Benzilic Acid Rearrangement

Supplementary Material

Experimental notes

This experiment aims at the preparation of 2-hydroxy-2-phenylbenzylic acid from benzil through a molecular rearrangement in basic medium. The experiment is very simple and adequate for 1st year chemistry students. The reaction is performed in a water/ethanol solution where the yellowish solid benzil reagent is soluble and thus the initial solution is slightly yellow. As the solution is heated under reflux the solution acquires a violet/blue colouration that becomes dark orange after heating for 20 min. The reaction is not complete but further heating does not lead to an increased yield.

The carboxylate salt present in the reaction mixture does not precipitate by simply putting the flask in an ice bath. It is necessary to scratch the flask to initiate the crystals formation. The crystals thus obtained are yellowish and very soluble in water. The addition of the H$_2$SO$_4$ solution leads to the immediate formation of the 2-hydroxy-2-phenylbenzilic acid that precipitates as white crystals. By the end of the H$_2$SO$_4$ addition all the aqueous solution becomes white. We chose to use a 2M solution of H$_2$SO$_4$ but either a more diluted solution or other strong acids, like HCl, can be used. The final product is isolated by filtration and washed with cold ethanol to remove traces of benzil. The recrystallization can be done with water (around 50 mL). The final product, 2-hydroxy-2-phenylbenzilic acid, is a white solid and the TLC and $^1$H NMR analysis confirm its purity. This experiment is very reproducible and the 2-hydroxy-2-phenylbenzilic acid can be isolated in one session of 2h, however, the measurement of the weight and melting point of the product can only be made after drying overnight in an oven. The yields vary between 32-64% and the melting point of product is 148-150 °C (lit 150-152 °C$^8$).

Photos of experiment

Figure SM 14.1.1. Initial yellowish solution of benzil
Figure SM 14.1.2. Reaction apparatus and the initial violet solution obtained after starting the heating

Figure SM 14.1.3. Reaction mixture after heating for 20 min
Figure SM 14.1.4. Addition of H₂SO₄ to the carboxylate aqueous solution and formation of the final product

Figure SM 14.1.5 - TLC plate. 80% diethyl ether/petroleum ether. a) Benzil b) Product
\(^1\)H NMR and IR Spectra

**Figure SM 14.1.6.** \(^1\)H NMR spectrum (400 MHz, CDCl\(_3\)) of the 2-hydroxy-2-phenylbenzilic acid.

**Figure SM 14.1.7.** IR spectra of the 2-hydroxy-2-phenylbenzilic acid.
Preparation of Phenyl Acetate and its Conversion
to 4-Hydroxyacetophenone

Supplementary Material

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Contents:

Experiment Notes

Step 1: Preparation of phenyl acetate .............................................................1
Step 1: Physical and safety data ........................................................................2

Step 2: Fries rearrangement: Conversion of phenyl acetate to 4-hydroxyacetophenone ......3
Step 2: Physical and safety data ........................................................................4

References .................................................................................................5

Figures

Figure SM 14.2.1. Photos of experimental set-up for Step 2 .................................................................7

Figure SM 14.2.2. Photo of TLC comparison between phenyl acetate and 4-hydroxyacetophenone ........................................................................................................7

Figure SM 14.2.3. Photo of different impurity levels present in 4-hydroxyacetophenone after recrystallization ........................................................................................................7

Figure SM 14.2.4. $^1$H and $^{13}$C NMR spectra for phenyl acetate ........................................................................................................8

Figure SM 14.2.5. $^1$H and $^{13}$C NMR spectra for 4-hydroxyacetophenone ........................................................................................................9
Figure SM 14.2.6. $^1$H NMR spectrum for a mixture of 2-hydroxyacetophenone, 4-hydroxyacetophenone and phenyl acetate obtained from a typical Lewis acid (AlCl$_3$) Fries rearrangement .................................................................10

Figure SM 14.2.7. Infrared spectra for phenyl acetate and 4-hydroxyacetophenone ..............................................................................................................................11

Experiment Notes

Step 1: Preparation of phenyl acetate:

This reaction is rapid and from an experimental perspective, relatively straightforward. Phenol readily dissolves in an excess of basic solution to generate the phenoxide ion. Because this is moderately exothermic we have found that, as directed, cooling the solution by adding ice-chilled water is beneficial. The subsequent reaction with acetic anhydride is practically instantaneous and despite a moderate excess of hydroxide the final yield of phenyl acetate is high. The work-up procedure is also standard and the inclusion of a saturated sodium bicarbonate wash is solely a precaution in case incorrect amounts of reagents have been added and acetic acid is present following the reaction. If the amounts are correctly measured, as directed, no carbon dioxide evolution is observed. Following drying (anhydrous MgSO$_4$ or Na$_2$SO$_4$), filtration and solvent removal under reduced pressure the phenyl acetate can be reliably distilled using a small, standard distillation apparatus, either at atmospheric pressure (b.p. approx. 190 °C/760 mmHg), or under reduced pressure (b.p. approx. 95 °C/20 mm Hg). Reasonable to good (50-80%) yields of a colourless mobile liquid are produced. This part of the experiment has been run successfully for several years in our second year undergraduate laboratories (30-60 students per class). Historically, the reaction, the work-up and the distillation was performed on the bench in the open laboratory, however, more recently the whole experiment has been relocated to fume cupboards. The mechanism of this reaction helps teaching/understanding of pK$_a$ values of alcohols and the resonance of the phenoxide anion, in addition to presenting nucleophilic acyl substitution and the chemistry of the carbonyl group more generally.

Physical and safety data Step 1:

Phenol: MWt.: 94.11 gmol$^{-1}$: Causes burns/corrosive, toxic (R = 23/24/25; 68); Avoid contact with skin, wear suitable protective equipment.
4 M NaOH solution: Causes burns/corrosive (R = 35); Avoid contact with skin, wear suitable protective equipment.

Acetic anhydride: MWt.: 102.09 g mol⁻¹; d = 1.08 g mL⁻¹; Causes burns (R = 22); flammable (R = 10); harmful (R 20/22); Avoid contact, wear suitable protective equipment.

Phenyl acetate MWt.: 136.15 g mol⁻¹; d = 1.073 g mL⁻¹; Harmful if swallowed (R = 22); Wear suitable protective equipment. Approx. b.pt. 190 °C/760 mm Hg; 95 °C/20 mm Hg.

Dichloromethane: Limited evidence of a carcinogenic effect (R = 40).

Sodium hydrogen carbonate solution: Liberates CO₂ on acidification.

**Step 2: Fries rearrangement: Conversion of phenyl acetate to 4-hydroxyacetophenone:**

In a fume cupboard, trifluoromethane sulfonic acid is transferred by syringe to a clean dry round bottom flask (RBF) equipped with a stirrer bar. The flask was cooled externally with an ice-water bath for 5 to 10 minutes before the appropriate amount of phenyl acetate was added in a dropwise fashion with another syringe. Under the conditions outlined, this reaction is fast and proceeds reliably to completion. In addition, only the para-isomer (4-isomer) is detected. This is in contrast to alternative methods using Lewis acids, such as AlCl₃, and using less polar media, in which typically significant amounts of the 2-isomer are encountered (see for example Figure SM 14.2.6).³ The literature,² used as a guide for this experiment, reports a general procedure using 0.28 mmol of the acetate with 3 mL of trifluoromethane sulfonic acid. We have found that one can significantly increase the relative ratio of phenyl acetate to trifluoromethane sulfonic acid to the 0.34 mmol to 0.5 mL level reported in this experiment. However, we have found that attempts to increase the concentration leads to formation of side-products that are difficult to remove by recrystallization (see Figure SM 14.2.3). Replacement of trifluoromethane sulfonic acid with alternative Brønsted acids, such as trifluoroacetic acid, proved unsatisfactory.

Please note trifluoromethane sulfonic acid is very corrosive so care and careful supervision should be taken introducing the trifluoromethane sulfonic acid to both the reaction vessel and the final solution of the reaction product to the separating funnel. These operations should only be performed in a fume cupboard. We found that the best way to perform the work-up was, in the fume cupboard, to transfer the contents of the reaction flask to ice-
chilled water in a beaker using a Pasteur pipette. Once this has been performed the contents of the RBF and the pipette may be safely washed out with dichloromethane and added to the same beaker. Following a standard extraction process it is recommended to discard this initial aqueous layer (containing trifluoromethane sulfonic acid) in a separate receptacle for disposal. Replacement of trifluoromethane sulfonic acid with alternative Brønsted acids, such as trifluoroacetic acid, proved unsatisfactory.

After drying, filtration and evaporation using a rotary evaporator, we found that the material isolated was rather pure and did not really require additional purification by recrystallization. However, clearly, this is dependent on the purity of the phenyl acetate produced in the initial step. Should further purification be required the solid can be recrystallized from the minimum volume (ca. 0.3 mmol to ca. 3 mL) of hot toluene. Following this protocol we obtained sharp melting points between 89 and 94 °C and a yield (after recrystallization) of approximately 80%. Note, the melting points encountered are somewhat lower than that reported in the literature, albeit using alternative solvent mixtures. However, in our hands use of this solvent is simpler than the reported alternatives and 1H NMR can also be used to confirm purity (see Figure SM 14.2.5).4

Mechanistically, precise details regarding the Fries rearrangement remain under debate, despite the fact that the reaction was first reported over 100 years ago.5 Under the Brønsted acid-based conditions reported here, using phenyl acetate (1) the 4-isomer (2) is almost exclusively formed. In contrast, using Lewis acidic (typically AlCl3 or BF3), or photochemical conditions, the 2-isomer (3) is formed in either, substantial amounts,3b or is the exclusive product.6 One explanation for the 2-selectivity involves a tight-ion pair 4, formed during the acyl fragmentation event in the Lewis acid reaction manifold. In contrast, in the Brønsted acid process a phenol and the acylium ion are formed 5, with parallels to Friedel-Crafts acylations (Scheme SM 14.2.1).

**Scheme SM 14.2.1.** Mechanistic pathways for the Fries rearrangement under Lewis, or Brønsted acid mediated reaction conditions
Evidence has also been collected to indicate that the Fries rearrangement, under certain conditions, is a reversible process and, thus, arguments of thermodynamic and kinetic control may be proposed.5c Finally, the reactive acylium ion may be intercepted by the conjugate base (trifluoromethane sulfonate anion), forming a mixed anhydride. This type of species is known and represents an excellent acylating reagent for Friedel-Crafts processes.7

**Physical and safety data Step 2:**

Phenyl acetate MWt.: 136.15 g mol⁻¹; d = 1.073 g mL⁻¹; Harmful if swallowed (R = 22); Wear suitable protective equipment.

4-Hydroxyacetophenone MWt.: 136.15 g mol⁻¹; Harmful if swallowed (R = 22); wear suitable protective equipment and avoid contact.

Trifluoromethane sulfonic acid: Causes severe burns (R = 35); wear suitable protective equipment (“breakthrough time” 0.4 mm nitrile gloves; 188 min). In case of contact wash area well with water and seek medical advice. It is recommended that laboratory supervisors oversee the dispensing of this material in a fume hood. General spillages can be neutralised with bicarbonate solutions.
Dichloromethane: Limited evidence of a carcinogenic effect (R = 40).

References


Figures

Figure SM 14.2.1. Photos of experimental set-up for Step 2: (a) Addition of phenyl acetate to 0.5 mL of trifluoromethane sulfonic acid in a 10 mL RBF; (b) The same reaction following addition

Figure SM 14.2.2. Photo of TLC comparison between phenyl acetate and 4-hydroxyacetophenone (c-Hex-EtOAc: 3:1; vanillin stain)

1: 4-Hydroxyacetophenone ($R_f = 0.25$);
2: Co-spot;
3: Phenyl Acetate ($R_f = 0.65$)
[minor impurity ($R_f = 0.55$)].
{2-hydroxyacetophenone has approximately the same $R_f$ as phenyl acetate in this solvent}

Figure SM 14.2.3. Photo of different impurity levels present in 4-hydroxyacetophenone after recrystallization in hot toluene: (a) $50 \mu$L phenyl acetate: 0.5 mL trifluoromethane sulfonic acid; (b) $100 \mu$L phenyl acetate: 0.5 mL trifluoromethane sulfonic acid
(a) 

(b) 

Chemical reactions and experimental setups are demonstrated in the images. The text and labels on the paper indicate specific chemical reactions and concentrations. For a more detailed understanding, please refer to the supplementary information in the book.
Figure SM 14.2.4. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra for phenyl acetate
Figure SM 14.2. $^1$H NMR (400 MHz, CDCl$_3$) and $^{13}$C NMR (100 MHz, CDCl$_3$) spectra for 4-hydroxyacetophenone (note: depending on concentration the phenol OH peak (@7.36 ppm in the spectrum below) differs in terms of chemical shift)
**Figure SM 14.2.6.** $^1$H NMR (400 MHz, CDCl$_3$) spectrum for a mixture of 2-hydroxyacetophenone, 4-hydroxyacetophenone (and phenyl acetate) obtained from a typical Lewis acid (AlCl$_3$) mediated Fries rearrangement.

The proton NMR spectrum provided above was recorded for the crude material obtained from a reaction conducted according to reference 3(b) {2-Hydroxyacetophenone:4-hydroxyacetophenone:phenylacetate (ca. 47.5:47.5:5 – based on relative integrals for methyl signals)}. 

![NMR spectra](image_url)
Figure SM 14.2.7. Infrared spectra (films) for: (a) phenyl acetate and (b) 4-hydroxyacetophenone
(b) 4-Hydroxyacetophenone
Multistep Synthesis of Dilantin

Supplementary Material

This experiment aims at the preparation of a pharmaceutical substance currently in use, starting with very common reagents and materials from any Organic Chemistry lab, which is very satisfying for the students.

The 3 steps can be used as independent experiments.

Part 1. Synthesis of Benzoin from Benzaldehyde

![Chemical structure of Benzoin from Benzaldehyde](image)

The structure of Vitamin B1 is as follows:

![Chemical structure of vitamin B1](image)

The mechanism of the catalyzed reaction is:

Step 1
Step 2

The ylide acts as a nucleophile and attacks the electropositive carbon of the C=O of benzaldehyde.

The benzylic hydrogen of the intermediate is acidic enough to be removed by the base present in the reaction.

Step 3

Next, this conjugate base of the intermediate acts as a nucleophile and attacks the electropositive carbon of another C=O of a second benzaldehyde molecule.

Finally, a proton exchange and elimination of the ylide anion produce benzoin:
Experimentally, it should be noticed:

*It is imperative that the benzaldehyde be from a newly opened bottle because of the ease of oxidation, producing benzoic acid, which will interfer with the reaction.* If the bottle of benzaldehyde used for the reaction appears to have any solids (benzoic acid) in it, don’t use it. Get a new one. Instructors should pay attention to this detail and distill benzaldehyde prior to class if necessary.

The Vitamin B₁ exists in the form of thiamine hydrochloride. *It must also be from a newly opened bottle, although it is not quite as critical as for the benzaldehyde.* It is stable in the acidic condition, but it absorbs water easily, and it is a heat-sensitive reagent, the thiamine in aqueous solution is easily oxidized by oxygen in the air. The rate of oxidation may be accelerated by light and some ions, such as cupric ion, ionic ion and magnesium ion. Vitamin B₁ should be stored in a refrigerator. Since the thiazole ring is easily broken in basic solution, both the aqueous solutions of thiamine hydrochloride and sodium hydroxide should be cooled thoroughly with an ice bath before use.

The addition of the sodium hydroxide solution must be very slow (dropwise). Realize it takes 10 minutes to add 3.3 mL! Don’t allow the reaction to reach above 20°C. Gloves must be worn when doing this stage.

For the purification procedure (session 2) it is important to use the minimum amount of hot solvent, otherwise crystallization is very difficult to occur. It takes a lot of scratching (Figure SM 14.3.1).
After purification, the yield of this reaction is usually under 40% (25-35% is the most common) so it may be a good idea to perform a bigger batch to have enough benzoin for the next step, should some students fail to obtain the recommended 1.0 g. We combine the synthetized and not used benzoin from previous years and it is stable.

**Part 2. Synthesis of Benzil from Benzoin**

\[ \text{Bezoin} \xrightarrow{\text{Cat. Cu(OAc)$_2$, NH$_4$NO$_3$, Acetic Acid}} \text{Benzil} \]
For the copper catalyzed benzoin oxidation, the sequence of two oxidations, both taking place at the same time in the same reaction mixture, is best represented using the convention of biochemistry for depicting redox reactions:

Scheme SM 14.3.1. Sequential oxidation of benzoin with Cu (II) acetate

*Note: Do not mistake this representation as a mechanism - it is a simple depiction of the overall changes taking place in the reaction.*

The mechanism of the catalytic oxidation is presented in Figure SM 14.3.3 and it is an interesting topic for discussing, depending on the level of studies and the theory background of the students. It can be omitted.
In the past, we used nitric acid to promote the oxidation of benzoin, with better yields. However, it is strongly exothermic and tricky to perform. For 7 mL of HNO₃ 5 g of benzoin is needed. Nitrous vapors are copiously produced. In recent years, the oxidation with copper (II) acetate was adopted. Typical yields are around 70%.

Some authors suggest monitoring the reaction by TLC. For that, they use silica gel plates, elute with 20 % ethyl acetate in hexanes (4:1 hexanes/EtoAc) and visualize the plates by UV. However, this demands the use of two necks round bottom flasks in order to obtain aliquots for analysis. Considering that the amount of liquid under reflux is very small, this leads to considerable losses.

During the reaction, there is an evolution of nitrogen. This can be followed by attaching some rubber tubing to the top of the condenser, connecting the other extremity to a Pasteur pipette and introducing the tip in water every 5 minutes (see Figure SM 14.3.2). When nitrogen stops bubbling in the side Erlenmeyer flask, mark the time and leaving the reaction going on for another 30 minute. The whole process should take no more than 90 minutes.
Part 3. Synthesis of Dilantin from Benzil

\[
\text{Benzil} \xrightarrow{\text{H}_2\text{NCONH}_2, \text{NaOH/Ethanol}} \text{5,5-diphenylhydantoin (Dilantin)}
\]

The mechanism of this reaction begins with the nucleophilic attack of the urea nitrogen atom on one of the carbonyls of benzil.
Benzilic acid rearrangement precedes through a 1,2-phenyl migration. Finally, dehydration produces the 5,5- diphenylhydantoin product.

It is important to make sure the benzil is of good purity. Usually, beautiful big pale yellow needles are obtained (Figure SM 14.3.5).
Melting point gives enough information to decide on purity, providing the available apparatus is calibrated. When in doubt, a FTIR spectrum should be obtained. Benzoin shows characteristic O-H stretch bands that are absent in benzyl (Figures SM 14.3.5 and SM 14.3.6).

If the IR spectrum shows a band over 3300 cm\(^{-1}\), do recrystallize benzyl prior to use.

The actual synthesis of phenytoin (Dilantin\(^{\circledast}\)) is straightforward, according to the described procedure for session 4. Point 5 (cooling to room temperature) can be speeded up by holding the flask under running tap water.

When adding distilled water to the mixture (point 6), it is common for some solid to form; this is unreacted benzyl and should be removed by filtration. Because the next step is acidification, where lots of solid is supposed to form, it can happen that, in point 6, students confuse the two and discard the filtrate instead of the unreacted solid material.

The addition of HCl leading to the formation of desired Dilantin can be easily followed by observation (Figure SM 14.3.4)
The obtained product is usually quite pure (yields 40-60% when performed by students, >75% when performed by instructors); if needed, Dilantin can be recrystallized from ethanol.

Overall yield, using average step yields will be ca. 12% (step 1: 35% x step 2: 70% x step 3: 50%)

**FTIR spectra**

The Infrared spectra were collected using a Perkin-Elmer Spectrum Two equipment, resolution 2 cm$^{-1}$, 32 scans, in transmission mode using KBr pellets.
Figure SM 14.3.5. FTIR spectrum of Benzoin, [main features at 3420, 3370 cm\(^{-1}\) (OH, s), 3050 cm\(^{-1}\) (C=CH, aromatic, w), 1680 cm\(^{-1}\) (C=O, s), 1590, 1585, 1480 cm\(^{-1}\) (C=C aromatic, m)]

Figure SM 14.3.6. FTIR spectrum of benzyl, [main features at 3050 cm\(^{-1}\) (C=CH, aromatic), 1680 cm\(^{-1}\) (C=O, s), 1595, 1585, 1450 cm\(^{-1}\) (C=C aromatic, m)]
Figure SM 14.3.7. FTIR spectrum of phenytoin, [main features at 3280 and 3208 cm⁻¹ (NH, s), 3060 cm⁻¹ (C=CH, aromatic, w), 1726 and 1720 cm⁻¹ (C=O, s), 1385 cm⁻¹ (C-N, m)]

¹H NMR spectra

NMR spectra were obtained using a Bruker Avance II 400MHz NMR spectrometer.
Figure SM 14.3.8. $^1$H NMR spectrum of benzoin (CDCl$_3$, 400 MHz) δ (ppm): 4.53 (s, 1×H, OH), 5.95 (s, 1×H, CH), 7.26, 7.92 (d, 2×H aromatic ring), 7.36-7.52 (t, 2×H);

Figure SM 14.3.9. $^1$H NMR spectrum of benzyl (CDCl$_3$, 400 MHz) δ (ppm): 7.50 - 7.54 (t, 2×H aromatic ring), 7.64 - 7.69 (t, 1×H), 7.97 - 7.99 (d, 2×H aromatic ring). The coupling constant is exactly the same for all hydrogens, J=7.6 Hz. The molecule is symmetrical; therefore the shifts are identical for the two “sides”. The substituted ketone groups influence the most the hydrogens in position ortho, then those para and, less of all, meta hydrogens.
Figure SM 14.3.10. $^1$H NMR spectrum of Dilantin (DMSO, 400 MHz) $\delta$ (ppm): 9.29 (NH), 7.30 - 7.42 (m, 10×H aromatic ring), 11.08 (s, 1×H, OH enol). 3.42 and 2.50 and signals from DMSO.

Physical properties of reagents and reaction products

Benzaldehyde

Form: colourless or yellowish liquid, very refractive ($n_0$ 1.5456)

Solubility: 0.695 g/ 100 mL in water, soluble in ethanol, ether

Boiling point: 178.1°C

Risk Codes: R22

Safety Statements: S24

http://www.scienclab.com/msds.php?msdsId=9927094
Benzoin
Form: white crystals
Solubility: slightly soluble in water
Melting point: 137°C
Risk Codes: R36/38
Safety Statements: S24
http://www.sciencelab.com/msds.php?msdsId=9923053

Benzil
Form: yellow crystals (needles or powder)
Solubility: insoluble in water, soluble in benzene
Melting point: 94-95°C
Risk Codes: R36/37/38
Safety Statements: S26-36-37/39
http://www.sciencelab.com/msds.php?msdsId=9923047

Phenytoin (Dilantin)
Form: white crystalline solid
Very slightly soluble in water, slightly soluble in chloroform, ethanol and ether, soluble in DMSO
Melting point: 295°C
Risk Codes: R22;R40;R45;R61;R63
Safety Statements: 53-45-36/37-16-7
http://www.sciencelab.com/msds.php?msdsId=9926522

This experiment has been performed by 2\textsuperscript{nd} year Chemistry and Biochemistry undergraduate students from Madeira University.
The 1st session usually takes no longer than 2 hours. A session has been introduced specifically for the purification of benzoin since the recrystallization can take a lot of effort. The need to re-dissolve and evaporate a bit of solvent is quite common. A 5th session for characterization was considered necessary, since phenytoin must be allowed to dry completely before yield can be calculated and spectra obtained.

All reactions are quite straightforward and very easy to perform in standard lab periods, providing that the student can make a reasonable distribution of tasks and have the work prepared in advance.
Preparation of isoborneol through the Wagner-Meerwein rearrangement reaction of (1R)-(+)\textsuperscript{-}camphene

Marek Krzemiński

Supplementary Material

Experiment Notes ...................................................................................................................... 1
........................................................................................................................................... 2
Figures ................................................................................................................................ 3
   Photos of experiment ........................................................................................................ 3
   \textsuperscript{1}H and \textsuperscript{13}C NMR spectra ........................................................... 6
   GC chromatograms ............................................................................................................ 12

This experiment is designed for students with previous experience in the organic chemistry lab. At Nicolaus Copernicus University, this experiment is routinely performed by graduate students at the laboratory of Chemistry of Natural Compounds.

The main objective of this experiment is to show students a rearrangement of the carbon skeleton in the reaction of camphene with acetic acid catalyzed by boron trifluoride etherate to isobornyl acetate. The second objective is to familiarize students with the alkaline hydrolysis of esters, by hydrolysis of isobornyl acetate, and sublimation as a method of purification of selected organic compounds. Students should also observe racemization of the product by measuring the optical rotation of the starting camphene and the product isoborneol. They should calculate the specific rotation of the substrate and the product, compare with literature data, and calculate their enantiomeric purity.

The reaction is carried out with (+)-camphene, but also (–)-camphene can be used. Commercially available (+)-camphene (Aldrich), which is of lower enantiomeric purity than (–)-camphene, may contain small amount of tricyclene, which does not interfere in the reaction. Other impurities are not recommended. As shown in the photographs of the first stage of the reaction (Figure SM 14.4.1-3), the reaction is carried out in a one-neck flask immersed in an oil bath at 55°C. In the absence of a magnetic stirrer hotplate with the temperature control, a two-neck flask equipped with a thermometer and a reflux condenser, heating mantle, and magnetic stirrer can be used. It is important to slowly
warm the reaction mixture to 60°C and maintain the reaction in the range of 50-60°C. In the synthesis of isobornyl acetate, the reaction mixture becomes dark brown as is shown in Figure SM 14.4.3.

In the second step of the isoborneol synthesis, alkaline hydrolysis of isobornyl acetate, it is important to use a good quality of potassium hydroxide. The combined organic solutions after extraction of isoborneol must be well dried to successfully complete sublimation of isoborneol. Another important factor for easy carry out sublimation process is complete evaporation of hexane using a rotary evaporator under reduced pressure. Sublimation apparatus is shown on Figures SM 14.4.7-8. Sublimation process is carried out under reduced pressure generated by water pump. Instead of a water-pump vacuum pump can be used which gives pressure 10-20 Torr. Sublimation takes place at a rather strong heating of the flask in a heating mantle. If you notice any liquid on the cooling finger of sublimation head, sublimation should be stopped, disconnect the vacuum, and use a paper towel to dry cooling finger. The heating gun is necessary to remove isoborneol from the walls of the of the flask (Figure SM 14.4.9-10).

The usual yield of the isobornyl acetate formation is in the range of 70-90%. The overall yield of the synthesis is an average of 40-60%, which was repeatedly confirmed at the laboratory of Chemistry of Natural Compounds, Faculty of Chemistry, Nicolaus Copernicus University in Toruń.
Photos of the experiment

**Figure SM 14.4.1** – Crystalline camphene

**Figure SM 14.4.2** – Reaction mixture (camphene in glacial acetic acid with BF₃·Et₂O) immersed in an oil bath (55°C) after 1-2 minutes

**Figure SM 14.4.3** – The entire set of equipment for the synthesis of isobornyl acetate

**Figure SM 14.4.4** – The reaction mixture poured into water in a separatory funnel after first extraction with hexane
Supplementary information for *Comprehensive Organic Chemistry Experiments for the Laboratory Classroom* © The Royal Society of Chemistry 2017

**Figure SM 14.4.5** – Alkaline hydrolysis of isobornyl acetate

**Figure SM 14.4.6** – Reaction mixture from the hydrolysis of isobornyl acetate poured into a separatory funnel contained water – separation of semi-solid isoborneol can be observed

**Figure SM 14.4.7** – Sublimation head
Figure SM 14.4.8 – Sublimation apparatus setup

Figure SM 14.4.9 – Sublimed isoborneol collected on a cooling finger

Figure SM 14.4.10 – Heating gun helps to remove product from the flask walls

Figure SM 14.4.11 – The end of sublimation (oily impurities stayed on the bottom of the flask)
1H and 13C NMR spectra

Figure SM 14.4.12 – 1H NMR spectrum (400 MHz, CDCl3) of (+)-camphene
Figure SM 14.4.13 – $^{13}$C NMR spectrum (100 MHz, CDCl₃) of (+)-camphene
Figure SM 14.4.14 – $^1$H NMR spectrum (400 MHz, CDCl$_3$) of the crude isobornyl acetate
Figure SM 14.4.15 – $^{13}$C NMR spectrum (400 MHz, CDCl$_3$) of the crude isobornyl acetate
Figure SM 14.4.16 – $^1$H NMR spectrum (400 MHz, CDCl$_3$) of isoborneol
Figure SM 14.4.17 – $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of isoborneol
GC analyses:

Column: Supelco wax 10, 15m x 0.53 mm x 1 μm
Carrier gas: helium,
Detector: FID,
Injector temperature: 220 °C
Detector temperature: 250 °C
Heating program: 2 min. in 60 °C, 15 °C/min. to 220 °C, 5 min. in 220 °C.

Figure SM 14.4.18 – GC chromatogram of (+)-camphene
Figure SM 14.4.19 – GC chromatogram of isobornyl acetate

<table>
<thead>
<tr>
<th>Ret.time (min.)</th>
<th>Area(%)</th>
</tr>
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<tbody>
<tr>
<td>6.065</td>
<td>1.874</td>
</tr>
<tr>
<td>6.740</td>
<td>94.205</td>
</tr>
<tr>
<td>7.358</td>
<td>3.921</td>
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</table>

Figure SM 14.4.20 – GC chromatogram of isoborneol

<table>
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<th>Ret.time (min.)</th>
<th>Area(%)</th>
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<tbody>
<tr>
<td>6.752</td>
<td>1.750</td>
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<tr>
<td>7.448</td>
<td>94.565</td>
</tr>
<tr>
<td>8.220</td>
<td>3.685</td>
</tr>
</tbody>
</table>
Umbelliferone: a natural scaffold suitable for the synthesis of ortho-acetylhydroxy coumarins via Fries rearrangement reaction

Supplementary Material

Experiment Notes
Table of results of different experiments ................................................................. 2
Product Isolation by flash column chromatography ................................................. 2

Figures
Photos of the experiment ......................................................................................... 4
$^1$H-NMR spectra ........................................................................................................ 5
IR spectra ....................................................................................................................... 8
TLC schemes ............................................................................................................... 9

The main goal of this experiment is to perform the Fries rearrangement reaction on a natural compound such as umbelliferone. Students who perform this reaction should have high skills in organic chemistry laboratory techniques.

The first step is the esterification of the OH group of the umbelliferone to produce the compound 7-acetoxycoumarin. This esterification reaction can be carried out at room temperature, but it would need at least 24 h. There are several methods described for the synthesis of the 7-acetoxycoumarin, but the one described here is the most appropriate for a laboratory session in a decent time with moderate to good yields. Quenching the reaction with ice-water solubilize the pyridine and ease the precipitation of the organic compound, facilitating the purification process. Neutralization with HCl forms the pyridinium salt that is highly soluble in water, avoiding future problems with pyridine. The aqueous solution containing the pyridinium salt can be placed in the basic water residues disposal. Recrystallization in methanol will take about 1 hour.

For the Fries rearrangement reaction, it is important to pulverize and homogenize quickly the solid mixture in the mortar. This step can also be carried out in a glovebox to ensure highly anhydrous conditions, but the yield is not highly affected if pulverization and homogenization process are done quickly (eg yields for compound 2: In glovebox: 83%; no glovebox: 77%). Anhydrous conditions during the reaction are important, but not critic, in order to give the Fries rearrangement in high yield. High volumes of white fumes are produced during the first 5 minutes of the reaction. Therefore for safety reasons it is rigorously needed to carry out the reaction in the fume hood. The initial yellow solid mixture will turn into a sticky yellowish mixture. After 2 h heating, it is important to allow the reaction to reach room temperature before quenching.
After quench the reaction, both compounds can be efficiently extracted by liquid-liquid extraction with ethyl acetate (3 x 30 mL).

This experiment will allow the students to rationalize the reaction mechanism of the acetylated final compound as a result of the Fries rearrangement. Students will also use the NMR as the main characterization technique. The structures of the final compounds are simple and the identification of both isomers is easy by $^1$H-NMR (see figures SM 14.5.5-8).

This experiment also tries to encourage students for a further bibliographic search about the importance of coumarins in the medicinal chemistry field.

The reproducibility of the experiment was assessed by its repetitive execution (Table SM 14.5.1) by first year Chemistry M.Sc. students from the Faculty of Pharmacy (Santiago de Compostela). Data of the yields and melting points reported in the literature are also included in Table SM 14.5.1.

### Table SM 14.5.1. Yields and melting points of compounds 1-3 obtained by first year Chemistry MSc students

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound 1</th>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Compound 2</th>
<th>Compound 3</th>
<th>Compound 3</th>
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<tbody>
<tr>
<td></td>
<td>Isolated Yield (%)</td>
<td>Melting Point (ºC)</td>
<td>Isolated Yield (%)</td>
<td>Melting Point (ºC)</td>
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<tr>
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<td>146-148</td>
<td>71</td>
<td>172-175</td>
<td>21</td>
<td>178-180</td>
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<td>2</td>
<td>96</td>
<td>144-147</td>
<td>67</td>
<td>167-169</td>
<td>27</td>
<td>175-178</td>
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<td>3</td>
<td>88</td>
<td>144-146</td>
<td>64</td>
<td>171-174</td>
<td>25</td>
<td>173-175</td>
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<tr>
<td>4</td>
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<td>143-145</td>
<td>82</td>
<td>168-174</td>
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<tr>
<td>5</td>
<td>97</td>
<td>145-147</td>
<td>72</td>
<td>167-171</td>
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<td>173-175</td>
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<tr>
<td>6</td>
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<td>143-145</td>
<td>77</td>
<td>169-172</td>
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<tr>
<td>Reported</td>
<td>97</td>
<td>142-143</td>
<td>71</td>
<td>166-167</td>
<td>29</td>
<td>173-175</td>
</tr>
</tbody>
</table>

**Product Isolation by flash chromatography:**

Prepare 3L of a hexane:acetone mixture (eluent) in a 6:1 v/v ratio. Take a column (60 cm high, 29/32 cm wide). Plug the stopcock end so that the silica will not drain out. This is normally done with a small piece of cotton or glass wool and a long stick or glass rod. Mount the column in your hood - due to the large volumes of volatile solvents used and the health risks associated with dry silica gel, you should never run a column outside of the hood. Check to see that your column is perfectly vertical - crooked columns make separation more difficult. Close the stopcock and add a few inches of your eluent. Add sand (dried and washed) to the column using a funnel to produce a thin layer of sand (no more than 1 cm) above the plug which will help prevent the silica from ending up in your collection flasks.
Make a slurry of the silica (80 g) by adding 100 mL of your eluent and mix it thoroughly by swirling vigorously to remove all the air from the silica (air bubbles will compromise the effectiveness of your column). Using a powder funnel, carefully and slowly pour the slurry into the column making sure not to disturb the layer of sand. Stop pouring frequently to swirl the slurry so that the silica is regularly mixed. Once you've finished pouring, rinse the Erlenmeyer several times with the eluent and add the remaining solvent/silica mixture to the column. Using a pipet and your solvent system, rinse any silica stuck to the sides of the top of the column into the solvent layer.

After loading, use gentle pressure compressed air to drain most of the eluent collecting above the silica layer off the column. **Caution: Never let the solvent level drop below the top of the column.** After loading the silica, the material solution must now be prepared and loaded on the column.

Add a protective layer of sand to the top of the silica. This should be relatively level and about 2 cm thick. Carefully fill the column with your eluent. At first, add the solvent via Pasteur pipet and keep adding the solvent by pipet until a few centimeters of solvent are above the column. Now slowly add the solvent through a powder funnel letting it first run down the side of the column. Run the column applying compressed air and collected fractions on test tubes (40 mL). Remember that a quick flow rate helps to give good separation (but not too fast). Adjust the air pressure to give a swift flow and keep the pressure on and change the test tubes once they become filled. Remember to replenish the solvent in the column frequently.

Monitor the progress of the column by TLC. Compounds are coloured so they are visible on the TLC. However, compounds are also visible under UV lamp, and therefore it can be useful to double-check the TLC under UV. The first compound to be eluted is compound 2 (8-acetyl-7-hydroxycoumarin), which will start to come out after around 9 tubes (fractions around 9-15 with pure compound). After this, there will be a few tubes with a mixture of compounds (tubes 16-20) and then the next compound (compound 3, 6-acetyl-7-hydroxycoumarin) will elute (tubes 21-23).

Once you have determined that all of the compounds you are interested in have eluted from the column, you are ready to wrap everything up. First, put a large Erlenmeyer flask underneath the column, and use a Keck clip to attached your compressed air source to the column. Allow the air to push all of the remaining solvent out of the column and then to dry the silica gel. (It's difficult to remove the silica from the column until it is completely dry.).

While the column is drying, start to combine fractions. Using TLC, determine which test tubes contain your pure compounds. Combine fractions of similar purity in large round bottom flasks and concentrate them on the rotovap.

Once the solvent is completely removed, analyze the compounds by NMR.
Photos of the experiment

**Figure SM 14.5.1.** Pulverization of the mixture of 7-acetoxy coumarin (1) and AlCl₃

**Figure SM 14.5.2.** Reaction setup apparatus needed to perform the Fries rearrangement reaction.
**Figure SM 14.5.3.** White fumes produced during the Fries rearrangement reaction.

**1H-NMR spectra**

![Umbelliferone](image)

**Figure SM 14.5.4.** Umbelliferone. $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ ppm 10.63 (bs, 1H, OH), 7.93 (d, $J = 9.4$ Hz, 1H, H-4), 7.52 (d, $J = 8.5$ Hz, 1H, H-5), 6.77 (dd, $J = 8.5$, 2.3 Hz, 1H, H-6), 6.70 (d, $J = 2.3$ Hz, 1H, H-8), 6.19 (d, $J = 9.4$ Hz, 1H, H-3).
Figure SM 14.5.5. 7-Acetoxycoumarin 1. $^1$H NMR (250 MHz, DMSO-$d_6$) δ ppm 8.06 (dd, $J = 9.5$, 1.2 Hz, 1H), 7.76 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.27 (t, $J = 1.7$ Hz, 1H), 7.15 (dt, $J = 8.4$, 1.7 Hz, 1H), 6.47 (dd, $J = 9.5$, 1.3 Hz, 1H), 2.30 (s, 3H).

Figure SM 14.5.6. 8-Acetyl-7-hydroxycoumarin 2. $^1$H NMR (250 MHz, DMSO-$d_6$) δ ppm 11.80 (bs, 1H), 7.97 (d, $J = 9.6$ Hz, 1H), 7.65 (d, $J = 8.6$ Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 1H), 6.28 (d, $J = 9.5$ Hz, 1H), 2.49 (s, 3H).
Figure SM 14.5.7. 6-Acetyl-7-hydroxycoumarin 3. $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ ppm 12.3 (bs, 1H), 8.33 (s, 1H), 8.02 (d, $J = 9.7$ Hz, 1H), 6.88 (s, 1H), 6.34 (d, $J = 9.5$ Hz, 1H), 2.65 (s, 3H).

Figure SM 14.5.7. Comparison of the aromatic region of the $^1$H-NMR spectra of 8-acetyl-7-hydroxycoumarin (compound 2, red), 6-acetyl-7-hydroxycoumarin (compound 3, blue) and a mixture of 2 and 3 (green).
Figure SM 14.5.8. Identification of the different isomers based on the different kind of signals present in the $^1$H-NMR spectra.

Figure SM 14.5.9. IR spectra of compound 2 $\nu_{\text{max}}$ (KBr) cm$^{-1}$, 3061 (O–H), 2791 (C–H), 1731 (C=O), 1613 (C=C), 1567 (aromatic), 1233 (O–C=O);
Figure SM 14.5.10. TLC scheme for the crude obtained in session 2. A) Umbelliferone; B) Compound 1 (7-Acetoxycoumarin); M) Mixture of A, B and C; C) Crude obtained in session 2.
Preparation of 4,5-functionalized cyclopentenone via cyclization of Stenhouse adduct

Supplementary Material

The aim of this experiment is to synthesize a 4,5-functionalized cyclopentenone from readily available starting materials (furfural, Meldrum’s acid and diethylamine) in 3 steps under mild reaction conditions. The synthesis of functionalized cyclopentenones from furan derivatives is a well-documented reaction and for further reading please see references 2-4. The reaction of furfural and two molecules of secondary amine under Lewis acid catalysis yield the corresponding 4,5-diaminocyclopentenone. All the products are easily isolated from the reaction mixture using simple techniques and the structure of the three products are confirmed by \(^1\text{H}\) and \(^{13}\text{C}\) NMR. Melting point determination is not possible as the samples suffer degradation with temperature (above 120 °C). The experimental procedure is based on the reports of Bigi (synthesis of activated furan) and Alaniz. The major modification to the protocol reported by Alaniz et al. is the use of sunlight instead of a bulb (GE Crystal Clear 200 bulb) for the cyclization step. The time for the sunlight induced reaction should be previously tested in each laboratory. As reported by Alaniz et al., several other secondary amines can also be used (however never tested by students).

The student body is students of advanced organic chemistry, in which the concepts of aldol reaction, conjugated additions, and Nazarov cyclization were learned.

This procedure was successfully implemented at the described scale and tested in the teaching laboratory by eight groups of two students from first year and by two upper-division undergraduate students (in this last case the reactions were performed in a scale 3 times smaller – 1 mmol of 2-furaldehyde). The yields obtained are in the range of 70-86% (activated furan, first step), 50-80% (Stenhouse adduct, second step) and 50-72% (cyclopentenone, third step).
Notes for the preparation of activated furan (session 1): Meldrum’s acid is not soluble in water at room temperature and starts to solubilize at reaction temperature. The reaction mixture will turn dark, and the product starts to precipitate during the reaction.

Figure SM 14.6.1 – Reaction for preparation of activated furan and aspect of the final product.

Figure SM 14.6.2 – Aspect of the isolated products from several groups in the teaching laboratory.

The analysis of the reaction completion by TLC can be performed directly to the reaction mixture however, since the $R_f$ of the product and starting material furfural are similar, evaporation of water should be performed after spotted in the TLC. As alternative, an aliquot of the reaction mixture can be extracted with ethyl acetate in a small vial and the TLC performed as normal. The observation of the reaction completion is not straightforward due to similar $R_f$ and a co-spot between the starting material and the reaction mixture should be done. This step is not completely necessary since 1.5 hours is
usually enough time to reach the reaction completion. Typically the amount of unreacted starting material is 0 – 10 mol% as determined by NMR of the isolated product. No purifications is necessary as this 2-furaldehyde does not react with amines without catalyst.

Figure SM 14.6.3 – Pictures of the TLC using UV identification (left) and using phosphomolybdic acid stain (right). F – furfural; P product (yellow colour); M – co-spot.

The reaction is known by Knoevenagel Condensation and the mechanism is represented in the next Scheme.
Notes for the preparation of the Stenhouse adduct (session 2): The reaction mixture immediately changes colour to red with the addition of the diethylamine. After cooling down the reaction mixture in an ice bath the solid is collected in a paper filter. Regarding the work-up protocol, is important to use cold diethyl ether, using a freezer or an ice bath to cool it down to around 5 ºC. The transfer to the vial should be performed after the solid is properly dried (5 to 10 minutes is enough to dried the solid with the fume hood ventilation)

![Aspect of the reaction](image1)

![Cooling down of the reaction mixture](image2)

![Product filtration](image3)

![Product in the filter paper](image4)

![Aspect of the isolated product](image5)

Figure SM 14.6.4

Regarding the mechanism, is believed that there is an initial conjugated addition of the amine to the furan ring activated, that promotes the furan ring opening by iminium ion formation, that forms that the enamine. The name “Stenhouse adduct” is given by the similarity to the Stenhouse salts. The red colour of the Stenhouse adduct can be explained based on the high conjugation.
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\[ \text{Stenhouse adduct} \xrightarrow{\text{hv}} \longrightarrow \text{4,5-functionalized cyclopentenone} \]
Example of NMR spectra of the activated furan (300 MHz, CDCl₃): From this $^1$H NMR there is 7-8% of furfural as unreacted starting material. The presence of this impurity does not affect the next step since furfural does not undergo formation of Stenhouse salt in the absence of acid catalysis.
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General NMR spectra (300 MHz, D₂O) of the cyclopentenone product obtained by the students:
Spectral data according to the literature (see compound 73 in Ref. 2b). Water suppression should not be used in the NMR program since there is one signal with chemical shift of 4.81 ppm.


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Synthesis of a chiral salen. Examples of the Schmidt rearrangement and ultrasound activation

Supplementary Material

This experiment, on a 50 mmol scale of camphoric acid, has been carried out by several final year graduate students and also by Masters Students. No problems were detected when these students carried out the experiment.

<table>
<thead>
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<th>SCALE (mmol camphoric acid)</th>
<th>YIELD (%)</th>
<th>TYPE OF STUDENT</th>
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<td>50</td>
<td>78</td>
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<td>5</td>
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</table>

The reaction (Figure SM 14.7.1) is usually carried out on a 50 mmol scale of camphoric acid. This can be reduced to a 5 mmol scale with identical results. The reaction mixture may be extracted with dichloromethane instead of chloroform but the yield of the isolated diamine is lower (40-50% instead of 70-90%). In the synthesis of the diamine, it is very important that the sodium azide is added slowly to avoid excessive evolution of gas. If the addition is not slow, the solution overheats causing the reaction mixture to climb up the condenser.

Figure SM 14.7.1. Reaction set-up.
If necessary the reaction may be left at room temperature and isolated later, even after a few days. When neutralizing the reaction mixture, it’s essential to control the temperature. In order to do this, more portions of ice should be added at intervals.

Usually, traces of water remain in the diamine even after drying with anhydrous sodium sulfate. It can be removed by adding one or two portions (15 mL) of toluene to the diamine and evaporating on the rotavapor. The resulting pale yellow oil is obtained in 70-90% yield and used directly in the salen synthesis.

In the synthesis of the salen, silica gel is used as catalyst and water sponge. In the isolation of the salen compound, dichloromethane is used to dissolve some of the product which often precipitates. This avoids low yields. The salen, a bright yellow solid is obtained in 80-90% yield and with a melting point of 156-157 °C.¹ When recrystallizing the salen, the process can be hastened if, instead of only hot ethyl acetate, a mixture of ethyl acetate/hexane is used.

Besides allowing the student to review fundamental carbonyl group reactivity related to the formation of the salen, this experiment introduces the student to more complex reaction mechanisms, namely, the Schmidt reaction, involving rearrangement with retention of stereochemistry (Scheme SM 14.7.1).

The student will use ¹H and ¹³C NMR in order to confirm the structure of the salen molecule.
$^1$H and $^{13}$C NMR Spectra:

Figure SM 14.7.2. $^1$H NMR spectrum of the salen compound.
Figure SM 14.7.3. $^{13}$C NMR spectrum of the salen compound.