Catalytic Epoxidation of *cis*-Cyclooctene with MTO (VII) and Pyrazole

Supplementary Material

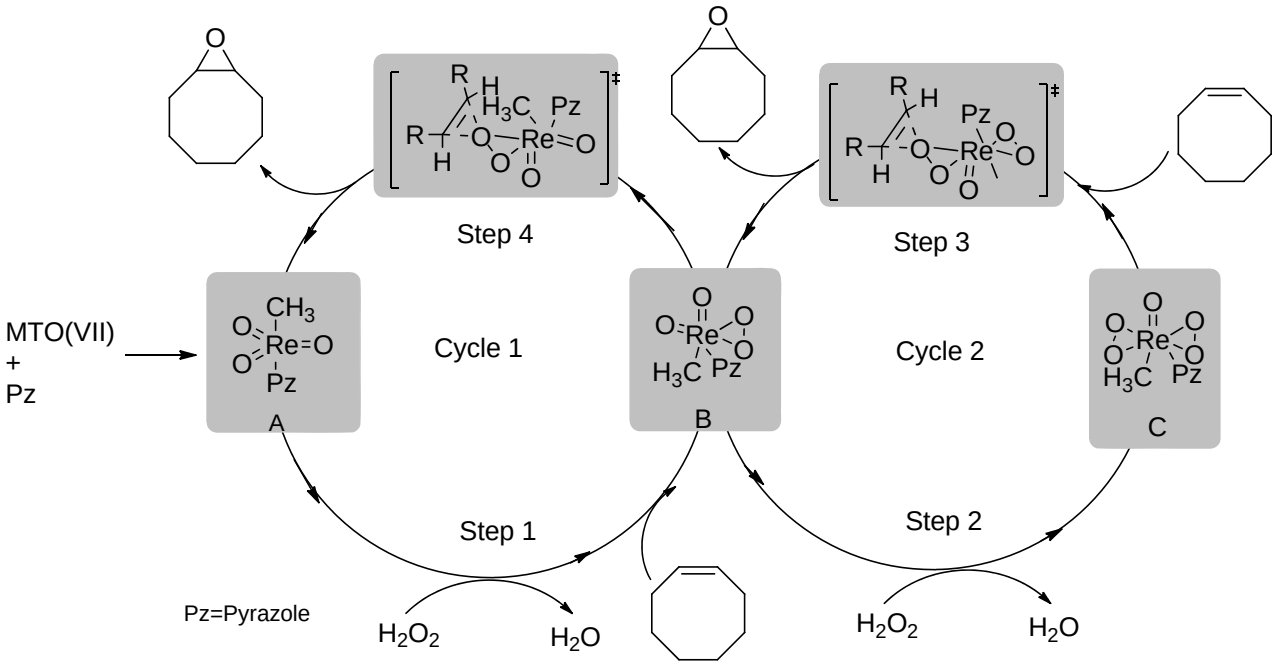
The goal of this experiment is the preparation of *cis*-cyclooctene oxide from the corresponding olefin in an anhydrous system. Two experiments are carried out simultaneously to compare the efficacy of the pyrazole ligand on the reaction acceleration. In the first step of the reaction, that has strong yellow color (Figure SM 12.3.1.1), this intense color indicates the formation of the active diperoxo complex (Scheme SM 12.3.1.1, **C**).[1]

Immediately after the addition of the olefin the color vanishes (Figure SM 12.3.1.2). To conclude the reaction it is necessary to decompose the UHP with the addition of a catalytic amount of MnO_2 and continue stirring until no more oxygen gas is released (Figure SM 12.3.1.3).

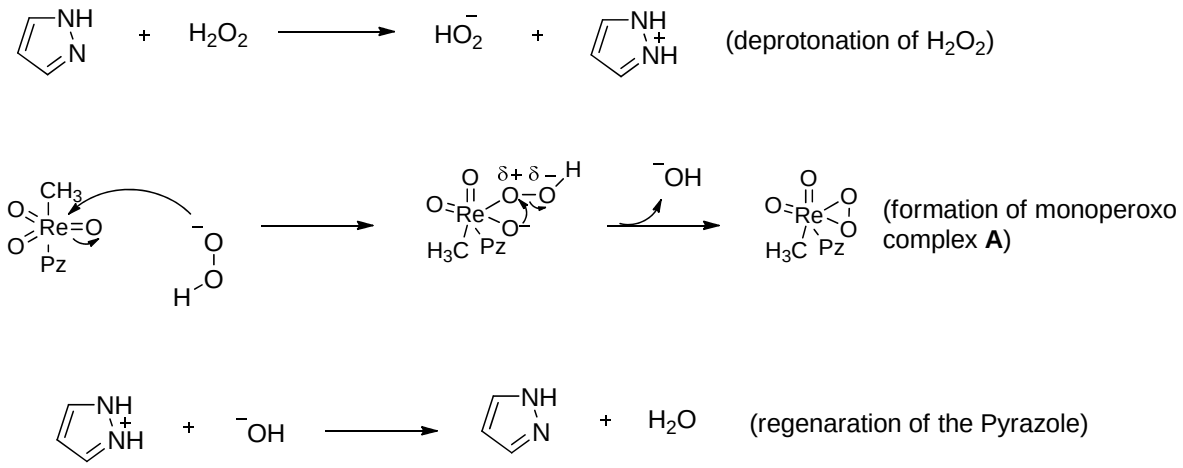
The proposed mechanism is depicted in the scheme SM 12.3.1.1,[2] in the first step the pyrazole is believed to coordinate to the MTO(VII) (this is a Lewis acid and thus acts as an electrophile) forming complex **A** with a bipyramid trigonal structure, which reacts with hydrogen peroxide forming the monoperoxo complex **B**. Hydrogen peroxide is a weak acid and is expected to be deprotonated by pyrazole forming HO_2^-. This anionic species is proposed to undergo a nucleophilic attack on the Re to form the metal peroxo unit with release of hydroxide anion. In Step 2, a similar event occurs to form the diperoxo complex **C**. In the Step 3 (Scheme SM 12.3.1.1) the reaction proceeds via what is commonly known as the "Butterfly Mechanism". The peroxide is viewed as an electrophile, and the alkene a nucleophile. The butterfly mechanism allows ideal positioning of the O-O σ^* orbital for the C-C π electrons to attack this vacant anti-bonding orbital (Scheme SM 12.3.1.3), complex **A** is regenerated and the cycle starts all over again. The mechanism for Step 4 in the catalytic cycle is similar to the mechanism presented for Step 3, but in this case complex **B** is regenerated, which can epoxidise the alkene.

Pyrazole is believed also to control the acidity of the peroxo complexes **B** and **C,** but in the case of more sensitive epoxides it is not enough to suppress acid-catalyzed oxirane ring

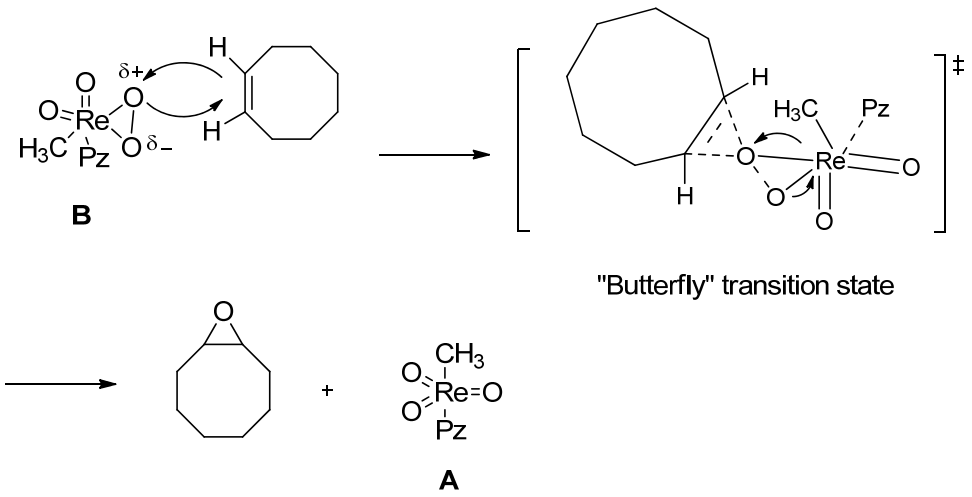
opening, for this reason is important use the UHP as the oxidant, urea can act as a buffer and reduce the acidity of the peroxo complexes thus limiting the hydrolysis side-reaction.[3]



Scheme SM 12.3.1.**1.** Proposed catalytic cycle.[2]



Scheme SM 12.3.1.**2. Proposed** mechanism for Step 1 in the catalytic cycle.



Scheme SM 12.3.1.**3**. Butterfly mechanism, for Step 3.

In Figures SM 12.3.1.4 and SM 12.3.1.5 the ^{1}H NMR spectra of the isolated product containing 1,3,5-trimethylbenzene (the internal standard) are shown, The student will also use ^{1}H NMR as a quantitative analytical technique, since they will calculate the reaction yield and conversion based on the ^{1}H NMR spectrum and using the equations presented in the experimental procedure.

This procedure was successfully executed at the described scale, and product yields of around 70% and a conversion of 100% for experiment **A**, and a conversion of 55% with a yield of 55% obtained for experiment **B** were obtained by the authors. When this experiment was repeated by M.Sc chemistry students in their 1st year at the University of Évora, it was possible to confirm the reproducibility of these reactions obtaining an average yield of 50 % (48-52 % range) and 98% average conversion (96-100% range) for experiment **A**. In the case of experiment **B**, the average yield was 45 % (43-47% range) and the average conversion 84% (82-87% range).

Photos of the Experiment:

	
Experiment **A**	Experiment **B**

Figure SM 12.3.1.**1 -** Reaction mixture, formation of the diperoxo complex – yellow color.

	
Experiment A	Experiment B

Figure SM 12.3.1.**2 -** Reaction mixture after addition of *cis*-cyclooctene.

Figure SM 12.3.1.**3** - Reaction mixture – decomposition of excess H_2O_2 with MnO_2.

^{1}H NMR spectra:

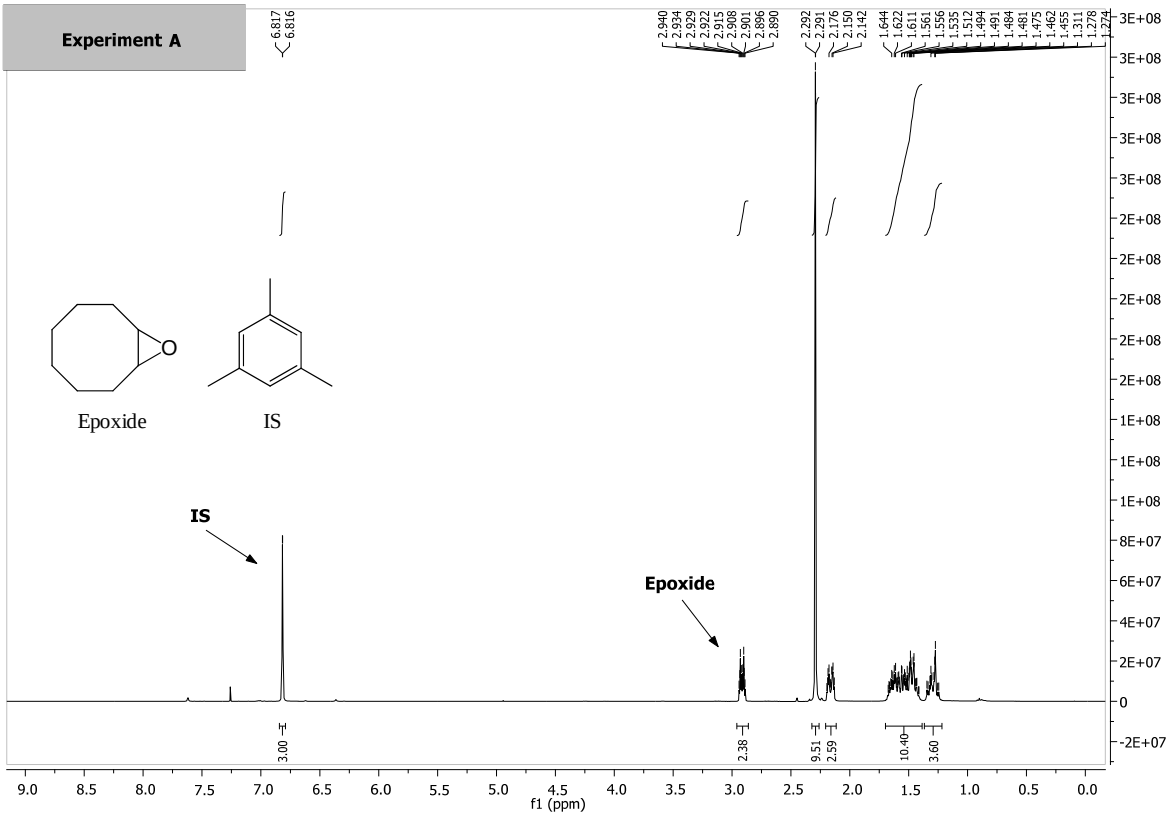


Figure SM 12.3.1.**4 –** ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of isolated product from Experiment A, yield of 70%, and conversion of 100%. Total reaction mass (m1) 0.257 g; reaction sample (m2) 0.020; IS mass (m3) 14.9 mg

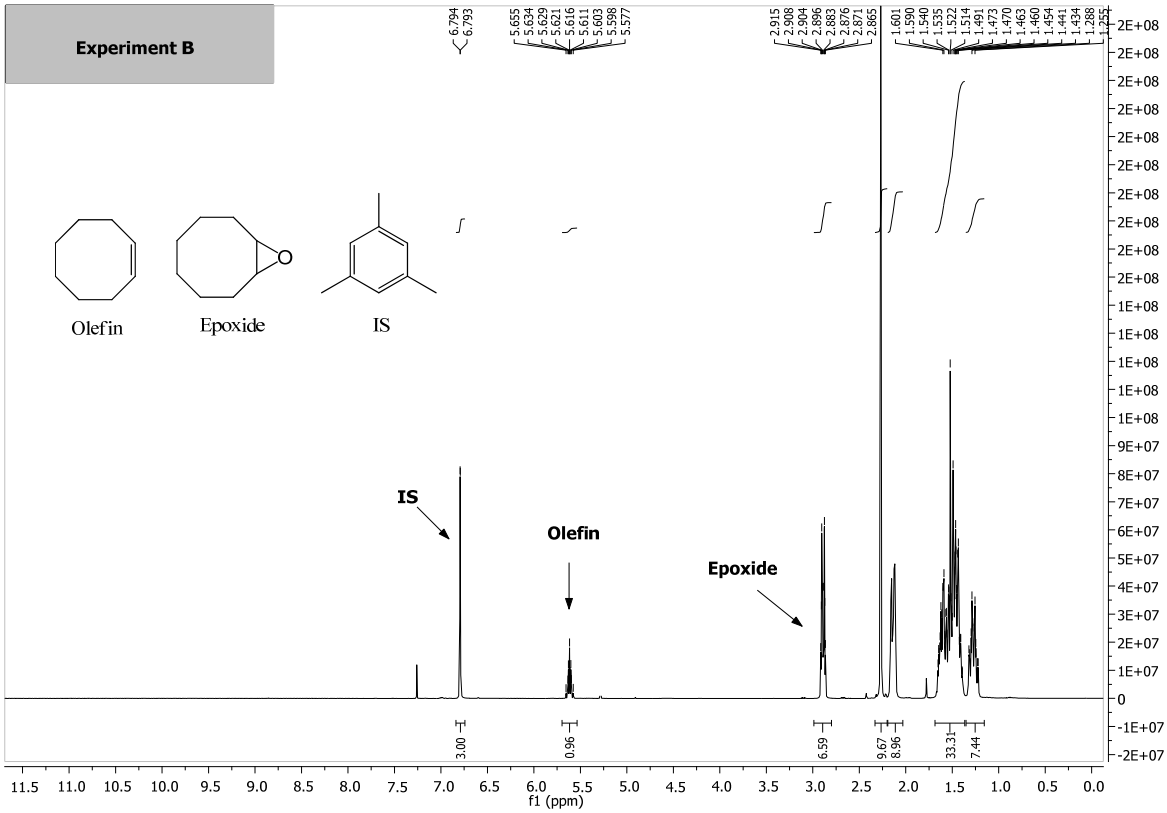


Figure SM 12.3.1.**5 –** ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of isolated product from Experiment B, yield of 55% and conversion of 87%. Total reaction mass (m1) 0.216 g; reaction sample (m2) 0.048 g; IS mass (m3) 12 mg.

[1] E.P. Carreiro, A.J. Burke, M.J.M. Curto, A.J.R. Teixeira, *J. Mol. Catal. A: Chem.* 2004, **217**, 69.
[2] F. E. Kühn, A. Scherbaum, W. A. Herrmann, *J. Organomet. Chem.* 2004, **689**, 4149, and references cited therein.
[3] W. Adam, C.M. Mitchell, *Angew. Chem. Int. Ed. Engl.* 1996, **35**, 533.

Stereoselective Epoxidation of Cholesterol by *m*-Chloroperoxybenzoic acid

Supplementary Material

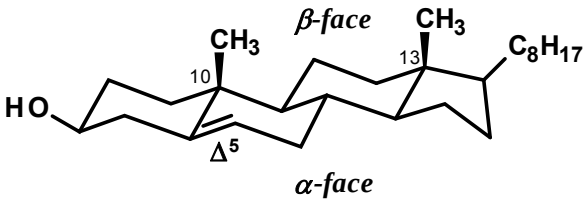
Experiment notes

The objective of this experimental work is to introduce the students to an easy and stereoselective epoxidation of cholesterol *via* peroxyacid use, as a double bond oxidizing agent. The experiment is multifaceted and can be used to teach students about epoxide synthesis, stereoselectivity in organic reactions, organic peroxyacids handling, TLC techniques as a tool to monitoring reaction progress, and the use of ^{1}H NMR to characterize the diastereomers.

The reaction is fast and complete. Another advantage of the experiment is that the reagents are common in the lab and generally not expensive.

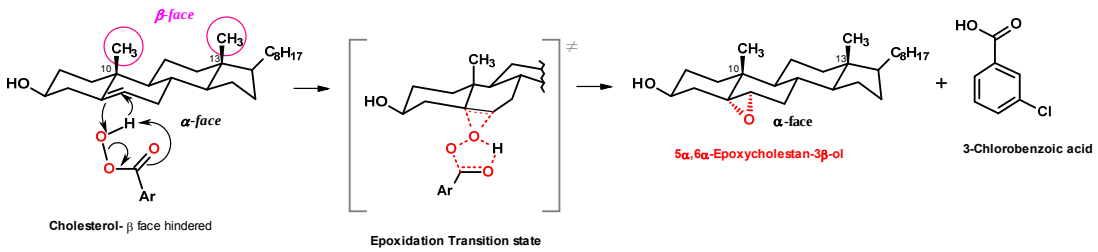
Mechanism and Stereo Chemistry Considerations

Cholesterol has a double bond between C5-C6 (Δ^5) in ring B and the two ring faces are denominated α and β faces. Since the β-face on the steroid nucleus is shielded by the two axial methyl groups at C10 and C13, epoxidation with a peroxyacid occurs preferentially on the less hindered α-face.



Cholesterol

The essence of the mechanism is electrophilic attack by the weak polarized O−O bond of the peroxyacid on the π orbital of the alkene. A proton has transferred from the epoxide oxygen to the carboxylic acid by-product. The transition state (marked ≠) for the reaction makes the bond -forming and -breaking processes clearer.[2] The steric hindrance of the C-10 methyl group prevents the *m*-CPBA from approaching to the top (β-face) of the molecule. (Scheme **SM 12.3.2.**1)



Scheme SM 12.3.2.1. Mechanism for the epoxidation of cholesterol by peroxyacid: the general electrophilic addition is believed to involve an intramolecular bonded spiro species (≠)

Because both new C−O bonds are formed on the same face of the alkene's *π* bond, the geometry of the alkene is reflected in the stereochemistry of the epoxide. The epoxidation is stereospecific and the proportions of the 5*α*,6*α*-isomer and its diastereomer, 5*β*,6*β*-epoxide, may vary with the epoxidation conditions. It has been described that the reaction with peroxyacid routinely yielded about 75% 5*α*,6*α*- and 25% 5*β*,6*β*-epoxides.[3,4]

Experimental Concerns

First the students prepare the reaction solutions (Figure **SM 12.3.2.**1-A). As soon as the first drop of the oxidizing peroxyacid is added to the cholesterol, students should collect the first sampling for TLC (time 0') (Figure **SM 12.3.2.**1-B) and start counting the 30' of reaction. The experimental technique implies a reflux assemble with low warming (40^{o}C) (Figure **SM 12.3.2.**1-C).

Regarding the TLC (Merck Silica Gel 60-F_{254} 250 µm precoated plates) visualization some remarks should be present:

- Always remember to look under UV light, in order to not miss any possibility of product identification (Figure **SM 12.3.2.**2-D, E).
- Always spray the stain reagents onto plates in a well ventilated hood while wearing safety glasses (Figure **SM 12.3.2.**2-F).
- With a 20 cm distance, apply (spray) moderate amounts of the stain reagent. This plate should be placed in an upright position, so that does not become soggy (if it looks wet, you have sprayed too much). You can always spray it again if necessary to enhance the detection.
- After spraying, the TLC spots are revealed in a hot plate, until the color appears and reveal the spot positions (Figure **SM 12.3.2.**3-G, H).

During the reflux, students have time available to prepare the alumina column chromatography (Al_2O_3, 90 active neutral, 70-230 mesh ASTM) by slurry method. This chromatography will allow the separation of the product epoxy-cholesterol. (Figure **SM 12.3.2.**4-I, J)

Table SM 12.3.2.1: Described melting points for cholesterol epoxydes

Stereoisomer	**Melting point (^{o}C)**	**Ref.**
5*α*,6*α*-Epoxycholesterol	142.5 141-141.5	(1a) (1b)
5*β*,6*β*-Epoxycholesterol	132	(1a)

Samples for NMR should contain 50 mg of the synthesized epoxy-cholesterol/600μL $CDCl_3$.

The ratio of *α*/*β*-epoxides is usually determined by integration of C6 proton signals in the ^{1}H NMR spectra of crude residues (*δ*=2.75-2.95 for *α*-epoxides and *δ*= 3.00-3.15 for *β*-epoxides).[4]

The reproducibility of the experiment was assessed by undergraduate students in the Medicinal Chemistry Department of Faculty of Pharmacy, University of Lisbon. The experience has been widely performed by students (about 200 students/year) since it is a routine work in the program of the Course of Pharmaceutical Chemistry on the Integrated Master of Pharmaceutical Sciences.

Yields obtained may vary between 50% and 80%. Melting points obtained: 138^o-143^{o}C (for reference see Table **SM 12.3.2.**1).
TLC examples may be seen in the supplied photos of the experiment.
^{1}H and ^{13}C NMR spectra for the cholesterol and epoxycholesterol are also supplied.
Table **SM 12.3.2.**2 summarize the main differences of the NMR spectra.Table **SM 12.3.2.**3 contains additional values in the ^{1}H NMR spectra for the epoxy-cholesterol.
It is evident a final proportion of 93% of *α*-epoxycholesterol to 7% of the *β*-stereoisomer. The percentages of the two isomers can vary slightly, possibly as a consequence of recrystallization. The *α*-epoxycholesterol isomer is clearly the majority. These spectra were run at 300 MHz using a Bruker Fourier spectrometer.

Photos of the experiment

A

Fig. **SM 12.3.2.**1. Reaction mixture preparation (A)

B

TLC sampling (B)

C

Reflux assemble (C)

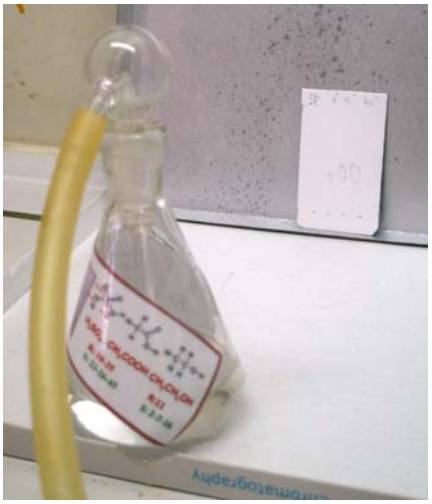
D

Fig. **SM 12.3.2.**2. TLC chromatographic elution (D)

E

TLC visualization with UV lamp for circumferential marking of the benzoic acid spots with pencil (E)

F



Spraying with sulphuric acid staining solution (F)

G

H

Fig. **SM 12.3.2.**3. TLC analysis of reaction mixture
TLC warming for spot revelation (G);
Chst=Cholesterol standard; 0', 15', 30': reaction mixture sample at 0 min, 15 min and 30 min respectively (H)
At time 0', we can see the unreacted cholesterol and already some product: epoxy-cholesterol. After 15' the reaction is already complete. The marking penciled indicates the *m*-chlorobenzoic acid that was previously observed in the UV lamp.

I

Fig. **SM 12.3.2.**4. Alumina Column Chromatography (I)

J

Elution of the column with 150mL of CH_2Cl_2 (J)

Spectra

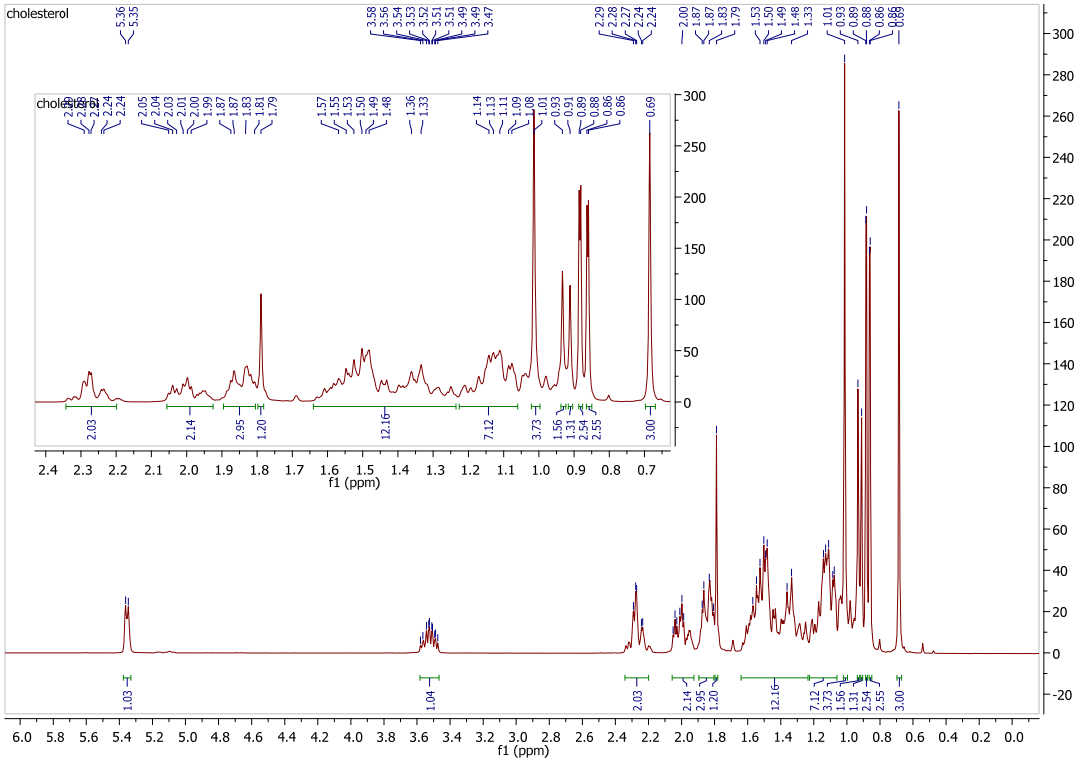


Fig. **SM 12.3.2.**5. ^{1}H NMR of Cholesterol

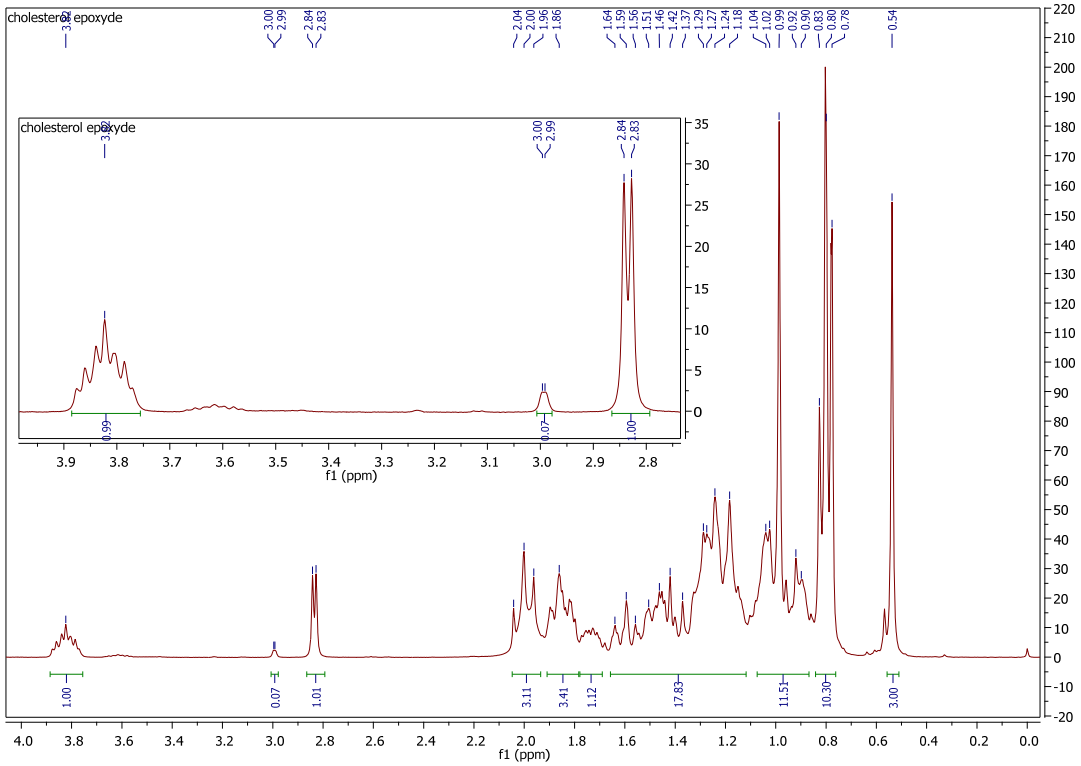


Fig. **SM 12.3.2.**6. ^{1}H NMR of the final product: epoxy-cholesterol

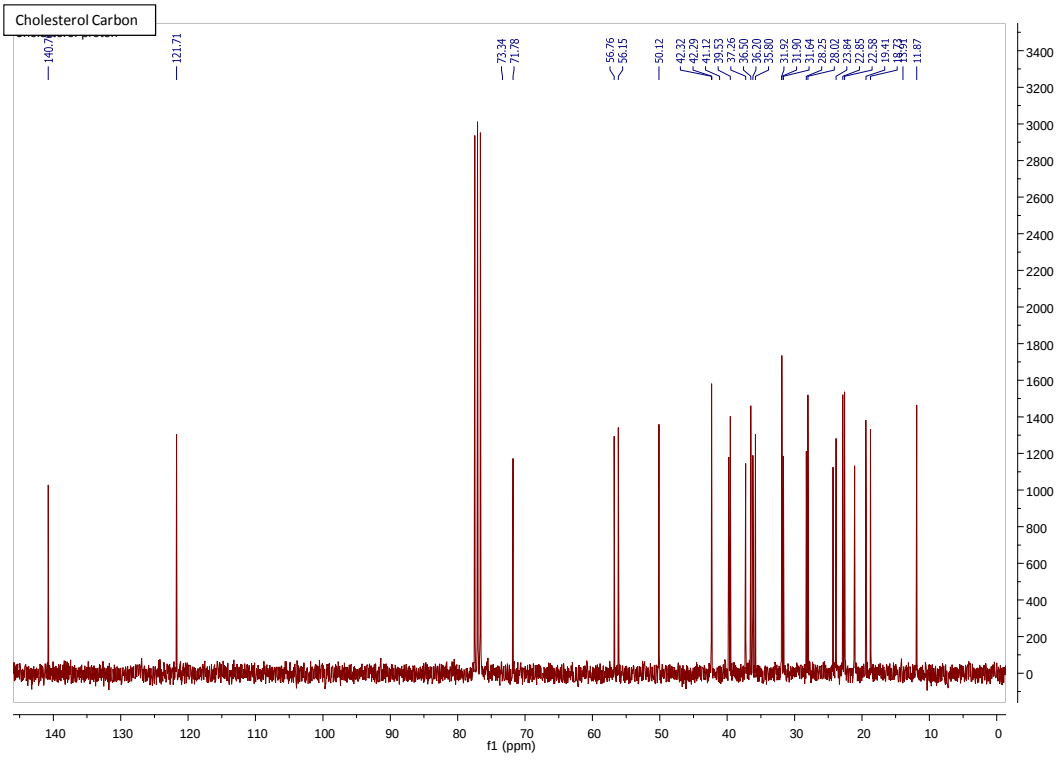


Fig. **SM 12.3.2.**7. ^{13}C NMR of cholesterol

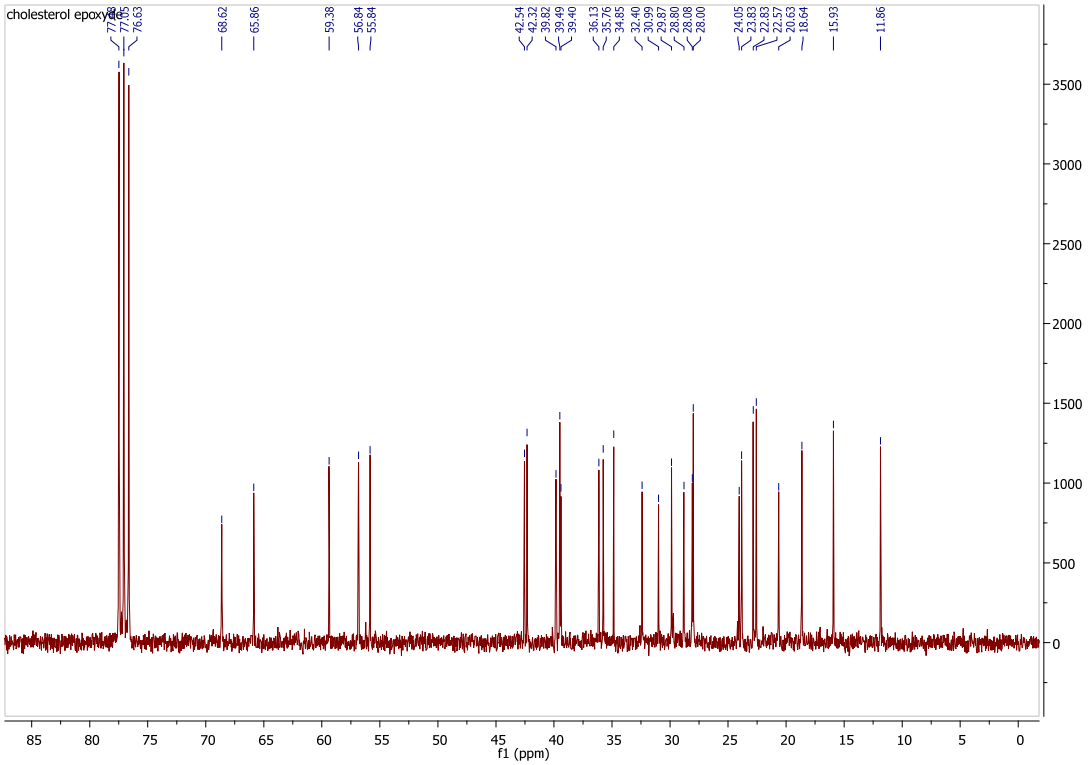
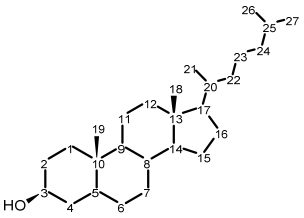


Fig. **SM 12.3.2.**8. ^{13}C NMR of the final product: epoxy-cholesterol



Cholesterol framework numbering for NMR interpretation

^{1}H NMR signal (frame number)	**Cholesterol (δ/ppm)**	**Epoxy-Cholesterol (δ/ppm)**
6	5.35-5.36	2.83-2.84 (α) and 2.99-3.00 (β)
3	3.52	3.82
^{13}C NMR signal (frame number)	**Cholesterol (δ/ppm)**	**Epoxy-Cholesterol (δ/ppm)**
3	71.8	68.62
5	140.8	65.86
6	121.7	59.38

Table SM 12.3.2.2. Key differences in the NMR spectra between the reagent cholesterol and the reaction product, epoxy-cholesterol.

^{1}H NMR signal (frame number)	**δ (ppm)**	**Pattern splitting**
18 (CH_3)	0.54	s
27	0.78	d
26	0.80	d
21	0.83	d
19 (CH_3)	0.99	s
7, 12	1.86	
4	2.0	m
3	3.82	m

Table SM 12.3.2.3. Additional values in the ^{1}H NMR spectra for the epoxy-cholesterol.

References:

1. (a) L. F. Fieser and M. Fieser, Steroids, 1959, Reinhold Publishing Corporation, New York, pp194, 197.

   (b) http://steraloids.com/cholest-basesd/cholestan-5-6-epoxy-3-ol.html- mp. 141-141.5ºC

2. J. Clayden, N. Greeves, S. Warren, P. Wothers, Organic Chemistry, Oxford University Press, First Ed., 2001, pp 506.
3. A. Sevanian and L.L. McLeod, *J Biol Chem*, 1986, **261**, 54.
4. M. Poirot, S.S.Poirot, *Biochimie*, 2012, **95**, 622.

Green Oxidation of Organic Compounds Using Metalloporphyrins

Supplementary Material

Experiment Notes

Figures

Experiment Notes:

The experiment involves the oxidation of organic substrates using H_2O_2 and metalloporphyrins as the catalyst. Two different catalyst systems are compared and the reaction catalyzed by Fe(TPPF5)Cl yields much better results in comparison to the Fe(TPP)Cl catalyzed reaction, see Table SM 12.3.3.1. Since the simple (and readily synthesized) Fe(TPP)Cl metalloporphyrin catalyst is not as robust, it degrades during the oxidation reactions leading to minimal oxidation product.[1] However, the use of chloro[tetrakis(pentafluorophenyl)porphyrinate iron(III), Fe(TPPF5)Cl, produces a higher yield of oxidized organic product.[2] The cyclooctene obtained from Sigma-Aldrich contained trace amounts of cyclooctene oxide that was quantified in the control experiment. After addition of Fe(TPPF5)Cl, the concentration of cyclooctene oxide increased by a factor of 50, from 1.8 mM to 100 mM. In comparison, the Fe(TPP)Cl catalyzed reaction showed no increase in cyclooctene oxide concentration.

Comparing the yields from the two metalloporphyrins introduces the students to a discussion on catalyst design and generational change in catalysts. The students are challenged to think of which would be better, a fluorinated catalyst that may not be considered “green” in terms of its chemistry but produce a desired product and is only used in small quantities. When using the Fe(TPPF5)Cl catalyst, the oxidation of cyclooctene produces a yield of 7% cyclooctene

oxide based on moles of product obtained divided by moles of reactant used times 100. The oxidation of cyclohexane produces a minimal amount (< 0.3 mM) of cyclohexanol, highlighting the difficulty of oxidizing alkanes in comparison to alkenes.

The experiment was reproduced multiple times during the development of the laboratory experiment by a junior undergraduate student (Anne E. Stock, co-Author). The experiment has been reproduced many times by students in a junior/senior level undergraduate course over three different semesters at Saint Francis University (PA, USA). During laboratory implementation, student results varied from zero substrate conversion to results comparable to those shown in the Figure SM 12.3.3.1, Figure SM 12.3.3.2, and Table SM 12.3.3.1 (produced by A.E.S). A key factor in obtaining good results was the student ability to prepare solutions and their pipetting skills. Students who were less proficient at pipetting microliter amounts did not achieve conversion rates obtained by the student co-author. It is suggested that the students pass a quality control test on their pipet technique before this experiment.

The experiment is designed to expand the student's view of green chemistry by focusing on catalysis and functionalizing alkanes and alkenes. The students performed the described experiment in groups within a 4 hour lab period. Each group prepared a set of solutions and performed the experiment and then loaded the aliquots onto a Thermo Trace GC/MS with an autosampler.

Note on Solutions: Instructors may want to prepare some of the solutions beforehand. Porphyrin solutions tend to be light sensitive so any pre-prepared solutions must be placed in a tightly sealed container protected from light.

Table SM 12.3.3.**1**: Comparison of concentrations of cyclooctene oxide formed with the two metalloporphyrin catalysts

	Fe(TPPF5)Cl (n=6)*		Fe(TPP)Cl (n=4)*	
	Average [cyclooctene oxide] (mM)	Std. Deviation	Average [cyclooctene oxide] (mM)	Std. Deviation
Substrate, Pre H_2O_2 addition	1.2	0.9	2.0	0.3
Substrate, Post H_2O_2 addition (Control 2)	0.7	0.9	1.3	0.6
Reaction Mixture with Catalyst, Pre H_2O_2 addition	1.8	0.9	2.0	1.0
Reaction Mixture with Catalyst, Post H_2O_2 addition	100	300	1.7	0.9

* n refers to the number of experimental trials completed

Figures:

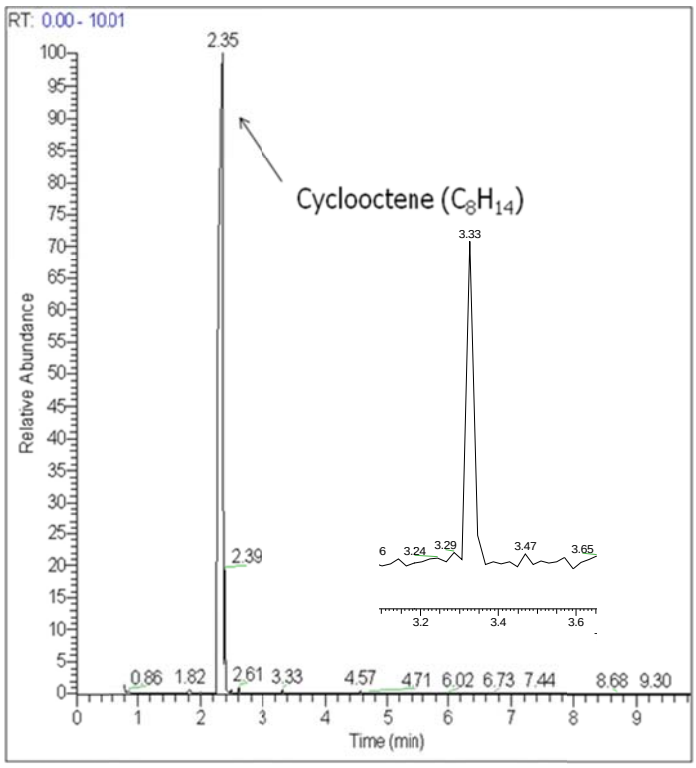


Figure SM 12.3.3.**1**: GC/MS response for cyclooctene prior to the oxidation. The decane peak is not visible compared to the relative abundance of cyclooctene. The inset on the right shows the magnified peak for the decane internal standard at 3.33 minutes.

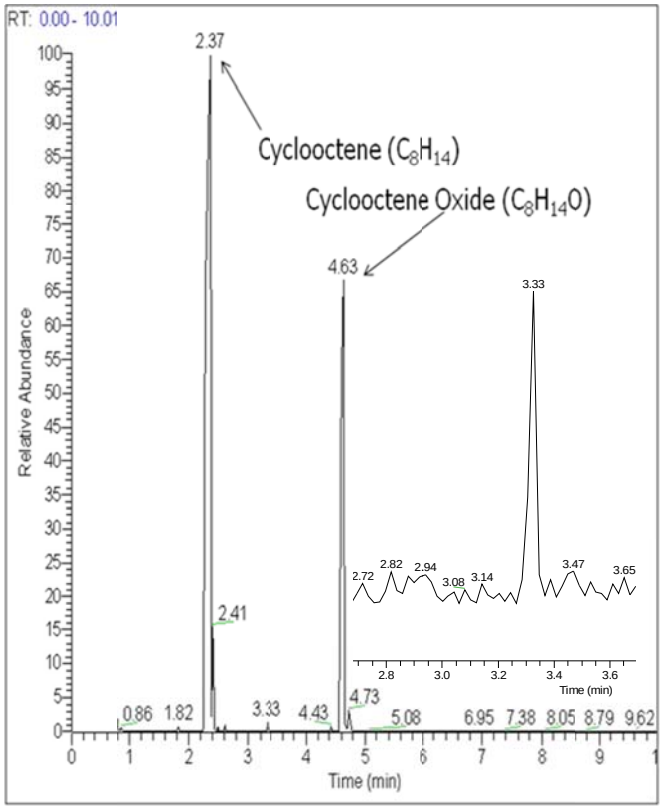


Figure SM 12.3.3.**2**: GC/MS response for cyclooctene after oxidation. The inset on the right shows the magnified peak for the decane internal standard at 3.33 minutes.

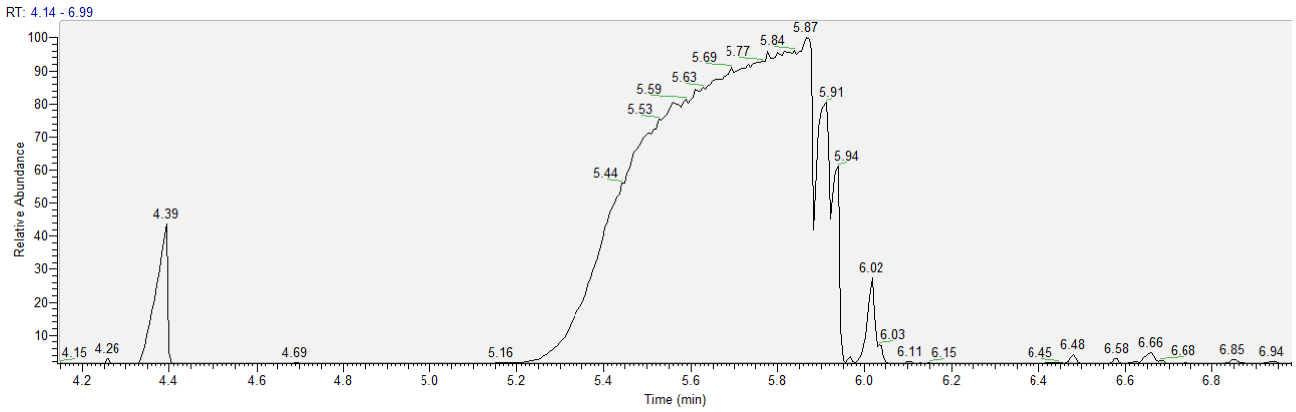


Figure SM 12.3.3.**3:** Screen capture of student collected GC/MS response for cyclooctene oxide after oxidation of cyclooctene by Fe(TPPF5)Cl . The peak at 4.39 minutes is the decane internal standard while the broad peak from 5.3-6 minutes is the cyclooctene oxide. The GC column used in Figure SM 12.3.3.1 and SM 12.3.3.2 is not the same as in Figure SM 12.3.3.3 and SM 12.3.3.4.

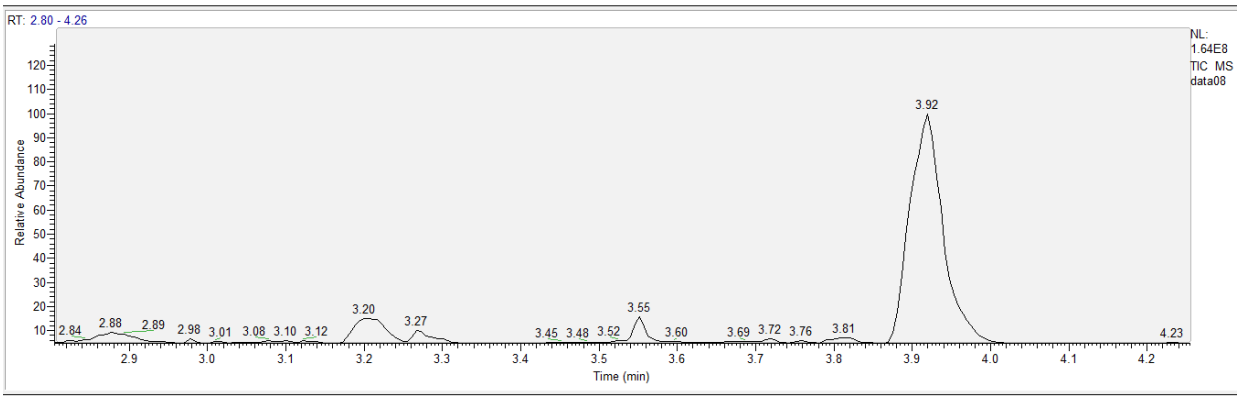


Figure SM 12.3.3.**4:** Screen capture of student collected GC/MS response of cyclohexanol after oxidation of cyclohexane by Fe(TPPF5)Cl . The peak at 3.92 is the decane internal standard while the peak at 3.20 minutes is the cyclohexanol. The GC column used in Figure SM 12.3.3.1 and SM 12.3.3.2 is not the same as in Figure SM 12.3.3.3 and SM 12.3.3.4.

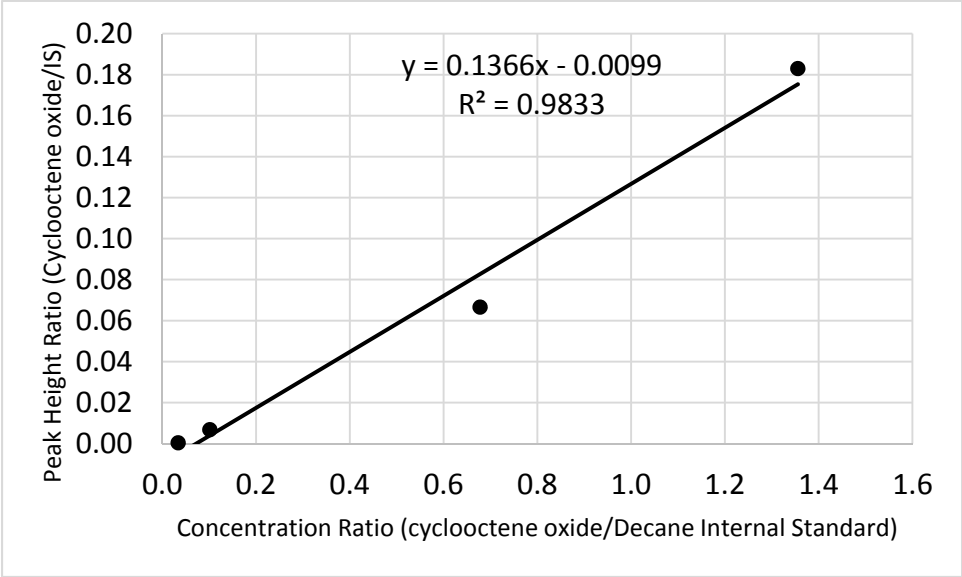


Figure SM 12.3.3.**5:** An example calibration plot for cyclooctene oxide/decane from student data.

Student Report Expectations:

Introduction: 20 points

Introduce why the functionalization of organics is important and why catalysis is critical for the success of these reactions. Why is it important for chemists to use green chemistry methods?

Data: 20 points

Ensure your tables are complete, have appropriate titles, center data

Discussion: 30 points

Analyze the data – was the process successful in transforming the organic substrates to a new oxygenated material. Reflect on the "green-ness" of the activity including:
Are the catalysts under study good examples (or not!) of Green Chemistry.
Examine the solvent system and decide if it fits Green Chemistry Principles.
Why is dichloromethane part of the solvent system in the procedure?

Conclusion: 10 points

References: 10 points

References:

1. Dolphin, D.; Traylor, T. G.; Xie, Lily Y. *Acc. Chem. Res.* 1997, **30**, 251.
2. Lane, B.S.; Burgess, K. *Chem. Rev.* 2003 **103**(7), 2457.

Catalytic epoxidation of carbamazepine

Supplementary Material

Experimental notes

Figures

Notes:

In this work, which is planned for a 4 hours session, around 12 students (in groups of two) will synthesise the carbamazepine 10,11-epoxide (**Epoxi-CBZ**) by the reaction of carbamazepine (**CBZ**) with hydrogen peroxide catalysed by the manganese(III) complex of 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphyrin in the presence of ammonium acetate (as co-catalyst), in acetonitrile at 25-30 °C. This work aims to introduce a greener, more sustainable approach for the epoxidation of double bonds, in contrast to the current methods presented in textbooks and developed in traditional laboratory classes. Students are therefore requested to use a safe, easily available and environmentally friendly oxidant (hydrogen peroxide) for the epoxidation of a highly prescribed drug via a biomimetic approach. The process known as the dismutation of hydrogen peroxide is responsible for the formation of water and molecular oxygen, thus diminishing the amount of hydrogen peroxide available for the catalytic epoxidation reaction. This is the reason why approximately four equivalents of oxidant instead of one are added during the 2 hours of reaction.

The addition of the oxidant diluted solution must be done with a micropipette.

The reaction can be monitored by TLC (silica gel plastic sheets with F_{254} indicator). Figure SM 12.3.4.1 represents a picture of the TLC plate obtained after 45 min of reaction. The carbamazepine control

spot is at the left ($R_{f\ (carbamazepine)}$ = 0.25) and the reaction mixture is at the right with the formation of a new spot corresponding to the epoxide product ($R_{f\ (epoxide)}$ = 0.18), using ethyl acetate as eluent.

The reaction can also be monitored by reverse phase HPLC equipped with a UV/Vis detector and a C18 (10 μm) reversed-phase column [CH_3CN/H_2O (30:70), λ = 215 nm, flow rate 1.0 mL/min, at room temperature]. The HPLC chromatogram of the **CBZ** epoxidation after 45 min of reaction is shown in Figure SM 12.3.4.2. Please note that each HPLC run will need about 10 min to be completed.

The structure of the **Epoxi-CBZ** is confirmed by ^{1}H NMR spectroscopy by comparison with the^{1}H NMR spectrum of the **CBZ**. The ^{1}H NMR spectra of **CBZ** and **Epoxi-CBZ** are shown in Figures SM 12.3.4.3 and SM 12.3.4.4, respectively. In the ^{1}H NMR spectrum of the epoxide the most important feature is the strong up field shift of the H-10,11 singlet from δ 6.95 ppm in **CBZ** to δ 4.28 ppm in the **Epoxi-CBZ**.

Figure SM 12.3.4.5 shows the typical profile for **CBZ** conversion *vs* time using a substrate/catalyst molar ratio of 150.

Depending on the substrate/catalyst molar ratio used, the reaction can be considered finished when:

- **CBZ** is completely consumed, as observed by TLC or by HPLC;
- no further **CBZ** conversion is observed by TLC or by HPLC.

When a substrate/catalyst molar ratio of 150 is used, the total conversion of **CBZ** is achieved after approximately 2 hours of reaction (Table SM 12.3.4.5). If a substrate/catalyst molar ratio of 300 is used instead, the total conversion of **CBZ** is achieved only after approximately 3 hours of reaction (Table SM 12.3.4.1). For a substrate/catalyst molar ratio of 600, the reaction is even slower and, after four hours of reaction, there is no evident increase of **CBZ** conversion (observed by HPLC). In the ^{1}H NMR spectrum of the extracted final reaction mixture, both the **Epoxi-CBZ** and the non-reacted **CBZ** can be identified, depending on the percentage of conversion of the substrate.

This experiment is intended for a fifth semester organic-inorganic-analytical-physical chemistry laboratory of the BSc Chemistry course, with weekly sessions of 4 hours. Normally, students who enrol in this laboratory have already attended two semesters of organic chemistry, one semester of a practical organic chemistry course, one semester of inorganic chemistry and one semester of a practical inorganic chemistry course.

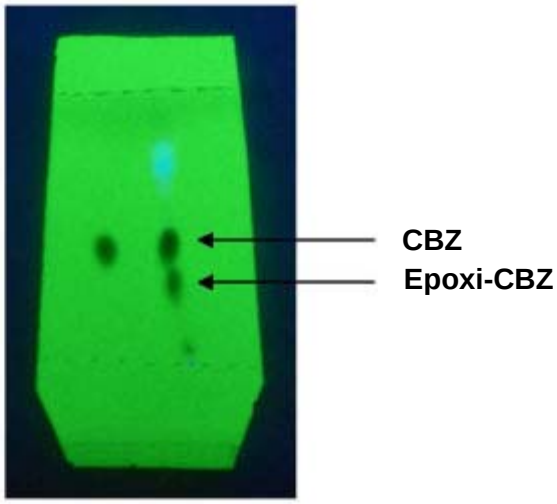


Figure SM 12.3.4.**1** - Picture of the TLC plate obtained after 45 min of reaction. The **CBZ** control spot is at the left and the reaction mixture is at the right with the formation of a new spot corresponding to the **Epoxi-CBZ** product, using ethyl acetate as eluent.

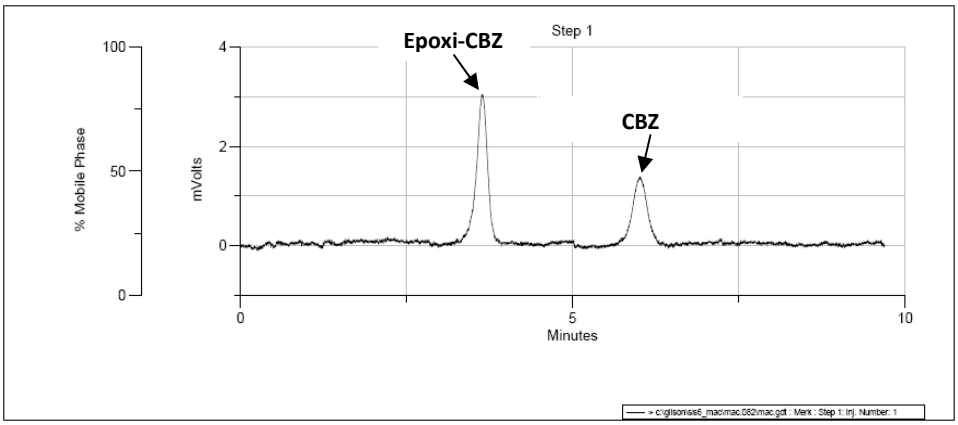


Figure SM 12.3.4.**2 -** HPLC chromatogram of the **CBZ** oxidation reaction after 45 min.

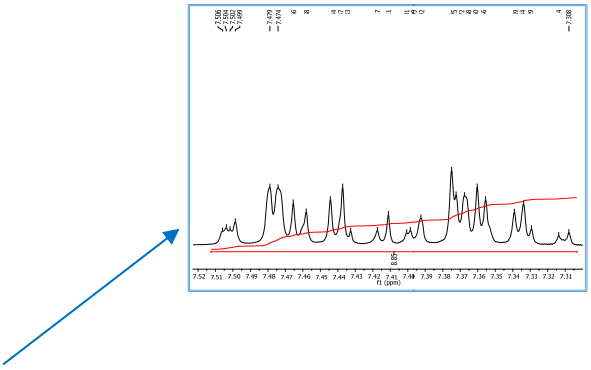


Figure SM 12.3.4.**3.** ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **CBZ**.

Figure SM 12.3.4.**4.** ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **Epoxi-CBZ**.

Figure SM 12.3.4.**5.** Carbamazepine conversion *vs* time of reaction for a substrate/catalyst molar ratio of 150 (6.67×10^{-4} mmol of catalyst) with H_2O_2 as oxidant.

Table SM 12.3.4.**1. Typical results for the oxidation of carbamazepine with hydrogen peroxide catalysed by Mn(TDCPP)Cl[(a)]**

Entry	Substrate/Catalyst Molar Ratio	Time (min)	H_2O_2 (mmol)	Conversion[(b)] (%)	Selectivity[(c)] (%)	TON[(d)]
1	without catalyst	120	4.0	0	—	—
2	150:1	120	without	0	—	—
3	150:1	120	4.0	99-100	100	148-150
4	300:1	180	6.0	99-100	100	297-300
5	600:1	240	8.0	96-98	100	575-587

[(a)]Reaction Conditions: 0.1 mmol of **CBZ**, 6.67 x 10^{-4} or 3.33 x 10^{-4} or 1.67 x 10^{-4} mmol of catalyst and 15 mg of ammonium acetate in a final total volume of 2.0 mL with CH_3CN. Aqueous 30% (w/w) H_2O_2 diluted (1:5) in CH_3CN is added every 15 min of reaction, each H_2O_2 addition corresponding to 0.05 mmol. [(b)]Determined by HPLC (mmol of **CBZ** consumed / initial mmol of **CBZ**). [(c)]Determined by HPLC (mmol of **Epoxi-CBZ** / mmol of **CBZ** consumed). (d) mmol of **Epoxi-CBZ** / mmol of catalyst.

Regioselective epoxidation of geraniol by $VO(acac)_2$ immobilised in polystyrene

Supplementary Material

This transformation allows an interconnection between organic chemistry and inorganic-organometallic chemistry in terms of rationalisation of the involved mechanism and also on the possibility of the utilization of the catalyst synthesised by students in the classes of inorganic-organometallic chemistry. This work was performed by several students of Chemistry Degree at Instituto Superior Técnico (IST) for several consecutive years in which the catalyst was prepared by the same students in another laboratory course. One group obtained 0.98 g (= 82%) of catalyst immobilised in polystyrene with a molecular weight inferior to the described (Mw = 45 000) and for the oxidation step the conversion was followed by TLC (Figure **SM 12.3.5.**1) and ^{1}H NMR (Figure **SM 12.3.5.**4) and was completed in 2.5 h. It was obtained 0.561 g (= 66%) of an oil.

In the ^{1}H NMR spectrum (Figure **SM 12.3.5.**3) it is possible to confirm the regioselective epoxidation of the olefin *b* relatively to the olefin *a* (Scheme **SM 12.3.5.**1), comparing it with the ^{1}H NMR spectra of the two possible epoxidation products.[1,2] The disappearance of the signal of H-c (Figure **SM 12.3.5.**2) at 5.43 ppm is an evidence that the epoxidation proceed in the double bond *b* instead of in the double bond *a* (Scheme **SM 12.3.5.**1). Also, the appearance of a new signal at 2.96 ppm integrating for one H is characteristic of the H-c (Scheme **SM 12.3.5.**1) of the epoxide. If the epoxidation occurred in the double bond *a*, in the ^{1}H NMR spectrum the signal at 5.06 ppm would disappear and a new one could be seen at 2.7 ppm, approximately. The disappearance of the signal at 4.17 ppm and the observation of a multiplet at 3.82-3.65 ppm is another evidence of the desired regioselective epoxidation. The smaller peaks are related with the epoxide opening as described in the literature[3].

The atom efficiency is calculated by dividing the molecular weight of the desired product by the total sum of the molecular weights of all substances produced in the stoichiometric equation of the reaction(s) involved.[4]

$$Atom\ efficiency = \frac{Molar\ mass\ of\ the\ desired\ product}{Molar\ mass\ of\ all\ the\ products} \times 100 \quad (1)$$

The products formed in this reaction are the epoxide and the *tert*-butyl alcohol:

$$C_{10}H_{18}O + C_4H_{10}O_2 \rightarrow C_{10}H_{18}O_2 + C_4H_{10}O$$

So, the molar mass of the desired product is 170.25 g/mol and the sum of the molar masses of the products formed is 244.37 g/mol (170.25 + 74.12). Applying equation (1) we obtain an atom efficiency of 70%.

The E factor is the actual amount of waste produced in the process, defined as everything without the desired product. It takes the chemical yield into account and includes reagents, solvent losses, all process aids, but there is one exception: we generally excluded water from the calculation of the E factor.[5]

The E factor is calculated using the following equation:

$$E\ factor = \frac{m_{waste}}{m_{product}} \qquad (2)$$

For the epoxidation step the waste is composed of hexane (13.1 g), $VO(acac)_2$ immobilised in polystyrene (0.3 g) and *tert*-butanol (0.481 g). Considering the production of 0.561 g of epoxide we have an E factor of:

$$E\ factor = \frac{13.1 + 0.3 + 0.481}{0.561} = 24.7$$

This reaction has a high E factor which is indicative that it has a negative impact in the environment (Table **SM 12.3.5.**1).

Table SM 12.3.5.1. The E factor[5].

Industry segment	Product tonnage	kg waste/kg product
Oil refining	10^6-10^8	< 0.1
Bulk chemicals	10^4-10^6	< 1-5
Fine chemicals	10^2-10^4	5 → > 50
Pharmaceuticals	10-10^3	25 - > 100

In organometallic catalysis the turnover number (*TON*) is calculated by the number of moles of substrate that a mole of catalyst can convert before becoming inactivated. Considering that 3.6 mol% of catalyst originates 3.3 mmoles of epoxide (= 66%) we have a TON=18.

Optionally, students performed the catalyst reuse and they observe the formation of the product in the two cycles has shown in the ^{1}H NMR spectra of Figures **SM 12.3.5.**4 and **SM 12.3.5.**5.

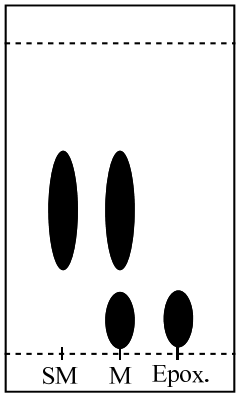
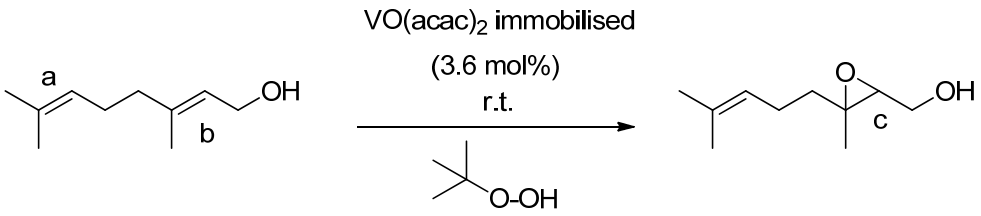


Figure SM 12.3.5.1. Schematic representation of the TLC for the reaction of geraniol epoxidation after 2 h (right) and comparison with geraniol (left). In the middle is the application of the two samples, left and right.



Scheme SM 12.3.5.1. Regioselective epoxidation of the allylic alcohol.

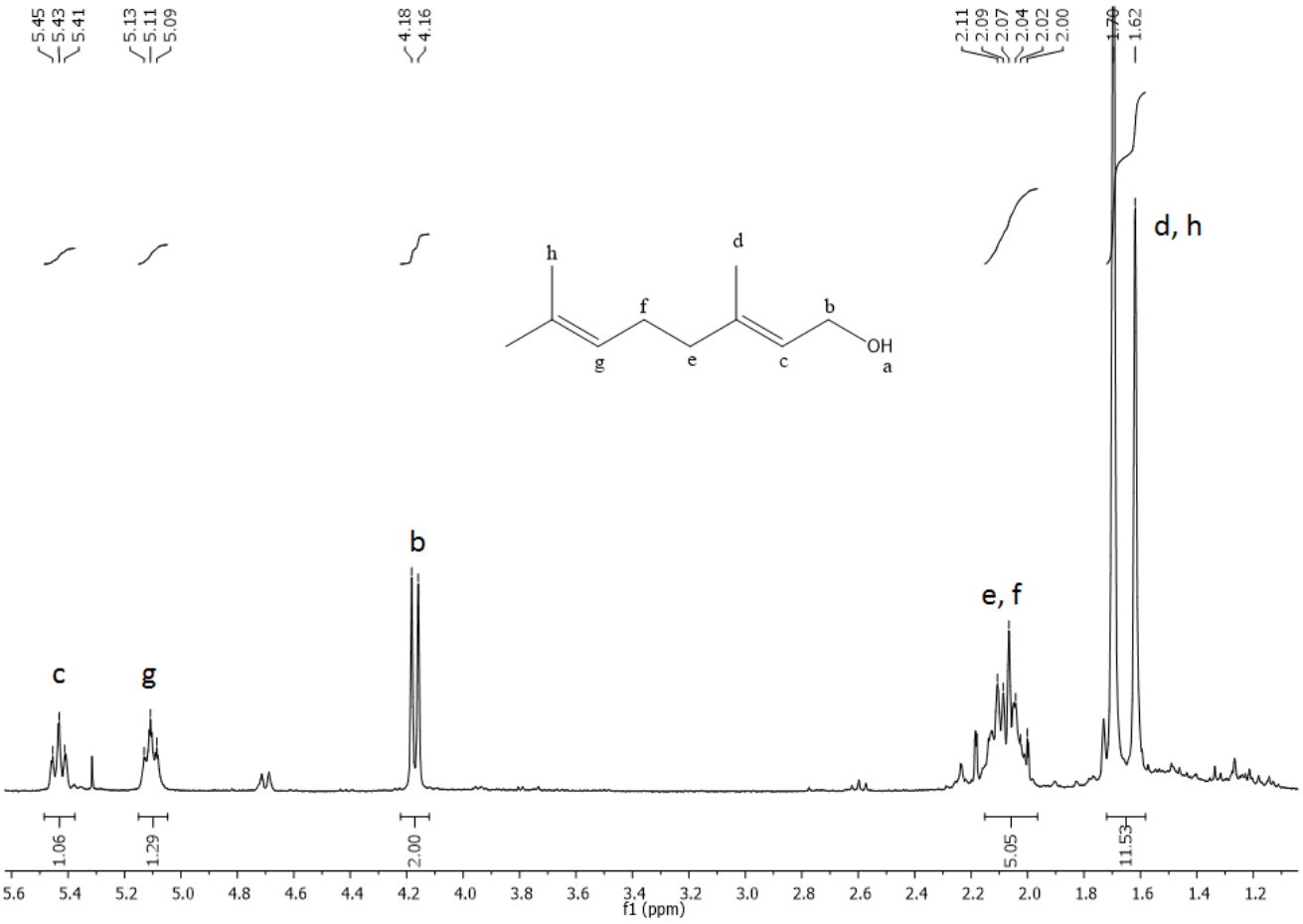


Figure SM 12.3.5.2. ^{1}H NMR ($CDCl_3$) spectrum of commercial geraniol.

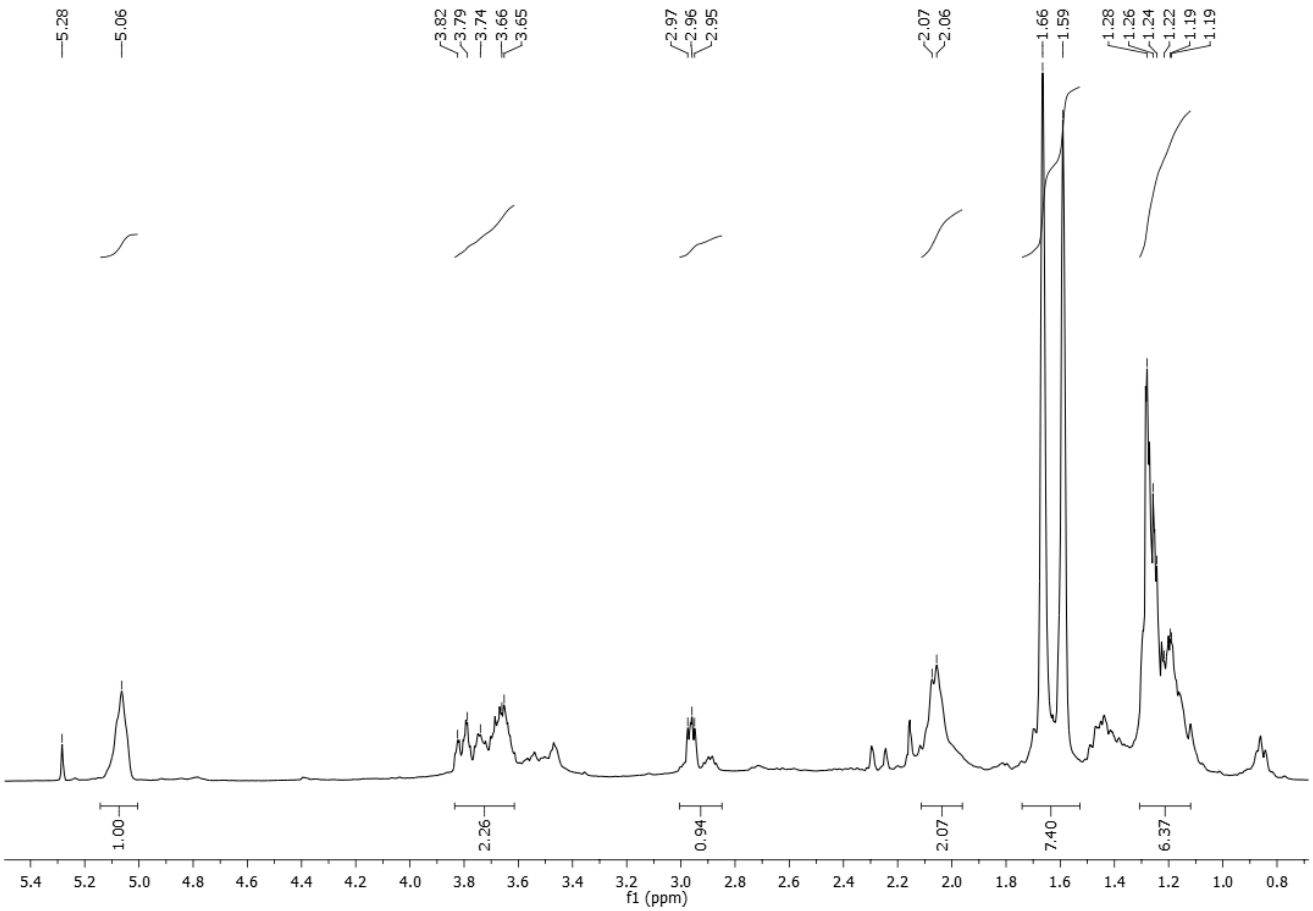


Figure SM 12.3.5.3. ^{1}H NMR ($CDCl_3$) spectrum of the product obtained from the epoxidation of geraniol.

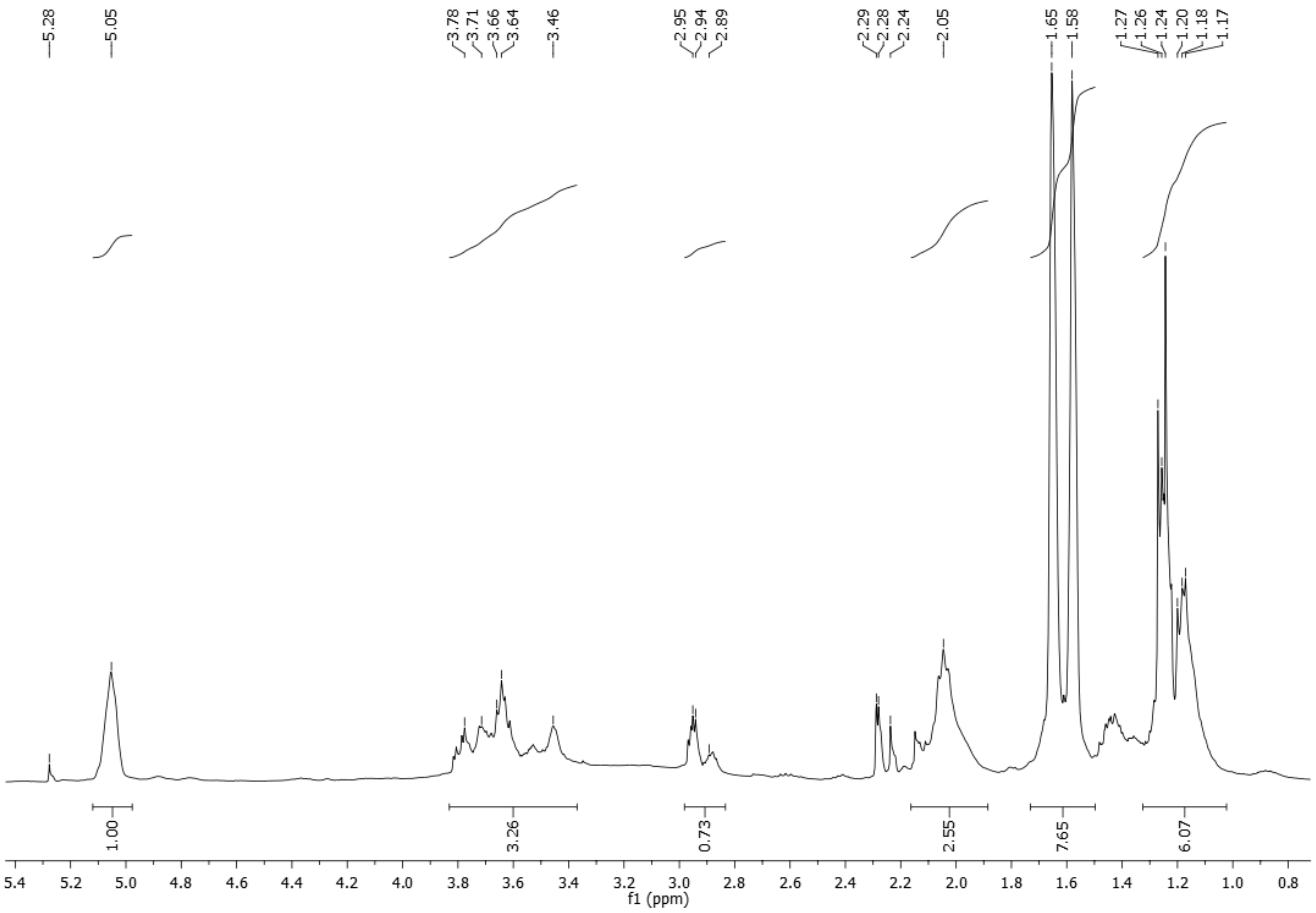


Figure SM 12.3.5.4. ^{1}H NMR ($CDCl_3$) spectrum obtained for the resulting product of geraniol epoxidation using *tert*-butyl hydroperoxide (1st cycle).

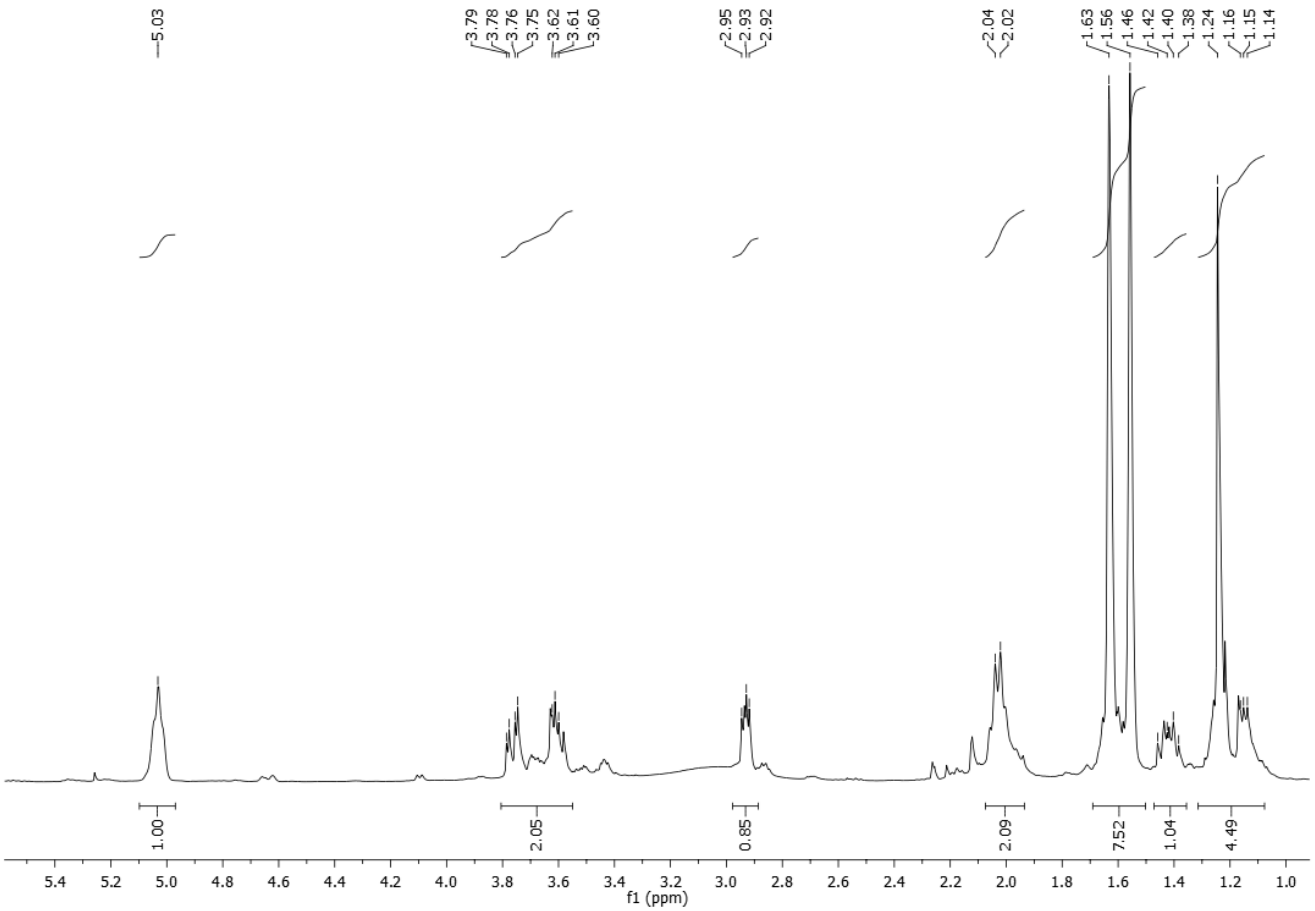


Figure SM 12.3.5.5. ^{1}H NMR ($CDCl_3$) spectrum obtained for the resulting product of geraniol epoxidation using using *tert*-butyl hydroperoxide (2nd cycle).

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[1] Saladino, R., Bernini, R., Neri, V., Crestini, C., *Appl. Catal., A*, **2009**, 360, 171.

[2] Surendra, K., Corey, E. J., *J. Am. Chem. Soc.*, **2008**, 130 (27), 8869.

[3] Wu, Z., *Beilstein J. Org. Chem*., **2013**, 9, 2374.

[4] Sheldon, R. A., *Pure Appl. Chem*., **2000**, 72, 7, 1233.

[5] Sheldon, R. A., *Green Chem.*, **2007**, 9, 1273.

Organocatalysed *trans*-dihydroxylation of olefins

Supplementary Material

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Experiment Notes

This experiment aims at the preparation of *trans*-1,2-cyclohexanediol from the correspondent alkene in a biphasic reaction. Since the starting alkene is not soluble in the reaction medium, it is possible to follow the reaction by direct observation of the disappearance of the starting material, whilst the reaction mixture proceeds to a homogeneous solution containing the solubilized product. As a heterogeneous reaction, it is of pivotal importance that vigorous stirring is used along the process.

After reaching completion, the reaction can be stored in the freezer until the next session.

The neutralization step should be performed before the reduction of the H_2O_2 excess, and the sodium sulfite addition should be done very slowly due to the exothermic character of the process.

The use of hydrogen peroxide water solution as reaction solvent avoids the use of organic solvents, although diethyl ether it is used for the isolation step. It is possible to efficiently isolate the product by the sublimation, avoiding the use of organic solvents, as described below. Hence, after neutralization and reduction of the reaction mixture, the solvent (water) is evaporated and resulting a white solid. This solid is transferred to a sublimation apparatus in order to achieve the isolation of the desired *trans*-1,2-cyclohexanediol. Although some of the *trans*-1,2-cyclohexanediol remains in the reaction

mixture after sublimation, probably due to inefficacy of diol and sodium *p*-toluenesulfonate separation, 90 % of the product is isolated in excellent purity after 4 h. The sublimation technique is emphasized in order to show the students that this technique can be used either as a purification technique or for the separation of compounds.

The reproducibility of the experiment was assessed by its repetitive execution (Table SM 12.3.6.1), namely by 1st year Chemistry M.Sc. students from Technical Superior Institute (Lisbon). Although the reaction does not reach completion in 4h at 75 ºC (one session), the reaction time can be extended to 21 h and yield higher than 95 % can be achieved.

Due to the cyclohexene low boiling point, when a reflux apparatus is used can suffer from leakage of the substrate through the joints, hence this situation can be avoided by using a closed vessel for the reaction.

The reaction can be conducted at 10, 25, or 50 mmol scale of alkene, although isolation by sublimation leads to higher yields if performed at lower scale (10 mmol). The entire product formed can be efficiently extracted by using liquid-liquid extraction with an organic solvent, regardless the initial amount of cyclohexene used.

Table SM 12.3.6.1 describes the results obtained with the use of 1 equivalent of *p*-toluenesulfonic acid. Nevertheless, *p*-toluenesulfonic acid can be reduced to 20 mol %, yielding the product in more than 90 % in longer reaction times (21 h, entry 14, Table SM 12.3.6.1).
This experiment will allow the students to rationalize the reaction mechanism *via* epoxide formation and also allows the use of NMR as a quantitative analytical technique, since they will calculate the reaction yield based on the ^{1}H NMR spectrum.

Several students performed this experience in three 4h sessions, and the feedback was very positive. This are some observations made by the students:

- ✓ “The experiment is quite easy to do, and it is nice to observe the reagent disappearance during the reaction”;
- ✓ “It was useful to perform sublimation and see the product separation without the need of organic solvents”.

Tips to answer the experiment questions

1. Interpret the ^{1}H NMR spectra obtained, and compare the obtained melting point with the literature.

The ^{1}H NMR spectra interpretation is presented in figure SM 12.3.6.5 of this Supplementary Material.

trans-1,2-cyclohexanediol melting point is 101-104ºC (www.aldrich.com).

2. Calculate the reaction conversion by NMR (Internal standard (IS) – chloroacetic acid):

$$mol = \frac{diol\ NMR\ peak\ (2.9\ ppm)}{IS\ NMR\ peack\ (3.8\ ppm)} * \frac{IS\ mass\ (m3)}{IS\ MW}$$

$$Diol\ total\ mass = mol\ diol * diol\ MW * \frac{Total\ sample\ (m1)}{NMR\ sample\ (m2)}$$

Example for Figure SM 12.3.6.5:

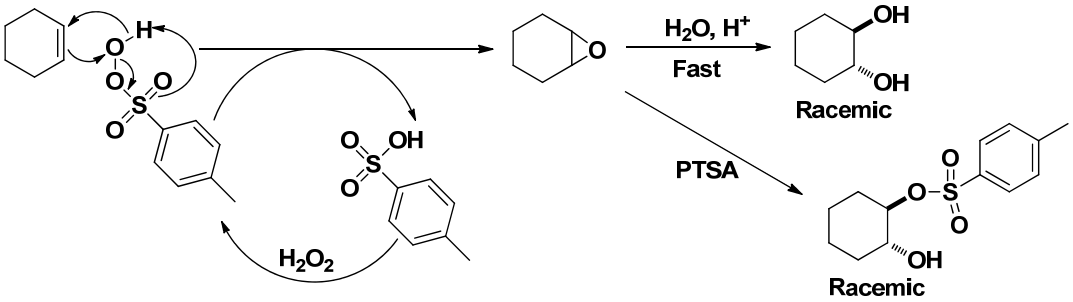
$$mol = \frac{2.19}{1.0} * \frac{0.010}{94.5} = 0.234\ mmol$$

$$Diol\ total\ mass = 0.234\ mmol * 116.16 * \frac{14.64}{0.14} = 2.84\ g$$

$$Diol\ conversion\ (\%) = \frac{Obtained\ mass\ (g)}{Theoretical\ value\ (g)} * 100 = \frac{2.84}{2.90} = 97.9\%$$

3. Calculate the yield, atom economy, and E factor for the overall process. Compare your atom economy and E factor with those reported in the previously reported experiment.
The E factor is defined as the mass ratio of waste to desired product, and the atom efficiency, calculated by dividing the molecular weight of the desired product by the sum of the molecular weights of all substances produced in the stoichiometric equation. [1]

4. Rationalize the involved mechanism of epoxidation and diol formation considering the epoxide ring-opening by water or by *p*-toluenesulfonic acid.



5. Discuss the importance of the promoter *p*-toluenesulfonic acid on the overall process

[1] Sheldon, R. A., *Green Chem.* 2007, **9 (12)**, 1273-1283.

p-Toluenesulfonic acid in the presence of hydrogen peroxide forms the corresponding peroxysulfonic acid that promote the oxidative reaction, resulting on the epoxide formation. This promoter is also important for the acid catalysed epoxide ring opening.

Isolation of *trans*-1,2-cyclohexanediol by sublimation

After the reaction is complete, add 1.2 g of $NaHCO_3$ to the stirred reaction mixture in order to neutralize the acid followed by slow addition of 1.0 g of Na_2SO_3 to reduce the excess H_2O_2. Remove the water by evaporation of the reaction mixture under reduced pressure. Grind the obtained white solid (Figure SM 12.3.6.1) in order to facilitate the sublimation process. Transfer the white solid into a sublimation apparatus, equipped with a magnetic stir bar, as indicated in Figure SM 12.3.6.2. While stirring, decrease the system pressure to 0.5 mm Hg, and then heat the mixture at 75 °C for 4h (Figure SM 12.3.6.3). Remove the sublimated compound (Figure SM 12.3.6.4), weight and determine the sublimation yield.

Table SM 12.3.6.1 – Experiments conducted in a round bottom flask coupled to a condenser[a], using cyclohexene as substrate, H_2O_2 (30 % sol. aq., 2 equiv.) as oxidant, and *p*-toluenesulfonic acid (1 equiv.) as reaction promoter.

Entry	Cyclohexene (mmol)	Temperature (°C)	Reaction Time (hours)	Yield (%, ^{1}H NMR)	Isolated Yield, % [b]	Melting Point (°C)[c]
1	10	65	4	62.1	58.0	99-100
2	10	75	4	65.0	56.0	97-100
3 [d]	10	75	4	64.4	61.2	88-98
4 [d]	10	75	4	65.9	62.3	79-81
5[d]	10	75	4	68.4	58.8	91-94
6	25	50	21	89.2	65.4	100-101
7	25	50	21	91.3	67.2	99-102
8	25	50	21	89.0	60.2	99-100
9	25	50	21	73.5	65.3	98-100
10	25	50	21	97.9[a]	65.4	94-97
11	50	50	21	89.2	63.1	89-94
12[d]	25	50	21	100[a]	55.7	97-100
13	25	25	21	50.0[e]	50.0	-
14[f]	25	50	21	95.5	95[g]	100-101

a) Entries 10-12: reaction perfomed in a sealed, capped tube, resitant to presures above atmospheric one. **b)** Isolated by sublimation. Note: It is possible to collect all compound formed by extraction of the aqueous layer with diethyl ether. **c)** Melting point of the sublimated product (literature m.p., *Aldrich* 100-103ºC)**. d)** Experiments executed by 1st year MSc students. **e)** Reaction performed at room temmperature. A secondary product (*trans*-2-hydroxycyclohexyl-p-toluenesulfonate) was formed in 50 % yield. Such product was isolated by the adding 10 mL of distilled water to the reaction mixture after 21 h at room temperature, inducing the precipitation of *trans*-2-hydroxycyclohexyl-p-toluenesulfonate which was further filtered and washed with more water. This solid was characterized by NMR (Figures SM 12.3.6.9 and SM 12.3.6.10). **f)** 20 mol% of *p*-toluenesulfonic acid were used. **g)** Product was isolated by extraction of the aqueous layer with diethyl ether.

Experiment Photos

Figure SM 12.3.6.**1** – Reaction mixture after water evaporation.

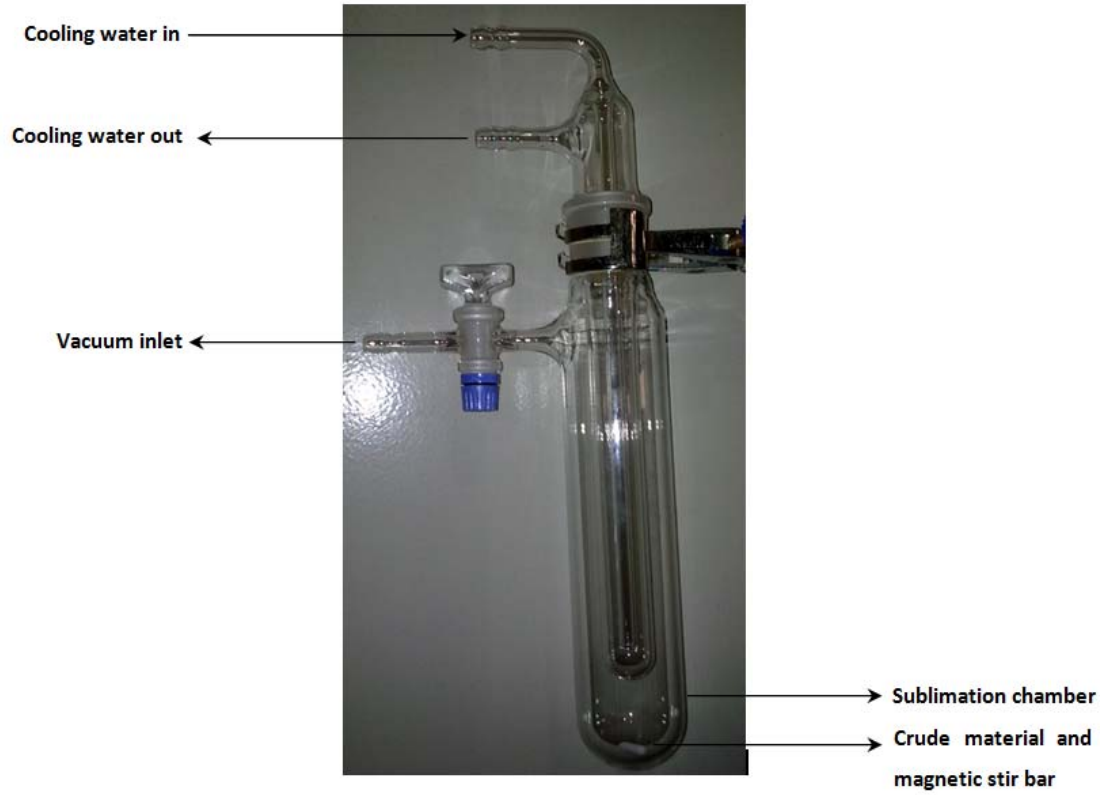


Figure SM 12.3.6.**2** – Sublimation apparatus used for the isolation of *trans*-1,2-cyclohexanediol from the reaction mixture

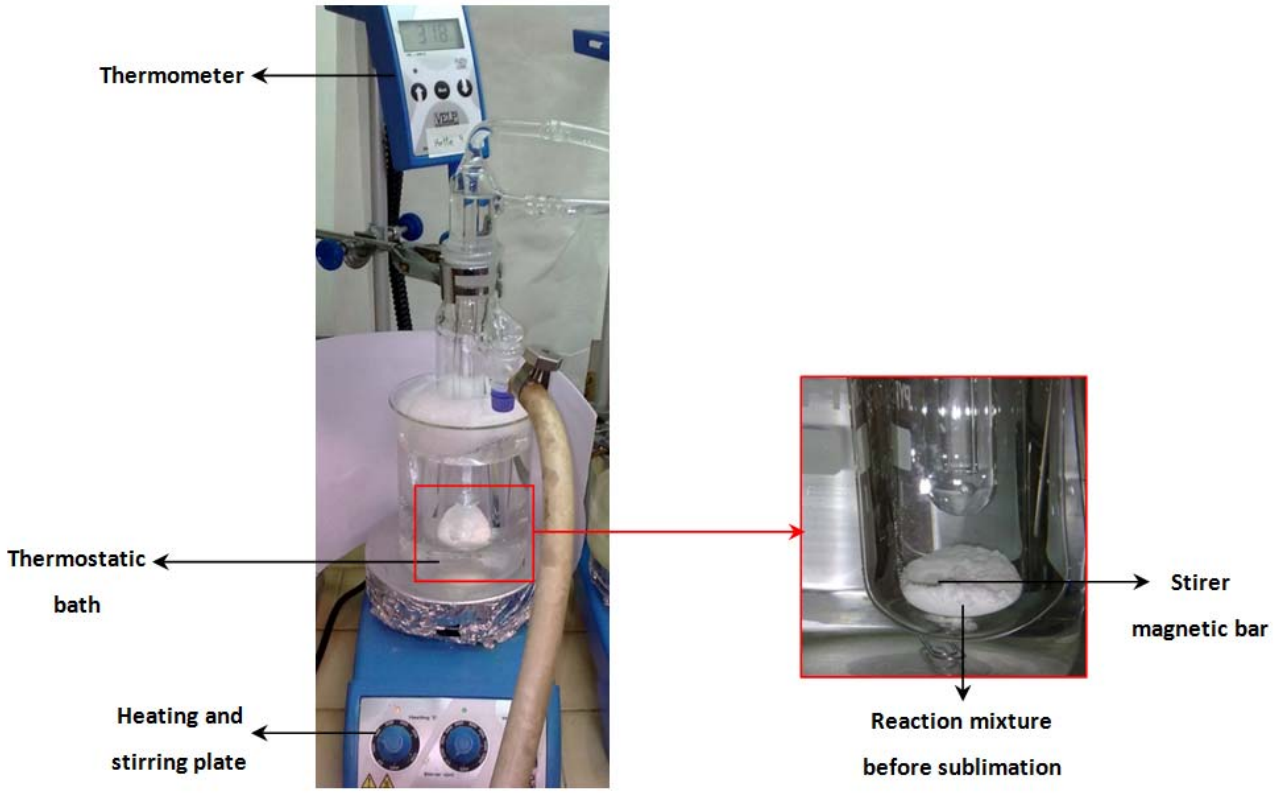


Figure SM 12.3.6.**3** – Early stage of the Sublimation

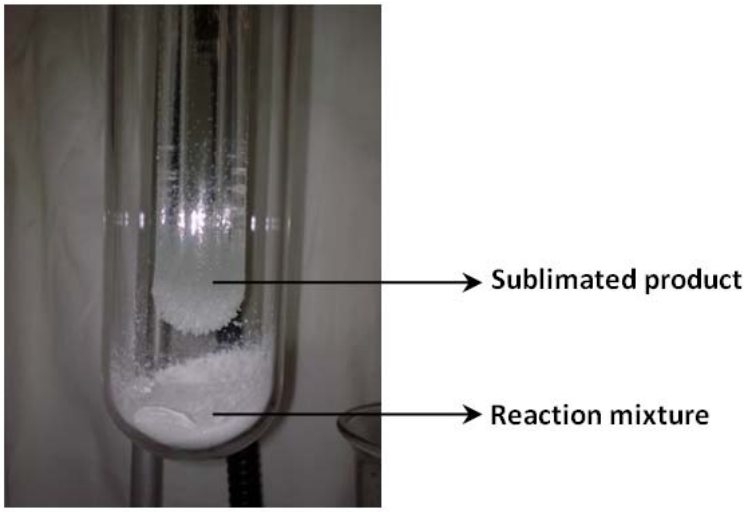


Figure SM 12.3.6.**4** – End of Sublimation

^{1}H and ^{13}C NMR spectra

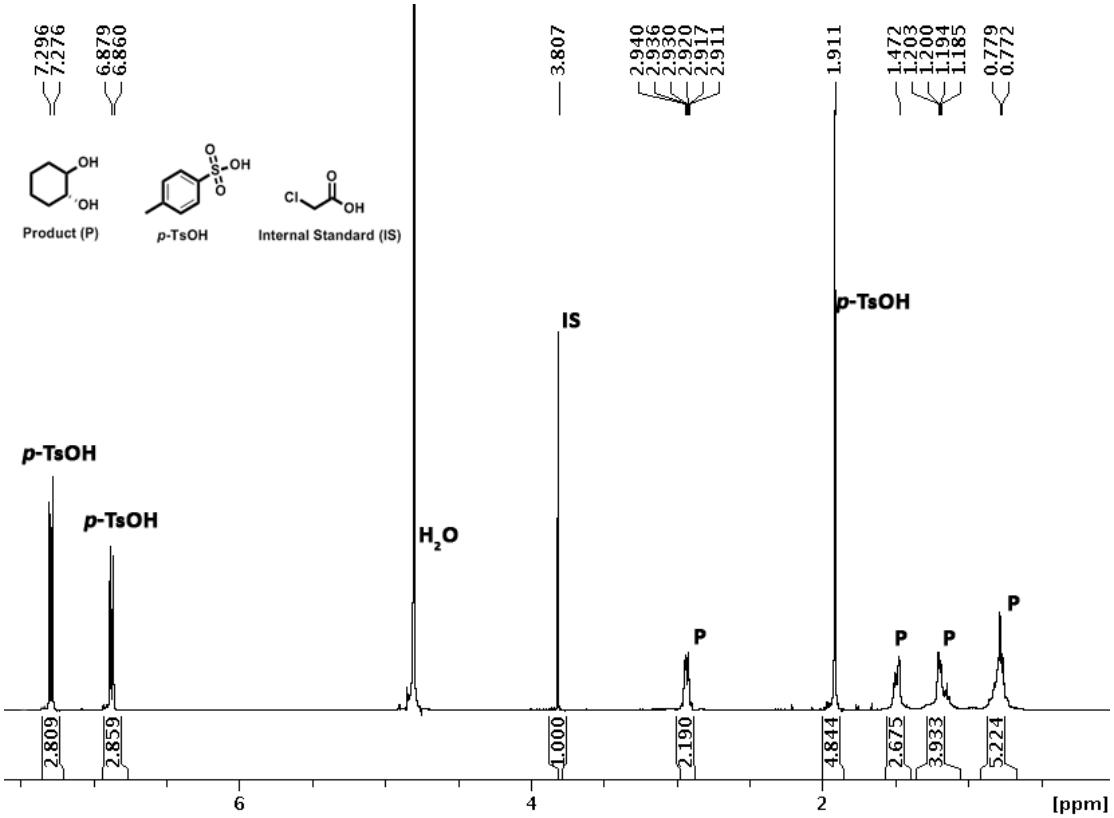


Figure SM 12.3.6.5 – ^{1}H NMR spectrum (400MHz, D_2O) of the crude mixture after 24h of reaction at 50 °C, with chloroacetic acid (IS) as internal standard. Total reaction mass (m1) 14.64g; reaction sample (m2) 0.14 g; IS mass (m3) 10.1 mg.

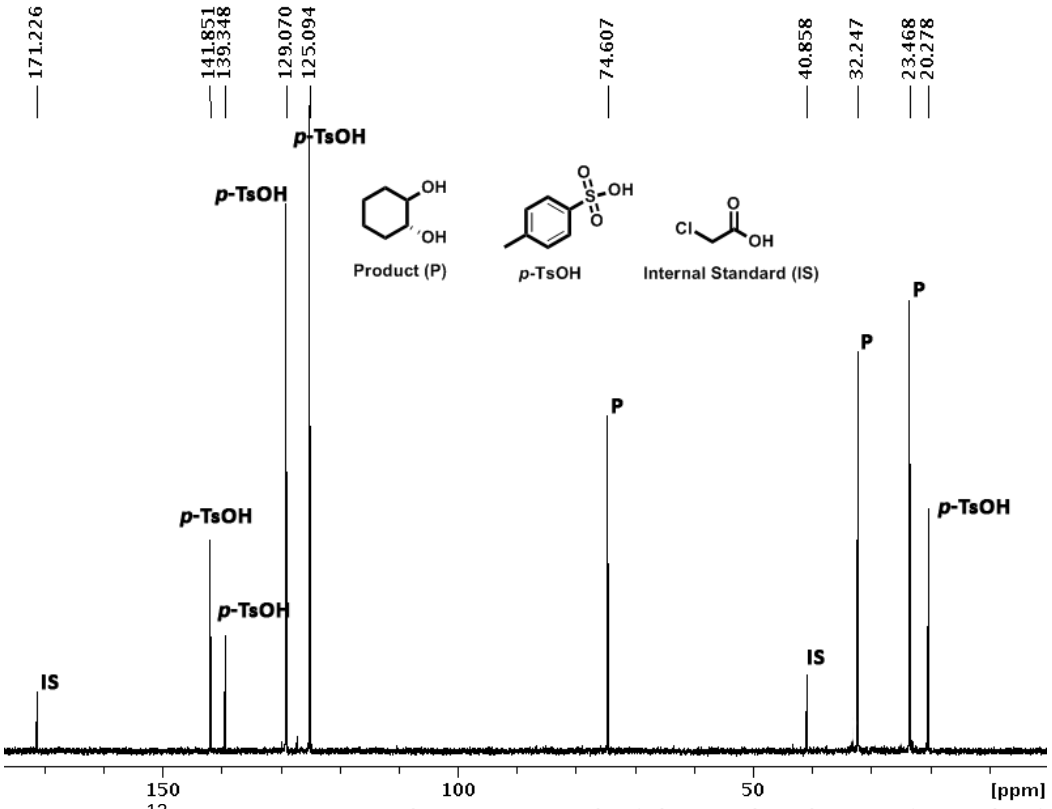


Figure SM 12.3.6.6 – ^{13}C NMR spectrum (100MHz, D_2O) of the crude mixture after 24h of reaction at 50 °C, with chloroacetic acid as internal standard (IS).

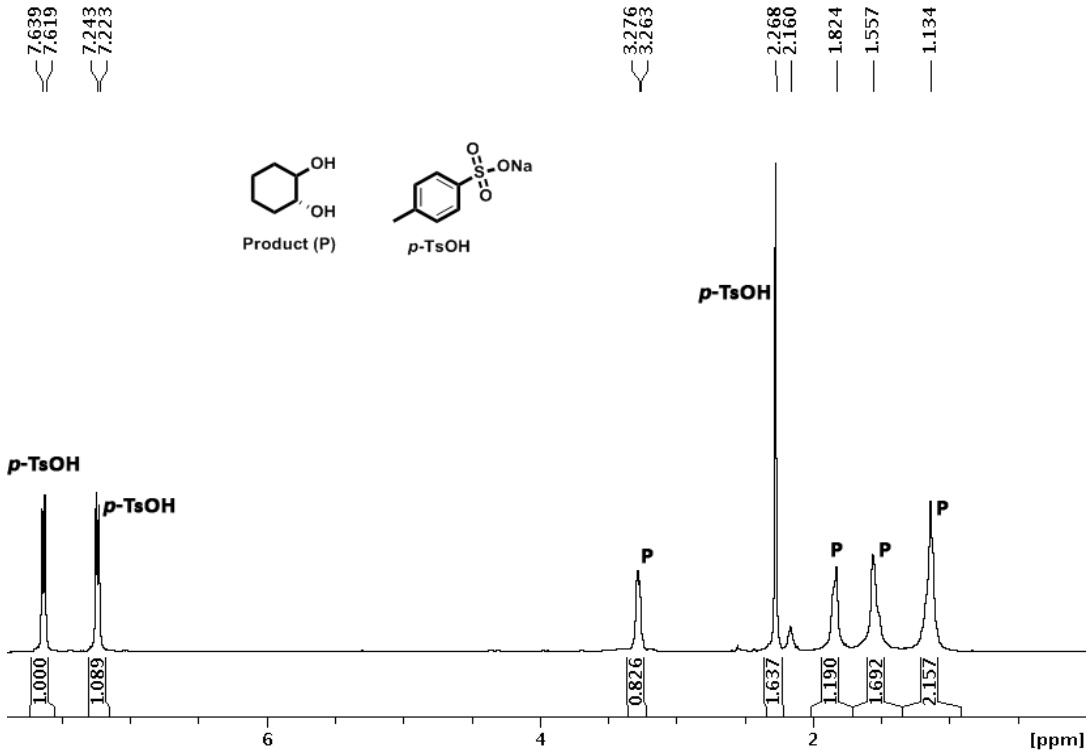


Figure SM 12.3.6.7 – ^{1}H NMR spectrum (400MHz, D_2O) of the reaction mixture after neutralization with $NaHCO_3$ and reduction with Na_2SO_3.

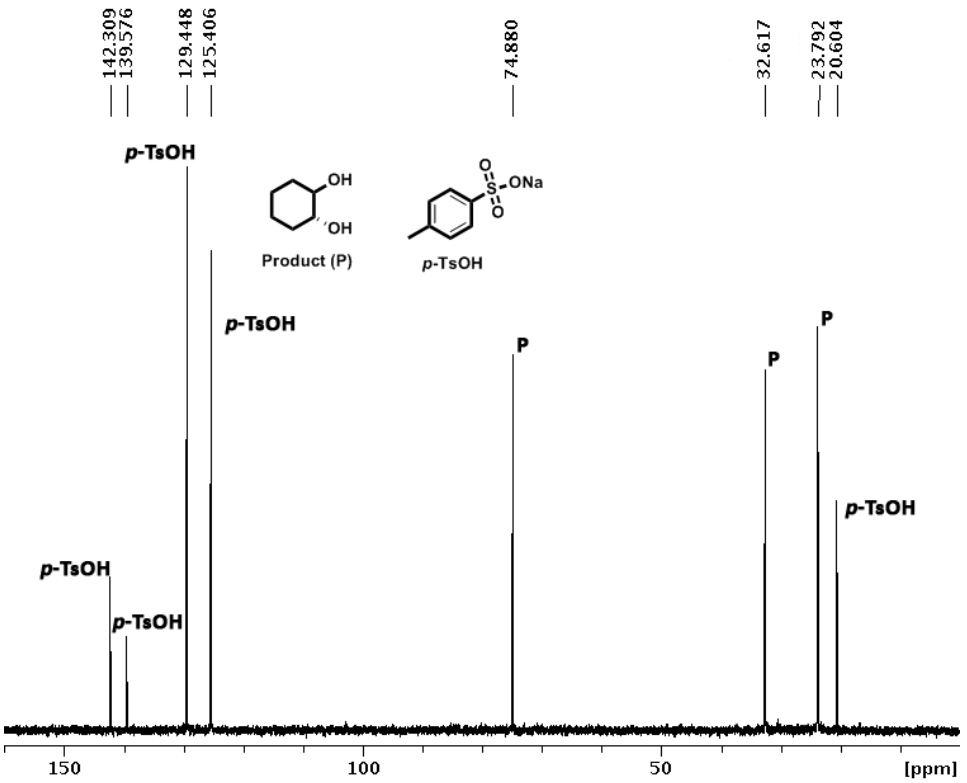


Figure SM 12.3.6.8 – ^{13}C NMR spectrum (100MHz, D_2O) of the reaction mixture after neutralization with $NaHCO_3$ and reduction with Na_2SO_3.

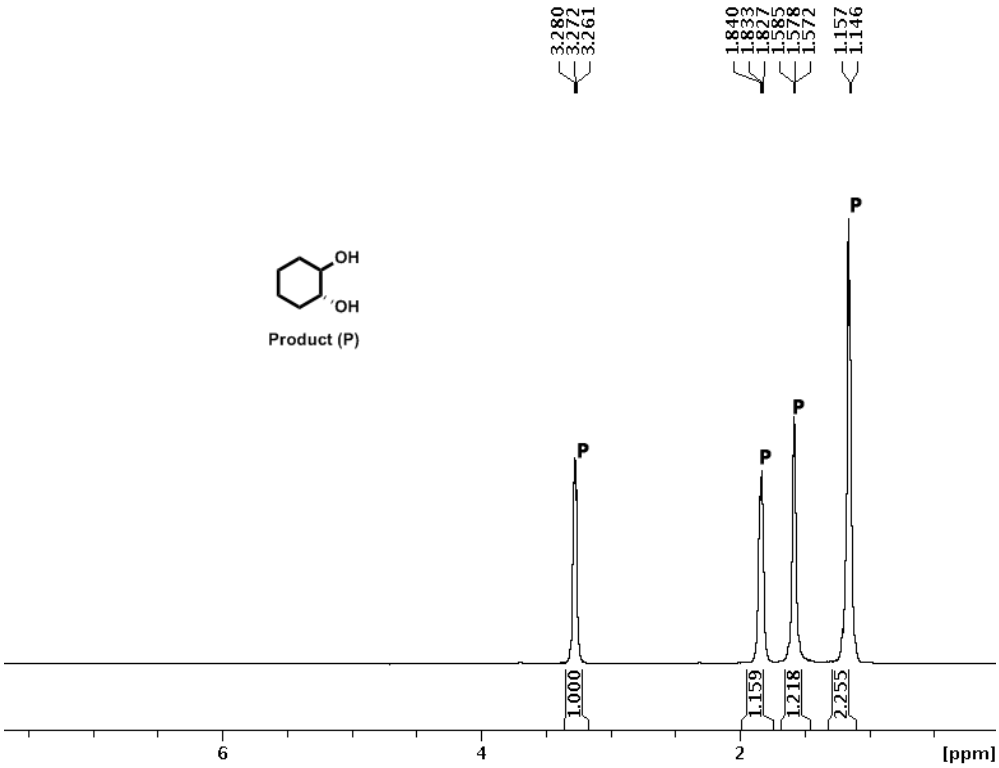


Figure SM 12.3.6.9 – ^{1}H NMR Spectrum (400MHz, D_2O) of *trans*-1,2-cyclohexanediol.

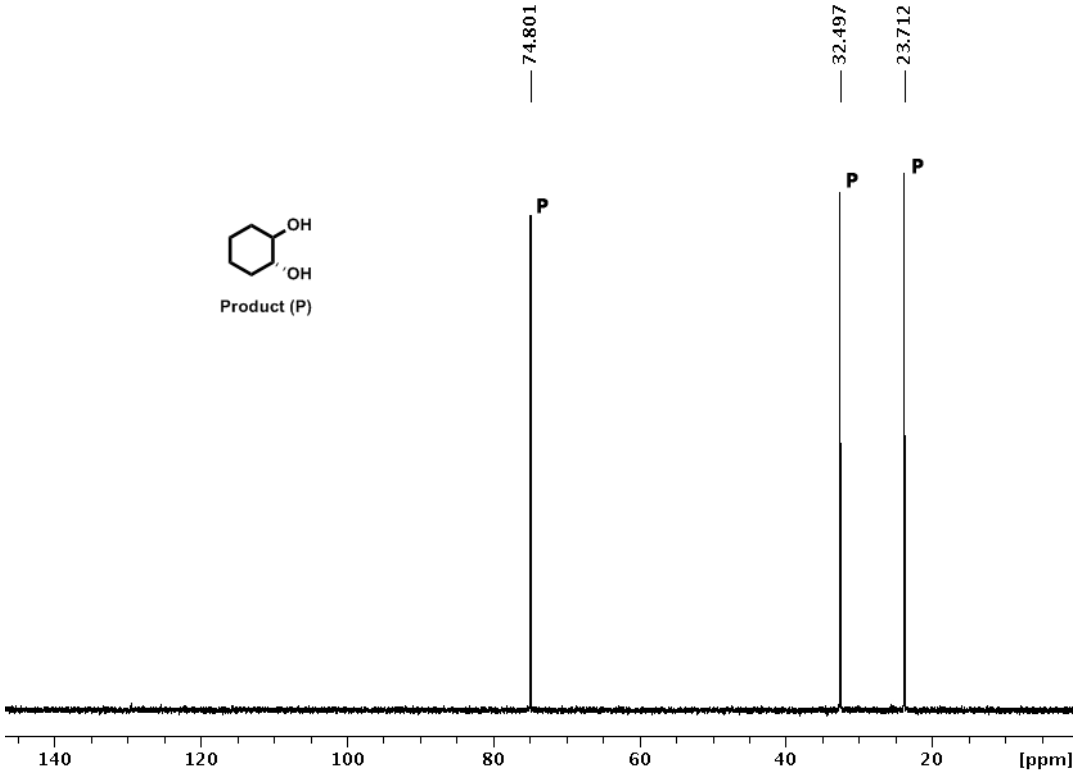


Figure SM 12.3.6.10 – ^{13}C NMR Spectrum (100MHz, D_2O) of *trans*-1,2-cyclohexanediol.

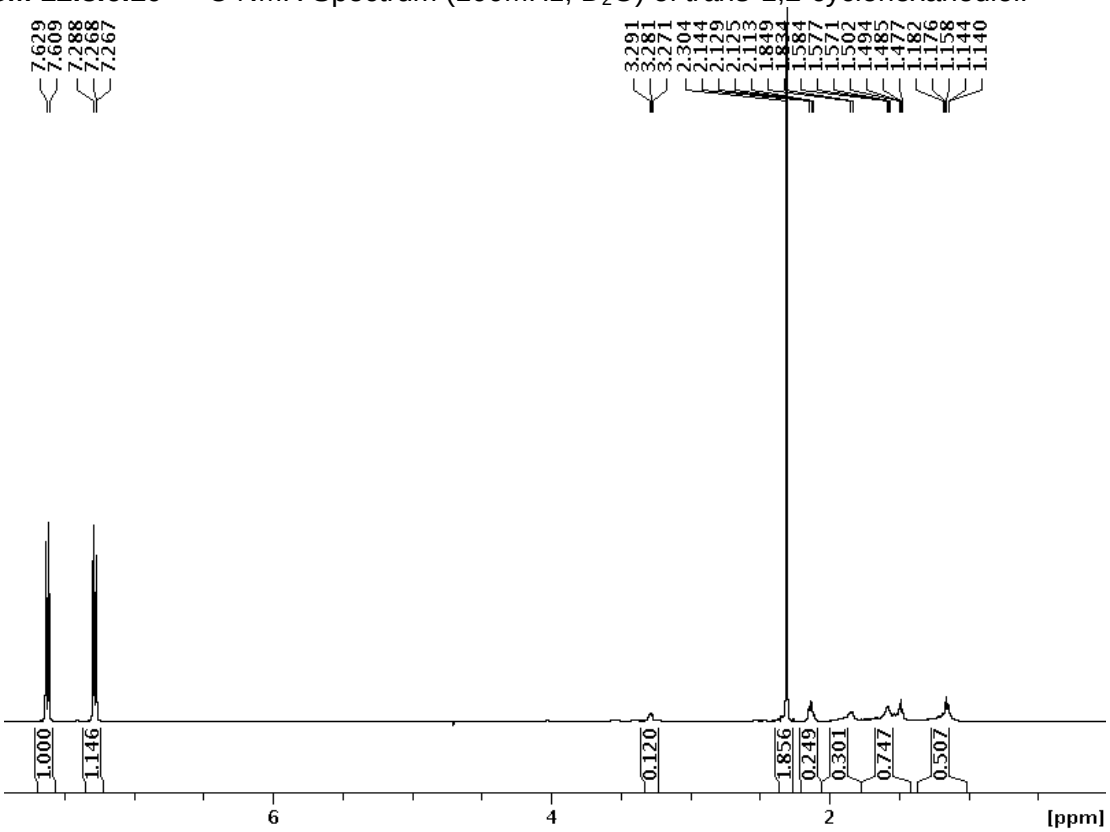


Figure SM 12.3.6.11 – ^{1}H NMR spectrum (400MHz, D_2O) of the remaining solid in the bottom of the sublimation apparatus after trans-1,2-cyclohexanediol sublimation.

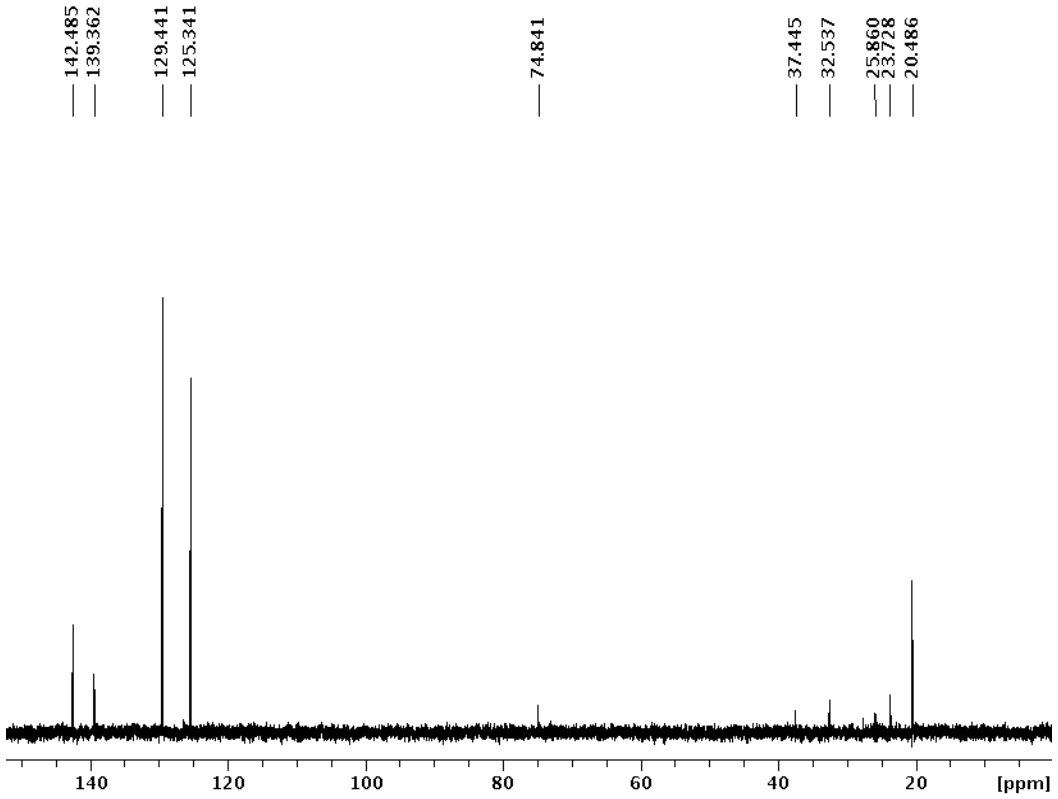


Figure SM 12.3.6.12 – ^{13}C NMR spectrum (100MHz, D_2O) of the remaining solid in the bottom of the sublimation apparatus after trans-1,2-cyclohexanediol sublimation.

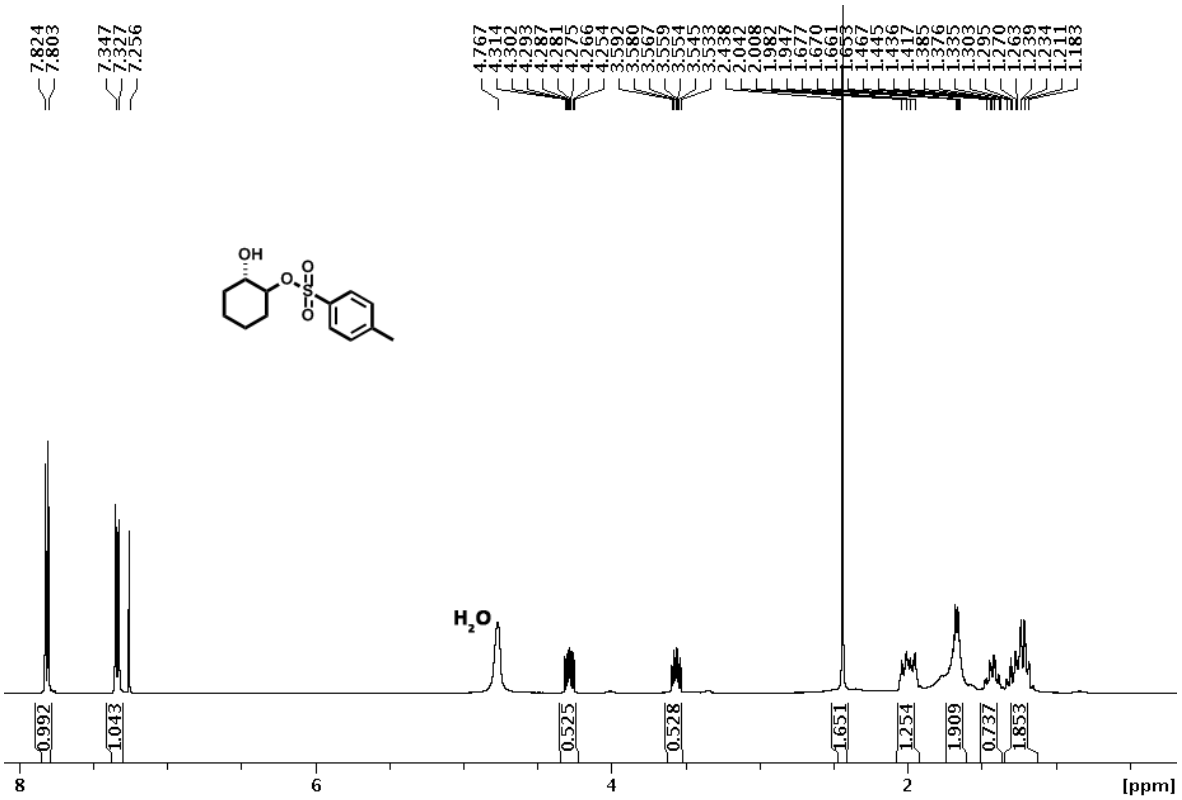


Figure SM 12.3.6.13 – ^{1}H NMR Spectrum (400MHz, $CDCl_3$) of *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate.

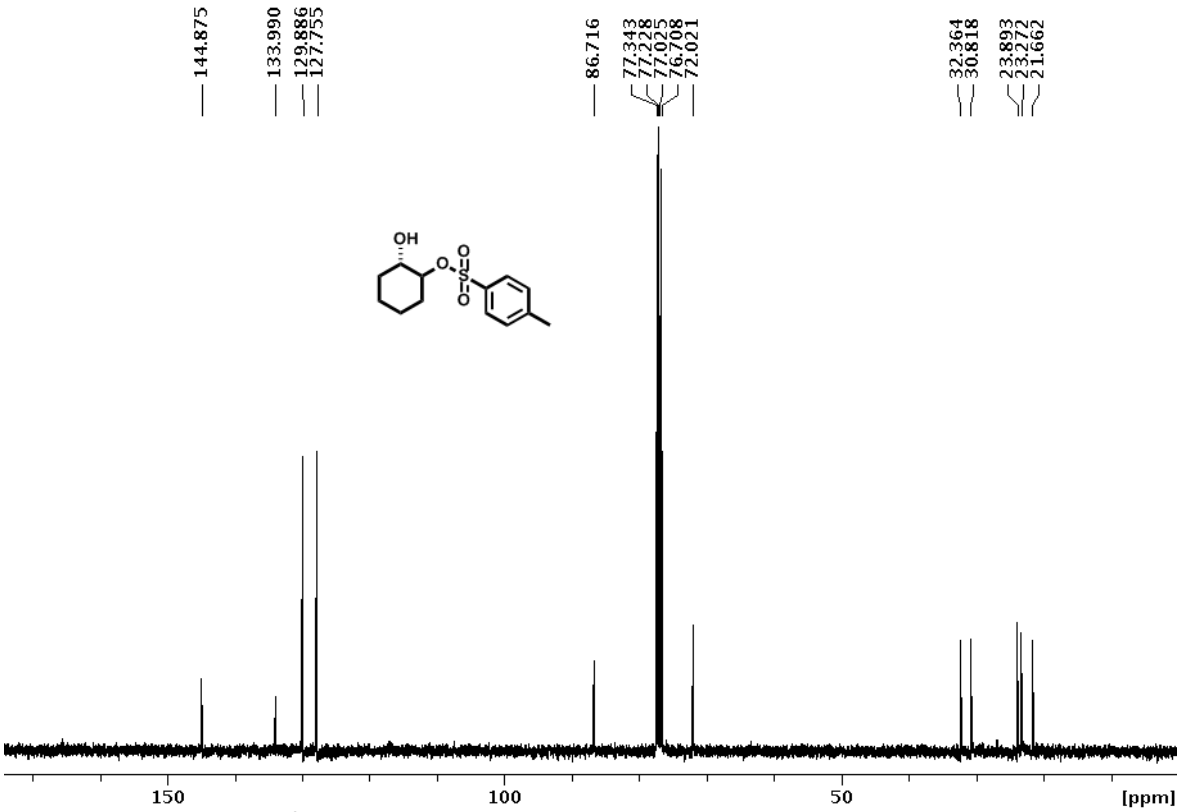


Figure SM 12.3.6.14 – ^{13}C NMR Spectrum (100MHz, $CDCl_3$) of *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate.