Bromination of Cinnamic acid

Supplementary Material

Experimental notes

This experiment aims at the preparation of the 2,3-dibromo-3-phenylpropanoic acid from cinnamic acid by bromine addition.

The cinnamic acid is soluble in dichloromethane at room temperature and thus before the bromine addition the reaction vessel holds a colourless solution. The bromine solution is intensively red-coloured and since the addition reaction is relatively fast at this temperature, the reaction evolution can be followed by the progressively disappearance of the red colour. The addition can be done in 30 min.

As the reaction proceeds, the product starts to precipitate and by the end of the bromine addition there is a significant amount of the product although usually the reaction mixture is still slightly coloured. 0.1-0.2 mL of cyclohexene are sufficient to remove all bromine traces and since the product of this reaction, 1,2-dibromocyclohexane, is soluble in CH_2Cl_2 it doesn't disturb the isolation of the desired product. Pay attention that cyclohexene stinks with a smell that resemble the additives present in the butane bottles which alert us to a gas leak.

The product isolation by filtration is simple and, as the dicloromethane is quite volatile, the product can be quickly air dried and the melting point determined in the same experimental session. As the cinnamic acid is soluble in cold CH_2Cl_2 the washing of the final product is essential to assure a good purity. TLC and ^{1}H NMR analysis confirm the purity of final product, without any cinnamic acid contamination, and thus it is not necessary to make any recrystallization.

The measurement of the melting point allows determining the addition mode of the bromine to the double bond. The values obtained confirm the erythro configuration of the product resulting from an *anti* addition. This experiment is very reproducible and was performed with students of the first year of the Chemistry degree. One session of 2 h is enough to perform the entire experiment which can also be conducted in a lower scale. The yields vary between 80-93% and the melting point of

product is 206-208 ºC (lit 202-204 ºC, Mayo, D., W., Pike, R., M., Forbes, D., C. Microscale organic laboratory: with multistep and multiscale synthesis, 5nd edition, Wiley Custom Services, chaper 7, pp 486).

Photos of the experiment

Figure SM 4.1.1.1.1.1. The cinnamic acid solubilization in CH_2Cl_2

Figure SM 4.1.1.1.1.2. Reaction apparatus before the Br_2 addition

Figure SM 4.1.1.1.1.3. Reaction apparatus after the Br_2 addition.

Figure SM 4.1.1.1.1.4. TLC plate. 60% diethyl ether/petroleum ether. a) cinnamic acid b) cinnamic acid and product c) Product

^{1}H NMR and IR spectra

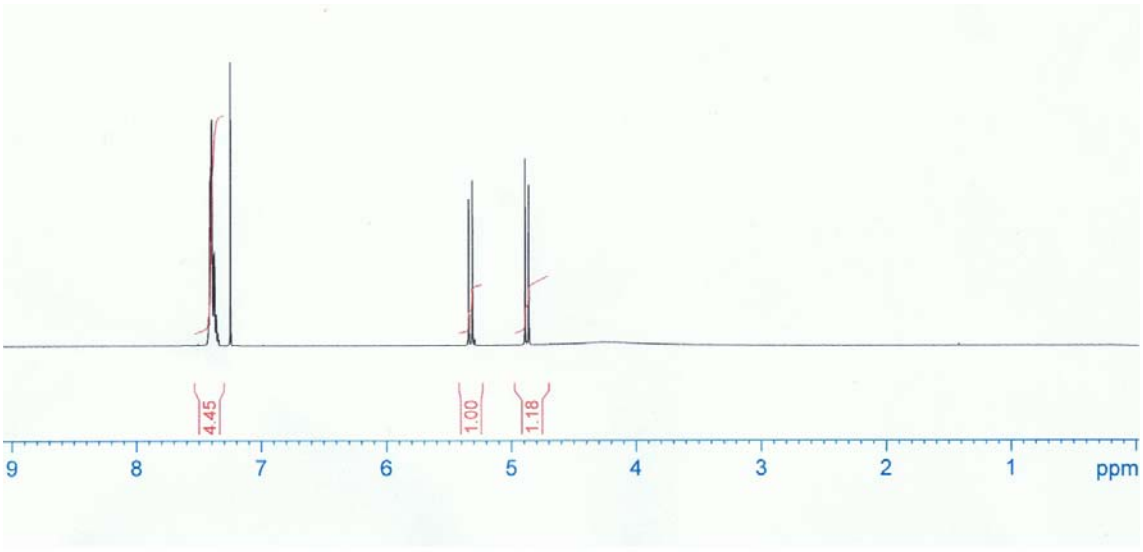


Figure SM 4.1.1.1.1.5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the reaction product

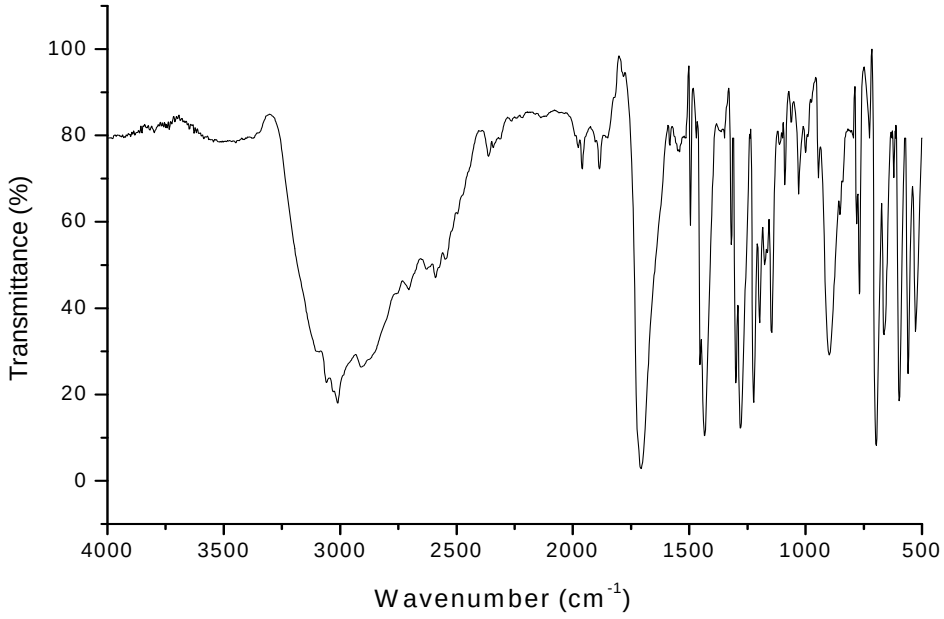


Figure SM 4.1.1.1.1.6. IR spectra of 2,3-dibromo-3-phenylpropanoic acid

Preparation of *meso*-1,2-Dibromo-1,2-diphenylethane

Supplementary Material

Experimental notes

Figures

Experimental notes

Background topics

This experiment illustrates a stereospecific electrophilic addition reaction to an alkene.

The experiment is appropriate to introductory/intermediate level students, who are encouraged to rationalise the mechanism of the reaction and some experimental details through the answers to a set of additional questions. It was already realized by over 100 students of the Faculty of Sciences and Technology, Universidade Nova de Lisboa (in classes of 22 students/class, 11 groups of two), who didn't experience any difficulties.

It is important that the students understand what a stereospecific reaction is. Suggest the students to write all the (3) stereoisomers of 1,2-dibromo-1,2-diphenylethane - the meso form and the racemic mixture of enantiomers (and to practice drawing Fischer projections). Discuss which are optically active. Identify enantiomers and diastereoisomers. Ask them about the results if the reaction were not stereospecific or if the *cis* stereoisomer of the starting alkene were used. (If the *cis* isomer of the starting material was used, the racemic mixture would be obtained).

Hints for the answers to the proposed questions and topic to discussion:

1. The crystalline perbromide is much less toxic and easier to handle than liquid bromine.
2. Stereospecificity results from the two-step mechanism explained in the Background section. No regioselectivity is possible when two identical (C-Br) new bonds are formed.
3. There are 3 stereoisomers (the meso form, optically inactive, and the two enantiomers, each one optically active). Optically active and inactive forms are diastereoisomers.
4. If the reaction were not stereospecific, all the isomers could be obtained, no matter which isomer of stilbene was used as starting reagent.

Experimental details

The experiment execution is very simple, the final product is easily isolated and doesn't need a further purification step.

The difficulty level is low, but the hazard level is moderate to high.

Pyridine and bromine are very toxic, requiring special caution in their manipulation (see Safety indications).

The main difficulty is drying the product; traces of acetic acid are not always easy to remove. More than one washing with methanol may be necessary.

The product is pure white. If some red color persists, traces of bromine are still present and must be efficiently removed (by further washing with methanol).

Some experimental results obtained by the students in the laboratory are presented in Table SM 4.1.1.2.1.

Table SM 4.1.1.2.1. Typical experimental results obtained in the Laboratory

Yield of product	70-85%
Melting point of product	236-237ºC

A very simple alternative to the experimental technique described is the direct reaction of trans-stilbene (in acetic acid solution) with bromine (added dropwise, with caution, in a fume hood). The final result is the same, although the use of the crystalline perbromide is less hazardous.

The preparation of samples for spectral analysis is also important.

Students should be familiarized with the technique of preparing a solid transparent disc for IR spectroscopy, by using a small amount of a dried sample of the compound and KBr and the adequate material. Ask them why this supporting material is adequate.

The only functional groups of the final product are the aromatic rings and the bromine atoms. Therefore, the IR spectrum shows no very significant absorption bands. The main ones are the following:

IR data (in KBr disc) of *meso* stilbene dibromide

3030-3090 cm^{-1}: =C-H

1450 and 1500 cm^{-1}: C=C

For ^{1}H-NMR spectroscopy $CDCl_3$ or DMSO-d_6 are suitable solvents.

Figures

Photos of the experiment

Fig. SM 4.1.1.2.1. Chemicals

Fig. SM 4.1.1.2.2. Preparation of the perbromide

Fig. SM 4.1.1.2.3. Recovery of the perbromide

Fig. SM 4.1.1.2.4. Addition of perbromide to stilbene

Fig. SM 4.1.1.2.5. Cooling the reaction mixture

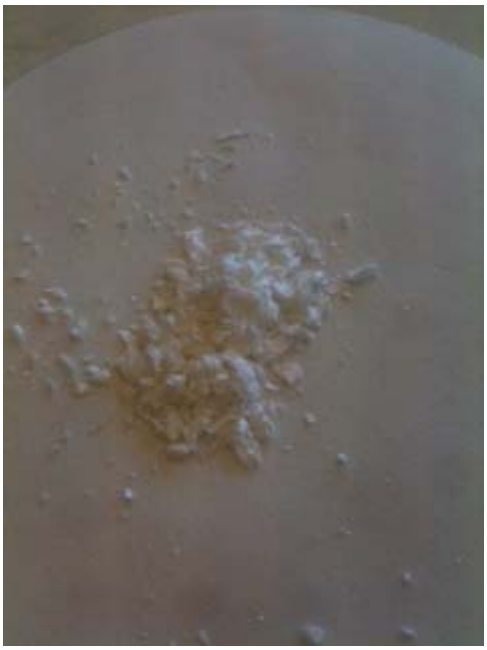


Fig. SM 4.1.1.2.6. Filtered and washed final product

Spectra

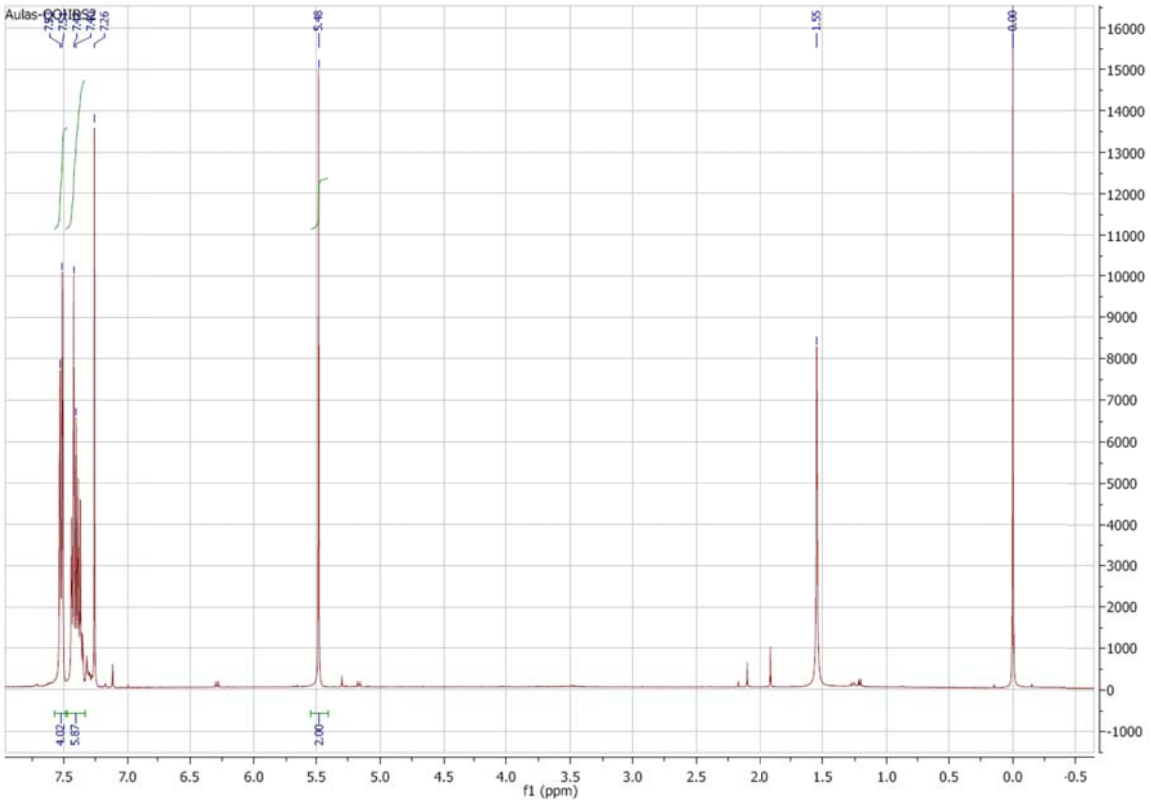


Fig. SM 4.1.1.2.7. ^{1}H-NMR spectrum of *meso*-1,2-dibromo-1,2-diphenylethane (in $CDCl_3$)

Bromination of (*E*)-chalcones [(*E*)-1,3-diarylprop-2-en-1-ones]

Supplementary Material

In this work, which is planned for a 4 hours session, students (individually or in groups of two) will synthesize 1,3-diaryl-2,3-dibromopropan-1-one derivatives by the reaction of bromine with (*E*)-chalcones. This experimental work illustrates the electrophilic addition reaction.

The desired product is obtained directly by filtration.

The bromine should be added slowly.

The 1,3-diaryl-2,3-dibromopropan-1-one derivatives are white. This experiment was performed by nearly 50 students and the yields and melting points are an average of the students' results.

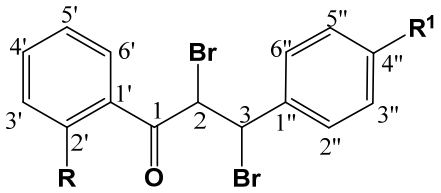


Figure SM 4.1.1.3.1 - 1,3-diaryl-2,3-dibromopropan-1-ones structure.

Table of Results: Reaction Yield and Melting Point of some 1,3-diaryl-2,3-dibromopropan-1-ones

Entry	Substituent R	Substituent R^1	Yield (%)	Melting point (°C)
1	H	H	70-80	200-202
2	H	OCH_3	65-75	190-192
3	$OCH_2C_6H_5$	H	60-75	179-181

The most important aspects in the NMR analysis is to confirm the disappearance of the vinylic protons and carbons of the starting (*E*)-chalcones and the appearance of signals due to the protons linked to a brominated carbon atom and also the effect of the bromine in the chemical shift of the carbon atoms. In the following figures are given, as examples, the ^{1}H and ^{13}C NMR and IR spectra of 2,3-dibromo-1,3-diphenylpropan-1-one.

Carbonyl groups are one of the most important structural units that can be revealed by IR spectroscopy. The carbon-oxygen double bond gives a characteristic peak in the 165-1800 cm^{-1} region.

Examples of IR, ^{1}H and ^{13}C NMR spectra:

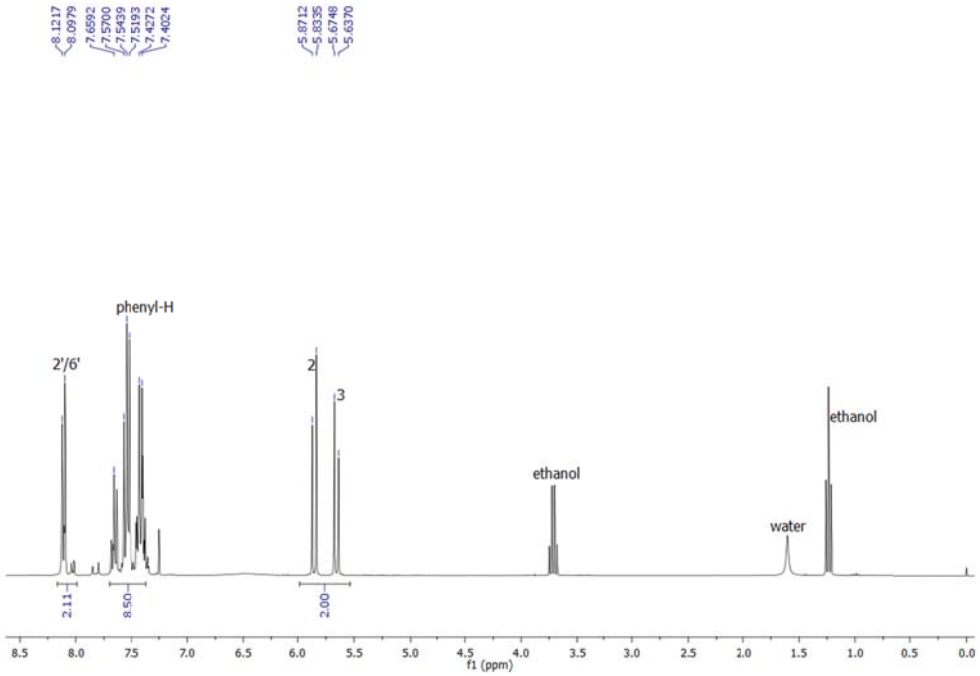


Figure SM 4.1.1.3.2 - ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the 2,3-dibromo-1,3-diphenylpropan-1-one (R=R[1]=H).

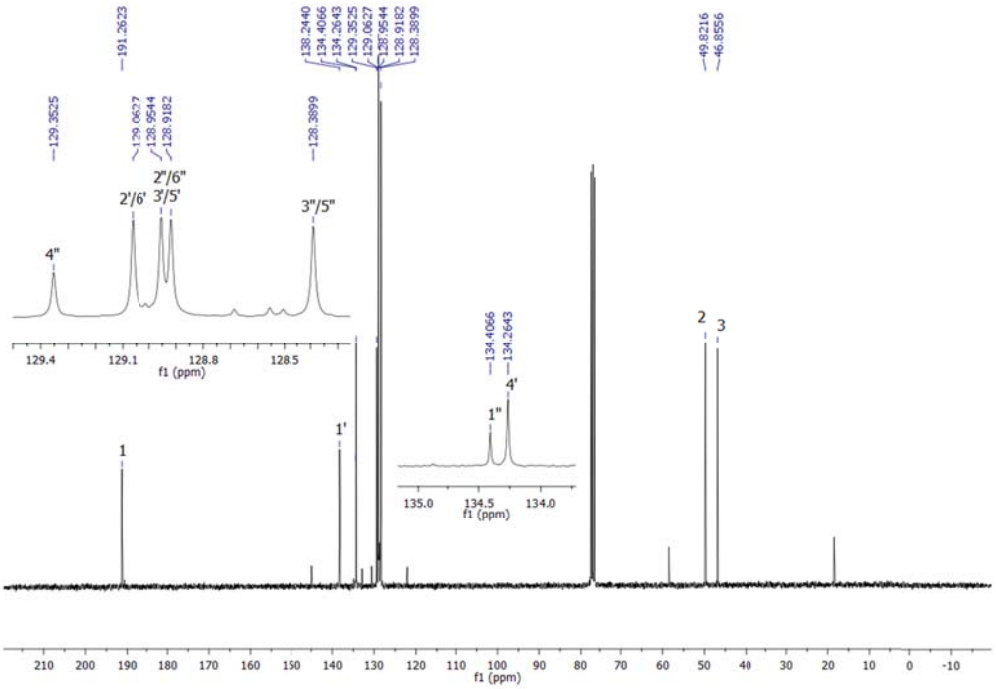


Figure SM 4.1.1.3.3 - ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of the 2,3-dibromo-1,3-diphenylpropan-1-one (R=R[1]=H).

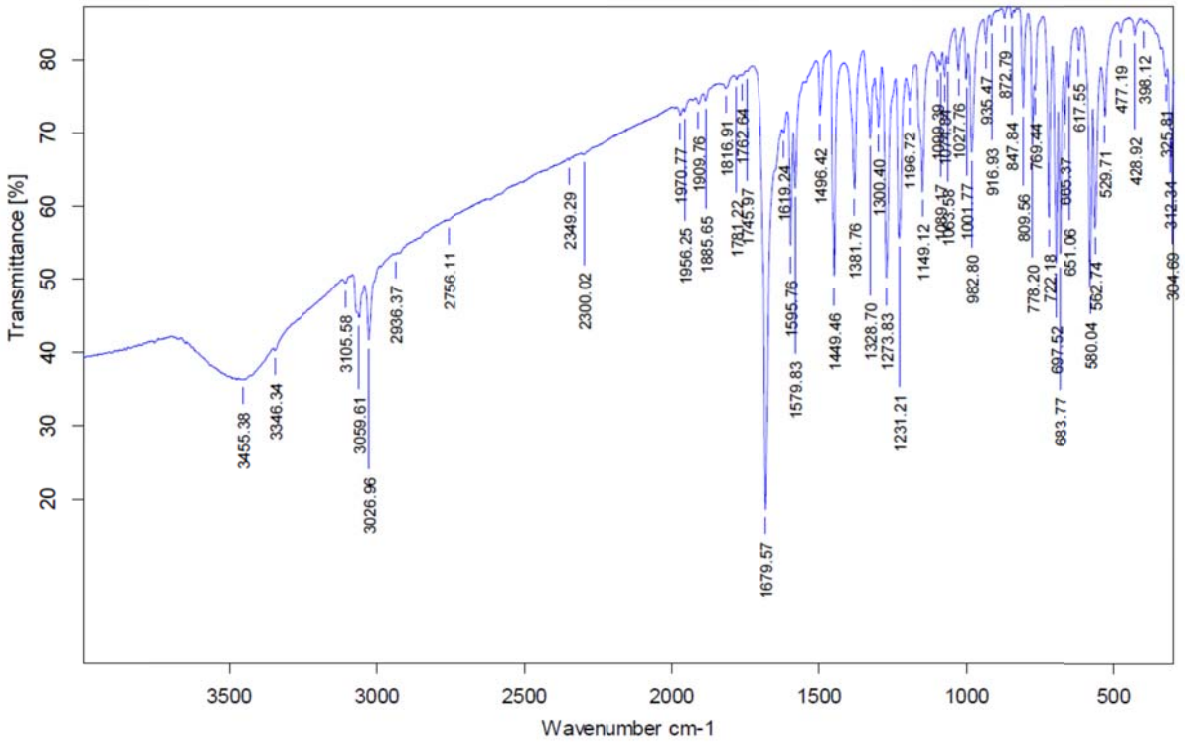


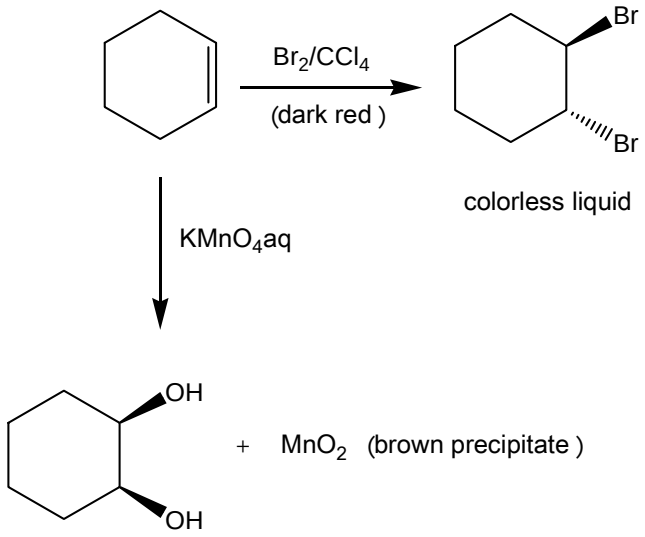
Figure SM 4.1.1.3.4 - IR spectrum of the 2,3-dibromo-1,3-diphenylpropan-1-one (R = R^1 = H).

Preparation of *trans*-2-Bromocyclohexanol from Cyclohexanol

Supplementary Material

Insaturation tests (cyclohexene):

- To probe the preparation of cyclohexene, both reactions with Br_2 in CCl_4 and $KMnO_4$ solutions can be performed. In the former, the dark red solution of Br_2 disappears when added to cyclohexene, according to Scheme SM 4.1.1.4.1; the second reaction with $KMnO_4$ solution (Baeyer test) generates a brown precipitate (MnO_2).



Scheme SM 4.1.1.4.1. Insaturation tests: Br_2 in CCl_4 and Baeyer test.

Infrared spectra of trans*-2-bromocyclohexanol and conformational analysis:*

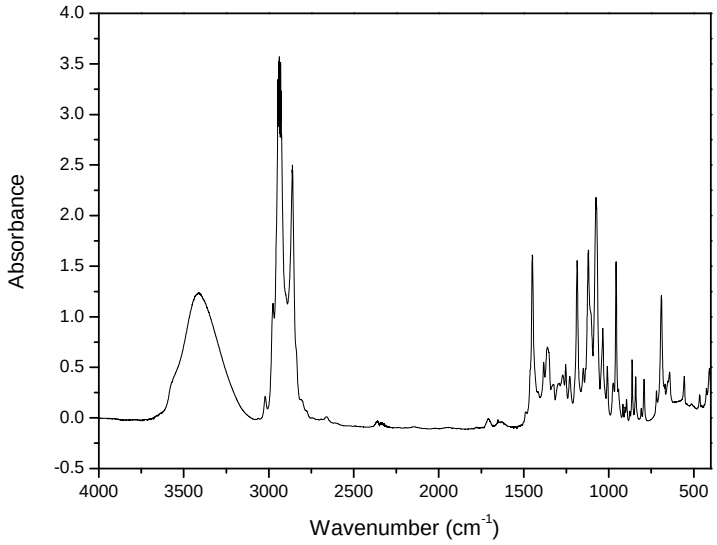


Figure SM 4.1.1.4.1. Infrared spectrum for the neat liquid (capillary film in KBr windows). The OH stretching band at 3400-3500 cm^{-1} and the lack of C=C stretching band at about 1600 cm^{-1} indicate the complete conversion of cyclohexene into *trans*-2-bromocyclohexanol.

Peak	Area	Centered at (cm^{-1})	Width	Height (Abs.)
1	13.376	3562.6	57.290	0.18629
2	165.69	3437.8	140.01	0.94427
3	130.33	3322.1	165.66	0.62770

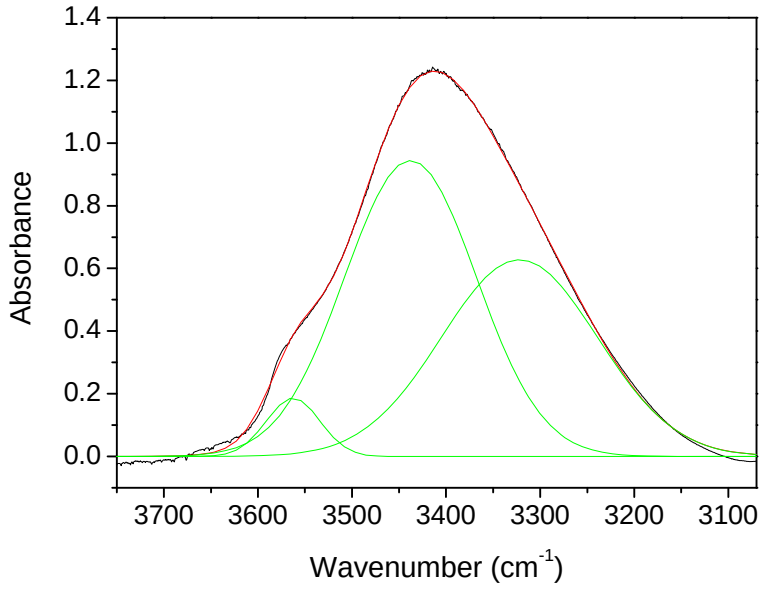


Figure SM 4.1.1.4.2. Expanded IR spectrum (neat liquid) in the O-H stretching region. The bands were deconvoluted using a Lorentzian function (main results are given above). The broad bands at 3322.1 and 3437.8 cm^{-1} indicate intermolecular H-bonded solute molecules. The low intensity band at higher wavenumber (3562.6 cm^{-1}) indicates free O-H. The associated molecules are predominantly in the diaxial conformation (60%, according to the relative band height: $[Abs_{diaxial}/Abs_{diaxial}+Abs_{diequatorial}]\times100$), because the higher intensity band centered at 3437.8 cm^{-1} corresponds to this conformer, according to the literature (Duarte, C. J., Freitas, M. P., "Hydrogen bonding and stereoelectronic effects in the conformational isomerism of *trans*-2-bromocyclohexanol", *J. Mol. Struct., 930*, 135-139, 2009).

Peak	Area	Centered at (cm^{-1})	Width	Height (Abs.)
1	0.84652	3591.2	11.644	0.046281
2	6.1779	3583.2	8.6885	0.45267

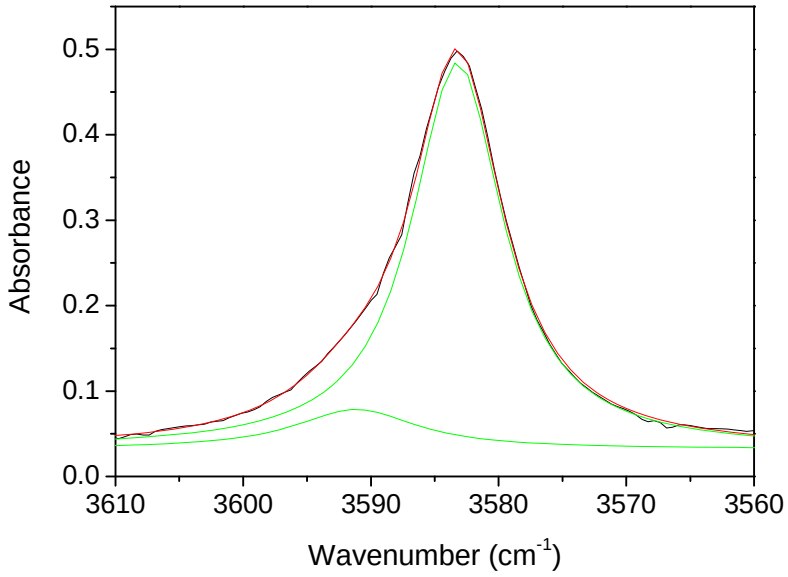
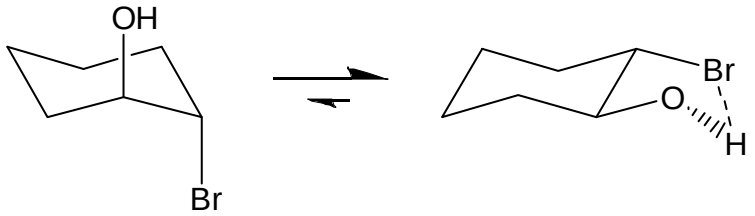


Figure SM 4.1.1.4.3. Expanded IR spectrum (in 0.02 cyclohexane solution) in the O-H stretching region. The bands were deconvoluted using a Lorentzian function (main results are given above). The bands are tighter and centered at higher wavenumbers than in the neat liquid due to the lack of intermolecular H-bond. The low intensity band at higher wavenumber (3591.2 cm^{-1}) corresponds to conformer diaxial, while the most intense band at 3583.2 cm^{-1} corresponds to the diequatorial conformer. The conformational preferences can be estimated by comparing the relative band intensities (9% diaxial and 91% diequatorial), and the diequatorial prevalence is due to the following intramolecular Br···HO hydrogen bond:



Synthesis of *trans*-cyclohexane-1,2-diol

Supplementary Material

This experiment has been performed since the 1960s by undergraduate second-year Chemistry students, and it is also appropriate for first year students since E1 elimination and *trans*-hydroxylation are reactions taught during the first semester of Organic Chemistry. They can explore the role of acids as catalysts in the conversion of alcohols in alkenes and realize that no nucleophilic substitution S_N1 can occur because there is not a nucleophile to attack the carbocation to lead substitution. In this experiment only one elimination product is possible. Starting from methylcyclohexanol for example, two alkenes products (regioisomers) can be obtained. The students can also compare anti hydroxylation with cis hydroxylation that can be accomplished using osmium tetroxide for example. This work combines several different unit operations, such as fractional, rotary evaporator and simple distillations, and liquid-liquid extractions. The instructor can decide to perform both steps on the classroom or choose one of them, depending on how much time is available. Dehydration of cyclohexanol to cyclohexane can be performed using phosphoric acid as catalyst[1]. Reaction scale could be reduced for a greener process using a small vigreux column.

Additional notes on the preparation of cyclohexene:

This reaction is reversible, so to drive the reaction forward, cyclohexene is removed continuously from the reaction mixture by fractional distillation (**Figure SM 4.1.1.5.1**) once it has a lower boiling point than cyclohexanol. This step takes at least 4 hours to complete. The oil baths should be heated initially to 160ºC and then the temperature should be lowered to 130-140ºC. The Vigreux columns used on this experiment were 50 cm tall (about 20 inches). The distillation is complete when there is roughly 4 mL of residue left. In the liquid-liquid extraction, the bottom layer is the aqueous. A saturated aqueous solution of NaCl (5 mL) can be used instead solid NaCl. Cyclohexene is purified by simple distillation; this step will be faster if an oil bath is used to heat the impure cyclohexene instead of a

water bath, despite the quite low boiling point of the product (81-83ºC[2]). For both distillation steps the receiving flask must be cooled in an ice/water bath because cyclohexene is very volatile.

Figure SM 4.1.1.5.1 – Fractional distillation apparatus.

It has a characteristic gas-like odor, which may alarm the students, so if possible the distillation should be carry out in the fume hood. According referee suggestion, this distillation can be carried out without Vigreux column with good results.

Average yield is 40-45%. The refractive index varies between 1.4425 and 1.4538, although most students obtained values between 1.4462 and 1.4468 (n_D=1.4465[2]).

Additional notes on the preparation of *trans*-cyclohexane-1,2-diol:

This step requires two sessions. Reaction apparatus for *trans*-cyclohexane-1,2-diol is shown in **Figure SM 4.1.1.5.2.** Temperature reaction is easily controlled and the cold water bath is rarely necessary. Cyclohexene should be added through a dropping funnel with pressure equalizer to minimize odor.

Figure SM 4.1.1.5.2 – Reaction set-up apparatus.

The peroxide test is always positive and so the reaction mixture is stirred with heating for 30 more minutes. Even after this time, the peroxide test remains positive and $FeSO_4$ must always be added to the reaction mixture. The distillation of water and formic acid with a rotary evaporator ends the first session. In the hydrolysis step warming can be extended for more than 15 min and may be followed by tlc. On the liquid-liquid extraction the aqueous layer is also on the bottom. The filtration step was skipped after removing the ethyl acetate on the rotary evaporator and the product was immediately recrystallized on the same flask, minimizing any losses. Alternatively, acetone can be used for

recrystallization. *Trans*-cyclohexane-1,2-diol is obtained with an average yield of 35-40%. Melting points are between 95 and 104ºC with a melting point range of 1-2ºC (lit.: 105ºC[2]).

IR spectra:

IR spectra of all products are available in the literature (Spectral Database for Organic Compounds, SDBS nº 569 for cyclohexene and nº 2416 for *trans*-cyclohexane-1,2-diol[3]). It is difficult to obtain the IR spectrum for cyclohexene due to its high volatility resulting in lower bands intensities. For that reason C=C absorption band at 1438 cm^{-1} is not visible. Nevertheless students easily identify in the **Figure SM 4.1.1.5.3** a strong band at 2930 cm^{-1} due to the aliphatic C-H absorption and at 3020 cm^{-1} for =C-H absorption.

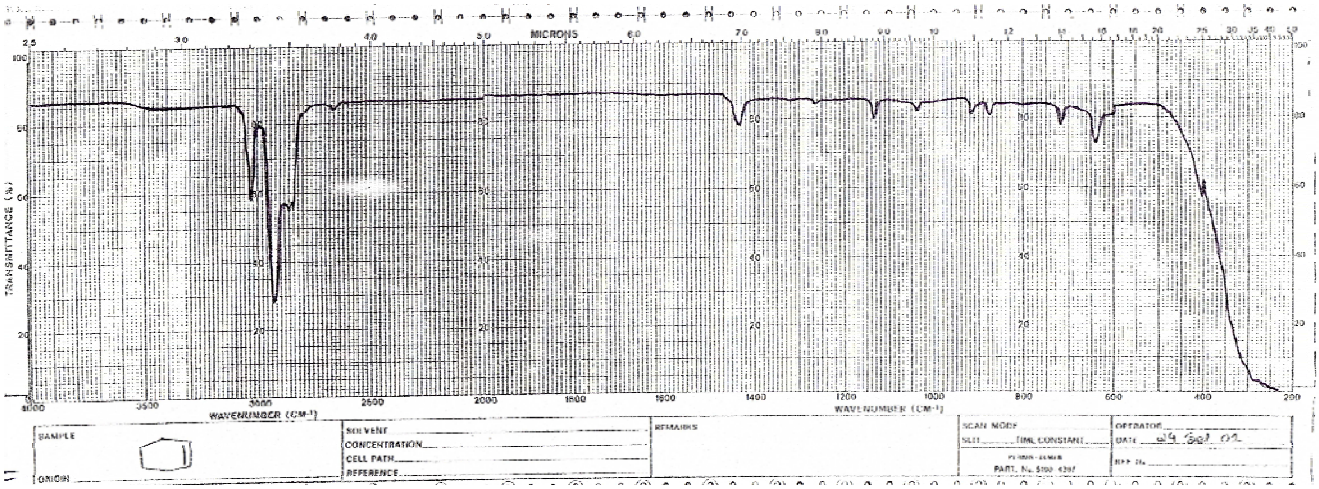


Figure SM 4.1.1.5.3: IR (liquid film) of cyclohexene

In the **Figure SM 4.1.1.5.4** is visible the strong O-H absorption band at 3100-3600 cm^{-1}.

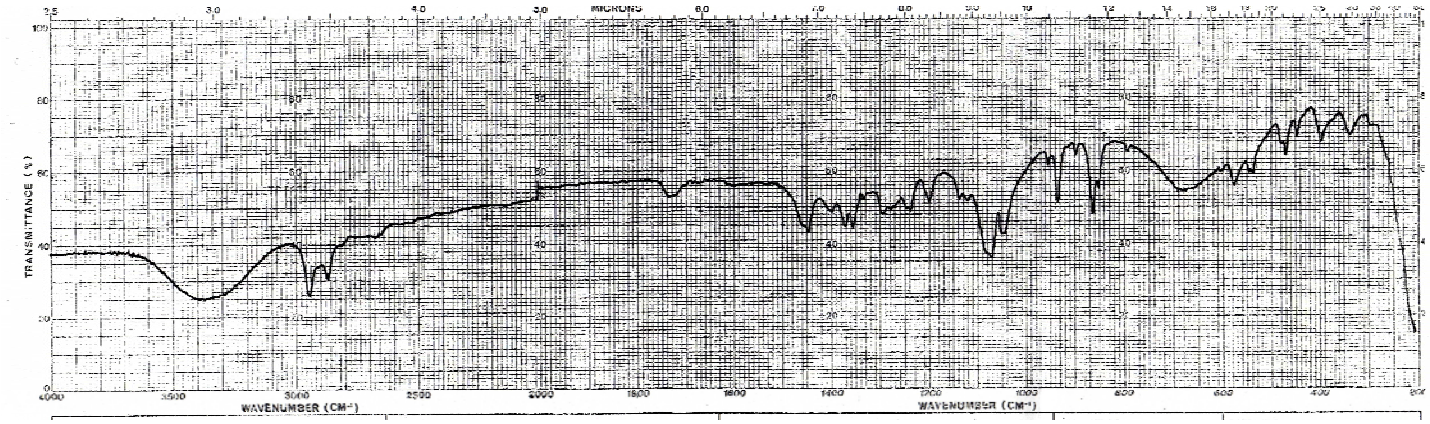


Figure SM 4.1.1.5.4: IR (KBr) of *trans*-cyclohexane-1,2-diol

^{1}H NMR spectrum

Students easily distinguish CH_2 protons from CH protons in **Figure SM 4.1.1.5.5** for cyclohexene.

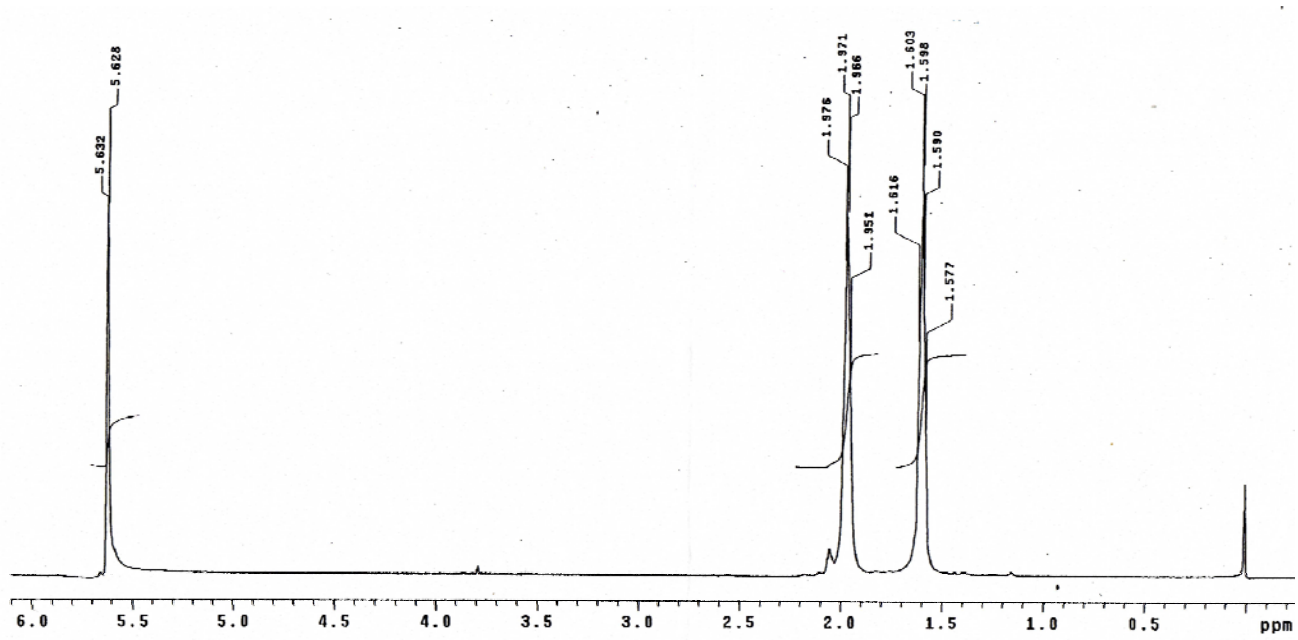


Figure SM 4.1.1.5.5: ^{1}H NMR ($CDCl_3$) of cyclohexene

The students analyzed the ^{1}H NMR spectrum of *trans*-cyclohexane-1,2-diol available in literature[3].

[1] Fieser, L. F.; Williamson, K. L. *Organic Experiments*, Houghton Mifflin Company: 8th ed., 1998, 235.
[2] R. Weast, *CRC Handbook of Chemistry and Physics*, 1st Student ed., 1988, C-230.
[3] URL: http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi, access in Sep 2015.

Synthesis of isobutylene and its use in esterification reactions

Supplementary Material

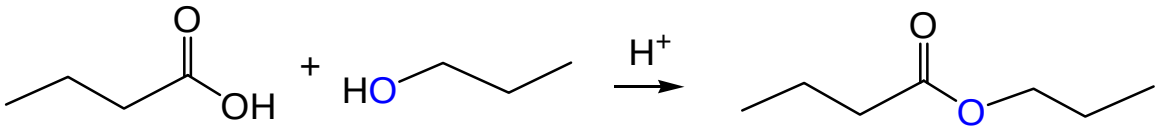
This experiment has been performed by students of the second year of the Biochemistry degree, in the course of Organic Chemistry (introduction level). Theoretical aspects of carbocation stability, alkene geometry, chemistry of the double bond, dehydration of alcohols and general principals of ester formation have been covered in class by the time this experiment is introduced. In previous lab sessions, student performed identification of alkenes by colorimetric tests based on addiction to the double bond and the (usual) synthesis of fruit aromas by Fischer esterification with primary and secondary alcohols, so the basic concepts have been discussed.

From the experimental point of view, the novelty is the manipulation of a reactant in the gas phase and its use *in situ*.

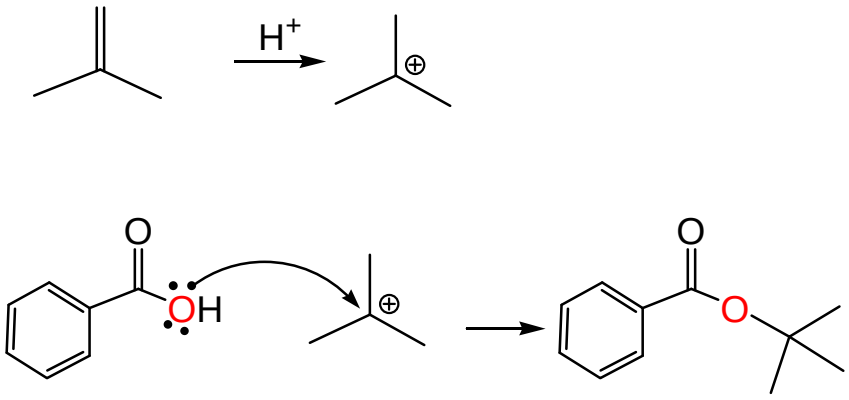
It can be used simply to illustrate the topic of alcohol elimination, instead of the more common cyclohexanol dehydration that requires a long, boring, reflux period (where on colorless liquid turns into another colorless liquid), or/and to introduce the discussion of heterogeneous *versus* homogeneous catalysis: it is possible to have groups using sulphuric acid as catalysts while others use oxalic acid; the latter is easily recovered (80% or more) and ready to reuse. Other heterogeneous catalysts can be evaluated and compared to oxalic acid.

The subsequent reaction that was chosen at this level was esterification of a carboxylic acid. Both benzoic and cinnamic acid are good choices.

During this step, isobutylene, generated in a separate apparatus, is again protonated by H_2SO_4 originating the tertiary carbocation (electrophile) which is then attacked by the oxygen of the carboxylic acid (nucleophile) in a different mechanism of the usual Fischer reaction, where the oxygen of the alcohol is the nucleophile.



Scheme SM 4.1.1.6.1. Acid-catalyzed Fischer esterification, involving primary (or secondary) alcohols. Notice that the oxygen atom of the ester originates from the **alcohol**, which is the nucleophile in this mechanism.



Scheme SM 4.1.1.6.2. Acid-catalyzed esterification, involving tertiary alcohols. Notice that the oxygen atom of the ester originates from the **carboxylic acid**, which is now the nucleophile.

On the first time this experiment was performed by our students, the setup was that described by Cunha *et al.* in Química Nova, 2003, 26(3) 425-427. The yields were very low (<30%) and, since then, we introduced several modifications to the protocol, mainly by sealing the connection between the gas producing system and the esterification vessel and keeping this at a low temperature all the time (see photos of experiment). A rubber stopper, suitable for the Erlenmeyer were the esterification was to occur, was bored to accommodate a glass Pasteur pipette, tightly fitting.

Some useful tips for better results:

- Use a new pipette, with a long tip and insert it the hole of the stopper while (or before) the oxalic acid/*tert*-butanol is being heated. Depending on the students´ dexterity, it may be better that this task is performed by the instructor or the lab technician to avoid nasty cuts.
- Clamp the piece by the stopper and insert the tip in a testing tube containing potassium permanganate solution. The first bubbles are just air being pushed out of the round bottom flask; after a few minutes, a brownish ring shows in the test tube: this is manganese oxide being formed and indicates that the gas bubbling in the tube is now the alkene. Using sodium carbonate solution to dissolve $KMnO_4$ can make this color change more evident, since in alkaline medium the manganese goes from oxidation state VII (purple) to IV (green) before forming Mn II (brown, insoluble). Bromine in water works just as well.
- When there is a regular production of gas bubbles and the reaction vessel is ready in its ice bath, clip the tip of the pipette so that is long enough to immerse in the reaction mixture when the stopper is firmly sealing the Erlenmeyer. This should be tested before starting the reactions. The stopper can be involved in parafilm. Regular stirring help gas dissolution and leads to better yields.

The longer the gas is allowed to bubble in the acid solution, the higher the yield will be. 2 hours will give about 30% conversion.

- Removing the pipette for storing between lab periods can be tricky since it is usually very tight. Taking off the stopper results in large losses of alkene; our solution was to remove the hose, leaving the pipette and close it with a piece of rolled up parafilm. The whole ensemble goes to the refrigerator.
- On the second session, it is important to cool down in an ice bath before opening the flask, since pressure can build up during storage.

The ester is easily obtained by liquid-liquid extraction as described. Care must be taken during the washing of the organic phase with sodium bicarbonate due to the presence of acid resulting in built up pressure and foaming. Phase separation is simple, although there is the need to dry the organic phase with Na_2SO_4.

The ester is obtained as a clear yellowish oil of low viscosity and good purity by removing the solvent in the rotavapor at 50ºC (benzoic acid as impurity could be detected in the NMR spectrum). Refractive index is 1.4900-1.4920, at 20ºC.

FTIR is a suitable technique to characterize the product, considering that its spectrum shows very clear changes from that of the parent acid (Figures SM 4.1.1.6.5 and SM 4.1.1.6.6, for benzoic and cinnamic products, respectively). Spectra of solid acids were obtained as KBr pellets and spectra of esters as thin films on KBr windows.

The main features are the disappearance of the complex bands in the region 3300-2500 cm^{-1} due to OH stretching and at 140 and 940 cm^{-1} (symmetric and asymmetric OH bending) of the acid and the shift from 1690 to 1725 cm^{-1} of the C=O stretching from acid to ester.

For students with more advanced knowledge on molecular spectroscopy techniques, NMR (both ^{1}H and ^{13}C) spectra can be obtained and discussed, as seen in Figures SM 4.1.1.6.7- SM 4.1.1.6.10.

When this experiment was performed by instructors, yields 60-65% were obtained. When performed by 2nd year students, the yields dropped to 35-55%. In lab classes, students also performed the recovery of unreacted benzoic acid and of catalyst, oxalic acid, by recrystallization.

Photos of experiment

Before

After

Figure SM 4.1.1.6.1 – Isobutylene set up, showing test tube before and after alkene bubbling

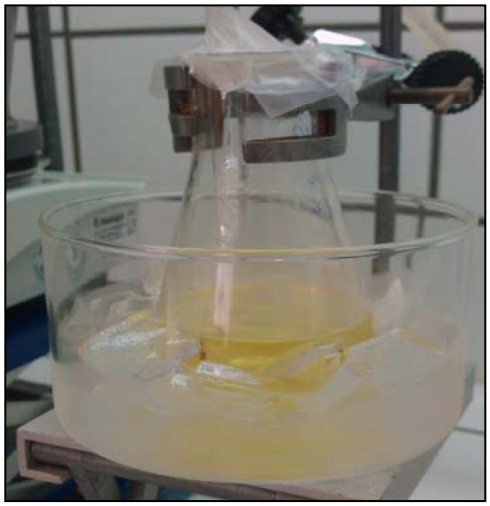


Figure SM 4.1.1.6.2 – Benzoic acid in dichloromethane and H_2SO_4

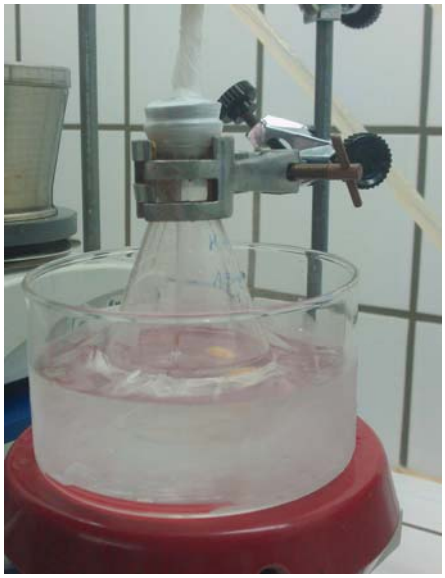


Figure SM 4.1.1.6.3 - Esterification in progress, pipette from isobutylene generation system inserted in acid mixture.

Figure SM 4.1.1.6.4 – Liquid-liquid extraction of ester, showing some emulsion in the organic phase. This clears up with the addition of sodium sulphate.

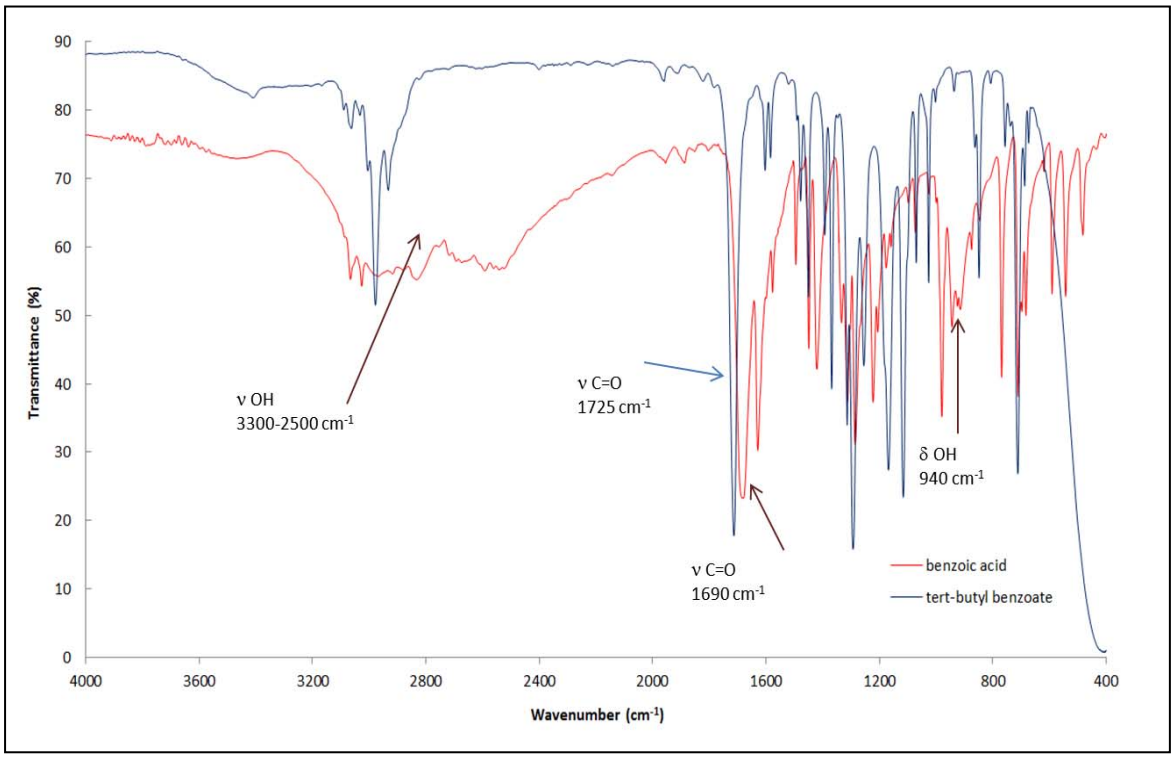


Figure SM 4.1.1.6.5 – FTIR spectra of benzoic acid (red) and tert-butyl benzoate (blue)

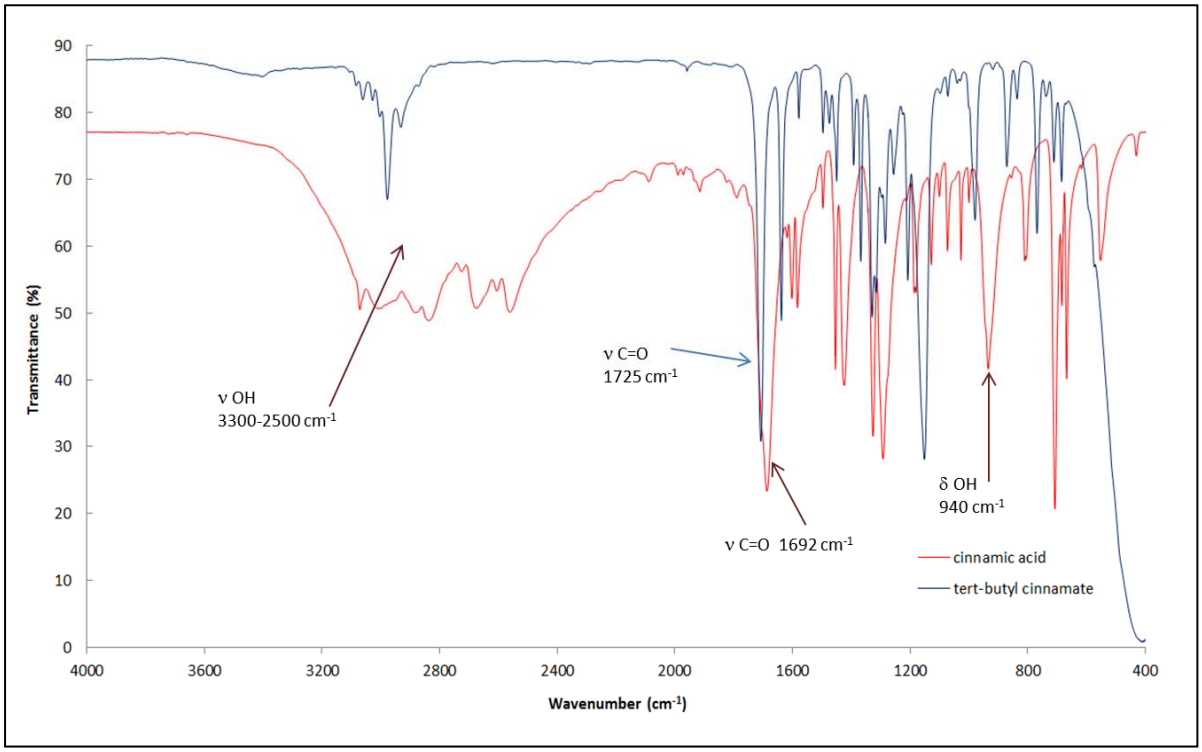


Figure SM 4.1.1.6.6 – FTIR spectra of cinnamic acid (red) and tert-butyl cinnamate (blue)

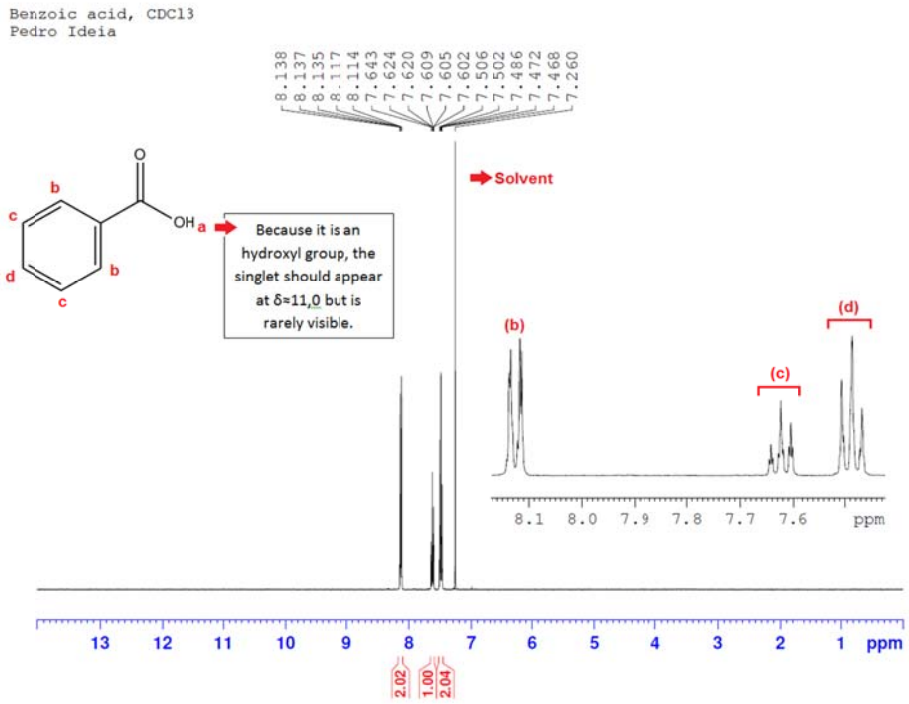


Figure SM 4.1.1.6.7 – ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of benzoic acid

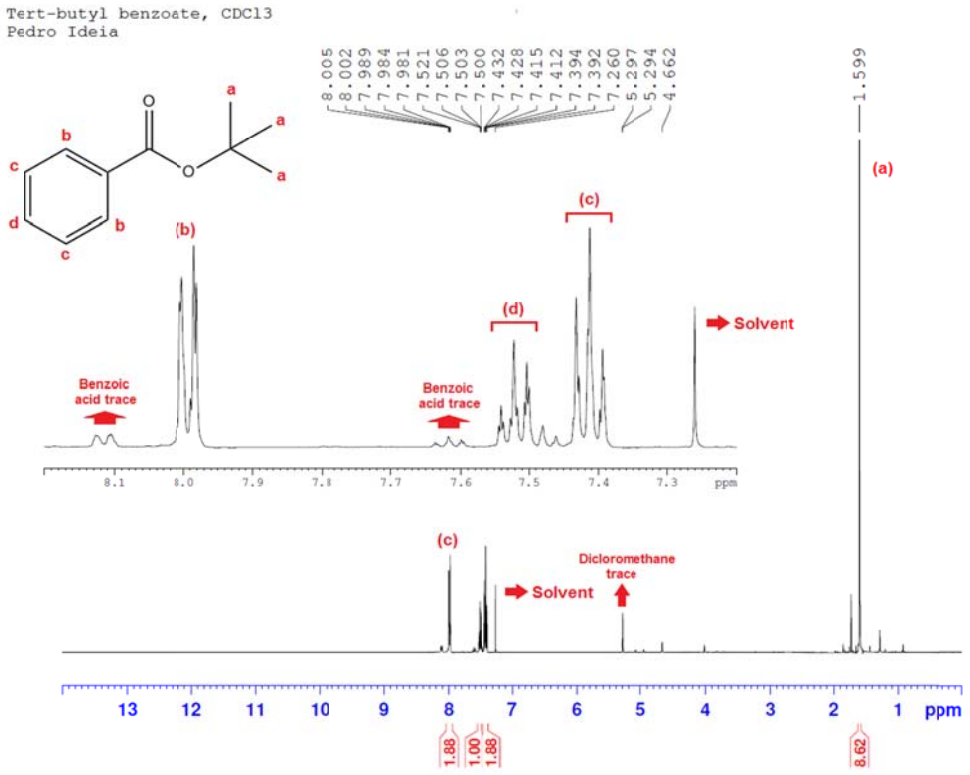


Figure SM 4.1.1.6.8 – ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of obtained tert-butyl benzoate

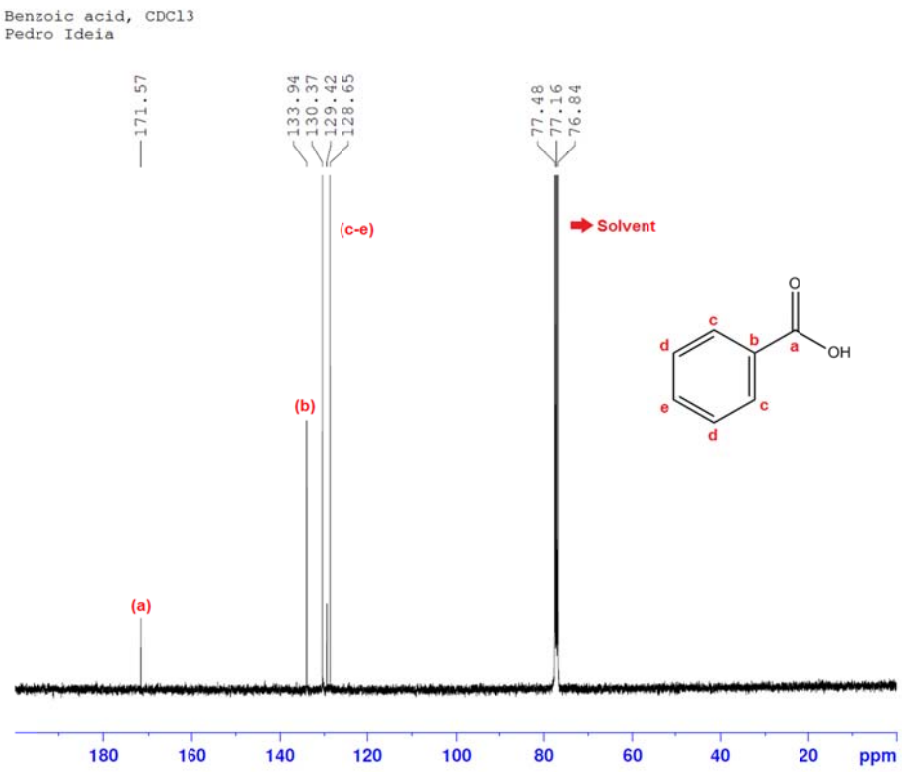


Figure SM 4.1.1.6.9 – ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of obtained benzoic acid

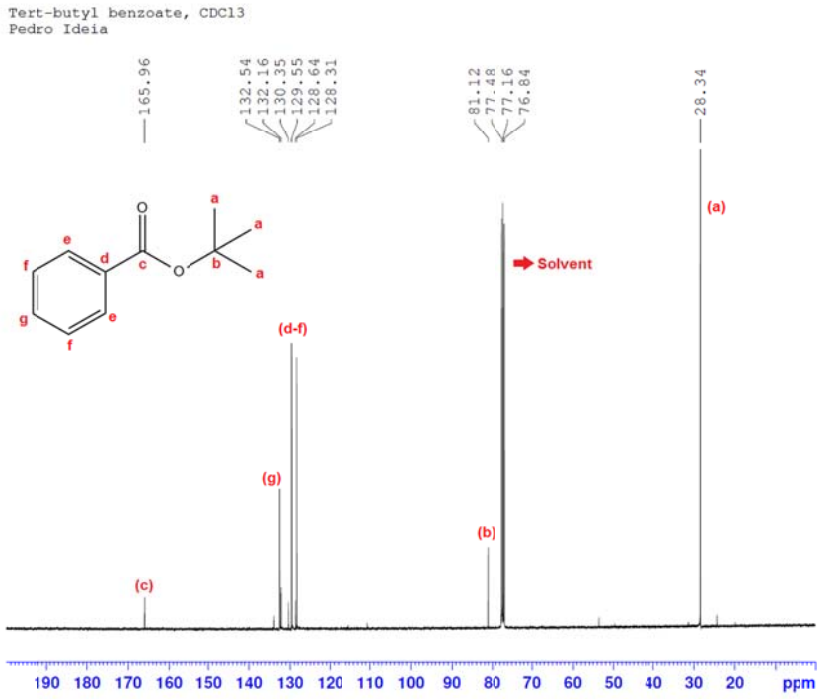


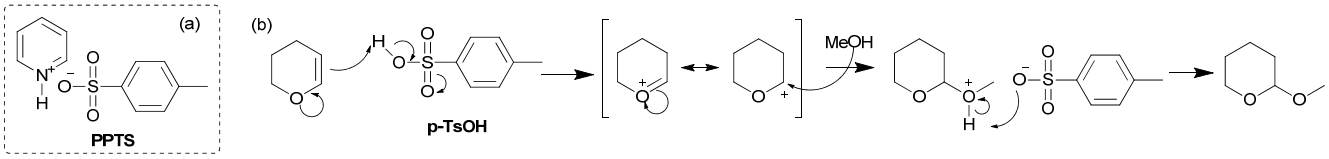
Figure SM 4.1.1.6.10 – ^{13}C NMR spectrum (400 MHz, $CDCl_3$) of obtained *tert*-butyl benzoate

Hydroxyl group protection *via* tetrahydropyranyl ether formation

Supplementary Material

Protecting groups play an important role in organic synthesis. This experiment aims the protection of hydroxyl group by tetrahydropyranyl ether formation. Among the various methods for protecting hydroxyl groups, the formation of tetrahydropyranyl ethers is one of the most widely used because of their easy formation and inertness to a range of reaction conditions.

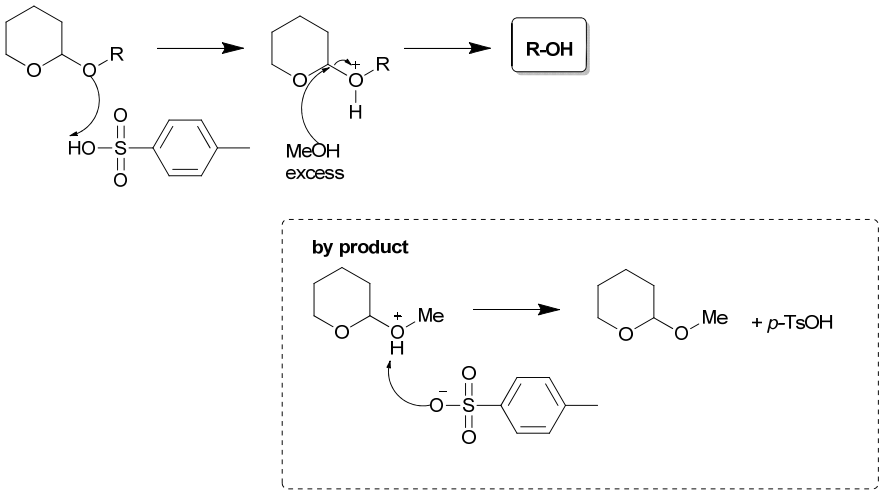
The mechanism of the tetrahydropyranyl ether formation (Scheme SM 4.1.1.7.1) is an acid-catalyzed addition of the alcohol to the double bond of the dihydropyran. Dihydropyran is especially reactive toward such an addition because the oxygen stabilize the carbocation that is initially produced in the reaction. In general, almost any acidic reagent or reagent that generates an acid in situ can be used to introduce the tetrahydropyranyl group.[1, 2] *p*-Toluenesulfonic acid (*p*-TsOH), (Scheme SM 4.1.1.7.1) and pyridinium *p*-toluenesulfonate (PPTS), a weakly acidic salt, are frequently used in this protection. The reaction mechanism of these acids is comparable, both protonate the dihydropyran, however in the PPTS case the proton comes from the pyridinium salt.



Scheme SM 4.1.1.7.1 – (a) Pyridinium *p*-toluenesulfonate structure. (b) Mechanism of the tetrahydropyranyl ether formation.

Most of the reported methods for tetrahydropyranyl ether formation use acidic reagents in an aprotic solvent, such as dichloromethane, tetrahydrofuran or toluene.1-Phenyl-cyclohexene may compete with dihydro-4H-pyran by reacting with the protic acid such as p-toluenesulfonic acid due to the formation of stable tertiary and benzylic carbocation. Additionally, acetic acid may compete with the alcohol by reacting with the carbocation derived from the protonation of dihydro-4H-pyran.

Although normal ethers are difficult to cleave, a tetrahydropyranyl ether is actually an acetal, and as such, it is cleaved under acidic conditions, such as *p*-toluenesulfonic acid, acetic acid, boric acid, etc. In this line, *p*-toluenesulfonic acid can be used as a promoter in tetrahydropyranyl ether formation and deprotection by using water or a simple alcohol such as methanol or ethanol as nucleophile for transacetalization (Scheme SM 4.1.1.7.2).



Scheme SM 4.1.1.7.2. – Mechanism of tetrahydropyranyl ether deprotection.

To understand the overall process is necessary to calculate atom economy and E factor. The E-factor is defined by the mass ratio of waste to desired product and is calculated by Equation SM 4.1.1.7.1.

$$\text{E factor} = \frac{\text{total of waste (g)}}{\text{total of product (g)}} \qquad \textbf{Equation SM 4.1.1.7.1.}$$

The atom economy is defined by the molecular mass ratio of desired product to all reactants and is calculated by Equation SM 4.1.1.7.2.

$$atom\ economy = \frac{\text{molecular mass of atoms of desired product}}{\text{molecular mass of atoms of all reactants}} \text{ x } 100\% \qquad \textbf{Equation SM 4.1.1.7.2.}$$

This experimental procedure has proved to be highly reproducible with yields within the 50% range. Those results were obtained by students conducting practical organic course during two consecutive semesters (aprox. 15 students/semester). Yields are lower than expected mainly due to losses that occurred during the distillation process, by the used of small scale glass material available in the teaching laboratories. The scale suggested in this work attempts to reconcile the minimization of the use of dihydro-4*H*-pyran with the need to have a sufficient amount of product to perform the distillation. The performance in a larger scale, would allow better yields.

The experimental procedure was developed in order to study the protection group concept, and the following aspects:

1) Hydroxyl group was used as a representative example of other functional groups and also because of its synthetic importance;

2) Tetrahydropyranyl ether formation was chosen because dihydro-4*H*-pyran is commercially available at a moderate price;
3) Although methanol is a poor example of alcohol from an educational point of view, its choice is due to the fact that other alcohols with longer chains could not be purified by distillation at atmospheric pressure and it is necessary to use distillation under reduced pressure or a chromatographic purification (more expensive).

In the case that these factors are not important, it will certainly be more interesting to exemplify this transformation with other natural substrates such as menthol, geraniol or cholesterol. Moreover geraniol and cholesterol allow further demonstration of the lack of reactivity of olefins under these experimental conditions.

Below is provided the observed ^{1}H NMR spectra of starting dihydro-4*H*-pyran (commercial sample) and the isolated product 2-methoxyhydropyran. The students can interpret those data and explore in more detail the conformational analysis by reading the reported literature.[3] In addition, the students can also analyze the infrared (IR) spectra of the isolated product 2-methoxyhydropyran and compare with the commercial materials methanol and dihydro-4*H*-pyran and the reported IR.

---

1. T. H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1999, 49-54.
2. J. M. Hornback, *Organic Chemistry*, Cengage Learning, 2005, 1011-1013.
3. R. J. Abraham, M. A. Warne and L. Griths, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1751-1757.

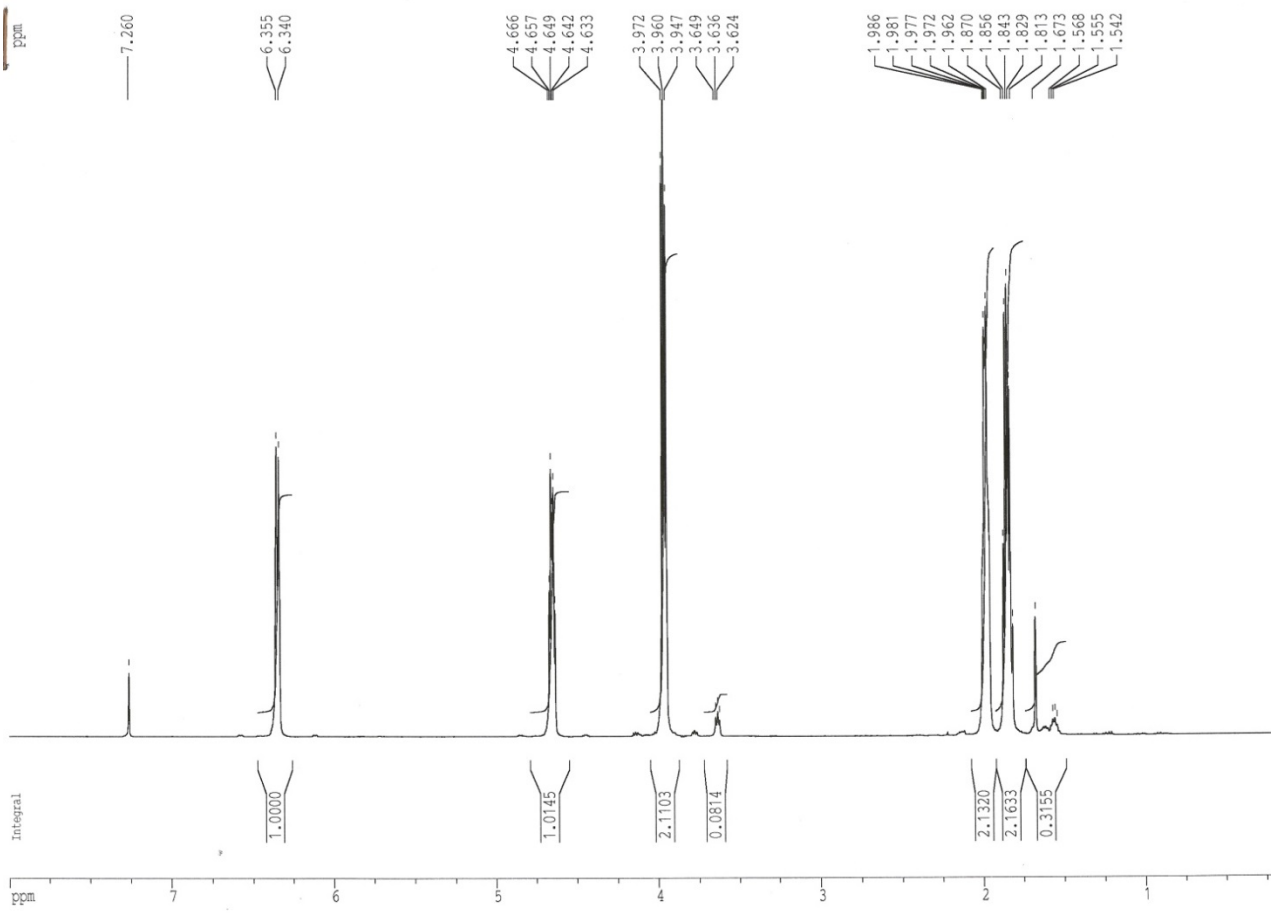


Figure SM 4.1.1.7.1 – ^{1}H NMR spectrum ($CDCl_3$) of dihydro-4*H*-pyran commercial available.

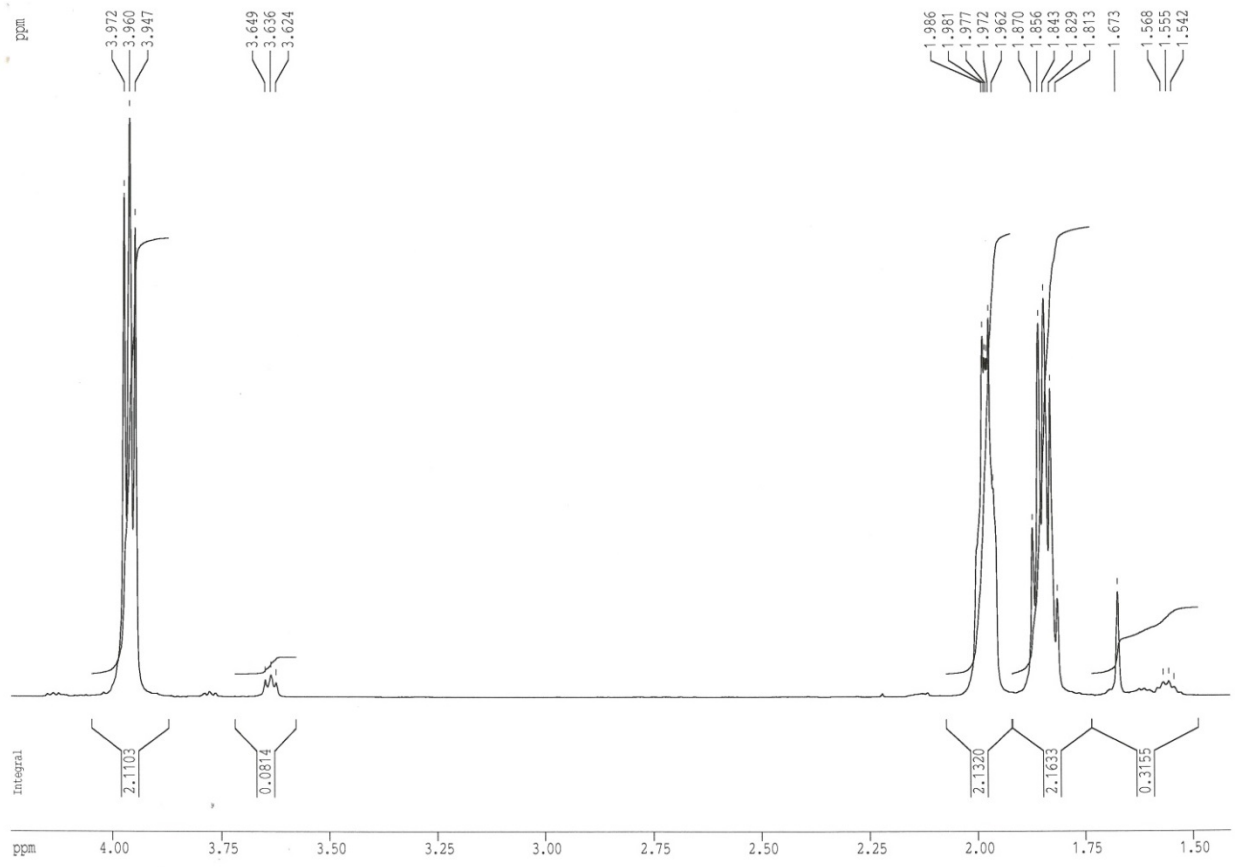


Figure SM 4.1.1.7.2 – Expansion of ^{1}H NMR spectrum ($CDCl_3$) of dihydro-4*H*-pyran commercial available.

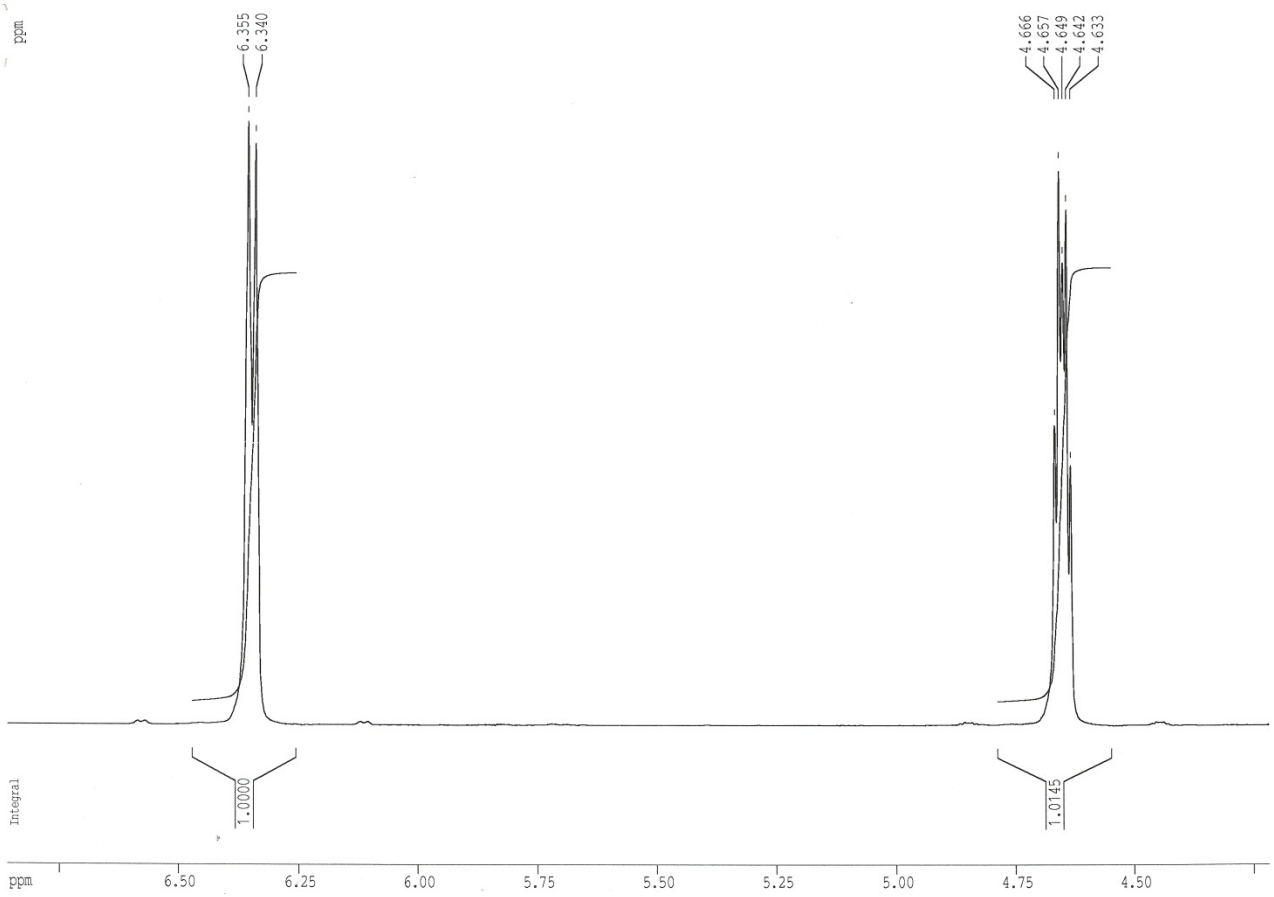


Figure SM 4.1.1.7.3 – Expansion of ^{1}H NMR spectrum ($CDCl_3$) of dihydro-4*H*-pyran commercial available.

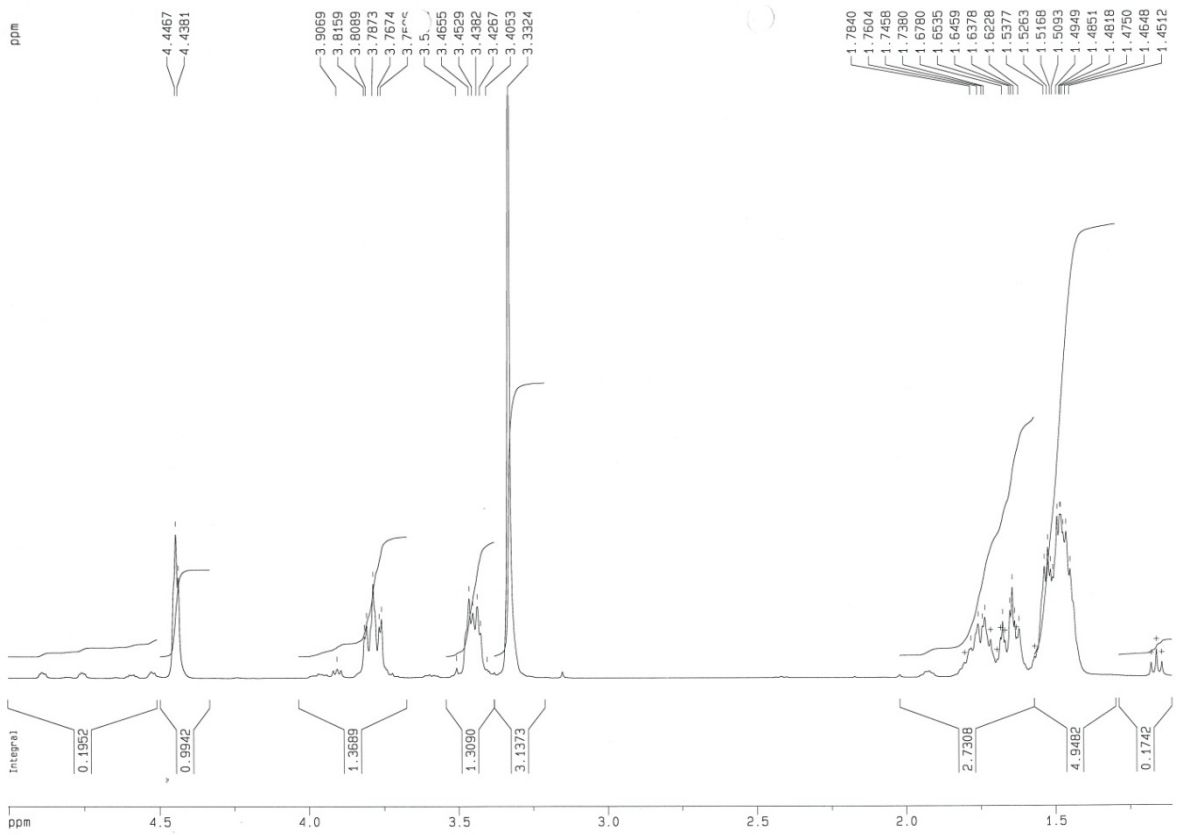


Figure SM 4.1.1.7.4 – ^{1}H NMR spectrum ($CDCl_3$) of the product of methanol protection obtained after distillation.

2-methoxytetrahydropyran IR: 2940, 1440, 1385, 1195, 1125, 1080, 1065, 1035, 955, 900, 875, 810 cm^{-1}.[4]

[4] P. J. Kropp, G. E. Fryxell, M. W. Tubergen, M. W. Hager, G. D. Harris, Jr., T. P. McDermott, Jr., and R. Tornero-Velez *J. Am. Chem. Soc.* **1991**, 113, 7300-7310.

Synthesis of (-)-Carvone from (+)-Limonene

Supplementary Material

Our experience shows that students tend to prefer laboratory works involving chemicals related to real life, and specifically products that are appealing to senses, like colorants with bright collors or fragrances. In this case, the laboratory work starts with the "citrus-smelling" (+)-limonene, extracted before from orange oil (see experiment 1.2), and results in (-)-carvone, the essence of spearmint. This experiment was performed for several years in our laboratory with students from the graduation in Chemistry and Chemical Engineering.

In the first step, the conversion of limonene to limonene nitrosochloride, mechanical stirring is more efficient than magnetic stirring, but complexity of the apparatus often limits the number devices to be used. In the absence of 4-neck flasks, a 3-neck round-bottomed flask can be used with a double-neck adapter. Alternatively, the second dropping funnel can be placed hanging on top of the reflux condenser, but without obstructing its end (it is important to remind the students that totally closed apparatus are dangerous). Average yields of limonene nitrosochloride are 20-26 g (50-56%). The product should be stored in a desiccator, and for long storage times a brown oily product starts forming, which should not be discarded, because its probably carvoxime. Although no further purification is needed, an analytical sample of limonene nitrosochloride may be obtained by recrystalization from ether (mp=111-112º C)[1]

The final washing of carvoxime (session 2) with isopropanol was eliminated from the original technique, since this strongly reduced the final yield of carvone. The average yield of carvoxime is 15-17 g (80-83%). Recrystalization of the product is not necessary, since the most probable contaminant is carvone. An analytical sample can be obtained by recrystalization from ethanol (mp=68-72º C).[1]

The use of a 10 % solution of oxalic acid in the hydrolysis of carvoxime to carvone improves the yield. Steam distillation can be stopped after collecting around 300 ml of water/carvone mixture. From this point on the distillate contains mostly water and carvacrol, which is always a by-product of the synthesis. Each group of students can perform the final fractional vacuum distillation, or alternatively, after weighting and measuring the refraction index (n_D= 1.4988 for pure (-)-carvone, the average yield is 8-10 g (60-65%)), the combined products of all groups can be distilled together. The boiling point of pure (-)-carvone at a given pressure can be obtained by the formula log P = - 2796/T_{eb} + 8.4782, where P is the pressure in mmHg and T_{eb} the boiling point in K.[2] Note the use of common logarithms (base 10). The specific rotation can be measured using a solution of 0.30 g of (-)-carvone in 50 ml of petroleum ether. The published value is $[\alpha]_D^{25}$= - 62.46º.[2] The residue of the distillation is mostly carvacrol, which can be obtained pure by combining the residues of all the groups and collecting the fraction that distils at 120-130º C (15

mm Hg). The boiling point of carvacrol can be obtained from log P = - 3008/T_{eb} + 8.7857.[2] Carvacrol raises the refraction index of Carvone, since pure carvacrol has n_D= 1.5230.[2]

Hints to the questions:

2) The electrophile part of the NO-Cl molecule is the NO group, and a formal addition of NO^+ to the double bond forms the most stable carbocation, i.e. the tertiary one. Addition of Cl^- to the carbocation affords the final product.

3) The endocyclic double bond is more substituted, and hence more stable.

4) The C=N double bond is conjugated with the carbon-carbon double bond, which increases the stability of this tautomer.

5) The optical rotation is an experimental quantity, there is no relation between an enantiomer being +/- and R/S.

Spectroscopic data:

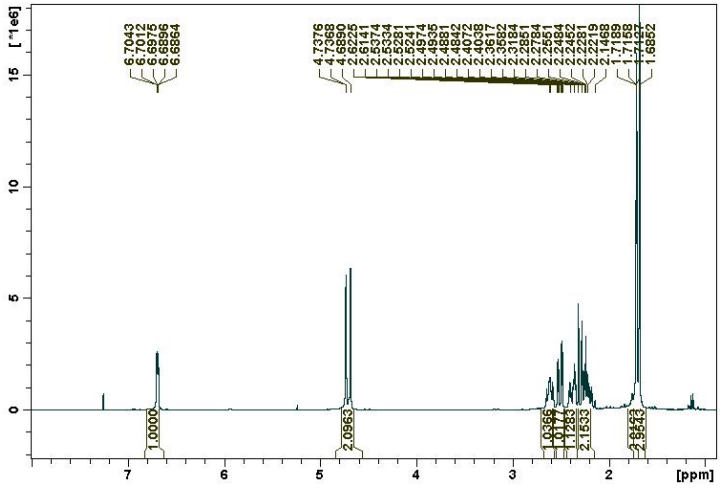


Figure SM 4.1.1.8.1 - ^{1}H RMN spectrum ($CDCl_3$) of (-)-Carvone

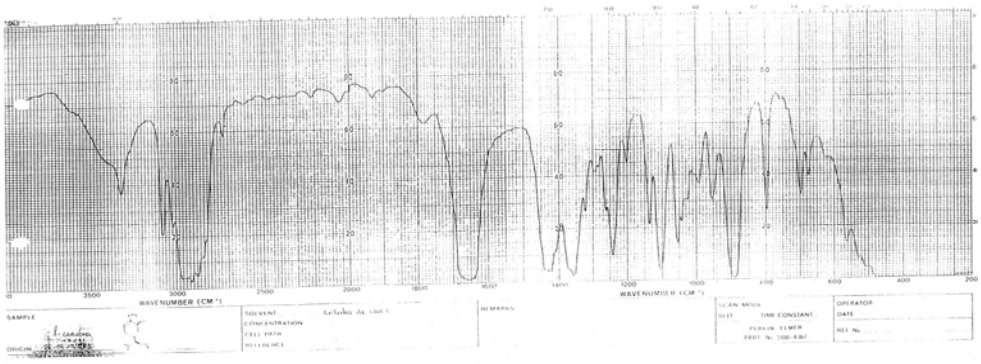


Figure SM 4.1.1.8.2 - IV spectrum (neat) of (-)-Carvone

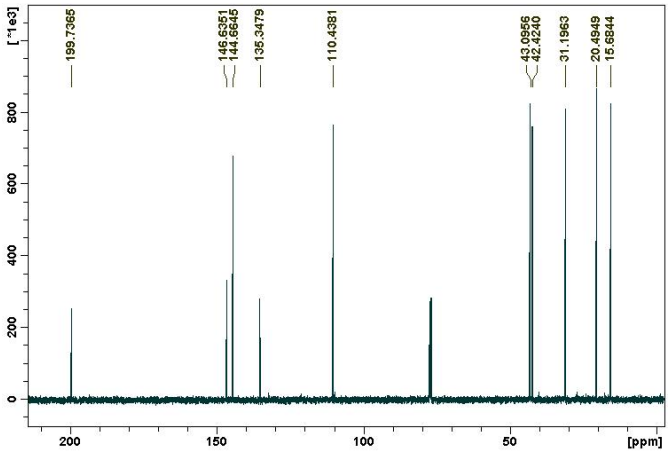


Figure SM 4.1.1.8.3 - ^{13}C RMN spectrum ($CDCl_3$) of (-)-Carvone

[1] O. S. Rothenberger, S. B. Krasnof, R. B. Rollins, *J. Chem. Ed.*, 1980, **57**, 741.
[2] R. Weast, CRC Handbook of Chemistry and Physics, 1st Student Ed. **1988** Florida.

Glycal transformation into surfactant 2-deoxy glycosides

Supplementary Material

Educational context

The goal of this experiment is to demonstrate the usefulness of carbohydrate chemistry for the generation of innovative structures with application in the medicinal chemistry field. In particular, the relevance of 1,2-unsaturated sugars as building blocks is highlighted. The full protocol was reproduced by 1st year Chemistry MSc students from Faculty of Sciences, University of Lisbon. The proposed experiment, and respective discussion, was conceived for a group of students with some theoretical background and experience working in an organic chemistry laboratory. This set of experiments can also be applied to a small project, when extended to other fatty alcohols. The need for a column chromatography to isolate major compounds from a reaction mixture with more than one impurity/secondary product, some of them with very close retention factors (R_f), offers students a valuable experience in advanced methodologies typical of a research unit daily basis.

Experiment Notes

- *Synthesis of* dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside

Reaction of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol with dodecanol in the presence of TPHB reaches total completion of the starting material after 2 h, when conducted at 40 ºC. The course of the reaction can be controlled by thin layer chromatography, eluted with cyclohexane (CyHex)/EtOAc 3:1. Although the reaction is highly stereoselective towards the dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside (**2**) due to the anomeric effect, formation of the β-anomer is also detected (**Figures SM 4.1.1.9.1 and SM 4.1.1.9.2**). Moreover, concomitant Ferrier rearrangement occurs, and traces of the 2,3-unsaturated glycoside can also be detected (**Figure SM 4.1.1.9.3**). Glycal hydrolysis can take place under poor anhydrous conditions, detected by vestigial TLC spots below the starting material. TLC of the glycosylation reaction is schematized in **Figure SM 4.1.1.9.4**.

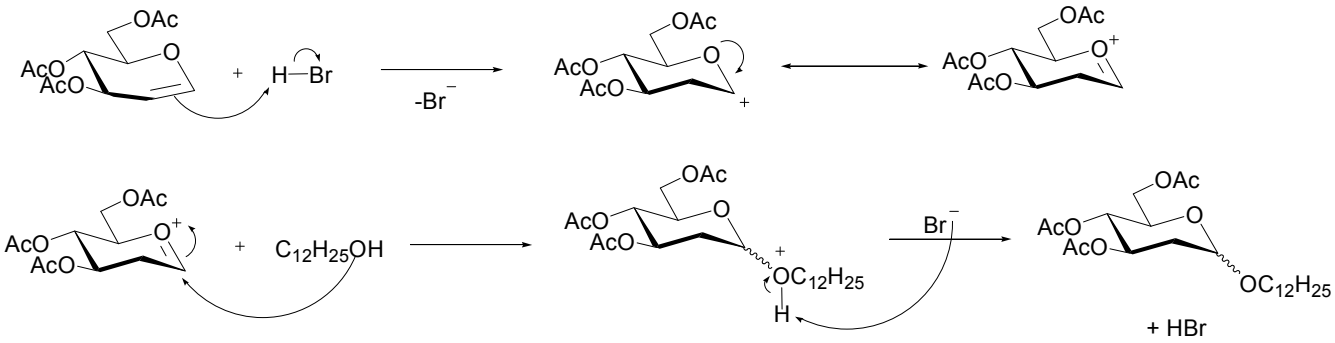


Figure SM 4.1.1.9.1. Mechanism of the glycosylation reaction catalyzed by acid.

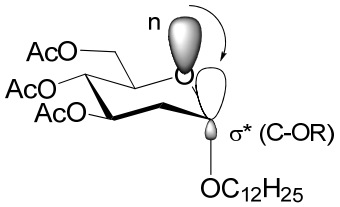


Figure SM 4.1.1.9.2. Anomeric effect. The lone pair of electrons of the anomeric centre is anti-periplanar to the C-X bond, favouring the formation of the α anomer.

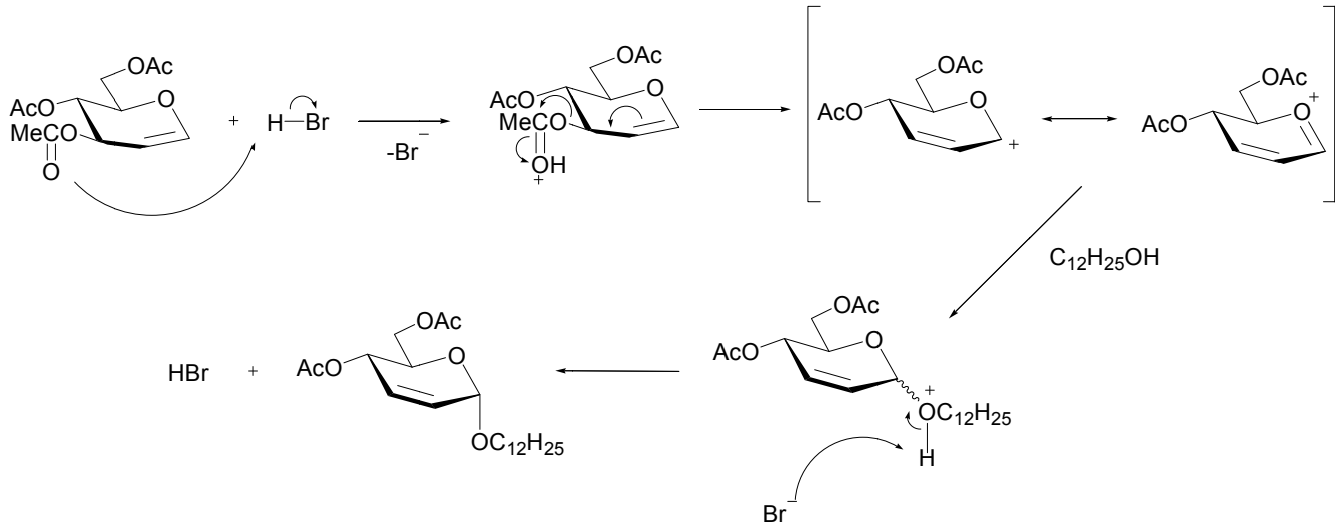


Figure SM 4.1.1.9.3. Mechanism of Ferrier rearrangement, catalysed by acid.

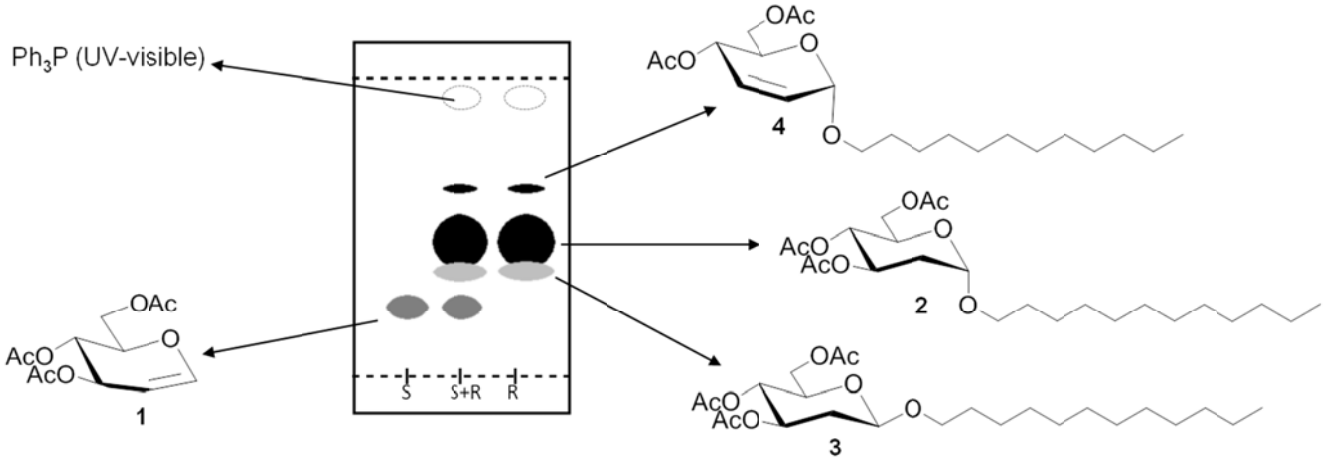


Figure SM 4.1.1.9.4 – Schematic TLC of the glycosylation reaction (R) with emphasis on starting material (i) and products structures (CyHex/EtOAc 3:1)

An efficient temperature control is important, as higher temperatures promote both Ferrier rearrangement and hydrolysis, and lower temperature results in longer reaction times.

Column chromatography is the most suitable method to isolate the compounds illustrated above. This can be accomplished using a column with 3 cm width packed with of silica gel 60 Å (0.040-0.630 mm) up to 12 cm height, eluted with CyHex/EtOAc 15:1 (**Figure SM 4.1.1.9.5**). After work-up, reaction

mixture is diluted in CyHex/EtOAc 15:1 (3 mL), with a few drops of dichloromethane (less than 1 mL), to ensure complete dissolution. Running the column under low pressure is highly recommended. After discharging ca. 80 mL (which will include the eluted triphenylphosphane), column fractions can be collected in 10 mL vials. Representative TLC plates for detection of the fraction composition are shown below (**Figure SM 4.1.1.9.6**).

Figure SM 4.1.1.9.5 – Column chromatography performed under external pressure applied by compressed N_2.

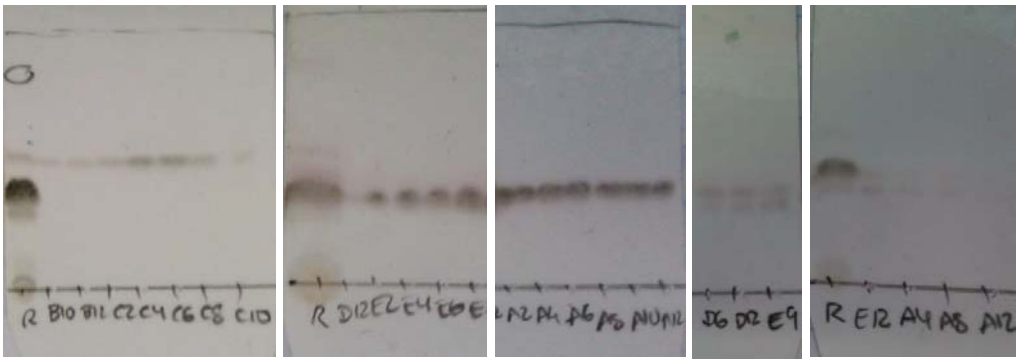


Figure SM 4.1.1.9.6 - Representative TLC plates of the column chromatography eluted fractions.

The first compound to be eluted is the Ferrier rearrangement product, the dodecyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**4**), which can be isolated in yields ranging from 5-7% (see NMR spectra in **Figures SM 4.1.1.9.14** and **SM 4.1.1.9.15**). Although dodecanol is not shown in **Figure SM 4.1.1.9.4**, it is eluted immediately after compound **4** and before the major compound, staining pink only after prolonged heating. Dodecanol is used in this reaction in a slight excess (1.05 equiv.) to overcome further isolation challenges. Hence, the use of a higher stoichiometric ratio of dodecanol is not recommended.

Prior to complete elution of dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside (**2**), fractions containing this compound start to be contaminated with the β-anomer 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside (**3**). Students can then run the column with a more polar eluent e.g. CyHex/EtOAc 10:1, to completely elute the α/β-anomeric mixture from the column. While the α-glycoside is isolated with this separation process, isolation of the β-anomer would only be possible running a second column chromatography with different eluent systems. The anomeric ratio of the mixture can be determined from the integration of the well resolved ^{1}H NMR signals of each anomer, namely H-1α and H-1β (**Figure SM 4.1.1.9.13**). For complete NMR spectra signal assignment for both anomers see **Figures SM 4.1.1.9.9** to **SM 4.1.1.9.12**. Students will be able to isolate the pure α-anomer in yields ranging from 45% to 50 %, and the anomeric mixture in yields (α/β between 3:1 and 2:1) from 25% to 30%. All compounds are isolated as colourless oils (**Figure SM 4.1.1.9.7**).

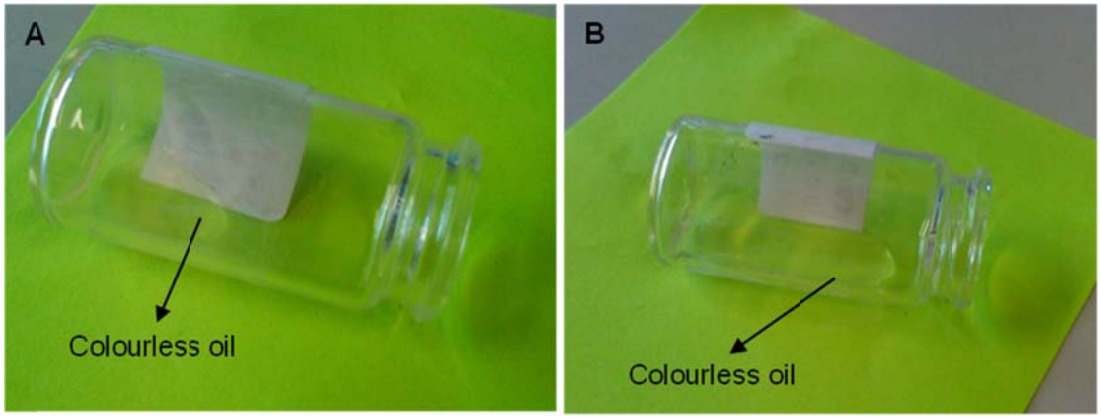


Figure SM 4.1.1.9.7 – A: Dodecyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**4**); B: dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside (**2**).

- *Synthesis of dodecyl 2-deoxy-α-D-arabino-hexopyranoside*

The efficient removal of the *O*-acetyl protecting groups can be carried out by Zemplén deacetylation, a classic methodology employing the use of a catalytic amount of sodium methoxide in methanol, at room temperature. The NaOMe suspension in methanol must be freshly prepared. The deprotection occurs straightforwardly and complete consumption of the starting material can be detected by TLC eluted with CyHex/EtOAc 1:1. The reaction can be quenched by adding acid resin, namely Amberlite (IR-120, H^+ form), previously washed with methanol. Solution pH should be controlled by a pH test paper, until complete neutralization. While neutralizing, the stir should be gentle to avoid breaking any resin beads. After filtration and evaporation, the product can be isolated in quantitative yield by silica-gel column chromatography, eluted with ethyl acetate. Nevertheless residue recrystallization from ethyl acetate/*n*-hexane 3:1 affords the pure product in 85-86% yield (**Figure SM 4.1.1.9.8**). In the experimental section it is suggested that students take the white solid to a high vacuum line before measuring the melting point, because time constrains make it impossible to keep it overnight in a vacuum desiccator containing desiccant and shredded paraffin wax for solvent

adsorption. For complete NMR signal assignment for compound **5**, see **Figures SM 4.1.1.9.16** and **SM 4.1.1.9.17**.

Figure SM 4.1.1.9.8 – Recrystalization of dodecyl 2-deoxy-α-D-*arabino*-hexopyranoside (**5**), from ethyl acetate/ *n*-hexane.

Physical and spectroscopic characterization of compounds:

Dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside (2): $[\alpha]_D^{20}$ +66 (*c* 1, CH_2Cl_2); R_f 0.58 (EtOAc/CyHex 1:3); IR (neat): 1748 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) *δ* 5.33 (ddd, 1H, $J_{3,2a}$ 11.9 Hz, $J_{3,2e}$ 5.5 Hz, $J_{3,4}$ 9.8 Hz, H-3), 5.00 (t, 1H, $J_{4,5}$ 10.0 Hz, H-4), 4.94 (d, 1H, $J_{1,2a}$ 3.1 Hz, H-1), 4.32 (dd, 1H, $J_{6a,5}$ 4.7 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.06 (dd, 1H, $J_{6b,5}$ 2.2 Hz, H-6b), 3.97 (ddd, 1H, $J_{5,4}$ = 10.0 Hz, H-5), 3.62 (dt, 1H, $J_{1'a,1'b}$ 9.4 Hz, $J_{1'a,2'}$ 6.2 Hz, H-1'a), 3.38 (dt, 1H, $J_{1'b,2'a,b}$ 6.2 Hz, H-1'b), 2.24 (dd, 1H, $J_{2e,2a}$ 12.9 Hz, $J_{2e,3}$ 5.7 Hz, H-2e), 2.10 (s, 3H, CH_3-Ac), 2.05 (s, 3H, CH_3-Ac), 2.02 (s, 3H, CH_3-Ac), 1.83 (td, 1H, H-2a), 1.63-1.53 (m, 2H, H- 2'a,b), 1.37-1.22 (m, 18H, H-3'- H-11'), 0.89 (t, 3H, $J_{12',11'}$ 7.1 Hz, H-12'); ^{13}C NMR ($CDCl_3$) *δ* 170.8 (C=O), 170.2 (C=O), 170.0 (C=O), 96.9 (C-1), 69.5 (C-4), 69.2 (C-3), 67.9 (C-1'), 67.7 (C-5), 62.4 (C-6), 35.1 (C-2), 31.9, 29.7, 29.6, 29.5, 29.4, 29.3 26.2, 22.7 (C-2'-C-11'), 21.0, 20.8, 20.7 (CH_3-Ac), 14.1 (C-12'). Anal. Calcd for $C_{24}H_{42}O_8$: C, 62.86; H, 9.23. Found: C, 63.20; H, 9.50.

Dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside (3): $[\alpha]_D^{20}$ -19 (*c* 1, CH_2Cl_2); R_f 0.47 (EtOAc/CyHex 1:3); IR (neat): 1748 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) *δ* 5.03-4.99 (m, 2H, H-3, H-4), 4.56 (dd, 1H, $J_{1,2a}$ 9.7 Hz, $J_{1,2e}$ 2.0 Hz, H-1), 4.30 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, $J_{5,6a}$ 5.0 Hz, H-6a), 4.11 (dd, 1H, $J_{6b,5}$ 2.5 Hz, H-6b), 3.87 (td, 1H, $J_{1'a,1'b}$ 9.6 Hz, $J_{1'a,2'a,b}$ 6.3 Hz, H-1'a), 3.60 (ddd, 1H, $J_{4,5}$ = 9.4 Hz, H-5), 3.46 (ddd, 1H, H-1'b), 2.32 (ddd, 1H, $J_{2e,3}$ 4.4 Hz, $J_{2a,2e}$ 12.4 Hz, H-2e), 2.10 (s, 3H, CH_3-Ac), 2.05 (s, 3H,CH_3-Ac), 2.02 (s, 3H, CH_3-Ac), 1.75 (ddd, 1H, $J_{2a,3}$ 10.0 Hz, H-2a), 1.63-1.53 (m, 2H, H-2'a,b), 1.33-1.22 (m, 18H, H-3'a,b-H-11'a,b), 0.84 (t, 3H, $J_{11',12'}$ 6.4 Hz, H-12'); ^{13}C NMR ($CDCl_3$) *δ* 99.6 (C-1), 71.9 (C-5), 71.0 (C-3), 70.8 (C-1'), 70.0 (C-4), 62.5 (C-6), 36.3 (C-2), 31.9, 29.7, 29.6, 29.5, 29.4, 26.0, 22.7 (C-2'- C-11'), 20.9, 20.8 (CH_3-Ac), 14.1 (C-12'). Anal. Calcd for $C_{24}H_{42}O_8$: C, 62.86; H, 9.23. Found: C, 63.20; H, 9.40.

Dodecyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (4): $[\alpha]_D^{20}$ +48 (*c* 1, CH_2Cl_2); R_f 0.71 (EtOAc/CyHex 1:3); IR (neat): 1757 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) *δ* 5.90 – 5.79 (m, 2H, H-2, H-3), 5.30 (br d, 1H, $J_{4,5}$= 9.7 Hz, H-4), 4.95 (br s, 1H, H-1), 4.28, 4.27, 4.25, 4.24 (Part AX of ABX system, 1H, $J_{6a,6b}$ = 12.1 Hz, $J_{6a,5}$ = 5.3 Hz, H-6a), 4.19, 4.16 (Part B of ABX system, 1H, $J_{5,6b}$ = 1.8 Hz, H-6b), 4.11 (ddd, 1H, H-5), 3.77 (dq, 1H, $J_{1'a,1'b}$ = 9.4 Hz, $J_{1'a,2'a,b}$ = 6.8 Hz, H-1'a), 3.50 (dq, 1H, $J_{1'b,2'a,b}$ = 6.6 Hz, H-1'b), 2.10 (s, 3H, CH_3-Ac), 2.09 (s, 3H, CH_3-Ac), 1.66–1.54 (m, 2H, H-2'a,b), 1.35–1.24 (m, 18H, H-3'a,b to H-11'a,b), 0.88 (t, 3H, $J_{11',12'}$= 7.1 Hz, H-12'); ^{13}C NMR ($CDCl_3$) *δ* 170.7 (C=O), 170.2 (C=O), 128.9, 127.9 (C-2, C-3), 94.3 (C-1), 68.9 (C-1'), 66.8 (C-5), 65.2 (C-4), 63.0 (C-6), 29.7 (C-2´), 31.8, 29.6, 29.6, 29.5, 29.4, 29.3, 26.2, 22.6 (C-3´-C-11'), 20.9, 20.7 (CH_3-Ac), 14.1 (C-12'). Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61. Found: C, 66.00; H, 9.90.

Dodecyl 2-deoxy-α-D-*arabino*-hexopyranoside (5). mp 113.9-115.5 ºC (EtOAc/*n*-hexane); mp by DSC 114.8 ºC; $[\alpha]_D^{20}$ +64 (*c* 1, MeOH); R_f 0.48 (EtOAc); IR (neat): 3354 cm^{-1} (C-OH); ^1H NMR (CD_3OD) *δ* 4.90 (d, 1H, $J_{1,2a}$ 2.8 Hz, H-1), 3.90-3.81 (m, 2H, H-3, H-6a), 3.75-3.67 (m, 2H, H-6b, H-1'a), 3.55 (ddd, 1H, $J_{5,4}$ 9.2 Hz, $J_{5,6a}$ 2.0 Hz, $J_{5,6b}$ 5.3 Hz, H-5), 3.38 (dt, 1H, $J_{1'b,2'a}$ = $J_{1'b,2'b}$ 6.3 Hz, $J_{1'b,1'a}$

9.8 Hz, H-1'b), 3.26 (t, 1H, $J_{4,3}$= $J_{4,5}$ =9.2 Hz, H-4), 2.07 (dd, 1H, $J_{2e,2a}$ 12.8 Hz, $J_{2e,3}$ 5.2 Hz, H-2e), 1.67–1.54 (m, 3H, H-2a, H-2'a, H-2'b), 1.45–1.26 (m, 18H, H-3'a,b-H-11'a,b), 0.93 (t, 3H, $J_{11',12'}$ 6.5 Hz, H-12'); ^{13}C NMR (CD_3OD) δ 99.4 (C-1), 74.8 (C-4), 74.2 (C-5), 70.9 (C-3), 69.1 (C-1'), 63.7 (C-6), 39.8 (C-2), 34.0, 31.7, 31.6, 31.6, 31.5, 31.4, 28.3, 24.6 (C-2'-C-11'), 15.3 (C-12'). Anal. Calcd for $C_{14}H_{36}O_5$: C, 65.03; H, 10.91. Found: C, 65.10; H, 11.20.

NMR Spectra

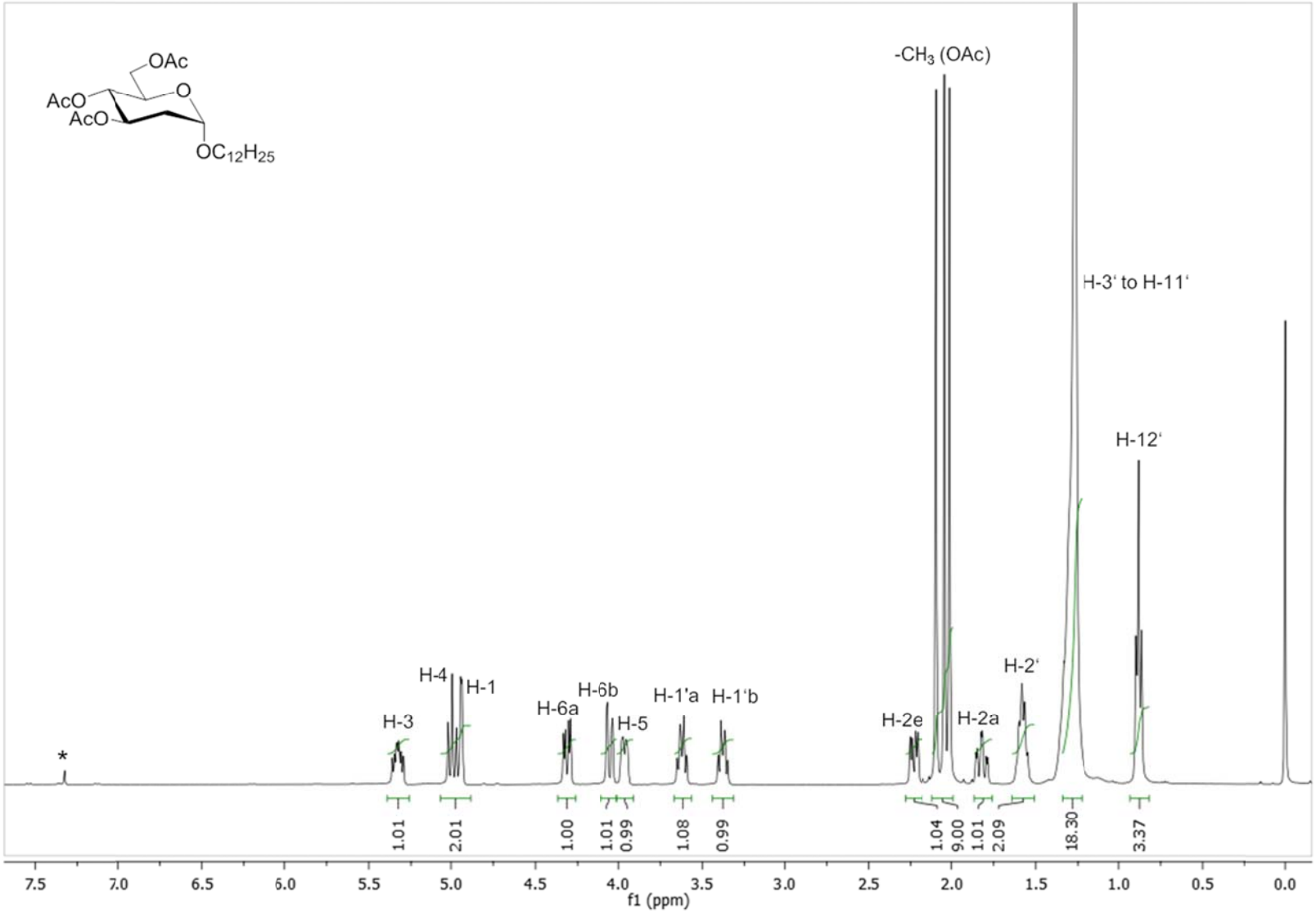


Figure SM 4.1.1.9.9 - ^{1}H NMR spectrum of dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside (**2**), in $CDCl_3$. *Solvent residual peak.

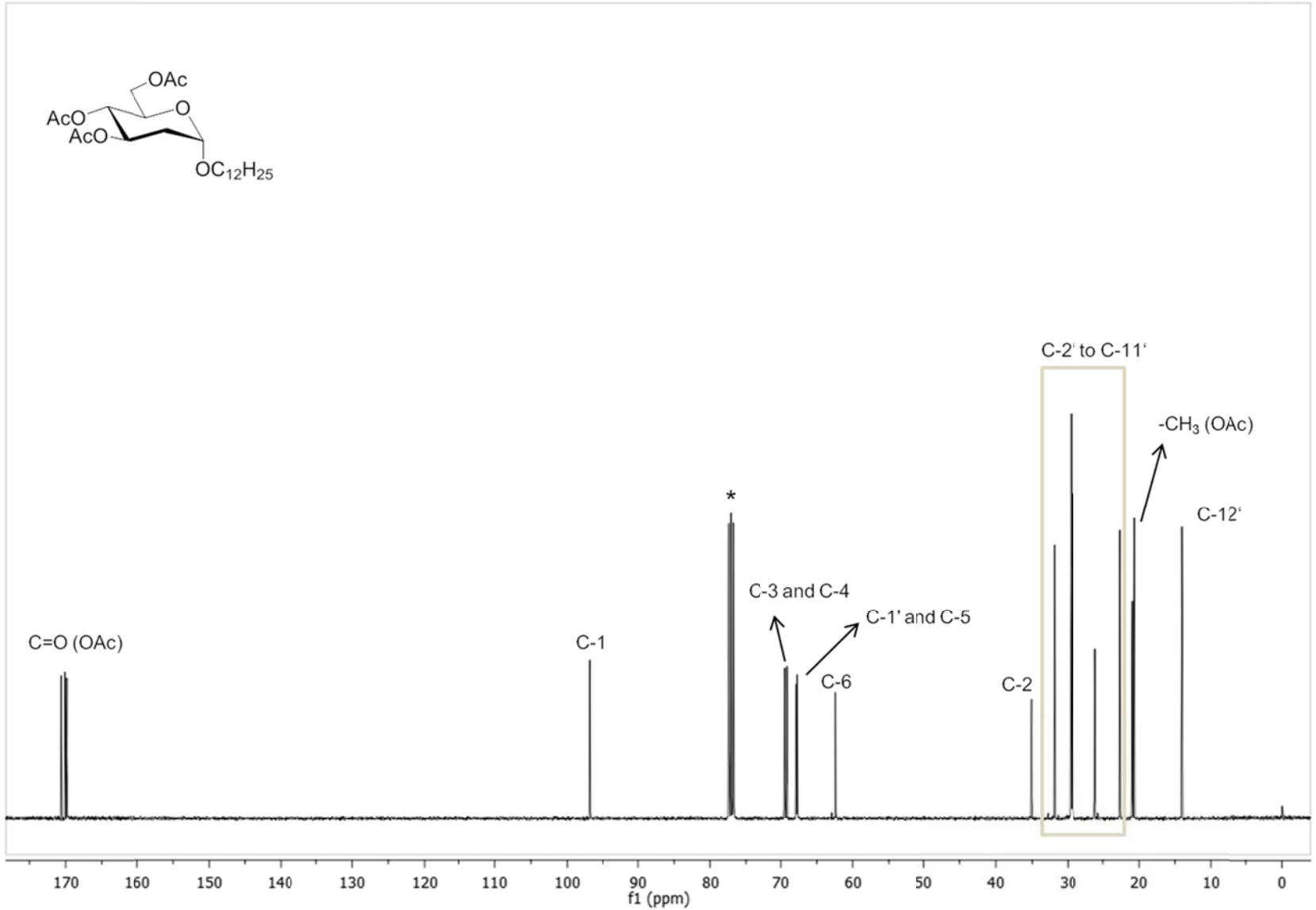


Figure SM 4.1.1.9.10 - ^{13}C NMR spectrum of dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranoside (**2**), in $CDCl_3$. *Solvent peak.

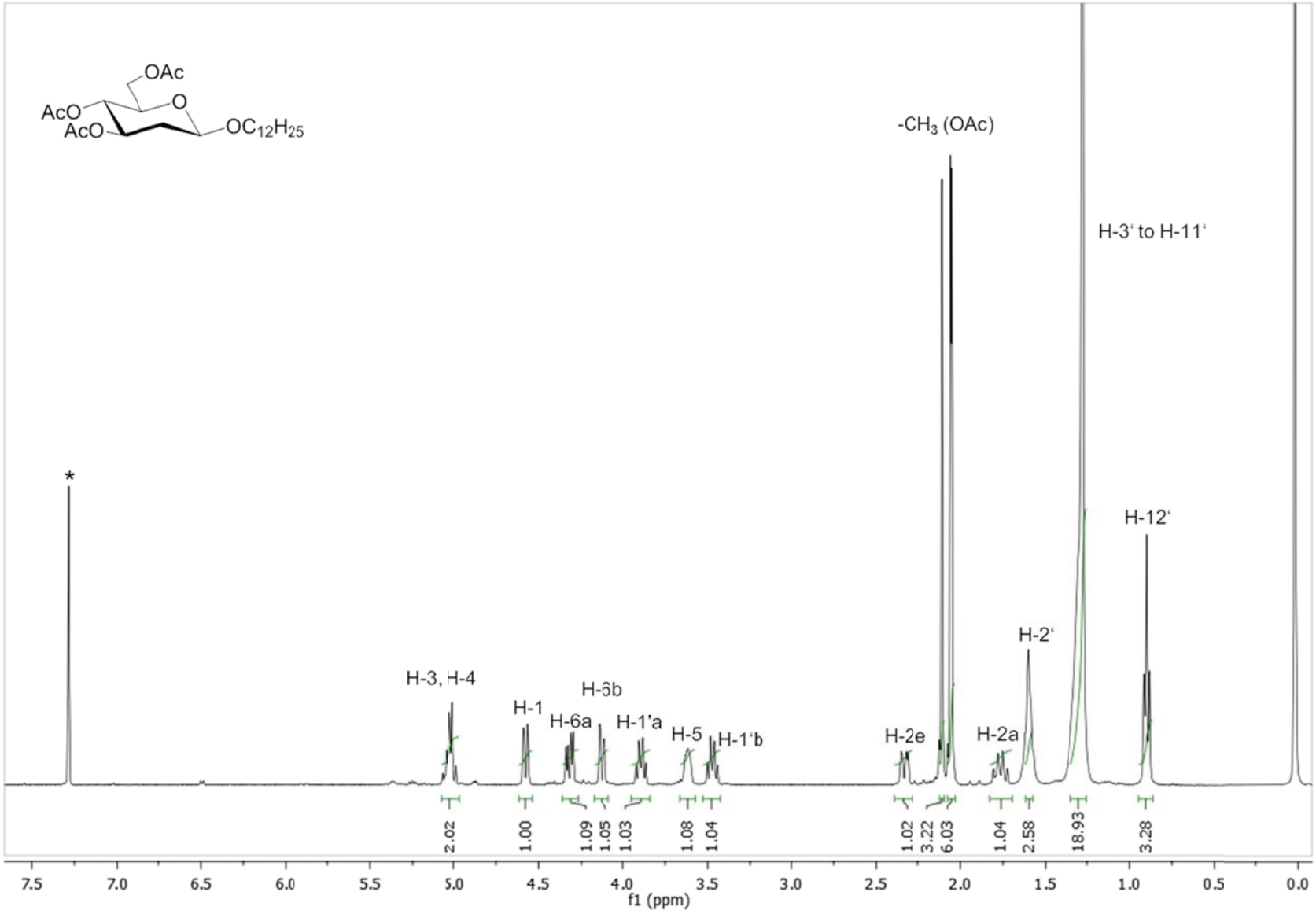


Figure SM 4.1.1.9.11 - ^{1}H NMR spectrum of dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside (**3**), in $CDCl_3$. *Solvent residual peak.

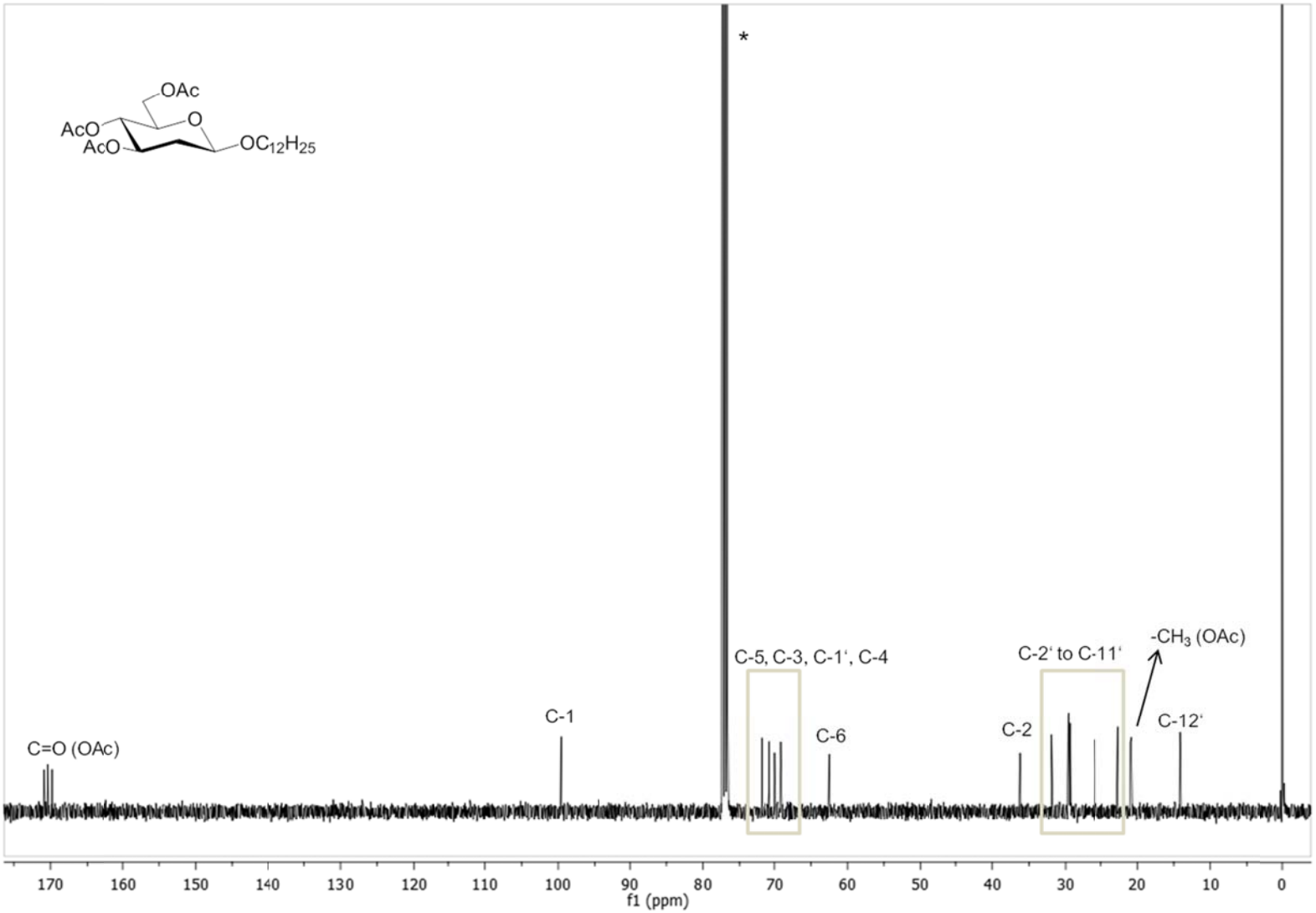


Figure SM 4.1.1.9.12- ^{13}C NMR spectrum of dodecyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside (**3**), in $CDCl_3$. *Solvent peak.

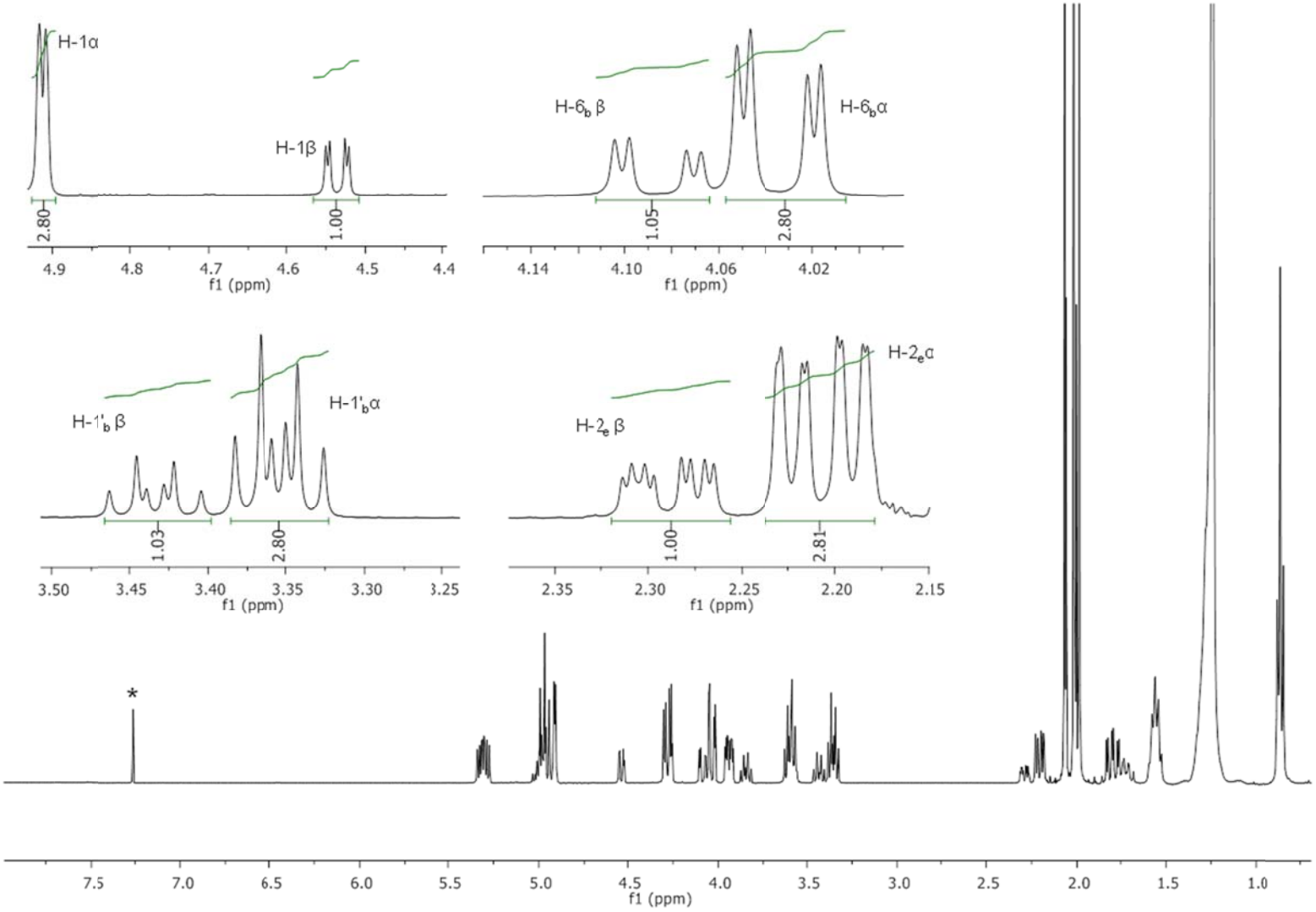


Figure SM 4.1.1.9.13 – ^{13}H NMR spectrum of glycosides **2** and **3** in α/β ratio of 2.8:1, in $CDCl_3$.*Solvent peak.

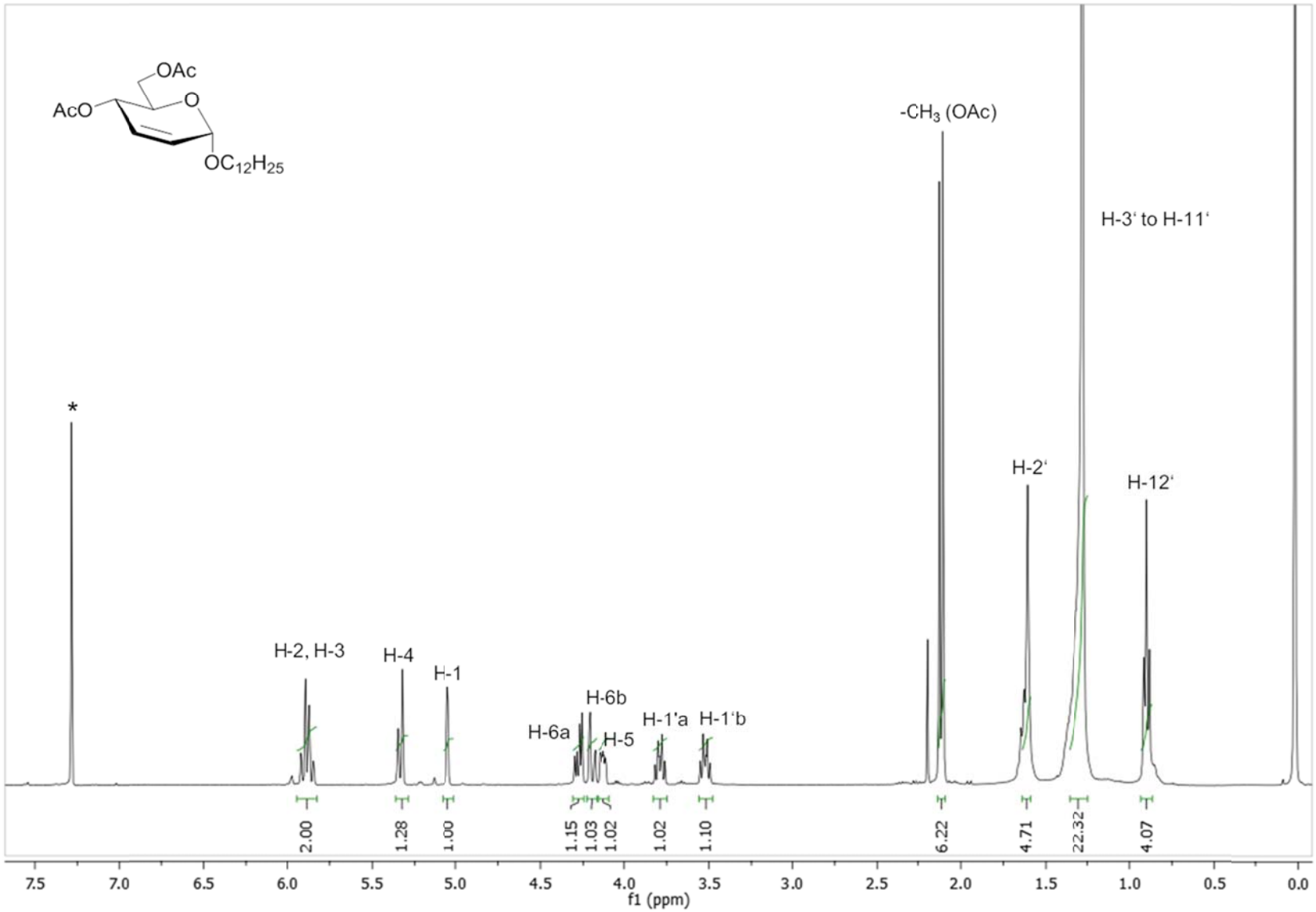


Figure SM 4.1.1.9.14 - ^{1}H NMR spectrum of dodecyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**4**), in $CDCl_3$.*Solvent residual peak. Integration of signals below δ 1.7 indicates contamination with dodecanol.

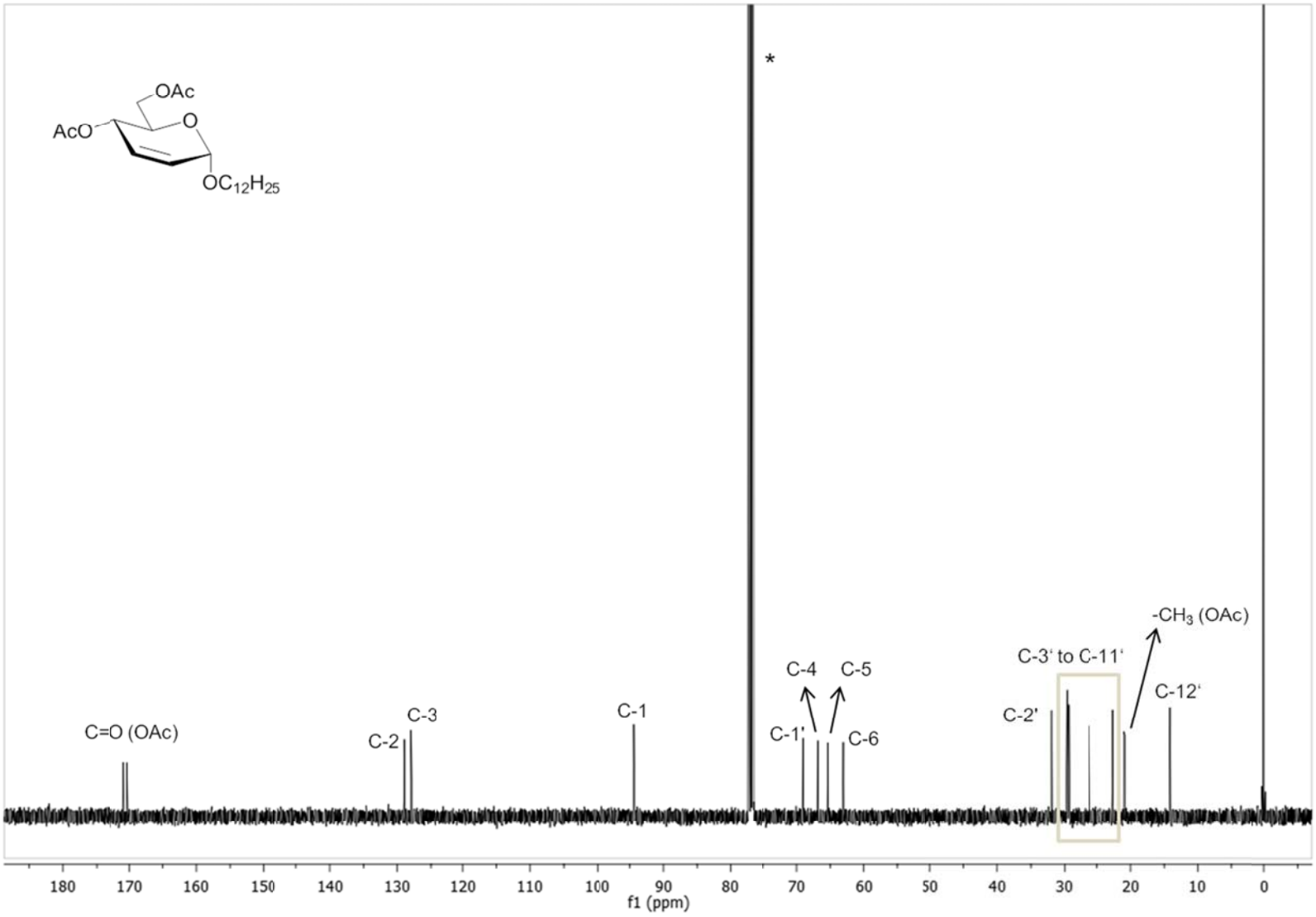


Figure SM 4.1.1.9.15 - ^{13}C NMR spectrum of dodecyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**4**), in $CDCl_3$. *Solvent peak.

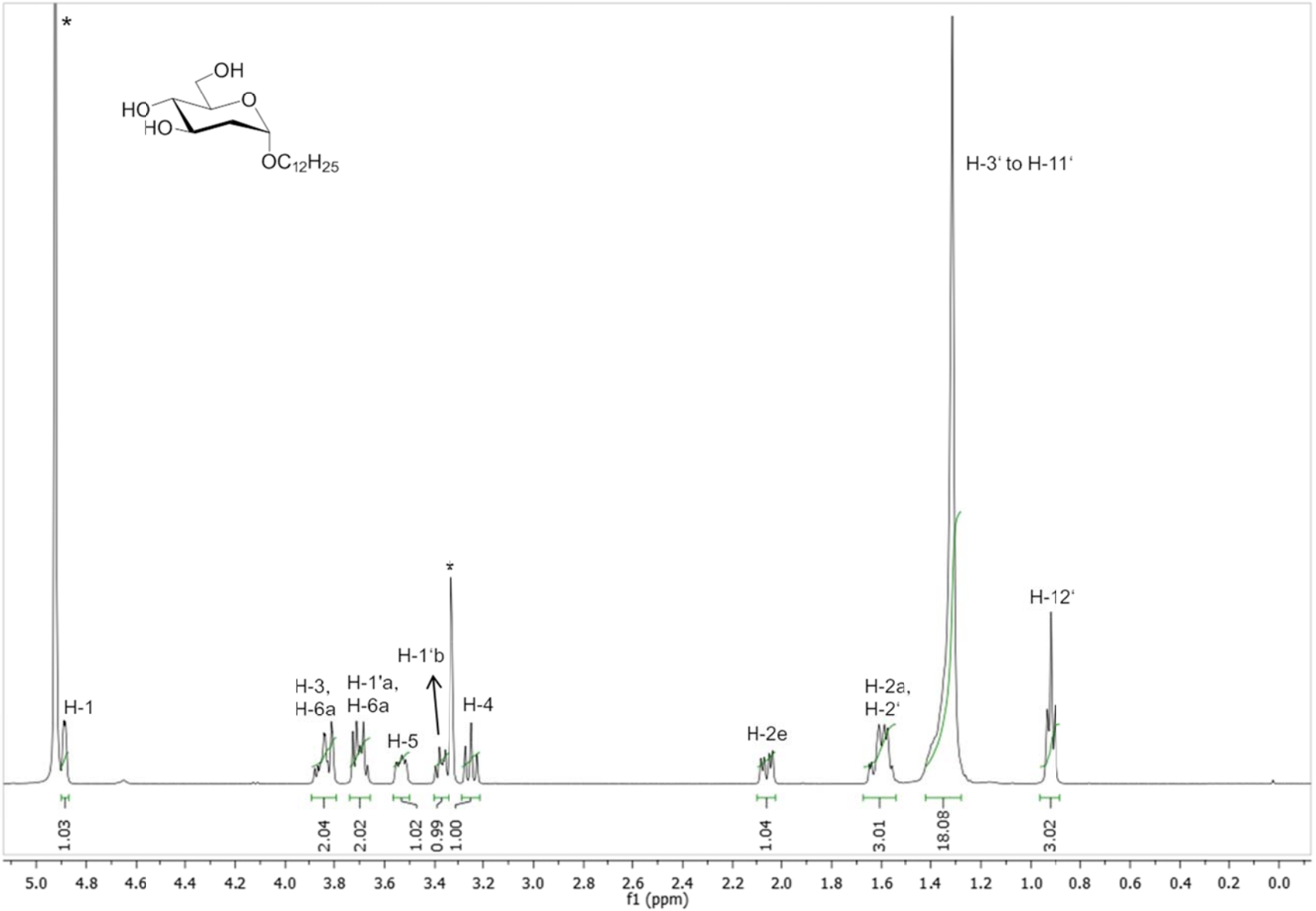


Figure SM 4.1.1.9.16 - ^{1}H NMR spectrum of dodecyl 2-deoxy-α-D-*arabino*-hexopyranoside (**5**), in MeOD.*Solvent residual peak.

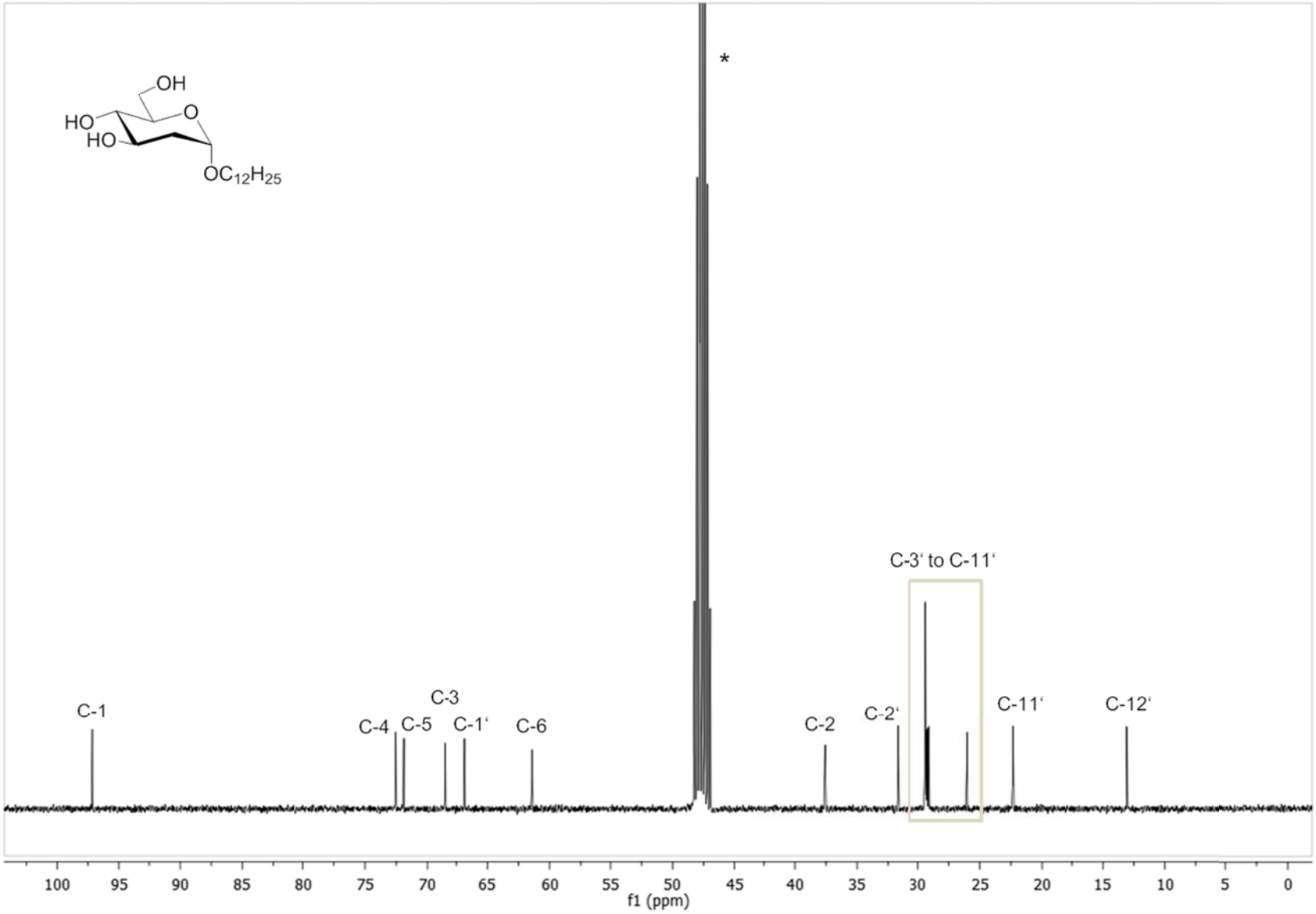


Figure SM 4.1.1.9.17 - ^{13}C NMR spectrum of dodecyl 2-deoxy-α-D-*arabino*-hexopyranoside (**5**), in MeOD.*Solvent peak.

Preparation of (1*R*,2*R*,3*R*,5*S*)-(–)-isopinocampheol through a hydroboration-oxidation reaction

Supplementary Material

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 Organic Synthesis.

The main objective of this experiment is to show students the hydroboration reaction and the oxidation of the organoborane. The second objective is to introduce students to the work under anhydrous conditions and in an inert gas atmosphere. Another purpose is to understand the regio- and stereoselectivity of hydroboration.

There are described two methods of carry out hydroboration step as well as oxidation step. In method 1, hydroboration of (+)-α-pinene followed by oxidation of the organoborane is performed on one laboratory session (Figure SM 4.1.1.10.1-SM 4.1.1.10.3). In method 2, an intermediate dialkylborane – diisopinocampheylborane (Ipc_2BH) is crystallized, isolated, and oxidized (Figure SM 4.1.1.10.4-SM 4.1.1.10.7). Instead of (+)-α-pinene, (–)-isomer can also be employed. Students should measure the optical rotation of the starting α-pinene, calculate the specific rotation, and based on the highest rotation given in the experiment description calculate the optical purity of the substrate. The optical rotation of the product isopinocampheol should also be measured. Students will compare optical purities of α-pinene and isopinocampheol. The can observe an increase of enantiomeric purity for isopinocampheol obtained in Method 2.

The reaction flask, as it is written, must be dried in a flame or by using a heat-gun and cool down in the stream of nitrogen or argon. The flask and gas-inlet adapter should be assembled while still hot.

Caution is advised when taking borane solution into the syringe.

When borane-THF complex is used for the synthesis, rather freshly purchased solution should be used. Borane-dimethyl sulfide adduct is a very stable compound when stored under nitrogen in

refrigerator, and particularly it should be used in the synthesis of crystalline, enantiomerically enriched Ipc_2BH.

Water or methanol is added to the reaction mixture to hydrolyze any unreacted borane and Ipc_2BH Both methods of oxidation of Ipc_2BH are described. A safer method utilizing sodium perborate and standard method with 30% hydrogen peroxide and 3M of sodium hydroxide.

It is mandatory to use protective gloves when handling 30% hydrogen peroxide.

Product after reaction is essentially pure, and if only the solvents are evaporated very well, isopinocampheol can be analyzed by ^{1}H and ^{13}C NMR. Small sample of isopinocampheol can be sublimed to measure melting point and/or optical rotation as it is shown on Figure SM 4.1.1.10.8 - SM 4.1.1.10.9.

In all syntheses following Method 1, students achieved yields in the range of 60-85%, Conducting experiments using Method 2, yields of isopinocampheol are lower (30-55%).

Photos of the experiment

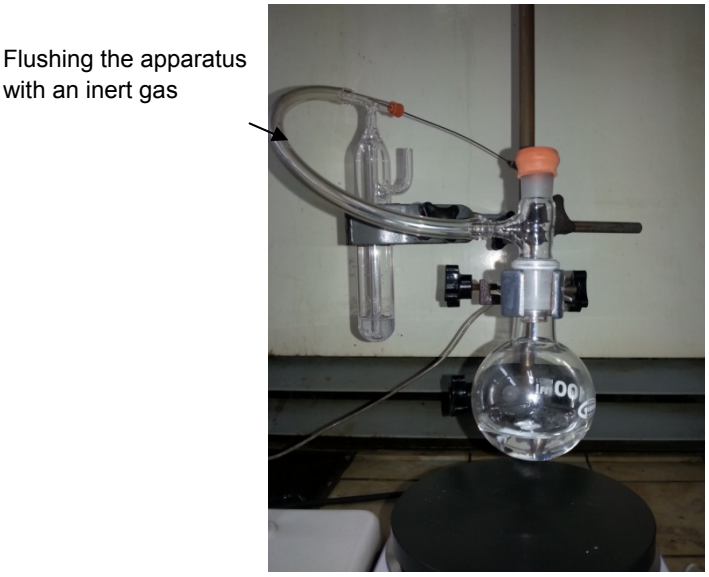


Figure SM 4.1.1.10.1 – An apparatus for hydroboration conducted under an inert gas atmosphere

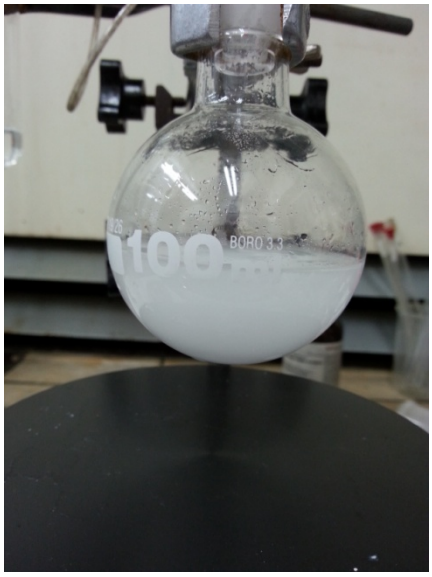


Figure SM 4.1.1.10.2 – The reaction mixture after addition of 3M sodium hydroxide an sodium perborate tetrahydrate

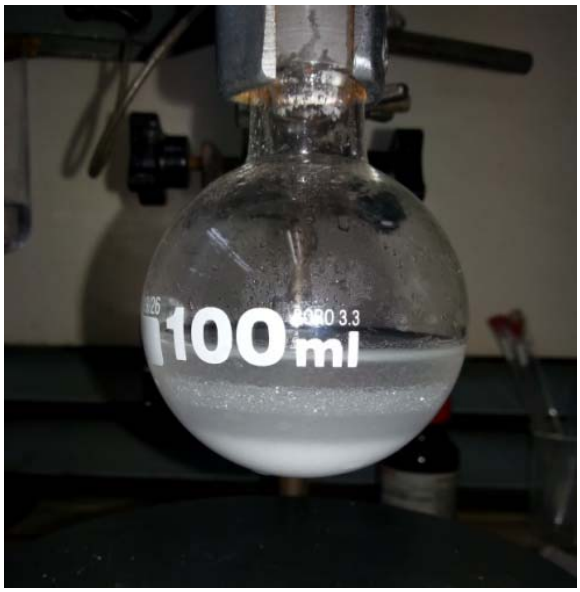


Figure SM 4.1.1.10.3 – Reaction mixture after 1 hour of oxidation (Method 1). Separation of the two phases after stopping the stirring.

Figure SM 4.1.1.10.4 – Crystallization of $^{d}Ipc_2BH$ in water/ice/salt bath (Method 2).

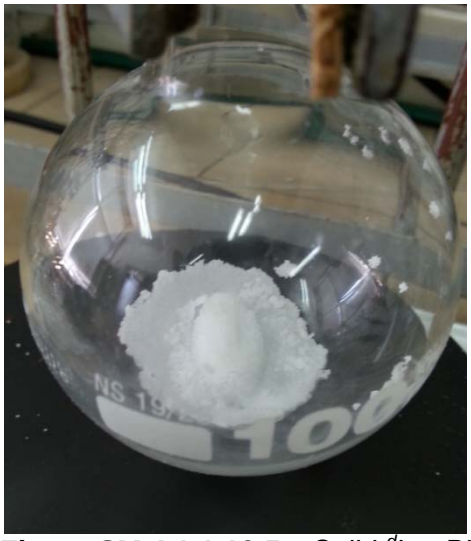


Figure SM 4.1.1.10.5 – Solid $^{d}Ipc_2BH$ after washing with hexane. This compound forms large hard crystals.

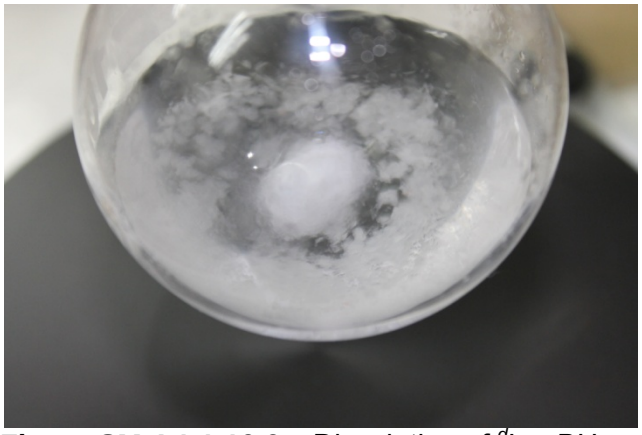


Figure SM 4.1.1.10.6 – Dissolution of $^{d}Ipc_2BH$ upon addition of methanol or water.

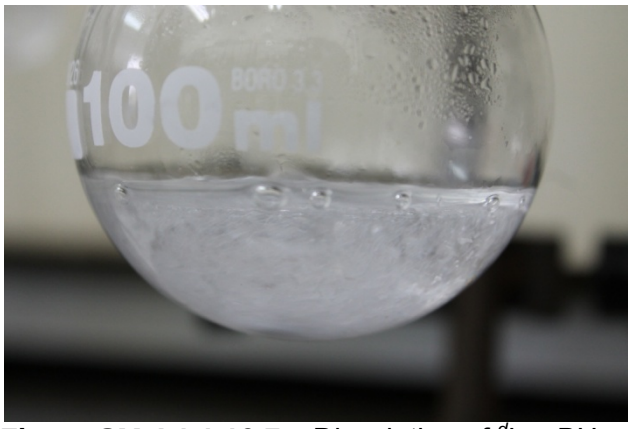


Figure SM 4.1.1.10.7 – Dissolution of $^{d}Ipc_2BH$ with hydrogen evolution upon addition of methanol.

Figure SM 4.1.1.10.8 – An apparatus for the sublimation of isopinocampheol under reduced pressure.

Figure SM 4.1.1.10.9 – Pure isopinocampheol collected on cooling finger after sublimation.

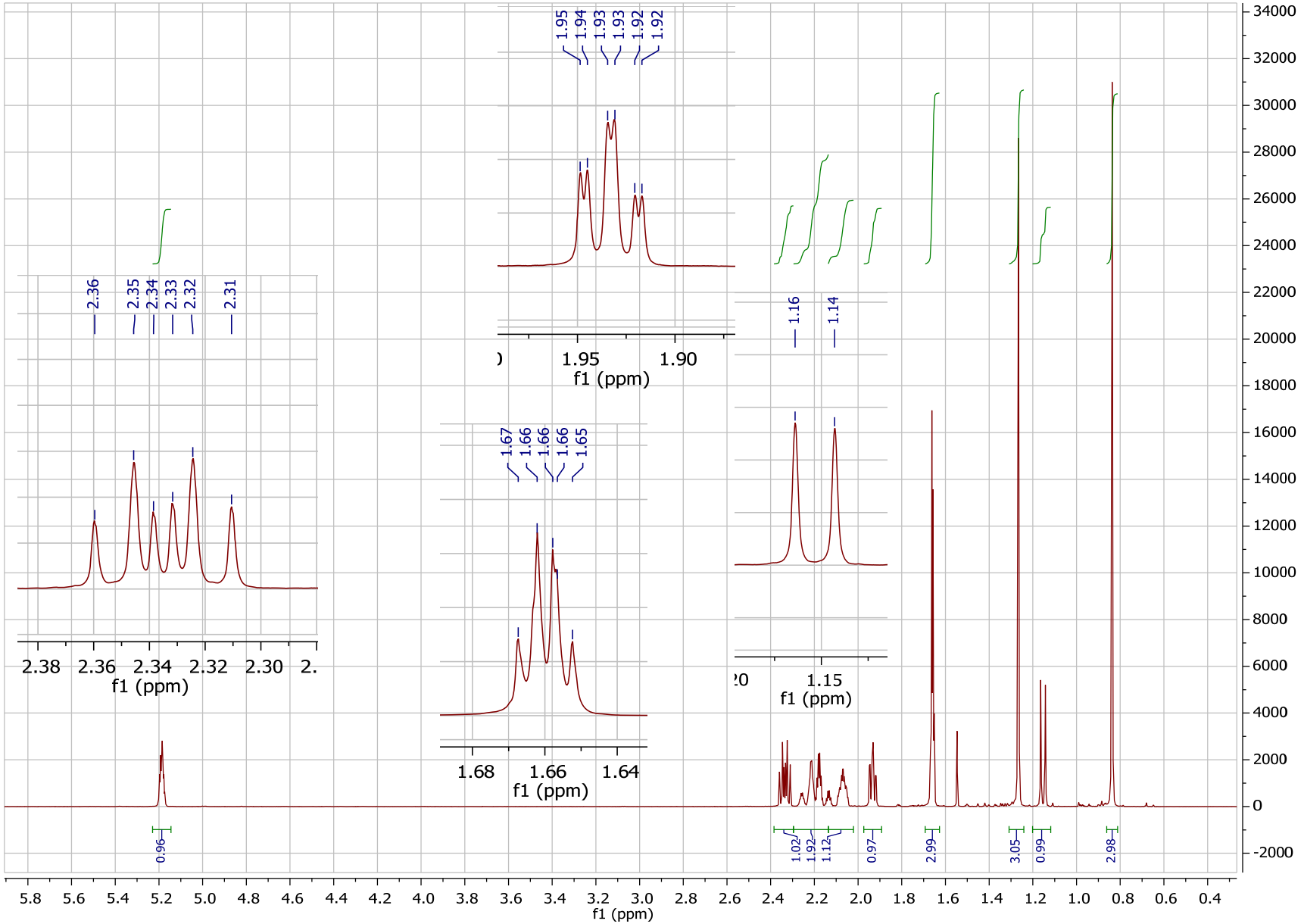


Figure SM 4.1.1.10.10 – ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the starting (+)-α-pinene

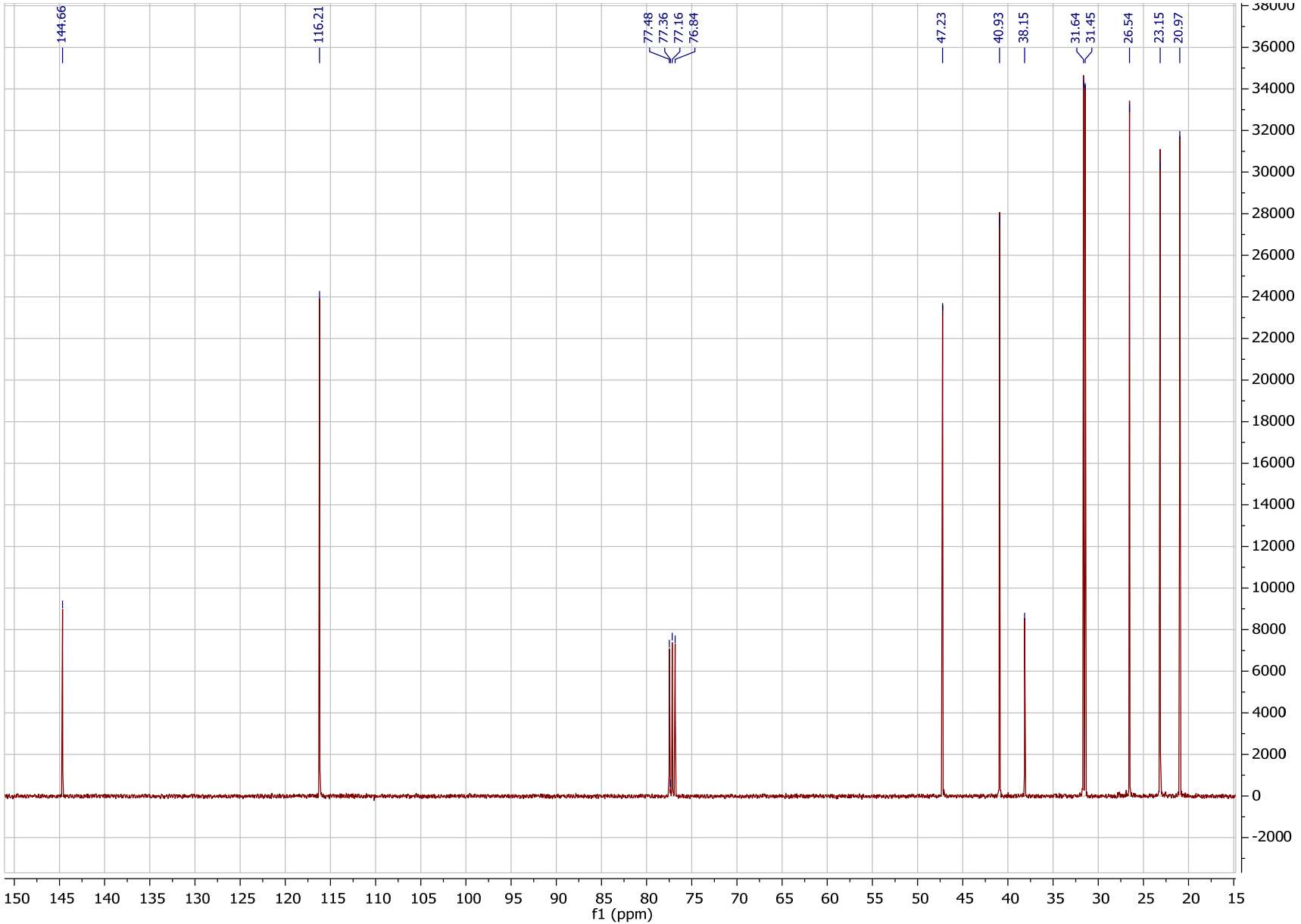


Figure SM 4.1.1.10.11 – ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of the starting (+)-α-pinene

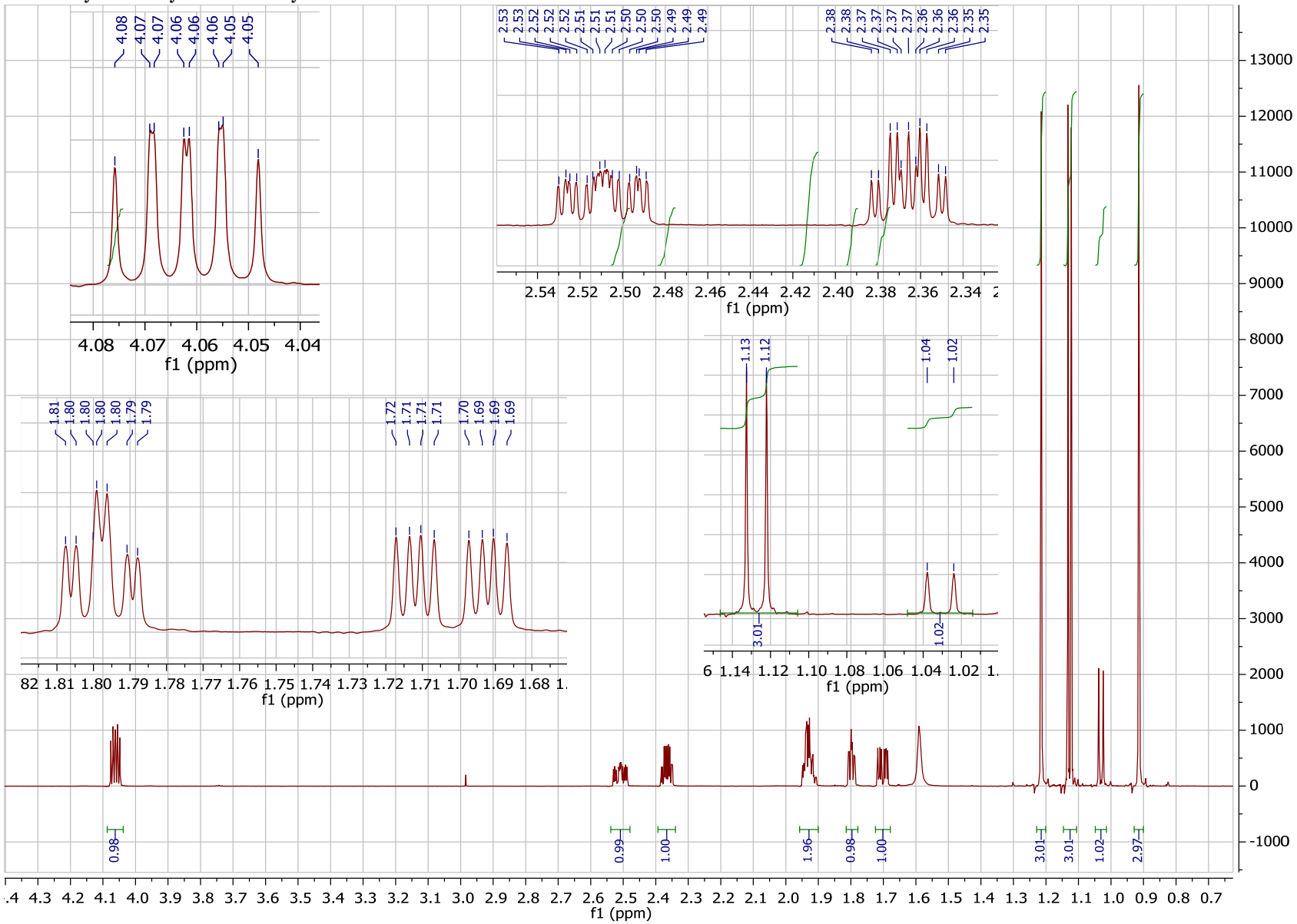


Figure SM 4.1.1.10.12 – ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the product (–)-isopinocampheol

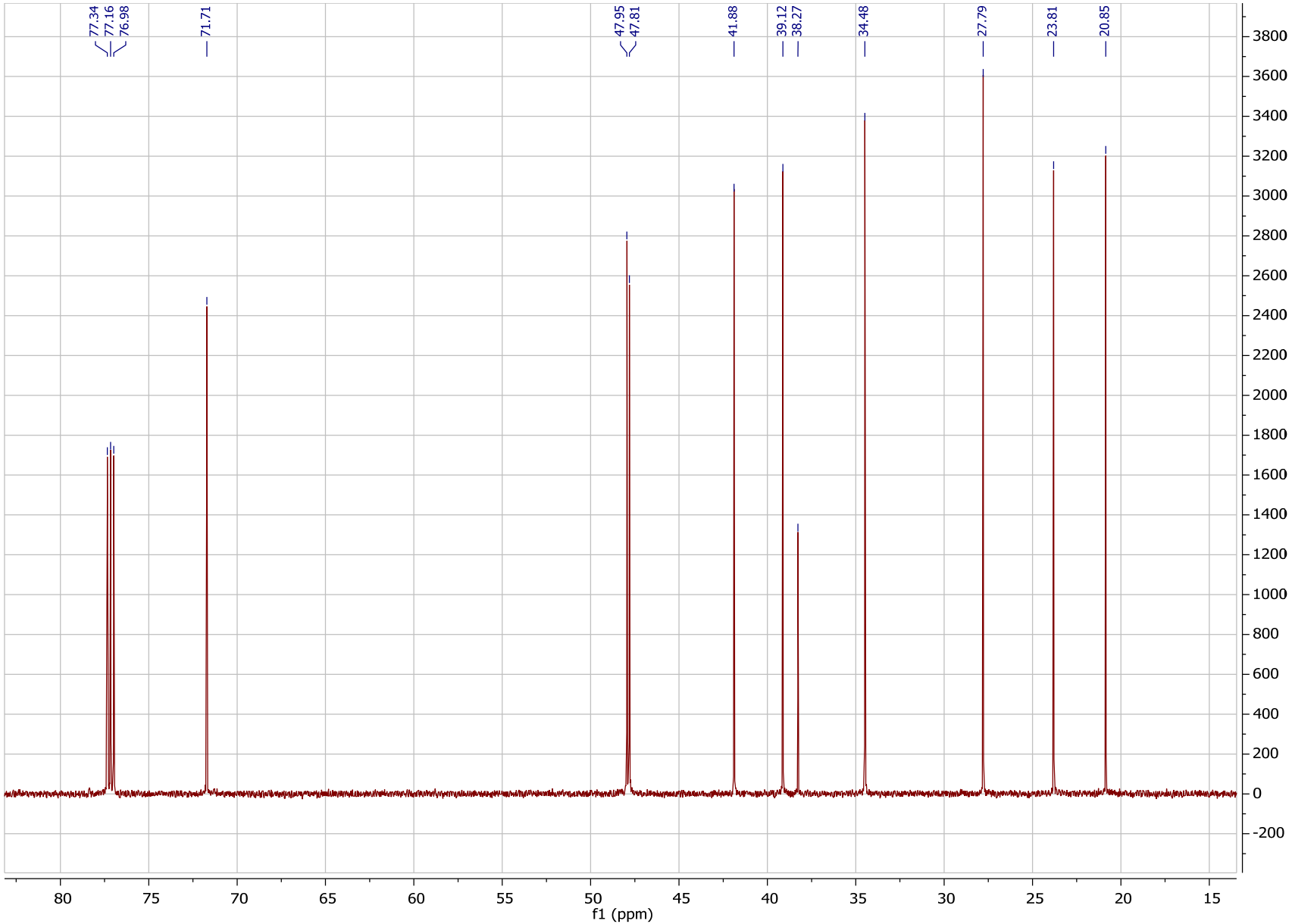


Figure SM 4.1.1.10.13 – ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of the product (–)-isopinocampheol

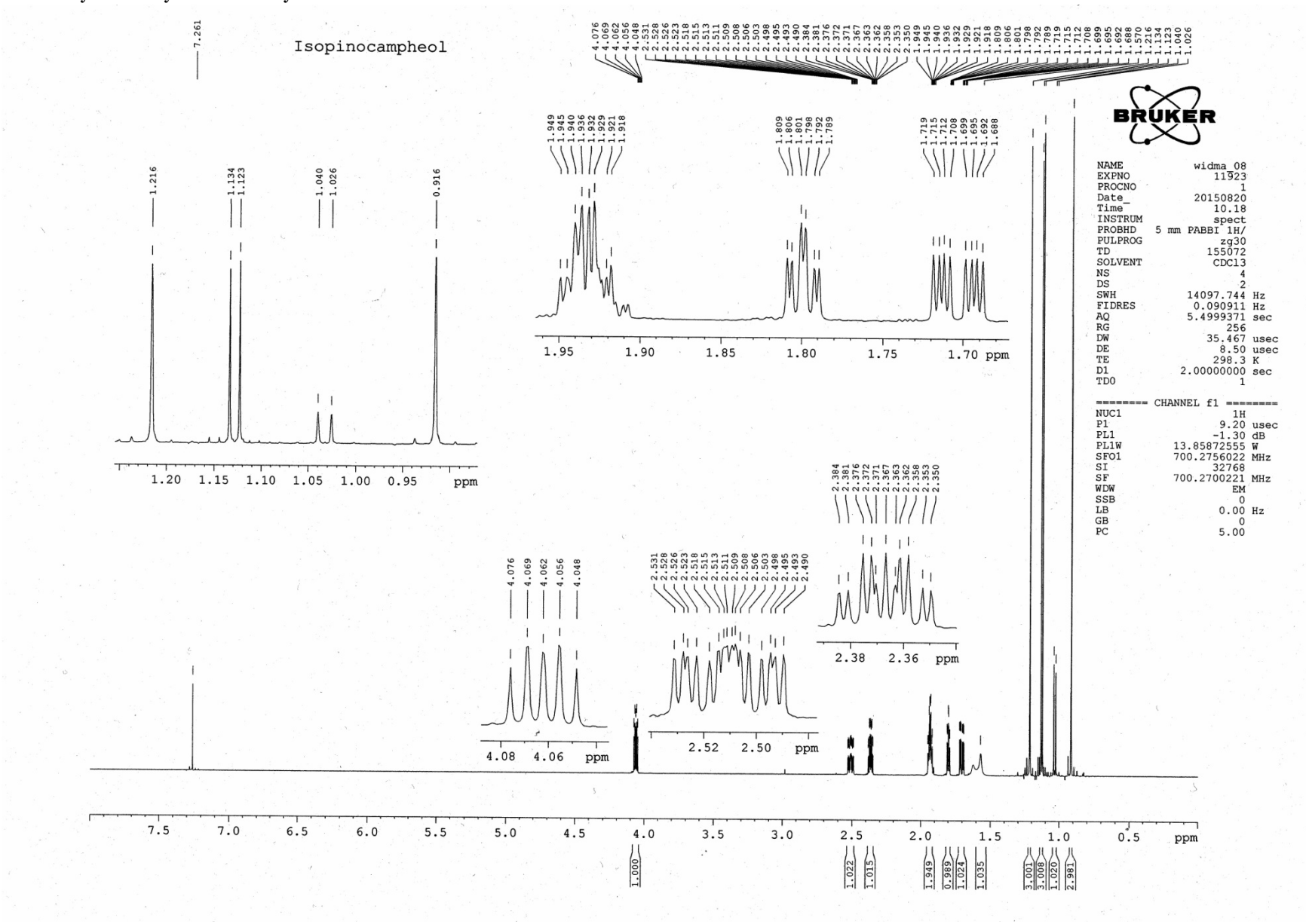


Figure SM 4.1.1.10.14 – ^{1}H NMR spectrum (700 MHz, $CDCl_3$) of the crude product (–)-isopinocampheol from the Method 2

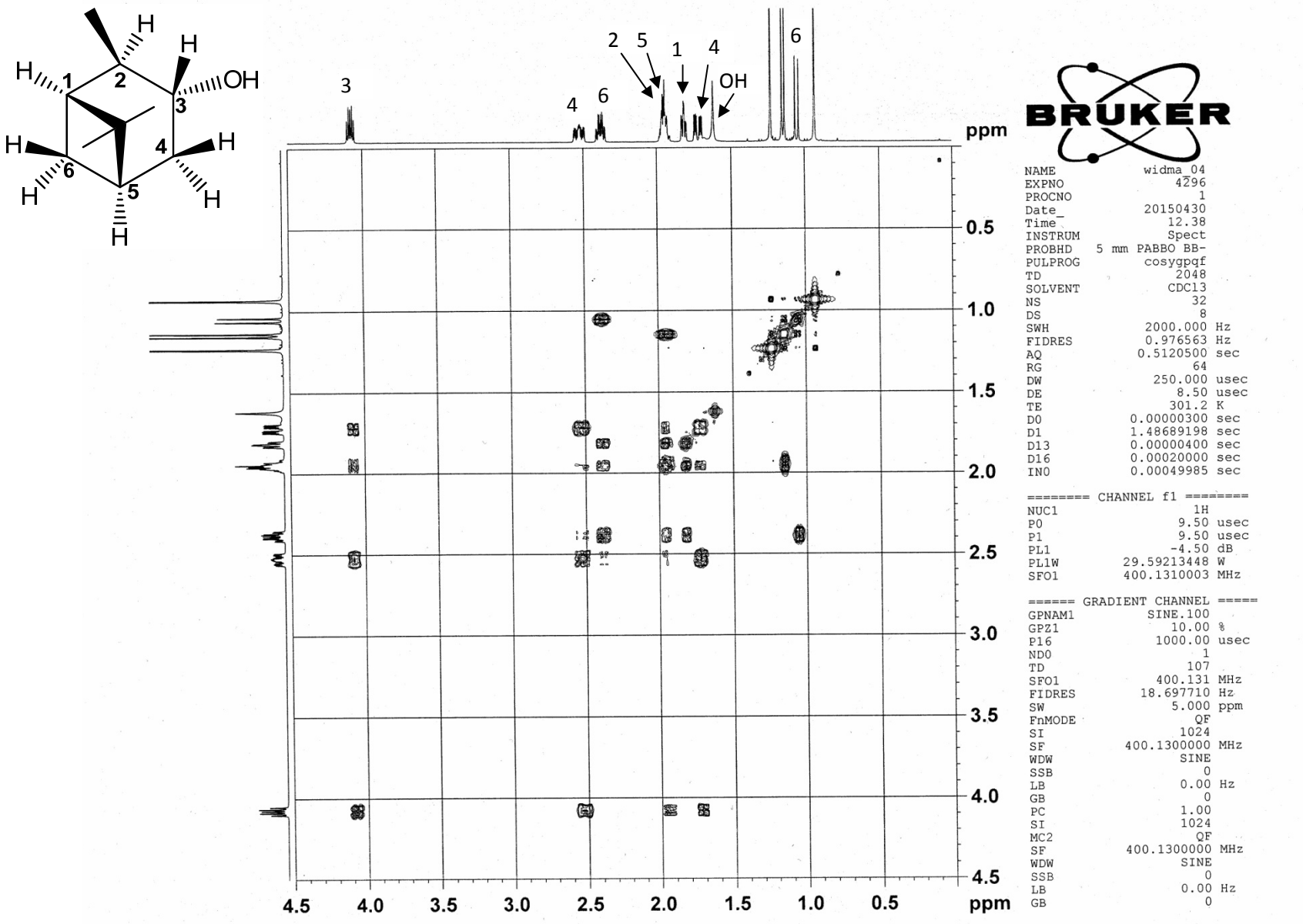


Figure SM 4.1.1.10.15 – ^{1}H x ^{1}H COSY NMR spectrum (400 MHz, $CDCl_3$) of the product (–)-isopinocampheol (numbers refer to the carbon atoms to which protons are attached)

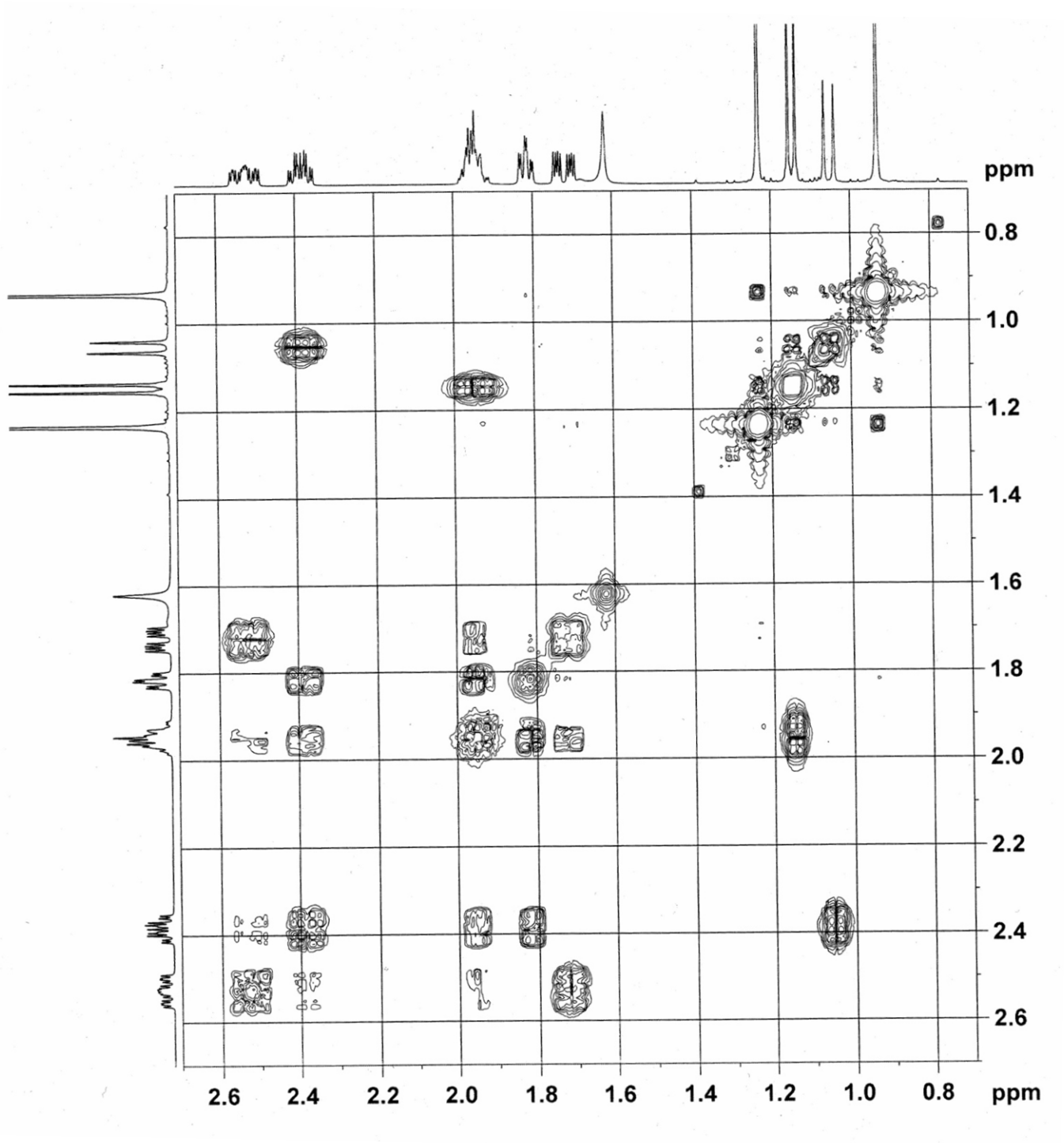


Figure SM 4.1.1.10.16 – ^{1}H x ^{1}H COSY NMR spectrum (400 MHz, $CDCl_3$) of the product (–)-isopinocampheol (expanded fragment of the spectrum)