UNIVERSITAT JAUME I

Organocatalytic synthesis of a fluorogenic substrate

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I can't thank enough to my tutor's job, Dr. Bea Escuder, because without her help, this work would not have taken form or content. Besides, there is one person more than I must name, she is Barbara Gimenez who has helped been day by day in the laboratory and she has always been there to help me with some question, so much experimental and academic.

Finally, also, thank the help of Rosa Martí, for resolving the doubts in the occasions where the results were not expected and to find another way for the synthesis.

Abstract

The aim of work has been the preparation of an organic compound, the methodol, that will be used as a reagent in an organocatalytic reaction which will turn into a fluorescent product. This job is included in a broader objective of the research group that consists in detecting the product of the catalytic reaction due to its fluorescence by using supramolecular catalysts. The job lies in the optimization of the preparation of the methodol, its characterization by ^{1}H NMR, ^{13}C NMR, COSY and MS, and the study of its reactivity through the use an organocatalysts as L-proline.

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Abbreviations

DMSO = Dimethyl sulfoxide

ESI = Electrospray ionization

EtOAc = Ethyl acetate

MeOH = Methanol

MS = Mass spectrometry

NMR = Nuclear Magnetic Resonance

PBS = Phosphate buffered saline

R.T =Room temperature

TLC = Thin layer chromatography

1. Introduction

In this work, we will evaluate the synthesis of an organic compound by aldol reaction. This reaction will be catalyzed by a purely organic substance without the presence of metals.

1.1 Aldol reaction

In organic chemistry, the aldol reaction is used to form carbon-carbon bonds. The reaction was found out by the Russian chemist Alexander Borodin in 1869 and by the French chemist Charles-Adolphe Wurtz in 1872.

The reaction combines two carbonyl compounds to form a more complex molecule. This reaction involves the nucleophilic addition of the enolate of a ketone to an aldehyde to form α,β-hydroxy carbonyl compound.

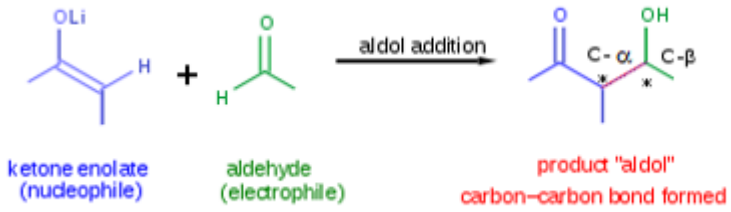


Figure 1. Aldol addition.

These products are known as aldols, which are composed of an aldehyde and an alcohol. Improved complexity arises because up to two new stereogenic centers are formed in the α and β carbon of aldol adduct. One of the most interesting properties is its ability to dehydrate easily through heating. In this manner, it is formed an α, β-unsaturated carbonyl compound. This process of dehydration is called aldol condensation.

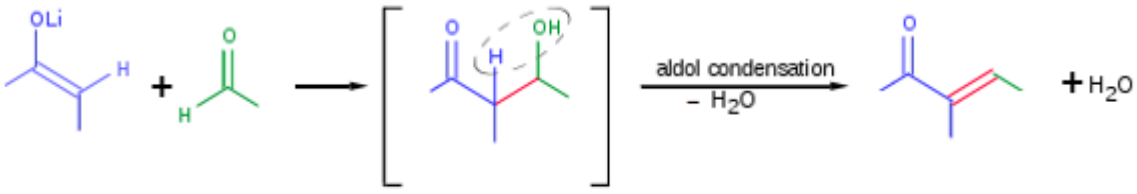


Figure 2. Aldol condensation.

A variety of nucleophiles can be used in the aldol reaction, including enols, enolates and enol ethers of ketones, aldehydes and many other carbonyl compounds. However, the electrophile is usually an aldehyde or a ketone.

When the nucleophile and the electrophile are different, the reaction is called the crossed aldol reaction. On the other hand, when the nucleophile and the electrophile are equal, the reaction is called aldol dimerization.

1.1.1. Mechanism

The aldol reaction may follow by two fundamentally different mechanisms. Carbonyl compounds, such as aldehydes and ketones, are nucleophilic species. These compounds can be converted into enols or enol ethers. The hydrogen atoms of the alpha carbon of these compounds are acidic and can be captured with suitable bases. These hydrogens be considered nucleophilic in the alpha carbon. They can especially attack reactive protonated carbonyls, such as protonated aldehydes.

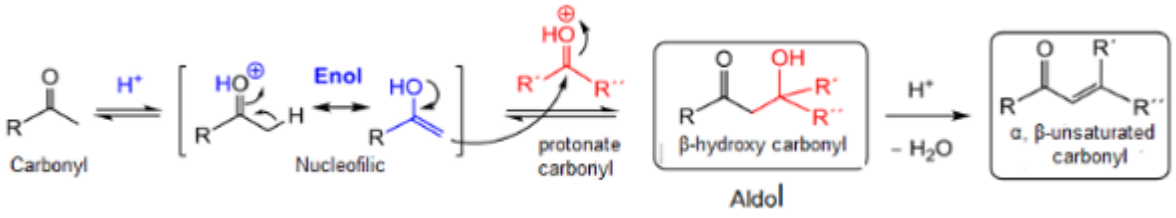


Figure 3. Enol mechanism.

Carbonyl compounds can also deprotonate to form enolates, which are much more nucleophilic than enols or enol ethers and can directly attack electrophiles. The usual electrophile is an aldehyde, as ketones are much less reactive.

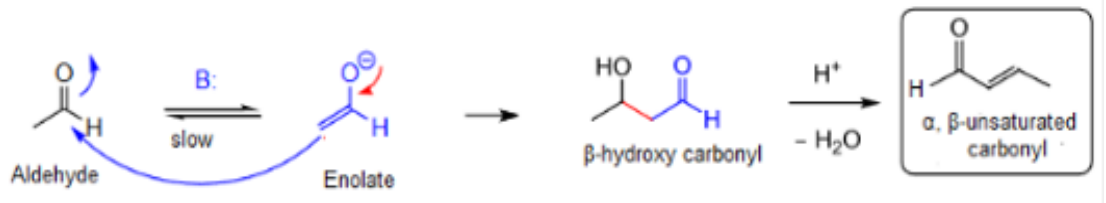


Figure 4. Enolate mechanism.

Besides, there is also the intramolecular aldol reaction which is the condensation reaction of two aldehyde groups or ketone groups in the same molecule. This reaction is important for the formation of carbon-carbon bonds in organic molecules that contain ring systems.

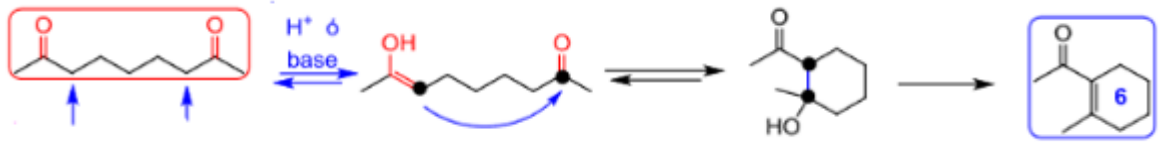


Figure 5. Intramolecular aldol reaction.

1.2 Organocatalysis

The great demand of new materials in the society and the concern for a less polluting chemistry, has caused the manifestation of a new generation of highly selective and sustainable organic catalysts.

Currently, the study of organic reactions catalyzed by purely organic substances is designated organocatalysis. These reactions are carried out in the absence of environmentally polluting metals. Organocatalysts are low molecular weight compounds. The most usual are proline derivatives, amines and thioureas.

Most chemical catalysts consist of metallic elements coordinated with ligands. However, McMillan demonstrated that The Asymmetric Reaction of Diels-Alder can be performed with a secondary amine derivative that doesn't contain any metallic elements (McMillan's catalyst), and proposed the concept of "organic molecular catalyst".

Until 1990s, it wasn't proved that organic catalysts could be used to solve major problems in chemical synthesis. The Hajos-Parrish reaction showed that small organic molecules (such as proline) could catalyze the same chemical reactions as much larger organic molecules (enzymes). The Hajos-Parrish reaction is based on the use of chiral secondary amine catalysts. These secondary amines form transient enamines when exposed to ketones, which can react enantioselectivity with suitable aldehyde electrophiles. Amine reacts with carbonyl to form an enamine. The enamine acts as nucleophile similar to enol and then the amine is released from the product. The best conditions for Hajos-Parrish were a catalytic amount of proline (3 mol%).

In the nature, the aldol reaction is catalyzed by enzymes to perform the coupling of unmodified substrates in aqueous medium thus achieving an absolute stereocontrol. Primary and secondary amines are able to catalyze intermolecular aldol reactions with acetone in aqueous media with organic solvents.

Although enzyme processes occur in an aqueous medium, water has been a solvent avoided in organic reactions as it was shown, for example, that proline catalyzes direct aldol reactions with high enantioselectivity in polar organic solvents DMSO. But, when it was carried out in the presence of water, racemic products were obtained. However, the use of water is preferred despite not being an organic solvent to reduce pollution.

2. Objective

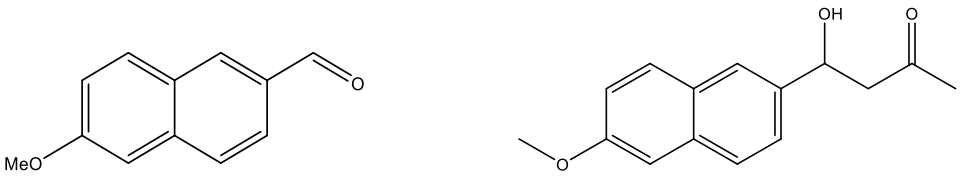
The main objective of this work is the synthesis of an organic compound with supramolecular catalysis application. Specifically, we focus on the synthesis and characterization of the methodol compound. We will investigate during different tests what are the best conditions to obtain the best yield. We will also try to perform the retro aldol reaction by checking for the occurrence of fluorescence in this reaction.

3. Results and discussion

In this section will set out the results obtained after the experimental section has been made for each of the different reactions. In this part, it's found the synthesis and characterization together with a brief discussion on them.

3.1. Synthesis and characterization of the methodol

Our studies start from a fluorescent organic compound (6-methoxy-2-naphthaldehyde) until to obtain an organic final product which hasn't fluorescence (4-hydroxy-4-(6-methoxy-2-naphthyl)-2-butanone).

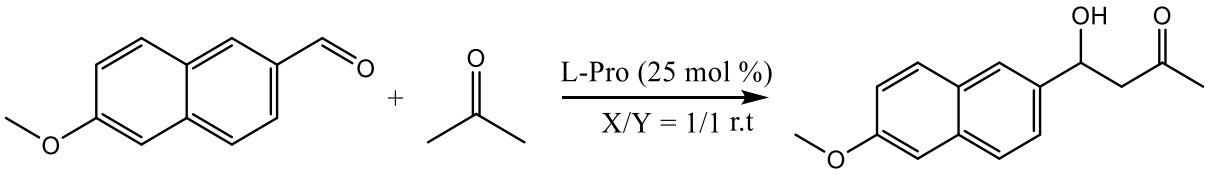


λext = 330nm, λem = 452nm λext = 347nm

Figure 6: Initial compound, 6-methoxy-2-naphthaldehyde (left) and product final,4-hydroxy-4-(6-methoxy-2-naphthyl)-2-butanone (right)

Based on the article by Armando Córdova, Wolfgang Notz, and Carlos F. Barbas III [1] was applied the methodology for the following reactions:

Table 1: Amine-catalysed aldol reactions between 6-methoxy-2-naphthaldehyde and acetone.



Entry	X	Y	Time
(1)	PBS	DMSO	24h
(2)	PBS	-	24h
(3)	PBS	MeOH	72h

The methodology consists in reacting an aldehyde (1mmol) with acetone in a buffer solution 1:1 of PBS and DMSO (10mL) catalyzed by L-proline (25 mol %) during 24 hours at room temperature and with agitation. Then, it is treated with NH_4Cl (sat) and extracted with AcOEt.

In the case (1) the result wasn't satisfactory since during the methodology, the DMSO couldn't be separated of our product. However, a small extraction was made to see the result, but as it can see in the Figure 27 in the annex, the product wasn't formed. This is known because the characteristic peak of NMR of the methodol (5.3 ppm) doesn't appear.

Then, we decided to use only PBS buffer with the same conditions (2) and the result, as in the previous case, wasn't satisfactory because the reaction wasn't performed and we obtained the starting compound. If we look at Figure 22 in the annex, it can see that the characteristic peak of the product wasn't formed. So that, we changed the line of action.

We decided to change the buffer dissolution to PBS/MeOH (3) as this way we can evaporate the MeOH. The reaction time was also changed from 24h to 72h.

Now, the result was good but we got very little quantity (0.402g of non-pure methodol). Despite the small amount, it could be seen that it could recrystallize.

In order to appreciate the progress of the reaction based on time it was decided to repeat the reaction in these conditions: 24, 48, 72 and 96h. The yield obtained was calculated to each test compared to the initial product using NMR.

Table 2: Progress of the reaction of methodol in function yield.

Reaction time	Yield
24h	20.00%
48h	43.00%
72h	60.00%
72h	70.00%
96h	0.00%

In the figure below ,it can be seen how the yield is calculated based on the characteristic peak of the starting compound against the characteristic peak of the methodol. The characteristic peak of the starting compound is approximately 10 ppm. This peak refers to hydrogen of the carbonyl aldehyde. In contrast, the peak approximately about 5.3 ppm refers to hydrogen of carbon bound to alcohol.

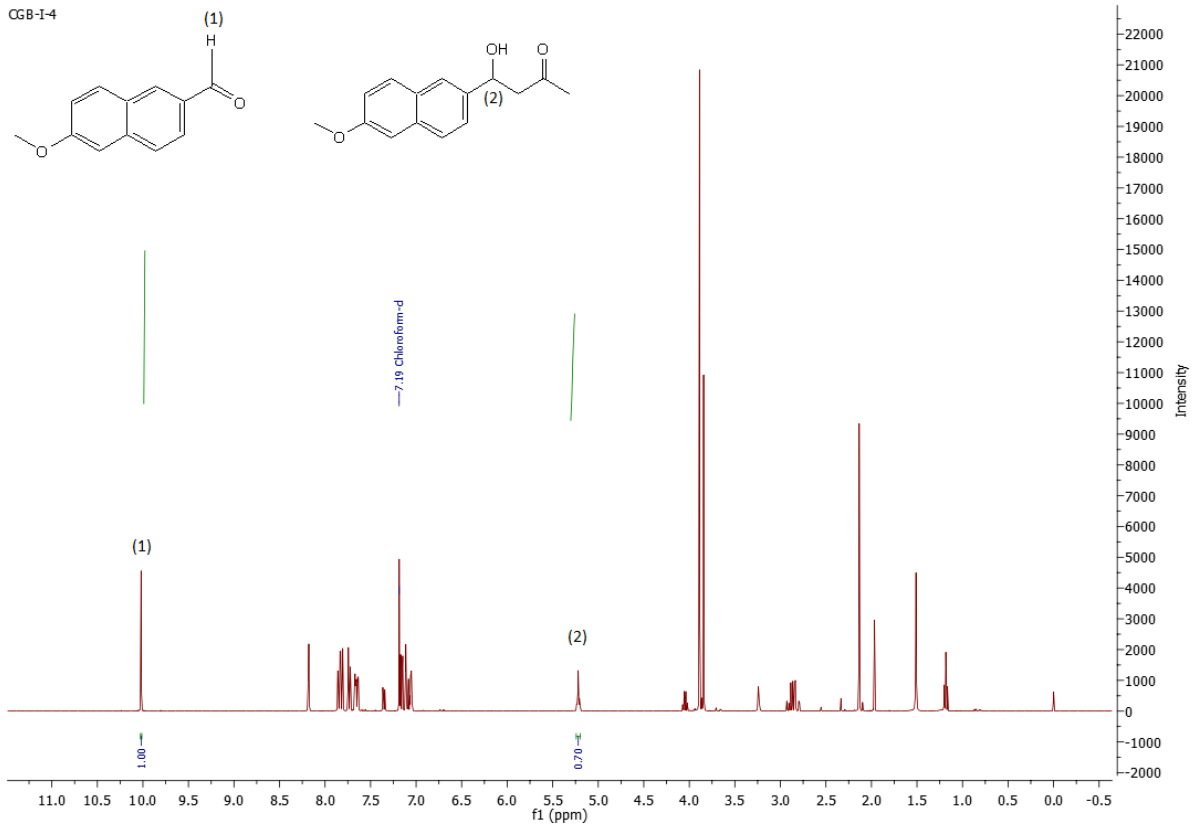


Figure 7: Progress of the reaction of methodol impure to 72h with 70% yield.

^{1}H NMR (400MHz, $CDCl_{3)}$

It must be said that the 72h reaction was made twice to obtain more quantity because with the 72h reaction, the best conditions were obtained. However, as the final product wasn't pure, since the reaction didn't occur at 100% and therefore the product contained traces of the initial product must be purified. As we can see in the table previous, it only got obtaining between 60% and 70%.

The product was purified by chromatographic column with a proportion of solvent 8mL hexane : 2mL EtOAc. Once purified, the results were characterized by ^{1}H NMR, ^{13}C,COSY and MS.

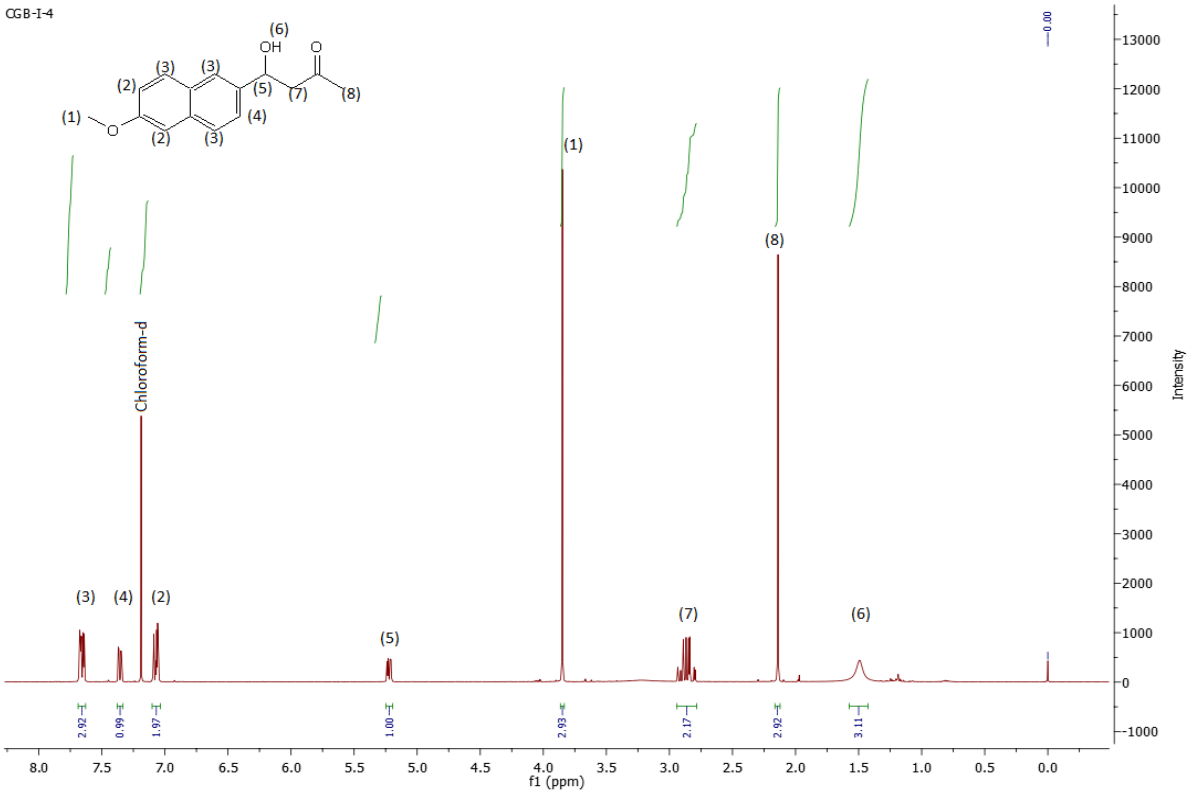


Figure 8: Pure methodol ^{1}H NMR (400MHz, $CDCl_3$)

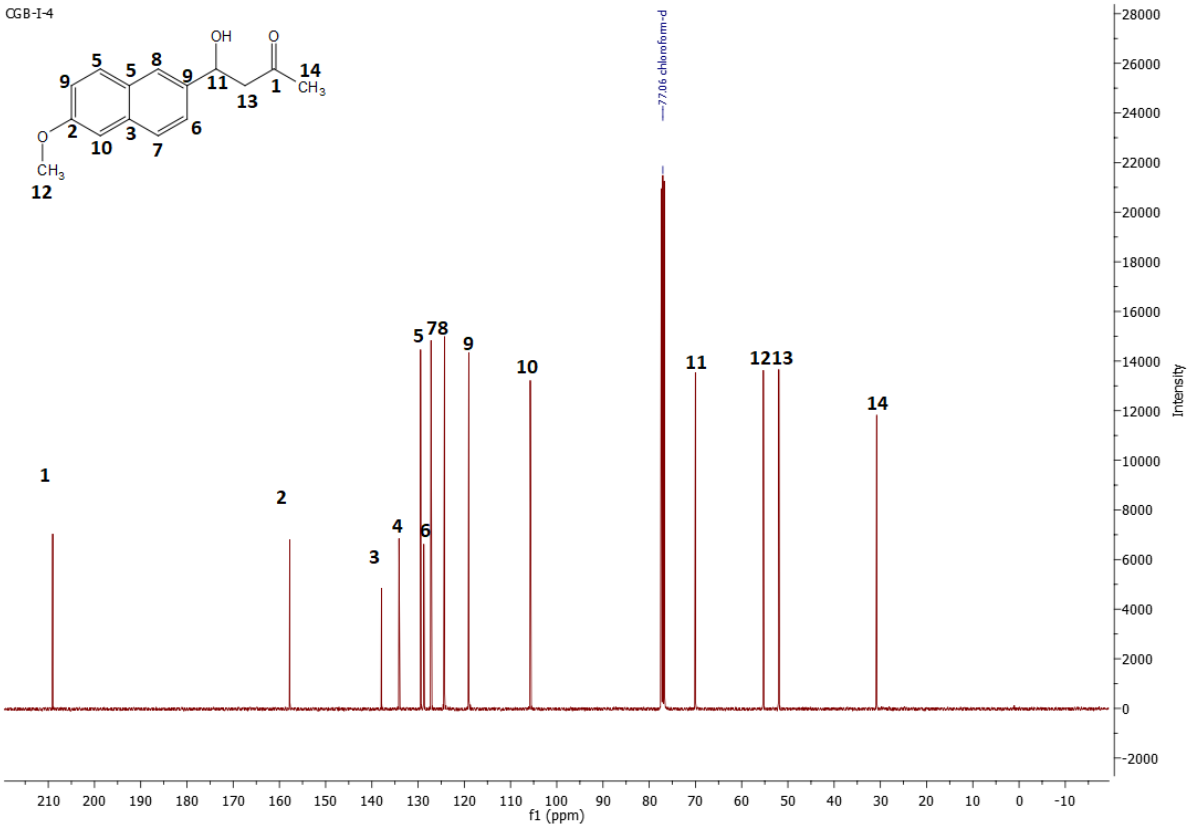


Figure 9: Pure methodol ^{13}C NMR (100 MHz, $CDCl_3$)

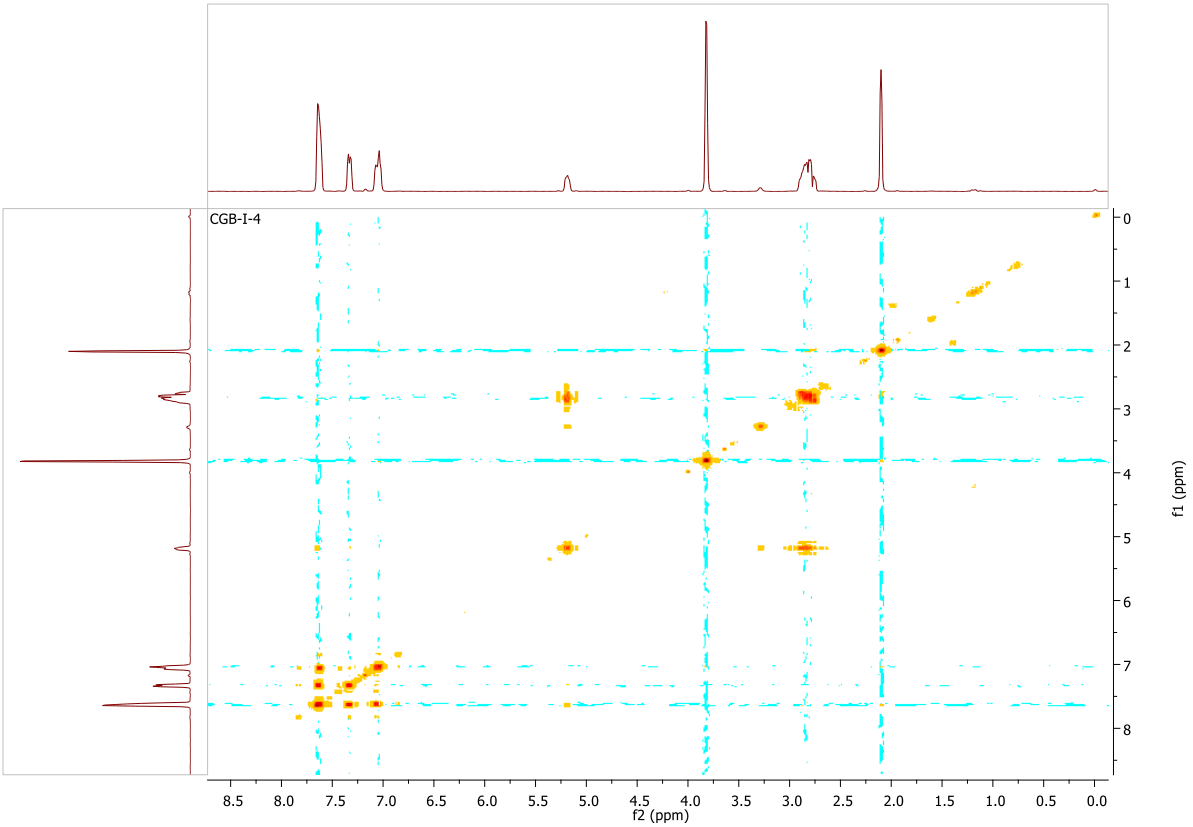
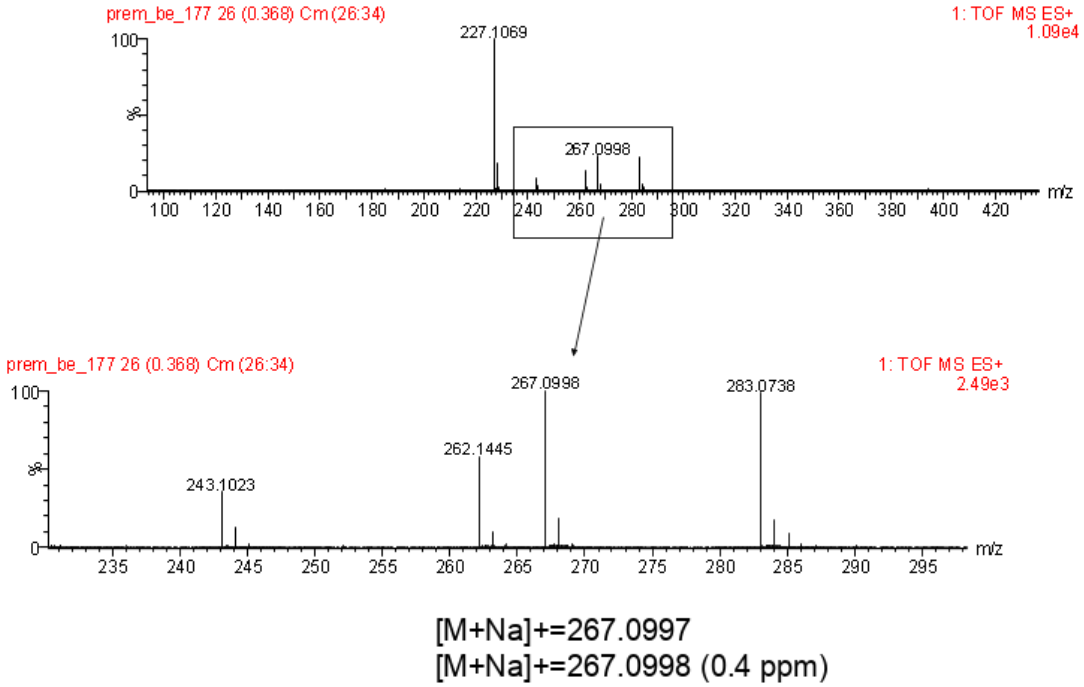


Figure 10: Pure methodol COSY NMR



[M+Na]+=267.0997
[M+Na]+=267.0998 (0.4 ppm)

Figure 11: Pure methodol ESI-MS

As we can know, there are substances that are able to absorb energy at a certain wavelength in the form of electromagnetic radiation and then emit some of that energy in the form of radiation. Fluorescent radiation is emitted when electronically excited molecules are relaxed to any of the vibrational states of the basal electronic state. These substances are called fluorescent substances.

In our case, the starting compound is fluorescent while the final product has not fluorescence. This is because the starting compound is a rigid organic molecule with the aromatic system conjugated with carbonyl, instead the final product does not present this conjugation.

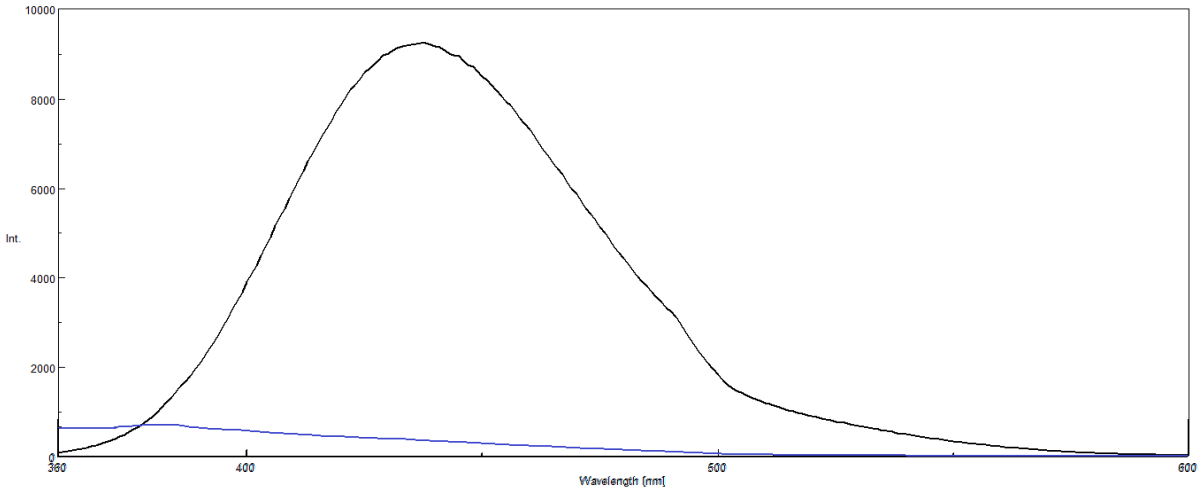
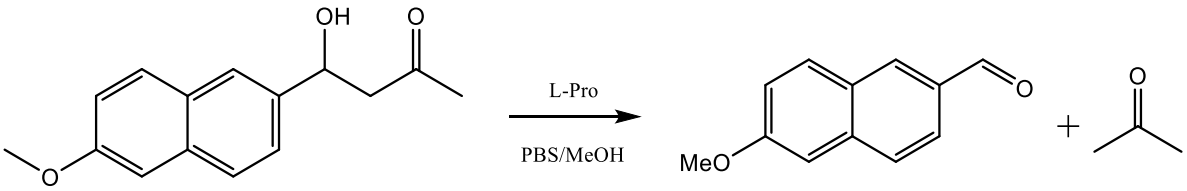


Figure 12: Fluorescence aldehyde (black) and fluorescence methodol (blue).

3.2. Retro aldol reaction

Once the methodol was synthesized and characterized, its reactivity was checked in organocatalyzed reactions by studying the retro aldol reaction in the presence and absence of an organocatalyst, in this case L-proline.

To follow the retro aldol reaction, two vials were used in which the same reaction was made with the difference that in the first vial, the catalyst (proline) was added but in the second vial not. In this way, the influence of the catalyst on the reaction would be appreciated. These reactions were evaluated to 6 days checking during different time intervals the reaction progress by observing fluorescence with and without the catalyst.



Scheme 1. Scheme of the retro aldol reaction with PBS/MeOH and L-proline as catalyst

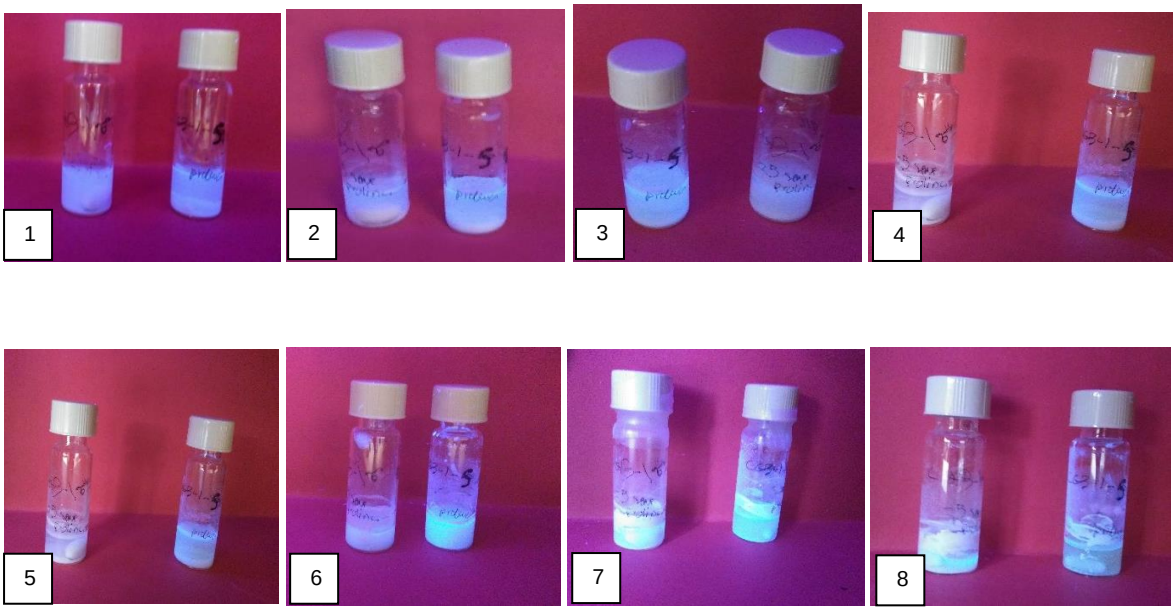


Figure 13. Fluorescence development in the retro aldol reaction of the methodol without proline (left) and methodol with proline (right). Conditions by proline reaction: 25 mg methodol, 0.5 mL PBS /0.5mL MeOH and 3 mg proline (%mol). Time intervals: (1) initial time, (2) 1 hour, (3) 2 hours, (4) 4 hours, (5) 1 day, (6) 2 days, (7) 3 days, (8) 6 days. The wells were irradiated with a standard long-wave UV lamp.

Figure 13 shows the occurrence of fluorescence in the retro aldol reaction of methodol. As we can see in figure 13 – picture 6, it can observe initially there aren't signs of fluorescence. However, after a while it appearances on the top the fluorescence. We also realize that with the catalyst (proline) the reaction progresses faster and therefore the fluorescence is shown earlier.

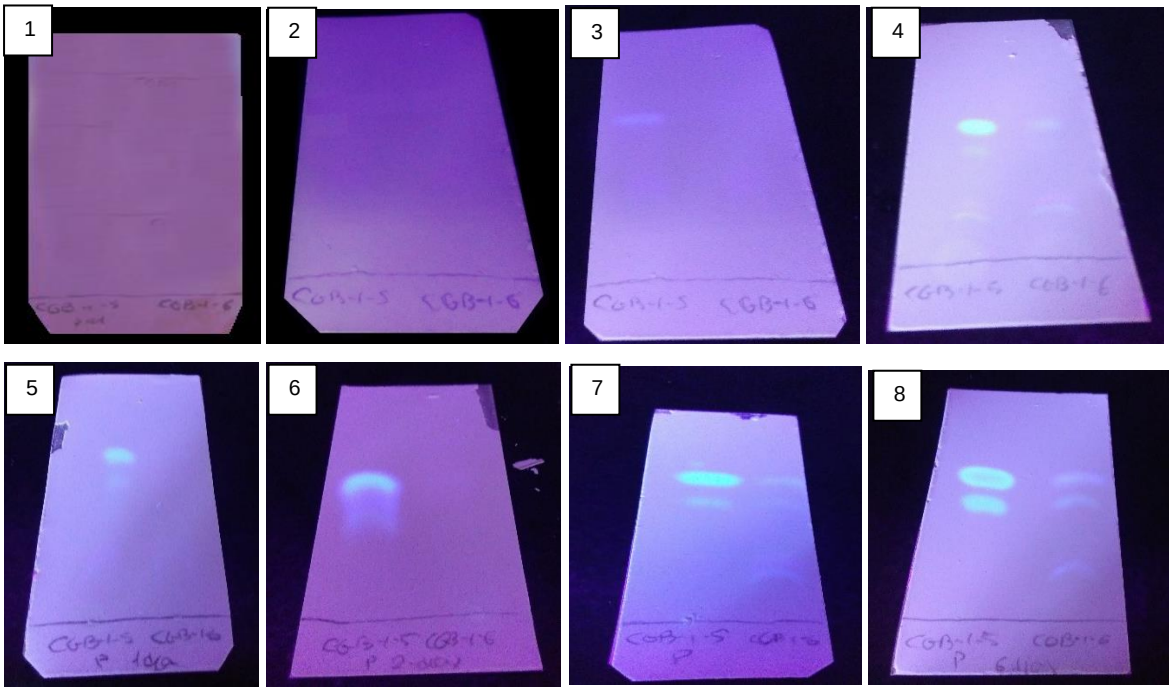
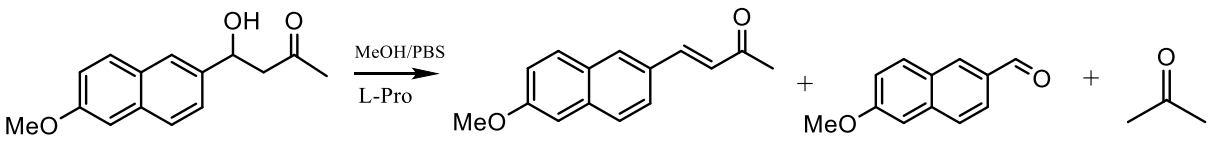


Figure 14. Development of the fluorescence in the retro aldol reaction of methodol with proline (left) and methodol without proline (right) by TLC. Conditions for the reaction with proline: 25 mg methodol, 0.5 mL PBS/0.5mL MeOH and 3 mg Proline(%mol). Time intervals: (1) initial time, (2) 1 hour, (3) 2 hours, (4) 4 hours, (5) 1 day,(6) 2 days, (7) 3 days, (8) 6 days. The TLCs were irradiated to a wavelength of 365nm, proportion of the eluent 2mL hexane: 8mL EtOAc.

As can be seen in Figure 14, initially, there aren't signs of fluorescence, instead after a while we can see the appearance of fluorescence. In addition, if we pay attention in the time interval of 3 days and 6 days, we can see the fluorescence on the one hand the aldehyde and the other hand, by-product.

Specifically, the stain above belongs to 6-methoxy-2-napthaldehyde and the stain located in lower part (E)-4-(6-methoxynaphthalen-2-yl)but-3-en-2-one, methodol dehydration product.



Scheme 2. Methodology retro aldol reaction with PBS/MeOH and L-proline with the by-product reaction

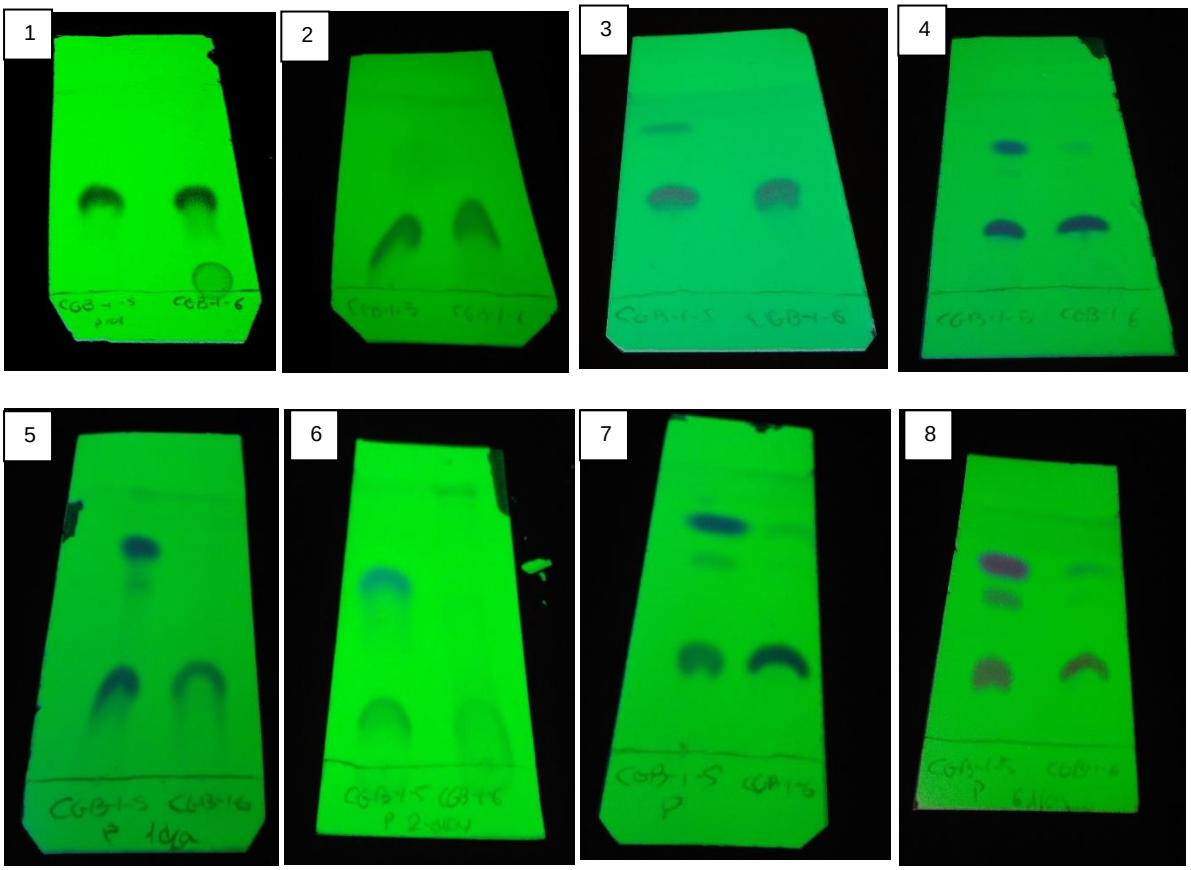


Figure 15.Development of the retro aldol reaction of methodol with proline (left) and methodol without proline (right). Condition for the proline reaction: 25 mg methodol, 0.5 mL PBS / 0.5mL MeOH and 3 mg Proline (%mol). Time intervals: (1) initial time, (2) 1 hour, (3) 2 hours, (4) 4 hours, (5) 1 day,(6) 2 days, (7) 3 days, (8) 6 days. The TLCs were irradiated to a wavelength of 254nm, eluent ratio 2 mL hexane : 8 mL EtOAc.

As we can see in Figure 15, initially the displacement of the reaction in both proline and without proline is the same. Over time, we pay attention that the starting product isn't eliminated. Gradually, the final product and the by-product are formed.

Specifically, if you look at the 6-day time interval we can see that the spot is higher belongs to 6-methoxy-2-napthaldehyde, the middle part to (E)-4-(6-methoxyhththalen-2-yl)but-3-in-2-one and the stain below 4-hydroxy-4-(6- methoxy-2-naphtyl)-2-butanone, methodol.

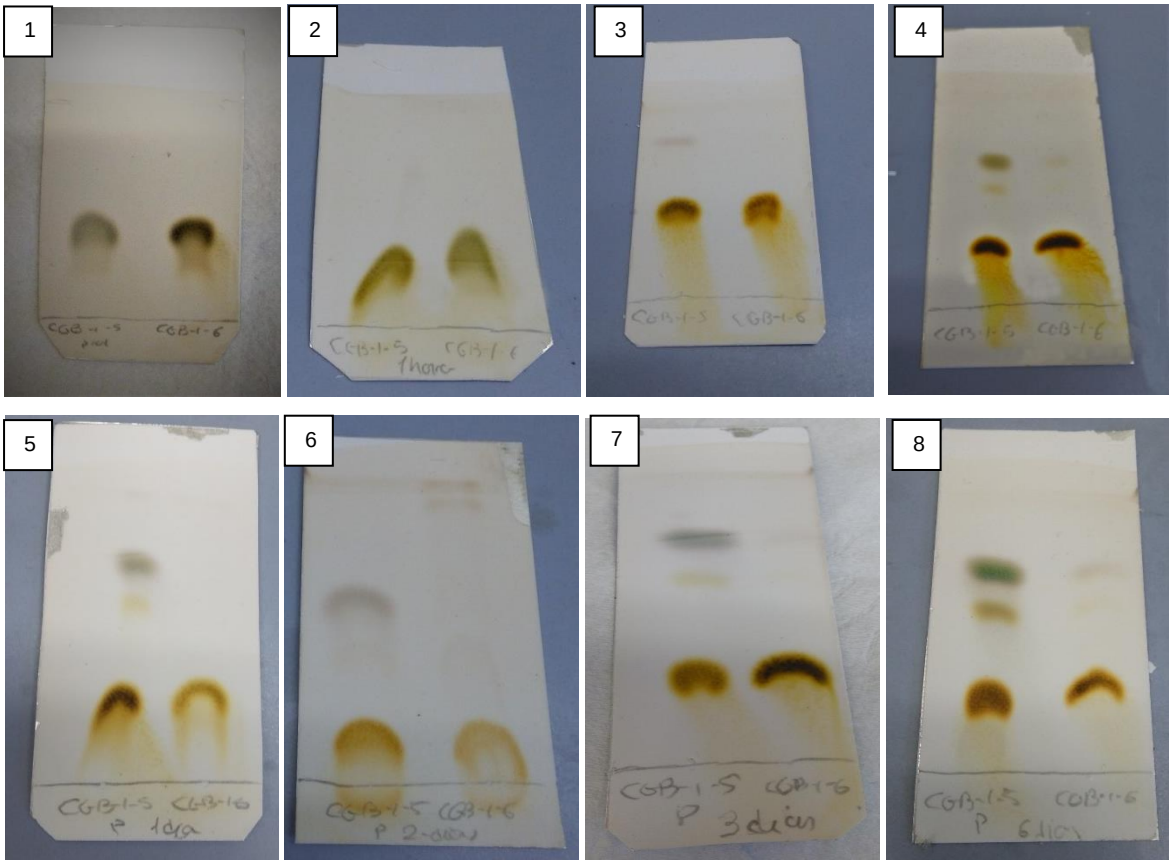


Figure 16. Revealed of the development of the retro aldol reaction of methodol with proline (left) and methodol without proline (right) through revealed in the TLC. Condition for the proline reaction: 25 mg Methodol, 0.5 mL PBS/0.5mL MeOH and 3 mg Proline. Time intervals: (1) initial time, (2) 1 hour, (3) 2 hours, (4) 4 hours, (5) 1 day,(6) 2 days, (7) 3 days, (8) 6 days. Ratio eluent 2mL hexane : 8mL EtOAc.

As you can see in Figure 16, initially the displacement of the reaction in both proline and without proline is the same. Over time, we pay attention that the starting product is not eliminated and gradually the final product and the by-product are formed.

Specifically, if you look at the 6-day time interval we can see that the grey spot belongs to 6-methoxy-2-napthaldehyde, the spot situated in the middle of the color orange belongs at (E)-4-(6-methoxynaphthalen-2-yl)but-3-in-2-one and the brown spot to 4-hydroxy-4-(6-methoxy-2-naphtyl)-2-butanone, methodol. We can also appreciate that the reaction without proline, despite having it 6 days, it doesn't form the final product in a lot.

3.3. Application of the use of the Methodol

The majority use of methodol is as a fluorogenic aldol sensor. This can be seen mostly in retro aldol reactions producing the fluorescent product.

The application lies in the use of aldol sensors as detection systems in synthetic libraries of possible enantioselective catalysts for aldol reaction.

As it's explained in the article by Benjamin List and co-worker[3] fluorescent molecules have played an important role in the chemical, biological and medical sciences. Its use ranges from the location of molecules in cells and tissues to the quantification of divalent cation fluctuations in metabolism.

The general idea is to introduce these genes into cell genomes as informants so that cells become "prefluorescent" constitutives. Such informing functions are widely used in transcription study and in temporal and spatial studies involving the expression of particular proteins. In addition, when the informant gene is an enzyme, such systems can be used to locate the binding of the ligand when the ligand binds to a fluorogenic substrate.

The use of fluorescence as a signaling tool stands out for its high sensitivity, which allows to obtain excellent sensor responses working at low analyte concentrations.

A fluorescent sensor is a system capable of interacting with the analyte in dissolution, signaling its presence by changing its fluorescent properties such as the emission wavelength, the intensity of the emission, or the appearance of a new band of emission absent in the spectrum of the free sensor.

Aldol sensors are now routinely used in catalysis displays of new antibodies with potential aldolase activity. Initial results indicate that neither substrates nor their fluorescent products are toxic to cells that express the antibody.

To demonstrate the application of fluorescence in my work, the retro aldol reaction was analyzed using the fluorimeter. We analyzed the reaction scheme 1 with and without the catalyst.

It was irradiated at the wavelength indicated in the article by Tolulope and co-workers [5]. The result was the follows:

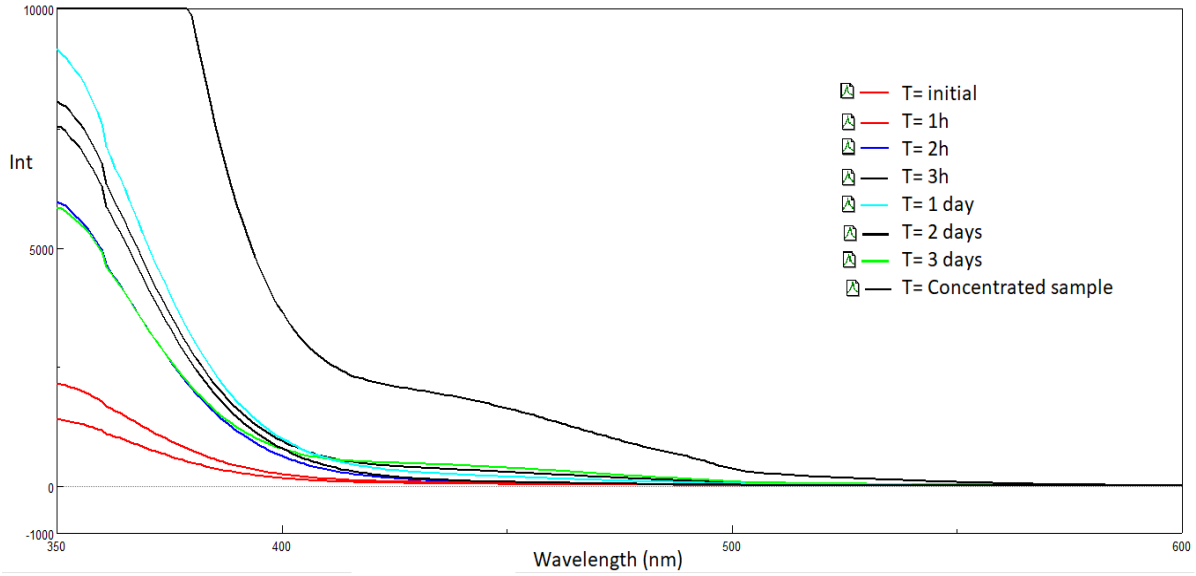


Figure 17. Development of the retro aldol reaction with the proline catalyst and solvents MeOH/PBS by fluorimeter irradiated to λ exc 330nm.

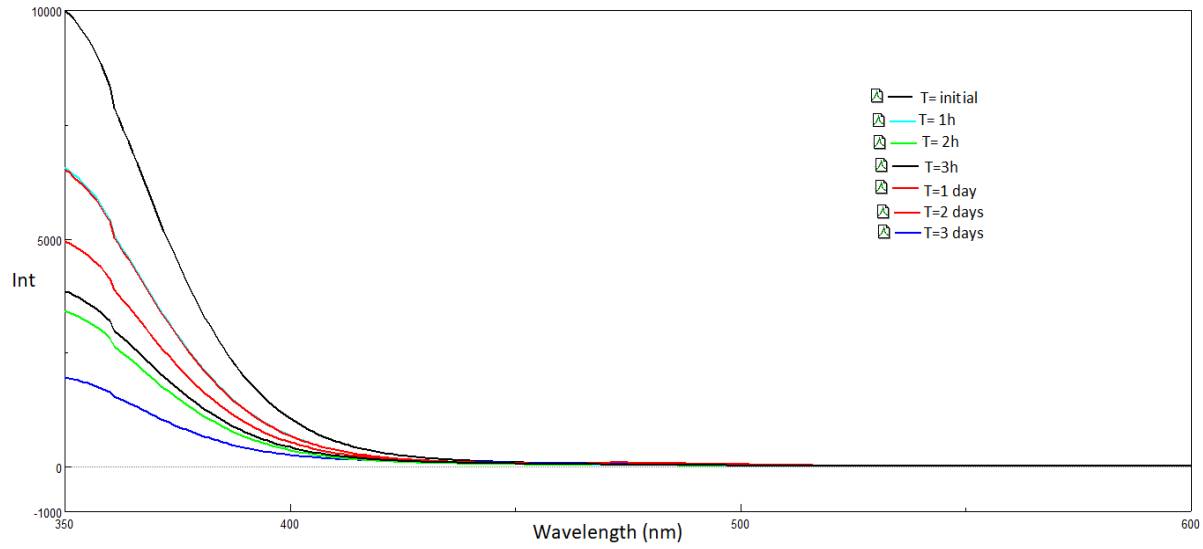


Figure 18. Development of the retro aldol reaction without the catalyst and with the PBS/MeOH dissolution by fluorimeter irradiated to λ exc 330nm.

However the results were not the expected as the appearance of fluorescence could not be seen. If we look at Figure 17 we can see a small amount of aldehyde formed, but still, we cannot see how the fluorescence of aldehyde increases and the starting product that in this

case is methodol also increases. It could say that what is mostly irradiating is the methodol and therefore we change the wavelength.

To this end, the absorbances of the two solutions, a solution of methodol and a solution of aldehyde (6-methoxy-2-naphtaldehyde) were analyzed. We also observed that the dissolution with MeOH/PBS didn't dissolve the product and therefore we would have an error in the concentration, since the matrix wouldn't look constant. For this reason, the new dissolution would be MeOH/PBS/DMSO.

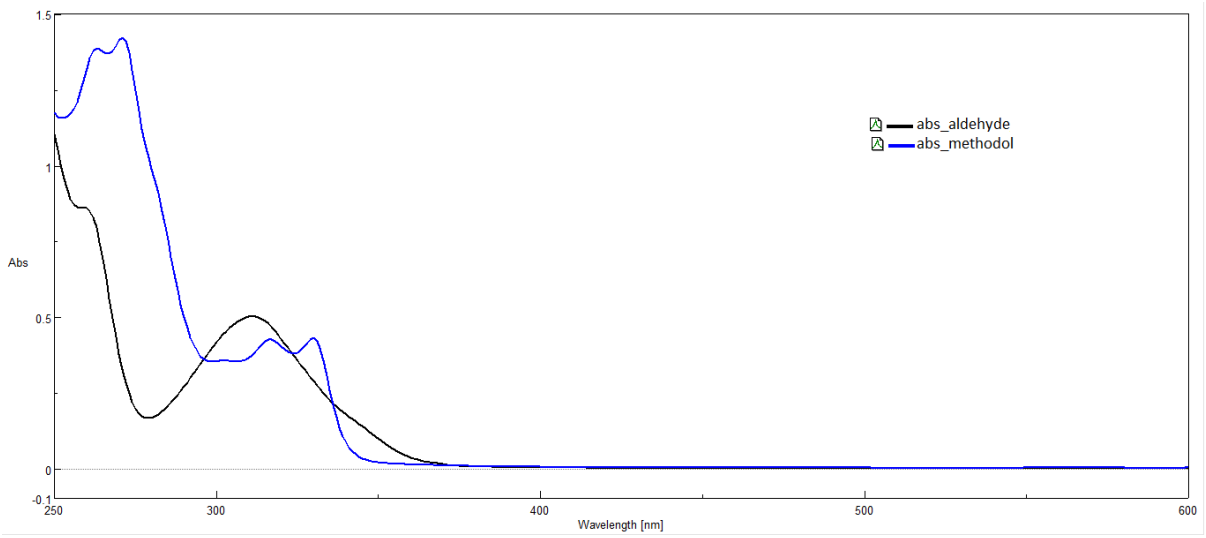


Figure 19. Spectrum of absorbance (6-methoxy-2-naphtaldehyde) and methodol dissolved in MeOH / PBS

In Figure 19, it can see that depending on the chosen excitation wavelength, it can absorb the two compounds, and therefore we will not be able to differentiate them or follow progress of the retro aldol reaction with and without proline.

Looking at Figure 19, we can see that irradiating at a wavelength of 305 nm approx. we have the maximum peak of aldehyde, but in turn, it also irradiates in less quantity to the methodol. So that, when we analise the fluorescence of these compounds, the signal would come out of the following form:

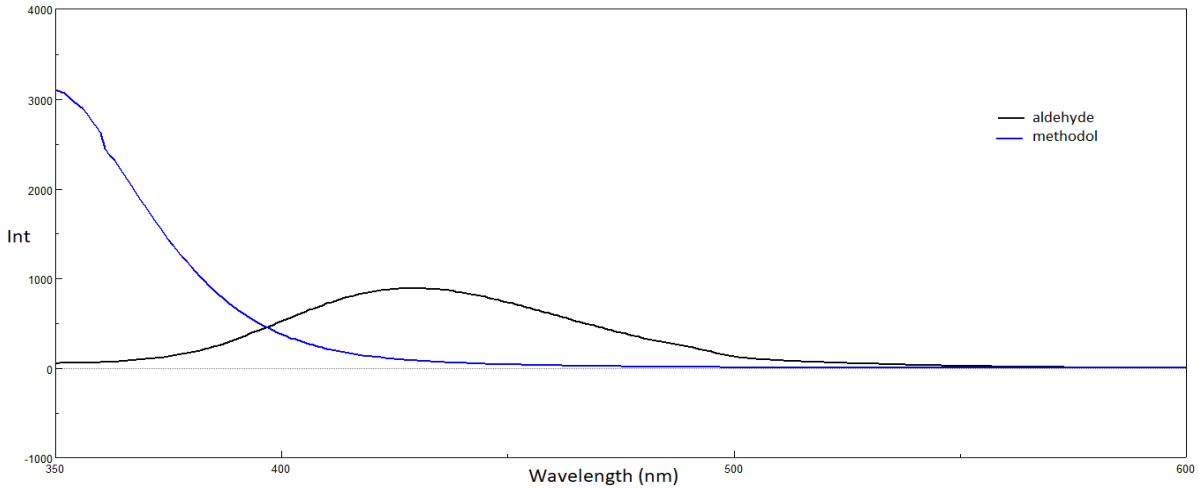


Figure 20. Spectrum of fluorescence of the (6-methoxy-2-naphtaldehyde) and methodol dissolved in MeOH/PBS by fluorimeter irradiated to λ exc 305nm.

Looking at Figure 20, we found that it can't be irradiated at 305nm as both compounds would be excited and therefore we couldn't appreciate the progress of the reaction. We can also look, that the methodol starts with an intensity greater than 3000. To know where the maximum peak of the methodol was checked by extending the wavelength parameters and it could be seen that the maximum of the irradiated methodol at 305nm was over 350nm.

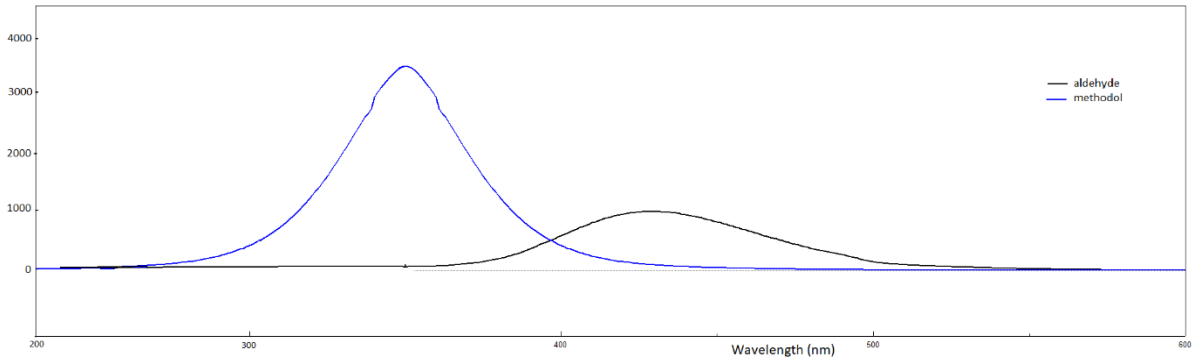


Figure 21. Fluorescence spectrum of (6-methoxy-2-naphtaldehyde) and methodol dissolved in MeOH/PBS by fluorimeter irradiated to λ exc 305nm.

Finally, as shown in Figure 19, if we irradiate to a length approximately 347nm, we can only irradiate only aldehyde since the intensity of the methodol is approximately 0. In this way, we can observe how the fluorescence in the retro aldol reaction appears.

To check that it was the correct excitation wavelength was done a test and came out correct.

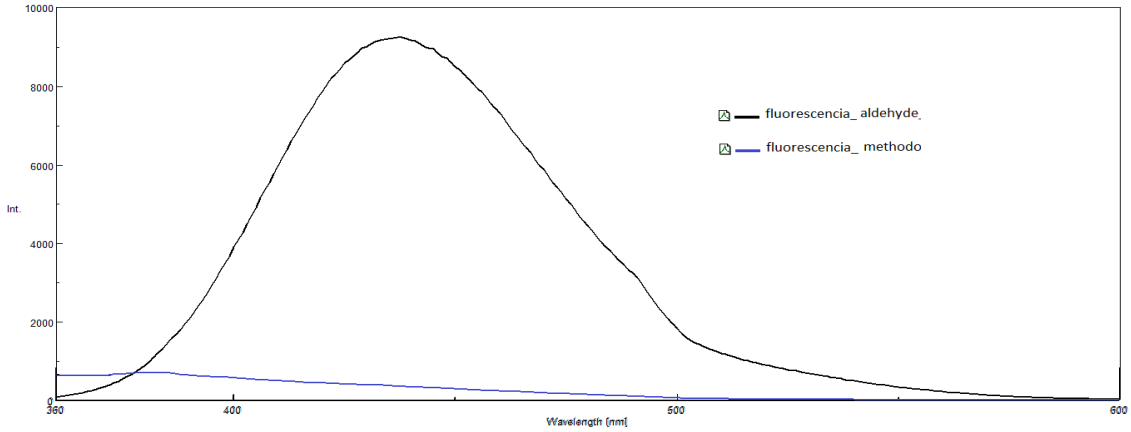


Figure 22. Fluorescence of (6-methoxy-2-naphtaldehyde) and methodol dissolved in MeOH/PBS by fluorimeter irradiated to λ exc 347nm.

Then, a calibration of 6-methoxy-2-naphtaldehyde was carried out for which standard solutions were prepared in MeOH/PBS/DMSO:

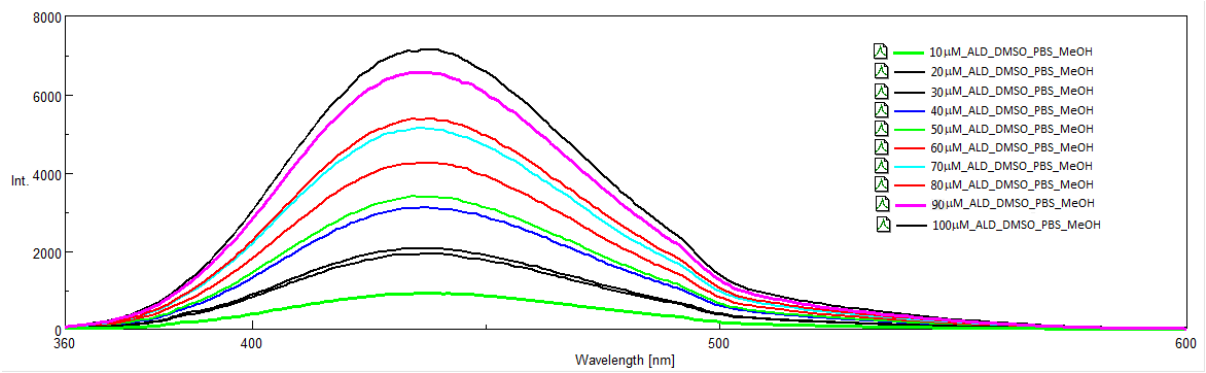


Figure 23.Calibration spectrum MeOH/DMSO/PBS/6-methoxy-2-naphtaldehyde

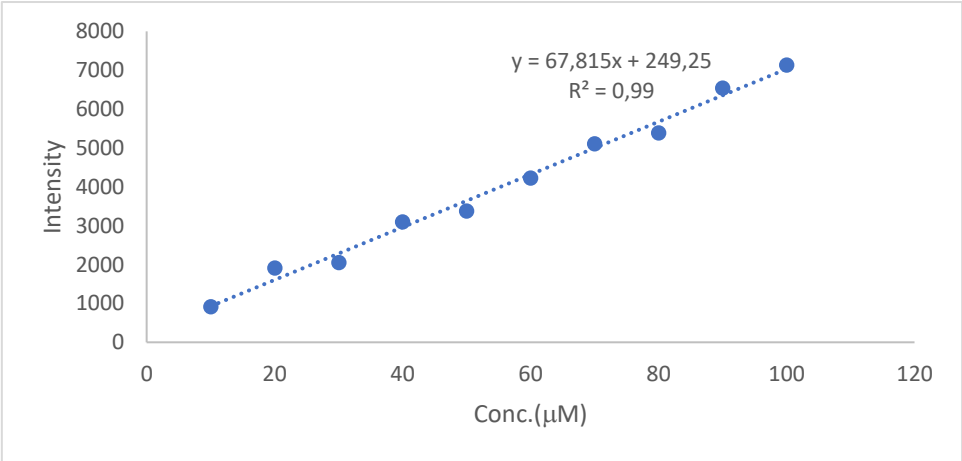
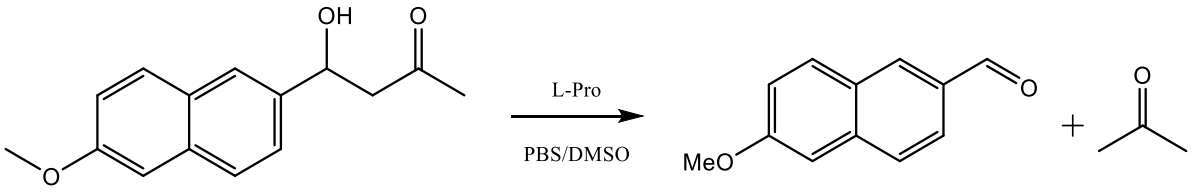


Figure 24. Calibration line with DMSO/PBS/MeOH/6-methoxy-2-naphtaldehyde

To correct the error in the concentration named previously, it was decided that instead of dissolving the methodol with MeOH : PBS, it would be dissolved with DMSO : PBS. Thus, as the samples were better dissolved, the measurements analyzed would have approximately the same concentration at different time intervals.



Scheme 3. Methodology retro aldol reaction with PBS/DMSO and L-proline.

The results for the proline reaction were the follows:

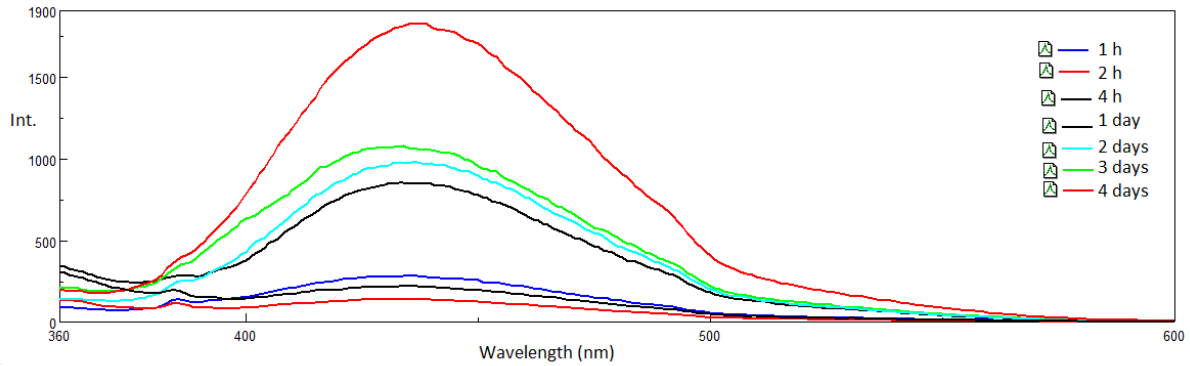


Figure 25.Fluorescencethe reaction retro aldol with proline catalyst and DMSO/PBS solvents by fluorimeter irradiated to λ exc 347nm.

As we can see the first hours of reaction, it can't appreciate the formation of aldehyde. Later already advancing in the days we appreciate the formation of the final product until you arrive with 4 days to form with an intensity of approximately 1850.

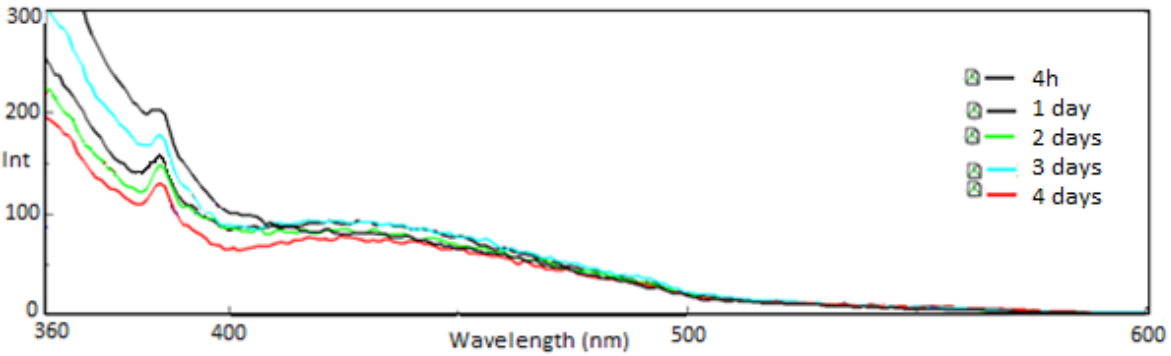


Figure 26. Fluorescence the reaction retro aldol without the proline catalyst and DMSO/PBS solvents using a fluorimeter irradiated to λ exc 347nm.

As we can see in figure 26, the reaction without catalyst is much slower. If we compare both images, we can see that without the catalyst with 4 days of reaction has approximately the same amount as with 4 hours of reaction, that is, the amount of product hasn't been increased. Instead if we look at image 19, which has catalyst, in 4 hours has an intensity of approximately 750 and in 4 days approximately 1850.

4. Experimental section

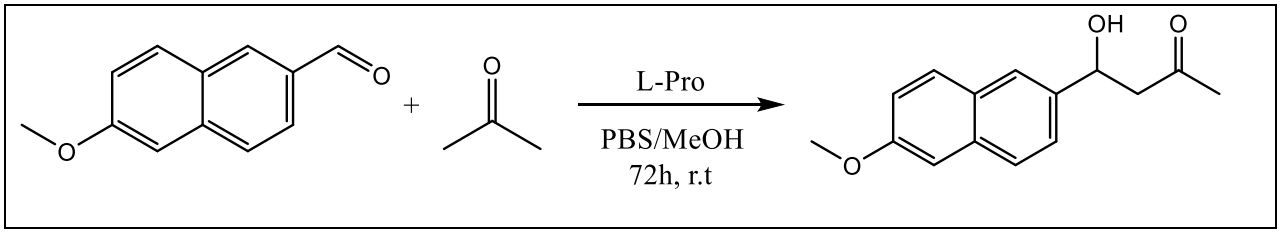


Table 3: Information of the reaction of methodol to yield 70%.

Compound	Amount	Pm(g/mol)	Amount in mmol
6-methoxy-2-naphtaldehyde	500 mg	186.21	2.68
Ketone	19.87mL	58.08 g/mol	268.5
MeOH	15mL	78.13 g/mol	
PBS	15mL		
L-proline	77mg	115.13 g/mol	0.00067
NH_4Cl	7 mL		
EtOAc	15 mL		

Inside a 50 ml round flask, 6-methoxy-2-naphthaleldehyde is dissolved with the buffer (PBS / MeOH). Then, ketone is added. Finally, the proline is introduced. The reaction must be 72 h in reaction with room temperature and agitation. The compound mustn't be in contact with light.

After those days, the reaction stops and takes to rotavapor. In this way, the MeOH evaporates. Then, washes with NH_4Cl and EtOAc to perform the extractions. Three extractions are performed. The aqueous part is maintained and the organic part is dried with Na_2SO_4 and then filtered with a filter paper with folds. The dissolution is taken back to rotavapor to

remove the EtOAc. Finally, when the whole solution is dry, it will be analyzed with NMR to see the amount of methodol that has been formed.

After this, it is re-dissolved in EtOAc to proceed to its purification by chromatographic column, using the ratio of (silica gel, 80 mL hexane : 20 mL ethyl acetate) as eluent. Fifty fractions of 2mL are collected. The product obtained was 0.102 gr of pure methodol and is characterized by ^{1}H NMR, ^{13}NMR and COSY.

Yield: 15% (pure, figure 9)

^{1}H NMR (400 MHz, $CDCl_3$) ppm 7.70 – 7.63 (m, 3H), 7.36 (dd, J x 8.5, 1.8 Hz, 1H), 7.07 (dt, J s 5.7, 2.5 Hz, 2H), 5.22 (dd, J s 9.0, 3.4 Hz, 1H), 3.85 (s, 3H), 2.86 (qd, J s 17.4, 6.2 Hz, 2H), 2.14 (s , 3H), 1.49 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) 209.04, 157.77, 137.92, 134.14, 129.46, 128.76, 127.21, 124.30, 119.03, 105.74, 70.01, 55.31, 51.97, 30.80 .

5. Conclusions

The results obtained in the different characterizations show us that the optimal titration for the synthesis of the organic compound methodol is reacting the starting compound with the PBS buffer dissolution/ MeOH and with the organic compound ketone and being catalyzed by the organic compound L-proline for 72h.

From the final product and with the same reaction conditions, the different tests have been performed to demonstrate the retro aldol reaction by thin layer chromatography. The results with the catalyst were optimal as both the appearance of fluorescence and the development of the reaction can be seen. Instead it can be seen that without the catalyst the reaction advances more slowly and therefore fluorescence doesn't appear.

Also, the different tests have been performed to demonstrate the retro aldol reaction with a fluorimeter. In these tests, reaction conditions had to be modified to improve the analysis matrix. This is because when taking the amount of sampling without being completely dissolved each time that the composition was analyzed, this wasn't the same. Therefore, the accuracy of the analysis wasn't correct.

Regarding the main objective of the project, synthesizing the organic compound methodol for catalytic application, it could be said that with the analyzed conditions, you get a good yield at 72h.

6. References

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[9] Chem 206, 215 Lecture Notes (2003, 2006)

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7. Annexes

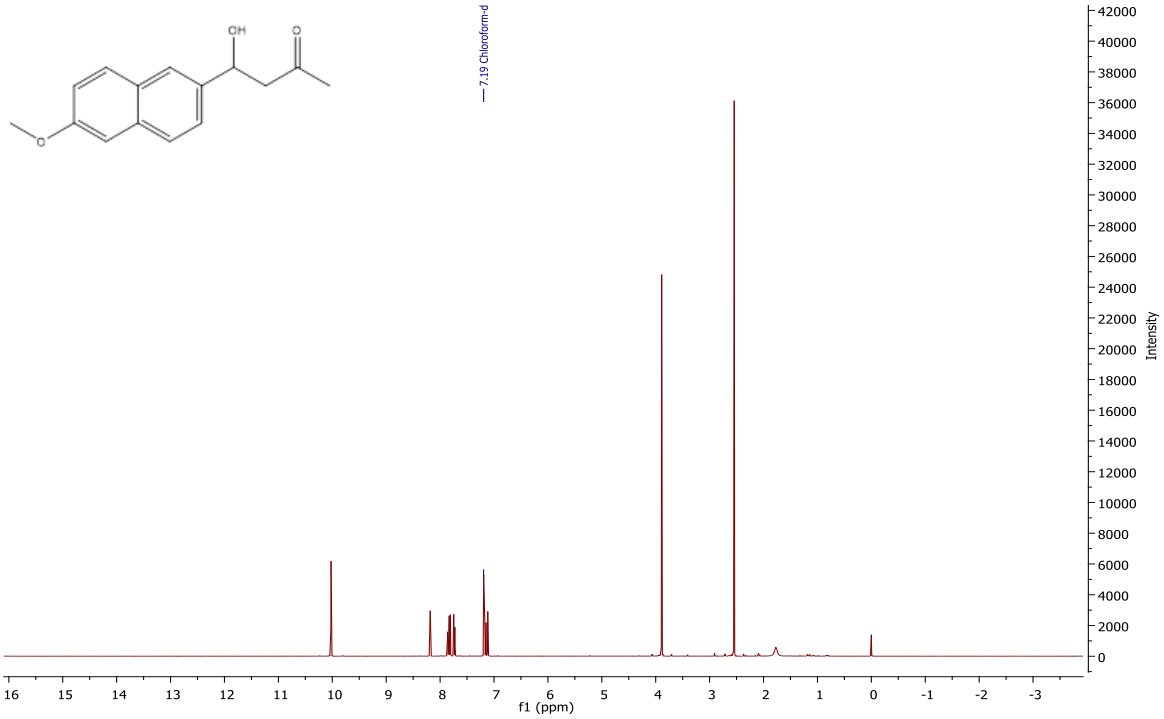

Figure 27. Progress of the reaction of methodol impure to 24h with PBS/DMSO. ^{1}H NMR (400MHz, $CDCl_3$).

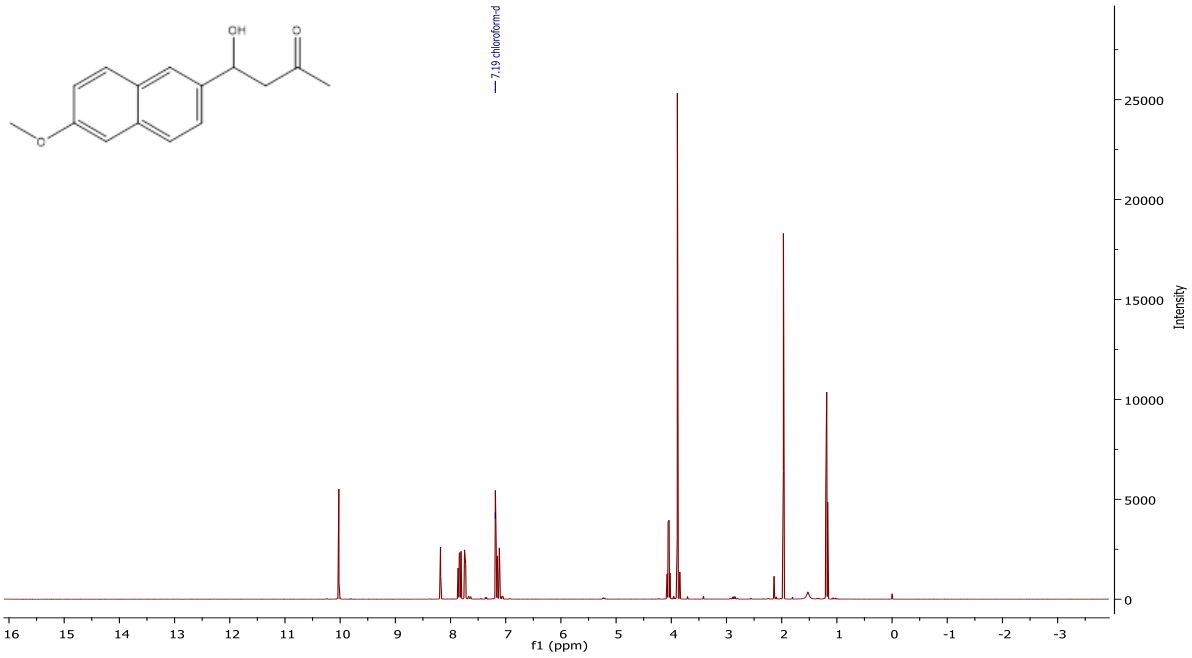

Figure 28. Progress of the reaction of methodol impure to 24h with PBS. ^{1}H NMR (400MHz, $CDCl_3$).

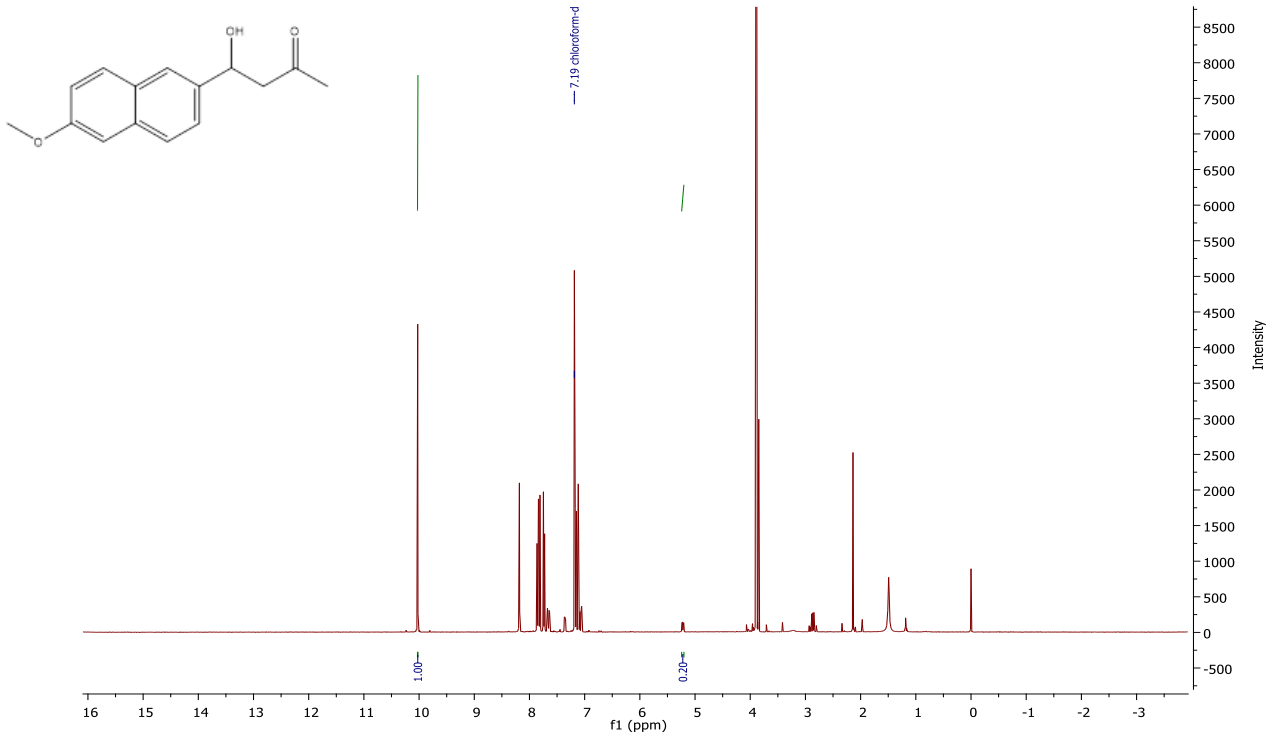

Figure 29: Progress of the reaction of methodol impure to 24h with 20% yield.

^{1}H NMR (400MHz, $CDCl_3$)

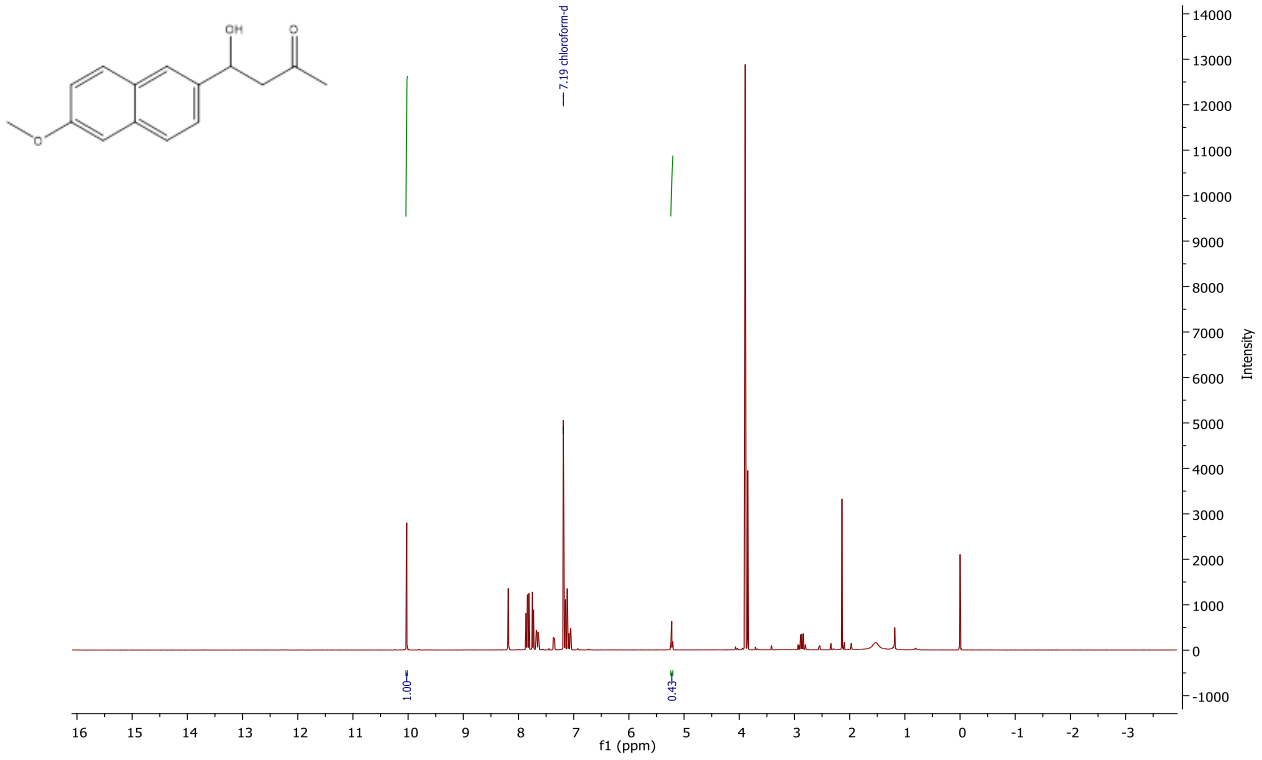

Figure 30: Progress of the reaction of methodol impure to 48h with 43% yield.

^{1}H NMR (400MHz, $CDCl_3$)

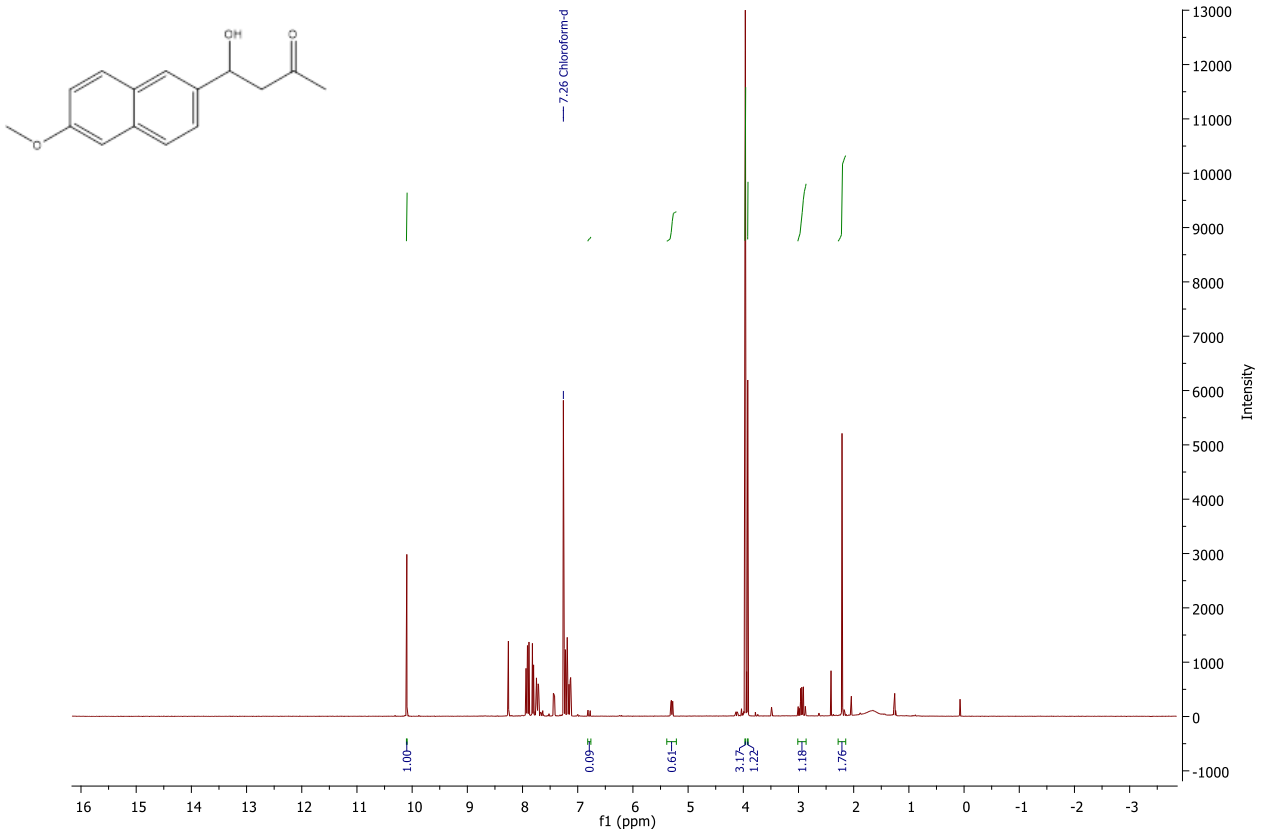

Figure 31: Progress of the reaction of methodol impure to 72h with 60% yield.

^{1}H NMR (400MHz, $CDCl_{3}$)

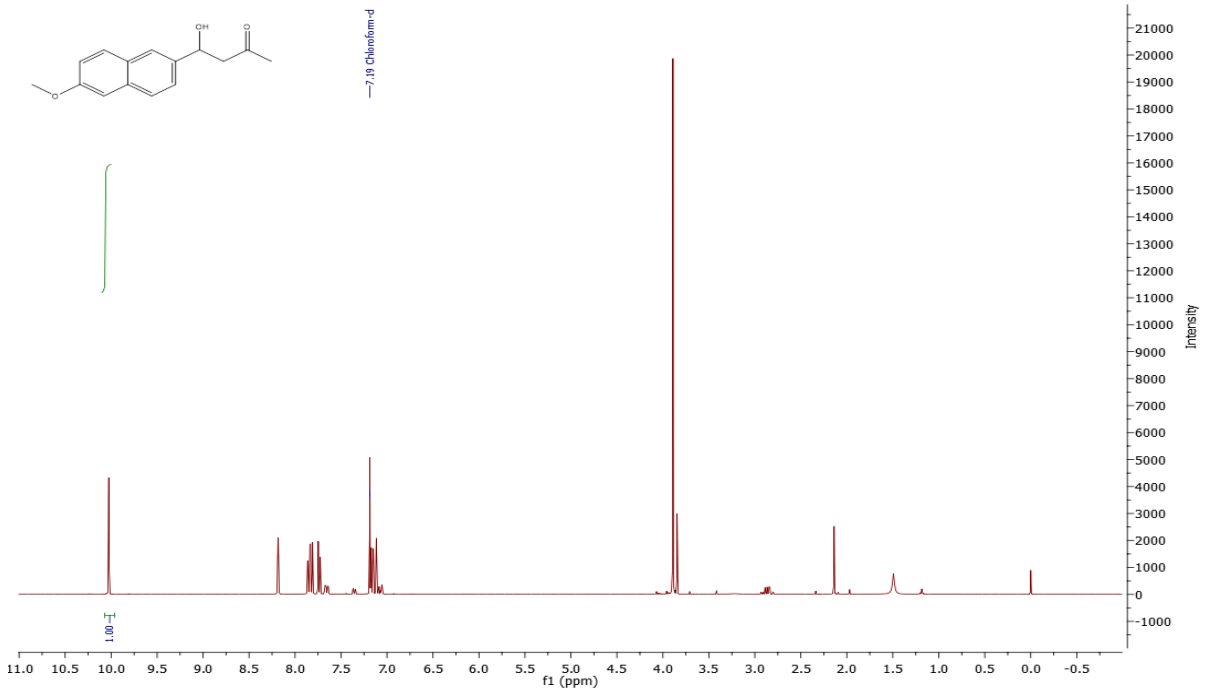

Figure 32: Progress of the reaction of methodol impure to 96h with 0% yield.

^{1}H NMR (400MHz, $CDCl_{3}$)