Supplementary materials A

Catalytic aldol condensation of bio-derived furanic aldehydes and acetone: challenges and opportunities

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Table of Contents

A1 - Reagents and solvents

All starting materials but furfural (99%, Sigma Aldrich) and HMF (min. 97%, Carbosynth) were obtained from commercial sources and used without further purification. Acetone (ACS reagent,

≥99.5%, Sigma Aldrich) was used as a solvent in the catalytic experiments. $Mg(NO_3)_2 \cdot 6H_2O$ (extra pure, Acros Organics) and $Al(NO_3)_3 \cdot 9H_2O$ (≥ 98 %, Fisher Chemical) were used in the preparation of the parent 2:1 Mg:Al HT, together with NaOH (Pellets, 98.9 %, Fisher Chemical) and Na_2CO_3 (Anhydrous, ≥ 99.5%, Fisher Chemical). The synthesis of HT and derived catalysts has already been described in detail elsewhere [1]. The zeolites used in the catalytic experiments were: H-beta (Zeolite catalyst, SiO_2/Al_2O_3 ratio: 27, Degussa); H-ZSM-5 (Union Carbide, 285 m^2/g); Zeolite Y (untreated and calcined, Heraeus Deutschland); Delaminated zeolite (ITQ2, Si/Al ratio: 15). The lysine used in the C8-OH synthesis was L-lysine monohydrate (≥99.0%, Loba Feinchemie). The water used in this preparation was deionized water obtained from a Simplicity UV water purification system, Merck Millipore, 18.2 MΩ·cm@ 25 °C. Silica (Silica gel 60, 0.03-0.2 mm, Carl Roth) and alumina (Neutral, Brockmann I, for chromatography, 50-200 µm, 60A, Acros Organics) were used in preparative chromatography. HCl (Hydrochloric acid, S.G. 1.18 (~37%), analytical reagent grade, Fischer Chemical) and NaOH (Pellets, 98.9 %, Fisher Chemical) were used in the homogeneous aqueous catalytic experiments. DAA (diacetone alcohol, min. 98.0%, TCI Chemicals) and MES (mesityl oxide, technical grade, 90%, Aldrich) were used as standards for the GC-FID quantification. Toluene (≥ 99.3%, Honeywell) was used as an internal standard for the GC-FID quantification. $CDCl_3$ (Chloroform-d for NMR, 99.8 atom % D, Acros Organics) was used as an NMR solvent, and CD_3COCD_3 (Acetone-d_6, 99.8 atom % D, Eurisotop) was used as an NMR solvent and as a reagent for in situ reactions.

A2 - Details and results of the synthesis and purification of reagents, intermediates and products

C9 and C15 are strongly retained by silica and separate readily in the column [2], possibly because of the different H-bonding patterns. On the other hand, C8 and C13 are more loosely retained and their separation required the use of alumina, which is more suitable for separating unsaturated compounds [3]. The preparation of pure aldols proved to be challenging not only in terms of

purification but of also in terms of selective synthesis. In the preparation of C8-OH, we could not selectively disfavour the dehydration over the aldol reaction at low temperatures with NaOH [4], so we ultimately had to resort to organocatalysis. L-lysine provided us with good quantities of C8-OH [5], although moderate concurrent dehydration was observed. The separation of C8-OH from the C8 was performed in silica since alumina promoted the dehydration of the latter. As for the remaining aldol intermediates, we were unable to synthesize any of them or detect them in our catalytic tests. To the best of our knowledge, these intermediates have never been observed.

A2.1 - Reagents

A2.1A - FUR

Furfural (b.p. 162 °C) was distilled with a simple distillation apparatus to remove the colourful impurities that the original batch contained, probably polyfurfurals/humins (Procedure A). Applying vacuum to the system speeds up the distillation and avoids contact of purified furfural with air, which could then re-degrade it. Even so, pure furfural should be a colourless oil, and the collected furfural was always a slightly yellow transparent oil (Figure A1). Since the obtained NMR spectrum for FUR was clean, and considering that even very small amount of degradation products stain FUR considerably [6], we considered FUR pure enough for our studies.

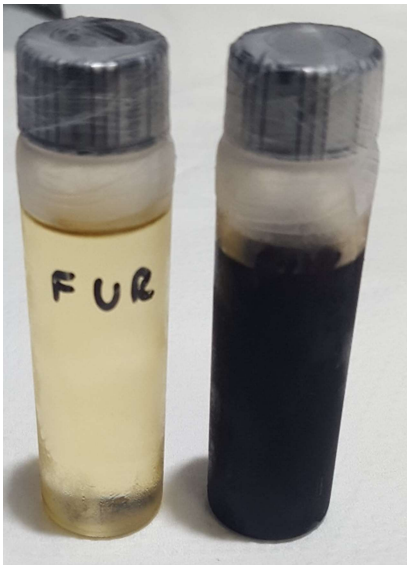

Figure A1. FUR after (left) and before purification (right).

Procedure A: 100 mL of FUR were loaded in a 250 mL rbf. A distillation apparatus, including a condenser and a collecting rbf, is assembled. The system is put under vacuum and the temperature of the 250 mL rbf containing furfural, immersed in an oil bath, is increased until reflux. At the end of the distillation a black tar is left in the original rbf, and the purified oil is transferred into a dark-glass vessel. The furfural is finally bubbled with N_2, the vessel sealed with parafilm and stored in a refrigerator.

A2.1B - HMF

In our experience, different batches of commercial HMF look different in terms of colour and texture. HMF cannot be distilled as it would degrade. For this, we adapted a recrystallization procedure from a post-HMF synthesis purification [7], and performed that instead. During the initial dissolution of the starting material in Et_2O, an insoluble part of it accumulated in the bottom (Figure A2). This solid, dark in colour, is probably responsible for the orange-ish colour of the commercial HMF. Even before the proper recrystallization took place, this black tar was separated as a means of preliminary purification. There is a considerable mass loss after recrystallization, which should be taken into account. The recrystallization does not seem to have a deep impact on the purification, as the ^{1}H-

NMR spectra before and after purification (Figures A29 and A30). It must be noted, however, that the impurity is insoluble also in $CDCl_3$ (Figure A3), which means that the impurity would not be easily revealed by liquid phase NMR. From this, it can be postulated that it is the separation after dissolution that is crucial for the purification.

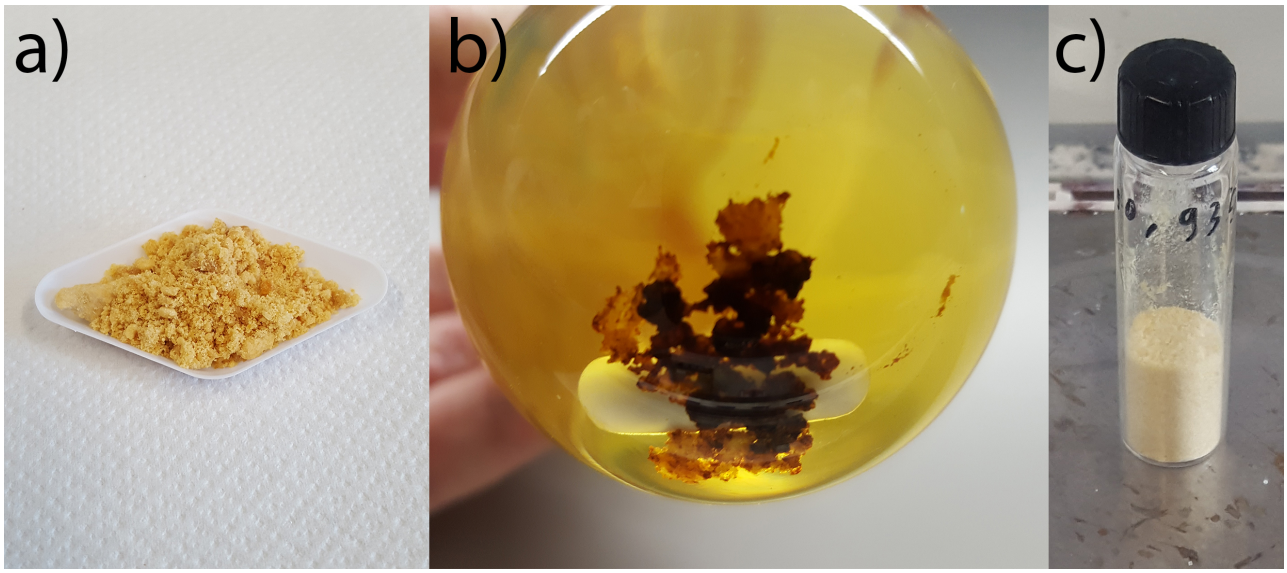

Figure A2. HMF recrystallization: original HMF (a), separated black tar (b), and recrystallized HMF (c).

Figure A3. $CDCl_3$ solution of HMF before (left) and after purification (right).

Procedure B [7]: 4 g of HMF were dissolved in ~ 40 mL of Et_2O, added dropwise under magnetic stirring. The yellow solution was transferred into another vessel to separate the black tar. The solution was left at -20 °C overnight. The solid was separated by filtration, crushed and dried under vacuum. The procedure afforded 2.65 g of recrystallized yellow HMF (66 % yield).

A2.2 - Mono-aldol reaction products

The key for the selective synthesis of the mono-aldol products is promoting the aldol reaction step while simultaneously suppressing the consecutive dehydration step, which, unfortunately, is catalysed by the same type of catalysts. While acid catalysts are more prone to dehydrate the substrate, basic catalysts are less so [8]. Organocatalysts are class of mild catalysts that oftentimes are employed in this type of reactions because they generally afford the β-hydroxy carbonyl product selectively; their nature also allows them to provide stereo-enriched products [9].

A2.2A - C8-OH

It has been reported that the aldol reaction of furfural and acetone in fair yields at low temperatures using NaOH [4]. Following this procedure (Procedure C), after 1 h of reaction in MeOH at -10 °C we obtained a very low conversion and detected only the presence of C8 and C13 in the mixture, implying that the aldol almost immediately dehydrates at these conditions. In a second run, we reproduced our own result. We then adapted a room temperature procedure for aqueous Henry reactions (Procedure D [10]), in the hope that the higher temperature could boost the conversion while increasing the C8-OH:C8 ratio; however, this time the reaction was almost instantaneous and total dehydration was observed together with complete furfural conversion. Instead of keeping on with NaOH and optimizing the conditions, we turned our attention to other catalysts. Zinc proline should supposedly afford C8-OH in excellent yields [11]; however the ^{1}H-NMR spectrum of the C8-OH obtained in this way, reported in the Supplementary Information to the article, contains intense C8 peaks. Finally, we followed a procedure that involves the amino acid L-lysine (Procedure E [5]). We could obtain decent

quantities of C8-OH in this way, although with moderate dehydration and with lower yields than the reported ones. We and the original inventors of the protocol used lysine in its L form because it is the naturally occurring and commercially available one; we did not analyse the optical activity of the species (it is completely irrelevant to our experiments), but we cannot discard that L-lysine managed to induce some enantiomeric excess on C8-OH (albeit probably a low one [11]).

With the reaction procedure in hand, we sought to purify the crudes chromatographically. Neutral alumina is generally the stationary phase of choice for the chromatographic purification of this type of acid-sensitive molecule. Even so, this purification (Procedure F) was unsuccessful: while the separation between C8 and C8-OH (which is more strongly retained) was smooth in TLC, during separation C8-OH thoroughly dehydrated to C8. Oddly enough, the dehydration does not substantially happen in silica, and thus we used that as a stationary phase (as it was proposed in the original preparation [5], procedure G). C8-OH is invisible in a normal TLC UV lamp (@254 nm), and therefore a potassium permanganate stain was required for it detection. The obtained pure C8-OH is an orange oil (Figure A4); while the intense colour is likely due to the presence of impurities, ^{1}H-NMR analysis of the compound do not highlight the presence of any concentrated impurity (Figure A23), which should then be a diluted, intensely coloured specie.

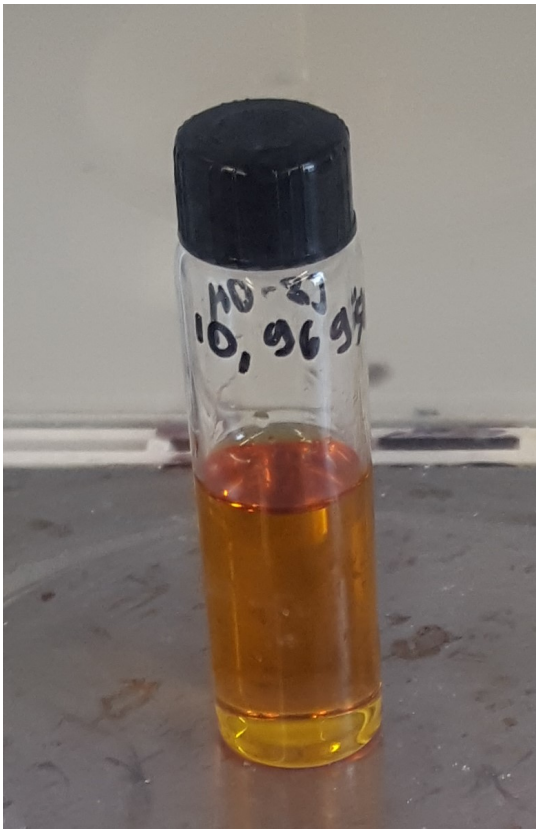

Figure A4. C8-OH after purification.

Procedure C [4]: A stirred solution of acetone (9.24 mL, 7.25 g, 0.125 mol) and furfural (6.47 mL, 7.50 g, 0.078 mol [*incorrectly reported as 0.049 mol in reference [4]*]) in 100 mL MeOH was cooled to -10 °C with an ice/NaCl bath. After this temperature was reached inside the rbf (checking it with a thermocouple), NaOH (6 mL of 2 M aqueous NaOH, 12 mmol) was added. After 15 min, the solution was poured in an Erlenmeyer flask containing 2 mL of acetic acid in an excess of ice. The mixture was extracted with 2:1 EtOAc:Hex v:v (3x100 mL), washed with 100 mL saturated $NaHCO_3$ and finally dried with Na_2SO_4. The mixture was analysed by GC-FID, estimating a very low conversion. The procedure was repeated letting the reaction for 1 h, with the same outcome. The crudes were then not purified.

Procedure D [10]: Acetone (9.24 mL, 7.25 g, 0.125 mol) and furfural (6.47 mL, 7.50 g, 0.078 mol) were dissolved in 150 mL of water. CTACl (1.653 mL, 1.6 g, 5 mmol) were added, followed by

NaOH (1.875 mL of 2M aqueous NaOH, 3.75 mmol). The reaction mixture was left stirring at room temperature for 1 h, then it was saturated with NaCl and extracted with Et_2O (4x40 mL), and finally dried with Na_2SO_4. The mixture was analysed by GC-FID, estimating complete conversion and a total dehydration. The crudes were then not purified.

Procedure E [5]: Acetone (50 mL, 39.2 g, 0.676 mol), furfural (8.6 mL, 9.97 g, 0.1 mol) and L-lysine (2.94 g, 0.02 mol) were dissolved in 400 mL of water. The reaction mixture was left stirring at room temperature for 28 h, then it was extracted with EtOAc (3x300 mL). The solution obtained was analysed by GC-FID: the conversion is not complete, but C8-OH is the major product, followed by C8. The mixture was concentrated in a rotavapor, dried under vacuum and purified by column chromatography (Procedures F and G).

Procedure F: An alumina column was prepared using an hexane:EtOAc 7:3 eluent. At these conditions, FUR, C8 and C13 are all rapidly eluted with the mobile phase ($R_f \sim 0.85$), while C8-OH is strongly retained ($R_f = 0.15$). During the chromatographic separation, a broad yellow band throughout the whole column appeared. Apparently, C8-OH started dehydrating over time, and since C8 elutes faster than the aldol, the produced C8 appears in a large number of fractions with no sight of C8-OH. The purification was therefore shut down.

Procedure G [5]: A silica column was prepared using an hexane:EtOAc 7:3 eluent. At these conditions, FUR, C8 and C13 all elute together ($R_f = 0.55$, Figure A5), while C8-OH is more strongly retained ($R_f = 0.25$). The separation proceeded smoothly, although the first the collected fractions were discarded because of partial overlap of FUR/C8 and C8-OH. The fact that the reaction (Procedure E) uses a lower acetone excess as compared to the neat reaction, and that the mild system disfavours acetone's self-reaction is important, since DAA ($R_f = 0.2$-0.4) overlaps with C8-OH. The

collected fractions were evaporated and the obtained orange oil was dried under vacuum (43 % yield). C8-OH was put under nitrogen and stored in a freezer before use.

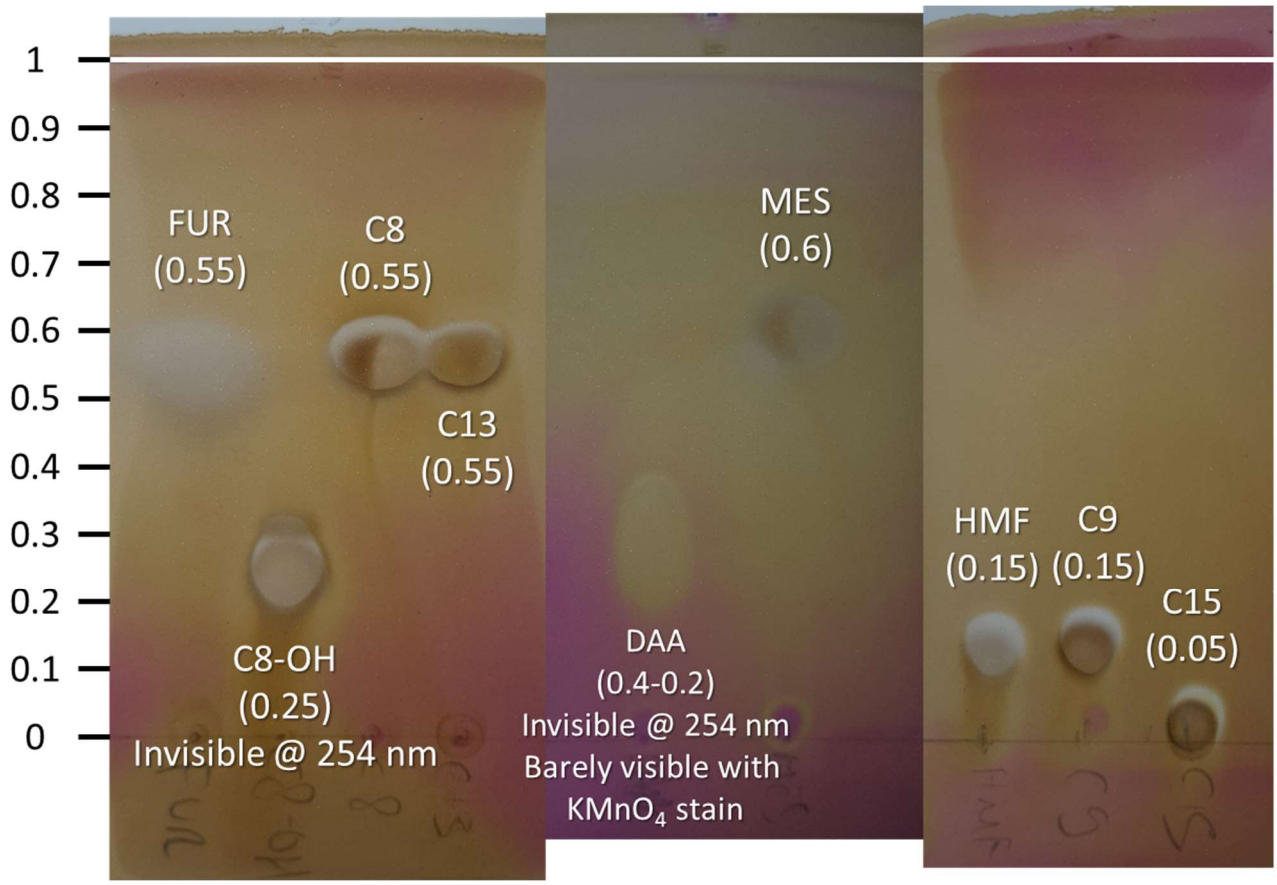

Figure A5. Silica TLCs of all reaction components with 7:3 hexane:EtOAc as the eluent, stained with a potassium permanganate-based solution.

A2.2B - C9-OH

Although in a report C9-OH is suggested as the product of the aldol condensation of acetone and HMF [12], the article only focuses on the conversion of HMF and C9-OH characterization is absent (and it probably corresponds to C9 in any case). This aside, C9-OH is absent in the literature as a detected product. In an attempt to prepare some via organocatalysis, we used Procedure E with HMF. Unfortunately, after 28 h HMF conversion was low and mostly lead to C9.

A2.3 - Mono-aldol condensation products

The mono-aldol reaction products were obtained by purifying the reaction crudes of the catalytic tests (described in Section B1) where they are the major products. The filtered reaction solutions were evaporated and unified in a single crude (one for ACE-FUR reactions and one for ACE-HMF ones). This crude would then afford the pure mono-condensation products after chromatographic separation. The first thing that should be noted is that, much like the starting materials, leaving the crudes at ambient conditions seem to trigger the degradation of the products, which causes a colour change (Figure A6).

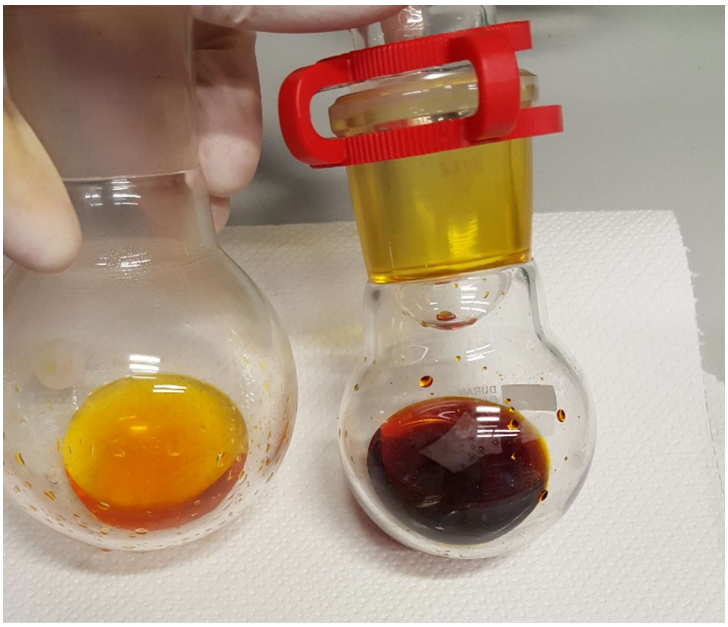

Figure A6. Fresh (left) and one-week-old ACE-FUR crudes (right).

Pre-column chromatography TLC analysis of the crude showed that the separation of the reaction components is rather troublesome. We could not find a combination of the most common solvents for column chromatography (hexane, EtOAc, DCM, MeOH) that could separate C8 from C13 in silica. We found, however, that alumina can (barely) separate them by virtue of the better interaction of the stationary phase with C=C bonds. The two spots are anyway not very distant from each other. On the other hand, C9 and C15 readily separate in silica with a hexane:EtOAc 1:1 eluent [2].

Importantly, the HMF derivatives are retained much more strongly than their FUR counterparts (Figure A5), perhaps because of the stronger O-H bonding network, as proposed in the main text. Unfortunately, in neither system it was possible to separate the starting material (FUR or HMF) from the mono-condensation product (C8 or C9). Hence, we brought the collected crudes to complete conversion before purification. We did so by adding chunks of NaOH to an acetone solution of the crude; this formed a thick slurry which proved to be impossible to separate in any way but a combination of centrifugation and membrane filtration. It is recommendable to leave the catalytic experiment ongoing until complete conversion before interrupting it instead of adding NaOH afterwards. In any case, this shows what happens when caustics are used as heterogeneous catalysts in acetone (we obtained the same outcome with KOH). The formation of degradation products in the crude appear as $R_f = 0$ spots on the TLC.

A2.3A - C8

Pure C8 is a yellow solid (Figure A7). Much like the reaction crude, this compound also seems to undergo some degradation over time, even with careful storage.

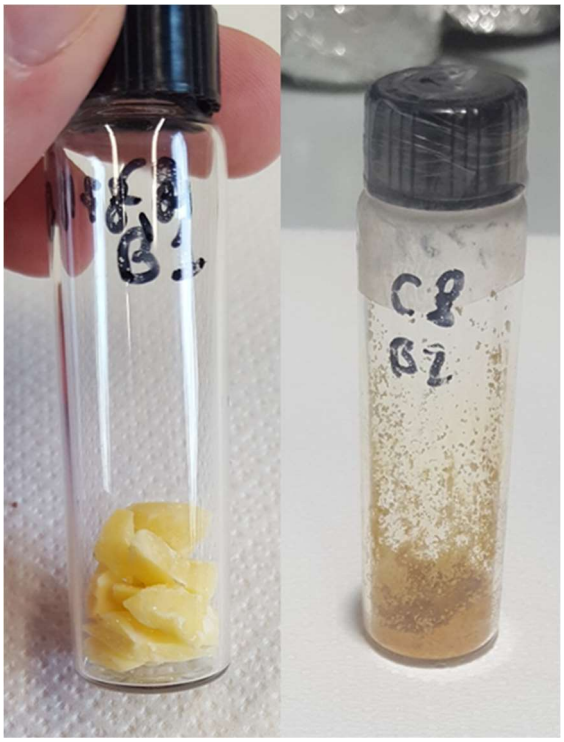

Figure A7. Pure C8 right after purification (left), and 6 months after that (right).

Procedure H: After ACE-FUR (or ACE-HMF) reactions (see Section B1), the heating was stopped and the mixture was let cool down. The reaction mixture was then filtered to separate the spent catalyst. This was then thoroughly washed with acetone (to remove all loosely adsorbed products from the recovered catalysts (see Section B2), and to recover as much product as possible). The collected solution was finally evaporated to remove acetone. The reaction crudes of all catalytic experiments were mixed together and stored. The united crudes were brought to complete conversion by adding 50 mL of acetone per crude and running a reaction at reflux progressively adding quantities of metal hydroxides until complete conversion of the aldehyde was reached. The suspension obtained was centrifuged to deposit most of the hydroxide, and the supernatant was filtered through a syringe filter, changing it every time it got clogged. The solution was evaporated again to remove acetone.

Procedure I: Since the final crude was too much to load it in one chromatographic column, this was progressively purified in different batches. An alumina column was prepared using hexane:EtOAc 95:5. At these conditions FUR (absent after complete conversion) and C8 elute together (R_f = 0.4,

Figure A8), while C13, DAA (present in major quantities) and C8-OH (also completely converted into C8) are more strongly retained. Partial overlap of C8 with C13/DAA required discarding of the last fractions for obtaining a spectroscopically pure sample. The collected fractions were evaporated and the obtained yellow oil was dried under vacuum. The oil has trouble to solidify even at low temperatures; scratching the glass with a spatula triggers the solidification. C8 was put under nitrogen and stored in a freezer before use.

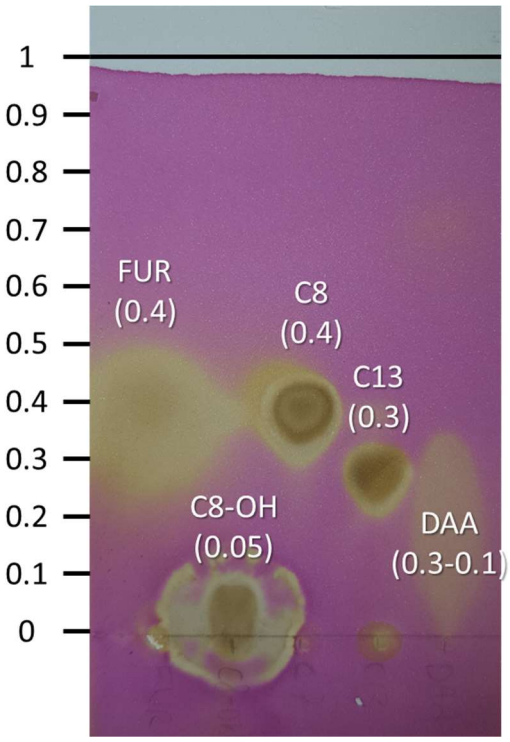

Figure A8. Alumina TLC of ACE-FUR reaction components with 95:5 hexane:EtOAc as the eluent, stained with a potassium permanganate-based solution.

A2.3B - C9

Pure C9 is a light yellow solid (Figure A7). Similarly to C8, C9 appears to undergo degradation over time, although this is perhaps slower in this case as indicated by the less dramatic colour change.

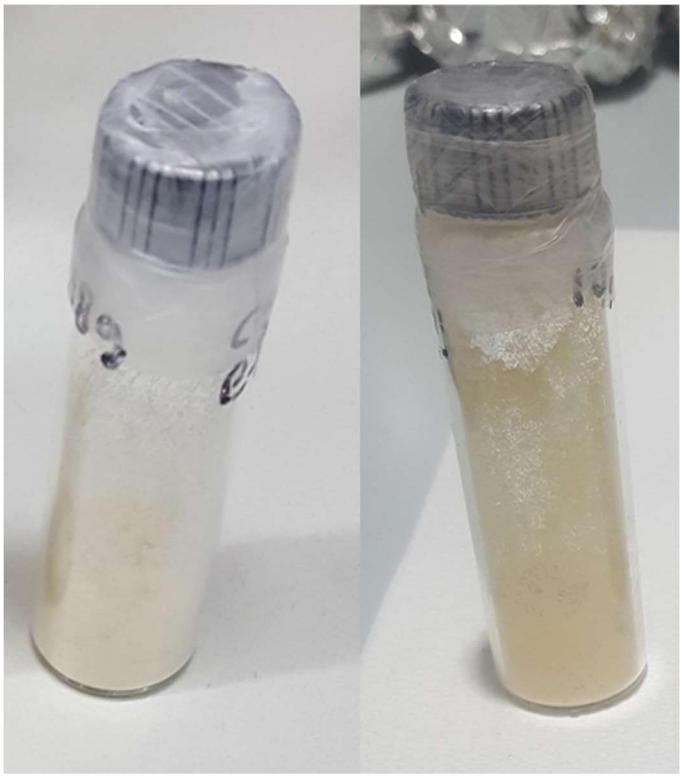

Figure A9. Pure C9 right after purification (left), and 6 months after that (right).

Procedure J: A silica column was prepared using an hexane:EtOAc 1:1 eluent. At these conditions, HMF (absent at complete conversion) and C9 elute together (R_f = 0.3, Figure A9), while C15 is more strongly retained (R_f = 0.1). DAA elutes earlier (R_f = 0.35-0.55). The collected fractions were evaporated and the obtained yellow oil was dried under vacuum. The oil has trouble to solidify even at low temperatures; scratching the glass with a spatula triggers the solidification. C9 was put under nitrogen and stored in a freezer before use.

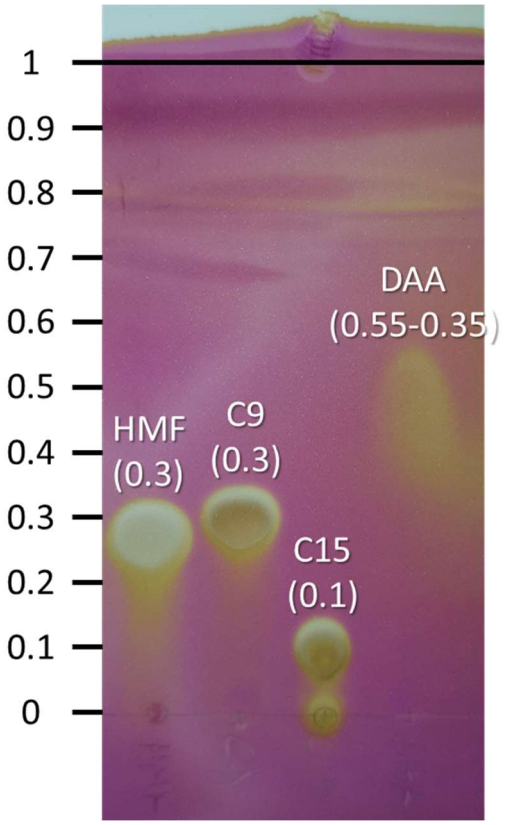

Figure A10. Silica TLCs of all reaction components with 1:1 hexane:EtOAc as the eluent, stained with a potassium permanganate-based solution.

A2.4 - Double-aldol reaction products

C13-OH and C15-OH must form at some point since their dehydration products are observed. We could not detect them in any of our experiments; as it happens, to the best of our knowledge nobody ever had.

A2.5 - Double-aldol condensation products

It is rather simple to obtain multi-gram quantities of the double-condensation products C13 and C15 by performing an NaOH-catalysed aqueous-phase aldol condensation and collect the solid that is filtered off at the end of the reaction, and this is what was done. Even though the various catalytic protocol claim that the products obtained have enough purity to be used as is, we observed $R_f = 0$ spots in the TLC analysis of both products. The nature of the species that originate them is unclear,

but they likely are strongly-retained polymerized degradation products. Indeed, they reappear after some time in batches of purified products. We must specify however that they are present in trace quantities, and that we performed purification only to obtain better quality spectroscopic data (i.e. this might not be necessary for other purposes). In any case, C13 could be purified with a short plug of silica, eluting with pure DCM. C15 is more strongly retained by silica, and pure EtOAc was used instead. However, this purification was not successful since the obtained solid had an orange-red colour, starting from a crude with the typical dark yellow of C15. Based on this and considering the acidic property of the stationary phase, we concluded that silica promoted the self-etherification of the product (the self-etherified HMF has a similar colour). The level of degradation appears to be low, but clearly the purification caused more problems than it solved and it was skipped altogether. Hence, C15 was finally used as is.

A2.5A - C13

Pure C13 is a bright yellow solid (Figure A11). This compound also seems to undergo some degradation over time, even with careful storage, and the colour change is quite clear like it was the case with C8.

Figure A11. Pure C13 right after purification (left), and 6 months after that (right).

Procedure K [13]: Furfural (11 mL, 12.8 g, 133 mmol), acetone (4.9 mL, 3.9 g, 66.6 mmol), NaOH (1 g, 25 mmol) were dissolved in 50 mL of deionized water in a rbf. The reaction was heated to 40 °C and let stir at this temperature for 5 h. After this time, the reaction was quenched by placing the rbf in an ice/water bath and let the product precipitate. The solid was filtered and washed with 0.5 M HCl (1.67 mL) followed by deionized water (100 mL). Finally, the obtained solid was dried at 50 °C for 16 h.

Procedure L: A silica column was prepared using DCM as an eluent. At these conditions, C13 elutes alone (R_f = 0.7) leaving the residue at the start. The collected fractions were evaporated and the obtained yellow solid was dried under vacuum (83 % yield).

A2.5B - C15

Pure C15 is a dark yellow solid (Figure A12). As for the rest of the compounds, C15 appears to undergo degradation.

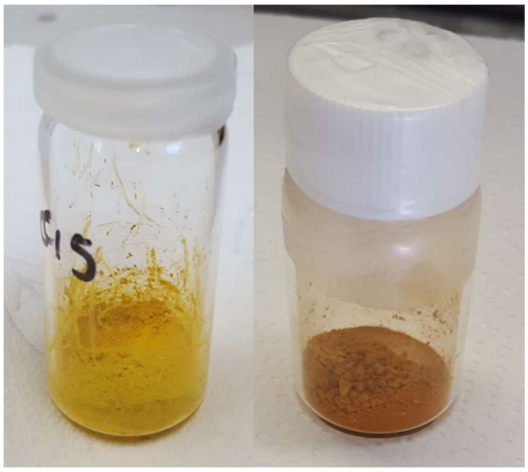

Figure A12. Pure C15 right after purification (left), and 6 months after that (right).

Procedure M [2]: HMF (1 g, 7.91 mmol) and acetone (0.29 mL, 231 mg, 3.96 mmol) were dissolved in 7 mL of deionized water in a rbf. The reaction was heated to 35 °C and let stir at this temperature for 15 min; NaOH (0.66 mL of aqueous 3M NaOH, 1.98 mmol) was then added. The solution was stirred at the same temperature for 60 min. After the required time had elapsed, HCl (2.75 mL of aqueous 0.5 M HCl, 1.37 mmol) solution was added to terminate the reaction. The neutralized solution was diluted 6.5 times with more deionized water. The precipitated C15 was separated by filtration. Finally, C15 was dried overnight in an oven at 50 °C to remove residual water. C15 obtained in this way was not further purified.

A2.5C - C14

There are three possible strategies to obtain C14: the first one is to react one pure mono-condensation product with the complementary aldehyde; the second one is to do a multi-component reaction with ACE, FUR and HMF; the last one is to prepare *in situ* one mono-condensation product and to add the complementary aldehyde some time after the outset of the reaction. In the first case, the reaction is pretty straightforward, and in principle only one product should be obtained. In the second case, a mixture of C13, C14 and C15 would be obtained; the ratio between the three of them would be defined

by the intrinsic reactivity of the two different aldehydes, and the molar ratio between them. In the third case, a mixture with variable composition will be produced according to the effectiveness of the *in situ* formation of the intermediate. For the first approach we decided to test the reaction of C9 and FUR, adapting the procedures developed by the group of Dumesic to our different components [2]. C9 is less soluble than an aldehyde, and for this more water was required to dissolve it (the predicted insolubility of C14 would create C14-covered C9 particles). The addition of NaOH provoked an instant colour change, almost right away a yellow suspended solid formed, while furfural appears to create a separated liquid phase. After some minutes however this second phase disappeared and a suspension similar to the one of C15 was obtained. C14 was obtained as a pure yellow solid (Figure A13, very similar to C13 and C15) which, like for C15, was not further purified.

Figure A13. Freshly-synthesized pure C14.

Procedure N: C9 (0.8 g, 4.82 mmol) and furfural (0.399 mL, 0.463 g, 4.82 mmol) were put in an rbf, and deionized water was added until all the C9 was dissolved when heating at 35 °C (at least 14 mL were required). Afterwards, NaOH (0.4 mL of aqueous 3 M NaOH, 1.2 mmol) was added. The solution was stirred at the same temperature for 60 min. After the required time had elapsed, HCl (1.68 mL of aqueous 0.5 M HCl, 0.84 mmol) solution was added to terminate the reaction. The neutralized solution was diluted 6.5 times with more deionized water. The precipitated C14 was

separated by filtration. Finally, C14 was dried overnight in an oven at 50 °C to remove residual water. C14 obtained in this way was not further purified (91% yield).

Procedure O: Furfural (0.399 mL, 0.463 g, 4.82 mmol), HMF (0.608 g, 4.82 mmol) [or a different mixture of FUR and HMF whose mole sum is 9.64 mmol (for instance 2:8 FUR:HMF 1.928 mmol:7.712 mmol 0.160 mL:0.973 g)] and acetone (0.357 mL, 0.280 g, 4.82 mmol) were dissolved in 8.5 mL of deionized water. Afterwards, NaOH (0.4 mL of aqueous 3 M NaOH, 1.2 mmol) was added. The solution was stirred at the same temperature for 60 min. After the required time had elapsed, HCl (1.68 mL of aqueous 0.5 M HCl, 0.84 mmol) solution was added to terminate the reaction. The neutralized solution was diluted 6.5 times with more deionized water. The mixture was then put in an ice bath to trigger precipitation. The precipitate obtained was separated by filtration. Finally, the precipitate was dried overnight in an oven at 50 °C to remove residual water. The precipitate was analysed by NMR to establish the C13:C14:C15 ratio, as explained in section C1.5.

Procedure P: HMF (0.608 g, 4.82 mmol) and acetone (0.357 mL, 0.280 g, 4.82 mmol) were dissolved in 8.5 mL of deionized water. Afterwards, NaOH (0.4 mL of aqueous 3 M NaOH, 1.2 mmol) was added. The solution was stirred at the same temperature for 5 min. Then, furfural (0.399 mL, 0.463 g, 4.82 mmol) was added and the reaction was let proceeding for 55 min. After the required time had elapsed, HCl (1.68 mL of aqueous 0.5 M HCl, 0.84 mmol) solution was added to terminate the reaction. The neutralized solution was diluted 6.5 times with more deionized water. The mixture was then put in an ice bath to trigger precipitation. The precipitate obtained was separated by filtration. Finally, the precipitate was dried overnight in an oven at 50 °C to remove residual water. The precipitate was analysed by NMR to establish the C13:C14:C15 ratio, as explained in section C1.5.

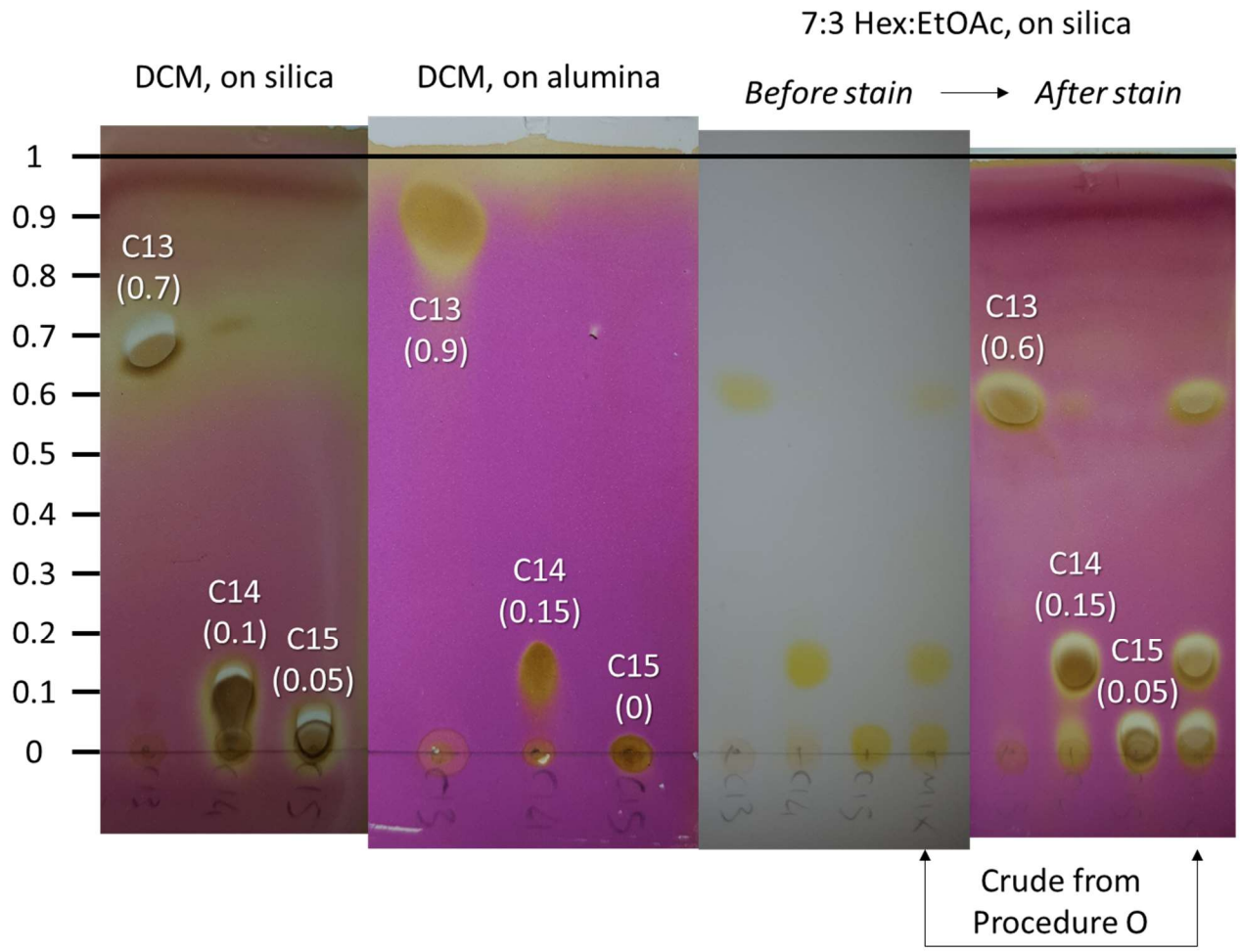

Figure A14 - TLCs of all double condensation products, stained with a potassium permanganate-based solution.

A2.6 - ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of the pure compounds in $CDCl_3$

^{1}H and ^{13}C NMR spectra are included for all reaction components that were purchased, or purified, or synthesized. The spectra were recorded on a Bruker Avance Neo 400 [the ones marked with the superscript ^{A} in the description of the related Figure], or a Bruker Avance 400 [with the superscript ^{B}].

A2.6A - ACE

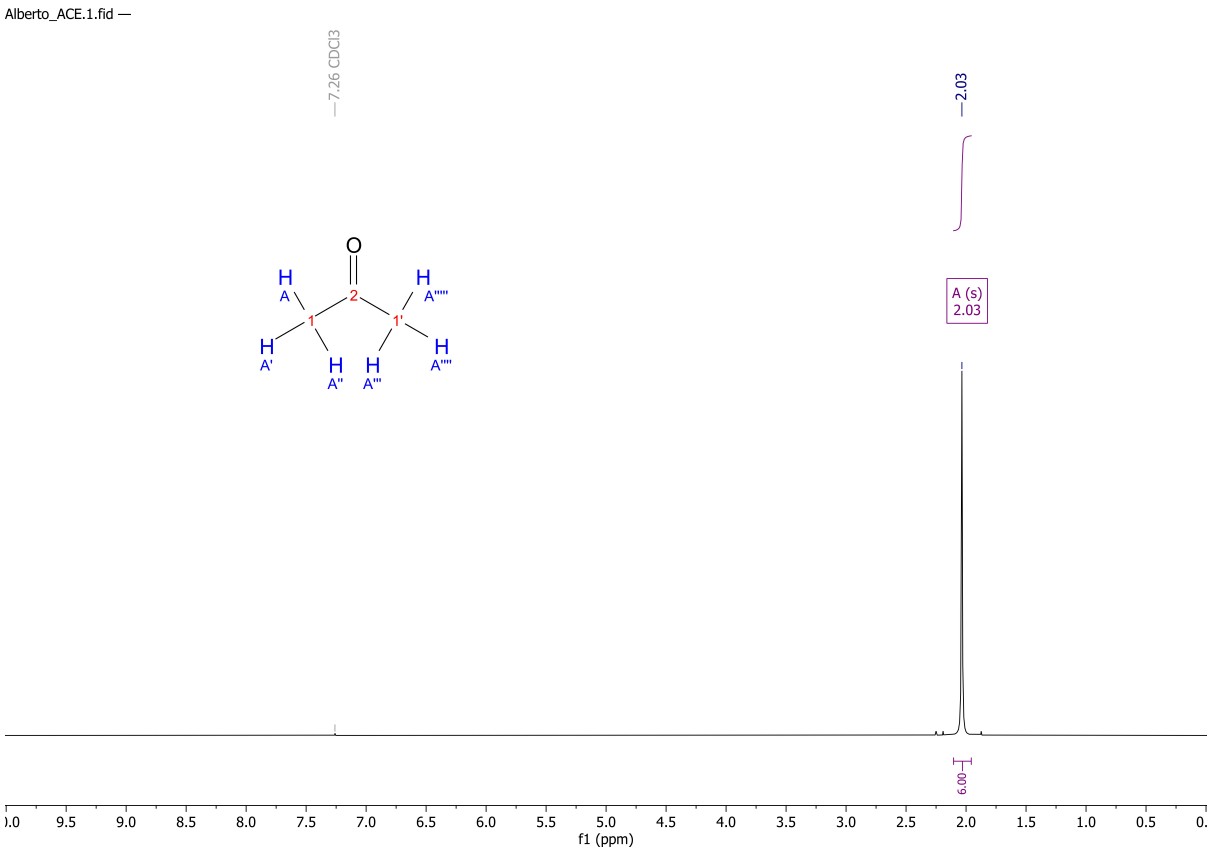

Figure A15[A]. ACE ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (s, 6H).

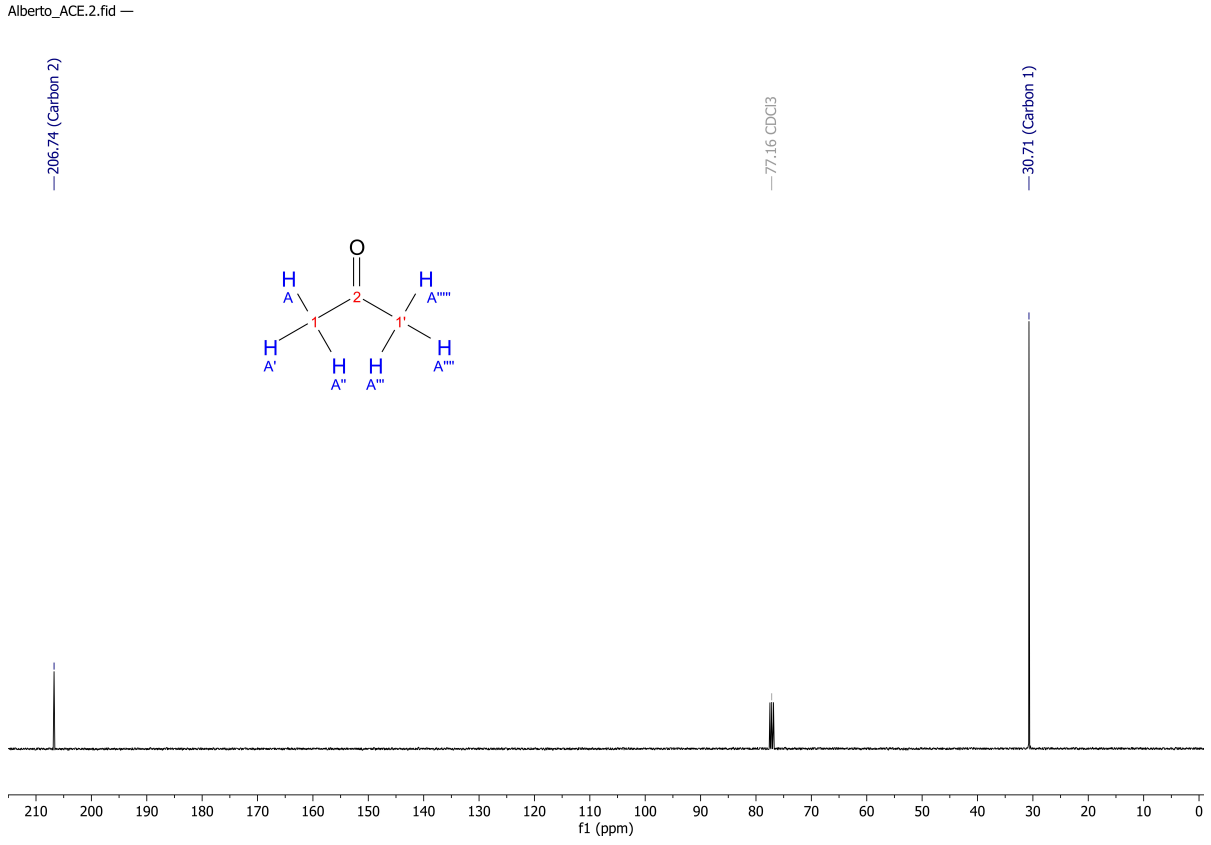

Figure A16[A]. ACE $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 206.74, 30.71.

A2.6B - DAA

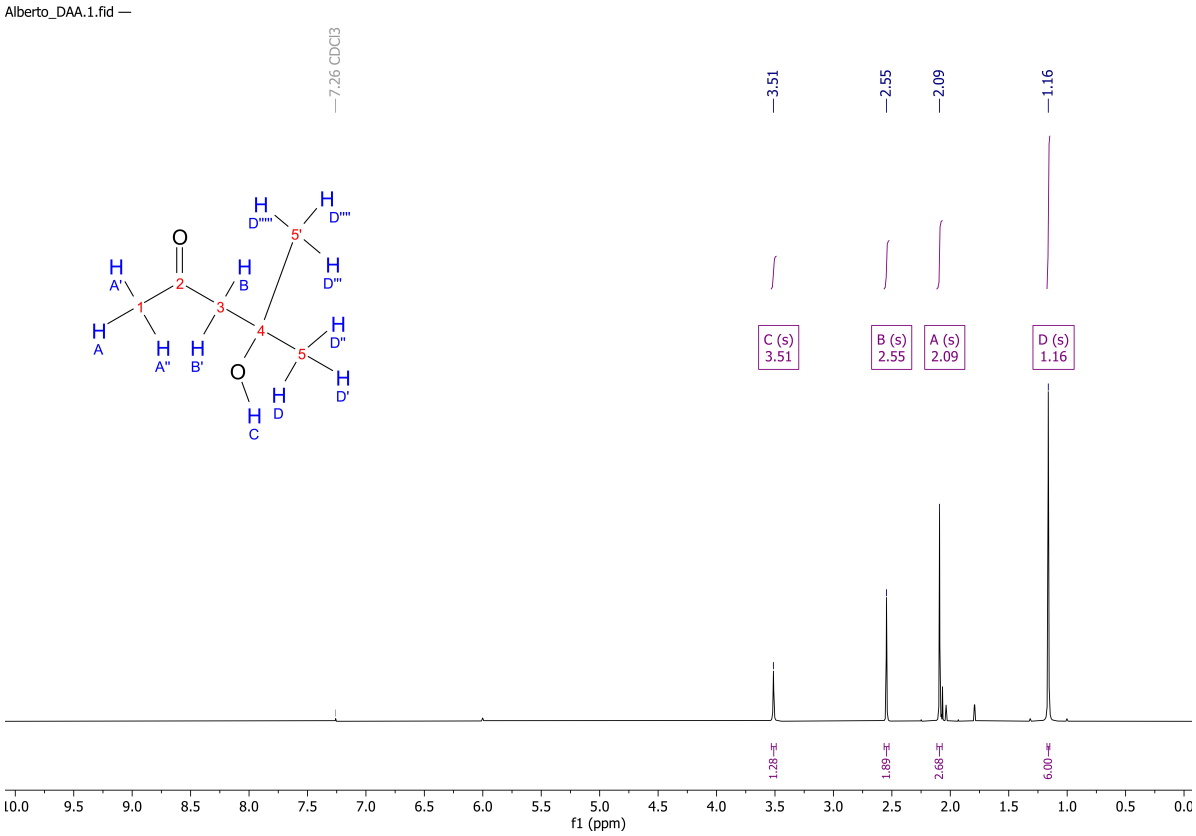

Figure A17[A]. DAA ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 1H), 2.55 (s, 2H), 2.09 (s, 3H), 1.16 (s, 6H).

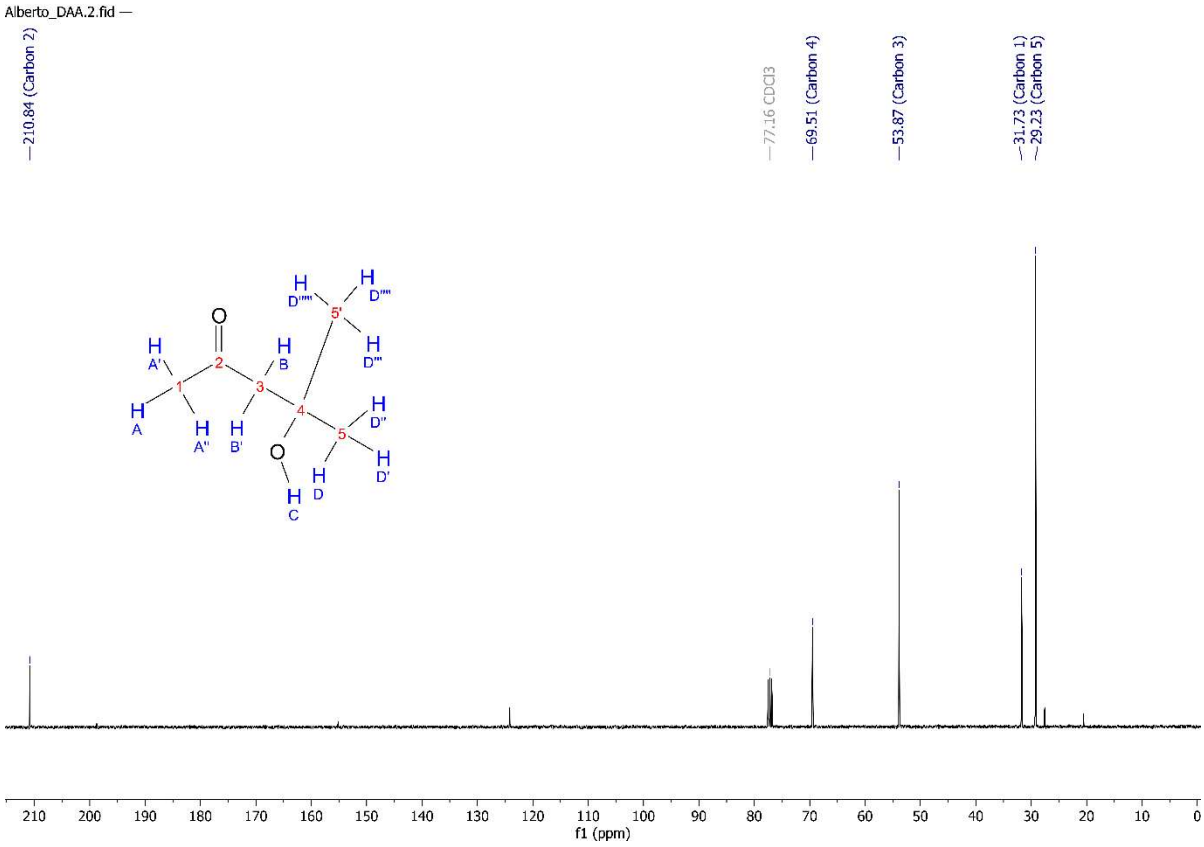

Figure A18[A]. DAA $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 210.84, 69.51, 53.87, 31.73, 29.23.

A2.6C - MES

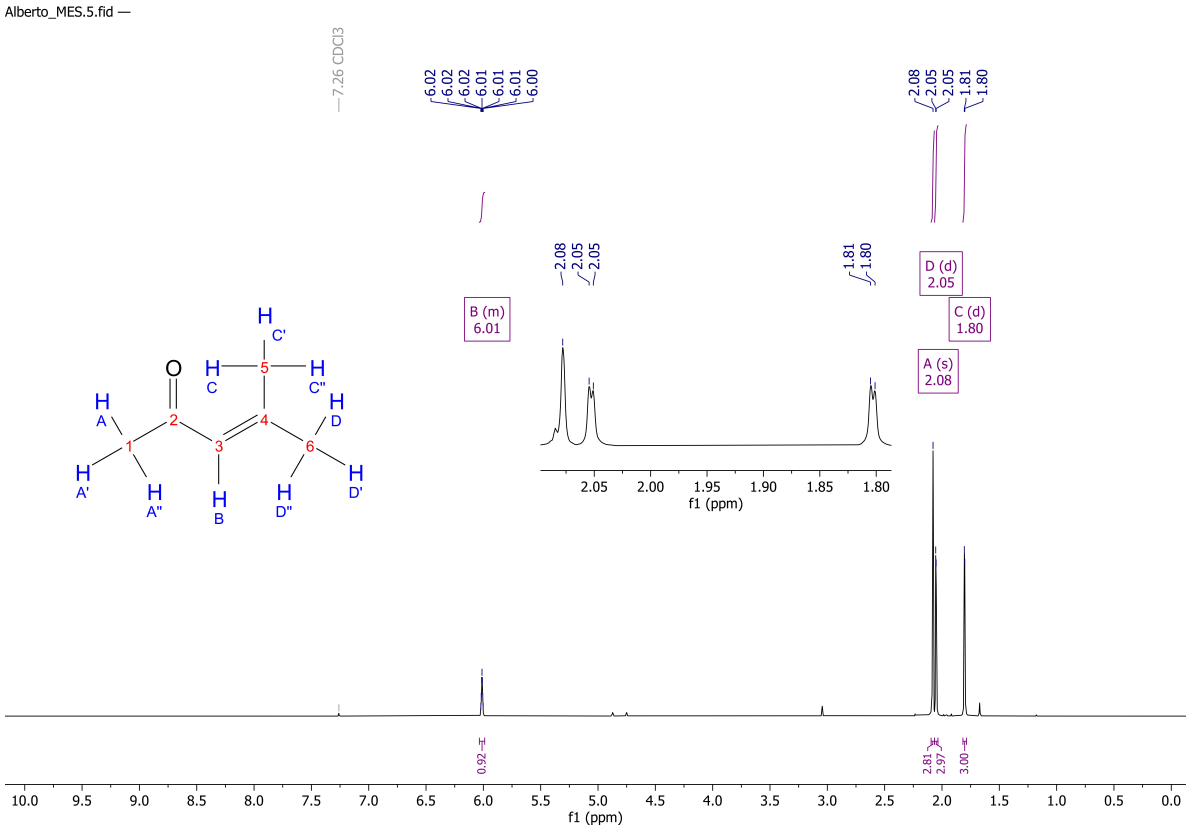

Figure A19[A]. MES ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 – 5.99 (m, 1H), 2.08 (s, 3H), 2.05 (d, J = 1.5 Hz, 3H), 1.80 (d, J = 1.6 Hz, 3H).

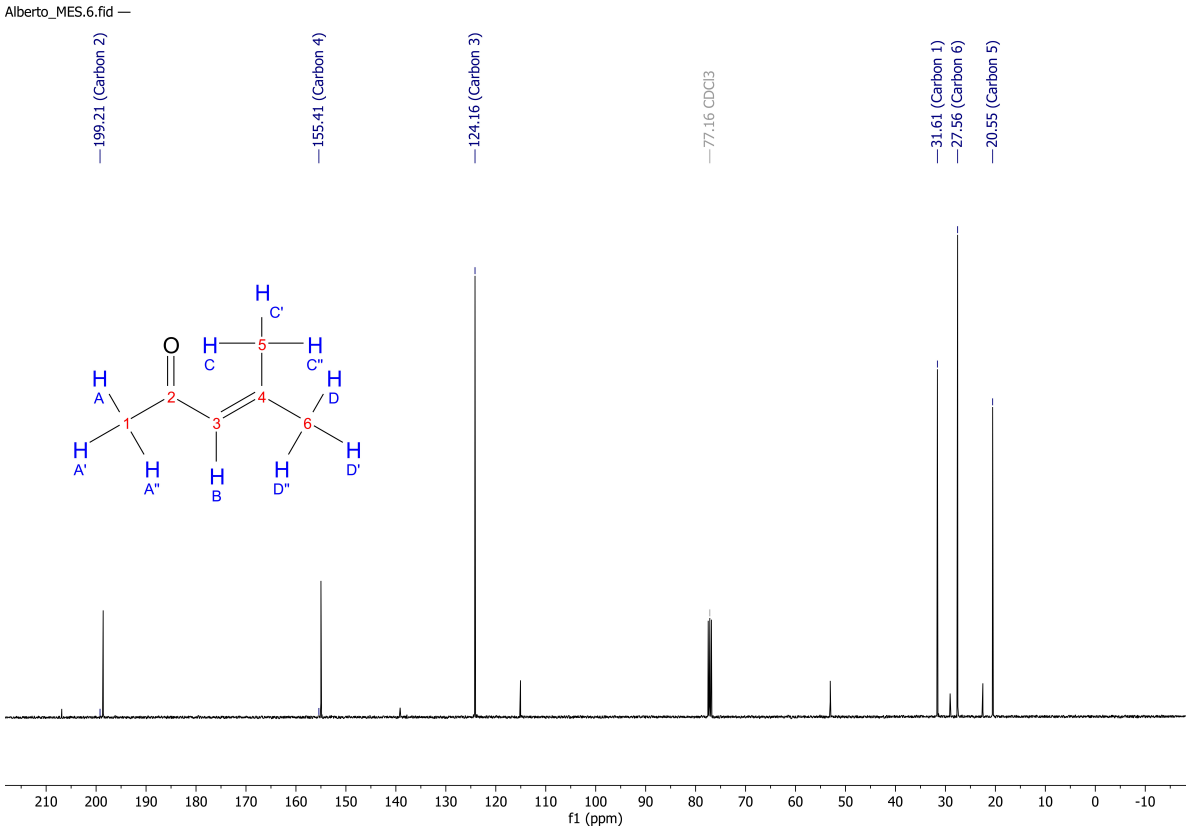

Figure A20[A]. MES ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 199.21, 155.41, 124.16, 31.61, 27.56, 20.55.

A2.6D - FUR

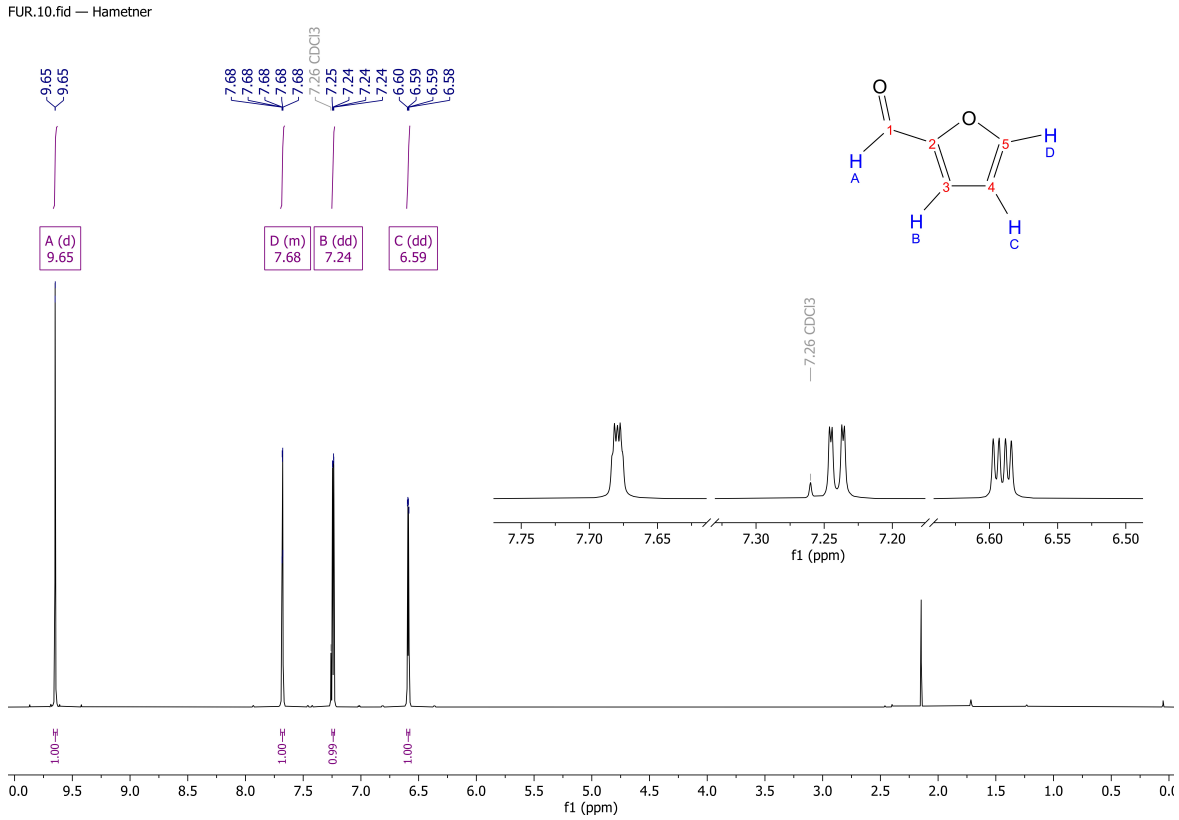

Figure A21[B]. FUR ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 0.7 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.24 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.59 (dd, *J* = 3.6, 1.7 Hz, 1H).

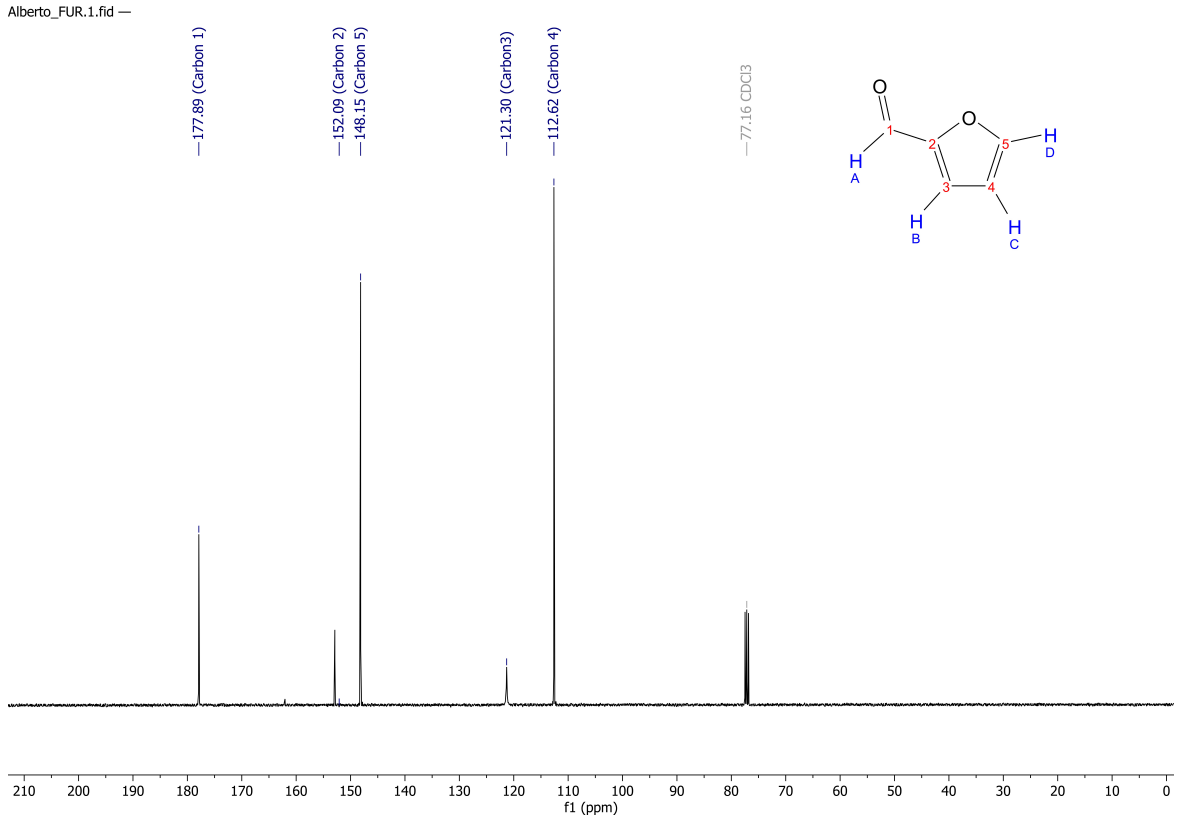

Figure A22[A]. FUR $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 177.89, 152.09, 148.15, 121.30, 112.62.

A2.6E - C8-OH

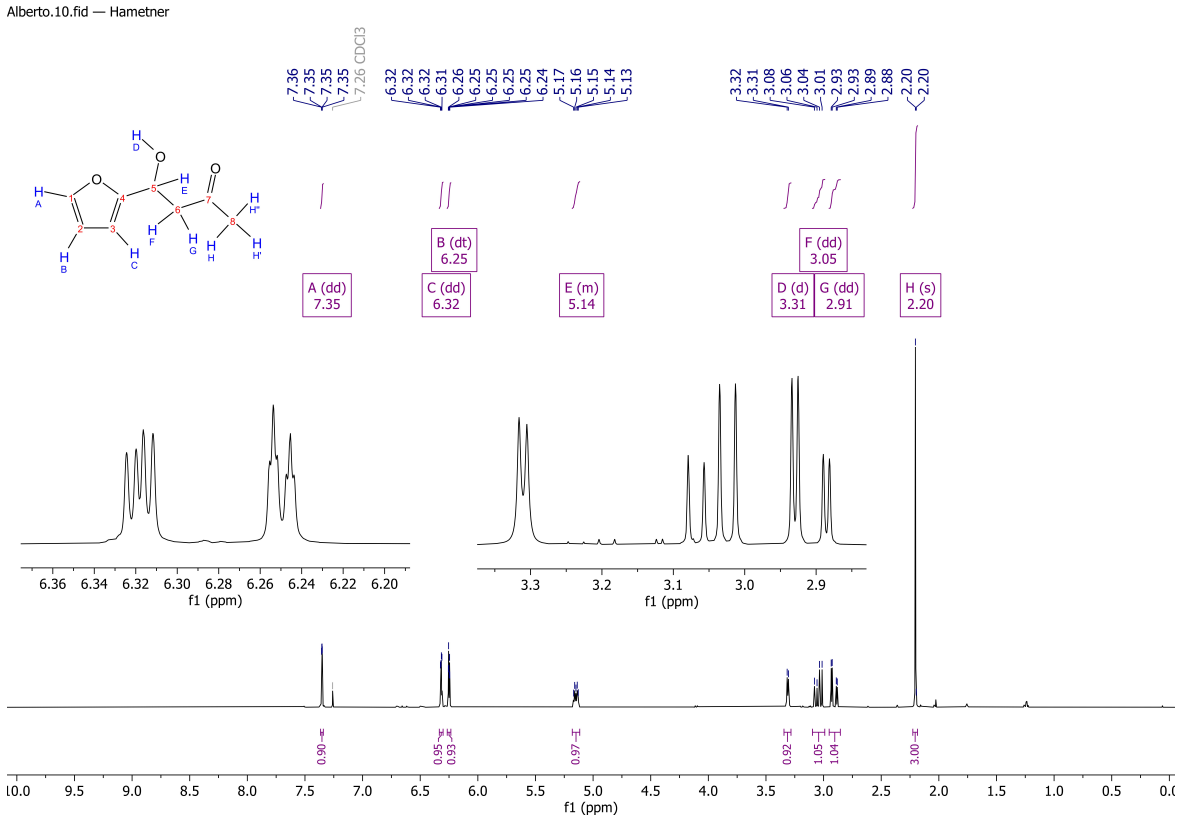

Figure A23[B]. C8-OH ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.25 (dt, *J* = 3.2, 0.8 Hz, 1H), 5.18 – 5.12 (m, 1H), 3.31 (d, *J* = 4.4 Hz, 1H), 3.05 (dd, *J* = 17.6, 8.9 Hz, 1H), 2.91 (dd, *J* = 17.6, 3.5 Hz, 1H), 2.20 (s, 3H).

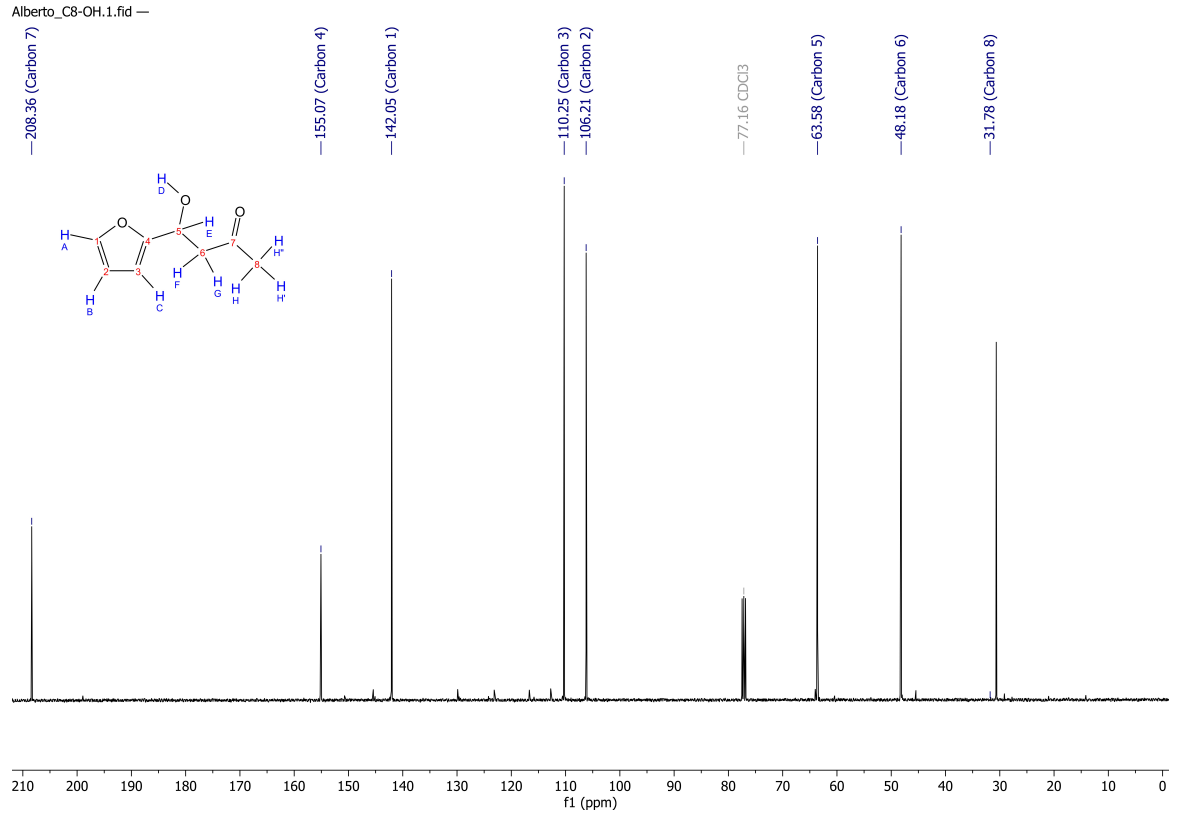

Figure A24[A]. C8-OH $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 208.36, 155.07, 142.05, 110.25, 106.21, 63.58, 48.18, 31.78.

A2.6F - C8

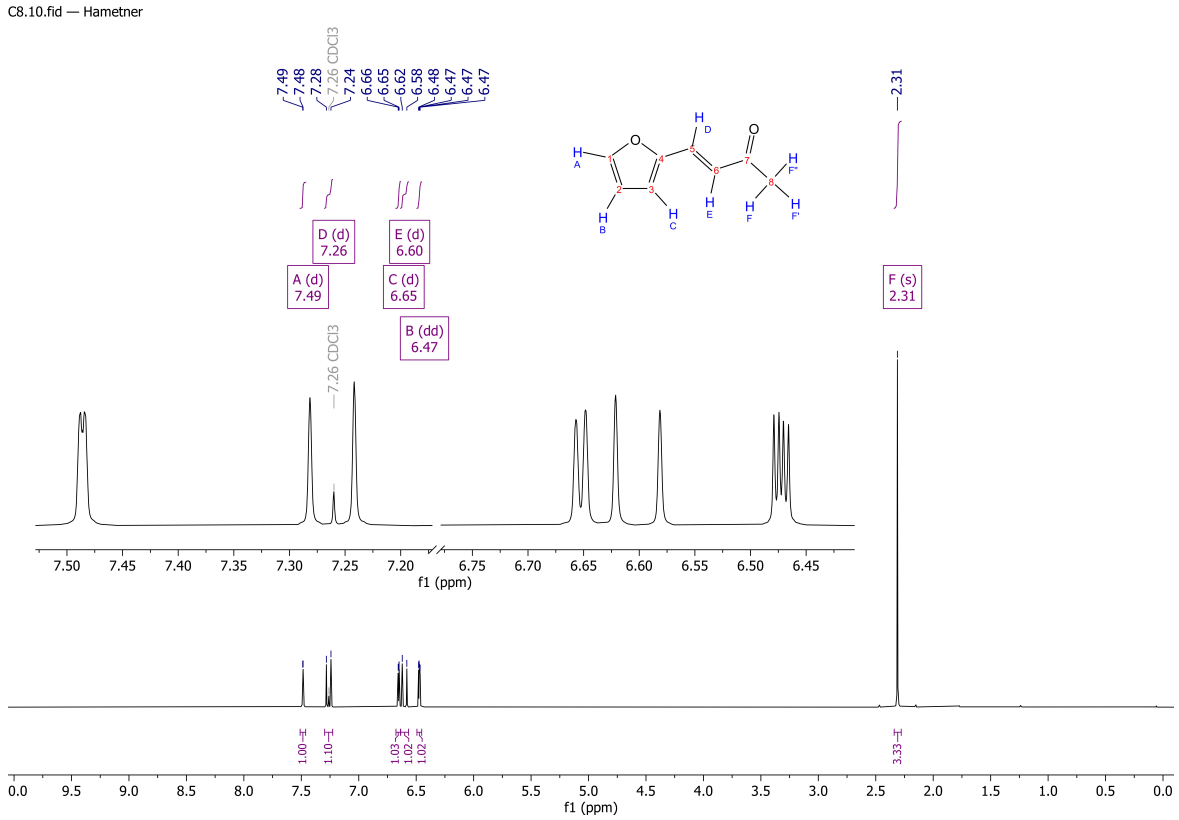

Figure A25[B]. C8 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 1.4 Hz, 1H), 7.26 (d, J = 15.9 Hz, 1H), 6.65 (d, J = 2.9 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.47 (dd, J = 3.5, 1.8 Hz, 1H), 2.31 (s, 3H).

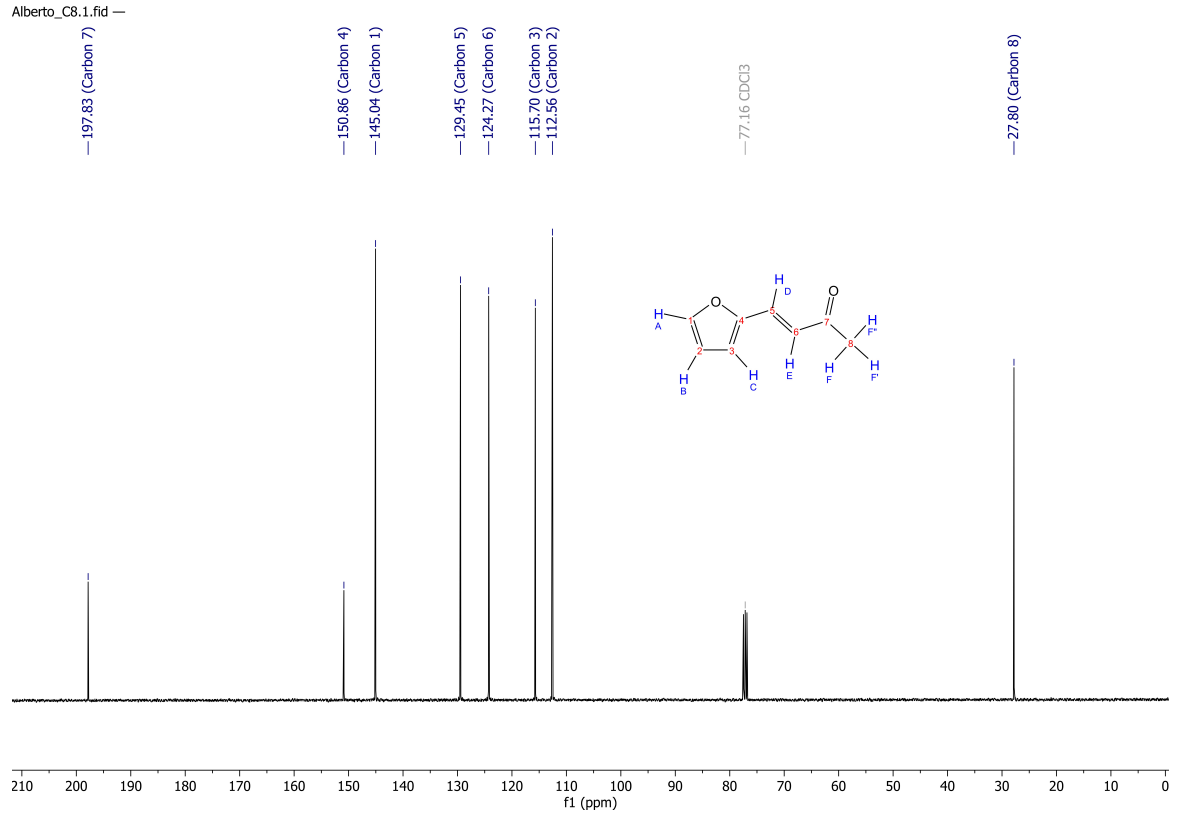

Figure A26[A]. C8 ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 197.83, 150.86, 145.04, 129.45, 124.27, 115.70, 112.56, 27.80.

A2.6G - C13

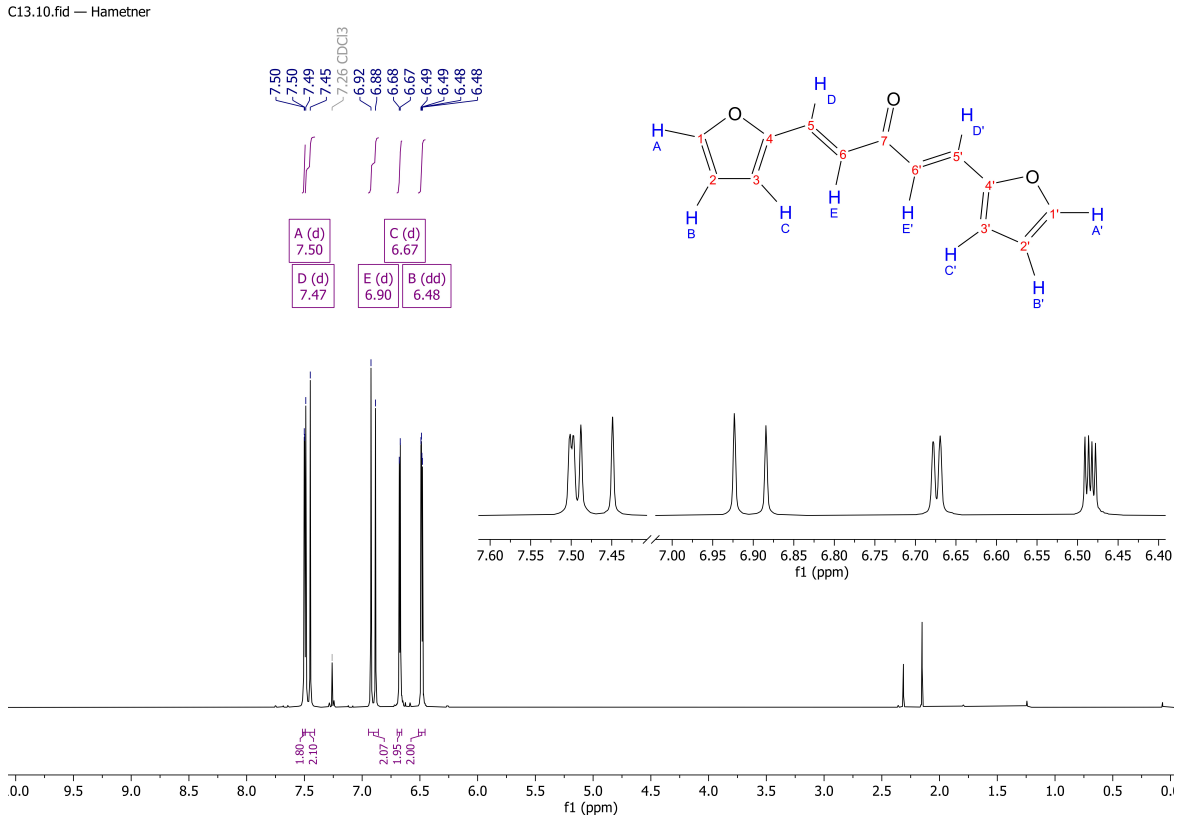

Figure A27[B]. C13 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 1.3 Hz, 2H), 7.47 (d, J = 15.6 Hz, 2H), 6.90 (d, J = 15.6 Hz, 2H), 6.67 (d, J = 3.4 Hz, 2H), 6.48 (dd, J = 3.4, 1.8 Hz, 2H).

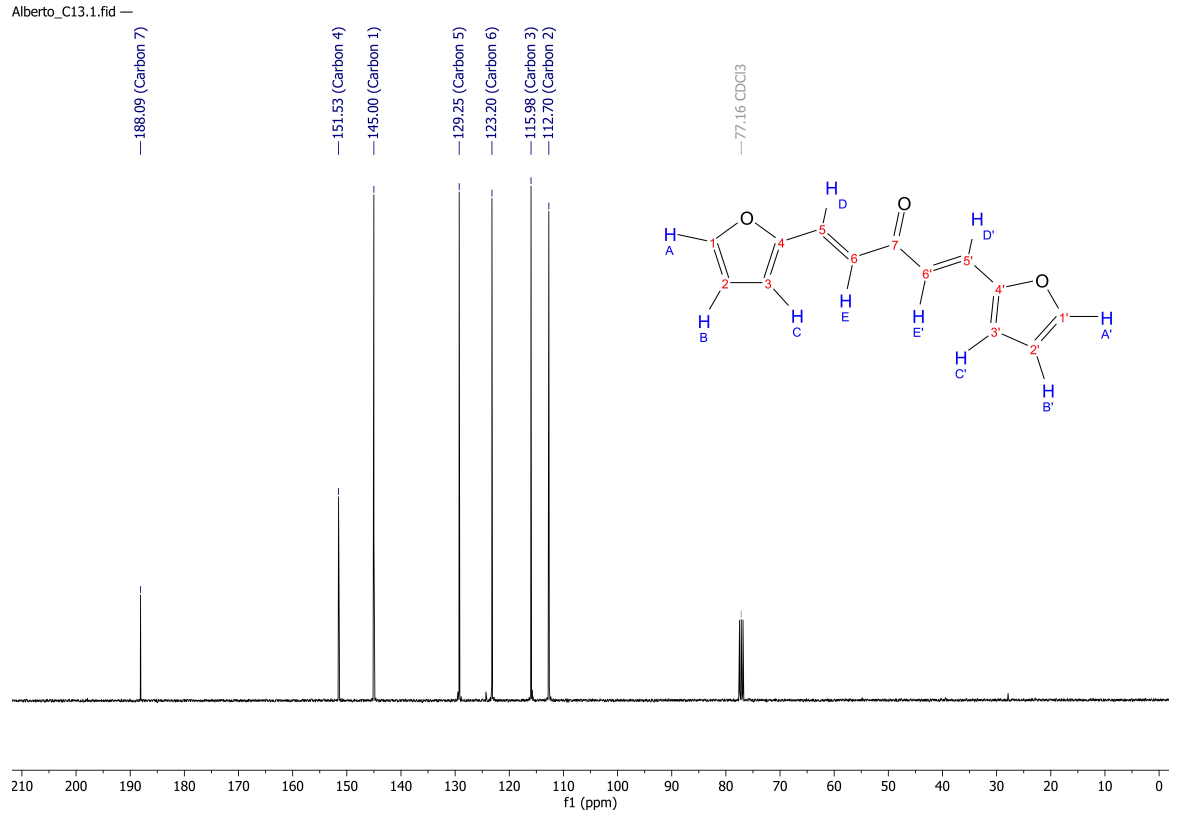

Figure A28[A]. C13 $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 188.09, 151.53, 145.00, 129.25, 123.20, 115.98, 112.70.

A2.6H - HMF

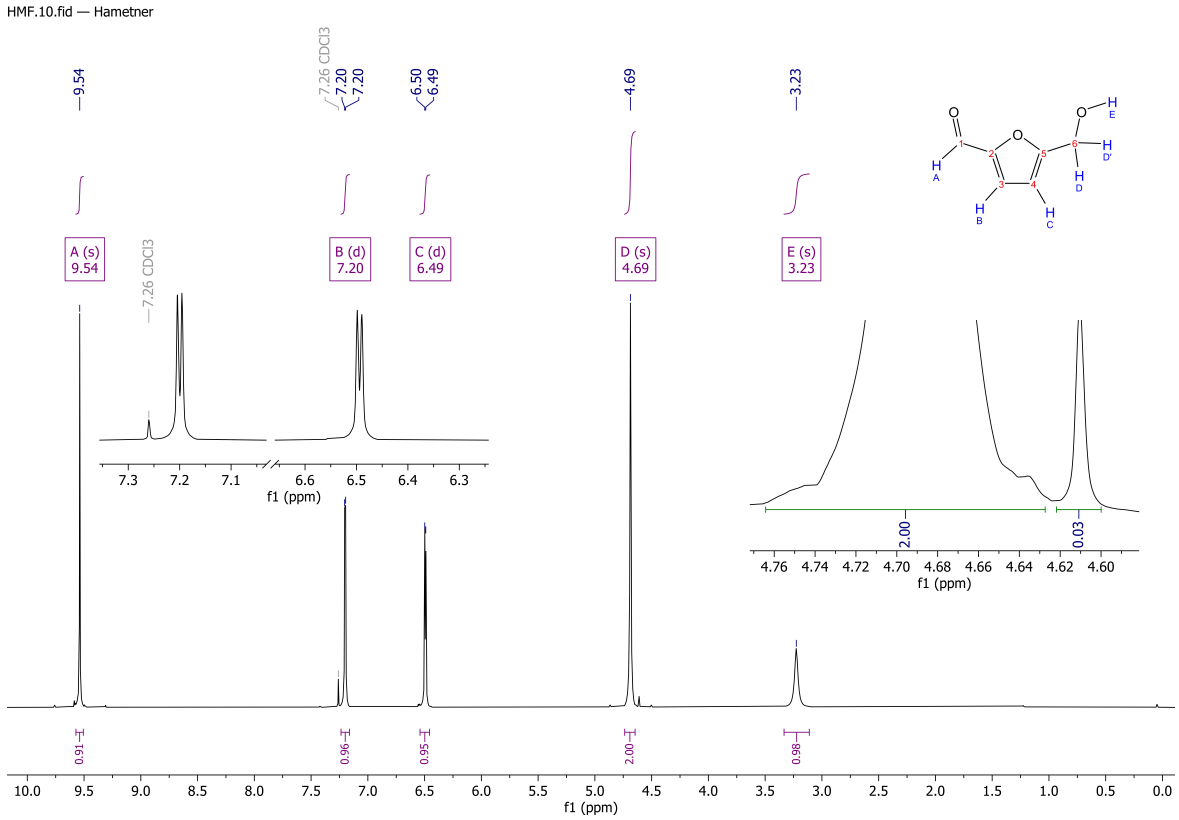

Figure A29[B]. HMF ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.20 (d, J = 3.5 Hz, 1H), 6.49 (d, J = 3.6 Hz, 1H), 3.23 (s, 1H).

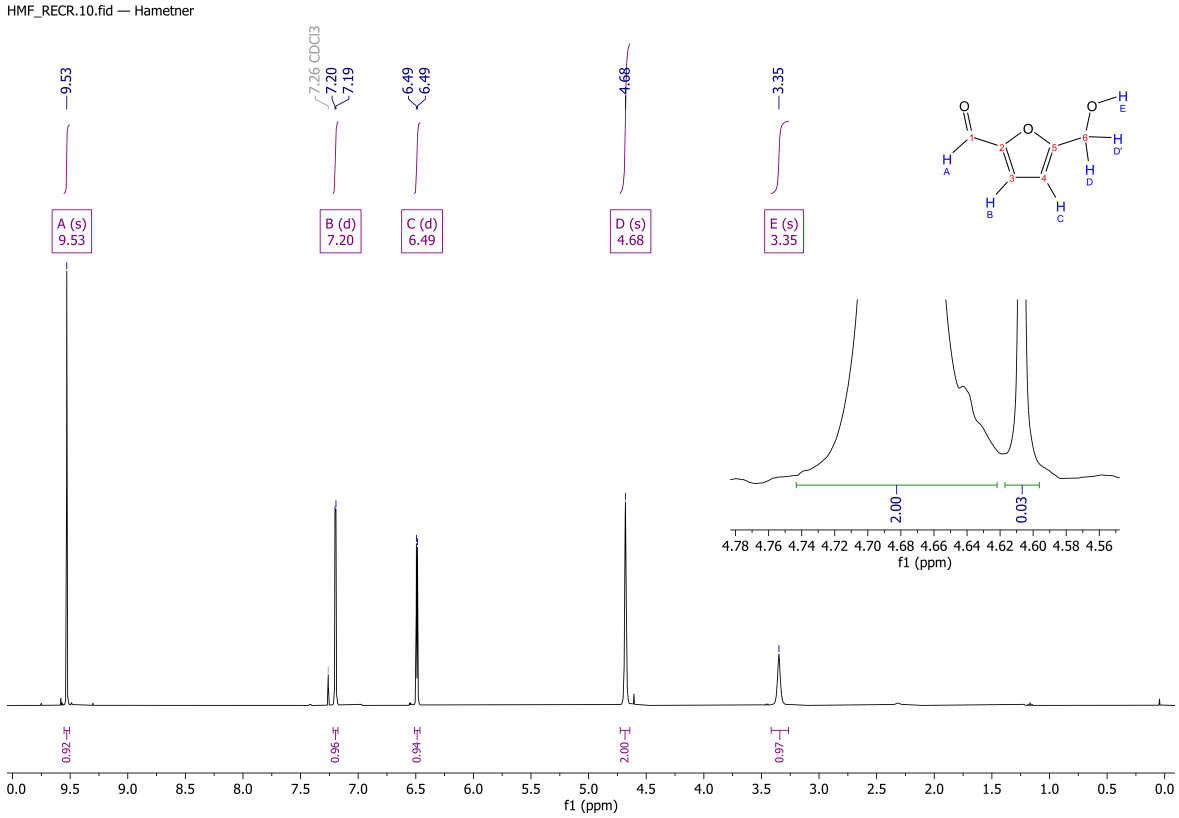

Figure A30[B]. HMF recr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.20 (d, J = 3.5 Hz, 1H), 6.49 (d, J = 3.6 Hz, 1H), 4.68 (s, 2H), 3.35 (s, 1H).

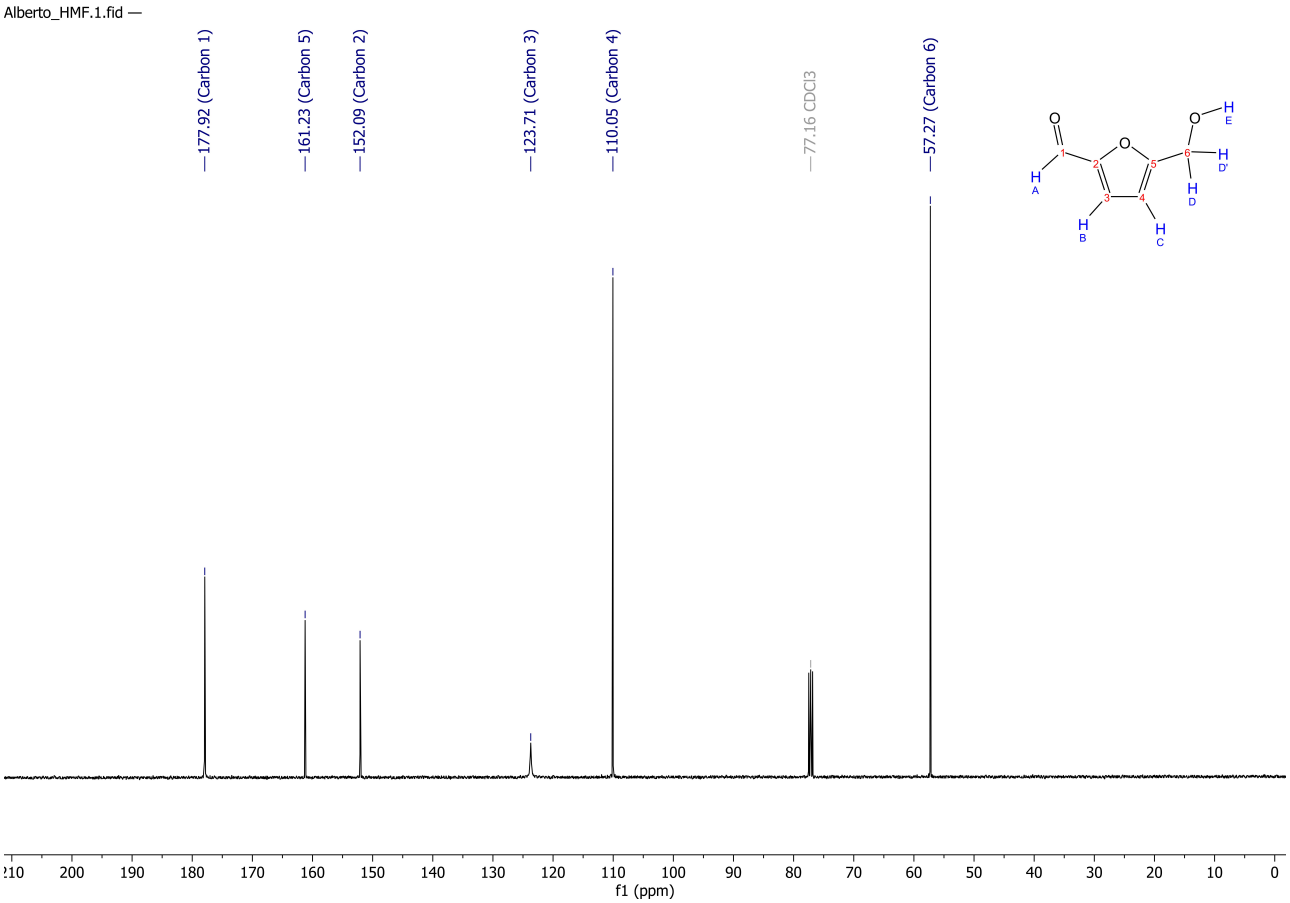

Figure A31[A]. HMF $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 177.92, 161. 23, 152.09, 123.71, 110.05, 57.27.

A2.6I - C9

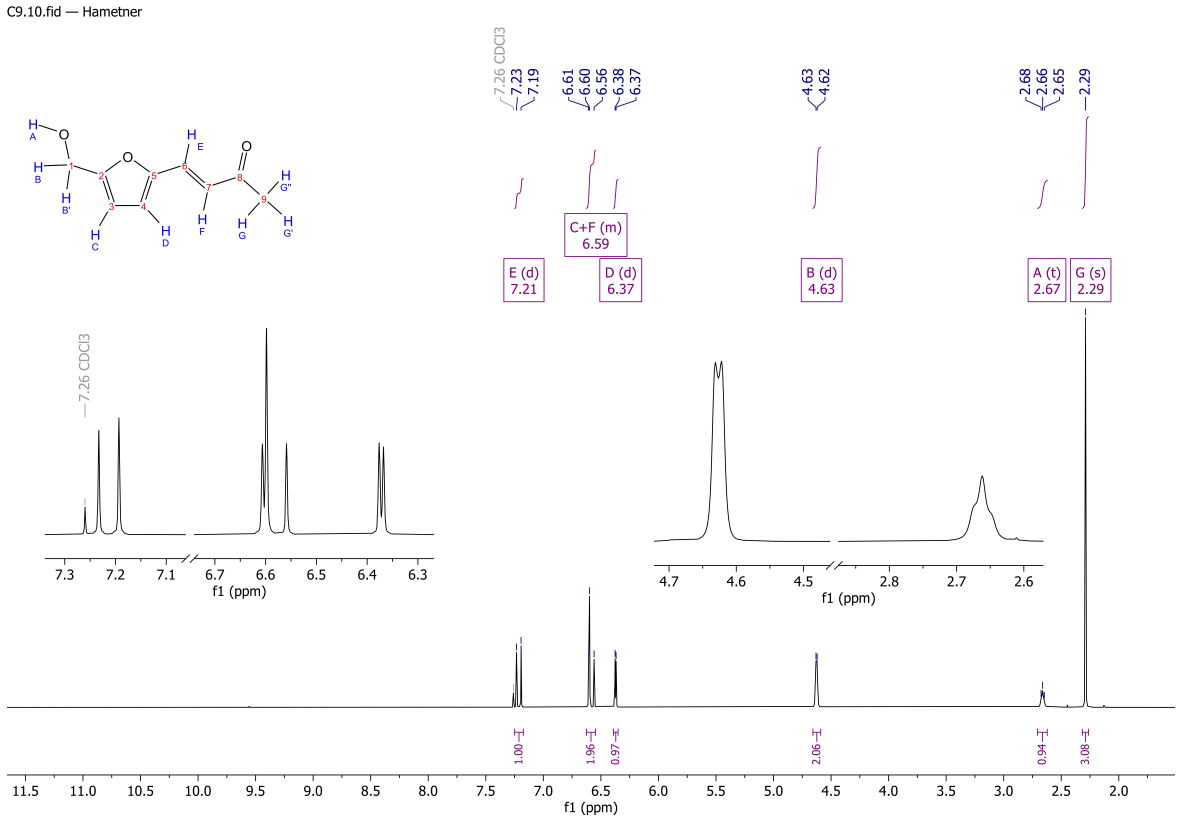

Figure A32[B]. C9 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 15.8 Hz, 1H), 6.62 – 6.55 (m, 2H), 6.37 (d, *J* = 3.4 Hz, 1H), 4.63 (d, *J* = 4.1 Hz, 2H), 2.67 (t, *J* = 5.4 Hz, 1H), 2.29 (s, 3H).

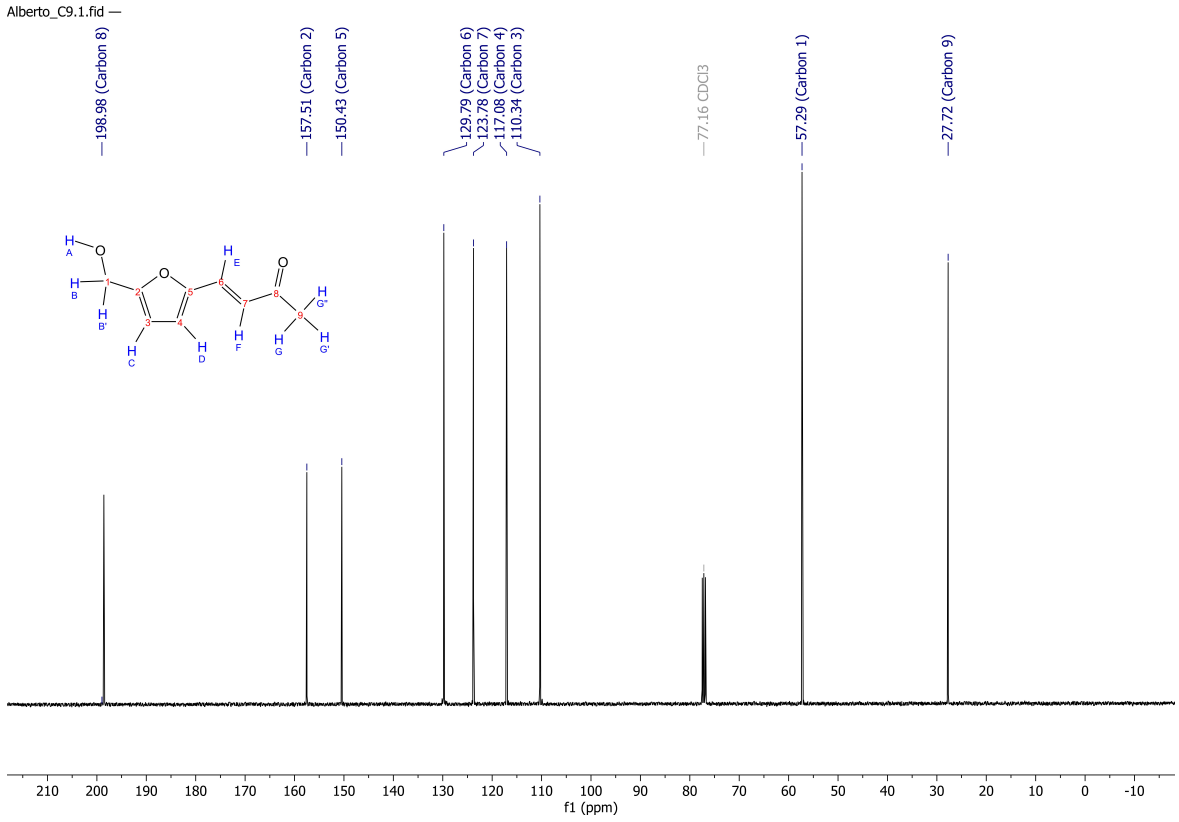

Figure A33[A]. C9 $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 198.98, 157.51, 150.43, 129.79, 123.78, 117.08, 110.34, 57.29, 27.72.

A2.6J - C15

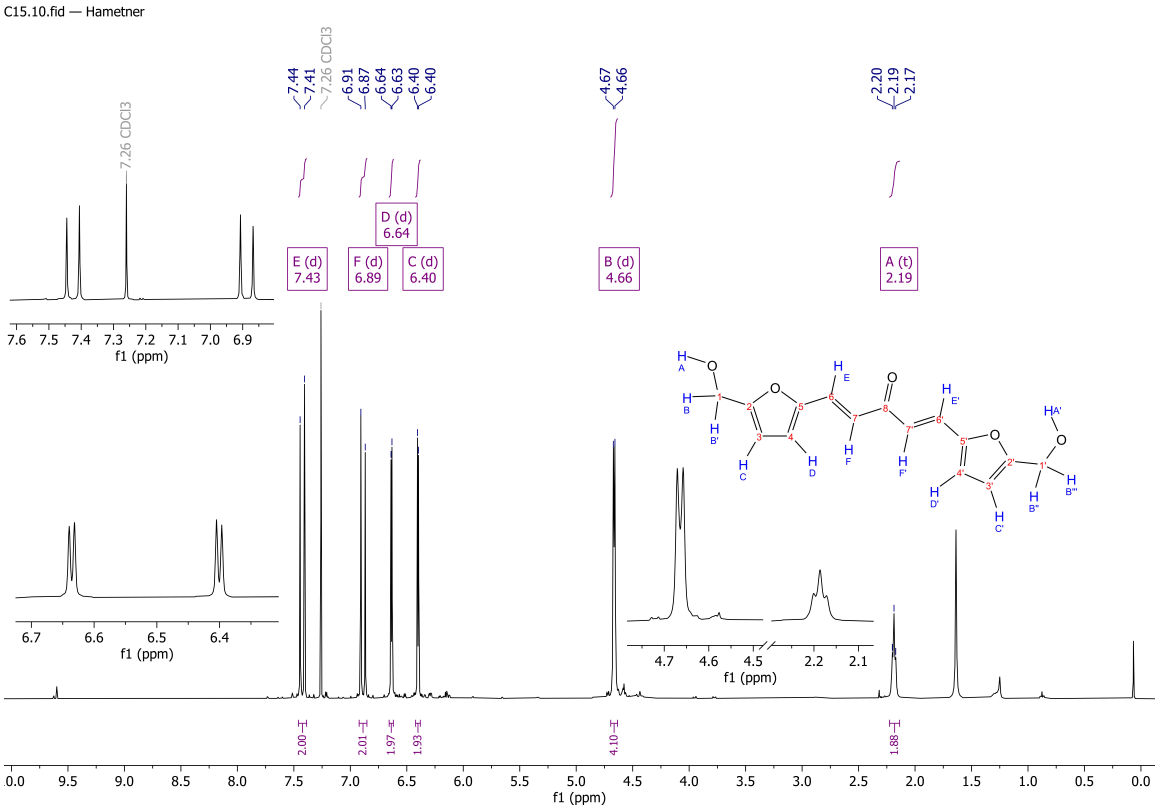

Figure A34[B]. C15 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 15.6 Hz, 2H), 6.89 (d, J = 15.5 Hz, 2H), 4.66 (d, J = 5.7 Hz, 4H), 2.19 (t, J = 6.0 Hz, 2H).

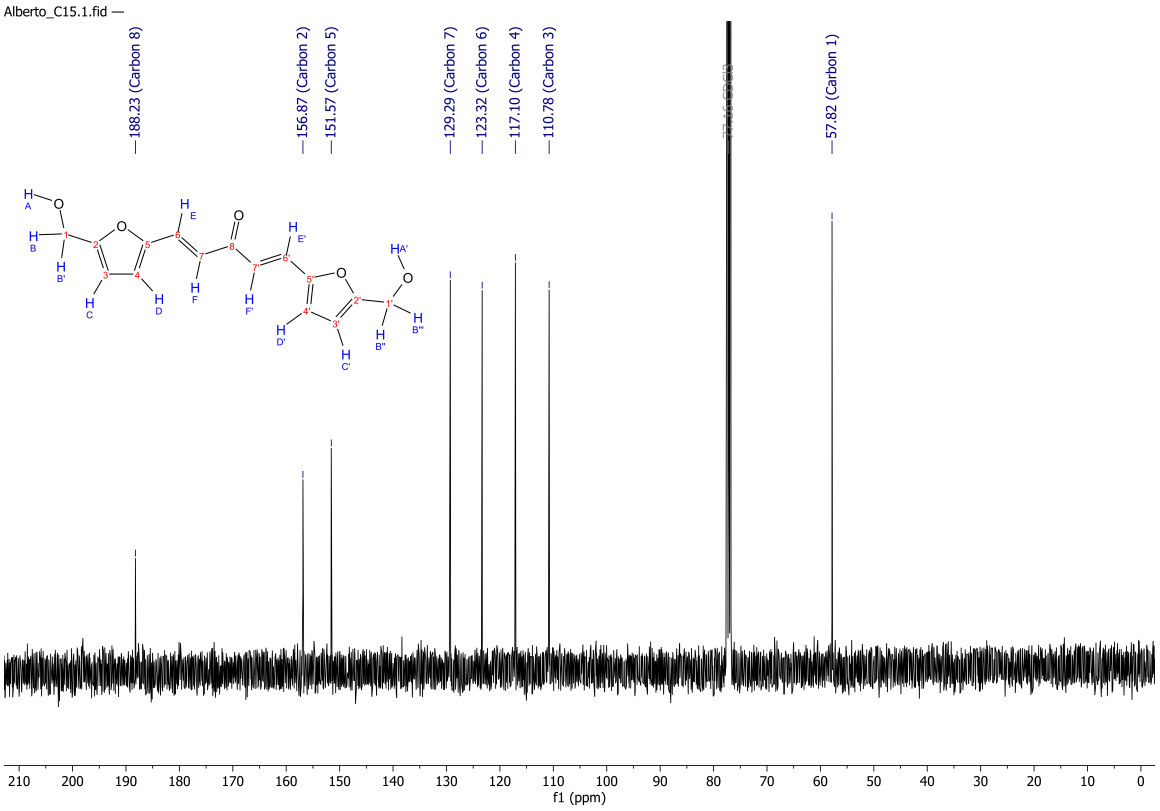

Figure A34[A]. C15 $^{13}C\{^{1}H\}$ NMR (400 MHz, $CDCl_3$) δ 188.23, 156.87, 151.57, 129.29, 123.32, 117.10, 110.78, 57.82.

A2.6K - C14

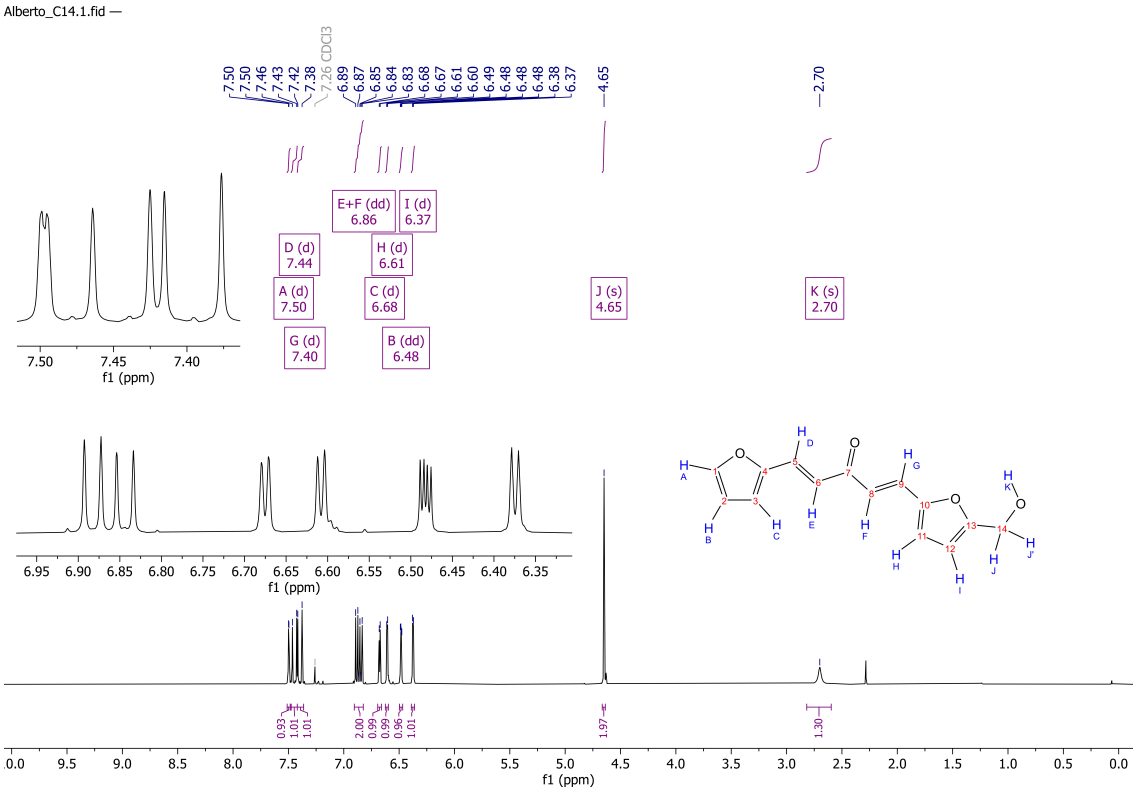

Figure A36[A]. C14 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 1.4 Hz, 1H), 7.44 (d, *J* = 15.6 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 6.86 (d+d, *J* = 15.6, 2H), 6.68 (d, *J* = 3.4 Hz, 1H), 6.61 (d, *J* = 3.3 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.37 (d, *J* = 3.3 Hz, 1H), 4.65 (s, 2H), 2.70 (s, 1H).

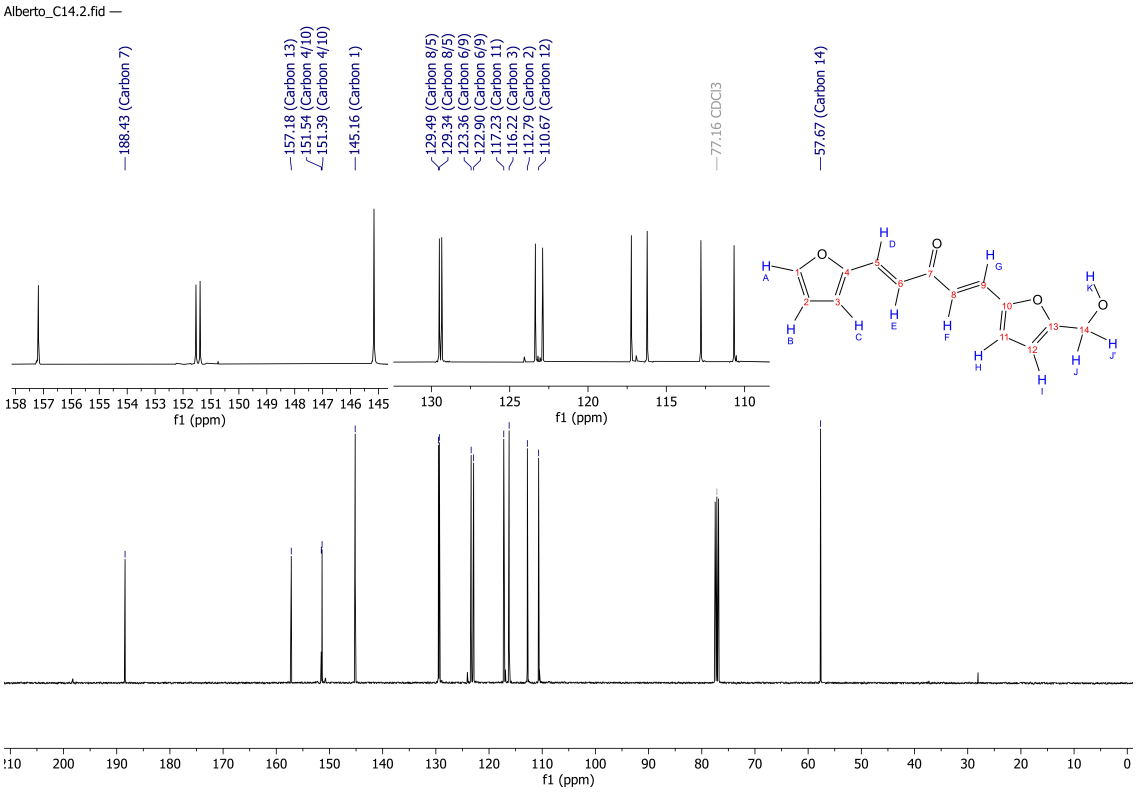

Figure A37[A]. C14 ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 188.43, 157.18, 151.54, 151.39, 145.16, 129.49, 129.34, 123.36, 122.90, 117.23, 116.22, 112.79, 110.67, 57.67.

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