THE SEX PHEROMONE OF SPRUCE BUDWORM (CHORISTONEURA FUMIFERANA CLEM): SYNTHESIS OF STEREOISOMERIC MIXTURES OF 11-TETRADECENAL

By

Martin Barasa Maniafu

BSc (Hons), Jomo Kenyatta University of Agriculture and Technology, 1998

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Supervisor:          David I MaGee, PhD, Chemistry/Organic
Examining Board:    John Neville, PhD, Chemistry/Physical
                    Sara Eisler, PhD, Chemistry/Organic
                    David MacLean, PhD, Forestry/Ecology

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ABSTRACT

Eastern spruce budworm (*Choristoneura fumiferana* Clem) continues to be a major insect pest that devastates millions of hectares of spruce and fir trees in Canada. Its pheromone has successfully been used to monitor insect populations as an early warning tool for forest managers. However, its effectiveness at helping to control insect populations as part of an integrated pest management strategy has yet to be determined. The current costs associated with manufacturing the pheromone makes it economically prohibitive if large sectors of land need to be treated. In an effort to elucidate a more economical route, a stereoselective synthesis of a mixture of E/Z-11-tetradecenal has been achieved from easily accessible symmetrical aliphatic diols. Environmentally benign protecting groups and oxidation reactions were used to help increase the yield and make the developed routes viable for scale up.
DEDICATION

Dedicated to my parents Ruth Naliaka and Eliud Maniafu Sabuni (late).
ACKNOWLEDGEMENTS

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<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
</tr>
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<tbody>
<tr>
<td>Ac₂O</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>AcONa</td>
<td>Sodium acetate</td>
</tr>
<tr>
<td>Conc</td>
<td>Concentrated</td>
</tr>
<tr>
<td>d</td>
<td>Doublet (spectra)</td>
</tr>
<tr>
<td>DDT</td>
<td>Dichlorodiphenyltrichloroethane</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-Dihydro-2H-pyran</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-Dimethoxyethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>DSS</td>
<td>Decision support system</td>
</tr>
<tr>
<td>E</td>
<td>German; entgegen = opposite, refers to stereochemistry about a double bond</td>
</tr>
<tr>
<td>Et₂O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transformed infrared</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas-liquid-mass spectrometry</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
<tr>
<td>ha</td>
<td>Hectare</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>IBD</td>
<td>Diacetoxy iodobenzene</td>
</tr>
<tr>
<td>IPM</td>
<td>Integrated pest management</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
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x
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>KHDMS</td>
<td>Potassium bis(trimethyl silyl) amide</td>
</tr>
<tr>
<td>Ltd</td>
<td>Limited</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet (spectra)</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>Methyl magnesium bromide</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>NMI</td>
<td>N-methyl imidazole</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>nr</td>
<td>No reaction</td>
</tr>
<tr>
<td>NY</td>
<td>New York</td>
</tr>
<tr>
<td>OPT</td>
<td>Phenyl tetrazolyl</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PPh₃</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>PTLC</td>
<td>Preparative thin layer chromatography</td>
</tr>
<tr>
<td>pTSA</td>
<td>para-Toluene sulfonic acid</td>
</tr>
<tr>
<td>pTsCl</td>
<td>para-Toluene sulfonyl chloride</td>
</tr>
<tr>
<td>Qty</td>
<td>Quantity</td>
</tr>
<tr>
<td>Rf</td>
<td>Retention factor</td>
</tr>
<tr>
<td>$</td>
<td>Canadian dollar</td>
</tr>
<tr>
<td>s</td>
<td>Singlet (spectra)</td>
</tr>
<tr>
<td>SBW</td>
<td>Spruce budworm</td>
</tr>
<tr>
<td>SC</td>
<td>South Carolina</td>
</tr>
<tr>
<td>SN₂</td>
<td>Second order nucleophilic substitution reaction</td>
</tr>
<tr>
<td>t</td>
<td>Triplet (spectra)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>TEAB</td>
<td>Tetraethyl ammonium bromide</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-tetramethyl-1-oxyl piperidine</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMANO</td>
<td>Trimethyl amine N-Oxide</td>
</tr>
<tr>
<td>TX</td>
<td>Texas</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>Z</td>
<td>German; zusammen = together, refers to stereochemistry about a double bond</td>
</tr>
</tbody>
</table>
Chapter one

Introduction

Canada’s Forest

Forty percent of Canada’s area is under forest cover. The forest and its resources partly shape the economy and way of life in Canada. It provides habitat to numerous creatures, freshens air, purifies water and its industry supports hundreds of thousands of direct jobs, which inject $22.1 billion to the country’s gross domestic product (GDP) in 2015.¹

In New Brunswick, 85% of the land surface is covered by forest and the province relies more on its forest industry than any other province in Canada.² The industry contributes over $1.5 billion directly to New Brunswick’s GDP and the wood industry is worth more than $500 million annually. The forest industry in New Brunswick is the largest employer with a workforce of nearly 22,000.²

The forest in New Brunswick has many tree species but only fir and spruce trees are destroyed by spruce budworm (SBW). The fir trees prevail in the north and northwest regions of the province, red spruce prevails in the east and southwest while black spruce prevails in the eastern lowlands ecoregion.³ However, the trees are vulnerable to spruce budworm (SBW) outbreaks as previous infestations have led to high volume growth loss and mortality of trees.⁴ ⁵ In 2002, MacLean predicted a 195 million m³ loss of timber in New Brunswick if a SBW outbreak was to occur.⁶ Such a significant loss of natural resources would deal a direct blow to any employment relying on the forest industry.
**Spruce budworm**

SBW is a tiny brown caterpillar with a characteristic black head and two rows patterned with white round spots on the back, and is prominent in most of North America. Spruce budworm is a moth species of the family *Tortricidae* and genus *Choristoneura*. *Choristoneura fumiferana, C. occidentalis, C. orae* and *C. biennis* are the four prevalent species that feed on spruce and fir trees in Canada. *Choristoneura fumiferana* Clements is known as the eastern SBW and is found in all the Canadian provinces and territories. *Choristoneura occidentalis* Freeman, the western SBW, ravages British Columbia and Alberta while *C. orae* Freeman and *C. biennis* Freeman are coastal SBW species found in British Columbia and partly in the territories.

The eastern SBW has a life cycle, Figure 1, which spans one year proceeding through egg, larval, pupal and adult stages. The larval stage passes through six instar levels. The adult moth, like many *Lepidoptera* species, lives for approximately two weeks mainly for mating, dispersal and oviposition.

In New Brunswick, the SBW caterpillar turns into a pupa in early or mid-July and may hang on silk threads from lower defoliated branches of balsam fir or spruce trees. The moths then emerge in late June to mid-July, and lay eggs on the underside of needles of fir and/or spruce trees in clusters of 10, with each female laying approximately 200 eggs. The yellow-orange oval shaped egg masses are about 1.2 mm in length and after incubation of 10-14 days they hatch into 1\textsuperscript{st} instar larvae that seek refuge in host trees or crevices weaving themselves in silk cocoons that molt into 2\textsuperscript{nd} instar larvae. The 2\textsuperscript{nd} instar larvae remain in the cocoon over the winter period. At the end of the winter period, late April or early May, the caterpillars free themselves and start feeding on
flower pollens or old needles. The caterpillars continue feeding on new shoots that appear until the end of June when they are in their 5th and 6th instar. These last two instars are the most voracious and cause the most damage. During an infestation they continue feeding on previous year’s needles if all current year foliage is completely destroyed. The larvae color transitions through the instars from yellow-green to pale brown and finally dark brown for the mature larvae. The mature caterpillar, about 22 mm in length, is characterized by a black head and two parallel rows of whitish spots on the back. The caterpillars pupate in early July for ten days. The pupae, which are brown in color and slightly curved, emerge into a grey-brown moth that has silvery white patches on the forewings and wingspan of 21 mm to 30 mm.\textsuperscript{12,13}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{SBW_life_cycle.png}
\caption{SBW life cycle}
\end{figure}
SBW Infestation

The history of SBW infestations in eastern Canada has been recorded for 200-300 years using dendroecological methods that utilize tree-ring width patterns to detect insect-induced reduction in foliage cover.\textsuperscript{14,15} The infestations recur every 35-40 years lasting 10-15 years.\textsuperscript{16} The most severe infestations in the 20\textsuperscript{th} century occurred thrice starting about 1910, 1940 and 1970, and affected mainly the provinces of Ontario, Quebec, New Brunswick and Newfoundland.\textsuperscript{16} The 1910 outbreak spread through eastern Canada until 1921. At its height, it extended from Lakes Kipewa and Expanse, in Western Quebec to Nova Scotia and Maine, then westward from Lake Expanse it spread to Welcome Lake Region, Ontario. The southern part of Cape Breton Island, west of Lake Superior in Ontario also experienced an extensive outbreak but only small infestations occurred in northern Manitoba and throughout New Brunswick. Twenty million cords of fir and spruce were killed in New Brunswick with mortality being severe on the Miramichi drainage.\textsuperscript{17} Severity increased in the infestation that began in 1940 and destroyed 25 million ha.\textsuperscript{14} The height of the infestation was realized in the 1950’s. In 1951 severe mortality of fir/spruce trees occurred on Cape Breton Island and it was not until 1953 that the northeastern mainland of Nova Scotia and Prince Edward Island suffered a similar fate. Infestation intensified in 1954 on Cape Breton Island while it declined on the Nova Scotia mainland and in southeastern New Brunswick. However, from 1952 until 1960, the northwestern region of New Brunswick was severely defoliated before the population density of the insects receded.\textsuperscript{18} Thereafter, population of the insects in the middle region of the province continued to rise triggering the last extensive infestation in 1970. The outbreak that began in 1970 was the most severe of the three
outbreaks in 20th century, covering northeastern Ontario, western Quebec, central New Brunswick, Newfoundland and Cape Breton Island in Nova Scotia.16 The infestation was so severe that young stands of fir and spruce trees in some regions were badly damaged despite initially thought to being immune from high budworm population densities.16 By 1981, 11.2 million ha of fir and spruce trees in Ontario and 10.2 million ha in Quebec had been destroyed. Overall, 55 million ha in eastern Canada had been destroyed equaling a loss of 44 million m³ of wood per year in Canada.19 At the end of the outbreak, mortality and slow growth of trees had cost Quebec annually 129-238 million m³ in timber loss,20 damaged 18 million ha in Ontario of which slightly over one third occurred in the Northwest region.21 In Newfoundland, 5.1 million m³ of balsam fir trees suffered mortality representing ninety percent of the island’s productive forest.22 Cape Breton experienced the severest infestation in Nova Scotia with eighty nine percent mortality of host trees translating into 21.5 million m³ loss of timber while New Brunswick lost 6.0 million m³ in 1982 alone.23-25 By 1993, the infestation had subsided in the majority of the areas with the exception of northwestern Ontario.26

The SBW infestation has now begun once again. Quebec has seen an increase in the SBW since 2006 leading to over 6.3 million hectares of severe defoliation by 2015.27 Defoliation in southern parts of Quebec spread into New Brunswick in 2014, prompting insecticide application. In the July of 2016, numerous moths were observed carpeting roads and buildings in Campbellton, Northern New Brunswick27 leading to concerns that another outbreak in New Brunswick is imminent.
SBW Chemical control

Historically, chemical insecticides, Figure 2, have been utilized to protect fir-spruce foliage rather than suppress SBW populations.\textsuperscript{14} The first aerial spray against SBW was conducted in northwestern Ontario using dichlorodiphenyltrichloroethane (DDT) in 1945 and 1946 at 1 kg/ha after initial successful trials of dosages ranging from 0.5- 5.0 kg/ha in the province between 1944 and 1945.\textsuperscript{28} It was not until 1952 that Quebec and New Brunswick began a similar campaign against SBW infestation, spraying 3200 ha and 48,000 ha, respectively.\textsuperscript{28, 29}

\begin{center}
\begin{tabular}{c}
\textbf{DDT} \\
\includegraphics[width=0.3\textwidth]{ddt.png} \\
\textbf{Phosphamidon} \\
\includegraphics[width=0.3\textwidth]{phosphamidon.png} \\
\textbf{Aminocarb} \\
\includegraphics[width=0.3\textwidth]{aminocarb.png} \\
\textbf{Fenitrothion} \\
\includegraphics[width=0.3\textwidth]{fenitrothion.png} \\
\textbf{Trichlorfon} \\
\includegraphics[width=0.3\textwidth]{trichlorfon.png}
\end{tabular}
\end{center}

\textbf{Figure 2:} Chemical insecticides used against SBW in New Brunswick

Throughout the 1950s and 1960s DDT was the control agent of choice with 6.6 tonnes being applied to forests in Canada.\textsuperscript{30} New Brunswick has been more aggressive than other provinces in its use of pesticides to contain the SBW infestations employing a variety of different chemicals from 1962. The pesticides were used at varying dosages and sprayed over millions of hectares. 2-Chloro-2-diethylcarbamoyl-1-methylvinyl
dimethyl phosphate (phosphamidon) was introduced in 1963 in New Brunswick and used until 1974.\textsuperscript{31} O,O-Dimethyl-O-(3-methyl-4-nitrophenyl) phosphorothioate (fenitrothion) was first introduced in 1967 and eventually replaced DDT in 1969 after its ban as the main insecticide. Dimethyl-(2, 2, 2-trichloro-1-hydroxyethyl) phosphonate (trichlorfon) and 4-(dimethylamino)-3-methylphenyl]methylcarbamate (aminocarb) were also used between 1974 and 1987 in Newfoundland, Quebec and New Brunswick.\textsuperscript{31}

DDT was used because it was cheap, very effective, readily available and applicable. However, persistence in the environment, reported resistance, and toxicity to birds and fish saw its withdrawal and subsequent ban in Canada in 1968.\textsuperscript{32-34} Phosphamidon was less toxic to fish than DDT but more expensive and was also withdrawn after it was realized it was killing many birds.\textsuperscript{32,35} Fenitrothion,\textsuperscript{36} which replaced DDT, was used in New Brunswick until 1984 and 1986 in Quebec as it was not toxic to fish and lasted longer after spraying. However, it was subsequently found to be toxic to pollinating insects, song birds and non-target aquatic organisms.\textsuperscript{36} Although aminocarb was very effective against SBW and less toxic and more environmentally friendly than fenitrothion, manufacture was discontinued in 1989 due to limited sales. Trichlorfon was used in New Brunswick until 1997 since it was not toxic to honey bees.\textsuperscript{36}

**SBW Biological control**

Continuous objections by the public on the use of chemical insecticides prompted the search for alternative control methods.\textsuperscript{37} The biological control agents tebufenozide (Mimic) and *Bacillus thuringiensis*, considered safe to the environment, non-toxic to humans and non-target insects, selective and biodegradable, then replaced chemical control of SBW in eastern Canada. *Bacillus thuringiensis* is an environmentally friendly
safe biopesticide that is highly selective for Lepidoptera larvae, non-toxic to humans, and exhibits negligible toxicity to fish and birds.\textsuperscript{38-40}

*Bacillus thuringiensis* is a bacterium that naturally occurs in soils forming spores that on maturity produces toxic protein crystals that are only released in the alkaline conditions found in the gut of Lepidoptera species. On ingestion, the toxin is released and then destroys the lining of the midgut. It then gets absorbed in the blood stream causing infection that stops the larvae from feeding, thus leading to death several days later.\textsuperscript{41}

*Bacillus thuringiensis* was first isolated in 1901 and scientifically described in 1911.\textsuperscript{42} It was registered in the US in the 1950s but not tested for insect control.\textsuperscript{40} It was registered in Canada in 1961\textsuperscript{43} and commercialized in 1970.\textsuperscript{44} In the 1970s, Canadian scientists extensively researched ways to use *Bacillus thuringiensis* in forests with a breakthrough coming by 1980 in which they had developed an economically efficient formulation using sorbitol that solved the evaporation problem in earlier formulation, enhanced adherence to the needles, and prevented contamination and spore fermentation.\textsuperscript{37} Millions of hectares have been sprayed with *Bacillus thuringiensis* since 1985 in an effort to control SBW, thus replacing chemical insecticides. Continued research has improved formulations leading to the use of more dilute amounts, better efficacy and lowered treatment costs.\textsuperscript{45-47}

*Bacillus thuringiensis* in typical conditions poses no risk to non-target organisms as it is applied to the foliage when the larvae start feeding and the insecticide lasts for weeks on foliage.\textsuperscript{47} Compared to chemical insecticides, *Bacillus thuringiensis* effectiveness has a high cost for preparation and application.\textsuperscript{47} There is no evidence of resistance to date by SBW to *Bacillus thuringiensis*. However, repeated use could lead to resistance,\textsuperscript{48}
jeopardizing efforts in controlling the insects. Furthermore, it is only applied to areas that have shown serious defoliation caused by 3\textsuperscript{rd} and 4\textsuperscript{th} instars of SBW to suppress spread, thus its effectiveness at higher insect populations is unknown.\textsuperscript{49}

Tebufenozide (Mimic), Figure 3, a growth regulator, is also currently used to control the SBW in Canada.\textsuperscript{50} It replaced organophosphates, due to their toxicity, and is a complement to the use of \textit{Bacillus thuringiensis} in controlling SBW in Canada.

![Figure 3: Tebufenozide.](image)

The formulation of Mimic used in Canada contains 25\% tebufenozide, the active ingredient.\textsuperscript{50} Tebufenozide behaves as an ecdysone molting hormone that causes premature molting of larvae.\textsuperscript{50} Mimic is not harmful to humans and does not harm non-target insects, but selectively kills SBW.\textsuperscript{50} Its advantage in controlling SBW is due to the fact that it is highly toxic to SBW, resistant to rain wash off, has longer residual times on foliage and there is evidence to suppression of SBW populations several years after application.\textsuperscript{51-54}

Tebufenozide was first sprayed in Manitoba to control SBW, and later in Alberta in 1999. After its formal registration for use to control forest and woodland pests in 2006, other provinces, particularly New Brunswick, have since utilized it in controlling low population densities of SBW.\textsuperscript{32} Although this makes it ideal as an integrated pest management (IPM) tool, high concentrations and exposure duration is harmful to
crustaceans. Additionally, Mimic is not permitted to be sprayed over open bodies of water since it remains in aquatic sediments for several weeks.\textsuperscript{50}

A pheromone is a chemical signal that members of the same species use to communicate.\textsuperscript{55} Releaser pheromones cause a response in insects while primer pheromones cause physiological changes in animals. Pheromones are classified into alarm, recruitment, aggregation, sex and many others.\textsuperscript{55} Most insects are selective and sensitive to the sex pheromone of their species. The sex pheromones released promote mating or function in a way related with sexual reproduction.\textsuperscript{55}

The SBW male attractant pheromone \textit{trans}-11-tetradecenal \textbf{1} was first isolated and identified by Weatherston \textit{et al.}\textsuperscript{56} Weatherston accomplished this by ether extraction of the cheesecloth and Mason jars that had contained moths for two days and biological activity was confirmed by both laboratory and field bioassays.\textsuperscript{56} For attraction of males a blend of the \textit{E} and \textit{Z} isomers was necessary as either isomer on its own was ineffective. Various blends of \textit{E/Z}-tetradecenal ranging from 85:15\textsuperscript{57} to 89:11\textsuperscript{58} have been shown to attract the male moths to some extent. It was initially shown that a 96:4 ratio was optimal, \textsuperscript{59} however, in 1980 it was confirmed that a 95\textit{E}:5\textit{Z} blend was most effective.\textsuperscript{60}

\begin{center}
\textbf{Figure 4:} The SBW pheromone, \textit{trans}-11-tetradecenal \textbf{1}.
\end{center}

The SBW pheromone has been an additional tool for the effective early management of this insect’s population. Specifically, it involves use of the sex pheromone in traps to monitor insect population densities and provide early warning of
outbreaks. The number of catches in traps in more than 500 hundred locations across Canada can be used to estimate the size of the SBW population and forecast migratory patterns of the insects.\textsuperscript{61} For example, a study in northwestern Ontario over a 21 year period showed that a warning for a possible extensive defoliation can be provided 6 years in advance. The findings were based on three successive years of increasing catches.\textsuperscript{62} With the ongoing outbreak of SBW in Quebec, both New Brunswick and Maine have deployed pheromone traps since 2008 in hot spots that have shown a dramatic rise in SBW population.

Figure 5: Number of catches in traps of SBW in New Brunswick.

Source: New Brunswick Department of Natural Resources

Figure 5 shows catches of SBW in New Brunswick since 1995 in three regions of the province. It reveals that there has been an overall steady rise in the population since 1995, more noticeably in northern New Brunswick. This has led the New Brunswick
government in the summer of 2016 to start spraying hot spots like Campbellton with *Bacillus thuringiensis* and with mimic in order to suppress SBW populations.\(^{63}\)

Miller *et al.* has shown that the SBW sex pheromone can also be used in mating disruption to monitor and control SBW without use of traps.\(^{64}\) Mating disruption involves use of synthetic insect sex pheromone applied to a specific area to prevent males from locating virgin females. The breakdown in the communication mechanism includes neurophysiological effects, false-trail following or a combination of these.\(^{64}\) Several trials in the laboratory and field have shown that the synthetic SBW sex pheromone disrupts mating behavior of the insects.\(^{65-70}\) Hercon\(^{\circledR}\) Disrupt Micro-flake\(^{\circledR}\) was highly successful in controlling the gypsy moth in the US with over 0.5 million acres of forest treated over a 15 year period.\(^{69}\) After a decade of research, an environmentally benign product, Disrupt Micro-flakes SBW\(^{\circledR}\), was developed and in 2007 registered in Canada with field trials in 2008 in Quebec showing mating disruption. However, the study in Quebec failed to suppress the SBW population, leading to Rhaind *et al.*’s suggestion that SBW mating success is dependent on the density of the population.\(^{69,70}\) Recently, independent studies by Silk and Riley indicated that the SBW pheromone does lower populations.\(^{71,72}\)

**Predicted impact of an uncontrolled SBW outbreak in New Brunswick**

Chang *et al.* in 2012 used the spruce budworm decision support system (SBW DSS), combined with a dynamic computable general equilibrium model to predict an economic loss of $3.3 billion and $4.7 billion for moderate and severe outbreaks, respectively, covering unprotected 2.8 million hectares for a 30 year period.\(^{73}\) MacLean *et al.* earlier in 2002 had predicted that the volume of wood loss would hit 83 million and 195 million m\(^3\) in normal and severe outbreaks, respectively.\(^{74}\) Since New Brunswick’s
economy depends heavily on the forest industry, with wood value of $500 million annually\textsuperscript{2}, this type of economic devastation would be disastrous for the province, thus a great deal of effort is being expended to explore the options available for mitigating the next SBW infestation. If the use of mating disruption technology is to be one these options then that ability to access large quantities of pheromone at an economical price is crucial.

**SBW Pheromone Synthesis**

**Previous syntheses of trans-11-tetradecenal (1)**

The first synthesis of *trans*-11-tetradecenal was achieved in six steps from commercially available 1, 8-octanediol\textsuperscript{2,56} A stereoselective preparation of the unsaturated aldehyde 1 employed a novel metal reduction of acetylenic intermediate 3 and its subsequent oxidation to 1. Reduction of the alkyne was the key step in the synthesis and introduced the requisite stereochemistry at C-11 to give a pure *E* unsaturated alcohol. Clayden showed that the stereospecificity of the reduction resulted from the stability of the intermediate radical anion due to steric interaction of unbound electrons and the alkyl groups, Figure 6.\textsuperscript{75}

![Scheme 1: Synthesis of trans-11-tetradecenal 1 by Weatherston *et al.*](attachment:image.png)

\textbf{Scheme 1}: Synthesis of *trans*-11-tetradecenal 1 by Weatherston *et al.*
Figure 6: Stability of radical anion intermediate.

Alcohol 4 was oxidized by chromic acid generated \textit{in situ} giving a poor yield of the product 1. Although the synthesis was stereoselective, the use of sodium metal to form alcohol 3, liquid ammonia, low temperatures and toxic chromic acid made the synthetic route unattractive for scale up.

Scheme 2: Wiesner and Tan synthesis.

In 1980, Wiesner and Tan synthesized the first stereoisomeric mixture of 11-tetradecenal starting from oleyl alcohol 5, Scheme 2.\textsuperscript{76} Oleyl alcohol 5 was reacted with thionyl chloride to produce the unsaturated chloride 6, which generated chloride 7 through ozonolysis and ketalization. A Grignard reagent was prepared from 7 and treating this with a catalytic amount of CuCl and a mixture of 3-chloropent-1-ene and 1-chloropent-3-ene allowed for formation of the carbon-carbon bond, thus resulting in the introduction of stereochemistry at C-11. A mixture of 8, 9 and 1 in a ratio of 1:1:8, respectively, was obtained. The terminal alkene 9 was removed by distillation, thus
providing an 89:11 mixture of 1 and 8 in an overall yield of 39% for the six-step sequence. Although the route was shorter than that reported by Weatherston et al., it was not commercialized because of the use of ozone, production of side products, and a tedious distillation.

Sharma and Lynch, Scheme 3, accomplished a synthesis of the SBW pheromone by coupling a C₁₀ and C₄ unit, much like Weatherston but using a different acetylenic route starting with 10-undecenal 10. They began by protecting the aldehyde 10 with triethylorthoformate in preparation for reduction of the aldehyde formed by ozonolysis of 11. The resulting alcohol 12 was subjected to an Appel reaction to form bromide 13 that was then coupled with lithium butynylide in dry DMSO to give the diethoxytetradecyne 14 in 87% yield after work up. The alkyne was then reduced with sodium in an ammonia/THF mixture resulting in a mixture of products consisting of 85% diethoxytetradecene 15 and 5% tetradecadiene 16. Acid catalyzed hydrolysis of the acetal yielded 94% E/Z-11-tetradecenal 1 with an isomeric ratio ranging from 98:2 to 96:4. The overall yield was 45-47%, which was an improvement on the synthesis of Wiesner and Tan, however, despite the improved yield and stereoselectivity, the method still suffered problems due to the use of ozone, liquid ammonia and solvents such as DMSO and carbon tetrachloride that are considered dangerous to the environment.
Scheme 3: Sharma and Lynch synthesis.

Ishumuratov *et al.* in 1997 approached the synthesis from a very different perspective, namely employing a modified Knoevenagel reaction for the stereospecific installation of the double bond. In seven steps, starting from 10-undecenoic acid 17, they prepared the SBW pheromone in an overall yield of 27%. Scheme 4. The unsaturated acid 17 was first reduced to alcohol 18 followed by oxidation to aldehyde 19. Grignard addition of vinyl magnesium bromide to aldehyde 19 followed by protection of the resulting alcohol as an ester set the stage for Grignard-copper mediated carbon-carbon bond formation via an $S_{N}2'$ reaction. Following coupling, anti-Markovnikov hydration of diene 24 with 9-BBN generated alcohol 4. Alcohol 4 was then oxidized using PCC to provide the desired SBW pheromone 1. Unfortunately the authors did not report the stereoisomeric ratio, therefore it is hard to assess the overall usefulness of this route. Regardless, the use of expensive starting materials, lower yields and employment of toxic
chromium compounds are significant impediments to the use of this route for any large scale synthesis.

Scheme 4: Ishumuratov et al. synthesis.

Justification of study

A review of earlier syntheses was desirable as this laid the foundation for the design of several short synthetic pathways to access a pheromone blend of 95:5 E/Z ratio of 11-tetradecenal. It is evident from the literature reported to date that all attempted syntheses employed few “green” approaches. In three of the syntheses, key steps involved alkylation using liquid ammonia, which is expensive, requires specific equipment setup, low temperature, use of a reactive moisture sensitive metal and gives varying yields. Toxic solvents such as DMSO, HMPA and reagents like chromic acid, and ozone were also utilized. Additionally, a number of steps employed low temperatures that are undesirable for large scale synthesis. With all these limitations combined, the synthesis of the SBW pheromone is prohibitively expensive for large scale application. To illustrate this point, currently there are a number of commercial suppliers of the SBW
pheromone and the price per gram is shown in Table 1. The cost per gram ranges from the lowest of $84 to the highest of $634.75. Also, it is clear from the table that it is more expensive to purchase the SBW pheromone from suppliers that have the purest isomer. To put this in perspective, 6 million hectares of forest in New Brunswick were sprayed during the last outbreak, applying the pheromone at 50 g/ha would cost $77.9 billion dollars to combat an infestation, using the prices noted in Table 1. Therefore, for the sex pheromone to be used as an effective IPM tool it must be produced at a significantly lower cost.

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Country</th>
<th>% Purity</th>
<th>Qty (g)</th>
<th>Price $/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yick-Vic Chemicals &amp; Pharmaceuticals</td>
<td>Hong Kong</td>
<td>90</td>
<td>10</td>
<td>84</td>
</tr>
<tr>
<td>ChemSampCo</td>
<td>Dallas, TX-USA</td>
<td>-</td>
<td>1</td>
<td>255.95</td>
</tr>
<tr>
<td>Matrix Scientific</td>
<td>Columbia, SC-USA</td>
<td>95</td>
<td>5</td>
<td>259.9</td>
</tr>
<tr>
<td>Finetech Industry Ltd</td>
<td>China</td>
<td>95</td>
<td>5</td>
<td>493.5</td>
</tr>
<tr>
<td>BOC Sciences</td>
<td>Shirley, NY-USA</td>
<td>96</td>
<td>5</td>
<td>634.75</td>
</tr>
</tbody>
</table>

**Table 1:** Retail price of *trans*-11-tetradecenal.
Objectives

This study embarked on developing short, efficient and economical routes to synthesize the SBW pheromone in the effective desired ratio of 95E:5Z, starting from readily and cheaply available aliphatic diols and unsaturated alkenols. Two approaches were envisaged:

1) Starting with a commercially available precursor containing a known alkene isomeric mixture. This had the advantage of retaining the known stereochemistry after the coupling. The key step in this approach utilized the Grignard copper mediated catalysis coupling to elongate the carbon chain. This reaction uses magnesium and copper (1) iodide, which are inexpensive, non-toxic, use mild conditions and are scalable.

2) The second approach employs the Julia olefination coupling as the key step to introduce the stereochemistry. This route would allow for the use of cheap starting materials, the ability to potentially control conditions such that the desired isomeric ratio could be obtained.

This resulted in seven short synthetic routes being targeted, four proceeding through five steps and the shortest via four steps. Disconnection of the molecule, Figure 7, at any of the identified locations led to the choice of relatively cheap commercially available symmetrical diols as starting material. Disconnection of carbon bonds at C11 and C12 allows the use cheap 1-propanes or propanal and 1, 11-undecanediol as starting materials. Cheap 1,10-decanediol and α-β unsaturated pentatonic acid are the starting materials by disconnecting at C10 and C11. Disconnection of the molecule at C10 and C9, C9 and C8 results into carbon units consisting of five, six, seven and nine carbons. Cheap and
readily commercially available unsaturated bromohalides and symmetrical diols of eight and nine carbons were starting materials for these routes.

Figure 7: Retrosynthetic disconnections for the synthesis of trans-11-tetradecenal.
Chapter two

Results and Discussion

Synthetic strategy

Analysis of the retrosynthetic disconnections of 1 at various C-C bonds, Figure 7, led to the design of viable synthetic routes to 1 via a Grignard-copper mediated reaction and modified Julia olefination. The Grignard-copper mediated route would entail the coupling of a n-halo-1-O-protected long chain alkane with a short chain unsaturated halide or some other appropriate leaving group, Figure 8. The use of copper makes the reaction fairly practical due to the ability of copper organometallics to tolerate many sensitive reactive functional groups.\(^\text{79}\) Julia olefination reaction would involve coupling of a 11-O-protected long chain aldehyde or propanal with 1-bromopropane or n-halo-1-O-protected long chain alkane respectively.

\[ \begin{align*}
   & \text{RO} \quad \text{X} \quad \text{6} \quad + \quad \text{C8} \quad + \quad \text{C6} \quad \text{24 and 25} \\
   & \text{C10} \quad + \quad \text{C4} \quad \text{42} \\
   & \text{C9} \quad + \quad \text{C5} \quad \text{28} \quad \text{"or"} \quad \text{24 and 25} \\
   & \text{C11} \quad + \quad \text{C3} \quad \text{29} \\
   & \text{RO} \quad \text{X} \quad \text{7} \quad + \quad \text{X} \quad \text{28} \quad \text{"or"} \quad \text{29} \\
   & \text{RO} \quad \text{X} \quad \text{8} \quad + \quad \text{X} \quad \text{46} \\
\end{align*} \]

Figure 8: Retrosynthetic disconnections leading to proposed units for the synthesis of SBW pheromone 1.
Preparation of homoallylic halides

My study began with preparation of the various unsaturated halides as shown in Schemes 5, 6 and 7 since commercially available halides are expensive. There are many inexpensive starting materials that contain the alcohol functionality and numerous studies that replace the hydroxyl group with chlorine, bromine and iodine have been reported. The search for milder conditions, shorter reaction times and higher yields are often the impetus for these studies. One method that has gained much favor in recent years is the Appel reaction that directly converts an alcohol to a halide in a single step usually in high yield, with very few side reactions, and is tolerant to a wide variety of functional groups. Additionally, the reaction conditions are neutral, thus suitable for alcohols that are acid and base sensitive.

Scheme 5: Synthesis of homoallylic halides 24 and 25.

The initial synthesis of 24 began with alcohol 23 taking advantage of the stereochemistry in the starting commercial trans-3-hexenol 23 (96%) and a chemoselective substitution of the alcohol functional group would not alter the
stereochemistry. The first attempt at utilizing the Appel reaction with alcohol 23 followed the procedure of Belmar et al. This reaction involved treating a cooled solution of triphenylphosphine (PPh₃) in CH₂Cl₂ at 0 °C with bromine to form a phosphonium dibromide salt. Alcohol 23 was then added at rt and allowed to react for 12 h. Unfortunately, after work up and purification a low yield of 35% was obtained. Although Belmar was able to demonstrate that this procedure routinely produced high yields of product, typically in excess of 85%, he used much larger quantities of starting material suggesting his method may not be as effective for small scale synthesis.

In an attempt to improve the yield it was decided to employ the procedure reported by Kabalka et al. To this end, conversion of alcohol 23 to tosylate 26 proceeded as expected in 94% yield. However, treatment of tosylate 26 with LiBr in acetone at rt for 20 h gave only a 50% yield of bromide. Attempts to improve this, including increasing the temperature, changing the solvent, increasing the amounts of LiBr, all proved fruitless. Unfortunately, this meant that the overall yield of transforming the alcohol to the halide was 47%. Although this was not an unworkable amount, it was felt that improvements could be made.

In an attempt to improve the yield it was decided to employ the procedure reported by Shakhmaev. Thus, alcohol 23 was again added to triphenylphosphonium dibromide, only this time the temperature was raised to 10 °C and retained the solvent as in previous reaction, CH₂Cl₂, instead of chloroform used by Shakhmaev. Following addition of the alcohol stirring was continued at room temperature for 2 h. In contrast to the previous result an excellent 85% yield of 24 was obtained.
With the success of this reaction it was decided to make the iodide as well since it was thought that the iodide might participate in the coupling reaction better than the bromide. Therefore, halide 25 was prepared by adding iodine to a solution of PPh$_3$ and imidazole in CH$_2$Cl$_2$ at 0 °C, stirring for 30 min and then adding alcohol 23. After stirring for 2 h, 25 was produced in an outstanding 92%.

**Preparation of allylic leaving groups**

With these halides in hand, the synthesis of C-5 allylic halides and a carbonate were investigated. This strategy was attractive as depending on the starting allylic halide the coupling could proceed through a S$_N$2 or a S$_N$2′ pathway. The S$_N$2′ pathway offered the possibility of using an extremely cheap starting material, but suffered from the unknown of how chemo- and regioselective the coupling would be.

The allylic halide mixtures 28 and 29, 30 and 31, Scheme 6, were prepared according to the procedure by Labrouillere in an E/Z ratio of 60:40. Allylic halogenation of the unsaturated secondary alcohol 27 using 0.5 eq of the Lewis acid bismuth (III) halide and drop-wise addition of chlorotrimethylsilane (Me$_3$SiCl) produced low yields (Table 2) of mixtures of 28 and 29 in only 10% yield and 30 and 31 in a slightly improved 15% yield. These yields are based on column chromatography separations on SiO$_2$ since distillation was practically impossible with such small amounts of product. The resulting yields were very poor compared to the 60% yield reported in the literature, and may reflect some loss due to evaporation of product after chromatography. Repeating the procedure by increasing the time to 1 h did not improve the yield, nor did doubling the equivalents of the Lewis acid. With lack of success in this green synthesis of the allylic halide, a different approach to converting the alcohol to a
suitable leaving group, such as a carbonate, was undertaken. We suspected that a carbonate would serve as a suitable partner for the regio-controlled copper-catalyzed Grignard coupling reaction since $S_{N}2'$ addition to allyl carbonates has been reported to result in products with high selectivity, $E/Z$ ratios of up to 99:1.\textsuperscript{87}

\[ 
\text{MeSiX, BiX}_3, \text{rt, 15 min} \rightarrow \begin{array}{c}
\text{OH} \\
\text{27}
\end{array} \rightarrow \begin{array}{c}
\text{X} \\
\text{X} = \text{Cl, Br}
\end{array} 
\]

**Scheme 6:** Synthesis of allylic halide and carbonate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Product</th>
<th>BiX₃</th>
<th>eq</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>28, 29</td>
<td>BiCl₃</td>
<td>0.5</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>30, 31</td>
<td>BiBr₃</td>
<td>0.5</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>28, 29</td>
<td>BiCl₃</td>
<td>0.5</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>30, 31</td>
<td>BiBr₃</td>
<td>0.5</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>28, 29</td>
<td>BiCl₃</td>
<td>1</td>
<td>15</td>
<td>10</td>
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<tr>
<td>6</td>
<td>27</td>
<td>30</td>
<td>BiBr₃</td>
<td>1</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 2:** Allylic halogenation of pent-1-ene-3-ol 29.
With this goal in mind, the carbonate 32 was prepared following the procedure by Li\(^8\) in which a solution of unsaturated allylic alcohol 27 in CH\(_2\)Cl\(_2\) at 0 °C was treated with isobutyl chloroformate and pyridine to give an excellent yield of 94%. Isobutyl chloroformate was preferred as it was believed that it would offer greater selectivity than methyl or ethyl carbonates since the bulky isobutyl group would provide greater steric hindrance to the incoming nucleophile and thus promote S\(_{N2}'\) reaction as opposed to S\(_{N2}\) reaction.\(^8\)

**Preparation of vinyl halide**

To wrap up the synthesis of the shorter carbon chain synths, attention was focused on the preparation of vinyl bromide 34, Scheme 7. It was believed that this could be accomplished in a straightforward manner following a recent report by Fursule\(^9\) where he demonstrated a highly chemoselective modified Hunsdiecker reaction to generate a number of vinyl bromides, Scheme 7. Accordingly, α, β-unsaturated carboxylic acid 33 was treated with 1.1 equivalents of tetraethylammonium bromide (TEAB) and 0.5 equivalents of diacetoxy iodobenzene (IBD). After stirring for 8 h the brown color had disappeared and a colorless solution was formed. Despite TLC analysis showing that the starting acid had been consumed, no vinyl bromide 34 was able to be isolated. Repeating the reaction by doubling the equivalents of IBD did not yield positive results. It is not clear why 34 was not isolatable, especially considering that Fursule had shown that the reaction worked for this exact compound. It may be that the reaction needs to be done on larger scale such that any halide formed can be isolated via distillation. Its
volatility was a worry from the start and it appears that extreme caution will need to be taken in future in order to try and obtain this compound.

![Scheme 7: Attempted synthesis of vinyl bromide 34.](image)

**Preparation of long chained saturated bromides**

With the short chain units now synthesized, attention was next focused on synthesizing the long carbon chain saturated bromides from symmetrical diols. Symmetrical diols are numerous, readily available and cheap. The monobromoalcohols 38, 39, 40 and 41, Scheme 8, were selectively synthesized from the commercially available symmetrical diols 1,8-octanediol 2, 1,9-nonanediol 35, 1,10-decanediol 36 and 1,11-undecanediol 37, respectively, following Chong’s procedure. The symmetrical diol in dry toluene was treated with 1 equivalent of 48% concentrated hydrobromic acid and initially heated at reflux for 36 h, then an additional amount (38 mol %) of the acid was added in order to complete the reaction and stirring continued for a further 36 h. Strictly adhering to these conditions routinely produced the n-bromo-1-alkanols in 88-92% yield. It should be noted that a small quantity of dibromide forms if the reaction is overheated but it is easily separated by SiO2 column chromatography. The yields are consistently outstanding and the yield is independent of the length of the carbon chain. The efficiency of this reaction is ascribed to the differences in solubility of the starting material and product in the solvent.
Scheme 8: Synthesis of bromo-alcohols 38-41.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 3: Yield of bromo-alcohols 38-41.

Preparation of bromoethers

To prepare for the coupling, the obtained bromo-alcohols were protected as their THP ethers 42, 43, 44 and 45 according to the procedure employed by Zarbin. Dihydro-2H-pyran (DHP) was used because it is cheap, inert to strong nucleophiles, scalable and easy to deprotect. Consequently, bromo-alcohols 38-41 were treated with a slight excess of DHP and a catalytic amount of pTSA at rt for 4 h to produce bromoethers 42-45 in 96%, 95%, 93% and 96%, respectively, Table 4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>95</td>
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<td>3</td>
<td>44</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 4: Yields of bromo-ethers 42-45.

$sp^3$-$sp^3$ and $sp^3$-$sp^2$ Cross coupling via copper mediated catalysis

With a variety of synthons now prepared, the first attempts at coupling utilizing the key copper catalyzed Grignard reaction was undertaken and is summarized in Scheme 10.

Grignard reagents 47, 48, 49 and 50 were prepared from the respective alkyl halides following the procedure of Belmar. The powdered magnesium was introduced to an oven dried flask which was fitted with a condenser while still hot and evacuated using argon for 2 h. Dry THF was introduced to the flask followed by a few drops of 1,2-dibromoethane. The flask was slightly warmed and the alkyl halide dissolved in THF was introduced very slowly while stirring over 15 min and maintaining reflux. Grignard reagent 47, Scheme 10, was prepared at various oil bath temperatures, Table 5, to optimize generation of the Grignard reagent. A small amount was syringed out of the
cooled mixture and titrated with 4-methylbenzaldehyde. The concentration of Grignard reagent was determined based on the amount of aldehyde consumed. From Table 5, entry 1 gave lowest mol eq of the Grignard reagent while higher temperatures, entries 4 and 5, showed the amount of Grignard reagent decreasing.

**Scheme 10:** Formation of Grignard reagent 47

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oil bath Temp °C</th>
<th>Aldehyde mmol</th>
<th>Grignard reagent volume used (mL)</th>
<th>Grignard reagent molarity (mol/dm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>1.0</td>
<td>2.50</td>
<td>0.40</td>
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<td>2</td>
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<td>84</td>
<td>1.0</td>
<td>1.85</td>
<td>0.54</td>
</tr>
</tbody>
</table>

**Table 5:** Optimization of Grignard formation.

With the concentration of Grignard reagent determined, coupling was attempted between Grignard reagent 47 and unsaturated halide 24, Figure 9, by varying the copper catalyst, the amount of catalyst used as well as the temperature of the reaction to optimize the coupling conditions, Table 6. When CuCl was used as a catalyst it did not favor coupling, regardless of the temperature or the amount of catalyst used, entries 1, 10 and 16. The use of CuBr improved the situation as yields in the 55% range could be obtained.
when 10 mol % of catalyst was used at rt, entry 5. Similar yields could be obtained at a lower temperature (0 °C) but more catalyst was required, 20 mol %. Finally, when CuI was used it gave the best coupling yields (76% – 78%), entries 6 and 9, required a shorter reaction time (2 h at rt), and could be performed equally efficiently at lower temperature (0 °C), although a higher catalyst loading was required, entry 18.

![Figure 9: Coupling Grignard reagent 47 with alkyl halide 24.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>mol eq</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
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</table>

**Table 6:** Optimization of coupling conditions.

No reaction (nr)
Using optimized conditions (oil bath temperature of 72 °C), the magnesium metal was all dissolved after 30 min using alkyl halides of a shorter carbon chain, but 1 h otherwise. Carbon-carbon coupling was achieved using a shorter reaction time than previously described,\textsuperscript{81} by reacting the generated nucleophile, catalyzed by CuI, with either 24, 25, 32, 42, 43, or 46. The yields for the coupling using optimized conditions are shown in Table 7. Examining Table 7, it appears that the coupling with the Grignard reagent from the alkyl iodide 25 gave the highest yield indicating that the strength of C-X bond presumably influences the ability to efficiently form the Grignard. Additionally, better yields were obtained by coupling C\textsubscript{8} + C\textsubscript{6} units rather than C\textsubscript{9} + C\textsubscript{5}.

Scheme 11: The Grignard-copper mediated cross coupling of alkyl halides.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Grignard reagent</th>
<th>Alkyl halide</th>
<th>% Yield</th>
<th>$E/Z$ ratio</th>
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<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>24</td>
<td>56</td>
<td>96:4</td>
</tr>
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<td>42</td>
<td>76</td>
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<td>42</td>
<td>82</td>
<td>96:4</td>
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<td>50</td>
<td>32$^a$</td>
<td>78</td>
<td>50:50</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>46</td>
<td>62</td>
<td>95:5</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>43</td>
<td>72</td>
<td>95:5</td>
</tr>
</tbody>
</table>

**Table 7:** Isolated yields of the key C–C coupling step using optimized conditions.

$^a$) A carbonate was used rather than an alkyl halide.

The $E/Z$ ratios are based on the stereochemistry of the starting material as it was not altered during the reaction. The one exception, however, is entry 6, Table 7, in which GC-MS analysis of the coupled product indicated that a virtual stereo-random $E/Z$ mixture was obtained. This was a surprising result considering that both Wiesner$^{76}$ and Ishumuratov et al.$^{78}$ demonstrated that similar allylic electrophiles generated products with much better stereoselectivity. With the halide or acetate leaving groups, it is suggested that the carbon-carbon double coordinates to the metal with no chelation to the leaving group, thus allowing slower reductive elimination of the alkyl ligand giving better selectivity since attack of the nucleophile comes from less hindered side,$^{93}$ while in this case it seems that the metal may chelate with the carbonate leaving group, thus allowing the nucleophile to attack the electrophile from either face of the intermediate allylic complex.
Unfortunately, coupling of vinyl halide 34 and alkyl halide 41 was not carried out since the modified Hunsdiecker reaction to form the vinyl halide was not successful. Hence the Grignard reagent could not be generated to explore the sp²-sp³ hybridized carbon-carbon formation of C₄-C₁₀ units. Similarly, the mixture of allylic halides 28 and 29, 30 and 31 could not be generated in desirable quantities, thus this coupling was not explored either. Clearly, these are routes that should be explored in future studies.

With the coupling complete, the resulting unsaturated ethers, Scheme 12, were then deprotected to alcohol 4 following standard conditions, MeOH and catalytic pTSA, in 86-90% yield. Subsequently oxidation using the recently developed “green chemistry” procedure by Hoover produced the desired pheromone 1 in 92% yield.

![Scheme 12: Oxidation of alcohol to pheromone 1.](image)

From the 7 pathways utilizing Grignard copper mediated catalysis, we report synthesis of predominantly E-11-tetradecenal in 5 steps, Scheme 13, with an overall yield of 57%. The overall reaction time of the synthesis of the pheromone is shorter than those previously reported since fewer steps were required, the coupling step took less than 2 h, and the highest overall yield of the pheromone was obtained by coupling of 1-iodohex-3-ene 25 with bromoether 49.
Scheme 13: Best Grignard copper mediated catalysis pathway.

**sp³ - sp² Cross coupling via modified Julia olefination**

With the copper catalyzed Grignard couplings complete, attention was now turned to the C11-C3 coupling strategy. A variety of regio and stereo controlled methods have been used to directly form olefins from carbonyl compounds. Examples include: Wittig, Horner-Wadsworth-Emmons, Peterson, Johnson and classical Julia olefination. A number of these olefinations have been used to synthesize insect pheromones, but are limited by the use of toxic solvents, expensive catalysts, formation of side products, and formation of mixtures of E/Z isomers that require additional steps to improve selectivity. The classical Julia olefination, Figure 10, involves many steps, including the use of sodium amalgam, thus making it unattractive for large scale synthesis. Improvements were made to the classical method by varying the heterocycle on the sulfone.

In this study the use of the modified Julia-Kocienski olefination reaction was targeted as it is superior to the classical Julia olefination for generating products with a high degree of stereoselectivity. The modified Julia-Kocienski is a single step reaction that is highly selective, more efficient and gives high yields. This apparently is due to the stability of phenyltetrazolyl sulfone anion which permits metallation before addition of
In addition, \textit{trans} selectivity increases with increasing size of the cation in the bulky base, polarity and coordinating ability of the solvent.\textsuperscript{102}

\textbf{Figure 10:} Classical Julia olefination reaction.

The mechanism\textsuperscript{103-106} of the modified Julia-Kocienski reaction, Figure 11, begins with the formation of a carbanion I, then addition of the aldehyde resulting in an unstable $\beta$-alkoxysulfone intermediate II (anti or syn) that undergoes Smiles rearrangement leading to a spirocyclic intermediate III that undergoes cleavage to a sulfinate salt IV by transfer of the heterocycle from sulfur to oxygen with antiperiplanar $\beta$-elimination V of sulfur dioxide. The mechanism for the modified Julia-Kocienski is believed to proceed via an open transition state rather than a closed transition state.\textsuperscript{107} The closed transition state occurs in non-polar solvents which promote metal coordination with small counter ions and thus leading to unfavorable steric hindrance between the large phenyl group and alkyl group as well as oxygen in the sulfone, Figure 12. However, in polar solvents coordination with large counter ions is favored and an open transition state predominates and this leads to an anti-configuration and less steric hindrance.\textsuperscript{105}
The second strategy in this study commenced with the formation of the sulfides 54 and 56, Scheme 14. Therefore, 1-phenyl-1H-tetrazole-5-thiol 53 was treated with sodium hydride\textsuperscript{108} to form the sulfide anion which was then reacted with 1-bromopropane and 54 respectively.
Scheme 14: Synthesis of sulfides and sulfones.

The reactions were complete after 8 h as shown by TLC and NMR and generated 54 and 56 in good yields, 82% and 65%, respectively. The sulfides were then oxidized uneventfully to sulfones 55 and 57 in 90-93% yield using a short reaction time according to the procedure of Kandasamy. This procedure utilized ammonium heptamolybdate catalyst, which is cheap, air stable, commercially available, and the reactions gave high yields at rt.

With sulfones in hand, the stage was set to prepare aldehydes 60, 61 and 62 via bromoalcohol 41, bromoether 45 and acetate 58, Scheme 15. This decision was made since a commercial source of the aldehydes was expensive compared to cheap readily available symmetrical diol 37.
Scheme 15: Preparation of C-11 aldehydes.

Bromoalcohol 41 and bromoether 45 were prepared as earlier described. Acetate 58 was prepared in 86% yield by refluxing diol 37 with glacial acetic acid catalyzed by concentrated H$_2$SO$_4$. This reaction was scalable and produced a high yield of monoacetate with very minute percentages of diacetate in a short reaction time. This reaction was remarkable as it is well known that mono-protection of symmetrical diols is difficult as it tends to give not more than 50% yield.$^{91}$ Exceptions to this are known. For example, symmetrical diols can be protected as their THP ethers in very high yields but the method has serious disadvantages because the ethers form very rapidly after most of the diols have been consumed requiring attention to stop the reaction, and longer chain diols are protected less efficiently.$^{110}$ Also, protection of diols using acetic anhydride gives moderate yields in very basic and strong refluxing conditions, however, work-up is tedious and on industrial scale, anhydrides are much more expensive compared to corresponding carboxylic acids.$^{111}$
Alcohols 41 and 58 were oxidized according to a recently reported procedure by Hoover,\textsuperscript{94} producing 60 and 62 in excellent yields 92-96%. The alcohols were treated sequentially with 0.05 eq each of CuOTf, 2, 2’ bipyridyl, TEMPO and 0.1 eq of N-methyl imidazole (NMI) at ambient temperature and stirred rapidly open to the atmosphere for 8 h. This catalytic system is highly selective for primary alcohols and tolerant to a wide number of functional groups.

Bromoether 45 was oxidized using trimethylamine N-oxide (TMANO) in DMSO in 65% yield.\textsuperscript{112} With all the synthons prepared, the key coupling step was accessed by utilizing the bulky base KHDSMS to generate the anion at -78 °C from the sulfones, Scheme 16, which were then coupled with aldehydes 60, 61, 62 and propanal.\textsuperscript{107} Isolated coupling yields and \(E/Z\) ratios were determined by GC-MS and are shown in Scheme 16. From this set of reactions it appears that the type of protecting group has little effect on \(E\)-selectivity. The acetate and bromide showed slightly higher selectivity than the THP protecting group, but this was not that significant.
Deprotection and subsequent oxidation of coupling products

Both the unsaturated ether and acetate, 63 and 64, respectively, were de-protected and oxidized as described earlier to give a mixture of E/Z-11-tetradecenal. With this accomplished, this study became the first to utilize the Julia-Kocienski olefination reaction for controlling the stereochemistry of 63 in a short synthesis of the SBW pheromone. The route allowed for the production of a stereoisomeric mixture of E/Z (87:12)-11-tetradecenal in four steps with an overall yield 28 %, Scheme 17. This has great promise as the isomeric mixture is close to the ideal mixture of 95E:5Z, therefore improvements to the stereoselectivity and overall yield, especially the olefination step, should be explored.
Scheme 17: Shortest synthetic pathway to the SBW pheromone 1.
CONCLUSIONS

This study embarked on developing short synthetic pathways that were economical and utilize green methods to synthesize the SBW pheromone as close to the optimum 95E:5Z ratio as possible. The most important step in this synthesis was the carbon-carbon coupling of two units of varying length that involved coupling primary alkyl halides or alkyl halides with aldehydes. To explore this, two well-known reactions, the Grignard reaction and Julia-Kocienski olefination, were used. Both reactions have been extensively utilized in forming carbon-carbon bonds and in particular the Julia-Kocienski reaction for the installation of high E-stereoselectivity, if carefully controlled. Though both reactions are moisture sensitive and temperature dependent, they are still applicable for large scale synthesis.

The seven Grignard coupling pathways involved the use of alkyl bromides and alkyl iodides. The results demonstrated that coupling of the Grignard derived from an alkyl iodide gave the best yield while coupling of C$_6$ and C$_8$ units gave better yield than coupling of C$_5$ and C$_9$ units. Use of an allyl carbonate as an electrophile in this reaction produced an undesirable 50:50 stereoisomeric mixture. Additionally, the yields of the coupling step indicated independence from length of the carbon chain used to form the Grignard reagent.

The Julia-Kocienski olefination reaction was explored for the first time in synthesis of the SBW pheromone but the yields in the coupling step were more modest when compared to the Grignard reaction. Three different Julia-Kocienski pathways were explored but the yields were unfortunately all in the mid 50% range. Further optimization should be explored in order to improve the yield and stereoselectivity. This is particularly
important as this route allows the SBW pheromone to be synthesized in just four simple steps.

**FUTURE STUDIES**

Grignard reagents are versatile nucleophiles in organic synthesis due to their high reactivity. They are among the most inexpensive organometallics that are readily prepared on large scale industrially and in the laboratory. However, they are extremely sensitive to moisture requiring anhydrous solvents and moisture free magnesium as a key in their preparation. The high basicity and reactivity of these hard nucleophiles is softened by the use of organocopper in $S_N2$ and $S_N2'$ reactions for cross coupling alkyl halides.

This study employed Grignard copper mediated catalysis in seven pathways that involved generating a Grignard reagent from long carbon chain aliphatic THP protected bromides and short chain unsaturated homoallylic and allylic halides. While initial preparation of the reagent was problematic, a key to its success was owed to complete elimination of air, drying of the magnesium powder under inert conditions, careful control of amount of solvent used and optimizing the temperature. Another problem posed was the solidifying of Grignard reagent on transfer, this resulted in the need for rapid addition of the Grignard reagent to the alkyl halide, which may have contributed to the reduced yield of coupling product and side products observed. Despite these limitations the method could be improved in future for synthesis of $trans$-11-tetradecenal.
by investigating the rate and order of addition of the reactants, reaction temperature, solvent effects and alternative catalysts.

No experiments were done where the halide was added to the already formed Grignard reagent. As the organometallic is likely to be stable at room temperature or lower this may allow for the addition of the catalyst and halide to be added to the anion. This could allow one to investigate whether the rapid or slow addition of halide has an effect on yield and overcome the problems of the Grignard reagent solidifying since it’s required to be added slowly.13

The Grignard experiments were carried out in THF and it would be interesting to investigate other aprotic solvents that enhance nucleophilicity for S\textsubscript{N}2, for example diethyl ether or dimethoxyethane (DME) which are both inexpensive. Future studies should also explore the use of ligands in Grignard copper mediated catalysis to improve the yields since the absence of ligands requires slow and regular addition of Grignard reagent for high yields.13

More studies need to be targeted towards allylic carbonates, acetates, halides, etc, as this would allow for the use of an extremely cheap starting material. As it was believed that there was increased coordination of the carbonyl oxygen in the carbonate to the metal, Figure 13, and that this may have contributed to a low stereoselectivity, then less basic acetates and halides may improve this. Coupled with these studies, more experiments need to be done with different copper (1) salts, like CuCN, and solvents to assess their impact on the selectivity.14
Figure 13: Regioselective S\textsubscript{N}2′ nucleophilic addition.

Another future consideration for exploration is searching ways to form a vinyl bromide to enable cross coupling between sp\textsuperscript{2} and sp\textsuperscript{3} hybridized carbons. This has not yet been explored for the synthesis of the SBW pheromone. These \textit{E}-vinyl bromides are useful precursors for vinyl anions and coupling partners in metal catalyzed coupling. A method by Abbas,\textsuperscript{115} Figure 14, could be used to prepare the vinyl bromide starting from propanal.

![Chemical structure](image)

**Figure 14:** Proposed pathway to prepare vinyl bromide.

Since only KHDMS base was used in the Julia olefination resulting in 87\textit{E}:12Z ratio, other bases should be explored to improve the ratio, particularly for the shortest pathway. Also using solvents of different polarities, like DME, and different temperatures may also prove beneficial.\textsuperscript{107}
Chemicals and Instrumentation

All solvents used were of analytical grade (Sigma Aldrich, Fluka, Fischer) or distilled and dried before use. Commercial reagents purchased from Sigma Aldrich, Alfa Aesar, AK Scientific, BDH and VWR analytical. The reagents were used without purification. Thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F$^{254}$ plates or alumina (20 x 20 cm, thickness 0.25 mm) with fluorescence indicator. Spots were visualized using a UV-254 nm lamp or by dipping the plates in a solution of potassium permanganate or phosphomolybidic acid stain and then heating on a hotplate at 350 °C for < 5 minutes. For preparative thin layer chromatography (PTLC), 20 x 20 cm, thickness 0.25 mm plates were used. Flash chromatography was performed with 40 - 63 μm (230 - 400 mesh), 60 Å irregular silica gel, superior grade purchased from SiliCycle Inc, Quebec, Canada.

$^1$H NMR was recorded at 300 MHz or 400 MHz using a Varian Inova 300 MHz or Varian Unity 400 MHz instrument at 25 °C. $^{13}$C NMR were recorded at 100 MHz using a Varian Unity 400 MHz instrument at 25 °C. All NMR spectra were processed and analyzed using the Mnova NMR program, Version 9.1.0-14011 or Version 10.0.2-15465 (Santiago de Compostela, Spain). Chemical shifts are reported in parts per million (ppm) and referenced to residual NMR solvent or tetramethylsilane. All proton-proton coupling constants are reported in Hertz (Hz). Alkene isomer ratio was determined by gas-liquid chromatography-mass spectrometry (GC/MS) using an Agilent Technologies 6890N Gas Chromatograph and Agilent 5973N Mass Selective Detector at Canadian Forest Service – Atlantic Forestry Centre, Fredericton, NB. A Zebron ZB-5MS capillary GC column of length 30 m, internal diameter 0.25 mm and 0.25 μm film thickness was
used with a temperature range from 50 to 220 °C. The sample was injected and the start temperature was held for 2 min, then a temperature ramp of 6.00 °C/min to 220 °C was performed. Once 220 °C was obtained it was held at 220 °C for 35 min. Fourier transformed infrared (FT-IR) spectra were recorded using a NEXUS 470 Infrared spectrometer. Neat samples were prepared on a 32 mm diameter KBr window by evaporating the solvent that resulted from dissolving the compounds in CH₂Cl₂.

Melting point was determined using Gallenkamp melting point apparatus and are uncorrected.

**Experimental procedures**

Synthesis of (E)-1-bromohex-3-ene 24.⁸⁴

\[ \text{OH} \quad \text{Br} \]

The compound was prepared following the procedure by Shakhmaev except with slight modifications. PPh₃ (2.21 g, 8.43 mmol) was dissolved in CH₂Cl₂ (40 mL) and the solution cooled to 10 °C in an ice-water bath. Bromine (8.00 mmol, 0.40 mL) dissolved in CH₂Cl₂ (10 mL) was then added drop-wise with stirring under argon over 5 minutes. After stirring for an additional 30 min while allowing the solution to warm to rt, a yellow suspension was formed. To this was added commercial E-3-hexen-1-ol (0.94 g, 8.20 mmol, 1.00 mL) in CH₂Cl₂ (10 mL) drop-wise over 5 minutes, after complete addition the solution was stirred at rt for 2 h. The mixture was diluted with hexane (150 mL) and then filtered over a pad of silica gel to yield a yellow liquid. Trace triphenylphosphine
oxide was removed by SiO$_2$ column chromatography eluting with hexane ($R_f = 0.5$) to give a bromide 24 as a pale yellow liquid. Yield: 1.26 g, 87%.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.59 (dtt, $J = 15.3$, 6.3, 1.3 Hz, 1H), 5.39 (dtt, $J = 15.2$, 6.7, 1.5 Hz, 1H), 3.37 (t, $J = 7.2$ Hz, 2H), 2.58 – 2.51 (m, 2H), 2.07 – 1.98 (m, 2H), 0.98 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 135.5, 125.4, 36.0, 32.9, 25.6, 13.6.

FT-IR (neat, cm$^{-1}$): 3056, 2967, 2996, 1460, 1262, 957.

Synthesis of (E)-1-iodohex-3-ene 25

The compound was prepared following the procedure by Myron except with some minor changes. PPh$_3$ (2.7 g, 10.4 mmol), 1H-imidazole (0.70 g, 9.60 mmol) and CH$_2$Cl$_2$ (20 mL) were sequentially added to a round bottom flask under argon. The mixture was stirred and cooled to 0 °C in an ice-water bath at which time I$_2$ (2.4 g, 9.6 mmol) was added in portions over 2-3 minutes. After complete addition the solution was stirred for 0.5 h and then commercial E-3-hexen-1-ol (0.80 g, 8.0 mmol, 1.00 mL) in CH$_2$Cl$_2$ (2 mL) was added drop-wise over 5 min and the mixture warmed slowly to rt. After stirring for 2 h, pentane (20 mL) was added and the solution stirred at rt for 30 min to precipitate excess PPh$_3$ and triphenylphosphine oxide. The solution was filtered over a pad of silica gel to give a brown liquid. Further purification by SiO$_2$ column chromatography eluting with hexane ($R_f = 0.50$) gave iodide 25 as a dark brown liquid.
Yield: 1.55 g, 92%.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.57 (dtt, $J = 15.1, 6.2, 1.3$ Hz, 1H), 5.35 (dtt, $J = 14.9, 6.6, 1.4$ Hz, 1H), 3.14 (t, $J = 7.3$ Hz, 2H), 2.68 – 2.41 (m, 2H), 2.15 – 1.88 (m, 2H), 0.99 (t, $J = 7.5$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 135.1, 127.3, 36.8, 25.5, 13.6, 6.1.

FT-IR (neat, cm$^{-1}$): 3029, 2958, 2359, 1454, 1166, 960.

Synthesis of [(E)-hex-3-enyl] 4-methylbenzenesulfonate 26. $^{82}$

Following the procedure of Kabalka, commercial $E$-3-hexen-1-ol (2.06 g, 20 mmol, 1.64 mL) was added to CH$_2$Cl$_2$ (20 mL) and cooled to 0 °C in an ice-water bath. To the stirring solution, pyridine (3.24 mL, 40 mmol) was added followed by p-toluenesulfonyl chloride (5.7 g, 30 mmol) in small portions over 2–3 min. The solution was warmed to room temperature and then stirred for 20 h. Water (14 mL) and ether (60 mL) were added and the separated organic phase was washed with 5% HCl (40 mL), saturated NaHCO$_3$ (20 mL x 2), brine (20 mL x 2) and dried (MgSO$_4$). Following filtration, the solution was concentrated and the crude extract purified by SiO$_2$ chromatography eluting with hexane/EtOAc (9:2, $R_f = 0.50$) to give a pale yellow oil.

Yield: 4.74 g, 94%.
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{):} \] \( \delta 7.82 - 7.76 \text{ (m, 2H), 7.37} - 7.32 \text{ (m, 2H), 5.51 (dtt, } J = 15.3, 6.3, 1.4 \text{ Hz, 1H), 5.23 (dtt, } J = 15.3, 6.8, 1.6 \text{ Hz, 1H), 4.01 (t, } J = 6.9 \text{ Hz, 2H), 2.45 (s, 3H), 2.33 (qq, } J = 6.9, 1.2 \text{ Hz, 2H), 2.01} - 1.92 \text{ (m, 2H), 0.93 (t, } J = 7.5 \text{ Hz, 3H).} \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3\text{):} \] \( \delta 144.6, 136.1, 133.3, 129.8, 127.9, 122.5, 70.2, 32.1, 25.5, 21.6, 13.5. \)

\[ \text{FT-IR (neat, cm}^{-1}\text{):} \] 3029, 2964, 1914, 1590, 1339, 1172, 1096, 966, 656.

Synthesis of 3-(pent-1-eneyl) isobutyl carbonate \(32\). \(^{88}\)

[Diagram]

In a dry 100 mL RBF, 1-penten-3-ol (2.4 mL, 23.2 mmol) and CH\(_2\)Cl\(_2\) (50 mL) were added and solution cooled to 0 °C. Isobutyl chloroformate (3.00 mL, 23.2 mmol) was added drop-wise over 10 min under argon while stirring, followed by pyridine (1.90 mL, 24.8 mmol). The solution was allowed to slowly warm to rt and stir for 12 h. The reaction was quenched by addition of 6 M HCl (25 mL), the organic phase was separated and the aqueous phase was washed with Et\(_2\)O (25 mL x 2). The combined organic extracts was washed with saturated NaHCO\(_3\) (25 mL), brine (25 mL x 2), dried (MgSO\(_4\)), filtered and concentrated to yield a yellow liquid. The crude product was purified by SiO\(_2\)
column chromatography eluting with hexane/EtOAc (2:1, \( R_f = 0.84 \)) to give a colourless liquid.

Yield: 4.24 g, 98 %.

\( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta 5.85 - 5.73 \) (m, 1H), \( 5.34 - 5.16 \) (m, 2H), \( 5.02 - 4.94 \) (m, 1H), \( 3.91 \) (dd, \( J = 7.0, 2.5 \) Hz, 2H), \( 2.10 - 1.86 \) (m, 1H), \( 1.84 - 1.60 \) (m, 2H), \( 0.95 \) (dq, \( J = 6.1, 2.3, 1.8 \) Hz, 9H).

\( ^{13}C \) NMR (100 MHz, CDCl\(_3\)): \( \delta 154.9, 135.9, 117.4, 80.1, 73.9, 27.9, 27.4, 18.9, 9.4 \).

FT-IR (neat, cm\(^{-1}\)): 3029, 2904, 1914, 1590, 1359, 1172, 1096, 966, 656.

General procedure for the synthesis of n-bromo-1-alcohols 38-41.\(^9\)

The n-bromo-1-alcohols were prepared according to the procedure outlined by Chong.\(^9\) In a dry round bottom flask was put the symmetrical diol, toluene and 48% concentrated HBr (1.05 mol eq). The solution was stirred and heated at reflux for 36 h, at which time an additional amount of concentrated HBr (0.40 mol eq) was added. The mixture was heated at reflux for a further 36 h. Upon cooling the mixture to rt, the lower aqueous phase was separated, and the organic layer was diluted with Et\(_2\)O and washed.
with 1 M NaOH, dried (MgSO₄) and solvent removed under reduced pressure. The residue was purified on SiO₂ flash chromatography column eluting with hexane/EtOAc.

Synthesis of 8-bromo-1-octanol 38. ⁹¹

Following the general procedure 1, 8-octane diol 2 (3.00 g, 20.0 mmol), toluene (100 mL) and 48% concentrated HBr (2.70 mL, 21.0 mmol) were used. An additional amount of concentrated HBr (1.00 ml, 8.00 mmol) was added. Purification using SiO₂ flash chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.52$) gave 38 as a colorless oil.
Yield: 3.95 g, 92 %.

$^{1}$H NMR (400 MHz, CDCl₃): \[ \delta 3.64 \text{ (t, } J = 6.9 \text{ Hz, 2H), 3.41 \text{ (t, } J = 6.8 \text{ Hz, 2H), 1.92} \text{ – 1.81} \text{ (m, 2H), 1.63} \text{ – 1.52} \text{ (m, 2H), 1.49} \text{ – 1.27} \text{ (m, 8H).} \]

$^{13}$C NMR (100 MHz, CDCl₃): \[ \delta 62.9, 33.9, 32.8, 32.7, 29.2, 28.7, 28.1, 25.6. \]

FT-IR (neat, cm⁻¹): \[ 3321, 2934, 1456, 1051. \]

Synthesis of 9-bromo-1-nonanol 39.

Following the general procedure 1, 9-nonane diol 35 (3.21 g, 20.0 mmol), toluene (100 mL) and 48% concentrated HBr (2.70 mL, 21.0 mmol) were used. An additional amount of concentrated HBr (1.00 ml, 8.00 mmol) was added. Purification using SiO₂ flash chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.50$) gave 39 as a white crystalline solid.
Yield: 4.02 g, 90 %.
MPt: 32-34 °C

$^1$H NMR (400 MHz, CDCl$_3$): δ 3.64 (t, $J = 6.6$ Hz, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 1.91 – 1.81 (m, 2H), 1.62 – 1.52 (m, 2H), 1.52 – 1.39 (m, 2H), 1.39 – 1.26 (m, 8H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 63.0, 34.0, 33.0, 32.8, 29.4, 29.3, 28.7, 28.1, 25.7.

FT-IR (neat, cm$^{-1}$): 3388, 2925, 1460, 1060.

Synthesis of 10-bromo-1-decanol 40.

Following the general procedure 1, 10-decane diol 36 (3.49 g, 20.0 mmol), toluene (100 mL) and 48% concentrated HBr (2.70 mL, 21.0 mmol) were used. An additional amount of concentrated HBr (1.00 mL, 8.00 mmol) was added. Purification using SiO$_2$ flash chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.50$) gave 40 as a white solid.

Yield: 4.17, 88%.

MPt: 42-45 °C

$^1$H NMR (400 MHz, CDCl$_3$): δ 3.64 (t, $J = 6.6$ Hz, 2H), 3.41 (t, $J = 6.8$ Hz, 2H), 1.90 – 1.81 (m, 2H), 1.56 (m, 2H), 1.48 – 1.39 (m, 2H), 1.32 (m, 10H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 63.0, 34.0, 32.8, 32.6, 29.5, 29.47, 29.36, 28.7, 25.7.

FT-IR (neat, cm$^{-1}$): 3553, 2930, 2845, 1465, 1043.
Synthesis of 11-bromo-1-undecanol 41.

Following the general procedure, 1,11-undecane diol 37 (3.77 g, 20.0 mmol), toluene (100 mL) and 48% concentrated HBr (2.70 mL, 21.0 mmol) were used. An additional amount of concentrated HBr (1.00 mL, 8.00 mmol) was added. Purification using SiO$_2$ flash chromatography eluting with hexane/EtOAc (2:1, $R_f=0.53$) gave 41 as a white crystalline solid.

Yield: 4.62 g, 92 %.

**MPt:** 46-50 °C.

**$^1$H NMR (400 MHz, CDCl$_3$):**

$\delta$ 3.64 (t, $J = 6.7$ Hz, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 1.93 – 1.77 (m, 2H), 1.65 – 1.50 (m, 2H), 1.52 – 1.21 (m, 14H).

**$^{13}$C NMR (100 MHz, CDCl$_3$):**

$\delta$ 63.1, 34.0, 33.0, 32.8, 29.54, 29.45, 29.41, 29.40, 28.8, 28.2, 25.7.

**FT-IR (neat, cm$^{-1}$):**

3375, 2930, 2845, 1465, 1052.

General synthesis of n-bromo-1-(tetrahydropyranoxy)-alkanes 42, 43, 44 and 45

Following the protocol of Zarbin,$^9$ to a solution of $n$-halo-1-alkanol in dry THF, was added pTSA (cat.) and dihydropyran. The reaction was stirred at rt for 4 h and then the mixture was washed with brine, dried over anhydrous MgSO$_4$, filtered and
concentrated under reduced pressure. The residue was purified using SiO₂ chromatography to give the halides 42, 43, 44 and 45.

Synthesis of 8-bromo-1-(tetrahydropyranloxy) octane 42

Following the general procedure, reaction of 38 (3.49 g, 16.7 mmol), THF (50 mL), pTSA (cat. 400 mg) and dihydropyran (1.67 mL, 18.4 mmol) gave after SiO₂ chromatography using hexanes/EtOAc (2:1, \( R_f = 0.66 \)) as eluent 42 a colorless oil. Yield: 4.70 g, 95%.

\[ ^1H \text{ NMR (400 MHz CDCl}_3): \delta 4.58 \ (dd, J = 4.6, 2.8 \ Hz, 1H), 3.94 - 3.83 \ (m, 1H), 3.74 \ (dtd, J = 9.5, 6.9, 0.7 \ Hz, 1H), 3.56 - 3.47 \ (m, 1H), 3.45 - 3.34 \ (m, 3H), 1.90 - 1.79 \ (m, 3H), 1.77 - 1.67 \ (m, 1H), 1.65 - 1.48 \ (m, 5H), 1.48 - 1.28 \ (m, 8H). \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3): \delta 98.9, 67.6, 62.4, 34.1, 32.8, 30.8, 29.7, 29.3, 28.7, 28.1, 26.1, 25.5, 19.7. \]

\[ \text{FT-IR (neat, cm}^{-1}) : 2930, 1739, 1460, 1029. \]

Synthesis of 9-bromo-1-(tetrahydropyranloxy) nonane 43.

Following the general procedure, reaction of 39 (3.73 g, 16.7 mmol), THF (50 mL), pTSA (cat. 400 mg) and dihydropyran (1.67 mL, 18.4 mmol) gave after SiO₂ chromatography using hexanes/EtOAc (2:1, \( R_f = 0.74 \)) as eluent 43 a colorless oil. Yield: 4.87 g, 95%.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.57 (dd, $J = 4.5$, 2.7 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.73 (dtd, $J = 9.6$, 6.9, 0.7 Hz, 1H), 3.55 – 3.46 (m, 1H), 3.45 – 3.34 (m, 3H), 1.91 – 1.78 (m, 3H), 1.76 – 1.66 (m, 1H), 1.65 – 1.48 (m, 5H), 1.47 – 1.26 (m, 10H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 98.9, 67.6, 62.5, 34.0, 30.8, 29.7, 29.4, 28.7, 28.2, 26.2, 25.5, 19.7.

FT-IR (neat, cm$^{-1}$): 2930, 1466, 1262, 1029.

Synthesis of 10-bromo-1-(tetrahydropyanyloxy) decane 44.

Following the general procedure, reaction of 40 (3.96 g, 16.7 mmol), THF (50 mL), pTSA (cat. 400 mg) and dihydropyran (1.67 mL, 18.4 mmol) gave after SiO$_2$ chromatography using hexanes/EtOAc (2:1, $R_f = 0.74$) as eluent 44 a colorless oil.

Yield: 4.99 g, 93%.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.57 (dd, $J = 4.5$, 2.7 Hz, 1H), 3.87 (ddd, $J = 11.1$, 7.4, 3.3 Hz, 1H), 3.73 (dt, $J = 9.5$, 6.9 Hz, 1H), 3.54 – 3.47 (m, 1H), 3.44 – 3.37 (m, 3H), 1.91 – 1.79 (m, 3H), 1.76 – 1.67 (m, 1H), 1.64 – 1.48 (m, 5H), 1.48 – 1.26 (m, 12H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 98.6, 67.6, 62.2, 33.8, 32.8, 30.6, 29.7, 29.4, 29.3, 28.6, 28.1, 26.2, 25.6, 19.6.

FT-IR (neat, cm$^{-1}$): 2921, 2845, 2252, 1452, 1034, 728.
Synthesis of 11-bromo-1-(tetrahydropyanyloxy) undecane 45.

Following the general procedure, reaction of 41 (4.20 g, 16.7 mmol), THF (50 mL), pTSA (cat. 400 mg) and dihydropyran (1.67 mL, 18.4 mmol) gave after SiO₂ chromatography using hexanes/EtOAc (2:1, \( R_f = 0.74 \)) as eluent 45 a colorless oil.

Yield: 5.36 g, 96%.

\(^1\)H NMR (400 MHz, CDCl₃): \( \delta 4.57 \) (dd, \( J = 4.5, 2.7 \) Hz, 1H), 3.87 (ddd, \( J = 11.1, 7.4, 3.6 \) Hz, 1H), 3.73 (dt, \( J = 9.6, 6.9 \) Hz, 1H), 3.54 – 3.46 (m, 1H), 3.43 – 3.35 (m, 4H), 1.91 – 1.80 (m, 3H), 1.64 – 1.48 (m, 5H), 1.46 – 1.24 (m, 15H).

\(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta 98.9, 67.7, 62.4, 34.0, 32.8, 30.8, 29.8, 29.53, 29.47, 29.42, 28.8, 28.2, 26.2, 25.5, 19.7 \).

FT-IR (neat, cm⁻¹): 2921, 1465, 1128, 1020.

Synthesis of 11-acetoxy-1-undecanol 58.

\[
\text{HO} \quad \bigg( \bigg)_{9} \quad \text{OH} \quad \rightarrow \quad \text{AcO} \quad \bigg( \bigg)_{9} \quad \text{OH}
\]

Toluene (20 mL), 1,11-undecanediol 37 (1.00 g, 5.30 mmol), glacial acetic acid (3.00 mL, 53.1 mmol), water (1.0 mL), and concentrated H₂SO₄ (10 drops) were added to a dry 100 mL round bottom flask. The mixture was stirred and heated at reflux for 4 h at 110 °C. After cooling to rt, the mixture was washed with water (10 mL), 10% NaHCO₃ (2 x 25 mL), brine (25 mL), dried (MgSO₄), filtered, and the solvent removed under reduced pressure to give a colorless liquid which solidified after standing at rt to a white
solid. Purification by SiO$_2$ column chromatography eluting with hexane/EtOAc (7:3, $R_f = 0.50$) gave 58 as a white crystalline solid.

Yield: 1.07 g, 88%.

**MPt:**

59-60 °C.

**$^1$H NMR (300 MHz, CDCl$_3$):**

δ 4.05 (t, $J = 6.8$ Hz, 2H), 3.64 (t, $J = 6.6$ Hz, 2H), 2.05 (s, 3H), 1.58 (dq, $J = 14.0$, 6.9 Hz, 8H), 1.42 – 1.17 (m, 10H).

**$^{13}$C NMR (100 MHz, CDCl$_3$):**

δ 171.2, 64.6, 62.9, 32.7, 29.4, 29.3, 29.27, 29.10, 29.09, 28.5, 25.8, 25.7, 21.0.

**FT-IR (neat, cm$^{-1}$):**

3455, 2926, 1732, 1235, 1033.

**Synthesis of 11-acetoxyundecanal 62.**

![Diagram](image)

94 Hoover’s procedure was followed. To a dry 25 ml RBF containing alcohol 58 (0.48 g, 2.00 mmol) was added dry CH$_3$CN (2 mL) followed sequentially by CuOTf (0.038 g, 0.10 mmol in 2 mL of CH$_3$CN), 2, 2'-bipyridine (0.016 g, 0.10 mmol in 2 mL of CH$_3$CN), TEMPO (0.016 g, 0.10 mmol in 2 mL of CH$_3$CN) and N-methylimidazole (0.008 g, 0.20 mmol in 2 mL of CH$_3$CN) at rt. The brown solution was rapidly stirred until the solution turned green, approximately 8 h, and $^1$H NMR showed reaction was complete. The mixture was neutralized with 1 M HCl (10 mL) and diluted with water (20 mL). The organic phase (pale green) was separated and the aqueous phase (pale blue) was washed with CH$_2$Cl$_2$ (25 mL x 5). The combined organic extracts was washed with
brine (25 mL x 2), dried (MgSO₄), filtered and concentrated to give a pale brown oil. Purification by SiO₂ column chromatography eluting with hexane/ EtOAc (2:1, R_f = 0.74) gave 62 as a brown oil.

Yield: 0.44 g, 96%.

**¹H NMR (400 MHz, CDCl₃):** \(\delta\) 9.77 (t, \(J = 1.8\) Hz, 1H), 4.05 (td, \(J = 6.8, 1.4\) Hz, 2H), 2.56 – 2.27 (m, 2H), 2.07 – 2.03 (m, 3H), 1.69 – 1.57 (m, 4H), 1.39 – 1.24 (m, 12H).

**¹³C NMR (100 MHz, CDCl₃):** \(\delta\) 202.9, 171.2, 64.6, 43.9, 29.4, 29.3, 29.2, 29.1, 28.6, 25.9, 22.1, 21.0.

**FT-IR (neat, cm⁻¹):** 3053, 2933, 2715, 2255, 1742.

Synthesis of 11-bromoundecanal 60.⁹⁴ Hoover’s procedure was followed. To a dry 25 ml RBF containing bromoalcohol 41 (0.50 g, 2.00 mmol) was added dry CH₃CN (2 mL) followed sequentially by CuOTf (0.04 g, 0.10 mmol in 2 mL of CH₃CN), 2, 2′-bipyridine (0.02 g, 0.10 mmol in 2 mL of CH₃CN), TEMPO (0.02 g, 0.10 mmol in 2 mL CH₃CN) and N-methylimidazole (0.008 g, 0.20 mmol in 2 mL of CH₃CN) at rt. The brown solution was rapidly stirred until the solution turned green, approximately 8 h, and ¹H NMR showed that the reaction was complete. The mixture was neutralized with 1 M HCl (10 mL) and diluted with water (20 mL). The organic phase (pale green) was separated and the aqueous phase (pale blue) was washed with CH₂Cl₂ (25 mL x 5). The combined organic extracts was washed with
brine (25 mL x 2), dried (MgSO₄), filtered and concentrated to give a pale brown oil. Purification by SiO₂ column chromatography eluting with hexane/ EtOAc (9:2, Rf = 0.59) gave 60 as a brown oil.

Yield: 0.46 g, 92 %.

**¹H NMR (400 MHz, CDCl₃):**

δ 9.77 (p, J = 1.9 Hz, 1H), 3.41 (tt, J = 6.9, 1.7 Hz, 3H), 2.43 (tq, J = 7.3, 1.6 Hz, 3H), 1.86 (dtt, J = 15.6, 6.9, 1.7 Hz, 3H), 1.68 – 1.59 (m, 3H), 1.48 – 1.39 (m, 2H), 1.37 – 1.26 (m, 6H).

**¹³C NMR (101 MHz, CDCl₃):**

δ 202.9, 43.9, 34.0, 32.8, 29.3, 29.26, 29.25, 29.1, 28.7, 28.1.

**FT-IR (neat, cm⁻¹):**

3032, 2926, 2701, 1721.

Synthesis of 11-[(tetrahydro-2H-pyran-2-yl)oxy]-undecanal 61.¹¹²

Anhydrous TMANO (0.59 g, 7.8 mmol) was added to a dry 25 mL RBF and flushed with Ar for 15 minutes. Dry DMSO (4 mL) was added under inert atmosphere at rt followed by bromide 45 (0.65 g, 1.94 mmol, in 1 mL of dry DMSO). The colorless mixture was stirred under an argon atmosphere for 5 h with the colour changing to a white gray opaque solution. The reaction was monitored using TLC and NMR, once complete it was quenched by pouring into ice cold brine (10 mL) and extracted with Et₂O (10 mL x 4). The combined organic extracts was washed with brine (10 mL x 2), dried (MgSO₄), filtered and concentrated to give a colorless oil. Purification using SiO₂ column
chromatography and eluting with hexane/EtOAc (9:2, \( R_f = 0.60 \)) gave 61 as a clear colorless liquid.

Yield: 0.33 g, 62%

\(^1\)H NMR (400 MHz, CDCl\(_3\)):
\[ \delta 9.77 (t, J = 3.7 \text{ Hz, 1H}), 4.57 (dd, J = 4.4, 2.5 \text{ Hz, 1H}), 3.92 – 3.83 (m, 1H), 3.78 – 3.69 (m, 1H), 3.55 – 3.46 (m, 1H), 3.43 – 3.34 (m, 1H), 2.41 (td, J = 7.4, 2.8 Hz, 2H), 1.90 – 1.78 (m, 1H), 1.77 – 1.68 (m, 1H), 1.67 – 1.48 (m, 7H), 1.41 – 1.22 (m, 10H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)):
\[ \delta 203.1, 98.9, 67.7, 62.4, 43.9, 30.8, 29.6, 29.5, 29.44, 29.4, 29.3, 29.2, 26.2, 25.5, 22.1, 19.7.

FT-IR (neat, cm\(^{-1}\)):
\[ 3061, 2930, 2854, 2719, 1716, 1137, 1034.

Synthesis of 1-phenyl-5-(11-tetrahydropyran-2-yloxyundecylsulfanyl) tetrazole 56.\(^{108}\)

\[ \text{Br} \quad \text{OTHP} \quad \text{45} \quad \rightarrow \quad \text{S} \quad \text{OTHP} \quad \text{10} \quad \text{56} \]

Following Dussart’s procedure\(^{108}\) but with some minor alterations, to a dry 100 mL round bottom flask under an argon atmosphere was put NaH (60 wt% in oil, 0.15 g, 6.40 mmol) and THF (15 mL). To this stirring suspension cooled in an ice bath, 1-phenyl-1H-tetrazole-5-thiol 53 (1.06 g, 6.0 mmol) in THF (5 mL) was added drop-wise. After stirring at this temperature for 10 min, bromide 45 (2.00 g, 6.00 mmol) in THF (4 mL) was added and then the solution was warmed slowly to rt and stirred for 8 h. The
mixture was quenched by the addition of saturated NH₄Cl (2 x 20 mL). The organic phase was separated and the aqueous phase was washed with EtOAc (2 x 10 mL). The combined organic phases was dried (MgSO₄), filtered and concentrated to give a colorless liquid that solidified on standing at rt. Purification by SiO₂ column chromatography eluting with hexane/ EtOAc (7:3, R_f = 0.15) gave 56 as a colorless liquid.

Yield: 1.68 g, 65%.

**¹H NMR (400 MHz, CDCl₃):**  δ 7.66 – 7.49 (m, 5H), 4.57 (dd, J = 4.5, 2.7 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.77 – 3.69 (m, 1H), 3.54 – 3.47 (m, 1H), 3.43 – 3.35 (m, 3H), 1.89 – 1.77 (m, 3H), 1.76 – 1.67 (m, 1H), 1.63 – 1.49 (m, 6H), 1.44 (p, J = 7.1 Hz, 2H), 1.39 – 1.23 (m, 11H).

**¹³C NMR (100 MHz, CDCl₃):**  δ 154.8, 130.1, 129.8, 129.3, 123.9, 123.7, 98.9, 67.8, 62.4, 33.4, 30.8, 29.7, 29.5, 29.47, 29.45, 29.41, 29.06, 29.02, 28.6, 26.2, 25.5, 19.7.

**FT-IR (neat, cm⁻¹):**  2916, 1739, 1586, 1505, 1375, 759, 687.

Synthesis of 1-phenyl-5-(11-tetrahydropyran-2-yloxyundecylsulfonyl) tetrazole 57.¹⁰⁹

![Synthesis of 1-phenyl-5-(11-tetrahydropyran-2-yloxyundecylsulfonyl) tetrazole 57.¹⁰⁹](image)
Using the procedure described by Kadasamy\textsuperscript{109} a dry 50 mL round bottom flask was charged with sulfide 56 (1.00 g, 2.31 mmol), ammonium heptamolybdate tetrahydrate (0.29 g, 0.23 mmol, 0.20 mmol) and MeOH (10 mL). Then 30\% aqueous H$_2$O$_2$ (0.94 mL, 9.24 mmol, 9.8 M) was added drop-wise at rt and a yellow solution resulted. After stirring for 8 h, MeOH was evaporated and the residue was diluted with EtOAc (10 mL), washed with aqueous NaHCO$_3$ (10 mL), brine (10 mL x 2), dried (MgSO$_4$), filtered and concentrated to give a colorless oil. The residue was purified by SiO$_2$ flash column chromatography eluting with hexane/EtOAc (7:3, $R_f = 0.41$) to give 57 as a colorless oil.

Yield: 1.0 g, 93%.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.73 – 7.67 (m, 1H), 7.64 – 7.57 (m, 4H), 4.58 (dd, $J = 4.6$, 2.6 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.77 – 3.69 (m, 2H), 3.55 – 3.46 (m, 1H), 3.42 – 3.35 (m, 2H), 2.01 – 1.90 (m, 1H), 1.64 – 1.45 (m, 6H), 1.40 – 1.24 (m, 14H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.5, 133.1, 131.4, 129.7, 125.1, 98.8, 67.7, 62.3, 56.0, 32.8, 30.8, 29.7, 29.5, 29.43, 29.38, 29.16, 28.9, 28.1, 26.2, 25.5, 22.0, 19.7.

FT-IR (neat, cm$^{-1}$): 2925, 1501, 1343, 1146, 1024, 755.
Synthesis of 5-[(1-propyl) sulfanyl]-1-phenyl-1H-tetrazole 54.

Using the procedure described for the formation of compound 56, reaction of NaH (60 wt% in oil, 0.23 g, 9.40 mmol), THF (15 mL), 1-phenyl-1H-tetrazole-5-thiol 53 (1.59 g, 9.00 mmol) and 1-bromopropane (1.11 g, 9.00 mmol) yielded, after purification by SiO2 column chromatography eluting with hexane/ EtOAc (7:3, Rf = 0.20) 54 as a colorless oil.

Yield: 1.63, 82%.

$^1$H NMR (400 MHz, CDCl$_3$)  \( \delta \) 7.60 – 7.56 (m, 1H), 7.56 – 7.53 (m, 4H), 3.43 – 3.34 (m, 2H), 1.94 – 1.81 (m, 2H), 1.06 (td, \( J = 7.3, 0.7 \) Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$)  \( \delta \) 154.5, 133.7, 130.0, 129.7, 123.8, 35.2, 22.6, 13.2.

FT-IR (neat, cm$^{-1}$):

2966, 2849, 2238, 1595, 1487, 1235, 921, 755, 687.

Synthesis of 1-phenyl-5-(propylsulfonyl)-1H-tetrazole 55.

Using the procedure described for the formation of compound 57, reaction of sulfide 54 (1.0 g, 4.54 mmol), ammonium heptamolybdate tetrahydrate (0.56 g, 0.45
mmol), MeOH (10 mL) and 30% aqueous H₂O₂ (1.85 mL, 18.2 mmol, 9.8 M) yielded, after purification by SiO₂ flash column chromatography eluting with hexane/EtOAc (7:3, R_f = 0.37), 55 as a white solid.

Yield: 1.1 g, 93%.

MPt: 47-50 °C

^1^H NMR (400 MHz, CDCl₃): δ 7.72 – 7.68 (m, 2H), 7.65 – 7.59 (m, 3H), 3.81 – 3.65 (m, 2H), 2.08 – 1.96 (m, 2H), 1.15 (td, J = 7.5, 0.7 Hz, 3H).

^1^C NMR (100 MHz, CDCl₃): δ 153.5, 133.3, 131.7, 129.5, 124.8, 57.6, 15.8, 12.8.

FT-IR (neat, cm⁻¹): 2970, 2872, 1596, 1156, 764.

Synthesis of (11E)-1-tetrahydropyanyloxytetradec-3-ene 52.⁸¹,¹⁰⁹

General procedure for the Grignard copper mediated coupling ⁸⁰

Method A

Following the procedure described by Belmar et al,⁸¹ a 50 mL oven dried (overnight) three necked flask was charged with powdered Mg (4.2 eq) and fitted with a reflux condenser while still hot. The flask and contents were flushed with argon gas for 1 h and then the whole apparatus was dried once more with a heat gun under inert gas. After cooling to rt and flushing with argon gas for a further 1 h, dry THF (5 mL) was added to the flask via syringe followed by 1, 2-dibromoethane (1 mL). Once reaction was
observed, as evidenced by the formation of bubbles and warming of the solution, the bromoether (4.0 eq) in dry THF (10 mL) was added drop-wise via syringe over 15-20 minutes while stirring. Once the solution began to reflux, an oil bath heated at 72 °C was introduced to maintain the reaction at reflux temperature. After complete addition the mixture was further stirred and heated at reflux for 30 minutes. The mixture was then cooled to rt and immediately transferred via syringe to a stirring suspension of CuI (cat. 10% mmol) in THF (10 mL) at rt which immediately formed a dark blue solution. Stirring was continued for 30 min and then unsaturated halide/carbonate (2.0 eq) in THF (5 mL) was then added at rt and the mixture stirred for 1-2 h. Saturated NH₄Cl solution (15 mL) was then added and mixture stirred for 30 min. The organic phase was separated and aqueous layer washed with Et₂O (15 mL x 3). The combined organic extract was washed with brine (20 mL), dried (MgSO₄), filtered, concentrated and purified by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, Rₖ = 0.63) to give 52 a colourless liquid.
Yield: 0.54 – 0.75 g, 56 – 78%

Following the general procedure, Mg (0.33 g, 13.7 mmol), 9-bromo-1-tetrahydropyranlyoxynonane 43 (4.00 g, 13.0 mmol) and bromo-2-pentene 46 (0.48 g,
3.25 mmol) yielded 52 following purification by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, \( R_f = 0.63 \)) as a clear colorless liquid.

Yield: 0.60 g, 62%.

\(^{1}\)H NMR (400 MHz, CDCl₃): \( \delta \ 5.54 - 5.26 \) (m, 2H), 4.58 (dd, \( J = 4.4, 2.7 \) Hz, 1H), 3.91 – 3.83 (m, 1H), 3.76 – 3.69 (m, 1H), 3.54 – 3.46 (m, 1H), 3.42 – 3.35 (m, 1H), 2.08 – 1.91 (m, 2H), 1.83 (dt, \( J = 10.4, 5.3 \) Hz, 4H), 1.77 – 1.67 (m, 3H), 1.64 – 1.41 (m, 3H), 1.40 – 1.16 (m, 14H), 0.96 (t, \( J = 7.5 \) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta \ 131.9, 131.5, 129.4, 129.3, 98.8, 67.7, 62.3, 32.6, 30.8, 30.3, 29.8, 29.7, 29.6, 29.5, 29.2, 26.3, 25.7, 19.8, 14.5, 14.0.

FT-IR (neat, cm\(^{-1}\)): 2970, 2871, 2359, 1595, 1487, 1343, 1155, 764.

Following the general procedure, Mg (0.33 g, 13.7 mmol), 8-bromo-1-(tetrahydropyranloxy)octane 42 (3.8 g, 13.0 mmol) and \((E)\)-1-bromohex-3-ene 24 (0.53 g, 3.25 mmol) yielded 52 following purification by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, \( R_f = 0.63 \)) as a clear colorless liquid.

Yield: 0.54 g, 56%.
Following the general procedure, Mg (0.33 g, 13.7 mmol), 8-bromo-1-(tetrahydropyranloxy)octane 42 (3.80 g, 13.0 mmol) and (E)-1-iodohex-3-ene 25 (0.68 g, 3.25 mmol) yielded 52 following purification by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, \( R_f = 0.63 \)) as a clear colorless liquid.

Yield: 0.75 g, 78%.

Following the general procedure, Mg (0.33 g, 13.7 mmol), 9-bromo-1-tetrahydropyranloxynonane 43 (4.00 g, 13.0 mmol) and (E)-1-bromo-2-pentene 46 (0.48 g, 3.25 mmol, 95% assay) yielded 52 following purification by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, \( R_f = 0.63 \)) as a clear colorless liquid.

Yield: 0.60 g, 62%.
Following the general procedure, Mg (0.33 g, 13.7 mmol), 9-bromo-1-tetrahydropyranlyoxynonane 43 (4.00 g, 13.0 mmol) and carbonate 32 (0.61 g, 3.25 mmol) yielded 52 following purification by SiO$_2$ column chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.63$) as a clear colorless liquid.

Yield: 0.72 g, 78%.

**Method B**

A 50 mL oven dried (overnight) three necked flask was charged with powdered Mg (0.12 g, 5.04 mmol) and fitted with a reflux condenser while still hot. The assembled apparatus was flushed with argon gas for 1 h and then it was dried with a heat gun once more. The apparatus was allowed to cool to rt while being flushed with Ar gas for an additional 1 h and then dry THF (2 mL) was added via syringe followed by 1, 2-dibromoethane (0.2 mL). After reaction was observed, as evidenced by bubbles and warming of the solution, (E)-1-iodohex-3-ene 25 (1.0 g, 4.8 mmol) in dry THF (3 mL) was added via syringe drop-wise over 5 minutes. Once the solution began refluxing, an
oil bath heated at 72 °C was introduced to maintain the solution at reflux. An additional amount of THF (5 mL) was added and the reaction was heated at reflux and stirred for 30 minutes. The mixture was cooled to rt and immediately transferred via syringe to a stirring suspension of CuI (cat. 91.4 mg, 0.48 mmol) in THF (2.5 mL) at rt forming immediately a dark blue solution. After stirring for 30 min, bromide 42 (0.47 g, 1.60 mmol) in THF (5 mL) was then added and the mixture stirred for an additional 1-2 h. Saturated NH₄Cl solution (10 mL) was added and the mixture stirred for 30 min. The organic phase was separated and the aqueous layer was washed with Et₂O (5 mL x 3). The combined extract was washed with brine (15 mL), dried (MgSO₄), filtered, concentrated and purified by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.63$) to give a colourless oil.

Following the general procedure, Mg (0.12 g, 5.00 mmol), (E)-1-bromohex-3-ene 24 (0.78 g, 4.80 mmol) and 8-bromo-1-(tetrahydropyranlyoxy)octane 42 (0.47 g, 1.60 mmol) yielded 52 following purification by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.63$) as a clear colorless liquid.

Yield: 0.732 g, 76%.
Following the general procedure, Mg (0.12 g, 5.00 mmol), (E)-1-bromo-2-pentene 46 (0.72 g, 4.80 mmol, 95% assay) and 9-bromo-1-tetrahydropyranoxynonane 43 (0.49 g, 1.60 mmol) yielded 52 following purification by SiO\(_2\) column chromatography eluting with hexane/EtOAc (2:1, \(R_f = 0.63\)) as a clear colorless liquid. Yield: 0.69 g, 72%.

General procedure for the Julia-Kocienski coupling\(^{106}\)

Following the procedure outlined by Blakemore,\(^{106}\) sulfone (1 eq) was added to a dry round bottom flask and flushed with Ar for about 15 min. Dry THF (20 mL) was added and the solution was cooled to -78 °C at which time potassium bis (trimethylsilyl) amide (KHDMS) (1.1 eq, 0.5 M in toluene) was added drop-wise over 1-2 min to form a yellow solution. After stirring for 1 h, aldehyde (1 eq) in THF (1 mL) was added drop-wise over 5 min and then the mixture was stirred at -78 °C for 1h. The mixture was poured into H\(_2\)O (15 mL), stirred for 30 min, the organic phase was separated and the aqueous phase was washed with Et\(_2\)O (10 mL). The combined organic extracts was washed with brine (10 mL x 2), dried (MgSO\(_4\)), filtered and concentrated to give a colorless oil. Purification by SiO\(_2\) column chromatography eluting with hexane/EtOAc (2:1, \(R_f = 0.63\)) gave a clear colorless liquid. Yield: 0.40-0.49 g, 50-56%.
Synthesis of \((E)-1\)-(tetrahydropyranloxy) tetradec-11-ene \(52\).

Following the general procedure above, propanal (0.19 g, 3.18 mmol), sulfone \(57\) (1.48 g, 3.18 mmol) and KHMDS (7.00 mL, 3.50 mmol) yielded \(52\) following purification by SiO\(_2\) column chromatography eluting with hexane/EtOAc (2:1, \(R_f = 0.63\)) as a clear colorless liquid.

Yield: 0.49 g, 52%.

\(^1\)H NMR (400 MHz, CDCl\(_3\)):
\[ \delta 5.55 - 5.26 (m, 2H), 4.68 - 4.44 (m, 1H), 3.92 - 3.83 (m, 1H), 3.77 - 3.69 (m, 1H), 3.55 - 3.46 (m, 1H), 3.43 - 3.34 (m, 1H), 2.06 - 1.93 (m, 3H), 1.88 - 1.79 (m, 1H), 1.76 - 1.67 (m, 1H), 1.64 - 1.47 (m, 6H), 1.45 - 1.19 (m, 10H), 0.96 (t, \(J = 7.5\) Hz, 3H). \]

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):
\[ \delta 131.6, 131.5, 129.38, 129.34, 98.8, 67.7, 62.3, 32.3, 31.6, 30.8, 29.8, 29.7, 29.6, 29.57, 29.52, 29.5, 29.2, 27.1, 26.3, 25.5, 22.7, 19.7, 14.1, 14.0. \]

FT-IR (neat, cm\(^{-1}\)):
\[ 2970, 2871, 2359, 1595, 1487, 1343, 1155, 764. \]
Following the general procedure above, aldehyde 61 (0.86 g, 3.18 mmol), sulfone 55 (0.80 g, 3.18 mmol) and KHMDS (7.0 mL, 3.50 mmol) yielded 52 following purification by SiO$_2$ column chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.63$) as a clear colorless liquid.
Yield: 0.61 g, 65%.

Synthesis of (E)-11-Tetradecenyl acetate 64.

Following the general procedure above, aldehyde 62 (0.73 g, 3.20 mmol), sulfone 55 (0.80 g, 3.18 mmol) and KHMDS (7.0 mL, 3.50 mmol) yielded 64 following purification by SiO$_2$ column chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.74$) as a clear colorless liquid.
Yield: 0.40 g, 50%.
$^1$H NMR (400 MHz, CDCl$_3$): \( \delta \) 5.59 – 5.32 (m, 2H), 4.05 (t, \( J = 6.8 \) Hz, 2H), 2.05 (s, 3H), 2.02 – 1.92 (m, 2H), 1.67 – 1.56 (m, 3H), 1.39 – 1.21 (m, 16H), 0.96 (t, \( J = 7.5 \) Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): \( \delta \) 171.3, 131.9, 129.4, 64.7, 32.6, 29.7, 29.5, 29.5, 29.5, 29.3, 29.2, 28.6, 25.9, 21.0, 14.0.

FT-IR (neat, cm$^{-1}$): 3160, 2935, 2858, 2260, 1721, 1267, 1034.

Synthesis of (E)-14-bromo-3-tetradecene 63.

Following the general procedure above, aldehyde 60 (0.79 g, 3.18 mmol), sulfone 55 (0.80 g, 3.18 mmol) and KHMDS (7.00 mL, 3.50 mmol) yielded 63 following purification by SiO$_2$ column chromatography eluting with hexane/EtOAc (2:1, \( R_f = 0.64 \)) as a clear colorless liquid.

Yield: 0.49 g, 56%.

$^1$H NMR (400 MHz, CDCl$_3$): \( \delta \) 5.54 – 5.28 (m, 2H), 3.41 (ddd, \( J = 9.1, 6.4, 4.2 \) Hz, 2H), 1.99 (dp, \( J = 19.4, 6.8 \) Hz, 2H), 1.84 (q, \( J = 7.5 \) Hz, 2H), 1.50 – 1.18 (m, 12H), 0.97 (q, \( J = 7.9, 5.5 \) Hz, 2H), 0.93 – 0.80 (m, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$):  δ 131.9, 129.3, 34.0, 32.8, 32.5, 29.6, 29.5, 29.4, 29.41, 29.1, 28.8, 28.2, 25.6, 14.0.

FT-IR (neat, cm$^{-1}$):  2926, 2845, 2355, 2112, 1452, 1375, 1087.

Synthesis of ($E$) - 11-tetradecen-1-ol 4.\textsuperscript{92}

\[
\begin{align*}
\text{Method A} \quad &
\end{align*}
\]

According to the method outlined by Zarbin,\textsuperscript{92} unsaturated ether 52 (0.5, 1.7 mmol), pTSA (0.08 g, 0.42 mmol) and MeOH (5 mL) were added to a dry 25 mL round bottom flask and the mixture stirred under Ar at rt for 6 h. The solvent was evaporated and the residue taken up in Et$_2$O (10 mL) and washed with saturated NaHCO$_3$ (10 mL), brine (10 mL), dried (MgSO$_4$), filtered and concentrated to yield a colorless liquid. Purification by SiO$_2$ column chromatography eluting with hexane/EtOAc (2:1, $R_f = 0.63$) gave a clear colorless oil.

Yield: 0.32 g, 90%.

$^1$H NMR (400 MHz, CDCl$_3$):  δ 5.54 – 5.28 (m, 2H), 3.64 (t, $J = 6.6$ Hz, 2H), 2.12 – 1.86 (m, 4H), 1.73 – 1.47 (m, 2H), 1.48 – 1.15 (m, 12H), 0.96 (td, $J = 7.4$, 0.7 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$):  δ 131.8, 129.3, 63.1, 32.8, 32.5, 29.6, 29.6, 29.5, 29.4, 29.1, 25.7, 25.6, 22.6, 14.0.

FT-IR (neat, cm$^{-1}$):  3339, 2925, 2849, 1460, 1375, 1047.
Method B

Following the procedure outlined by Bates, acetate 64 (0.42 g, 1.65 mmol), K$_2$CO$_3$ (0.68 g, 4.95 mmol) and MeOH (10 mL) were added to a flask and stirred at rt for 2.5 h. The solvent was evaporated and the residue taken up in Et$_2$O (10 mL) and washed with saturated NaHCO$_3$ (10 mL), brine (10 mL), dried (MgSO$_4$), filtered and concentrated to yield a colorless liquid. Purification by SiO$_2$ column chromatography eluting with hexane/EtOAc (2:1, $R_f$ = 0.63) gave a clear colorless oil.

Yield: 0.35 g, 92%.

Synthesis of (E)-11-tetradecenal 1.

Method A

Hoover’s procedure was followed. To a dry 25 mL RBF containing unsaturated alcohol 4 (0.43 g, 2.0 mmol) was added dry CH$_3$CN (2 mL) followed sequentially by CuOTf (0.04 g, 0.10 mmol in 2 mL of CH$_3$CN), 2,2'-bipyridine (0.02 g, 0.10 mmol in 2 mL of CH$_3$CN), TEMPO (0.02 g, 0.10 mmol in 2 mL of CH$_3$CN) and N-methyl imidazole (0.008 g, 0.20 mmol in 2 mL of CH$_3$CN) at rt. The brown solution was rapidly stirred until it turned greened in approximately 8 h, and $^1$H NMR showed reaction was complete. The mixture was neutralized with 1 M HCl (10 mL) and diluted with water (20 mL). The organic phase (pale green) was separated and the aqueous phase (pale blue)
was washed with CH₂Cl₂ (25 mL x 5). The combined organic extracts was washed with brine (25 mL x 2), dried (MgSO₄), filtered and concentrated to give a pale brown oil. Purification by SiO₂ column chromatography eluting with hexane/ EtOAc (2:1, \( R_f = 0.76 \)) gave 1 as a colourless oil.

Yield: 0.42 g, 100%.

\(^{1}\text{H NMR (400 MHz, CDCl₃):}\) \( \delta \) 9.77 (q, \( J = 1.7 \) Hz, 1H), 5.40 (dq, \( J = 15.1, 9.4, 7.3 \) Hz, 2H), 2.41 (td, \( J = 7.2, 3.4 \) Hz, 2H), 1.98 (h, \( J = 7.1 \) Hz, 5H), 1.79 – 1.47 (m, 3H), 1.29 (d, \( J = 11.2 \) Hz, 10H), 1.07 – 0.89 (m, 3H).

\(^{13}\text{C NMR (100 MHz, CDCl₃):}\) \( \delta \) 202.9, 131.9, 129.3, 43.9, 32.5, 29.6, 29.4, 29.3, 29.2, 29.1, 25.6, 22.1, 14.0.

\(^{\text{FT-IR (neat, cm}^{-1})\):\) 3020, 2925, 2849, 2714, 1716, 1456, 1375, 957.

**Method B**

Anhydrous TMANO (0.59 g, 7.83 mmol) was added to a dry 25 mL RBF and flushed with Ar for 15 minutes. Dry DMSO (4 mL) was added under inert atmosphere at rt followed by bromide 63 (0.53 g, 1.94 mmol, in DMSO (1 mL) and the colorless mixture stirred under argon for 5 h with the colour changing to a white gray opaque solution. The reaction was monitored using TLC and NMR, and when complete was quenched by pouring into ice cold brine (10 mL) and extracted with Et₂O (10 mL x 4). The combined organic extracts was washed with brine (10 mL x 2), dried (MgSO₄).
filtered and concentrated to give a colorless solution. Purification by SiO₂ column chromatography eluting with hexane/EtOAc (2:1, \( R_f = 0.76 \)) gave 1 as a clear colorless liquid. Yield: 0.25 g, 60%.
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Appendix 1: $^1$H NMR Spectra
Appendix 2: $^{13}$C NMR Spectra
-62.927
-33.998
-32.781
-32.699
-29.216
-28.714
-28.088
-25.640
Appendix 3: IR Spectra
**Vitae**

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<thead>
<tr>
<th>Candidate’s full Name:</th>
<th>Martin Barasa Maniafu.</th>
</tr>
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