Honors Cup Synthetic Proposal

Section: 271
Group Members: Roshan Najafi, Ye Hu, Chris Hanes, Paul Dinh

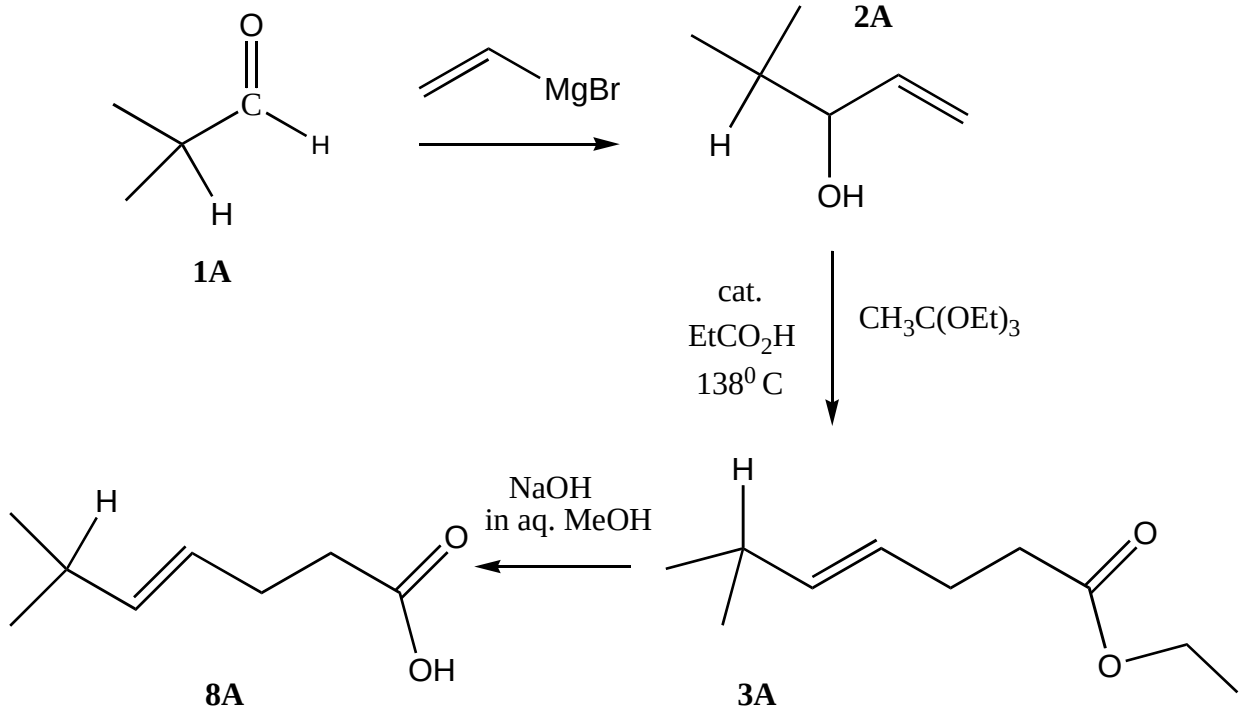
Title: A General Synthesis of (E)-6-methyl-4-heptenoic acid, a precursor to the final Synthesis of Capsaicinoids

Introduction:

The chemistry of flavors has constantly been a topic of interest for research scientists. In the article by Harumi Kaga, Kouhei Goto, Tomiki Takahashi, Masao Hino, Takashi Tokuhashi, and Kazuhiko Orito, the origin of the "heat" in hot peppers was investigated. Hot peppers, including paprika, tabascos, and red peppers are part of the genus *Capsicum*. Capsaicinoids are the chemical compounds that cause the burning sensation one gets upon eating red peppers, by acting directly on the pain receptors in the mouth. In addition, the 15 natural capsaicinoids are used as important ingredients in spices, preservatives, and drugs. Aside from edible substances, capsaicinoids have also been reported to take part in certain biological activities, including carcinogenic activities.

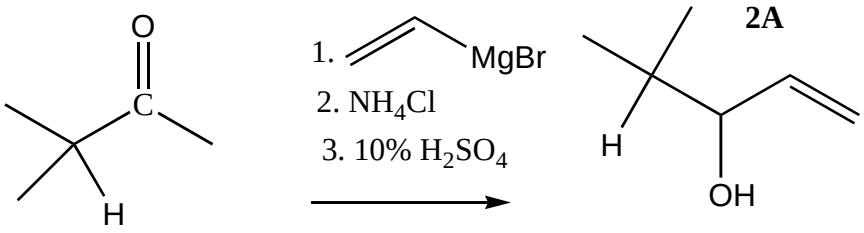
There are multiple methods of synthesizing natural capsaicinoids. The synthesis of natural capsaicinoids is relatively difficult, due to the contamination of the natural capsaicinoids by related amides, and because of the difficulty of obtaining certain minor components in a pure state. In the following proposal, we have outlined a method for synthesizing (E)-6-methyl-4-heptenoic acid, a compound that, upon addition of thionyl chloride and vanillylamine, gives Nornorcapsaicin. However, due to cost concerns, we will not be able to complete the final synthesis of Nornorcapsaicin and will only be synthesizing up to **8A**.

Overall synthetic reaction scheme:



Step 1

Synthetic transformation 1:



1A

Experimental 1:

Note: Quantitative amounts within the 3 steps have been scaled up by a factor of 1.325 in order to obtain 0.55 g yield of our desired product, (E)-6-methyl-4-heptenoic acid.

Isobutyraldehyde **(1A**, 9.54 g, 129.85 mmol) in dry THF (39.75 mL) was added drop-wise to a stirred solution of vinylmagnesium bromide (145.75 mL, 1 M solution, 0.14575 mol) at 0º C over 15 minutes. NOTE: The experimental of the article specifies that the above solution should then at this point be stirred at room temperature for 15 hours, however this step is not feasible for our laboratory purposes. The only way to accomplish this stirring step would be to have the 15 hours scaled down to 4 hours, our lab period. Unfortunately, the productivity and feasibility of this is not very high, and therefore this must be noted within the experimental. After stirring, saturated ammonium chloride (NH_4Cl, 19.88 mL) was added, and THF (tetrahydrofuran) was evaporated. The remaining residue was acidified with 10% H_2SO_4 to a pH of 3. The residue was then extracted with ether (39.8 mL x 2). The residue (oily) was distilled using the distillation techniques known to us to give the first product, 4-methyl-1-penten-3-ol (**2A**, 9.6725, 73%). H-NMR analysis can be done to confirm the existence of the prepared product.

Safety caution: During the procedure, THF is evaporated into the air. Since THF is a carcinogen, it needs to be done under the hood, where there is air ventilation. It would be best to carry out the rest of the reaction under a hood as well.

Expected yield:

The expected yield of **2A** (4-methyl-1-penten-3-ol) for this first step is 9.6725 g at 73% yield.

Safety, disposal and green issues 1:

Note: The following compounds used in Step 1 of the synthesis all cause eye and skin irritation. They may cause respiratory tract and digestive tract irritation if inhaled or swallowed. Be sure to wear safety goggles and gloves at all times, and do not swallow anything.

Isobutyraldehyde: Highly flammable and harmful if swallowed. Not stable with oxidizing agents, strong reducing agents, and strong bases. Needs to be ventilated, therefore be sure to use under a hood. Do not empty any waste into drains but rather into proper organic waste disposal bucket. Be sure to wear safety goggles and gloves at all times.

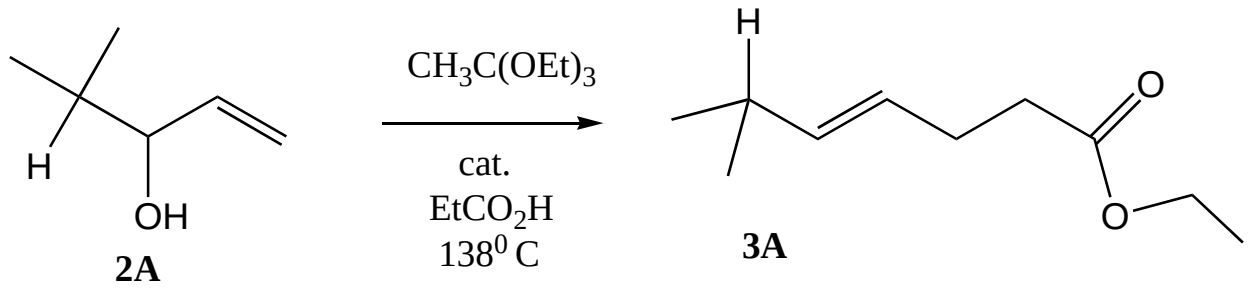
Vinyl Magnesium Bromide: Highly flammable and corrosive. Reacts violently with water to liberate extremely flammable gases and form explosive peroxides, therefore must be handled in anhydrous solution. Moisture sensitive, light sensitive, and air sensitive: use only in a chemical fume hood. May decompose to carbon monoxide, carbon dioxide, bromine fumes, and oxides of magnesium. Contains tetrahydrofuran, a carcinogen. Use only under a fume hood.

Sulfuric Acid: Irritant, highly flammable, corrosive. Wash hands thoroughly after handling and store in a cool, dry place in a tightly closed container. May decompose to oxides of sulfur and hydrogen sulfide, use under fume hood.

Ammonium Chloride: Harmful. It is stable at room temperature in closed containers under normal storage and handling conditions, therefore avoid excess heat. Decomposes to ammonia and hydrochloric acid fumes

Step 2

Synthetic transformation 2:



Experimental 2:

Note: Quantitative amounts within the 3 steps have been scaled up by a factor of 1.325 in order to obtain 0.55 g yield of our desired product, (E)-6-methyl-4-heptenoic acid.

Using 6.96 g (72.88 mmol) of the obtained product **2A**, a mixture was created by addition of triethyl orthoacetate ($CH_3C(OEt)_3$, 82.95 g, 0.52 mol) and proprionic acid ($EtCO_2H$, 0.325 g, 4.37 mmol) as a catalyst. The mixture was heated at 138º C for three hours, using a Claisen distillation head (view attached image in references) under an atmosphere of argon. Then, EtOH was distilled off in 30 minutes using simple distillation. The residue after this first distillation was then distilled to give 9.6725 g of (E)-Ethyl-6-methyl-4-heptanoate (ester **3A**).

Expected yield:

The expected yield of **3A** ((E)-Ethyl-6-methyl-4-heptanoate) for the second step is 9.6725 g at 73% yield.

Safety, disposal and green issues 2:
Note: The following compounds all cause eye, skin, and digestive tract irritation, be sure to wear safety goggles and gloves at all times, and appropriate clothing. Do not inhale or swallow anything.

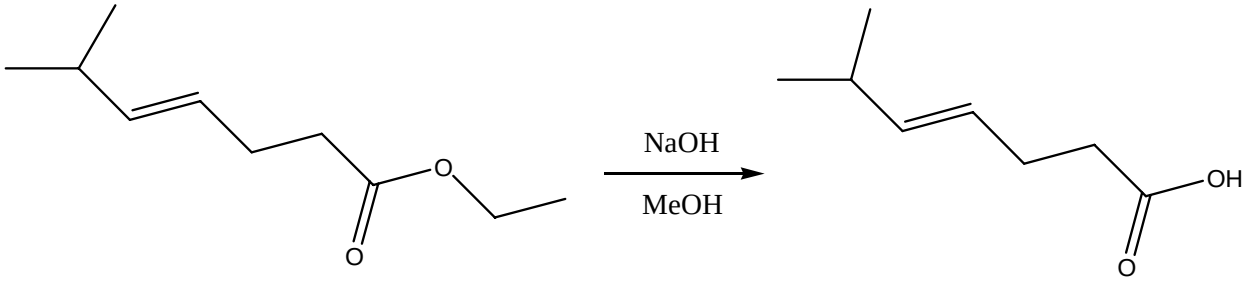
Triethylorthoacetate: Irritant. Keep away from sources of ignition and store in a cool, dry place in a tightly closed container, preferably in the area for flammables. Use adequate ventilation under a hood. Decomposes to carbon monoxide, carbon dioxide, ethyl alcohol, acetic acid. Avoid entering into waters or underground water.

Propionic acid: Corrosive. Empty containers retain product residue, and can be dangerous: should be handled with care and properly cleaned. Needs ventilation, keep under hood. Stable under normal temperatures and pressures. Decomposes to carbon monoxide, carbon dioxide. May be a carcinogen. Dump waste into acid container.

Ethyl alcohol: Highly flammable. Avoid exposure to moist air or water. Keep away from sources of ignition. Stable under normal conditions and temperatures. Decomposes to carbon dioxide and carbon monoxide.

Step 3

Synthetic transformation 3:



Ester 3A **8A, (E)-6-Methyl-4-heptenoic acid**

Experimental 3:

Note: Quantitative amounts within the 3 steps have been scaled up by a factor of 1.325 in order to obtain 0.55 g yield of our desired product, (E)-6-methyl-4-heptenoic acid.

0.73935 g (4.346 mmol) of Ester **3A** was refluxed in a solution of 50% aqueous MeOH (5.3 mL) and 15% NaOH for 3 hours. Aqueous $NaHSO_4$ and then $(NH_4)_2SO4$ were used to saturate the mixture, which was then extracted with ether-hexane (1:1, 13.25 mL × 3). Combining the three extracts, this mixture was then washed with saturated brine (6.625 ml) and dried over anhydrous MgSO4, evaporated, and short-path distilled. (Short-path distillation is used to remove unwanted components and to purify minor compounds. It permits the separation of heat-sensitive materials with high boiling points at much lower temperatures.) 0.550 g of the final product, (E)-6-Methyl-4-heptenoic acid (**8A**), was produced at 89% yield.

Expected yield:
The expected yield for this final step and end product is 0.550 g of **8A** at 89% yield.

Safety, disposal and green issues 3:
Note: The following compounds are known to cause eye, skin, gastrointestinal, and respiratory irritation, do not inhale or swallow, and be sure to wear safety goggles and gloves at all times. Prepare this step entirely under ventilation, under a fume hood.

Sodium Hydroxide: Irritant. Corrosive. Stable at room temperature in closed containers under normal storage and handling conditions. Waste goes into bases container.

Methanol: Toxic if inhaled or swallowed. Highly flammable. Pressure builds if container is near heat. Do not dump in drain, can cause environmental damage. Wash thoroughly after handling. Ground containers when transferring material and store in a cool, dry place in a tightly closed container in the flammables area. Waste goes into non-halogen container.

Sodium bisulfate: Harmful. Avoid generating dusty conditions. Store in a cool, dry place. Keep from contact with oxidizing materials. Keep away from strong acids. Can decompose to oxides of sulfur. Has a moderate potential to affect aquatic organisms.

Overall budget:

Chemical	Supplier	Product number	Cost	Amt. Needed	Total
Isobutyraldehyde	Sigma Aldrich	240788-100ML	$0.49/g	10 g	$38.60
Vinyl magnesium bromide	Aldrich	225584-800ML	$0.117/g	110 mL	$91.90
Ammonium Chloride	Sigma Aldrich	326372-100G	$0.663/g	20 mL	$66.30
Triethylorthoacetate	Aldrich	T60402-100ML	$0.27/g	83 g	$23.90
Propionic acid	Sigma Aldrich	P1386 500 mL	$0.036/g	0.4 g	$18.00
Methanol	Sigma Aldrich	179337 500 mL	$0.047/g	6 mL	$18.70
Ammonium Sulfate	Sigma Aldrich	A6387 500G	$0.067/g	Not specific (However much is needed)	$33.70
Sodium bisulfate	Sigma Aldrich	307823 25G	$0.796/g	Not specific	$19.90
Magnesium sulfate	Sigma Aldrich	246972 100G	$0.213/g	Not specific	$21.30

Total costs per synthesis: __$295.30__

References:

Step 1:

1) Kaga, H.; Goto, H.; Takahashi, T.; Hino, M.; Tokuhashi, T.; Orito, K. *Tetrahedron* **1996**, *52*, 8451-8470.
2) Midland, M.M.; Koops, R.W. *J. Org. Chem.* **1990**, *55*, 5058-5065.
3) Greeves, N.; Lee, W.M; Barkley, J.V. *Tetrahedron Letters* **1997**, *38*, 6453-6456.

Step 2:

1) Kaga, H.; Goto, H.; Takahashi, T.; Hino, M.; Tokuhashi, T.; Orito, K. *Tetrahedron* **1996**, *52*, 8451-8470.

2) See claisendistillationhead.jpeg attached.

Step 3:

1) Kaga, H.; Goto, H.; Takahashi, T.; Hino, M.; Tokuhashi, T.; Orito, K. *Tetrahedron* **1996**, *52*, 8451-8470.
2) Kaga, H.; Goto, K.; Fukuda, T.; Orito, K. *Biosci. Biotech. Biochem.* **1992**, *56*, 946-948.