# University of Alberta

The Use of Canola Oil as a Carbon Feedstock in the Synthesis of Value-Added Materials

by

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# Abstract

With the increased strain on the world's petroleum supplies, research efforts are turning toward establishing renewable sources of carbon in the generation of materials that are essential for consumer products ranging from pharmaceuticals to polymers. Canola oil is one such renewable resource that can be used as a carbon source. Transesterification of canola oil results in the liberation of unsaturated fatty acid methyl esters. Chemical manipulation of these unsaturated methyl esters can lead to more diverse chemical functionalities that would be useful in the preparation of value-added materials. Alkynes are one such functional group that can be used in the synthesis of more complex molecules. One special type of alkyne is benzyne. Benzyne can undergo cycloaddition reactions that can result in aromatic hydrocarbon scaffolds.

This thesis will focus on the synthesis of terminal alkynes from canola oil, featuring a novel tandem ozonolysis-dibromoolefination reaction. The terminal alkynes will be used to synthesise aromatic rings through a [2+2+2] cycloaddition reaction.

Alkyl-sustituted aromatic rings will be used as model compounds to the aromatic rings synthesised from canola oil. The synthesis of benzyne from these aromatic rings will be explored.

# Acknowledgements

This page represents the most important page in this entire dissertation. No one makes it to this place without the support of a team of people. First and foremost, the Department of Chemistry and the University of Alberta represent an institution I am proud to be associated with. The Department of Chemistry is filled with many talented people without whom the quality of research accomplished would pale: Wayne Moffat and his team in Analytical and Instrumentation Laboratories; Mark Miskolzie in the NMR Laboratory; Dr. Randy Whittal and his team in the Mass Spectrometry Laboratory; Bonnie Gover; and Anita Weiler, who has done an amazing job at making sure I have met all of my program requirements.

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# List of Abbreviations

| | |
|---|---|
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| PFO | 9,9'-dioctylfluorene |
| R | alkyl group (general) |
| Å | angstrom |
| app | apparent |
| BP | boiling point |
| br | broad |
| calcd | calculated |
| $^{13}$C NMR | carbon-13 nuclear magnetic resonance |
| cm | centimetre |
| CN | cetane number |
| δ | chemical shift |
| *J* | coupling constant |
| °C | degrees Celsius |
| DAG | diacylglycerol |
| DBO | dibromoolefin |
| DCM | dichloromethane |
| DMF | dimethyl formamide |
| DMS | dimethyl sulphide |
| DMSO | dimethylsulphoxide |
| DMG | directing metalation group |
| d | doublet |
| EI | electron impact |
| ES | electrospray |
| eq | equivalents |
| Et | ethyl |
| FAE | fatty acid ester |
| FAME | fatty acid methyl ester |
| FCC | flash column chromatography |
| FFA | free fatty acid |
| FBW | Fritch-Buttenberg-Weichell |
| g | gram |
| GHG | green house gas |
| Hz | hertz |
| HMBC | heteronuclear multiple bond correlation |
| HMQC | heteronuclear multiple quantum correlation |
| h | hour |
| IR | infrared |
| kcal | kilocalorie |
| LAH | lithium aluminium hydride |
| m/z | mass to charge ratio |
| MHz | megahertz |
| [M] | metal catalyst |

| | |
|---|---|
| Me | methyl |
| µ | micro |
| mL | millilitre |
| mm | millimetre |
| mmol | millimole |
| min | minute |
| mol | mole |
| $M^+$ | molecular ion |
| MAG | monoacylglycerol |
| $^n$Bu | *n*-butyl |
| NMO | *N*-methylmorpholine-*N*-oxide |
| DMAP | *N,N*-dimethylaminopyridine |
| Nf | nonafluorobutanesulfonyl |
| Nu | nucleophile |
| ppm | parts per million |
| PLED | polymer light emitting diode |
| PPE | polyphenylether |
| PU | polyurethane |
| PVC | polyvinyl chloride |
| psi | pound per square inch |
| Pr | propyl |
| PG | protecting group |
| $^1$H NMR | proton nuclear magnetic resonance |
| PDC | pyridinium dichromate |
| q | quartet |
| RED | renewable energy directive |
| $R_f$ | retention factor |
| rt | room temperature |
| $^s$Bu | *sec*-butyl |
| sept | septet |
| SiPG | silyl protecting group |
| s | singlet |
| $^t$Bu | *tert*-butyl |
| THF | tetrahydrofuran |
| TMEDA | tetramethylethylenediamine |
| TPAP | tetrapropylammonium peruthenate |
| TLC | thin layer chromatography |
| Ts | tosyl |
| TAG | triacylglycerol |
| TEA | triethylamine |
| TES | triethylsilyl |
| OTf | triflate |
| TIPS | triisopropylsilyl |
| TMS | trimethylsilyl |
| t | triplet |
| XRD | x-ray diffraction |

Z/C/P $Zn/CBr_4/PPh_3$

# Chapter 1

## Introduction

*"The cure for boredom is curiosity. There is no cure for curiosity."*
*-Dorothy Parker*

The United Nations Conference on Sustainable Development, held in Rio de Janeiro, Brazil in 2012, known as Rio+20, resulted in world governments committing to sustainable development goals that balance economic, social, and environmental concerns.[1] The twelve principles of green chemistry provide a framework in the development or improvement of processes and products that can allow the chemical industry to contribute to the sustainable development goals.[2,3] The twelve priniciples are: 1) prevention of waste; 2) atom economy; 3) less hazardous synthesis; 4) design of benign chemicals; 5) benign solvents and auxiliaries; 6) design for energy efficiency; 7) use of renewable feedstocks; 8) reduction of derivatives; 9) catalysis; 10) design for degradation; 11) real time analysis from pollution prevention; 12) inherently benign chemistry for accident prevention. The work presented in this thesis will focus on principle #7, the use of renewable feedstocks. It is estimated that over 80 billion tons of oil equivalents (toe) of carbon is produced annually across in the globe in biomass.[4] Chemically, biomass is comprised mainly of carbohydrates, lignins, and fats and oils. For this thesis, vegetable oil, specifically canola oil, was chosen as the source of renewable carbon.

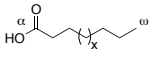
In this Chapter, the history of vegetable oil as a carbon source will be explored. It will begin with a brief introduction to plant oils and their chemical structure. In Section 1.2, a short review on materials made from plant oils will be presented; this will be followed with a discussion on the use of fatty acids derived from plant oils to synthesise materials. Section 1.3 presents the advantages of canola oil over

other vegetable oils and why it was chosen as the carbon source for this thesis. The Chapter will end with a succinct outline of the overall thesis, presenting the work that will be discussed in more detail in the following chapters.

### 1.1 Plant Oils

The annual global production of major vegetable oils was 158 million metric tonnes in 2012/13, a number that has shown a steady increase over the last decade.[5]

Fats and oils are comprised of triacylglycerols (triglycerides): three fatty acids esterified on a glycerol backbone. A general triacylglycerol is shown in Figure 1.1 with the glycerol backbone highlighted in red. The "R" goups (highlighted in blue in Figure 1.1) vary depending on the fatty acid. In natural fatty acids this "R" group consists of an unbranched hydrocarbon chain with an even number of carbons, commonly between the range of 12-22 carbons atoms (though acids are known that have carbon atom chains between 2-80).[6] Unsaturated fatty acids will also possess one or more olefins in the R group; these olefins are in the *cis* configuration and will appear at preferred positions, most commonly the ω-9 position.* The three fatty acids present in the triacylglycerol can all be the same, but can also be a mixture of different fatty acids. The fatty acid profile of fats and oils determines their properties, and varies among sources. Table 1-1 shows the

* Fatty acid terminology where the α terminus is the end bearing the carbonyl group and the ω terminus is the end bearing the methyl group. ω-9 position refers to nine carbons from the end methyl group. 

fatty acid profiles of a series of vegetable oils. From Table 1-1 it can be seen that vegetable oils are rich in unsaturated fatty acids with coconut and palm oils being notable exceptions.

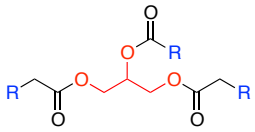
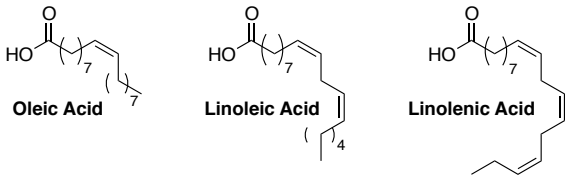


**Figure 1.1: A general triacylglycerol.**

**Table 1-1. Average Composition of Fatty Acids in Vegetable Oils (wt %).**




| Oil Type | Saturated Fats | Oleic Acid | Linoleic Acid | Linolenic Acid |
|---|---|---|---|---|
| Canola oil | 7 | 61 | 21 | 11 |
| Flaxseed oil | 9 | 18 | 16 | 57 |
| Sunflower oil | 12 | 16 | 71 | 1 |
| Olive oil | 15 | 75 | 9 | 1 |
| Soybean oil | 15 | 23 | 56 | 6 |
| Palm oil | 51 | 39 | 10 | Trace |
| Coconut oil | 91 | 7 | 2 | - |

"Skipped" or "methylene-interrupted" fatty acids make up the most common type of polyunsaturated fatty acids. This terminology stems from the placement of a methylene ($CH_2$) group between olefins, as opposed to direct conjugation. There are, however, examples of acids that have unusual patterns of unsaturation (Figure 1.2). Calendic acid (**1.1**), α-eleostearic acid (**1.2**), and punicic acid (**1.3**) all

contain olefins that are conjugated rather than separated by a methylene group. It is noteworthy that the *trans*-configuration of olefins is prevalent in conjugated unsaturated fatty acids, whereas in methylene-interrupted acids (linoleic or linolenic), the *trans* configuration is only produced by ruminant animals or by processes such as partial hydrogenation. Otherwise, these fatty acids exist solely in the *cis*-configuration. Though rare, there are also examples of fatty acids containing acetylenes, such as santalbic acid (**1.4**) and bolekic acid (**1.5**).[6,4]

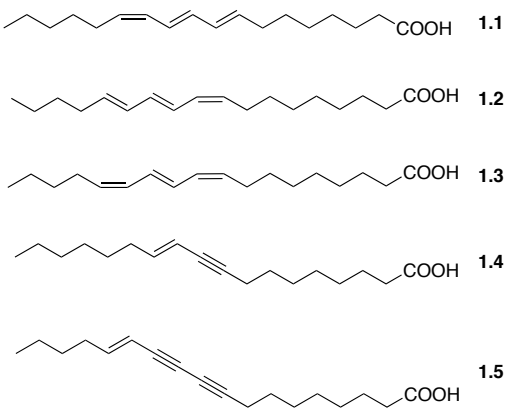



**Figure 1.2: Conjugated and acetylenic fatty acids: 1.1 calendic acid; 1.2 α-eleostearic acids; 1.3 punicic acid; 1.4 santalbic acid; 1.5 bolekic acid.**

## 1.2 Plant Oil Materials

Triacylglycerols (triglycerides) possess a number of chemically-reactive sites (Figure 1.3) that can be used in the synthesis of value-added materials ranging from thermosetting polymers to biodiesels.[7,8] The work presented in the thesis will focus on chemistry at the olefin position.

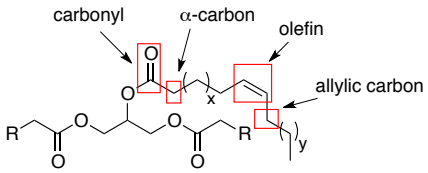



**Figure 1.3. Reactive sites on a triglyceride.**

### 1.2.1 Direct Polymerisation of Olefin

Highly unsaturated oils, like linseed (flaxseed) oil or soybean oil, are classified as "drying oils" and are susceptible to autoxidation and polymerisation.[†] Drying oils are used in coatings, paints, varnishes etc., because they polymerise into a solid upon exposure to oxygen or other driers.[9] The mechanism of this oxidation polymerisation ("drying") has been studied by FT-IR and FT-Raman spectroscopy.[10,11,12] Though complicated, the mechanism is generally accepted to be a free radical reaction beginning with hydrogen abstraction from an interrupting methylene group in polyunsaturated fatty acids to form a pentadienyl radical, **1.6** (Scheme 1.1).[13,14,15] These radicals react with oxygen to form hydroperoxy radicals that propagate the reaction by abstracting hydrogen from alkyl groups (RH in Scheme 1.1), resulting in conjugated hydroperoxides **1.7**. Hydroperoxide decomposition results in alcohols, aldehydes, ketones, ethers, carboxylic acids, and epoxides. The radical recombination of alkyl, alkoxyl, or peroxyl radicals produced during the reaction result in a cross-linked material ideal for paints, coatings, or resins.[13,15,14]

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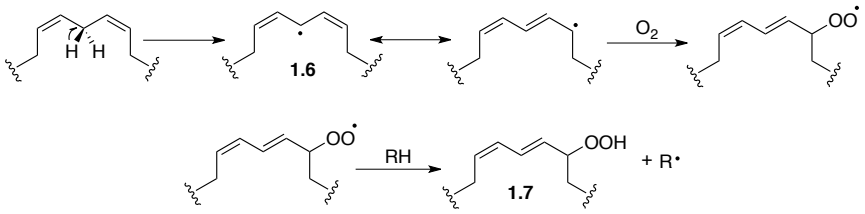
[†] The degree of unsaturation of oils can be described by the iodine value, which is defined at the amount of iodine (in grams) that is taken up by 100g of that oil. Oils are divided into three classes according to their iodine value: drying oils have an iodine value greater that 170, *e.g.,* linseed (flaxseed) oil; semi-drying oils have an iodine value between 100 and 170, *e.g.,* sunflower oil; non-drying oils have an iodine value less than 100, *e.g.,* palm oil.[15]




**Scheme 1.1: Autoxidation of polyunsaturated fatty acids.**

As long as there are radicals, or functionalities that can produce radicals, still present, a film is not considered dry. The drying process can be accelerated with the addition of a catalyst, called a drier. Mallégol *et al.* found that the addition of cobalt drier to linseed oil resulted in an accelerated drying process without affecting the overall mechanism. The authors attributed this to changes in kinetics.[13] The authors noted that in thick films through-dry‡ became slow due to surface-hardening, where the under layers remain viscous while the surface is solid.

The olefins present in unsaturated oils can also be polymerised by cationic polymerisation and their utility can be further increased by copolymerisation with other olefins. Larock *et al.* have extensively studied the cationic polymerisation of soybean oils. The authors used three types of soybean oil: regular soybean oil, low saturated soybean oil, and conjugated low saturated soybean oil, each increasing in reactivity toward cationic polymerisation.[16] While it was found that soybean oil does not homopolymerise through cationic polymerisation, it can be copolymerised with divinylbenzene as a comonomer. Divinylbenzene is very

‡ Through-dry: the curing of the oil coating through all layers.

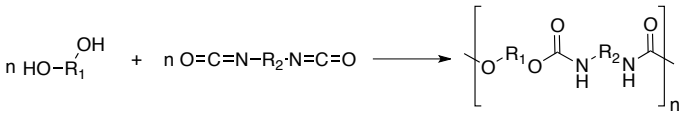
reactive to cationic polymerisation. The authors found that the cross-linking density was not even throughout the material resulting in uneven mechanical properties. This was attributed to poor miscibility between the initiator, $BF_3$•$OEt_2$, and the soybean oil. Modifications to the initiator resulted in improved polymerisation. The resulting materials were rigid, hard polymers with a high crosslinking density and nonuniform crosslink structure, making the materials brittle.

In an effort to establish polymers with controlled mechanical properties, Larock *et al.* included styrene as the main comonomer in the copolymerisation of soybean oil, adding small amounts of divinylbenzene, norbornadiene, or dicyclopentadiene to control the crosslinking density.[17] By controlling the oil, stoichiometry, and crosslinker the authors were able to control the properties in the final material. It was found that the higher crosslink densities (materials made from low saturated soybean oil, styrene, and either divinylbenzene or norbornadiene) resulted in hard plastics with a high glass transition temperature and increased tensile strength, while the materials with low crosslink densities were soft rubbers with a lower glass transition temperature.[18,19,20,21] The mechanical properties of these soybean oil based polymers were shown to be comparable to petroleum-based polymers, suggesting that these soybean oil materials can be substituted for current plastics.

### 1.2.2 Polyols and Polyurethanes

The synthesis of polyols from vegetable oils represents one of the largest potential applications of this feedstock in materials chemistry. Polyols from vegetable oils are of most interest in their application to the synthesis of polyurethanes. While a brief overview of this chemistry will be discussed herein, the interested reader is directed toward any of number of the review articles published on this subject for further detail.[22,23,24,25]

Polyurethanes (PUs) are arguably one of the most polytropic polymers available due a wide variety of applications. PUs are mainly used for the production of flexible and rigid foams; however, they are also used in coatings, adhesives, sealants, and elastomers.[23] The synthesis of PUs involves the reaction of a diisocyanate with a diol or polyol (Scheme 1.2). The synthesis of PUs using polyfunctional polyols, like those obtained from vegetable oils, results in highly crosslinked materials.[22] Industrially there are only a few diisocyanates used to produce PUs; they are typically aromatic, specifically 2,4-toluene diisocyanate and methylene diphenyl diisocyanate. Aliphatic diisocyanates have been shown to have slow kinetics during the polymerisation process.[24] Since vegetable oils are aliphatic, they are used as precursors for the polyol partners rather than the diisocyanates.



**Scheme 1.2: General polyurethane synthesis from diol and diisocyanate.**

Castor oil is 90% ricinoleic acid (Figure 1.4) making it a rare example of a vegetable oil that naturally contains a hydroxyl group. Castor oil is therefore used as a polyol without further modification, as it contain approximately 2.7 hydroxyl groups per triglyceride molecule. The even distribution of the hydroxyl groups throughout the oil result in uniformly crosslinked PU materials with good mechanical properties.[25]

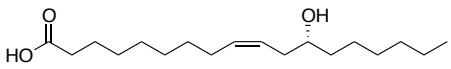
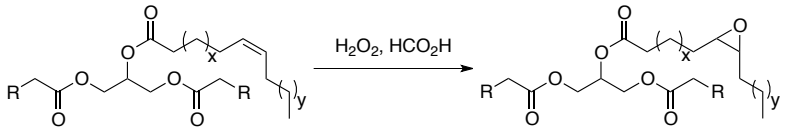


**Figure 1.4: Ricinoleic acid.**

Since most vegetable oils do not contain the requisite hydroxyl groups naturally, they must be installed. This can be done in one of several ways: epoxidation followed by oxirane ring opening; transesterification or transamidation; ozonolysis followed by reduction; hydroformylation followed by reduction.[25] As it is the most common method to produce vegetable oil polyols, this discussion will focus on epoxidation. Ozonolysis will be presented in Chapter 2 as part of larger discussion. All of these reactions take advantage of the carbon-carbon double bonds present in vegetable oils to introduce the hydroxyl group. To produce a polyol with sufficient hydroxyl groups to result in a PU with the correct

properties, the starting vegetable oil must be highly unsaturated, typically requiring more than 2.5 double bonds per triglyceride molecule.[25] For example, many polyols are synthesised from soybean oil, which has an average of 4.6 double bonds per triglyceride molecule.

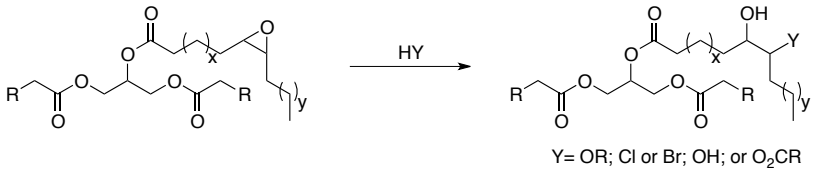
Commercially, epoxidised vegetable oils are synthesised by reaction with hydrogen peroxide and formic acid to produce a peracid *in situ* (Scheme 1.3).[26] There has been some use of vegetable oil epoxides in the synthesis of epoxy resins.[27] They are also used as plasticisers and stabilisers in PVC by increasing polymer flexibility and scavenging any hydrogen chloride that is produced by exposure to heat or light.[6,4]



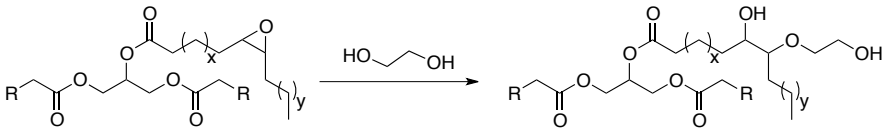

**Scheme 1.3: Epoxidation of a triglyceride.**

To increase the utility of epoxidised oils, the epoxide is reacted with a proton donor causing a ring opening reaction and results in polyols. [23,25,28] The most reliable proton donors tend to be alcohols; however, the drawback of using alcohols is that the resulting hydroxyl groups are secondary, which are less reactive in PU synthesis (Scheme 1.4).[23] To circumvent this challenge diols, such as ethylene glycol, can be used (Scheme 1.5). Not only does this result in a primary hydroxyl group, but it also results in two hydroxyl groups for every one

epoxy group, meaning a higher hydroxyl functionality.[25] The primary hydroxyl groups have also been shown to result in more thermally stable PUs.[22] 1,3-Propanediol has been added as a chain extender in PU synthesis, and has resulted in improved mechanical properties.[29]

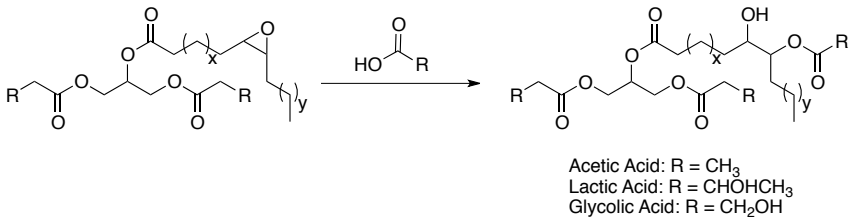



**Scheme 1.4: Reaction of epoxidised vegetable oil with a general proton donor.**




**Scheme 1.5: Reaction of expoxidised vegetable oil with ethylene glycol.**

Alcohols and diols are not the only proton donors: PUs have been synthesised from polyols produced from epoxidised soybean oil reacted with biobased acids acetic acid, lactic acid, and glycolic acid (Scheme 1.6).[30] Both acetic acid and lactic acid result in polyols that have only secondary hydroxyl groups available for reaction with isocyanates, while glycolic acid results in a primary hydroxyl group. This difference had little affect on the observed properties in the corresponding PUs but there was a noticeable change in gel time, as gel time is affected by the reactivity of the hydroxyl group. Expectedly, the PUs produced from glycolic acid polyols had a shorter gel time due to the presence of the more reactive primary hydroxyl group.

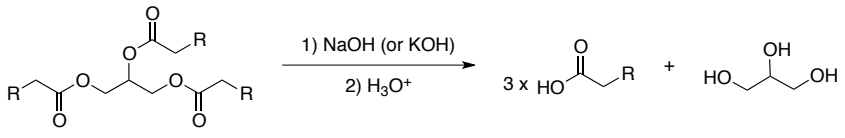



**Scheme 1.6: Polyol synthesis by reaction of epoxidised vegetable oil with biobased acids.**

While these are only a few examples of the synthesis of PUs from vegetable oil polyols, there are many more examples, underscoring the large potential for vegetable oils to be used as a starting material in the synthesis of this valuable and versatile material.[31,32,33,34,35]

### 1.2.3 Breaking Apart the Triglyceride: Fatty Acids and Glycerol Materials

While it is possible to use vegetable oils in their starting triglyceride form, it is also possible to break apart the triglyceride into its components and use the pieces for further chemistry. By reacting the triglyceride with a base, such as sodium or potassium hydroxide, the oil is saponified into three equivalents of free fatty acid (FFA) and one equivalent of glycerol (Scheme 1.7).




**Scheme 1.7: Saponification of triglyceride.**

**Biodiesels**

Triglycerides can also be transesterified to produce fatty acid esters upon reaction with an alcohol in the presence of an acid or base catalyst. One of the largest markets for fatty acid esters is in the production of biodiesel. Biodiesel is a fuel made up of long-chain fatty acid esters obtained from a renewable source of fat or oil.[36] Though any alcohol is suitable for fatty acid ester production, the most common is methanol, chosen because it is inexpensive. While either base or acid catalysts are suitable for the transesterification reaction, industrially base catalysis is preferred.[37] Over 60% of biodiesel plants use the catalyst sodium methoxide to initiate transesterification. The result of this process is fatty acid methyl esters (FAMEs).

There are a number of advantages to the use of biodiesels: first and foremost is the overall net reduction in green house gas emissions because of the carbon sequestration that occurs in the growth of the oilseed producing plants.[38,39] With biodiesels there are no sulphates or polycyclic aromatic hydrocarbons; there is a reduction in the amount of carbon monoxide emitted; and there is less soot and odour. Further, this fuel can be used directly in current compression-ignition diesel engines and can be blended with petrodiesel, as biodiesel is soluble in petrodiesel in all concentrations. When blended, there is an observed reduction in the total hydrocarbon, carbon monoxide, and particulate emissions.[40] Despite an

overall decrease in exhaust emissions with the use of biodiesels, there is no reduction of nitrogen oxide emissions.[37,41]

The suitability of a material for use as a diesel fuel is determined by cetane number (CN),[§] viscosity, cold flow, oxidative stability, and lubricity.[42] Gerhard Knothe summarises five approaches to improving biodiesel properties by altering fatty acid composition in a 2009 Energy and Environmental Science paper.[42] With the exception of lubricity, all properties are impacted by the fatty acid ester (FAE) composition, where both the acid and the alcohol chosen for esterification can have an impact. From Knothe's paper it is clear that altering FAE composition is not trivial. Alteration that favours one property can result in a deleterious effect on other properties. For example, while an increase in saturation can improve the cetane number, decrease $NO_x$ emissions, and increase oxidative stability, saturation also reduces cold flow and increases viscosity. It seems that fuels high in methyl oleate result in a reasonable compromise between oxidative stability and cold flow while keeping CN within acceptable limits. This results in oils high in oleic content, such as canola oil, being selected for biodiesel production. The European Union represents the world's largest biodiesel market and over 80% of these biodiesels are composed of canola (rapeseed) oil.

Reduction in the emission of greenhouse gasses (GHG) is touted as the major advantage of biodiesels. Europe's Renewable Energy Directive (RED), which was

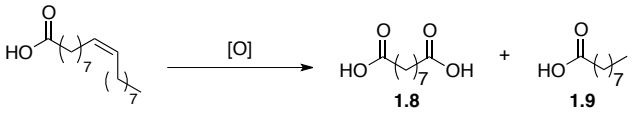
[§] Cetane number describes the ignition delay time of a fuel between entering the combustion chamber and ignition. The number is dimensionless; higher numbers indicate a shorter delay. The standard for the United States is 47 and for Europe is 51.

introduced in 2009, requires a reduction in greenhouse gas emissions of 35% (compared to petroleum-based fuels) for biodiesels up 2017, when the reduction requirement will be increased to 50%. The European Commission's studies report that canola oil biodiesels have a "typical" GHG emission reduction of 45%, but often use a default number of 38% emission reduction to describe the benefits of canola oil based biodiesels.[43] Based on these numbers it seems that canola biodiesel meets RED sustainability requirements; however, a recent independent study by Gernot Pehnelt and Christoph Vietze refutes these claims and points to GHG savings of, at best, 29.7%.[44] The authors claim there was a lack of transparency in the calculations performed by the European Commission. Running a life cycle analysis using the same basic methodology and background data as RED, and only utilising publicly available and published data in their calculations, the authors were unable to replicate the numbers reported by RED. Further, these calculations did not take into account any of the other environmental or social impacts associated with using available agriculture land for fuel, which they argue would further decrease the sustainability of canola oil biodiesel.

One other major concern is vegetable oil biofuels is that a large amount of glycerol is produced as a by-product, and with the growing use of biodiesels, the amount of glycerol produced has exceeded the global demand.[45] For this reason, deoxygenation of glycerol is being investigated in the synthesis of platform chemicals; however, this chemistry remains beyond the scope of this thesis.

## Linear Diacids

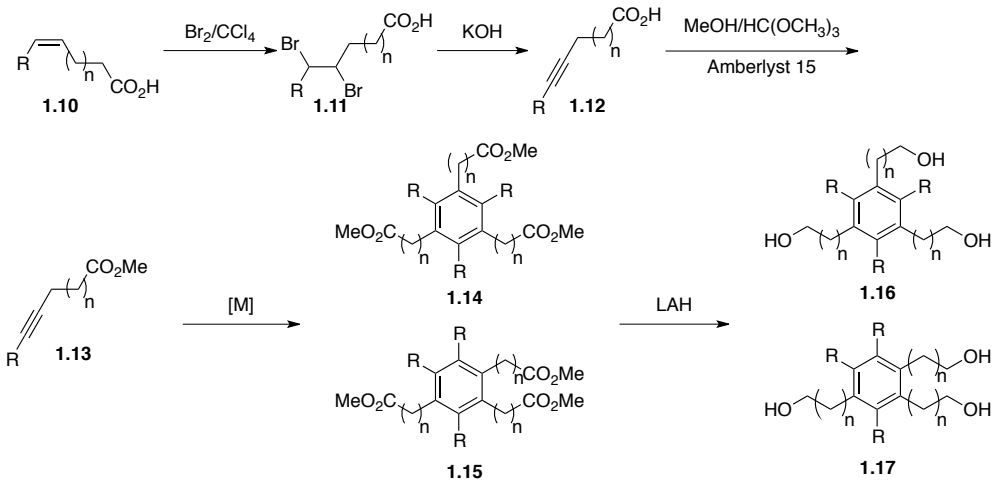
Oxidative cleavage of FFAs and FAMEs produces medium- to long-chain diacids that are valuable monomers in the synthesis of polyesters, polyamides, and polyurethanes.[46,4] Azelaic acid (**1.8**) is one of the largest produced diacids; it is used in a number of applications ranging from pharmaceuticals to plasticisers and lubricants.[47] Azelaic acid (**1.8**) is produced from the oxidative cleavage of oleic acid, isolated from oleic-rich oils, such as canola or olive, forming pelargonic acid (**1.9**) as a by-product (Scheme 1.8). Chapter 2 will deal with the oxidative cleavage of FAMEs isolated from canola oil.




**Scheme 1.8: Oxidative cleavage of methyl oleate.**

## Aromatic Rings

One of the most pertinent transformations of the olefins in vegetable oil for this thesis is their conversion to alkynes for use in aromatic ring synthesis (Scheme 1.9).[48,49] Bromination of the olefin followed by elimination of HBr results in an internal alkyne, **1.12**. The alkyne can undergo trimerisation with using an appropriate metal catalyst, resulting in two aromatic isomers: the symmetric **1.14**; and the anti-symmetric **1.15**. These aromatic esters are reduced to triols, **1.16** and **1.17**, for use in polyurethane synthesis. The synthesis of aromatic triols has been applied to fatty acids derived from canola oil.[50,51]



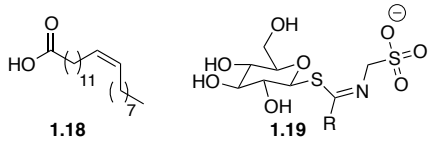

**Scheme 1.9: Synthesis of aromatic triols from fatty acids.**

## 1.3 Canola Oil: Canada's Crop

In many places around the world the terms "canola" and "rapeseed" are used synonymously, but while these two crops are related, there is a discrete difference between the two species. In the 1970s Canadian scientists, through a research initiative led by Dr. Keith Downey, Dr. Baldur Steffanson, and Dr. Burton Craig, genetically modified rapeseed to reduce the amount of "anti-nutritional" components: erucic acid (**1.18**) and glycosinolates (**1.19**) (Figure 1.5), both of which make rapeseed unfit for human consumption.[52] In order to be referred to as "canola," the amount of erucic acid has to be less than 2%, and the amount of glycosinolates has to be less than 30 μmol.[53] The term "canola" stands for "**Can**adian **o**il, **l**ow **a**cid," and is widely considered to be "Canada's crop." Table 1-2 shows a comparison of Canada's principle field crops,[**] and from this information it we begin to understand the canola industry's claim of Canada's most valuable crop. In a report published by the Canola Council of Canada in

[**] Information available from Statistics Canada

2011, the impact of canola on the Canadian economy is described.[††41] The contents are also summarised on their website.[53] The canola industry contributes $15.4 billion to the Canadian economy per year, providing 228 000 Canadian jobs and over $8.2 billion in wages. These jobs are spread over the areas of farming, seed handling, transportation, crushing, refining, and end uses. The acreage dedicated to canola is increasing due to the profitability and resilience of this crop. In 2007, the industry set the goal of producing 15 million tonnes of oil by 2015. In 2011, a record 14 million tonnes was produced by Canadian canola growers, further underscoring the economic importance of this crop.




1.18 1.19

**Figure 1.5: Antinutritional components of rapeseed-erucic acid and glycosinolates.**

**Table 1-2: Comparison of Canada's Principle Crops for 2011-2012 Crop Year.**

| Crop | | Average Price/tonne[a] | Acreage Harvested (KHa) | Production (Kt) |
|---|---|---|---|---|
| Wheat | durum | 345 | 8553 | 25 288 |
| | other | 290 | | |
| Canola | | 601 | 7589 | 14 608 |
| Flax | | 525 | 291 | 399 |

[a] Price in Canadian dollars.

From a consumer perspective, canola oil is widely regarded as one of the healthiest vegetable oils available: it is primarily comprised of the

[††] This report uses data collected from three crop years: 2007-08, 2008-09, and 2009-10. A crop year is from August through to July.

monounsaturated fatty acid oleic acid (Table 1-1), which is viewed as a "heart healthy" fatty acid having been shown to lower low-density lipoprotein levels and assist in controlling blood glucose levels.[54] Further, in comparison to other oleic acid-rich oils, like olive oil, canola oil is low in saturated fatty acids, at less than 7%. The remainder of the oil is comprised of α-linolenic (ω-3) and linoleic (ω-6) fatty acids in the nutritionally ideal 1:2 ratio. Canola oil has also been defined as "zero-trans fat" by government regulatory agencies. The seeds are 44% (by weight) oil, making the canola crop high yielding in oil production. Further, the remaining 56% is a high-protein meal that is ideal for livestock feed. Oil for human consumption and meal for livestock feed represent the largest consumer uses for canola.

From a chemistry perspective, canola makes an excellent choice as a renewable source of carbon. This increase in production along with the proclivity for high oil yields makes it abundant. The high oleic content is what makes it so attractive as a source of biodiesel despite the drawbacks discussed *vide supra*. But, as also discussed, this high oleic content also allows for a number of chemical manipulations at the olefin position. Being mostly monounsaturated, it is more oxidatively stable compared to other common oils being used as carbon sources, namely soybean oil.

While the work presented in this thesis focuses on canola oil as the carbon feedstock, it is not limited to only canola oil. Domestic production of carbon

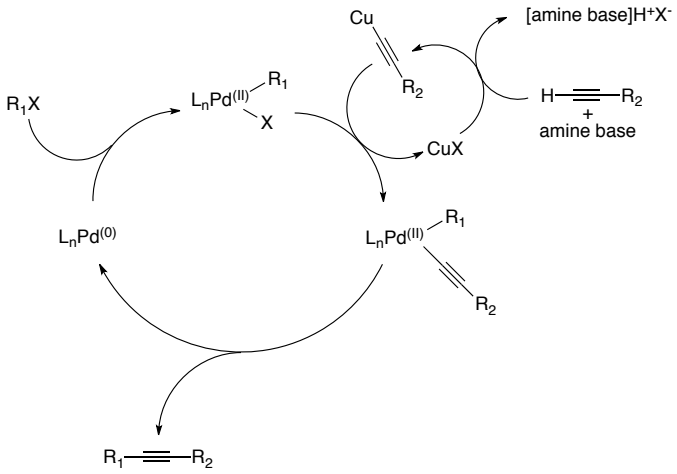
feedstocks is one advantage of the production of biodiesels over petrodiesels for many countries, and this can naturally be extended to the production of any material, as fuel is just one application of petroleum resources. By developing chemistry that can take advantage of any unsaturated vegetable oil crop allows each country to apply these processes to the crops available in their own region. For Canada, canola is the crop of choice, for another country, olive oil might be a better choice. Further, the waste products in the refining of canola oil (and other vegetable oils) as well as soapstock production result in FAMEs. This allows for the application of the chemistry discussed in this thesis to the use of these waste materials.

### 1.4 Terminal Alkynes

Because the focus of this thesis is on the synthesis of materials rather than fuels, the conversion of FAMEs isolated from canola oil into a versatile functional group is a necessity. Terminal alkynes became the functional group target of choice. Terminal alkynes play an integral role in the syntheses of complex organic scaffolds. The low pKa of the sp C-H bond on terminal alkynes relative to $sp^2$ and $sp^3$ C-H bonds[‡‡] allows for deprotonation and conversion to organolithium or organomagnesium nucleophiles used to form carbon-carbon bonds (Scheme 1.10). Terminal alkynes can also be used in the formation of carbon-carbon bonds through various cross coupling reactions, such as the Sonagashira, Stille, and Cadiot-Chodkiewicz couplings to name a few (Scheme 1.11).[55,56,57]

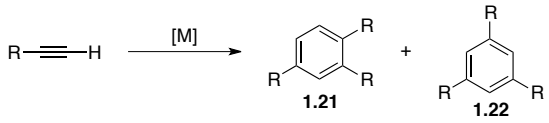
[‡‡] pKa of sp C-H: 25; $sp^2$ C-H: 43; $sp^3$ C-H: 50


**Scheme 1.10: Synthesis of alkynyllithium species from terminal alkyne.**




**Scheme 1.11: General mechanism for Sonogashira cross-coupling reaction.**

The use of internal alkynes synthesised from canola oil FAMEs to produce hexasubstituted aromatic rings was discussed in Section 1.2.3, Scheme 1.9. This same [2+2+2] cycloaddition chemistry can be applied to terminal alkynes as well and the result is trisubstituted aromatic rings (Scheme 1.12).[58,59] Just as with the hexasubstituted aromatic rings, a mixture of symmetric (**1.22**) and anti-symmetric (**1.21**) rings are formed; however, the metal catalyst used can select for one regioisomer preferrentially.[60] The synthesis of trisubstituted aromatic rings from FAMEs over hexasubstituted aromatic rings would open up the possibility of chemistry on the ring itself as well as on the substituents.




**Scheme 1.12: [2+2+2] cycloaddition of terminal alkynes.**

Terminal alkynes can be used to build carbon scaffolds by behaving as dienophiles in Diels-Alder chemistry, or by 1,3-dipolar addition via a "click" reaction.[61] They can be conjugated to form extended π-systems, a crucial component in organic materials with non-linear optical response;[62] they can also be found in a number of valuable natural products.[63,64,65]

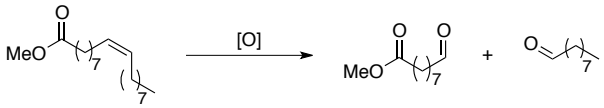
Because of this wide-ranging versatility, the synthesis of terminal alkynes from a renewable resource, such as canola oil, would allow for the production of a variety of value-added materials made of renewable carbon. This will form the basis of the work discussed in Chapter 3 of this thesis.

## 1.5 Outline for Thesis Work

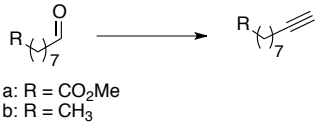
The goal of this work is to demonstrate the synthesis of building blocks for value-added materials from the renewable carbon source canola oil by separating the FAMEs isolated from canola oil and converting these into terminal alkynes that can then be used in the synthesis of a number of different materials (Scheme 1.13). The conversion of FAMEs to terminal alkynes presents two key challenges: the first challenge is to find a robust oxidative cleavage method of the olefins in the FAMEs, ideally resulting in the production of aldehydes (Scheme 1.14). This

forms the basis of the work presented in Chapter 2. The second challenge is the separation and conversion of the aldehydes into terminal alkynes (Scheme 1.15).

**Scheme 1.13: Conversion of canola oil to terminal alkynes and their potential uses.**

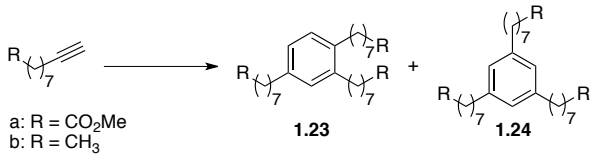



**Scheme 1.14: Oxidative cleavage of methyl oleate to produce aldehydes.**




**Scheme 1.15: Conversion of aldehydes to alkynes.**

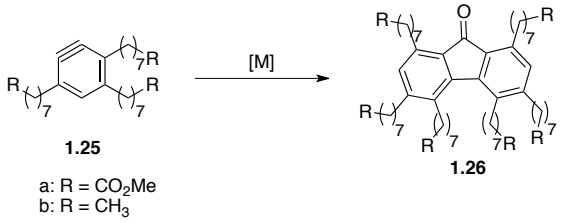
While there are a number of different potential applications for the terminal alkynes, as shown in Scheme 1.13, this thesis targets the synthesis of trisubstituted aromatic rings with, ideally control over the regiochemistry in favour of the anti-symmetric ring (**1.23**) (Scheme 1.16). The synthesis of terminal alkynes and aromatic rings will be discussed in Chapter 3.




**Scheme 1.16: [2+2+2] cycloaddition of terminal alkynes.**

Aromatic rings allow for the synthesis of polyphenylenes, which are used in the synthesis of polymeric semiconductors for organic electronic applications.[66] By

targeting the anti-symmetric trisubstituted aromatic ring, the synthesis of a unique alkyne, benzyne (**1.25**), is possible. Benzyne can be used in cycloaddition reactions resulting in bridged phenylenes, such as fluorenone (**1.26**) (Scheme 1.17). Bridged polyphenylenes based on fluorenone have been well researched by the Veinot group and therefore seemed a suitable target for the proof of concept for this thesis work.[67,68,69] A more detailed discussion of fluorenone, bridged polyphenylene materials, and efforts toward the synthesis of benzyne is presented in Chapter 4.




**Scheme 1.17: Conversion of benzyne into fluorenone via [2+2+1] cycloaddition.**

The final chapter of this thesis features a summary and the conclusions of this work. It highlights some of the unanswered questions and challenges, such as the impact on sustainable development, including atom economy and socio-economic concerns. It also addresses the numerous possible future directions using the work presented in this thesis as a foundation.

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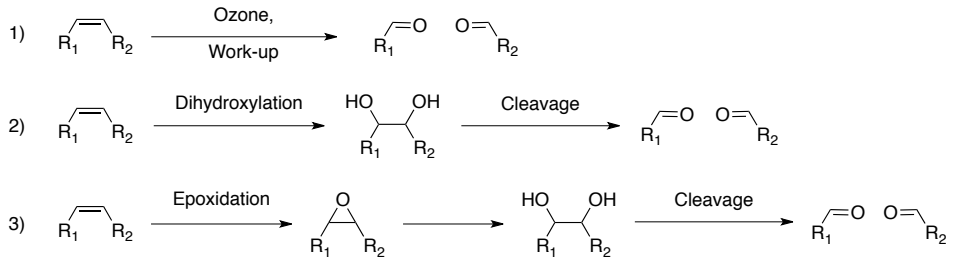
# Chapter 2

## Oxidative Cleavage of Fatty Acid Methyl Esters

*"Perplexity is the beginning of knowledge."*
*-Khalil Gibran*

## 2.1 Introduction to Oxidative Cleavage

In this thesis, one of the key aspects to the successful synthesis of valuable chemical building blocks from canola oil is cleaving FAMEs at their unsaturation points. This process, known as oxidative cleavage, results in carbonyl compounds that serve as starting points for more complex synthetic manipulation. Generally, there are three main methods used for the oxidative cleavage of double bonds: 1) ozonolysis; 2) dihydroxylation followed by vicinal diol cleavage; 3) epoxidation, followed by ring opening and then vicinal diol cleavage (Scheme 2.1). To minimise the total number of steps required for the presented syntheses, only methods 1 and 2 were looked at in any detail.

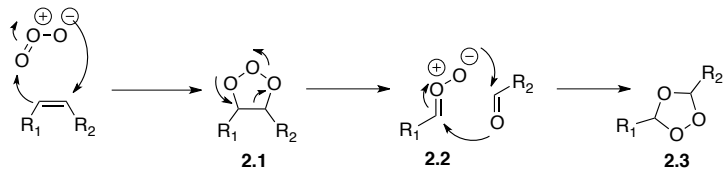



**Scheme 2.1: General oxidative cleavage methods.**

### 2.1.1 Ozonolysis

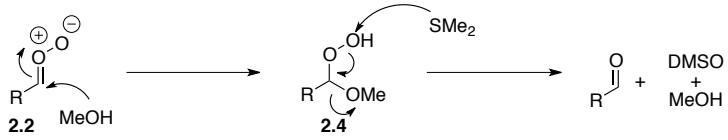
Ozone, an allotrope of oxygen, is highly reactive molecule that can undergo a 1,3-dipolar addition across alkenes, forming a 1,2,3-trioxolane **2.1** (Scheme 2.2).[1] This compound is unstable and undergoes a cycloreversion to form a carbonyl compound as well as a carbonyl oxide, **2.2**. These compounds then proceed through a second 1,3-dipolar addition to form an ozonide, also known as a 1,2,4-

trioxolane, **2.3**.[1,2] To complete the cleavage of the alkene, the ozonolysis is followed by a work-up designed to break apart the ozonide.




**Scheme 2.2: Mechanism of ozonolysis on alkenes.**

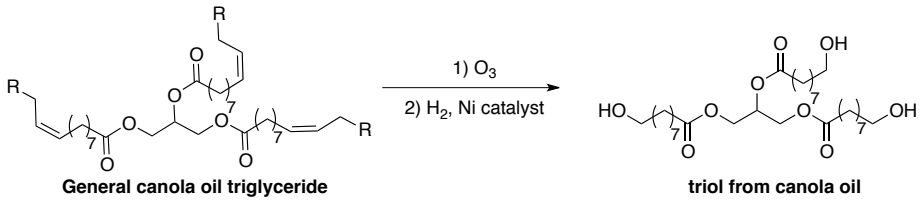
The most common work up procedures uses dimethyl sulphide (DMS) in the presence of methanol.[3,4] Methanol reacts with the carbonyl oxide to form a hydroperoxy acetal, **2.4**, and this is in turn reduced by the dimethyl sulphide (Scheme 2.3). It is possible for the dimethyl sulphide to reduce the ozonide as well, albeit slowly.[5]




**Scheme 2.3: Formation of methoxy hydroperoxide followed by reduction using DMS.**

Another common approach used to work-up ozonides and carbonyl oxides employs phosphines: $Ph_3P$ or $(MeO)_3P$.[6,7] This method, like the DMS method, results in formation of ketones and/or aldehydes. Alternatively, ozonides may be reduced to alcohols by reaction with $NaBH_4$ or $BH_3 \bullet SMe_2$,[8] or conversely, the ozonides may be oxidised to carboxylic acids by reaction with hydrogen peroxide.

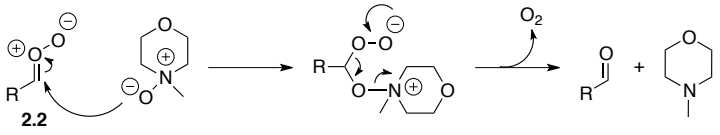
Ozonolysis has already been extensively examined on canola oil.[9] As discussed in Chapter 1, there are a number of methods used to synthesise polyols from vegetable oils, and one such method is ozonolysis. Narine *et al.* have found it possible to produce polyols from canola oil by ozonolysing the oil and following this with a reductive work up using hydrogen gas and a nickel catalyst (Scheme 2.4).[10] These polyols were then used in the production of PUs with a variety of properties.[11,12] It was found that solvent plays a critical role in the success of the ozonolysis and that a mixture of methanol and ethyl acetate was most appropriate for the ozonolysis of canola oil.




**Scheme 2.4: Ozonolysis of canola oil to produce polyols.**

Polyols are not the only possible products accessable from the ozonolysis of vegetable oils. Pryde *et al*. synthesised aldehyde oils from soybean oil.[13,14] Here, the authors reduced the ozonolysis mixture with zinc dust and acetic acid. The result was a mixture rich in carbonyls. These aldehyde oils readily reacted with urea, polyols, phenolic compounds, and even themselves to produce a series of soft, flexible, insoluble resins.

Though there are many advantages, one of largest concerns associated with ozonolysis is that hydroperoxy acetals and ozonides are unstable and prone to spontaneous decomposition, making these intermediates potentially explosive. Using the mild reducing agents noted above leads to the risk of incomplete removal of these intermediates. To address this issue, Dussault *et al.* have found additives, such as water, pyridine, and *N*-methylmorpholine-*N*-oxide (NMO), preclude ozonide formation by interacting immediately with the carbonyl oxide (**2.2**), circumventing the need for a reductive work-up (Scheme 2.5).[15,16,17]




**Scheme 2.5: Proposed mechanism for reaction of NMO with carbonyl oxide.**

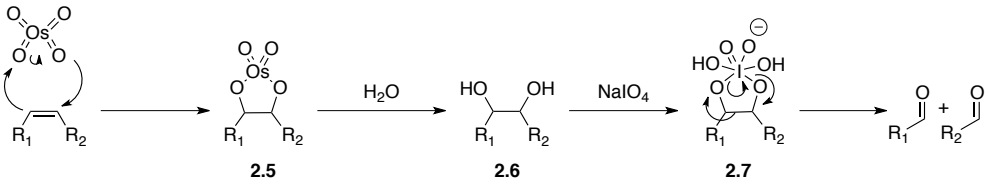
### 2.1.2 Vicinal Diol Cleavage

Vicinal diol cleavage is another very common method employed in the cleavage of double bonds. The first step is the use of an oxidising agent to convert the alkene to a 1,2-diol; the second step involves the use of a co-oxidant to cleave the 1,2-diol into two carbonyl compounds (Scheme 2.1, part 2). There are three common reagents used for this purpose: $OsO_4$, $RuO_4$, and $KMnO_4$.

The first reagent, $OsO_4$, is a gentle oxidiser. One of the advantages of using this reagent over ozone is $OsO_4$ reacts with both electron rich and electron poor alkenes.[18] In addition, unlike other dihydroxylation reagents, $OsO_4$ will not over-

oxidise the cleavage products and the carbonyls remain at the aldehydic oxidation state.[19] To achieve cleavage, an excess of $NaIO_4$ is added to the reaction. This will cleave the diol, and reoxidises the Os(VI) back to Os(VIII) hence, $OsO_4$ can be used in catalytic amounts.

The mechanism of the cleavage reaction starts with $OsO_4$ undergoing a [3+2] cycloaddition with the alkene to form an osmate ester (**2.5**) (Scheme 2.6). This is hydrolysed to the 1,2-diol, **2.6**. The diol reacts with the $NaIO_4$, **2.7**, breaking the C-C bond, resulting in two carbonyl compounds. The major limitation of $OsO_4$ is its acute toxicity. It may be fatal if inhaled, ingested, or absorbed through skin. Further, it sublimes well below its boiling point (BP = 129 °C), increasing the risk of inhaling vapours.




**Scheme 2.6: Oxidative cleavage with $OsO_4$ and $NaIO_4$.**

Another common oxidant related to $OsO_4$ is $RuO_4$. Both are group 8 metals, but as ruthenium is more easily reduced, it becomes the stronger oxidising agent, and instead of the reaction stopping at the aldehydic oxidation state, carboxylic acids are obtained from reactions performed with $RuO_4$.[20,21] Frunzke *et al.* performed a series of quantum chemical calculations to determine why it was that $OsO_4$ produced diols, while $RuO_4$ cleaved carbon-carbon double bonds and attributed

this difference to the fact that Os(VIII) compounds are more stable than Ru(VIII) compounds.[22]

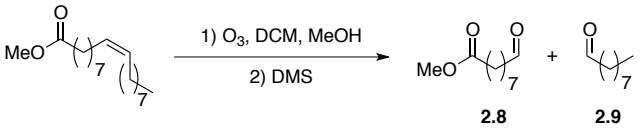
$KMnO_4$ is an oxidant that is similar to $OsO_4$ and $RuO_4$. It exhibits pH dependent reactivity. Under neutral or basic conditions, $KMnO_4$ converts alkenes into diols or α-hydroxy ketones (acyloins). Under acidic conditions, an oxidative decomposition occurs, resulting in double bond cleavage.[23,24,25] Lemieux and von Rudloff successfully completed oxidative cleavage of alkenes in a pH range of 7-8[26] by adding $NaIO_4$ as a co-oxidant, similar to the reactions done with $OsO_4$ and $RuO_4$. With $NaIO_4$ alone, no oxidation occurred, indicating the actual oxidising agent was $KMnO_4$.

This chapter will focus on applying various oxidative cleavage methods to the unsaturated fatty acids found in canola oil. It begins by looking at a series of cleavage reactions intended to produce carbonyl derivatives from the FAMEs. In the final section of this chapter, a method developed to couple ozonolysis with a carbon-carbon bond forming reaction will be discussed.

**2.2 Oxidative Cleavage to Generate Nonanal**

The first attempt made at the oxidative cleavage was done using ozonolysis of methyl oleate in a solution of methanol and dichloromethane, followed by a DMS work up (Scheme 2.7). The expected products of this reaction were aldehydes **2.8** and **2.9**; however, what was isolated was consistent with methoxy

hydroperoxyacetals that were not reduced by the DMS. The TLC of the crude product isolated from the reaction showed three different spots. This mixture of compounds was separated using flash column chromatography (FCC). The first isolated fractions were a mixture of nonanal (**2.9**), and methoxy hydroperoxide (**2.10**). This was confirmed by $^{1}$H NMR spectroscopy, which showed a peak at δ = 9.77 ppm, consistent with the aldehyde proton of **2.9**. A large peak at δ = 3.32 ppm, consistent with a methoxy group, and a peak at δ = 4.36 ppm (t, $J$ = 5.7 Hz), which is consistent with a proton adjacent to the peroxide, support the presence of **2.10** (Figure 2.1). The second fractions isolated showed no peaks indicative of an aldehyde; however, there were two peaks that may be assigned to methoxy groups: one at δ = 3.67 ppm, which is consistent with the protons from the methyl ester; the second signal was at δ = 3.32 ppm, which is consistent with the methoxy group of the corresponding hydroperoxy acetal. A triplet was also noted at δ = 4.35 ppm ($J$ = 5.7 Hz), which is consistent with a proton adjacent to the hydroperoxy and methoxy functional groups (Figure 2.2). The third fractions isolated from the column was shown to be a mixture of aldehyde **2.8**, as evidenced by the presence of a peak in the $^{1}$H NMR spectrum at δ = 9.76 ppm, which is consistent with an aldehyde proton, and the corresponding methoxy hydroperoxide **2.11**, consistent with the remaining peaks. Because each fraction was a mixture of compounds, FCC was not efficient at separating the aldehydes from the methoxy hydroperoxides.




**Scheme 2.7: Ozonolysis of methyl oleate.**

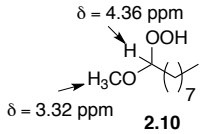



**Figure 2.1: Methoxy hydroperoxy acetal of nonanal isolated from ozonolysis reaction.**

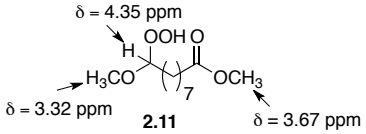
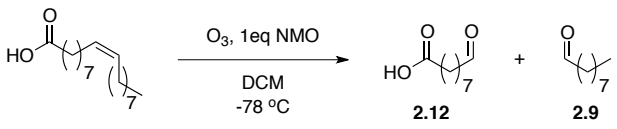



**Figure 2.2: Methoxy hydroperoxy acetal of 2.8 isolated from ozonolysis reaction.**

The methoxy hydroperoxy acetals proved to be extraordinarily difficult to remove from the aldehyde products; to avoid this complication, addition of *N*-methylmorpholine-*N*-oxide (NMO) to the ozonolysis mixture was explored (Scheme 2.8).[15] We also investigated the possibility of using of oleic acid in place of methyl oleate as the starting material. This was thought to improve the separation of the expected aldehydes, **2.12** and **2.9**, because a straightforward acid-base extraction could be applied.




**Scheme 2.8: Ozonolysis with NMO additive on oleic acid starting material.**

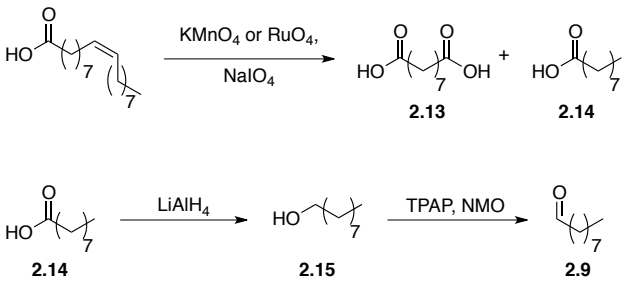
After surveying a number of conditions, the ideal ozonolysis conditions were determined to be 1 equivalent of NMO additive in DCM, a 15 minute flush of ozone followed by a 30 minute sparge of oxygen to ensure that any unreacted ozone had been flushed from the reaction mixture. All procedures were performed at −78 °C. Unfortunately, separation of the cleavage products proved difficult. Product separation via Acid-base extraction was unsuccessful, and column chromatography remained necessary. The compounds isolated from the column were a mixture of the desired aldehydes with their corresponding carboxylic acids, azelaic acid (**2.13**) and pelargonic acid (**2.14**).

When methyl oleate was used as a starting material the relative quantity of the over-oxidised products was reduced; however, the aldehydes still proved difficult to separate, particularly **2.9**. By evaluating the crude reaction mixture immediately after ozonolysis, it was observed that very little carboxylic acid was present. After passing the crude product through a column, a large amount of pelargonic acid (**2.14**) was obtained.* These data suggest **2.9** was oxidised on the silica of the column.

To circumvent challenges associated with isolation of the halves of the oleate molecule as aldehydes, we opted to explore isolating the corresponding carboxylic acids by using a stronger oxidative cleavage reagent ($KMnO_4$ or $RuO_4$).

* This change in products was easily identifiable from the $^1$H NMR spectrum, where a distinct decrease in the aldehyde proton at δ = 9.76 ppm was visible along with a shift in the protons adjacent to the carbonyl from a doublet of triplets at δ = 2.41 ppm (*J* = 7.5 Hz, 2 Hz) to a triplet at δ = 2.34 ppm (*J* = 7.5 Hz).

Following isolation of pelargonic acid (**2.14**) it could be converted to nonanal **2.9** using reductive chemistry that would require little purification (Scheme 2.9).




**Scheme 2.9: Oxidative cleavage of oleic acid followed by conversion of pelargonic acid to nonanal.**

$RuO_4$ proved to be the superior reagent. $KMnO_4$ failed to completely convert the starting material; therefore, there was always some oleic acid that remained in the sample resulting in low yields.

One of the advantages of producing carboxylic acids over aldehydes was that the azelaic acid readily precipitated out of solution as a white solid, making it easy to remove via gravity filtration. The isolated pelargonic acid was reduced to nonanol (**2.15**) using lithium aluminium hydride (LAH) and isolated in greater than 90% yield. The nonanol was re-oxidised to nonanal (**2.9**) either under Swern conditions,[27,28] or using tetrapropylammonium peruthenate (TPAP) with an NMO co-oxidant. The utility of the TPAP oxidation was limited by the fact that it was necessary to remove the catalyst via filtration of the product through a silica plug, converting the desired aldehyde to pelargonic acid.

The Swern reaction proved equally unsuccessful. These reactions produce inexplicably odd results: The $^{1}H$ NMR spectrum showed two triplets at $\delta = 4.30$ and 3.67 ppm ($J = 6.5$ Hz) consistent with those adjacent to esters. There was a small peak at $\delta = 9.79$ ppm, confirming that a small amount of aldehyde was present. The IR spectrum showed a peak at 1744 $cm^{-1}$, consistent with the carbonyl stretch of an ester. Another peak at 1169 $cm^{-1}$ consistent with a C−O stretch was also observed. The most perplexing data arises from the mass spectrum where no molecular ion was observed and the highest mass fragment was 299.2946 m/z, consistent with a molecular formula of $C_{19}H_{39}O_2$. In attempts to reproduce these results to understand what happened, only mixtures of nonanal and the starting material nonanol were isolated. This method of oxidation was subsequently abandoned.

## 2.3 Synthesis of Dibromoolefins via a Tandem Ozonolysis-Dibromoolefination Reaction

In light of the reactivity of the aldehydes obtained from the oxidative cleavage, we opted to explore the possibility of avoiding complications associated with their isolation and develop a strategy that would combine the ozonolysis with a dibromoolefination in a single step. There are some examples of coupling the oxidation of alcohols to aldehydes with reaction of aldehydes with ylides;[29,30,28] however, there are only a limited number combining this type of carbon-carbon bond formation with ozonolysis.[31,32,33] The existing examples typically all involve terminal alkenes, whereas we are using internal alkenes.

As a model system for this reaction, we investigated the reactions of *trans*-stilbene. It was chosen because, as a symmetric alkene, only a single product would be produced. Furthermore, being relatively electron-rich, it was expected proceed smoothly through the ozonolysis procedure.

Using 2.0 equivalents of each Zn, $CBr_4$, and $PPh_3$ (Z/C/P) for each equivalent of aldehyde produced, the reaction was not complete after six days (Table 2-1, Entry 1), as indicated by the presence of two compounds clearly separable using TLC ($R_f$ = 0.35 and 0.62 in 8:1 hexanes:ethyl acetate), as well as a downfield peak in the $^1$H NMR spectrum at 10.06 ppm, consistent with the presence of benzaldehyde. Of important note, there was no evidence of the *trans*-stilbene starting material in either the TLC or the $^1$H NMR analyses. These observations suggest the alkene proceeds efficiently through the ozonolysis and the delay in reaction is likely occurring in the dibromoolefination. It is also worth noting the $^1$H NMR spectrum shows no evidence of over-oxidation to benzoic acid.

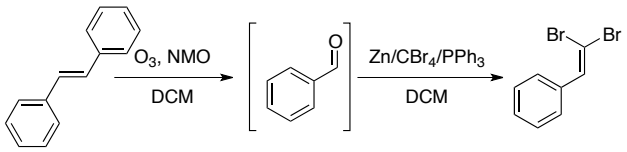
To reduce the reaction time, the Z/C/P mixture was reacted for six hours in refluxing dichloromethane (DCM) before addition of the ozonolysis mixture (Table 2-1, Entry 2). After over 7 days of reaction, no dibromoolefin was detected by TLC and the reaction was stopped.

To facilitate a more efficient reaction, the relative proportions of Z/C/P were increased from 2.0 to 2.5 equivalents per equivalent of aldehyde (Table 2-1, Entry

3). The yield increased to 79%, and though there was no evidence of unreacted aldehyde or starting material in the product, the reaction time required for this conversion remained quite long, at 120 hours. Increasing the Z/C/P concentrations to 3.0 equivalents per equivalent of aldehyde resulted in conversion to dibromoolefin in only 3 hours, and the reaction yield increased to 85% (Table 2-1, Entry 7). The resulting product, 1,1-dibromo-2-phenylethene, was isolated as a light yellow oil and required no further purification.

With the reaction conditions optimised, this method was applied to a variety of alkenes to evaluate the generality of the approach (See: Table 2-2). 3.0 equivalents of each Zn, $CBr_4$, and $PPh_3$ for each equivalent of aldehyde were reacted for 24 h, after which the alkene was ozonolysed and added to the reaction mixture. The reactions were monitored by TLC and $^1H$ NMR spectroscopy. It was immediately evident that yields had dropped compared to reaction with *trans*-stilbene; however, they are comparable to literature yields when a two-step process is employed. No further purification was required for Entries 1-4.

**Table 2-1. Reaction Conditions Used in the Synthesis of 1,1-Dibromo-2-phenylethene.**[a]

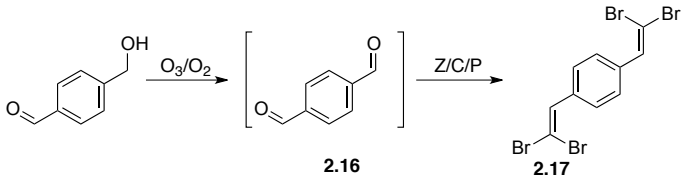



| Entry | $Zn/CBr_4/PPh_3$ (equiv)[b] | Reaction Time (h)[c] | Total Time (h)[d] | Yield (%)[e] |
|---|---|---|---|---|
| 1 | 4.0[f] | 120 | 146 | 58 |
| 2 | 4.0[f,g] | - | - | 0 |
| 3 | 5.0[h] | 120 | 167 | 79 |
| 4 | 6.0[i] | 120 | 165 | 83 |
| 5 | 6.0[i] | 72 | 118 | 75 |
| 6 | 6.0[i] | 24 | 48 | 74 |
| 7 | 6.0[i] | 3 | 27 | 85 |

[a] General procedure: Zn, $CBr_4$, $PPh_3$ were added to an argon filled, flame-dried round bottom flask and then suspended in DCM (0.45 M). The mixture was stirred between 23-48 hours followed by addition of the post-ozonoylsis mixture by canula. The reaction was stirred until complete, as determined by TLC. [b] Number of equivalents for each Zn, $CBr_4$, and $PPh_3$. [c] Reaction time following addition of ozonolysis mixture. [d] Total reaction time including time for reacting the $Zn/CBr_4/PPh_3$. [e] All yields are for isolated product. [f] 2.0 eq of each Zn, $CBr_4$, $PPh_3$ for 1.0 eq of aldehyde produced. [g] $Zn/CBr_4/PPh_3$ was reacted in refluxing DCM. [h] 2.5 eq of each $Zn/CBr_4/PPh_3$ for 1.0 eq of aldehyde produced. [i] 3.0 eq of each $Zn/CBr_4/PPh_3$ for 1.0 eq of aldehyde produced.

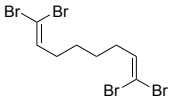
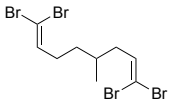
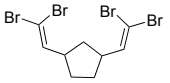
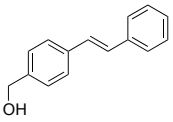
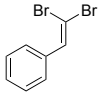
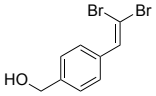
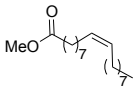
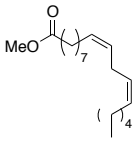
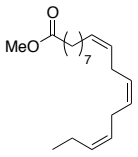
Unexpected results were obtained when the starting material was *trans*-4-stilbenemethanol (Table 2-2, Entry 5). Conspicuously absent from the $^1H$ NMR spectrum were peaks arising from benzylic methylene protons at about $\delta = 4.8$ ppm. The crude $^1H$ NMR spectrum showed the expected peaks associated with

1,1-dibromo-2-phenylethene, as well as an unexpected singlet at δ = 7.57 ppm. To separate this unknown impurity from the 1,1-dibromo-2-phenylethene, it was selectively precipitated as a cream-colored solid at low temperature (–20 – 0 °C) in a minimum amount of hexanes. The $^{1}$H NMR spectrum showed only two singlets: δ = 7.57 ppm (4H) and δ = 7.49 ppm (2H). The IR spectrum of the sample did not show signals consistent with O−H or $sp^3$ C−H functional groups and the mass spectrum provides a molecular formula of $C_{10}H_6Br_4$. Based on these data we assert this product is **2.17** (Scheme 2.10). Oxidation of the benzylic alcohol during ozonolysis could result in the formation of **2.16**, which reacts with the excess Z/C/P to form **2.17**.




**Scheme 2.10: Reaction of *trans*-4-stilbenemethanol under ozonolysis conditions.**

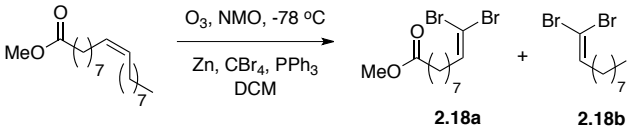
**Table 2-2. Tandem Ozonolysis-Dibromoolefination on Alkenes.**

| Entry | Alkene | DBO | Yield (%)[a] |
|---|---|---|---|
| 1 |  |  | 64 |
| 2 |  |  | 56 |
| 3 |  |  | 65 |
| 4 |  |  | 24 |
| 5 |  |  | 86 |
| | |  | - |
| 6 |  | **2.18a** | 69 |
| | | **2.18b** | 85 |
| 7 |  | **2.18a** | 54 |
| | | **2.19b** | 54 |
| 8 |  | **2.18a** | 69 |
| | |  | -[b] |

[a] Isolated yields. [b] Yield not determined because of the rapid decomposition of the product.

After applying this method successfully with a variety of internal alkenes, we

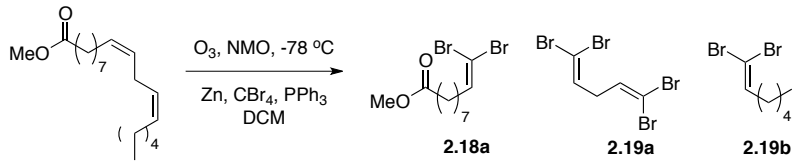
revisited the oxidative cleavage of methyl oleate, (Table 2-2, Entry 6, Scheme 2.11). The two resulting dibromoolefins, **2.18a** and **2.18b**, were separated using FCC. The large difference between the $R_f$ values of **2.18a** and **2.18b**, (0.44 and 0.73, respectively) allowed for effective isolation of the two products. While yields were remained lower than those observed for the *trans*-stilbene reaction, (69% for **2.18a**, 85% for **2.18b**) they are substantially higher than those obtained when we employed the two-step procedure.



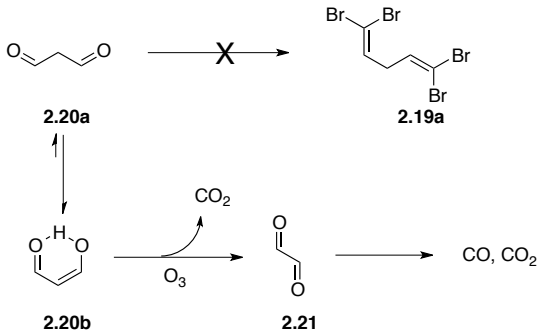

**Scheme 2.11: Tandem ozonolysis-dibromoolefination on methyl oleate.**

To ensure the complete utility of this method, we subjected the two remaining FAMEs of canola oil, methyl linoleate and methyl linolenate, to the process (Table 2-2, Entries 7 and 8, respectively). What makes these two examples particularly interesting is the presence of multiple double bonds accessible for cleavage. In methyl linoleate there are two double bonds: one at the C9 position and one at the C12 position. In methyl linolenate there are three double bonds: one at the C9 position, one at the C12 position, and one at the C15 position. Starting with methyl linoleate, we adjusted the amount of reactants to account for this extra double bond. A second equivalent of NMO was added and the ozonolysis time was doubled from 15 minutes to 30 minutes. Expecting 4.0 equivalents of aldehyde to be produced from the ozonolysis, 12.0 equivalents of

the Z/C/P were used (Scheme 2.13). What was most interesting about this reaction was that compound **2.19a** was completely absent from both the $^1$H NMR spectrum and the TLC of the crude product. FCC was used to separate the products (8:1 hexane: ethyl acetate eluent) and only compounds **2.18a** and **2.19b** were isolated. Isolation of these two compounds suggests that the oxidative cleavage was successful and that the absence of **2.19a** is occurring after this point, but before conversion to the DBO. **2.19a** is expected from reaction of the malondialdehyde, **2.20a**, with the dibromophophonium ylide (Scheme 2.13). Further investigation into malondialdehyde showed that it actually prefers to exist in the enol form rather than the keto form, and specifically the *cis*-enol form, **2.20b**.[34] This structure results in *another* double bond that can be cleaved to give $CO_2$ and glyoxal **2.21** which can degrade into other compounds.[35]




**Scheme 2.12: Tandem ozonolysis-dibromoolefination on methyl linoleate.**




**Scheme 2.13: Proposed reaction of malondialdehyde under ozonolysis conditions.**

Because of the reaction of malondialdehyde during the ozonolysis, only 2.0 equivalents of aldehyde would actually be available to react with the dibromophosphonium ylide; therefore, we reduced the number of equivalents of the Z/C/P to 6.0 from 12.0.

## 2.4 Conclusions

The first challenge of this work was to find a successful method to cleave the FAMEs isolated from canola oil. After numerous unsuccessful attempts to cleave the double bonds and isolate simply the aldehydes, it was found that instead it was possible to couple the ozonolysis with a dibromoolefination reaction and isolate the corresponding DBOs directly. This method was explored with a variety of internal alkenes, including all three of the unsaturated FAMEs that comprise canola oil. The method proved to be straightforward to carry out and provided one of few examples of coupling an ozonolysis reaction with a carbon-carbon bond forming reaction. The application of this method to the synthesis of alkyne building blocks from canola oil FAMEs will be explored in chapter 3.

## 2.5 Experimental

**General Information.** Unless otherwise stated, all glassware was oven-dried. Transfer of solvents and reaction mixtures was done using oven-dried syringes and cannulae. All starting materials were purchased from Sigma-Aldrich and used without further purification. Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra

($^1$H NMR) were recorded at 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Standard notation was used to describe the multiplicity of signals observed in $^1$H NMR spectra: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), etc. Carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded at 125 MHz and are reported (ppm) relative to the centre line of the triplet from chloroform-d (77.26 ppm). Ozonolysis was performed using a Welsbach T-816 Ozone Generator set with a shell pressure of 8.0 psi and a voltage of 90.

**Representative procedure.** In a flame-dried round bottom flask under a positive pressure of argon, Zn powder (1.18 g, 18.0 mmol), $CBr_4$ (5.97, 18.0 mmol), and $PPh_3$ (4.72, 18.0 mmol) (Z/C/P) were suspended in $CH_2Cl_2$ (40 mL). This mixture was allowed to stir for 24 hours at room temperature. To an oven-dried 100 mL three-neck round bottom flask was added methyl oleate (0.89 g, 3.0 mmol), $CH_2Cl_2$ (20 mL), and *N*-methylmorpholine *N*-oxide (NMO) (0.35 g, 3.0 mmol). This solution was cooled to -78 °C and a stream of $O_2/O_3$ was bubbled through the solution at a rate of 2.0 L/min through a glass pipette for 15 minutes. The solution was then sparged with $O_2$ for 30 minutes. This mixture was then put under a positive pressure of argon and transferred to the Z/C/P mixture via cannula. The ozonolysis flask was rinsed with $CH_2Cl_2$ (3 x 5 mL) and this was added to the reaction mixture. The reaction was stirred until completion, determined by TLC and $^1$H NMR spectroscopy. The solvent was partially removed *in vacuo* and the residue was filtered through a plug of silica gel using 5% EtOAc in hexane as eluent. The filtrate was concentrated on the *in vacuo*.

All other alkenes were treated with the same procedure, replacing methyl oleate with the appropriate alkene.

**1,1-dibromo-2-phenylethene:**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.49 (s, 1H), 7.39-7.34 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 136.9, 135.6, 128.6, 128.4, 89.6; IR ($CDCl_3$, cast) 3054, 3024, 1595, 1439, 1444, 920, 863, 778, 745, 692 $cm^{-1}$; HRMS (EI, $M^{\bullet+}$) for $C_8H_6{}^{79}Br^{81}Br$ calcd 261.8816, found: m/z 261.8814.

These data matched those previously reported for 1,1-dibromo-2-phenylethene.[36]

**1,1,8,8-tetrabromooctadiene, Table 2-2, Entry 1:**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.38 (t, $J$ = 7.5 Hz, 2H), 2.15-2.10 (m, 4H), 1.49-1.43 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 136.5, 87.4, 31.0, 25.4; IR ($CDCl_3$, cast) 2933, 2860, 1786, 1716, 1458, 1438, 839, 789, 722, 713 $cm^{-1}$; HRMS (EI, $M^{\bullet+}$) for $C_8H_{10}{}^{79}Br_2{}^{81}Br_2$ calcd 425.7475, found: m/z 425.7467.

These data matched those previously reported for 1,1,8,8-tetrabromooctadiene.[37]

**1,1,8,8-tetrabromo-4-methyloctadiene, Table 2-2, Entry 2:**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.41-6.35 (m, 2H), 2.18-2.07 (m, 3H), 2.04-1.96 (m, 1H), 1.68-1.59 (m, 1H), 1.51-1.42 (m, 1H), 1.34-1.25 (m, 1H), 0.94 (d, $J$ = 10 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.1, 89.5, 88.9 39.8, 34.2, 31.9, 30.6, 19.3; IR ($CDCl_3$, cast) 3020, 2958, 2925, 2872, 2854, 1784, 1620, 1456, 780 $cm^{-1}$; HRMS (EI, [$M^{\bullet+}$-3H]) for $C_9H_9{}^{79}Br_2{}^{81}Br_2$ calcd 436.7397, found: m/z 436.7410.

**1,1-dibromohexene, Table 2-2, Entry 3:**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.36 (t, *J* = 7.5 Hz, 1H), 2.09 (app q, *J* = 7.5 Hz, 2H), 1.43-1.32 (m, 4H), 0.92-0.89 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.9, 88.4, 32.7, 29.9, 22.1, 13.8; IR ($CDCl_3$, cast) 2957, 2927, 2872, 2857, 1811, 1783, 1465, 806, 768 cm$^{-1}$; HRMS (EI, $M^{\bullet+}$) for $C_6H_{10}{}^{79}Br^{81}Br$ calcd 241.9129, found: m/z 241.9129.

These data matched those previously reported for 1,1-dibromohexene.[38]

**1,3-di-(*gem*-dibromoethenyl)cyclopentane, Table 2-2, Entry 4:**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, *J* = 9 Hz, 2H), 2.82-2.76 (m, 2H), 2.18 (app dt, *J* = 6, 12 Hz, 1H), 1.98-1.94 (m, 2H), 1.50-1.42 (m, 2H), 1.14 (app dt, *J* = 10.5, 12.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) 142.4, 88.3, 43.5, 37.9, 30.7; IR ($CHCl_3$, cast) 2955, 2867, 1617, 1447, 1259, 835, 792, 669 cm$^{-1}$; HRMS (EI, $M^{\bullet+}$) for $C_9H_{10}{}^{79}Br_2{}^{81}Br_2$ calcd 437.7475, found: m/z 437.7472.

**1,4-di-(*gem*-dibromoethenyl)benzene, 2.17:**

0.075 g; 6%; cream coloured solid; $^{1}$H NMR (500 MHz, $CD_2Cl_2$) δ 7.57 (s, 4H), 7.49 (s, 2H); $^{13}$C NMR (125 MHz, $CD_2Cl_2$) δ 136.8, 135.8, 128.8, 90.5; IR ($CHCl_3$, cast) 3023, 1931, 1675, 1594, 1504, 1404, 884, 835, 739 cm$^{-1}$; HRMS (EI, $M^{\bullet+}$) for $C_{10}H_6{}^{79}Br_2{}^{81}Br_2$ calcd 445.7162, found: m/z 455.7164; mp (°C): 81-85 (note: sample degraded soon after melting.)

These data matched those previously reported for 1,4-di-(*gem*-dibromoethenyl)benzene.[39]

**1,1-dibromodecene, 2.18b:**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.38 (t, *J* = 7.5 Hz, 1H), 2.08 (app q, *J* = 7.5 Hz, 2H), 1.44-1.39 (m, 2H), 1.32-1.27 (m, 10H), 0.90-0.87 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.9, 88.4, 33.0, 31.8, 29.3, 29.2, 29.0, 27.8, 22.6, 14.1; IR ($CDCl_3$, cast) 2955, 2926, 2855, 1790, 1465, 803, 782 cm$^{-1}$; HRMS (EI, $M^{\bullet+}$) for $C_{10}H_{18}{}^{79}Br_2$ calcd 295.9775, found: m/z 295.9779.

These data matched those previously reported for 1,1-dibromodecene.[40]

**Methyl 1,1-dibromodecenoate, 2.18a:**

$^{1}$H NMR (500 MHz, $CDCl_3$) δ 6.37 (t, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.08 (app q, *J* = 7.0 Hz, 2H), 1.65-1.59 (m, 2H), 1.44-1.38 (m, 2H), 1.32-1.31 (app s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.2, 138.8, 88.5, 51.4, 34.0, 32.9, 29.0, 28.9, 28.8, 27.7, 24.9; IR ($CDCl_3$, cast) 2930, 2857, 1789, 1739, 1436, 1247, 1198, 1172 cm$^{-1}$; HRMS (EI, $[M\text{-}H]^{\bullet+}$) for $C_{11}H_{17}{}^{79}Br^{81}BrO_2$ calcd 340.9575, found: m/z 340.9564.

These data matched those previously reported for methyl 1,1-dibromodecenoate.[41]

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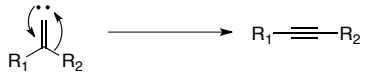
# Chapter 3

## Synthesis of Terminal Alkynes from Fatty Acid Methyl Esters

*"As knowledge increases, wonder deepens."*
*-Charles Morgan*

## 3.1 Introduction

As outlined in Chapter 1, terminal alkynes make up a valuable class of functional groups. Because of their utility in making functional materials they became the ideal target for demonstrating the potential of using a renewable source of carbon. Despite their efficacy as building blocks, there are few methods available for synthesising terminal alkynes. The most dominant procedures involve homologation of an aldehyde via reaction of a phophorus ylide or phosphonate-stabilised carbanion. These reactions produce an alkylidenecarbene, **3.1**, that in turn undergoes a 1,2 rearrangement to produce the alkyne (Scheme 3.1).[1,2] This rearrangement is commonly referred to as the Fritsch-Buttenberg-Weichell (FBW) rearrangement and was first observed in the late 19$^{th}$ century in the synthesis of tolans from diarylcholorethene derivatives.[3,4,5] More than a century later, this rearrangement has become a valuable synthetic tool in the synthesis of acetylene materials.[6,7,8] The migrating group ($R_2$ in Scheme 3.1) can be a hydrogen atom, aryl, heteroaryl, alkyl, alkenyl, or an alkynyl moiety. The migrating of ability of the alkynyl moiety has been studied extensively by Tykwinski *et al.* as part of their pursuit of polyynes.[9,10,11] There are two general approaches used to synthesise terminal alkynes: the Seyforth-Gilbert homologation and the Corey-Fuchs reaction. Both reactions employ a rearrangement of an alkylidenecarbene to produce the terminal alkyne, but differ in their synthesis of the alkylidenecarbene.




**Scheme 3.1: General rearrangement of alkylidenecarbene.**

### 3.1.1 Seyferth-Gilbert Homologation

In the Seyferth-Gilbert homologation, the alkylidenecarbene is formed via break-down of an oxaphosphetane-type intermediate, **3.5**, which is produced when an aldehyde (or ketone) reacts with a phosphonate carbanion (**3.4**) (Scheme 3.2).[12,13,14] One drawback of the Seyferth-Gilbert homologation is that the necessary α-diazophosphonate, **3.2**, is not commercially available; however, it can be readily prepared.[15] Moreover, the reaction conditions require low temperatures, inert atmosphere, and strong bases in order to produce the required phosphonate carbanion, **3.4**. These harsh conditions mean that only the most robust starting materials can be used in the Seyferth reaction, severely limiting its utility. A variation of this homologation, the Ohira-Bestmann modification, uses dimethyl-1-diazo-2-oxopropylphosphonate, **3.3**, which can generate **3.4** *in situ*.[16,17] Though still not commercially available, **3.2** is produced in a single step.[18] The reaction conditions are also mild, avoiding the use of strong bases, low temperature, and inert atmosphere, making it tolerant of most functional groups.[19,20] These milder conditions, however, limit the Ohira-Bestmann modification to the synthesis of terminal alkynes only, while the Seyferth-Gilbert homologation can be used to synthesise internal and terminal alkynes. Since its inception, the Ohira-Bestmann modification has been expanded to one-pot

procedures involving the simultaneous oxidation of alcohols to aldehydes followed by the conversion to alkynes (Scheme 3.3).[21,22]

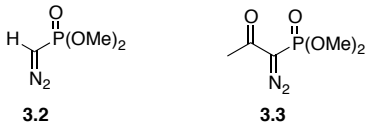
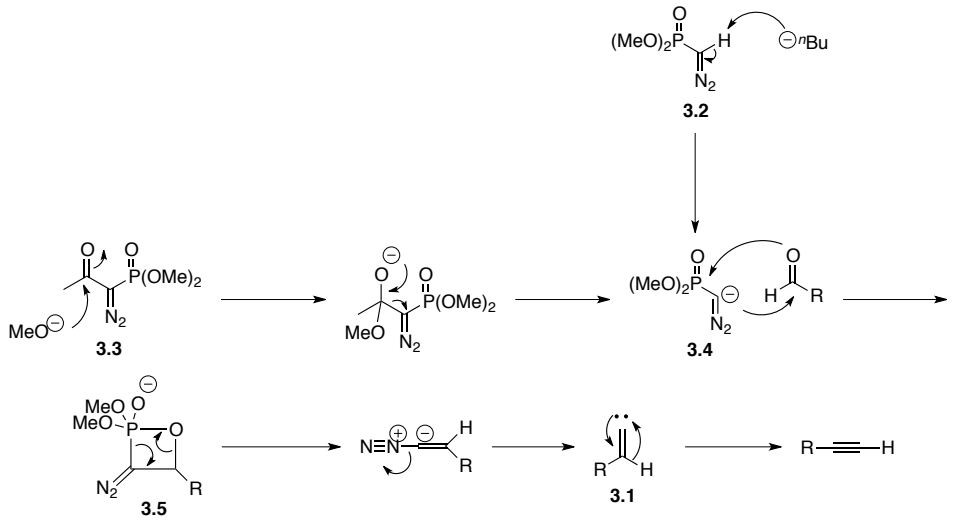
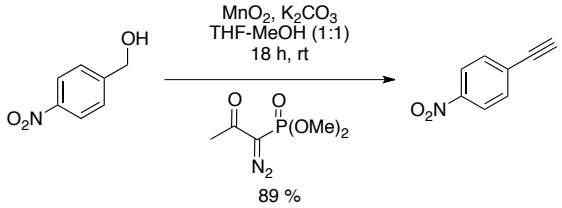



**Figure 3.1: α-Diazophosphonates used in the Seyferth-Gilbert and Ohira-Bestmann reactions, respectively.**




**Scheme 3.2: Mechanism for the Seyferth-Gilbert and Ohira-Bestmann reaction.**

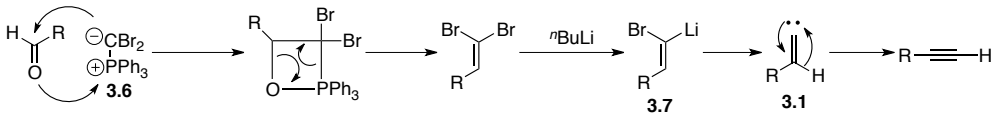



**Scheme 3.3: One-pot Ohira-Bestmann Homologation of Alcohol to Terminal Alkyne.**

### 3.1.2 Corey-Fuchs Reaction

The other commonly employed method for the generation of the alkynes is the Corey-Fuchs reaction (Scheme 3.4). In this reaction, an aldehyde is reacted with a

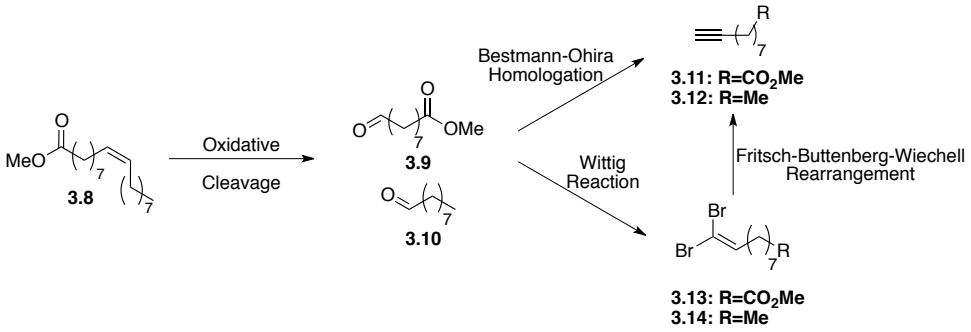
phophorus ylide to form a dibromoolefin (DBO) through a Wittig-type reaction.[23] The DBO is further reacted with an organolithium compound to form an alkylidene carbenoid **3.7** that can α-eliminate to an alkylidenecarbene followed by migration of a pendent group to form a terminal alkyne.[24,25] The alkyne could also be formed by β-elimination on **3.7**.




**Scheme 3.4: Mechanism for the Corey-Fuchs alkyne synthesis.**

## 3.2 Proposed Synthetic Pathway

To begin exploring the synthesis of terminal alkynes using FAMEs isolated from canola oil, it was first decided that the chemistry should be developed and optimised with commercially available methyl oleate, **3.8**, the simplest and most abundant of the FAMEs that comprise canola oil. The first step in the proposed synthetic pathway (Scheme 3.5) involved first oxidatively cleaving the double bond to generate aldehydes **3.9** and **3.10**. These aldehydes can then be reacted with phosphorus anions or ylides to either produce alkynes **3.11** and **3.12** (the Bestmann-Ohira reaction) or to produce the dibromoolefins (DBOs) **3.13** and **3.14**, which can then undergo an FBW rearrangement (*vide supra*) to the alkynes **3.11** and **3.12**.

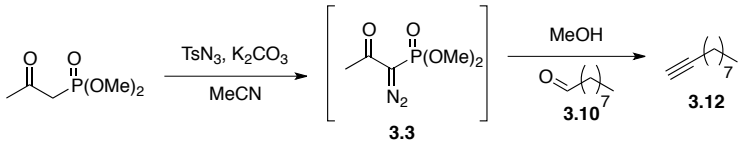



**Scheme 3.5: Proposed synthetic pathway.**

## 3.3 Synthesising Alkynes from Pure FAMEs

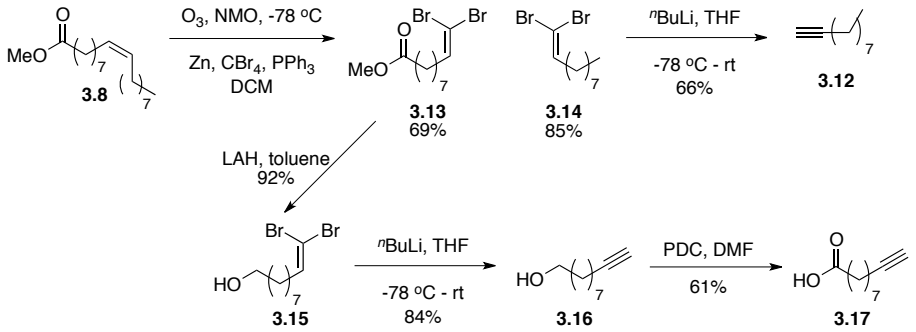
### 3.3.1 Methyl Oleate

Initial attempts to synthesise alkynes from methyl oleate were accomplished using the Bestmann-Ohira homologation (Scheme 3.6). The aldehydes were produced from one of the oxidative cleavage methods discussed in Chapter 2, Section 2.2. Dimethyl-2-oxopropylphosphonate was reacted with tosyl azide ($TsN_3$) under basic conditions in acetonitrile to produce the Bestmann reagent (**3.3**), which was then reacted *in situ* with nonanal, **3.10**. This produced 1-decyne, **3.12**. Though this reaction was successful in producing the target alkyne, 1-decyne, the yields were poor (less than 10%) and the product was not pure.




**Scheme 3.6: Bestmann-Ohira synthesis of 1-decyne.**

The poor yields of the Bestmann-Ohira reaction, combined with the challenges associated with isolating pure nonanal (discussed in Chapter 2) led to the application of the tandem ozonolysis-dibromoolefination reaction in the synthesis of alkynes from FAMEs.



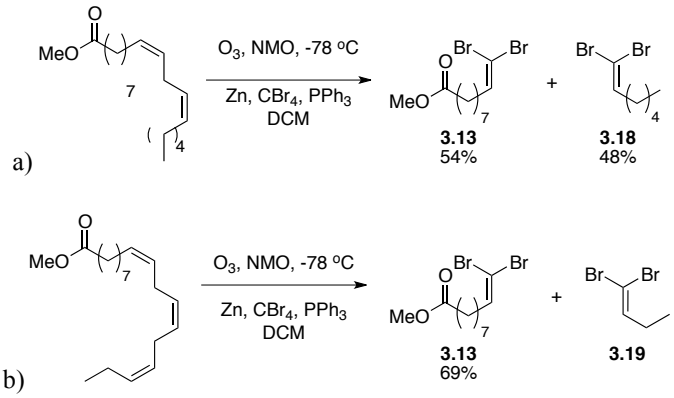

**Scheme 3.7: Synthesis of 1-decyne and decynoic acid from methyl oleate.**

The tandem ozonolysis-dibromoolefination was applied to methyl oleate in the manner described in Chapter 2. Following the isolation of **3.14**, it was converted to the corresponding terminal alkyne by inducing a Fritsch-Buttenberg-Wiechell (FBW) rearrangement using $^{n}$BuLi in THF (Scheme 3.7). Because of the reactivity of carbonyl compounds with organolithium reagents, **3.13** could not be converted to the terminal alkyne **3.11** by reaction with $^{n}$BuLi directly. Instead, it was reduced to alcohol **3.15** using lithium aluminium hydride (LAH) in 92% yield (Scheme 3.7). The FBW rearrangement was performed to give yne-ol **3.16** in an 84% yield. The yne-ol **3.17** could be a useful terminal alkyne in its own right, because the alcohol functionality offers numerous avenues for creating a variety of other terminal alkynes. Here we demonstrate one example of the possible transformations of**3.18**, the conversion of the oxygen-bearing carbon to its

original oxidation state by reacting it with pyridinium dichromate (PDC) in dimethyl formamide (DMF). This resulted in the generation of alkyne **3.17** in a 61% yield.

### 3.3.2 Methyl Linoleate and Methyl Linolenate

Methyl linoleate and methyl linolenate were subjected to the same tandem ozonolysis-dibromoolefination reaction (Scheme 3.8). The results are discussed in Chapter 2. It is important to note that the shorter alkyl dibromoolefins isolated from these starting materials are light sensitive and will readily degrade upon exposure to ambient light, limiting their utility. This also precluded detailed characterisation of these compounds.




**Scheme 3.8: Tandem oznolysis-dibromoolefination reaction of a) methyl linoleate and b) methyl linolenate.**

## 3.4 Synthesis of Terminal Alkynes From Methyl Oleate Obtained From Refined Canola Oil

Having successfully demonstrated our method with the individual FAMEs, we applied it to methyl oleate separated from refined canola oil purchased from a

supermarket. 50 mL of Compliments® brand 100% pure canola oil was dissolved in 100 mL of methanol and 5 mL of concentrated sulphuric acid was added. This mixture was heated to reflux for a period of 24 hours to produce FAMEs and glycerol. The resulting FAMEs were extracted from glycerol using diethyl ether. Methyl oleate was isolated from other FAMEs by low temperature crystallisation in an acetonitrile/dry ice bath with acetone as a solvent.[26] With a melting point of -20 °C, the methyl oleate selectively crystallised from the solution while other FAMEs remained dissolved. 14.5 g of methyl oleate was isolated. The $^{1}$H NMR spectrum of the methyl oleate was consistent with that reported in the literature.[27] The sample was free of glycerol, unreacted triacylglycerols (TAGs), diacylglycerols (DAGs), or monoacylglycerols (MAGs). GC-MS analysis of the methyl oleate sample revealed it to be 78% methyl oleate, with methyl palmate, methyl linolenate, methyl sterate, and methyl eicosenate making up the majority of the remaining 22% of the sample.*

This methyl oleate was subjected to the previously described protocol and DBOs **3.13** and **3.14** were successfully isolated in 75% and 54% yield respectively. These DBOs were converted into the terminal alkynes **3.12**, **3.16**, and **3.17.**

The previous source of methyl oleate was 99% pure methyl oleate obtained from Sigma-Aldrich at a price of $222.50 (CDN) for 25 g.† Comparatively, 50 mL of

* GC-MS data available in Appendix A

† Price from online Sigma-Aldrich catalogue.

Compliments® brand canola oil is approximately $0.29.[‡] Even taking into account the cost of 100 mL of methanol ($3.10) and 5 mL of sulphuric acid ($0.25),[§] the reaction cost of using refined canola oil as the source of methyl oleate is significantly reduced. What's more, is that the methyl oleate does not have to be scrupulously pure to be successful in the conversion to DBOs; however, the reduced purity may account for the lower yields compared to when the 99% pure methyl oleate was used.

### 3.5 Synthesis of Aromatic Rings

To synthesise aromatic rings, 1-decyne was reacted with palladium on graphite. The reaction was monitored by TLC. Preliminary results suggest that the synthesis of **3.20** was successful. The sudden appearance of a UV active spot on the TLC and small peaks in the $^1$H NMR spectrum between δ 7.8-6.6 ppm, which are consistent with aromatic ring protons were observed; however, the large number of aliphatic protons make detection of aromatic protons in NMR difficult. These results suggest that it is possible to synthesise tri-substituted aromatic rings from canola oil.


**3.12** **3.20**

**Scheme 3.9: Cyclotrimerisation of 1-decyne.**

[‡] Price from online Sobey's catalogue.

[§] Prices calculated from online Fisher Scientific catalogue: methanol is $124.21/4 L; sulphuric acid is $126.62/2.5 L.

## 3.6 Conclusions

In this Chapter, canola oil FAMEs were used to give access to a variety of reagents bearing valuable functional groups (e.g., alkyne and alcohol functionalities) in good to moderate yields. Further, it was demonstrated that the source of methyl oleate could be from refined canola oil obtained from a local supermarket. The work described lays the groundwork for future studies aimed at the manipulations of plant-derived oils and their associated FAMEs into a variety of value-added products that exploit the terminal alkynes presented in this chapter.

## 3.7 Experimental

**General Information.** Unless otherwise stated, all glassware was oven-dried. Transfer of solvents and reaction mixtures was done using oven-dried syringes and cannulae. All starting materials were purchased from Sigma-Aldrich and used without further purification. Flash chromatography columns were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra ($^{1}$H NMR) were recorded at 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Standard notation was used to describe the multiplicity of signals observed in $^{1}$H NMR spectra: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), etc. Carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were recorded at 125 MHz and are reported (ppm) relative to the centre line of the triplet from chloroform-d (77.26 ppm). Ozonolysis was performed using a Welsbach T-816 Ozone Generator set with a shell pressure of 8.0 psi and a

voltage of 90.

**General procedure for synthesis of DBOs**

The procedure for the synthesis of DBOs can be found in Chapter 2, along with the characterisation data for 1,1-dibromodecene (**3.14**), Methyl 1,1-dibromodecenoate (**3.13**).

**1,1-Dibromoheptene, 3.18:**

$^1$H NMR (300 MHz, $CDCl_3$) δ 6.39 (t, *J* = 7.2Hz, 1H), 2.09 (app q, *J* = 6.9 Hz, 2H), 1.46-1.40 (m, 2H), 1.34-1.29 (m, 4H), 0.93-0.88 (m, 3H).

**1,1-Dibromo-10-decanol, 3.15:**

To a flame dried round bottom flask under a positive pressure of argon was added lithium aluminum hydride (LAH) (0.12 g, 3.1 mmol) and freshly distilled toluene (5 mL) to create a slurry. The slurry was cooled in an ice-water bath. Compound **3.13** (0.77 g, 2.25 mmol) was added to a separate flamed-dried round bottom flask under a positive pressure of argon and dissolved in freshly distilled toluene (6 mL). The solution was transferred to the LAH slurry via cannula. After transfer of starting material was complete, the ice-water bath was removed and the reaction was stirred at room temperature until complete, as determined by TLC. After reaction was complete, it was cooled once more and dilute HCl (less than 2 M) was added until all of the LAH was consumed. The resulting solution was extracted with $Et_2O$ (3 x 10 mL). The combined organic phases were washed with

water (1 x 10 mL) and brine (1 x 10 mL). The organic phase was isolated and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

$^1$H NMR (500 MHz, $CDCl_3$) δ 6.38 (t, *J* = 7 Hz, 1H), 3.64 (t, *J* = 7 Hz, 2H), 2.08 (q, *J* = 7 Hz, 2H), 1.60-1.54 (m, 2H), 1.45-1.40 (m, 2H), 1.39-1.30 (m, 8H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 138.8, 88.5, 63.0, 32.9, 32.7, 29.3, 28.9, 27.7, 25.7; IR (cast, $CDCl_3$) 3338, 2928, 2855, 1710, 1623, 1463, 1372, 1056, 801, 783, 723 $cm^{-1}$

**General procedure for the synthesis of alkynes:**

In a flame dried round bottom flask under a positive pressure of argon the starting DBO (1.9 mmol) was dissolved in freshly distilled THF (10 mL). This was cooled to −78 °C and $^n$BuLi (4.8 mL, 1.6 M in hexanes) was added dropwise to the solution. The reaction was stirred at −78 °C for 1 hour and then stirred at room temperature until complete, as determined by TLC. Reaction was diluted with water and extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL) and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated *in vacuo*.

**9-Decyn-ol 3.16**:

The product was purified by FCC (3:1 hexanes:EtOAc eluent). $^1$H NMR (500 MHz, $CDCl_3$) δ 3.64-3.62 (m, 2H), 2.18 (dt, *J* = 2.5, 7 Hz), 1.93 (t, *J* = 2.5 Hz, 1H), 1.60-1.51 (m, 4H), 1.44-1.30 (m, 8H), 1.20 (br s, 1H); $^{13}$C NMR (125 MHz,

$CDCl_3$) δ 84.7, 68.1, 63.0, 32.8, 29.2, 29.0, 28.6, 28.4, 25.7, 18.4; IR (cast, $CDCl_3$) 3310, 2931, 2857, 2117, 1465, 1432, 1055 $cm^{-1}$

These data matched those previously reported for 9-decynol.[28]

**1-Decyne, 3.12:**

$^1H$ NMR (500 MHz, $CDCl_3$) δ 2.18 (dt, *J* = 2.5, 7 Hz, 2H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.55-1.49 (m, 2H), 1.42-1.35 (m, 2H), 1.31-1.23 (m, 8H), 0.90-0.86 (m, 3H); IR (cast, $CDCl_3$) 3313, 2956, 2926, 2214, 1465, 1378 $cm^{-1}$

These data matched those previously reported for 1-decyne.[29]

**9-Decynoic Acid, 3.17:**

In a flame-dried round bottom flask under a positive pressure of argon compound **3.15** (0.20 g, 1.3 mmol) was dissolved in of dimethyl formamide (3 mL). Pyridinium dichromate (0.65 g, 1.74 mmol) was added and the reaction was stirred at room temperature until completion, as determined by TLC. The reaction was diluted with water and then extracted with $Et_2O$ (3 x 5 mL). The combined organic layers were washed with water (1 x 5 mL), washed with brine (1 x 5 mL), dried over anhydrous $MgSO_4$, and filtered and concentrated *in vacuo*.

$^1H$ NMR (500 MHz, $CDCl_3$) 2.36-2.33 (m, 2H), 2.19-2.16 (m, 2H), 1.41-1.93 (m, 1H), 1.68-1.61 (m, 2H), 1.55-1.49 (m, 2H), 1.42-1.30 (m, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 84.6, 68.1, 33.8, 29.0, 28.9, 28.7, 28.5, 28.4, 24.6, 18.3; IR (cast, $CDCl_3$) 3303, 3100-2850, 3035, 2935, 2859, 2118, 1710, 1463, 1431, 1413, 1287,

937 $cm^{-1}$; HRMS (ES, $[M-H]^-$) for $C_{10}H_{15}O_2$ calcd 167.1078, found: m/z 167.1076.

These data matched those previously reported for 9-decynoic acid.[30]

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# Chapter 4

## The Synthesis of Benzyne from Alkyl-Substituted Aromatic Rings

*"The pursuit of knowledge makes all manner of hardship worthwhile."*
*-Jacqueline Carey*

## 4.1 Introduction to Fluorenone

Conjugated polymers represent a vast area of research for their interesting optical and semiconducting properties, and those based on phenylene monomers are by far the most widely used.[1,2] Phenylene-based polymers have been studied in polymer light-emitting diodes (PLEDs)[3,4] and organic lasers.[5] What makes organic semiconducting materials so interesting is that they are lightweight, flexible, and inexpensive to produce. They exhibit high photoluminescent quantum efficiencies, excellent solubility, and readily form films. A brief overview of polyfluorene-based materials will be discussed herein; however, the interested reader is directed to any number of extensive reviews on this subject for more detail.[1,3,6,7,8]

### 4.1.1 Fluorene-based Materials

Though a variety of light-emitting polymers based on phenylenes have been produced, the most popular are based on the bridged phenylene fluorene (Figure 4.1).[2] Substitution on the methylene group, the 9-position, increases the solubility, and therefore the processibility, of the polymer, without interrupting the conjugation. This results in an intense blue-emitting polymer without a deleterious hypsochromic shift. Examples of polymers based on substituted fluorenes are shown in Figure 4.2, the most popular polymer being poly-9,9'-dioctylfluorene (PFO), where the R groups in **4.1** are octyl chains. Alkyl substituted fluorenes are most known for their intense blue emission, but they can also be copolymerised

with other monomers, resulting in emissive polymers across the whole visible spectrum.

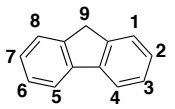



**Figure 4.1: Fluorene, shown with the accepted numbering system.**

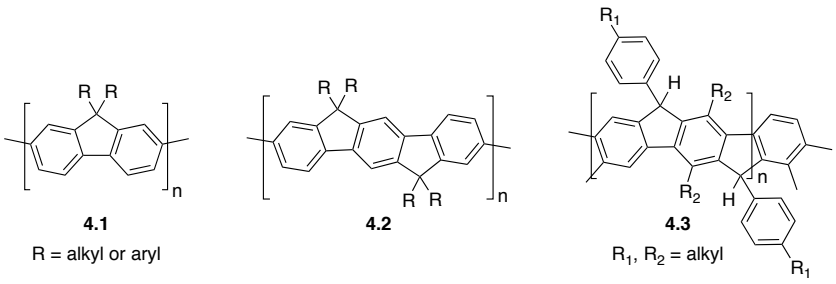
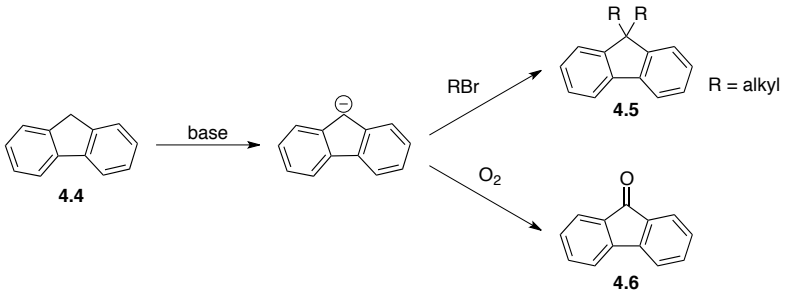
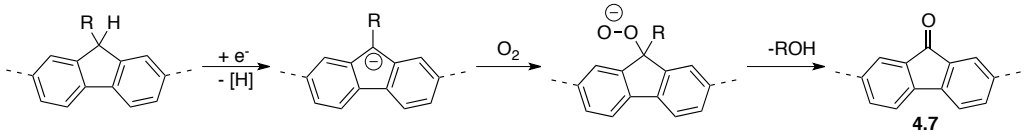



**Figure 4.2: Examples of bridged polyphenylene polymers based on fluorene.**

9,9'-Dialkylfluorenes are synthesised by reacting fluorene (**4.4**) with a base (Scheme 4.1). The resulting ion can be reacted with alkyl bromides to produce **4.5**, which can then be polymerised. However, if oxygen is present, fluorenone (**4.6**) will be produced as a by-product. When polymerised, the poly(dialkylfluorenes) are thermo-oxidatively unstable. Over time, ketone defects within the material are produced by oxidation of the 9 position. Scheme 4.2 shows the proposed mechanism for the oxidation.[2] These keto-defects are associated with a bathochromic shift from the characteristic blue emission to a green emission.

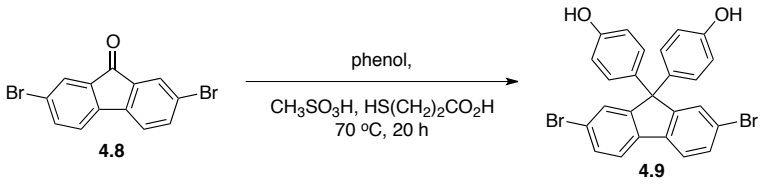



**Scheme 4.1: Alkyl substitution of fluorene.**

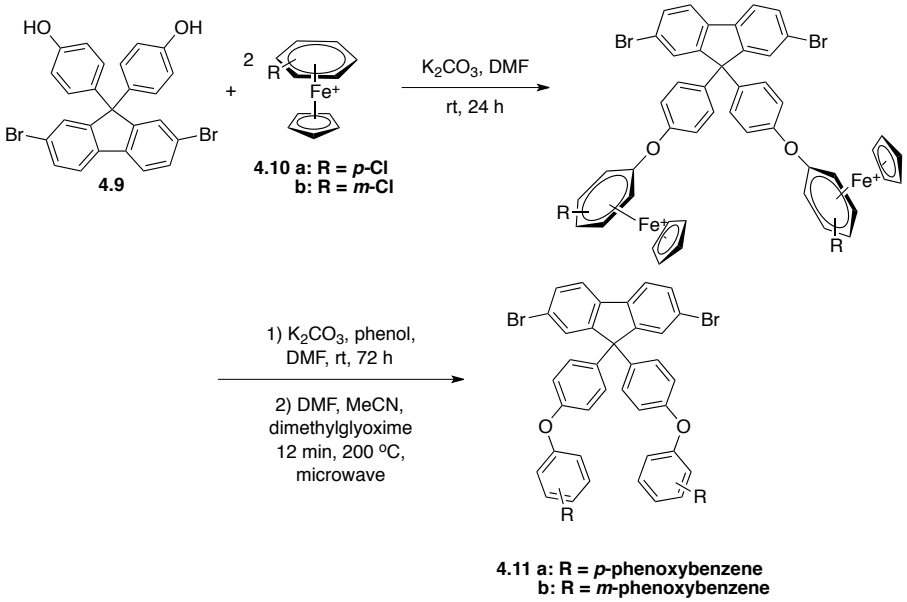



**Scheme 4.2: Proposed oxidation mechanism.**

In place of alkyl groups, aryl groups can be substituted on the 9 position of fluorene. The result is more oxidatively stable materials; however, the synthetic process must be altered because the aryl groups cannot generally be added directly to fluorene. Instead, the starting monomer can be fluorenone (Scheme 4.3). Previous work in the Veinot group has demonstrated that 2,7-dibromofluorenone, **4.8**, can be reacted successfully with phenol to produce 2,7-dibromo-9,9′-di(4-hydroxyphenyl)-9H-fluorene, **4.9**.[9] Compound **4.9** was reacted with $\eta^6$-1,4-dichlorobenzene-$\eta^5$-cyclopentadienyliron hexafluorophosphate to extend the phenol substitution into aromatic ethers of three benzene units in length, **4.11** (Scheme 4.4). The result, when polymerised, was a more thermo-oxidatively stable blue-emitting material.




**Scheme 4.3: Aryl substitution on the 9-position of fluorenone.**




**Scheme 4.4: Aromatic ether monomer synthesis.**

### 4.1.2 The Green Emission Debate

As already mentioned, the thermo-oxidative instability of fluorene-based materials remains a significant drawback to their use. The source of the green emission remains under debate and there are two schools of thought as to the source: 1) keto-defects present within the polyfluorene chain (Figure 4.3a). These are thought to lead to an intramolecular $\pi$–$\pi^*$ charge transfer state between C=O

functionalities in the polymer;[10] or 2) aggregation of the fluorenone moieties within the polymer chain produce an excimer (Figure 4.3b).[11,*]

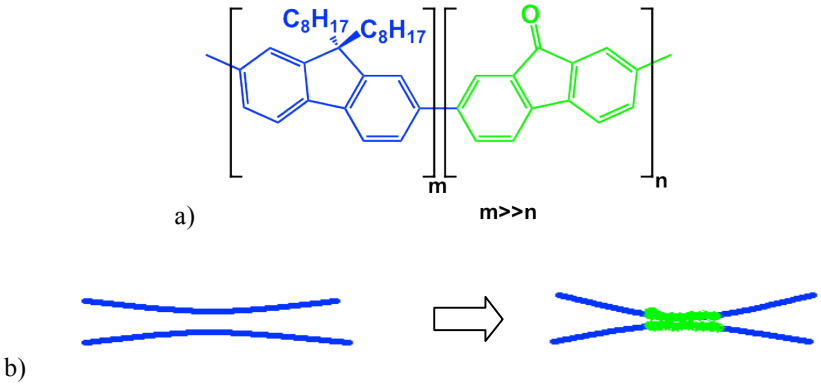



**Figure 4.3: a) Green emission from keto-defects, b) green emission from aggregation.**

The evidence is clear that a ketone moiety must be present to result in green emission; however, the most compelling evidence suggests that these ketone groups must aggregate to result in green emission (Figure 4.4).[10] Chan *et al.* studied the crystal packing structure of polyfluorene oligomers with ketone defects by X-ray diffraction (XRD) and found there was face-to-face overlap of the fluorenone carbonyl groups with an inter-planar difference of 3.50 Å, which is typical for π-stacked materials that form excimers.[11] These results are further augmented by studies that show no green emission when polyfluorenes are intercalated into clays, despite the harsh oxidative conditions,[12] or when poly(9.9'-dihexylfluorene) chains are isolated in a polystyrene matrix.[13] Previous studies done in the Veinot group have shown that blending polyfluorene with polyphenylether (PPE) precludes green emission. However, even more interesting

* An excimer is a short-lived bound excited state between two molecules at a distance of 3–5 Å. In polymer chemistry, this may also be referred to as an exiplex, where the bound state is between two polymers.

is that blue emission can be restored by blending oxidised, green emitting polyfluorene with PPE.[14] This observation of a return to blue emission following blending with PPE greatly underscores the likelihood of excimer formation, as PPE reduces fluorenone–fluorenone interaction, but does not reduce the presence of the fluorenone moiety. All of this evidence together suggests that anything that reduces fluorenone–fluorenone interaction should increase material stability, and thereby reduce green emission.

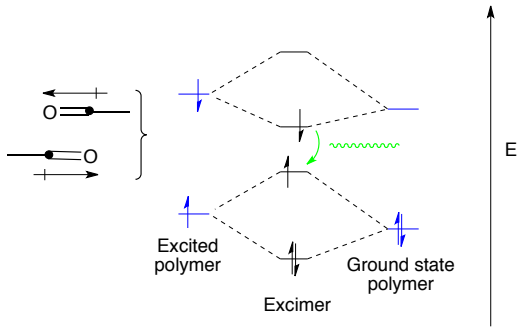
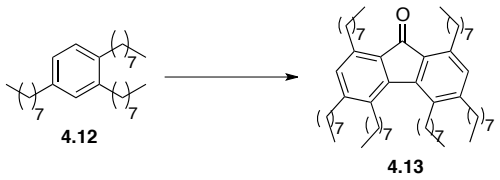



**Figure 4.4: Dipole-mediated stacking of ketone moieties resulting in excimer formation and green emission.**

### 4.1.3 From Canola Oil to Fluorenone

As discussed in Chapter 3, FAMEs isolated from canola oil can be converted into trisubstituted aromatic rings (**4.12**). If these aromatic rings were converted into fluorenone (Scheme 4.5), the result would be **4.13** where long alkyl chains are substituted on the fluorenone backbone. The long alkyl chains should create enough steric repulsion between polymer chains made of **4.13** to preclude aggregation and thus prevent excimer formation, resulting in a more stable light-emitting material (Figure 4.5).




**Scheme 4.5: Fluorenone from canola oil-based trisubstituted aromatic rings.**

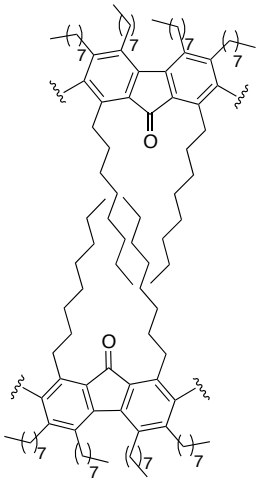


**Figure 4.5: Steric repulsion between alkyl substituted fluorenone moities.**

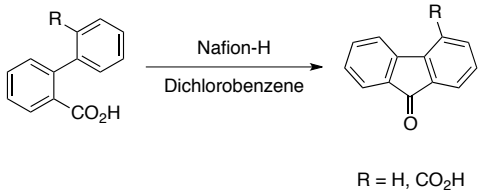
### 4.1.4 Synthesising Fluorenone

Beyond lending itself as a starting material for the synthesis of monomers for polymer electronics, fluorenone, and its derivatives, are found in natural products,[15] marine sediments,[16] weathered, surface-retorted shale oil,[17] and kerogen pyrolyzates.[†18] Fluorenones are also used in pharmaceuticals,[19,20] and in biomedical applications.[21] For example, fluorenone is found in potent anti-methicillin-resistant staphylococci (MRS) agents, which show improved pharmocokinetics compared to vancomycin, the most common antibiotic for

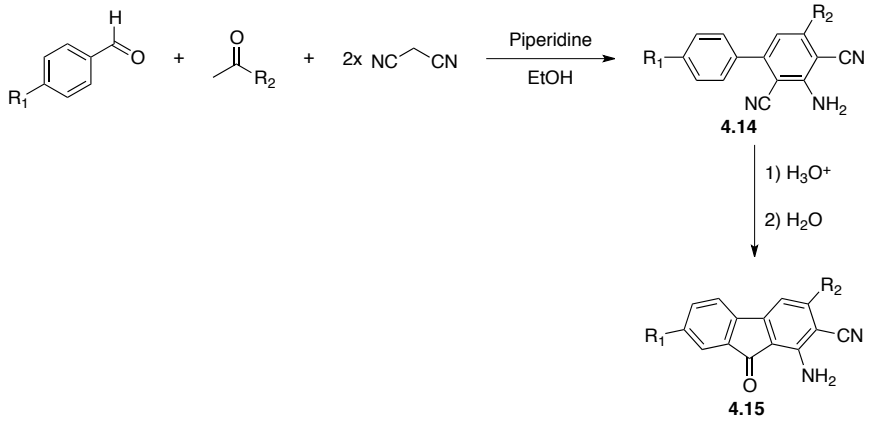
[†] Surface-retorted shale oil and kerogen pyrolyzates are crude oil-like products isolated from the processing of oil shales.

treating MRS infections.[22] This means that methods of synthesising fluorenone and its derivatives have been well explored. There are generally two approaches used for fluorenone synthesis: 1) intramolecular ring closure of biaryl compounds; 2) cycloaddition reactions involving arynes.

Intramolecular Friedel–Crafts acylations represent an obvious method to ring closure on biaryls.[23] Olah *et al.* demonstrated that Nafion-H could be used to catalyse intramolecular acylations, resulting in a variety of cyclic ketones and heterocycles, including fluorenones (Scheme 4.6).[24] The compounds were produced in excellent yield (greater than 80% for fluorenones) with no other by-products in a short reaction time (1–3 hours). Yu and Velasco synthesised multiply substituted fluorenones, and, more specifically, asymmetrically substituted fluorenones, with the intention of generating the high dipole moment required for liquid crystalline order (Scheme 4.7).[25] In this synthesis, the authors use aromatic aldehydes, alkylketones, and two equivalents of malononitrile in the presence of piperidine to produce 2-aminobenzene-1,3-dicarbonitriles (**4.14**). This species undergoes an intramolecular Friedel–Crafts acylation, where the nitrile group acts as the acylating agent, to produce fluorenone (**4.15**).

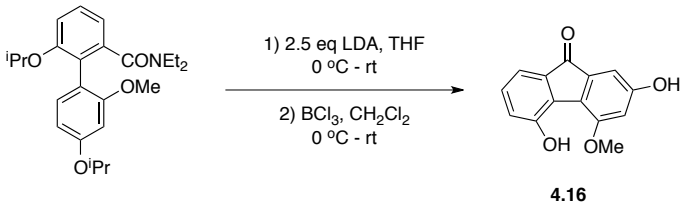



**Scheme 4.6: Friedel–Crafts acylation using Nafion-H as catalyst.**



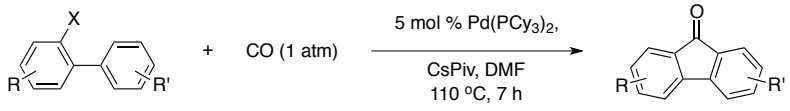

**Scheme 4.7: Synthesis of multiply substituted fluorenones featuring Friedel–Crafts acylation.**

From the group of Victor Snieckus, the fluorenone dengibsin (**4.16**) was synthesised using a remote direct metalation of biarylcarbamoates (Scheme 4.8).[26] This method circumvented the need for a classical Friedel–Crafts acylation, which had previously failed in the synthesis of dengibsin.[27]



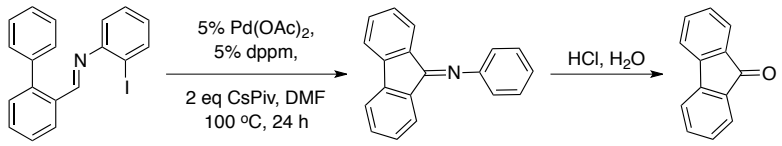

**Scheme 4.8: Synthesis of dengibsin featuring a remote directed metalation.**

Campo and Larock induced a palladium-catalysed cyclocarbonylation of *ortho*-halobiaryls to produce a series of fluorenones through a relatively short, straightforward synthesis (Scheme 4.9).[28]




**Scheme 4.9: Pd-catalysed cyclocarbonylation of *ortho*-halobiaryls.**

Intramolecular C–H activation is another way to accomplish intramolecular cyclisation of biaryl compounds. Zhao *et al.* synthesised a variety of fluorenones using an aryl to imidoyl palladium migration followed by an intramolecular arylation. This approach features a novel activation of imidoyl C–H bonds by catalytic palladium (Scheme 4.10), which appears to proceed through a previously unprecedented organopalladium(IV) hydride intermediate (Figure 4.6).[29]




**Scheme 4.10: Fluorenone synthesis via aryl to imidoyl palladium migration.**

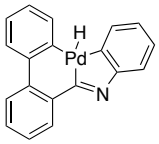
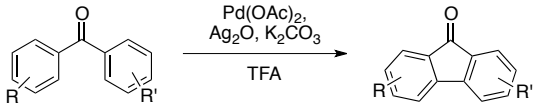


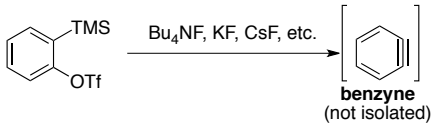

**Figure 4.6: Organopalladium(IV) hydride intermediate.**

Most intramolecular ring closure reactions to form fluorenones involve acylation of biaryls. Li *et al.* used a different approach and instead used a palladium-catalysed dehydrogenation of benzophenones (Scheme 4.11).[30] This was accomplished by a unique example of dual palladium-catalysed C–H activation. The result was a series of substituted fluorenones produced in good to excellent yields. This method also exhibited good functional group compatibility.

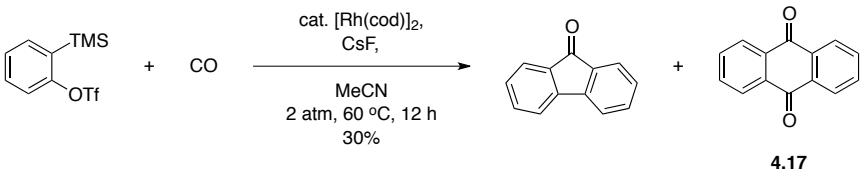



**Scheme 4.11: Pd-catalysed dehydrogenative cyclisation on benzophenones.**

The above examples all demonstrate intramolecular ring closing reactions on cyclic molecules to synthesise fluorenones. As already mentioned, another common strategy in synthesising fluorenones is the use of cycloaddition reactions involving arynes (Scheme 4.12). Arynes, or benzynes, will be discussed in detail later in this Chapter. Chatani *et al.* reported the first example of a transition-metal catalysed carbonylation of benzyne to synthesise fluorenone (Scheme 4.13).[31] The challenge with this method is that the yield was low, 30%, and the corresponding quinone, **4.17**, was isolated as a side product.



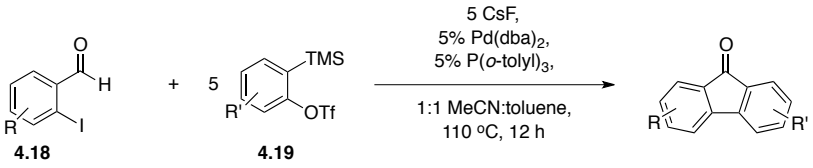

**Scheme 4.12: Benzyne synthesis.**




**Scheme 4.13: Carbonylation of benzyne to synthesise fluorenone.**

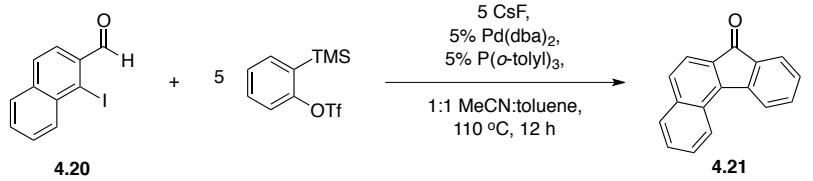
In another example of cycloadditions with arynes, Waldo *et al.* used a palladium-catalysed annulation of arynes with 2-haloarenecarboxaldehydes, **4.18** (Scheme

4.14).[15] In their approach, the authors explored the scope of the reaction, producing a large number of differently substituted fluorenones. They explored the substitution on **4.18**, as well as the substitution on the benzyne precursor, **4.19**. This allowed for the modular synthesis of a large number of fluorenones that could be asymmetrically substituted. The authors used both commercially available and laboratory synthesised *o*-haloarenecarboxaldehydes and found that more electrophilic aldehydes produced better results.




**Scheme 4.14: Pd-catalysed annulation of arynes by 2-haloarenecarboxaldehydes.**

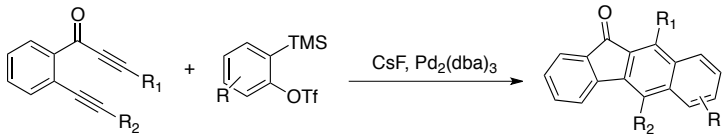
To expand the scope of this method, the authors used 2-iodonaphthalene-1-carboxaldehyde, **4.20**, in place of **4.18** and isolated **4.21** (Scheme 4.15). This allows for the synthesis of more complicated polycyclic aromatic hydrocarbon skeletons. The naphthalene rings can also be substituted, further increasing the utility of this reaction.




**Scheme 4.15: Pd-catalysed annulation of arynes by 2-iodonaphthalene-1-carboxaldehyde.**

This method of fluorenone synthesis allowed for a modular synthetic approach with readily available starting materials. Moreover, it produced no competing quinones and it avoids harsh oxidising agents and strong mineral acids, making it tolerant of a number of functional groups.

An interesting example of cycloaddition chemistry is in the synthesis of benzo[*b*]fluorenones by Peña *et al.* Here, the authors employ what they term a partially intramolecular [2+2+2] cyclotrimerisation reaction with benzyne to form benzo[*b*]fluorenones (**4.23**), which make up the polycyclic skeleton of the anitiumor antibiotics kinamycins (Scheme 4.16).[19] The authors found that the yields were strongly dependent on the substituent groups and electronics of **4.22**; smaller R groups and more electron-deficient alkynes produced better yields.

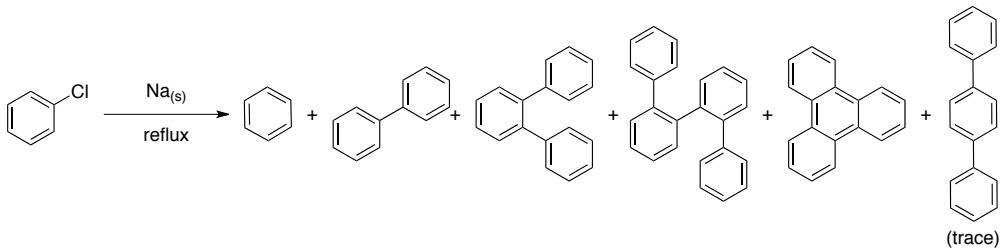



**Scheme 4.16: Pd-catalysed partially intramolecular [2+2+2] cyclotrimerisation reaction.**

The cycloaddition strategies are all dependent on benzyne, **4.24**. Its unique structure and reactivity make a valuable synthetic target. The ability to convert aromatic rings synthesised from methyl oleate into benzyne would allow for the synthesis of a large variety of complex carbon materials from a renewable carbon source. The remainder of this chapter is devoted to the molecule benzyne, and its synthesis.

## 4.2 Introduction to Benzyne

The history of benzyne (**4.24**), also referred to as dehydrobenzene, begins with its existence being proposed as a reactive intermediate in a Wurtz–Fittig reaction of boiling chlorobenzene and sodium metal (Scheme 4.17).[32,33]




**Scheme 4.17: Wurtz-Fittig coupling of chlorobenzene.**

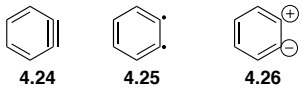
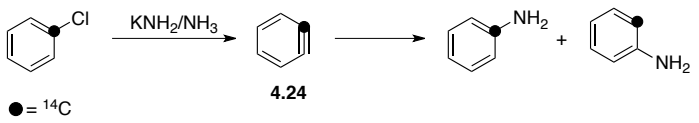



**Figure 4.7: Proposed structures of benzyne.**

### 4.2.1 Structure and Electronics of Benzyne

Three possible structures of benzyne have been postulated (Figure 4.7). The structure first proposed by Bachmann and Clarke in 1927 was biradical **4.25**. In 1942, the zwitterion **4.26** was proposed as the structure to explain observations by Wittig.[33] However, it was experiments by John D. Roberts in 1953 that supported **4.24** as the structure of benzyne.[34,35] Roberts reacted $^{14}$C-labelled chlorobenzene with potassium amide in liquid ammonia (Scheme 4.18). The aniline products were obtained in a 1:1 ratio, which supported the electronically neutral **4.24**

intermediate over the zwitterionic intermediate **4.26**. These results were further augmented by experiments by Huisgen and Rist.[36,37]




**Scheme 4.18: Roberts' 1953 $^{14}$C-labelling experiment.**

Benzyne has since been characterised by infrared spectroscopy,[38] $^{1}$H and $^{13}$C NMR spectroscopy,[39,40,41] and ultraviolet photoelectron spectroscopy.[42] The bond order is somewhere between a triple bond and a double bond. The IR absorption peak for the C≡C bond is reported at 1846 $cm^{-1}$, and the bond length was measured to be 1.25 Å. While this is closer to the typical acetylene bond of 1.20 Å than that of an alkene (1.33 Å), the increased length suggests the bond is slightly weaker than a "true" alkyne triple bond. Current theoretical and experimental evidence suggests that benzyne is a ground-state singlet molecule with a singlet–triplet energy difference of 37.5 kcal/mol. This strong bonding interaction is attributed to the overlap of the two adjacent $sp^2$ orbitals residing in the same plane on the molecule.[42,43] These data suggest that **4.24**, rather than **4.25**, is the best representation of benzyne.

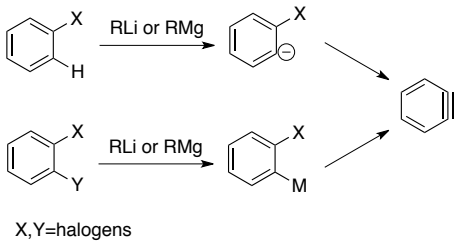
### 4.2.2 Methods of Generating Benzyne

There are four general approaches used to produce benzyne: 1) base-promoted elimination of haloarenes and 1,2-dihaloarenes, 2) fluorine-mediated elimination

of silylated benzenes, 3) thermolysis of diazotised anthranilic acid, and 4) oxidation 1-aminobenzotriazole.[44]

**Base-Promoted Elimination of Haloarenes and 1,2-Dihaloarenes**

In these reactions organolithium or organomagnesium reagents are reacted with haloarenes or 1,2-dihaloarenes to either deprotonate or induce halogen–metal exchange, followed by elimination to produce benzyne (Scheme 4.19). The drawback of this method is it requires harsh conditions, which are not compatible with a number of functional groups. Despite this, benzynes generated via this method have been applied to several total syntheses.[45,46,47,48]

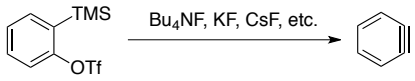



**Scheme 4.19: synthesis of benzyne from haloarenes or 1,2-haloarenes under basic conditions.**

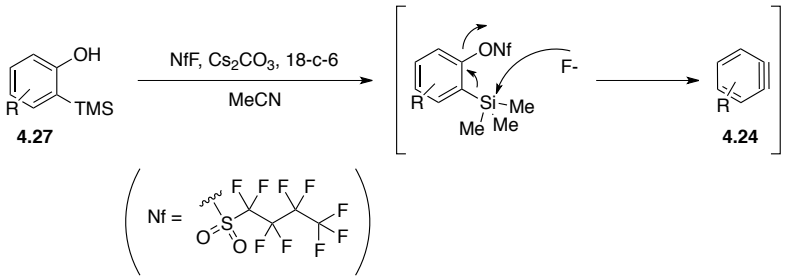
**Fluorine-Mediated Elimination of Silylated Benzenes**

The predominant method for generating benzyne is from *o*-silylphenyl triflates, with 2-(trimethylsilyl)phenyl triflate being the most common (Scheme 4.20).[49] The advantage of this method is that the conditions are typically mild and neutral, making it compatible with a wide variety of functional groups. However, aryl triflates have low hydrolytic stability, which has prompted the use of other leaving groups. For example, nonafluorobutanesulfonyl fluoride has been reacted with *o*-(trimethylsilyl)phenols, **4.27**, to produce benzynes via a domino reaction where

the nonafluorobutanesulfonyl (Nf) group activates the phenolic hydroxyl group to produce a leaving group and the resulting free fluoride ion attacks the TMS moiety causing elimination to benzyne (Scheme 4.21).[50]

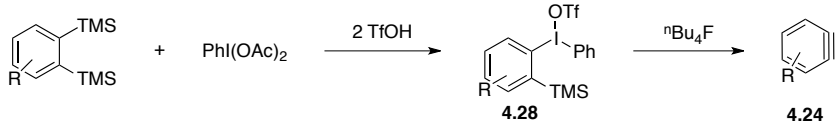



**Scheme 4.20: Generation of benzyne using silylated triflates and fluoride ions.**




**Scheme 4.21: Benzyne synthesis from *o*-(trimethylsilyl)phenols and nonafluorobutanesulfonyl fluoride.**

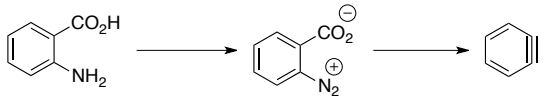
Another leaving group explored in place of triflate is the hypervalent iodine group phenyliodanyl, which is reported to have a $10^6$ times greater leaving group ability compared to triflate (Scheme 4.22).[51] This leads to the synthesis of benzyne under milder conditions. The drawback of using hypervalent iodine benzyne precursors (**4.28**) is these compounds tend to have poor solubility in standard solvents used in organic reactions. This has been circumvented by the use of precursors bearing alkyl chains.[52,53]




**Scheme 4.22: Benzyne synthesis with a hypervalent iodine leaving group.**

### Thermolysis of Diazotised Antranilic Acid

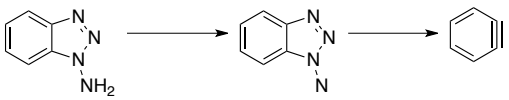
This method uses diazotised anthranilic acid as a benzyne precursor (Scheme 4.23). The starting material, anthranilic acid is widely available, and the release of $CO_2$ and $N_2$ gas makes the formation of benzyne entropically favourable.




**Scheme 4.23: Generation of benzyne by thermolysis.**

### Oxidation of 1-Aminobenzotriazole

This method for generating benzyne is less common, but affords benzyne products in good yields from the oxidation of 1-aminobenzotriazole (Scheme 4.24). The typical oxidant is lead tetraacetate ($Pb(OAc)_4$); however, *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) have also been used.[54,55]




**Scheme 4.24: Generation of benzyne by oxidation.**

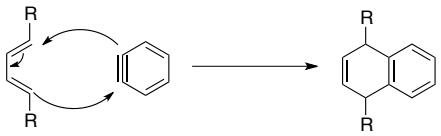
### 4.2.3 Reactions of Benzyne

Benzyne has been used in numerous reactions to build organic scaffolds. This work has been reviewed extensively.[56,57,58,59] These reactions can be divided into three broad categories: pericyclic reactions, transition metal-catalysed reactions, and nucleophilic additions. Though benzyne can add to a seemingly endless array

of nucleophiles,[56,60] of most importance to the work presented in this thesis are percyclic reactions and transition metal-catalysed reactions.

**Pericyclic Reactions**

The electrophilic nature of benzyne allows it to undergo cycloaddition reactions with dienes, 1,3-dipoles, and alkenes. Probably the most extensively explored is cycloaddition with dienes: the Diels–Alder reaction, a [4+2] cycloaddition between a *cis*-conjugated diene and a typically electrophilic dienophile (Scheme 4.25). The reactivity of benzyne and the ease of the Diels–Alder reaction make it well-suited to the detection of benzyne, usually through addition to furan. Benzyne is such a strong dienophile that it has even been shown to undergo a Diels–Alder reaction with benzene.[61] Diels–Alder reactions with benzyne are extensive and even applied in the building of polycyclic aromatic hydrocarbons.[62]




**Scheme 4.25: [4+2] cycloaddition of benzyne.**

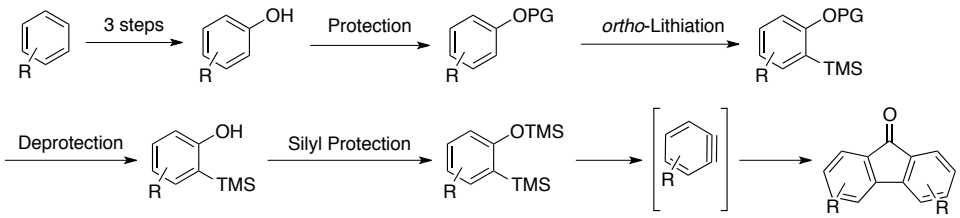
**Transition Metal-Catalysed Reactions**

Similar to [4+2] cycloaddition reactions are [2+2+2] and [2+2+1] cycloaddition reactions, which lend themselves well to the production of complex aromatic scaffolds. While these reactions are theoretically thermally allowed, the large entropic penalty precludes them from occurring.[63] Transition metal catalysts have

allowed the use of benzynes in cyclotrimerisation reactions, and similar [2+2+1] cycloaddition reactions, which are valuable in the synthesis of complex organic structures.[64] Often employing a palladium catalyst, benzyne has been a precursor in the synthesis of 9-fluorenones,[15] 9-fluorenylidenes,[65] benzo[*b*]fluorenones,[19] phenanthrenes,[66] and a number of other materials. These reactions were discussed in more detail in the previous sections.

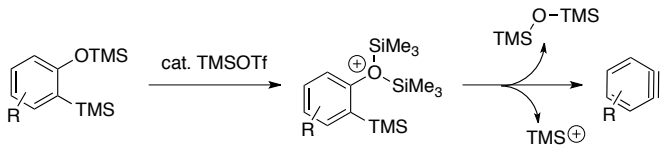
### 4.3 Proposed Synthetic Plan

Because of its importance in the synthesis of electronic polymers, the synthesis of 9-fluorenone from the alkyl substituted aromatic rings made from canola oil was the ultimate end goal of this project. This chapter is devoted to the synthesis of the penultimate target in fluorenone synthesis: benzyne. The proposed synthetic pathway is outlined in Scheme 4.26. To begin, the alkyl substituted aromatic rings are transformed into a phenol through three straightforward synthetic steps. The phenol will be protected; this will serve the dual purpose of masking the acidic proton and directing the following *ortho*-lithiation, which will install a silyl group adjacent to the phenol. The protecting group on the phenol will be removed and replaced with a silyl group. This compound will then be converted to benzyne, which can then undergo a transition metal-catalysed [2+2+1] cycloaddition to form 9-fluorenone with alkyl substituents on the backbone.




**Scheme 4.26: Proposed synthetic pathway.**

In an effort to develop new synthetic methodology, as well as to limit the total number of synthetic steps, a novel method for the production of benzyne will be explored (Scheme 4.27). The direct benzyne precursor will be a silylated silynol instead of a silylated triflate. It is hypothesised that addition of a catalytic amount of TMSOTf will result in the generation of benzyne following the elimination of hexamethyldisiloxane, regenerating the $TMS^{+}$ catalyst. This method would be catalytic, using a small amount of a reagent that is less toxic than the commonly employed fluoride reagents (CsF, KF etc.) that are used stoichiometrically to produce benzyne.




**Scheme 4.27: Novel method for the generation of benzyne.**

Rather than exploring this somewhat unprecedented synthesis with alkyl substituted aromatic rings obtained from canola oil, this synthesis was explored using a series of model phenols **4.29** (Figure 4.8) that are structurally similar, but sterically less demanding, than the aromatic rings derived in the previous chapter.

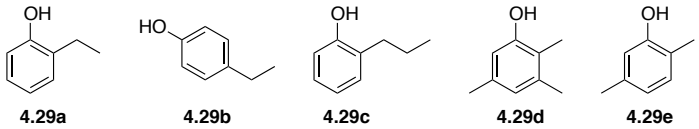
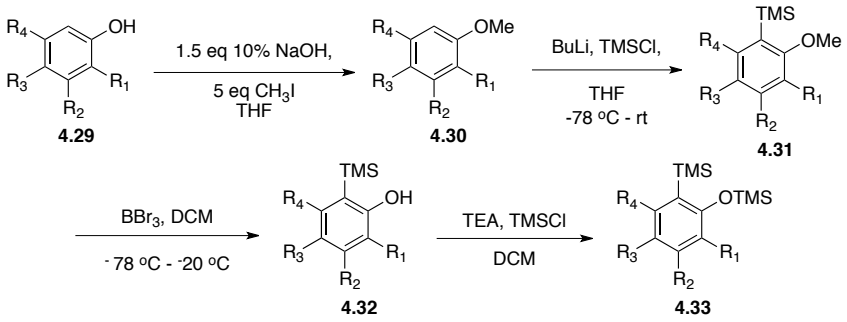



**Figure 4.8: Model compounds.**

## 4.4 Discussion

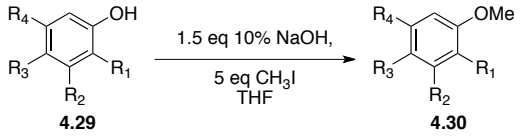
The first step of the synthesis was to choose an appropriate protecting group for the phenol. This serves the dual purpose of tying up the acidic phenolic proton as well as directing the subsequent *ortho*-lithiation step.[67] A methoxy group was explored first (Scheme 4.28).




**Scheme 4.28: Synthesis of benzyne precursor using a methoxy protecting group.**

The protecting group was introduced by reacting 10% NaOH with the starting phenol, followed by the addition of an excess of $CH_3I$. This produced **4.30** in good yield and the products did not require further purification. The results for each phenol protection are presented in Table 4-1. In the case where a larger alkyl group is present *ortho* to the phenol functional group, the yields were consistently lower, indicating steric bulk plays a role in the success of this protection (Table 4-1, Entries 1 and 3).

**Table 4-1. Methoxy Protection of Starting Phenols.**




| Entry | Starting Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Product | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | **4.29a** | Et | H | H | H | **4.30a** | 76 |
| 2 | **4.29b** | H | H | Et | H | **4.30b** | 80 |
| 3 | **4.29c** | Pr | H | H | H | **4.30c** | 60 |
| 4 | **4.29d** | Me | Me | H | Me | **4.30d** | 82 |
| 5 | **4.29e** | Me | H | H | Me | **4.30e** | 83 |

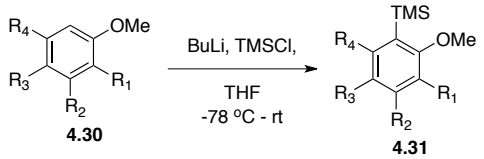
[a] isolated yields

The next step was *ortho*-lithiation. This was accomplished using 2.5 equivalents of either *sec*- or *tert*-butyllithium at –78 °C for one hour, followed by addition of 2.5 equivalents of TMSCl.[68] The reaction was then warmed to room temperature. The results of this step are presented in Table 4-2. The *ortho*-lithiation was most successful with **4.30b**, providing the target product in an 85% yield. Presumably this is because of the reduced steric hindrance around the methoxy protecting group. When a methyl group was present *ortho* to the methoxy group, the expected product, **4.31**, was not isolated (Table 4-2, Entries 4 and 5). Instead, the TMS group was introduced onto one of the methyl groups, resulting in compounds **4.34**, **4.35a** and **4.35b** (Figure 4.9). Using HMQC and HMBC NMR experiments to augment the 1D $^{1}$H NMR and $^{13}$C NMR experiments, the regioisomers **4.35a** and **4.35b** were determined.[‡] It was found that **4.35a** was the major regioisomer, while **4.35b** was the minor isomer, making up approximately 36% of the sample. These products are most likely because the benzylic protons

[‡] Full NMR spectroscopic characterisation data can be found in Appendix B.

are more slightly more acidic, and sterically less encumbered than the aryl protons, making their removal more favourable using $^{t}$BuLi (Figure 4.10). Further, the unexpected regioisomer **4.35b** is most likely a result of the poor directing ability of the methoxy functional group.[69]

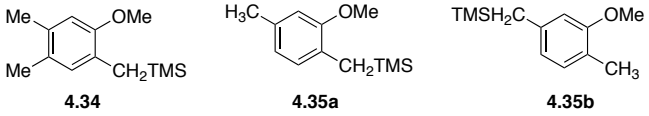
**Table 4-2. *Ortho*-lithiation of Methoxy-protected Phenols.**




**4.30** **4.31**

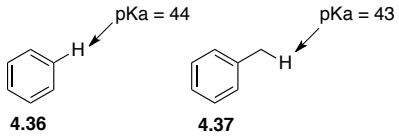
| Entry | S.M. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Base | Product | Yield (%)[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | **4.30a** | Et | H | H | H | $^{t}$BuLi | **4.31a** | 56 |
| 2 | **4.30b** | H | H | Et | H | $^{s}$BuLi | **4.31b** | 85 |
| 3 | **4.30c** | Pr | H | H | H | $^{t}$BuLi | **4.31c** | - |
| 4 | **4.30d** | Me | Me | H | Me | $^{t}$BuLi | **4.34** | 86 |
| 5 | **4.30e** | Me | H | H | Me | $^{t}$BuLi | **4.35a/b** | 86 |

[a] isolated yields.




**4.34** **4.35a** **4.35b**

**Figure 4.9: *ortho*-Lithiation side products.**

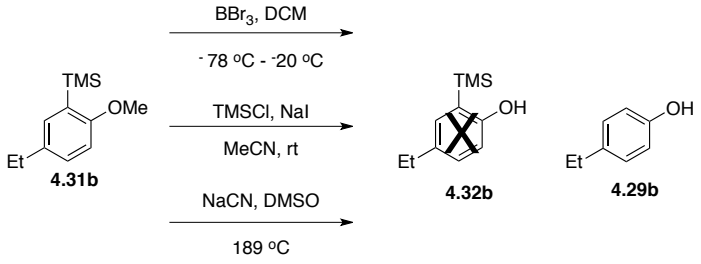



**4.36** **4.37**

**Figure 4.10: Comparison of phenylic and benzylic pKas.**

After *ortho*-lithiation, the following step of the synthesis was to remove the methoxy protecting group. Compound **4.31b** was used as the starting material to

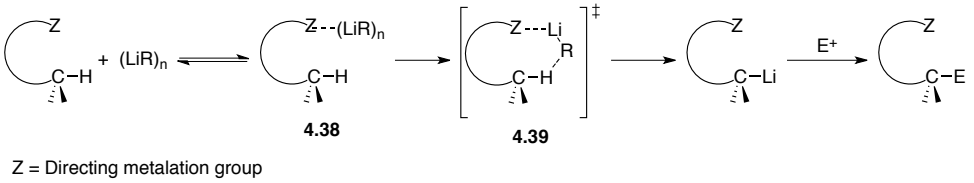
explore the appropriate conditions. This was first attempted using boron tribromide.[70,71,72] Instead of isolating desired product, **4.23b**, the starting phenol, **4.30b**, was isolated (Scheme 4.29). Studies by Snieckus *et al.* indicate $BBr_3$ is capable of inducing *ipso*-desilylation, explaining these observations.[73] With this in mind, two other deprotection methods were explored: the first involving generation of TMSI *in situ*,[74] and the second using a Krapcho-type reaction involving NaCN in DMSO at reflux.[75] These methods also resulted in the concurrent removal of the *ortho* TMS group as well as the removal of the methoxy protecting group. These results suggest that the methoxy group is not a good choice as the protecting group.




**Scheme 4.29: Attempted removal of methoxy protecting group.**

To overcome the challenges associated with the methoxy group, directed *ortho* metalation (DoM) was explored.[76] DoM, pioneered by Victor Snieckus, allows for contiguous substitution on aromatic rings with excellent regiochemical control.[77,78] DoM is regarded as a complex-induced proximity effect (CIPE) where the reactive groups are brought together by the formation of a premetalation complex (**4.39**) that promotes deprotonation at the *ortho* position on an aromatic ring (Scheme 4.30).[79] The directed metalation group (DMG,

represented as "Z" in Scheme 4.30) should be resistant to nucleophilic attack by the metalating agent, it must contain a heteroatom capable of coordinating the metalating agent in proximity to the *ortho* position through a 4, 5, or 6 membered ring, and should be sterically demanding.[80,81] The efficiency of various directing groups is shown in Figure 4.11. The efficiency of a group is dependent on the base, solvent, and temperature.




**Scheme 4.30: Complex-induced proximity effect.**

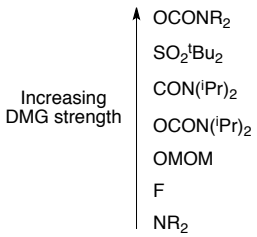
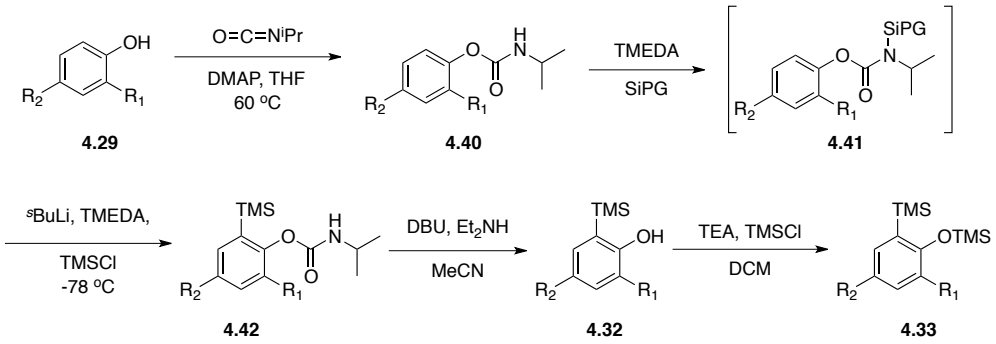



**Figure 4.11: Efficiency of directed metalation groups in $^{n}$BuLi/THF/–78 °C.**

*O*-carbamates are a notably powerful directing group; however, these groups typically require harsh removal conditions that would not be compatible with the TMS group.[69] This challenge was addressed by the work of Kauch and Hoppe where they found *N*-isopropylcarbamate was a stronger directing group compared to the methoxy group, but could be removed under mildly basic conditions

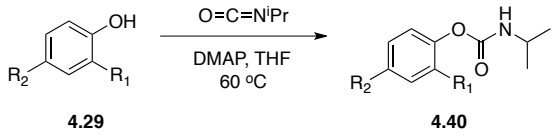
without affecting an *ortho*-TMS group.[82,69,83] This method was applied to the model compounds **4.29a**, **4.29b**, and **4.29c** (Scheme 4.31).




**Scheme 4.31: Synthesis of a benzyne precursor with an *N*-isopropylcarbamate protecting group.**

*N*-isopropylcarbamates, **4.40**, were formed by reacting starting phenols **4.29** with isopropylisocyanate and *N,N*-dimethylaminopyridine (DMAP). It was found that increasing the amount of DMAP from 0.1 equivalents to 1.0 equivalents, and stirring with the phenol for 10 minutes prior to the addition of the isopropylisocyanate, increased the yields significantly (Table 4-3).

**Table 4-3. *N*-isopropylcarbamate Protection of Starting Phenols.**



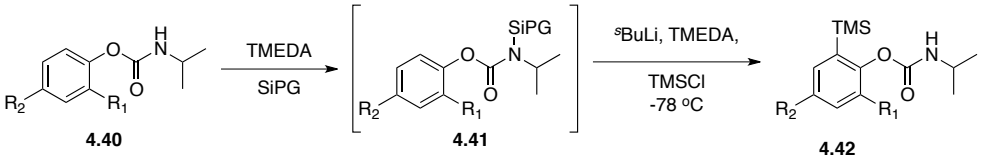

| Entry | S.M. | $R_1$ | $R_2$ | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **4.29a** | Et | H | **4.40a** | 80 |
| 2 | **4.29b** | H | Et | **4.40b** | 76 |
| 3 | **4.29c** | Pr | H | **4.40c** | 66 |

[a] isolated yields

To *ortho*-lithiate *N*-isopropylcarbamate-functionalized arenes successfully, Kauch and Hoppe found it necessary to place a silicon protecting group (SiPG) on the

nitrogen atom to prevent reaction at the carbonyl carbon by the alkyllithium reagent (**4.41**). This modification effectively hindered the carbonyl carbon from nucleophilic attack. The authors found this conversion could be done in one pot with the *ortho*-lithiation, and the SiPG could be removed during work up.

**Table 4-4. *Ortho*-lithiation Using the *N*-isopropylcarbamate Directing Group.**




| Entry | S.M. | $R_1$ | $R_2$ | SiPG | Base | E+ | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4.40a** | Et | H | TIPSOTf | $^{s}$BuLi | TMSCl | -[a] |
| 2 | **4.40a** | Et | H | TIPSOTf | $^{n}$BuLi | TMSCl | -[b] |
| 3 | **4.40a** | Et | H | TIPSOTf | $^{n}$BuLi | TMSCl | -[a] |
| 4 | **4.40a** | Et | H | TIPSOTf | $^{n}$BuLi | TMSCl | -[a] |
| 5 | **4.40a** | Et | H | TMSOTf | $^{n}$BuLi | TMSCl | 8[c,e] |
| 6 | **4.40a** | Et | H | TMSOTf | $^{n}$BuLi | TMSCl | 18[c,e] |
| 7 | **4.40a** | Et | H | TMSOTf | $^{s}$BuLi | TMSCl | 4[c,e] |
| 8 | **4.40a** | Et | H | TMSOTf | $^{n}$BuLi | TMSCl | 35[c,e] |
| 9 | **4.40a** | Et | H | TMSOTf | $^{n}$BuLi | TMSCl | 29[c,e] |
| 10 | **4.40a** | Et | H | TMSOTf | $^{n}$BuLi | TMSCl | 5[c,e] |
| 11 | **4.40a** | Et | H | TESOTf | $^{n}$BuLi | TMSCl | 47[d] |
| 12 | **4.40a** | Et | H | TESOTf | $^{n}$BuLi | TMSOTf | 60[d] |
| 13 | **4.40a** | Et | H | TESOTf | $^{n}$BuLi | TMSOTf | 61[d] |
| 14 | **4.40a** | Et | H | TESOTf | $^{n}$BuLi | TMSOTf | - |
| 15 | **4.40a** | Et | H | TESOTf | $^{s}$BuLi | TMSCl | -[a,e] |
| 16 | **4.40b** | H | Et | TIPSOTf | $^{s}$BuLi | TMSCl | - |
| 17 | **4.40b** | H | Et | TMSOTf | $^{s}$BuLi | TMSCl | 26[f] |
| 18 | **4.40b** | H | Et | TMSOTf | $^{n}$BuLi | TMSCl | 38[f] |
| 19 | **4.40b** | H | Et | TESOTf | $^{n}$BuLi | TMSCl | -[g] |
| 20 | **4.40b** | H | Et | TESOTf | $^{n}$BuLi | TMSOTf | - |
| 21 | **4.40b** | H | Et | TESOTf | $^{n}$BuLi | TMSCl | - |
| 22 | **4.40b** | H | Et | TESOTf | $^{s}$BuLi | TMSCl | - |

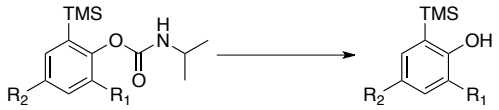
[a] Isolated only starting material. [b] Post *ortho*-lithiation product with TIPS SiPG still present on carbamate. [c] Yield calculated by NMR spectroscopy. [d] Yield based on recovered starting material. [e] side product also present: starting phenol **4.29a** [f] Isolated yield. [g] Double *ortho*-substituted product.

The Kauch–Hoppe procedure was applied to **4.40a** and **4.40b**. The results are summarised in Table 4-4. When TIPSOTf was used as the SiPG, it was found that only starting material or product with the TIPS group still present on the carbamate was isolated; none of the desired compound was formed (Table 4-4, Entries 1-4, and 16). This suggested the need for a more labile SiPG. The next SiPG group examined was TMSOTf (Table 4-4, Entries 5-10, 17, and 18). Now it was possible to isolate small amounts of the desired product **4.42**; however, nearly always there was a 1:1 ratio of the starting phenol **4.29** to the product. This suggested that the SiPG was not large enough to protect the carbamate carbonyl carbon from attack by the alkyllithium. To overcome this drawback, a third SiPG was explored: TESOTf. Being larger than TMS, it was proposed that TES would prevent attack at the carbonyl carbon, but the group is still more labile than TIPS. With this SiPG it was found that reasonable amounts of **4.42** could be isolated without any phenol present (Table 4-4, Entries 11-15, and 19-22).

To remove the *N*-isopropylcarbamate protecting group, **4.42** was mixed with a base; the results are summarised in Table 4-5. The isolated yields of **4.42** were low to moderate and almost always had large amounts of starting phenol **4.29** isolated as a side product. In some cases (Table 4-5, Entries 2, 5, and 6) **4.29** was the only product isolated. Following a report by Bronner and Garg, a different deprotection method was attempted, this time using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and diethylamine (Table 4-5, Entries 9-11).[84] Bronner and Garg reported that this deprotection method could be used in tandem with TMS

protection to produce **4.33** without having to isolate **4.32** (Scheme 4.32). Using the one pot approach proposed by Bronner and Garg was not successful in isolating **4.33** as predicted; however, the use of DBU did result in the removal of the carbamate protecting group in moderate to good yields (60–80%) without concurrent removal of the *ortho*-TMS group (Table 4-5, Entries 9-11).

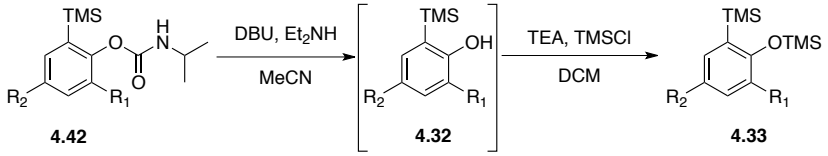
**Table 4-5. Removal of *N*-isopropylcarbamate Protecting Group.**




**4.42** **4.32**

| Entry | S.M. | $R_1$ | $R_2$ | Base | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **4.42b** | H | Et | 10% NaOH | 62 |
| 2 | **4.42b** | H | Et | 10% NaOH | -[b] |
| 3 | **4.42a** | Et | H | 10% NaOH | - |
| 4 | **4.42a** | Et | H | 10% NaOH | 14[b] |
| 5 | **4.42a** | Et | H | 10% NaOH | -[b] |
| 6 | **4.42a** | Et | H | 10% NaOH | -[b] |
| 7 | **4.42a** | Et | H | 10% NaOH | 47 |
| 8 | **4.42a** | Et | H | 10% NaOH | 6 |
| 9 | **4.42a** | Et | H | DBU/$NHEt_2$ | 68 |
| 10 | **4.42a** | Et | H | DBU/$NHEt_2$ | 56 |
| 11 | **4.42c** | Pr | H | DBU/$NHEt_2$ | 83 |

[a] Isolated yields [b] Starting phenol **4.29** obtained as side product



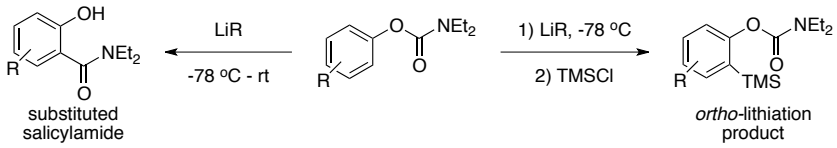

**4.42** **4.32** **4.33**

**a: $R_1$ = Et; $R_2$ = H**
**b: $R_1$ = H; $R_2$ = Et**

**Scheme 4.32: Tandem carbamate removal and TMS protection.**

While using the *N*-isopropylcarbamate protecting group did allow for the synthesis of **4.32**, the poor yields of the *ortho*-lithiation reaction and the moderate

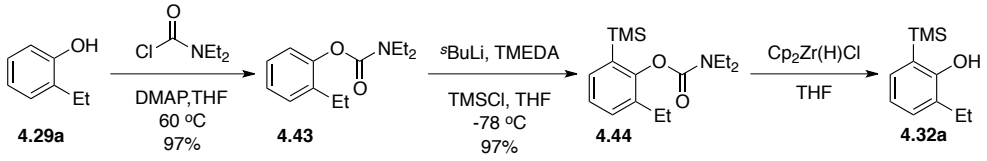
yields of the deprotection step suggested revisiting the directing metallation group on the phenol. Snieckus *et al.* have studied directed *ortho*-metalation extensively and have concluded that *N,N*-diethylcarbamate is one of the most powerful directing groups. These groups are known to undergo an intramolecular [1,3]-acyl migration to give substituted salicylamides at room temperature, referred to as an anionic *ortho*-Fries rearrangement; however, this can be avoided by keeping the reaction at low temperature (Scheme 4.33).[76,77,78, 80, 81,85,86,87] The Snieckus group have also shown this group can be removed without removing TMS substituents using the Schwartz reagent ($Cp_2Zr(H)Cl$).[88]




**Scheme 4.33: Competing anionic *ortho*-Fries rearrangement.**

To explore this possibility, 2-ethylphenol (**4.29a**) was reacted with *N,N*-diethylcarbamoyl chloride to produce **4.43** in a 97% yield (Scheme 4.34). The protected product required no further purification. This compound was *ortho*-lithiated to synthesise **4.44**, also in 97% yield. This was then exposed to the Schwartz reagent. These preliminary results suggest the product of the reaction was **4.32a**, as the $^1$H NMR spectrum showed the appearance of a peak at $\delta = 4.82$ ppm, consistent with the proton of an OH functional group. The TLC data was also consistent with **4.32a** isolated by other means. As sufficient quantities of **4.32** had been obtained for the following synthetic steps, this reaction was not explored

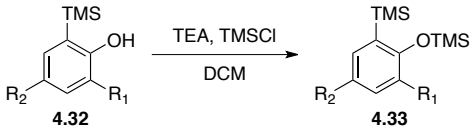
further; however, the results remain as a promising method for the synthesis of **4.32**.




**Scheme 4.34: Use of *N,N*-diethylcarbamate protecting group.**

After synthesising **4.32**, it was converted to the benzyne precursor, **4.33**, by reaction with triethylamine (TEA) and TMSCl. The results are presented in Table 4-6. Silyl ether **4.33** was not stable to silica gel chromatography, resulting in some starting material (**4.32**) being isolated alongside the desired product. Any unreacted starting material could be recycled through the reaction once more. Because the crude product of the reaction was reasonably clean to begin with, it was found that further purification was unnecessary, and **4.33** could be carried forward as is.

**Table 4-6. Synthesis of the Benzyne Precursor.**

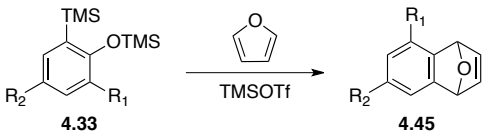



| Entry | S.M. | $R_1$ | $R_2$ | Product | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **4.32b** | H | Et | **4.33b** | - |
| 2 | **4.32b** | H | Et | **4.33b** | 69 |
| 3 | **4.32a** | Et | H | **4.33a** | 66 |
| 4 | **4.32a** | Et | H | **4.33a** | 6 |
| 5 | **4.32a** | Et | H | **4.33a** | 52 |
| 6 | **4.32c** | Pr | H | **4.33c** | 70 |

[a] Isolated yields

After the successful synthesis of benzyne precursor **4.33**, the synthesis of benzyne was attempted using a catalytic amount of TMSOTf. The test reaction was a Diels–Alder cycloaddition using furan as the diene. A variety of conditions were explored (Table 4-7). The solvent, temperature, equivalents of furan, and equivalents of TMSOTf were all varied, and in each case only the original phenol, **4.29**, was isolated.

**Table 4-7. Synthesis of Benzyne using TMSOTf as a Catalyst.**




| Entry | Substrate | $R_1$ | $R_2$ | Furan eq. | TMSOTf eq. | Solvent | Temperature |
|---|---|---|---|---|---|---|---|
| 1 | **4.33b** | H | Et | 10 | 0.3 | Toluene | reflux |
| 2 | **4.33b** | H | Et | 10 | 0.3 | Toluene | rt |
| 3 | **4.33a** | Et | H | 10 | 0.3 | Toluene | reflux |
| 4 | **4.33a** | Et | H | 10 | 0.3 | Toluene | rt |
| 5 | **4.33a** | Et | H | 15 | 0.3 | Toluene | reflux |
| 6 | **4.33a** | Et | H | 15 | 0.3 | Toluene | rt |
| 7 | **4.33a** | Et | H | 30 | 0.3 | $CH_2Cl_2$ | reflux |
| 8 | **4.33a** | Et | H | 50 | 1.0 | Toluene | rt |

Despite the fact that the main goal of this work was to synthesise benzyne for the synthesis of fluorenone, the conversion of **4.27** into an *o*-silylphenyltriflate for fluoride-mediate elimination was not pursued due to time constraints.

## 4.4 Conclusions

In this Chapter, a series of model compounds used to represent the aromatic rings previously discussed were exposed to a number of synthetic manipulations to provide an alternate method for generating benzyne, with the hope of establishing a catalytic method for benzyne production. After surveying a number of conditions, it was found that *N,N*-diethylcarbamate was the ideal protecting group for the phenol and the group could be removed using the Schwartz reagent. All attempts at using catalytic TMSOTf to generate benzyne from **4.33** were unsuccessful. However, it is well established that **4.33** is a precursor for *o*-silylphenyl aryl triflates used to generated benzyne. Therefore, this is a promising direction for further investigation.

## 4.5 Experimental

**General Information.** Unless otherwise stated, all glassware was oven-dried. Transfer of solvents and reaction mixtures was done using oven-dried syringes and cannulae. All starting materials were purchased from Sigma–Aldrich and used without further purification. Flash chromatography columns were packed with 230–400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra ($^1$H NMR) were recorded at 300 MHz or 400 MHz and coupling constants (*J*) are reported in Hertz (Hz). Standard notation was used to describe the multiplicity of signals observed in $^1$H NMR spectra: broad (br), apparent (app), multiplet (m), singlet (s), doublet (d), triplet (t), etc. Carbon nuclear magnetic resonance spectra

($^{13}$C NMR) were recorded at 125 MHz and are reported (ppm) relative to the centre line of the triplet from chloroform-*d* (77.26 ppm).

### 4.5.1 Protection of Phenols

**General procedure for methoxy protection**

The starting phenol (2.0 mmol) was dissolved in freshly distilled THF (7 mL) and 10% aqueous NaOH (1.2 mL, 3.0 mmol) and $CH_3I$ (0.62 mL, 10.0 mmol) were added. The mixture was stirred at room temperature until the reaction was complete, determined by TLC (8:1 hexanes:EtOAc eluent). The mixture was then extracted with $Et_2O$ (3 x 10 mL). The combined organic phases were washed with water (1 x 10 mL) and brine (1 x 10 mL). The organic phase was isolated and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

**2-ethylmethoxybenzene, 4.5a:**

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.21–7.12 (m, 2H), 6.93–6.82 (m, 2H), 3.84 (s, 3H), 2.65 (q, $J$ = 7.5 Hz, 2H), 1.20 (t, $J$ = 7.5 Hz, 3H)

These data matched those previously reported for 2-ethylmethoxybenzene.[89]

**4-ethylmethoxybenzene, 4.5b:**

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.15–7.10 (m, 2H), 6.86–6.81 (m, 2H), 3.80 (s, 3H), 2.60 (q, $J$ = 7.5 Hz, 2H), 1.22 (t, $J$ = 7.5 Hz, 3H)

These data matched those previously reported for 4-ethylmethoxybenzene.[89]

**2-propylmethoxybenzene, 4.5c:**

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.20–7.12 (m, 2H), 6.91–6.84 (m, 2H), 3.83 (s, 3H), 2.62–2.57 (m, 2H), 1.65–1.58 (m, 2H), 0.96 (t, $J$ = 7.2 Hz, 3H)

These data matched those previously reported for 2-propylmethoxybenzene.[90]

**2,3,5-trimethylmethoxybenzene, 4.5d:**

$^1$H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.55 (s, 1H), 3.80 (s, 3H), 2.30 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H)

These data matched those previously reported for 2,3,5-trimethylmethoxybenzene.[91]

**2,5-dimethylmethoxybenzene, 4.5e:**

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.04–7.00 (app d, 1H), 6.70–6.65 (app d, 1H), 3.83 (s, 3H), 2.35 (s, 3H), 2.19 (s, 3H)

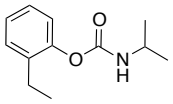
These data matched those previously reported for 2,5-dimethylmethoxybenzene.[92]

**General procedure for *N*-isopropylcarbamate protection[§]**

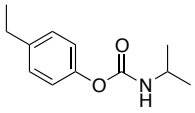
In a flame-dried, three-neck round bottom flask, affixed with a condenser, under a positive pressure of argon, the phenol (20.0 mmol) was dissolved in freshly distilled THF (10 mL). *N*,*N*-dimethylaminopyridine (DMAP, 1.22 g, 10.0 mmol) was added and the mixture was cooled in an ice-water bath. After stirring for 10 min, isopropyl isocyanate (2.3 mL, 24.0 mmol) was added. The mixture was then

[§] Compounds were only partially characterised.

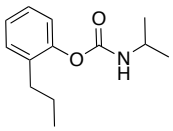
heated to 60 °C, and stirred until complete as determined by TLC (4:1 hexanes:EtOAc). The reaction was cooled to room temperature and quenched by the addition of 2M HCl (1 mL:1 mmol phenol). The solution was extracted with $Et_2O$ (3 x 10 mL) and the combined organic layers were washed saturated aqueous sodium bicarbonate (1 x 10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

**2-ethylphenyl-*N*-isopropylcarbamate, 4.11a:** 

$^1$H NMR (400 MHz, $CDCl_3$) δ 7.25–7.21 (m, 1H), 7.20–7.12 (m, 2H), 7.09–7.06 (m, 1H), 4.86 (br s, 1H), 3.90 (sept, *J* = 6.8 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.26 (d, *J* = 6.4 Hz, 6H), 1.20 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 153.8, 149.0, 136.3, 129.2, 126.7, 125.6, 122.5, 43.4, 23.1, 22.9, 14.2; IR ($CDCl_3$, cast) 3320, 3038, 2972, 2936, 2876, 1710, 1531, 1488 $cm^{-1}$

**4-ethylphenyl-*N*-isopropylcarbamate, 4.11b:** 

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.17 (app d, *J* = 8.4 Hz, 2H), 7.03 (app d, *J* = 8.4 Hz, 2H), 4.86 (br s, 1H), 3.90 (sept, *J* = 6.6 Hz, 1H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.24 (d, *J* = 6.6 Hz, 6H), 1.23 (t, *J* = 7.5 Hz, 3H); IR ($CDCl_3$, cast) 3327, 3038, 2975, 2962, 2934, 2875, 1706, 1592, 1544, 1512 $cm^{-1}$

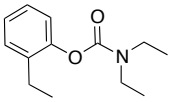
**2-propylphenyl-*N*-isopropylcarbamate, 4.11c:** 

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.23–7.18 (m, 1H), 7.17–7.12 (m, 2H), 7.09–7.05 (m, 1H), 4.86 (br s, 1H), 3.90 (sept, *J* = 6.6 Hz, 1H), 2.54 (m, 2H), 1.61 (appt sext,

$J$ = 7.5 Hz, 2H), 1.25 (d, $J$ = 6.6 Hz, 6H), 0.95 (t, $J$ = 7.5 Hz, 3H); IR ($CDCl_3$, cast) 3323, 3037, 2967, 2933, 2873, 1710, 1532, 1488, 1453 $cm^{-1}$

**General Procedure for *N*,*N*-diethylcarbamate protection**[**]

The procedure as described for the *N*-isopropylcarbamate protection, replacing isopropyl isocyanate with *N*,*N*-diethylcarbamoyl chloride (1.5 mL, 12.0 mmol), was employed.

**2-ethylphenyl-*N*,*N*-diethylcarbamate, 4.14:** 

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.25–7.06 (m, 4H), 3.50–3.38 (m, 4H), 2.60 (q, $J$ = 7.5 Hz, 2H), 1.30–1.19 (m, 6H), 1.21 (t, $J$ = 7.5 Hz, 3H)

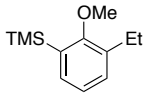
**4.5.2 *ortho*-Lithiation of Protected Phenols**[††]

**General procedure for the *ortho*-lithiation of methoxy phenols and diethylcarbamates**

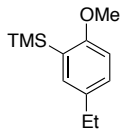
In a flame-dried round bottom flask under a positive pressure of argon, the starting material (4.9 mmol) was dissolved in freshly distilled THF (25 mL). The reaction was cooled to –78 °C and TMEDA (1.8 mL; 12.2 mmol) was added. $^n$BuLi (7.6 mL, 1.6 M in hexanes) was added dropwise to the solution. After complete addition, the mixture was stirred for 1 h at room temperature. TMSCl (2.2 mL, 17.1 mmol) was added dropwise. The mixture was stirred at –78 °C until the reaction was complete as determined by TLC (4:1 hexanes:EtOAc). When

[**] Only the $^1$H NMR spectrum for this compound was obtained.
[††] Compounds were only partially characterised.

complete, the reaction was quenched at –78 °C with the addition of methanol and 2M HCl. It was then allowed to warm to room temperature. The solution was diluted with water (30 mL) and extracted with $Et_2O$ (3 x 30 mL). The combined organic layers were washed with saturated sodium bicarbonate (1 x 30 mL) and with brine (1 x 30 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.

**2-ethyl-6-trimethylsilylanisole, 4.6a:** 


$^1$H NMR (300 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 7.10–7.06 (m, 1H), 3.76 (s, 3H), 2.70 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H), 0.13–0.10 (m, 9H)

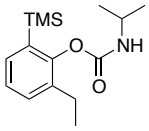
**4-ethyl-2-trimethylsilylanisole, 4.6b:** 


$^1$H NMR (300 MHz, $CDCl_3$) δ 7.20–7.11 (m, 2H), 6.85–6.73 (m, 1H), 3.76 (s, 3H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H), 0.13–0.10 (m, 9H); HRMS (EI, $[M]^{\bullet+}$) for $C_{12}H_{20}OSi$ calcd 208.1283, found: m/z 208.1283

**General procedure for the *ortho*-lithiation of *N*-isopropylcarbamates**

In a flame-dried round bottom flask under a positive pressure of argon the starting material (16.4 mmol) was dissolved in freshly distilled THF (80 mL). The mixture was cooled to 0 °C and TMEDA (2.7 mL, 18.0 mmol) was added, followed by the SiPG (18.0 mmol). The mixture was allowed to warm to room temperature over a period of 30 min and more TMEDA (4.9 mL, 32.8 mmol) was added. The solution was then cooled to –78 °C and $^s$BuLi (23.4 mL, 32.8 mmol, 1.4 M in

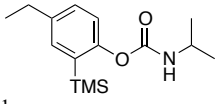
cyclohexane) was added slowly, over an hour. After the addition was complete, the reaction was stirred at –78 °C for 1 h. TMSCl (7.2 mL, 57.3 mmol) was added dropwise over 30 min. The reaction was stirred at –78 °C until complete, determined by TLC (4:1 hexanes:EtOAc eluent). When complete, the reaction was quenched at –78 °C with the addition of methanol and 2M HCl. It was then allowed to warm to room temperature. The solution was diluted with water (50 mL) and extracted with $Et_2O$ (3 x 50 mL). The combined organic layers were washed with saturated sodium bicarbonate (1 x 50 mL) and with brine (1 x 50 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*.




**2-(trimethylsilyl)-6-ethylphenyl-*N*-isopropylcarbamate, 4.13a:**

$^1$H NMR (300 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.20–7.15 (m, 1H), 4.86 (br s, 1H), 3.90 (sept, *J* = 6.6 Hz, 1H), 2.51 (q, *J* = 7.5 Hz, 2H), 1.23 (d, *J* = 6.6 Hz, 6H), 1.19 (t, *J* = 7.5, 3H), 0.26 (s, 9H); IR ($CDCl_3$, cast) 3316, 3044, 2970, 2877, 1705, 1540 $cm^{-1}$

**2-(trimethylsilyl)-4-ethylphenyl-*N*-isopropylcarbamate, 4.13b:**




$^1$H NMR (300 MHz, $CDCl_3$) δ 7.25–7.18 (m, 2H), 7.03–7.00 (m, 1H), 4.76 (br s, 1H), 3.92 (sept, *J* = 7.5 Hz, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.24 (d, *J* = 6.6 Hz, 6H), 1.24 (t, *J* = 7.5 Hz, 3H), 0.28 (s, 9H)

### 4.5.3 Removal of Silicon Protecting Groups

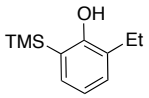
**General procedure for removal of *N*-isopropylcarbamate**

In a flame-dried round bottom flask under a positive pressure of argon, the starting material (0.92 mmol) was dissolved in freshly distilled acetonitrile (10 mL) and DBU (0.21 g, 1.38 mmol) and diethylamine (0.11, 1.11 mmol) were added. The reaction was heated to 40 °C for 45 min and then cooled to room temperature. TMSCl (0.18 mL, 1.38 mmol) was added dropwise and the mixture was stirred until the reaction was complete as determined by TLC (4:1 hexanes:EtOAc eluent). When complete, the solution was diluted with $Et_2O$ (20 mL). The organic phase was washed with saturated sodium bicarbonate (2 x 10 mL) and with 10% sodium hydroxide (2 x 10 mL). The organic phase was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*.

**General procedure for removal of *N,N*-diethylcarbamate**

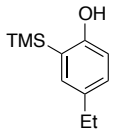
In a glovebox, the Schwartz reagent (1.54 g, 5.96 mmol) was added to a flame-dried round bottom flask equipped with a stir bar. In a separate flame-dried round bottom flask under a positive pressure of argon, the starting material (1.99 mmol) was dissolved in freshly distilled THF (20 mL) and stirred for 10 min. The solution was transferred to the flask with the Schwartz reagent via cannula. The reaction was stirred at room temperature until complete, determined by TLC (4:1 hexanes:EtOAc eluent). When complete, the reaction was quenched with 2M HCl. The solution was extracted with $Et_2O$ (3 x 15 mL), and the combined organic

phases were washed with brine (1 x 15 mL). The organic phase was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*.

**2-ethyl-6-trimethylsilylphenol, 4.7a:** 


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.24 (app dd, *J* = 7.2, 2.0 Hz, 1H), 7.17 (app d, *J* = 7.2 Hz, 1H), 6.91 (app t, *J* = 7.2 Hz, 1H), 4.82 (s, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.78 (t, *J* = 7.6 Hz, 3H), 0.32 (s, 9H); IR ($CDCl_3$, cast) 3613, 3575, 3056, 2964, 2899, 1576, 1426 $cm^{-1}$; HRMS (EI, $[M]^{\bullet+}$) for $C_{11}H_{18}OSi$ calcd 194.1127; found, m/z 194.1128.

These data matched those previously reported for 2-ethyl-6-trimethylsilylphenol.[93]

**4-ethyl-2-trimethylsilylphenol, 4.7b:** 


$^1$H NMR (400 MHz, $CDCl_3$) δ 7.17 (app d, *J* = 2.0 Hz, 1H), 7.07 (app dd, *J* = 8.0, 2.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H), 0.31 (s, 9H)

### 4.5.4 Synthesis of Benzyne Precursor

In a flame-dried round bottom flask under a positive pressure of argon, the starting material (1.26 mmol) was dissolved in $CH_2Cl_2$ (12 mL) and triethylamine (0.19 mL, 1.39 mmol) was added. The reaction was stirred for 10 min and TMSCl (0.17 mL, 1.39 mmol) was added dropwise. The reaction was stirred at room

temperature until complete, as determined by TLC (4:1 hexanes:EtOAc eluent). When complete, the reaction was diluted with water (10 mL) and extracted with $CH_2Cl_2$ (3 x 10 mL), and the combined organic phases were washed with brine (1 x 10 mL). The organic phase was dried over anhydrous $MgSO_4$, and concentrated *in vacuo*.

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# Chapter 5

## Conclusions and Future Directions

*"The important thing is not to stop questioning.*
*Curiosity has its own reason for existing."*
*-Albert Einstein*

The overall goal of the work described in this thesis was to demonstrate that canola oil could be used as a renewable source of carbon in the synthesis of value-added materials. This unique approach to the synthesis of aliphatic terminal alkynes opens the door for a modular approach to a variety of more complex organic scaffolds. While the original focus of this project was to build monomers for the synthesis of organic polymer electronics, the lessons learned throughout the work can be applied to various other syntheses. Herein, this Chapter will provide a summary of the work discussed, as well as provide some potential future directions.

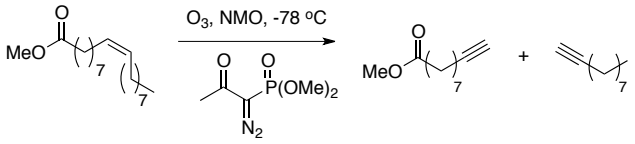
## 5.1 Oxidative Cleavage of FAMEs-Chapter 2

### 5.1.1 Conclusions

After surveying several oxidative cleavage methods, it became apparent that isolation of the corresponding aliphatic aldehydes from fatty acid methyl esters (FAMEs) was impractical and poor yielding. To overcome this obstacle, a method to combine the oxidative cleavage with the subsequent dibromoolefination reaction was developed. The coupling of ozonolysis with dibromoolefination was optimised and then applied to a number of different internal olefins including the three unsaturated FAMEs that comprise canola oil, resulting in a series of dibromoolefins. This Chapter outlined one of the few examples of an ozonolysis reaction coupled to a carbon-carbon bond forming reaction.

### 5.1.2 Future Work

In this work, only one type of reaction was coupled to the ozonolysis: dibromoolefination. However, this reaction proceeds by the reaction of a phosphorous ylide with an aldehyde, a mechanism not unique to dibromoolefination. It therefore stands to reason that it would be possible to use analogous phosphorous ylides. A recent publication by Willand-Charnley and Dussault demonstrated the Wittig and the Horner-Wadsworth-Emmons reactions can be successfully coupled with ozonolysis.[1] Notably absent from their examples is the synthesis of alkynes through the Seyforth-Gilbert (or Bestmann-Ohira modification) reaction. Because of this thesis's focus on the synthesis of alkynes, this would be a reasonable extension of the current work (Scheme 5.1). This would result in a significant reduction in the number of synthetic steps required to make terminal alkynes.




**Scheme 5.1: Proposed tandem ozonolysis-Bestmann-Ohira reaction to produce terminal alkynes.**

## 5.2 Synthesis of Terminal Alkynes-Chapter 3

### 5.2.1 Conclusions

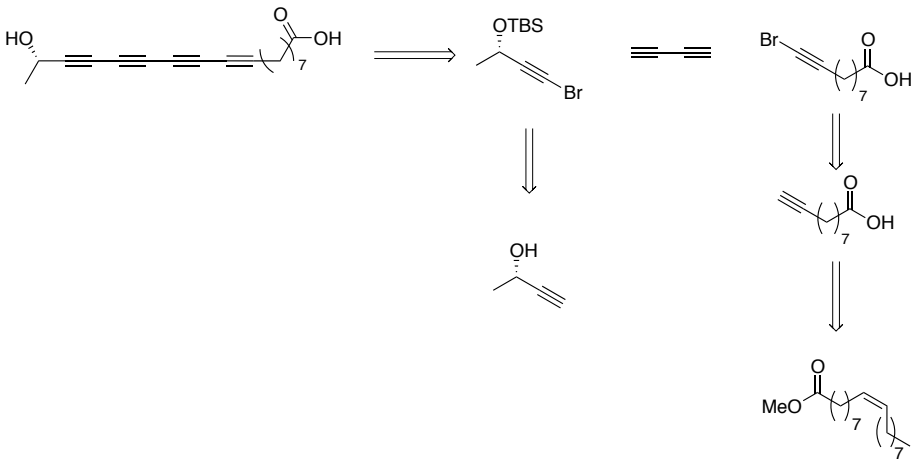
This Chapter presented the synthesis of a series of terminal alkynes, both from pure fatty acid methyl esters, as well as store-bought canola oil. These alkynes contained valuable functional groups that would allow for further manipulation, making them well-suited as chemical building blocks. To demonstrated their utility in the synthesis

of more complex organic framework, preliminary results on their cyclotrimerisation were discussed.

### 5.2.2 Future Work

The synthesis of trisubstituted aromatic rings remains an incomplete part of this project. Given the positive preliminary results, a full study with complete characterisation of the aromatic rings is warranted.

One of the most promising alkynes synthesised in this Chapter was decynoic acid. What makes this alkyne so interesting is its use in the total synthesis of minquartynoic acid: a natural product that has promising anti-tumor and anti-HIV activity.[2,3] Using decynoic acid synthesised from canola oil in the synthesis of minquartynoic acid, 50% of the carbon mass of this polyyne would be from a renewable starting material (Scheme 5.2).




**Scheme 5.2: Retrosynthetic analysis of (-)-minquartynoic acid.**

### 5.3 Making Benzyne from Alkyl Substituted Aromatic Rings-Chapter 4

#### 5.3.1 Conclusions

This Chapter addressed the synthesis of benzyne from a number of alkyl-substituted phenols, serving as model compounds for the aromatic rings made from canola oil alkynes. While benzyne itself was not synthesised in this work, one of its precursors, *o*-(trimethylsilyl)-4-ethylphenyl trimethylsilanol was successfully synthesised.

#### 5.3.2 Future Work

The next step for this aspect of the project is to actually synthesise benzyne from the model phenols, and to use benzyne to make 9-fluorenone: one of the target molecules of the present study. After making 9-fluorenone, it would be possible to synthesise a series of oligomers to study the impact of alkyl substitution on the fluorenone backbone on its electronic properties.

### 5.4 The Path Forward for Canola Oil Materials and Sustainable Development

In a climate where sustainability is common topic of discussion, and the limitation and environmental impact of petroleum resources has become a front-runner of concerns plaguing modern society, canola oil offers a potential solution to some concerns. Compared with other plant oils, the high unsaturated content of canola increases its utility in chemical manipulations like those described in this thesis; however, chemical methods developed to manipulate canola oil are not limited to only this oil, but can be readily applied to any unsaturated oil. The production of canola as a carbon feedstock requires a low energy input and it is high yielding,

increasing its attractiveness. Canola's low oxygen content compared with other renewable carbon sources also make it well-suited for the production of hydrocarbon materials.

While the work presented in this thesis is a step forward in sustainable development, there are a number of unanswered problems that keep this chemistry from being regarded as "green". First and foremost, this work was designed to use a renewable resource in current, well-established synthetic processes. These synthetic steps are all done in organic solvents, primarily dichloromethane, and under inert atmosphere. The most glaring challenge is the synthesis of alkynes. Existing methods for making alkynes are outlined in Chapter 3; none of these methods are atom-economical and all produce large quantities of waste, something that at an industrial scale would be significant. The major by-product of this type of plant oil chemistry is glycerol. The amount of glycerol being produced around the world has increased dramatically as the desire for biofuels has increased. The production of glycerol now outstrips its common uses. The recent report by the European Commission suggesting that rapeseed biodiesels fail the sustainability test is a poignant example of the numerous challenges faced in developing a more sustainable chemical industry.[4]

From a socio-economic perspective, one of the biggest concerns arises when considering the increasing acreage of usable farmland being dedicated to canola. As the profitability of the crop continues to grow, the amount of cropland being used for

food crops, such as wheat, decline. This will likely result in significant impacts on the availability and price of food globally.

Sustainable development is a problem that must be tackled socially, economically, and scientifically. Since the 18$^{th}$ century, we have shifted from the use of renewable natural resources to the use of petroleum resources; a shift that faciliated the industrial revolution and our current commodities-based consumer culture. This shift allowed for the growth of our global, specialised culture. It has resulted in the inextricable dependence on petroleum, and has had significant environmental and social impacts. Because of this, it would be naive to assume that sustainability is an issue that can be solved in 10 years by a small group of individuals in a single field. The work presented in this thesis represents one small piece of the solution, one small contribution that will hopefully inspire more questions, more creativity, more curiosity and further the drive toward a more sustainable culture.

## 5.5 References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# Appendix A

## GC-MS data for methyl oleate from refined canola oil

Area Percent Report

Data File : F:\20130516\0801001.D Vial: 8
Acq On : 17 May 20113 8:5 Operator: WDM
Sample : BROWN BAB6-70B NEAT Inst : GCMS1
Misc : Multiplr: 1.00
Sample Amount: 0.00
MS Integration Params: autoint1.e

Method : C:\HPCHEM\1\METHODS\DEFAULT.M (Chemstation Integrator)
Title :

Signal : TIC

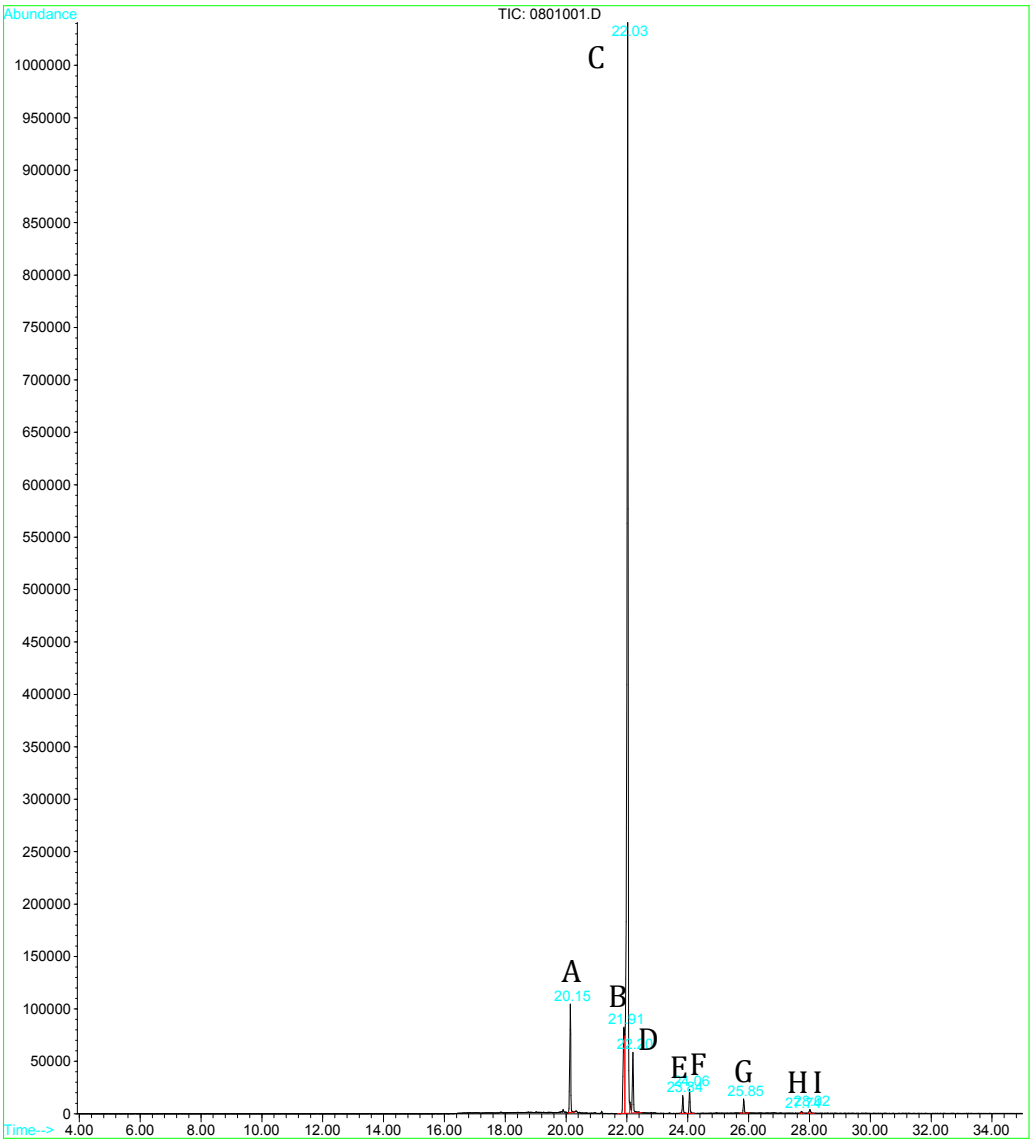
| peak # | R.T. min | first scan | max scan | last scan | PK TY | peak height | peak area | peak % max. | % of total |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 20.141 | 1416 | 1422 | 1432 | PV | 98590 | 2437822 | 8.40% | 6.573% |
| 2 | 21.904 | 1558 | 1576 | 1579 | BV 2 | 82000 | 2821001 | 9.72% | 7.606% |
| 3 | 22.029 | 1579 | 1587 | 1593 | VV 2 | 1004568 | 29023277 | 100.00% | 78.254% |
| 4 | 22.200 | 1598 | 1602 | 1625 | VB | 56462 | 1406665 | 4.85% | 3.793% |
| 5 | 23.847 | 1737 | 1746 | 1759 | PV 2 | 16562 | 410203 | 1.41% | 1.106% |
| 6 | 24.064 | 1759 | 1765 | 1775 | PV | 23254 | 527520 | 1.82% | 1.422% |
| 7 | 25.850 | 1911 | 1921 | 1932 | BV | 12452 | 291095 | 1.00% | 0.785% |
| 8 | 27.731 | 2082 | 2086 | 2093 | 7 | 1786 | 51636 | 0.18% | 0.139% |
| 9 | 28.017 | 2104 | 2111 | 2123 | BV 2 | 3499 | 119237 | 0.41% | 0.321% |

Sum of corrected areas: 37088456

0801001.D DEFAULT.M Fri May 17 11:03:36 2013

- Sample obtained from methyl oleate from canola oil
- Chromatographs shown on pages 132 and 133
- Total of 9 peaks eluted; relative percentages reported under "% total"
- The corresponding mass spectra for each peak are presented on pages 134 to 142

File : F:\20130516\0801001.D
Operator : WDM
Acquired : 17 May 20113 8:5 using AcqMethod GCMS-DB5
Instrument : GCMS1
Sample Name: BROWN BAB6-70B NEAT
Misc Info :
Vial Number: 8



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Operator   : WDM
Acquired   : 17 May 20113   8:5     using AcqMethod GCMS-DB5
Instrument :   GCMS1
Sample Name: BROWN BAB6-70B NEAT
Misc Info  :
Vial Number: 8
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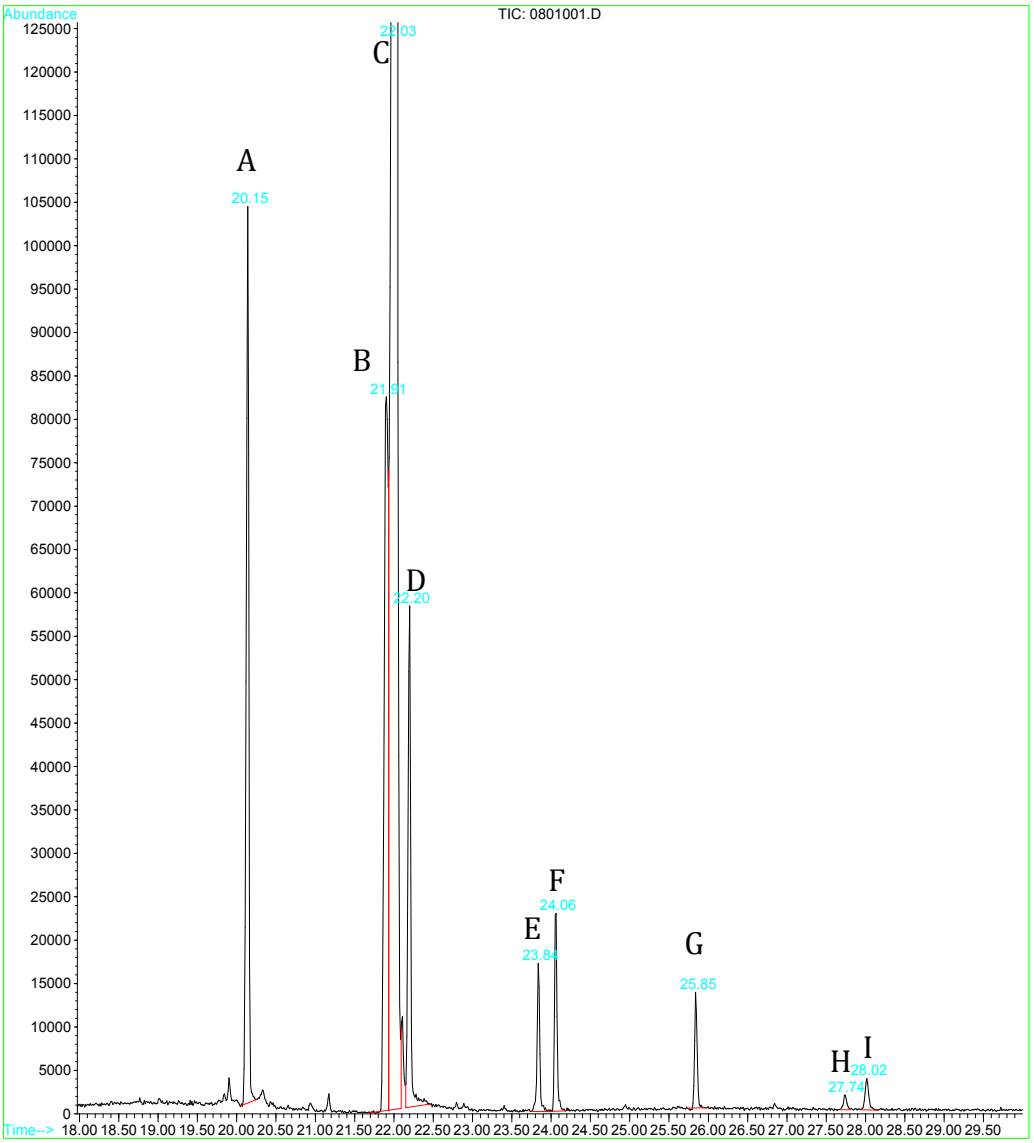
Expanded view of chromatograph



# Mass Spectrum of Peak A and Library Matches

** Search Report Page 1 of 1 **

Unknown: Scan 1422 (20.141 min): 0801001.D
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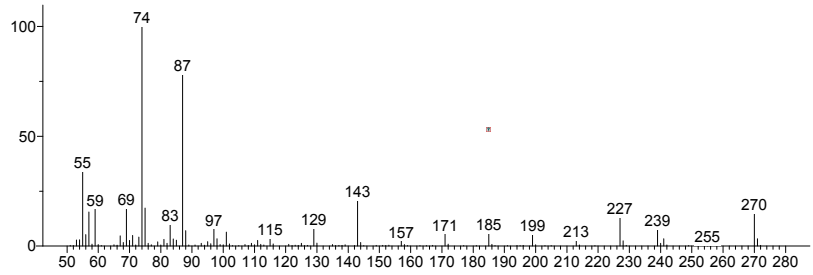
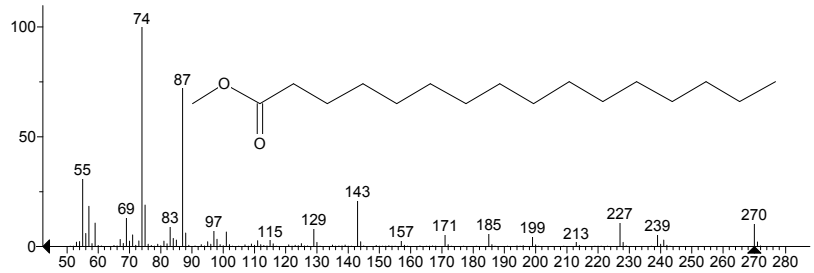
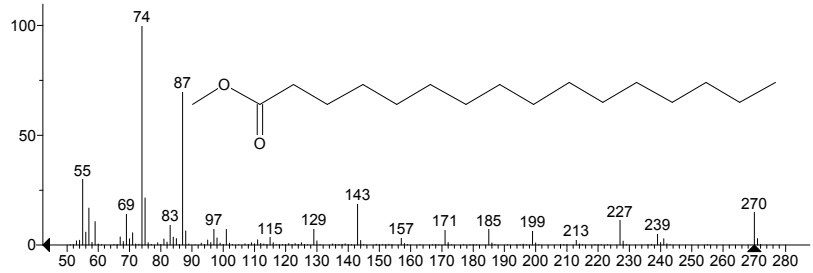



Hit 1 : Hexadecanoic acid, methyl ester
C17H34O2; MF: 931; RMF: 932; Prob 82.0%; CAS: 112-39-0; Lib: mainlib; ID: 40690.




Hit 2 : Hexadecanoic acid, methyl ester
C17H34O2; MF: 927; RMF: 928; Prob 82.0%; CAS: 112-39-0; Lib: replib; ID: 9770.



# Mass Spectrum of Peak B and Library Matches

** Search Report Page 1 of 1 **

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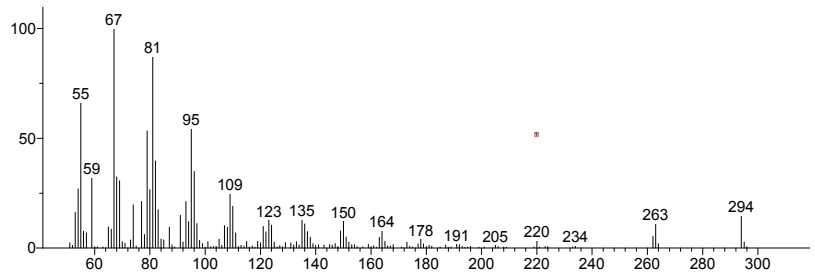
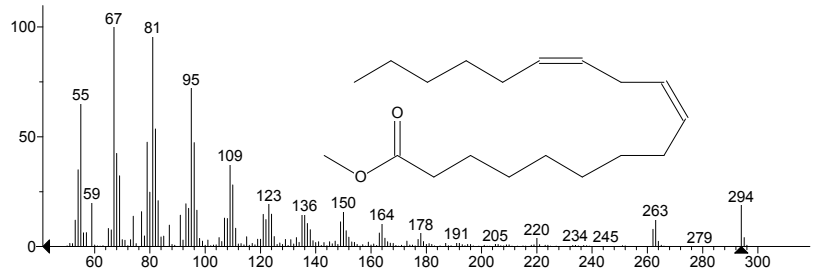
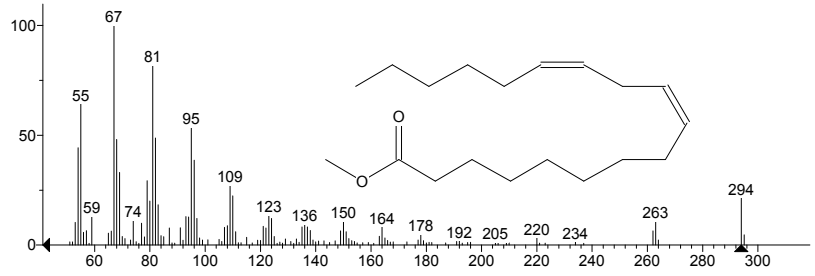
Compound in Library Factor = -107




Hit 1 : 9,12-Octadecadienoic acid (Z,Z)-, methyl ester
C19H34O2; MF: 926; RMF: 926; Prob 26.4%; CAS: 112-63-0; Lib: mainlib; ID: 30167.




Hit 2 : 9,12-Octadecadienoic acid (Z,Z)-, methyl ester
C19H34O2; MF: 913; RMF: 923; Prob 26.4%; CAS: 112-63-0; Lib: replib; ID: 7669.



# Mass Spectrum of Peak C and Library Matches

** Search Report Page 1 of 1 **

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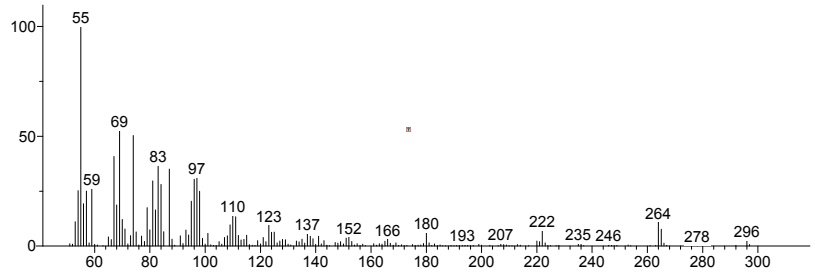


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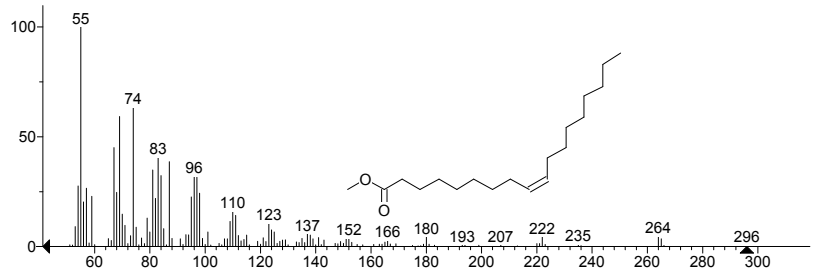


Hit 2 : 9-Octadecenoic acid, methyl ester, (E)-
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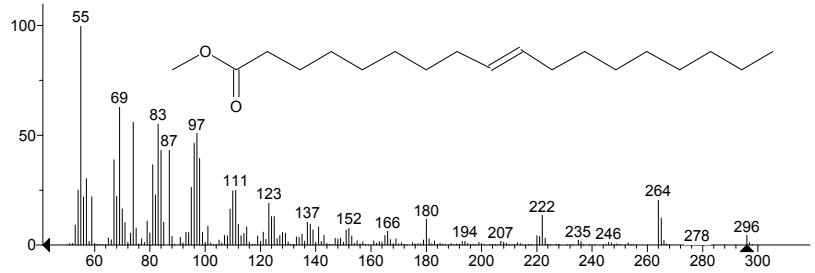

# Mass Spectrum of Peak D and Library Matches

** Search Report Page 1 of 1 **

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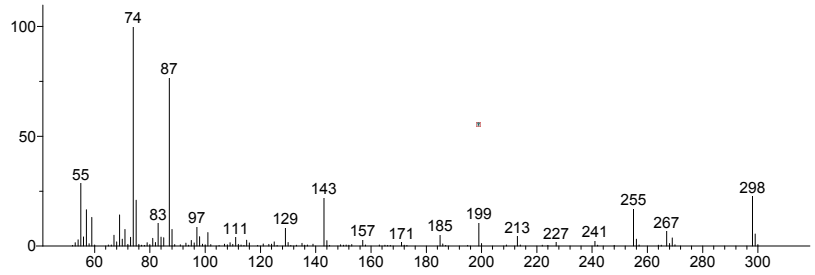
Compound in Library Factor = 103

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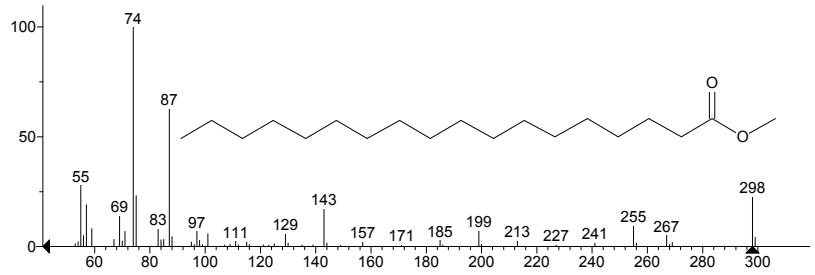


Hit 2 : Methyl stearate
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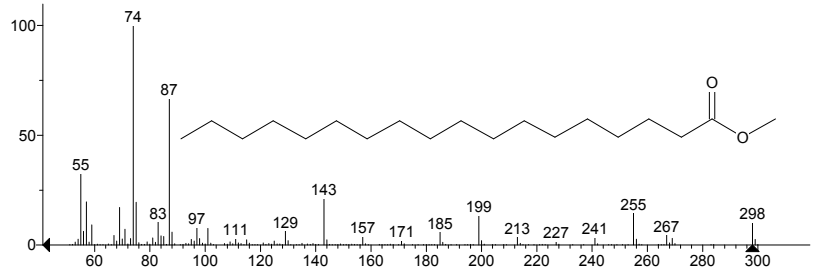

# Mass Spectrum of Peak E and Library Matches



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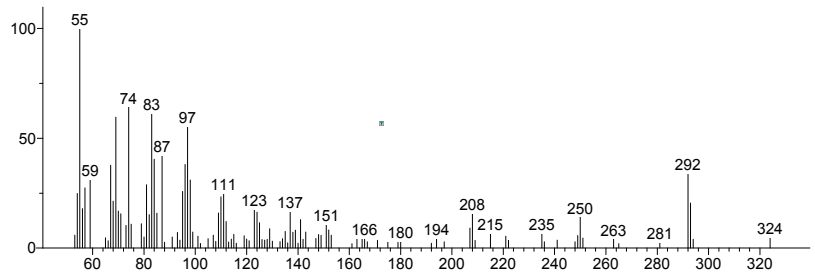
Compound in Library Factor = -118




Hit 1 : cis-11-Eicosenoic acid, methyl ester
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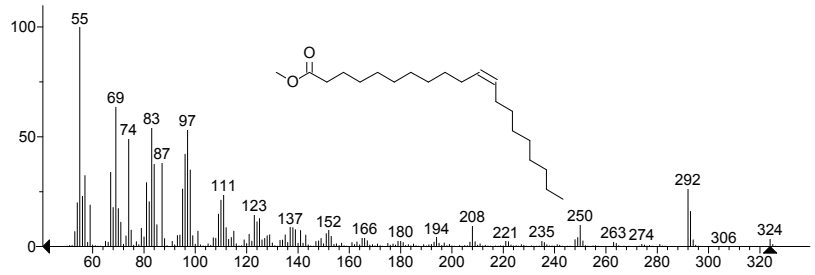


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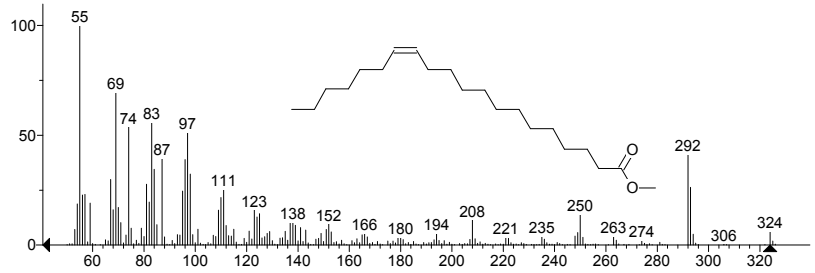

# Mass Spectrum of Peak F and Library Matches

** Search Report Page 1 of 1 **

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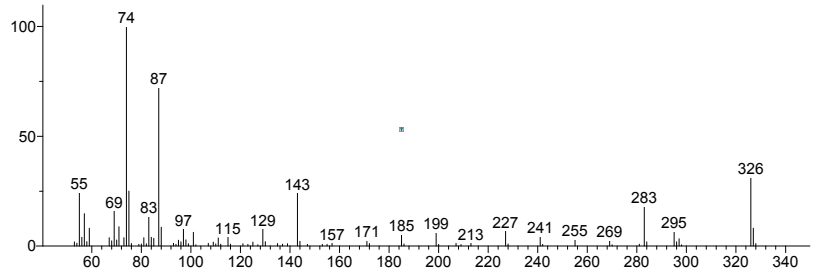


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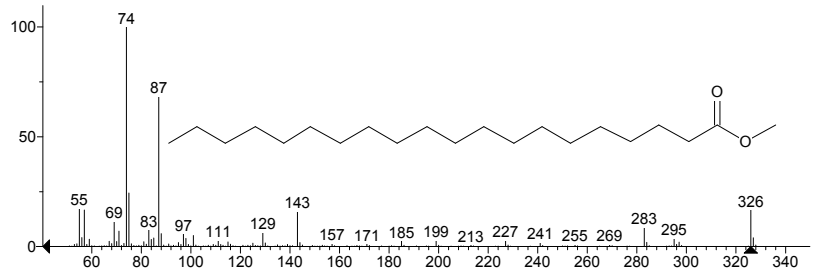


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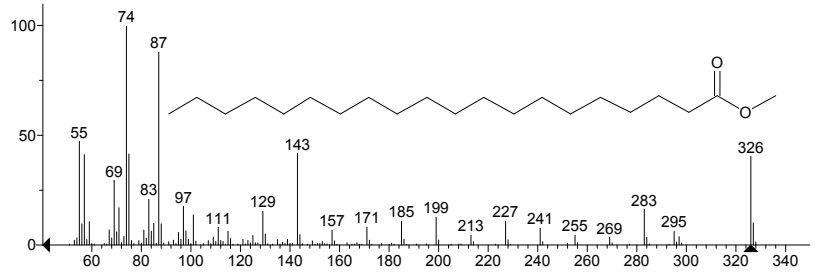

# Mass Spectrum of Peak G and Library Matches

** Search Report Page 1 of 1 **

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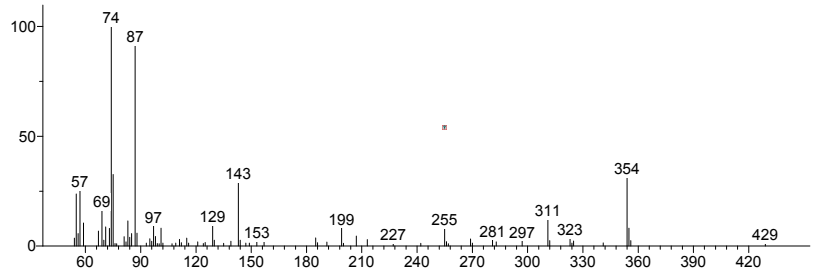


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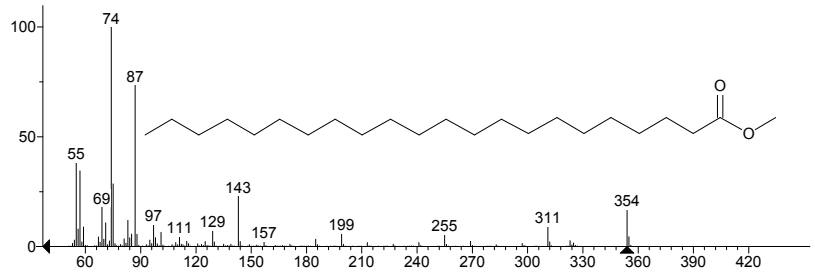


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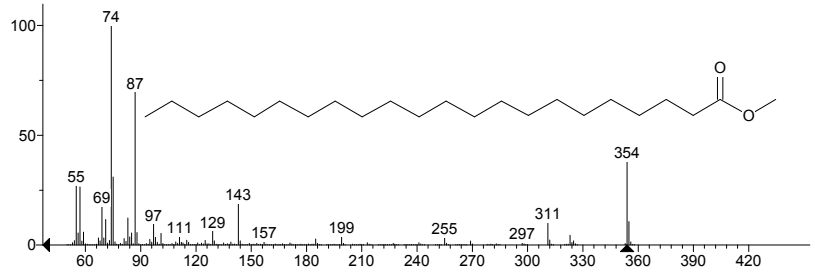
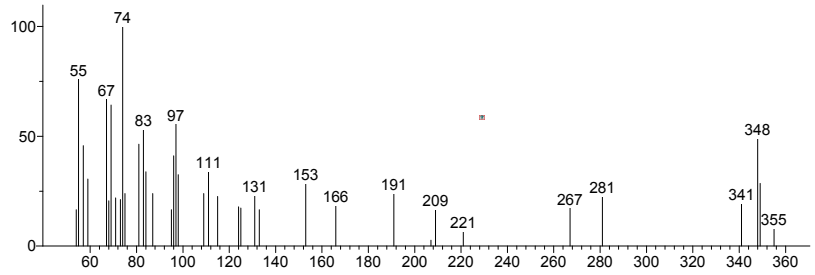


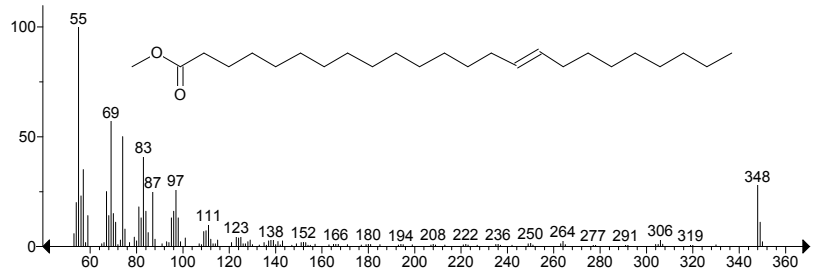
# Mass Spectrum of Peak H and Library Matches

** Search Report Page 1 of 1 **

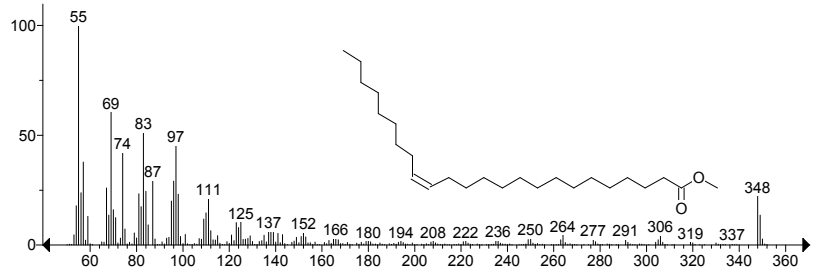
Unknown: Scan 2086 (27.731 min): 0801001.D
Compound in Library Factor = -1230




Hit 1 : 15-Tetracosenoic acid, methyl ester
C25H48O2; MF: 571; RMF: 659; Prob 60.8%; CAS: 56554-33-7; Lib: mainlib; ID: 17829.



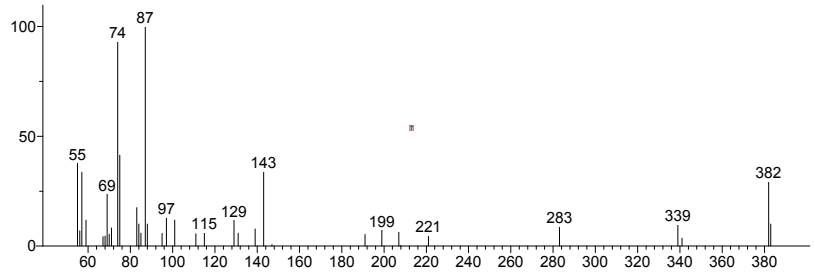

Hit 2 : 15-Tetracosenoic acid, methyl ester, (Z)-
C25H48O2; MF: 546; RMF: 571; Prob 18.5%; CAS: 2733-88-2; Lib: replib; ID: 4753.



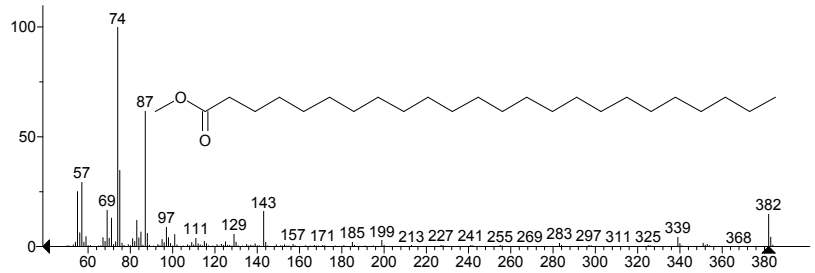
# Mass Spectrum of Peak I and Library Matches



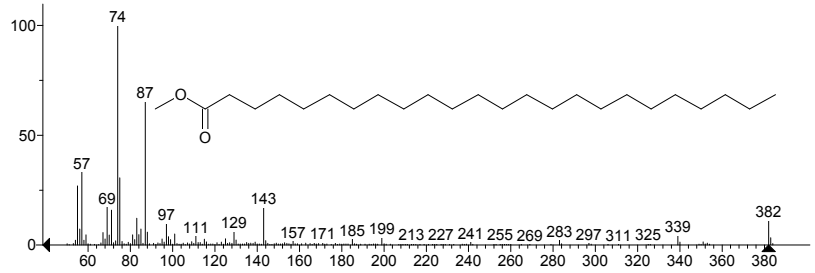
Unknown: Scan 2111 (28.017 min): 0801001.D
Compound in Library Factor = -150




Hit 1 : Tetracosanoic acid, methyl ester
C25H50O2; MF: 755; RMF: 774; Prob 80.8%; CAS: 2442-49-1; Lib: mainlib; ID: 40715.

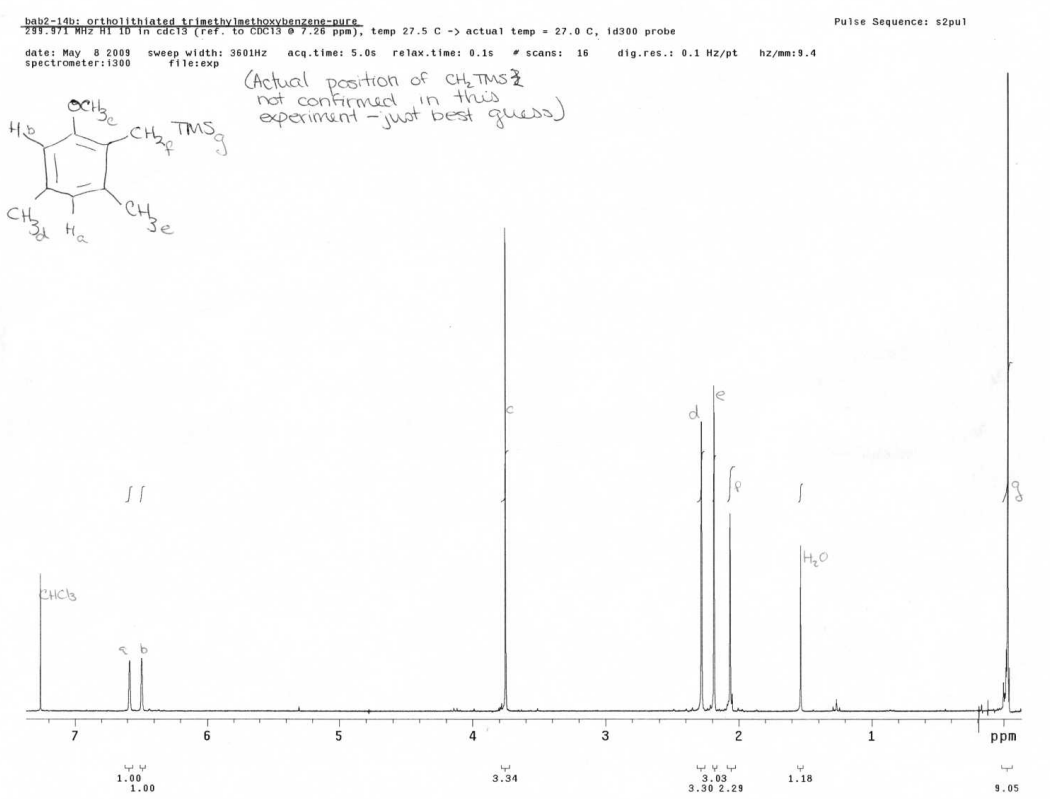


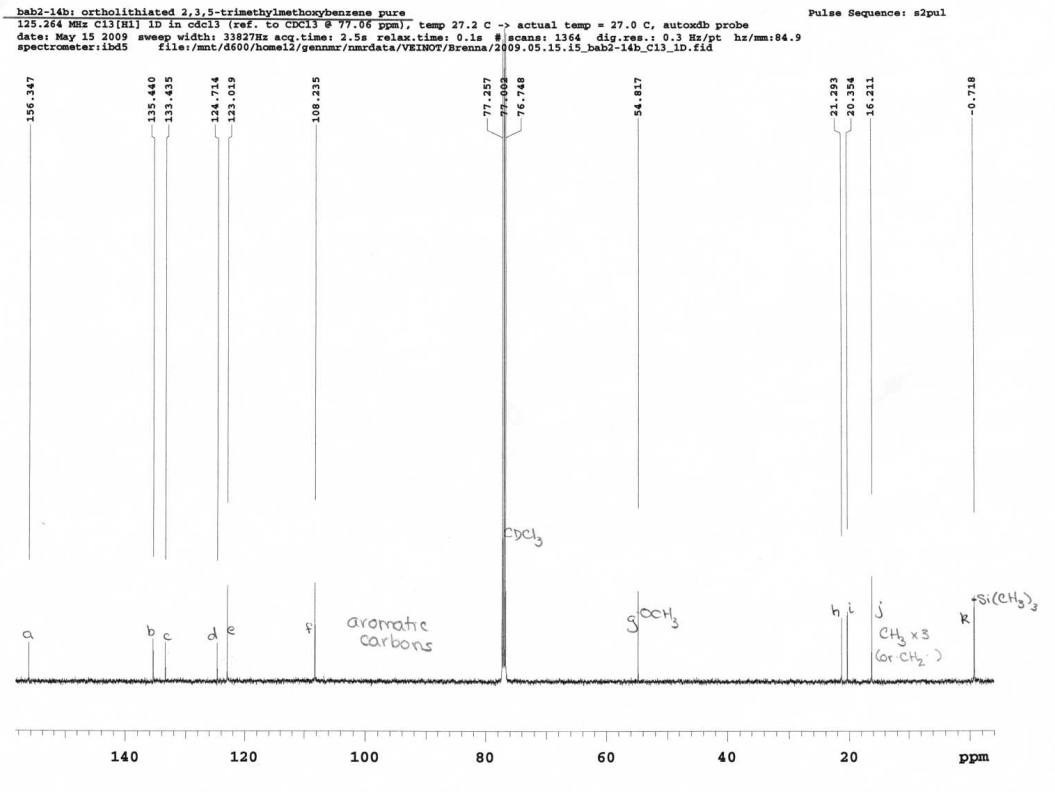

Hit 2 : Tetracosanoic acid, methyl ester
C25H50O2; MF: 674; RMF: 682; Prob 80.8%; CAS: 2442-49-1; Lib: replib; ID: 9814.



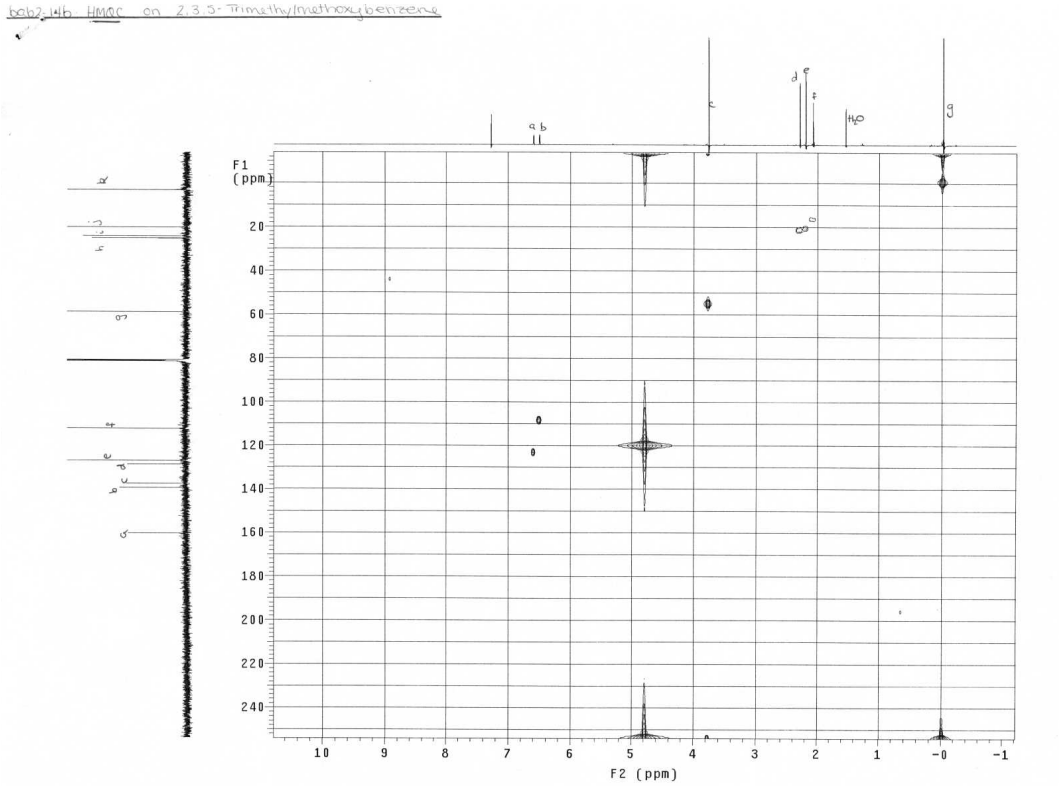
# Appendix B

## Full NMR characterisation data for compounds 4.34, 4.35a and b


bab2-14b: ortholithiated trimethylmethoxybenzene-pure
299.971 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, id300 probe
Pulse Sequence: s2pul
date: May 8 2009 sweep width: 3601Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:9.4
spectrometer:i300 file:exp
(Actual position of CH2TMS not confirmed in this experiment - just best guess)
CHCl3
H2O
ppm
1.00
1.00
3.34
3.03
3.30 2.29
1.18
9.05


bab2-14b: ortholithiated 2,3,5-trimethylmethoxybenzene pure
125.264 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.2 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
date: May 15 2009 sweep width: 33827Hz acq.time: 2.5s relax.time: 0.1s # scans: 1364 dig.res.: 0.3 Hz/pt hz/mm:84.9
spectrometer:ibd5 file:/mnt/d600/home12/gennmr/nmrdata/VEINOT/Brenna/2009.05.15.i5_bab2-14b_C13_1D.fid
156.347
135.440
133.435
124.714
123.019
108.235
77.257
77.002
76.748
54.817
21.293
20.354
16.211
-0.718
CDCl3
aromatic carbons
OCH3
CH3 x3 (or CH2)
Si(CH3)3
ppm

bab2-14b HMBC on 2,3,5-Trimethylmethoxybenzene



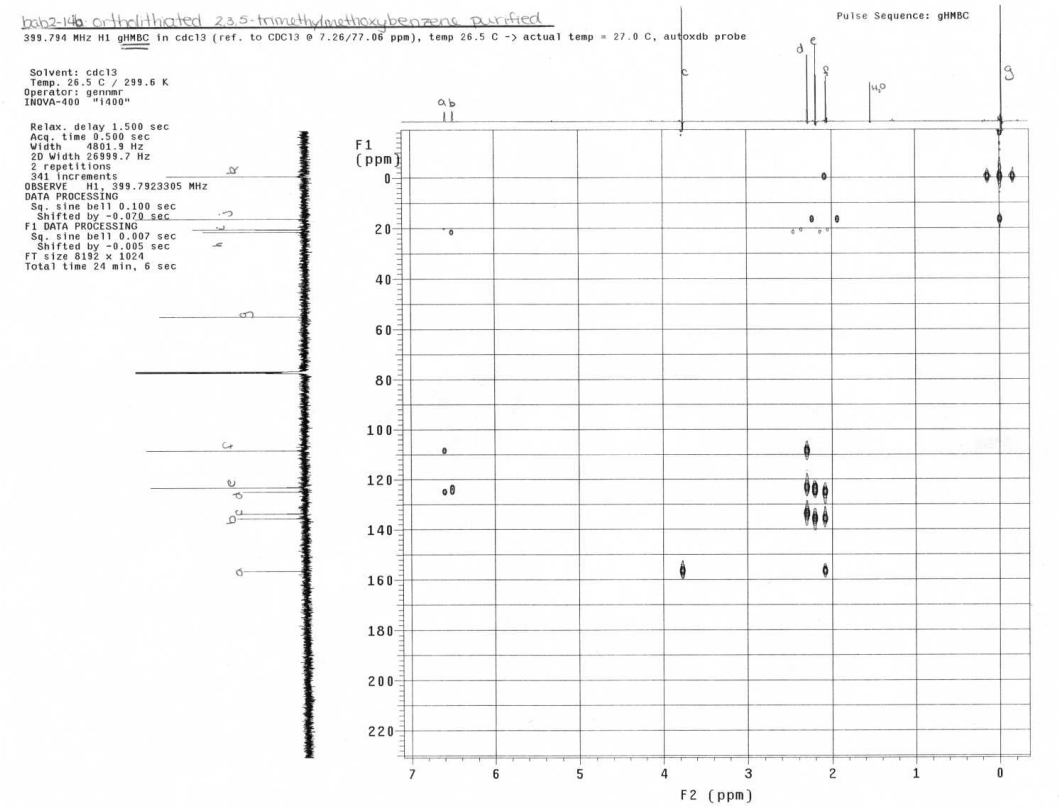

bab2-14b orthlithiated 2,3,5-trimethylmethoxybenzene purified

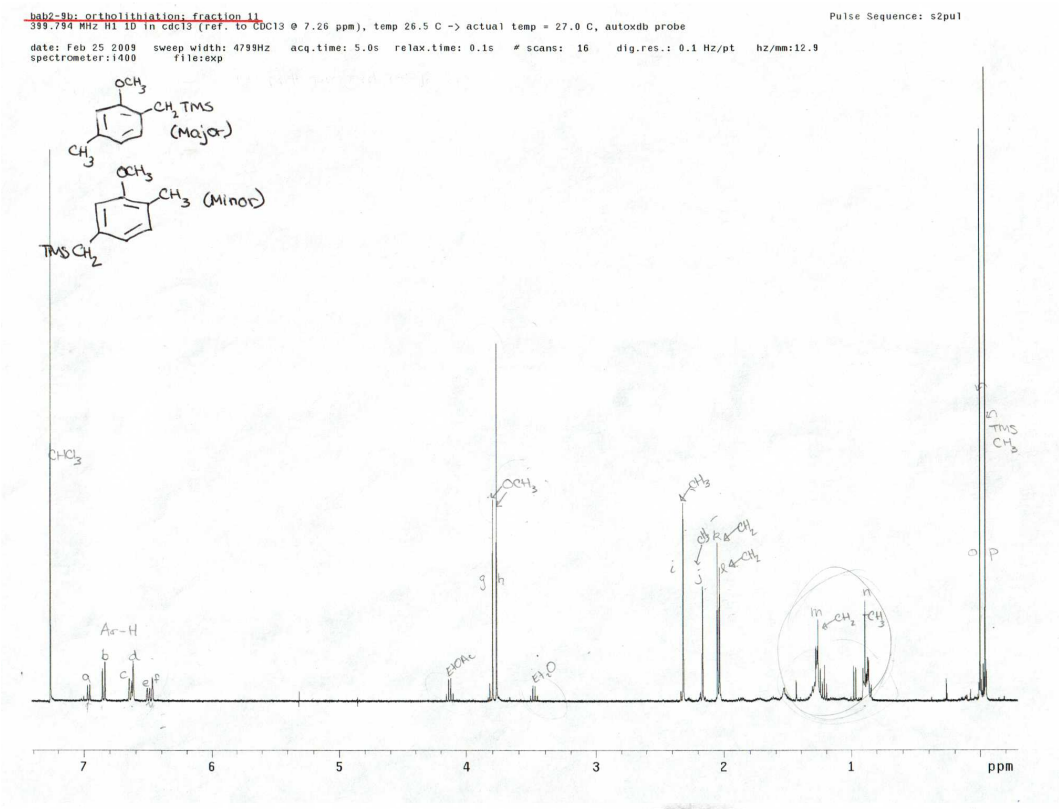
399.794 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe

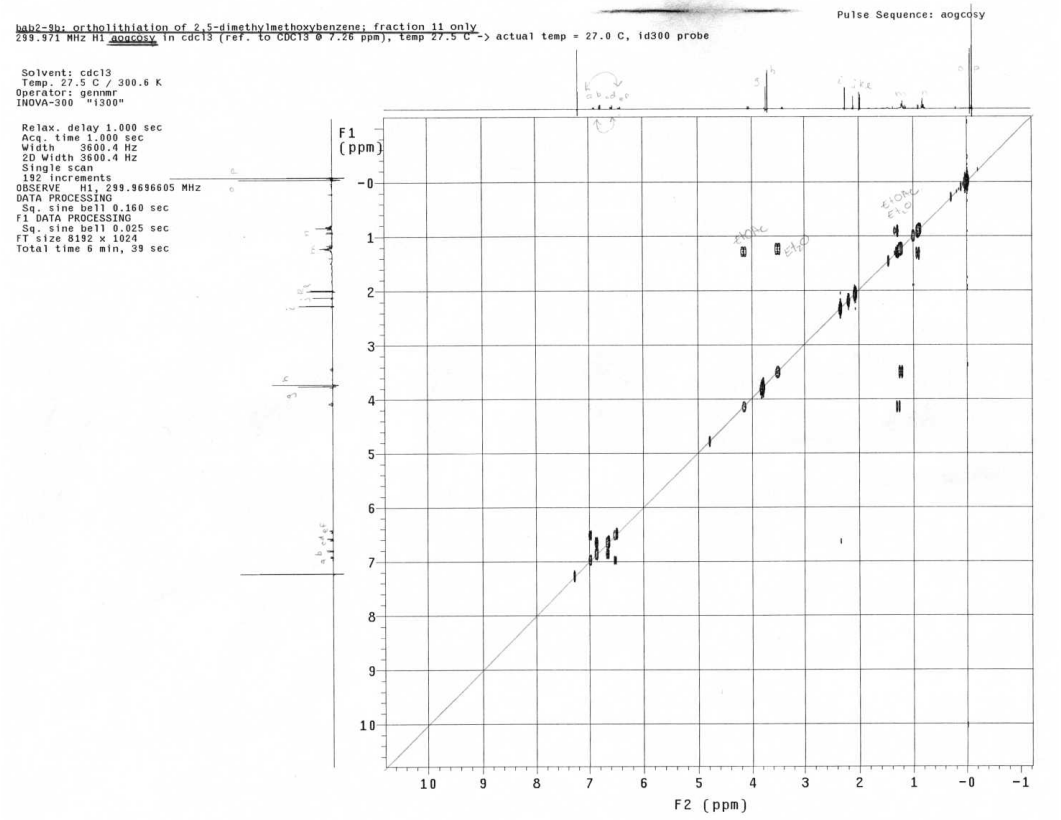
Pulse Sequence: gHMBC

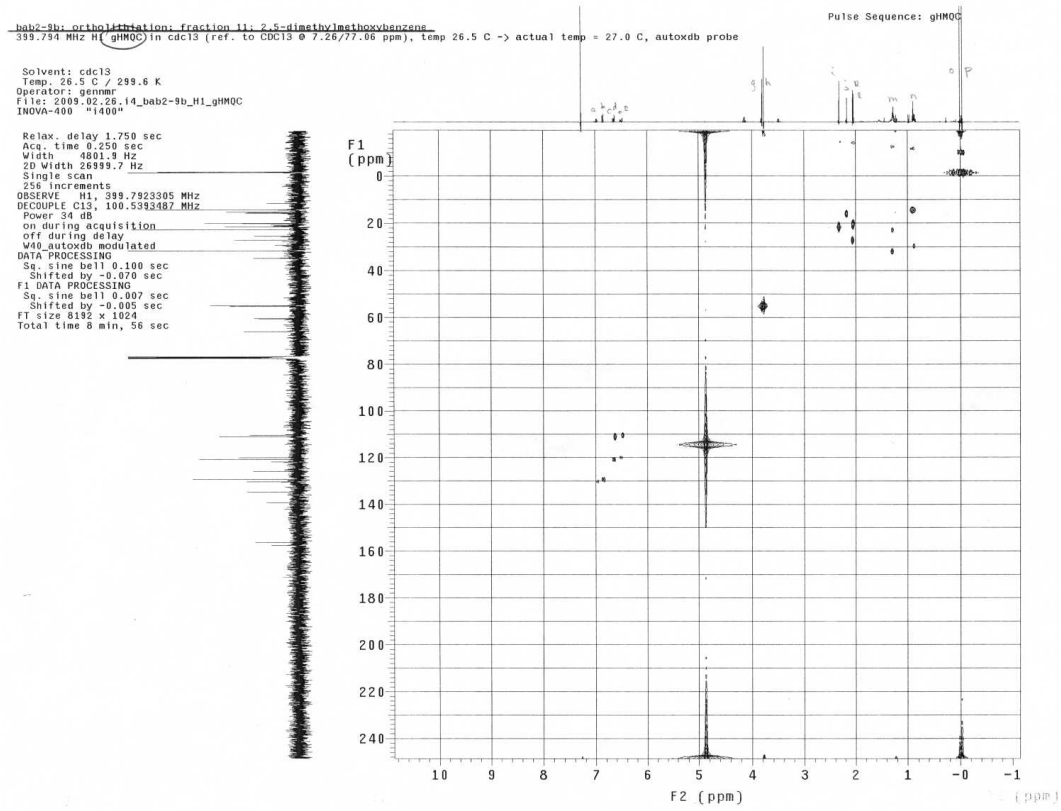
Solvent: cdcl3
Temp. 26.5 C / 299.6 K
Operator: genmmr
INOVA-400 "i400"

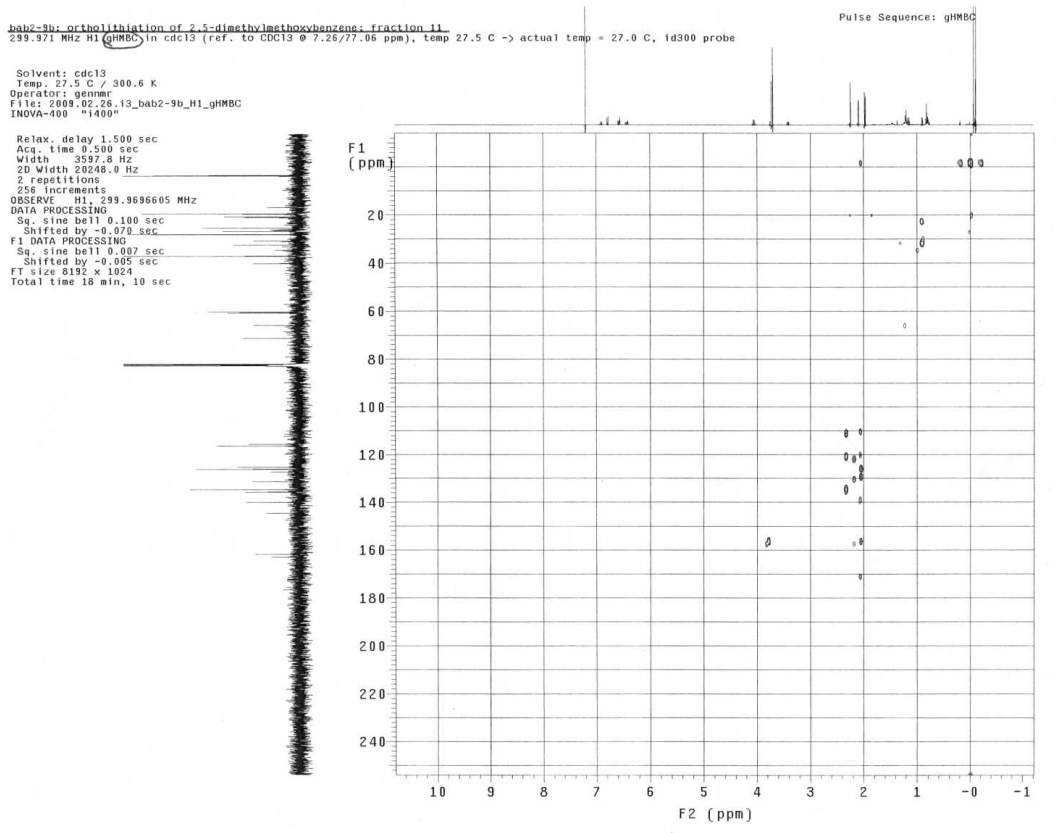
Relax. delay 1.500 sec
Acq. time 0.500 sec
Width 4801.9 Hz
2D Width 26999.7 Hz
2 repetitions
341 increments
OBSERVE H1, 399.7923305 MHz
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.007 sec
Shifted by -0.005 sec
FT size 8192 x 1024
Total time 24 min, 6 sec

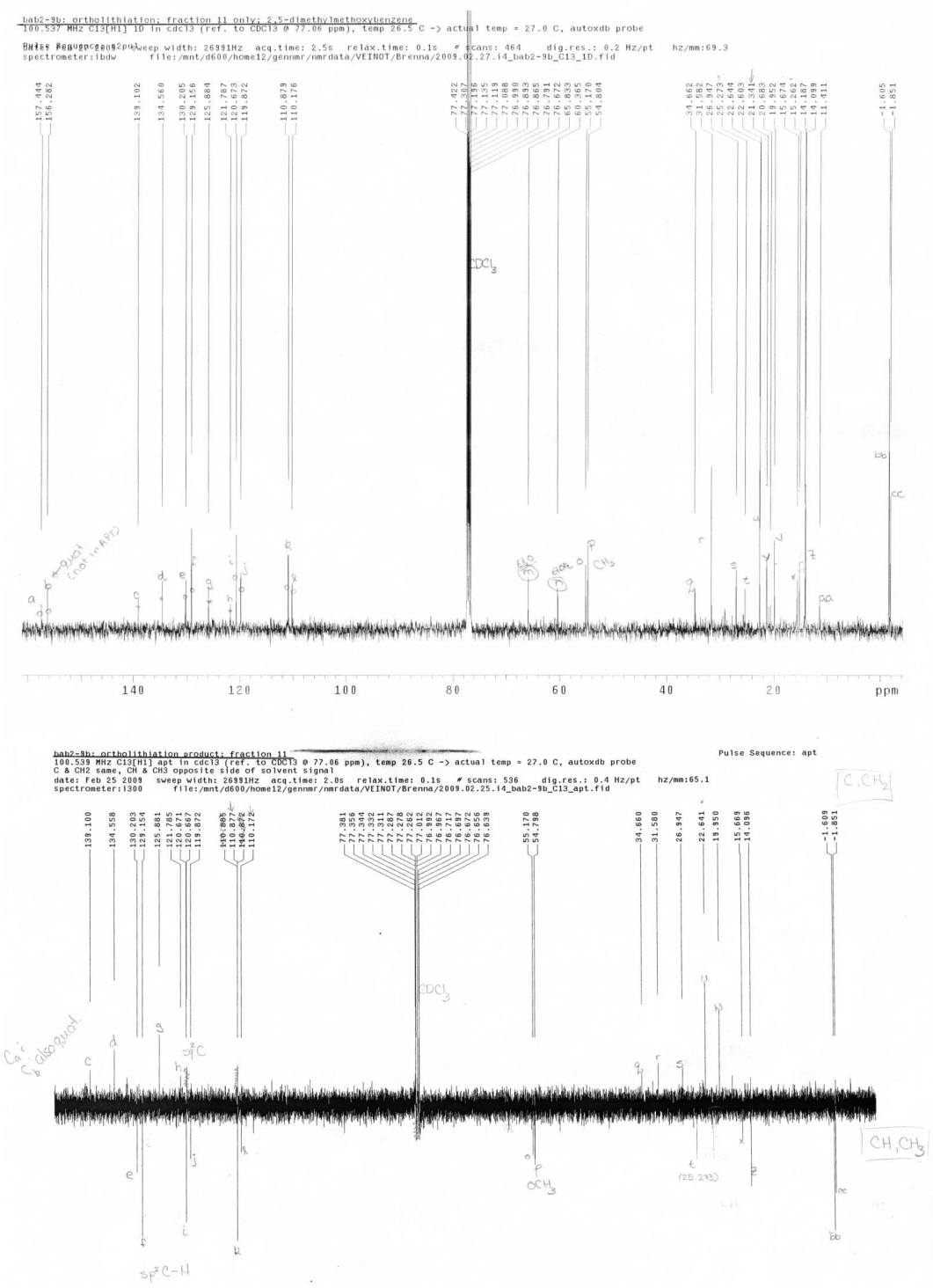



bab2-9b: ortholithiation; fraction 11
399.794 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
date: Feb 25 2009 sweep width: 4789Hz acq.time: 5.0s relax.time: 0.1s # scans: 16 dig.res.: 0.1 Hz/pt hz/mm:12.9
spectrometer:i400 file:exp
OCH3
CH2TMS
(Major)
CH3
OCH3
CH3 (Minor)
TMSCH2
CHCl3
Ar-H
a
b
d
c
e
f
EtOAc
Et2O
OCH3
g
h
CH3
i
j
k
CH2
CH2
l
m
CH2
CH3
n
o
p
TMS
CH3
7
6
5
4
3
2
1
ppm


bab2-9b: ortholithiation of 2,5-dimethylmethoxybenzene; fraction 11 only
299.971 MHz H1 aogcosy in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, id300 probe
Pulse Sequence: aogcosy
Solvent: cdcl3
Temp. 27.5 C / 300.6 K
Operator: genmmr
INOVA-300 "i300"
Relax. delay 1.000 sec
Acq. time 1.000 sec
Width 3600.4 Hz
2D Width 3600.4 Hz
Single scan
192 increments
OBSERVE H1, 299.9696605 MHz
DATA PROCESSING
Sq. sine bell 0.160 sec
F1 DATA PROCESSING
Sq. sine bell 0.025 sec
FT size 8192 x 1024
Total time 6 min, 39 sec
F1 (ppm)
F2 (ppm)
EtOAc
Et2O


bab2-9b: ortholithiation: fraction 11: 2,5-dimethylmethoxybenzene
399.794 MHz H1 gHMQC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: gHMQC
Solvent: cdcl3
Temp. 26.5 C / 299.6 K
Operator: genmmr
File: 2009.02.26.i4_bab2-9b_H1_gHMQC
INOVA-400 "i400"
Relax. delay 1.750 sec
Acq. time 0.250 sec
Width 4801.9 Hz
2D Width 26999.7 Hz
Single scan
256 increments
OBSERVE H1, 399.7923305 MHz
DECOUPLE C13, 100.5393487 MHz
Power 34 dB
on during acquisition
off during delay
W40_autoxdb modulated
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.007 sec
Shifted by -0.005 sec
FT size 8192 x 1024
Total time 8 min, 56 sec
F1 (ppm)
F2 (ppm)


bab2-9b: ortholithiation of 2,5-dimethylmethoxybenzene: fraction 11
299.971 MHz H1 gHMBC in cdcl3 (ref. to CDCl3 @ 7.26/77.06 ppm), temp 27.5 C -> actual temp = 27.0 C, id300 probe
Pulse Sequence: gHMBC
Solvent: cdcl3
Temp. 27.5 C / 300.6 K
Operator: genmmr
File: 2009.02.26.i3_bab2-9b_H1_gHMBC
INOVA-400 "i400"
Relax. delay 1.500 sec
Acq. time 0.500 sec
Width 3597.8 Hz
2D Width 20248.0 Hz
2 repetitions
256 increments
OBSERVE H1, 299.9696605 MHz
DATA PROCESSING
Sq. sine bell 0.100 sec
Shifted by -0.070 sec
F1 DATA PROCESSING
Sq. sine bell 0.007 sec
Shifted by -0.005 sec
FT size 8192 x 1024
Total time 18 min, 10 sec
F1 (ppm)
F2 (ppm)


bab2-9b: ortholithiation; fraction 11 only; 2,5-dimethylmethoxybenzene
100.537 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe
Pulse Sequence: s2pul
date: Feb 25 2009 sweep width: 26991Hz acq.time: 2.5s relax.time: 0.1s # scans: 464 dig.res.: 0.2 Hz/pt hz/mm:69.3
spectrometer:ibdw file:/mnt/d600/home12/gennmr/nmrdata/VEINOT/Brenna/2009.02.27.14_bab2-9b_C13_1D.fid
157.444
156.282
139.102
134.560
130.205
129.156
125.884
121.787
120.673
119.872
110.879
110.176
77.402
77.107
76.812
77.135
77.119
77.088
76.990
76.883
76.685
76.791
76.672
65.833
60.365
55.170
54.804
34.662
31.582
26.973
25.273
22.644
22.603
21.341
20.683
19.952
15.674
15.262
14.187
14.099
11.411
-1.605
-1.851
CDCl3
140
120
100
80
60
40
20
ppm
bab2-9b: ortholithiation product; fraction 11
Pulse Sequence: apt
100.539 MHz C13[H1] apt in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.5 C -> actual temp = 27.0 C, autoxdb probe
C & CH2 same, CH & CH3 opposite side of solvent signal
date: Feb 25 2009 sweep width: 26991Hz acq.time: 2.0s relax.time: 0.1s # scans: 536 dig.res.: 0.4 Hz/pt hz/mm:65.1
spectrometer:i300 file:/mnt/d600/home12/gennmr/nmrdata/VEINOT/Brenna/2009.02.25.14_bab2-9b_C13_apt.fid
139.100
134.558
130.203
129.154
125.881
121.785
120.671
120.667
119.872
140.005
110.877
110.672
110.172
77.381
77.356
77.344
77.332
77.311
77.287
77.278
77.262
77.012
76.992
76.817
76.717
76.697
76.672
76.656
76.639
55.170
54.798
34.660
31.580
26.947
22.641
19.950
15.669
14.096
-1.609
-1.851
CDCl3
C,CH2
CH,CH3
sp2C
sp2C-H
(25.232)