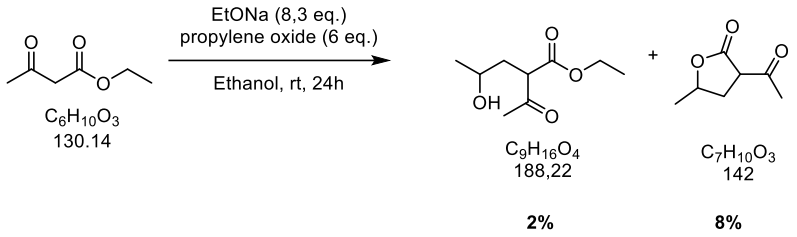
EXPERIMENT # NFA-24-003 Nucleophilic addition on epoxide

START DATE Tuesday, April 23, 2024 **END DATE** Wednesday, April 24, 2024

REFERENCES CN 114524914 A, 2022 and J. CHEM. SOC. PERKIN TRANS (1985), 2585-2598

OBJECTIVE Remake the EXPERIMENT 2 adding a fresh prepared sodium ethoxide in ethanol.

REACTION SCHEME



$C_6H_{10}O_3$
130.14

$C_9H_{16}O_4$
188,22

$C_7H_{10}O_3$
142

2% **8%**

EXPERIMENT DATA

Reagents	Formula	CAS #	Origin	Eq.	M	n (mmol)	m (g)	V (mL)	d (g/mL)	C (moL/L)	Pur.
SM	C6H10O3	141-97-9	12133	1,00	130,14	**3,842**	0,500	0,388	1,29		
Sodium Hydride	HNa	7646-69-7		8,32	24,00	**32,0**	**0,768**	######	-		60%
Propilene oxide	C3H6O	75-56-9	6283	6,03	58,08	**23,2**	**1,366**	1,646	0,83		
Solvent	Ethanol							38			
[SM] initial=	**0,100**	mol/L									

Desired product	C9H16O4	**Expected**	188.22	**3.842**	**0.723**	**Yield =** **10%**
		Obtained	**188.22**	**0.389**	0.073	

PROCEDURE

In a schlenk ballon with Ar atmosphere and room temperature, was added 38 ml of ethanol and 0,768 g of HNa (60% in mineral oil), leave stir until the generation of H_2 be complete. The mixture color was gray because of the HNa powder color.

Commented [NA1]: I notice now that Ihave made a mistake, I supose to add only 31 mg of NaH.

To the solution, was added 500 mg (0,388 mL) of ethyl acetoacetate and toluene (5 mL), stirring at room temperature, and propylene oxide 268 mg (0,323 mL), dropwise.

The mixture was heated to 90°C, while the temperature raising, was added more 1,2 eq of epoxide, and it bubbles, that means the epoxide is volatilized, the mixture was cold down to the room temperature and after leaving stirring overnight was added an excess of epoxide (1 mL), one TLC was take compare the reaction before and after put this excess.

The TLC showed tree spots, the middle one apparently has the same Rf of the ethyl acetoacetate, the bottom one must be the open ring product, the upper one could be the epoxide, but it appears even just with UV, which isn't the case of the epoxide, so it must be a subproduct. Since I have put an excess of EtONa by mistake, its not absurd think that this is the lactone that we don't want.

Commented [NA2]: Think, the white spot when it was revelade with KMnO4 is the ethanol, I don't dry the TLC before run it because I don't wanted to lost the ethyl epoxide.

The reaction was maintained in stirring at room temperature and after 24 h, looking for the TLC, at first apparently the starting material has been consumed, 1 mL of the reactional mixture was added to 1 mL of H_2O, the pH of this mixture was around 12.

For the workup, the solvent was evaporated at reduced pressure, the residue was resolubilized in AcOEt (25 mL) and washed with NH_4Cl (2x15 mL) and brine (2x15mL), the organic phase was dried with Na_2SO_4, and the solvent was evaporated in reduced pressure. A pale yellow liquid was obtained.

React. Cond.	**ON**		**24 h**				**After workup**			
Eluent	AcOEt in pentane 15%		AcOEt in pentane 10%		AcOEt in pentane 50%	AcOEt in pentane 80%	AcOEt in ciclohexane 20%		AcOEt in ciclohexane 10%	
TLC pic.										
Legend	SM R* R**	SM R* R**	SM R M	SM R M	SM R M	SM R M	SM R M	SM R M	SM R M	SM R M
Rev.	UV 254 mn	$KMnO_4$	$KMnO_4$	PMA	$KMnO_4$	$KMnO_4$	$KMnO_4$	PMA	$KMnO_4$	PMA

*Reaction before add epoxide excess

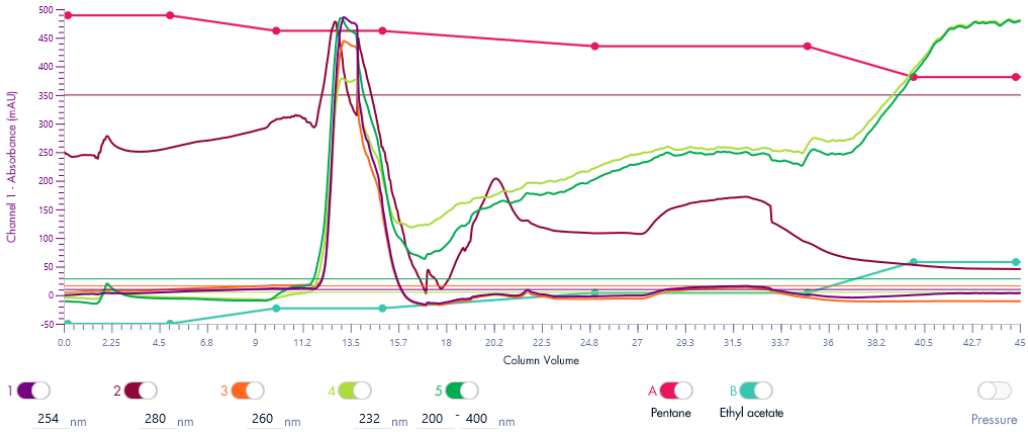
**Reaction after add epoxide excess

Crude 1,9576 g
NMR [$CDCl_3$, 300 MHz] **300cX** = ^1H →

PURIFICATION

Colum size: PFSiHP 25g
Elution: 100% pentane (5CV) - 0 to 5% AcOEt in Pentane (5CV) - 5% AcOEt in Pentane (5CV) - 5 to 10% AcOEt in Pentane

(10CV) - 10% AcOEt in Pentane (10CV) - 10 to 20% AcOEt in Pentane (5CV) - 20% AcOEt in Pentane (5CV).



Fractions*: F1 (TUBES 30-32) = 153.8 mg; → 63.5 mg**

F2 (TUBES 33-44) = 1.2549 g; → 3.8 mg**

F3 (TUBES 49-61) = 208 mg; → 73.3 mg**

F4 (TUBES 74-90) = 94.6 mg.

*verify by TLC ,** after dried again

CHARACTERIZATION

The figure 1 show the NMR spectrum of the sample F1 that appears in the TLC as a white spot that quickly disappears when the TLC warm up but don't have significant UV absorbance to be seem during the puriflash separation. Make the spectrum analysis we the presence of 6 signals between 1-5.2 ppm, probably, 2 of then belong to our compound: 1.2 ppm (t,3H); 3.4 ppm (m,2H). The other signals are from ethyl acetate (the signals in 2.07ppm and 1.26 ppm). Some of these signals are in agree with the literature for the propylene oxide, our reagent but the signal in 5.08 ppm don't seems to belong either the ethyl acetate, one of the expected products or reagents.

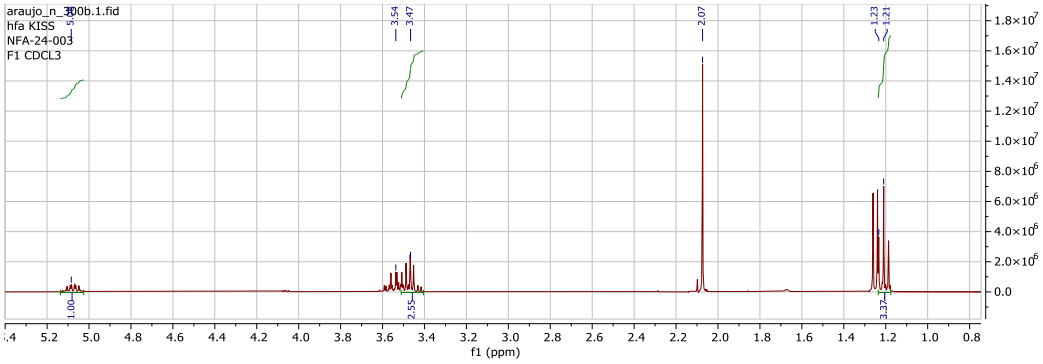


Figure 1 - NMR ^{1}H [$CDCl_3$, 300 MHz] spectrum of the sample F1.

A GCMS analysis of this sample was made (Figure 2). The chromatogram shows the presence of only one compound that are found at 4.95 min. In the MS spectra we can observe the expected peaks for the propylene oxide (m/z= 59, 58 and 43) but also one unexpected peak of m/z = 86.

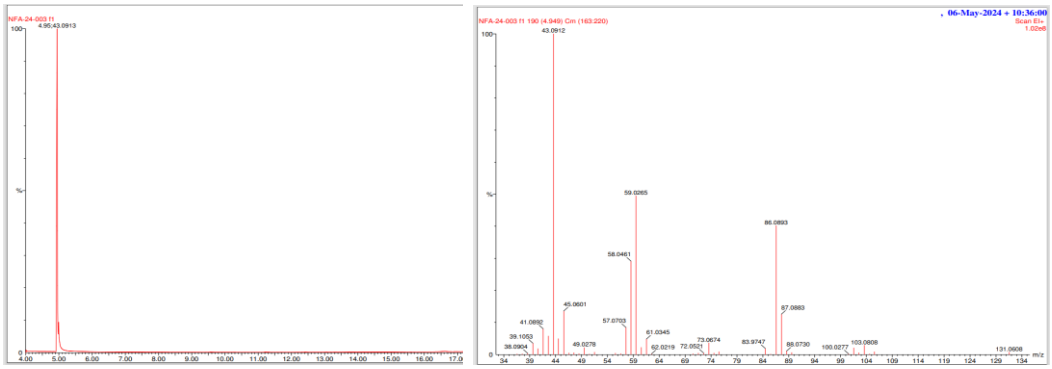
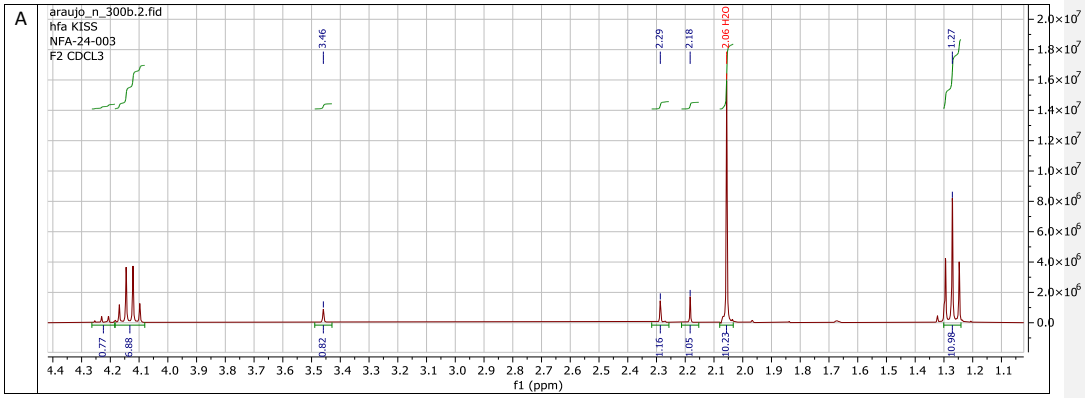


Figure 2 – Chromatogram and mass spectrum of the sample F1.

The figure 3 shows the NMR H of the F2, this fraction hade the highest UV absorbance in the puriflash leaving between 12 and 16 CV, we can see the signals from the ethyl acetate (1.26 ppm; 2.06 ppm and 4.2 ppm) and some other less intense signals, if we compare this spectrum with the ethyl acetoacetate (one of our reagents) spectrum, we can see that these signals matching.



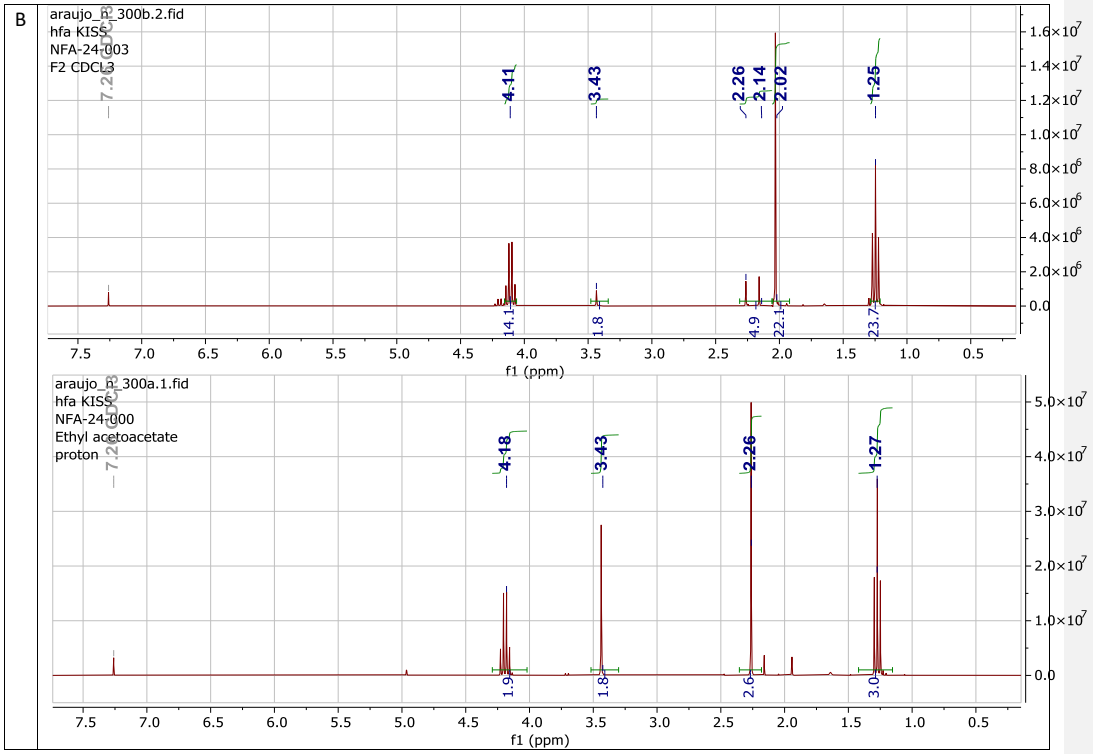


Figure 3 –A. NMR ^{1}H [$CDCl_3$, 300 MHz] spectrum of the F2 sample; B. Comparation of the F2 NMR spectrum (up) and the ethyl acetoacetate spectrum(bottom).

The figure 4 shows the NMR spectrum of the F3 sample, the second signal showed on the puriflash UV spectrum. We can see again the signals from ethyl acetate and some others signals probably from the product, the NMR spectrum of the sample F4 when compared presenting the exact same signals, so the two samples were put together and dried. Another NMR H spectrum (Figure 5) was taken where we can see that we have a mixture of compounds, the multiples with the chemical shift in 4.6 ppm(1H) and 3.78 ppm (1H), the doublet in 2.46 ppm (3H), the double doublet in 3.38 ppm (1H), the triplet in 1.43 ppm (3H) and the singlet in 1.25 ppm (1H) are the most abundant ones, this tell us that probably the lactone product that we are trying to avoid was formed and is the major product. The others signals have integration for 0.5

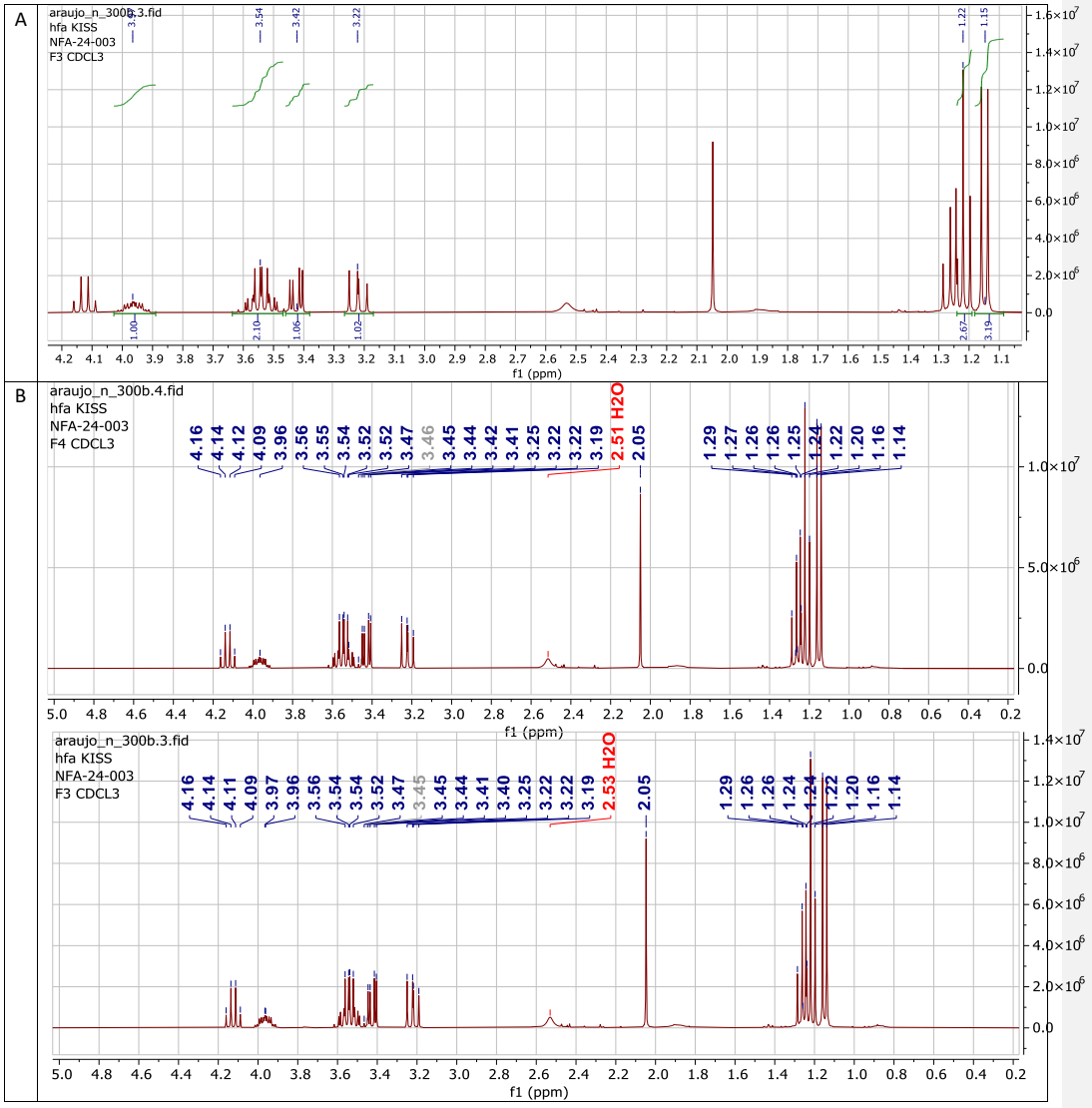


Figure 4 – A. NMR ^{1}H [$CDCl_3$, 300 MHz] spectrum of the F3 sample; B. Comparation between the NMR H spectrum of F3 (up) and F4 (bottom).

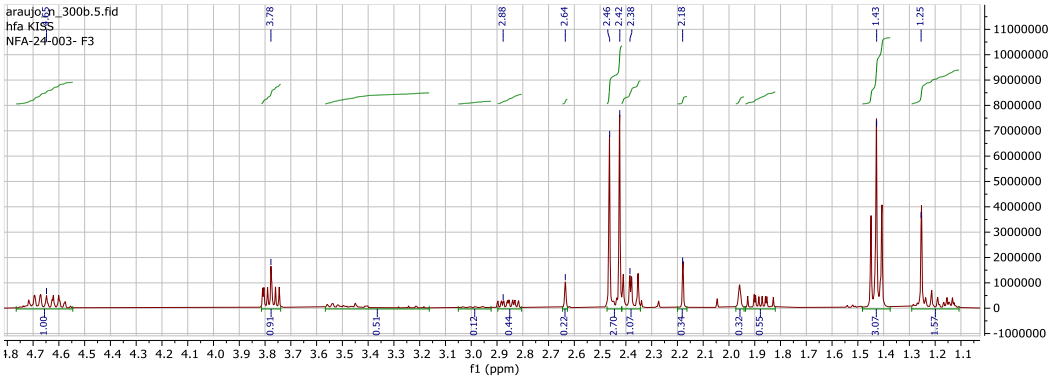


Figure 5 – NMR ^{1}H [$CDCl_3$, 300 MHz] spectrum of the samples F3 and F4 combined and dried.

A GC-MS analysis of this sample was conducted, in the chromatogram (Figure 6) we can see tree signals at 2.9, 3.9 and 7.2 min. The mass spectrum at 2.9 min (Figure 7) shows some of the principals expected fragmentations for our desired product: the peaks with m/z 84, 59 and 45, but also shows the peak whit m/z 31 typical of primary alcohols and we can't see anything heavier than m/z 82.

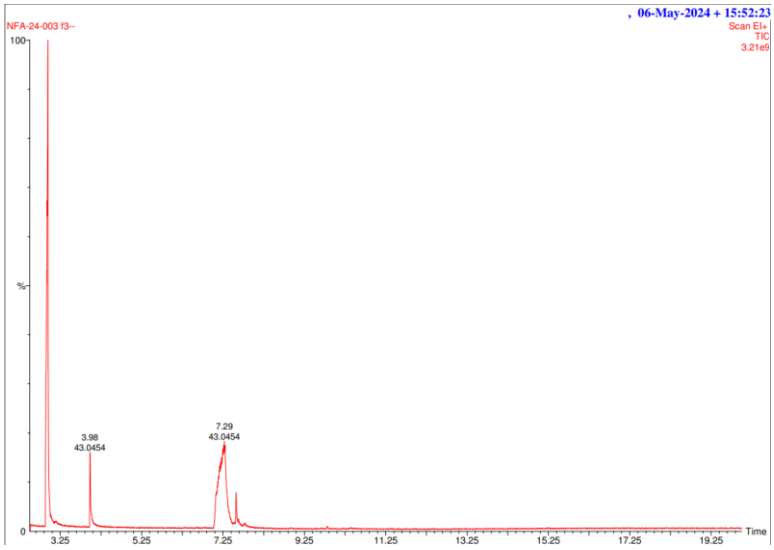


Figure 6 – Chromatogram of the combined samples F3 and F4

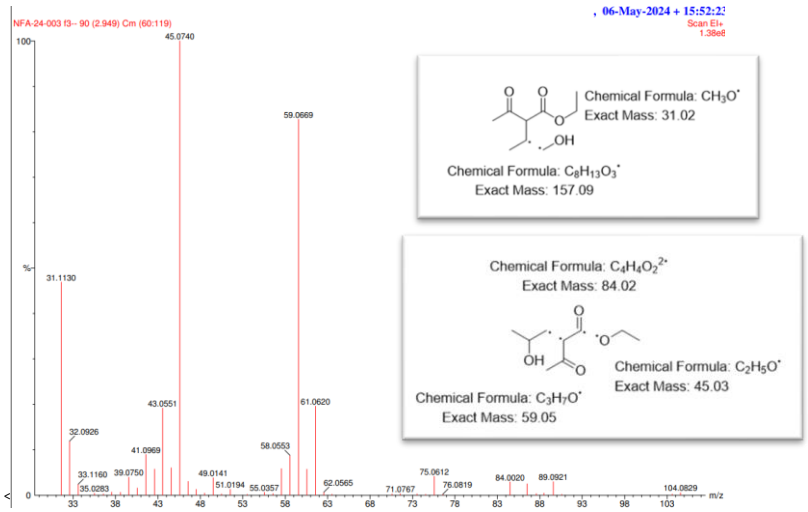


Figure 7 – Mass spectrum of the combined F3 and F4 at 2.9 min and some proposed fragmentations.

The mass spectrum at 3.9 min also shows some of the expected peaks for our desired product: m/z 101, 59 and 43, but again we don't observe noting heavier than m/z 102, another peak observed is m/z 32, maybe the lost off O_2.

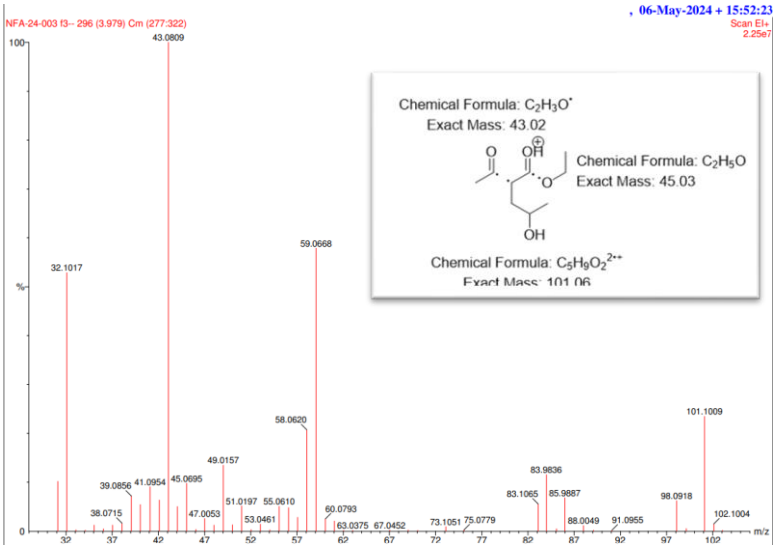


Figure 8 - Mass spectrum of the combined F3 and F4 at 3.9 min and proposed fragmentations.

At 7.2 min the mass spectrum (Figure 9) showed 7 peaks m/z 143, 114, 100, 83, 71, 55 and 43. We can attribute all of then at the lactone side product as we can see in the proposed fragmentation (Figure 10), the protonated molecule loses an hydrogen, than a CO molecule and finally divide in two fragments or loses an acetyl, than an hydroxyl and carbon monoxide.

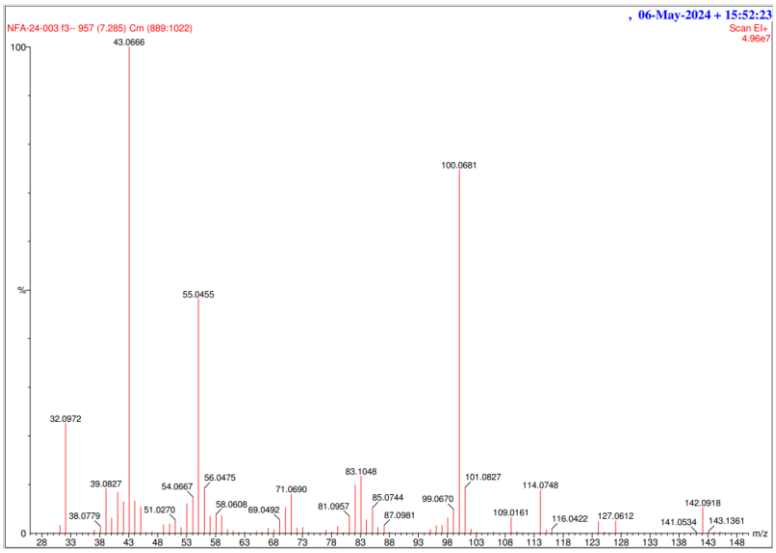


Figure 9 - Mass spectrum of the combined F3 and F4 at 7.2 min.

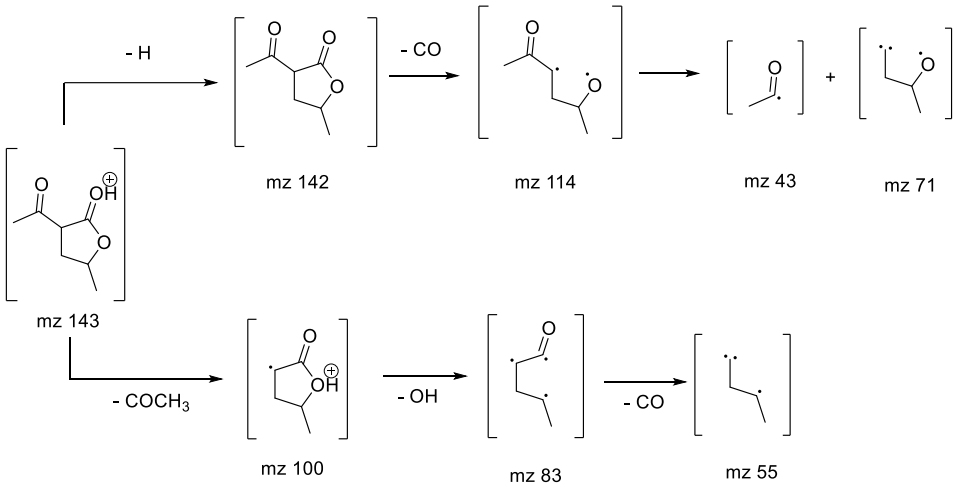


Figure 10 – Fragmentation of the lactone side product.

CONCLUSION

Probably the amount of NaH left the mixture to basic and this caused the formation of the lactone as major product, the reaction wasn't completed, there's 3.8 mg of starting material left in the reactional mixture.

Commented [NA3]: but we only get 10% of yield, where is the rest of the SM?

We must take care of the drying process; the compounds are too similar to ethyl acetate is hard to take it off.

Now we have to break the lactone ring with ethanol to obtain our product.