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Studies of the Reaction of Rongalite with Epoxides

Anuj Aryal
Montclair State University

Abstract

Reactions between Rongalite ($Na^+O^-SOCH_2OH$) and epoxides were studied with the aim of developing new synthetic routes for the procurement of sulfone diols. This class of compounds contains essential building blocks in the construction of sulfur heterocycles, which have been implied in the development of several medicinal compounds. Thus far, the desired diols have not been isolated. During control experiments with bromo alcohols, an unknown product was isolated but remains to be identified.

Keywords: Rongalite, epoxides, sulfones, diol synthesis

MONTCLAIR STATE UNIVERSITY

Studies of the reaction of Rongalite with epoxides

by

Anuj Aryal

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Thesis Committee:

[redacted]

Dr. Magnus Bebbington
Thesis Sponsor

[redacted]

Dr. Amrita Sarkar
Committee Member

[redacted]

Dr. David Konas
Committee Member

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Rongalite

Rongalite (IUPAC: Sodium Hydroxymethylsulfinate) is an organic salt with a tubular crystal structure. Industrially, sodium dithionite ($Na_2S_2O_4$) and formaldehyde are used to produce Rongalite. It is registered under trademark of BASF in the form Sodium Hydroxymethylsulfinate dihydrate ($Na^+HOCH_2SO_2^-$). [1] In the past, Rongalite has been used to treat mercury poisoning since it is an excellent metal chelator [2] whereas in the present, it has many applications. It has a reducing property, which makes it useful in various industrial applications such as redox initiator in emulsion polymerization.[1] It is also used as a printing and dyeing agent. The origin of this compound goes back to 1908 when formaldehyde and sulfur dioxide were reduced in presence of zinc to produce zinc formaldehydesulfoxylate. This paste could be then converted to the sodium salt with sodium hydroxide or sodium carbonate.[3] Rongalite is stable under ambient conditions but can decompose upon long term exposure to air or moisture. Likewise, Rongalite is also sensitive to heat and can decompose when heated above 100°C. Rongalite is a white powder that is soluble in water and alcohols such as methanol.[1,4]

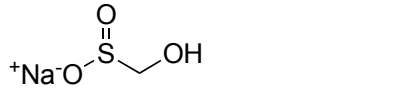
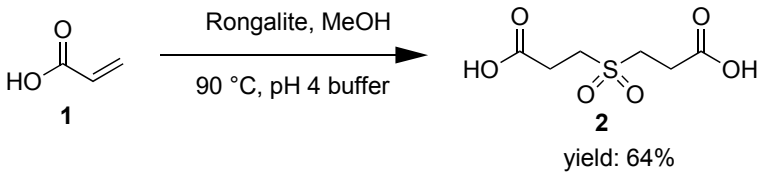


Figure 1 Structure of Rongalite

Rongalite in Synthetic chemistry

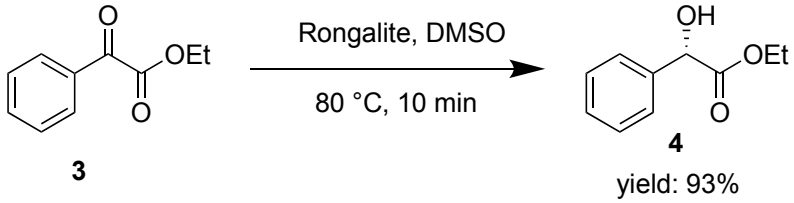
With the chemical formula of $Na^+HOCH_2SO_2^-$, Rongalite is an equivalent of the normally unstable SO_2^{2-}, the hyposulfite dianion. Therefore, its possible application in organic synthesis is as a reducing agent as well as to introduce SO_2 groups into organic molecules. For example, Rongalite has been used to synthesize sulfones via reaction with various organic compounds

such as alkene. One such example is shown by Scheme 1 where Rongalite reacts with alkene with carboxylic acid tail to form sulfone.[5]



Scheme 1 Rongalite as a sulfonyl group surrogate

Rongalite can be used to reduce various functional groups, such as carbonyl groups, nitro groups, and azo compounds. It is often used in the synthesis of pharmaceuticals, dyes, and other organic compounds.[1,5] An example of such reduction is illustrated by Scheme 2. Here, Rongalite has been used as a reducing agent to form a hydroxyl group from a ketone.[6]



Scheme 2 Use of Rongalite as a reducing agent

Sulfones

Sulfones are a class of organic compounds that contain a sulfonyl group (Figure 2) attached to two organic substituents, usually hydrocarbons. These results from the sulfur atom bonding to two organic groups via single bonds and two oxygen atoms via a double each. Sulfone and its derivatives are present very commonly in licensed drugs as well as in polymers.[7] Dapsone (brand name: Aczone) is an antibiotic used in the treatment of leprosy.[8] Similarly, Hydrochlorothiazide (brand name: Microzide) is a diuretic medicine which treats high blood

pressure caused by fluid build ups.[9] The structures of these drugs are shown by Figure 3 respectively.

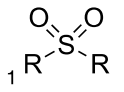


Figure 2 Structure of a Sulfone

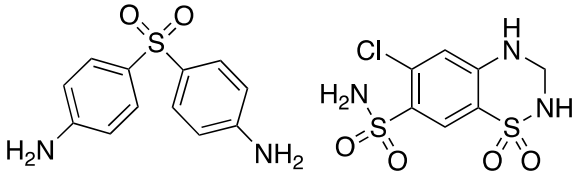


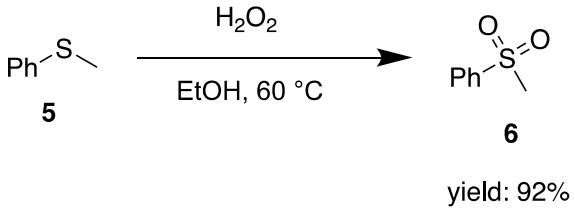
Figure 3 Dapsone (left), an antibiotic drug Hydrochlorothiazide (Right), for high blood pressure

1. Sulfone Synthesis

The most familiar sulfone synthesis is the oxidation of sulfides and sulfoxides as well as alkylation of sulfinates, aromatic sulfonylation and addition to alkenes and arenes.[9] In addition, sulfones can also be synthesized using a sulfur dioxide (SO_2) surrogate.

1.1 Oxidation of sulfides

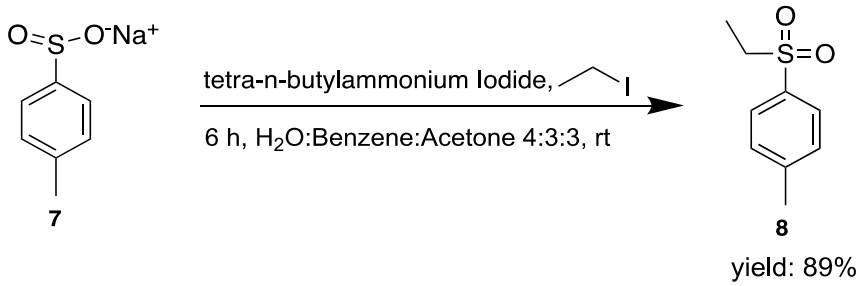
Oxidation of sulfides is the most common and straightforward reaction to synthesize sulfones. The excess oxidant, either hydrogen peroxide or peracids, is required along with high temperatures and longer reaction times for a complete oxidation of sulfides or sulfoxides to sulfone. The reaction is often mixed in acetic acid.[11] The drawback of this reaction is that it can be costly since peroxide is expensive.[12] An example from most recent advances is shown by Scheme 3 where the aromatic sulfide **5** is converted to sulfone **6** via oxidation.[11]



Scheme 3 Oxidation of sulfide and sulfoxide

1.2 Alkylation of sulfinates

Sulfinate salts are strong nucleophiles, and they can react with different electrophiles to produce sulfones. An example is shown by Scheme 4 where sodium *p*-toluenesulfinate **7** is alkylated by alkyl halide to produce sulfone.[13] This reaction requires tetra-n-butylammonium salts of halides for catalysis which can raise toxicity and safety issues. Sulfinate salts are non-corrosive solids and most of them exist in their hydrated forms. These salts are usually stable at standard conditions and can be stored for long period without decomposition.[14] For these reasons sulfinate salts are studied for their potential use as building blocks for many sulfonyl compounds such as sulfones and sulfonamides.

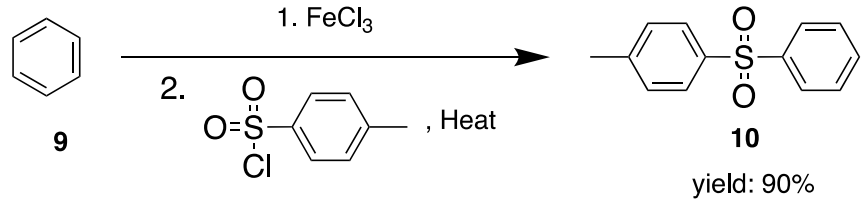


Scheme 4 Alkylation of sulfinate to prepare sulfones

1.3 Aromatic sulfonylation

In the Friedel-crafts sulfonylation of aromatic hydrocarbons, the hydrocarbon is treated with a sulfonyl chloride in the presence a Lewis acid catalyst such as $FeCl_3$ which activates the sulfonyl chloride making it more reactive towards the arene group.[15] The limitations of these reactions

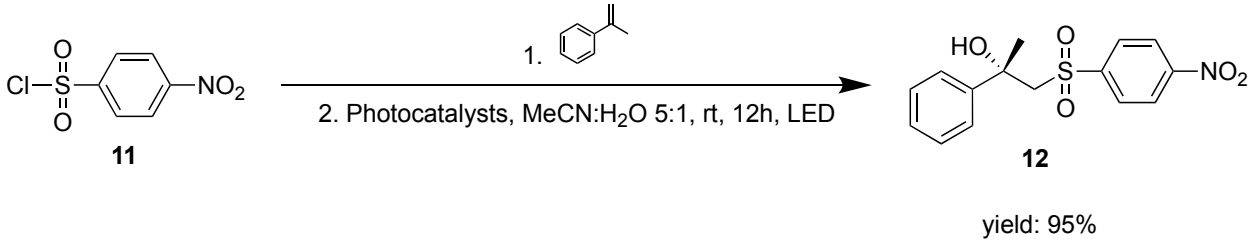
are that they can lead to other by products due to Lewis acid catalysts which can be difficult to dispose of. However, aromatic sulfonylation is still a widely used reaction to produce sulfones industrially.[16]



Scheme 5 Aromatic Sulfonylation using Lewis acid

1.4 Addition to alkenes and arenes

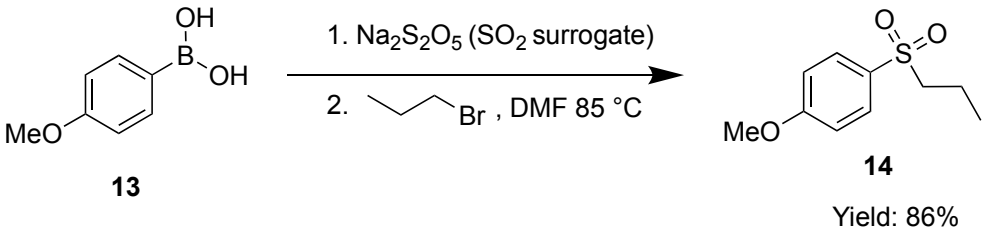
Sulfones are also synthesized by addition to alkenes and alkynes. This reaction follows the process of atom transfer radical addition (ATRA) which involves transfer of a halogen atom from a halogenated radical initiator species to the unsaturated hydrocarbons to form a carbon-radical intermediate which further undergoes reaction (Scheme 6).[17] ATRA also has some limitations which is the need for halogenated starting materials which can be costly, in addition to the possible unwanted side reactions such as homocoupling of the halogenated radicals unless performed in inert atmosphere.



Scheme 6 ATRA reaction to synthesize sulfones

1.5 Other Reactions

There are other reactions involving sulfur dioxide to synthesize sulfones. These are three component reactions in which a sulfur dioxide surrogate is used (Scheme 7). However, sulfur dioxide surrogates can be toxic which causes asthma like allergies, adding to the hazard. [18, 19]



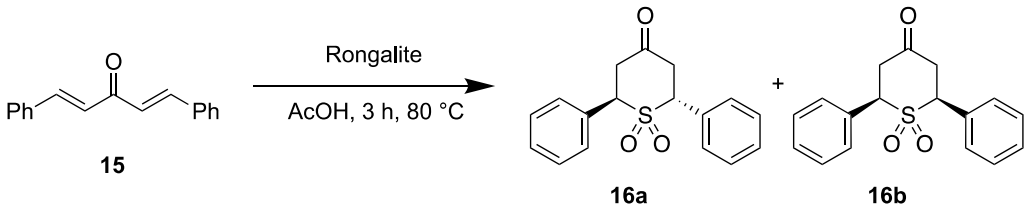
13 **14**

Yield: 86%

Scheme 7 Sulfone synthesis via SO_2 surrogate

Motivation

There is a growing need for non-expensive and eco-friendly synthetic methods to synthesize sulfones. Sulfones and derivatives are favored starting reagent in many organic synthetic routes. However, despite their importance, preparing sulfones can be a difficult task. Since Rongalite is cheap, easy to handle and a very good reagent for sulfonyl groups, it can shorten the reaction route to synthesize sulfones which has several drawbacks otherwise. In our preliminary studies, Rongalite was used to synthesize cyclic sulfones **16** via a double conjugate addition to dionines **15**. In one of the reactions represented by Scheme 8, diastereomeric ratio was 6:1. This gave us a perspective to try a different electrophile.

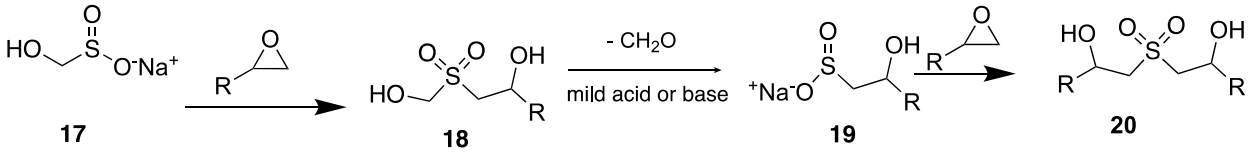


15 **16a** **16b**

yield: 88%

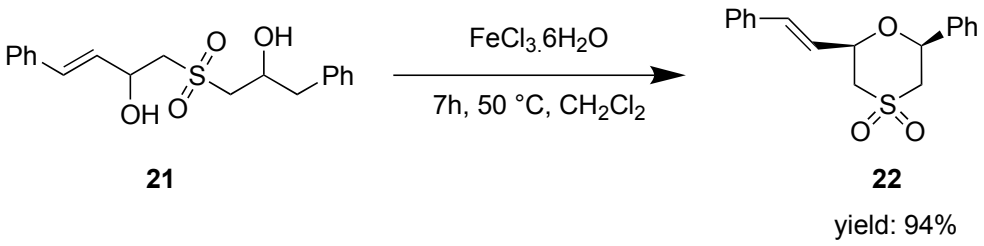
Scheme 8 Sulfone synthesis via double conjugate addition to Rongalite

For these reasons, the potential use of Rongalite as a source of nucleophile (SO_2^{2-}) in a catalytic ring opening reaction of epoxides is studied. In a proposed reaction (Scheme 9), these asymmetric ring openings of epoxides lead to synthesis of sulfones with a chiral diol.



Scheme 9 Proposed reaction of Rongalite as a nucleophile with two consecutive electrophiles

Organosulfur heterocycles are important building blocks in medicinal drugs. The sulfone diols synthesized from these reactions can easily be converted to drugs of medicinal interest.[20] One example is represented by Scheme 10 where a sulfone diol **21** is converted to a sulfone heterocycle **22** in a 98:2 diastereomeric selectivity.



Scheme 10 Conversion of sulfone diol to sulfone heterocycles

We hypothesize for this project that Rongalite can be used as an inexpensive surrogate for SO_2^{2-} ion in double ring opening reactions. This will give rise to an enantioselective sulfone synthesis the detail is represented by Figure 5. In an enantioselective reaction, one or more products with different stereochemistry are formed in unequal amounts. Once successfully synthesized, this study will also look to acquire the data of enantioselectivity of the sulfone diols.

Sulfone via epoxide ring opening by Rongalite

For our studies epoxides **23** 2,2-dibutyl-oxirane and **26** Cis-stilbene oxide were made according to previously described procedures whereas **24** cyclohexene oxide and **25** 1,2-epoxy octane were purchased. [21, 22] The preparation methods for **23** and **26** are shown by Schemes 11 and 12 respectively.

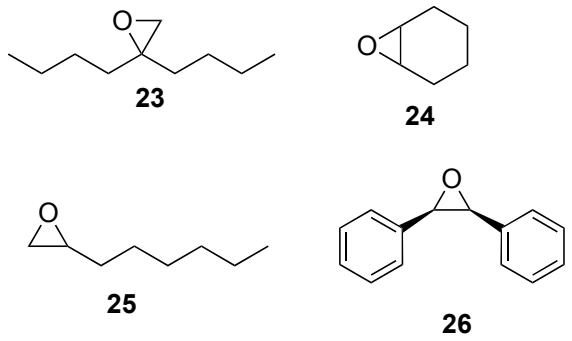
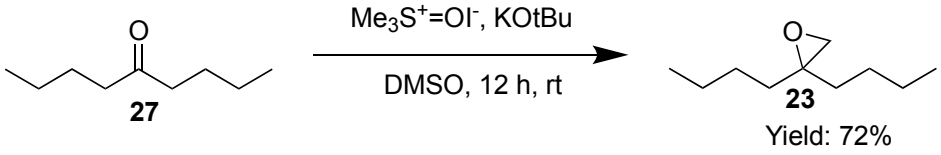
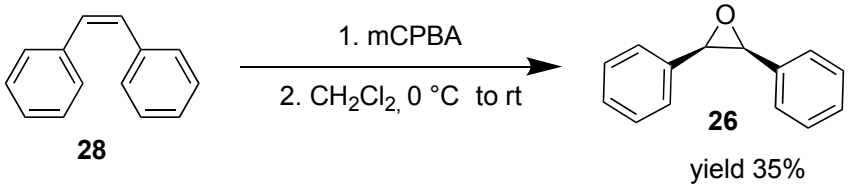


Figure 4 Epoxides used for the study



Scheme 11 Preparation of 2,2-dubutyl oxirane



Scheme 12 Preparation of cis stilbene oxide

The proposed mechanism of the reaction is shown (Figure 5). For this mechanism, 1,2-epoxy octane **25** is taken as the example. First, mild acid or catalyst will form a hydrogen bond with the oxygen on epoxide. The hydroxymethanesulfinate, as a nucleophile, will react with the activated

epoxide at the less hindered carbon atom in the ring. This will lead to the formation of intermediate **29**. In the presence of acid or base this intermediate will lose a formaldehyde, which will result structure **30**. The hyposulfite then attacks epoxide for electrophile addition forming a sulfone **31**. Double ring opening will occur sequentially. If the first epoxide ring is opened with electrophile added to hydroxymethanesulfinate to form intermediate **29**, and the second epoxide is the same enantiomer, the product **31a** will be chiral. If intermediate **29** reacts with the other epoxide enantiomer, **31b** will be achiral. This will give rise to two diastereomers as illustrated by Figure 5. This study looks to optimize the use of Rongalite as a nucleophile under different conditions as well as observe enantioselectivity for the double ring opening. For example, use of different solvents and combinations if needed, which include water, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), tetrahydrofuran (THF) and so on. Similarly, different pH conditions, temperature and stoichiometric ratios of the reactants are tried. Most importantly, the effects of catalyst are also studied and used to optimize the reaction. Some catalysts used are thiourea which proposedly help in either the ring opening or the increase the rate at which the double addition of electrophile takes place by forming hydrogen bond.

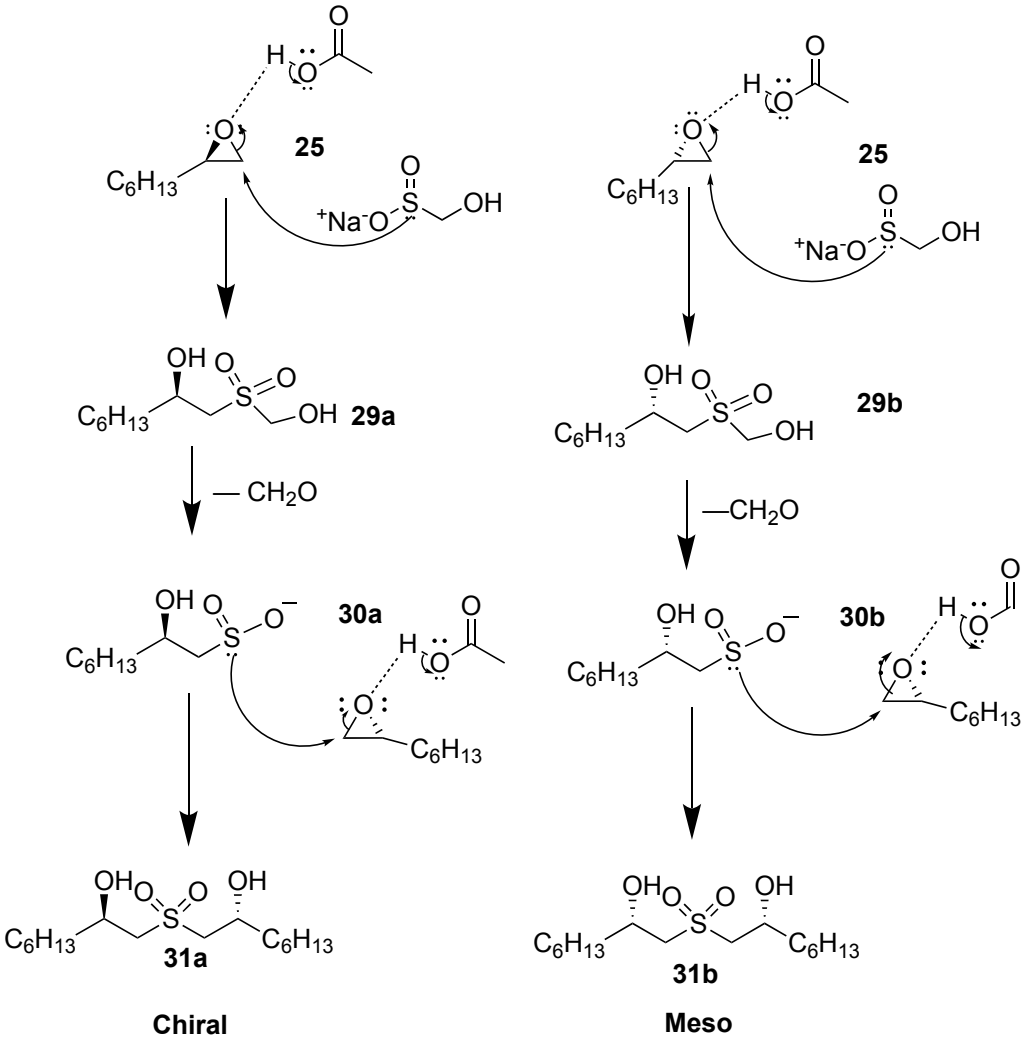


Figure 5 Proposed mechanism for double ring opening via Rongalite

The expected products for reaction with epoxides **23** and **26** are **32a** and **33a** respectively with diastereomers **32b** and **33b** (Figure 6).

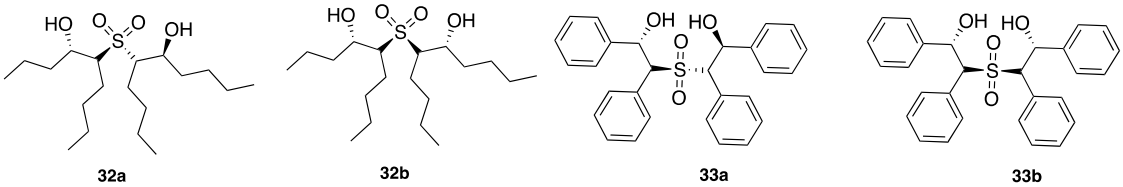
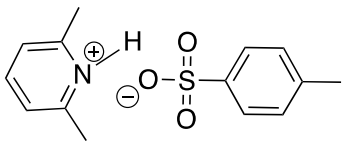


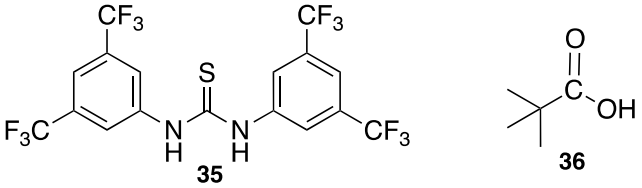
Figure 6 Expected products from epoxides 23 and 26 with their diastereomers

For catalysis, in addition to acetic acid (pKa: 4.76), 2,6-dimethyl-pyridinium-*p*-toluenesulfonate **34** (pKa~ 5.0), thiourea **35** and pivalic acid (pKa: 5.03) **36** have been used under different conditions (Table 1).



34

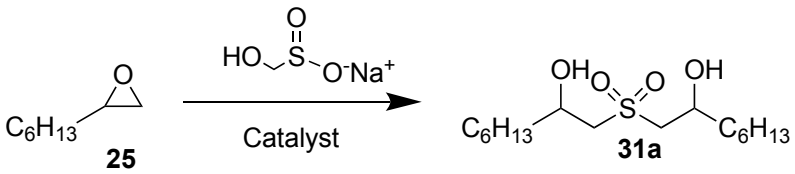
Figure 7 Structure of 2,6-dimethyl-pyridinium-p-toluenesulfonate



35 **36**

Figure 8 Structures of Thiourea catalyst and Pivalic acid

The proposed overall transformation is shown (Scheme 13). However, the results shows that these reactions were not successful in synthesizing sulfone diols and instead yielded ester **37** and alkyl diol **38** with 1,2-epoxyoctane while other epoxides showed no reactivity. The results are with **25** 1,2-epoxyoctane are summarized in Table 1.



25 **31a**

Scheme 13 Overall transformation from epoxide to sulfone diol

37 **38**

Figure 9 Structures of 2-Hydroxyoctyl-1-acetate and 1,2-octanediol

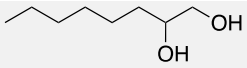
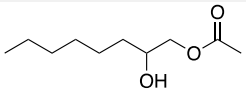
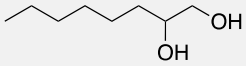
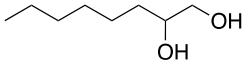
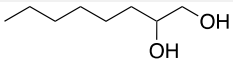
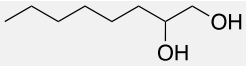
Entry	Solvent	Conditions	Time	Product	Yield
1	Water	70°C	Overnight		1:20 product: reactant
2	DMSO	80°C, acetic acid	Overnight		14%
3	DMSO	80°C, pyridinium salt **34**	Overnight		44%
4	DMSO	80°C, pyridinium salt **34**	3 hr		29%
5	DMSO	rt, pyridinium salt **34,** thiourea **35**	4 hr	Recovered Starting Material	
6	DMSO	40°C, pyridinium salt **34,** thiourea **35**	4 hr		13%
7	DMSO	60°C, pivalic acid **36**	Overnight		26%

Table 1 Reactions of 1,2-epoxy octane with Rongalite under different conditions

According to a previously described method, sulfones were synthesized in water using sodium salt of sulfinate. [23] Epoxide **23** 2,2-dibutyl-oxirane showed no reactivity under similar procedure, and with the change of the solvent to isopropyl alcohol and to DMSO with increase in temperature. A possible explanation is the steric effect that arises due to the presence of a long chain alkyl group on either side of the epoxide. Similarly, we tried epoxide **25** 1,2-epoxyoctane in water which showed hints of reactivity. In an unpurified crude mix, 1:20 product to reactant mixture was measured. To increase the reactivity, water was replaced with DMSO, and acetic acid was added to the mixture for a slightly acidic condition. Mild acidic conditions would allow activation of the epoxide and allow nucleophile to add to less sterically hindered carbon. The

analysis of the product showed that acetic acid behaved as a nucleophile and formed an ester as a ring opened product **37**. The results were comparable to a similar reaction of 1,2-epoxyoctane and acetic acid which targeted the synthesis of compound **37** 2-hydroxyoctyl-1-acetate. [24] To prevent this, we used something less nucleophilic but with a similar pKa, **34** 2,6-dimethyl-pyridinium-*p*-toluenesulfinate in the next sets of the reaction. We prepared 2,6-dimethyl-pyridinium-*p*-toluenesulfonate **34** by reaction of 2,6-lutidine with acetone *p*-toluene sulfonic acid monohydrate. [25] In theory, it would act as a weakly acidic catalyst in the reaction mixture and help prevent from getting it more basic. However, this reaction yielded the alkyl diol **38** as the ring opened product when run overnight and 3 hrs. Thiourea catalyst **35** was added to the mixture, which forms hydrogen bond with the oxygen and like acetic acid, would allow activation of the ring opening reaction. In a reaction described as amino lysis of epoxides, thiourea showed efficient catalytic activity as a double hydrogen bond donor.[26] In the next set of reactions with epoxide **25** 1,2-epoxy octane at room temperature there was no signs of reactivity and at 40 °C showed some reactivity. The product in the NMR corresponded to the same diol **38**. Thiourea **35** was replaced by pivalic acid **36** (pKa 5.03) which has a similar pKa as acetic acid and forms hydrogen bond with oxygen on epoxide, facilitating the reaction by allowing the nucleophile to attack the less sterically hindered carbon in the epoxide. However, in analysis of NMR and mass spectrum it was observed that the product was 1,2-octan-diol **38** with an increased yield. When 1,2-epoxy octane **25** was replaced by cis-stilbene-oxide **26**, it did not

show any reactivity under similar conditions. Most of the reaction used 1,2-epoxy octane as the model substrate since it showed more reactivity than the other epoxides.

Control reactions

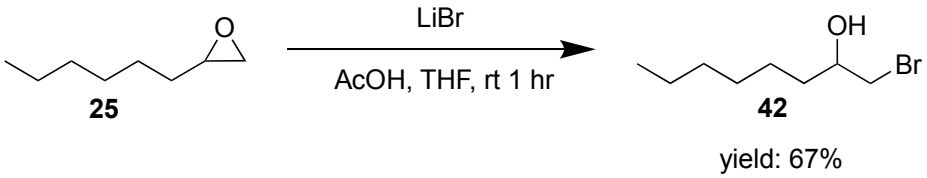
Since our target compound was a sulfone diol, we have also tried to synthesize sulfones via other synthetic routes. In addition to a reaction of bromo alcohols with Rongalite, other reactions use a salt Sodium *p*-toluenesulfinate to open the epoxide ring [14, 30] as well as oxidation of sulfide to synthesize sulfone using a method described before.

Control via Bromo Alcohols

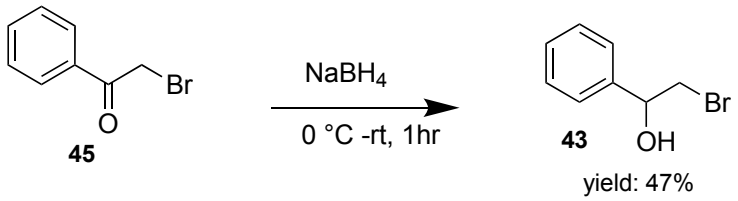
In order to provide reference for the sulfonyl diol that was expected from the epoxide ring opening with Rongalite and make it easier to identify products in those reactions, a new scheme was proposed. In this proposed scheme, bromo alcohol is generated either from the epoxide as a ring opened product or from the reduction of bromo ketone. The bromo alcohol is then reacted with Rongalite to produce sulfones in a nucleophilic substitution reaction. The reaction mechanism is described as a one pot synthesis from alkylation of Rongalite (Scheme 17).[27] The reaction of Rongalite and 1,2-epoxyoctane in acetic acid showed that acetic acid reacted as a nucleophile and formed **37**. Therefore, this gave us a possible synthetic route analogous to Scheme 13 with the ring opening of epoxides with Rongalite. The difference in this method is the substitution of Br group with nucleophilic hyposulfite ion.

Typically, bromo alcohols are prepared via synthetic reactions by the bromination of alcohol using either bromine or hydrogen bromide. This class of chemical compound can also be used as chiral building blocks in organic synthesis such as intermediates in production of

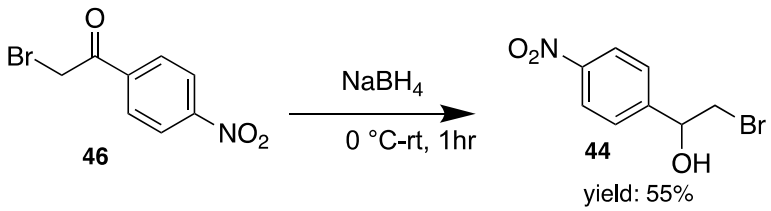
pharmaceuticals and many other agrochemical compounds. For these reactions, bromo alcohols **40, 41,** and **42** have been used in a double alkylation of Rongalite.[28]1-bromo-2-octanol **40** was synthesized from 1,2-epoxy octane **23** using Lithium Bromide according to a known reaction Scheme 14.[29] 2-bromo-1-phenylethanol **41** and 2-bromo-1(4-nitrophenyl)-ethanol **42** were both made via a reduction reaction of 2-Bromoacetophenone **43** and 2-Bromo-4-nitroacetaphenone **44** respectively according to Schemes 15 and 16.[30]



Scheme 14 Bromination of 1,2-epoxy octane

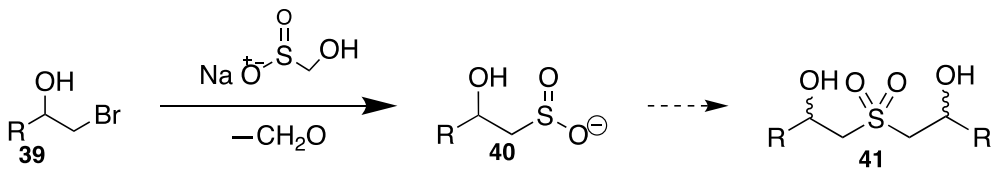


Scheme 15 Reduction of 2-Bromo-Acetophenone



Scheme 16 Reduction of 2-Bromo-4-nitroacetaphenone

Scheme 17 shows that the intermediate is similar to the one in reactions with epoxide, formed by a loss of formaldehyde. The dotted arrow represents the proposed formation of sulfone diol although which was not the product isolated. The results are shown in Table 2 and the spectral features of the products in Table 3.



Scheme 17 Transformation of bromo alcohol to sulfone in a one pot synthesis

Entry	Bromo alcohol	Solvent	Base	Conditions	Time	Product
1	**42**	DMF	$KHCO_3$	80°C	4 hr	Recovered starting material
2	**42**	DMSO	K_2CO_3	rt	Overnight	**42a**
3	**43**	DMSO	K_2CO_3	rt	Overnight	**43a**
4	**44**	DMSO	K_2CO_3	rt	Overnight	**44a**
5	**44**	DMSO	K_2CO_3	rt	3 hr	**44a**

Table 2 Reaction summary between Rongalite and bromo alcohols

In these reactions, formation of epoxides was commonly observed which is expected because of the presence of base in the mix. In a control reaction of 1-bromo-2-octanol **42** only in the presence of the base K_2CO_3, epoxide was observed in a 1:3 ratio with starting material. This reaction is depicted by the expected mechanism described as intramolecular SN_2 mechanism (Figure 10).

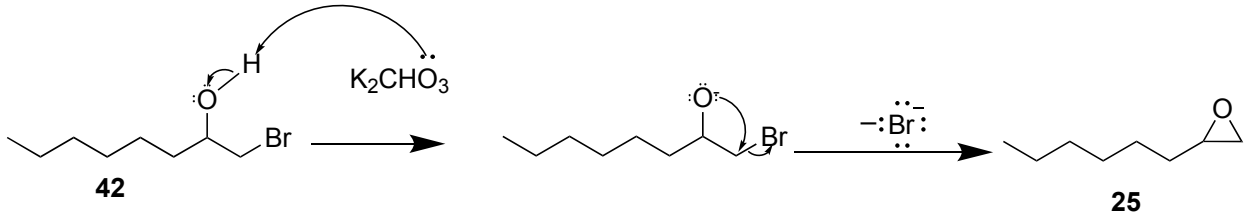


Figure 10 Mechanism of epoxide formation in presence of base in a control reaction using 1,2-epoxyoctane

Formation of epoxides **47** and **48** were also observed in corresponding reactions with bromo alcohols and **43** and **44** respectively. A possible use of these epoxides for the future is that it can be tested in ring opening reactions according to proposed Scheme 13. The presence of aromatic rings contributes to more reactivity of the epoxides in general.

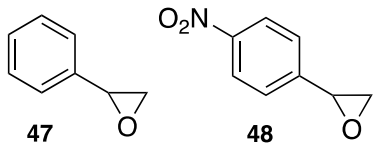


Figure 11 Epoxides formed in the presence of base with 2-bromo-1-phenylethanol and 2-bromo-1(4-nitrophenyl)-ethanol

During analysis of the other product formed, the presence of a carbonyl group was evident in all products as shown by a sharp peak in the IR spectrum at around 1770-1790 cm^{-1} and formation of a diol could be ruled out by the absence of the hydroxyl stretch. The NMR spectra hint at formation of analogous compounds for corresponding Bromo alcohol. The spectral features are summarized in Table 3.

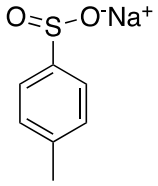
Compound	**IR**	**^{1}H NMR**	**^{13}C NMR**
42a, Viscous liquid	1791 cm^{-1}, No OH stretch	δ0.91(m, 3H), 1.40 (m, 8H), 1.70 (m,1H), 1.84(m, 1H), δ4.12 (m, 1H), 4.60 (m,1H), 4.76(m,1H).	δ13.98, 22.45, 24.31, 28.79, 31.50, 33.88, 69.40, 77.07, 155.11
43a, white solid	1769 cm^{-1}, No OH stretch	δ4.40 (m, 1H), 4.87 (m, 1H), 5.74 (m,1H), 7.42 (m, 5H).	δ71.17, 78.00, 125.87, 129.26, 129.75, 135.79, 154.8
44a, white solid	1785 cm^{-1}, No OH stretch	δ4.38 (m, 1H), 4.86 (m, 1H), 5.74 (m,1H), 7.50 (m, 5H)	δ70.65, 76.36, 124.55, 126.50, 142.75, 148.79, 155.60

Table 3 Spectral features of the products formed in reactions between Rongalite and bromo alcohols

For a better analysis and structural determination, a crystal analysis is required. Product **43a** is a possible candidate for that study since the it formed a clear crystalline structure.

Control Reaction via Sodium *p*-toluenesulfinate

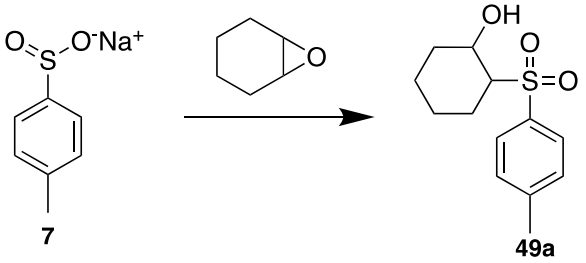
Like Rongalite, Sodium *p*-toluenesulfinate **7** is also used as a mild reducing agent in organic synthesis, particularly for the reduction of ketones, aldehydes, and imines. Similarly, its reaction with epoxides is proposed to be analogous where it can be used as a nucleophile in addition reactions, and as a chiral auxiliary in asymmetric synthesis



7

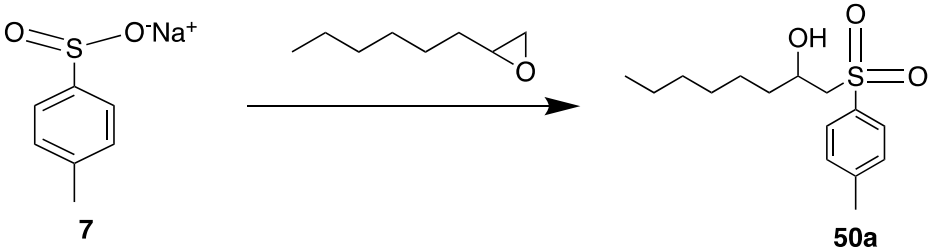
Figure 12 Structure of Sodium p-toluenesulfinate

We have tried analogous reactions with this salt to test the reactivities of Epoxides. These transformations are given by Schemes 18 and 19. In each reaction, there will be two enantiomers because the ring opening will take place from either side of the epoxide.



7 **49a**

Scheme 18 Transformation of Sodium p-toluene sulfinate to sulfone



7 **50a**

Scheme 19 Transformation of Sodium p-toluene sulfinate to sulfone

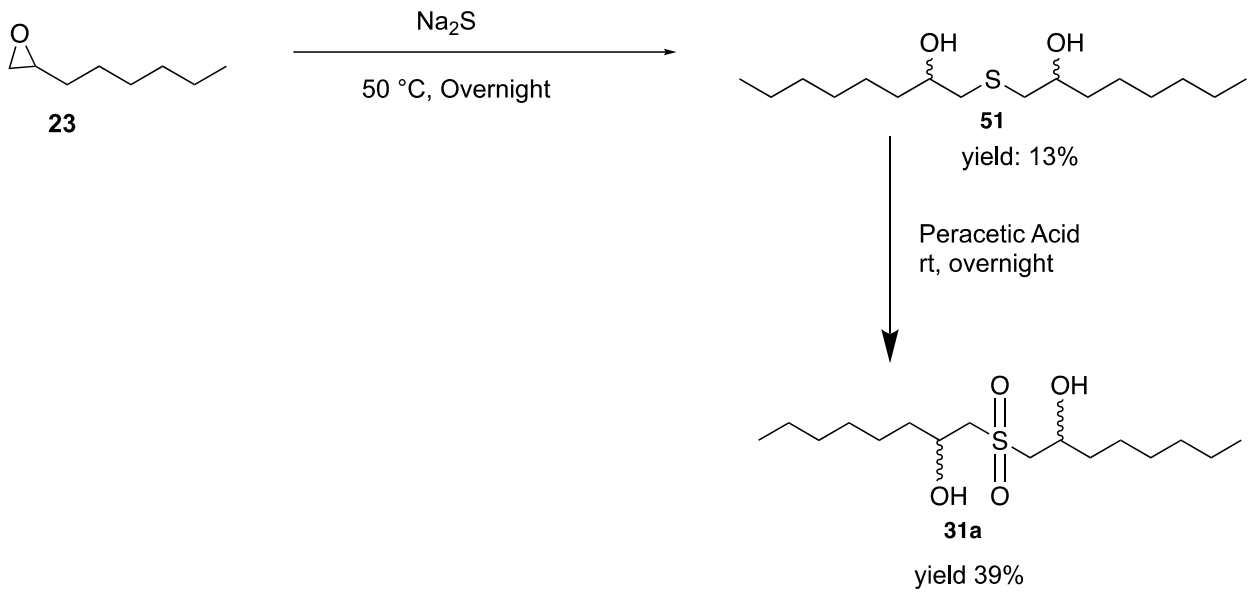
The reactions are summarized below in Table 4. Polyethylene glycol 400 (PEG400) has been used in a catalytic ring opening reaction between epoxides and sodium *p*-toluene sulfinate salt.[32] However, epoxide **23** showed no reactivity with sodium *p*-toluenesulfinate whereas unoptimized reactions with **24** and **25** showed promising signs. For the reaction with epoxide **24**, montmorillonite clay was used for catalytic ring opening in reference to a previous work.[33] These are corresponding to the reactivity shown by these epoxides with Rongalite, which shows the steric hindrance on the epoxides because of the alkyl group.

epoxide	solvent	conditions	Yield
23	Water+toluene 1:1	PEG 400, 110 °C	Recovered starting material
24	Water+toluene+Acetone 2:1:1	Montmonillonite clay, rt, 15hr	22%
25	DMSO	2,6 dimethyl pyridinium *p*-toluene sulfinate	12%

Table 4 Reaction summary between reactions of epoxides and sodium p-toluenesulfinate salt

Control via oxidation of sulfide

For a better characterization of the sulfone that we had hypothesized using 1,2-epoxy octane, we took the conventional synthetic route to synthesize sulfone from oxidation of sulfide. For this scheme, the choice of epoxide was 1,2-epoxy octane because it showed more reactivity. First, 1,2-epoxyoctane was reacted with odium sulfide to produce **51** 1,1-thiobis(2-Octanol).[34] The resultant compound was oxidized using excess peracetic acid in DCM to produce **31** 1,1-sulfonyldi-2-octanol (Scheme 20).[35]



Scheme 20 Sulfone synthesis via sulfide oxidation

Conclusions and Future work

The reaction of Rongalite with epoxides yielded alkyl diols and sulfonyl diols are yet to be isolated. The desired sulfonyl diol was successfully synthesized via oxidation of sulfide which will be used as a reference for future studies. In a control reaction of Rongalite with bromo alcohols, unknown products were isolated. Future studies will focus on better characterization and determination of these products. Possible strategies will be the growth of crystals as well as trying out different epoxides that might form analogous structures. This might also present better explanations as to why the reactions between Rongalite and epoxides did not go as proposed. The reactivity of epoxides with aromatic rings formed in the reactions between bromo alcohol and Rongalite can also be tested in further studies.

The control reactions with sulfinate salt reflected steric hinderance on the epoxides. Now that we understood the steric effects, different methods and formulations will be developed, including the test for Lewis acid catalysts in the future studies, that will continue investigating the application of Rongalite as a surrogate for hyposulfite ion SO_2^- in epoxide ring opening reactions.

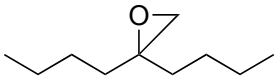
Materials and Methods

All the reactions involving Rongalite were carried out under an inert argon atmosphere. All the solvents and reagents were acquired in their commercial form from vendors, unless specified otherwise. ^{1}H and ^{13}C NMR Spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ unless specified otherwise. All the thin layer chromatography (TLC) was performed using silica plate and $KMnO_4$ stain to visualize. Column chromatography was performed using silica gel 60-200 mesh. Mass spectrometer analysis was performed in Q-Exative™ Plus Hybrid Quadrupole-Orbitrap™ Mass Spectrometer, a FTMS.

Experimental

Preparation of 2,2-dibutyl Oxirane **23**

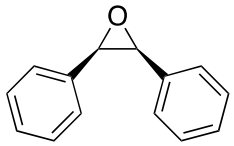
To a mixture of 8.67mL (50 mmol) 5-nonane, 11.22g (55mmol) trimethyl sulfonium iodide and 6.17g (55mmol) potassium tert-butoxide were added respectively. The mixture was stirred at room temperature for 12 hours. The reaction mixture is quenched with 50 ml water and the product and brine and then dried over sodium sulfate. Final product: 5.76g, gel and the yield were 72%. ^{1}H NMR ($CDCl_3$) δ0.88-0.92 (m, 6H), 1.33 (m, 8H), 1.56-1.62(m, 4H), 2.56(s, 2H).



Preparation of cis-stilbene oxide **26**

2.02g (11.1 mmol) cis-stilbene is mixed in 40mL dichloromethane at 0 °C and in an ice bath. Slowly, 3.40g (13.9 mmol) m-chloroperbenzoic acid (mCPBA) was added to the mix and stirred for 30 mins. Organic layer separated using ethyl acetate, while also adding 20mL 10% Sodium

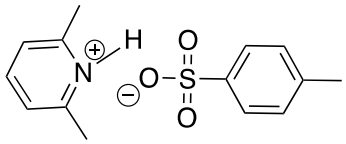
Sulfite to get rid of excess mCPBA and 20mL 10% sodium bicarbonate to separate by products into aqueous layer. The solvent was removed under reduced pressure after drying over Sodium Sulfate. Purified by column chromatography with ethyl acetate in hexane (1:9) to obtain final product 0.76g and the percent yield was 35%. NMR ($CDCl_3$) δ4.45 (s, 2H), 7.23 (s, 10H).



Preparation of 2,6-dimethyl pyridinium p-toluenesulfinate **34**

5.0g (47 mmol) 2,6-lutidine was added to 45mL acetone and stirred at room temperature. To the mix, mole equivalent *p*-toluene sulfonic acid monohydrate (8.914g) in 100mL acetone was added. White precipitation was obtained and washed with 50 mL acetone after filtration. Final product was white crystalline solid, and the yield was 96%.

^1H NMR δ1.77 (s, 3H), 2.42 (s, 2H), 2.90 (s, 5H), 7.25 (m, 2H), 7.48 (m, 2H), 7.90 (m, 2H), 8.15 (m, 1H)

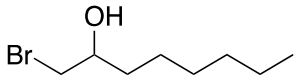


Bromination of 1,2-epoxyoctane **42**

2.98mL (19.5 mmol) 1,2-epoxyoctane was mixed with 25mL THF and 5 mL acetic acid. 2.7g (31 mmol) Lithium bromide was added to the mix and the reaction was run for 1 hour and monitored by Thin Layer Chromatography. The mixture was extracted by water and ethyl acetate. The organic layer was washed with sodium sulfate and solvent removed under reduced

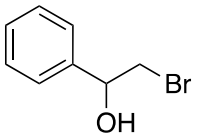
pressure. Purification was performed by column chromatography using a solvent mixture of 1:9 Ethyl acetate in hexane. Final mass of the purified product was 2.75 crystalline solid and the yield was 67%.

^{1}H NMR δ0.92 (m, 3H), 1.48- δ1.60 (m, 10H), 2.81 (s, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 3.45 (m, 1H)



Preparation of 2-Bromo-1phenylethanol **43**

3.98g (20 mmol) 2-Bromo-acetophenone in methanol is stirred and cooled to 0°C. 0.83g (22 mmol) $NaBH_4$ was added to the mix and after gradual increase to room temperature, it was stirred for an hour. A few drops of 1M HCl was added to the reaction after complete disappearance of 2-Bromo-acetophenone. Extracted by ethyl acetate, dried over Na_2SO_4 and solvent removed under reduced pressure. Column chromatography performed in 1:19 ethyl Acetate and hexane. Final mass of the purified: 1.88g, yield 47%. ^{1}H NMR δ2.93 (s, 1H), 3.60 (m, 1H), 3.70 (m, 1H), 4.98 (m, 1H), 7.40 (m, 5H)

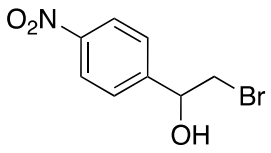


Preparation of 2-bromo-1(4-nitrophenyl) ethanol via reduction **44**

4.42g (18.1 mmol) 2-Bromo-4-nitroacetaphenone added to 100ml MeOH and was brought to 0°C in an ice bath. 240mg (6.34 mmol) $NaBH_4$ was slowly added to the mixture. The reaction mixture was slowly allowed to warm to room temperature and stirred for an hour. Extracted by

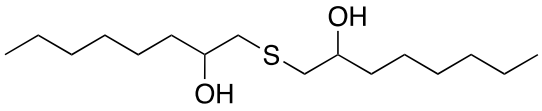
ethyl acetate, dried over Na_2SO_4, the solvent was removed under reduced pressure. Column chromatography was performed in 1:4 ethyl acetate in hexane. Final mass 3.45g and yield was 55%.

^{1}H NMR δ2.87 (s, 1H), 3.59 (m, 1H), 3.75 (m, 1H), 5.1 (m, 1H), 7.64 (m, 2H), 8.30 (m, 2H)



Preparation of 1,1'-Thiobis(2-octanol) **51**

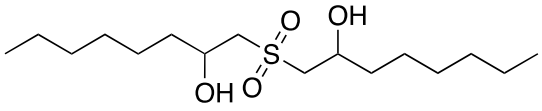
2.16g (9 mmol) Sodium sulfide was dissolved in water and 1.16g (9 mmol) 1,2-epoxyoctane was added to the mix. The reaction was stirred overnight at 50 °C and the organic extracted by Ethyl acetate. After drying over sodium sulfate, solvent was removed under reduced pressure. Raw weight of the product was 71mg. Column Chromatography was performed using ethyl acetate and hexane in a 1:4 ratio. Final mass of the purified was 340mg, yield was 13%. ^{1}H NMR: δ0.88 (d, 3H), 1.29- 1.49 (d, 11H), 2.55 (m, 1H), 2.74 (m, 1H), 3.46 (d, 1H), 3.67 (s,1H). HRMS (ESI) Calculated for $C_{16}H_{34}O_2SNa$: $[M+ Na]^+$: 313.218, found: *m/z* 313.219



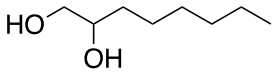
Oxidation of 1,1'-Thiobis(2-octanol) **31**

184mg (0.634 mmol) 1,1′-Thiobis(2-octanol) in dichloromethane (2.26 mL) was stirred. Slowly, dropwise peracetic acid (32% w/v in acetic acid) (0.40mL, 2.6 equivalent) was added dropwise. The reaction mixture was stirred overnight at room temperature. The reaction was quenched by addition of aqueous sodium metabisulfite 2mL and the mixture was further stirred at room temperature. The excess acid was removed by sodium carbonate until gas evolvement stopped.

The phases were separated, and the aqueous phase was extracted with dichloromethane 3x10ml. The organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. Purification was performed by chromatography on silica gel 1:4 ethyl acetate/hexane and increased to 1:1 Final mass: 80 mg, yield 39%. ^{1}H NMR: δ0.94 (m, 3H), 1.34 (m, 10H), 3.044-3.45 (m, 3H), 4.33 (s, 1H). ^{13}C NMR δ14.11 22.54, 25.01, 28.99, 31.67, 37.02, 60.88, 66.60. HRMS (ESR): Calculated for $C_{16}H_{34}O_4SNa$: $[M+Na]^+$: 345.208, found: *m/z* 345.205.



Characterization of 1,2 octan-diol **38:** viscous gel like liquid. ^{1}H NMR δ0.92(m, 3H), 1.32-1.48(m, 10H), 3.46(m, 1H), 3.64(m, 4H). ^{13}C NMR δ14.01, 22.60, 25.57, 29.35, 31.77, 33.07, 66.74, 72.41. IR (Neat): 571, 1069, 1458, 2925, 3339 cm^{-1}. HRMS (ESI): Calculated for $C_8H_{16}(OH)_2Na$: $[M+Na]^+$ 169.120, Found: *m/z* 169.119.



Characterization of unknowns

42a viscous liquid

^{1}H NMR δ0.91 (m, 3H), 1.40 (m, 8H), 1.70 (m,1H), 1.84 (m, 1H), 4.12(m, 1H), 4.60 (m,1H), 4.76 (m,1H). ^{13}C NMR δ13.98, 22.45, 24.31, 28.79, 31.50, 33.88, 69.40, 77.07, 155.11. IR (neat): 774, 1060, 1166, 1791, 2927 cm^{-1}. Epoxide also extracted from the reaction, in a 7:10 ratio to the product.

43a white solid

^{1}H NMR δ4.40 (m, 1H), 4.87 (m, 1H), 5.74 (m,1H), 7.42 (m, 5H). ^{13}C NMR δ71.17, 78.00, 125.87, 129.26, 129.75, 135.79, 154.8. IR (neat): 697, 758, 1050, 1167, 1769, 2925 cm^{-1}. Epoxide formed in roughly 1:1 ratio.

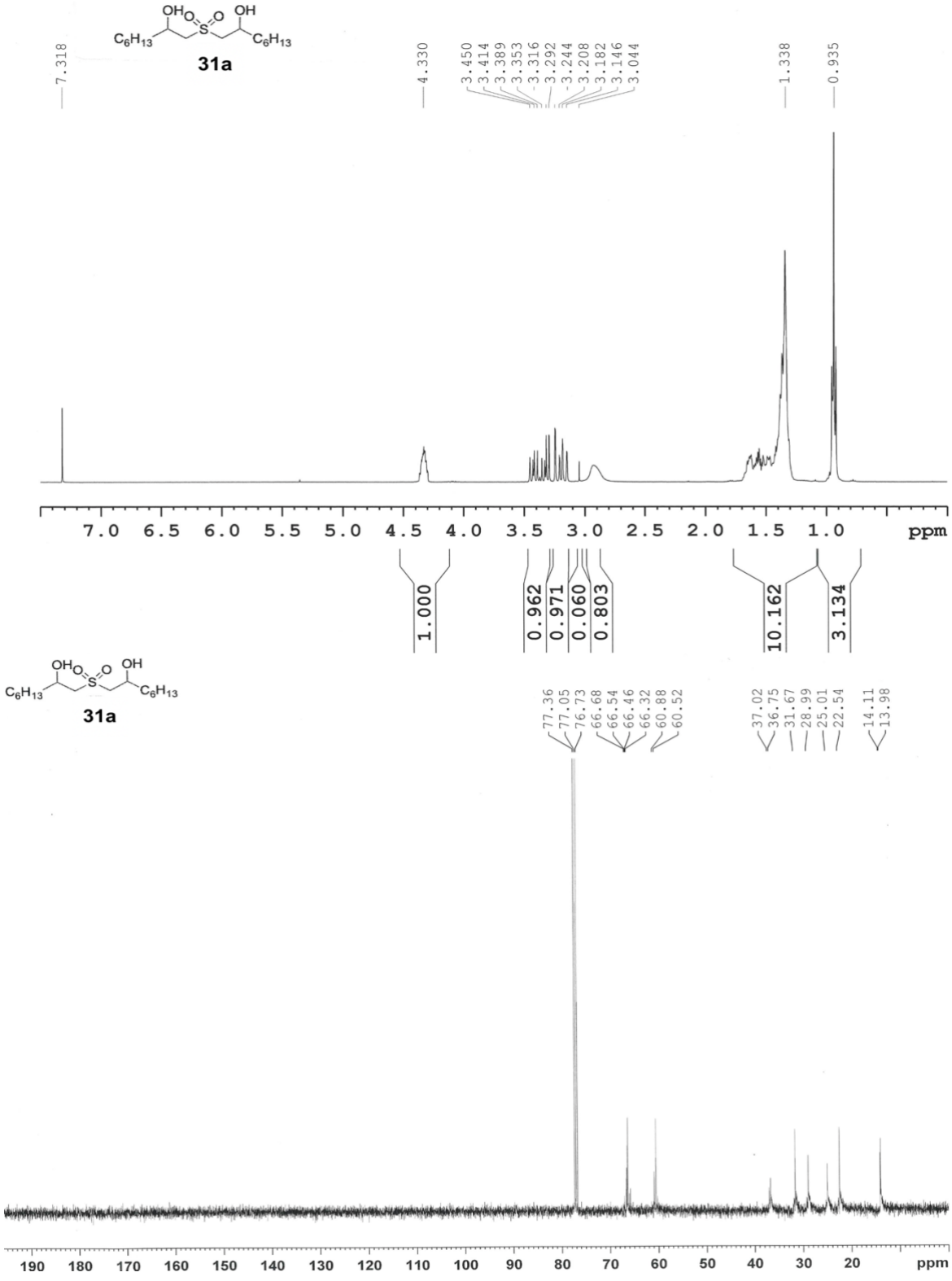
44a white solid

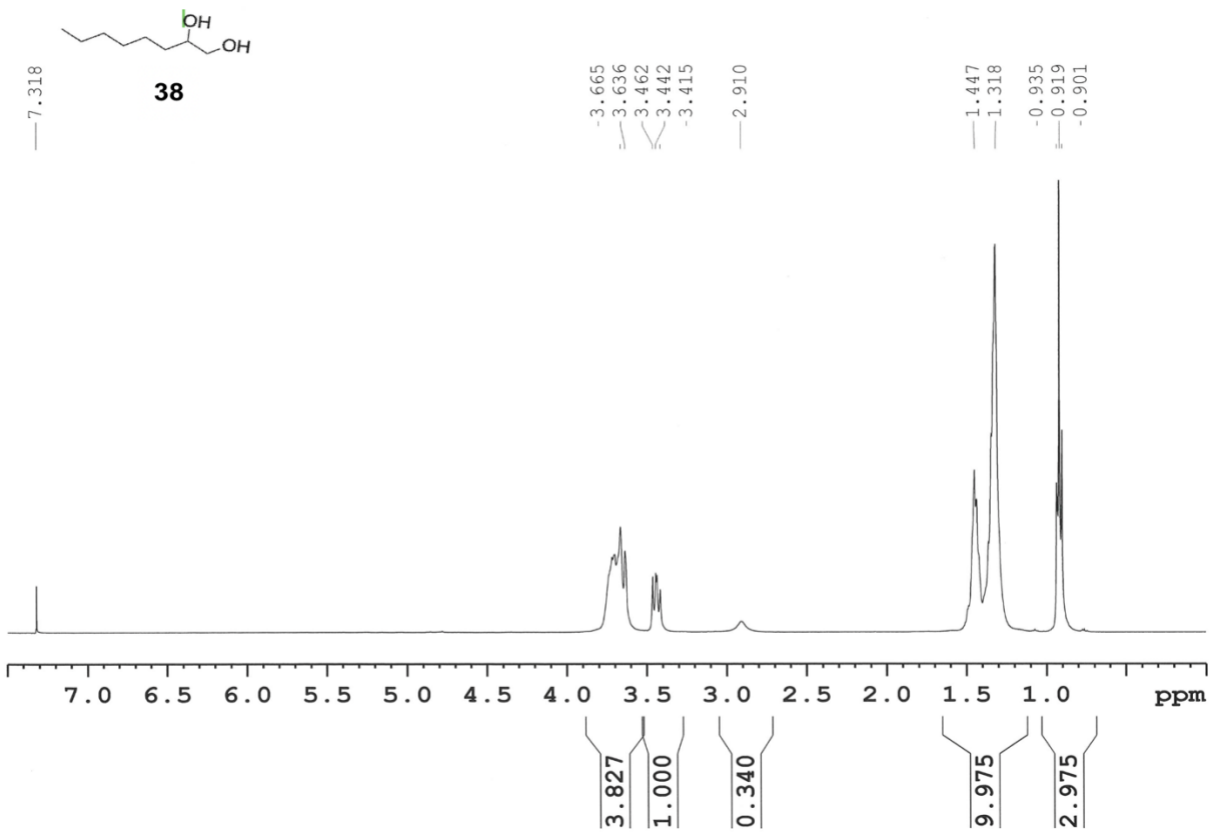
^{1}H NMR δ4.38 (m, 1H), 4.86 (m, 1H), 5.74 (m,1H), 7.50 (m, 5H)

^{13}C NMR δ70.65 76.36 124.55 126.50 142.75 148.79 155.60. IR (neat): 695, 770, 1077, 1185, 1344, 1519, 1785, 3086 cm^{-1}. Epoxide formed in 1:1 ratio.

Supplemental Figures and Illustrations

NMR Spectra

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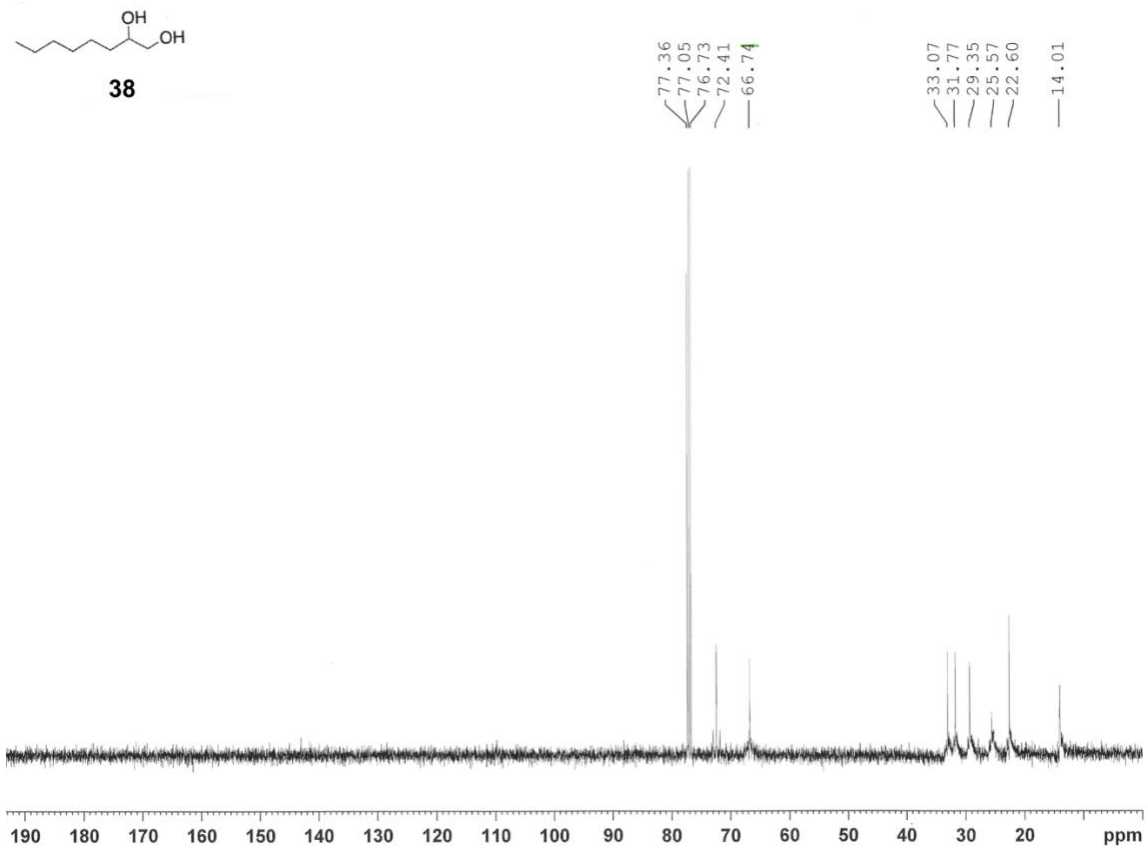
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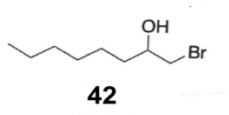
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Br

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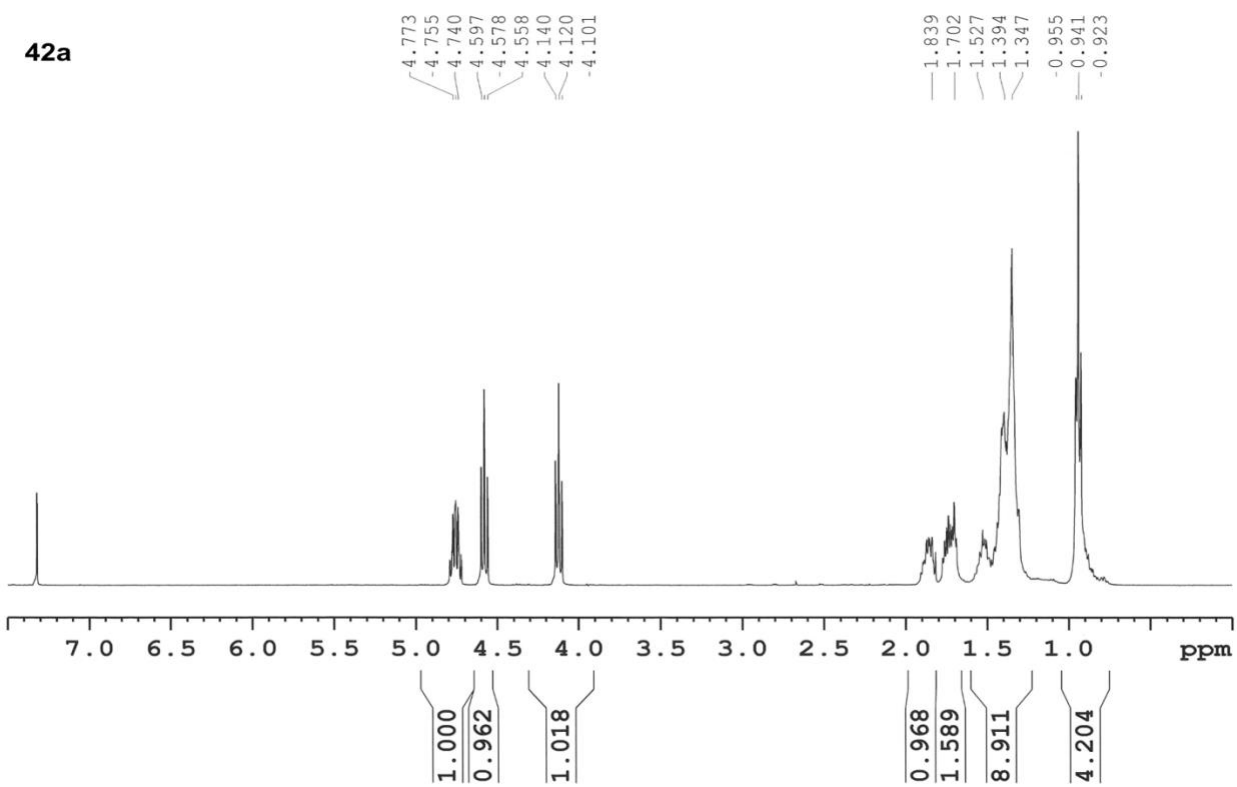
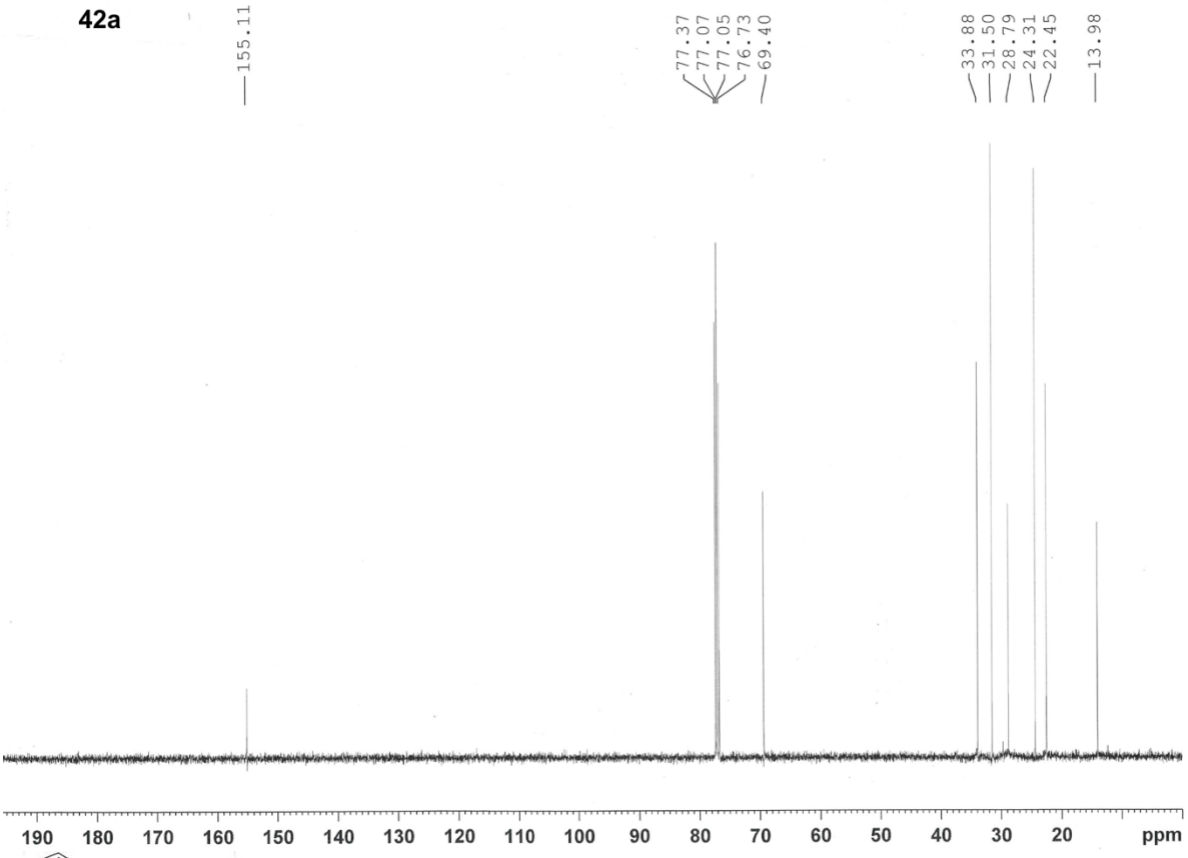
3.605
3.597
3.579
3.571
3.510
3.452
3.434
3.426
3.408
2.281
2.090
1.606
1.583
1.567
1.479
1.332
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.024
1.000
0.989
1.053
1.158
10.774
3.885

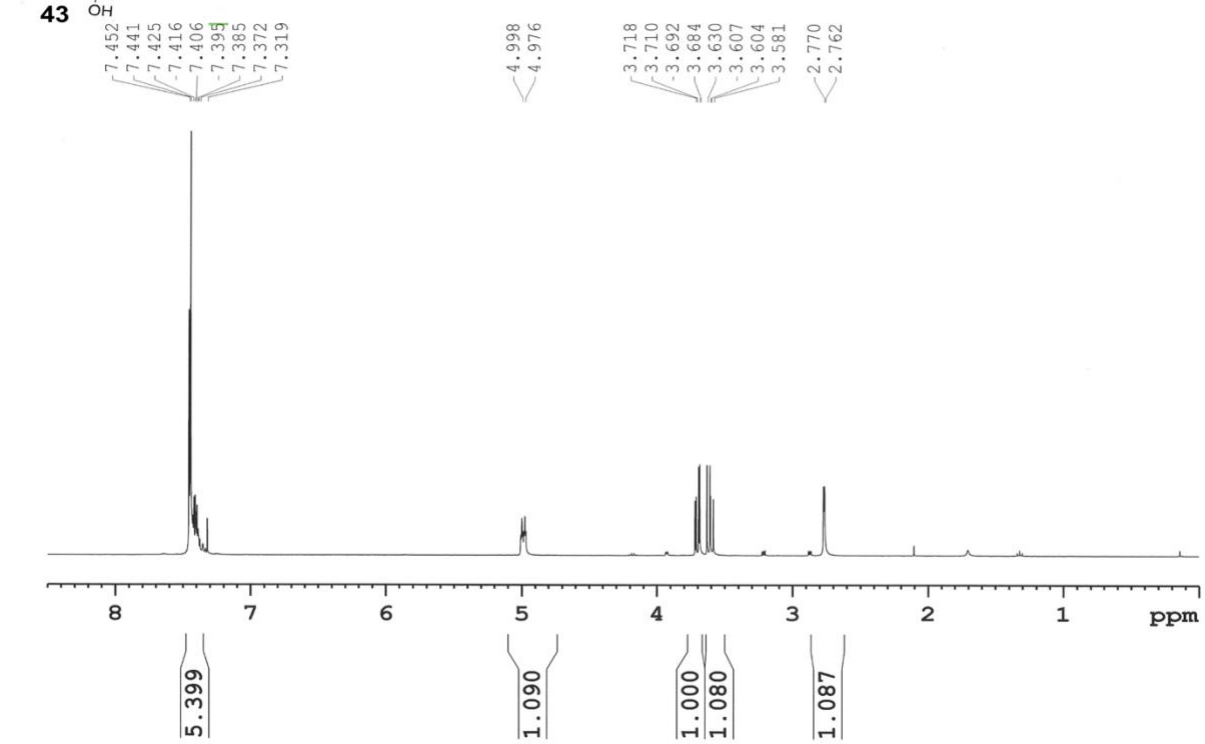
42a

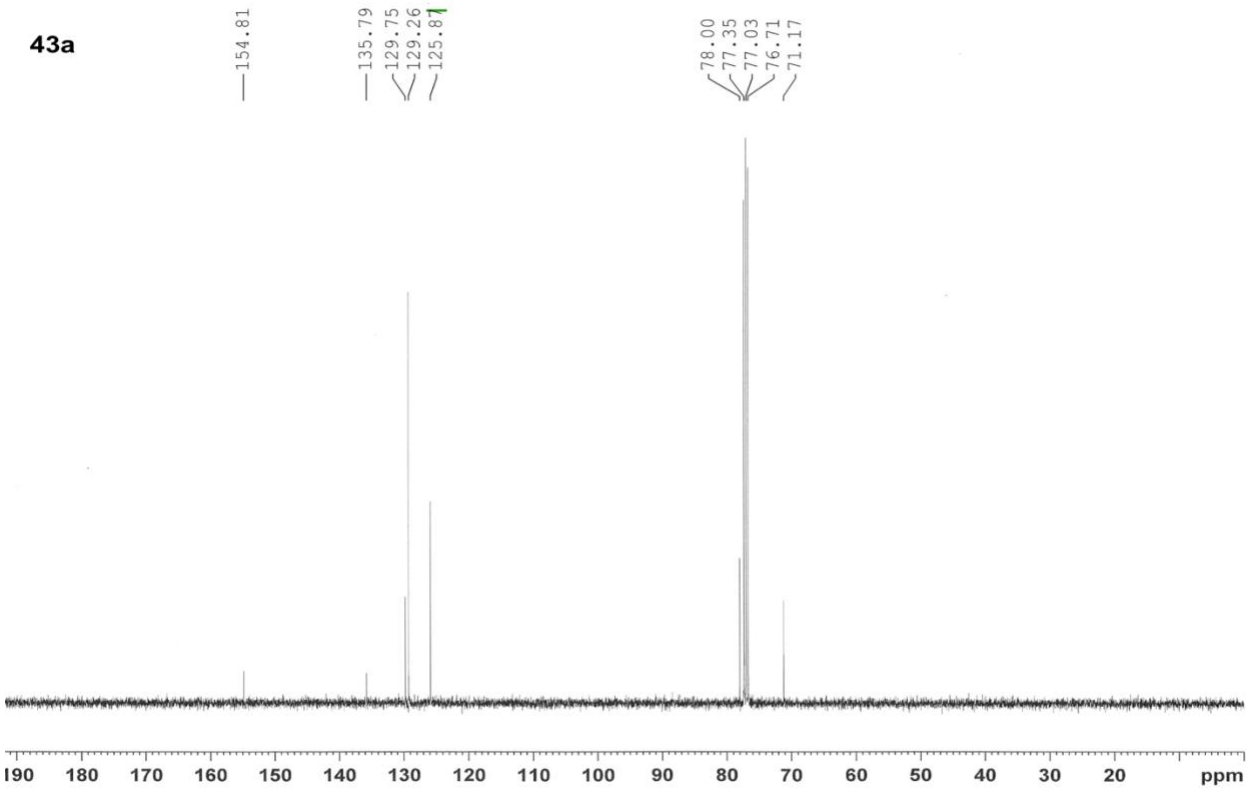

4.773
4.755
4.740
4.597
4.578
4.558
4.140
4.120
4.101
1.839
1.702
1.527
1.394
1.347
0.955
0.941
0.923
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.000
0.962
1.018
0.968
1.589
8.911
4.204

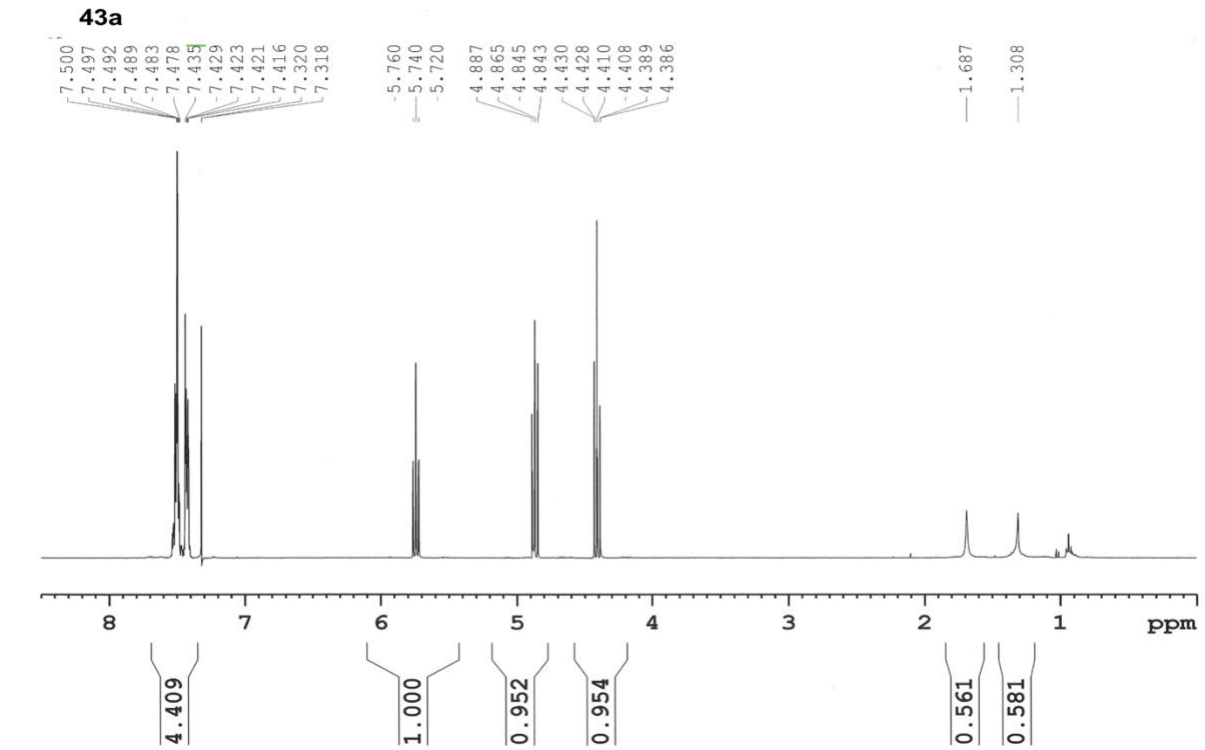
42a

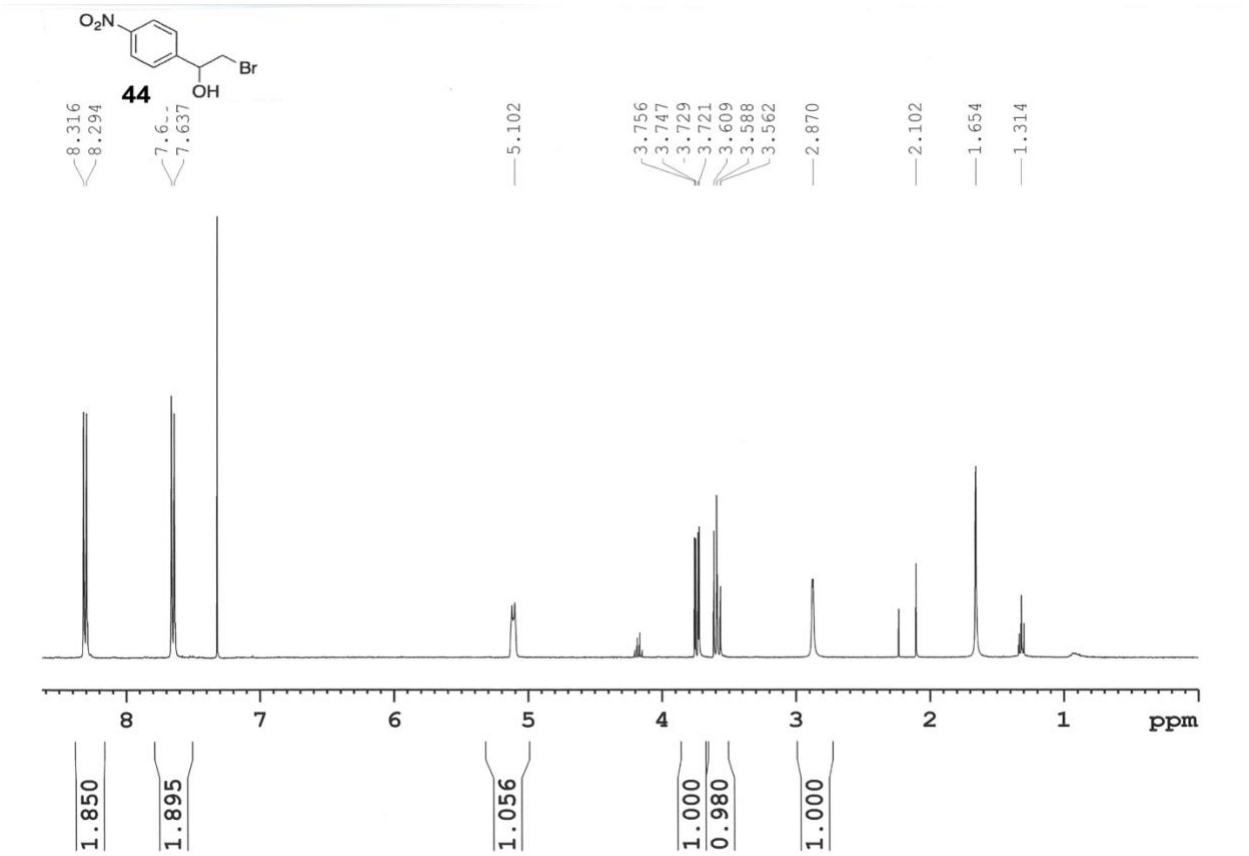

155.11
77.37
77.07
77.05
76.73
69.40
33.88
31.50
28.79
24.31
22.45
13.98
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

43

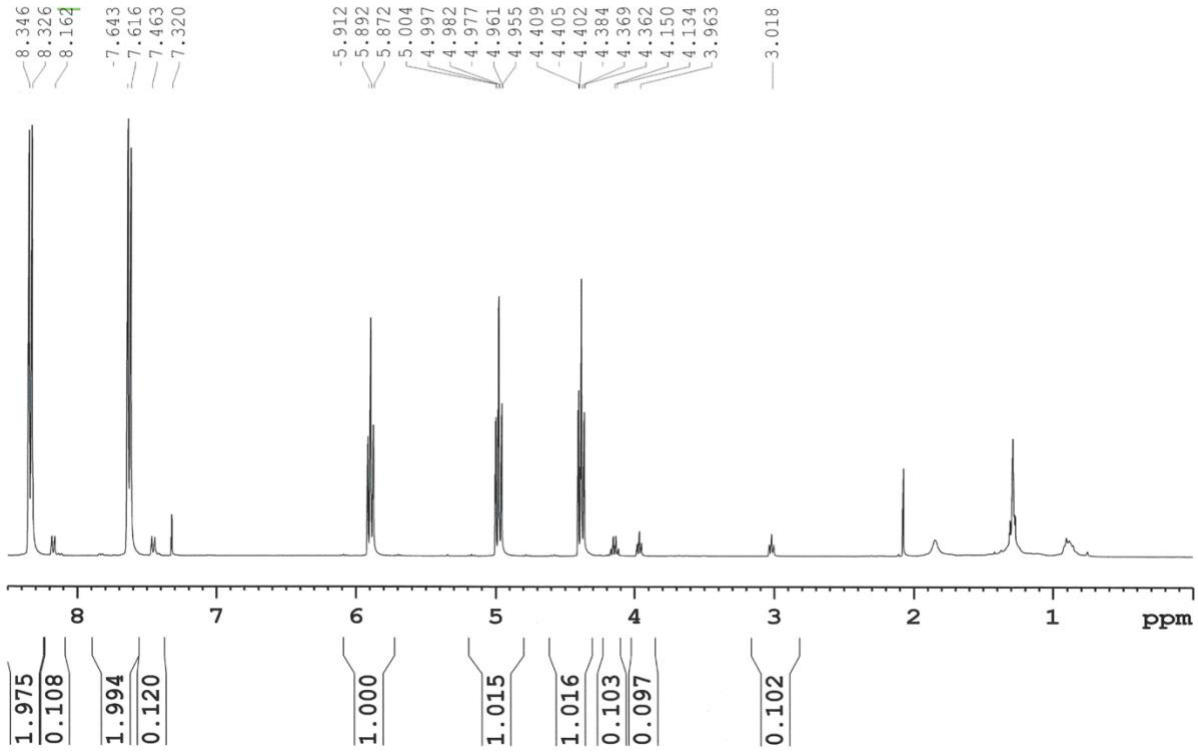

7.452
7.441
7.425
7.416
7.406
7.385
7.372
7.319
4.998
4.976
3.718
3.710
3.692
3.684
3.630
3.607
3.604
3.581
2.770
2.762
8 7 6 5 4 3 2 1 ppm
5.399
1.090
1.000
1.080
1.087


43a
154.81
135.79
129.75
129.26
125.81
78.00
77.35
77.03
76.71
71.17
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

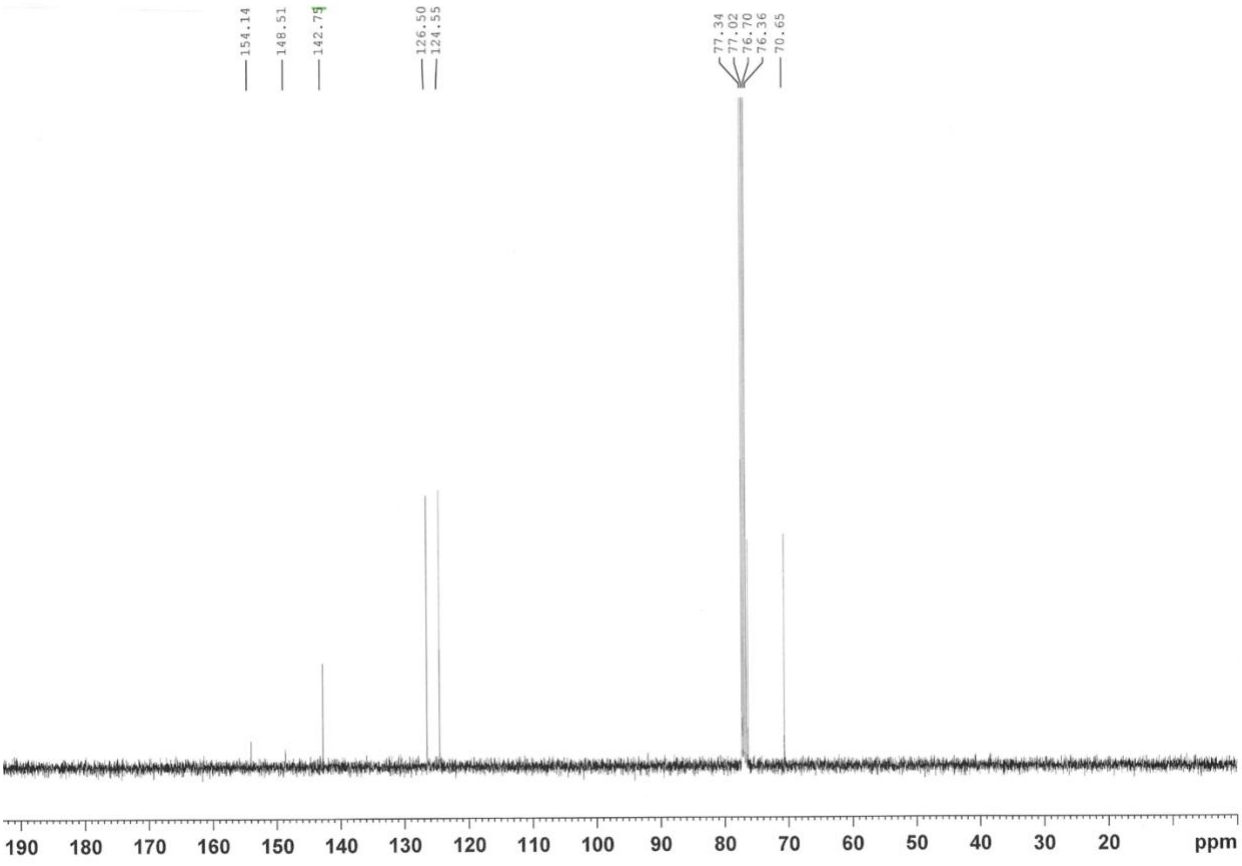

43a
7.500
7.497
7.492
7.489
7.483
7.478
7.435
7.429
7.423
7.421
7.416
7.320
7.318
5.760
5.740
5.720
4.887
4.865
4.845
4.843
4.430
4.428
4.410
4.408
4.389
4.386
1.687
1.308
8 7 6 5 4 3 2 1 ppm
4.409
1.000
0.952
0.954
0.561
0.581


O2N
Br
OH
44
8.316
8.294
7.6..
7.637
5.102
3.756
3.747
3.729
3.721
3.609
3.588
3.562
2.870
2.102
1.654
1.314
8
7
6
5
4
3
2
1
ppm
1.850
1.895
1.056
1.000
0.980
1.000

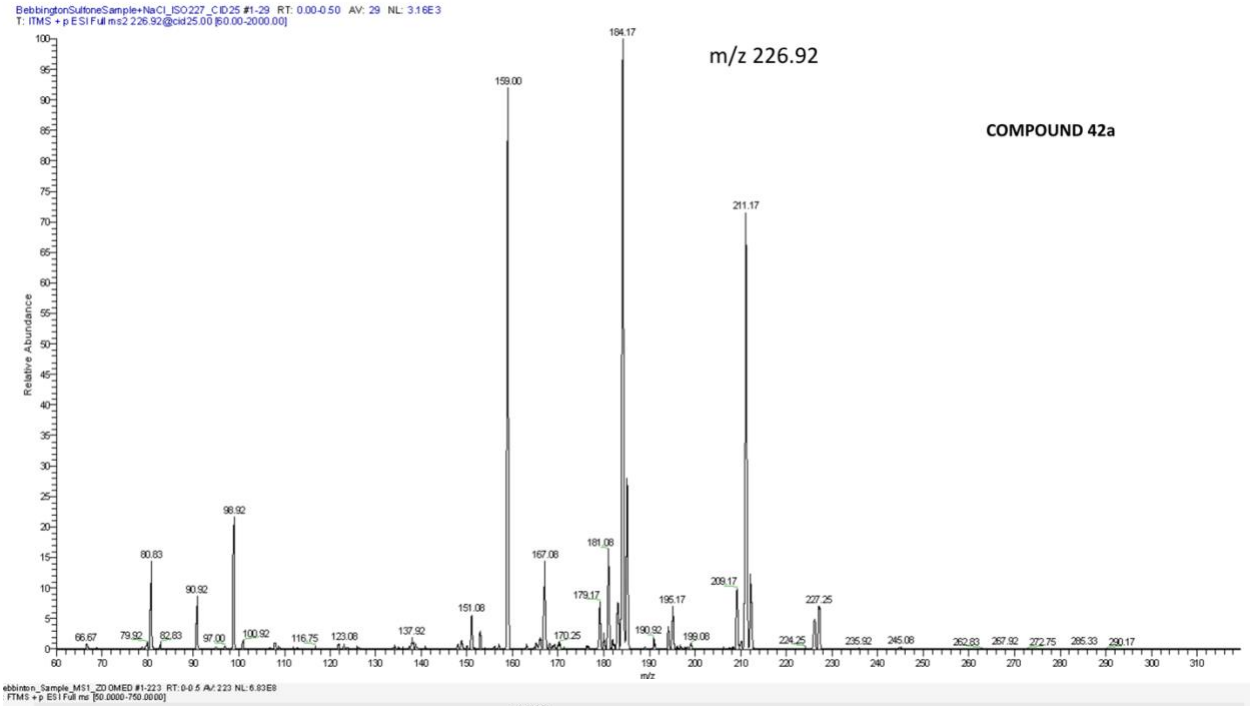
44a

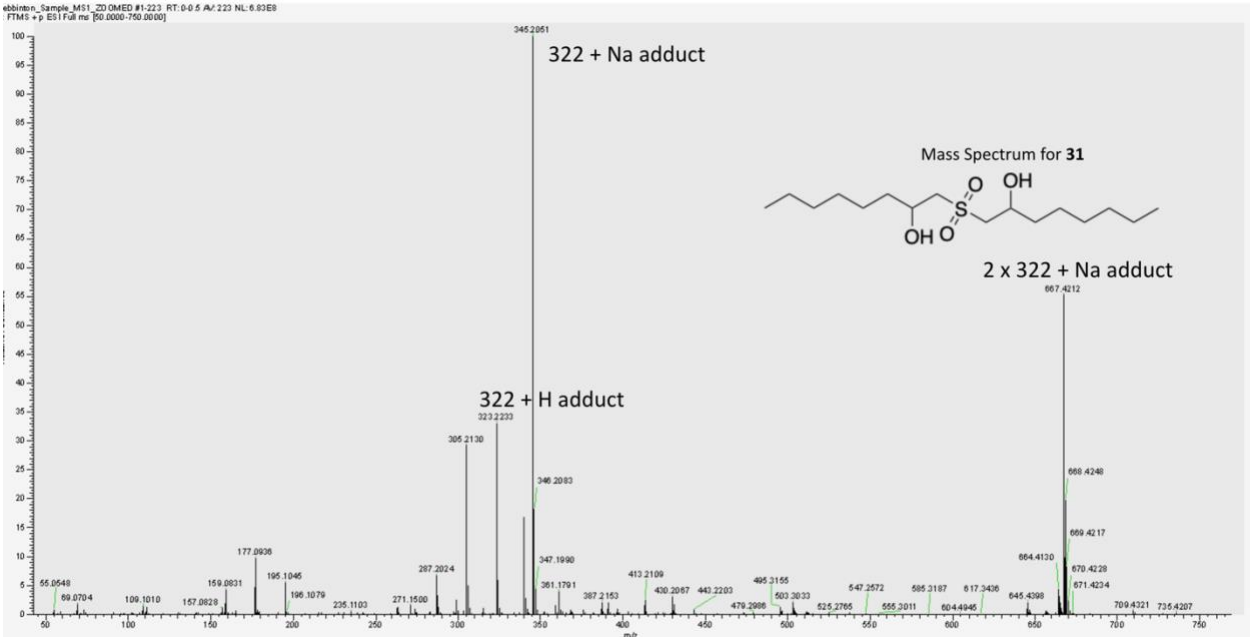

8.346
8.326
8.162
7.643
7.616
7.463
7.320
5.912
5.892
5.872
5.004
4.997
4.982
4.977
4.961
4.955
4.409
4.405
4.402
4.384
4.369
4.362
4.150
4.134
3.963
3.018
8
7
6
5
4
3
2
1
ppm
1.975
0.108
1.994
0.120
1.000
1.015
1.016
0.103
0.097
0.102

44a


154.14
148.51
142.79
126.50
124.55
77.34
77.02
76.70
76.36
70.65
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

Mass Spectra





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