Synthesis of Flosal

by

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ABSTRACT

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Flosal (Jasmonal, Jasmine Aldehyde, (*E*)-2-benzylideneheptanal) is an important commercial fragrance compound. The principal method for its preparation involves a crossed aldol condensation reaction of heptanal and benzaldehyde. The method has a serious drawback as the synthesis of jasmine aldehyde is accompanied by self-condensation of heptanal to produce foul-smelling 2-pentyl-2-nonenal. We optimized the reaction conditions to maximize yield of jasmine aldehyde while preventing formation of 2-pentyl-2-nonenal. The desired product was obtained in ~60% yield, with a room for future improvement.

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Introduction

Crossed aldol condensation reactions occurs when there is at least one carbonyl aldehyde compound that lacks an α-hydrogen to react with itself, so that another aldehyde with an α-hydrogen can bind [1]. The flosal experiments are meant to optimize the reaction conditions for synthesis of Jasmine Aldehyde (Flosal) rather than extract it from the Jasmine flower. Jasmine Aldehyde is a key ingredient in some perfumes. It is produced artificially through a crossed aldol condensation reaction of heptanal and benzaldehyde (Figure 1) [2]. Different conditions and techniques were employed to maximize yield of the desired product, (*E*)-2-benzylideneheptanal while both the undesired product, (*E*)-2-pentylnon-2-enal and benzaldehyde left over are minimized. The techniques, such as slow addition and use of a phase-screen, were employed in the experiment to identify the most efficient procedure [3].

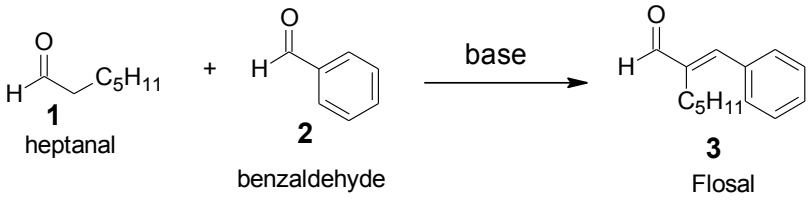


Figure 1: Flosal reaction

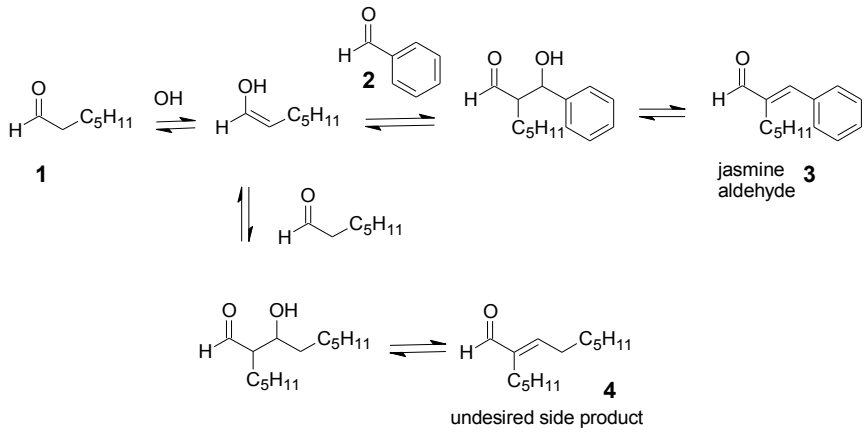


Figure 2: Jasmine aldehyde pathway

As shown in Figure 3, the desired pathway produces flosal (jasmine aldehyde) rather than (*E*)-2-pentylnon-2-enal mostly due to the steric hindrance of heptanal, but the ultimate goal of the experiment is minimizing the undesired product to nearly zero percent [2].

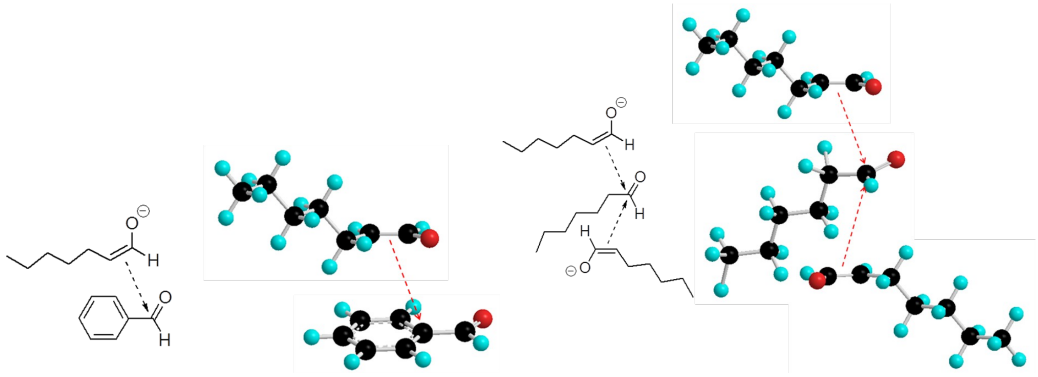


Figure 3: Benzaldehyde (left) is less sterically hindered compared to heptanal (right).

Materials and Methods

Data Acquisition:

GC-MS analyses were carried out by means of Agilent 6890N Gas Chromatograph equipped with an HP-5 MS 30 m x 0.25 mm column and an Agilent 5973N Mass Spectrum Detector.

Solvents and Reagents:

Heptanal, benzaldehyde, sodium hydroxide, FC-72, methanol, sodium hydride were obtained from Fischer Scientific. Distilled H_2O, diethylether, hexane, and pentane were solvents used to perform the reaction and the work-up.

General Work-Up Procedure:

A crossed aldol condensation reaction is carried through both a base and the benzaldehyde reacting with heptanal to produce the desired product, jasmine aldehyde. In most techniques, the base is added together with benzaldehyde to a container with 10-20mL

of solvent. The heptanal is mixed into the container at a controlled rate, reaction was carried out for 30 minutes or longer. Three phases of extraction were carried out: (1) 3 extractions with the appropriate organic solvent, (2) 5 extractions with deionized (DI) H_2O, (3) 3 extractions with saturated aqueous NaCl. Extracted solution was analysed by means of GC-MS.

Experimental Procedures

Phase-screen techniques:

FC-72 (2mL) was added to beaker. An open-ended tube was placed in the solution. 1M KOH (3mL) was added to the perflouroalkane and benzaldehyde (0.24mL) was injected into the solution. Heptanal (0.28mL) was placed within the tube and allowed to react for a few days. The top layer (remaining heptanal) within the tube was removed. The solution was transferred to a separatory funnel and extracted with diethylether or hexane. The organic layer was removed and stored for future experiments, the aqueous layer was extracted three times to obtain some flosal. A second trial of phase-screen begins the same as the previous experiment except the solvent diethylether is replaced with hexane for extraction. Three samples, the flosal, aqueous, and organic layers are analyzed through GC-MS.

The last experiment for phase-screen was carried with hexane acting as the phase-screen. H_2O (2mL) was added to NaOH (0.5g) and the solution was poured into a test tube. A stirrer is placed in the test tube to begin spinning. EtOH (2mL) was added to the test tube, and benzaldehyde (1.1mL) was injected into the solution. Hexane (4mL) was overlayed on the top of the solution before heptanal (0.7mL) in hexane (4mL) was injected by syringe. Addition of heptanal solution lasts for ten minutes, and the experiment was left to complete in 30 minutes. Extraction, storage, and analysis were repeated from earlier addition experiments except pentane instead of hexane was used for extraction.

PTFE tape technique:

1M KOH (4mL) in isopropanol (100mL) was added to a round bottom flask. Benzaldehyde (0.4mL) was injected into the flask. PTFE tape was applied to the bottom of the tube to separate the heptanal from the solution. A stirrer was placed in the flask. A solution of heptanal (0.28mL) in hexanes (20mL) was placed into the tube. The reaction was allowed to proceed for 1 hour. Same extraction procedures were used from the previous addition.

In the second experiment, isopropanol was replaced with ethanol. The rest of the procedure remains the same, and a sample is prepared for analysis.

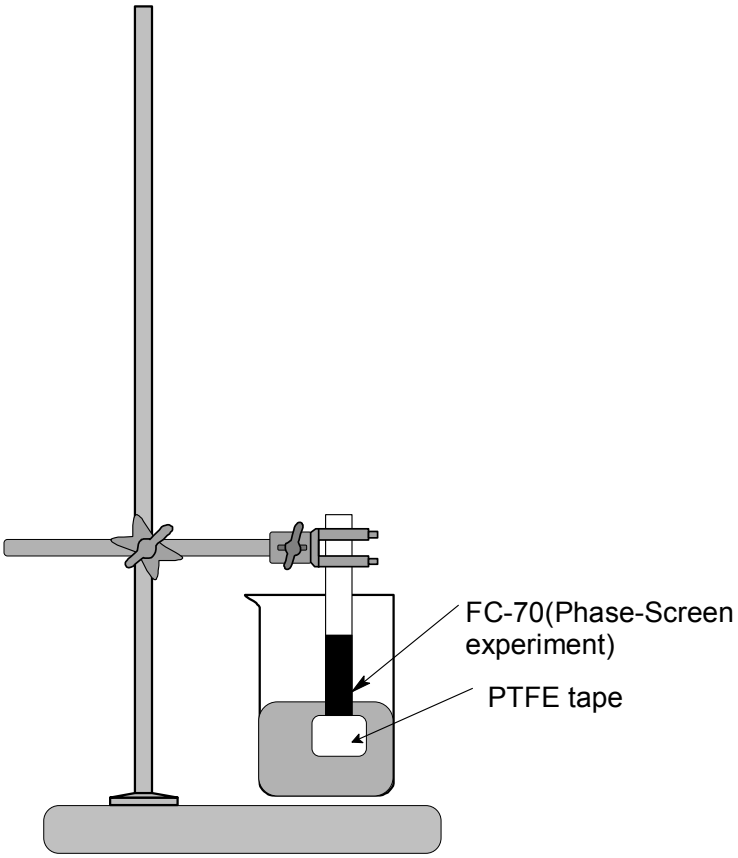


Figure 4: Setup of Phase-screen and PTFE tape

Slow addition techniques:

1M NaOH (4mL) in methanol was added to a round bottom flask equipped with a stirring bar. Benzaldehyde (0.4mL) was placed in the solution and hexane (20mL) was added. Heptanal (0.28mL) and hexane (1mL) are placed in a dropping funnel. The heptanal solution was slowly added for 30 minutes. The experiment was left to complete for another 30 minutes. The methanol was extracted 3 times with hexanes (6mL). The hexane layer was purified by 3 extractions of H_2O (5mL). The organic layer was further purified by 3 extractions of saturated NaCl (2mL).The sample was analyzed by means of GC-MS.

The first experiment was repeated for the second trial except that the second phase required five extractions of H_2O (5mL).

In the third experiment, the base was replaced with 1:1 water/ethanol and the rest of the procedure remained the same.

A new base, sodium methoxide was used for the fourth experiment of slow addition. Sodium hydride (0.2g) was mixed with methanol (4-5mL). The procedure, beginning with the benzaldehyde, was repeated twice.

H_2O (2mL) was added to NaOH (0.5g) and the solution was poured into a test tube. A stirrer was placed in the test tube to start stirring. EtOH (2mL) was added to the test tube, and benzaldehyde (0.1mL) was injected into the solution. Addition of heptanal (0.07mL) in EtOH (5mL) solution lasted for ten minutes, and the experiment was left to complete in 30 minutes. Extraction, storage, and analysis are repeated from earlier addition experiments except pentane instead of hexane is used for extraction.

The final experiment in slow addition repeats the previous trial except that the reactants' volumes were increased, benzaldehyde (1.1mL) and heptanal (0.7mL).

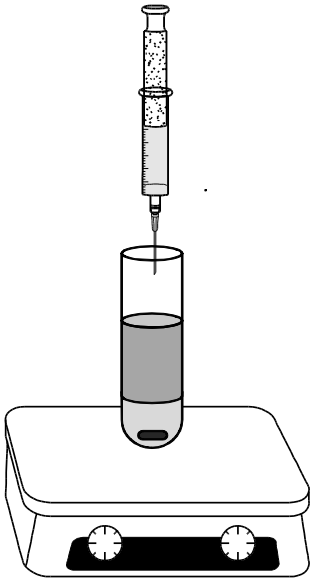


Figure 5: Setup for slow addition w/ syringe

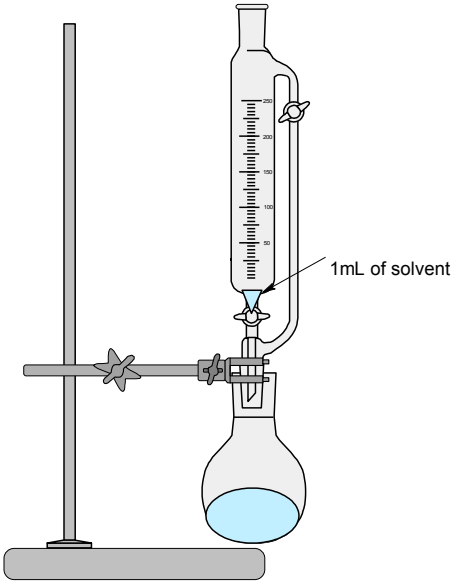


Figure 6: Setup for slow addition w/ dropping funnel

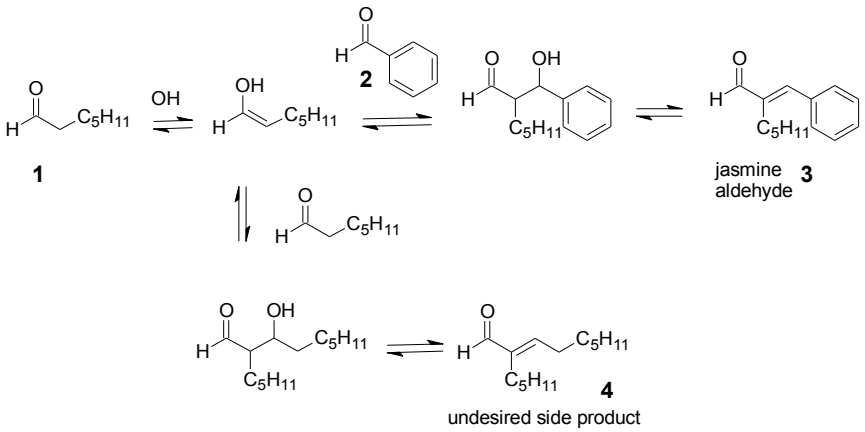
Results and Discussion

Phase-screen:

Eight experiments were completed with the phase-screen technique, and only one

provided a good yield of Jasmine Aldehyde as seen in table 1.

Table 1. Phase-screen



		Yield (%)[a]			
Entry	**Conditions**	**1**	**2**	**3**	**4**
1	FC-72, ethyl-ether, 2 days, rt	71	5	19	4
2	FC-72, ethyl-ether, 2 days, rt	N/A	N/A	85	N/A
3	FC-72, ethyl-ether, 2 days, rt, FC-72 layer	17	25	1	4
4	FC-72, ethyl-ether, 2 days, rt, aqueous layer	54	37	N/A	N/A
5	FC-72, ethyl-ether, 2 days, rt, organic layer	38	44	N/A	2
6	FC-72, hexane, 2 days, rt, FC-72 layer	13	16	9	3
7	FC-72, hexane, 2 days, rt, aqueous layer	41	16	7	3
8	FC-72, hexane, 2 days, rt, organic layer	30	42	8	1
9	Hexane,benzaldehyde(1.1), heptanal(0.7)in hexane(4mL), 10min, rt	8	N/A	38	11
10	Hexane,benzaldehyde(1.1), heptanal(0.7)in hexane(4mL), 10min, rt	16	6	39	12

a) As determined by GC-MS analysis

Slow Addition:

The results shown in table 2 indicate that slow addition provided low yields of jasmine aldehyde, but also relatively small amounts of (*E*)-2-pentylnon-2-enal. The protocol created for the slow addition technique may not have yielded enough flosal for the goal of the experiment, but it has prevented the heptanal to bind to itself. With sodium methoxide as the base, the yields were even lower. The ethanol addition provided the best results as indicated by a high yield of jasmine aldehyde, low yield of (E)-2-pentylnon-2-enal, and high conversion.

Table 2. Slow Addition

		Yield (%)[a]			
Entry	**Conditions**	**1**	**2**	**3**	**4**
1	hexane(1mL), 30 min, rt, 3x ext. of H_2O(5mL)	35	1	46	11
2	hexane(1mL), 30 min, rt, 5x ext. of H_2O(5mL)	24	N/A	47	18
3	1:1 H_2O/ethanol base, 30min, rt, 5x of H_2O(5mL)	37	N/A	23	11
4	sodium hydride(0.2g)/methanol(4-5mL), 30min, rt, 5x of H_2O(5mL)	43	N/A	29	17
5	sodium hydride(0.2g)/methanol(4-5mL), 30min, rt, 5x of H_2O(5mL)	27	N/A	38	13
6	sodium hydride(0.2g)/methanol(4-5mL), 30min, rt, 5x of H_2O(5mL)	35	N/A	40	12
7	Pentane,benzaldehyde(0.1), heptanal(0.07) in EtOH(5mL), 10min, rt	3	N/A	62	23
8	Pentane, benzaldehyde(1.1), heptanal(0.7)in EtOH(5mL), 10min, rt	7	N/A	24	11
9	Pentane, benzaldehyde(1.1), heptanal(0.7)in EtOH(5mL), 10min, rt	7	N/A	57	14

a) As determined by GC-MS analysis

PTFE Tape as a phase-screen:

There was no appreciable reaction when PTFE was used as a phase-screen. The problem may lie on the amount of solvent used in the protocol. The benzaldehyde and base

were too diluted in the solvent solution to reach the PTFE tape and dissolve towards the heptanal.

Overall Discussion:

Most of the experiments gave jasmine aldehyde in poor yields. Furthermore, the reaction product was accompanied by significant amount of (*E*)-2-pentylnon-2-enal as well as other byproducts. Moreover, removal of the excess of benzaldehyde presented a problem. Yield of jasmine aldehyde was improved by adding a dilute solution of heptanal to a mixture of sodium hydroxide and an excess of benzaldehyde. Under such conditions, heptanal enolate ion was surrounded by numerous molecules of benzaldehyde and very few other heptanal molecules. Thus, it was much more likely to react with benzaldehyde than with another heptanal molecule. Purity of the isolated jasmine aldehyde was increased by repeated water rinses of the organic extract, which successfully removed excess of benzaldehyde.

Conclusion

A simple addition of heptanal to a mixture of base and an excess of benzldehyde provided the best results. The reaction conditions allowed heptanal to be deprotonated by the base and to immediately react with benzaldehyde while minimizing self-condensation. Better results might be obtained if there was a more efficient barrier between the heptanal and the base/benzaldehyde phase. The barrier would enable even slower addition of heptanal thus completely eliminating self-condensation. For future phase-screen experiments, a different perflouroalkane compound should be implemented to possibly observe better results.

References

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2. Hornback, J.M. *Organic Chemistry, 2nd ed.* 2006 Thompson Brooks/Cole, Belmont, CA 94002, p.886.

3. Dragojlovic, Veljko. CHM 2205L (*Organic Chemistry 2) Summer 2013 Lab Manual*. Synthesis of Jasmine Aldehyde.

Appendix

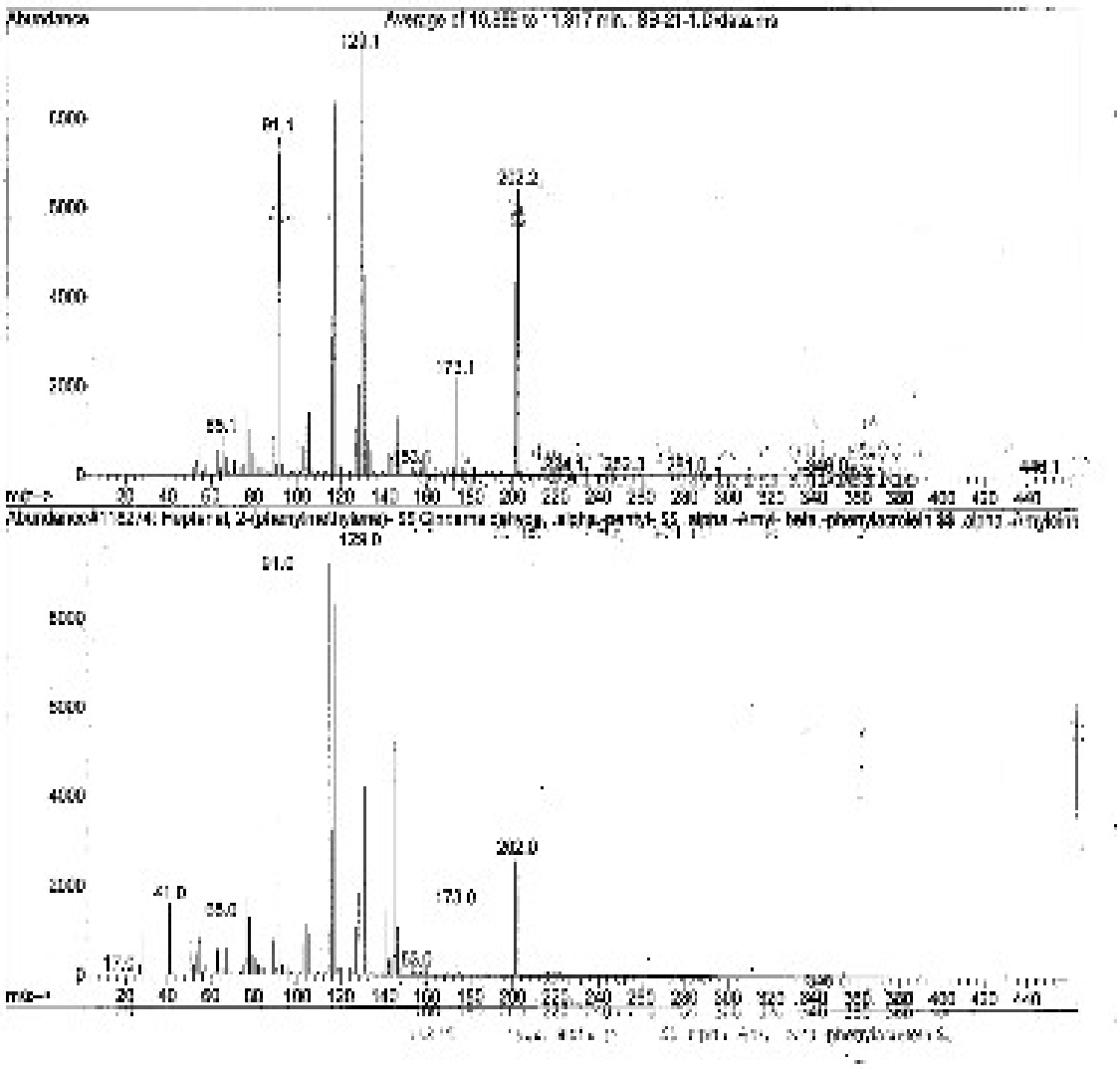

Figure 7: GC-MS of Jasmine Aldehyde(Flosal)

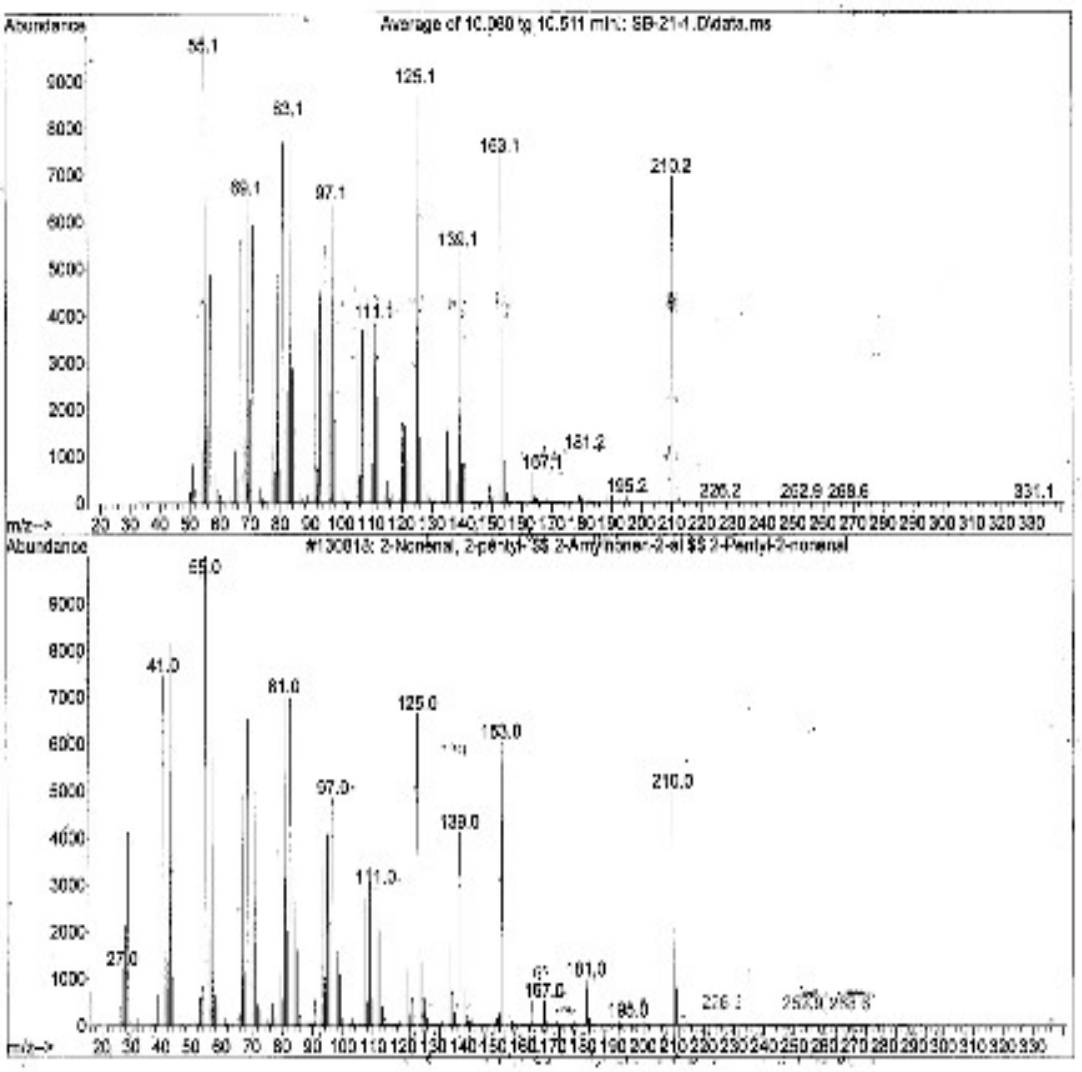

Figure 8: GC-MS of (*E*)-2-pentylnon-2-enal