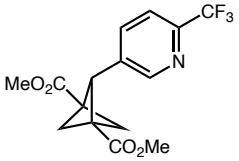
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.42 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.12 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.04 (d, *J* = 6.4 Hz, 1H), 3.70 (s, 6H), 2.81 (dd, *J* = 9.6, 3.3 Hz, 1H), 2.47 – 2.43 (m, 4H), 2.36 – 2.32 (m, 2H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.1, 158.8, 147.6, 136.7, 129.4, 120.9, 67.2, 52.2, 51.6, 47.5, 41.0, 21.9.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3016.1, 1717.7, 1571.7, 1439.0, 1342.3, 1282.7, 1209.1, 1136.6, 1122.6, 1106.1, 1050.0, 1031.1, 917.4, 818.5, 790.8, 783.5, 744.4, 732.0, 710.6, 577.3, 511.6, 444.7, 418.4.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{18}NO_4$ ($[M+H]^+$) 276.1236, found 276.1229.

**Dimethyl 2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (30)**




Prepared according to the general procedure slowly adding a solution of 5-bromo-2-(trifluoromethyl)pyridine (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 122 mg (371 μmol, 74% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.70 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.91 (ddt, *J* = 8.0, 2.1, 0.7 Hz, 1H), 7.65 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.01 (d, *J* = 6.7 Hz, 1H), 3.75 (s, 6H), 2.64 (dd, *J* = 9.6, 3.3 Hz, 1H), 2.50 – 2.43 (m, 3H).

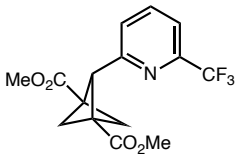
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.7, 150.4, 146.9 (q, *J* = 34.8 Hz), 138.0, 135.4, 121.7 (q, *J* = 274.0 Hz), 120.1 (q, *J* = 2.7 Hz), 63.9, 53.0, 52.4, 48.8, 41.2.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -67.92 (s, 3F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 3017.2, 1724.2, 1438.0, 1335.7, 1289.3, 1206.8, 1177.8, 1128.4, 1086.6, 1047.0, 1026.2, 916.2, 879.8, 834.1, 788.8, 762.4, 744.2, 689.4, 638.2, 597.8.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{15}NO_4F_3$ ($[M+H]^+$) 330.0953, found 330.0948.

**Dimethyl 2-(6-(trifluoromethyl)pyridin-2-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (31)**




Prepared according to the general procedure slowly adding a solution of 2-bromo-6-(trifluoromethyl)pyridine (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 127 mg (386 μmol, 77% yield) of the desired product as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.81 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 4.05 (d, *J* = 6.8 Hz, 1H), 3.74 (s, 6H), 2.55 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.45 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.41 (d, *J* = 1.8 Hz, 1H), 2.37 (dd, *J* = 6.8, 3.1 Hz, 1H).

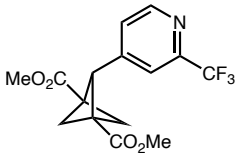
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.2, 157.1, 147.7 (q, *J* = 34.6 Hz), 137.6, 126.4, 121.5 (q, *J* = 274.1 Hz), 118.8 (q, *J* = 2.7 Hz), 66.9, 52.5, 52.1, 48.6, 41.5.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -68.35 (s, 3F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 2961.9, 1727.2, 1596.3, 1463.2, 1440.1, 1337.0, 1294.7, 1241.2, 1203.0, 1184.4, 1160.0, 1115.0, 1101.9, 1085.0, 1052.3, 1037.0, 1019.8, 992.2, 946.0, 927.1, 875.2, 839.8, 817.1, 791.8, 775.8, 750.2, 741.8, 693.3, 655.9, 556.5, 515.9, 476.8, 434.1, 416.6.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{15}NO_4F_3$ ($[M+H]^+$) 330.0953, found 330.0951.

**Dimethyl 2-(2-(trifluoromethyl)pyridin-4-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (32)**




Prepared according to the general procedure slowly adding a solution of 4-bromo-2-(trifluoromethyl)pyridine (113 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 125 mg (380 μmol, 76% yield) of the desired product as a colorless oil.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (d, *J* = 5.0 Hz, 1H), 7.72 (s, 1H), 7.50 (d, *J* = 5.0 Hz, 1H), 3.97 (d, *J* = 6.7 Hz, 1H), 3.76 (s, 6H), 2.61 (dd, *J* = 9.6, 3.3 Hz, 1H), 2.48 – 2.40 (m, 3H).

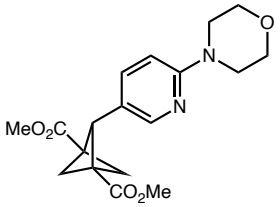
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.6, 150.1, 148.4 (q, *J* = 34.4 Hz), 147.4, 126.7, 121.6 (q, *J* = 274.4 Hz), 121.0 (q, *J* = 2.9 Hz), 65.2, 52.8, 52.4, 49.0, 41.4.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -68.11 (s, 3F).

**IR (film):** $\nu_{max}(cm^{-1})$ 2955.9, 1728.5, 1609.5, 1436.1, 1371.9, 1324.9, 1288.2, 1243.2, 1201.7, 1180.2, 1134.9, 1119.8, 1090.6, 1052.5, 996.0, 927.0, 844.1, 788.3, 741.3, 690.4, 623.5, 517.6.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{15}NO_4F_3$ ($[M+H]^+$) 330.0953, found 330.0951.

**Dimethyl 2-(6-morpholinopyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (33)**




Prepared according to the general procedure slowly adding a solution of 4-(5-bromo-2-pyridyl)morpholine (122 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-

dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–75% EtOAc/hexane) gave 116 mg (335 μmol, 67% yield) of the desired product as a pale yellow solid.

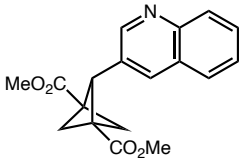
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 2.4 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 8.7 Hz, 1H), 3.88 (d, *J* = 6.6 Hz, 1H), 3.84 – 3.79 (m, 4H), 3.72 (s, 6H), 3.52 – 3.46 (m, 4H), 2.70 (dd, *J* = 9.4, 3.1 Hz, 1H), 2.41 – 2.35 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.1, 158.8, 147.6, 136.7, 129.4, 120.9, 67.2, 52.2, 51.6, 47.5, 41.0, 21.9.

**IR (film):** $\nu_{max}(cm^{-1})$ 3006.5, 2955.3, 2856.2, 1721.3, 1604.8, 1554.1, 1492.2, 1449.9, 1433.7, 1407.5, 1371.3, 1333.6, 1316.2, 1289.8, 1245.6, 1228.2, 1201.9, 1155.0, 1118.9, 1077.1, 1047.6, 1031.6, 1004.6, 944.5, 919.4, 859.0, 806.2, 788.2, 764.2, 734.3, 652.0, 550.7, 478.4.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{23}N_2O_5$ ($[M+H]^+$) 347.1607, found 347.1604.

**Dimethyl 2-(quinolin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (34)**




Prepared according to the general procedure slowly adding a solution of 3-bromoquinoline (104 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–75% EtOAc/hexane) gave 110 mg (353 μmol, 71% yield) of the desired product as a pale yellow solid.

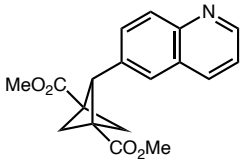
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.86 (d, *J* = 2.3 Hz, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 4.16 (d, *J* = 6.7 Hz, 1H), 3.77 (s, 6H), 2.78 (dd, *J* = 10.0, 3.2 Hz, 1H), 2.51 – 2.45 (m, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.1, 151.4, 147.2, 135.4, 129.6, 129.4, 129.3, 128.0, 127.7, 127.0, 64.9, 53.0, 52.3, 48.6, 41.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3002.4, 2951.2, 1716.7, 1570.4, 1493.2, 1445.6, 1432.9, 1379.7, 1330.8, 1285.3, 1209.7, 1183.7, 1161.6, 1131.4, 1110.0, 1052.6, 1025.7, 985.7, 961.9, 922.1, 887.6, 863.7, 831.9, 794.6, 763.7, 756.5, 738.7, 642.7, 623.7, 505.8, 483.8, 454.3, 419.0.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{18}NO_4$ ($[M+H]^+$) 312.1236, found 312.1231.

**Dimethyl 2-(quinolin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (35)**




Prepared according to the general procedure slowly adding a solution of 6-bromoquinoline (104 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–100% EtOAc/hexane) gave 98.9 mg (318 μmol, 64% yield) of the desired product as a pale yellow solid.

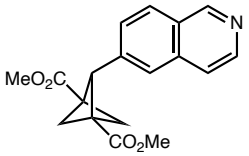
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.90 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.75 (t, *J* = 0.9 Hz, 1H), 7.65 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.18 (d, *J* = 6.6 Hz, 1H), 3.77 (s, 6H), 2.80 (dd, *J* = 9.4, 3.1 Hz, 1H), 2.48 – 2.41 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.3, 150.3, 147.3, 136.5, 135.0, 130.7, 129.4, 128.1, 127.2, 121.4, 67.1, 52.9, 52.2, 48.4, 41.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3012.9, 1718.8, 1594.2, 1496.3, 1439.7, 1340.3, 1322.9, 1284.1, 1219.4, 1201.7, 1134.6, 1119.2, 1109.7, 1053.6, 1030.3, 985.9, 934.5, 918.2, 885.7, 841.7, 832.4, 803.5, 789.8, 762.3, 741.0, 620.8, 539.8, 526.1, 510.0, 480.8, 515.6.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{18}NO_4$ ($[M+H]^+$) 312.1236, found 312.1234.

**Dimethyl 2-(isoquinolin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (36)**




Prepared according to the general procedure slowly adding a solution of 6-bromoisoquinoline (104 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in *t*BuOH/$PhCF_3$ (v/v = 1/3, 5 mL total) *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)$Br_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–100% EtOAc/hexane) gave 102 mg (328 μmol, 66% yield) of the desired product as a white solid.

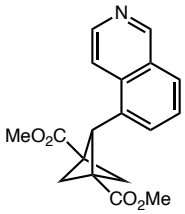
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.24 (s, 1H), 8.52 (d, *J* = 5.8 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 5.9 Hz, 1H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.18 (d, *J* = 6.6 Hz, 1H), 3.77 (s, 6H), 2.77 (dd, *J* = 9.3, 3.1 Hz, 1H), 2.49 – 2.41 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.2, 152.0, 142.9, 139.4, 135.9, 128.6, 127.9, 127.7, 125.9, 120.9, 67.2, 52.9, 52.3, 48.5, 41.5.

**IR (film):** $\nu_{max}(cm^{-1})$ 3005.2, 2951.4, 1726.1, 1631.5, 1585.9, 1489.5, 1435.0, 1358.1, 1335.6, 1285.8, 1202.6, 1153.9, 1050.9, 909.4, 830.6, 786.8, 768.4, 729.3, 658.0, 645.2, 472.9.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{18}NO_4$ ($[M+H]^+$) 312.1236, found 312.1232.

**Dimethyl 2-(isoquinolin-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (37)**




Prepared according to the general procedure slowly adding a solution of 5-bromoisoquinoline (104 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in *t*BuOH/$PhCF_3$ (v/v = 1/3, 5 mL total) *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2%

$Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂** in $PhCF_3$. Purification *via* flash column chromatography (5–100% EtOAc/hexane) gave 99.3 mg (319 μmol, 64% yield) of the desired product as a white solid.

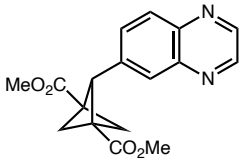
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.25 (d, *J* = 1.0 Hz, 1H), 8.51 (d, *J* = 6.1 Hz, 1H), 7.92 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.74 (dt, *J* = 6.0, 1.0 Hz, 1H), 7.63 – 7.55 (m, 2H), 4.51 (d, *J* = 6.3 Hz, 1H), 3.64 (s, 6H), 2.91 (dd, *J* = 9.6, 3.2 Hz, 1H), 2.60 (dd, *J* = 9.5, 2.0 Hz, 1H), 2.43 (d, *J* = 2.0 Hz, 1H), 2.39 (dd, *J* = 6.3, 3.2 Hz, 1H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.2, 153.2, 142.9, 135.8, 131.2, 130.6, 128.9, 127.6, 126.8, 116.7, 66.9, 52.1, 51.9, 47.6, 41.1.

**IR (film):** $\nu_{max}(cm^{-1})$ 2950.5, 1724.4, 1619.8, 1589.0, 1490.2, 1434.4, 1383.5, 1359.3, 1340.8, 1284.1, 1204.1, 1153.6, 1111.6, 1043.7, 924.6, 865.8, 829.3, 813.0, 798.0, 758.6, 738.5, 666.5, 643.0, 497.4, 473.3, 413.0.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{18}NO_4$ ($[M+H]^+$) 312.1236, found 312.1234.

**Dimethyl 2-(quinoxalin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (38)**




Prepared according to the general procedure slowly adding a solution of 6-bromoquinoxaline (105 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in *t*BuOH/$PhCF_3$ (v/v = 1/1, 5 mL total) *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂** in $PhCF_3$. Utilizing **alternate workup procedure B**, purification *via* flash column chromatography (5–100% EtOAc/hexane) gave 93.0 mg (298 μmol, 60% yield) of the desired product as a pale yellow solid.

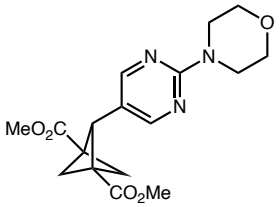
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.84 (d, *J* = 1.9 Hz, 1H), 8.83 (d, *J* = 1.9 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 8.01 (t, *J* = 1.6 Hz, 1H), 7.74 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.21 (d, *J* = 6.6 Hz, 1H), 3.78 (s, 6H), 2.80 (dd, *J* = 9.5, 3.0 Hz, 1H), 2.50 – 2.43 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.1, 145.3, 145.0, 142.9, 142.3, 139.0, 131.4, 129.5, 128.9, 66.7, 53.0, 52.3, 48.5, 41.5.

**IR (film):** $\nu_{max}(cm^{-1})$ 3020.1, 2950.1, 1736.5, 1718.2, 1619.0, 1495.2, 1436.3, 1369.2, 1351.7, 1329.3, 1283.7, 1207.2, 1134.3, 1099.0, 1050.3, 1026.5, 958.9, 942.1, 919.6, 895.9, 876.3, 842.2, 789.0, 765.6, 743.4, 656.7, 614.7, 614.6, 565.4, 531.9, 511.7, 442.1, 420.5.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{17}N_2O_4$ ($[M+H]^+$) 313.1188, found 313.1183.

**Dimethyl 2-(2-morpholinopyrimidin-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (39)**




Prepared according to the general procedure slowly adding a solution of 4-(5-bromopyrimidin-2-yl)morpholine (122 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–75% EtOAc/hexane) gave 112 mg (322 μmol, 64% yield) of the desired product as a pale yellow solid.

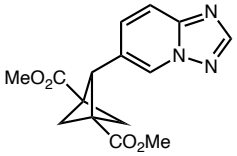
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.29 (s, 2H), 3.81 – 3.74 (m, 9H), 3.72 (s, 6H), 2.67 (dd, *J* = 9.6, 3.2 Hz, 1H), 2.43 – 2.40 (m, 2H), 2.37 (dd, *J* = 9.5, 2.0 Hz, 1H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.0, 160.8, 158.0, 118.1, 67.0, 62.2, 53.0, 52.2, 48.5, 44.4, 40.7.

**IR (film):** $\nu_{max}(cm^{-1})$ 2958.0, 2865.3, 1721.9, 1599.6, 1532.7, 1477.8, 1463.0, 1442.5, 1404.1, 1355.6, 1306.7, 1282.1, 1270.4, 1251.7, 1210.5, 1187.4, 1173.4, 1142.4, 1117.0, 1076.2, 1047.6, 1028.4, 1008.0, 986.4, 952.6, 932.7, 920.7, 881.6, 860.3, 847.7, 792.8, 759.0, 733.7, 654.2, 601.9, 588.2, 554.0, 530.7, 484.8, 471.8.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{22}N_3O_5$ ($[M+H]^+$) 348.1560, found 348.1557.

**Dimethyl 2-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (40)**



Prepared according to the general procedure slowly adding a solution of 6-bromo-[1,2,4]triazolo[1,5-*a*]pyridine (99.0 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in *t*BuOH/$PhCF_3$ (v/v = 1/3, 5 mL total) *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)$Br_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–100% EtOAc/hexane) gave 83.7 mg (278 μmol, 56% yield) of the desired product as a white solid.

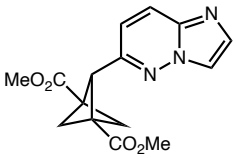
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.72 (dt, *J* = 2.0, 1.0 Hz, 1H), 8.34 (s, 1H), 7.73 (dd, *J* = 9.2, 1.0 Hz, 1H), 7.55 (dd, *J* = 9.2, 1.7 Hz, 1H), 4.03 (d, *J* = 6.5 Hz, 1H), 3.77 (s, 6H), 2.76 (dd, *J* = 9.6, 3.2 Hz, 1H), 2.50 – 2.46 (m, 2H), 2.43 (dd, *J* = 9.6, 2.0 Hz, 1H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.8, 154.0, 149.5, 131.7, 128.0, 123.4, 116.4, 63.6, 52.9, 52.4, 49.1, 41.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3005.9, 1715.8, 1639.2, 1544.0, 1510.5, 1439.8, 1429.7, 1414.3, 1331.9, 1320.3, 1290.3, 1254.7, 1207.3, 1189.6, 1152.3, 1106.7, 1052.8, 1027.6, 944.9, 931.2, 915.9, 870.7, 839.0, 820.0, 800.3, 789.5, 779.6, 759.8, 743.4, 663.5, 601.7, 588.2, 454.2, 429.6.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{16}N_3O_4$ ($[M+H]^+$) 302.1141, found 302.1137.

**Dimethyl 2-(imidazo[1,2-*b*]pyridazin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (41)**



Prepared according to the general procedure slowly adding a solution of 6-bromoimidazo[1,2-*b*]pyridazine (99.0 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in *t*BuOH/$PhCF_3$ (v/v = 1/1, 5 mL total) *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium

carbonate (2.0 equiv), 2% Ir(dF($CF_3$)ppy)$_2$(dtbpy)$PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Utilizing **alternate workup procedure A**, purification *via* flash column chromatography (10–100% MeCN/$CH_2Cl_2$) gave 63.5 mg (211 μmol, 42% yield) of the desired product as a pale yellow solid.

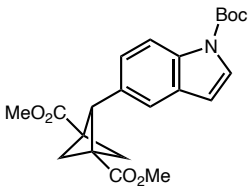
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.89 (dd, *J* = 9.4, 0.7 Hz, 1H), 7.86 (t, *J* = 0.9 Hz, 1H), 7.73 (d, *J* = 1.2 Hz, 1H), 7.14 (d, *J* = 9.3 Hz, 1H), 4.01 (d, *J* = 6.5 Hz, 1H), 3.76 (s, 6H), 2.76 (dd, *J* = 10.3, 3.1 Hz, 1H), 2.48 – 2.41 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.8, 150.3, 138.3, 133.8, 125.5, 118.5, 117.0, 64.6, 53.3, 52.2, 48.6, 41.3.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3136.4, 3008.0, 2955.7, 1720.5, 1542.4, 1463.7, 1438.5, 1317.6, 1292.9, 1276.8, 1208.7, 1156.4, 1131.7, 1109.1, 1053.3, 1032.5, 1019.7, 917.1, 907.8, 890.0, 856.9, 800.0, 789.2, 775.0, 748.7, 736.6, 638.1, 589.3, 530.0, 469.8, 444.8, 419.8.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{16}N_3O_4$ ($[M+H]^+$) 302.1141, found 302.1134.

**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (42)**




Prepared according to the general procedure slowly adding a solution of *N*-Boc-5-bromoindole (148 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2 Ir(dF($CF_3$)ppy)$_2$(dtbpy)$PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–40% EtOAc/hexane) gave 158 mg (396 μmol, 79% yield) of the desired product as a colorless oil.

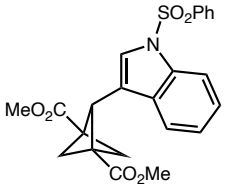
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.05 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 3.7 Hz, 1H), 7.45 (t, *J* = 0.8 Hz, 1H), 7.19 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.53 (dd, *J* = 3.7, 0.8 Hz, 1H), 4.14 (d, *J* = 6.6 Hz, 1H), 3.75 (s, 6H), 2.78 (dd, *J* = 9.4, 2.9 Hz, 1H), 2.42 (dd, *J* = 9.4, 1.7 Hz, 1H), 2.39 (d, *J* = 1.6 Hz, 1H), 2.36 (dd, *J* = 6.7, 2.9 Hz, 1H), 1.67 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.6, 149.9, 134.3, 130.8, 130.7, 126.4, 124.8, 120.7, 115.1, 107.5, 83.9, 67.6, 52.8, 52.1, 48.0, 41.3, 28.3.

**IR (film):** $\nu_{max}(cm^{-1})$ 2951.5, 1726.0, 1471.4, 1435.6, 1365.8, 1336.1, 1284.6, 1257.6, 1227.2, 1201.0, 1154.6, 1134.3, 1081.9, 1022.6, 926.6, 846.4, 808.3, 765.4, 727.3, 602.3, 521.8, 478.9, 425.3.

**HRMS (ESI)** m/z calcd. for $C_{22}H_{26}NO_6$ ($[M+H]^+$) 400.1760, found 400.1756.

**Dimethyl 2-(1-(phenylsulfonyl)-1*H*-indol-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (43)**




Prepared according to the general procedure slowly adding a solution of *N*-benzenesulfonyl-3-bromoindole (168 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 145 mg (328 μmol, 66% yield) of the desired product as a pale yellow solid.

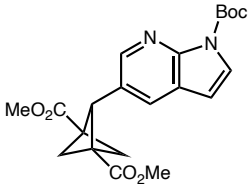
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.97 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.92 – 7.84 (m, 2H), 7.60 (d, *J* = 1.3 Hz, 1H), 7.58 – 7.39 (m, 4H), 7.30 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H), 3.99 (dd, *J* = 6.4, 1.3 Hz, 1H), 3.67 (s, 6H), 2.96 (dd, *J* = 9.5, 3.0 Hz, 1H), 2.47 (dd, *J* = 9.5, 2.0 Hz, 1H), 2.42 (d, *J* = 2.0 Hz, 1H), 2.39 (dd, *J* = 6.5, 2.9 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.1, 138.3, 135.1, 134.0, 131.2, 129.4, 126.9, 125.1, 124.7, 123.4, 120.1, 117.5, 113.7, 60.8, 52.8, 52.1, 48.6, 40.7.

**IR (film):** $\nu_{max}(cm^{-1})$ 2951.2, 1726.3, 1447.2, 1435.3, 1370.4, 1286.4, 1204.5, 1174.3, 1123.2, 1087.2, 1051.0, 1021.1, 978.1, 928.5, 787.5, 746.9, 724.6, 685.0, 672.1, 592.6, 581.5, 570.8, 551.3, 471.7, 424.8.

**HRMS (ESI)** m/z calcd. for $C_{23}H_{22}NO_6S$ ($[M+H]^+$) 440.1168, found 440.1165.

**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrrolo[2,3-b]pyridin-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (44)**




Prepared according to the general procedure slowly adding a solution of *tert*-butyl 5-bromopyrrolo[2,3-*b*]pyridine-1-carboxylate (149 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br₂** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 114 mg (285 μmol, 57% yield) of the desired product as a white solid.

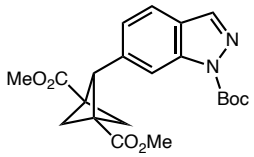
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.44 (d, *J* = 2.2 Hz, 1H), 7.87 (dd, *J* = 2.1, 0.8 Hz, 1H), 7.63 (d, *J* = 4.0 Hz, 1H), 6.49 (d, *J* = 4.0 Hz, 1H), 4.12 (d, *J* = 6.6 Hz, 1H), 3.75 (s, 6H), 2.71 (dd, *J* = 10.1, 3.1 Hz, 1H), 2.46 – 2.43 (m, 2H), 2.41 (dd, *J* = 6.7, 3.1 Hz, 1H), 1.67 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.2, 148.0, 147.3, 145.4, 129.5, 127.2, 126.9, 122.8, 104.7, 84.4, 65.0, 53.1, 52.3, 48.3, 41.2, 28.3.

**IR (film):** $\nu_{max}(cm^{-1})$ 3002.8, 1744.4, 1718.1, 1531.7, 1474.8, 1441.8, 1395.6, 1357.5, 1324.9, 1288.0, 1273.9, 1207.7, 1196.7, 1164.8, 1142.3, 1097.5, 1050.7, 1026.5, 919.1, 905.1, 854.9, 839.4, 823.4, 788.0, 769.1, 747.8, 732.8, 663.3, 626.0, 610.3, 466.9.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{25}N_2O_6$ ($[M+H]^+$) 401.1713, found 401.1711.

**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-indazol-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (45)**




Prepared according to the general procedure slowly adding a solution of *tert*-butyl 6-bromoindazole-1-carboxylate (149 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 117 mg (293 μmol, 59% yield) of the desired product as a white solid.

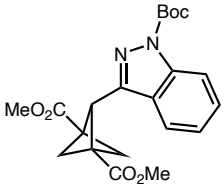
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.20 (t, *J* = 1.2 Hz, 1H), 8.13 (d, *J* = 0.9 Hz, 1H), 7.66 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.24 (ddd, *J* = 8.3, 1.4, 0.6 Hz, 1H), 4.17 (d, *J* = 6.7 Hz, 1H), 3.78 (s, 6H), 2.77 (dd, *J* = 9.4, 3.0 Hz, 1H), 2.48 – 2.37 (m, 3H), 1.71 (s, 9H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.3, 149.3, 140.0, 139.4, 137.7, 124.9, 124.5, 120.9, 114.6, 85.0, 67.6, 52.8, 52.2, 48.3, 41.5, 28.3.

**IR (film):** $\nu_{max}(cm^{-1})$ 2952.2, 1727.5, 1618.9, 1481.7, 1435.2, 1412.2, 1380.3, 1369.9, 1344.2, 1284.7, 1254.5, 1203.3, 1146.9, 1031.7, 950.3, 915.8, 847.0, 778.3, 751.4, 666.1, 621.8, 582.7, 473.9.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{25}N_2O_6$ ($[M+H]^+$) 401.1713, found 401.1706.

**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-indazol-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (46)**




Prepared according to the general procedure slowly adding a solution of 1-Boc-3-bromoindazole (149 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 119 mg (297 μmol, 59% yield) of the desired product as a white solid.

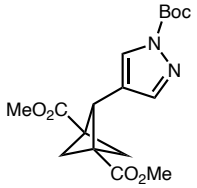
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.71 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.49 (ddd, *J* = 8.4, 7.1, 1.1 Hz, 1H), 7.32 – 7.23 (m, 1H), 4.16 (d, *J* = 6.5 Hz, 1H), 3.70 (s, 6H), 3.06 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.55 (dd, *J* = 9.5, 1.8 Hz, 1H), 2.46 (d, *J* = 1.7 Hz, 1H), 2.44 (dd, *J* = 6.6, 3.0 Hz, 1H), 1.68 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.1, 149.3, 146.3, 140.7, 128.8, 125.9, 123.4, 120.7, 114.8, 84.3, 59.8, 54.0, 52.1, 48.7, 41.2, 28.3.

**IR (film):** $\nu_{max}(cm^{-1})$ 2950.9, 1724.7, 1517.5, 1439.1, 1415.1, 1382.1, 1370.5, 1353.2, 1345.8, 1312.3, 1288.8, 1247.9, 1202.1, 1158.7, 1103.3, 1084.3, 1049.9, 1016.3, 930.8, 913.8, 889.1, 868.9, 854.0, 835.2, 787.0, 774.4, 759.8, 748.0, 568.5, 477.4, 431.8.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{25}N_2O_6$ ($[M+H]^+$) 401.1713, found 401.1710.

**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (47)**




Prepared according to the general procedure slowly adding a solution of *tert*-butyl 4-bromopyrazole-1-carboxylate (124 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 76.0 mg (217 μmol, 43% yield) of the desired product as a white solid.

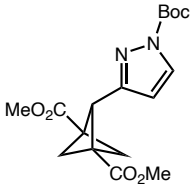
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.08 (s, 1H), 7.70 (s, 1H), 3.73 – 3.71 (m, 7H), 2.74 (dd, $J$ = 9.6, 2.9 Hz, 1H), 2.43 (d, $J$ = 2.1 Hz, 1H), 2.38 (dd, $J$ = 6.8, 2.8 Hz, 1H), 2.34 (dd, $J$ = 9.6, 2.1 Hz, 1H), 1.65 (s, 9H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.9, 147.8, 144.7, 129.9, 119.4, 85.6, 58.0, 52.8, 52.2, 49.6, 40.9, 28.1.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2958.7, 1739.5, 1719.7, 1426.6, 1399.2, 1369.4, 1328.2, 1294.6, 1277.0, 1254.5, 1211.8, 1193.7, 1153.5, 1110.1, 1054.7, 1027.6, 990.8, 956.7, 924.1, 889.5, 845.1, 799.7, 788.2, 768.4, 741.3, 655.0, 604.3, 483.4, 462.7.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{22}N_2O_6Na$ ($[M+Na]^+$) 373.1376, found 373.1373.

**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (48)**




Prepared according to the general procedure slowly adding a solution of *tert*-butyl 3-bromopyrazole-1-carboxylate (124 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. The reaction mixture was irradiated for 4 h and the solution of both the heteroaryl bromide and silylamine was added at a rate of 1.5 mL/h. Purification *via* flash column chromatography (20–100% EtOAc/hexane) gave 70.4 mg (201 μmol, 40% yield) of the desired product as a colorless oil.

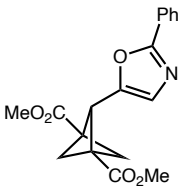
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 2.7 Hz, 1H), 3.88 (d, *J* = 6.9 Hz, 1H), 3.72 (s, 6H), 2.82 (dd, *J* = 9.3, 2.9 Hz, 1H), 2.43 – 2.35 (m, 3H), 1.62 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.0, 152.4, 147.6, 131.2, 109.2, 85.1, 61.0, 53.1, 52.1, 49.0, 41.3, 28.1.

**IR (film):** $\nu_{max}(cm^{-1})$ 2952.3, 1770.0, 1729.9, 1540.8, 1435.6, 1411.1, 1370.2, 1354.1, 1285.0, 1257.9, 1233.7, 1203.1, 1144.3, 1046.2, 965.0, 927.8, 840.4, 766.8, 482.9.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{23}N_2O_6$ ($[M+H]^+$) 351.1556, found 351.1550.

**Dimethyl 2-(2-phenyloxazol-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (49)**




Prepared according to the general procedure slowly adding a solution of 5-bromo-2-phenyloxazole (112 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump

to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **5% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 87.1 mg (266 μmol, 53% yield) of the desired product as a white solid.

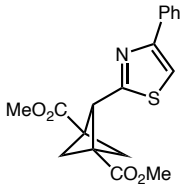
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.00 – 7.97 (m, 2H), 7.47 – 7.42 (m, 3H), 7.12 (d, *J* = 1.2 Hz, 1H), 3.90 (dd, *J* = 6.7, 1.2 Hz, 1H), 3.74 (s, 6H), 2.93 (ddd, *J* = 9.3, 3.0, 0.8 Hz, 1H), 2.49 – 2.40 (m, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.4, 161.6, 147.8, 130.5, 128.9, 127.5, 127.0, 126.4, 58.5, 52.9, 52.3, 49.6, 41.0.

**IR (film):** $\nu_{max}(cm^{-1})$ 2952.2, 1729.0, 1593.4, 1548.5, 1482.3, 1435.1, 1350.9, 1287.8, 1201.2, 1155.8, 1123.9, 1052.6, 1024.6, 985.3, 925.9, 845.4, 816.7, 777.0, 755.8, 712.6, 691.1, 492.0.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{18}NO_5$ ($[M+H]^+$) 328.1185, found 328.1183.

**Dimethyl 2-(4-phenylthiazol-2-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (50)**




Prepared according to the general procedure slowly adding a solution of 2-bromo-4-phenylthiazole (120 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (1.6 equiv) in $PhCF_3$ *via* syringe pump to a solution of dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (263 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (2.0 equiv), 2% $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ and **10% Ni(dtbpy)Br$_2$** in $PhCF_3$. Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 46.2 mg (135 μmol, 27% yield) of the desired product as a yellow oil.

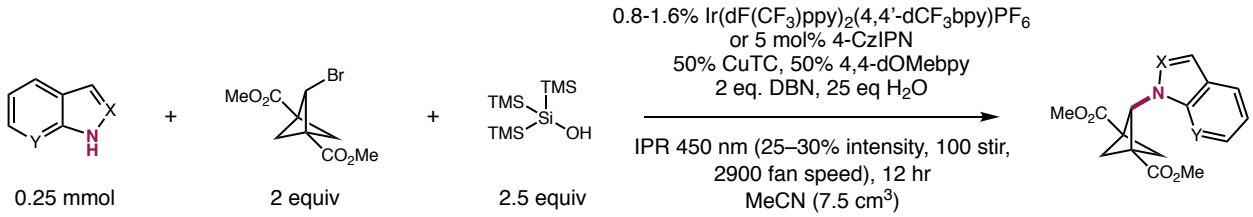
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.89 – 7.85 (m, 2H), 7.45 (s, 1H), 7.42 – 7.37 (m, 2H), 7.34 – 7.29 (m, 1H), 4.12 (d, *J* = 6.7 Hz, 1H), 3.77 (s, 6H), 2.99 (dd, *J* = 10.1, 3.1 Hz, 1H), 2.48 – 2.43 (m, 3H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.6, 164.2, 154.9, 134.5, 128.8, 128.2, 126.5, 113.4, 63.4, 53.0, 52.2, 49.0, 42.3.

**IR (film):** $\nu_{max}(cm^{-1})$ 2951.3, 1728.2, 1491.2, 1435.6, 1291.0, 1205.1, 1155.5, 1051.1, 1028.2, 908.1, 856.9, 787.6, 727.4, 692.2, 647.8, 467.8.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{18}NO_4S$ ($[M+H]^+$) 344.0957, found 344.0949.

## Cross-Electrophile Coupling for 2-Amination of BCP Bromides




### General Procedure A for BCP-Amination

To an oven-dried 40 mL vial equipped with a Teflon stir bar was added *N*-nucleophile (0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]2[4,4'-d($CF_3$)bpy]$PF_6$ (0.002–0.004 mmol, 0.008-0.016 equiv.) or 4-CzIPN (2.0 mg, 0.0025 mmol, 0.05 equiv.) and MeCN (7.5 mL, 0.03 M). 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.) and water (0.11 mL, 6.25 mmol, 25 equiv.) were then added, and the resulting solution was stirred for 1–2 minutes under air to ensure complete ligation of the nucleophile to the copper precatalyst. Following this complexation period, brominated bicyclo[1.1.1]pentane (0.50 mmol, 2.0 equiv.) and supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.) were added to the mixture, after which the vial was capped and an 18 G vent needle was inserted through the Teflon-lined septum. The reaction mixture was subsequently stirred under air within the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). After 12 hours, MeOH (0.25 mL) was added. This resulting solution was stirred under air for 2 hours, filtered through a short plug of celite or silica and concentrated in vacuo to obtain the crude product. The crude product was then purified by flash chromatography on silica gel to afford the desired product.

### General Procedure B for BCP-Amination

To an oven-dried 40 mL vial equipped with a Teflon stir bar was added *N*-nucleophile (0.25 mmol, 1.0 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (0.002–0.004 mmol, 0.008-0.016 equiv.) or 4-CzIPN (2.0 mg, 0.0025 mmol, 0.05 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.) and MeCN (3.75 mL). To a separate oven-dried 40 mL vial equipped with a Teflon stir bar was added CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.) and acetonitrile (3.75 mL). The resulting mixtures were stirred

for 1–2 minutes under air to ensure complete ligation of the ligand to the copper catalyst and deprotonation of the amine base. Next, the CuTC/4,4'-dimethoxy-2,2'-bipyridine/MeCN mixture was added to the vial containing the *N*-nucleophile, photocatalyst and base solution. Water (0.11 mL, 6.25 mmol, 25 equiv.) was then added to the resulting combined solution, and the solution was stirred for 1–2 minutes to ensure complete ligation of the *N*-nucleophile to the copper precatalyst. Following this complexation period, brominated bicyclo[1.1.1]pentane (0.50 mmol, 2.0 equiv.) and supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.) were added to the mixture, after which the vial was capped and an 18 G vent needle was inserted through the Teflon-lined septum. The reaction mixture was subsequently stirred under air within the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). After 12 hours, MeOH (0.25 mL) was added. This resulting solution was stirred under air for 2 hours, filtered through a short plug of celite or silica and concentrated in vacuo to obtain the crude product. The crude product was then purified by flash chromatography on silica gel to afford the desired product.

*Notes:*

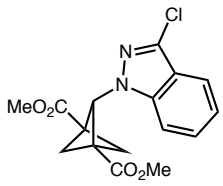
- **Reaction Setup**: Appreciable yields are still observed using a Kessil 450 nm lamp setup (1 vial per light, ~6 cm from each light), but optimal yields were obtained using the Integrated Photoreactor. Light intensity is an important parameter for reaction yield, so it is important to make sure the light intensities are comparable between reaction setups.
- **Stir Rate**: Low stir rates are critical for good yields of aminated product. The ideal stir rates were less than 500 RPM, with 100 RPM being optimal.
- **Solvents**: Acetonitrile was found to be the optimal solvent by far. Small amounts (<10%) of other solvents such as methanol, dichloromethane and acetone, did not hurt reaction yield.
- **Electrophile stoichiometry**: Increasing the BCP bromide equivalents significantly over 2.0 equiv tends to give reduced yield. However, reducing the BCP bromide equivalents to 1.5 equiv tends to not hurt yield for most substrates.
- **Photocatalyst**: 5 mol% 4-CzIPN and 0.8–1.6 mol% $[Ir(dF(CF_3)ppy)_2(4,4'\text{-}dCF_3bpy)]PF_6$ were the two best photocatalysts using supersilanol (Cas no. 7428-60-6), with the optimal catalyst being different for each substrate. Higher photocatalyst loadings up to 5 mol% for iridium photocatalysts and 10 mol% for organic photocatalysts tend to lead to higher yields (potentially due to photocatalyst degradation over the course of the reaction). If incomplete conversion of

BCP bromide is observed, we recommend increasing the photocatalyst loading to improve yield. When using (adamantylamino)supersilane (Sigma-Aldrich, cat.-no. 915319), the following commercially available photocatalysts could also be used (in lower yields):

- $[Ir(dFCF_3ppy)_2(4,4'\text{-dtbbpy})]PF_6$
- $[Ir(ppy)_2(dtbbpy)]PF_6$

- **Cu loading**: 50 mol% of the copper catalyst was found to be optimal across every substrate.
- **Cu catalyst system**: Other ligand scaffolds, such as diketonates or phenanthrolines, gave diminished yield for most amine classes. Other Cu(I) precatalysts, such as $Cu(MeCN)_4PF_6$ and $Cu(MeCN)_4BF_4$ gave comparable yields for some substrates, but this was not consistent across every substrate or amine class. Cu(II) pre-catalysts, such as $Cu(OTf)_2$, tended to give diminished yields.
- **Base**: A range of inorganic bases led to diminished yield. Other organic bases, such as DBU and TMG, can give comparable yields, but this is not consistent across every substrate and amine class. Lower base equivalencies tend to lead to diminished yields.
- **Silyl radical precursor**: Supersilanol (Cas no. 7428-60-6) was identified as the best silyl radical precursor for this transformation, but (Adamantylamino)supersilane (Sigma-Aldrich, cat.-no. 915319) could also be used with slightly diminished yield of the cross-coupling product for a number of different substrates. Other silanes led to either significantly diminished yields or no desired product. Increased supersilyl radical precursor equivalents led to diminished yields for a number of substrates.
- **Unsuccessful amine classes**: Amides, sulfonamides, carbamates and anilines gave no yield of cross-coupled product for dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate.

**Dimethyl 2-(3-chloro-1*H*-indazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (51)**




Prepared following general procedure A using 3-chloro-1*H*-pyrazole (38.2 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13

mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–15% EtOAc/hexane) on silica gel afforded the desired product (67.1 mg, 80% yield) as a colorless oil.

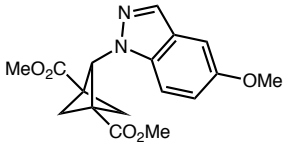
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 8.5 Hz, 1H), 7.23 (t, 1H, *J* = 8.5 Hz), 5.08 (d, *J* = 6.4 Hz, 1H), 3.72 (s, 6H), 3.11 (dd, *J* = 9.7, 3.3 Hz, 1H), 2.58–2.35 (m, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.0, 141.5, 133.8, 127.8, 121.9*, 119.8, 110.0, 72.5, 52.2, 48.7, 47.0, 43.0. (* two peaks at this position)

**IR (film):** $\nu_{max}$($cm^{-1}$) 2951.9, 1728.4, 1571.5, 1504.9, 1479.8, 1457.8, 1435.1, 1422.0, 1390.7, 1338.5, 1295.9, 1209.7, 1156.7, 1048.7, 907.7, 844.7, 789.2, 763.3, 725.8, 646.7, 627.9, 548.3, 472.9.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{15}ClN_2O_7$ ($[M+H]^+$) 335.0793, found 335.0809.

**Dimethyl 2-(5-methoxy-1*H*-indazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (52)**




Prepared following general procedure A using 5-methoxy-1*H*-indazole (37.0 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M) using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–25% EtOAc/hexane)

on silica gel afforded the desired product (52.4 mg, 63% yield) as a white solid with 5% bromobicyclo[1.1.1]pentane-1,3-dicarboxylate as impurity.

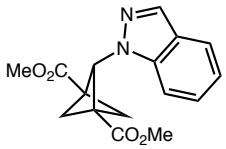
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 1.0 Hz, 1H), 7.43 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.10–7.00 (m, 2H), 5.11 (d, *J* = 6.3 Hz, 1H), 3.84 (s, 3H), 3.72 (s, 6H), 3.04 (dd, *J* = 9.7, 3.2 Hz, 1H), 2.50 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.44 (d, *J* = 2.4 Hz, 1H), 2.38 (dd, *J* = 9.7, 2.4 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.4, 155.1, 136.2, 133.2, 125.1, 118.7, 110.6, 100.4, 72.9, 55.8, 52.3, 48.8, 47.0, 43.1.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2924.2, 2853.4, 1730.6, 1505.5, 1451.6, 1435.2, 1364.2, 1296.7, 1209.8, 1152.6, 1048.0, 1016.6, 919.3, 854.0, 788.6, 753.4, 603.0, 467.1.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{19}N_2O_5$ ($[M+H]^+$) 331.1288, found 331.1299.

**Dimethyl 2-(1*H*-indazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (53)**




Prepared following general procedure B using 1*H*-indazole (29.5 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), $Ir[dF(CF_3)ppy]_2[4,4'\text{-}d(CF_3)bpy]PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M) using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–20% EtOAc/hexane) on silica gel afforded the desired product (67.5 mg, 90% yield) as a white solid.

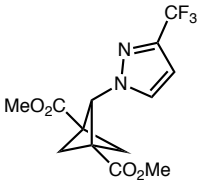
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 1.1 Hz, 1H), 7.72 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.54 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.38 (ddd, J = 8.4, 6.9, 1.1 Hz, 1H), 7.17 (ddd, *J* = 8.4, 6.9, 1.1 Hz, 1H), 5.15 (d, *J* = 6.3 Hz, 1H), 3.72 (s, 6H), 3.07 (dd, *J* = 9.7, 3.2 Hz, 1H), 2.51 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.46 (d, *J* = 2.4 Hz, 1H), 2.41 (dd, *J* = 9.7, 2.4 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.4, 140.3, 133.9, 126.7, 124.7, 121.3, 121.2, 109.6, 72.9, 52.3, 48.9, 47.0, 43.1.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2967.6, 1725.4, 1502.1, 1459.3, 1433.9, 1392.4, 1355.6, 1316.6, 1299.2, 1266.1, 1206.1, 1181.6, 1138.0, 1048.4, 967.9, 893.2, 836.6, 750.8, 622.2, 470.5.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{19}N_2O_5$ ($[M+H]^+$) 301.1183, found 301.1191.

**Dimethyl 2-(3-(trifluoromethyl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (54)**




Prepared following general procedure A using 3-(trifluoromethyl)-1*H*-pyrazole (34.0 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M) using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–50% EtOAc/hexane) on silica gel afforded the desired product (58.0 mg, 73% yield) as a colorless oil.

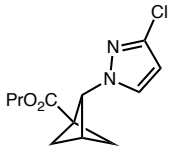
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.77 (s, 1H), 6.65 – 6.37 (m, 1H), 4.94 (d, *J* = 6.4 Hz, 1H), 3.77 (s, 6H), 2.59 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.52–2.43 (m, 2H), 2.31 (dd, J = 9.8, 2.6 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 167.6, 142.6 (q, *J* = 38.2 Hz), 131.5, 121.3 (q, *J* = 268.5 Hz), 104.9 (q, *J* = 2.1 Hz), 73.7, 52.5, 48.2, 47.6, 42.6.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2966.9, 1725.0, 1502.2, 1459.0, 1433.8, 1392.2, 1355.7, 1316.8, 1266.2, 1206.1, 1181.8, 1138.1, 1048.4, 967.9, 893.0, 751.3, 622.6, 472.5.

**HRMS (ESI)** m/z calcd. for $C_{13}H_{14}F_3N_2O_4$ ($[M+H]^+$) 319.0900, found 319.0908.

**(±)-Propyl 2-(3-chloro-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (55)**




Prepared following general procedure A using 3-chloro-1H-pyrazole (25.6 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), propyl 2-bromobicyclo[1.1.1]pentane-1-carboxylate (116.6 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–15% EtOAc/hexane) on silica gel afforded the desired product (52.6 mg, 83% yield) as a colorless oil.

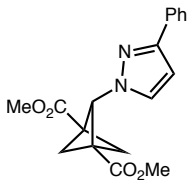
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.61 (d, *J* = 2.4 Hz, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 4.62 (d, *J* = 6.4 Hz, 1H), 4.09 (t, *J* = 6.8 Hz, 2H), 3.02 (s, 1H), 2.42 (dd, *J* = 9.8, 3.3 Hz, 1H), 2.30 – 2.14 (m, 2H), 1.99 (dd, *J* = 9.8, 2.8 Hz, 1H), 1.68 (dt, *J* = 7.6, 6.8 Hz, 2H), 0.94 (t, *J* = 7.6 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.0, 139.5, 132.1, 105.3, 73.3, 66.9, 47.3, 47.2, 45.0, 32.8, 22.1, 10.6.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2968.1, 1723.9, 1503.7, 1459.2, 1434.9, 1393.0, 1356.0, 1317.6, 1266.8, 1206.7, 1182.0, 1139.0, 1048.9, 968.7, 907.4, 837.2, 728.2, 647.1, 621.6.

**HRMS (ESI)** m/z calcd. for $C_{12}H_{16}ClN_2O_2$ ($[M+H]^+$) 255.0895, found 255.0906.

**Dimethyl 2-(3-(phenyl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (56)**




Prepared following general procedure A using 3-(phenyl)-1*H*-pyrazole (36.0 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13

mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M) using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–20% EtOAc/hexane) on silica gel afforded the desired product (54.6 mg, 67% yield) as a colorless oil.

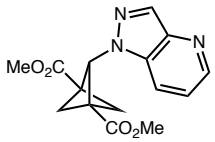
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.3 Hz, 2H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 4.97 (d, *J* = 6.3 Hz, 1H), 3.80 (s, 6H), 2.70 (dd, *J* = 9.7, 3.3 Hz, 1H), 2.54 – 2.40 (m, 2H), 2.32 (dd, *J* = 9.7, 2.5 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.1, 151.2, 133.5, 131.0, 128.6, 127.7, 125.7, 103.3, 73.9, 52.4, 48.3, 47.4, 42.6.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2924.7, 2854.1, 1731.6, 1502.9, 1457.4, 1435.0, 1368.0, 1297.2, 1210.5, 1157.1, 1098.0, 1047.3, 1018.6, 959.3, 919.0, 844.1, 788.7, 753.6, 725.0, 628.1, 602.8, 444.4.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{19}N_2O_4$ ($[M+H]^+$) 327.1339, found 327.1360.

**Dimethyl 2-(1*H*-pyrazolo[4,3-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (57)**




Prepared following general procedure A using 1*H*-pyrazolo[4,3-b]pyridine (29.8 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (4.6 mg, 0.004 mmol, 0.016 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–60% EtOAc/hexane) on silica gel afforded the desired product (55.0 mg, 73% yield) as a colorless oil.

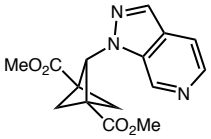
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.57 (dd, *J* = 4.4, 1.2 Hz, 1H), 8.21 (d, *J* = 1.0 Hz, 1H), 7.97 (dt, *J* = 8.6, 1.2 Hz, 1H), 7.28 (dd, *J* = 8.6, 4.4 Hz, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 3.72 (s, 6H), 3.00 (dd, *J* = 9.8, 3.3 Hz, 1H), 2.60 – 2.43 (m, 2H), 2.38 (dd, *J* = 9.8, 2.4 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.1, 146.1, 142.5, 134.7, 133.2, 120.9, 117.9, 72.4, 52.4, 48.9, 47.3, 43.0.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2952.2, 1727.7, 1594.4, 1565.3, 1504.3, 1433.9, 1421.7, 1354.4, 1294.9, 1267.2, 1209.5, 1172.9, 1155.7, 1046.7, 1005.6, 918.4, 844.4, 788.9, 762.2, 729.7, 627.9, 580.8, 476.3

**HRMS (ESI)** m/z calcd. for $C_{15}H_{16}N_3O_4$ ($[M+H]^+$) 302.1135, found 302.1145.

**Dimethyl 2-(1*H*-pyrazolo[3,4-c]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (58)**




Prepared following general procedure A using 1*H*-pyrazolo[3,4-c]pyridine (29.8 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), $Ir[dF(CF_3)ppy]_2[4,4'\text{-}d(CF_3)bpy]PF_6$ (4.6 mg, 0.004 mmol, 0.016 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–75% EtOAc/hexane) on silica gel afforded the desired product (37.6 mg, 50% yield) as a colorless oil.

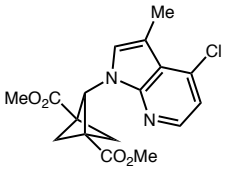
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 9.08 (s, 1H), 8.35 (d, *J* = 5.6 Hz, 1H), 8.03 (s, 1H), 7.61 (d, *J* = 5.6, 1H), 5.23 (d, *J* = 6.3 Hz, 1H), 3.74 (s, 6H), 3.01 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.55 (dd, *J* = 6.4, 3.4 Hz, 1H), 2.51 (d, *J* = 2.5 Hz, 1H), 2.42 (dd, *J* = 9.8, 2.5 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 167.9, 139.7, 136.9, 134.4, 133.2, 128.5, 114.8, 72.6, 52.5, 48.8, 47.3, 43.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2924.3, 2854.1, 1730.9, 1457.8, 1434.3, 1421.6, 1366.9, 1295.5, 1266.7, 1210.8, 1154.5, 1047.1, 1018.0, 919.2, 844.8, 788.8, 761.8, 726.2, 628.4, 598.8.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{16}N_3O_4$ ($[M+H]^+$) 302.1135, found 302.1138.

**Dimethyl 2-(4-chloro-3-methyl-1*H*-pyrrolo[2,3-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (59)**




Prepared following general procedure A using 4-chloro-3-methyl-1*H*-pyrrolo[2,3-b]pyridine (41.7 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), $Ir[dF(CF_3)ppy]_2[4,4'\text{-}d(CF_3)bpy]PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–50% $Et_2O$/hexane) on silica gel afforded the desired product (55.6 mg, 63% yield) as a colorless oil.

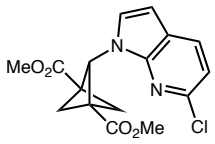
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 5.1 Hz, 1H), 7.15 (s, 1H), 6.98 (d, *J* = 5.1 Hz, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 3.74 (s, 6H), 2.75 (dd, *J* = 9.6, 3.4 Hz, 1H), 2.48 (s, 3H), 2.45 (dd, *J* = 6.4, 3.4 Hz, 1H), 2.43 (d, J = 2.6 Hz, 1H), 2.38 (dd, *J* = 9.6, 2.6 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.4, 150.0, 143.0, 136.6, 126.0, 118.4, 116.8, 110.6, 71.8, 52.34, 48.3, 47.0, 42.7, 12.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2952.2, 1729.0, 1492.1, 1435.9, 1381.7, 1298.4, 1257.7, 1205.7, 1155.9, 1104.7, 1056.1, 1020.9, 921.3, 876.2, 840.2, 787.8, 752.5, 725.8, 693.8, 640.5.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{18}ClN_2O_4$ ($[M+H]^+$) 349.0950, found 349.0960.

**Dimethyl 2-(6-chloro-1*H*-pyrrolo[2,3-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (60)**




Prepared following general procedure A using 6-chloro-1H-pyrrolo[2,3-b]pyridine (38.2 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), $Ir[dF(CF_3)ppy]_2[4,4'\text{-}d(CF_3)bpy]PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–15% EtOAc/hexane) on silica gel afforded the desired product (50.0 mg, 60% yield) as a colorless oil.

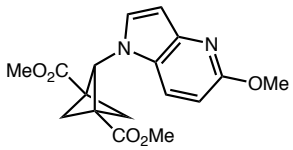
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 3.6 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.47 (d, *J* = 3.6 Hz, 1H), 5.07 (d, *J* = 6.5 Hz, 1H), 3.82 (s, 6H), 2.71 (dd, *J* = 9.6, 3.5 Hz, 1H), 2.55 – 2.30 (m, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.3, 147.7, 144.4, 131.1, 128.1, 118.9, 116.6, 101.1, 71.6, 52.5, 48.5, 47.0, 42.7.

**IR (film):** $\nu_{max}(cm^{-1})$ 2948.2, 1726.2, 1591.4, 1460.1, 1418.6, 1388.9, 1330.6, 1292.8, 1206.5, 1159.5, 1049.2, 1033.0, 908.1, 825.7, 771.5, 730.5, 563.8, 521.5, 476.8, 468.0

**HRMS (ESI)** m/z calcd. for $C_{16}H_{15}ClN_2O_7$ ($[M+H]^+$) 335.0793, found 335.0794.

**Dimethyl 2-(5-methoxy-1*H*-pyrrolo[3,2-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (61)**




Prepared following general procedure A using 5-methoxy-1*H*-pyrrolo[3,2-b]pyridine (37.0 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–75% $Et_2O$/hexane) on silica gel afforded the desired product (55.1 mg, 67% yield) as a white solid.

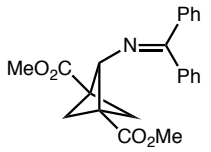
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.62 (dd, *J* = 8.9, 0.8 Hz, 1H), 7.36 (d, *J* = 3.3 Hz, 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 6.54 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.04 (d, *J* = 6.3 Hz, 1H), 3.98 (s, 3H), 3.71 (s, 6H), 2.98 (dd, *J* = 9.7, 3.6 Hz, 1H), 2.50 (dd, *J* = 6.3, 3.6 Hz, 1H), 2.43 (d, *J* = 2.7 Hz, 1H), 2.37 (dd, *J* = 9.7, 2.7 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.1, 160.6, 143.5, 129.0, 125.8, 121.1, 105.8, 102.3, 73.1, 53.5, 52.5, 48.1, 47.1, 42.6.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2951.0, 1729.7, 1600.0, 1574.4, 1487.1, 1435.0, 1413.8, 1367.8, 1346.2, 1294.3, 1258.3, 1214.8, 1199.9, 1159.1, 1089.2, 1047.6, 1026.9, 912.2, 811.0, 778.1, 727.5, 607.3, 470.2.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{19}N_2O_5$ ($[M+H]^+$) 331.1288, found 331.1295.

**Dimethyl 2-((diphenylmethylene)amino)bicyclo[1.1.1]pentane-1,3-dicarboxylate (62)**




Prepared following general procedure A using diphenylmethanimine (45.3 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), $Ir[dF(CF_3)ppy]_2[4,4'\text{-}d(CF_3)bpy]PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–20% $Et_2O$/hexane) on silica gel afforded the desired product (50.0 mg, 55% yield) as a colorless oil.

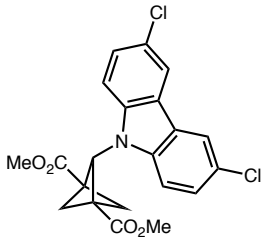
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.67 (d, *J* = 7.4 Hz, 2H), 7.58 – 7.41 (m, 3H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.19 (m, 2H), 4.37 (d, *J* = 5.9 Hz, 1H), 3.89 (dd, *J* = 9.4, 1.8 Hz, 1H), 3.65 (s, 6H), 2.49 (dd, *J* = 5.9, 1.8 Hz, 1H), 2.31 (d, J = 2.4 Hz, 1H), 1.97 (dd, J = 9.4, 2.4 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.0, 168.9, 139.9, 136.4, 130.5, 129.0, 128.7, 128.5, 128.4, 128.1, 79.8, 51.9, 48.6, 48.2, 43.6.

**IR (film):** $\nu_{max}(cm^{-1})$ 2999.0, 2949.6, 1726.7, 1614.9, 1597.8, 1575.6, 1491.4, 1434.1, 1376.3, 1346.4, 1315.5, 1283.6, 1203.1, 1153.6, 1117.4, 1073.3, 1051.0, 1027.4, 1000.2,967.6, 918.2, 782.4, 731.5, 694.3, 649.7, 615.5, 582.1, 455.6.

**HRMS (ESI)** m/z calcd. for $C_{22}H_{22}NO_4$ ($[M+H]^+$) 364.1543, found 364.1551.

**Dimethyl 2-(3,6-dichloro-9*H*-carbazol-9-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (63)**




Prepared following general procedure A using 3,6-dichloro-9*H*-carbazole (59.0 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]2[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–15% EtOAc/hexane) on silica gel afforded the desired product (63.9 mg, 61% yield) as a white solid.

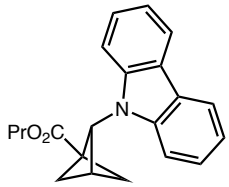
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 2.1 Hz, 2H), 7.37 (dd, *J* = 8.8, 2.1 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 5.13 (d, *J* = 6.8 Hz, 1H), 3.66 (s, 6H), 3.19 (dd, *J* = 9.7, 3.7 Hz, 1H), 2.68 (dd, *J* = 6.8, 3.7 Hz, 1H), 2.56 – 2.38 (m, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.4, 139.8, 127.0, 126.0, 124.1, 120.2, 111.2, 74.1, 52.6, 49.3, 47.9, 44.10.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3011.9, 2951.4, 1727.1, 1504.8, 1472.4, 1438.4, 1359.7, 1336.4, 1315.6, 1282.6, 1240.3, 1210.9, 1154.2, 1081.8, 1055.7, 1034.6, 905.8, 867.2, 848.9, 800.2, 729.5, 687.6, 643.2, 567.6, 526.7, 423.0.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{18}Cl_2NO_4$ ($[M+H]^+$) 418.0607, found 418.0614.

**(±)-Propyl 2-(9*H*-carbazol-9-yl)bicyclo[1.1.1]pentane-1-carboxylate (64)**




Prepared following general procedure A using 9*H*-carbazole (41.8 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]2[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), propyl 2-bromobicyclo[1.1.1]pentane-1-carboxylate (116.6 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–10% EtOAc/hexane) on silica gel afforded the desired product (36.1 mg, 45% yield) as a white solid.

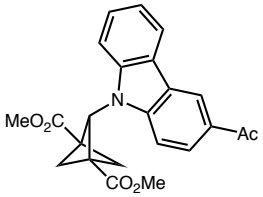
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.07 (dt, *J* = 7.7, 1.0 Hz, 2H), 7.60 – 7.33 (m, 4H), 7.25 – 7.20 (m, 2H), 4.98 (d, *J* = 6.7 Hz, 1H), 4.07 – 3.78 (m, 2H), 3.51 (s, 1H), 2.86 (dd, *J* = 9.5, 3.4 Hz, 1H), 2.30 (dd, *J* = 6.8, 3.4 Hz, 1H), 2.26 – 2.16 (m, 2H), 1.46 (q, *J* = 7.3 Hz, 2H), 0.70 (t, *J* = 7.3 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.8, 141.5, 126.0, 123.5, 120.2, 119.6, 110.2, 74.0, 66.7, 50.0, 46.6, 45.1, 33.2, 21.7, 10.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2968.2, 2936.7, 1721.6, 1623.9, 1596.0, 1490.6, 1450.4, 1392.1, 1328.8, 1315.5, 1228.4, 1212.2, 1164.7, 1120.7, 1085.7, 1019.7, 926.8, 884.8, 749.5, 723.0, 620.1, 565.7.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{22}NO_2$ ($[M+H]^+$) 320.1645, found 320.1660.

**Dimethyl 2-(3-acetyl-9*H*-carbazol-9-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (65)**




Prepared following general procedure A using 1-(9*H*-carbazol-3-yl)ethan-1-one (52.3 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–50% EtOAc/hexane) on silica gel afforded the desired product (67.2 mg, 69% yield) as a white solid.

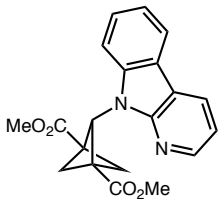
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.23 – 7.98 (m, 3H), 7.88 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.47 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 5.26 (d, *J* = 6.9 Hz, 1H), 3.71 (s, 6H), 3.24 (dd, *J* = 9.8, 3.9 Hz, 1H), 2.76 – 2.63 (m, 4H), 2.55 – 2.45 (m, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 198.2, 168.5, 142.5, 140.6, 135.0, 127.8, 127.7, 122.9, 121.2, 120.6, 120.5, 120.0, 110.5, 110.3, 74.2, 52.6, 49.4, 47.8, 44.1, 27.1.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2924.5, 2853.1, 1731.4, 1624.1, 1595.8, 1567.7, 1505.0, 1452.1, 1434.2, 1364.5, 1294.8, 1209.3, 1172.0, 1151.6, 1047.3, 1019.7, 919.5, 844.3, 798.4, 788.5, 741.6.

**HRMS (ESI)** m/z calcd. for $C_{23}H_{22}NO_5$ ($[M+H]^+$) 392.1492, found 392.1475.

**Dimethyl 2-(9*H*-pyrido[2,3-b]indol-9-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (66)**




Prepared following general procedure A using 9*H*-pyrido[2,3-b]indole (42.1 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–50% EtOAc/hexane) on silica gel afforded the desired product (63.6 mg, 73% yield) as a white solid.

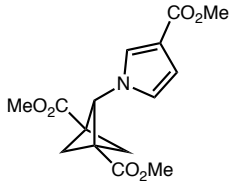
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.30 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.26 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.52 – 7.40 (m, 2H), 7.29 (ddd, *J* = 7.7, 6.5, 1.6 Hz, 1H), 7.13 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.08 (d, *J* = 6.6 Hz, 1H), 3.69 (s, 6H), 2.97 (dd, *J* = 9.6, 3.5 Hz, 1H), 2.58 (dd, *J* = 6.6, 3.5 Hz, 1H), 2.50 – 2.40 (m, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.1, 152.3, 145.5, 140.2, 128.0, 127.0, 121.1, 121.0, 120.8, 116.0, 115.8, 110.2, 71.8, 52.1, 49.1, 47.3, 43.9.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3012.7, 2989.9, 2948.8, 2920.8, 1729.6, 1625.4, 1591.3, 1591.3, 1459.9, 1434.8, 1421.2, 1388.9, 1339.4, 1293.6, 1229.0, 1207.3, 1158.3, 1136.3, 1060.7, 1050.4, 1034.1, 772.5, 731.4

**HRMS (ESI)** m/z calcd. for $C_{20}H_{19}N_2O_4$ ($[M+H]^+$) 351.1339, found 351.1355.

**Dimethyl 2-(3-(methoxycarbonyl)-1*H*-pyrrol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (67)**




Prepared following general procedure A using methyl 1*H*-pyrrole-3-carboxylate (31.3 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–25% EtOAc/hexane) on silica gel afforded the desired product (34.6 mg, 45% yield) as a colorless oil.

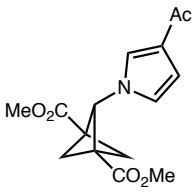
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.43 (t, *J* = 1.7 Hz, 1H), 6.76 (t, *J* = 2.8 Hz, 1H), 6.58 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.81 (d, *J* = 6.3 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 6H), 2.71 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.51 (dd, *J* = 6.3, 3.4 Hz, 1H), 2.44 (d, *J* = 2.6 Hz, 1H), 2.24 (dd, *J* = 9.8, 2.6 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 167.7, 165.2, 125.9, 121.9, 116.5, 110.4, 72.6, 52.6, 51.2, 48.5, 47.6, 42.5.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2952.7, 1728.9, 1706.8, 1542.5, 1499.0, 1435.5, 1376.0, 1292.4, 1245.8, 1205.0, 1156.9, 1124.4, 1055.1, 1023.3, 998.5, 924.1, 818.2, 788.9, 761.8, 727.7, 696.0, 619.0, 469.6.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{18}NO_6$ ($[M+H]^+$) 308.1129, found 308.1138.

**Dimethyl 2-(3-acetyl-1*H*-pyrrol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (68)**




Prepared following general procedure A using methyl 1-(1*H*-pyrrol-3-yl)ethan-1-one (27.3 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–40% EtOAc/hexane) on silica gel afforded the desired product (34.6 mg, 50% yield) as a colorless oil.

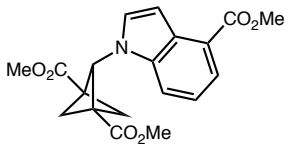
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.47 (t, *J* = 1.7 Hz, 1H), 6.79 (dd, *J* = 3.0 Hz, 1.7 Hz, 1H), 6.59 (dd, J = 3.0, 1.7 Hz, 1H), 4.81 (d, *J* = 6.4 Hz, 1H), 3.77 (s, 6H), 2.73 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.52 (dd, *J* = 6.4, 3.4 Hz, 1H), 2.46 (d, *J* = 2.6 Hz, 1H), 2.38 (s, 3H), 2.25 (dd, *J* = 9.8, 2.6 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 193.6, 167.7, 126.5, 125.9, 122.5, 109.5, 72.5, 52.6, 48.4, 47.8, 42.5, 27.3.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2953.6, 1727.8, 1658.8, 1530.9, 1499.9, 1435.1, 1379.5, 1348.9, 1291.7, 1249.0, 1205.8, 1157.3, 1105.6, 1054.9, 1021.2, 931.4, 800.7, 789.4, 763.2, 727.2, 659.6, 617.0, 474.1.

**HRMS (ESI)** m/z calcd. for $C_{15}H_{18}NO_5$ ($[M+H]^+$) 292.1179, found 292.1193.

**Dimethyl 2-(4-(methoxycarbonyl)-1*H*-indol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (69)**



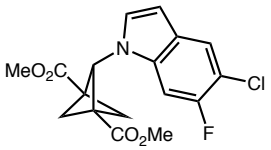

Prepared following general procedure A using methyl 1H-indole-4-carboxylate (43.8 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (4.6 mg, 0.004 mmol, 0.016 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–15% EtOAc/hexane) on silica gel afforded the desired product (53.2 mg, 60% yield) as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 3.3 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 3.3 Hz, 1H), 5.12 (d, *J* = 6.4 Hz, 1H), 3.98 (s, 3H), 3.69 (s, 6H), 3.01 (dd, *J* = 9.6, 3.7 Hz, 1H), 2.50 (dd, *J* = 6.4, 3.7 Hz, 1H), 2.46 – 2.29 (m, 2H).
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.1, 168.0, 137.7, 129.2, 128.4, 123.9, 121.9, 121.4, 114.9, 103.5, 73.2, 52.5, 52.0, 48.1, 47.1, 42.7.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2951.8, 1730.5, 1713.2, 1505.7, 1435.7, 1380.3, 1353.8, 1321.7, 1286.9, 1268.6, 1213.1, 1195.1, 1154.2, 1048.1, 1020.2, 905.0, 845.5, 788.5, 753.1.

**HRMS (ESI)** m/z calcd. for $C_{19}H_{20}NO_6$ ($[M+H]^+$) 358.1285, found 358.1315.

**Dimethyl 2-(5-chloro-6-fluoro-1*H*-indol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (70)**




Prepared following general procedure B using 5-chloro-6-fluoro-1*H*-indole (42.4 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]$_2$[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–20% EtOAc/hexane) on silica gel afforded the desired product (61.2 mg, 70% yield) as a colorless oil.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.43 (dd, *J* = 6.1, 0.9 Hz, 1H), 7.33 (d, *J* = 9.5 Hz, 1H), 7.30 (d, *J* = 3.3 Hz, 1H), 6.44 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.01 (d, *J* = 6.3 Hz, 1H), 3.74 (s, 6H), 2.95 (dd, *J* = 9.7, 3.6 Hz, 1H), 2.50 (dd, *J* = 6.4, 3.6 Hz, 1H), 2.44 (d, *J* = 2.7 Hz, 1H), 2.39 (dd, *J* = 9.7, 2.7 Hz, 1H).

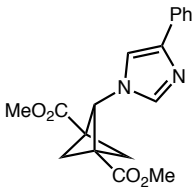
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.0, 153.5 (d, *J* = 238.6 Hz), 133.3, 129.2, 127.7 (d, *J* = 9.0 Hz), 115.9 (d, *J* = 21.3 Hz), 111.5, 107.0 (d, *J* = 23.3 Hz), 102.4, 73.1, 52.5, 48.1, 47.0, 42.6.

**$^{19}$F NMR (282 MHz, $CDCl_3$)** δ -126.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2952.8, 1728.5, 1503.2, 1470.1, 1435.3, 1390.9, 1353.7, 1295.4, 1261.7, 1208.1, 1144.3, 1050.1, 968.0, 925.6, 849.6, 817.7, 788.5, 754.1, 714.5, 691.8.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{16}ClFNO_4$ ($[M+H]^+$) 352.0746, found 352.0750.

**Dimethyl 2-(4-phenyl-1*H*-imidazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (71)**




Prepared following general procedure A using 4-phenyl-1*H*-imidazole (7.2 mg, 0.05 mmol, 1.0 equiv.), CuTC (4.8 mg, 0.025 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 0.025 mmol, 0.5 equiv.), 4-CzIPN (2.0 mg, 0.0025 mmol, 0.05 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (12.3 mg, 0.10 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (26.3 mg, 0.10 mmol, 2.0 equiv.), supersilanol (33 μL, 0.13 mmol, 2.5 equiv.), water (23 μL, 1.25 mmol, 25 equiv.) and MeCN (1.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification of five combined 0.05 mmol scale crude reaction vials (0.25 mmol total) by flash chromatography (0–75% EtOAc/hexane) provided the title compound (43.0 mg, 53% yield, >20:1 r.r.) as a colorless oil.

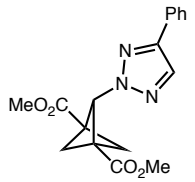
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.80 – 7.72 (m, 3H), 7.41 (d, *J* = 1.4 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.26 – 7.21 (m, 1H), 4.83 (d, *J* = 6.3 Hz, 1H), 3.78 (s, 6H), 2.79 (dd, *J* = 9.8, 3.5 Hz, 1H), 2.56 (dd, *J* = 6.3, 3.5 Hz, 1H), 2.51 (d, *J* = 2.7 Hz, 1H), 2.29 (dd, *J* = 9.8, 2.7 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 167.6, 142.1, 137.3, 133.9, 128.7, 127.0, 125.0, 114.9, 70.4, 52.63, 48.6, 48.1, 42.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2954.0, 1732.4, 1493.0, 1436.6, 1361.2, 1354.4, 1297.0, 1212.4, 1159.0, 1057.6, 1020.0, 827.8, 789.7, 780.1, 753.7, 719.1, 695.5, 627.4, 487.7, 479.2, 446.5, 436.9, 420.4.

**HRMS (ESI)** m/z calcd. for $C_{18}H_{19}N_2O_4$ ($[M+H]^+$) 327.1339, found 327.1329.

**Dimethyl 2-(4-phenyl-2*H*-1,2,3-triazol-2-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (72)**




Prepared following general procedure A using 4-phenyl-2*H*-1,2,3-triazole (36.3 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), 4-CzIPN (9.8 mg, 0.013 mmol, 0.05 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (30% light intensity, 2900 fan speed and 100 stir rate). Purification by flash chromatography (0–20% EtOAc/hexane) on silica gel afforded the desired product (35.2 mg, 43% yield) as a white solid.

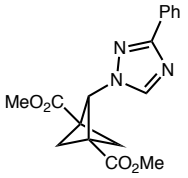
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.88 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 5.19 (d, *J* = 6.4 Hz, 1H), 3.78 (s, 6H), 2.80 (dd, *J* = 9.8, 3.5 Hz, 1H), 2.52 – 2.43 (m, 2H), 2.39 (dd, *J* = 9.8, 2.5 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 167.4, 148.1, 131.7, 130.2, 129.0, 128.7, 126.1, 75.7, 52.5, 48.5, 46.8, 43.1.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2952.9, 1727.5, 1503.4, 1458.3, 1434.7, 1390.0, 1355.4, 1299.2, 1263.0, 1207.0, 1183.7, 1139.6, 1050.9, 977.5, 968.0, 922.5, 892.6, 847.9, 789.0, 753.3, 694.4.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{18}N_3O_4$ ($[M+H]^+$) 328.1292, found 328.1290.

**Dimethyl 2-(3-phenyl-1*H*-1,2,4-triazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (73)**




Prepared following general procedure A using 4-phenyl-2*H*-1,2,3-triazole (7.3 mg, 0.05 mmol, 1.0 equiv.), CuTC (4.8 mg, 0.025 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (5.4 mg, 0.025 mmol, 0.5 equiv.), 4-CzIPN (2.0 mg, 0.0025 mmol, 0.05 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (12.3 mg, 0.10 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (26.3 mg, 0.10 mmol, 2.0 equiv.), supersilanol (33 μL, 0.13 mmol, 2.5 equiv.), water (23 μL, 1.25 mmol, 25 equiv.) and MeCN (1.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification of five combined 0.05 mmol scale crude reaction vials (0.25 mmol total) by flash chromatography (0–50% EtOAc/hexane) provided the title compound (43.5 mg, 53% yield, >20:1 r.r.) as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.44 (s, 1H), 8.17 – 7.87 (m, 2H), 7.58 – 7.31 (m, 3H), 4.95 (d, *J* = 6.5 Hz, 1H), 3.79 (s, 6H), 2.72 (dd, *J* = 9.8, 3.5 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.35 (dd, J = 9.8, 2.7 Hz, 1H).

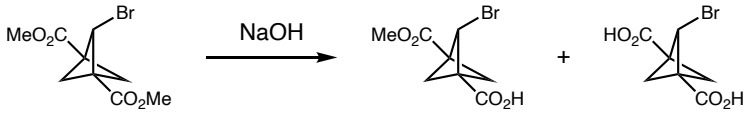
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 167.5, 162.1, 144.7, 130.8, 129.4, 128.6, 126.5, 71.6, 52.6, 48.4, 47.9, 42.5.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2952.9, 1728.3, 1522.6, 1492.6, 1436.2, 1382.2, 1348.3, 1299.0, 1257.0, 1204.9, 1157.6, 1104.6, 1056.6, 1022.6, 970.7, 919.4, 840.5, 788.2, 725.8, 694.0, 640.8, 470.9.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{18}N_3O_4$ ($[M+H]^+$) 328.1292, found 328.1297.

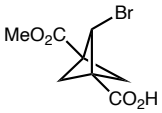
## Sequential Functionalization

### Hydrolysis of Brominated Methyl BCP Diester




An oven-dried 250 mL round-bottom flask was charged with a stir bar and dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (2.63 g, 10 mmol). $Et_2O$ (76 mL) was added, followed by NaOH (0.5 M in MeOH, 24 mL, 12 mmol, 1.2 equiv) and the reaction mixture was stirred vigorously for 2 h during which a white precipitate is forming. The mixture is placed in a water bath, aqueous HCl (0.1 M, 150 mL) was added slowly and the resulting clear mixture was transferred into a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine (150 mL) and dried ($M_g2SO_4$). After filtration and removal of the solvent, the crude material was purified *via* flash column chromatography (0–5% AcOH/$CH_2Cl_2$) to obtain 329 mg (1.25 mmol, 13% recovery) of the diester starting material as a white solid, 1.90 g (7.63 mmol, 76% yield, 87% b.r.s.m.) of the desired monoester as a white solid and 259 mg (1.10 mmol, 11% yield) of the diacid as a white solid.

### (±)-2-Bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (S8)



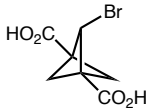

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.57 (d, *J* = 7.5 Hz, 1H), 3.74 (s, 3H), 3.07 (ddd, *J* = 10.1, 3.1, 0.7 Hz, 1H), 2.87 (d, *J* = 2.8 Hz, 1H), 2.46 (dd, *J* = 7.5, 3.2 Hz, 1H), 2.35 (dd, *J* = 10.0, 2.9 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.1, 166.8, 61.2, 52.5, 50.6, 50.1, 43.1, 42.8.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2849.0, 2593.6, 1729.9, 1692.7, 1435.7, 1352.2, 1304.7, 1257.4, 1219.3, 1200.8, 1173.9, 1125.7, 1083.8, 1058.8, 1016.5, 1003.9, 939.8, 908.3, 881.8, 796.1, 767.5, 755.2, 723.0, 700.2, 589.1, 535.8, 493.4, 445.1.

**HRMS (ESI)** m/z calcd. for $C_8H_8O_4Br$ ($[M–H]^+$) 246.9611, found 246.9609.

**2-Bromobicyclo[1.1.1]pentane-1,3-dicarboxylic acid (3)**



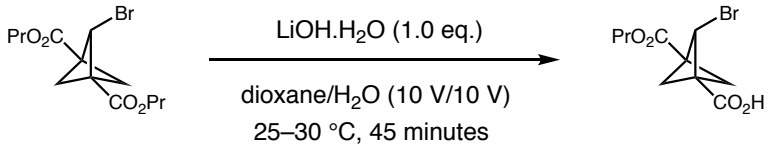

**$^{1}$H NMR (400 MHz, MeOD)** δ 4.61 (d, *J* = 7.5 Hz, 1H), 2.91 (dd, *J* = 10.1, 3.0 Hz, 1H), 2.81 (d, *J* = 2.6 Hz, 1H), 2.36 (dd, *J* = 7.5, 3.0 Hz, 1H), 2.30 (dd, *J* = 9.9, 2.6 Hz, 1H).

**$^{13}$C NMR (126 MHz, MeOD)** δ 170.0, 62.9, 50.6, 50.4, 44.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2851.4, 2600.7, 1694.5, 1212.9, 1091.3, 1003.7, 917.3, 763.9, 744.9, 722.6, 502.5, 470.0.

**HRMS (ESI)** m/z calcd. for $C_7H_6O_4Br$ ($[M–H]^+$) 232.9455, found232.9455.

**Hydrolysis of Brominated Propyl BCP Diester**

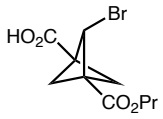



To a 40 mL vial equipped with a stir bar was added dipropyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (957.6 mg, 3 mmol, 1 equiv.) and lithium hydroxide monohydrate ($LiOH•H_2O$, 251.8 mg, 3 mmol, 2 equiv.). Then, dioxane (15 mL) and $H_2O$ (15 mL) was added. The solution was allowed to stir at room temperature for 90 min.

The reaction mixture was diluted with diethyl ether ($Et_2O$, 50 mL) and $H_2O$ (50 mL). The $Et_2O$ phase was then washed with $Na_2CO_3$ aq. solution (0.3 M, 10 mL), and all of the aqueous phases were combined. The $Et_2O$ phase was dried over $Na_2SO_4$, filtered, and concentrated in vacuo to provide the starting material dipropyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate in 191.5 mg (0.6 mmol, 20% yield).

The combined aqueous phase was acidified with concentrated hydrochloric acid (HCl, 5 mL), and then extracted with DCM (3 x 40 mL). The combined DCM phase was then washed with $H_2O$ (3 x 20 mL), and dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to provide 498.8 mg (1.8 mmol, 60% yield) of desired product as a white solid.

**(±)-2-Bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (S9)**

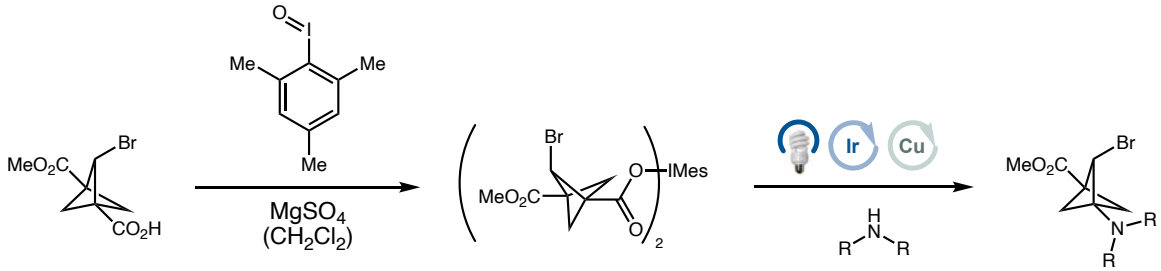



**$^1$H NMR (500 MHz, $CDCl_3$)** δ 4.58 (d, *J* = 7.5 Hz, 1H), 4.10 (td, *J* = 6.7, 1.9 Hz, 2H), 3.07 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.87 (d, *J* = 2.8 Hz, 1H), 2.46 (dd, *J* = 7.5, 3.1 Hz, 1H), 2.35 (dd, *J* = 10.0, 2.9 Hz, 1H), 1.77 – 1.58 (m, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 172.0, 166.6, 67.0, 61.3, 50.5, 50.0, 43.2, 43.0, 22.0, 10.4.

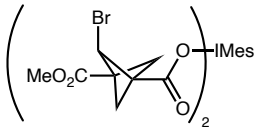
**IR (film):** $\nu_{max}$($cm^{-1}$) 2971.3, 2015.9, 1733.1, 1395.7, 1296.8, 1263.2, 1209.7,1141.8, 1058.0, 920.7, 771.6.

**Decarboxylative C–N Cross-Coupling of Monoacid**




**Step 1)** According to a modified procedure previously developed by the MacMillan group,[8] iodosylmesitylene (786 mg, 3.0 mmol) and 2-Bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (1.49 g, 6.0 mmol, 2.0 equiv) were added to an oven-dried 100 mL round-bottom flask equipped with a stir bar, followed by anhydrous $CH_2Cl_2$ (30 mL) and $MgSO_4$ (1.08 g, 9.0 mmol, 3.0 equiv). The reaction mixture was stirred vigorously in the dark for 30 min and then filtered (Celite), rinsing with $CH_2Cl_2$. After removal of the solvent, 2.21 g (2.98 mmol, >99% yield) of the diacyloxymesitylene was obtained as a white solid, which was used in the subsequent step without further purification.

**(±)-Bis-2-bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carbonyl)oxy)iodomesitylene (S10)**



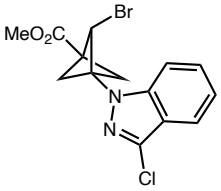

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.09 (s, 2H), 4.39 (d, *J* = 7.5 Hz, 2H), 3.69 (s, 6H), 2.88 (dd, *J* = 10.0, 3.1 Hz, 2H), 2.75 – 2.68 (m, 8H), 2.38 (s, 3H), 2.29 (dd, *J* = 7.5, 3.1 Hz, 2H), 2.17 (dd, *J* = 10.0, 2.8 Hz, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 170.9, 167.0, 143.7, 141.7 (t, *J* = 11.8 Hz), 130.5, 129.3 (t, *J* = 1.6 Hz), 62.1, 52.3, 50.8, 50.1, 43.0, 42.1, 26.8, 21.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2949.4, 1732.1, 1657.4, 1588.9, 1436.8, 1378.7, 1296.9, 1255.3, 1208.1, 1104.8, 1047.8, 1011.5, 942.3, 911.0, 883.3, 851.3, 809.8, 789.7, 766.0, 693.2, 526.9, 490.3, 465.0.

**HRMS (ESI)** m/z calcd. for $C_{25}H_{27}O_8Br_2INa$ ($[M+Na]^+$) 762.9015, found 762.9008.

**(±)-Methyl 2-bromo-3-(3-chloro-1*H*-indazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S11)**




An oven-dried 40 mL vial equipped with a cross-shaped stir bar was charged with the 3-chloroindazole (229 mg, 1.50 mmol), the BCP-diacyloxymesitylene (1.67 g, 2.25 mmol, 1.5 equiv), $Ir(ppy)_3$ (19.7 mg, 30.0 µmol, 0.02 equiv) and $Cu(acac)_2$ (196 mg, 750 µmol, 0.50 equiv), capped and sealed with parafilm. The vial was evacuated and subsequently filled with nitrogen, repeated three times. Dioxane (previously degassed by sparging with nitrogen for 15 min, 15 mL) was added and the mixture was sonicated for 5 min before placing it in the Integrated Photoreactor and stirring while irradiating for 4 hours (450 nm, 100% light intensity, 600 rpm stir rate, 5200 rpm fan rate). Afterwards, the vial was removed from the photoreactor, cooled to room temperature and opened to air. Aqueous tetrasodium EDTA (0.1 M, 30 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with

saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$) and filtered. After removal of the solvent, the crude material was purified *via* flash column chromatography (3–25% EtOAc/hexane) to obtain 449 mg (1.26 mmol, 84% yield) of the C–N coupling product as a white solid.

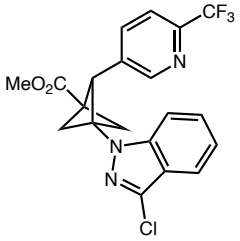
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.68 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.57 (dt, *J* = 8.6, 0.9 Hz, 1H), 7.47 (ddd, *J* = 8.5, 6.9, 1.1 Hz, 1H), 7.30 – 7.21 (m, 1H), 4.88 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H), 3.60 (ddd, *J* = 10.0, 2.9, 0.6 Hz, 1H), 3.08 (d, *J* = 2.8 Hz, 1H), 2.89 (dd, *J* = 7.5, 2.8 Hz, 1H), 2.81 (dd, *J* = 9.9, 2.9 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 166.8, 141.1, 135.6, 128.6, 122.3, 122.0, 120.2, 110.3, 63.7, 54.8, 52.7, 52.3, 51.3, 40.7.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2950.9, 1728.1, 1616.0, 1504.7, 1492.2, 1467.8, 1434.8, 1412.2, 1397.9, 1349.8, 1334.9, 1301.7, 1264.0, 1230.3, 1208.6, 1174.1, 1155.6, 1144.4, 1133.7, 1124.1, 1032.9, 1013.9, 961.6, 924.5, 896.5, 871.0, 794.8, 766.5, 758.3, 747.1, 687.9, 630.5, 590.1, 574.7, 565.3, 556.4, 496.6, 478.1, 427.2.

**HRMS (ESI)** m/z calcd. for $C_{14}H_{13}N_2O_2ClBr$ ($[M+H]^+$) 354.9849, found 354.9842.

**(±)-Methyl 3-(3-chloro-1*H*-indazol-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (74)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of 5-bromo-2-(trifluoromethyl)pyridine (67.8 mg, 0.30 mmol) and *N*-adamantyl-*N*-supersilylamine (191 mg, 0.48 mmol, 1.6 equiv) in $PhCF_3$ (3 mL) *via* syringe pump to a solution of the *N*-(3-chloroindazolyl)-BCP bromide (213 mg, 0.60 mmol, 2.0 equiv), cesium carbonate (195 mg, 0.60 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (6.73 mg, 6.00 µmol, 0.02 equiv) and $Ni(dtbpy)Br_2$ (7.30 mg, 15.0 µmol, 0.05 equiv) in $PhCF_3$ (6 mL). Purification *via* flash column chromatography (5–30% EtOAc/hexane) gave 95.5 mg (227 µmol, 76% yield) of the desired

product as a white solid and 89.7 mg (252 µmol, 84% recovery) of the *N*-functionalized BCP bromide starting material.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.47 (d, *J* = 1.5 Hz, 1H), 7.72 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.56 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.48 – 7.36 (m, 2H), 7.29 – 7.24 (m, 1H), 4.47 (d, *J* = 6.7 Hz, 1H), 3.83 (s, 3H), 3.14 (dd, *J* = 9.6, 3.1 Hz, 1H), 2.99 (dd, *J* = 6.8, 3.0 Hz, 1H), 2.92 (dd, *J* = 9.6, 2.0 Hz, 1H), 2.75 (d, *J* = 2.0 Hz, 1H).

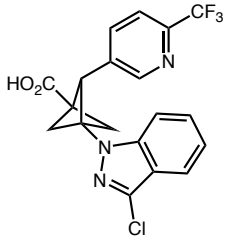
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.6, 150.2, 147.0 (q, *J* = 34.7 Hz), 140.9, 137.9, 135.5, 134.8, 128.7, 122.4, 122.1, 121.6 (q, *J* = 273.8 Hz), 120.5, 120.2 (q, *J* = 2.4 Hz), 109.8, 65.6, 55.5, 53.7, 52.7, 50.6, 39.0.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -68.00 (s, 3F).

**IR (film):** $\nu_{max}(cm^{-1})$ 2953.8, 1730.5, 1615.5, 1508.1, 1492.7, 1465.9, 1391.6, 1333.0, 1292.8, 1227.5, 1203.9, 1173.3, 1131.5, 1086.2, 1028.0, 962.8, 932.5, 903.2, 870.9, 832.3, 793.0, 765.3, 742.4, 693.0, 630.9, 603.1, 557.8, 476.3, 426.2.

**HRMS (ESI)** m/z calcd. for $C_{20}H_{16}N_3O_2F_3Cl$ ($[M+H]^+$) 422.0883, found 422.0881.

**(±)-3-(3-chloro-1*H*-indazol-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (S12)**




An 8 mL vial equipped with a cross-shaped stir bar was charged with the methyl ester (63.3 mg, 150 µmol), followed by the addition of MeOH (900 µL), $H_2O$ (1500 µL) and NaOH (0.5 M in MeOH, 600 µL, 300 µmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 24 h, during which the cloudy mixture gradually became clear. Then, the vial was opened and saturated $NH_4Cl$ (2 mL) and HCl, (1 M, 400 µL) were added and the aqueous layer was extracted with EtOAc (4 x 3 mL). The combined organic layers were washed with brine (5 mL), dried ($Mg_2SO_4$) and filtered (Celite). After removal of the solvent, the free carboxylic acid (60.6 mg,

149 µmol, >99% yield) was obtained as an off-white solid which was used in the subsequent step without further purification.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.72 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.32 – 7.23 (m, 1H), 4.51 (d, *J* = 6.5 Hz, 1H), 3.14 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.07 – 2.94 (m, 2H), 2.81 (s, 1H).

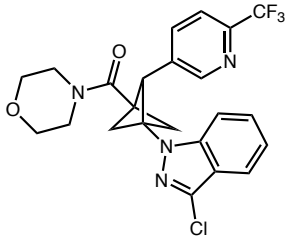
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.7, 150.0, 146.6 (q, *J* = 35.5 Hz), 140.9, 138.4, 135.6, 135.4, 128.8, 122.4, 122.1, 121.5 (q, *J* = 274.5 Hz), 120.53, 120.49 (q, *J* = 2.8 Hz), 109.9, 65.5, 55.5, 53.7, 50.6, 39.1.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -67.88 (s, 3F).

**IR (film):** $\nu_{max}(cm^{-1})$ 3005.4, 1714.6, 1616.2, 1508.3, 1492.1, 1467.5, 1407.4, 1335.2, 1230.6, 1205.7, 1174.0, 1131.3, 1088.1, 1031.2, 1006.7, 946.6, 914.8, 875.2, 834.0, 745.5, 696.0, 667.2, 648.1, 631.0, 603.5, 560.8, 426.4.

**HRMS (ESI)** m/z calcd. for $C_{19}H_{14}N_3O_2F_3Cl$ ($[M+H]^+$) 408.0727, found 408.0727.

**(±)-(3-(3-chloro-1*H*-indazol-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentan-1-yl)(morpholino)methanone (S13)**




An oven-dried 8 mL vial equipped with a cross-shaped stir bar was charged with the free carboxylic acid (40.8 mg, 100 µmol) and $CH_2Cl_2$ (1 mL) under nitrogen atmosphere and the reaction mixture was cooled to 0 °C. Morpholine (13.8 µL, 13.9 mg, 160 µmol, 1.6 equiv) was added, followed by HATU (57.0 mg, 150 µmol, 1.5 equiv) and DIPEA (70.0 µL, 51.7 mg, 400 µmol, 4.0 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 12 h during which the cloudy mixture gradually became clear. After addition of saturated $NH_4Cl$ (2 mL), the aqueous layer was extracted with $CH_2Cl_2$ (3 x 2 mL) and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and filtered. Purification *via* flash column

chromatography (5–100% EtOAc/hexane) gave 44.1 mg (92.5 μmol, 92% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.44 (d, *J* = 2.1 Hz, 1H), 7.75 – 7.66 (m, 2H), 7.56 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.47 – 7.35 (m, 2H), 7.28 – 7.23 (m, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 3.78 – 3.61 (m, 8H), 3.22 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.06 (dd, *J* = 6.8, 3.2 Hz, 1H), 2.98 (dd, *J* = 9.6, 2.2 Hz, 1H), 2.78 (d, *J* = 2.1 Hz, 1H).

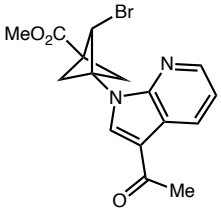
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 165.8, 150.1, 147.0 (q, *J* = 34.9 Hz), 140.9, 138.1, 135.6, 135.0, 128.8, 122.4, 122.0, 121.5 (q, *J* = 274.2 Hz), 120.5, 120.3 (q, *J* = 2.6 Hz), 109.8, 67.0, 66.7, 66.4, 56.5, 54.6, 51.5, 46.3, 42.9, 40.9.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -68.01 (s, 3F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 2858.0, 1616.4, 1506.3, 1464.5, 1437.1, 1409.1, 1390.1, 1334.1, 1307.9, 1283.6, 1266.8, 1230.8, 1207.6, 1175.4, 1114.8, 1086.5, 1031.9, 998.2, 954.6, 906.5, 833.4, 765.6, 743.0, 691.7, 602.2, 558.5, 473.9, 427.1.

**HRMS (ESI)** m/z calcd. for $C_{23}H_{21}N_4O_2F_3Cl$ ($[M+H]^+$) 477.1305, found 477.1302.

**(±)-Methyl 3-(3-acetyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-bromobicyclo[1.1.1]pentane-1-carboxylate (S14)**




An oven-dried 40 mL vial equipped with a cross-shaped stir bar was charged with 3-acetyl-7-azaindole (240 mg, 1.50 mmol), the BCP-diacyloxymesitylene (1.67 g, 2.25 mmol, 1.5 equiv), $Ir(ppy)_3$ (19.7 mg, 30.0 μmol, 0.02 equiv) and $Cu(acac)_2$ (196 mg, 750 μmol, 0.50 equiv), capped and sealed with parafilm. The vial was evacuated and subsequently filled with nitrogen, repeated three times. Dioxane (previously degassed by sparging with nitrogen for 15 min, 15 mL) was added and the mixture was sonicated for 5 min before placing it in the Integrated Photoreactor and stirring while irradiating for 4 hours (450 nm, 100% light intensity, 600 rpm stir rate, 5200 rpm fan rate). Afterwards, the vial was removed from the photoreactor, cooled to room temperature

and opened to air. Aqueous tetrasodium EDTA (0.1 M, 30 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$) and filtered. After removal of the solvent, the crude material was purified *via* sequential flash column chromatography (first column: 5–60% EtOAc/hexane, second column: 5% MeCN isocratic) to obtain 398 mg (1.10 mmol, 73% yield) of the C–N coupling product as a white solid.

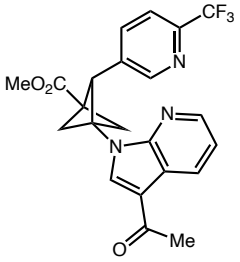
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.36 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.79 (s, 1H), 7.29 – 7.22 (m, 1H), 5.13 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H), 3.39 (dd, *J* = 9.9, 2.7 Hz, 1H), 3.21 (d, *J* = 2.8 Hz, 1H), 3.06 (dd, *J* = 9.9, 2.9 Hz, 1H), 2.90 (dd, *J* = 7.4, 2.7 Hz, 1H), 2.55 (s, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 193.1, 166.7, 148.9, 145.1, 131.9, 131.3, 119.3, 119.1, 116.6, 63.4, 52.6, 52.5, 52.2, 51.4, 41.3, 27.5.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3105.7 2953.5, 1727.2, 1652.4, 1594.7, 1573.6, 1530.4, 1502.9, 1481.3, 1436.3, 1370.5, 1342.3, 1292.4, 1251.9, 1233.8, 1204.3, 1184.1, 1159.7, 1137.4, 1108.8, 1086.1, 1009.1, 963.2, 937.3, 925.1, 899.1, 855.1, 811.8, 799.1, 780.5, 762.9, 644.9, 627.6, 601.2, 562.9, 487.6, 470.9, 436.0, 409.4.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{16}N_2O_3Br$ ($[M+H]^+$) 363.0344, found 363.0342.

**(±)-Methyl 3-(3-acetyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (75)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of 5-bromo-2-(trifluoromethyl)pyridine (67.8 mg, 0.30 mmol) and *N*-adamantyl-*N*-supersilylamine (191 mg, 0.48 mmol, 1.6 equiv) in $PhCF_3$ (3 mL) *via* syringe pump to a solution of the *N*-(3-acetyl-7-indolyl)-BCP bromide (218 mg, 0.60 mmol, 2.0 equiv), cesium carbonate (195 mg, 0.60 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (6.73 mg, 6.00 μmol, 0.02 equiv) and

Ni(dtbpy)$Br_2$ (7.30 mg, 15.0 µmol, 0.05 equiv) in $PhCF_3$ (6 mL). Purification *via* flash column chromatography (5–60% EtOAc/hexane) gave 86.3 mg (201 µmol, 67% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.63 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.39 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.35 (s, 1H), 7.61 (s, 1H), 7.58 – 7.51 (m, 2H), 7.29 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.82 (d, *J* = 6.6 Hz, 1H), 3.84 (s, 3H), 3.20 (dd, *J* = 9.6, 1.9 Hz, 1H), 3.04 (dd, *J* = 9.6, 2.8 Hz, 1H), 2.90 (dd, *J* = 6.7, 2.8 Hz, 1H), 2.64 (d, *J* = 1.9 Hz, 1H), 2.51 (s, 3H).

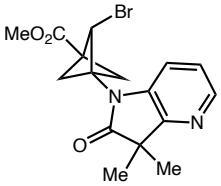
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 193.2, 168.9, 150.1, 149.0, 147.2 (q, *J* = 34.7 Hz), 145.6, 137.9, 135.3, 132.0, 131.8, 121.8 (q, *J* = 274.2 Hz), 120.5 (q, *J* = 2.7 Hz), 119.7, 119.6, 117.0, 65.1, 55.5, 53.0, 52.0, 50.2, 39.4, 27.8.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -68.03.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2953.8, 1730.5, 1615.5, 1508.1, 1492.7, 1465.9, 1391.6, 1333.0, 1292.8, 1227.5, 1203.9, 1173.3, 1131.5, 1086.2, 1028.0, 962.8, 932.5, 903.2, 870.9, 832.3, 793.0, 765.3, 742.4, 693.0, 630.9, 603.1, 557.8, 476.3, 426.2.

**HRMS (ESI)** m/z calcd. for $C_{20}H_{16}N_3O_2F_3Cl$ ($[M+H]^+$) 422.0883, found 422.0881.

**(±)-Methyl 2-bromo-3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S15)**




An oven-dried 40 mL vial equipped with a cross-shaped stir bar was charged with the 3,3-dimethyl-4-azaoxindole (195 mg, 1.20 mmol), the BCP-diacyloxymesitylene (1.34 g, 1.80 mmol, 1.5 equiv), Ir(ppy)$_3$ (15.8 mg, 24.0 µmol, 0.02 equiv) and Cu(acac)$_2$ (157 mg, 600 µmol, 0.50 equiv), capped and sealed with parafilm. The vial was evacuated and subsequently filled with nitrogen, repeated three times. Dioxane (previously degassed by sparging with nitrogen for 15 min, 12 mL) was added and the mixture was sonicated for 5 min before placing it in the Integrated Photoreactor and stirring while irradiating for 4 hours (450 nm, 100% light intensity, 600 rpm stir

rate, 5200 rpm fan rate). Afterwards, the vial was removed from the photoreactor, cooled to room temperature and opened to air. Aqueous tetrasodium EDTA (0.1 M, 30 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$) and filtered. After removal of the solvent, the crude material was purified *via* flash column chromatography (5–50% EtOAc/hexane) to obtain 203 mg (556 µmol, 46% yield) of the C–N coupling product as a pale yellow solid.

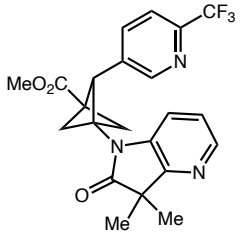
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.25 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.31 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.13 (dd, *J* = 8.0, 5.0 Hz, 1H), 5.00 (d, *J* = 7.6 Hz, 1H), 3.78 (s, 3H), 3.53 – 3.47 (m, 1H), 3.00 (d, *J* = 2.9 Hz, 1H), 2.93 – 2.85 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 180.7, 166.6, 155.6, 143.7, 136.0, 122.5, 115.7, 63.3, 52.8, 52.6, 51.1, 51.0, 44.8, 42.4, 23.0, 22.9.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2965.8, 1746.7, 1708.6, 1601.4, 1498.5, 1458.8, 1440.6, 1387.7, 1349.0, 1319.6, 1302.3, 1279.0, 1256.4, 1204.5, 1182.0, 1140.5, 1091.3, 1073.2, 1023.8, 998.5, 958.8, 916.4, 867.1, 840.1, 798.1, 776.9, 761.1, 679.2, 669.7, 579.4, 555.6, 503.1, 417.4.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{18}N_2O_3Br$ ($[M+H]^+$) 365.0501, found 365.0496.

**(±)-Methyl 3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (76)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of 5-bromo-2-(trifluoromethyl)pyridine (67.8 mg, 0.30 mmol) and *N*-adamantyl-*N*-supersilylamine (191 mg, 0.48 mmol, 1.6 equiv) in $PhCF_3$ (3 mL) *via* syringe pump to a solution of the *N*-(3,3-dimethyl-4-azaoxindolyl)-BCP bromide (219 mg, 0.60 mmol, 2.0 equiv), cesium carbonate (195 mg, 0.60 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (6.73 mg, 6.00 µmol, 0.02 equiv) and $Ni(dtbpy)Br_2$ (7.30 mg, 15.0 µmol, 0.05 equiv) in $PhCF_3$ (6 mL). Purification *via*

sequential flash column chromatography (first column: 5–75% EtOAc/hexane, second column: 0-10% MeCN/$CH_2Cl_2$) gave 91.7 mg (213 μmol, 74% yield) of the desired product as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.51 (d, *J* = 2.1 Hz, 1H), 8.26 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.74 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.62 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.18 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.11 (dd, *J* = 8.0, 5.0 Hz, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 3.17 (dd, *J* = 9.7, 3.3 Hz, 1H), 2.99 (dd, *J* = 6.8, 3.4 Hz, 1H), 2.96 (dd, *J* = 9.7, 2.1 Hz, 1H), 2.63 (d, *J* = 2.0 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H).

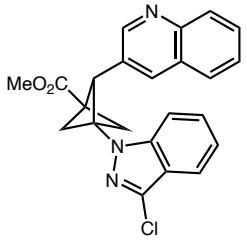
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 180.7, 168.3, 155.8, 149.8, 147.1 (q, *J* = 34.9 Hz), 143.9, 137.6, 136.0, 135.1, 122.6, 121.6 (q, *J* = 273.9 Hz), 120.3 (q, *J* = 2.7 Hz), 115.5, 65.0, 54.5, 52.6, 51.4, 49.7, 44.9, 40.6, 23.0, 22.9.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ – 67.96 (s, 3F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 2970.4, 1722.4, 1599.3, 1506.2, 1436.1, 1381.7, 1333.8, 1296.6, 1269.8, 1204.5, 1170.1, 1133.2, 1086.3, 1027.2, 963.4, 931.9, 871.2, 831.9, 793.7, 776.5, 753.8, 693.3, 680.4, 638.6, 602.5, 578.2, 554.4, 503.3.

**HRMS (ESI)** m/z calcd. for $C_{22}H_{21}N_3O_3F_3$ ($[M+H]^+$) 432.1535, found 432.1530.

**(±)-Methyl 3-(3-chloro-1*H*-indazol-1-yl)-2-(quinolin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (77)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of 3-bromoquinoline (62.4 mg, 0.30 mmol) and *N*-adamantyl-*N*-supersilylamine (191 mg, 0.48 mmol, 1.6 equiv) in $PhCF_3$ (3 mL) *via* syringe pump to a solution of the *N*-(3-chloroindazolyl)-BCP bromide (213 mg, 0.60 mmol, 2.0 equiv), cesium carbonate (195 mg, 0.60 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (6.73 mg, 6.00 μmol, 0.02 equiv) and

Ni(dtbpy)$Br_2$ (7.30 mg, 15.0 µmol, 0.05 equiv) in $PhCF_3$ (6 mL). Purification *via* flash column chromatography (5–60% EtOAc/hexane) gave 83.0 mg (206 µmol, 69% yield) of the desired product as a yellow solid.

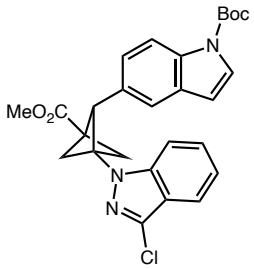
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.60 (d, *J* = 2.2 Hz, 1H), 8.02 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.94 (dt, *J* = 2.1, 1.0 Hz, 1H), 7.75 – 7.62 (m, 3H), 7.50 (td, *J* = 7.4, 1.2 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.25 (ddd, *J* = 7.9, 4.5, 3.3 Hz, 1H), 4.61 (dd, *J* = 6.7, 1.0 Hz, 1H), 3.85 (s, 3H), 3.30 (dd, *J* = 9.6, 2.9 Hz, 1H), 2.98 (ddd, *J* = 8.6, 4.8, 2.4 Hz, 2H), 2.76 (d, *J* = 1.9 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.0, 151.0, 147.1, 141.0, 135.5, 135.3, 129.7, 129.3, 128.7, 128.6, 127.9, 127.6, 127.0, 122.2, 122.1, 120.4, 110.0, 66.6, 55.4, 53.8, 52.6, 50.5, 39.0.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2949.6, 1727.5, 1614.7, 1570.6, 1505.3, 1492.3, 1464.8, 1435.8, 1407.3, 1393.9, 1329.6, 1291.5, 1227.5, 1205.0, 1171.8, 1151.1, 1122.5, 1013.0, 985.0, 957.1, 917.2, 860.7, 796.6, 765.3, 740.8, 687.1, 648.7, 629.3, 558.5, 478.6, 426.7.

**HRMS (ESI)** m/z calcd. for $C_{23}H_{19}N_3O_2Cl$ ($[M+H]^+$) 404.1166, found 404.1167.

**(±)-*tert*-Butyl 5-(1-(3-chloro-1*H*-indazol-1-yl)-3-(methoxycarbonyl)bicyclo[1.1.1]pentan-2-yl)-1*H*-indole-1-carboxylate (78)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of *N*-Boc-5-bromoindole (88.9 mg, 0.30 mmol) and *N*-adamantyl-*N*-supersilylamine (191 mg, 0.48 mmol, 1.6 equiv) in $PhCF_3$ (3 mL) *via* syringe pump to a solution of the *N*-(3-chloroindazolyl)-BCP bromide (213 mg, 0.60 mmol, 2.0 equiv), cesium carbonate (195 mg, 0.60 mmol, 2.0 equiv), Ir(dF($CF_3$)ppy)$_2$(dtbpy)$PF_6$ (6.73 mg, 6.00 µmol, 0.02 equiv) and Ni(dtbpy)$Br_2$ (14.6 mg, 30.0 µmol, 0.1 equiv) in $PhCF_3$ (6 mL). Purification *via* flash column chromatography (25–100% $CH_2Cl_2$/hexane + 1% MeCN) gave 106 mg (223 µmol, 74% yield) of the desired product as a white solid.

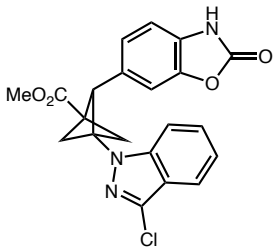
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.6 Hz, 1H), 7.70 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.54 (d, *J* = 3.8 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.27 – 7.20 (m, 2H), 6.94 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.42 (dd, *J* = 3.8, 0.8 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 3.31 (dd, *J* = 9.5, 2.6 Hz, 1H), 2.93 – 2.86 (m, 2H), 2.64 (d, *J* = 1.8 Hz, 1H), 1.63 (s, 9H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.6, 149.8, 141.1, 134.7, 134.3, 130.6, 129.9, 128.2, 126.4, 124.7, 122.0, 121.9, 120.7, 120.2, 115.2, 110.4, 107.4, 83.9, 69.0, 55.1, 53.9, 52.4, 50.1, 39.1, 28.3.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2978.1, 1728.0, 1615.2, 1504.4, 1465.8, 1436.9, 1407.4, 1361.2, 1332.8, 1291.3, 1257.8, 1226.5, 1201.9, 1164.8, 1151.9, 1134.2, 1081.7, 1022.1, 971.7, 948.5, 900.1, 846.0, 831.2, 806.4, 765.3, 742.9, 727.2, 630.1, 558.6, 520.7, 476.8, 426.7.

**HRMS (ESI)** m/z calcd. for $C_{27}H_{27}N_3O_4Cl$ ($[M+H]^+$) 492.1690, found 492.1689.

**(±)-Methyl 3-(3-chloro-1*H*-indazol-1-yl)-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)bicyclo[1.1.1]pentane-1-carboxylate (79)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of 6-bromo-3*H*-1,3-benzoxazol-2-one (64.2 mg, 0.30 mmol) and *N*-adamantyl-*N*-supersilylamine (191 mg, 0.48 mmol, 1.6 equiv) in *t*BuOH/$PhCF_3$ (v/v = 1/3, 3 mL total) *via* syringe pump to a solution of the *N*-(3-chloroindazolyl)-BCP bromide (213 mg, 0.60 mmol, 2.0 equiv), cesium carbonate (195 mg, 0.60 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (6.73 mg, 6.00 μmol, 0.02 equiv) and $Ni(dtbpy)Br_2$ (14.6 mg, 30.0 μmol, 0.1 equiv) in $PhCF_3$ (6 mL). Purification *via* flash column chromatography (5–50% EtOAc/hexane) gave 86.9 mg (212 μmol, 71% yield) of the desired product as a pale yellow solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.15 (bs, 1H), 7.71 (dt, *J* = 8.3, 1.1 Hz, 1H), 7.45 – 7.34 (m, 2H), 7.25 (ddd, *J* = 8.0, 6.2, 1.6 Hz, 1H), 6.97 (dd, *J* = 1.6, 0.8 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.82

(ddd, $J$ = 8.1, 1.6, 0.7 Hz, 1H), 4.46 (d, $J$ = 6.7 Hz, 1H), 3.83 (s, 3H), 3.23 (dd, $J$ = 9.5, 2.8 Hz, 1H), 2.91 (dd, $J$ = 6.7, 2.7 Hz, 1H), 2.86 (dd, $J$ = 9.5, 1.9 Hz, 1H), 2.66 (d, $J$ = 1.8 Hz, 1H).

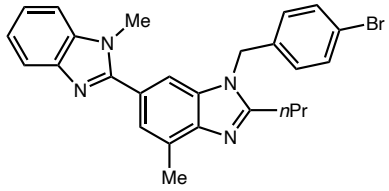
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.2, 154.9, 144.0, 141.0, 135.1, 130.8, 128.5, 128.2, 124.3, 122.2, 122.0, 120.4, 110.6, 110.1, 109.6, 68.1, 55.0, 53.9, 52.5, 50.3, 39.1.

**IR (film):** $\nu_{max}$($cm^{-1}$) 3218.3, 2951.3, 1760.9, 1727.9, 1615.6, 1501.8, 1464.9, 1437.1, 1406.7, 1393.0, 1329.9, 1292.1, 1227.2, 1204.7, 1173.3, 1151.4, 1123.4, 1013.9, 971.6, 916.3, 878.7, 835.3, 799.8, 766.5, 728.5, 705.8, 647.4, 630.2, 581.0, 558.3, 536.2, 476.3, 427.7.

**HRMS (ESI)** m/z calcd. for $C_{21}H_{17}N_3O_4Cl$ ($[M+H]^+$) 410.0908, found 410.0906.

## Synthesis of BCP Drug Analogs

**3'-(4-Bromobenzyl)-1,7'-dimethyl-2'-propyl-1*H*,3'*H*-2,5'-bibenzo[*d*]imidazole (S16)**



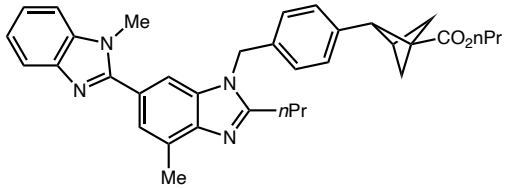

An oven-dried 40 mL vial equipped with a cross-shaped stir bar was charged with 7-methyl-5-(1-methylbenzimidazol-2-yl)-2-propyl-1*H*-benzimidazole (913 mg, 3.00 mmol) and 4-bromobenzyl bromide (787 mg, 3.15 mmol, 1.05 equiv). DMA (10 mL) was added, followed by $K_2CO_3$ (456 mg, 3.30 mmol, 1.1 equiv) and the reaction mixture was stirred vigorously for 16 h after which the mixture was filtered into a separatory funnel, rinsing the residue with EtOAc. $H_2O$ (100 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (75 mL), dried ($MgSO_4$) and filtered, the solvent was removed and the crude material was purified *via* flash column chromatography (0–10% MeOH/$CH_2Cl_2$) to give 1.13 g (2.39 mmol, 80% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.83 – 7.77 (m, 1H), 7.42 (dd, *J* = 8.7, 1.9 Hz, 4H), 7.39 – 7.35 (m, 1H), 7.34 – 7.28 (m, 2H), 6.99 – 6.83 (m, 2H), 5.34 (s, 2H), 3.80 (s, 3H), 2.91 – 2.84 (m, 2H), 2.77 (s, 3H), 1.84 (h, *J* = 7.4 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 159.0, 156.6, 143.2, 136.6, 135.1, 135.0, 132.3, 130.3, 129.8, 128.0, 124.2, 124.0, 122.9, 122.8, 122.1, 119.5, 109.8, 109.2, 46.9, 32.0, 30.0, 22.0, 17.0, 14.2.

The spectroscopic data matched those reported in the literature.[9]

**(±)-Propyl 2-(4-((1,7'-dimethyl-2'-propyl-1*H*,3'*H*-[2,5'-bibenzo[*d*]imidazol]-3'-yl)methyl)phenyl)bicyclo[1.1.1]pentane-1-carboxylate (S17)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of the parent bromide (237 mg, 0.50 mmol) and *N*-adamantyl-*N*-supersilylamine (318 mg, 0.80 mmol, 1.6 equiv) in $PhCF_3$ (5 mL) *via* syringe pump to a solution of propyl 2-bromobicyclo[1.1.1]pentane-1-carboxylate (233 mg, 1.00 mmol, 2.0 equiv), cesium carbonate (326 mg, 1.00 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (11.2 mg, 10.0 μmol, 0.02 equiv) and $Ni(dtbpy)Br_2$ (24.3 mg, 50.0 μmol, 0.10 equiv) in $PhCF_3$ (10 mL). Purification *via* flash column chromatography (0–5% $MeOH/CH_2Cl_2$) gave 210 mg (384 μmol, 77% yield) of the desired product as a white solid.

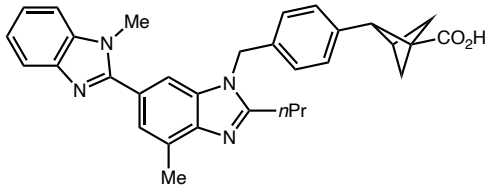
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.84 – 7.76 (m, 1H), 7.44 (d, *J* = 9.7 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.32 – 7.27 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 5.38 (s, 2H), 4.03 (t, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 3.67 (d, *J* = 6.7 Hz, 1H), 2.95 – 2.86 (m, 2H), 2.76 (s, 3H), 2.72 (s, 1H), 2.32 (dd, *J* = 9.6, 2.8 Hz, 1H), 2.13 (d, *J* = 1.9 Hz, 1H), 2.11 – 2.06 (m, 2H), 1.85 (h, *J* = 7.4 Hz, 2H), 1.63 (h, *J* = 7.2 Hz, 2H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 169.4, 156.6, 154.8, 143.3, 143.0 (2C), 138.7, 136.8, 135.2, 134.0, 129.5, 129.2, 126.0, 123.9, 122.6, 122.5, 119.7, 109.7, 109.1, 66.2, 64.7, 49.9, 47.7, 47.2, 45.8, 31.9, 30.9, 30.0, 22.1, 22.0, 17.1, 14.2, 10.5.

**IR (film):** $\nu_{max}(cm^{-1})$ 2965.6, 1721.4, 1513.8, 1451.5, 1403.4, 1389.1, 1316.7, 1281.3, 1247.5, 1224.9, 1200.8, 1121.7, 921.3, 866.4, 741.8, 660.3, 499.6, 448.6.

**HRMS (ESI)** m/z calcd. for $C_{35}H_{39}N_4O_2$ ($[M+H]^+$) 547.3073, found 547.3072.

**(±)-2-(4-((1,7'-Dimethyl-2'-propyl-1*H*,3'*H*-[2,5'-bibenzo[*d*]imidazol]-3'-yl)methyl)phenyl)bicyclo[1.1.1]pentane-1-carboxylic acid (80)**




An oven-dried 8 mL vial equipped with a cross-shaped stir bar was charged with the propyl ester (27.3 mg, 50.0 µmol), the vial was capped and sealed with parafilm. The vial was evacuated and filled with nitrogen, repeated three times and NaOH (0.5 M in MeOH, 500 µL, 250 µmol, 5.0 equiv) was added. The reaction mixture was stirred vigorously at room temperature for 24 h after which $H_2O$ (500 µL) was added and the mixture was stirred for 120 min, after which complete consumption of both propyl and methyl ester was observed via TLC. HCl (0.2 M, 2 mL) was added and the mixture was extracted with $CHCl_3$/*i*PrOH (v/v = 3/1, 3 x 2 mL), the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and filtered. After removal of the solvent, the crude material was purified *via* flash column chromatography (0–20% MeOH/$CH_2Cl_2$) to give 20.7 mg (41.0 µmol, 82% yield) of the BCP-Telmisartan analog as a white solid.

**$^1$H NMR (500 MHz, MeOD)** δ 7.66 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.47 (d, *J* = 1.1 Hz, 1H), 7.32 (pd, *J* = 7.2, 1.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.55 (s, 2H), 3.73 (s, 3H), 3.64 (d, *J* = 6.5 Hz, 1H), 3.04 – 2.95 (m, 2H), 2.72 (s, 3H), 2.71 (s, 1H), 2.24 (dd, *J* = 9.5, 2.7 Hz, 1H), 2.10 – 2.05 (m, 2H), 2.01 (dd, *J* = 6.8, 2.7 Hz, 1H), 1.80 (h, *J* = 7.4 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, MeOD)** δ 173.9, 158.8, 155.5, 143.6, 142.3, 140.3, 137.4, 136.0, 135.8, 130.3, 130.1, 127.5, 125.3, 124.3, 124.2, 124.1, 119.0, 111.5, 111.0, 65.9, 50.6, 48.1, 48.0, 47.5, 32.2, 31.4, 30.2, 22.8, 16.9, 14.2.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2963.8, 2928.6, 1703.3, 1513.7, 1451.5, 1412.1, 1320.5, 1280.6, 1248.5, 1226.6, 1202.0, 1156.3, 1123.7, 1089.6, 1007.0, 922.4, 866.1, 764.5, 741.3, 660.2, 574.9, 522.9, 447.9.

**HRMS (ESI)** m/z calcd. for $C_{32}H_{33}N_4O_2$ ($[M+H]^+$) 505.2604, found 505.2603.

Chiral separation:

Column & Dimensions: IZ, 21X250 mm, 5 um

UV Wavelength: 215 nm

Flow Rate: 70 mL/min

Modifier: 25% MeOH w/ 0.1% $NH_4OH$

Outlet Pressure: 100 bar

Sample Amount: 30.6 mg

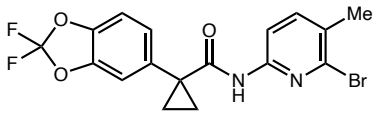
Diluent: 1:1 MeOH/ACN

Diluent Volume: 3 mL

Injection Volume: 1 mL

Instrument: Sepiatec 2

**_N_-(6-Bromo-5-methylpyridin-2-yl)-1-(2,2-difluorobenzo[_d_][1,3]dioxol-5-yl)cyclopropane-1-carboxamide (S18)**




In an oven-dried 100 mL round-bottom flask equipped with a stir bar, 1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropanecarboxylic acid (969 mg, 4.00 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and two drops of DMF at 0 °C. Oxalyl chloride (700 µL, 1.02 g, 8.00 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was dried under high vacuum for 1 h before redissolving in $CH_2Cl_2$ (20 mL) and cooling to 0 °C. 6-Bromo-5-methyl-pyridin-2-amine (898 mg, 4.80 mmol, 1.2 equiv) and $NEt_3$ (840 µL, 607 mg, 6.00 mmol, 1.5 equiv) were added and the reaction mixture was stirred for 12 h after which HCl (0.1 M, 40 mL) was added. After separation of the layers and extraction of the aqueous layer with $CH_2Cl_2$ (3 x 20 mL), the combined organic layers were washed with $H_2O$ (40 mL) and saturated $NaHCO_3$ (40 mL), dried ($MgSO_4$) and filtered. The solvent was removed and the crude material was purified *via* flash column chromatography (15% EtOAc/hexane isocratic) to give 1.38 g (3.36 mmol, 84% yield) of the desired product as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.62 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.21 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.17 (d, *J* = 1.7 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 2.31 (s, 3H), 1.73 (q, *J* = 3.9 Hz, 2H), 1.17 (q, *J* = 4.0 Hz, 2H).

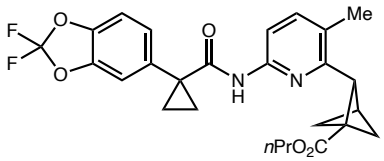
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.8, 149.0, 144.4, 143.9, 141.3, 141.0, 134.6, 131.8 (t, *J* = 256.5 Hz), 130.7, 126.8, 112.7, 112.5, 110.4, 31.3, 21.3, 17.6.

**$^{19}$F NMR (282 MHz, $CDCl_3$)** δ -49.55 (2F, s).

**IR (film):** $\nu_{max}$($cm^{-1}$) 3216.0, 1672.9, 1591.8, 1567.9, 1492.1, 1440.0, 1414.4, 1352.5, 1335.1, 1300.0, 1282.6, 1223.4, 1155.7, 1125.9, 1066.6, 1028.8, 992.5, 967.7, 938.4, 911.3, 900.4, 875.8, 832.0, 818.3, 769.6, 750.1, 832.4, 723.9, 705.2, 680.1, 654.5, 631.9, 606.1, 543.7, 444.0, 426.6.

**HRMS (ESI)** m/z calcd. for $C_{17}H_{14}N_2O_3F_2$ ($[M+H]^+$) 411.0156, found 411.0153.

**(±)-Propyl 2-(6-(1-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)cyclopropane-1-carboxamido)-3-methylpyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (S19)**




Prepared according to the **general procedure for cross-electrophile BCP 2-arylation**, slowly adding a solution of the parent bromide (123 mg, 0.30 mmol) and *N*-adamantyl-*N*-supersilylamine (191 mg, 0.48 mmol, 1.6 equiv) in $PhCF_3$ (3 mL) *via* syringe pump to a solution of propyl 2-bromobicyclo[1.1.1]pentane-1-carboxylate (140 mg, 0.60 mmol, 2.0 equiv), cesium carbonate (195 mg, 0.60 mmol, 2.0 equiv), $Ir(dF(CF_3)ppy)_2(dtbpy)PF_6$ (6.73 mg, 6.00 μmol, 0.02 equiv) and $Ni(dtbpy)Br_2$ (14.6 mg, 30.0 μmol, 0.10 equiv) in $PhCF_3$ (6 mL). Purification *via* flash column chromatography (20% EtOAc/hexane isocratic) gave 55.0 mg (114 μmol, 38% yield) of the desired product as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.47 (s, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.19 (d, *J* = 1.7 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 3.78 (qt, *J* = 10.7, 6.5 Hz, 2H), 3.57 (d, *J* = 6.7 Hz, 1H), 2.78 (s, 1H), 2.18 (s, 3H), 2.14 (dd, *J* = 9.6, 2.7 Hz, 1H), 2.06 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.02 (d, *J* = 1.7 Hz, 1H), 1.97 (dd, *J* = 6.8, 2.8 Hz, 1H), 1.77 (ddd,

*J* = 9.5, 5.9, 2.7 Hz, 1H), 1.67 (ddd, *J* = 7.9, 6.0, 2.8 Hz, 1H), 1.56 – 1.45 (m, 2H), 1.14 (dtdd, *J* = 12.7, 9.5, 6.3, 3.1 Hz, 2H), 0.80 (t, *J* = 7.4 Hz, 3H).

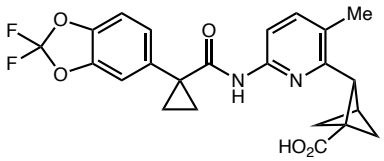
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.5, 169.5, 154.7, 148.0, 144.2, 143.6, 139.7, 135.4, 131.8 (t, *J* = 256.2 Hz), 128.3, 126.8, 112.4, 111.3, 110.3, 65.4, 65.3, 49.8, 46.8, 45.5, 31.7, 31.3, 22.0, 17.4, 17.3, 16.7, 10.4.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -49.73, -49.75 (rotameric).

**IR (film):** $\nu_{max}(cm^{-1})$ 3393.3, 2975.8, 1728.3, 1677.0, 1593.8, 1511.8, 1495.6, 1460.8, 1441.6, 1380.8, 1360.5, 1309.4, 1239.5, 1228.1, 1197.6, 1130.5, 1119.3, 1076.1, 1034.8, 992.3, 967.2, 945.3, 909.3, 839.2, 827.0, 743.1, 726.4, 702.7, 672.3, 637.1, 612.0, 550.9, 450.0, 427.4.

**HRMS (ESI)** m/z calcd. for $C_{26}H_{27}N_2O_5F_2$ ($[M+H]^+$) 485.1888, found 485.1882.

**(±)-2-(6-(1-(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)cyclopropane-1-carboxamido)-3-methylpyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (81)**




An oven-dried 8 mL vial equipped with a cross-shaped stir bar was charged with the propyl ester (24.2 mg, 50.0 μmol), the vial was capped and sealed with parafilm. The vial was evacuated and filled with nitrogen, repeated three times and NaOH (0.5 M in MeOH, 500 μL, 250 μmol, 5.0 equiv) was added. The reaction mixture was stirred vigorously at room temperature for 24 h after which $H_2O$ (500 μL) was added and the mixture was stirred for 120 min, after which complete consumption of both propyl and methyl ester was observed via TLC. HCl (0.2 M, 2 mL) was added and the mixture was extracted with $CHCl_3$/*i*PrOH (v/v = 3/1, 3 x 2 mL), the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and filtered. After removal of the solvent, the crude material was purified *via* flash column chromatography (0–5% MeOH/$CH_2Cl_2$) to give 22.1 mg (40.7 μmol, 81% yield) of the BCP-Lumacaftor analog as a white solid.

**$^{1}$H NMR (500 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.25 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 3.56 (d, *J* = 6.9 Hz, 1H), 2.87 (s, 1H), 2.28 – 2.21

(m, 5H), 2.15 (dd, $J$ = 7.0, 2.9 Hz, 1H), 2.02 (dd, $J$ = 9.7, 2.7 Hz, 1H), 1.77 – 1.70 (m, 2H), 1.28 – 1.17 (m, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.9, 170.1, 154.1, 146.8, 144.5, 144.1, 142.0, 134.2, 131.8 (t, $J$ = 256.7 Hz), 129.8, 126.4, 113.5, 112.2, 110.9, 64.3, 51.2, 47.7, 46.7, 32.4, 31.4, 17.4, 17.3, 17.3.

**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -49.77 (s, 2F).

**IR (film):** $\nu_{max}$($cm^{-1}$) 3407.4, 2989.4, 1730.6, 1689.5, 1592.8, 1483.2, 1445.1, 1381.3, 1323.2, 1235.6, 1225.7, 1204.0, 1129.7, 1081.5, 1032.3, 992.1, 958.9, 942.2, 909.3, 865.6, 831.9, 786.9, 757.2, 739.7, 742.4, 704.7, 678.6, 657.2, 635.5, 625.4, 592.1, 532.7, 446.9, 429.9, 413.5.

**HRMS (ESI)** m/z calcd. for $C_{23}H_{21}N_2O_5F_2$ ($[M+H]^+$) 443.1419, found 443.1416.

Chiral separation:

Column & Dimensions: Lux-2, 21X250 mm, 5 um

UV Wavelength: 215 nm

Flow Rate: 70 mL/min

Modifier: 30% MeOH w/ 0.1% $NH_4OH$

Outlet Pressure: 100 bar

Sample Amount: 30.2 mg

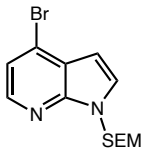
Diluent: 1:1 MeOH/ACN

Diluent Volume: 2 mL

Injection Volume: 0.4 mL

Instrument: Sepiatec 2

**4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (S20)**




In an oven-dried 40 mL vial equipped with a cross-shaped stir bar, a suspension of 4-bromo-7-azaindole (985 mg, 5.00 mmol) in $CH_2Cl_2$ (20 mL) was cooled to 0 °C before DIPEA (1.3 mL, 7.50 mmol, 1.5 equiv) was added, followed by SEMCl (1.1 mL, 6.00 mmol, 1.2 equiv). The ice

bath was removed and the reaction mixture was stirred at room temperature for 2 h after which the mixture was a clear solution. Saturated $NH_4Cl$ (40 mL) was added, layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 20 mL). The combined organic layers were washed with $H_2O$ (30 mL) and brine (30 mL) and then dried ($MgSO_4$) and filtered. Purification *via* flash column chromatography (5–25% EtOAc) gave 1.55 g (4.74 mmol, 95% yield) of the SEM-protected azaindole as a yellow oil.

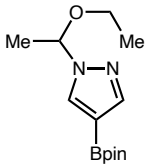
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.13 (d, *J* = 5.1 Hz, 1H), 7.40 (d, *J* = 3.6 Hz, 1H), 7.29 (d, *J* = 5.1 Hz, 1H), 6.57 (d, *J* = 3.6 Hz, 1H), 5.66 (s, 2H), 3.52 (dd, *J* = 8.8, 7.7 Hz, 2H), 0.90 (dd, *J* = 8.9, 7.7 Hz, 2H), -0.07 (s, 9H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 148.1, 143.5, 128.6, 125.3, 122.3, 119.7, 101.3, 73.4, 66.5, 17.9, -1.3.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2951.3, 1589.6, 1550.9, 1508.8, 1480.6, 1413.5, 1371.9, 1334.9, 1306.3, 1278.1, 1248.2, 1201.4, 1119.6, 1090.8, 1074.1, 917.8, 901.8, 856.4, 831.9, 809.1, 782.8, 742.1, 719.5, 693.3, 644.0, 609.2, 588.4, 532.5.

**HRMS (ESI)** m/z calcd. for $C_{13}H_{20}N_2OSiBr$ ($[M+H]^+$) 327.0528, found 327.0523.

**1-(1-Ethoxyethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (S21)**




In an oven-dried 40 mL vial equipped with a cross-shaped stir bar, ethyl vinyl ether (2.1 mL, 1.62 g, 22.5 mmol, 3.0 equiv) and HCl (4 M in dioxane, 190 uL, 750 μmol, 0.1 equiv) were added to a suspension of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.46 g, 7.50 mmol) in PhMe (15 mL) and the reaction mixture was stirred vigorously at 40 °C for 12 h after which the suspension has turned into a clear solution. $NaHCO_3$ (126 mg, 1.50 mmol, 0.2 equiv) was carefully added and the reaction mixture was stirred at 40 °C for 60 min and then filtered (Celite), rinsing with PhMe. After removal of the solvent, the crude product was purified

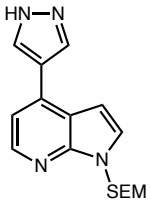
*via* flash column chromatography (5–50% EtOAc/hexane) to obtain 1.76 g (6.61 mmol, 88%) of the protected pyrazole as a white solid.

**$^1$H NMR (500 MHz, DMSO-$d_6$)** δ 8.09 (s, 1H), 7.63 (s, 1H), 5.56 (q, *J* = 6.0 Hz, 1H), 3.43 – 3.33 (m, 1H), 3.13 (dq, *J* = 9.6, 7.0 Hz, 1H), 1.57 (d, *J* = 5.9 Hz, 3H), 1.25 (s, 12H), 1.01 (t, *J* = 7.0 Hz, 3H).

**$^{13}$C NMR (126 MHz, DMSO-$d_6$)** δ 144.6, 135.3, 85.9, 83.1, 63.0, 24.73, 24.68, 21.2, 14.7.

The spectroscopic data matched those reported in the literature.[11]

**4-(1*H*-Pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridine (S22)**




1-SEM-4-Bromo-7-azaindole (1.31 g, 4.00 mmol), ethoxyethyl-protected pyrazole-4-pinacolatoboronate (1.28 g, 4.80 mmol, 1.2 equiv), $K_2CO_3$ (1.66 g, 12.0 mmol, 3.0 equiv) and $Pd(dppf)Cl_2•CH_2Cl_2$ (163 mg, 200 µmol, 0.05 equiv) were dissolved in dioxane (15 mL, previously degassed by sparging with $N_2$ for 15 min) and $H_2O$ (5 mL, previously degassed by sparging with $N_2$ for 15 min) and the deep red reaction mixture was stirred vigorously at 100 °C for 16 h. The now dark mixture was cooled to room temperature and filtered, rinsing with $H_2O$ (50 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL), the combined organic layers were then washed with brine (30 mL) and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was redissolved in a 1:2 mixture of EtOAc/hexane and filtered through a silica plug, rinsing with EtOAc/hexane (1:2). The solvent was removed *in vacuo* to give a yellow oil.

The resulting yellow oil was redissolved in THF (2 mL), HCl (1 M, 20 mL) was added and the reaction mixture was stirred vigorously for 2 h. Then, a 10% solution of $K_2CO_3$ (50 mL) was slowly added, the mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (30 mL) and dried. The solvent was removed in vacuo and the resulting pale yellow crude product was re-dissolved in a minimal amount of EtOAc and triturated with

hexane, resulting in the precipitation of a white solid. The suspension was filtered, washing the residue with hexane, affording 1.00 g (3.18 mmol, 80%) of the desired compound as a white solid.

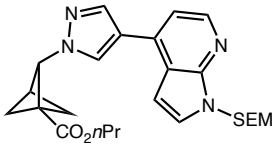
**$^1$H NMR (500 MHz, DMSO-*d*$_6$)** δ 13.26 (s, 1H), 8.50 (s, 1H), 8.22 (d, *J* = 5.0 Hz, 1H), 8.19 (s, 1H), 7.66 (d, *J* = 3.7 Hz, 1H), 7.37 (d, *J* = 5.0 Hz, 1H), 6.91 (d, *J* = 3.6 Hz, 1H), 5.63 (s, 2H), 3.55 – 3.49 (m, 2H), 0.87 – 0.79 (m, 2H), -0.10 (s, 9H).

**$^{13}$C NMR (126 MHz, DMSO-*d*$_6$)** δ 148.5, 143.0, 137.8, 133.1, 129.0, 127.8, 118.5, 116.3, 113.0, 100.3, 72.4, 65.3, 17.2, -1.4..

**IR (film):** $\nu_{max}$(cm$^{-1}$) 3165.1, 2953.9, 2916.8, 1591.5, 1513.6, 1495.3, 1428.1, 1391.1, 1347.9, 1330.2, 1280.4, 1247.9, 1204.2, 1156.6, 1084.9, 1075.9, 1056.2, 1015.6, 991.5, 933.0, 899.4, 855.9, 825.8, 790.4, 751.4, 711.8, 659.9, 641.1, 609.6, 583.9, 534.5.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{23}N_4OSi$ ([M+H]$^+$) 315.1641, found 315.1638.

**(±)-Propyl 2-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S23)**




Prepared following the **general procedure A BCP 2-amination coupling** using 1-SEM-4-(4-pyrazolyl)-7-azaindole (78.6 mg, 0.25 mmol), CuTC (23.8 mg, 125 µmol, 0.5 equiv), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 125 µmol, 0.5 equiv), 4-CzIPN (9.9 mg, 12.5 µmol, 0.05 equiv), 1,5-diazabicyclo(4.3.0)non-5-ene (59.6 µL, 62.1 mg, 0.50 mmol, 2.0 equiv), propyl 2-bromobicyclo[1.1.1]pentane-1-carboxylate (120 mg, 0.50 mmol, 2.0 equiv), supersilanol (192 µL, 0.63 mmol, 2.5 equiv), water (110 µL, 110 mg, 1.25 mmol, 25 equiv) and MeCN (7.5 mL, 0.03 M) using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate), performing two runs in parallel. Purification *via* flash chromatography (5–50% EtOAc/hexane) afforded 104 mg (223 µmol, 45% yield) as a yellow oil.

**$^1$H NMR (500 MHz, CDCl$_3$)** δ 8.31 (d, *J* = 5.0 Hz, 1H), 8.23 (s, 1H), 8.04 (s, 1H), 7.39 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 5.0 Hz, 1H), 6.72 (d, *J* = 3.7 Hz, 1H), 5.71 (s, 2H), 4.80 (d, *J* = 6.4 Hz,

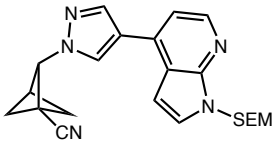
1H), 4.14 (td, *J* = 6.8, 1.1 Hz, 2H), 3.60 – 3.52 (m, 2H), 3.11 (s, 1H), 2.51 (dd, *J* = 9.9, 3.3 Hz, 1H), 2.31 (dd, *J* = 6.5, 3.2 Hz, 1H), 2.27 (d, *J* = 2.8 Hz, 1H), 2.08 (dd, *J* = 9.8, 2.8 Hz, 1H), 1.71 (h, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 – 0.89 (m, 2H), -0.07 (s, 9H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.0, 148.6, 143.2, 138.3, 133.6, 129.1, 128.1, 120.4, 117.7, 113.7, 100.7, 73.2, 66.8, 66.3, 47.3, 47.3, 45.0, 32.8, 22.1, 17.9, 10.5, -1.3.

**IR (film):** $\nu_{max}(cm^{-1})$ 2951.3, 1725.4, 1590.9, 1512.3, 1314.9, 1276.1, 1248.3, 1231.4, 1206.1, 1138.5, 1072.7, 993.9, 918.3, 897.8, 857.1, 833.0, 746.4, 715.8, 651.4, 611.4, 592.0.

**HRMS (ESI)** m/z calcd. for $C_{25}H_{35}N_4O_3Si$ ($[M+H]^+$) 467.2478, found 467.2472.

**(±)-2-(4-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carbonitrile (S24)**




An oven-dried 8 mL vial equipped with a cross-shaped stir bar was charged with the propyl ester (56.0 mg, 120 µmol), the vial was capped and sealed with parafilm. The vial was evacuated and filled with nitrogen, repeated three times and NaOH (0.5 M in MeOH, 1.2 mL, 600 µmol, 5.0 equiv) was added. The reaction mixture was stirred vigorously at room temperature for 24 h after which $H_2O$ (1.2 mL) was added and the mixture was stirred for 120 min, after which complete consumption of both propyl and methyl ester was observed via TLC. HCl (1 M, 800 µL) was added and the mixture was extracted with $CHCl_3$/*i*PrOH (v/v = 3/1, 4 x 2 mL), the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the material was dried under high vacuum for 3 h.

A cross-shaped stir bar was added to the vial containing the resulting yellow solid and THF (2.4 mL) was added under nitrogen atmosphere. The solution was cooled to 0 °C and *N*-methylmorpholine (33 µL, 30.3 mg, 300 µmol, 2.5 equiv) was added, followed by isobutyl chloroformate (31 µL, 32.8 mg, 240 µL, 2.0 equiv). The reaction mixture was stirred at 0 °C for 60 min, then aqueous ammonia (120 µL) was added and the reaction mixture was stirred vigorously at room temperature for 16 h. Saturated aqueous $NH_4Cl$ (4 mL) was added and the

mixture was extracted with EtOAc (4 x 2 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$), then the solvent was removed *in vacuo* and the material was dried under high vacuum for 3 h.

The vial containing the resulting yellow solid was charged with a cross-shaped stir bar and $CH_2Cl_2$ (2.4 mL) was added under nitrogen atmosphere. The reaction mixture was cooled to 0 °C, then $NEt_3$ (50 µL, 36.4 mg, 360 µmol, 3.0 equiv) and trifluoroacetic anhydride (33 µL, 50.4 mg, 240 µmol, 2.0 equiv) were added. The ice bath was removed and the reaction mixture was stirred at room temperature for 60 min. Saturated aqueous $NH_4Cl$ (4 mL) was added and the mixture was extracted with EtOAc (4 x 2 mL). The combined organic layers were washed with brine (5 mL) and dried. After removal of the solvent, the crude material was purified *via* flash column chromatography (5–60% EtOAc/hexane) to obtain 44.8 mg (110 µmol, 92% yield) of the SEM-protected BCP cyanide as a yellow oil.

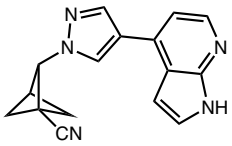
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.33 (d, *J* = 5.0 Hz, 1H), 8.10 (s, 1H), 8.08 (s, 1H), 7.42 (d, *J* = 3.7 Hz, 1H), 7.21 (d, *J* = 5.0 Hz, 1H), 6.72 (d, *J* = 3.7 Hz, 1H), 5.71 (s, 2H), 4.88 (d, *J* = 6.4 Hz, 1H), 3.61 – 3.52 (m, 2H), 3.08 (s, 1H), 2.73 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.48 (dd, *J* = 5.9, 3.2 Hz, 2H), 2.28 (dd, *J* = 9.8, 3.1 Hz, 1H), 0.95 – 0.89 (m, 2H), -0.06 (s, 9H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 140.6, 139.2, 128.6, 127.8, 125.6, 121.2, 118.1, 115.6, 113.9, 100.8, 74.5, 73.6, 66.5, 50.2, 46.5, 36.6, 32.9, 17.9, -1.3.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2950.3, 1590.8, 1511.7, 1337.7, 1311.8, 1276.1, 1246.9, 1201.4, 1070.9, 993.6, 939.1, 898.5, 857.1, 832.1, 745.6, 716.3, 651.3, 610.6.

**HRMS (ESI)** m/z calcd. for $C_{22}H_{28}N_5OSi$ ($[M+H]^+$) 406.2063, found 406.2057.

**(±)-2-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carbonitrile (82)**




An oven-dried 8 mL vial equipped with a cross-shaped stir bar was charged with the SEM-protected azaindole (43.4 mg, 107 µmol), the vial was capped and sealed with parafilm. The vial

was evacuated and filled with nitrogen, repeated three times and $CH_2Cl_2$ (1 mL) and TFA (500 µL) were added. The reaction mixture was stirred at room temperature for 3 h, then the volatiles were removed, PhMe (2 mL) was added and the volatiles were removed again. The resulting material was dried under high vacuum for 2 h, then dissolved in dioxane (1 mL) and ethylene diamine (500 µL) and stirred vigorously at 50 °C for 60 min. After removal of the solvent, the crude material was purified *via* flash column chromatography (0–10% MeOH/EtOAc) to obtain 28.4 mg (103 µmol, 96% yield) of the desired product as a white solid.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.30 (d, *J* = 5.0 Hz, 1H), 8.11 (s, 1H), 8.09 (s, 1H), 7.38 (d, *J* = 3.6 Hz, 1H), 7.21 (d, *J* = 5.0 Hz, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 3.08 (s, 1H), 2.73 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.49 (dd, *J* = 6.4, 3.3 Hz, 2H), 2.28 (dd, *J* = 9.8, 3.1 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 149.1, 143.6, 139.1, 132.7, 127.6, 124.9, 121.5, 117.1, 115.7, 113.6, 100.5, 74.5, 50.2, 46.5, 36.6, 32.9.

**IR (film):** $\nu_{max}(cm^{-1})$ 3103.4, 2992.1, 2875.3, 1597.6, 1490.3, 1443.1, 1403.3, 1382.9, 1359.3, 1332.1, 1268.5, 1229.5, 1201.3, 1186.8, 1141.9, 1117.4, 1076.7, 1024.8, 995.9, 898.7, 867.6, 840.4, 821.0, 806.9, 790.7, 708.3, 679.2, 645.8, 623.4, 591.6, 566.5, 512.1.

**HRMS (ESI)** m/z calcd. for $C_{16}H_{14}N_5$ ($[M+H]^+$) 276.1249, found 276.1245.

Chiral separation:

Column & Dimensions: Lux-2, 21X250 mm, 5 um

UV Wavelength: 215 nm

Flow Rate: 70 mL/min

Modifier: 35% MeOH w/ 0.1% $NH_4OH$

Outlet Pressure: 100 bar

Sample Amount: 30.6 mg

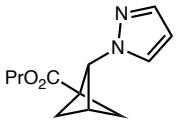
Diluent: 1:1 MeOH/ACN

Diluent Volume: 6 mL

Injection Volume: 1 mL

Instrument: Sepiatec 2

**(±)-Propyl 2-(1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S25)**




**Prepared according to the general procedure A for BCP 2-amination** using 1*H*-pyrazole (17.0 mg, 0.25 mmol, 1.0 equiv.), CuTC (23.8 mg, 0.13 mmol, 0.5 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (27.0 mg, 0.13 mmol, 0.5 equiv.), Ir[dF($CF_3$)ppy]2[4,4'-d($CF_3$)bpy]$PF_6$ (2.3 mg, 0.002 mmol, 0.008 equiv.), 1,5-diazabicyclo(4.3.0)non-5-ene (61.5 mg, 0.50 mmol, 2.0 equiv.), dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (131.5 mg, 0.50 mmol, 2.0 equiv.), supersilanol (0.17 mL, 0.63 mmol, 2.5 equiv.), water (0.11 mL, 6.25 mmol, 25 equiv.) and MeCN (7.5 mL, 0.03 M). using the Integrated Photoreactor (450 nm irradiation) for 12 hours (25% light intensity, 2900 fan speed and 100 stir rate). Purification of three combined 0.25 mmol scale crude reaction vials (0.75 mmol total) by flash chromatography (0–100% $Et_2O$/hexane) on silica gel afforded the desired product (68.0 mg, 41% yield) as a colorless oil.

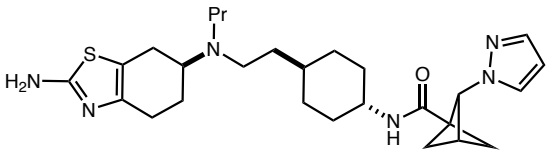
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 6.27 (t, *J* = 1.8 Hz), 4.70 (d, *J* = 6.5 Hz, 1H), 4.10 (t, *J* = 7.4 Hz, 2H), 3.03 (s, 1H), 2.38 (dd, *J* = 9.8, 3.2 Hz, 1H), 2.28 – 2.12 (m, 2H), 2.02 (dd, *J* = 9.8, 2.7 Hz, 1H), 1.68 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 168.1, 139.3, 129.7, 105.6, 73.0, 66.7, 47.1, 47.0, 45.1, 32.7, 22.1, 10.4.

**IR (film):** $\nu_{max}$($cm^{-1}$) 2950.7, 1727.0, 1471.9, 1436.1, 1359.0, 1335.6, 1315.3, 1282.6, 1240.1, 1210.8, 1153.4, 1081.4, 1054.4, 1033.5, 849.5, 798.6, 728.5, 686.6, 642.5, 615.8, 565.4, 524.7, 468.9, 460.7, 449.9, 422.3.

**HRMS (ESI)** m/z calcd. for $C_{12}H_{17}N_2O_2$ ($[M+H]^+$) 221.1285, found 221.1288.

**(2*R*)-N-((1*S*,4*R*)-4-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-2-(1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxamide and (2*S*)-N-((1*S*,4*R*)-4-(2-(((S)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-2-(1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxamide (83)**




An oven-dried 8 mL vial equipped with a cross-shaped stir bar was charged with (±)-Propyl 2-(1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (19.0 mg, 1 equiv., 86.2 μmol). The vial was evacuated and filled with nitrogen, repeated three times and NaOH (0.5 M in MeOH, 863 μL, 431.3 μmol, 5.0 equiv.) was added. The reaction mixture was stirred vigorously at room temperature for 24 h after which $H_2O$ (863 μL) was added and the mixture was stirred for 120 min. HCl (0.5 M, 3 mL) was added and the mixture was extracted with $CHCl_3$/iPrOH (v/v = 3/1, 3 x 3 mL), the combined organic layers were washed with brine (4 mL), dried ($Na_2SO_4$) and filtered into a 40 mL vial. After removal of the solvent, the crude 2-pyrazole BCP acid was used directly in the next step.

To the crude 2-pyrazole BCP in a 40 mL vial was added dichloromethane (1.34 mL) and triethylamine (22.1 μL, 1.3 equiv. 112.1 μmol). The resulting mixture was cooled to –10 °C, and then chloromethylformate (8.1 μL, 1.2 equiv. 103.2 μmol) was added. After 1 h, amine (37.7 mg, 1.3 equiv. 112.1 μmol) was added and the reaction was stirred at room temperature overnight. Next, 3 mL of $Na_2CO_3$ and 3 mL of EtOAc was added to the mixture. The reaction was extracted with EtOAc (3 x 3 mL) and then dried over $Na_2SO_4$. Purification by preparative HPLC (XBridge BEH C18 OBD column, 30–60% MeCN/$H_2O$ with 0.1% $NH_4OH$) afforded the desired product (20.1 mg, 47% yield over 2 steps) as a mixture of diastereomers and rotamers.

**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.65 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 6.31 (t, *J* = 2.1 Hz, 1H), 4.80 (s, 2H), 4.57 (d, *J* = 6.4 Hz, 1H), 3.64 (dtd, *J* = 11.5, 7.6, 3.9 Hz, 1H), 3.01 (tdd, *J* = 9.9, 5.2, 2.4 Hz, 1H), 2.90 (s, 1H), 2.75 – 2.35 (m, 8H), 2.32 – 2.25 (m,

2H), 2.22 (dd, *J* = 9.9, 3.1 Hz, 1H), 2.10 – 1.89 (m, 3H), 1.87 (dd, *J* = 9.9, 3.1 Hz, 1H), 1.81–1.62 (m, 3H), 1.43 (h, *J* = 7.4 Hz, 2H), 1.38 – 1.12 (m, 5H), 1.11 – 0.97 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 167.0, 165.5, 145.3, 139.0, 129.5, 117.8, 105.5, 72.4, 57.5, 52.8, 49.1, 48.7, 48.7, 48.6, 43.2, 36.3, 35.2, 33.0, 32.7, 32.0, 32.0, 32.0, 31.6, 26.8, 26.0, 26.0, 25.0, 25.0, 22.4, 12.0.

**IR (film):** $\nu_{max}(cm^{-1})$ 3287.7, 3193.3, 2927.1, 2850.4, 1643.8, 1559.4, 1528.4, 1448.7, 1339.0, 1366.3, 1312.4, 1266.3, 1225.8, 1167.8, 1096.0, 1052.9, 982.6, 918.5, 879.4, 832.6, 757.4, 731.1, 645.6, 631.4, 617.0, 599.4, 560.1, 547.8, 537.8, 521.0, 512.5, 505.8, 458.8, 447.2, 438.2, 430.2, 425.1, 416.8, 407.6.

**HRMS (ESI)** m/z calcd. for $C_{27}H_{41}N_6OS$ ($[M+H]^+$) 497.3057, found 497.3061.

Chiral separation:

Column & Dimensions: AD-H, 21X250 mm, 5 um

UV Wavelength: 208 nm

Flow Rate: 70 mL/min

Modifier: 40% MeOH w/ 0.1% $NH_4OH$

Outlet Pressure: 100 bar

Sample Amount: 17.6 mg

Diluent: 1:1 MeOH/ACN

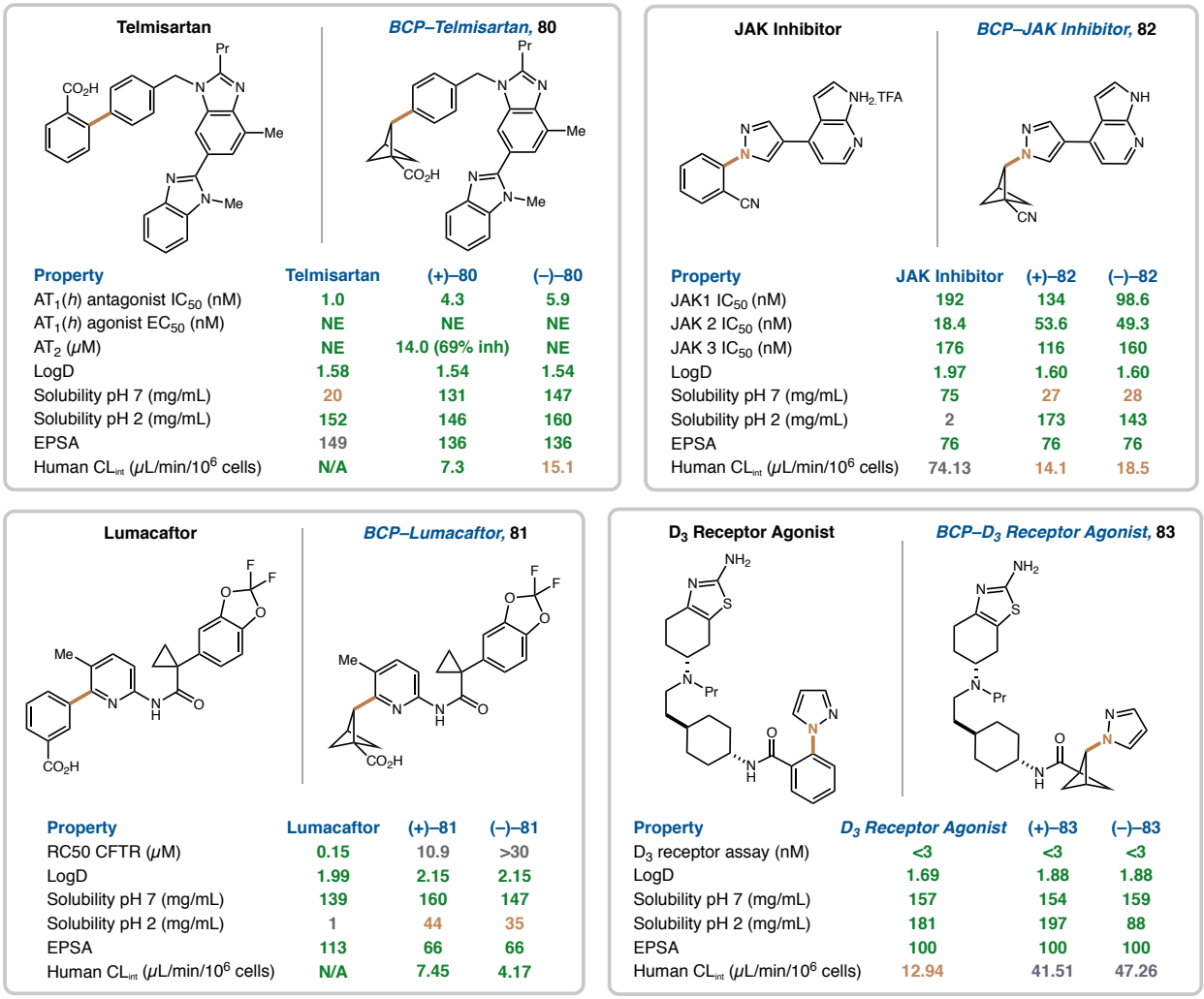
Diluent Volume: 2 mL

Injection Volume: 0.5 mL

Instrument: Sepiatec 3

# ADME Properties and Potency

## Summary of Data




| Property | Telmisartan | (+)–80 | (–)–80 |
|---|---|---|---|
| $AT_1$(*h*) antagonist $IC_{50}$ (nM) | 1.0 | 4.3 | 5.9 |
| $AT_1$(*h*) agonist $EC_{50}$ (nM) | NE | NE | NE |
| $AT_2$ (μM) | NE | 14.0 (69% inh) | NE |
| LogD | 1.58 | 1.54 | 1.54 |
| Solubility pH 7 (mg/mL) | 20 | 131 | 147 |
| Solubility pH 2 (mg/mL) | 152 | 146 | 160 |
| EPSA | 149 | 136 | 136 |
| Human $CL_{int}$ (μL/min/$10^6$ cells) | N/A | 7.3 | 15.1 |

| Property | JAK Inhibitor | (+)–82 | (–)–82 |
|---|---|---|---|
| JAK1 $IC_{50}$ (nM) | 192 | 134 | 98.6 |
| JAK 2 $IC_{50}$ (nM) | 18.4 | 53.6 | 49.3 |
| JAK 3 $IC_{50}$ (nM) | 176 | 116 | 160 |
| LogD | 1.97 | 1.60 | 1.60 |
| Solubility pH 7 (mg/mL) | 75 | 27 | 28 |
| Solubility pH 2 (mg/mL) | 2 | 173 | 143 |
| EPSA | 76 | 76 | 76 |
| Human $CL_{int}$ (μL/min/$10^6$ cells) | 74.13 | 14.1 | 18.5 |

| Property | Lumacaftor | (+)–81 | (–)–81 |
|---|---|---|---|
| RC50 CFTR (μM) | 0.15 | 10.9 | >30 |
| LogD | 1.99 | 2.15 | 2.15 |
| Solubility pH 7 (mg/mL) | 139 | 160 | 147 |
| Solubility pH 2 (mg/mL) | 1 | 44 | 35 |
| EPSA | 113 | 66 | 66 |
| Human $CL_{int}$ (μL/min/$10^6$ cells) | N/A | 7.45 | 4.17 |

| Property | $D_3$ Receptor Agonist | (+)–83 | (–)–83 |
|---|---|---|---|
| $D_3$ receptor assay (nM) | <3 | <3 | <3 |
| LogD | 1.69 | 1.88 | 1.88 |
| Solubility pH 7 (mg/mL) | 157 | 154 | 159 |
| Solubility pH 2 (mg/mL) | 181 | 197 | 88 |
| EPSA | 100 | 100 | 100 |
| Human $CL_{int}$ (μL/min/$10^6$ cells) | 12.94 | 41.51 | 47.26 |

**Figure S4.** Full dataset for all synthesized BCP pharmaceuticals. $CL_{int}$ = hepatic intrinsic clearance; Inh = inhibition; NE = No significant effect.

Telmisartan potency data as corroborated from cited papers.[12–24]
JAK inhibitor as exemplified in cited patents.[25,26]
Dopamine $D_3$ receptor agonist as exemplified in cited papers and patents[27,28]

## Assay Details

<u>Angiotension assay</u>

Assay was performed as reported by Martin and coworkers.[29]

Kinase assay

Z'-LYTE Screening Protocol and Assay Conditions was performed as cited and copied below.[30]

*Test Compounds:* The test compounds are screened in 1% DMSO (final) in the well.

*Peptide/Kinase Mixtures:* All Peptide/Kinase Mixtures are diluted to a 2X working concentration in the appropriate Kinase Buffer
(see below kinase specific assay conditions for a complete description).

*ATP Solution:* All ATP Solutions are diluted to a 4X working concentration in Kinase Buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA).
ATP Km apparent is previously determined using a Z′-LYTE assay.

*Development Reagent Solution:* The Development Reagent is diluted in Development Buffer (see section kinase specific assay conditions for a complete description).

*10X Novel PKC Lipid Mix:* 2 mg/ml Phosphatidyl Serine, 0.2 mg/ml DAG in 20 mM HEPES, pH 7.4, 0.3% CHAPS

*For 5 mL 10X Novel PKC Lipid Mix:*
1. Add 10 mgs Phosphatidyl Serine (Avanti Polar Lipids Part# 8400032C or 840039C) and 1 mg DAG(Avanti Polar Lipids Part# 800811C) to a glass tube.
2. Remove the chloroform from lipid mixture by evaporating to a clear, thin film under a stream of nitrogen. Continuous rotation of the tube, at an angle to ensure maximum surface area of the lipid solution, will promote the thinnest film.
3. Add 5 mLs resuspension buffer, 20 mM HEPES, 0.3% CHAPS, pH 7.4, to the dried lipid mix
4. Heat gently to 50-60 °C for 1-2 minutes and vortex in short intervals until the lipids are dissolved to a clear or slightly hazy solution. The lipids are typically in solution after 2-3 heat/vortex cycles.
5. Cool to room temperature, aliquot into single use volumes and store at –20 □C.

*Assay Protocol*
Bar-coded Corning, low volume NBS, black 384-well plate (Corning Cat. #4514)
1. 100 nL – 100X Test Compound in 100% DMSO
2. 2.4 µL – Kinase buffer
3. 5 µL – 2X Peptide/Kinase Mixture
4. 2.5 µL – 4X ATP Solution
5. 30-second plate shake
6. 60-minute Kinase Reaction incubation at room temperature
7. 5 µL – Development Reagent Solution
8. 30-second plate shake
9. 60-minute Development Reaction incubation at room temperature
10. Read on fluorescence plate reader and analyze the data

The following controls are made for each individual kinase and are located on the same plate as the kinase:

*0% Phosphorylation Control (100% Inhibition Control)*

The maximum Emission Ratio is established by the 0% Phosphorylation Control (100% Inhibition Control), which contains no ATP and therefore exhibits no kinase activity. This control yields 100% cleaved peptide in the Development Reaction.

*100% Phosphorylation Control*

The 100% Phosphorylation Control, which consists of a synthetically phosphorylated peptide of the same sequence as the peptide substrate, is designed to allow for the calculation of percent phosphorylation. This control yields a very low percentage of cleaved peptide in the Development Reaction.

The 0% Phosphorylation and 100% Phosphorylation Controls allow one to calculate the percent Phosphorylation achieved in a specific reaction well. Control wells do not include any kinase inhibitors.

*0% Inhibition Control*

The minimum Emission Ratio in a screen is established by the 0% Inhibition Control, which contains active kinase. This control is designed to produce a 10–50%* phosphorylated peptide in the Kinase Reaction.

* Cascade assays may produce up to 70% phosphorylated peptide.

*Known Inhibitor*

A known inhibitor control standard curve, 10 point titration, is run for each individual kinase on the same plate as the kinase to ensure the kinase is inhibited within an expected IC50 range previously determined.

The following controls are prepared for each concentration of Test Compound assayed:

*Development Reaction Interference*

The Development Reaction Interference is established by comparing the Test Compound Control wells that do not contain ATP versus the 0% Phosphorylation Control (which does not contain the Test Compound). The expected value for a non-interfering compound should be 100%. Any value outside of 90% to 110% is flagged.

*Test Compound Fluorescence Interference*

The Test Compound Fluorescence Interference is determined by comparing the Test Compound Control wells that do not contain the Kinase/Peptide Mixture (zero peptide control) versus the 0% Inhibition Control. The expected value for a non-fluorescence compound should be 0%. Any value > 20% is flagged.

The following equations are used for each set of data points:

| | Equation |
|---|---|
| **Correction for Background Fluorescence** | $FI_{Sample} - FI_{TCFI\ Ctl}$ |
| **Emission Ratio** (using values corrected for background fluorescence) | $\frac{\text{Coumarin Emission (445 nm)}}{\text{Fluorescein Emission (520 nm)}}$ |
| **% Phosphorylation (% Phos)** | $\left\{ 1 - \frac{(\text{Emission Ratio} \times F_{100\%}) - C_{100\%}}{(C_{0\%} - C_{100\%}) + [\text{Emission Ratio} \times (F_{100\%} - F_{0\%})]} \right\} * 100$ |
| **% Inhibition** | $\left\{ 1 - \frac{\%\ Phos_{Sample}}{\%\ Phos_{(0\%\ Inhibition\ Ctl)}} \right\} * 100$ |
| **Z´** (using Emission Ratio values) | $1 - \frac{3*Stdev_{(0\%\ Phos\ Ctl)} + 3*Stdev_{(0\%\ Inhibition)}}{Mean_{(0\%Phos\ Ctl)} - Mean_{(0\%\ Inhibition)}}$ |
| **Difference Between Data Points** (single point only) | $\lvert \%\ Inhibition_{Point\ 1} - \%\ Inhibition_{Point\ 2} \rvert$ |
| **Development Reaction Interference (DRI)** (no ATP control) | $\frac{Emission\ Ratio_{DRI\ Ctl}}{Emission\ Ratio_{0\%\ Phos\ Ctl}}$ |
| **Test Compound Fluorescence Interference (TCFI)** (check both Coumarin and Fluorescein emissions) | $\frac{FI_{TCFI\ Ctl}}{FI_{0\%\ Inhibitor\ Ctl}}$ |

**FI** = Fluorescence Intensity
$C_{100\%}$ = Average Coumarin emission signal of the 100% Phos. Control
$C_{0\%}$ = Average Coumarin emission signal of the 0% Phos. Control
$F_{100\%}$ = Average Fluorescein emission signal of the 100% Phos. Control
$F_{0\%}$ = Average Fluorescein emission signal of the 0% Phos. Control
**DRI** = Development Reaction Interference
**TCFI** = Test Compound Fluorescence Interference

*Graphing Software*
SelectScreen Kinase Profiling Service uses XLfit from IDBS. The dose response curve is curve fit to model number 205 (sigmoidal dose-response model). If the bottom of the curve does not fit between -20% & 20% inhibition, it is set to 0% inhibition. If the top of the curve does not fit between 70% and 130% inhibition, it is set to 100% inhibition.

*JAK1*
The 2X JAK1 / Tyr 06 mixture is prepared in 50 mM HEPES pH 6.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA, 0.02% NaN3. The final 10 µL Kinase Reaction consists of 22.9 - 91.5 ng JAK1 and 2 µM Tyr 06 in 50 mM HEPES pH 7.0, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA, 0.01% NaN3. After the 1 hour Kinase Reaction incubation, 5 µL of a 1:128 dilution of Development Reagent A is added.

*JAK2*
The 2X JAK2 / Tyr 06 mixture is prepared in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA. The final 10 µL Kinase Reaction consists of 0.12 - 0.5 ng JAK2 and 2 µM Tyr 06 in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA. After the 1 hour Kinase Reaction incubation, 5 µL of a 1:128 dilution of Development Reagent A is added.

*JAK3*
The 2X JAK3 / Tyr 06 mixture is prepared in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA. The final 10 µL Kinase Reaction consists of 0.5 - 2.7 ng JAK3 and 2 µM Tyr 06 in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 1 mM EGTA. After the 1 hour Kinase Reaction incubation, 5 µL of a 1:128 dilution of Development Reagent A is added

## References


(1.) Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C., *Science* **2018,** *360*, 1010-1014.

(2.) Sakai, H. A.; Liu, W.; Le, C. C.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2020,** *142*, 11691-11697.

(3.) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics* **1996,** *15*, 1518-1520.

(4.) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A., *J. Org. Chem.* **1997,** *62*, 7512-7515.

(5). Le, C. "Chip"; Wismer, M. K.; Shi, Z.-C.; Zhang, R.; Conway, D. V.; Li, G.; Vachal, P.; Davies, I. W.; MacMillan, D. W. C. *ACS Cent. Sci.* **2017**, *3* (6), 647–653.

(6.) Ripenko, V.; Vysochyn, D.; Klymov, I.; Zhersh, S.; Mykhailiuk, P. K., *J. Org. Chem.* **2021,** *86*, 14061-14068.

(7.) Sun, R.; Qin, Y.; Nocera, D. G., *Angew. Chem. Int. Ed.* **2020,** *59*, 9527-9533.

(8.) Liang, Y.; Zhang, X.; MacMillan, D. W. C., *Nature* **2018,** *559*, 83-88.

(9.) Kumar, A. S.; Ghosh, S.; Mehta, G. N., *Journal of Chemical Research* **2010,** *34*, 95-97.

(10.) Zhu, Y.-F.; Wei, B.-L.; Wei, J.-J.; Wang, W.-Q.; Song, W.-B.; Xuan, L.-J., *Tetrahedron Lett.* **2019,** *60*, 1202-1205.

(11.) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J., *Org. Lett.* **2009,** *11*, 1999-2002.

(12.) Hansen, J. L.; Haunsø, S.; Brann, M. R.; Sheikh, S. P.; Weiner, D. M. *Molecular Pharmacology*, **2004**, *65(3)*, 770.

(13.) Foster, J. R.; Ueno, S.; Chen, M. X.; Harvey, J.; Dowell, S. J.; Irving, A. J.; Brown, A. J. *Pharmacol. Res. Perspect.* **2019**, *7*, e00542.

(14.) Casimiro-Garcia, A.; Filzen, G. F.; Flynn, D.; Bigge, C. F.; Chen, J.; Davis, J. A.; Dudley, D. A.; Edmunds, J. J.; Esmaeil, N.; Geyer, A.; Heemstra, R. J.; Jalaie, M.; Ohren, J. F.; Ostroski, R.; Ellis, T.; Schaum, R. P.; Stoner, C. *J. Med. Chem.* **2011,** *54* (12), 4219.

(15.) Casimiro-Garcia, A.; Heemstra, R. J.; Bigge, C. F.; Chen, J.; Ciske, F. A.; Davis, J. A.; Ellis, T.; Esmaeil, N.; Flynn, D.; Han, S.; Jalaie, M.; Ohren, J. F.; Powell, N. A. *Bioorganic & Medicinal Chemistry Letters* **2013**, *23* (3), 767.

(16.) Zhang, J.; Wang, J.-L.; Zhou, Z.-M.; Li, Z.-H.; Xue, W.-Z.; Xu, D.; Hao, L.-P.; Han, X.-F.; Fei, F.; Liu, T.; Liang, A.-H. *Bioorganic & Medicinal Chemistry* **2012**, *20* (14), 4208.

(17.) Zhang, J.; Wang, J.-L.; Yu, W.-F.; Zhou, Z.-M.; Tao, W.-C.; Wang, Y.-C.; Xue, W.-Z.; Xu, D.; Hao, L.-P.; Han, X.-F.; Fei, F.; Liu, T.; Liang, A.-H. *European Journal of Medicinal Chemistry* **2013,** *69*, 44.

(18.) Le, M. T.; Pugsley, M. K.; Vauquelin, G.; Van Liefde, I. *British Journal of Pharmacology* **2007**, *151* (7), 952.

(19.) Mathews, W. B.; Szabo, Z. *Current Topics in Medicinal Chemistry,* **2010**, *10* (16), 1585.

(20.) Zhu, W.; Bao, X.; Ren, H.; Da, Y.; Wu, D.; Li, F.; Yan, Y.; Wang, L.; Chen, Z. *European Journal of Medicinal Chemistry* **2016,** *115,* 161.

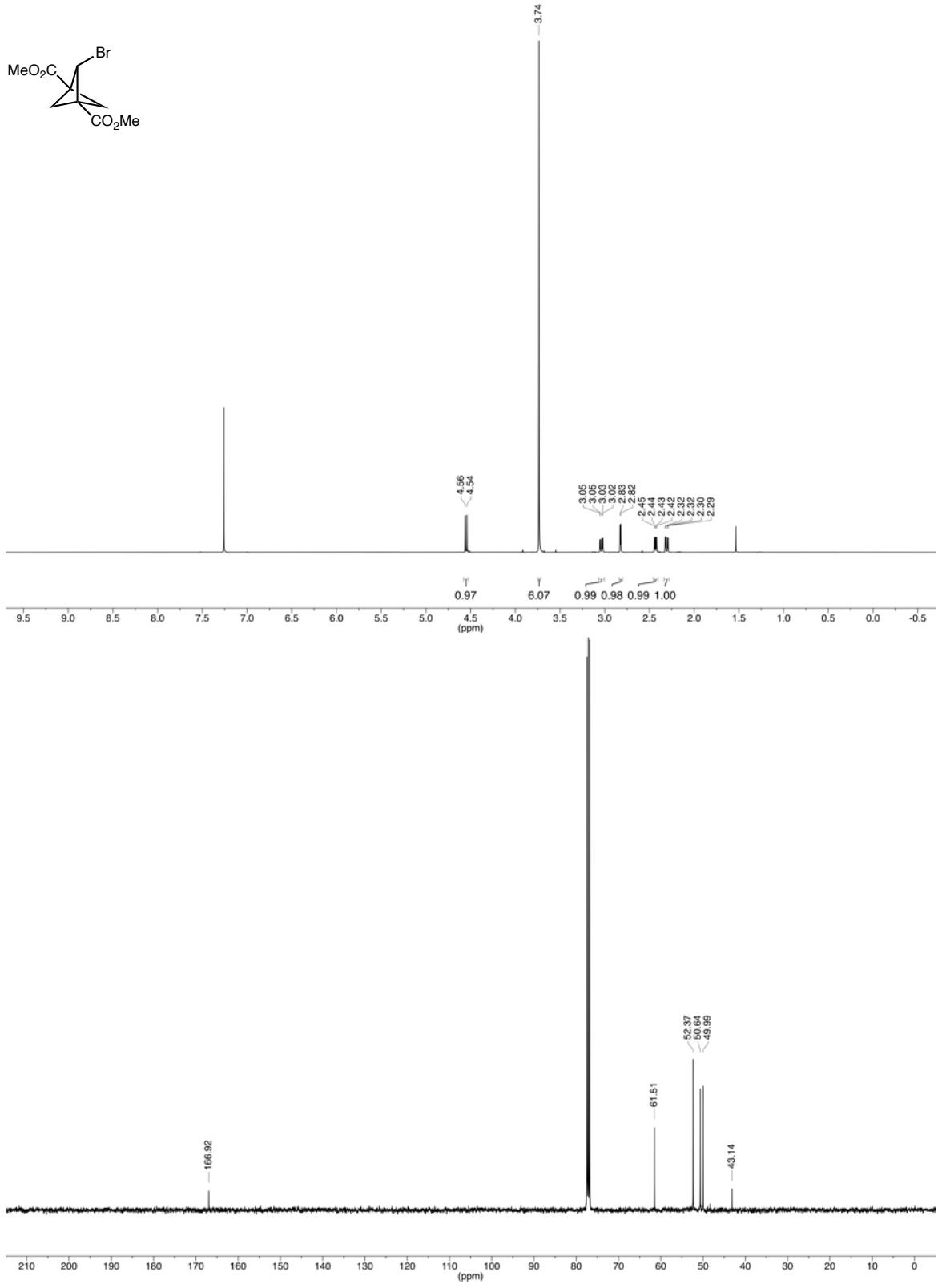
(21.) Wu, Z.; Xia, M.-B.; Bertsetseg, D.; Wang, Y.-H.; Bao, X.-L.; Zhu, W.-B.; Tao-Xu; Chen, P.-R.; Tang, H.-S.; Yan, Y.-J.; Chen, Z.-L. *Bioorganic Chemistry* **2020**, *101*, 104042.

(22.) Qu, L.; Wang, J.; Hou, T.; Zhou, H.; Wang, Z.; Zhang, X.; Liang, X. S. *Journal of Pharmacological and Toxicological Methods* **2020**, *102,* 106682.

(23.) Ojima, M.; Igata, H.; Tanaka, M.; Sakamoto, H.; Kuroita, T.; Kohara, Y.; Kubo, K.; Fuse, H.; Imura, Y.; Kusumoto, K.; Nagaya, H. *J. Pharmacol. Exp. Ther.* **2011**, *336*(3), 801.
(24.) Maillard, M. P.; Perregaux, C.; Centeno, C.; Stangier, J.; Wienen, W.; Brunner, H.-R.; Burnier, M. *J. Pharmacol. Exp. Ther.* **2002**, *302* (3), 1089..
(25.) Rodgers, J. D.; Shepard, S.; Maduskuie, T. P., Jr.; Wang, H.; Falahatpisheh, N.; Rafalski, M.; Arvanitis, A. G.; Storace, L.; Jalluri, R. K.; Fridman, J. S.; Vaddi, K. Heteroaryl substituted pyrrolo[2,3-b]pyridines and pyrrolo[2,3-b]pyrimidines as Janus kinase inhibitors. WO 2007/0135461 Al. (2007).
(26.) Rodgers, J. D.; Shepard, S.; Maduskuie, T. P. Jr.; Wang, H.; Falahatpisheh, N.; Rafalski, M.; Arvanitis, A. G.; Storace, L.; Jalluri, R. K.; Fridman, J. S.; Vaddi, K. Heteroaryl substituted pyrrolo[2,3-b]pyridines and pyrrolo[2,3-b]pyrimidines as Janus kinase inhibitors. WO 2009/0181959 Al. (2009).
(27.) Chen, J.; Levant, B.; Wang, S. *Bioorganic & Medicinal Chemistry Letters.* **2012**, *22*(17), 5612.
(28.) Wang, S.; Chen, J.; Collins, G.; Woods, J. H.; Levant, B. Selective ligands for the dopamine 3 ($D_3$) receptor and methods of using the same. WO 2010/025235 A1
(29.) Martin, M. M.; Willardson, B. M.; Burton, G. F.; White, C. R.; McLaughlin, J. N.; Bray, S. M.; Oglivie, J. W. Jr.; Elton, T. S. *Mol. Endocrinol.* **2001**, *15*(2), 281.
(30.) https://www.thermofisher.com/us/en/home/products-and-services/services/custom-services/screening-and-profiling-services/selectscreen-profiling-service/selectscreen-kinase-profiling-service.html

# Spectral Data for Isolated Products

## Dimethyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (4)



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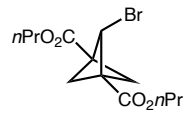





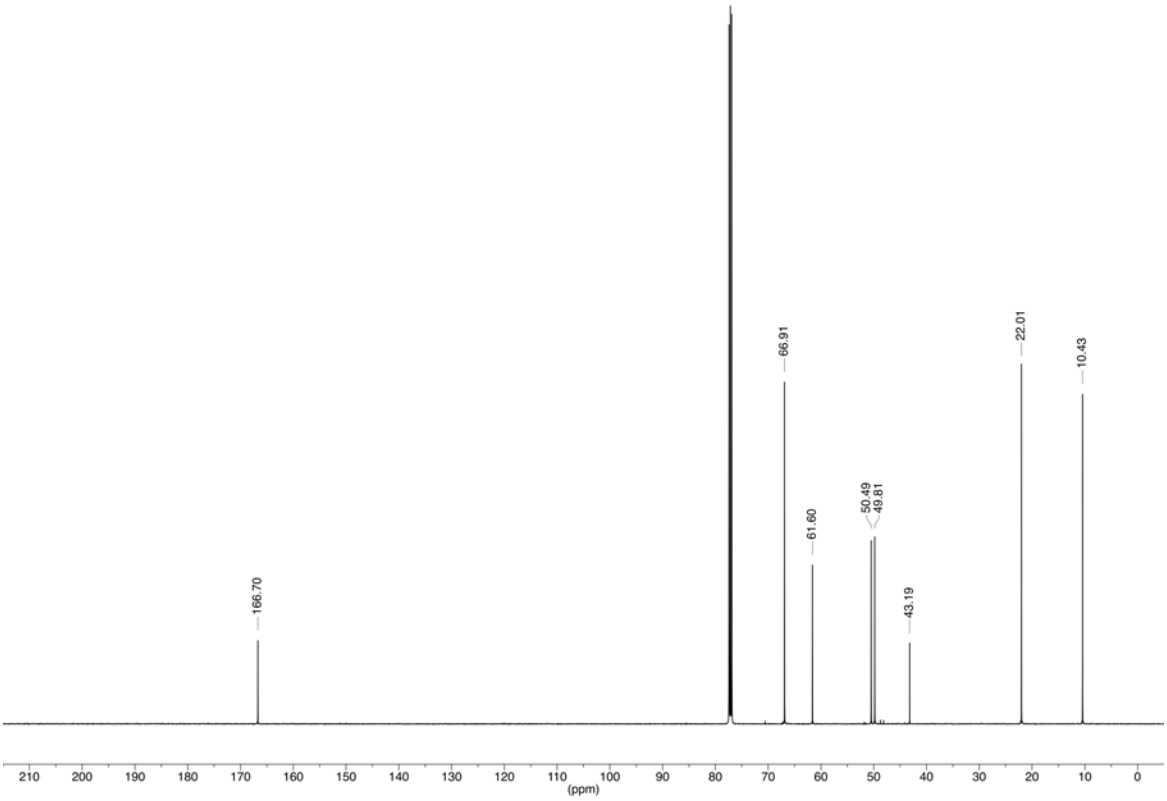

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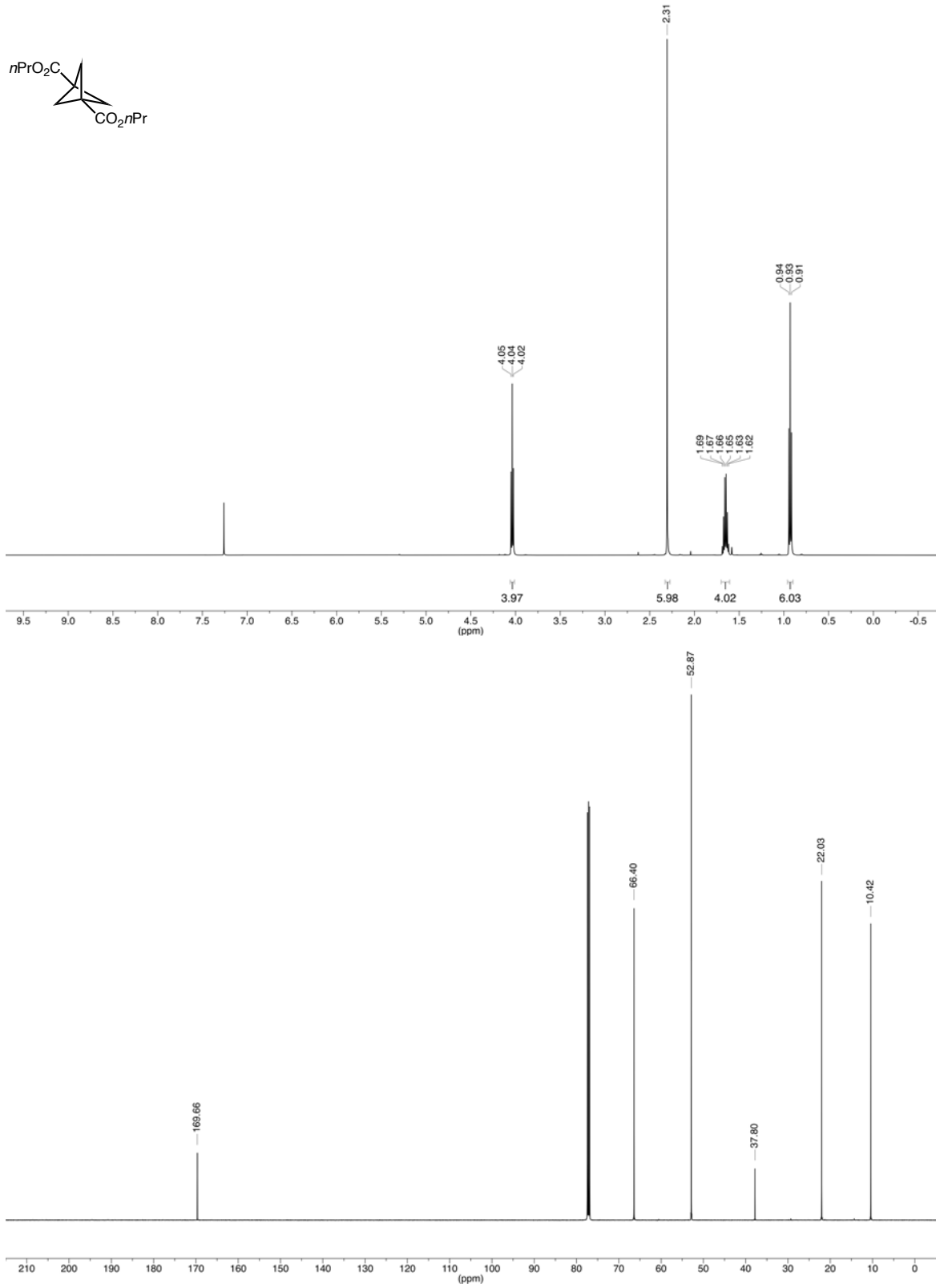

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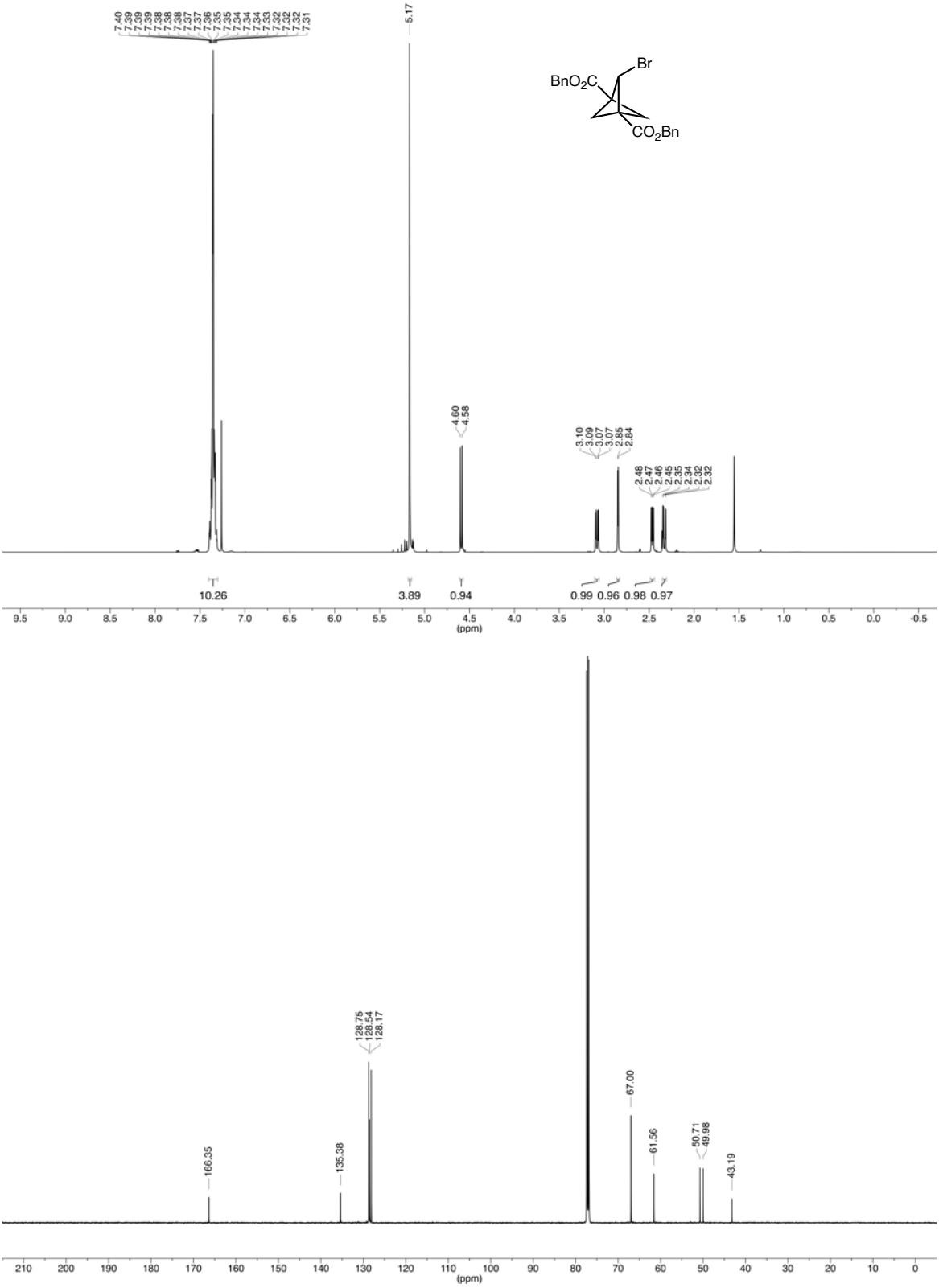

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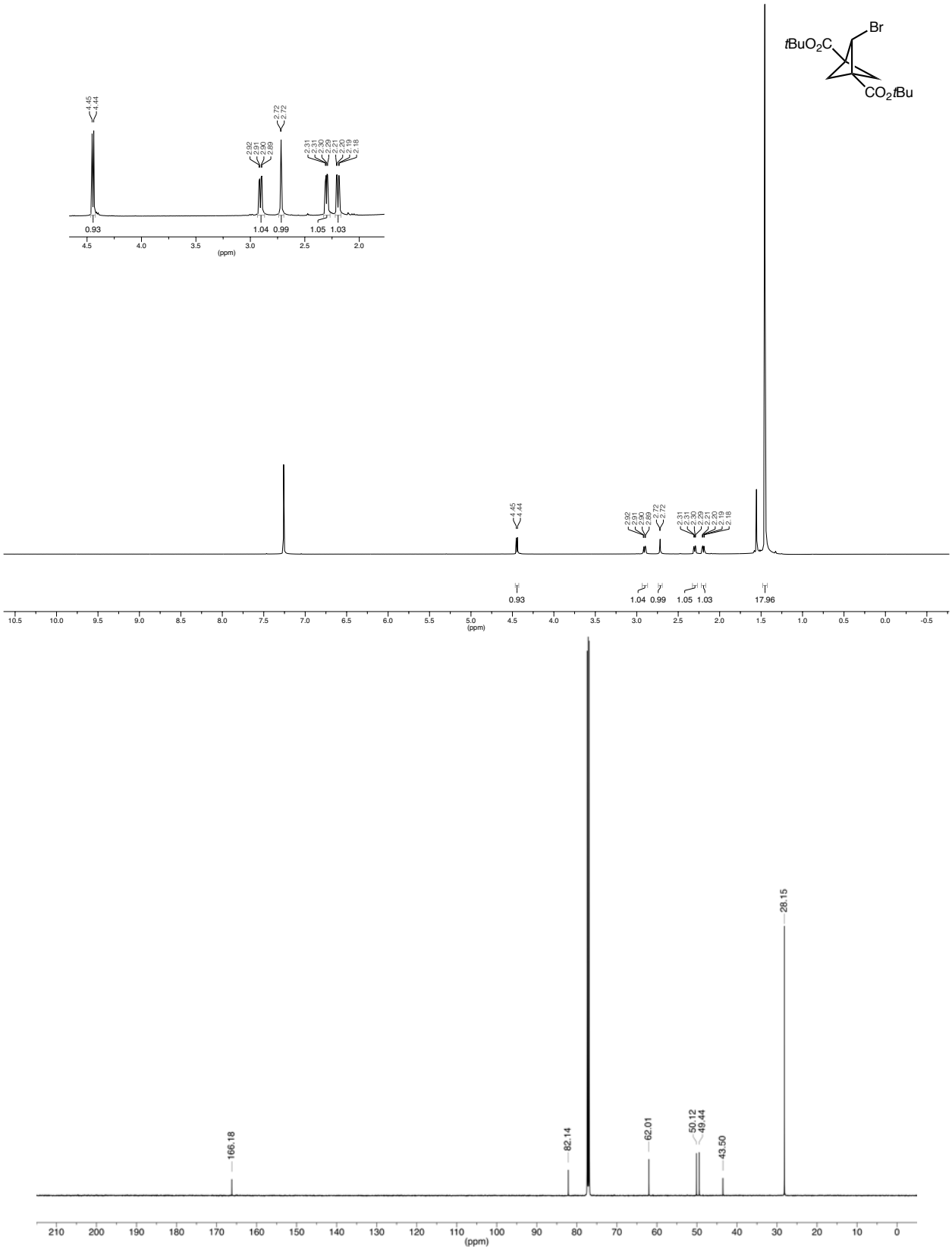

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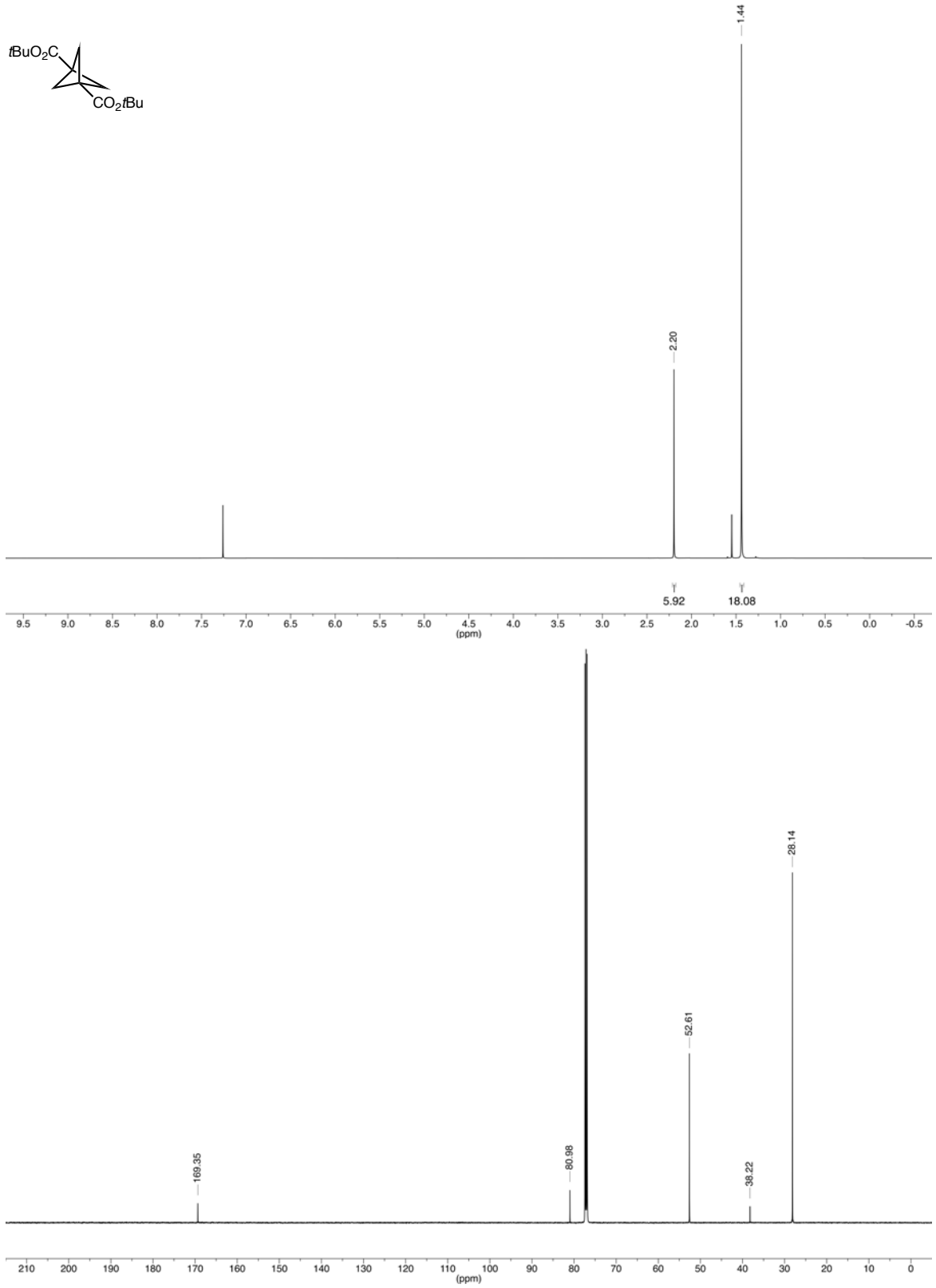
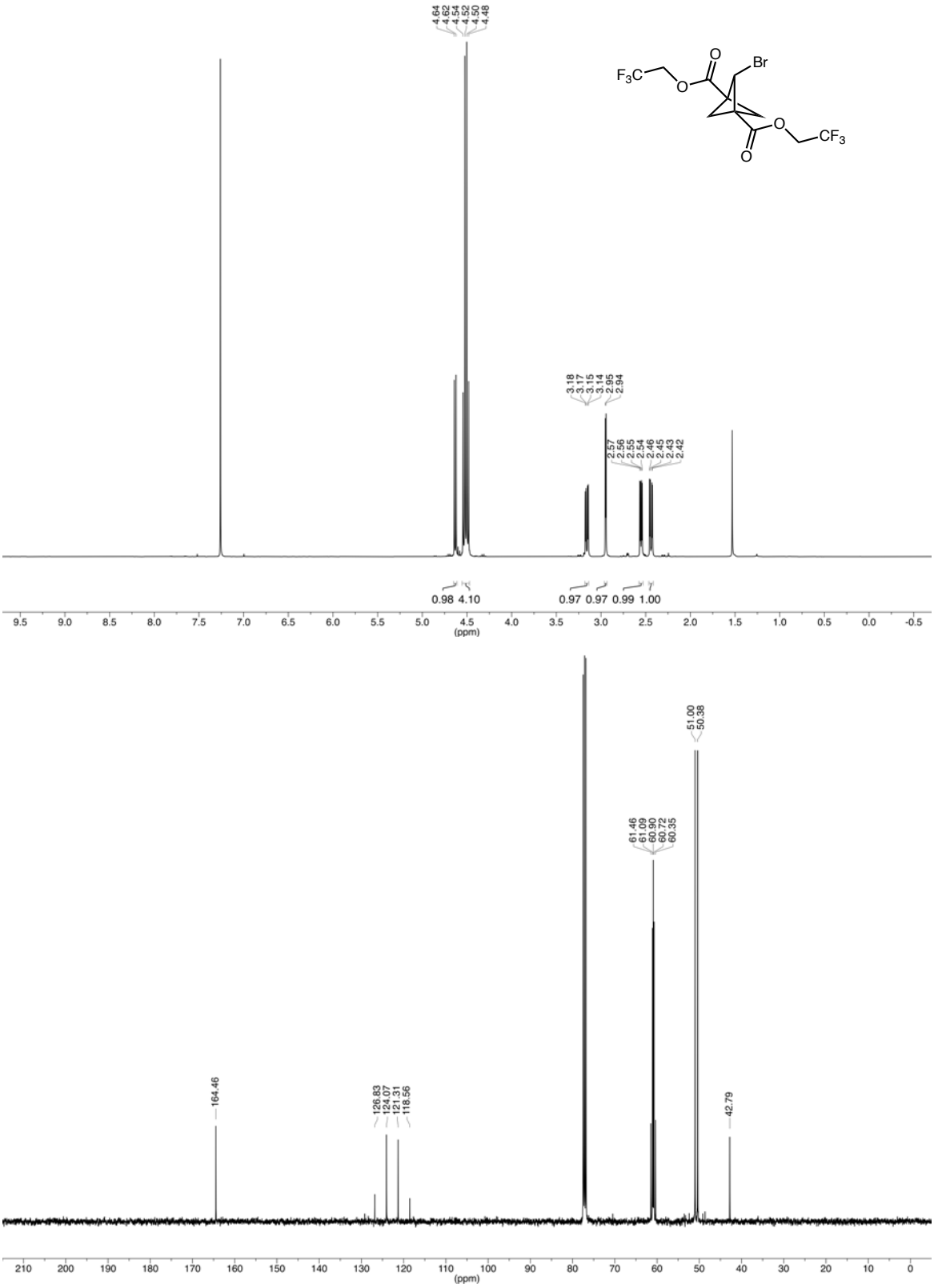
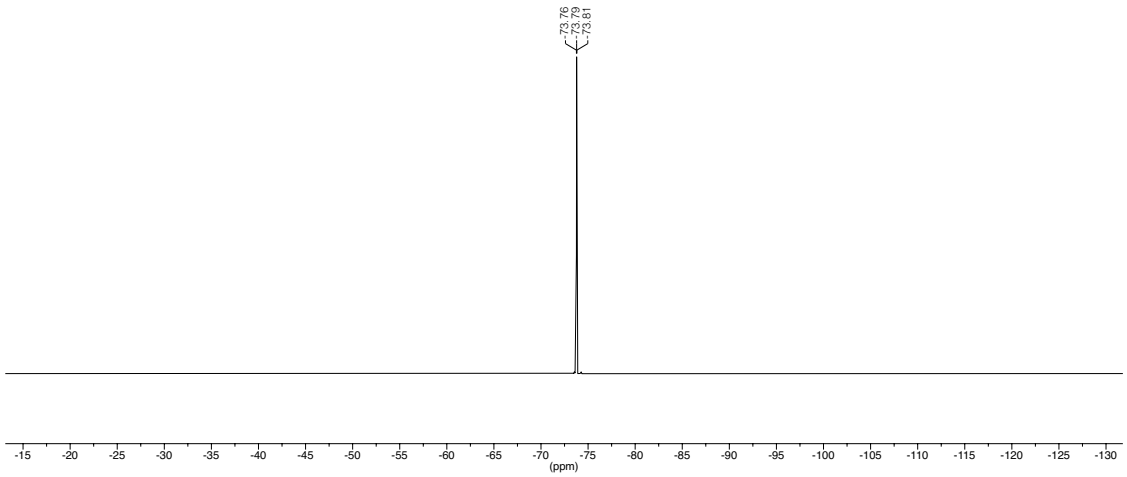


**Bis(2,2,2-trifluoroethyl) 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (8)**



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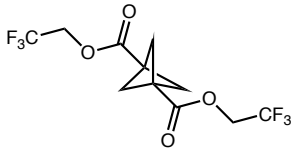

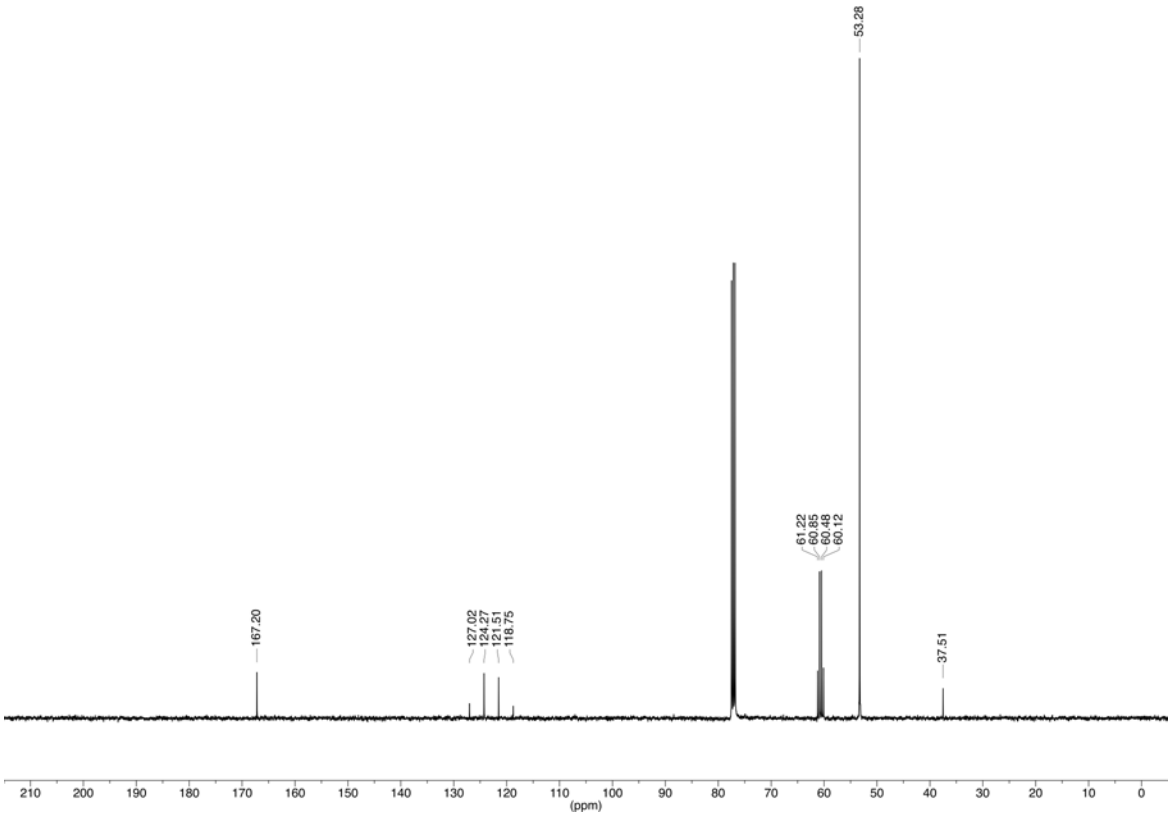
167.20
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124.27
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118.75
61.22
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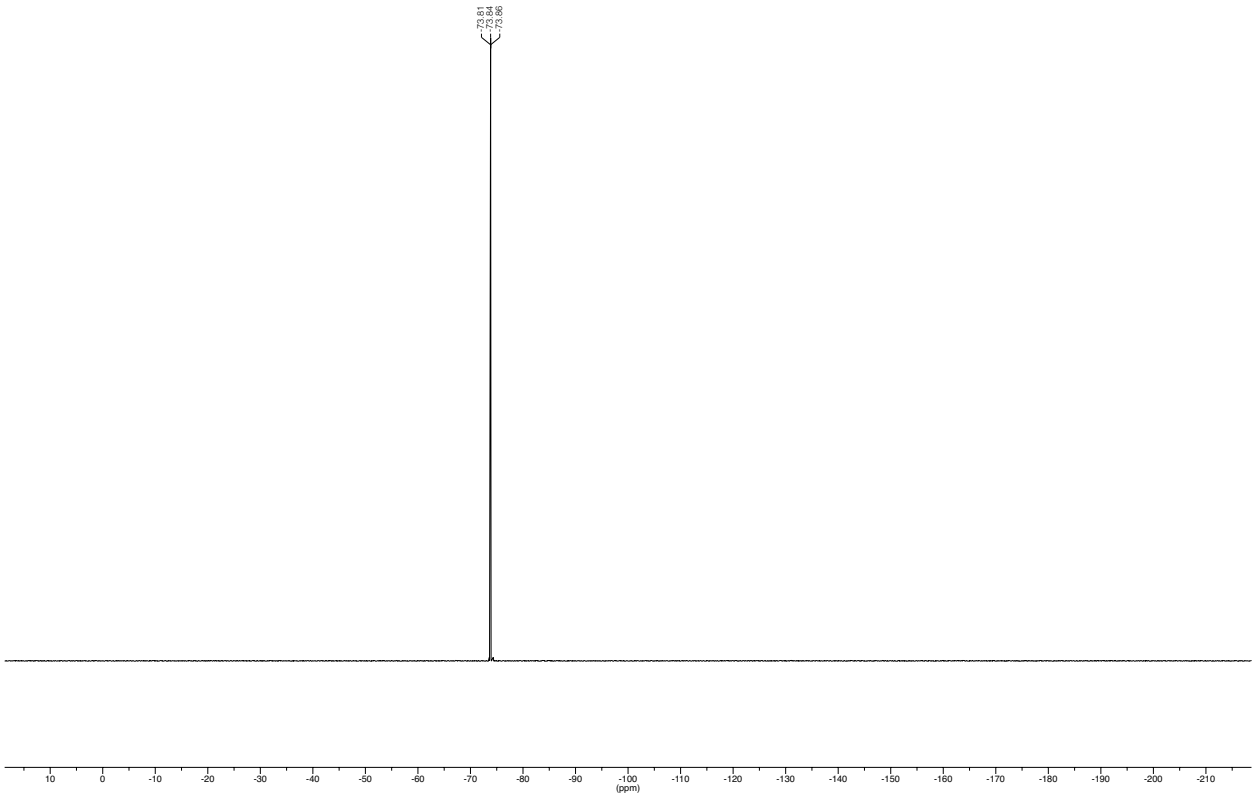
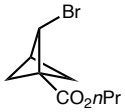
60.48
60.12
53.28
37.51
(ppm)

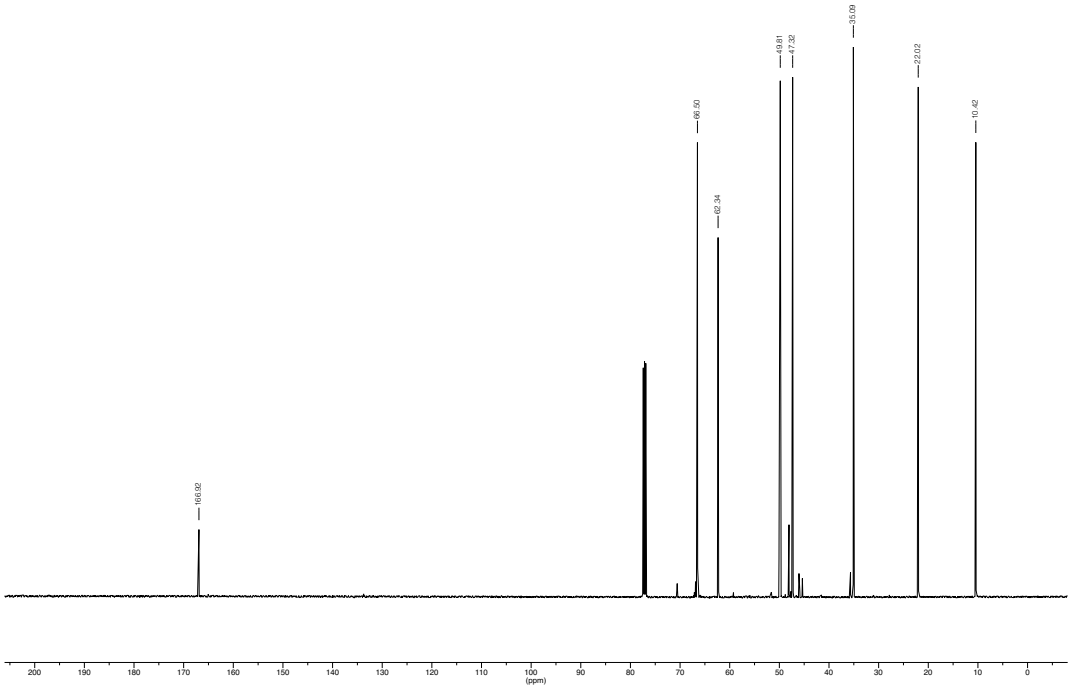

-73.81
-73.84
-73.86
(ppm)

**(±)-Propyl 2-bromobicyclo[1.1.1]pentane-1-carboxylate (9)** – 92% purity

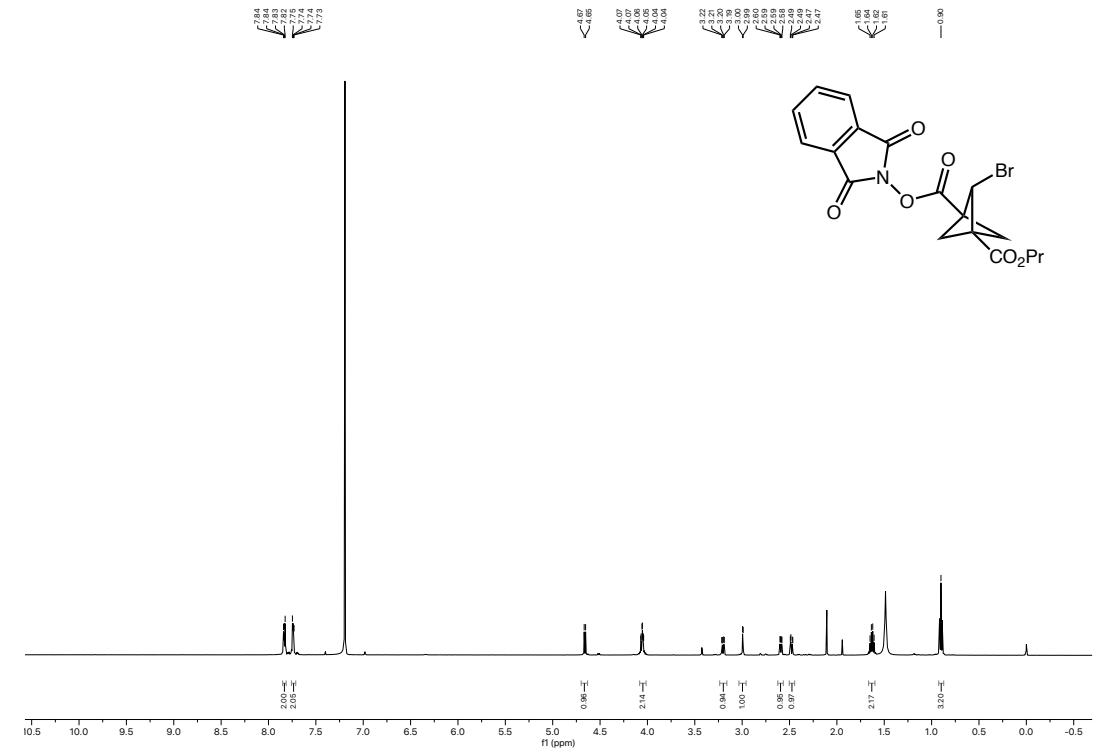


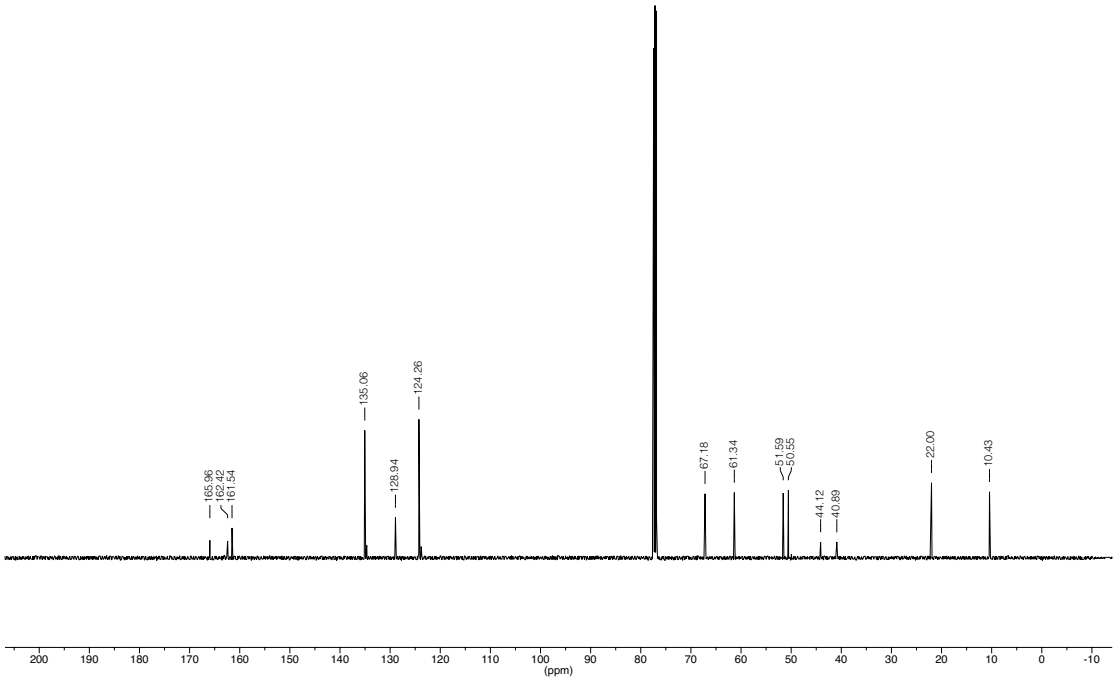




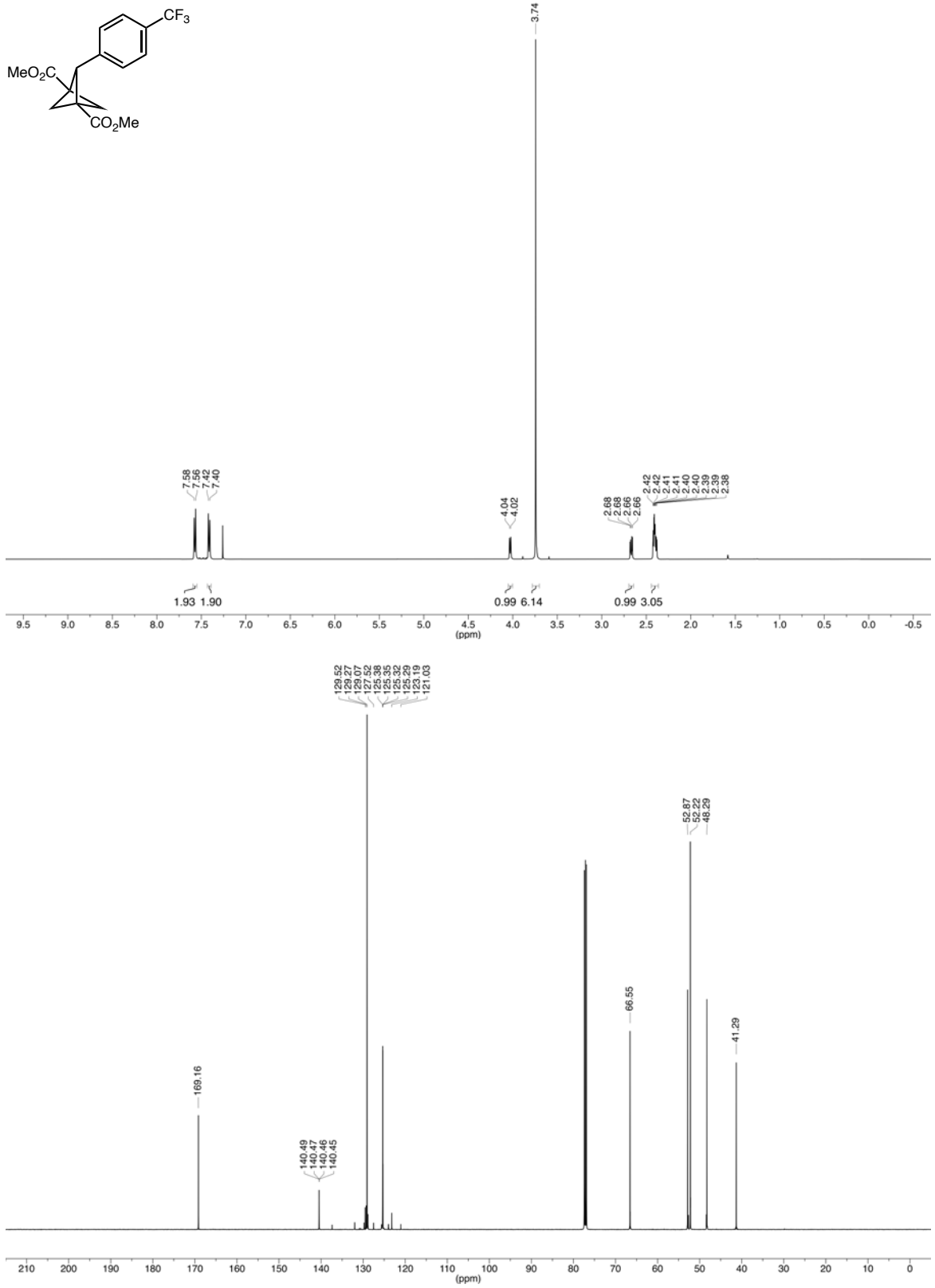


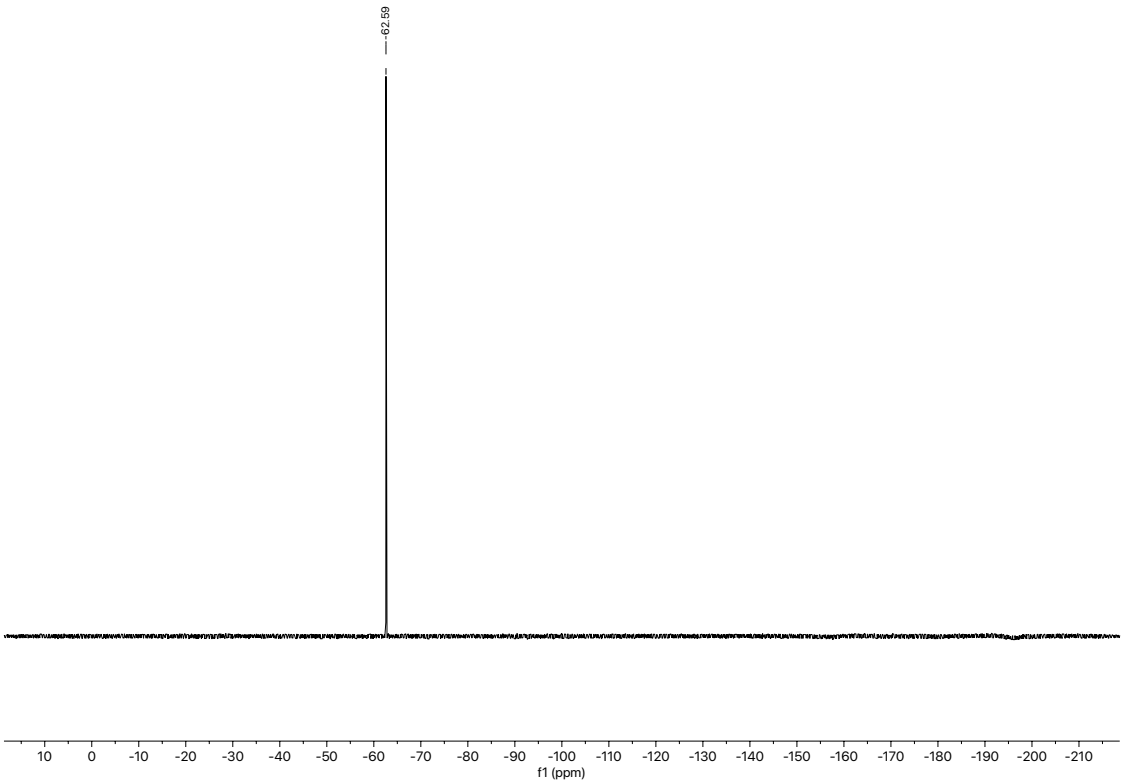
**(±)-1-(1,3-dioxoisoindolin-2-yl) 3-propyl 2-bromobicyclo[1.1.1]pentane-1,3-dicarboxylate (S6)**



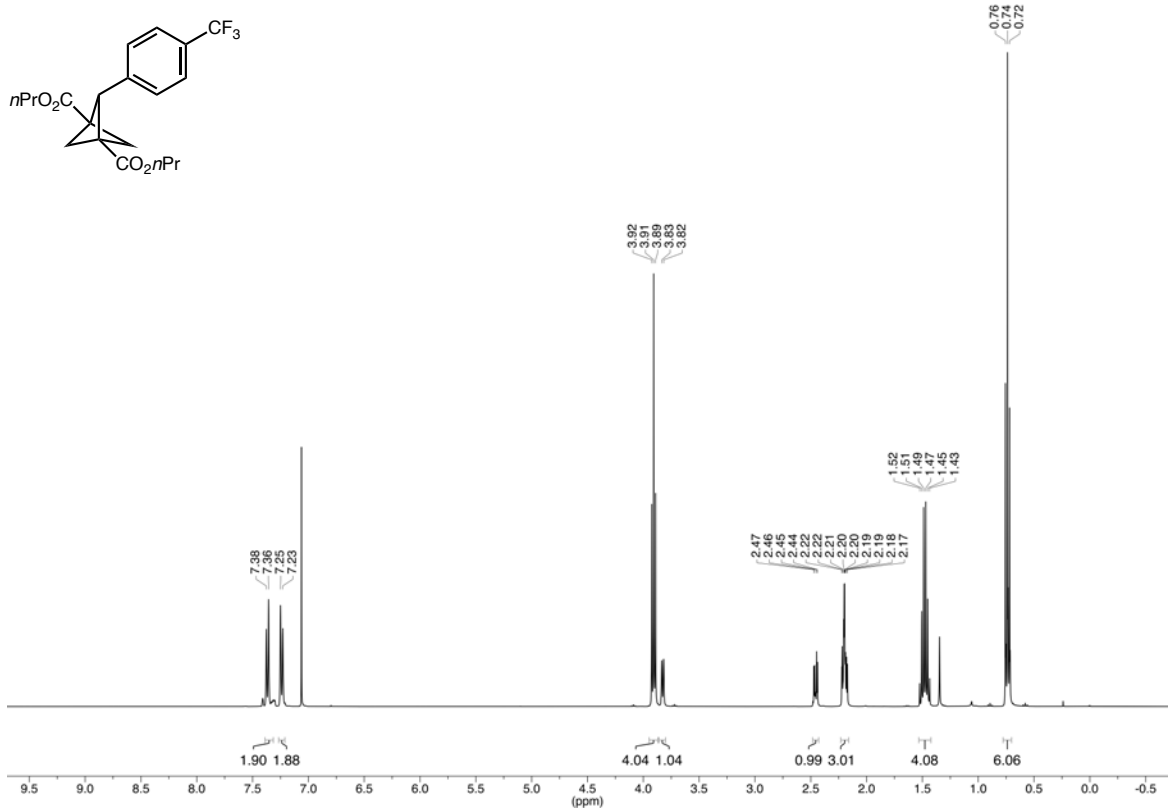



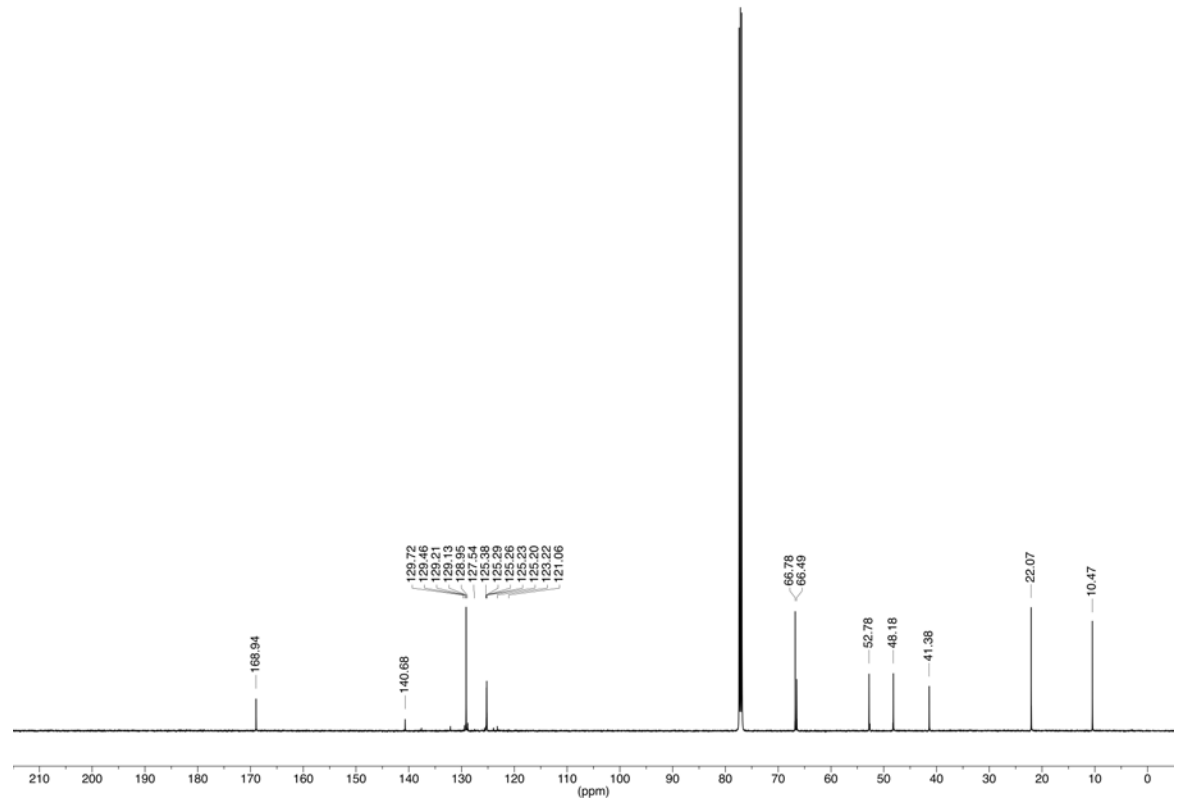
**Dimethyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (10)**

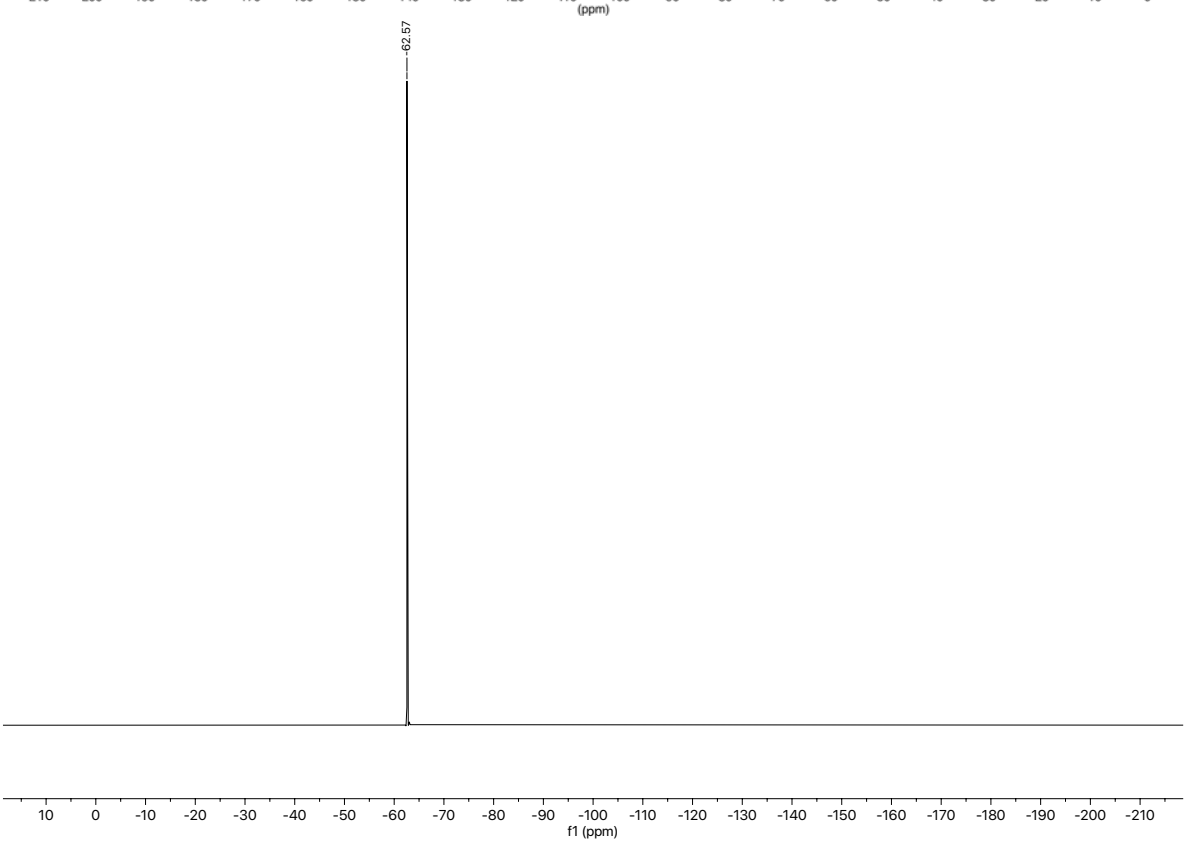




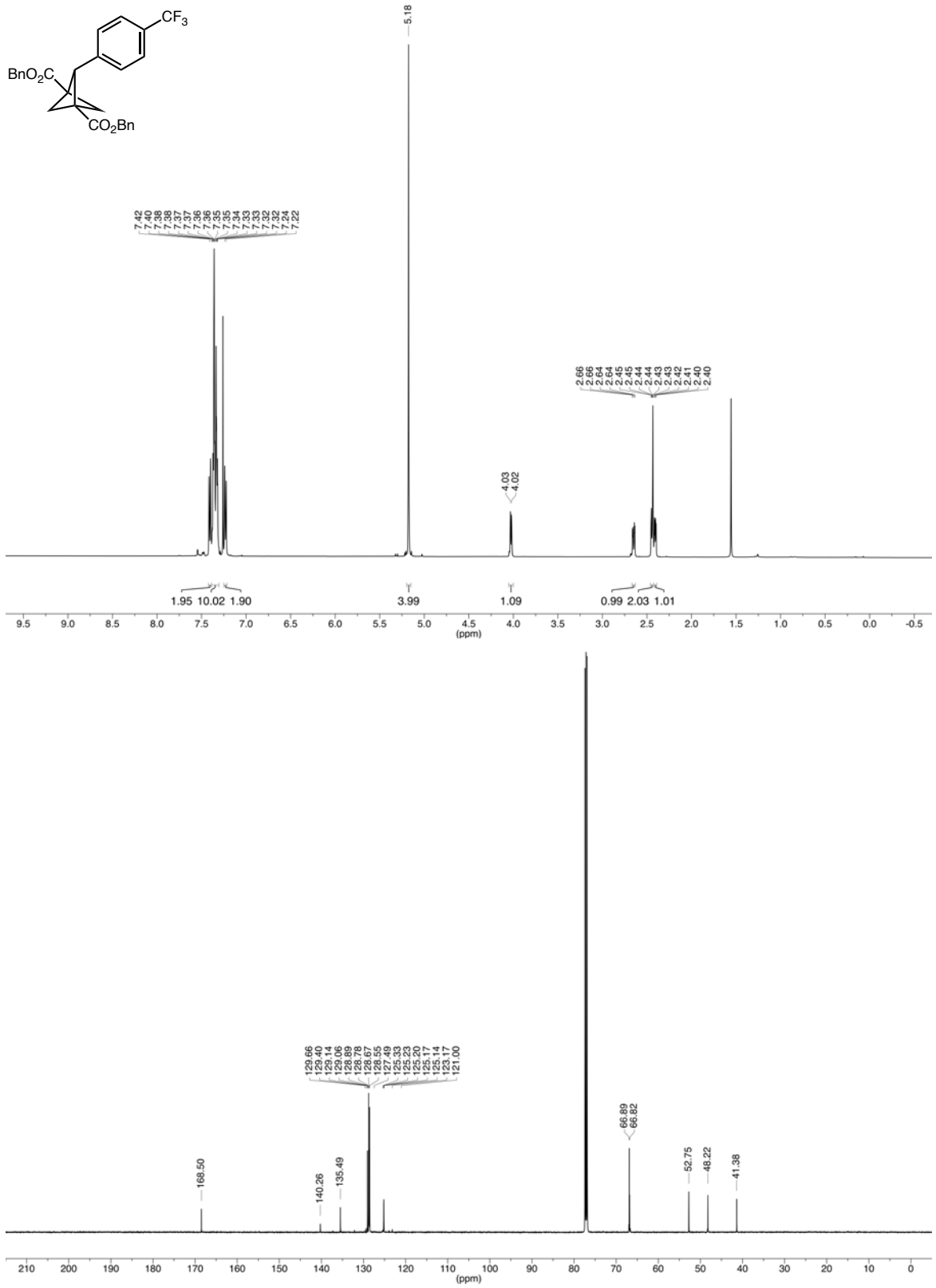

**Di-*n*-propyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (11)**

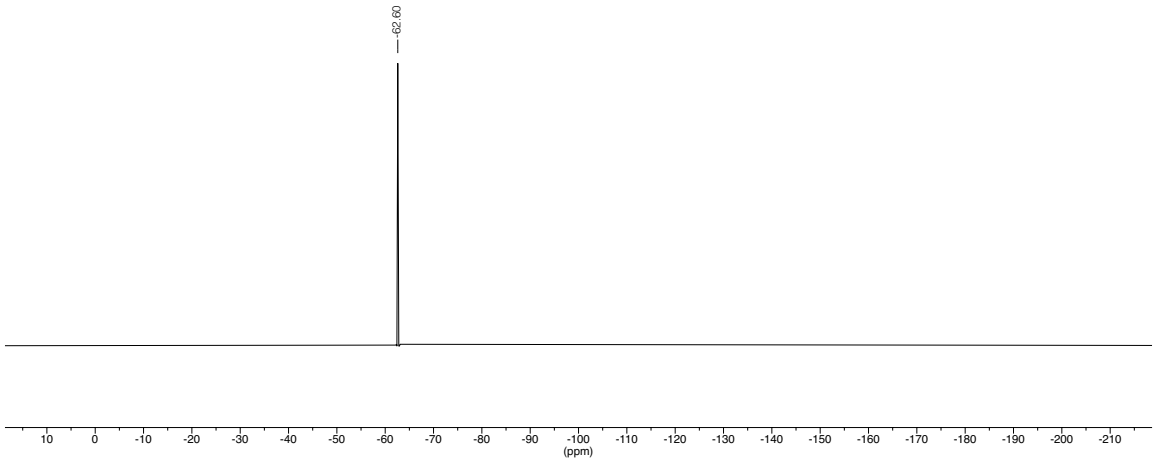



168.94
140.68
129.72
129.46
129.21
129.13
128.95
127.54
125.38
125.29
125.26
125.23
125.20
123.22
121.06
66.78
66.49
52.78
48.18
41.38
22.07
10.47
(ppm)

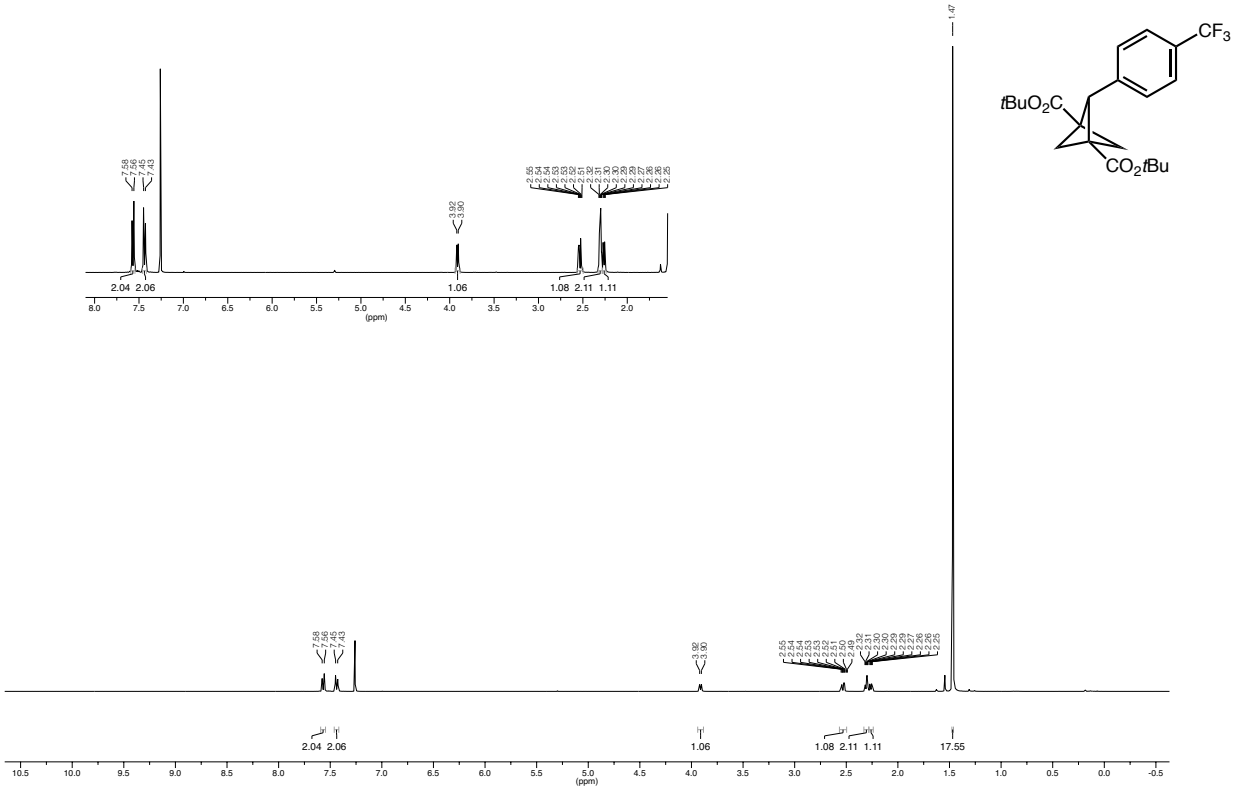

-62.57
f1 (ppm)

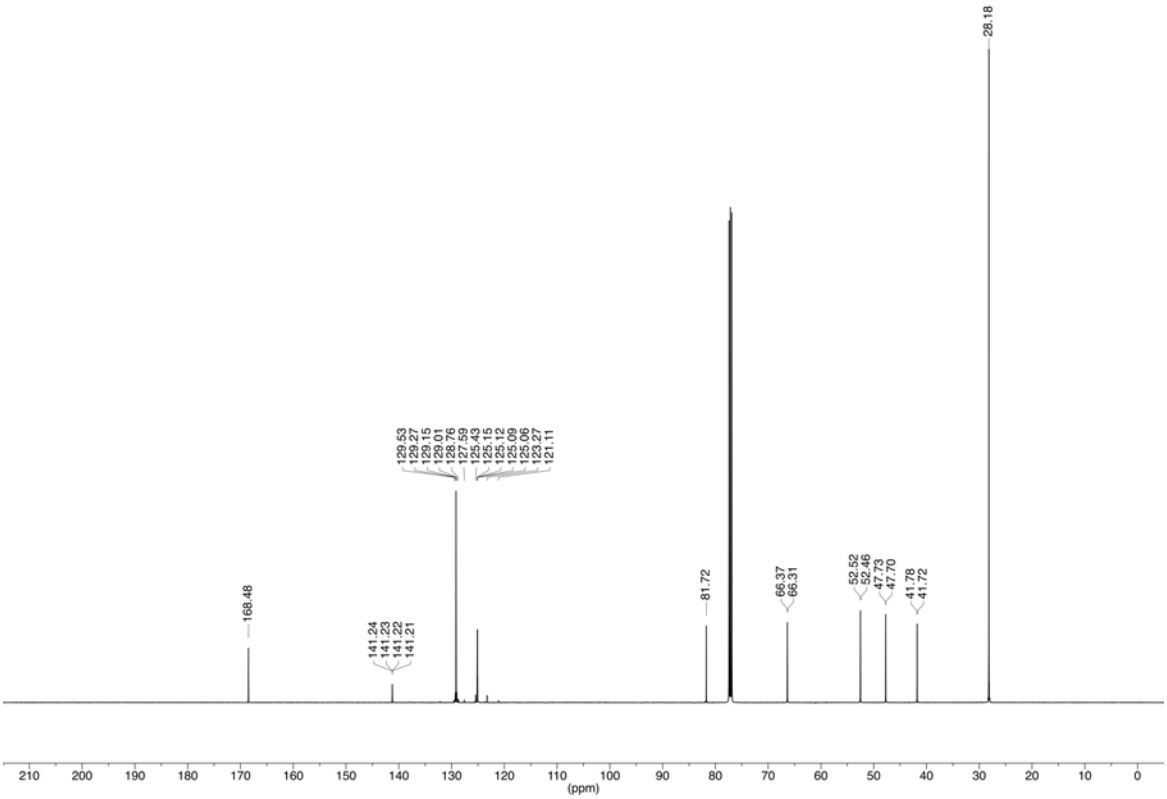
**Dibenzyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (12)**

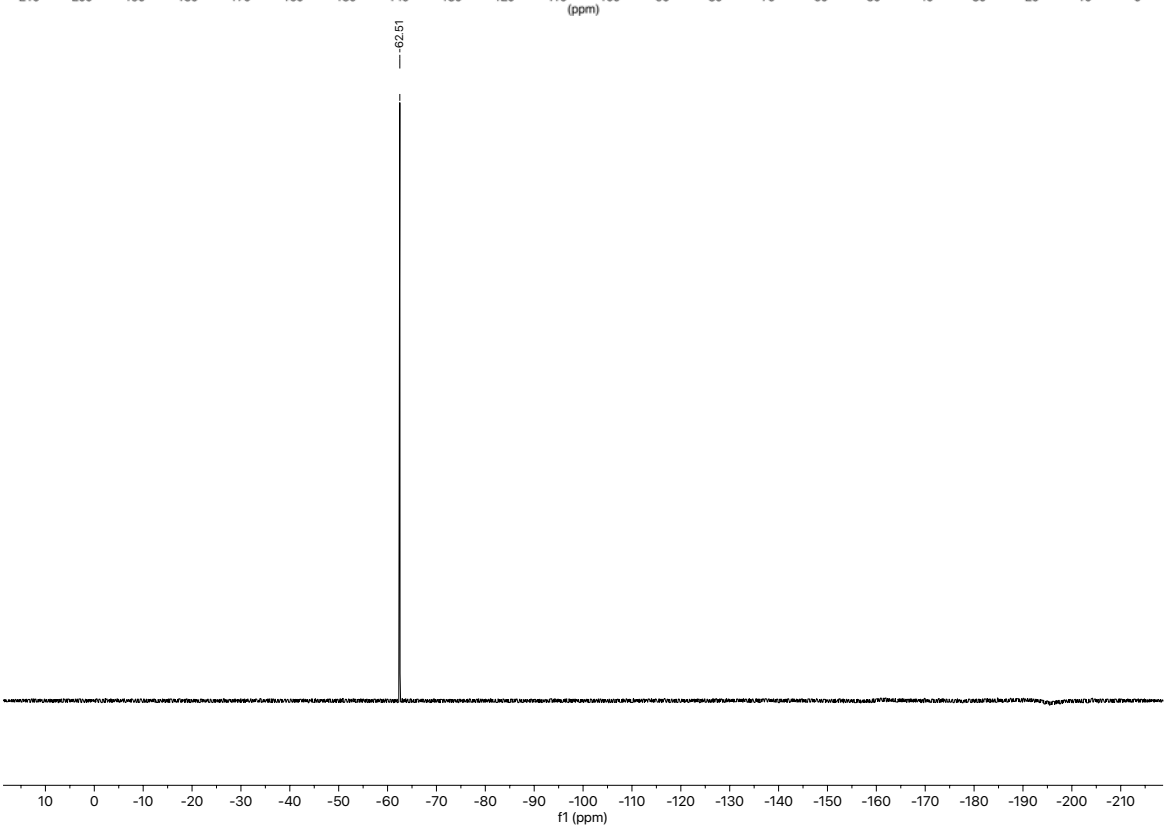




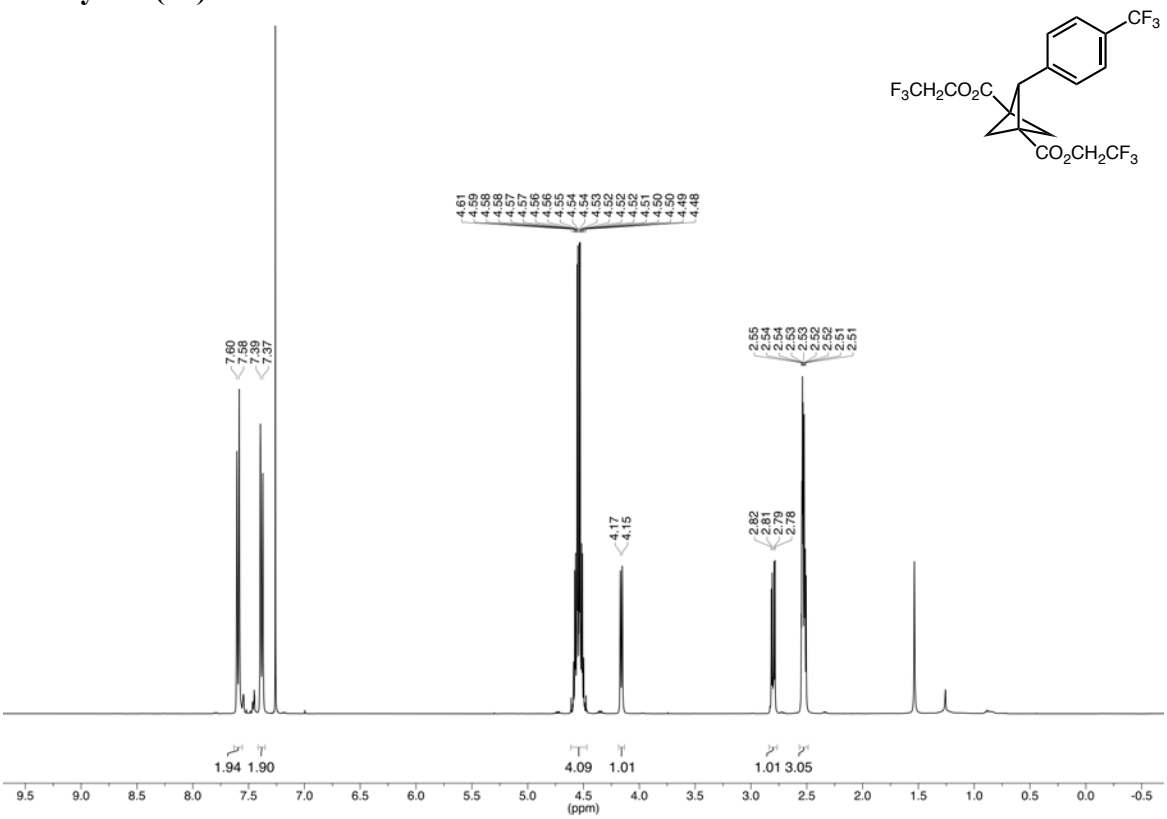

**Di-*tert*-butyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (13)**

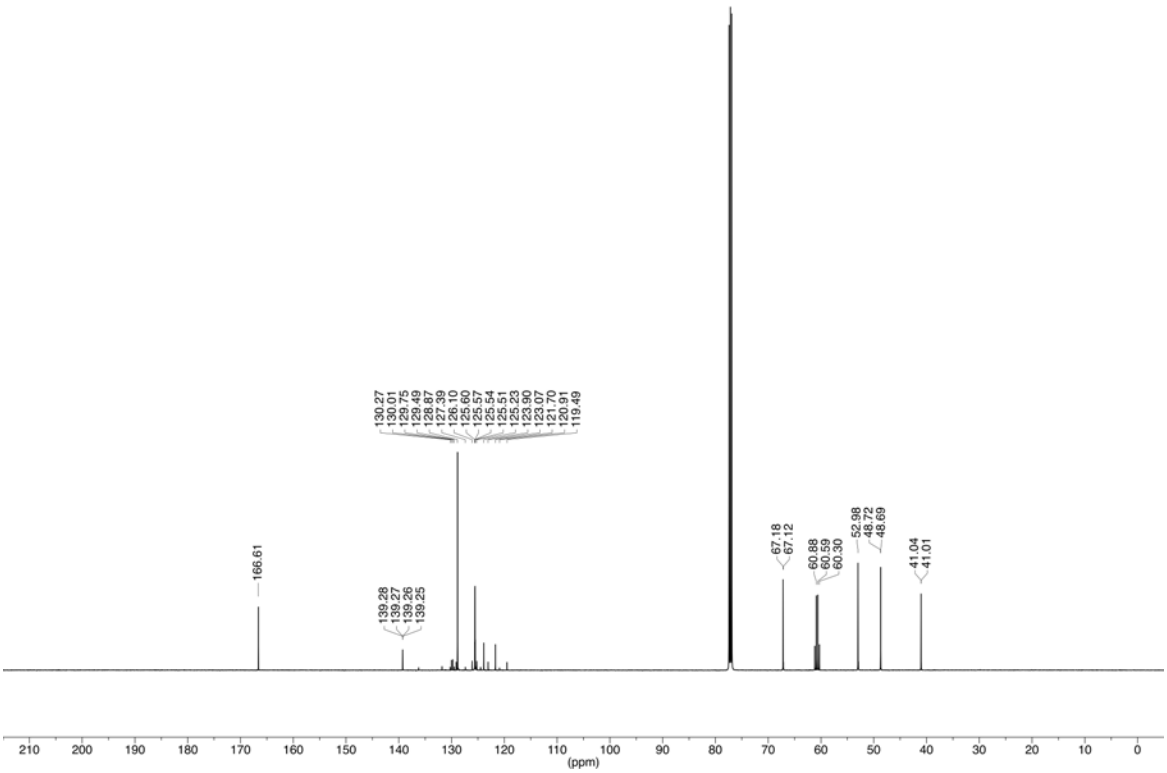


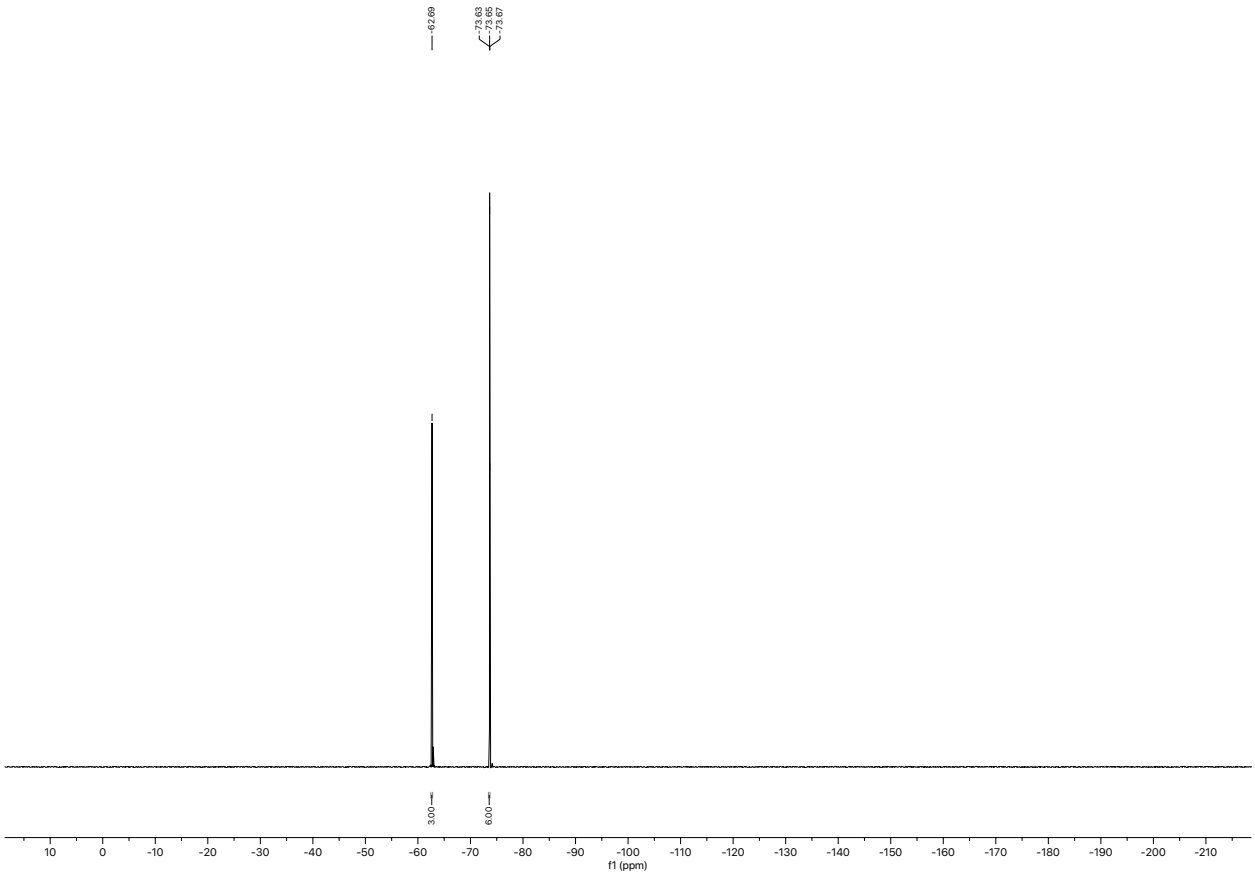

28.18
129.53
129.27
129.15
129.01
128.76
127.59
125.43
125.15
125.12
125.09
125.06
123.27
121.11
168.48
141.24
141.23
141.22
141.21
81.72
66.37
66.31
52.52
52.46
47.73
47.70
41.78
41.72
(ppm)


-62.51
f1 (ppm)

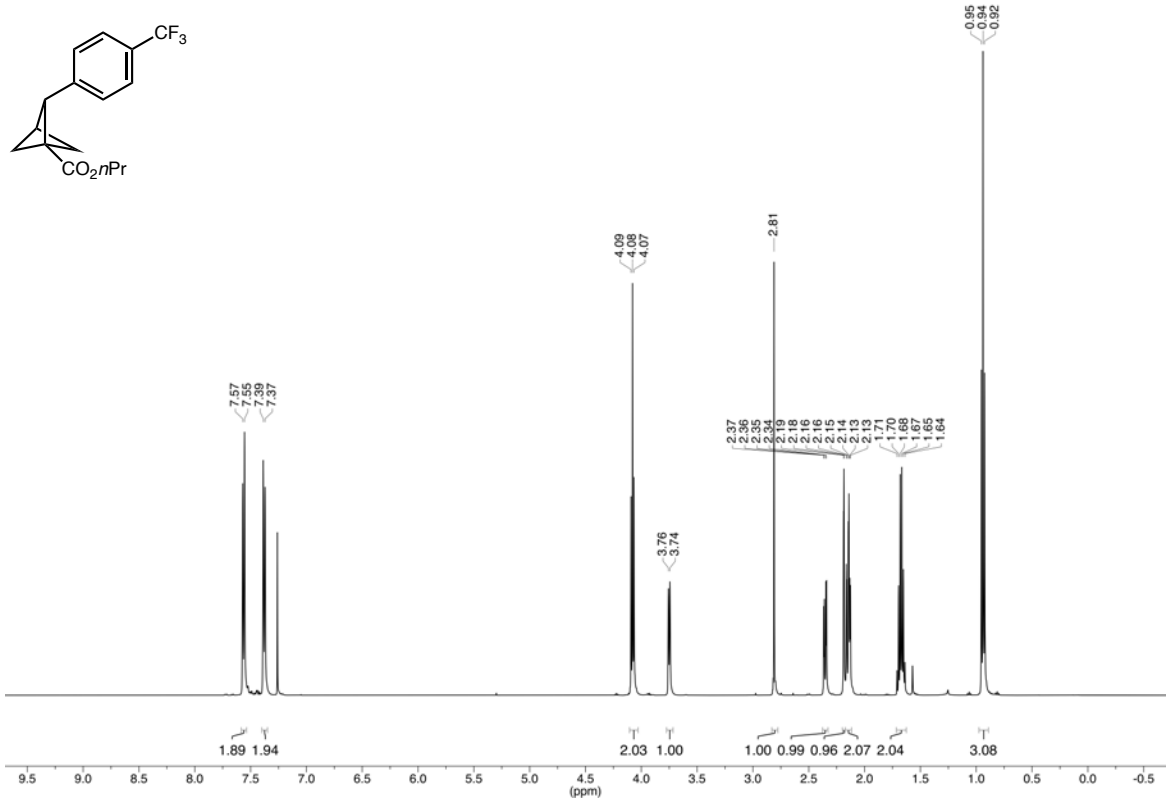
**Bis(2,2,2-trifluoroethyl) 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (14)**

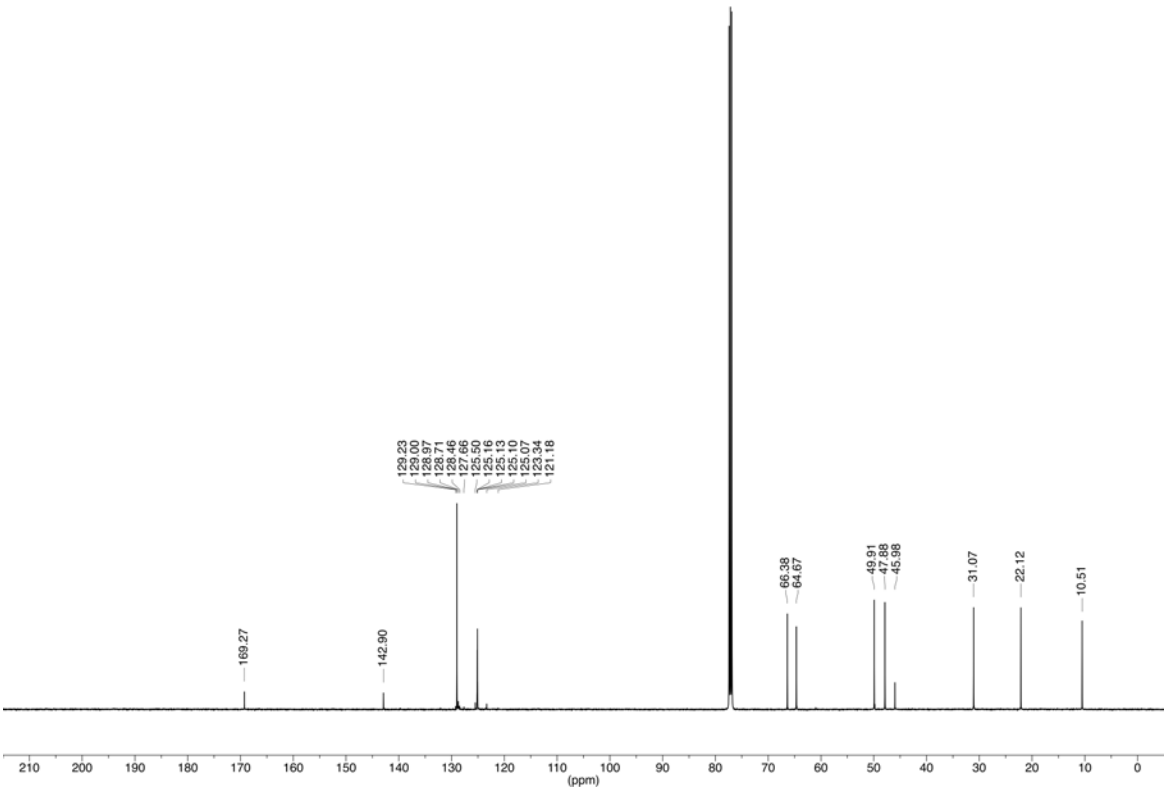


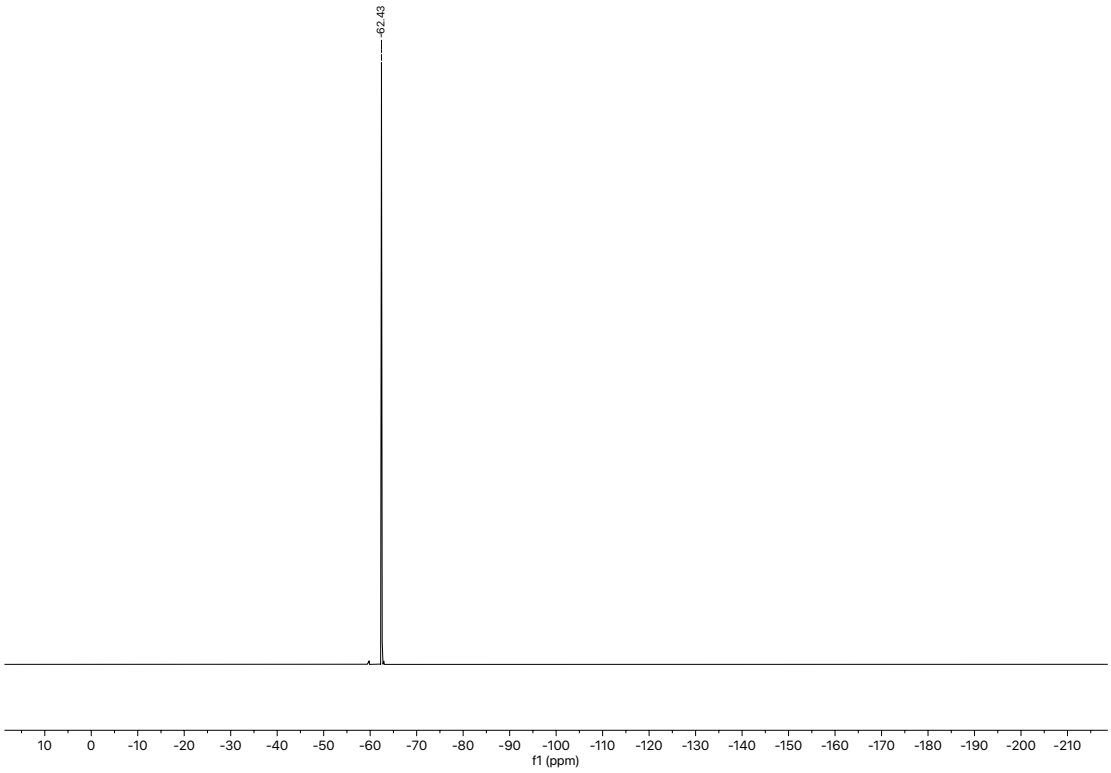





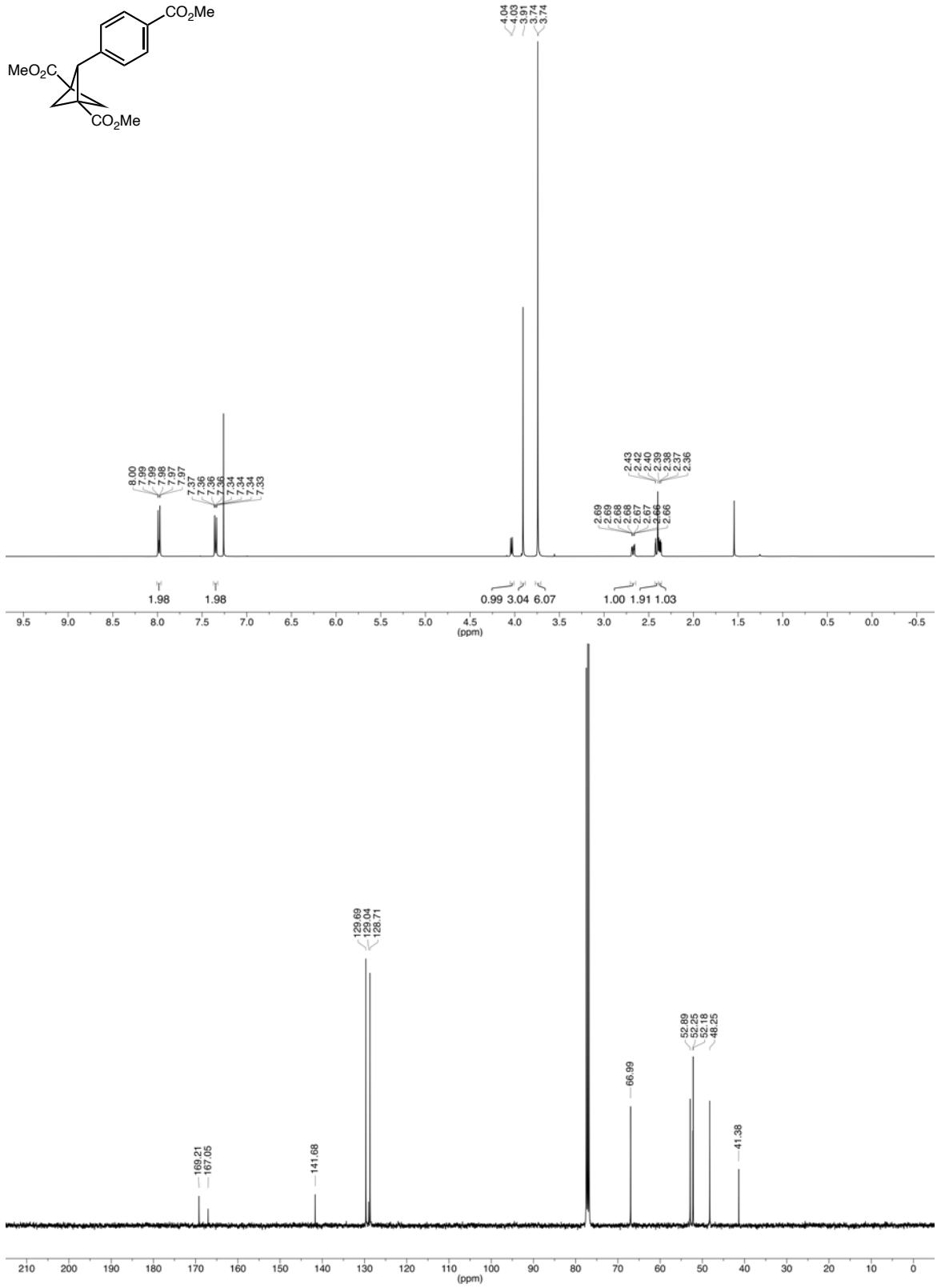

**(±)-Propyl 2-(4-(trifluoromethyl)phenyl)bicyclo[1.1.1]pentane-1-carboxylate (15)**



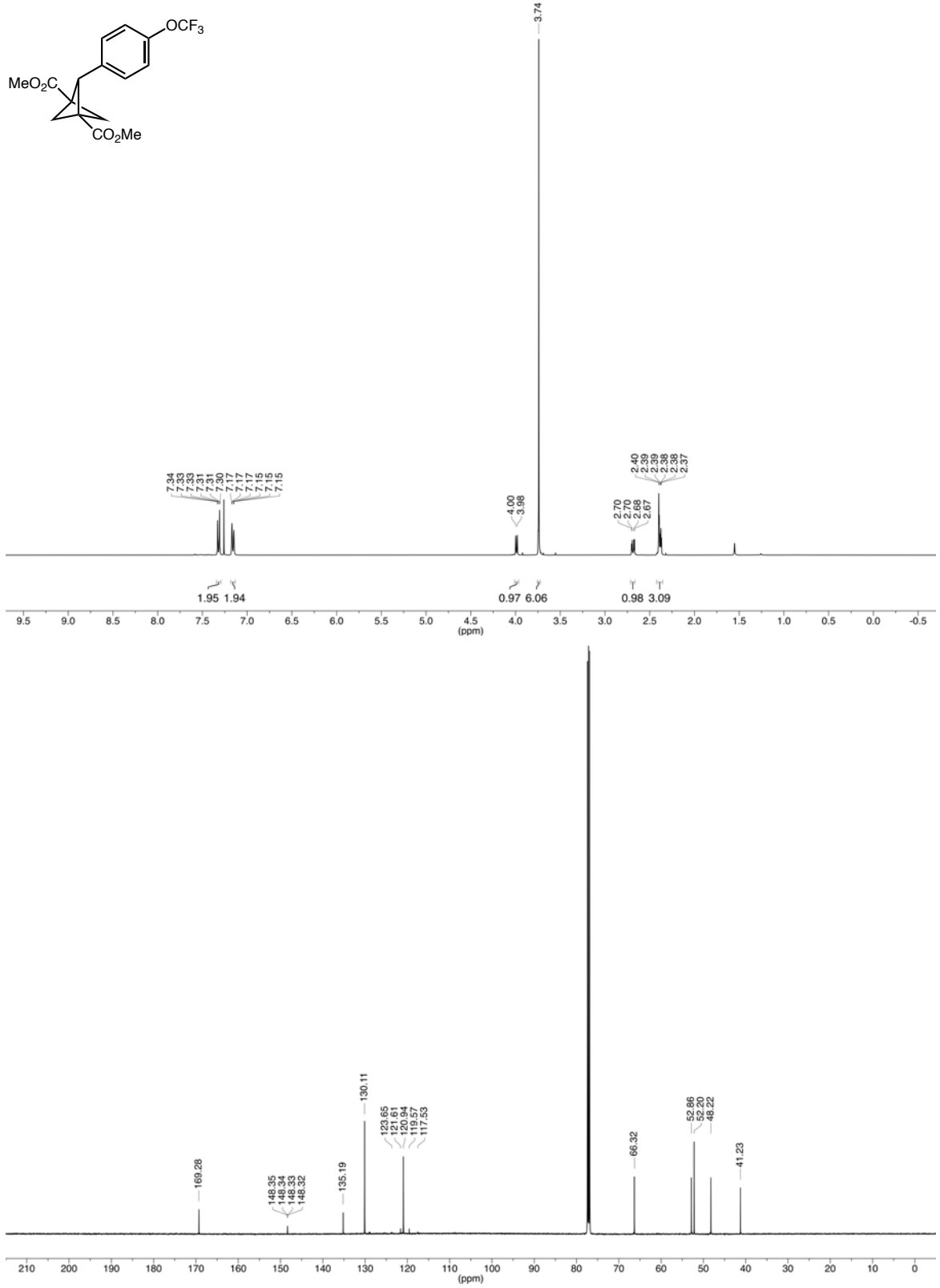

129.23
129.00
128.97
128.71
128.46
127.66
125.50
125.16
125.13
125.10
125.07
123.34
121.18
169.27
142.90
66.38
64.67
49.91
47.88
45.98
31.07
22.12
10.51
(ppm)

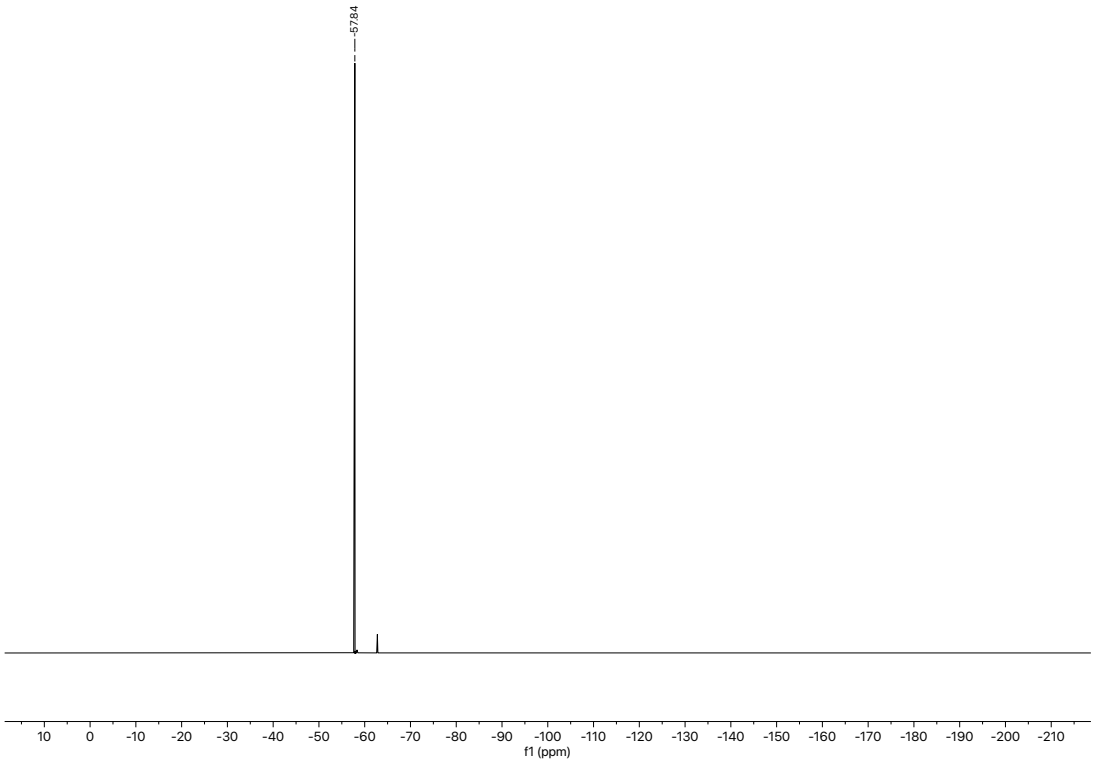

-62.43
f1 (ppm)

**Dimethyl 2-(4-(methoxycarbonyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (16)**

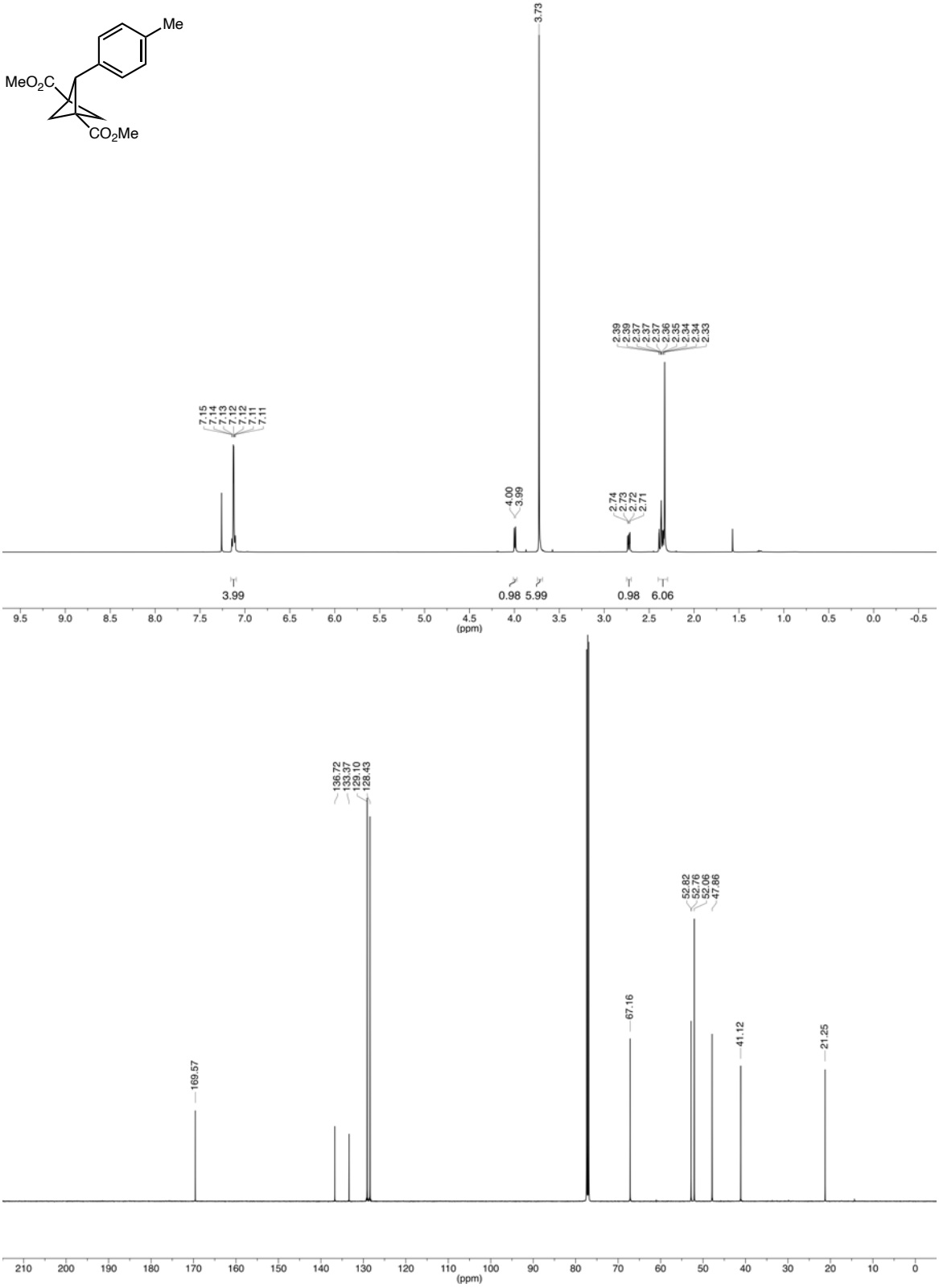


**Dimethyl 2-(4-(trifluoromethoxy)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (17)**

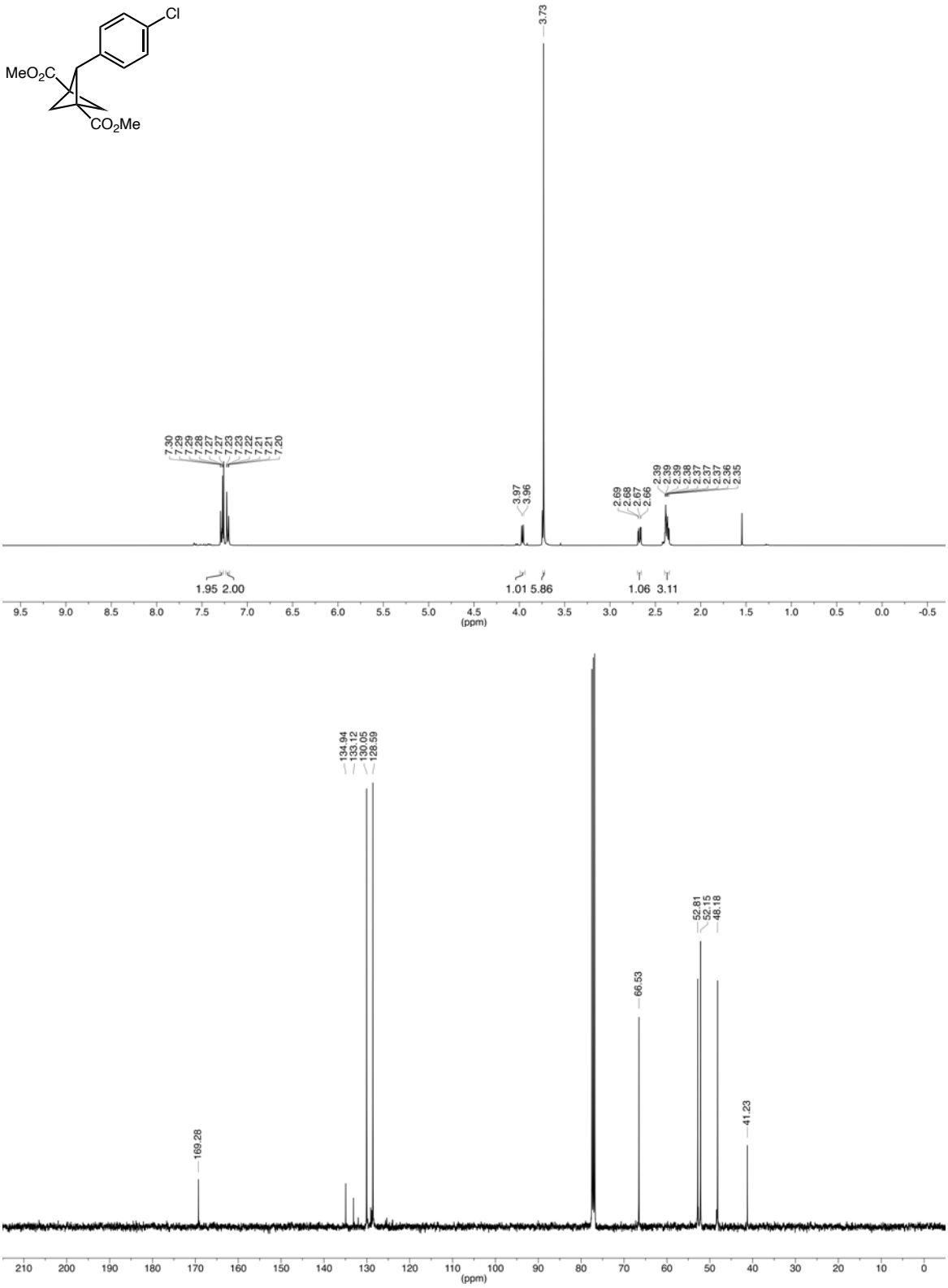



-57.84
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

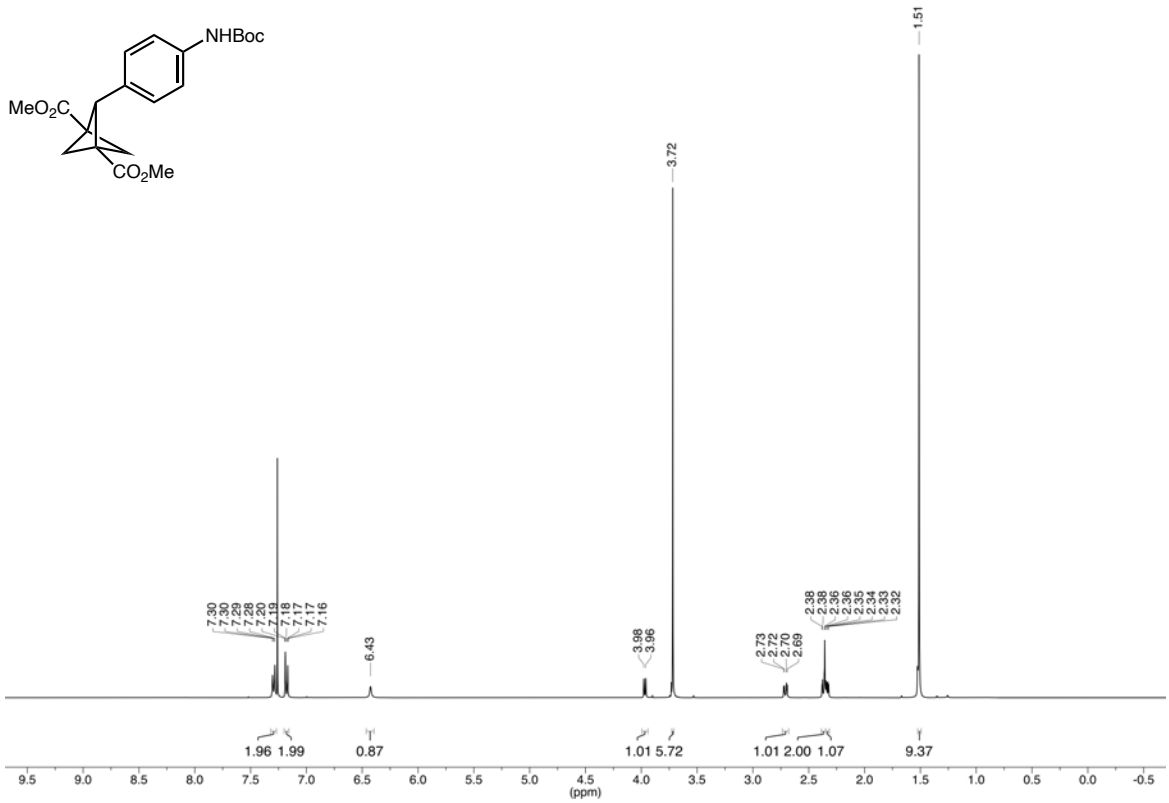
**Dimethyl 2-(*p*-tolyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (18)**

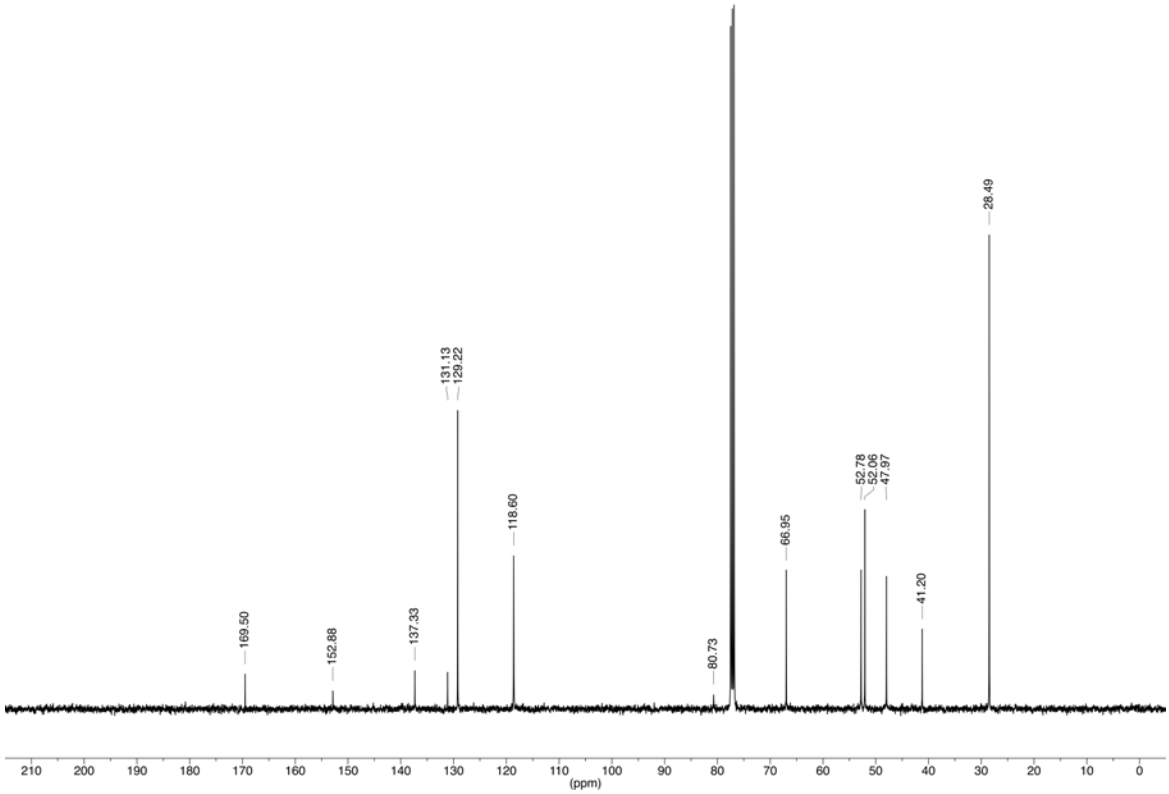


**Dimethyl 2-(4-chlorophenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (19)**

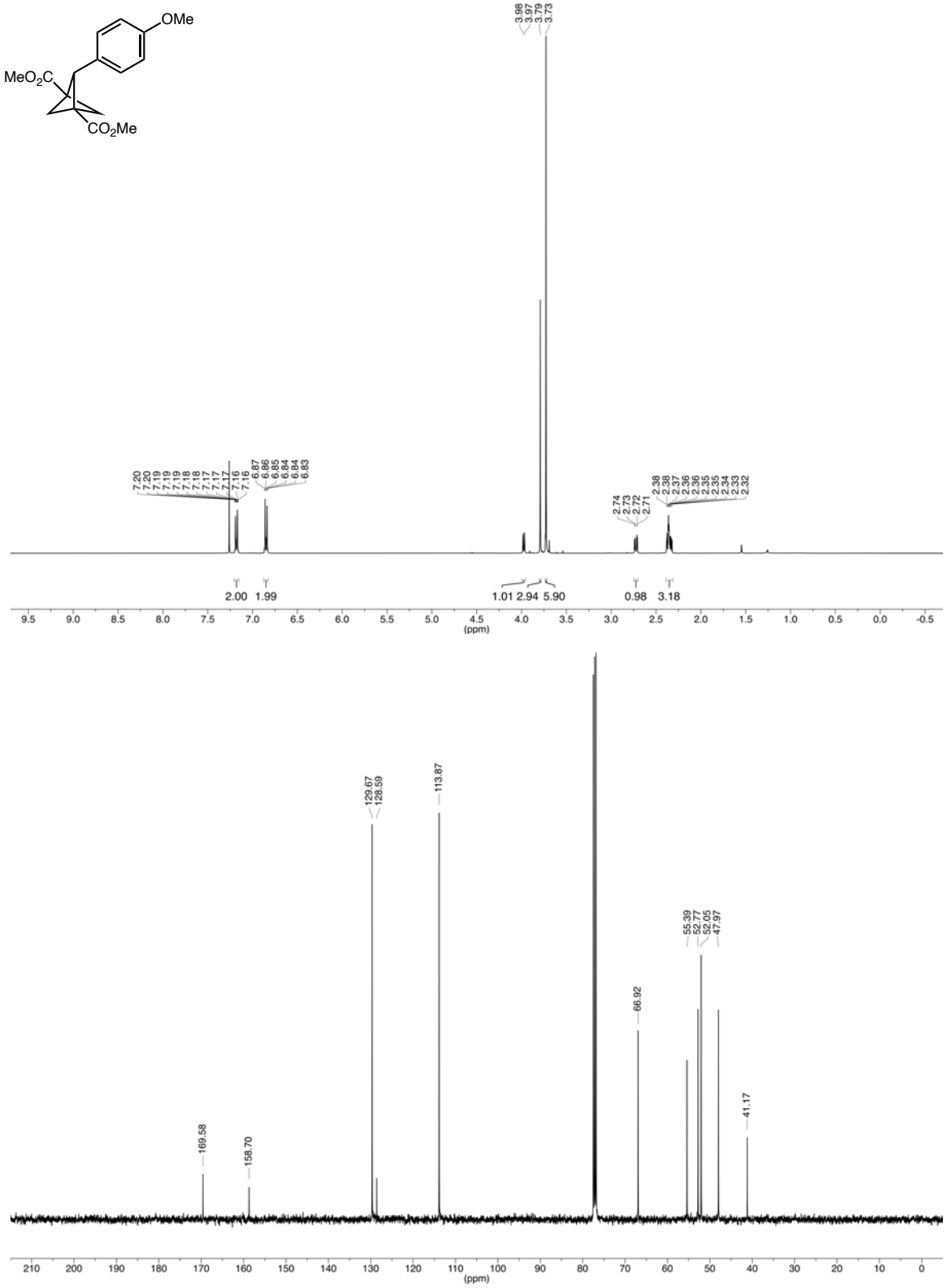


**Dimethyl 2-(4-((*tert*-butoxycarbonyl)amino)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (20)**

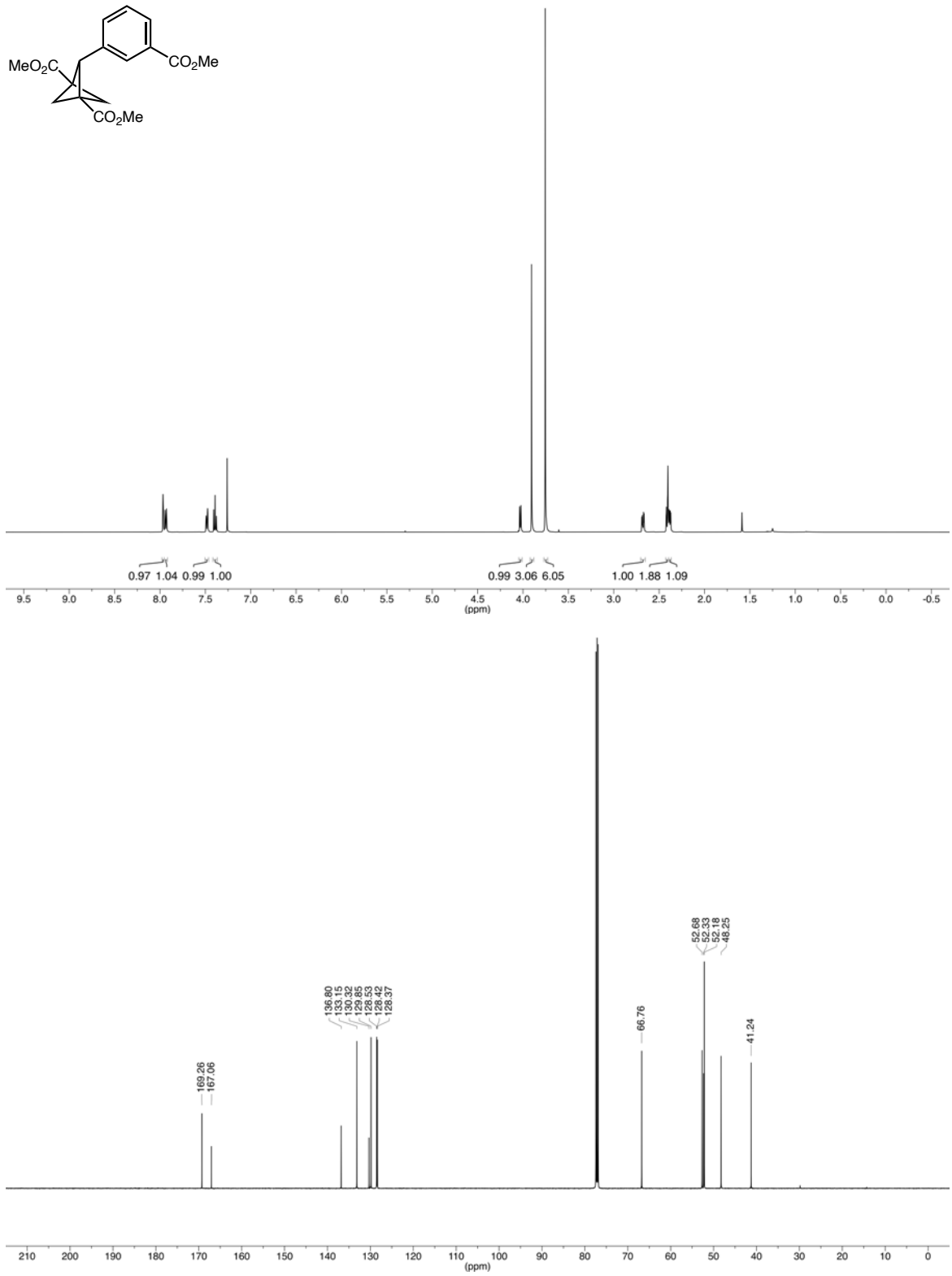


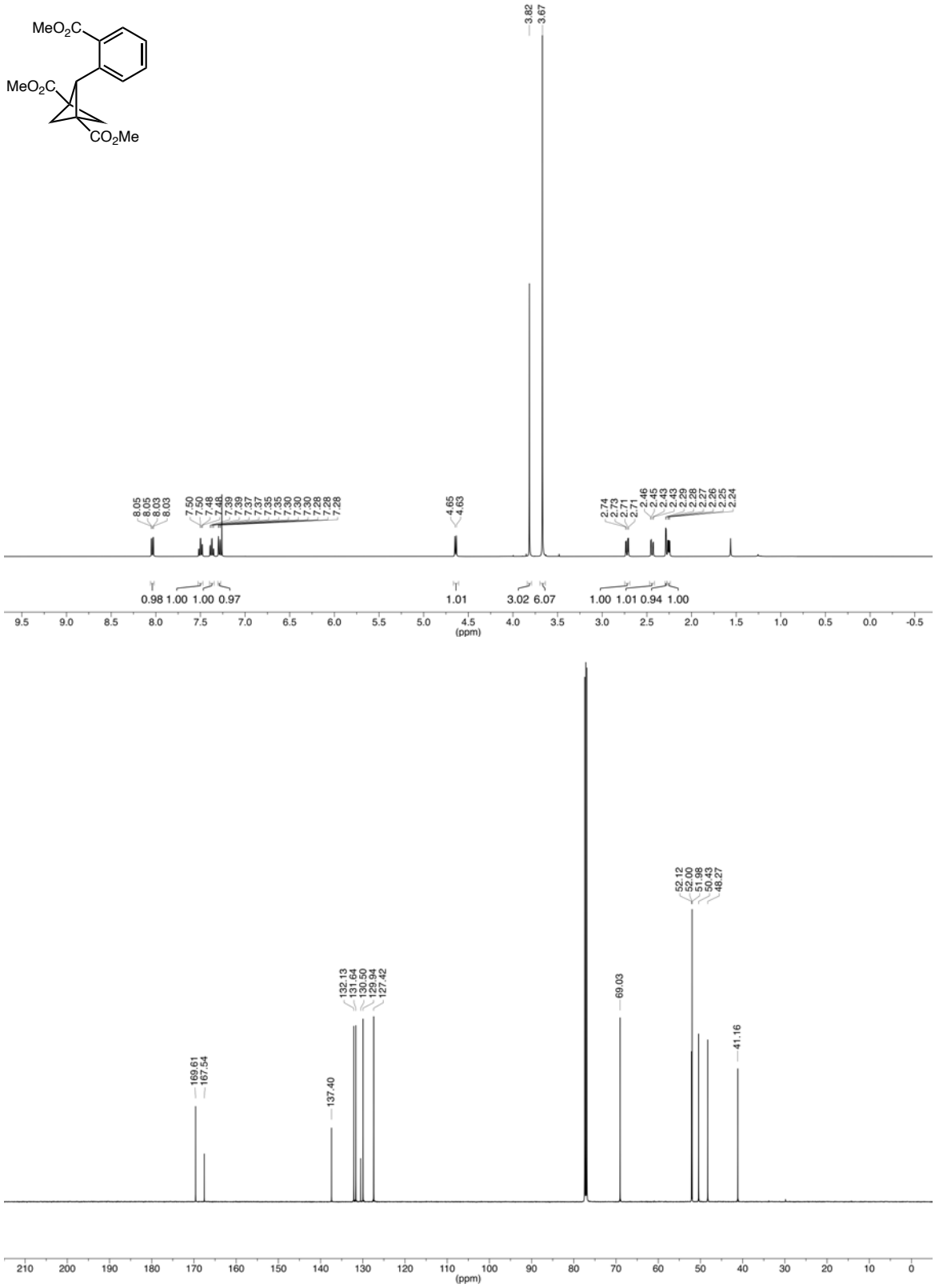
**Dimethyl 2-(4-methoxyphenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (21)**



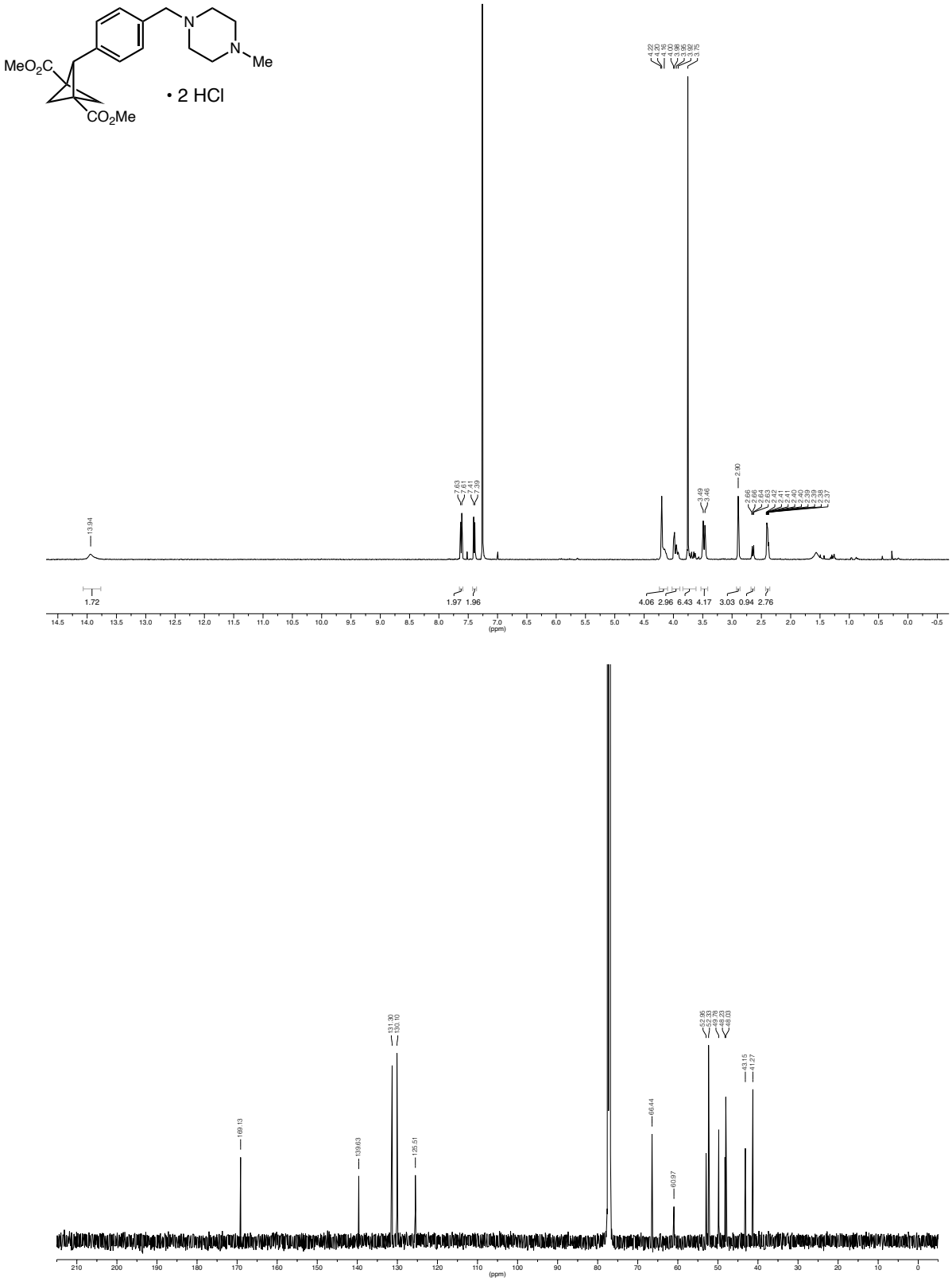
**Dimethyl 2-(3-(methoxycarbonyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (22)**



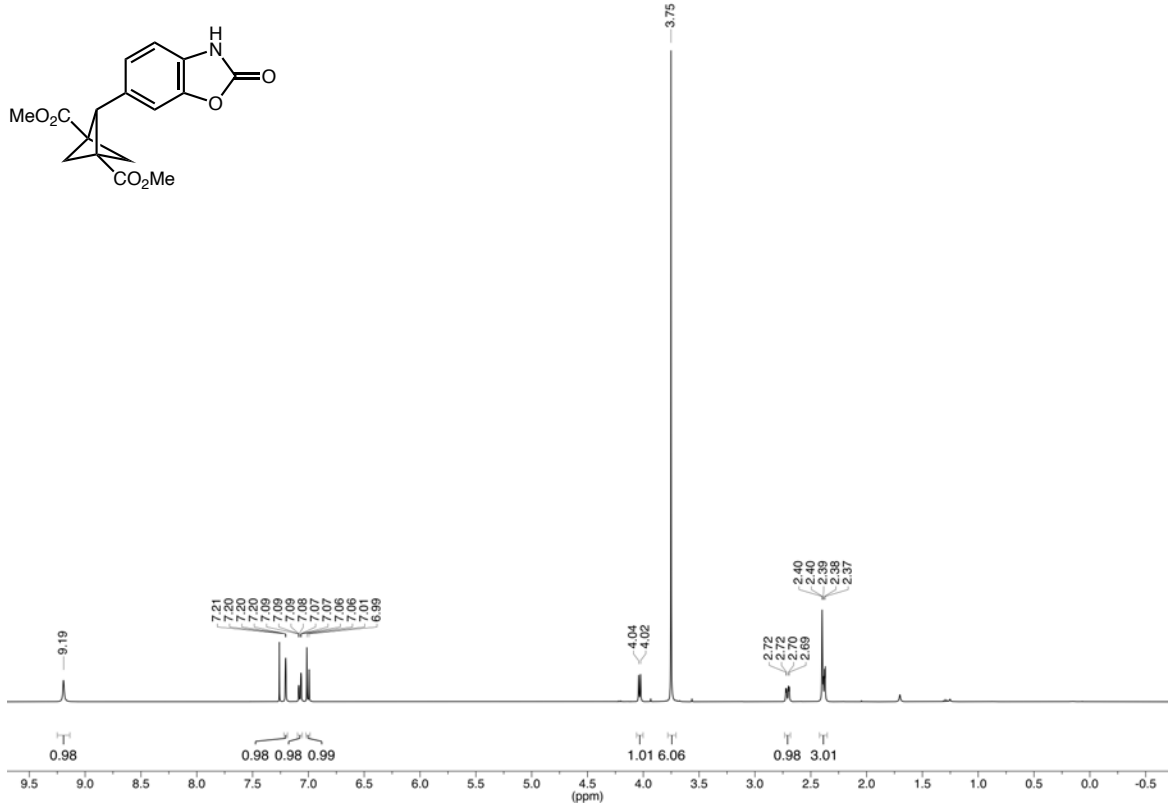
**Dimethyl 2-(2-(methoxycarbonyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (23)**

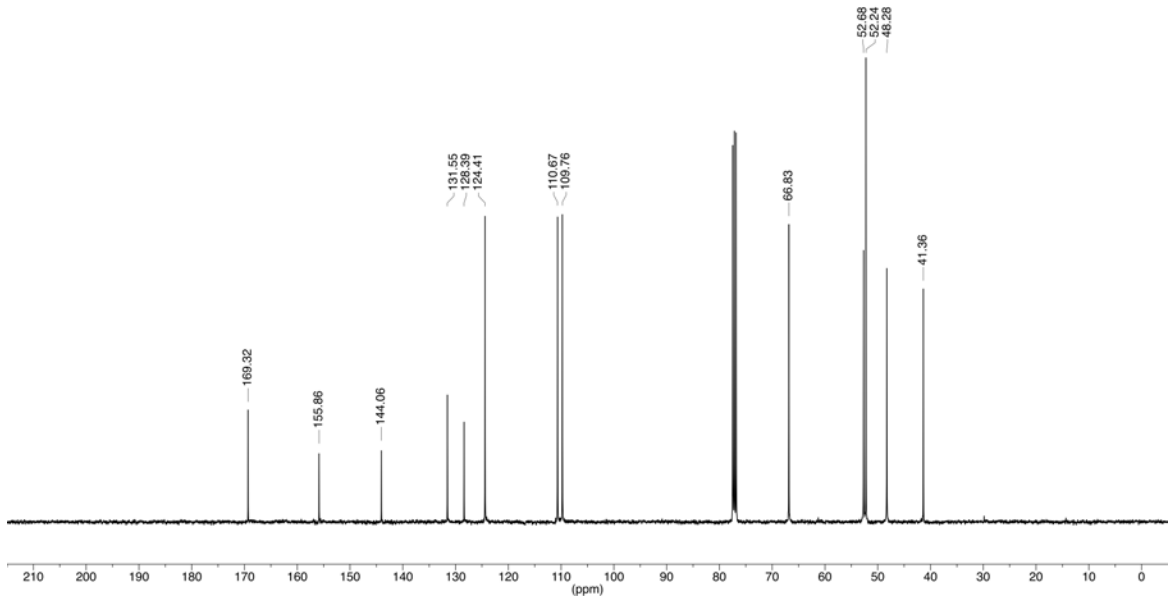


**Dimethyl 2-(4-((4-methylpiperazin-1-yl)methyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate dihydrochloride (24)**

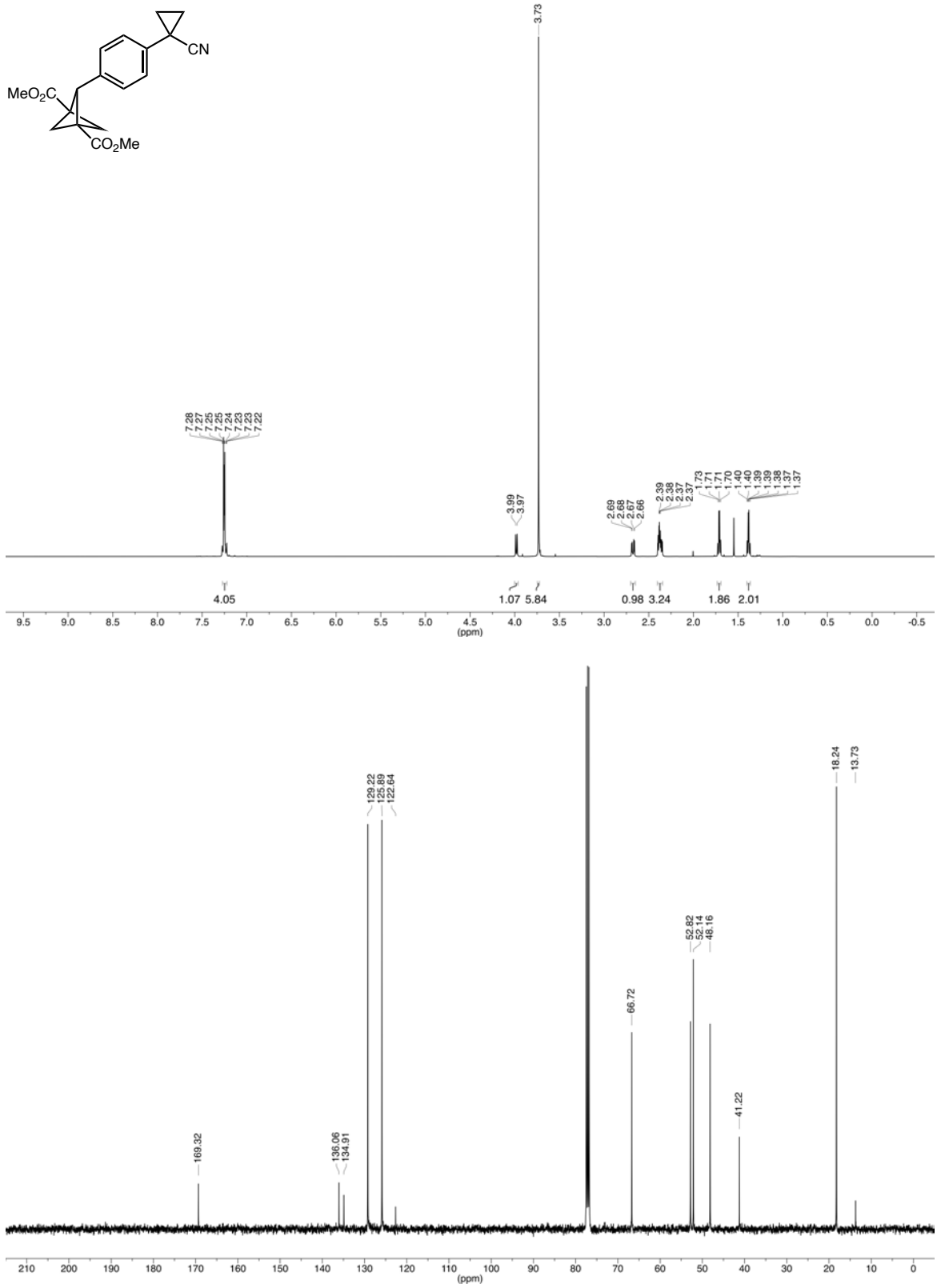


**Dimethyl 2-(2-oxo-2,3-dihydrobenzo[d]oxazol-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (25)**

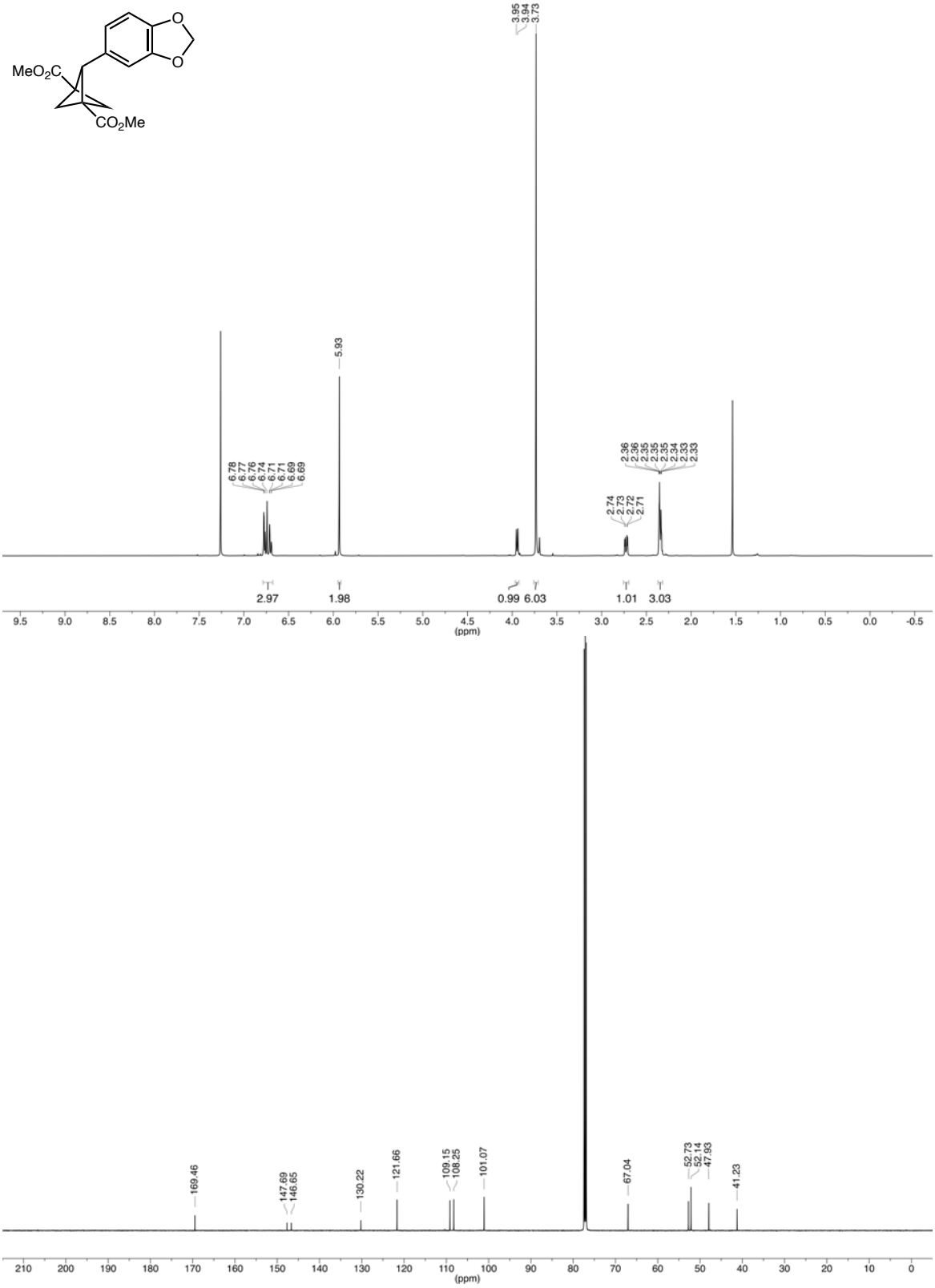


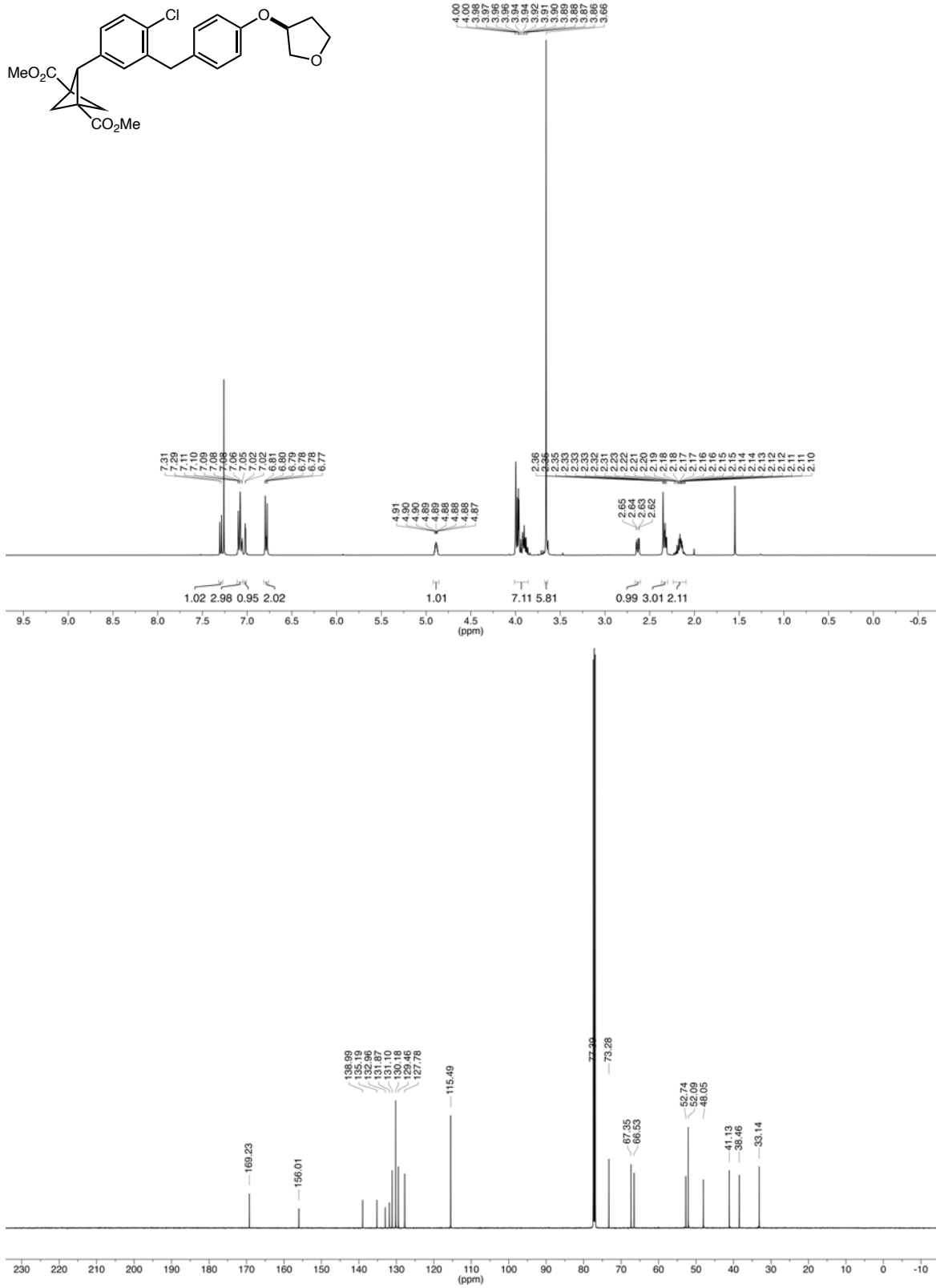
**Dimethyl 2-(4-(1-cyanocyclopropyl)phenyl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (26)**



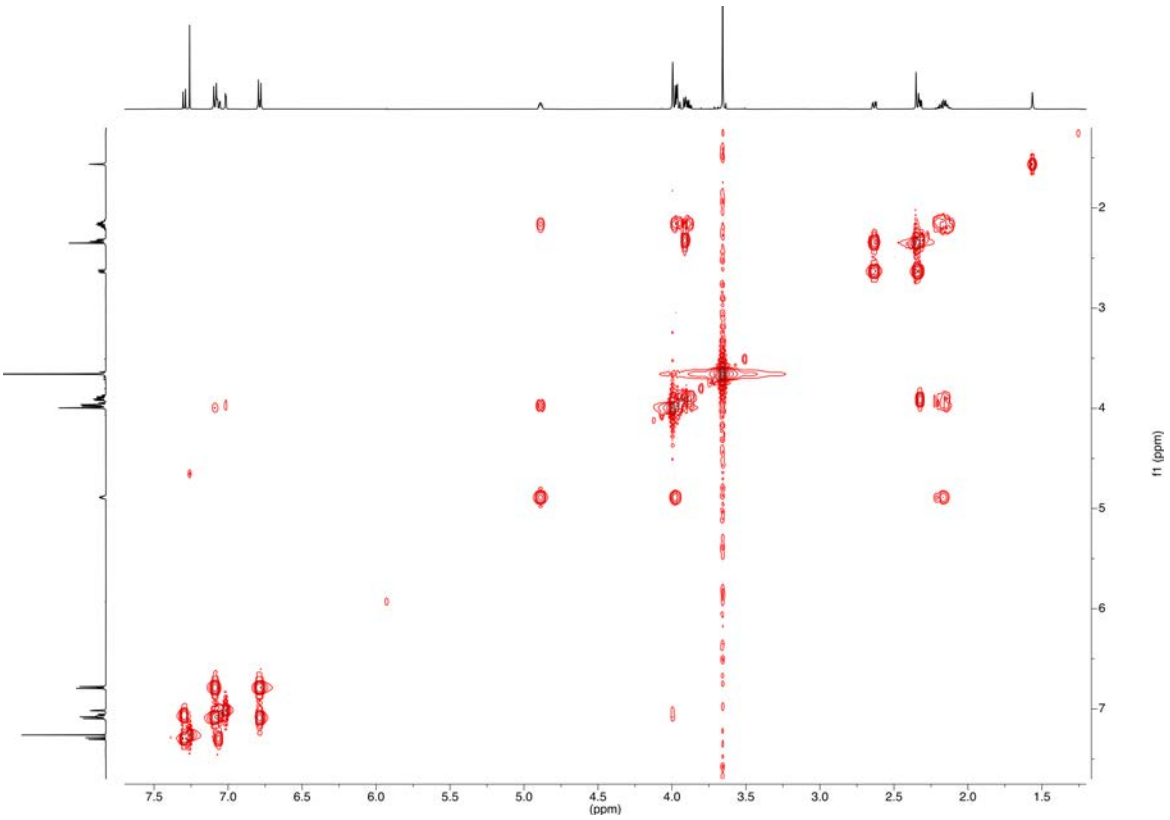
**Dimethyl 2-(benzo[*d*][1,3]dioxol-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (S7)**



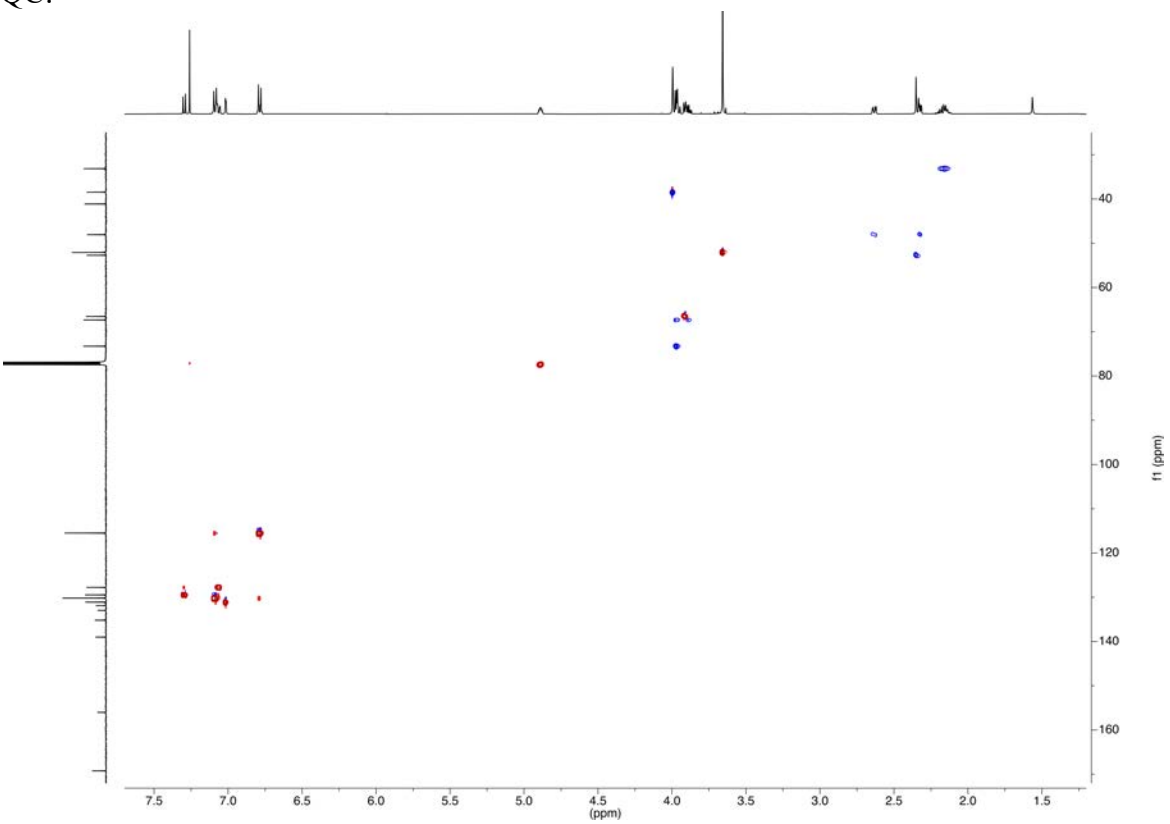
**rac-Dimethyl (S)-2-(4-chloro-3-(4-((tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-bicyclo[1.1.1]pentane-1,3-dicarboxylate (27)**



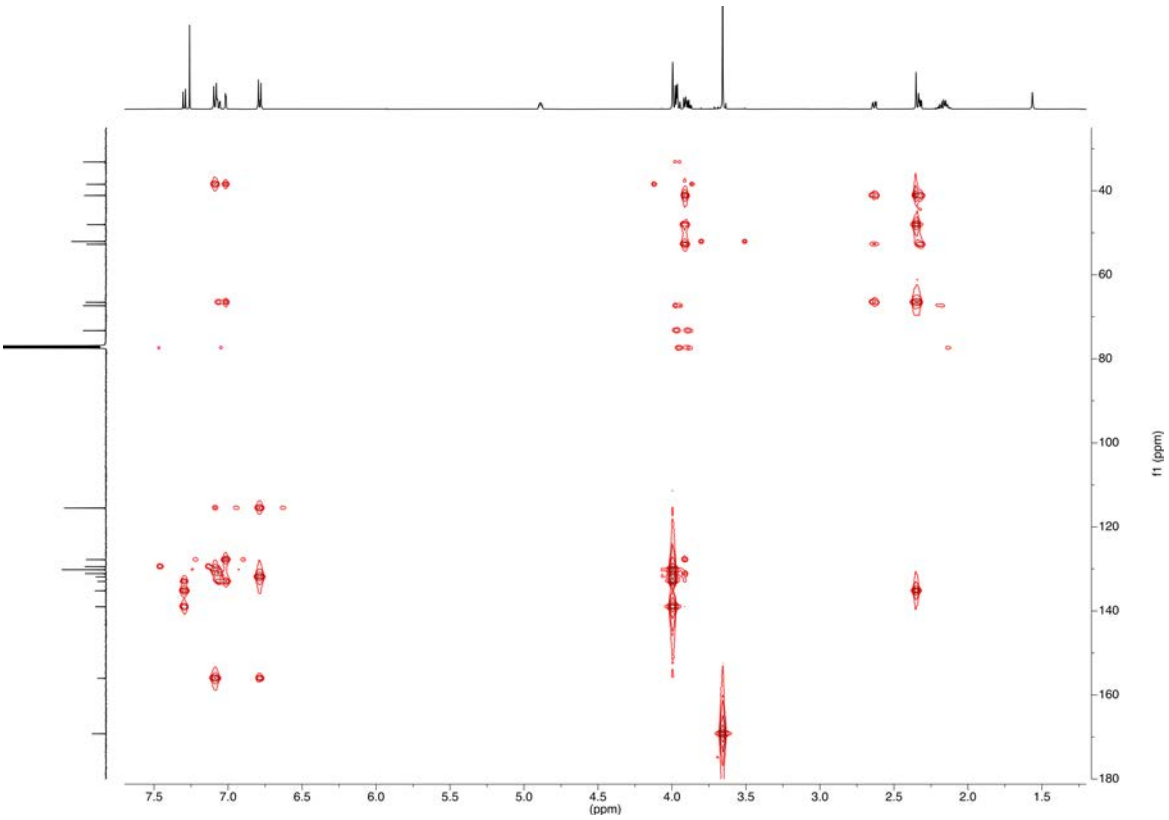
COSY:


7.5
7.0
6.5
6.0
5.5
5.0
4.5
(ppm)
4.0
3.5
3.0
2.5
2.0
1.5
2
3
4
5
6
7
f1 (ppm)

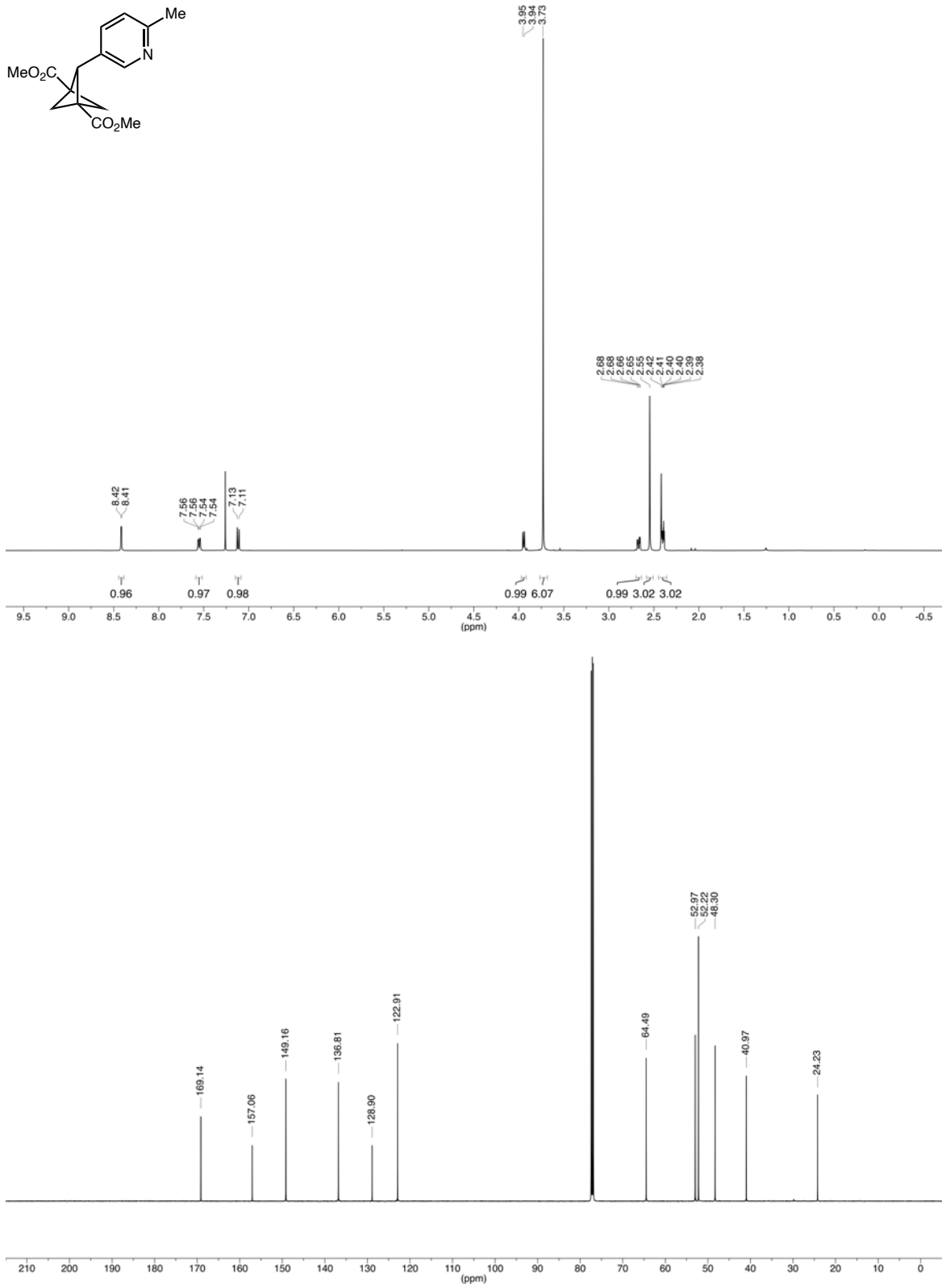
HSQC:


7.5
7.0
6.5
6.0
5.5
5.0
4.5
(ppm)
4.0
3.5
3.0
2.5
2.0
1.5
40
60
80
100
120
140
160
f1 (ppm)

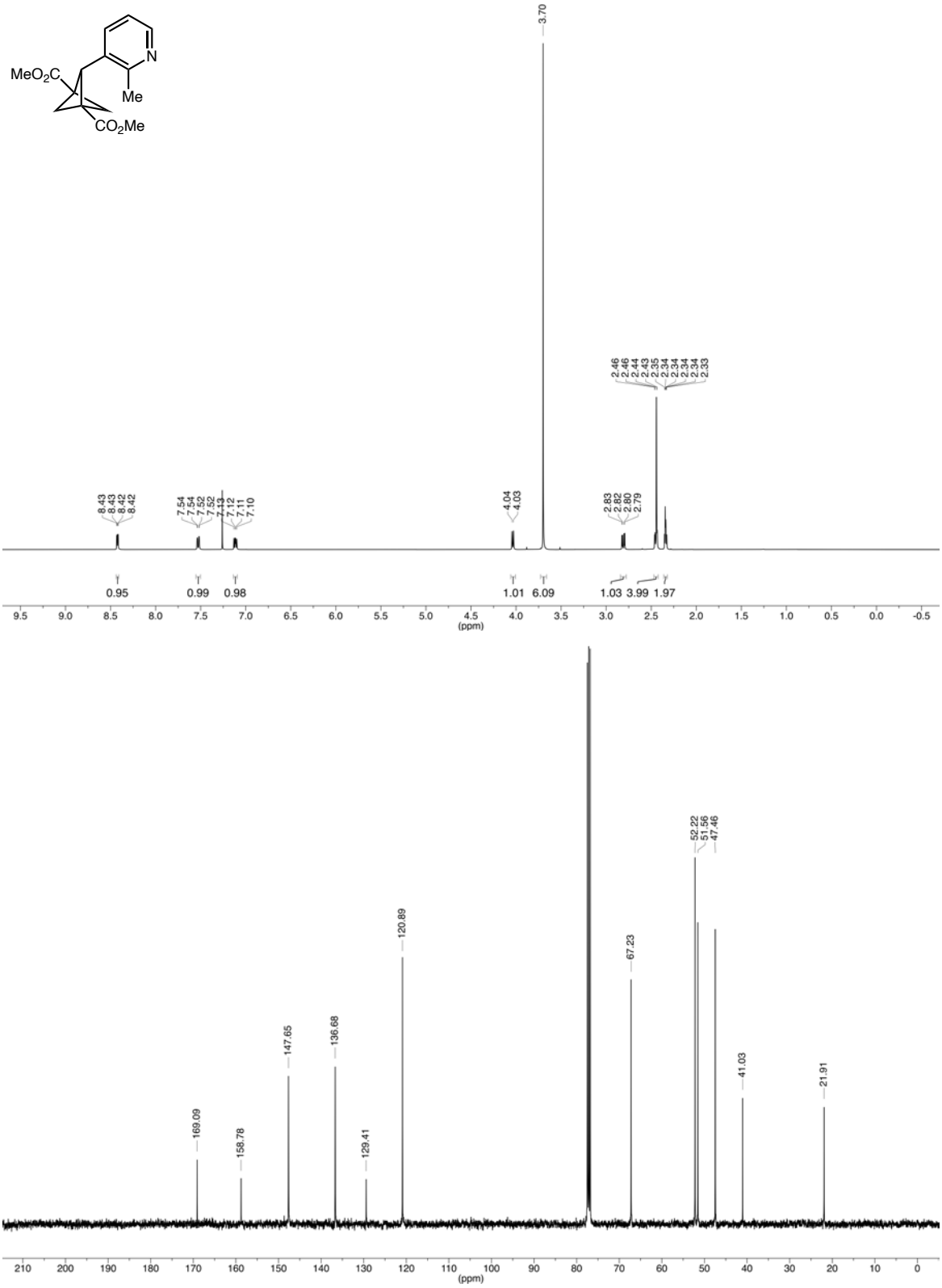
HMBC:


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)
40
60
80
100
120
140
160
180
f1 (ppm)

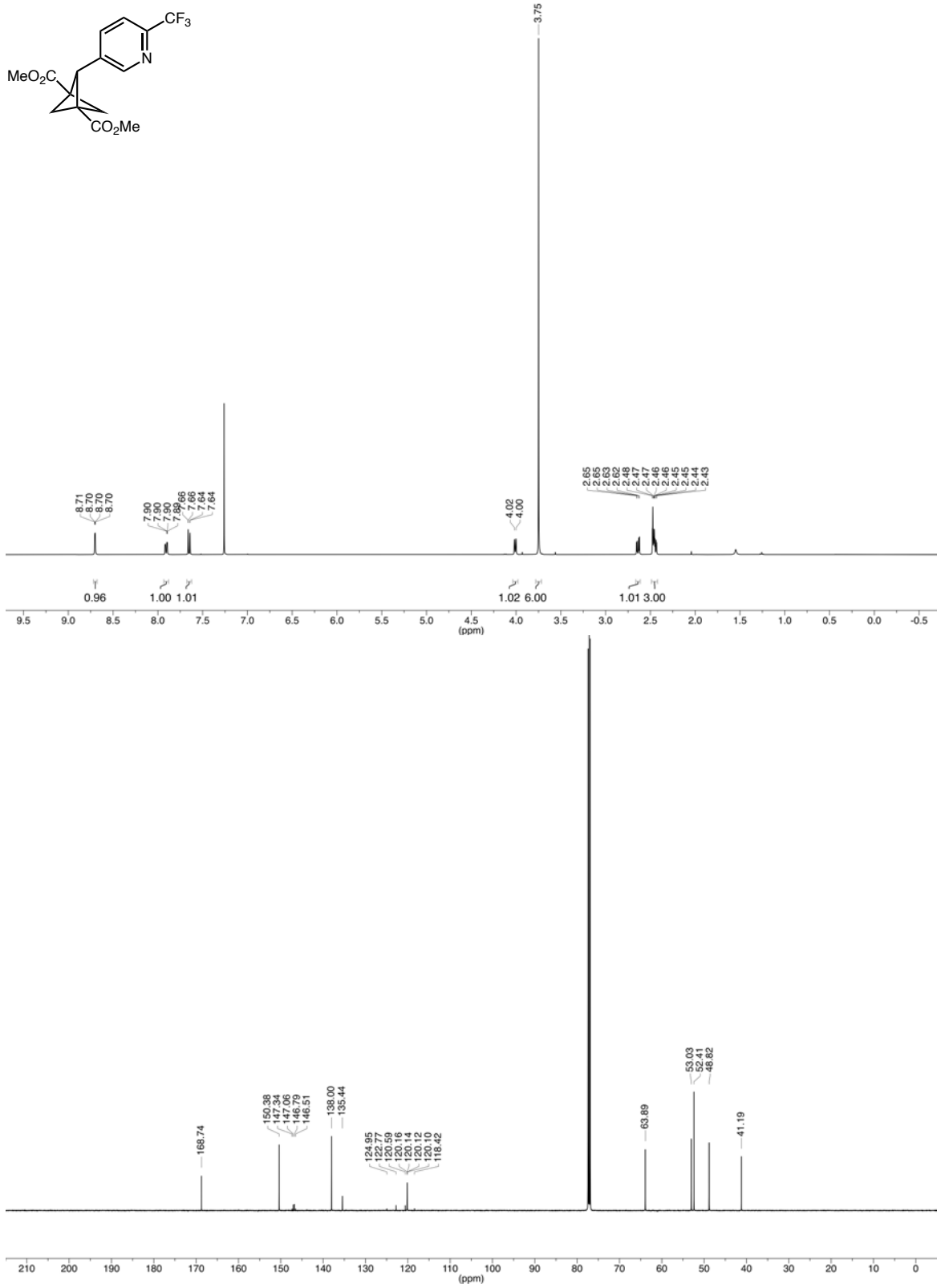
**Dimethyl 2-(6-methylpyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (28)**

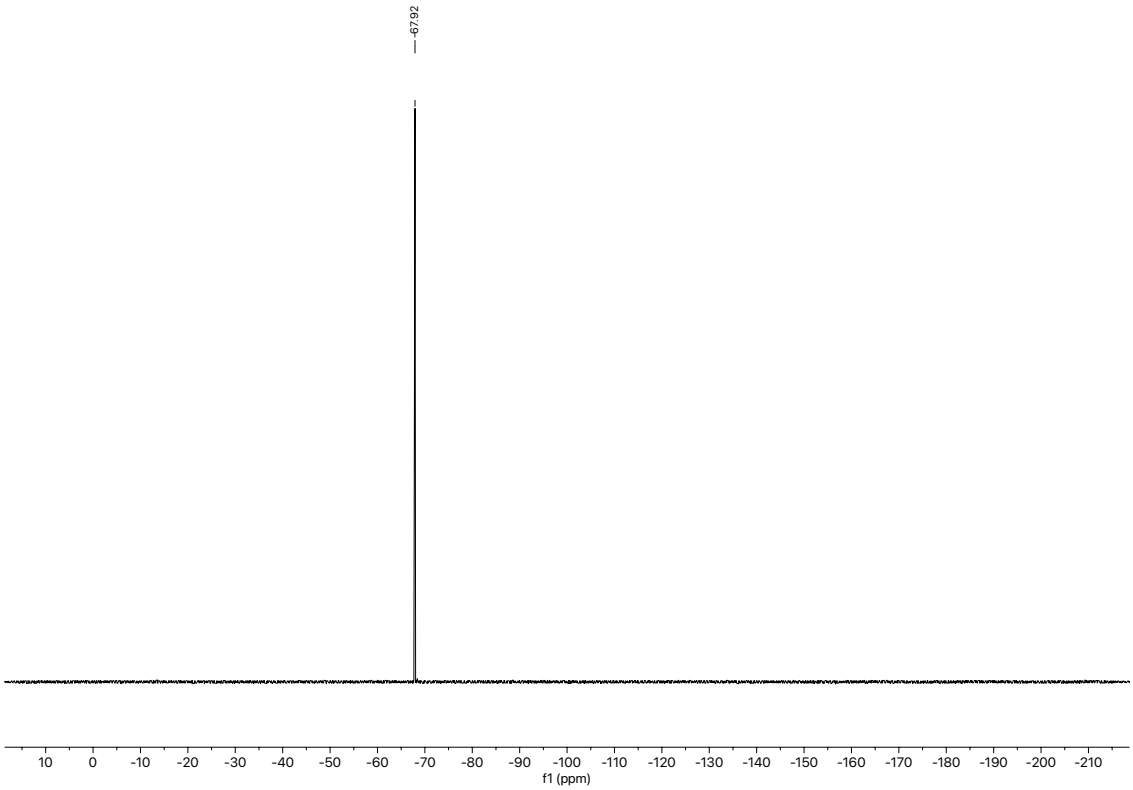


**Dimethyl 2-(2-methylpyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (29)**

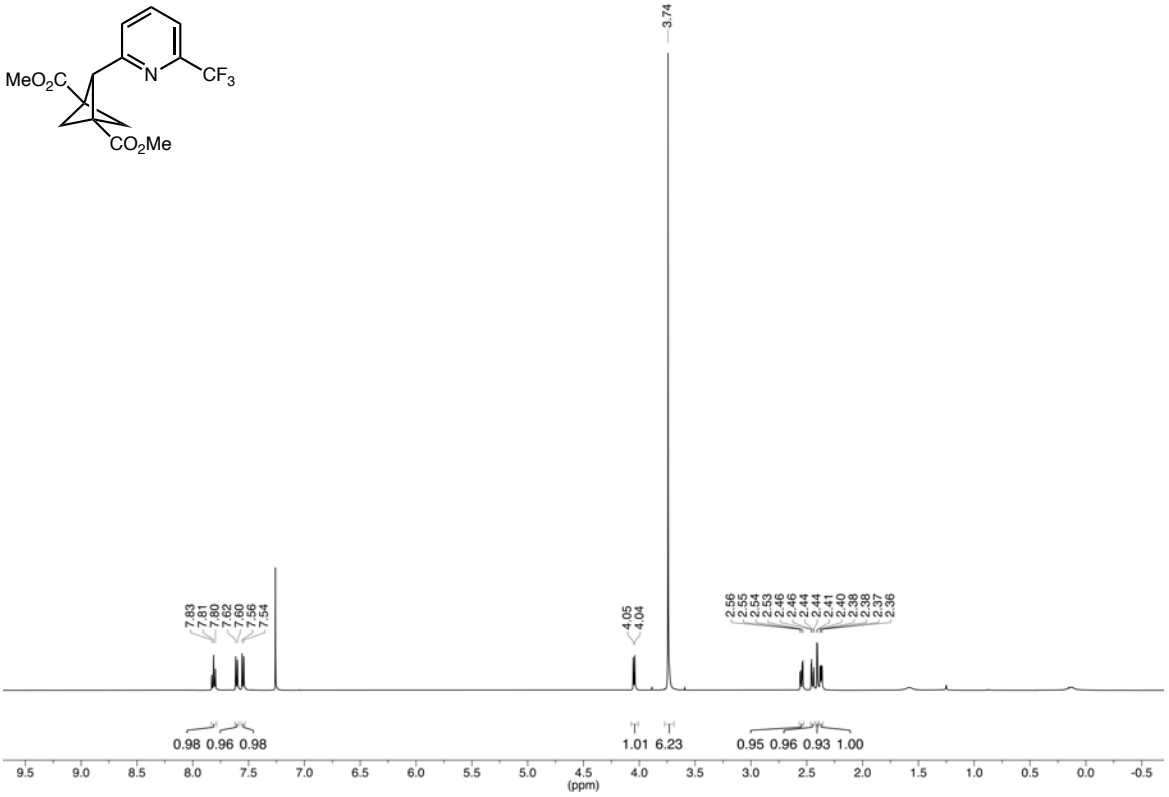


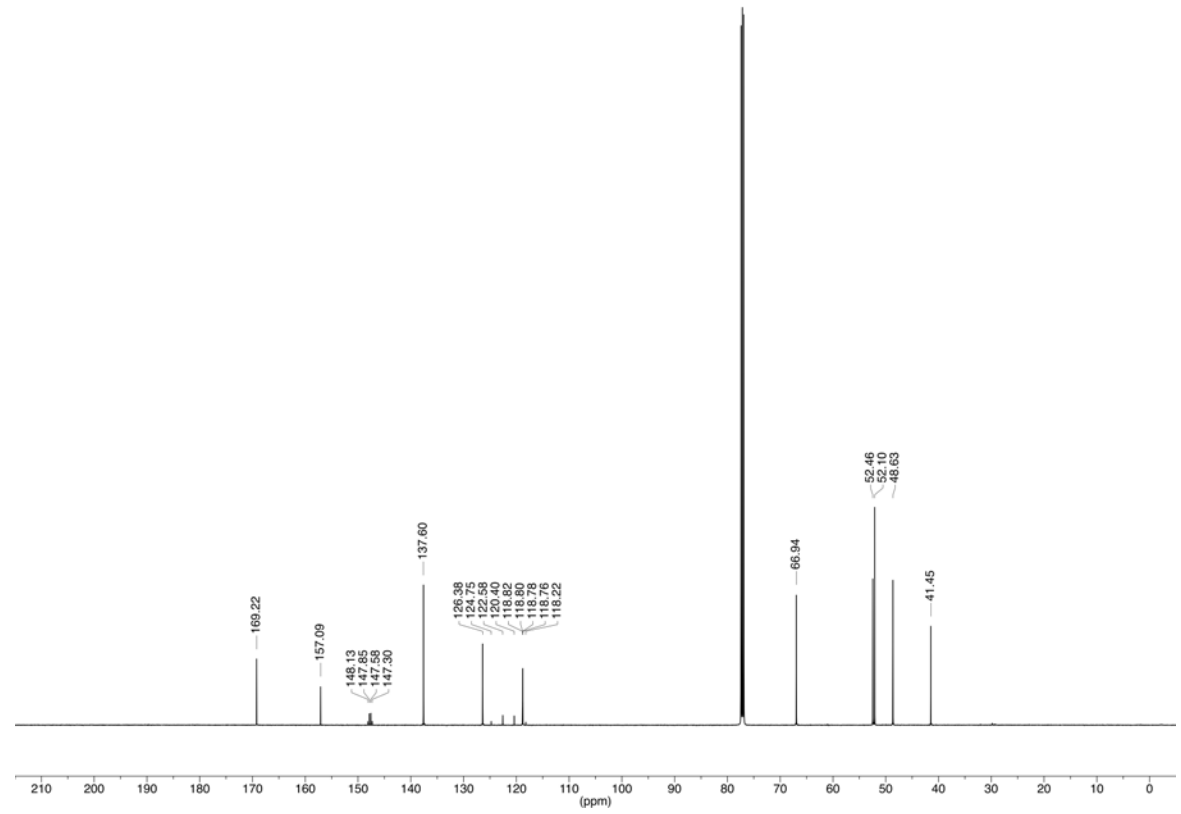
**Dimethyl 2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (30)**

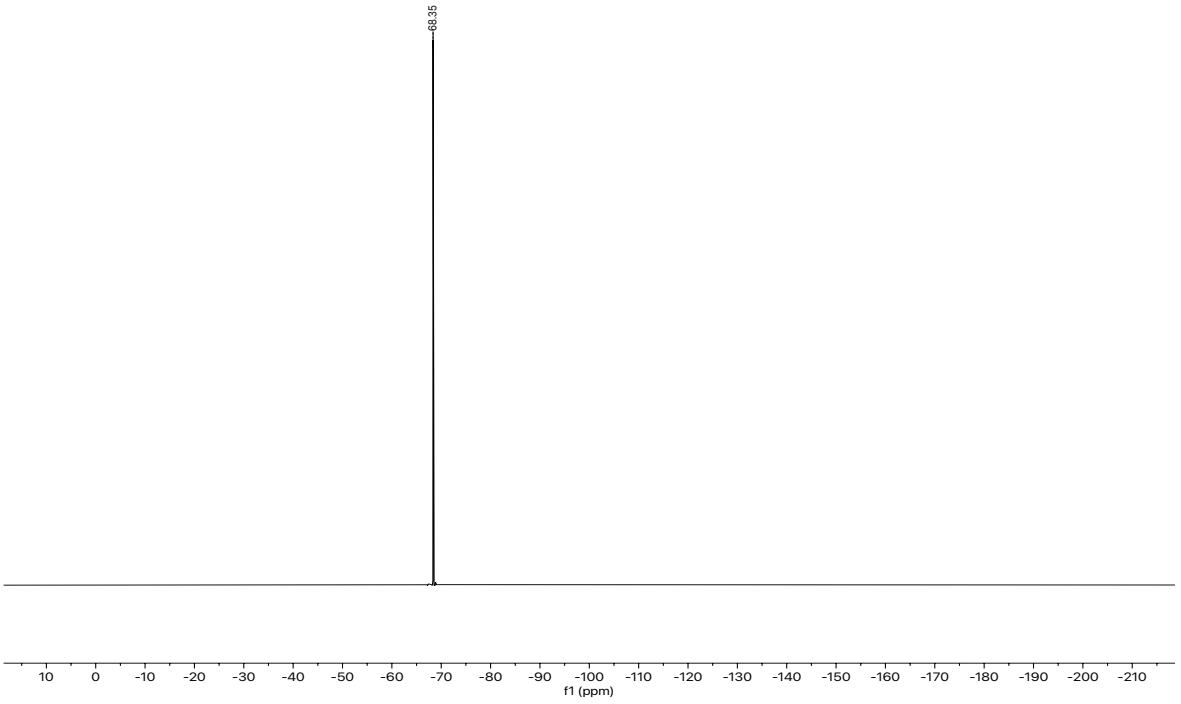




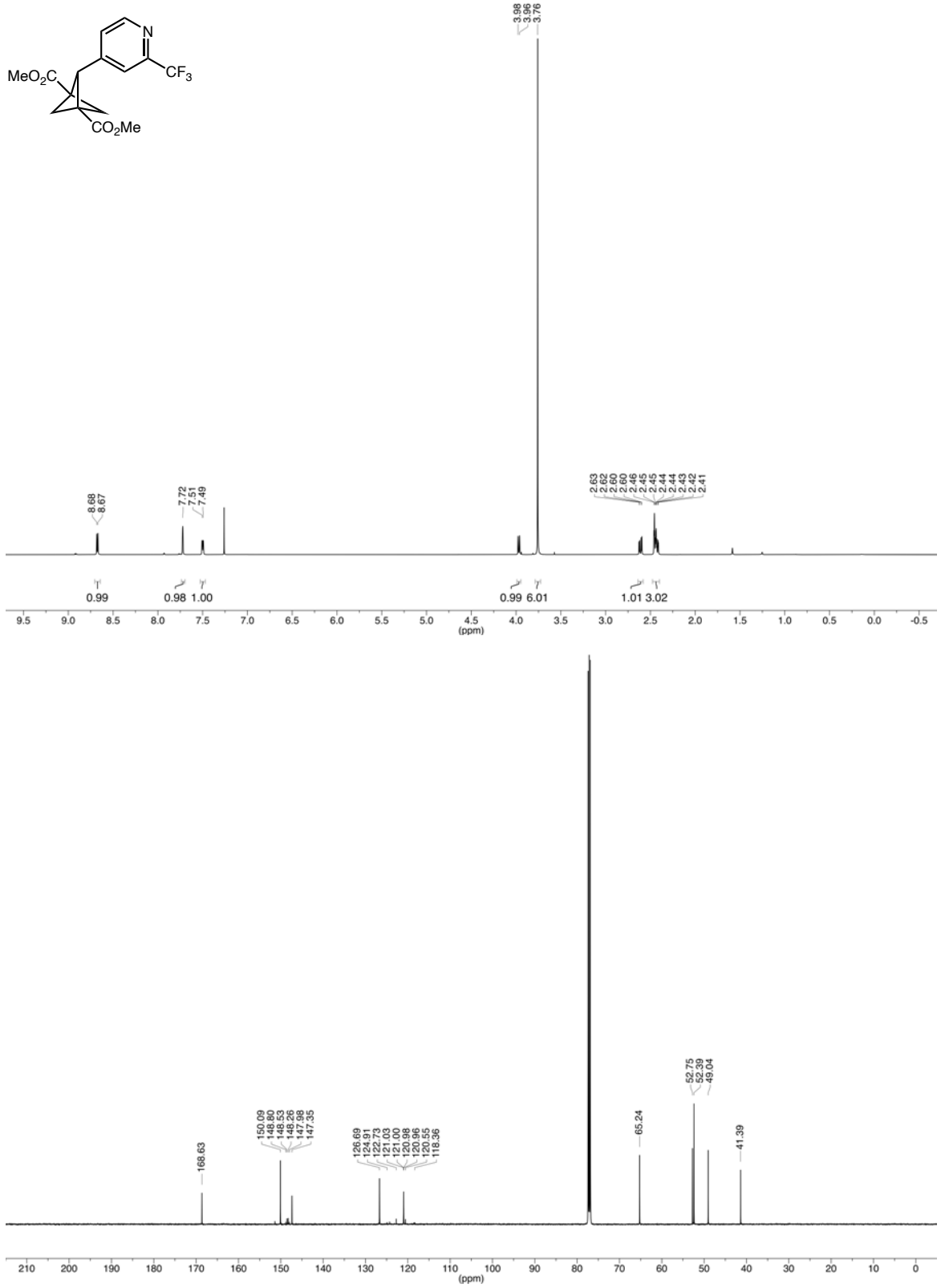

**Dimethyl 2-(6-(trifluoromethyl)pyridin-2-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (31)**

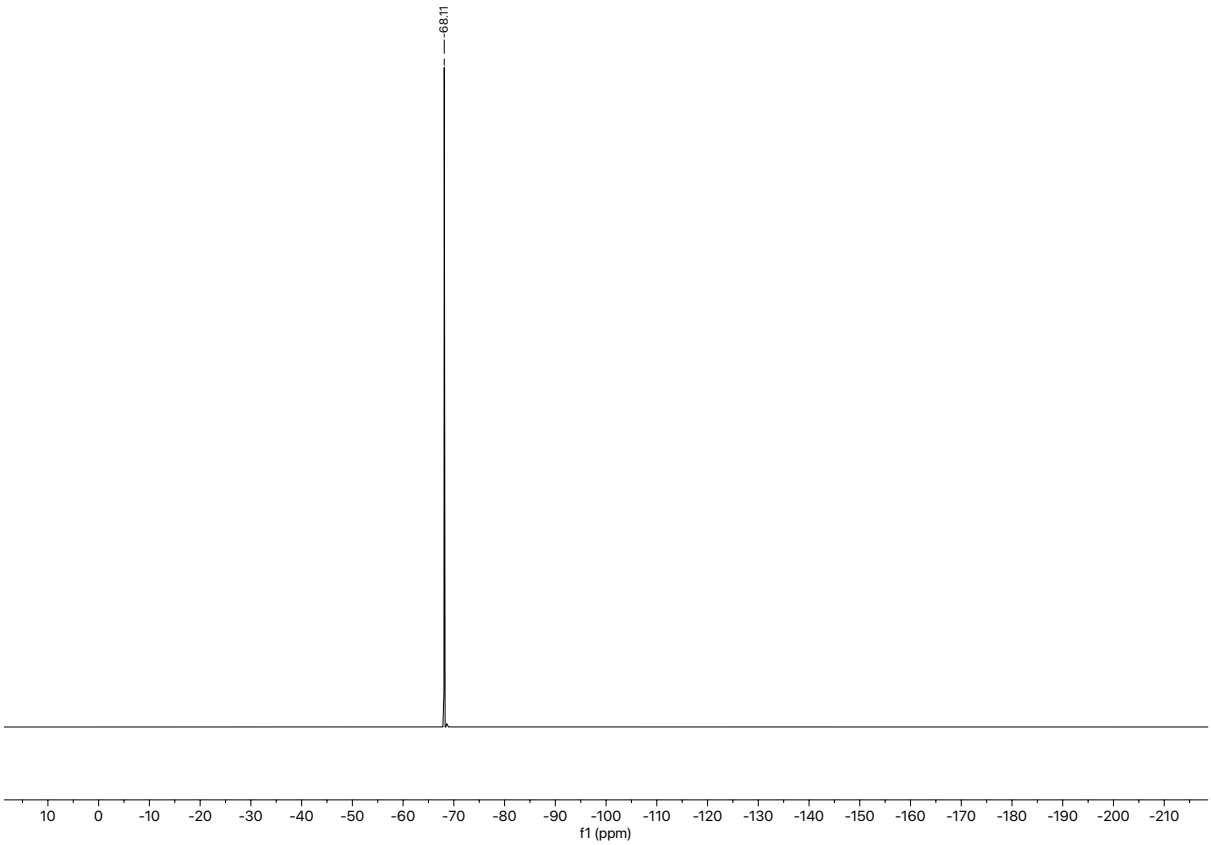



169.22
157.09
148.13
147.85
147.58
147.30
137.60
126.38
124.75
122.58
120.40
118.82
118.60
118.38
118.76
118.22
66.94
52.46
52.10
48.63
41.45
(ppm)

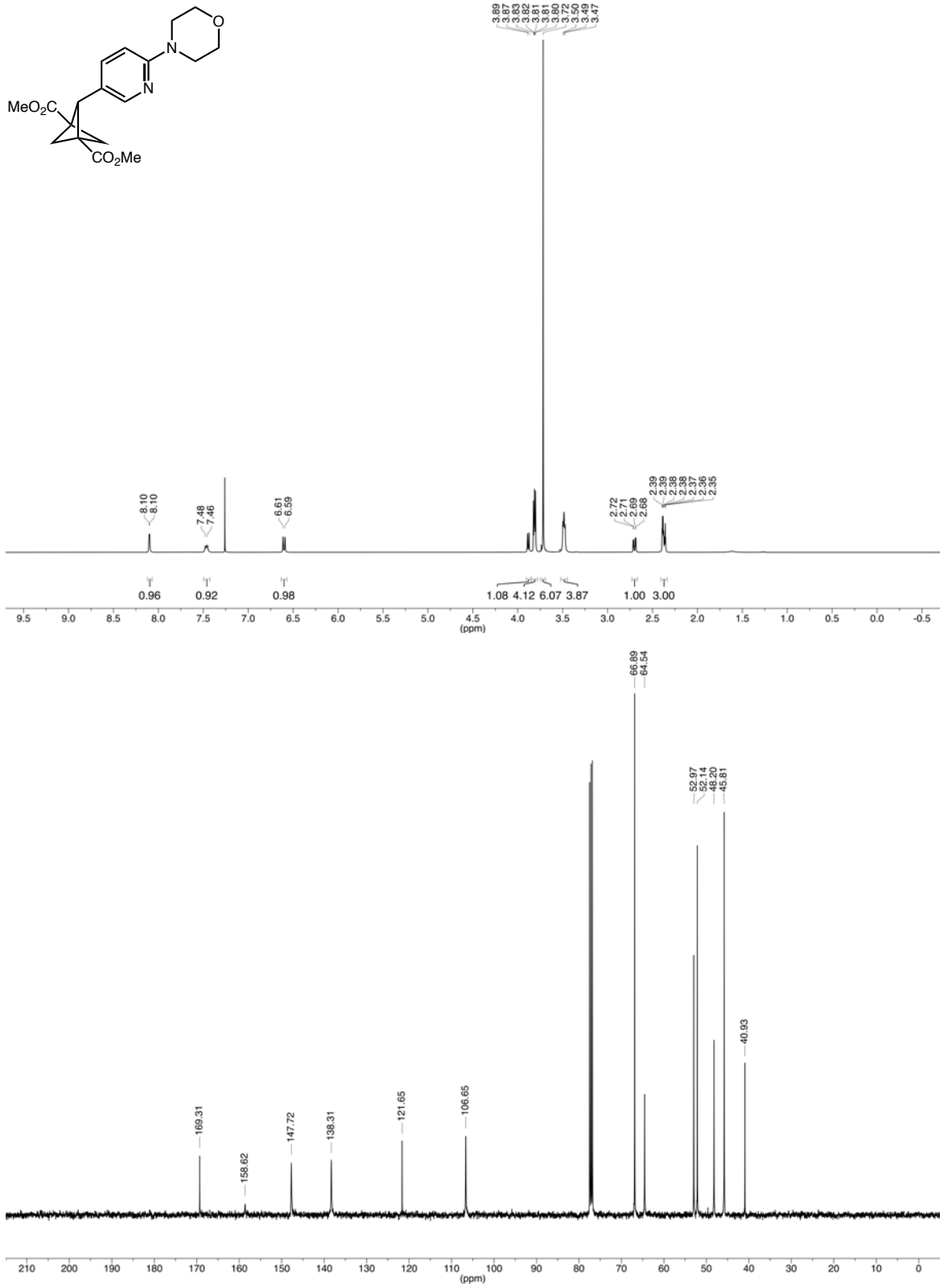

68.35
f1 (ppm)

**Dimethyl 2-(2-(trifluoromethyl)pyridin-4-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (32)**

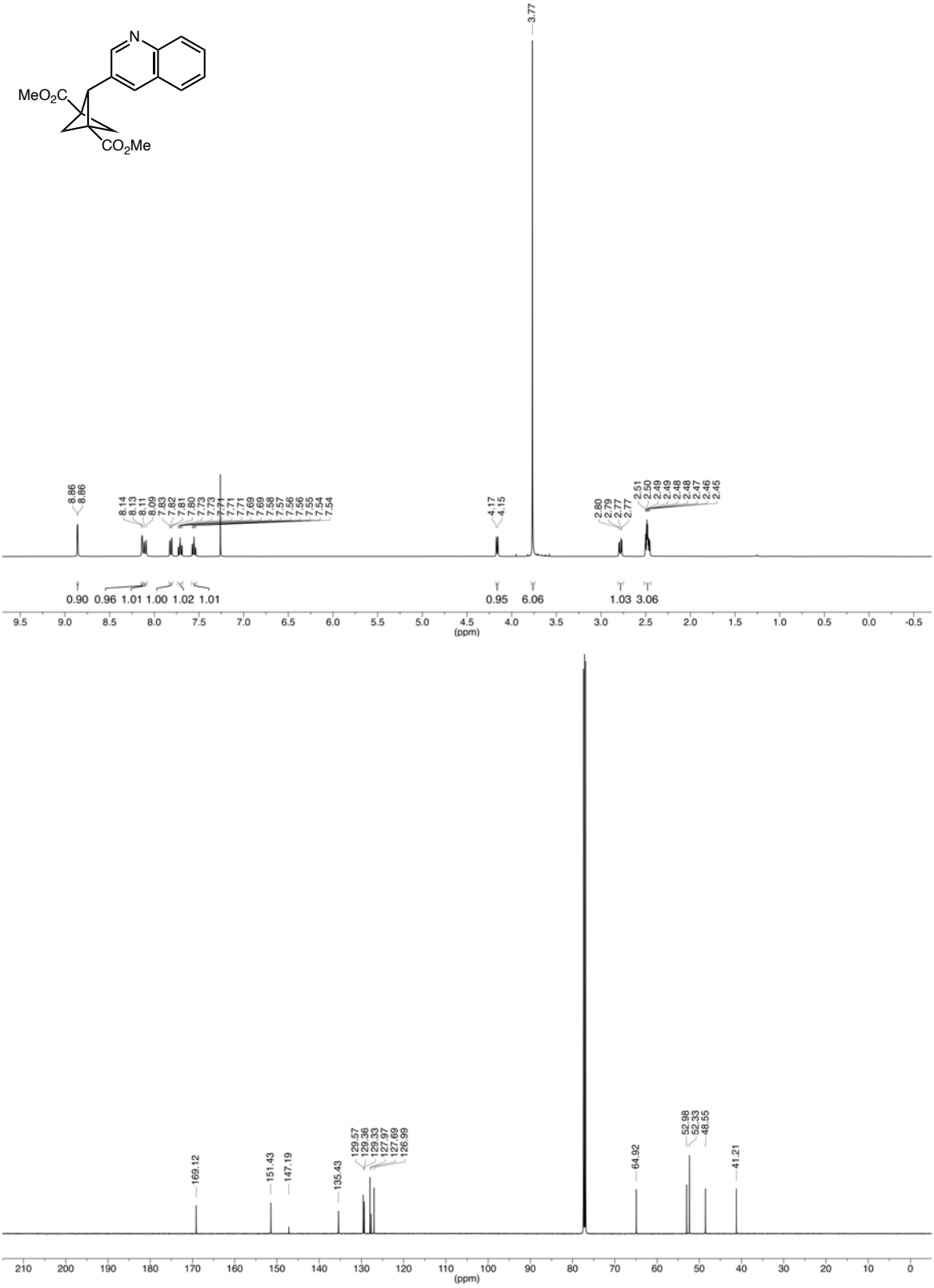



-68.11
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

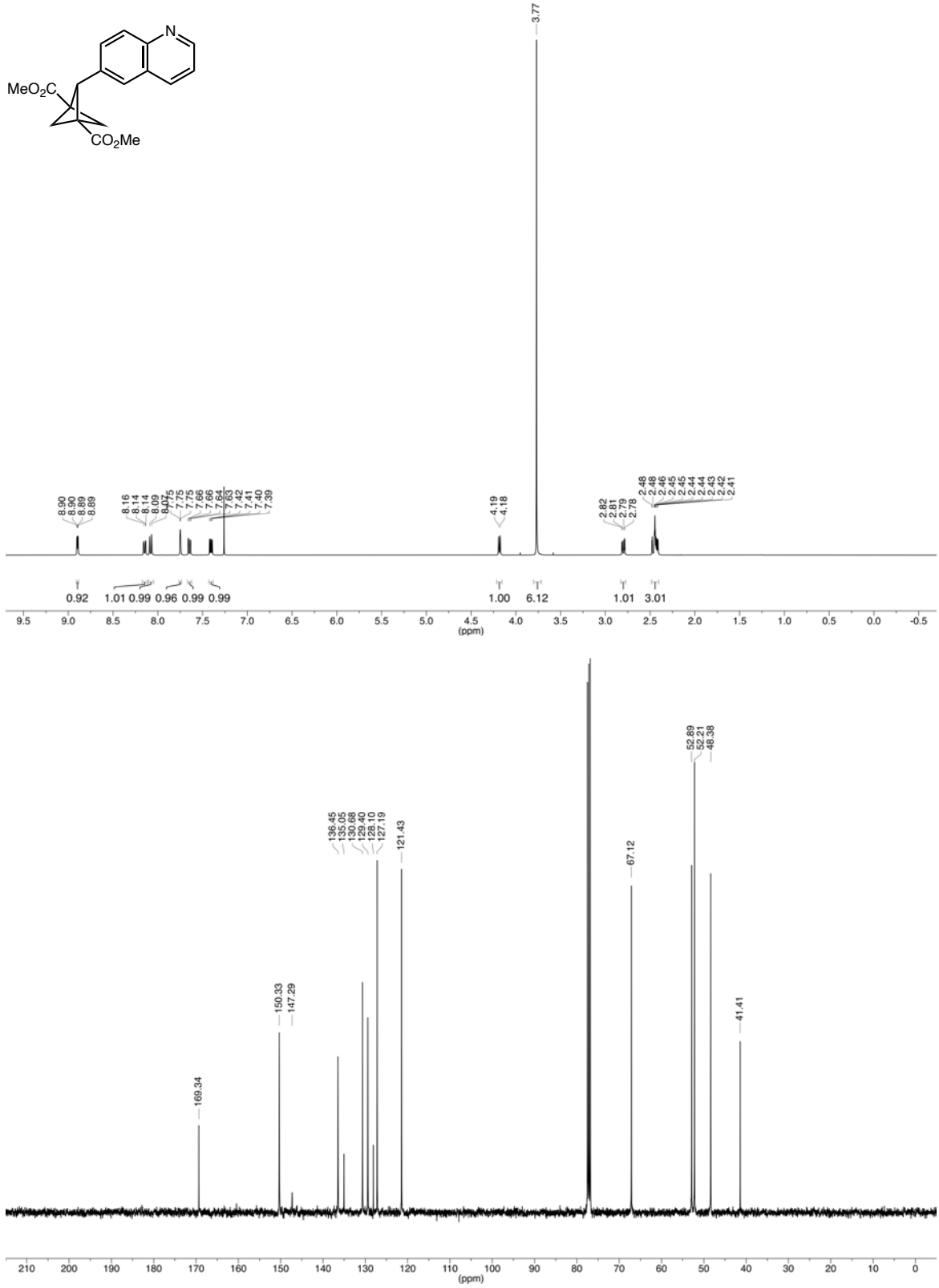
**Dimethyl 2-(6-morpholinopyridin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (33)**



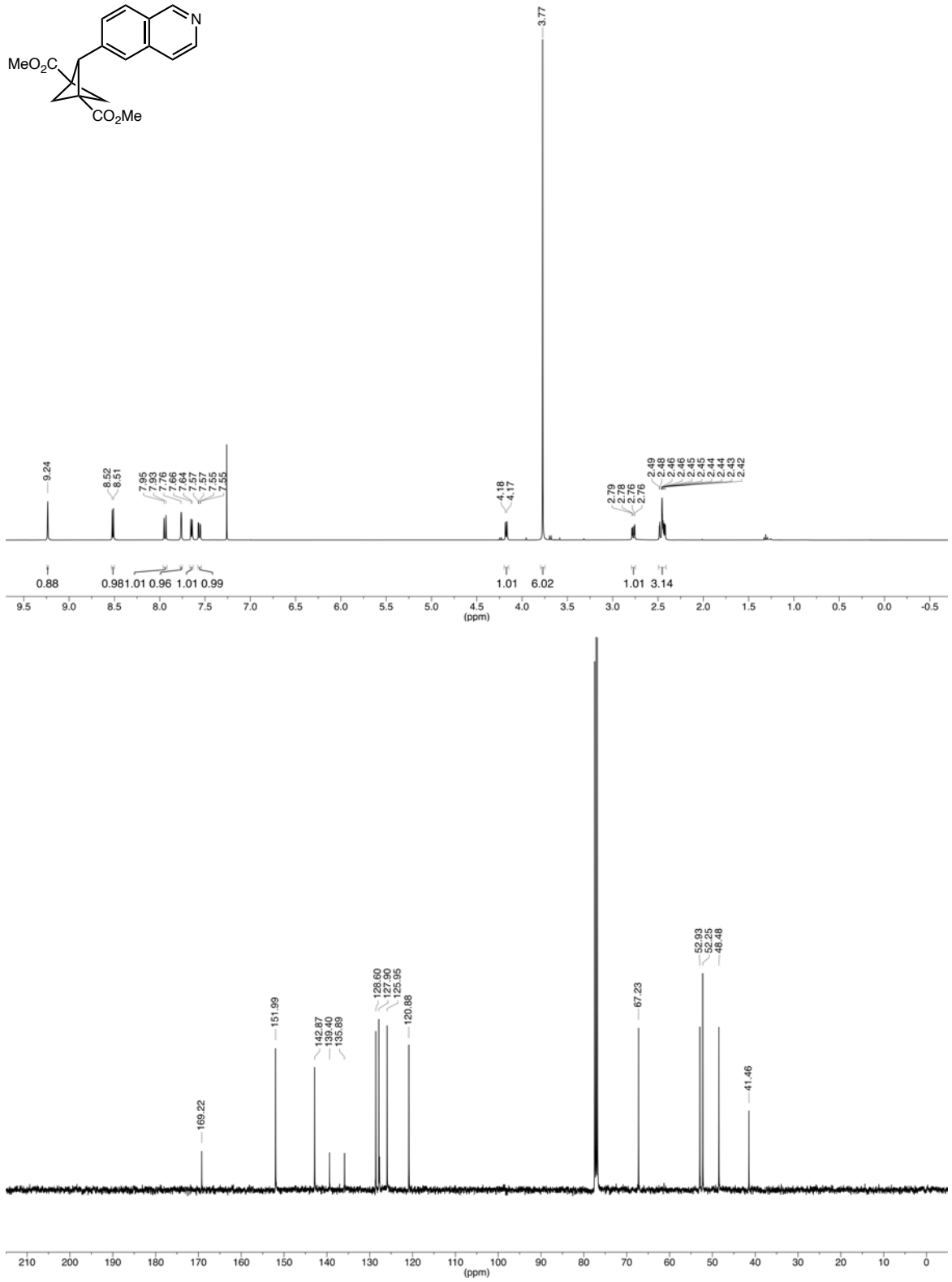
**Dimethyl 2-(quinolin-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (34)**



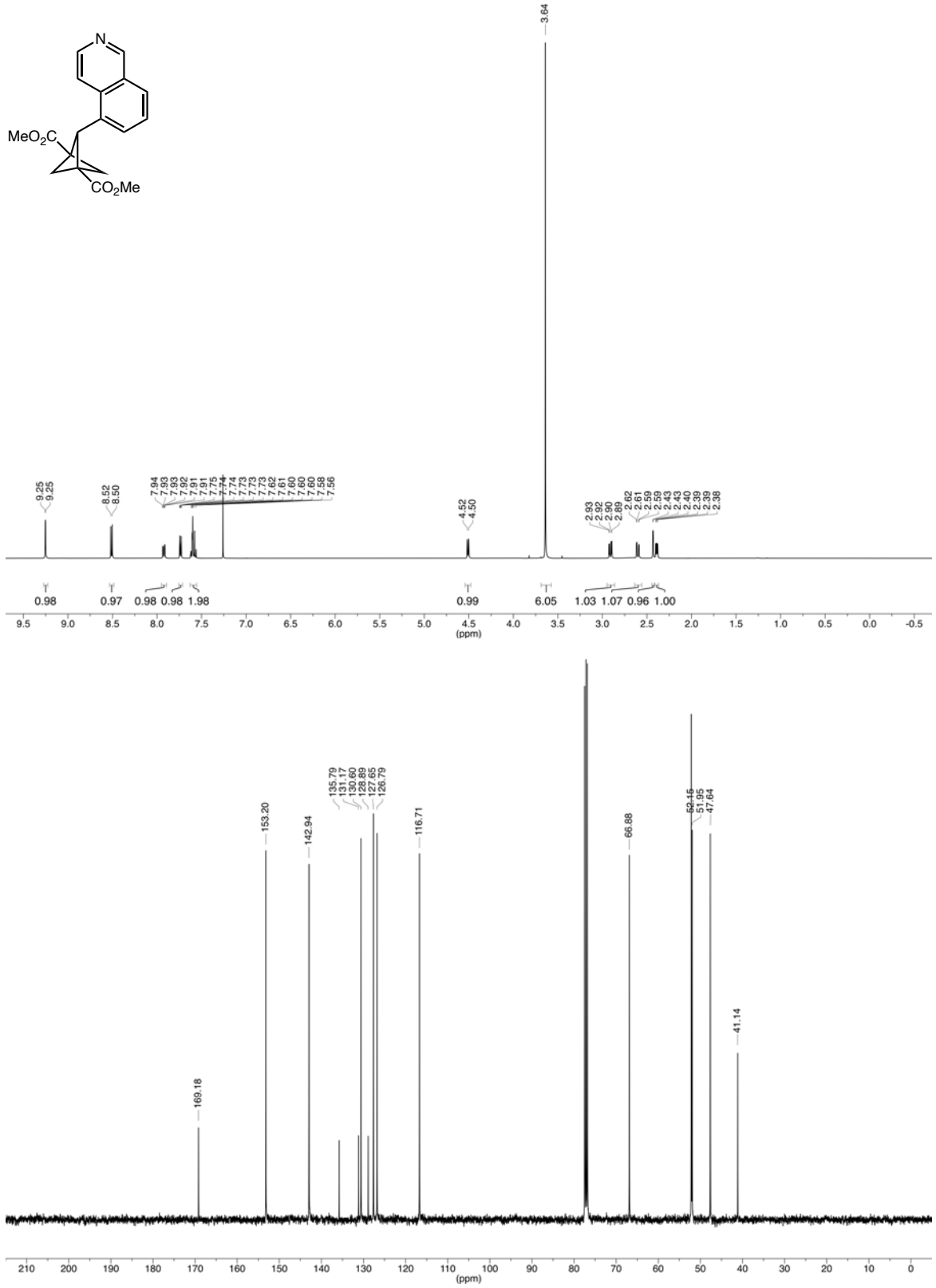
**Dimethyl 2-(quinolin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (35)**



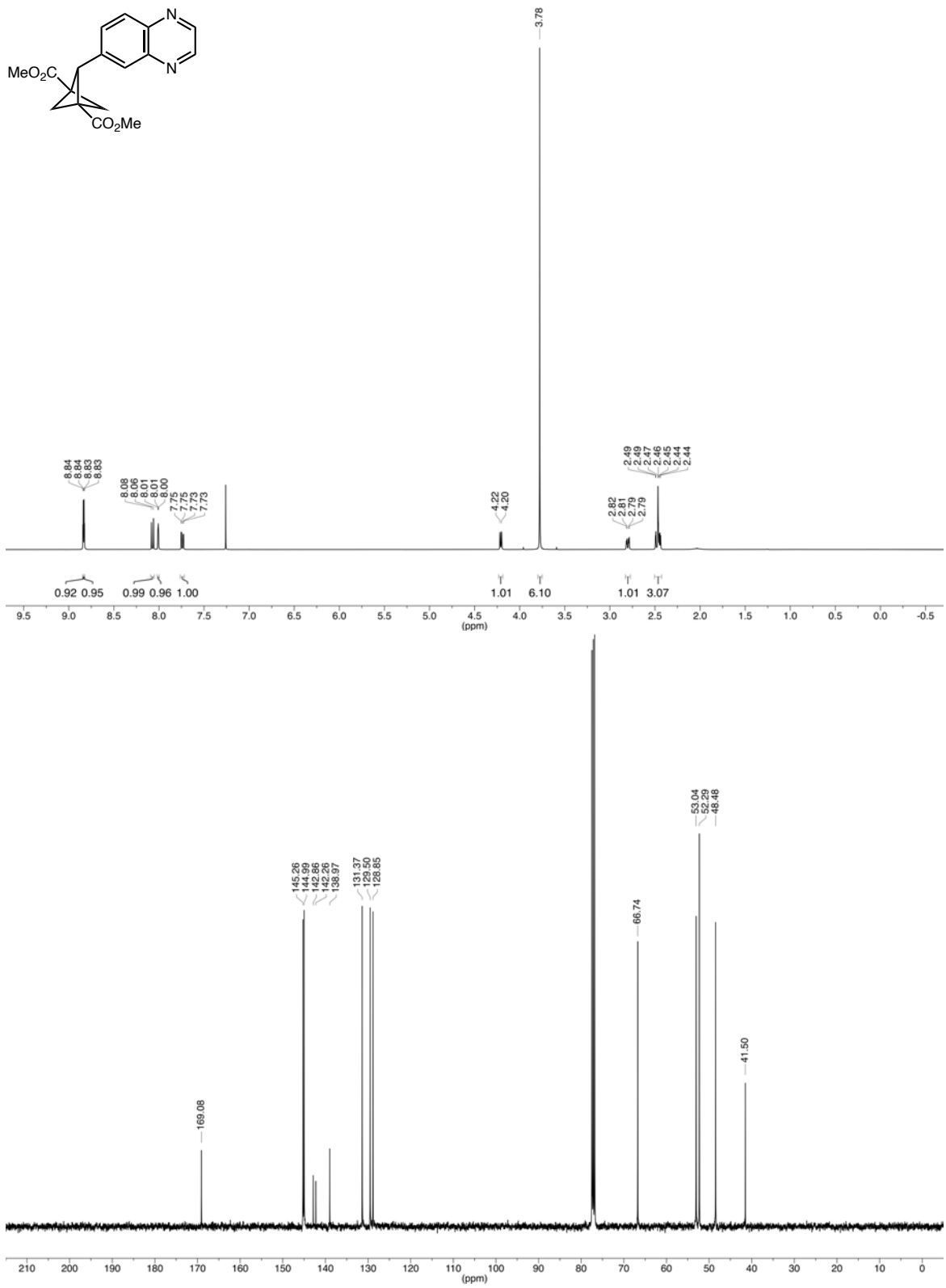
**Dimethyl 2-(isoquinolin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (36)**



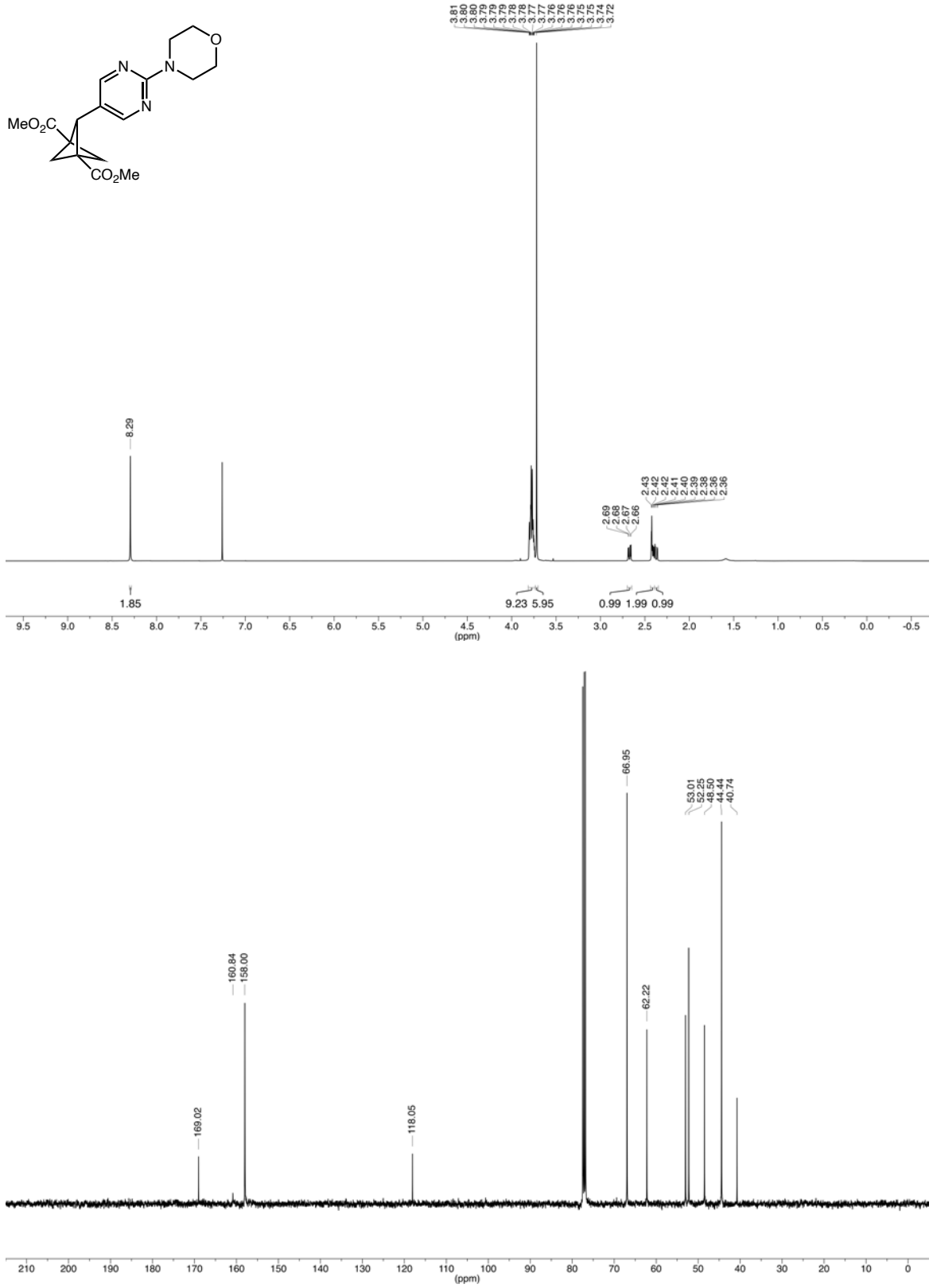
**Dimethyl 2-(isoquinolin-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (37)**



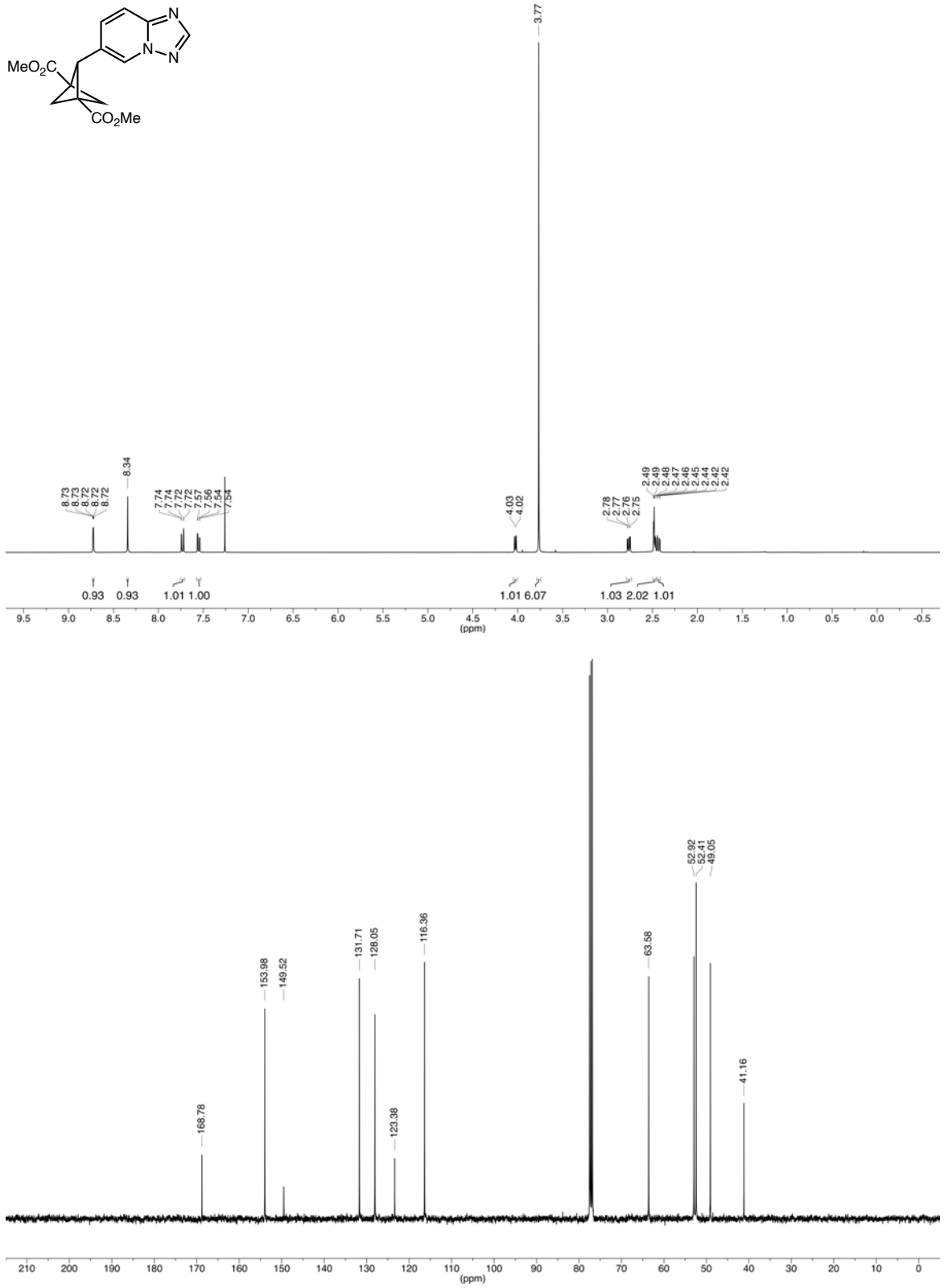
**Dimethyl 2-(quinoxalin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (38)**



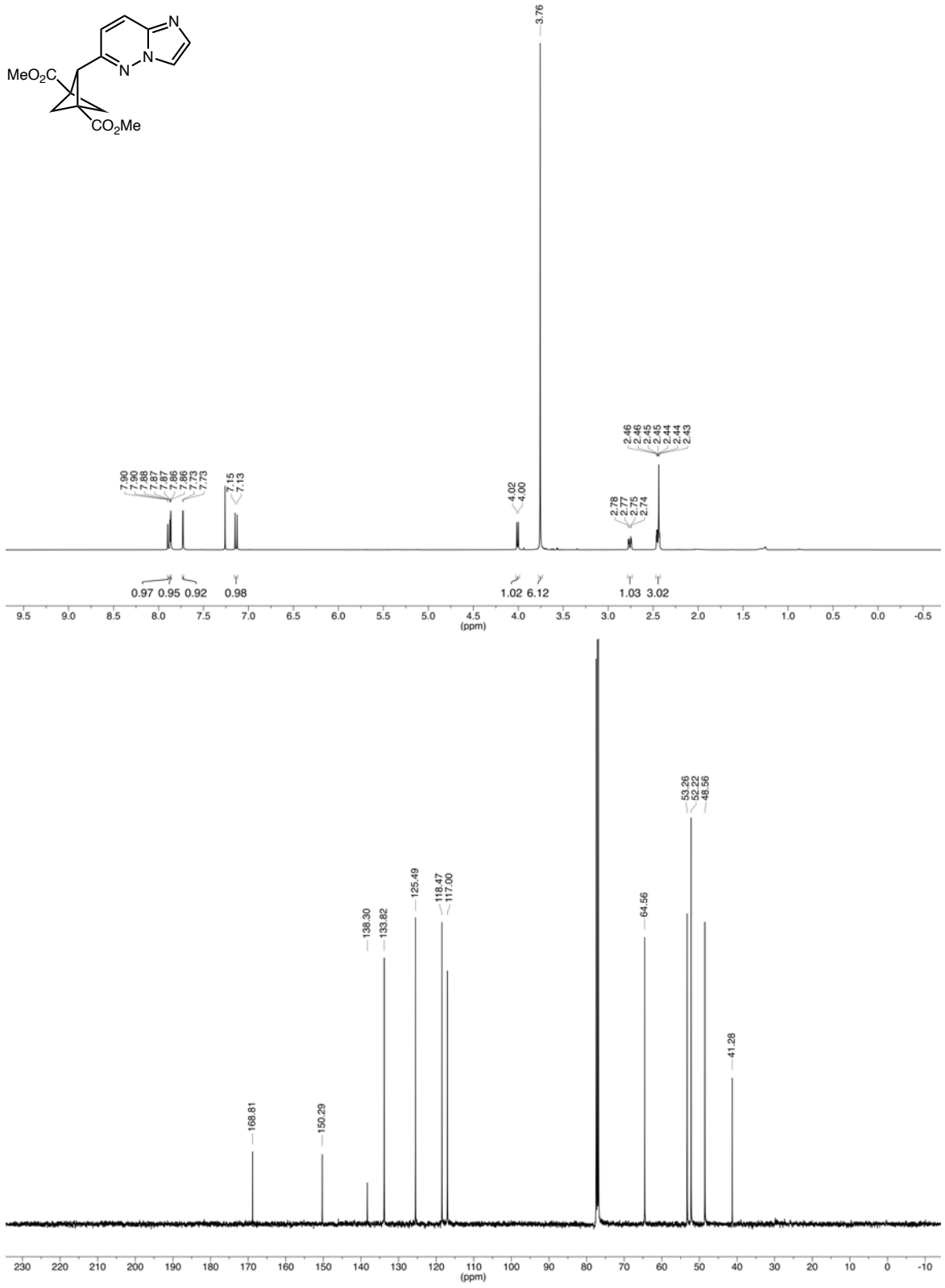
**Dimethyl 2-(2-morpholinopyrimidin-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (39)**



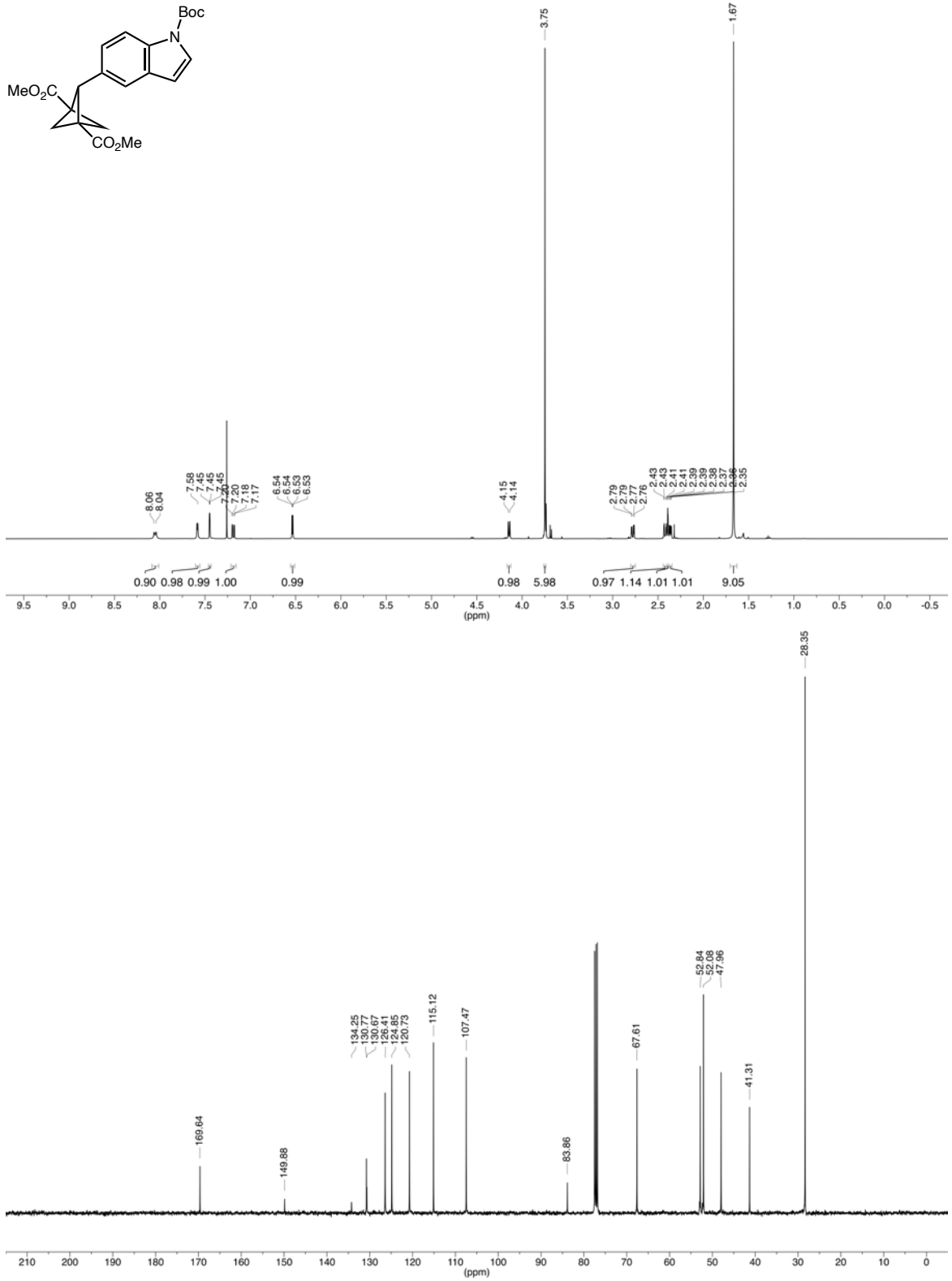
**Dimethyl 2-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (40)**



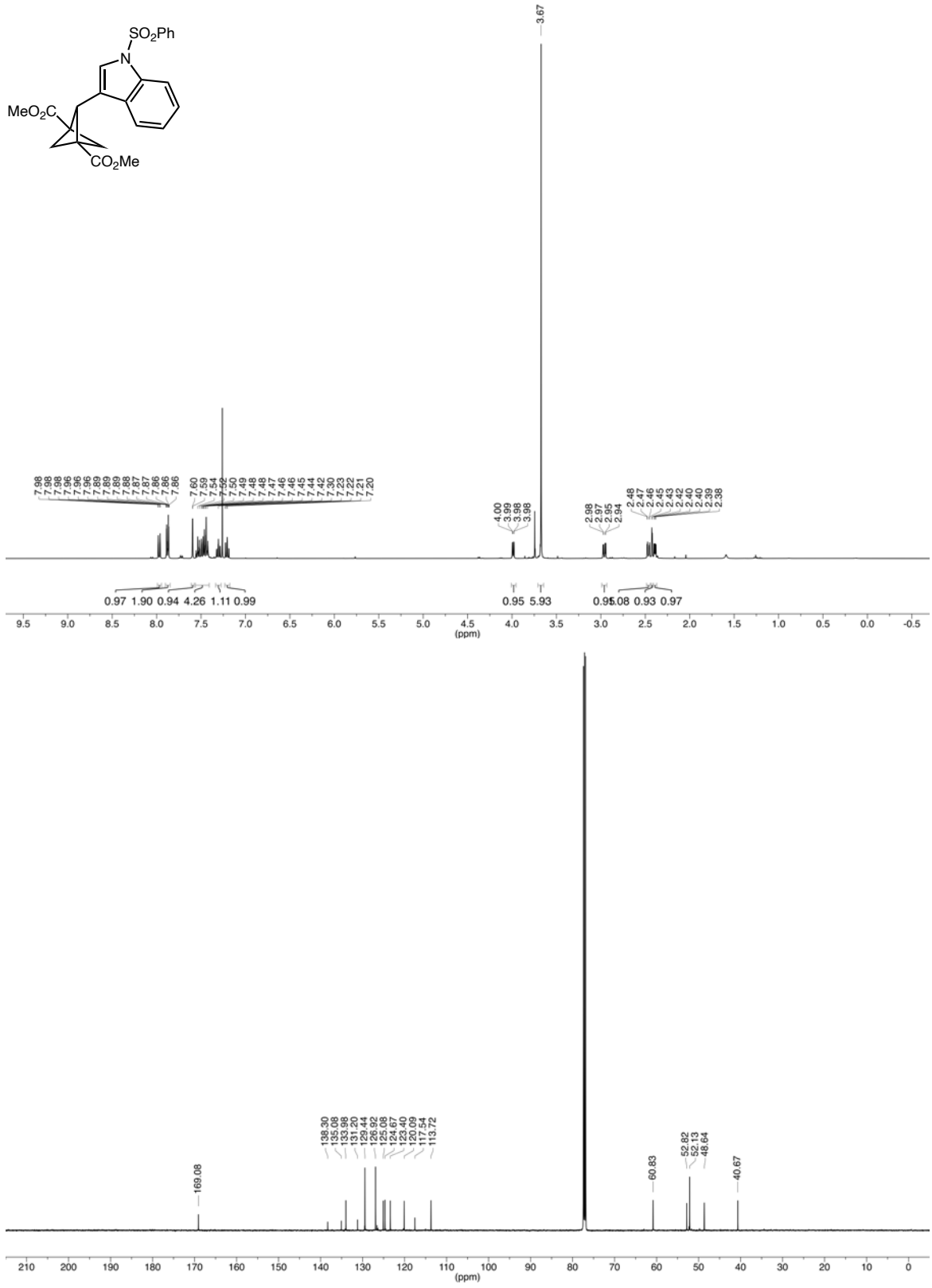
**Dimethyl 2-(imidazo[1,2-*b*]pyridazin-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (41)**



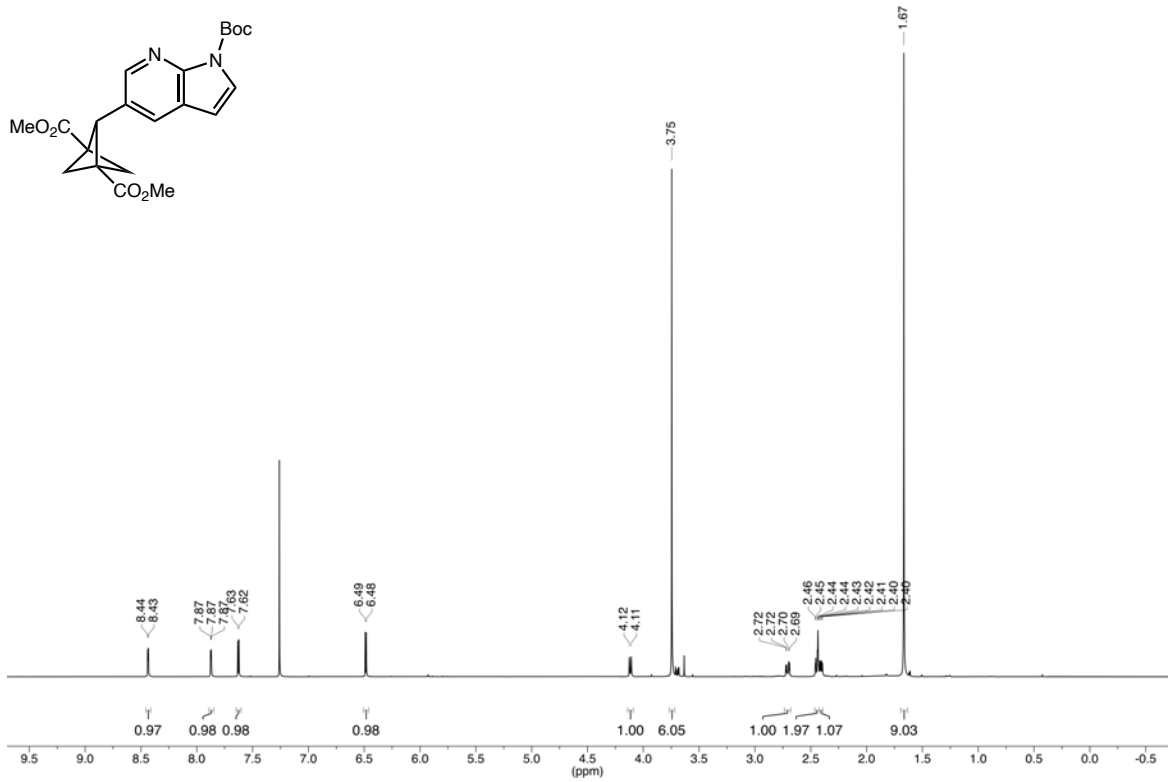
**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (42)**

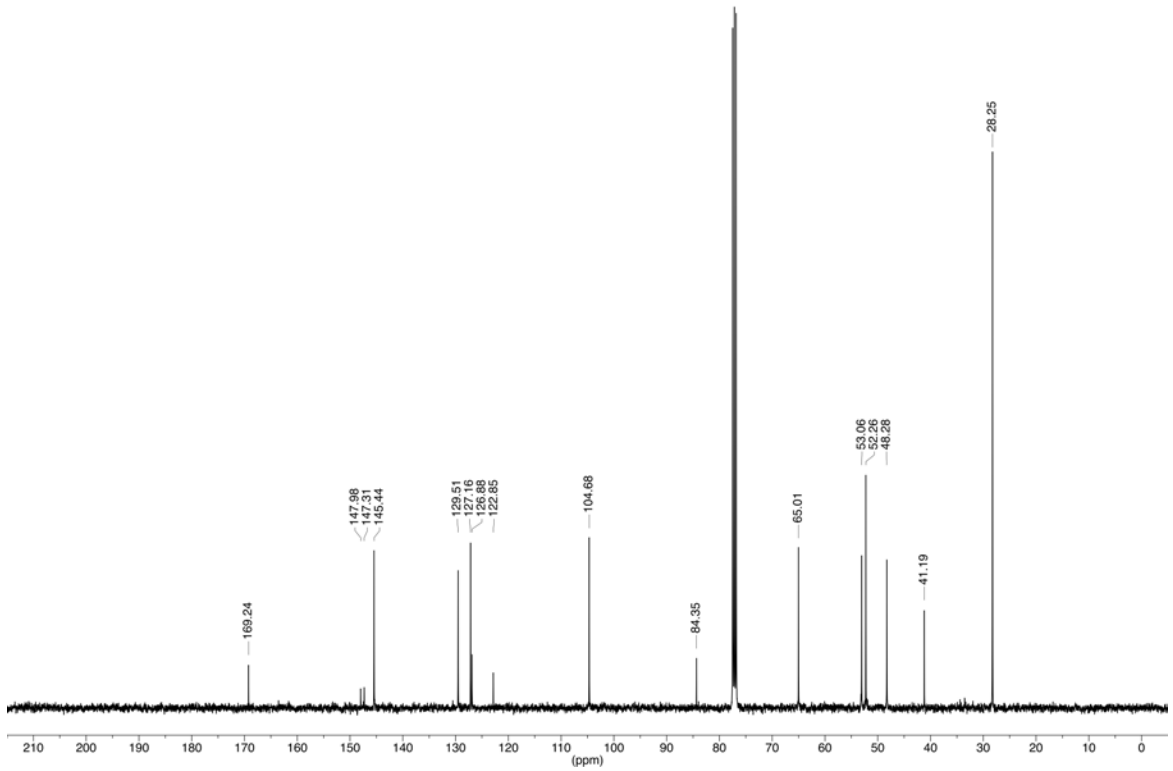


**Dimethyl 2-(1-(phenylsulfonyl)-1*H*-indol-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (43)**

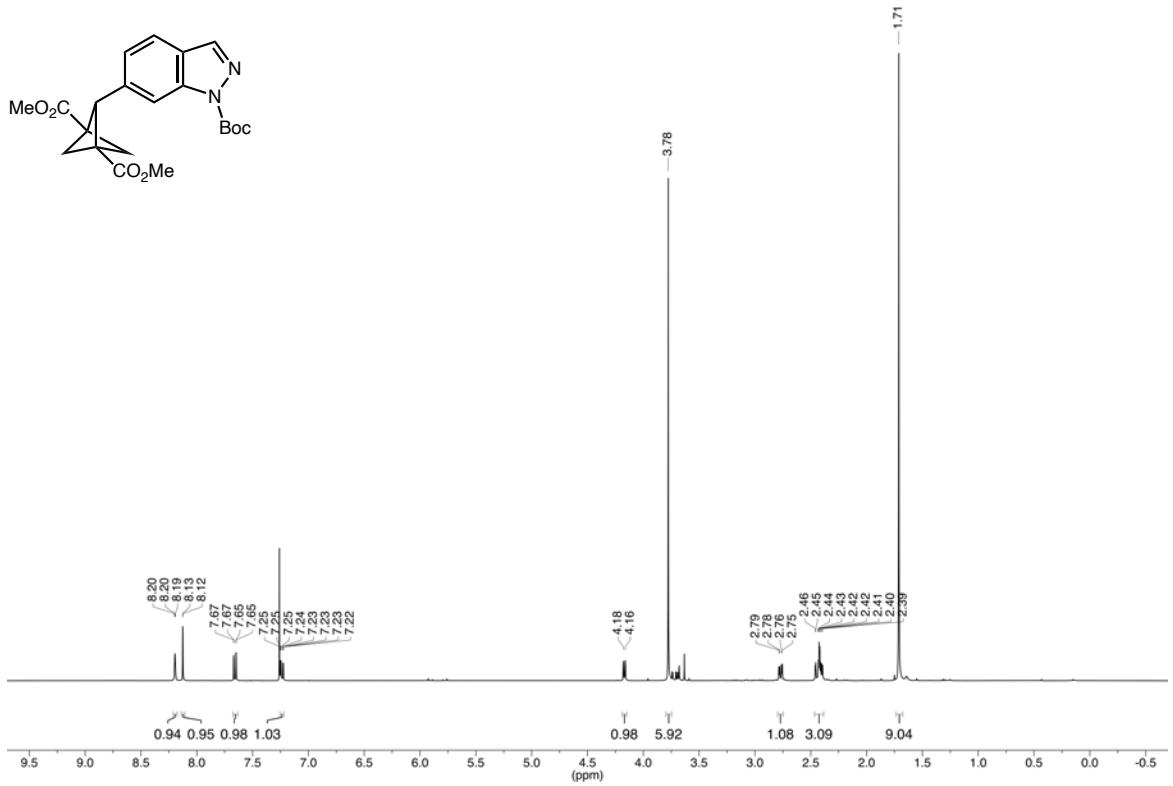


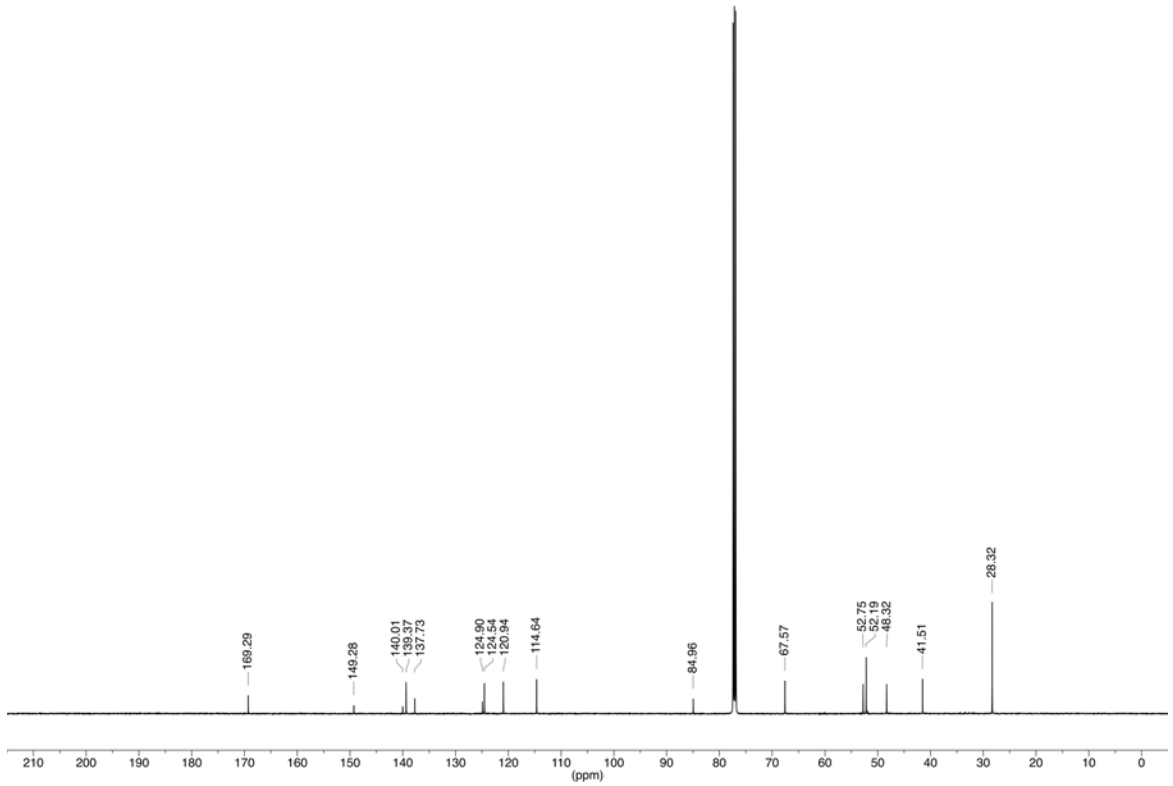
**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrrolo[2,3-b]pyridin-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (44)**



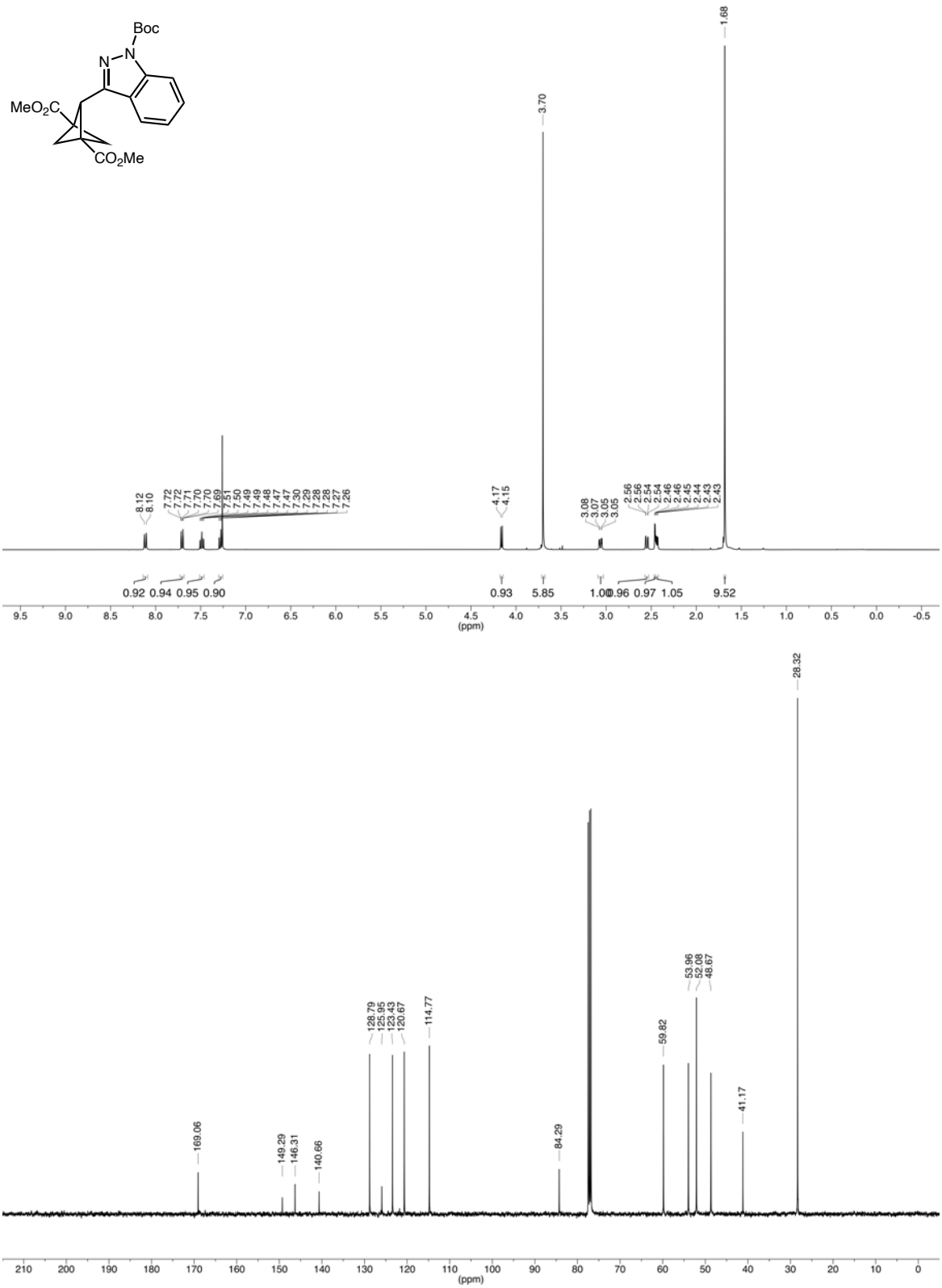



**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-indazol-6-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (45)**

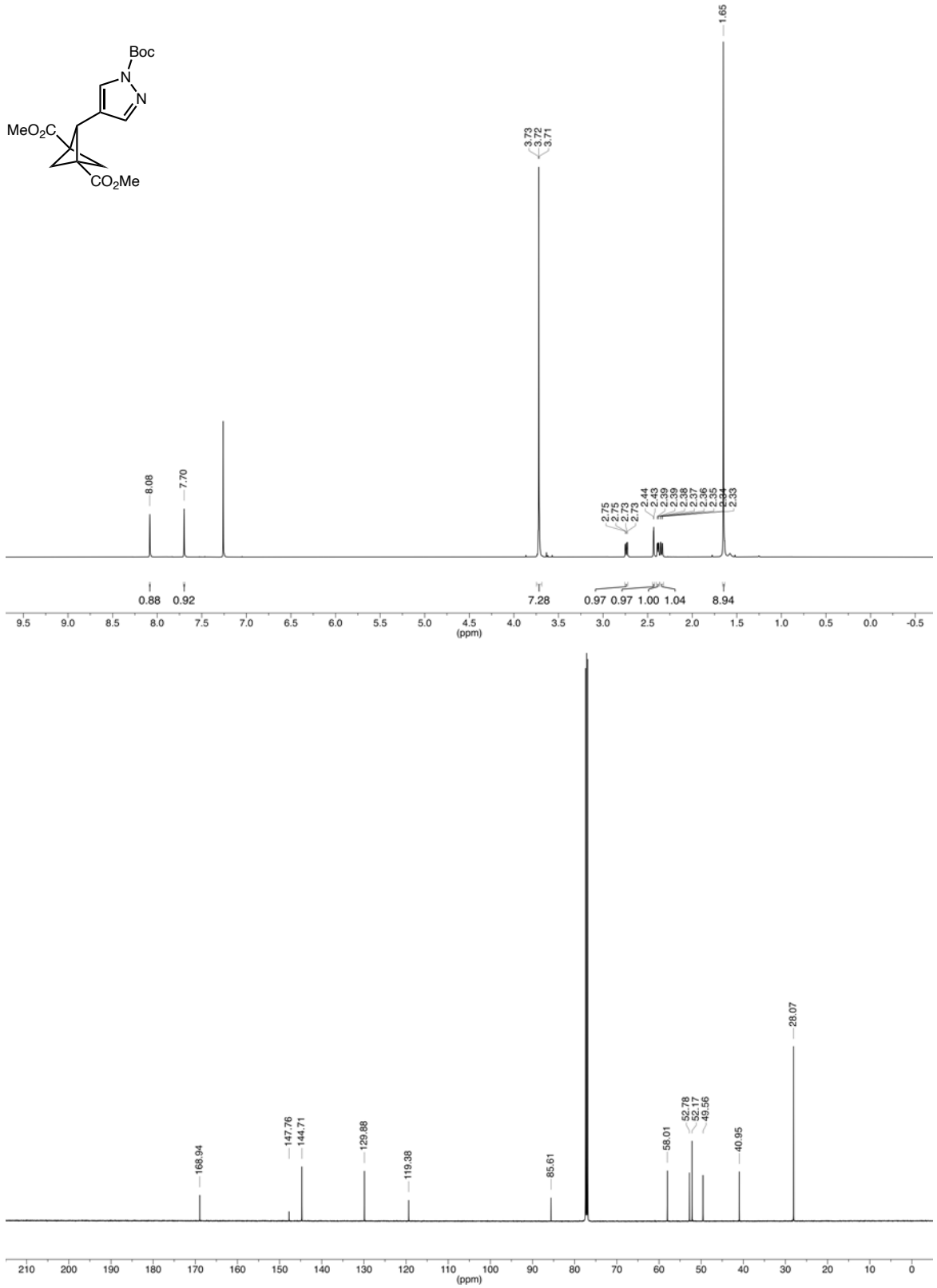


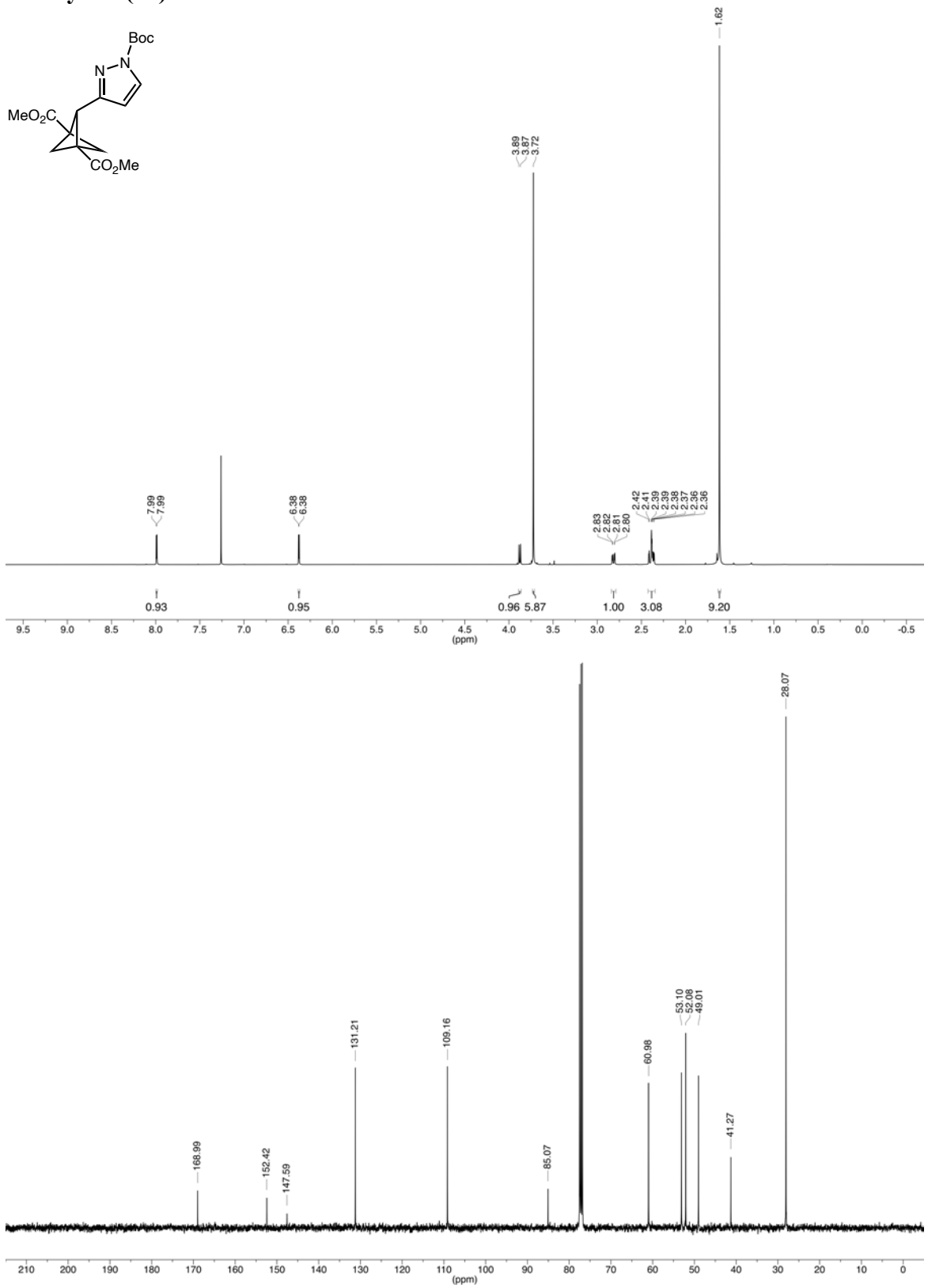
**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-indazol-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (46)**



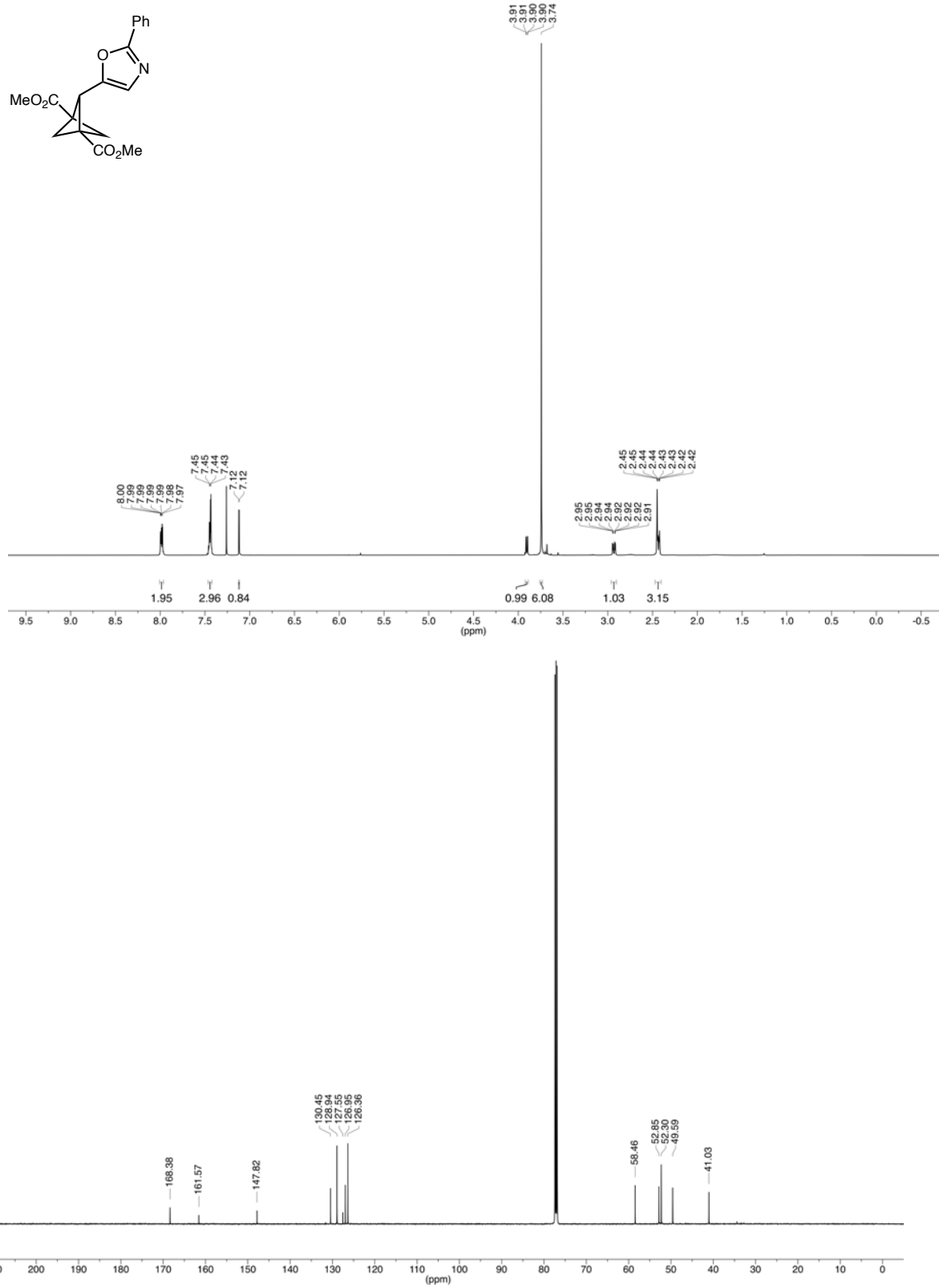
**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (47)**



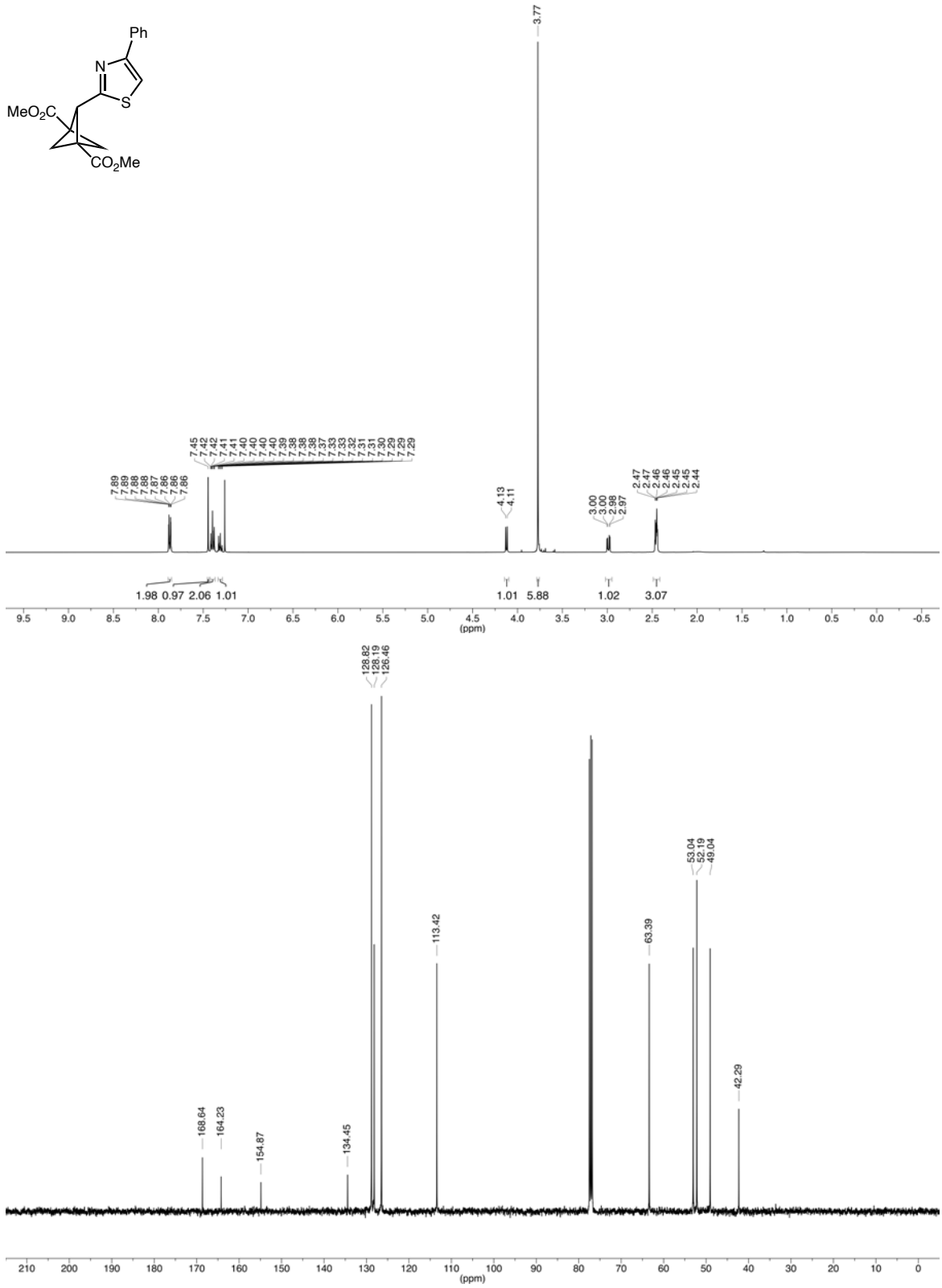
**Dimethyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-3-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (48)**



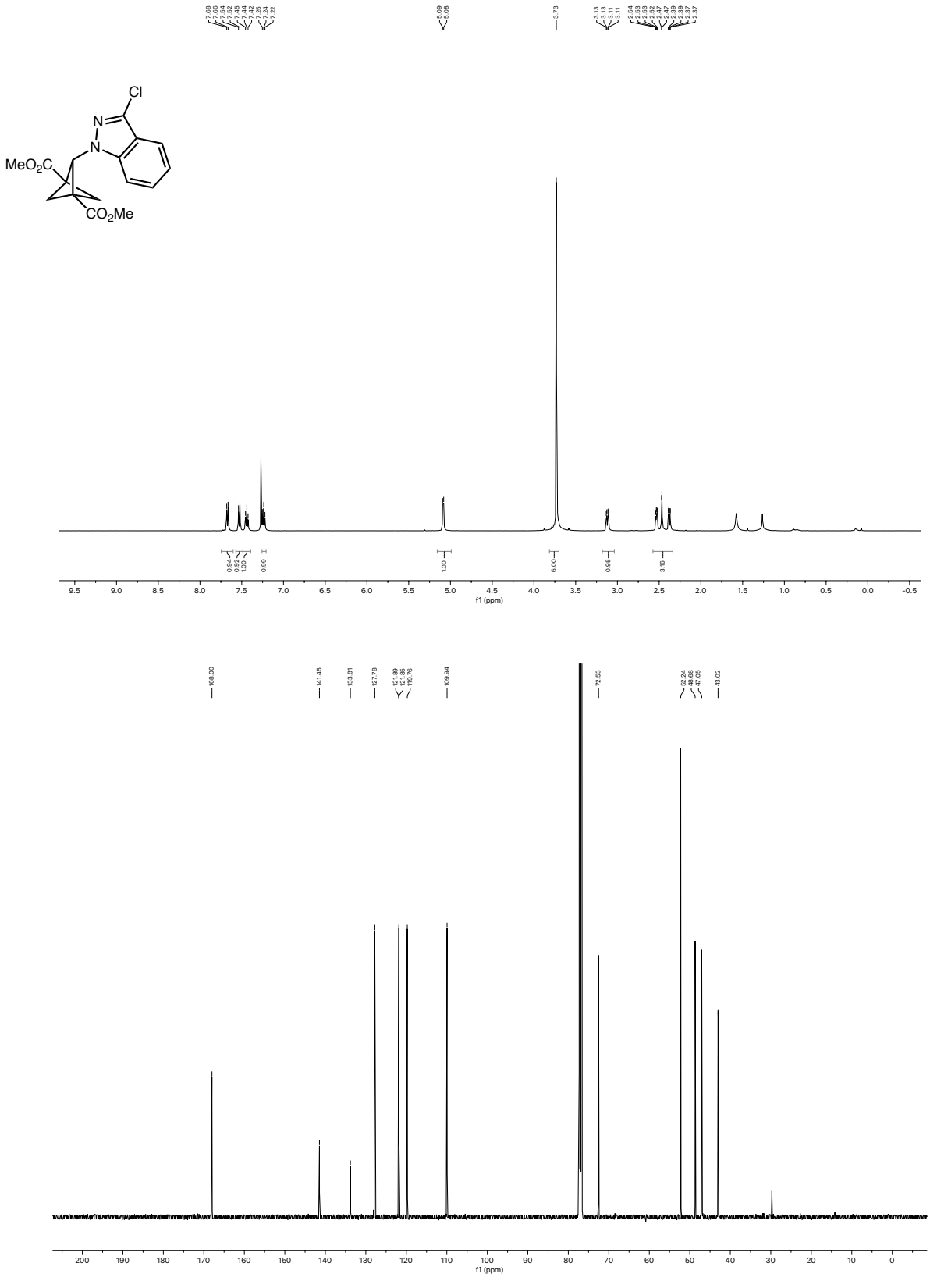
**Dimethyl 2-(2-phenyloxazol-5-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (49)**



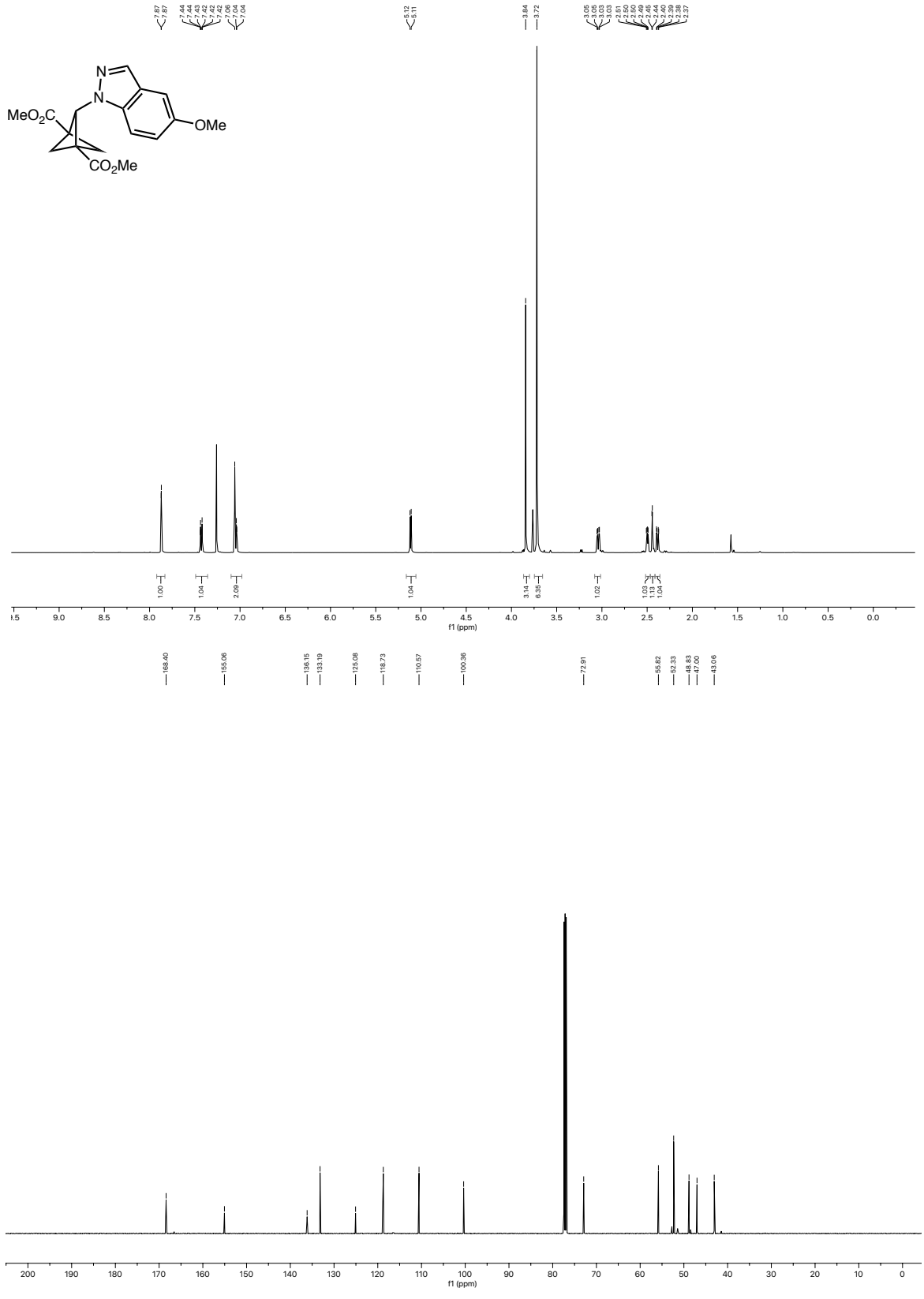
**Dimethyl 2-(4-phenylthiazol-2-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (50)**



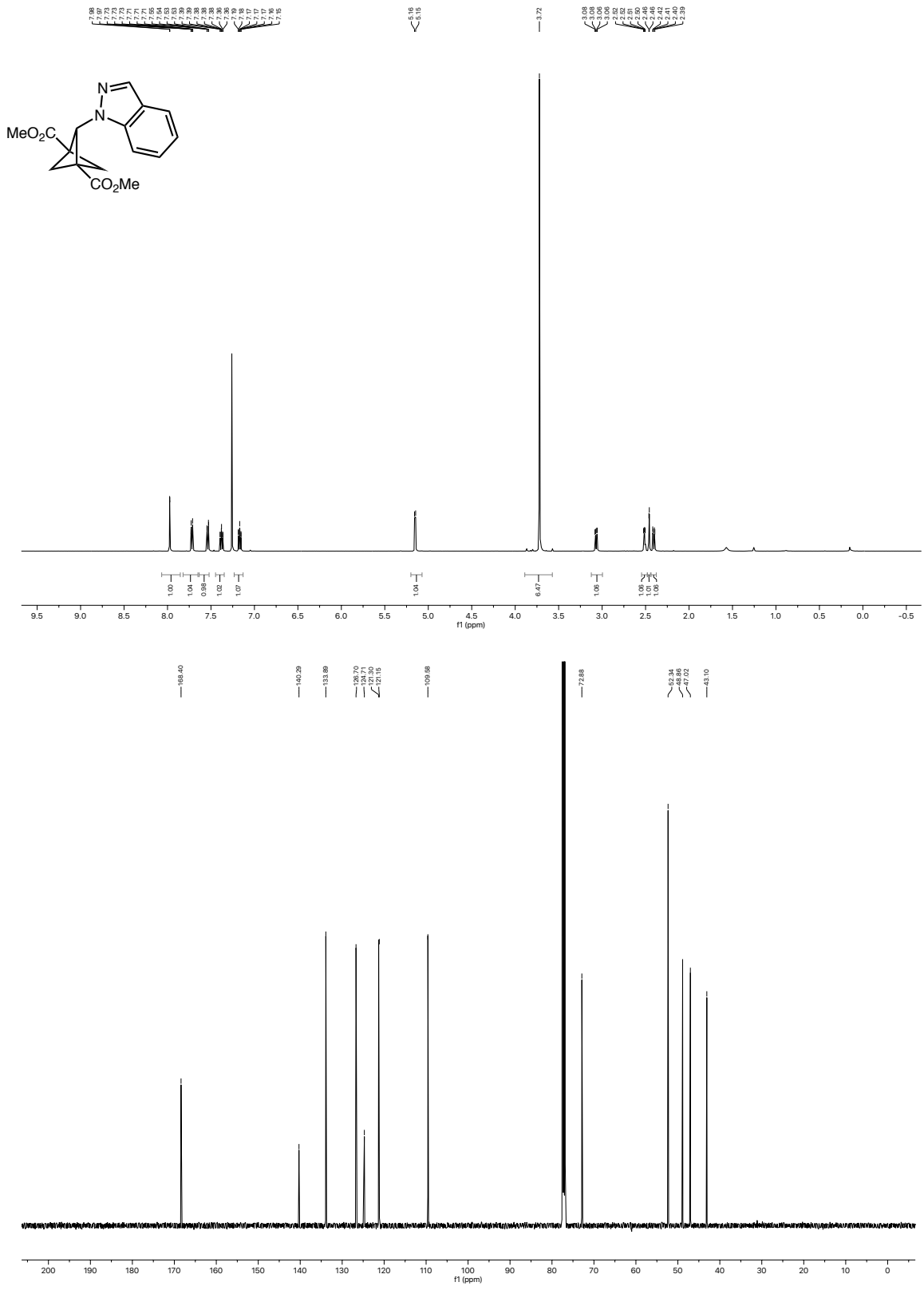
**Dimethyl 2-(3-chloro-1H-indazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (51)**



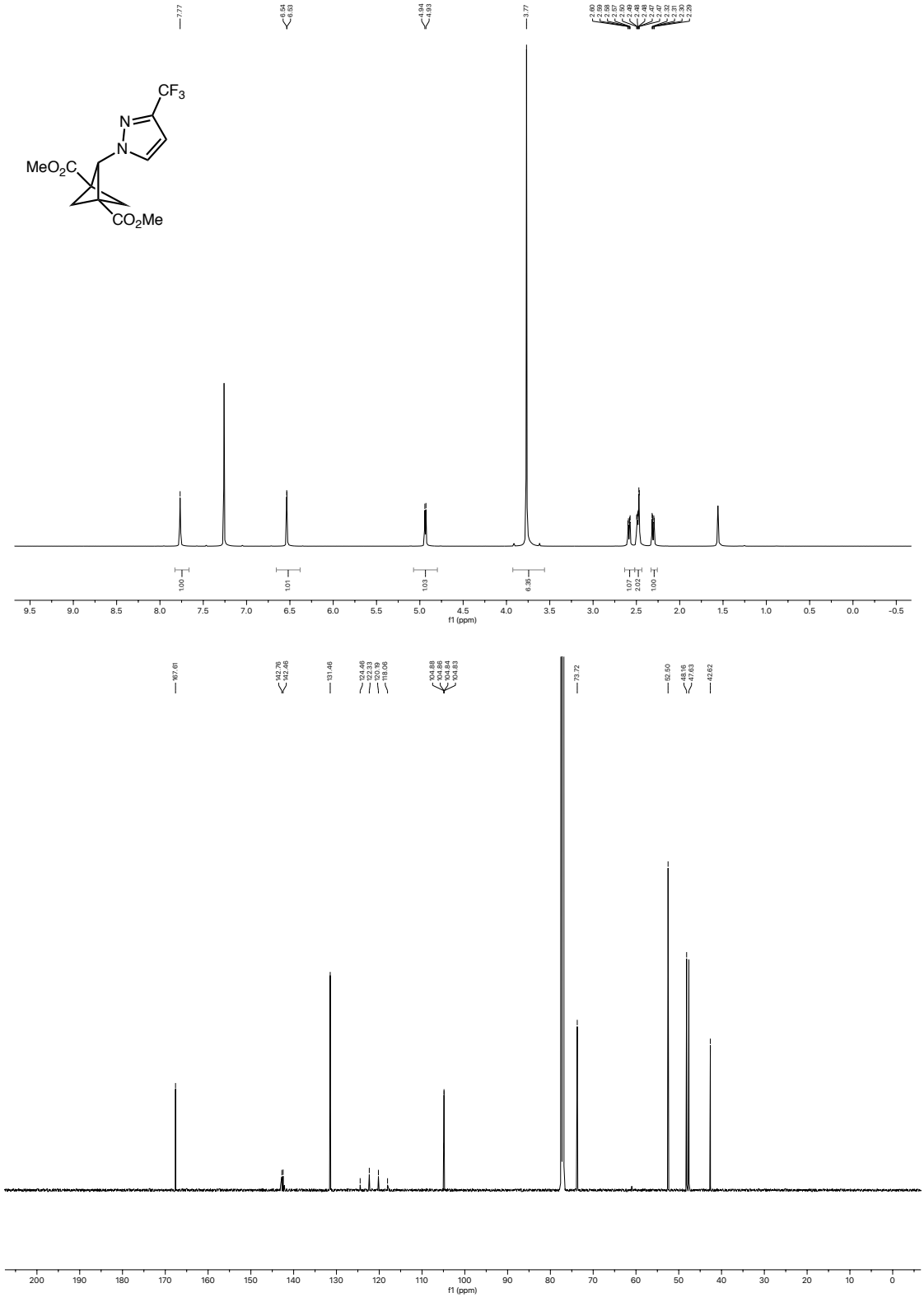
**Dimethyl 2-(5-methoxy-1H-indazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (52)**



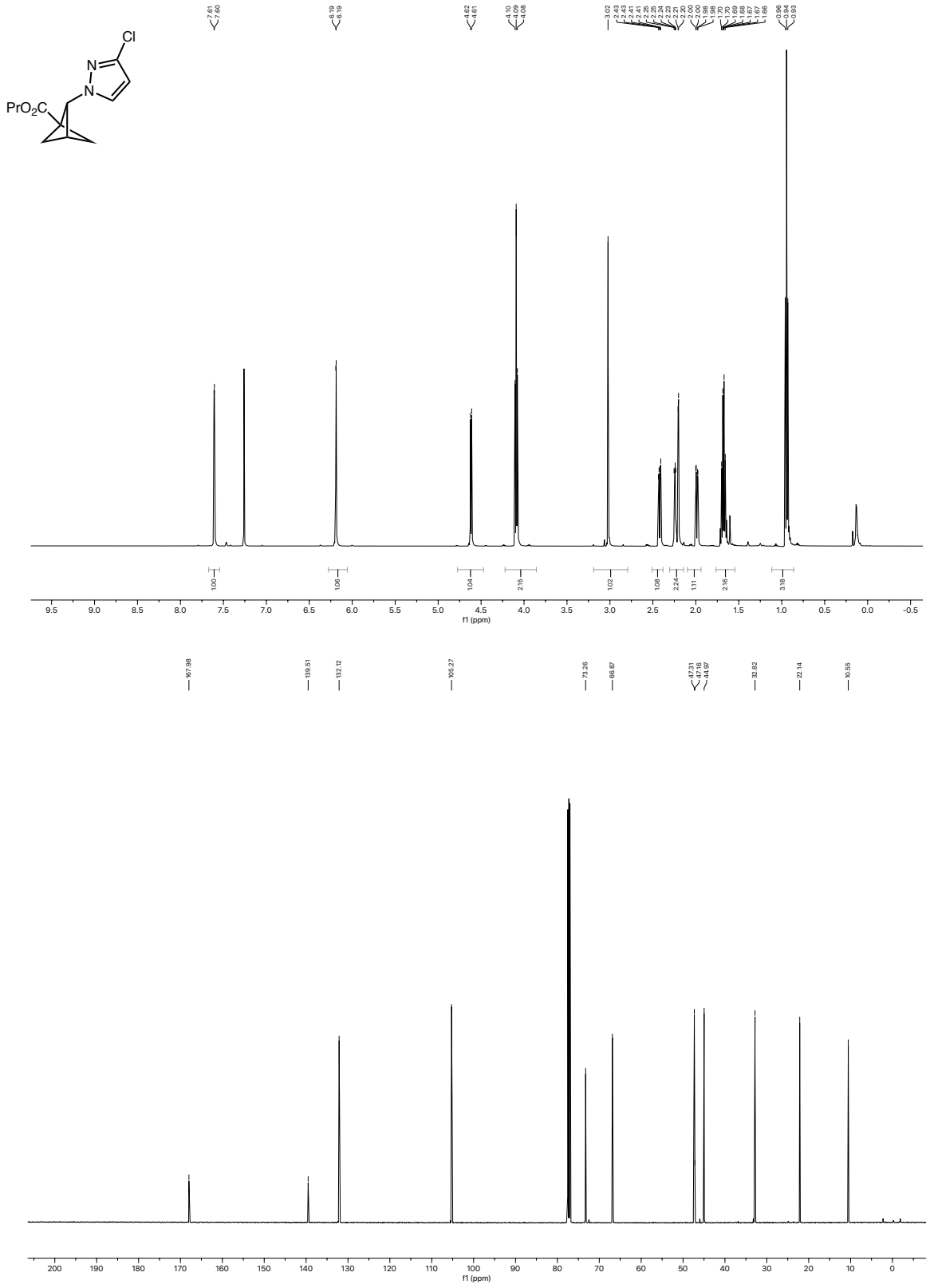
**Dimethyl 2-(1*H*-indazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (53)**



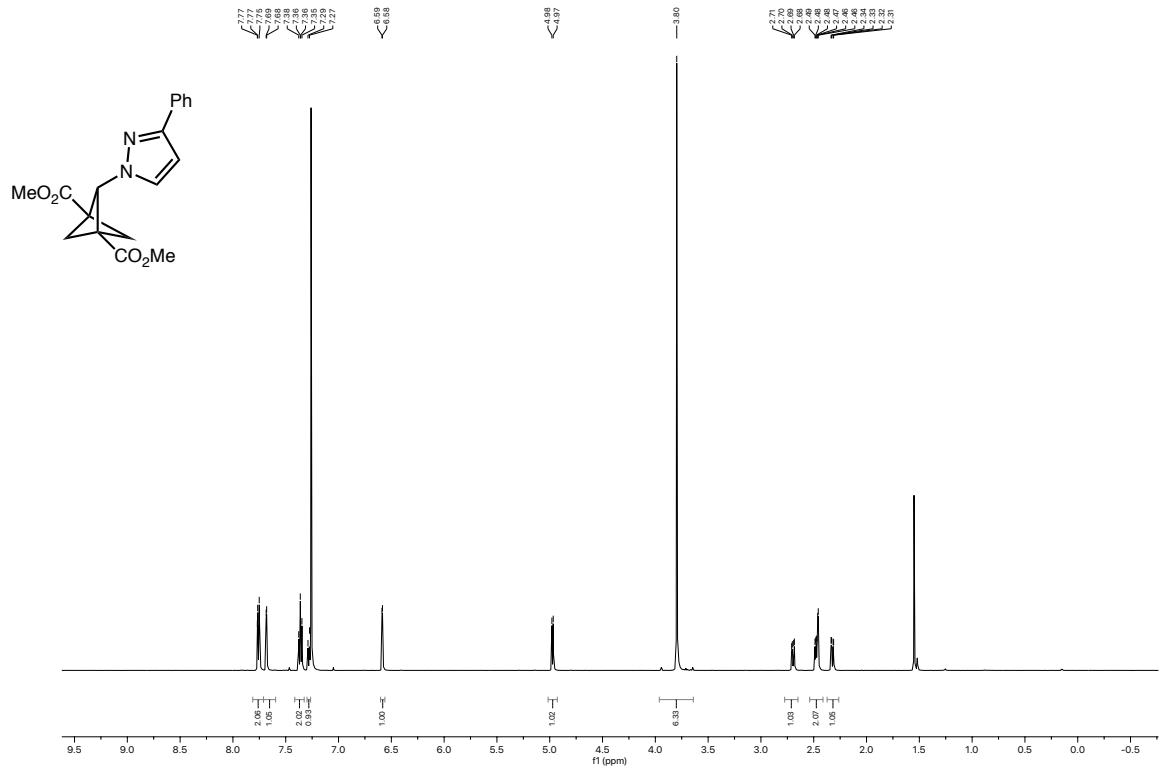
**Dimethyl 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (54)**

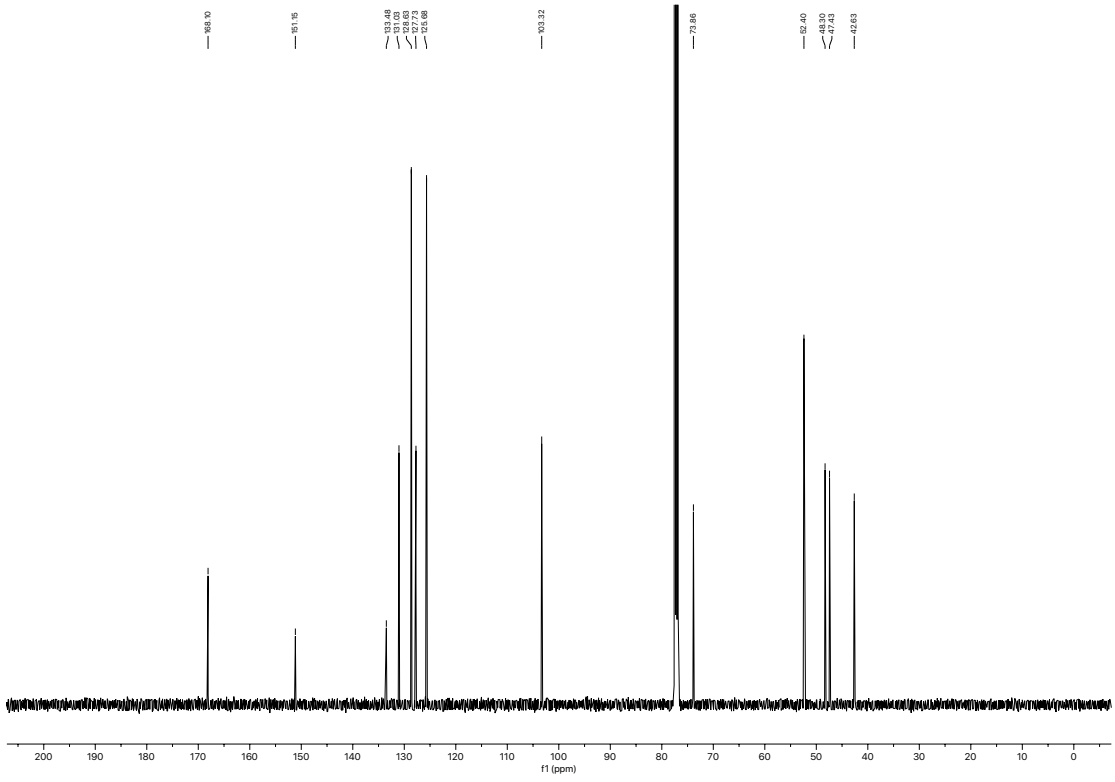


**(±)-Propyl 2-(3-chloro-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (55)**

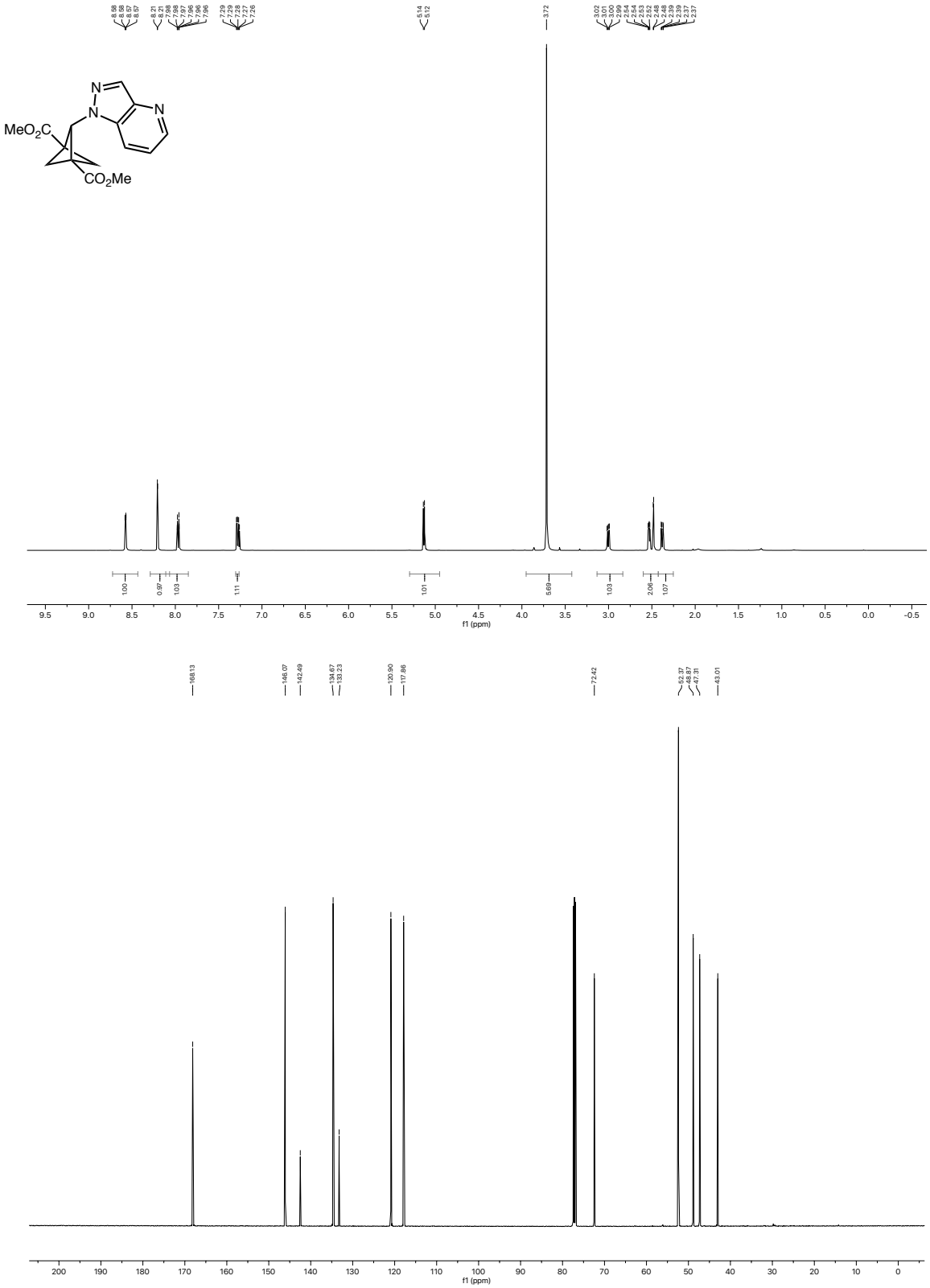


**Dimethyl 2-(3-(phenyl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (56)**

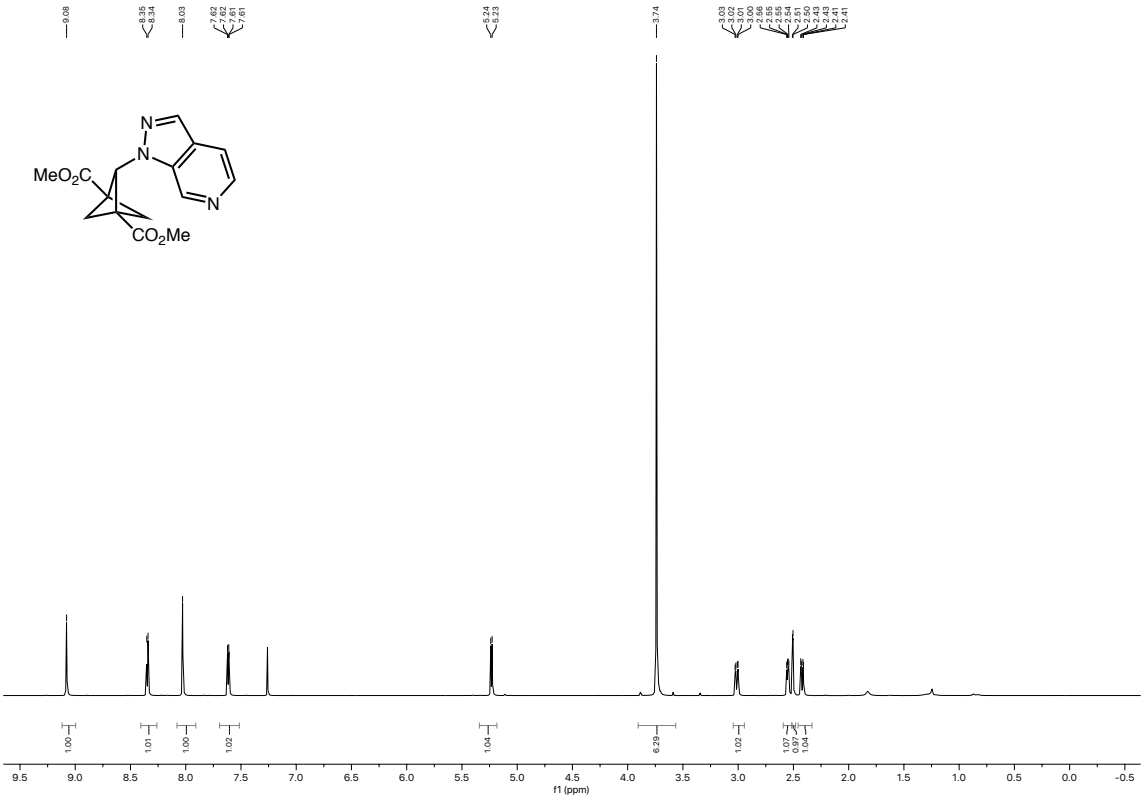


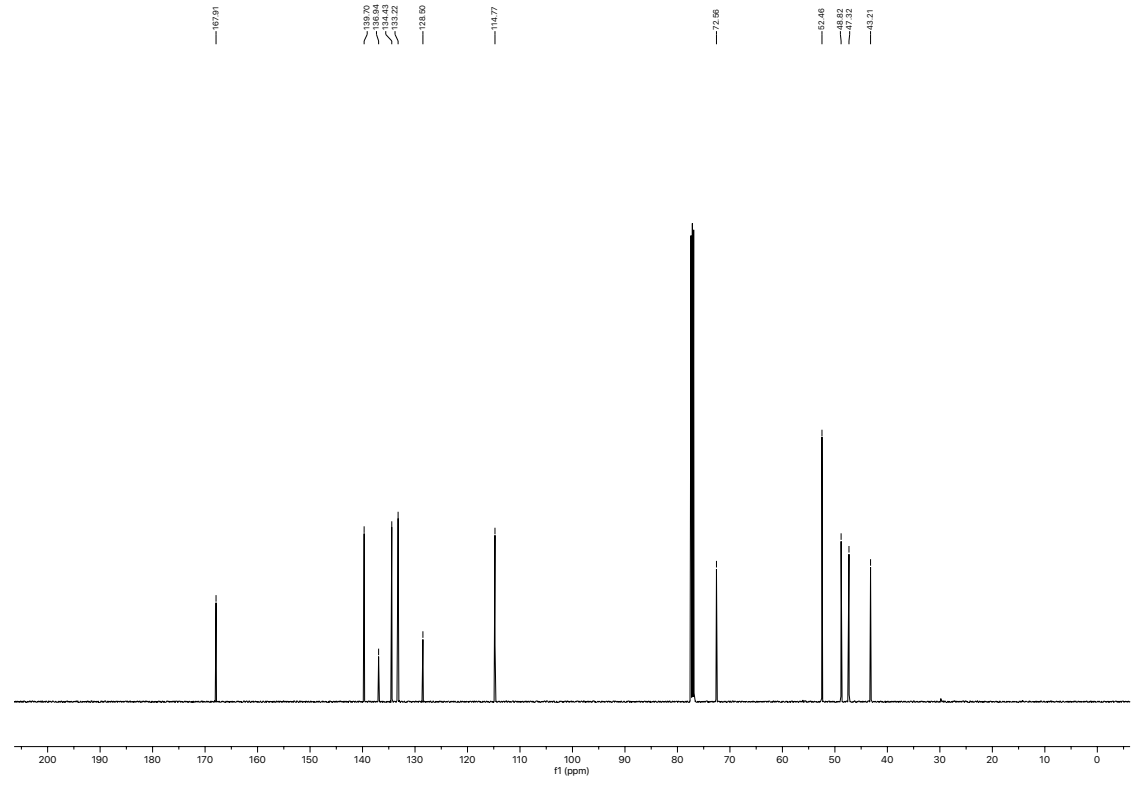



**Dimethyl 2-(1H-pyrazolo[4,3-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (57)**

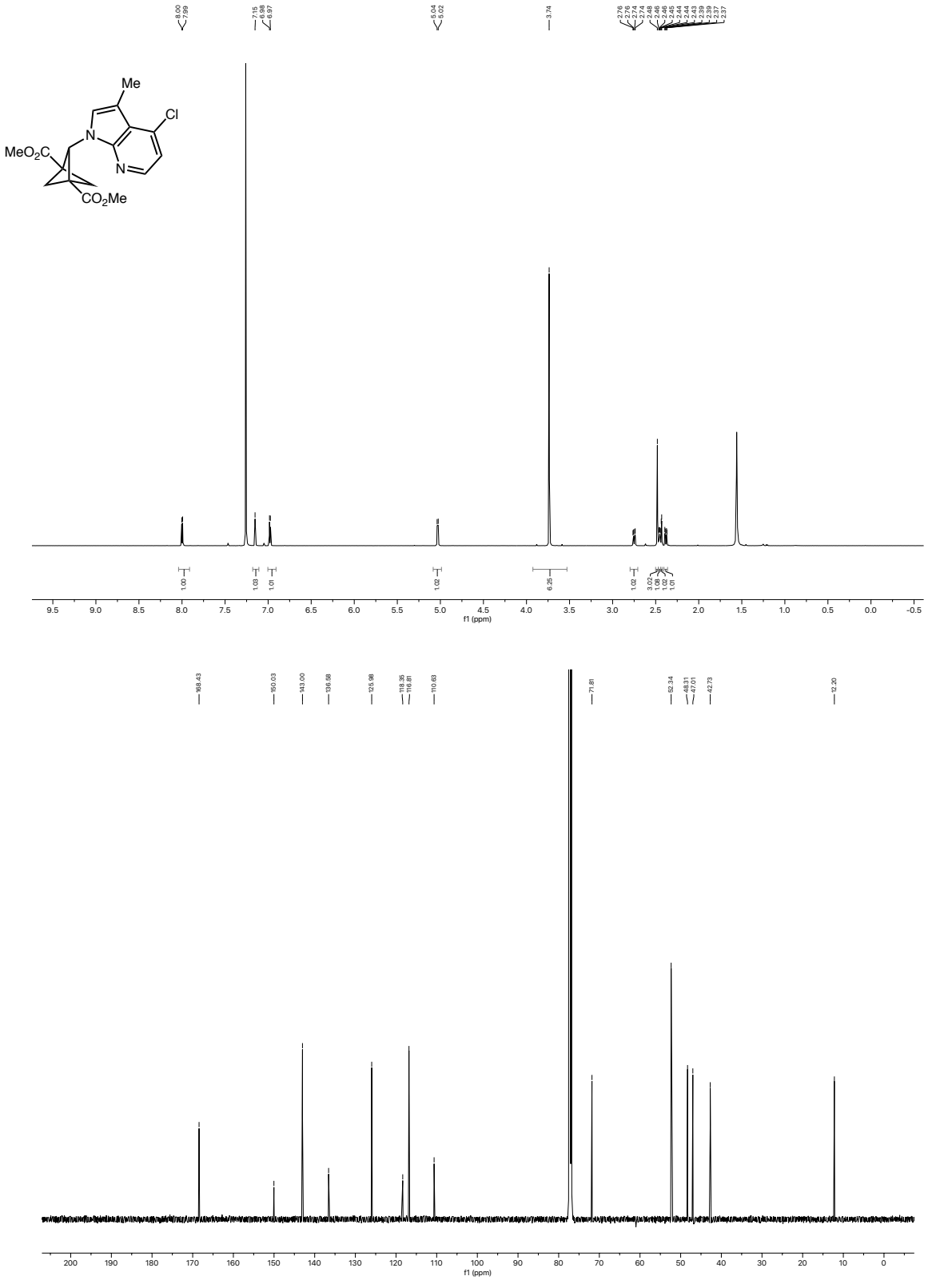


**Dimethyl 2-(1H-pyrazolo[3,4-c]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (58)**

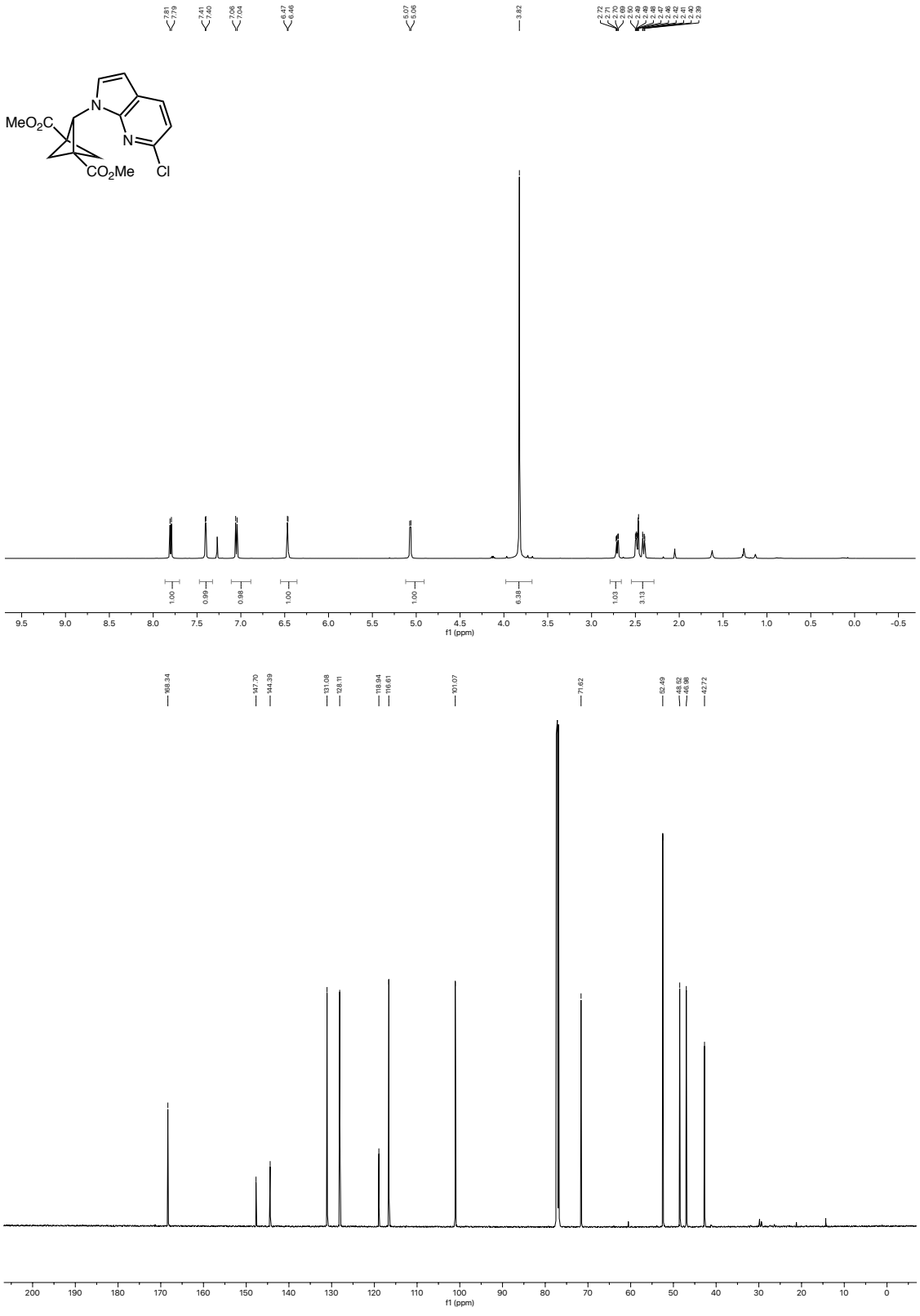


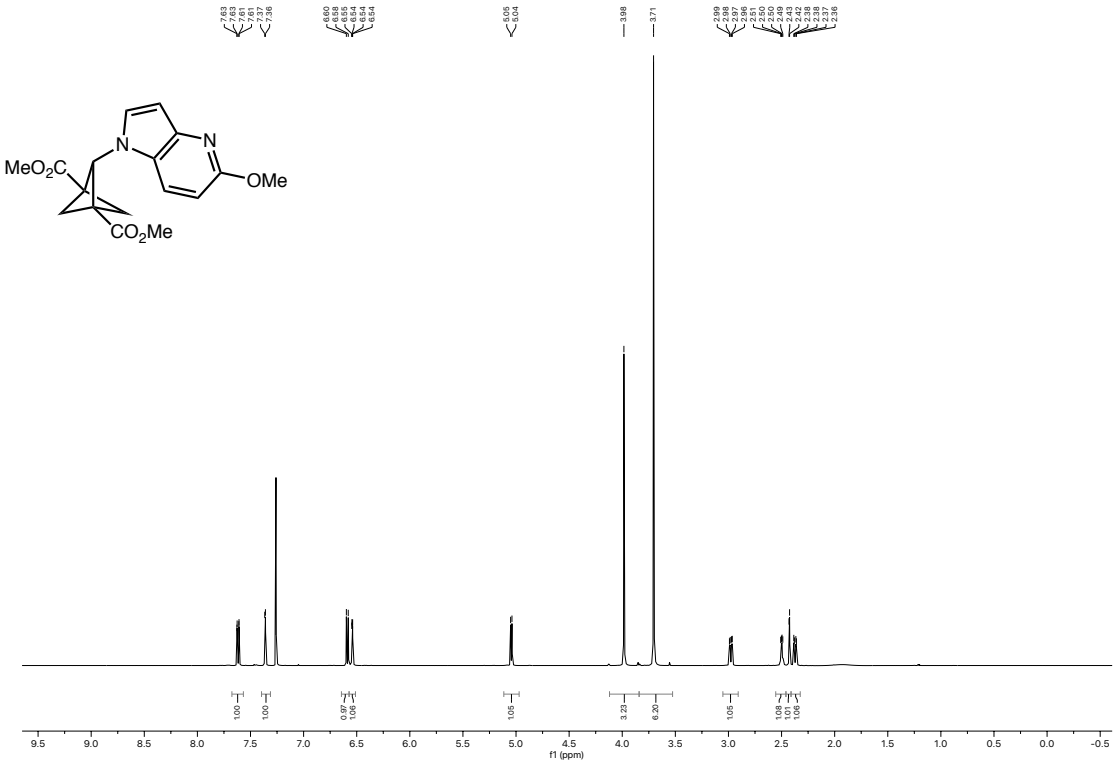
**Dimethyl 2-(4-chloro-3-methyl-1H-pyrrolo[2,3-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (59)**

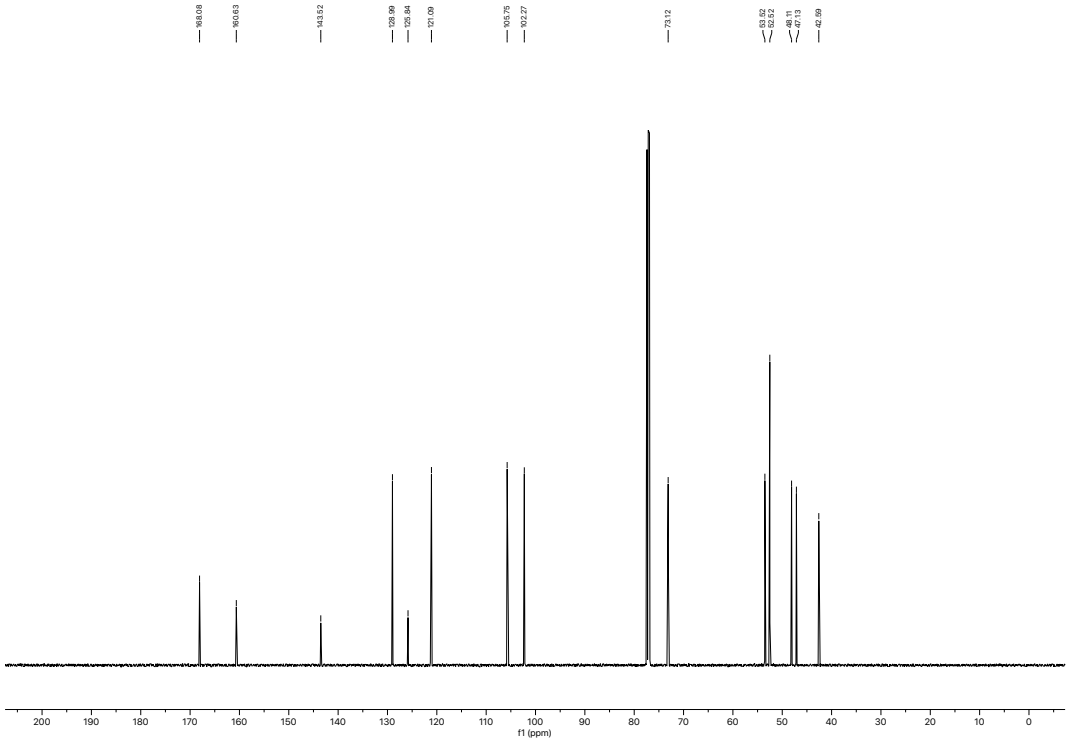


**Dimethyl 2-(6-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (60)**

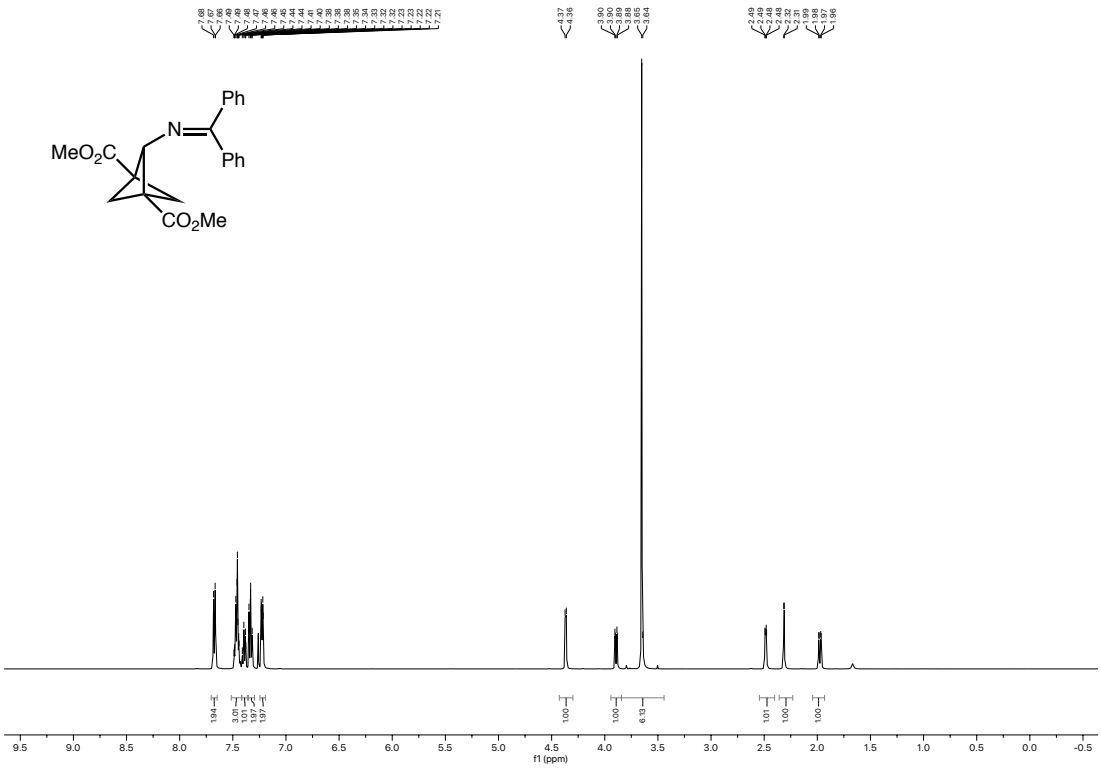


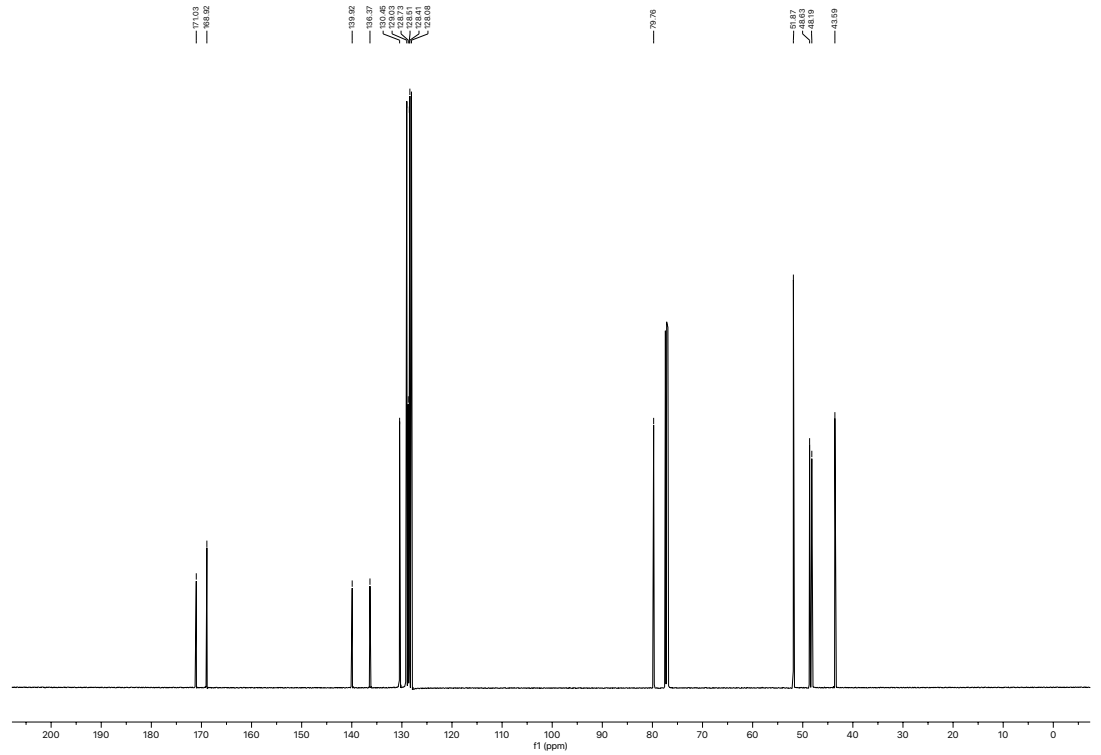
**Dimethyl 2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (61)**



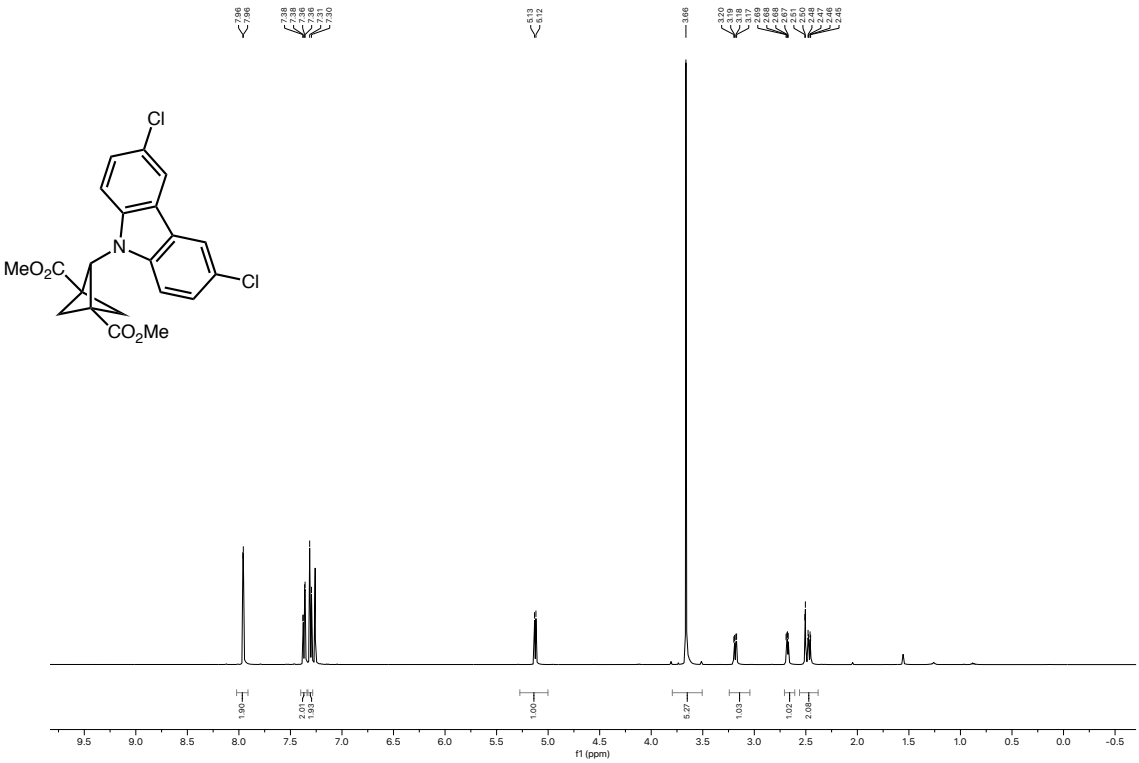



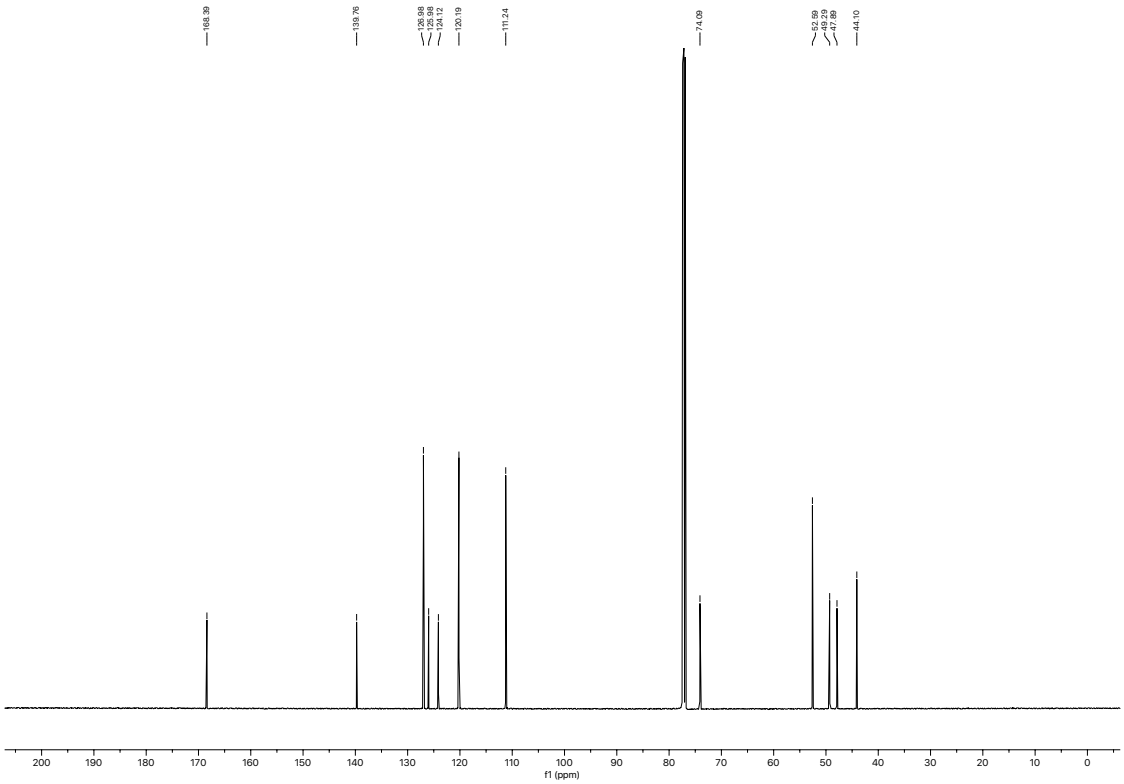
**Dimethyl 2-((diphenylmethylene)amino)bicyclo[1.1.1]pentane-1,3-dicarboxylate (62)**



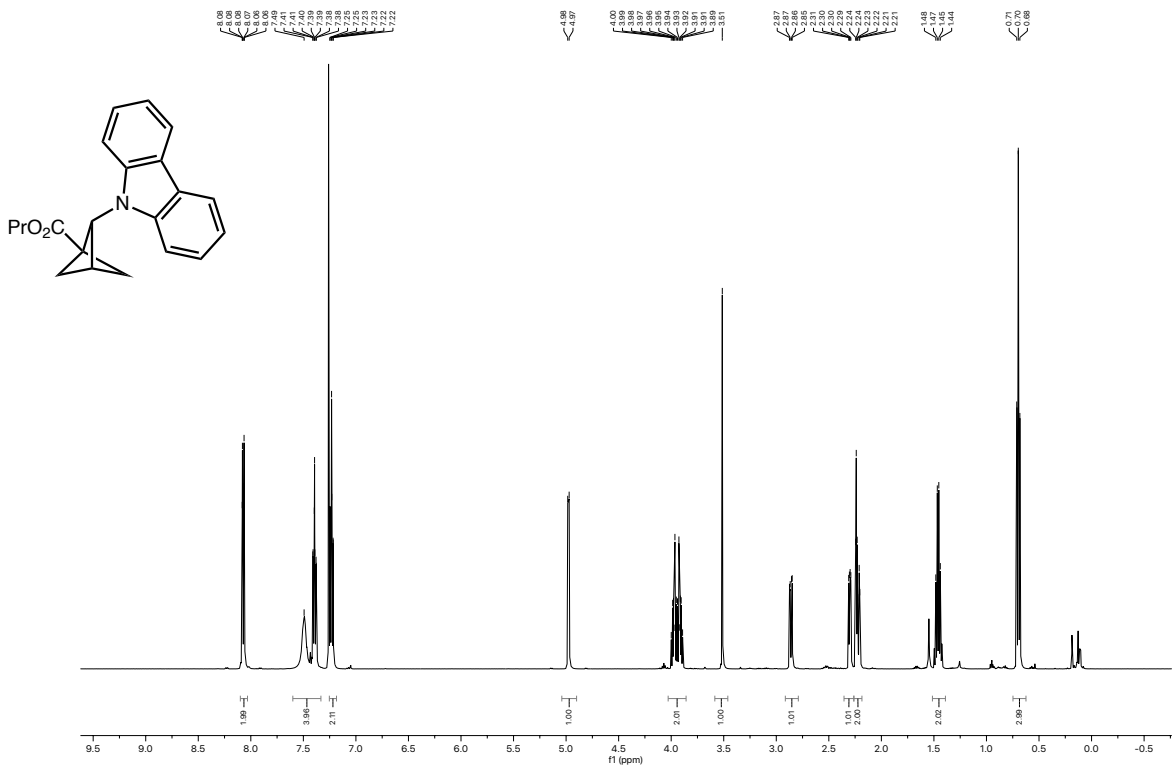



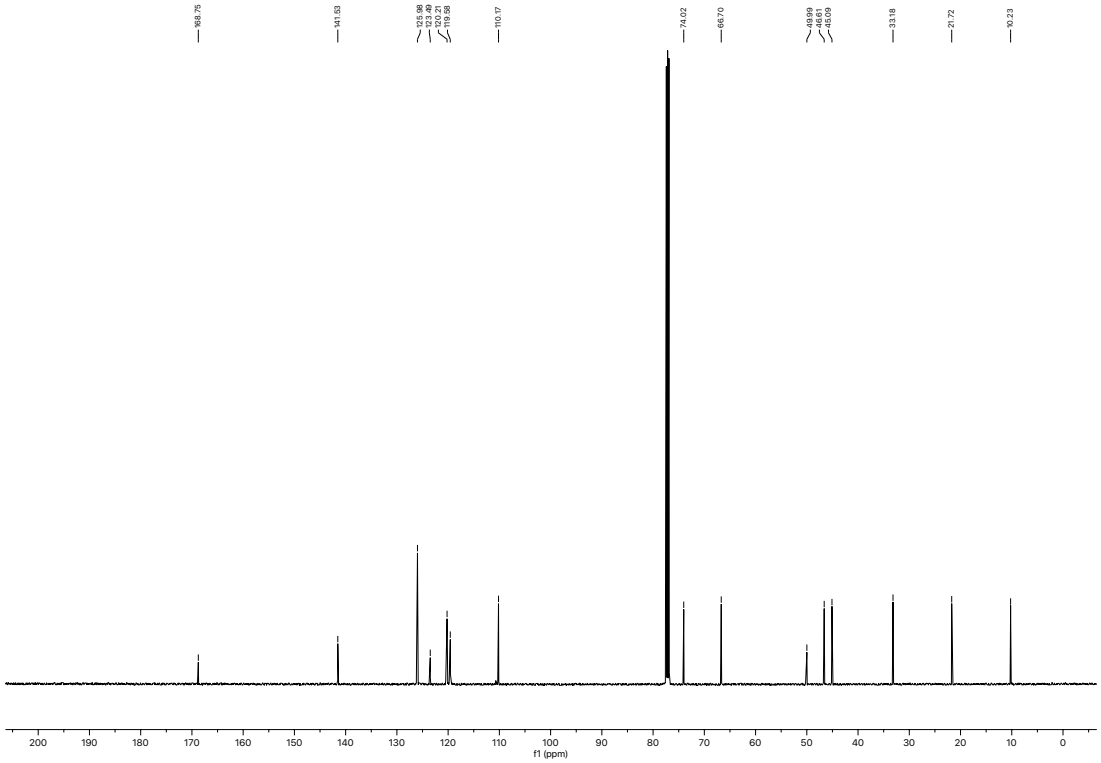
**Dimethyl 2-(3,6-dichloro-9H-carbazol-9-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (63)**



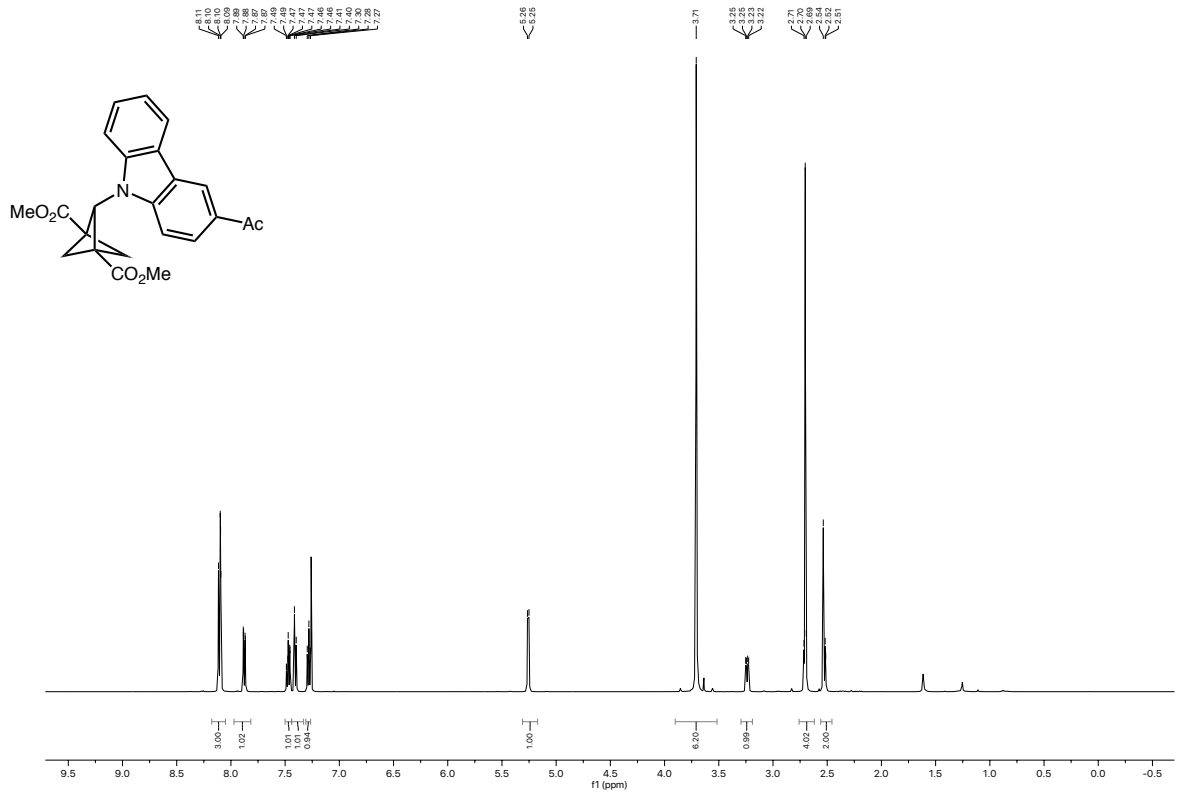



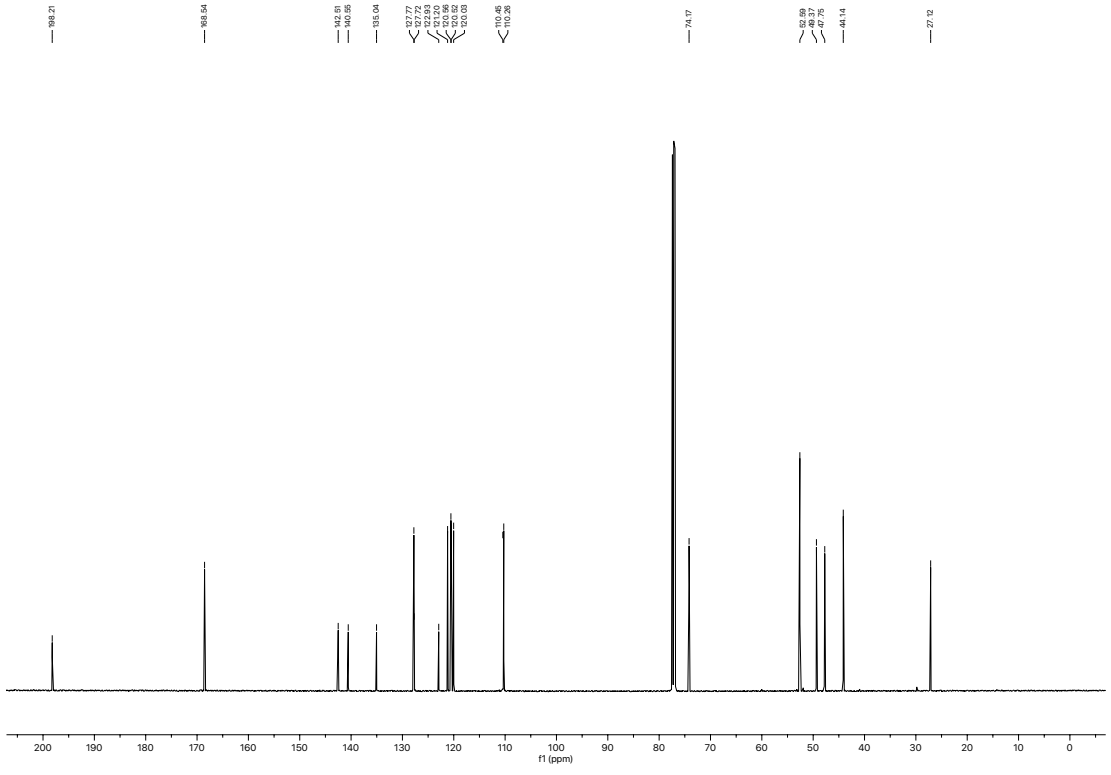
**(±)-Propyl 2-(9*H*-carbazol-9-yl)bicyclo[1.1.1]pentane-1-carboxylate (64)**



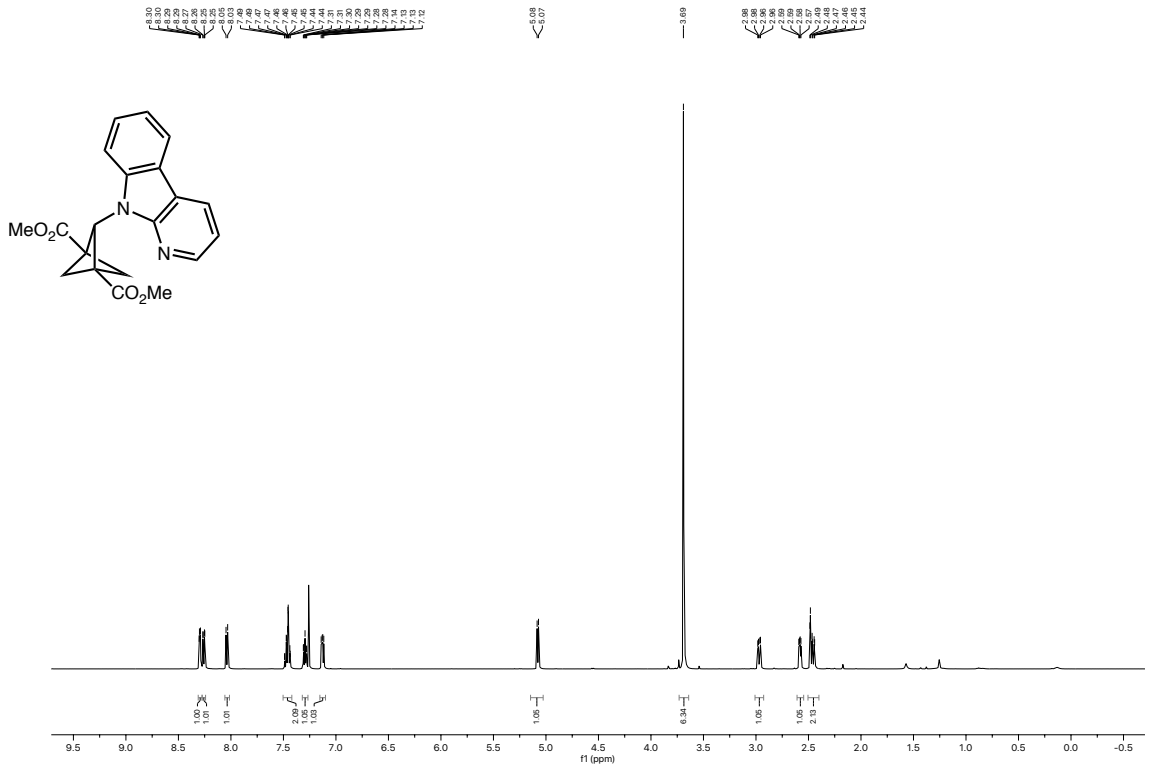



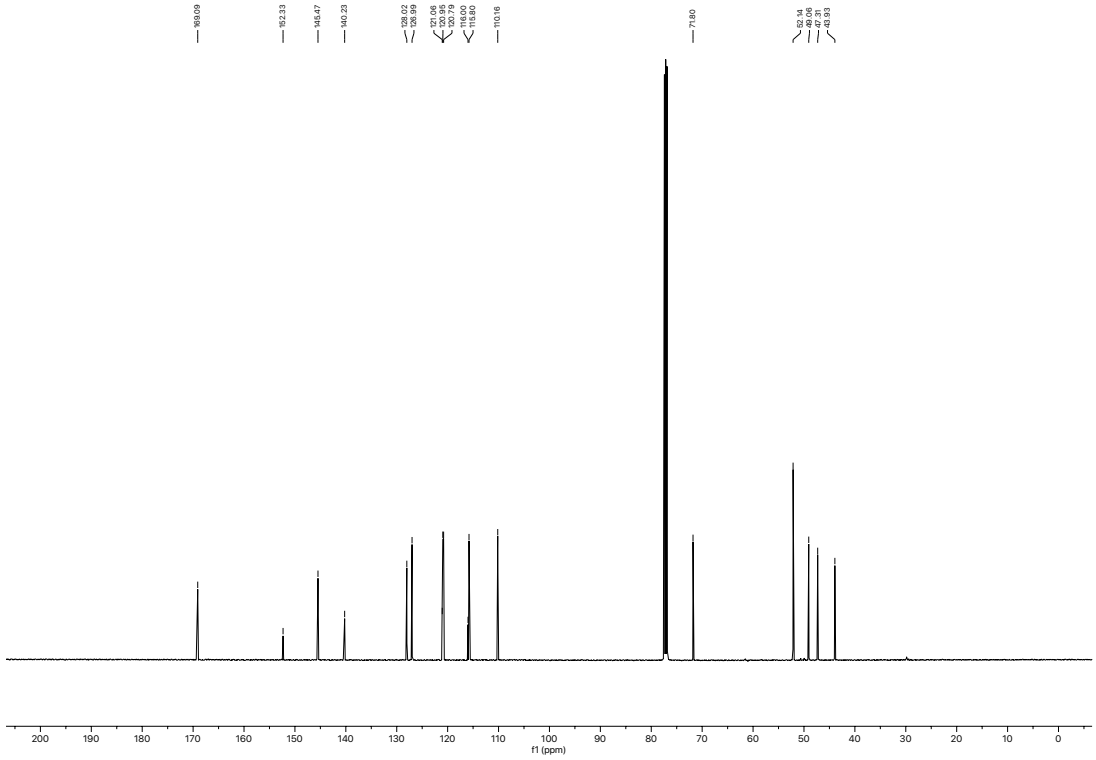
**Dimethyl 2-(3-acetyl-9*H*-carbazol-9-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (65)**



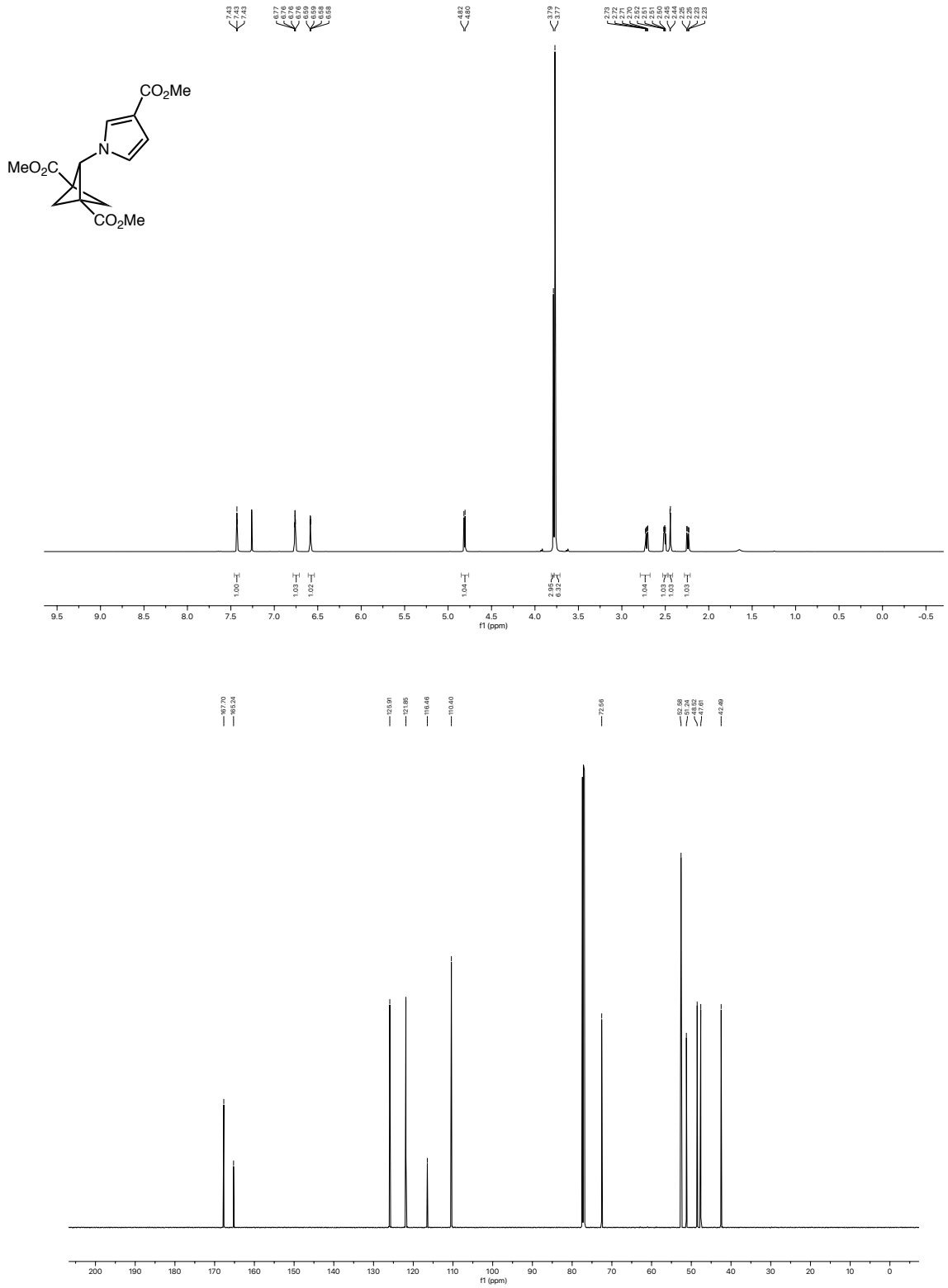



**Dimethyl 2-(9H-pyrido[2,3-b]indol-9-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (66)**

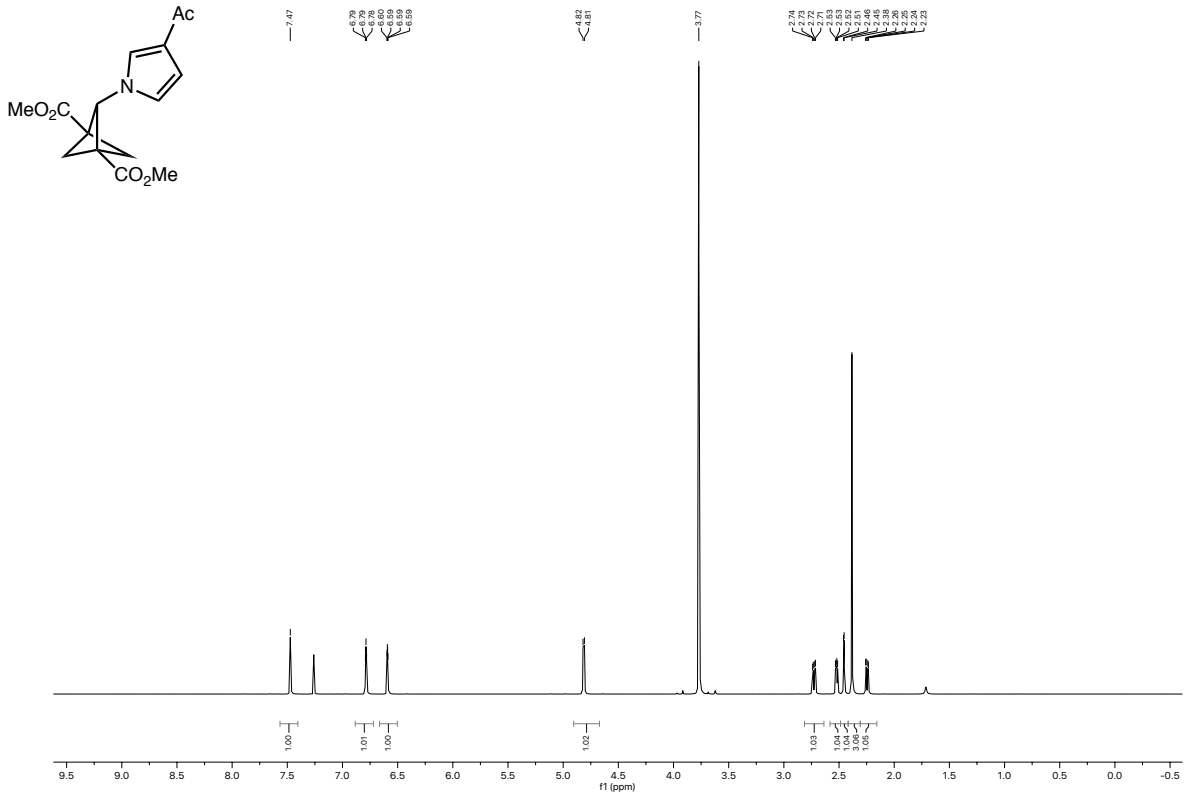


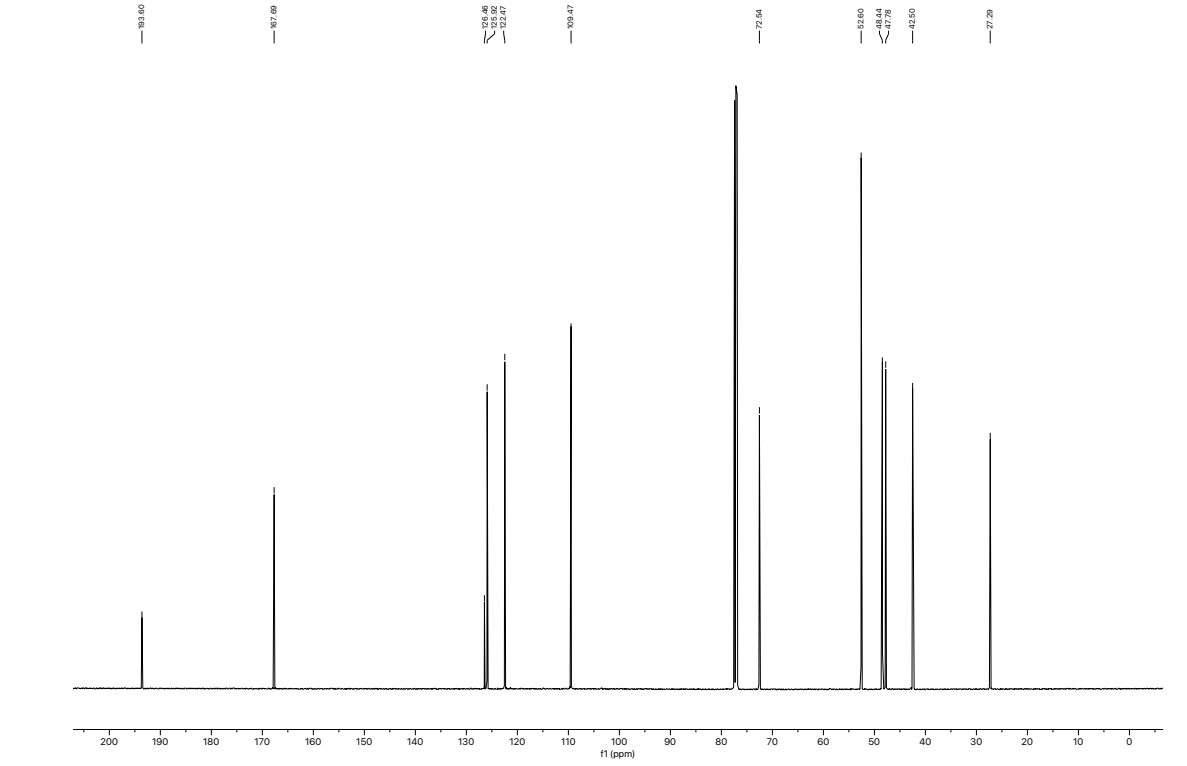



**Dimethyl 2-(3-(methoxycarbonyl)-1*H*-pyrrol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (67)**

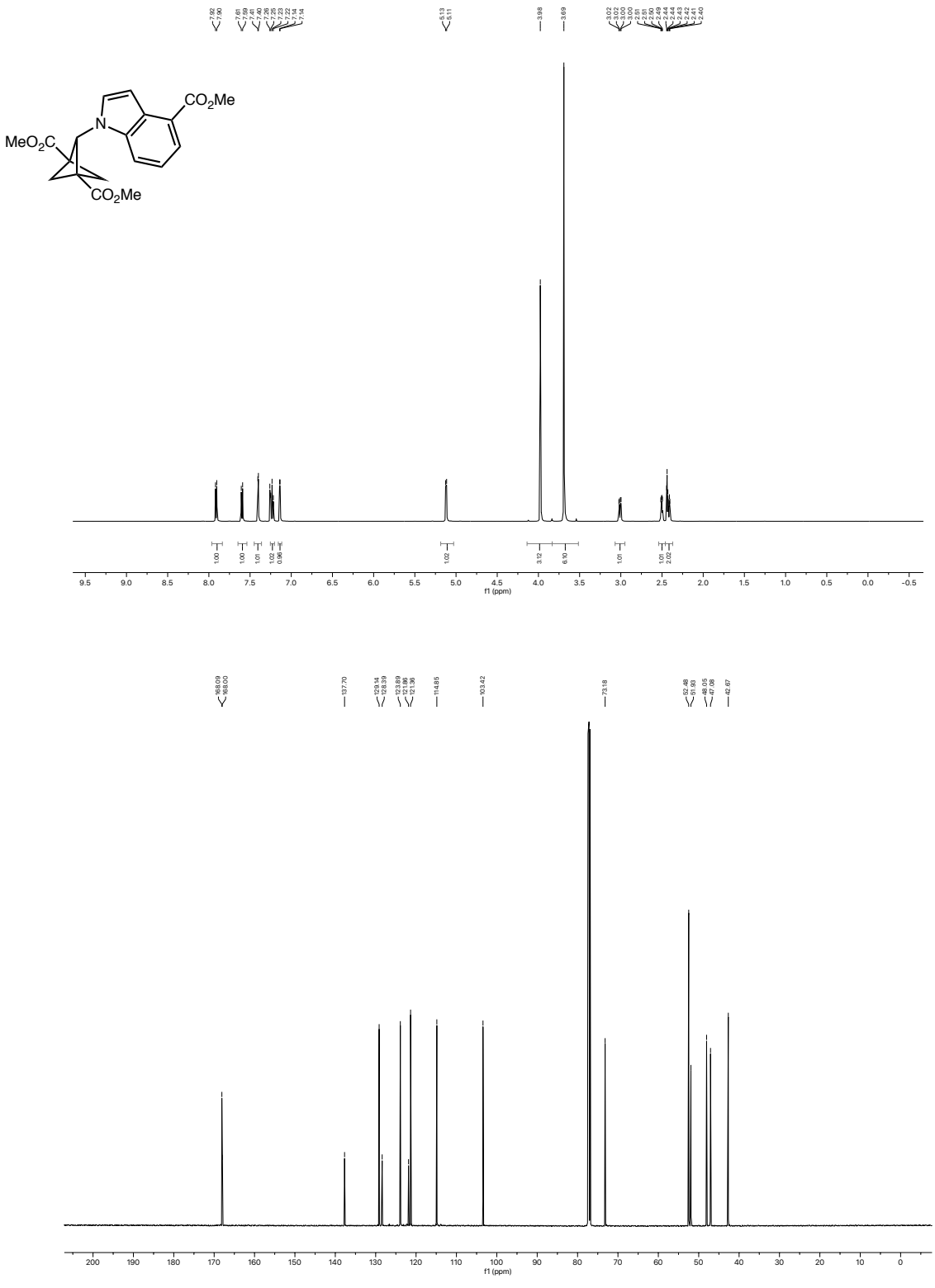


**Dimethyl 2-(3-acetyl-1H-pyrrol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (68)**

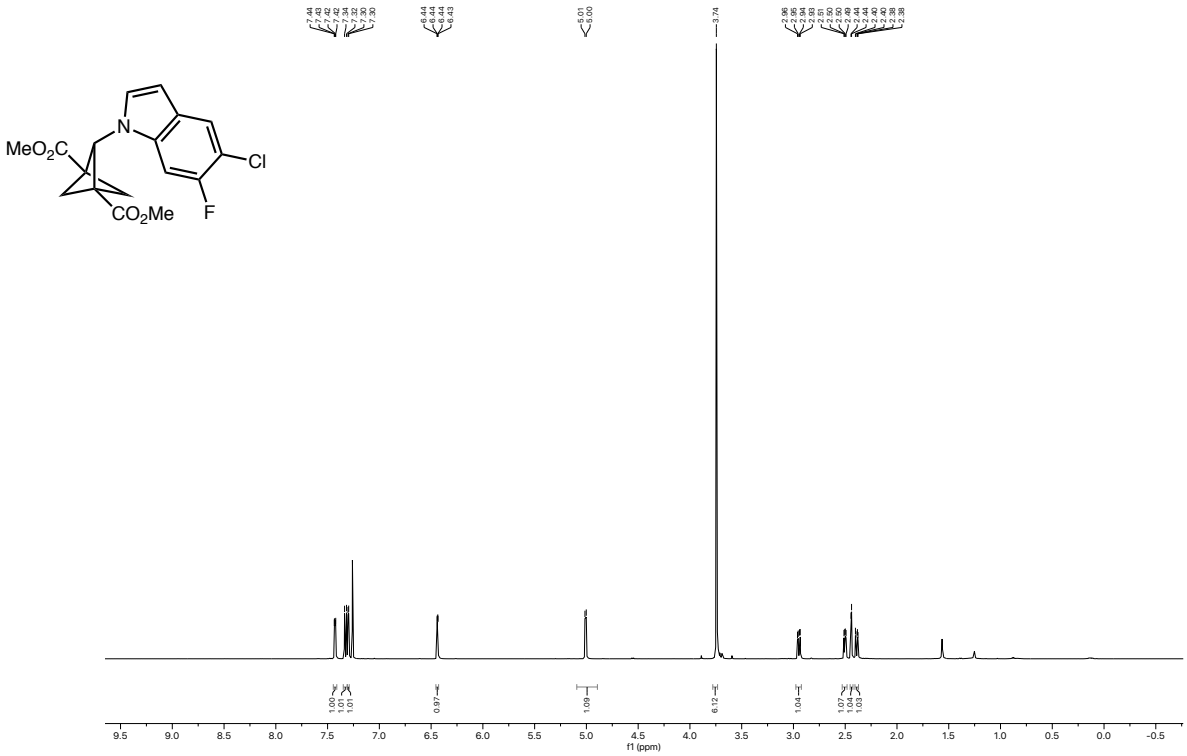


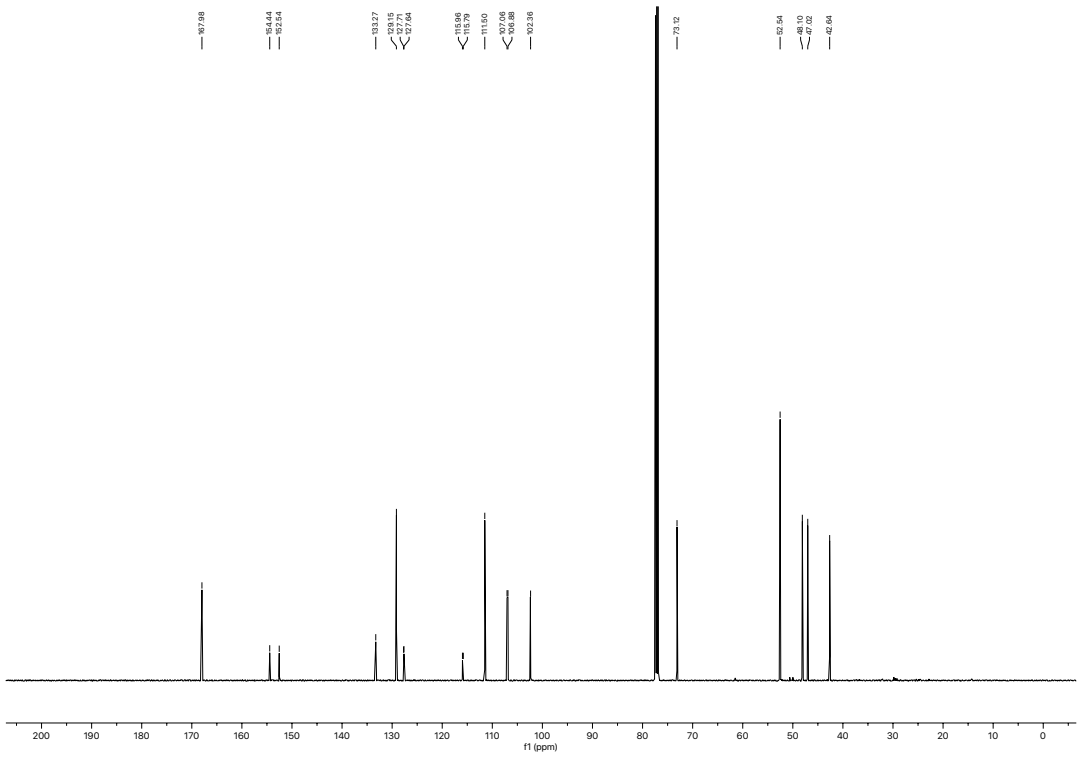



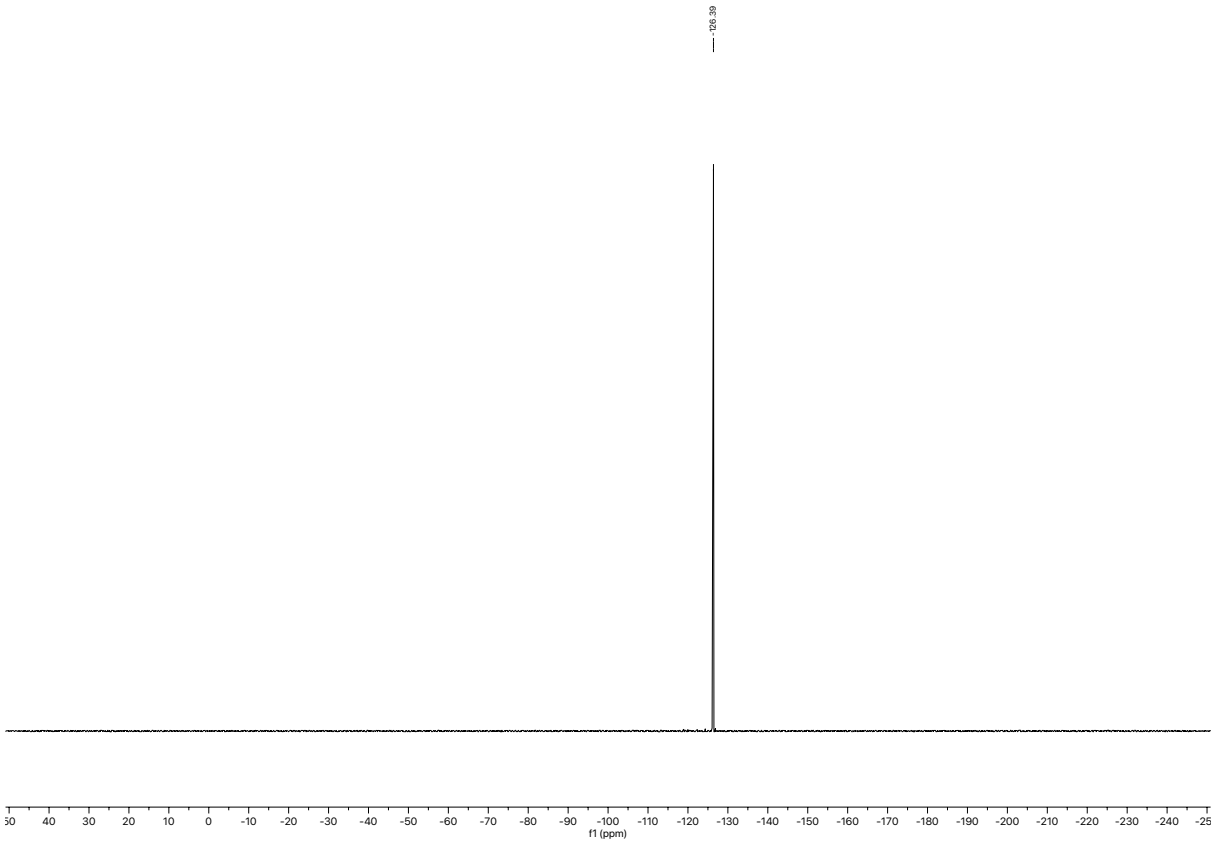
**Dimethyl 2-(4-(methoxycarbonyl)-1H-indol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (69)**



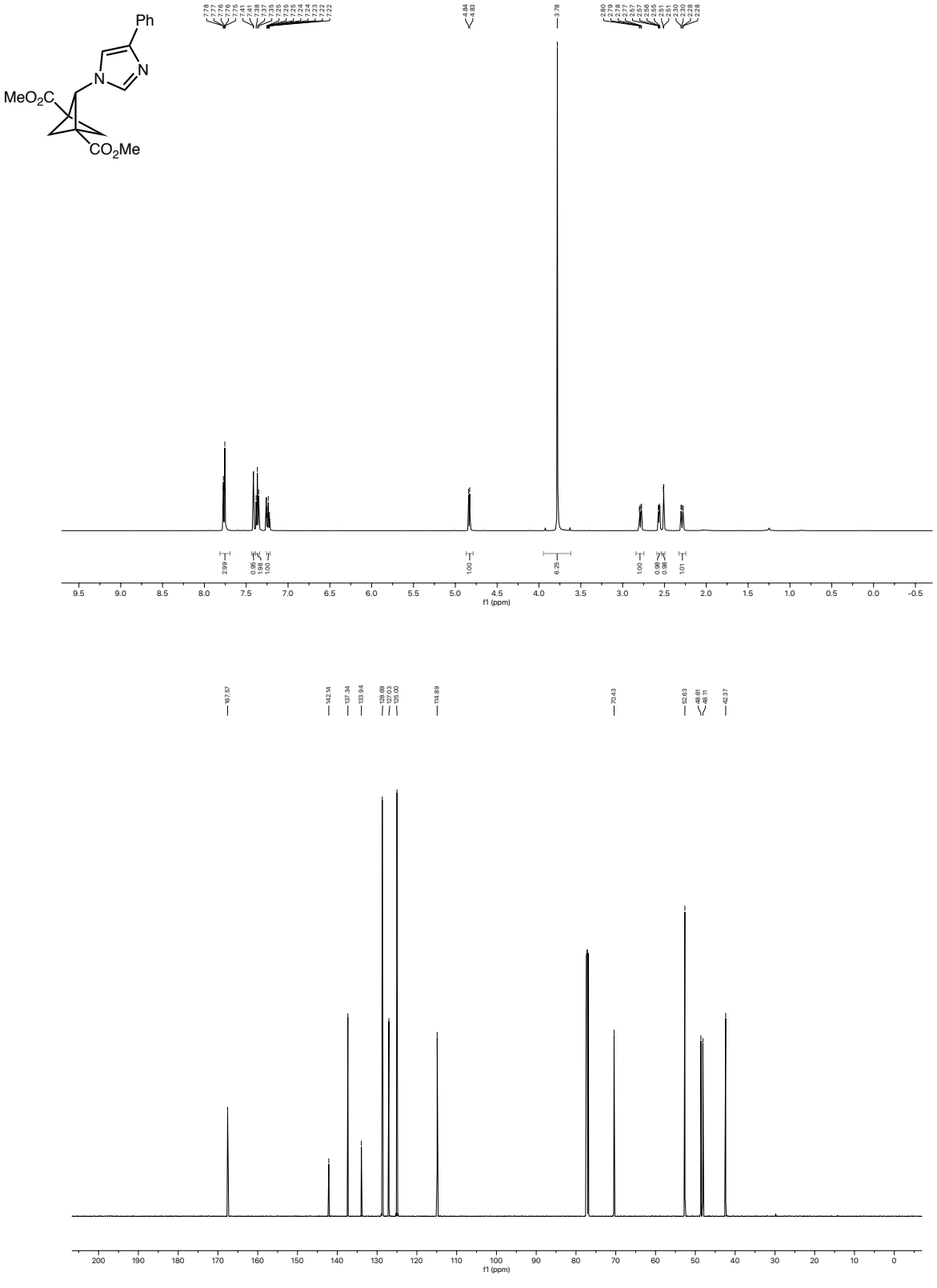
**Dimethyl 2-(5-chloro-6-fluoro-1*H*-indol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (70)**



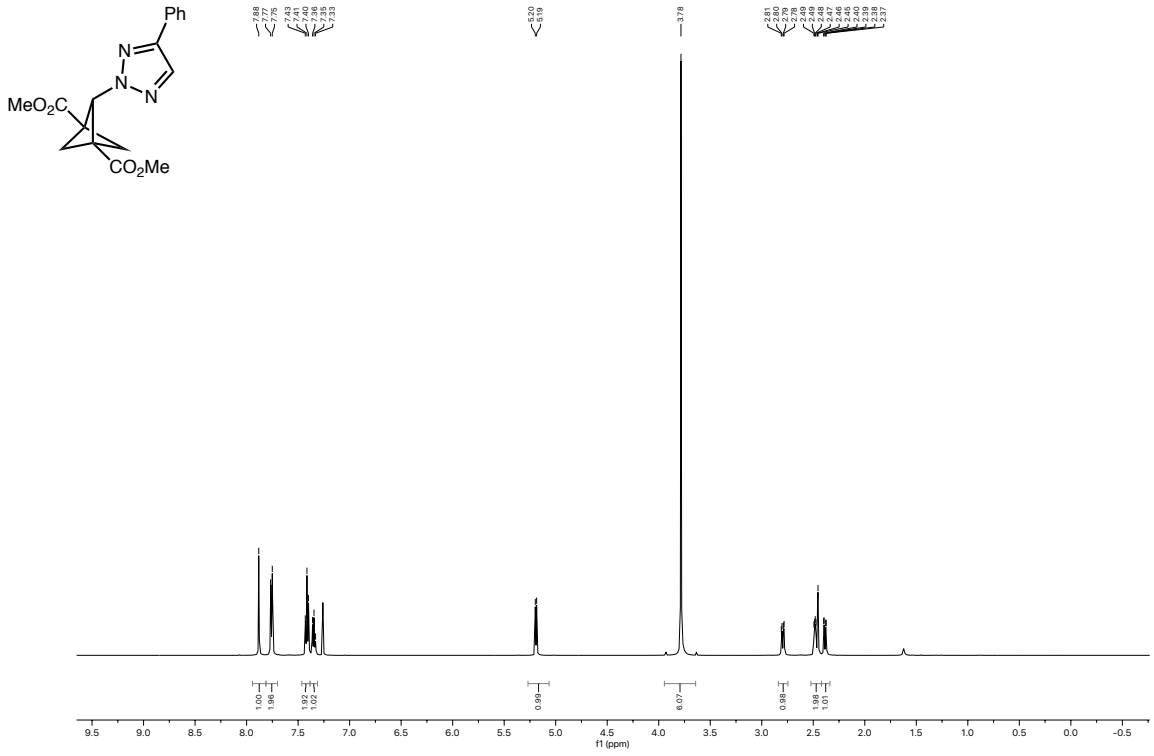



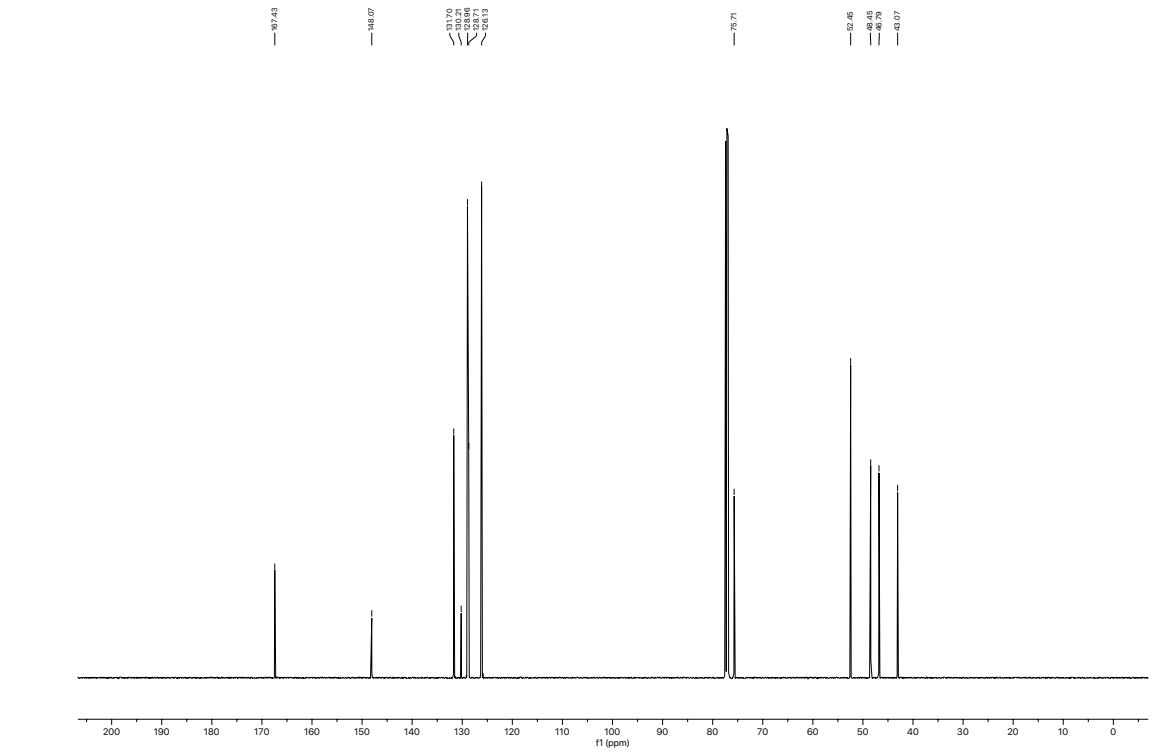

-126.39
50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -25
f1 (ppm)

**Dimethyl 2-(4-phenyl-1*H*-imidazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (71)**

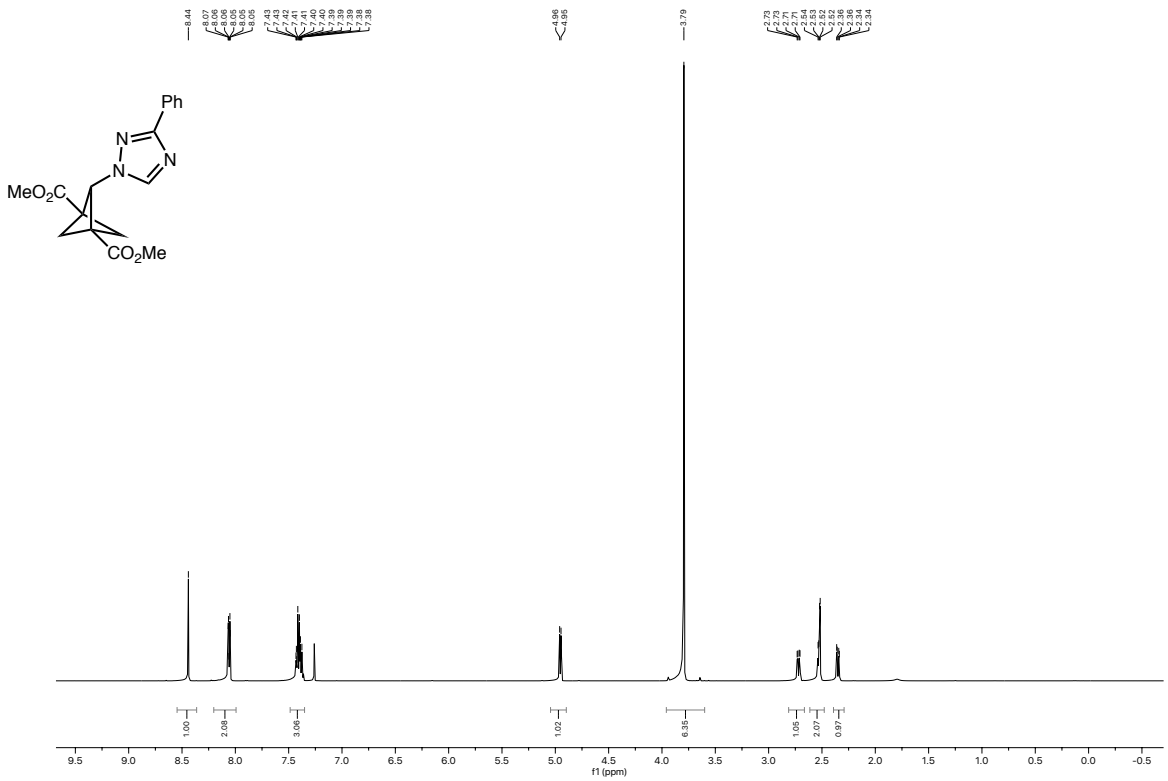


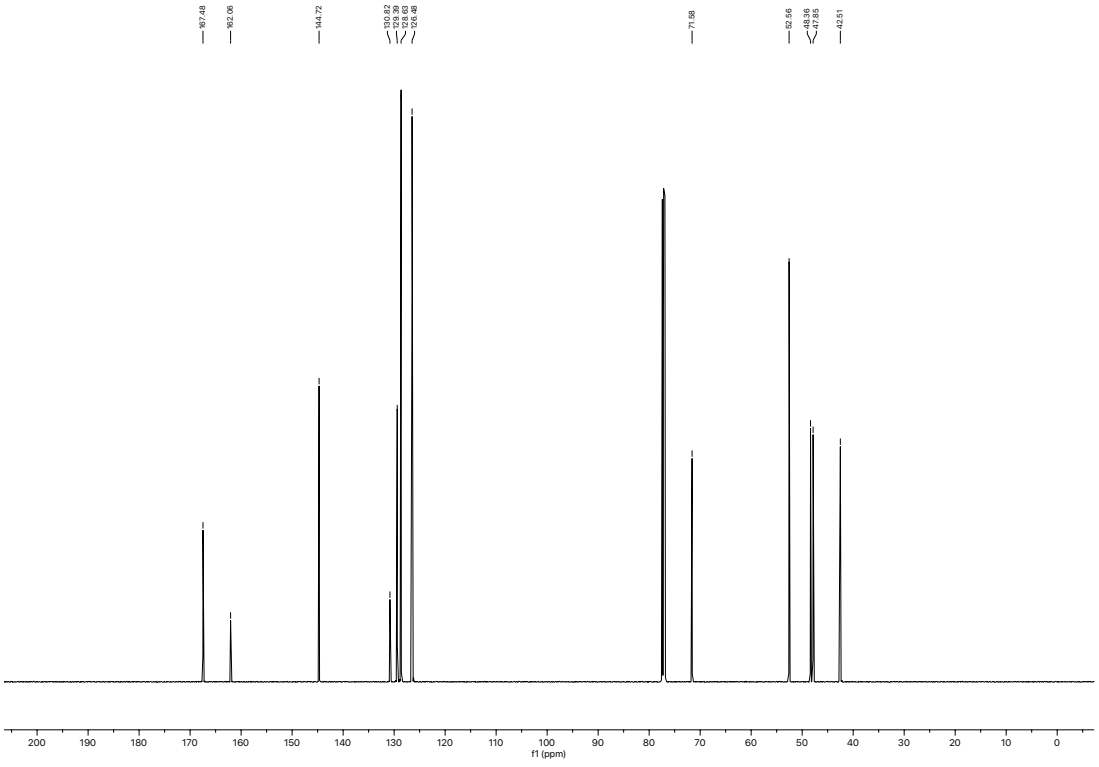
**Dimethyl 2-(4-phenyl-2*H*-1,2,3-triazol-2-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (72)**



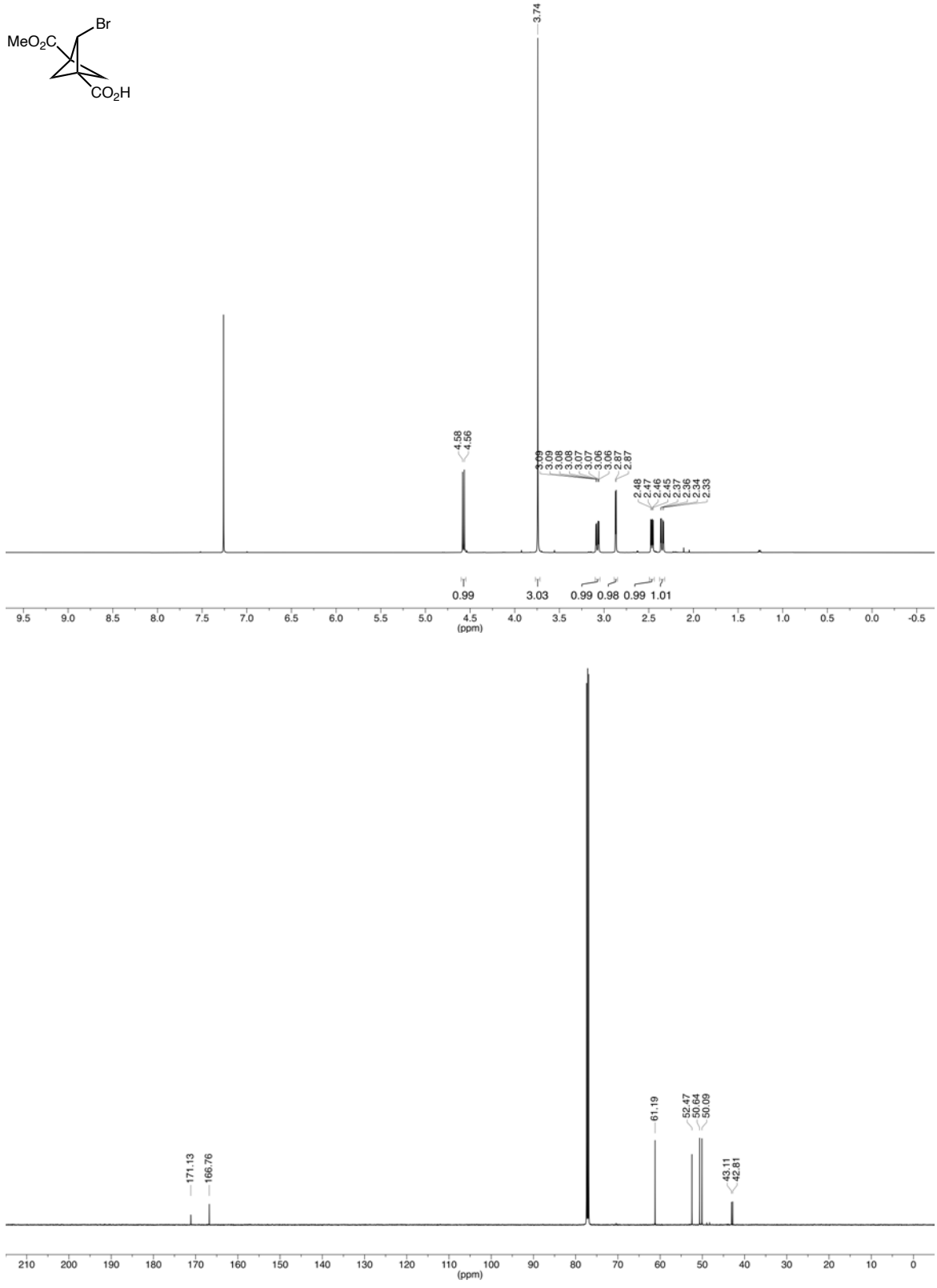



**Dimethyl 2-(3-phenyl-1*H*-1,2,4-triazol-1-yl)bicyclo[1.1.1]pentane-1,3-dicarboxylate (73)**

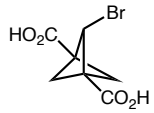


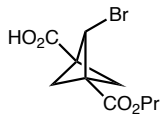
**(±)-2-Bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (S8)**



**2-Bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (3)**

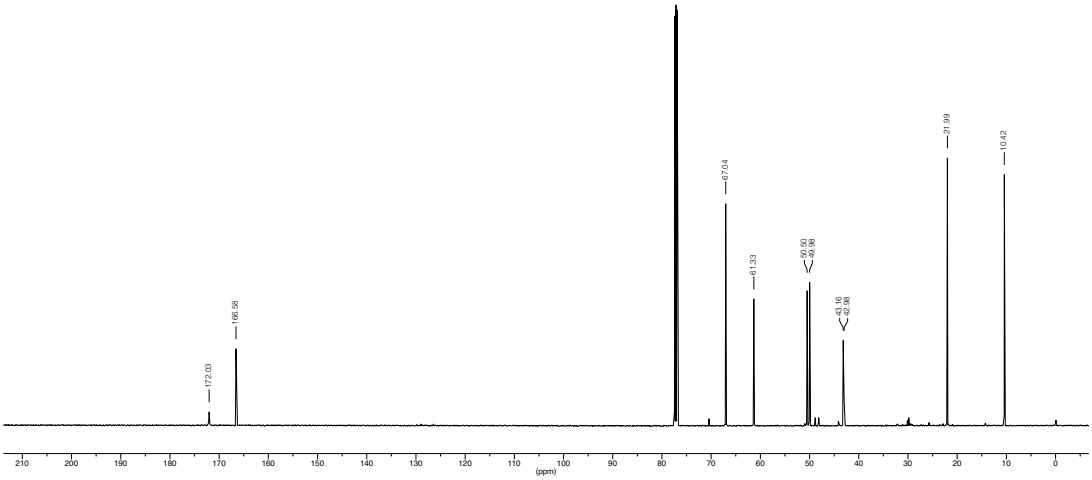


**(±)-2-Bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (S9)**

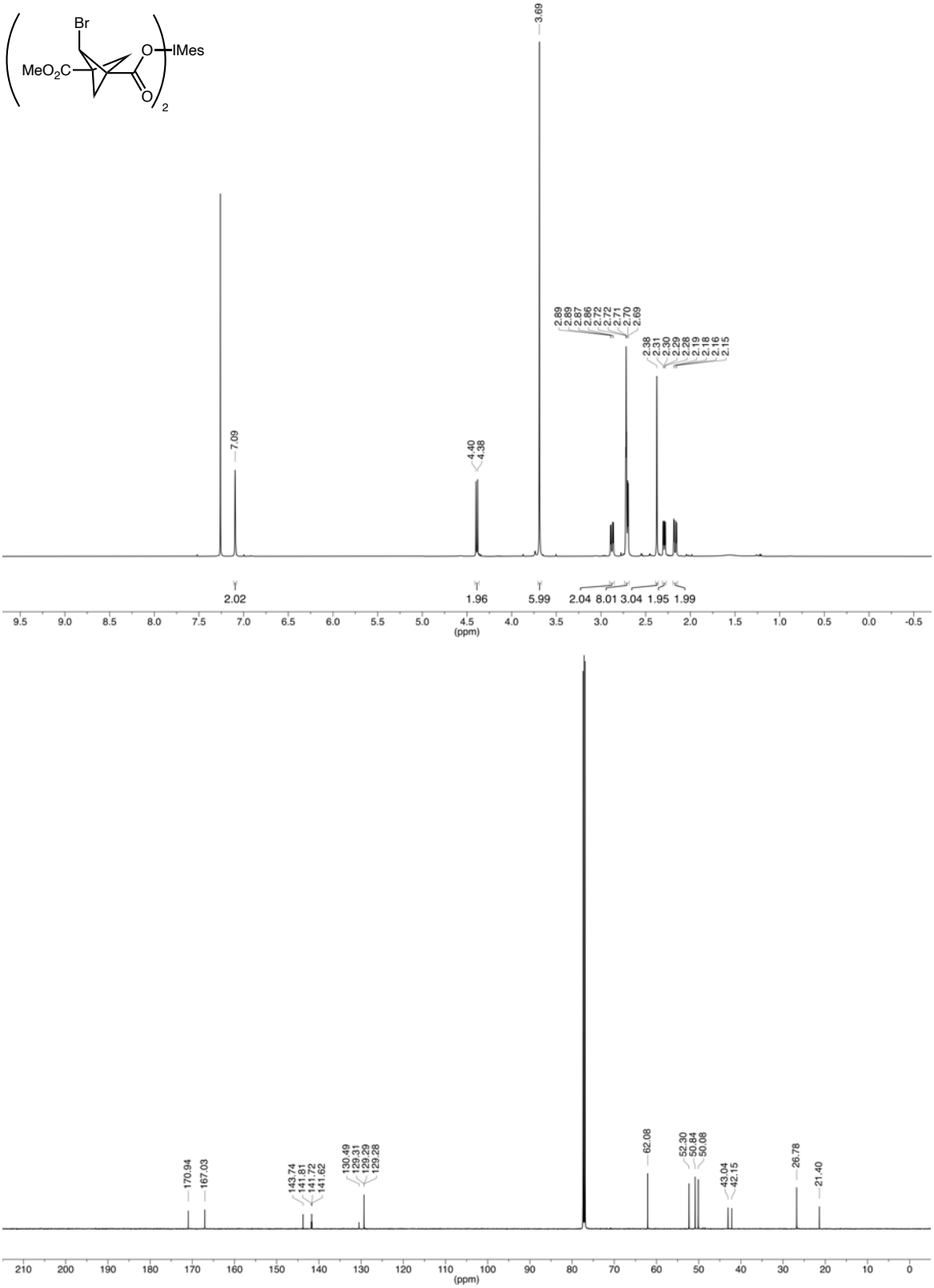




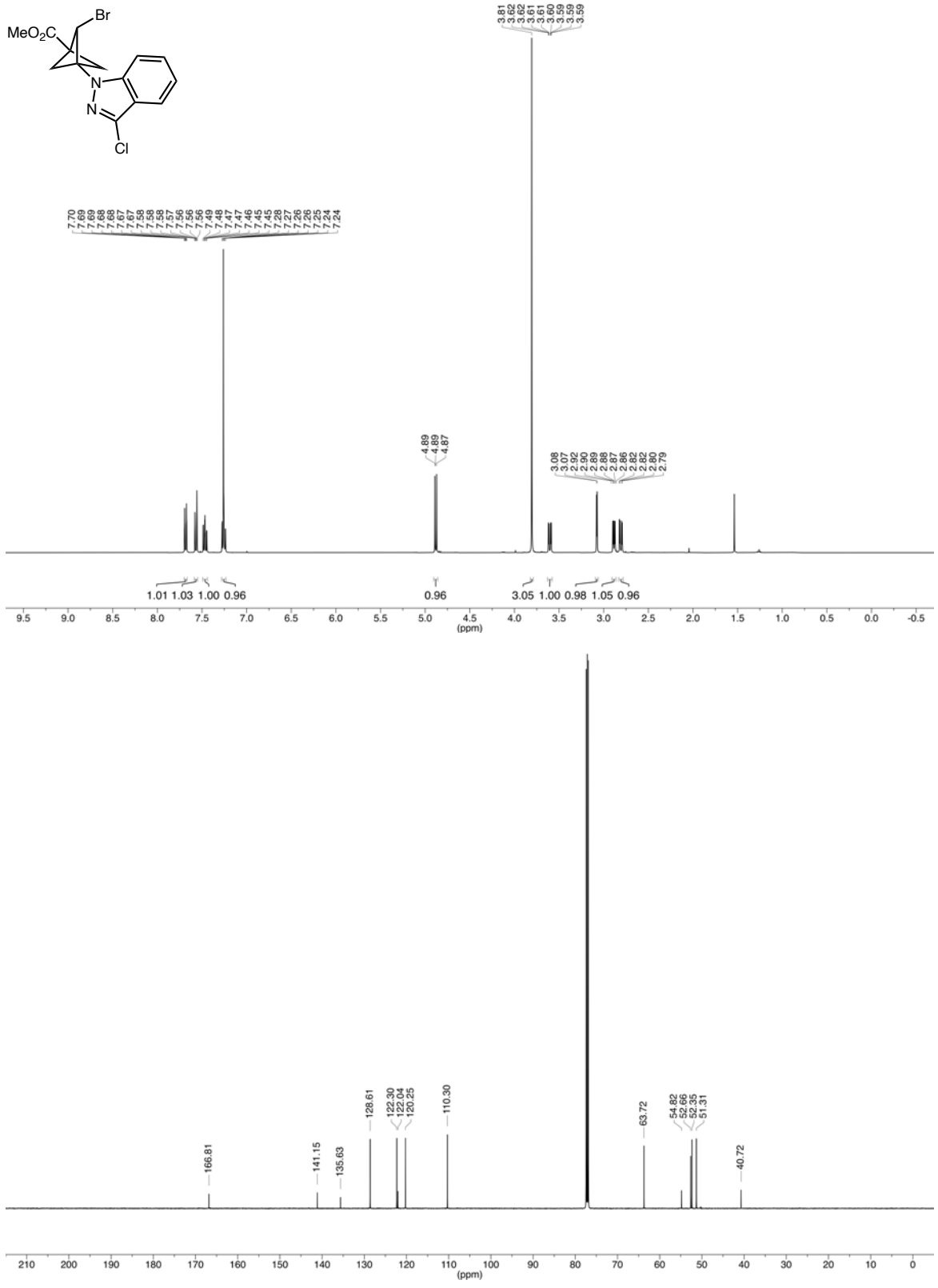




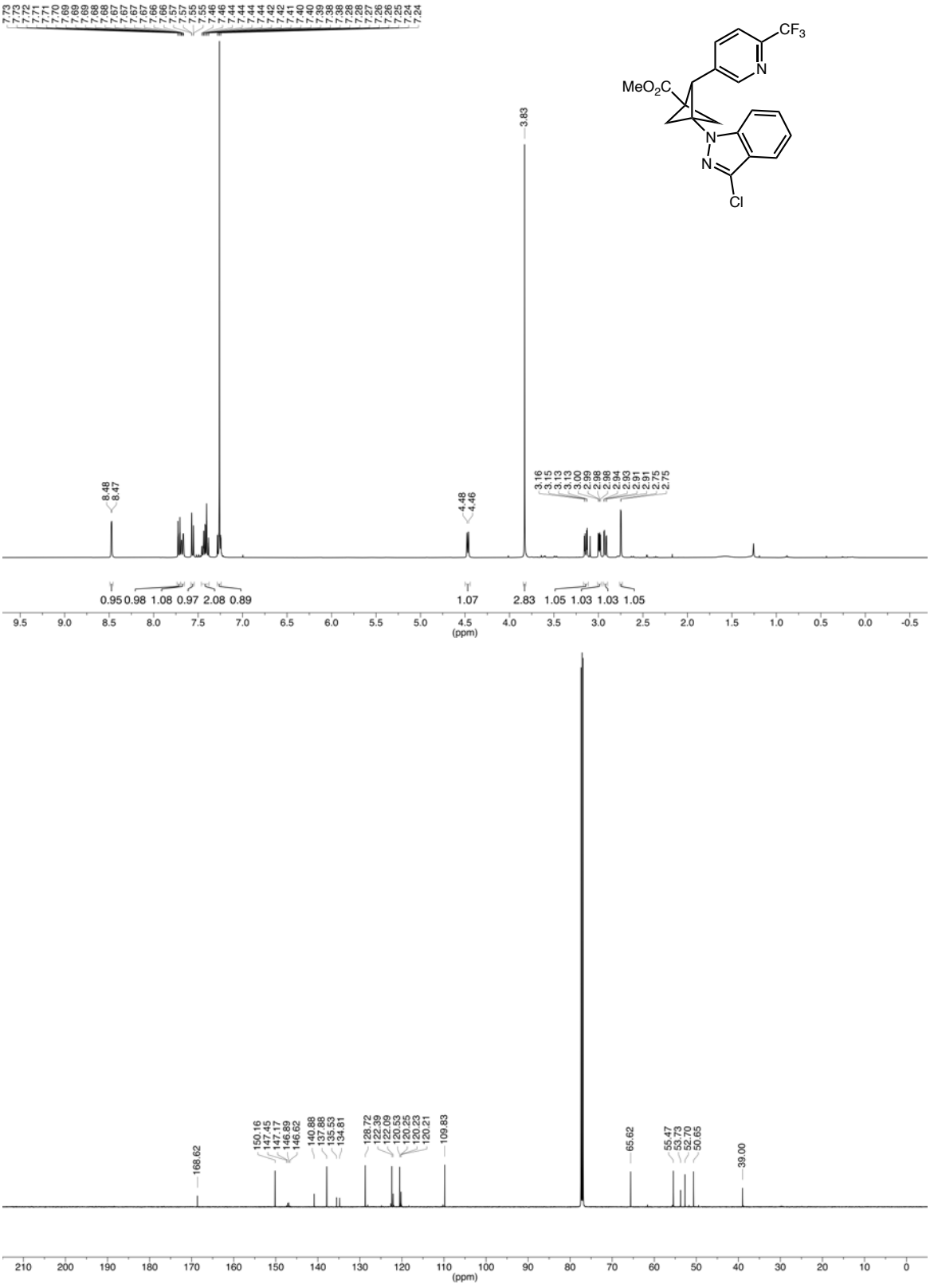
**(±)-Bis-2-bromo-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carbonyl)oxy)iodomesitylene (S10)**

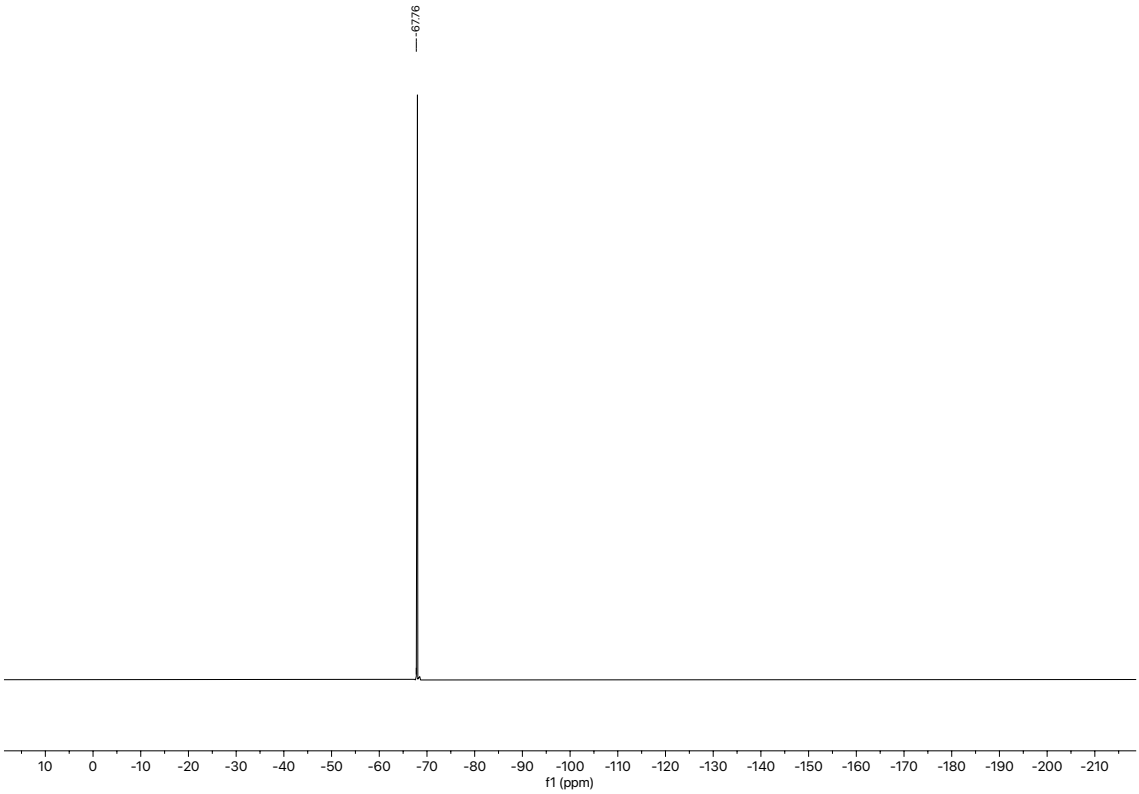


**(±)-Methyl 2-bromo-3-(3-chloro-1*H*-indazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S11)**

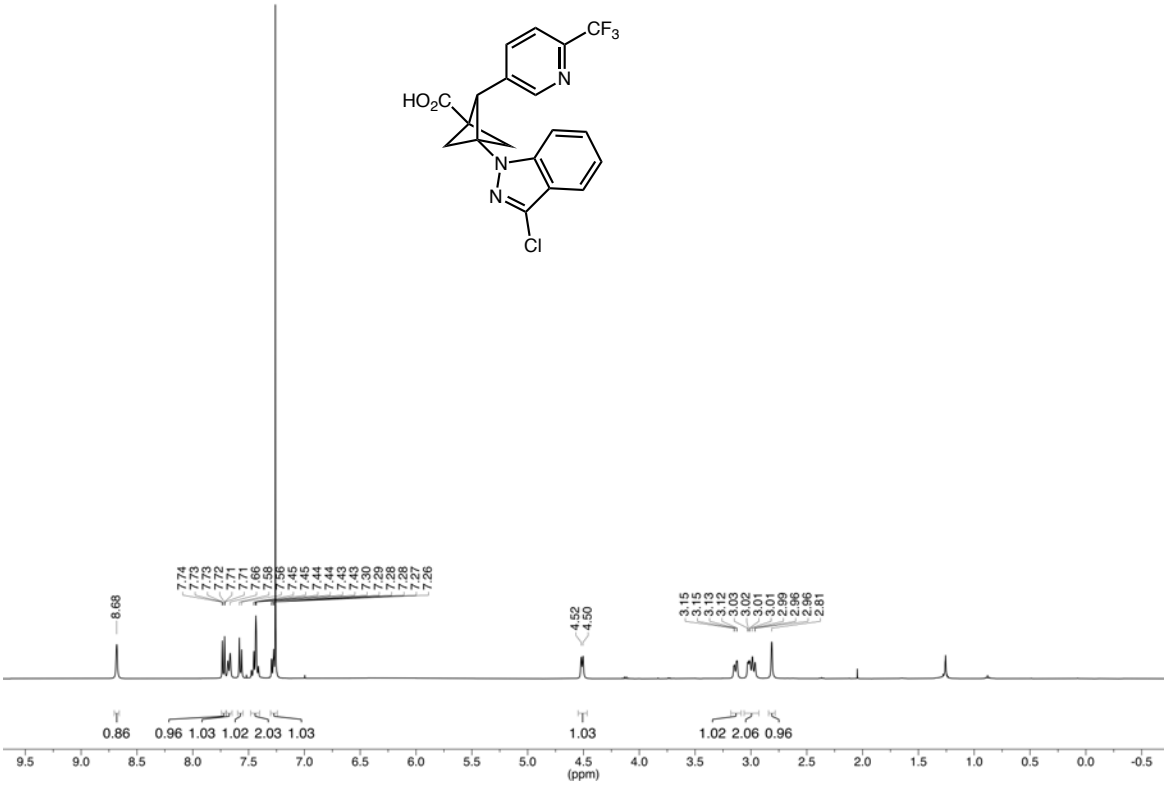


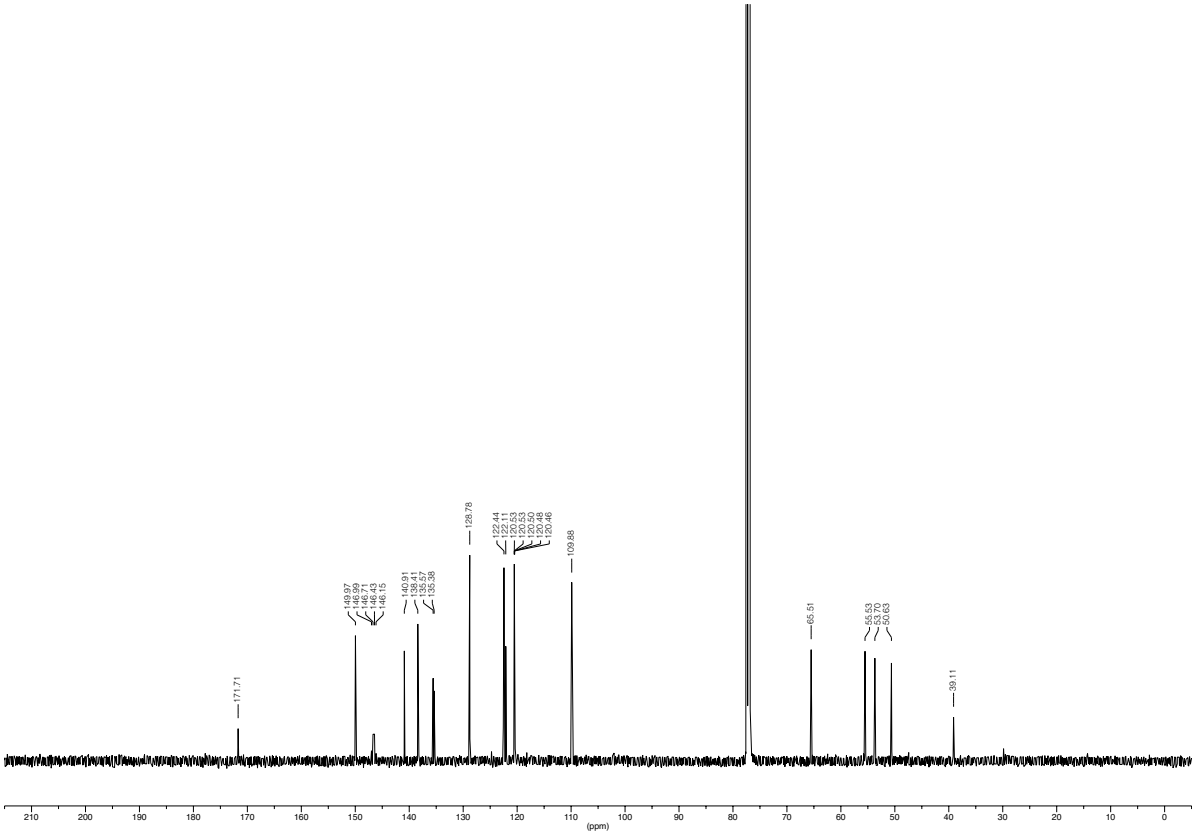
**(±)-Methyl 3-(3-chloro-1*H*-indazol-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (74)**

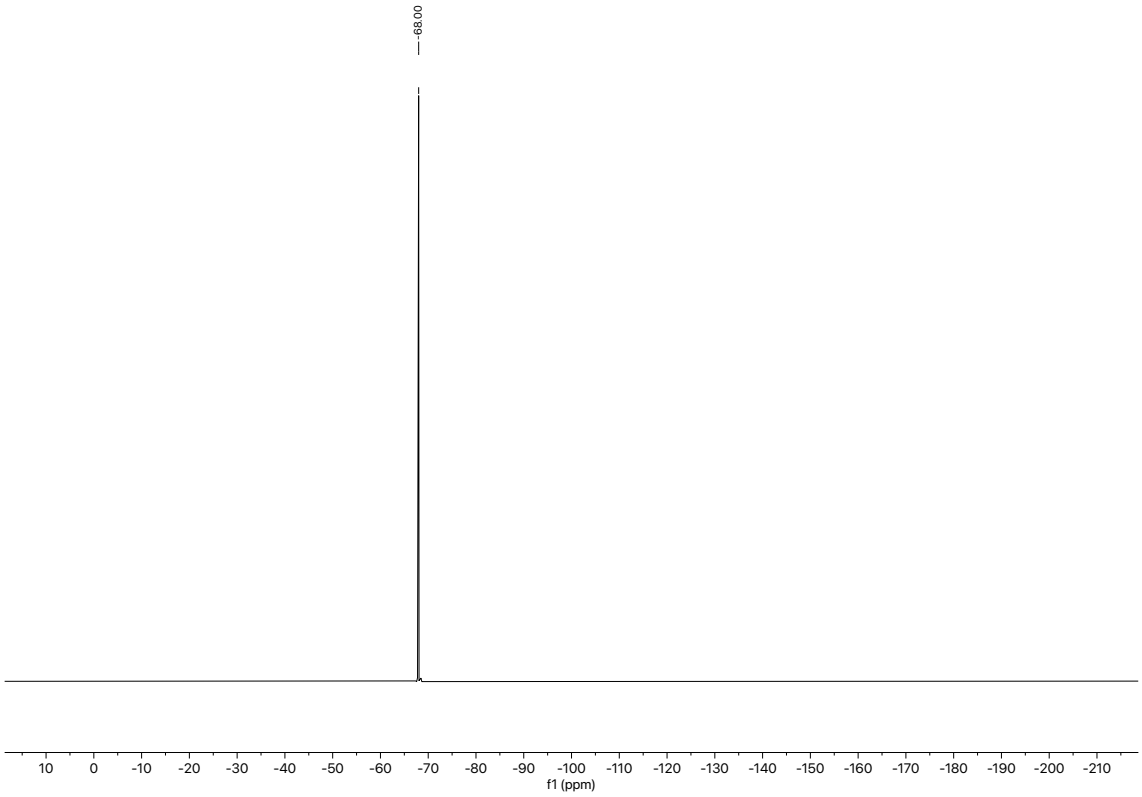




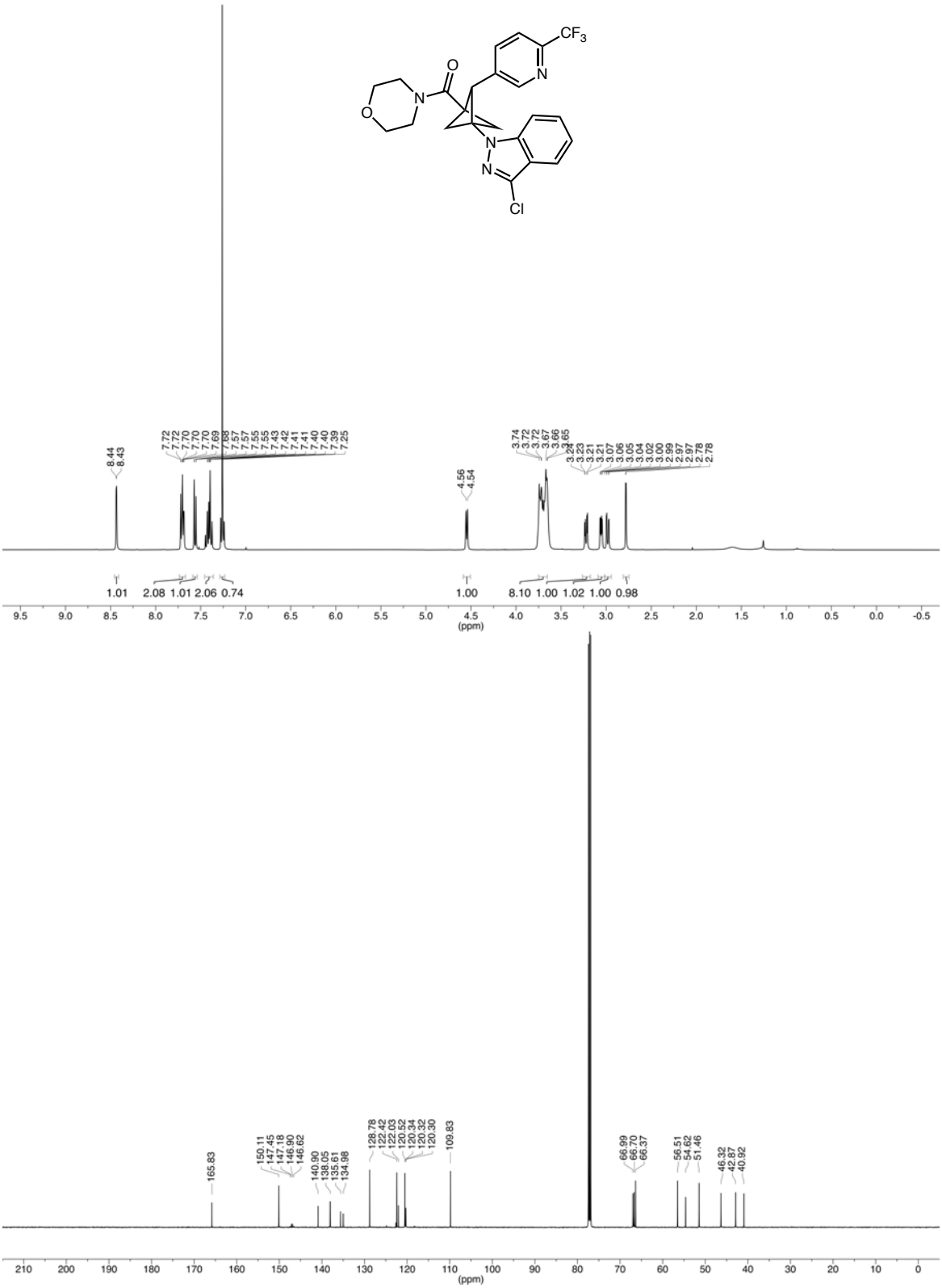

**(±)-3-(3-chloro-1*H*-indazol-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (S12)**

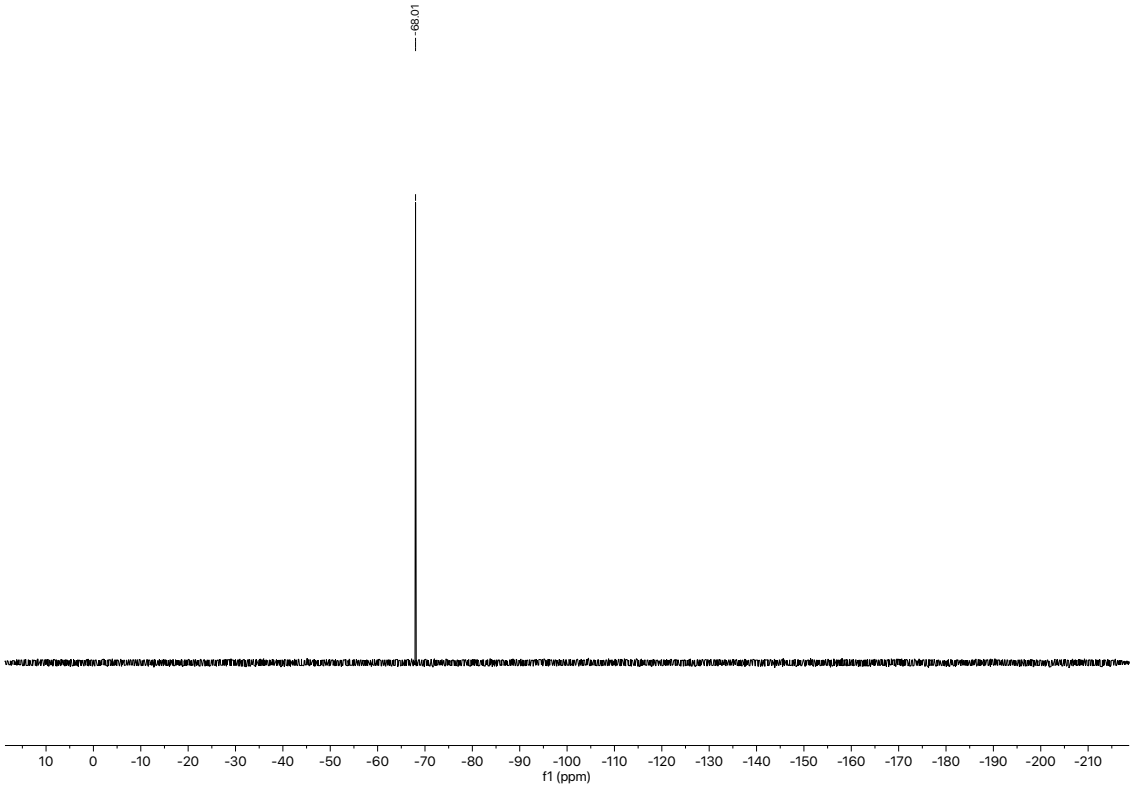



171.71
149.97
149.59
147.71
146.43
146.15
140.91
138.41
135.57
135.38
128.78
122.44
122.11
120.53
120.53
120.50
120.48
120.46
109.88
65.51
55.53
53.70
50.63
39.11
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

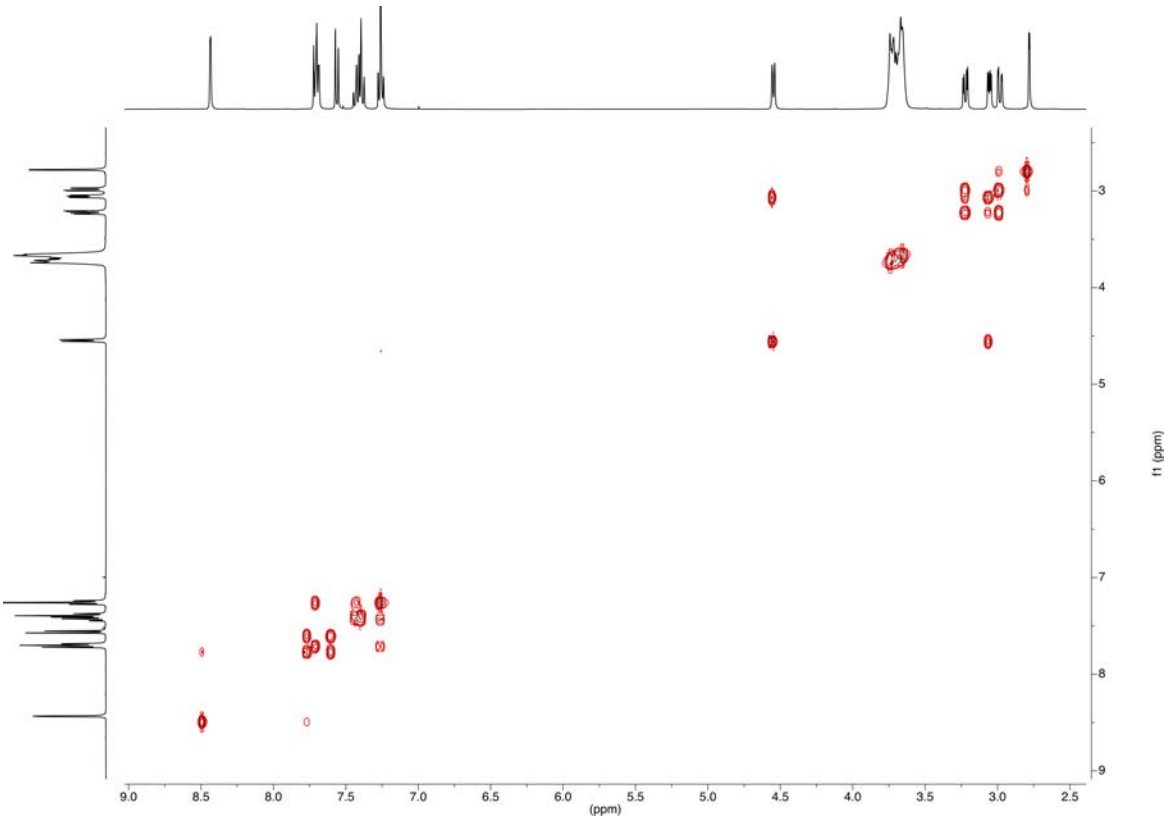

-68.00
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

**(±)-(3-(3-chloro-1*H*-indazol-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentan-1-yl)(morpholino)methanone (S13)**

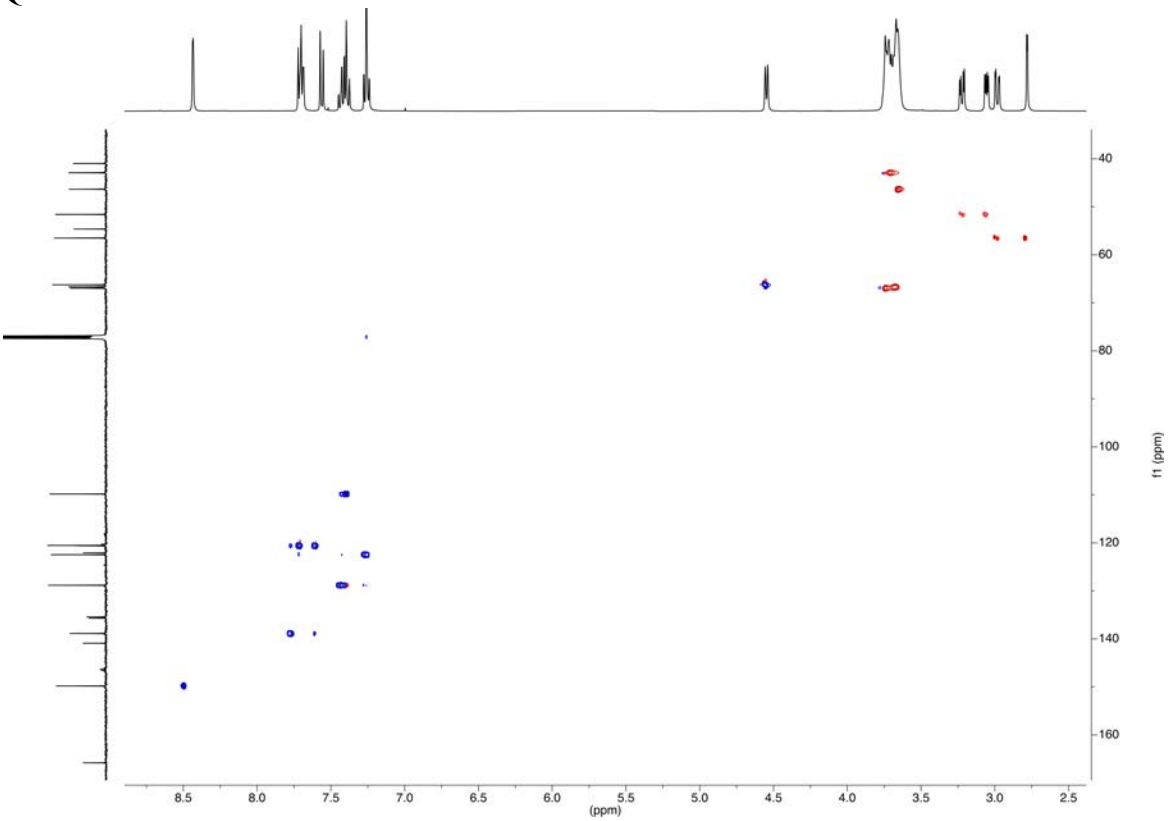



-68.01
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

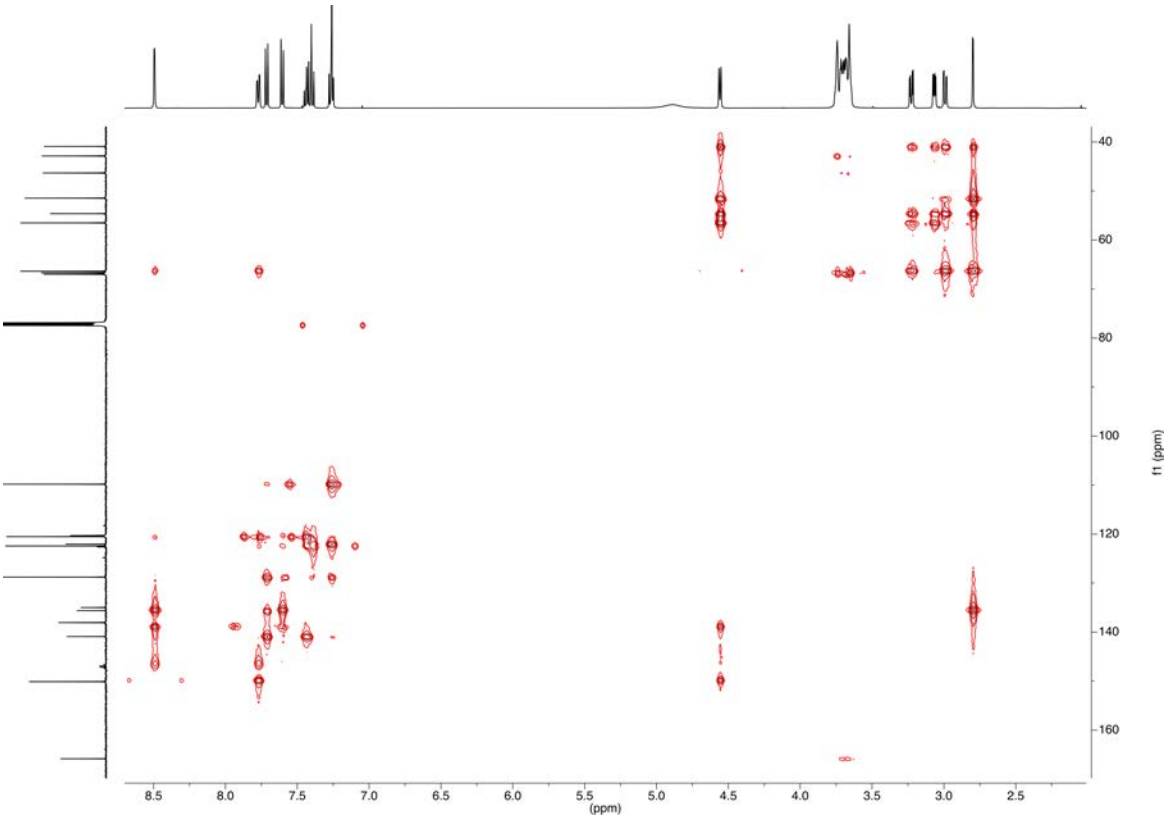
COSY:


9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5
(ppm)
3 4 5 6 7 8 9
f1 (ppm)

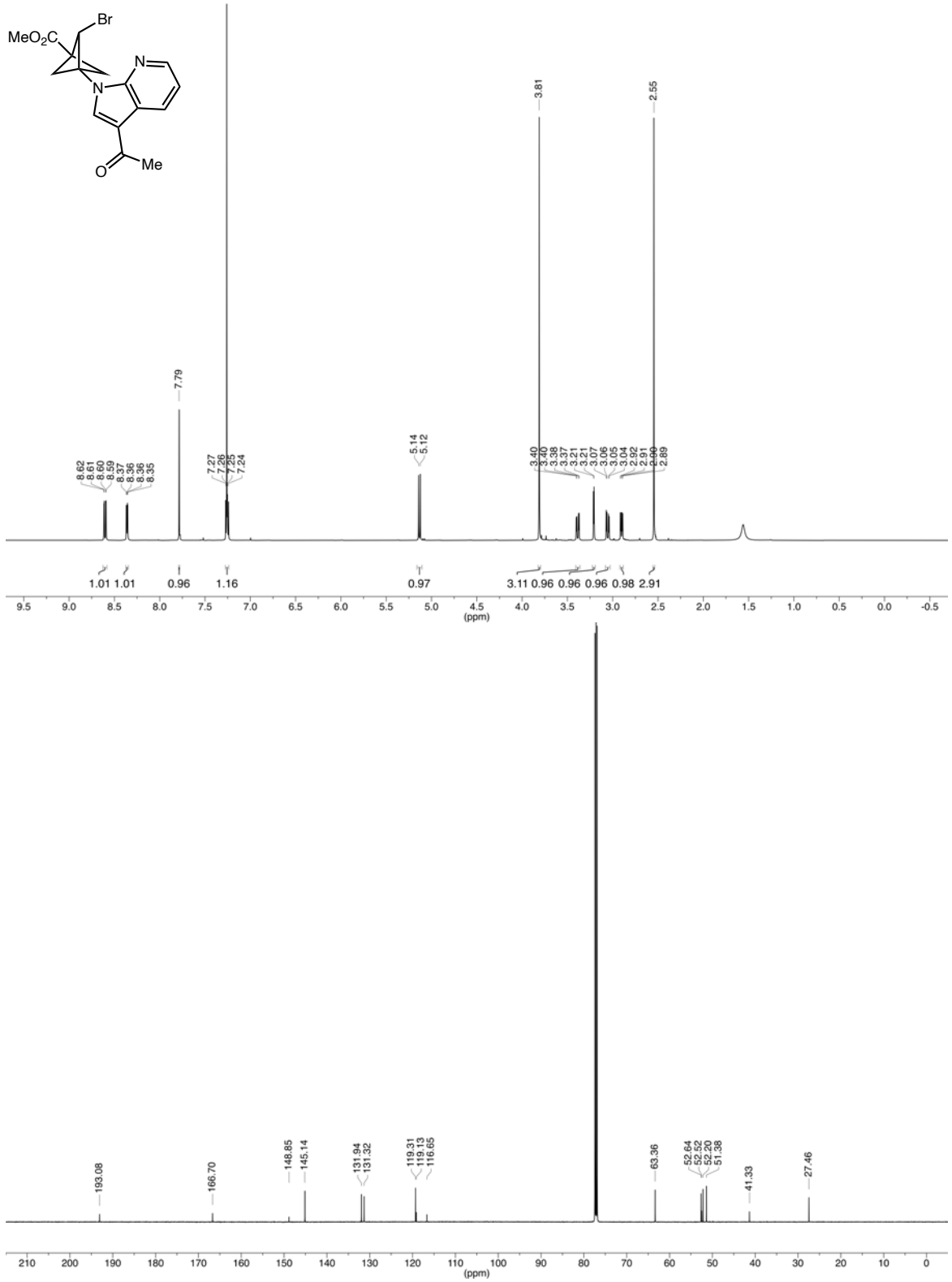
HSQC:


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
(ppm)
40
60
80
100
120
140
160
f1 (ppm)

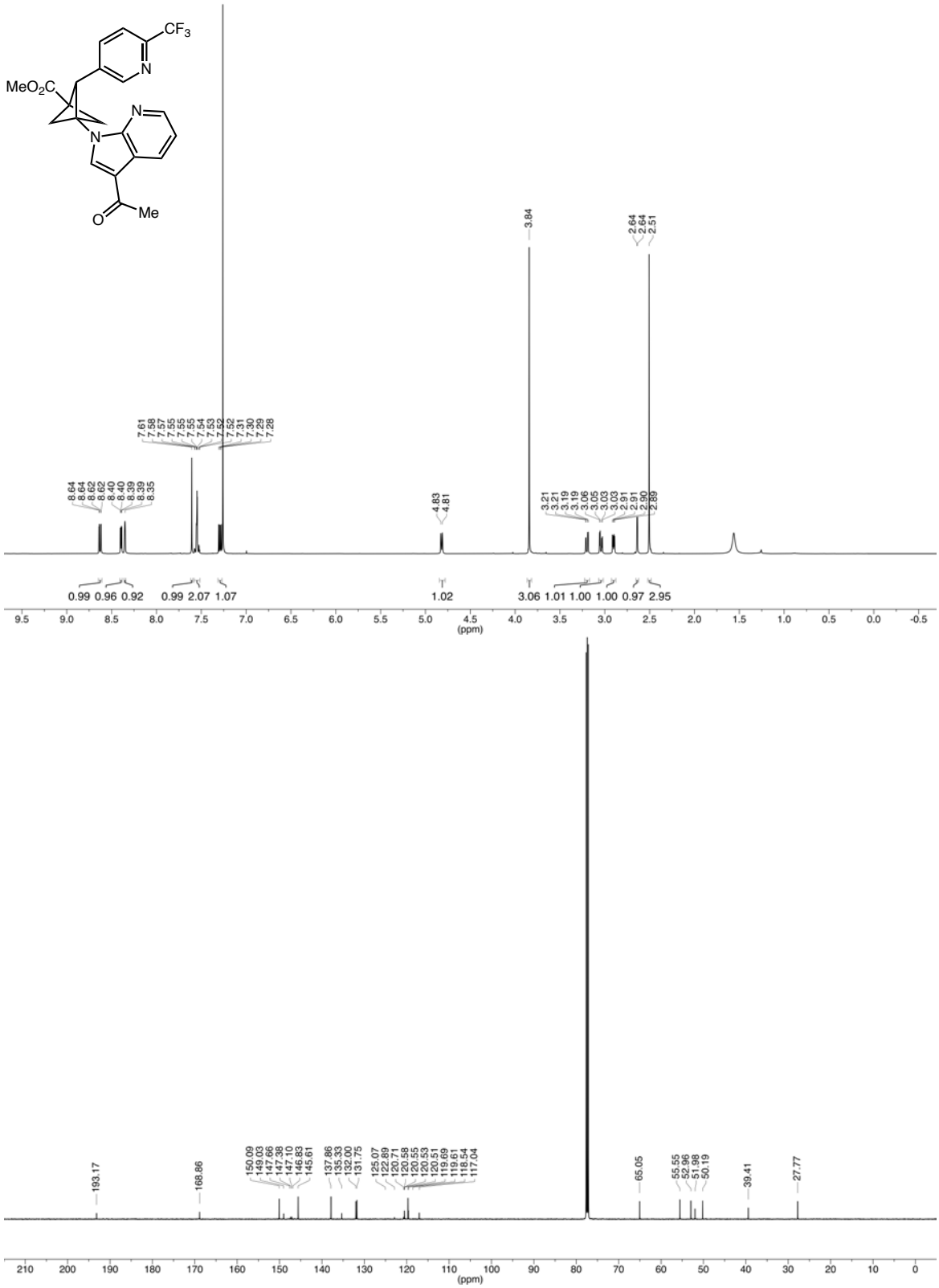
HMBC:

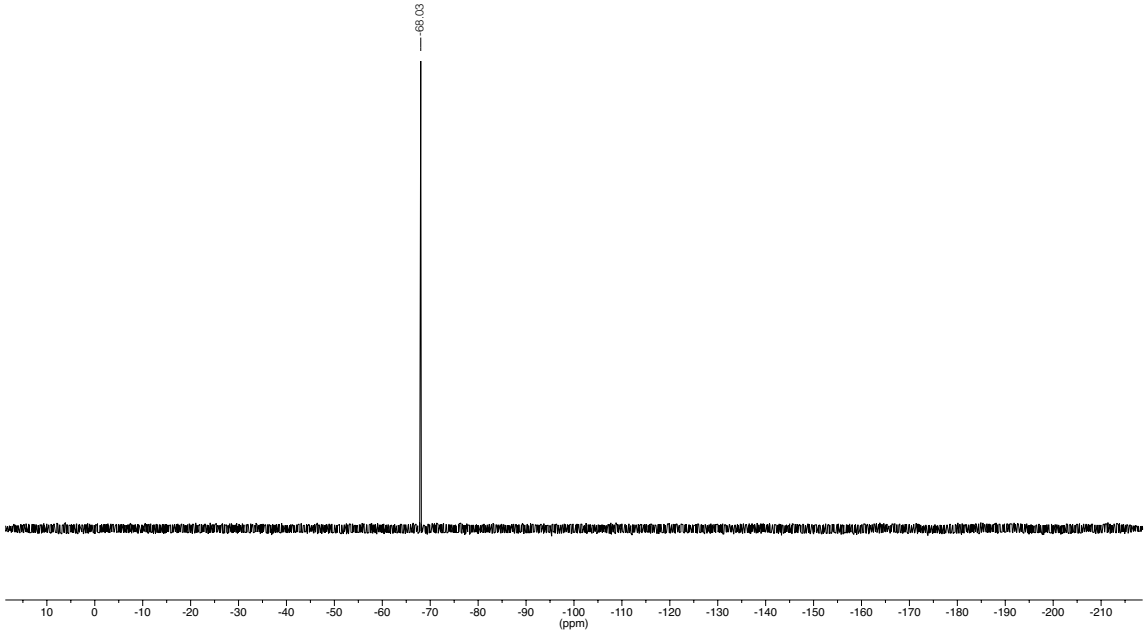

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
(ppm)
40
60
80
100
120
140
160
f1 (ppm)

**(±)-Methyl 3-(3-acetyl-1H-pyrrolo[2,3-b]pyridin-1-yl)-2-bromobicyclo[1.1.1]pentane-1-carboxylate (S14)**

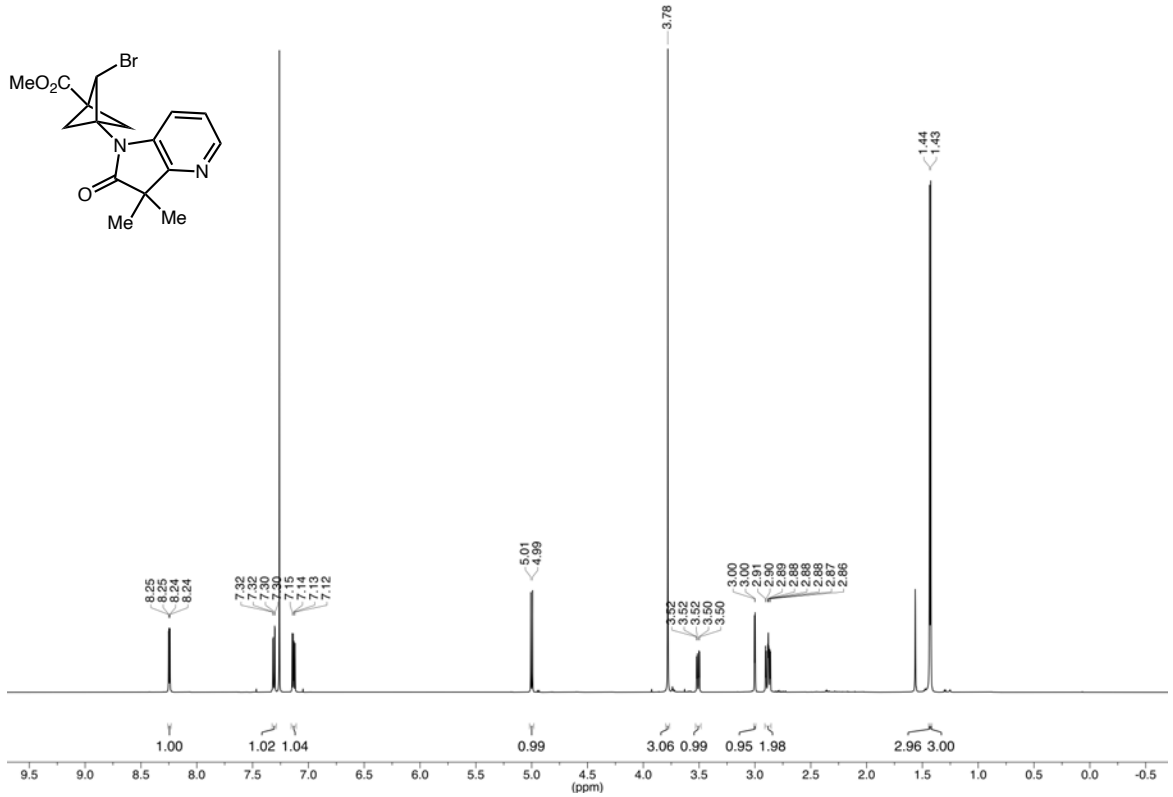


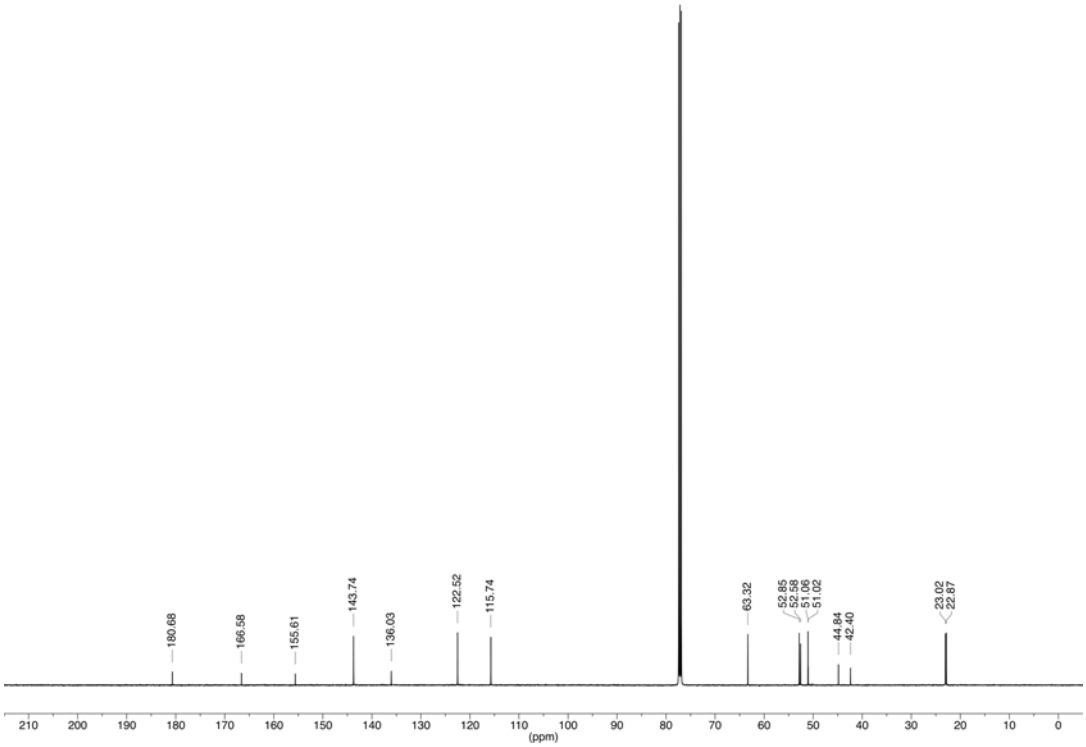
**(±)-Methyl 3-(3-acetyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (75)**



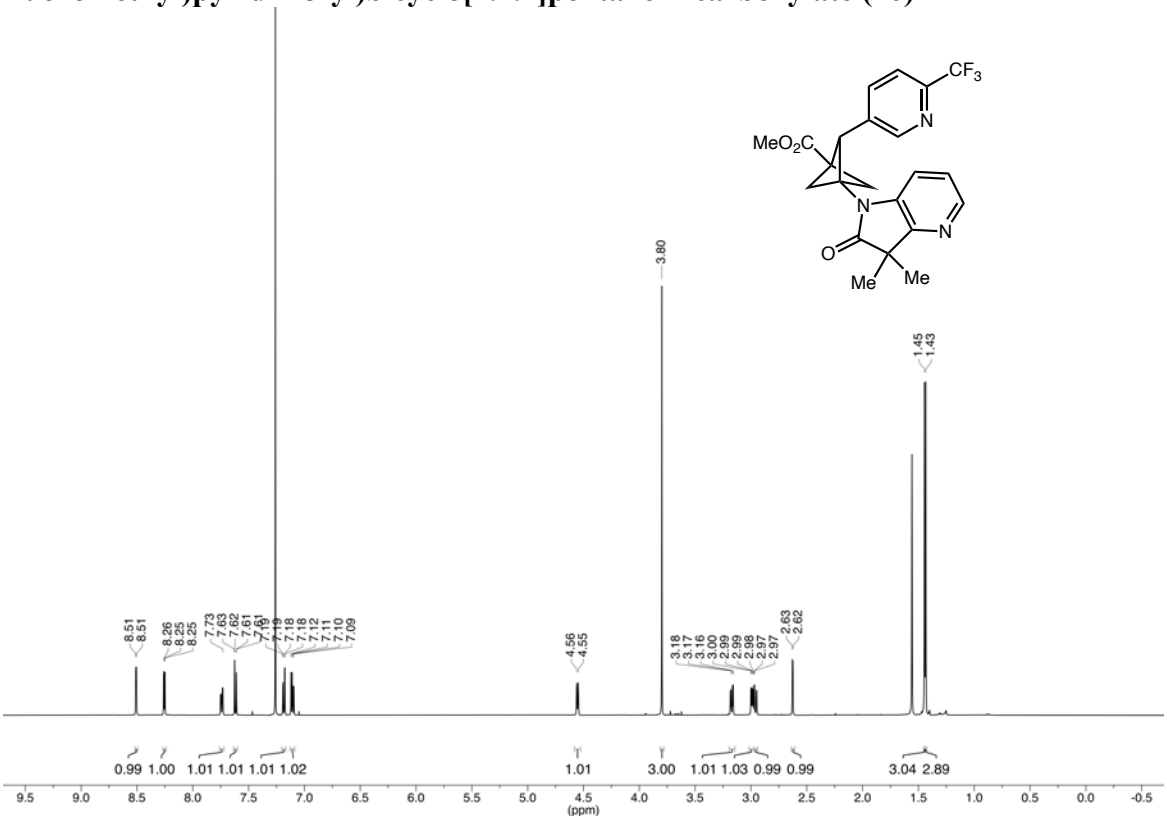


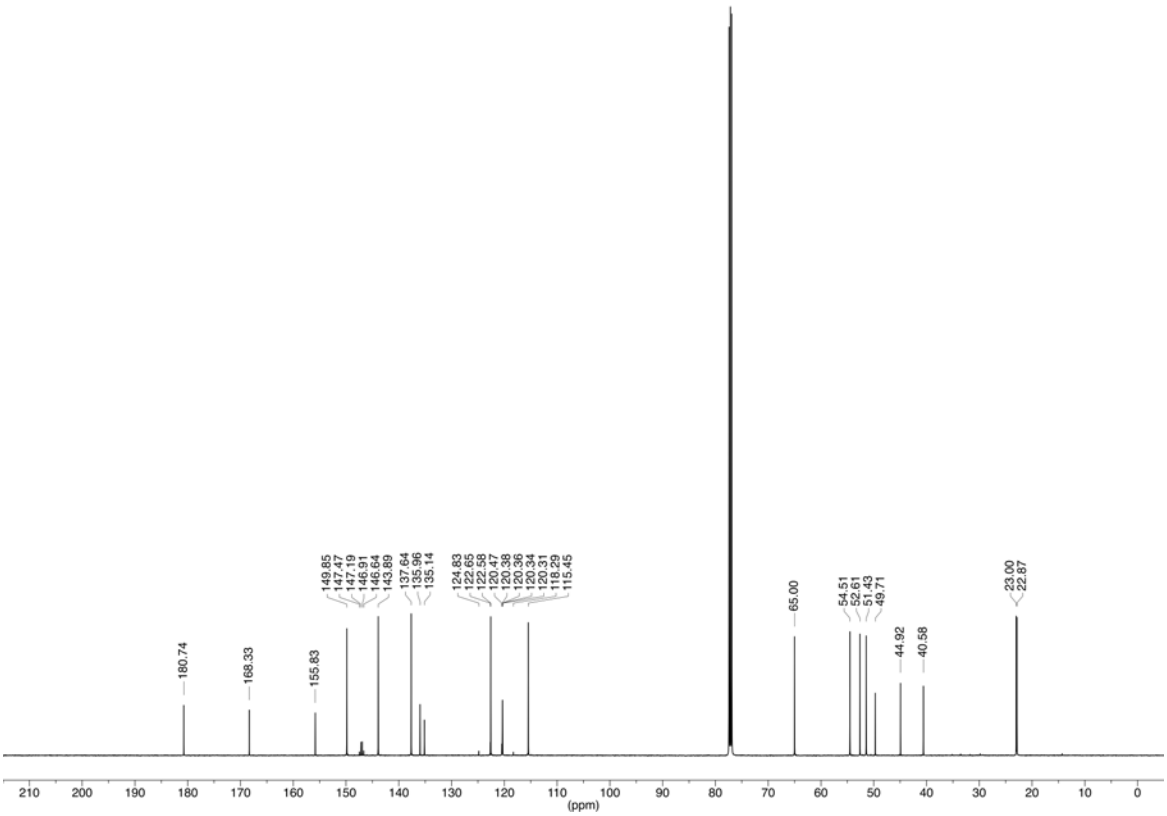

**(±)-Methyl 2-bromo-3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S15)**

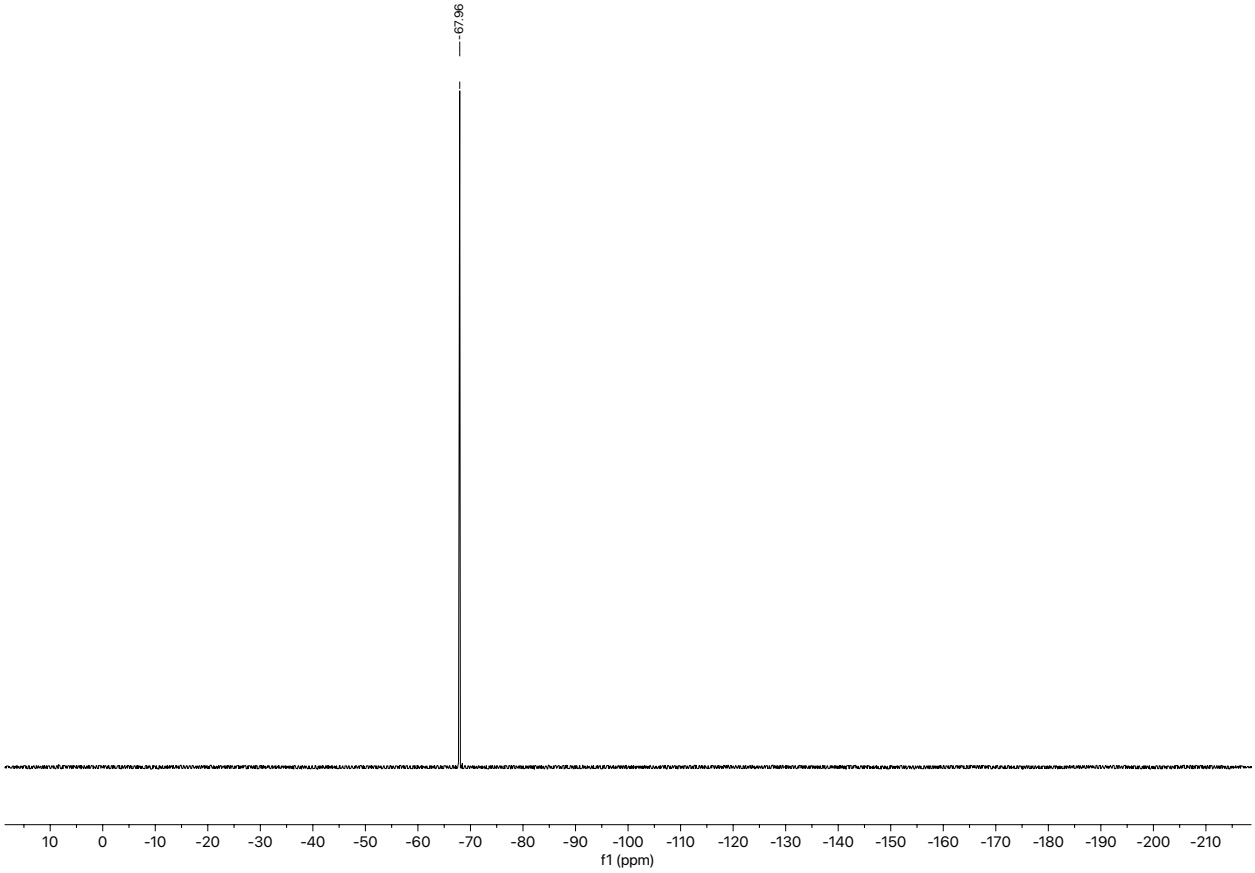




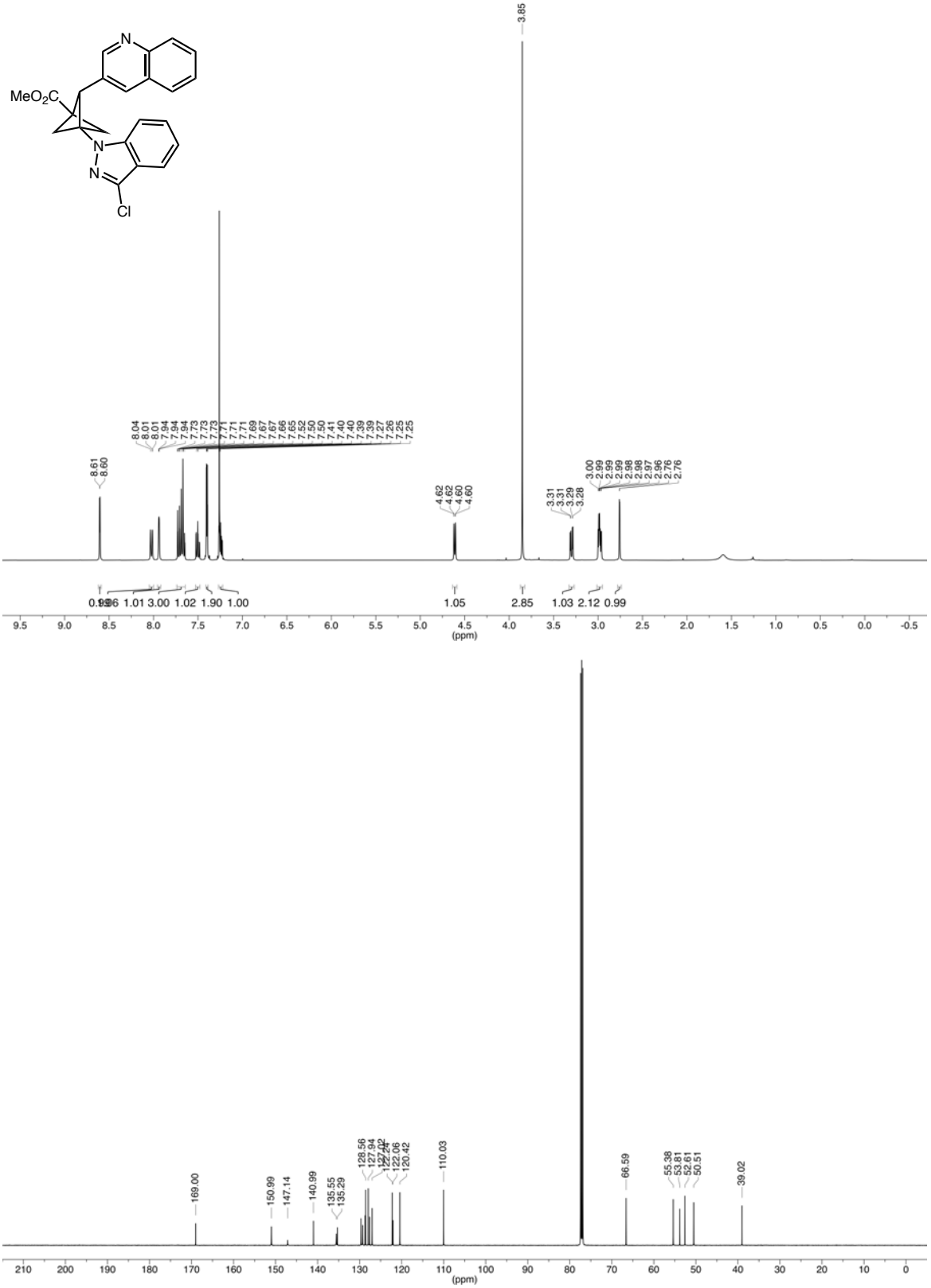

**(±)-Methyl 3-(3,3-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-2-(6-(trifluoromethyl)pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (76)**



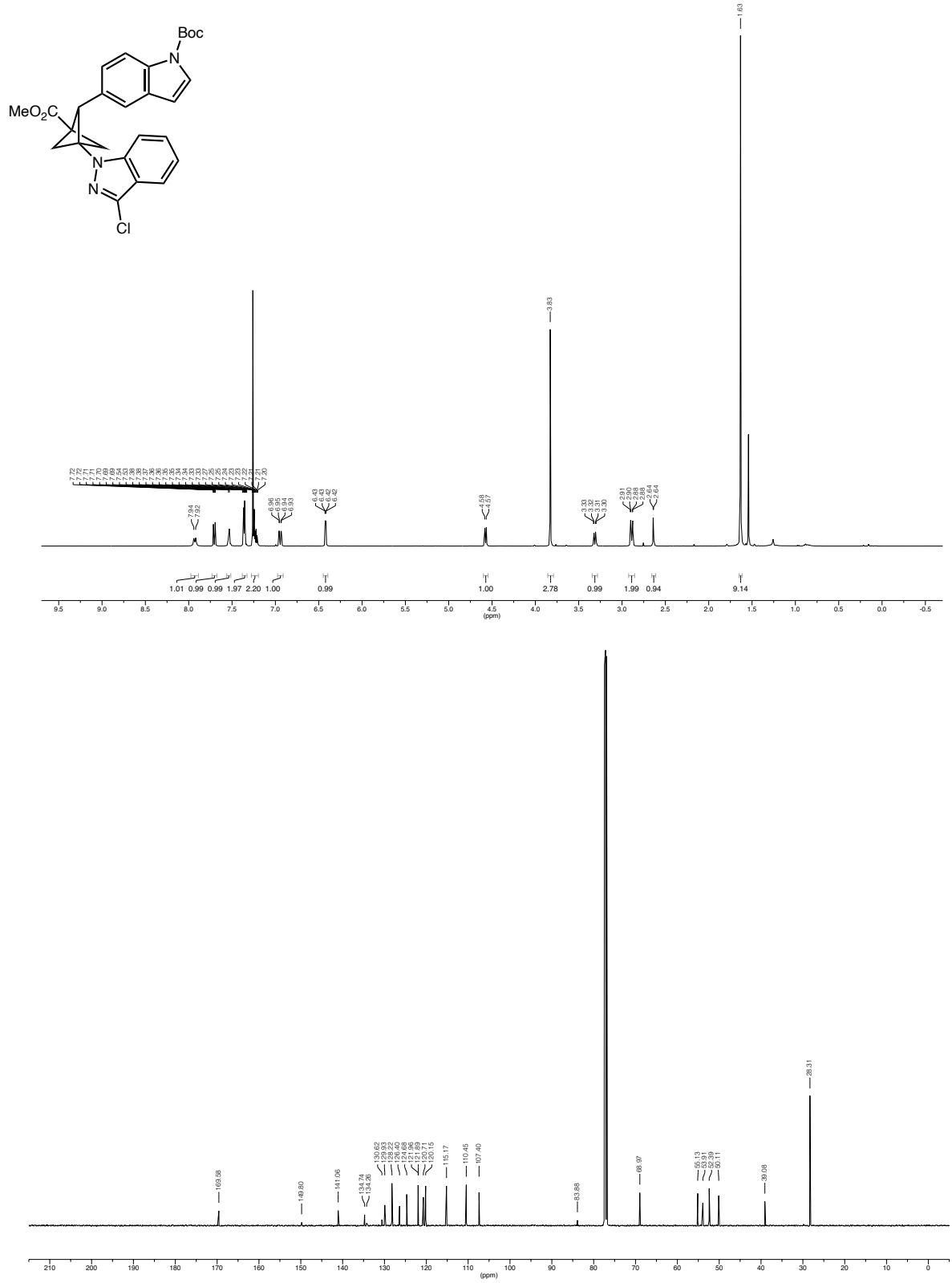

180.74
168.33
155.83
149.85
147.77
147.19
146.91
146.64
143.89
137.64
135.96
135.14
124.83
122.65
122.58
120.47
120.38
120.36
120.34
120.31
118.29
115.45
65.00
54.51
52.61
51.43
49.71
44.92
40.58
23.00
22.87
(ppm)


-67.96
f1 (ppm)

**(±)-Methyl 3-(3-chloro-1*H*-indazol-1-yl)-2-(quinolin-3-yl)bicyclo[1.1.1]pentane-1-carboxylate (77)**

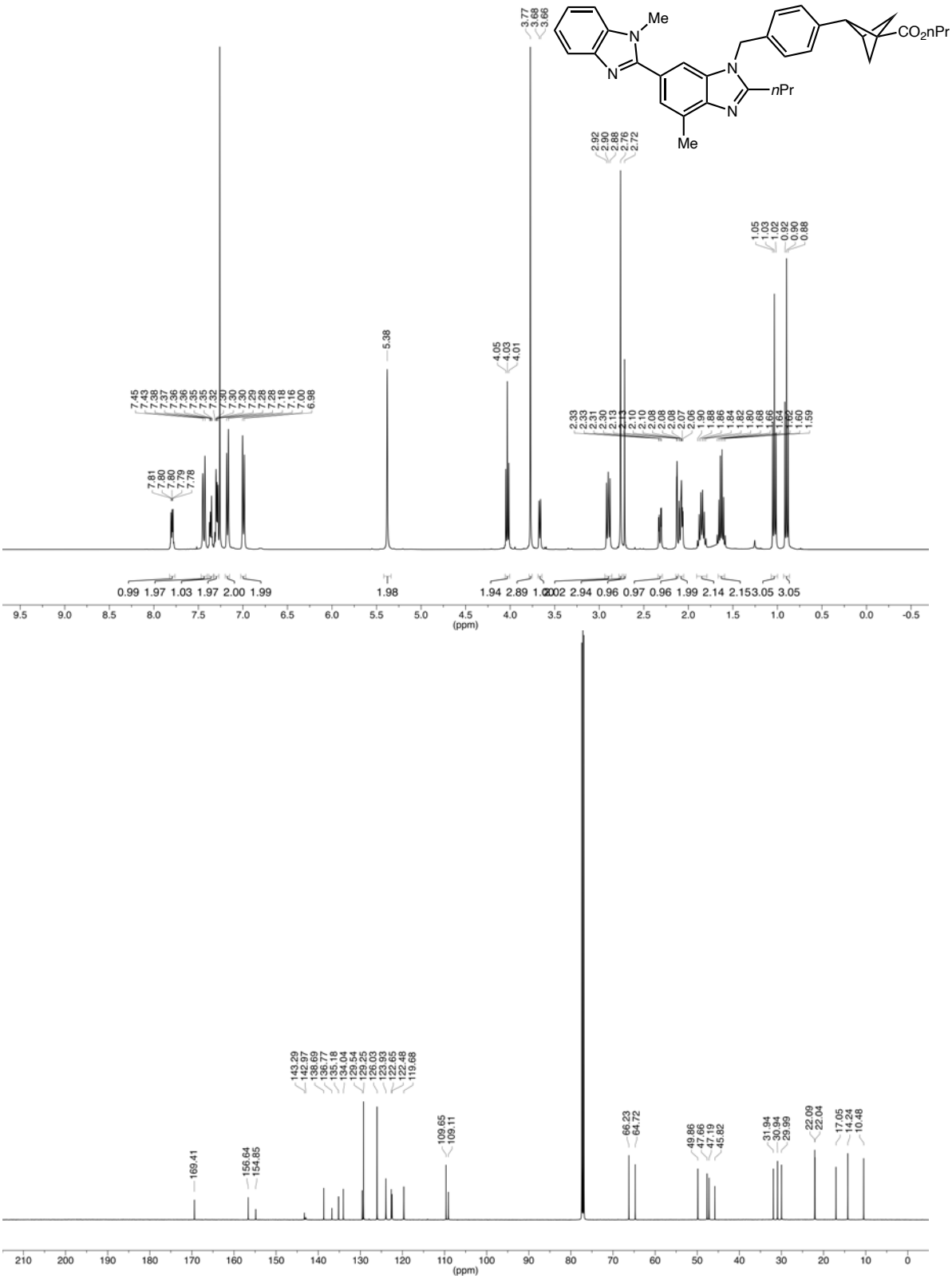


**(±)-*tert*-Butyl 5-(1-(3-chloro-1*H*-indazol-1-yl)-3-(methoxycarbonyl)bicyclo[1.1.1]pentan-2-yl)-1*H*-indole-1-carboxylate (78)**

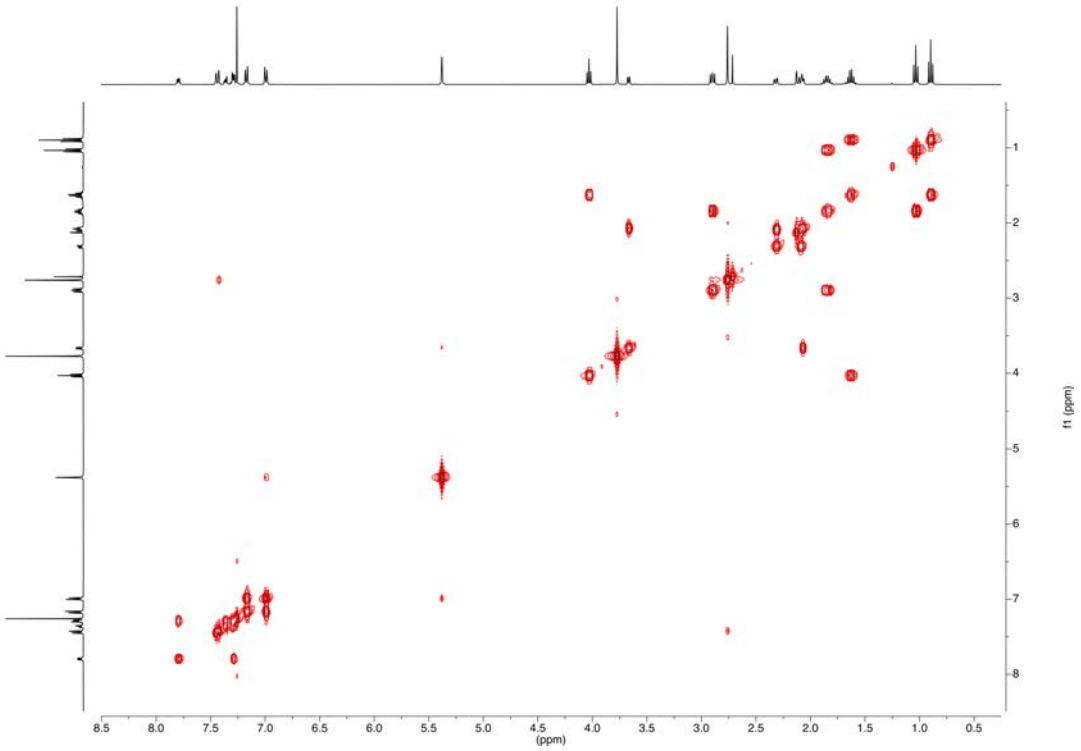


**(±)-Methyl 3-(3-chloro-1*H*-indazol-1-yl)-2-(2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl)bicyclo[1.1.1]pentane-1-carboxylate (79)**

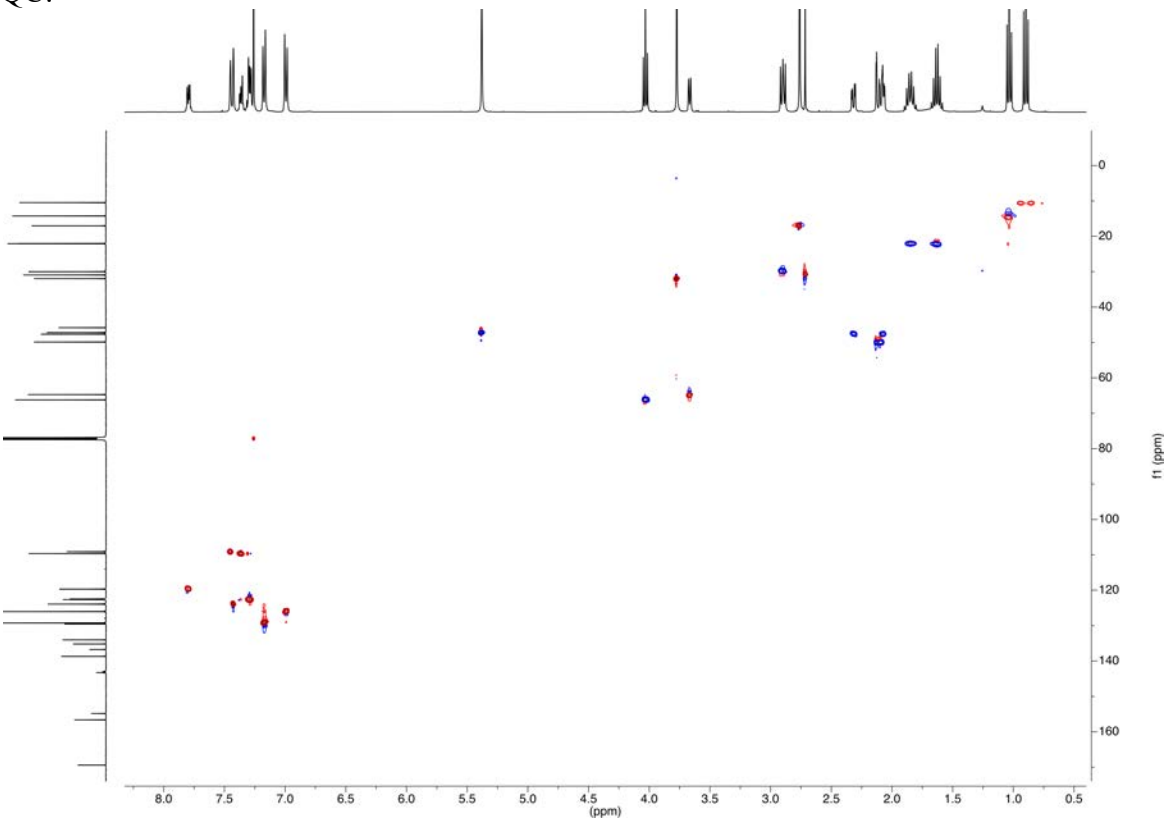
**(±)-Propyl 2-(4-((1,7'-dimethyl-2'-propyl-1*H*,3'*H*-[2,5'-bibenzo[*d*]imidazol]-3'-yl)methyl)phenyl)bicyclo[1.1.1]pentane-1-carboxylate (S17)**



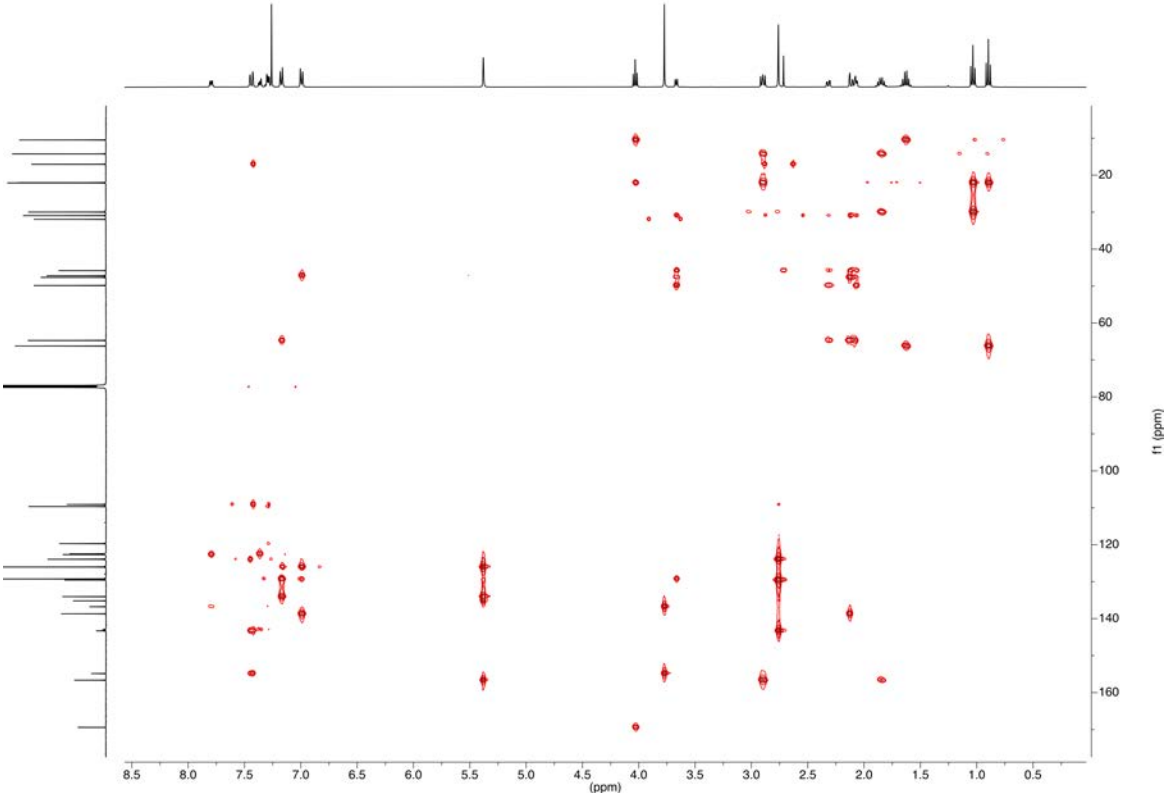
COSY:


8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)
1 2 3 4 5 6 7 8
f1 (ppm)

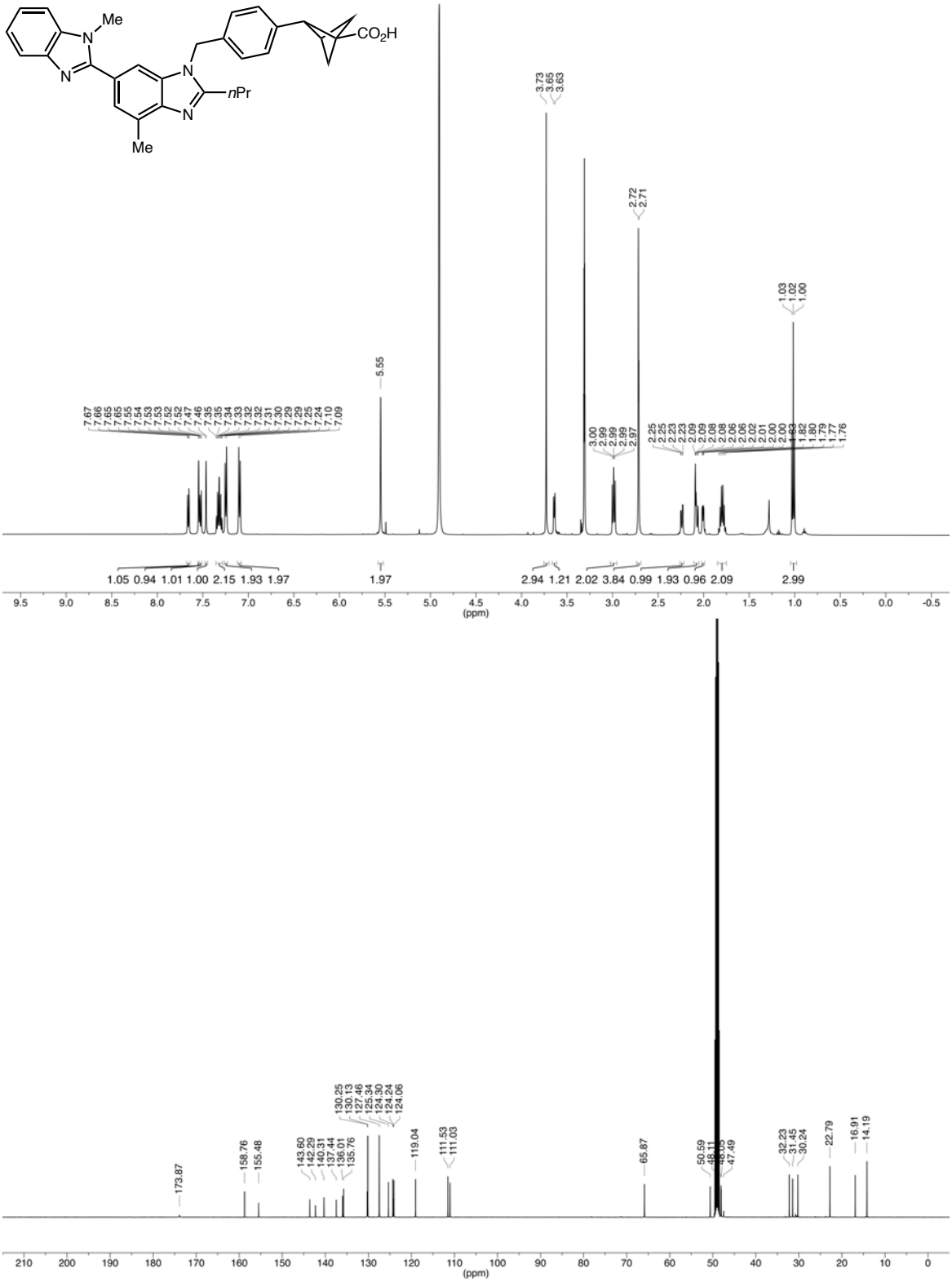
HSQC:


8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)
0 20 40 60 80 100 120 140 160
f1 (ppm)

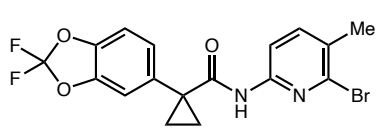
HMBC:


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)
20
40
60
80
100
120
140
160
f1 (ppm)

**(±)-2-(4-((1,7'-Dimethyl-2'-propyl-1*H*,3'*H*-[2,5'-bibenzo[*d*]imidazol]-3'-yl)methyl)phenyl)bicyclo[1.1.1]pentane-1-carboxylic acid (80)**

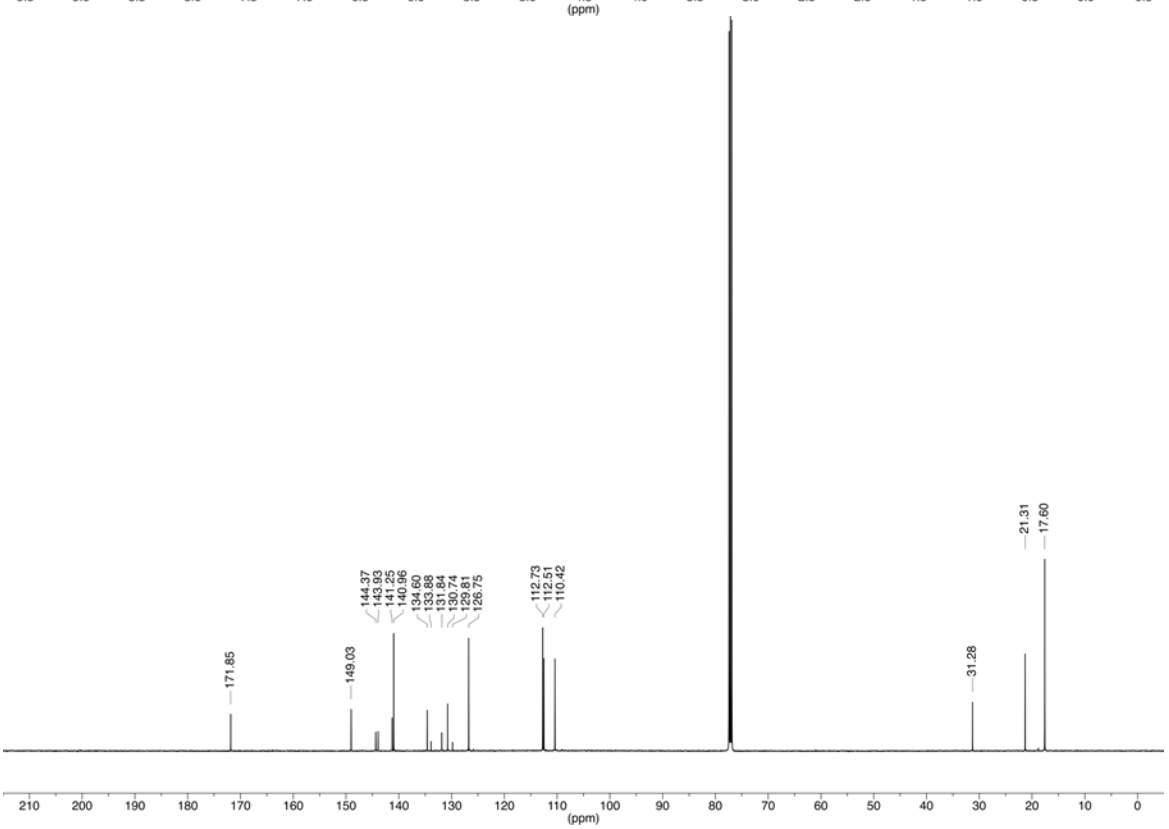


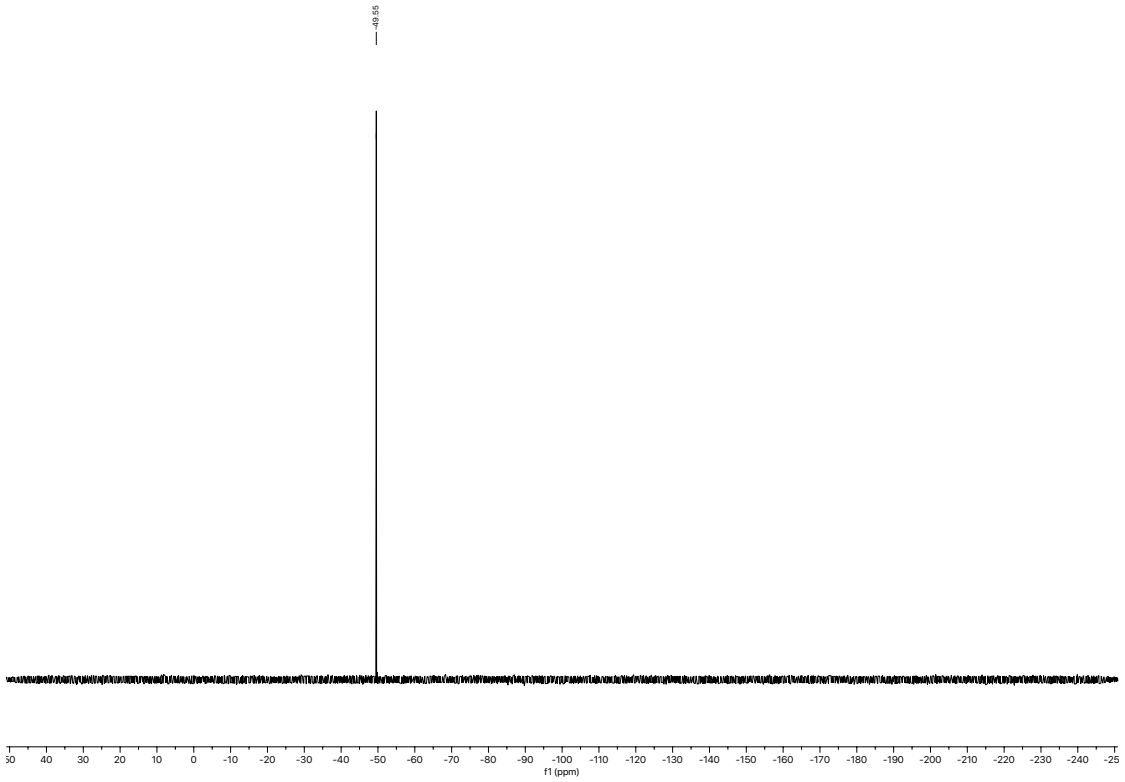
***N*-(6-Bromo-5-methylpyridin-2-yl)-1-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)cyclopropane-1-carboxamide (S18)**



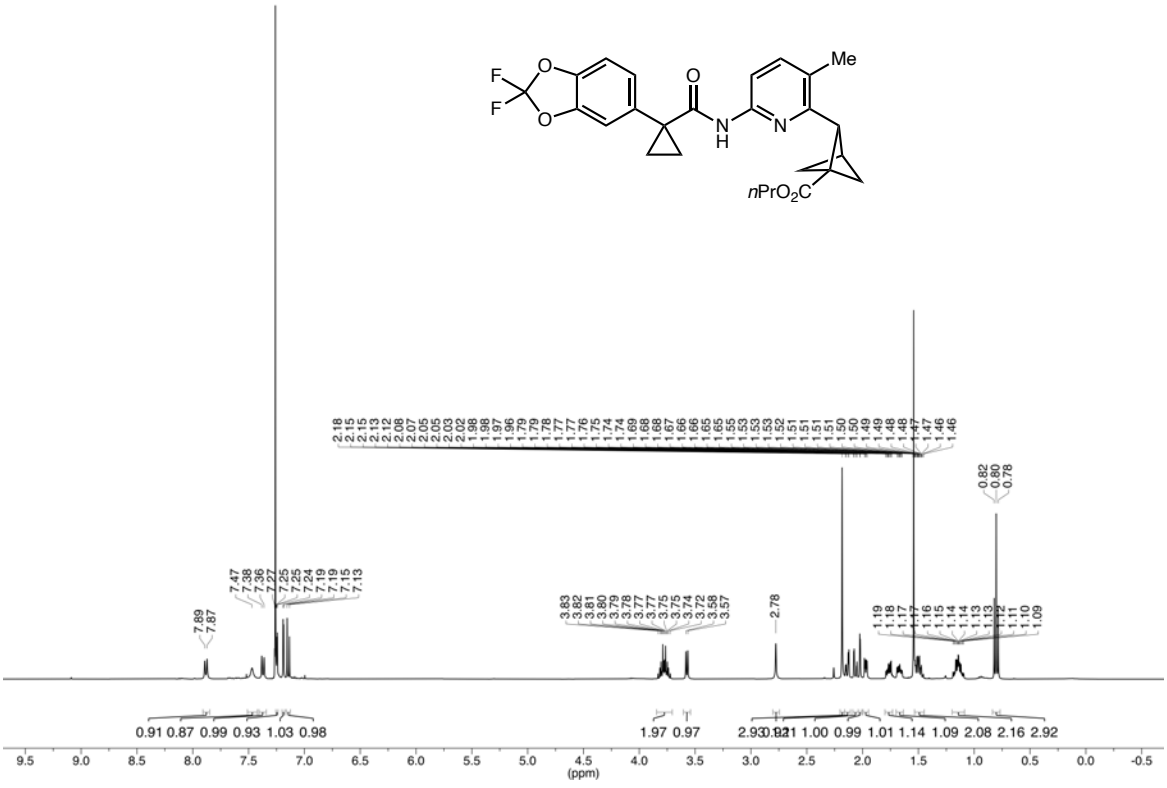


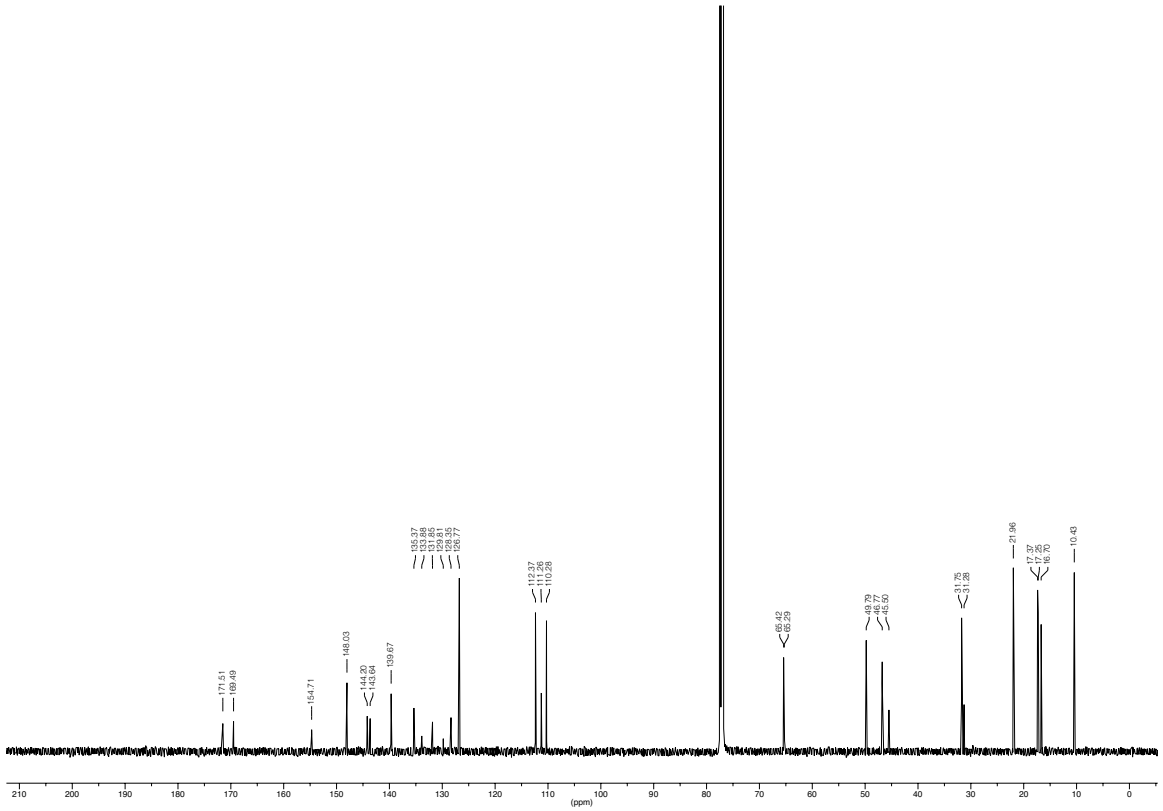


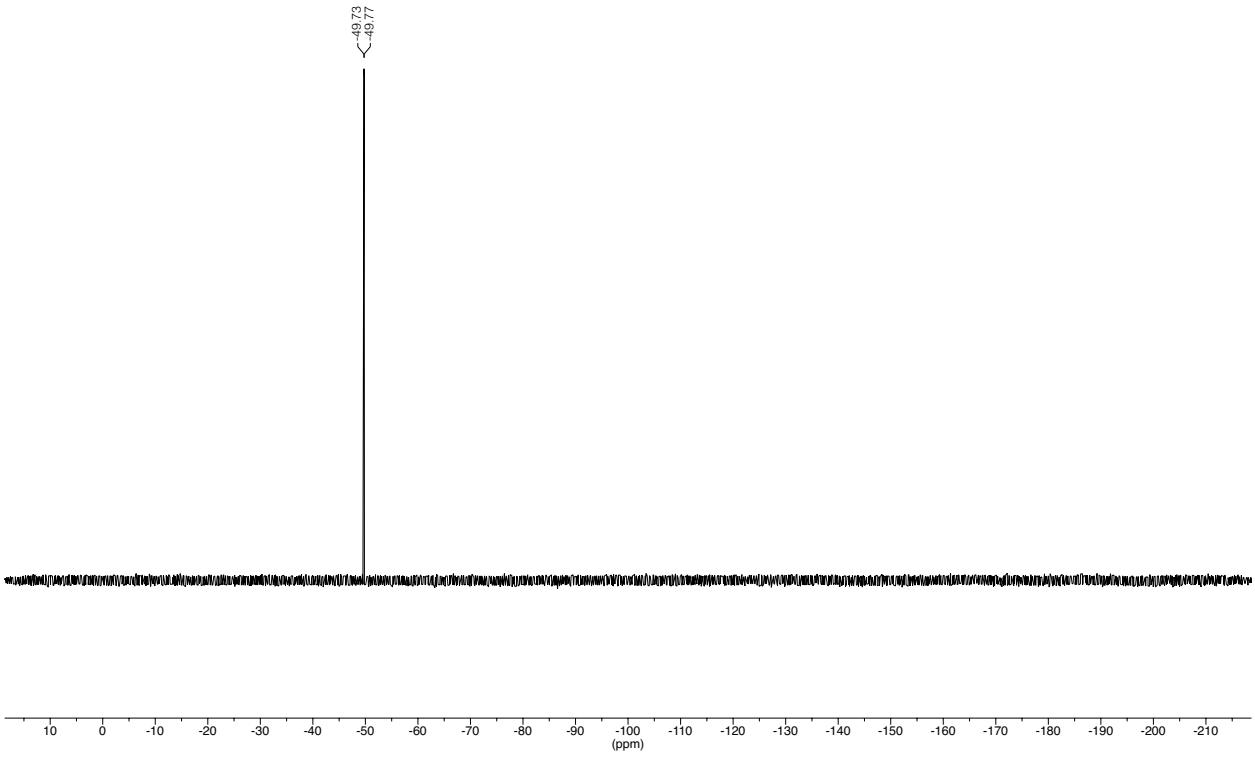




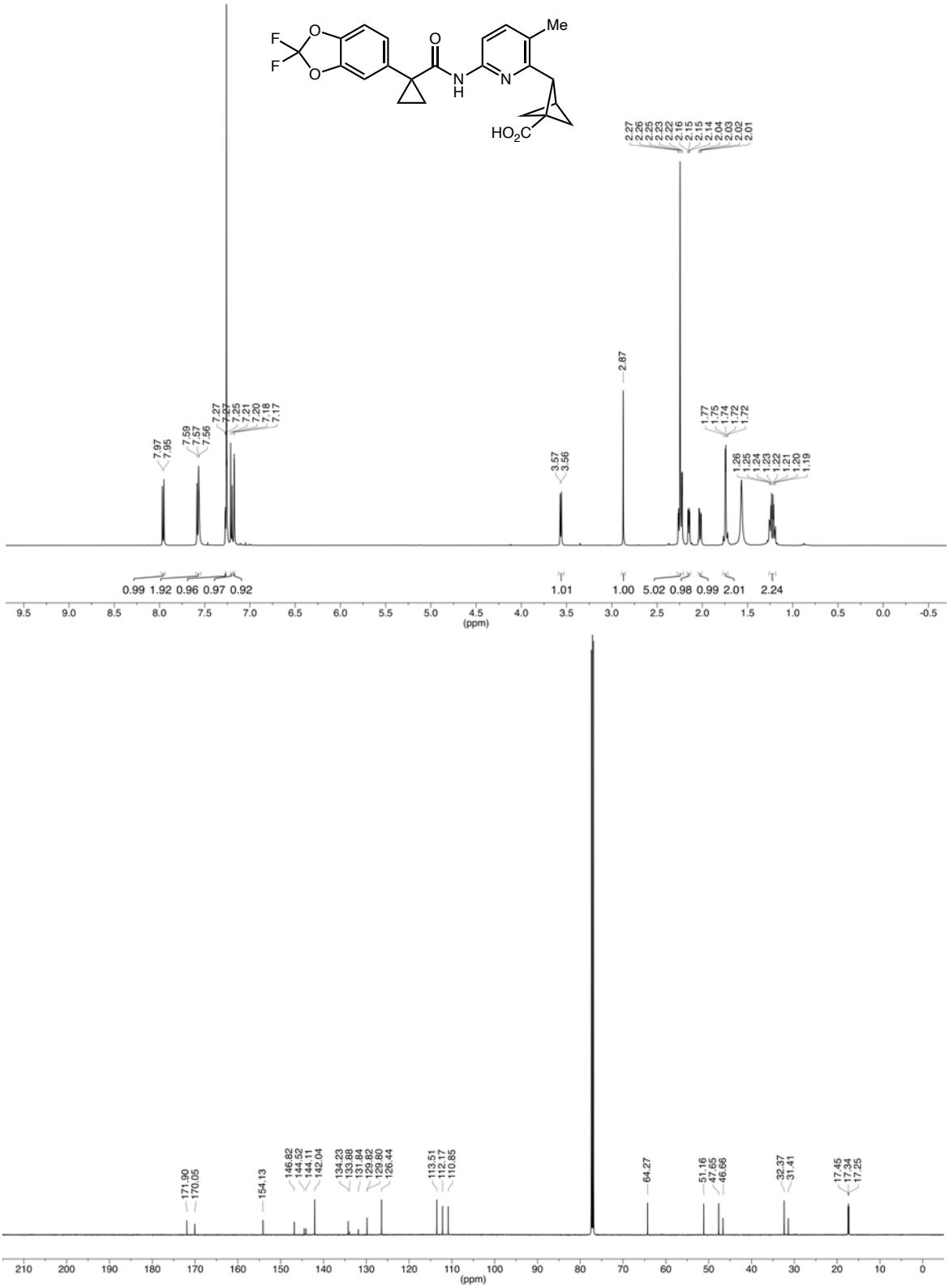

**(±)-Propyl 2-(6-(1-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)cyclopropane-1-carboxamido)-3-methylpyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (S19)**

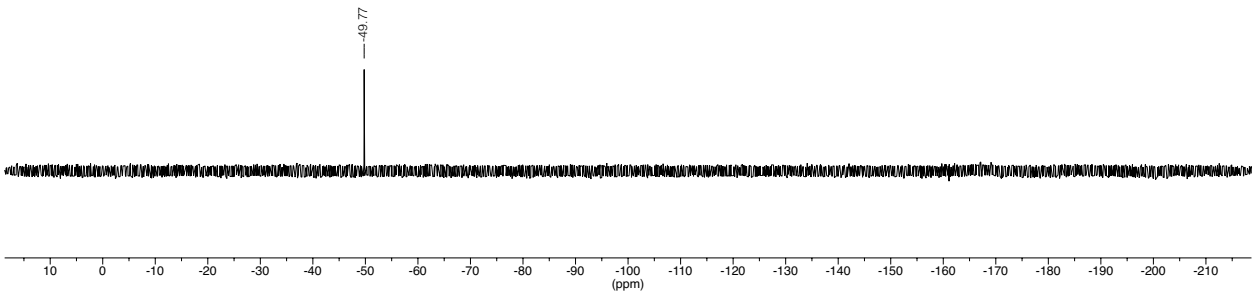



171.51
169.49
154.71
148.03
144.20
143.64
139.67
135.37
133.89
131.86
129.81
128.45
126.77
112.37
111.26
110.28
65.42
65.29
49.79
46.77
45.50
31.75
31.28
21.96
17.37
17.25
16.70
10.43
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

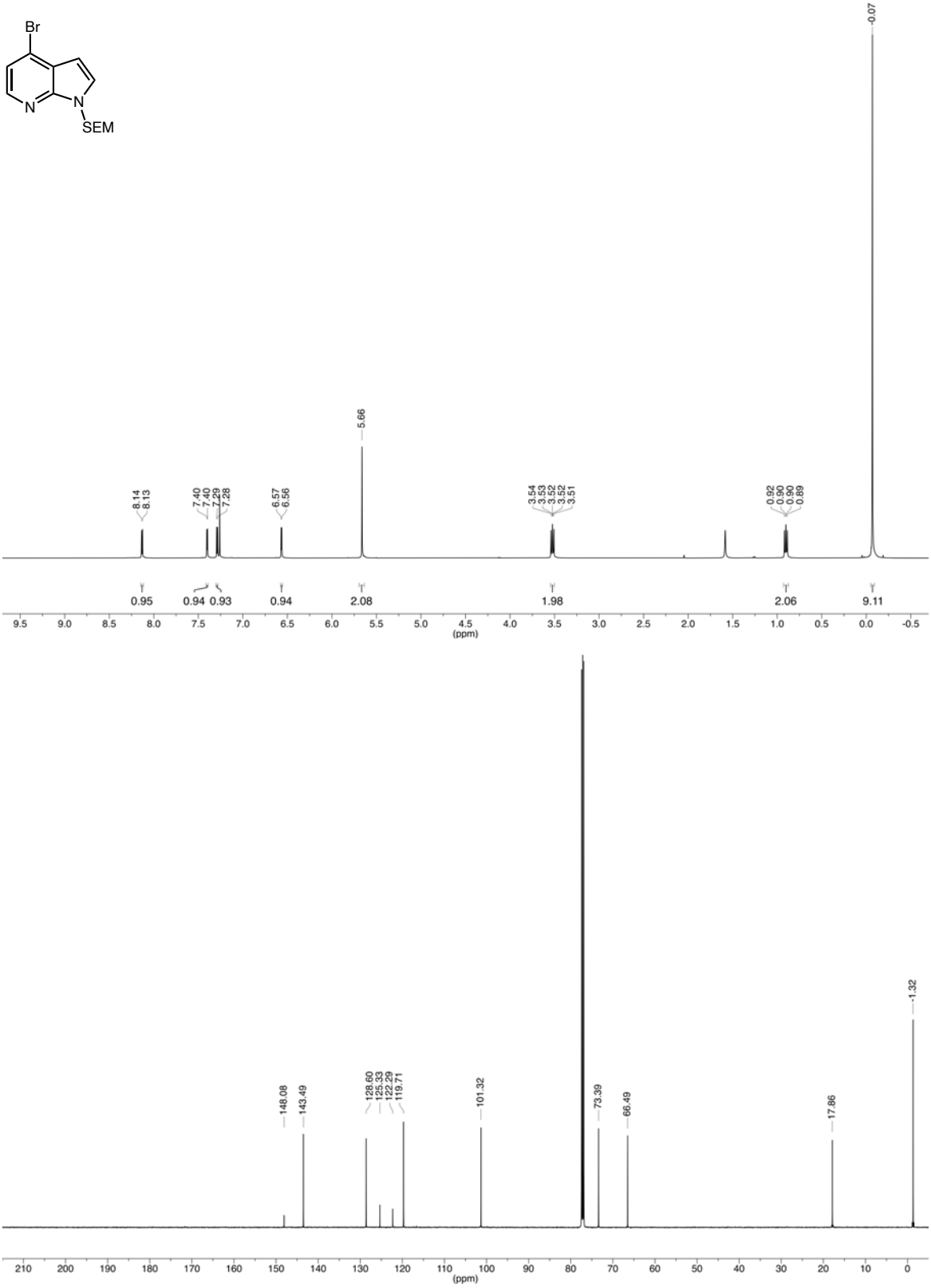

-49.73
-49.77
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
(ppm)

**(±)-2-(6-(1-(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)cyclopropane-1-carboxamido)-3-methylpyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (81)**

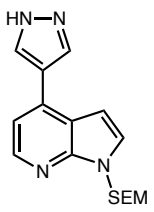



-49.77
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
(ppm)

**4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (S20)**

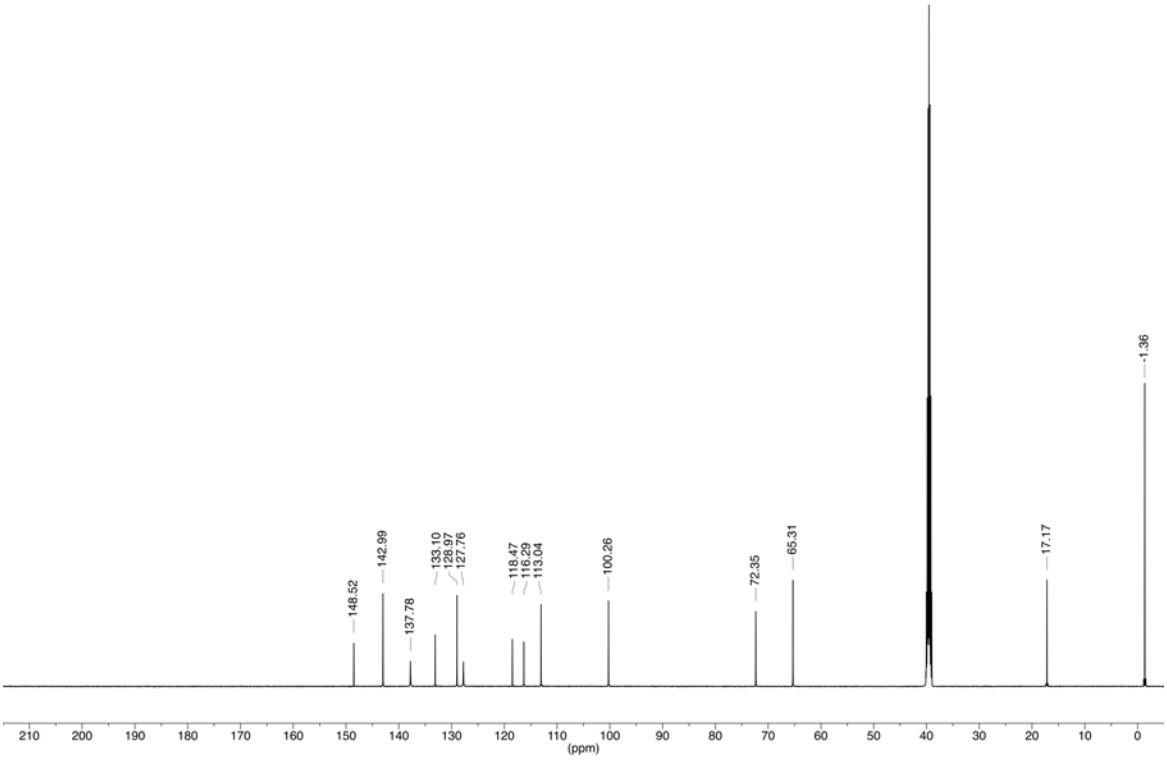


**4-(1*H*-Pyrazol-4-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-b]pyridine (S22)**

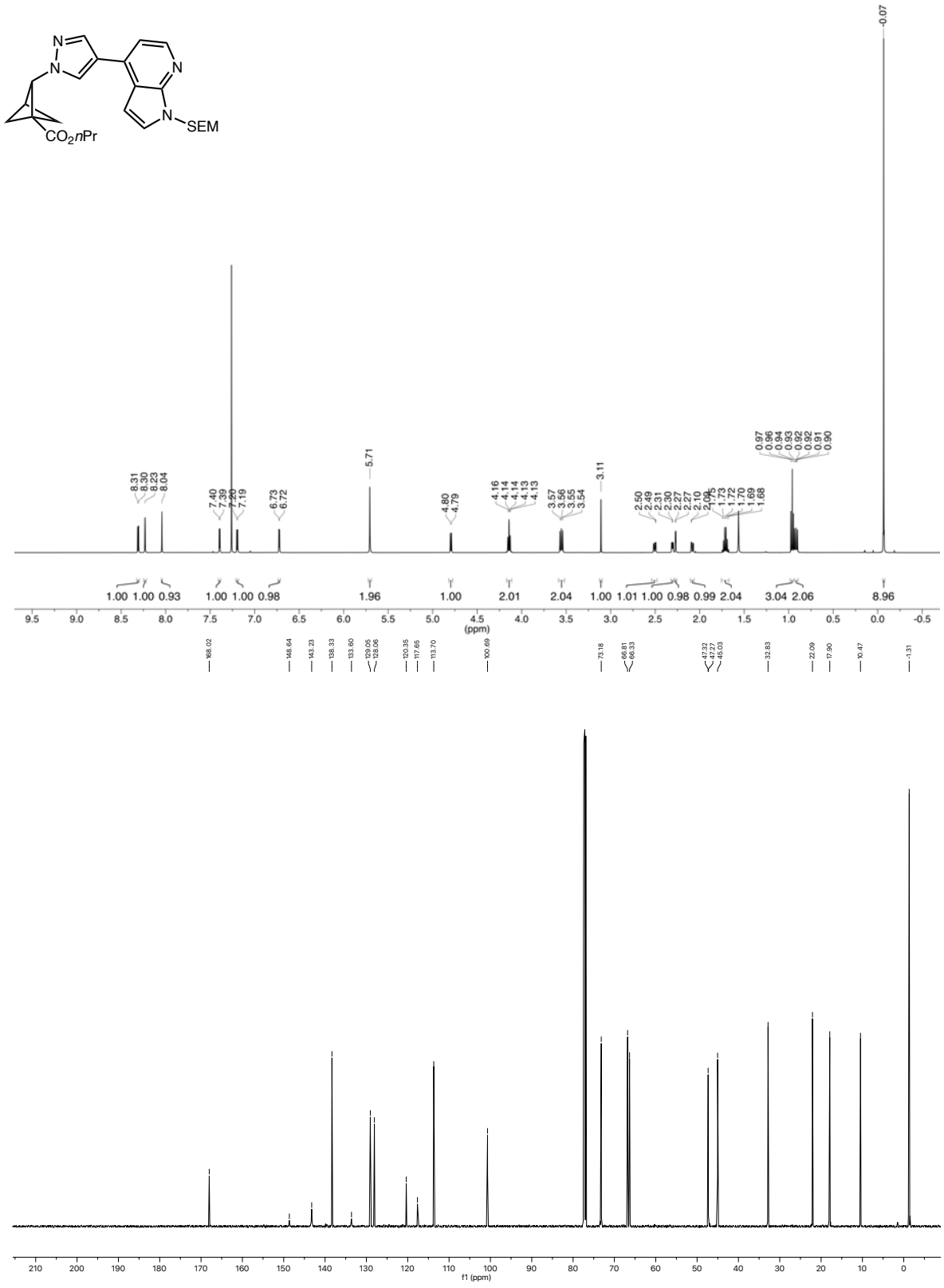




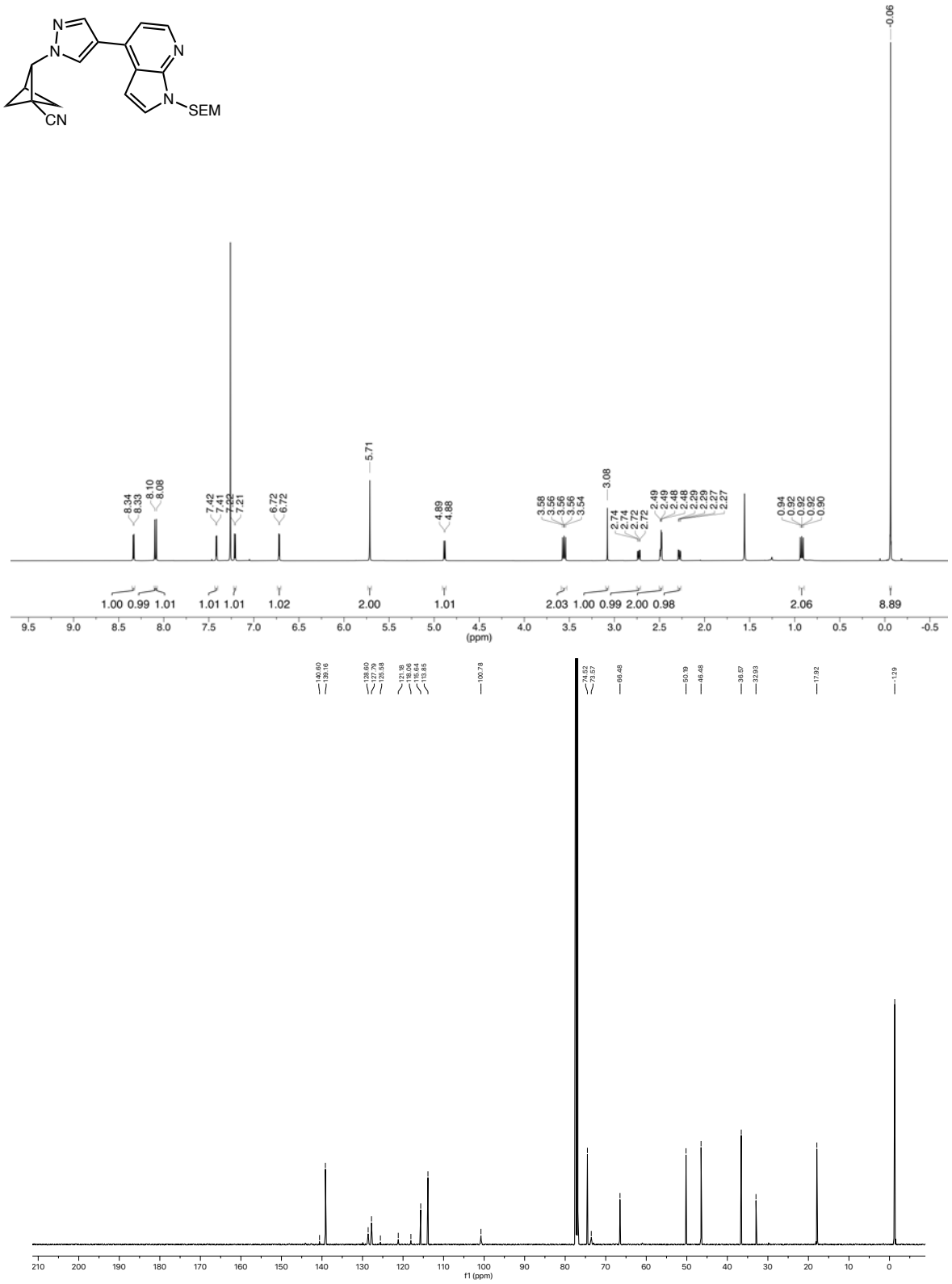




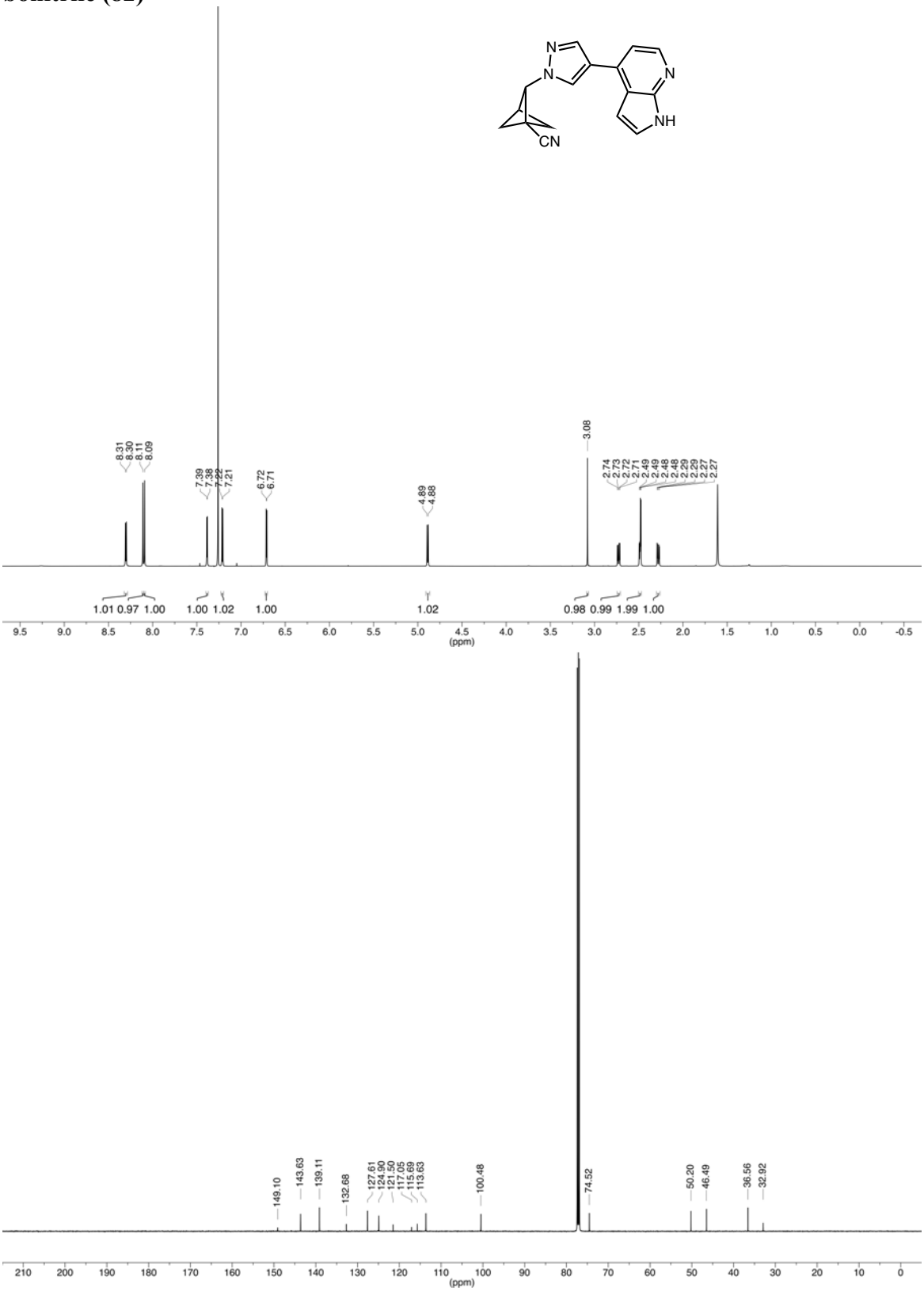
**(±)-Propyl 2-(4-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S23)**



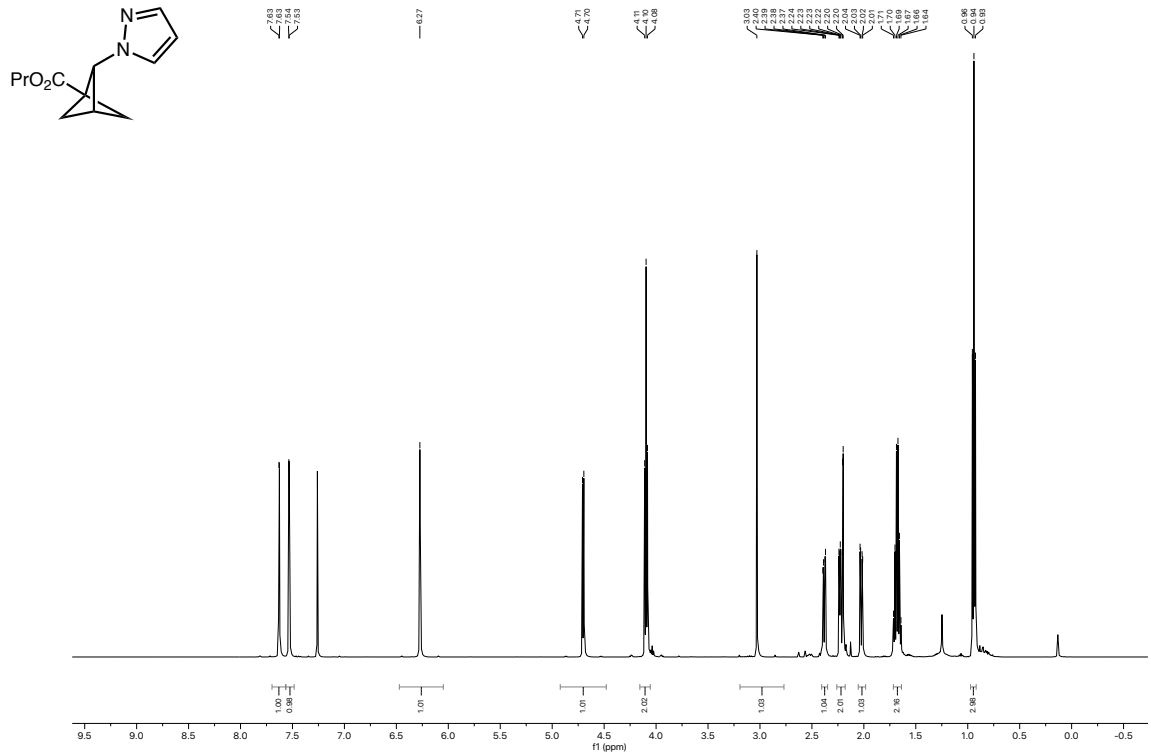
**(±)-2-(4-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carbonitrile (S24)**

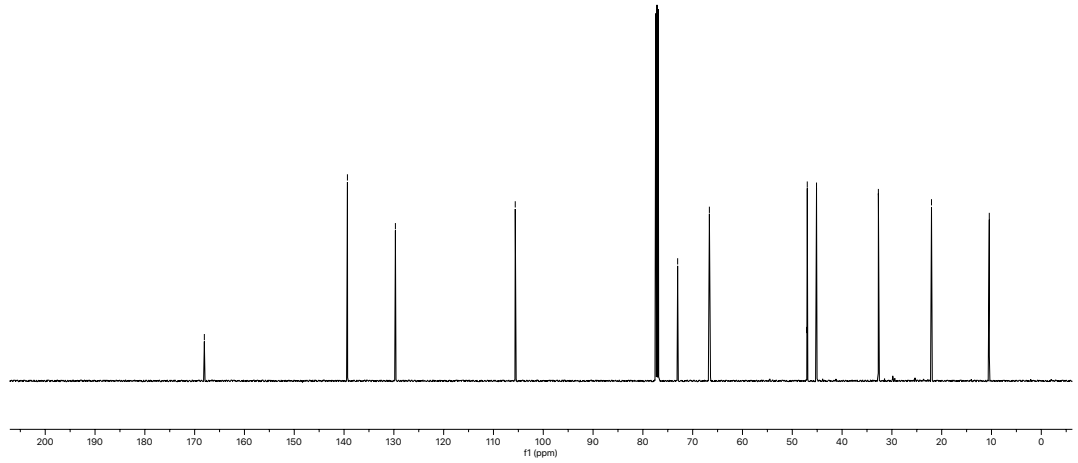


**(±)-2-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carbonitrile (82)**



**(±)-Propyl 2-(1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (S25)**



**(2*R*)-N-((1*S*,4*R*)-4-(2-(((*S*)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-2-(1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxamide and (2*S*)-N-((1*S*,4*R*)-4-(2-(((*S*)-2-amino-4,5,6,7-tetrahydrobenzo[d]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-2-(1*H*-pyrazol-1-yl)bicyclo[1.1.1]pentane-1carboxamide(83)**