



The Synthesis of Orthoesters and their Role as Delivery Systems for Lubricant Additives

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To Andy, my husband, I simply could not have done this without you. Thank you for your continued support, love and inspiration.

Abstract

Improving the efficiency of vehicles is crucial to reducing the emissions of internal combustion engines and lessen their impact on the environment. Lubricant friction modifiers successfully reduce the frictional losses within vehicles, but their poor durability limits their potential. Utilising an *in situ* delivery system for friction modifiers could improve their durability and performance. An ideal approach could use [3,3]-sigmatropic rearrangements, driven by heat, to allow for the *in situ* formation of esters.

This thesis describes the synthetic approaches to the development of a delivery system for friction modifiers. The main investigation centres around the synthesis of ketene acetals and orthoesters, followed by the direct orthoester Johnson-Claisen rearrangement of those orthoesters. This novel delivery system successfully produced a friction modifier capable of reducing the friction within the high frequency reciprocating rig (HFRR) bench test. This reduction in friction was found to be a small but significant improvement compared to a commercially available friction modifier.

The investigation into the synthesis of orthoesters also led to a second approach to a delivery system. The degradation of orthoesters to release a friction modifier is discussed. Orthoesters successfully solubilised and then released friction modifiers when subjected to heat or acid. The highlighted improved storage stability and solubility within lubricant oil packages gives this approach real advantages as a potential commercial delivery system.

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Abbreviations

ACEA	European Automobile Manufacturers' Association
Coefficient of Friction	A measure of the amount of resistance that a surface exerts on or substances moving over it
DCM	Dichloromethane
DFT	Density Functional Theory
DGDE	Diethylene Glycol Dimethyl Ether
DIBAL-H	Diisobutylaluminium Hydride
DMF	Dimethylformamide
FM^1	Friction Modifier 1 (due to the confidential nature of these molecules they are not included in the experimental)
FM^2	Friction Modifier 2 (due to the confidential nature of these molecules they are not included in the experimental)
GMO	Glycerol Monooleate
HFRR	High Frequency Reciprocating Rig
HMDS	Bis(trimethylsilyl)amine
ICE	Internal Combustion Engine
IPA	Isopropanol
KO^tBu	Potassium t*ert*-Butoxide
L-85-99	Oxidative Resistance Test as defined by ACEA
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide

OFMs	Organic Friction Modifiers
OIT	Oxidative Induction Time
PAO	Poly Alpha Olefin
*p*PTS	Pyridinium *p*-Toluenesulfonate
PSCD	Pressure Differential Scanning Calorimetry
PTC	Phase Transfer Catalyst
TBAB	Tetra-*n*-*B*utylammonium Bromide
THF	Tetrahydrofuran
TIBA	Triisobutylaluminium
UNFCCC	United Nations Framework Convention on Climate Change
ZDDPs	Zinc Dithiophosphate

1.0. Introduction

Improving the efficiency of vehicles is crucial to reduce the emissions of internal combustion engines and lessen their impact on the environment. This thesis will discuss how friction modifiers can be used to reduce the frictional losses within vehicles. Furthermore, the design of novel friction modifiers which can be synthesised *in situ* of the engine or transmission, to improve on their durability, will be described.

1.1. The Automotive Industry and Climate Change

Over recent years climate change and global warming has increasingly become a worldwide interest discussed in the media, scientific communities and governments. Committees such as the United Nations Framework Convention on Climate Change (UNFCCC) have led a global effort to unite countries to pledge to decrease greenhouse gases and to halt the increase in global average temperature.[1] More specifically there has been a huge amount of interest in more efficient and cleaner transportation systems. This has led to government regulations and pledges, including the UK, which stated in 2018 that their mission was "for all new cars and vans to be effectively zero emission by 2040".[2] This has influenced a drive towards electric vehicles, since these are known to have zero emissions during consumer use. However, it is important to note that electric vehicles still have an emissions impact relating to their manufacture as well as the generation of the electricity.[3]

Although it is important to think of future technology, such as electric cars, the energy and environmental impacts of transportation is too damaging to not apply fuel economy and emissions standards to current internal combustion engine (ICE) vehicles on the market. Especially since 12% of the EU total CO_2 emissions comes from cars.[4] There is a sense of urgency in this area which is highlighted by stricter emissions targets coming into play from 2020/2021; moving from 130 g CO_2/km to 95 g CO_2/km, which relates to a fuel economy of 68.9 miles per gallon. In order to achieve these strict fuel economy and emissions targets, the automotive industry needs to understand where the energy losses are coming from. Holmberg *et al*.

and Ali Erdemir, provide a detailed look into the energy losses in both ICE and electric cars.[3,5] For a typical passenger ICE car, only 21% of fuel is used to move the car, the remaining fuel accounts for overcoming energy losses. Friction losses stand out as the highest, with 200,000 million liters of fuel (petrol and diesel) worldwide used to overcome friction. Therefore, if frictional losses can be reduced then this would drastically reduce CO_2 emissions and start paving the way for more environmentally responsible transportation.

Lubricants are used in automotive industry to help overcome energy losses. Lubricant packages are comprised of 80% of a base oil and 20% additives. The additives help to increase the lifetime of engines, gears and axles by reducing friction and wear on the moving parts, dispersing deposits formed and improve the efficiency of the vehicle. A range of additives are used in order to provide these benefits. Figure 1 shows an example of a typical composition of a commercial lubricant oil package, however this can vary depending on the final application.

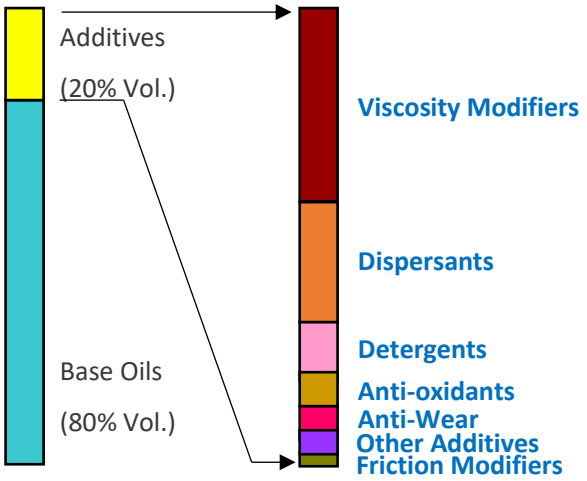


Figure 1: The additives that go into an average automotive lubricant package

The viscosity of the lubricant can also help to reduce energy losses in a vehicle. Moving to lower viscosities allows the lubricant to flow through the moving parts more easily, which reduces friction and improves fuel economy.[6] However, these lower viscosity lubricant packages can lead to thinner oil film thicknesses and increased boundary contact, which results in potentially higher friction and wear.[7,8] In order to overcome frictional losses in a vehicle both low viscosity

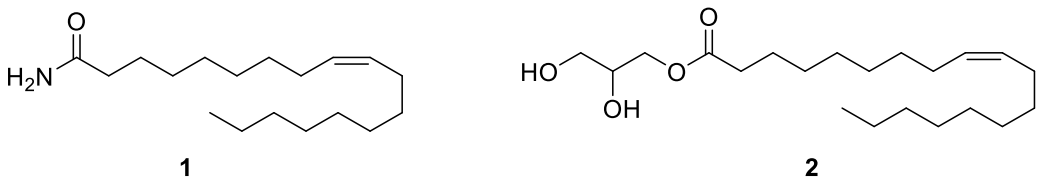
packages and friction modifiers are required. Although lower viscosity oils are an important part in reducing friction, this thesis will only describe the synthesis of novel friction modifiers.

1.2. Lubricant Friction Modifiers

Friction modifiers are used to overcome frictional losses within vehicles. Frictional losses can be described as energy losses that account for friction, which is defined as the resistance to motion of one object relative to another object. Within automotive vehicles there are many moving parts in both the engine and transmission, including axels, gears and pistons, which can result in significant frictional losses.

There are four different types of lubricant friction modifiers; organic friction modifiers (OFMs), organo-molybdenum compounds[9–11], functionalised polymers[12–15] and dispersed nanoparticles[16,17]. OFMs and organo-molybdenum compounds have been known for decades, whilst functionalised polymers and dispersed nanoparticles are much more recent technology. As this thesis describes the synthesis of novel organic friction modifiers, only organic friction modifiers will be discussed.

Organic friction modifiers have a polar head group attached to a long apolar aliphatic chain, they come in the form of carboxylic acids, alcohols, esters, amines, amides and imides.[18] Figure 2 shows some OFMs used within automotive lubricant packages today such as oleylamide[19,20] (**1**) and glycerol monooleate (GMO)[21,22] (**2**).



1 **2**

Figure 2: OFMs used within automotive lubricant packages

The mechanism of action of OFMs was initially described by Hardy who suggested that OFMs self-assemble on solid surfaces to form vertically orientated monolayers, wherein methyl groups on opposing monolayers slide against each other.[23] Bowden and Leben further developed this model by suggesting that the monolayer needs to repair itself in order to maintain protection, meaning a suitable supply of lubricant must be readily available.[24] The most accepted model today, with this model believed to be the mechanism of action for GMO, was described by Bowden and Tabor. They measured the behaviour of sliding similar solids against each other with a lubricant and suggested that OFMs only partially separate the surfaces and thus reduce the extent of solid adhesion.[25] Hardy's and the Bowden-Tabor model are shown in Figure 3.

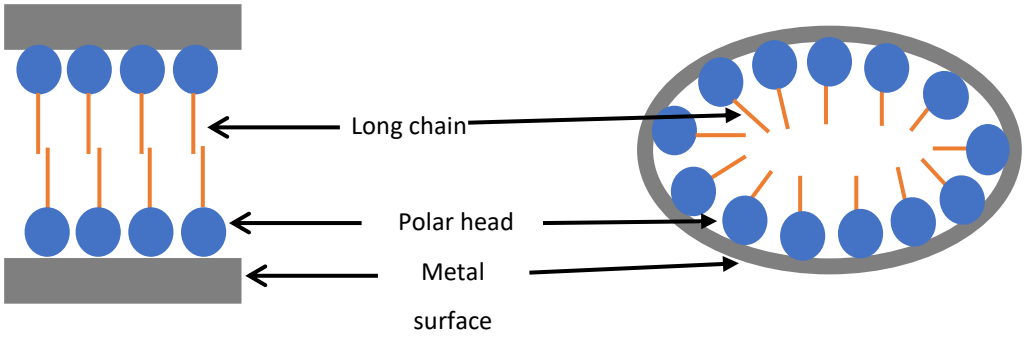


Figure 3: a) Hardy's model of lubrication; b) The Bowden-Tabor model of lubrication

OFMs form monolayers by the polar head group either adsorbing or chemically interacting with the polar metal surface, while the long aliphatic chains orientate themselves to maximize Van der Waals interactions. The cumulative short range Van der Waals interactions between the close packed aliphatic chains creates a strong film.[26] In fact, Bowden and Tabor suggested these interactions were thought to be as important as the strength of the polar head group attachment to the surface.[25] It is important to note here that the monolayer mechanism of action was determined through model systems, it is not yet proven whether this is still the case when moving to real-world conditions, such as engines.

The structure of the OFM can have an impact on its performance and mechanism of action. The features discussed the most in the literature include the chain length and the saturation of the molecule. Firstly, many studies have shown that chain length (of acids or alcohols) has a large impact on the coefficient of friction.[23,25,27–31] Increasing the chain length results in more cohesive forces (Van der Waals interactions), which makes the OFM film strong enough to be more resistant to temperatures and pressures and thus reduce metal-metal contact. Jahanmir[28] suggests that under their test conditions a chain length of C_{18} or larger (for fatty acids) produces a minimum coefficient of friction (Figure 4). The coefficient of friction is defined as a measure of the amount of resistance that a surface exerts on or substances moving over it. However, other work from Levine and Zisman[27] and Briscoe and Evans[30] has shown that no chain length effect was observed for C_{14}-C_{22} chains (for fatty acids) (Figure 5). This suggests that test conditions are important when investigating chain length, but all current research indicates a chain length effect up to at least C_{10} before the coefficient of friction begins to level out.

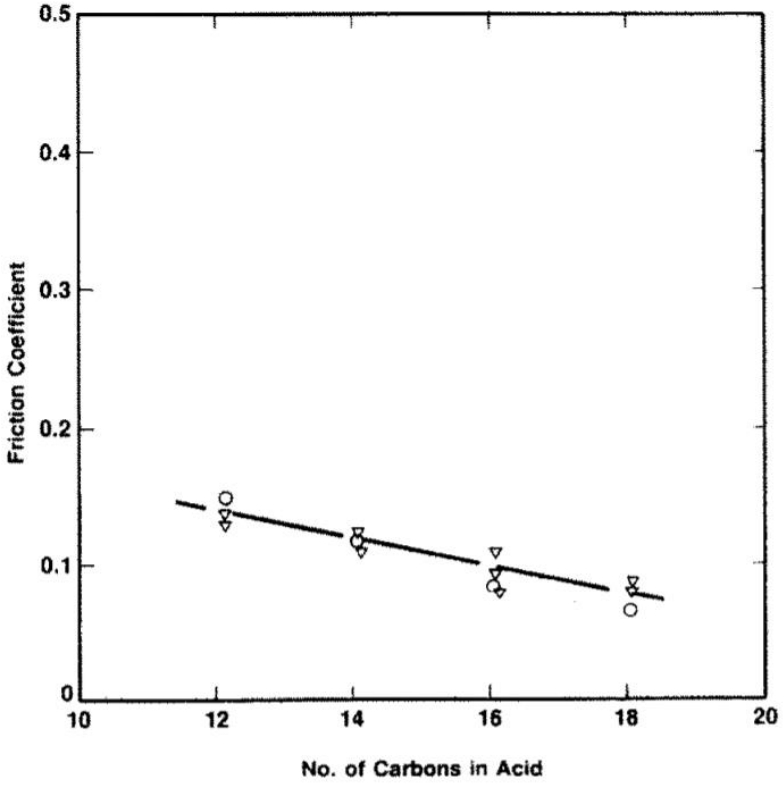


Figure 4: The effect of chain length on the coefficient of friction for fatty acids studied by Jahanmir[28] Friction coefficient was measured by rubbing a steel ball on a steel cylinder coated with the acid dosed in n-hexadecane at 1 wt%. Image reproduced with permission of the rights holder, Elsevier. Copyright © 1985 Elsevier.

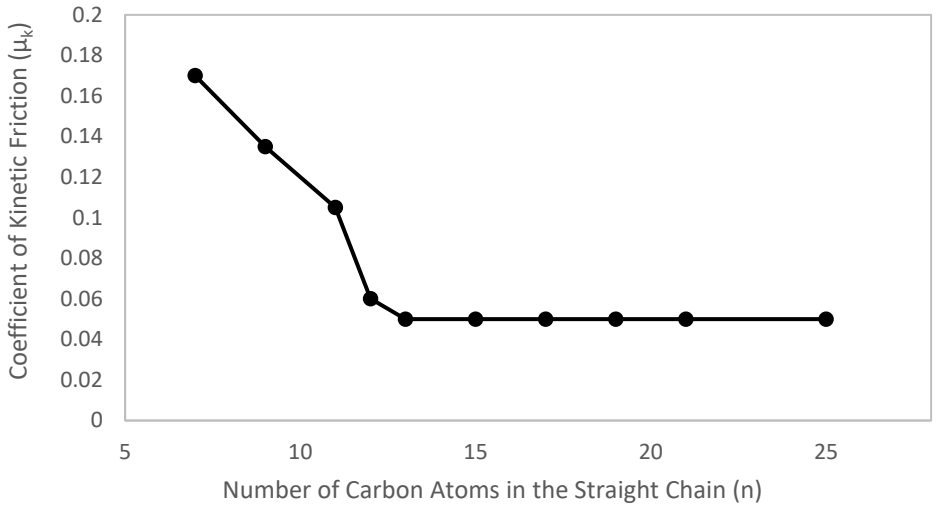


Figure 5: The effect of chain length on the coefficient of friction for fatty acids studied by Levine and Zisman[27] Friction coefficient was measured by rubbing a steel ball on a glass plate coated with a monolayer solution of the acid. Image reproduced with permission of the rights holder, American Chemical Society. Copyright ©1957 American Chemical Society.

The other characteristic feature of OFMs discussed in the literature is saturation. There is a consensus that a straight long chain saturated OFM gives the lowest coefficient of friction, with significant experimental data to validate this theory.[8,32–34] Some research in this area has involved looking at stearic (**3**), elaidic (**4**) and oleic acid (**5**) (Figure 6). Spike *et al*., shows that stearic acid (**3**) produces the lowest coefficient of friction, followed by elaidic acid (**4**) and then oleic acid (**5**) (Figure 7).[8,32] These results are not unexpected since cumulative forces between close packed chains are believed to make strong films and thus reduce friction. Packing is described as how close together the molecules can get and interact with each other. Stearic acid (**3**) produces the closest packed chains, whilst oleic acid (**5**) struggles to closely pack due to the *cis* alkene. There are also differences in how sliding speed affects the coefficient of friction (Figure 7); stearic and elaidic gave low friction at low speeds that increased approximately linearly with speed. Whereas oleic acid had relatively low friction which stayed almost constant with speed. These differences suggest that there could be a difference between the type of film formed and frictional behaviour of molecules that can closely pack with linear configurations compared to those that struggle to closely pack.

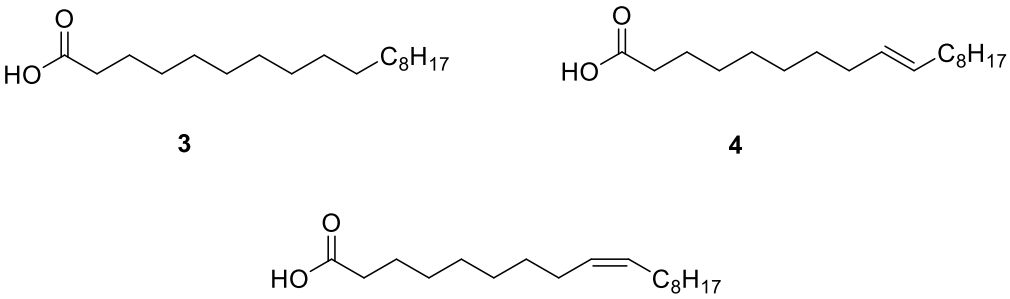


Figure 6: Stearic acid (3), elaidic acid (4) and oleic acid (5)

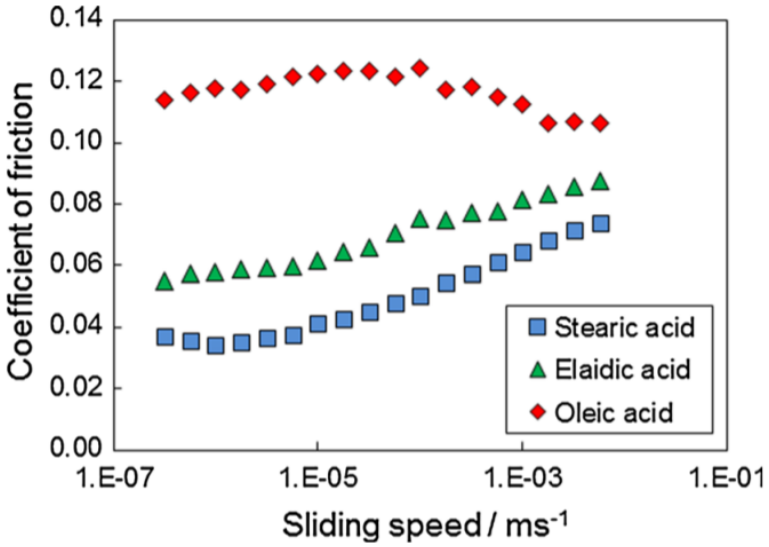
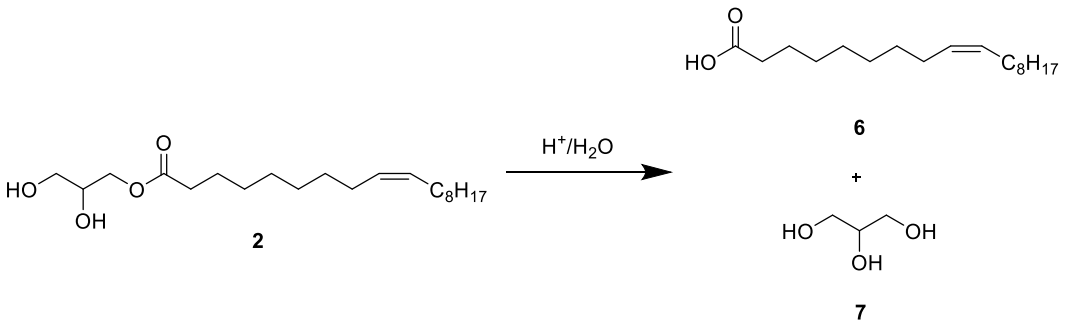


Figure 7: Friction versus sliding speed for three 0.01M fatty acid solutions in hexadecane at 100 °C.[8] Image reproduced with permission of the rights holder, Springer Nature. Copyright © 2015 Springer Nature.

It is known from Spike *et al*., that stearic acid (**3**) and elaidic acid (**4**) produce lower coefficients of friction compared to oleic acid (**5**). However, as shown above in Figure 2, the majority of commercial OFMs incorporate an oleic chain. This is a result of both cost and solubility within lubricant packages. Oleic acid is significantly cheaper than elaidic acid and provides improved solubility over stearic acid, making oleic derivatives more commercially viable for OFMs in lubricant packages.

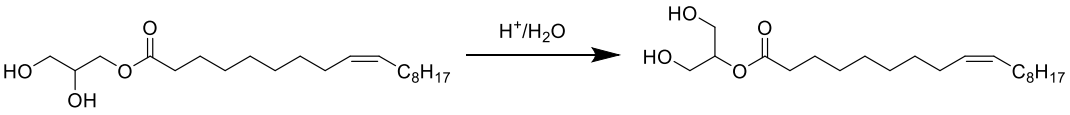
Despite significant research undertaken on OFMs the mechanism of action is still relatively poorly understood. This is due to several reasons including that most of the academic work mainly investigated saturated compounds, even though the

majority of the OFMs used in lubricant formulations incorporates some form of unsaturation to help improve solubility. Furthermore, it is not totally understood if the OFM in its original form is the active friction modifier, or whether it is its degradation products. For example, Tang and Li propose that GMO (**2**) lubricates metal surfaces by hydrolysing to oleic acid (**6**) and glycerol (**7**) (Scheme 1), and then behaves according to the Bowden-Tabor model.[18] This hydrolysis can occur *in situ* of the engine due to the lubricant becoming more acidic as it ages through the formation of organic acids in combustion and water leaching from combustion. However, Campen has shown GMO to have an immediate low coefficient of friction.[33] To complicate things further, the surface in question for lubrication could also have an impact with Spikes *et al*.[35] and Okuda *et al*.[36], suggesting that GMO in its original form interacts with diamond-like carbon surfaces. Furthermore, the monolayer model is still not universally accepted, with many academics believing thicker films are actually formed since the monolayer model cannot explain all experimental observations, discussed by Allen and Dragulis in 1969.[37] This area is still controversial but recent work published by Shaigan and Neill *et al*. in 2020 suggests that multilayers can form but requires film thickness measurements to validate this theory.[38] Finally, it is not known whether the OFM interacts solely with the metal surface or if there are interactions with other components within the lubricant. For example, OFMs are known to interact, both synergistically and antagonistically, with anti-wear agents such as zinc dithiophosphates (ZDDPs).[39]



Scheme 1: The degradation of GMO under acidic hydrolysis conditions which occurs due to the lubricant becoming more acidic as it ages and water leaching from combustion

Friction modifiers are highly beneficial to lubricant packages due to their ability to reduce friction. Unfortunately, a main drawback of friction modifiers is that they are known to degrade over time resulting in poorer frictional performance as the lubricant ages.[40] Looking at GMO as an example, as mentioned earlier many academics think that the degradation, to oleic acid and glycerol, allows it to behave well as a friction modifier. However, oleic acid and glycerol are not the only degradation products of GMO and the composition of these products can vary dependent on water content and temperature.[41,42] GMO can also undergo an acyl migration to give its isomer (**8**) (scheme 2) and has the potential to undergo oxidations, although these are more than likely not to occur in the conditions of an engine. Further to this, after GMO has degraded to oleic acid, the oleic acid can form salts with free metallic cations, from detergents or dispersants within the lubricant package, whilst also undergoing degradations itself. These can be a result of oxidations to form epoxides, dihydroxystearic acids and ketostearic acids, which can also all undergo degradations.[43] All of these further degradations will have an impact on the frictional performance of GMO and can help to explain why lubricants degrade over time. Further to this Camp *et al*. in 2018, undertook frictional measurements of a few of the degradation products; oleic acid, glycerol and calcium oleate.[42] They suggest that the degradation of GMO forms species which do not adsorb to surfaces as well as GMO, shown by an increase in the coefficient of friction, suggestive that degradation over time causes poorer frictional performance.

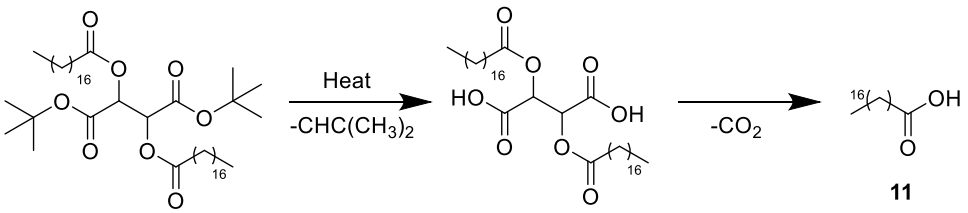


2 **8**

Scheme 2: Acyl migration of GMO

1.3. Improving the Durability of Friction Modifiers

During the course of undertaking the research described in this thesis studies attempting to improve upon the durability of friction modifiers were reported. Instead of usual degradation, the friction modifier was shown to be released over time allowing for a reduction in friction.[44,45] Uhrich *et al*., investigated the use of esters as thermocleavable friction modifiers. This work investigated the degradation (β-ester pyrolysis) of an ester (**9**) (Scheme 3) to release a novel friction modifier (**10**) in a controlled manner, resulting in a reduction in coefficient of friction over time. The novel dicarboxylic acid friction modifier (**10**), had a coefficient of friction approximately one-third lower than that of its mono-acid derivative (**11**), measured by high frequency reciprocating rig (HFFR). They hypothesised that the increased performance was a result of enhanced surface activity from the two polar head groups as well as the two neighbouring long chains, which increases the amount of cohesive forces. Although these novel dicarboxylic acids were shown to be capable of undergoing decarboxylative eliminations (step 2 of Scheme 3) the degradation products are that of commercially known friction modifiers, such as stearic acid (**11**) and thus will still provide friction modification performance.



9 **10** **11**

Scheme 3: The β-ester pyrolysis to form dicarboxylic acids followed by decarboxylative elimination to form mono-acids by Uhrich *et al.*[44]

The controlled release performance of the thermocleavable friction modifiers was supported by results from a controlled release test, in which the bulk oil with 1% of the novel compound was exposed to 130 °C followed by brief temperature ramps to 215 °C to mimic an engine. The novel friction modifier (**10**) was shown to be released from (**9**) in a controlled manner up to 6 hours, after which some decarboxylative degradations, forming stearic acid (**11**), resulted in some loss in activity (Figure 8). Despite the promising performance of these friction modifiers, this work seems to only suggest a controlled release of 6-8 hours and does not show what happens to the coefficient of friction after 8 hours. In order to truly enhance the durability, the controlled release of these friction modifiers would need to be sustained over a longer period of time. Furthermore, it must be noted that the lubricant used in the controlled release test, as well as all HFRR testing, only involved the friction modifier blended into a base oil (polyalpha-olefin, PAO). Realistically it would be required to be tested in a fully formulated package, including other additives such as detergents and dispersants, to further mimic real world conditions. Finally, this approach produced carboxylic acids which are known to cause corrosion within vehicles. It would be more beneficial to produce neutral species such as esters.

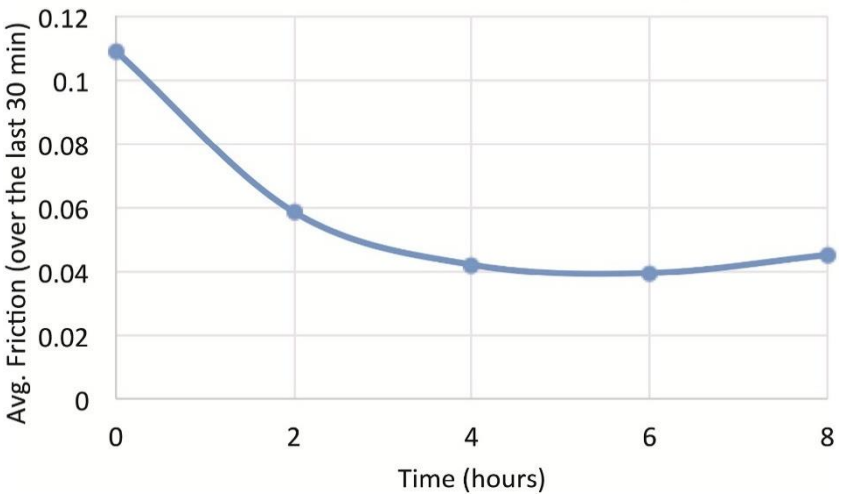
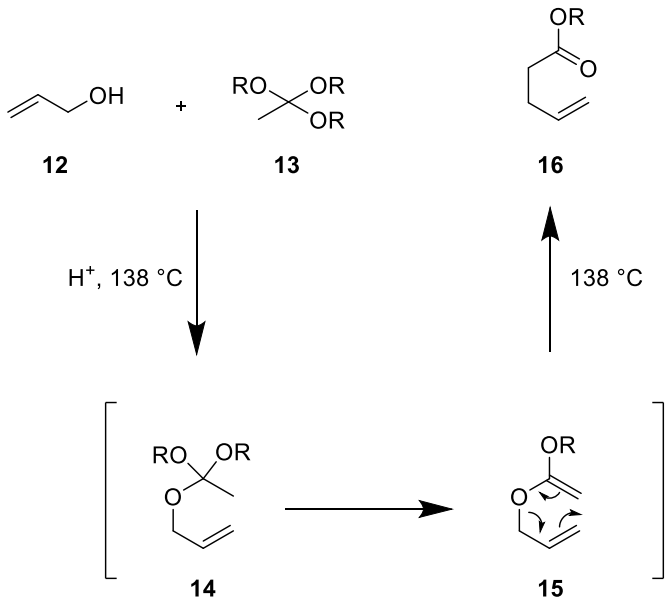


Figure 8: A graph showing the average coefficient of friction of 1 wt% of (9) in PAO over time measured by HFRR from Uhrich *et al*.[44] Image reproduced with permission of the rights holder, Elsevier. Copyright © 2018 Elsevier.

2.0. Aims

The aims of this research are to develop an *in situ* delivery system for friction modifiers, which uses the conditions of the engine or transmission, such as heat. The use of this delivery system should improve the durability of the friction modifier and fuel efficiency. Ideally the final delivered friction modifier should have a similar structure to GMO (**2**) since it is known to significantly reduce the coefficient of friction.

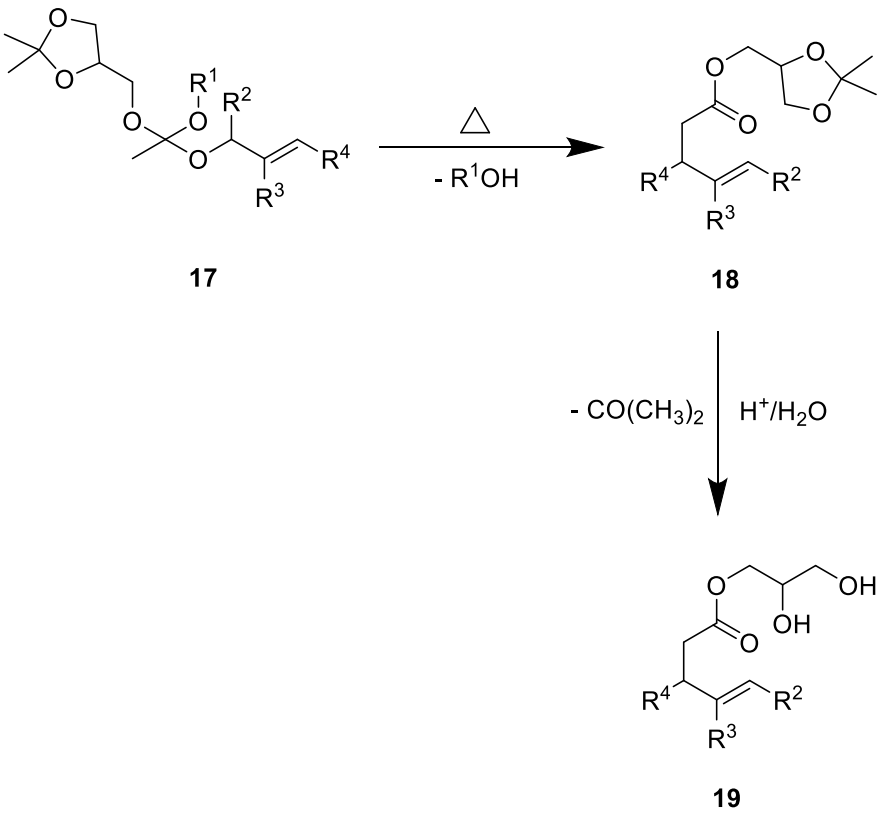
The proposed delivery system is the orthoester Johnson-Claisen rearrangement (Scheme 4). The rearrangement has many advantages for this application. Firstly, the rearrangement is known to require temperatures above 100 °C which matches the temperature of the sump of the engine. Secondly, an ester is produced which has friction modification capabilities, whilst not adversely affecting corrosion compared to carboxylic acids. Finally, the rate of the [3,3]-sigmatropic rearrangement is known to be influenced by functionality and thus the rearrangement can be designed to undergo a controlled and slow rearrangement.[46–52] This is an important aspect of this application because if the ester is released too fast, the durability of the friction modifier will not be improved.



Scheme 4: The orthoester Johnson-Claisen rearrangement

For the orthoester Johnson-Claisen rearrangement to be useful for this application it is required to be modified. This is due to the fact that the original orthoester Johnson-Claisen rearrangement (Scheme 4) uses two starting materials: the allylic alcohol (**12**) and trialkyl orthoester (**13**). In a lubricant package there are a range of additives dosed in at varying amounts dependent on the final application (Figure 1). Friction modifiers are often dosed into a package at very low percentages (less than 5%) which means the two starting materials of the rearrangement would be unlikely to interact and react. In order to overcome this, the delivery system is required to a be a single component. During the orthoester Johnson-Claisen rearrangement, prior to the actual rearrangement, a mixed orthoester (**14**) is formed *in situ* (Scheme 4). Although not normally done, mixed orthoesters (**14**) can be prepared[53–56] and therefore are ideal candidates for friction modifier delivery systems.

The final proposed delivery system is therefore the direct orthoester Johnson-Claisen rearrangement (Scheme 5). The orthoester can be designed to incorporate functionality, such as the solketal head group, which will allow it to mimic GMO (**2**). Furthermore, the orthoester can be designed to influence both the selectivity and the rate of the rearrangement by altering the R_1 group. Moreover, the protected diol in the solketal head group enhances the delivery system concept, since an *in situ* acetal deprotection would be required. This deprotection could be promoted by the increase in the acidity of the lubricant oil as it ages. Therefore, both the rearrangement and deprotection can act as *in situ* delivery systems and should provide a long, controlled release of the friction modifier.



17 **18** **19**

Scheme 5: The proposed *in situ* delivery system for friction modifiers using the direct orthoester Johnson-Claisen rearrangement

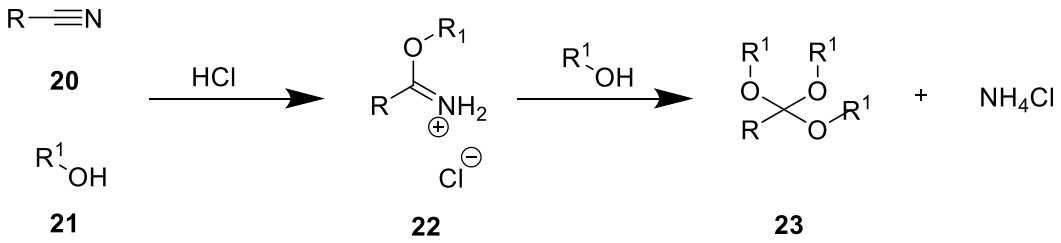
3.0. Synthesising Orthoesters

This chapter will describe two modified approaches to synthesising orthoesters. The use of these approaches to design orthoesters capable of behaving as delivery systems for friction modifiers will also be discussed.

3.1. Review of the Synthesis of Orthoesters

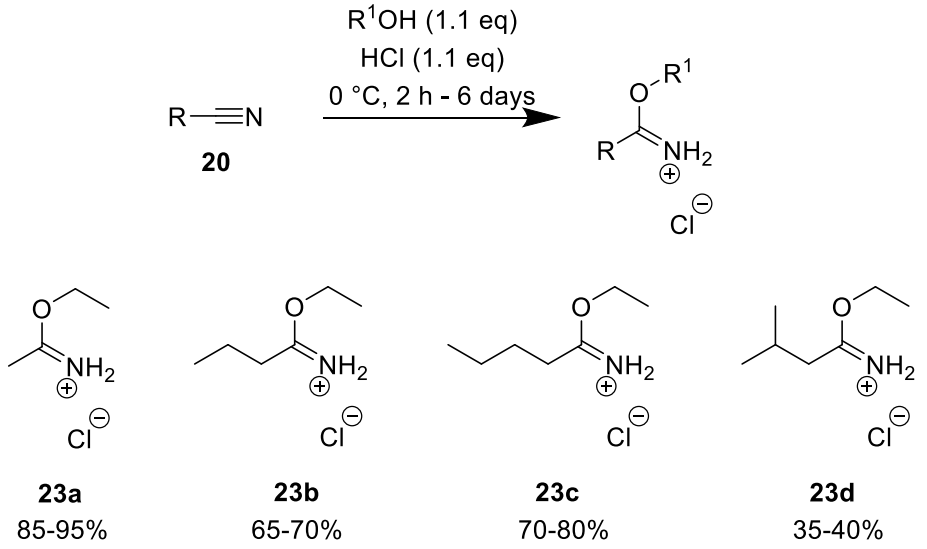
From Salts

Orthoesters have been known for over a century, with the first synthesis reported in 1883.[57] The Pinner reaction (Scheme 6) forms orthoesters (**23**) through the alcoholysis of an imidate hydrochloride (**22**).



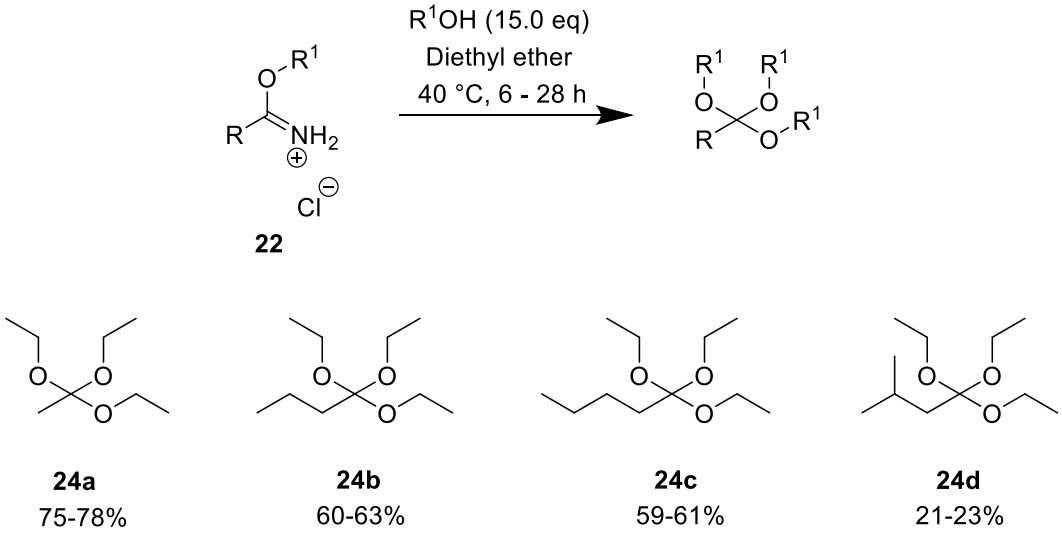
Scheme 6: The Pinner Reaction

The synthesis of the imidate hydrochlorides (**23a-d**), for a wide variety of aliphatic substrates, was found to be high yielding. However, McElvain found the reaction to be dependent on steric and electronic effects. For example sterically hindered products were obtained in significantly lower yields (Scheme 7).[58]



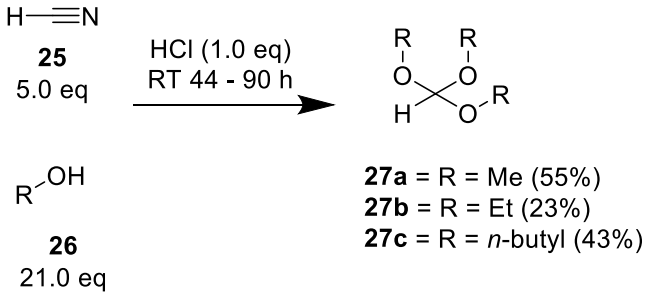
Scheme 7: Examples of imidate hydrochlorides synthesised by McElvain[58]

The synthesis of orthoesters from imidate hydrochlorides and alcohols has been investigated by several research groups. Reiter and Hess synthesised triethyl orthoacetate (**24a**) in 40-64% yield by leaving the reaction at room temperature for 8-14 days.[59] McElvain improved upon the rate and the yield by heating the reaction to 46 °C for 6 hours and produced triethyl orthoacetate (**24a**) in 75-78% yield. McElvain also described how sterically hindered imidate hydrochlorides also led to a decrease in yield of the orthoesters (Scheme 8).



Scheme 8: Examples of triethyl orthoesters synthesised by McElvain via the Pinner reaction

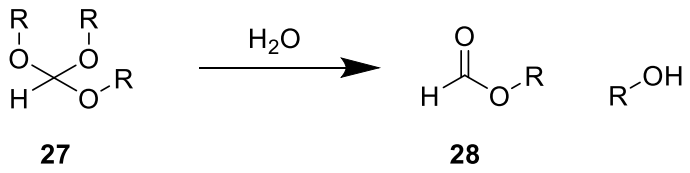
The Pinner reaction was further modified by Erickson in 1955. Erickson described the synthesis of orthoformates (**27a-c**) *via* a one-step Pinner reaction in yields of 23-55% (Scheme 9).[60]



Scheme 9: Synthesis of orthoformates *via* a one-step synthesis

Erickson found there was a correlation between the yield of the one-step Pinner reaction and the molar ratio of HCl:HCN:ROH. Erikson theorised that using an excess of hydrogen cyanide prevented degradation of the orthoformate (Scheme

10). When the reaction was attempted without an excess of hydrogen cyanide, the alcohol and HCl reacted to form water, which led to the degradation of the orthoformate and caused a reduction in yield.

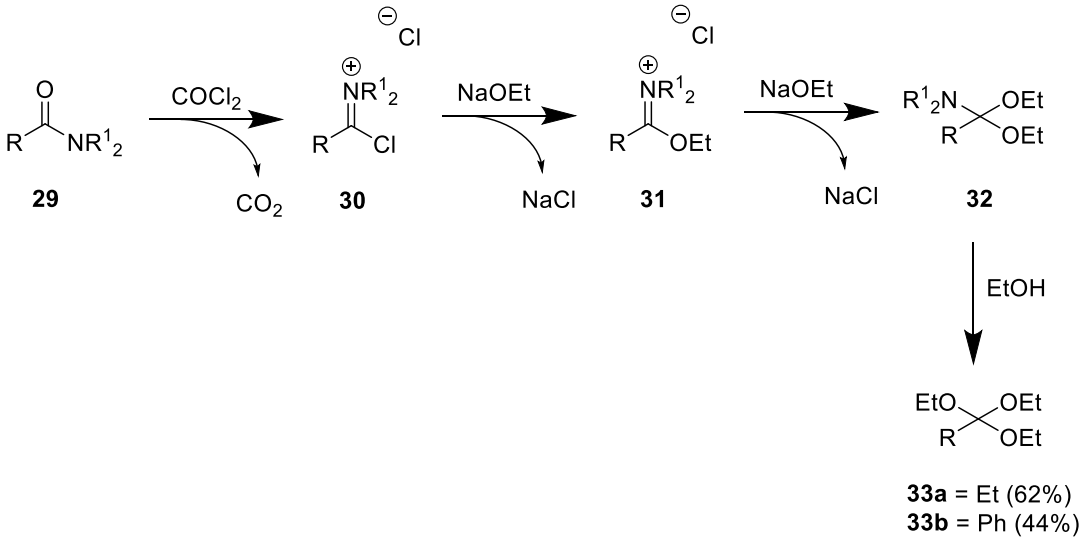


27 **28**

Scheme 10: Degradation of orthoformates

Unfortunately, the Pinner reaction, even with modifications from McElvain and Erickson, suffers from toxicity and scalability due to the use of HCl gas and HCN. Further to this, there is a significant lack of substrate scope, with just short chain aliphatic alcohols used in the synthesis of orthoesters and orthoformates.

A related method to the Pinner reaction was described in 1963 by Eilingsfeld *et al*.[61] Similarly to the Pinner reaction, this method involved the alcoholysis of salts (**30**-**31**) through addition of sodium alkoxides and alcohols to amide chlorides (Scheme 11). Although HCl gas is no longer needed, this method requires the use of phosgene, which is highly toxic. This method also has a limited substrate scope by only using sodium ethoxide/ethanol.

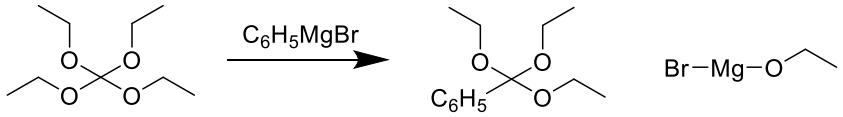


29 **30** **31** **32**

Scheme 11: Synthesis of orthoesters *via* amide chlorides

From Carbonates

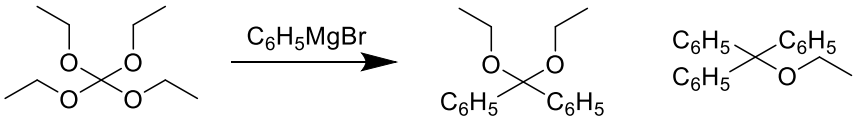
In 1905, Tachitschibabin, described the synthesis of orthoesters (**35**) from the reaction of a Grignard reagent with ethyl orthocarbonate (**34**) (Scheme 12).[62]



34 **35** **36**

Scheme 12: Tachitschibabin procedure to orthoesters

Unfortunately, Tachitschibabin did not describe a preparative experimental procedure for the synthesis of orthoesters from ethyl orthocarbonate that was reproducible. This was highlighted in 1942 when McElvain and McBane attempted to repeat this work and was only able to produce a ketal (**37**) and ether (**38**) as products (Scheme 13).[58] However, the yields and reaction conditions were not reported.

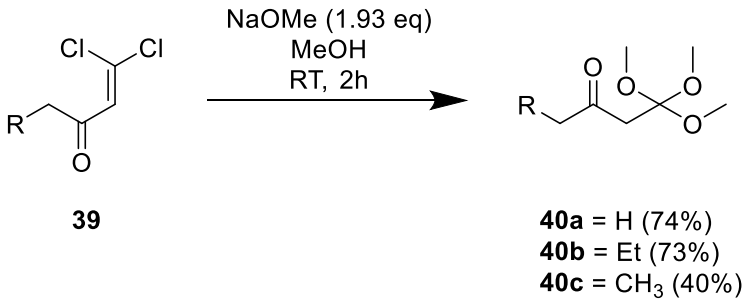


35 **37** **38**

Scheme 13: McElvain's products of the Tachitschibabin reaction

From Vinylidene Chlorides

In 1976, Brassard and Banville discovered the synthesis of orthoesters from vinylidene chlorides, whilst attempting to synthesise ketene acetals.[63] They found that acyl vinylidene chlorides (**39**) reacted with sodium methoxide/methanol at room temperature to form a range of orthoesters (**40a-c**) (Scheme 14). Unfortunately, other derivatives of vinylidene chlorides were not investigated so only acyl orthoesters were synthesised.



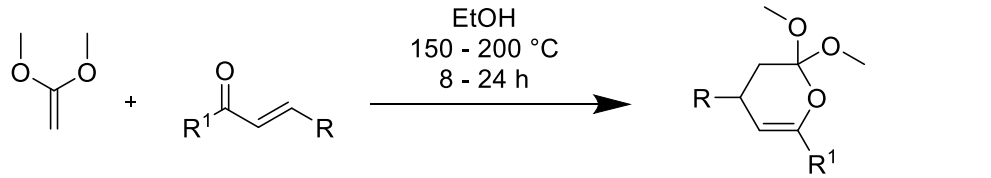
39

40a = H (74%)
40b = Et (73%)
40c = CH_3 (40%)

Scheme 14: Synthesis of orthoesters from vinylidene chlorides

From Cycloaddition Reactions

The synthesis of orthoesters from the reaction of ketene acetals and aldehydes was described by McElvain and Behun in 1954.[64] They reported that unsaturated O-internal cyclic orthoesters (**43a-c**) were synthesised when ketene dimethyl acetal (**41**) and an aldehyde or ketone were reacted together in a hydrogenation bomb (Scheme 15).



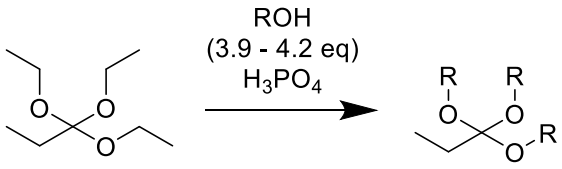
41 **42**

43a = R = R^1 = H (70%)
43b = R = Ph; R_1 = H (59%)
43c = R = Ph; R_1 = Me (30%)

Scheme 15: The synthesis of mixed O-internal cyclic orthoesters through condensation reactions

From Orthoesters

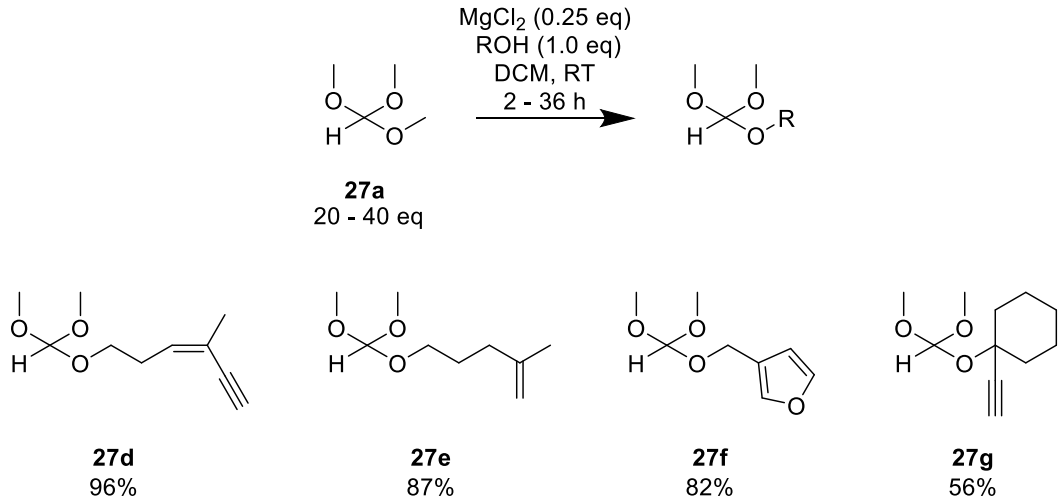
Orthoesters can also be synthesised from other orthoesters *via* etherification reactions. In 1954, Arbuzov and Shavash-Tolkacheva described the synthesis of a small range of simple symmetric orthopropionates (**44a-d**) from triethyl orthopropionate (**44**) in the presence of phosphoric acid (Scheme 16).[65,66] Unfortunately, little experimental detail was provided.



44 **44a-d**
R = propyl, *n*-butyl, *n*-hexyl, *n*-octyl

Scheme 16: Synthesis of orthopropionates *via* an etherification reaction

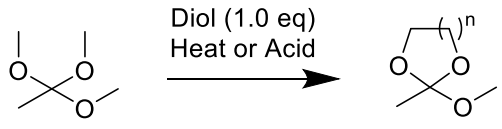
The etherification of orthoesters was also used to synthesise mixed orthoesters. Perron *et al*., described $MgCl_2$ catalysed etherification of trimethyl orthoformate (**27a**) to form a range of mixed orthoesters (**27d-g**) (Scheme 17).[56] A large excess of trimethyl orthoformate (**27a**) (20-40 equivalents) was used to allow for the formation of only the mono-substituted orthoester (**27d-g**) in moderate to good yields of 54-96%. However, further exchange was observed if any other catalyst or acid was used, including the small amounts of HCl present in deuterated chloroform.



Scheme 17: Synthesis of mixed orthoesters *via* $MgCl_2$ catalysed etherification

Cyclic orthoesters (**46**) have been shown to be synthesised *via* the etherification of orthoesters (Scheme 18). There has been a significant interest in cyclic orthoesters since they are used as protecting groups for diols, especially in carbohydrate synthesis.[67,68] Therefore there are many examples of etherification

to form cyclic orthoesters (**46**) all with varying preparations. Most describe the use of an acid catalyst including benzoic acid[69], *p*-toluenesulfonic acid[70], $GeCl_4$[71], $Yb(OTf)_3$[72] and $MgCl_2$[73]. However, Yokoyama *et al*., produced cyclic orthoesters by heating to 100 °C whilst removing the methanol formed.[74] Despite the differences in preparation, the research groups all suggest greater ease of synthesis compared to acyclic variants.

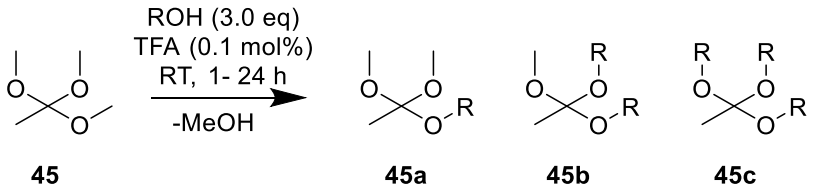


45 **46**
n = 1- 3

Scheme 18: General scheme of the etherification of trimethyl orthoesters to cyclic orthoesters

The most recent development in the etherification of orthoesters was described by Brachvogel and Delius in 2015.[75] This work focussed on the etherification of a range of aliphatic alcohol and diols with trimethyl orthoester. Instead of describing the synthesis of the fully substituted orthoester (**45c**), they investigated the equilibrium that formed during the exchange. They found that under acidic conditions (0.1 mol% TFA) a mixture of the mono-(**45a**), di-(**45b**), and tri-(**45c**) substituted orthoesters were synthesised (Table 1).They also showed that the ratio of products and rate of the reaction could be influenced by the substrate used and by changing the concentration, acid equivalents, removing the methanol formed and using a metal template. Although Brachvogel and Delius described how the ratio of etherification products can be manipulated, no preparative examples to isolated orthoesters were described as all reaction products were mixtures.

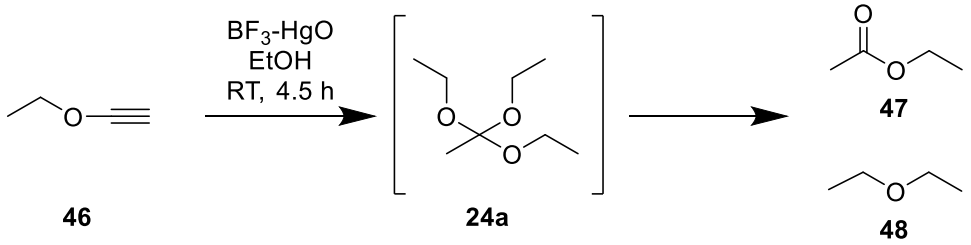
Table 1: Etherification of trimethyl orthoester described by Brachvogel and Delius, product ratios determined by ^{1}H-NMR[68]



	R	45	45a	45b	45c
1	*n*-Butyl	22	44	27	8
2	Ph	89	11	-	-
3	^{i}Pr	74	26	-	-
4	$(CH_2)_2OMe$	42	42	14	2

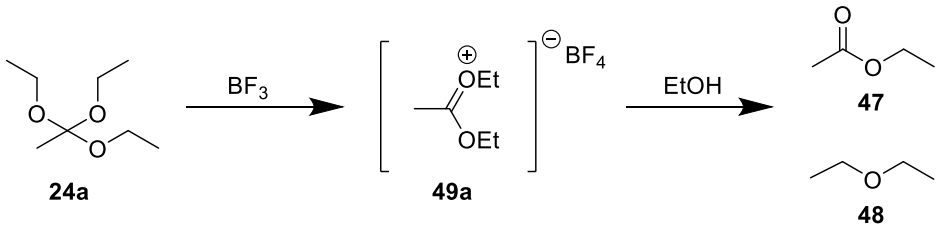
From Alkynes

Lewis acid catalysed addition of alcohols to alkynes is another method of synthesising orthoesters. Addition of alcohols to alkynes is well known with a range of catalysts used, such as molybdenum[76], tungsten[77], ruthenium[78], palladium[79,80], platinum[81], zinc[82], iron[83], iridium[84,85] and gold[86–88]. However, additions to alkoxy alkynes (alkoxy acetylenes) to produce orthoesters are less well reported. Cramer *et al*. described the boron trifluoride/mercuric oxide catalysed addition of ethanol to ethoxyacetylene (**46**).[89,90] Unfortunately, triethyl orthoester (**24a**) was not isolated during this reaction. The resulting products were polymers of ethoxyacetylene and ethyl acetate (**47**) and diethyl ether (**48**) (Scheme 19). Cramer theorised that degradation of the orthoester, catalysed by boron trifluoride/mercuric oxide, produced ethyl acetate (**47**) and diethyl ether (**48**).



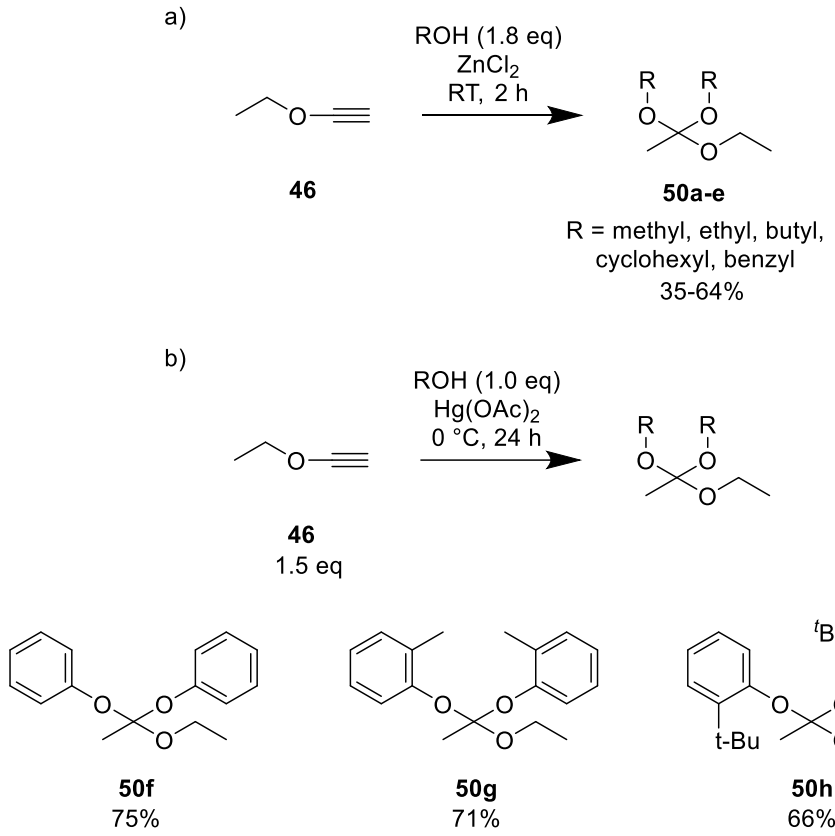
Scheme 19: Boron trifluoride and mercuric oxide catalysed addition of alcohols to alkoxy acetylenes

The boron trifluoride catalysed degradation of orthoesters is known in the literature.[91–93] The formation of a carbocation (**49a**) (Scheme 20), followed by reaction with ethanol produced the observed products (**47-48**) of the boron trifluoride/mercuric oxide catalysed addition of alcohols to ethoxyacetylene described by Cramer *et al*.



Scheme 20: The boron catalysed degradation of orthoesters

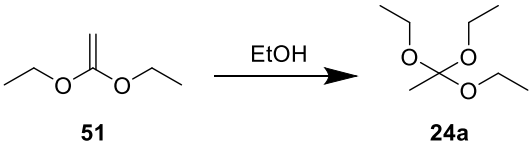
Broekema further developed the addition of alcohols to alkoxy acetylenes in 1975. They described the synthesis of aliphatic (**50a-e**) and aryl (**50f-h**) orthoesters, in poor to moderate yields (35 – 75%), from the addition of alcohols and phenols to ethoxyacetylene (**46**) in the presence of $ZnCl_2$ and $Hg(OAc)_2$ respectively (Scheme 21). Unfortunately, orthoesters (**50c-e**) were reported to contain impurities, which were theorised to be products from the decomposition of the orthoester during distillation, although the identity of the impurities was not disclosed.



Scheme 21: a) $ZnCl_2$ catalysed addition of aliphatic alcohols to ethoxyacetylene; b) $Hg(OAc)_2$ catalysed addition of phenols to ethoxyacetylene

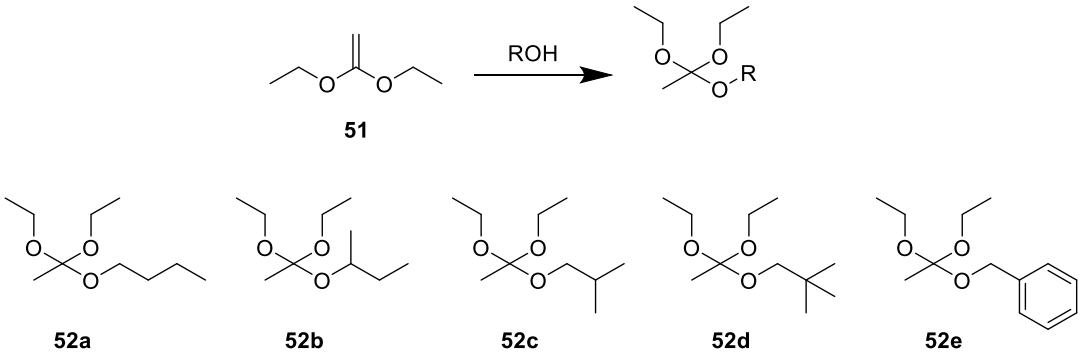
From Ketene Acetals

Another method of synthesising orthoesters involved the addition of alcohols to ketene acetals. McElvain *et al*. reported the first example in 1936, where ketene diethyl acetal (**51**) was reacted with ethanol and formed triethyl orthoester (**24a**) (Scheme 22).[94] However, no yields were reported.



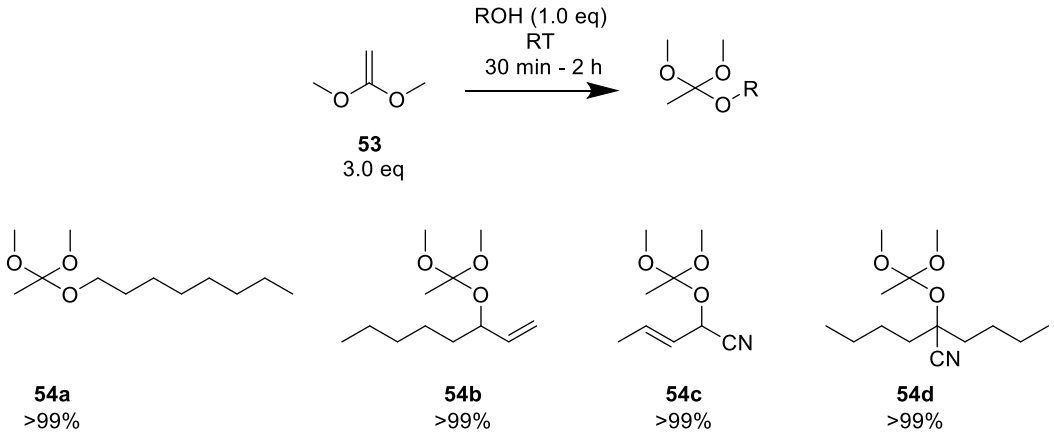
Scheme 22: Reaction of diethyl ketene acetal with ethanol

In 1942, McElvain advanced their work on the addition of alcohols to ketene acetals by describing the formation of mixed orthoesters.[95] They suggested that mixed orthoesters (**52a-e**) were formed by the direct addition of the alcohol to ketene diethyl acetate (**51**) (Scheme 23), and did not report any workup or purification procedures. Furthermore, no yields were reported.



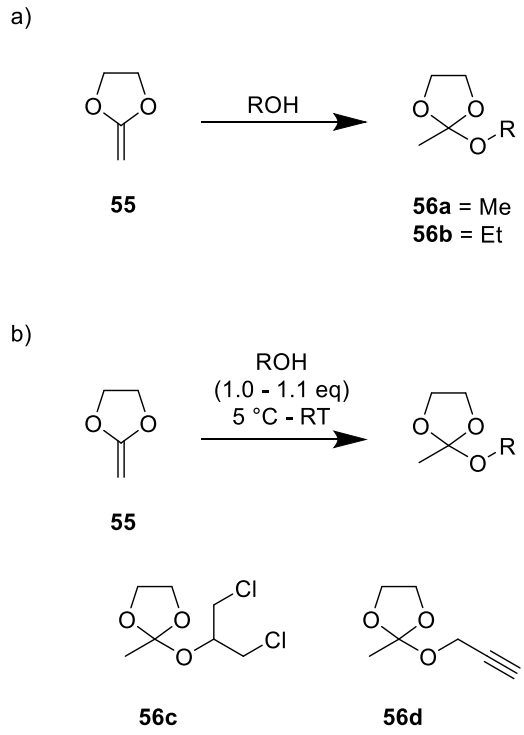
Scheme 23: The synthesis of mixed orthoesters by addition of alcohols to ketene diethyl acetal

The catalyst and solvent free addition of alcohols to ketene acetals has had little investigation since the work reported by McElvain *et al*. in 1942. In 2008, McGeary and Cosgrove described the addition of a range of primary, secondary and tertiary alcohols to dimethyl ketene acetal (**53**), without catalyst or solvent, to form mixed orthoesters (**54a-d**) in quantitative yields (Scheme 24).[54,96] Unfortunately the large excess of ketene acetal (**53**) required could cause issues with purification when moving to less volatile ketene acetals.



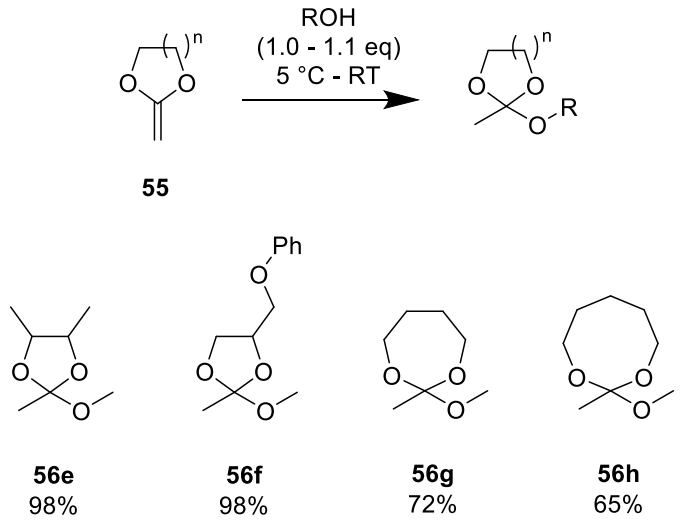
Scheme 24: Examples of the mixed orthoesters formed by McGeary and Cosgrove

There are also limited examples of the solvent and catalyst free addition of alcohols to cyclic ketene acetals. In 1948, McElvain and Curry first observed the addition of alcohols to 2-methyl-1,3-dioxloane (**55**) to produce cyclic orthoesters (**56a-b**) (Scheme 25a).[97] This was further demonstrated by Capon *et al*. in 1985 with unsaturated and halogen containing alcohols (Scheme 25b).[98] Unfortunately, yields were not reported for any of the cyclic orthoesters synthesised.



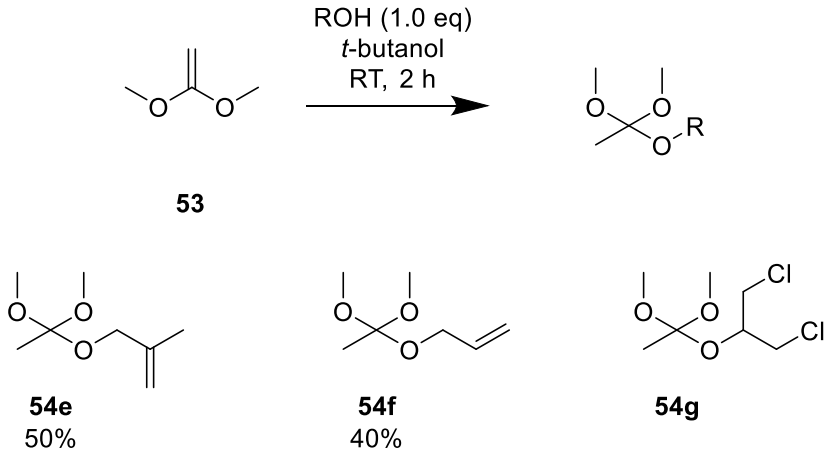
Scheme 25: a) Cyclic orthoester synthesised by McElvain; b) Cyclic orthoesters synthesised by Capon *et al*.

Fukuda *et al*., further developed the addition of alcohols to cyclic ketene acetals by using 5, 7 and 8 membered cyclic ketene acetals (**56e-h**) (Scheme 26).[99] Fukuda demonstrated that 5-membered cyclic orthoesters (**56e-f**) were formed in 98% within 1 hour at room temperature, whilst the larger ring orthoesters (**56g-h**) were only formed in 65-75% yield even after 48 hours at room temperature. They postulated that the 5-membered ketene acetals were more reactive because the electron density on the unsaturated methylene group was larger. However, no spectral data was reported for the mixed orthoester products.



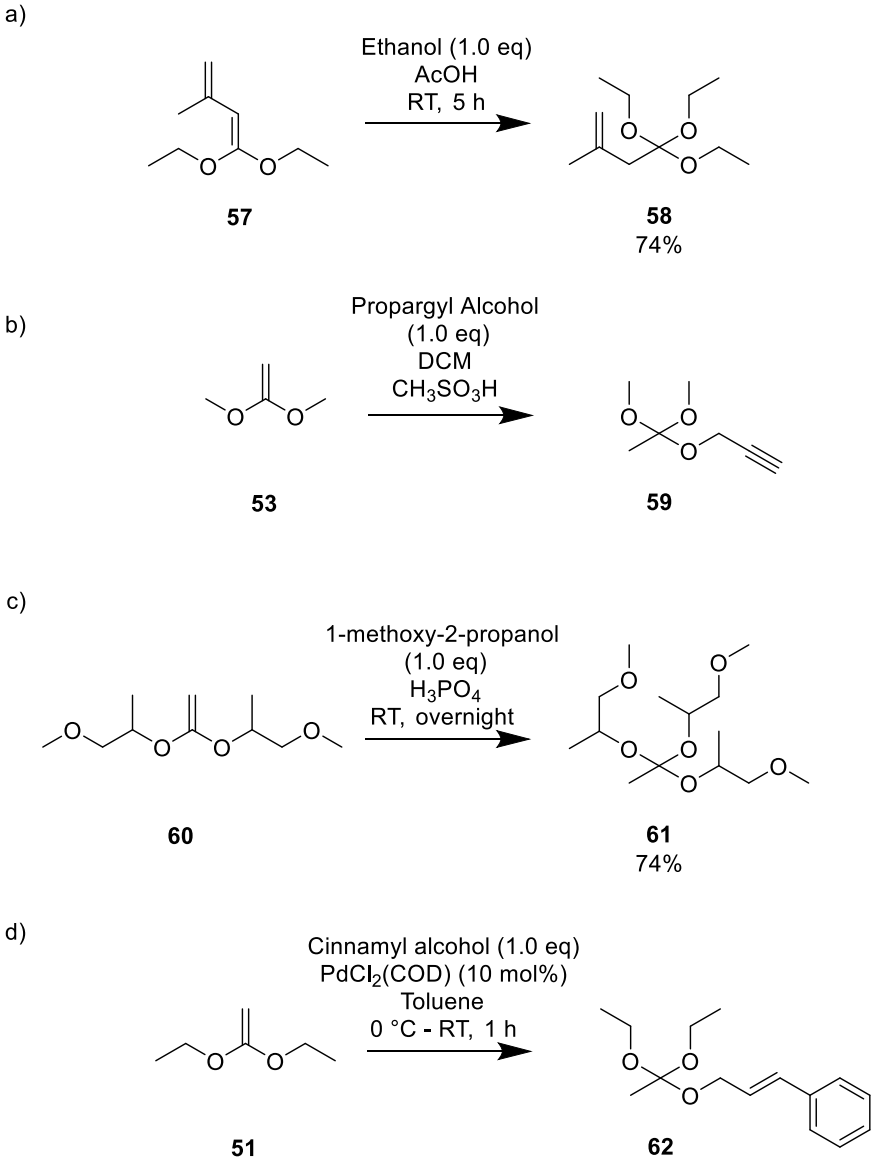
Scheme 26: Synthesis of cyclic ketene acetals

In 1984, Capon and Siddhanta reported the addition of alcohols to ketene acetals utilising *t*-butanol as a solvent.[98,100] A small range of unsaturated and halogen containing alcohols were added to ketene dimethyl acetal (**53**) producing mixed orthoesters (**54e-g**) (Scheme 27). However, the mixed orthoesters were only synthesised in yields of 40-50%, which were significantly lower than the quantitative yields reported by McGeary and Cosgrove.



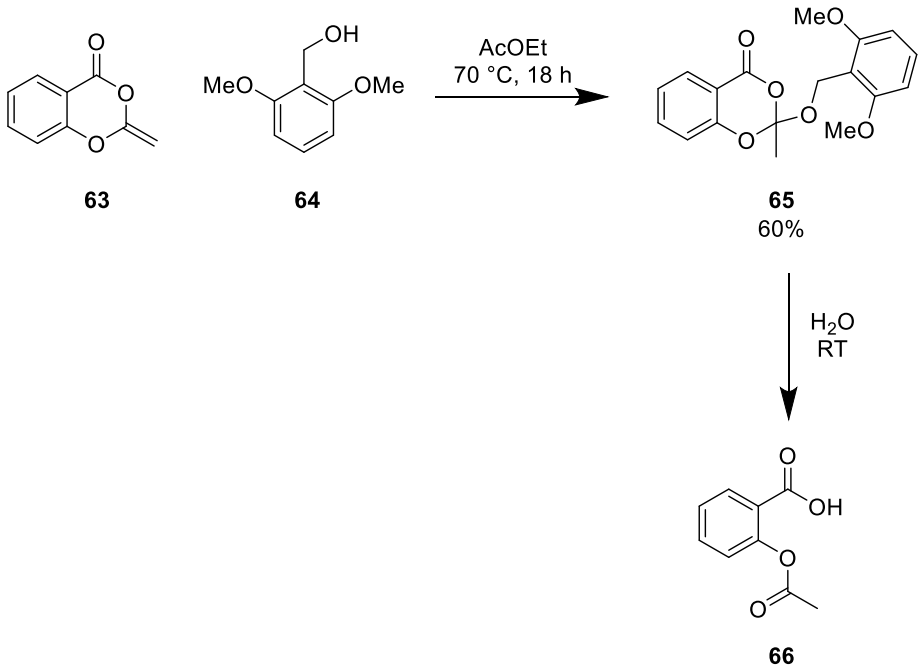
Scheme 27: The addition of alcohols to ketene acetals with *t*-butanol as the solvent

The acid catalysed addition of alcohols to ketene acetals has received significantly more investigation over the years. A range of acid catalysts have been studied (Scheme 28); including acetic acid[101], methane sulfonic acid[98], phosphoric acid[102] and $PdCl_2(COD)$[103]. Although yields were not always reported.



Scheme 28: Examples of the addition of alcohols catalysed by a) acetic acid; b) methane sulfonic acid; c) phosphoric acid; d) $PdCl_2(COD)$

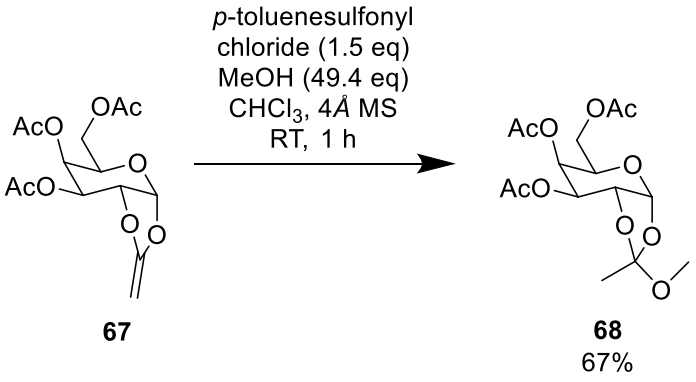
The synthesis of orthoesters by the addition of alcohols to cyclic ketene acetals has also been used to synthesise aspirin prodrugs (**65**).[104] Since orthoesters are known to undergo hydrolysis reactions, these orthoesters could readily hydrolyse to release aspirin (**66**) (Scheme 29). However, no yields or conditions for the hydrolysis were reported.



63 **64** **65** 60% **66**

Scheme 29: Synthesis of orthoester aspirin prodrugs by addition of alcohols to ketene acetals

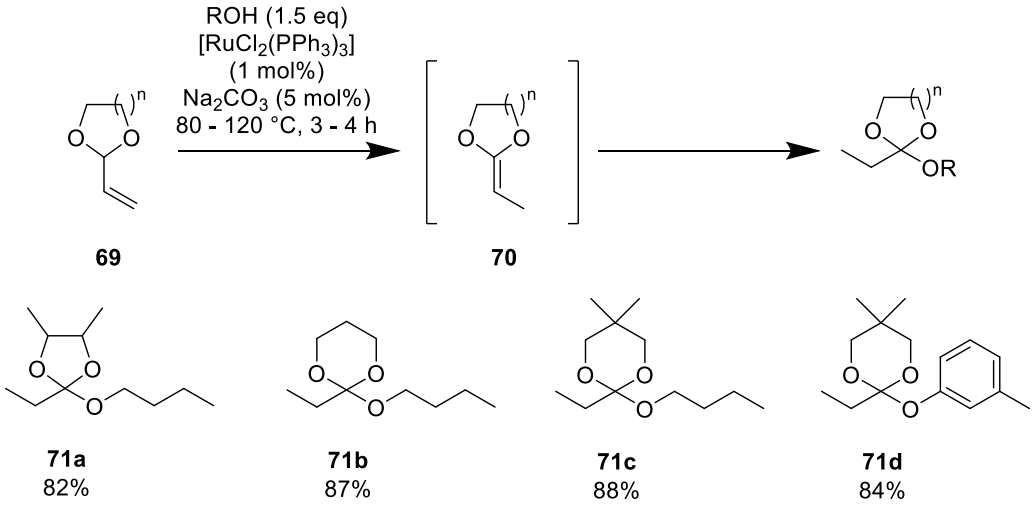
Orthoesters can also be used as protecting groups for carbohydrates.[105] Carbohydrate orthoesters (**67**) can be synthesised by the addition of alcohol to a carbohydrate ketene acetal (**68**), using *p*-toluenesulfonyl chloride as a catalyst (Scheme 30).[106]



67 **68** 67%

Scheme 30: The synthesis of carbohydrate orthoesters through the addition of an alcohol to a ketene acetal

The synthesis of orthoesters from the *in situ* formation of ketene acetals has also been reported. Krompiec *et al*. described the formation of cyclic mixed orthoesters through [Ru] catalysed addition of alcohols to O-allyl acetals.[55,107] They proposed that the O-allyl acetal (**69**) underwent a [Ru] catalysed isomerisation[108] to form a ketene acetal (**70**) which then allows for addition of the alcohol to form mixed orthoesters (**71a-d**) (Scheme 31). Unfortunately, due to the nature of the O-allyl acetals, this method only allows for the formation of orthopropionates and higher carbon chains.



Scheme 31: Synthesis of mixed orthoesters from O-allyl acetals

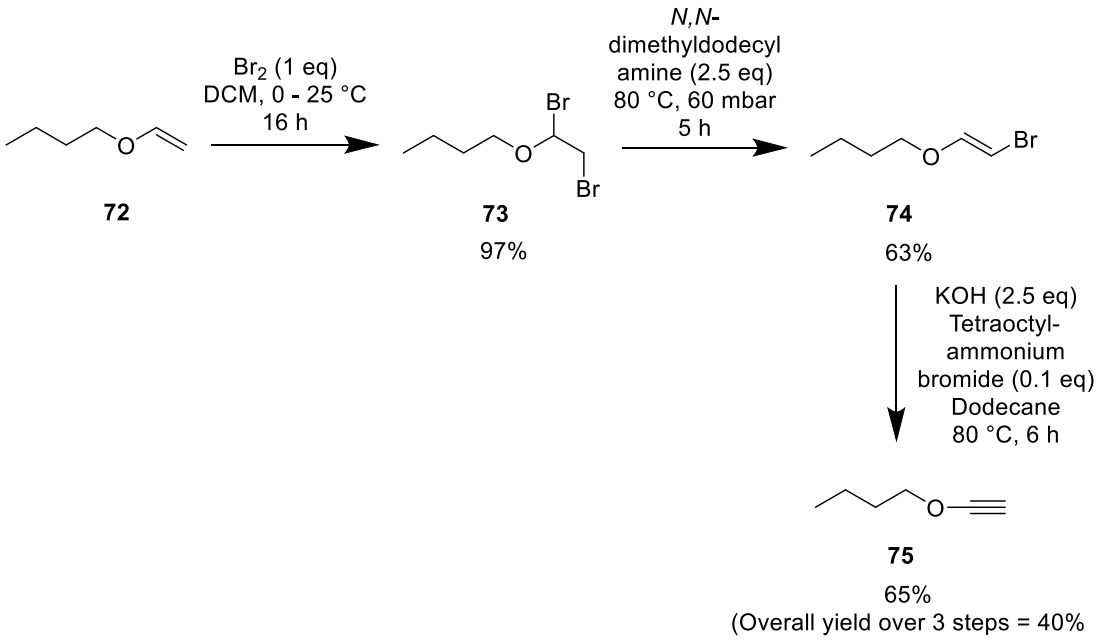
The use of ketene acetals to make orthoesters has not been popular in the past due to difficulties in synthesising the ketene acetal.[109] This is noted by the fact that the examples discussed were reported at least 10 years ago, with most reported between 1930-1985. However, over the last 50 years the synthesis of ketene acetals, particularly cyclic variants, have been intensively investigated due to their potential as monomers for biodegradable polymers[110,111], therefore making this now a more viable approach.

3.2 Results and Discussion

3.2.1 Synthesis of Orthoesters from Alkoxy Acetylenes

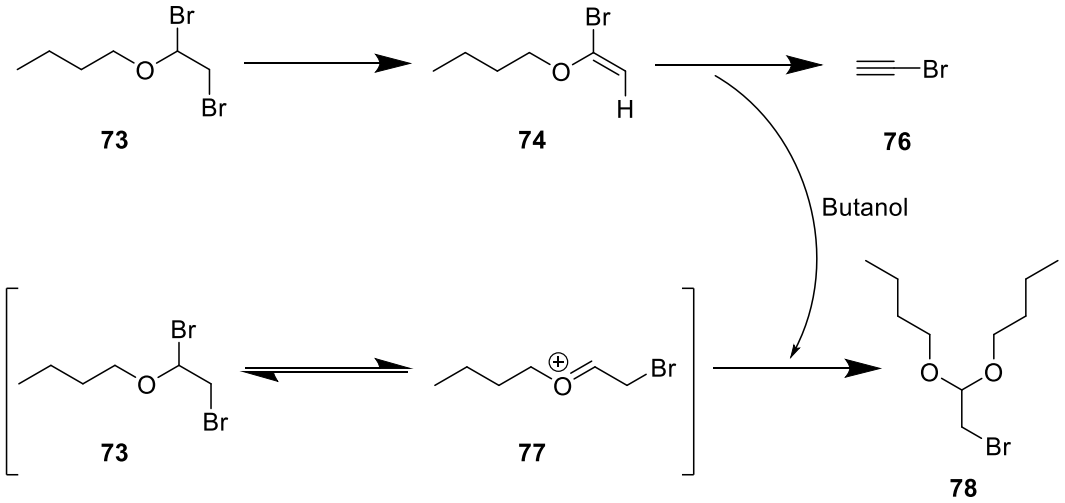
The first synthetic route towards orthoesters investigated was a zinc catalysed addition of alcohols to alkoxy acetylenes, originally developed by Broekema.[53] Although this research was from 1975 it is one of the more recent developments in the syntheses of orthoesters. Short reaction times, use of a cheap catalyst and moderate yields made this an attractive route to di-substituted orthoesters. In order to expand the substrate scope of this reaction, it was important to be able to access a range of alkoxy acetylenes. Unfortunately, commercially available alkoxy acetylenes are limited to ethoxyacetylene. However, they are well known in the literature, with a wide variety of different reaction routes.[89,112–115] As an aim of this project was to devise a reliable, cheap and scalable method of synthesising orthoesters, reaction routes using highly pyrophoric, toxic and hard to use chemicals like *n*-BuLi, LDA and sodium amide were avoided.

Butoxyacetylene was chosen as the first candidate since it was well known in the literature and would be a good model of the reaction route.[89,112-113] The synthetic route (Scheme 32) began with the bromination of vinyl ether (**72**) followed by two subsequent dehydrobrominations.[89,116–118]



Scheme 32: Synthesis route to butoxyacetylene

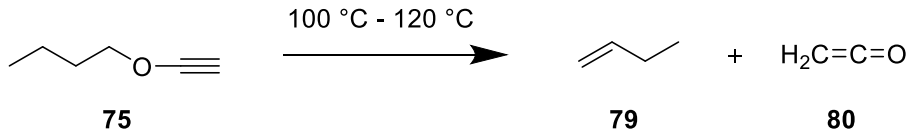
Although this route allowed for the successful synthesis of butoxyacetylene (**75**), there were several difficulties which could impact the viability of the route for other substrates. The first problem was a result of the first dehydrobromination step to produce mono-bromide (**74**). Di-bromide (**73**) can degrade to form butanol and an alkyne (**76**). The butanol can then react with intermediate (**77**) to form bromoacetal (**78**) as a side product (Scheme 33). Unfortunately, rigorous attempts to prevent the side product from forming, including using a range of different bases, were unsuccessful. The only method of obtaining mono-bromide (**74**) cleanly involved distilling the product out of the reaction as it formed. *N,N*-dimethyldodecylamine was used as the base due to its boiling point being higher than that of mono-bromide (**74**), allowing for easy separation and distillation. However, this may not be the case for all substrates and therefore it is more than likely that the base would have to be optimised for each substrate to allow easy separation.



Scheme 33: Synthesis of side product bromoacetal (78) through unfavoured dehydrobrominations

The second problem resulted from the final dehydrobromination. Butoxyacetylene (**75**) is known to undergo a thermally activated degradation to form butene (**79**) and ketene (**80**) (Scheme 34).[119–121] Preventing this thermal degradation during the reaction was easily achieved by maintaining the reaction temperature below 100 °C. If the reaction was performed at 100 °C or above, butoxyacetylene (**75**) was contaminated with butene (**79**). Remarkably attempts to remove the butene (**79**) were unsuccessful despite its low boiling point. Therefore, the reaction was

conducted at 80 °C for 6 h and obtaining butoxyacetylene (**75**) in 65% yield (Scheme 32).



Scheme 34: Thermal degradation of butoxyacetylene to form butene

Attempts to synthesise other acetylenes, such as cyclohexyl or *n*-octyl, were unsuccessful. Problems arose in both dehydrobromination steps. For example, for the cyclohexyl derivative (**81**) the acetylene could not be isolated without the formation of the thermal degradation products, cyclohexene and ketene. On the other hand, for the *n*-octyl derivative (**82**), the monobromide could not be isolated without contamination from *N,N*-dimethyldodecylamine. Alternative bases tested proved ineffective.

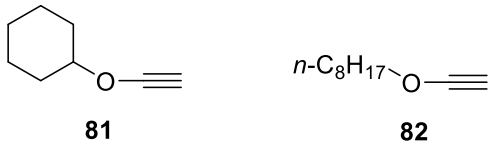
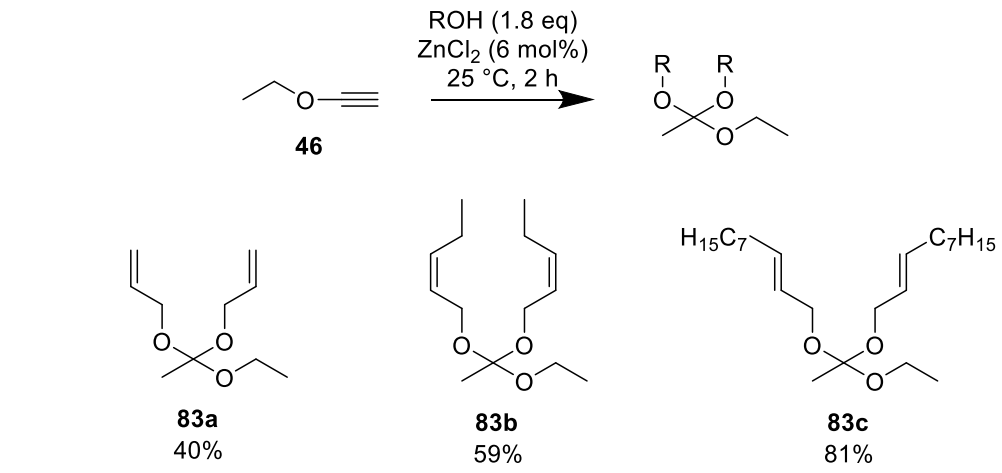


Figure 9: Cyclohexyl and n-octyl acetylene

Unfortunately, despite rigorous efforts this method of synthesising alkoxy acetylenes is not reliable, facile or scalable. Formation of simple alkoxy acetylenes was challenging, therefore using this method to allow for the synthesis of more complex acetylenes, which would have the potential to behave as the active group for the orthoester delivery systems is not viable. Nevertheless, commercially available ethoxyacetylene (**46**) and synthetically made butoxyacetylene (**75**) were both used in the Lewis acid catalysed synthesis of orthoesters.

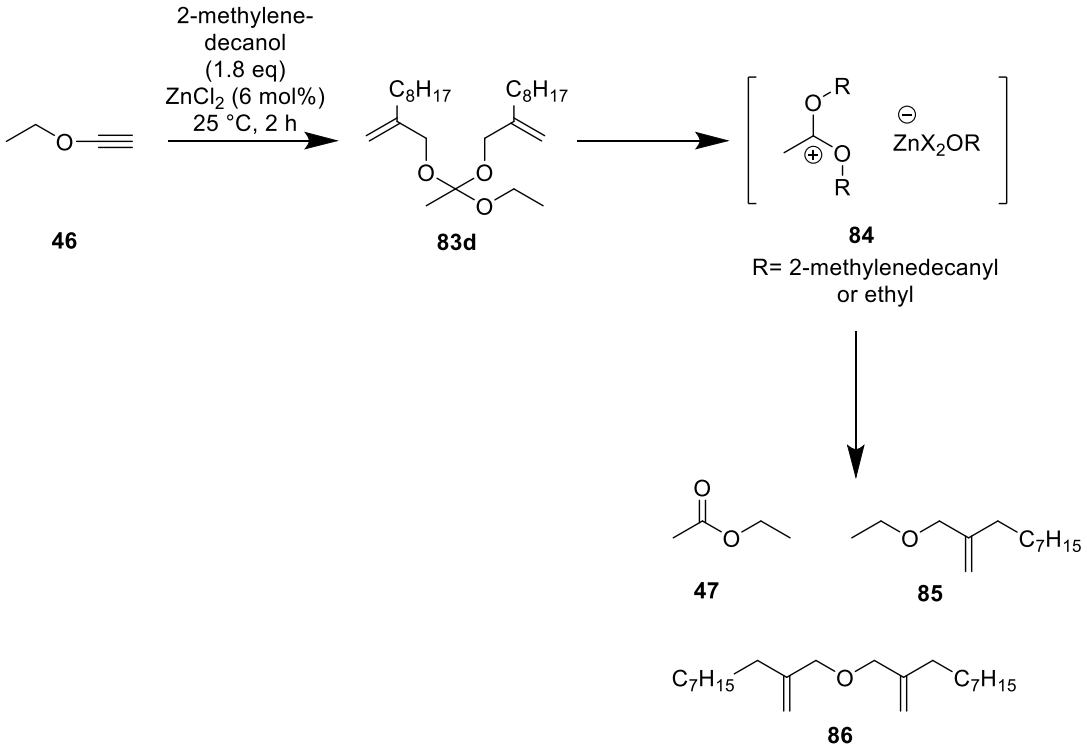
Initial attempts to synthesise orthoesters *via* acetylenes involved applying Broekema's conditions to allylic alcohols, using commercially available ethoxyacetylene. Straight chain allylic alcohols produced orthoesters (**83a-c**) in good to moderate yields, while only requiring a filtration as purification. Importantly for the application of delivery systems for automotive lubricant oils

this reaction was tolerant to a long chain ($C_{10}H_{18}$) allylic alcohol, which would provide solubility within a lubricant package.



Scheme 35: Synthesis of orthoesters using Broekema's conditions[53]

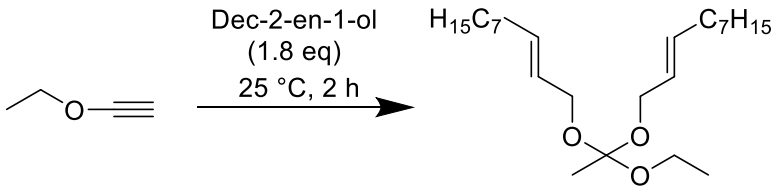
To further the scope of the reaction, Broekema's conditions were attempted for allylic alcohols with different substitution patterns around the alkene. When using an allylic alcohol with an external alkene (2-methyldecanol) the reaction was found to produce a complex range of side products. A potential theory for these side products could be a zinc mediated degradation (Scheme 36).[122]



Scheme 36: Zinc mediated degradation of orthoesters

Optimisation of the reaction conditions whilst still using $ZnCl_2$ continued to produce these side products. Therefore, a Lewis acid catalyst screen was undertaken with dec-2-enol due to the success of the reaction with $ZnCl_2$ (Table 2). These Lewis acids were chosen due to their success in the addition of alcohols to acetylenes.[123]

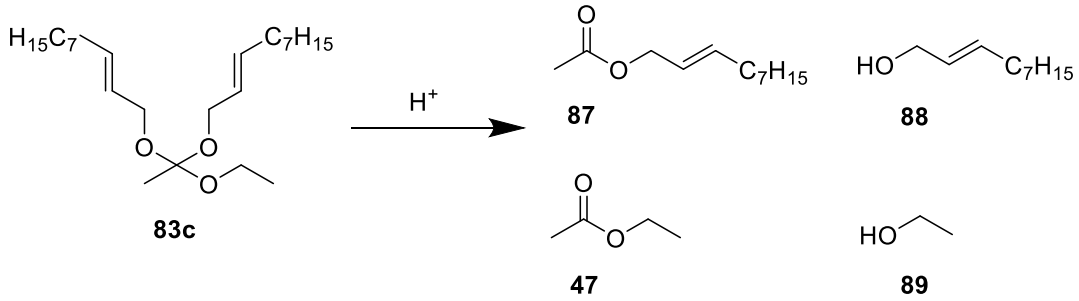
Table 2: Lewis acid screening for the synthesis of dec-2-en-1-ol mixed orthoester; [a] Product conversion determined by ^{1}H NMR alcohol:product



46 **83c**

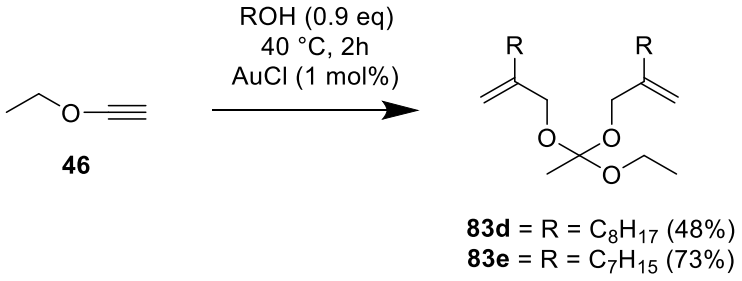
Entry	Catalyst	Catalyst Loading (mol%)	Product Conversion (%)[a]
1	$Sc(OTf)_2$	2	Degradation
2	AuCl	1	100
3	AuCl	2	100
4	AuCl	3	Degradation
5	AuCl	5	Degradation
6	$AuCl_3$	1	Degradation
7	$AuCH_3.P(C_6H_5)_3$	2	0
8	InCl	2	0
9	CuCl	2	20
10	CuCl	10	30
11	$CuCl_2$	2	20
12	$Cu(OAc)_2$	2	0
13	$Cu(OTf)_2$	1	Degradation
14	$FeCl_3$	2	0

It is widely known in the literature that orthoesters are unstable to acids resulting in degradation to their corresponding acetate esters (**47, 87**) and alcohols (**88-89**) (Scheme 37).[124–130] Therefore, it was not a surprise when several of the acids in the screen led to the degradation of the orthoester, suggesting that they were too acidic for this transformation. Further to this it was also found that an optimum amount of acid was required for the addition; using too much acid also led to degradation of the orthoester. AuCl was determined to be the best catalyst producing full conversion with a low loading of 1 mol%.



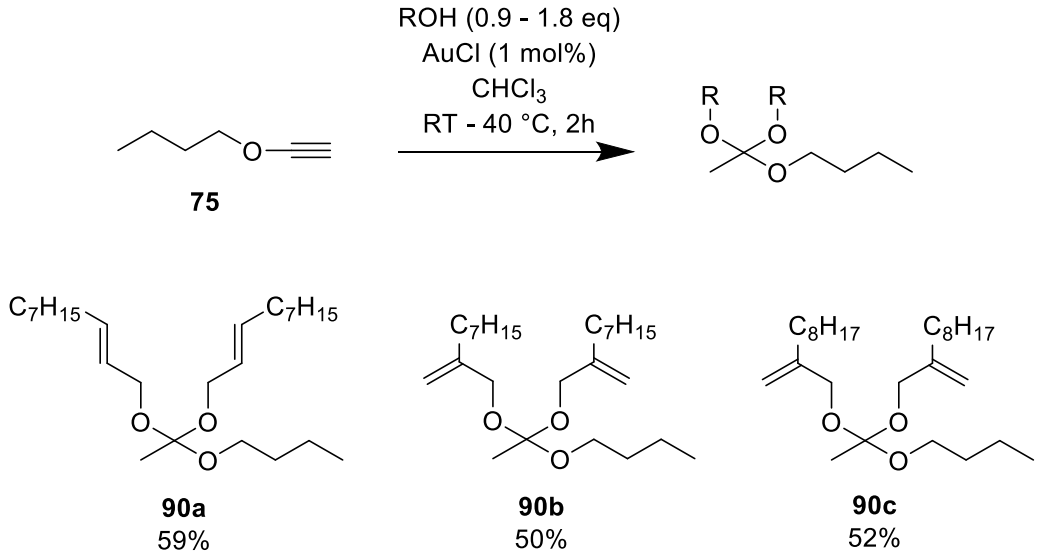
Scheme 37: Example of the degradation of orthoesters

Moving from $ZnCl_2$ to AuCl for the addition of branched alkene allylic alcohols to ethoxyacetylene to produce orthoester (**83d**) led to no observed side products, however the reaction stalled, with only 25% conversion of the allylic alcohol, determined by ^{1}H-NMR ratio alcohol:orthoester. Optimising the reaction, by increasing the temperature and using excess acetylene resulted in 100% alcohol consumption and a yield of 48%, as well as the formation of another derivative in 73% (**83e**) (Scheme 38).



Scheme 38: Optimised conditions of AuCl catalysed addition of external allylic alcohols to ethoxyacetylene

These optimised conditions were also found to tolerate the addition of allylic alcohols to butoxyacetylene (**75**) (Scheme 39).



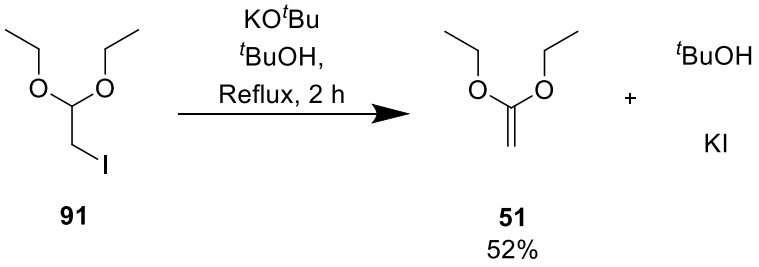
Scheme 39: Addition of allylic alcohols to butoxyacetylene using the improved conditions

3.2.2 Synthesis of Orthoesters from Ketene Acetals

3.2.2.1 Review of the Synthesis of Ketene Acetals

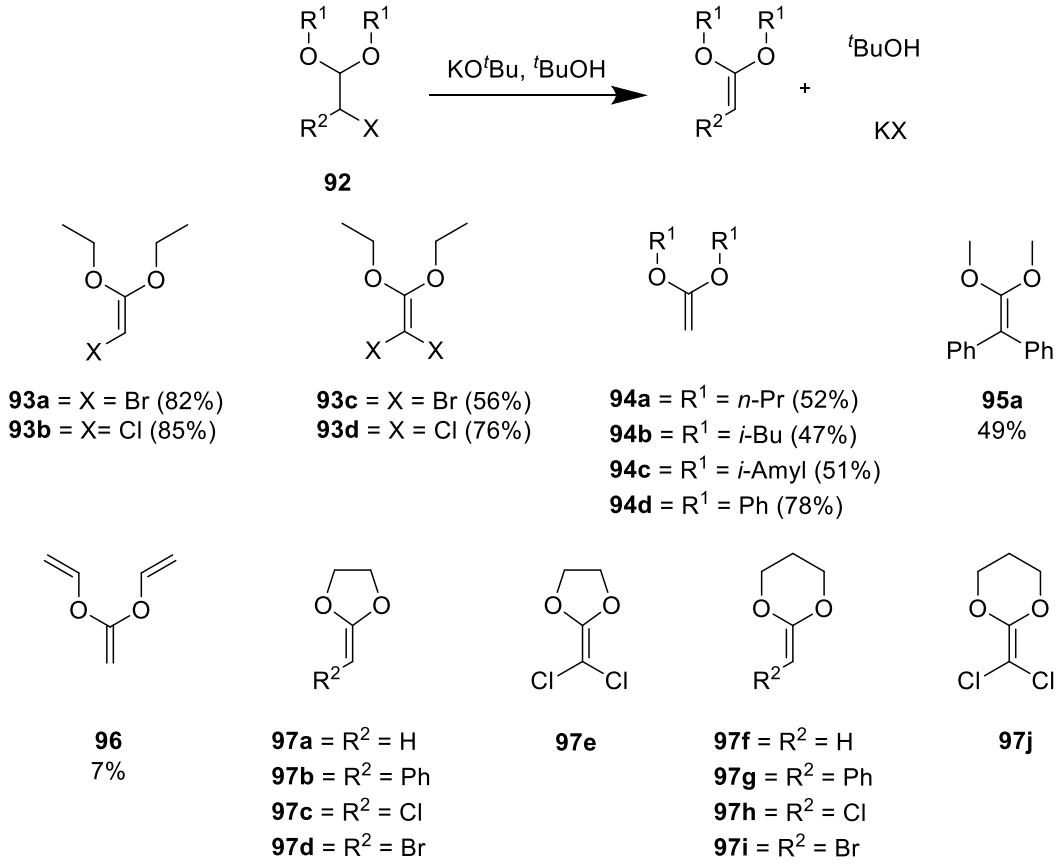
From Haloacetals

The first reported synthesis of ketene acetals from haloacetals was described by Beyerstedt and McElvain in 1936.[94] They demonstrated that an iodoacetal (**91**) could undergo dehydroiodination in the presence of potassium *t*-butoxide, in *t*-butanol, to produce a ketene acetal (**51**) (Scheme 40). The use of *t*-butanol as the solvent was important, since primary or secondary alcohols reacted with the ketene acetal to form orthoesters. Later work by McElvain *et al*. highlighted that ketene dimethylacetal (**53**) could also be synthesised in yields of 67 – 75% from the bromoacetal.[131,132]



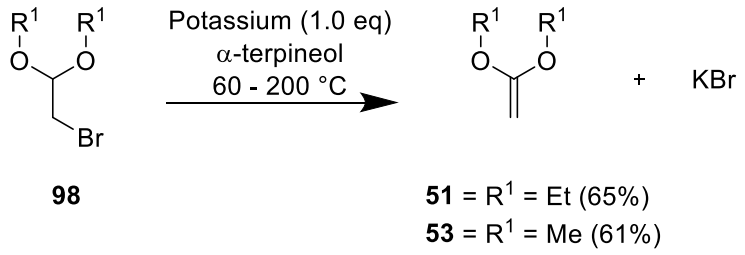
Scheme 40: Dehydroiodination of an iodoacetal into a ketene acetal

Over the years the dehydrohalogenation of haloacetals to form ketene acetals has been expanded to a range of substrates. From 1936 – 1955, McElvain *et al*. demonstrated the synthesis of bromo- and chloro-ketene acetals (**93a-d**)[133–135], ketene dialkyl acetals (**94a-d**)[136-137], diphenyl ketene dimethylacetal (**95a**)[138], ketene divinylacetals (**96**)[139] and ketene cyclic acetals (**97a-j**)[97] (Scheme 41).



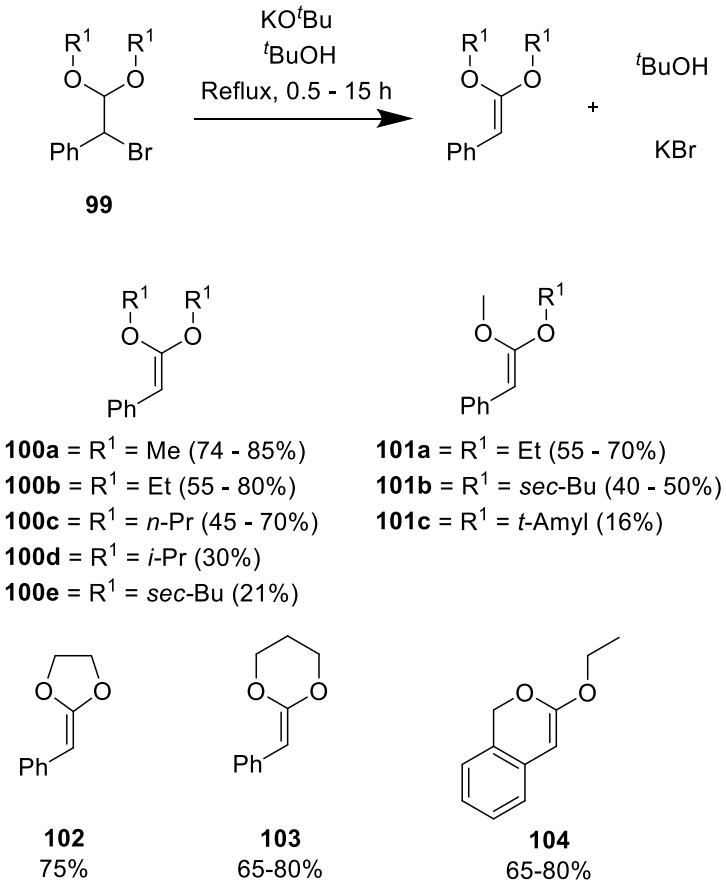
Scheme 41: Range of ketene acetals synthesised by McElvain[97,133-139]

In 1964, Corey *et al*. developed a new method of dehydrohalogenating bromoacetals to form ketene acetals.[140] They utilised potassium metal in anhydrous α-terpineol to convert bromo dimethylacetal to ketene dimethylacetal (**53**) (Scheme 42). This method was later utilised by Griffiths *et al*. to synthesise ketene diethylacetal (**51**).[141]



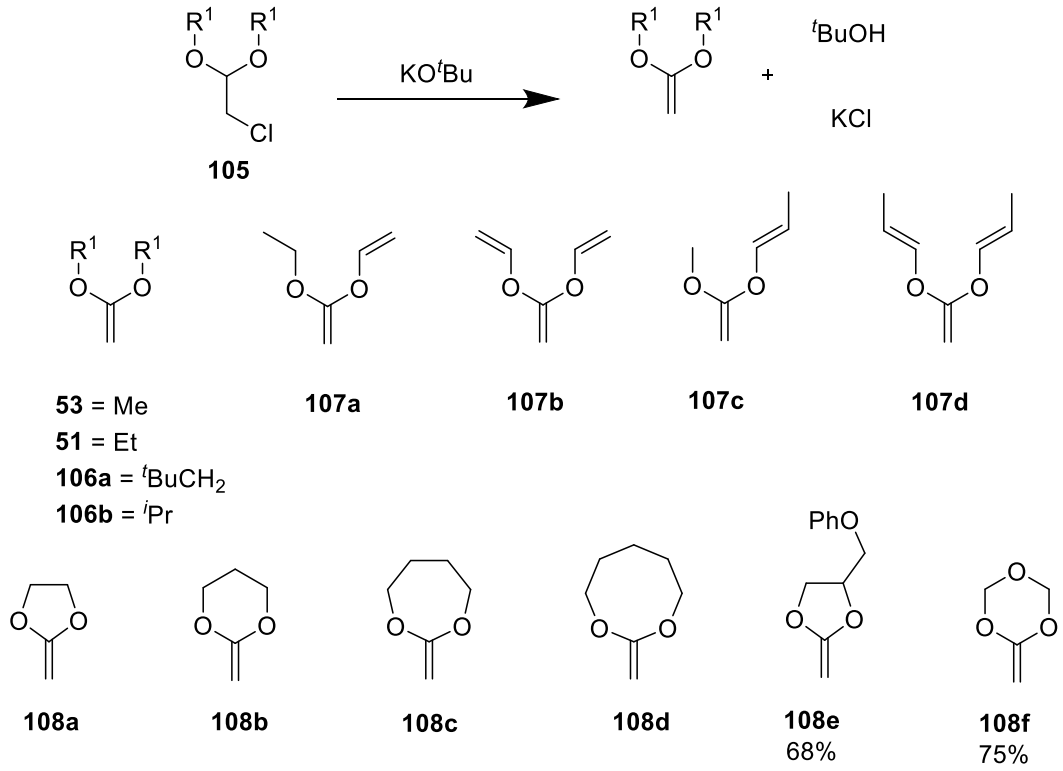
Scheme 42: Dehydrohalogenation of bromoacetals using potassium metal

In 1966, Baldwin and Walker continued to further the substrate scope by synthesising a range of phenyl ketene acetals from the dehydrohalogenation of the corresponding haloacetals (Scheme 43).[142] They demonstrated that this method tolerated primary, secondary and cyclic substrates, specifically this method allowed for the formation of mixed ketene acetals (**101a-c**) and O-internal cyclic ketene acetals (**104**). It must be noted though that the purity of the ketene acetals was between 70 – 95% depending on the substrate.



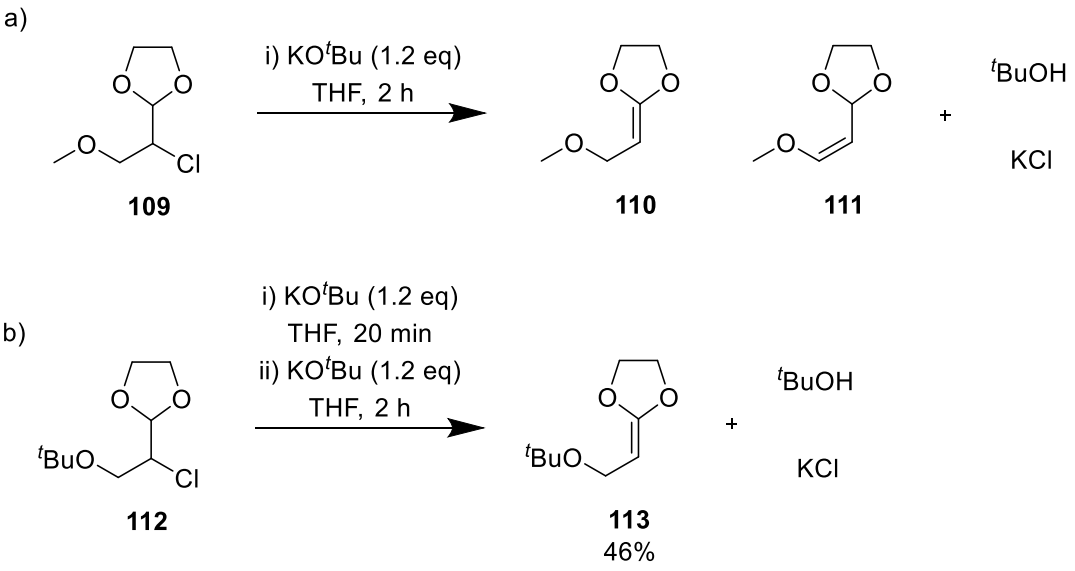
Scheme 43: Synthesis of a range of phenyl ketene acetals

The substrate scope was further investigated in 1978 by Taskinen and Pentihainen.[143] They described the dehydrochlorination of a range of acylic and cyclic bromoacetals to form ketene acetals (Scheme 44). Primary, secondary and vinyl substrates were all tolerated by this dehydrochlorination, as well as allowing for the formation of mixed ketene acetals (**107a, 107c**) and a range of ring sizes (**108a-f**). This method was later utilised by Fukuda *et al*. to synthesise other cyclic ketene acetal derivatives (**116e-f**) (Scheme 44).[99]



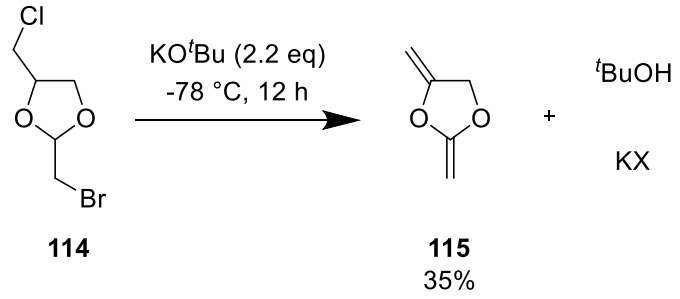
Scheme 44: Synthesis of a range of acylic and cyclic ketene acetals from chloroacetals

The synthesis of longer carbon chain analogue ketene acetals was successfully undertaken by Scheeren and Aben in 1988.[144] They demonstrated that longer chain haloacetals without any steric bulk result in a mixture of the ketene acetal (**110**) and the enol ether (**111**) when they are subjected to dehydrohalogenation (Scheme 45a). Addition of more steric bulk to the haloacetal (**112**) resulted in the exclusive formation of the ketene acetal (**113**) (Scheme 45b).



Scheme 45: a) Dehydrochlorination of 109 to produce the ketene acetal and enol ether; b) Dehydrochlorination of 112 to form exclusively the ketene acetal

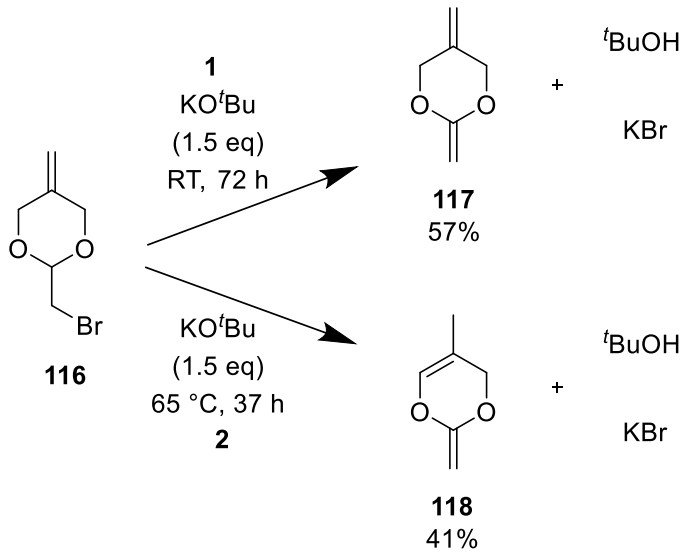
The synthesis of *exo*-methylene cyclic ketene acetals was developed in 1990 by Hayashi *et al*.[145] A double dehydrohalogenation of haloacetal (**114**) at -78 °C for 12 hours produced exo-methylene cyclic ketene acetal (**115**) in 35% isolated yield (Scheme 46). Difficulties in separation from *t*-butanol was described as the cause of the low isolated yield compared to 65% yield by ^{1}H-NMR. Other bases, such as DBU, NaH, n-Buli, sodium dimsylate and sodium cumyl alkoxide were also investigated but did not produce the desired product (**115**).



Scheme 46: Double dehydrohalogenation to form *exo*-methylene ketene acetals

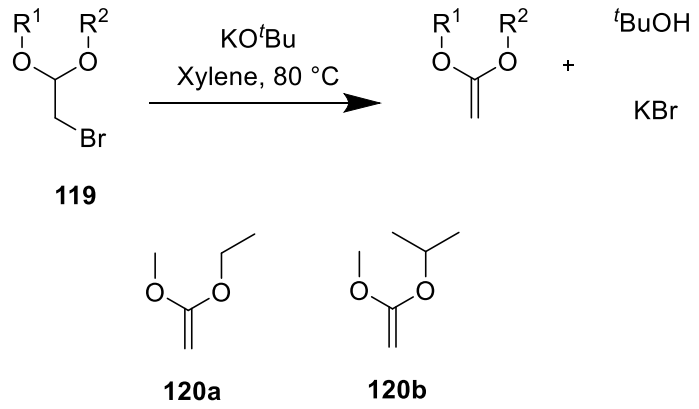
Hayashi *et al*. also synthesised *exo*-methylene ketene acetals by installing the exo-methylene prior to the dehydrohalogenation, in the bromoacetal (**116**). They demonstrated that the temperature of the reaction could lead to the isomerisation of the exo-methylene to form ketene acetal (**118**). The desired exo-methylene ketene acetal (**117**) could be exclusively formed by holding the reaction at room

temperature for 72 hours (Scheme 47, route 1). To obtain exclusively the internal-methylene ketene acetal (**118**) the reaction was heated to 65 °C for 37 hours (Scheme 47, route 2). They postulated that the isomerisation was a result of abstraction of the allylic proton with KO^{t}Bu, since [1,3]-H migration is thermally forbidden.



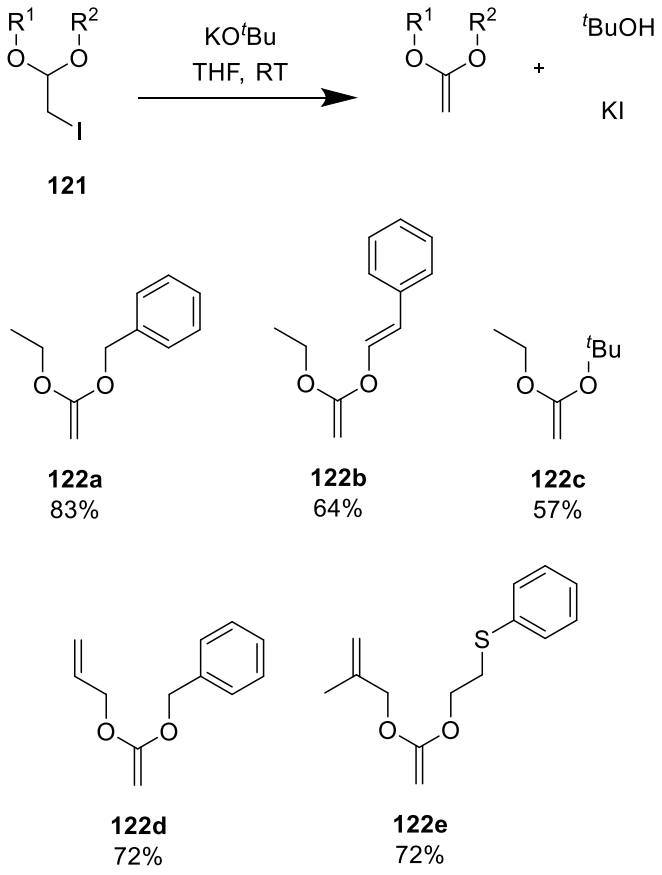
Scheme 47: Dehydrohalogenation products of bromoacetal (116) under different conditions

Mixed ketene acetals have been investigated over the years. In 1975 Cliff and Dunn modified the dehydrohalogenation method described by McElvain[94] by using xylene as a solvent and heating the reaction to 80 °C.[146] This method allowed for the dehydrobromination of two mixed bromoacetals (**119**) to the corresponding ketene acetal (**120a-b**) (Scheme 48).



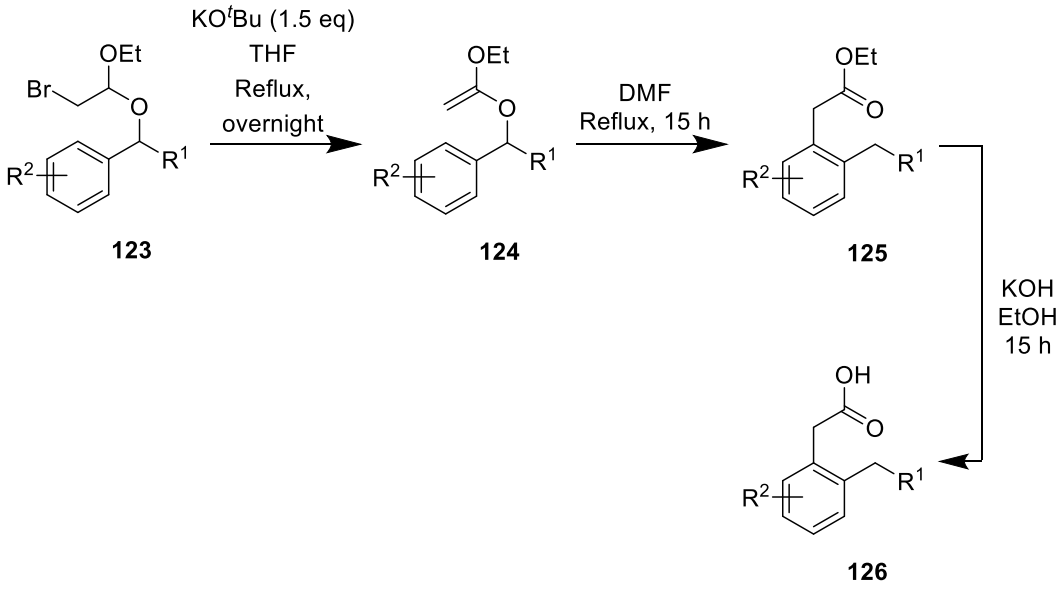
Scheme 48: Synthesis of mixed ketene acetals

In 1989, Middleton and Simpkins described the dehydroiodination of a range of mixed iodoacetals (**121**) to form their corresponding ketene acetals (**122a-e**) (Scheme 49).[147] They demonstrated that this method tolerated primary, tertiary, vinyl, benzylic and allylic substrates. The isolation of the benzylic and allylic ketene acetals (**122a,d-e**) was surprising since they are known to undergo the orthoester Johnson-Claisen rearrangement.[148]



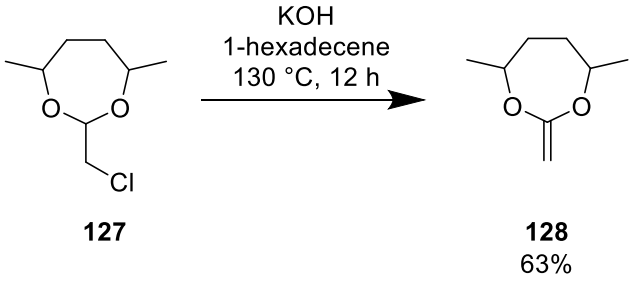
Scheme 49: Synthesis of mixed ketene acetals from iodoacetals

Benzylic mixed ketene acetals were further synthesised by McGeary *et al*. in 2017.[149] The dehydrobromination of a range of benzyl bromoacetals produced benzyl ketene acetals (**124**) which were immediately taken on to undergo the Claisen rearrangement, followed by hydrolysis to form alcohols (**126**) (Scheme 50). Unfortunately, the ketene acetals were only isolated crude from the reaction mixture and therefore have limited characterisation data.



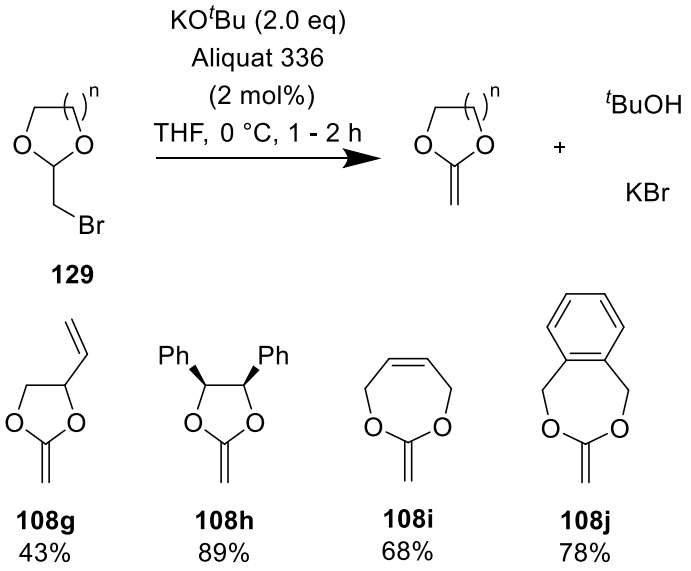
Scheme 50: Synthesis of benzylic mixed ketene acetals

The synthesis of cyclic ketene acetals *via* the dehydrohalogenation of haloacetals has been intensively researched over the years due to their potential as monomers for biodegradable polymers.[110] A range of different conditions have been employed to improve upon the yield and ease of reaction. Bailey *et al*., demonstrated that KOH could be used as the dehydrohalogenating agent, producing cyclic ketene acetal (**128**) in 63% yield (Scheme 51).[150]



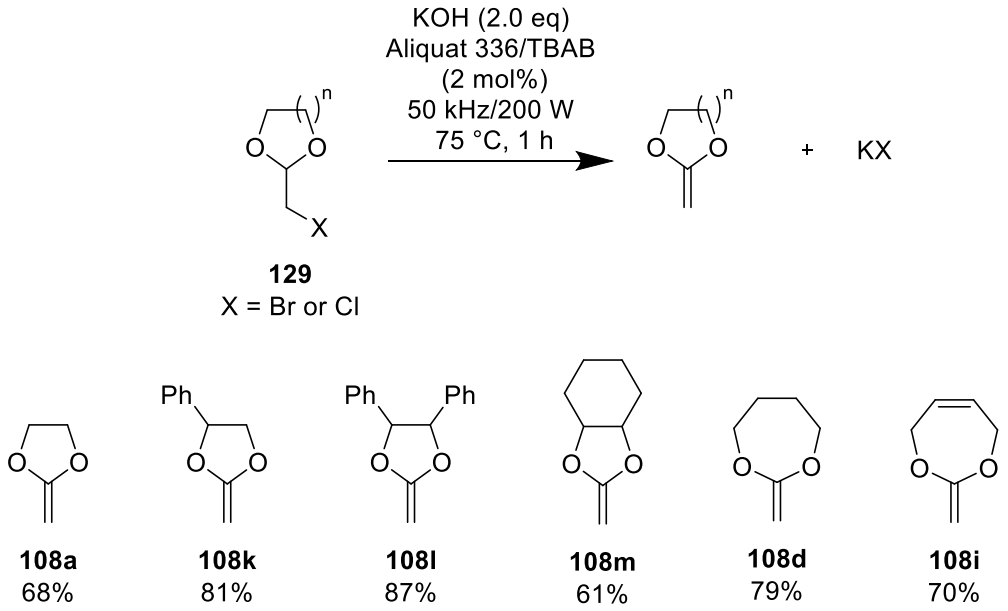
Scheme 51: Formation of ketene acetals using KOH

A phase transfer catalysed dehydrohalogenation was developed by Bailey and Zhou in 1991.[151] A range of cyclic ketene acetals (**108g-j**) were produced from the KO^{t}Bu and Aliquat 336 catalysed dehydrobromination (Scheme 52). They postulated that the $RO^-/^+NR_4$ ion pair in Aliquat 336 dissociated more readily when dissolved in an organic solvent, such as THF, which increased the basicity and promoted elimination to form the ketene acetals.



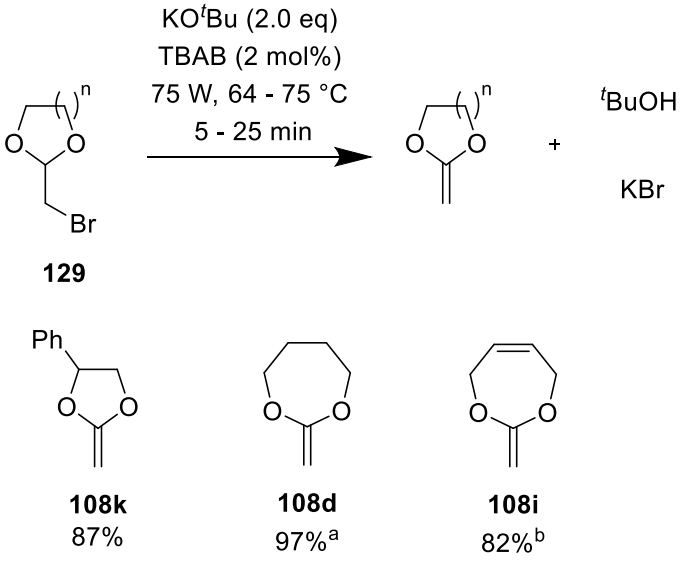
Scheme 52: Synthesis of cyclic ketene acetals catalysed by Aliquat 336

In 1992 and 1993, ultrasonic irradiation partnered with phase transfer catalysis in solvent free conditions was utilised for the dehydrohalogenation of bromoacetals to form ketene acetals (**108**) (Scheme 53).[152,153] This method involved the use of KOH and either tetrabutylammonium bromide (TBAB) or Aliquat 336, with both phase-transfer catalysts producing similar yields. They highlighted that the dehydrohalogenation was incomplete even after 2 hours when ultrasonic irradiation was not used, and that yields significantly dropped when a phase transfer catalyst was not used. KOH was used instead of the commonly used KO^{t}Bu because KO^{t}Bu caused a too rapid release of HBr. Since HBr is a strong acid the considerable build up from rapid release led to decomposition of the ketene acetal. They postulated that the use of ultrasonic irradiation led to fragmentation and reduction in the particle size, which increased the reaction surface and created a better dispersion. However, some yields showed little improvement compared to the original phase-transfer catalysed route described by Bailey and Zhou (Scheme 52) which questions the part the ultrasonic irradiation played in this reaction.



Scheme 53: Ultrasonic irradiation and phase transfer catalysed dehydrohalogenation to form ketene acetals

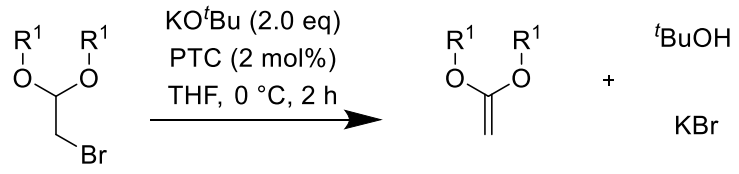
In 1996, Prieto *et al*. also developed a microwave irradiation assisted dehydrohalogenation of bromoacetals to form cyclic ketene acetals (Scheme 54).[154] In partnership with a phase transfer catalyst (TBAB) and KO^{t}Bu this method was found to be much quicker (5 – 25 minutes) compared to other routes and was higher yielding (82 – 97%). Furthermore, they discussed that in some cases (**108d**) KO^{t}Bu was a strong enough base and the use of TBAB was not required and in other cases (**108i**) a milder base, such as KOH, alongside TBAB was needed to isolate the ketene acetal.



Scheme 54: The microwave and phase transfer catalyst assisted dehydrohalogenation; [a] No TBAB used; [b] 2.5 eq KOH used

In 1999 Zheng and Su further developed the phase transfer catalysed dehydrohalogenation by investigating a range of phase transfer catalysts and their effect on the yield (Table 3).[155] They highlighted that all the phase transfer catalysts used increased the yield of the reaction compared to when no catalyst was used. Further to this, 18-crown-6 performed very well (91% yield) due to the fact the potassium ion radius equals that of the 18-crown-6. In terms of PEG, the yield increased along with the number of oxyethylene units up to 23 units (Table 3, line 10), before the yield decreased again at 34 units. They postulated that it was not just the strength of the complex formed but also the solubility in relation to the extraction procedure that affected the yield. This meaning that the phase transfer catalysis of the PEG increased with the number of oxyethylene units, but the hydrophobic nature also increased which led to issues in the extraction. Throughout this work Zheng and Su also determined that a solvent was required to control the dehydrohalogenation and allowed for better solubility of the ion pairs and the complex.

The dehydrohalogenation method described by Zheng and Su was also used for the synthesis of acyclic ketene acetals (Scheme 55).[155] The same effects of changing the phase transfer catalyst shown for the cyclic ketene acetals were also observed for the acyclic variants.

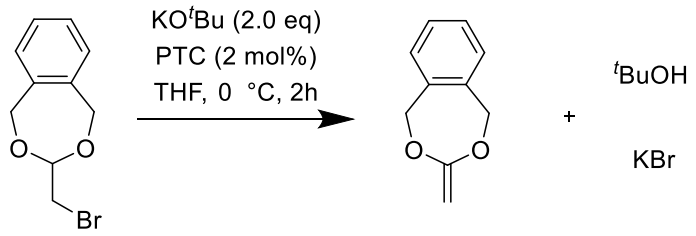


98

53 = R^1 = Me (50 - 60%)
51= R^1 = Et (63 - 70%)
106b = R^1 = *i*-Pr (55 - 63%)

Scheme 55: Phase transfer catalysed synthesis of acylic ketene acetals

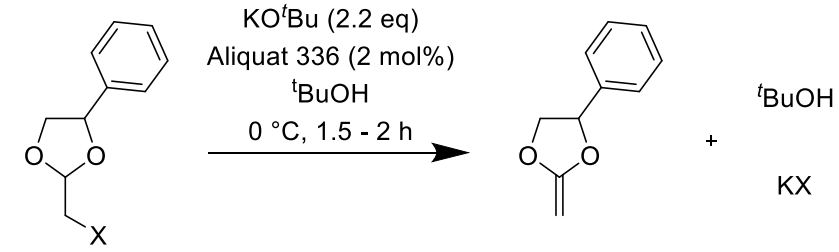
Table 3: Phase transfer catalyst (PTC) screening; [a] PEG = poly(ethylene glycol) figures indicate nominal average; [n] average number of oxyethylene units (-OCH_2CH_2-); [c] isolated after distillation or recrystallization



130 **108j**

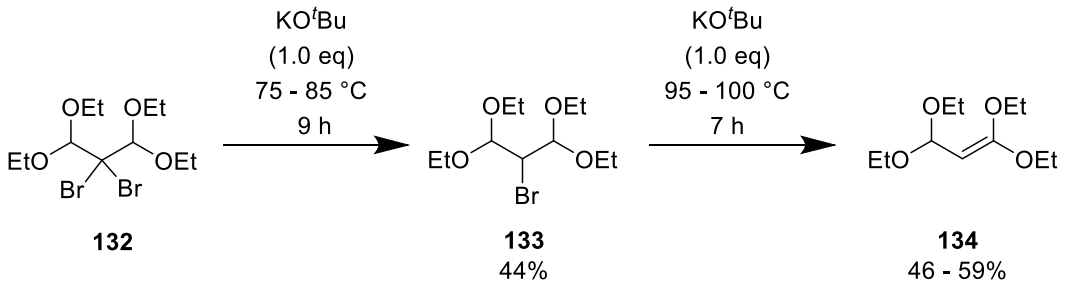
Entry	PTC	n[b]	Yield (%)[c]
1	None	-	51
2	Aliquat 336	-	78
3	TBAB	-	76
4	12-crown-4	-	58
5	15-crown-5	-	63
6	18-crown-6	-	91
7	PEG400[a]	9	65
8	PEG600[a]	14	70
9	PEG900[a]	20	89
10	PEG1000[a]	23	91
11	PEG1500[a]	34	73
12	PEG2000[a]	45	68

The effect of the halogen on the ease and yield of the dehydrohalogenation step was investigated by Nicolas *et al*. in 2016.[156] They synthesised cyclic chloro-, bromo-, and iodo-acetals (**131a-c**) which were then subsequently dehydrohalogenated with KO^{t}Bu to form ketene acetal (**108k**) (Scheme 56). This was the first reported dehydroiodination of a cyclic iodoacetal. Unsurprisingly the results were consistent with the reactivity of the halogens; the iodoacetal produced ketene acetal (**108k**) in 85% within 1.5 hours, the bromoacetal 81% in 2 hours and the chloroacetal only 23% after 2 hours.



Scheme 56: Dehydrohalogenation of a cyclic haloacetal

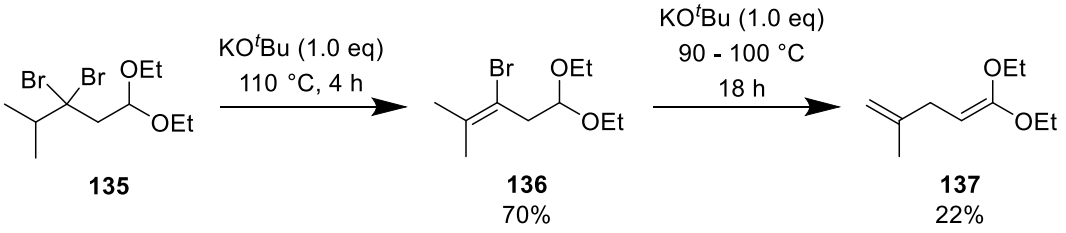
The dehydrohalogenation of haloacetals to form ketene acetals could also be applied to α,α-dibromoacetals (**132**). In 1951, McElvain and Morris discovered that α,α-dibromoacetals required two separate dehydrobromination reactions in order to form ketene acetals in successful yields (Scheme 57).[157] Attempts were made to dehydrobrominate (**132**) to ketene acetal (**134**) in one dehydrobromination step by using two equivalents of KO^{t}Bu, however this resulted in a mixture of the mono-bromide (**133**) and ketene acetal (**134**) in yields of 29% and 10% respectively.



Scheme 57: Dehydrobromination of α,α-dibromoacetals

In 1952, McElvain and Morris furthered the substrate scope of the dehydrohalogenation of α,α-dibromoacetals.[101] Isopropenylketene diethylacetal (**137**) was synthesised from the double dehydrobromination of the dibromoacetal (**135**) (Scheme 58). They postulated that the rearrangement of the alkene in (**136**) occurred before the elimination to form the ketene acetal as similar systems (bromo α,β-unsaturated acids) had been shown to undergo rearrangements before replacement of the halogen.[158]

The dehydrohalogenation of haloacetals to form ketene acetals has proved to be a fruitful method, tolerating a range of substrates and functionalities. However, a significant amount of this work reported limited characterisation data and yields. Furthermore, with a range of modifications to the method for specific substrates spread across different papers, a uniformed, reliable method for the formation of O,O-ketene acetals has not been fully described.

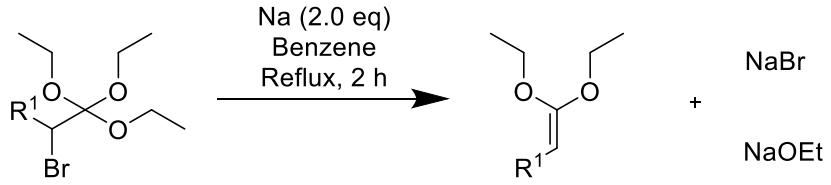


135 **136** 70% **137** 22%

Scheme 58: Dehydrobromination and rearrangement of α,α-dibromoacetal to form isopropenylketene diethylacetal

From the Reaction of Sodium with α-Bromoorthoesters

A similar method to the dehydrohalogenation of haloacetals was reported in 1940 and 1942 by McElvain *et al*. They discovered that α-bromoorthoesters (**138**) could be converted in ketene acetals (**51, 139a-c**) by the action of sodium (Scheme 59).[95,159,160] They highlighted that the main advantage of this approach was that the loss of NaOEt only allowed for the formation of the ketene acetal, the double bond could not form anywhere else in the molecule.



138

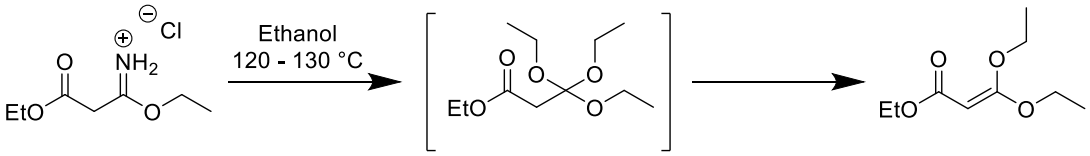
51 = R^1 = H (66%)
139a = R^1 = Me (80%)
139b = R^1 = ^{i}Pr (65%)
139c = R^1 = Pr (71%)

Scheme 59: Formation of ketene acetals from α-bromoorthoesters

In 1946, McElvain and Stevens attempted to synthesise phenylketene acetals through the reaction of the corresponding bromoorthoesters and sodium.[161] Unfortunately, they discovered that instead of the desired ketene acetal, the products of this reaction were a complex sodium salt of the ester moiety and sodium bromide. Furthermore, this method has had no further investigation since 1946, limiting its applicability.

From the Pyrolysis of Orthoesters

In 1907, Reitter and Weindel were attempting to synthesise orthoesters through the Pinner reaction.[57] Attempting purification, by distillation, of the orthoester (**141**) resulted in the formation of the ketene acetal (**142**), although no yield was reported (Scheme 60).[162] They postulated that the high temperatures of the distillation caused the orthoester (**141**) to undergo pyrolysis to form the ketene acetal (**142**).

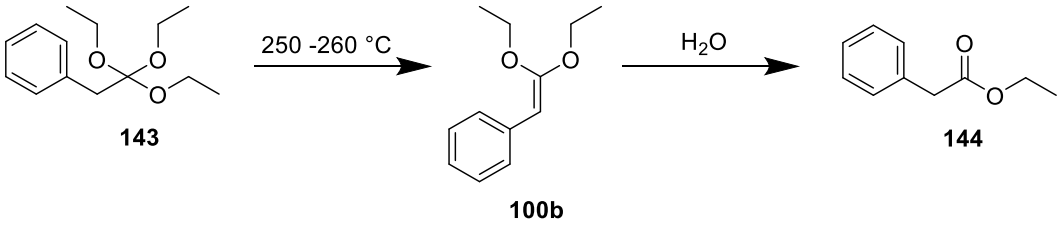


140 **141** **142**

Scheme 60: Pyrolysis of orthoesters *in situ* to form ketene acetals

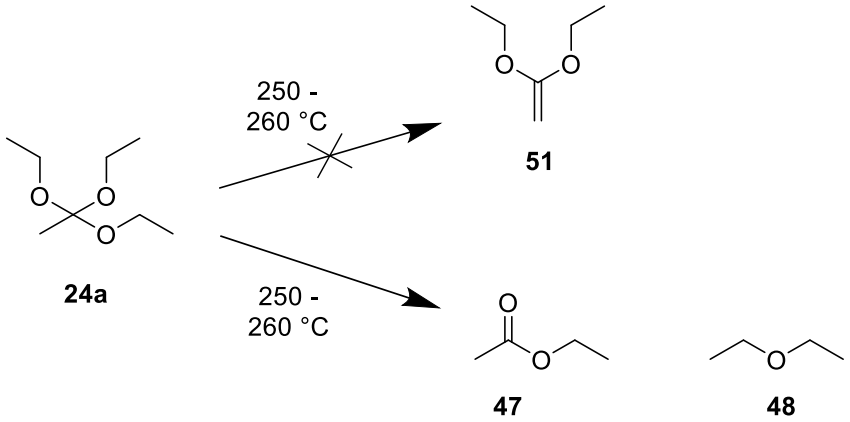
Staudinger and Rathsam, in 1922, undertook the first intentional pyrolysis of an orthoester to form ketene acetals.[163] They successfully converted ethyl orthophenylacetate (**143**) to phenylketene diethylacetal (**100b**) (Scheme 61). However, they noted on exposure to water the ketene acetal (**100b**) degraded to

an ester (**144**). This hydrolysis of ketene acetals is now well-known in the literature.[164–166]



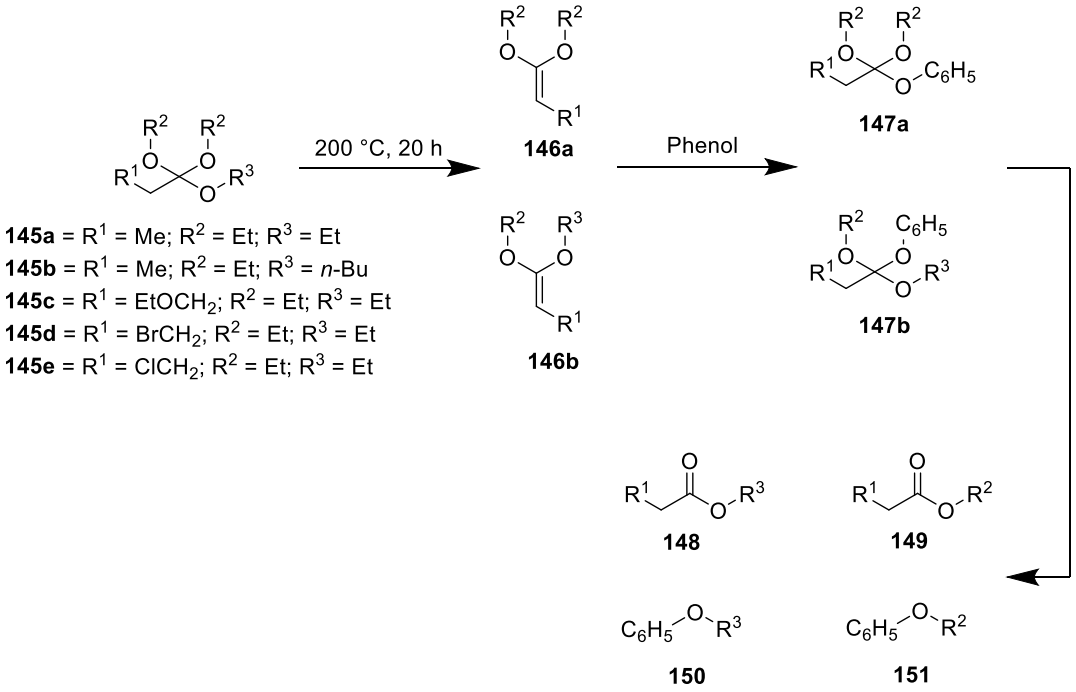
Scheme 61: Pyrolysis of ethyl orthophenylacetate (143) to phenylketene diethylacetal (100b) and subsequent hydrolysis to the ester (144)

Staudinger and Rathsam attempted to extend the scope of the pyrolysis to aliphatic orthoesters such as triethyl orthoester (**24a**). Unfortunately, instead of forming the ketene acetal (**51**), ethyl acetate (**47**) and diethyl ether (**48**) was formed (Scheme 62). They postulated that an activated α-hydrogen was required to undergo successful pyrolysis.



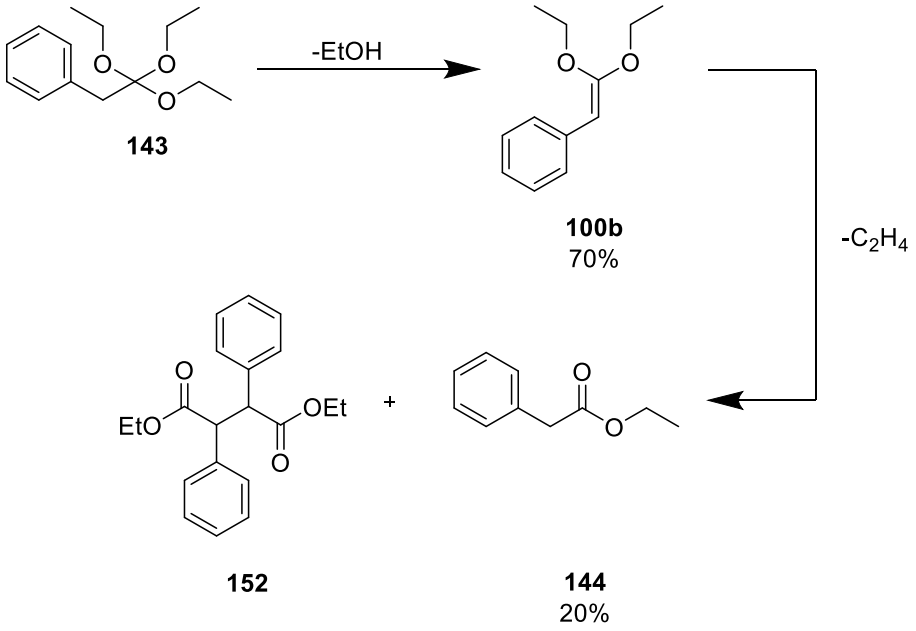
Scheme 62: Pyrolysis of triethyl orthoester (24a) to ethyl acetate (47) and diethyl ether (48)

McElvain *et al*. further investigated the pyrolysis of orthoesters in 1942.[95] The pyrolysis of a range of orthoesters (**145**), in the presence of phenol was investigated. In all cases the isolation of the ketene acetal (**146a-b**) was unsuccessful and instead a range of esters (**148-149**) and ethers (**150-151**) were formed (Scheme 63). The use of the phenol allowed for the *in situ* formation of mixed orthoesters (**147a-b**) and thus allowed investigation into the pyrolysis of those mixed orthoesters (**147a-b**).



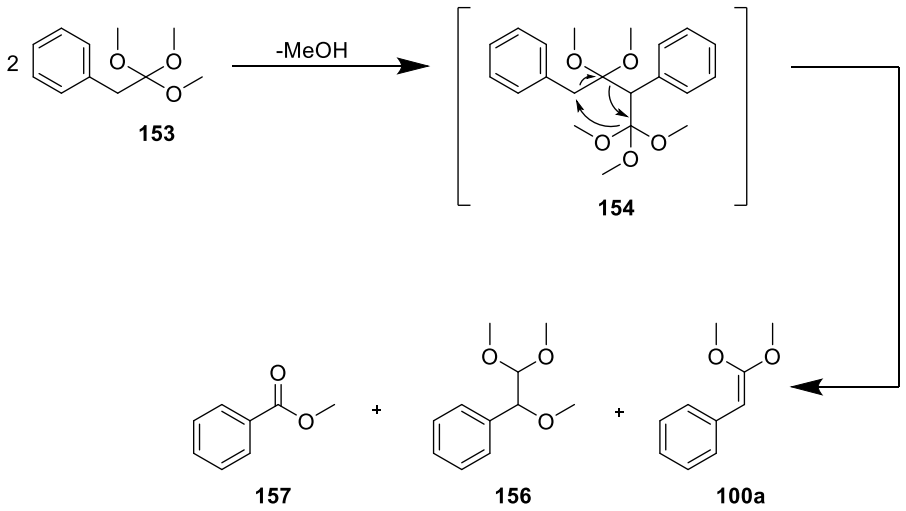
Scheme 63: Examples of the pyrolysis of a range of orthoesters *via* ketene acetals to form esters and ethers

McElvain and Stevens also investigated the pyrolysis of ethyl orthophenylacetate (**143**), in 1946.[161] They successfully produced phenylketene diethylacetal (**100b**) using the same method as Staudinger and Rathsam[163] in 70% isolated yield (Scheme 64). However, they also produced ethyl phenylacetate (**144**) in 20% yield, as well as a small amount of *meso*-diethyl α,α'-diphenylsuccinate (**152**). They suggested that ethyl phenylacetate was formed by the loss of ethylene during the pyrolysis. Specifically, the ethylene was determined to be lost from the ketene acetal since the evolution of the alcohol occurred prior to evolution of the ethylene (Scheme 64). This was further supported by the fact that on redistillation phenylketene diethylacetal (**100b**) produced a small amount of ethyl phenylacetate (**144**).



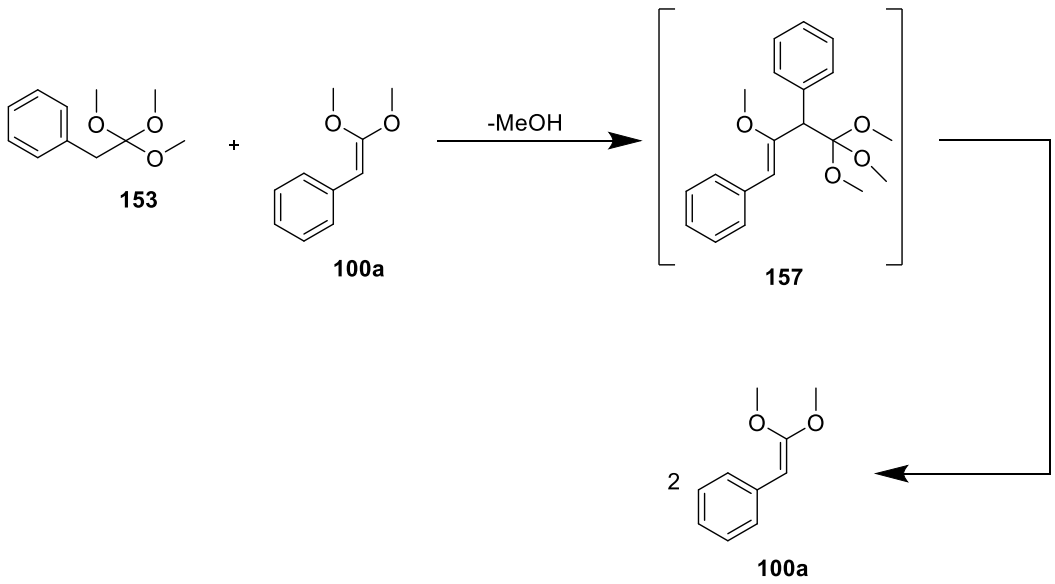
Scheme 64: The pyrolysis of ethyl orthophenylacetate (143)

McElvain and Stevens also investigated the pyrolysis of methyl orthophenylacetate (**153**). Since methyl orthophenylacetate (**153**) cannot undergo the same mechanism as ethyl orthophenylacetate, as it cannot lose ethylene, it was thought that the ester (**156**) side product would not be synthesised. However, they observed that methyl orthophenylacetate produced higher yields (33%) of the ester (**156**) and lower yields (59%) of the ketene acetal (**100a**) compared to ethyl orthophenylacetate (**143**). Further to this, they found methyl orthophenylacetate to be significantly more stable to pyrolysis, requiring temperatures of 250 – 260 °C, whilst only 40 – 50% of the expected amount of methanol was produced. They postulated that the reaction proceeded through a dimer of the orthoesters (**154**), Although they proposed a complex and unusual mechanism of the formation of the ester (**155**) from the ketene acetals, its formation could simply be attributed to the degradation of the orthoester.



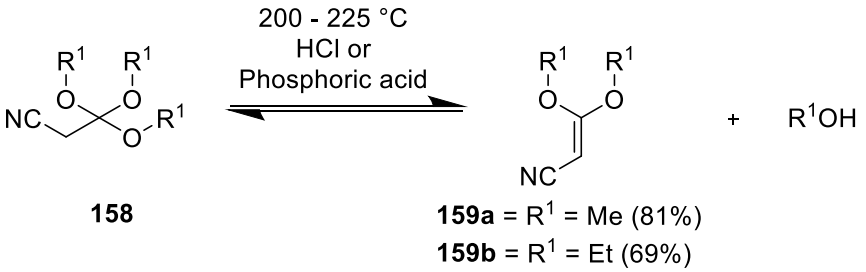
Scheme 65: Proposed mechanism of the pyrolysis of methyl orthophenylacetate

Further investigation into the orthoester dimer complex (**154**) formed from the pyrolysis of methyl orthophenylacetate led McElvain and Stevens to pyrolyse the orthoester (**153**) in the presence of the ketene acetal (**100a**). This reaction was in stark contrast to the pyrolysis of the orthoester (**153**) on its own. All the expected alcohol evolved rapidly and phenylketene dimethyl acetal was isolated in 88% yield and no methyl phenylacetate was isolated. McElvain and Stevens suggested a different intermediate (**157**) was formed (Scheme 66).



Scheme 66: Change in mechanism when orthoester is pyrolysed in the presence of the ketene acetal

In 1949, McElvain and Schroeder discovered that the pyrolysis of methyl orthocyanoacetate (**158**) to cyanoketene dimethylacetal (**159a**) (Scheme 67), was a reversible reaction catalysed by acid.[167,168] In order to push the pyrolysis to cyanoketene dimethylacetal (**159a**) the alcohol was required to be removed as it was produced. This work further supported the conclusion from Staudinger and Rathsam that an active α-hydrogen was required for the pyrolysis of orthoesters to ketene acetals to be successful.

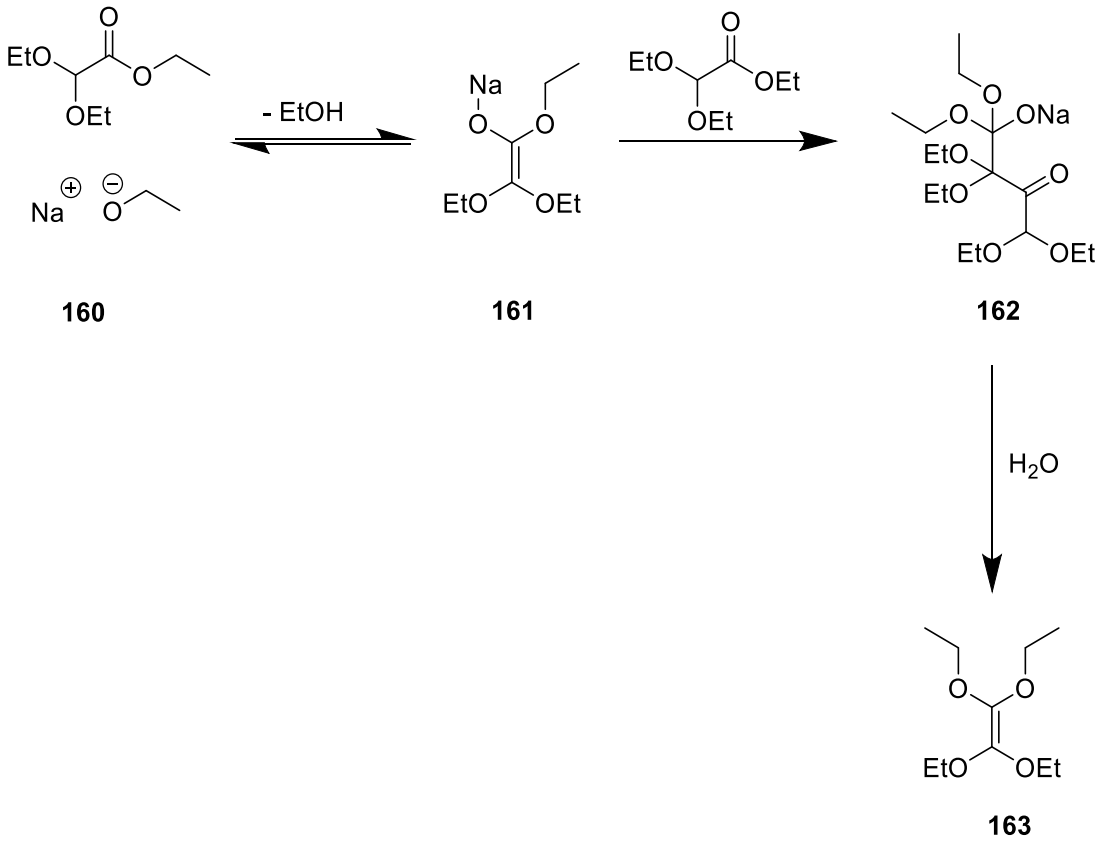


Scheme 67: Pyrolysis of methyl orthocyanoacetate

The pyrolysis of orthoesters is a good tool towards the synthesis of ketene acetals. However, the pyrolysis only works for orthoesters with an active α-hydrogen and the high temperatures required often lead to the formation of side products or the subsequent pyrolysis of the ketene acetal.

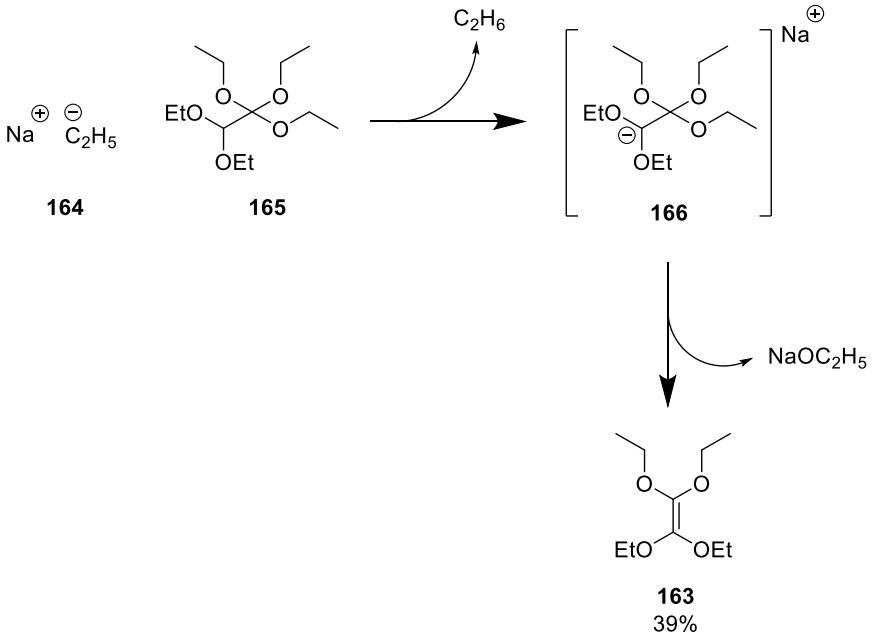
From Reaction of Strong Bases with Orthoesters

In 1926, Scheibler reported the synthesis of ketene acetals from sodium ethoxide and an ester.[169] They suggested that the reaction formed an sodium alkoxide orthoester (**162**), which underwent a hydrolysis reaction to form a ketene acetal (**163**) (Scheme 68). However, Scheiblers' work was questioned in 1927 and 1930 by Adickes.[170,171]



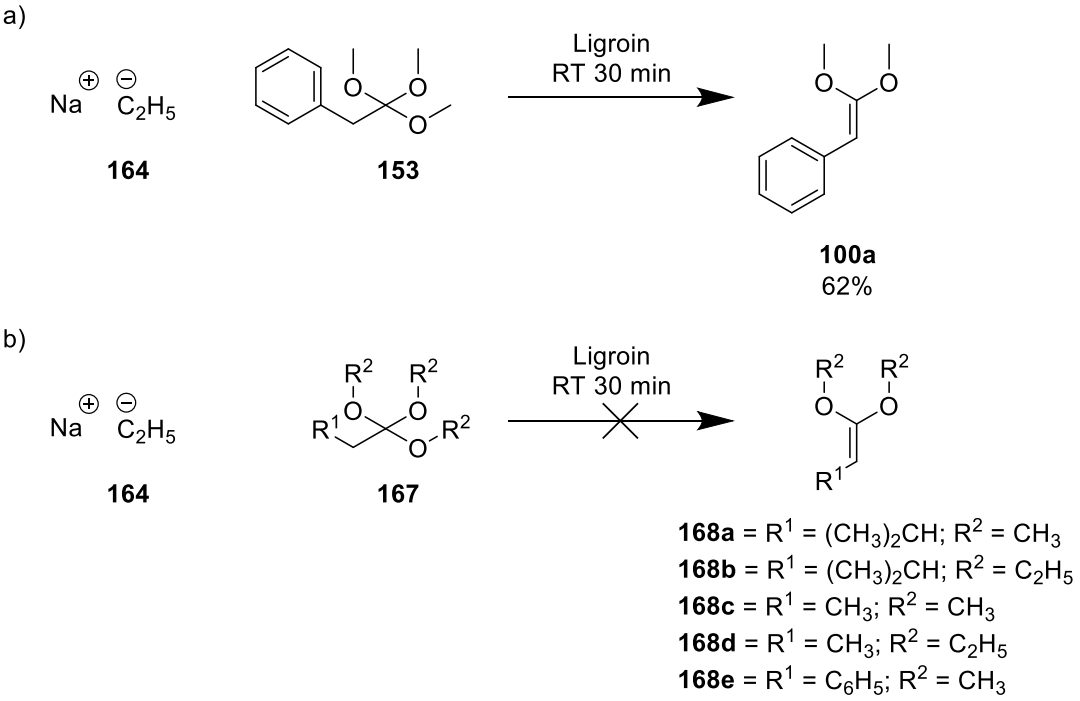
Scheme 68: The proposed synthesis route to ketene acetals using sodium ethoxide

Further attempts to synthesise ketene acetal (**163**) from the dealcoholation of orthoesters were undertaken by McElvain and Clarke in 1947.[172] Instead of forming a sodium alkoxide orthoester (**162**), they formed a triethyl orthoester (**165**) and reacted that with ethyl sodium (**164**) (Scheme 69). They assumed the reaction proceeded as a simple acid-base reaction, in which the strong base extracts a proton from the orthoester (**165**) to form ethane and a carbanion (**166**). The elimination of an ethoxy anion produced the ketene acetal (**163**) in 39% yield. However, the formation of 160% of ethane and 235% sodium ethoxide (based on the amount of orthoester used) suggested that the reaction is significantly more complex than just an acid-base reaction, although McElvain and Clarke did not elaborate.



Scheme 69: Synthesis of a ketene acetal via the reaction of an orthoesters with a strong base

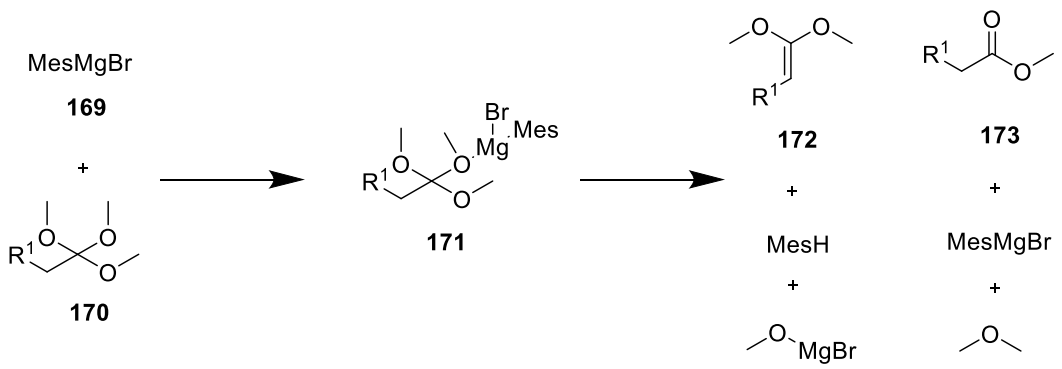
In 1950, McElvain and Venerable furthered the synthesis of ketene acetals from the reaction of orthoesters with sodium ethyl.[173] Unfortunately they found that only methyl orthophenylacetate (**153**) converted to the ketene acetal (**100a**) (Scheme 70a). Other purely aliphatic orthoesters (**167**) were not converted to the corresponding ketene acetal (**168a-e**) (Scheme 70b). McElvain and Venerable proposed that the base preferentially attacked the alkoxyl groups due to the production of excessive yields of ethane.



Scheme 70: a) Dealcoholation of methyl orthophenylacetate using ethyl sodium; b) aliphatic orthoesters do not undergo the dealcoholation using ethyl sodium

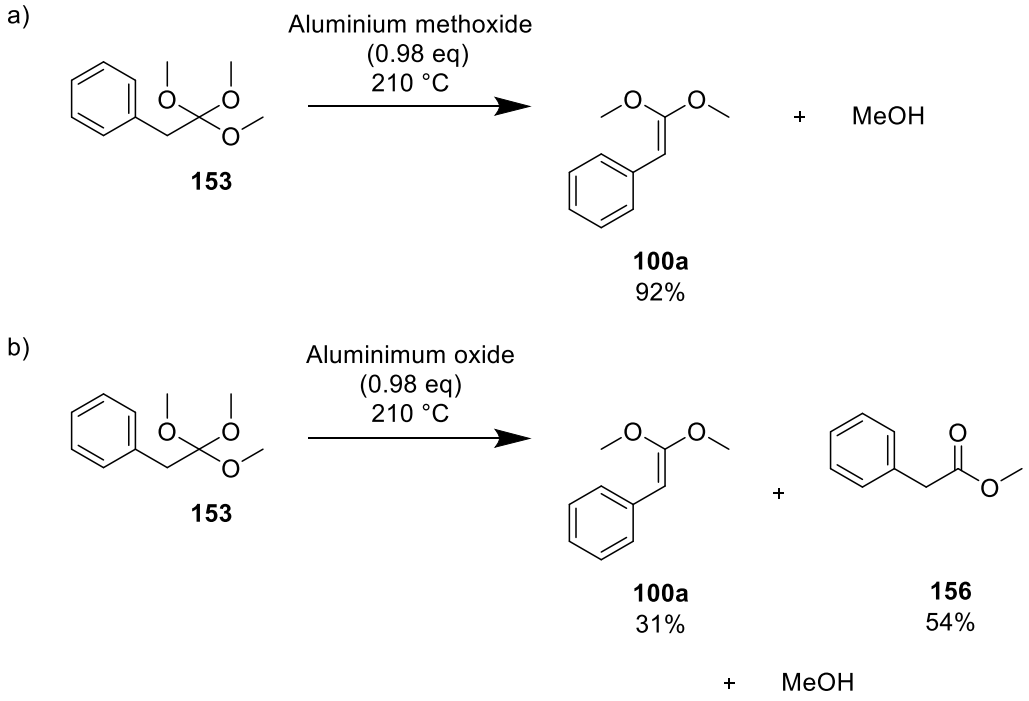
Sodium ethyl proved to be an unsuitable general reagent for the dealcoholation of orthoesters to form ketene acetals. McElvain and Venerable proceeded to investigate the suitability of a range of strong bases in the dealcoholation of methyl orthophenylacetate (**153**). The bases investigated included sodium triphenylmethyl, which resulted in no reaction, sodium naphthalene, in which the naphthalene couldn't be separated from the reaction products, and sodium allyl benzene, lithium butyl and isopropyl, *t*-butyl and mesitylmagnesium bromide which produced ketene acetal in yields of 14-56%.

Further investigation into the mechanism of the dealcoholation of orthoesters using mesitylmagnesium bromide was taken. McElvain and Venerable postulated that mesitylmagnesium bromide formed a coordination complex (**170**) with the orthoester, which could then undergo decomposition to either the ketene acetal (**172**) or the ester (**173**) (Scheme 71). They suggested that in the coordination complex (**171**) the Grignard reagent was behaving as an acid instead of a base.



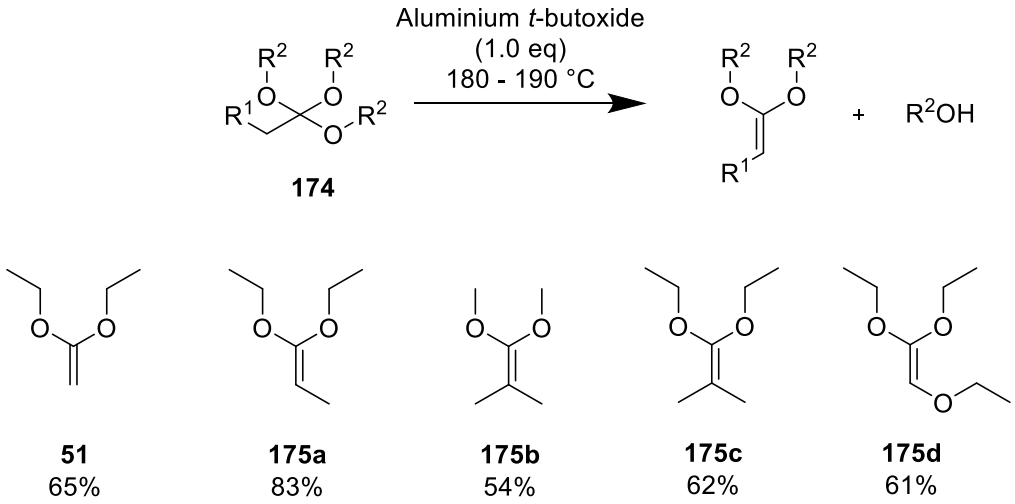
Scheme 71: Proposed mechanism of the dealcoholation of orthoesters using Grignard reagents

McElvain and Venerable suggested that aprotic acids might behave as effective dealcoholation catalaysts due to their ability to coordinate. Aluminium methoxide was utilised and when reacted with methyl orthophenylacetate (**153**) at 210 °C, the ketene acetal (**100a**) was produced in 92% isolated yield (Scheme 72a). This method was found to produce purer ketene acetals with lower temperatures compared to the pyrolysis route discussed earlier.[161] Interestingly they demonstrated that aluminium oxide was a poorer choice of catalyst for the dealcoholation; producing the ketene acetal in only 31% yield and the major product was the ester (**156**) in 54% yield (Scheme 72b). The difference in products from the aprotic acids was postulated to be due to the ability of aluminium oxide to coordinate simultaneously to two oxygens in the orthoesters, which produced a complex that eliminated dimethyl ether rather than methanol.



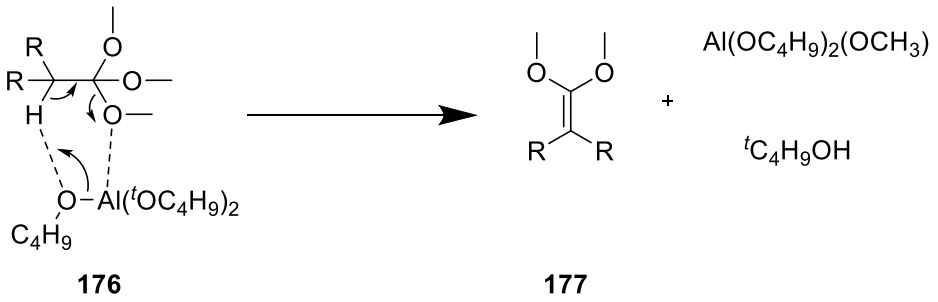
Scheme 72: a) Dealcoholation using aluminium methoxide; b) dealcoholation using aluminium oxide

McElvain and Davie furthered the dealcoholation of orthoesters in 1951 by increasing the substrate of the orthoesters.[174] They demonstrated that aluminium *t*-butoxide was an effective catalyst for the dealcoholation of a range of orthoesters, including aliphatic orthoesters, which previously were unaffected (Scheme 73). They postulated that aluminium *t*-butoxide was a more effective catalyst due to its greater ability to coordinate to the orthoesters which prevented the lower boiling (aliphatic) orthoesters from distilling away before they are dealcoholated to the ketene acetals.



Scheme 73: Dealcoholation of orthoesters using aluminium *t*-butoxide

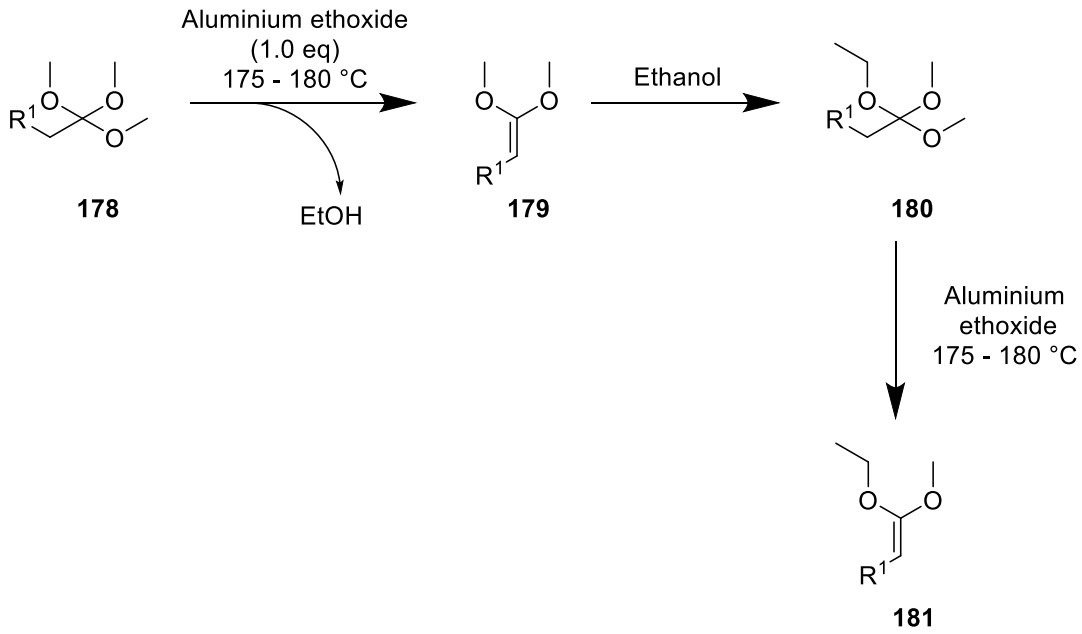
The use of aluminium *t*-butoxide allowed for further speculation of the mechanism of the dealcoholation of orthoesters. McElvain and Davie noted the formation of pure *t*-butanol from the reaction of aluminium *t*-butoxide and methyl orthoesters. They proposed the production of *t*-butanol supported the mechanism in which the alkoxide coordinates with the orthoester and then undergoes a concerted elimination (Scheme 74).



Scheme 74: Mechanism of the dealcoholation of orthoesters to form ketene acetals

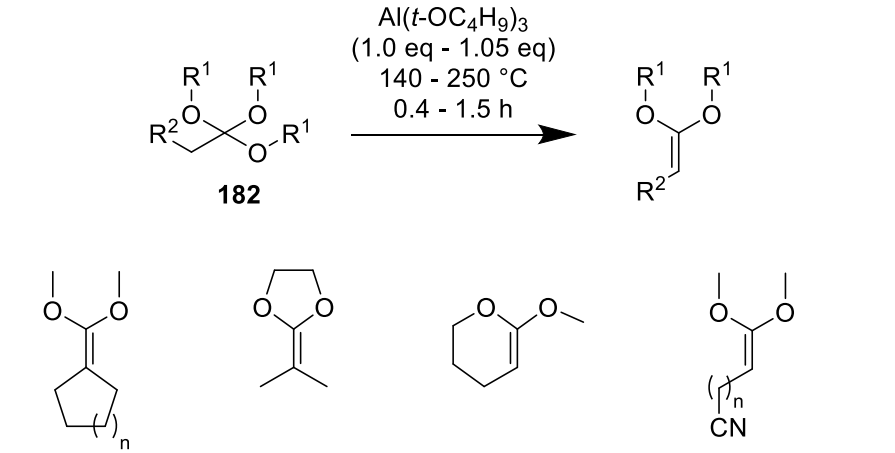
A range of other aluminium alkoxides were investigated as catalysts for the dealcoholation of orthoesters. Unfortunately, utilising both aluminium ethoxide and isopropoxide resulted in the formation of mixed ketene acetals (**181**) (Scheme 75). McElvain and Davie determined these products were formed through the addition of ethanol/isopropanol to the initially formed ketene acetal (**179**), which

produced mixed orthoesters (**179**). These orthoesters could then undergo dealcoholation to produce the mixed ketene acetals (**181**).



Scheme 75: Synthesis of mixed ketene acetals by using aluminium ethoxide as the dealcoholation reagent

McElvain *et al*. investigated the aluminium *t*-butoxide mediated dealcoholation of orthoesters with several other substrates over the years. The dealcoholation was found to tolerate cyclic ketene acetals (**183a-b,183**)[175,176], O-internal cyclic ketene acetals (**185**)[177] and cyano-substituted ketene acetals (**186a-c**) (Scheme 76)[178].

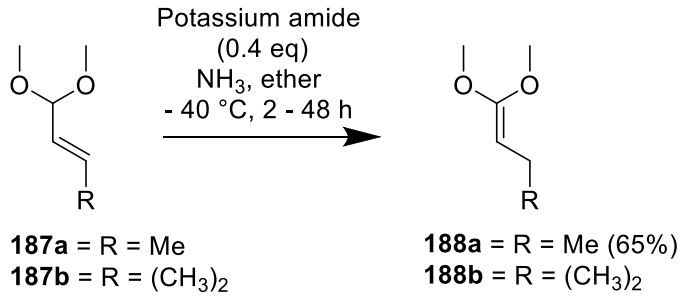


Scheme 76: Dealcoholation of orthoesters to form a range of ketene acetals; [a] aluminium methoxide used

The dealcoholation of orthoesters to form ketene acetals via the use of a strong base or aprotic acid produces ketene acetals that are higher in purity and are more tolerant to a range of substrates compared to the pyrolysis method. However, the main problem for the formation of ketene acetals from orthoesters, is that the orthoesters need to be synthesised first. Unfortunately, the synthesis of orthoesters has been known to be difficult.[109]

Allyl Acetal Migrations and Isomerisations

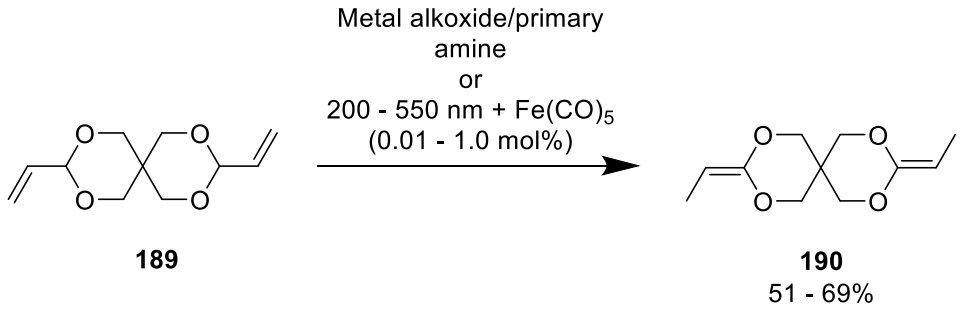
The first base catalysed rearrangement of 3,3-dialkoxyalkenes was described by Scheeren *et al*. in 1977.[179] A small range of 3,3-dialkoxyalkenes were converted into ketene acetals using potassium amide/ammonia (Scheme 77). They noted that increasing the steric bulk around the alkene of the 3,3-dialkoxyalkene resulted in much longer reaction times, for example 3,3-dimethoxyisobutene (**188b**) took 48 hours to go to conversion compared to 3,3-dimethoxypropene (**188a**) which only took 2 hours. Unfortunately, only boiling points were reported for characterisation of these compounds.



Scheme 77: Isomerisation of 3,3-dialkoxyalkenes with potassium amide/NH_3

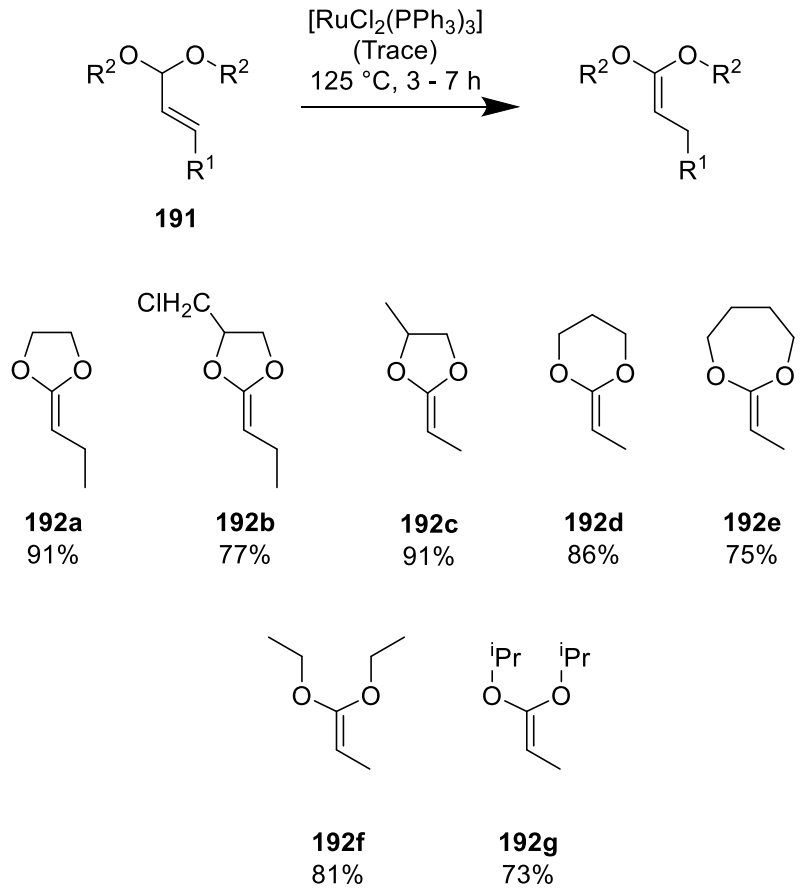
The rearrangement of diallyl acetals to produce diketene acetals has been explored, due to the fact that the diketene acetals can be utilised as monomers for a range of polymers.[180,181] In particular the rearrangement of diallylidene pentaerythritol (**189**) to diketene acetal (**190**) (Scheme 78), has been extensively studied. The rearrangement has been reported to be catalysed by metal alkoxide/primary amine solutions, such as potassium *t*-butoxide/diethylene diamine[182] and *n*-BuLi/diethylene diamine[183]. Furthermore, the

photoisomerization of diallylidene pentaerythritol (**188**) using iron pentacarbonyl as a sensitizer has also been reported.[184]



Scheme 78: The rearrangement of diallylidene pentaerythritol to diketene acetals

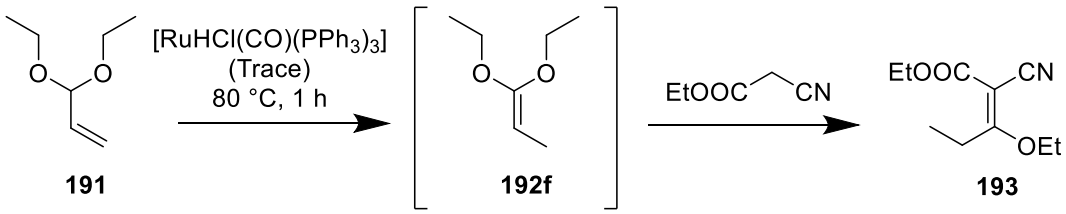
A ruthenium catalysed rearrangement of allyl acetals was reported by by Crivello *et al.* in 1996.[108] They described how a range of allyl acetals (**191**) underwent a ruthenium catalysed isomerisation to form ketene acetals (**192a-g**) (Scheme 79). Both cyclic and acylic allyl acetals were tolerated by this approach producing ketene acetals with good to excellent yields of 68 – 91%.



Scheme 79: Examples of the [Ru] isomerisation of allyl acetals to form ketene acetals

Crivello *et al*. noted that the reaction conditions of the [Ru] isomerisation had a big impact on the reaction products. They observed that undertaking the reaction at higher temperatures increased the rate of isomerisation but also increased the formation of side products which were difficult to separate from the ketene acetals. Further to this, undertaking the reaction at temperatures lower than 120 °C resulted in long reaction times which correlated to a reduced yield. This was found to be a result of polymerisation of the ketene acetal, as well as oxidative side reactions.

In 2017, Sato *et al*. described the [Ru] catalysed isomerisation of allyl acetals with a new [Ru] catalyst and reaction conditions.[185] They described the isomerisation of acrolein diethyl acetal with [$RuHCl(CO)(PPh_3)_3$] at 80 °C for 1 hour. However, the ketene acetal (**192f**) was not isolated and was immediately reacted further with ethyl cyanoacetate (**193**) (Scheme 80).

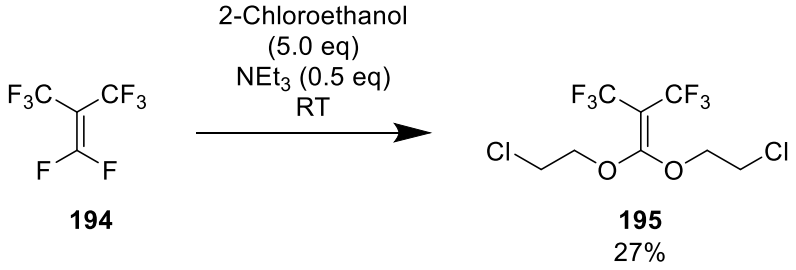


Scheme 80: [Ru] catalysed isomerisation of diethyl acrolein acetal followed by addition of ethyl cyanoacetate

The isomerisation of allyl acetals successfully produces a range of ketene acetals, under a variety of reaction conditions, including base, ruthenium and photochemistry. Unfortunately, due to the nature of the allyl acetals this method only allows for the synthesis of ketene acetals with some form of substitution on both carbons of the alkene, which makes this method not suitable as a general approach to ketene acetals.

From Vinylidene Halides

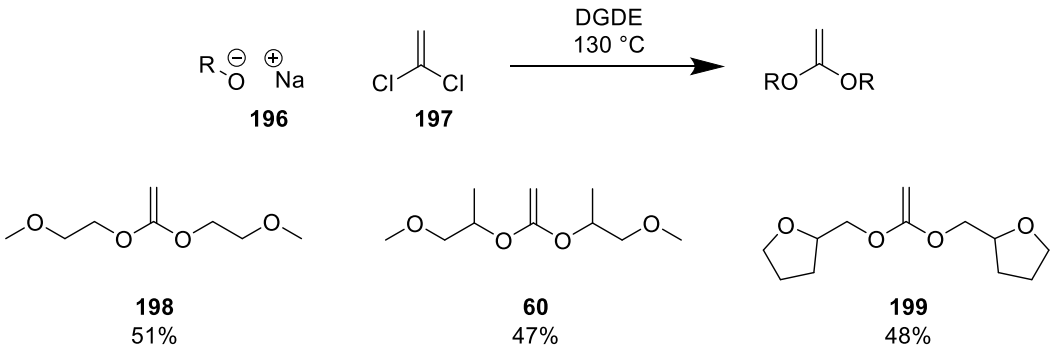
The first reported synthesis of ketene acetals from vinylidene halides was described by Hoffman *et al.* in 1957. They described the base catalysed substitution of octafluoroisobutene (**194**) to form ketene acetal (**195**) (Scheme 81).



194 **195** 27%

Scheme 81: Synthesis of ketene acetals from vinylidene fluorides

In 1964, Kuryla and Leis reported the synthesis of ketene acetals (**60, 198-199**) from the reaction of β- and γ-alkoxy alcoholates with vinylidene chloride (**197**) (Scheme 82).[102] They demonstrated that the reaction was only successful when using β- and γ-alkoxy alcoholates, other alcohols including simple aliphatic alcohols (e.g. methanol and ethanol) were unsuccessful.

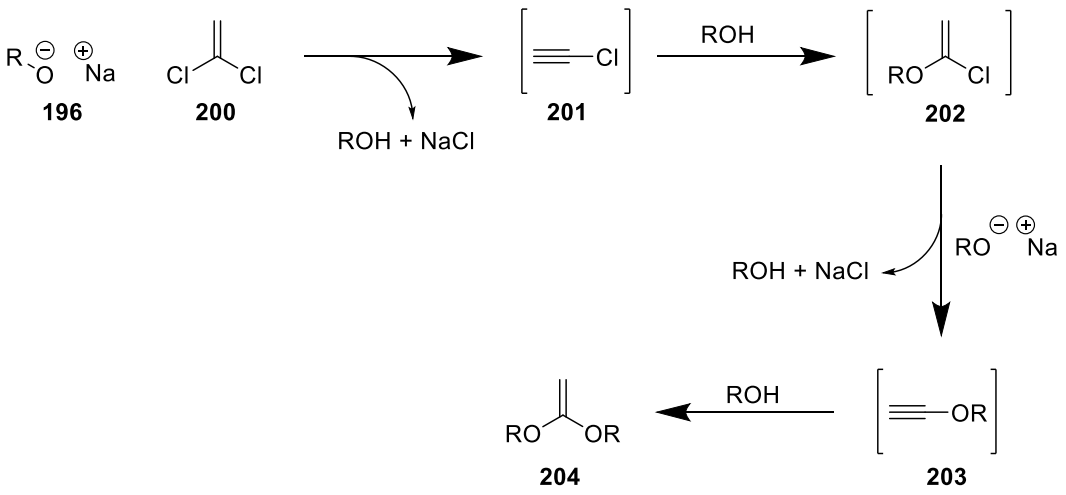


196 **197**

198 51% **60** 47% **199** 48%

Scheme 82: The formation of ketene acetals from vinylidene chloride;
[a]DGDE = diethylene glycol dimethyl ether

Kuryla and Leis proposed the mechanism of the ketene acetal synthesis from vinylidene chloride (Scheme 83). They suggested that the alkoxy alcoholate (**196**) dehydrohalogenated vinylidene chloride (**200**) to form chloroacetylene (**201**). Chloroacetylene then reacted with the alcohol to form 1-chloro-alkoxyethene (**202**), which underwent a further dehydrohalogenation to form alkoxyacetylene (**203**). The alkoxyacetylene (**203**) then reacted with another equivalent of alcohol to form the ketene acetal (**204**).



Scheme 83: The mechanism of the reaction of alkoxy alcoholates and vinylidene chloride

In 1965, Kuryla reported that other halo-olefins could also be used to synthesise ketene acetals in the same manner as vinylidene chloride (**200**).[186] *Cis*-1,2-dichloroethene (**205**), *trans*-1,2-dichloroethene (**206**), 1-bromo-2-ethoxyethene (**207**) and 1,1,2-trichloroethene (**208**) (Figure 10), could all be used to produce ketene acetals. However, the yields of the ketene acetals were noted to be inversely proportional to how easily the dichloroethane underwent the dehydrochlorination.

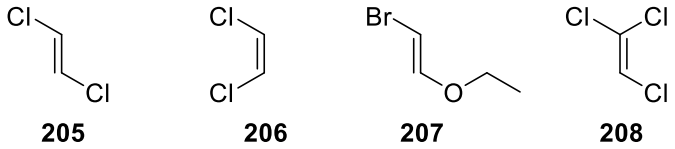
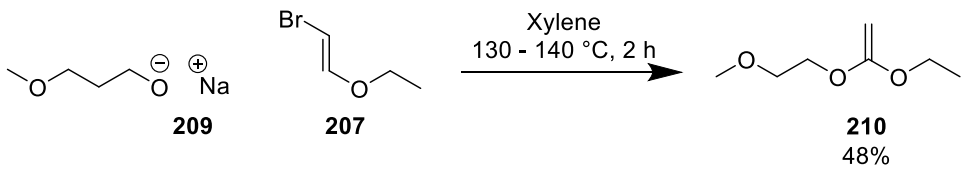


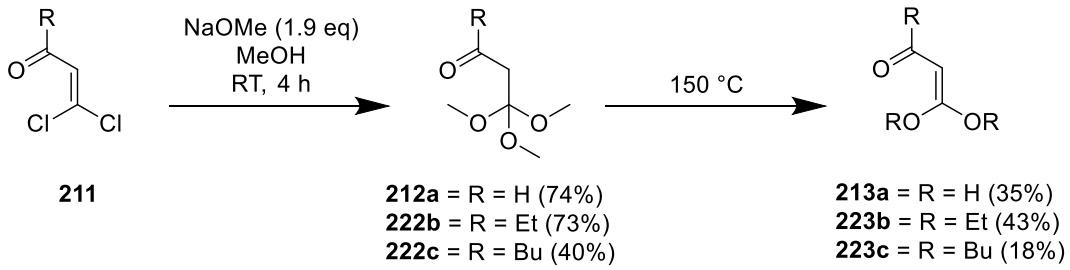
Figure 10: Examples of the halo-olefins that could be used to synthesise ketene acetals

Kuryla also reported the synthesis of a mixed ketene acetal (**210**) through the reaction of alkoxy alcoholates with 1-bromo-2-ethoxyethene (**207**) (Scheme 84).[186] However, this was the only example of its kind reported and full characterisation data was not reported



Scheme 84: The formation of a mixed ketene acetal from 1-bromo-2-ethoxyethene and an alkoxy alcoholate

Brassard and Banville utilised acyl-substituted vinylidene chlorides (**211**) to form acylketene acetals (**213a-c**).[63] The room temperature reaction of vinylidene chlorides with NaOMe/MeOH resulted in the orthoester (**212a-c**) product rather than the ketene acetal. However, they demonstrated that the ketene acetal (**213a-c**) could easily be isolated by pyrolysis of the crude orthoester (**212a-c**) at 150 °C (Scheme 85).



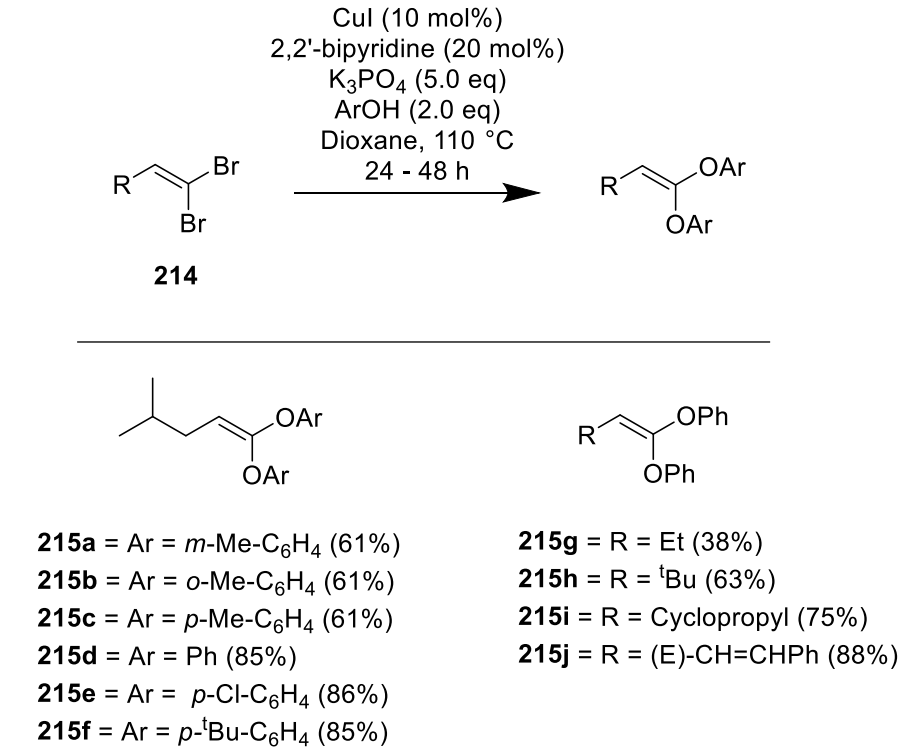
211

212a = R = H (74%)
222b = R = Et (73%)
222c = R = Bu (40%)

213a = R = H (35%)
223b = R = Et (43%)
223c = R = Bu (18%)

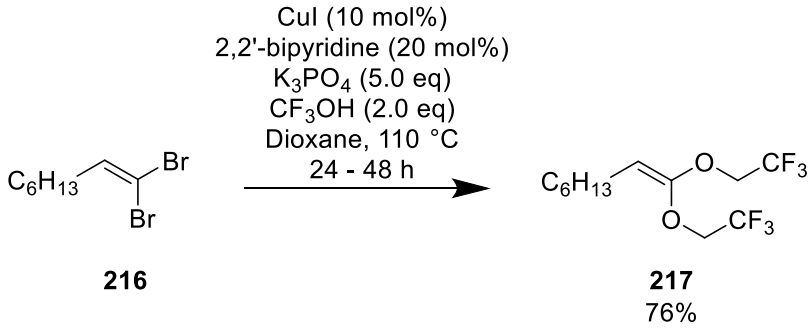
Scheme 85: The synthesis of ketene acetals from acylvinylidene chlorides

Vinylidene bromides were also used in the synthesis of ketene acetals. In 2012, Evano *et al*. developed a copper catalysed double cross coupling of phenols with readily available 1,1-dibromoalkenes to form ketene acetals.[187] The scope of the cross coupling was demonstrated with a range of phenols and 1,1-dibromoalkenes (Scheme 86). Interestingly they discussed that there was no effect of sterics or electronics on the yield of the reaction, shown by no change in yield for ketene acetals (**215a-c**) where the methyl group was moved around the phenol. However, the ketene acetals (**215a-j**) were found to be unstable to acid and water and resulted in ketene acetals that were isolated "virtually pure" (~95%, with some residual 2,2'-bipyridine).



Scheme 86: Copper catalysed double cross coupling of vinylidene bromides to form ketene acetals

Evano *et al*. described only one example of the double cross coupling with a substrate that was not a phenol derivative. Trifluoroethanol was successfully used to synthesise ketene acetal (**217**) (Scheme 87). The use of aliphatic alcohols resulted in homodimerization of the 1,1-bromoalkene.

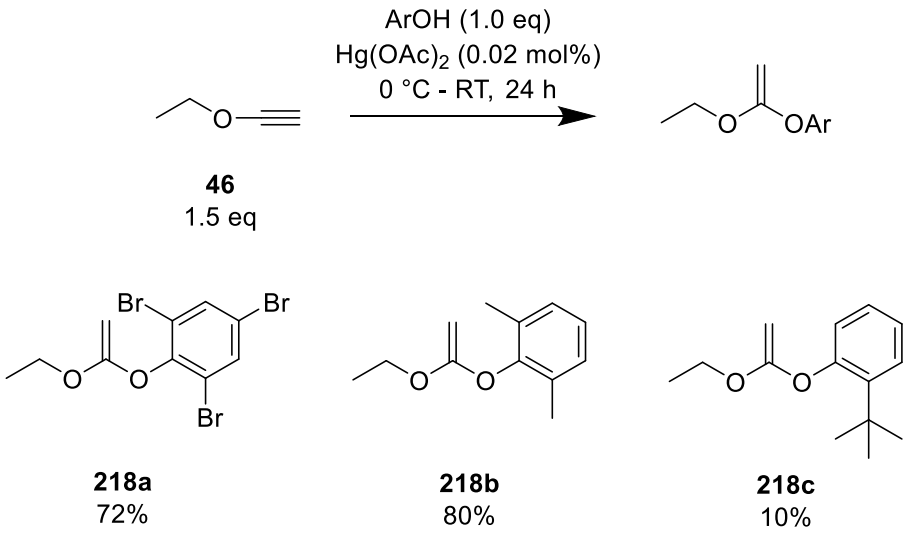


Scheme 87: Copper catalysed cross coupling using trifluoroethanol

The use of vinylidene halides towards the synthesis of ketene acetals has proven to be tolerant towards acyl, aryl, primary and secondary alkyl groups, as well as producing mixed ketene acetals. However, the yields of the ketene acetals produced from vinylidene halides are poor (<50%).

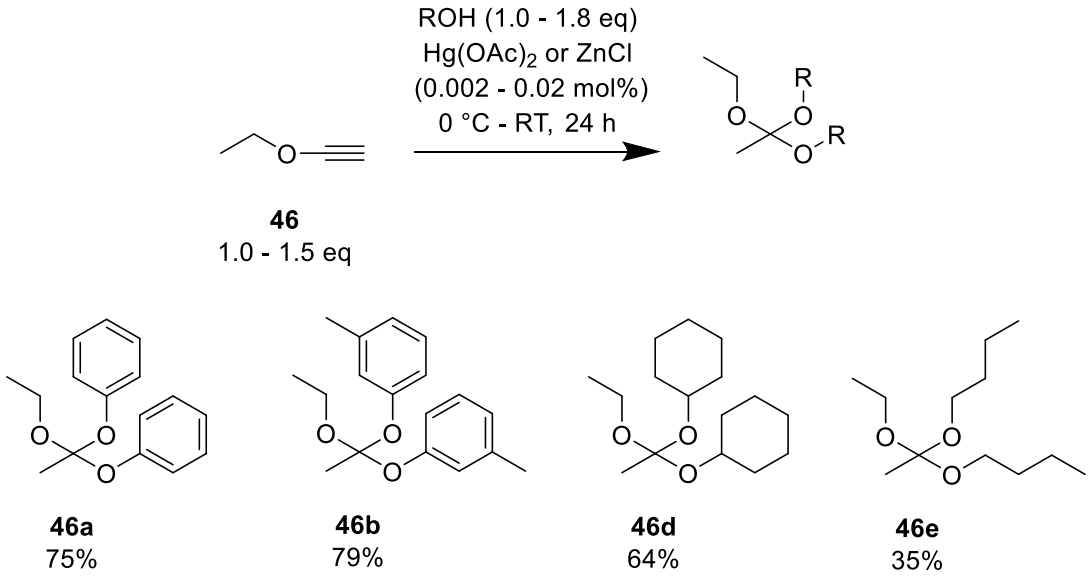
From Alkoxy Acetylenes

The formation of mixed ketene acetals from the mercury catalysed addition of phenols to alkoxy acetylenes was described by Broekema in 1975.[53] They demonstrated that sterically hindered phenols could be used to form the mixed ketene acetals (**218a-c**) (Scheme 88).



Scheme 88: The synthesis of mixed ketene acetals from the mercury catalysed addition of phenols to ethoxyacetylene

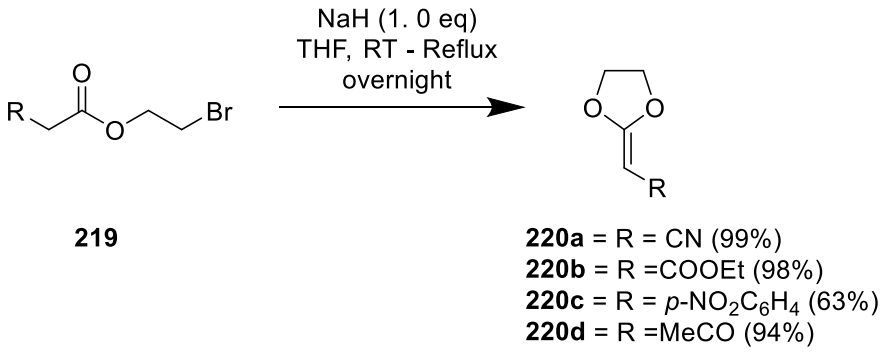
Broekema showed that if non-sterically hindered phenols or alcohols were used then a double addition to ethoxyacetylene (**46**) occurred which resulted in mixed orthoesters (**46a-e**) (Scheme 89).



Scheme 89: Examples of orthoesters synthesised from the mercury/zinc catalysed addition of alcohols to ethoxyacetylene

From Alkylation of ester-enolates

The first described alkylation of enolisable esters was described by Parker in 1956.[188] They described a base catalysed intramolecular O-alkylation of enolisable esters; sodium hydride was utilised as the base and produced ketene acetals (**220a-d**) (Scheme 90).

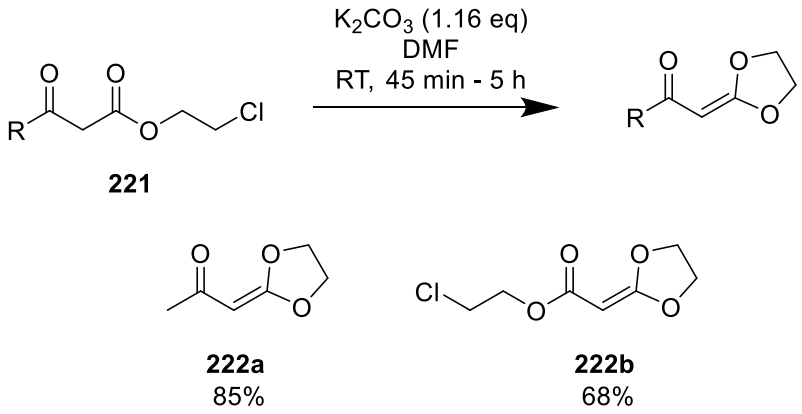


219

220a = R = CN (99%)
220b = R =COOEt (98%)
220c = R = *p*-$NO_2C_6H_4$ (63%)
220d = R =MeCO (94%)

Scheme 90: Synthesis of ketene acetals from enolisable esters

In 1985, Broadhurst described the synthesis of acylketene acetals from an intramolecular base-catalysed O-alkylation of ester-enolates.[189] Two different ester-enolates (**221**) were reacted with K_2CO_3 at room temperature which produced acylketene acetals (**222a-b**) (Scheme 91).



221

222a
85%

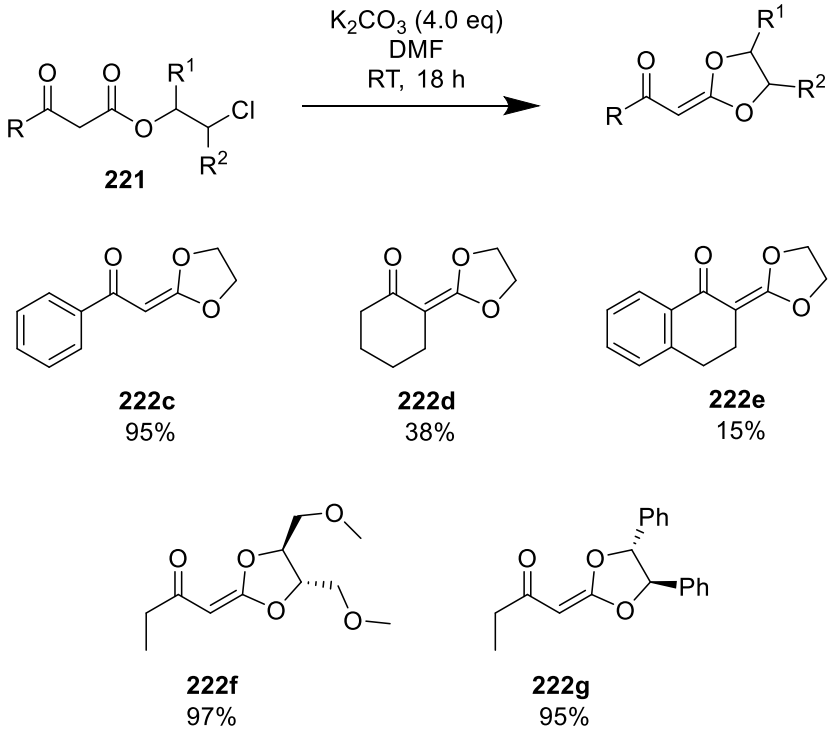
222b
68%

Scheme 91: Synthesis of acylketene acetals from base catalysed alkylations of ester-enolates

The exclusive O-alkylation of the ester-enolates, compared to C-alkylation was surprising. Broadhurst postulated that the constraints of the intramolecularity could increase the sterics of the transition state and increase O-alkylation.[190] Furthermore, they suggested that participation of the neighbouring carbonyl could

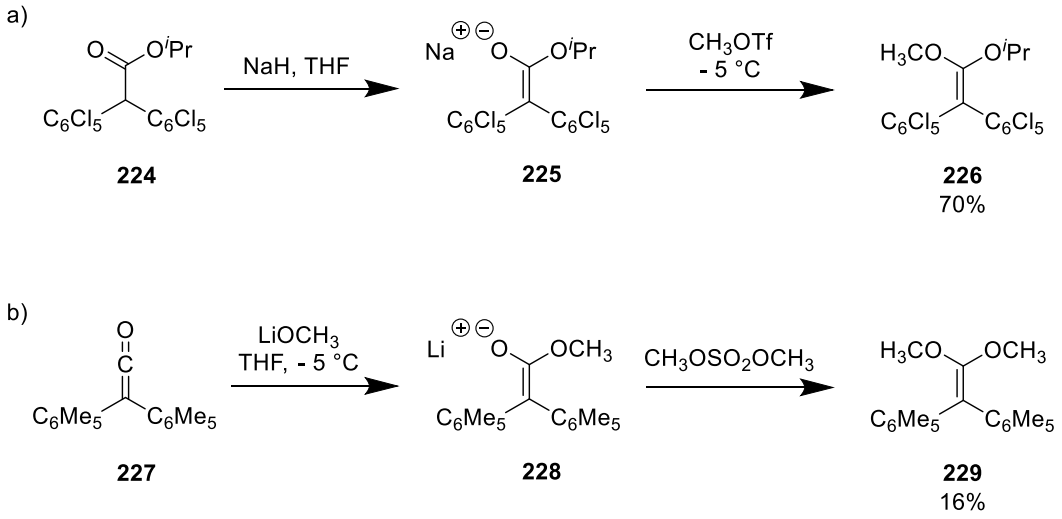
increase the stability of the proposed transition state, and also directed towards O-alkylation.

Eid and Konopelski, in 1991, furthered the acylketene acetal synthesis by Broadhurst, by increasing the substrate scope by incorporating aromatic and non-aromatic rings (Scheme 92).[191] Further to this, they also synthesised enantiomerically pure ketene acetals (**229**), which could be used towards the synthesis of natural products (rice and maize weevil aggregation pheromone "sitophilure").



Scheme 92: Synthesis of acylketene acetals from ester-enolates

In 1987, Hegarty *et al*. also reported the exclusive O-alkylation of ester-enolates.[192] They described the alkylation of sterically hindered enolates of diarylcarboxylic acids (**224**) and ketenes (**227**), which produced ketene acetals (**226, 229**) (Scheme 93). These acids (**225, 228**) were defined as the most hindered diarylacetic acids due to the "buttressing effect of the *meta*-substituents".



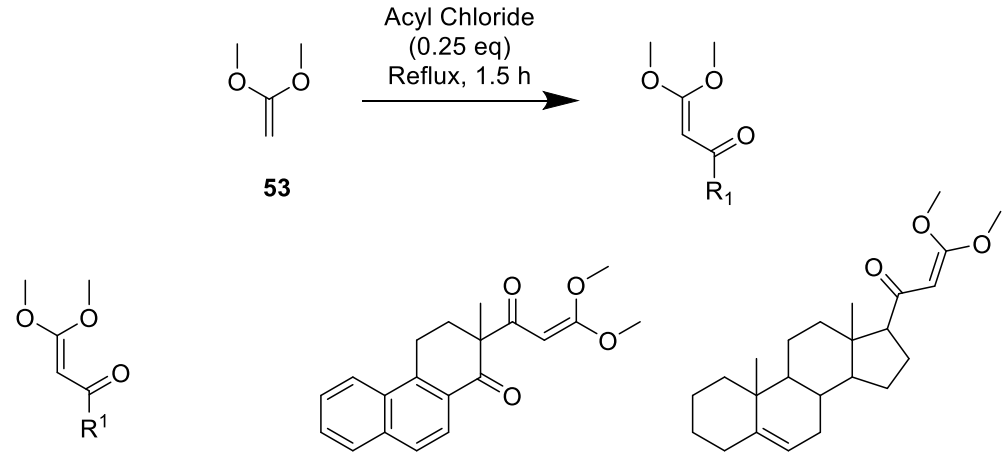
Scheme 93: Synthesis of ketene acetals from sterically hindered ester-enolates and ketenes

Hegarty demonstrated that these highly sterically hindered ketene acetals (**226, 229**) had greater acid resistance compared to previously reported ketene acetals.[164] In fact (**226**) could not be hydrolysed even when subjected to 6.23 M TFA in methanol for 24 hours at room temperature. They postulated that the bulky aryl groups resulted in resistance to proton transfer above and below the plane of the ketene acetal double bond.

The use of ester-enolates in the synthesis of ketene acetals allows for the formation of significantly more complex ketene acetals. This makes them more useful in synthetic chemistry when looking to use ketene acetals in the synthesis of natural products, especially with the simple reaction conditions employed. Furthermore, this approach produces ketene acetals with improved properties such as acid resistance, which has not been observed before in the literature. However, the highly substituted nature means that this route is not ideal for a general approach towards ketene acetals.

From Reaction of Ketene Acetals with Chlorides

Acyl ketene acetals can be synthesised by the addition of acyl chlorides to ketene acetals, demonstrated by McElvain and McKay in 1956.[193] A wide variety of aryl and aliphatic acyl chlorides were added to ketene dimethylacetal (**53**) to yield acyl ketene dimethylacetals (**230a-i**) (Scheme 94). The reaction initially used triethylamine but McElvain and McKay noted a series of side reactions on use and the yield was limited to 50 - 55%. The use of a 4-fold excess of the ketene acetal allowed for the formation of the acyl ketene acetal in high yields, making it an ideal method for expensive acyl chlorides (**230h-i**).



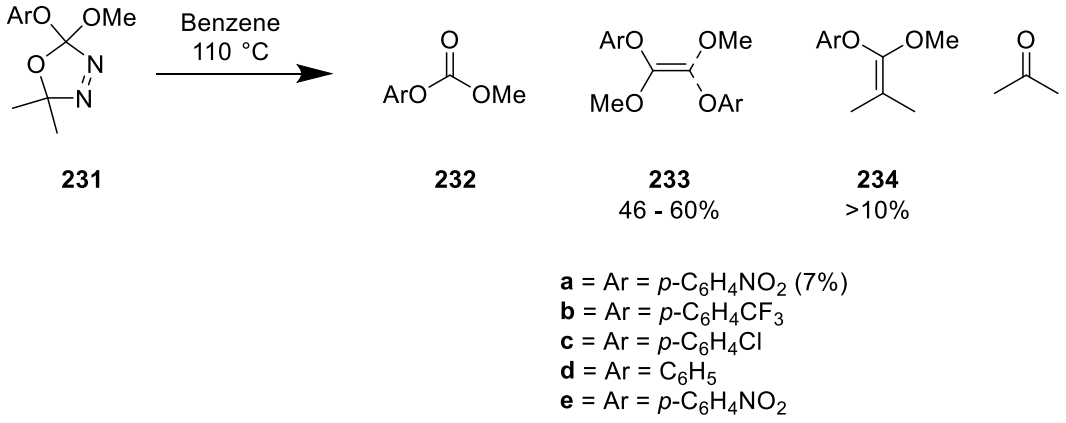
230a = R^1 = Ph (84%)
230b = R^1 = *p*-CH_3OPh (81%)
230c = R^1 = *p*-NO_2Ph (88%)
230d = R^1 = *o*-NO_2Ph (90%)
230d = R^1 = $(CH_3)_3C$ (75%)
230e = R^1 = Cl_3C (81%)
230f = R^1 = $(Ph)_2CH$ (67%)
230g = R^1 = $CH_3(CH_2)_{10}$ (67%)

Scheme 94: Synthesis of acyl ketene acetals from ketene dimethylacetal

From Thermolysis of Aryloxy Methoxy Oxadiazolines

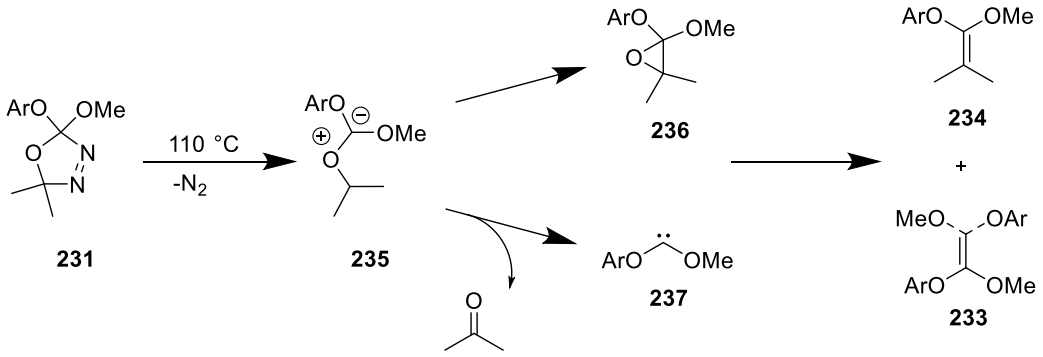
Mixed ketene acetals were reported as the minor product of the thermolysis of aryloxy methoxy oxadiazolines, by Warkentin *et al*.[194] The thermolysis of aryloxy methoxy oxadiazolines (Scheme 95), resulted in the formation of carbonates (**232**), dimers of an aryloxylcarbene intermediate (**233**) and ketene acetals (**234**). Unfortunately, the ketene acetals were the minor product and made up less than 10% of the product. Further to this only ketene acetal (**234a**) could be isolated

through chromatography; the other ketene acetals (**234b-e**) underwent hydrolysis too readily.



Scheme 95: Thermolysis of oxadiazolines to form carbonates, dimers and ketene acetals

Warkentin *et al*. postulated the formation of the ketene acetal (**234**) was through an oxirane (**236**) (Scheme 96). They "tentatively assigned" the oxirane (**236**) by GC-MS. They proposed the mechanism wherein a carbonyl ylide (**235**) is formed. This ylide (**235**) underwent fragmentation to release acetone and a carbene (**247**), which can dimerise (**233**). These carbenes (**237**) can then deoxygenate the oxirane (**236**), which is formed from the electrocyclic ring closure of the ylide (**235**).

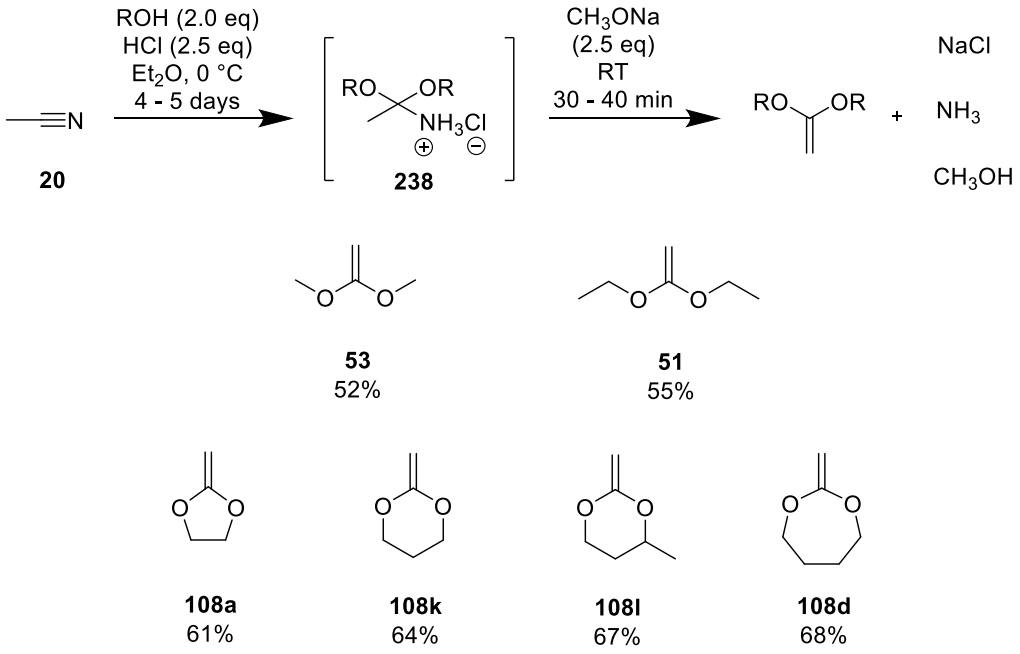


Scheme 96: The mechanism of the synthesis of ketene acetals from the thermolysis of aryloxy methoxy oxadiazolines

From the Pinner Approach

Argade modified the Pinner reaction by reducing the equivalents of alcohol used to stop the reaction at the salt intermediate (**238**).[195] They then showed that the salt intermediate (**238**) underwent a deamination, in the presence of base, to form ketene acetals (Scheme 97). Both aliphatic ketene acetals (**51, 58**) and cyclic

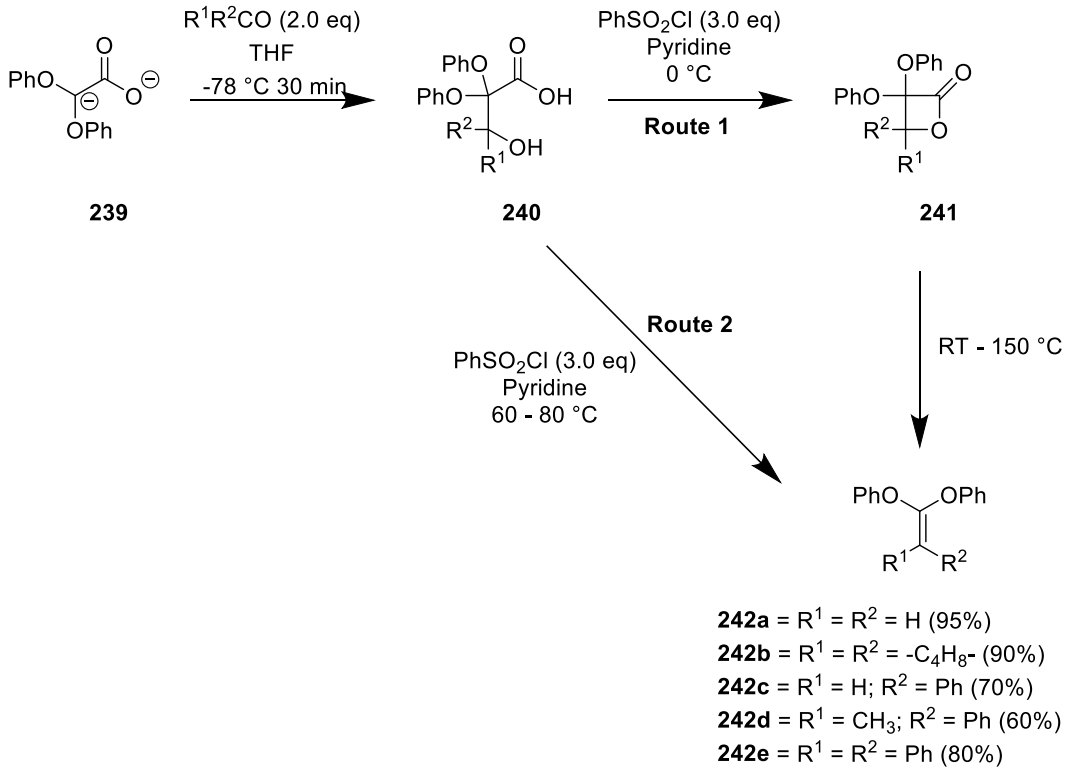
ketene acetals (**106a,d,k,l**) were successfully synthesised in moderate yields of 52 – 68% (Scheme 97). However, the reaction suffers from long reaction times, specifically the formation of the salt intermediate (**238**) can take 4 – 5 days.



Scheme 97: Formation of aliphatic and cyclic ketene acetals through the Pinner approach

From β-Lactones

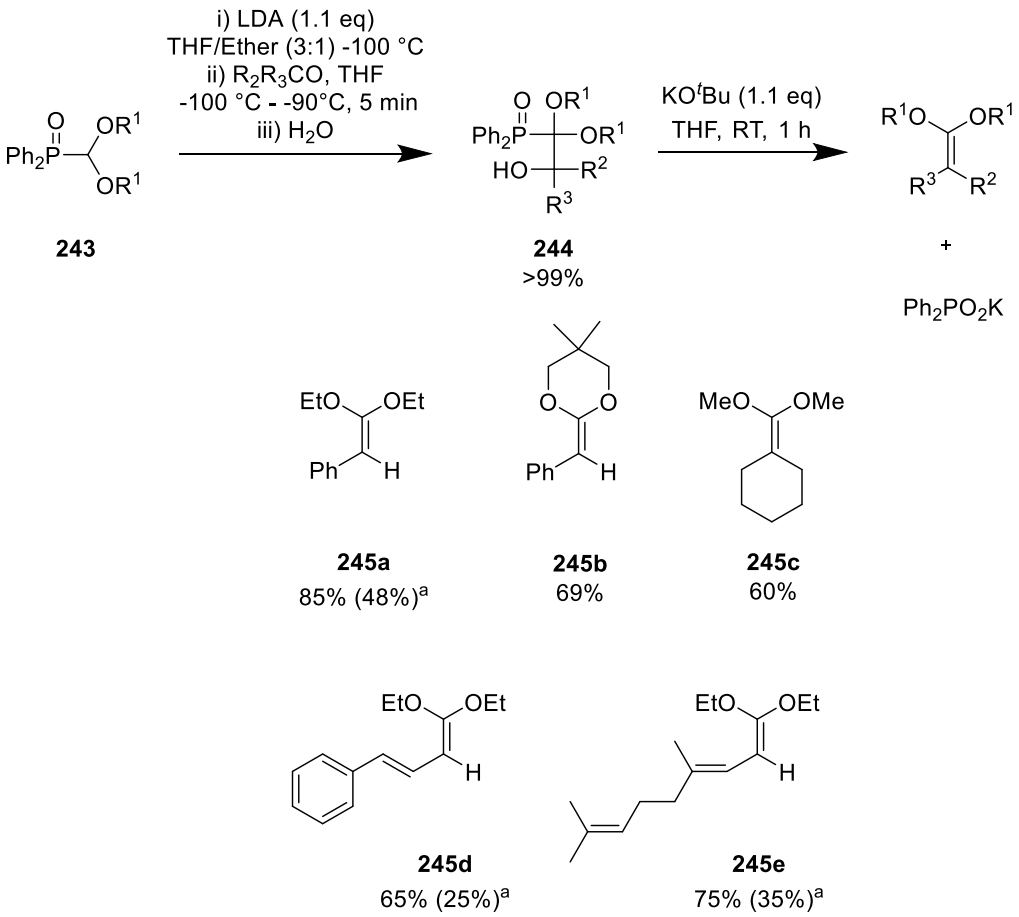
In 1979, Adam and Fich described the synthesis of diphenyl ketene acetals (**242a-e**) from the decarboxylation of β-lactones (**241**), as shown by route 1 in Scheme 98.[196] They noted that the ease of the decarboxylation of the β-lactones was substituent dependent, for example **(242c-e)** underwent decarboxylation at room temperature, whilst (**242a-b**) required temperatures around 150 °C. Further to this, Adam and Fich also described how the ketene acetals could also be synthesised from the precursor of the β-lactone; β-hydroxy acid (**240**) (route 2 of Scheme 98). Utilising elevated temperatures with the pyridine-benzenesulfonyl chloride and β-hydroxy acid resulted in the ketene acetals (**242a-e**). However, this route was only described in a generic manner suggesting yields of 30-40% without citing yields of specific substrates.



Scheme 98: Synthesis of ketene acetals *via* β-lactones (route 1) and β-hydroxy acids (route 2); yields shown are for route 1 only

From a Horner-Wittig approach

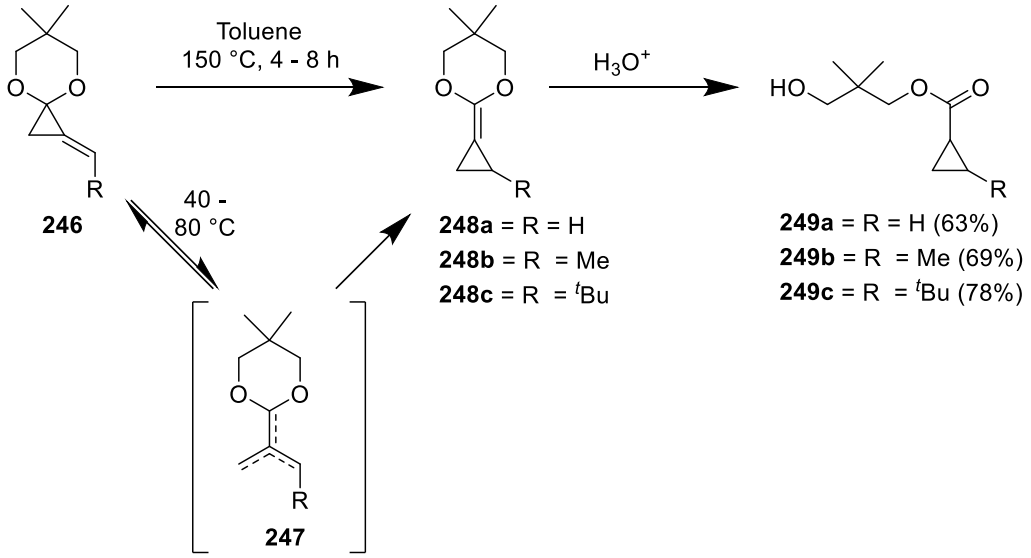
The Horner-Wittig reaction has been reported to be used to form ketene acetals.[197] In 1983, Gen *et al*. described the Horner-Wittig reaction of dialkoxymethyl diphenyl phosphine oxides (**243**) with a variety of aldehydes and ketones to produce ketene acetals (**245a-e**) (Scheme 99). They demonstrated that saturated, unsaturated and aromatic ketones and aldehydes could be tolerated. This method also allowed for the ketene alkoxy groups (R_1) to be modified, to produce both acylic (**245a, d, e**) and cyclic ketene acetals (**245b-c**). Although the ketene acetals were produced "synthetically pure for synthetic purposes", further purification, by distillation, to produce analytically pure ketene acetals was undertaken. Unfortunately, the ketene acetals were found to be thermally unstable, which resulted in significantly lower yields. For example, (**245a**) before purification had an isolated yield of 85%, after distillation the isolated yield was 48%.



Scheme 99: Examples of ketene acetals formed from ketene acetals from phosphine oxides; [a] isolated yields

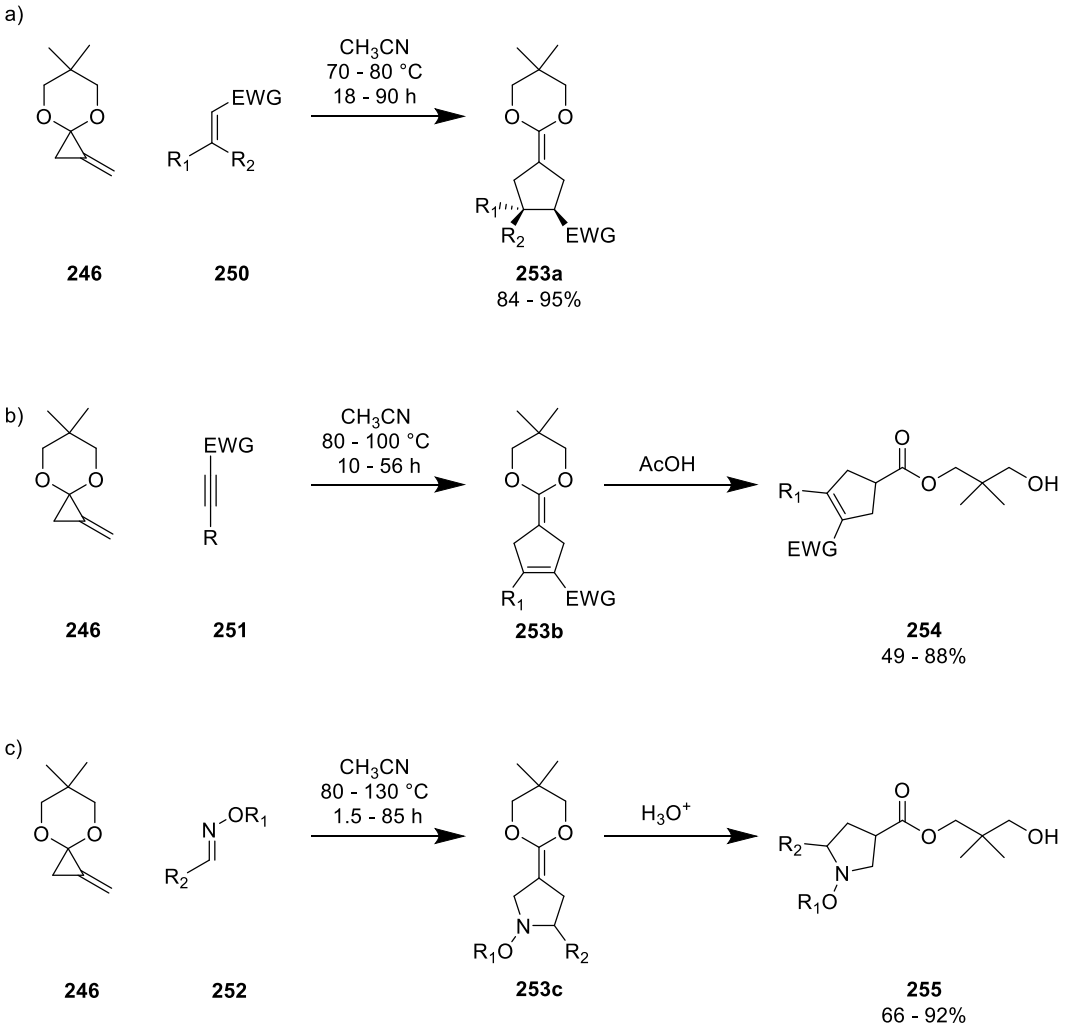
From Methylenecyclopropane

Nakamura *et al*. demonstrated that the thermolysis of methylenecyclopropane (**246**) produced ketene acetals (**248a-c**) (Scheme 100).[198] Unfortunately, the ketene acetals were not isolated due to their hydrolytic instability and instead were fully hydrolysed to esters (**249a-c**) to prove characterisation. They postulated that undertaking the reaction at 150 °C caused an alternative ring closure and was irreversible compared to when undertaking the reaction at 40 – 80 °C and the reaction was irreversible (Scheme 100).



Scheme 100: The synthesis of ketene acetals from the thermolysis of methylenecyclopropane

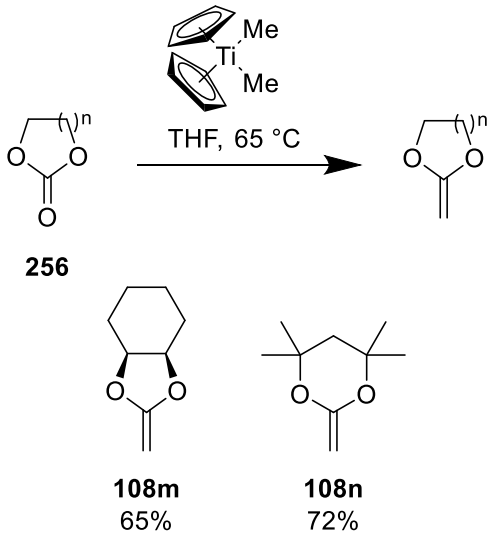
Nakamura *et al*. also demonstrated the formation of ketene acetals from cycloaddition reactions of methylenencyclopropane (**246**) with olefins[199] (Scheme 101a), alkynes[200] (Scheme 101b) and imines[201] (Scheme 101c). The ketene acetals (**253a-c**) produced were highly functionalised, with a range of electron deficient functionalities including esters, nitriles and ketones on the cyclopentane ring. Due to the hydrolytic instability of the ketene acetals they were often hydrolysed to esters (**254-255**) to allow for further characterisation.



Scheme 101: a) Cycloaddition of olefins; b) Cyloadditon of alkynes; c) Cycloaddition of oxime

From the Petasis Reaction

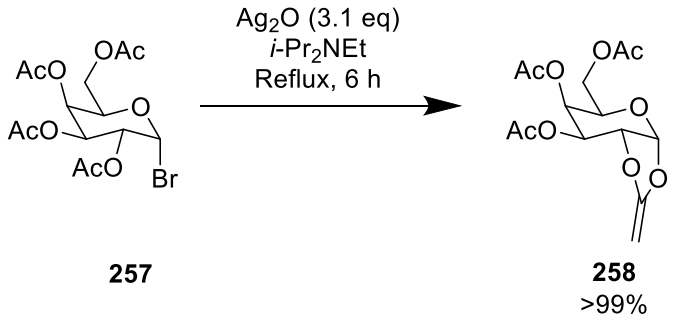
In 1995, Petasis *et al.* described an enhanced version of the Tebbe reaction[202], in which dimethyl titanocene behaves as an effective methylenation agent.[203] They highlighted that cyclic carbonates (**256**) could undergo methylation to form cyclic ketene acetals (**108m-n**) (Scheme 102).



Scheme 102: Petasis reaction to form ketene acetals from carbonates

From Silver catalysed reactions with Halogeno Sugars

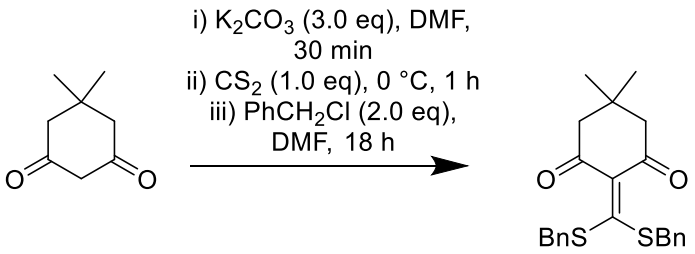
In 1995, Hecht *et al*. discovered a silver oxide catalysed O-alkylation of halogeno sugars (**257**), which produced cyclic ketene acetals (**258**) (Scheme 103).[106] This method was found to be highly effective, producing ketene acetal (**258**) in quantitative yields.



Scheme 103: Silver catalysed O-alkylation to form cyclic ketene acetals

From S,S-Ketene Acetals

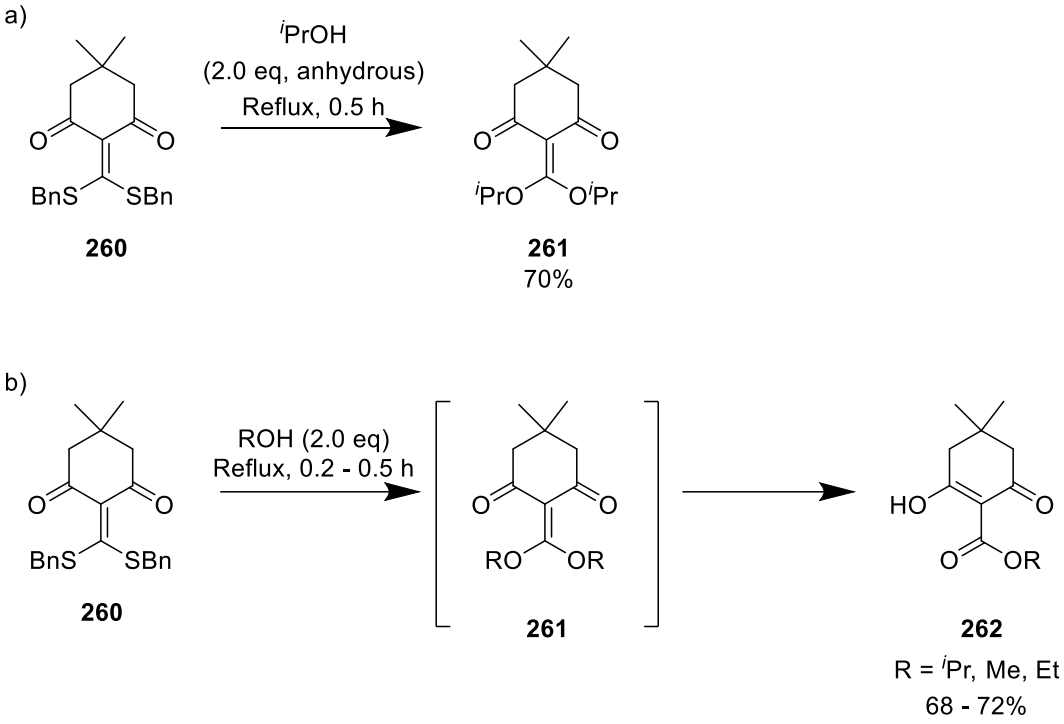
Substitution reactions of S,S-ketene acetals have also been shown to produce O,O-ketene acetals. These S,S-ketene acetals (**260**) were formed by the reaction of ketones with carbon disulfide and benzyl chloride in the presence of potassium carbonate (Scheme 104).[204]



259 **260**
90%

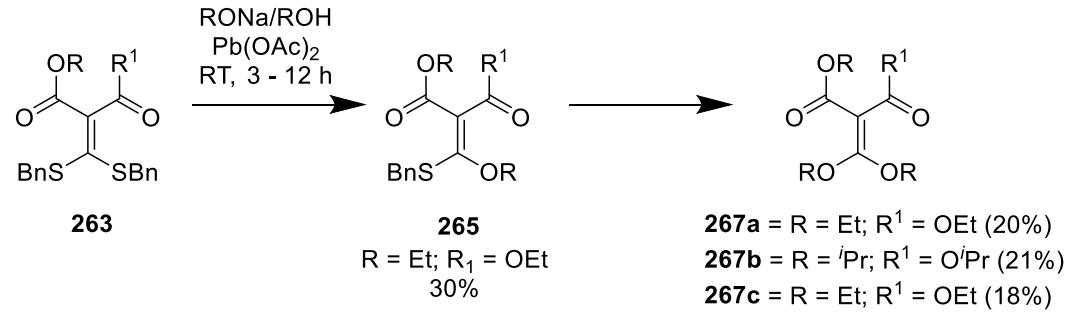
Scheme 104: Synthesis of S,S-ketene acetals

The substitution of alkylthio groups, of α,α'-dioxo ketene dibenzylthioacetals (**260**), by alkoxy groups to form O,O-ketene acetals has been reported by Liu *et al*.[205] The substitution was originally performed on cyclic α,α'-dioxo ketene dibenzylthioacetals (**260**) in the presence of refluxing alcohol to form O,O-ketene acetals (**261**). Unfortunately, the O,O-ketene acetal was only isolated when absolutely anhydrous isopropanol was utilised (Scheme 105a); other alcohols and any presence of water resulted in the formation of the corresponding ester (**262**) (Scheme 105b). They postulated that the slight steric hindrance of the isopropanol group increased the ketene acetals' (**261**) stability compared to other alcohol derivatives, such as methanol and ethanol.



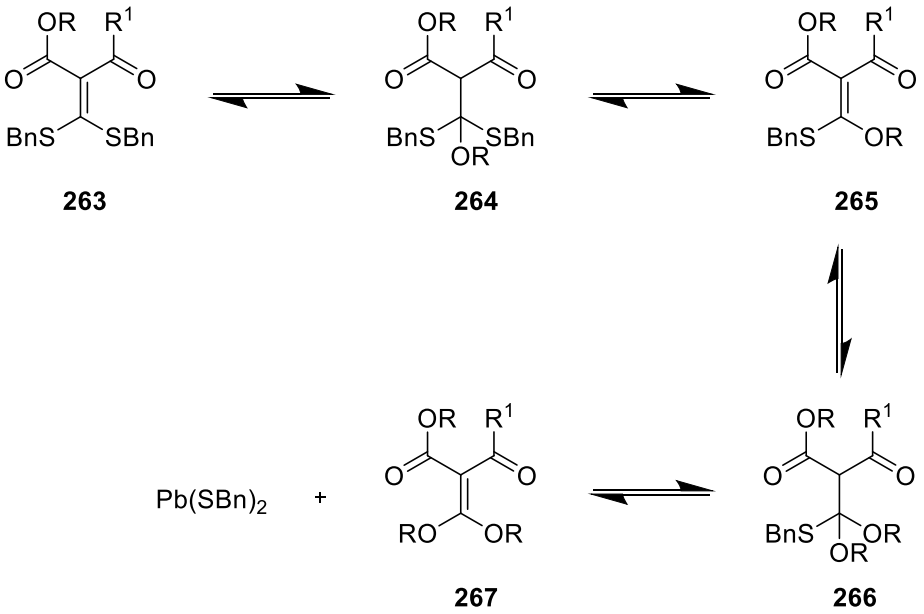
Scheme 105: a) Synthesis of O,O-ketene acetal using anhydrous isopropanol; b) formation of esters using non-anhydrous alcohols

Acyclic derivatives of α,α'-dioxo ketene dibenzylthioacetals were also subjected to substitution reactions with alcohols. Unfortunately, they found that the acylic derivatives were not sensitive to refluxing alcohols and instead the substitution was only successful when utilising sodium alkoxide nucleophiles catalysed by $Pb(OAc)_2$. A range of O,O-ketene acetals (**267a-c**) were synthesised in poor yields (18-21%) (Scheme 106). S,O-ketene acetals (**265**) could also be isolated by reducing the length of time of the reaction.



Scheme 106: Substitution of α,α'-dioxo ketene dibenzylthioacetals with sodium alkoxides to form O,S and O,O-ketene acetals

Lui *et al*. proposed that the substitution of α,α'-dioxo ketene dibenzylthioacetals was a result of addition reactions followed by subsequent eliminations (Scheme 107). The formation of the O,O-ketene acetals was driven by the weakened S-C sp^2 *p*-π conjugation, the strong electron withdrawing nature of the α-carbonyls, the formation of more stable ester products, through hydrogen-bonding, and the formation of complexes between benzylthio and $Pb(OAc)_2$.



Scheme 107: Mechanism for the substitution of S,S-ketene acetals to O,O-ketene acetals

Over the years there has been a great interest in the synthesis of O,O-ketene acetals, and this has been matched with numerous different methods of their preparation. McElvain and co-workers were at the forefront of the investigation into O,O-ketene acetals, making a significant contribution to the area with 37 papers published and the development of three different methods of their synthesis.

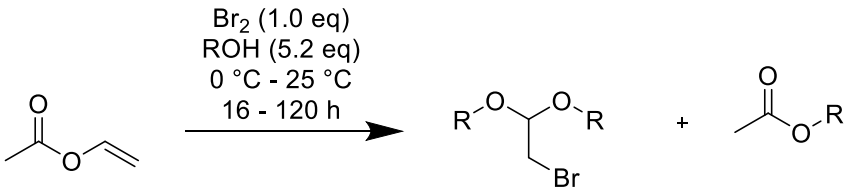
The synthetic routes to ketene acetals described in this review all have their advantages and disadvantages dependent on the target ketene acetal desired. The dehydrohalogenation method proved to be the most general method to the formation of ketene acetals, allowing for a wide variety of functionalities to be incorporated, compared to other methods which were often substrate specific. However, a significant number of the studies into the dehydrohalogenation of haloacetals were completed in the 1930s-1950s; a time where the characterisation

of compounds was more difficult. Additionally, the more recent studies often neglected to include yields or characterisation data and often highlighted a dependence on phase transfer catalysis to produce the ketene acetals in good yields and reaction times.

This chapter will now highlight how modifications to the literature methods of the dehydrohalogenation of haloacetals allowed for a wide variety of ketene acetals to be synthesised. The use of these ketene acetals in the synthesis of orthoesters will then be discussed.

3.2.2.2. Results and Discussion - Synthesis of Haloacetals

Three synthetic routes towards haloacetals were envisaged. The first route involved the bromination of vinyl acetate (**268**) in the presence of an excess of the desired alcohol substrate to form symmetric bromoacetals (**269a-g**).[206,207] This method was found to tolerate a small range of aliphatic primary and secondary alcohols (Scheme 108). Unfortunately, utilising secondary alcohols (**269d**) resulted in a significant drop in the yield (8%) even after the reaction was held at room temperature for 5 days. Nevertheless, for primary aliphatic alcohols this method proved to be scalable, with the bromoacetals (**269a-c,e-g**) synthesised on scales of 50 – 100 g, with little impact on the purity or yield.

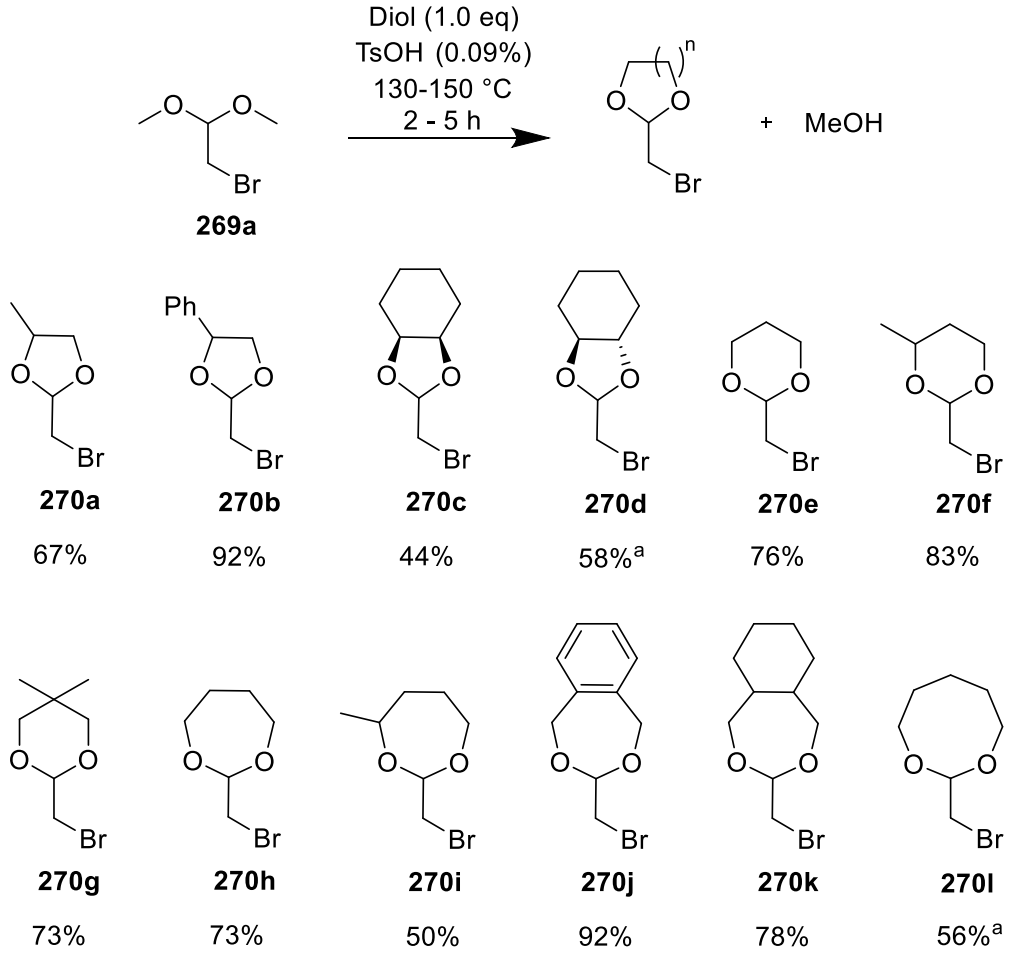


268

269a = R = Me (73%)
269b = R = Et (70%)
269c = R = Bu (71%)
269d = R = ^{i}Pr (8%)
269e = R = *n*-hexyl (79%)
269f = R = 2-ethylhexyl (71%)
269g = R = *n*-decyl (52%)

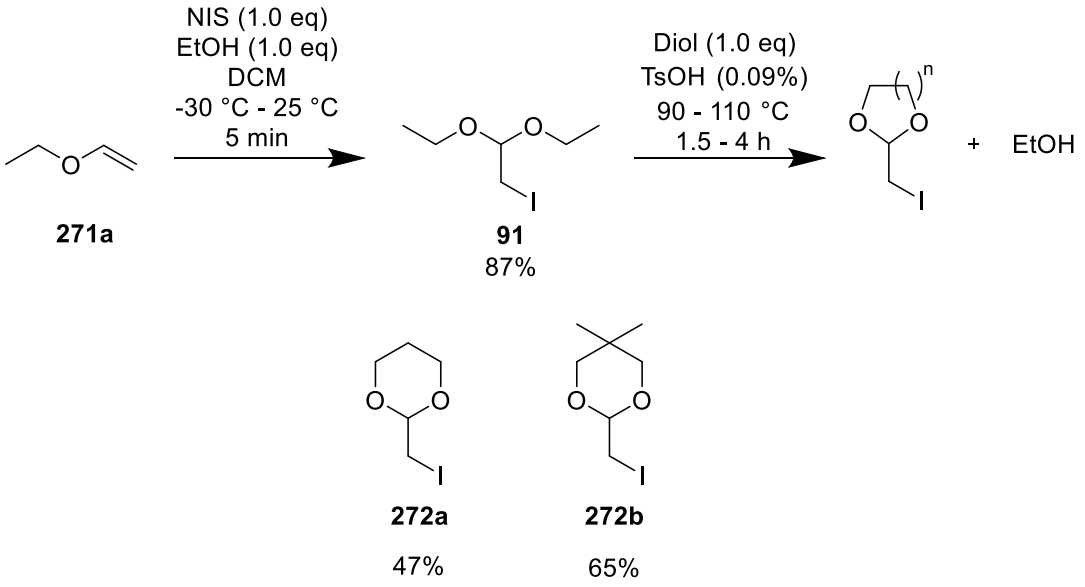
Scheme 108: The synthesis of bromoacetals from vinyl acetate

The second method of synthesising haloacetals involved the transacetalisation of methyl bromoacetal (**269a**) with diols to form cyclic bromoacetals (Scheme 109).[153,208] The majority of the bromoacetals were purely one diastereoisomer, with exceptions of (**270a,b,i**). This method was found to be moderate to high yielding, only required a simple distillation for purification and could also be used on scale, with 20 g of cyclic bromoacetals (**270a-l**) produced.



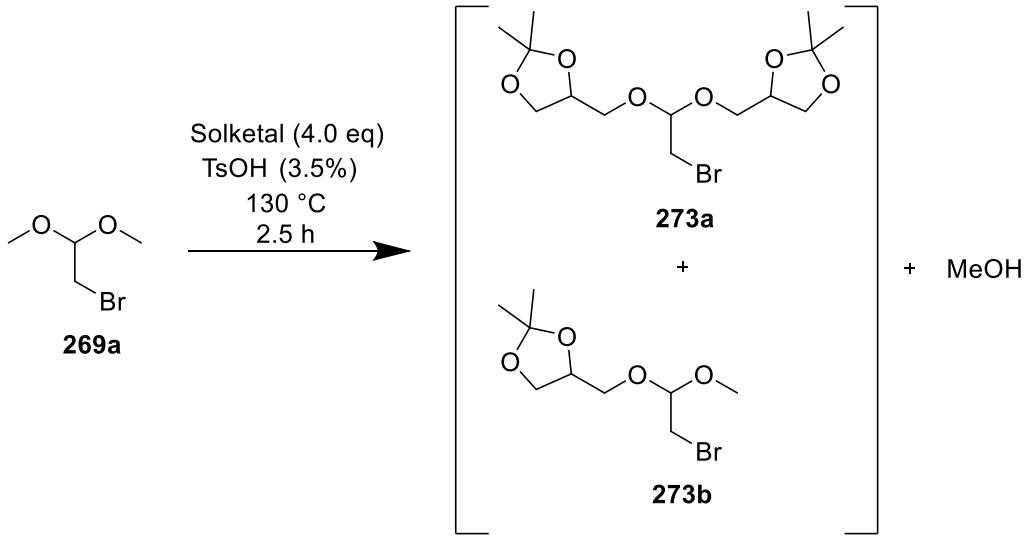
Scheme 109: Synthesis of a range of cyclic bromoacetals via transacetalisation of methyl bromoacetal (269a); [a] 1.2 eq of 269a

As mentioned earlier, the dehydrohalogenation of iodoacetals has been found to be significantly faster and higher yielding than that of bromo or chloroacetals. Cyclic iodoacetals have been synthesised previously using Finkelstein's iodination procedure, however this method often requires high reaction temperatures and long reaction times.[156,209] As an alternative, the transacetalisation method used for bromoacetals can also be used for the synthesis of cyclic iodoacetals (Scheme 110).



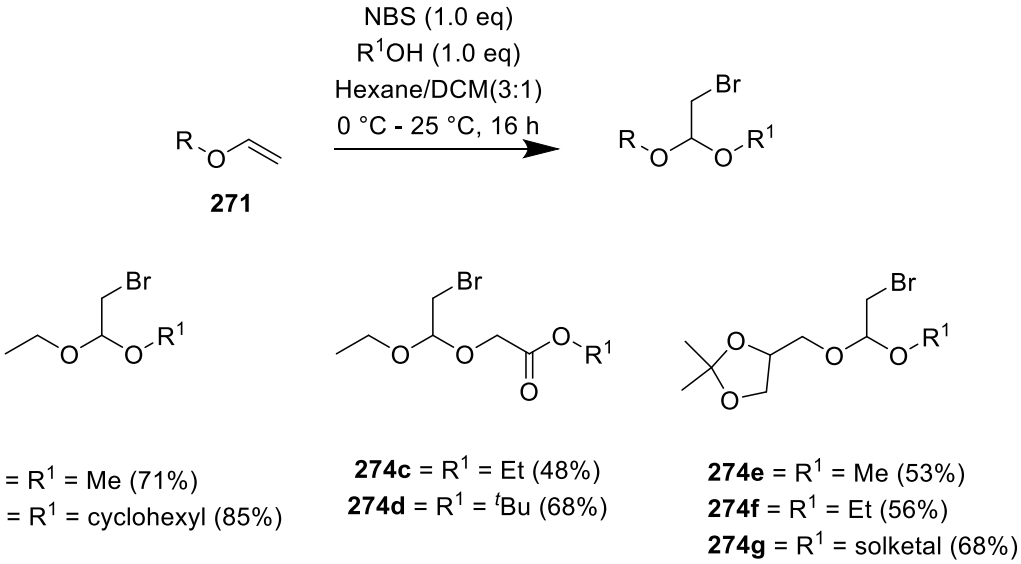
Scheme 110: The transacetalisation of ethyl iodoacetal to form cyclic iodoacetals

The synthesis of aliphatic bromo and iodoacetals was also attempted by the transacetalisation approach. Attempts to synthesise more complex primary aliphatic bromoacetals, such as di-solketal bromoacetal (**273a**) proved challenging. Unfortunately, even when a two-fold excess of solketal was used the mixed methyl/solketal bromoacetal (**273b**) was produced alongside the desired bromoacetal (**273a**) (Scheme 111). Efforts to prepare secondary symmetric bromo and iodoacetals *via* this method also proved challenging and the haloacetals were not isolated.



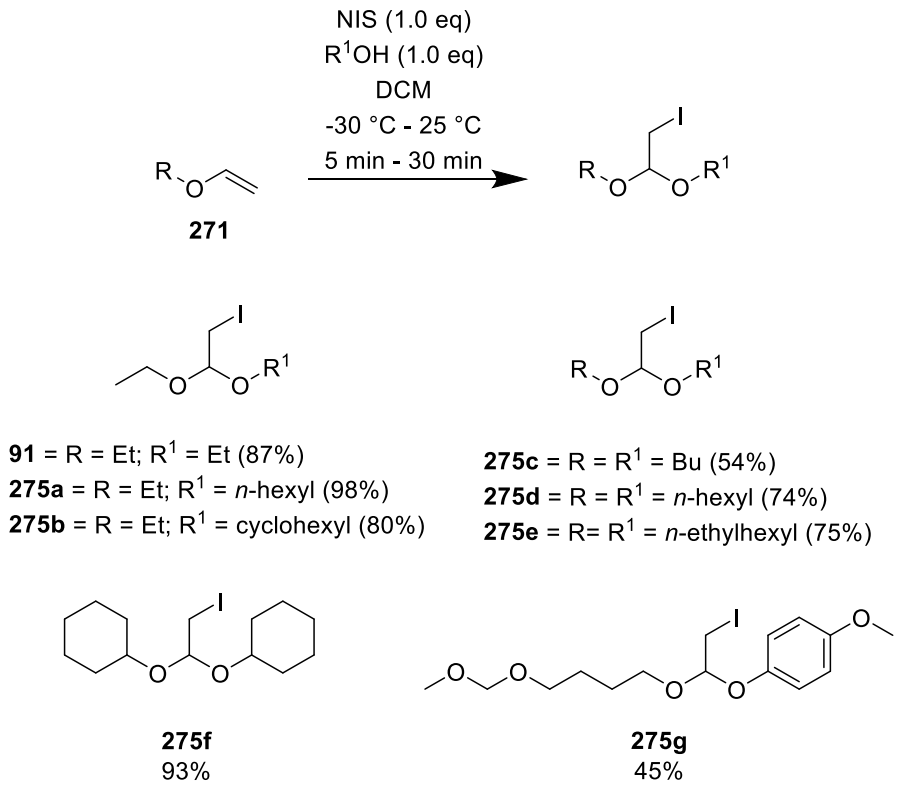
Scheme 111: Transacetalisation of 269a with solketal resulted in a mixture of both the mono- (273a) and di- (273b) solketal bromoacetal

The final method of synthesising haloacetals involved the halogenation of vinyl ethers (**271**).[147,210] This approach was utilised first to make a range of bromoacetals (Scheme 112). Primary and secondary alcohols were tolerated by this approach and both symmetric and mixed bromoacetals could be synthesised. Further to this, the only purification required was to remove the succinimide by-product and any residual NBS, which could be done by cooling the product in *n*-pentane and filtering out the NBS and succinimide or through washes with sat. aq. $NaHCO_3$. Alternatively, any residual NBS or succinimide could also be removed during the dehydrohalogenation step.



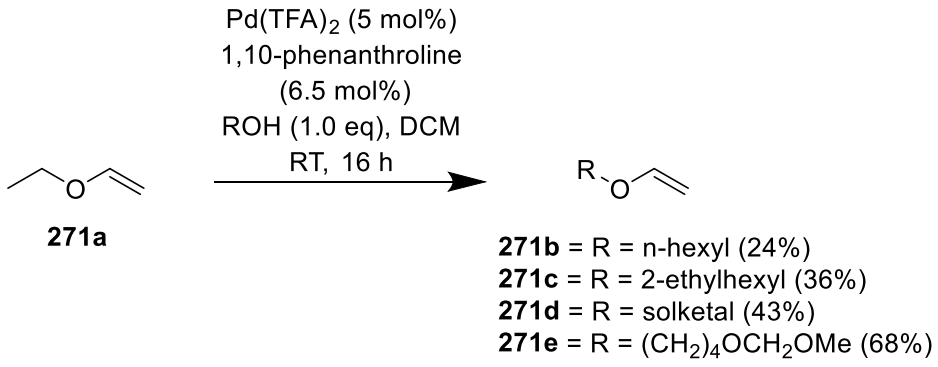
Scheme 112: The formation of a range of bromoacetals from vinyl ethers; R = Et or solketal

The halogenation of vinyl ethers was also used to synthesise iodoacetals. The synthesis of iodoacetals occurred much more rapidly than the bromoacetals and a wide variety of a symmetric and mixed iodoacetals were synthesised (Scheme 113). A range of substrates were tolerant of this approach, including primary (**91, 275a,c-d**) and secondary alcohols (**275b,f**) and protected hydroxyls (**275j**). Furthermore, the method was also tolerant to phenols, such as 4-methoxyphenol (**275j**). However, successful synthesis with phenols was only achieved by changing the order of addition. Under the original conditions, iodination of 4-methoxyphenol occurred rather than formation of the iodoacetal. To overcome this, the NIS was added only to the vinyl ether at -30 °C and held for 10 minutes, followed by addition of the 4-methoxyphenol.



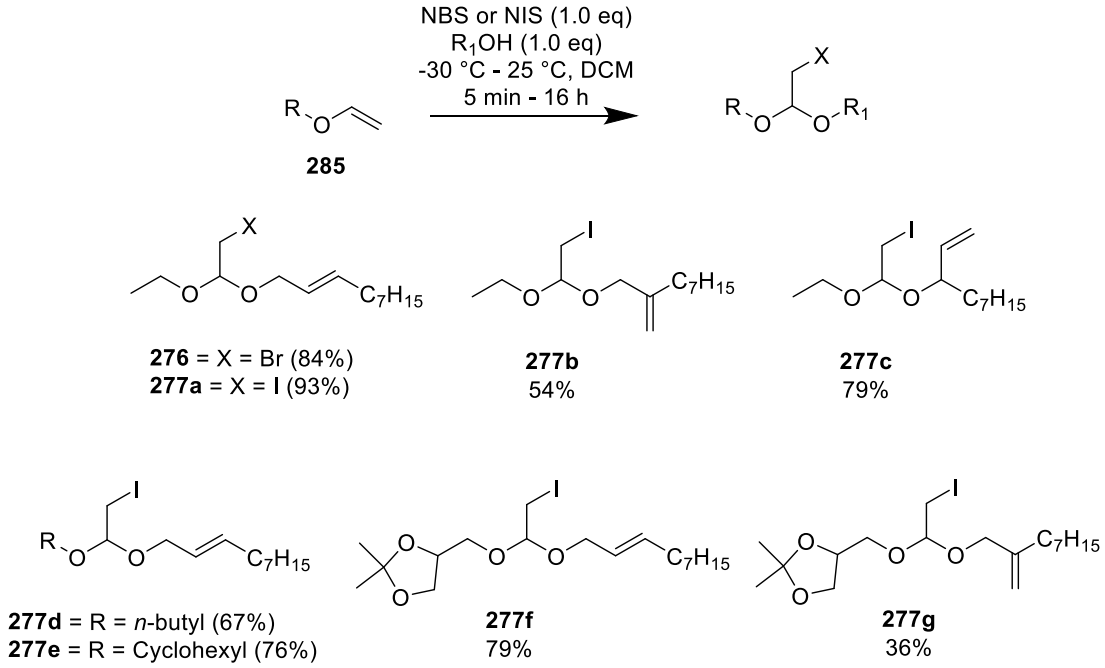
Scheme 113: Synthesis of a range of iodoacetals from vinyl ethers

The synthesis of haloacetals *via* the vinyl ether route proved to be a quick and easy method to both symmetric and mixed haloacetals. However, the limited commercial viability of the vinyl ethers was a major disadvantage to this route. Although a small range of vinyl ethers (**271b-e**) (Scheme 114), could be synthesised, the method involved expensive palladium catalysis and was poor yielding due to degradation which occurred during purification.



Scheme 114: Synthesis of higher chain vinyl ethers from ethyl vinyl ether

The iodination of vinyl ethers also tolerated allylic alcohols, which had been previously demonstrated by Middleton and Simpkins in 1989.[147] To improve upon the substrate scope, a range of long chain primary and secondary allylic alcohols, with different substitution patterns around the alkene, were utilised to produce mixed haloacetals (Scheme 115). Unfortunately, synthesising iodoacetals (**277b, g**), using 2-methylenenonanol, resulted in poor conversion of the alcohol into the iodoacetal. Attempts to improve the conversion, including increasing the length of the reaction, changing the temperature and increasing the equivalents of vinyl ether were unsuccessful. In order to isolate iodoacetals (**277b, g**), the unreacted alcohol had to be distilled out of the product, which resulted in 36-54% isolated yield. This drop in yield for the 2-methylenenonanol iodoacetals (**277b, g**) was mirrored in attempts to synthesise similar iodoacetals described by Middleton and Simpkins.



Scheme 115: The formation of a range of allylic haloacetals from vinyl ethers

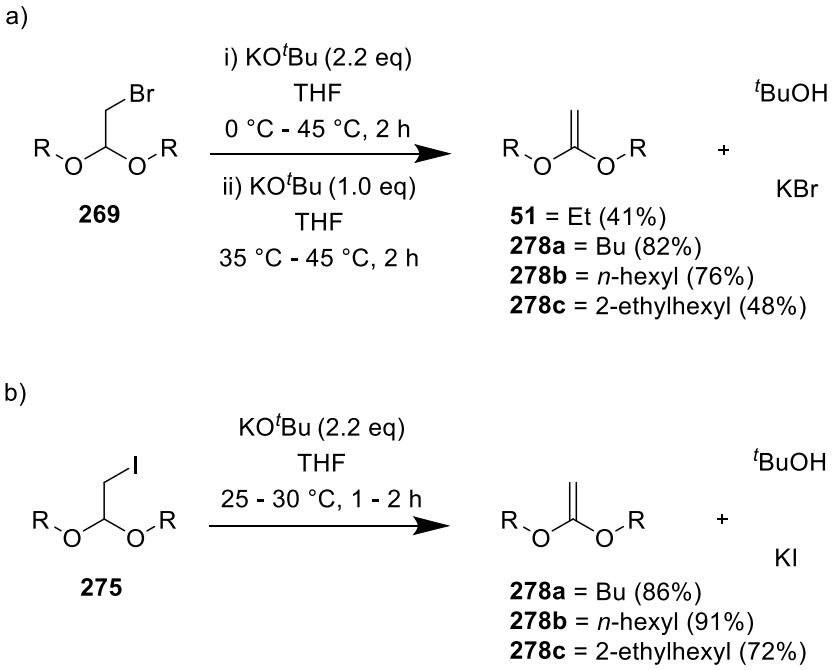
The allylic fragment of these haloacetals was important for the design and application of the orthoesters. The allylic nature will provide the orthoesters with the ability to undergo [3,3]-sigmatropic rearrangements and behave as delivery systems for lubricant additives, which will be described in chapter 4 and 5. Incorporating the allylic alcohol into the haloacetal, rather than at the orthoester

synthesis step, allowed for more creative flexibility when designing the orthoesters. This was especially important when it was found that certain groups, such as carbonyls (**274c-d**), did not survive the dehydrohalogenation step. In fact, utilising all three methods of synthesising haloacetals allowed for ease in the design of the final orthoester product.

3.2.2.3. Results and Discussion - Synthesis of Ketene Acetals

Initial attempts at the dehydrohalogenation involved utilising 18-crown-6 as a phase transfer catalyst because it showed increased isolated yields in the literature. However, even though using a phase transfer catalyst increased the rate of the elimination, removing it at the end of the reaction was difficult. Due to the instability of the ketene acetals, filtering out the phase transfer catalyst through even neutral alumina caused degradation of the ketene acetal.

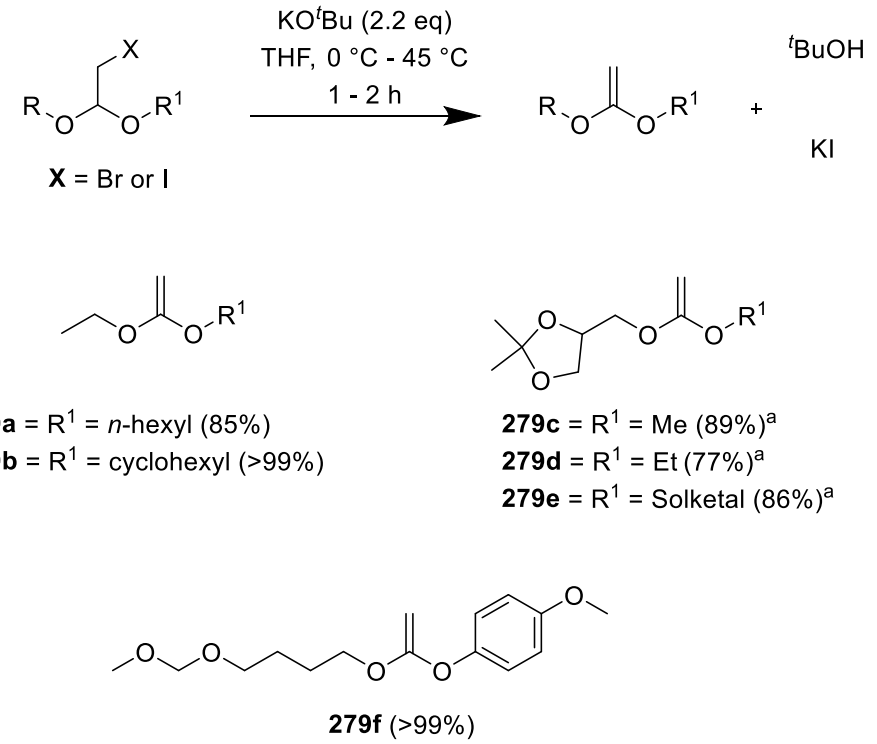
Undertaking the dehydrohalogenation without a phase transfer catalyst allowed for the isolation of the ketene acetals in moderate to good yields (Scheme 116). The halogen used to produce the haloacetals was found to have a real impact on the dehydrohalogenation. Significant differences in the ease of the elimination were observed between the symmetric primary aliphatic bromo and iodoacetals. In order to fully convert the aliphatic bromoacetals, temperatures of 35 – 45 °C and 3.2 equivalents of KO^{t}Bu were required (Scheme 116a). However, the iodoacetals were fully converted after 1 – 2 hours at room temperature with only 2.2 eq of KO^{t}Bu (Scheme 116b).



Scheme 116: Dehydrobromination of a range of symmetric bromoacetals

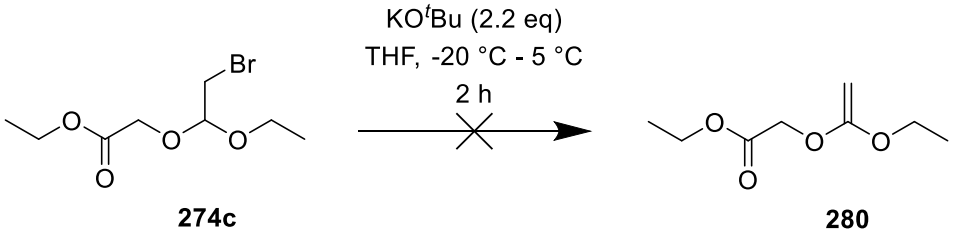
The iodoacetals unquestionably increased the rate and ease of the dehydrohalogenation. However, the synthetic route to some of the iodoacetals was significantly more difficult than the bromoacetals, which was discussed in section 3.2.2.2. The payoff arising from easier dehydrohalogenation from the iodoacetals did not overcome the challenging route to the iodoacetals and therefore the bromoacetals were easier to synthesise and use in the synthetic route to symmetric primary aliphatic ketene acetals. Furthermore, the dehydrohalogenation conditions used for the bromoacetals have the potential to be further optimised to improve this route.

The conditions used for the dehydrohalogenation of the symmetric haloacetals were then used for other aliphatic substrates. In most cases the iodoacetal was used due to the ease in the dehydrohalogenation. However, for the solketal substrates (**293c-e**) the bromoacetal was deemed suitable with full conversion of the bromoacetal occurring after 2 hours at room temperature. A range of other mixed and symmetric ketene acetals were synthesised in this way (Scheme 117).



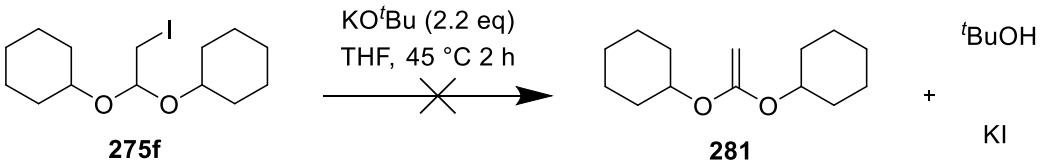
Scheme 117: Dehydrohalogenation of haloacetals to form ketene acetals; [a] bromoacetal used

The success of the dehydrohalogenation of aliphatic haloacetals was substrate dependent. For example, haloacetals (**274c**) which incorporated a carbonyl group at the β-carbon to the acetal did not form the ketene acetal (**280**) (Scheme 118). A range of side reactions could take place during this dehydrohalogenation, such as cyclisations, which could prevent the isolation of the ketene acetal. However, no characteristic peaks or products could be identified in the ^{1}H NMR spectrum.



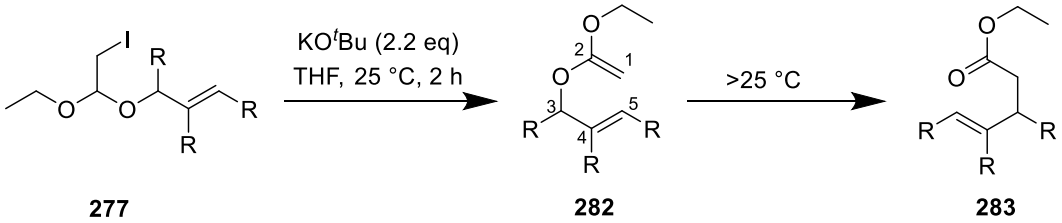
Scheme 118: The dehydrobromination of a bromoacetal with a β-carbonyl (274c) produced a range of unknown side products instead of 280

The dehydrohalogenation of secondary haloacetals also proved challenging; the elimination required harsher reaction conditions to fully convert the iodoacetal (**275f**) to the ketene acetal (**281**) (Scheme 119). Despite full conversion to the ketene acetal, the reaction also produced a side product. Unfortunately, the side product could not be removed by distillation and its identity could not be determined.



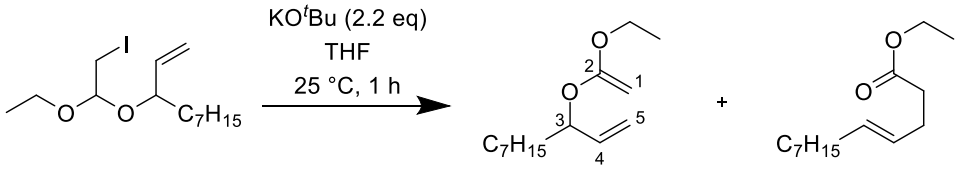
Scheme 119: The dehydroiodination of secondary iodoacetals resulted in the formation of an unknown side product preventing the isolation of 281

The dehydrohalogenation of allylic haloacetals (**277**) proved more challenging than the aliphatic haloacetals. The challenge was not related to the elimination of the halogen but rather in the isolation of the ketene acetal. The allylic ketene acetals (**282**) were prone to undergo [3,3]-sigmatropic rearrangements, specifically the orthoester Johnson-Claisen rearrangement (Scheme 120) leading to ester (**283**). In order to prevent the rearrangement from occurring the reaction mixture had to be maintained at temperatures no higher than room temperature throughout the reaction and isolation, including the removal of the solvent. Furthermore, it was important to either store the allylic ketene acetal (**282**) in the freezer or use immediately to prevent any rearrangement on storage.



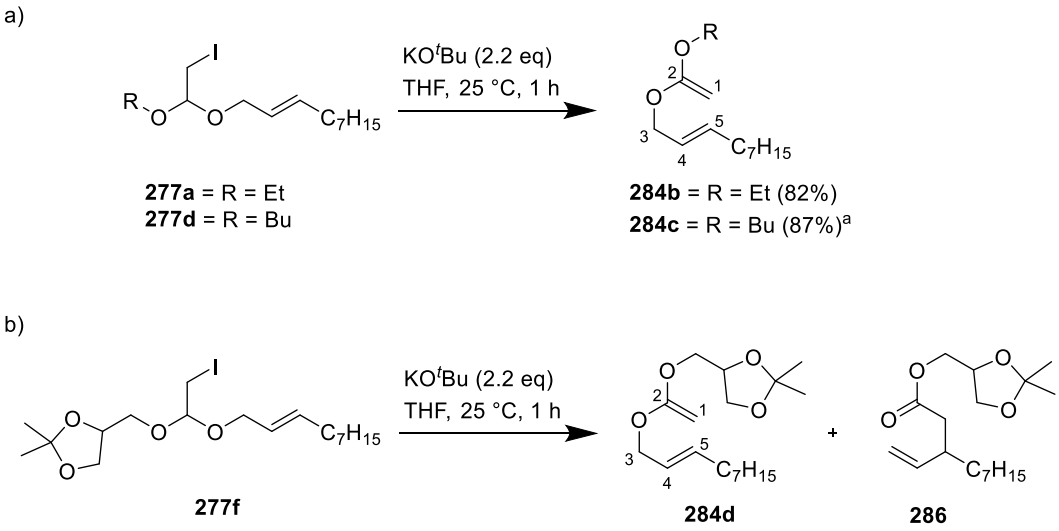
Scheme 120: Dehydrohalogenation of allylic haloacetals and the subsequent [3,3]-sigmatropic rearrangement

The substitution pattern around the alkene of the allylic iodoacetals had an impact on the ability of the ketene acetal to undergo the rearrangement and thus impacted the success of the isolation. Substitution at position 3 (**284a**) (Scheme 121) resulted in formation of the rearrangement product (**285**), even when the temperature of the reaction was maintained below 25 °C. This led to a mixture of the ketene acetal (**284a**) and ester (**285**), which could both be observed by IR (~1640 cm^{-1} and ~1730 cm^{-1}). The approximate ratio could not be determined by ^{1}H NMR since the ketene acetal rearranged to the ester whilst in the NMR queue (approx.15-30 min).



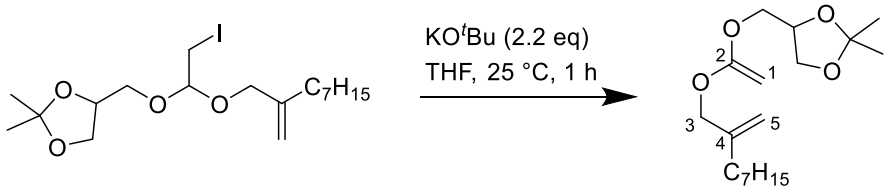
Scheme 121: Substitution at position 3 resulted in a mixture of both the ketene acetal (284a) and the rearrangement ester (285)

Isolation of ketene acetals with substituents at position 5 was dependent on the substrate of the non-allylic fragment (R in Scheme 122) of the haloacetal. For example, when a simple aliphatic group was used the ketene acetal (**284b**) could be isolated in 82% yields (Scheme 122a). Other simple aliphatic ketene acetals (**284c**) could be synthesised but characterisation data could not be collected due to rapid rearrangement whilst in the NMR queue. Successful formation of the ketene acetal was determined by reacting it immediately with an alcohol, before the ^{1}H-NMR data returned, to form the orthoester. This will be further discussed later in this chaper. For more complex substrates such as using a solketal group the ketene acetal (**284d**) could not be isolated without significant amounts of the rearrangement product, (Scheme 122b).



Scheme 122: a) The dehydroiodination of simple iodoacetals with alkene substitution at position 5; [a] used immediately without collecting characterisation data; b) Synthesis of ketene acetals and rearrangement ester using solketal/dec-2-enol iodoacetal

Allylic alcohols with substituents at position 4, allowed for the formation of ketene acetals (**284e**) with a solketal group (Scheme 123).

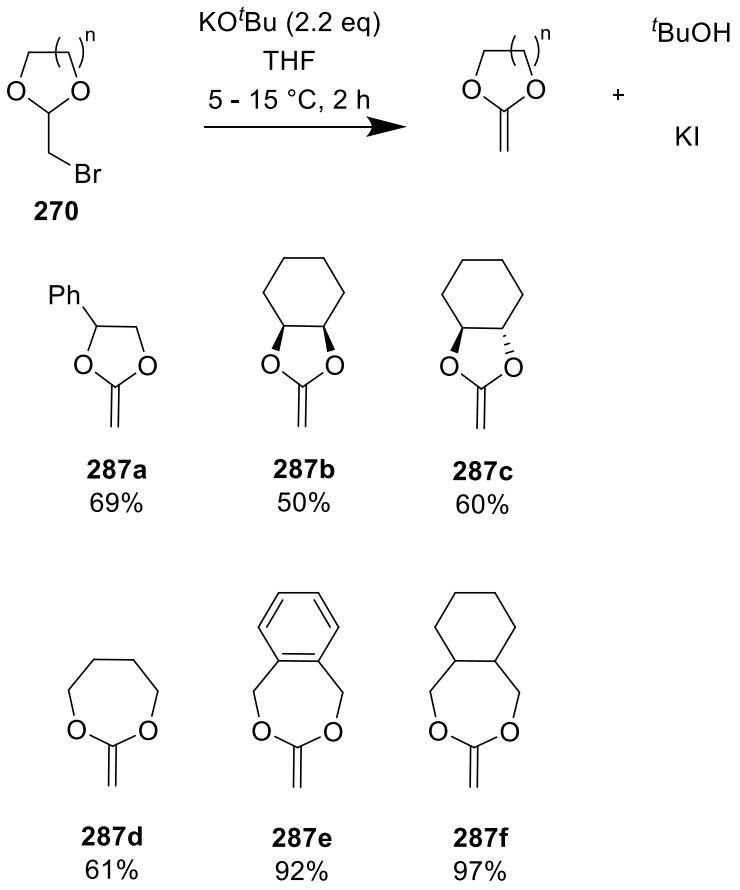


277g **284e** >99%

Scheme 123: Dehydroiodination of iodoacetals with substituents at position 4

The allylic substitution pattern effect on the isolation of ketene acetals can be explained as a result of the rate of the rearrangement. It is known in the literature that the substitution pattern of the alkene in the ketene acetal impacts the rate of the rearrangement[211–217]. The substitution rate effects match the ability to isolate the ketene acetal. For example, substitution at position 3 is known to rearrange the fastest, therefore occurs so readily it forms at room temperature and the ketene acetal cannot be isolated. Further to this, the substrate dependence highlighted for substitution at position 5, also suggests that the non-allylic fragment of the iodoacetal also impacts the rate of the rearrangement. The rate of the rearrangement will be discussed further in chapter 4.

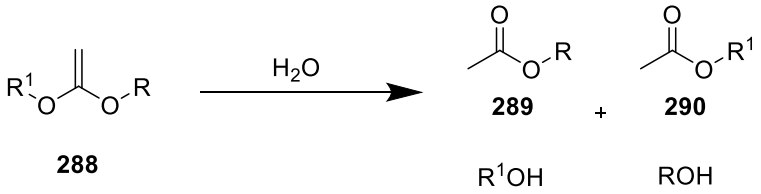
The dehydrohalogenation reaction conditions used for the synthesis of aliphatic and allylic ketene acetals were used for cyclic ketene acetals. However, milder reaction conditions were required in order to isolate the ketene acetal without degradation. This resulted in the use of the bromoacetals and cooler reaction temperatures (5 - 15 °C) (Scheme 124). Unfortunately, this method did not tolerate the isolation of 6-membered ketene acetals without degradation, despite changing the temperature, length of time of reaction, using iodoacetals and attempted purifications *via* distillations. Although the cyclic ketene acetals produced were not novel compounds, the synthesis of many of them without a phase transfer catalyst was novel.



Scheme 124: Synthesis of cyclic ketene acetals through dehydrobromination

It is important to note that the ketene acetals (**287**) synthesised in this chapter were found to be unstable to air and moisture and rapidly underwent hydrolysis reactions to form acetate esters (**289-290**) and the corresponding alcohols (Scheme 125). In order to prevent the degradation, the ketene acetals were required to be kept under anhydrous conditions, both during reaction and on storage. Storage of the ketene acetals was difficult, ideally the ketene acetal was used immediately, but when this was not possible the ketene acetals could be stored in the freezer under inert conditions for short periods of times. The acyclic ketene acetals could be easily purified by distillation if any degradation did occur. The instability of the ketene acetal also had an impact on the NMR data collected as they were found to often start to degrade whilst in the NMR queue. The quickest analysis of the ketene acetals purity was by IR. Since the degradation products were esters and alcohols (Scheme 125), they could easily be observed by IR,

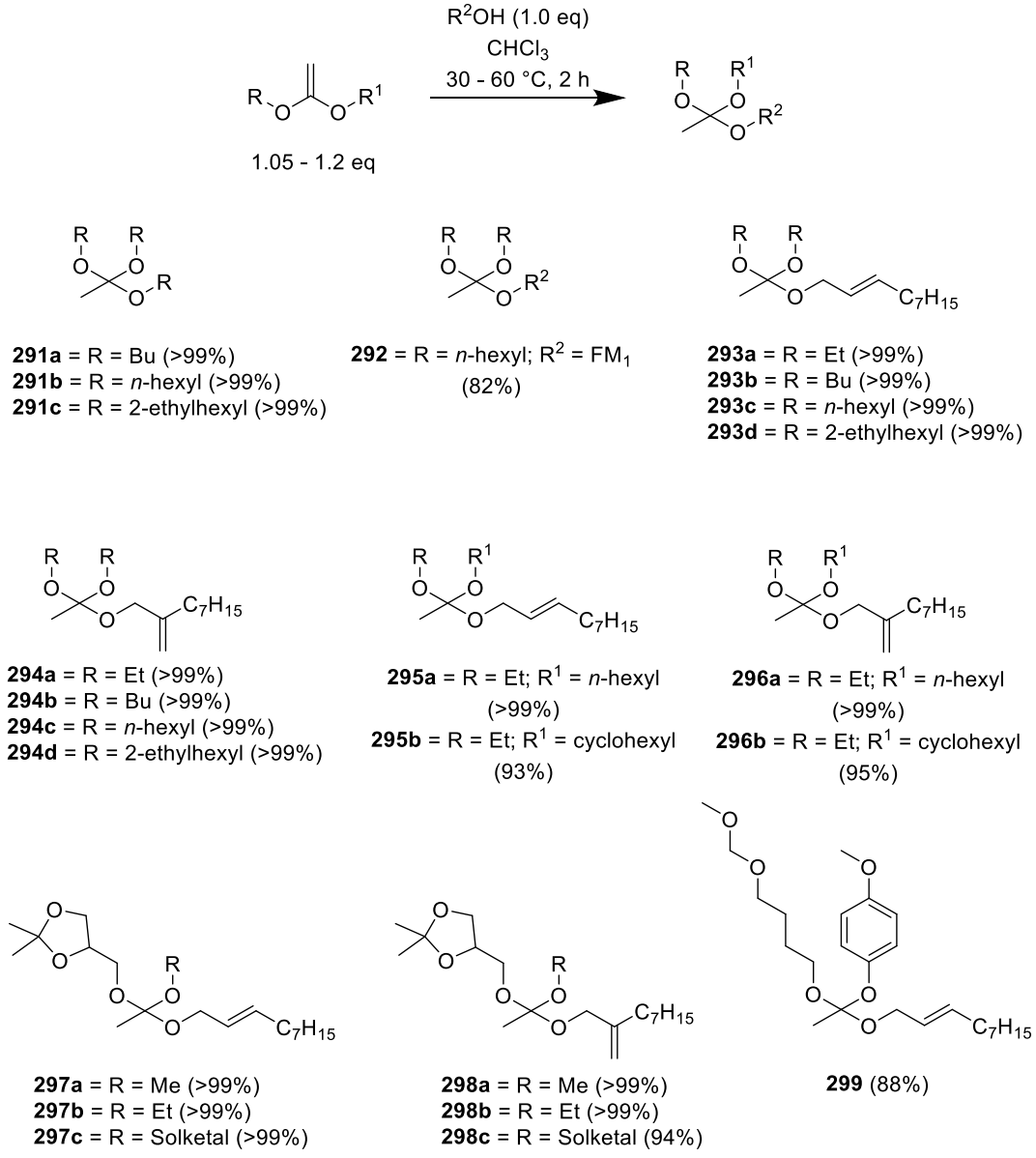
especially as there was a difference between the ketene acetal peak (~1650 cm^{-1}) and the ester degradation product (~1720 cm^{-1}).



Scheme 125: Degradation of ketene acetals

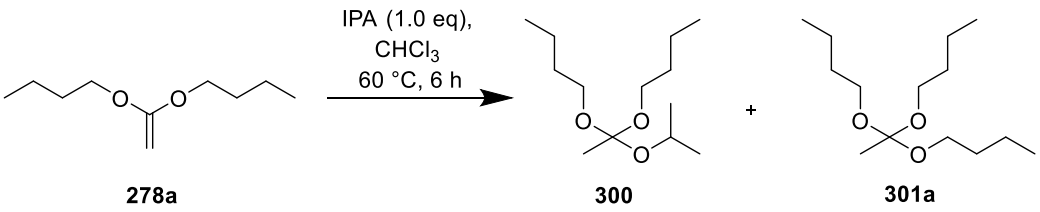
3.2.2.4. Results and Discussion - Addition of Alcohols to Ketene Acetals

Initial attempts to synthesise orthoesters from the addition of alcohols to ketene acetals involved the modification of McGeary and Cosgrove's studies.[54] Unfortunately, utilising the solvent free conditions resulted in a complex mixture of products which was more than likely a result of the exothermic reaction. After optimisation, the best reaction conditions were found to be the addition of a solution of ketene acetal to the alcohol, followed by heating the reaction for 2 hours. A small excess of the ketene acetal (1.05 – 1.2 equivalents) was required for the full conversion of the alcohol, however this was a large reduction compared to McGeary and Cosgrove's work. A range of solvents could be used, including hexane, ethyl acetate, THF and chloroform, however it was important that these were anhydrous, and used in an inert atmosphere, to prevent degradation of the orthoester. Utilising this method allowed for the formation of a range of orthoesters (Scheme 126). Both allylic and aliphatic alcohols could be added to ketene acetals. Furthermore, this is the first reported synthesis of tri-substituted mixed orthoesters, wherein all three of the alkoxy groups on the orthoester are different. In most cases the orthoesters were synthesised without the need for purification, but if required then this could be undertaken *via* careful distillation. However, in some cases there were baseline impurities in the ^{1}H-NMR, which could not be removed by distillation. Attempts to remove these impurities by column chromatography was unsuccessful due to the instability of the orthoesters towards silica, acid and moisture.



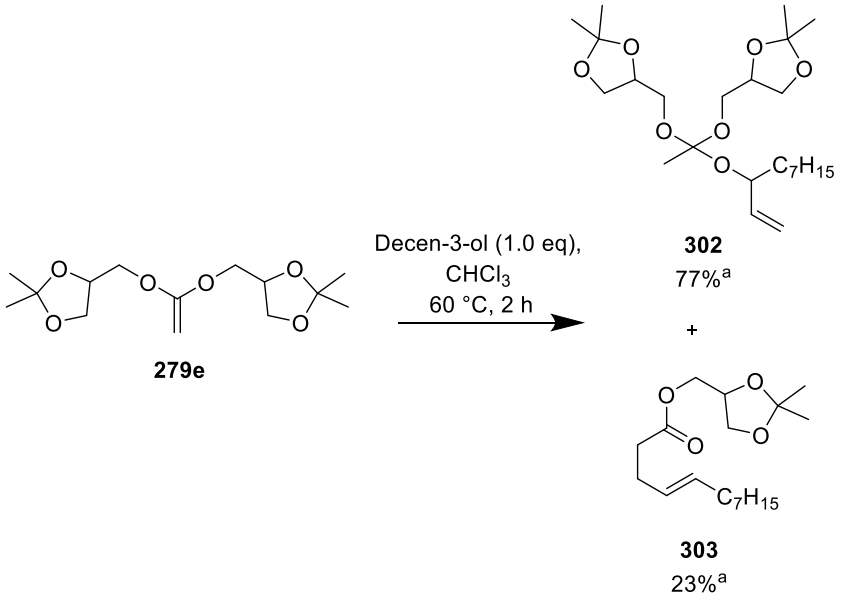
Scheme 126: Synthesis of symmetric and mixed orthoesters through the addition of alcohols to ketene acetals; [a] 6 hours at 60 °C

The addition of secondary alcohols to ketene acetals proved more difficult than primary alcohols. In order to add simple aliphatic secondary alcohols, such as 2-propanol, the temperature of the reaction had to be increased to 60 °C and the length of the reaction extended to 6 hours. Unfortunately, the harsh conditions required resulted in the scrambling of the orthoester, producing tributyl orthoester (**301**) as well as the desired mixed orthoester (**300**) (Scheme 127). This was based on the presence of an additional methyl group in the ^{1}H-NMR spectrum. An approximate ratio of the products could not be determined due to difficulties in characterising which methyl peak corresponded to which orthoester.



Scheme 127: The attempted addition of a secondary alcohol to a ketene acetal, which resulted in scrambling of the orthoester

The addition of allylic secondary alcohols, such as decen-3-ol, was unsuccessful. The temperatures required for the ketene acetal and alcohol to react resulted in the orthoester to undergo a [3,3]-sigmatropic rearrangement once it was formed (Scheme 128). This resulted in a mixture of products and the orthoester could not be isolated.

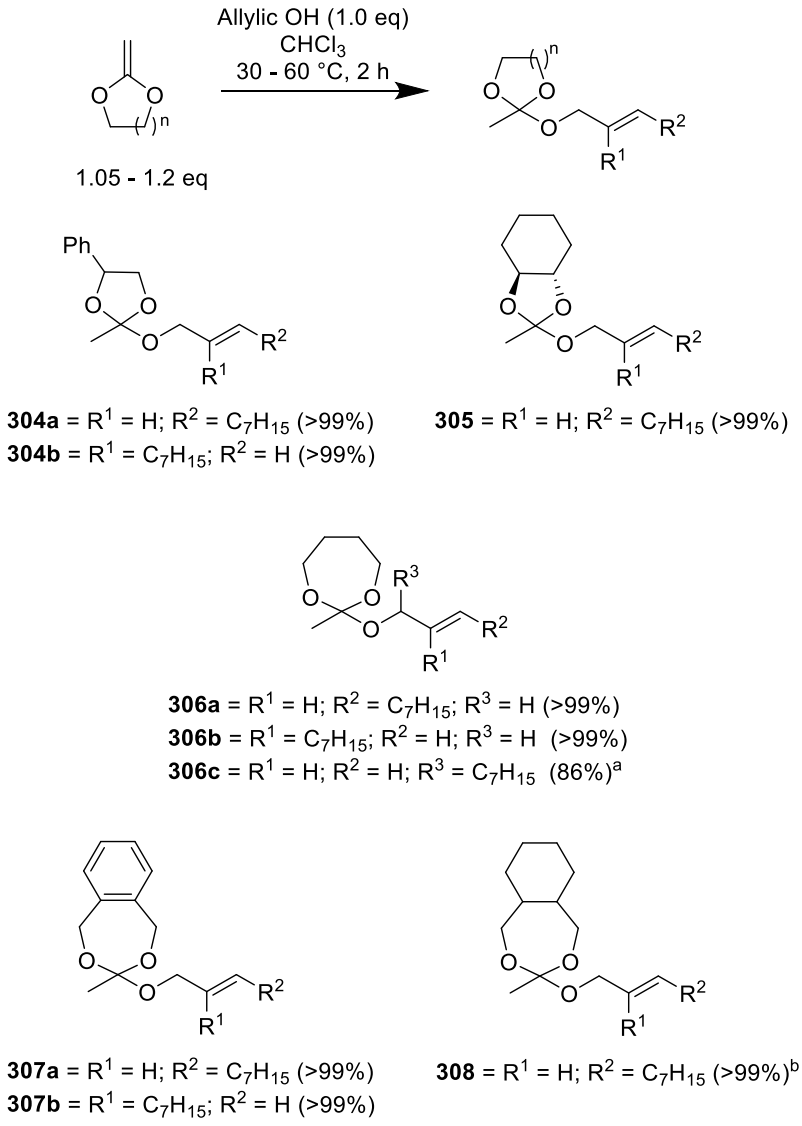


Scheme 128: The addition of secondary allylic alcohols to ketene acetals resulted in a mixture of products; [a] yields are based on ^{1}H-NMR ratio

The addition of more complex functionality, such as friction modifier 1 (FM[1]), to ketene acetals was also successful and produced orthoester (**292**). The ability to incorporate this functionality has an impact on the application of these orthoesters, which will be discussed further in chapter 5.

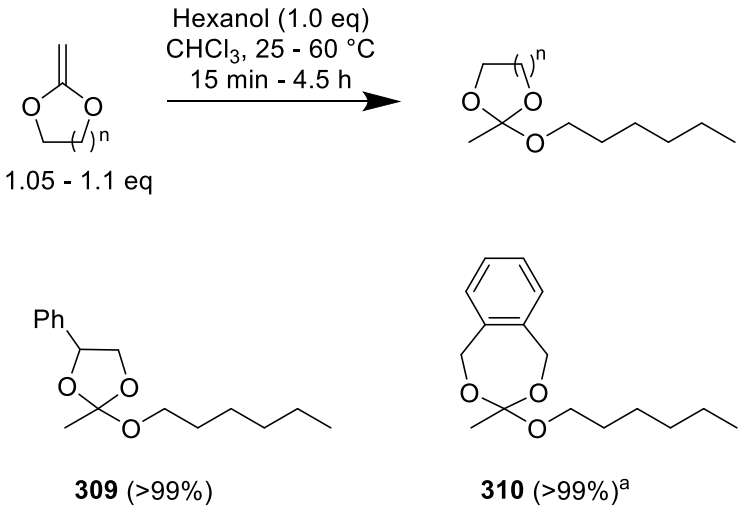
The synthetic method used to synthesise acylic orthoesters could also be used to prepare cyclic orthoesters. Primary allylic alcohols added to cyclic ketene acetals without problems to produce a range of cyclic orthoesters (Scheme 129). However, similarly to acyclic ketene acetals, the addition of secondary allylic alcohols proved

challenging and often resulted in the [3,3]-sigmatropic rearrangement of the orthoester due to the temperature of the reaction. Surprisingly, no rearrangement occurred when decen-3-ol was added to the 7-membered ketene acetal, although the reaction stalled after 6 hours, the secondary allylic orthoester (**306c**) was isolated in 85% yield. The ability to isolate this orthoester was determined to be due to the rearrangement occurring at a higher temperature than that of both the reaction and the temperature required to remove the unreacted alcohol, however it is unclear why this particular orthoester has higher rearrangement temperatures compared to the other cyclic orthoesters synthesised.



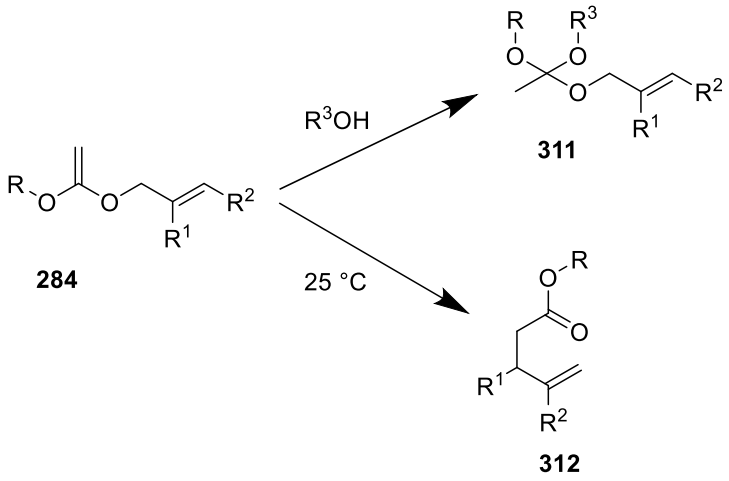
Scheme 129: Synthesis of cyclic orthoesters from the addition of alcohols to ketene acetals; [a] 6 hours at 60 °C; [b] 24 hours at 60 °C

There was a marked difference in the reactivity of the cyclic ketene acetals with aliphatic alcohols compared to allylic alcohols. The ease of the addition of the aliphatic alcohol was dependent on the size of the ring of the cyclic ketene acetal. Smaller rings reacted with aliphatic alcohols with greater ease than larger rings, for example, 5-membered orthoesters (**309**) were formed after 4.5 hours at 60 °C, whilst 7-membered orthoesters (**310**) stalled after 22 hours at 60 °C. In fact, in order to successfully add aliphatic alcohols to 7-membered ketene acetals, acid catalysis (pyridinium *p*-toluenesulfonate *p*PTS) was required (Scheme 130). The ring size effect has already been described in the literature by Fukuda.[99] Fukuda postulated that a smaller ring had greater p-π conjugation, which resulted in greater electron density on the alkene and thus increased reactivity. These results were also matched to the NMR chemical shift of the alkene, effectively creating a prediction tool of the reactivity of cyclic ketene acetals, wherein the more upfield the shift the more reactive the ketene acetal will be. For example, the 5-membered ketene acetal (**302a**) has a shift of 3.73-3.69 ppm for the alkene compared to 3.96 ppm for the 7-membered ketene acetal (**302e**). These shifts suggest that the 5-membered ketene acetal is more reactive, which matches the observed reactivity. The difference between the ease of addition of allylic and aliphatic alcohols can be postulated to be due to the slight differences in acidity. This will be further discussed later in this chapter when proposing a mechanism.



Scheme 130: Addition of aliphatic alcohols to cyclic ketene acetals;
[a] 1 mol% *p*PTS

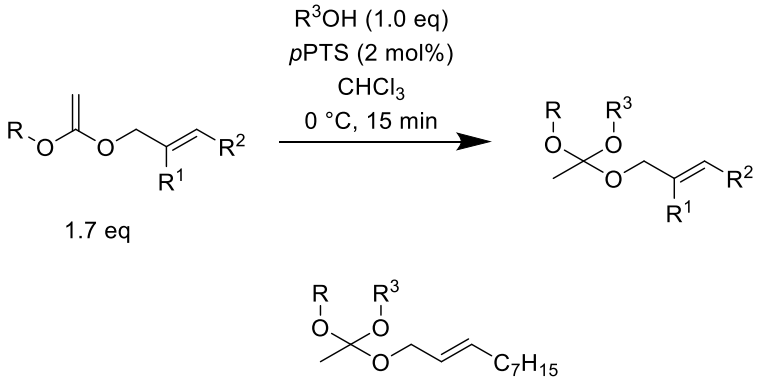
The synthesis of orthoesters from the addition of alcohols to allylic ketene acetals was challenging. The allylic ketene acetals (**284**) were found to react slowly with alcohols at room temperature, often taking 24 - 48 hours to fully consume the ketene acetal. Furthermore, the competing [3,3]-sigmatropic rearrangement (Scheme 131) prevented the reaction from being heated in order to promote addition. In fact, the [3,3]-sigmatropic rearrangement was still observed if the reaction was held at room temperature. The difference in reactivity of allylic ketene acetals compared to aliphatic ketene acetals was speculated to be due to the electron withdrawing nature of the allylic alkene, effectively reducing the electron density of the reactive alkene. This was based on the chemical shifts of the ketene acetals. For example, the alkene in the aliphatic solketal ketene acetal (**279e**) had a shift of 3.15 ppm compared to 3.75-3.61 ppm for the allylic solketal ketene acetal (**284c**).



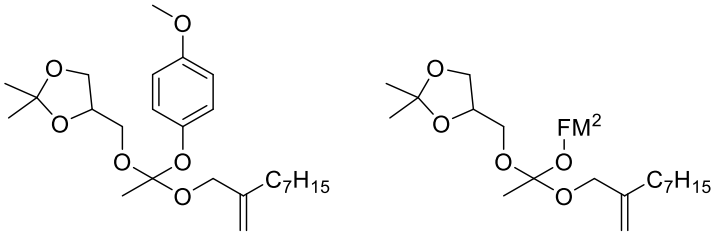
Scheme 131: The addition of alcohols to allylic ketene acetals to form orthoesters (311) and the competing rearrangement to form esters (312)

Acid catalysis facilitated the addition of alcohols into allylic ketene acetals. The optimised conditions involved acidifying the alcohol, followed by a 15-minute addition to an excess of the ketene acetal, which was cooled to 0 °C. It was necessary to keep the ketene acetal cool to prevent the competing rearrangement. Furthermore, the acid catalyst had to be added to the alcohol and not the ketene acetal, if the acid was added directly to the ketene acetal it resulted in degradation or scrambling of the orthoester. Unfortunately, despite using an excess of the ketene acetal, in most cases, the alcohol was not fully consumed. The removal of

the residual alcohol is a major drawback to this reaction since the purification of orthoesters can be difficult, especially when there is an allylic group installed. Orthoesters can only be purified by distillation and it was found that the allylic orthoesters undergo rearrangements at elevated temperatures. Therefore, the addition alcohol was limited to reasonably low boiling alcohols (<100 °C) or alcohols which can be removed by basic aqueous washes (**313**) or filtrations (**314**). Nevertheless, this method tolerated a range of functionality, including aliphatic, phenolic and friction modifiers (FM^2) (Scheme 132). The significance of the inclusion of FM^2 will be discussed in chapter 4 and 5. Interestingly, some of the more acidic functionalities, such as 4-methoxyphenol (**295e, 313**) and trifluoroethanol (**295f**) underwent the addition without the acid catalyst.



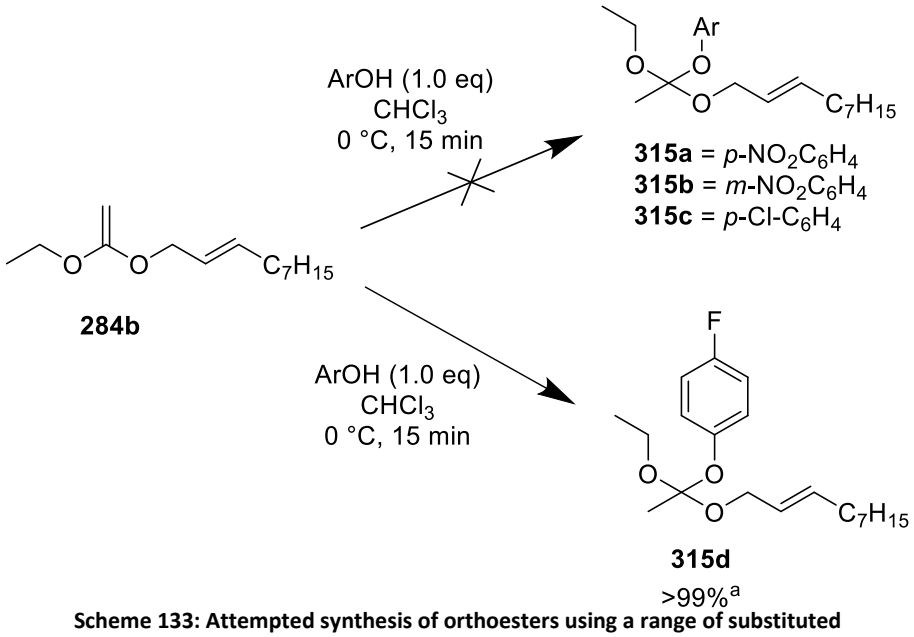
295a = R = Et; R^3 = *n*-hexyl (>99%)
295c = R = Et; R^3 = Me (67%)[a]
295d = R = Et; R^3 = $(CH_2)_4OCH_2OMe$ (52%)[a]
295e = R = Et; R^3 = C_6H_4OMe (>99%)[b]
295f = R = Et; R^3 = CH_2CF_3 (>99%)[b]
295g = R = Bu; R^3 = *n*-hexyl (56%)[a]



313 (>99%)[b] **314** (>99%)

Scheme 132: Synthesis of orthoester by addition of alcohols to allylic ketene acetals; [a] 2.0 eq ketene acetal, no *p*PTS, 25 °C 24-72 h; [b] No *p*PTS

To further investigate how the acidity of the alcohol affected the addition of alcohols to ketene acetals a range of substituted phenols were utilised (Scheme 133). The chloro- and nitro- phenols were found to be too acidic (pKa = 7.2 – 9.1) and resulted in immediate degradation of the orthoesters (**315a-c**). The fluorophenol (pKa = 9.9), however, successfully formed the orthoester (**315d**), which could be observed by IR. Although the orthoester (**315d**) could be observed by ^{1}H NMR it proved too unstable to collect full characterisation data. Overall, the acidity of the alcohol was paramount to the success of the reaction, not acidic enough and the addition was slow and required catalysis, too acidic and the orthoester degraded.



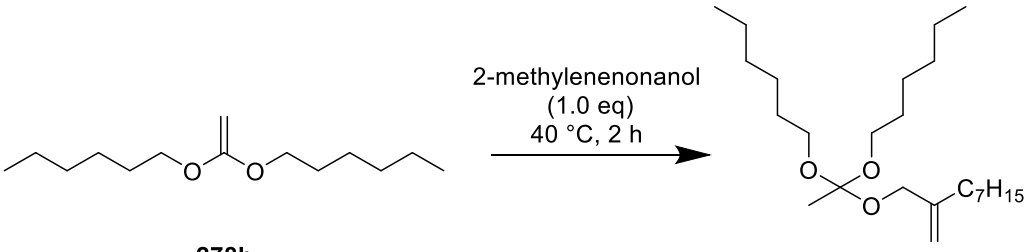
Scheme 133: Attempted synthesis of orthoesters using a range of substituted phenols; [a] started to degrade whilst in the ^{1}H NMR queue, resulting in poor purity

3.2.2.5. Results and Discussion - Mechanism of the Addition of Alcohol to Ketene Acetals

The scope and reaction conditions of the synthesis of orthoesters through the addition of alcohols to ketene acetals has been investigated over years by numerous research groups. However, the mechanism of the reaction has not been discussed. Our initial investigation was into the effect of external acid sources, such as the glass reaction vessel and solvents, on the reaction. A PTFE reaction flask was utilised for the reaction of a simple aliphatic ketene acetal (**278b**) with 2-methylenenonanol. The original reaction conditions, which included an inert

atmosphere, were used (Table 4, line 2). The outcome was comparable to the glass reaction vessel (Table 4, line 1). The reaction was then undertaken in anhydrous ethyl acetate (Table 4, line 3) and neat (Table 4, line 4), both in a PTFE flask, to confirm that the solvent was not catalysing the reaction. In both cases the yield was comparable to the original conditions. Finally, the alcohol was passed through basic alumina before use to remove any acidic components (Table 4, line 5). Overall, it was found that the reaction was not facilitated by any external acidic sources.

Table 4: Investigation of the effect of external acidic sources on the addition of alcohols to ketene acetals; [a] alcohol subjected to a basic alumina plug; [b] isolated yields



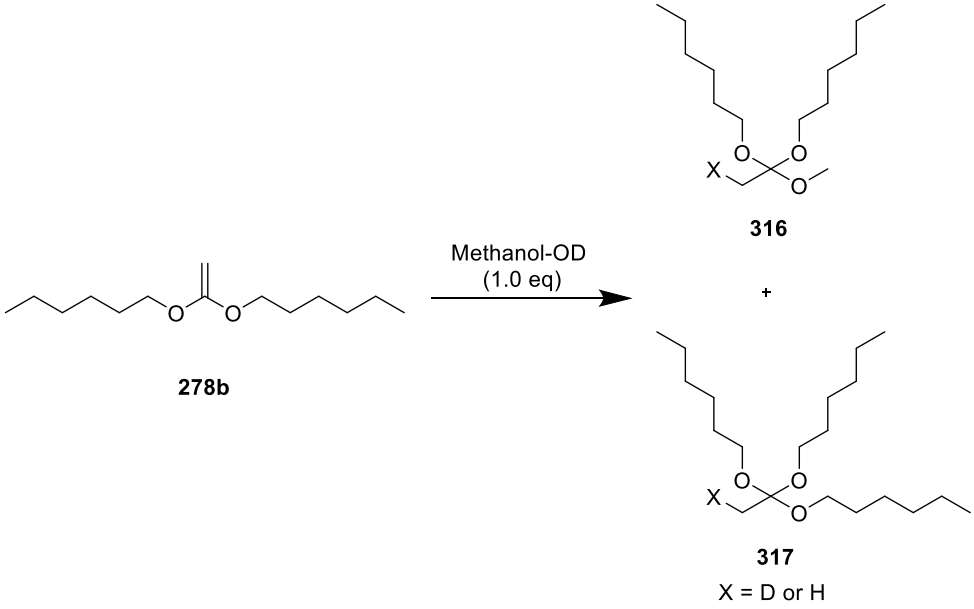
278b
1.2 eq

294c

Entry	Reaction Vessel	Solvent	Condition change	Yield (%)
1	Pyrex glass	$CHCl_3$	-	>99
2	PTFE	$CHCl_3$	-	94
3	PTFE	EtOAc	-	95
4	PTFE	-	-	>99
5	PTFE	$CHCl_3$	Basify Alcohol[a]	>99

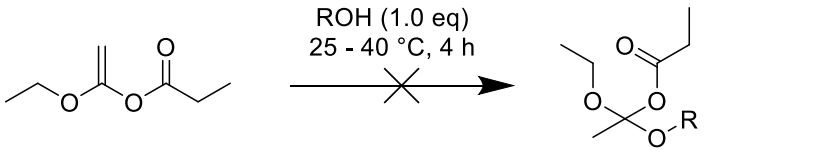
To investigate further the mechanism, a deuterated alcohol was used to determine whether the proton on the alcohol was transferred to the methylene of the ketene acetal to form the methyl group of the orthoester. Using methanol-OD in a reaction with hexyl ketene acetal (**278b**) successfully produced an orthoester. The first observation was that full conversion was achieved immediately after the 45-minute room temperature addition. Secondly, there were two methyl orthoester

peaks noted in both the ^{1}H-NMR and ^{13}C-NMR, as well as two quaternary carbons in the ^{13}C-NMR, which suggested that there were 2 different orthoesters present. This could be as a result of scrambling of the orthoester, in which both the mixed orthoester (**316**) and symmetric orthoester (**317**) are formed (Scheme 134). Nevertheless, some deuterium was incorporated at the orthoester methyl, observed in the ^{13}C-NMR. However, since the reaction produced another orthoester, integral measurements could not be taken, due to overlap in the ^{1}H-NMR. Therefore, the use of deuterated alcohols cannot be conclusive proof of proton transfer from the alcohol to the ketene acetal.



Scheme 134: The reaction of ketene acetal with deuterated methanol resulted in a mixture of both deuterated and non-deuterated orthoesters and a mixture of mixed orthoesters due to scrambling

Throughout the investigation into the synthesis of orthoesters, the substituents around the ketene acetal were found to have an impact on its reactivity and ease of the reaction. For example, both large rings and allylic groups were found to decrease the reactivity. This was postulated to be since these groups cause a reduction in the electron density of the alkene. This suggested that the alkene behaved as the nucleophile. To further investigate this another electron withdrawing ketene acetal (**318**) was synthesised. This ketene acetal was found to be stable and did not react with either allylic or aliphatic alcohols (Scheme 135). The resulting ^{1}H-NMR showed both the alcohol and the ketene acetal, no orthoester and no degradation of the ketene acetal.

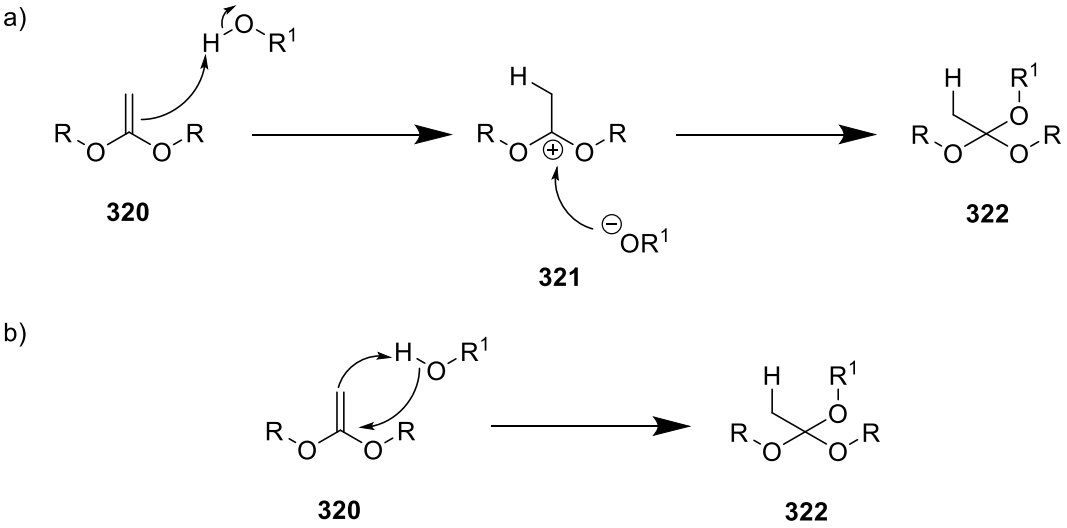


318

319a = R = *n*-hexyl
319b = R = $CH_2CHC(CH_2)_7$

Scheme 135: The addition of alcohols to electron poor ketene acetals resulted in no reaction

A mechanism of the addition of alcohols to ketene acetals can now be proposed (Scheme 136a). It is proposed that the ketene acetal behaves as a nucleophile and abstracts a proton from the alcohol. The alkoxide can then react with the carbocation to form the orthoester. There is also potential that this reaction behaves in a concerted manner (Scheme 136b). This mechanism was proposed because of three reasons. The first was that the proton must come from the alcohol since there are no other acid sources present. The second was that the ease of reaction increased with more acidic alcohols since they can more readily form the alkoxides. The final reason was that the ease of the reaction decreased with electron poor ketene acetals since it reduced the nucleophilicity and electron density of the alkene. Further work should be undertaken on the deuterium studies to obtain conclusive proof that the proton from the alcohol is abstracted by the alkene.



Scheme 136: The proposed mechanism of the addition of alcohols to ketene acetals; a) two step; b) concerted

3.3. Conclusion

This chapter described two successful syntheses of orthoesters. The novel gold-catalysed addition of allylic alcohols to alkoxy acetylenes was proven to be moderate yielding whilst requiring no further purification. This method was shown to tolerate a small range of chain lengths, substitution patterns around the alkene and acetylene substrates. However, the use of an expensive gold catalyst and the limited flexibility in the design of the orthoesters makes this approach not suitable for the application of a delivery system for friction modifiers.

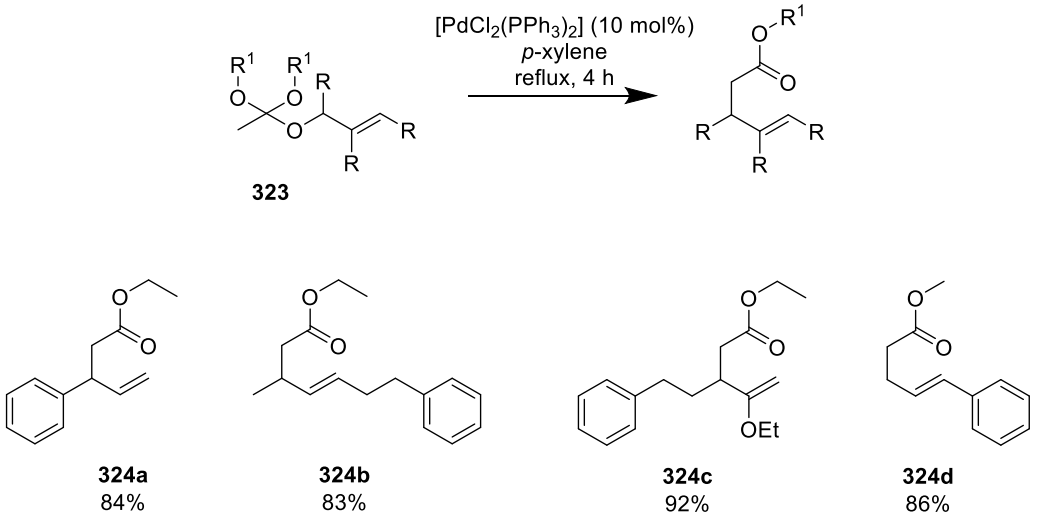
The modified preparation of orthoesters from the addition of alcohols to ketene acetals improved upon examples in the literature[54] by reducing the equivalents of ketene acetal, using a wide variety of different ketene acetals and expanding the substrate scope. Furthermore, the synthesis of mixed tri-substituted orthoesters, which were not known in the literature, was described. Finally, the mechanism for the addition was discussed.

4.0. Modifications to the Orthoester Johnson-Claisen Rearrangement

The orthoester Johnson-Claisen rearrangement has been used for decades in a wide variety of applications.[218] This chapter will discuss modifications to the rearrangement which could allow for the rearrangement to behave as a delivery system for friction modifiers.

4.1. Review of the Direct Orthoester Johnson-Claisen Rearrangement

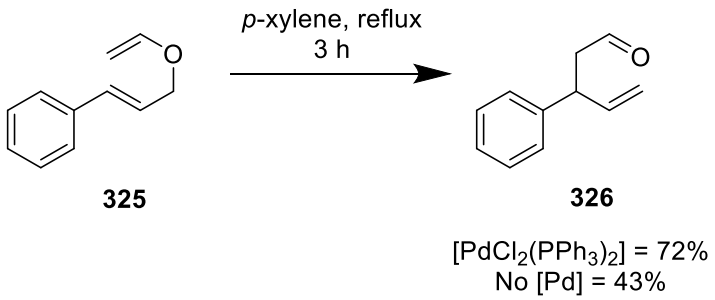
There has been limited investigation into the orthoester Johnson-Claisen rearrangement directly from mixed orthoesters (**323**). Mukaiyama *et al*., described a palladium catalysed variant.[219] A small range of crude allylic derived mixed orthoesters were heated to reflux in the presence of $[PdCl_2(PPh_3)_2]$ to yield the corresponding esters (**324a-d**) in 83-92% yield (Scheme 137).



Scheme 137: The orthoester Johnson-Claisen rearrangement from mixed orthoester from Mukaiyama *et al*.[219]

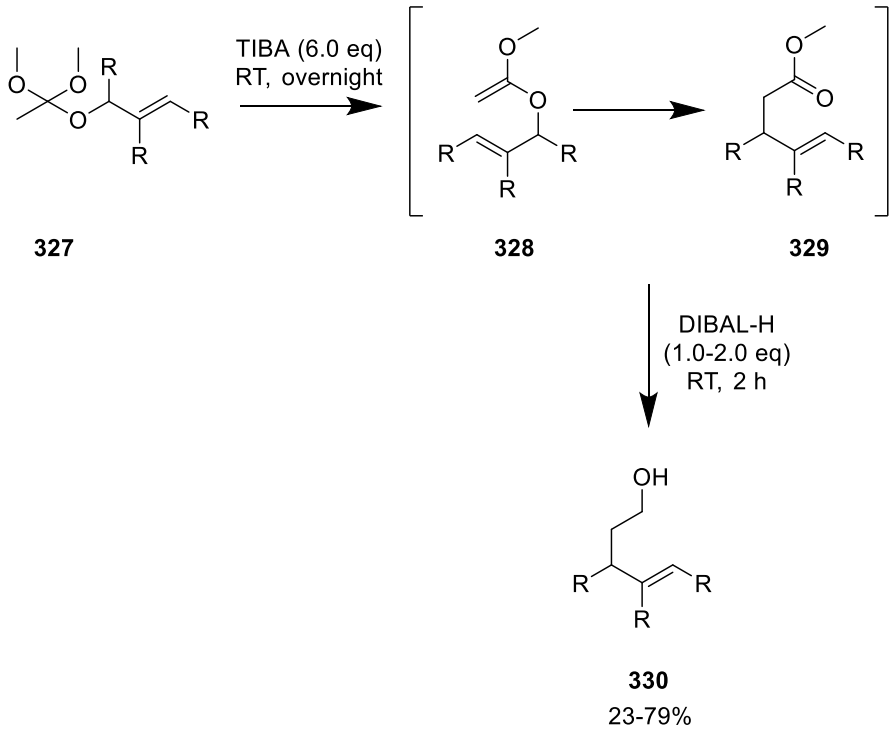
Mukaiyama *et al*., theorised that the palladium complex facilitated the elimination of the ethanol/methanol and the [3,3]-sigmatropic rearrangement. The rearrangement was shown to be assisted by palladium by rearranging a ketene acetal intermediate, 3-phenyl-2-propenyl vinyl ether (**325**), with and without $[PdCl_2(PPh_3)_2]$ (Scheme 138). Using palladium resulted in a higher yield (72%) compared to undertaking the reaction without it (43%). Unfortunately, all these

results were only reported in a communication paper, without any experimental data to confirm successful synthesis and no follow up paper was ever published.



Scheme 138: Rearrangement of 325 with and without $[PdCl_2(PPh_3)_2]$

Another example of using mixed orthoesters as starting materials to the orthoester Johnson-Claisen rearrangement was described by McGeary and Cosgrove.[96] In this instance triisobutylaluminium (TIBA) was used to promote the rearrangement of a range of primary, secondary and tertiary allylic derived mixed orthoesters (Scheme 139). TIBA was already known in the literature to promote both the elimination of methanol to form ketene acetals[220] (**327**) and the Claisen rearrangement[221,222] but this was the first instance of its use in the orthoester Johnson-Claisen rearrangement. Although TIBA promoted the rearrangement it also led to the reduction of the esters (**329**) to alcohols (**330**) (Scheme 139). The authors also suggested that to fully reduce any trace ester DIBAL-H was required.



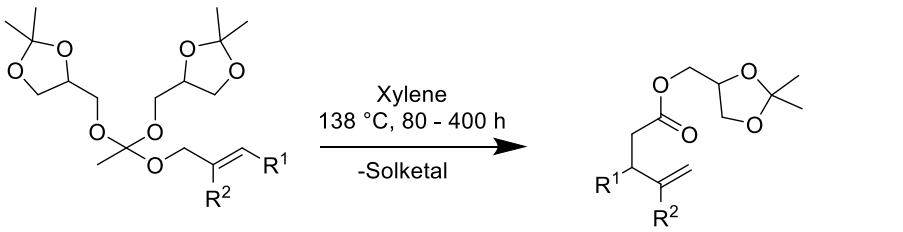
Scheme 139: TIBA promoted orthoester Johnson-Claisen rearrangement

The orthoester Johnson-Claisen rearrangement directly from mixed orthoesters described by Mukaiyama *et al*. and McGeary and Cosgrove highlight the potential for this rearrangement. However, there are many issues to be overcome if this rearrangement was to be used in the application of an *in situ* delivery system of friction modifiers for automotive lubricants. Firstly, TIBA and $[PdCl_2(PPh_3)_2]$ would not be present in the automotive lubricant, ideally this rearrangement would be catalysed thermally and/or by organic acidic components within the lubricant. Secondly, the TIBA method only required room temperature conditions, whilst the $[PdCl_2(PPh_3)_2]$ method was completed after 4 hours at 138 °C. As mentioned earlier, in order to keep friction lower for longer the formation of the ester (friction modifier) would need be much slower. Overall, both routes are unsuitable and need to be modified in order to produce a useful *in situ* delivery system.

4.2. Results and Discussion – The Direct Orthoester Johnson Claisen Rearrangement

4.2.1. Aliphatic Mixed (Di-substituted) Orthoesters

The rearrangement of the disolketal orthoesters (**297c and 298c**) was initially investigated (Scheme 140), since these orthoesters included the functionality to potentially deliver a friction modifier. The rearrangement was successful using heat alone and only produced the desired ester (**331a-b**). Furthermore, the long reaction times (80 – 400 h) made these orthoesters ideal for delivery systems. The differences in reaction times was attributed to the allylic substitution pattern; the orthoester (**298c**) with substitution at R^2 took 400 hours at 138 °C, while the orthoester (**297c**) with substitution at R^1 only took 80 hours at 138 °C. These rate differences will be discussed in more detail later in this chapter.



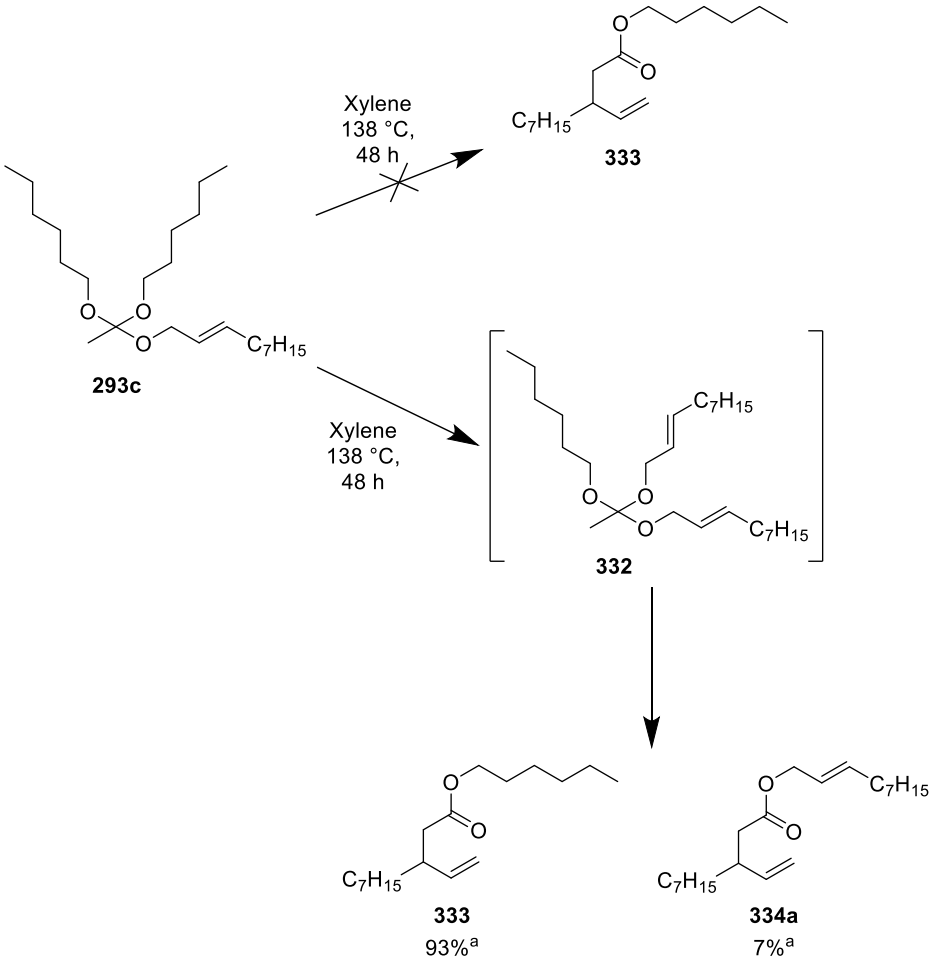
297c = $R^1 = C_7H_{15}$; R^2 = H
298c = R^1 = H; $R^2 = C_7H_{15}$

331a = $R^1 = C_7H_{15}$; R^2 = H (62%)
331b = R^1 = H; $R^2 = C_7H_{15}$ (71%)

Scheme 140: The direct orthoester Johnson-Claisen rearrangement of solketal orthoesters

The direct orthoester Johnson-Claisen of simple aliphatic chain orthoesters, such as the hexyl orthoester (**293c**) was found to be produce more than one product. Under the same reaction conditions as the solketal derivatives (**297c/298c**) the hexyl orthoester (**293c**) formed the desired ester (**333**) and a second ester which was determined to be the allylic ester (**334a**) (Scheme 141). The formation of the allylic ester (**334a**) suggested that the orthoester underwent a scrambling reaction, wherein substitution of the groups on the orthoester occurs to produce other orthoesters (**332**) (Scheme 141). This scrambling is required in the original orthoester Johnson-Claisen rearrangement in order to form the mixed orthoester precursor and acid is used to promote this. These results highlight that the

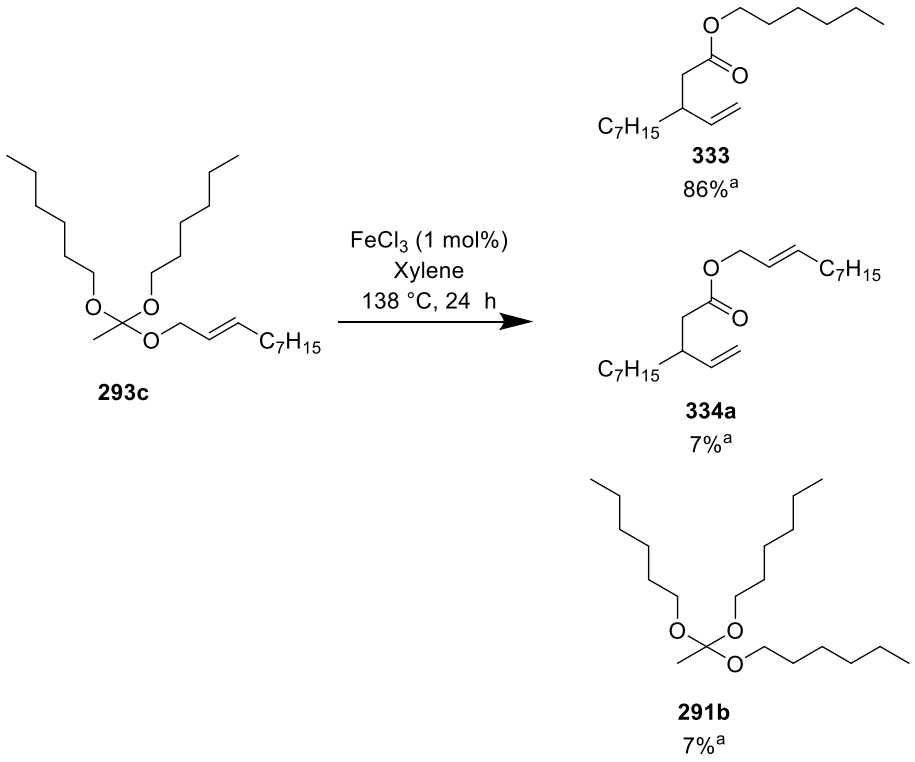
scrambling reactions can occur without acid, under elevated temperatures. Furthermore, this indicated that the orthoester Johnson-Claisen rearrangement involves competing substitution (scrambling of the orthoester) and elimination (formation of the ketene acetal and thus ester) reactions. Unfortunately, the formation of the desired ester (**333**) could not be separated from the allylic ester (**334a**) by column chromatography or distillation. These results were also mirrored for the other simple aliphatic orthoesters (**293-294**), including those with the different allylic substitution pattern.



Scheme 141: The direct orthoester Johnson-Claisen of orthoester (293c); [a] yields are based on normalised integrals by ^{1}H NMR spectroscopy

To further investigate the effect of scrambling on the direct orthoester Johnson-Claisen rearrangement the use of 1 mol% of acid (propionic acid, $FeCl_3$ and $ZnCl_2$) was studied. Acid catalysis resulted in the formation of trihexyl orthoester (**293c**), as well as the desired ester (**333**) and allylic ester (**334a**) (Scheme 142). This confirms that scrambling also occurs in the presence of acid and leads to the

formation of orthoesters which cannot undergo the rearrangement. Surprisingly though the amount of allylic ester (**334a**) produced was comparable to when no acid was used. The use of acid was also found to increase the rate of the reaction; with catalysis the reaction required 24 hours to go to completion compared to 48 hours when no acid is used.

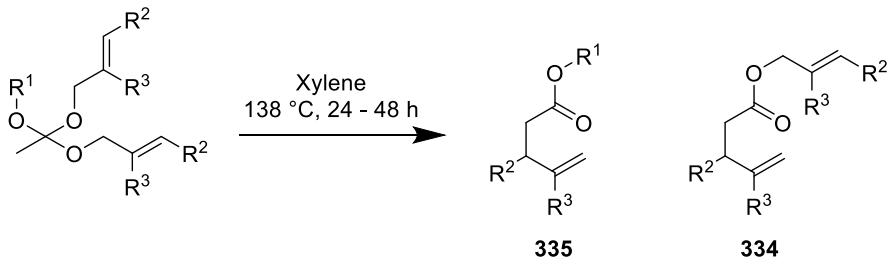


Scheme 142: The products produced from the acid catalysed orthoester Johnson-Claisen rearrangement; [a] yields are based on normalised integrals by ^{1}H NMR spectroscopy

4.2.2. Allylic Mixed (Di-substituted) Orthoesters

The rearrangement of a range of di-allylic orthoesters (**83/90**) was investigated (Table 5). Unsurprisingly, both the aliphatic ester (**335**) and allylic ester (**334**) were produced. This further supports the theory that scrambling during both the original and direct orthoester Johnson-Claisen rearrangement, forming di-allylic (**83/90**) orthoesters, results in the formation of the allylic ester (**334**).

Table 5: The impact of substituents around the orthoester on the rearrangement products; [a] yields are based on normalised integrals by ^{1}H NMR spectroscopy



335 334

Orthoester	R^1	R^2	R^3	335 Yield (%)[a]	334 Yield (%)[a]
83c	Et	C_7H_{15}	H	45	55
83e	Et	H	C_7H_{15}	67	33
90a	Bu	C_7H_{15}	H	42	58
90b	Bu	H	C_7H_{15}	93	7

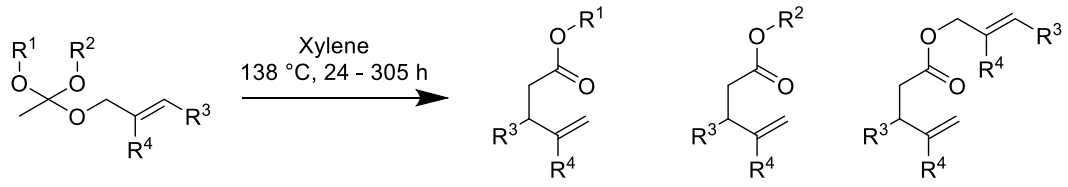
The functionality attached to the orthoester was found to have an impact on the selectivity of the rearrangement (Table 5). When R_1 was an ethyl group (**83c,e**, Table 5, line 1 and 2) the substitution pattern of the allylic group had an impact on the ratio of ester products. For example, substitution at R_3 of the alkene (**83e**, Table 5, line 2) caused an increase in the amount of aliphatic ester formed. The same effect was observed when R_1 was butyl (**90a,b**, Table 5, line 3 and 4), but the trend was more pronounced. The chain length difference of R_1 had little effect when the ester had substitution at R_2 (**83c, 90a** , Table 5, line 1 and 3). However, when there was substitution at R_3 of the alkene (**83e, 90b**, Table 5, line 2 and 4) there was a large increase of the aliphatic ester with the longer butyl chain length. Overall, these studies highlight that leaving group propensity and steric hindrance impacts the selectivity of the reaction. For example, steric hindrance could drive the formation of the aliphatic ester (**335**) when the allylic fragment has the external double bond (**90a,b**). Despite this, it is important to note that the synthesis of these orthoesters, described in chapter 3, required the use of AuCl. Although every attempt was made to remove the AuCl, there is the potential of residual AuCl remaining, which could promote scrambling of the orthoester during

the rearrangement, as well as also potentially catalysing transesterification reactions.

4.2.3. Aliphatic Mixed (Tri-substituted) Orthoesters

The direct orthoester Johnson-Claisen rearrangement of mixed (tri-substituted) orthoesters was investigated. Unsurprisingly, a mixture of esters was produced for all the mixed (tri-substituted) orthoesters (Table 6). To confirm that this was due to the selectivity of the rearrangement not due to transesterification reactions, the final products (for the ethyl and *n*-hexyl derivatives) were isolated and heated separately in the presence of the other alcohol. In both cases no transesterification was observed. The allylic ester (**334**) was also observed in most cases, although it was more likely to be produced when the linear allylic orthoesters (**293c, 295b**) were used. When using a good leaving group, such as 4-methoxphenol, the rearrangement was still not fully selective, producing the desired esters in 94-96% selectivity. Unsurprisingly, the use of a good leaving group increased the rate of the rearrangement. For example, the solketal/4-methoxyphenol derivative (**313**) underwent complete rearrangement within 24 hours, while the solketal/Et derivative (**298b**) took 305 hours.

Table 6: The direct orthoester Johnson-Claisen rearrangement of tri-substituted orthoesters; [a] yields are based on normalised integrals by ^{1}H NMR spectroscopy; [b] could not be determined by ^{1}H NMR spectroscopy due to overlap; [c] isolated yields



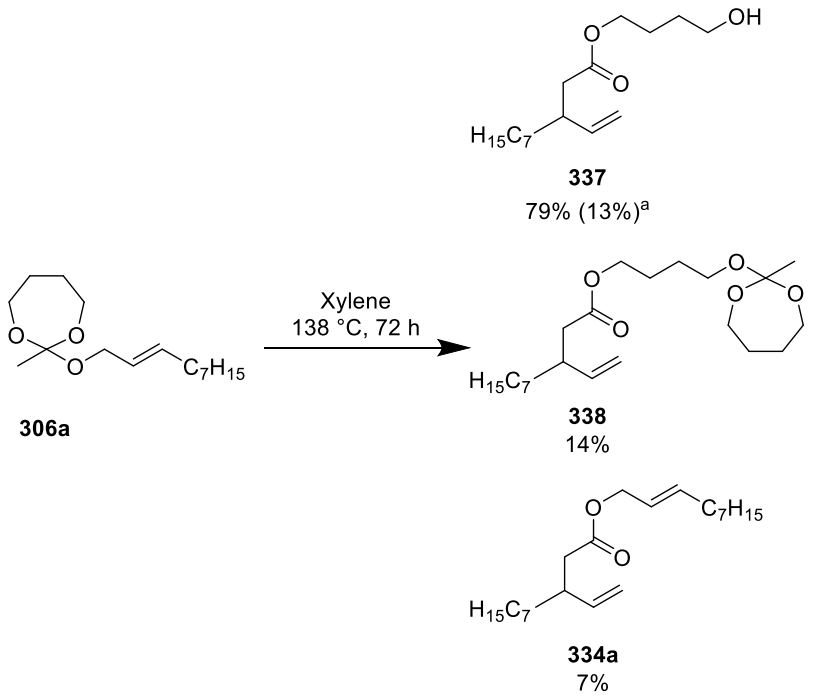
335 **336** **334**

Orthoester	Time (h)	R^1	R^2	R^3	R^4	335 Yield (%)[a]	336 Yield (%)[a]	334 Yield (%)[a]
293c	24	Et	*n*-Hexyl	C_7H_{15}	H	6	74	20
294c	24	Et	*n*-Hexyl	H	C_7H_{15}	21	86	-
295b	24	Et	Cyclohexyl	C_7H_{15}	H	8	85	7
296b	24	Et	Cyclohexyl	H	C_7H_{15}	7	93	-
298b	305	Et	Solketal	H	C_7H_{15}	-[b]	-[b]	-[b]
314	30	FM[2]	Solketal	H	C_7H_{15}	23 (20)[c]	66 (41)[c]	11
313	24	C_6H_4OMe	Solketal	H	C_7H_{15}	4	96 (79)[c]	-
299	24	C_6H_4OMe	$(CH_2)_4OCH_2OMe$	C_7H_{15}	H	6	94 (79)[c]	Trace

4.2.4. Cyclic Orthoesters

The orthoester Johnson-Claisen rearrangement of cyclic orthoesters was also investigated and were found to be significantly more challenging than the aliphatic variants. Only one of the orthoesters (**306a**) underwent the rearrangement (Scheme 143) but also produced another side product. The side product was determined to be orthoester (**338**), which was believed to be a result of the newly

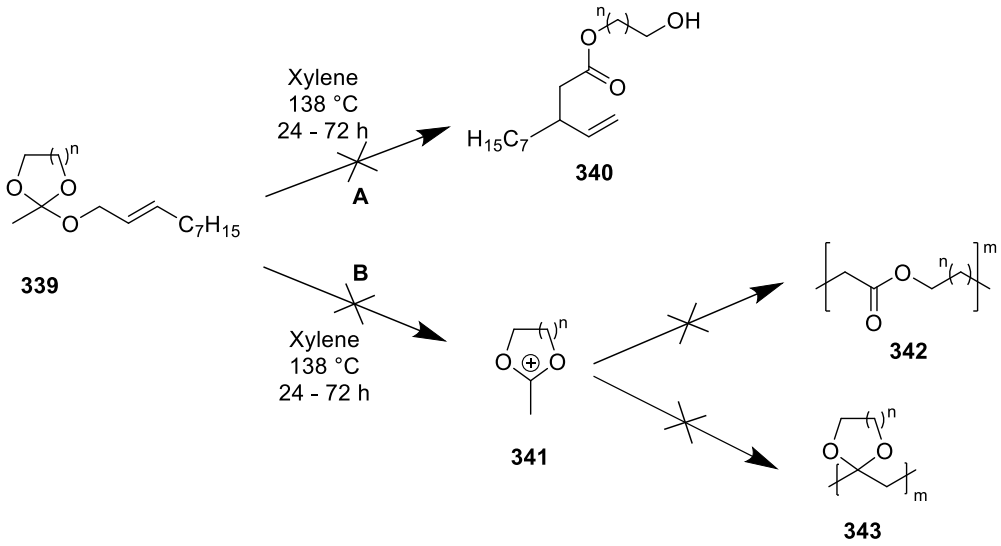
formed ester product (**337**) partaking in the scrambling of the unreacted orthoester (**306a**). Further to this, the allylic ester (**334a**) was also observed, further suggesting that scrambling reactions occur. In comparison to the aliphatic variants, the side product orthoester (**338**) and allylic ester (**334a**) were easily removed by column chromatography. The direct orthoester Johnson-Claisen rearrangement of cyclic orthoesters further highlighted that the formation of the ketene acetal intermediate and thus the effect of the competing substitution/elimination reactions had a large impact on the products of the rearrangement.



Scheme 143: Orthoester Johnson-Claisen rearrangement of cyclic orthoesters; yields are based on normalised integrals by ^{1}H NMR spectroscopy; [a] isolated yield

The direct orthoester Johnson-Claisen rearrangement of a range of 5-membered and substituted 7-membered cyclic orthoesters was also investigated. Unfortunately, these rearrangements proved challenging. In most cases, a small amount of rearrangement ester was observed, which could not be isolated by column chromatography. Furthermore, the formation of a significantly larger alkyl region in the ^{1}H-NMR spectrum was observed. Initially, it was thought this side product could be due to cationic polymerisation of the acetal (**341**) (Scheme 144).[111] However, there was little evidence of the characteristic peaks of these polymers, such as the acetate protons (-**CH$_2$**-CO) (**342**) or the acetal protons (-**CH$_2$**-

C(O(CH$_2$)$_n$O)-) (**343**), although the nature of the ^{1}H-NMR caused problems when attempting to determine the products synthesised. Further work is still required to determine the products of these rearrangements, specifically the large alkyl region, and the differences between the behaviour of the 7-membered cyclic orthoester (**306a**) and the other cyclic orthoesters.



Scheme 144: The potential pathways of cyclic orthoesters at 138 °C. When subjected to rearrangement conditions most cyclic orthoesters did not undergo the rearrangement (pathway a) and the theorised cationic polymerisation (pathway b) was also not observed.

Attempts were made to try to promote the direct orthoester Johnson-Claisen rearrangement of cyclic orthoesters using acid catalysis. Both substituted 5- and 7-membered cyclic orthoesters were exposed to acid under the rearrangement conditions. Unfortunately the use of 1 mol% of a range of Bronsted and Lewis acids ($FeCl_3$, propionic acid, $Sc(OTf)_3$) resulted in the scrambling of the orthoester, indicated by the formation of an additional methyl peak in the ^{1}H-NMR, as well as some degradation of the orthoester. When $FeCl_3$ and propionic acid were used the degradation occurred through the hydrolysis pathway resulting in acetate esters and alcohols. When $Sc(OTf)_3$ was used the degradation resulted in a complex mixture of products which could not be identified.

4.2.5. Quantitative Rate Studies

4.2.5.1. Review of the Rate Studies of [3,3]-Sigmatropic Rearrangements

The factors affecting the rates of the Claisen rearrangement have been studied intensively over the past century.[48–52,213,215–217,223–245] However, there is still disagreement in the community regarding the transition state and mechanism, which would help to rationalise the substituent effects observed. Most substituents can be used to stabilise each of the potential transition states, which led to a variety of interpretations of the transition state. Four reaction mechanisms have been described over the years.[246] The first mechanism was described as a synchronous concerted reaction, wherein the transition state is aromatic in nature (blue line, Figure 11). DFT and deuterium secondary kinetic isotope effect calculations were used to determine this transition state and were found to have good agreement with experimental results.[247–249] The second mechanism was an asynchronous stepwise reaction utilising a bis-allyl transition state (black line, Figure 11). This mechanism suggested that the C^4-O^3 bond breaks first. Bonding evolution theory and DFT calculations determined the C^4-O^3 bond to be completely broken before bond formation took place.[250] Additionally, deuterium kinetic isotope effect calculations for 2-Me_3SiO substitution (the Ireland-Claisen rearrangement) found that bond breaking was more prevalent and thus described the bis-allyl transition state.[251] The third mechanism was an asynchronous stepwise reaction through a 1,4-diyl transition state (grey line, Figure 11). This mechanism suggested that the C^1-C^6 bond forms first. MNDO/MINDO calculations were used as evidence to support this transition state. These calculations and subsequent transition state were used to predict rate enhancements of certain substituents, for example a cyano group at position C2, which were proven through experimental results.[252]

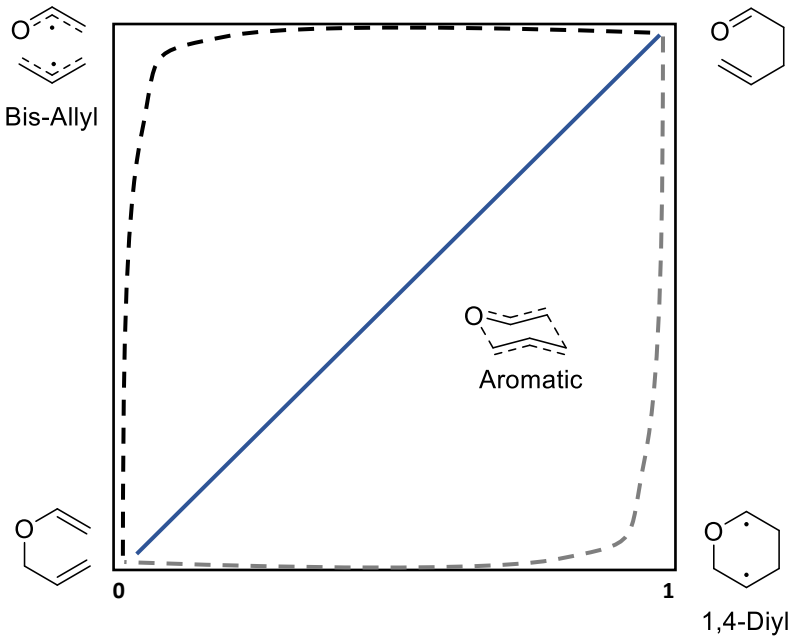
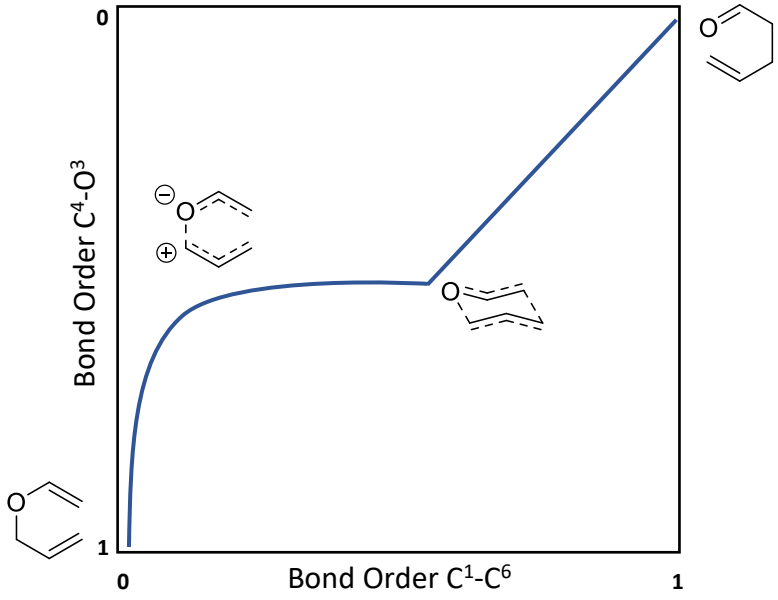


Figure 11: Three proposed mechanisms of the Claisen rearrangement.[244] Image reproduced with the permission of the rights holder, CC BY-NC-SA 3.0.

The final mechanism, described in 2013 by Kobayashi *et al.*, described a three step pathway (Figure 12a), wherein the C^4-O^3 bond is initially weakened which generates a bis-allyl transition state.[244,253] The C^1-C^6 bond is then weakly formed which results in the formation of an aromatic 6-membered intermediate. The C^4-O^3 bond breaking and C^1-C^6 formation then occur simultaneously. This mechanism was determined as a result of molecular vibration frequency changes and ultra-short pulse laser spectroscopy, wherein all of the transition state bonds can be accounted for (Figure 12b).

a)



b)

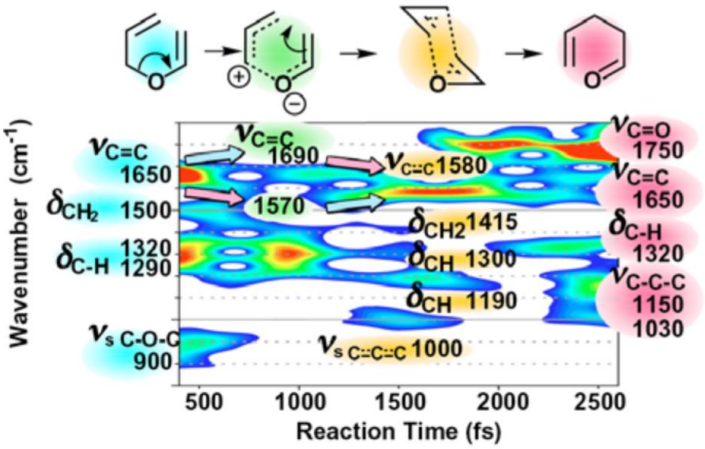
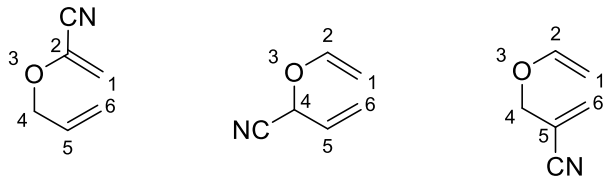
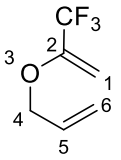


Figure 12: a) A more recent postulation of the mechanism of the Claisen rearrangement; b) A Claisen rearrangement induced by 5 fs pulses of visible wavelength light as described by Kobayashi *et al.*[244] Images reproduced with the permission of the rights holder, CC BY-NC-SA 3.0.

A range of substituents and models were investigated when examining the rates of the Claisen rearrangement. For example, Carpenter investigated the effect of cyano groups.[213] They observed that cyano groups present at C2, C4 and C5 resulted in a rate acceleration (Figure 13), whilst cyano groups at C1 and C6 resulted in a rate deceleration. The results were rationalised using Hückel molecular orbital theory (HMO) resulting in a model which allowed for evaluation of the transition state and the reactant(s).[214] Unfortunately, there was a significant downside to this model; cyano groups can also behave as radical stabilising groups, so the acceleration at C2 and C4 could be due to this radical stabilising behaviour rather than the electron-withdrawing nature. In order to investigate whether these results were due to radical stabilising behaviour or electron-withdrawing character, a trifluoro group at C2 and C4 was investigated, since trifluoro groups cannot stabilise radicals. Gajewski *et al*., found that acceleration at C2 is still observed for trifluoro groups, however the acceleration at C4 is no longer observed.[215] This is suggestive that the C4 acceleration observed for a cyano group is due to radical stabilisation.



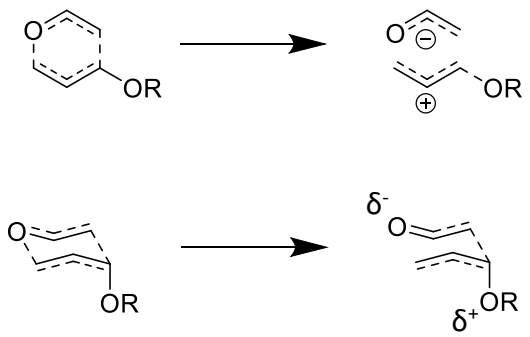
344a **344b** **344c**



344d

Figure 13: Cyano and trifluroro group positioning which produced a rate acceleration of the Claisen rearrangement

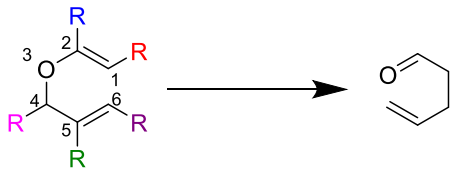
Further models of the kinetics of the Claisen rearrangement, included work by Curran which contradicts findings by Carpenter. Curran investigated the effects of alkoxy groups, and highlighted a large acceleration at C6[230,254], even though Carpenter suggested there should be a deceleration due to the electron-donating character[213]. Curran's model was rationalised by a "vinylogous anomeric effect" which resulted in a π → σ* stabilisation. The model suggests that the process goes through an early transition state in which bond breaking is more advanced than bond making (Scheme 145). Therefore, an alkoxy group at the C6 position will stabilise this transition state and cause a rate acceleration.



Scheme 145: The "vinylogous anomeric effect" which explains the C6 alkoxy acceleration

The general effects of specific substituents around the ether core have been summarised (Table 7).[246,255]

Table 7: The effects of substituent groups on the Claisen rearrangement collated by Castro[46]



	Position	Electron Donating	Electron Withdrawing
Acceleration	1	-O, $-NH_2$, -F, $-CH_3$	
	2	$-OSi(CH_3)_3$, - CH_3, $-CH^-$ SO_2Ph, - F	-CN, $-CO_2^-$, $-CO_2CH_3$, $-CF_3$
	4	$-CH_3$, $-OCH_3$	-CN
	5		-CN
	6	$-CH_3$, $-OCH_3$	
Deceleration	1		-CN, $-CO_2CF_3$
	5	$-CH_3$, $-OCH_3$	
	6		-CN

This review highlights that the rate of [3,3]-sigmatropic rearrangements can be significantly impacted by the substituents attached to the central ether core. This is detrimental to this research because the rate of the rearrangement should ideally be slow enough to only reach full conversion towards the end of an engine test, which is usually a week under extreme conditions. This would equate to a much longer reaction time in real-world conditions.

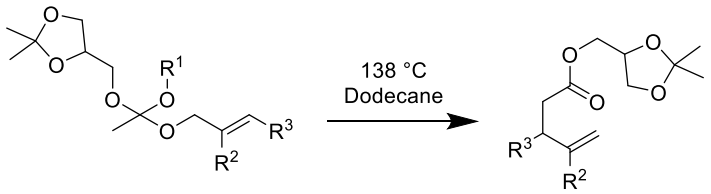
4.2.5.2. Results and Discussion

Before the rate studies were conducted, the effect of concentration on the rearrangement directly from the orthoester was investigated. The concentration was found to heavily impact the rate of the formation of the ester; most likely impacting the formation of the ketene acetal prior to the sigmatropic rearrangement. This concentration effect caused issues when investigating the rates of the rearrangement for the application of a delivery system for friction modifiers. Friction modifiers are dosed in the final lubricant oil packages at <5 wt%, which makes them very dilute and thus should result in a slow rearrangement. However, when a system is that dilute it can be difficult to sample and monitor the rate. Attempts to monitor the reaction by GC-MS and HPLC were unsuccessful due to degradation of the orthoester. ^{1}H NMR could be used to monitor the reaction, but the concentration had to be increased to allow for a good signal to noise ratio on the baseline. Therefore, any rates determined from the quantitative studies would be significantly faster than when the rearrangement occurs in the real-world application.

The rate studies were undertaken at a concentration of 0.0024 mol/L (50 wt%) in dodecane since this allowed easy interpretation by ^{1}H NMR and the dodecane mimicked an oil-like environment. The studies were all undertaken in an inert atmosphere to limit the influence of moisture on the rate. To better replicate real world conditions, the rate of the rearrangement when exposed to air should also be measured. Bis(trimethylsilylamine) (HMDS) was used as an internal standard for the NMR studies. The candidates chosen for the rate studies all had the potential to form an ester capable of behaving as a lubricant additive. Unfortunately, the quantitative rate studies proved challenging. Following the reaction by wt% did not correlate with the normalised integrals. Therefore, although reaction rates could be determined from this method, which matched the rates observed qualitatively, the reliability and accuracy is questionable. The rate data is shown in Table 8. Firstly, the position of the substitution of the alkene impacted the rate. When there was substitution at position R^3 (**297c**) of the alkene the rate was significantly faster than when there was substitution at position R^2

(**298c**). These results also match the literature.[46] Secondly, the group (R^1) lost from the orthoester to form the ketene acetal also impacted the rate. When R^1 was a better leaving group, such as 4-methoxphenol (**313**), the rate of the reaction was significantly faster. Although, the leaving propensity of R^1 obviously effects the rate of the formation of the ketene acetal (**284**), the substitution pattern on the alkene could have an impact on both the formation of the ketene acetal (**284**) and the rearrangement to the ester (**331**). Therefore, in order to further understand the rate of the direct orthoester Johnson-Claisen rearrangement, quantitative rate studies of the rearrangement from the isolated ketene acetal (**284**) is required. The rates of the formation of the ketene acetal (**284**) would also be beneficial, as this would allow investigation into the conditions which impact the competing elimination and substitution reactions of the orthoester. However, attempts to isolate the ketene acetal (**284**) directly from the orthoester have been unsuccessful, and the ketene acetal (**284**) was not observed during the rearrangement.

Table 8: The reaction rates of the direct orthoester Johnson-Claisen rearrangement of a range of solketal orthoesters calculated by integrations relative to an internal standard of HMDS by ^{1}H NMR spectroscopy; all reactions were undertaken at 0.0024 mol/L in dodecane at 138 °C; [a] rate of reaction is measured in moles/litre/hour



331

Orthoester	R^1	R^2	R^3	Rate of Reaction (M/h)[a]
297c	Solketal	H	C_7H_{15}	0.00889
298c	Solketal	C_7H_{15}	H	0.00059
313	4-Methoxyphenol	C_7H_{15}	H	0.228
314	FM^2	C_7H_{15}	H	0.00184

The rate studies undertaken also produced plots of the normalised integrals (Figure 14-16), by ^{1}H NMR spectroscopy, of the orthoester and ester vs time. Unfortunately for orthoester (**313**) the reaction occurred too quickly to produce a plot.

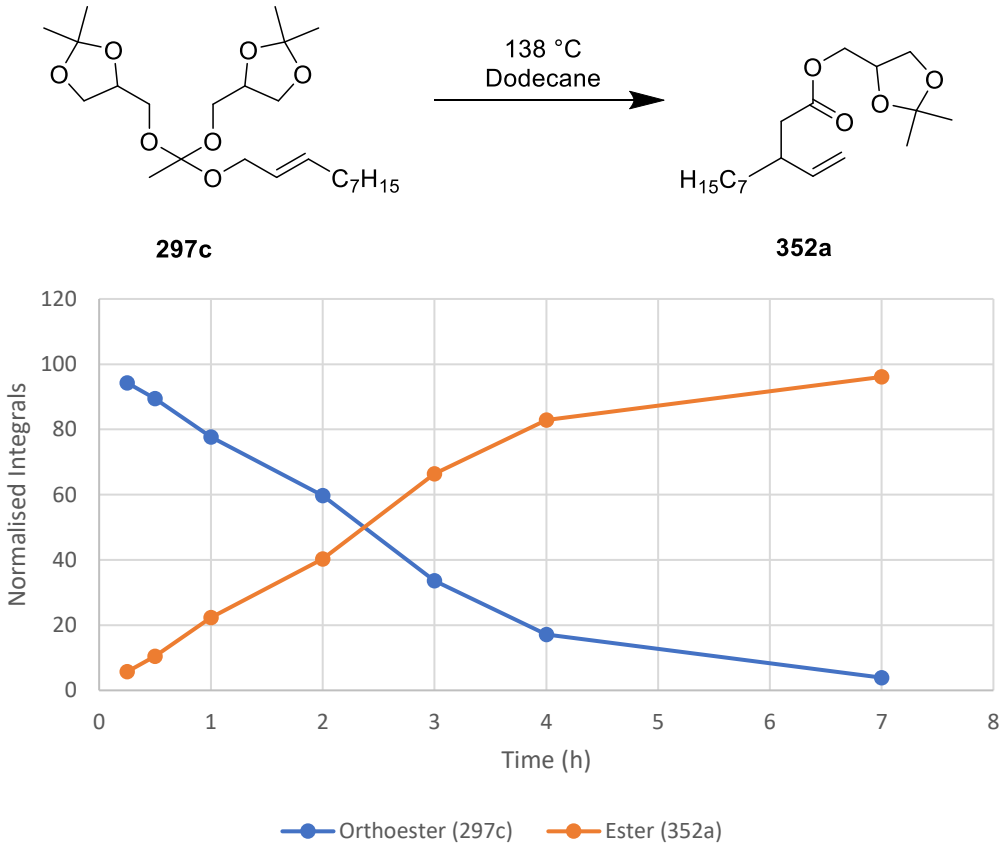


Figure 14: A graph showing the normalised integrals of orthoester (297c) and ester (352a) vs time by ^{1}H NMR spectroscopy; all reactions were undertaken at 0.0024 mol/L in dodecane at 138 °C

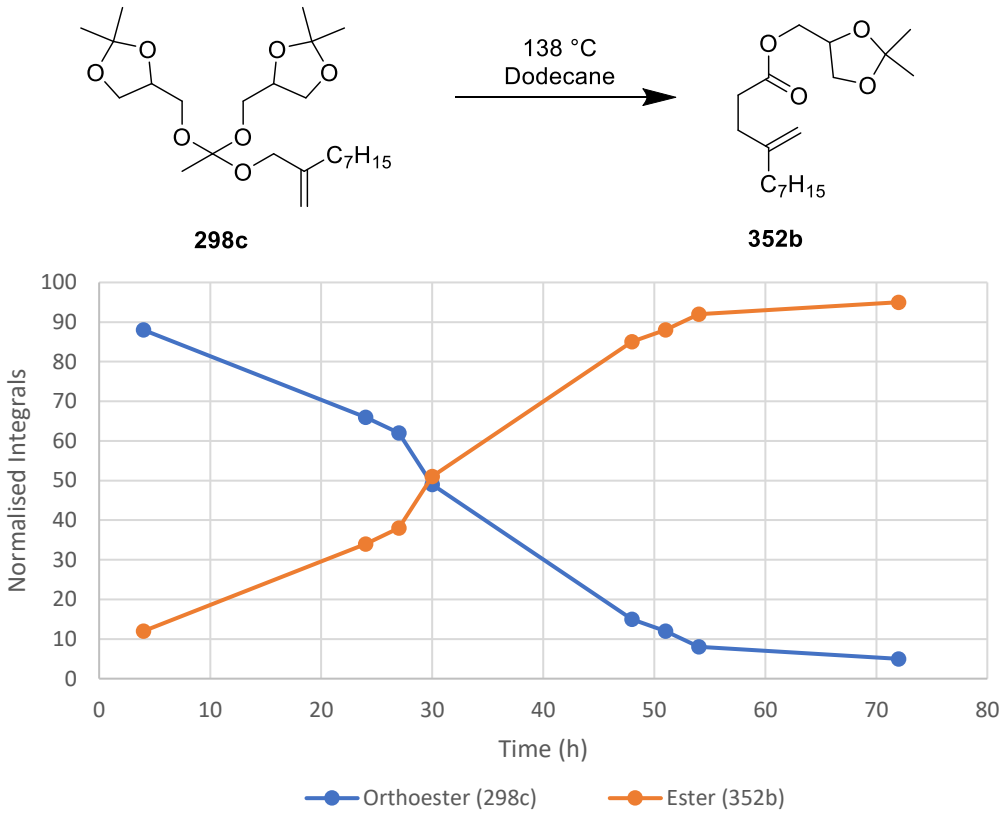


Figure 15: A graph showing the normalised integrals of orthoester (298c) and ester (352b) vs time by ^{1}H NMR spectroscopy; all reactions were undertaken at 0.0024 mol/L in dodecane at 138 °C

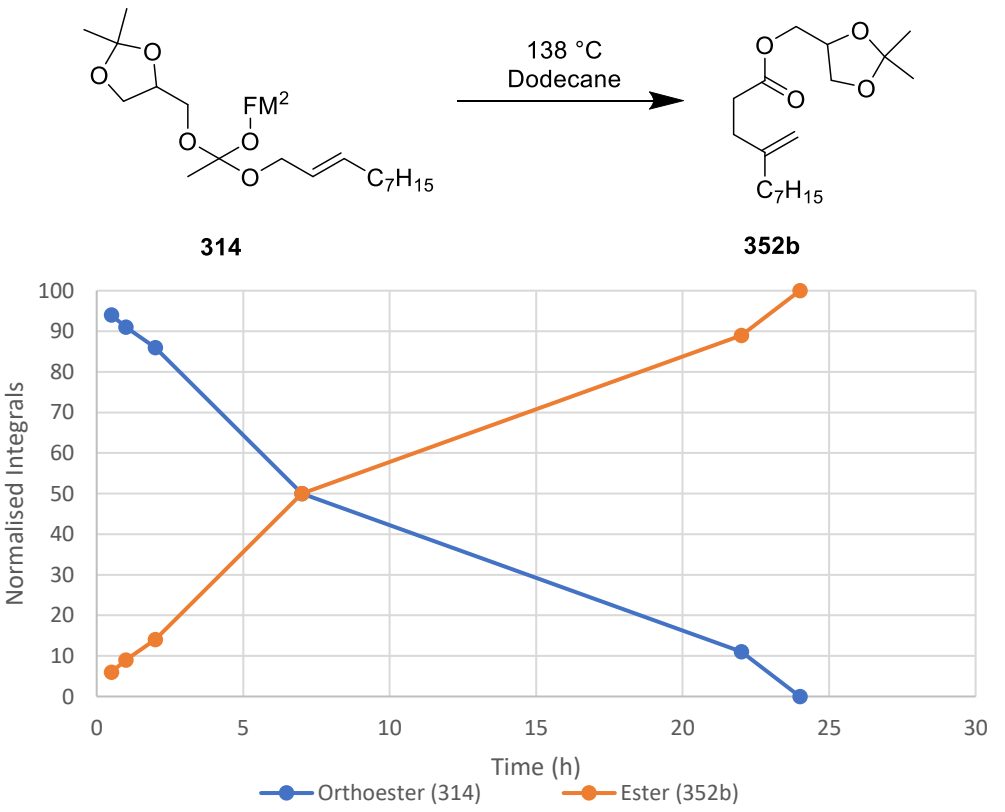
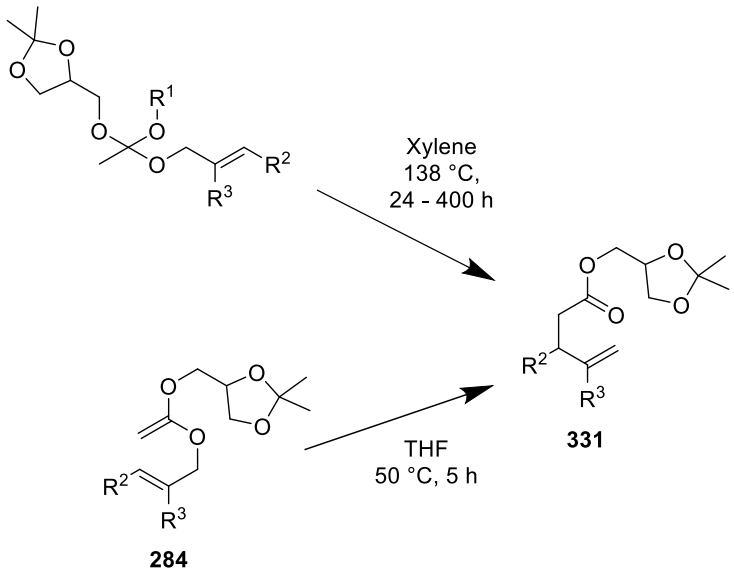


Figure 16: A graph showing the normalised integrals of orthoester (314) and ester (352b) vs time by ^{1}H NMR spectroscopy; all reactions were undertaken at 0.0024 mol/L in dodecane at 138 °C

Work was undertaken to determine the rate limiting step of the direct orthoester Johnson-Claisen rearrangement. The solketal ketene acetal (**284e**) was synthesised and subjected to the conditions of the rearrangement. 100% conversion to the ester (**331b**) was observed within 5 hours at only 50 °C. The reaction was monitored by the reduction of the ketene acetal peak (~1646 cm^{-1}) observed by IR. The ketene acetal rearrangement was found to be significantly faster, even at a lower temperature, compared to all the orthoester rearrangements which incorporated a solketal group (Table 9); 5 hours at 50 °C compared to 24 – 400 hours at 138 °C. These results suggest that the rate limiting step is the formation of the ketene acetal.

The hypothesis of the formation of the ketene acetal being the rate limiting step can be further supported by the fact that the R^1 group on the solketal orthoesters also impacted the rate of the overall rearrangement, indicated by a difference in reaction length (Table 9). It can be hypothesised that the R^1 groups have different leaving propensities and therefore impact the competing elimination and substitution reactions of the orthoester. For example, when R^1 is solketal (Table 9, line 2 and 3) substitution is favoured, leading to scrambling of the orthoester rather than formation of the ketene acetal. But, when R^1 is 4-methoxyphenol (Table 9, line 5), a better leaving group, elimination is favoured and the ketene acetal readily forms, highlighted by short reaction times. The substitution pattern of the allylic alcohol, on the other hand, had an impact on the rate of the overall rearrangement; substitution at R^2 of the alkene (Table 9, line 2) was significantly slower compared to substitution at R^3 of the alkene (Table 9, line 3). It is unsure whether the allylic substitution just affects the [3,3]-rearrangement or both the ketene acetal formation and the [3,3]-rearrangement. It is known that the differences in the allylic substitution pattern affects the rate of the [3,3]-rearrangement.[46] But, the observation of the allylic ester throughout many of these rearrangements also suggests that the allylic alcohol partakes in a substitution reaction (scrambling) and thus may impact the ketene acetal formation. Further work in this area, specifically quantitative rate studies of the ketene acetal rearrangement, is required to fully support this hypothesis.

Table 9: The comparison of the orthoester Johnson-Claisen rearrangement from orthoesters and ketene acetals; [a] calculated by normalised integrals by ^{1}H NMR spectroscopy; [b] 50 °C, 5 h



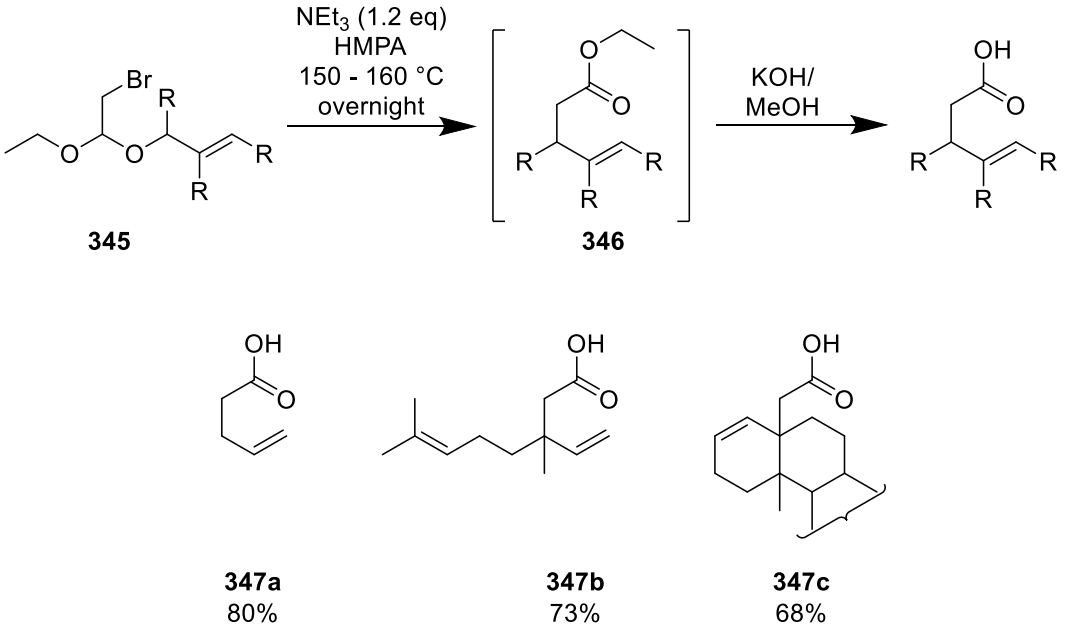
Orthoester	Ketene Acetal	R^1	R^2	R^3	Time (h)	Conversion (%)[a]
-	**284e**	-	H	C_7H_{15}	5[b]	100
297b	-	Et	H	C_7H_{15}	305	100
297c	-	Solketal	H	C_7H_{15}	400	100
298c	-	Solketal	C_7H_{15}	H	80	100
314	-	FM[2]	H	C_7H_{15}	30	100
313	-	*p*-$OMeC_6H_5$	H	C_7H_{15}	24	100

4.3. Base mediated Claisen Rearrangement

As an alternative to the direct orthoester Johnson-Claisen rearrangement, the base mediated equivalent was investigated. This involved an elimination-rearrangement of haloacetals. Utilising haloacetals over orthoesters would allow for a reduction in the number of overall steps to the final ester. Furthermore, haloacetals are more stable than orthoesters; they can be stored without degradation for longer periods of time and can be easily purified. Both of these advantages would be beneficial for potential commercialisation for the application of a delivery system for friction modifiers.

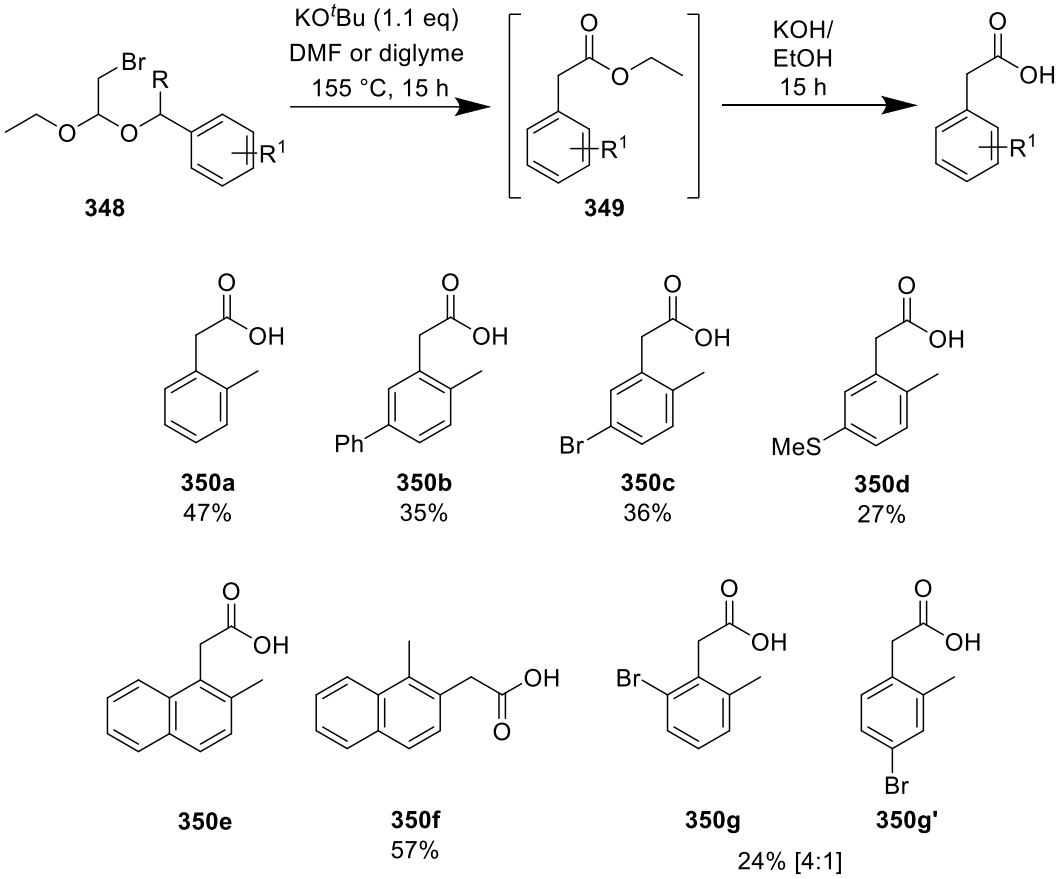
4.3.1. Review of the Base mediated Claisen

The base mediated orthoester Johnson-Claisen rearrangement is reported sparsely in the literature. The rearrangement from bromoacetals (**345**) was first described in 1986 by Lidbetter and Marples (Scheme 146).[256] However, they immediately hydrolysed the resulting esters (**346**) into carboxylic acids (**347a-c**) and therefore no characterisation data for the ester was produced.



Scheme 146: Base mediated Claisen rearrangement developed by Lidbetter and Marples[256]

A more recent example of the rearrangement was described by McGeary *et al.* in 2017.[257] They described the base-mediated rearrangement of benzyl bromoacetals (Scheme 147). However, as with Lidbetter and Marples, they immediately hydrolysed the resulting esters to carboxylic acids.

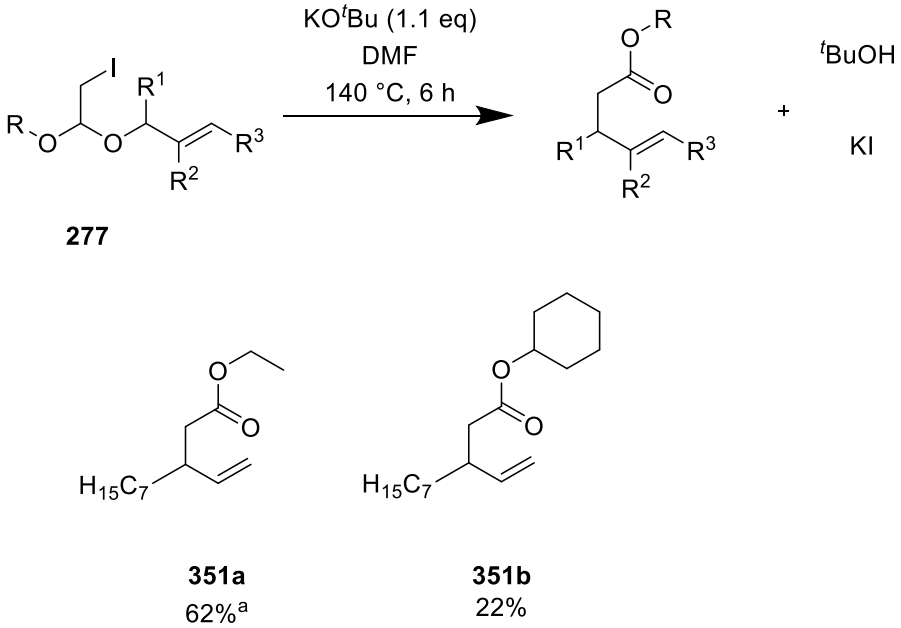


Scheme 147: Base mediated aryl Claisen described by McGeary *et al.*[257]

The isolation of the ester, rather than the subsequent reduction to the alcohol, was of great interest since this thesis investigated the delivery of lubricant additives, specifically esters which behave as friction modifiers. Therefore, attempts were made to undergo the base mediated Claisen rearrangement and isolate the ester.

4.3.2. Results and Discussion

Initial investigation involved applying the conditions developed by McGeary *et al*. however, using iodoacetals rather than bromoacetals due to the greater ease of the elimination. When utilising a simple iodoacetal (**277**) the reaction was found to undergo the elimination-rearrangement at 140 °C within 6 hours (Scheme 148). Despite successful isolation of the ester (**351a**), there were baseline impurities in the ^{1}H NMR which could not be removed by column chromatography. Nevertheless, secondary esters (**351b**) could also be tolerated by this approach (Scheme 148), without the baseline impurities present that were found in the primary ester, although the yield was poor at only 22%. Although initial results are promising, this work requires further optimisation to improve upon yields and purity, as well as investigation into the substrate scope.



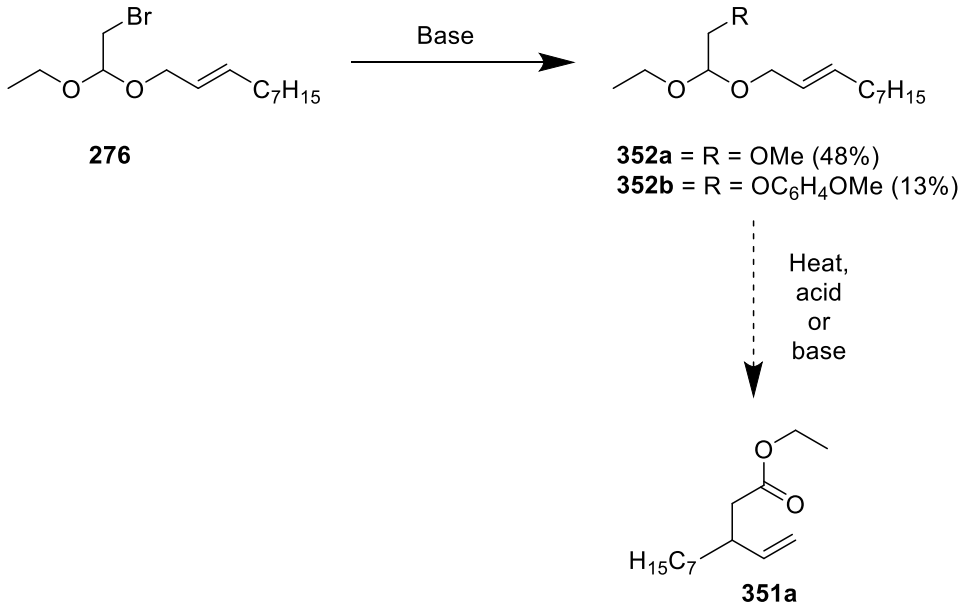
Scheme 148: Base mediated Claisen of iodoacetals; [a] Baseline impurities by ^{1}H NMR

The base mediated Claisen rearrangement, to isolate both esters and alcohols, has the potential to be a useful rearrangement within synthetic organic chemistry. It has advantages over both the original orthoester Johnson-Claisen rearrangement and the direct orthoester Johnson-Claisen rearrangement developed in this thesis. Firstly, the base mediated Claisen does not require large excesses of reagents, compared to the original orthoester Johnson-Claisen which often uses 3-7 equivalents of the trialkyl orthoester. Furthermore, the use of haloacetals instead

of orthoesters produces “cleaner” rearrangements as the haloacetals cannot undergo scrambling. Finally, the rate of the rearrangement also has the potential to be controlled by the halogen used, for example using iodoacetals should lead to a rate increase compared to the use of chloroacetals.

The application of the base mediated Claisen is limited for the development of a delivery system for lubricant additives. This is for two reasons; the first is that lubricant oils would not be basic enough to facilitate the elimination, in fact lubricant oils become more acidic over time. The second reason is that the presence of halogens within lubricant oils is restricted due to their human health and environmental impact. Therefore, a more useful approach for this application would be to use non-halogenated acetals.

Preliminary work was undertaken on the rearrangement directly from non-halogenated acetals. A small range of acetals with different leaving groups (**352a-b**) were synthesised (Scheme 149). However, attempts to undergo the rearrangement was unsuccessful. Heat proved to be ineffective on its own, with the acetals remaining unconverted, by ^{1}H NMR spectroscopy, after 24 h at 138 °C. Further investigation is now required into both acid and base catalysis of the rearrangement.



276

352a = R = OMe (48%)
352b = R = OC_6H_4OMe (13%)

351a

Scheme 149: The formation of a range of acetals and the desired rearrangement

4.4. Conclusion

In conclusion, the orthoester Johnson-Claisen rearrangement can be modified by undertaking the rearrangement directly from a haloacetal, ketene acetal or orthoester. This chapter has highlighted that scrambling of the orthoester during the rearrangement can lead to the formation of side products. Furthermore, the leaving group propensity of the groups around the orthoester can impact the selectivity and rate of the rearrangement. Understanding the scrambling of the orthoester and the conditions that impact it will allow for greater development of the direct orthoester Johnson-Claisen rearrangement. Additionally, with further investigation to improve upon yield and purity, the base-mediated Claisen rearrangement could be a welcome addition to the [3,3]-sigmatropic rearrangement toolbox.

5.0. Applications to Lubricant Additives

This chapter will highlight how orthoesters are a valuable tool in overcoming issues in the lubricant additive industry. The use of orthoesters which can transform into friction modifiers will first be discussed. Additionally, the use of orthoesters as solubilising agents and delivery systems, to improve the solubility and durability of friction modifiers in lubricant oil packages, will be described.

5.1. Use of Orthoesters as Delivery Systems for Lubricant Additives

The orthoesters were designed to firstly produce an ester which would provide a frictional benefit. Since the aims of this work were not to synthesise new friction modifiers but rather to develop a new delivery method, the head group functionality of commercially known friction modifiers, such as glycerol monooleate (GMO), was targeted (Figure 17). Unfortunately, the GMO head group was required to be protected in order to incorporate it into an orthoester, therefore the protected ester (**331**) was the target molecule of the rearrangement (Figure 17).

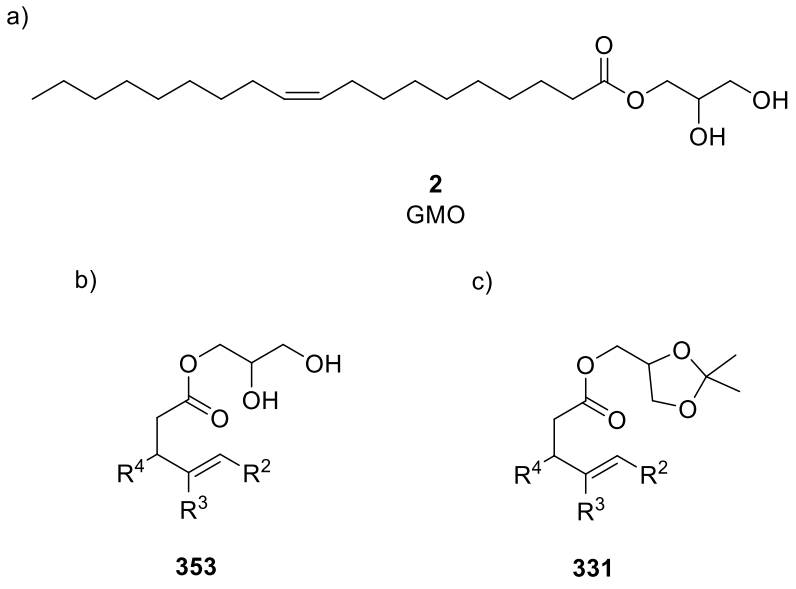
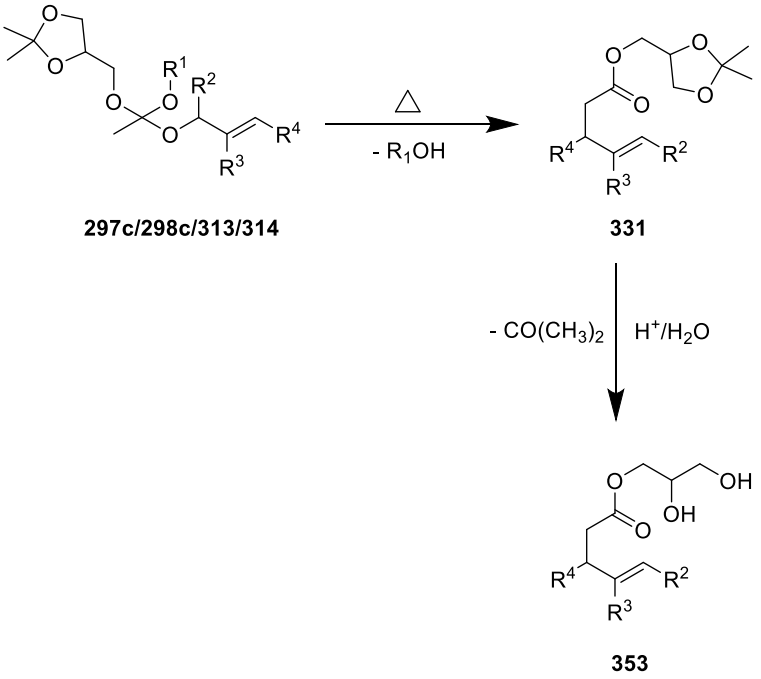


Figure 17: a) Glycerol monooleate; b) GMO ester target; c) Protected GMO target

The formation of the protected solketal ester (**331**) from the orthoester was a benefit to the application. This is because, in order to get through to the friction modifier (**353**), two *in situ* reactions need to occur (Scheme 150). Firstly, the

rearrangement must take place, which can be promoted by the heat of the engine (or transmission). Secondly, the acetal must be deprotected, which can be promoted by the increase in the acidity of the lubricant oil as it ages. Overall, these two steps should provide a long, controlled *in situ* release of the friction modifier.



Scheme 150: The proposed delivery system of a friction modifier

5.1.2. Lubricant Additive Performance Testing

5.1.2.1. High Frequency Reciprocating Rig (HFRR)

In order to provide proof of concept of the use of orthoesters as delivery systems for lubricant additives, specifically friction modifiers, friction performance data was needed to be collected. In the lubricant industry, bench tests are used to indicate the performance of a lubricant additive before more expensive and time-consuming testing, such as engine tests, are undertaken. A bench test for friction is the High Frequency Reciprocating Rig (HFRR) test (Figure 18). This test involves a polished steel ball and disc, which are put under load. The ball is then moved in a reciprocating motion across the stationary steel disc. The resulting wear scar and friction (coefficient of friction) can then be measured; the coefficient of friction is defined as a measure of the amount of resistance that a surface exerts on or

substances moving over it, which represents the friction between two surfaces. The HFRR can be run at different temperatures to help mimic the conditions of an engine. In order to test the friction performance of a lubricant oil, the steel surface is coated in the lubricant oil.

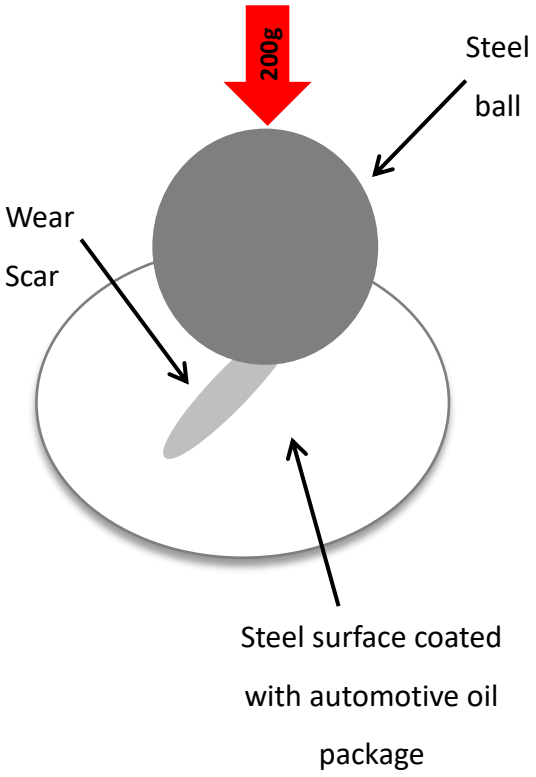


Figure 18: The HFRR friction bench test

Bench tests are important as low cost and quick methods to screen potential new lubricant additives. However, a single bench test cannot simulate all the conditions of an engine and using a variety of different bench tests add additional variables which can therefore make interpretation of the results difficult. Therefore, bench tests should only be used as an indication of their performance. In order to fully understand the performance of a lubricant additive it should be subjected to an engine test.

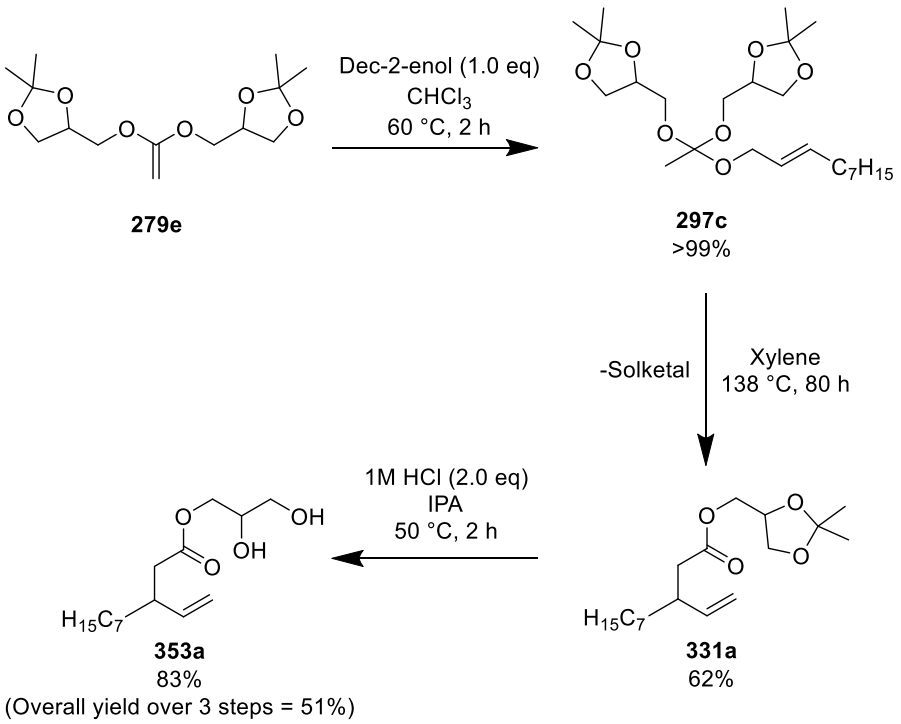
5.1.2.2. HFRR Test Protocol

Load	200 g
Duration	60 minutes
Frequency	20 Hz
Temperature	Isothermal at 120 °C
Metallurgy	Standard steel ball on hardened steel disc

For each of the new components tested, they were dosed into a fully formulated lubricant oil at 2 wt%. A fully formulated oil contains a range of other lubricant additives, such as detergents, dispersants, anti-wear agents and viscosity modifiers. The use of a fully formulated package replicates real-world conditions. A baseline sample, of the lubricant oil on its own, was used as a reference to compare the friction performance. This test was completed by John Durham and Megan Williams at Lubrizol Ltd. in Hazelwood. The HFRR test used was from an internal Lubrizol test method using the conditions above.

5.1.2.3. Disolketal Derivatives

Initial HFRR testing was undertaken to evaluate the friction performance of orthoester (**297c**), protected ester (**331a**) and deprotected ester (**353a**). This orthoester was chosen due to the ability to synthesise large quantities of the products quickly. Ideally, the orthoester (**297c**) and protected ester (**331a**) should have little to no friction performance, whereas the deprotected ester (**353a**) should have the greatest friction performance. The definition of good friction performance is to have a lower coefficient of friction compared to when no FM is present. All three of the components were isolated and tested separately (Figure 19).



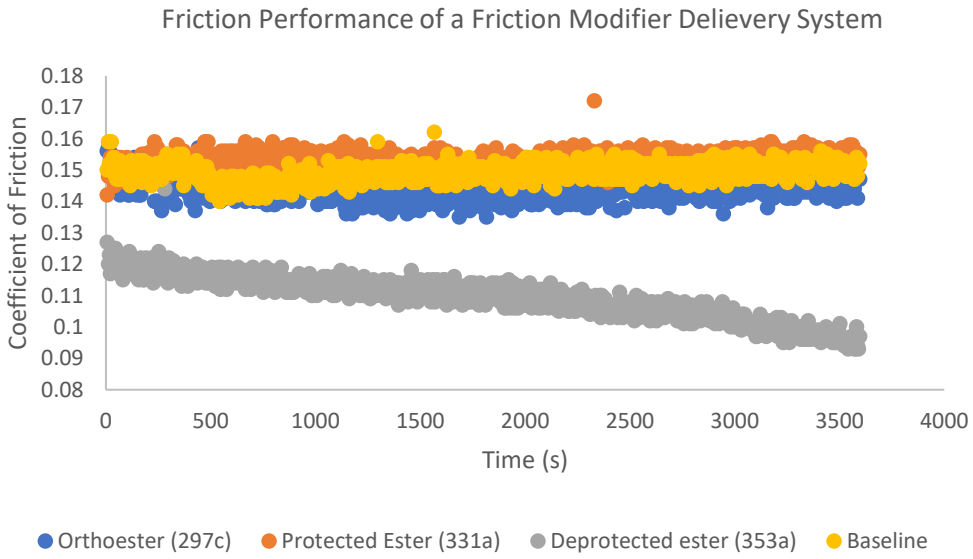
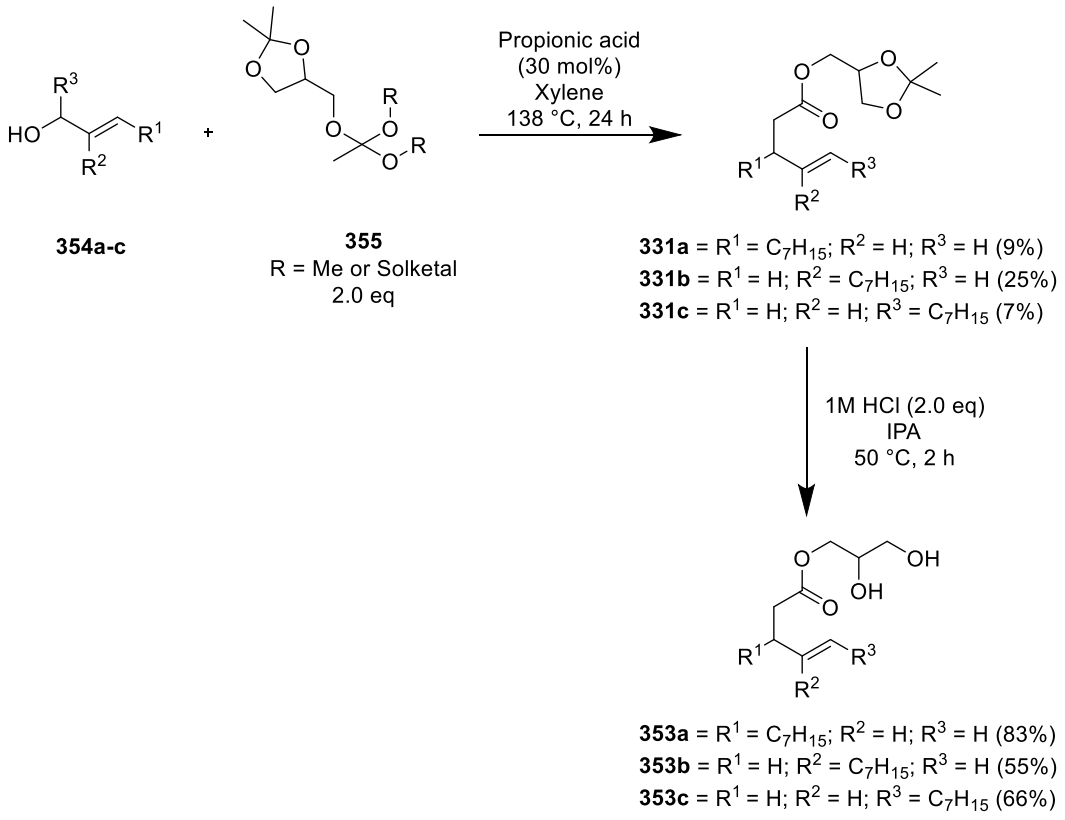


Figure 19: A graph showing the coefficient of friction vs time for 3 different components

The HFRR results (Figure 19) show that the only component that had any lowering friction performance was the deprotected ester (**353a**). This was identified by a large decrease in the coefficient of friction of the deprotected ester (**353a**) in comparison to the baseline. The steady decline in the coefficient of friction for the deprotected ester (**353a**) could be a result of the ester degrading to the acid under the conditions of the test, as it is well known that acids produce low coefficient of friction values. In fact, in some literature studies, the degradation of the ester to

the acid is believed to be the mechanism of action.[18] Furthermore, there could be other reasons for the decrease in coefficient of friction, for example the surface of the metal could be becoming more saturated.

The deprotected ester (**353a**) was the only component of the delivery system to provide any friction performance. Therefore, the deprotected ester was further investigated to improve upon performance. The substitution pattern of the alkene on the ester was investigated since this could have impact on the packing of the molecules and thus the friction performance. The deprotected esters (**353a-c**), were synthesised independently from the orthoester route (Scheme 151), since the formation of the orthoester for ester (**353c**) was unsuccessful. The development and optimisation of the synthesis of the solketal orthoester (**355**) is discussed in section 5.2.1.

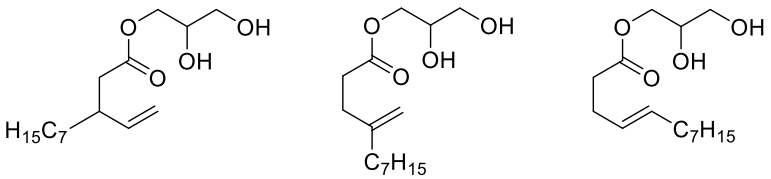


Scheme 151: The synthesis route to the deprotected esters (353a-c)

The HFRR results for the effect of the substitution pattern (Figure 20) highlighted that there was a difference in the friction performance depending on the substitution. The trend showed that branching of the ester had an impact on the

coefficient of friction. For example, the most branched ester (**353a**) was shown to give the highest coefficient of friction, while the linear ester (**353c**) gave the lowest coefficient of friction and therefore was the best performing friction modifier. This branching effect was not surprising, since it affects how the esters can pack at the surface of the metal. Esters that can densely pack, such as the linear derivative (**353c**), are more likely to reduce friction.

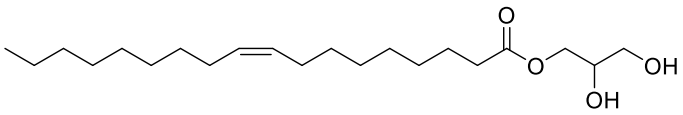
The deprotected esters (**353a-c**) were also compared to a commercially known friction modifier, GMO (**2**), which was sourced from Sigma Aldrich. Although the deprotected esters (**353a-c**) were designed to look like GMO, there were some big differences between the molecules. Firstly, the chain length on the deprotected esters was significantly shorter than GMO ($C_{12}H_{21}$ compared to $C_{18}H_{33}$). Secondly, both the position and orientation of the alkene in the deprotected ester was different compared to GMO. In GMO the alkene was *cis*-orientated at position C9 on the chain; the *cis*-orientation is used to improve the solubility. In the deprotected esters (**353a-c**) the alkene is significantly closer to the carbonyl at position C5, and for the linear ester (**353c**) the alkene is *trans*-orientated. Comparing the friction performance from the HFRR data (Figure 20), showed that two of the deprotected esters (**353b-c**) were found to have a greater decrease in the coefficient of friction over some or all the test compared to GMO. This could suggest that the deprotected esters (**353b-c**) and GMO have a different mechanism of action. Furthermore, when looking at the average coefficient of friction of the test the linear deprotected ester (**353c**) was lower than GMO, whilst the branched esters (**353a-b**) were higher (Figure 21). The slight improved friction performance of the linear deprotected ester (**353c**) compared to GMO was surprising, since the literature suggests that longer chain lengths will afford lower friction.[27,28,30] The potential reasoning for the improved performance of the linear deprotected ester (**353c**) versus GMO could be that it has better molecular packing as a result of the *trans*-alkene compared to the *cis*-alkene in GMO.[8,32–34]



353a

353b

353c



2
GMO

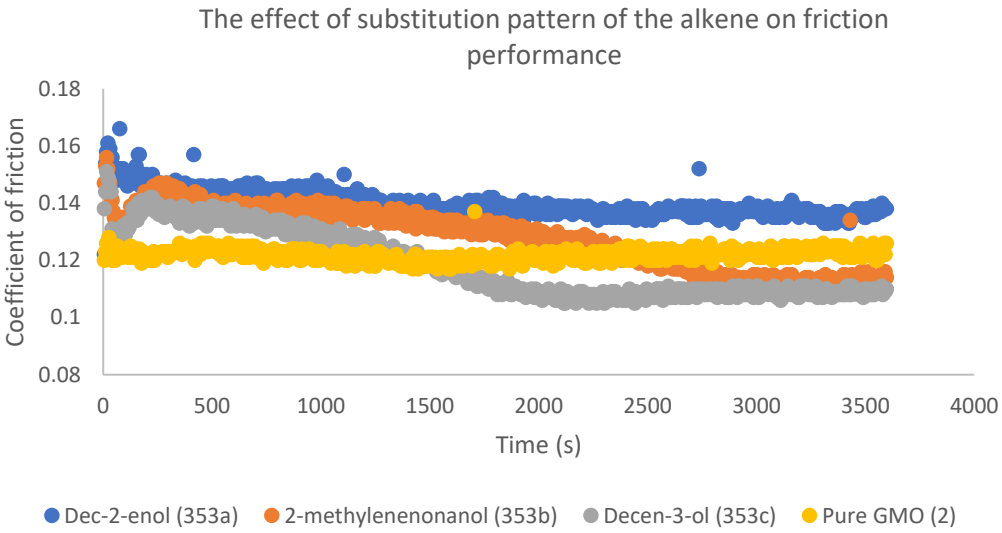


Figure 20: A graph showing the effect of changing the substitution pattern of the alkene on the friction performance

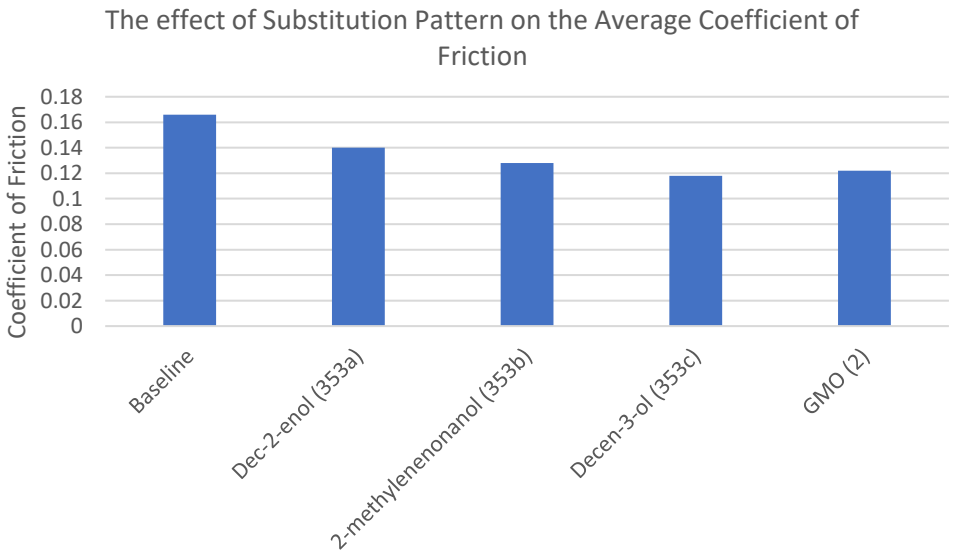
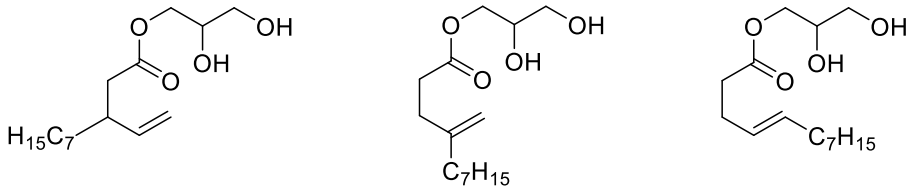


Figure 21: A graph showing the effect of the substitution pattern on the alkene on the average coefficient of friction

The friction performance is an important part of the process to determining a lead candidate. However, the solubility of the component in the lubricant oil is as important as the friction performance, as drop-out and sediment can impact the overall performance and compatibility of a lubricant oil. For example, GMO incorporates a *cis*-alkene, even when the *trans*-alkene derivative is known to reduce friction more, in order to improve on the solubility. Interestingly, it was found that all three of the deprotected esters (**353a-c**) were soluble within the lubricant oil used for testing, even when the linear *trans*-alkene was used (Figure 22). Further work could involve the use of spectroscopic techniques to measure the solubility, haze and compatibility of the oils.



353a **353b** **353c**

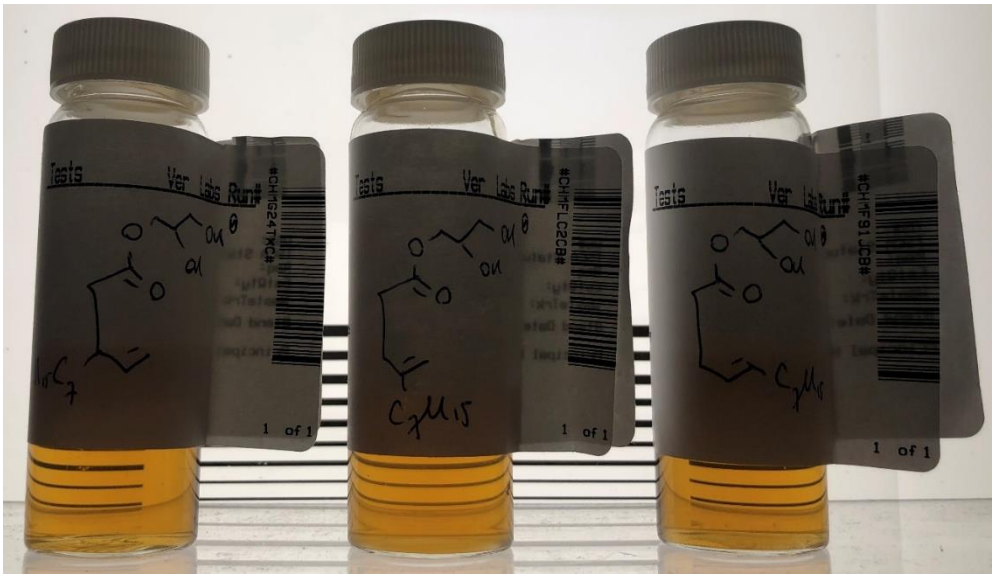
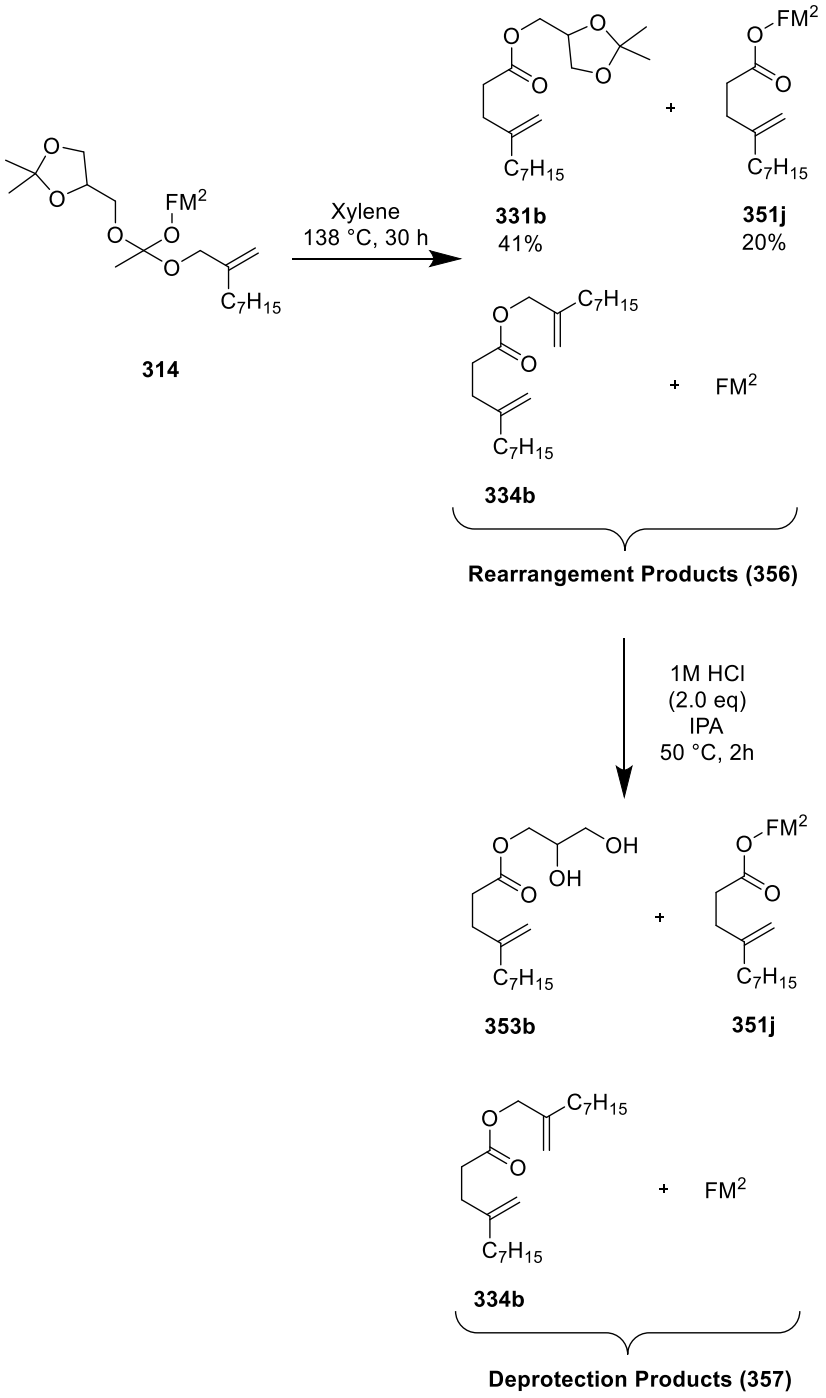


Figure 22: The solubility of the three deprotected esters in the lubricant oil

5.1.2.4. HFRR Results - Orthoesters that Release more than one Friction Modifier

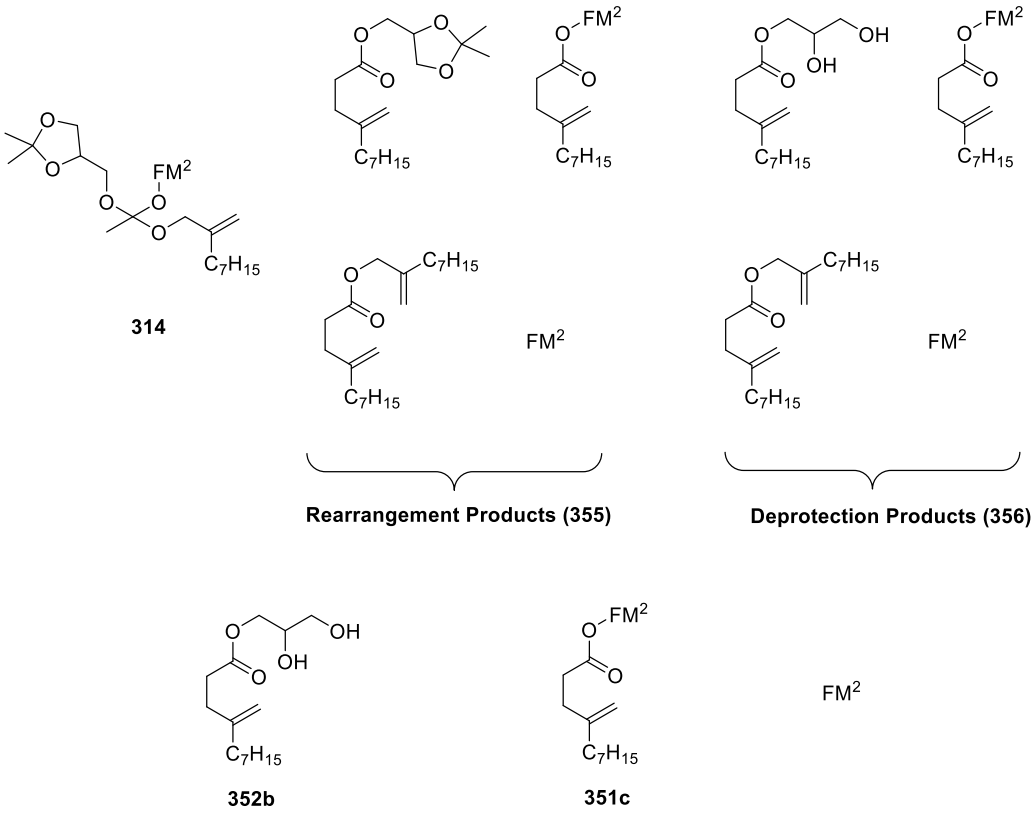
HFRR testing was also undertaken on the orthoester which was designed to release both the solketal protected ester and another friction modifier (FM^2) on rearrangement. The selectivity of this rearrangement was poorer than the disolketal rearrangement previously discussed, and as a result there was a mixture of rearrangement products (Scheme 152) , including the FM^2 ester (**351c**) and allylic ester (**334b**). Although products from the mixture could be identified, not all the product yields could be determined due to the complex nature of the NMR or unsuccessful isolation. Ideally in this case, the rearrangement products (**356**) should also show some friction performance, due to the release of the FM^2, followed by a further reduction in the coefficient of friction on deprotection. The orthoester (**314**), mixture of protected ester rearrangement products (**356**) and mixture of deprotected rearrangement products (**357**) were all isolated from the rearrangement process and tested for HFRR. Furthermore, the solketal deprotected ester (**353c**), FM^2 ester (**351c**) and FM^2 were also isolated and tested for HFRR.



Scheme 152: Orthoesters designed to release more than one lubricant additive

The HFRR data (Figure 23) firstly demonstrates that the orthoester (**314**) caused a small drop in the coefficient of friction compared to the baseline, which could be a result of some of the functionality in FM^2 interacting with the surface of the metal. Secondly, there was a large drop in coefficient of friction on rearrangement (**356**), which can be assumed to be a result of the release of FM^2. However, there

was little difference in the coefficient of friction between the rearrangement products (**356**) and the deprotection products (**357**). This suggests that most of the friction performance was a result of non-glycerol products. To further investigate this, the FM^2 ester (**351c**) was isolated and tested for HFRR. The FM^2 ester (**351c**) was found to have a low average coefficient of friction (Figure 24), but a decrease in the coefficient of friction over the test was also observed. The drop in the coefficient of friction over the test is likely to be a result of the degradation of the ester to the corresponding acid and FM^2. When the rearrangement (**356**) and deprotection (**357**) products are compared to the isolated solketal deprotected ester (**353b**), they had a significantly lower coefficient of friction. Furthermore, there were differences in the curve of the coefficient of friction over the test, for example the solketal deprotected ester (**353b**) showed a decrease in coefficient of friction over the test, whilst the rearrangement (**356**) and deprotection (**357**) products were shown to stay constant throughout the test. This could suggest differences in how the products interact with the surface of the metal and potentially the mechanism of action of the products.



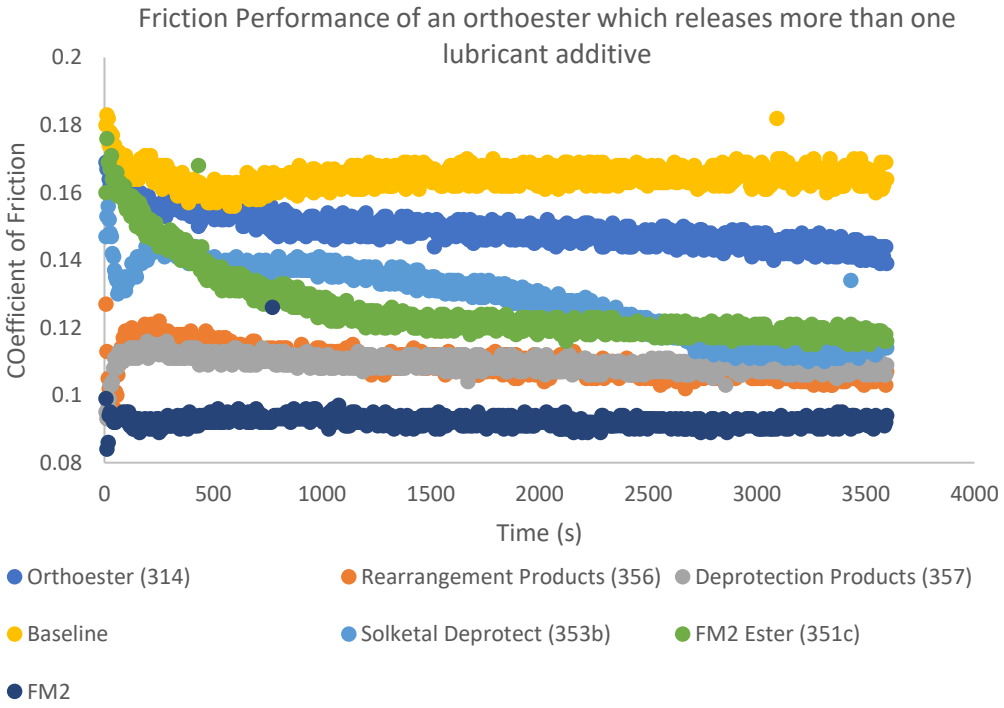


Figure 23: A graph showing the friction performance of an orthoester which can release more than one lubricant

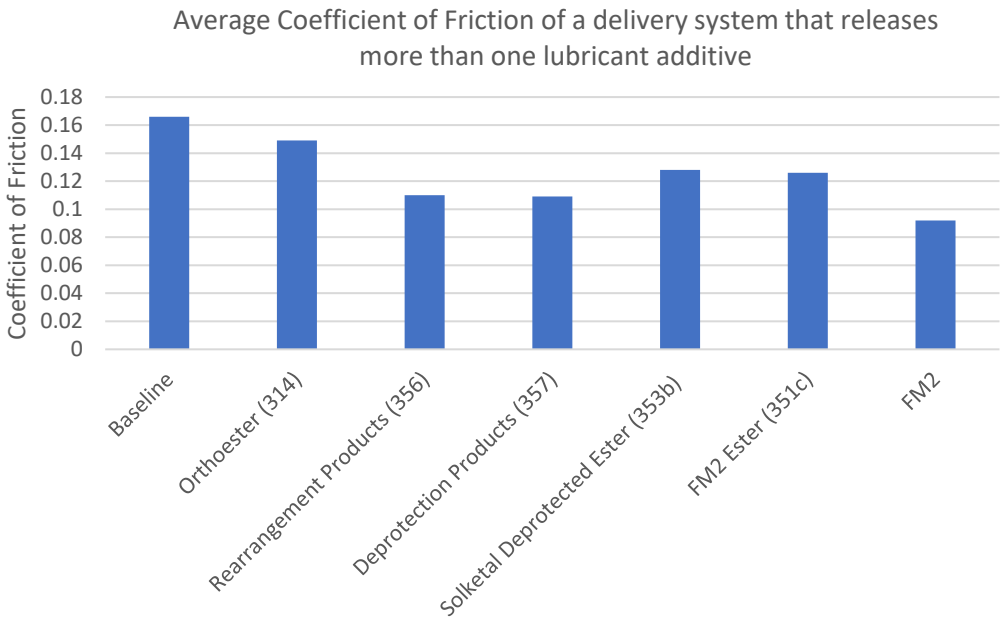
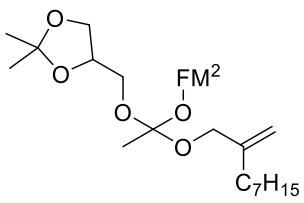


Figure 24: A graph showing the average coefficient of friction of a delivery system which releases more than one lubricant additive

As alluded to earlier, the solubility of the component within the lubricant oil is as important factor of developing new components. Although FM^2 is a better friction modifier than the rearrangement products of the orthoester delivery system, indicated by a lower coefficient of friction, FM^2 has poor solubility in lubricant oils. When FM^2 is incorporated into the orthoester (**314**) it is fully soluble, with no precipitate, haze or sediment (Figure 25). The use of orthoesters as solubilising agents for lubricant additives will be further discussed later in this chapter.



314

FM^2

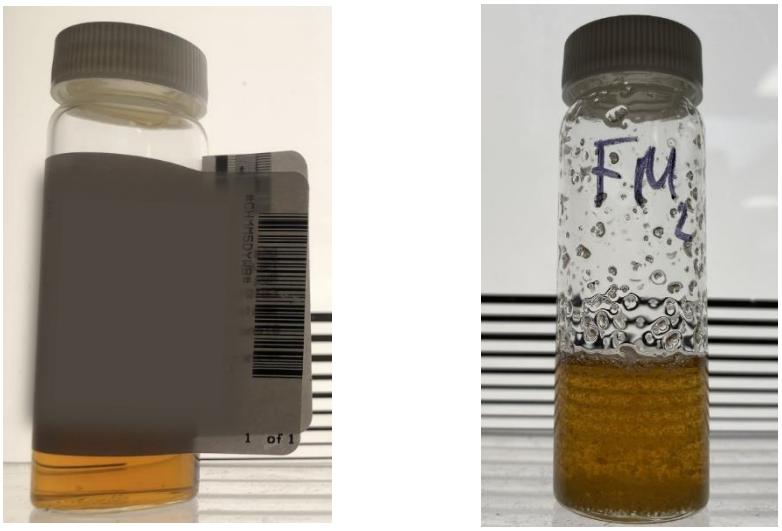
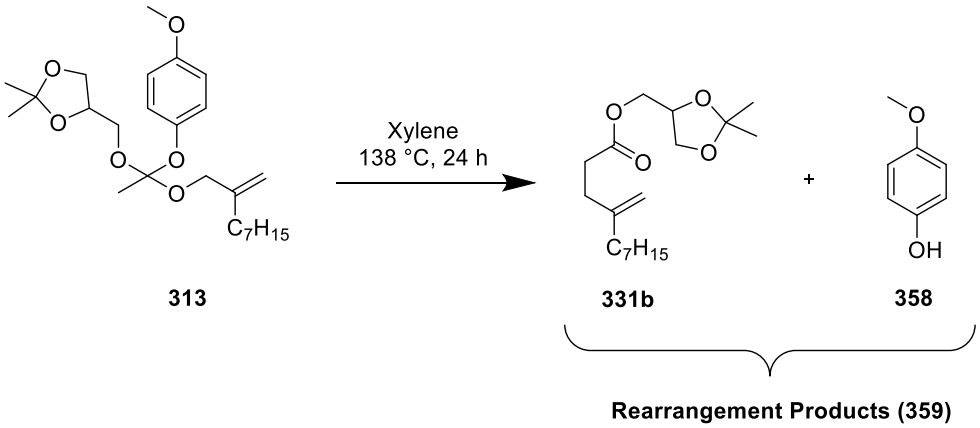


Figure 25: The improved solubility of an orthoester containing FM^2 (left hand side) compared to FM^2 on its own (right hand side)

5.1.2.5. Oxidative Resistance Test

An orthoester was also designed to release 4-methoxyphenol (**358**), a potential antioxidant, through the rearrangement (Scheme 153). This would improve the atom efficiency of the orthoester since both the rearrangement product (**331b**) and the 4-methoxyphenol (**358**) could improve the performance of the lubricant additive.



Scheme 153: The release of 4-methoxyphenol during the direct orthoester Johnson-Claisen rearrangement

Antioxidants are used within lubricant oils to increase the oxidative resistance of the base oil and thus prolong the life of the lubricant. Base oils are susceptible to degradation by oxygen, which can result in thickening and the formation of sludge. Since the oxidation process is initiated through the formation of free radicals and peroxides, antioxidants work by preventing further propagation of the radical chains. The oxidative resistance of a lubricant oil is tested using Pressure Differential Scanning Calorimetry (PSCD). This test measures the ability of the oil to resist oxidation in an oxygen-rich environment at elevated temperatures. The results of this test are reported as the oxidation induction time (OIT)/minute. This is defined as "the time between the start of the exposure to oxygen and the onset of the exothermic reaction in isothermic conditions".[258] This means that the greater the time it takes for the exothermic reaction to occur then the better the oxidative resistance.

5.1.2.6. Oxidative Resistance (L-85-99) Test Protocol

Pan Type	Tzero
Weight of sample	2.0 mg ± 0.05 mg
Air Atmosphere	100 (±7) psig, 690 (±48) KPa g
Flow Rate	Static, no flow
Sample Loading Temperature	<40 °C
Equilibrium Temperature	50 °C (±2 °C)
Equilibrium Time at 50 °C	5 minutes
Temperature Ramp Rate	40 (± 10) °C / minute
Isothermal Test Temperature	210 (± 0.5) °C
Test Duration	240 minutes

For each of the new components tested, they were dosed into a fully formulated lubricant oil at 2 wt%. A fully formulated oil contains a range of lubricant additives,

such as detergents, dispersants, anti-wear agents and viscosity modifiers. The use of a fully formulated package replicates real-world conditions. A baseline sample, of the lubricant oil on its own, was also run as a reference to compare the oxidative resistance performance. The tests were run by technicians in the Blend Test Services at Lubrizol Ltd. In Hazelwood.

5.1.2.7. Oxidative Resistance (L-85-99) Test Results

In order to determine whether the orthoester would deliver an antioxidant through the direct orthoester Johnson-Claisen rearrangement, the oxidative resistance of the rearrangement mixture (**359**) was tested (Table 10). The results demonstrated that that the rearrangement mixture, which included 4-methoxyphenol (**358**), improved the oxidative resistance of the lubricant oil. This was indicated by an increase in the oxidative induction time compared to the lubricant oil. This therefore provides proof of concept for using the orthoester Johnson-Claisen rearrangement as a delivery system for antioxidants. Furthermore, although the friction performance of the solketal ester (**331b**) and deprotected ester (**353b**) produced is known, it would be important to also undertake the HFRR test in the presence of 4-methoxyphenol (**358**) to make sure no adverse interactions take place and therefore obtain proof of the use of orthoesters as double lubricant additive delivery systems, improving both friction and oxidative resistance.

Table 10: The oxidative resistance of rearrangement products tested using L-85-99

Sample	OIT/min
Lubricant oil	77.5
Lubricant oil + 2 wt% Rearrangement mixture (359)	84.2

5.1.2.8. Lubricant Additive Testing Conclusions

Both the HFRR and oxidative resistance testing demonstrated proof of concept of using the orthoester Johnson-Claisen rearrangement as delivery systems for

lubricant additives. The HFRR testing highlighted that some of the rearrangement products had a small but significant increase in friction performance when compared to a commercially available friction modifier, with the potential of increased durability due to the novel delivery system. Additionally, the HFRR testing showed that the friction modification could be further improved when a high performing friction modifier was released during the rearrangement. Finally, the oxidative resistance testing indicated the potential of using the orthoester Johnson-Claisen rearrangement as a delivery system for other lubricant additives, such as antioxidants.

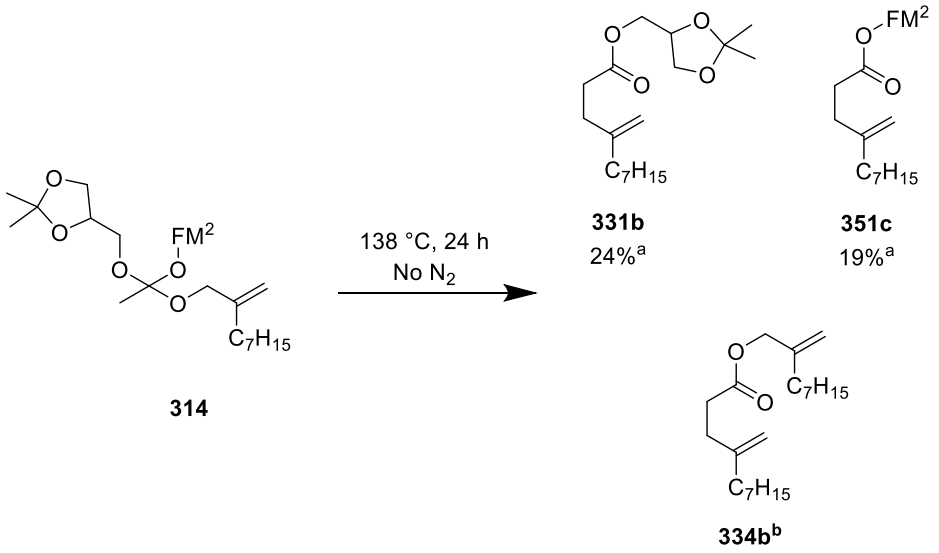
5.1.3. Mimicking the Lubricant Oil Environment

The initial rearrangement studies of the solketal orthoesters were all undertaken in environments that would be completely different to that of the lubricant oil. Therefore, studies were undertaken to consider the effect of the lubricant oil, including the effect of exposure to air, using iron mimics, as well as running the rearrangement in a lubricant oil.

Initial investigation into mimicking the lubricant oil environment involved looking into the effect of undertaking the rearrangement without an inert atmosphere. The use of air resulted in an increase in the rate of the reaction, in all cases the rearrangement was complete after 24 hours at 138 °C, compared to the reaction times originally observed (Table 9). As it was postulated that the increase in the rate was a result of moisture in the air, further investigation into the atmosphere was undertaken. The rearrangement was found to not be accelerated when using a CO_2 atmosphere. Furthermore, when water was dosed into the rearrangement, both when under N_2 and CO_2, no rate acceleration was observed. However, since the rearrangement occurred at temperatures above the boiling point of water, the water effect is not surprising and further work is required.

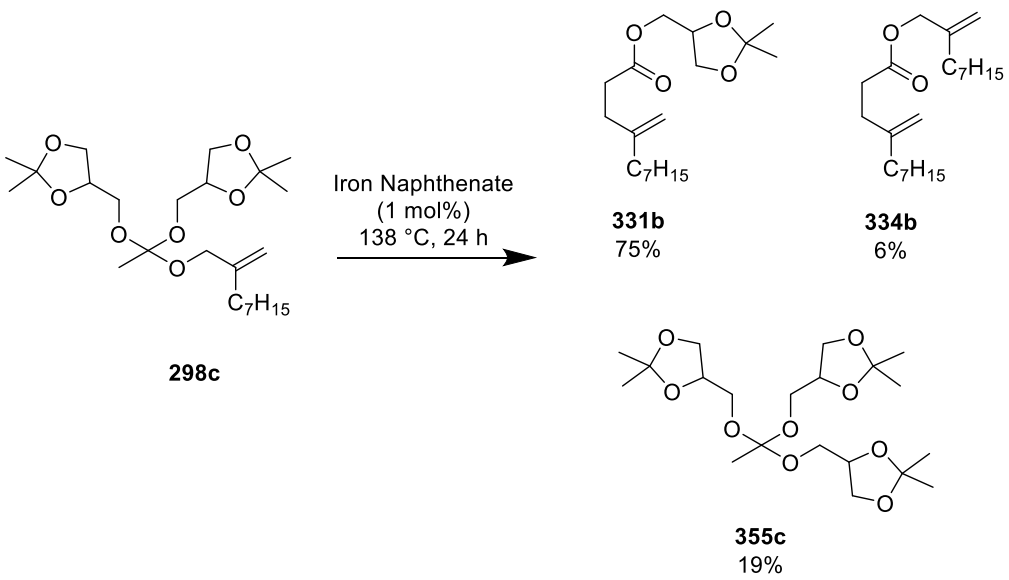
The use of air also impacted the selectivity of the rearrangement, possibly because of the increased scrambling of the orthoester which occurred due to the presence of moisture. This was highlighted by the solketal/ FM^2 orthoester, wherein only 24% of the solketal ester (**331b**) and 19% of the FM^2 ester (**351c**) was isolated, with

the remainder of the reaction mixture being a mixture of the allylic ester (**334b**) and another unknown allylic product (Scheme 154). This was compared to 41% and 20% of the solketal (**331b**) and FM^2 ester (**351c**) isolated respectively when exposed to an inert atmosphere.



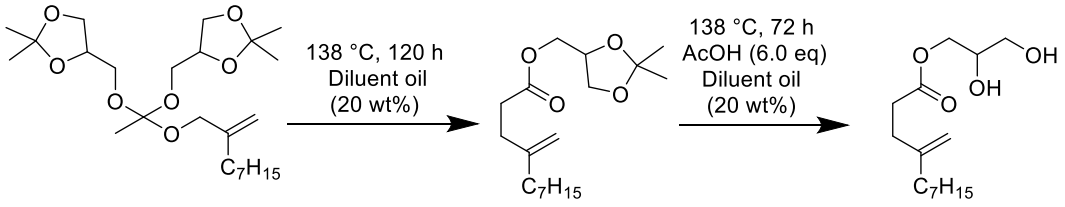
Scheme 154: The effect of air on the direct orthoester Johnson-Claisen rearrangement; [a] isolated yields; [b] observed but not isolated

The effect of using an iron mimic was also investigated. This was investigated since wear on the moving parts can cause iron to be present within the lubricant oil. Iron naphthenate has been used in lubricant oil testing as a surrogate for wear debris. Therefore, the rearrangement of disolketal/2-methylenenonanol orthoester (**298c**) was undertaken using 1 mol% iron naphthenate. As with the air studies, the rearrangement was complete after only 24 hours at 138 °C, compared to 400 hours under the original conditions. Furthermore, both the allylic ester (**334b**) and tri-solketal orthoester (**355c**) were produced (Scheme 155). This suggests that the iron naphthenate caused the orthoester to undergo more scrambling, resulting in the formation of unwanted side products. This can be postulated to be due to the Lewis acidity of iron naphthenate. As discussed in chapter 4, the presence of acid resulted in increased scrambling. Interestingly, the use of iron naphthenate did not result in the deprotection of the acetal.



Scheme 155: The effect of an iron mimic on the direct orthoester Johnson-Claisen rearrangement; yields are based on normalised integrals by ^{1}H NMR spectroscopy

The final study into mimicking the lubricant oil environment was to undertake the rearrangement in an oil. A base oil (diluent oil, supplied by Lubrizol) was chosen since base oils do not contain any lubricant additives, as these could interact with the rearrangement, and allowed for monitoring by ^{1}H NMR. Disolketal/2-methylenenonanol orthoester (**298c**) successfully underwent the rearrangement in a base oil in 120 hours (Scheme 156). The increase in the rate of the rearrangement can be attributed to both the increased concentration, to allow for monitoring by ^{1}H-NMR, and the slightly acidic nature of the base oil. The acetal deprotection of the solketal was then undertaken in the base oil. Acetic acid was used to replicate an organic acid within the lubricant oil and was added portion wise to the reaction mixture over 72 hours. ESI-MS was used to observe that the deprotection had been successful, but as this technique was not quantitative and the acetal region of the ^{1}H-NMR overlapped with the base oil, the length of time and equivalents of acetic acid required for full conversion could not be determined. Furthermore, both reactions were undertaken using an inert atmosphere. Ideally these reactions should be undertaken under air to fully mimic the lubricant oil environment, but with previous work in this area it is believed that this will only further increase the rate of the reaction and produce the allylic ester (**334b**) by-product.



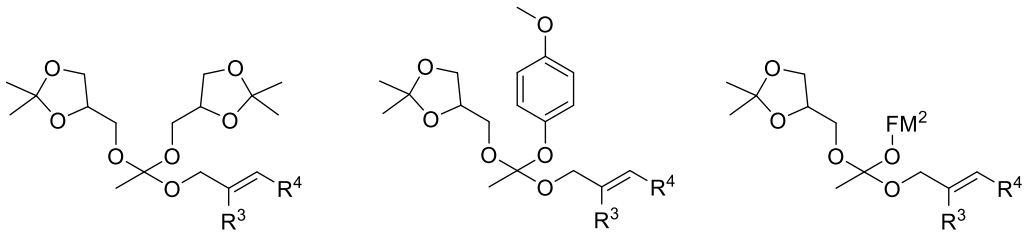
298c **331b** **353b**

Scheme 156: Undertaking the rearrangement and deprotection in a lubricant oil environment

Mimicking the conditions of a lubricant oil environment have shown that the direct orthoester Johnson-Rearrangement is not an ideal delivery system for lubricant additives. The characteristics of the rearrangement that were chosen for this application, such as the ability to tune the rate, are lost. Furthermore, the formation of side products and detrimental effect on the selectivity of the rearrangement when using air or an iron source highlights the issues of using this rearrangement in a lubricant environment.

5.1.4. Determination of a Lead Candidate

Utilising the selectivity, rate and performance data described in this thesis, an orthoester lead candidate for the delivery system of lubricant additives can be determined. The potential lead candidates are shown in Figure 26. Although orthoesters (**313, 314**) were shown to produce more than one lubricant additive, improving on their atom efficiency and performance, the rates of the rearrangements were too fast. This would result in little improvement on the durability of the lubricant additives. The orthoester (**298c**) was shown to have a long rearrangement rate and the resulting friction modifier (**353b**) was found to have friction performance similar to a commercial friction modifier (GMO), despite having a significantly shorter chain length. Therefore, orthoester (**298c**) was chosen as the lead candidate. Further work would be to investigate whether increasing the chain length to match GMO improves friction performance and if it impacts the rate of the rearrangement.



297c = R^3 = H; R^4 = C_7H_{15}
298c = R^3 = C_7H_{15}; R^4 = H

313 = R^3 = C_7H_{15}; R^4 = H

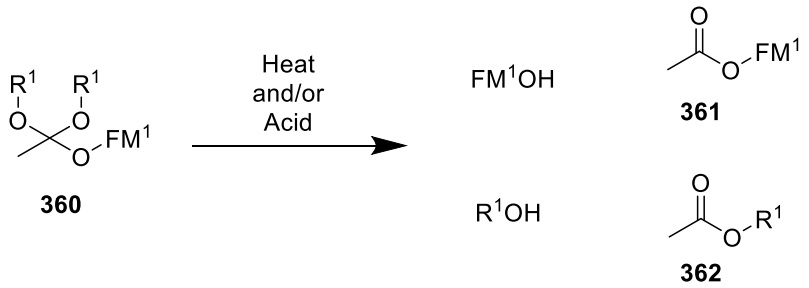
314 = R^3 = H; R^4 = C_7H_{15}

Figure 26: Potential orthoester lead candidates for the delivery system of lubricant additives

The use of the orthoester Johnson-Claisen rearrangement as a delivery system for lubricant additives is an interesting and novel approach. Although the orthoester successfully rearranges and can be modified to impact the selectivity and rate of the rearrangement, as well as the performance of the resulting lubricant additive, the rearrangement suffers from real-world applicability issues. The main problem is the impact of the air on the rearrangement since it increases both the formation of side products and the rate of the reaction. This results in a loss of control of both the rate and the selectivity, which were the main reasons the direct orthoester Johnson-Claisen rearrangement was chosen for this application. Furthermore, further exploration is required to confirm that the transformation of the orthoester to the deprotected ester improves the durability. For example, *in situ* testing is required to observe the drop in the coefficient of friction as the orthoester goes through the rearrangement and deprotection, rather than isolated components.

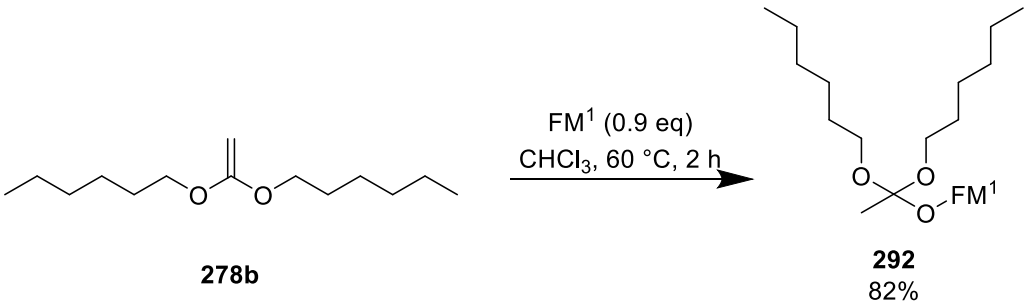
5.2. Use of Orthoesters as Solubilising Agents for Lubricant Additives

The development of a delivery system for lubricant additives *via* the direct orthoester Johnson-Claisen rearrangement was found to have little applicability to real-world conditions. However, the investigation did highlight that orthoesters could be used as solubilising agents for lubricant additives that were poorly soluble in lubricant oils. Therefore, instead of an elaborate rearrangement, the conditions of the engine/transmission could be used to degrade the orthoester and deliver a lubricant additive (Scheme 157). This would still produce an *in situ* delivery system that enhances the durability but would also improve the compatibility of an already developed lubricant additive, for example a friction modifier (FM^1), in lubricant oil packages.



Scheme 157: Using the degradation of orthoesters as *in situ* delivery systems for lubricant additive

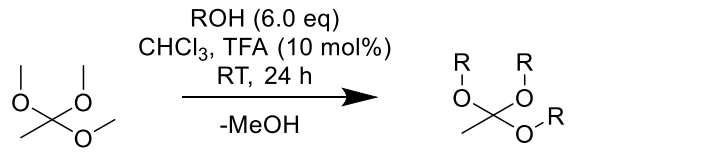
The synthesis of orthoesters incorporating FM^1 was previously described in chapter 3, *via* the addition to ketene acetals (Scheme 158). Although this approach allowed isolation of the mono-FM^1 orthoester (**308**), the synthesis route is not commercially viable due to the number of steps. Therefore, a new route to orthoesters was developed for this application.



Scheme 158: The synthesis of FM^1 orthoesters via the ketene acetal approach as described in chapter 3

5.2.1. Results and Discussion - Synthesising Orthoesters from Orthoesters

A modified version of the orthoester exchange approach, originally described by both Arbusov[65] and Brachvogel *et al.*[75], was used in order to synthesise orthoesters capable of solubilising lubricant additives. Initial investigation involved optimising the method to produce a range of simple symmetric (trialkyl) orthoesters. Reacting trimethyl orthoester with a 3-fold excess of alcohol and 10 mol% of TFA produced symmetric orthoesters within 24 hours. Subsequent purification by simple distillation to remove the excess alcohol and any acetate ester formed from the acid-mediated degradation of the orthoester, produced five symmetric orthoesters (**291a-e**) in yields of 60-75% (Scheme 159).



45

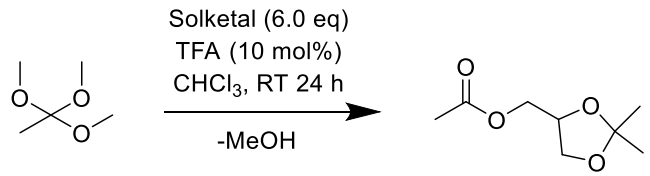
291a = R = *n*-butyl (60%)
291b = R = *n*-hexyl (72%)
291c = R = *n*-octyl (75%)
291d = R = *n*-decyl (62%)
291e = R = *n*-dodecyl (75%)

Scheme 159: Synthesis of symmetric (trialkyl) orthoesters via the modified orthoester exchange approach

Investigation into the optimisation of the orthoester exchange involved undertaking the reaction without solvent. Unfortunately, removing the solvent resulted in poorer conversion. This can be reasoned by an increased equilibrium since the molecules can interact more easily. To overcome this, the reaction could be heated, and the methanol distilled off. Further optimisation could involve reducing the acid mol% in the reaction. Since the use of 10 mol% of acid causes some degradation of the orthoester, using fewer equivalents may reduce the degradation but also may impact the rate of the reaction.

The symmetric orthoesters (**291a-e**) could easily be scaled up to 50-100 g; with further optimisation, such as investigating solvent more thoroughly and acid mol%, this reaction could certainly be industrially viable.

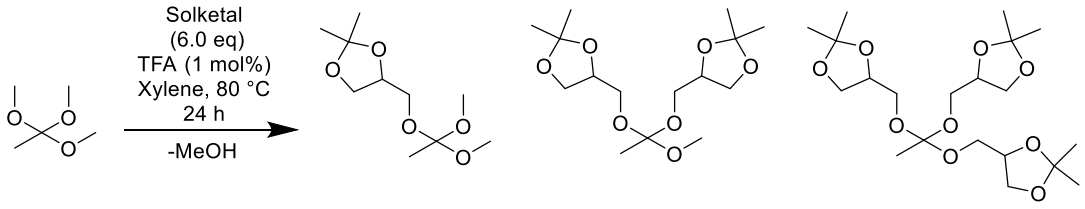
The success of the orthoester exchange approach prompted the use of the method to synthesise other orthoesters which could be used in the orthoester Johnson-Claisen rearrangement. This was especially useful for the synthesis of the deprotected esters (**353a-c**) which underwent the HFRR testing (section 5.1.2.3.). Using the same conditions as the simple aliphatic alcohols, 6 equivalents of alcohol and 10 mol% TFA, produced solketal acetate (**363**), with only residual amounts of any of the desired orthoester observed (Scheme 160). This was due to the hydrolytic instability of the orthoester, with the bulky nature of the solketal groups increasing its susceptibility to hydrolysis.



45 **363**

Scheme 160: Orthoester exchange of trimethyl orthoacetate and solketal with 10 mol% TFA

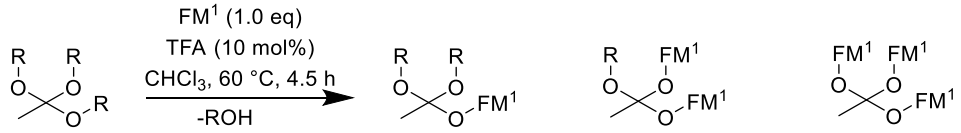
Reducing the amount of TFA used in the exchange to 1 mol% allowed for the isolation of the solketal orthoesters. However, instead of just the desired orthoester (**354a**), a mixture of the mono-(**354a**), di-(**354b**), and tri-orthoesters (**354c**) were synthesised. The ratio of the orthoester mixture was determined by ^{1}H NMR, since there was good baseline separation between the orthoester methyl groups. It was established to be 0.36:0.50:0.14 (mono-(**354a**), di-(**354b**), tri-(**354c**)). Attempts to push the conversion by heating the reaction to 80 °C, using xylene as the solvent, resulted in a small increase in the amount of di-(**354b**) and tri-orthoester (**354b**) synthesised, with a ratio of 0.17:0.62:0.22 (mono- (**354a**), di-(**354b**), tri-(**354c**)) (Scheme 161).GC-MS was investigated to validate the ratios observed by NMR however only one major component was observed, even though ESI-MS confirmed the presence of all three orthoesters. There is potential for the exchange to be further optimised by increasing the length of time of the reaction or increasing the temperature even further, although this would be limited by the boiling point of the trimethyl orthoester (**45**).



45 **354a** 0.17[a] **354b** 0.62[a] **354c** 0.22[a]

Scheme 161: Orthoester exchange of trimethyl orthoacetate (45) and solketal with 1 mol% TFA; a ratio determined by normalised integrals by ^{1}H NMR

The orthoester exchange approach was then further optimised to allow for the incorporation of a friction modifier (FM_1). A small variety of symmetric (trialkyl) orthoesters were reacted with one equivalent of FM^1, supplied by Lubrizol, producing a range of orthoesters (**365-368**) (Scheme 162). The symmetric orthoesters were either commercially available (trimethyl/triethyl) or synthesised in house following the orthoester exchange method described above, resulting in a one or two step reaction.



364

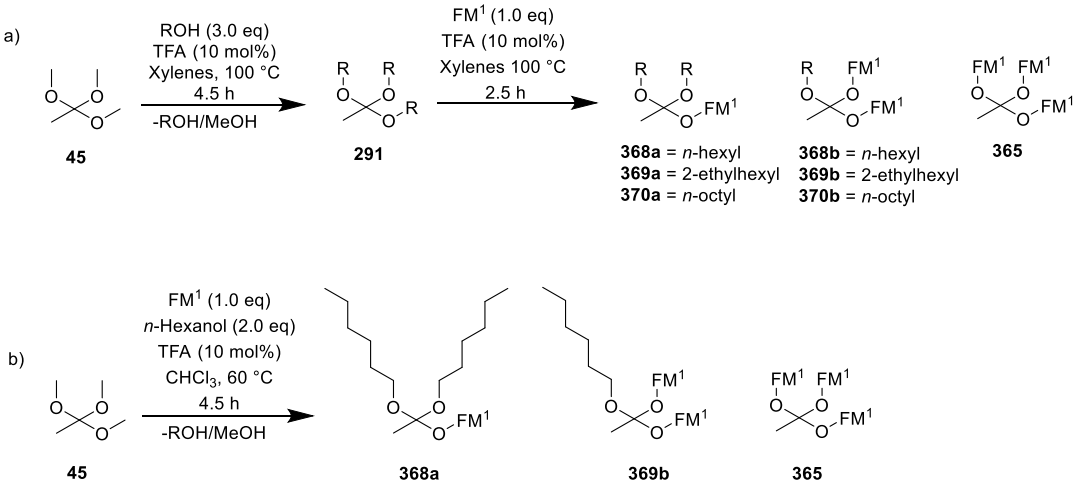
366a = R = Me
367a = R = Et
368a = R = *n*-hexyl

366b = R = Me
367b = R = Et
368b = R = *n*-hexyl

365

Scheme 162: The synthesis of orthoesters incorporating FM^1

To further improve the commercial viability and scope of this route, a one-step reaction from the trialkyl orthoester that are not commercially available is desirable. There were two different ways that achieved this. The first was a one-pot two-step approach (Scheme 163a), where a long chain symmetric orthoester was synthesised first and then FM^1 was introduced. This produced longer chain derivatives, such as *n*-hexyl (**368**), 2-ethylhexyl (**369**) and *n*-octyl (**370**). The second method was an all-in approach (Scheme 163b), where both the longer chain alcohol and FM^1 were introduced at the same time. This method was also used to synthesise the *n*-hexyl derivative (**368**).



Scheme 163: a) one-pot two-step approach to forming orthoesters; b) the all-in approach to forming orthoesters

The orthoester exchange approach allows for the quick and easy incorporation of FM^1 into orthoesters. However, due to the nature of the orthoester exchange a wide variety of products can be formed. Using *n*-hexyl derivatives as an example, the range of potential products can be identified, note that the same product types could be formed with the other derivatives. Firstly, a mixture of the desired mono-(**368a**), di-(**368b**) and tri-substituted (**365**) orthoester products can be formed. There is also the potential for residual FM^1 that has not reacted to be present, since it cannot be removed by purification methods such as filtration, distillation, or chromatography. Further to this, in the one-pot two-step and the all-in approach there is the potential to form side products. These first come in the form of orthoesters which still have a methoxy group incorporated (**366a-b, 371**) (Figure 27). These orthoesters are still productive in terms of incorporating FM^1 but are not the desired products of this reaction, and therefore could have an impact on its application.

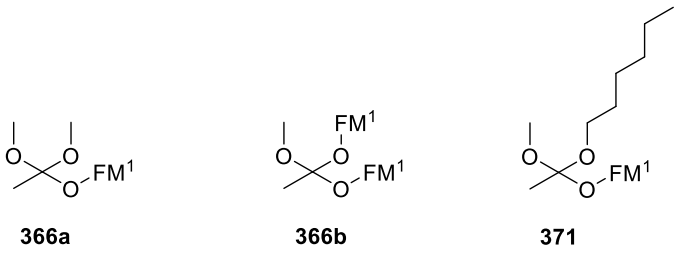
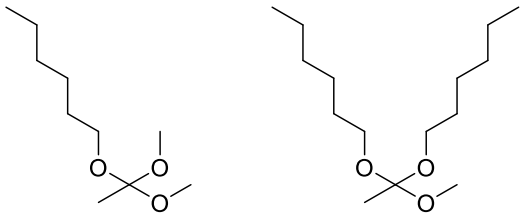


Figure 27: The three non-desired FM^1 orthoesters that could be formed in the FM^1 orthoester exchange

The final side products were orthoesters which are classed as unproductive since they do not contain FM[1] (**372-373**) (Figure 28). These can form as a result of using stoichiometric amounts of *n*-hexanol, compared to the original conditions of the orthoester exchange, which used an excess of alcohol to promote conversion.



372 **373**

Figure 28: The two unproductive orthoesters that could be formed in the FM[1] orthoester exchange

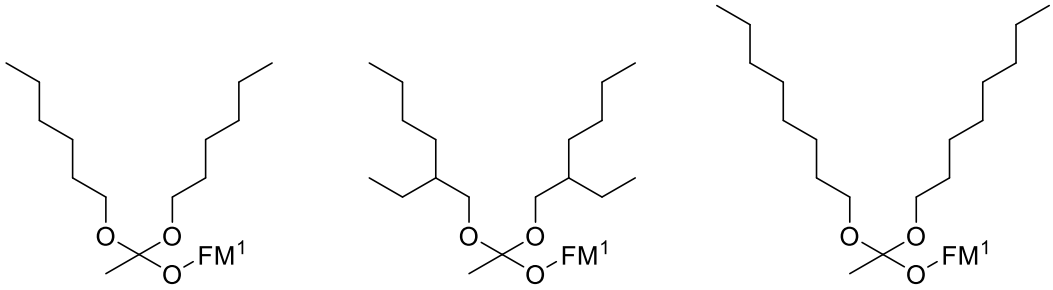
A range of analytical techniques, including ^{1}H-NMR, ESI-MS and GC-MS, were used to try to qualitatively and quantitatively describe the reaction products. Unfortunately, there were issues with all these techniques. Despite ^{1}H NMR qualitatively showing at least three orthoester methyl groups, overlapping of the peaks within the ^{1}H NMR meant that the ratio of the potential products could not be determined. ESI-MS initially looked like a good tool for qualitatively describing these orthoesters. In the all-in and one-pot two-step methods for the *n*-hexyl derivative all three desired substituted orthoesters (**368a-b, 365**), FM[1] and in the case of the one-pot two-step approach, some unproductive orthoester was observed (**373**). The other potential products mentioned above and the starting orthoesters were not observed by ESI-MS. However, in the case of the *n*-hexyl (**368**) derivative from the original orthoester exchange approach (i.e. directly from trihexyl orthoester) (Scheme 162) ESI-MS only revealed the mono-(**368a**), and di-substituted (**368b**) orthoesters, despite the fact there were at least three distinct orthoester methyl peaks present in the ^{1}H NMR, making this method unreliable. This could be due to ion suppression resulting in any less abundant peaks to not be visible. Finally, although Brachvogel *et al*.[75] used GC-MS to determine ratios in their orthoester exchange, the high molecular weights of the products in this work made GC-MS impossible.

The inability to quantitatively determine the ratio of mono-, di- and tri-substituted orthoesters present made it difficult to understand the effects, if any, of the different routes, and if the alcohol used had an impact on the products formed. Unless a method of determining the ratio of products can be identified, the effect of changing any of the reaction variables will remain unknown. Nevertheless, the data does show that FM[1] can be incorporated into the orthoesters *via* routes that would be more commercially viable than the ketene acetal route.

5.2.2. Results and Discussion - Effect of Substitution and Reaction Conditions on Orthoester Solubility

The effect of the chain length of R group on the orthoesters was initially investigated to explore the impact of substitution on the solubility. Increasing the chain length would be beneficial to the solubility of the orthoester. However, it would impact how much FM[1] would be released because the orthoester would be dosed into the oil at >5 wt%, and the longer the chain length, the greater the molecular weight and thus less moles of the orthoester would be used. The orthoesters (**368,369,370**) which had chain lengths of C_6H_{13} or greater were soluble in a lubricant oil package at 2 wt% (Figure 29a). In fact, these orthoesters were found to remain solubilised within the package even after storage at room temperature for at least 5 months (Figure 29b). The stability of the orthoesters, as intermediates, was also monitored over a period of 4 months. A small amount of degradation was observed after 4 months, noted by the formation of an acetate ester in the ^{1}H NMR. However, due to the nature and overlap of signals in the ^{1}H NMR spectrum it was not possible to quantify how much degradation had occurred.

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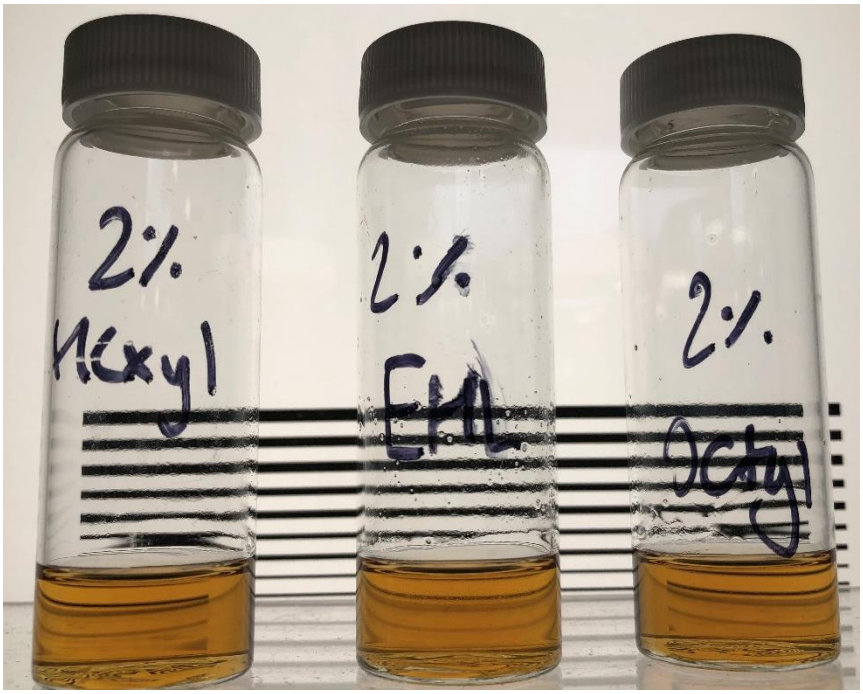
368
Idealised Structure

369
Idealised Structure

370
Idealised Structure

a)

b)



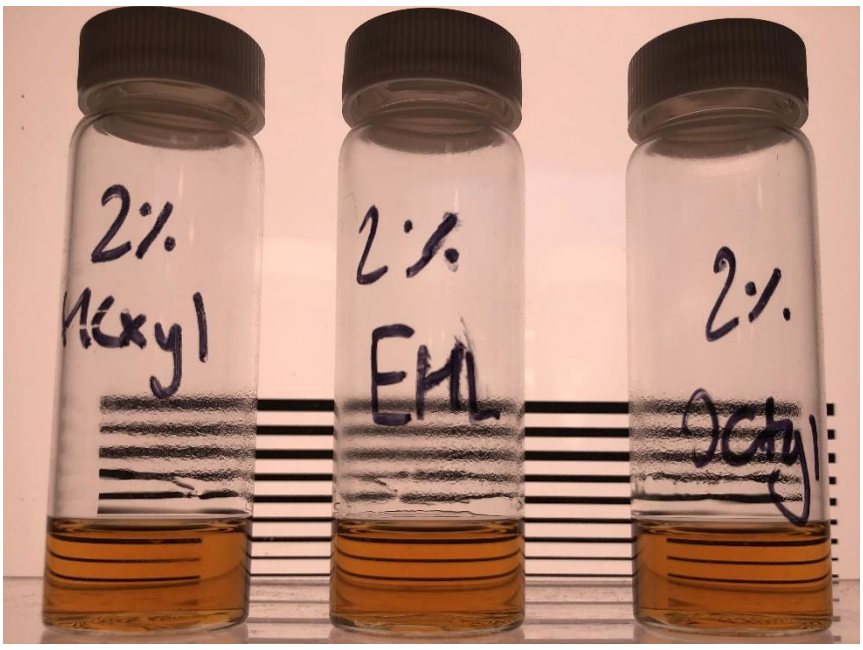
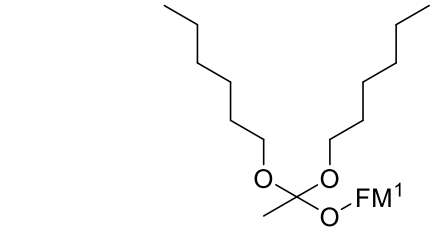


Figure 29: a) Initial solubility of the FM[1] orthoesters in a lubricant oil package; b) after 5 months the solubility has not changed

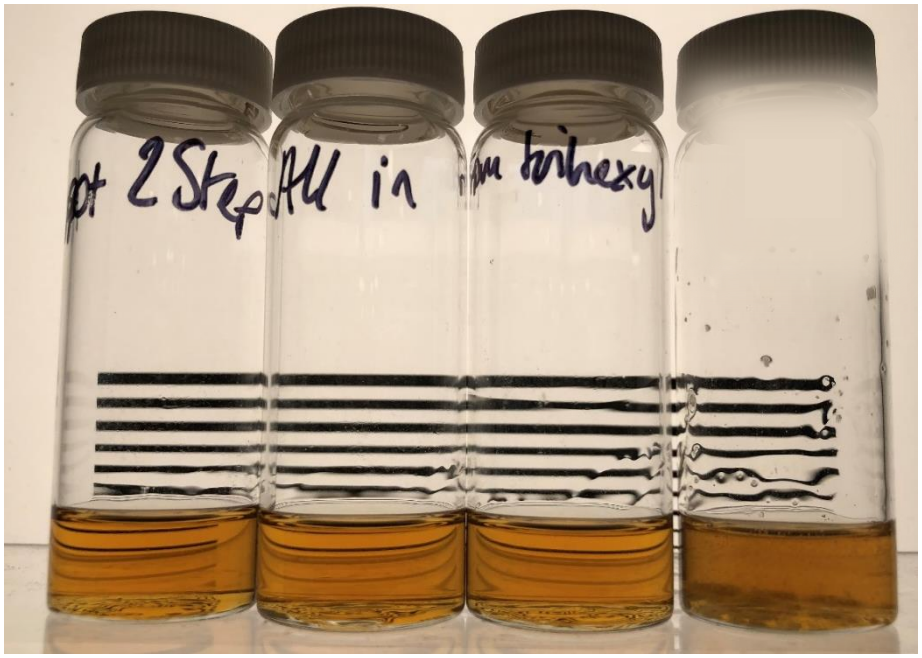
The impact of the reaction route of the orthoesters on the solubility in a lubricant oil package was also investigated. The hexyl derivative (**368**) was explored since it was the shortest chain to provide the desired solubility. The orthoester could be synthesised in three ways; from the original orthoester exchange, the one-pot two-step and the all-in reaction conditions. The orthoester (**368**) synthesised from all three methods was found to be soluble (Figure 30a). Furthermore, the orthoesters were also found to be soluble even after 3 months at room temperature (Figure 30b). This highlighted that the reaction route had no impact on the solubility and thus the best route to the FM^1 orthoester was the all-in reaction due to its commercial viability.



368
Idealised Structure

One-pot two-step **All-in** **Original exchange** FM^1OH

a)



b)

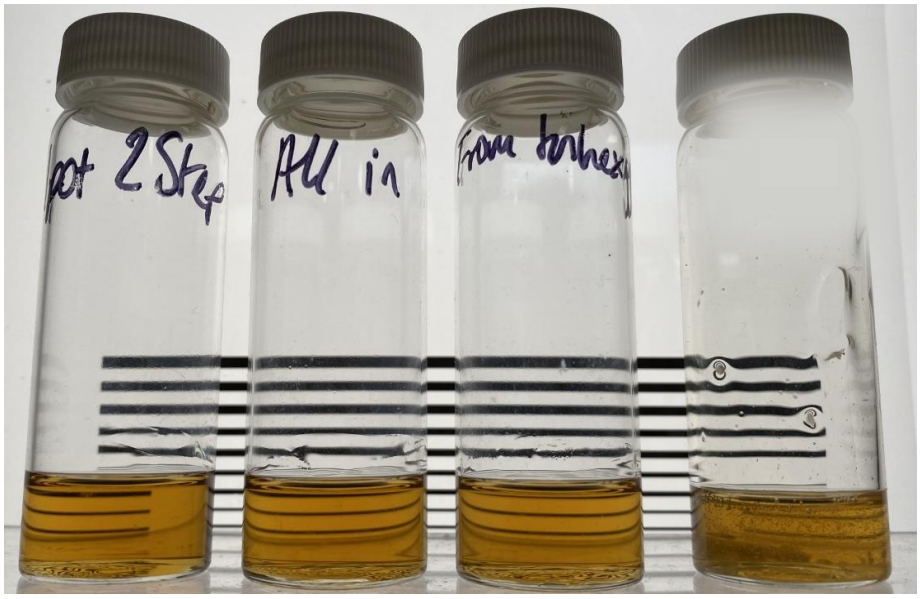
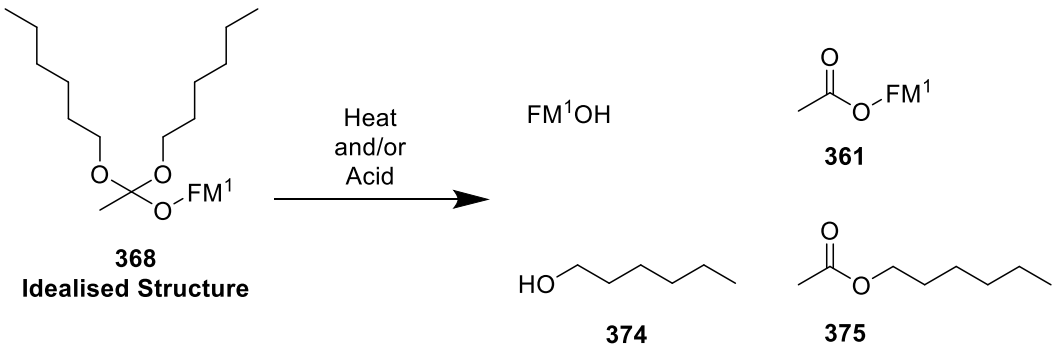


Figure 30: a) The solubility of orthoesters made using different reactions conditions and compared to FM^1; b) after 3 months the solubility has not changed

5.2.3. Results and Discussion - Delivery of FM^1 - Degradation of the Orthoester

Orthoesters have been shown to behave as solubilising agents for FM^1. However, since the orthoester will provide little friction modification performance, the orthoester must release FM^1 *in situ* of the lubricant oil to behave as a delivery system for FM^1. Orthoesters can degrade *via* a hydrolysis reaction when exposed to moisture and acid and since lubricant oils are known to become more acidic as they age, this degradation can be used as the *in situ* delivery system. However, this degradation does result in a range of products (Scheme 164). This means that some of the FM^1 could be incorporated into an acetate ester (**361**) rather than released, which could impact the friction performance. Nevertheless, the acetate ester (**361**) could also be prone to degradation itself through hydrolysis and thus release the FM^1. Therefore, the lack of control over the selectivity of the degradation does not pose a significant problem to the application. The *n*-hexyl orthoester derivative (**366**) was chosen to investigate the degradation due to the promising solubility results.

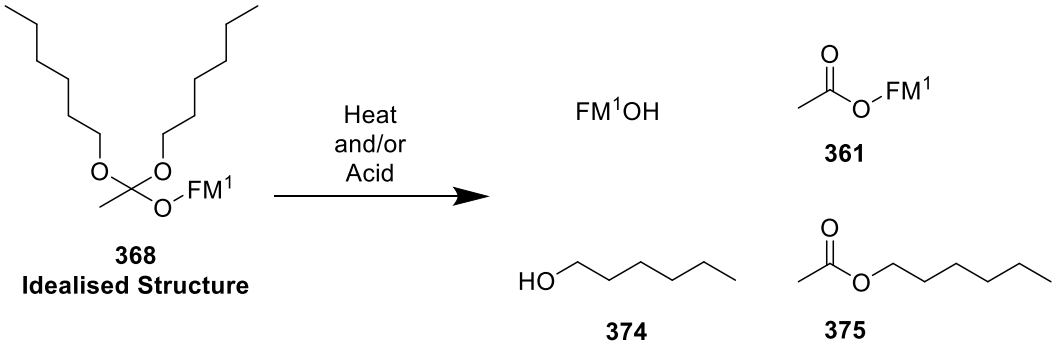


Scheme 164: Using the degradation of hexyl/FM^1 orthoester to release FM^1

The conditions for the degradation of the orthoesters were developed to be as close as possible to real-world conditions. The concentration of the orthoester (2 wt%) was similar to the concentration it would be in a lubricant oil package and the solvents were chosen to mimic oil-like environments, such a pentane, nonane and a base oil (diluent oil, supplied by Lubrizol). The acid used was decanoic acid as it mimics the organic acids that may be present in the lubricant oil. Finally, all the degradations were undertaken under air to further mimic the lubricant oil environment. The effect of acid and temperature on the degradation was

investigated (Table 11). Unfortunately, due to the overlap in the ^{1}H-NMR it was only possible to qualitatively determine whether partial or full degradation had occurred. Further work is required to develop a technique to allow for quantification of the degradation. Furthermore, the yield of the FM^{1} from the degradation could also not be calculated due to the formation of a white solid which stuck the reaction flask, ^{1}H-NMR of this material showed that it was FM^{1}.

Table 11: The effect of temperature and acid on the degradation of orthoesters; [a] ^{1}H NMR yield determined by normalised integrals of FM^{1}OH to 361; [b] observed but could not be quantified; [c] orthoester concentration was 20 wt%



368
Idealised Structure

Entry	Decanoic acid (mol %)	Temp (°C)	Time (h)	Solvent	Degradation – Partial or Full	360 Yield (%)[a]
1	10	25	24	*n*-Pentane	Partial	0
2	20	25	24	*n*-Pentane	Partial	-[b]
3	50	25	24	*n*-Pentane	Partial	-[b]
4	10	138	24	*n*-Nonane	Full	13
5	0	138	24	*n*-Nonane	Full	14
6	10	138	24	Diluent oil[c]	Full	22
7	0	138	24	Diluent oil[c]	Full	20

The results in Table 11 show that the degradation of the orthoester was more dependent on the temperature of the reaction rather than acid. In all cases where heat was used, both with and without decanoic acid, there was full degradation. When decanoic acid was used at room temperature, only partial degradation was observed even when 50 mol% was used. The temperature effect was not surprising since the investigation into orthoesters throughout this thesis has shown that orthoesters readily undergo scrambling at elevated temperatures. Therefore, the presence of moisture and elevated temperatures increases the rate of the degradation (*via* hydrolysis) of the orthoester. Pleasingly the degradation was also successful in diluent oil, both with and without acid. In most cases, the FM^1 acetate ester (**361**) was also formed, however this was the minor FM^1 product and was only produced in 13% – 22% yield by ^1H NMR. There was a subtle increase in the formation of the FM^1 acetate ester (**361**) when the degradation was undertaken in diluent oil, this can be postulated to be because diluent oil is slightly acidic.

The use of orthoesters as liquidising agents and their subsequent degradation as a delivery system for lubricant additives, such as FM^1, has been proven to be a feasible approach. However, there are many other variables that need to be investigated in order to fully understand the degradation and if the selectivity and rate can be controlled. For example, the effects of time, temperature, inorganic acids and the presence of other lubricant additives all need to be studied. Furthermore, performance testing is required to make sure that the use of orthoesters and their degradation does not the impact the ability of FM^1 to reduce the coefficient of friction.

5.3. Conclusion

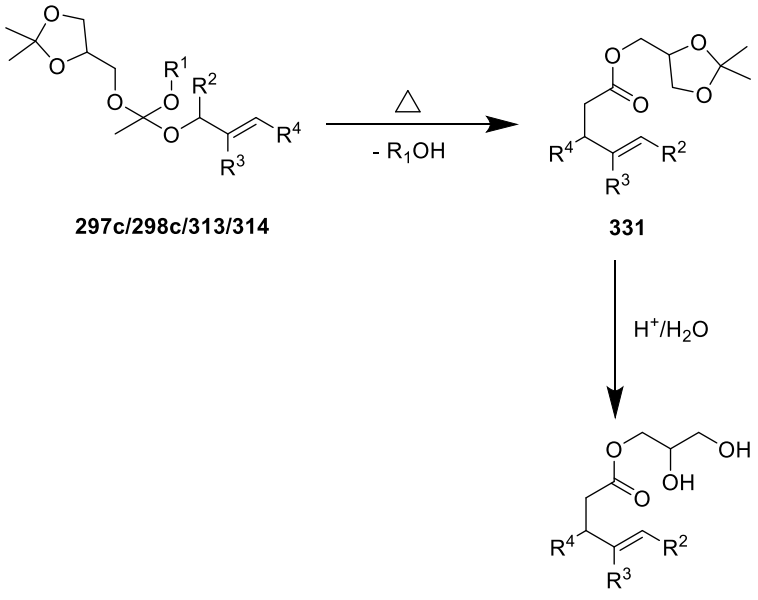
This chapter has highlighted that orthoesters can be used to deliver lubricant additives. Rearrangement and degradation of the orthoester have been harnessed as methods of releasing friction modifiers. However, both methods have their advantages and disadvantages. The rearrangement approach allowed for the rate and selectivity to be controlled whilst under inert conditions, which allowed for the design of a novel friction modifier with a slow rearrangement and good friction

performance. However, the conditions of the lubricant environment, such as the presence of air, had a detrimental impact on the rate and selectivity of the rearrangement. Additionally, the rearrangement was prone to forming side products. Conversely, the degradation approach allowed for the incorporation and release of a known high performing friction modifier, under the conditions of the lubricant oil environment. However, there was little control over the rate and selectivity, highlighted by full degradation occurring after 24 hours and formation of the undesirable acetate ester (**361**). Furthermore, the synthesis of the orthoester *via* the orthoester exchange approach resulted in a mixture of orthoester products and the ratio of these products could not be determined. This could result in poor synthetic reproducibility.

Overall, the orthoester degradation approach is the most suitable delivery method for the application in lubricant oil packages. The synthesis of the orthoester *via* the orthoester exchange approach is a more commercially viable route and the degradation works under the conditions of a lubricant oil environment without forming any unexpected or unknown side products. Furthermore, the FM^1 acetate ester (**361**) produced has the potential to also degrade to release FM^1. Therefore, further work should be devoted to further understanding the degradation of orthoesters, as well as creating a testing method to measure the ratio of the orthoester products synthesised *via* the orthoester exchange approach.

6.0. Conclusion

Herein, two new methods of delivering friction modifiers *in situ* of the engine or transmission of automotive vehicles have been developed. Firstly, friction modifiers, in the form of esters, have been synthesised through the direct orthoester Johnson-Claisen rearrangement. This rearrangement could be promoted by the heat of the engine sump and the increased acidity of the oil as it ages (Scheme 165). A range of orthoesters were shown to undergo the rearrangement, with the R^1 group affecting both the rate and selectivity of the reaction. The rate was particularly important as it would be desirable for the transformation to occur slowly to allow the friction modifier to be delivered over a long period of time to improve upon durability. The lead friction modifier (**353b**) was selected because it was shown to have the slowest rate of formation, demonstrated by quantitative rate studies, did not form any undesired side products and resulted in a reduction of the coefficient of friction similar to that of a commercial friction modifier (GMO). Unfortunately, the use of the orthoester Johnson-Claisen rearrangement as a delivery system was limited by the fact that the rearrangement rate and selectivity were dependent on both the reaction atmosphere (i.e. inert or air) and the concentration.

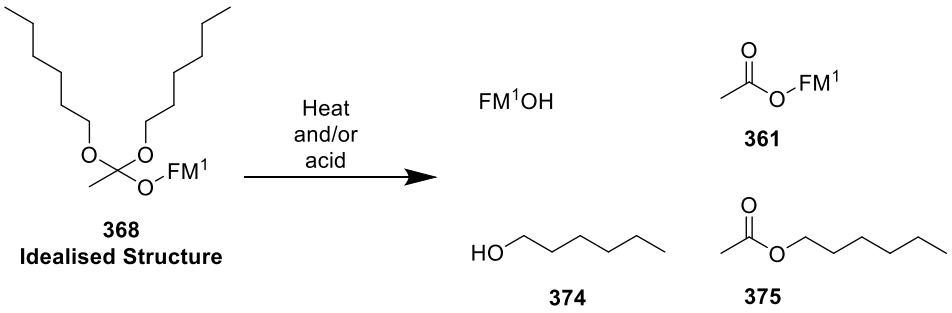


297c/298c/313/314 **331**

353a = R^2 = H; R^3 = H; R^4 = C_7H_{15}
353b = R^2 = H; R^3 = C_7H_{15}; R^4 = H
353c = R^2 = C_7H_{15}; R^3 = H; R^4 = H

Scheme 165: The delivery of ester friction modifiers via the orthoester Johnson-Claisen rearrangement

The second delivery method of friction modifiers took advantage of the instability of orthoesters. This method was also particularly useful since it allowed the use of novel friction modifiers that had already been developed. These friction modifiers (FM^1) were incorporated into orthoesters and when subjected to heat or acid, similar to the conditions of engine oil within the sump, the orthoesters were shown to degrade to release the friction modifier (Scheme 166). The method had further applications since incorporation of FM^1 into orthoesters significantly improved its solubility within lubricant packages, even when stored at room temperature for 4 months. The improved storage stability and solubility are significant advantages of the approach as they are important aspects of developing and commercialising novel additives. Further investigation into the degradation conditions, stability and particularly the impact on the friction performance would be instrumental to progressing this approach towards use in automotive vehicles.



368
Idealised Structure

361

374

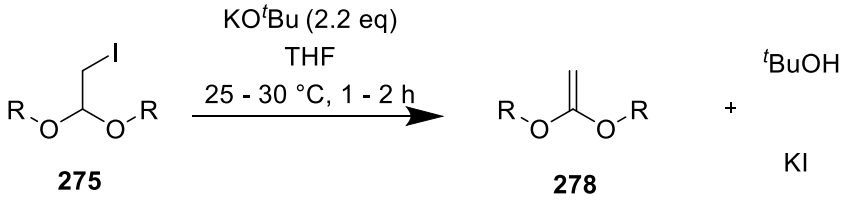
375

Scheme 166: The delivery of friction modifiers via the degradation of orthoesters

The use of the mixed orthoester Johnson-Claisen rearrangement and the degradation of orthoesters as delivery systems for friction modifiers improves upon work completed by Uhrich *et al.*[44] They demonstrated that esters could be pyrolyzed over time to produce acids and thus reduce friction. Whilst the method did successfully reduce friction over time, the reduction was only demonstrated in a base oil rather than a fully formulated package. Interactions with other components in a fully formulated package could affect the friction performance observed. All the HFRR testing completed in this thesis were undertaken in fully formulated packages to account for this. Furthermore, Uhrich *et al*. developed carboxylic acid friction modifiers which are known to cause corrosion problems within the automotive vehicle, the synthesis of neutral esters, as discussed in this

thesis, is much more favourable. Finally, the synthetic route proposed by Uhrich *et al.* was lengthy and expensive, which limits the viability of the work for commercial applications. Even though the synthesis of the orthoesters (**297c, 298c, 313, 314**) designed to undergo the rearrangement was also lengthy, the synthesis of the orthoesters (**368**) designed to undergo degradations could be undertaken in one step using commercially available starting materials.

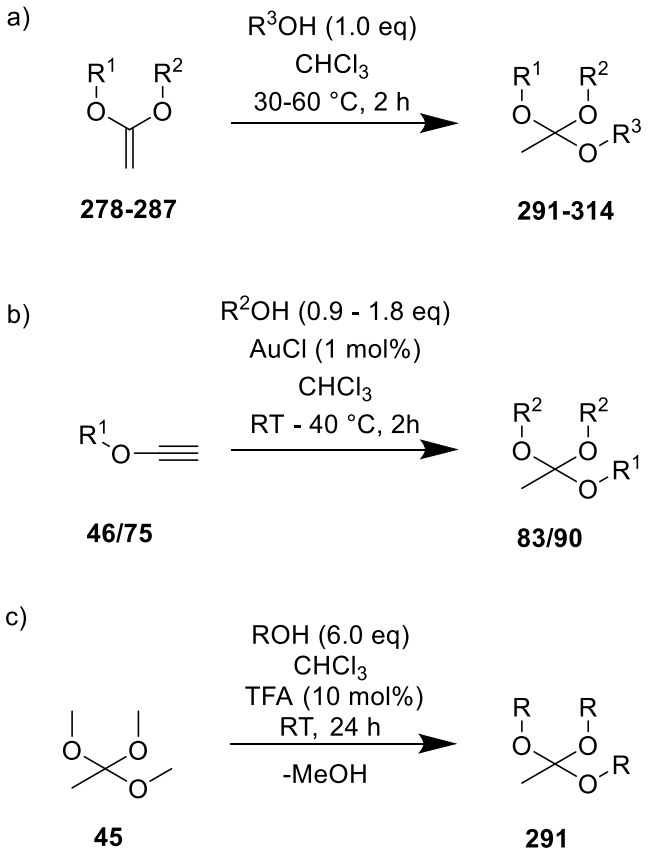
Whilst the main aim of this thesis was to develop an *in situ* delivery system for friction modifiers, there were several other developments in other areas along the way. Firstly, this work demonstrated that the dehydrohalogenation of haloacetals (**275**) to form ketene acetals (**278**) (Scheme 167) could be undertaken without a phase transfer catalyst. The use of phase transfer catalysis in this transformation has been favoured over recent years[151–153,156,208], although investigation without the catalysis has been undertaken, many of these studies provided little to no characterisation data and yields.[94,99,143,146,147] Removing the phase transfer catalysis made the work up procedure of the ketene acetal easier and often eliminated the need for further purification.



Scheme 167: Examples of the dehydrohalogenation of haloacetals without the use of phase transfer catalysis

Three modified methods towards to the synthesis of orthoesters were also described. Firstly, the synthesis of orthoesters from the addition of alcohols to ketene acetals (Scheme 168a) was modified from McGeary and Cosgrove's[54] work by reducing the equivalents of the ketene acetal required. This improved the applicability of this method to a wide variety of ketene acetals, which was demonstrated by the formation of a range of orthoesters, including previously unknown mixed tri-substituted orthoesters wherein all the groups are different. Secondly, the gold catalysed addition of alcohols to acetylenes (Scheme 168b) was shown to produce a small range of orthoesters, with the gold catalysis tolerating

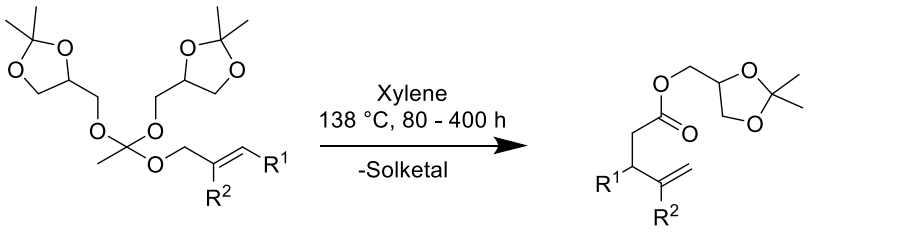
more sterically hindered alcohols compared to the zinc and mercury catalysts originally described by Broekema.[53] Finally, the orthoester exchange approach (Scheme 168c), which was previously limited to orthoformates[130,259] and orthopropionates[65], generated trialkyl orthoesters (**291**) in scales of up to 100 g within 24 hours. However, this approach was limited to trialkyl orthoesters since attempts to synthesise mixed orthoesters resulted in mixtures of the mono-, di- and tri-substituted products.



Scheme 168: The synthesis of orthoesters by a) Addition of alcohols to ketene acetals; b) Addition of alcohols to alkoxy acetylenes; c) The orthoester exchange approach

The mixed orthoester Johnson-Claisen rearrangement promoted by heat alone was also described (Scheme 169). Whilst the rearrangement had previously been developed by Mukaiyama[219] and McGeary and Cosgrove[96], both of these rearrangements used expensive catalysts and recorded limited characterisation data of the esters produced. Furthermore, this thesis emphasised the effect of the scrambling that occurs during the rearrangement which can impact the purity of the final ester. Moreover, the synthesis and isolation of allylic ketene acetals led

to the conclusion that the formation of the ketene acetal was the rate limiting step in the orthoester Johnson-Claisen rearrangement. A study into the effect of substituents and temperature on the scrambling of the orthoester would be invaluable to further understanding the rates of both the original and direct orthoester Johnson-Claisen rearrangement.

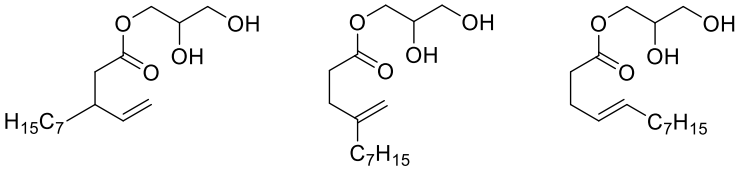


297c = $R^1 = C_7H_{15}$; $R^2 = H$
298c = $R^1 = H$; $R^2 = C_7H_{15}$

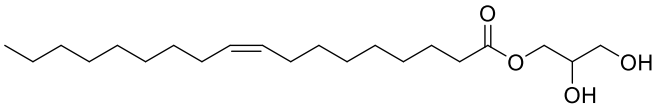
331a = $R^1 = C_7H_{15}$; $R^2 = H$ (62%)
331b = $R^1 = H$; $R^2 = C_7H_{15}$ (71%)

Scheme 169: An example of the direct orthoester Johnson-Claisen rearrangement

Investigation into the friction performance of the final ester products synthesised by the direct orthoester Johnson-Claisen rearrangement (Scheme 170) highlighted the impact of the position of the alkene on the performance. Although the reasoning behind the differences in performance is well known, branching prevents dense packing at the surface of the metal, there is little evidence in the literature to prove this theory. The HFRR testing undertaken on esters (**353a-c**) validated this trend. Additionally, the comparison of these esters (**353a-c**) compared to a commercially known friction modifier (GMO, **2**) demonstrated that the linear ester (**353c**) had a small but significant reduction in the coefficient of friction. These results were contrary to literature precedent suggesting that longer chain lengths result in lower reductions in the coefficient of friction.[27,28,30] Therefore, these results could be used to develop novel friction modifiers, even without the delivery system described in this thesis.



353a **353b** **353c**



2
GMO

Scheme 170: The final ester products of the direct orthoester Johnson-Claisen rearrangement and GMO (2)

7.0. Experimental

General Information

All commercially purchased reagents were used without further purification, including all dry solvents. Specifically, the chloroform used for the synthesis of orthoesters was anhydrous and stabilised by amylenes, which was obtained from Sigma Aldrich. GMO was also obtained from Sigma Aldrich. Diluent oil and FM^1 were supplied by Lubrizol Ltd. NMR spectra were recorded on a Bruker AVANCE 500 (^1H: 500 MHz) spectrometer at 298 K. NMR spectra were referenced to the residual solvent peak (^1H: $CDCl_3$, 7.27 ppm; C_6H_6, 7.16 ppm). Chemical shifts (δ) are denoted in ppm. All reactions were carried out under a "non-rigorous" nitrogen atmosphere (no degassing of the reaction solution), unless stated otherwise.

Mass spectra analysis was undertaken by Emma Haywood and Anthony Shacklock from the Analytical Services department of Lubrizol Ltd. in Hazelwood. For certain compounds, the mass spectra data is not included due to the fact that the desired mass ion was not observed during the test. This could be a result of the method used at Lubrizol Ltd. The ketene acetals were too unstable to obtain mass spectra analysis.

Compounds which incorporate FM^1 or FM^2 are not described in this experimental due to confidentiality reasons.

NMR Rate Studies

Orthoester and dodecane, at a concentration of 0.0024 mol/L, was heated to 138 °C. Samples were taken initially after 30 min and then periodically until the reaction was complete (as monitored by ^1H NMR spectroscopy). The analyte samples were prepared by dissolving 25 mg of material into 900 mg of $CDCl_3$ with a known amount of the wt% standard HMDS added, and then mixed to generate homogenous samples. The rate of the reaction was then calculated by integrations relative to HMDS by ^1H NMR spectroscopy. The NMR analysis of the samples was completed on a Bruker AVANCE 500 spectrometer with a 5mm probe and using standard conditions for the acquisition of ^1H NMR data using a d1=4sec. and zg30

to ensure full relaxation of protons. Whilst the 25 mg samples were collected by Charlotte Roy, the addition of $CDCl_3$ and subsequent analysis was completed by the NMR team (Adam Clarke, Emma Haywood, Gareth Hickinbotham) at Lubrizol. Ltd. in the Analytical Services department.

HFRR Test Procedure

Tests were undertaken by John Durham and Megan Williams in the Applied and Strategic Science department of Lubrizol Ltd. in Hazelwood. The HFRR test used was from an internal Lubrizol test method using the conditions below. The following testing protocol was used:

Load	200 g
Duration	60 minutes
Frequency	20 Hz
Temperature	Isothermal at 120 °C
Metallurgy	Standard steel ball on hardened steel disc

For each of the components tested, they were dosed into a fully formulated lubricant oil at 2 wt%. A baseline sample, of the lubricant oil on its own, was always collected as a reference.

Oxidative Resistance (L-85-99) Test Procedure

Tests were undertaken by technicians in the Blend Test department of Lubrizol Ltd. in Hazelwood. The tests were run using the standard L-85-99 procedure as described by The Coordinating European Council for the Development of Performance Tests for Fuels, Lubricants and Other Fluid (CEC). The standard L-85-99 protocol is as follows:

Pan Type	Tzero
Weight of sample	2.0 mg ± 0.05 mg
Air Atmosphere	100 (±7) psig, 690 (±48) KPa g
Flow Rate	Static, no flow
Sample Loading Temperature	<40 °C
Equilibrium Temperature	50 °C (±2 °C)
Equilibrium Time at 50 °C	5 minutes
Temperature Ramp Rate	40 (± 10) °C / minute
Isothermal Test Temperature	210 (± 0.5) °C
Test Duration	240 minutes

For each of the new components tested, they were dosed into a fully formulated lubricant oil at 2 wt%. A baseline sample, of the lubricant oil on its own, was always collected as a reference.

General Procedure A

To a solution of alcohol (mmol as stated) and acetylene (425 µL, 1.77 mmol, 40% wt in hexanes) was added Lewis acid (mmol as stated), at 5 °C, before being stirred at 25 °C for 2 h. Hexane (30 mL) was added and the solution was filtered and concentrated to dryness by reduced pressure to yield the title compound.

General Procedure B

To a solution of vinyl acetate (mmol as stated) and alcohol (mL as stated) at -10 °C, was added bromine (mol as stated) dropwise over the stated time. The solution was then allowed to warm to 25 °C and left stirring for 16 h. DCM (100 mL) was then added and washed with water (100 mL). The organic layer was separated and the aqueous extracted with further DCM (150 mL). The combined organic layers

were then dried with $MgSO_4$ and concentrated to dryness by reduced pressure to yield the crude bromoacetal, which was purified by distillation.

General Procedure C

To a solution of *p*-toluenesulfonic acid (mmol as stated) and 2-bromo-1,1-dimethoxyethane (mmol as stated) was added diol (mmol as stated). The solution was heated with stirring to 130 °C for the time stated with a Dean-Stark apparatus. The crude bromoacetal was then purified by distillation to yield the title compound.

General Procedure D

To a solution of vinyl ether (mmol as stated), alcohol (mmol as stated) and hexane/DCM (0.12 M, 3:1 v/v) was added NBS (mmol as stated) at 0 °C. Then stirred at 25 °C for 16 h. Pentane (20 mL) was added and the reaction mixture was cooled to -50 °C for 30 min. Pentane (150 mL) was added and the reaction mixture was filtered, washed water (2 x 100 mL), Sat. aq. $NaHCO_3$ (4 x 250 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound.

General procedure E

To a solution of vinyl ether (mmol as stated), alcohol (mmol as stated) and DCM (0.35 M) was added NIS (mmol as stated) at -30 °C portion wise over 10 mins. Pentane (100 mL) was added and the reaction mixture was, washed $Na_2S_2O_3$ (100 mL), Sat. aq. $NaHCO_3$ (2 x 200 mL) and brine (100 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound.

General Procedure F

To a solution of ethyl vinyl ether (mmol stated), palladium(II) trifluoroacetate (mmol stated), 1,10-phenanthroline (mmol stated) and DCM (5.6 M) was added alcohol (mmol as stated) and triethylamine (4 drops). The solution was stirred at 25 °C for 18 h. Diethyl ether (150 mL) was added and the solution was filtered through celite and concentrated to dryness by reduced pressure, which was purified by silica gel chromatography.

General Procedure G

To a solution of bromoacetal (mmol as stated) and THF (0.14 M), at 0 °C, was added KO^{t}Bu (mmol as stated) portion wise over 45 - 50 min. The solution was then heated to 30 °C for 2 h. The reaction mixture was cooled to 0 °C and further KO^{t}Bu (mmol stated) was added portion wise over 10 min. The solution was then heated to 30 °C for 2 h. Hexane (200 mL) was added, the solution was filtered through a small cotton wool plug and concentrated to dryness by reduced pressure to yield the title compound.

General Procedure H

To a stirring solution of KO^{t}Bu (mmol stated) in THF (0.33 M) was added iodoacetal (mmol as stated) in THF (0.5 M) dropwise over 45 min – 1 h. The solution was then stirred at stirred at 25 °C for 1.25 h. Hexane (100 mL) was then added and the solution was concentrated to dryness by reduced pressure. Further hexane (100 mL) was added and the solution was filtered through a small pad of cotton wool before being concentrated to dryness to yield the title compound.

General Procedure I

To a solution of bromoacetal (mmol as stated) and THF (0.14 M), at 0 °C, was added KO^{t}Bu (mmol as stated) portion wise over 30 - 40 min. The solution was then stirred at the stated temperature for 2 h. Hexane (100 mL) was then added and the solution was concentrated to dryness by reduced pressure. Further hexane (100 mL) was added and the solution was filtered through a small pad of cotton wool before being concentrated to dryness to yield the title compound.

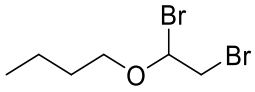
General Procedure J

To alcohol (mmol stated) was added ketene acetal (mmol stated) in $CHCl_3$ (0.2 M), *via* syringe pump, over 45 min. The solution was then heated to the stated temperature for 2 h before being concentrated to dryness by reduced pressure to yield the title compound.

General Procedure K

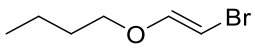
To a stirring solution of alcohol (mmol/mol stated) in chloroform (0.6 M) was added trimethyl orthoacetate (mmol/mol stated) and trifluoroacetic acid (mmol/mol stated). The solution was then left to stir at 25 °C for 24 h before being concentrated to dryness by reduced pressure. The crude orthoester was then purified by distillation to yield the title compound.

1-(1,2-Dibromoethoxy)butane (73)



To a solution of butyl vinyl ether (92.8 ml, 720 mmol) in DCM (240 mL), at 0 °C, was added bromine (36.8 mL, 720 mmol) in DCM (80 mL) dropwise over 2.5 h. The solution was held at 25 °C for 18 h and then concentrated to dryness by reduced pressure to yield the title compound (180.1 g, 97%) as an orange liquid. ν_{max}/cm^{-1}; 2959, 2935, 2874, 1464, 1422, 1114 and 573; ^{1}H NMR (500 MHz, $CDCl_3$); 6.02 (1H, dd, J 9.4, 2.6 Hz, CH), 3.96 (1H, dd, J 10.8, 9.4 Hz, CH_2), 3.92-3.87 (2H, m, CH_2), 3.56 (1H, dt, J 9.5, 6.5 Hz, CH_2), 1.70-1.62 (2H, m, CH_2), 1.49-1.38 (2H, m, CH_2), 0.95 (3H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 91.7 (CH), 72.6 (CH_2), 34.5 (CH_2), 30.6 (CH_2), 19.3 (CH_2), 13.8 (CH_3).[a] The data was consistent with the literature.[116]

(*E*)-1-((2-Bromovinyl)oxy)butane (74)



To a solution of *N,N*-dimethyldodecylamine (82.0 g, 384 mmol) heated to 80 °C was added 1-(1,2-dibromoethoxy)butane (40.0 g, 154 mmol) dropwise over 2 h. Vacuum was then applied (60 mbar) and the temperature increased to 100 °C. The reaction was held with stirring for 5 h to yield a colourless distillate. The crude product was then redistilled (70 °C, 60 mbar) to yield the title compound (17.4 g, 63%) as a colourless liquid. ν_{max}/cm^{-1}; 3109, 2960, 2934, 2874, 1641, 1097 and 688; ^{1}H NMR (500 MHz, $CDCl_3$); 6.60 (1H, d, J 4.2 Hz, CH), 5.09 (1H, d, J 4.2 Hz, CH), 3.92

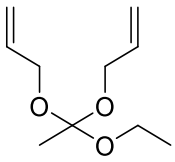
[a] Mass spectra analysis was run but the desired mass ion was not observed.

(2H, t, J 6.7 Hz, CH_2), 1.71-1.62 (2H, m, CH_2), 1.48-1.32 (2H, m, CH_2), 0.95 (3H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 147.9 (CH), 82.0 (CH), 73.4 (CH_2), 32.0 (CH_2), 18.8 (CH_2), 14.0 (CH_3).[a] The data was consistent with the literature.[116]

Butoxyacetylene (75)

To a solution of (*E*)-1-((2-bromovinyl)oxy)butane (2.00 g, 11.2 mmol) was added dodecane (10 mL), KOH (1.56 g, 27.9 mmol) and tetraoctylammonium bromide (610 mg, 1.12 mmol). The solution was then heated to 80 °C for 6 h. The crude acetylene was then distilled (80 °C, 60 mbar) to yield the title compound (593 mg, 65%) as a colourless liquid. ν_{max}/cm^{-1}; 3319, 2952, 2877, 2150, 1739 and 1466; ^1H NMR (500 MHz, $CDCl_3$); 4.08 (2H, t, J 6.5 Hz, CH_2), 1.78-1.69 (2H, m, CH_2), 1.52 (1H, s, CH), 1.48-1.38 (2H, m, CH_2), 0.95 (3H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 91.4 (CH), 78.9 (CH_2), 31.0 (CH_2), 18.5 (CH_2), 13.7 (CH_3).[a] The data was consistent with the literature.[118]

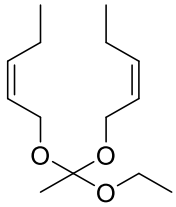
3-(1-(Allyloxy)-1-ethoxyethoxy)prop-1-ene (83a)



Following general procedure A with ethoxyacetylene (5.00 g, 28.5 mmol, 40% wt in hexanes), allyl alcohol (3.51 mL, 51.3 mmol) and $ZnCl_2$ (20.0 mg, 0.150 mmol). Purification by distillation (105 °C, 60 mbar) gave the title compound (2.12 g, 40%) as a colourless liquid. ν_{max}/cm^{-1}; 3082, 2980, 2933, 2873 and 1648; ^1H NMR (500 MHz, $CDCl_3$); 5.93 (2H, ddt, J 17.2, 10.7, 5.4 Hz, CH), 5.29 (2H, app. dq, J 17.2, 1.6 Hz, CH), 5.14 (2H, app. dq, J 10.4, 1.6 Hz, CH), 4.06 (4H, dt, J 5.4, 1.6 Hz, CH_2), 3.58 (2H, q, J 7.0 Hz, CH_2), 1.51 (3H, s, CH_3), 1.21 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.6 (CH), 116.0 (CH_2), 114.4 (C), 63.3 (CH_2), 58.2 (CH_2), 20.3 (CH_3), 15.2 (CH_3); HRMS *m/z* (ESI^+) 209.1137 ($M + Na^+$) $C_{10}H_{18}O_3Na^+$ requires 209.1148.

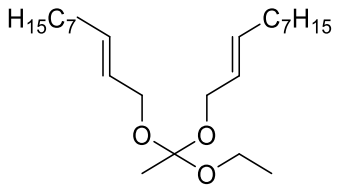
[a] Mass spectra analysis was run but the desired mass ion was not observed.

(*Z*)-1-(1-Ethoxy-1-(((Z)-pent-2-en-1-yl)oxy)ethoxy)pent-2-ene (83b)



Following general procedure A with ethoxyacetylene (5.00 g, 28.5 mmol, 40% wt in hexanes), *cis*-2-penten-ol (5.18 mL, 51.3 mmol) and $ZnCl_2$ (20.0 mg, 0.150 mmol). Purification by distillation (145 °C, 60 mbar) gave the title compound (4.06 g, 59%) as a colourless liquid. ν_{max}/cm^{-1}; 2936, 2966, 2877, 1658 and 1462; ^1H NMR (500 MHz, $CDCl_3$); 5.54-5.50 (4H, m, CH), 4.11 (4H, dd, J 4.1, 1.7 Hz, CH_2), 3.57 (2H, q, J 7.1 Hz, CH_2), 2.08 (4H, qdd, J 7.4, 5.4, 2.4 Hz, CH_2), 1.51 (3H, s, CH_3), 1.22 (3H, t, J 7.1 Hz, CH_3), 0.98 (6H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.3 (CH), 125.4 (CH), 58.0 (CH_2), 57.9 (CH_2), 20.9 (CH_2), 20.4 (CH_3), 15.2 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 265.1493 ($M + Na^+$) $C_{14}H_{25}O_3Na^+$ requires 265.1774.

(*E*)-1-(1-(((E)-Dec-2-en-1-yl)oxy)-1-ethoxyethoxy)dec-2-ene (83c)



Synthesis by reaction of ethoxyacetylene and $ZnCl_2$

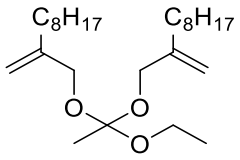
Following general procedure A with dec-2-en-1-ol (2.00 g, 12.8 mmol), ethoyxacetylene (1.24 g, 7.11 mmol, 40% wt in hexanes) and $ZnCl_2$ (6.00 mg, 0.0440 mmol) gave the title compound (2.2 g, 81%) as an orange liquid.

Synthesis by reaction of ethoxyacetylene and AuCl

Following general procedure A with dec-2-en-1-ol (500 mg, 3.20 mmol), ethoyxacetylene (425 µL, 1.77 mmol, 40% wt in hexanes) and AuCl (4.00 mg, 0.0172 mmol) gave the title compound (508 mg, 75%) as a brown/orange liquid.

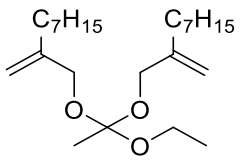
ν_{max}/cm^{-1}; 2955, 2924, 2855, 1456 and 1378; ^{1}H NMR (500 MHz, $CDCl_3$) 5.74-5.64 (2H, m, CH), 5.60-5.49 (2H, m, CH), 3.99 (4H, dd, J 6.1, 1.3 Hz, CH_2), 3.57 (2H, q, J 7.1 Hz, CH_2), 2.08-1.98 (4H, m, CH_2), 1.49 (3H, s, CH_3), 1.41-1.34 (4H, m, CH_2), 1.34-1.24 (16H, m, CH_2), 1.21 (3H, t, J 7.1 Hz, CH_3), 0.92-0.86 (6H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 134.0 (CH), 126 (CH), 114.3 (C), 63.0 (CH_2), 57.9 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 22.6 (CH_2), 20.5 (CH_3), 15.2 (CH_3), 14.1 (CH_3); HRMS *m/z* (ESI^+) 405.3344 ($M + Na^+$) $C_{24}H_{46}O_3Na^+$ requires 405.3339.

2-((1-Ethoxy-1-((2-methylenedecyl)oxy)ethoxy)methyl)dec-1-ene (83d)



Following general procedure A with 2-methylenedecan-1-ol (500 mg, 2.94 mmol), ethoxyacetylene (780 µL, 3.26 mmol, 40% wt in hexanes) and AuCl (8.00 mg, 0.0344 mmol) at 40 °C, gave the title compound (506 mg, 84%) as a brown liquid. ν_{max}/cm^{-1}; 2956, 2925, 2855, 1740,1652 and 1459; ^{1}H NMR (500 MHz, $CDCl_3$) 5.05 (2H, d, J 2.0 Hz, CH), 4.85 (2H, d, J 2.0 Hz, CH), 3.97 (4H, s, CH_2), 3.60 (2H, q, J 7.1 Hz, CH_2), 2.06 (2H, t, J 7.6 Hz, CH_2), 1.51 (3H, s, CH_3), 1.49-1.40 (2H, m, CH_2), 1.33-1.23 (24H, m, CH_2), 1.21 (3H, t, J 7.1 Hz, CH_3), 0.89 (6H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 146.5 (C), 114.6 (C), 110.2 (CH_2), 65.1 (CH_2), 58.0 (CH_2), 33.6 (CH_2), 32.1 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 15.4 (CH_3), 14.3 (CH_3); HRMS *m/z* (ESI^+) 433.3646 ($M + Na^+$) $C_{26}H_{50}O_3Na^+$ requires 433.3652.

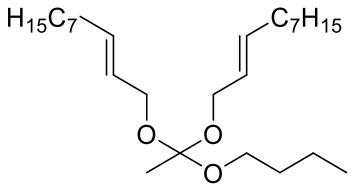
2-((1-Ethoxy-1-((2-methylenenonyl)oxy)ethoxy)methyl)non-1-ene (83e)



Following general procedure A with 2-methylenenonanol (500 mg, 3.20 mmol), ethoxyacetylene (850 µL, 3.54 mmol, 40% wt in hexanes) and AuCl (8.00 mg, 0.0320 mmol) at 40 °C, gave the title compound (447 mg, 73%) as a brown liquid.

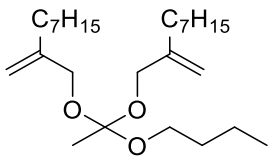
ν_{max}/cm^{-1}; 2956, 2925, 2856, 1741, 1652 and 1459; ^{1}H NMR (500 MHz, $CDCl_3$); 5.04 (2H, d, J 2.0 Hz, CH), 4.84 (2H, d, J 2.0 Hz, CH), 3.96 (4H, s, CH_2), 3.59 (2H, q, J 7.1 Hz, CH_2), 2.05 (4H, t, J 7.7 Hz, CH_2), 1.50 (3H, s, CH_3), 1.44 (4H, m, CH_2), 1.27 (16H, m, CH_2), 1.20 (3H, t, J 7.1 Hz, CH_3), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.3 (C), 114.5 (C), 110.3 (CH_2), 65.1 (CH_2), 58.0 (CH_2), 33.6 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 15.4 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 405.3333 ($M + Na^+$) $C_{24}H_{46}O_3Na^+$ requires 405.3339.

(*E*)-1-(1-Butoxy-1-(((*E*)-dec-2-en-1-yl)oxy)ethoxy)dec-2-ene (90a)



Following general procedure A with dec-2-en-1-ol (429 mg, 2.75 mmol), butoxyacetylene (150 mg, 1.53 mmol) and AuCl (4.00 mg, 0.0172 mmol) at 40 °C, gave the title compound (333 mg, 59%) as a brown liquid. ν_{max}/cm^{-1}; 2956, 2924, 2855, 1744, 1465 and 1378; ^{1}H NMR (500 MHz, $CDCl_3$); 5.74-5.64 (2H, m, CH), 5.60-5.51 (2H, m, CH), 3.99 (4H, dd, J 6.2, 1.3 Hz, CH_2), 3.49 (2H, q, J 6.7 Hz, CH_2), 2.08-1.98 (4H, m, CH_2), 1.51-1.46 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.43-1.34 (6H, m, CH_2), 1.33-1.23 (16H, m, CH_2), 0.93 (3H, t, J 7.4 Hz, CH_3), 0.89 (6H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.4 (CH), 126.2 (CH), 63.2 (CH_2), 62.3 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 29.33 (CH_2), 29.32 (CH_2), 29.30 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 19.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS *m/z* (ESI^+) 433.3669 ($M + Na^+$) $C_{26}H_{50}O_3Na^+$ requires 433.3652.

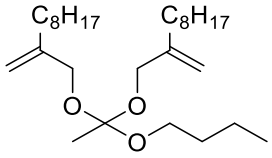
2-((1-Butoxy-1-((2-methylenenonyl)oxy)ethoxy)methyl)non-1-ene (90b)



Following general procedure A with 2-methylenenonanol (215 mg, 1.50 mmol), hexane (100 µL), butoxyacetylene (150 mg, 1.53 mmol) and AuCl (4.00 mg, 0.0172

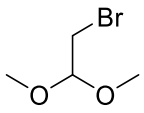
mmol) at 40 °C, gave the title compound (286 mg, 50%) as a brown liquid. ν_{max}/cm^{-1}; 2957, 2926, 2857, 1653, 1464 and 1378; ^{1}H NMR (500 MHz, $CDCl_3$); 5.05 (2H, d, J 2.0 Hz, CH_2), 4.85 (2H, d, J 2.0 Hz, CH_2), 3.97 (4H, s, CH_2), 3.54-3.48 (2H, m, CH_2), 2.06 (4H, t, J 7.6 Hz, CH_2), 1.58-1.54 (4H, m, CH_2), 1.51 (3H, s, CH_3), 1.46-1.42 (2H, m, CH_2), 1.32-1.23 (16H, m, CH_2), 0.93 (3H, t, J 7.3 Hz, CH_3), 0.89 (6H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.4 (C), 114.6 (C), 110.1 (CH_2), 65.0 (CH_2), 62.4 (CH_2), 33.6 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 19.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS *m/z* (ESI$^+$) 433.3654 (M + Na$^+$) $C_{26}H_{50}O_3Na^+$ requires 433.3652.

2-((1-Butoxy-1-((2-methylenedecyl)oxy)ethoxy)methyl)dec-1-ene (90c)



Following general procedure A with 2-methylenedecanol (234 mg, 1.50 mmol), hexane (100 µL), butoxyacetylene (150 mg, 1.53 mmol) and AuCl (4.00 mg, 0.0172 mmol) at 40 °C, gave the title compound (315 mg, 52%) as a brown liquid. ν_{max}/cm^{-1}; 2957, 2925, 2855, 1653, 1465 and 1377; ^{1}H NMR (500 MHz, $CDCl_3$); 5.05 (2H, d, J 2.0 Hz, CH_2), 4.85 (2H, d, J 2.0 Hz, CH_2), 3.96 (4H, s, CH_2), 3.54-3.48 (2H, m, CH_2), 2.05 (4H, t, J 7.5 Hz, CH_2), 1.60-1.53 (4H, m, CH_2), 1.42-1.37 (4H, m, CH_2), 1.32-1.22 (18H, m, CH_2), 0.93 (3H, t, J 7.3 Hz, CH_3), 0.89 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.5 (C), 114.6 (C), 110.1 (CH_2), 65.0 (CH_2), 62.4 (CH_2), 33.6 (CH_2), 33.58 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 19.6 (CH_2), 14.2 (CH_3), 14.0 (CH_3); HRMS *m/z* (ESI$^+$) 461.3958 (M + Na$^+$) $C_{26}H_{50}O_3Na^+$ requires 461.3965.

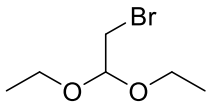
2-Bromo-1,1-dimethoxyethane (269a)



Following general procedure B with vinyl acetate (42.8 mL, 465 mmol), methanol (98 mL) and bromine (24.0 mL, 465 mol). Addition was completed over 4 h.

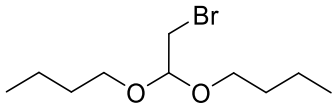
Concentration to dryness resulted in the title compound (57.6 g, 73%) as a yellow liquid. ν_{max}/cm^{-1}; 2937, 2833, 1447, 1118 and 1058; ^{1}H NMR (500 MHz, $CDCl_3$); 4.55 (1H, t, J 5.4 Hz, CH), 3.40 (6H, s, CH_3), 3.37 (2H, d, J 5.4 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 103.3 (CH), 54.2 (CH_3), 31.0 (CH_2).[a] The data was consistent with the literature.[260]

2-Bromo-1,1-diethoxyethane (269b)



Following general procedure B with vinyl acetate (38.5 mL, 417 mmol), methanol (127 mL) and bromine (21.4 mL, 417 mmol). Addition was completed over 4 h. Addition was completed over 4 h. Concentration to dryness resulted in the title compound (58.8 g, 70%) as a yellow liquid. ν_{max}/cm^{-1}; 2977, 2930, 2882 and 1054; ^{1}H NMR (500 MHz, $CDCl_3$); 4.67 (1H, t, J 5.5 Hz, CH), 3.70 (2H, dq, J 9.4, 7.1 Hz, CH_2), 3.58 (2H, dq, J 9.4, 7.1 Hz, CH_2), 3.37 (2H, d, J 5.5 Hz, CH_2), 1.24 (3H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 101.5 (CH), 62.4 (CH_2), 31.9 (CH_2), 15.2 (CH_3).[a] The data was consistent with the literature.[261]

1-(2-Bromo-1-butoxyethoxy)butane (269c)

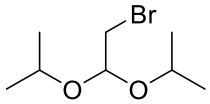


Following general procedure B with vinyl acetate (21.4 mL, 232 mmol), butanol (110 mL) and bromine (12.0 mL, 232 mmol). Addition was completed over 2 h. Purification by distillation (70 °C, 60 mbar) gave the title compound (41.6 g, 71%) as a colourless liquid. ν_{max}/cm^{-1}; 2958, 2933, 2873, 1464, 1112, 1067 and 1042; ^{1}H NMR (500 MHz, $CDCl_3$); 4.76 (1H, t, J 5.5 Hz, CH), 3.64 (2H, dt, J 9.3, 6.6 Hz, CH_2), 3.51 (2H, dt, J 9.3, 6.6 Hz, CH_2), 3.37 (2H, d, J 5.5 Hz, CH_2), 1.63-1.55 (2H, m, CH_2),

[a] Mass spectra analysis was run but the desired mass ion was not observed.

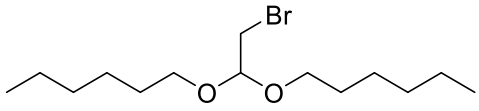
1.45-1.36 (2H, m, CH_2), 0.93 (3H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 102.0 (CH), 66.7 (CH_2), 31.93 (CH_2), 31.92 (CH_2) 19.5 (CH_2), 14.3 (CH_3).[a]

2-(2-Bromo-1-isopropoxyethoxy)propane (269d)



Following general procedure B with vinyl acetate (5.40 mL, 58.1 mmol), isopropanol (23.0 mL) and bromine (3.00 mL, 58.1 mmol). Addition was completed over 45 min. Purification by distillation (90 °C, 60 mbar) gave the title compound (1.4 g, 8%) as a yellow liquid. ν_{max}/cm^{-1}; 2973, 2931 and 1021; ^1H NMR (500 MHz, $CDCl_3$); 4.72 (1H, t, J 5.3 Hz, CH), 3.88 (2H, app. sept, J 6.2 Hz, CH), 3.32 (2H, d, J 5.3 Hz, CH_2), 1.23 (6H, d, J 6.2 Hz, CH_2), 1.19 (6H, t, J 6.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 99.3 (CH), 69.2 (CH), 33.3 (CH_2), 23.1 (CH_3), 22.4 (CH_3).[a] The data was consistent with the literature.[261]

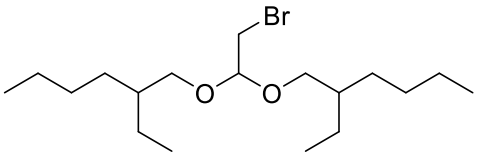
1-2(Bromo-1-(hex0yloxy)ethoxy)hexane (269e)



Following general procedure B with vinyl acetate (21.4 mL, 232 mmol), hexanol (150 mL) and bromine (12.0 mL, 0.23 mmol). Addition was completed over 3 h. Purification by distillation (90 °C, 60 mbar) gave the title compound (55.8 g, 79%) as a slightly cloudy colourless liquid. V_{max}/cm^{-1}; 2955,2930, 2859, 1467, 1114, 1062 and 1024; ^1H NMR (500 MHz, $CDCl_3$); 4.66 (1H, t, J 5.5 Hz, CH), 3.63 (2H, dt, J 9.2, 6.6 Hz, CH_2), 3.50 (2H, dt, J = 9.2, 6.6 Hz, CH_2), 3.37 (2H, d, J 5.5 Hz, CH_2), 1.60 (4H, q, J 6.6 Hz, CH_2), 1.41-1.34 (4H, m, CH_2), 1.34-1.26 (8H, m, CH_2), 0.9 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (500 MHz, $CDCl_3$); 101.7 (CH), 67.0 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3); HRMS *m/z* (ESI^+) 331.1243 and 333.1243 ($M + Na^+$) $C_{14}H_{91}BrO_2Na^+$ requires 331.1278 and 333.1243.

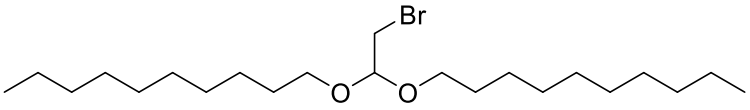
[a] Mass spectra analysis was run but the desired mass ion was not observed.

3-((2-Bromo-1-((2-ethylhexyl)oxy)ethoxy)methyl)heptane (269f)



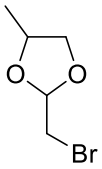
Following general procedure B with vinyl acetate (21.4 mL, 232 mmol), 2-ethylhexanol (188 mL) and bromine (12.0 mL, 232 mmol) Addition was completed over 2 h. Purification by distillation (120 °C, 60 mbar) gave the title compound (60.0 g, 71%) as a slightly cloudy colourless liquid. ν_{max}/cm^{-1}; 2958, 2926, 2873, 2860, 1461, 1117 and 1047; ^{1}H NMR (500 MHz, $CDCl_3$); 4.63 (1H, t, J 5.5 Hz, CH), 3.58-3.49 (2H, m, CH_2), 3.40-3.33 (4H, m, CH_2), 1.51 (2H, hept, J 5.9 Hz, CH), 1.46-1.24 (16H, m, CH_2), 0.93-086 (12H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); Diastereoisomers present; 102.2 (CH), 69.6 (CH_2), 39.9 (CH), 31.9 (CH_2), 30.61 (CH_2), 30.57 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 23.92 (CH_2), 23.90 (CH_2), 23.2 (CH_2), 14.3 (CH_3), 11.24 (CH_3), 11.21 (CH_3); HRMS *m/z* (ESI^+) 387.1814 and 389.1849 ($M + Na^+$) $C_{18}H_{37}BrO_2Na^+$ requires 387.1814 and 389.1846.

1-(2-Bromo-1-(decyloxy)ethoxy)decane (269g)



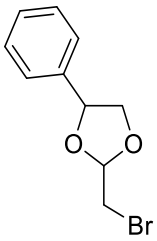
Following general procedure B with vinyl acetate (10.7 mL, 116 mmol), decanol (115 mL) and bromine (6.00 mL, 116 mmol). Addition was completed over 2 h. Purification by distillation (160 °C, 60 mbar) gave the title compound (25.5 g, 52%) as a yellow liquid. ν_{max}/cm^{-1}; 2922, 2853, 1456 and 1117; ^{1}H NMR (500 MHz, $CDCl_3$); 4.66 (1H, t, J 5.5 Hz, CH), 3.62 (2H, dt, J 9.2, 6.6 Hz, CH_2), 3.50 (2H, dt, J 9.2, 6.6 Hz, CH_2), 3.37 (2H, d, J 5.5 Hz, CH_2), 1.60 (4H, p, J 6.7 Hz, CH_2), 1.40-1.34 (4H, m, CH_2), 1.34-1.23 (24H, m, CH_2), 0.89 (6H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 101.9 (CH), 67.1 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 26.3 (CH_2), 22.8 (CH_2), 14.3 (CH_3); HRMS m/z (ESI^+) 443.2495 and 445.2467 ($M + Na^+$) $C_{22}H_{45}BrO_2Na^+$ requires 443.2460 and 445.2487.

2-(Bromomethyl)-4-methyl-1,3-dioxolane (270a)



Following general procedure C with *p*-toluenesulfonic acid (50.0 mg, 0.263 mmol), 2-bromo-1,1-dimethoxyethane (5.00 g, 29.6 mmol) and 1,2-propanediol (2.17 mL, 29.6 mmol) for 2 h. Purification by distillation (155 °C, 60 mbar) resulted in crude bromoacetal. DCM (50 mL) was then added and washed with water (2 x 100 mL). The aqueous layer was then extracted DCM (100 mL) and the combined organic layers were dried $MgSO_4$ and concentrated to dryness to yield the title compound (3.55 g, 67%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2975, 2880, 2932 and 668; ^1H NMR (500 MHz, $CDCl_3$); 5.27 (1.0H, t, J 4.1 Hz, CH), 5.14 (1.0H, t, J 4.1 Hz, CH), 4.33 (1.0H, dp, J 7.1, 6.0 Hz, CH_2), 4.25 (1.0H, dp, J 7.1, 6.0 Hz, CH_2), 4.18 (1.0H, dd, J 7.9, 5.6 Hz, CH_2), 4.04 (1.0H, dd, J 7.5, 6.3 Hz, CH_2), 3.51 (1.0H, t, J 7.7 Hz, CH_2), 3.47 (1.0H, dp, J 7.7 Hz, CH_2), 3.40 (1.0H, dd, J 3.9, 1.8 Hz, CH), 3.37 (1.0H, dd, J 4.1, 2.0 Hz, CH), 1.83 (3H, d, J 6.0 Hz, CH_3), 1.29 (3H, d, J 6.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 102.2 (CH), 101.8 (CH), 74.0 (CH), 73.1 (CH), 72.2 (CH_2), 71.6 (CH_2), 33.1 (CH_2), 32.9 (CH_2), 18.2 (CH_3), 18.0 (CH_3). Diastereomeric ratio 1:1.[a] The data was consistent with the literature.[262]

2-(Bromomethyl)-4-phenyl-1,3-dioxolane (270b)

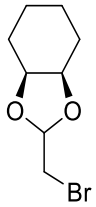


Following general procedure C with *p*-toluenesulfonic acid (50.0 mg, 0.263 mmol), 2-bromo-1,1-dimethoxyethane (5.00 g, 29.6 mmol) and 1-phenyl-1,2-ethanediol (4.09 g, 29.6 mmol) for 30 min. Purification by distillation (160 °C, 60 mbar) gave the title compound (6.60 g, 92%) as a slight yellow liquid. ν_{max}/cm^{-1}; 3064, 3032,

[a] Mass spectra analysis was run but the desired mass ion was not observed.

2967, 2884, 1135 and 697; ^{1}H NMR (500 MHz, $CDCl_3$); 7.46-7.41 (2H, m, CH), 7.41-7.31 (8H, m, CH), 5.52 (1H, t, J 4.2 Hz, CH), 5.36 (1H, t, J 3.8 Hz, CH), 5.20 (1H, dd, J 7.7, 6.2 Hz, CH_2), 5.12 (1H, dd, J 7.9, 6.5 Hz, CH_2), 4.48 (1H, dd, J 8.4, 6.0 Hz, CH_2), 4.48 (1H, dd, J 7.9, 6.5 Hz, CH_2), 3.84 (1H, t, J 7.7 Hz, CH), 3.80 (1H, t, J 7.9 Hz, CH), 3.57 (1H,d, J 3.8 Hz, CH_2), 3.54-3.45 (1H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 138.4 (C), 137.9 (C), 128.80 (CH), 128.78 (CH), 128.6 (CH), 128.5 (CH), 126.6 (CH), 126.2 (CH), 102.9 (CH), 102.6 (CH), 79.4 (CH), 78.7 (CH), 72.9 (CH_2), 72.4 (CH_2), 32.9 (CH_2), 32.7 (CH_2). Diastereomeric ratio 1:0.72.[a] The data was consistent with the literature.[153]

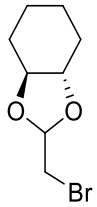
2-(Bromomethyl)hexahydrobenzo[1,3]dioxole (270c)



Following general procedure C with *p*-toluenesulfonic acid (25.0 mg, 0.131 mmol), 2-bromo-1,1-dimethoxyethane (2.50 g, 14.8 mmol) and *cis*-1,2-cyclohexanediol (1.70 g, 14.8 mmol) for 1 h. Purification by distillation (150 °C, 60 mbar) gave the title compound (1.44 g, 44%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2936, 2865, 1131 and 993; ^{1}H NMR (500 MHz, $CDCl_3$); 5.15 (1H, t, J 4.6 Hz, CH), 4.08 (2H, p, J 5.2 Hz, CH), 3.42 (2H, d, J 4.6 Hz, CH_2), 1.84-1.75 (4H, m, CH_2), 1.61-1.51 (2H, m, CH_2), 1.36-1.26 (2H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 102.0 (CH), 75.2 (CH), 33.0 (CH_2), 28.6 (CH_2), 20.9 (CH_2).[a] The data was consistent with the literature.[153]

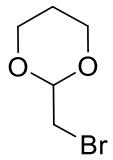
[a] Mass spectra analysis was run but the desired mass ion was not observed.

2-(Bromomethyl)hexahydrobenzo[d][1,3]dioxole (270d)



Following general procedure C with *p*-toluenesulfonic acid (50.0 mg, 0.263 mmol), 2-bromo-1,1-dimethoxyethane (5.00 g, 29.6 mmol) and *trans*-1,2-cyclohexanediol (3.44 g, 29.6 mmol) for 3 h. Further 2-bromo-1,1-dimethoxyethane (1.00 g, 5.92 mmol) was added and stirred at 130 °C for 1 h. Purification by distillation (150 °C, 60 mbar) gave the title compound (3.78 g, 58%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2943, 2872, 1446 and 1108; ^{1}H NMR (500 MHz, $CDCl_3$); 5.32 (1H, t, J 4.3 Hz, CH), 3.41 (2H, d, J 4.3 Hz, CH_2), 3.36-3.27 (2H, m, CH_2), 2.22-2.13 (2H, m, CH_2), 1.88-1.78 (2H, m, CH_2), 1.58-1.38 (2H, m, CH_2), 1.32-1.24 (2H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 101.9 (CH), 82.4 (CH), 80.5 (CH), 33.3 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 23.74 (CH_2), 23.69 (CH_2).[a] The data was consistent with the literature.[153]

2-(Bromomethyl)-1,3-dioxane (270e)

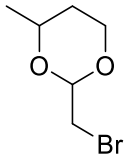


Following general procedure C with p-toluenesulfonic acid (200 mg, 1.40 mmol), 2-bromo-1,1-dimethoxyethane (20.0 g, 11.8 mol) and 1,3-propanediol (8.80 mL, 11.8 mol) for 2 h. Further 2-bromo-1,1-dimethoxyethane (2.0 g, 11.8 mmol) was added and then heated to 130 °C for 1 h. Purification by distillation (150 °C, 20 mbar) gave the title compound (16.2 g, 76%) as a yellow liquid. V_{max}/cm^{-1}; 2972, 2928, 2855, 1469, 1139, 1127 and 1003; ^{1}H NMR (500 MHz, $CDCl_3$); 4.72 (1H, t, J 4.5 Hz, CH), 4.17 (2H, ddt, J 10.6, 5.0, 1.4 Hz, CH_2), 3.86-3.76 (2H, m, CH_2), 3.34 (2H, d, J 4.5 Hz, CH_2), 2.12 (1H, dtt, J 13.6, 2.7 , 1.4 Hz, CH_2), 1.36 (1H, dtt, J 13.6, 2.7,

[a] Mass spectra analysis was run but the desired mass ion was not observed.

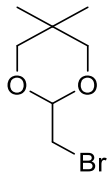
1.4 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 99.8 (CH), 67.3 (CH_2), 32.1 (CH_2), 25.4 (CH_2).[a] The data was consistent with the literature.[263]

2-(Bromomethyl)-4-methyl-1,3-dioxane (270f)



Following general procedure C with *p*-toluenesulfonic acid (100 mg, 0.526 mmol), 2-bromo-1,1-dimethoxyethane (10.0 g, 58.1 mmol) and 1,3-butanediol (5.20 mL, 58.1 mmol) for 2 h. Purification by distillation (150 °C, 60 mbar) gave the title compound (9.60 g, 83%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2974, 2858 and 1119; ^1H NMR (500 MHz, $CDCl_3$); 4.73 (1H, t, J 4.6 Hz, CH), 4.14 (1H, ddd, J 11.5, 5.0, 1.4 Hz, CH), 3.85-3.74 (2H, m, CH_2), 3.34 (2H, d, J 4.6 Hz, CH_2), 1.73-1.63 (1H, m, CH_2), 1.44 (1H, dtd, J 13.3, 2.5, 1.4 Hz, CH_2), 1.25 (3H, d, J 6.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 99.9 (CH), 73.3 (CH), 66.9 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 21.7 (CH_3).[a] The data was consistent with the literature.[155]

2-(Bromomethyl)-5,5-dimethyl-1,3-dioxane (270g)

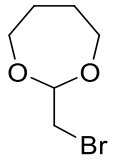


Following general procedure C with *p*-toluenesulfonic acid (50.0 mg, 0.263 mmol), 2-bromo-1,1-dimethoxyethane (5.00 g, 29.6 mmol) and 2,2-dimethyl-1,3-propanediol (3.10 g, 29.6 mmol) for 2 h. Purification by distillation (150 °C, 60 mbar) gave the title compound (4.88 g, 73%) as a slight yellow liquid. V_{max}/cm^{-1}; 2956, 2858 and 1127; ^1H NMR (500 MHz, $CDCl_3$); 4.62 (1H, t, J 4.4 Hz, CH), 3.67 (2H, d, J 11.2 Hz, CH_2), 3.49 (2H, d, J 11.2 Hz, CH_2), 3.39 (2H, d, J 4.4 Hz, CH_2), 1.21 (3H, s, CH_3), 0.74 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 99.6 (CH), 77.3 (CH_2), 31.9

[a] Mass spectra analysis was run but the desired mass ion was not observed.

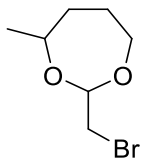
(CH_2), 30.4 (C), 23.0 (CH_3), 21.7(CH_3).[a] The data was consistent with the literature.[264]

2-(Bromomethyl)-1,3-dioxepane (270h)



Following general procedure C with *p*-toluenesulfonic acid (200 mg, 1.00 mmol), 2-bromo-1,1-dimethoxyethane (20.0 g, 11.8 mol) and 1,4-butanediol (10.5 mL, 11.8 mol) for 2 h. Further 2-bromo-1,1-dimethoxyethane (2.00 g, 11.8 mmol) was added and heated to 130 °C for 30 min. Purification by distillation (150 °C, 60 mbar) gave the title compound (16.9 g, 73%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2942, 2877, 2845 and 1122; ^1H NMR (500 MHz, $CDCl_3$); 4.90 (1H, t, J 5.3 Hz, CH), 3.94 (2H, dq, J 12.0 and 3.2 Hz, CH_2), 3.67 (2H, dq, J 12.0 and 3.2 Hz, CH_2), 3.33 (2H, d, J 5.3 Hz, CH_2), 1.80-1.65 (4H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 100.7 (CH), 66.7 (CH_2), 32.4 (CH_2), 29.3 (CH_2).[a] The data was consistent with the literature.[265]

2-(bromomethyl)-4-methyl-1,3-dioxepane (270i)

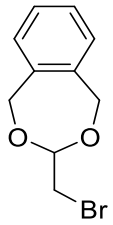


Following general procedure C with *p*-toluenesulfonic acid (50.0 mg, 0.263 mmol), 2-bromo-1,1-dimethoxyethane (5.00 g, 29.6 mmol) and 1,4-pentanediol (3.10 mL, 29.6 mmol) for 2 h. Purification by distillation (150 °C, 60 mbar) gave the title compound (3.3 g, 50%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2942, 2877, 2845 and 1122; ^1H NMR (500 MHz, $CDCl_3$); 4.86 (1H, t, J 5.1 Hz, CH), 4.87 (1H, t, J 5.1 Hz, CH), 4.02-3.98 (1H, m, CH_2), 3.98-3.94 (1H, m, CH_2), 3.82-3.77 (1H, m, CH_2), 3.77-3.72 (1H, m, CH_2), 3.68 (1H, dtt, J 10.9, 3.6, 2.6 Hz, CH_2), 3.55 (1H, ddd,, J 11.9, 10.9, 2.6 Hz, CH_2), 3.27 (2H, dd, J 5.4, 1.0 Hz, CH_2), 3.25 (2H, d, J 5.4 Hz, CH_2), 1.76-1.67 (3H,

[a] Mass spectra analysis was run but the desired mass ion was not observed.

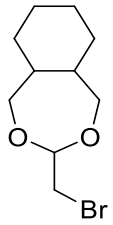
m, CH_2), 1.67-1.58 (3H, m, CH_2), 1.51-1.44 (1H, m, CH_2), 1.44-1.37 (1H, m, CH_2), 1.18 (3H, d, J 6.4 Hz, CH_3), 1.16 (3H, d, J 6.4 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 100.2 (CH), 99.2 (CH), 76.4 (CH), 69.6 (CH), 69.0 (CH_2), 64.6 (CH_2), 36.3 (CH_2), 36.2 (CH_2), 32.8 (CH_2), 32.2 (CH_2), 29.0 (CH_2), 28.4 (CH_2), 22.5 (CH_3), 22.3 (CH_3).[a] The data was consistent with the literature.[266]

3-(Bromomethyl)-1,5-dihydrobenzo[1,3]dioxepine(270j)



Following general procedure C with *p*-toluenesulfonic acid (100 mg, 0.526 mmol), 2-bromo-1,1-dimethoxyethane (10.0 g, 59.2 mmol) and 1,2-benzenedimethanol (8.18 g, 59.2 mmol) for 2 h. DCM (50 mL) was added and the reaction mixture was filtered and concentrated to dryness to yield the title compound (13.2 g, 92%) as a cream crystalline solid. ν_{max}/cm^{-1}; 3043, 2980, 2955, 2861 and 696; ^{1}H NMR (500 MHz, $CDCl_3$); 7.30-7.25 (2H, m, CH), 7.24-7.18 (2H, m, CH), 5.16 (1H, t, J 5.1 Hz, CH), 4.97 (4H, d, J 5.1 Hz, CH_2), 3.49 (2H, d, J 5.1 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 138.6 (C), 127.9 (CH), 127.6 (CH), 106.0 (CH), 71.9 (CH_2), 31.7 (CH_2).[a] The data was consistent with the literature.[267]

3-(Bromomethyl)octahydrobenzo[1,3]dioxepine (270k)

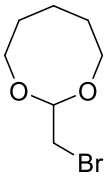


Following general procedure C with *p*-toluenesulfonic acid (17.0 mg, 0.0894 mmol), 2-bromo-1,1-dimethoxyethane (1.76 g, 10.4 mmol) and *trans*-1,2-cyclohexanedimethanol (1.50 g, 10.4 mmol) for 30 min. Further 2-bromo-1,1-

[a] Mass spectra analysis was run but the desired mass ion was not observed.

dimethoxyethane (527 mg, 3.12 mmol) and *p*-toluenesulfonic acid (17.0 mg, 0.0894 mmol) was added and stirred at 130 °C for 1 h. Purification by distillation (190 °C, 60 mbar) gave the title compound (1.96 g, 78%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2921, 2852, 1127 and 693; ^{1}H NMR (500 MHz, $CDCl_3$); 4.94 (1H, t, J 5.3 Hz, CH), 3.81 (1H, dd, J 11.4, 2.4 Hz, CH_2), 3.61 (1H, dd, J 11.4, 9.8 Hz, CH_2), 3.45 (1H, dd, J 12.1, 2.1 Hz, CH_2), 3.38 (1H, t, J 11.0 Hz, CH_2), 3.35-3.27 (2H, m, CH_2), 1.83-1.70 (2H, m, CH), 1.61-1.50 (2H, m, CH_2), 1.35-1.16 (4H, m, CH_2), 0.94-0.79 (2H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 100.2 (CH), 74.1 (CH_2), 67.8 (CH_2), 45.8 (CH), 45.7 (CH), 32.3 (CH_2), 28.8 (CH_2), 28.2 (CH_2), 26.2 (CH_2), 26.0 (CH_2).[a]

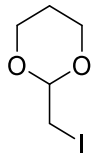
2-(Bromomethyl)-1,3-dioxocane (270l)



Following general procedure C with *p*-toluenesulfonic acid (50.0 mg, 0.263 mmol), 2-bromo-1,1-dimethoxyethane (5.00 g, 29.6 mmol) and 1,5-pentanediol (3.10 mL, 29.6 mmol) for 1.5 h. Further 2-bromo-1,1-dimethoxyethane (2.00 g, 11.8) was added and heated with stirring to 130 °C for 1h. Purification by distillation (150 °C, 60 mbar) gave the title compound (3.5 g, 56%) as a colourless liquid. ν_{max}/cm^{-1}; 2937, 2867, 1474, 1117, 1049 and 1020; ^{1}H NMR (500 MHz, $CDCl_3$); 4.63 (1H, t, J 5.5 Hz, CH), 3.62 (2H, dt, J 9.3, 6.5 Hz, CH_2), 3.48 (2H, dt, J 9.3, 6.5 Hz, CH_2), 3.34 (2H, d, J 5.5 Hz, CH_2), 1.61 (4H, p , J 6.9 Hz, CH_2), 1.42-1.40 (2H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 101.8 (CH), 66.8 (CH_2), 31.8 (CH_2), 29.5 (CH_2), 22.9 (CH_2).[a] The data was consistent with the literature.[265]

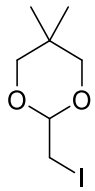
[a] Mass spectra analysis was run but the desired mass ion was not observed.

2-(Iodomethyl)-1,3-dioxane (272a)



To a solution of *p*-toluenesulfonic acid (37.0 mg, 0.195 mmol) and 2-iodo-1,1-diethoxyethane (5.00 g, 22.3 mmol) was added 1,2-propanediol (1.70 g, 22.3 mmol). The solution was heated with stirring to 90 °C for 1 h, followed by 100 °C for 2 h and 110 °C for 2 h with a dean-Stark apparatus. DCM (100 mL) was added, washed with water (2 x 100 mL) and brine (2 x 100 mL), dried MgSO4 and concentrated to dryness. The crude bromoacetal was then purified by distillation (150 °C, 60 mbar) to yield the title compound (2.4 g, 47%) as a red liquid. ν_{max}/cm^{-1}; 2968, 2925, 2852, 2723, 991 and 637; ^{1}H NMR (500 MHz, $CDCl_3$); 4.50 (1H, t, J 4.4 Hz, CH), 4.14 (2H, ddt, J 10.4, 4.9, 1.4 Hz, CH_2), 3.86-3.79 (2H, m, CH_2), 3.18 (2H, d, J 4.4 Hz, CH_2), 2.09 (1H, dtt, J 13.5, 12.5, 4.9 Hz, CH_2), 1.32 (1H, dtt, J 13.5, 2.6, 1.4 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 99.6 (CH), 67.1 (CH_2), 25.3 (CH_2), 5.2 (CH_2).[a] The data was consistent with the literature.[268]

2-(Iodomethyl)-5,5-dimethyl-1,3-dioxane (272b)

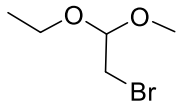


To a solution of *p*-toluenesulfonic acid (22.0 mg, 0.116 mmol) and 2-iodo-1,1-diethoxyethane (3.00 g, 13.4 mmol) was added 2,2-dimethylpropanediol (1.39 g, 13.4 mmol). The solution was heated with stirring to 90 °C for 1.5 h with a dean-Stark apparatus to yield the title compound (2.2 g, 65%) as a red liquid. ν_{max}/cm^{-1}; 2955, 2848, 2905, 1122 and 668; ^{1}H NMR (500 MHz, $CDCl_3$); 4.34 (1H, t, J 4.1 Hz, CH), 3.65 (2H, d, J 10.8 Hz, CH_2), 3.49 (2H, d, J 10.8 Hz, CH_2), 3.23 (2H, d, J 4.1 Hz,

[a] Mass spectra analysis was run but the desired mass ion was not observed.

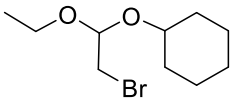
CH_2), 1.21 (3H, s, CH_3), 0.73 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 99.1 (CH), 77.3 (CH_2), 23.2 (CH3), 21.6 (CH3), 5.5 (CH_2).[a]

2-Bromo-1-ethoxy-1-methoxyethane (274a)



Following general procedure D with ethyl vinyl ether (3.80 mL, 40.0 mmol), methanol (1.60 mL, 40.0 mmol) and NBS (7.20 g, 40.0 mmol) gave title compound (5.2 g, 71%) as a colourless liquid. ν_{max}/cm^{-1}; 2978, 2932, 2832, 1057 and 682; ^1H NMR (500 MHz, $CDCl_3$); 4.61 (1H, t, J 5.4 Hz, CH), 3.70 (1H, dq, J 9.5, 7.0 Hz, CH_2), 3.59 (1H, dq, J 9.5, 7.0 Hz, CH_2), 3.39 (3H, s, CH_3), 3.37 (2H, dd, J 5.4, 1.6 Hz, CH_2), 1.24 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 102.3 (CH), 62.9 (CH_2), 53.8 (CH_3), 31.4 (CH_2), 15.3 (CH_3).[a]

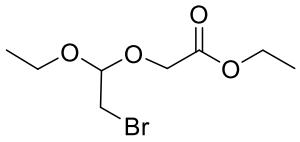
(2-Bromo-1-ethoxyethoxy)cyclohexane (274b)



Following general procedure D with ethyl vinyl ether (1.90 mL, 20.0 mmol), cyclohexanol (2.10 mL, 20.0 mmol) and NBS (3.60 g, 20.0 mmol) gave the title compound (4.2 g, 85%) as a colourless liquid. ν_{max}/cm^{-1}; 2976, 2932, 2857, 1049, 1024 and 686; ^1H NMR (500 MHz, $CDCl_3$); 4.75 (1H, t, J 5.5 Hz, CH), 3.68 (1H, dq, J 9.1, 7.0 Hz, CH_2), 3.61-3.56 (1H, m, CH_2), 3.56-3.52 (1H, m, CH), 3.36 (2H, qd, J 5.5, 4.9 Hz, CH_2), 1.93-1.84 (2H, m, CH_2), 1.80-1.72 (2H, m, CH_2), 1.57-1.50 (1H, m, CH_2), 1.45-1.24 (5H, m, CH_2), 1.23 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 100.3 (CH), 75.9 (CH), 61.6 (CH_2), 33.3 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 24.2 (CH_2), 15.3 (CH_3).[a]

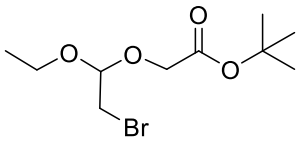
[a] Mass spectra analysis was run but the desired mass ion was not observed.

Ethyl 2-(2-bromo-1-ethoxyethoxy)acetate (274c)



Following general procedure D with ethyl vinyl ether (1.45 mL, 15.1 mmol), ethyl glycolate (1.43 mL, 15.1 mmol) and NBS (2.70 g, 15.1 mmol). Purification by column chromatography (EtOAc:Hexane 1:3, Rf = 0.31) gave the title compound (1.9 g, 48%) as a yellow liquid. ν_{max}/cm^{-1}; 2980, 2902, 1753, 1737 and 683; ^{1}H NMR (500 MHz, $CDCl_3$); 4.84 (1H, d, J 4.8 Hz, CH), 4.83 (1H, d, J 4.8, CH), 4.24 (2H, dd, J 7.2, 1.0 Hz, CH_2), 4.21 (2H, dd, J 7.2, 1.0 Hz, CH_2), 4.20 (2H, s, CH_2), 4.19 (2H, s, CH_2), 3.74 (2H, dq, J 9.4, 7.1 Hz, CH_2), 3.63 (2H, dq, J 9.4, 7.1 Hz, CH_2), 3.45 (2H, dd, J 10.9, 6.1 Hz, CH_2), 3.40 (2H, dd, J 10.9, 6.1 Hz, CH_2), 1.29 (6H, t, J 7.1 Hz, CH_3), 1.23 (6H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 169.9 (C), 101.0 (CH), 63.0 (CH_2), 62.7 (CH_2), 60.9 (CH_2), 30.8 (CH_2), 15.0 (CH_3), 14.2 (CH_3).[a]

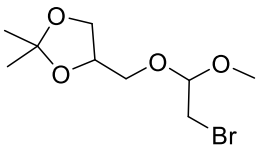
***t*-Butyl 2-(2-bromo-1-ethoxyethoxy)acetate (274d)**



Following general procedure D with ethyl vinyl ether (2.90 mL, 30.2 mmol), *t*-butyl-2-hydroxyacetate (2.90 mL, 30.2 mmol) and NBS (5.40 g, 30.2 mmol) gave the title compound (5.8 g, 48%) as a colourless liquid. ν_{max}/cm^{-1}; 2978, 2932, 1746 and 682; ^{1}H NMR (500 MHz, $CDCl_3$); 4.83 (1H, d, J 4.6 Hz, CH), 4.81 (1H, d, J 4.6 Hz, CH), 4.09 (2H, s, CH_2), 4.08 (2H, s, CH_2), 3.74 (2H, dq, J 9.3, 7.1 Hz, CH_2), 3.63 (2H, dq, J 9.3, 7.1 Hz, CH_2), 3.46 (2H, dd, J 10.9. 6.3 Hz, CH_2), 3.39 (2H, dd, J 10.9, 6.3 Hz, CH_2), 1.48 (18H, s, CH_3), 1.23 (6H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 169.2 (C), 101.3 (CH), 82.0 (CH_2), 63.6 (CH_2), 62.8 (CH_2), 31.3 (CH_2), 28.1 (CH_3), 15.1 (CH_3).[a]

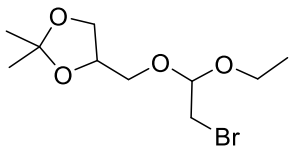
[a] Mass spectra analysis was run but the desired mass ion was not observed.

4-((2-Bromo-1-methoxyethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (274e)



Following general procedure D with 2,2-dimethyl-4-((vinyloxy)methyl)-1,3-dioxolane (450 mg, 2.84 mmol), methanol (115 µL, 2.84 mmol) and NBS (506 mg, 2.84 mmol) gave the title compound (392 mg, 53%) as a yellow liquid. ν_{max}/cm^{-1}; 2986, 2935, 1052 and 686; ^{1}H NMR (500 MHz, $CDCl_3$); 4.67 (1H, td, J 5.4, 1.5 Hz, CH), 4.28 (1H, p, J 5.8 Hz, CH), 4.07 (1H, ddd, J 8.3, 6.4, 4.5 Hz, CH_2), 3.78 (1H, ddd, J 15.8, 8.1, 5.8 Hz, CH_2), 3.7 (0.5H, dd, J 10.0, 5.5 Hz, CH_2), 3.61 (1H, d, J 5.8 Hz, CH_2), 3.54 (0.5H, dd, J 10.0, 5.5 Hz, CH_2), 3.41 (3H, s, CH_3), 3.37 (2H, d, J 5.4 Hz, CH_2), 1.42 (3H, s, CH_3), 1.36 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 109.6 (C), 109.59 (C), 102.7 (CH), 102.5 (CH), 74.6 (CH), 74.5 (CH), 67.5 (CH_2), 67.4 (CH_2), 66.9 (CH_2), 66.8 (CH_2), 54.1 (CH_2), 54.09 (CH_2), 30.9 (CH_2), 30.89 (CH_2), 26.89 (CH_3), 26.87 (CH_3), 25.5 (CH_3), 25.4 (CH_3).[a]

4-((2-Bromo-1-ethoxyethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (274f)

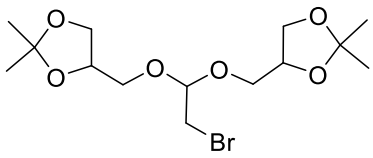


Following general procedure D with ethyl vinyl ether (1.70 mL, 18.1 mmol), solketal (1.90 mL, 18.1 mmol) and NBS (506 mg, 2.84 mmol) gave the title compound (2.4 g, 56%) as a yellow liquid. ν_{max}/cm^{-1}; 2981, 2933, 2878, 1052 and 683; ^{1}H NMR (500 MHz, $CDCl_3$); 4.74 (1H, td, J 5.5, 2.5 Hz, CH), 4.28 (1H, p, J 6.0 Hz, CH), 4.08 (1H, ddd, J 8.5, 6.4, 4.5 Hz, CH_2), 3.79 (1H, ddd, J 14.4, 8.3, 6.1 Hz, CH_2), 3.75-3.57 (3.5H, m, CH_2), 3.54 (0.5H, dd, J 9.8, 5.8 Hz, CH_2), 3.38 (2H, dd, J 5.5, 2.5 Hz, CH_2), 1.43 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.24 (3H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 109.63 (C), 109.58 (C), 101.9 (CH), 101.6 (CH), 74.62 (CH), 74.59 (CH), 67.3 (CH_2), 67.2 (CH_2), 67.0 (CH_2), 66.9 (CH_2), 63.0 (CH_2), 62.9 (CH_2), 31.51 (CH_2), 31.47 (CH_2), 26.91 (CH_3), 26.90 (CH_3), 25.47 (CH_3), 25.44 (CH_3), 15.3 (CH_3), 15.2 (CH_3); HRMS *m/z*

[a] Mass spectra analysis was run but the desired mass ion was not observed.

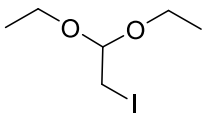
(ESI$^+$) 305.0408 and 307.0338 (M + Na$^+$) $C_{10}H_{19}O_4Na^+$ requires 305.0359 and 307.0391.

4,4'-(((2-Bromoethane-1,1-diyl)bis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (274a)



Following general procedure D with 2,2-dimethyl-4-((vinyloxy)methyl)-1,3-dioxolane (200 mg, 1.26 mmol), solketal (157 µL, 1.26 mmol) and NBS (224 mg, 1.26 mmol) gave the title compound (317 mg, 68%) as a yellow liquid. ν_{max}/cm^{-1}; 2986, 2935, 2877, 1049, 841 and 513; ^{1}H NMR (500 MHz, $CDCl_3$); 4.80 (1H, tt, J 5.6, 1.8 Hz, CH), 4.28 (2H, p, J 6.0 Hz, CH), 4.07 (2H, ddd, J 8.4, 6.5, 4.3 Hz, CH_2), 4.79 (1H, ddd, J 8.1, 4.5, 3.7 Hz, CH_2), 3.77-3.70 (2H, m, CH_2), 3.56 (1H, ddd, J 10.0, 5.6, 1.9 Hz, CH_2), 3.39 (2H, dd, J 5.6, 1.8 Hz, CH_2), 1.42 (6H, s, CH_3), 1.35 (6H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 109.7 (C), 109.6 (C), 102.2 (CH), 102.0 (CH), 101.8 (CH), 74.6 (CH), 74.54 (CH), 74.53 (CH), 67.58 (CH_2), 67.57 (CH_2), 67.50 (CH_2), 67.49 (CH_2), 66.86 (CH_2), 66.84 (CH_2), 66.7 (CH_2), 66.6 (CH_2), 31.05 (CH_2), 31.03 (CH_2), 30.9 (CH_2), 26.89 (CH_3), 26.87 (CH_3), 25.46 (CH_3), 25.42 (CH_3); HRMS *m/z* (ESI$^+$) 391.0727 and 393.0710 (M + Na$^+$) $C_{14}H_{25}O_6Na^+$ requires 391.0729 and 393.0710.

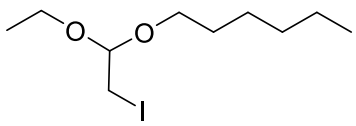
1,1-Diethoxy-2-iodoethane (91)



Following general procedure E with ethyl vinyl ether (4.60 mL, 48.0 mmol), ethanol (2.30 mL, 40.0 mmol) and NIS (9.00 g, 40.0 mmol) gave the title compound (8.5 g, 87%) as a colourless liquid. ν_{max}/cm^{-1}; 2975, 2879, 1050 and 639; ^{1}H NMR (500 MHz, $CDCl_3$); 4.61 (1H, t, 5.5 Hz, CH), 3.68 (2H, dq, J 9.3, 7.2 Hz, CH_2), 3.56 (2H, dq, J 9.3, 7.2 Hz, CH_2), 3.22 (2H, d, J 5.5 Hz, CH_2), 1.23 (6H, t, J 7.1 Hz, CH_3); ^{13}C NMR

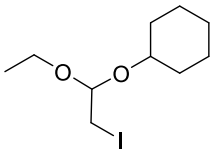
(125 MHz, $CDCl_3$); 101.8 (CH), 62.3 (CH_2), 15.3 (CH_3), 5.7 (CH_2).[a] The data was consistent with the literature.[269]

1-(1-Ethoxy-2-iodoethoxy)hexane (275a)



Following general procedure E with ethyl vinyl ether (2.30 mL, 24.0 mmol), hexanol (2.50 mL, 20.0 mmol) and NIS (4.50 g, 20.0 mmol) gave the title compound (5.9 g, 98%) as a colourless liquid. ν_{max}/cm^{-1}; 2929, 2860, 1054 and 640; ^1H NMR (500 MHz, $CDCl_3$); 4.61 (1H, t, J 5.5 Hz, CH), 3.68 (1H, dq, J 9.4, 7.1 Hz, CH_2), 3.64-3.51 (2H, m, CH_2), 3.51-3.43 (1H, m, CH_2), 3.22 (2H, d, J 5.5 Hz, CH_2), 2.33 (2H, q, J 6.8 Hz, CH_2), 1.42-1.26 (6H, m, CH_2), 1.23 (3H, t, J 7.1 Hz, CH_3), 0.89 (3H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 101.9 (CH), 66.8 (CH_2), 62.3 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 15.2 (CH_3), 14.2 (CH_3), 5.6 (CH_2); HRMS *m/z* (ESI^+) 323.0533 ($M + Na^+$) $C_{10}H_{21}IO_2Na^+$ requires 323.0478.

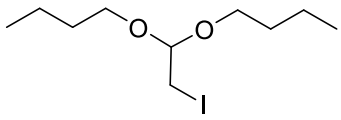
(1-Ethoxy-2-iodoethoxy)cyclohexane (275b)



Following general procedure E with ethyl vinyl ether (2.30 mL, 24.0 mmol), cyclohexanol (2.10 mL, 20.0 mmol) and NIS (4.50 g, 20.0 mmol) gave the title compound (4.7 g, 80%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2974, 2930, 2856, 1048 and 604; ^1H NMR (500 MHz, $CDCl_3$); 4.69 (1H, t, J 5.3 Hz, CH), 3.65 (1H, dq, J 9.4, 7.3 Hz, CH_2), 3.59-3.47 (2H, m, CH/CH_2), 3.24-3.16 (2H, m, CH_2), 1.92-1.82 (2H, m, CH_2), 1.80-170 (2H, m, CH_2), 1.56-1.48 (1H, m, CH_2), 1.43-1.24 (5H, m, CH_2), 1.22 (3H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 100.5 (CH), 75.6 (CH), 61.2 (CH_2), 33.3 (CH_2), 32.5 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 24.1 (CH_2), 15.3 (CH_3), 6.7 (CH_2); HRMS *m/z* (ESI^+) 321.0372 ($M + Na^+$) $C_{10}H_{19}IO_2Na^+$ requires 321.0322.

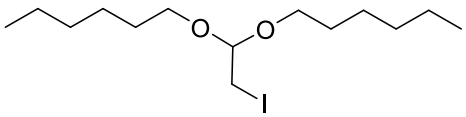
[a] Mass spectra analysis was run but the desired mass ion was not observed.

1-(1-Butoxy-2-iodoethoxy)butane (275c)



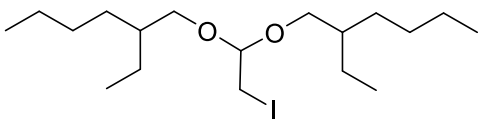
Following general procedure E with butyl vinyl ether (2.58 mL, 20.0 mmol), butanol (1.82 mL, 20.0 mmol) and NIS (4.49 g, 20.0 mmol) gave the title compound (3.2 g, 54%) as a colourless liquid. ν_{max}/cm^{-1}; 2958, 2932, 2871, 1037 and 641; ^{1}H NMR (500 MHz, $CDCl_3$); 4.60 (1H, t, J 5.6 Hz, CH), 3.61 (2H, dt, J 9.2, 6.5 Hz, CH_2), 3.48 (2H, dt, J 9.2, 6.5 Hz, CH_2), 3.22 (2H, d, J 5.6 Hz, CH_2), 1.63-1.52 (4H, m, CH_2), 1.46-1.35 (4H, m, CH_2), 0.93 (6H, t, J 7.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 102.0 (CH), 66.4 (CH_2), 31.8 (CH_2), 19.5 (CH_2), 14.0 (CH_3), 5.6 (CH_2); HRMS *m/z* (ESI^+) 321.0516 ($M + Na^+$) $C_{10}H_{21}IO_2Na^+$ requires 323.0478.

1-(1-(Hexyloxy)-2-iodoethoxy)hexane (275d)



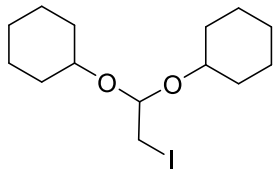
Following general procedure E with hexyl vinyl ether (1.40 g, 10.9 mmol), hexanol (1.37 mL, 10.9 mmol) and NIS (2.45 g, 10.9 mmol). Stirred at – 30 °C for 30 min. Purification by distillation (135 – 140 °C, 0 mbar) gave the title compound (2.86 g, 74%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2955, 2928, 2859, 1108, 725 and 642; ^{1}H NMR (500 MHz, $CDCl_3$); 4.61 (1H, t, J 5.6 Hz, CH), 3.6 (2H, dt, J 9.1, 6.6 Hz, CH_2), 3.47 (2H, dt, J 9.1, 6.6 Hz, CH_2), 3.22 (2H, d, J 5.6 Hz, CH_2), 1.63-1.54 (4H, m, CH_2), 1.40-1.33 (4H, m, CH_2), 1.33-1.24 (8H, m, CH_2), 0.89 (6H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 102.1 (CH), 66.8 (CH_2), 31.7 (CH_2), 29.7 (CH_2), 25.8 (CH_2),22.7 (CH_2), 14.1 (CH_3), 5.5 (CH_2); HRMS *m/z* (ESI^+) 379.1158 ($M + Na^+$) $C_{14}H_{29}IO_2Na^+$ requires 379.1104.

3-((1-((2-Ethylhexyl)oxy)-2-iodoethoxy)methyl)heptane (275e)



Following general procedure E with 2-ethylhexyl vinyl ether (1.00 g, 6.39 mmol), 2-ethylhexanol (1.00 mL, 6.39 mmol) and NIS (1.44 g, 6.39 mmol). Stirred at – 30 °C for 10 min. Purification by distillation (135 – 140 °C, 0 mbar) gave the title compound (2.0 g, 75%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2957, 2925, 2873, 2859, 1043 and 610; ^{1}H NMR (500 MHz, $CDCl_3$); 4.58 (1H, t, J 5.5 Hz, CH), 3.51 (2H, dt, J 9.0, 5.8 Hz, CH_2), 3.35 (2H, dt, J 9.0, 5.8 Hz, CH_2), 3.22 (2H, d, J 5.5 Hz, CH_2), 1.50 (2H, q, J 5.9 Hz, CH), 1.43-1.26 (16H, m, CH_2), 0.93-0.86 (12H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 102.52 (CH), 102.48 (CH), 102.45 (CH), 69.24 (CH_2), 69.22 (CH_2), 69.19 (CH_2), 69.16 (CH_2), 39.9 (CH_2), 30.63 (CH_2), 30.59 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 23.93 (CH_2), 23.92 (CH_2), 23.2 (CH_2), 14.26 (CH_3), 11.3 (CH_3), 5.5 (CH_2); HRMS *m/z* (ESI^+) 435.1816 ($M + Na^+$) $C_{18}H_{37}IO_2Na^+$ requires 435.1730.

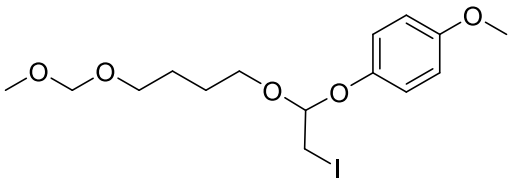
<u>((2-Iodoethane-1,1-diyl)bis(oxy))dicyclohexane (275f)</u>



Following general procedure E with cyclohexyl vinyl ether (1.15 mL, 8.06 mmol), cyclohexanol (807 mg, 8.06 mmol) and NIS (1.81 g, 8.06 mmol), stirred at – 30 °C for 10 min, gave the title compound (2.6 g, 93%) as a colourless liquid. ν_{max}/cm^{-1}; 2929, 2855, 1015 and 604; ^{1}H NMR (500 MHz, $CDCl_3$); 4.75 (1H, t, J 5.3 Hz, CH), 3.52 (2H, tt, J 9.1, 3.7 Hz, CH), 3.18 (2H, d, J 5.3 Hz, CH_2), 1.92-1.80 (4H, m, CH_2), 1.80-1.69 (4H, m, CH_2), 1.57-1.48 (2H, m, CH_2), 1.44-1.33 (4H, m, CH_2), 1.33-1.16 (8H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 99.4 (CH), 74.9 (CH), 33.4 (CH_2), 32.6 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 24.1 (CH_2), 7.9 (CH_2).[a]

[a] Mass spectra analysis was run but the desired mass ion was not observed.

1-(2-Iodo-1-(4-(methoxymethoxy)butoxy)ethoxy)-4-methoxybenzene (275g)

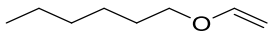


To a solution of 1-(methoxymethoxy)-4-(vinyloxy)butane (500 mg, 3.12 mmol) and DCM (10 mL) was added NIS (702 mg, 3.12 mmol) at -30 °C portion wise over 5 min. 4-methoxyphenol (387 mg, 3.12 mmol) dissolved in DCM (1 mL) was then added over 5 min. Pentane (200 mL) was added and the reaction mixture was, washed $Na_2S_2O_3$ (4 x 250 mL), Sat. aq. $NaHCO_3$ (5 x 250 mL), dried $MgSO_4$ and concentrated to dryness (100 105 °C, 60 mbar) to yield the title compound (569 mg, 45%) as a slight yellow liquid. ν_{max}/cm^{-1}; 2933, 2880, 1505 and 1035; ^1H NMR (500 MHz, $CDCl_3$); 7.0-6.96 (2H, m, CH), 6.85-6.81 (2H, m, CH), 5.15 (1H, dd, J 5.2, 4.9 Hz, CH), 4.61 (2H, s, CH_2), 3.78 (3H, s, CH_3), 3.61-3.50 (4H, m, CH_2) 3.37-3.33 (2H, m, CH_2), 3.35 (3H, s, CH_3), 1.69 (4H, p, J 3.0 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 155.5 (C), 150.2 (C), 119.5 (CH), 114.7 (CH), 102.92 (CH), 96.4 (CH_2), 67.5 (CH_2), 67.1 (CH_2), 55.7 (CH_3), 55.2 (CH_3), 26.47 (CH_2), 26.48 (CH_2), 4.9 (CH_2); HRMS *m/z* (ESI^+) 433.0511 ($M + Na^+$) $C_{15}H_{23}IO_5Na^+$ requires 433.0482.

$Pd(TFA)_2$

To $Pd(OAc)_2$ (1.7 g, 7.57 mmol) was added TFA (85.0 mL, 1.11 mmol) and stirred at 25 °C for 1 h before being concentrated to dryness. To the resulting brown solid was added TFA (140 mL, 1.83 mmol) and stirred at 25 °C for 15 min. The solution was then concentrated to dryness to yield a brown solid (1.1 g), which was stored in a vacuum oven (60 – 100 mbar) for 48 h before use.[270]

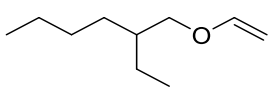
Hexyl vinyl ether (271b)



Following general procedure F with ethyl vinyl ether (143 mL, 1.49 mol), palladium(II) trifluoroacetate (928 mg, 2.79 mmol), 1,10-phenanthroline (652 mg, 3.62 mmol) and hexanol (6.99 mL, 55.7 mmol). Purification by silica gel chromatography (2% Ether :Hexane, R_f = 0.5) gave the title compound (1.73 g, 24%)

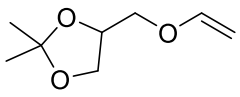
as a colourless liquid. ν_{max}/cm^{-1}; 2931, 2861, 1636, 1609 and 1200; ^{1}H NMR (500 MHz, $CDCl_3$); 6.48 (1H, dd, J 14.4, 6.9 Hz, CH), 4.18 (1H, dd, J 14.4, 2.1 Hz, CH_2), 3.98 (1H, dd, J 6.9, 2.1 Hz, CH_2), 3.68 (2H, t, J 6.6 Hz, CH_2), 1.66 (2H, p, J 6.6 Hz, CH_2), 1.43-1.35 (2H, m, CH_2), 1.35-1.29 (4H, m, CH_2), 0.91 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 152.1 (CH), 86.3 (CH_2), 68.3 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3).[a] The data was consistent with the literature.[271]

2-Ethylhexyl vinyl ether (271c)



Following general procedure F with ethyl vinyl ether (200 mL, 2.09 mol), palladium(II) trifluoroacetate (1.30 g, 3.90 mmol), 1,10-phenanthroline (914 mg, 5.07 mmol) 2-ethylhexanol (12.2 mL, 78.0 mmol). Purification by silica gel chromatography (2%EtOAc:Hexane, $R_f = 0.5$) gave the title compound (4.48 g, 37%) as a colourless liquid. ν_{max}/cm^{-1}; 2960, 2927, 2861, 1649, 1635, 1608 and 1463; ^{1}H NMR (500 MHz, $CDCl_3$); 6.49 (1H, dd, J 14.3, 6.8 Hz, CH), 4.17 (1H, dd, J 14.4, 1.8 Hz, CH), 3.96 (1H, dd, J 6.8, 1.9 Hz, CH), 3.57 (2H, d, J = 5.8 Hz, CH_2), 1.64-1.54 (1H, m, CH), 1.45-1.36 (2H, m, CH_2), 1.36-1.26 (6H, m, CH_2), 0.94-0.86 (6H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 152.4 (CH), 85.9 (CH_2), 70.4 (CH_2), 39.4 (CH), 30.7 (CH_2), 29.2 (CH_2), 24.0 (CH_2), 23.2 (CH_2), 14.3 (CH_3), 11.2 (CH_3).[a] The data was consistent with the literature.[272]

Solketal vinyl ether (271d)

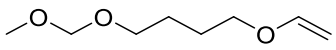


Following general procedure F with ethyl vinyl ether (131 mL, 1.37 mol), palladium(II) trifluoroacetate (851 mg, 2.56 mmol), 1,10-phenanthroline (585 mg, 3.25 mmol) and solketal (6.34 mL, 50.99 mmol). Purification by silica gel chromatography (10% Ether:Hexane, $R_f = 0.3$) gave the title compound (3.5 g, 43%) as a yellow liquid. ν_{max}/cm^{-1}; 2988, 2935, 2880, 1637, 1617 and 1199; ^{1}H NMR (500

[a] Mass spectra analysis was run but the desired mass ion was not observed.

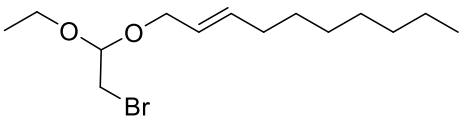
MHz, $CDCl_3$); 6.49 (1H, dd, J 14.3, 6.8 Hz, CH), 4.36 (1H, p, J 5.9 Hz, CH), 4.20 (1H, dd, J 14.3, 2.2 Hz, CH_2), 4.10 (1H, dd, J 8.3, 6.4 Hz, CH_2), 4.04 (1H, dd, J 6.8, 2.2 Hz, CH_2), 3.81-3.77 (1H, m, CH_2), 3.77-3.73 (1H, m, CH_2), 3.69 (1H, dd, J 10.1, 5.4 Hz, CH_2), 1.44 (3H, s, CH_3), 1.38 (3H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 151.7 (CH), 109.7 (C), 87.2 (CH_2), 74.0 (CH), 68.7 (CH_2), 66.8 (CH_2), 26.9 (CH_3), 25.5 (CH_3).[a] The data was consistent with the literature.[270]

1-(Methoxymethoxy)-4-(vinyloxy)butane (271e)



Following general procedure F with ethyl vinyl ether (19.5 mL, 0.203 mmol), palladium trifluoroacetate (124 mg, 0.372 mmol), 1,10-phenanthroline (87.0 mg, 0.483 mmol), 4-(methoxymethoxy)butan-1-ol (1.00 g, 7.45 mmol) and triethylamine (1 drop). Purification by silica gel chromatography (10% EtOAc:Hexane, R_f = 0.4) gave the title compound (815 mg, 68%) as a colourless liquid. ν_{max}/cm^{-1}; 2930, 2876, 1631, 1614 and 1042; ^1H NMR (500 MHz, $CDCl_3$); 6.46 (1H, CH, J 14.4, 6.9 Hz, CH), 4.61 (2H, s, CH_2), 4.17 (1H, dd, J 14.4, 2.1 Hz, CH_2), 3.97 (1H, dd, J 6.9, 2.1 Hz, CH_2), 3.70 (2H, t, J 6.0 Hz, CH_2), 3.55 (2H, t, J 6.0 Hz, CH_2), 3.35 (3H, s, CH_3), 1.79-1.72 (2H, m, CH_2), 1.72-1.65 (2H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 152.0 (CH), 96.5 (CH_2), 86.4 (CH_2), 67.8 (CH_2), 67.4 (CH_2), 55.2 (CH_3), 26.5 (CH_2), 26.0 (CH_2).[a]

(*E*)-1-(2-Bromo-1-ethoxyethoxy)dec-2-ene (276)

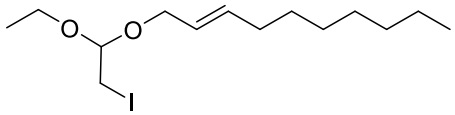


Following general procedure D with ethyl vinyl ether (2.94 mL, 30.7 mmol), dec-2-enol (4.00 g, 25.6 mmol) and NBS (4.56 g, 25.6 mmol), gave the title compound (6.6 g, 84%) as a yellow liquid. ν_{max}/cm^{-1}; 2956, 2924, 2855 and 685; ^1H NMR (500 MHz, $CDCl_3$); 5.77-5.67 (1H, m, CH), 5.60-5.51 (1H, m, CH), 4.71 (1H, t, J 5.5 Hz, CH), 4.11 (1H, ddd, J 11.7, 6.1, 0.9 Hz, CH_2), 4.03 (1H, ddd, J 11.7, 6.7, 0.9 Hz, CH_2), 3.70

[a] Mass spectra analysis was run but the desired mass ion was not observed.

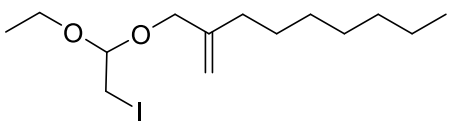
(1H, dq, J 9.2, 7.0 Hz, CH_2), 3.59 (1H, dq, J 9.2, 7.0 Hz, CH_2), 3.38 (2H, d, J 5.5 Hz, CH_2), 2.04 (2H, q, J 6.8 Hz, CH_2), 1.42-1.35 (2H, m, CH_2), 1.35-1.26 (8H, m, CH_2), 1.24 (3H, t J 7.0 Hz, CH_3), 0.88 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 135.7 (CH), 125.6 (CH), 100.8 (CH), 67.8 (CH_2), 62.4 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.28 (CH_2), 29.27 (CH_2), 29.1 (CH_2), 22.8 (CH_2), 15.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 329.1165 and 331.1066 (M + Na^+) $C_{14}H_{27}BrO_2Na^+$ requires 329.1168 and 331.1145 .

(*E*)-1-(1-Ethoxy-2-iodoethoxy)dec-2-ene (277a)



Following general procedure E with ethyl vinyl ether (2.94 mL, 30.1 mmol), dec-2-enol (4.00 g, 25.6 mmol) and NIS (5.76 g, 25.6 mmol), stirred at – 30 °C for 30 min, gave the title compound (8.4 g, 93%) as a yellow liquid. ν_{max}/cm^{-1}; 2956, 2923, 2854, 1026, 723 and 638; ^1H NMR (500 MHz, $CDCl_3$); 5.77-5.68 (1H, m, CH), 5.60-5.51 (1H, m, CH), 4.65 (1H, t, J 5.5 Hz, CH_2), 4.09 (1H, ddd, J 12.0, 6.1, 1.2 Hz, CH_2), 4.01 (1H, ddd, J 12.0, 6.5, 0.8 Hz, CH_2), 3.68 (1H, dq, J 9.4, 6.9 Hz, CH_2), 3.56 (1H, dq, J 9.4, 6.9 Hz, CH_2), 3.23 (2H, d, J 5.5 Hz, CH_2), 2.04 (2H, q, J 7.1 Hz, CH_2), 1.43-1.34 (2H, m, CH_2), 1.34-1.26 (8H, m, CH_2), 1.24 (3H, t, J 7.2 Hz, CH_3), 0.89 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 135.6 (CH), 125.6 (CH), 101.1 (CH), 67.6 (CH_2), 62.2 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.30 (CH_2), 29.27 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 15.3 (CH_3), 14.2 (CH_3), 5.7 (CH_2); HRMS *m/z* (ESI^+) 377.1023 (M + Na^+) $C_{14}H_{27}IO_2Na^+$ requires 377.0948.

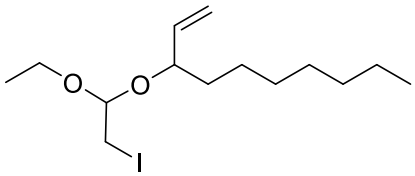
2-((1-Ethoxy-2-iodoethoxy)methyl)non-1-ene (277b)



Following general procedure E with ethyl vinyl ether (737 µL, 7.70 mmol), 2-methylenenonanol (1.00 g, 6.39 mmol) and NIS (1.44 g, 6.39 mmol), stirred at – 30 °C for 30 min. Purification by distillation (130 °C, 0 mbar) gave the title compound (1.3 g, 54%) as a yellow liquid. ν_{max}/cm^{-1}; 2924, 2855, 1652, 1051, 723 and 606; ^1H

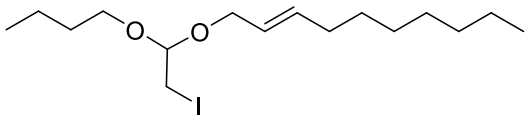
NMR (500 MHz, $CDCl_3$); 5.04 (1H, s, CH_2), 4.91 (1H, s, CH_2), 4.65 (1H, t, J 5.5 Hz, CH), 4.07 (1H, d, J 12.5 Hz, CH_2), 3.98 (1H, d, J 12.5 Hz, CH_2), 3.68 (1H, dq, J 9.0, 6.8 Hz, CH_2), 3.58 (1H, dq, J 9.0, 6.8 Hz, CH_2), 3.24 (2H, d, J 5.5 Hz, CH_2), 2.09 (2H, t, J 7.6 Hz, CH_2), 1.49-1.42 (2H, m, CH_2), 1.32-1.26 (8H, m, CH_2), 1.24 (3H, t, J 7.0 Hz, CH_3), 0.89 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 145.9 (C), 111.9 (CH_2), 101.3 (CH), 69.5 (CH_2), 62.2 (CH_2), 33.3 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 15.3 (CH_3), 14.2 (CH_3), 5.4 (CH_2); HRMS *m/z* (ESI^+) 377.1024 (M + Na^+) $C_{14}H_{27}IO_2Na^+$ requires 377.0948.

3-(1-Ethoxy-2-iodoethoxy)dec-1-ene (277c)



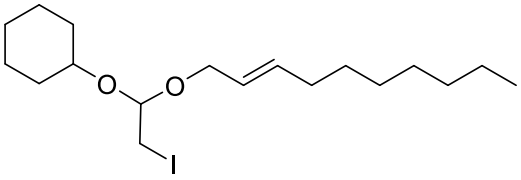
Following general procedure E with ethyl vinyl ether (735 µL, 7.70 mmol), decen-3-ol (1.00 g, 6.39 mmol) and NIS (1.44 g, 6.39 mmol), stirred at – 30 °C for 30 min, gave the title compound (1.7 g, 79%) as a yellow liquid. ν_{max}/cm^{-1}; 2925, 2856, 1011, 723 and 639; ^1H NMR (500 MHz, $CDCl_3$); 5.78 (0.5H, ddd, J 17.6, 10.5, 7.9 Hz, CH), 5.68 (0.5H, ddd, J 17.6, 10.5, 7.9 Hz, CH), 5.24-5.09 (2H, m, CH_2), 4.62 (1H, dt, J 8.8, 5.5 Hz, CH), 3.99 (0.5H, q, J 6.5 Hz, CH) 3.86 (0.5H, q, J 6.5 Hz, CH), 3.68 (0.5, dq, J 9.3, 6.9 Hz, CH_2), 3.64-3.54 (1H, m, CH_2), 3.48 (0.5H, dq, J 9.3, 6.9 Hz, CH_2), 3.20 (2H, dd, J 8.8, 5.5 Hz, CH_2), 1.68-1.61 (1H, m, CH_2), 1.53-1.43 (1H, m, CH_2) 1.40-1.25 (10H, m, CH_2), 1.21 (3H, dt, J 11.1, 6.8 Hz, CH_3), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 139.4 (CH), 138.8 (CH), 117.8 (CH_2), 116.5 (CH_2), 100.8 (CH), 99.2 (CH), 79.5 (CH), 78.7 (CH), 62.4 (CH_2), 61.1 (CH_2), 35.6 (CH_2), 35.5 (CH_2), 31.95 (CH_2), 31.94 (CH_2), 29.63 (CH_2), 29.60 (CH_2), 29.36 (CH_2), 29.35 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 22.8 (CH_2), 15.4 (CH_3), 15.1 (CH_3), 14.2 (CH_3), 6.6 (CH_2), 6.3 (CH_2); HRMS *m/z* (ESI^+) 377.1029 (M + Na^+) $C_{14}H_{27}IO_2Na^+$ requires 377.0948.

(*E*)-1-(1-Butoxy-2-iodoethoxy)dec-2-ene (277d)



Following general procedure E with butyl vinyl ether (828 µL, 6.39 mmol), dec-2-enol (1.00 g, 6.39 mmol) and NIS (1.44 g, 6.39 mmol), stirred at – 30 °C for 30 min, gave the title compound (1.6 g, 67%) as a yellow liquid. ν_{max}/cm^{-1}; 2956, 2924, 2854, 1032, 723 and 641; ^{1}H NMR (500 MHz, $CDCl_3$); 5.77-5.68 (1H, m, CH), 5.59-5.50 (1H, m, CH), 4.65 (1H, t, J 5.6 Hz, CH), 4.10 (1H, ddd, J 11.8, 6.0, 1.0 Hz, CH_2), 4.01 (1H, ddd, J 11.8, 6.0, 1.0 Hz, CH_2), 3.61 (1H, dq, J 9.0, 6.4 Hz, CH_2), 3.49 (1H, dq, J 9.0, 6.4 Hz, CH_2), 3.23 (2H, dd, J 5.6, 0.9 Hz, CH_2), 2.05 (2H, q, J 7.0 Hz, CH_2), 1.62-1.56 (2H, m, CH_2), 1.45-1.36 (4H, m, CH_2), 1.31-1.24 (8H, m, CH_2), 0.94 (3H, t, J 7.4 Hz, CH_3), 0.89 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 135.6 (CH), 125.5 (CH), 101.1 (CH), 67.5 (CH_2), 66.4 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 19.5 (CH_2), 14.2 (CH_3), 14.0 (CH_3), 5.5 (CH_2).[a]

(*E*)-(1-(Dec-2-en-1-yloxy)-2-iodoethoxy)cyclohexane (277e)

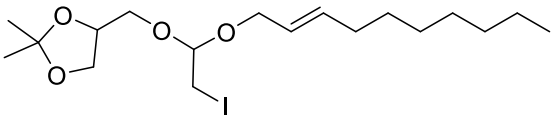


Following general procedure E with cyclohexyl vinyl ether (906 µL, 6.39 mmol), dec-2-enol (1.00 g, 6.39 mmol) and NIS (1.44 g, 6.39 mmol), stirred at – 30 °C for 30 min, gave the title compound (2.0 g, 76%) as a yellow liquid. ν_{max}/cm^{-1}; 2926, 2855, 1022, 723 and 604; ^{1}H NMR (500 MHz, $CDCl_3$); 5.77-5.65 (1H, m, CH), 5.60-5.50 (1H, m, CH), 4.73 (1H, t, J 5.6 Hz, CH), 4.07 (1H, ddd, J 12.0, 6.3, 1.2 Hz, CH_2), 4.0 (1H, ddd, J 12.0, 6.5, 1.2 Hz, CH_2), 3.54 (1H, tt J 9.4, 4.1 Hz, CH), 3.24-3.18 (2H, m, CH_2), 2.05 (2H, q, J 7.2 Hz, CH_2), 1.91-1.83 (2H, m, CH_2), 1.80-1.73 (2H, m, CH_2), 1.53-1.49 (1H, m, CH_2), 1.41-1.34 (5H, m, CH_2), 1.34-1.19 (10H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 135.3 (CH), 125.8 (CH), 99.8 (CH), 75.6

[a] Mass spectra analysis was run but the desired mass ion was not observed.

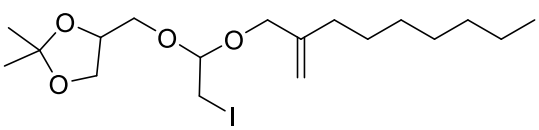
(CH), 66.6 (CH_2), 33.4 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.7 (CH_2), 24.3 (CH_2), 24.1 (CH_2), 22.9 (CH_2), 14.2 (CH_3), 6.8 (CH_2).[a]

(*E*)-4-((1-(Dec-2-en-1-yloxy)-2-iodoethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (277f)



Following general procedure E with 2,2-dimethyl-4-((vinyloxy)methyl)-1,3-dioxolane (1.01 g, 6.39 mmol), dec-2-enol (1.00 g, 6.39 mmol) NIS (1.44 g, 6.39 mmol), stirred at – 30 °C for 30 min, gave the title compound (2.0 g, 76%) as a yellow liquid. ν_{max}/cm^{-1}; 2924, 2855, 1050, 723 and 641; ^1H NMR (500 MHz, $CDCl_3$); 5.77-5.68 (1H, m, CH), 5.59-5.49 (1H, m, CH), 4.71 (1H, t, J 5.6 HZ, CH), 4.28 (1H, pd, J 6.1, 2.3 Hz, CH), 4.14-4.09 (1H, m, CH_2), 4.09-4.05 (1H, m, CH_2), 4.04-3.97 (1H, m, CH_2), 3.80 (1H, ddd, J 14.3, 8.4, 6.0 Hz, CH_2), 3.68 (0.5H, dd, J 9.7, 5.4 Hz, CH_2), 3.62-3.54 (1H, m, CH_2), 3.51 (0.5H, dd, J 9.7, 6.0 Hz, CH_2), 3.23 (2H, dd, J 5.6, 1.3 Hz, CH_2), 2.05 (2H, q, J 7.0 Hz, CH_2), 1.43 (3H, d, J 2.5 Hz, CH_3), 1.40-1.37 (2H, m, CH_2), 1.36 (3H, s, CH_3), 1.32-1.24 (8H, m, CH_2), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 136.0 (CH), 135.9 (CH), 125.3 (CH), 109.6 (C), 109.5 (C), 101.3 (CH), 101.1 (CH), 74.6 (CH), 74.5 (CH), 67.9 (CH_2), 67.8 (CH_2), 67.1 (CH_2), 67.0 (CH_2), 66.8 (CH_2), 67.7 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 29.26 (CH_2), 29.1 (CH_2), 26.9 (CH_3), 25.5 (CH_3), 25.4 (CH_3), 22.8 (CH_2), 14.1 (CH_3), 5.0 (CH_2), 4.9 (CH_2); HRMS *m/z* (ESI^+) 463.1362 ($M + Na^+$) $C_{18}H_{33}IO_4Na^+$ requires 463.1316.

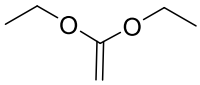
4-((2-Iodo-1-((2-methylenenonyl)oxy)ethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (277g)



Following general procedure E with 2,2-dimethyl-4-((vinyloxy)methyl)-1,3-dioxolane (1.01 g, 6.39 mmol), dec-2-enol (1.00 g, 6.39 mmol) and NIS (1.44 g, 6.39 mmol), stirred at – 30 °C for 30 min. Purification by distillation (125-130 °C, 0 mbar)

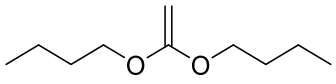
gave the title compound (1.0 g, 36%) as a brown liquid. ν_{max}/cm^{-1}; 2925, 2855, 1652, 1051 and 723; ^{1}H NMR (500 MHz, $CDCl_3$); 5.04 (1H, s, CH_2), 4.92 (1H, s, CH_2), 4.72 (1H, t, J 5.5 Hz, CH), 4.29 (1H, pd, J 12.2, 6.0, 2.4 Hz, CH_2), 4.11-4.04 (2H, m, CH_2), 3.98 (1H, dd, J 12.4, 3.2 Hz, CH_2), 3.80 (1H, ddd, J 14.5, 8.3, 6.1 Hz, CH_2), 3.69 (0.5H, dd, J 9.9, 5.4 Hz, CH_2), 3.63-3.56 (1H, m, CH_2), 3.55 (0.5H, dd, J 9.9, 5.4 Hz, CH_2), 3.25 (2H, dd, J 5.5, 1.5 Hz, CH_2), 2.08 (2H, t, J 7.4 Hz, CH_2), 1.49-1.44 (2H, m, CH_2), 1.43 (3H, d, J 2.9 Hz, CH_3), 1.37 (3H, s, CH_3), 1.33-1.23 (10H, m, CH_2), 0.89 (3H, t, J 6.6 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 145.8 (C), 145.6 (C), 112.0 (CH_2), 111.9 (CH_2), 111.8 (C), 101.6 (CH), 101.4 (CH), 74.6 (CH), 74.5 (CH), 69.9 (CH_2), 69.7 (CH_2), 67.0 (CH_2), 66.9 (CH_2), 66.8 (CH_2), 33.3 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 27.7 (CH_2), 26.9 (CH_3), 25.5 (CH_3), 25.4 (CH_3), 22.7 (CH_2), 14.2 (CH_3), 4.7 (CH_2), 4.6 (CH_2); HRMS *m/z* (ESI^+) 463.1401 ($M + Na^+$) $C_{18}H_{33}IO_4Na^+$ requires 463.1316.

1,1-Diethoxyethene (51)



Following general procedure G with 1-(2-bromo-1-ethoxy)butane (5.00 g, 25.4 mmol), KO^{t}Bu (6.27 g, 55.8 mmol) and KO^{t}Bu (2.85 g, 25.4 mmol) gave the title compound (1.2 g, 41%) as yellow liquid. ν_{max}/cm^{-1}; 2980, 2932, 1643, 1279 and 1048; ^{1}H NMR (500 MHz, C_6D_6); 3.56 (4H, q, J 7.1 Hz, CH_2), 3.19 (2H, s, CH_2), 1.03 (6H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 63.4 (CH_2), 56.6 (CH_2), 14.4 (CH_3).[a] The data was consistent with the literature.[155]

1-((1-Butoxyvinyl)oxy)butane (278a)



***Via* Bromoacetal:**

Following general procedure G with 1-(2-bromo-1-butoxyethoxy)butane (5.00 g, 19.8 mmol), KO^{t}Bu (4.89 g, 43.6 mmol) and KO^{t}Bu (2.22 g, 19.8 mmol) gave the title compound (2.8 g, 82%) as yellow liquid.

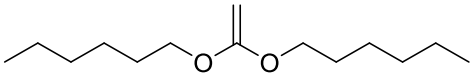
[a] Mass spectra analysis was run but the desired mass ion was not observed.

***Via* Iodoacetal:**

Following general procedure H with KO^{t}Bu (822 mg, 7.33 mmol) and 1-(1-butoxy-2-iodoethoxy)butane (1.00 g, 3.33 mmol) gave the title compound (490 mg, 86%) as a yellow liquid.

ν_{max}/cm^{-1}; 2959, 2934, 2874, 1642 and 1280; ^{1}H NMR (500 MHz, C_6D_6); 3.62 (4H, t, J 6.4 Hz, CH_2), 3.24 (2H, s, CH_2), 1.48 (4H, q, J 6.4 Hz, CH_2), 1.33-1.23 (4H, m, CH_2), 0.77 (6H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 166.1 (C), 67.7 (CH_2), 56.5 (CH_2), 31.4 (CH_2), 19.5 (CH_2), 13.9 (CH_3).[a]

1-((1-(Hexyloxy)vinyl)oxy)hexane (278b)



***Via* Bromoacetal:**

Following general procedure G with 1-2(Bromo-1-(hexyloxy)ethoxy)hexane (6.12 g, 19.8 mmol), KO^{t}Bu (4.89 g, 43.6 mmol), addition over 25 min, and KO^{t}Bu (2.22 g, 19.8 mmol) gave the title compound (3.4 g, 76%) as yellow liquid.

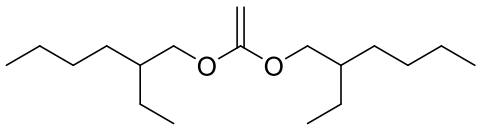
***Via* Iodoacetal:**

Following general procedure H with KO^{t}Bu (831 mg, 7.41 mmol) and 1-(1-(hexyloxy)-2-iodoethoxy)hexane (1.20 g, 3.37 mmol). Heating to 30 °C for 2 h gave the title compound (702 mg, 91%) as a yellow liquid.

ν_{max}/cm^{-1}; 2955, 2930, 2859, 1642 and 1281; ^{1}H NMR (500 MHz, C_6D_6); 3.65 (4H, t, J 6.5 Hz, CH_2), 3.27 (2H, s, CH_2), 1.57-1.49 (4H, m, CH_2), 1.31-1.23 (4H, m, CH_2), 1.22-1.09 (8H, m, CH_2), 0.82 (6H, t, J 7.1 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 165.7 (C), 67.7 (CH_2), 66.1 (CH_2), 31.5 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.5 (CH_2), 13.8 (CH_3).[a]

[a] Mass spectra analysis was run but the desired mass ion was not observed.

3-(((1-((2-Ethylhexyl)oxy)vinyl)oxy)methyl)heptane (278c)



***Via* Bromoacetal:**

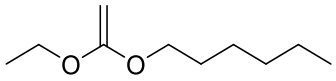
Following general procedure G with 3-((2-bromo-1-((2-ethylhexyl)oxy)ethoxy)methyl)heptane (7.23 g, 19.8 mmol), KO^{t}Bu (6.67 g, 59.4 mmol) and KO^{t}Bu (6.67 g, 59.4 mmol). Heating to 45 °C for 2 h after both additions gave the title compound (2.7 g, 48%) as yellow liquid.

***Via* Iodoacetal:**

Following general procedure H with KO^{t}Bu (898 mg, 8.00 mmol) and 3-((1-((2-ethylhexyl)oxy)-2-iodoethoxy)methyl)heptane (1.50 g, 3.64 mmol). Heating to 30 °C for 2 h gave the title compound (947 mg, 72%) as a yellow liquid.

ν_{max}/cm^{-1}; 2958, 2926, 2874, 2860, 1643 and 1279; ^{1}H NMR (500 MHz, $CDCl_3$); 3.66 (4H, dd, J 5.6, 1.2 Hz, CH_2), 3.32 (2H, s, CH_2), 1.58-1.52 (2H, m, CH), 1.46-1.38 (4H, m, CH_2), 1.38-1.24 (12H, m, CH_2), 0.85 (6H, t, J 6.9 Hz, CH_3), 0.82 (6H, t, J 7.5 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 165.7 (C), 70.4 (CH_2), 56.3 (CH_2), 39.2 (CH), 30.5 (CH_2), 29.0 (CH_2), 23.8 (CH_2), 23.0 (CH_2), 13.9 (CH_3), 10.9 (CH_3).[a]

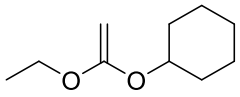
1-((1-Ethoxyvinyl)oxy)hexane (279a)



Following general procedure G with KO^{t}Bu (1.65 g, 14.7 mmol) and 1-(1-ethoxy-2-iodoethoxy)hexane (1.98 g, 6.66 mmol) gave the title compound (1.3 g, 85%) as a yellow liquid. ν_{max}/cm^{-1}; 2930, 2860, 1643 and 1280 ^{1}H NMR (500 MHz, C_6D_6); 3.64-3.56 (4H, m, CH_2), 3.22 (2H, dd, J 14.4, 3.3 Hz, CH_2), 1.55-1.47 (2H, m, CH_2), 1.29-1.23 (2H, m, CH_2), 1.20-1.07 (4H, m, CH_2), 1.05 (3H, t, J 7.1 Hz, CH_3), 0.82 (3H, t, J

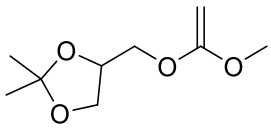
7.1 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 165.7 (C), 68.0 (CH_2), 63.5 (CH_2), 56.5 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 22.9 (CH_2), 14.5 (CH_3), 14.2 (CH_3).[a]

((1-Ethoxyvinyl)oxy)cyclohexane (279b)



Following general procedure G with KO^{t}Bu (830 mg, 7.39 mmol) and (1-ethoxy-2-iodoethoxy)cyclohexane (1.00 g, 3.35 mmol) gave the title compound (630 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2980, 2933, 2858, 1640 and 1257; ^1H NMR (500 MHz, C_6D_6); 4.06 (1H, tt, J 8.1, 3.6 Hz, CH), 3.56 (2H, q, J 7.0 Hz, CH_2), 3.39 (1H, d, J 3.0 Hz, CH_2), 3.26 (1H, d, J 3.0 Hz, CH_2), 1.85-1.79 (2H, m, CH_2), 1.65-1.56 (2H, m, CH_2), 1.52-1.46 (2H, m, CH_2), 1.18-1.06 (4H, m, CH_2), 1.04 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 164.1 (C), 75.2 (CH), 63.4 (CH_2), 59.3 (CH_2), 31.8 (CH_2), 25.9 (CH_2), 23.7 (CH_2), 14.5 (CH_3).[a]

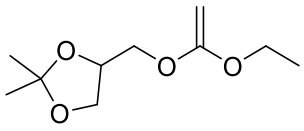
4-(((1-Methoxyvinyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (279c)



Following general procedure I with 4-((2-bromo-1-methoxyethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (1.00 g, 3.72 mmol) and KO^{t}Bu (999 mg, 8.17 mmol), 25 °C, gave title compound (625 mg, 89%) as yellow liquid. ν_{max}/cm^{-1}; 2986, 2939, 2883, 1646, 1282 and 1026; ^1H NMR (500 MHz, C_6D_6); 4.15-4.06 (1H, m, CH), 3.75-3.70 (2H, m, CH_2), 3.62 (2H, ddd, J 10.8, 7.3, 1.0 Hz, CH_2), 3.17 (1H, d, J 3.7 Hz, CH_2), 3.16 (3H, s, CH_3), 3.07 (1H, d, J 3.8 Hz, CH_2), 1.37 (3H, s, CH_3), 1.24 (3H, s, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 116.4 (C), 109.5 (C), 74.0 (CH), 68.9 (CH_2), 66.9 (CH_2), 56.5 (CH_2), 54.9 (CH_3), 27.0 (CH_3), 25.6 (CH_3).

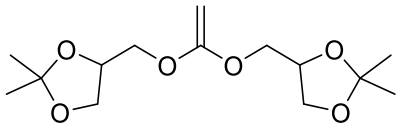
[a] Mass spectra analysis was run but the desired mass ion was not observed.

4-(((1-Ethoxyvinyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (279d)



Following general procedure I with 4-((2-Bromo-1-ethoxyethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (5.00 g, 17.7 mmol) and KO^{t}Bu (4.36 g, 38.8 mmol), at 25 °C, gave the title compound (2.7 g, 77%) as yellow liquid. ν_{max}/cm^{-1}; 2985, 2935, 1645, 1280 and 1033; ^{1}H NMR (500 MHz, C_6D_6); 4.14 (1H, p, J 6.0 Hz, CH), 3.75 (2H, ddd, J 8.5, 6.4, 3.5 Hz, CH_2), 3.63 (2H, ddd, J 13.0, 8.5, 6.0 Hz, CH_2), 3.51 (2H, q, J 6.8 Hz, CH_2), 3.19 (1H, d, J 3.6 Hz, CH_2), 3.12 (1H, d, J 3.6 Hz, CH_2), 1.36 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.0 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 163.3 (C), 109.4 (C), 74.0 (CH), 68.8 (CH_2), 66.9 (CH_2), 63.7 (CH_2), 57.3 (CH_2), 27.0 (CH_3), 25.6 (CH_3), 14.4 (CH_3).[a]

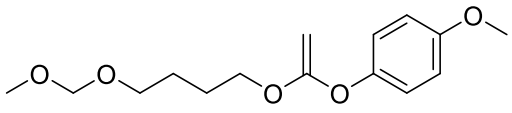
4,4'-((Ethene-1,1-diylbis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (279e)



Following general procedure I with 4,4'-(((2-bromoethane-1,1-diyl)bis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (1.00 g, 2.71 mmol) and KO^{t}Bu (669 mg, 5.96 mmol), at 25 °C, gave the title compound (630 mg, 81%) as yellow liquid. ν_{max}/cm^{-1}; 2987,2936, 2886, 1685, 1648 and 1455; ^{1}H NMR (500 MHz, $CDCl_3$); 4.14-4.07 (2H, m, CH_2), 3.75-3.66 (4H, m, CH_2), 3.62-3.54 (4H, m, CH_2), 3.15 (2H, d, J 0.7 Hz, CH_2), 1.36 (6H, d, J 0.7 Hz, CH_3), 1.24 (6H, m, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 164.6 (C), 164.6 (C), 109.2 (C), 73.55 (CH), 73.54 (CH), 68.61 (CH_2), 68.58 (CH_2), 66.6 (CH_2), 66.5 (CH_2), 57.78 (CH_2), 57.76 (CH_2), 26.6 (CH_3), 25.1 (CH_3).[a]

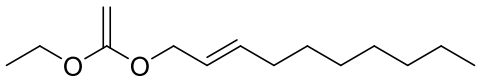
[a] Mass spectra analysis was run but the desired mass ion was not observed.

1-Methoxy-4-((1-(4-(methoxymethoxy)butoxy)vinyl)oxy)benzene (279f)



Following general procedure H with KO^{t}Bu (301 mg, 2.68 mmol) and 1-(2-iodo-1-(4-(methoxymethoxy)butoxy)ethoxy)-4-methoxybenzene (500 mg, 1.22 mmol) gave the title compound (360 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2928, 1650 and 1505; ^{1}H NMR (500 MHz, C_6D_6); 7.03 (2H, dd, J 6.7, 2.2 Hz, CH), 6.65 (2H, dd, J 6.7, 2.2 Hz, CH), 4.43 (2H, s, CH_2), 3.60 (2H, t, J 6.2 Hz, CH_2), 3.59 (1H, d, J 3.2 Hz, CH_2), 3.42 (1H, d, J 3.2 Hz, CH_2), 3.31 (2H, t, J 6.2 Hz, CH_2), 3.24 (3H, s, CH_3), 3.14 (3H, s, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 164.8 (C), 156.6 (C), 149.2 (C), 120.7 (CH), 114.9 (CH), 96.4 (CH_2), 68.5 (CH_2), 67.2 (CH_2), 64.0 (CH_2), 55.1 (CH_3), 54.8 (CH_3).[a]

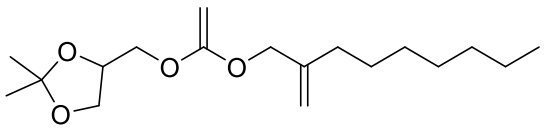
(*E*)-1-((1-Ethoxyvinyl)oxy)dec-2-ene (284a)



Following general procedure H with KO^{t}Bu (697 mg, 6.21 mmol) and (E)-1-(1-ethoxy-2-iodoethoxy)dec-2-ene (1.00 g, 2.82 mmol) gave the title compound (520 mg, 82%) as a yellow liquid. The temperature of the reaction, including work up and concentration, was kept at 25 °C or below. ν_{max}/cm^{-1}; 2956, 2925, 2855, 1644 and 1276; ^{1}H NMR (500 MHz, $CDCl_3$); 5.64-5.57 (2H, m, CH), 4.19 (2H, d, J 5.4 Hz, CH_2), 3.58 (2H, q, J 6.9 Hz, CH_2), 3.27 (1H, d, J 3.3 Hz, CH_2), 3.23 (1H, d, J 3.3 Hz, CH_2), 1.90 (2H, q, J 6.8 Hz, CH_2), 1.37-1.28 (8H, m, CH_2), 1.04 (3H, t, J 7.2 Hz, CH_3), 0.91-0.89 (3H, m, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 165.6 (C), 134.9 (CH), 125.2 (CH), 68.7 (CH_2), 63.6 (CH_2), 57.4 (CH_2), 32.6 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 14.5 (CH_3), 14.3 (CH_3).[a]

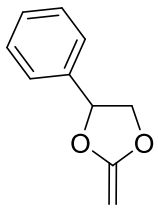
[a] Mass spectra analysis was run but the desired mass ion was not observed.

2,2-Dimethyl-4-(((1-((2-methylenenonyl)oxy)vinyl)oxy)methyl)-1,3-dioxolane (284e)



Following general procedure H with KO^{t}Bu (561 mg, 4.99 mmol) and 4-((2-iodo-1-((2-methylenenonyl)oxy)ethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (1.00 g, 2.27 mmol) gave the title compound (800 mg, >99%) as yellow liquid. The temperature of the reaction, including work up and concentration, was kept at 25 °C or below. ν_{max}/cm^{-1}; 2955, 2925, 2855, 1646, 1457 and 1371; ^{1}H NMR (500 MHz, $CDCl_3$); 5.09 (1H, d, J 1.7 Hz, CH_2), 4.89 (1H, d, J 1.7 Hz, CH_2), 4.15 (2H, s, CH_2), 3.75-3.71 (2.5H, m, CH_2/CH), 3.66-3.61 (2.5H, m, CH_2/CH), 3.26 (2H, q, J 3.7 Hz, CH_2), 2.01 (2H, t, J 7.9 Hz, CH_2), 1.40 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.29-1.18 (8H, m, CH_2), 0.90-0.88 (3H, m, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 165.1 (C), 144.9 (C), 111.9 (CH_2), 109.4 (C), 74.0 (CH), 71.1 (CH_2), 68.9 (CH_2), 67.0 (CH_2), 58.3 (CH_2), 33.4 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 27.0 (CH_3), 25.5 (CH_3), 14.3 (CH_3).[a]

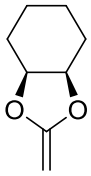
2-Methylene-4-phenyl-1,3-dioxolane (287a)



Following general procedure I with 2-(bromomethyl)-4-phenyl-1,3-dioxolane (2.50 g, 10.3 mmol) and KO^{t}Bu (2.54 g, 22.6 mmol), at 5-10 °C, gave the title compound (1.2 g, 69%) as yellow liquid. ν_{max}/cm^{-1}; 3035, 2957, 2901 and 1679; ^{1}H NMR (500 MHz, C_6D_6); 7.04-6.96 (5H, m, CH), 4.72 (1H, t, J 7.1 Hz, CH), 3.76-3.73 (1H, m, CH_2), 3.73-3.69 (2H, m, CH_2), 3.46 (1H, dd, J 7.36, 0.7 Hz, CH_2); ^{13}C NMR (125 MHz, C_6D_6); 164.8 (C), 137.8 (C), 128.9 (CH), 126.2 (CH), 78.9 (CH), 72.2 (CH_2), 54.6 (CH_2).[a] The data was consistent with the literature.[153]

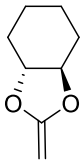
[a] Mass spectra analysis was run but the desired mass ion was not observed.

(3aR,7aS)-2-Methylenehexahydrobenzo[d][1,3]dioxole (287b)



Following general procedure I with 2-(bromomethyl)hexahydrobenzo[1,3]dioxole (1.00 g, 4.52 mmol) and KO^{t}Bu (1.12 g, 10.0 mmol), at 5-10 °C, gave the title compound (316 mg, 50%) as yellow liquid. ν_{max}/cm^{-1}; 2938, 2865, 1677, 1022 and 996; ^{1}H NMR (500 MHz, C_6D_6); 3.81-3.76 (2H, m, CH), 3.67 (2H, s, CH_2), 1.63-1.55 (2H, m, CH_2), 1.29-1.15 (4H, m, CH_2), 0.84-0.74 (2H, m, CH_2); ^{13}C NMR (125 MHz, C_6D_6); 75.2 (CH), 55.5 (CH_2), 26.8 (CH_2), 20.5 (CH_2).[a] The data was consistent with the literature.[153]

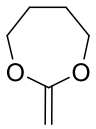
(3aR,7aR)-2-Methylenehexahydrobenzo[d][1,3]dioxole (287c)



Following general procedure I with 2-(bromomethyl)hexahydrobenzo[d][1,3]dioxole (2.50 g, 11.3 mmol) and KO^{t}Bu (2.79 g, 24.9 mmol), at 5-10 °C, gave the title compound (950 mg, 60%) as yellow liquid. ν_{max}/cm^{-1}; 2947, 2866, 1682, 1220 and 1107; ^{1}H NMR (500 MHz, C_6D_6); 3.74 (2H, s, CH_2), 3.22-3.12 (2H, m, CH), 1.77-1.71 (2H, m, CH_2), 1.20-1.14 (2H, m, CH_2), 1.14-1.05 (2H, m, CH_2), 0.70-0.58 (2H, m, CH_2); ^{13}C NMR (125 MHz, C_6D_6); 164.9 (C), 82.3 (CH), 56.3 (CH_2), 28.4 (CH_2), 23.4 (CH_2).[a]

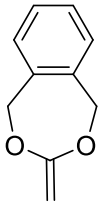
[a] Mass spectra analysis was run but the desired mass ion was not observed.

2-Methylene-1,3-dioxepane (287d)



Following general procedure I with 2-(bromomethyl)-1,3-dioxepane (1.50 g, 7.77 mmol) and KO^{t}Bu (1.92 g, 17.09 mmol), at 5-15 °C, gave the title compound (540 mg, 61%) as yellow liquid. ν_{max}/cm^{-1}; 2945, 2886, 2849, 1671, 1656 and 1029; ^{1}H NMR (500 MHz, C_6D_6); 3.84 (2H, s, CH_2), 3.61-3.56 (4H, m, CH_2), 1.16 (4H, dt, J 5.1, 2.2 Hz, CH_2); ^{13}C NMR (125 MHz, C_6D_6); 164.5 (C), 69.9 (CH_2), 68.0 (CH_2), 29.0 (CH_2).[a] The data was consistent with the literature.[265]

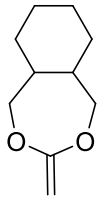
3-Methylene-1,5-dihydrobenzo[e][1,3]dioxepine (287e)



Following general procedure I with 3-(Bromomethyl)-1,5-dihydrobenzo[1,3]dioxepine (2.50 g, 10.3 mmol) and KO^{t}Bu (2.55 g, 22.7 mmol), at 5-10 °C, gave the title compound (1.5 g, 92%) as yellow liquid. ν_{max}/cm^{-1}; 2957, 2922,2868, 1672 and 1602; ^{1}H NMR (500 MHz, C_6D_6); 6.88 (2H, dd, J 5.7, 3.4 Hz, CH), 6.54 (2H, dd, J 5.7, 3.4 Hz, CH), 4.77 (4H, s, CH_2), 3.96 (2H, s, CH_2); ^{13}C NMR (125 MHz, C_6D_6); 165.1 (C), 136.3 (C), 127.4 (CH), 126.3 (CH), 72.1 (CH_2), 69.9 (CH_2).[a] The data was consistent with the literature.[267]

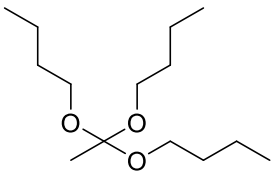
[a] Mass spectra analysis was run but the desired mass ion was not observed.

3-Methyleneoctahydrobenzo[e][1,3]dioxepine (287f)



Following general procedure I with 3-(bromomethyl)octahydrobenzo[1,3]dioxepine (1.50 g, 6.02 mmol) and KO^{t}Bu (1.48 g, 13.2 mmol), at 5-10 °C, gave the title compound (990 g, 97%) as yellow crystalline solid. ^{1}H NMR (500 MHz, C_6D_6); 3.89 (2H, s, CH_2), 3.59 (2H, dd, J 11.4, 2.6 Hz, CH_2), 3.43 (2H, dd, J 11.4, 10.0 Hz, CH_2), 1.47-1.40 (2H, m, CH), 1.11-0.99 (4H, m, CH_2), 0.92-0.86 (2H, m, CH_2), 0.44-0.35 (2H, m, CH_2); ^{13}C NMR (125 MHz, C_6D_6); 165.6 (C), 74.5 (CH_2), 67.7 (CH_2), 45.1 (CH), 29.9 (CH_2), 26.0 (CH_2).[a]

Tributyl Orthoester (291a)



From addition to ketene acetal:

Following general procedure J with butanol (172 mg, 2.32 mmol) and 1-((1-butoxyvinyl)oxy)butane (400 mg, 2.32 mmol), at 60 °C, gave the title compound (540 mg, >99%) as a yellow liquid.

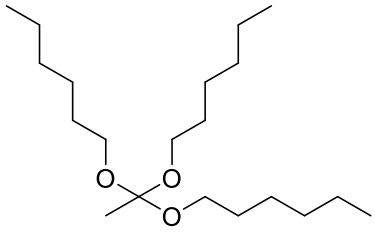
From the orthoester exchange approach:

Following general procedure K with butanol (161 mL, 1.75 mol), trimethyl orthoacetate (37.4 mL, 0.290 mol) and trifluoroacetic acid (2.25 mL, 0.0290 mol). Purification by distillation (85 °C, 80 mbar) gave tributyl orthoacetate (42 g, 60%) as a clear liquid.

[a] Mass spectra analysis was run but the desired mass ion was not observed.

ν_{max}/cm^{-1}; 2958, 2935, 2879, 1465 and 1372; ^{1}H NMR (500 MHz, C_6D_6); 3.46 (6H, t, J 6.9 Hz, CH_2), 1.59-1.51 (6H, m, CH_2), 1.44 (3H, s, CH_3), 1.43-1.34 (6H, m, CH_2), 0.92 (3H, t, J 7.4 Hz, CH_3); ^{13}C NMR (125 MHz, C_6D_6); 114.1 (C), 61.7 (CH_2), 31.9 (CH_2), 20.2 (CH_3), 19.5 (CH_2), 14.0 (CH_3); HRMS *m/z* (ESI$^+$) 269.2100 (M + Na$^+$) $C_{14}H_{20}O_3Na^+$ requires 269.2087. The data was consistent with the literature.[75]

Trihexyl Orthoester (291b)



From addition to ketene acetal:

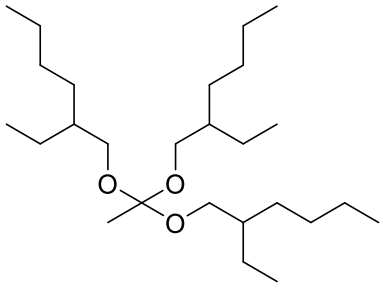
Following general procedure J with hexanol (134 mg, 1.31 mmol) and 1-((1-(hexyloxy)vinyl)oxy)hexane (300 mg, 1.31 mmol), at 60 °C, gave the title compound (469 mg, >99%) as a yellow liquid.

From the orthoester exchange approach:

Following general procedure K with hexanol (22.1 mL, 176 mmol), trimethyl orthoacetate (3.74 mL, 29.4 mmol) and trifluoroacetic acid (225 µL, 2.94 mmol). Purification by distillation (100 °C, 20 mbar) gave the title compound (6.96 g, 72%) as a clear liquid.

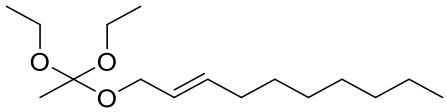
ν_{max}/cm^{-1}; 2929, 2873, 2859, 1467 and 1372; ^{1}H NMR (500 MHz, $CDCl_3$); 3.46 (6H, t, J 6.9 Hz, CH_2), 1.57 (6H, p, J 6.9 Hz, CH_2), 1.45 (3H, s, CH_3), 1.40-1.23 (18H, m, CH_2), 0.89 (9H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 114.2 (C), 62.0 (CH_2), 31.7 (CH_2), 29.8 (CH_2),26.0 (CH_2), 22.7 (CH_2), 20.2 (CH_3), 14.0 (CH_3); HRMS *m/z* (ESI$^+$) 353.3066 (M + Na$^+$) $C_{20}H_{42}O_3Na^+$ requires 353.3026. The data was consistent with the literature.[273]

Tri-2-ethylhexyl orthoester (291c)



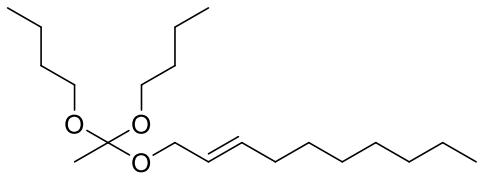
Following general procedure J with 2-ethylhexanol (69.0 mg, 0.527 mmol) and 3-(((1-((2-ethylhexyl)oxy)vinyl)oxy)methyl)heptane (150 mg, 0.527 mmol), at 40 °C for 2.5 h, gave the title compound (215 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2958, 2927, 2873, 2860, 1461 and 1371; ^{1}H NMR (500 MHz, $CDCl_3$); 3.37 (6H, dd, J 5.8, 1.3 Hz, CH_2), 1.53-1.45 (3H, m, CH), 1.33 (3H, s, CH_3), 1.42-1.24 (24H, m, CH_2), 0.94-0.84 (18H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 114.1 (C), 64.68 (CH_2), 64.66 (CH_2), 64.5 (CH_2), 39.9 (CH), 30.8 (CH_2), 29.3 (CH_2), 24.1 (CH_2), 23.3 (CH_2), 20.5 (CH_3), 14.2 (CH_3), 11.2 (CH_3); HRMS *m/z* (ESI^+) 437.4005 ($M + Na^+$) $C_{26}H_{54}O_3Na^+$ requires 437.3965.

(*E*)-1-(1,1-Diethoxyethoxy)dec-2-ene (293a)



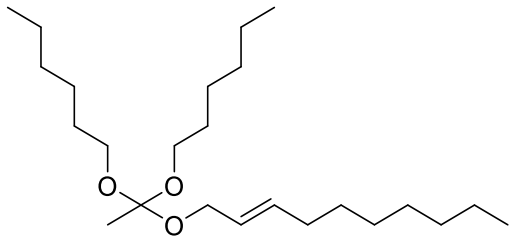
Following general procedure J with dec-2-enol (244 mg, 1.56 mmol) and 1,1-diethoxyethene (200 mg, 1.72 mmol), at 40 °C. Further 1,1-diethoxyethene (18.1 mg, 0.15 mmol) was added and held at 25 °C for 5 min. Purification by distillation (80 °C, 0 mbar) gave the title compound (430 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2925, 2855, 1458 and 1376; ^{1}H NMR (500 MHz, $CDCl_3$); 5.73-5.64 (1H, m, CH), 5.59-5.49 (1H, m, CH), 3.97 (2H, dd, J 6.0, 1.0 Hz, CH_2), 3.55 (4H, q, J 7.0 Hz, CH_2), 2.06-1.98 (2H, m, CH_2), 1.47 (3H, s, CH_3), 1.39-1.33 (2H, m, CH_2), 1.32-1.23 (8H, m, CH_2), 1.20 (6H, t, J 7.1 Hz, CH_3), 0.87 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (500 MHz, $CDCl_3$); 134.1 (CH), 126.3 (CH), 114.2 (C), 62.9 (CH_2), 57.6 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.29 (CH_2), 29.26 (CH_2), 29.2 (CH_2), 22.7 (CH_2), 20.37 (CH_3), 15.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) ($M + Na^+$) 295.2246 $C_{16}H_{32}O_3Na^+$ requires 295.2244.

(*E*)-1-(1,1-Dibutoxyethoxy)dec-2-ene (293b)



Following general procedure J with dec-2-enol (363 mg, 2.32 mmol) and 1-((1-butoxyvinyl)oxy)butane (440 mg, 2.55 mmol), at 40 °C, gave the title compound (772 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2958, 2927, 2873, 1465 and 1378; ^{1}H NMR (500 MHz, $CDCl_3$); 5.73-5.64 (1H, m, CH), 5.59-5.51 (1H, m, CH), 3.97 (2H, dd, J 6.2, 1.2 Hz, CH_2), 3.48 (2H, t, J 6.7 Hz, CH_2), 2.06-2.00 (2H, m, CH_2), 1.61-1.52 (4H, m, CH_2), 1.47 (3H, s, CH_3), 1.44-1.34 (6H, m, CH_2), 1.32-1.23 (8H, m, CH_2), 0.93 (6H, t, J 7.4 Hz, CH_3), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.0 (CH), 126.4 (CH), 114.4 (C), 62.9 (CH_2), 62.1 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 31.97 (CH_2), 29.32 (CH_2), 29.31 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 20.4 (CH_3), 19.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS *m/z* (ESI^+) (M + Na^+) 351.2902 $C_{20}H_{40}O_3Na^+$ requires 351.2870.

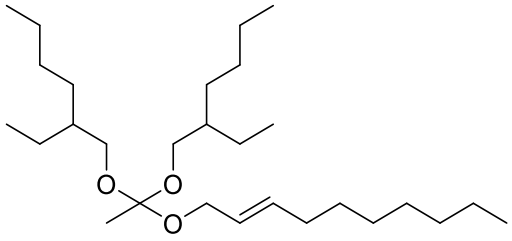
(*E*)-1-(1,1-Bis(hexyloxy)ethoxy)dec-2-ene (293c)



Following general procedure J with dec-2-enol (274 mg, 1.75 mmol) and 1-((1-(hexyloxy)vinyl)oxy)hexane (440 mg, 1.93 mmol), at 40 °C, gave the title compound (670 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 3955, 2925, 2856, 1466 and 1376; ^{1}H NMR (500 MHz, $CDCl_3$); 5.73-5.66 (1H, m, CH), 5.59-5.52 (1H, m, CH), 3.97 (2H, dd, J 6.2, 1.2 Hz , CH_2), 3.47 (4H, t, J 6.7 Hz, CH_2), 2.08-2.00 (2H, m, CH_2), 1.58 (4H, p, J 6.9 Hz, CH_2), 1.47 (3H, s, CH_3), 1.41-1.33 (6H, m, CH_2), 1.33-1.24 (16H, m, CH_2), 0.92-0.86 (9H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.1 (CH), 126.2 (CH), 114.4 (C), 62.9 (CH_2), 62.4 (CH_2), 32.48 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.33 (CH_2),

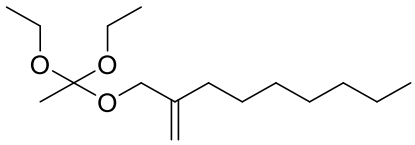
29.32 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 22.78 (CH_2), 20.5 (CH_3), 14.23 (CH_3), 14.20 (CH_3); HRMS *m/z* (ESI^+) (M + Na^+) 407.3531 $C_{24}H_{48}O_3Na^+$ requires 407.3496.

(*E*)-1-(1,1-Bis(hexyloxy)ethoxy)dec-2-ene (293d)



Following general procedure J with dec-2-enol (200 mg, 1.28 mmol) and 3-(((1-((2-ethylhexyl)oxy)vinyl)oxy)methyl)heptane (400 mg, 1.41 mmol), at 40 °C for 2.5 h, gave the title compound (620 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2958, 2925, 2858, 1461 and 1378; ^1H NMR (500 MHz, $CDCl_3$); 5.72-5.64 (1H, m, CH), 5.61-5.51 (1H, m, CH), 3.99 (2H, dd, J 6.2, 0.9 Hz, CH_2), 3.39-3.35 (4H, m, CH_2), 2.07-1.99 (2H, m, CH_2), 1.53-1.48 (2H, m, CH), 1.47 (3H, s, CH_3), 1.44-1.37 (4H, m, CH_2), 1.37- 1.23 (22H, m, CH_2), 0.93-0.86 (15H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.0 (CH), 126.5 (CH), 114.3 (C), 64.89 (CH_2), 64.97 (CH_2), 64.8 (CH_2), 62.9 (CH_2), 39.9 (CH), 32.5 (CH_2), 32.0 (CH_2), 30.8 (CH_2), 30.75 (CH_2), 30.7 (CH_2), 29.32 (CH_2), 29.31 (CH_2), 29.28 (CH_2), 29.25 (CH_2), 24.09 (CH_2), 24.05 (CH_2), 23.3 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 14.3 (CH_3), 11.3 (CH_3), 11.2 (CH_3); HRMS *m/z* (ESI^+) 463.4182 (M + Na^+) $C_{28}H_{56}O_3Na^+$ requires 463.4122.

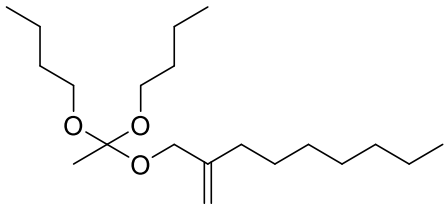
2-((1,1-Diethoxyethoxy)methyl)non-1-ene (294a)



Following general procedure J with 2-methylenonanol (244 mg, 1.56 mmol) and 1,1-diethoxyethene (240 mg, 2.06 mmol), at 40 °C. Further 1,1-diethoxyethene (18.1 mg, 0.15 mmol) was added and held at 25 °C for 5 min. Purification by distillation (80 °C, 0 mbar) gave the title compound (441 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2976, 2927, 2857, 1654, 1489, 1376; ^1H NMR (500 MHz, $CDCl_3$); 5.04 (1H, d, J 2.1 Hz, CH_2), 4.84 (1H, d, J 2.1 Hz, CH_2), 3.94 (2H, s, CH_2), 3.56 (4H, q,

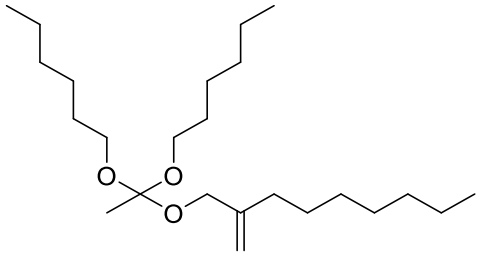
J 7.3 Hz, CH_2), 2.05 (2H, t, J 7.6 Hz, CH_2), 1.48 (3H, s, CH_3), 1.46-1.40 (2H, m, CH_2), 1.35-1.23 (8H, m, CH_2), 1.20 (6H, t, J 7.1 Hz, CH_3), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.4 (C), 114.5 (C), 110.1 (CH_2), 64.6 (CH_2), 57.8 (CH_2), 33.5 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 20.4 (CH_3), 15.4 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) (M + Na^+) 295.2238 $C_{16}H_{32}O_3Na^+$ requires 295.2351.

2-((1,1-Dibutoxyethoxy)methyl)non-1-ene (294b)



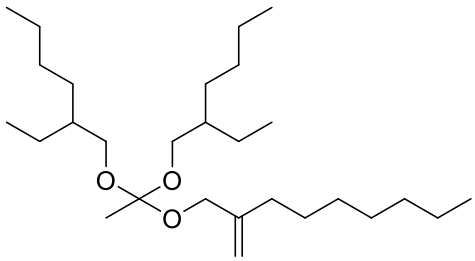
Following general procedure J with 2-methylenenonanol (363 mg, 2.32 mmol) and 1-((1-butoxyvinyl)oxy)butane (479 mg, 2.78 mmol) at 40 °C, gave the title compound (791 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2957, 2928, 2873, 1652, 1463 and 1375; ^1H NMR (500 MHz, $CDCl_3$); 5.04 (1H, d, J 2.1 Hz, CH_2), 4.84 (1H, d, J 2.1 Hz, CH_2), 3.94 (2H, s, CH_2), 3.49 (4H, t, J 6.7 Hz, CH_2), 2.05 (2H, t, J 7.5 Hz, CH_2), 1.59-1.51 (4H, m, CH_2), 1.48 (3H, s, CH_3), 1.46-1.42 (2H, m, CH_2), 1.42-1.35 (4H, m, CH_2), 1.32-1.22 (8H, m, CH_2), 0.92 (6H, t, J 7.5 Hz, CH_3), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.5 (C), 114.3 (C), 110.1 (CH_2), 64.6 (CH_2), 62.1 (CH_2), 33.6 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 20.4 (CH_3), 19.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS *m/z* (ESI^+) 351.2877 (M + Na^+) $C_{20}H_{40}O_3Na^+$ requires 351.2870.

2-((1,1-Bis(hexyloxy)ethoxy)methyl)non-1-ene (294c)



Following general procedure J with 2-methylenenonanol (274 mg, 1.75 mmol) and 1-((1-(hexyloxy)vinyl)oxy)hexane (480 mg, 2.10 mmol) at 40 °C, gave the title compound (680 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2926, 2857, 1652, 1466 and 1375; ^{1}H NMR (500 MHz, $CDCl_3$); 5.04 (1H, d, J 2.1 Hz, CH_2), 4.84 (1H, d, J 2.1 Hz, CH_2), 3.95 (2H, s, CH_2), 3.49 (4H, t, J 6.7 Hz, CH_2), 2.05 (2H, t, J 7.6 Hz, CH_2), 1.57 (4H, p, J 6.8 Hz, CH_2), 1.48 (3H, s, CH_3), 1.47-1.43 (2H, m, CH_2), 1.39-1.33 (4H, m, CH_2), 1.33-1.23 (16H, m, CH_2), 0.92-0.86 (9H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.5 (C), 114.4 (C), 110.1 (CH_2), 64.6 (CH_2), 62.5 (CH_2), 33.6 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 22.77 (CH_2), 20.4 (CH_3), 14.22 (CH_3), 14.18 (CH_3); HRMS *m/z* (ESI^+) 407.3153 ($M + Na^+$) $C_{24}H_{48}O_3Na^+$ requires 407.3496.

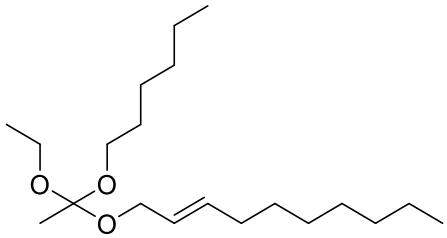
2-((1,1-Bis((2-ethylhexyl)oxy)ethoxy)methyl)non-1-ene (294d)



Following general procedure J with 2-methylenenonanol (200 mg, 1.28 mmol) and 3-(((1-((2-ethylhexyl)oxy)vinyl)oxy)methyl)heptane (437 mg, 1.54 mmol) at 40 °C, gave the title compound (632 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2958, 2926, 1655, 1460 and 1377; ^{1}H NMR (500 MHz, $CDCl_3$); 5.04 (1H, d, J 2.1 Hz, CH_2), 4.84 (1H, d, J 2.1 Hz, CH_2), 3.96 (2H, s, CH_2), 3.39 (4H, dd, J 6.0, 2.0 Hz, CH_2), 2.06 (2H, t, J 7,6 Hz, CH_2), 1.52-1.48 (2H, m, CH), 1.47 (3H, s, CH_3), 1.46-1.38 (6H, m, CH_2), 1.36-1.22 (20H, m, CH_2), 0.92-0.85 (15H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.7 (C), 114.3 (C), 109.9 (CH_2), 64. 89 (CH_2), 64. 88 (CH_2), 64.85 (CH_2), 64.68 (CH_2), 64.66

(CH_2), 64.60 (CH_2), 39.85 (CH), 39.84 (CH), 32.0 (CH_2), 30.79 (CH_2), 30.77 (CH_2), 30.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 24.06 (CH_2), 24.05 (CH_2), 23.2 (CH_2), 22.8 (CH_2), 20.57 (CH_3), 14.3 (CH_3), 11.3 (CH_3), 11.2 (CH_3); HRMS *m/z* (ESI^+) 463.4156 (M + Na^+) $C_{28}H_{56}O_3Na^+$ requires 463.4122.

(*E*)-1-(1-Ethoxy-1-(hexyloxy)ethoxy)dec-2-ene (295a)



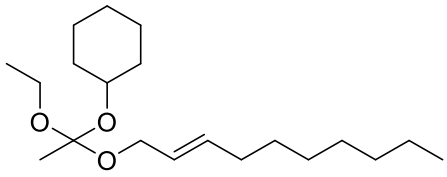
Following general procedure J with dec-2-enol (181 mg, 1.16 mmol) and 1-((1-ethoxyvinyl)oxy)hexane (220 mg, 1.28 mmol) at 30 °C, gave the title compound (398 mg, >99%) as a yellow liquid.

To a stirring solution of KO^tBu (697 mg, 6.21 mmol) in THF (3.5 mL) was added (*E*)-1-(1-ethoxy-2-iodoethoxy)dec-2-ene (1.00 g, 2.82 mmol) in THF (700 µL) dropwise over 30 min. The solution was then stirred at stirred at 25 °C for 1 h. Hexane (100 mL) was then added and the solution was concentrated to dryness, keeping the temperature below 25 °C. Further hexane (100 mL) was added and the solution was filtered through a small pad of cotton wool before being concentrated to dryness by reduced pressure, keeping the temperature below 25 °C, to yield the (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (520 mg, 82%) as a yellow liquid. At 0 °C, to (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (300 mg, 1.33 mmol) was added a mixture of hexanol (81.0 mg, 0.795 mmol) and *p*PTS (4.00 mg, 0.0159 mmol) dissolved in $CHCl_3$ (2 mL) over 15 min *via* a syringe pump. Further *p*PTS (2 mg, 0.008 mmol) dissolved in $CHCl_3$ (2 mL) was added before being concentrated to dryness to yield the title compound (294, >99%) as a yellow liquid.

ν_{max}/cm^{-1}; 2956, 2925, 1466 and 1376; ^1H NMR (500 MHz, $CDCl_3$); 5.74-5.63 (1H, m, CH), 5.59-4.49 (1H, m, CH), 3.97 (2H, dd, J 6.3, 1.0 Hz, CH_2), 3.55 (2H, q, J 7.2 Hz, CH_2), 3.47 (2H, t, J 6.9 Hz, CH_2), 2.07-1.99 (2H, m, CH_2), 1.57 (2H, p, J 7.0 Hz, CH_2), 1.47 (3H, s, CH_3), 1.39-1.34 (4H, m, CH_2), 1.33-1.25 (12H, m, CH_2), 1.21 (3H, t, CH_3),

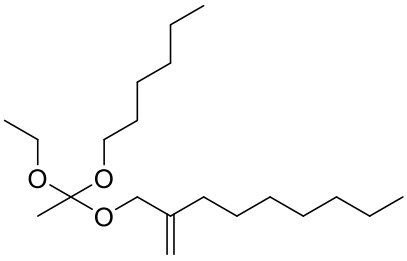
0.92-0.86 (6H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.1 (CH), 126.2 (CH), 114.4 (C), 62.9 (CH_2), 62.4 (CH_2), 57.8 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.31 (CH_2), 29.30 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 22.76 (CH_2), 20.4 (CH_3), 15.4 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 351.2908 ($M + Na^+$) $C_{20}H_{40}O_3Na^+$ requires 351.2870.

(*E*)-(1-(Dec-2-en-1-yloxy)-1-ethoxyethoxy)cyclohexane (295b)



Following general procedure J with dec-2-enol (167 mg, 1.07 mmol) and ((1-ethoxyvinyl)oxy)cyclohexane (200 mg, 1.17 mmol) at 30 °C. Purification by distillation (75 °C, 0 mbar) gave the title compound (326 mg, 93%) as a yellow liquid. ν_{max}/cm^{-1}; 2926, 2855, 1451 and 1377; ^1H NMR (500 MHz, $CDCl_3$); 5.73-5.64 (1H, m, CH), 5.58-5.49 (1H, m, CH), 3.99 (2H, qdd, J 12.4, 5.9, 1.2 Hz, CH_2), 3.72 (1H, tt, J 9.7, 4.0 Hz, CH), 2.60-3.52 (2H, m, CH_2), 2.06-1.99 (2H, m, CH_2), 1.89-183 (2H, m, CH_2), 1.76-1.69 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.39-1.33 (4H, m, CH_2), 1.33-1,22 (14H, m, CH_2), 1.19 (3H, t, J 7.2 Hz, CH_3), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 133.7 (CH), 126.4 (CH), 114.7 (C), 70.9 (CH) 63.0 (CH_2), 57.8 (CH_2), 34.31 (CH_2), 34.26 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 29.29 (CH_2),29.28 (CH_2), 29.26 (CH_2), 25.8 (CH_2), 24.81 (CH_2), 24.80 (CH_2), 22.77 (CH_2), 21.7 (CH_3), 15.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 349.2786 ($M + Na^+$) $C_{20}H_{40}O_3Na^+$ requires 349.2713.

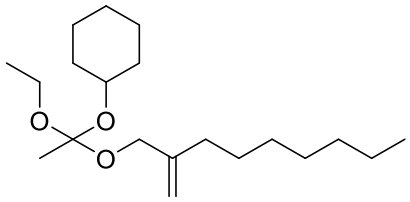
2-((1-Ethoxy-1-(hexyloxy)ethoxy)methyl)non-1-ene (296a)



Following general procedure J with 2-methylenenonanol (181 mg, 1.16 mmol) and 1-((1-ethoxyvinyl)oxy)hexane (240 mg, 1.39 mmol) at 30 °C, gave the title compound (385 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2927, 2857, 1652, 1459 and 1376; ^1H NMR (500 MHz, $CDCl_3$); 5.04 (1H, d, J 2.1 Hz, CH_2), 4.84 (1H, d, J 2.1

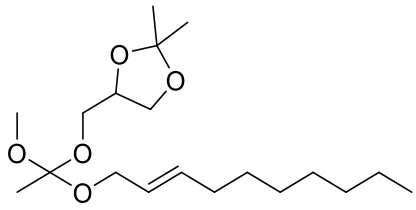
Hz, CH_2), 3.94 (2H, s, CH_2), 3.56 (2H, q, J 7.1 Hz, CH_2), 3.48 (2H, t, J 7.1 Hz, CH_2), 2.05 (2H, t, J 7.7 Hz, CH_2), 1.56 (2H, p , J 7.0 Hz, CH_2), 1.48 (3H, s, CH_3), 1.46-1.41 (2H, m, CH_2), 1.38-1.33 (2H,m, CH_2), 1.31-1.24 (14H, m, CH_2), 1.20 (3H, t, J 7.1 Hz, CH_3), 0.91-0.85 (6H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.5 (C), 114.4 (C), 110.1 (CH_2), 64.6 (CH_2), 57.7 (CH_2), 33.6 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 26.1 (CH_2), 22.78 (CH_2), 22.75 (CH_2), 20.4 (CH_3), 15.4 (CH_3), 14.2 (CH_3), 14.15 (CH_3); HRMS *m/z* (ESI^+) 351.2905 (M + Na^+) $C_{20}H_{40}O_3Na^+$ requires 351.2870.

(1-Ethoxy-1-((2-methylenenonyl)oxy)ethoxy)cyclohexane (296b)



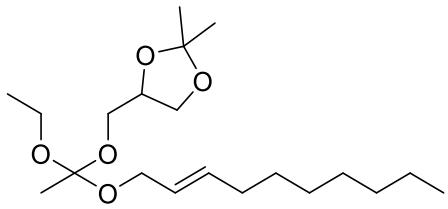
Following general procedure J with 2-methylenenonanol (169 mg, 1.08 mmol) and ((1-ethoxyvinyl)oxy)cyclohexane (240 mg, 1.41 mmol) at 30 °C, gave the title compound (350 mg, 95%) as a yellow liquid. ν_{max}/cm^{-1}; 2928, 2855, 1652, 1451 and 1377; ^1H NMR (500 MHz, $CDCl_3$); 5.04 (1H, d, J 2.1, CH_2), 4.84 (1H, d, J 2.1 Hz, CH_2), 4.02-3.88 (2H, m, CH_2), 3.74 (1H, tt, J 9.6, 3.9 Hz, CH), 3.61-3.54 (2H, m, CH_2), 2.05 (2H, t, J 7.4 Hz, CH_2), 1.89-1.83 (2H, m, CH_2), 1.76-1.70 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.48-1.42 (2H, m, CH_2), 1.39-1.34 (2H, m, CH_2), 1.34-1.24 (12H, m, CH_2), 1.18 (3H, t, J 7.2 Hz, CH_3), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.7 (C), 114.8 (C), 109.6 (CH_2), 71.1 (CH), 64.9 (CH_2), 57.8 (CH_2), 34.34 (CH_2), 34.32 (CH_2), 34.29 (CH_2), 33.6 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 25.8 (CH_2), 24.8 (CH_2), 22.8 (CH_2), 21.7 (CH_3), 15.4 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 349.2784 (M + Na^+) $C_{20}H_{40}O_3Na^+$ requires 349.2713.

(*E*)-4-((1-(Dec-2-en-1-yloxy)-1-methoxyethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (297a)



Following general procedure J with dec-2-enol (151 mg, 0.966 mmol) and 4-(((1-methoxyvinyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (200 mg, 1.06 mmol) at 60 °C, gave the title compound (339 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2926, 2856, 1458 and 1379; ^{1}H NMR (500 MHz, $CDCl_3$); 5.74-5.65 (1H, m, CH), 5.57-5.50 (1H, m, CH), 4.26 (1H, p, J 6.4 Hz, CH), 4.07 (1H, dd, J 8.4, 6.5 Hz, CH_2), 3.78 (2H, d, J 6.2 Hz, CH_2), 3.78 (1H, dd, J 8.4, 6.2 Hz, CH_2), 3.60 (1H, ddd, J 10.0, 5.7, 3.2 Hz, CH_2), 3.50 (1H, ddd, J 9.8, 6.2, 3.5 Hz, CH_2), 3.28 (3H, d, J 1.7 Hz, CH_3), 2.05-1.99 (2H, m, CH_2), 1.48 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.39-1.33 (2H, m, CH_2), 1.32-1.23 (8H, m, CH_2), 0.88 (3H, t, 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$); 134.4 (CH), 125.9 (CH), 114.7 (C), 109.5 (C), 74.68 (CH), 74.66 (CH), 67.25 (CH_2), 67.24 (CH_2), 63.5 (CH_2), 63.4 (CH_2), 63.3 (CH_2), 50.2 (CH_3), 50.1 (CH_3), 32.4 (CH_2), 32.0 (CH_2), 29.29 (CH_2), 29.27 (CH_2), 29.2 (CH_2), 26.9 (CH_3), 25.5 (CH_3), 22. 8 (CH_2), 19.83 (CH_3), 19.80 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 367.2476 ($M + Na^+$) $C_{19}H_{36}O_5Na^+$ requires 367.2455.

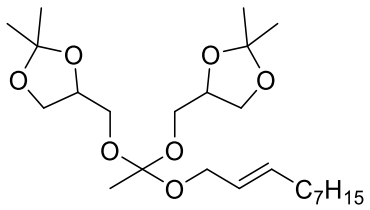
(*E*)-4-((1-(Dec-2-en-1-yloxy)-1-ethoxyethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (297b)



Following general procedure J with dec-2-enol (772 mg, 4.49 mmol) and 4-(((1-ethoxyvinyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (1.00 g, 4.94 mmol) at 60 °C, gave the title compound (1.75 g, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2926, 2856, 1457, 1379 and 1371; ^{1}H NMR (500 MHz, $CDCl_3$); 4.74 (1H, m, CH), 5.57-5.49 (1H,

m, CH), 4.26 (1H, p, J 6.2 Hz, CH), 4.07 (1H, dd, J 8.3, 6.2 Hz, CH_2), 3.99-3.95 (2H, m, CH_2), 3.78 (1H, ddd, J 7.7, 6.0, 1.6 Hz, CH_2), 3.61 (1H, ddd, J 9.0, 3.3, 0.9 Hz, CH_2), 3.58-3.53 (2H, m, CH_2), 3.49 (1H, dd, J 10.0, 6.4 Hz, CH_2), 2.06-1.99 (2H, m, CH_2), 1.48 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.31-1.23 (8H, m, CH_2), 1.20 (3H, td, J 7.1, 2.6 Hz, CH_3), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.3 (CH), 126.0 (CH), 114.5 (C), 109.4 (C), 74.69 (CH), 74.68 (CH), 67.3 (CH_2), 63.41 (CH_2), 63.39 (CH_2), 63.3 (CH_2), 63.2 (CH_2), 58.1 (CH_2), 58.0 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 29.29 (CH_2), 29.27 (CH_2), 29.2 (CH_2), 26.9 (CH_3), 25.54 (CH_3), 25.53 (CH_3), 22.8 (CH_2), 20.42 (CH_3), 20.41 (CH_3), 15.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 381.2635 ($M + Na^+$) $C_{20}H_{38}O_5Na^+$ requires 381.2611.

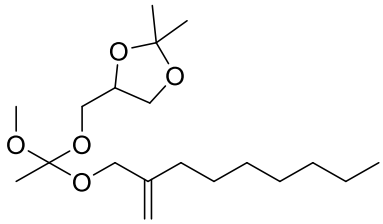
(*E*)-4,4'-(((1-(Dec-2-en-1-yloxy)ethane-1,1-diyl)bis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (297c)



Following general procedure J with dec-2-enol (96.0 mg, 0.624 mmol) and 4,4'-((ethene-1,1-diylbis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (180 mg, 0.624 mmol) in $CHCl_3$ (1.5 mL) at 60 °C for 3h, gave the title compound (275 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2987, 2926, 2856, 1458, 1380 and 1371; ^{1}H NMR (500 MHz, $CDCl_3$); 5.72-5.62 (1H, m , CH), 5.56-5.46 (1H, m, CH), 4.24 (2H, pd, J 6.0, 2.6 Hz, CH), 4.05 (2H, ddd, J 14.7, 8.2, 1.8 Hz, CH_2), 3.98 (2H, d, J 6.3 Hz, CH_2), 3.77 (2H, ddd, J 13.9, 6.1, 1.8 Hz, CH_2), 3.63-3.56 (2H, m, CH_2), 3.55-3.48 (2H, m, CH_2), 2.01 (2H, q, J 7.0 Hz, CH_2), 1.49 (3H, s, CH_3), 1.40 (6H, s, CH_3), 1.35 (6H, s, CH_3), 1.36-1.33 (2H, m, CH_2), 1.30-1.22 (8H, m, CH_2), 0.87 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.4 (CH), 125.7 (CH), 114.5 (C), 109.5 (C), 74.63 (CH), 74.60 (CH), 67.15 (CH_2), 67.14 (CH_2), 67.12 (CH_2), 63.7 (CH_2), 63.60 (CH_2), 63.57 (CH_2), 63.55 (CH_2), 63.42 (CH_2), 63.39 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 29.26 (CH_2), 29.25 (CH_2), 29.16 (CH_2), 26.88 (CH_3), 26.86 (CH_3), 25.52 (CH_3), 25.51 (CH_3), 22.7 (CH_2),

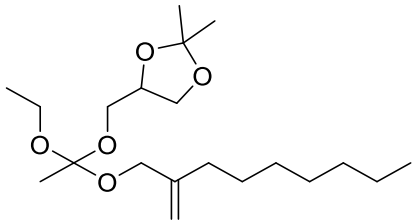
20.44 (CH_3), 20.41 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 467.3001 (M + Na^+) $C_{24}H_{44}O_7Na^+$ requires 467.2979.

4-((1-Methoxy-1-((2-methylenenonyl)oxy)ethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (298a)



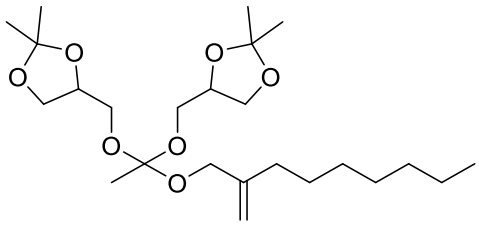
Following general procedure J with 2-methylenenonanol (151 mg, 0.966 mmol) and 4-(((1-methoxyvinyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (219 mg, 1.16 mmol) in $CHCl_3$ (1.6 mL) at 60 °C, gave the title compound (342 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2928, 2857, 1652, 1457 and 1379; ^1H NMR (500 MHz, $CDCl_3$); 5.04 (1H, d, J 2.1 Hz, CH_2), 4.85 (1H, d, J 2.1 Hz, CH_2), 4.26 (1H, pd, J 6.2, 1.8 Hz, CH), 4.07 (1H, dd, J 8.5, 6.5 Hz, CH_2), 3.95 (2H, s, CH_2), 3.78 (1H, ddd, J 8.2, 6.0, 1.8 Hz, CH_2), 3.61 (1H, ddd, J 9.9, 5.6, 2.1 Hz, CH_2), 3.52 (1H, ddd, J 9.6, 6.1, 3.4 Hz, CH_2), 3.30 (3H, d, J 1.3 Hz, CH_3), 2.06-2.02 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.46-1.42 (2H, m, CH_2), 1.42 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.34-1.22 (10H, m, CH_2), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.1 (C), 114.7 (C), 110.4 (CH_2), 109.5 (C), 74.71 (CH), 74.69 (CH), 67.19 (CH_2), 65.2 (CH_2), 65.1 (CH_2), 63.42 (CH_2), 63.39 (CH_2), 50.2 (CH_3), 50.1 (CH_3), 33.5 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.9 (CH_3), 25.57 (CH_3), 25.56 (CH_3), 22.8 (CH_2), 19.83 (CH_3), 19.81 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 367.2493 (M + Na^+) $C_{19}H_{36}O_5Na^+$ requires 367.2455.

4-((1-Ethoxy-1-((2-methylenenonyl)oxy)ethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (298b)



Following general procedure J with 2-methylenenonanol (772 mg, 4.93 mmol) and 4-(((1-methoxyvinyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (1.00 g, 4.93 mmol) at 60 °C for 2.5 h, gave the title compound (1.8 g, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2928, 2858, 1652, 1457 and 1379; ^{1}H NMR (500 MHz, $CDCl_3$); 5.03 (1H, d, J 2.1 Hz, CH_2), 4.84 (1H, d, J 2.1 Hz. CH_2), 4.26 (1H, p, J 6.2 Hz, CH), 4.07 (1H, ddd, J 8.1, 6.4, 1.4 Hz, CH_2), 3.95 (2H, s, CH_2), 3.78 (1H, ddd, J 10.0, 5.6, 1.0 Hz, CH_2), 3.61 (1H, dd, J 9.8, 5.6 Hz, CH_2), 3.59-3.55 (2H, m, CH_2), 3.51 (1H, ddd, J 10.0, 6.1, 1.4 Hz, CH_2), 2.04 (2H, t, J 8.7 Hz, CH_2), 1.49 (3H, s, CH_3), 1.47-1.42 (2H, m, CH_2), 1.41 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.32-1.24 (10H, m, CH_2), 1.20 (3H, td, J 7.0, 2.2 Hz, CH_3), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.2 (C), 114.5 (C), 110.3 (CH_2), 109.4 (CH), 74.7 (CH), 67.26 (CH_2), 67.25 (CH_2), 65.1 (CH_2), 64.9 (CH_2), 63.4 (CH_2), 63.38 (CH_2), 58.2 (CH_2), 58.0 (CH_2), 33.5 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.9 (CH_3), 25.55 (CH_3), 25.54 (CH_3), 22.8 (CH_2), 20.43 (CH_3), 20.42 (CH_3), 15.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 381.2622 ($M + Na^+$) $C_{20}H_{38}O_5Na^+$ requires 381.2611.

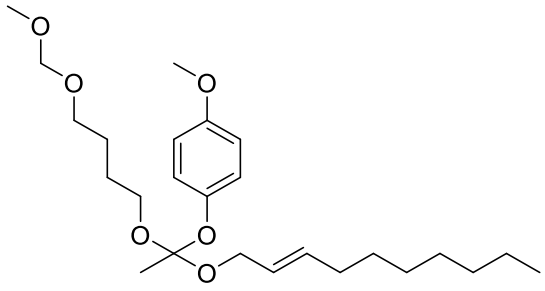
4,4'-(((1-((2-Methylenenonyl)oxy)ethane-1,1-diyl)bis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (298c)



Following general procedure J with 2-methylenenonan-1-ol (99.0 mg, 0.634 mmol) and 4,4'-((ethene-1,1-diylbis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane)

(200 mg, 0.694 mmol) at 60 °C for 2.5 h, gave the title compound (263 mg, 94%) as a yellow liquid. ν_{max}/cm^{-1}; 2986, 2928, 2857, 1457, 1371, 1379 and 1047; ^{1}H NMR (500 MHz, $CDCl_3$); 5.01 (1H, d, J 2.1 Hz, CH_2), 4.84 (1H, d, J 2.1 Hz, CH_2), 4.24 (2H, pd, J 6.0, 2.2 Hz, CH_2), 4.05 (2H, ddd, J 8.2, 6.1, 1.9 Hz, CH_2), 3.95 (2H, s, CH_2), 3.76 (2H, ddd J 8.5, 6.4, 1.9 Hz, CH_2), 3.64-3.58 (2H, m, CH_2), 3.56-3.50 (2H, m, CH_2), 2.02 (2H, q, J 7.5 Hz, CH_2), 1.50 (3H, s, CH_3), 1.46-1.41 (2H, m, CH_2), 1.40 (6H, s, CH_3), 1.35 (6H, s, CH_3), 1.31-1.22 (8H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.0 (C), 114.5 (C), 110.3 (CH_2), 109.4 (C), 74.65 (CH), 74.64 (CH), 74.62 (CH), 67.11 (CH_2), 67.10 (CH_2), 67.09 (CH_2), 65.4 (CH_2), 65.3 (CH_2), 65.2 (CH_2), 63.6 (CH_2), 63.5 (CH_2), 63.4 (CH_2), 33.5 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.9 (CH_3), 26.8 (CH_3), 25.52 (CH_3), 25.49 (CH_3), 22.8 (CH_2), 20.43 (CH_3), 20.41 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 467.2975 ($M + Na^+$) $C_{24}H_{44}O_7Na^+$ requires 467.2979.

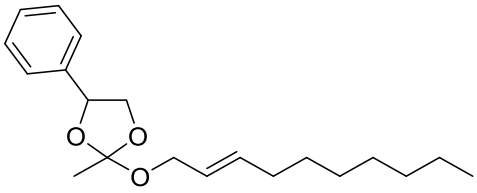
(*E*)-10-(4-Methoxyphenoxy)-10-methyl-2,4,9,11-tetraoxahenicos-13-ene (299)



Following general procedure J with decen-1-ol (251 mg, 1.61 mmol) and 1-methoxy-4-((1-(4-(methoxymethoxy)butoxy)vinyl)oxy)benzene (500 mg, 1.77 mmol) in $CHCl_3$ (2.5 mL) at 40 °C for 1.5 h, followed by 60 °C for 1.5 h. Further decen-2-ol (50.0 mg, 0.320 mmol) was added and heated to 60 °C for 3 h. Purification by distillation (96 °C, 0 mbar) gave the title compound (620 mg, 88%) as a yellow liquid. ν_{max}/cm^{-1}; 2925, 2856, 1506 and 1378; ^{1}H NMR (500 MHz, $CDCl_3$); 7.12 (2H, dd, J 8.9 Hz, CH), 6.81 (2H, dd, J 8.9 Hz, CH), 5.72-5.63 (1H, m, CH), 5.58-5.50 (1H, m, CH), 4.61 (2H, s, CH_2), 3.98 (2H, d, J 5.9 Hz, CH_2), 3.78 (3H, s, CH_3), 3.57-3.50 (4H, m, CH_2), 3.36-3.34 (3H, m, CH_3), .08-1.99 (2H, m, CH_2), 1.72-1.64 (4H, m, CH_2), 1.49 (3H, s, CH_3), 1.39-1.34 (2H, m, CH_2), 1.34-1.21 (8H, m, CH_2), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 155.8 (C), 147.5 (C), 134.2 (CH), 126.1

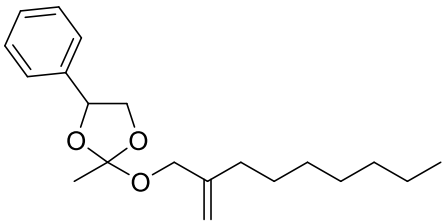
(CH), 122.1 (CH), 114.3 (CH), 114.5 (C), 144.4 (C), 96.5 (CH_2), 67.7 (CH_2), 67.6 (CH_2), 63.2 (CH_2), 62.3 (CH_2), 62.2 (CH_2), 55.7 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 29.29 (CH_2), 29.2 (CH_2), 26.7 (CH_2), 26.63 (CH_2), 26.61(CH_2), 26.4 (CH_2), 22.8 (CH_3), 21.7 (CH_3), 14.2 (CH_3).[a]

(*E*)-2-(Dec-2-en-1-yloxy)-2-methyl-4-phenyl-1,3-dioxolane (304a)



Following general procedure J with decen-1-ol (193 mg, 1.23 mmol) and 2-methylene-4-phenyl-1,3-dioxolane (220 mg, 1.36 mmol) at 60 °C, gave the title compound (410 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 3002, 2955, 2924, 2854, 2854, 1456 and 1387; ^1H NMR (500 MHz, $CDCl_3$); 7.40-7.31 (5H, m, CH), 5.79-5.70 (1H, m, CH), 5.64-5.55 (1H, m, CH), 5.26 (1H, t, J 7.3 Hz, CH), 4.47 (1H, dd, J 7.9, 6.9 Hz, CH_2), 4.15-4.047 (2H, m, CH_2), 3.79 (1H, t, J 7.6 Hz, CH_2), 2.09-2.00 (2H, m, CH_2), 1.74 (3H, s, CH_3), 1.42-1.35 (2H, m, CH_2) 1.34-1.23 (8H, m, CH_2), 0.90 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 139.3 (C), 134.5 (CH), 134.47 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 126.3 (CH), 126.2 (CH), 122.2 (C), 79.0 (CH), 78.1 (CH), 72.2 (CH_2), 71.7 (CH_2), 63.9 (CH_2), 63.6 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 29.33 (CH_2), 29.31 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 23.0 (CH_3), 22.6 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 341.2075 ($M + Na^+$) $C_{20}H_{30}O_3Na^+$ requires 341.2087.

2-Methyl-2-((2-methylenenonyl)oxy)-4-phenyl-1,3-dioxolane (304b)

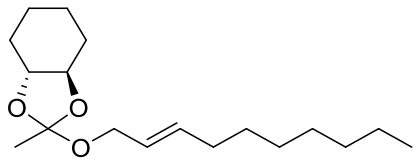


Following general procedure J with 2-methylenenonanol (289 mg, 1.85 mmol) and 2-methylene-4-phenyl-1,3-dioxolane (300 mg, 1.85 mmol) at 60 °C, gave the title

[a] Mass spectra analysis was run but the desired mass ion was not observed.

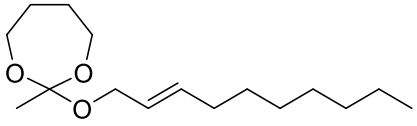
compound (618 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2929, 2856, 1652, 1456 and 1382; ^{1}H NMR (500 MHz, $CDCl_3$); 7.40-7.30 (5H, m, CH), 5.25 (1H, t, J 7.3 Hz, CH), 5.06 (1H, d, J 2.1 Hz, CH_2), 4.88 (1H, d, J 2.1 Hz, CH_2), 4.46 (1H, dd, J 7.8, 6.9 Hz, CH_2), 4.10-4.0 (2H, m, CH_2), 3.80 (1H, t, J 7.6 Hz, CH_2), 2.12-2.06 (2H, m, CH_2), 1.74 (3H, s, CH_3), 1.50-1.42 (2H, m, CH_2), 1.34-1.22 (8H, m, CH_2), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.4 (C), 139.2 (C), 128.8 (CH), 128.74 (CH), 128.72 (CH), 128.4 (CH), 126.6 (CH), 126.3 (CH), 122.4 (C), 79.1 (CH), 78.1 (CH), 72.1 (CH_2), 71.7 (CH_2), 66.1 (CH_2), 65.8 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 22.8 (CH_2), 22.8 (CH_3), 22.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 341.2035 ($M + Na^+$) $C_{20}H_{30}O_3Na^+$ requires 341.2087.

(3aR,7aR)-2-(((*E*)-Dec-2-en-1-yl)oxy)-2-methylhexahydrobenzo[d][1,3]dioxole (305)



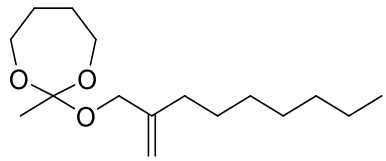
Following general procedure J with dec-2-enol (334 mg, 2.14 mmol) and (3aR,7aR)-2-methylenehexahydrobenzo[d][1,3]dioxole (300 mg, 2.14 mmol) at 60 °C, gave the title compound (633 mg, quant) as a yellow liquid. ν_{max}/cm^{-1}; 2999, 2925, 2857, 1458, 1379 and 1112; ^{1}H NMR (500 MHz, $CDCl_3$); 5.75-5.67 (1H, m, CH), 5.61-5.53 (1H, m, CH), 4.13 (1H, ddd, J 11.2, 6.2, 1.1 Hz, CH), 4.05 (1H, ddd, J 11.2, 6.2, 1.1 Hz, CH), 3.52 (1H, ddd, J 11.2, 9.2, 3.7 Hz, CH_2), 3.36 (1H, ddd, J 11.6, 9.2, 3.8 Hz, CH_2), 2.16-2.11 (2H, m, CH_2), 2.06-1399 (2H, m, CH_2), 1.86-1.79 (2H, m, CH_2), 1.59 (3H, s, CH_3), 1.46-1.35 (4H, m, CH_2), 1.33-1.25 (8H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (500 MHz, $CDCl_3$); 134.7 (CH), 126.2 (CH), 121.4 (C), 81.7 (CH), 81.1 (CH), 63.2 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 29.32 (CH_2), 29.30 (CH_2), 29.21 (CH_2), 29.20 (CH_2), 28.6 (CH_2), 24.6 (CH_3), 23.8 (CH_2), 23.8 (CH_2), 22.8 (CH_2), 14.3 (CH_3); HRMS *m/z* (ESI^+) ($M + Na^+$) 319.2221 $C_{18}H_{40}O_3Na^+$ requires 319.2244.

(*E*)-2-(Dec-2-en-1-yloxy)-2-methyl-1,3-dioxepane (306a)



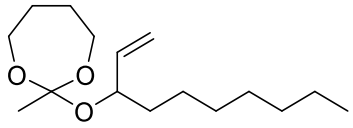
Following general procedure J with dec-2-enol (497 mg, 3.18 mmol) and 2-methylene-1,3-dioxepane (400 mg, 3.50 mmol) at 60 °C, gave the title compound (860 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2924, 2855, 1464 and 1380; ^{1}H NMR (500 MHz, $CDCl_3$); 5.74-5.64 (1H, m, CH), 5.59-5.52 (1H, m, CH), 3.97 (2H, dd, J 6.1, 1.2 Hz, CH_2), 3.94-3.88 (2H, m, CH_2), 3.62-3.54 (2H, m, CH_2), 2.02 (2H, q, J 6.9 Hz, CH_2), 1.70-1.59 (4H, m, CH_2), 1.45 (3H, s, CH_3), 1.40-1.33 (2H, m, CH_2), 1.31-1.23 (8H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 133.7 (CH), 126.3 (CH), 115.7 (C), 64.1 (CH_2), 62.7 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 29.23 (CH_2), 29.20 (CH_2), 22.8 (CH_2), 21.1 (CH_3), 14.3 (CH_3); HRMS *m/z* (ESI^+) 293.2094 ($M + Na^+$) $C_{16}H_{30}O_3Na^+$ requires 239.2087.

2-Methyl-2-((2-methylenedecyl)oxy)-1,3-dioxepane (306b)



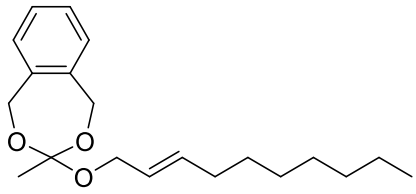
Following general procedure J with 2-methylenenonanol (374 mg, 2.39 mmol) and 2-methylene-1,3-dioxepane (327 mg, 2.87 mmol) at 60 °C for 3 h, gave the title compound (671 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2997, 2924, 2854, 1464, 1380 and 1154; ^{1}H NMR (500 MHz, $CDCl_3$); 5.05 (1H, d, J 2.1 Hz, CH_2), 4.85 (1H, d, J 2.1 Hz, CH_2), 3.94 (2H, s, CH_2), 3.93-3.89 (2H, m, CH_2), 3.62-3.57 (2H, m, CH_2), 2.08 (2H, t, J 7.5 Hz, CH_2), 1.69-1.63 (4H, m, CH_2), 1.45 (3H, s, CH_3), 1.47-1.42 (2H, m, CH_2), 1.30-1.24 (10H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.6 (C), 115.8 (C), 110.7 (CH_2), 66.1 (CH_2), 62.9 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 29.50 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.74 (CH_2), 22.73 (CH_2), 21.1 (CH_3), 14.3 (CH_3); HRMS *m/z* (ESI^+) 307.2250 ($M + Na^+$) $C_{17}H_{32}O_3Na^+$ requires 307.224.

2-(Dec-1-en-3-yloxy)-2-methyl-1,3-dioxepane (306c)



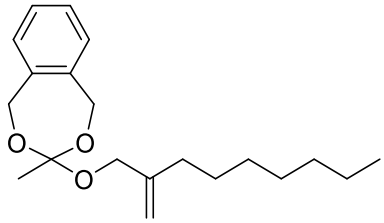
Following general procedure J with decen-3-ol (374 mg, 2.39 mmol) and 2-methylene-1,3-dioxepane (300 mg, 2.63 mmol) at 60 °C for 6 h. Purification by distillation (70 – 90 °C, 0 mbar) gave the title compound (556 mg, 86%) as a yellow liquid. ν_{max}/cm^{-1}; 2925, 2855, 1464 and 1380; ^{1}H NMR (500 MHz, $CDCl_3$); 5.79 (1H, ddd, J 17.7, 10.3, 7.1 Hz, CH), 5.14-4.99 (2H, m, CH_2), 4.08 (1, q, J 7.1 Hz, CH), 3.93-3.82 (2H, m, CH_2), 3.57-3.46 (2H, m, CH_2), 1.68-1.55 (6H, m, CH_2) 1.41 (3H, s, CH_3), 1.32-1.19 (10H, m, CH_2), 0.85 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 140.8 (CH), 115.9 (C), 114.5 (CH_2), 74.7 (CH), 63.1 (CH_2), 62.9 (CH_2), 36.5 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.33 (CH_2), 29.28 (CH_2), 29.1 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 22.2 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 293.2119 ($M + Na^+$) $C_{16}H_{30}O_3Na^+$ requires 293.2087.

(*E*)-3-(Dec-2-en-1-yloxy)-3-methyl-1,5-dihydrobenzo[e][1,3]dioxepine (307a)



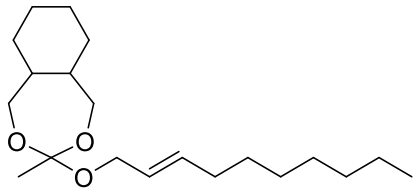
Following general procedure J with dec-2-enol (209 mg, 1.34 mmol) and 3-methylene-1,5-dihydrobenzo[e][1,3]dioxepine (238 mg, 1.47 mmol) at 60 °C, gave the title compound (430 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2924, 2855, 1450 and 1381; ^{1}H NMR (500 MHz, $CDCl_3$); 7.19 (2H, dd, J 5.5, 3.3 Hz, CH), 7.09 (2H, dd, J 5.5, 3.3 Hz, CH), 5.81-5.72 (1H, m, CH), 5.66-5.58 (1H, m, CH), 5.15 (2H, d, J 14.6 Hz, CH_2), 4.68 (2H, d, J 14.6 Hz, CH_2), 4.10 (2H, dd, J 6.1, 1.2 Hz, CH_2), 2.05 (2H, q, J 6.9 Hz, CH_2), 1.62 (3H, s, CH_3), 1.42-1.37 (2H, m, CH_2), 1.34-1.23 (8H, m, CH_2), 0.89 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 137.8 (C), 134.3 (CH), 127.0 (CH), 126.4 (CH), 125.9 (CH), 116.1 (C), 64.9 (CH_2), 65.6 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 29.28 (CH_2), 29.27 (CH_2), 29.17 (CH_2), 22.8 (CH_2), 20.0 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 341.2109 ($M + Na^+$) $C_{20}H_{30}O_3Na^+$ requires 341.2087.

3-Methyl-3-((2-methylenenonyl)oxy)-1,5-dihydrobenzo[e][1,3]dioxepine (307b)



Following general procedure J with 2-methylenenonanol (289 mg, 1.85 mmol) and 3-methylene-1,5-dihydrobenzo[e][1,3]dioxepine (330 mg, 2.04 mmol) at 60 °C for 3 h, gave the title compound (616 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2926, 2856, 1652, 1450 and 1381; ^{1}H NMR (500 MHz, $CDCl_3$); 7.20 (2H, dd, J 5.5, 3.2 Hz, CH), 7.10 (2H, dd, J 5.5, 3.2 Hz, CH), 5.16 (2H, d, J 14.8 Hz, CH_2), 5.13 (1H, d, J 2.1 Hz, CH_2), 4.91 (1H, d, J 2.1 Hz, CH_2), 4.69 (2H, d, J 14.8 Hz, CH_2), 4.08 (2H, s, CH_2), 2.12 (2H, t, J 7.6 Hz, CH_2), 1.63 (3H, s, CH_3), 1.53-1.45 (2H, m, CH_2), 1.37-1.25 (8H, m, CH_2), 0.90 (3H, t, J 6.6 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 146.0 (C), 137.7 (C), 127.0 (CH), 126.4 (CH), 116.2 (C), 110.7 (CH_2), 66.5 (CH_2), 64.9 (CH_2), 33.4 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 22.8 (CH_2), 18.9 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 341.2109 ($M + Na^+$) $C_{20}H_{30}O_3Na^+$ requires 341.2087.

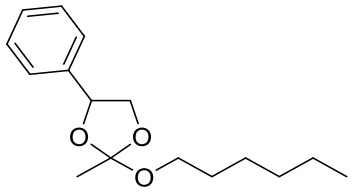
(*E*)-3-(Dec-2-en-1-yloxy)-3-methyloctahydrobenzo[e][1,3]dioxepine (308)



Following general procedure J with dec-2-enol (253 mg, 1.62 mmol) and 3-methyleneoctahydrobenzo[e][1,3]dioxepine (300 mg, 1.78 mmol) at 60 °C for 26 h, gave the title compound (581 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2922, 2854, 1459 and 1377; ^{1}H NMR (500 MHz, $CDCl_3$); 5.73-5.63 (1H, m, CH), 5.60-5.50 (1H, m, CH), 4.00-3.92 (2H, m, CH_2), 3.85 (1H, t, J 11.4 Hz, CH_2), 3.51-3.40 (2H, m, CH_2), 3.28 (1H, dd, J 11.9, 3.2 Hz, CH_2), 2.02 (2H, q, J 6.4 Hz, CH_2), 1.80-1.74 (2H, m, CH_2), 1.56-1.51 (2H, m, CH_2), 1.43 (3H, s, CH_3), 1.39-1.31 (4H, m CH_2/CH), 1.30-1.20 (12H, m, CH_2), 0.88 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 133.9 (CH), 126.3 (CH), 115.4 (C), 68.7 (CH_2), 66.4 (CH_2), 64.2 (CH_2), 46.2 (CH), 45.4 (CH), 32.4

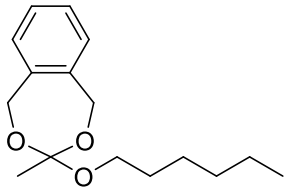
(CH_2), 31.9 (CH_2), 29.29 (CH_2), 29.28 (CH_2), 29.18 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 22.8 (CH_2), 21.1 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 347.2637 (M + Na^+) $C_{20}H_{36}O_3Na^+$ requires 347.2557.

2-(Hexyloxy)-2-methyl-4-phenyl-1,3-dioxolane (309)



Following general procedure J with hexanol (186 mg, 1.82 mmol) and 2-methylene-4-phenyl-1,3-dioxolane (300 mg, 1.91 mmol) at 60 °C for 4.5 h, gave the title compound (490 mg, >99%) as a yellow liquid. ν_{max}/cm^{-1}; 2925, 2855, 1451 and 1377; ^1H NMR (500 MHz, $CDCl_3$); 7.41-7.32 (5H, m, CH), 5.25 (1H, t, J 7.1 Hz, CH), 4.46 (1H, dd, J 7.9, 7.1 Hz, CH_2), 3.79 (1H, t, J 7.7 Hz, CH_2), 3.63-3.57 (2H, m, CH_2), 1.73 (3H, s, CH_3), 1.65-1.58 (2H, m, CH_2), 1.43-1.39 (2H, m, CH_2), 1.33-1.30 (4H, m, CH_2), 0.92 (3H, t, 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 139.3 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.35 (CH), 126.7 (CH), 126.3 (CH), 122.2 (C), 79.0 (CH), 78.05 (CH), 72.1 (CH_2), 72.7 (CH_2), 62.9 (CH_2), 62.7 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 26.0 (CH_2), 22.8 (CH_2), 22.7 (CH_3), 22.2 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 287.1682 (M + Na^+) $C_{16}H_{24}O_3Na^+$ requires 287.3542.

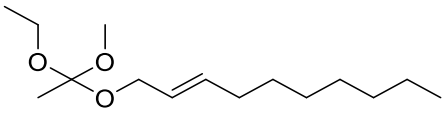
3-(Hexyloxy)-3-methyl-1,5-dihydrobenzo[e][1,3]dioxepine (310)



To 3-methylene-1,5-dihydrobenzo[e][1,3]dioxepine (300 mg, 1.85 mmol) was added a mixture of hexanol (172 mg, 1.68 mmol) and pPTS (4.00 mg, 0.0168 mmol) dissolved in $CHCl_3$ (3.3 mL), *via* syringe pump, over 15 min. The solution was then stirred at 25 °C for 15 min before being concentrated to dryness by reduced pressure to yield the title compound (503 mg, >99%) as a colourless liquid. ν_{max}/cm^{-1}; 3003, 2930, 2871, 1450 and 1380; ^1H NMR (500 MHz, $CDCl_3$); 7.19 (2H, dd, J 5.6,

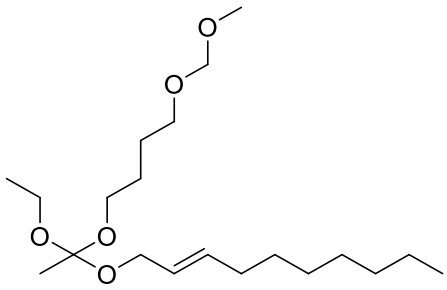
3.3 Hz, CH), 7.09 (2H, dd, J 5.6, 3.3 Hz, CH), 5.12 (2H, d, J 14.4 Hz, CH_2), 4.69 (2H, d, J 14.4 Hz, CH_2), 3.59 (2H, t, J 6.5 Hz, CH_2), 1.69-1.62 (2H, m, CH_2), 1.61 (3H, s, CH_3), 1.47-1.39 (2H, m, CH_2), 1.36-1.30 (4H, m, CH_2), 0.91 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 137.8 (C), 127.0 (CH), 126.6 (CH), 116.1 (C), 64.8 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 19.6 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 287.1662 ($M + Na^+$) $C_{16}H_{24}O_3Na^+$ requires 287.1618.

(*E*)-1-(1-Ethoxy-1-methoxyethoxy)dec-2-ene (295c)



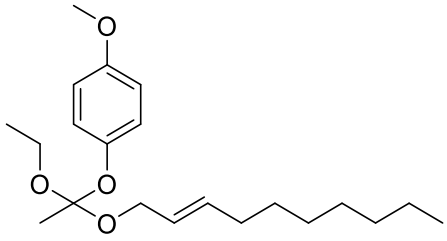
To a stirring solution of KO^tBu (697 mg, 6.21 mmol) in THF (3.5 mL) was added (*E*)-1-(1-ethoxy-2-iodoethoxy)dec-2-ene (1.00 g, 2.82 mmol) in THF (700 µL) dropwise over 30 min. The solution was then stirred at stirred at 25 °C for 1 h. Hexane (100 mL) was then added and the solution was concentrated to dryness, keeping the temperature below 25 °C. Further hexane (100 mL) was added and the solution was filtered through a small pad of cotton wool before being concentrated to dryness, keeping the temperature below 25 °C, to yield the (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (520 mg, 82%) as a yellow liquid. To (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (300 mg, 1.34 mmol) was added methanol (27.0 µL, 0.655 mmol) and stirred at 25 °C for 5 h. Further methanol (27.0 µL, 0.655 mmol) was added and stirred at 25 °C for 16 h before being concentrated to dryness (96 °C, 0 mbar) to yield the title compound (115 mg, 67%) as a yellow liquid. ν_{max}/cm^{-1}; 2924, 2854, 1459 and 1377; ^1H NMR (500 MHz, $CDCl_3$); 5.75-5.66 (1H, m, CH), 5.60-5.52 (1H, m, CH), 3.97 (2H, dd, J 6.2, 1.1 Hz, CH_2), 3.56 (2H, q, J 6.8 Hz, CH_2), 3.28 (3H, s, CH_3), 2.03 (2H, q, J 7.2 Hz, CH_2), 1.47 (3H, s, CH_3), 1.40-1.34 (2H, m, CH_2), 1.33-1.24 (8H, m, CH_2), 1.23 (3H, t, J 7.1 Hz, CH_3), 0.88 (3H, t, J 6.6 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 134.2 (CH), 126.1 (CH), 114.6 (C), 63.0 (CH_2), 57.8 (CH_2), 49.9 (CH_3), 32.5 (CH_2), 32.0 (CH_2), 29.31 (CH_2), 29.30 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 19.8 (CH_3), 15.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 281.2176 ($M + Na^+$) $C_{15}H_{30}O_3Na^+$ requires 281.2087.

(*E*)-10-Ethoxy-10-methyl-2,4,9,11-tetraoxahenicos-13-ene (295d)



To a stirring solution of KO^{t}Bu (697 mg, 6.21 mmol) in THF (3.5 mL) was added (*E*)-1-(1-ethoxy-2-iodoethoxy)dec-2-ene (1.00 g, 2.82 mmol) in THF (700 µL) dropwise over 30 min. The solution was then stirred at stirred at 25 °C for 1 h. Hexane (100 mL) was then added and the solution was concentrated to dryness by reduced pressure, keeping the temperature below 25 °C. Further hexane (100 mL) was added and the solution was filtered through a small pad of cotton wool before being concentrated to dryness, keeping the temperature below 25 °C, to yield the (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (520 mg, 82%) as a yellow liquid. To (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (300 mg, 1.34 mmol) was added 4-(methoxymethoxy)butan-1-ol (80.0 mg, 0.655 mmol) and stirred at 25 °C for 28 h before being concentrated to dryness (96 °C, 0 mbar) to yield the title compound (120 mg, 52%) as an orange liquid. ν_{max}/cm^{-1}; 2924, 2855, 1651, 1465 and 1376; ^{1}H NMR (500 MHz, $CDCl_3$); 5.73-5.65 (1H, m, CH), 5.59-5.51 (1H, m, CH), 4.62 (2H, s, CH_2), 3.97 (2H, dd, J 6.1, 1.2 Hz, CH_2), 3.55 (4H, q, J 7.1 Hz, CH_2), 3.54-3.50 (2H, m, CH_2), 3.36 (3H, s, CH_3), 2.03 (2H, q, J 7.0 Hz, CH_2), 1.72-164 (4H, m, CH_2), 1.47 (3H, s, CH_3), 1.39-1.34 (2H, m, CH_2), 1.33-1.23 (8H, m, CH_2), 1.20 (3H, t, J 7.1 Hz, CH_3), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.2 (CH), 126.2 (CH), 114.4 (C), 96.5 (CH_2), 67.7 (CH_2), 63.0 (CH_2), 57.8 (CH_2), 55.2 (CH_3), 32.5 (CH_2), 31.9 (CH_2), 29.31 (CH_2), 29.29 (CH_2), 29.21 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 22.8 (CH_2), 20.4 (CH_3), 15.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI$^+$) 383.2894 (M + Na$^+$) $C_{20}H_{40}O_5Na^+$ requires 383.2768.

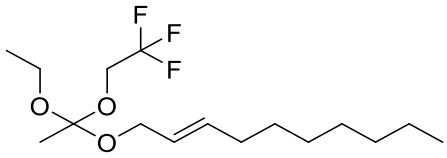
(*E*)-1-(1-(Dec-2-en-1-yloxy)-1-ethoxyethoxy)-4-methoxybenzene (295e)



To a stirring solution of KO^{t}Bu (697 mg, 6.21 mmol) in THF (3.5 mL) was added (*E*)-1-(1-ethoxy-2-iodoethoxy)dec-2-ene (1.00 g, 2.82 mmol) in THF (700 µL) dropwise over 30 min. The solution was then stirred at stirred at 25 °C for 1 h. Hexane (100 mL) was then added and the solution was concentrated to dryness, keeping the temperature below 25 °C. Further hexane (100 mL) was added and the solution was filtered through a small pad of cotton wool before being concentrated to dryness by reduced pressure, keeping the temperature below 25 °C, to yield the (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (520 mg, 82%) as a yellow liquid. To (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (306 mg, 1.35 mmol) was added 4-methoxyphenol (99.0 mg, 0.795 mmol) dissolved in $CHCl_3$ (2 mL) over 15 min *via* a syringe pump, at 0 °C. The reaction mixture was then stirred at 0 °C for 15 min before being concentrated to dryness by reduced pressure to yield the title compound (300 mg, >99%) as an orange liquid. ν_{max}/cm^{-1}; 2955, 2925, 2855, 1505, 1465 and 1378; ^{1}H NMR (500 MHz, $CDCl_3$); 7.08 (2H, dd, J 6.9, 2.5 Hz, CH), 6.81 (2H, dd, J 6.9, 2.5 Hz, CH), 5.79-5.70 (1H, m, CH), 5.63-5.56 (1H, m, CH), 4.17 (2H, ddd, J 6.0, 2.9, 1.2 Hz, CH_2), 3.78 (3H, s, CH_3), 3.75-3.69 (2H, m, CH_2), 2.06 (2H, q, J 6.7 Hz, CH_2), 1.49 (3H, s, CH_3), 1.41-1.36 (2H, m, CH_2), 1.34-1.24 (11H, m, CH_2/CH_3), 0.89 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 155.5 (C), 147.9 (C), 134.6 (CH), 125.8 (CH), 121.8 (CH), 115.9 (C), 114.2 (CH), 63.3 (CH_2), 58.1 (CH_2), 55.6 (CH_3), 32.5 (CH_2), 32.0 (CH_2), 29.31 (CH_2), 29.30 (CH_2), 29.21 (CH_2), 22.8 (CH_2), 21.0 (CH_3), 15.2 (CH_3), 14.2 (CH_3).[a]

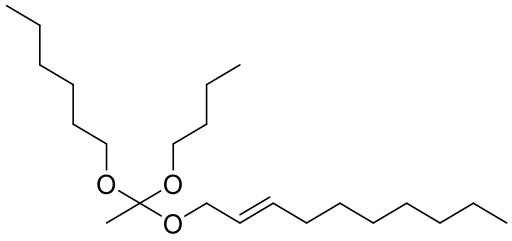
[a] Mass spectra analysis was run but the desired mass ion was not observed.

(*E*)-1-(1-Ethoxy-1-(2,2,2-trifluoroethoxy)ethoxy)dec-2-ene (295f)



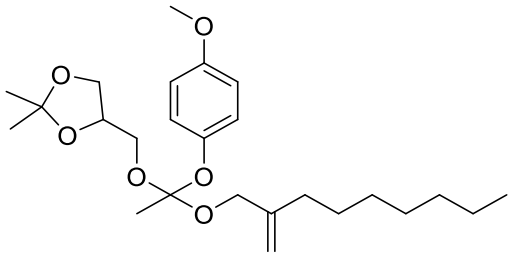
To a stirring solution of KO^{t}Bu (697 mg, 6.21 mmol) in THF (3.5 mL) was added (*E*)-1-(1-ethoxy-2-iodoethoxy)dec-2-ene (1.00 g, 2.82 mmol) in THF (700 µL) dropwise over 30 min. The solution was then stirred at stirred at 25 °C for 1 h. Hexane (100 mL) was then added and the solution was concentrated to dryness, keeping the temperature below 25 °C. Further hexane (100 mL) was added and the solution was filtered through a small pad of cotton wool before being concentrated to dryness by reduced pressure, keeping the temperature below 25 °C, to yield the (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (520 mg, 82%) as a yellow liquid. To (*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (220 mg, 0.972 mmol) was added trifluoroethanol (57.0 mg, 0.570 mmol) dissolved in $CHCl_3$ (1.5 mL) over 15 min *via* a syringe pump, at 0 °C. The reaction mixture was then stirred at 0 °C for 15 min before being concentrated to dryness by reduced pressure to yield the title compound (235 mg, >99%) as an orange liquid. ν_{max}/cm^{-1}; 2927, 2857, 1656, 1460 and 1380; ^{1}H NMR (500 MHz, $CDCl_3$); 5.74-5.65 (1H, m, CH), 5.59-5.48 (1H, m, CH), 4.01 (2H, ddd, J 6.2, 4.9, 1.1 Hz, CH_2), 3.90 (2H, q, J 8.9 Hz, CH_2), 3.63-3.55 (2H, m, CH_2), 2.04 (2H, q, J 7.1 Hz, CH_2), 1.53 (3H, s, CH_3), 1.40-1.35 (2H, m, CH_2), 1.32-1.25 (8H, m, CH_2), 0.89 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.7 (CH), 125.5 (CH), 114.8 (C), 64.0 (CH_2), 60.3 (CH_2), 60.0 (CH_2), 59.7 (CH_2), 59.4 (CH_2), 58.7 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.29 (CH_2), 29.28 (CH_2), 29.17 (CH_2), 22.7 (CH_2), 20.3 (CH_3), 15.2 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI$^+$) 349.2743 (M + Na$^+$) $C_{16}H_{29}F_3O_3Na^+$ requires 349.1961.

(*E*)-1-(1-Butoxy-1-(hexyloxy)ethoxy)dec-2-ene (295g)



To a solution of KO^tBu (647 mg, 5.76 mmol) in THF (3.0 mL) was added (*E*)-1-(1-butoxy-2-iodoethoxy)dec-2-ene (1.00 g, 2.62 mmol) dissolved in THF (1.4 mL) dropwise over 25 min. The solution was then stirred at 25 °C for 1 h. Hexane (100 mL) was added and the reaction mixture was concentrated to dryness. Further hexane (150 mL) was added, the solution was filtered through a small cotton wool plug and concentrated to dryness by reduced pressure to yield (*E*)-1-((1-butoxyvinyl)oxy)dec-2-ene (580 mg, 87%) as yellow liquid. To (*E*)-1-((1-butoxyvinyl)oxy)dec-2-ene (250 mg, 0.982 mmol) was added hexanol (50.0 mg, 0.489 mmol). The reaction mixture was then stirred at 25 °C for 60 h before being concentrated to dryness (96 - 110 °C, 0 mbar) to yield the title compound (98 mg, 56%) as a dark yellow liquid. ν_{max}/cm^{-1}; 2956, 2925, 2856, 1465 and 1377; ^1H NMR (500 MHz, $CDCl_3$); 5.74-5.64 (1H, m, CH), 5.60-5.51 (1H, m, CH), 3.97 (2H, dd, J 6.2, 1.1 Hz, CH_2), 3.51-3.45 (4H, m, CH_2), 2.03 (2H, q, J 7.2 Hz, CH_2), 1.59-1.53 (4H, m, CH_2), 1.47 (3H, s, CH_3), 1.41-1.35 (6H, m, CH_2), 1.33-1.21 (12H, m, CH_2), 0.93 (3H, t, J 7.5 Hz, CH_3), 0.91-0.87 (6H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 134.0 (CH), 126.3 (CH), 114.4 (C), 62.9 (CH_2), 62.4 (CH_2), 62.1 (CH_2), 32.5 (CH_2), 32.0 (CH_2), 31.97 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.32 (CH_2), 29.31 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.8 (CH_2), 22.77 (CH_2), 20.44 (CH_3), 19.6 (CH_2), 14.23 (CH_3), 14.20 (CH_3), 14.1 (CH_3); HRMS *m/z* (ESI^+) 379.3259 ($M + Na^+$) $C_{22}H_{44}O_3Na^+$ requires 379.3183.

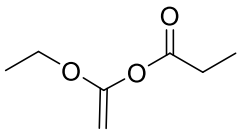
4-((1-(4-Methoxyphenoxy)-1-((2-methylenenonyl)oxy)ethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (313)



To a solution of KO^{t}Bu (561 mg, 5.00 mmol) in THF (3.0 mL) was added 4-((2-iodo-1-((2-methylenenonyl)oxy)ethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (1.00 g, 2.35 mmol) dissolved in THF (1.0 mL) dropwise over 50 min. The solution was then stirred at 25 °C for 1.25 h. Hexane (100 mL) was added and the reaction mixture was concentrated to dryness. Further hexane (150 mL) was added, the solution was filtered through a small cotton wool plug and concentrated to dryness by reduced pressure to yield 2,2-dimethyl-4-(((1-((2-methylenenonyl)oxy)vinyl)oxy)methyl)-1,3-dioxolane (800 mg, >99%) as yellow liquid. To 2,2-dimethyl-4-(((1-((2-methylenenonyl)oxy)vinyl)oxy)methyl)-1,3-dioxolane (250 mg, 0.800 mmol) was added 4-methoxyphenol (58.0 mg, 0.467 mmol) dissolved in $CHCl_3$ (1.2 mL) over 15 min *via* a syringe pump, at 0 °C. The reaction mixture was then stirred at 0 °C for 15 min. Hexane (20 mL) was then added and the solution was washed with 5% NaOH (4 x 20 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (220 mg, >99%) as a brown liquid. ν_{max}/cm^{-1}; 2956, 2926, 1652, 1506, 1464 and 1380; ^{1}H NMR (500 MHz, $CDCl_3$); 7.12-7.03 (2H, m, CH), 6.82-6.75 (2H, m, CH), 5.08 (1H, d, J 1.7 Hz, CH_2), 4.89 (1H, d, J 1.7 Hz, CH_2), 4.33 (1H, tt, J 6.1, 3.4 Hz, CH), 4.19-4.11 (2H, m, CH_2), 4.11-4.07 (1H, m, CH_2), 3.83-3.70 (3H, m, CH_2), 3.78 (3H, s, CH_3), 2.07 (2H, t, J 7.3 Hz, CH_2), 1.50 (3H, d, J 4.0 Hz, CH_3), 1.48-1.45 (2H, m, CH_2), 1.44 (3H, d, J 3.7 Hz, CH_3), 1.38 (3H, s, CH_3), 1.34-1.21 (8H, m, CH_2), 0.89 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 155.7 (C), 147.7 (C), 145.9 (C), 122.1 (CH), 116.1 (C), 114.2 (CH), 110.5 (CH_2), 109.5 (C), 74.7 (CH), 74.6 (CH), 67.2 (CH_2), 67.1 (CH_2), 65.4 (CH_2), 65.38 (CH_2), 63.7 (CH_2), 63.4 (CH_2), 55.7 (CH_3), 33.6 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.9 (CH_3), 26.9 (CH_3), 25.60 (CH_3), 25.56 (CH_3), 22.8

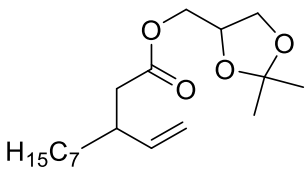
(CH_2), 21.0 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 459.2728 ($M + Na^+$) $C_{21}H_{34}O_3Na^+$ requires 436.2825.

1-Ethoxyvinyl propionate (318)



To a solution of propionic acid (493 µL, 6.66 mmol), THF (14 mL) and [$RuCl_2$(*p*-cymene)$_2$] (20.0 mg, 0.0327 mmol) was added ethoxyacetylene (2.00 mL, 8.34 mmol), at 0 °C. The solution was then heated to 40 °C for 15 min. The reaction mixture was then distilled (50-55 °C) to yield the title compound (136 mg, 18%) as yellow liquid. ν_{max}/cm^{-1}; 2985, 2955, 2888, 1772 and 1672; ^1H NMR (500 MHz, $CDCl_3$); 3.87 (2H, q, J 7.0 Hz, CH_2) 3.82 (1H, d, J 3.7 Hz, CH_2), 3.76 (1H, d, J 3.7 Hz, CH_2), 2.46 (2H, q, J 7.6 Hz, CH_2), 1.34 (3H, t, J 6.8 Hz, CH_3), 1.19 (3H, t, J 7.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 171.8 (C), 157.4 (C), 71.7 (CH_2), 64.8 (CH_2), 27.3 (CH_2), 14.2 (CH_3), 8.81 (CH_3). The data was consistent with the literature.[274]

(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 3-vinyldecanoate (331a)



***Via* the original Orthoester Johnson-Claisen:**

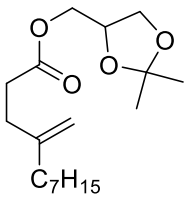
To dec-2-enol (1.00 g, 6.39 mmol), xylene (45 mL) and solketal orthoester (**354**) (4.00 g, 12.8 mmol) was added propionic acid (144 µL, 1.93 mmol). The solution was heated to 138 °C for 24 h. EtOAc (100 mL) was then added and the solution was washed 0.5 HCl (6 x 100 mL), sat. aq. $NaHCO_3$ (100 mL), brine (100 mL), dried $MgSO_4$ and concentrated to dryness (150 - 170 °C, 0 mbar). The crude ester was then purified by column chromatography (10% EtOAc:Hexane, R_f = 0.3) to yield the title compound (163 mg, 9%) as a yellow liquid.

***Via* the direct Orthoester Johnson-Claisen:**

(*E*)-4,4'-(((1-(dec-2-en-1-yloxy)ethane-1,1-diyl)bis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (100 mg, 0.225 mmol) and xylene (1 mL) was heated to 138 °C for 80h. DCM (50 mL) was then added and the reaction mixture was washed water (6 x 50 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (42 mg, 62%) as a yellow liquid.

ν_{max}/cm^{-1}; 2926, 2856, 1739 and 1641; ^1H NMR (500 MHz, $CDCl_3$); 5.68-5.55 (1H, m, CH), 5.05-4.97 (2H, m, CH_2), 4.29 (1H, p, J 5.9 Hz, CH), 4.14 (1H, ddd, J 11.4, 4.6, 1.1 Hz, CH_2), 4.11-4.05 (2H, m, CH_2), 3.73 (1H, dd, J 8.4, 6.2 Hz, CH_2), 2.52 (1H, dq, J 8.1, 2.6 Hz, CH_2), 2.41 (1H, dd, J 14.8, 6.0 Hz, CH_2), 2.32 (1H, ddd, J 14.8, 8.7, 1.1 Hz, CH_2), 1.44 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.33-1.18 (12H, m, CH_2), 0.88 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 172.5 (C), 141.2 (CH), 115.2 (CH_2), 109.9 (C), 73.7 (CH), 66.6 (CH_2), 66.6 (CH_2), 64.73 (CH_2), 64.65 (CH_2), 40.63 (CH), 40.61 (CH), 40.09 (CH_2), 40.07 (CH_2), 34.6 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.08 (CH_2), 27.07 (CH_2), 26.8 (CH_3), 25.53 (CH_3), 25.52 (CH_3), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* 335.2245 ($M + Na^+$) $C_{18}H_{32}O_5Na^+$ requires 335.2193.

(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 4-methyleneundecanoate (331b)



***Via* the original Orthoester Johnson-Claisen:**

To 2-methylenenonanol (1.00 g, 6.39 mmol), xylene (45 mL) and solketal orthoester (**354**) (5.40 g, 12.8 mmol) was added propionic acid (144 µL, 1.93 mmol). The solution was heated to 138 °C for 24 h. EtOAc (50 mL) was then added and the solution was washed 0.5 HCl (6 x 70 mL), sat. aq. $NaHCO_3$ (70 mL), brine (70 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure. The crude ester was then purified by column chromatography (10% EtOAc:Hexane, R_f = 0.3) to yield the title compound (510 mg, 25%) as a yellow liquid.

***Via* the direct Orthoester Johnson-Claisen:**

4,4'-(((1-((2-methylenenonyl)oxy)ethane-1,1-diyl)bis(oxy))bis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (66.0 mg, 0.149 mmol) and xylene (660 µL) was heated to 138 °C for 400 h. DCM (20 mL) was then added and the reaction mixture was washed water (6 x 50 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (45 mg, 71%) as a yellow liquid.

Solketal/FM^2/2-methylenenonanol Orthoester (155 mg, 0.242 mmol) and xylene (1 mL) was heated to 138 °C for 24 h before being concentrated to dryness. Hexane (25 mL) was added and the solution was filtered and concentrated to dryness by reduced pressure to yield a brown semi-solid. The crude ester was purified by column chromatography (20% EtOAc:Hexane, R_f = 0.4) to yield the title compound (31 mg, 41%) as a yellow liquid.

4-((1-(4-methoxyphenoxy)-1-((2-methylenenonyl)oxy)ethoxy)methyl)-2,2-dimethyl-1,3-dioxolane (140 mg, 0.32 mmol) and xylene (1.1 mL) was heated to 138 °C for 24 h. Hexane (20 mL) was added and the solution was washed 5% NaOH (4 x 50 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (78 mg, 79%) as a brown liquid.

***Via* coupling to the acid:**

To a stirring solution of 2-methylenenonanol (3.00 g, 19.2 mmol), triethyl orthoacetate (24.6 mL, 0.134 mmol) and xylene (144 mL) was added propionic acid (402 µl, 5.39 mmol). The solution was then heated to 138 °C for 24 h. EtOAc (50 mL) and 1M HCl (50 mL) was then added. The solution was washed 1M HCl (3 x 150 mL), sat. aq. $NaHCO_3$ (150 mL), brine (150 mL), dried $MgSO_4$ and concentrated to dryness to yield ethyl 4-methyleneundecanoate (3.4 g, 79%) as a yellow liquid. To 4-methyleneundecanoate (3.00 g, 13.3 mmol) was added KOH (30 mol%, 6.4 mL, 33.1 mmol) and heated to 85 °C for 2.5 h. The reaction mixture was then acidified to pH 1 using conc. Sulfuric acid. The organic layer was separated and concentrated to dryness to yield 4-methyleneundecanoic acid (2.1 g, 78%) as an orange liquid. To a solution of 4-methyleneundecanoic acid (1.00 g, 4.99 mmol), solketal (570 µL,

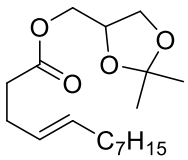
4.59 mmol) and DCM (10 mL) was added EDCl (957 mg, 4.99 mmol) and DMAP (122 mg, 0.998 mmol). The solution was then stirred at 25 °C for 24 h before being concentrated to dryness. Hexane (3 mL) was added and the solution was filtered and concentrated to dryness by reduced pressure. The crude ester was purified by column chromatography (20% EtOAc:Hexane, R_f = 0.4) to yield the title compound (860 mg, 57%) as a yellow liquid.

***Via* Ketene Acetal:**

2,2-dimethyl-4-(((1-((2-methylenenonyl)oxy)vinyl)oxy)methyl)-1,3-dioxolane (78.0 mg, 0.250 mmol) in THF (1.1 mL) was heated to 50 °C for 5 h before being concentrated to dryness by reduced pressure to yield the title compound (60 mg, 76%) as an orange liquid.

ν_{max}/cm^{-1}; 2927, 2856, 1740 and 1646; ^1H NMR (500 MHz, $CDCl_3$); 4.74 (1H, d, J 1.7 Hz, CH_2), 4.70 (1H, d, J 1.7 Hz, CH_2), 4.34-4.27 (1H, m, CH), 4.16 (1H, dd, J 11.5, 5.0 Hz, CH_2), 4.12-4.04 (2H, m, CH_2), 3.73 (1H, dd, J 8.5, 6.3 Hz, CH_2), 2.53-2.47 (2H, m, CH_2), 2.36-2.31 (2H, CH_2), 2.0 (2H, t, J 7.5 Hz, CH_2), 1.43 (3H, s, CH_3), 1.42-1.38 (2H, m, CH_2), 1.37 (3H, s, CH_3), 1.30-1.23 (8H, m, CH_2), 0.88 (3H, t, J 6.9, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 173.2 (C), 148.2 (C), 109.9 (C), 109.2 (CH_2), 73.7 (CH), 66.5 (CH_2), 64.8 (CH_2), 36.4 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 30.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.8 (CH_3), 25.5 (CH_3), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* 335.2230 ($M + Na^+$) $C_{18}H_{32}O_5Na^+$ requires 335.2193.

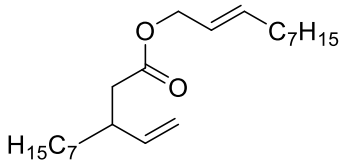
(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl (*E*)-dodec-4-enoate (331c)



To decen-3-ol (500 mg, 3.20 mmol), xylene (26 mL) and solketal orthoester (**354**) (2.05 g, 6.40 mmol) was added propionic acid (72.0 µL, 0.958 mmol). The solution was heated to 138 °C for 24 h. EtOAc (50 mL) was then added and the solution was washed 0.5 HCl (6 x 80 mL), sat. aq. $NaHCO_3$ (80 mL), brine (80 mL), dried $MgSO_4$ and concentrated to dryness (150 – 155 °C, 0 mbar). The crude ester was then

purified by column chromatography (10% EtOAc:Hexane, R_f = 0.3) to yield the title compound (64 mg, 7%) as a yellow liquid. ν_{max}/cm^{-1}; 2957, 2925, 2855 and 1741; ^1H NMR (500 MHz, $CDCl_3$); 5.51-5.43 (1H, m, CH), 5.43-5.34 (1H, m, CH), 4.35-4.27 (1H, m, CH), 4.17 (1H, dd, J 11.5, 4.9 Hz, CH_2), 4.12-4.05 (2H, m, CH_2), 3.74 (1H, dd, J 8.5, 6.1 Hz, CH_2), 2.45-2.38 (2H, m, CH_2), 2.36-2.28 (2H, m, CH_2), 1.96 (2H, q, J 7.0 Hz, CH_2), 1.44 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.34-1.23 (10H, m, CH_2), 0.89 (3H, t, J 6.8 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 173.2 (C), 132.2 (CH), 127.8 (CH), 109.7 (C), 73.8 (CH), 66.5 (CH_2), 64.7 (CH_2), 34.3 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 26.8 (CH_3), 25.5 (CH_2), 22.8 (CH_3), 14.2 (CH_3); HRMS *m/z* 335.2244 ($M + Na^+$) $C_{18}H_{32}O_5Na^+$ requires 335.2193.

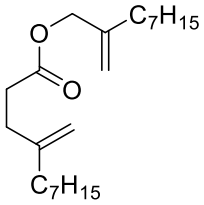
(*E*)-Dec-2-en-1-yl 3-vinyldecanoate (334a)



To a stirring solution of dec-2-enol (2.00 g, 12.8 mmol), triethyl orthoacetate (16.4 mL, 89.6 mmol) and xylene (96 mL) was added propionic acid (286 µl, 3.84 mmol). The solution was then heated to 138 °C for 24 h. EtOAc (50 mL) and 1M HCl (50 mL) was then added. Further EtOAc (50 mL) added and the solution was washed 1M HCl (3 x 100 mL), sat. aq. $NaHCO_3$ (100 mL), brine (100 mL), dried $MgSO_4$ and concentrated to dryness to yield Ethyl 3-vinyldecanoate (2.2 g, 75%) as a yellow liquid. To ethyl 3-vinyldecanoate (1.8 g, 8.0 mmol) was added KOH (30 mol%, 3.8 mL, 19.9 mmol) and heated to 85 °C for 2.5 h. The reaction mixture was then acidified to pH 1 using conc. Sulfuric acid. Diethyl ether (20 mL) was added and the organic layer was separated and concentrated to dryness to yield 3-vinyldecanoic acid (945 mg, 65%) as a yellow liquid. To a solution of 3-vinyldecanoic acid (500 mg, 2.50 mmol), dec-2-enol (359 mg, 2.30 mmol) and DCM (5.5 mL) was added EDCl (479 mg, 2.50 mmol) and DMAP (61.0 mg, 0.499 mmol). The solution was then stirred at 25 °C for 24 h. DCM (30 mL) was added and the solution was filtered through a small silica pad before being concentrated to dryness. Hexane (30 mL) was added and the solution was filtered through a small silica pad and concentrated to dryness (120 °C, 0 mbar). The crude ester was purified by column

chromatography (1% EtOAc:Hexane, R_f = 0.16) to yield the title compound (350 mg, 45%) as a yellow liquid. ν_{max}/cm^{-1}; 2956, 2925, 2855, 1737, 1677 and 1642; ^1H NMR (500 MHz, $CDCl_3$); 5.79-5.72 (1H, m, CH), 5.67-5.58 (1H, m, CH), 5.58-5.50 (1H, m, CH), 5.07-4.95 (2H, m, CH_2), 4.50 (2H, d, J 6.4 Hz, CH_2), 2.52 (2H, dq, J 7.8, 2.4 Hz, CH_2), 2.37 (2H, dd, J 14.7, 6.2 Hz, CH_2), 2.29 (2H, dd, J 14.7, 8.2 Hz, CH_2), 2.09-2.00 (2H, m, CH_2), 1.41-1.32 (4H, m, CH_2), 1.32-1.18 (17H, m, CH_2), 0.90-0.85 (6H, m, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 172.4 (C), 142.3 (CH), 136.7 (CH), 124.0 (CH), 115.0 (CH_2), 65.3 (CH_2), 40.6 (CH), 40.3 (CH_2), 34.6 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.28 (CH_2), 29.25 (CH_2), 29.0 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* 359.2912 ($M + Na^+$) $C_{22}H_{40}O_2Na^+$ requires 359.2921.

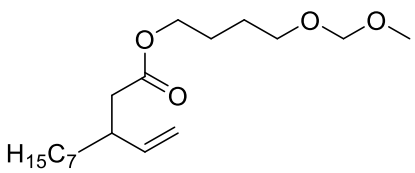
2-Methylenenonyl 4-methyleneundecanoate (334b)



To a stirring solution of 2-methylenenonanol (1.50 g, 9.60 mmol), triethyl orthoacetate (12.3 mL, 67.2 mmol) and xylene (70 mL) was added propionic acid (215 µl, 2.88 mmol). The solution was then heated to 138 °C for 24 h. EtOAc (50 mL) and 1M HCl (50 mL) was then added. The solution was washed 1M HCl (3 x 100 mL), sat. aq. $NaHCO_3$ (100 mL), brine (100 mL), dried $MgSO_4$ and concentrated to dryness to yield ethyl 4-methyleneundecanoate (1.7 g, 79%) as a yellow liquid. To 4-methyleneundecanoate (1.50 g, 6.63 mmol) was added KOH (30 mol%, 3.20 mL, 16.6 mmol) and heated to 85 °C for 2.5 h. The reaction mixture was then acidified to pH 1 using conc. Sulfuric acid. Diethyl ether (20 mL) was added and the organic layer was separated and concentrated to dryness to yield 4-methyleneundecanoic acid (1.0 g, 77%) as a dark red liquid. To a solution of 4-methyleneundecanoic acid (500 mg, 2.50 mmol) and DCM (3.8 mL) was added thionyl chloride (356 mg, 3.00 mmol) dropwise over 5 min. The solution was heated to 35 °C for 30 min before being concentrated to dryness. The acid chloride (305 mg, 1.41 mmol) was then

added to a mixture of 2-methylenenonanol (200 mg, 1.28 mmol), NEt_3 (259 mg, 2.56 mmol) and DCM (3 mL) dropwise over 5 min at 0 °C. The solution was then stirred at 25 °C for 1 h. The reaction was then quenched with sat. aq. NH_4Cl (3 mL) and extracted diethyl ether (3 x 30 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure. The crude ester was purified by column chromatography (5% EtOAc:Hexane, R_f = 0.5) to yield the title compound (140 mg, 17%) as a yellow liquid. ν_{max}/cm^{-1}; 2956, 2924, 2855, 1739 and 1648; ^1H NMR (500 MHz, $CDCl_3$); 5.02 (1H, d, J 1.7 Hz, CH_2), 4.93 (1H, d, J 1.7 Hz, CH_2), 4.76 (1H, d, J 1.7 Hz, CH_2), 4.72 (1H, d, J 1.7 Hz, CH_2), 4.53 (2H, s, CH_2), 2.51 (2H, dd, J 7.0 Hz, CH_2), 2.39-2.33 (2H, m, CH_2), 2.10-1.98 (2H, m, CH_2), 1.49-1.40 (4H, m, CH_2), 1.34-1.22 (16H, m, CH_2), 0.89 (6H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 173.2 (C), 148.4 (C), 144.3 (C), 112.1 (CH_2), 109.2 (CH_2), 66.9 (CH_2), 36.4 (CH_2), 33.4 (CH_2), 32.9 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.32 (CH_2), 29.27 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* 359.2916 ($M + Na^+$) $C_{22}H_{40}O_2Na^+$ requires 359.2921.

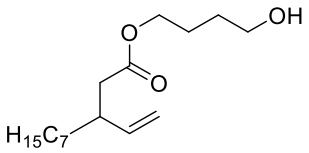
4-(Methoxymethoxy)butyl 3-vinyldecanoate (336a)



(E)-10-(4-methoxyphenoxy)-10-methyl-2,4,9,11-tetraoxahenicos-13-ene (500 mg, 1.14 mmol) and xylene (5 mL) was heated to 138 °C for 24 h before being concentrated to dryness. Hexane (40 mL) was added and the solution was washed 5% NaOH (4 x 100 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield a yellow liquid. The crude ester was purified by column chromatography (20% Diethyl ether:Hexane, R_f = 0.16) to yield the title compound (282 mg, 79%) as a yellow liquid. ν_{max}/cm^{-1}; 2927, 2857, 1738 and 1641; ^1H NMR (500 MHz, $CDCl_3$); 5.63 (1H, ddd, J 18.6, 8.3, 1.5 Hz, CH), 5.05-4.96 (2H, m, CH_2), 4.62 (2H, s, CH_2), 4.09 (2H, t, J 6.3 Hz, CH_2), 3.55 (2H, t, J 6.3 Hz, CH_2), 3.37 (3H, s, CH_3), 2.56-2.46 (1H, m, CH), 2.37 (1H, dd, J 14.6, 6.3 Hz, CH_2), 2.28 (1H, dd, J 14.6,

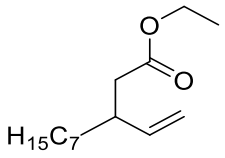
8.5 Hz, CH_2), 1.76-1.62 (4H, m, CH_2), 1.40-1.22 (12H, m, CH_2), 0.88 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 172.7 (C), 141.3 (CH), 114.9 (CH_2), 96.5 (CH_2), 67.3 (CH_2), 64.1 (CH_2), 55.3 (CH_3), 40.7 (CH), 40.3 (CH_2), 34.7 (CH_2), 32.0 (CH_2),29.7 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 26.4 (CH_2), 25.7 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* (ESI^+) 337.2387 ($M + Na^+$) $C_{18}H_{34}O_4Na^+$ requires 337.2349.

4-Hydroxybutyl 3-vinyldecanoate (337)



(*E*)-2-(dec-2-en-1-yloxy)-2-methyl-1,3-dioxepane (300 mg, 1.11 mmol) and xylene (5.5 mL) was heated to 138 °C for 72 h before being concentrated to dryness by reduced pressure. The crude ester was purified by column chromatography (25% EtOAc:Hexane, R_f = 0.17) to yield the title compound (38 mg, 13%) as a yellow liquid. ν_{max}/cm^{-1}; 3419, 2925, 2855, 1735 and 1641; ^1H NMR (500 MHz, $CDCl_3$); 5.62 (1H, ddd, J 18.8, 8.5, 1.4 Hz, CH), 5.04-4.95 (2H, m, CH_2), 4.09 (2H, t, J 6.3 Hz, CH_2), 3.67 (2H, t, J 6.3 Hz, CH_2), 2.55-2.45 (1H, m, CH), 2.36 (1H, dd, J 14.6, 6.0 Hz, CH_2), 2.27 (1H, dd, J 14.6, 8.4 Hz, CH_2), 1.74-1.66 (2H, m, CH_2), 1.65-1.61 (2H, m, CH_2), 1.40-1.19 (13H, m, CH_2), 0.87 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 172.8 (C), 141.2 (CH), 114.9 (CH_2), 64.2 (CH_2), 62.4 (CH_2), 40.7 (CH), 40.3 (CH_2), 34.7 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.34 (CH_2), 29.26 (CH_2), 27.1 (CH_2), 25.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* (ESI^+) 293.2101 ($M + Na^+$) $C_{16}H_{30}O_3Na^+$ requires 293.2087.

Ethyl 3-vinyldecanoate (351a)



***Via* Iodoacetal:**

To a stirring solution of KO^tBu (173 mg, 1.54 mmol) and DMF (2 mL) was added a mixture of (*E*)-1-(1-ethoxy-2-iodoethoxy)dec-2-ene (500 mg, 1.41 mmol) in DMF (1 mL) dropwise over 15 min. The solution was then stirred at 25 °C for 1 h and then

heated to 140 °C for 6 h. Hexane (30 mL) was then added and the solution was washed water (100 mL) and extracted hexane (2 x 50 mL). The combined organic layers were washed water (3 x 80 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (195 mg, 62%) as a yellow liquid.

***Via* Ketene Acetal:**

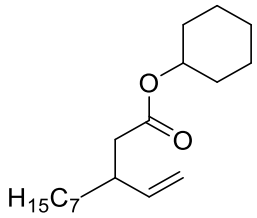
(*E*)-1-((1-ethoxyvinyl)oxy)dec-2-ene (867, 3.83 mmol) in THF (1 mL) was heated to 50 °C for 4 h before being concentrated to dryness by reduced pressure to yield the title compound (617 mg, 71%) as a yellow liquid.

***Via* the Orthoester Johnson-Claisen Rearrangement:**

To a stirring solution of dec-2-en-ol (2.00 g, 12.8 mmol) and xylene (96 mL) was added triethyl orthoacetate (16.4 mL, 89.6 mmol) and propionic acid (286 µL, 3.84 mmol). The solution was then heated to 138 °C for 24 h. EtOAc (50 mL) and 1M HCl (50 mL) was added and stirred for 5 min. Further EtOAc (50 mL) was added and the solution was then washed with 1M HCl (3 x 100 mL), $NaHCO_3$ (100 mL) and brine (100 mL), dried with $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (2.2 g, 76%) a yellow liquid.

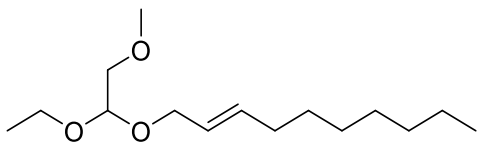
ν_{max}/cm^{-1}; 2957, 2926, 2855, 1737, 1641 and 1464; ^1H NMR (500 MHz, $CDCl_3$); 5.63 (1H, ddd, J 18.6, 8.4, 1.5 Hz, CH), 5.06-4.95 (2H, m, CH_2), 4.12 (2H, q, J 7.1 Hz, CH_2), 2.56-2.47 (1H, m, CH), 2.36 (1H, dd, J 14.7, 6.2 Hz, CH_2), 2.27 (1H, dd, J 14.7, 8.5 Hz, CH_2), 1.39-1.19 (15H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 172.5 (C), 141.0 (CH), 114.7 (CH_2), 60.4 (CH_2), 40.5 (CH), 40.2 (CH_2), 34.5 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.3 (CH_3), 14.1 (CH_3); HRMS *m/z* 249.184 ($M + Na^+$) $C_{14}H_{26}O_2Na^+$ requires 249.1825.

Cyclohexyl 3-vinyldecanoate (351b)



To a stirring solution of KO^{t}Bu (173 mg, 1.54 mmol) and DMF (2 mL) was added a mixture of (*E*)-(1-(dec-2-en-1-yloxy)-2-iodoethoxy)cyclohexane (572 mg, 1.40 mmol) in DMF (1 mL) dropwise over 15 min. The solution was then stirred at 25 °C for 1 h and then heated to 140 °C for 6 h. The reaction mixture was poured into water (100 mL) and extracted hexane (2 x 50 mL). The combined organic layers were washed water (3 x 100 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (85 mg, 22%) as a yellow liquid. ν_{max}/cm^{-1}; 2925, 2856, 1733 and 1641; ^{1}H NMR (500 MHz, $CDCl_3$); 5.63 (1H, ddd, J 18.6, 8.4, 1.4 Hz, CH), 5.05-4.96 (2H, m, CH_2), 4.76 (1H, tt, J 9.0, 4.0 Hz, CH), 2.51 (1H, dq, J 7.9, 2.9 Hz, CH), 2.34 (1H, dd, 14.3, 6.4 Hz, CH_2), 2.26 (1H, dd, J 14.3, 8.2 Hz, CH_2), 1.87-1.79 (2H, m, CH_2), 1.76-1.69 (2H, m, CH_2), 1.58-1.49 (2H, m, CH_2), 1.43-1.34 (6H, m, CH_2), 1.34-1.21 (10H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 172.3 (C), 141.3 (CH), 114.9 (CH_2), 72.5 (CH), 40.8 (CH), 34.6 (CH_2), 32.0 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 27.0 (CH_2), 25.5 (CH_2), 23.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* 303.2320 (M + Na^+) $C_{18}H_{32}O_2Na^+$ requires 303.2295.

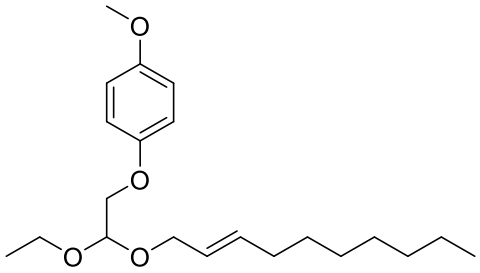
(*E*)-1-(1-ethoxy-2-methoxyethoxy)dec-2-ene (352a)



A stirring solution of (*E*)-1-(2-bromo-1-ethoxyethoxy)dec-2-ene (300 mg, 0.976 mmol), methanol/THF (1.7 mL, 60:40 v/v) and NaOMe (1.12 mL, 4.88 mmol) was heated to 50-55 °C for 24 h. TBME (0.5 mL) was added and the solution heated to 50-55 °C for 78 h. DCM (20 mL) and water (20 mL) was added and the solution was

washed brine (50 mL). The aqueous layer was extracted DCM (50 mL) and the combined organic layers were dried $MgSO_4$ and concentrated to dryness. The crude acetal was purified by silica gel chromatography (10% EtOAc:Hexane, R_f = 0.29) to yield the title compound (121 mg, 48%) as a yellow liquid. ν_{max}/cm^{-1}; 2924, 2855, 1457 and 1115; ^1H NMR (500 MHz, $CDCl_3$); 5.74-5.68 (1H, m, CH), 5.59-5.52 (1H, m, CH), 4.68 (1H, t, J 5.2 Hz, CH), 4.11 (1H, ddq, J 11.7, 6.1, 1.1 Hz, CH_2), 4.03 (1H, ddq, J 11.7, 6.6, 1.1 Hz, CH_2), 3.70 (1H, dq, J 9.4, 7.0 Hz, CH_2), 3.58 (1H, dq, J 9.4, 7.0 Hz, CH_2), 3.46 (2H, d, J 5.1 Hz, CH_2), 3.40 (3H, s, CH_3), 2.04 (2H, q, J 7.2 Hz, CH_2), 1.41-1.35 (2H, m, CH_2), 1.23-1.25 (8H, m, CH_2), 1.23 (3H, t, J 7.0 Hz, CH_3), 0.89 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 135.2 (CH), 126.0 (CH), 100.2 (CH), 73.3 (CH_2), 67.6 (CH_2), 62.2 (CH_2), 59.5 (CH_3), 33.4 (CH_2), 32.0 (CH_2), 29.30 (CH_2), 29.29 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 15.5 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 281.2227 ($M + Na^+$) $C_{15}H_{30}O_3Na^+$ requires 281.2087.

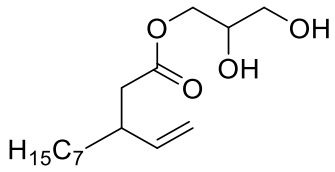
(*E*)-1-(2-(dec-2-en-1-yloxy)-2-ethoxyethoxy)-4-methoxybenzene (352b)



A solution of (*E*)-1-(2-bromo-1-ethoxyethoxy)dec-2-ene (1.20 g, 4.01 mmol), DMF (10 mL), 4-methoxyphenol (331 mg, 2.67 mmol) and KOH (300 mg, 5.35 mmol) was heated to 150 °C for 1 h. The reaction mixture was poured into water (600 mL) and extracted diethyl ether (3 x 150 mL). The combined organic layers were washed 5% NaOH (3 x 150 mL), water (600 mL), dried $MgSO_4$ and concentrated to dryness. The crude acetal was purified by silica gel chromatography (5% EtOAc:Hexane, R_f = 0.23) to yield the title compound (220 mg, 13%) as a yellow liquid. ν_{max}/cm^{-1}; 2956, 2925, 2855, 1508 and 1459; ^1H NMR (500 MHz, $CDCl_3$); 6.89-8.45 (2H, m, CH), 8.45-6.80 (2H, m, CH), 5.78-5.68 (1H, m, CH), 5.63-5.51 (1H, m, CH), 4.86 (1H, t, J 5.2 Hz, CH), 4.16 (1H, ddd, J 11.7, 61, 1.1 Hz, CH_2), 4.08 (1H, ddd, J 11.7, 6.6, 1.1 Hz, CH_2), 3.98 (2H, d, J 5.3 Hz, CH_2), 3.77 (3H, s, CH_3), 3.76-3.71 (1H, m, CH_2), 3.67-

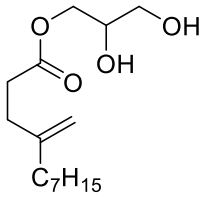
3.61 (1H, m, CH_2), 2.05 (2H, q, J 6.9 Hz, CH_2), 1.41-1.27 (8H, m, CH_2), 1.25 (3H, t, J 7.1 Hz, CH_3), 0.89 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 154.1 (C), 152.9 (C), 135.4 (CH), 125.8 (CH), 115.8 (CH), 114.7 (CH), 99.9 (CH), 69.4 (CH_2), 67.8 (CH_2), 62.5 (CH_2), 62.5 (CH_2), 55.8 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 29.31 (CH_2), 29.29 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 15.5 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI$^+$) 373.2382 (M + Na^+) $C_{21}H_{34}O_4Na^+$ requires 373.2349.

2,3-Dihydroxypropyl 3-vinyldecanoate (353a)



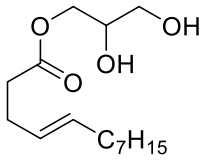
To a solution of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 3-vinyldecanoate (100 mg, 0.320 mmol) in IPA (1.3 mL) was added 1M HCl (640 µL, 0.640 mmol). The solution was then heated to 50 °C for 2 h. Diethyl ether (25 mL) was added and the solution was washed brine (30 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (72 mg, 83%) as a thick yellow liquid. ν_{max}/cm^{-1}; 3392, 2956, 2925, 2855, 1736 and 1641^{1}H NMR (500 MHz, $CDCl_3$); 5.63 (1H, ddd, J 18.6, 8.4, 1.5 Hz, CH), 5.07-4.99 (2H, m, CH_2), 4.21-4.06 (2H, m, CH_2), 3.91 (1H, p, J 5.1 Hz, CH), 3.68 (1H, dd, J 11.4, 3.9 Hz, CH_2), 3.59 (1H, dd, J 11.4, 5.9 Hz, CH_2), 2.55-2.49 (1H, m, CH), 2.43 (1H, dd, J 14.6, 5.7 Hz, CH_2), 2.33 (1H, dd, J 14.6, 8.8 Hz, CH_2), 1.39-1.22 (13H, m, CH_2), 0.89 (3H, t, J = 6.6 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 173.2 (C), 141.2 (CH), 115.3 (CH_2), 70.3 (CH), 65.2 (CH_2), 63.4 (CH_2), 40.7 (CH), 40.1 (CH_2), 34.7 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3); HRMS *m/z* 295.1931 (M + Na^+) $C_{15}H_{28}O_4Na^+$ requires 295.1880.

2,3-Dihydroxypropyl 4-methyleneundecanoate (353b)



To a solution of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methyleneundecanoate (250 mg, 0.800 mmol) in IPA (6.8 mL) was added 1M HCl (1.6 mL, 1.60 mmol). The solution was then heated to 50 °C for 2 h. Diethyl ether (20 mL) was added and the solution was washed brine (40 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure. The crude ester was then purified by column chromatography (50% EtOAc:Hexane, R_f = 0.11) to yield the title compound (124 mg, 55%) as a thick yellow liquid. ν_{max}/cm^{-1}; 3397, 2926, 2856, 1737 and 1646; ^1H NMR (500 MHz, $CDCl_3$); 4.77 (1H, d, J 1.7 Hz, CH_2), 4.71 (1H, d, J 1.7 Hz, CH_2), 4.21-4.09 (2H, m, CH_2), 3.95-3.88 (1H, m, CH), 3.70 (1H, dd, J 11.4, 3.4 Hz, CH_2), 3.60 (1H, dd, J 11.4, 5.6 Hz, CH_2), 2.57-2.46 (2H, m, CH_2), 2.36-2.30 (2H, m, CH_2), 2.00 (2H, t, J 7.6 Hz, CH_2), 1.46-1.36 (2H, m, CH_2), 1.31-1.24 (8H, m, CH_2), 0.89 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 173.9 (C), 148.2 (C), 109.4 (CH_2), 70.3 (CH), 65.3 (CH_2), 63.4 (CH_2), 36.3 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 30.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3); HRMS *m/z* 295.1928 (M + Na^+) $C_{15}H_{28}O_4Na^+$ requires 295.1880.

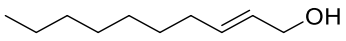
2,3-Dihydroxypropyl (*E*)-dodec-4-enoate (353c)



To a solution of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl (*E*)-dodec-4-enoate (37.0 mg, 0.118 mmol) in IPA (1.0 mL) was added 1M HCl (240 µL, 0.236 mmol). The solution was then heated to 50 °C for 2 h. Diethyl ether (25 mL) was added and the solution was washed brine (30 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (21 mg, 66%) as a thick yellow liquid. ν_{max}/cm^{-1}; 3405, 2924, 2854 and 1735; ^1H NMR (500 MHz, $CDCl_3$); 5.54-5.44 (1H, m, CH), 5.44-5.35 (1H, m, CH), 4.22 (1H, dd, J 11.7, 4.7 Hz, CH_2), 4.16 (1H, dd, J 11.7, 6.3 Hz, CH_2), 3.97-3.90 (1H, m, CH), 3.70 (1H, dd, J 11.5, 4.2 Hz, CH_2), 3.61 (1H, dd,

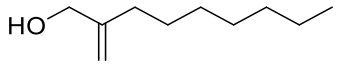
J 11.5, 5.8 Hz, CH_2), 2.45-2.40 (2H, m, CH_2), 2.33 (2H, q, 7.0 Hz, CH_2), 1.98 (2H, q, J 7.0 Hz, CH_2), 1.37-1.23 (8H, m, CH_2), 0.89 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 173.8 (C), 132.4 (CH), 127.7 (CH), 70.4 (CH), 65.3 (CH_2), 63.4 (CH_2), 34.4 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 22.8 (CH_2), 14.2 (CH_3); HRMS *m/z* 295.1927 (M + Na^+) $C_{15}H_{28}O_4Na^+$ requires 295.1880.

Dec-2-en-1-ol (354a)



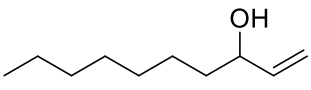
Triethyl phosphonoacetate (36.8 mL, 182 mmol) was added dropwise to a stirring suspension of NaH (8.00 g, 182 mmol) in diethyl ether (400 mL) at 0 °C. After hydrogen evolution was complete (5 min), octanal (26.4 mL, 166 mmol) was added dropwise. The solution was then stirred at 0 °C for 1.5 h before being quenched with sat. aq. NH_4Cl (100 mL). Diethyl ether (200 mL) was added and the solution was washed with water (2 x 200 mL) and brine (2 x 200 mL), dried over $MgSO_4$ and concentrated to dryness to yield ethyl dec-2-enoate (29.6 g, 90%) as a colourless liquid, which was used without further purification. To DIBAL-H (72.0 mL, 72.0 mmol, 1M in THF) was added Ethyl dec-2-enoate (5.70 g, 28.8 mmol) in anhydrous DCM/Hexane (149 mL, 2:1 v/v) at -78 °C. The reaction was stirred at -78 °C for 3 h. The mixture was then quenched with methanol (45 mL) and 1M Rochelle's salt (30 mL) and held without stirring at 25 °C for 18 h. To the solution was added water (400 mL) and was extracted with EtOAc (3 x 200 mL). The combined organic layers were then washed with brine (2 x 200 mL), dried over $MgSO_4$ and concentrated to dryness by reduced pressure to yield the title compound (4.2 g, 93%). ν_{max}/cm^{-1}; 3326, 2955, 2923, 2854 and 1670; ^{1}H NMR (500 MHz, $CDCl_3$) 5.75-5.55 (2H, m, CH), 4.08 (2H, d, J 5.5 Hz, CH_2), 2.04 (2H, q, J 7.4 Hz, CH_2), 1.53 (1H, s, OH), 1.42-1.21 (2H, m, CH_2), 1.28 (8H, m, CH_2), 0.88 (3H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 133.7 (CH), 128.9 (CH), 63.9 (CH_2), 32.3 (CH_2), 32.0 (CH_2), 29.29 (CH_2), 29.28 (CH_2), 29.27 (CH_2), 22.7 (CH_2), 14.2 (CH_3); HRMS *m/z* (ESI^+) 179.1423 (M + Na^+) $C_{10}H_{20}ONa^+$ requires 179.1441. The data was consistent with the product.[275]

2-Methylenenonanol (354b)



To a stirring solution of p-toluic acid (1.00 g, 7.34 mmol), pyrrolidine (306 µL, 3.67 mmol) and DCM (50 mL) was added formaldehyde (~37% wt in water, 36.7 mmol) and nonanol (6.30 mL, 36.7 mmol). The solution then heated to 40 °C for 1h before cooling to 25 °C. 7% $NaHCO_3$ (100 mL) was then added and extracted with DCM (3 x 100 mL). The combined organic layers were then washed with brine (100 mL), dried Na_2SO_3 and concentrated in vacuo to yield 2-methylenenonal (5.4 g, 96%) as a clear liquid, which was used immediately. 2-methylenenonanal (5.40 g, 35.0 mmol) in DCM/Hexane (2:1, 180 mL) was added to a solution of DIBAL (87.5 mL, 87.5 mmol, 1M in hexanes) at -78 °C. The solution was kept at -78 °C for 3h before the addition of methanol (20 mL) and 1M Rochelle's salt (60 mL). Then left to sit for 16h before extraction with EtOAc (3 x 200 mL). The combined organic layers were then washed with brine (250 mL), dried $MgSO_4$ and concentrated to dryness by reduced pressure to yield crude alcohol, which was then purified by silica gel chromatography (10% EtOAc:Hexane, R_f = 0.28) to yield 2-methylenenonan-1-ol (2.91 g, 53%) as a colourless liquid. ν_{max}/cm^{-1}; 3320, 2956, 2925, 2855, 1744, 1725, 1654 and 1459; ^1H NMR (500 MHz, $CDCl_3$) 5.04-4.99 (1H, m, CH), 4.87 (1H, d, J = 1.3 Hz, CH), 4.07 (2H, s, CH_2), 2.06 (2H, t, J 7.8 Hz, CH_2), 1.54 (1H, s, OH), 1.48-1.40 (2H, m, CH_2), 1.35-1.22 (8H, m, CH_2), 0.89 (3H, t, J 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 149.5 (C), 109.1 (CH_2), 66.12 (CH_2), 33.1 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 22.8 (CH_2), 14.3 (CH_3); HRMS *m/z* (ESI^+) 155.1423 (M – $[H]^-$) $C_{10}H_{20}OH^-$ requires 155.1441. The data was consistent with the product.[276]

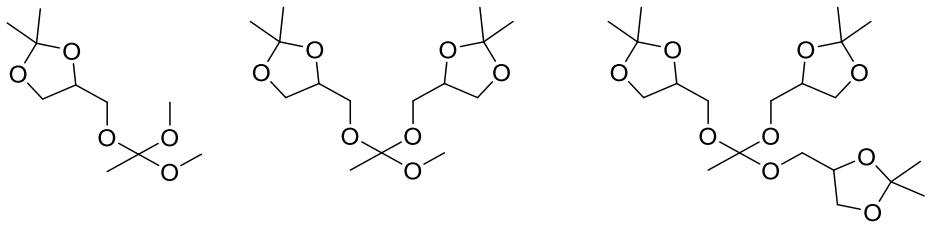
Dec-1-en-3-ol (354c)



To a stirring solution of octanal (7.80 mL, 50.0 mmol) in anhydrous THF (200 mL) was added vinylmagnesium bromide (50.0 mL, 1M in THF) dropwise at 0 °C. The solution was then stirred at 25 °C for 1 h. The solution was then cooled back to 0 °C and quenched with 1M HCl (55 mL). The aqueous layer was then extracted with

EtOAc (4 x 50 mL). The combined organic layers were then dried with $MgSO_4$ and concentrated to dryness by reduced pressure to yield the crude alcohol, which was then purified by silica gel chromatography (20% EtOAc:Hexane, R_f = 0.35) to yield dec-1-en-3-ol (4.37 g, 56%) as a yellow liquid. ν_{max}/cm^{-1}; 3358, 2957, 2926, 2856, 1744 and 1728; NMR (500 MHz, $CDCl_3$) 5.86 (1H, ddd, J 17.0, 10.8, 6.5 Hz, CH), 5.21 (1H, dt, J 17.3, 1.4 Hz, CH_2), 5.09 (1H, dt, J 10.8 Hz, 1.4 Hz, CH_2), 4.10 (1H, app. q, J 6.5 Hz, CH), 1.76 (1H, S, OH), 1.59-1.45 (2H, m, CH_2), 1.45-1.25 (10H, m, CH_2), 0.87 (3H, t, J 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 141.4 (CH), 114.6 (CH_2), 73.2 (CH), 37.1 (CH_2), 31.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.1 (CH); HRMS *m/z* (ESI^+) 157.1620 ($M + H^+$) $C_{10}H_{20}OH^+$ requires 157.1587. The data was consistent with the product.[277]

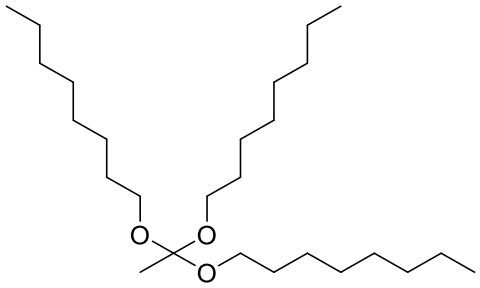
Solketal Orthoester (355)



Following general procedure K with solketal (124 mL, 996 mmol), trimethyl orthoacetate (21.0 mL, 166 mmol), xylene (286 mL) and TFA (137 µL, 1.66 mmol) at 80 °C for 24 h. The crude orthoester was then washed water (6 x 200 mL), dried $MgSO_4$ and concentrated to dryness. Purification by distilation (110 °C, 0 mbar) gave a mixture of mono-, di- and tri-substituted solketal orthoester (14.1 g) as a colourless liquid. ν_{max}/cm^{-1}; 2986, 2939, 2885, 1457 and 1380; ^1H NMR (500 MHz, $CDCl_3$); 4.26-4.19 (2H, m, CH), 4.07-4.00 (2H, m, CH_2), 3.79-3.70 (2H, m, CH_2), 3.60-3.54 (2H, m, CH_2), 3.53-3.44 (2H, m, CH_2), 3.28-3.23 (3H, m, CH_3), 1.48-1.42 (3H, m, CH_3), 1.39 (6H, s, CH_3), 1.33 (6H, s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 114.8 (C), 114.6 (C), 114.4 (C), 109.47 (C), 109.46 (C), 109.43 (C), 109.41 (C), 74.59 (CH), 74.56 (CH), 74.53 (CH), 74.49 (CH), 67.12 (CH_2), 67.06 (CH_2), 67.03 (CH_2), 67.00 (CH_2), 66.99 (CH_2), 66.97 (CH_2), 66.95 (CH_2), 63.65 (CH_2), 63.61 (CH_2), 63.47 (CH_2), 63.44 (CH_2), 63.42 (CH_2), 63.3 (CH_2), 63.2 (CH_2), 50.2 (CH_3), 50.1 (CH_3), 50.03 (CH_3), 49.97 (CH_3), 49.8 (CH_3), 26.84 (CH_3), 26.83 (CH_3), 26.81 (CH_3), 25.48 (CH_3), 25.46 (CH_3), 19.66

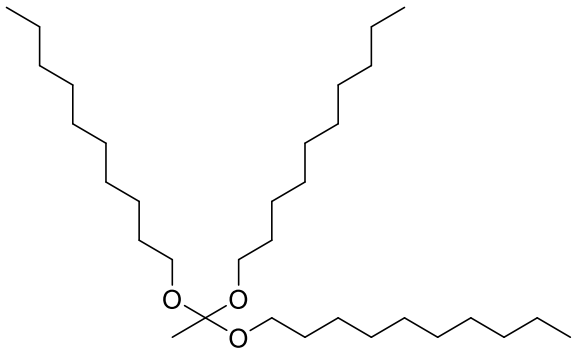
(CH_3), 19.62 (CH_3), 19.57 (CH_3); HRMS *m/z* (ESI^+) 243.1233 ($M + Na^+$) $C_{10}H_{20}O_5Na^+$ requires 243.1203; HRMS *m/z* (ESI^+) 343.1799 ($M + Na^+$) $C_{15}H_{28}O_7Na^+$ requires 343.1727; HRMS *m/z* (ESI^+) 443.1319 ($M + Na^+$) $C_{20}H_{36}O_9Na^+$ requires 443.2252.

Trioctyl orthoester (291d)



Following general procedure K with octanol (278 mL, 176 mmol), trimethyl orthoacetate (37.4 mL, 0.294 mmol) and trifluoroacetic acid (2.25 mL, 0.0294 mol). Purification by distillation (130 °C, 20 mbar) gave the title liquid (90.0 g, 75%) as a colourless liquid. ν_{max}/cm^{-1}; 2924, 2855, 1466 and 1372; ^1H NMR (500 MHz, $CDCl_3$) 3.46 (6H, t, J 6.9 Hz, CH_2), 1.57 (6H, p, J 6.9 Hz, CH_2), 1.45 (3H, s, CH_3), 1.40-1.19 (30H, m, CH_2), 0.88 (9H, t, J 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 114.2 (C), 62.2 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 22.8 (CH_2), 20.3 (CH_3), 14.2 (CH_3); HRMS *m/z* (ESI^+) 437.4030 ($M + Na^+$) $C_{26}H_{54}O_3Na^+$ requires 437.3965.

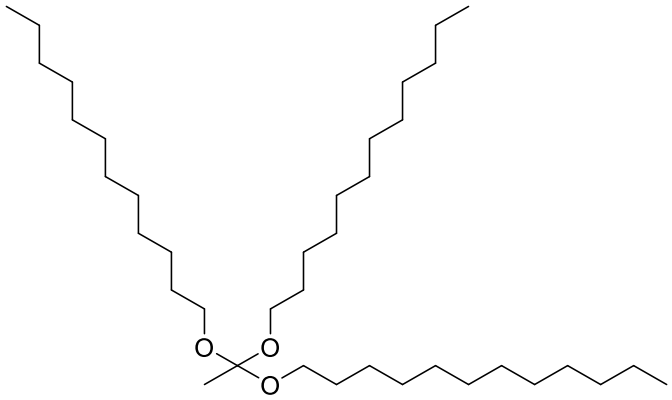
Tridecyl Orthoester (291e)



Following general procedure K with decanol (33.6 mL, 176 mol), trimethyl orthoacetate (3.74 mL, 29.4 mmol) and trifluoroacetic acid (225 µL, 2.94 mmol). Purification by distillation (145 °C, 20 mbar) gave tridecyl orthoacetate (9.27 g, 62%) as a clear liquid. ν_{max}/cm^{-1}; 2922, 2853, 1466 and 1372; ^1H NMR (500 MHz,

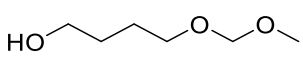
$CDCl_3$); 3.4.6 (6H, t, J 6.9 Hz, CH_2), 1.61-1.53 (6H, m, CH_2), 1.45 (3H, s, CH_3), 1.39-1.21 (42H, m, CH_2), 0.89 (3H, t, J 6.7 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 114.3 (C), 61.9 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.3 (CH_2), 22.7(CH_2), 20.2 (CH_3), 14.1 (CH_2); HRMS *m/z* (ESI^+) 521.4932 (M + Na^+) $C_{32}H_{66}O_3Na^+$ requires 521.4904.

Tridodecyl orthoester (291f)



Following general procedure K with dodecanol (336 mL, 1.50 mol), trimethyl orthoacetate (30.2 mL, 249 mmol) and trifluoroacetic acid (1.93 ml, 0.0249 mol). Purification by distillation (170 °C, 80 mbar) gave tridodecyl orthoacetate (114 g, 75%) as a clear liquid. ν_{max}/cm^{-1}; 2921, 2853, 1466 and 1372; ^1H NMR (500 MHz, $CDCl_3$); 3.46 (6H, t, J 7.2 Hz, CH_2), 1.61-1.52 (6H, m, CH_2), 1.45 (3H, s, CH_3), 1.32-1.12 (54H, m, CH_2), 0.89 (9H, t, J 7.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$); 114.1 (C), 62.1 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.3 (CH_2), 22.7 (CH_2), 20.2 (CH_3), 14.1 (CH_3); HRMS *m/z* (ESI^+) 605.5858 (M + Na^+) $C_{14}H_{20}O_3Na^+$ requires 605.5843.

4-(Methoxymethoxy)butan-1-ol



To a stirring solution of NaH (1.60 g, 40.0 mmol, 60% mineral oil) and THF (15 mL) was added 1,4-butanediol (7.93 g, 88.0 mmol) in THF (30 mL) dropwise over 30 min. The solution was left stirring at 25 °C for 45 min. Chloromethyl methyl ether (3.20 mL, 40.0 mmol) in THF (30 mL) was then added. The solution was stirred at 25 °C for 45 min before being quenched with sat. aq. $NaHCO_3$ (80 mL). The aqueous

layer was then washed with diethyl ether (3 x 150 mL) and the combined organic layers were dried $MgSO_4$ and concentrated to dryness by reduced pressure. The crude alcohol was purified by silica gel column chromatography (50% EtOAc:Hexane, R_f = 0.11) to yield the title compound (4.8 g, 88%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$); 4.63 (2H, s, CH_2), 3.66 (2H, t, J 5.9 Hz, CH_2), 3.57 (2H, t, J 5.9 Hz, CH_2), 3.66 (3H, s, CH_3), 1.73-1.62 (4H, m, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$); 96.6 (CH_2), 67.9 (CH_2), 62.7 (CH_2), 55.4 (CH_3), 29.9 (CH_2), 26.6 (CH_2).[a] The data was consistent with the product.[278]

[a] Mass spectra analysis was run but the desired mass ion was not observed.

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