A Short Multi-step Flow Synthesis of a Potential Spirocyclic Fragrance Component

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Abstract:
The search for novel chemical architectures displaying improved biological properties is a never-ending synthetic challenge. In this context many new test structures are often conceived by selecting and replicating specific design elements from naturally occurring molecules and displaying them in an alternative format by way of a new chemical assembly. Constructing these newly designed compounds can be a timely and expensive process especially when a large quantity of the target material is required for physiochemical and property testing. To permit easier scale up and safer working practice many chemical researchers are employing flow chemistry approaches to aid in their synthesis challenges. Herein we report on the preparation of a key spirocyclic lactone using flow based reaction processing techniques.

Keywords:
Flow synthesis, meso reactor, multi-step, Diels Alder reaction, Baylis Hillman reaction

Introduction:
Within the flavours and fragrance industries terpenoid structures dominate the chemical portfolios of most supply houses. The *gem*-dimethylcyclohexene unit being particularly prevalent as occurring in the carotenoids (retinal, vitamin A, β -carotene) and many bench mark fragrances classes such as the ionones and damascones (figure 1).[1] As part of a collaboration exploring new fragrance components we were recently challenged to formulate a scalable synthesis to the target 2-oxaspiro[4.5]decan-1-one molecule **1** which had been identified as a compound of interest from biological isolation.[2] The crude extraction containing the proposed structure **1** had shown modest antimicrobial activity and promising indicators as a base fragrance note.

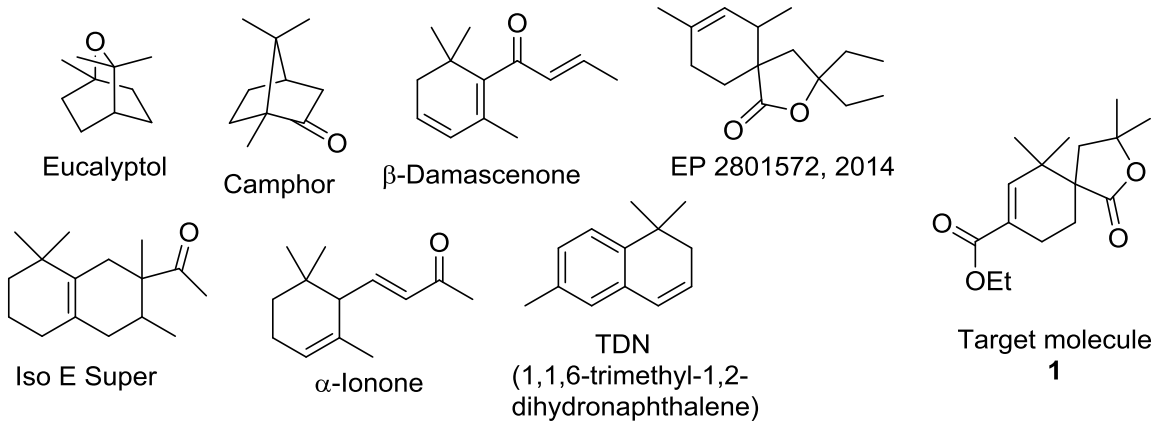
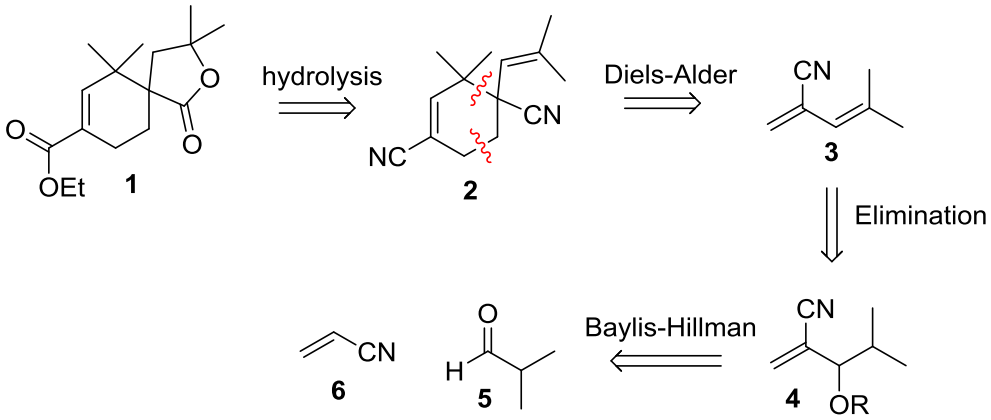


Figure 1. *Common structural motifs in fragrances and flavours.*

Retrosynthesis:
Our synthetic approach aimed to make use of the inherent symmetry invested in the core structure which we perceived could be assembled from a Diels-Alder cycloaddition reaction (Scheme 1). A survey of the literature indicated that elimination from an appropriately functionalised allylic system **4** could be used to *in-situ*

generate the necessary diene component **3**.[3] Correspondingly, a Baylis–Hillman reaction between the low cost starting materials isobutyraldehyde (**5**) and acrylonitrile (**6**) would furnish the target allylic system which could be activated to induce elimination using various mediators. Indeed, we discovered a similar tactic had been previously used in the preparation of a related but simplified structure mikanecic acid.[4] Encouraged by this we set out to devise a flow based synthesis to the target structure.[5]



Scheme 1. *Retrosynthesis of the target 2-oxaspiro[4.5]decan-1-one **1**.*

Synthesis:

The Baylis–Hillman reaction is a very versatile and powerful bond forming reaction however it is normally associated with prolonged reaction times (up to 7 days).[6] To provide sufficient residence time to achieve high conversions we elected to progress the reaction through a set of continuous-flow stirred tank reactors (6 × CFSTR) operated in series, each of 100 mL internal volume. The reactors were stirred at a constant 280 rpm and isothermally incubated at 65 °C.[7] Two feed lines were prepared as stock solutions; *solution 1*) 6 M isobutyraldehyde (**5**) containing 15 mol% 1,4-diazabicyclo[2.2.2]octane (DABCO) and *solution 2*) 6.6 M solution of acrylonitrile (**6**). A mixed solvent system of 2-methyl tetrahydrofuran and trifluoroethanol (15:2 volumetric ratio) was used as the makeup solvent. The presence of hydrogen donor solvents have been shown to significantly improve the kinetics of the Balyis-Hillman reaction.[8b] Although water or MeOH is often used we found the use of the more acidic trifluoroethanol to be particularly beneficial for this transformation. Equal flow rates of 0.3 mL/min were used for dispensing of each feed line. The output flow from the 6th consecutive CFSTR yielded >95% conversion (^{1}H NMR analysis) running at steady state (20.2 h as determined by GC analysis). This crude output was directly coupled with an additional feed of neat acetic anhydride (10.6 M, 1.1 equiv., 0.17 mL/min) and directed into a second stage reactor group comprising of three sequentially linked Polar bear plus reactors (3 × 52 mL) (Figure 2).[9] The reactors were maintained at 135 °C providing a combined residence time of approximately 202 min. During solution progression through this second reactor group the Baylis-Hillman adduct was first acylated (**4** R = OH → **5** R = Ac) and then underwent a thermally promoted elimination to furnish the butadiene species **3**.[10] This material was relatively short lived at the elevated working temperature and was seen to rapidly convert via a Diels-Alder cycloaddition to the desired cyclohexene derivative **2** (residence time 202 min). The process was easily monitored by GC-MS sampling (Figure 3).

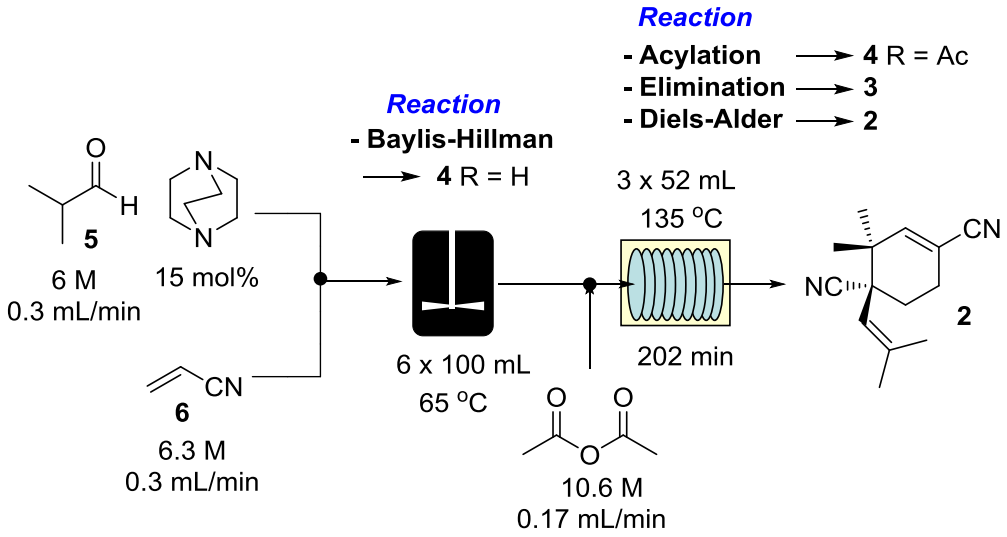


Figure 2. *Reactor step-up for the dual stage formation of cycloadduct **2*** (overall 89% purity crude).

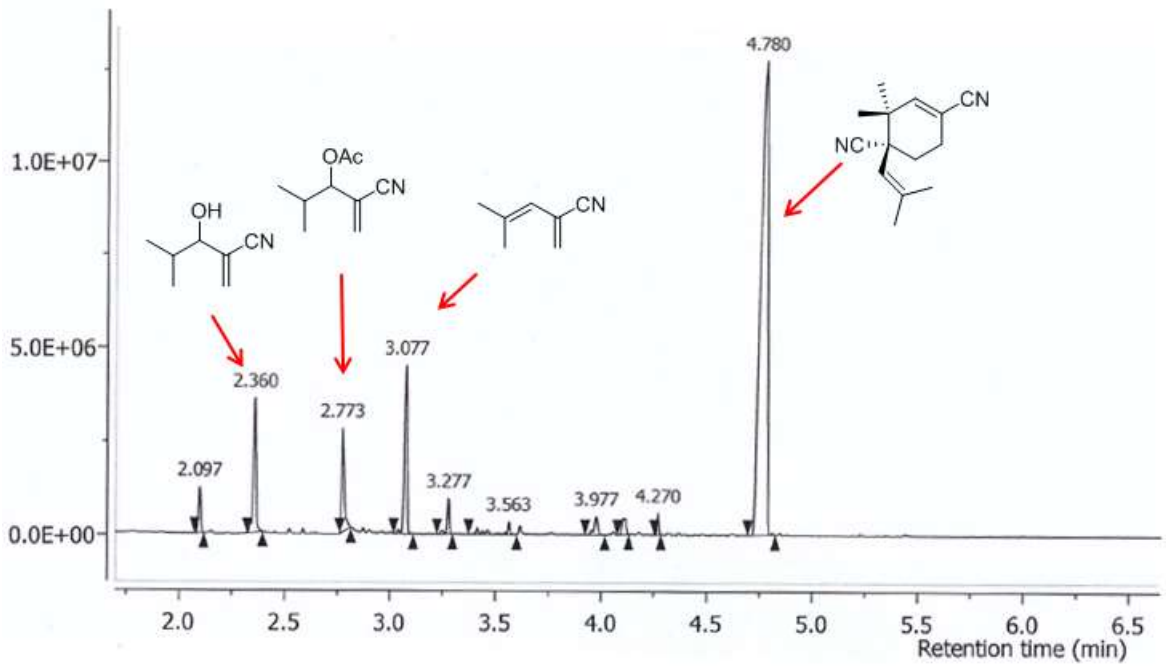


Figure 3. Representative reaction sampling and analysis via *GC-MS TIC plot for the thermal Diels-Alder sequence **4** R = H → **2**.*

Isolation of compound **2** was readily effected by direct evaporation of the reactor output. The residual brown oil then upon standing crystallised to yield large orange/brown crystals (figure 4). The material could be readily recrystallized from ethanol to give a colourless transparent crystal. However, the purity of the crude solid was sufficient to progress through the later stages of the sequence. The process to this stage running at steady state gave a throughput of ~23 g/h and proved very robust being run as an uninterrupted sequence for 6.5 days generating over 3.58 kg of isolated material **2**.

Figure 4. *Crystallisation of crude intermediate compound **2** upon standing (rt, 2 days).*

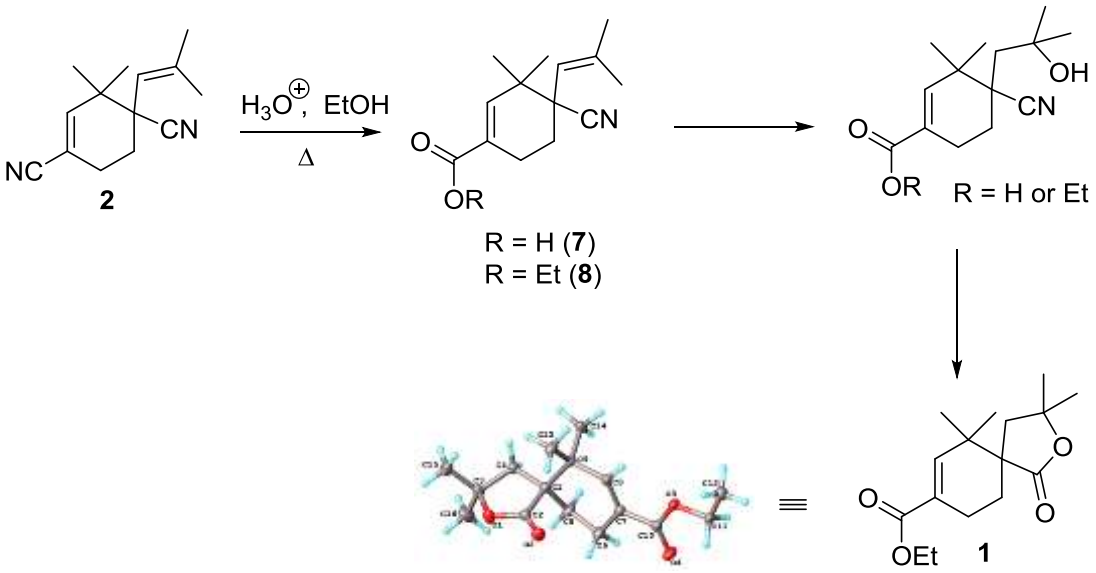
Having successfully devised a flow route to key intermediate **2** we next turned our attention to transformations for the subsequent esterification and lactonisation (**2** → **1**). As nitriles are normally more easily hydrolysed under basic conditions we first elected to use aqueous NaOH to generate the corresponding carboxylates which we anticipated would under a pH switch, to acidic conditions in the presence of ethanol, generate the desired final product **1**. However, our initial attempts using a range of basic conditions gave only partial hydrolysis resulting in exclusive formation of compound **7** upon acidification albeit in very high isolated yields and purity (>90% conversion, >95% purity ^{1}H-NMR). For example, an ethanolic stock solution of intermediate **2** (2 M) was pumped (0.5 mL/min) to mix with a 4 M solution of NaOH (0.5 mL/min) before passing into a heated reactor coil (2 × 52 mL, residence time 104 min) maintained at 125 °C. The reactor output was collected and the ethanol evaporated under reduced pressure. The mixture was acidified with aqueous hydrochloric acid (2 M, pH 2) which resulted in the precipitation of a white solid which was filtered, washed with cold water, cold EtOH and dried under vacuum to yield compound **7** (91% isolated yield).

The quaternary cyano group of **2** being flanked by the *gem*-dimethyl and allyl group is sterically very hindered and so proved resistant to hydrolysis. This was additionally exemplified by the fact that even heating a 6 M NaOH solution of the dinitrile **2** (0.1 M in 10% v/v EtOH) for 7 days at 120 °C gave only the mono acid derivative **7**. By extension compound **7** was shown to be easily converted to the corresponding ethyl ester **8** under standard esterification conditions (batch: 1 M in EtOH, cat H_2SO_4, reflux 6 h). We therefore concluded that the most promising approach would be to alternatively first induce hydration of the pendant alkene group. Our rationale was to thus use the generated tertiary alcohol formed under Markovnikov conditions to subsequently assist in an intramolecular hydration of the adjacent nitrile (Scheme 2). In this scenario the proximity of the alcohol and presence of the double *gem*-dimethyl group would result in an enhanced Thorpe-Ingold effect[11] and would help promote the intramolecular attack onto the proximal nitrile. Additionally although the molecule **2** contains two olefinic functionalities the significant difference in their nucleophilic character should allow them to be chemically distinguished in an acid catalysed hydration.

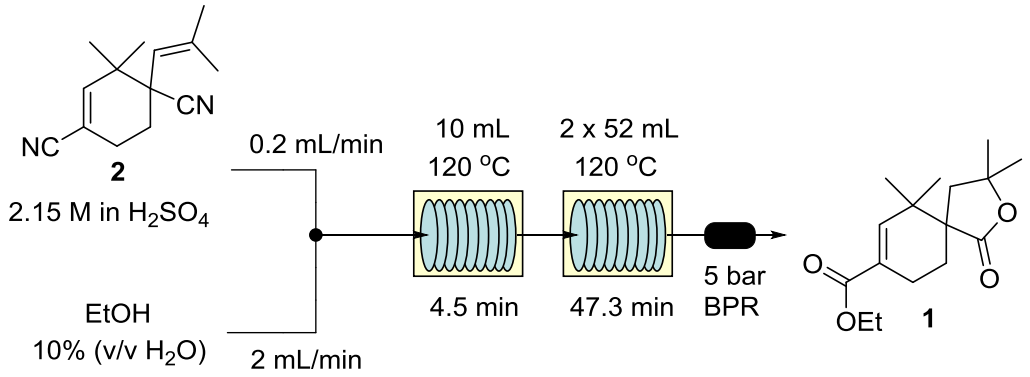
Consequently we evaluated the acid promoted direct lactonisation and concurrent esterification. Initial exploration using acidic ethanolic conditions (1 M in EtOH with 10% 4 M HCl v/v, 102 °C) rapidly generated the ethyl ester **8** starting from either compound **7** or **2** but even after prolonged reaction times did not realise the required alkene hydration. Eventually it was determined that much stronger acidic conditions were required.

Therefore compound **2** (or intermediate **7**) was dissolved in cold (0 °C) conc. H_2SO_4 to create a 2.15 M solution. As this mixture was relatively viscous a peristaltic pumping unit (Vapourtec MedChem – E series [12]) was used to drive the fluidic flow (0.2 mL/min). This mixture was united with a flow stream of ethanol (10% H_2O v/v) pumped via the second peristaltic pump (2 mL/min) to mix at a teflon T-piece before passing into a heated

(120 °C) FEP coil reactor (10 mL). The mixture was then progressed into a further residence time flow coil also maintained at 120 °C (104 mL; 2 × 52 mL FEP conjoined coils). System pressure was ensured using a 5 bar back pressure regulator which was placed just before the exit of the system (Scheme 3). The output flow was collected as batches (528 mL; 4 h processing time) and further processed by evaporation of the volatiles and extraction of the residue with dichloromethane (3 × 150 mL).[13] This allowed the final product **1** to be isolated by solvent evaporation (note the dichloromethane was recycled for subsequent extractions). Upon standing the pale yellow oil isolated started to crystallise, a small sample was removed washed with ether and dried. This material was recrystallized from hexane and used as seeding material for future batch of the product. Following this procedure a final yield of **1** derived from compound **2** or **7** was 72-74% respectively.



Scheme 2. Proposed *hydration strategy to compound **1**.*



Scheme 3. Reactor set-up for conversion of compound **2** into **1**.

Conclusion:

We have demonstrated the application of flow chemistry to the scale-up synthesis of a previously identified target validation structure derived from a natural product screening campaign of new fragrance components. The multi-step sequence constructed was robust and easily scaled to allow the kilo production of the target material and its intermediates (1.42 kg of compound **1** was eventually generated). Several options for improving the synthesis were determined though the course of the study based upon both reactor designs and chemical synthesis. We believe the work presented demonstrates the potential value of flow chemistry as applied to target synthesis in the flavours and fragrance industries.

Experimental:

Materials and methods

Unless specified, reagents were obtained from commercial sources and used without further purification. Solvents were obtained from Fisher scientific, and H_2O refers to deionised water.

NMR spectra were recorded on a Bruker Avance-400, Varian VNMRS-600 or Varian VNMRS-700 instruments and are calibrated to the residual solvent peaks. Assignments are based on additional 2D experiments such as DEPT-135, COSY, HSQC and HMBC spectra. Liquid chromatography-mass spectrometry (LCMS) was performed on an Agilent HP 1100 series chromatograph (Mercury Luna 3µ C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of MeCN–water containing 0.1% formic acid. Gradient = 0–1 min: hold MeCN 5%, 1–4 min: ramp MeCN 5–95%, 4–5 min: hold MeCN 95%, 5–7 min: ramp MeCN 95–5%, 7–8 min: hold MeCN 5%. Retention times are reported as Rt. High resolution mass spectra (HRMS) were recorded on a Waters Micromass LCT Premier spectrometer using time of flight with positive electrospray ionisation (ESI+), an ABI/MDS Sciex Q-STAR Pulsar with ESI+ and an ASAP (atmospheric pressure solids analysis probe ionisation), or a Bruker BioApex II 4.7e FTICR utilising either ESI+ or a positive electron ionisation (EI+) source equipped with a direct insertion probe. The mass reported is that containing the most abundant isotopes (35Cl and 79Br). Limit: ± 5 ppm. IR spectra were recorded neat on a Perkin-Elmer Spectrum One or Perkin-Elmer Spectrum Two FT-IR spectrometer using Universal ATR sampling accessories. Letters in parentheses refer to the relative absorbency of the peak: w – weak (<40% of the most intense peak), m – medium (40–75% of the most intense peak), s – strong (>75% of the most intense peak) and br – broad. Melting points were recorded on an Optimelt 100 automated melting point system with a heating rate of 2 °C/min (70% onset point and 10% clear point) and are uncorrected.

See supplementary information for spectra and X-ray information.

Continuous flow synthesis of 3,3-dimethyl-4-(2-methylprop-1-enyl)cyclohexen-1-ene-1,4-dicarbonitrile 2: A bespoke in series continuous-flow stirred tank reactors set-up (6 × CFSTR) was used. Each reactor chamber consisted of a 100 mL internal volume stainless steel vessel (internal height 82 mm, 40 mm ID). The reactors were stirred at a constant 280 rpm using a teflon coated 3 × 1 cm half-moon paddle. The reactors were isothermally incubated at 65 °C using jacketed covers (OMEGA Beaker Heater, SRBH Series product No. SRBH0250-1 with a hermetically sealed PTFE coated thermocouple HSTC-TT-KI-24S-1M and temperature controller Rydine DX340077). A 1 L stock solution of isobutyraldehyde (**5**, 6 M, 432.7 g, 548 mL) containing 15 mol% 1,4-diazabicyclo[2.2.2]octane (DABCO, 0.9 M, 101 g) and a stock solution of acrylonitrile (**6**, 6.6 M, 350.2 g, 432.3 mL) were prepared. A mixed solvent system of 2-methyl tetrahydrofuran (2-Me-THF, containing 300 ppm of butylated hydroxytoluene stabiliser) and trifluoroethanol (15:2 volumetric ratio) was used as the makeup solvent. Refill stock solutions were prepared freshly as required to enable continuous running of the reactor. A Uniqsis FlowSyn was used to pump the two flow streams (through the pump heads at 0.3 mL/min per channel) into the CFSTR combining at a Teflon T-piece just prior to entry. The reactor output from the 6th CFSTR was coupled with an additional feed of acetic anhydride (10.6 M, 0.17 mL/min, Knauer K120 pump) and directed into a reactor comprising of three sequentially linked Polar bear plus coil reactors (3 × 52 mL equating to a combined residence time of 202 min) which were all maintained at 135 °C. A 75 psi back pressure regulator was placed at the end of the reactor series. The flow output was collected into a 1 L pear shaped flask and when filled to approximately 750 mL replaced. The reaction mixture was rotary evaporated to remove volatiles and the mixture poured into a 1 L large necked flask to crystallise. The product showed a crude purity of >89% by 1H NMR against 2,4-dimethoxybenzene as an internal standard. Clear crystalline solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.38 (1H, s), 4.95 (1H, s), 2.39 (1H, m), 2.32 (dtd, *J* = 18.4, 6.1, 1.9 Hz, 1H) 2.12 (1H, m), 2.05 (dtt, *J* = 13.3, 6.1, 1.4 Hz, 1H), 1.99 (t, *J* = 1.3 Hz, 3H), 1.81 (3H, s), 1.30 (3H, s), 1.11 (d, *J* = 2.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 151.2 (CH_2), 139.6 (C), 121.4 (C), 119.3 (CH), 118.8 (C), 110.8 (C), 42.5 (C), 40.0 (C), 29.0 (CH_2), 28.0 (CH_3), 26.5 (CH_3), 24.3 (CH_2), 24.1 (CH_3), 19.4 (CH_3); IR ν cm^{-1} 2974.4 (m), 2915.5 (w), 2234.7 (w), 2214.2 (m), 1759.7 (w), 1639.1 (w), 1452.9 (m), 1432.7 (m), 1398.1 (s), 1377.2 (m), 1361.1 (m), 1220.0 (w), 1189.8 (w), 1032.8 (m), 966.1 (m), 892.1 (s), 804.6 (s), 540.0 (s); Melting point 79.5-81.5 °C (EtOAc, uncorrected); GC-MS Rt = 4.780 min, $C_{14}H_{18}N_2$; m/z = 214.15 (20.63%), 199.10 (7.07%), 157.10 (1.49%), 109.10 (1.77%), 108.10 (23.99%), 107.10 (100%), 106.1 (12.7%). GC-MS Rt = 4.780 min, $C_{14}H_{18}N_2$; m/z = 214.15 (20.63%), 199.10 (7.07%), 157.10 (1.49%), 109.10 (1.77%), 108.10 (23.99%), 107.10 (100%), 106.1 (12.7%). LC-MS (ESI - LC MeCN (TQD)) Rt 3.11 $^{m}/_{z}$ $[M+H]^+$ = 215.0; Acc. Mass. Calc. $C_{14}H_{19}N_2$ 215.1548, found 215.1552 (1.9 ppm). The structure of 3,3-dimethyl-4-(2-methylprop-1-enyl)cyclohexen-1-ene-1,4-dicarbonitrile **2** was

unambiguously confirmed by X-ray crystallography and the structure has been deposited at the Cambridge Crystallographic Centre with the unique reference 1052030. Summary of Data; Formula: $C_{14}H_{18}N_2$, Unit Cell Parameters: a 12.0639(2) b 6.9251(1) c 15.2108(3) Space group P21/n.

Characterisation of intermediates in the synthesis of 3,3-dimethyl-4-(2-methylprop-1-enyl)cyclohexen-1-ene-1,4-dicarbonitrile 2 (compounds 4 and 5):

2-(1-hydroxy-2-methylpropyl)acrylonitrile 4:[6] Colourless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 1.95 (1H, m), 2.51 (1H, s), 2.95 (1H, d, *J* = 6.1 Hz), 5.96 (1H, m), 6.00 (1H, m); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 131.3 (CH_2), 126.1 (C), 117.5 (C), 82.4 (CH), 28.3 (CH), 19.2 (CH_3), 16.9 (CH_3). GC-MS (EI) Rt = 3.077 min, C_7H_9N; m/z = 125.1 (4.9%), 108.15 (5.1%), 107.1 (100.0%), 106.1 (22.4%), 81.1 (16.6%), 80.1 (20.5%), 43.05 (56%).

2-(1-acetoxy-2-methylpropyl)acrylonitrile 5: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.1 (1H, s), 5.92 (1H, s), 4.98 (1H, d, *J* = 8.0 Hz), 2.12 (3H, s), 2.10 (1H, m), 1.13 (1H, m), 0.90 (6H, m); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.2 (C), 134.3 (CH_2), 122.4 (C), 116.8 (C), 78.2 (CH), 31.1 (CH_3), 21.8 (CH), 17.9 (CH_3), 18.0 (CH_3). GC-MS (EI) Rt = 2.773 min, $C_9H_{13}NO_2$; m/z = 168.2 (0.61%), 126.1 (4.79%), 125.1 (59.4%), 124.1 (15.3%), 83.05 (46.9%), 82.1 (38.7%), 53.05 (7.19%), 43.05 (100%).

Synthesis of 4-cyano-4-(2-methylprop-1-enyl)cyclohexen-1-ene carboxylic acid 7: A solution of compound **2** (2.5 M) in EtOH was pumped (0.5 mL/min, Knauer K120 pump) to mix at a PEEK T-piece with an aqueous solution of NaOH (5 M, 2 equiv., 0.5 mL/min) and then directed into a heated tubular reactor coil (Polar bear plus 2 × 52 mL, residence time 104 min) which was maintained at 125 °C. A short 10 mL FEP coil reactor (vapourtec) was placed at the reactor exit and submerged in a water bath (14-16 °C) to aid cooling. The output was collected and the volatiles evaporated under reduced pressure. The mixture was acidified with aqueous hydrochloric acid (2 M, pH 2) and the resulting precipitation filtered, washed with cold water, cold EtOH and dried under vacuum to yield compound **7** (91% isolated yield, 200 mmol scale). White crystalline solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.01 (s, 1H), 6.81 (t, *J* = 1.9 Hz, 1H), 4.95 (p, *J* = 1.4 Hz, 1H), 2.51 (dtd, *J* = 18.6, 6.4, 1.9 Hz, 1H), 2.34 (dtd, *J* = 18.6, 6.2, 1.9 Hz, 1H), 2.12 (dt, *J* = 13.6, 6.2 Hz, 1H), 2.03 (m, 1H), 1.97 (d, *J* = 1.4 Hz, 3H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.1 (C), 147.8 (CH), 138.3 (C), 127.1 (C), 121.8 (C), 119.6 (CH), 42.5 (C), 39.5 (C), 29.1 (CH_2), 27.6 (CH_3), 26.3 (CH_3), 23.9 (CH_3), 21.0 (CH_2), 19.0 (CH_3); IR ν cm^{-1} 2959.6 (w), 2871.2 (w), 2642.8 (w), 1679.5 (s), 1634.9 (m), 1433.0 (m), 1386.5 (w), 1364.2 (w), 1291.9 (m), 1252.7 (m), 971.2 (m), 949.3 (m), 916.8 (m), 859.1 (w), 824.0 (w), 751.7 (m), 735.5 (w), 713.8 (w), 591.1 (w), 545.3 (w), 519.2 (w); Melting point 167.7-168.8 °C (EtOH, uncorrected); LC-MS (ESI - LC MeCN (TQD)) Rt 2.62 $^m/_z$ $[M]^+$ = 233.1; Acc. Mass. Calc. $C_{14}H_{19}NO_2$ 233.1654, found 233.1654. The structure of 4-cyano-4-(2-methylprop-1-enyl)cyclohexen-1-ene carboxylic acid **7** was unambiguously confirmed by X-ray crystallography and the structure has been deposited at the Cambridge Crystallographic Centre with the unique reference 1061814. Summary of Data; Formula: $C_{14}H_{19}NO_2$, Unit Cell Parameters: a 6.9841(3) b 11.3829(4) c 16.7282(8) Space group $P2_1/c$.

Synthesis of ethyl 4-cyano-4-(2-methylprop-1-enyl)cyclohexen-1-ene carboxylate 8: A 500 mL stock solution of compound **2** or compound **7** (0.5 M) in absolute EtOH containing HCl (3.5 mL) was pumped (0.5 mL/min, Knauer K120 pump) into a heated tubular reactor coil (Polar bear plus 52 mL, residence time 104 min) which was maintained at 120 °C. A 75 psi back pressure regulator was placed at the reactor terminus to control outgassing. The reactor output was collected and the volatiles evaporated under reduced pressure. The mixture was then dissolved in EtOAc (250 mL) and washed with saturated $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$) and the solvent removed under vacuum to yield title compound **8** (quantitative, 250 mmol scale).Clear oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.67 (1H, s), 4.95 (1H, s), 4.20 (2H, q, J = 6.7 Hz), 2.40 (1H, m), 2.34 (1H, m), 2.12 (1H, m), 2.04 (1H, m), 2.01 (3H, s), 1.79 (3H, s), 1.31 (3H, s), 1.30 (3H, t, J = 6.7 Hz), 1.15 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.9 (CH), 144.9 (C), 138.0 (C), 127.5 (C), 121.9 (C), 119.4 (CH), 60.6 (CH_2), 43.9 (C), 40.3 (C), 27.6 (CH_3), 26.4 (CH_3),26.2 (CH_2), 24.0 (CH_3), 23.7 (CH_2), 21.6 (CH_3), 14.2 (CH_3); IR ν cm^{-1} 2975.9 (w), 1758.3 (w), 1708.5 (s), 1654.2 (w), 1454.8 (w), 1390.0 (w), 1378.5 (w), 1269.7 (s), 1246.9 (s), 1226.2 (m), 1178.3 (m), 1130.1 (w), 1086.4 (m), 1027.5 (m), 965.8 (w), 950.7 (w), 865.1 (w), 734.0 (m); LC-MS (ESI - LC MeCN (TQD)) Rt 3.45 $^m/_z$ $[M+H]^+$ = 262.1; Acc. Mass. Calc. $C_{16}H_{23}NO_2$ 262.1807, found 262.1819 (4.6 ppm).

Synthesis of ethyl 3,3,6,6-tetramethyl-1-oxo-2-oxaspiro[4,5]dec-7-ene-8-carboxylate 1: A solution of compound **2** (460 g; 2.15 M) was prepared in cold (0 °C) conc. H_2SO_4 (1 L). The stock solution pumped (Vapourtec – E series, 0.2 mL/min) to mix (teflon T-piece) with a flow stream of ethanol (10% H_2O v/v, 2 mL/min) and passed into a heated zone (120 °C) comprising of FEP coils (1 × 10 mL + 2 × 52 mL). A 5 bar back pressure regulator (compression tube) was placed at the exit of the system to maintain system pressure. The output flow was batched (528 mL) and the volatiles evaporated under reduced pressure. The residue was extracted with DCM (3 × 150 mL), dried ($MgSO_4$) and evaporated under reduced pressure. A small seed crystal of compound **1** was added to the viscous oil and the material was left to stand for 3 days to crystallise. The solid was filtered and washed with cold hexane and dried under vacuum to yield the title compound **1** (445.7 g, 74%). Clear crystalline solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.67 (dd, *J* = 2.4, 1.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.56 – 2.34 (m, 2H), 2.28 (d, *J* = 13.6 Hz, 1H), 2.12 (ddd, *J* = 14.1, 6.2, 3.2 Hz, 1H), 1.94 (ddd, *J* = 14.1, 10.0, 6.3 Hz, 1H), 1.85 (d, *J* = 13.7 Hz, 1H), 1.48 (d, *J* = 17.0 Hz, 6H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 177.0 (C), 167.1 (C), 145.6 (CH), 127.4 (C), 79.8 (C), 60.4 (CH_2), 50.1 (C), 43.9 (CH_2), 36.85 (C), 30.5 (CH_3), 30.2 (CH_3), 29.8 (CH_2), 25.7 (CH_3), 23.5 (CH_3), 21.65 (CH_2), 14.25 (CH_3); IR ν cm^{-1} 2972.8 (w), 1750.8 (m), 1696.0 (s), 1467.7 (w), 1269.2 (s), 1249.9 (s), 1182.9 (m), 1127.0 (m), 1048.1 (m), 9505 (m), 761.5 (w), 731.0 (w), 616.1 (w), 602.4 (w); Melting point 56.9-58.0 °C (Hexane, uncorrected); LC-MS (ESI - LC MeCN (TQD)) Rt 3.04 $^m/_z$ $[M+H]^+$ = 281.2 and $[2M+H]^+$ = 561.2; Acc. Mass. Calc. $C_{16}H_{24}O_4$ 280.1753, found 280.1761 (2.8 ppm). The structure of ethyl 3,3,6,6-tetramethyl-1-oxo-2-oxaspiro[4,5]dec-7-ene-8-carboxylate **1** was unambiguously confirmed by X-ray crystallography and the structure has been deposited at the Cambridge Crystallographic Centre with the unique reference 1061813. Summary of Data; Formula: $C_{16}H_{24}O_4$, Unit Cell Parameters: a 9.1034(5) b 18.2570(7) c 9.4207(5) Space group $P2_1/n$.

Acknowledgments:

We gratefully acknowledge financial support from the Royal Society (IRB). Furthermore we are very grateful to John Davies (Department of Chemistry, University of Cambridge) for solving the X-ray crystal structure of compound **2**. We would also like to thank Dr D. S. Yufid (Department of Chemistry, Durham University) for solving the X-ray crystal structures of compounds **1** and **7**.

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[2] Comparison to the original natural sample indicated the material did not match the synthesised compound **1**. Further analysis is currently underway to elucidate a revised structural assignment for the naturally isolated compound.

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[13] This process was preformed manually at larger scales but could be conducted using an in-line membrane extraction procedure at smaller scale. Currently scale-up is being investigated.

A Short Multi-step Flow Synthesis of a Potential Spirocyclic Fragrance Component

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Supporting information

The X-ray single crystal data have been collected on a Bruker SMART CCD 6000 (compound **1**) and Agilent XCalibur Saphire-3 (compound **7**) diffractometers (graphite monochromators, λMoKα, λ =0.71073Å) equipped with a Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats at the temperatures 120(2). Both structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using Olex2 [1] and SHELXTL[2] software. All non-disordered non-hydrogen atoms were refined anisotropically, hydrogen atoms were refined isotropically.

Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1061813 (**1**) and 1061814 (**7**).

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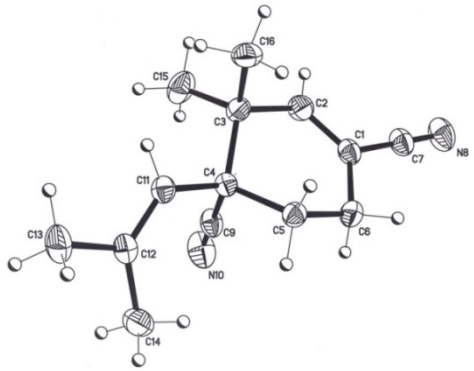
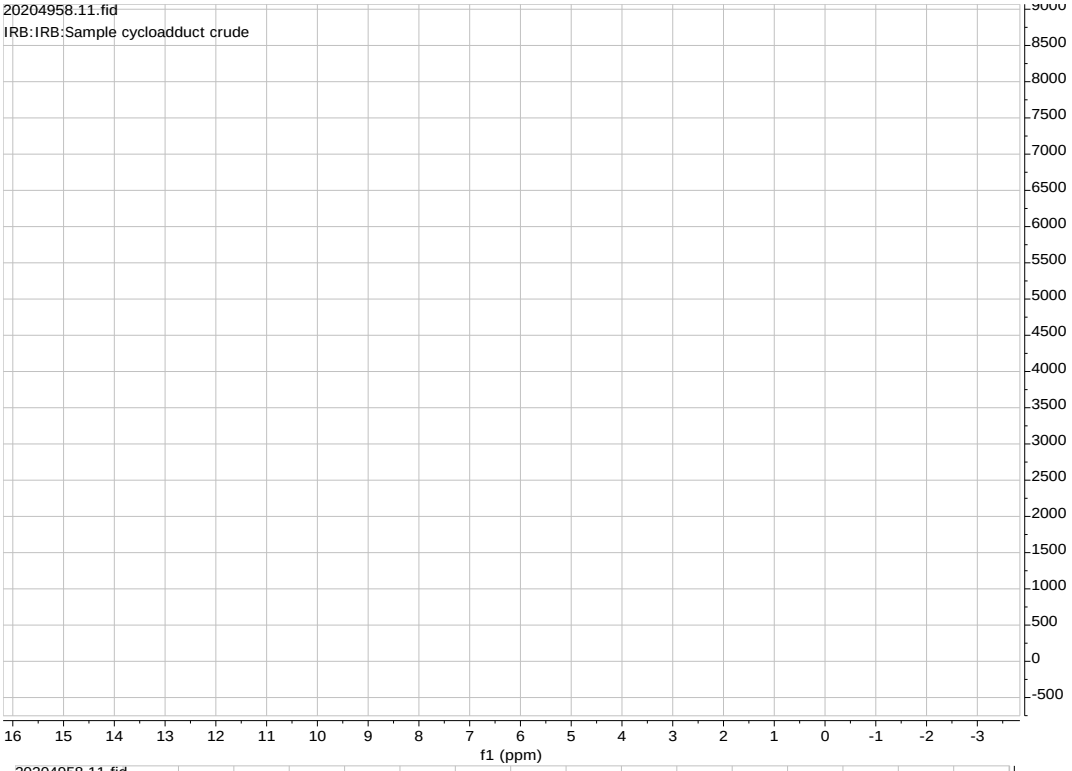
2. G. M. Sheldrick, *Acta Cryst., Sect. A*: **2008**, *64*, 112-122. DOI: 10.1107/S0108767307043930.

Spectra for 3,3-dimethyl-4-(2-methylprop-1-enyl)cyclohexen-1-ene-1,4-dicarbonitrile 2:

The structure of 3,3-dimethyl-4-(2-methylprop-1-enyl)cyclohexen-1-ene-1,4-dicarbonitrile **2** was unambiguously confirmed by X-ray crystallography and the structure has been deposited at the Cambridge Crystallographic Centre with the unique reference 1052030. Summary of Data; Formula: $C_{14}H_{18}N_2$, Unit Cell Parameters: a 12.0639(2) b 6.9251(1) c 15.2108(3) Space group P21/n.

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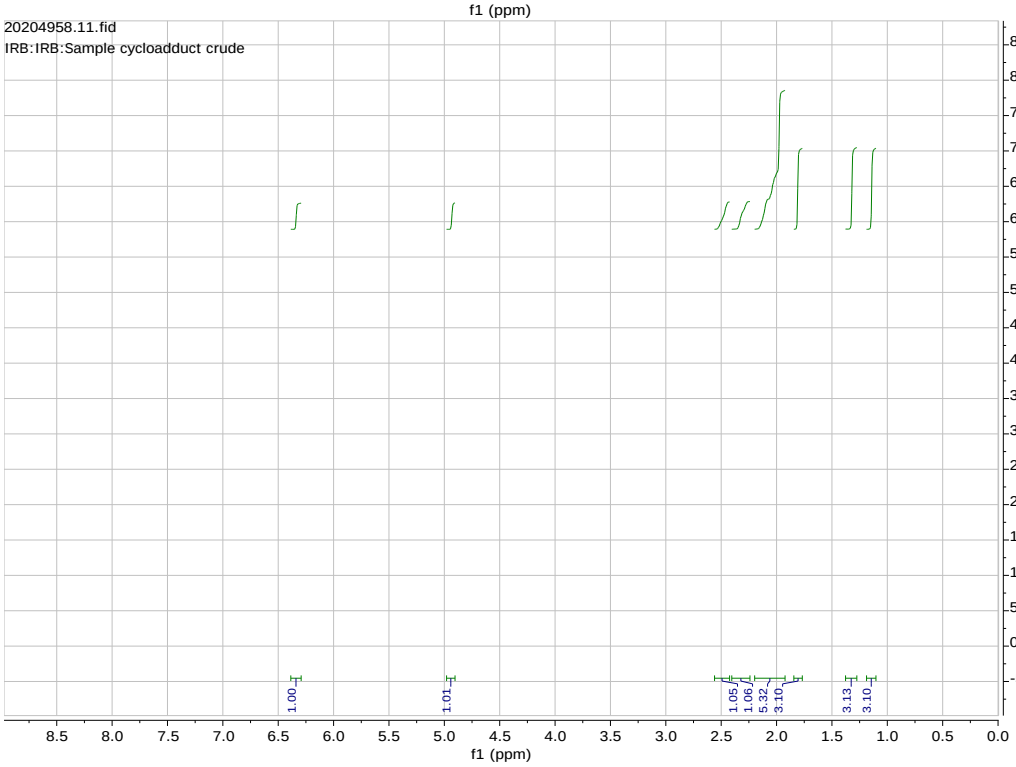
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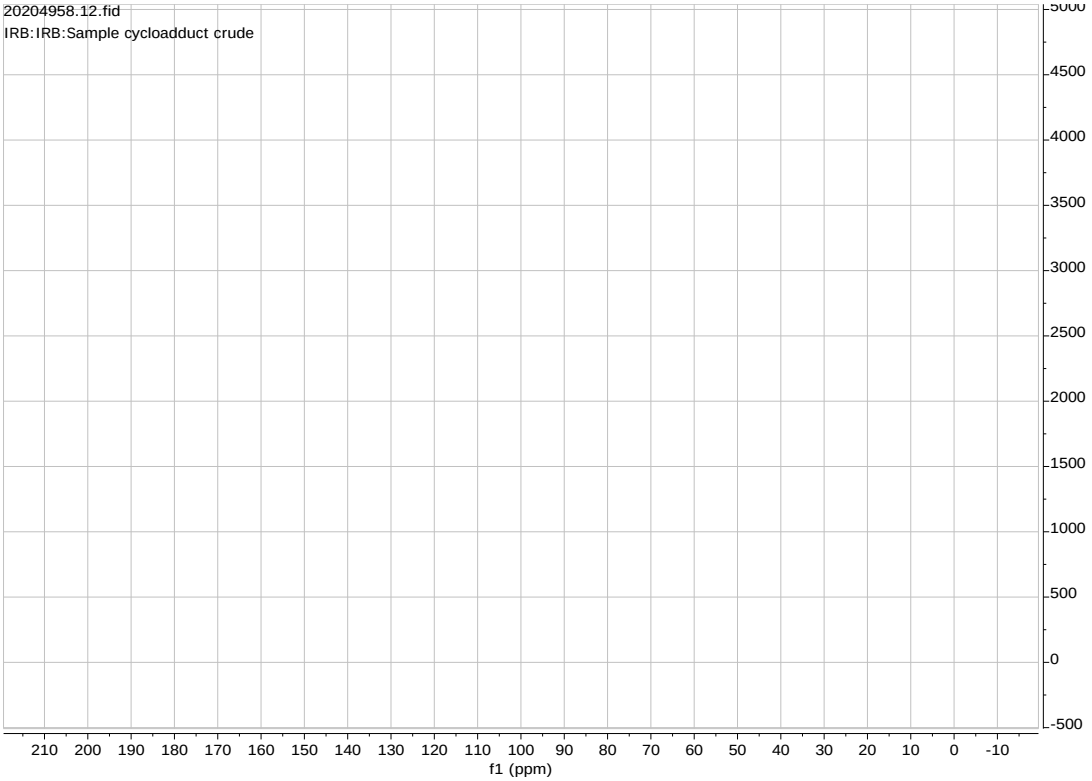
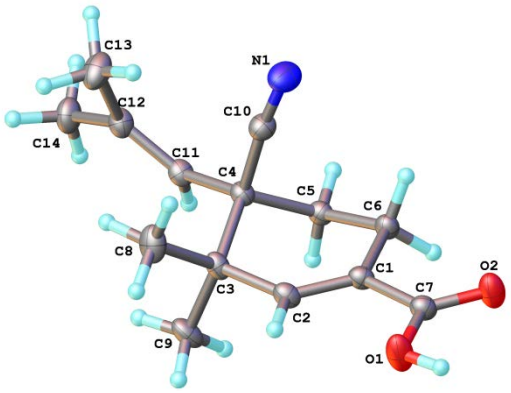
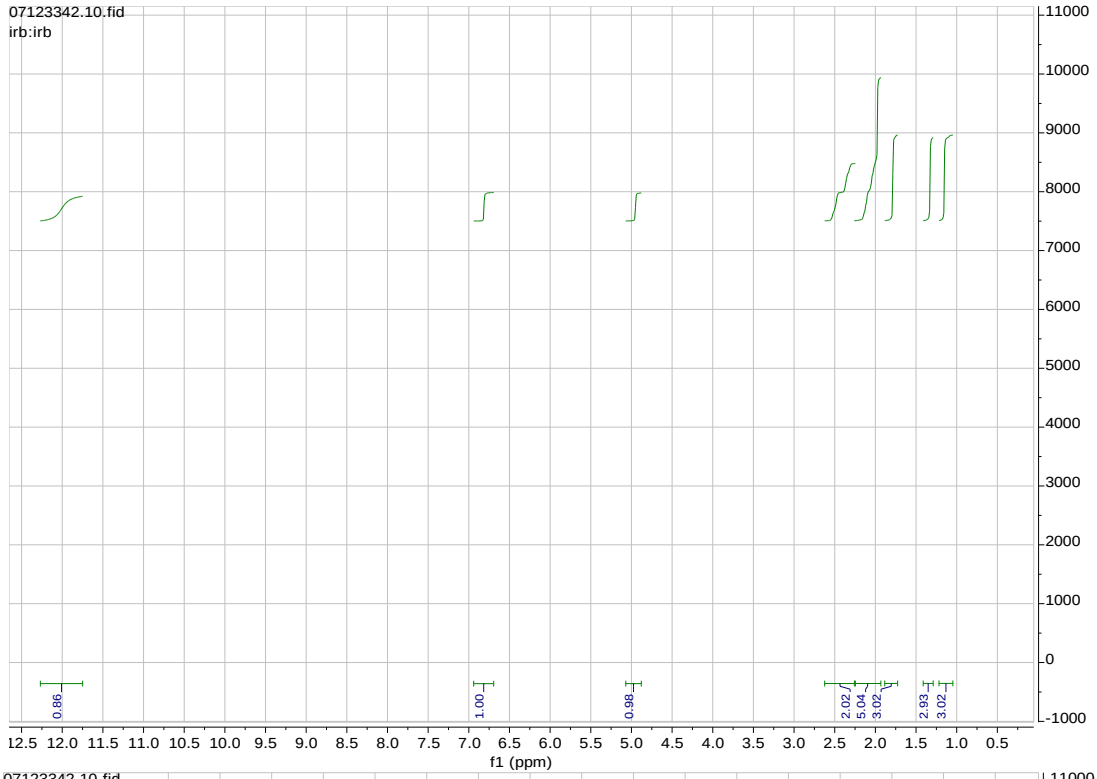


Spectra for 4-cyano-4-(2-methylprop-1-enyl)cyclohexen-1-ene carboxylic acid 7:



The structure of 4-cyano-4-(2-methylprop-1-enyl)cyclohexen-1-ene carboxylic acid **7** was unambiguously confirmed by X-ray crystallography and the structure has been deposited at the Cambridge Crystallographic Centre with the unique reference 1061814. Summary of Data; Formula: $C_{14}H_{19}NO_2$, Unit Cell Parameters: a 6.9841(3) b 11.3829(4) c 16.7282(8) Space group $P2_1/c$.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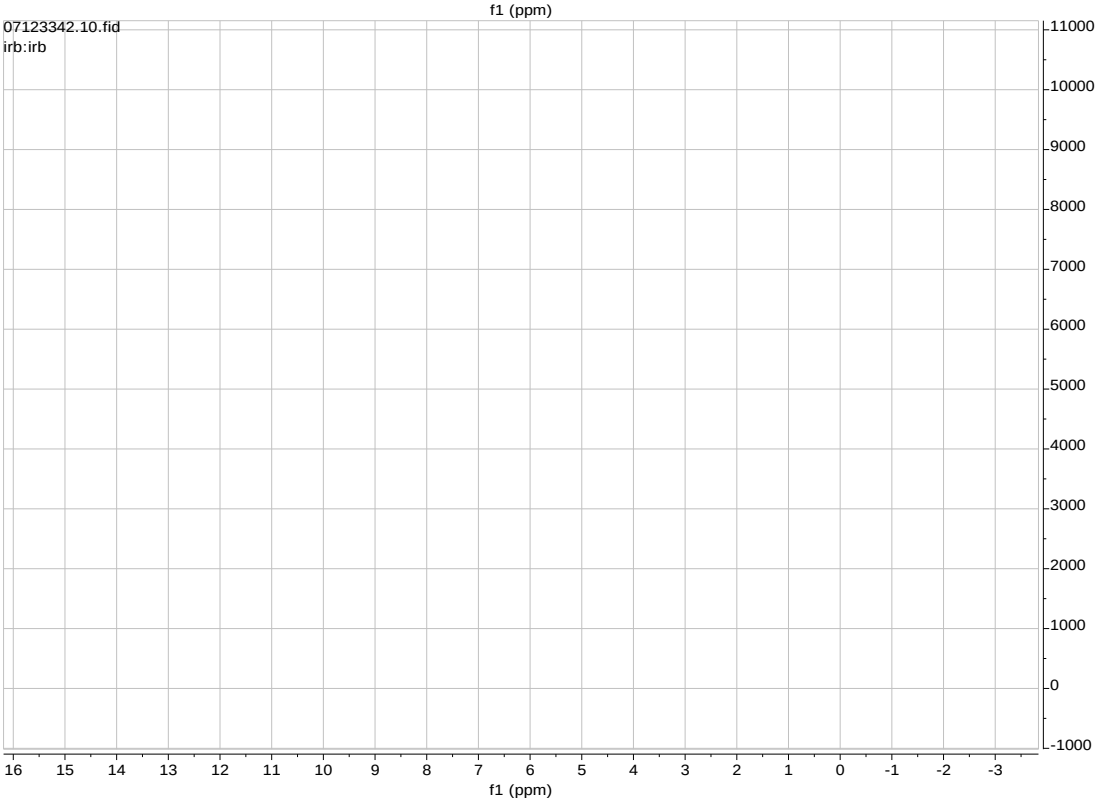
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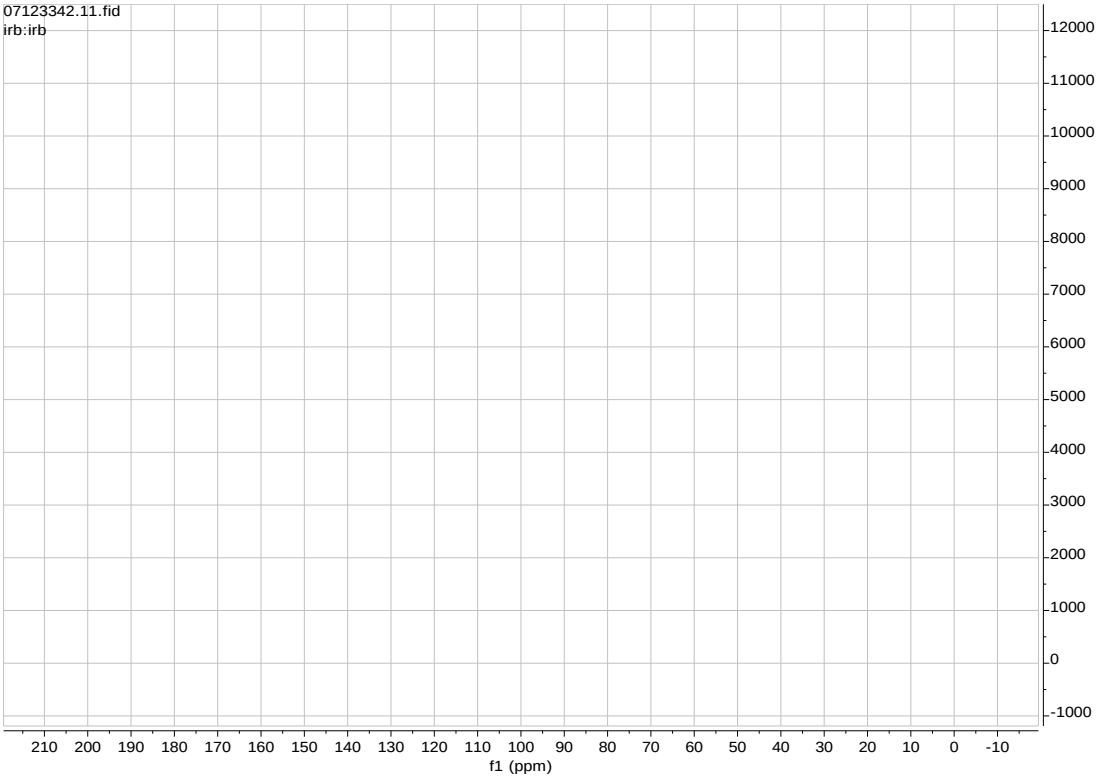
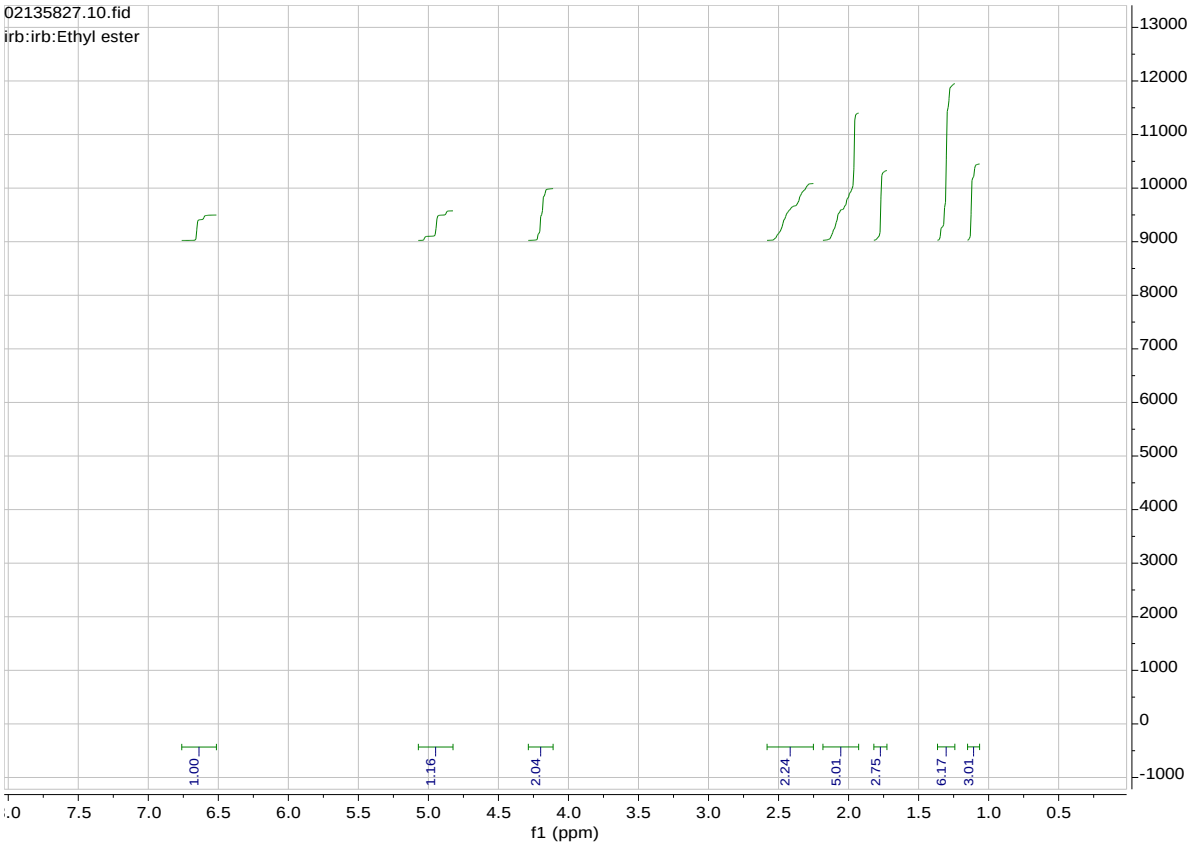
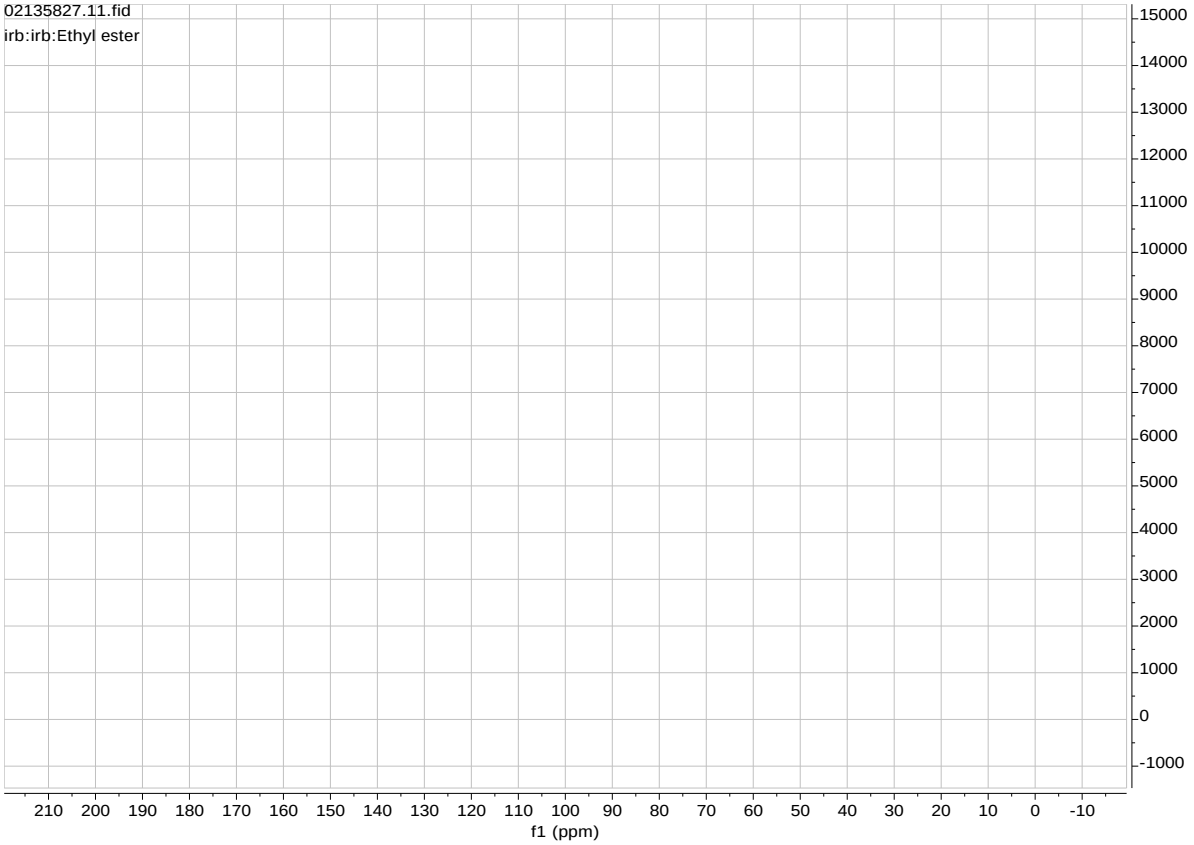


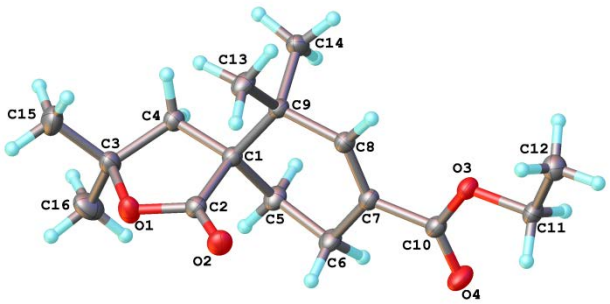
Spectra for ethyl 4-cyano-4-(2-methylprop-1-enyl)cyclohexen-1-ene carboxylate 8:

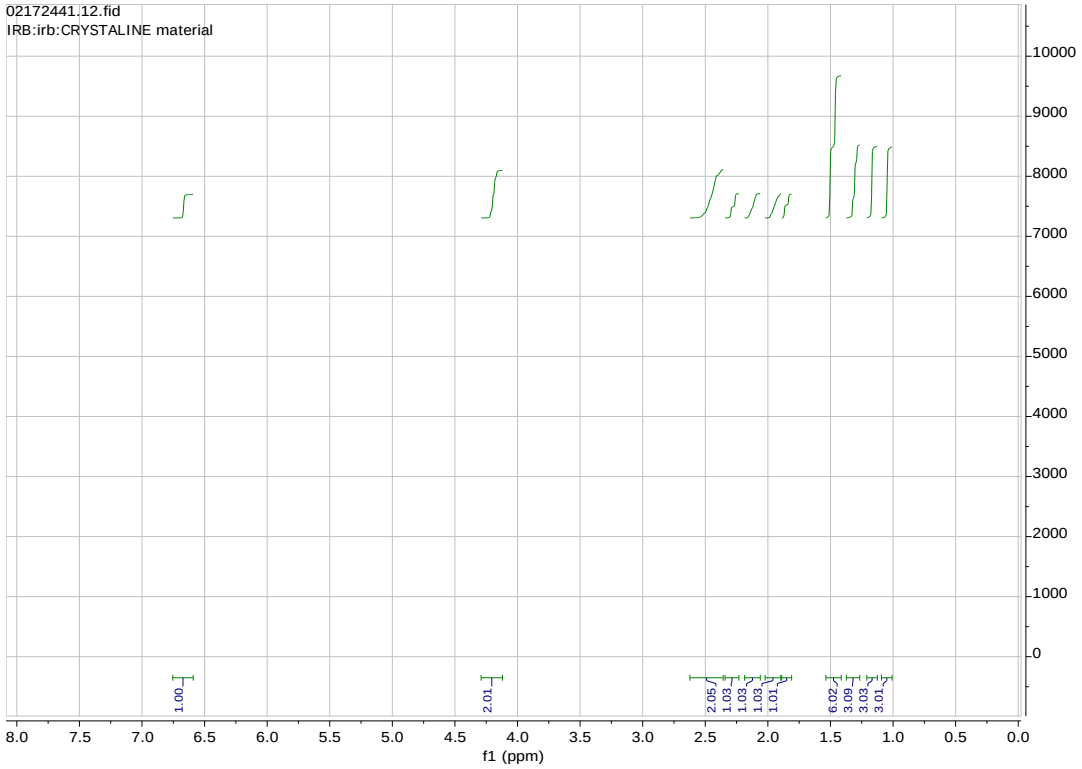




Spectra for ethyl 3,3,6,6-tetramethyl-1-oxo-2-oxaspiro[4,5]dec-7-ene-8-carboxylate 1:

The structure of ethyl 3,3,6,6-tetramethyl-1-oxo-2-oxaspiro[4,5]dec-7-ene-8-carboxylate **1** was unambiguously confirmed by X-ray crystallography and the structure has been deposited at the Cambridge Crystallographic Centre with the unique reference 1061813. Summary of Data; Formula: $C_{16}H_{24}O_4$, Unit Cell Parameters: a 9.1034(5) b 18.2570(7) c 9.4207(5) Space group $P2_1/n$.

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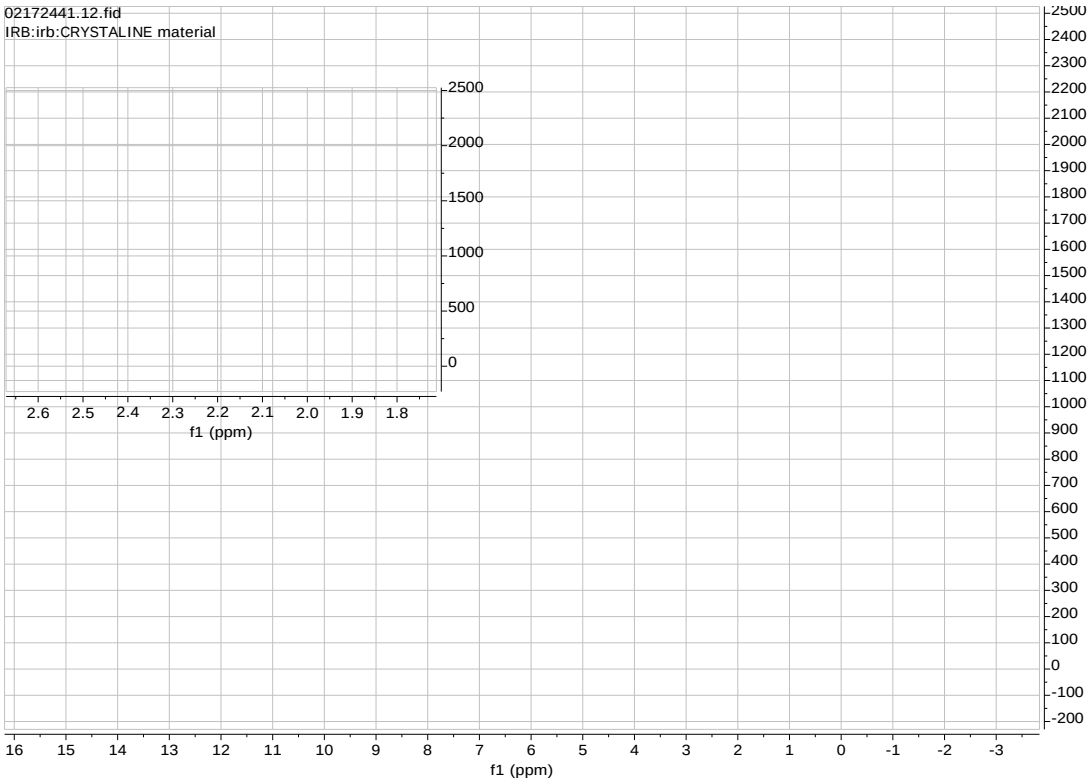
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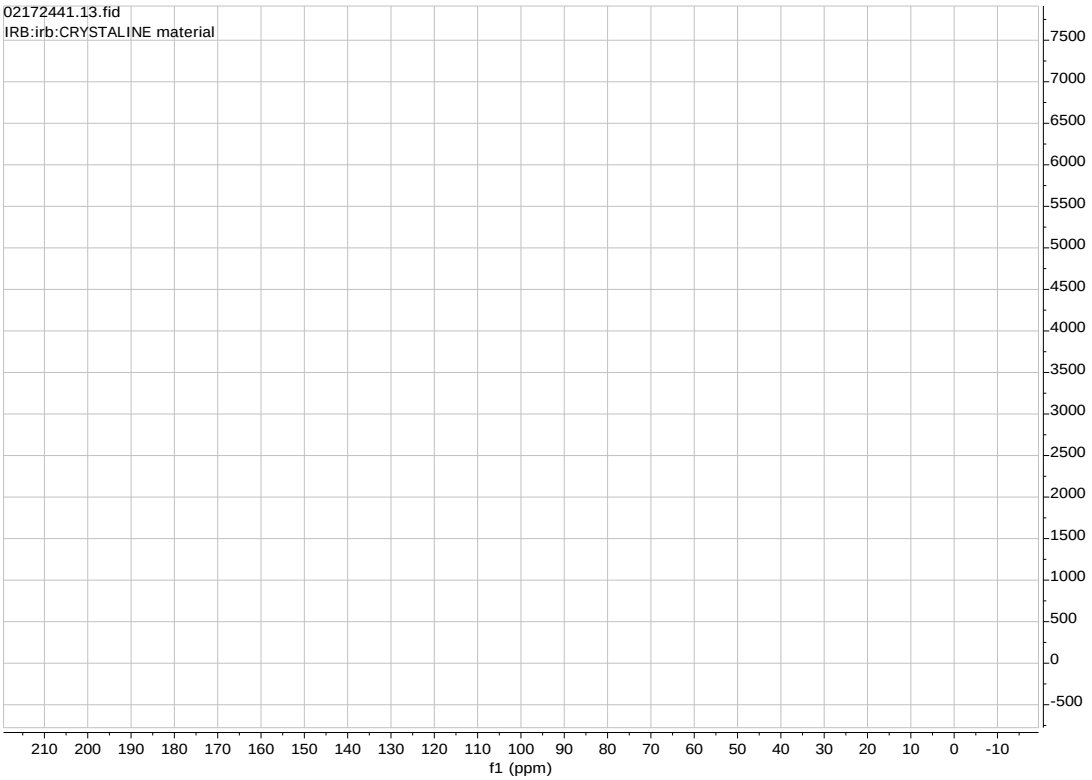
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