**Supporting Information**

# Highly Efficient Synthesis of HIV NNRTI Doravirine

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## 1. Optimization of Aldol Reaction in Batch Mode:

Aldol execution in batch mode requires pre-formation of an ester enolate, a reactive intermediate with inherent instability. Enolates derived from bulky esters are more stable and can be handled at higher temperatures, therefore our initial efforts focused on *tert*-butyl ester **7c**. A screen of solvent, temperature and base identified NaHMDS in toluene at -10 °C as a set of robust reaction conditions when conducted on gram scale (Table 1). However, upon scale-up to >10g the exotherm produced by the enolate formation required modifying the conditions to include slower NaHMDS addition rate and a lower initial batch temperature of -30 °C. In preparation for executing the aldol reaction on kilogram scale where NaHMDS addition rate would be extended even further, enolate stability over time was measured by evaluating the reaction performance after a hold period. The enolate generated from **7c** was found to degrade over time, showing ~7-9% lower yield in the aldol reaction per 1 hour of additional hold time at -10 °C.

Identical conditions were used to conduct the aldol reaction with ethyl ester **7a** and iPr ester **7b**, except that these substrates required -40 °C to produce aldol adduct yields comparable to **7c**. However, subsequent conversion of **8a** was found to be a much higher yielding pathway to pyridone **10**. In all cases, transformation of aldol adducts to dienes **8a-c** went smoothly using TFAA with triethylamine and the bulky ester intermediates were more prone to non-productive pathways upon exposure to the cycloamination conditions. Consequently, we focused efforts to improve the aldol yield of ethyl ester **7a**. Unfortunately, further investigation showed that preformation of the enolate derived from ethyl ester **7a** was not suitable for scale-up as aldol yields worsened on attempts to scale. Our next approach was to investigate Barbier conditions with **7a** thereby avoiding preformation of the unstable enolate; however, this approach met with significantly diminished yields of aldol product **8a**.

Due to enolate instability and robustness issues with the aldol reaction upon scale-up, tert-butyl ester **7c** was deemed the only viable enolate precursor suitable for scale-up in batch mode, even though the overall conversion of **7c** to pyridone **10** occurred in the lowest overall yield. However, the tert-butyl ester **7c** derived enolate was not free of instability and robustness issues and would require significant development before scale-up. Therefore we began to look at alternate processing technologies such as Continuous Flow to avoid generation of the enolate at scale.

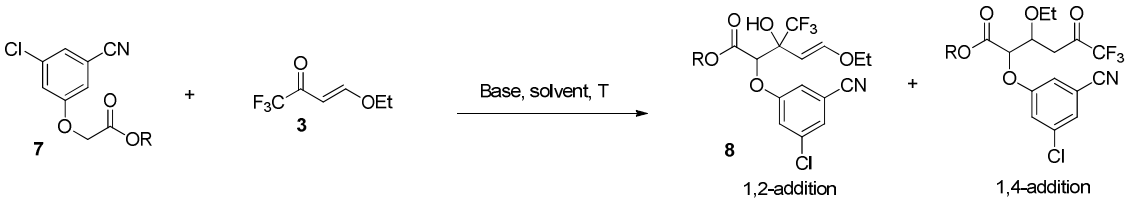


**Table 1. Selected results from aldol optimization studies (all reactions run on ≤ 1g scale unless noted)**

| R | Base | Solvent | Temp (°C) | Conversion (assay yield) | 1,2 : 1,4 |
|---|---|---|---|---|---|
| $^t$Bu | LiHMDS | THF | -78 | 91% | 2.5 : 1 |
| $^t$Bu | NaHMDS | THF | -78 | 83% | 8.5 : 1 |
| $^t$Bu | KHMDS | THF | -78 | 43% | ND |
| $^t$Bu | NaHMDS | DME | -60 | 72% | 1.3 : 1 |
| $^t$Bu | NaHMDS | Toluene | -30 | 89% (72%) | 13 : 1 |
| $^t$Bu | KO$^t$Amyl | Toluene | -30 | 80% (23%) | ND |
| $^t$Bu | NaHMDS | Toluene | -10 | 95% (77%) | 13 : 1 |
| $^t$Bu | NaHMDS | Toluene | -10 | 95% (63%)[1] | 13 : 1 |
| $^t$Bu | NaHMDS | Toluene | 0 | 98% (49%) | 13 : 1 |
| Et | NaHMDS | Toluene | -40 | 87% (65%) | 12 : 1 |
| Et | NaHMDS | Toluene | -10 | 65% (26%) | ND |
| Et | NaHMDS | Toluene | -40 | 79% (43%)[1] | ND |
| $^i$Pr | NaHMDS | Toluene | -40 | 93% (70%) | 13 : 1 |
| $^i$Pr | NaHMDS | Toluene | -10 | 60% (35%) | 13 : 1 |

[1] Reaction run on 10g scale.

**2. Micro-Batch Screening of the Aldol Reaction**

The following procedure is representative of the micro-batch experimentation reactions described in this publication. Micro-batch experiments were conducted directly in 1.5mL HPLC vials equipped with magnetic stir-bars. Stock solutions of 0.5M ester **7a** with the indicated ratio of enone **3** were prepared and the dispensed directly into the HPLC vials. Further dilutions were made if necessary to obtain the desired solvent composition. The HPLC vials were loaded into a stainless steel HPLC 100-well auto-sample rack which was placed in a cooling bath at the indicated temperature. With vigorous stirring, the bases were added in a single quick injection. Reaction age times were monitored accurately with a stopwatch timer ranging between 5 and 60 seconds with the intention to simulate resonance time in a flow reactor. After the allotted age period, each reaction was quenched by quickly adding 1mL 10% aqueous $H_3PO_4$. Note: each reaction was handle individually and completed to quench before moving to the next vial. The completed reaction set was analyzed using an Agilent Technologies 1200 series HPLC. To alleviate concerns of decomposition while in queue to be analyzed, a typical quenched micro-batch aldol reaction was shown to be stable by quantitative HPLC for at least 6 hours at room temperature. Percent conversion was measured by comparison of HPLC peak area of starting ester **7a** vs. product aldol adduct **8a** (Table 2). Reactions that provided >80% conversion were diluted up to 10mL with MeCN in a volumetric flask and assay yield was calculated vs. reference standard of **8a** (~0.2 mg/mL in MeCN).

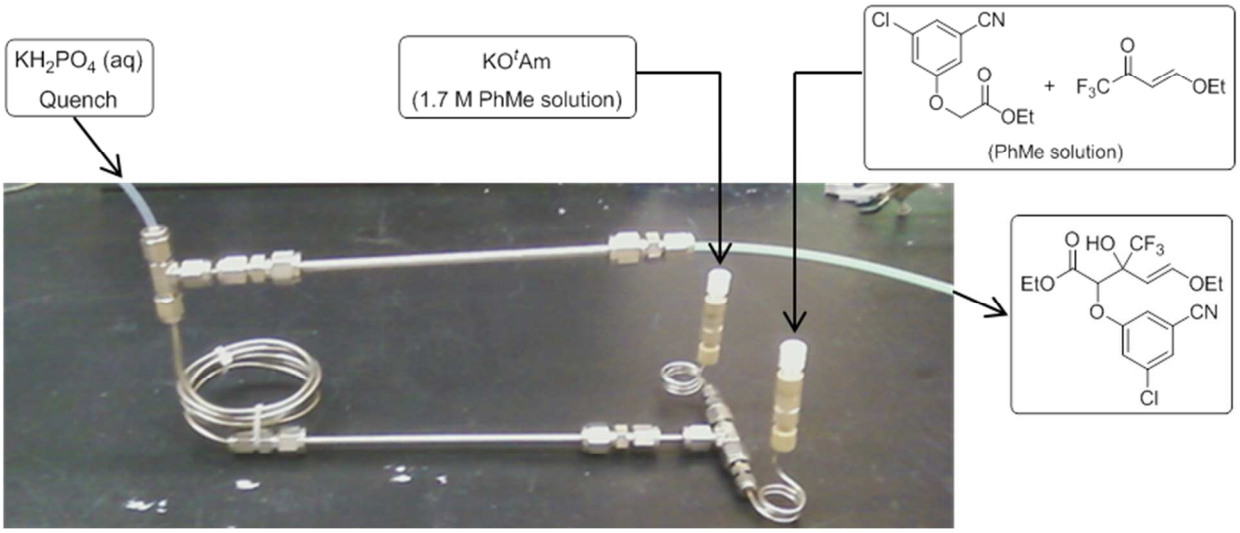
**Table 2: Sample Results from Micro-Batch Snapshot Experiments**


| **3** / **7a** | Time (seconds) | Temp °C | solvent | Base (equiv.) | % conv (% yield **8a**) |
|---|---|---|---|---|---|
| 1.0 | 20 | 23 | toluene | NaHMDS (1.5) | 50 (28) |
| 1.25 | 20 | 23 | toluene | NaHMDS (1.5) | 89 (53) |
| 1.5 | 20 | 23 | toluene | NaHMDS (1.5) | 99 (57) |
| 1.2 | 20 | -20 | toluene | NaHMDS (1.3) | 91 (72) |
| 1.2 | 60 | -20 | toluene | NaHMDS (1.3) | 95 (73) |

| | | | | | |
|---|---|---|---|---|---|
| 1.3 | 20 | 0 | toluene | NaHMDS (1.3) | 98 (73) |
| 1.2 | 20 | -20 | THF | NaHMDS (1.3) | 75 (66) |
| 1.2 | 20 | 23 | THF | NaHMDS (1.3) | 95 (67) |
| 1.2 | 20 | -20 | THF | nBuLi (1.0) | 7 |
| 1.2 | 20 | -20 | MTBE | NaHMDS (1.3) | 75 (70) |
| 1.2 | 60 | 50 | toluene or THF | various amine bases | No rxn |
| 1.2 | 20 | -20 | toluene | Li$O^t$Bu (1.3) | 5 |
| 1.2 | 20 | -20 | toluene | Na$O^t$Bu (1.3) | 67 (45) |
| 1.2 | 20 | -20 | toluene | K$O^t$Bu (1.3) | 97 (85) |
| 1.2 | 20 | -20 | THF | K$O^t$Bu (1.3) | 94 (77) |
| 1.2 | 20 | -50 | toluene | K$O^t$Am (1.3) | 94 (86) |
| 1.2 | 20 | -20 | toluene | K$O^t$Am (1.3) | 97 (85) |
| 1.2 | 20 | 0 | toluene | K$O^t$Am (1.3) | 94 (79) |
| 1.2 | 5 | -20 | toluene | K$O^t$Am (1.3) | 96 (84) |
| 1.2 | 60 | -20 | toluene | K$O^t$Am (1.3) | 98 (85) |

**3. Development of Continuous Aldol Reaction**

After using small-scale experiments to establish viable conditions for the continuous aldol addition, the reaction was evaluated in a continuous fashion. A 4.4 mL reactor was constructed from 1/8" stainless steel tubing as shown pictorially below:

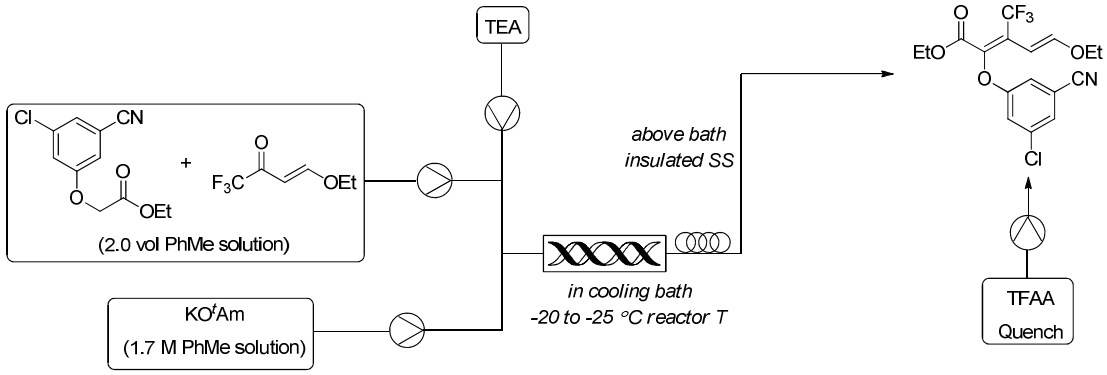



A solution of ester **7a**, enone **3** in toluene was prepared to a final concentration of 1 M in ester. This solution was pumped into one reactor inlet at 9.35 mL/min. A commercial solution of potassium *tert*-amylate in toluene (1.7 M) was pumped into the second reactor inlet at 8.25 mL/min. The reactor up to the second T-Mixer was submerged in a dry ice acetone batch maintained at -25 °C. At the second T-mixer the aqueous quench was introduced at a rate of 6.7 mL/min. The residence time (τ) in the reactor was 15 seconds. At completion of the reaction the aqueous phase was removed and the organic solution assayed by quantitative HPLC to determine yield of aldol adduct.

Initially the aqueous quench was evaluated to identify conditions which would deliver an organic solution with sufficient stability for downstream processing. Using a 10 wt% solution of potassium phosphate dibasic in 5 wt% aqueous phosphoric acid delivered an aqueous pH after quench of 8-11. The organic solution obtained showed no degradation as measured by quantitative HPLC after 3 days at 40 °C and 8 days at room temperature. In comparison an aqueous quench solution of 15 wt% potassium phosphate monobasic delivered an organic solution that showed 3% degradation after 3 days at 40 °C.

Though viable conditions to quench the aldol reaction were identified there was a desire to simplify the process through direct elimination of the aldol reaction stream. Attempts to include the trifluoroacetic anhydride in the receiver vessel required an additional 1-2 equiv of TFAA to push the reaction to complete conversion. As such a protocol where trifluoroacetic acid was added continuously to the receiver vessel was adopted.

This procedure was evaluated on kilogram scale using a reactor constructed from ¼" stainless steel tubing shown schematically below. The reactor volume was 82.2 mL, corresponding to a residence time (τ) of 53 seconds (see experimental procedure for flow rates) and a total processing time for a 1 kg batch of 1 h 45 min.




To assist with scale-up of the flow process the impact of temperature on the yield of the aldol reaction and subsequent cyclization to pyridone **10** was evaluated as shown in the table below.

**Table 3: Impact of Bath Temperature on Continuous Aldol Reaction**

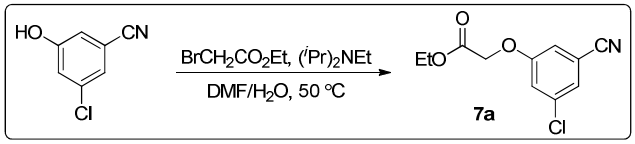
| *Aldol Reaction* | | | | | *Heterocyclization* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Solution KF | Bath T (°C) | Reactor T (°C) | Diene (LCAP) | Rel. Assay | NH3 P (psi) | NH3 P (equiv) | T (°C) | Time (h) | Pyridone (LCAP) | Assay (g) | AY |
| 353 | -25 | -20 | 78.56 | "Standard" | 50 | 35 | 60 | 6 | 75.36 | 23.51 | 72% |
| 537 | -25 | -20 | 79.52 | 100% | 50 | 34 | 60 | 6 | 71.39 | 24.37 | 74% |
| 228 | -10 | 0 | 78.61 | 97% | 48 | 36 | 60 | 6 | 71.54 | 21.87 | 67% |
| 233 | 0 | 10 | 77.41 | 95% | 70 | 43 | 60 | 6 | 67.72 | 22.49 | 69% |
| 234 | 9 | 20 | 76.29 | 94% | 52 | 38 | 60 | 6 | 68.44 | 21.53 | 66% |
| 226 | 14 | 26 | 73.60 | 90% | 55 | 38 | 60 | 6 | 64.94 | 20.18 | 61% |

**4. HPLC Conditions**

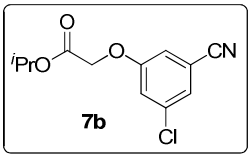
Fused-core C-18 (4.6x100 mm, 2.7 µm particle); 210 + 280 nm; 1.8 mL/min; 40 °C, solvent channel A: $CH_3CN$; solvent channel B: aqueous 0.1% $H_3PO_4$). 10% A to 95% A over 8 min, hold 2min.

| Peak | Retention time |
|---|---|
| Enone **3**: | 3.74 min (absorbs only at 280 nm) |
| Ethyl ester **7a**: | 4.45 min |
| Toluene: | 4.66 min |
| Aldol product **8a**: | 5.26 min |
| Diene **9a** | 5.96 min |
| Pyridone **10** | 4.13 min |

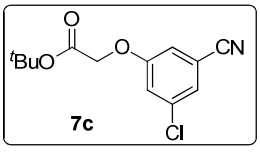
**5. Experimental Procedures and Compound Characterization**




**Ethyl 2-(3-chloro-5-cyanophenoxy)acetate (7a)**. A 1L round bottom flask equipped with overhead stirring was charged with 3-chloro-5-hydroxybenzonitrile (50.0 g, 98 wt% purity, 319 mmol) and 15% aqueous DMF (200 mL DMF + 35.5 mL $H_2O$). To the resulting solution was added diisopropylethylamine (61.3 mL, 99.0% purity, 1.1 equiv) and ethyl 2-bromoacetate (35.7 g, 1.15 equiv) at ambient temperature. The resulting solution was warmed to 50 °C and aged for 12 h. Upon completion of the reaction the mixture was cooled to 0-5 °C. To the clear to slightly cloudy solution was added 5% seed crystals of product (3.8g, 16.0 mmol) to induce crystallization. Water (64.5mL) was added to the thin suspension *via* syringe pump over 3 h while maintaining the temperature at 0-5 °C. Additional water (200mL) was added over 1 h while maintaining the temperature at 0-5 °C. The final DMF/water ratio was 1:1.5. The resulting slurry was aged for 1 h at 0-5 °C and filtered. The cake was washed with 2:1 DMF/water (150 mL) and water (200 mL). The wet cake was dried under a nitrogen stream at ambient temperature to afford 73.4 g of **7a** as a light tan solid, 96% yield, 99.5% purity. *Characterization Data:* $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.29 (m, 1H), 7.15 (m, 1H), 7.06 (m, 1H), 4.67 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 1.35 (t, J = 7 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ = 167.5, 158.6, 136.2, 125.2, 120.3, 117.2, 116.4, 114.4, 65.5, 61.8, 14.1 ppm. HRMS (ESI) cald for $C_{11}H_{11}NO_3Cl$ $[M+H]^+$ 240.0427, found 240.0418. Melting point: 41-42 °C.

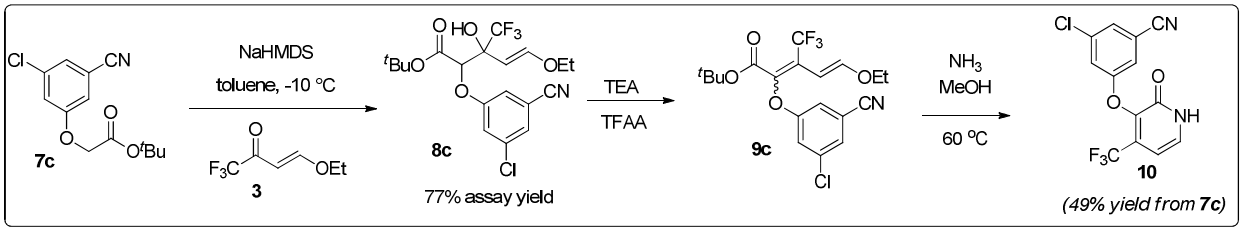



**Isopropyl 2-(3-chloro-5-cyanophenoxy)acetate (7b)**. To a solution of 3-chloro-5-hydroxybenzonitrile (20 g, 129 mmol) in acetone (200 mL) was added $K_2CO_3$ (27.0 g, 195 mmol) and isopropyl 2-bromoacetate (27.1 g, 150 mmol). The mixture was warmed to 50 °C and aged for 4h. The reaction mixture was allowed to cool to 23 °C and then filtered to remove inorganic precipitate. The filter cake was washed with acetone (70 mL). The combined filtrate and wash was concentrated to a volume of ~80mL. Heptane (200 ml) was charged over 4h. The resulting slurry was filtered, washed with heptane and dried under $N_2$ to give 29.75g (90% yield) of white crystalline solid (99% purity). *Characterization Data:* $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.29 (m, 1H), 7.16 (m, 1H), 7.07 (m, 1H), 5.17 (p, J = 6.5 Hz, 1 H), 4.62 (s, 2H), 1.30 (d, J = 6.5 Hz, 6H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz) δ = 167.0, 158.7, 136.1, 125.1, 120.3, 117.2, 116.5, 114.4, 69.8, 65.7, 21.7 ppm. HMRS (ESI) calcd for $C_{12}H_{13}NO_3Cl$ $[M+H]^+$ 254.0584, found 254.0581.




***tert*-Butyl 2-(3-chloro-5-cyanophenoxy)acetate (7c)**. To a 2L round bottom flask equipped with an overhead mechanical stirrer was charged 3-chloro-5-hydroxybenzonitrile (80 g, 505 mmol), followed by acetone (800 ml), $K_2CO_3$ (92 g, 667 mmol) and *tert*-butyl 2-bromoacetate (85 ml, 561 mmol). The reaction was warmed to 50-55 °C and aged 4h. The reaction mixture was filtered and then washed with acetone (240 mL). The filtrate was concentrated on a rotovap to ~half the volume (~400mL) during which time the product began to crystallize. To the resulting slurry was added heptane (400 mL) over 2h, then aged at RT over night. Under mechanical stirring, n-heptane (400 mL, 5 vol) was added slowly over 2h, then stirred at RT overnight. The batch was filtered, washed with n-heptane (160 mL x 2) and dried under $N_2$. Isolated 128.6g (94.0 % yield) of a white crystalline solid (99.0% purity). *Characterization Data:* $^1$H NMR ($CDCl_3$, 500 MHz) δ = 7.29 (m, 1H), 7.15 (m, 1H), 7.06 (m, 1H), 4.56 (s, 2 H), 1.52 (s, 9H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz) δ = 166.6, 158.7, 136.1, 125.0, 120.2, 117.2, 116.4, 114.3, 83.3, 65.9, 28.0 ppm. HMRS (ESI) calcd for $C_{13}H_{15}NO_3Cl$ $[M+H]^+$ 268.0740, found 268.0736.

**Procedure for the Synthesis of Pyridone 10 via Aldol Run in Batch Mode:**

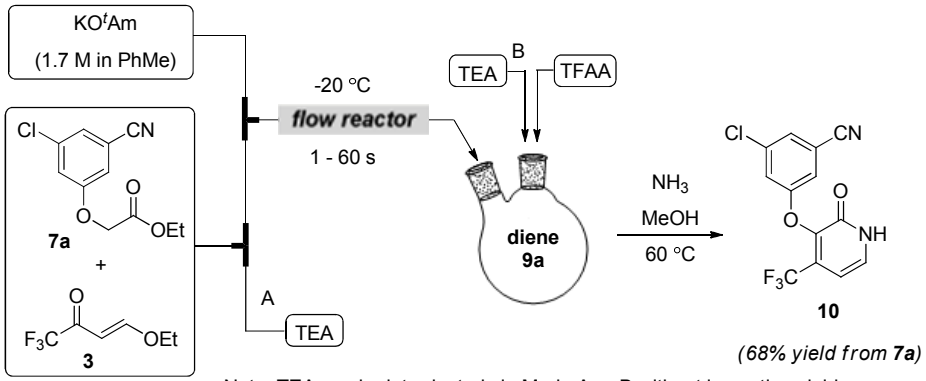



**3-Chloro-5-((2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile (10)**. To a -15 °C solution of 0.6M sodium bis(trimethylsilyl)amide in toluene (7.47 ml, 4.48 mmol) was added a solution of *tert*-butyl 2-(3-

chloro-5-cyanophenoxy)acetate (1.0 g, 3.74 mmol) in toluene (5.0 ml) dropwise via an addition funnel over 15 min with internal temp <-10 °C. The resulting suspension was aged at -10 °C for 15min. Neat (E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**3**) (0.646 ml, 4.48 mmol) was added over 15min while maintaining the internal reaction temp to < -10 °C. The mixture was aged 15min at -10 °C then allowed to warm to 0 °C. The reaction was quenched with $H_2O$ (10 mL), and the layers were allowed to settle. The organic layer was washed again with $H_2O$ (10 mL). The org layer was next azeotropically dried by distillation. The volume was adjusted to 5 mL and the final water content was determined to be < 300ppm by Karl Fisher coulometric titration. The solution was assayed against an authentic reference and found to contain 1.26g (77% yield) of **8c**.

The solution of **8c** (1.26 g, 2.89 mmol) in toluene at 23 °C was treated triethylamine (1.21 ml, 8.67 mmol) followed by dropwise addition of trifluoroacetic anhydride (0.613 ml, 4.34 mmol) over 15 min. The temperature was maintained at <30 °C during the TFAA addition. The resulting heterogeneous mixture was aged 1h.

The crude reaction mixture of diene **9c** in toluene was added MeOH (6.5 mL) and the inorganic precipitate dissolved to give a clear yellow solution. The solution of **9c** was found to be exceptionally stable; however, attempts to isolate by chromatography resulted in decomposition. The reaction was transferred to a pressure vessel, anhydrous ammonia (2.5 ml, 107.2 mmol) was charged and the vessel was aged 12h @ 80 °C. The resulting dark solution was concentrated in vacuo to remove ammonia and during the ammonia distillation pyridone **10** precipitated out of solution. The distillation continued to remove most of the MeOH while maintaining a relatively constant volume by replenishing with toluene. The mixture was filtered, washed with 4:1 toluene/MeOH (2.0mL) and dried over a $N_2$ stream to afford 0.576g (49% overall yield from **7c**) of a white crystalline solid. *Characterization Data:* $^1$H NMR (DSMO-$d_6$, 500 MHz) δ = 13.13-12.33 (br s, 1H), 7.71 (t, 1H, $J$ = 1.56 Hz), 7.60 (d, 1H, $J$ = 6.72 Hz), 7.57 (dd, 1H, $J$ = 2.4, 1.2 Hz), 7.51 (t, 1H, $J$ = 2.1 Hz), 6.46 (d, 1H, $J$ = 6.86 Hz) ppm. $^{13}$C (125 MHz, DMSO-$d_6$) δ = 157.4, 156.9, 140.7 (q, $J$ = 1.77 Hz), 134.9, 134.1, 130.8 (q, $J$ = 31.43 Hz), 126.4, 121.9 (q, $J$ = 275.79 Hz), 121.2, 118.3, 117.0, 113.7, 100.0 (q, $J$ = 4.37 Hz) ppm. HMRS (ESI) calcd for $C_{13}H_7N_2O_2F_3Cl$ $[M+H]^+$ 315.0148, found 315.0152. Melting point: 272 °C.




Note: TEA can be introducted via Mode A or B without impacting yield

**Procedure for the Synthesis of Pyridone 10 via Continuous Aldol Reaction (TEA added via mode A):**

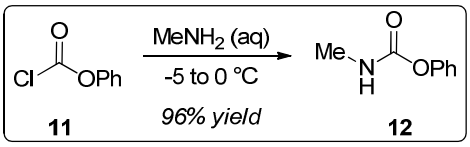
**3-Chloro-5-((2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile (10)**. A solution of ethyl ester **7a** (1.00 kg, 4.17 mol, 1.00 equiv) and enone **3** (1.05 kg, 6.27 mol, 1.50 equiv) in toluene (1.74 kg, 2.00 L) transferred at a rate of 35 mL/min was combined with triethylamine (2.33 L, 16.7 mol, 4.00 equiv) transferred at a rate of 22.5 mL/min and pumped to one reactor inlet. The commercial solution of 1.7 M potassium *tert*-amylate in toluene (3.56 L, 6.05 mol, 1.45 equiv) was pumped to the second reactor inlet at a rate of 35 mL/min. The receiver vessel was a 30 L cylindrical jacketed vessel charged with toluene (1.2 L) and potassium trifluoroacetate[1] (44 g, 0.292 mol, 5 wt% of theoretical). Trifluoroacetic anhydride (1.74 L, 12.5 mol, 3.00 equiv) was added to the receiver vessel at a rate of 17.2 mL/min. The reactor was submerged in a dry ice/acetone batch maintained at -30 to -42 °C for the course of the run. The receiver vessel was maintained at 6 to 8 °C. At completion of the reaction the receiver vessel was warmed to room temperature and methanol (2.7 L) was added. Qualitative HPLC analysis showed the desired diene was generated in 83.55 LCAP.

The resulting solution was transferred to a 10 gallon stainless steel autoclave using methanol (0.861 kg) as a forward rinse of the transfer line. The vessel was charged with ammonia (1.9 kg, 117 mol, 28 equiv) to a pressure of 6 psi. The mixture was warmed to 60 °C resulting in a pressure increase to 51 psi and aged for 6 h. The reaction was

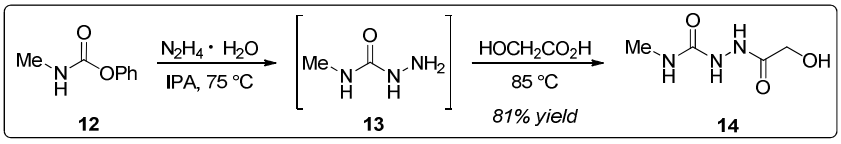
cooled to room temperature and the system vented. The solution was transferred out of the stainless steel autoclave using methanol (8 L) as a forward rinse of the transfer line.

A 22 L four neck round bottom flask was equipped with a thermocouple, vacuum adapter, distillation head and overhead stirrer. The batch and methanol rinse were transferred to the round bottom flask in portions to maintain a volume of 8-12 L while concentrating at 19 inHg and 40 °C. During concentration the product crystallized from solution. At completion of the concentration the system was vented and cooled to room temperature. Methanol (1.5 L) was added to bring the final reaction volume to 9.5 L and aged overnight.

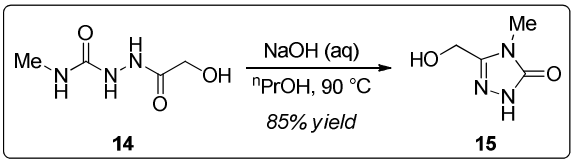
The resulting slurry was filtered and the cake washed with methanol (8 L). The solid was dried on the frit under a nitrogen stream. Obtained 0.909 kg (68% corrected yield) of pyridone **10** as an off-white solid with 99.04 HPLC LCAP and 98.5 LCWP. *Characterization Data:* $^1$H NMR (DSMO-$d_6$, 500 MHz) δ = 13.13-12.33 (br s, 1H), 7.71 (t, 1H, $J$ = 1.56 Hz), 7.60 (d, 1H, $J$ = 6.72 Hz), 7.57 (dd, 1H, $J$ = 2.4, 1.2 Hz), 7.51 (t, 1H, $J$ = 2.1 Hz), 6.46 (d, 1H, $J$ = 6.86 Hz) ppm. $^{13}$C (125 MHz, DMSO-$d_6$) δ = 157.4, 156.9, 140.7 (q, $J$ = 1.77 Hz), 134.9, 134.1, 130.8 (q, $J$ = 31.43 Hz), 126.4, 121.9 (q, $J$ = 275.79 Hz), 121.2, 118.3, 117.0, 113.7, 100.0 (q, $J$ = 4.37 Hz) ppm. HMRS (ESI) calcd for $C_{13}H_7N_2O_2F_3Cl$ $[M+H]^+$ 315.0148, found 315.0152. Melting point: 272 °C.




**Phenyl methylcarbamate (12)**. Aqueous methylamine (500 g, 6.44 mol, 40 wt%) was charged to a 2 L vessel equipped with heat/cool jacket, overhead stirrer, temperature probe and nitrogen inlet. The solution was cooled to -5 °C. Phenyl chloroformate (500.0 g, 3.16 mol) was added over 2.5 h maintaining the reaction temperature between -5 and 0 °C. On complete addition the white slurry was stirred for 1 h at 0 °C. The slurry was filtered, washed with water (500 mL) and dried under $N_2$ sweep overnight to afford 465g (96% yield) of the desired product as a white crystalline solid. *Characterization Data:* $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.36 (t, 2H, $J$ = 7.9 Hz), 7.19 (t, 1H, $J$ = 7.4 Hz), 7.13 (d, 2H, $J$ = 7.7 Hz), 5.23 (br s, 1H), 2.82 (d, 3H, $J$ = 4.63 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz) δ = 155.4, 151.1, 129.3, 125.3, 121.7, 27.7 ppm. HMRS (ESI) calcd for $C_8H_{10}NO_2$ $[M+H]^+$ 152.0712, found 152.0709. Melting point: 66 °C.

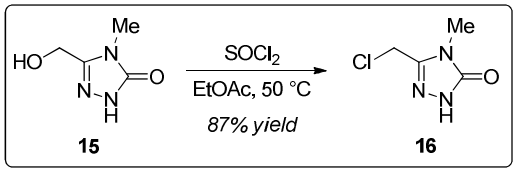



**2-(2-Hydroxyacetyl)-*N*-methyl-hydrazinecarboxamide (14)**. Phenyl methylcarbamate (300 g, 1.95 mol) was charged to a 2 L vessel with cooling jacket, overhead stirrer, temperature probe, reflux condenser and nitrogen inlet. Charged IPA (390 mL) and hydrazine hydrate (119 g, 2.33 mol). The resulting slurry was warmed to 75 °C and aged for 6 h. Charged IPA (810 mL) and glycolic acid (222 g, 2.92 mol) and the resulting solution was aged at 83-85 °C for 10-12 h. The mixture was seeded with product (0.5 g) after 4 h at 83-85 °C. The slurry was slowly cooled to 20 °C over 2 h and aged for 1 h. The slurry was filtered and washed with IPA (600 mL). The cake was dried under nitrogen sweep to afford 241.8g (81% yield) of the desired product as a white crystalline solid. *Characterization data:* $^1$H NMR ($D_2O$, 400 MHz): δ = 4.10 (s, 2H), 2.60 (s, 3H). $^{13}$C NMR ($D_2O$, 100 MHz) δ = 175.1, 160.4, 60.5, 26.0 ppm. HMRS (ESI) calcd for $C_4H_{10}N_3O_3$ $[M+H]^+$ 148.0722, found 148.0719.

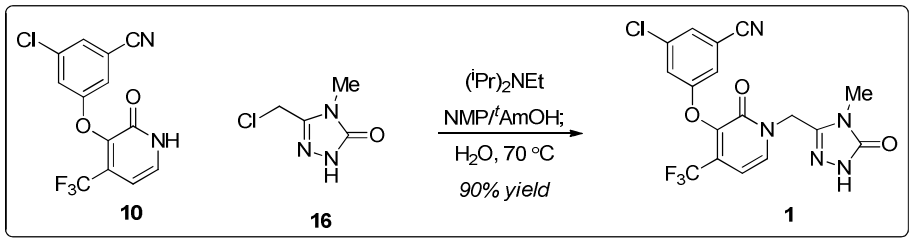



**3-(Hydroxymethyl)-4-methyl-1*H*-1,2,4-triazol-5(4*H*)-one (15)**. Compound **14** (130 g, 0.84 mol, 95 wt%), *n*-propanol (130 mL) and water (130 mL) were charged to a 1 L vessel with jacket, overhead stirrer, temperature probe, reflux condenser and nitrogen inlet. Sodium hydroxide (16.8 g, 0.42 mol) was added and the slurry warmed to reflux and aged for 3 h. The reaction mixture was cooled to 20 °C and the pH adjusted to 6.5 (+/- 0.5) using concentrated aqueous hydrochloric acid (28.3 mL, 0.34 mol). Water was azeotropically removed under vacuum at 40-50 °C by reducing the volume to ~400 mL and maintaining that volume by the slow addition of n-propanol (780 mL). The final water content should be <3000 ug/mL. The resultant slurry (~ 400 mL) was cooled to 23 °C and heptane (390 ml) was added. The slurry was aged for 1 h at 23 °C, cooled to 0 °C and aged 2 h. The slurry was filtered, the cake washed with 1:2 n-PrOH/heptane (100 mL) and dried to provide 125g (85% yield) of an off-white crystalline solid. The solid was ~73 wt% due to residual inorganics (NaCl). *Characterization data:* $^1$H NMR ($D_2O$, 400 MHz): δ =

4.43 (s, 2H), 3.16 (s, 3H) ppm. $^{13}$C NMR ($D_2O$, 100 MHz) δ = 156.3, 148.2, 54.4, 27.0 ppm. HMRS (ESI) calcd for $C_4H_8N_3O_2$ $[M+H]^+$ 130.0617, found 130.062.




**3-(Chloromethyl)-4-methyl-1*H*-1,2,4-triazol-5(4*H*)-one (16)**. A mixture of **15** (54 g, at 73wt%, 307 mmol) in ethyl acetate (540 mL) was stirred at 45 °C. Thionyl chloride (26.9 mL, 369 mmol) was added over 30-45 min and the mixture aged at 50 °C for 2 h. The warm suspension was filtered and the filter cake (mainly NaCl) was washed with ethyl acetate (108 mL). The combined filtrate and wash were concentrated at 50-60 °C under reduced pressure to approximately 150 mL. The resulting slurry was cooled to -10 °C and aged for 1 h. The slurry was filtered and the filter cake washed with ethyl acetate (50 mL). The cake was dried under a nitrogen sweep to afford 40.1g (86% yield) of the desired product as a bright yellow solid. *Characterization Data:* $^1$H NMR (DMSO-$d_6$, 500 MHz): δ = 3.18 (s, 3H), 4.72 (s, 2H), 11.83 (s, 1H) ppm. $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz) δ = 26.7, 35.5, 143.8, 154.9 ppm. HMRS (ESI) calcd for $C_4H_7N_3OCl$ $[M+H]^+$ 148.0278, found 148.0279.




**Doravirine (1)**. A 75 L flask was charged a 9.63 wt% solution of **16** in NMP (11.6 kg, 7.55 mol). Charged **10** (2.00 kg, 6.29 mol), NMP (3.8 L) and 2-methyl-2-butanol (6.0 L). To the resulting suspension was slowly added *N,N*-diisopropylethylamine (4.38 L, 25.2 mol) over 4 h. The reaction was aged for 18 h at ambient temperature. The tan solution was quenched with acetic acid (1.26 L, 22.0 mol) and aged at ambient temperature overnight. The tan solution was warmed to 70 °C. Water (2.52 L) was added and the batch was seeded with crystalline **1** (134 g) to induce crystallization. The thin suspension was aged 1 h at 70 °C. Additional water (14.3 L) was added over 7 h. The slurry was aged for 2 h at 70 °C and slowly cooled to 20 °C over 5 h. The slurry was filtered and washed with 2:1 NMP/water (6 L), followed by water (6 L x 2). The filter cake was dried under nitrogen to give 2.53 kg (85% yield) of **1** as a white solid. *Characterization Data :* $^1$H NMR (DMSO-$d_6$, 500 MHz): δ 3.11 (s, 3H), 5.17 (s, 2H), 6.66 (d, 1H, *J* = 7.4 Hz), 7.52 (m, 1H), 7.61 (dd, 1H, *J* = 2.4, 1.3 Hz), 7.74 (dd, 1H, *J* = 1.8, 1.4 Hz), 7.89 (d, 1H, *J* = 7.4 Hz), 11.68 (s, 1H) ppm. $^{13}$C NMR (DMSO-$d_6$, 125.7 MHz): δ 26.7, 43.3, 100.2, 113.6, 116.8, 118.4, 121.1, 121.6, 126.5, 129.9, 134.9, 137.3, 140.1, 143.2, 155.0, 156.0, 157.2 ppm. $^{19}$F NMR (DMSO-$d_6$, 470.5 MHz): δ -62.3 ppm. HMRS (ESI) calcd for $C_{17}H_{12}N_5O_3F_3Cl$ $[M+H]^+$ 426.0581, found 426.0588.

**6. X-Ray Crystal Data and Structure Refinement for Compound 8a**

A single crystal was grown by vapor diffusion of n-heptane into a concentrated isopropyl acetate solution of Compound **8a**. The crystal was a small colorless plate with dimensions of 0.07 mm x 0.27 mm x 0.31mm. Data collection was performed on a Bruker Apex II system at 100K. The unit cell was determined to be monoclinic in space group $P2_1/n$. Crystallographic data is summarized in **Table 3**. The compound crystallized as a racemate (2R,3R / 2S,3S) and the C4-C5 double bond is in the trans configuration. **Figure 1** shows an ORTEP representation of Compound **8a** with thermal ellipsoids set at the 30% probability level. Full structural details have been deposited with Cambridge Crystallographic Data Centre (CCDC 1044760).

**Figure 1: ORTEP representation of Compound 8a with thermal ellipsoids set at the 30% probability level.**

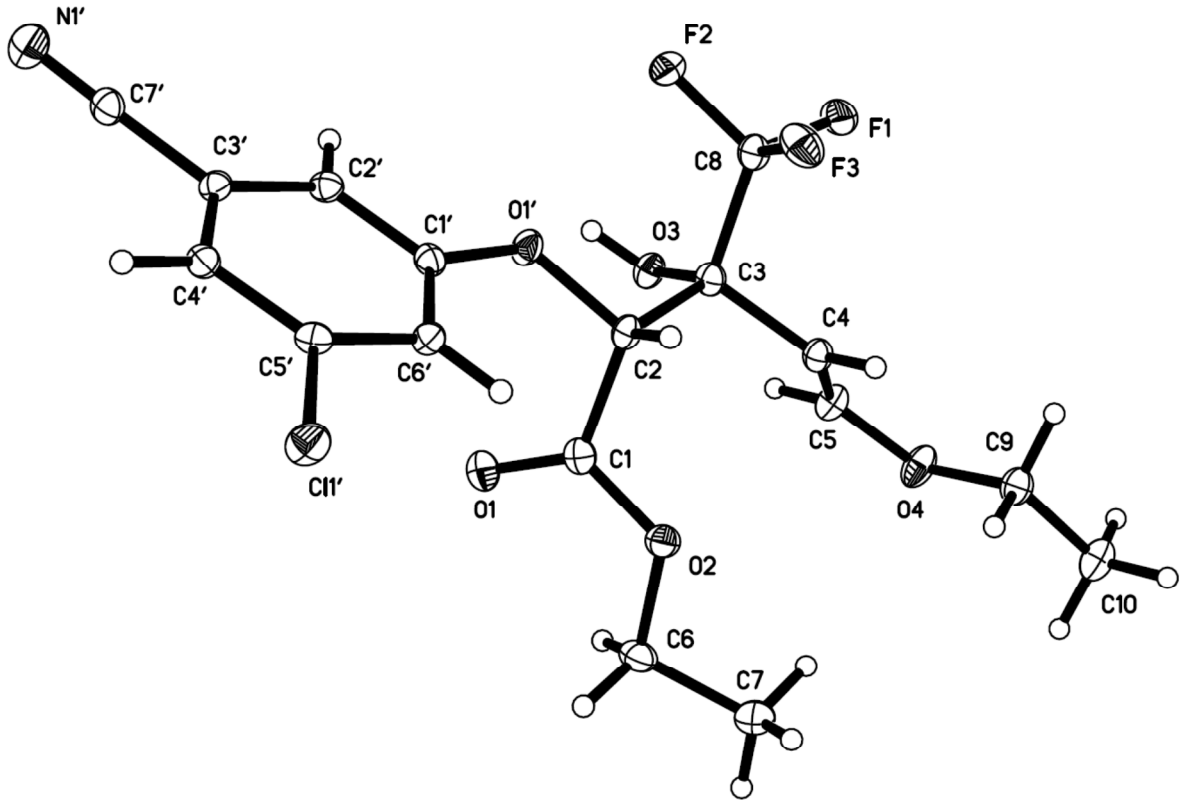
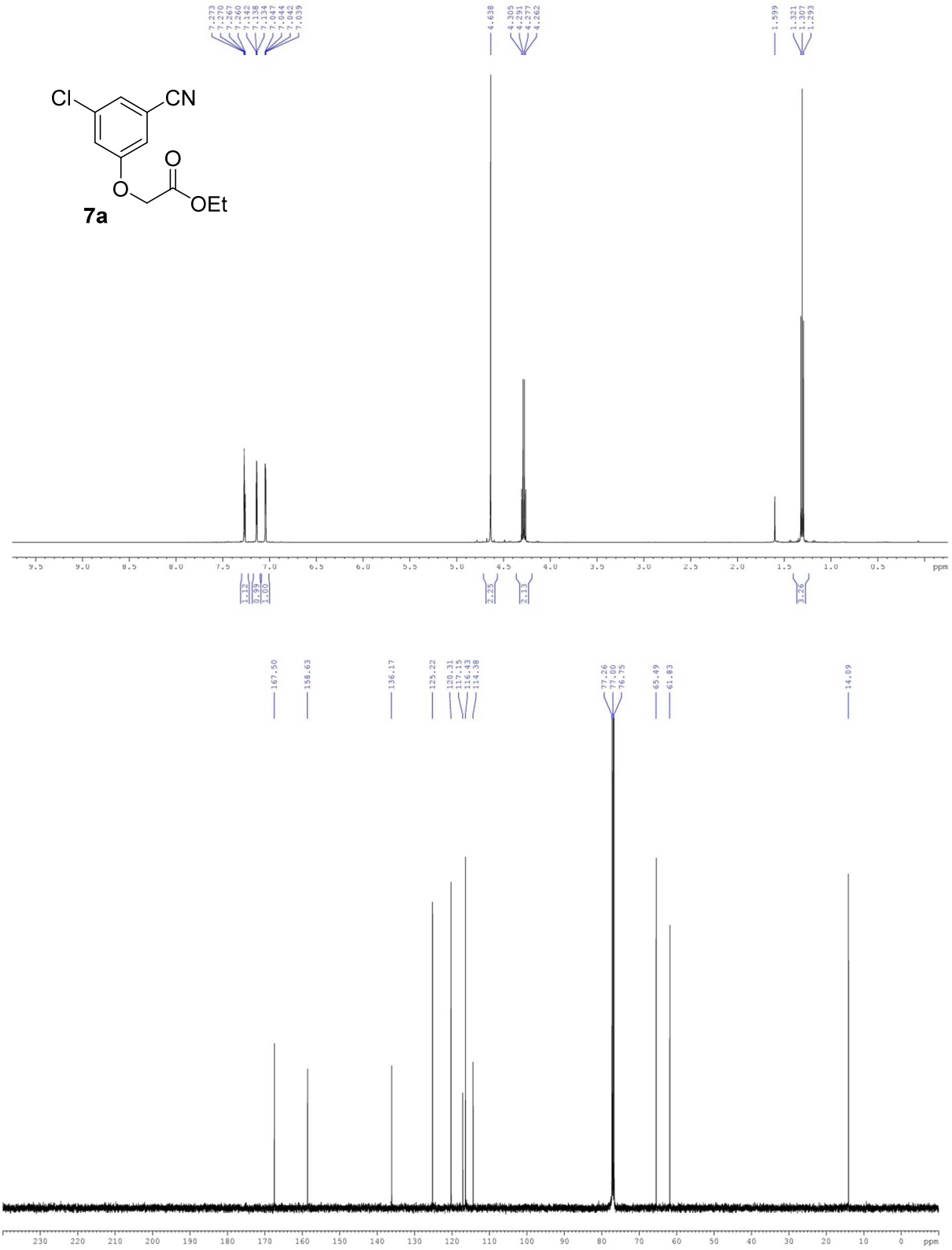


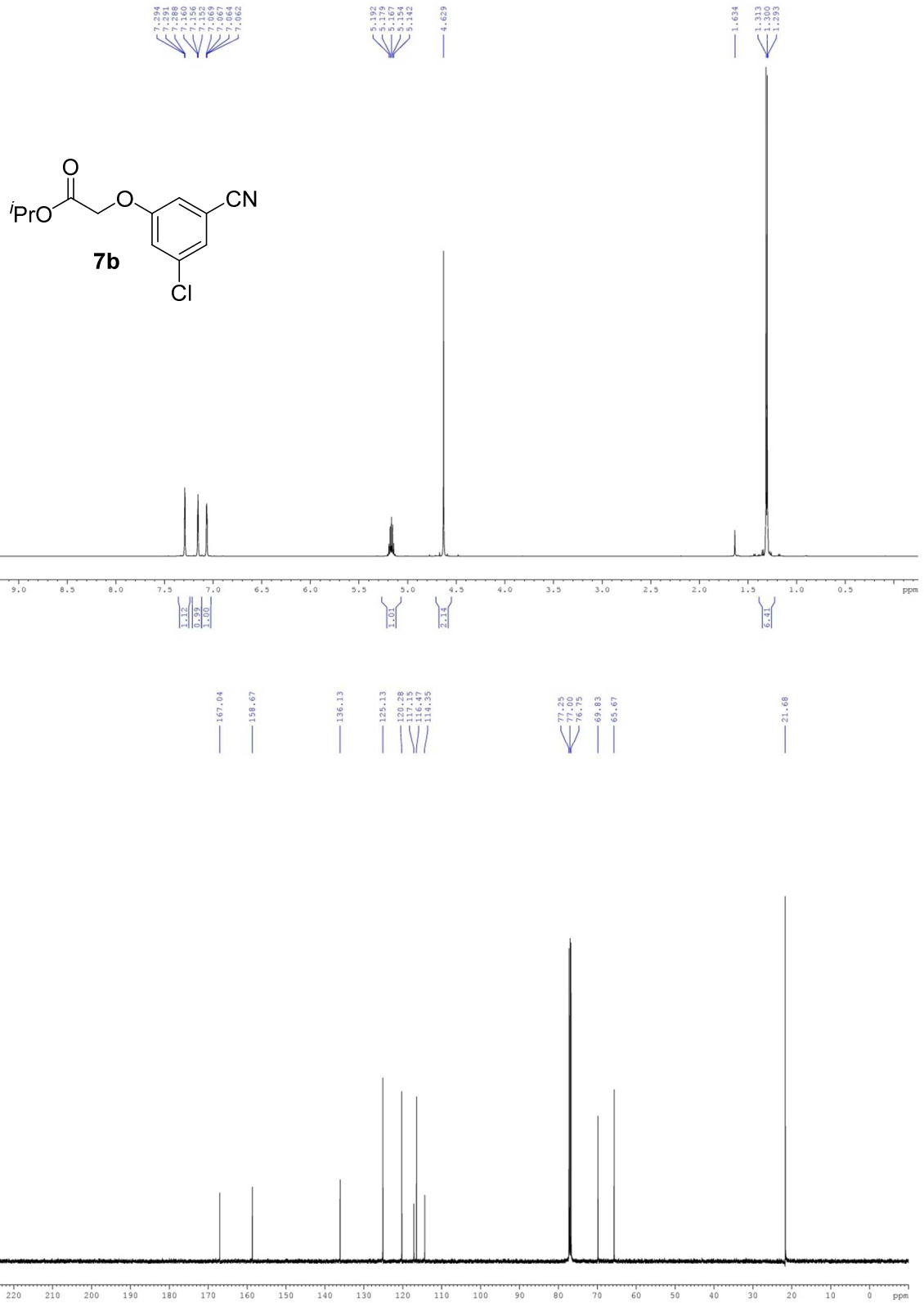

**Table #. Crystal data and structure refinement for Compound 8a**

| | | |
|---|---|---|
| Empirical formula | $C_{17}\ H_{17}\ Cl\ F_3\ N\ O_5$ | |
| Formula weight | 407.76 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1/n$ | |
| Unit cell dimensions | a = 11.9780(8) Å | a= 90°. |
| | b = 7.5434(5) Å | b= 94.087(3)° |
| | c = 20.4174(13) Å | g = 90°. |
| Volume | 1840.1(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.472 $g/cm^3$ | |
| Absorption coefficient | 2.384 $mm^{-1}$ | |
| F(000) | 840 | |
| Crystal size | 0.312 x 0.272 x 0.066 $mm^3$ | |

| | |
|---|---|
| Theta range for data collection | 4.154 to 66.448°. |
| Index ranges | -14<=h<=14, -7<=k<=8, -24<=l<=24 |
| Reflections collected | 26879 |
| Independent reflections | 3201 [R(int) = 0.0403] |
| Completeness to theta = 66.500° | 98.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.854 and 0.630 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3201 / 0 / 247 |
| Goodness-of-fit on $F^2$ | 1.027 |
| Final R indices [I>2sigma(I)] | R1 = 0.0304, wR2 = 0.0815 |
| R indices (all data) | R1 = 0.0331, wR2 = 0.0836 |
| Largest diff. peak and hole | 0.339 and -0.243 e.$Å^{-3}$ |

## 7. Copies of $^{1}H$ and $^{13}C$ Spectra

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Cl
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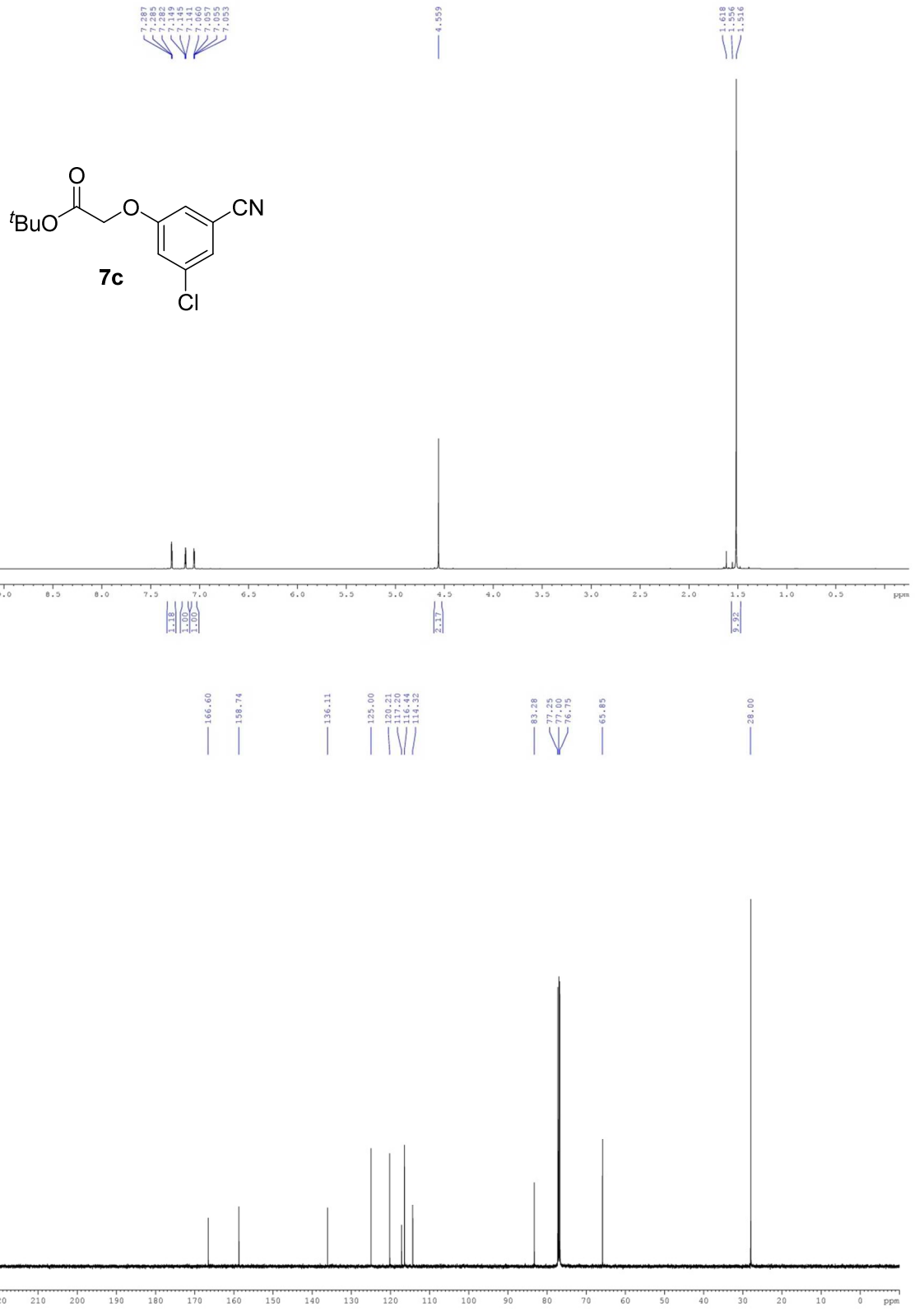
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7.145
7.141
7.060
7.057
7.055
7.053
4.559
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1.556
1.516
O
tBuO
O
CN
Cl
7c
1.18
1.00
1.00
2.17
9.92
166.60
158.74
136.11
125.00
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116.44
114.32
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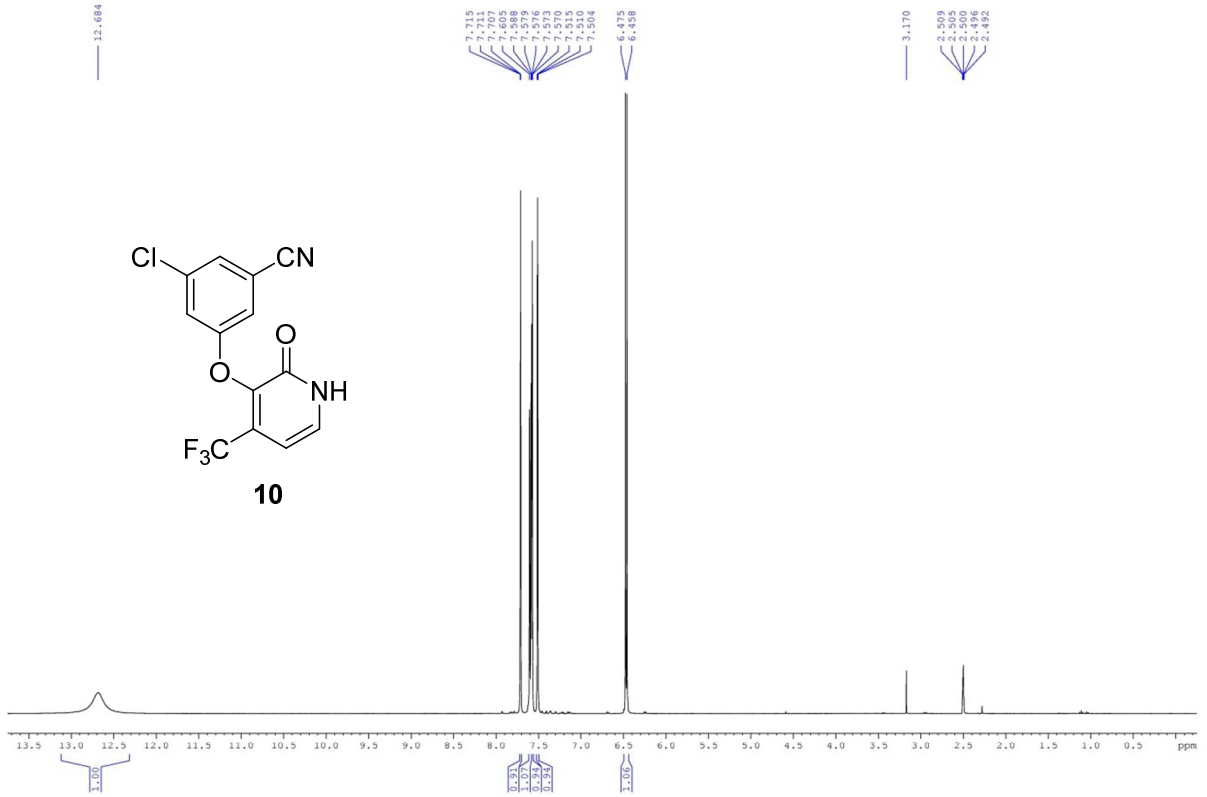
77.00
76.75
65.85
28.00
ppm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7.573
7.570
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7.510
7.504
6.475
6.458
3.170
2.509
2.505
2.500
2.496
2.492
Cl
CN
O
O
NH
F3C
10
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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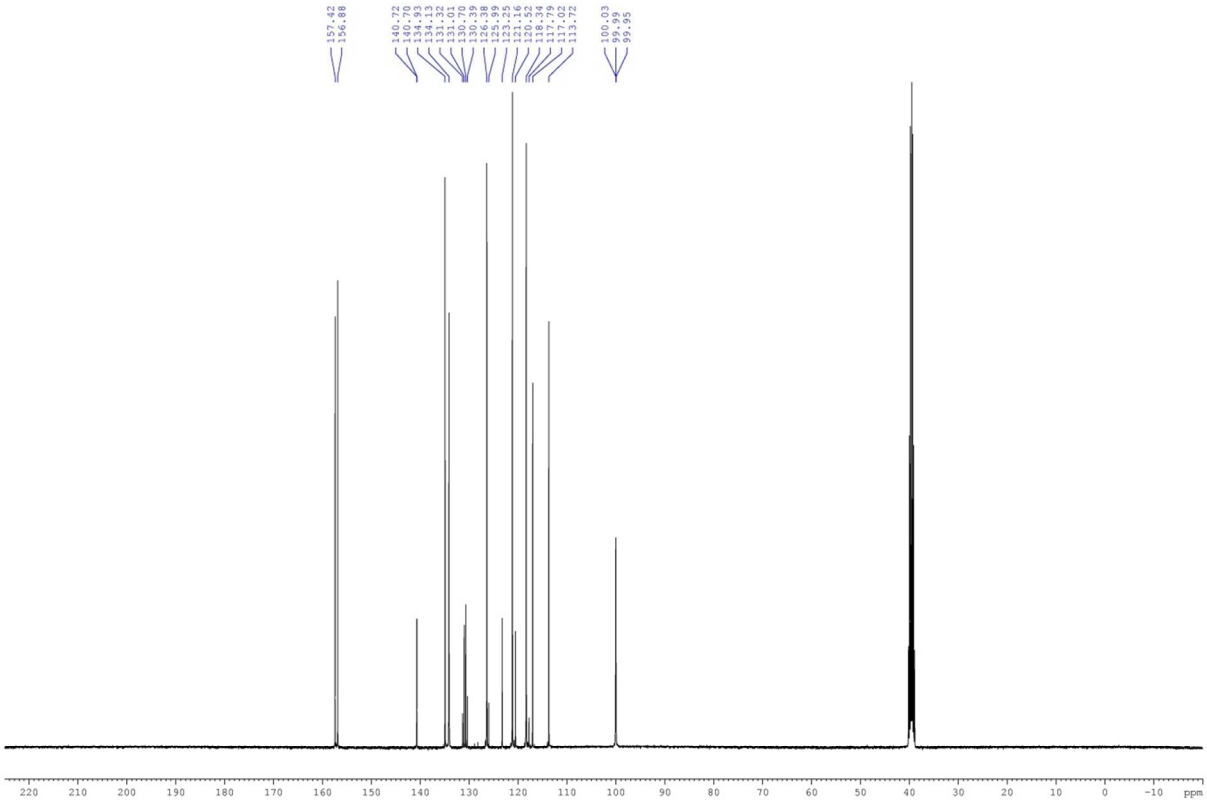
0.94
0.94
1.06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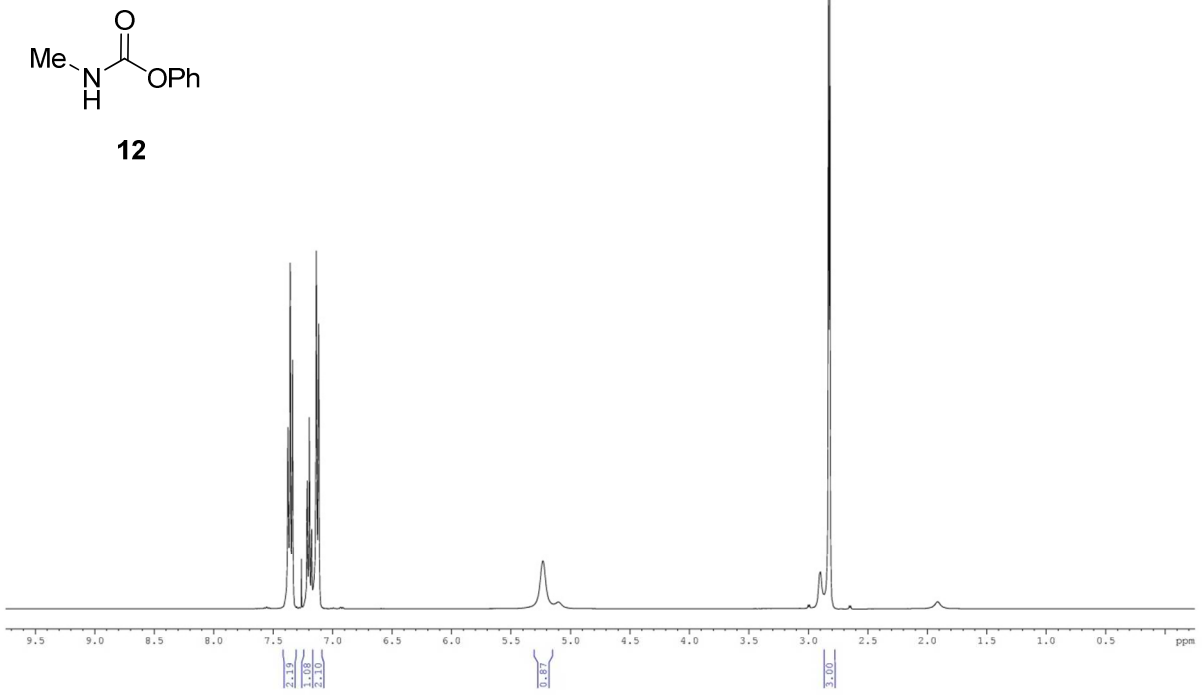
140.70
140.03
134.13
131.32
131.01
130.70
130.39
126.38
125.99
123.25
121.16
120.32
118.34
117.79
117.02
113.72
100.03
99.99
99.95
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm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7.261
7.213
7.194
7.176
7.135
7.116
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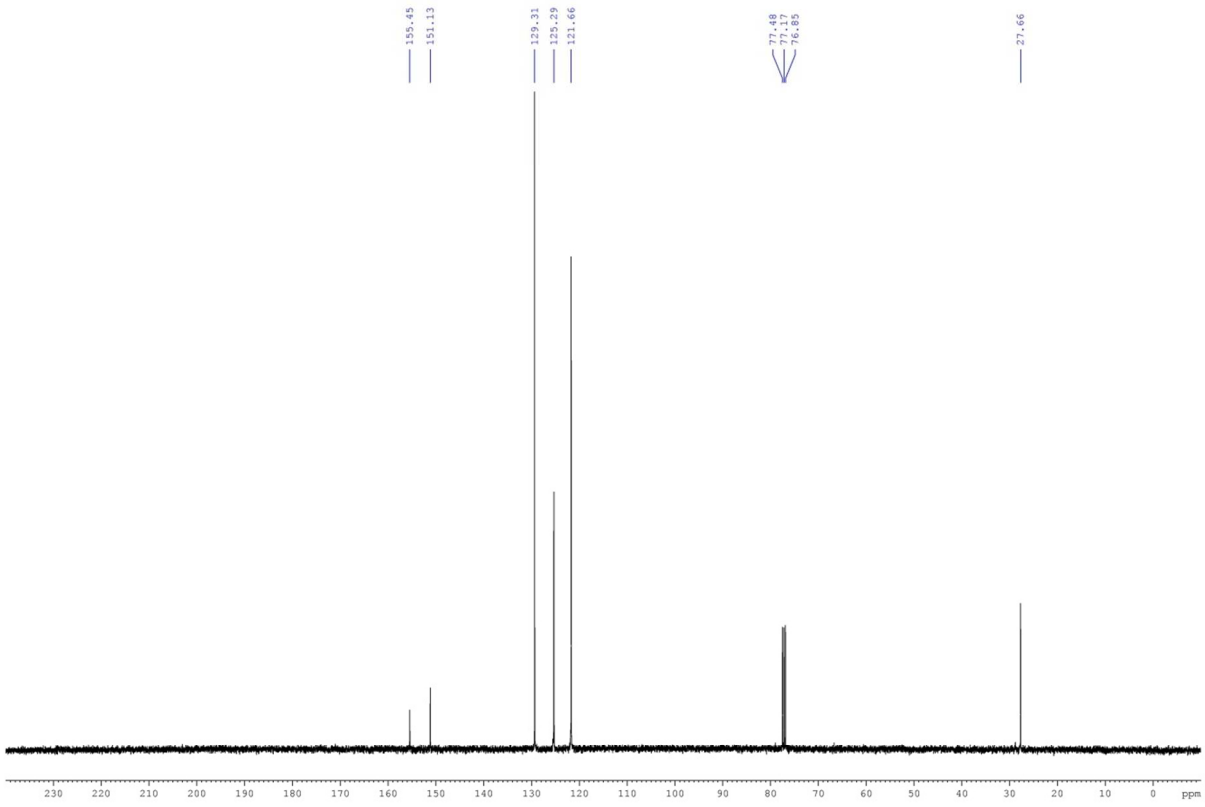
1.08
2.10
0.87
3.00
ppm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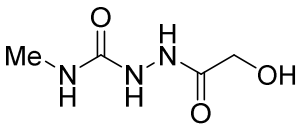
27.66
ppm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N
H
O
N
H
H
N
O
OH

**14**


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2.592
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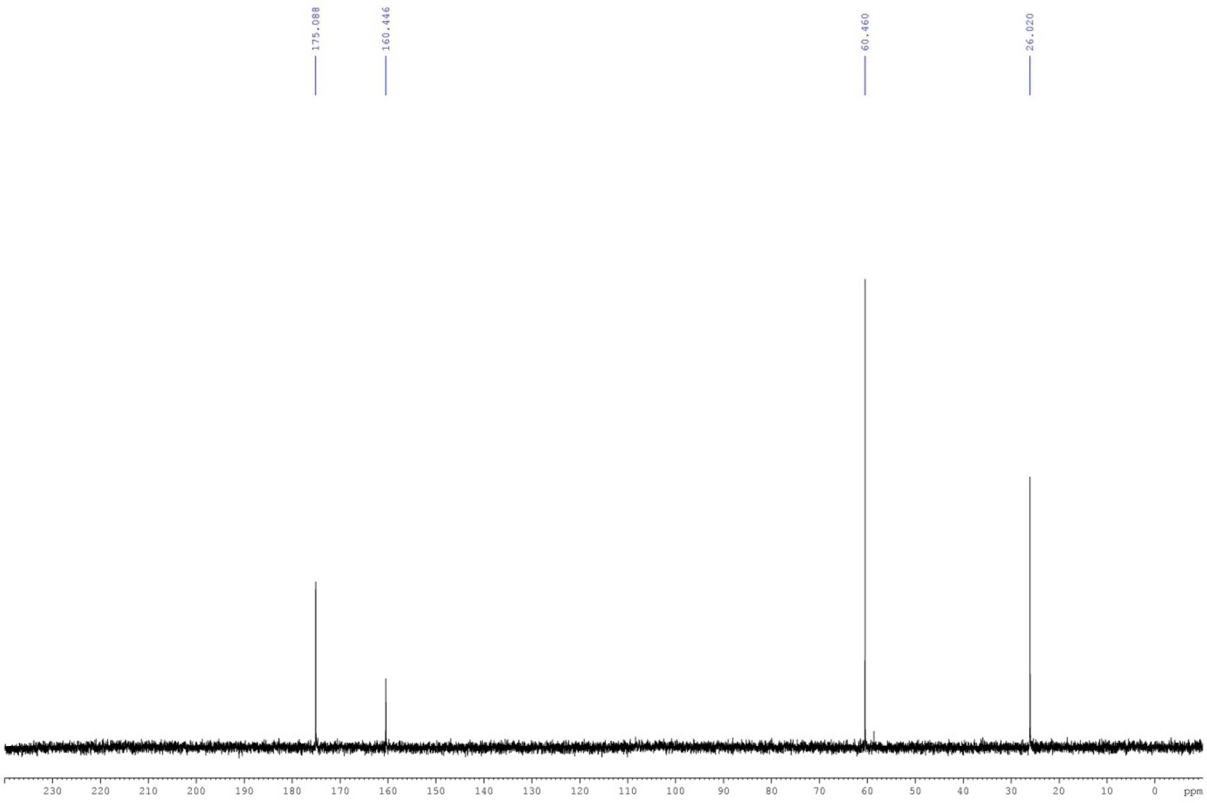
3.05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26.020
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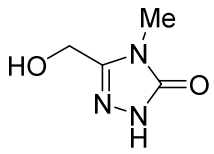
Me
HO
N
O
N
N
H

**15**


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2.566
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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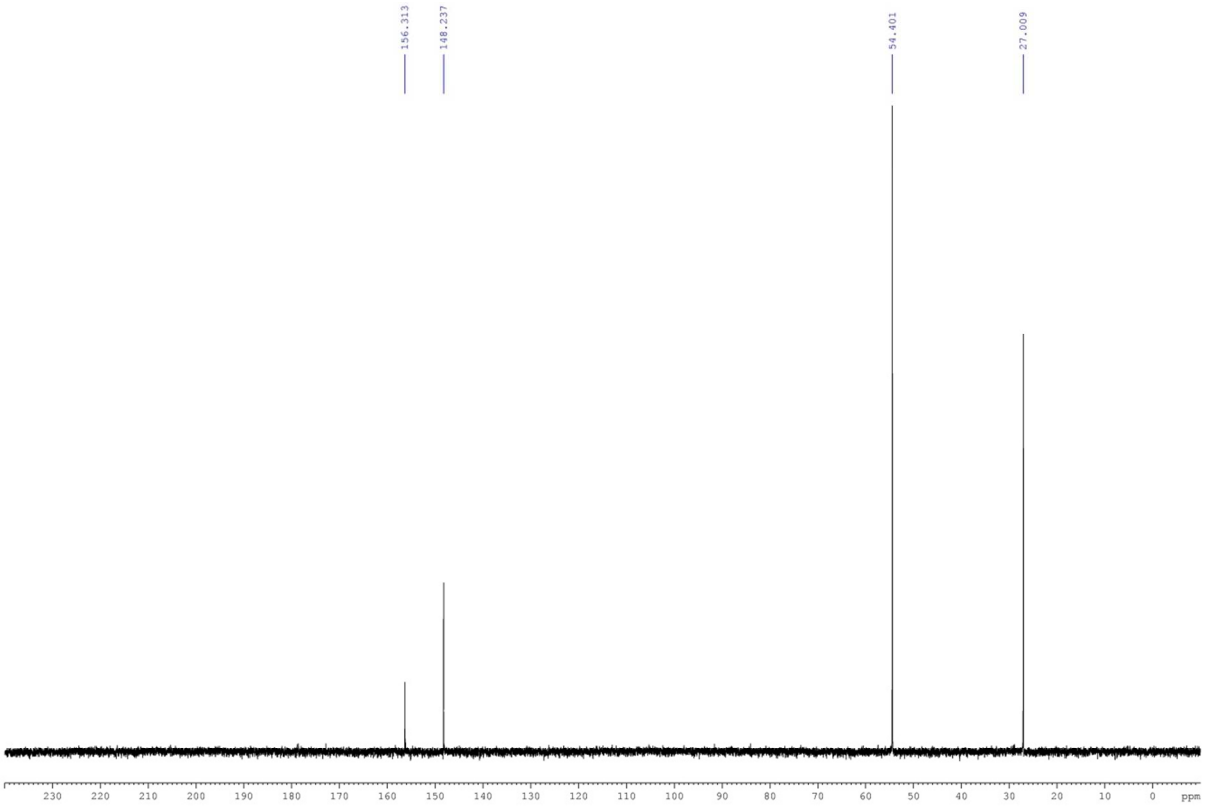
3.00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70
60
50
40
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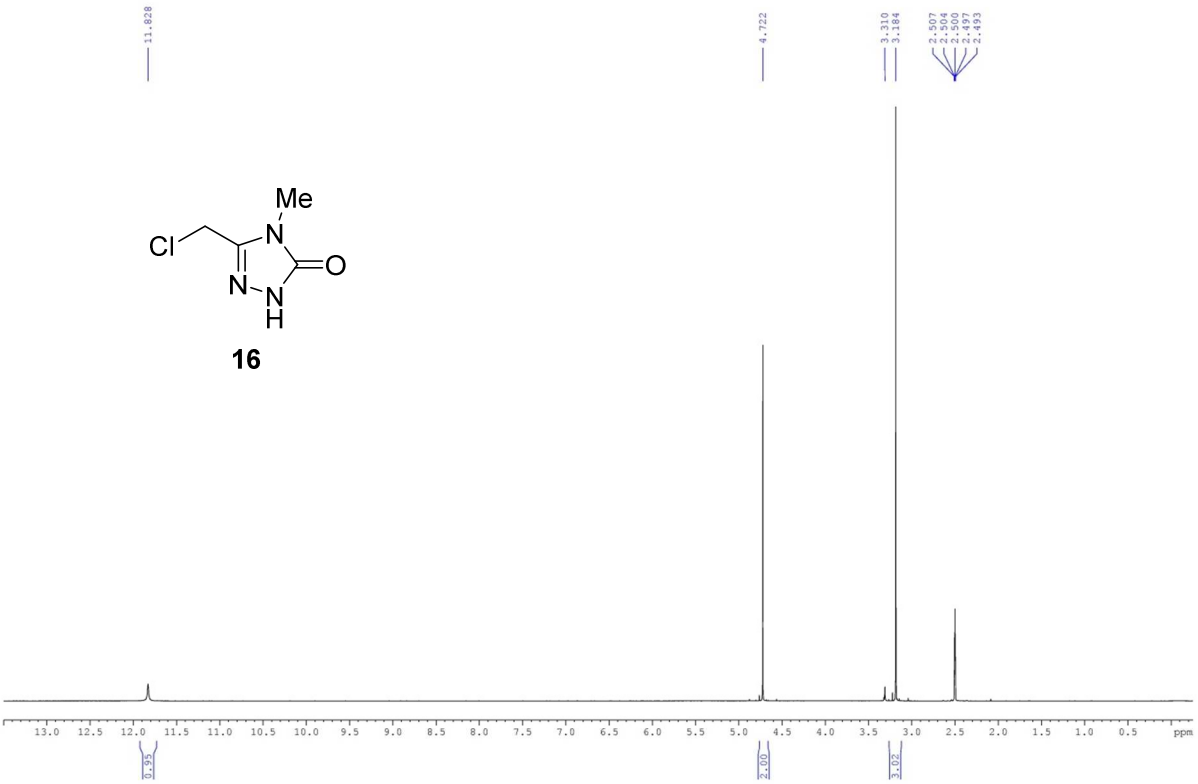
20
10
0
ppm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3.184
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2.497
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Me
N
Cl
O
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H
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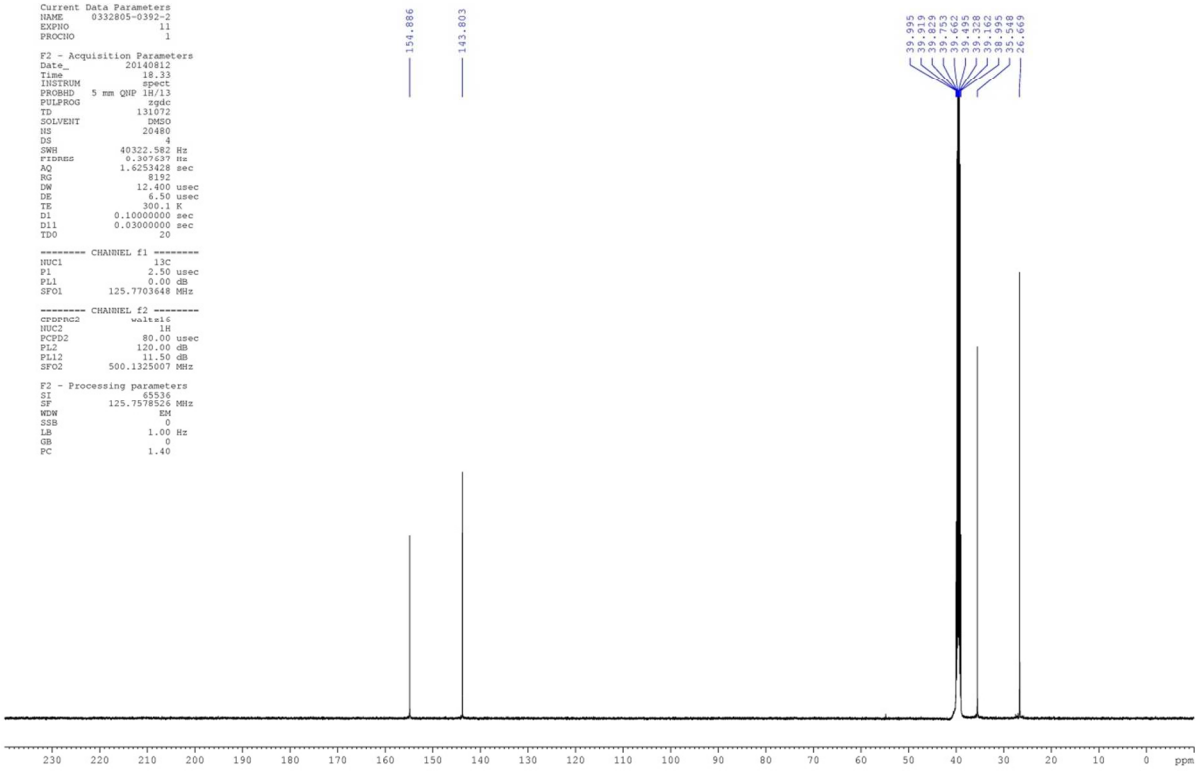
2.00
3.02

16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DS 4
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FIDRES 0.307637 Hz
AQ 1.6253428 sec
RG 8192
DW 12.400 usec
DE 6.50 usec
TE 300.1 K
D1 0.10000000 sec
D11 0.03000000 sec
TD0 20
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P1 2.50 usec
PL1 0.00 dB
SFO1 125.7703648 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 120.00 dB
PL12 11.50 dB
SFO2 500.1325007 MHz
F2 - Processing parameters
SI 65536
SF 125.7578526 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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143.803
39.995
39.919
39.829
39.733
39.662
39.495
39.328
39.162
38.995
35.548
26.669
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


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7.874
7.742
7.739
7.738
7.736
7.610
7.608
7.605
7.603
7.589
7.525
7.521
6.671
6.656
5.168
3.318
3.112
Cl
CN
O
O
N
Me
N
N
N
H
O
F3C
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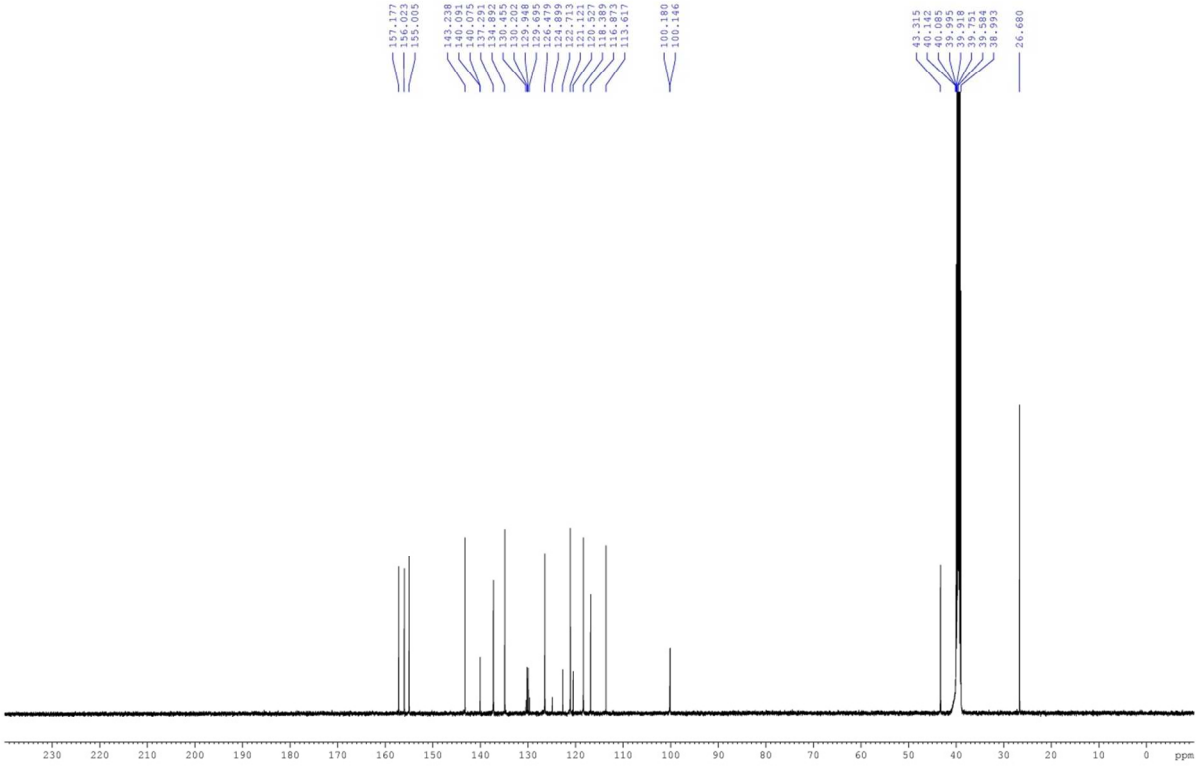
0.85
1.03
2.06
3.06
ppm

**1**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43.315
40.142
40.085
39.995
39.918
39.751
39.584
38.993
26.680
ppm

[1] Potassium trifluoroacetate seed is added to aid in the precipitation of the inorganic by-product. In the absence of seed potassium trifluoroacetate precipitates as a gummy, gelatinous solid.