Honors Cup Synthetic Proposal

Section: 251
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Title: 3 Step Synthesis of 3,7-dimethyl-1,5 (E), 7-Octatrien-3-ol (Hotrienol)

Introduction: (what makes your target interesting?)
Hotrienol is a naturally occurring compound found in the Japanese Ho Tree (*Cinnamomum*). It is a major component of the Ho leaf oil. Because of this, Hotrienol is classified as a Monoterpene, which are primary constituents of the essential oils of many types of plants and flowers. Essential oils are used widely as natural flavor additives for food, as fragrances in perfumery, in aromatherapy, and in traditional and alternative medicines. Synthetic variations and derivatives of natural terpenes and terpenoids also greatly expand the variety of aromas used in perfumery and flavors used in food additives. Hotrienol has a distinct fruity aroma and is used widely as a flavoring agent in the food and wine industry. The production of Hotrienol starts with the ene-type chlorination of Linalyl Propionate and then dehydrochlorinated by lithium bromide and lithium carbonate in DMF, followed by hydrolysis of dehydro-alpha-linalyl acylate to form Hotrienol in 55% yield.

Overall synthetic reaction scheme: (a Chemdraw or similar drawing of all three steps)
Step 1

Synthetic transformation 1: (Chemdraw picture of first transformation)

\[
\begin{align*}
\text{OCOEt} & \quad \text{OCOEt} \\
\text{linalyl acetate} & \quad \text{CH}_2\text{Cl}_2 \\
60\% \text{ calcium hypochlorite} & \quad \text{boric acid} \\
\text{H}_2\text{O} & \quad \text{sodium sulfide} \\
10\% \text{ NaCl} & \\
\end{align*}
\]

Experimental 1 (notes if this transformation is not exactly the one reported in literature (e.g. on a different scale) and how it was modified):

NOTE: All substrates and reagents were scaled down by a factor of 0.5 (this included quantities as well as molarities, however did not include time, concentrations, or temperature). Although this means that the initial substrate is used in the amount of 5.25g, everything could be scaled down further to reduce this value. 500-mL vessels were used due to laboratory restrictions and the R group that was used from the experiment was in the form of C2H5.

A 500-mL, three-necked, round-bottomed flask with a reflux condenser and an addition funnel were used. Linalyl propionate (25 mmol) was added in CH2Cl2 (25mL), along with 60% calcium hypochlorite (2.9 g, 12.25mmol) and boric acid (3.1g, 50mmol). This mixture was stirred at 5 degrees Celsius as water (5mL) was added dropwise over 3.5 hours. The reaction was stirred at the same temperature for one hour, and then sodium sulfide (1.25g, 9.95mmol) was added. The inorganic salt was filtered off, and then organic layer was separated and washed twice with 10% NaCl solutions. The solvent was removed under vacuum, and the product was distilled under reduced pressure.

Expected yield: % g
A 5.3g (87% yield) product was recovered as an oil (purity was 94%).

Safety, disposal and green issues 1:

Dichloromethane is an eye and skin irritant. It is also possibly carcinogenic in humans. Thus when working with this reagents, should wear goggles, gloves, and apron to avoid contact. Also it is harmful if inhaled, thus should work in the hood. Incompatible with alkali metals,
aluminum, strong oxidizing agents, strong caustics, some form of plastic, titanium. Dispose in waste bottle labeled “chlorinated organic solvents”

**Calcium hypochlorite** is water-sensitive. Upon contact with moisture, it will produce chlorine gas, which is toxic. Thus should take care to work in anhydrous conditions. It is also a strong oxidant, thus want to avoid contact with eyes and skin. Goggles, gloves and aprons should be wore. Avoid contact with strong acids, ammonium compounds, amines, metal salts, metals, metal oxides, strong bases, sulfur, halocarbons, organic fuels. Dispose in waste bottle labeled “hazardous waste”

**Boric Acid** is also water sensitive and extremely hygroscopic, thus should also take care to work in anhydrous conditions. Wear goggles and gloves and work in hood. Reacts violently with potassium and acid anhydrides, thus should make sure glassware aren’t contaminated with those compounds. Dispose in waste bottle labeled “acids”

**Sodium sulfide** is corrosive upon contact with skin. Thus should wear goggles and gloves when handling reagent. It is also water sensitive and decomposes upon contact with moisture to form hydrogen sulfide, which is toxic and combustible. Thus should work in hood and anhydrous conditions. Avoid heat, flames, ignition sources, and acids. Dispose in waste bottle labeled “hazardous waste”

**Step 2**

**Synthetic transformation 2:** (Chemdraw picture of second transformation)

![Chemdraw image of second transformation]

**Experimental 2** (notes if this transformation is not exactly the one reported in literature (e.g. on a different scale) and how it was modified):

NOTE: All substrates and reagents were scaled down by a factor of 0.5 (this included quantities as well as molarities, however did not include time, concentrations, or temperature). Again, the 500-mL vessel was used for laboratory restrictions.
A 500-mL, three-necked, round-bottomed flask with a reflux condenser were used. Previous product (4.3g, 17.5mmol) was added in DMF (35mL), lithium carbonate (3.23g, 43.75mmol), and lithium bromide (5.85g, 26.25mmol). The reaction was stirred at 130 degrees Celsius for 2 hours. The conversion and selectivity were 98% and 78%, respectively. The vessel was cooled to 70 degrees Celsius and DMF was recovered under vacuum. Toluene (50mL) and water (50mL) were added to the residue. The organic layer was washed with water (50mL) and then 10% NaCl (50mL) solution. The solvent was recovered under vacuum, and the product was distilled under reduced pressure.

**Expected yield:** % g
A 2.4g (71% yield) product was recovered as an oil (purity was 94%).

**Safety, disposal and green issues 2:**

Both DMF and Lithium bromide are moisture sensitive. They require anhydrous conditions. Toluene is a highly flammable solvent, take precaution to avoid, thus avoid heat. All organic solvents are highly volatile, therefore, should be worked under a hood. Goggles and gloves should be worn. DMF should be disposed in the waste bottle labeled “chlorinated organic solvents”. Lithium carbonate and Lithium bromide should be disposed in waste bottle labeled “lithium compounds”.

**Step 3**

**Synthetic transformation 3:** (Chemdraw picture of third transformation)

**Experimental 3** (notes if this transformation is not exactly the one reported in literature (e.g. on a different scale) and how it was modified):

NOTE: All substrates and reagents were scaled down by a factor of 0.005. The reason for the large down scale is due to the fact that the original procedure was an increase of 100-fold which
would mean a factor of 0.01 would be necessary to reverse that process. However, we also needed to scale down an additional 0.5, thus the 0.005 down-scale (this included quantities as well as molarities, however did not include concentrations, or temperature). *The original stirring time for this step was 5 hours. However, due to time restrictions it is possible to stir for 3 hours and sacrifice %yield in order to have ample time for the experiment. If time permits, the original 5 hours should be kept.

A 500-mL, three-necked, round-bottomed flask with a reflux condenser and an addition funnel were used. Previous product (2.45g, 11.5mmol) was added to the vessel. The mixture was stirred at 20-30 degrees Celsius while 10% NaOH in 50% MeOH aqueous solution (5.06g) was added dropwise over 1 hour and stirred for *3 hours. The conversion and selectivity were 100 and 95%, respectively. The vessel was cooled to room temperature and acetic acid (0.1036g, 1.75mmol) was added and concentrated under vacuum. To the residue, EtOAc (2.5mL) and water (2.5mL) were added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2.5mL x 2). The combined organic layer was washed with 5% NaHCO3 (1mL) and 5% NaCl solution (1mL), and then concentrated under vacuum to crude product (1.98g). Product was purified by using a five theoretical plate column distillation with helipac No. 3.

**Expected yield: % g**

1.53g (85% yield) product of hotrienol (purity was 98%)

**Safety, disposal and green issues 3:**

*Ethyl Acetate and Acetic Acid* are both flammable. When handling these reagents, should work in a hood as well as take care to avoid heat. Goggles and gloves should be worn. Dispose Ethyl Acetate in “chlorinated organic solvents” and dispose Acetic Acid in “acids”.

**Overall budget:**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Supplier</th>
<th>Cost</th>
<th>Amt. Needed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichloromethane</td>
<td>Sigma Aldrich</td>
<td>$24.20/500mL</td>
<td>25mL</td>
<td>$1.21</td>
</tr>
<tr>
<td>60% calcium hypochlorite</td>
<td>Sigma Aldrich</td>
<td>$16.20/250g</td>
<td>2.9g</td>
<td>$0.19</td>
</tr>
<tr>
<td>boric acid</td>
<td>Sigma Aldrich</td>
<td>$19.20/500g</td>
<td>3.1g</td>
<td>$0.12</td>
</tr>
<tr>
<td>sodium sulfide</td>
<td>Sigma Aldrich</td>
<td>$160.50/50g</td>
<td>1.25g</td>
<td>$4.01</td>
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<td>DMF</td>
<td>Sigma Aldrich</td>
<td>$26.30/L</td>
<td>35mL</td>
<td>$0.92</td>
</tr>
<tr>
<td>lithium carbonate</td>
<td>Sigma Aldrich</td>
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<td>3.23g</td>
<td>$0.88</td>
</tr>
<tr>
<td>lithium bromide</td>
<td>Sigma Aldrich</td>
<td>$34.40/100g</td>
<td>5.85g</td>
<td>$2.01</td>
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<tr>
<td>Toluene</td>
<td>Sigma Aldrich</td>
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<td>50 mL</td>
<td>$1.44</td>
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<tr>
<td>acetic acid</td>
<td>Sigma Aldrich</td>
<td>$20.50/100g</td>
<td>0.1036g</td>
<td>$0.02</td>
</tr>
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<td>Ethyl Acetate</td>
<td>Sigma Aldrich</td>
<td>$40.80/L</td>
<td>7.5mL</td>
<td>$0.30</td>
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<td>Sodium Bicarbonate (note: 5% needed)</td>
<td>Sigma Aldrich</td>
<td>$65.30/Kg</td>
<td>1 mL</td>
<td>&lt;$0.05</td>
</tr>
</tbody>
</table>

**Total costs per synthesis:** ~$11.86

**References (include at least two different sources for your experimentals):**

1st step:


* This article PDF file was too big, so I could not attach it on email. We will hand in a hard copy before class on Monday.

2nd step:


**Emerson, W.S.; Patrick, T. M. Organic Syntheses, Coll. 1963. 4, 980.

** This article also talks about a dehydrochlorination step. The reagent that acts as a base to perform the elimination mechanism is pyridine, its basicity is very similar to that of lithium bicarbonate, which is the base in the original article of step 2. Therefore, even though pyridine is not the exact reagent, we thought it should serve similar functions as lithium bicarbonate in the dehydrochlorination step.


***This article PDF file was also too big. We will also hand in a hard copy before class on Monday.

3rd step:
