# Table of Contents

# 1. General information

Alkyl bromides, titanium isopropoxide, alkenes, benzaldehydes and other electrophiles were distilled before use and then stored under argon. Anhydrous LiCl was bought from Merck, stored in glovebox and used without further purification. Carbon dioxide (CO2) was purchased at the 4.5 grade and used as received. Solvents were dried over molecular sieves for 48 hours and after removal of sieves, degassed with freeze-pump-thaw technique.

NMR spectra was measured with Bruker Advance Neo 400. $^{1}H$ and $^{13}C$ were referenced with residual solvent residue of $CDCl_3$ and $^{19}F$ was referenced with internal standard of hexafluorobenzene set to -164.90 ppm. The spectra were processed with Mestrenova 14.2.0 with mainly automatic assignments and manual corrections where required. All coupling constants (J) are quoted to the nearest 0.1 Hz with the involved nuclei subscripted, and the resonances are noted as follows: δ chemical shift in ppm (number of nuclei, multiplicity, J value(s), assignment). Splitting patterns are denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (heptet), m (multiplet), or br (broad resonance). In case of signal overlap, 2D NMR experiments (HSQC and/or HMBC) were used as additional techniques for NMR signal assignments.

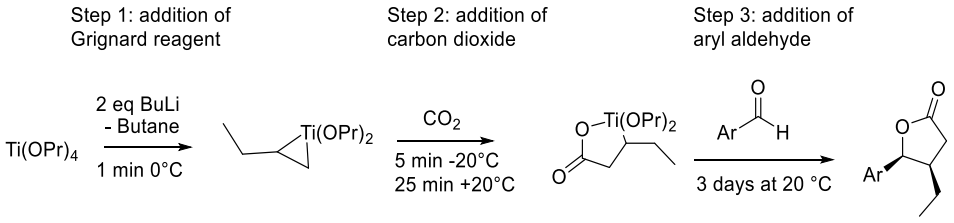
Gas chromatographic analyses were carried out an Agilent 6890N GC equipped with 5973 MSD using a HP-5MS UI (30 m, 0.25 mm, 0.25 µm) column.

High-resolution mass spectra (HRMS) were recorded on Bruker microTOF mass spectrometer by electrospray ionization time of flight reflectron experiments. The mass detector was calibrated with HCOONa solution in 1:1 $H_2O$:iPrOH. All HRMS experiments were recorded with positive ion detector and the recorded masses were under 5 ppm error unless otherwise noted.

## Abbreviations

THF = Tetrahydrofuran
NMR = Nuclear magnetic resonance
ESI-MS = Electrospray ionization mass spectrometry
GC-MS = Gas Chromatography – Mass spectrometry
TMEDA = N,N,N,N-Tetramethylethylenediamine
DMMEA = N,N-Dimethyl-2-methoxyethylamine
HMPA = Hexamethylphosphoramide

# 2. Optimization with butyl lithium




**Scheme S1**: Lactone formation with BuLi

**Table S1**: Reaction optimization for BuLi, Yield is calibrated GC yield. [a] BuLi:Ti(OiPr)$_4$:p-fluorobenzaldehyde [b] NMR-yield, the coloration is for emphasizing the changed variable. Step 3 time was optimized by running gas chromatogram twice a day to see, when starting material was fully consumed or there was no change to it from previous gas chromatogram. Leaving reaction to stir at room temperature for longer time had no effect on the reaction.

| | Temperature (°C) | Solvent | Stoichiometry[a] | Step 1 reaction time | Step 2 reaction time | Additive | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | 20 | THF | 2.1:1.05:1 | 5 min | 2h | | Trace |
| 2 | 0 | THF | 2.1:1.05:1 | 5 min | 2h | | 26 |
| 3 | -20 | THF | 2.1:1.05:1 | 5 min | 2h | | 26 |
| 4 | -40 | THF | 2.1:1.05:1 | 5 min | 2h | | 2 |
| 5 | 0 | $Et_2O$ | 2.1:1.05:1 | 5 min | 2h | | 27 |
| 6 | 0 | Toluene | 2.1:1.05:1 | 5 min | 2h | | 0 |
| 7 | 0 | Hexane | 2.1:1.05:1 | 5 min | 2h | | 0 |
| 8 | 0 | THF | 2.0:1.2:1 | 5 min | 2h | | 27 |
| 9 | 0 | $Et_2O$ | 2.0:1.2:1 | 5 min | 2h | | 20 |
| 10 | 0 | THF | 2.6:1.3:1 | 5 min | 2h | | 39 |
| 11 | 0 | $Et_2O$ | 2.6:1.3:2 | 5 min | 2h | | 19 |
| 12 | 0 | THF | 3.0:1.5:1 | 5 min | 2h | | 36 |
| 13 | 0 | $Et_2O$ | 3.0:1.5:2 | 5 min | 2h | | Trace |
| 14 | 0 | THF | 2.6:1.3:1 | 5 min | 5 min | | 41 |
| 15 | 0 | THF | 2.6:1.3:1 | 5 min | 15 min | | 44 |
| 16 | 0 | THF | 2.6:1.3:1 | 5 min | 30 min | | 53 |
| 17 | 0 | THF | 2.6:1.3:1 | 5 min | 1h | | 34 |
| 18 | 0 | THF | 2.6:1.3:1 | 15 min | 30 min | | 22 |
| 19 | 0 | THF | 2.6:1.3:1 | 2 min | 30 min | | 63 |
| 20 | 0 | THF | 2.6:1.3:1 | 1 min | 30 min | | 75 |
| 21 | 0 | THF | 2.6:1.3:1 | 30 sec | 30 min | | Variable |
| 21 | 0 | THF | 2.6:1.3:1 | 1 min | 30 min | LiCl | 71[b] |
| 22 | 0 | THF | 2.6:1.3:1 | 1 min | 30 min | | 77[b] |

Reaction at the optimized conditions (#22 in table S1): An oven-dired 25 ml Schlenk tube with stirrer bar was filled with argon and sealed with rubber septum. 3 ml of dry degassed THF and 0.394 ml of titanium isopropoxide (1.3 mmol) were added. The solution was cooled to 0°C and 1.625 ml of 1.6 M BuLi in hexanes (2.6 mmol) was added over

10 seconds, and the reaction turned black. After further 50 seconds $CO_2$ is flushed through a 0.4 mm diameter needle for 5 minutes. The tube is taken from the cold bath to room temperature and stirred for further 25 minutes. 1 mmol of aldehyde was added as one portion and the mixture was stirred for 3 days at room temperature to give a slightly yellow solution. 4 ml of 3 M HCl is added slowly to the solution (foaming) and stirred for 30 minutes to free the lactone. Organic phase is extracted with 3x2 ml of EtOAc and the combined organic phase is evaporated. Yield is determined from the crude by GC/MS with 0,5 mmol of mesitylene as standard (#1-21) or by 1H NMR with 0.33 mmol of 1,3,5-trimethoxy benzene as standard (#21-22)

## Study of titanium sources

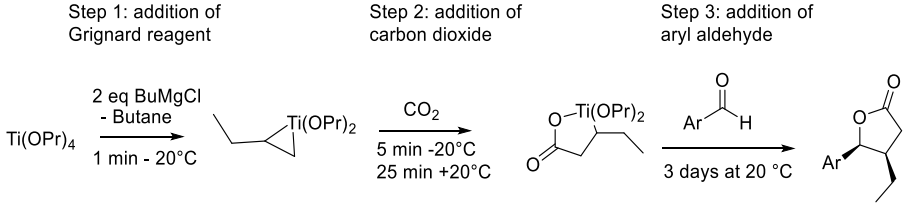
**Table S2:** *cis*-diastereomer NMR-yield for different titanium sources. $TiCl(OiPr)_3$ had higher amounts of minor impurities visible in gas chromatograms similar to what was observed when the reaction was performed with $Ti(OiPr)_4$ higher temperature, which may indicate that it's higher reactivity wasn't suitable for these conditions. $Ti(OMe)_4$ and $Ti(OBu)_4$ solutions formed gel like black solid after adding BuLi and there was also precipitation in the solution before work-up, which would indicate that the problem is the solubility of the formed intermediates.

| Titanium | Yield |
|---|---|
| $Ti(OiPr)_4$ | 77% |
| $TiCl(OiPr)_3$ | 56% |
| $Ti(OMe)_4$ | <5% |
| $Ti(OBu)_4$ | 25 % |
| $TiCp_2Cl_2$ | 0% |
| $TiCl_4$ | 0% |

# 3. Optimization with butyl magnesium chloride

Reaction with commercial Grignard reagent: An oven-dried 25 ml Schlenk tube with stirrer bar was brought into am argon filled glovebox and 3 ml of dry degassed THF, 0.394 ml of titanium isopropoxide (1.3 mmol) and 110 mg of LiCl (2.6 mmol) were added. Tube was sealed with rubber septum and brought out of the glovebox and stirred 15 minutes in room temperature to dissolve most of the lithium chloride. The solution was cooled to -20°C and 1.3 ml of 2 M Grignard in THF (2.6 mmol) was added over 10 seconds, and the reaction turned black (occasionally the reaction may form a gel at this point and the tube has to be shaken by hand to enable magnetic stirring). After further 50 seconds, $CO_2$ is flushed through a 0.4 mm diameter needle for 5 minutes. The tube is taken from the cold bath to room temperature and stirred for further 25 minutes. 1 mmol of aldehyde was added as one portion and the mixture was stirred 3 days at room temperature to give a yellow-brown solution. 4 ml of 3 M HCl is added slowly to the solution (foaming) and stirred for 30 minutes to free the lactone. Organic phase is extracted with 3x2 ml of EtOAc and the combined organic phase is evaporated. Yield is determined from the crude by 1H NMR with 0.33 mmol of 1,3,5-trimethoxy benzene as standard.

Products were isolated by column chromatography with 100:10:1 hexane:EtOAc:iPrOH eluent, (for **11n** and **11o** 100:25:1 ratio was used instead). For **11o**, after quenching with the 4 ml of 3 M HCl and stirring for 30 minutes, the mixture was made basic with $Na_2CO_3$ before extracting. Some products may have carboxylic acid impurity, from direct addition of Grignard reagent to carbon dioxide, that is not completely removed by column chromatography, but it could be removed by DCM/$Na_2CO_3$(aq) extraction.




**Scheme S2**: Lactone formation with BuMgCl

**Table S3**: Reaction optimization for BuMgCl. Yield is NMR-yield with trimethoxybenzene as standard [a] Grignard reagent ; Titanium isopropoxide ; Aldehyde, the coloration is for emphasizing the changed variable

| # | Temperature | Solvent | Stoichiometry[a] | Cyclopropyl reaction time | CO2 addition | Additive (2.6 eq) | Yield(%) |
|---|---|---|---|---|---|---|---|
| 1 | 0 | THF | 2.6;1.3;1 | 5 min | 30 min | | 0 |
| 2 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | | 5 |
| 3 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | LiCl | 29 |
| 4 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | TMEDA | 0 |
| 5 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | DMMEA | 0 |
| 6 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | HMPA | 0 |
| 7 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | LiBr | 2 |
| 8 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | NaCl | 9 |
| 9 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | ZnCl2 | 0 |
| 10 | -40 | THF | 2.6:1.3:1 | 5 min | 30 min | CuBr | 23 |
| 11 | -20 | THF | 2.6:1.3:1 | 5 min | 30 min | LiCl | 10 |
| 12 | -20 | THF | 2.6:1.3:1 | 2 min | 30 min | LiCl | 51 |
| 13 | -20 | THF | 2.6:1.3:1 | 1 min | 30 min | LiCl | 73 |
| 14 | -20 | THF | 2.6:1.3:1 | 15 min | 30 min | LiCl | Trace |

# 4. Grignard reagent screening

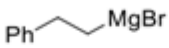
Butyl-, propy-l, octyl- and phenylethylmagnesium chloride were purchased from sigma Aldrich and used directly in the reactions. Rest of the Grignard reagents were synthesized from corresponding alkyl bromide in THF activated magnesium turings. Magnesium turnings were activated by washing them with 0.1 M HCl, followed by distilled water and ethanol. They were dried in vacuum and then heated to 300 °C for 1 hour in vacuum, and then stored under argon.

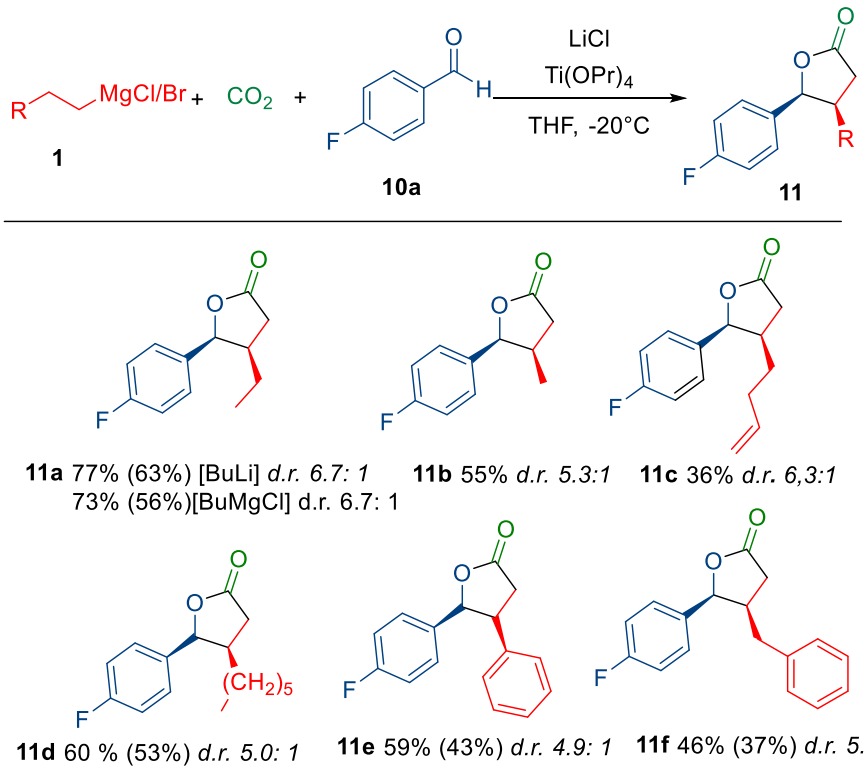
## 4.1. Grignard reagent synthesis

10 mmol of organobromide (RBr) dissolved in ~1:10 in THF and was added dropwise over 3-5 minutes into a reaction vessel containing activated magnesium turnings (11 mmol) in 5ml of THF under argon. The reaction was refluxed at for 1 hour as a clear grey solution evolved. After 1 hour, the concentration of the organomagnesium bromide (RMgBr) was determined by titrating against iodine in a 1.0 M LiCl in tetrahydrofuran (THF). The endpoint of this titration, proposed by Krasovskiy et al., is characterised by the colour change from dark brown to colourless upon complete consumption of the iodine.[1]

The prepared Grignard reagent was directly used with the method optimized to BuMgCl and the cis diastereomer yield was determined with $^{1}$H NMR using 1,3,5-trimethoxybenzene as standard.

**Table S4**: Grignard synthesis yield, Yield by titration.

| Entry | Grignard reagent | Solvent | Yield/ % |
|---|---|---|---|
| 1 |  | THF | 75 |
| 2 |  | THF | 85 |
| 3 |  | THF | 78 |
| 4 |  | THF | 68 |
| 5 |  | THF | 83 |
| 6 |  | THF | 68 |
| 7 |  | THF | 94 |
| 8 |  | THF | 94 |
| 9 |  | THF | 0 |
| 10 |  | THF | 0 |




**Scheme S3**: Lactone formation with various primary Grignard reagents

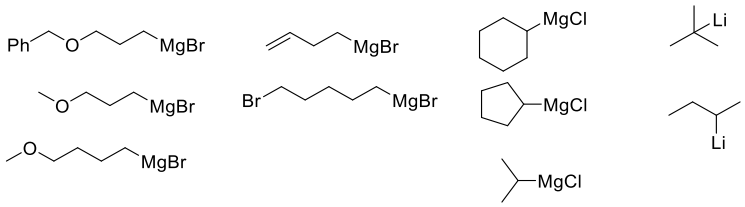



**Figure S1:** Grignard reagents and alkyl lithiums that didn't give any product

# 5. Screening of electrophiles

Screening was done using the optimized conditions for BuMgCl and p-fluorobenzaldehyde without further optimization.

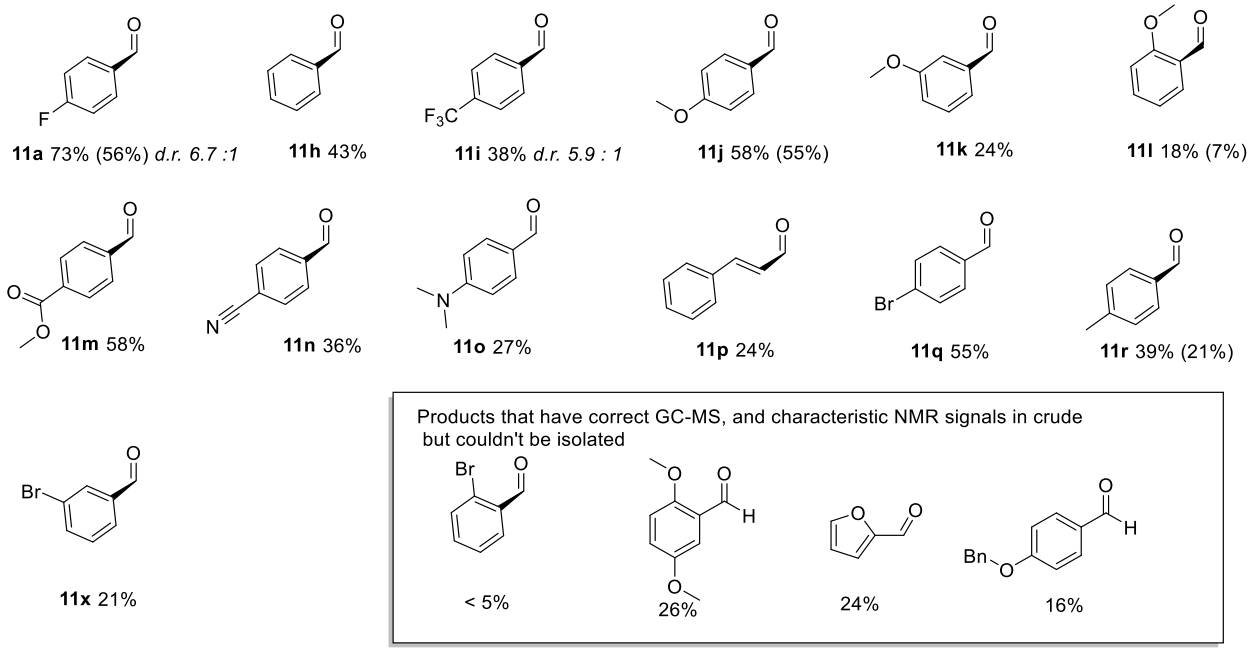
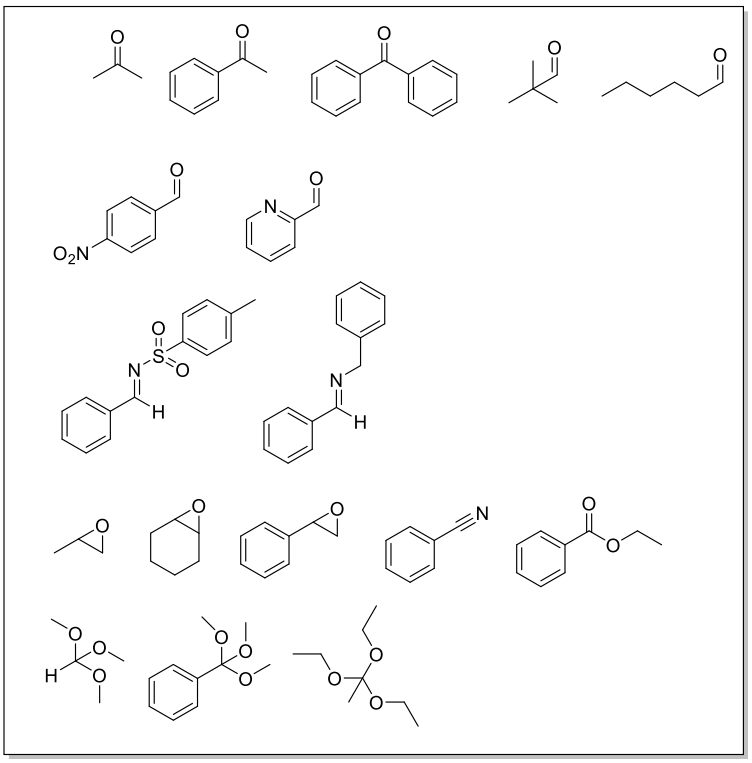



**Figure S2:** Aldehydes that yielded product, NMR yield of cis-lactone, isolated yield in parenthesis



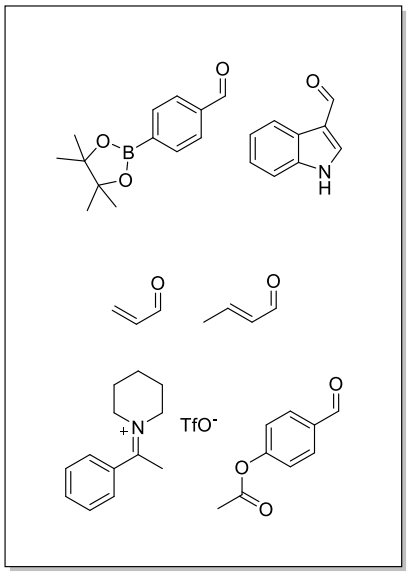
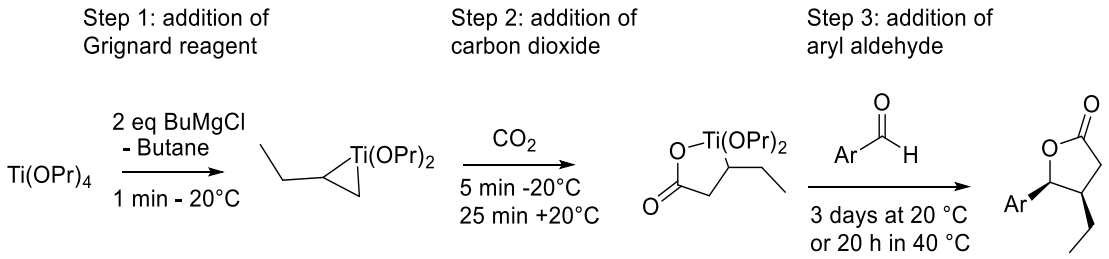




**Figure S3:** Studied electrophiles, that did not yield any product

# 6. Investigation for the effectiveness of lithium chloride




**Scheme S4:** Reaction scheme for the lactone formation with primary Grignard reagents. LiCl dissolved in THF was added before each step to figure out its effect on the reaction.

**Table S5**: Effect of lithium chloride in a reaction with BuMgCl. [a]

| # | LiCl addition | Yield of 11a (%) |
|---|---|---|
| 1 | LiCl (s) | 73 |
| 2 | LiCl mixed with BuMgCl before addition | 68 |
| 3 | LiCl (THF) before step 1 | 65 |
| 4 | LiCl (THF) before step 2 | 25 |
| 5 | LiCl (THF) before step 3 | 29 |
| 6 | No LiCl | 31 |
| 7 | 0 °C | 3 |
| 8 | 0°C No LiCl | 0 |

[a]2.6 eq of LiCl added either before the reaction as solid or as a saturated THF solution

To a 25 ml Schlenk tube was added under argon 2 ml of dry degassed THF, 0.394 ml of titanium isopropoxide (1.3 mmol). To test the effect of lithium chloride on each step, 2 ml of saturated LiCl in THF was added before each step (1. before adding the Grignard, 2. between Grignard and $CO_2$ addition and 3. right before adding the aldehyde.) The solution was cooled to -20°C and 1.3 ml of 2 M Grignard in THF (2.6 mmol) was added over 30 seconds, and the reaction turned black (occasionally the reaction may solidify at this point and the tube has to be shaken by hand to enable magnetic stirring). After 30 seconds $CO_2$ is flushed through a 0.4 mm for 5 minutes. The tube is taken from the cold bath to room temperature and stirred for further 25 minutes. 1 mmol of aldehyde was added as on portion and the mixture was stirred 3 days at room temperature to give a slightly brown solution. 4 ml of 3 M HCl is added slowly to the solution and stirred for 30 minutes to free the lactone. Organic phase is extracted with 3x2 ml of EtOAc and the combined organic phase is evaporated. Yield is determined from the crude by $^1$H NMR with 0.33 mmol of trimethoxy benzene as standard. Purification by column chromatography (usually 100:10:1 hexane:EtOAc:i-PrOH)or by distillation to receive mixture of diastereomers.

# 7. 11o 5-(4-(dimethylamino)phenyl)-4-ethyldihydrofuran-2(3H)-one diastereomer selectivity

Unlike all the other lactones, **11o** 5-(4-(dimethylamino)phenyl)-4-ethyldihydrofuran-2(3H)-one was selective to the *trans*-diastereomer. 27% of *trans* and 5 % *cis*-diastereomers was observed in NMR. To investigate this, we repeated the reaction by using BuLi instead of BuMgCl, and the NMR showed 20% *trans* and 21% *cis*. However, after column chromatography only *trans*-lactone could be obtained. To check, if the cis-diastereomer was decomposing or transforming into to *trans*-diastereomer, a new reaction with BuLi was made, which had 24 % *trans* and 19 % *cis* in crude NMR. The crude was dissolved in dichloromethane and 300 mg of silica was added. The mixture was stirred for 60 minutes. Silica was filtered and the washed with EtOH to eluate everything. After this treatment NMR showed near full conversion to *trans*-diastereomer, with 42% *trans* and < 3% *cis*. Analogous isomerization was not detected with any other lactone products. If silica catalyzed isomerization was happening in other lactones, then we would expect the diastereomeric ratios of lactone coming from column chromatography to be uniform in all fractions, which was not the case.

This conversion also proceeds quickly in basic, neutral and acidic alumina. Also, slow conversion can be observed over several days when the crude is dissolved in $CDCl_3$. Since the cis-diastereomer couldn't be isolated, crude NMR ($^{1}H$, $^{13}C$, HSQC, HMBC, end of the NMR spectra section) with 2:1 *trans*:*cis* ratio was used to make sure that the 5.6 ppm doublet is truly a signal originating from the cis-lactone.

Since the reactions with BuLi and BuMgCl have different diastereomer ratios, we also investigated the effect of added magnesium. When 2.6 eq $MgCl_2$ was added before adding the aldehyde, 16 % *trans* and 10% *cis* was obtained. When $MgCl_2$ was added 2 days after adding the aldehyde, 18% *trans* and 19% *cis* was obtained. Therefore, magnesium might also have some effect on the selectivity of the insertion step of the aldehyde, instead of catalyzing the isomerization. Additionally, computational data showed a 0.9 kcal/mol difference between the two possible inner sphere TS, in favour of the one leading to the *trans*-diastereomer (see SI Table S9 for details). However, this data does not take in to account explicit effect that magnesium might have on the reaction mechanism for this specific substrate.

# 8.Alkene exchange reaction

$Ti(OiPr)_4$ (1.3 mmol), LiCl (2.6 mmol) and THF (3 ml) were added in a argon filled glovebox to an oven-dried Schlenk flask containing magnetic stirrer bar and sealed with rubber septum. The flask was brought out of the glovebox and stirred for 15 minutes. 1-Hexene (8 mmol) was added to the flask. The mixture was cooled to -20°C. Cyclohexyl magnesium chloride in $Et_2O$ was added over 10 seconds. The mixture is stirred for 5 minutes, during which the reaction turns slightly yellow-orange (unlike with primary Grignard reagents where the reaction turns black almost immediately). $CO_2$ is flushed to the flask for 5 minutes and the reaction starts to slowly turn darker. After the $CO_2$ flush, the mixture is brought to room temperature for 1 hour, during which it turns completely black. Aldehyde is added in one-portion under $CO_2$ flow. After 3 days in room temperature, the reaction is quenched with 3 M HCl (4 ml) and extracted with 3x2 ml EtOAc to yield the crude product. Yield was analyzed by 1H-NMR with trimethoxyhexene as standard. Purification by column chromatography 200:20:1 Hexene:EtOAc:iPrOH 4 column volumes into 50:5:1 Hexene:EtOAc:iPrOH

**Table S5:** Optimization of alkene exchange reaction with 1-hexene. Yield by $^1$H-NM, with trimethoxy benzene as standard a: Slightly lower yield, but side product composition is better for purification, see figures SI5-6.

| # | Equivalents(1-hexene) | step 1 time | Additive | Yield(%) |
|---|---|---|---|---|
| 1 | 8 | 1 | 2.6 eq LicL | 23 |
| 2 | 4 | 1 | 2.6 eq LicL | 16 |
| 3 | 2 | 1 | 2.6 eq LicL | 15 |
| 4 | 4 | 2 | 2.6 eq LicL | 22 |
| 5 | 4 | 5 | 2.6 eq LicL | 31 |
| 6 | 4 | 15 | 2.6 eq LicL | 36 |
| 7 | 4 | 15 | | 34[a] |
| 8 | 8 | 15 | | 29 |
| 9 | 8 | 5 | | 27 |
| 10 | 4 | 30 | | 32 |
| 11 | 2 | 15 | | 22 |
| 12 | 1.3 | 15 | | 19 |

$Ti(OiPr)_4$ (1.3 mmol) and THF (3 ml) were added under argon to an oven-dried Schlenk flask containing magnetic stirrer bar and sealed with rubber septum. 1-Hexene (4 mmol) was added to the flask. The mixture was cooled to -20°C. 1.6 ml of 2.0 M Cyclohexyl magnesium chloride in $Et_2O$ was added over 10 seconds. The mixture is stirred for 15 minutes, during which the reaction turns slightly yellow-orange (unlike with primary Grignard reagents where the reaction turns black almost immediately). $CO_2$ is flushed to the flask for 5 minutes and the reaction starts to slowly turn darker. After the $CO_2$ flush, the mixture is brought to room temperature for 1 hour, during which it turns completely black. Aldehyde is added in one-portion under $CO_2$ flow. After 3 days in room temperature, the reaction is quenched with 3 M HCl (4 ml) and extracted with 3x2 ml EtOAc to yield the crude product. Yield was analyzed by 1H-NMR with trimethoxybenze as standard. Purification by column chromatography 200:20:1 Hexene:EtOAc:iPrOH 4 column volumes into 50:5:1 Hexene:EtOAc:iPrOH

**Table S7**: Effect of Grignard reagent or alkyl lithium source. Yield is calibrated GC-MS yield with mesitylene as standard (GC was used since NMR overlap was too high for to separate exchange and non-exchange product) Exchange product incorporates the added 1-hexene, whereas the non-exchange product incorporates the organometallic reagent as in Scheme S1 or S2.

| Organometallic reagent | Exchange product | Non-exchange |
|---|---|---|
| c-HexMgCl (2.0 M Et2O) | 34% | 0% |
| c-HexMgCl (2.0 M THF:Toluene | 31% | 0% |
| c-HexMgCl (1.0 M MeTHF) | 18% | 0% |
| c-PentMgCl (2.0 M Et2O) | 7% | 0% |
| c-PentMgBr (2.0 M Et2O) | 15% | 0% |
| BuLi (1.6 M Hexane) | 18% | 38% |
| BuMgCl (2.0 M THF) | 4% | 18% |
| tBuLi (1.7 M Hexane) | 6% | 0% |
| iPrMgCl | 6% | 0% |
| iPrMgCl-LiCl | < 1% | 0% |

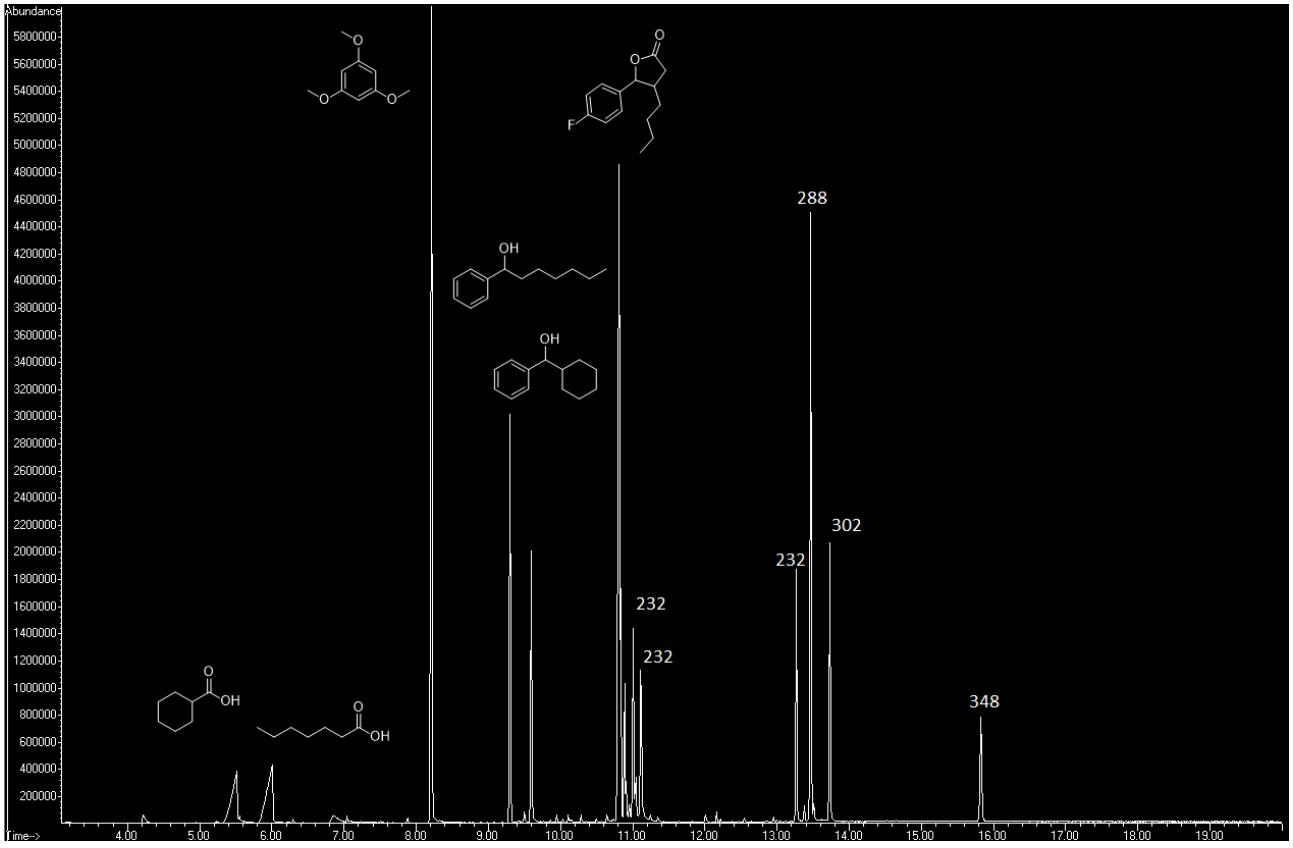


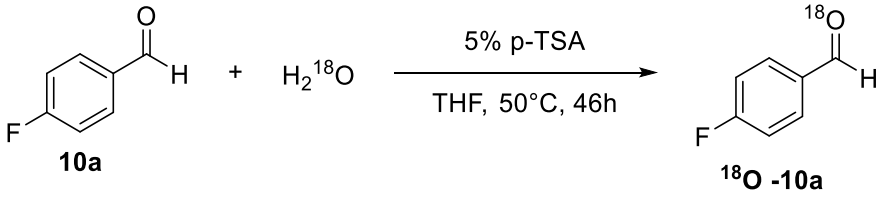

**Figure S4:** Gas chromatograms for 1-Hexene exchange reaction with lithium chloride (trimethoxybenzene is a standard). The numbers above the peaks are the mass for $M^+$ ion if the compound could not be identified. Separation of compound with $M^+$ 232 at 11 min is extremely difficult.


**Figure S5:** Gas chromatograms for 1-Hexene exchange reaction without lithium chloride. More pinacol coupling product (1,2-bis(4-fluorophenyl)ethane-1,2-diol) is formed instead which is not visible here and is very easy to separate. The numbers above the peaks are the mass for $M^+$ ion if the compound could not be identified.

**Table S8**: Scope of alkenes. [a] NMR-yield, [b] 1,3 eq of alkene and additional 1,3 equivalent of c-hexyl magnesium chloride to deprotonate was used.

| Alkene | Yield(%)[a] |
|---|---|
| 1-hexene | 34 |
| 1-octene | 28 |
| 1,5-hexadiene | 32 |
| styrene | < 2 |
| allylbenzene | 31 |
| allylTMS | 27 |
| 6-bromo-1-hexene | 33 |
| vinylbutyl ether | 0 |
| 1-vinyl-4-cyclohexene | < 2 |
| 4-penten-1-ol[b] | 0 |
| 3-buten-1-ol[b] | 0 |
| 3-butenoic acid[b] | 0 |

# 9. $^{18}$O-labeled experiment




**Scheme S5**: Synthesis of $^{18}$O-labeled p-fluorobenzaldehyde. Adapted method from Tang et al.[2]

$H_2{}^{18}O$ (500 µl, 24.9 mmol) was adeed to a solution of p-fluorobenzaldehyde (500 µl, 4.66 mmol) and p-TSA (50 mg, 0.29 mmol), in dry THF (5 ml) under argon. The mixture was stirred for 46 hours at 50 °C. The work-up is also done under argon, and the $K_2CO_3$(aq) and $Et_2O$ were degassed by bubbling argon for 5 minutes before addition. Aqueous 2M $K_2CO_3$ (5 ml) was added to the solution and the mixture was extracted with $Et_2O$ (3x3 ml). Combined organic phase was dried with anhydrous $MgSO_4$ and filtered with syringe filter. Volatiles were removed in vacuo to get the $^{18}$O-**10a** (512 mg, 87%, 4,06 mmol). The $^{18}$O content was determined to be 76% from peak heights in ESI-MS.

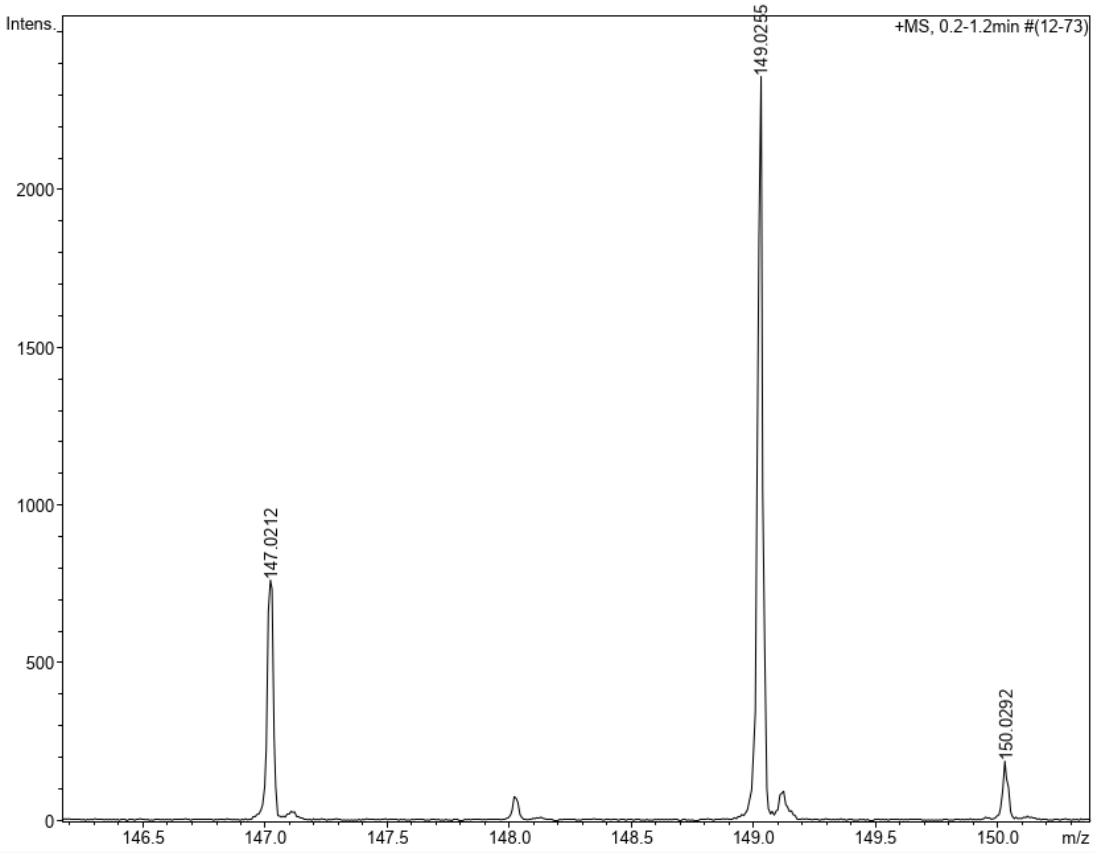
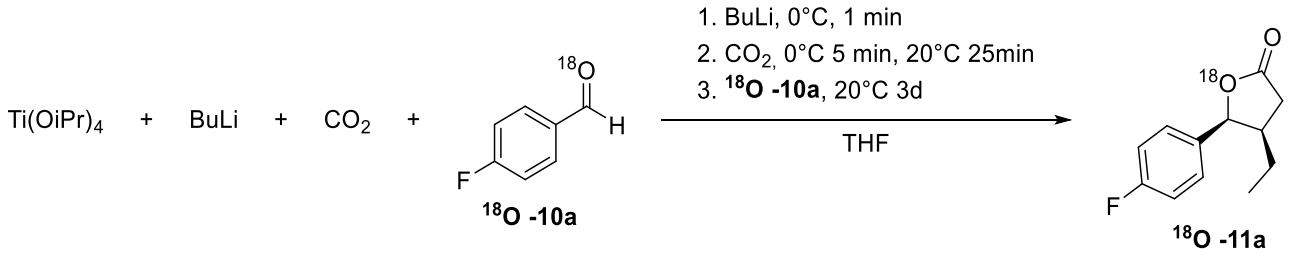



**Figure S6**: High resolution mass spectra of the isolated product. $^{16}$O: $[M+Na]^+$ calculated 147.02222, detected 147.0212 intesity: 764. $^{18}$O: $[M+Na]^+$ calculated: 149.0265, detected: 149.0255 intensity: 2360. Total $^{18}$O-content: 76%




**Scheme S6**: Synthesis of $^{18}O$-labeled cis-lactone

The $^{18}O$-**10a** was used in the optimized reaction with BuLi. The reaction gave 152 mg of cis-lactone (72%), with 69 % $^{18}O$-content, which was determined from peak heights in ESI-MS. In the $^{13}C$-NMR the $^{18}O$ adjacent carbons are shifted upfield.

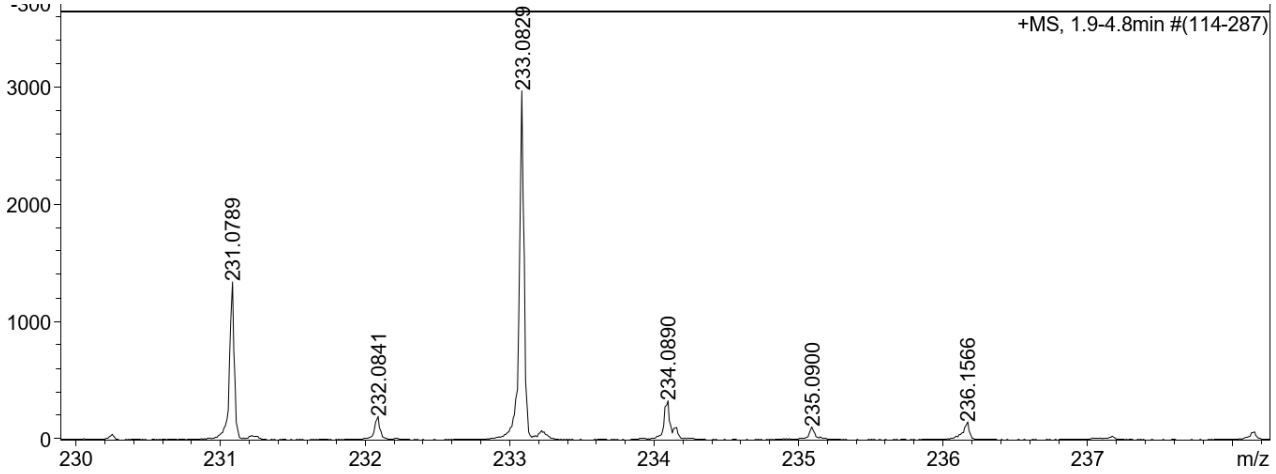



**Figure S7**: High resolution mass spectra of the isolated product. $^{16}O$: $[M+Na]^+$ calculated 231.0797, detected 231.0789 intesity: 1295. $^{18}O$: $[M+Na]^+$ calculated: 233.0840, detected: 233.0829 intensity: 2867. Total $^{18}O$-content: 69%

# 10. Computational details

The computational molecular model was composed of the full Ti complex and full substrates, without truncations or symmetry constraints. Calculations were carried out using the Gaussian 16 program, Revision B.01.[3] Geometries were optimized at the B3LYP/6-31+G(d,p) level,[4] including the D3 version of Grimme's empirical dispersion correction[5] and the CPCM[6] solvent model with the parameters of tetrahydrofuran (THF). Transition states and minima were verified through frequency calculations (no imaginary frequencies for minima, one imaginary frequency for transition states). B3LYP-D3/def2-TZVP[7] (CPCM) single point energies were performed to obtain more accurate electronic energies. Counterpoise corrections computed at the def2-TZVP level and a standard state conversion to a 1M standard state were included in the final standard state Gibbs free energies. All energies are given at 298.15 K, unless explicitly noted otherwise. Geometries for all the calculated structures are given in the separate Supporting Information file.

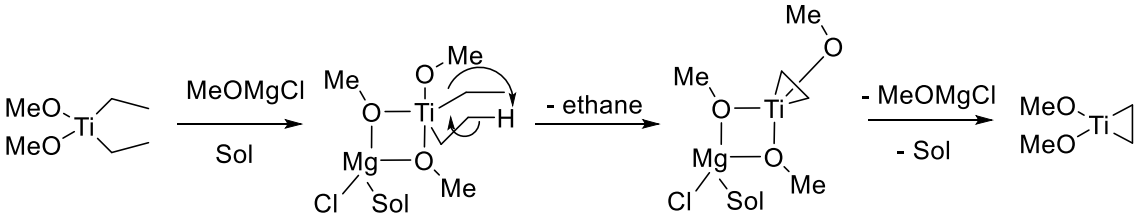



**Figure S8.** Mechanism for formation of titanacyclopropane from dialkyltitanium, as proposed by Bertus.[8] A magnesium salt species (formed as a byproduct in the mixture) is proposed to bind to the dialkyltitanium species, followed by a direct proton transfer from one alkyl to the other, without formation of a distinct Ti-hydride. As this transformation has been studied in great detail by Bertus, it was not modelled here.

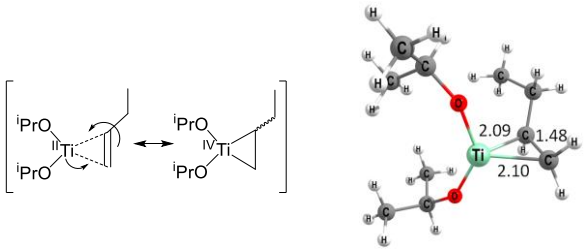



**Figure S9.** *Left*: Possible resonance structures of **3a**. *Right*: Optimized geometry of **3a** (B3LYP-D3/6-31+G(d,p), CPCM[THF]). Initially we evaluated if **3a** may be best described as a titana(IV)cyclopropane or as a titanium(II)alkene species. The optimized C-C bond in **3a** shows a length of 1.48 Å (Figure 1), which is closer to a single bond bond (1.53 Å in free butane) than a double bond (1.34 Å in free butene). Thus, **3a** is best described as a titanacyclopropane, in line with computational studies on similar systems.[9]

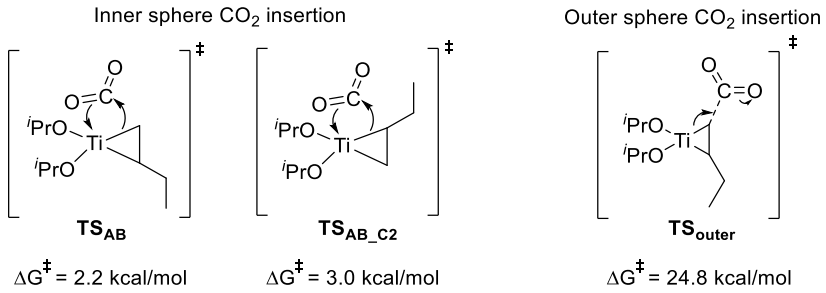
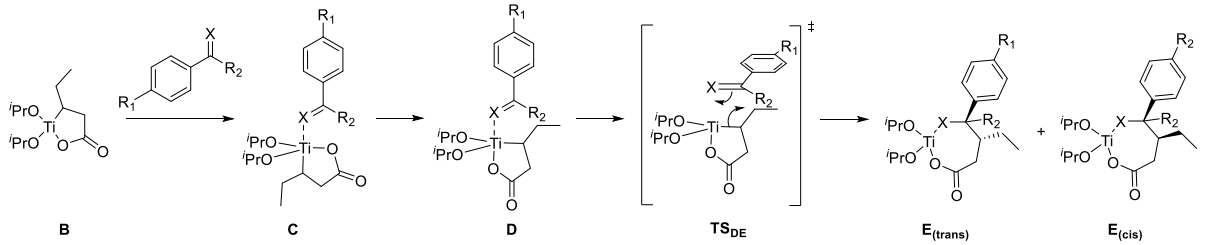



**Figure S10.** Putative TSs computed here for transformation of **3a** to titanalactone **C** (energies given relative to **3a** + $CO_2$). It can be noted that the reaction mixture contains LiCl which may have an effect on carboxylation reactions with $CO_2$, if an outer sphere mechanism is operative. However, it is not assumed to influence the inner sphere mechanism,[10] which is strongly preferred in our calculations, see main text.

**Table S9.** Gibbs free energies (kcal/mol) comparing insertion of aldehyde, ketone or imine into B (298 K, energies given relative to 3a + $CO_2$ + aldehyde/ketone/imine). It can be observed that the stability of C appears to determine the activation barrier for $TS_{DE}$. For the 4-dimethylaminobenzaldehyde, the 0.9 kcal/mol difference between the barriers could explain the majority of *trans*-diastereomer product observed experimentally for **11o**.




| | B | C | D | $TS_{DE(trans)}$ | $TS_{DE(cis)}$ | $E_{(trans)}$ | $E_{(cis)}$ | Overall barrier |
|---|---|---|---|---|---|---|---|---|
| **4-fluorobenzaldehyde** | -23.1 | -23.7 | -20.0 | -6.9 | -6.8 | -49.8 | -51.6 | 16.8 |
| **acetophenone** | -23.1 | -25.0 | -21.2 | -4.1 | / | -46.5 | -46.4 | 20.9 |
| **phenylmethanimine** | -23.1 | -29.5 | -25.6 | -0.9 | / | -43.9 | -42.0 | 28.6 |
| **4-dimethylaminobenzaldehyde** | -23.1 | -26.6 | -22.7 | -8.5 | -7.6 | -45.7 | -48.4 | 18.1 |

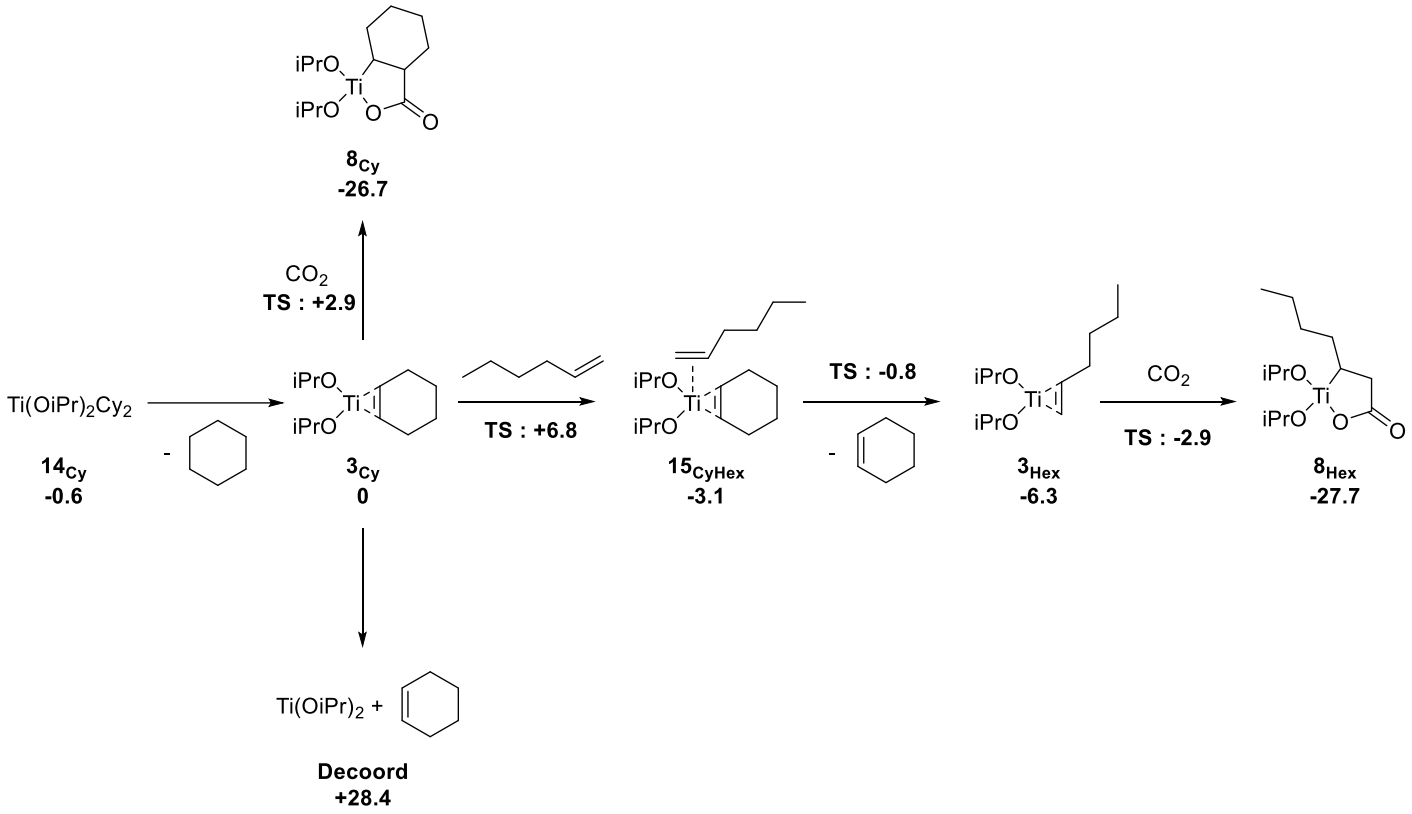



**Figure S11.** Putative alkene exchange mechanism, with CyMgCl (Cy = cyclohexyl) as main Grignard reagent and hexene as exchange alkene(note that standard state conversion and counterpoise corrections were not included in the shown energies). Three possible pathways are shown here, all starting from coordinated species $\mathbf{3_{Cy}}$:

- The first pathway (up) shows the non-exchange mechanism where the $CO_2$ is inserted directly into structure $\mathbf{3_{Cy}}$, leading to the formation of titanalactone $\mathbf{8_{Cy}}$ with a barrier of 2.9 kcal/mol.
- The second pathway (down) shows the dissociative exchange mechanism, where the cyclohexene firsts decoordinates from $\mathbf{3_{Cy}}$ before the hexene can take its place. Thermodynamically, the decoordination of the cycle from the complex is largely disfavored (+28.4 kcal/mol), so this pathway was not further studied.
- The third pathway (right) corresponds to the exchange mechanism. The hexene first coordinates to species $\mathbf{3_{Cy}}$ with a barrier of 6.8 kcal/mol, forming $\mathbf{15_{CyHex}}$. The subsequent decoordination of the cyclohexene leads to the exchange titanacyclopropane $\mathbf{3_{Hex}}$ onto which $CO_2$ can insert itself with a barrier of 3.4 kcal/mol to form $\mathbf{8_{Hex}}$.

Looking at the doubly-coordinated species $\mathbf{15_{CyHex}}$, it can either decoordinate the cyclohexene to come back to species $\mathbf{3_{Cy}}$ or decoordinate the cyclohexene to lead to the alkene exchange. The barriers for both possibilities are 9.9 kcal/mol and 2.3 kcal/mol respectively. This difference of 7.6 kcal/mol between the two barriers explains why the exchange was observed experimentally in these conditions.

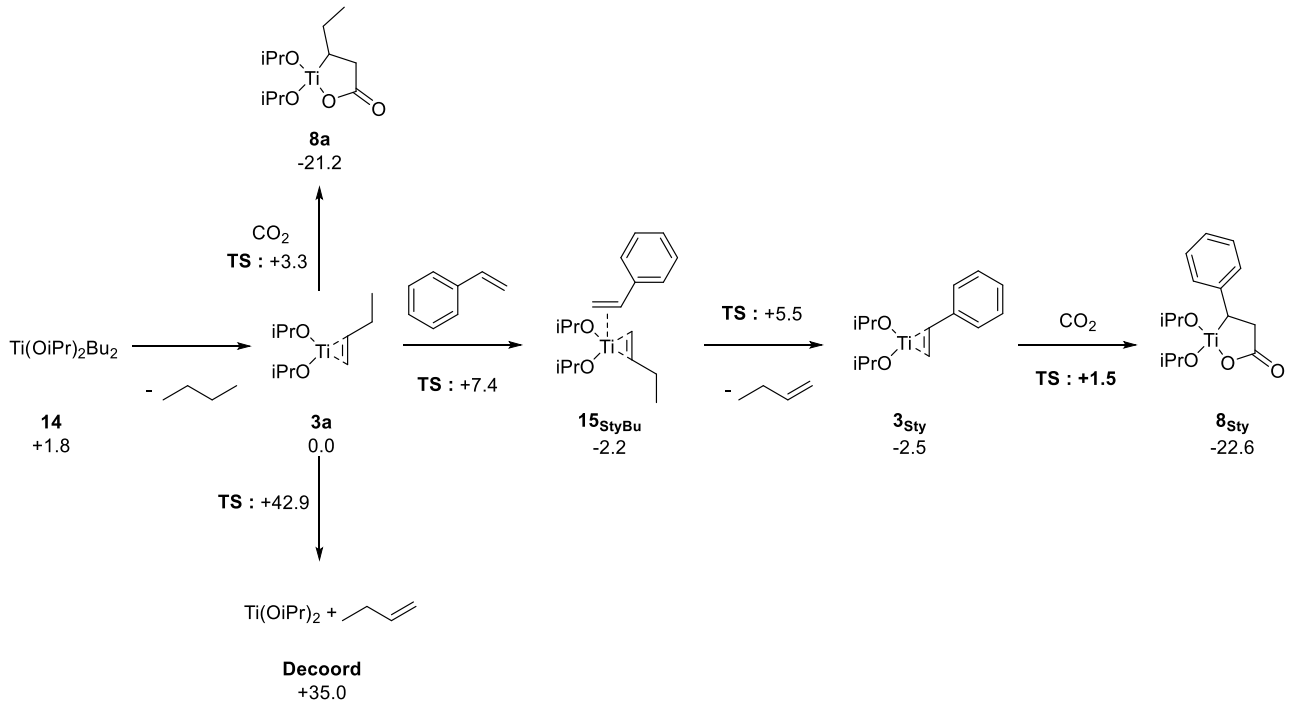



**Figure S12.** Putative alkene exchange mechanism, with BuMgCl (Bu = butyl) as main Grignard reagent and styrene as exchange alkene (note that standard state conversion and counterpoise corrections were not included in the shown energies). The same three pathways are shown as in Figure S9. Compared to Figure S9, the two possible pathways originating from doubly coordinated structure **15$_{StyBu}$** have much closer barriers: the decoordination of styrene back to titanacyclopropane **3** has a barrier of 9.6 kcal/mol, while the decoordination of butene leading to the exchange species **3$_{Sty}$** has a barrier of 7.7 kcal/mol. Considering these values, the exchange should be occurring, contradicting experimental results. We hypothesize that the high reactivity of styrene might lead to more favorable side reactions rather than the exchange.

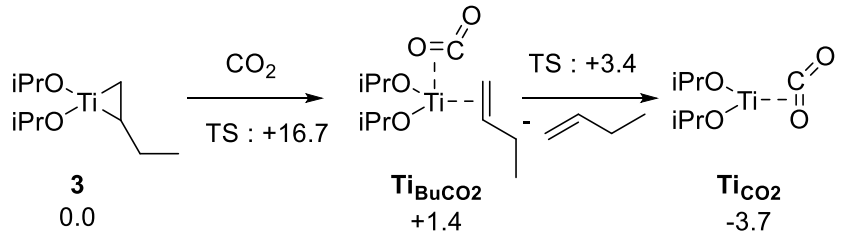



**Figure S13.** Putative $CO_2$ exchange mechanism. The observed barrier for the coordination of $CO_2$ to species **3** (16.7 kcal/mol) is much higher than that of the calculated inner sphere $CO_2$ insertion (2.2 kcal/mol, see Figure S8). So even though the decoordination of butene from **Ti$_{BuCO2}$** has a low barrier (2.0 kcal/mol) and is thermodynamically favored, the exchange does not happen, as structure **Ti$_{BuCO2}$** is not expected to be formed.

# 11. Characterization data

## 11a *cis*-4-ethyl-5-(4-fluorophenyl)dihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 2H), 7.12 – 7.03 (m, 2H), 5.59 (d, *J* = 6.7 Hz, 1H), 2.82 – 2.58 (m, 2H), 2.44 (dd, *J* = 17.0, 5.7 Hz, 1H), 1.22 – 0.99 (m, 1H), 0.97 – 0.81 (m, 1H), 0.84 – 0.75 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.70, 162.62 (d, *J* = 247.0 Hz), 132.21 (d, *J* = 3.3 Hz), 127.56 (d, *J* = 8.1 Hz), 115.65 (d, *J* = 21.7 Hz), 83.70, 77.36, 42.22, 34.06, 22.64, 12.00.

$^{19}$F NMR (376 MHz, $CDCl_3$) -116.3

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{12}H_{13}FO_2Na$: 231.0797 Found: 231.0805

## 11b *cis*-5-(4-fluorophenyl)-4-methyldihydrofuran-2(3H)-one

$^{1}$H NMR($CDCl_3$, 400 MHz): δ = 7.28 – 7.18 (m, 2H), 7.18 – 7.02 (m, 2H), 5.60 (d, 1H, *J*=5.7 Hz), 2.95 – 2.85 (m, 1H), 2.90 – 2.79 (m, 1H), 2.43 – 2.29 (m, 1H), 0.76 – 0.66 (m, 3H) ppm

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.54, 162.44 (d, *J* = 246.6 Hz), 131.91 (d, *J* = 3.2 Hz), 127.16 (d, *J* = 8.1 Hz), 115.52 (d, *J* = 21.7 Hz), 83.50, 37.10, 34.94, 15.13.

$^{19}$F NMR (376 MHz, $CDCl_3$) -117.1

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{11}H_{11}FO_2Na$: 217.0641 Found: 217.0639

## 11c *cis*-4-(but-3-en-1-yl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.17 (m, 2H), 7.21 – 7.00 (m, 2H), 5.73 – 5.52 (m, 2H), 5.09 – 4.89 (m, 2H), 2.88 – 2.72 (m, 2H), 2.52 – 2.35 (m, 1H), 2.18 – 1.96 (m, 1H), 1.89 (dddt, *J* = 14.5, 8.6, 7.3, 1.3 Hz, 1H), 1.38 – 1.11 (m, 1H), 1.07 – 0.77 (m, 1H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.41, 162.56 (d, *J* = 247.2 Hz), 137.05, 131.98 (d, *J* = 3.2 Hz), 127.47 (d, *J* = 8.3 Hz), 115.73 (d, *J* = 2.2 Hz), 115.52, 83.45, 39.62, 34.08, 31.45, 28.70.

$^{19}$F NMR (376 MHz, $CDCl_3$) -116.7

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{14}H_{15}FO_2Na$: 257.0954 Found: 257.0941

## 11d *cis*-5-(4-fluorophenyl)-4-hexyldihydrofuran-2(3H)-one

1 H NMR (400 MHz, CDCl3) δ 1H NMR (400 MHz, CDCl3) δ 7.27 – 7.17 (m, 2H), 7.15 – 7.01 (m, 2H), 5.61 (d, J = 6.4 Hz, 1H), 2.82 – 2.70 (m, 2H), 2.51 – 2.33 (m, 2H), 1.40 – 1.00 (m, 10H), 0.94 – 0.80 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.70, 162.50 (d, *J* = 247.0 Hz), 132.08 (d, *J* = 3.2 Hz), 127.46 (d, *J* = 8.2 Hz), 117.06 – 113.72 (m), 83.64, 40.40, 34.28, 31.60, 29.45, 29.08, 27.47, 22.50, 14.00.

$^{19}$F NMR (376 MHz, $CDCl_3$) = -116.9

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{16}H_{21}FO_2Na$: 287.1423 Found: 287.1421

## 11e *cis*-5-(4-fluorophenyl)-4-phenyldihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.09 (m, 3H), 6.93 – 6.78 (m, 6H), 5.83 (d, 1H, *J*=6.7 Hz), 4.06 (ddd, 1H, *J*=8.2, 6.7, 5.9 Hz), 3.09 (dd, 1H, *J*=17.5, 8.3 Hz), 2.95 (dd, 1H, *J*=17.5, 5.8 Hz) ppm

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.56, 162.22 (d, *J*=246.7 Hz), 136.57, 131.38 (d, *J*=3.2 Hz), 128.18 (d, *J*=50.7 Hz), 129.58 – 125.52 (m), 114.94 (d, *J*=21.7 Hz), 84.12, 77.29, 46.86, 34.99 ppm

$^{19}$F NMR (376 MHz, $CDCl_3$) = -117.09

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{16}H_{13}FO_2Na$: 279.0797 Found: 279.0809

## 11f *cis*-4-benzyl-5-(4-fluorophenyl)dihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 4H), 7.27 – 7.18 (m, 1H), 7.17 – 7.09 (m, 2H), 7.09 – 6.98 (m, 2H), 5.71 (d, *J* = 6.4 Hz, 1H), 3.10 (dddt, *J* = 11.4, 7.9, 6.5, 4.9 Hz, 1H), 2.65 (ddd, *J* = 17.5, 7.9, 0.6 Hz, 1H), 2.52 – 2.35 (m, 2H), 2.09 (dd, *J* = 14.0, 11.6 Hz, 1H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.10, 175.65, 162.60 (d, *J* = 247.3 Hz), 138.33, 131.74 (d, *J* = 3.3 Hz), 128.70, 128.67, 127.42 (d, *J* = 8.2 Hz), 126.65, 115.72 (d, *J* = 21.8 Hz), 83.12, 77.26, 41.84, 35.45, 34.14.

$^{19}$F NMR (376 MHz, $CDCl_3$) δ -116.58.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{17}H_{15}FO_2Na$: 293.0948 Found: 293.0952

## 11g *cis*-4-ethyl-5-(4-fluorophenyl)dihydrofuran-1-$^{18}$O-2(3H)-one*

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.19 (dddd, *J* = 8.0, 5.1, 2.5, 1.4 Hz, 2H), 7.11 – 6.99 (m, 2H), 5.58 (d, *J* = 6.7 Hz, 1H), 2.81 – 2.58 (m, 2H), 2.43 (dd, *J* = 17.1, 5.7 Hz, 1H), 1.17 – 1.03 (m, 1H), 0.97 – 0.79 (m, 1H), 0.82 – 0.74 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.69, 162.58 (d, *J* = 247.0 Hz), 132.20 (d, *J* = 3.3 Hz), 127.53 (d, *J* = 8.2 Hz), 115.61 (d, *J* = 21.6 Hz), 83.64, 42.17, 34.02, 22.61, 11.96.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{12}H_{13}FO^{18}ONa$: 233.0840 Found: 233.0829

*69% $^{18}$O-content, There is an upfield chemical shift change on $^{18}$O adjacent carbons on $^{13}$C NMR, which results in peak splitting. In these cases, the lower intensity signal is ignored.

## 11h *cis*-4-ethyl-5-phenyldihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 4H), 7.25 – 7.17 (m, 2H), 5.61 (d, *J* = 6.6 Hz, 1H), 2.84 – 2.56 (m, 2H), 2.52 – 2.28 (m, 1H), 1.22 – 0.99 (m, 1H), 0.97 – 0.82 (m, 1H), 0.82 – 0.75 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 177.00, 136.44, 128.62, 128.30, 125.85, 84.31, 42.29, 34.08, 22.70, 12.05.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{12}H_{14}O_2Na$: 213.0891 Found: 213.0890

## 11i *cis*-4-ethyl-5-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.39 (dt, *J* = 8.7, 0.9 Hz, 2H), 5.68 (d, *J* = 6.5 Hz, 1H), 2.87 – 2.67 (m, 2H), 2.49 (dd, *J* = 16.9, 4.9 Hz, 1H), 1.18 – 1.01 (m, 1H), 0.99 – 0.84 (m, 1H), 0.87 – 0.78 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.29, 140.39, 130.48 (q), 126.04, 125.55 (q), 125.27(q), 83.30, 77.23, 41.93, 33.93, 29.71, 22.39, 11.77, 1.03.

$^{19}$F δ -65.80

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{13}H_{13}F_3O_2Na$: 281.0765 Found: 281.0748

## 11j *cis*-4-ethyl-5-(4-methoxyphenyl)dihydrofuran-2(3H)-one

$^1$H NMR(400 MHz, $CDCl_3$) δ 7.20 – 7.11 (m, 2H), 6.92 (dq, 2H, *J*=9.6, 3.0, 2.4 Hz), 5.59 (d, 1H, *J*=6.7 Hz), 3.83 (s, 3H), 2.82 – 2.58 (m, 2H), 2.45 (dd, 1H, *J*=16.9, 6.2 Hz), 1.24 – 1.09 (m, 1H), 0.99 – 0.84 (m, 1H), 0.81 (t, 3H, *J*=7.2 Hz) ppm

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 177.01, 159.45, 127.05, 113.87, 84.15, 55.30, 42.29, 33.96, 22.67, 12.00 ppm

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{13}H_{16}O_2Na$: 243.0997 Found: 243.0995

## 11k *cis*-4-ethyl-5-(3-methoxyphenyl)dihydrofuran-2(3H)-one

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.30 (dt, *J* = 13.3, 8.0 Hz, 1H), 6.99 – 6.85 (m, 1H), 6.89 – 6.79 (m, 1H), 6.83 – 6.76 (m, 1H), 5.60 (d, *J* = 6.7 Hz, 1H), 3.83 (s, 2H), 2.84 – 2.61 (m, 1H), 2.47 (dd, *J* = 16.8, 5.5 Hz, 1H), 1.27 – 1.11 (m, 1H), 1.01 – 0.89 (m, 1H), 0.92 – 0.78 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.84, 159.76, 137.93, 117.96, 113.40, 111.49, 84.05, 42.14, 33.98, 22.42, 11.92.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{13}H_{16}O_2Na$: 243.0997 Found: 243.0991

## 11l *cis*-4-ethyl-5-(2-methoxyphenyl)dihydrofuran-2(3H)-one

$^1$H NMR(400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 2H), 7.00 (m, 1H), 6.96 – 6.88 (m, 1H), 5.87 (d, 1H, *J*=6.1 Hz), 3.86 (s, 3H), 2.85 – 2.71 (m, 2H), 2.54 – 2.38 (m, 1H), 1.17 – 1.06 (m, 1H), 0.94 – 0.83 (m, 1H), 0.79 (t, 3H, *J*=7.3 Hz) ppm

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 177.19, 155.99, 129.48, 129.03, 126.70, 120.57, 110.13, 81.04, 55.32, 40.52, 34.37, 29.71, 22.30, 11.80 ppm

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{13}H_{16}O_2Na$: 243.0997 Found: 243.0991

## 11m *cis*-Methyl 4-(3-ethyl-5-oxotetrahydrofuran-2-yl)benzoate

$^1$H NMR(400 MHz, $CDCl_3$) δ 8.07 (d, 2H, *J*=8.4 Hz), 7.34 (d, 2H, *J*=8.1 Hz), 5.68 (d, 1H, *J*=6.6 Hz), 3.95 (s, 3H), 2.86 – 2.77 (m, 1H), 2.78 – 2.66 (m, 1H), 2.48 (dd, 1H, *J*=16.8, 5.0 Hz), 1.19 – 1.05 (m, 1H), 0.96 – 0.77 (m, 4H) ppm

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.37, 166.59, 141.38, 130.09, 129.81, 125.68, 83.54, 52.23, 41.98, 33.95, 22.43, 11.81 ppm

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{14}H_{16}O_4Na$: 271.0946 Found: 271.0945

## 11n *cis*-4-(3-ethyl-5-oxotetrahydrofuran-2-yl)benzonitrile

$^1$H NMR(Chloroform-*d*, 400 MHz): δ = 7.76 – 7.64 (m, 2H), 7.43 – 7.35 (m, 2H), 5.66 (d, 1H, *J*=6.5 Hz), 2.82 (dd, 1H, *J*=17.0, 8.0, 0.7 Hz), 2.80 – 2.67 (m, 1H), 2.49 (dd, 1H, *J*=17.0, 4.6 Hz), 1.16 – 0.99 (m, 1H), 0.96 – 0.78 (m, 4H) ppm

$^{13}$C NMR(Chloroform-*d*, 101 MHz): δ = 175.91, 141.71, 132.39, 126.41, 118.35, 112.21, 83.00, 41.83, 33.93, 22.35, 11.72 ppm

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{13}H_{13}NO_2Na$: 238.0844 Found: 238.0839

## 11o *trans*-5-(4-(dimethylamino)phenyl)-4-ethyldihydrofuran-2(3H)-one

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 6.72 (d, *J* = 8.3 Hz, 2H), 4.94 (d, *J* = 7.9 Hz, 1H), 2.97 (s, 6H), 2.85 – 2.72 (m, 1H), 2.46 – 2.26 (m, 2H), 1.63 (dqd, *J* = 13.6, 7.5, 4.7 Hz, 1H), 1.49 – 1.31 (m, 1H), 0.95 – 0.76 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.66, 150.96, 127.69, 125.43, 112.36, 87.53, 46.15, 40.57, 35.59, 25.11, 12.16.

HRMS-ESI(pos): $[M+H]^+$ Calculated for $C_{14}H_{20}NO_2$: 234.1494 Found: 234.1496

$[M+Na]^+$ Calculated for $C_{14}H_{19}NO_2Na$: 256.1313 Found: 256.1313

## 11p *cis*-4-ethyl-5-styryldihydrofuran-2(3H)-one

$^1$H NMR(400 MHz, $CDCl_3$) δ 7.54 – 7.20 (m, 5H), 6.70 (dd, 1H, *J*=15.9, 1.2 Hz), 6.20 (ddd, 1H, *J*=15.9, 7.1, 2.2 Hz), 5.19 (td, 1H, *J*=7.0, 1.3 Hz), 2.80 – 2.54 (m, 2H), 2.44 – 2.25 (m, 1H), 1.72 – 1.52 (m, 1H), 1.50 – 1.32 (m, 1H), 1.12 – 0.88 (m, 3H) ppm

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.58, 176.20, 135.82, 133.62, 128.73, 128.34, 126.70, 123.01, 83.22, 41.82, 33.65, 22.71, 12.14.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{14}H_{16}O_2Na$: 239.1048 Found: 239.1050

## 11q *cis*-5-(4-bromophenyl)-4-ethyldihydrofuran-2(3H)-one

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.49 (m, 2H), 7.17 – 7.08 (m, 2H), 5.58 (d, *J* = 6.7 Hz, 1H), 2.83 – 2.59 (m, 2H), 2.45 (dd, *J* = 17.0, 5.5 Hz, 1H), 1.20 – 1.02 (m, 1H), 0.98 – 0.84 (m, 1H), 0.84 – 0.78 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.53, 135.37, 131.70, 127.39, 122.12, 83.49, 77.26, 41.92, 33.91, 22.48, 11.85.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{12}H_{13}BrO_2Na$: 290.9997 Found: 290.9982

## 11r *cis*-4-ethyl-5-(p-tolyl)dihydrofuran-2(3H)-one

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H), 7.14 – 7.07 (m, 2H), 5.58 (d, *J* = 6.7 Hz, 1H), 2.78 – 2.58 (m, 2H), 2.49 – 2.40 (m, 1H), 2.36 (s, 3H), 1.22 – 1.07 (m, 1H), 0.95 – 0.82 (m, 1H), 0.82 – 0.75 (m, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 177.12, 138.10, 133.41, 129.29, 125.84, 84.41, 42.34, 34.08, 22.77, 21.29, 12.11.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{13}H_{16}O_2Na$: 227.1048 Found: 227.1037

## 11s *cis*-4-butyl-5-(4-fluorophenyl)dihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.07 (td, *J* = 8.7, 2.1 Hz, 2H), 5.59 (d, *J* = 6.3 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.49 – 2.35 (m, 1H), 1.33 – 1.16 (m, 1H), 1.20 – 1.06 (m, 2H), 1.10 – 0.98 (m, 2H), 0.92 – 0.80 (m, 1H), 0.78 (td, *J* = 7.2, 2.2 Hz, 3H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.76, 162.47 (d, *J* = 246.8 Hz), 132.14 (d, *J* = 3.2 Hz), 127.48 (d, *J* = 8.2 Hz), 115.49 (d, *J* = 21.6 Hz), 83.63, 40.31, 34.25, 29.59, 29.08, 22.43, 13.82.

$^{19}$F NMR (376 MHz, $CDCl_3$) δ -116.85.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{14}H_{17}FO_2Na$: 259.1105 Found: 259.1107

## 11t *cis*-5-(4-fluorophenyl)-4-((trimethylsilyl)methyl)dihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.15 (m, 2H), 7.15 – 7.07 (m, 2H), 5.56 (d, *J* = 6.5 Hz, 1H), 2.86 (ddtd, *J* = 12.5, 7.8, 6.6, 2.5 Hz, 1H), 2.76 (dd, *J* = 16.9, 7.8 Hz, 1H), 2.34 (dd, *J* = 16.9, 6.8 Hz, 1H), 0.32 (dd, *J* = 14.6, 2.6 Hz, 1H), 0.10 (dd, *J* = 14.6, 12.7 Hz, 1H), -0.01 (s, 9H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.67, 162.50 (d, *J* = 246.9 Hz), 132.13 (d, *J* = 3.2 Hz), 127.66 (d, *J* = 8.1 Hz), 115.54 (d, *J* = 21.7 Hz), 85.07, 77.23, 36.98, 36.06, 16.94, -1.10.

$^{19}$F NMR (376 MHz, $CDCl_3$) δ -116.97.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{14}H_{19}FO_2SiNa$: 289.1031 Found: 289.1028

## 11u *cis*-4-(4-bromobutyl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 2H), 7.14 – 7.03 (m, 2H), 5.60 (d, *J* = 6.4 Hz, 1H), 3.29 (td, *J* = 6.5, 1.0 Hz, 2H), 2.82 – 2.68 (m, 2H), 2.52 – 2.38 (m, 1H), 1.71 (ddt, *J* = 8.5, 7.6, 6.4 Hz, 2H), 1.46 – 1.19 (m, 2H), 1.07 (ddt, *J* = 15.8, 10.4, 5.1 Hz, 1H), 0.90 (dtd, *J* = 13.3, 10.4, 5.1 Hz, 1H).

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.40, 162.70 (d, *J* = 247.2 Hz), 131.98 (d, *J* = 3.2 Hz), 127.57 (d, *J* = 8.1 Hz), 115.82 (d, *J* = 21.6 Hz), 83.52, 40.45, 34.38, 33.36, 32.44, 28.81, 26.19.

$^{19}$F NMR (376 MHz, $CDCl_3$) δ -116.55.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{14}H_{16}BrFO_2Na$: 337.0210 Found: 337.0197

11x *cis*-5-(3-bromophenyl)-4-ethyldihydrofuran-2(3H)-one

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.49 (ddd, 1H, *J*=7.9, 2.1, 1.0 Hz), 7.41 (t, 1H, *J*=1.9 Hz), 7.28 (t, 1H, *J*=7.8 Hz), 7.18 (ddd, 1H, *J*=6.9, 1.8, 0.9 Hz), 5.59 (d, 1H, *J*=6.7 Hz), 2.84 – 2.73 (m, 1H), 2.76 – 2.62 (m, 1H), 2.48 (dd, 1H, *J*=17.0, 5.3 Hz), 1.21 – 1.09 (m, 1H), 0.95 – 0.79 (m, 4H) ppm

$^{13}$C NMR (101 MHz, $CDCl_3$) δ 176.33, 138.65, 131.32, 130.10, 128.73, 124.31, 122.79, 83.21, 41.97, 33.89, 22.46, 11.84.

HRMS-ESI(pos): $[M+Na]^+$ Calculated for $C_{12}H_{13}BrO_2Na$: 290.9997 Found: 290.9993

# 12. References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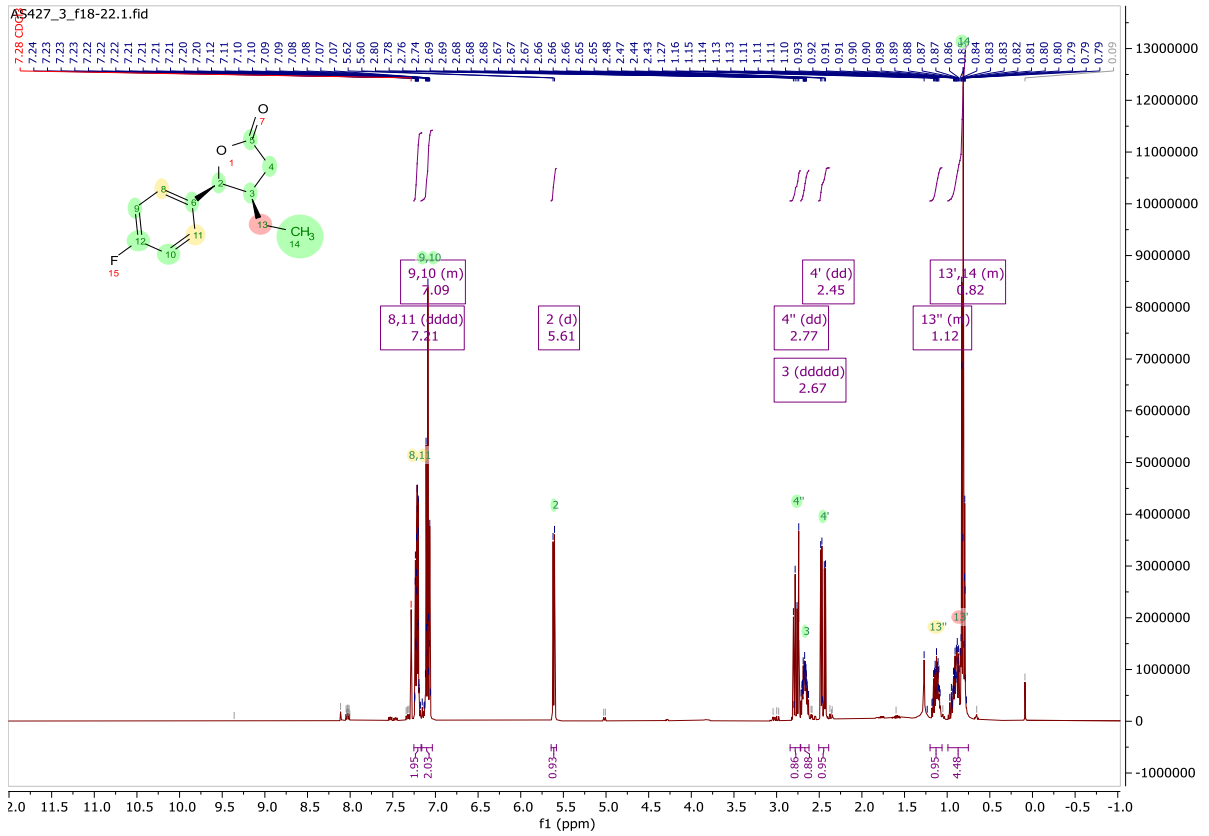
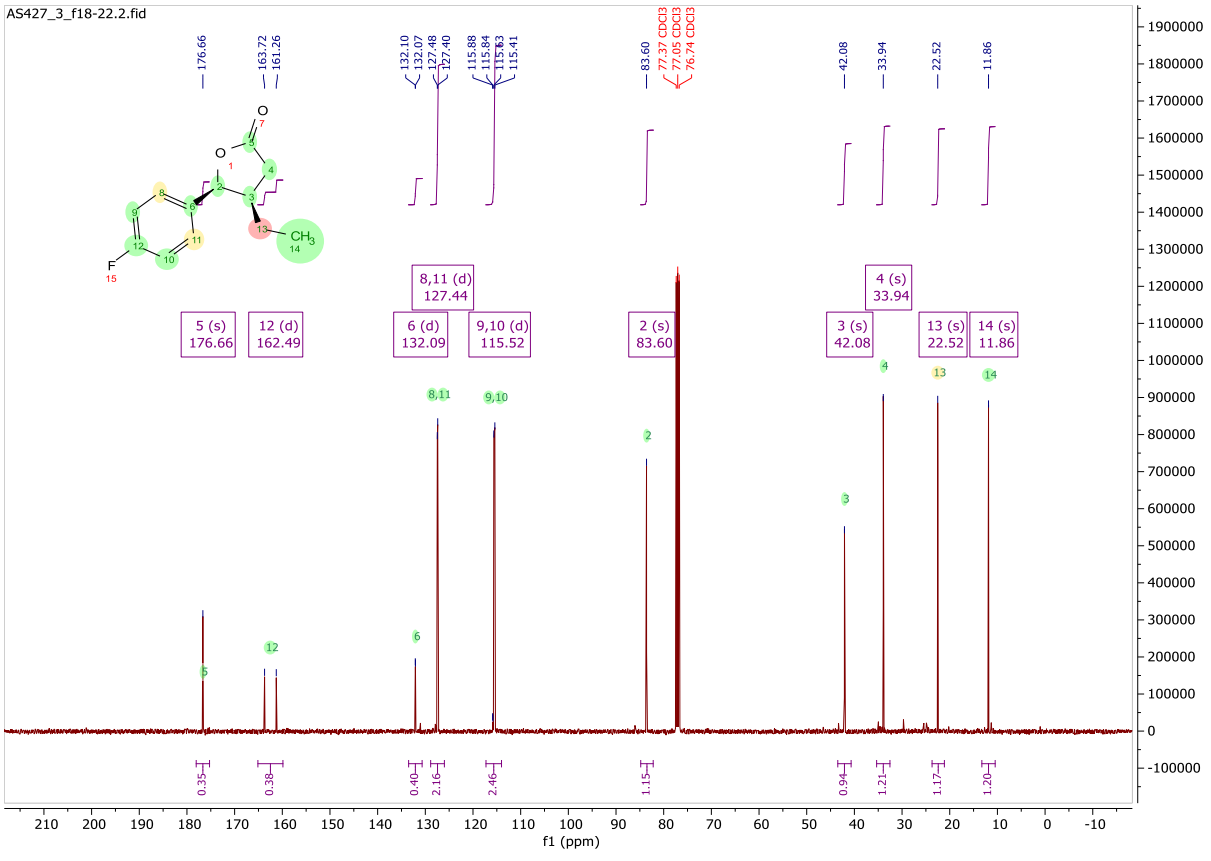
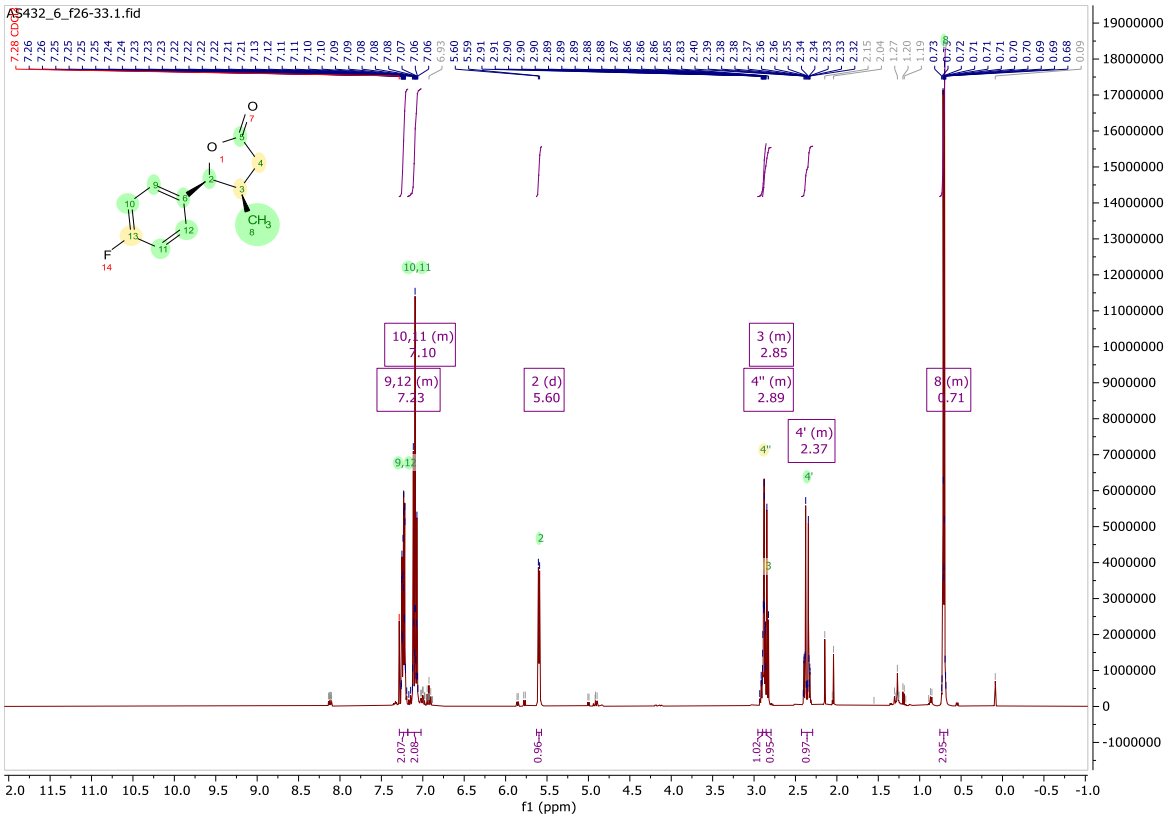
# 13. NMR-spectra

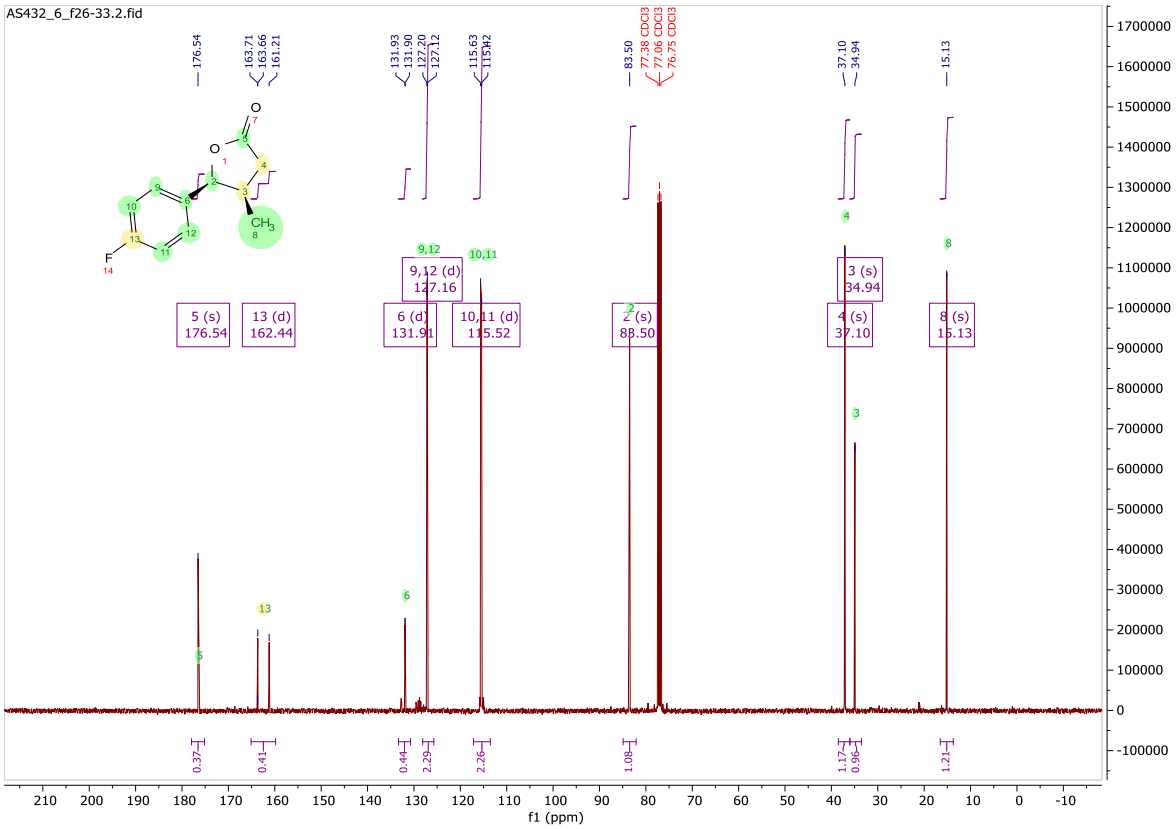
## **11a** *cis*-4-ethyl-5-(4-fluorophenyl)dihydrofuran-2(3H)-one



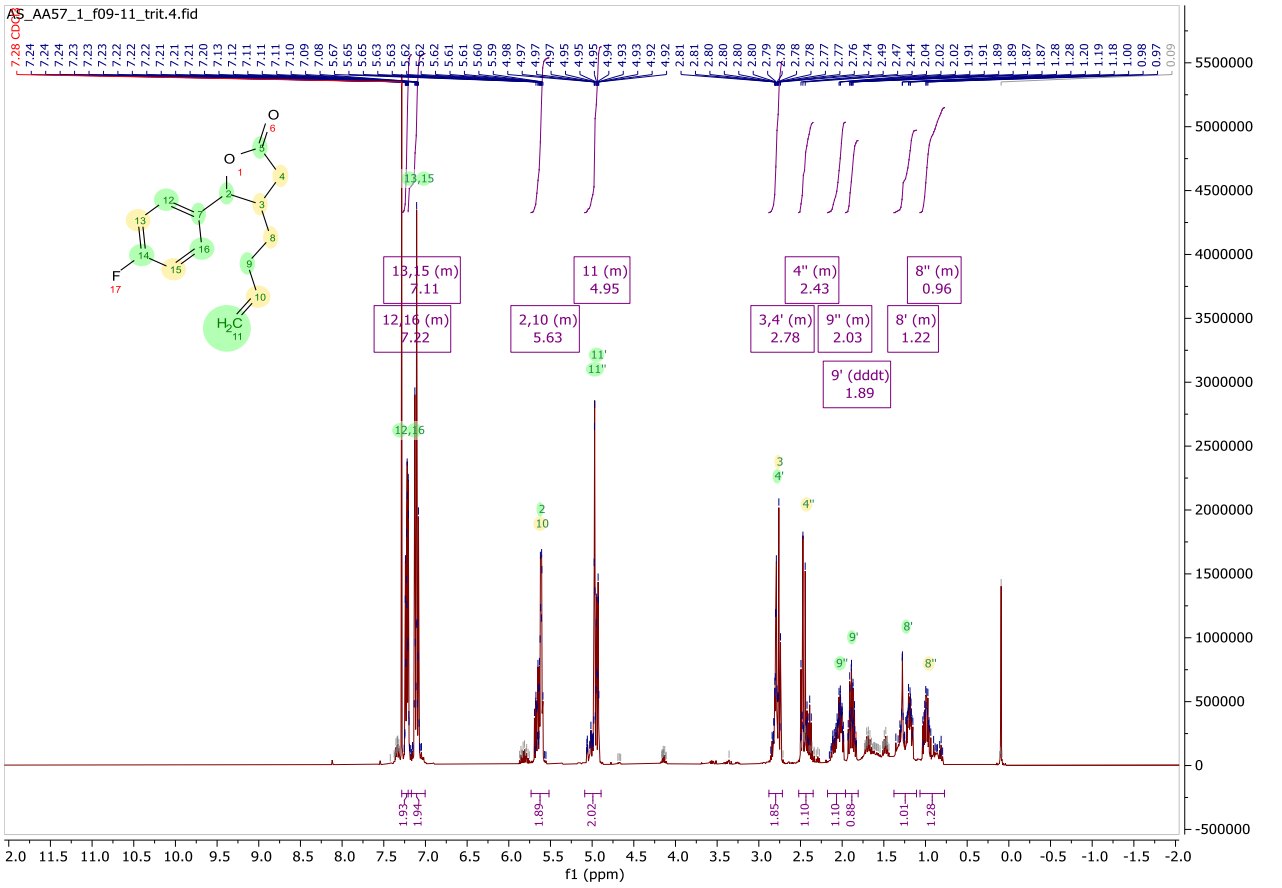



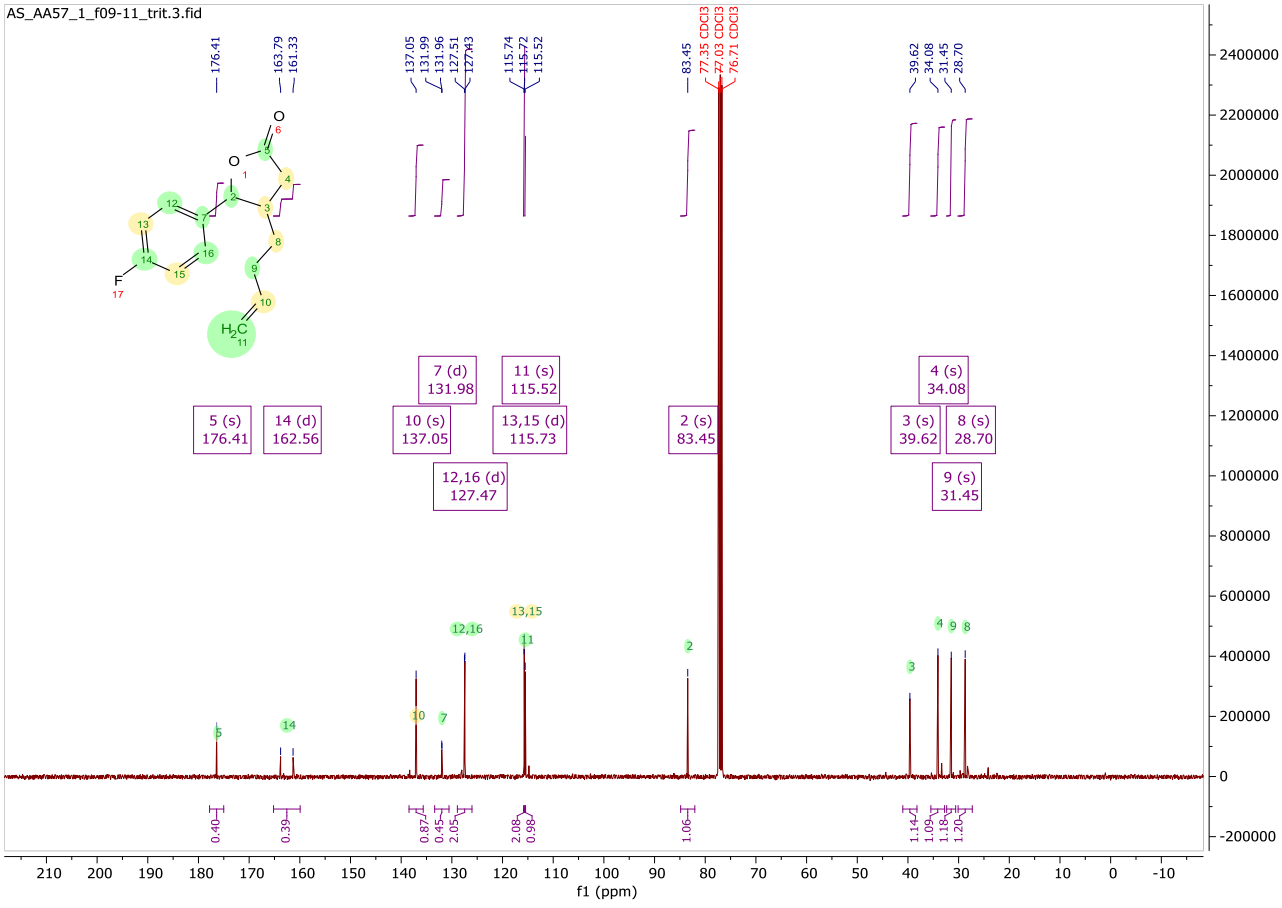
**11b** *cis*-5-(4-fluorophenyl)-4-methyldihydrofuran-2(3H)-one



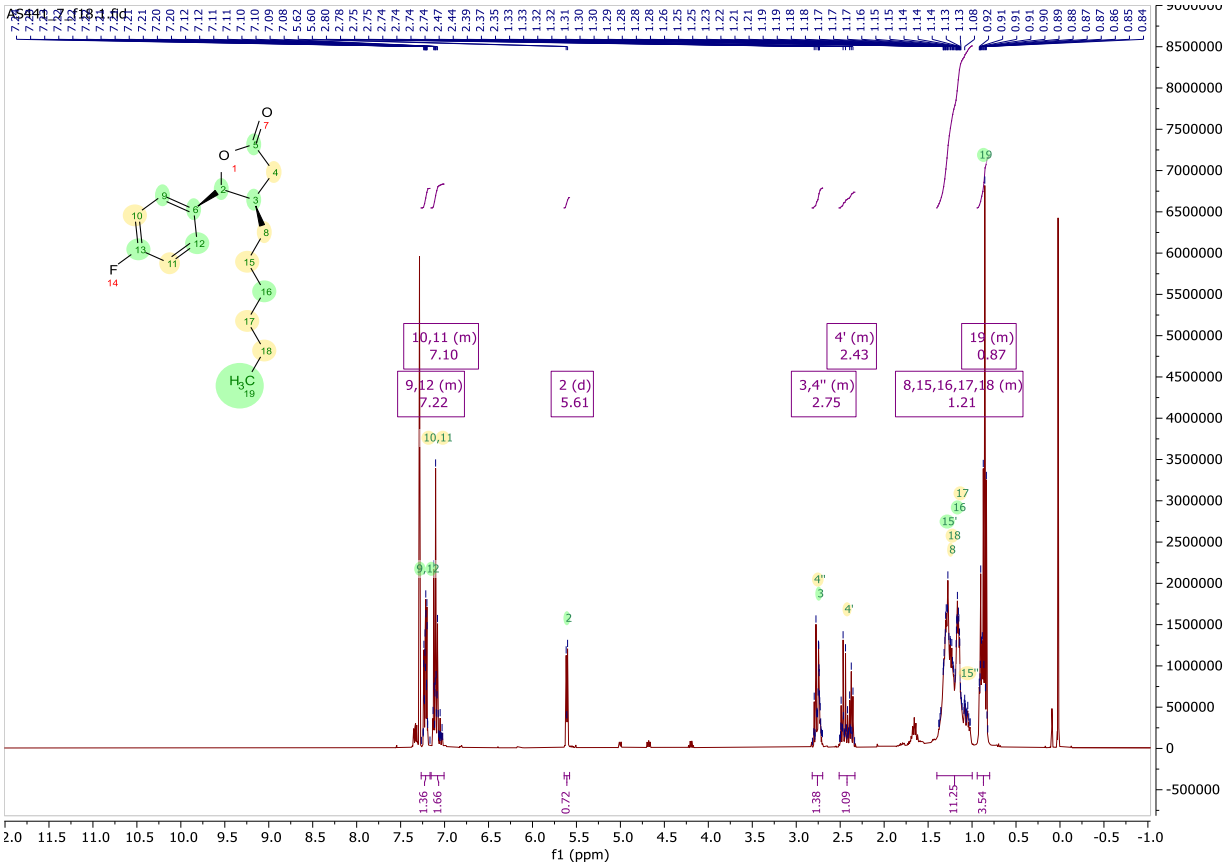



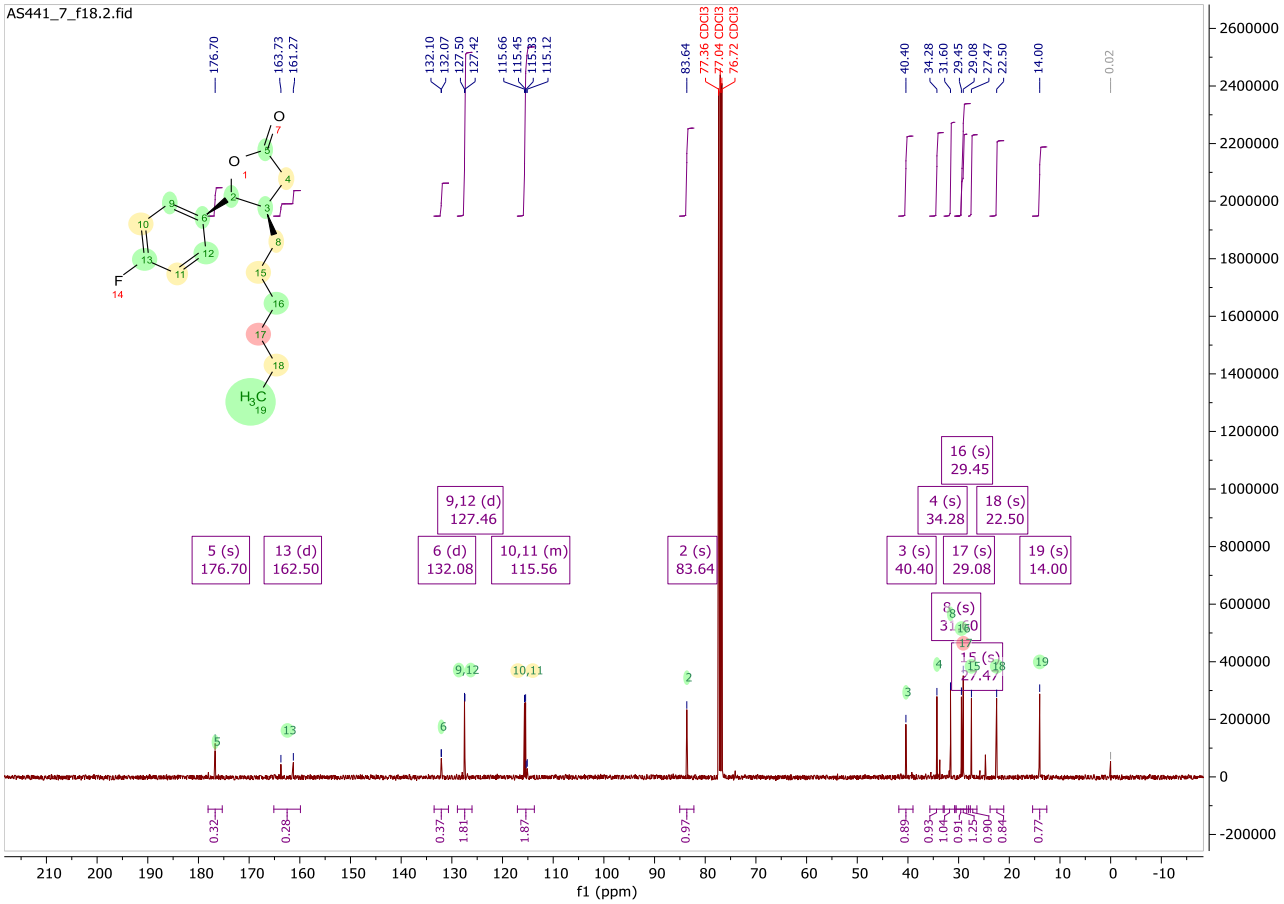
## **11c** *cis*-4-(but-3-en-1-yl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one



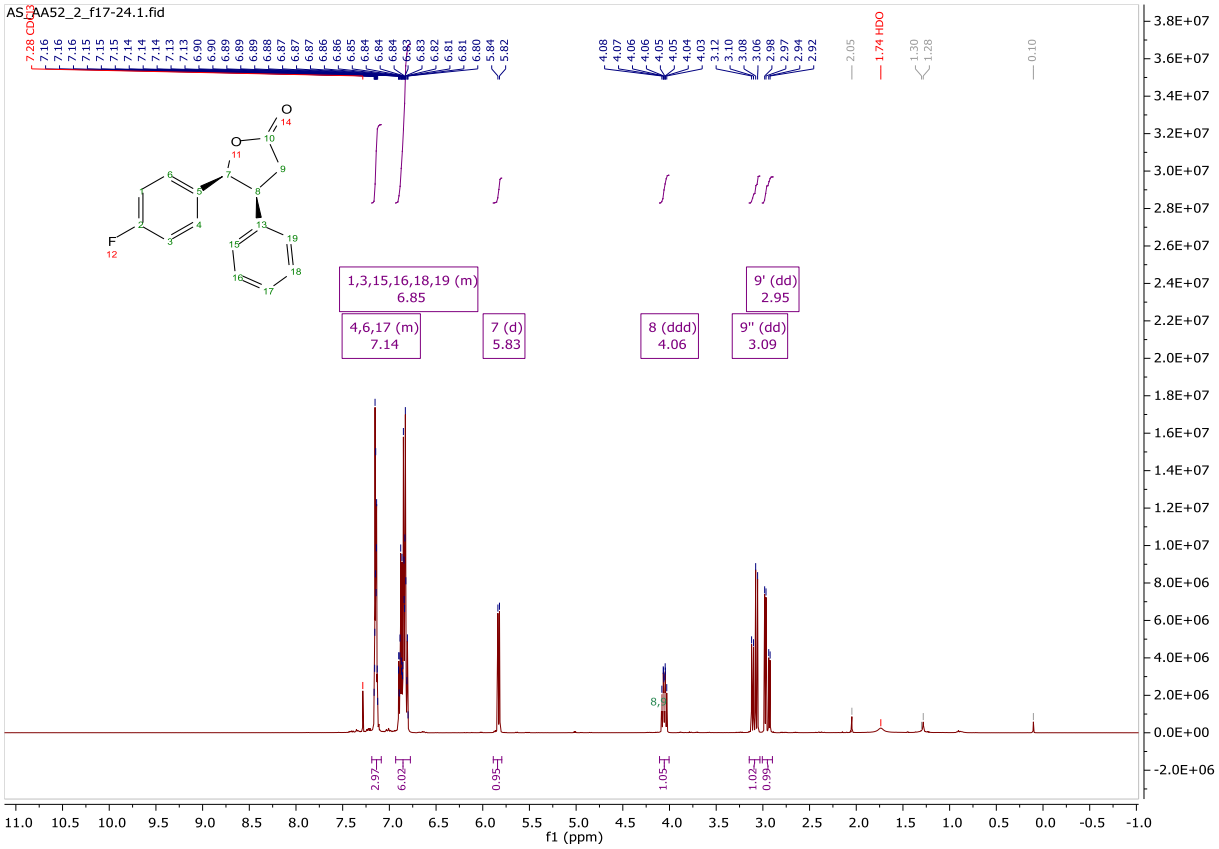



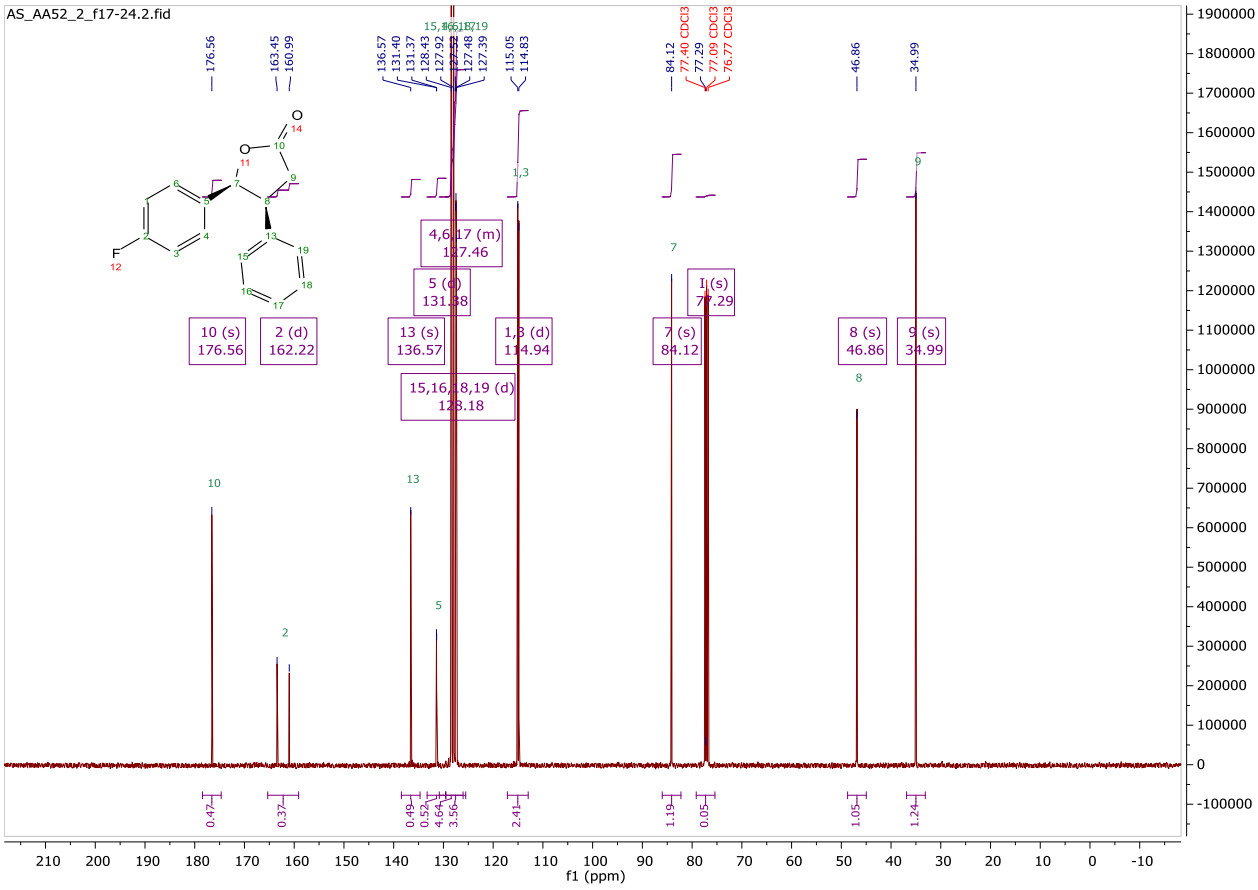
**11d** *cis*-5-(4-fluorophenyl)-4-hexyldihydrofuran-2(3H)-one



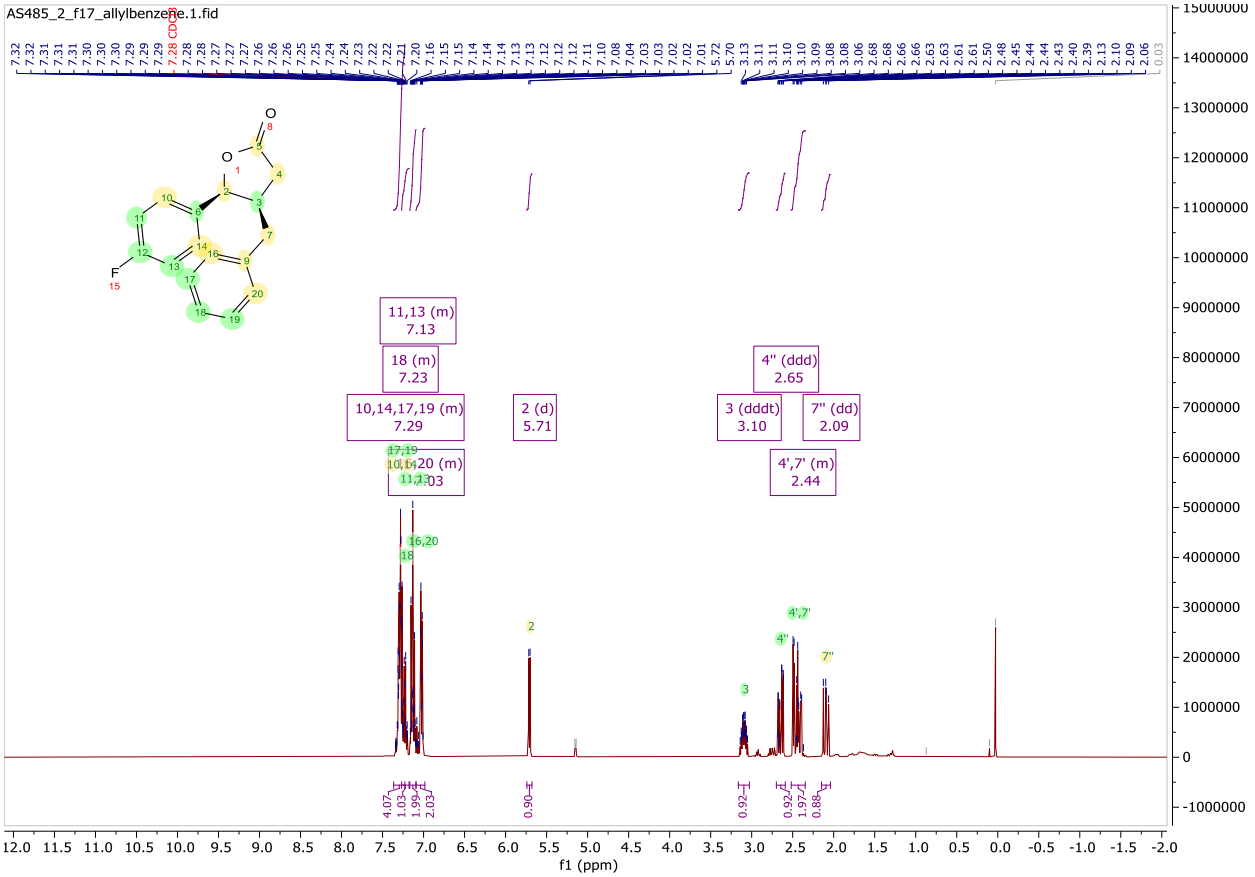



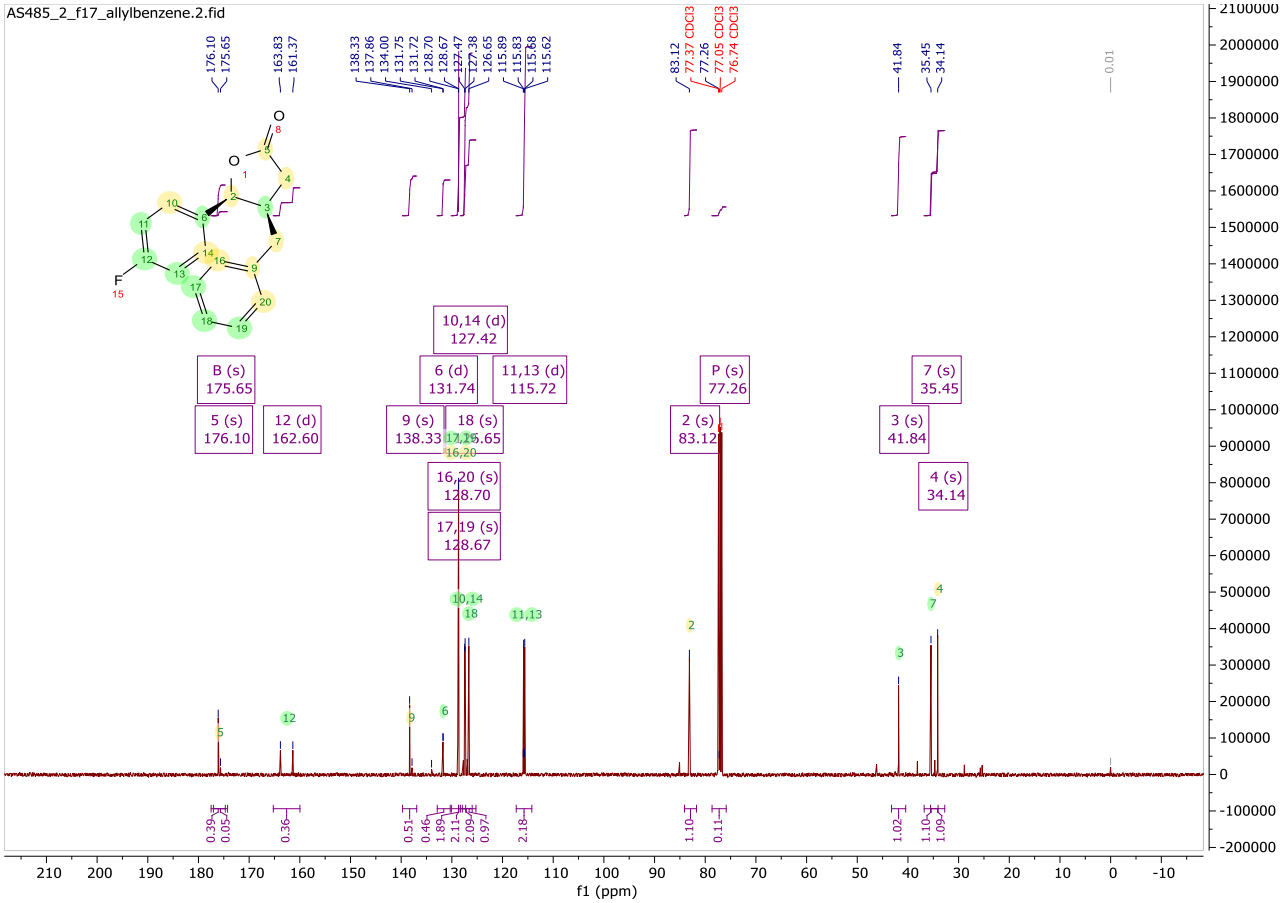
## **11e** *cis*-5-(4-fluorophenyl)-4-phenyldihydrofuran-2(3H)-one



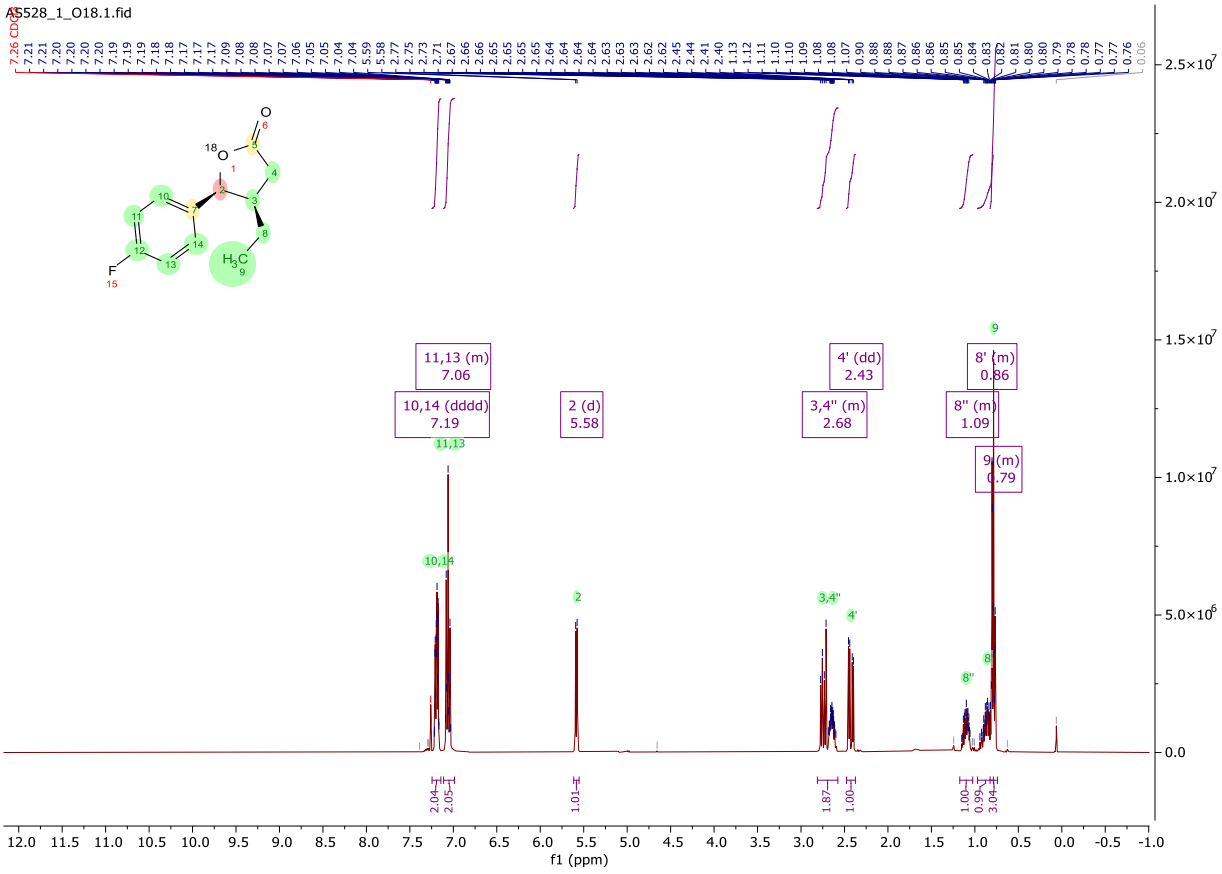



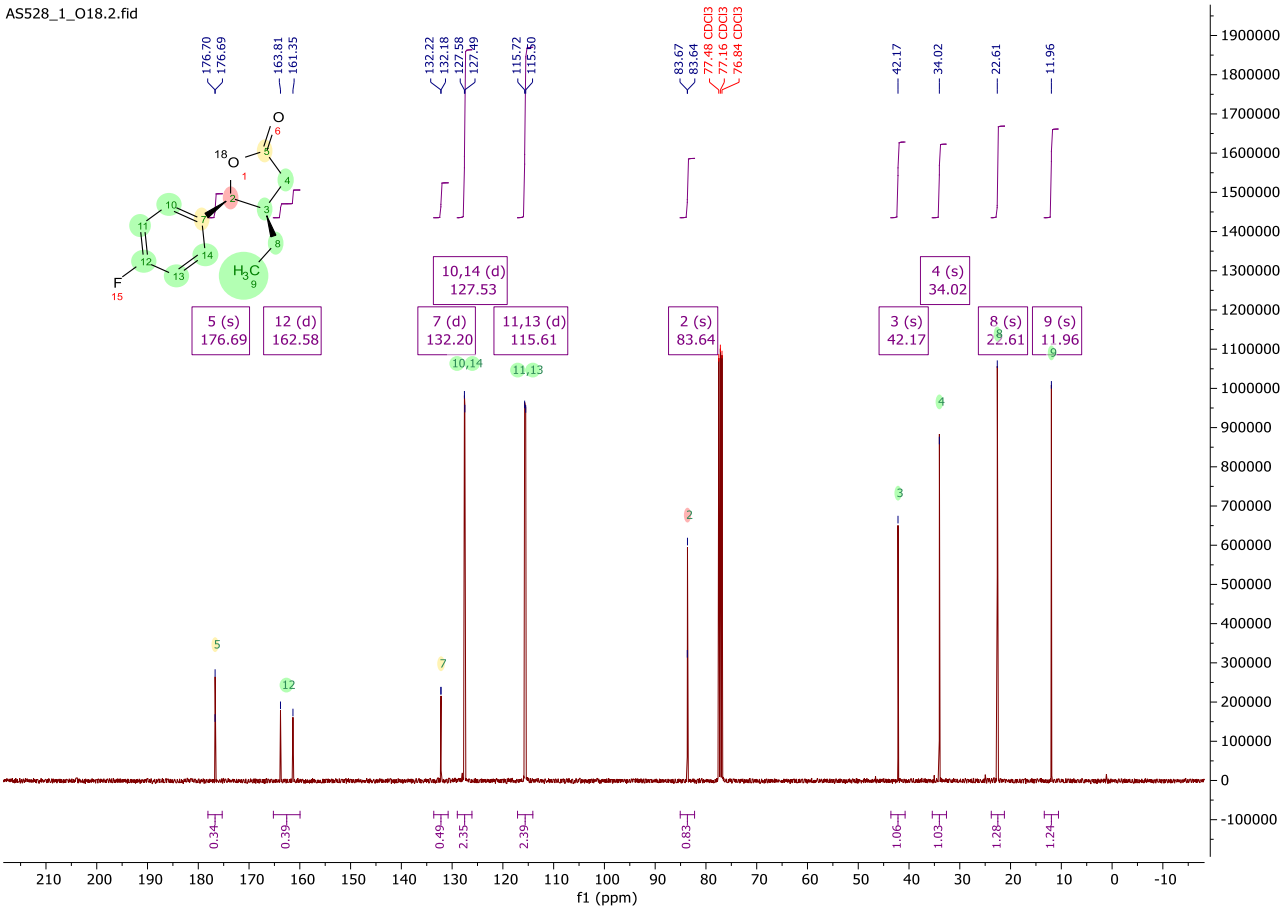
**11f** *cis*-4-benzyl-5-(4-fluorophenyl)dihydrofuran-2(3H)-one 10:1 mixture of cis-trans isomers



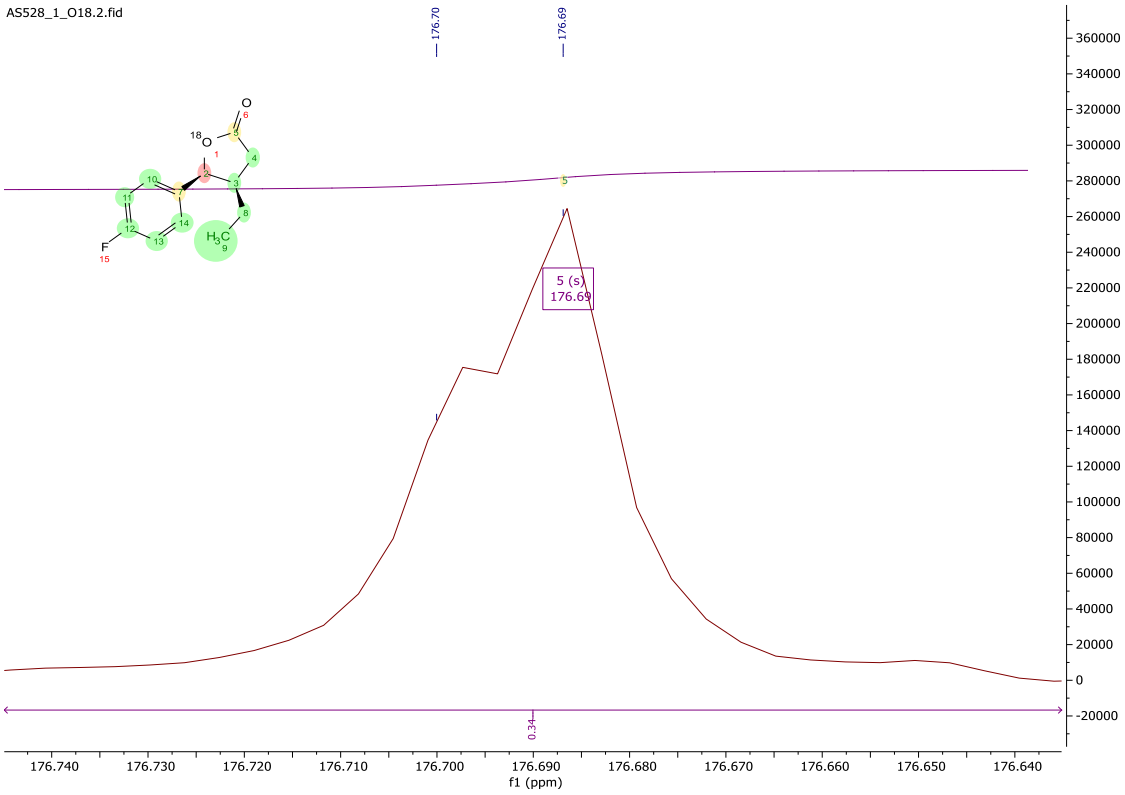



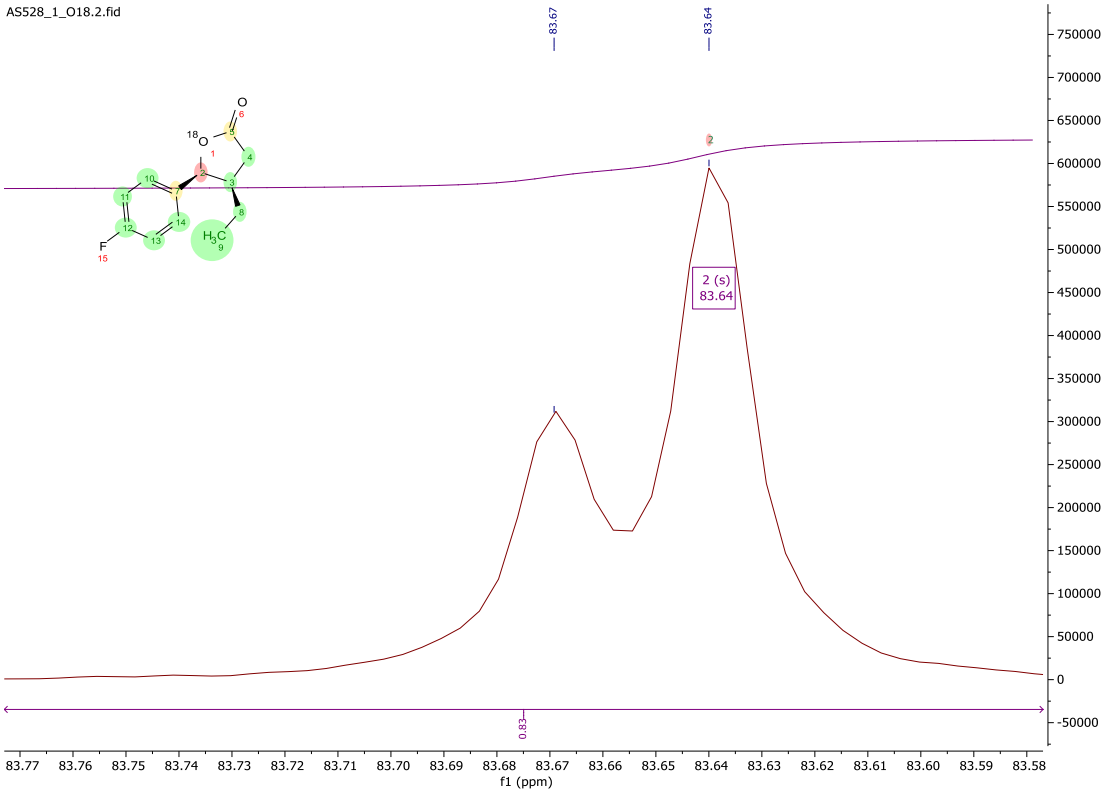
**11g** *cis*-4-ethyl-5-(4-fluorophenyl)dihydrofuran-1-$^{18}$O-2(3H)-one

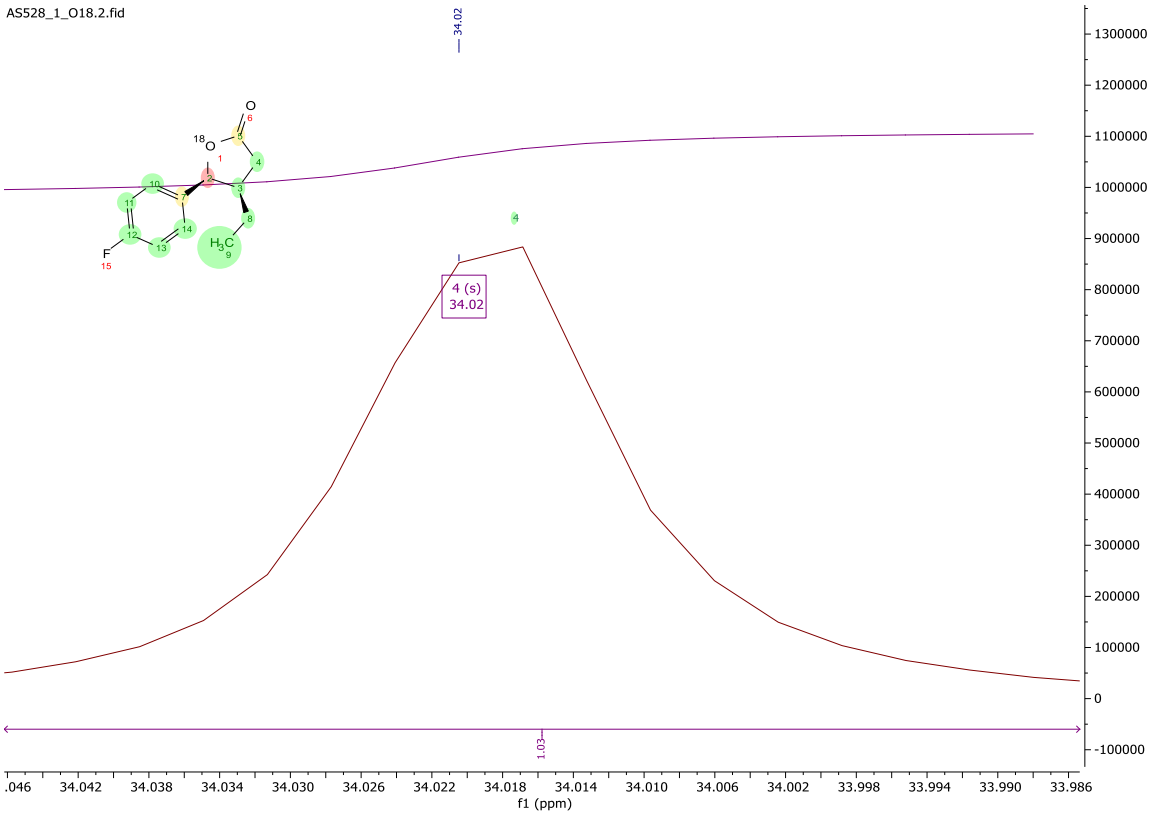


$^{18}O$ has small effect on the closest carbon signals, where the major signal is the $^{18}O$-product and theminor signal is the $^{16}O$-product.

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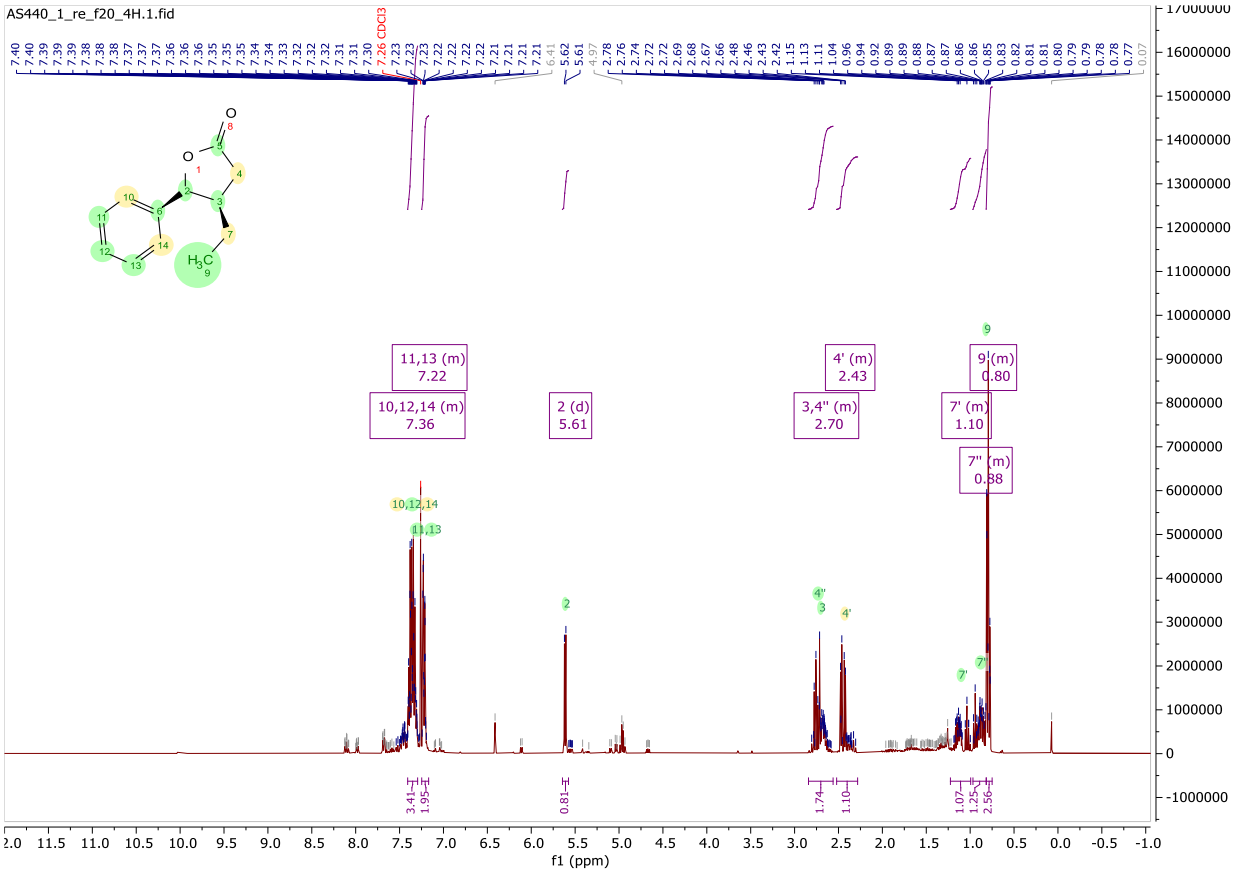
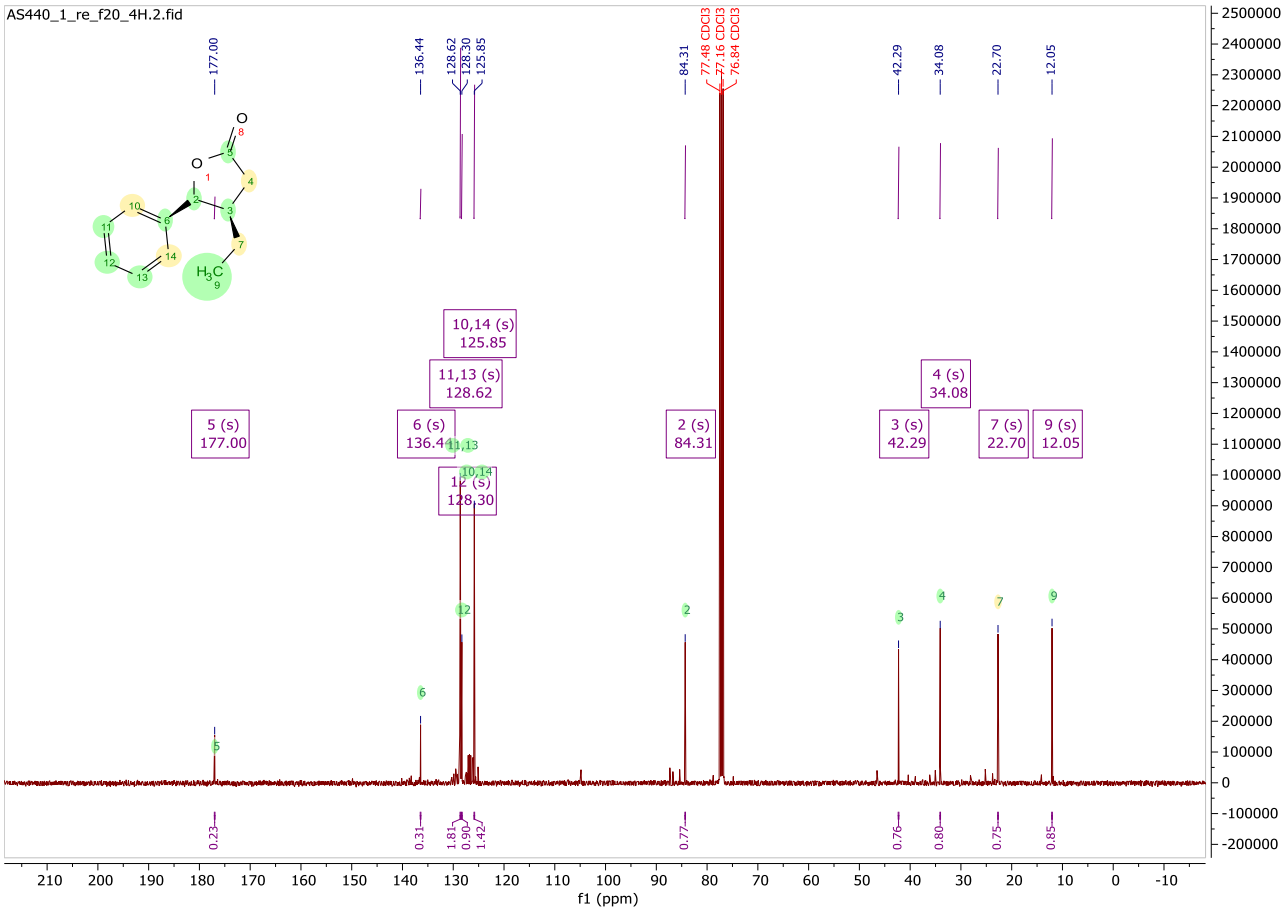
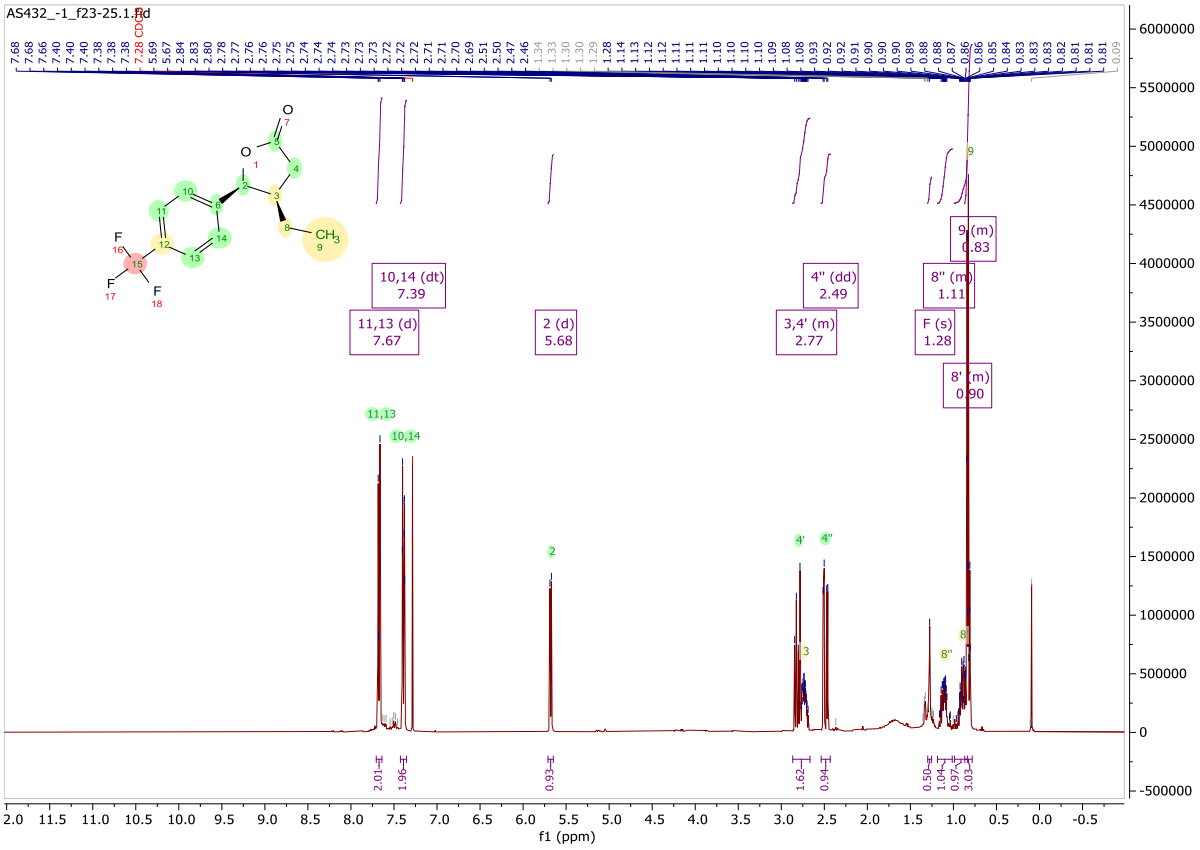
34.02
4 (s)
34.02
1.03
f1 (ppm)

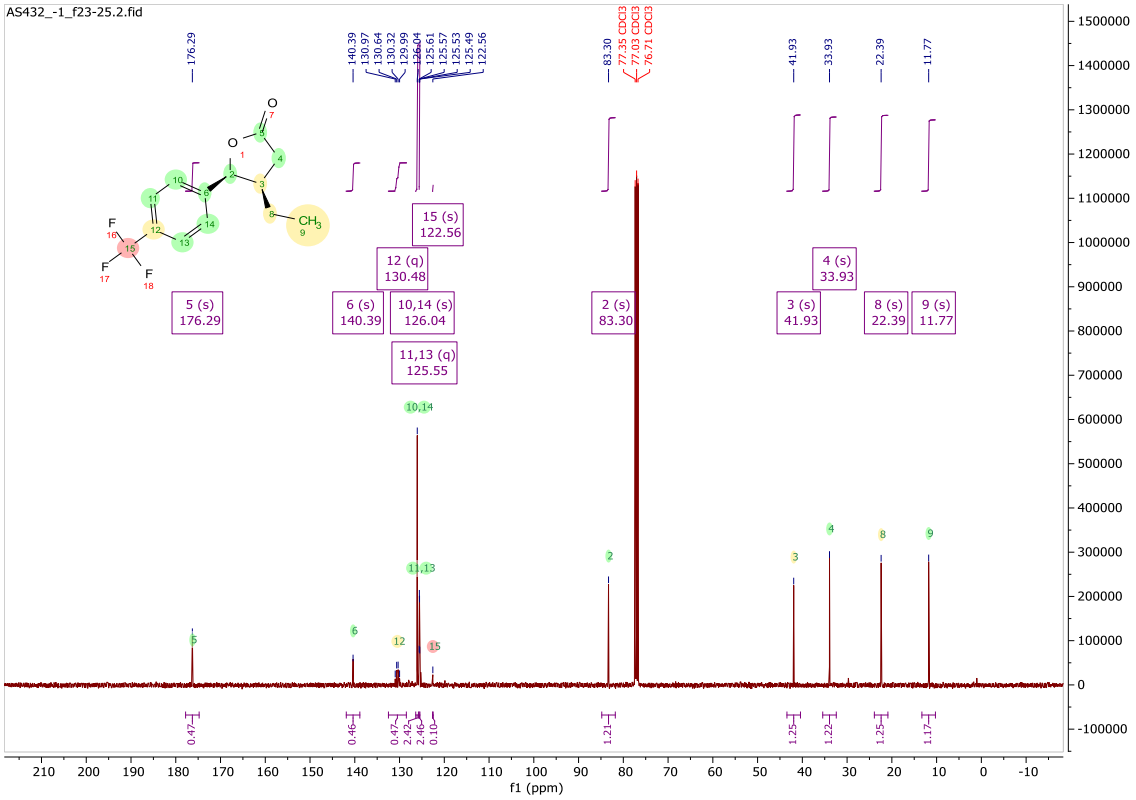
## **11h** *cis*-4-ethyl-5-phenyldihydrofuran-2(3H)-one



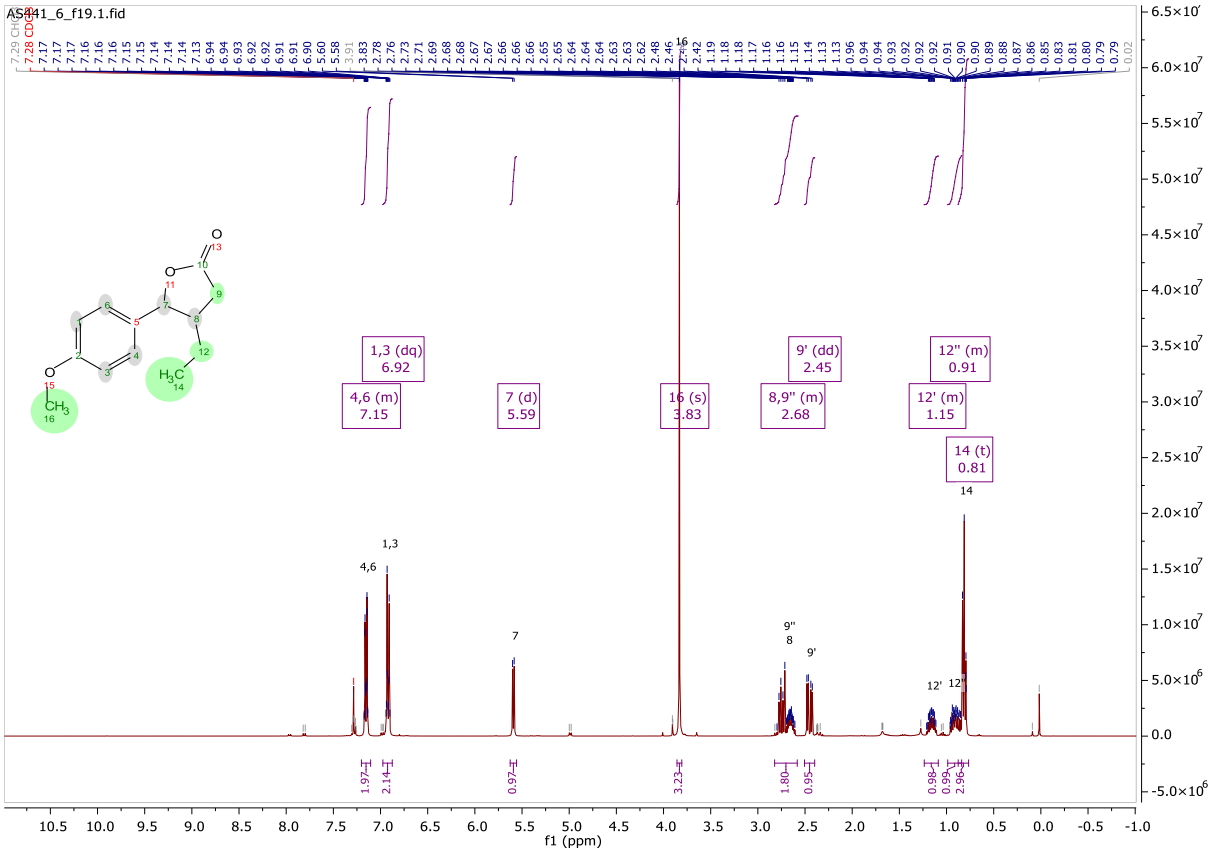



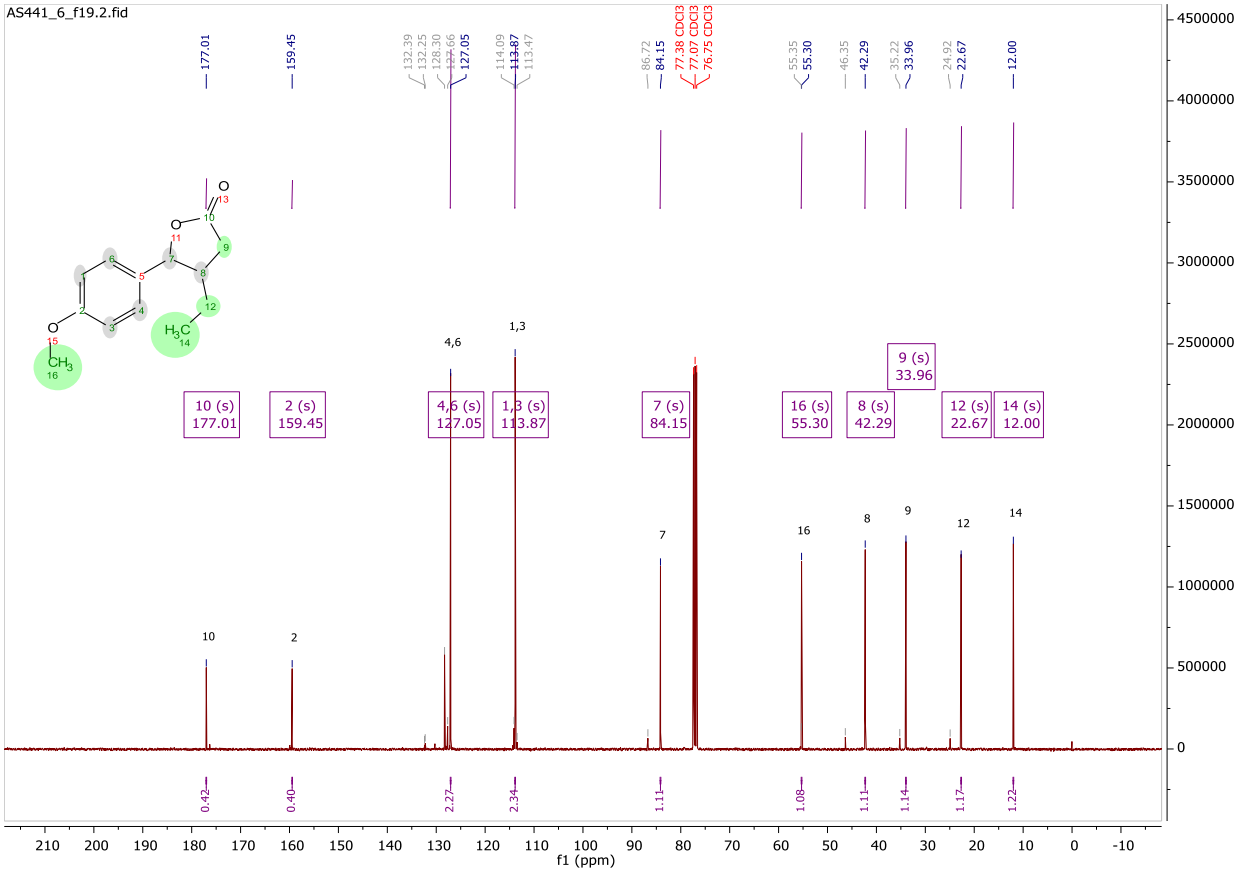
**11i** *cis*-4-ethyl-5-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one



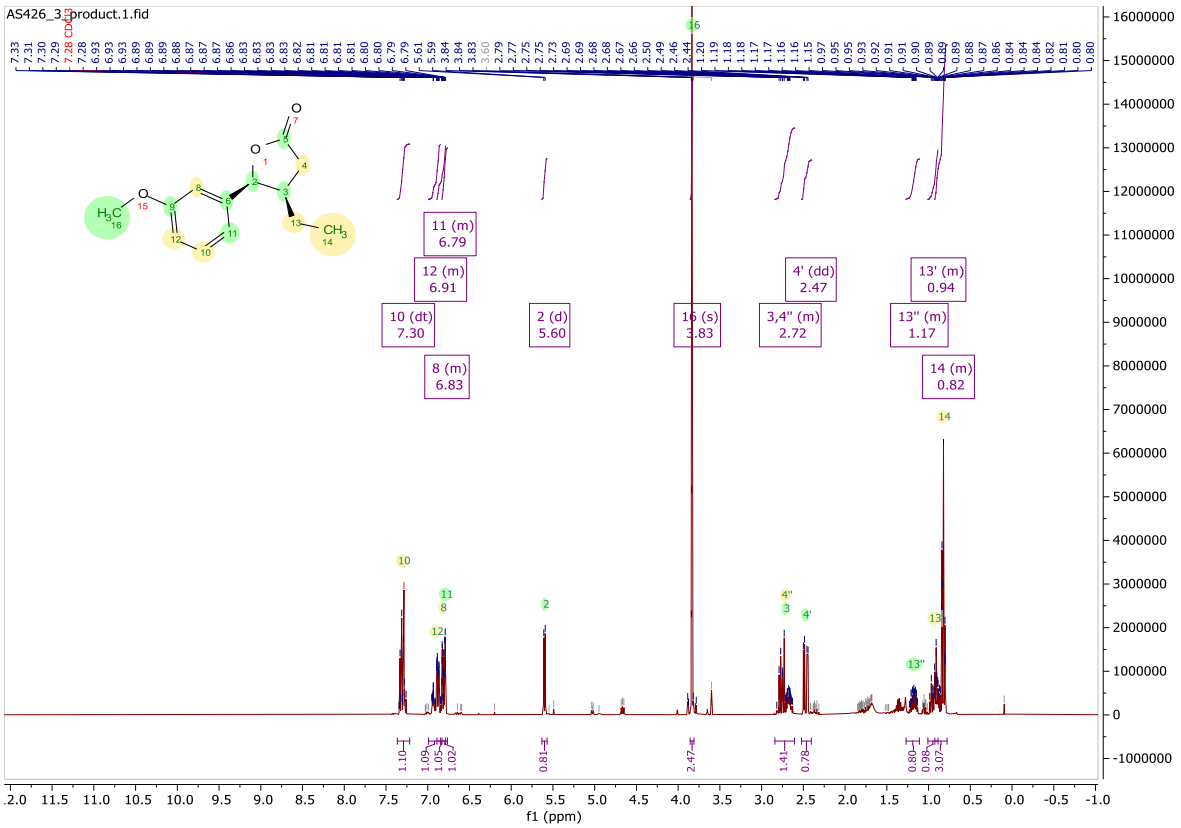
## **11j** *cis*-4-ethyl-5-(4-methoxyphenyl)dihydrofuran-2(3H)-one

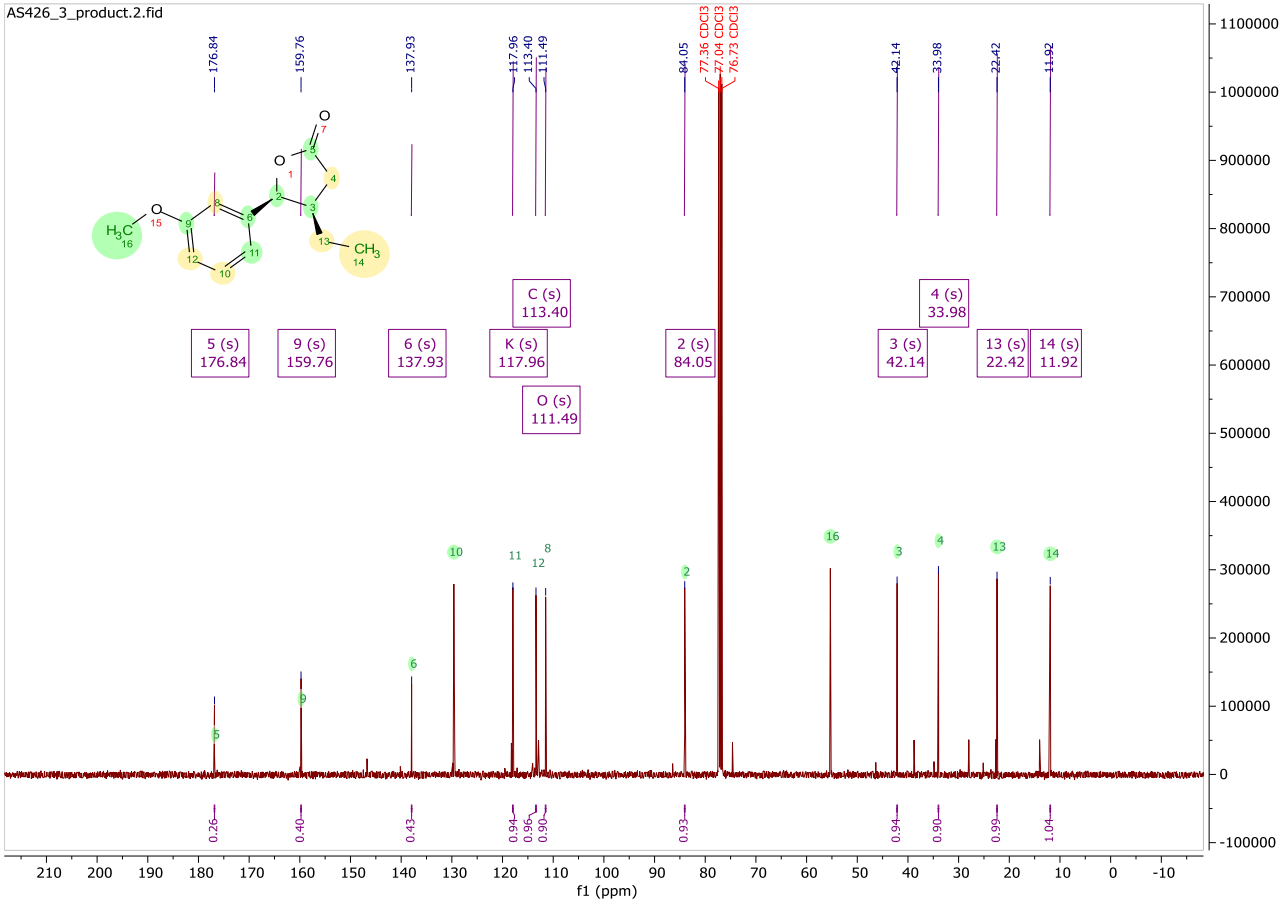


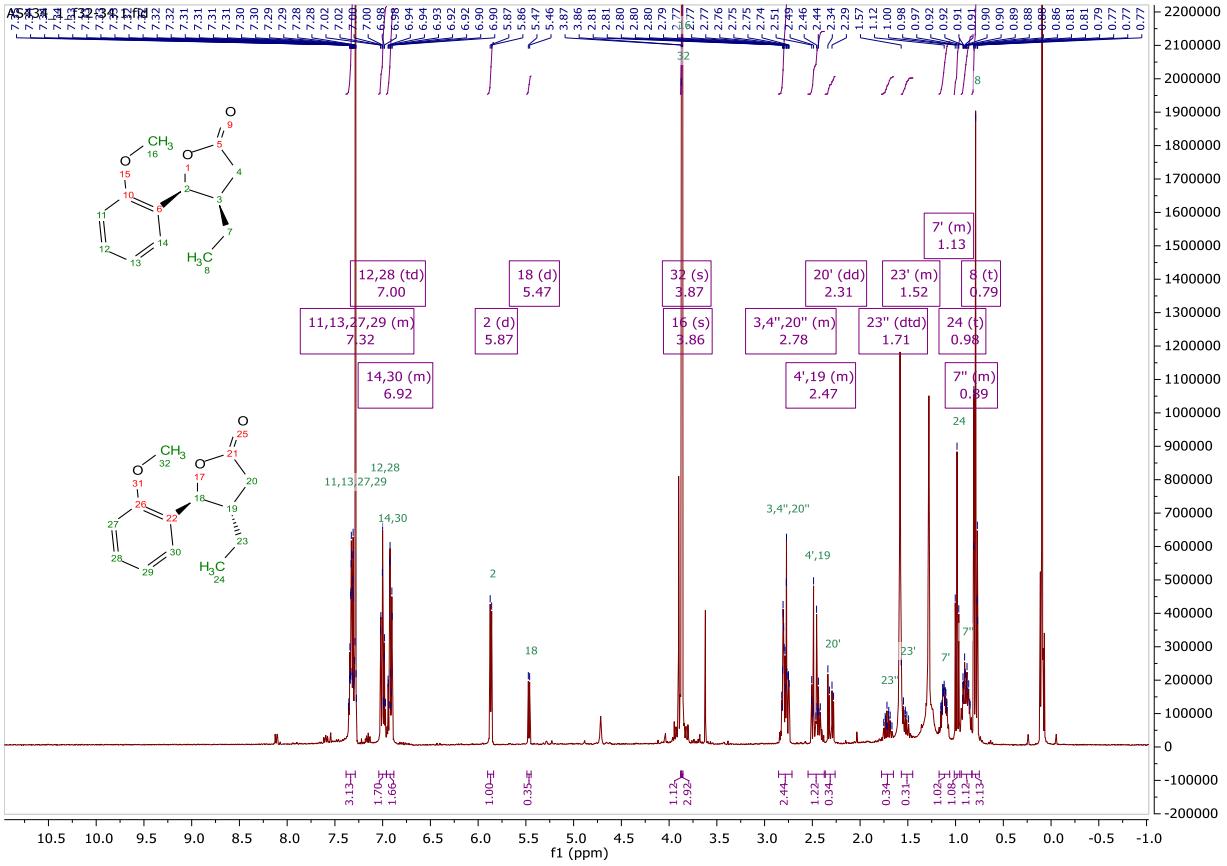
**11k** *cis*-4-ethyl-5-(3-methoxyphenyl)dihydrofuran-2(3H)-one

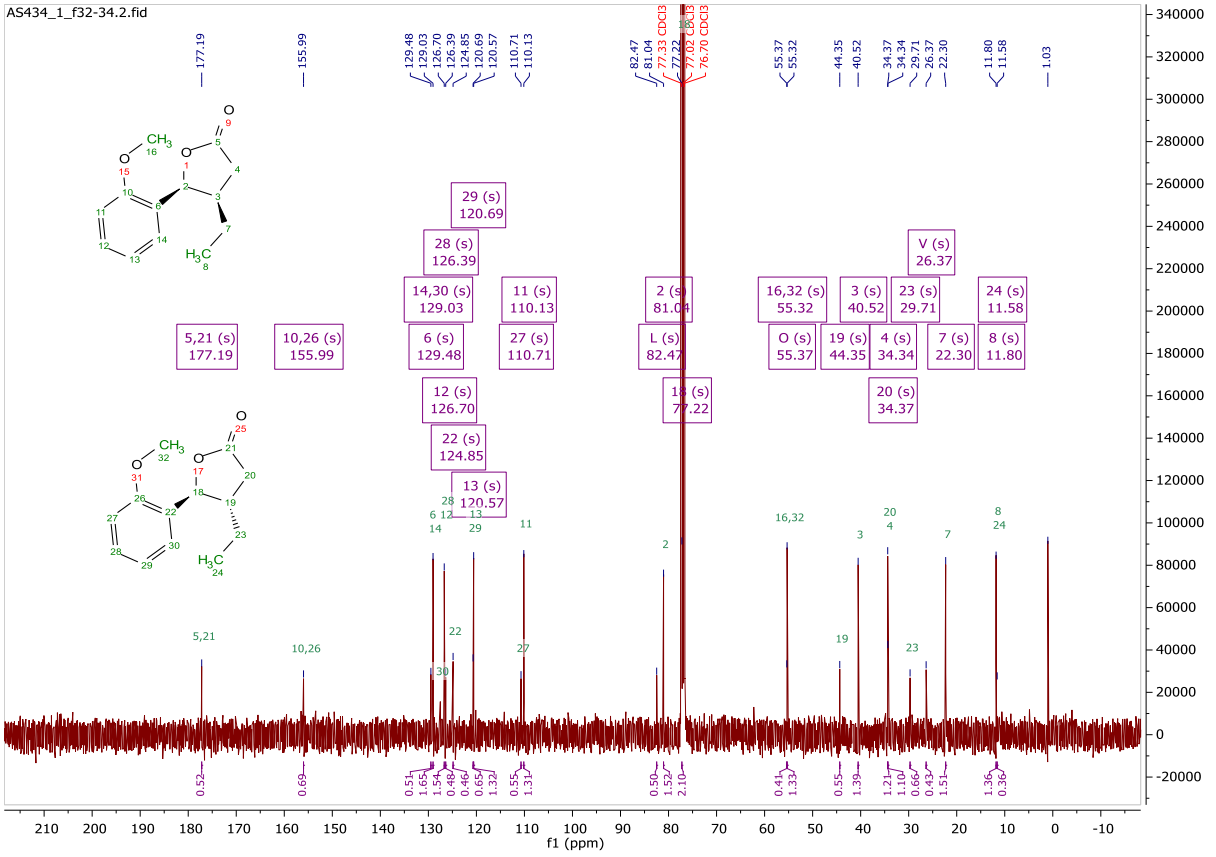
(11:1 mixture of diastereomers)



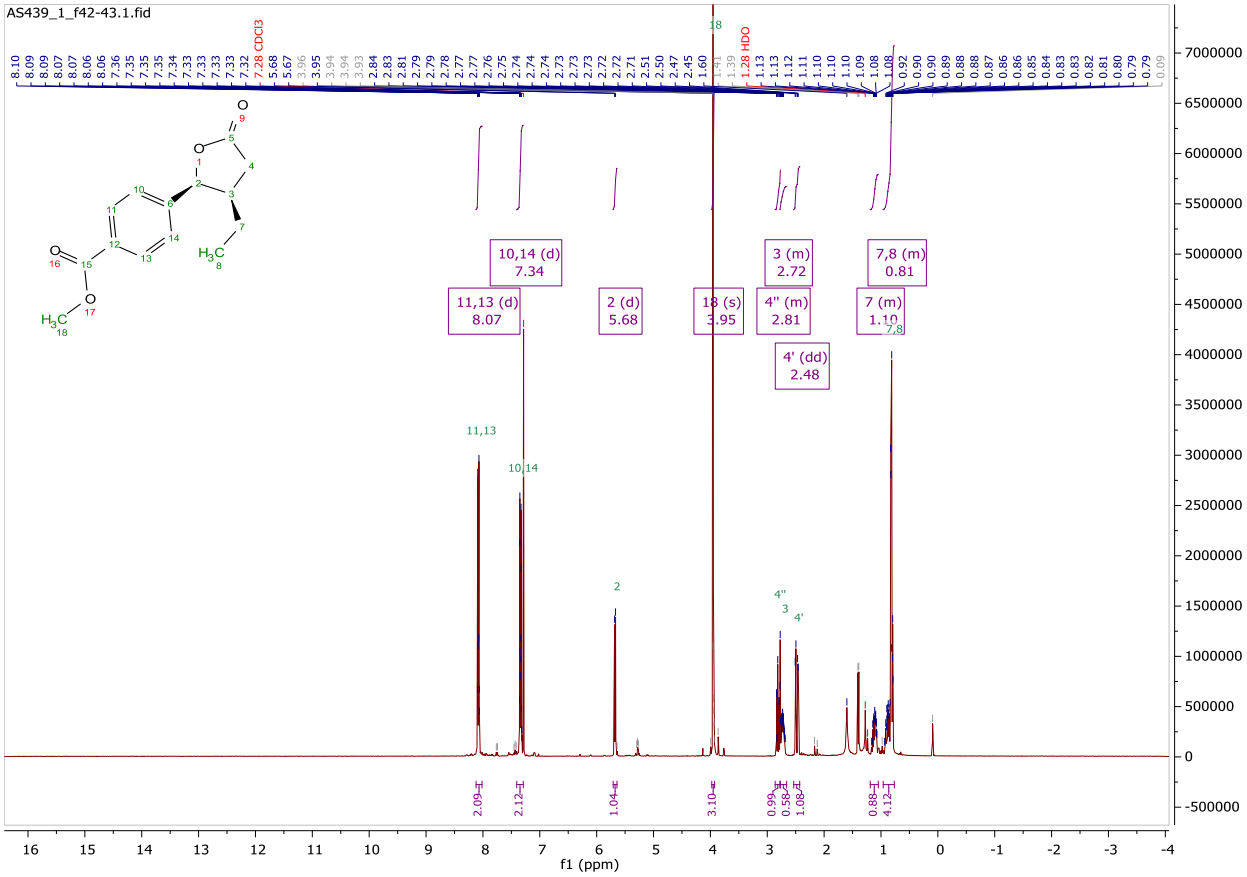



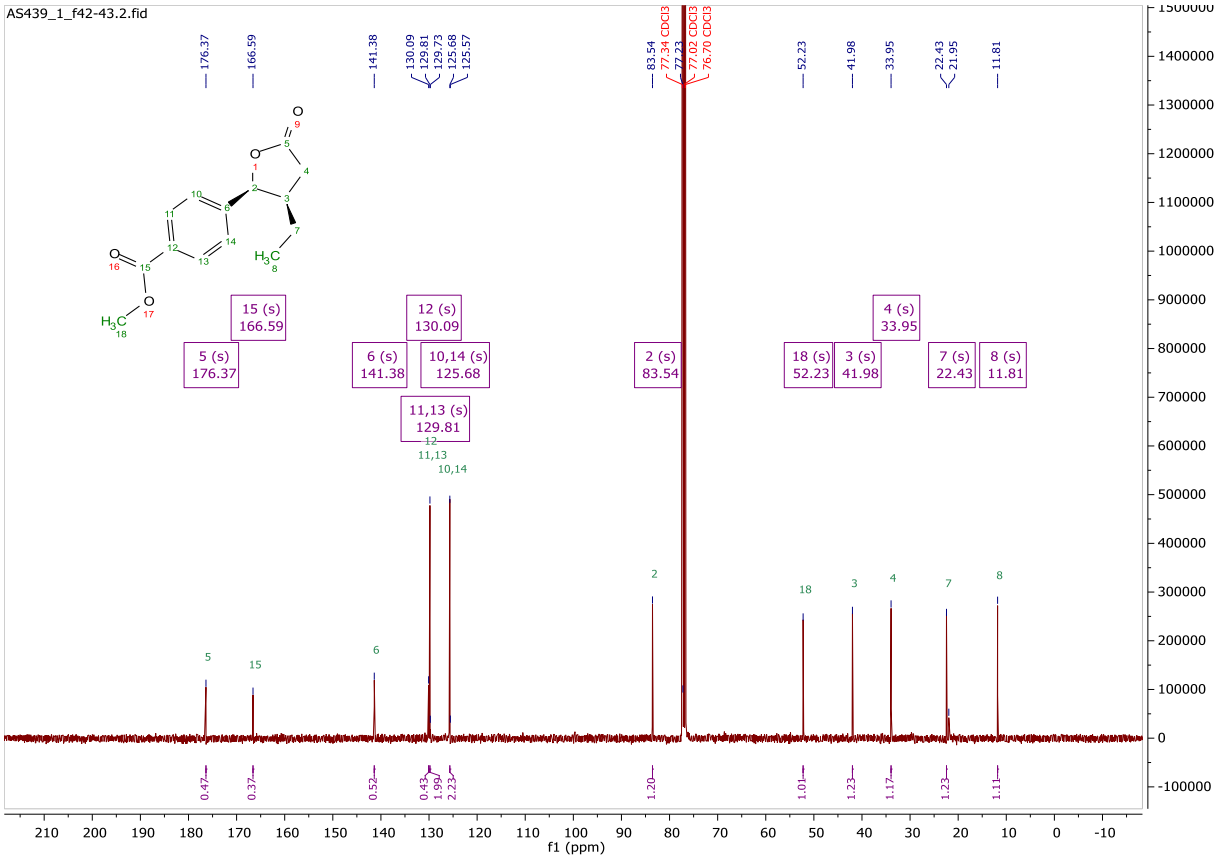
**11l** *cis*-4-ethyl-5-(2-methoxyphenyl)dihydrofuran-2(3H)-one (3:1 mixture of isomers)



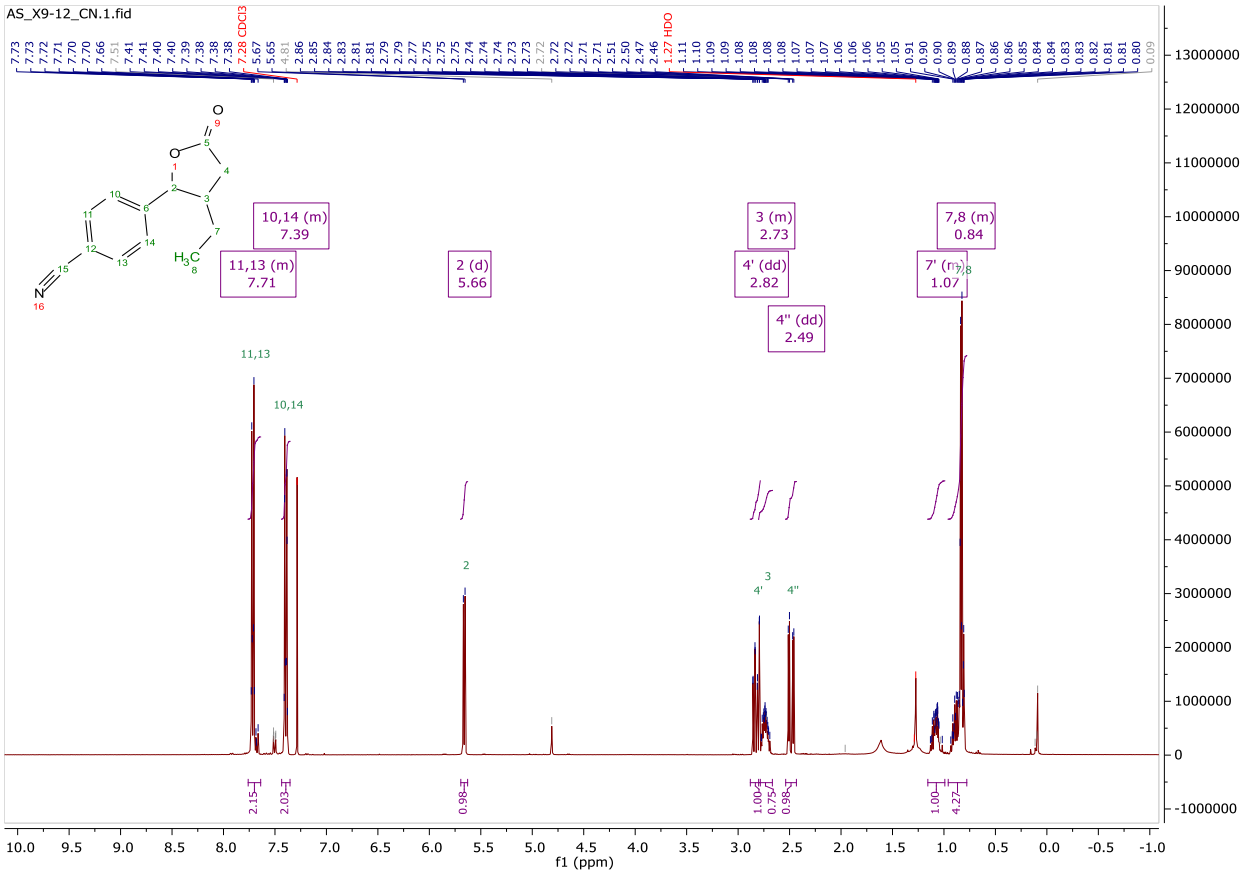



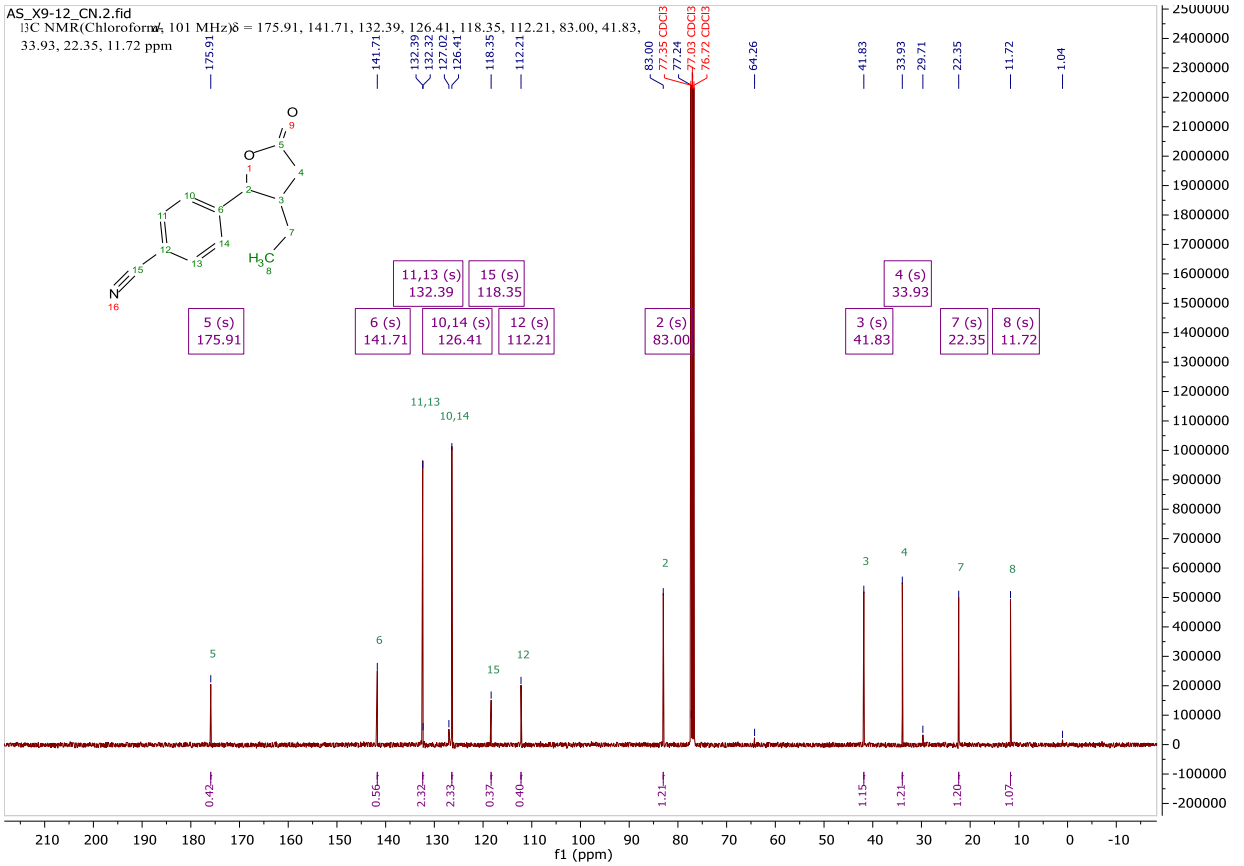
## **11m** *cis*-Methyl 4-(3-ethyl-5-oxotetrahydrofuran-2-yl)benzoate



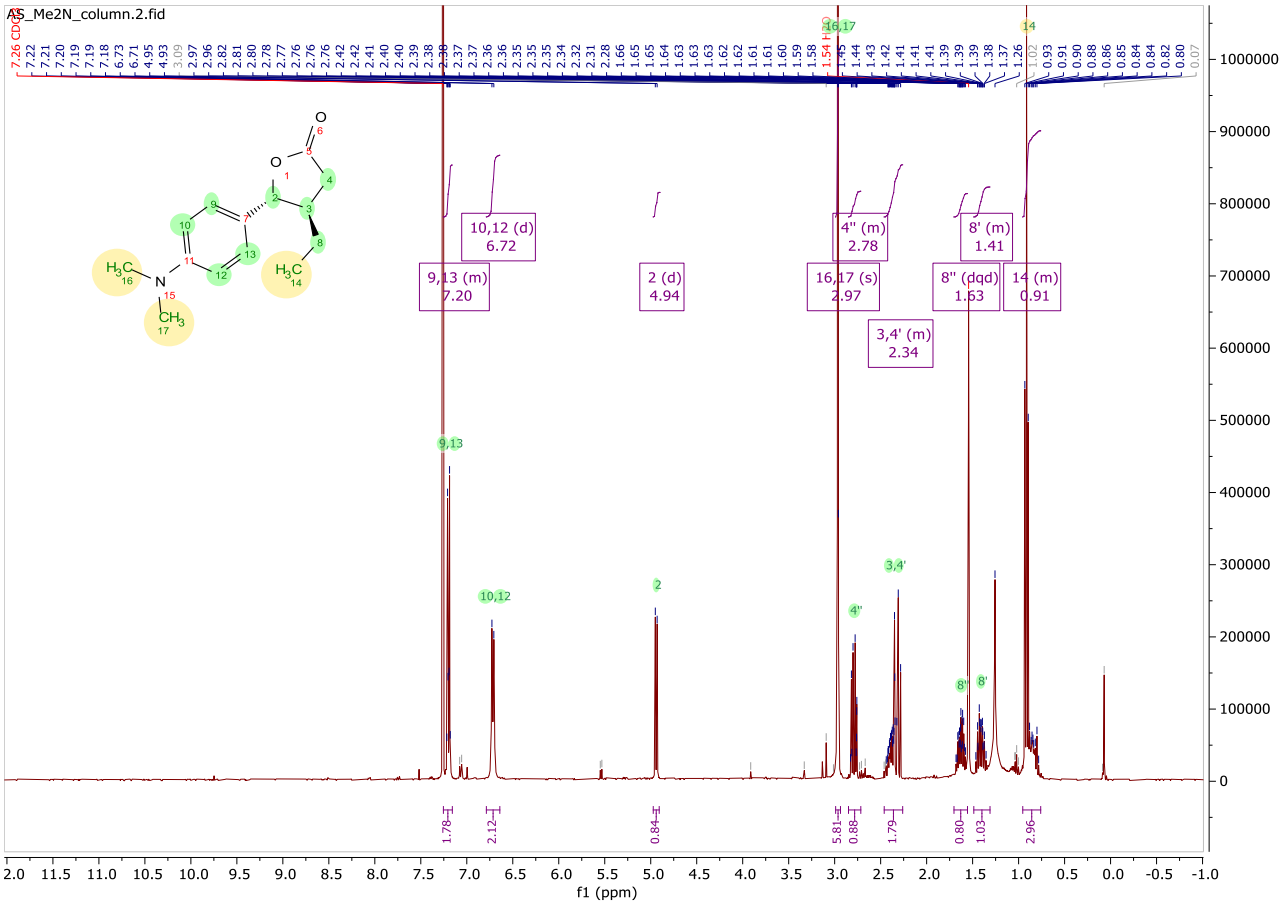



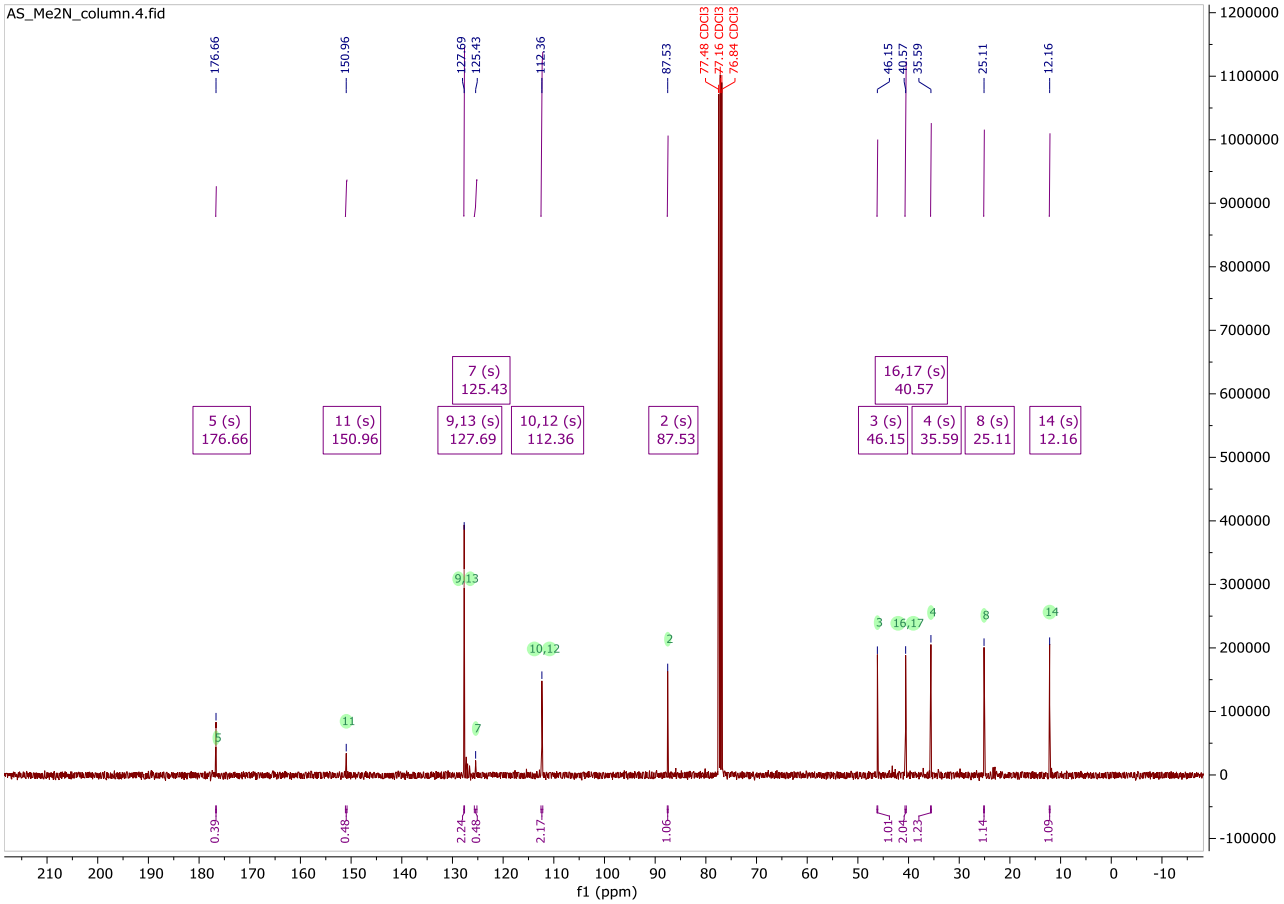
## **11n** *cis*-4-(3-ethyl-5-oxotetrahydrofuran-2-yl)benzonitrile



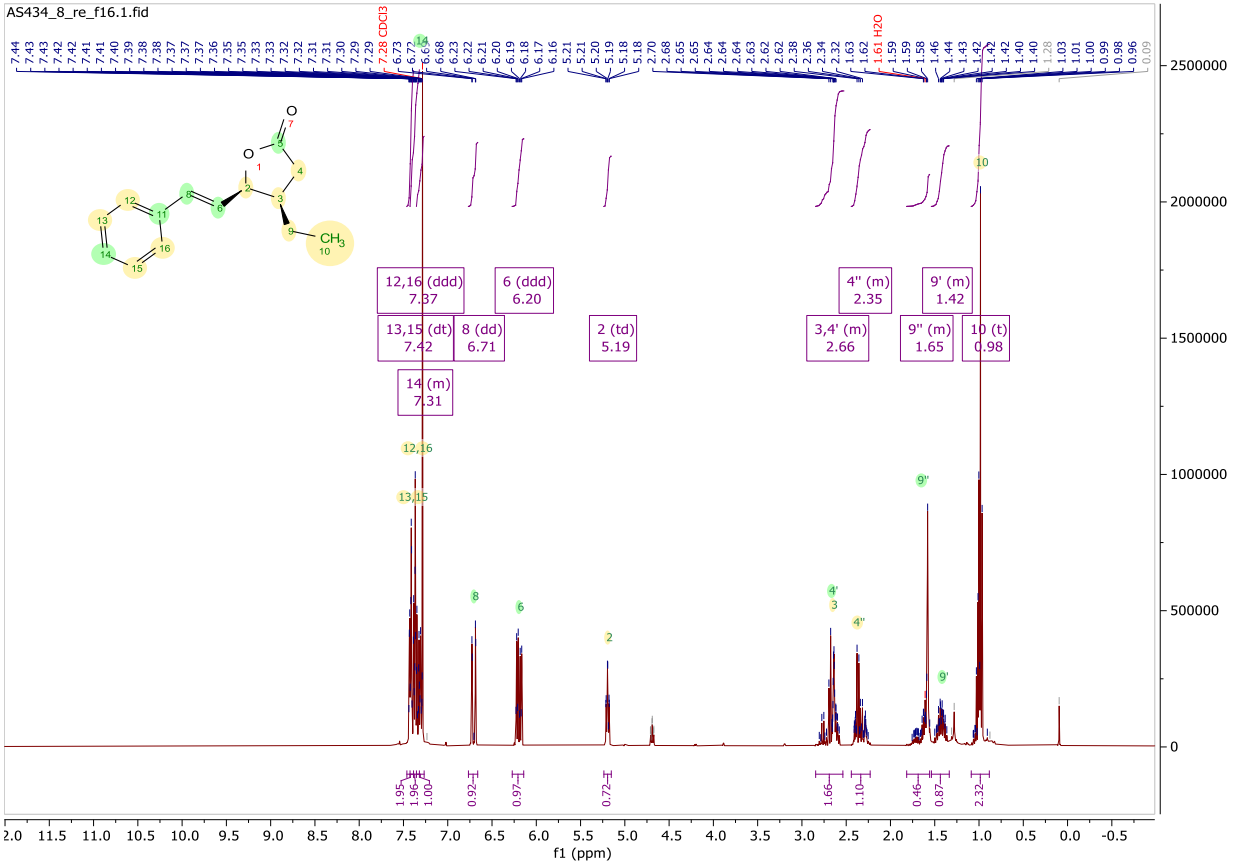



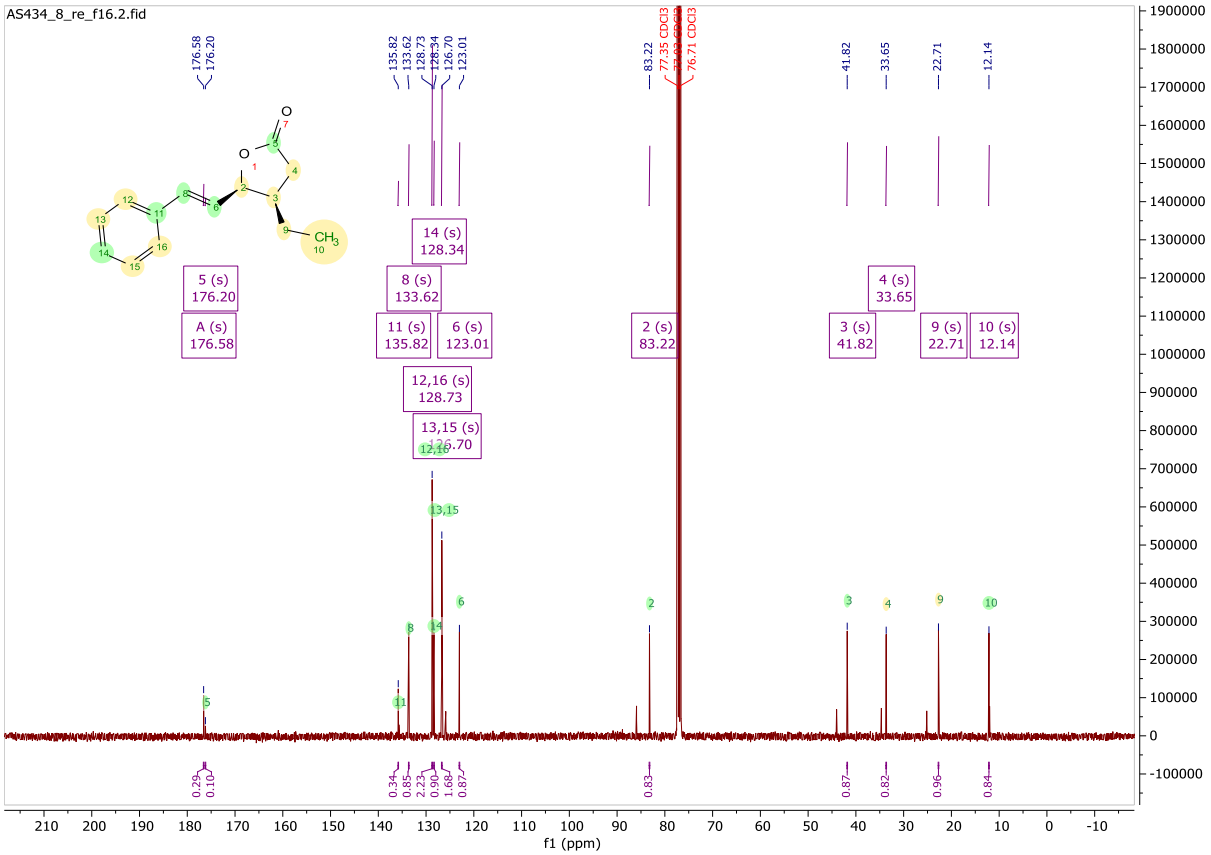
## **11o** *trans*-5-(4-(dimethylamino)phenyl)-4-ethyldihydrofuran-2(3H)-one



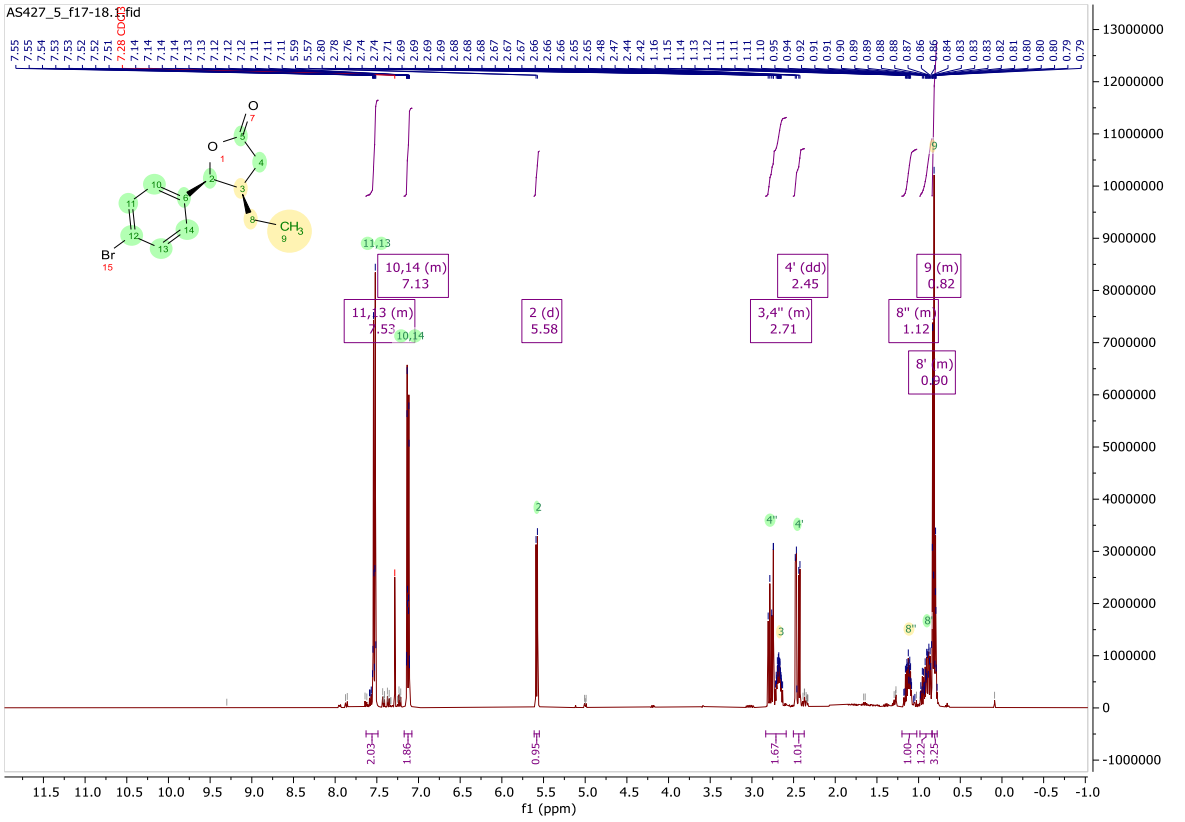



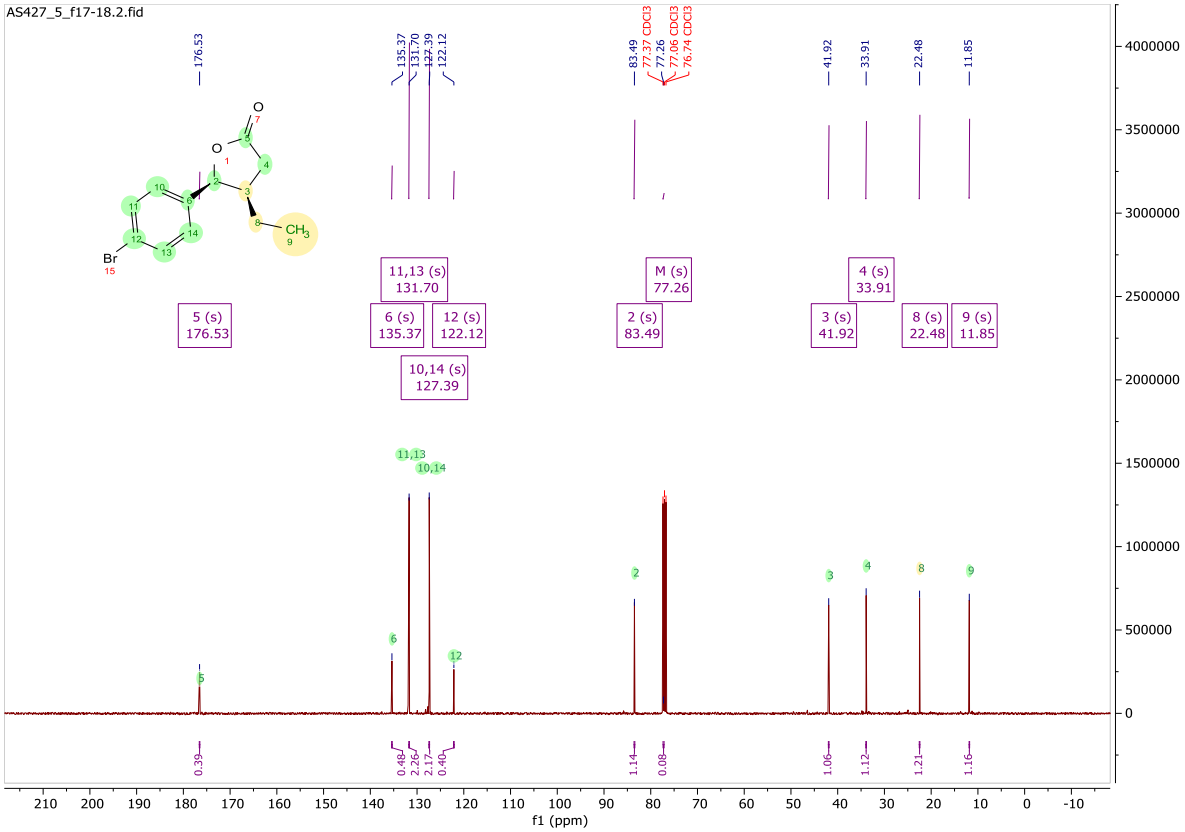
## **11p** *cis*-4-ethyl-5-styryldihydrofuran-2(3H)-one



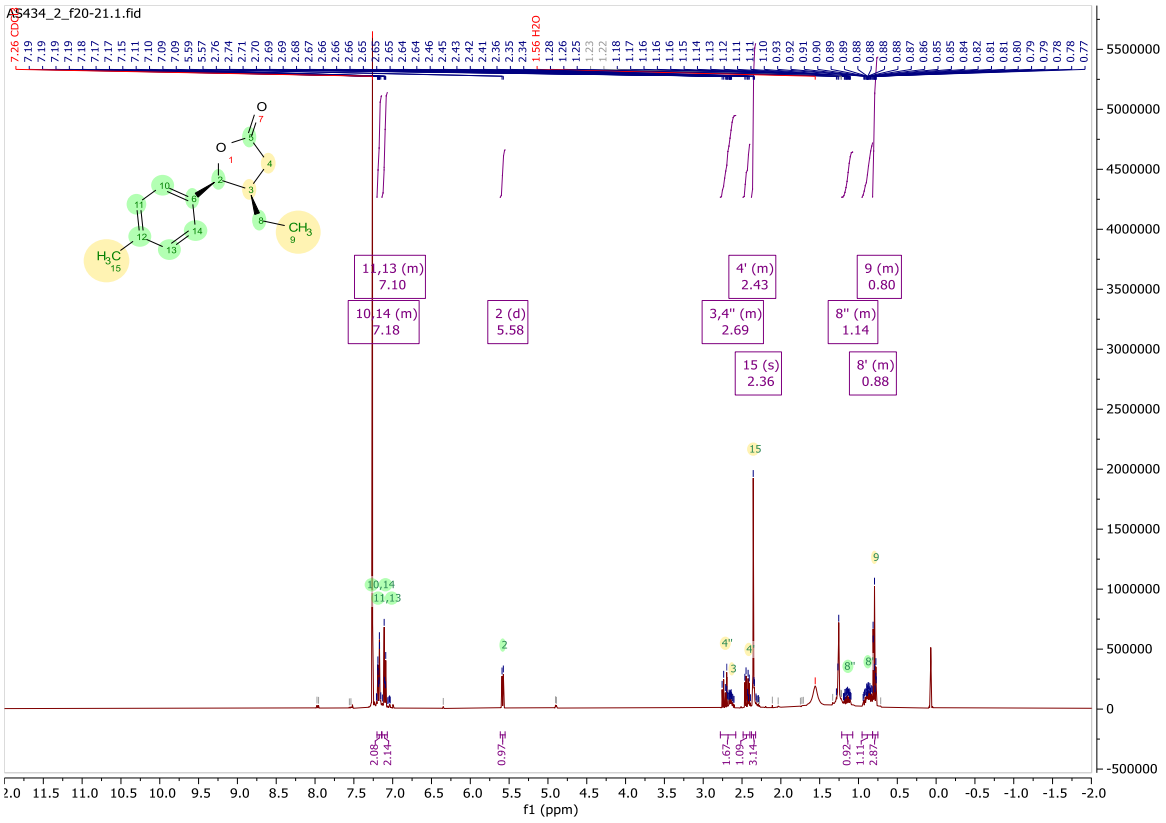



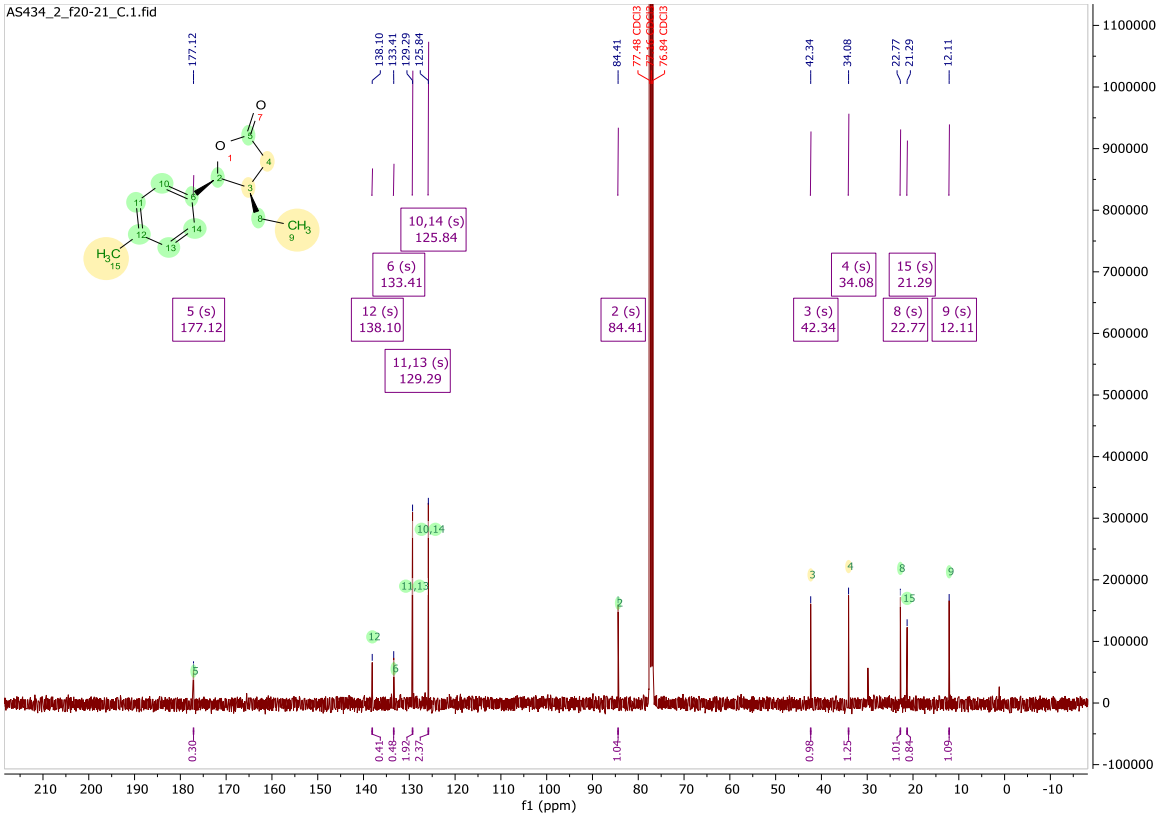
**11q** *cis*-5-(4-bromophenyl)-4-ethyldihydrofuran-2(3H)-one



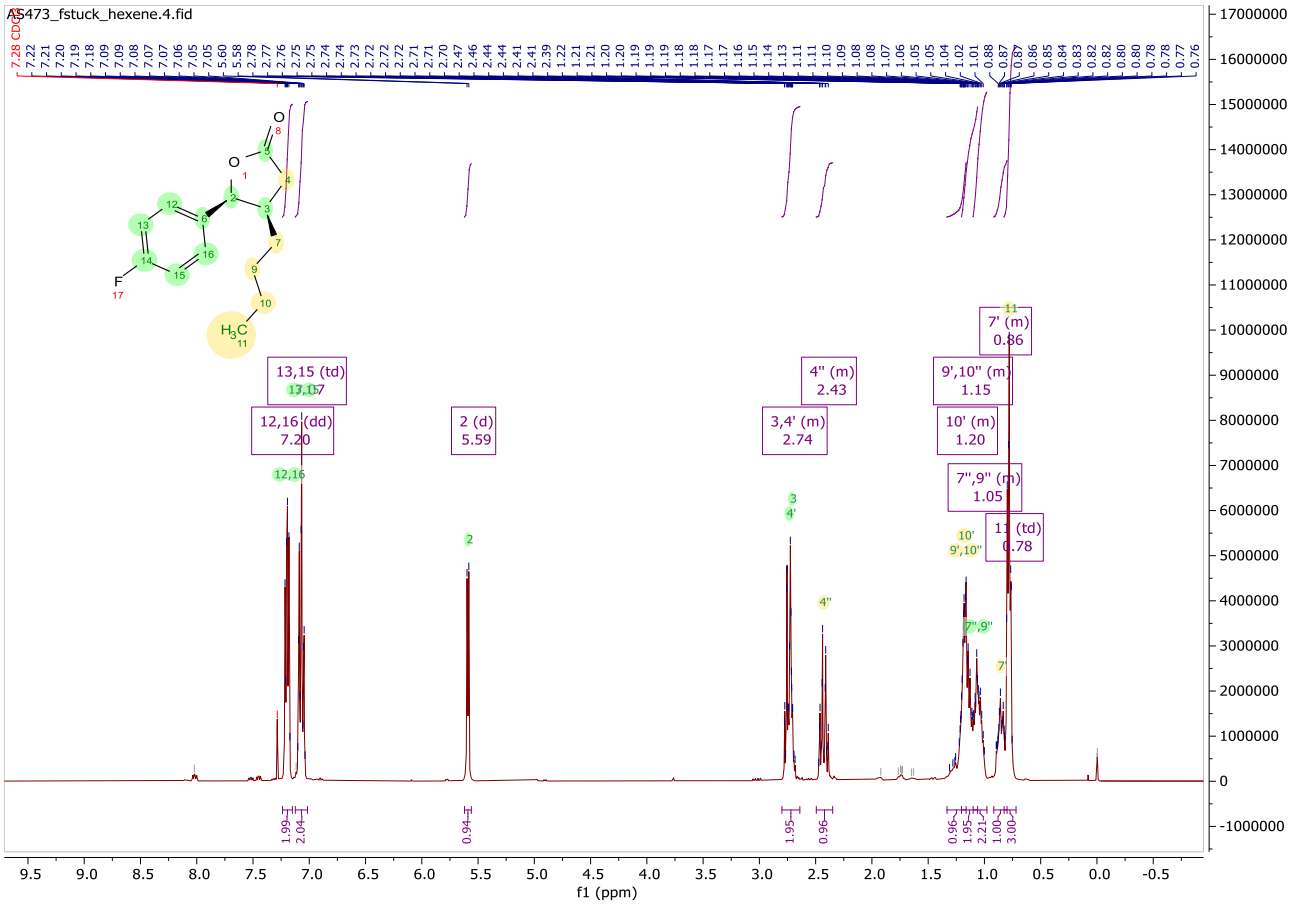



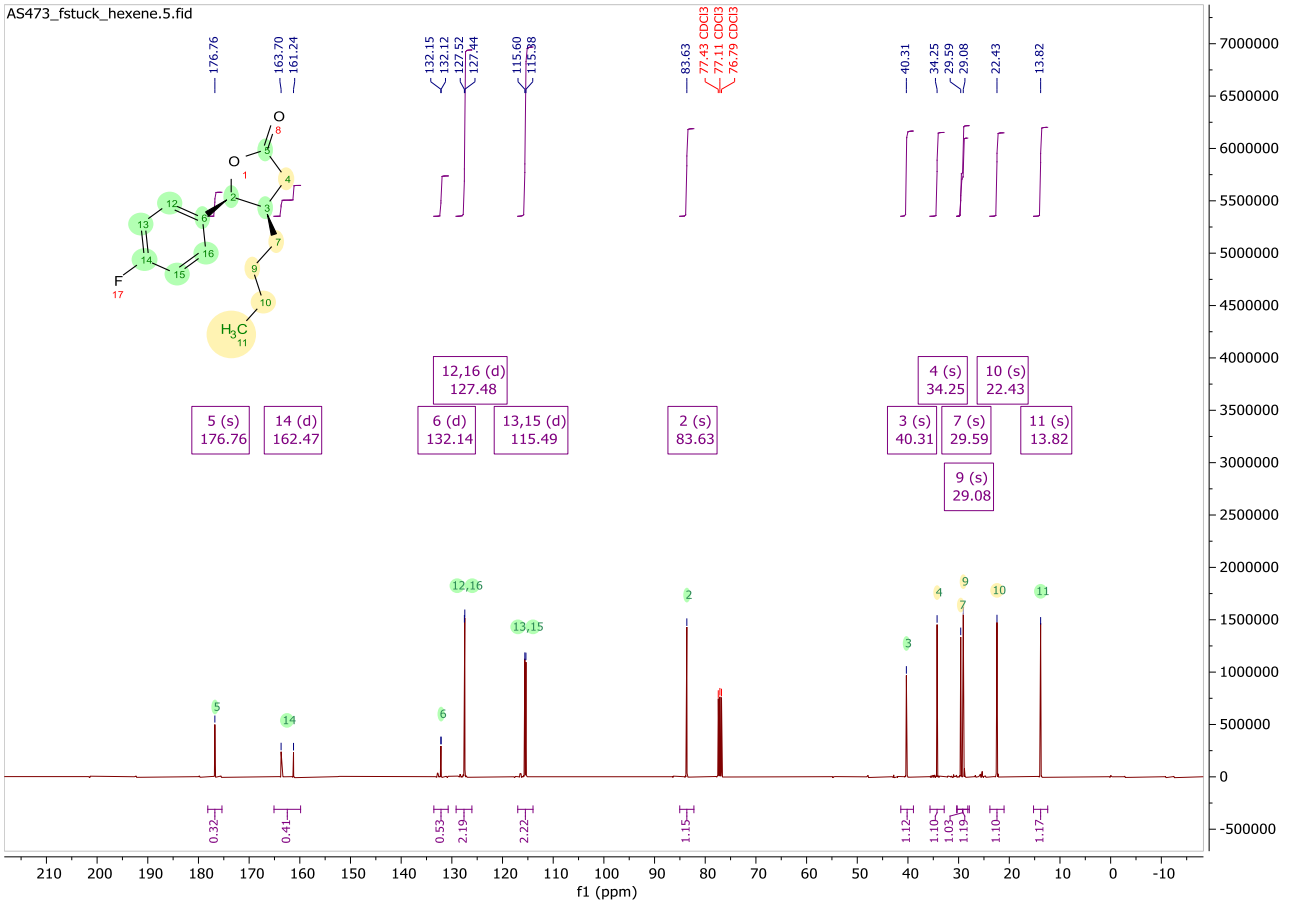
## **11r** *cis*-4-ethyl-5-(p-tolyl)dihydrofuran-2(3H)-one



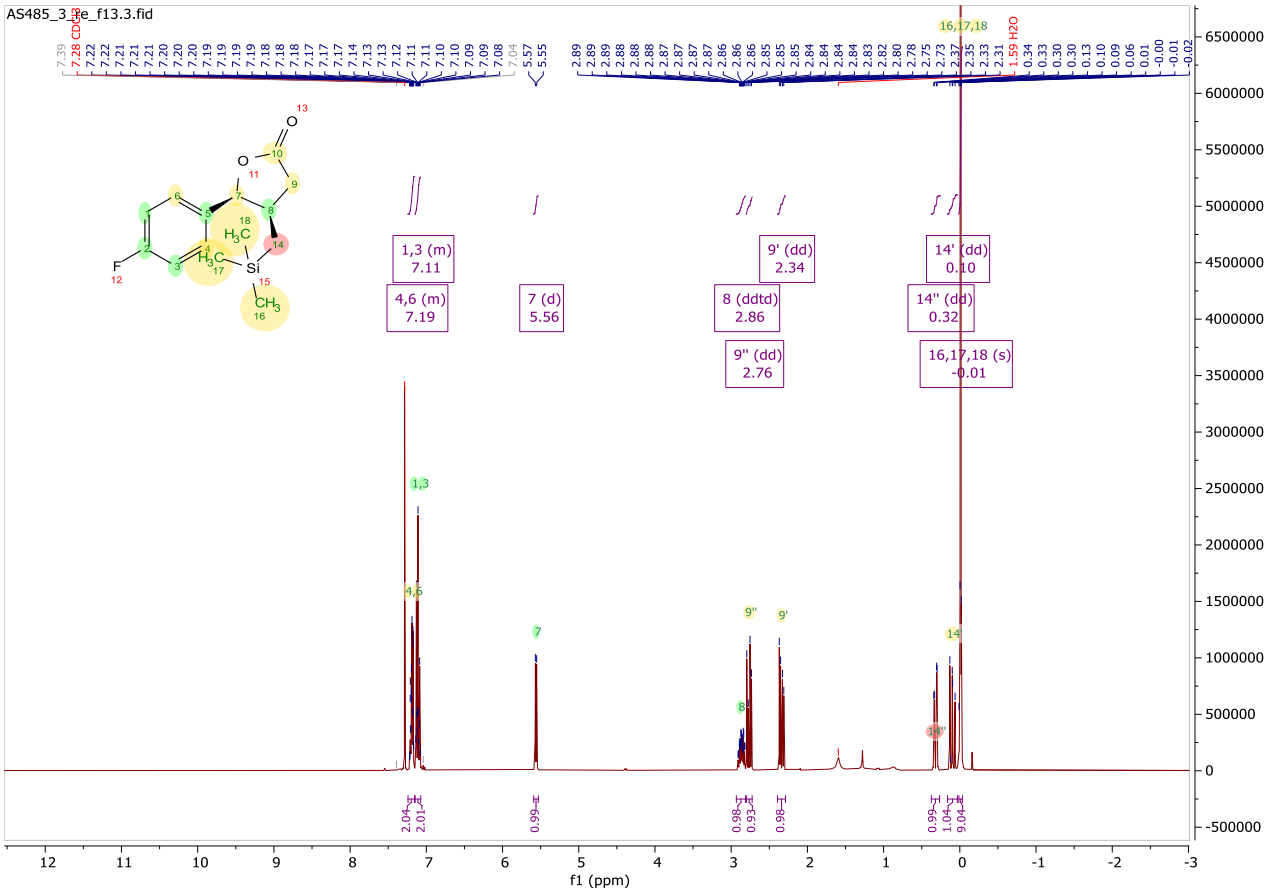



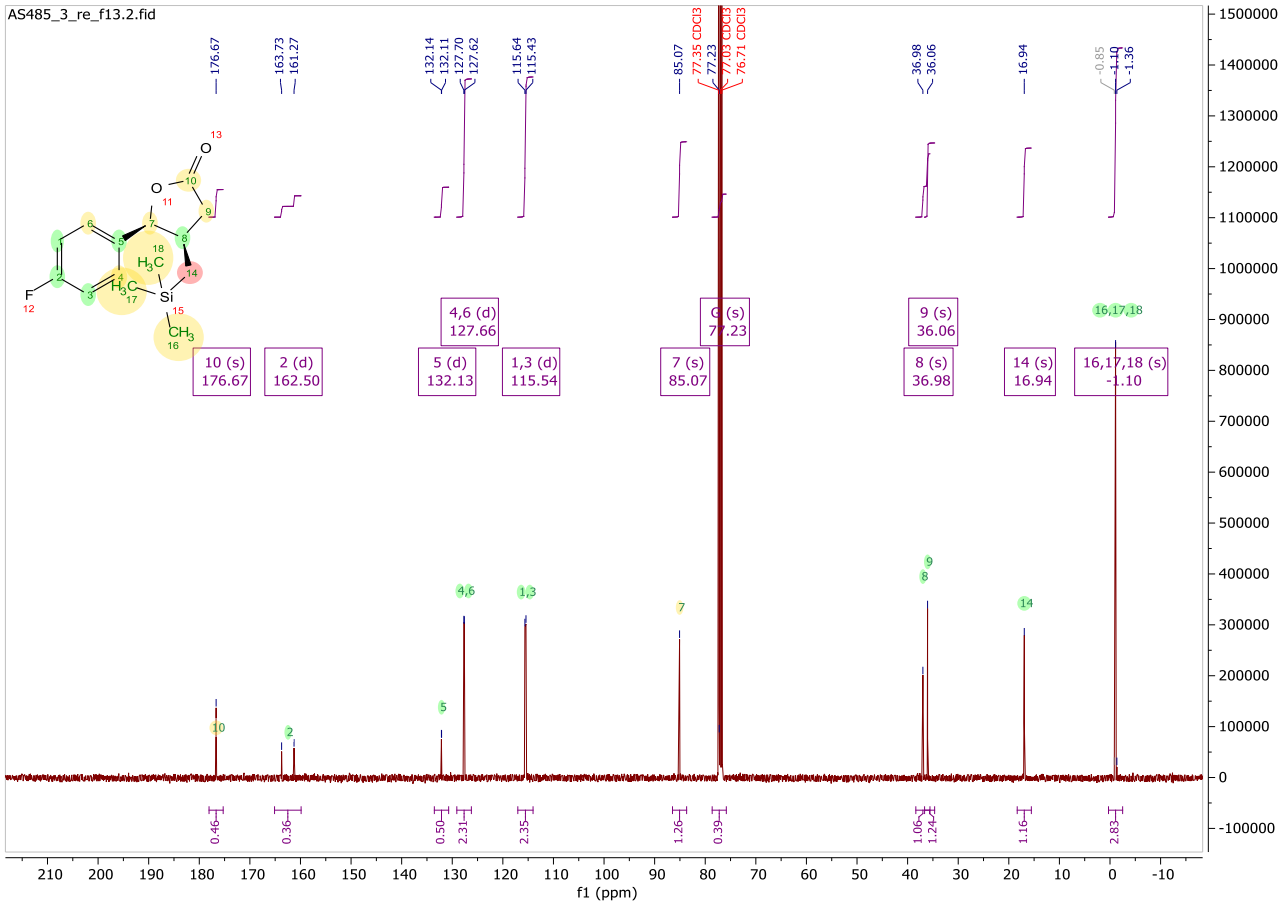
## **11s** *cis*-4-butyl-5-(4-fluorophenyl)dihydrofuran-2(3H)-one



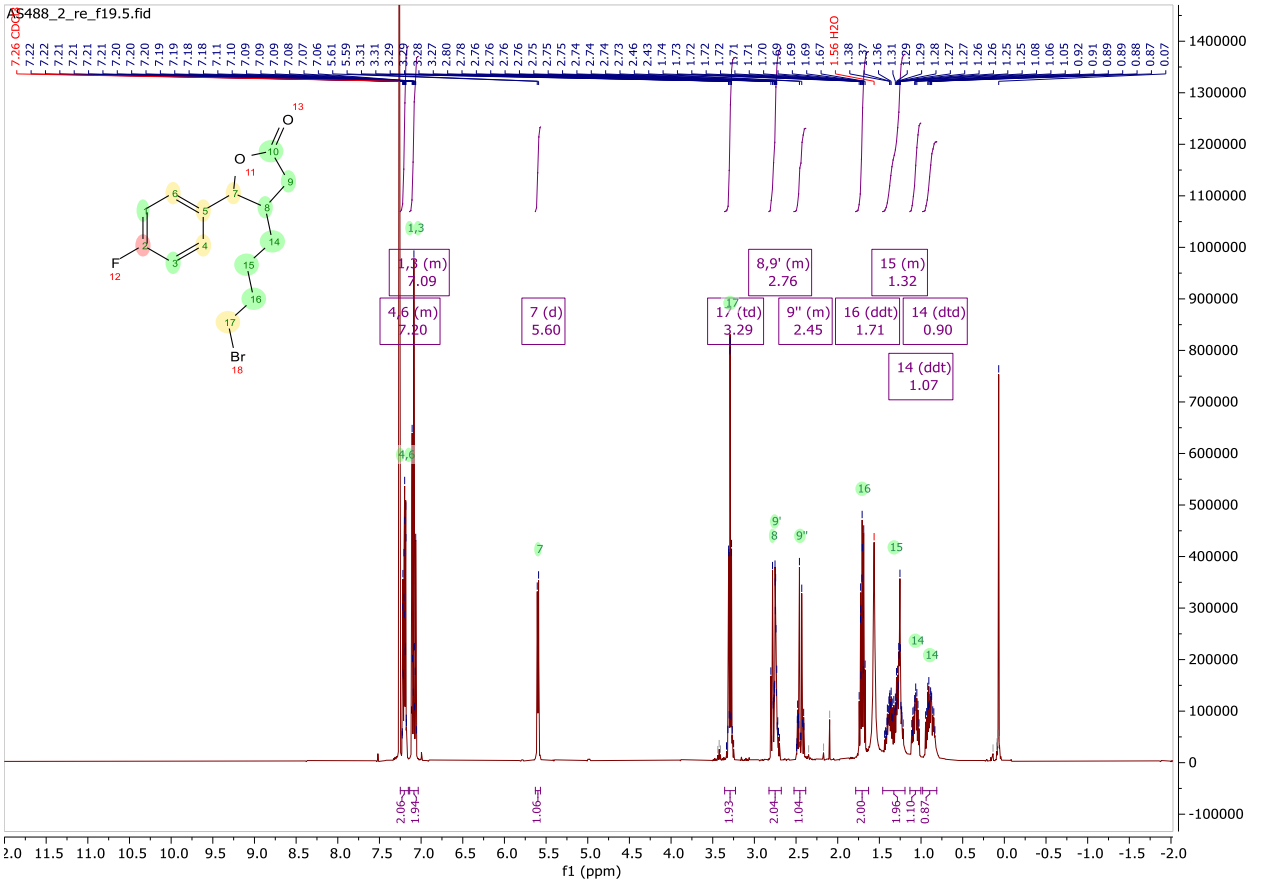



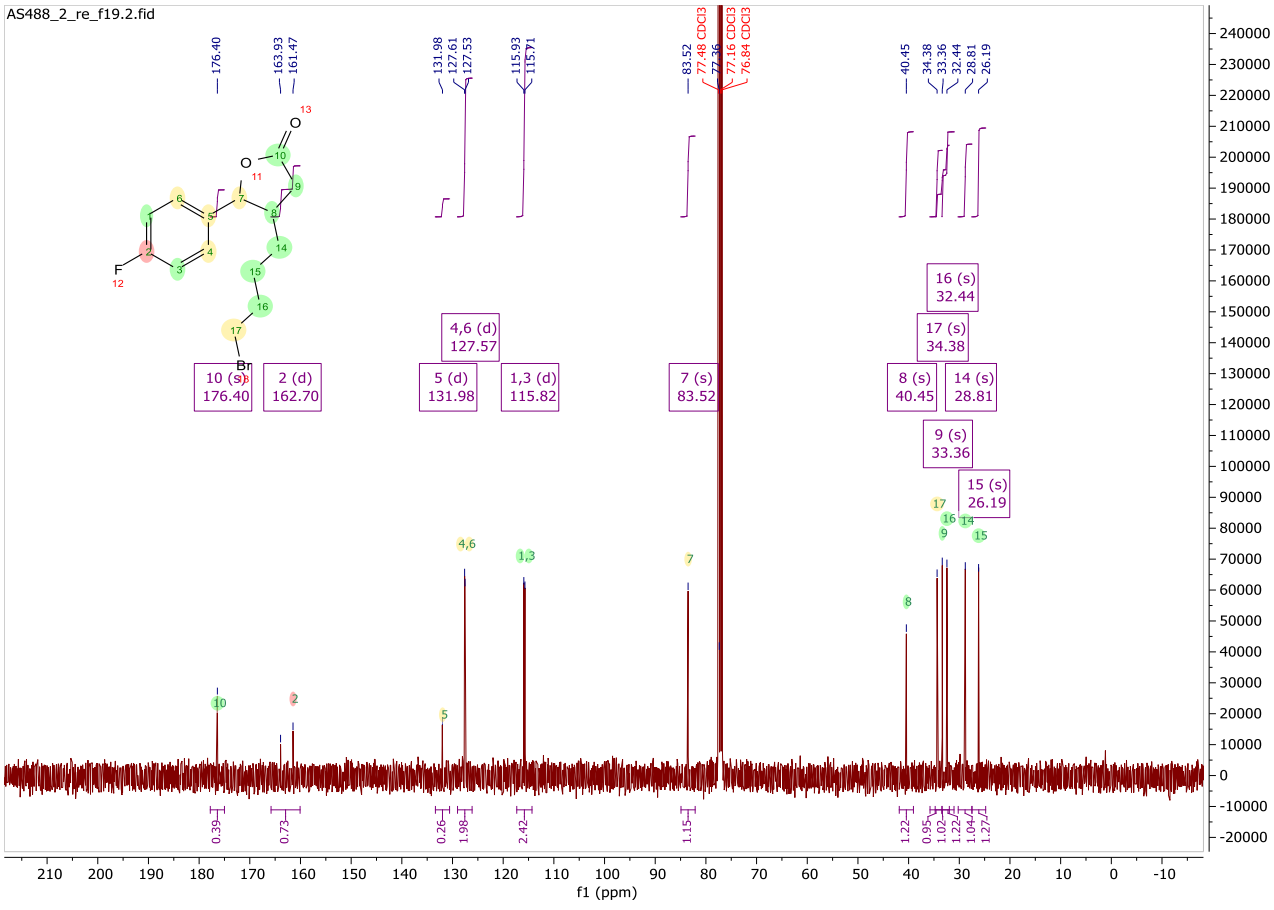
**11t** *cis*-5-(4-fluorophenyl)-4-((trimethylsilyl)methyl)dihydrofuran-2(3H)-one



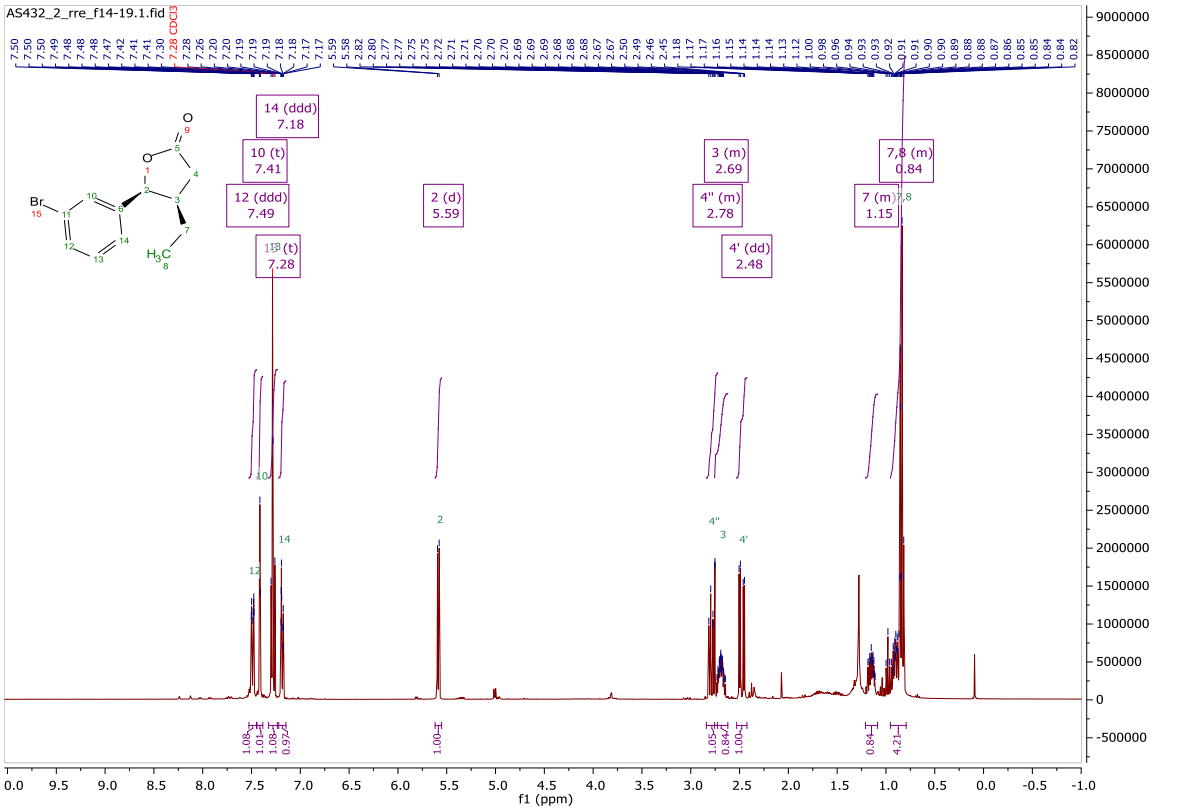



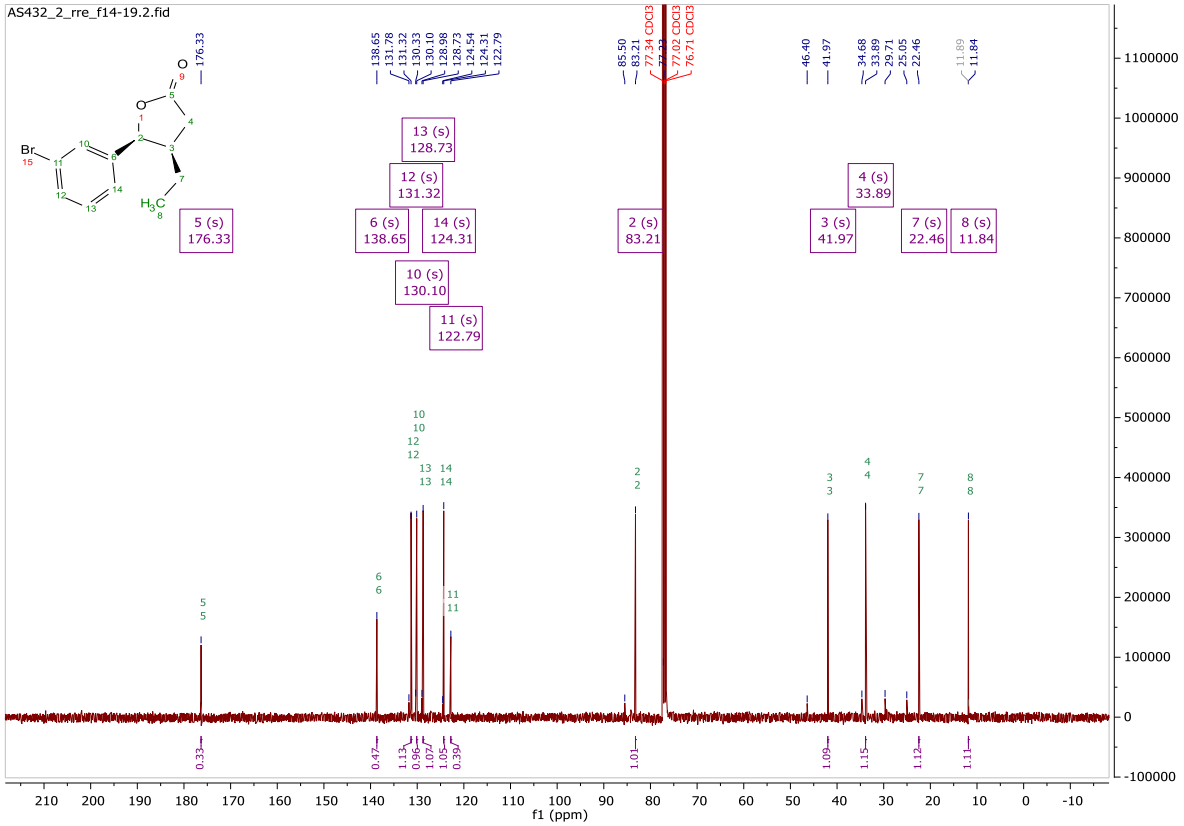
## **11u** *cis*-4-(4-bromobutyl)-5-(4-fluorophenyl)dihydrofuran-2(3H)-one



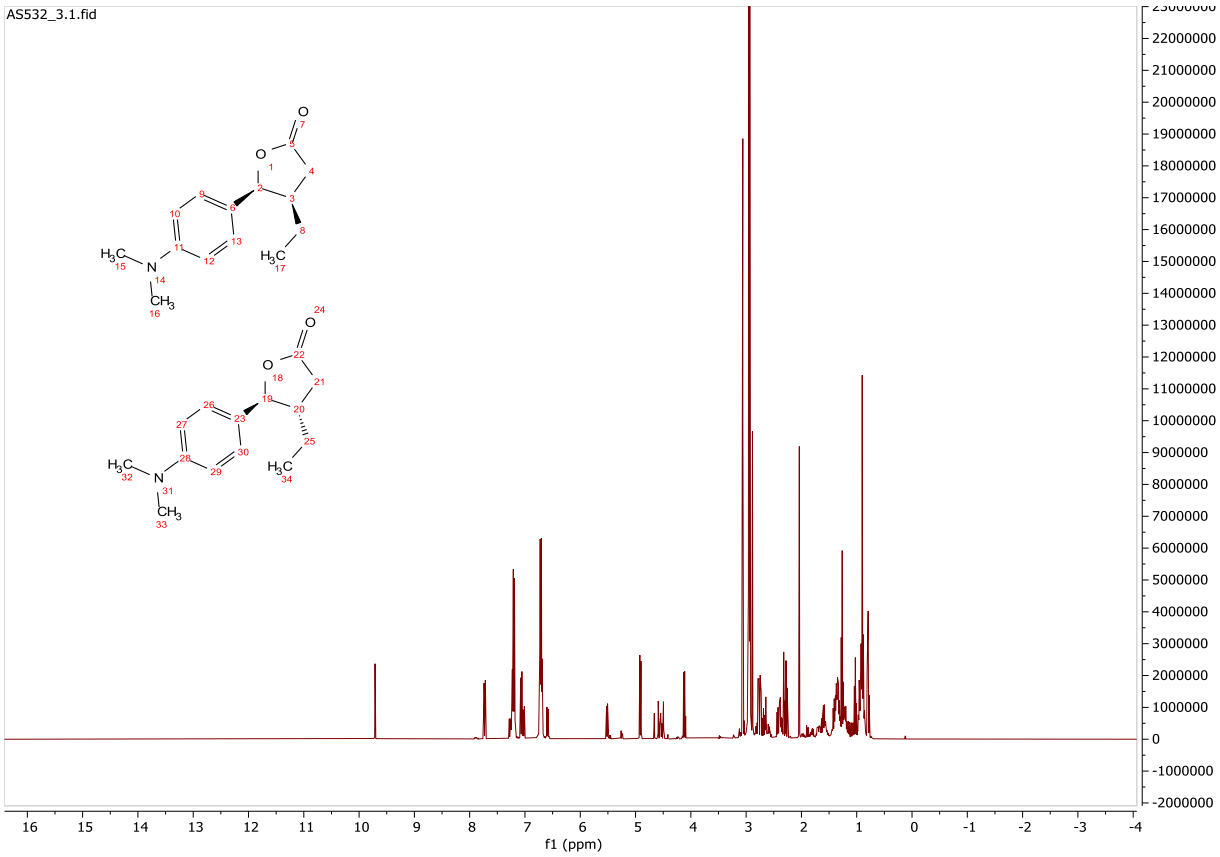
**11x** *cis*-5-(3-bromophenyl)-4-ethyldihydrofuran-2(3H)-one

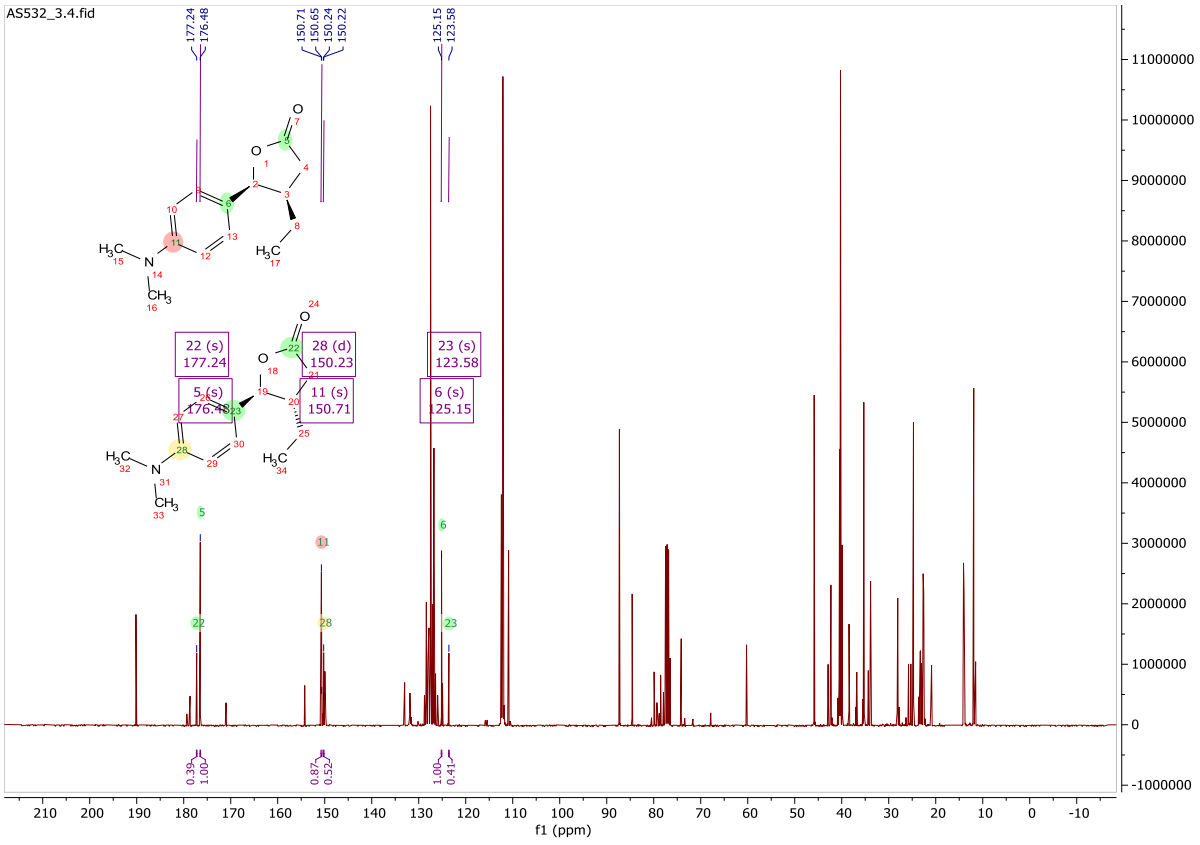


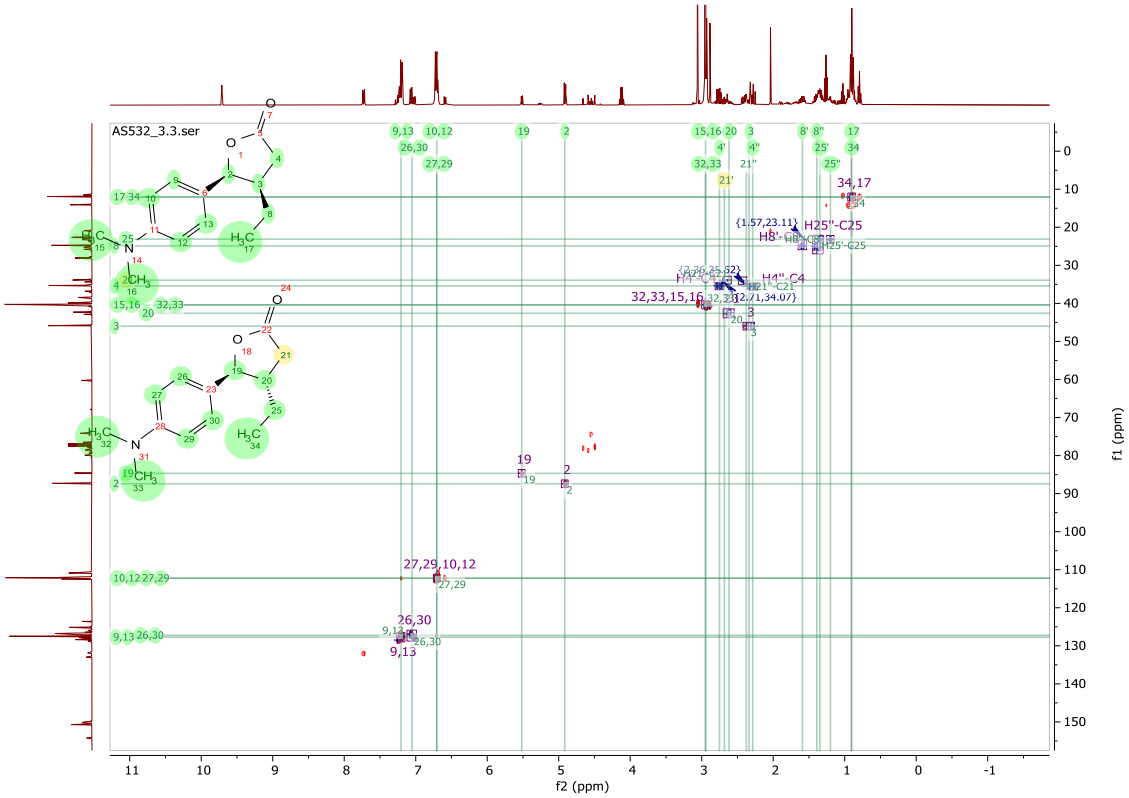
Crude NMR of **11o** with 2:1 ratios of *trans* : *cis*

C-H designations are only in HSQC, except quaternary and carbonyl carbons, which are in $^{13}C$.

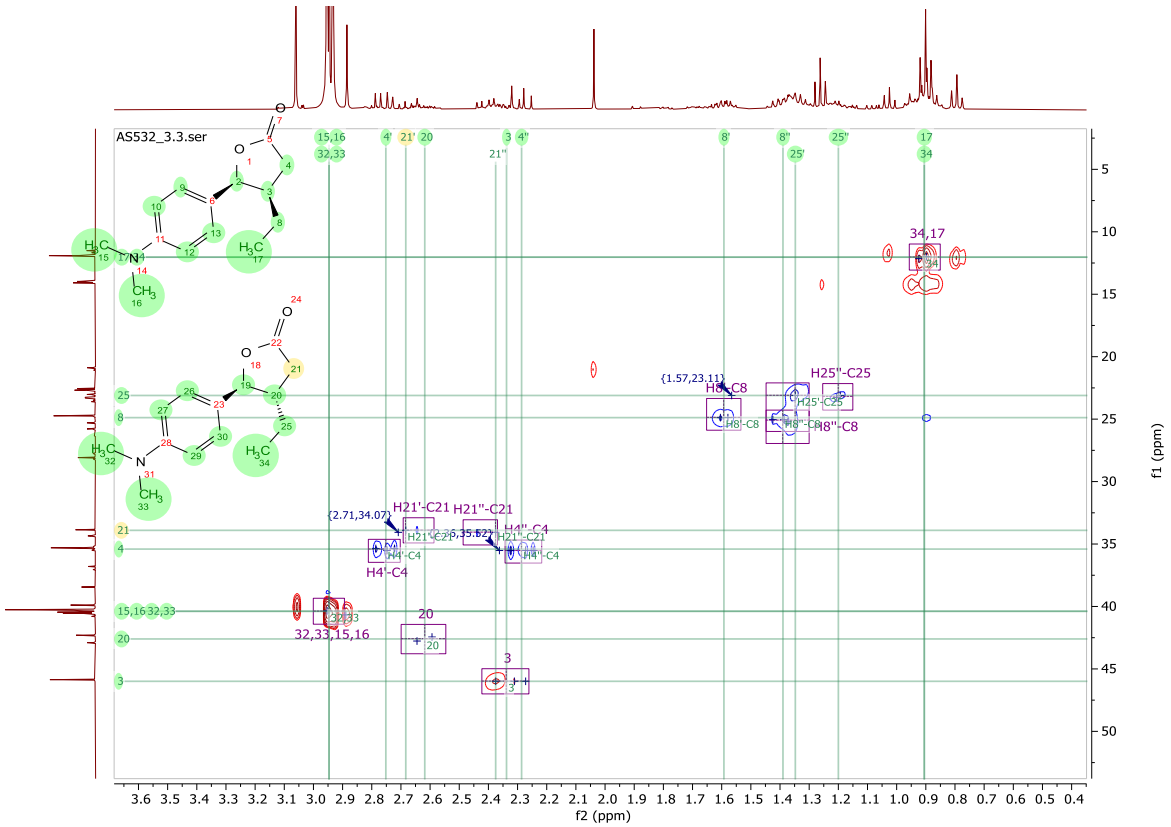


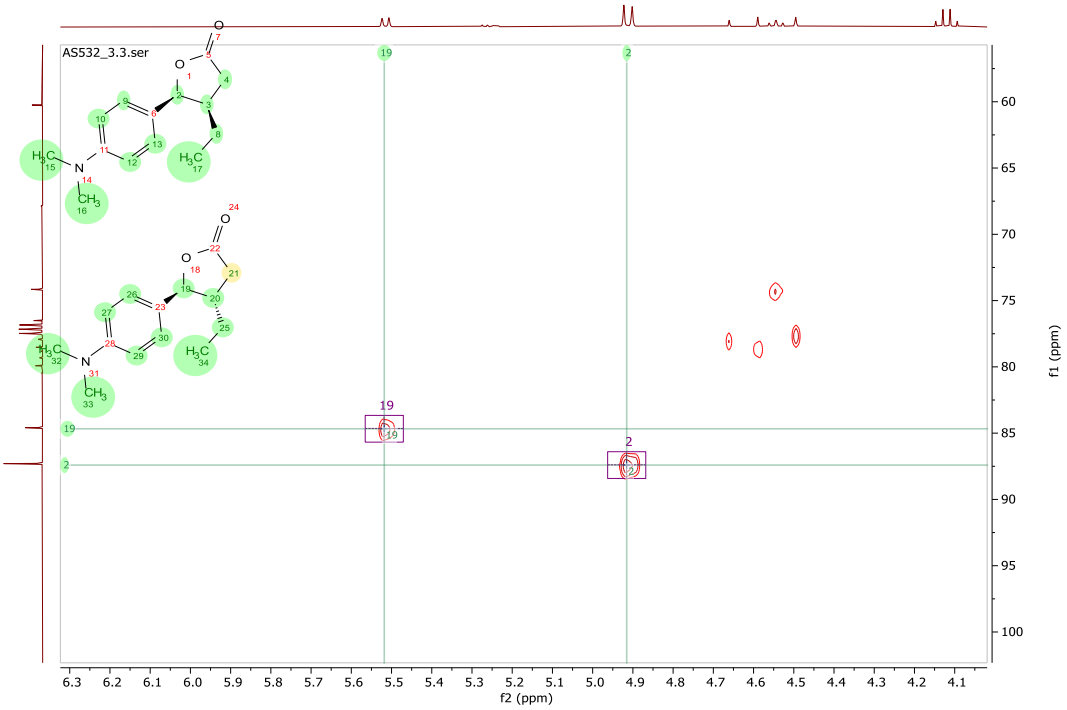

HSQC: full



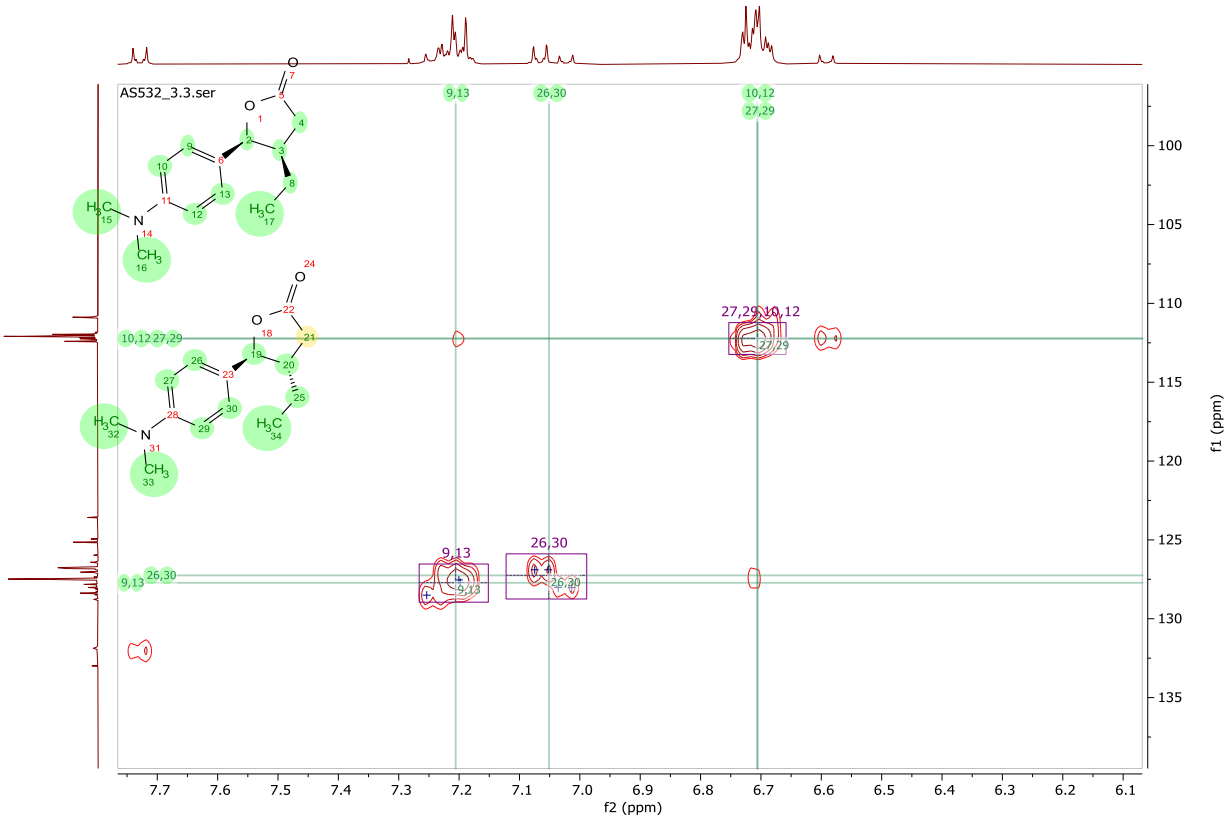

HSQC: zoomed



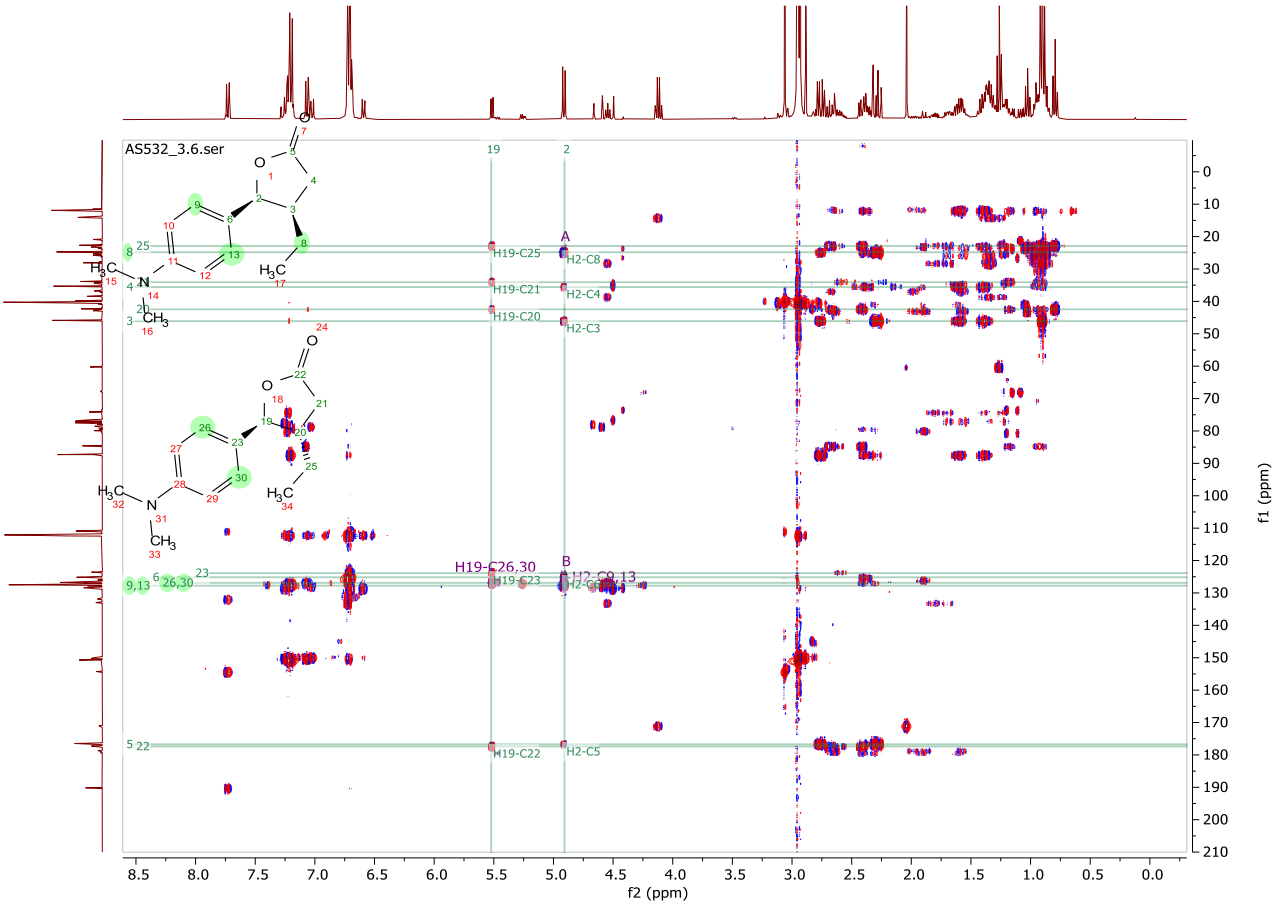
HSQC: zoomed




HSQC:zoomed



HMBC


AS532_3.6.ser
H19-C25
H19-C21
H19-C20
H19-C26,30
H19-C23
H19-C22
H2-C8
H2-C4
H2-C3
H2-C8,13
H2-C5
A
B
f2 (ppm)
f1 (ppm)