

# Lab Exp G. Synthesis of Methyl Diantilis

MARK REJNA

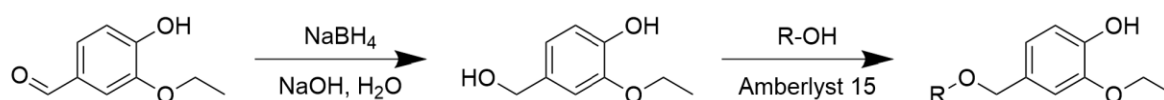
University of California, Berkeley

## I. INTRODUCTION

Methyl Diantilis has a unique, pleasant aroma that is described by Givaudan as elegant, spicy, and sweet; having notes of carnation and vanilla.<sup>1</sup> For this reason, Methyl Diantilis is widely used in the Fragrance Industry as an important ingredient in the production of beauty, cosmetics, and fragrances such as perfumes and shampoos. For commercial synthetic compounds such as Methyl Diantilis which are frequently used in many industries, it is important to study the methods of synthesising the compound in order to optimise its production. The aroma and bioactivity of Methyl Diantilis is caused and affected by the ether group in the aromatic compound, similar to that of ethylvanillin.<sup>2</sup> The method to synthesise Methyl Diantilis in this experiment is based on the investigation conducted by Willaim H. Miles and Katelyn B. Connell. This method of synthesising Methyl Diantilis utilises sodium borohydride as a reducing agent, whereas the synthesis of Methyl Diantilis on a large scale uses hydrogen as a reducing agent.<sup>3</sup>

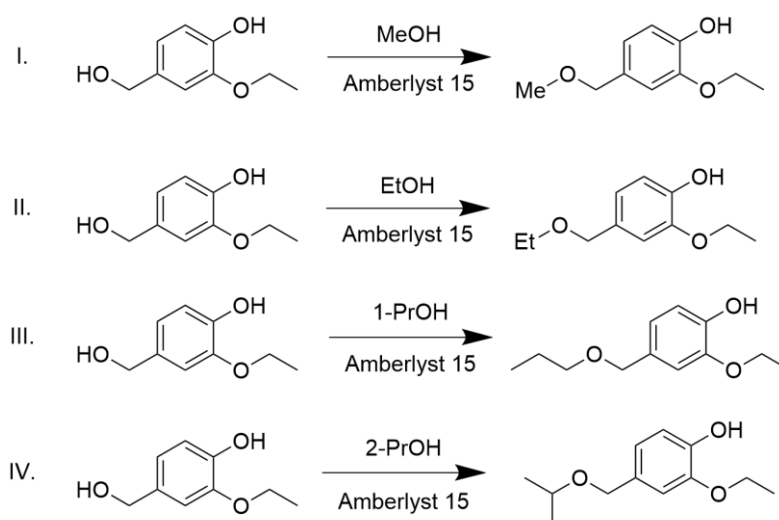
In this experiment, Methyl Diantilis as well as similar 4-hydroxy-3-ethoxybenzyl alkyl ethers will be synthesised as outlined in *Scheme 1* and *Scheme 2* below, where the hydroxyl groups used in this experiment are methanol, ethanol, 1-propanol, and 2-propanol.

*Scheme 1: Synthesis Overview (Step 1 and generalised Step 2)*



This two-step synthesis mechanism will start with the reagent ethylvanillin. The first step is a nucleophilic addition reaction where the aldehyde functional group on ethylvanillin is reduced to a hydroxyl group with sodium borohydride, sodium hydroxide, and water. The second step is a nucleophilic substitution reaction where the hydroxyl group undergoes etherification to become an ether. This is done by reacting the product of step 1 with a hydroxyl group and Amberlyst 15.

*Scheme 2: Step 2 with Methanol, Ethanol, 1-Propanol, and 2-Propanol*



## II. EXPERIMENTAL PROCEDURE

This experiment was conducted in a group of 5 members: Mark Rejna, Parker Gravel, Floria Li, Pierson Sauberan, and Anjali Pisharaly. Each member performed Step 1 of the procedure and Step 2 was conducted by each group member using a different alcohol (methanol, ethanol, 1-propanol, or 2-propanol). It should be noted that the measurements of mass and volume in Step 1 correspond to my experiment and not other group member's.

### Step 1: Sodium Borohydride Reduction of 3-Ethoxy-4-hydroxybenzaldehyde (Ethylvanillin)

A magnetic stir bar was placed into a 25 mL Erlenmeyer flask. A mass of 0.245 g of ethylvanillin was dissolved into 3 mL of 0.5 M sodium hydroxide (NaOH) and added to the

flask. The flask was then cooled in an ice bath and a mass of 0.073 g of sodium borohydride ( $\text{NaBH}_4$ ) was added to the flask in small amounts. Next, the flask was removed from the ice bath and left for 20 minutes in order to raise the temperature of the flask to room temperature. The flask was then cooled again by placing it back into the ice bath and 2.5 mL of 2.5 M hydrochloric acid ( $\text{HCl}$ ) was added to the flask slowly. The flask quickly foamed and this was caused by the formation hydrogen ( $\text{H}_2$ ) which was escaping the flask. The acidity of the reaction mixture was checked when the formation of gas slowed and it was confirmed to be very acidic. The flask was left in the ice bath for 5 minutes. The flask was vacuum filtered to isolate a solid white precipitate. The precipitate was washed with 2 mL of cold water three times and then dried on filter paper under a vacuum for 15 minutes. The precipitate yield weighed 0.2001 grams. A thin-layer chromatography (TLC) was conducted comparing the solid product dissolved in 2 mL of acetone to ethylvanillin using a 1:1 ratio of hexanes to ethyl acetate solvent. Finally, a sample of the precipitate produced by Anjali was dissolved in  $\text{DMSO-d}_6$  and analysed using  $^1\text{H}$  NMR.

#### Step 2: Etherification of 3-ethoxy-4-hydroxybenzyl Alcohol

Step 2 of the experiment was conducted by each group member using a different alcohol: Floria used methanol, Pierson used ethanol, Parker used 1-propanol, and Mark used 2-propanol. A mass of 0.1000 g of 'wet' Amberlyst 15 was added into a small round bottom flask. The Amberlyst was washed with 1 mL of the assigned alcohol three times, the alcohol was removed carefully using a Pasteur pipette. Next, 2 mL of the assigned alcohol was added to the flask, followed by the addition of 0.1000 g of the product from Step 1 (3-ethoxy-4-hydroxybenzyl alcohol) which was added to the flask in small proportions whilst being stirred vigorously. One drop of this reaction mixture was removed for TLC analysis. The flask was then attached to a condenser and heated to reflux for 15 minutes. An additional 1 mL of the assigned alcohol was added to the flask during heating. One drop of this reaction

mixture was removed and diluted with 5 drops of acetone for TLC analysis. A mass of 0.0500 g of sodium bicarbonate ( $\text{NaHCO}_3$ ) was then added to the flask and left to stir for another 5 minutes. The reaction mixture was filtered through a glass fibre plug using a Pasteur pipette and then the reaction flask was washed with small volumes of assigned alcohol three times. The product was then isolated from the solvent by heating the mixture on a hot plate with a gentle stream of air. The product using 2-propanol was an oily liquid substance with a yellow-brown color which weighed 0.0508 g. Finally, a sample of the product was dissolved in  $\text{DMSO-d}_6$  and analysed using  $^1\text{H}$  NMR.

### III. DISCUSSION

#### RESULTS AND DATA ANALYSIS

**3-ethoxy-4-hydroxybenzyl alcohol.**  $^1\text{H}$  NMR (80 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.32 (t,  $J = 7.2$  Hz, 3H), 3.10-3.76 (broad s, 1H), 3.95 (q,  $J = 7.2$  Hz, 2H), 4.36 (s, 2H), 6.71 (s, 2H), 6.86 (s, 1H)

**2-ethoxy-4-(methoxymethyl)phenol (methyl Diantilis).**  $^1\text{H}$  NMR (80 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.31 (t,  $J = 7.2$  Hz, 3H), 3.22 (s, 2H), 3.95 (m, 2H), 4.24 (s, 3H), 4.78-5.99 (broad s, 1H), 6.79 (t,  $J = 11.2$  Hz, 3H)

**2-ethoxy-4-(ethoxymethyl)phenol.**  $^1\text{H}$  NMR (80 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.06 (t,  $J = 7.2$  Hz, 6H), 1.20 (m, 2H), 3.22-3.63 (m, 4H), 3.63-4.20 (broad s, 2H), 4.35 (t,  $J = 5.2$  Hz, 2H), 6.19-6.87 (m, 3H),  $\delta$  8.51 (broad s, 1H)

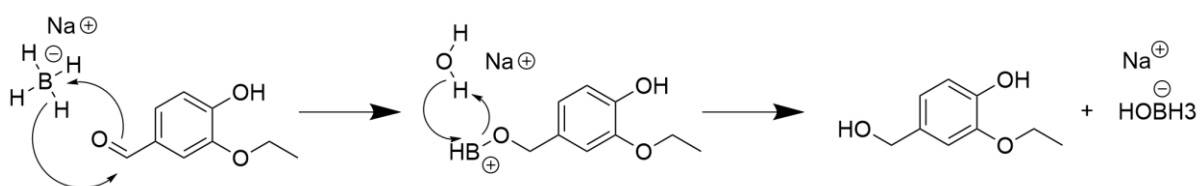
**2-ethoxy-4-(propoxymethyl)phenol.**  $^1\text{H}$  NMR (80 MHz,  $\text{DMSO-d}_6$ )  $\delta$  0.94-1.49 (m, 9H), 3.59 (t,  $J = 6.4$ , 2H), 4.31 (s, 2H), 6.52 (s, 1H), 6.72 (s, 1H), 6.84 (s, 1H), 8.74 (broad s, 1H)

**2-ethoxy-4-(isopropoxymethyl)phenol.**  $^1\text{H}$  NMR (80 MHz,  $\text{DMSO-d}_6$ )  $\delta$  0.86 (t,  $J = 7.2$  Hz, 3H), 1.05-1.78 (m, 6H), 3.33 (t,  $J = 6.8$  Hz, 3H), 3.95 (q,  $J = 7.2$  Hz, 2H), 4.3 (s, 2H), 6.72 & 6.84 (s, 3H), 8.76 (broad s, 1H)

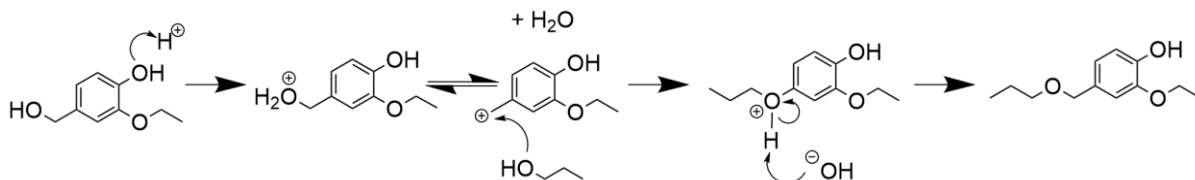
As seen in *Table 1* in the *Appendix*, the yield of the product using methanol was the smallest at 26.2%. The yield of the product using 2-propanol was significantly higher at 40.6%. The yield of the product using ethanol was also higher at 43.8%, and the product using 1-propanol was the highest at 55.8%. It should be noted that the products of all of the iterations of this experiment were oily liquid substances with a yellow-brown color. Because the yield was an oily liquid and not a solid precipitate, the values for actual mass are very inaccurate and higher than they should be, and thus the values for yield are higher. The main experimental factors that led to a lower than expected yield are the loss of precipitate in *Step 1* when transferring the mass, incomplete reactions in *Step 1*, and product loss in *Step 2* during vacuum evaporation. The mass of the oily liquid was measured and then evaporated was continued fully, leaving no residue behind, therefore indicating that the oily liquid was the product and for this reason it is unknown how much product was lost through vacuum evaporation not being stopped early enough.

The mechanisms of the reactions conducted in *Step 1* and *Step 2* with *1-propanol* are outlined in *Schemes 3* and *4*, respectively.

*Scheme 3: Mechanism of Step 1*



*Scheme 4: Mechanism of Step 2 Step 2 with 1-Propanol*



The analysis of  $^1\text{H}$  NMR spectrums is interpreting the chemical shifts, multiplicity, and integration in the data above which can also be visualised in the  $^1\text{H}$  NMR spectrums in

*Figures 7- 11 in the Appendix.* The intermediate, 3-ethoxy-4-hydroxybenzyl alcohol, has a broad singlet integrated to 1 between  $\delta$  3.10-3.17 ppm which corresponds to the overlapping signals of the hydroxyl group hydrogens labelled B and F. The reason that their chemical shifts are lower than expected is because they form hydrogen bonds with H<sub>2</sub>O which typically has a chemical shift of 3.31 in DMSO-d<sub>6</sub>. There is also an overlapping signal at  $\delta$  6.86 where aromatic hydrogens labelled A and H overlap. The <sup>1</sup>H NMR spectrum for Methyl Diantilis has an unknown singlet impurity signal at  $\delta$  3.22 ppm with an integration of 2H, as well as overlapping signals at  $\delta$  3.95 corresponding to hydrogens labelled D, and G. In the <sup>1</sup>H NMR spectrum for 2-ethoxy-4-(ethoxymethyl)phenol there are two impurities present, one is an unknown impurity at  $\delta$  1.20 and the other is identified to be H<sub>2</sub>O between  $\delta$  3.63-4.20. This spectrum also contains overlapping signals of aromatic hydrogens labelled A, E, and I between  $\delta$  6.19-6.87. The <sup>1</sup>H NMR spectrum for 2-ethoxy-4-(propoxymethyl)phenol does not contain any impurities or overlapping signals, the aromatic hydrogens have chemical shifts of 6.52, 6.72, and 6.84 ppm. Similarly, the <sup>1</sup>H NMR spectrum for 2-ethoxy-4-(isopropoxymethyl)phenol does not contain any impurities, however, the aromatic hydrogens overlap such that there are two main peaks at  $\delta$  6.72 and 6.84 ppm which have an integration of 3H.

After analysing the corresponding TLC diagrams and <sup>1</sup>H NMR spectrums in *Figures 1-11*, respectively, it is clear that the samples followed a similar trend where some impurities were present in the mother liquor of *Step 2*, however, these impurities were removed by heating the mother liquor to reflux for 15 minutes. This can be seen visually in *Figures 1-4* where the lane S2-1 on the TLC plates has either 2 distinct dots or a cone-like shape indicating an impurity is present whereas the final TLC lane, S2-2, only contains one dot which corresponds to a pure product. The reason for this trend is because the reaction in *Step 2* was incomplete and after heating to reflux, the reaction proceeded to completion removing

the impurities. It should be noted that as seen in the  $^1\text{H}$  NMR spectrum, impurities were still detected in reaction I. and II. that were not detected by TLC. There were no impurities identified in  $^1\text{H}$  NMR spectrums of reaction, III. and IV. which suggests that the TLC analysis is accurate. Furthermore, from the  $^1\text{H}$  NMR of the intermediate (product from *Step 1*), the impurity of  $\text{H}_2\text{O}$  was identified.

Example calculation - the molar ration between desired product and impurity (reaction II.  $\text{H}_2\text{O}$  impurity):

$$\text{H}_2\text{O impurity: } \frac{\text{observed peak integration}}{\text{expected peak integration}} = \frac{2}{2} = 1$$

$$\text{Desired product (used signal for hydrogen labelled C\&F): } \frac{\text{observed peak integration}}{\text{expected peak integration}} = \frac{6}{6} = 1$$

$$\text{Molar ratio: } \text{desired product: impurity} = 1:1$$

The intermediate, 3-ethoxy-4-hydroxybenzyl alcohol (product from *Step 1*), has a molar ration of *desired product:  $\text{H}_2\text{O}$  impurity* = 3: 1, therefore, it can be stated that the intermediate is 75% pure. The product from reaction II., 2-ethoxy-4-(ethoxymethyl)phenol, has a molar ratio of *desired product:  $\text{H}_2\text{O}$  impurity* = 1: 1, indicating that the desired product is 50% pure with respect to  $\text{H}_2\text{O}$ . This reaction also has another impurity with an unknown identity which is a wide multiplet with an integration of 2H. Furthermore, the product from reaction I, Methyl Diantilis, has an unknown impurity that is a singlet with an integration of 2H, thus the product is not 100% pure. Conversely, products from reactions III. and IV. did not have any impurities identified in either the S2-2 TLC lane or in their  $^1\text{H}$  NMR spectrums.

## CONCLUSION

Overall, the multi-step synthesis reactions conducted in this experiment were successful. The first step of the reaction was a nucleophilic addition which synthesised an intermediate. The second step of the reaction was a nucleophilic substitution using alcohols methanol, ethanol, 1-propanol, and 2-propanol. The reaction in *Step 2* involving methanol synthesised Methyl Diantilis, the other reactions synthesised 4-hydroxy-3-ethoxybenzyl alkyl ethers which have a similar structure. The highest yield in this experiment was from reaction

III. (the reaction with 1-propanol) which was 55.8%, and the lowest yield in this experiment was from reaction I. (the reaction with methanol) which was 26.2%. All products were analysed using TLC and  $^1\text{H}$  NMR. Reactions I. and II. were identified to be impure and contain impurities whereas reactions III. and IV. did not contain any impurities and thus are pure. Therefore, this experiment was completed successfully as the theoretical products for the synthesis reactions were ultimately synthesised even though some of the reactions had a low yield. Improvements to increase the yield can be made to the method of this experiment which are discussed in the next section.

## FURTHER DISCUSSION

To improve this experiment and increase yield of products, more solvent can be used to rinse the Erlenmeyer flask in *Step 1* in order to minimise the loss of precipitate during transfer. Additionally, a real reflux condenser can be used instead of the DIY condenser which was constructed in this experiment and used in *Step 2*. This would only evaporate the liquids at the bottom of the round bottom flask yielding a better final product.

## V. REFERENCES

### BIBLIOGRAPHY

1. Givaudan; *Methyl Diantilis*; <https://www.givaudan.com/fragrance-beauty/eindex/methyl-diantilism> (accessed 2024-11-28).
2. Wardani, E. A.; Fadlan, A.; Santoso, M.; J. Synthesis of 2-ethoxy-1-((3-methyl-2-buten-1-yl)oxy-4-((3-methyl-2-buten-1-yl)oxymethyl))benzene ; *J. AIP Conf.* 2018, DOI: 10.1063/1.5082492
3. Miles, W. H.; Connell, K. B.; Synthesis of Methyl Diantilis, a Commercially Important Fragrance; *J. Che. E.* 2006; 83 (2), 285; DOI: 10.1021/ed083p285

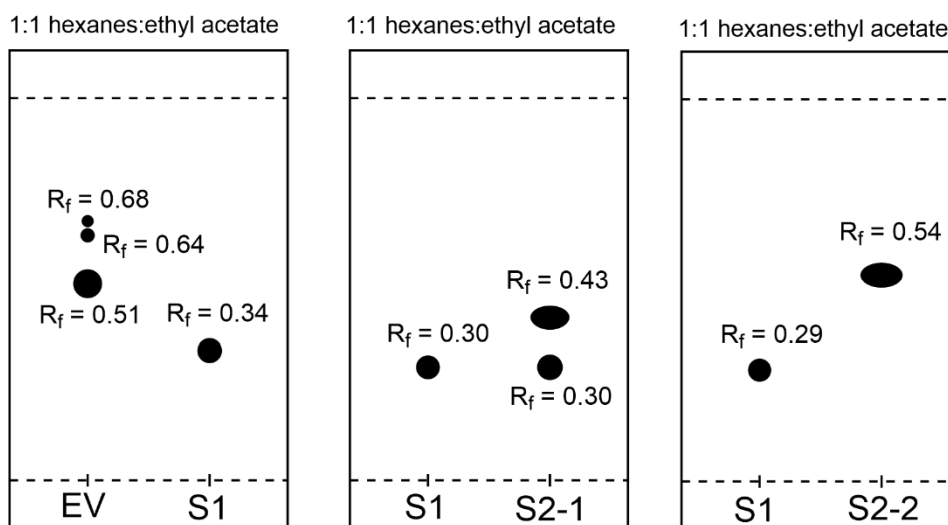


## APPENDIX

*Table 1: Mass data and percent yield from Step 2 of experiment*

Alcohol	Theoretical Mass (g)	Actual Mass (g)	Percent Yield (%)
<b>Methanol</b>	0.108	0.0261	26.2
<b>Ethanol</b>	0.117	0.0512	43.8
<b>1-Propanol</b>	0.125	0.0697	55.8
<b>2-Propanol</b>	0.125	0.0508	40.6

*Figure 1: TLC plates for Reaction I. - Methanol*



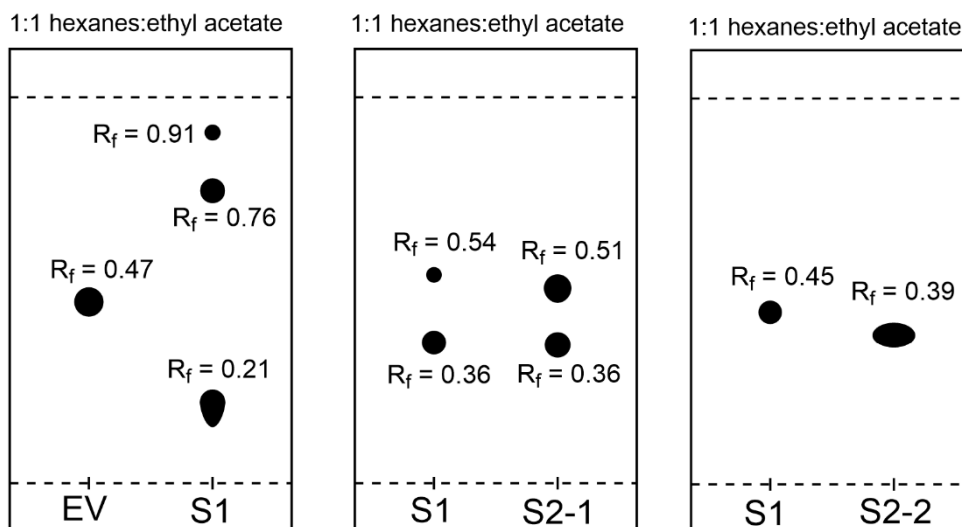
EV: pure ethylvanillin

S1: product from Step 1 (3-ethoxy-4-hydroxybenzyl alcohol)

S2-1: first drop from S2 (sample with R-OH)

S2-2: second drop from S2 (after 15 min heating)

Figure 2: TLC plates for Reaction II. - Ethanol



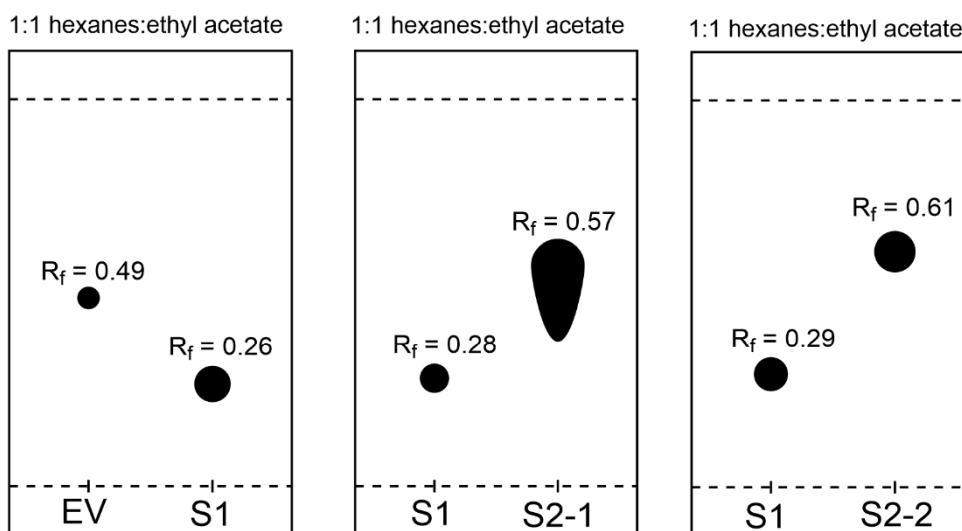
EV: pure ethylvanillin

S1: product from Step 1 (3-ethoxy-4-hydroxybenzyl alcohol)

S2-1: first drop from S2 (sample with R-OH)

S2-2: second drop from S2 (after 15 min heating)

Figure 3: TLC plates for Reaction III. - *l*-Propanolo



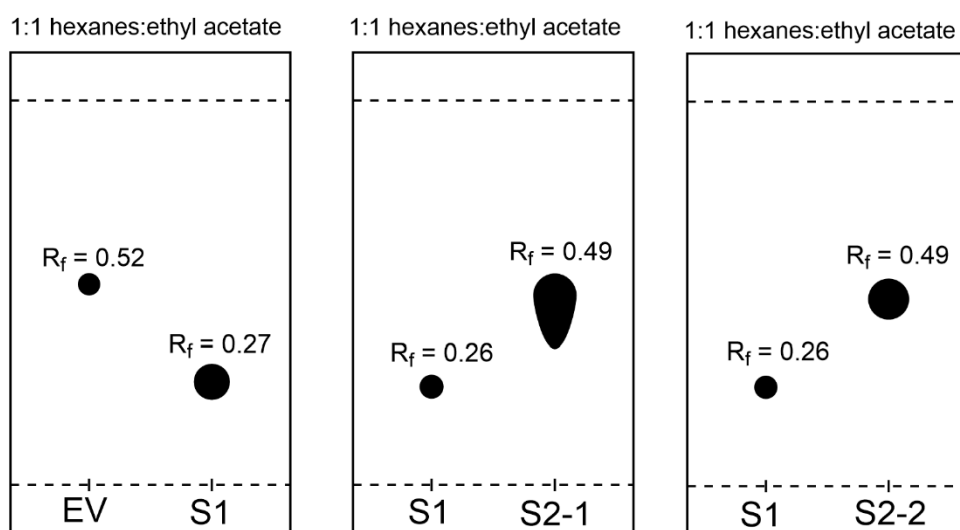
EV: pure ethylvanillin

S1: product from Step 1 (3-ethoxy-4-hydroxybenzyl alcohol)

S2-1: first drop from S2 (sample with R-OH)

S2-2: second drop from S2 (after 15 min heating)

Figure 4: TLC plates for Reaction IV. - 2-Propanol



EV: pure ethylvanillin

S1: product from Step 1 (3-ethoxy-4-hydroxybenzyl alcohol)

S2-1: first drop from S2 (sample with R-OH)

S2-2: second drop from S2 (after 15 min heating)

Figure 5: Ethylvanillin Standard  $^1\text{H}$  NMR Spectrum

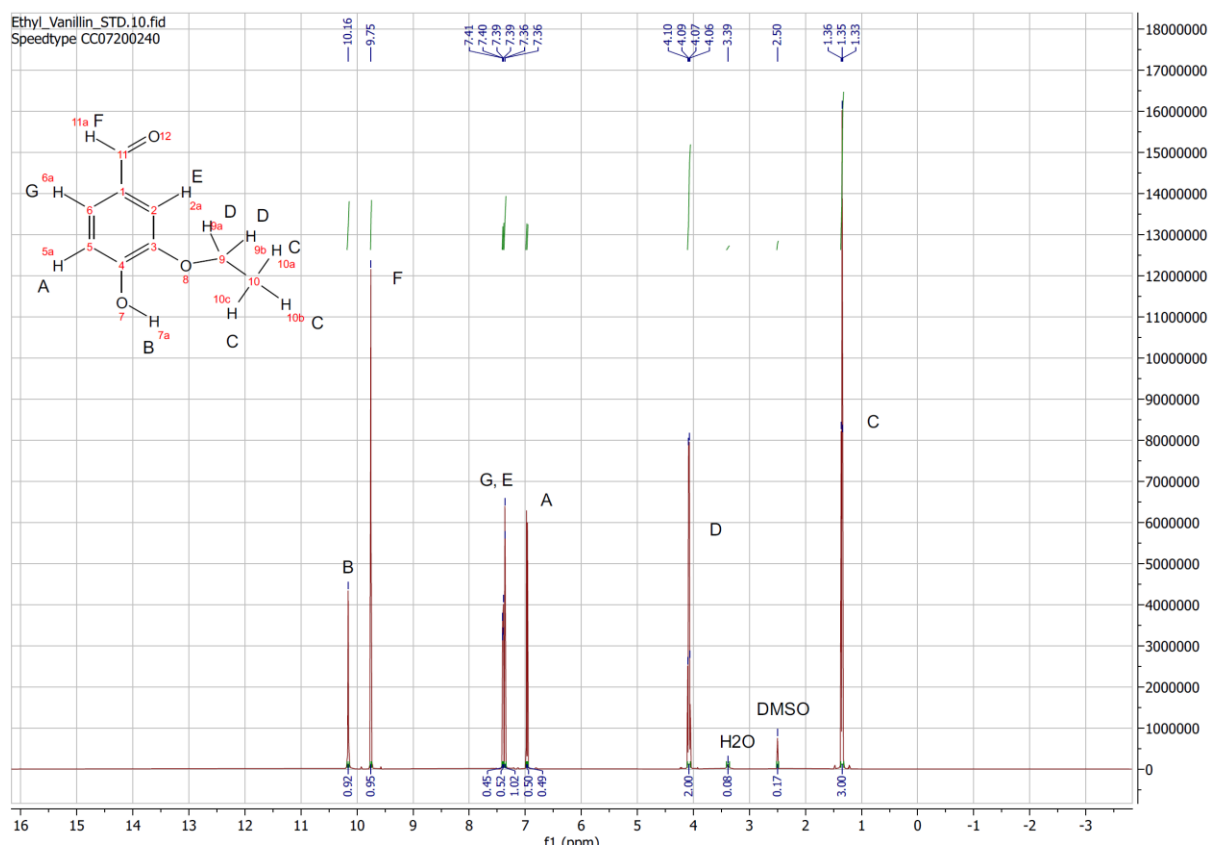


Figure 6: Ethylvanillin Standard  $^{13}\text{C}$  NMR Spectrum

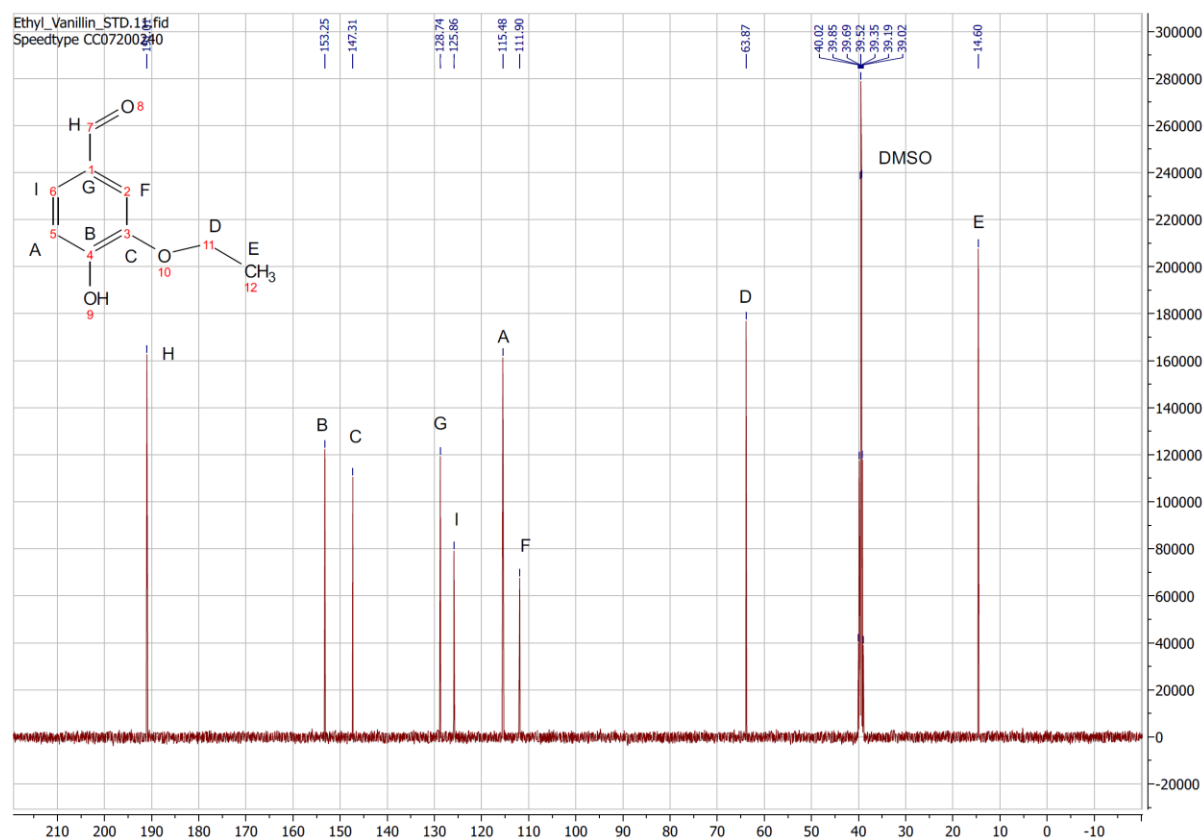


Figure 7: 3-ethoxy-4-hydroxybenzyl alcohol (product from step 1)  $^1\text{H}$  NMR Spectrum

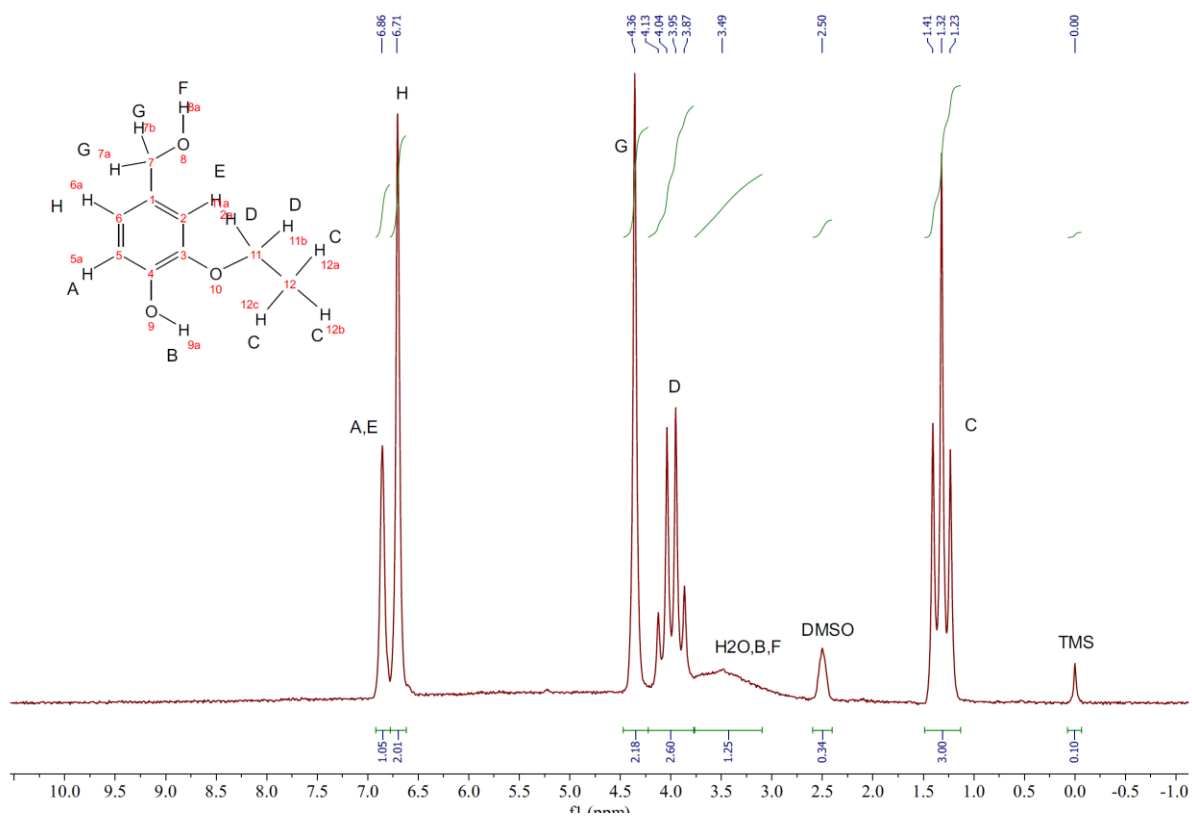


Figure 8: RXN I. - Sample From Step 1 and Methanol (Methyl Diantilis)  $^1\text{H}$  NMR Spectrum

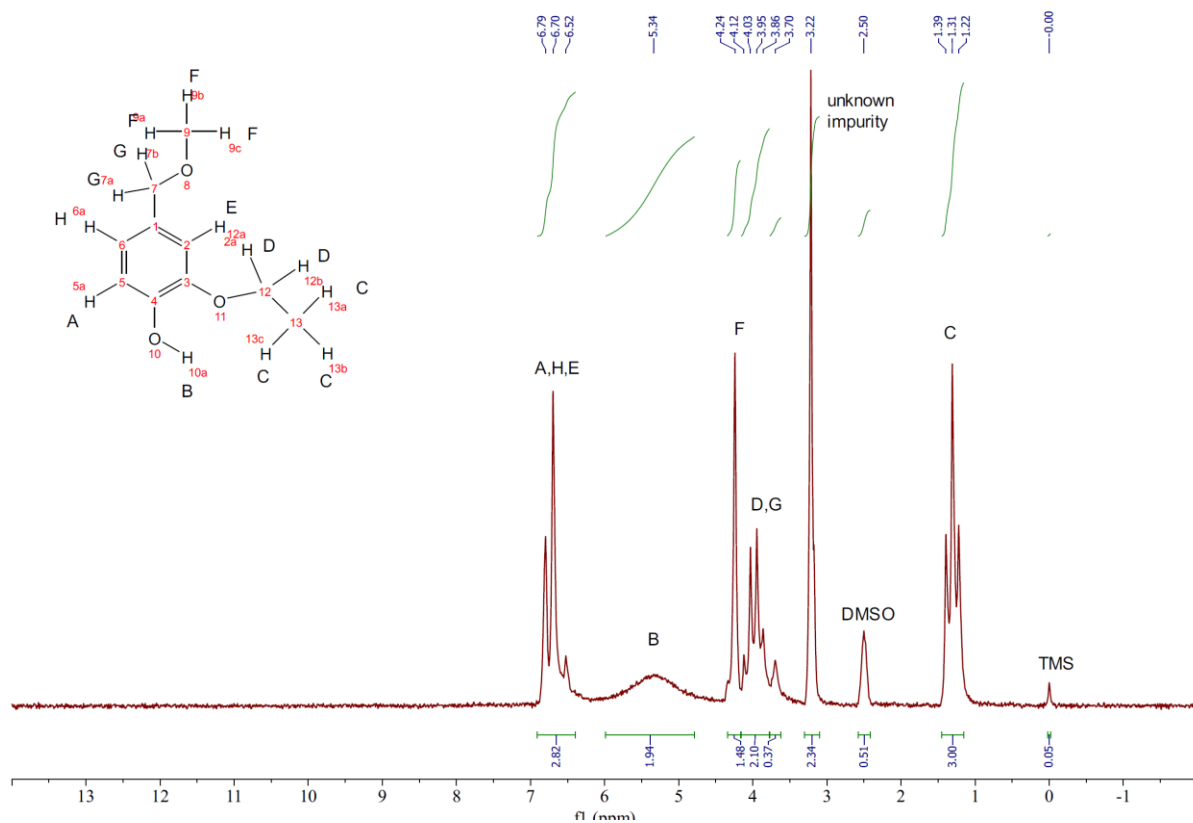


Figure 9: RXN II. - Sample From Step 1 and Ethanol  $^1\text{H}$  NMR Spectrum

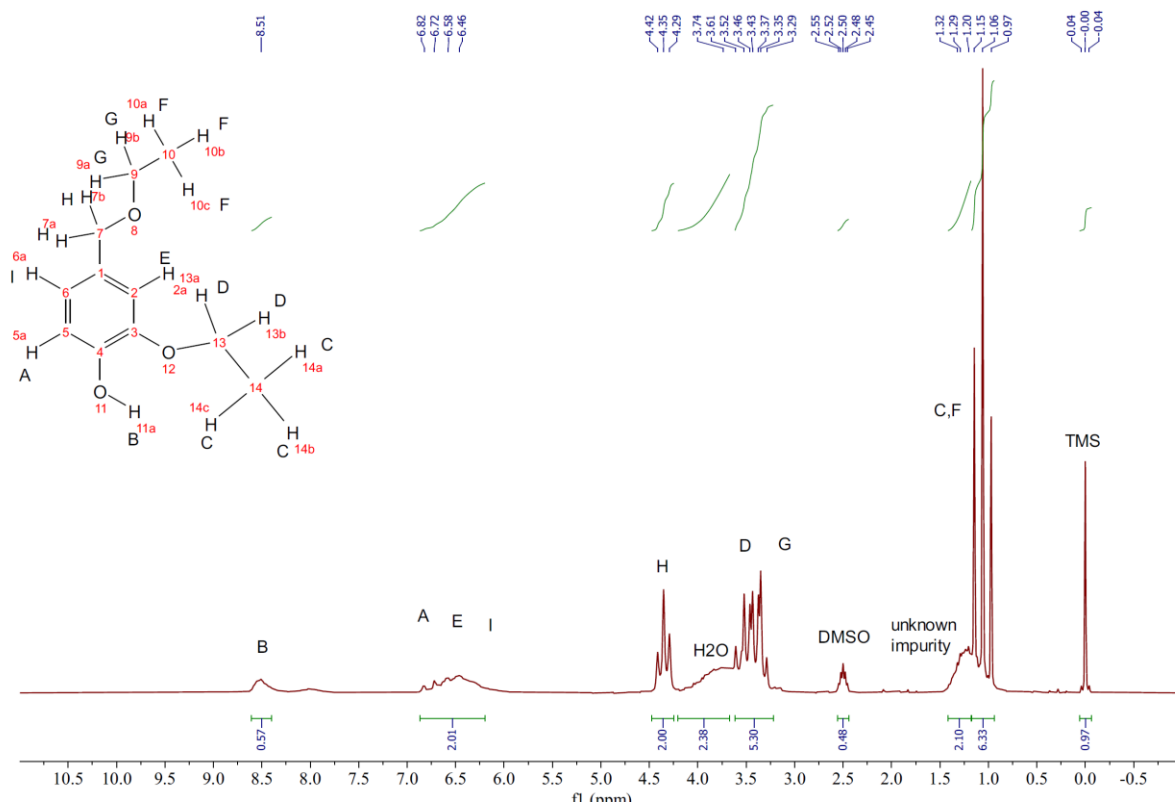


Figure 10: RXN III. - Sample From Step 1 and 1-Propanol  $^1\text{H}$  NMR Spectrum

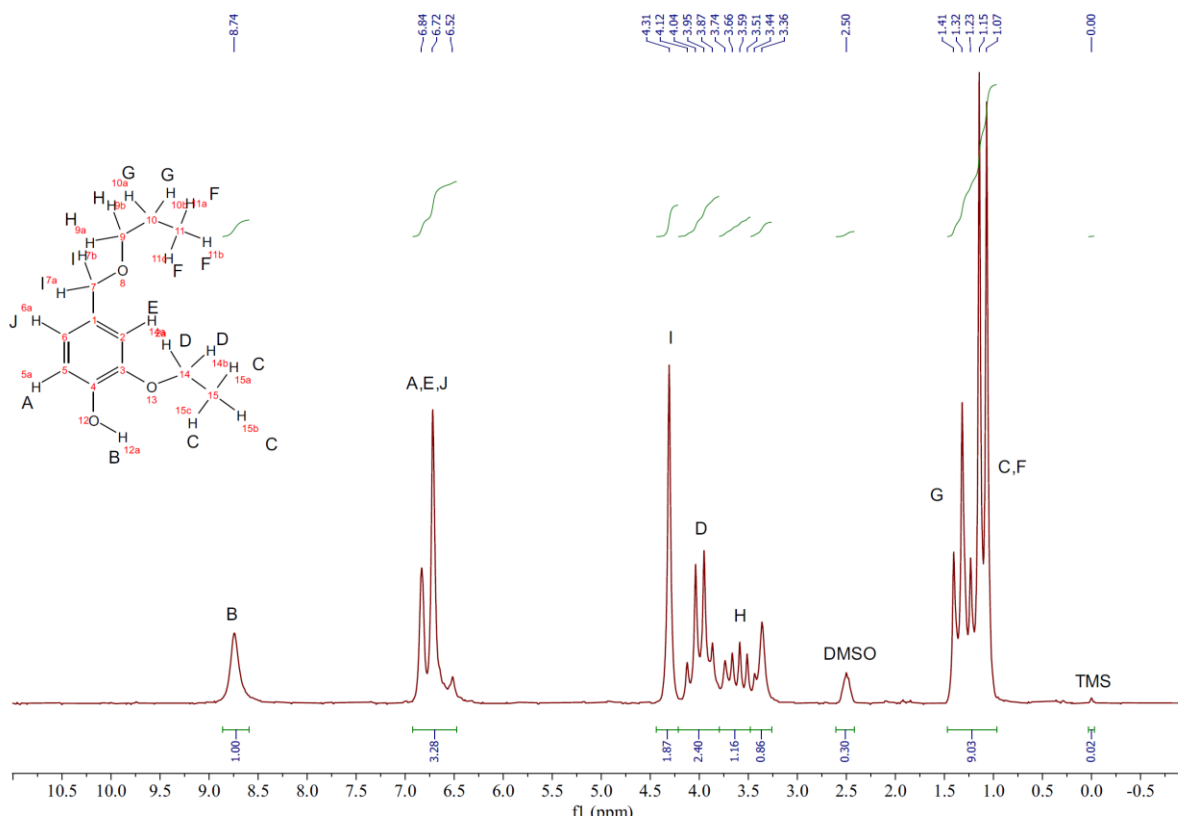


Figure 11: RXN IV. - Sample From Step 1 and 2-Propanol  $^1\text{H}$  NMR Spectrum

