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Studies Towards the Synthesis of Novel, Renewable Monomers Sourced from Terpenes

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Abstract

The multitude of commercially available plastics, ubiquitous in modern society, with uses from food contains to surgical tools, is vast. However, the major feedstock for these materials is crude oil, which accounts for 7% of oil consumption worldwide – a figure that is predicted to rise substantially in the near future.

To address this problem, a wide range of renewable resources have been identified as potential feedstocks of new, sustainably sourced polymer materials. Terpenes represent one of these potential feedstock options, and are mainly sourced from waste streams of existing industries – most notably paper and citrus juice production. This class of compounds provides an opportunity for the polymer industry to explore novel materials and potentially reduce dependency on non-renewable resources.

This report details the studies towards synthesis of potential monomers from terpenes using sustainable organic transformations. Short (3 synthetic steps or less) syntheses, involving reactions utilising high atom economy and/or catalysis, form the main focus of the investigations. Of the successful reactions performed, these protocols have been extensively optimised to provide the best yield and selectivity for the desired products, as well as operational simplicity and sustainable chemical reagents involved in carrying out the transformations themselves.

The monomers produced during this work are suitable for a variety of polymerisation techniques, including free radical polymerisation, ring-opening polymerisation and other step-growth methods. The resulting polymers have also shown promise in a variety of applications when tested by collaborators, with particular focuses on vaccine adjuvants and alternating hard and soft tri-block co-polymers for thermoplastic elastomer formation.

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Abbreviations

2-MeTHF = 2-methyltetrahydrofuran

3-NBA = 3-nitrobenzaldehyde

AA = acrylic acid

Ac = acetyl

acac = acetylacetonate

ACVA = 4,4'-azobis(4-cyanovaleric acid)

AIBN = 2,2'-azobis(*iso*-butyronitrile)

app = apparent

aq. = aqueous

ATR = attenuated total reflectance

ATRP = atom transfer radical polymerisation

BDI = bis(dimesityl)iminopropionate

BHT = 2,6-di-*tert*-butyl-4-methylphenol

Bn = benzyl

bpy = 2,2'-bipyridine

BQ = 1,4-benzoquinone

br = broad

BVMO = Baeyer-Villiger mono-oxidase

Bz = benzoyl

Cat = catechol

cat. = catalytic

CL = ε-caprolactone

CPAD = 4-cyano-4-(phenylcarbonylthioylthio)pentanoic acid

Cy = cyclohexyl

d = days

Đ = polydispersity

d.e. = diastereomeric excess

d.r. = diastereomeric ratio

Da = Daltons

DAF = 4,5-diazafluoren-9-one

DBTTC = dibenzyl trithiocarbonate

DCE = 1,2-dichloroethane

DCM = dichloromethane

DDM = dodecyl mercaptan

decomp. = decomposition

DFT = density functional theory

DIP-Cl = *B*-chlorodi-*iso*-pinocampheylborane

DIP-EI = direct insertion probe electron ionisation

DMA = N,N-dimethylacetamide

DMAP = N,N-dimethyl-4-aminopyridine

DMC = dimethyl carbonate

DMDO = dimethyldioxirane

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

DSC = differential scanning calorimetry

dtbpx = 1,2-bis((di-*tert*-butyl)phosphinomethyl)benzene

e.e. = enantiomeric excess

EBrP = ethyl 2-bromopropionate

eq. = molar equivalents

ESI = electro-spray ionisation

Et = ethyl

G6P = glucose-6-phosphate

G6PDH = glucode-6-phosphate dehydrogenase

GDH = glucose de-hydrogenase

GPC = gel permeation chromatography

h = hours

HMTETA = 1,1,4,7,10,10-hexamethyltriethylenetetramine

HOMO = highest occupied molecular orbital

HOSA = hydroxylamine-*O*-sulfonic acid

HRMS = high resolution mass spectrometry

^{i}Bu = *iso*-butyl

^{i}Pr = *iso*-propyl

IR = infra-red

Irgacure = 2-hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone

K_a = acid dissociation equilibrium constant

LAH = lithium aluminium hydride

LUMO = lowest un-occupied molecular orbital

m.p. = melting point

MA = methyl acrylate

MAA = methacrylic acid

MAO = methylaluminoxane

MCH = methylcyclohexane

*m*CPBA = *meta*-chloroperbenzoic acid

Me = methyl

MMA = methyl methacrylate

M_n = number average molecular mass

mol = moles

mol% = percentage equivalence by molar amount

MPV = Meerwein-Ponndorf-Verley

Ms = methanesulfonyl

MS = molecular sieves

M_w = mass average molecular mass

NADPH = nicotinamide adenine dinucleotide phosphate (reduced form)

NBS = *N*-bromosuccinimide

^{n}Bu = *n*-butyl

NMI = *N*-methylimidazole

NMR = nuclear magnetic resonance

nOe = nuclear Overhauser effect

NOESY = nuclear Overhauser effect correlation spectroscopy

oct = 2-ethylhexanoate

PDP = 1,1'-bis(2-pyridinylmethyl)-2,2'-bipyrrolidine

PET = poly(ethylene terephthalate)

Ph = phenyl

PMMA = poly(methyl methacrylate)

PPA = polyphosphoric acid

ppm = parts per million

PPN = bis(triphenylphosphine)iminium

psi = pounds per square inch

PTSA = *para*-toluenesulfonic acid

PTZ = phenothiazine

quant. = quantitative

r.t. = room temperature

RAFT = reversible addition-fragmentation chain transfer

R_f = retention factor

SEC = size exclusion chromatography

T3P® = 1-propanephosphonic acid cyclic anhydride

TBA = tetra-*n*-butylammonium

TBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene

^{t}Bu = *tert*-butyl

TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical

Tf = trifluoromethanesulfonyl

T_g = glass transition temperature

TGA = thermogravimetric analysis

THF = tetrahydrofuran

TLC = thin layer chromatography

TMNO = trimethylamine-*N*-oxide

TOF = time of flight

tris = 6,6',6''-(nitrilotris(methylene))tris(2,4-di-*tert*-butylphenolate)

Ts = *para*-toluenesulfonyl

TV = tele-vision

UV = ultra-violet

vac. = vacuum

VMA = vinyl methacrylate

w/w = mass to mass ratio

wt.% = percentage equivalence by mass

1. Introduction

1.1 Plastics and Polymers

1.1.1 The History of Plastics

From their commercial emergence as a household material in 1933 [1], plastics have since become ubiquitous in modern society. The range of potential applications for various different materials within this large family is almost limitless, and as such purposes are determined, the demand for these materials increases rapidly as time progresses. It is predicted that by 2050, there will be a demand for 1800 million tonnes of plastic worldwide during that year [2].

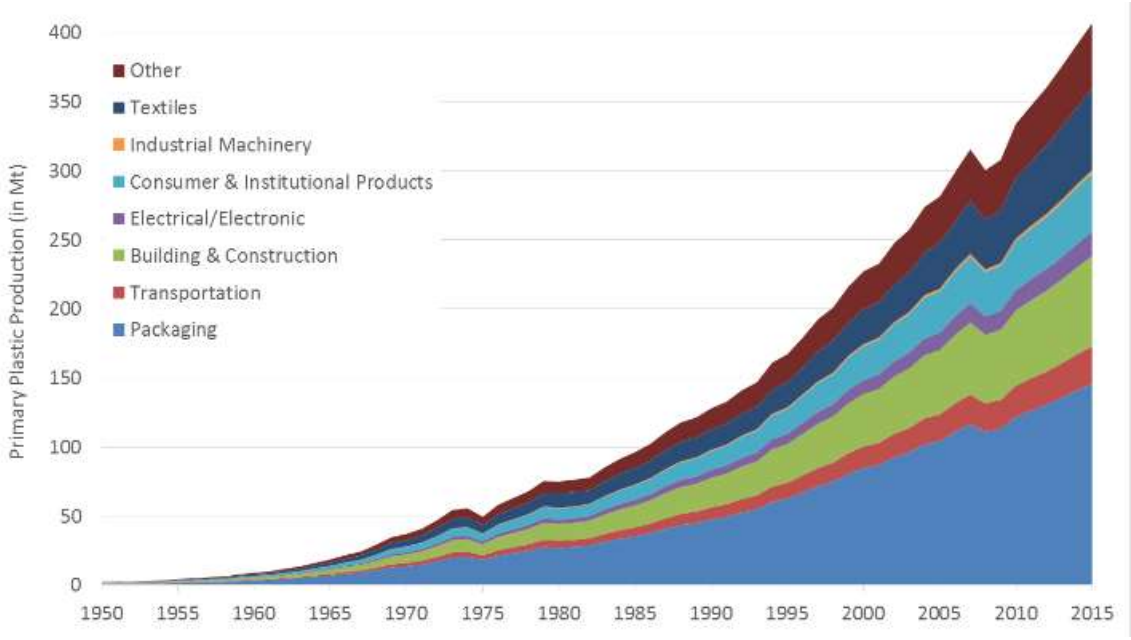


Figure 1. A graph depicting plastic production from 1950 to 2015, as well as a breakdown of the proportions of the different purposes that these materials were used for. Reproduced from the literature [3].

The universal nature of many of these materials is represented not only by the worldwide demand for plastic-based commercial products, but also the vast number of industries that require them in order to be able to carry out their purposes efficiently (Figure 1). Furthermore, as the lesser economically

developed countries of the world begin to industrialise their economies, the demand for plastics proliferates due to the requirement for these materials in more efficient industrial processes.

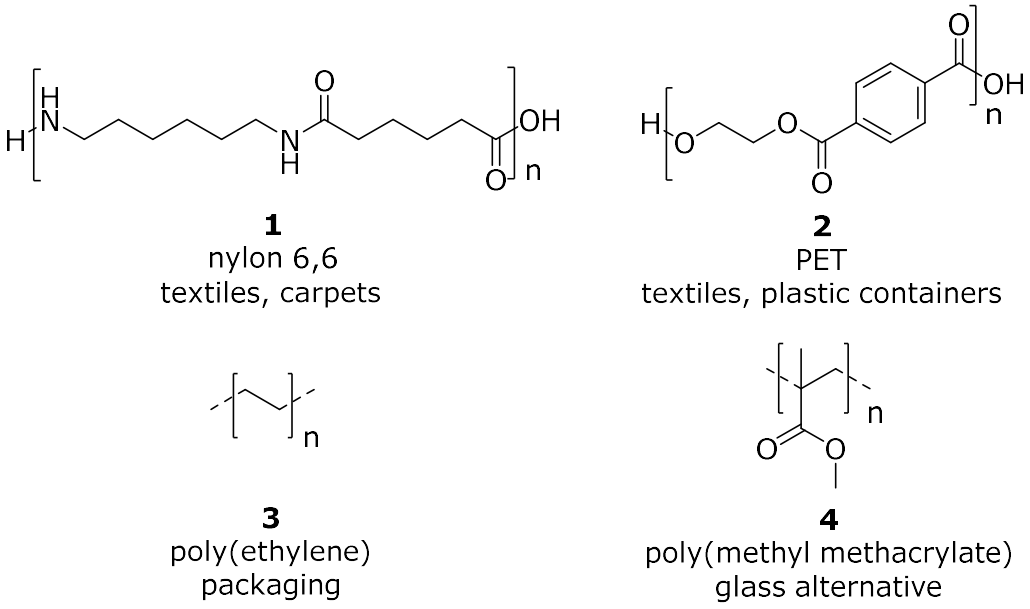


Figure 2. The structures of many of the polymers used in domestic applications, annotated with their major purpose.

Most initial developments in polymer science, and hence the range of plastics and materials containing them that became commercially available, were made during the 1930's, with companies such as ICI and Dupont becoming a major source for these new products. [4] Materials like nylon-6,6 (**1**), poly(ethylene terephthalate) (PET, **2**) and poly(methyl methacrylate) (PMMA, **4**) were all developed during this period [5], which have since found major uses in both industrial and domestic purposes (Figure 2).

1.1.2 Polymer Synthesis

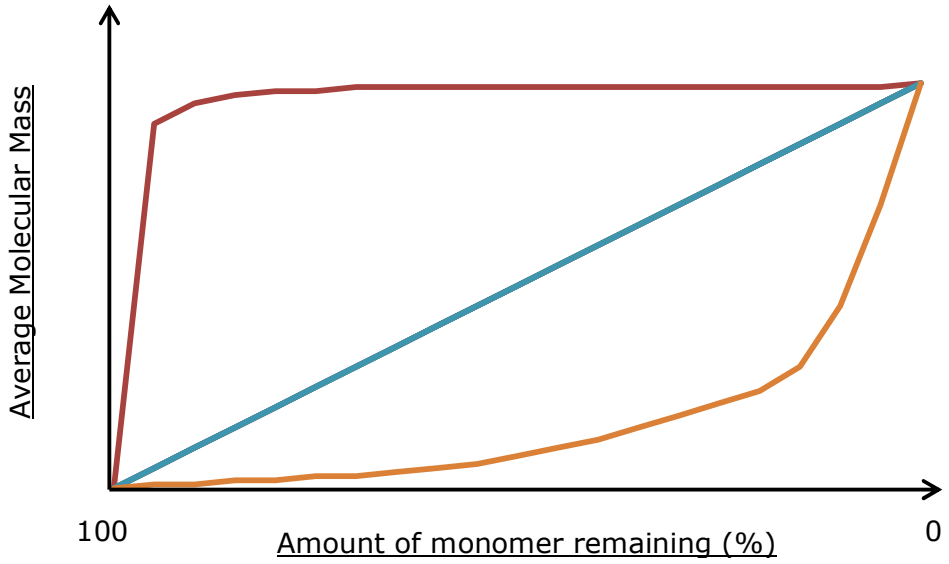
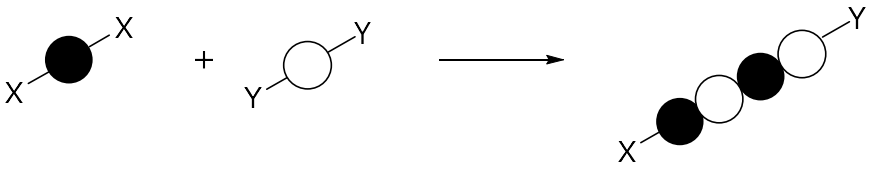


Figure 3. The average profiles of step-growth (orange), chain-growth (red) and "living" (blue) polymerisation synthesis methods, with the average molecular mass of the polymer chains present in the reaction mixture plotted against the amount of the starting monomer material remaining in the reaction mixture [6].

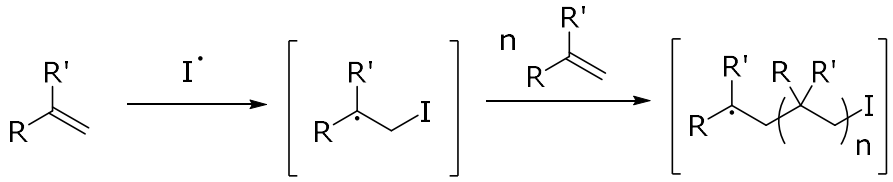
There are three major mechanisms of polymerisation, and these are known as step-growth (or condensation) polymerisation, chain-growth (or addition) polymerisation, and "living" (or controlled) polymerisation. Any synthesis of polymeric material can be attributed to one of these mechanisms by plotting the average molecular mass of the polymer against conversion of the starting monomer (Figure 3).



Scheme 1. The general reaction scheme for the synthesis of polymers via *step-growth (or condensation) polymerisation. X and Y represent complimentary reactive functional groups (e.g. amines and acid chlorides to synthesise polyamides).*

Step-growth polymerisation processes involve the condensation of monomers with two or more chemically reactive functional groups (alcohols, carboxylic acids, amines, acid chlorides, among many more) (Scheme 1). These polymerisations typically begin with the formation of dimers, then trimers, then tetramers, and so on until all of the monomer has been consumed.

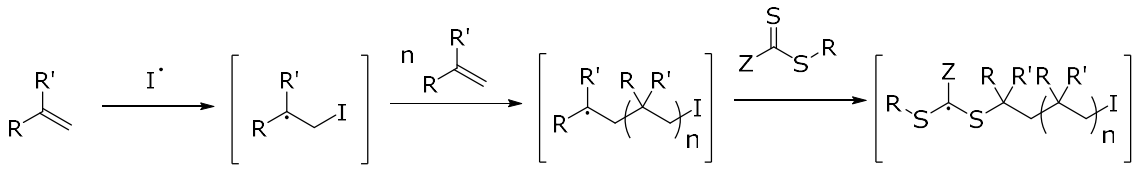
This means that the larger polymer chains are not formed until conversion reaches a high value (Figure 3, orange trace). As a result, the polydispersity (Đ) values of these polymers are most commonly high, indicating a broad distribution of molecular weights of the polymer chains.



Scheme 2. The general reaction scheme for the synthesis of polymers via *chain-growth (or addition) polymerisation.*

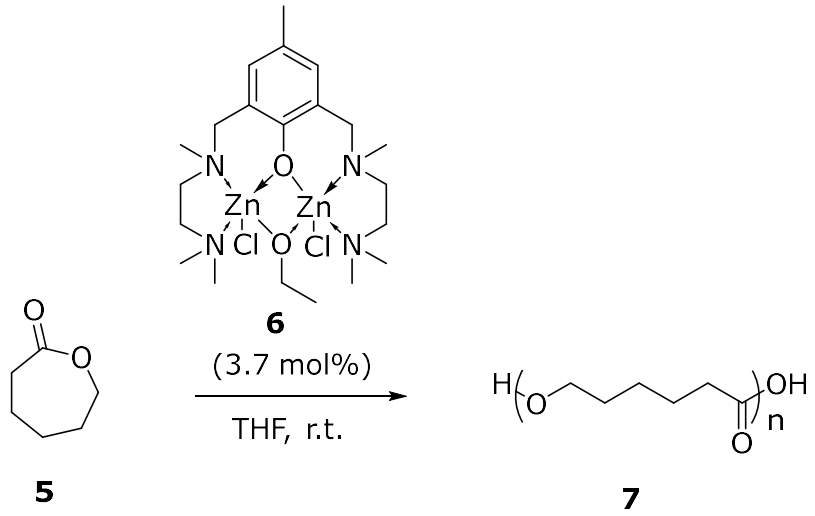
Conversely, chain-growth (or addition) polymerisation involves radicals, generated from reactive alkene-containing substrates (such as acrylate and methacrylate esters [7]) by a radical initiator, as the propagating species (Scheme 2). This can be split into three distinct processes: initiation (the generation of a radical-based monomer species using an external chemical initiator), propagation (the growth of the polymer chain through radical addition into further monomer molecules), and termination (radicals being removed from the system through various means).

Due to the reactive nature of radicals in general, large amounts of propagation occur at high monomer concentration, leading to the formation of high molecular weight materials at low conversion values (Figure 3, red trace). Again, this process also leads to reasonably high polydispersity values, although these tend to be slightly lower than analogous step-growth processes [8].



Scheme 3. The general scheme for a chain-growth polymerisation controlled by a dithioester RAFT agent – an example of a "living" polymerisation.

Finally, "living" polymerisation is defined by the molecular weight of the growing polymer chains increasing at a constant rate, allowing for greater control of the process, and hence a much lower polydispersity value (Figure 3, blue trace). In chain-growth polymerisations, this often involves the addition of a chain transfer additive which can control the rate of propagation by lowering the reactivity of the radical species [9]. One family of these additives are known as RAFT agents (Scheme 3) – dithioesters that intercept the propagating polymer chain radical to form a more stabilised intermediate, allowing for a much slower consumption rate of the monomer present [10].



*Scheme 4. The ring-opening polymerisation of ε-caprolactone (**5**), catalysed by **6**, a zinc(II) complex utilising a pentadentate phenolate ligand [11].*

Another "living" polymerisation process is ring-opening polymerisation – the use of a catalyst to cause opening of a lactone, lactam or other ring containing a reactive functional group, which then propagates. An example is the polymerisation of ε-caprolactone (**5**) using **6** as a catalyst (Scheme 4). [11] As there is only ever a substoichiometric amount of the ring-opened, propagating

intermediate at a low concentration, with only one reactive functional group able to perform the propagation, the average molecular weight also increases steadily with conversion and is classed as “living” polymerisation [12].

1.1.3 The Problems with Plastics



Figure 4. A graph depicting the potential scale of the issue of plastic waste in the environment in the future, with three different scenarios. Reproduced from the literature [13].

The massive scale on which plastics are produced, as well as the inherent stability of the materials, leads to significant challenges. Due to their stability, many plastics persist for inordinate amounts of time in the environment (Figure 4). [13] Those materials produced by step-growth procedures, such as polyesters and polyamides, contain functional groups that are widely found in nature, and can therefore be broken down by bacteria or other enzyme-containing organisms [14]. However, those that involve the formation of a substituted poly(ethylene) backbone – all examples that are produced by chain-growth processes, "living" or otherwise – are much more persistent. Indeed, the literature contains only a select few examples of the successful deconstruction of this (poly)ethylene backbone [15]. As a result, waste plastic builds up to such levels that entire ecosystems begin to detrimentally change – an issue that has been highlighted in many forms of mainstream media in recent years, with the Blue Planet TV series presented by David Attenborough at the forefront.

Another issue arising from the sheer scale of plastic production, is the source of the feedstocks required for synthesis of the materials. 7% of crude oil production currently is used for the production of plastic materials [16]. Conversely however,

over 99% of plastics arise from crude oil – a material that is currently very cheap at approximately $40 per barrel, especially due to the recent global coronavirus crisis, but is also a non-renewable resource [17]. Estimates of the size of crude oil reserves change readily, due to the discovery of new oil wells across the globe, but this value is thought to be in the region of 45 years supply at their current level [18]. However, the status of this is clear – crude oil will eventually be depleted, and an alternative source for these materials, so crucial to modern society, will have to be discovered.

1.2 Bioplastics

1.2.1 An introduction to bioplastics

There are many possible feedstocks for plastics which could be considered as renewable, and this is not a new concept, with many literature reviews available on the subject [19-21]. Indeed, polymers that have been entirely sourced from such feedstocks are found abundantly in nature, in the form of proteins and polysaccharides. However, in order to generate materials with the required properties for specific functions in society, alternative starting compounds and polymer synthesis methods need to be explored, as naturally occurring polymers often do not match a lot of these requirements.

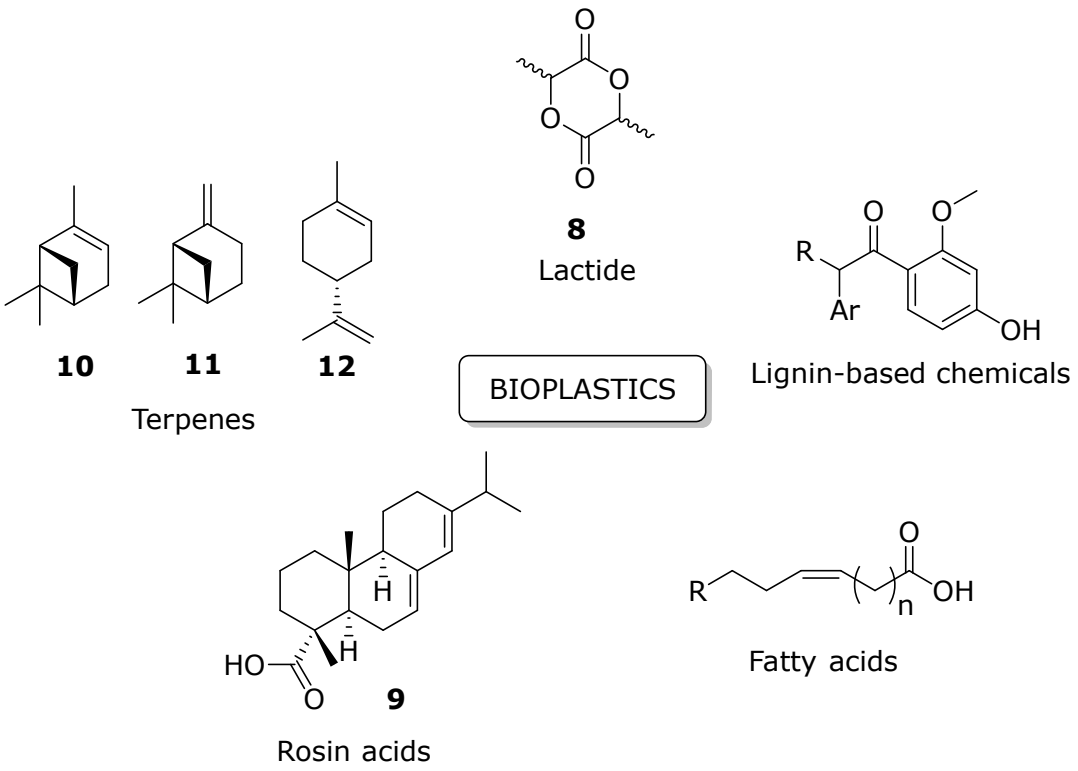
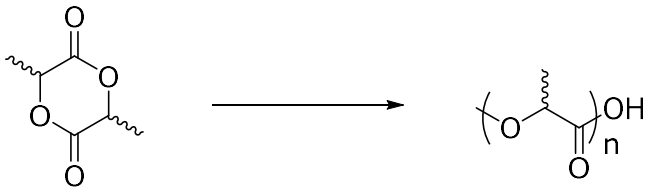


Figure 5. An example of some renewable feedstocks that can be used to create bioplastics.

A selection of the options available for use as feedstocks for renewable bioplastics are shown in Figure 5, with each example detailed in literature reviews for their use as bioplastic starting materials [22-24].

1.2.2 Lactide



8 **13**

*Scheme 5. The homopolymerisation of lactide (**8**) to form polyester **13**.*

One of the most extensively researched bioplastics involves the polymerisation of lactide (**8**), the dimer of lactic acid, using ring-opening polymerisation methods (Scheme 5). Lactide is produced on a scale of 300 kT per annum, sourced from mainly bacterial fermentation on an industrial scale. [25] However, poly(lactide) (**13**) unfortunately suffers from limited uses as a plastic, due to problems with thermal degradation of the material at relatively low temperatures, compared to other alternatives [26]. Also, despite the range of properties that can be achieved by varying the degree of polymerisation in the material [27], there are applications which require entirely different physical behaviour, such as those that need to have high tensile strength. This means additional alternatives to **13** would also need to be explored in order to satisfy societal demands for bioplastics.

1.2.3 Lignin-based chemicals

Lignin is a collection of phenol-based compounds obtained from the breakdown of polymeric material obtained from wood-based feedstocks. This is a significant advantage over other feedstocks in that production of this material would not directly interfere with food supply. As part of the "food versus fuel" debate that is often mentioned with both biofuels and bioplastics [28], arable land would not need to be used in this instance.

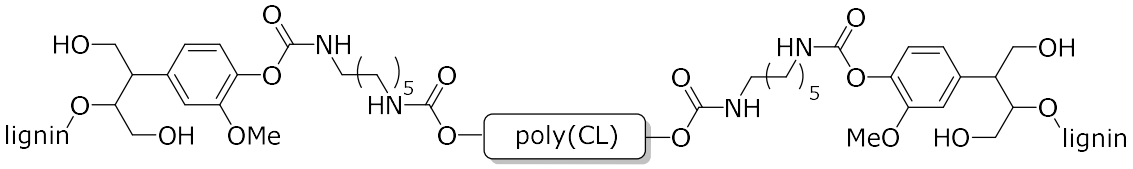
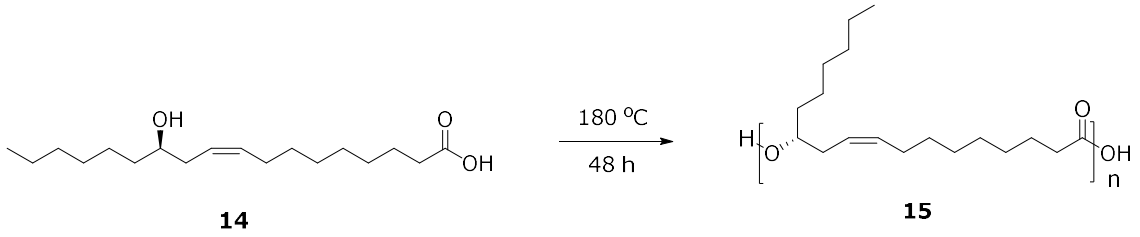


Figure 6. An example of a bioplastic incorporating a lignin-based structure along with poly-caprolactone, linked together by urethane functionalities. [29]

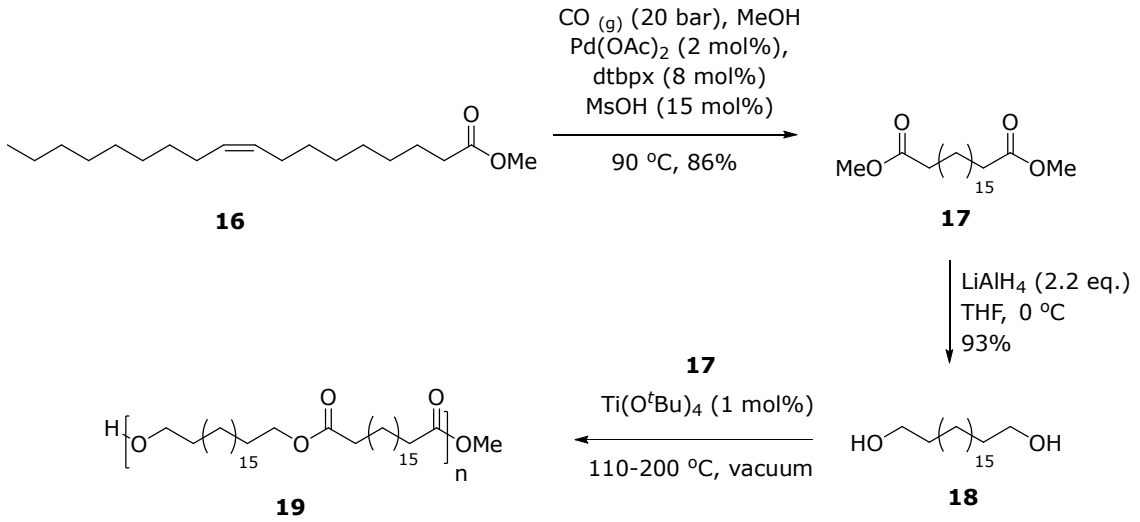
An example of bioplastic production from lignin biomass is shown in Scheme 6. [29]. The main issue with using lignin as a feedstock for renewable materials is that they are often hard to characterise, due to the complex nature of the starting material. As a result, it is then difficult to tailor properties of resulting polymers, and often lead to materials which are difficult to replicate many times over due to the erratic nature of the lignin-based structures. [30]

1.2.4 Fatty Acids



14 **15**

*Scheme 6. Formation of a renewable polyester **15** from **14**, sourced from castor oil.* [31]



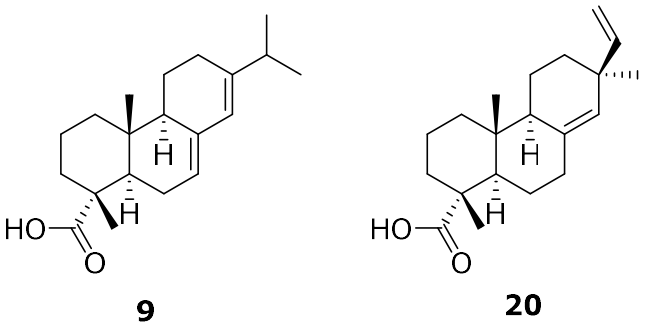
16 **17** **17** **19** **18**

Scheme 7. An example of the synthesis of renewably sourced monomers and subsequent polymers from fatty acids. [32]

Plant-based oils offer another alternative feedstock, as they contain a variety of triglycerides – three medium to long chain carboxylic acids attached to glycerol via ester linkages. Depending on the source of these oils, the corresponding hydrolysis of the triglycerides can yield a multitude of different acid species. In a limited number of cases, these fatty acid molecules can contain two reactive functional groups suitable for polymerisation – for example, **14** (Scheme 6) which contains a hydroxyl group in addition to the carboxylic acid and can be used to make polyesters. [31] Alternatively, such reactive functionalities can be introduced into the molecules using chemical modifications, such as the example in Scheme 7, using di-ester **17** and diol **18**. [32]

The issue with using fatty acids as large-scale feedstocks for renewable polymers is that the crops that provide the oils needed for extraction of these materials often compete with the land required for farming edible crops. As food shortages are predicted to become ever more common with the passing of time, with 24% of children in Asia and sub-Saharan Africa predicted to be malnourished in 2050 [33], this is a problem that may hinder the progress of bioplastic research in this area.

1.2.5 Rosin Acids



9 **20**

*Figure 7. The structure of some examples of rosin acids, abietic acid (**9**) and pimaric acid (**20**), available in nature.*

Rosin acids offer another option for potential bioplastic production (Figure 7). Like fatty acids, these materials contain a carboxylic acid group in conjunction with several alkenes. Direct esterification of these alkenes, or their conversion into alcohols *via* a Brown hydroboration/oxidation prior to esterification, could potentially allow the production of polyesters from these starting materials.

Unfortunately, the problem with the use of rosin acids on a large scale is that they are not produced in large quantities in nature when compared with other bioplastic options. Most of the rosin acids come from crude tall oil and the scale of rosin acid production is 300 kg annually in North America, with the majority of this going towards the production of diesel additives [34]. Therefore, achieving the amounts required for mass polymer production would be a significant challenge. Also, the structures within the family of rosin acids are reasonably limited, and providing a multitude of materials with different properties would also be difficult – however some examples are documented in the literature. [35-36]

Rosin acids are synthesised in nature from isoprene, a ubiquitous starting material which is also the source of many other compounds found in nature, forming the terpenes family. It is this wider family that gives a lot more options for the production of bioplastics from isoprene-based materials.

1.3 Terpenes

1.3.1 An Introduction to Terpenes

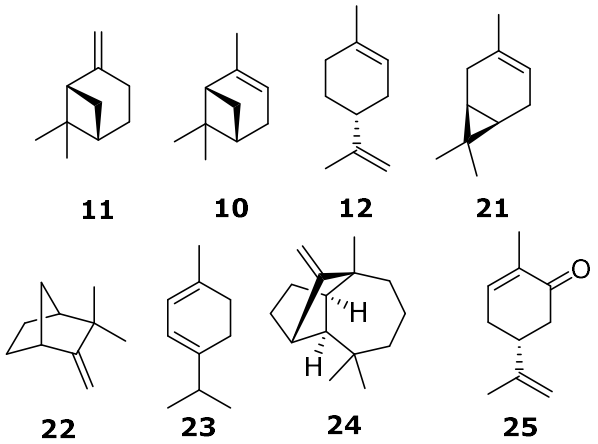


Figure 8. The structures of some of the most abundant monoterpenes, sesquiterpenes and related terpenoids.

Terpenes are a broad family of hydrocarbon species found as secondary metabolites in a multitude of plants, and as mentioned previously, are biosynthesised from isoprene. By far the most abundant moieties of this family are monoterpenes, which involves the use of 2 units of isoprenyl pyrophosphate to synthesise, and have the general formula $C_{10}H_{16}$. Some of the most abundant of this sub-family of compounds include β-pinene (**11**), α-pinene (**10**), limonene (**12**), 3-carene (**21**), camphene (**22**), and α-terpinene (**23**) (Figure 8).

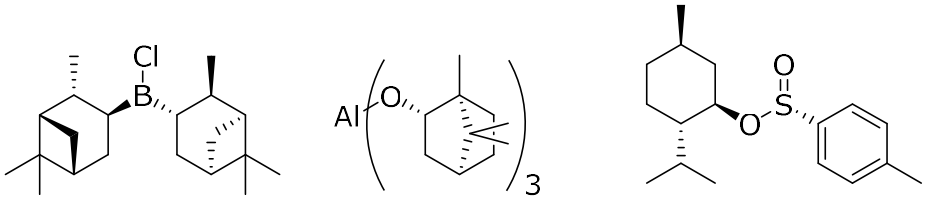
Further, less common examples include sesquiterpenes (such as α-longifolene (**24**)), diterpenes and triterpenes, made from 3, 4 and 6 units of isoprenyl pyrophosphate respectively, with the latter most commonly associated as biosynthetic precursors to steroids. [37] Steroids and other such oxidised variants of terpenes, such as carvone (**25**), can also be referred to as terpenoids.

Most terpenes are isolated in the largest quantities from turpentine, although other sources, such as citrus peel oil for the isolation of **12**, also exist. Turpentine is extracted from various species of pine trees, and as a result is a common waste stream from the industrial production of paper. Similarly, **12** and **25** are obtained from citrus peel oil and spearmint oil respectively, which are

also waste streams of the citrus juice and mint flavouring industries. [38] The fact that these materials can be obtained from waste streams of industries that already operate on a large scale is a significant advantage. This ensures the supply of these materials is plentiful, and available at very low cost. In addition to this, the most common method of disposing of these waste streams currently is incineration – therefore using these species as renewable feedstocks for bioplastics has a significant positive environmental impact.

1.3.2 Terpenes in Organic Chemistry

Due to their interesting structures, terpenes have been extensively studied in the chemical literature. The unique rearrangement chemistry that the family of compounds is associated with, especially with regards to carbocation intermediates, was the focus of many studies by Meerwein [39-40]. The understanding in this area was then further expanded with the advent of ^{13}C NMR spectroscopy, in which these proposed carbocation intermediates could actually be observed using this technique [41-42].



26 **27** **28**

Figure 9. The structures of some terpene-based reagents used in organic synthesis for various transformations.

Some specific reagents have also been developed with terpene-based components, which have been used for asymmetric transformations in organic chemistry. Examples of these include DIP-Cl (**26**) and tri-isobornylaluminium(III) (**27**) (Figure 9), which can be used for the asymmetric reduction of functional groups such as ketones. [43-44] Menthol can also be used to generate Andersen's auxiliary (**28**), a chiral reagent used for the synthesis of enantiomerically enriched sulfoxides and sulfinimines [45-46].

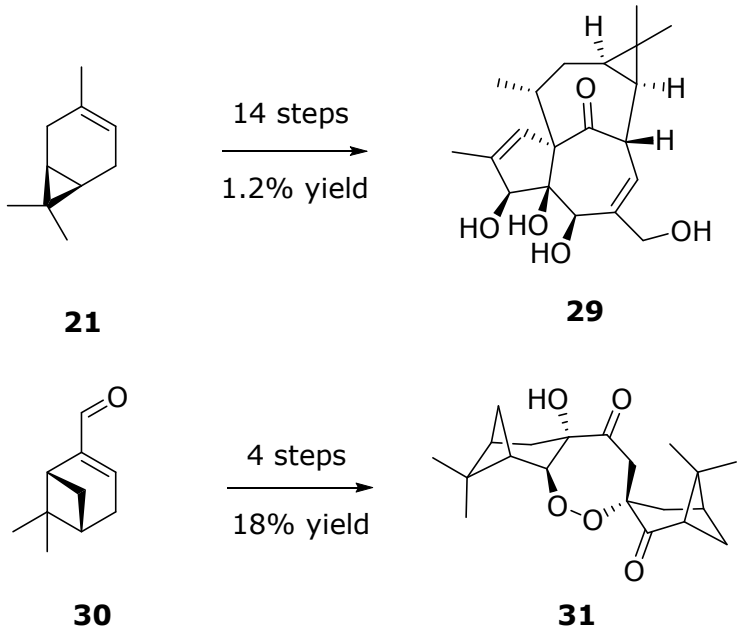
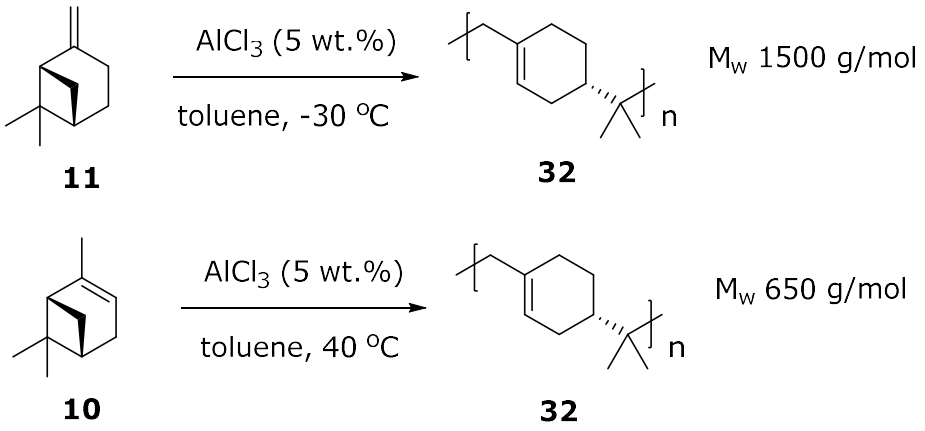


Figure 10. Some examples of total syntheses starting from monoterpenes.

Due to the presence of chiral centres in the terpene moieties, the compounds are considered part of the "chiral pool" [47] – a term referring to molecules obtained from nature which already contain asymmetry and can be used to produce more complex targets with the chirality carried through the syntheses. Examples of this include the total synthesis of ingenol (**29**) from **21**, [48] and cardamom peroxide (**31**) from myrtenal (**30**) (Figure 10). [49] α-Longifolene (**24**) was also the target of total synthesis in earlier literature reports. [50]

However, for the purpose of this study, the polymer chemistry that terpenes exhibit is interesting. With the presence of substituted alkenes and small rings in the chemical structures of the compounds, the provision of potential cationic ring opening polymerisation, or radical-mediated polymerisation is possible.

1.4 Polymers from Terpenes

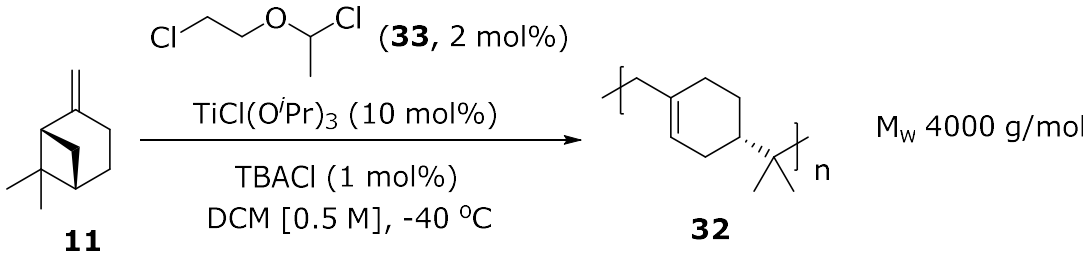


*Scheme 8. The homopolymerisation of β-pinene (**11**) and α-pinene (**10**) using aluminium chloride as a catalyst.* [51]

Attempts at direct homopolymerisation of terpenes have been conducted as early as 1950, when Roberts and Day trialled a cationic ring-opening polymerisation of β-pinene (**11**) and α-pinene (**10**) using aluminium chloride as the Lewis acid catalyst (Scheme 8). [51] **11** required a temperature of −30 °C to achieve full conversion to **32**, yet only achieved an average molecular weight (M_w) value of 1500 g/mol. Conversely, the subjection of **10** to the optimised polymerisation conditions for this substrate, which required a temperature of 40 °C, only achieved a maximum conversion value of 35%. This was mainly due to the formation of a dimeric species, which was unable to propagate further under the reaction conditions. Additionally, the material obtained provided a M_w value of 650 g/mol, indicating the material was unlikely to progress beyond oligomeric species.

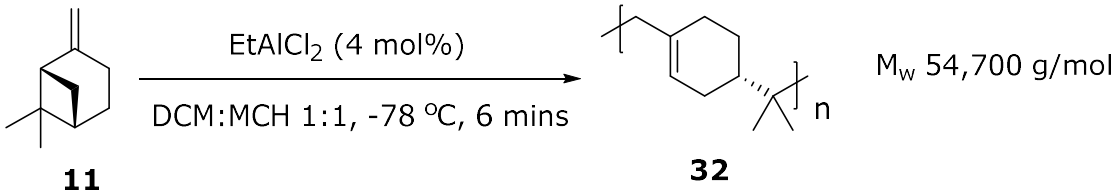
1.4.1 Polymers from β-pinene

The direct homopolymerisation of β-pinene has been a topic that has been investigated thoroughly in the literature, and a review has been published that involves the topic. [52] The substrate contains a reactive exo-methylene double bond that can be used to initiate ring-opening polymerisation with an acidic catalyst – with Lewis acids being the most commonly used catalytic species.



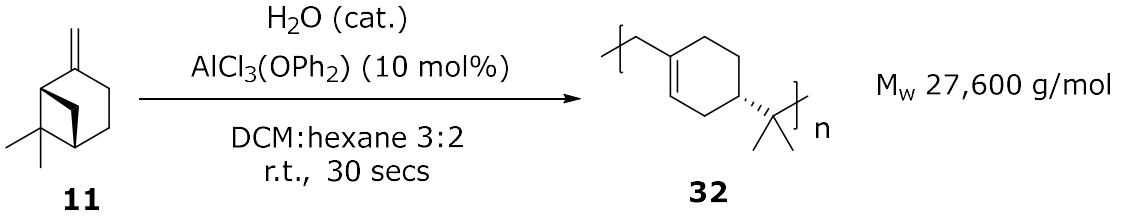
*Scheme 9. The synthesis of a polymer (**32**) from **11** using a titanium-based Lewis acid catalyst, in conjunction with substoichiometric amounts of **33** and TBACl.* [53]

In 1997, Lu and co-workers documented the use of chlorotri-*iso*-propoxytitanium(IV) as a Lewis acid catalyst for the polymerisation of **11**, using **33** and TBACl as co-catalysts (Scheme 9). [53] At −40 °C, a polymer with a M_w value of 4000 g/mol was obtained with a polydispersity (Đ) value of 1.3, indicating a reasonable degree of control occurs in the process. The authors also noted that the use of TBACl as a co-catalyst was crucial for both achieving conversion values above 70%, and also for attaining low polydispersity values in the resulting materials. However, these conditions involve relatively high catalyst stoichiometry, and the reaction mixture is dilute (0.5 M) when compared to other standard polymerisation procedures (typically in excess of 2 M).



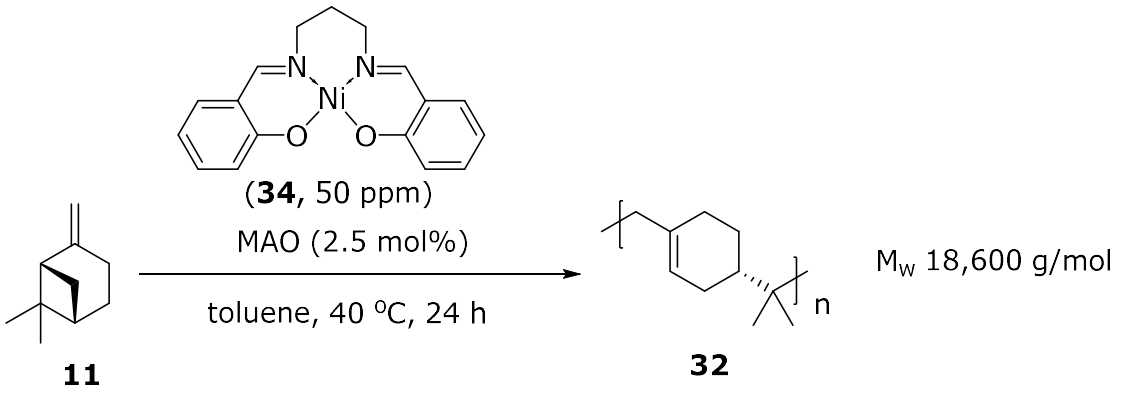
*Scheme 10. The synthesis of a polymer from **11** with a M_w value of over 50,000, using ethylaluminium dichloride as a catalyst.* [54]

Truly high M_w values for the polymerisation of **11** remained elusive until 2006, when Satoh and co-workers identified a protocol for the synthesis of a polymer from **11** with a recorded M_w of 54,700 g/mol (Scheme 10). [54] The material produced had a polydispersity value of 2.18, therefore the process occurs with a lesser degree of control than the previous example (Scheme 9). Due to the high degree of polymerisation, a clearly defined glass transition temperature (T_g) of 90 °C for the product could also be determined – a rare instance for a terpene-based homopolymer.



*Scheme 11. The synthesis of a polymer from **11** using aluminium chloride diphenyl ether complex as a catalyst, in just 30 seconds.* [55]

In 2011, a procedure was developed that was based on the original conditions used by Roberts and Day (Scheme 8) to generate a polymer from **11** with a much improved M_w of 27,600 g/mol (Scheme 11). [55] Using a stabilised complex of aluminium chloride and diphenyl ether, at an increased catalytic loading of 10 mol% compared to the original conditions [51], allowed the polymerisation to proceed to high conversion at room temperature in just 30 seconds. The product had a polydispersity value of 2.05, which is typical for polymerisation processes without additional species such as chain transfer agents [56]. A T_g value of 86.5 °C for the resulting material was also recorded.

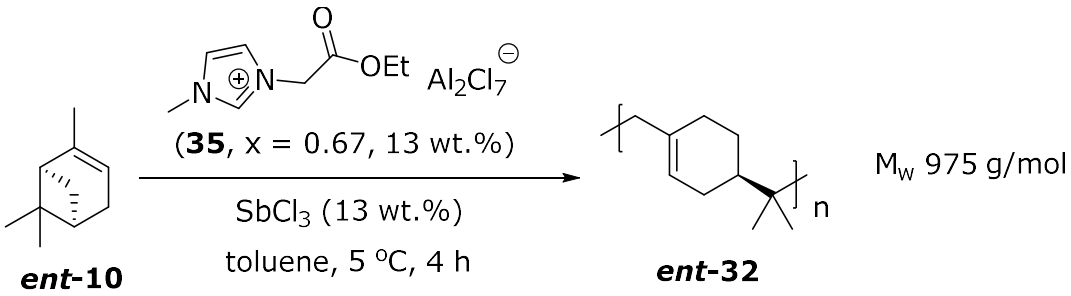


*Scheme 12. The synthesis of a polymer from **11** using a nickel-salen complex (**34**) as a catalyst, and MAO as an initiator.* [57]

Chloride salts of aluminium and titanium are not the only species that can induce cationic ring-opening polymerisation of **11** however. Yu and co-workers produced a polymer with a M_w of 18,600 g/mol and a polydispersity value of 1.70 using just 50 ppm of a nickel-based salen catalyst (**34**), in conjunction with 2.5 mol% of MAO as an initiator (Scheme 12). [57] While using relatively mild conditions for a cationic ring-opening polymerisation, no T_g was reported for the material, meaning the degree of polymerisation is not quite as high as desired. Furthermore, the use of MAO as an initiator adds considerable cost to the process as a whole. [58]

1.4.2 Polymerisation of α-pinene

As previously discussed (Scheme 9), the polymerisation of **10** proves even more difficult than that of **11**, due to the more stable, tri-substituted internal alkene present in the structure. However, this has not dissuaded some researchers, and some attempts have been reported in the literature since the original study.



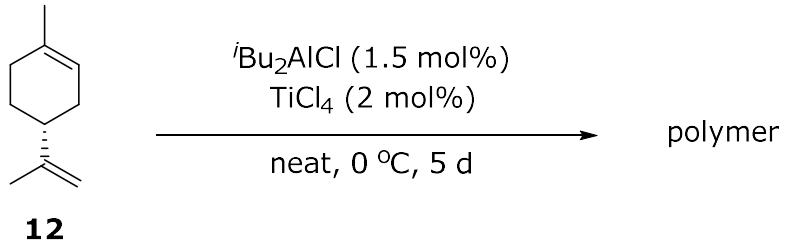
Scheme 13. The synthesis of a low molecular weight polymer from **ent-*10*** *using an aluminium chloride based ionic liquid, in conjunction with antimony(III) chloride, as the catalyst and additive respectively.* [59] *x refers to the molar fraction of* $AlCl_3$ *present in the ionic liquid.*

Liu and co-workers documented the use of an ionic liquid containing aluminium chloride (**35**) in a process attempting to polymerise ***ent*-10** (Scheme 13). [59] The procedure managed to initiate polymerisation, but only resulted in a material with an average molecular weight of 975 g/mol – slightly better than the degree of polymerisation achieved in the study by Roberts and Day. The authors managed to measure a value for the softening point of the material, which was found to be 116 °C.

Another attempt at α-pinene polymerisation was conducted in the gas phase, using an aerosolised buffer mixture of ammonium sulfate and sulfuric acid. [60] Unfortunately, no parameters such as molecular weight or polydispersity were published along with this study.

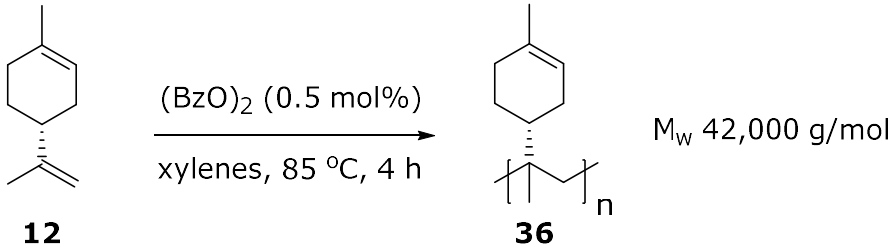
1.4.3 Attempts at polymerisation of limonene

Homopolymerisation of limonene (**12**) is also under-represented in the literature, due to the challenges it poses in polymerisation reactions. With no driving force from the opening of a strained 4-membered ring in this case, cationic polymerisation is exceedingly difficult. Therefore, chain growth addition polymerisation using radical initiators tends to be the most employed procedure for polymerisation attempts involving **12**.



Scheme 14. The attempted cationic homopolymerisation of limonene using Ziegler-type Lewis acidic catalysis. [61]

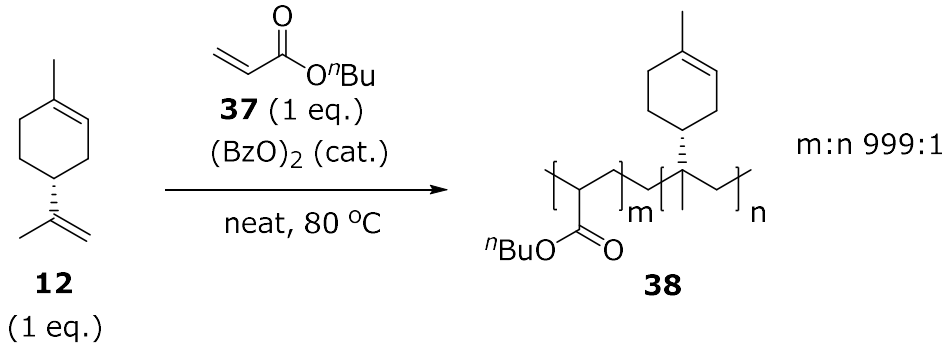
One of the earliest attempts at homopolymerisation of limonene was conducted by Modena and co-workers in 1965 (Scheme 14). [61] The procedure involved cationic polymerisation through a combination of aluminium and titanium based catalysts, and achieved 67% monomer conversion. The material produced did not have the structure, M_w, polydispersity or T_g values reported however.



*Scheme 15. The attempted radical-mediated polymerisation of **12** at 85 °C using benzoyl peroxide as an initiator.* [62]

Singh and Kamal have reported the radical polymerisation of **12** to form a polymer with a M_w value of 42,000 g/mol (Scheme 15). [62] However, the NMR and GPC analyses presented in this report raise some doubts as to whether this degree of polymerisation was actually achieved. Literature found elsewhere also

backs up the fact that these results may not be as good as they appear, as limonene is often used as a chain transfer agent in radical polymerisations [63]. Therefore, the observed M_w value of 42,000 g/mol may not be entirely reproducible.



*Scheme 16. The attempted radical co-polymerisation of **12** and* n*-butyl acrylate (**37**) using benzoyl peroxide as an initiator.* [64]

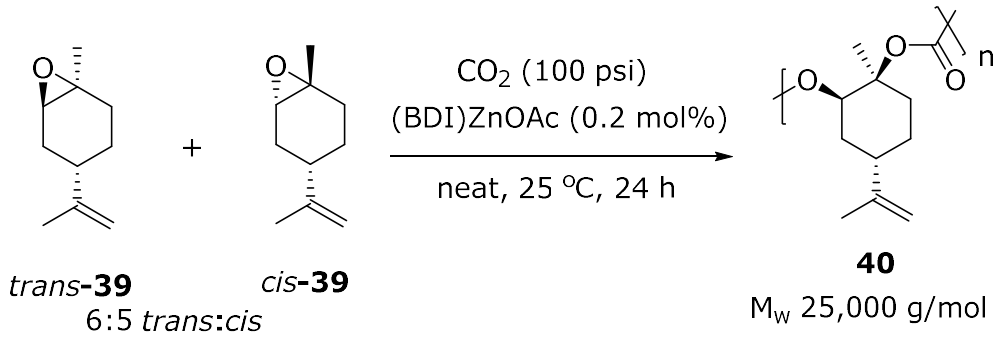
An attempt to co-polymerise **12** with *n*-butyl acrylate (**37**), in equal stoichiometries, was conducted by Ren and co-workers (Scheme 16). [64] Unfortunately, when the two monomers were subjected to the reaction conditions, the product contained only 0.1% limonene. Poor uptake of the terpene moiety in the final polymer product is a common problem when trying to co-polymerise terpenes with other, more efficient monomers such as maleic anhydride, isobutene and styrene. [65-67]

1.5 Organic Modification of Terpenes for the Synthesis of Terpene-Derived Polymers

With reports of successful homopolymerisation of terpenes being limited in the literature, and the resulting materials produced from these examples having a narrow distribution of properties, a new approach for the synthesis of terpene-based polymers was required. As many of the terpene structures contain alkene functional groups, it is feasible to use organic chemistry techniques to introduce further functionality into the molecules, which would allow polymerisation processes to occur more reliably.

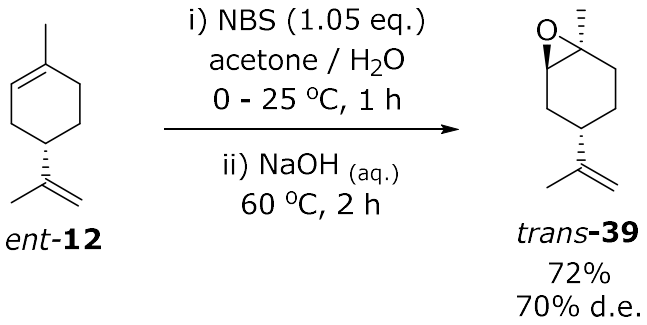
This is an approach that has been gaining popularity significantly throughout the past decade, with a large variety of different polymer structures being generated from the same group of starting materials. As a result, the organic modification of terpenes for the synthesis of new bio-based polymers is a subject covered by many recent reviews. [52, 68–69].

1.5.1 Polycarbonates



Scheme 17. The synthesis of a polycarbonate from a commericially available mixture of trans-***39 and*** cis-***39****, plus carbon dioxide under pressure, using a bis-diiminate zinc complex as a catalyst.* [70]

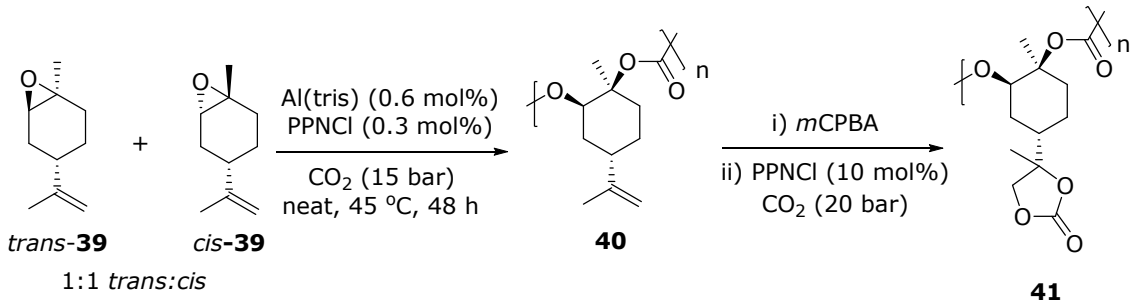
A process was developed by Coates and co-workers to synthesise a polycarbonate from a commercially available diastereomeric mixture of limonene oxide (**39**) and carbon dioxide under pressurised conditions (Scheme 17). [70] Interestingly, the resulting polymer was formed entirely from the *trans*- isomer, with *cis*-**39** remaining unreacted during the process. The resulting polymer displayed a M_w value of above 25,000 g/mol when reacted for 24 hours, with a well-controlled polydispersity of 1.19.



Scheme 18. The optimised synthesis of trans-***39*** *on a kilogram scale.* [71]

As *cis*-**39** was unreactive, a new approach to the synthesis of *trans*-**39** from the much cheaper and more readily available *ent*-**12**, on a reasonable scale suitable for polymerisation, was required in order to enhance the impact of the work of Coates and co-workers. As a result, Hauenstein *et al.* developed a low cost, kilogram scale synthesis of *trans*-**39** with the desired isomer formed in 70% d.e.

(Scheme 18) [71]. A more detailed set of properties for the resulting polymer **40** was also published in this report.

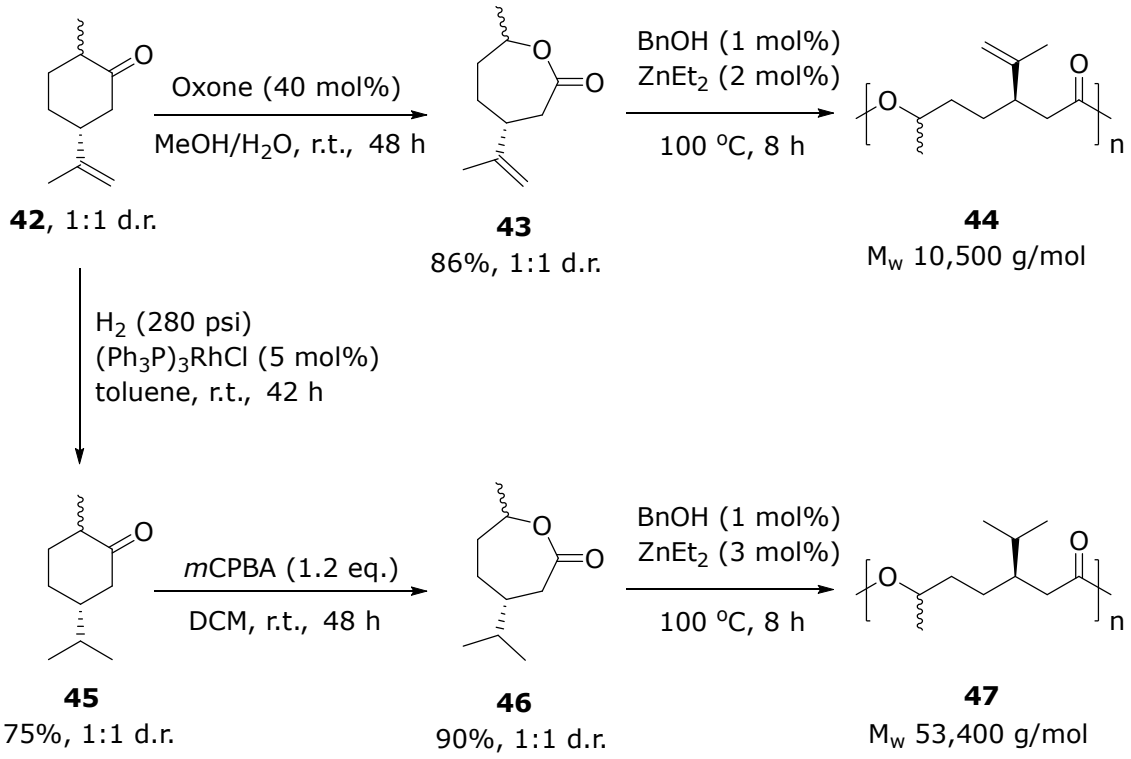


*Scheme 19. The polymerisation of a diastereomeric mixture of **39** using an aluminium-based catalyst, followed by post-polymerisation modification of **40** to introduce a further carbonate functionality.* [72]

Further expansion on the application of this chemistry was published by Kindermann and co-workers, who used an aluminium complex to polymerise a diastereomeric mixture of **39** (Scheme 19), with the *cis*- isomer again being unreactive. [72] Post-polymerisation modifications were then carried out on **40** to introduce a second carbonate functionality from the pendant alkene groups in the polycarbonate material. These modifications caused the final polymer product **41** to have an observed T_g value of 180 °C. Furthermore, the carbonate functionality could be modified further if desired, potentially leading to complex polymer architectures through cross-linking with other reactants [73].

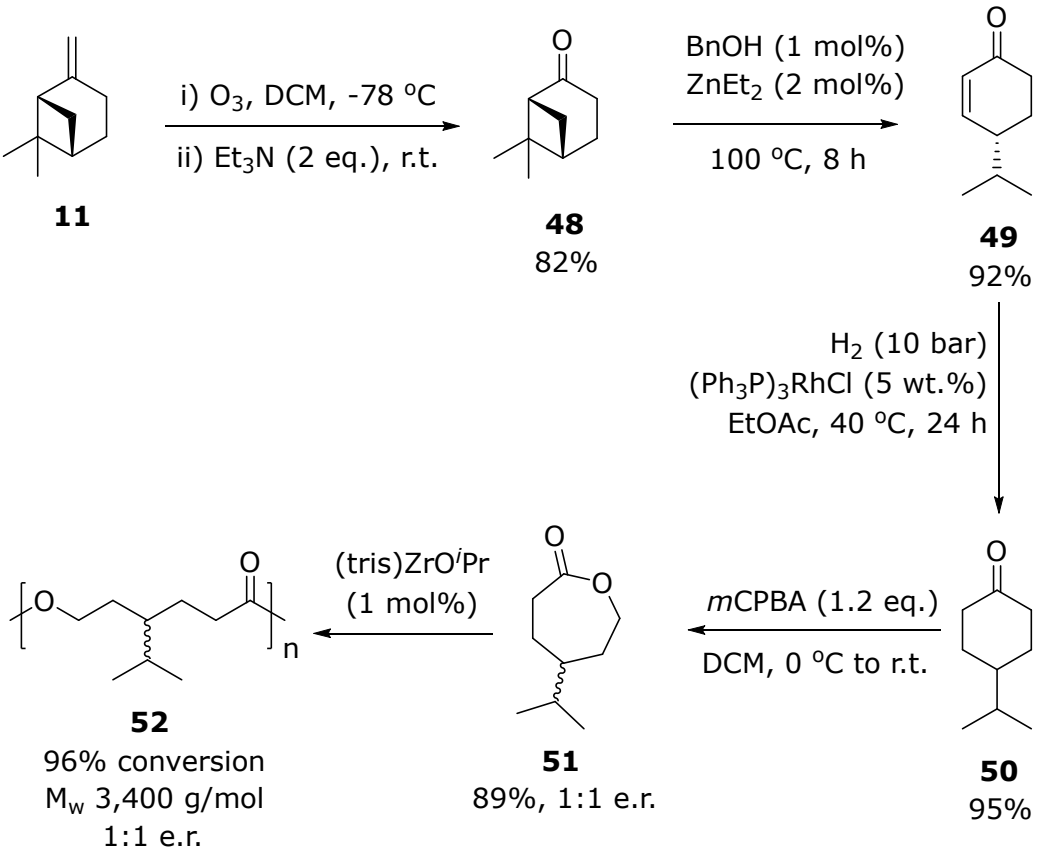
1.5.2 Polyesters

Polyesters synthesised from terpenes have also been investigated significantly, due to the variety of reactions which can install oxygen-containing functionalities into alkene containing substrates.



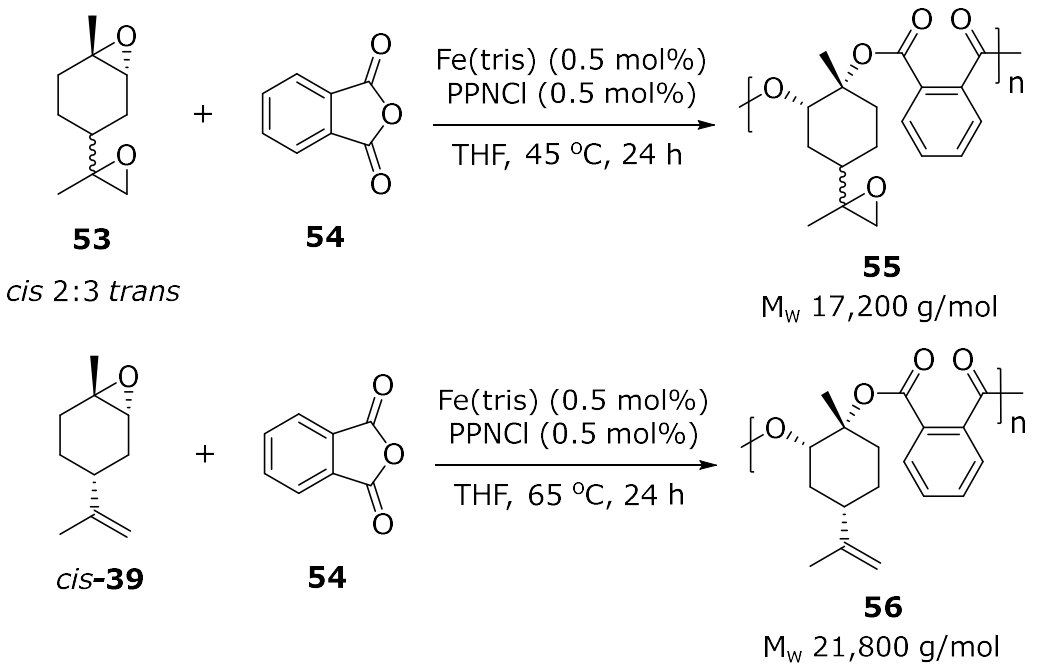
*Scheme 20. The synthesis of corresponding polyesters from two different ε-lactones **43** and **46**, both synthesised from a diastereomeric mixture of dihydrocarvone (**42**).* [74]

Lowe and co-workers synthesised two different 7-membered lactones from a common starting material **42** (Scheme 20) [74] – a terpenoid isolated primarily from spearmint oil [75]. Direct Baeyer-Villiger oxidation of **42** and subsequent polymerisation furnished one polyester **44**. The second polyester **47** was synthesised by hydrogenation of **42**, followed by Baeyer-Villiger oxidation and subsequent polymerisation. Polyester **44** exhibited an M_w value of 10,500 g/mol and a T_g of −20 °C, while polyester **47** showed an M_w of 53,400 g/mol and a T_g of −27 °C. In both cases, the polymerisations gave products with polydispersity values lower than 1.3, showing the process had a high degree of control.



*Scheme 21. The synthesis of ε-lactone **51** in 4 steps from **11**, followed by a zirconium-catalysed ring-opening polymerisation.* [76]

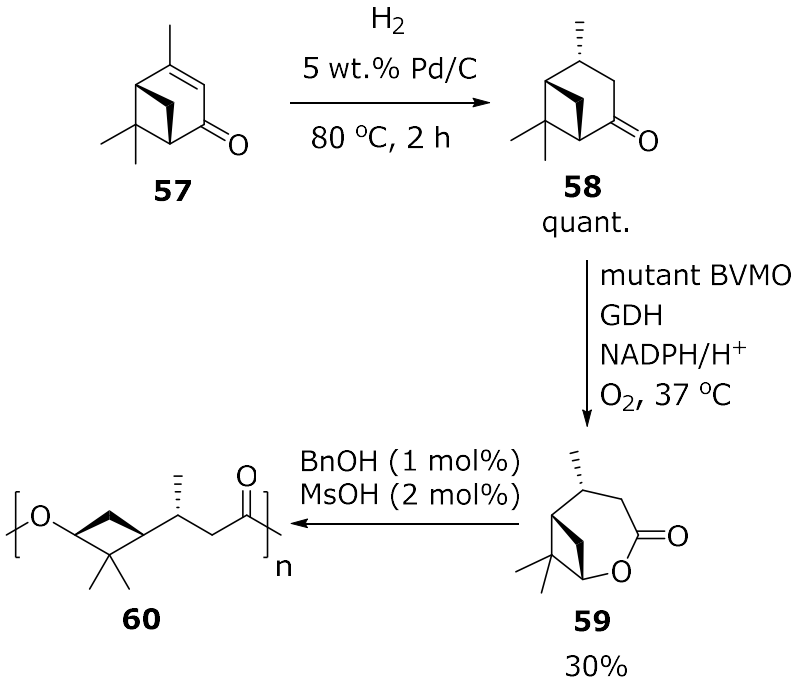
Quilter and co-workers have also documented formation of a polyester from a terpene-based ε-lactone **51**, synthesised in 4 steps from **11** (Scheme 21). [76] Each synthetic step in the route had a yield of at least 82%, and could be performed on a multi-gram scale – both factors which greatly enhance the route's use for preparing sufficient quantities for polymerisation. A zirconium-based tris(phenolate) complex was used as the polymerisation catalyst, generating polymer **52** with excellent conversion. The resulting material displayed an M_w of 3400 g/mol and a Đ value of 1.57.



*Scheme 22. The synthesis of partially terpene-based polyesters from phthalic anhydride **54**, and* cis***-39** or **53**.* [77]

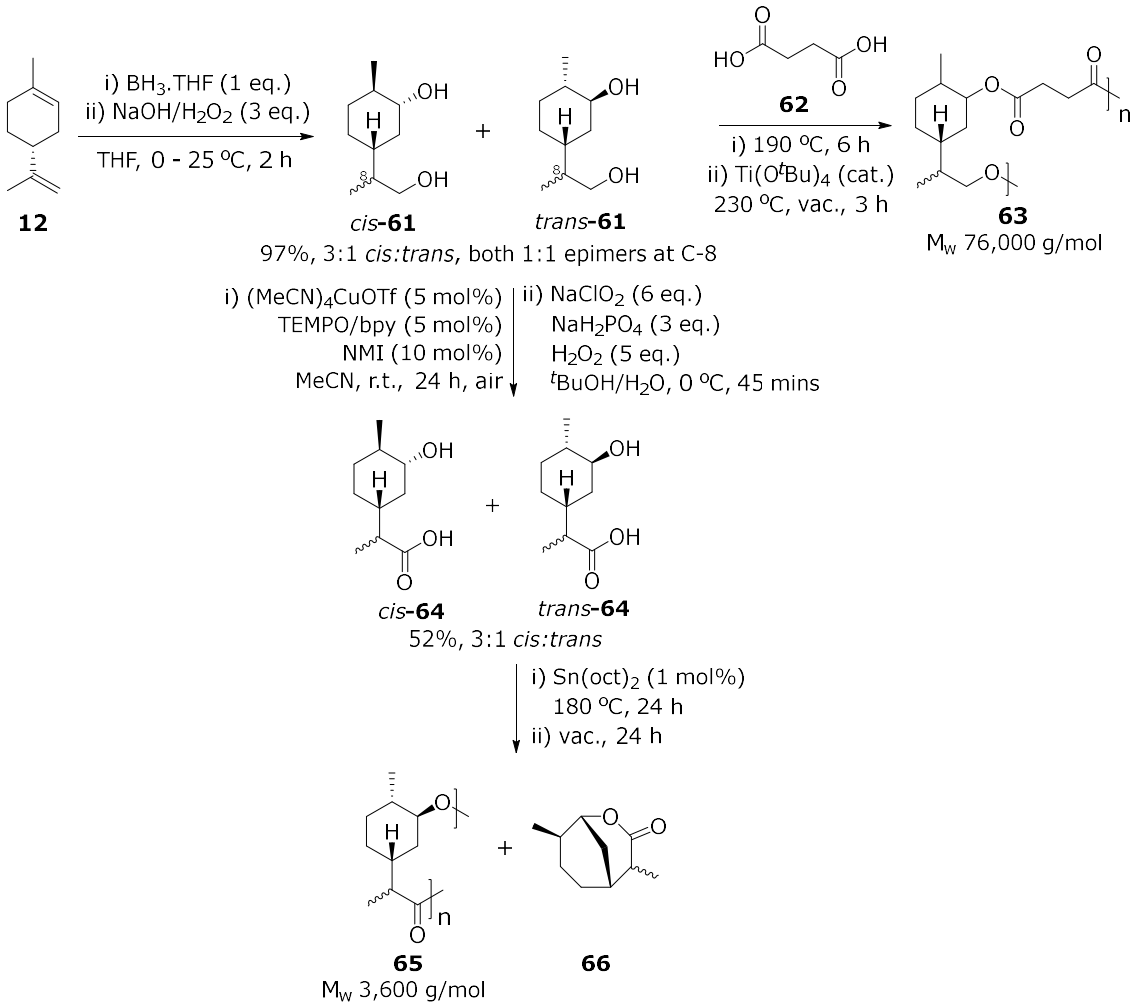
Polyesters have been synthesised from *cis*-**39** and **53** in conjunction with **54** to form a partially terpene-based material, using an iron(III) tris(phenolate) complex as the polymerisation catalyst in tandem with PPNCl (Scheme 22). [77] When **53** was used as the substrate, polyester **55** was formed with an M_w of 17,200 g/mol, a Đ value of 1.94, and a T_g of 59 °C. Interestingly, the tri-substituted epoxide in **53** was almost exclusively favoured over the 1,1-disubstituted epoxide in this polymerisation reaction.

Alternatively, when *cis*-**39** was used as the substrate, polyester **56** was formed with an M_w of 21,800 g/mol, a Đ value of 1.33, and a T_g of 141 °C. The vast difference in glass transition temperature between the two materials may be down to a small degree of cross-linking between the pendant alkene groups in **56**, although this hypothesis was not proven with evidence.



*Scheme 23. The synthesis of ε-lactone **59** from verbenone (**57**) in 2 steps, including a biocatalytic Baeyer-Villiger oxidation as the key step, and subsequent polymerisation.* [78]

Stamm and co-workers developed the synthesis of ε-lactone **59** from verbenone (**57**) in 2 steps (Scheme 23). [78] The key step involves a biocatalytic oxidation using a mutant Baeyer-Villiger monooxygenase enzyme along with several co-factors, using oxygen as the sole oxidant. Unfortunately, this step could only be optimised to a maximum conversion of 30% from **58** despite trying numerous different enzyme mutants. Nonetheless, **59** was polymerised using methanesulfonic acid as the catalyst to give polyester **60** in 94% conversion, with an M_w of 3,760 g/mol, a low Đ value of 1.14, and an observed T_g of 26 °C.



*Scheme 24. The synthesis of a terpene co-polymer **63** in 2 steps from **12**, and an entirely terpene-based polyester **65** in 4 steps from **12**.* [79]

Terpene-containing polyesters **63** and **65** have also been synthesised from **12** (Scheme 24). [79] A partially terpene-based co-polymer (in conjunction with succinic acid **62**) was synthesised from **61**, with an M_w of 76,000 g/mol, a Đ value of 2.5 (typical for an uncontrolled step-growth polymerisation) and a T_g of 16 °C.

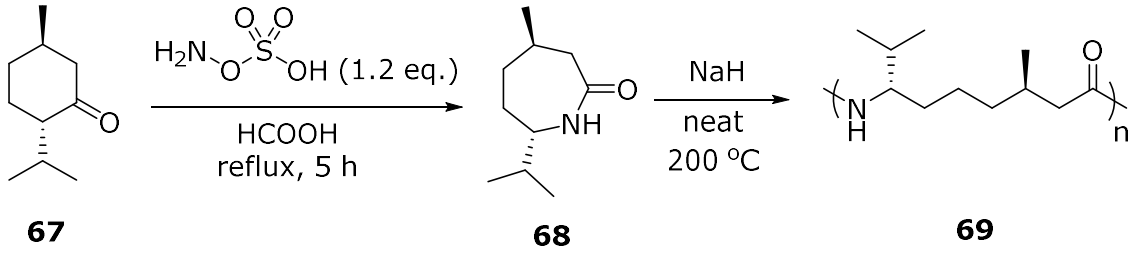
The terpene-based diol precursor **61** (as a mixture of isomers) was then also reacted further, generating hydroxy-acid **64** in 2 steps. Multiple 2-step routes to **64** were trialled and examined using Green Motion, a metric for examining the sustainability of a synthesis route [80], with the best performing route shown (Scheme 25). Relatively harsh polymerisation conditions were then employed, as secondary alcohols often react slowly in polyesterification reactions. [81] When

subjected to polymerisation conditions, the *trans*-isomer of **64** formed **65** cleanly, while the *cis*-isomer of **64** exclusively and irreversibly ring closed to form lactone **66** under these reaction conditions. The polymerisation was also modelled by DFT (protocol mR062XD3/6-311++g(2d,p)/cpcm = ethylethanoate) in the study, which confirmed these were the most likely thermodynamic outcomes. Nonetheless, polymer **65** was formed which displayed an M_w of 3,600 g/mol, a reasonably low Đ value of 1.4, and a T_g of 44 °C.

Furthermore, depolymerisation of polyester **63** under alkaline conditions to refurnish diol **61** was also proven, enabling the possibility of recycling the terpene-containing polyester **63** once the use of the initial material had been fulfilled.

1.5.3 Polyamides

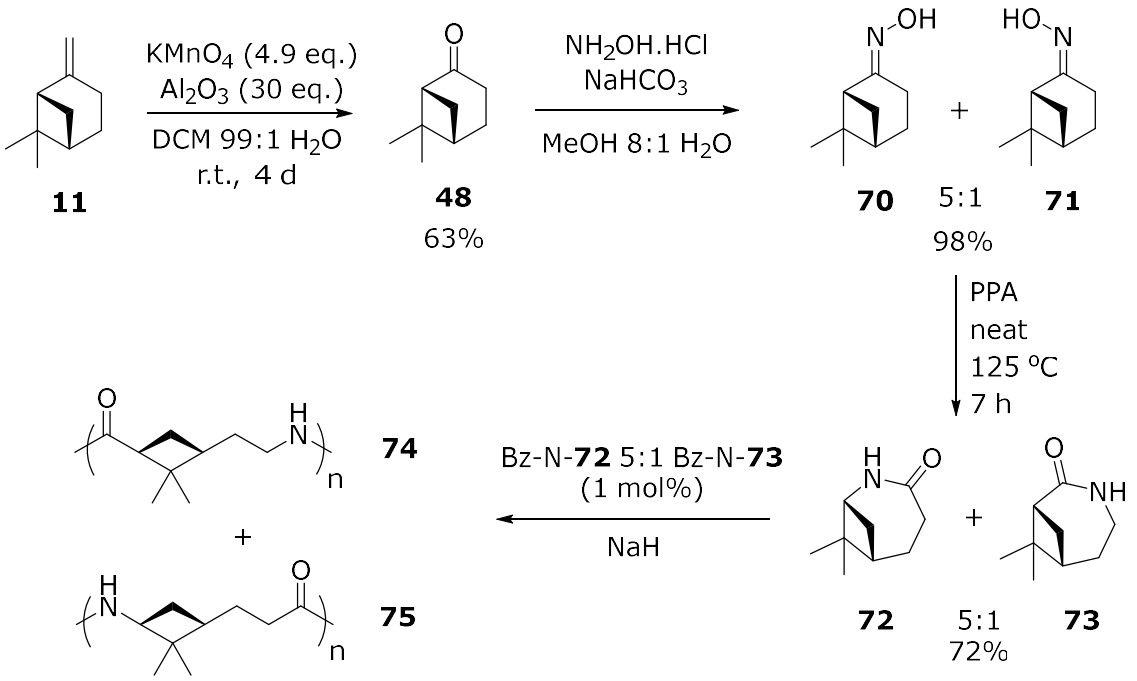
Polyamides have also proved to be a common target for terpene-derived polymers in relatively recent literature publications. The nitrogen-containing functionality was introduced via Beckmann rearrangement from a terpenoid-based oxime-containing precursor in most of the highlighted cases, although limited examples of other strategies are also documented.



67 **68** **69**

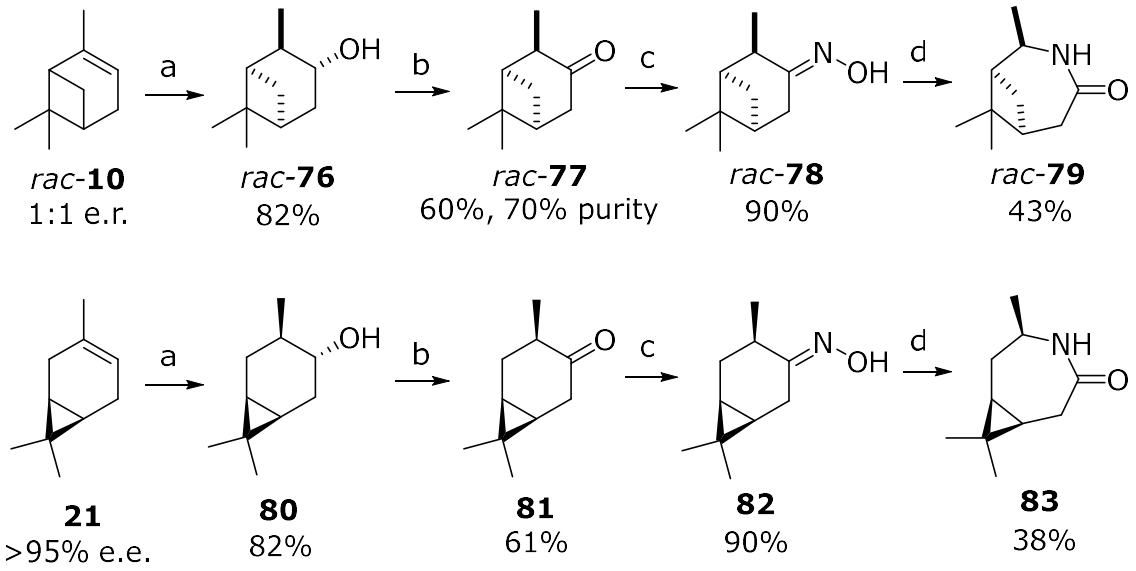
*Scheme 25. The synthesis of a terpene-based polyamide **69** from the naturally-occurring terpenoid menthone (**67**).* [82]

Menthone (**67**) is a naturally occurring terpenoid containing a ketone functionality. This substrate was utilised to synthesise a terpene-derived polyamide in 2 steps, via the 7-membered lactam **68**, using a Beckmann rearrangement (Scheme 25) [82]. The use of hydroxylamine-*O*-sulfonic acid (HOSA) as the reagent caused the Beckmann rearrangement to occur spontaneously as soon as the intermediate oxime had been formed in the reaction mixture, removing the need for an extra synthetic step. When subjected to anionic ring-opening polymerisation conditions using sodium hydride as the catalyst, a polyamide with a molecular weight of 3500 Da and a polydispersity value of 2.5. Due to the relatively low M_w of the formed material, a glass transition temperature was not determined.



*Scheme 26. The synthesis of two different terpene-based polyamides **74** and **75**, both in 4 steps from β-pinene (**11**).* [83]

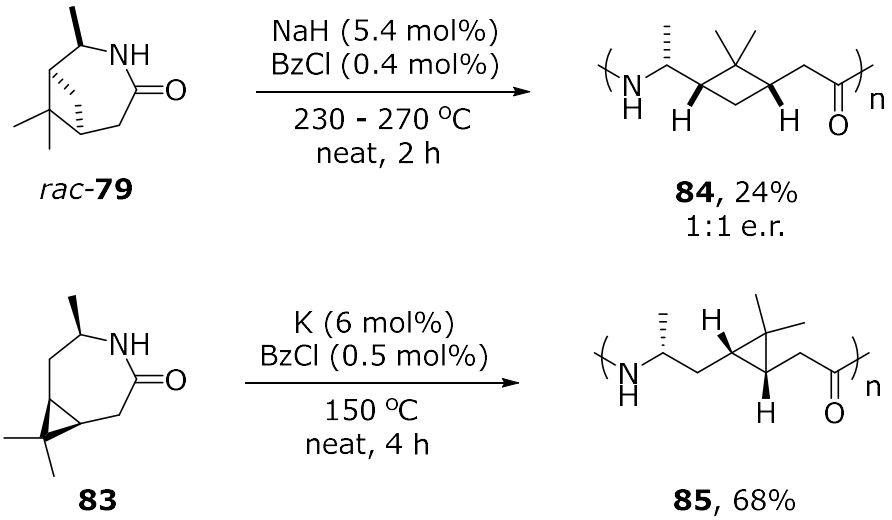
Winnacker and co-workers have also synthesised two different polyamides in 4 steps from **11** (Scheme 26). [83] Oxidative cleavage of the alkene functionality gave **48** in 63% yield, containing the required carbonyl for oxime formation and subsequent Beckmann rearrangement. Interestingly, both possible stereo-isomers of oxime were formed, in a 5:1 ratio of **70** to **71** in 98% yield. A separate synthetic step using poly-phosphoric acid was also required to form the desired ε-lactam compounds in 72% yield – however, these could not be successfully separated at any stage. The mixture of **72** and **73** were then subjected to anionic ring-opening polymerisation conditions, using sodium hydride in conjunction with a substoichiometric amount of the *N*-benzoylated variants of the lactam compounds, to aid the initiation step. This yielded a material with a molecular weight of 8000 Da, and a recorded T_g of 150 °C – a high value for a terpene-based material. This study built on original work conducted by Hall, which synthesised the ε-lactams **72** and **73**. [84] Further detail was also provided about the materials by Winnacker *et al.* in a subsequent publication. [85]



a = i) $NaBH_4$, $Et_2O.BF_3$, THF, -10 °C ii) NaOH, H_2O_2
b = $Al(O^iPr)_3$ (5 mol%), 3-NBA (1.2 eq.), toluene, r.t., 12 h
c = $NH_2OH.HCl$ (2.1 eq.), NaOAc (2.1 eq.), EtOH:H_2O 1:1, 65 °C, 4 h
d = i) NaOH (3 eq.), THF:H_2O 1:1, 0 °C ii) TsCl (1.1 eq.), 0 °C

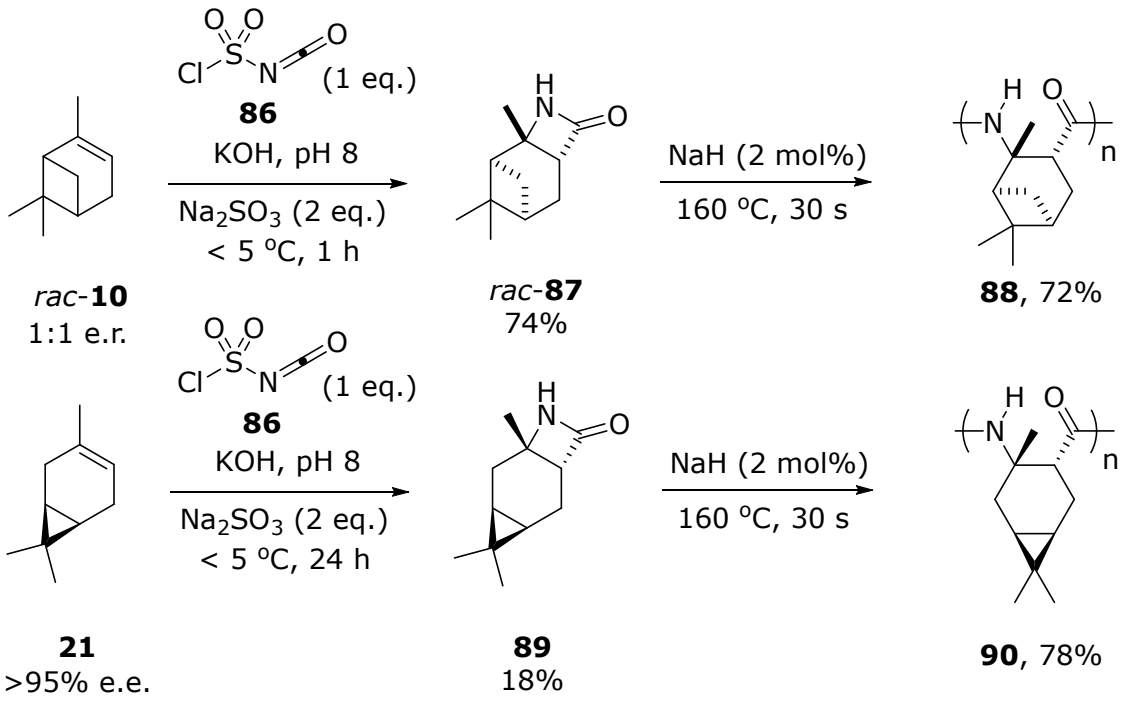
*Scheme 27. The synthesis of ε-lactams **79** and **83** from α-pinene (**10**) and (+)-3-carene (**21**) respectively.* [86]

Two novel terpene-based ε-lactams **79** and **83** were also synthesised from **10** and **21** in work published by Stockmann *et al.* (Scheme 27). [86] Using a procedure originally developed by Lochyński and co-workers, alcohols **76** and **80** were synthesised in 82% yield in both cases. [87] The alcohols were then subjected to a modified Oppenauer oxidation protocol using 3-nitrobenzaldehyde (3-NBA) as the oxidising agent with aluminium *iso*-propoxide as the catalyst. [88] This protocol gave yields of the desired ketones **77** and **81** in 60% and 61% respectively. Oxime formation and subsequent Beckmann rearrangement initiated by tosylation of the intermediate oximes gave the desired ε-lactams **79** and **83** selectively.



*Scheme 28. The polymerisation of ε-lactams **79** and **83**.*

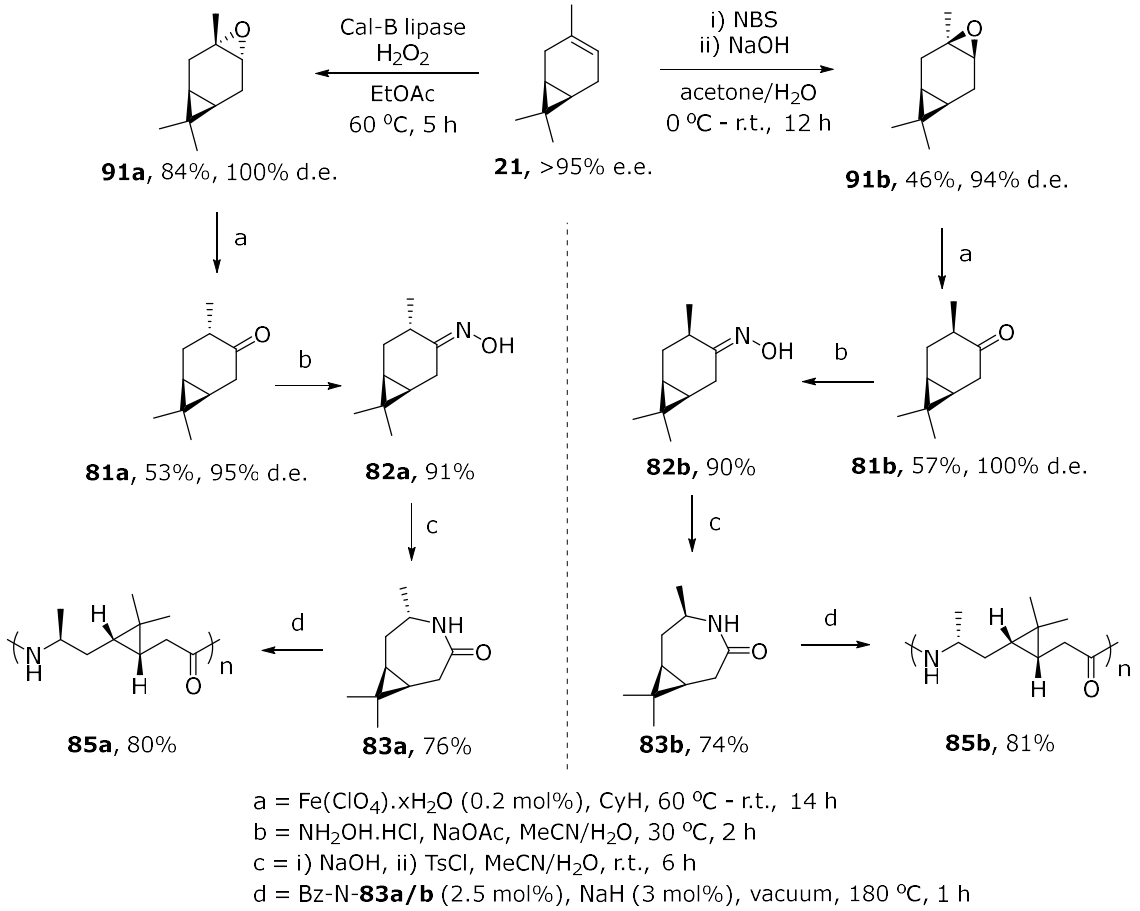
79 and **83** were then subjected to anionic ring-opening polymerisation conditions (Scheme 28). For **79**, a combination of catalytic sodium hydride and benzoyl chloride was identified as the optimal initiator combination, giving polyamide **84** with an M_w value of 2900 Da and a polydispersity of 1.48. However, these optimal conditions still only provided 24% conversion to polymeric material. Conversely, **83** was polymerised using potassium metal and a higher loading of benzoyl chloride as catalysts, yielding polymer **85** with a molecular weight of 22,300 Da and a T_g value of 120 °C, with 68% conversion achieved.



*Scheme 29. The synthesis of two polyamides **88** and **90** in 2 steps, from **10** and **21** respectively.*

In the same publication, Stockmann *et al.* also reported the synthesis of two different polyamides, **88** and **90**, from the same starting materials as previously described (Scheme 29). The terpenes were reacted with chlorosulfonyl isocyanate (**86**) in a [2+2] cycloaddition reaction under weakly basic conditions, adopted from a previous literature example. [89] The reaction with **10** proved much more successful with a yield of 74%, however **21** only produced a 18% yield of the fused β-lactam product **89**.

Polymerisation of these species proved extremely fast, reaching >70% conversion in just 30 seconds in both cases. Polyamide **88** was obtained with a molecular weight of 3300 Da and a very low polydispersity value of 1.0. Conversely, polyamide **90** was obtained with a M_w value of 1500 Da and a Đ value of 1.07. While these polydispersity values for both polymers are excellent and show a great deal of control in the process, due to the low M_w value an accurate determination of the glass transition temperature was not possible in both cases.



*Scheme 30. The diastereoselective synthesis of both variants of ε-lactam **83** from (+)-3-carene (**21**) and their subsequent polymerisation.* [90]

In order to try and improve the polymerisation of lactam **83**, Stockmann and co-workers set about making the pure diastereomers of **83** separately (Scheme 30). [90] The synthesis involved epoxidation of the alkene functionality, via two different methods. The first involved enzymatic oxidation with hydrogen peroxide as the terminal oxidant, giving **91a** in 84% yield with total diastereoselectivity. For the other diastereomer, the use of *N*-bromosuccinimide followed by the addition of sodium hydroxide gave the desired epoxide **91b** in a moderate 46% yield, but with 94% d.e.

The epoxidation was then followed by a Lewis acid-catalysed ring opening using iron(II) perchlorate to give the desired ketones **81a** and **81b** in 95% and 100% d.e. respectively. Oxime formation and subsequent Beckmann rearrangement then furnished the desired ε-lactams **83a** and **83b**. Anionic ring-opening

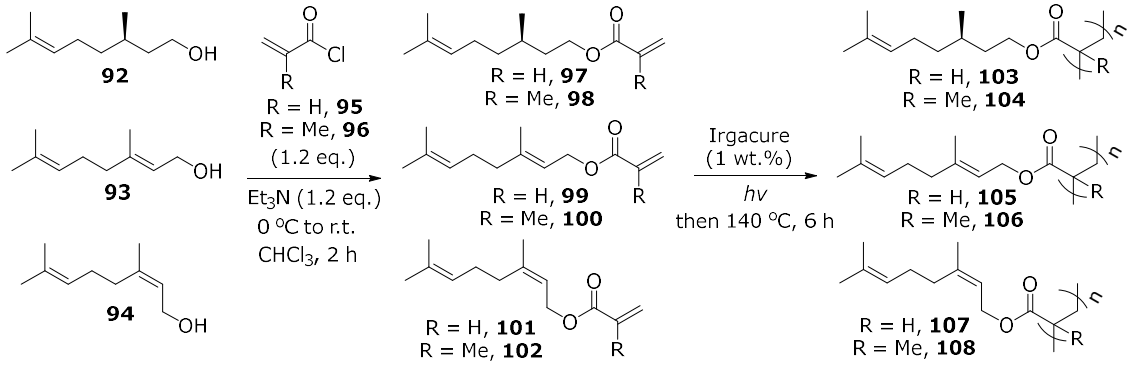
polymerisation catalysed by sodium hydride and initiated by the corresponding benzoylated lactams then gave the desired polyamides.

Polyamide **85a** was obtained with 80% conversion, a molecular weight of 10,200 Da, a Đ value of 1.59, and a glass transition temperature of 105 °C. Alternatively, polyamide **85b** was obtained with 81% conversion, an M_w value of 19,900 Da, a polydispersity value of 1.65, and a T_g value of 111 °C. These differences in polymer parameters highlight the effect of what such a subtle change in substrate structure can do to the overall polymerisation of a species.

Finally, the polyamides were converted into transparent films by slow evaporation of a solution of the polymers in hexafluoro-*iso*-propanol, and their optical properties were examined by comparison with Fraunhofer lines. While the homopolymers did not exhibit transparency, 1:1 co-polymers of each polyamide in conjunction with ε-caprolactone (**5**) proved to be transparent.

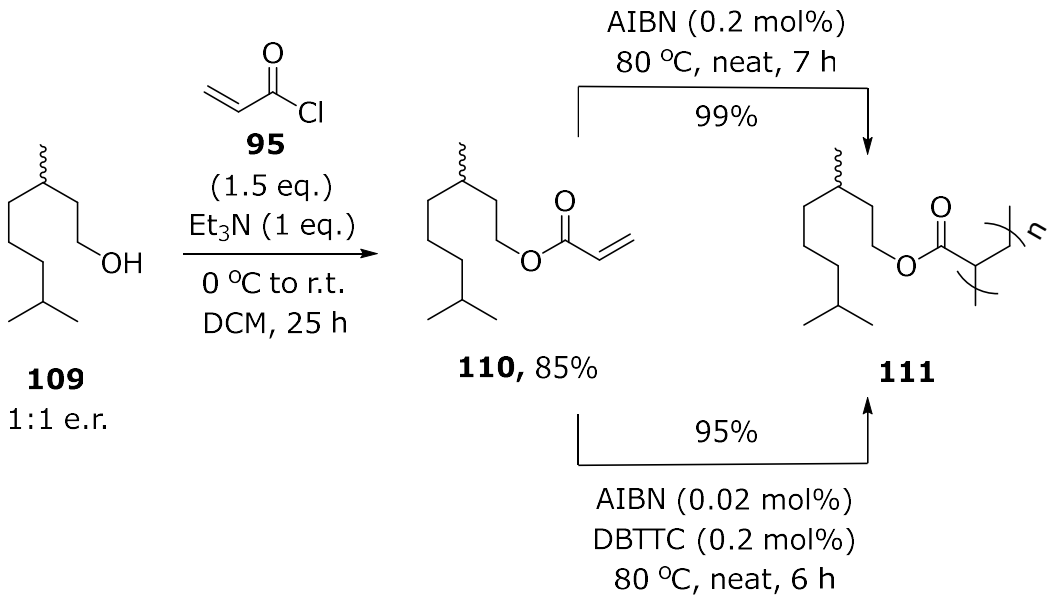
1.5.4 Poly(meth)acrylates

For chain-growth polymerisation, a vastly significant proportion of materials are generated from acrylate or methacrylate esters. As these structures are so reliable for radical-based polymerisation techniques, there have been a steadily increasing number of recent publications focused on the synthesis and subsequent polymerisation of terpene-containing (meth)acrylate based monomers.



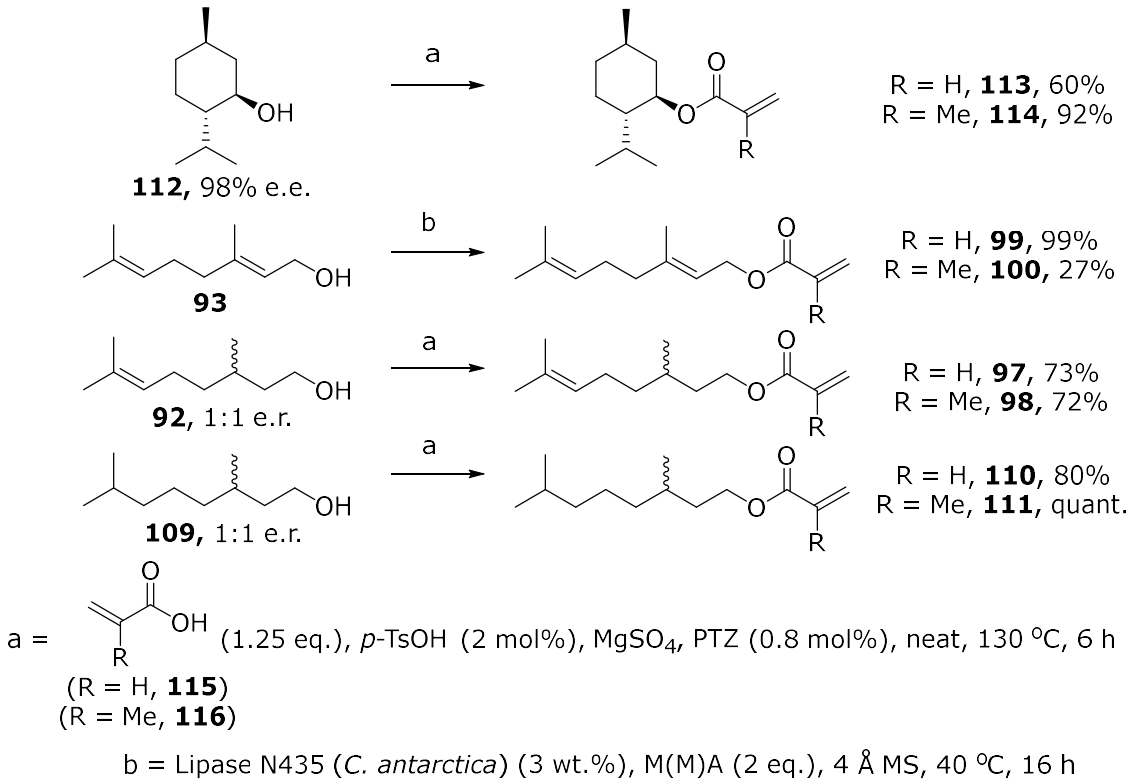
*Scheme 31. The synthesis of poly(acrylates) and poly(methacrylates) from the naturally occurring acyclic mono-hydroxylated terpenoids citronellol (**92**), geraniol (**93**) and nerol (**94**).* [91-93]

Worzakowska and co-workers have published three studies, in relatively quick succession, about the synthesis and polymerisation of acrylate and methacrylate esters from the naturally occurring acyclic terpenoids citronellol (**92**), geraniol (**93**) and nerol (**94**) using the corresponding acid chloride reagents as the source of the meth(acrylate) functionality (Scheme 31). [91-93] The monomers were then subjected to ultra-violet irradiation using Irgacure® as the polymerisation initiator. The corresponding polymers were then subjected to thermal stability and decomposition testing in these studies. While the chemistry to synthesise these monomers may not be particularly complex, these studies are some of the first examples of terpene-based (meth)acrylate esters being investigated as potential renewably sourced materials.



*Scheme 32. The synthesis and subsequent polymerisation (using two alternative methods) of acrylate **110**, derived from tetrahydrogeraniol (**109**).* [94]

A subsequent study by Noppalit and co-workers detailed the synthesis of a polymer from tetrahydrogeraniol acrylate **110** by chain-growth polymerisation both in the presence and absence of a RAFT chain transfer agent (Scheme 32). [94] The monomer could be synthesised in 85% yield using acryloyl chloride as the esterifying agent. In the absence of a RAFT agent, a polymer was achieved with an excellent M_w value of 278,000 Da, a polydispersity of 2.4, and a T_g of −46 °C – an extremely low value which remains one of the lowest glass transition temperatures reported for a bio-based material. Conversely, when the RAFT agent DBTTC was also present in the polymerisation mixture, a material was achieved with a much more controlled polydispersity of 1.1, but only at 46,000 Da and with no recorded T_g value. **110** was also used as the soft-block source in the synthesis of both combinations of ABA tri-block co-polymers, using styrene as the second monomer - these more complex materials often find use as thermoplastics. [95] Also, while tetrahydrogeraniol is not a prevalent compound found in nature, it can be manufactured from the total reduction of the much more available geraniol (**93**). [96]

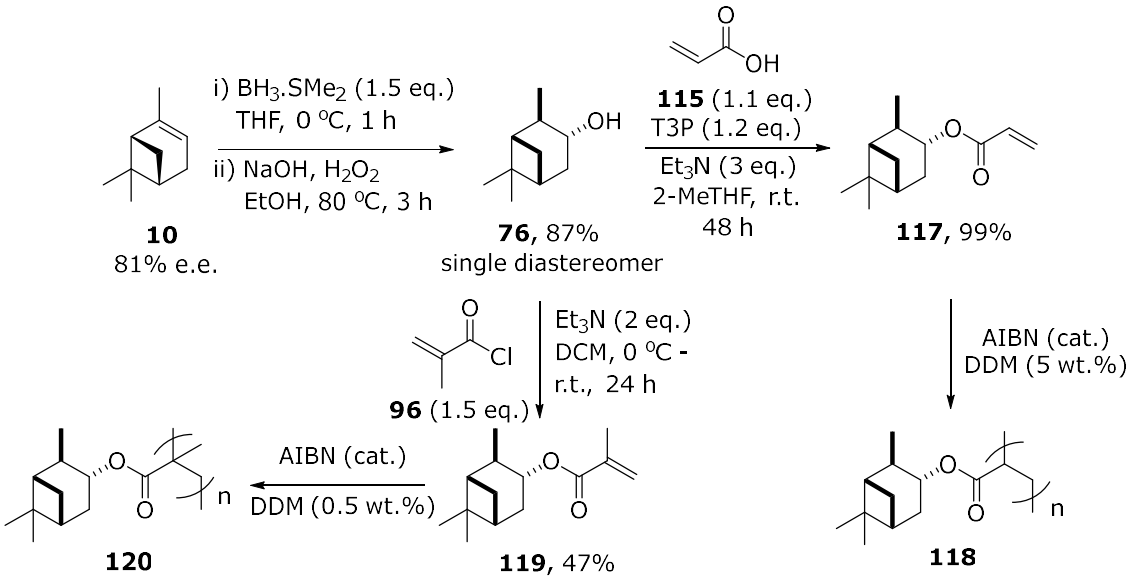


Scheme 33. The optimisation of the synthesis of various (meth)acrylate esters from terpenoid-based alcohols, with a focus on sustainability. [97]

A recent study compiled by Droesbeke and Du Prez examined the synthesis of acrylate and methacrylate esters from various terpenoid alcohols, using protocols considered to be more sustainable than traditional esterification conditions, which often use acid chloride reagents (Scheme 33). [97] The research found that for three of the four starting materials examined in the study, a traditional Fischer esterification using tosic acid as the catalyst, in the presence of phenothiazine (PTZ) as a radical inhibitor and magnesium sulfate as a dehydrating agent respectively, was the procedure that gave the highest yields of the corresponding acrylate and methacrylate ester products.

For **93** however, this procedure was outperformed by the use of a lipase-catalysed transesterification procedure with methyl (meth)acrylate (M(M)A). This procedure gave an excellent yield of 99% for the synthesis of the acrylate, yet this result fell to 27% when the same conditions were used for methacrylate formation. The reasoning behind this is most likely due to the extra steric bulk

created by the methyl substituent not providing an ideal fit into the active site of the enzyme, rendering the catalysis much less efficient.



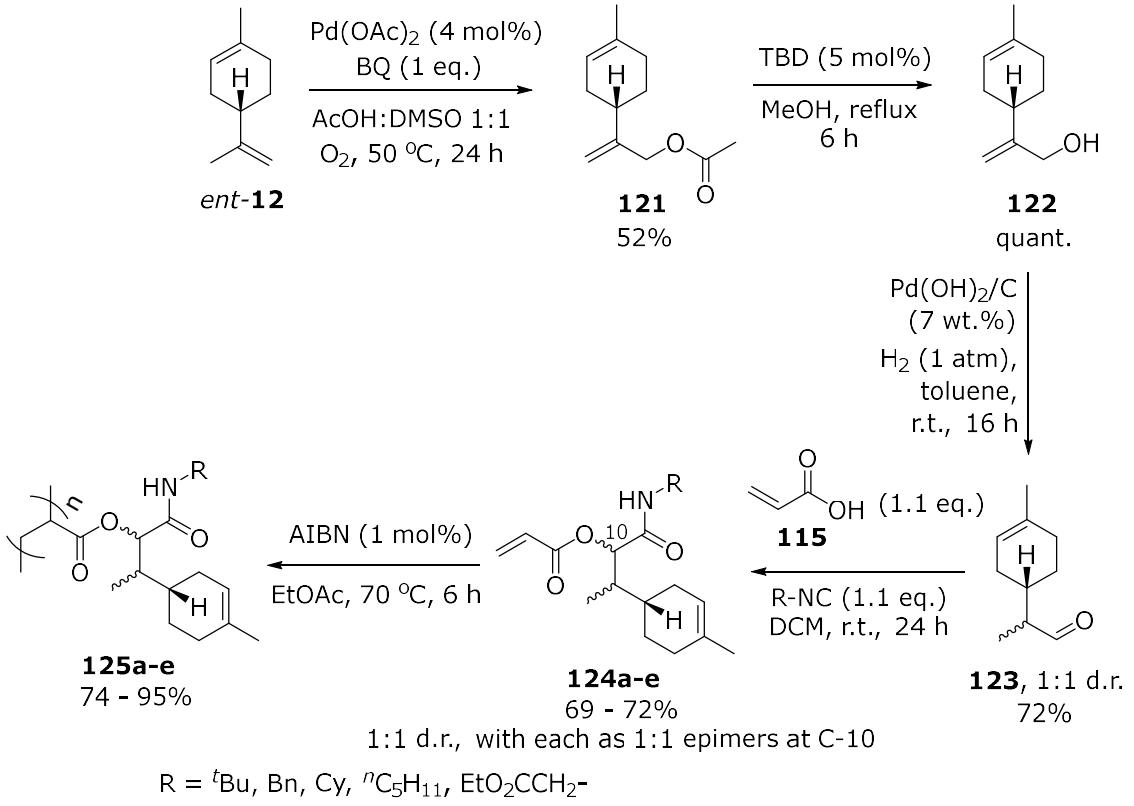
*Scheme 34. The synthesis and polymerisation of acrylate and methacrylate monomers **117** and **119** from **10** via a hydroboration/oxidation and subsequent esterification protocol.* [98]

Terpenoids prove excellent as renewable sources of hydroxylated compounds available for esterification, but are quite often more difficult to source than the related terpene hydrocarbon substances. As a result, procedures that can start with these much more abundant species would be even more attractive than those discussed previously. A collaboration between researchers in the groups of Stockman and Howdle detailed the synthesis of acrylate and methacrylate monomers from **10**, **11** and **12** via hydroboration/oxidation of the alkene-containing compounds, followed by esterification (Scheme 34, only **10** shown for clarity – the use of the hydroboration/oxidation protocol on **12** leads to a 1:1 diastereomeric mixture of the corresponding alcohol product). [98]

In the case of acrylates, the coupling agent T3P® could be used with acrylic acid for the esterification, generating a much more benign phosphate-containing aqueous waste stream. However this did not work for the corresponding methacrylates, and the acid chloride reagent was required instead. Polymerisation was conducted in the presence of dodecyl mercaptan (DDM), a

chain transfer agent, and gave materials **118** and **120** with vastly different glass transition temperatures of 12 °C and 142 °C respectively.

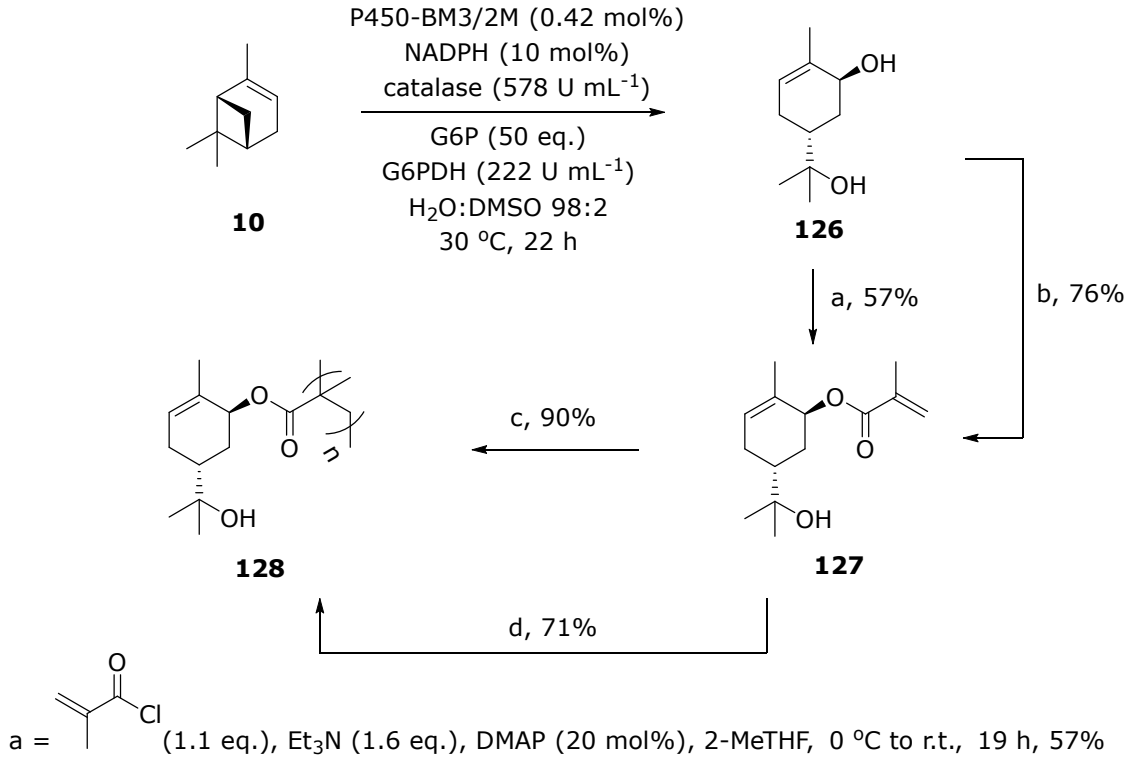
Applications of the resulting polymers were subsequently investigated, with the use of the materials as coatings being explored. Scratch tests were also performed on the resulting terpene polymer-coated substances to determine their effectiveness as a protective coating.



*Scheme 35. The synthesis of poly(acrylates) in 5 steps from **12** using the Passerini reaction for introduction of the acrylate functionality.* [99]

In Meier's research group, a protocol was devised to install the acrylate ester functionality into a terpene-based monomer structure via the Passerini reaction, using commercially available isocyanides and acrylic acid in conjunction with aldehyde **123**, synthesised in 3 steps from **12** (Scheme 35). [99] Each of these 3 steps used catalysis in the transformations, adding to the sustainability parameter of the process. A selection of 5 terpene-based poly(acrylates) were formed from the 5 commercially available isocyanides used in the study, giving

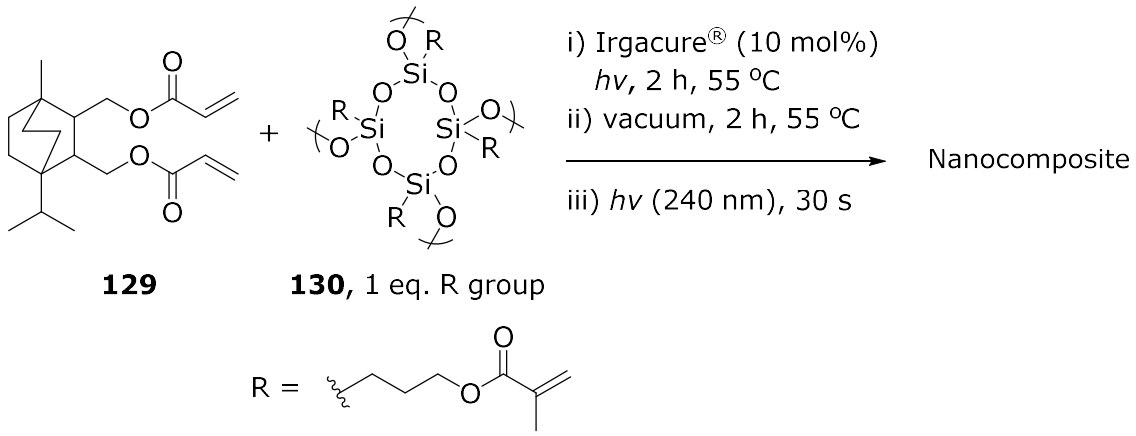
materials with a range of T_g values from 86 – 143 °C and polymer conversion values from 74% to 95%.



Scheme 36. The synthesis of a poly(methacrylate) ***128*** *from* ***10*** *in 3 steps, using two alternative methods for the esterification and polymerisation steps.* [100]

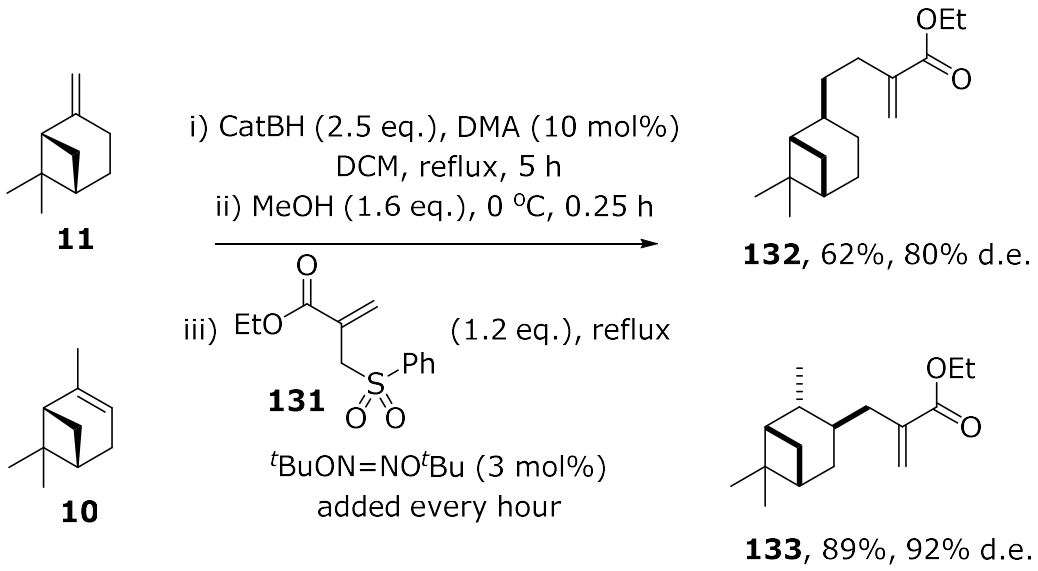
A recent procedure published by Stamm and co-workers details the synthesis of a terpene-derived poly(methacrylate) (**128**) in 3 steps from **10** (Scheme 36). [100] Interestingly, both transformations could be carried out using enzymatic processes – with the esterification reaction giving a significantly better yield of 76%, compared with 57%, for the monomer **127** when conducted using the detailed biotransformation. RAFT-mediated polymerisation gave polymer **128** with a 90% conversion, an average molecular weight of 8600 Da, a polydispersity of 1.2 and a glass transition temperature of 116 °C. However, when ATRP was used as the polymerisation method, an M_w of 20,900 Da and a T_g value of 141 °C with the same polydispersity value was recorded for the

resulting material, albeit with a lower conversion of 71%. This suggests that for this example ATRP was the superior procedure in terms of generating a useful material.



*Scheme 37. The synthesis of an organic-inorganic nanocomposite from a terpene-based diacrylate **129** (stereochemistry and synthesis not specified in the literature example) and poly(silylsesquioxane) **130** using ultraviolet induced polymerisation.* [101]

Ando and co-workers have detailed the formation of an organic-inorganic nanocomposite material from a methacrylate ester-containing functionalised poly(silylsesquioxane) **130** and a terpene-based diacrylate compound **129**, donated to the researchers from a supporting industrial company. These species were polymerised together in a random fashion using ultraviolet irradiation in conjunction with Irgacure® as the initiator (Scheme 37). [101] Due to the random nature of the polymerisation as opposed to a structured block formation, the chemical structure of the product was undetermined – however, the material produced displayed a high T_g of 167 °C. Mechanical and optical properties of the nanocomposite were also investigated, including the flexural strength and transparency of the resulting material.



*Scheme 38. The synthesis of α-substituted-α,β-unsaturated esters **132** and **133** from **11** and **10** respectively in a diastereoselective fashion using a hydroboration and subsequent radical addition approach.* [102]

Schaffner and Renaud have described the synthesis of α-substituted acrylate type esters from terpenes in a diastereoselective fashion (Scheme 38). [102] The approach provides products **132** and **133** with reasonable diastereoselectivity in both cases, and is presented as a general method for the functionalisation of unactivated alkenes.

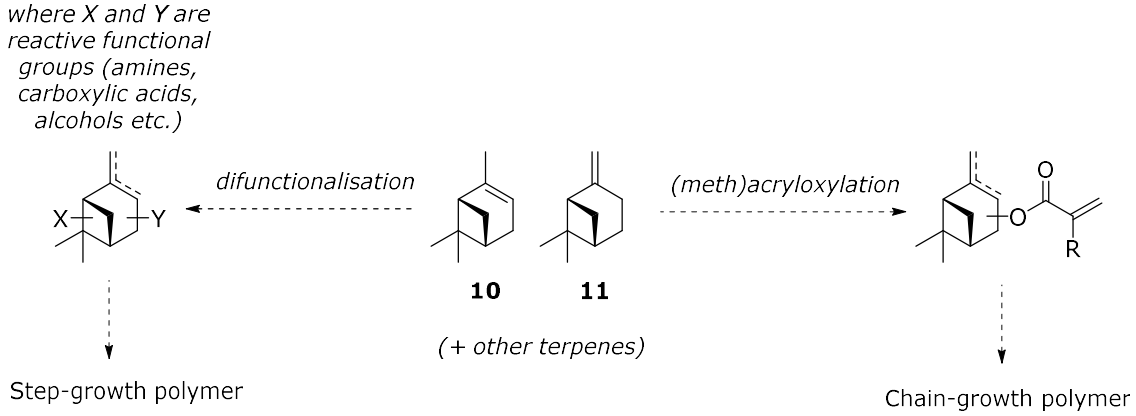
This work contrasts from that of the Zard [103] or Baran [104] research groups as it allows the preservation of an α,β-unsaturated ester in the final product, whereas the other methods remove this functionality when the radical addition process occurs. The products **132** and **133** could have potential use as monomers due to their similarity to the other acrylates shown earlier in this section, however this potential was not realised by the authors of this study and no further work was conducted in this area.

With most of these literature examples of terpene modifications and subsequent polymerisations coming in the last 5 years approximately, the field is still relatively in its infancy in the research community. The area of research is potentially vast, with the only applicable limits being the creativity of the chemical community itself, along with the number of transformations required to achieve a monomer in a reasonable quantity and yield. This means that there is

plenty of chemical space still to explore in this area, and this project will aim to fill some of this space with a selection of novel terpene-based monomers.

2. Aims and Objectives

The vast swathe of potential chemical space for the synthesis of polymers derived from terpenes is still very much underexplored. The limited examples of acrylate and methacrylate containing materials, discussed in the previous section, allows for much more possible exploration of novel monomers containing these crucial functional groups. Additionally, the currently documented examples of terpene-based polymers synthesised via step-growth (condensation) polymerisation, or ring-opening polymerisation methods, can also be expanded on greatly.



Scheme 39. A summary of the proposed hypothetical procedures that will be utilised to synthesise monomers, suitable for either step-growth or chain-growth polymerisation methods, from terpenes.

The aim of this project will be to synthesise novel terpene-based monomers suitable for the polymerisation techniques detailed thus far (Scheme 39). This involves installation of either an acrylate or methacrylate ester functionality, which will allow for polymers to be produced *via* free radical polymerisation. Conversely, installation of either two reactive functional groups, such as alcohols, amines or carboxylic acids, or a functionalised ring system (a lactone or lactam) will provide monomers suitable for condensation or ring-opening polymerisation respectively.

In addition to this primary objective, the syntheses of these monomers will also be designed and conducted to some further guidelines, with efficiency and sustainability in mind. These criteria are as follows:

- A maximum of 3 synthetic steps will be employed in the generation of viable monomer species. This is the maximum length of a synthetic route that is deemed acceptable to specialist monomer production in industry. The main reason for this is mostly to do with yield, as additional synthetic steps, however high-yielding they may be, do ultimately cause some loss of material. Coupled with this is the time and energy required to perform such syntheses, especially on a scale large enough to provide enough material for polymer synthesis purposes.
- Any waste generated during the monomer synthesis must be minimised. This also includes considerations of the stoichiometry of reagents, the amount of solvent and/or catalyst required for transformations, and any purification procedures required after each step. Maximisation of atom economy in such procedures will also prove beneficial with regards to minimising the amount of waste produced.
- Solvent use should be minimised wherever possible. Also, the utilisation of environmentally benign solvents should be prioritised, and recycling of any solvent used should also be considered to minimise the overall waste of the process further.
- Catalysis should be prioritised, to minimise the necessity for stoichiometric reagents.
- Where possible, the use of reagents with low toxicity (along with the toxicity of any by-products) should be preferred during these syntheses.

These criteria are primarily derived from some of the Principles of Green Chemistry, outlined in the literature. [105-106] These principles will also be used to further assess the sustainability of any successful monomer synthesis identified during this research, and they will help to guide optimisation of processes that are deemed to require improvement with regards to the above objectives.

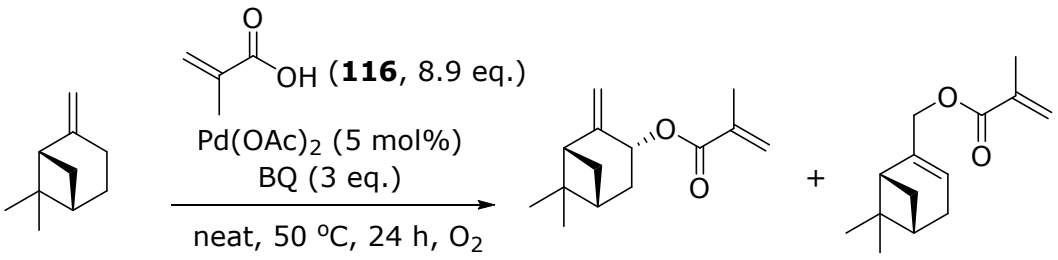
As a further point, where catalysis is used, there will be a substantial effort to prioritise methods which are successful when earth-abundant transition metals, or metal-free catalysts, are employed in the synthetic transformations. Due to the potential scale of monomer synthesis, on the order of kilograms even for specialist polymer production, the cost of using noble metals in transformations required to produce these monomers would be astronomical, and therefore unsuitable for this purpose. Noble metal waste residues often have high costs

regarding their disposal also, so the necessity for identifying transformations that require more cost-effective alternatives is high in this case.

3 Results and Discussion

3.1 Palladium-catalysed methacryloxylation

In this project, (-)-α-pinene (**10**) and (-)-β-pinene (**11**) were supplied as a scalemic mixture with 81% e.e. The major stereoisomers are shown in the schemes throughout this section, and all subsequent sections of the thesis.



11 **134** **135**

82%, **134** 10:1 **135**

*Scheme 40. The literature procedure for the synthesis of **134** and **135** from **11** using a palladium-catalysed methacryloxylation process [98].*

Previous work in the group had established a protocol for the methacryloxylation of β-pinene (**11**) in a single step using methacrylic acid (**116**) as both the reactant and solvent, in conjunction with palladium(II) acetate and 1,4-benzoquinone as catalyst and oxidant respectively (Scheme 40) [98]. The ratio of products obtained from this procedure was interesting, and an investigation was carried out to see if additives in the reaction mixture had any effect on the yield or product ratio of the protocol. The results of this investigation are shown in Table 1.

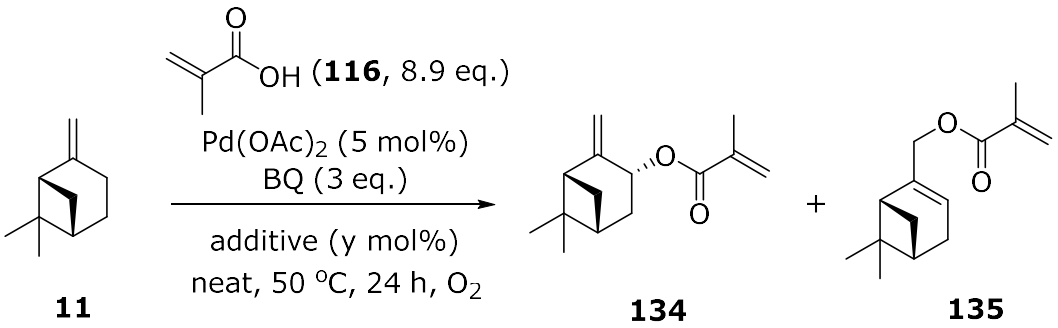


*Table 1. The results of the investigation into the effect of additives on the palladium-catalysed methacryloxylation of **11**.*

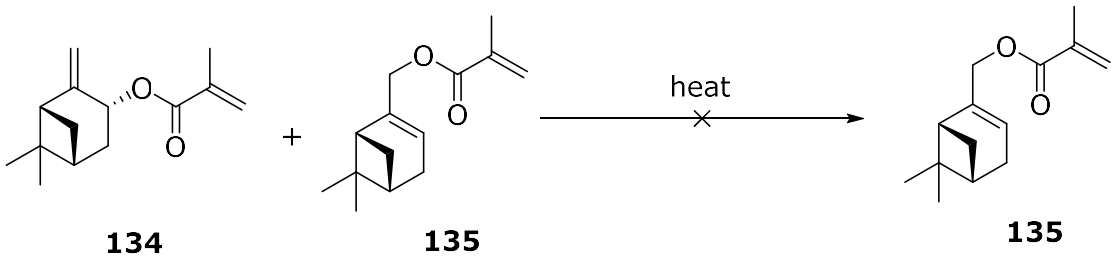
Entry	Additive (y mol%)	Yield (%)	Product ratio (**134** : **135**)
literature [98]	-	82	10 : 1
1	*p*TsOH·H_2O (10)	36	1 : 1
2	DAF (5)	13	1 : 14

When PTSA (entry 1) was used as an additive, the selectivity of the process was entirely diminished and a 36% yield of a 1:1 mixture of products **134** and **135** was the result of the reaction. The reasoning for the reduced selectivity has not yet been determined, but could possibly be due to the increased acidity of the reaction mixture accelerating the formation of **135** through proton-mediated rearrangement of the palladium-π-allyl intermediate to the more thermodynamically stable tri-substituted alkene substrate. The depreciation of product yield from the original procedure is most likely due to hydrolysis of organopalladium intermediates by the quantity of water present in the additive, as water is a much more nucleophilic species when compared with a carboxylic acid.

4,5-diazafluoren-9-one (DAF) is a well-established ligand for palladium(II) complexes, and has been shown in the literature to cause enhanced activity and selectivity in many palladium(II)-catalysed reactions [107]. When DAF was used as the additive in this reaction (entry 2), a remarkable reversal of selectivity was observed, with a 14:1 ratio favouring **135** as the major product. However, the yield of the process was significantly reduced, most likely due to the acidic

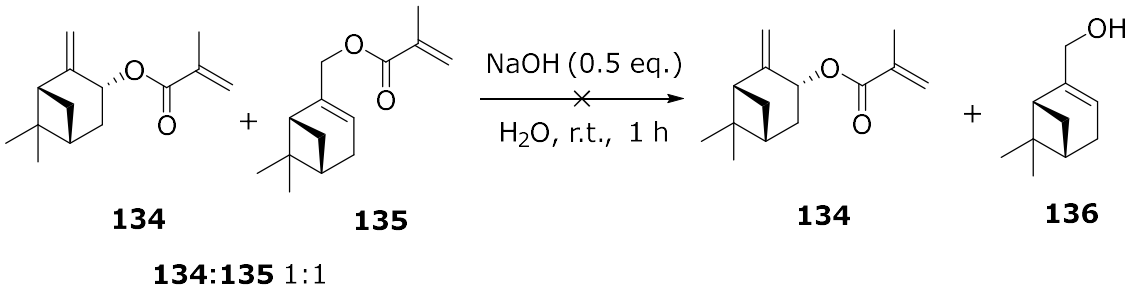
reaction mixture protonating the DAF ligand, leading to a loss of catalytic activity.

The compounds in the product mixture that this reaction yields could not be separated by either chromatography or distillation under reduced pressure. If these components could not be separated, it would be impossible to achieve a homopolymer of either methacrylate species when subjected to free radical polymerisation conditions.



*Scheme 41. The attempted thermal conversion of a mixture of **134** and **135** to solely **135**.*

It was hypothesised that **134** could be converted to the more thermodynamically stable tri-substituted alkene **135** by a [3,3]-sigmatropic rearrangement. Therefore, the product mixture was heated in an attempt to convert all of the mixture to **135** (Scheme 41). This resulted in decomposition of the sample to an intractable mixture of species, which is most likely caused by uncontrolled polymerisation of the methacrylate functionalities in both **134** and **135**.



*Scheme 42. The attempted hydrolysis of **135** to **136** in the presence of **134**.*

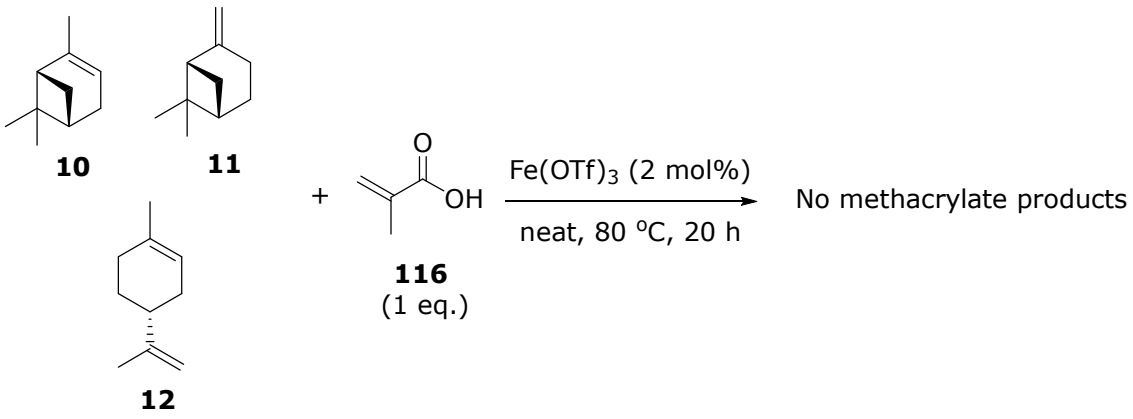
Hydrolysis of the ester groups presented another opportunity to separate **134** and **135**. As **135** is the methacrylate ester of a primary alcohol, it was proposed that this would hydrolyse to the corresponding alcohol at a faster rate than the

secondary ester functionality present in **134**. Unfortunately, attempts at selectively hydrolysing **135** using sodium hydroxide resulted in either no reaction, or hydrolysis of both species at similar reaction rates (Scheme 42).

With the difficulty of separating **134** and **135** from each other following the palladium-catalysed reactions, it was decided that the procedure would not be developed further. A new process was required that provided compounds which could either be produced selectively, or separated from other by-products easily. The palladium catalyst was also an issue – a loading of 5 mol% was required for a reasonable degree of activity to be achieved. On the scale of reaction required to yield a desirable amount of product for polymerisation and subsequent materials testing purposes, the quantity of palladium catalyst required becomes too expensive for the process to remain commercially viable. Even with the relatively low cost of palladium(II) acetate, this is still a significant amount at approximately £11,700 per mole (Merck). Therefore, a process involving the synthesis of a methacrylate species in one step from a commercially available terpene, using a catalyst with a much lower cost, was required.

3.2 Acid-catalysed methacryloxylation

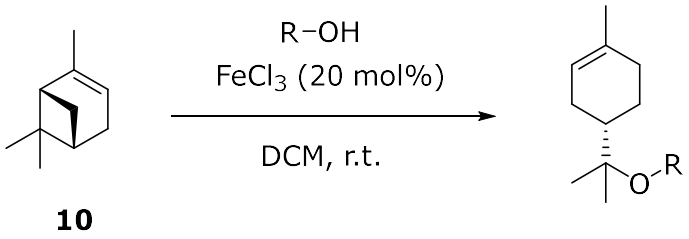
There has been a significant amount of interest in alkene hydrofunctionalisation reactions in recent literature, as detailed in several reviews [108-110]. In particular, the use of iron(III) triflate, whether generated *in situ* [111] or used from a commercial source [112], has gained a significant amount of attention with regards to hydrofunctionalisation reactions, both intramolecular [111] and intermolecular [112]. It was hypothesised that iron(III) triflate may be used as a catalyst to initiate the coupling of readily available terpenes with methacrylic acid – albeit a species much less nucleophilic than any alcohols used in the literature examples.



*Scheme 43. The attempted direct methacryloxylation of **10**, **11** and **12** with iron(III) triflate as a catalyst.*

Using the conditions outlined in the literature for intermolecular reactions [112], direct methacryloxylation of **10**, **11** and **12** was attempted (Scheme 43). In all cases, the starting material was entirely consumed, yet all of the reactions failed to yield any isolable methacrylate ester products. Only an intractable mixture of apparent hydrocarbons could be isolated, with a very low proportion of alkene protons compared to the amount of alkane protons in the ^{1}H NMR spectrum Furthermore, this mixture could not be separated to any degree by either chromatography or distillation. This suggests that cationic rearrangements and possibly some degree of oligomerisation is occurring. Coupled with this, the rate of these processes must be significantly faster than that of the methacrylic acid intercepting a resulting cationic intermediate to form the desired methacrylate

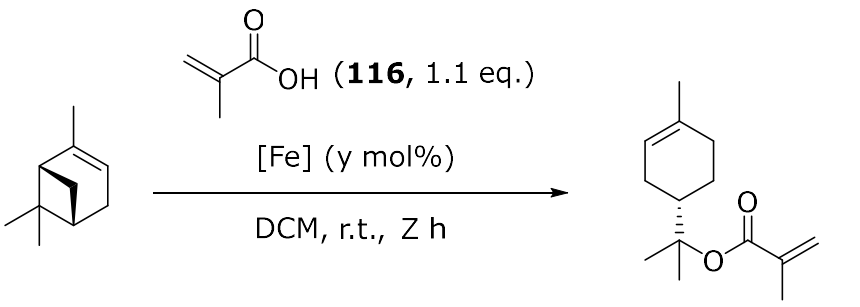
ester products that were targeted. In order to combat this, it was proposed that a change of conditions, including the use of a solvent, would hopefully stabilise the cationic intermediate for a period of time long enough for nucleophilic attack of the carboxylic acid to occur.



10

*Scheme 44. The iron-catalysed hydroalkoxylation of **10** as reported in the literature [113].*

Iron(III) chloride had been found as a catalyst, albeit in a reasonably high loading of 20 mol%, for the hydroalkoxylation of terpenes with various alcohols (Scheme 44) [113]. Using these conditions, it was hypothesised that at least some desired methacrylate product could be isolated if the alcohol in this procedure was swapped for methacrylic acid. A variety of iron(III) catalysts were trialled for this reaction using similar conditions to those outlined in Scheme 44, and the results are shown in Table 2.



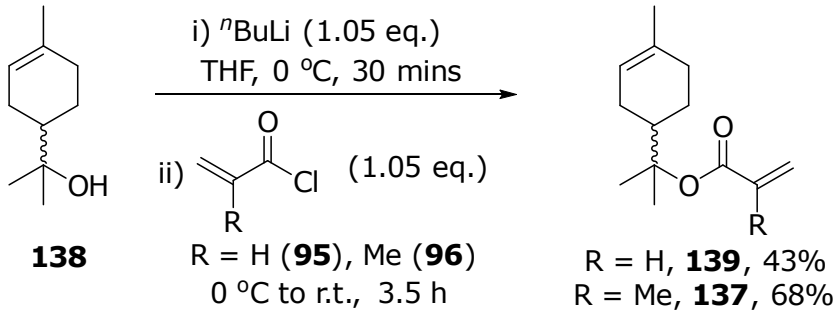
10 **137**

expected product

*Table 2. The results of the investigation into methacryloxylation of **10** with various iron(III) catalysts.*

Entry	Catalyst	y (mol%)	Z (h)	Result
1	$FeCl_3$	20	4	No methacrylate products
2	$FeCl_3$	5	20	No methacrylate products
3	$Fe(acac)_3$	5	20	No methacrylate products
4	$Fe(NO_3)_3 \cdot 9H_2O$	5	20	No methacrylate products
5	$Fe(OTf)_3$	5	20	Methacrylate isolated (12% yield)

The original literature conditions [113] in conjunction with methacrylic acid as the reactant (entry 1) did not yield any desired methacrylate products. Again, the reaction produced a mixture of unidentifiable and inseparable hydrocarbon species. A reduction in catalyst loading (entry 2) provided the same outcome, albeit with a noticeable increase in peak definition shown in the ^1H NMR spectrum. Iron(III) acetylacetonate and ferric nitrate nonahydrate (entries 3 and 4 respectively) were also trialled, yet did not provide any isolable methacrylate-containing products. However, the use of iron(III) triflate as the catalyst (entry 5) furnished a 12% yield of a methacrylate ester containing compound after chromatographic separation.



*Scheme 45. The synthesis of **139** and **137** from α-terpineol (**138**) using a deprotonation and subsequent esterification protocol.*

While this was a promising result, the structure of the product as determined by both ^{1}H and ^{13}C NMR did not seem to match the corresponding structure that had been proposed in the literature alkoxylation reactions. To confirm this suspicion, the proposed structure was synthesised from α-terpineol (**138**) by a deprotonation and subsequent esterification using methacryloyl chloride (**96**). This process yielded the desired product **137** in 68% yield. For reference in the future, the corresponding acrylate **139** was also produced from **138** and acryloyl chloride (**95**) in a yield of 43%.

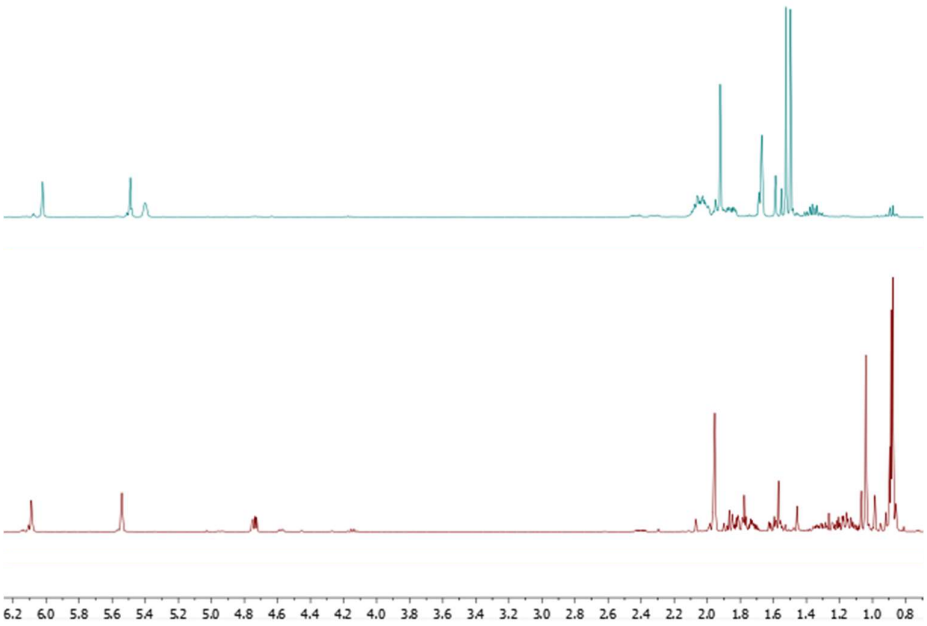
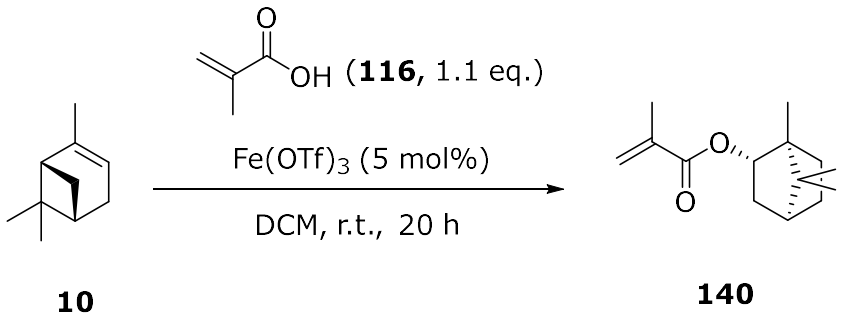
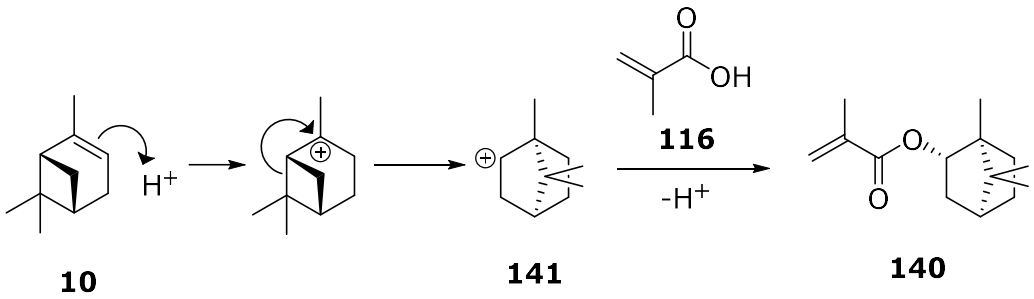


*Figure 11. The stacked ^{1}H NMR spectra of **137** (blue) and the methacryloxylation product (red).*

The ^{1}H NMR spectrum of the methacryloxylation product was then compared with that of **137** (Figure 11). The comparison shows that the two products are not the same – the methacryloxylation product does not contain any other alkene apart from that in the methacrylate functionality.

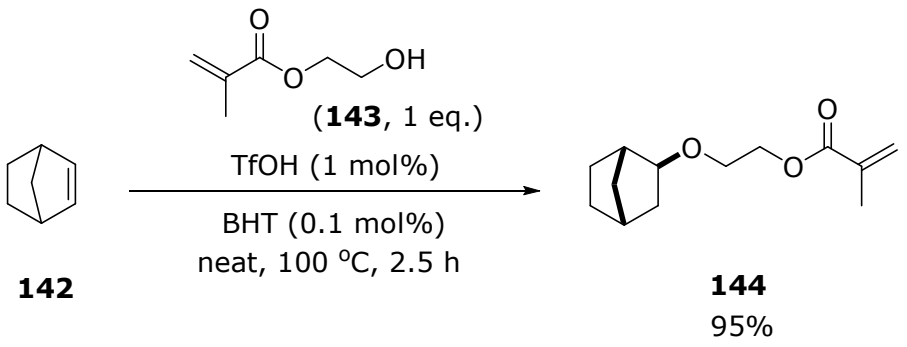


*Scheme 46. The identified structure of **140**.*



*Scheme 47. The mechanism of the acid-mediated formation and subsequent interception of the isobornyl cation (**141**).*

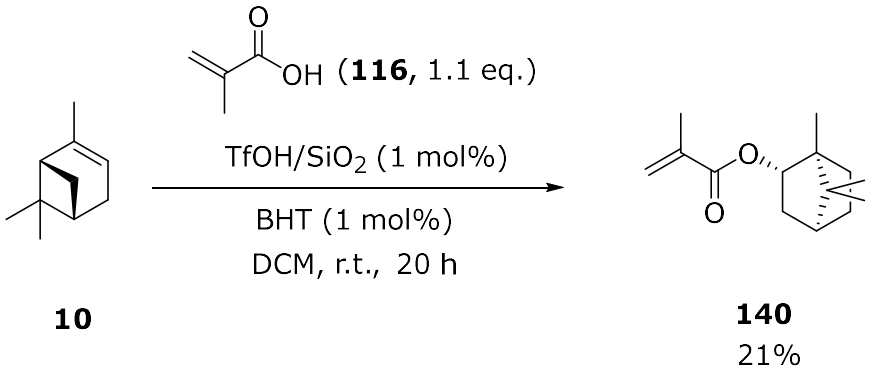
Closer inspection of the ^{1}H, ^{13}C and 2-dimensional NMR spectra revealed that the correct structure of the product was isobornyl methacrylate (**140**). Under the reaction conditions, the cationic intermediate produced from **10** undergoes a Wagner-Meerwein rearrangement to form the relatively stable isobornyl cation (**141**), which is then intercepted by **116** to form **140**. This compound has also been recently synthesised in the literature. [114]



*Scheme 48. The triflic acid catalysed reaction between norbornene (**142**) and hydroxyethyl methacrylate (HEMA, **143**) as detailed in the literature [115].*

Triflate salts of Earth abundant metals have been used in alkene hydrofunctionalisation reactions previously in the literature [116]. One in-depth study showed that when copper(II) triflate was used as the catalyst for a hydroalkoxylation reaction (Scheme 48), the active catalyst in this case is actually triflic acid itself, often formed from the metal triflate salt by adventitious water in the reaction medium [115]. In this instance (Scheme 48), the triflic acid catalyst protonates the alkene functionality to generate the norbornyl cation, which is then intercepted by HEMA to generate the desired product **144**.

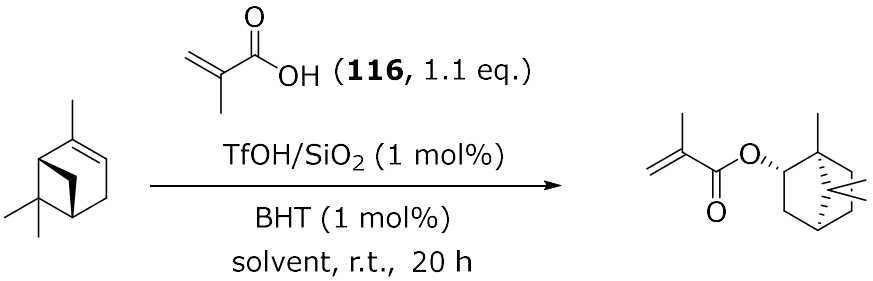
This is advantageous from both a commercial and waste aspect – triflic acid itself is less costly to use than the corresponding metal triflate salts, and also there is no need to remove any metals from the reaction mixture after completion.



*Scheme 49. The synthesis of **140** from **10** using triflic acid as a catalyst.*

To investigate this hypothesis, triflic acid was used as a catalyst in the synthesis of **140** from **10**. However, as triflic acid is a highly corrosive and volatile

reagent, it was first adsorbed onto silica gel in order to provide a catalyst that was easier to handle. Using a catalyst loading of 1 mol% triflic acid, which mimics that used in the literature example, along with BHT in a 1 mol% loading as a radical inhibitor, **140** was synthesised in 21% yield (Scheme 49). Scaling the reaction up by a factor of 25 also resulted in a 21% yield of **140**.



10 **140**

*Table 3. Optimisation of the solvent used in the synthesis of **140** from **10**. Yield values are determined by ^{1}H NMR using an internal standard (methyl benzoate).*

Entry	Solvent	Yield of **140** (%)
1	DCM	20
2	neat	1
3	MeCN	<1
4	THF	<1
5	Et_2O	<1
6	EtOAc	<1
7	Acetone	1
8	2-MeTHF	<1

With the procedure yielding **140** in a low yield, optimisation of the reaction conditions was carried out. Firstly, the solvent was varied to see if any increase in yield could be identified (Table 3). However, only dichloromethane (entry 1) seemed to give a viable yield of **140**, at 20%. Using no solvent (entry 2) only provided **140** in 1% yield by NMR. All other solvents contained either a nitrogen or oxygen functionality, which could have intercepted the triflic acid proton and initiated side reactions.

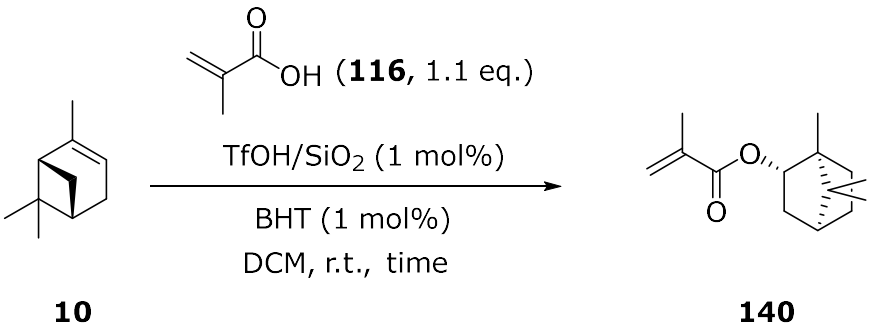
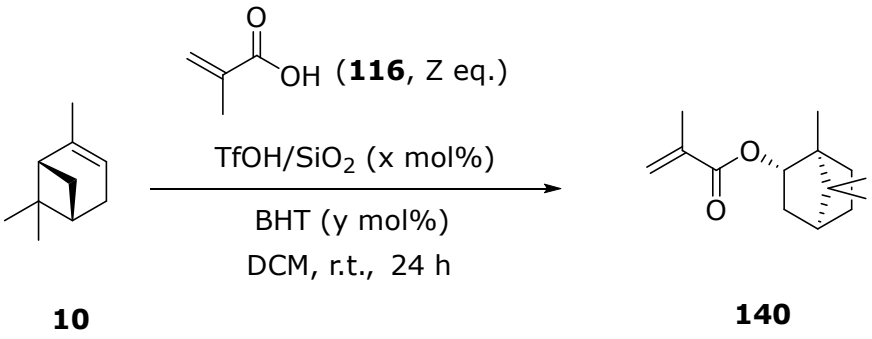


*Table 4. The optimisation of reaction time and its effect on the yield of **140**. Yields of **140** were determined by ^{1}H NMR using an internal standard (methyl benzoate).*

Entry	Time (h)	Yield of **140** (%)
1	1	<1
2	2	<1
3	3	<1
4	4	<1
5	6	1
6	8	1
7	16	12
8	24	22
9	48	22

Reaction time was then investigated (Table 4). The yield of **140** slowly increased from 1 through to 16 hours (entries 1-7) and reached a maximum of 22% at 24 hours (entry 8). After 48 hours (entry 9) there was no significant improvement in yield, therefore 24 hours was taken as the optimum reaction time for the procedure.



10 **140**

*Table 5. The optimisation of catalyst loading, BHT loading and methacrylic acid loading and their effect on the yield of **140**. Yields of **140** were determined by ^{1}H NMR using an internal standard (methyl benzoate).*

Entry	x (mol%)	y (mol%)	Z (eq.)	Yield of **140** (%)
1	1	1	1.1	20
2	1	1	1.2	16
3	1	1	1.5	13
4	1	1	2	9
5	1	1	3	23
6	1	1	5	25
7	0.5	1	5	4
8	3	1	5	25
9	5	1	5	21
10	1	0	5	23
11	1	0.5	5	25
12	1	5	5	4

The next parameters to investigate in the optimisation of the process were the loadings of the triflic acid catalyst, the BHT additive and the methacrylic acid (**116**) reactant (Table 5). Increasing the methacrylic acid equivalents (entries 1-6) showed a peculiar trend of decreasing the yield of **140** up to 2 equivalents (entry 4) and then increasing up to 5 equivalents. However, using 5 equivalents (entry 6) furnished **140** in 25% yield – a reasonable improvement on the original conditions.

Decreasing the loading of triflic acid (entry 7) caused a sharp drop-off in yield, and increasing the loading (entries 8 and 9) provided no further improvement in the yield of **140**, therefore 1 mol% was taken as the optimal value.

Finally, the loading of the radical inhibitor BHT as an additive was investigated – decreasing the loading had no major effect on yield (entries 10 and 11). However, increasing to 5 mol% caused the yield of **140** to decrease to 4% (entry 12). As BHT is a phenol, albeit sterically hindered, it may have been nucleophilic enough to intercept the cationic intermediates in the reaction at a faster rate than methacrylic acid.

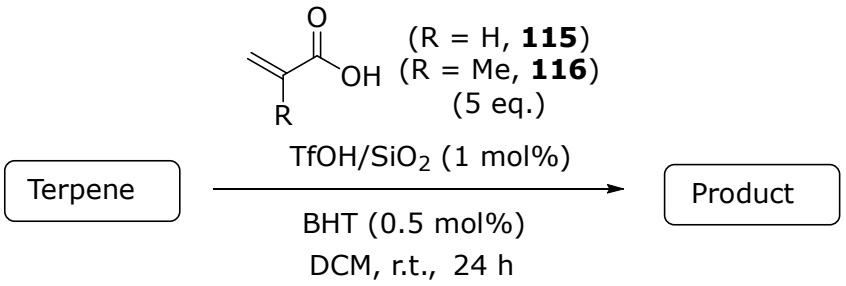
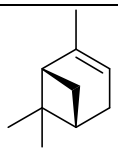
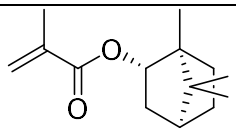
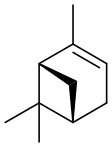
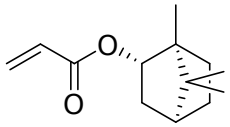
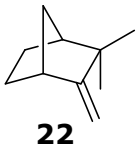
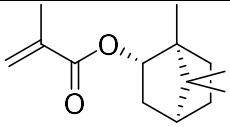
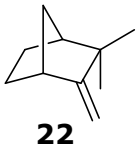
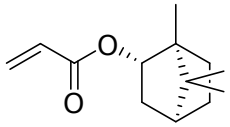
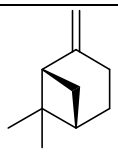
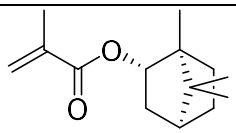
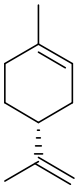


Table 6. The scope of the optimised methacryloxylation conditions using silica-supported triflic acid as a catalyst.

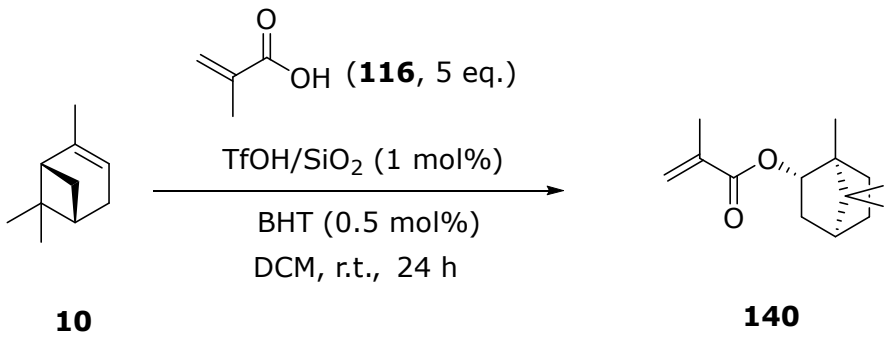
Entry	Terpene	Scale (mmol)	R =	Product	Yield (%)
1	 **10**	100	Me	 **140**	35
2	 **10**	10	H	 **145**	22
3	 **22**	10	Me	 **140**	78
4	 **22**	10	H	 **145**	85
5	 **11**	1	Me	 **140**	18
6	 **12**	1	Me	No methacrylate products	N/A

With optimised conditions identified, the scope of the reaction was then explored (Table 6). Scaling the original reaction to 100 mmol of **10** (entry 1) resulted in an improved yield of 35% of the desired product **140**. Alternatively, when acrylic acid (**115**) was used as the reactant on a 10 mmol scale (entry 2), **145** was produced in 22% yield.

The use of camphene (**22**) as the starting material with methacrylic acid (entry 3) was also trialled, and gave **140** in 78% yield on a 10 mmol scale. Also, when **115** was used as the reactant with **22** on the same scale (entry 4), **145** was formed in an 85% yield. The marked improvement in yield is most likely due to camphene undergoing a very reliable Wagner-Meerwein rearrangement to the isobornyl cation, as detailed in the literature [39-40, 117-118]. By contrast, α-pinene cationic rearrangements can often lead to a multitude of products as there are more possible charged intermediates, and indeed most naturally occurring terpenes are produced from some of these species [119]. However, the cost of camphene as a starting material is considerably higher than α-pinene, due to the former material not being available in large quantities as a waste product from existing industries. Therefore, on a large scale a cost analysis would be required that took availability of the materials and the yield of the process into account, to decide the best method for the production of **140** in that instance.

Using β-pinene (**11**) as the starting material on a small scale (entry 5) also provided **140** in 18% yield. However, using limonene (**12**) as the substrate (entry 6) failed to provide any isolable methacrylate ester product. This result suggests that an important driving force of the reaction is the release of strain when the 4-membered ring in the pinene skeleton is opened.

Although these optimised conditions work to some degree, there are some issues to do with sustainability about the process. Firstly, the necessity for a chlorinated solvent, in dichloromethane, in order to generate products is an issue. Dichloromethane is a toxic solvent to both humans and organisms in the wider ecosystem, therefore if the process is to be truly considered sustainable and safely operable on a large scale – which is required for materials used to manufacture polymers - this factor will need to be changed.



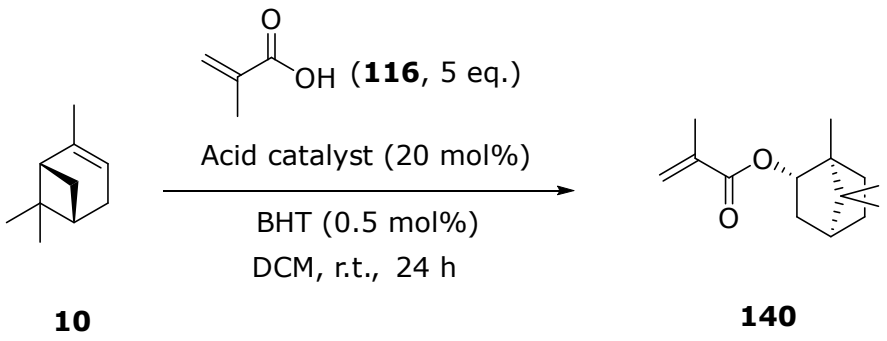
10 **140**

Table 7. The attempts at recycling the silica-supported triflic acid catalyst for use in multiple reactions. Yields were calculated by ^{1}H NMR using an internal standard (methyl benzoate).

Entry	Number of times catalyst used previously	Yield of **140** (%)
1	0	20
2	1	1
3	2	>1

Secondly, triflic acid is quite an expensive catalyst relative to other Brønsted acids, and its use on a large scale would make a commercial polymer production process not economically viable. It was hypothesised that recycling of the silica-supported triflic acid for use in further reactions would lessen the financial impact of using a triflic acid catalyst. Unfortunately, attempts to recycle the catalyst were unsuccessful, leading to a large depreciation of the yield of **140** when used again in subsequent reactions (Table 7, entries 2 and 3). This suggests that the triflic acid species is leaching into the solvent during the reaction, leading to loss of catalyst activity when the heterogeneous catalyst support is recycled. Coupled with this drawback, special and expensive reaction vessels would be needed to avoid corrosion when equipment comes into contact with the triflic acid catalyst or, due to leaching, any of the reaction mixture in a prospective chemical plant.

With all of these drawbacks considered, further optimisation of the process was carried out to try and identify a process that did not require a chlorinated solvent, or triflic acid as the catalytic species.



10 **140**

*Table 8. The variation of Brønsted acid catalyst and its effect on the yield of **140**. Yields were calculated by ^{1}H NMR using an internal standard (1,3,5-trimethoxybenzene).*

Entry	Catalyst	Yield of **140** (%)
1	H_2SO_4	10
2	*ortho*-H_3PO_4	<1
3	PPA	7
4	Amberlyst-15	2

As the acid catalyst loading was reasonably low at 1 mol%, the activity of Brønsted acids with less negative pK_a values than triflic acid at this stoichiometry may not have been enough to initiate catalysis of the methacryloxylation procedure. Therefore, for the Brønsted acid screen (Table 8), the loading was increased to 20 mol%, in order to ensure activity of a species would be displayed. Sulfuric acid (entry 1) gave the best yield in the screen of 10%, whereas *ortho*-phosphoric acid (entry 2) failed to show any reasonably activity in producing **140**. Both polyphosphoric acid (entry 3) and the sulfonic acid resin Amberlyst-15 (entry 4) showed some degree of activity, but not to the extent of that exhibited by sulfuric acid.

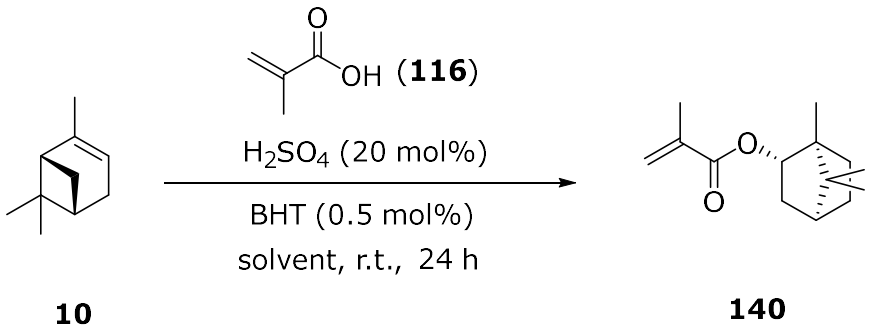


*Table 9. The optimisation of solvent and concentration, and their effect on the yield of **140**. Yields of **140** were calculated by ^{1}H NMR using an internal standard (1,3,5-trimethoxybenzene).*

Entry	Solvent	Concentration (relative to **10**) (mol dm^{-3})	Yield of **140** (%)
1	DCM	1	17
2	$CHCl_3$	1	17
3	DCE	1	9
4	DMC	1	8
5	neat	1	17
6	neat	0.5	11
7	neat	2	15
8	neat	4	11

With dichloromethane the only solvent providing any viable yield of **140** so far, chlorinated solvents were investigated in a solvent optimisation screen (Table 9, entries 1-3). Chloroform (entry 2) provided a similar yield to that of dichloromethane (entry 1), yet 1,2-dichloroethane (entry 3) only furnished **140** in 9% yield. Dimethyl carbonate, a solvent recently documented as a more sustainable alternative to dichloromethane with similar properties [120], was also trialled in the reaction (entry 4), yet only produced an 8% yield of **140**.

Using a neat reaction mixture, yet maintaining the same concentration of **10** by increasing the amount of methacrylic acid, was also attempted (entry 5). This produced a 17% yield of **140**, comparable to that when DCM was used as the reaction solvent (entry 1). Attempts at both reducing (entry 6) and increasing

(entries 7 and 8) the concentration of the reaction mixture led to depreciation in the yield of **140**.

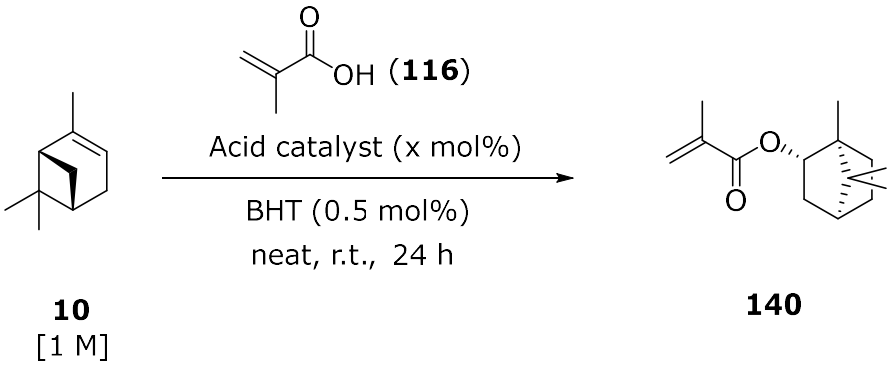


*Table 10. The investigation into sulfuric acid catalyst loading, and its effect on the yield of **140**. Yields were calculated using ^{1}H NMR with an internal standard (1,3,5-trimethoxybenzene).*

Entry	x (mol%)	Yield of **140** (%)
1	10	19
2	20	22
3	30	22
4	50	20

Sulfuric acid catalyst loading was the final reaction parameter to be optimised (Table 10). Reducing the loading to 10 mol% (entry 1) caused a slight worsening of the yield of **140** compared to the original conditions (entry 2), whereas increasing to 30 mol% or 50 mol% (entries 3 and 4) caused no further improvement of the reaction yield.

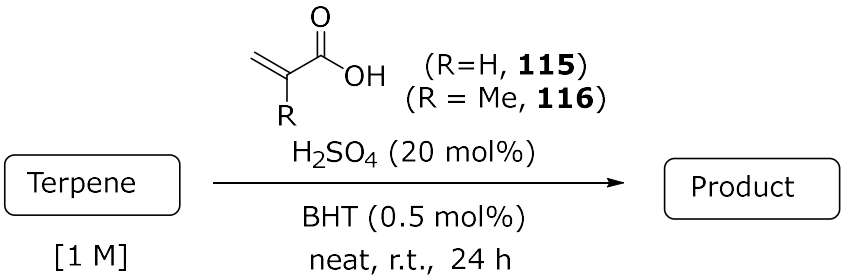
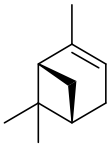
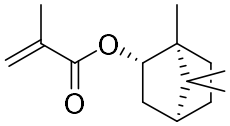
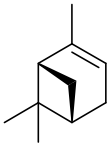
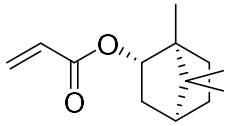
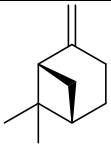
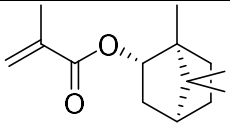
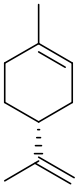
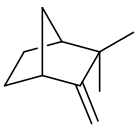
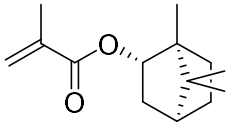
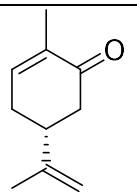
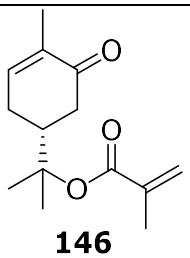
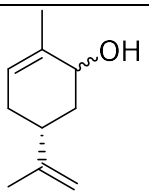
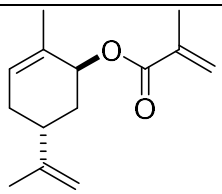
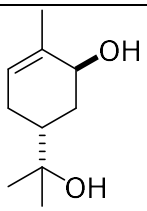
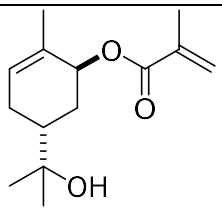


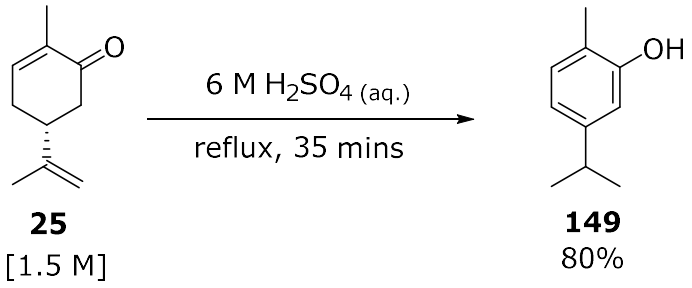
Table 11. The investigation into the scope of the optimised sulfuric acid catalysed (meth)acryloxylation reaction conditions.

Entry	Terpene/Terpenoid	R =	Product	Yield (%)	d.r.
1	 **10**	Me	 **140**	22	N/A
2	 **10**	H	 **145**	11	N/A
3	 **11**	Me	 **140**	22	N/A
4	 **12**	Me	No methacrylate products	0	N/A
5	 **22**	Me	 **140**	83	N/A

6	 **25**	Me	 **146**	11	N/A
7	 **147** 1:1 d.r.	Me	 **148**	50	6:1
8	 **126** >20:1 d.r.	Me	 **127**	10	>20:1

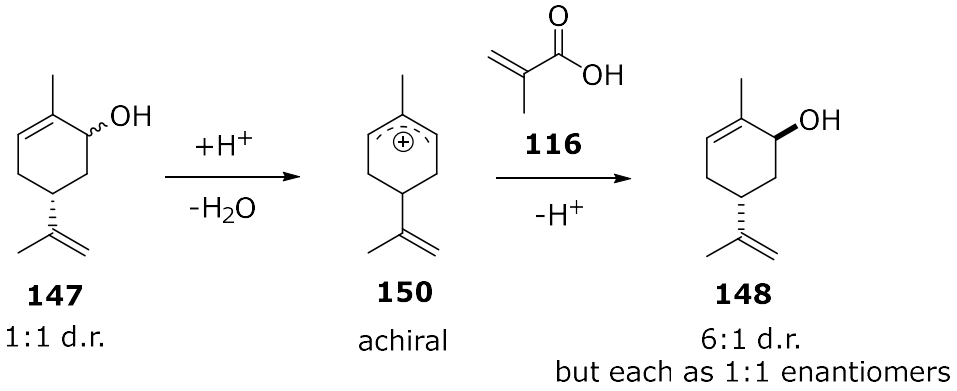
An investigation into the scope of the reaction using the optimised conditions was then carried out (Table 11). Firstly, using the original reactants (entry 1) generated **140** in an isolated yield of 22%. Using acrylic acid (**115**, entry 2) gave acrylate **145** in 11% yield – a significant decrease compared to the corresponding methacrylate product, which suggests that acrylic acid is either a worse nucleophile and intercepts resulting carbocationic intermediates at a reduced rate, or that acrylic acid itself is less stable to the reaction conditions.

When **11** was used as the substrate with methacrylic acid (entry 3), **140** was also isolated in a 22% yield. However, **12** (entry 4) failed to furnish any methacrylate ester products. In conjunction with the result obtained from the scope of the triflic acid catalysed methacryloxylation procedure (Table 7, entry 6), this suggests that the release of the ring strain from the 4-membered unit of the pinene skeleton is an important thermodynamic driving force for product formation in both procedures. As also previously seen before, **22** (Table 12, entry 5) tolerated the reaction conditions well, and produced **140** in 83% yield.



*Scheme 50. The literature procedure to generate **149** from **25** using acidic conditions [121].*

Terpenoids were also used as substrates in this investigation of reaction scope (entries 6-8). When **25** (entry 6) was submitted to the reaction conditions, methacrylate **146** was furnished in 11% yield. This result was unexpected, as the enone functionality remained intact – it has been documented in the literature that carvone readily aromatises in acidic conditions (Scheme 50) [121]. This phenol-containing species **149** most likely accounted for the remaining mass, but was not isolated as it may have been left in the aqueous work-up fraction after washing with aqueous sodium hydroxide.



*Scheme 51. The formation of **148** from **147** with a degree of diastereoselectivity, but with each diastereomer as a racemic pair of enantiomers.*

Using carveol as a 1:1 mixture of isomers (**147**) as the substrate (entry 7) gave **148** in 50% yield. Interestingly, the d.r. of the product had been enriched to 6:1, which suggests that the allylic cationic intermediate (**150**, Scheme 51) had been formed and then intercepted by the methacrylic acid, as opposed to a sulfuric acid-catalysed Fischer esterification mechanism. **148** has also

alternatively been synthesised via a palladium catalysed C-H activation process. [122]

When *trans*-sobrerol (**126**) was submitted to the reaction conditions (entry 8), **127** was furnished in 10% yield, with the diastereomeric ratio of the product similar to that observed in the starting material. With this substrate the similar occurrence of an achiral allylic cation intermediate also occurs, therefore **127** is also most likely a scalemic mixture of enantiomers.

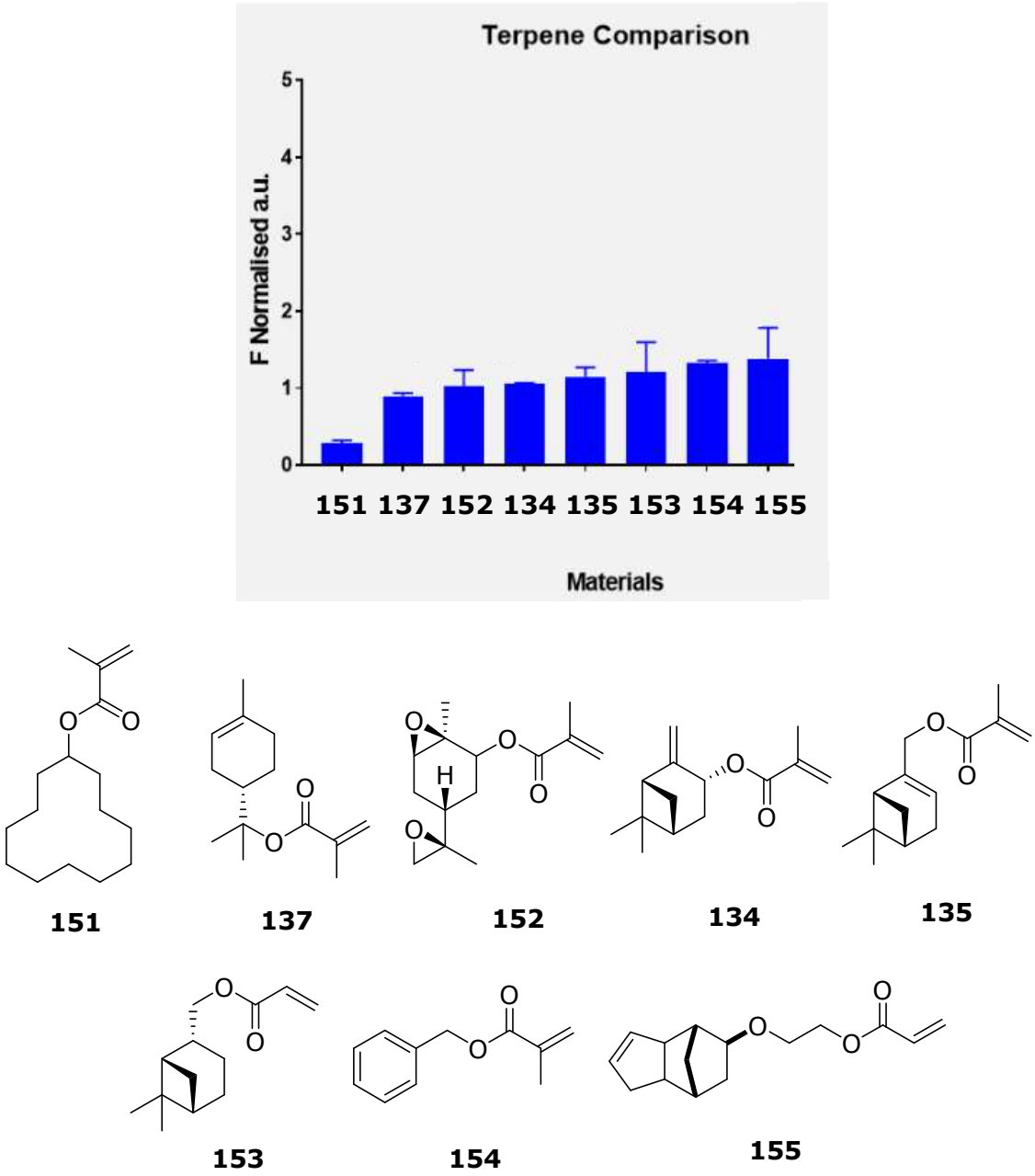
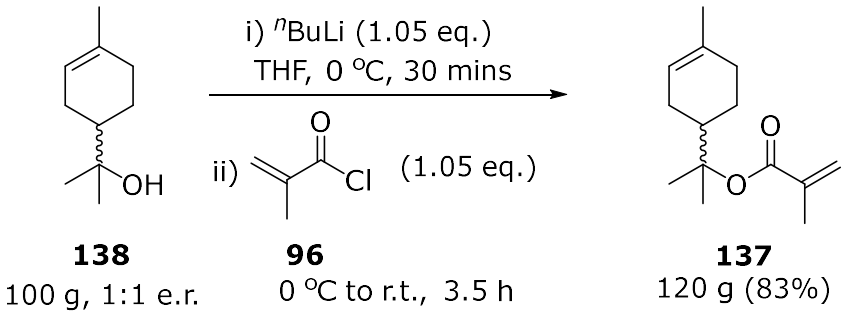


Figure 12. The results of the anti-attachment assay, conducted by Olutoba Sanni, a PhD student in the Department of Engineering.

With a selection of novel compounds produced by the reaction scope, the identification of an application for any potential materials made from the monomers was necessary. The compounds were given to colleagues in the Department of Engineering for an assay of anti-attachment testing (Figure 12). This process involves deposition of a solution containing the monomer and an

ultra-violet initiator onto a surface, followed by ultra-violet irradiation and then solvent removal. The coated surface is then placed into an aqueous medium containing bacteria, and the quantity of bacteria that can adhere to the surface is determined and recorded as an arbitrary value (the A value). A lower A value corresponds to a lesser degree of bacterial adhesion on the surface, and materials with low A values have potential use as coatings in medical applications.

From the assay, **137** was highlighted as an excellent monomer for the production of materials for anti-attachment purposes. The Engineering department had recently received approval for the use of **155** in coatings for medical applications, yet **137** had a lower A value. Only the monomer **151** had a lower A value in the assay, and **151** was modelled computationally to have a very low A value. Other monomers from the wider terpene project, including **134**, **135** and **153** were found to have low A values, but not to the same degree as **137**. However, monomers that are not shown in the graph, including **140**, did not exhibit any significant anti-attachment activity in the assay.



138
100 g, 1:1 e.r.

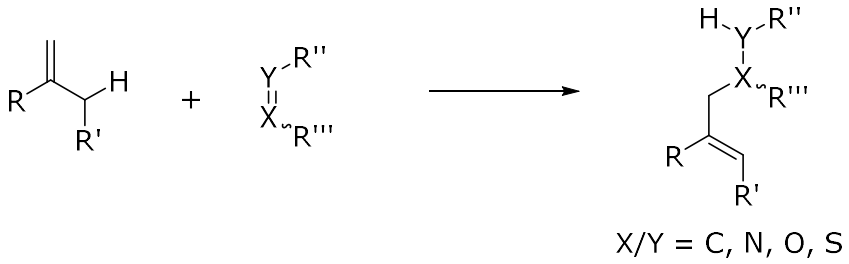
96
0 °C to r.t., 3.5 h

137
120 g (83%)

*Scheme 52. The reaction to produce **137** from **138** on a 100 gram scale. This reaction was performed in collaboration with Dr. Alexander Ilchev, a post-doctoral research associate in the group of Prof. Derek Irvine.*

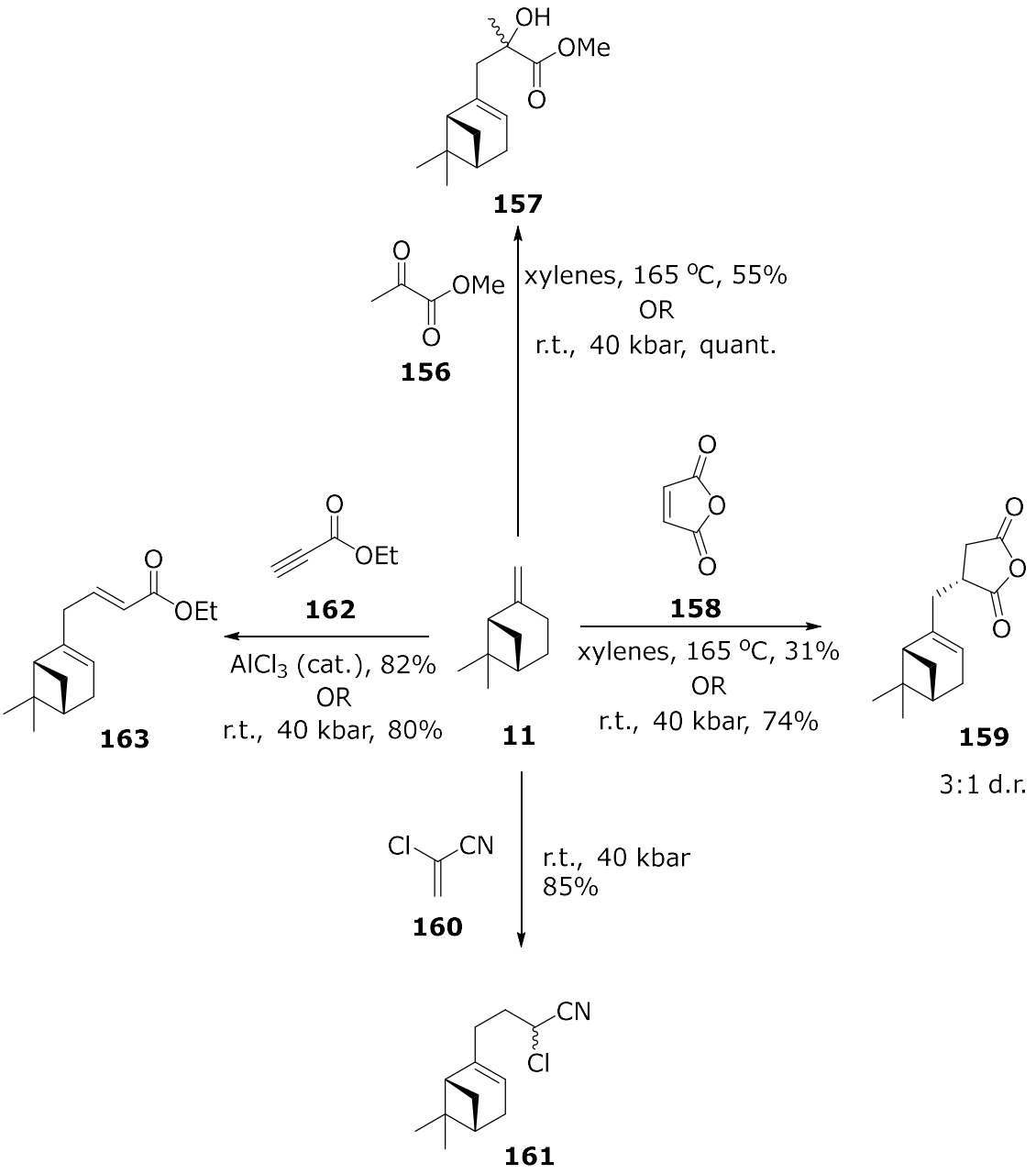
As **137** had been shown to have excellent anti-attachment activity, the Department of Engineering required approximately 100 grams of the material in order to provide enough quantity for various further tests. The original synthesis was then carried out using 100 grams of **138** as the starting material. This reaction provided 120 grams (83% yield) of **137**. The material is currently being used in the Department of Engineering to explore the application of **137** as both a catheter coating, and a vaccine adjuvant.

3.3 Synthesis of potential monomers using the Alder ene reaction



Scheme 53. A generalised reaction scheme for the Alder ene reaction.

Since the discovery of the Alder ene reaction (Scheme 53) [123] in 1943, there have been many applications of the process in complex target synthesis [124-125]. However, the reaction comes with a major drawback - as a group transfer reaction, the activation energy is typically higher than other pericyclic processes such as the Diels-Alder [4+2] cycloaddition. As a result, only certain privileged structures are able to participate in the Alder ene reaction in a synthetically useful transformation. Alkenes with multiple electron-donating or electron-withdrawing groups in order to raise the HOMO or lower the LUMO enough respectively are often required in order for the reaction to proceed [126], which limits the scope of synthetic possibility with this class of transformation.



*Scheme 54. A selection of Alder ene reactions involving **11** from the literature [127-130].*

11 has been extensively used in Alder ene reactions in the literature (Scheme 54). Under thermally-mediated reaction conditions, **11** can be used in conjunction with methyl pyruvate (**156**) [127] or maleic anhydride (**158**) [128] to generate **157** in 55% yield, or **159** in 31% yield respectively. Lewis acid catalysts such as $AlCl_3$ can also be used to mediate Alder ene reactions, and is used to generate **163** in 82% yield when **162** is used as the enophile [129].

Alternatively, Alder ene reactions have also been shown to occur at ambient temperature under very high pressures of 40 kbar [130], effective on a wide variety of substrates and with consistently superior yields when compared to thermal or Lewis acid initiated reactions (Scheme 54).

Of particular interest is the Alder ene reaction with **11** and **158**. [127-8] In the two literature examples, the studies discuss that the observed product directly isolated from the reaction mixture is a 3:1 diastereomeric mixture of **159**, with the major diastereomer able to be purified through crystallisation (the minor diastereomer not crystallising nearly as well and therefore remaining in solution during the crystallisation process). [127] The studies also show that the major diastereoisomer has (*R*)-configuration at the chiral centre located on the anhydride ring.

The product **159** is a substituted succinic anhydride, which have been used in condensation polymerisations as both a "masked" di-carboxylic acid for polyesterifications [131] or directly to make poly(anhydride) materials [132]. Di-carboxylic acid species are often relatively insoluble in organic solvents due to their high degree of hydrophilicity, which limits the versatility of the procedure. Masking the di-acid functionality as a cyclic anhydride improves the hydrophobicity and hence solubility of the moiety, while also improving the reaction rate of the initial esterification at the start of the polymerisation procedure.

It was hypothesised that a robust procedure could be developed to produce **159** with a high degree of sustainability. The transformation has an atom economy of 100%, and literature examples have shown that the use of a Lewis acid catalyst can traverse the activation energy barrier for the process at temperatures close to that of ambient conditions – with this specific example being used as part of this article [129].

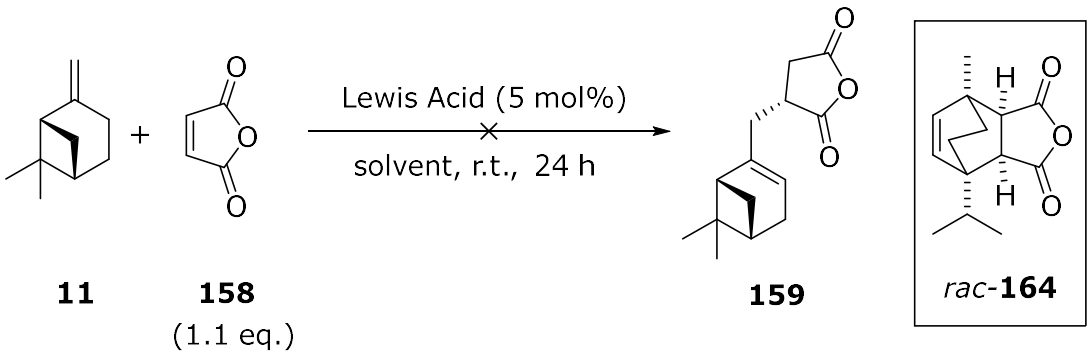
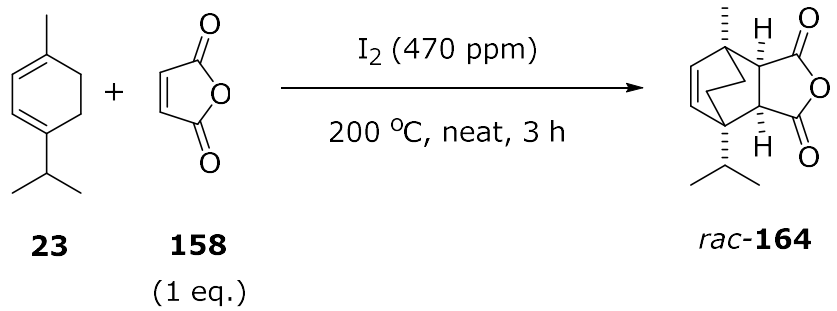


*Table 12. The results of the Lewis acid catalyst screen for the synthesis of **159** from **11** and **158**.*

Entry	Lewis Acid	Solvent	Yield of **159** (%)	Yield of *rac*-**164** (%)
1	$FeCl_3$	EtOAc	0	7
2	$FeCl_3$	DCM	0	0
3	$AlCl_3$	EtOAc	0	0
4	$AlCl_3$	DCM	0	0
5	$ZnCl_2$	EtOAc	0	0
6	$ZnCl_2$	DCM	0	0
7	$ZrCl_4$	EtOAc	0	0
8	$ZrCl_4$	DCM	0	0
9	$TiCl_4$	EtOAc	0	0
10	$Ti(OEt)_4$	EtOAc	0	0
11	$SnCl_4$	EtOAc	0	0
12	$BF_3{\cdot}OEt_2$	EtOAc	0	0

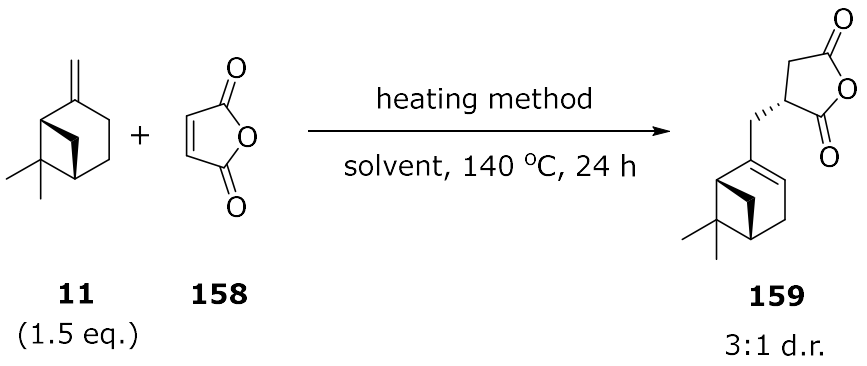
A screen of various Lewis acid catalysts was conducted to attempt to synthesise **159** using ambient conditions (Table 12). However, none of the trialled combinations of Lewis acids and solvent systems were able to yield **159**, with almost all conditions (entries 2-12) yielding no terpene-based anhydride species, which suggests that the activation energy of the process is still too high for most Lewis acids to be used as catalysts at room temperature.



Scheme 55. The literature synthesis of rac-***164*** *from a Diels-Alder cycloaddition between* ***23*** *and* ***158*** *[133].*

Despite most Lewis acid and solvent combinations yielding no product, the combination of iron(III) chloride and ethyl acetate as catalyst and solvent respectively (entry 1) did lead to a small amount of a new product forming. After isolation, the result of the reaction was not the desired anhydride product **159**, but was a different terpene-based anhydride species, *rac*-**164**. This species is most readily formed as a Diels-Alder adduct from a reaction between α-terpinene (**23**) and **158** (Scheme 55) [133]. No specific determination of the product was carried out to determine *endo*- or *exo*- configuration in this investigation, as this was not the desired product – however, previous literature studies have shown that achiral terpene-based dienes exclusively produce the *endo*- isomer in Diels-Alder reactions with **158** [134-135], so the configuration of *rac*-**164** was tentatively assigned as *endo*- in this case.

Therefore, α-terpinene must have been formed in the reaction conditions from **11** *via* Lewis acid catalysed carbocationic rearrangements. The industrial synthesis of **23** uses such rearrangements, catalysed by Brønsted acids, in its synthesis from α-pinene (**10**) [136]. This suggests that the proposed mechanism is possible under these reaction conditions. However, why only the conditions highlighted in entry 1 produced *rac*-**164** whereas all of the other trialled conditions did not remains to be seen.



11 (1.5 eq.) **158** **159** 3:1 d.r.

*Table 13. The investigation into the synthesis of **159** using high temperature. Yields were calculated using ^{1}H NMR with an internal standard (pyrazine).*

Entry	Solvent	Heating method	Yield of **159** (%)
1	xylenes	conventional	38
2	xylenes	microwave	10
3	-	conventional	0
4	-	microwave	6

With the Lewis acid catalysis screen failing to yield **159** in all instances, an approach to a thermally mediated Alder ene reaction was attempted (Table 13). Initially, conditions described in the literature were used (entry 1) [126] and gave **159** in 38% yield by ^{1}H NMR. Switching to microwave irradiation (entry 2) led to a sharp decrease in yield, as did the attempts at carrying out a solvent-free reaction (entries 3 and 4).

With conditions identified for the synthesis of **159**, the next step was to ascertain a standard operating procedure that could isolate **159** reliably. The main issue with this reaction is that it is very difficult to achieve higher than 50% conversion of the starting material – using higher reaction temperatures and longer reaction times both did not improve this value further.

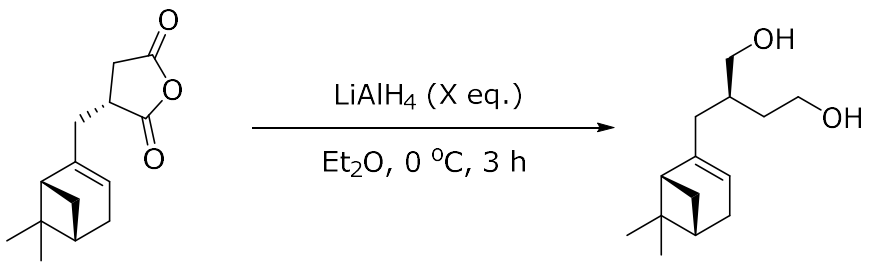
After the reaction, the solvent and excess **11** was removed under reduced pressure at 50 °C. The remaining crude solid residue contained a lot of unreacted **158** due to the poor degree of conversion. As a result of this, a multitude of solvents for standard hot recrystallisation procedures to yield pure **159** from the crude reaction mixture were trialled, but all failed to produce **159**

to a reasonable degree of purity. Moreover, all of the solvents that showed some degree of success were very low yielding. Therefore, it was decided that a precipitation strategy to achieve isolation of **159** would be investigated.

Treatment of the crude solid residue with ethyl acetate caused full dissolution of all of the components within it. It was discovered that upon adding petroleum ether to make the solvent mixture in a 1:1 ratio, a colourless precipitate was formed. Filtration and subsequent NMR analysis of the precipitate determined that it was **158** that first crashed out of solution. Further addition of petroleum ether to the filtrate caused no extra precipitate to form. Subsequent evaporation of the solvent from the filtrate under reduced pressure yielded a pale yellow solid in 41% yield.

^{1}H NMR analysis showed this solid to be **159**, contaminated with approximately 2% **158**. Further purification of this material was challenging, but can be achieved using a recrystallisation from hot petroleum ether. Unfortunately, this process is prone to poor mass recovery – mimicking the initial problems earlier identified with hot recrystallisation techniques. A potential reason for this could be the process only yielding the major diastereomer in this case, as this was previously observed in literature examples. [127-128] However, the pale yellow solid obtained after the precipitation process was deemed of a sufficient purity for further use. Most importantly, this investigation has found a way of purifying **159** to a reasonable degree without requiring the need for column chromatography – an important factor in increasing the scale to those required for polymerisation purposes.

The next step was to synthesise a terpene-based diol, to partner the anhydride **159** in a polyesterification process that yielded a material made almost entirely from terpene-based substrates (Table 14). It was evident that this could be achieved by a total reduction of the anhydride functionality present in **159**.



159
3:1 d.r.

165
3:1 d.r.

*Table 14. The investigation into the synthesis of **165** by reduction of **159** with $LiAlH_4$.*

Entry	Scale (mmol of **159**)	X (eq.)	Yield of **165** (%)
1	0.5	4	35
2	0.5	8	98
3	2.5	8	74
4	10.0	8	74

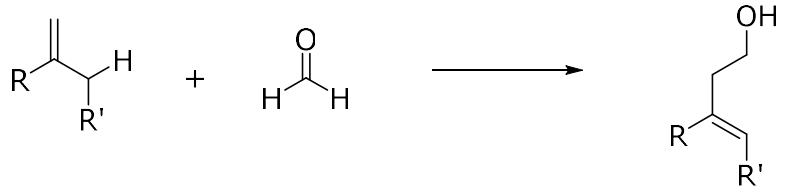
Initial trials on a small scale (0.5 mmol) were conducted using 4 equivalents of lithium aluminium hydride (LAH, entry 1), but only produced the desired diol **165** in 35% yield. This disappointing result was most likely attributed to quenching of the LAH reagent by adventitious water present in the solvent and/or on the equipment used prior to the addition of the anhydride, even though care had been taken to make sure neither of these were present through use of alumina-dried solvent and dried glassware.

To combat this issue, glassware was dried multiple times under vacuum. In combination with an increase in loading of LAH to 8 equivalents (entry 2), the yield was improved to 98%. An increase in scale by a factor of 5 (entry 3) led to a depreciation in yield to 74%, but this value was maintained through a further increase in scale by a factor of 4 (entry 4).

Another advantage of this process was the absence of any further purification required after the reaction work-up. When a Fieser work-up protocol was used to remove the aluminium-containing by-products [137], the desired terpene-based diol **165** was isolated cleanly.

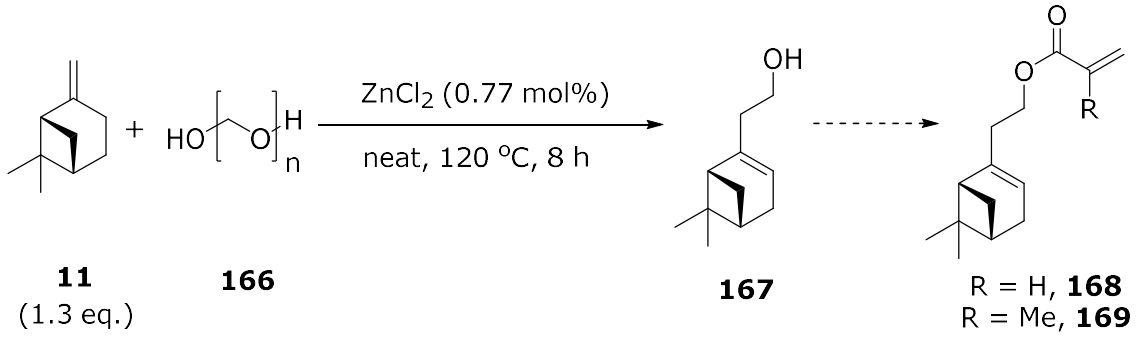
With synthesis methods now established for both a di-acid equivalent and a diol, the respective compounds **159** and **165** are ready for polymerisation tests. Polyesters made entirely from renewable feedstocks could be formed from the reaction of **159** and **165**, the reaction of **159** with other renewably sourced diols [138], or the reaction of **165** with other examples of sustainably sourced di-carboxylic acids [139].

3.4 Synthesis of (meth)acrylate esters from 11 using the Prins reaction



Scheme 56. The general reaction scheme for a Prins reaction to produce a homoallylic alcohol product.

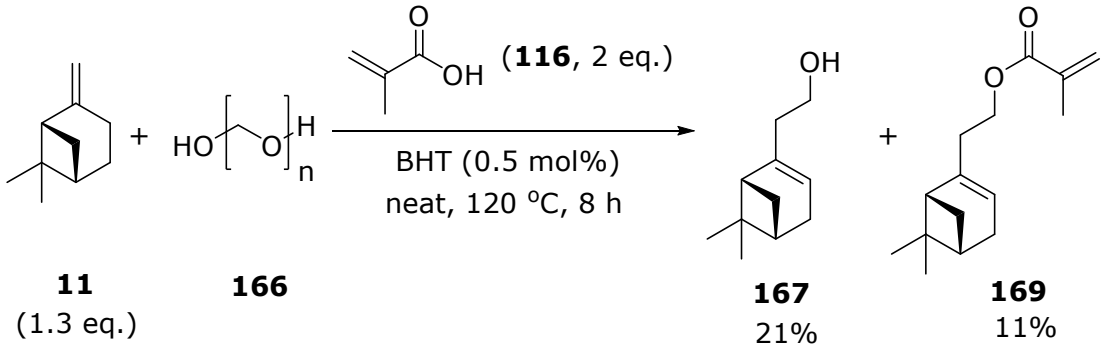
One example of an Alder ene reaction has been used so often that it has become a named reaction in its own right. The use of formaldehyde as a reaction partner in an Alder ene reaction was first conducted in 1919 [140] and has since become known as the Prins reaction (Scheme 56) - and has been used in total syntheses of natural products [141]. Because of the high reactivity of formaldehyde as the enophile, a wider variety of alkenes can be used as reacting partners, and operating conditions are often less harsh than those mediating standard Alder ene reactions.



*Scheme 57. An example from the literature of the synthesis of nopol (**167**) from **11** and paraformaldehyde (**166**) [142], followed by the proposed (meth)acryloylation to produce **168** and **169**.*

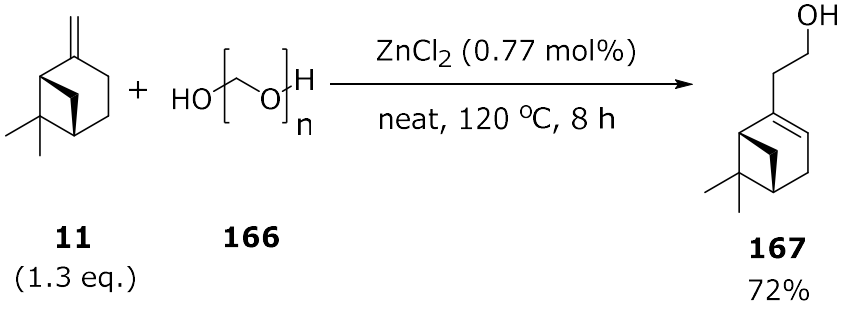
11 has been used in such procedures previously in the literature, to generate the homoallylic alcohol species **167**, using either Brønsted or simple Lewis acids as catalysts (Scheme 57) [142], or using a heterogeneous Lewis acidic catalyst [143]. It was hypothesised that nopol could then be converted to the

corresponding acrylate (**168**) or methacrylate (**169**) using standard esterification conditions to generate viable monomers in 2 steps from **11** (Scheme 57). These are compounds which have not yet been reported, as well as their corresponding polymers, in the literature.



*Scheme 58. The synthesis of **169** in one step from **11** using methacrylic acid (**116**) as the Brønsted acid and reacting partner.*

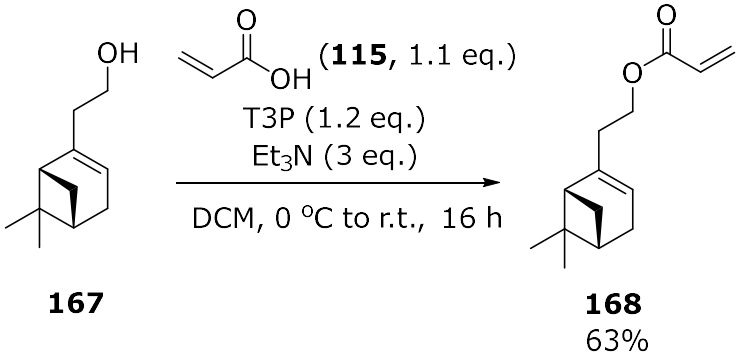
The literature documented a synthesis of the acetate ester of nopol using acetic acid in conjunction with **11** and **166** [142]. It was hypothesised that using **116** instead of acetic acid would yield **169** in 1 step from **11**. With BHT as an additive to inhibit polymerisation of either **116** or **169** under the reaction conditions, **169** was synthesised in 11% yield after purification by column chromatography, with a further 21% of **167** also isolated during the purification process (Scheme 58).



*Scheme 59. The synthesis of **167** from **11** using zinc chloride as a Lewis acid catalyst.*

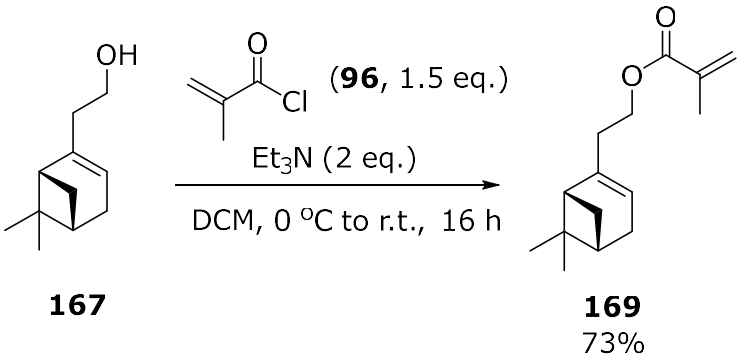
While this result was interesting, it was proposed that the overall yield would be greater than 11% over 2 steps. Therefore, **167** was synthesised from **11**, using

zinc chloride as a Lewis acid, to synthesise **167** in a 72% yield (Scheme 59) using conditions outlined in the literature [142].



*Scheme 60. Acryloylation of **167** to synthesise **168** using a T3P®-mediated ester coupling procedure.*

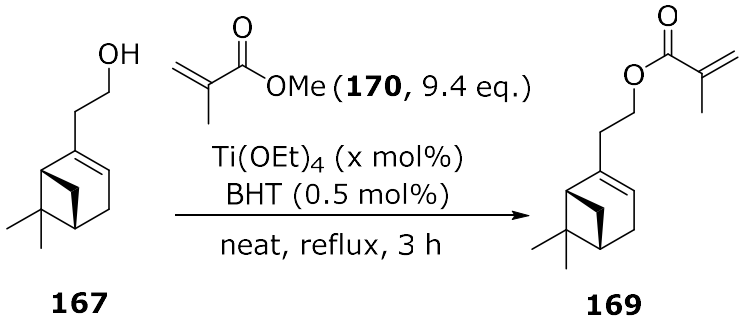
167 was then submitted to esterification conditions with acrylic acid (**115**) in order to synthesise **168**, using T3P® as the coupling agent (Scheme 60). The benefit of using T3P® over other coupling agents is that the by-product is a water-soluble triphosphate anion that can be washed away during an aqueous work-up. Moreover, the triphosphate species is much more environmentally benign than other by-products, such as chloride ions [144]. Using this protocol, **168** was synthesised in 63% yield.



*Scheme 61. Esterification of 157 with methacryloyl chloride (**96**) to synthesise **169**.*

However, methacrylic acid (**116**) is not compatible with T3P® due to steric hindrance, as has been documented in the literature by the Stockman and Howdle groups [98]. Therefore, for the initial synthesis procedure of **169**,

methacryloyl chloride (**96**) was using as the reacting partner (Scheme 61). The desired product **169** was synthesised in 73% yield – a good result, but the sustainability of the process needed to be improved to make the synthesis viable on scales required for further polymerisation studies.



167 **169**

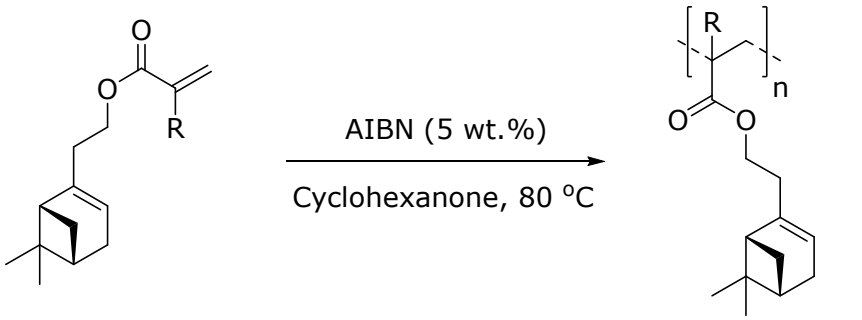
*Table 15. The optimisation of catalyst loading in the synthesis of **169** from **167** by a titanium-catalysed transesterification procedure. Yields of **169** were calculated by ^{1}H NMR using an internal standard (pyrazine).*

Entry	x (mol%)	Yield of **169** (%)
1	10	87
2	20	91

Transesterification provides a useful method of synthesising esters from alcohols under relatively mild conditions, and is the subject of comprehensive reviews in the literature [145-146]. It was hypothesised that a titanium-catalysed transesterification procedure could be used to synthesise **169** from **167**, using methyl methacrylate (**170**) as the source of the methacryloyl group, while also being the solvent for the reaction. Titanium(IV) ethoxide was selected as the catalyst, and the catalyst loading was varied in order to find the optimal stoichiometry for the synthesis of **169** (Table 15). Using 10 mol% of titanium catalyst (entry 1) gave a ^{1}H NMR yield of 87% of **169**, whereas increasing the catalyst loading to 20 mol% (entry 2) gave **169** in 91% yield.

The process was repeated using 10 mol% of titanium catalyst, as it was considered that using double the loading was not worth the extra 4% yield of **169**. The desired product **169** was isolated in 87% yield, with no further purification required. This is an excellent result because the transesterification

reaction yields **169** in a better yield than the corresponding acid chloride esterification (Scheme 59) and with no purification steps required. The process also provides the opportunity for the excess methyl methacrylate to be recycled into further reactions, improving the sustainability of the process even more.



R = H, **168**
R = Me, **169**

R = H, **171**
R = Me, **172**

*Table 16. The polymerisation of **168** and **169**, as conducted by Dr. Olivia Monaghan, a post-doctoral research associate previously in the group of Prof. Steven Howdle.*

Entry	R =	Conversion (%)	Đ	T_g (°C)
1	H (**168**)	22	-	-
2	Me (**169**)	cross-linked	-	-

With synthesis routes identified to the new (meth)acrylate compounds **168** and **169**, the next step was to trial homo-polymerisations of the potential monomers. These reactions were conducted by Dr. Olivia Monaghan in the group of Prof. Steven Howdle, and unfortunately did not produce polymers reliably (Table 16). With the acrylate **168** (entry 1), conversion only reached a maximum of 22% and a reliable polydispersity (Đ) and glass transition temperature (T_g) value could not be determined because of the low conversion of the process. When **169** was submitted to the polymerisation conditions (entry 2), a highly cross-linked material was produced that did not dissolve in organic solvents, therefore no parameters such as Đ or T_g could be determined.

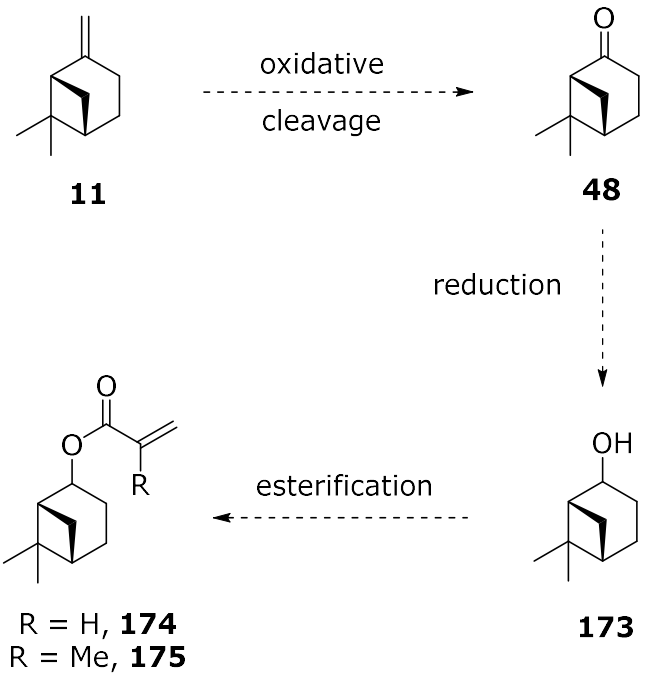
3.5 Synthesis of sterically hindered terpene-based monomers

3.5.1 Identification and Planned Synthesis

The terpenes collaboration had produced a reasonable amount of novel acrylate and methacrylate monomers, with a selection of them published [98]. Of these published monomers, a range of T_g values was achieved, from 12 °C to 142 °C. However, a certain selection of applications for polymers require much higher T_g values than 142 °C in order for the corresponding materials to excel at these purposes with the correct properties.

These purposes include thermoplastic coatings and "hard" blocks as part of co-polymer materials [147] – where "hard" block refers to a polymer fragment with a high T_g, and "soft" block refers to a polymer fragment with a much lower T_g. These materials in particular have a wide range of applications [148-149], such as thermoplastic elastomers. Therefore, being able to access these functionalities using terpene-based monomers would be an excellent avenue to explore in the grand scheme of the collaborative project.

It is notoriously difficult to predict the properties of a polymer based solely on the structure of a monomer [150], with many examples not following proposed trends. However, there are some guidelines which do apply to most structures, in particular with regards to degrees of freedom [151]. It was hypothesised that reducing the number of rotatable bonds by bringing the (meth)acrylate ester unit closer to the bicyclic ring system in a pinene-based monomer would impose a degree of steric hindrance on the corresponding polymer backbone. This would increase rigidity of the material by allowing the polymer chains to stack closer together, which would in turn raise the T_g value of the material.



*Scheme 62. The proposed synthesis of hindered acrylate (**174**) and methacrylate (**175**) monomers from β-pinene (**11**) in 3 steps.*

With this hypothesis in mind, a synthesis was devised of sterically hindered (meth)acrylate species from **11** in 3 steps (Scheme 62). Oxidative cleavage of **11** would generate the ketone, nopinone (**48**). Subsequent reduction of the carbonyl functionality would yield the corresponding alcohol, nopinol (**173**) which could then be submitted to esterification conditions to produce the desired (meth)acrylate monomers **174** and **175**. Due to the increased substitution in the corresponding polymer backbone of the methacrylate **175**, it was most likely that this species would produce the highest T_g value – a trend consistently seen in the literature [152].

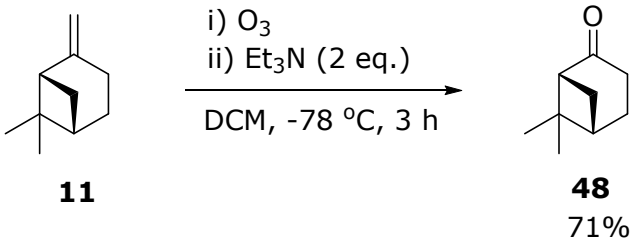
Another point to address in this synthetic route is the length – at 3 steps, this is the longest synthesis route proposed in the collaboration. Communication from industrially-based collaborators in the project stated that this was acceptable, as 3 steps was the maximum length of route to a monomer that would be commercially viable. However, in order to make this effective, the synthesis would need to be robust, high-yielding and both as cheap and sustainable as possible to carry out.

3.5.2 Oxidative cleavage of 11 to form 48

3.5.2.1 Synthesis of 48 by ozonolysis

Firstly, the synthesis of **48** needed to be identified. Fortunately, this is a transformation that has been documented extensively in the literature, and is even the sole subject of a review [153]. Methods to synthesise **48** from **11** have included ozonolysis [154-155], Lemieux-Johnson oxidation [156], ruthenium(III) chloride catalysed oxidative cleavage in conjunction with sodium periodate [157-158] and oxidative cleavage using potassium permanganate [159].

It was decided that ozonolysis would be the best starting point for the reaction, in order to produce **48** reliably. Most importantly, the literature documented ozonolysis procedures performed using large scale amounts of **11** as the substrate [76] – which would be required for the scale of monomer needed for polymerisation testing.



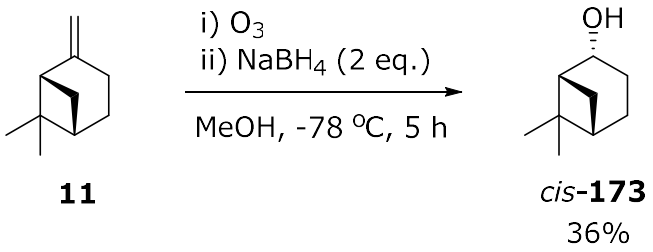
11 **48** 71%

*Scheme 63. The initial ozonolysis procedure to synthesise **48**.*

The initial attempt at ozonolysis of **11** mimicked the literature conditions almost exactly (Scheme 63) – with the only differences being the scale of the reaction (this attempt was half that of the literature procedure) and the reaction time (slightly shorter at 3 hours as opposed to 6). This procedure yielded **48** in 71% after purification by column chromatography – a pleasing result which provided plenty of material for further synthesis.

Over the course of the project, the ozonolysis reaction has been repeated 5 times, providing yields between 75 and 81%. This produced a large quantity of **48** throughout the project, which was used to advance the synthesis route further (see Section 3.5.3). However, it should be noted that this procedure does contain a significant drawback. The quench of the intermediate ozonide

with triethylamine causes a reasonably large exotherm, and can easily run away if slow, careful addition of the triethylamine is not performed while keeping the mixture at -78 °C throughout. This has the potential to cause a significant runaway reaction, which may cause issues if the reaction is scaled up further – especially as heat transfer from external coolants into a larger vessel is less efficient.

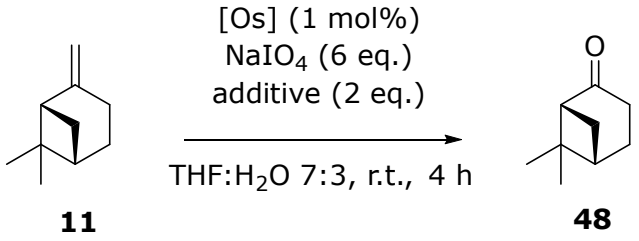


Scheme 64. The synthesis of cis-***173*** *directly through ozonolysis, using sodium borohydride as the quenching reagent for the intermediate ozonide.*

In an ozonolysis procedure, the choice of reagent for the quenching of the intermediate ozonide can influence which oxidation level is present in the received product. When sodium borohydride is used as the quenching reagent, the products obtained are alcohols [160]. It was hypothesised that using sodium borohydride instead of triethylamine would lead to the synthesis of *cis*-**173** without the need for an extra synthetic step (Scheme 64). Unfortunately, when this proposal was trialled, an extremely large exotherm occurred. Even with careful control of the temperature of the reaction mixture, and slow addition of the reagent, the exotherm proved too violent to contain entirely, leading to a significant loss of product material. However, the desired alcohol *cis*-**173** was obtained in 36% yield. Even though this result is promising, the procedure was not attempted again as the two step procedure (Section 3.5.3), with isolation of **48**, gave a superior yield of 64% over the two separate transformations.

3.5.2.2 Synthesis of 48 by Lemieux-Johnson oxidation

It was therefore suggested that a Lemieux-Johnson oxidation protocol to synthesise **48** should be investigated next. Since the discovery of the reaction in 1956 [161], it has become a vital tool in organic synthesis for the oxidative cleavage of alkenes in either a separate two-step [162] or one-pot [163] protocol. Additionally, the reaction has also been used in the literature for this particular transformation [156,164].



11 **48**

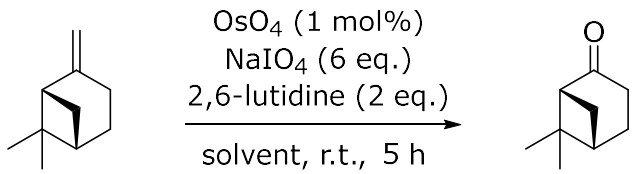
*Table 17. The initial attempts at the synthesis of **48** from **11** using a Lemieux-Johnson oxidation protocol. Both conversion and yield values were determined by ^{1}H NMR using an internal standard (pyrazine).*

Entry	Catalyst	Additive	Conversion (%)	Yield of **48** (%)
1	$K_2OsO_2(OH)_4$	-	30	14
2	$K_2OsO_2(OH)_4$	2,6-lutidine	35	3
3	OsO_4	-	>95	16
4	OsO_4	2,6-lutidine	>95	67

The initial attempt at the synthesis of **48** by Lemieux-Johnson oxidation followed conditions outlined in the literature, using potassium osmate(VI) dihydrate as the catalytic species (Table 17, entry 1) [165]. However, this only produced a 35% conversion of **11** by ^{1}H NMR, and only gave **48** in 14% yield, also determined by ^{1}H NMR.

The literature had also documented the use of tertiary amine bases as additives in the Lemieux-Johnson oxidation, with 2.6-lutidine in particular greatly enhancing the yield of the oxidative cleavage product [166]. When these conditions were trialled (entry 2), a similar degree of conversion and worse yield were achieved however.

With these poor results obtained, it was decided that osmium(VIII) tetroxide would be used as the catalyst, both with and without the 2,6-lutidine as an additive. When not using an additive (entry 3) the conversion appeared to be total by ^{1}H NMR, yet the yield of **48** was poor at only 16%. However, when the additive was used (entry 4), a full conversion of **11** was observed, in conjunction with a 67% yield of the desired product **48**.



11 **48**

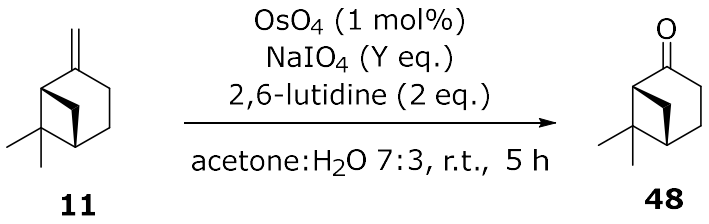
Table 18. The results of the solvent optimisation screen for the Lemieux-Johnson oxidation protocol. Conversion and yield values were determined by ^{1}H NMR using an internal standard (pyrazine).

Entry	Solvent	Conversion (%)	Yield of **48** (%)
1	MeCN:H_2O 7:3	>95	48
2	acetone:H_2O 7:3	>95	89
3	MeOH:H_2O 7:3	93	69
4	H_2O	64	3

With a set of conditions identified for a reasonable yield of **48** using a Lemieux-Johnson oxidation, the next task was to optimise the procedure in order to improve the yield of **48**. The first parameter to investigate was the solvent (Table 18). As sodium periodate is used as the oxidant, the reaction solvent needed to be quite polar, and most likely contain some degree of water in order to achieve a reasonable degree of dissolution. Therefore, only solvents that were miscible with water were investigated.

Acetonitrile (entry 1) and acetone (entry 2) (both as a 7:3 mixture with water) both achieved full conversion by NMR after 5 hours, and gave **48** in yields of 48% and 89% respectively. Using methanol as the organic part of the solvent mixture (entry 3) achieved slightly less than full conversion but a better yield of 69% than that of acetonitrile. Also, it was shown that an organic component in

the solvent was necessary, as using water as the sole solvent (entry 4) caused a large depreciation in both conversion and yield of **48**. This was most likely due to the poor solvation of **11** in an entirely aqueous reaction medium.

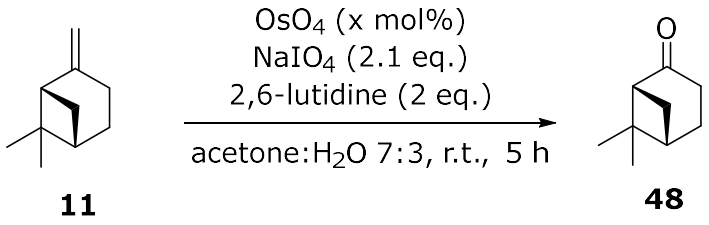


11 **48**

Table 19. The results of the oxidant loading optimisation screen for the Lemieux-Johnson oxidation protocol. Conversion and yield values were determined by ^{1}H NMR using an internal standard (pyrazine).

Entry	Y (eq.)	Conversion (%)	Yield of **48** (%)
1	1.1	62	49
2	2.1	>95	74
3	3	44	5
4	4	55	16

The loading of sodium periodate was the next reaction parameter to be optimised (Table 19), as 6 equivalents seemed rather excessive for this particular procedure. Reducing the oxidant loading to 1.1 equivalents resulted in a diminished conversion and hence yield (entry 1), while using 2.1 equivalents (entry 2) gave a comparative conversion and yield value to those of the original conditions. Increasing the oxidant loading beyond this (entries 3 and 4) seemed to stall the reaction – a peculiar set of results, given that 6 equivalents performed well earlier in the optimisation process. As 2.1 equivalents (entry 2) gave a good yield of **48**, this loading of periodate was taken forward without further investigation.

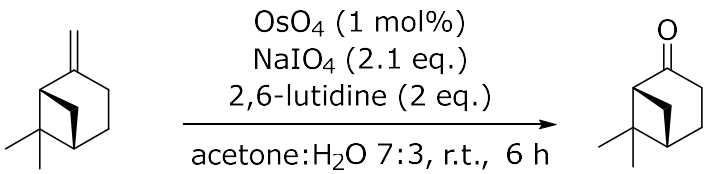


11 **48**

Table 20. The catalyst loading optimisation screen for the Lemieux-Johnson oxidation protocol. Conversion and yield values were determined by ^{1}H NMR using an internal standard (pyrazine).

Entry	x (mol%)	Conversion (%)	Yield of **48** (%)
1	0.5	>95	44
2	0.2	>95	35
3	0.1	77	23
4	0.05	49	32

A loading of 1 mol% of osmium catalyst is reasonably high and quickly becomes very expensive once the reaction is scaled up beyond that of a screening level. Therefore, optimisation of this parameter was investigated (Table 20). Reducing the catalyst loading to 0.5 mol% and 0.2 mol% (entries 1 and 2) caused reductions in the yield of **48** while maintaining full conversion. Reducing the loading further (entries 3 and 4) caused a drop off in conversion of **11**, while keeping the yield of **48** at somewhat the same level. The results of this screen were disappointing, as it showed that in order to maintain a good yield of **48**, the catalyst loading had to be maintained at 1 mol%.



11
10 mmol

48
76%

Scheme 65. Scale up of the optimised Lemieux-Johnson oxidation protocol.

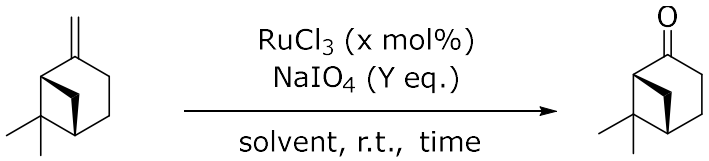
Despite the disappointing catalyst loading result, the Lemieux-Johnson oxidation was scaled up. 10 mmol of **11** was used as the starting material, and **48** was

isolated after column chromatography in 76% yield. This result is only very slightly lower than that achieved by the original ozonolysis procedure, and presents much less of a risk with regard to exotherms and potential quenching. This means it could be more of a successful option for larger scale-up if required.

However, using an osmium(VIII) species as the catalyst is both extremely expensive and highly toxic – requiring a specialist disposal method which adds to the cost of the procedure further. The cost could be mitigated slightly by using osmium(VIII) tetroxide supported on an ion-exchange resin, which would allow separation of the catalyst from the reaction mixture by simple filtration. This would allow the catalyst to be re-used in further transformations, providing minimal leaching occurred, and this has been shown in literature examples [167]. The high toxicity of the material still remains an issue for truly large scale procedures however.

3.5.2.3 Synthesis of 48 by ruthenium-catalysed oxidative cleavage

An alternative to the traditional Lemieux-Johnson oxidation is to use a ruthenium precatalyst instead of osmium(VIII). When used in conjunction with sodium periodate, the ruthenium species is oxidised to the ruthenate(VII) anion, RuO_4^-. This active catalytic moiety then performs the initial 1,3-dipolar cycloaddition with the alkene substrate. This protocol is extensively documented in the literature [168-170]. The procedure has also been reported as a way of synthesising **48** from **11** [157-158]. It was hypothesised that this method could be used instead of the Lemieux-Johnson oxidation, as ruthenium is significantly cheaper and less toxic than the corresponding osmium catalyst.



11 **48**

*Table 21. Initial investigations into the synthesis of **48** using ruthenium(III) chloride and sodium periodate as catalyst and oxidant respectively.*

Entry	x (mol%)	Y (eq.)	Solvent	Time (h)	Yield of **48** (%)
1	1	2.1	MeCN:H_2O 3:2	3	<1[a]
2	2	2.1	MeCN:H_2O 3:2	3	<1[a]
3	5	2.1	MeCN:H_2O 3:2	3	<1[a]
4	1	2.1	MeCN:H_2O 3:1	3	1[a]
5	2	2.1	MeCN:H_2O 3:1	3	<1[a]
6	5	2.1	MeCN:H_2O 3:1	3	1[a]
7 [155]	1	4	$CHCl_3$:MeCN:H_2O 2:2:3	2	0
8	1	4	DCM:MeCN:H_2O 2:2:3	2	0
9	1	4	DCM:MeCN:H_2O 2:2:3	2.5	0
10[b] [172]	1	2.1	EtOAc:H_2O 1:1	24	0

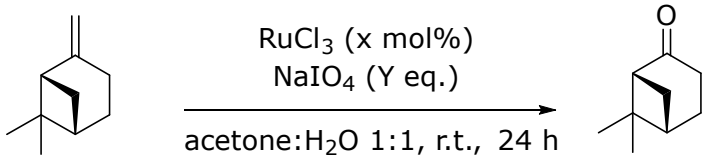
a = determined by ^{1}H NMR using an internal standard (pyrazine).

b= tetra-*n*-butylammonium bromide (TBABr) used as an additive (3 mol%).

Initial studies used conditions similar to those found in the literature [168], varying the catalyst loading and solvent proportions of acetonitrile and water (Table 21, entries 1-6). Unfortunately, all of these conditions were unsuitable for the synthesis of **48**, with full conversion but only trace amounts of the desired product detected by ^{1}H NMR.

A different publication detailed the use of a three-component solvent system, utilising carbon tetrachloride, acetonitrile and water in a 2:2:3 ratio [157]. However, carbon tetrachloride is no longer acceptable for use as a solvent due to its high degree of toxicity, suspected carcinogenic activity, and sustained persistence in the environment [171]. Therefore, chloroform (entry 7) and dichloromethane (entries 8 and 9) were substituted for the halogenated solvent portion of the mixture. Unfortunately, these attempts also failed to produce any viable quantity of **48**.

Finally, conditions were trialled using a mixture of ethyl acetate and water with the addition of a phase transfer catalyst, TBABr (entry 10). The literature documented a yield of 85% of **48** for this procedure [172], but this was not replicated in the result obtained, with failure to isolate **48** being the outcome of the reaction once again.



11 **48**

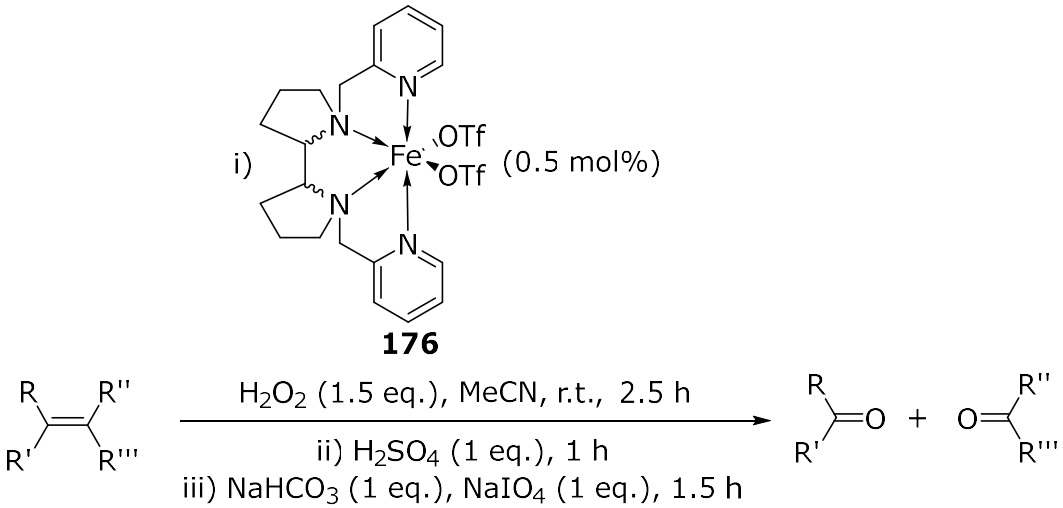
*Table 22. The attempted synthesis of **48** using a ruthenium(III) chloride catalysed oxidative cleavage in a 1:1 mixture of acetone and water.*

Entry	Scale (mmol of **11**)	x (mol%)	Y (eq.)	Yield of **48** (%)
1	1	2.5	3	6[a]
2	10	1	2.1	35
3	10	1	2.1	41

a = determined by ^{1}H NMR using an internal standard (pyrazine).

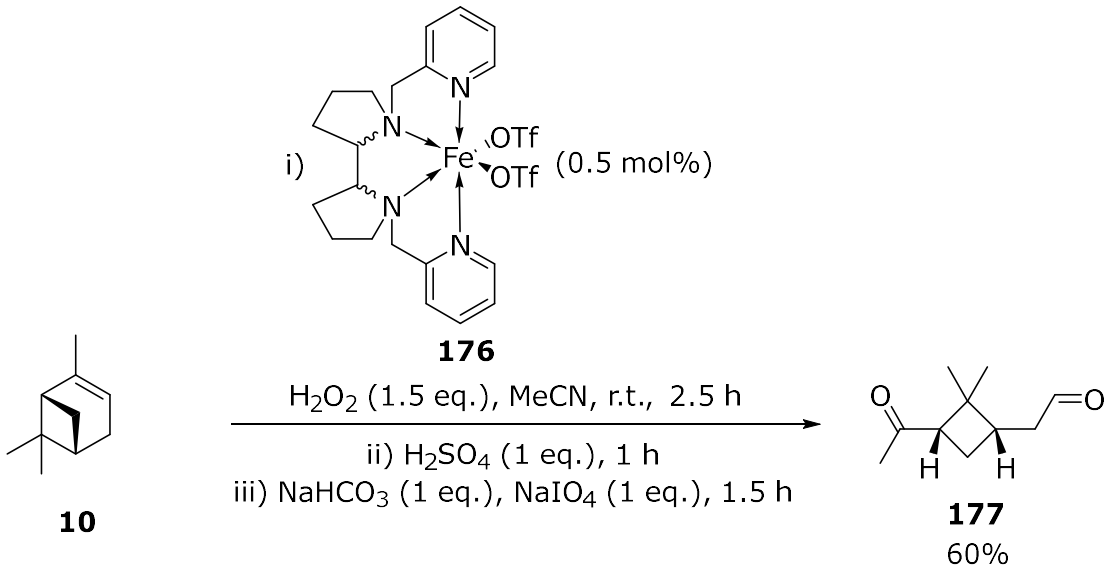
As a mixture of acetone and water worked best for the Lemieux-Johnson oxidation, it was hypothesised that this would also provide a good solvent system for the ruthenium catalysed procedure (Table 22). However, using 2.5 mol% of catalyst (entry 1) only produced a 6% yield of **48** by ^{1}H NMR. Applying the optimised conditions to the reaction further, by reducing the loading of catalyst to 1 mol% and oxidant to 2.1 equivalents (entry 2) improved the reaction enormously, giving an isolated yield of 35% of **48** at the first attempt, and an improved yield of 41% (entry 3) at the second attempt. While this was a good improvement on the initial results for ruthenium-catalysed reactions, it was suggested that the degree of Lewis acidity present in ruthenium(III) species was causing side reactions to occur. As the yield of **48** was average at best in all cases, this may have been happening at too fast a rate for the yield to be improved further. Therefore, other methods of oxidative cleavage were considered to be a more attractive option at this stage.

3.5.2.4 Synthesis of 48 by an iron-catalysed one-pot epoxidation/hydrolysis/ oxidative cleavage procedure



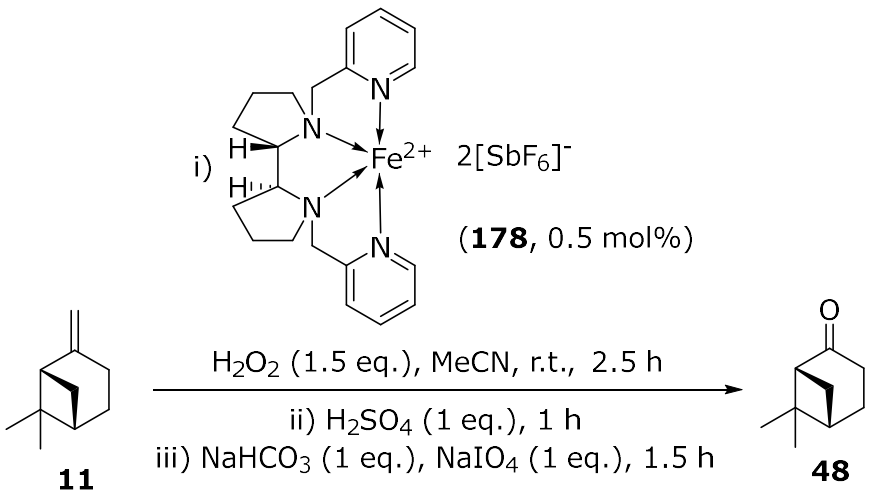
Scheme 66. The literature procedure for the iron-catalysed oxidative cleavage of aliphatic alkenes using a 3 step, one-pot protocol [173].

A procedure reported in the literature detailed the use of an iron-catalysed oxidative cleavage reaction utilising 3 sequential reaction steps all conducted in one pot (Scheme 66) [173]. The procedure consists of an epoxidation catalysed by an iron(II) complex (**176**), followed by a Brønsted acid-mediated hydrolysis of the resulting epoxide. A mixture of sodium bicarbonate and sodium periodate is then added to both neutralise the acid and cleave the resulting diol to the desired carbonyl products.



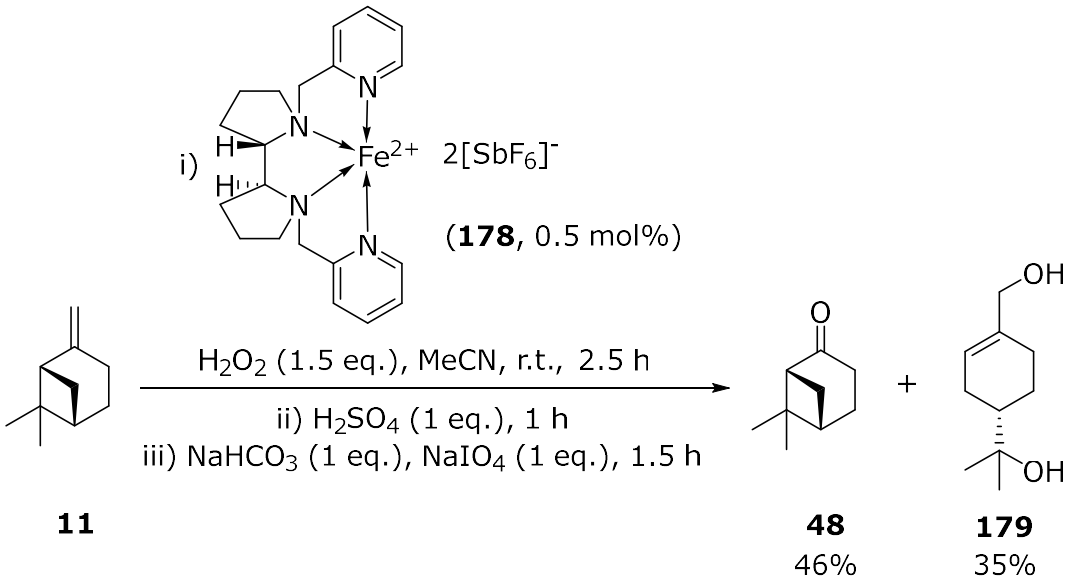
*Scheme 67. The synthesis of **177** from α-pinene (**10**) using the iron-catalysed 3 step, one-pot oxidative cleavage protocol [173].*

Each of the steps was examined individually during the reported investigation to determine what was happening with each reagent addition, before the one-pot protocol was developed. Interestingly, the investigation's substrate scope also included the use of **10** with a 60% yield of the desired carbonyl products (Scheme 67). Therefore, it was hypothesised that this protocol could be applied to **11** to produce **48**.



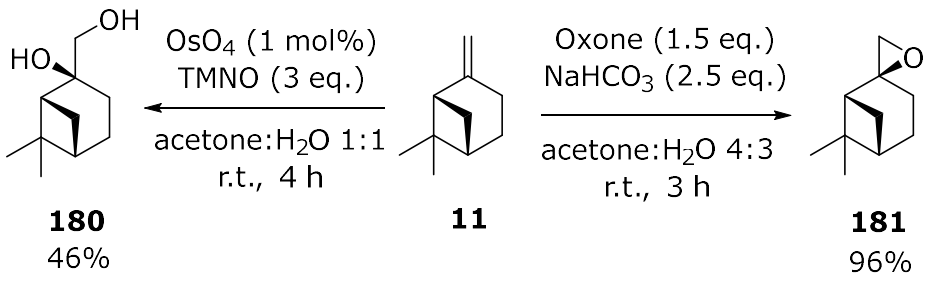
*Scheme 68. The initial attempt at the synthesis of **48** using the iron(II)-catalysed 3 step, one-pot oxidative cleavage procedure.*

The initial attempt at the reaction using **11** as the starting material proved promising (Scheme 68). For the first test, the commercially available White-Chen catalyst (**178**) was used – an enantiomerically enriched version of the catalyst used in the literature procedure, which has been used in many oxidation reactions [174-175]. On a small scale, **48** was seen in the ^{1}H NMR of the crude mixture with full conversion of **11**. However, there appeared to be formation of an unidentified side product which was also present in the spectrum. The attempt at identification of the side product was unsuccessful due to the small scale of the initial reaction – not enough material could be isolated for full analysis.



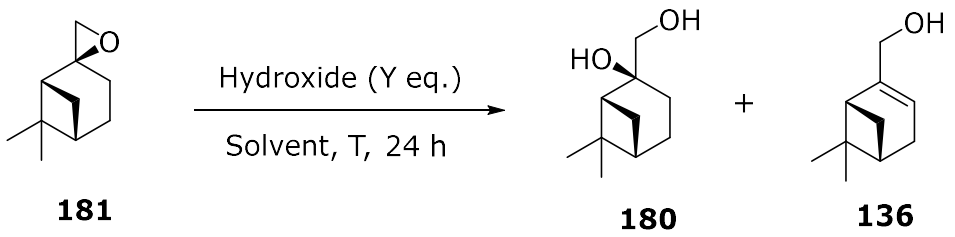
*Scheme 69. The scaled up synthesis of **48**, followed by identification of the side product **179** after purification.*

Scaling up the reaction by a factor of 5 allowed for the components of the crude mixture to be separated by column chromatography (Scheme 69). **48** was isolated in 46% yield, and the side product was determined to be **179**, which was isolated in 35% yield. It was evident that **179** was the product of a cascade of ring opening processes initiated by the addition of sulfuric acid. In order to circumvent this issue, alternative methods of hydrolysing β-pinene oxide would need to be investigated.



*Scheme 70. The synthesis of the proposed epoxide (**181**) and diol (**180**) intermediates in the 3 step, one-pot oxidative cleavage reaction.*

In order to carry out the investigation, the proposed desired intermediates in the 3 step, one-pot synthesis of **48** needed to be synthesised. Firstly, β-pinene oxide (**181**) was synthesised from **11** using a combination of Oxone® and acetone in a slightly basic medium (Scheme 70), which is proposed to form dimethyl dioxirane (DMDO) *in situ* in the reaction mixture [176]. This process gave a yield of 96%. Similarly, the proposed diol intermediate that results in the synthesis of **48** when combined with sodium periodate, **180**, was synthesised in 46% yield using a catalytic Upjohn dihydroxylation protocol previously developed in the literature, with slight modifications to stoichiometry and solvent used [177].



181 **180** **136**

*Table 23. The screen of epoxide hydrolysis conditions in the attempted synthesis of **180** from **181**.*

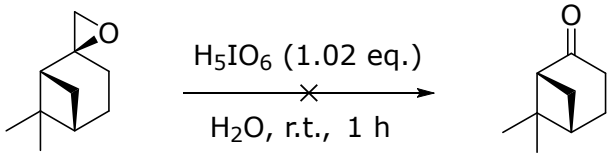
Entry	Hydroxide	Y = (eq.)	Solvent	T (°C)	Result
1	LiOH	3	acetone:H_2O 1:1	20	recovered SM
2	NaOH	3	acetone:H_2O 1:1	20	recovered SM
3	KOH	3	acetone:H_2O 1:1	20	recovered SM
4	LiOH	3	H_2O	20	recovered SM
5	NaOH	3	H_2O	20	recovered SM
6	KOH	3	H_2O	20	recovered SM
7	KOH	7.6	H_2O	60	decomposition
8	$Ba(OH)_2$	1.5	H_2O	60	decomposition
9	LiOH	3	H_2O	reflux	**136** (53%)
10	NaOH	3	H_2O	reflux	**136** (51%)
11	KOH	3	H_2O	reflux	**136** (75%)
12	$Ba(OH)_2$	1.5	H_2O	reflux	**136** (60%)

With Brønsted acids initiating the ring-opening cascade to form **179**, it was suggested that hydroxide would be the best reagent for the attempted synthesis of **180** from **181** (Table 23). Lewis acids were also considered, but not trialled, as they were most likely to initiate formation of **179** also. Initial tests (entries 1-6) were conducted at room temperature in both 1:1 solvent mixtures of acetone and H_2O (entries 1-3) and just water as the solvent (entries 4-6), but all attempts resulted in minimal conversion.

Increasing the loading of hydroxide and increasing the temperature to 60 °C simultaneously (entry 7) resulted in decomposition. Barium hydroxide was suggested as a viable alternative, and has been used in epoxide hydrolysis

previously in the literature [178]. However, using this reagent at 60 °C with 3 equivalents of the hydroxide anion (entry 8) again caused decomposition.

When the temperature of the reaction was increased to reflux (entries 9-12), only **181** was observed after 6 hours by TLC in all cases. However, when left for 24 hours, it was discovered that **136** was produced in varying yields from 51-75% depending on the cation of the hydroxide reagent. With the combination of the TLC results after 6 hours, it seems that upon hydrolysis of the epoxide to the desired diol **180**, the hydroxide reagent then reacts further. **180** appears to be deprotonated to initiate a formal elimination of a molecule of water, resulting in the formation of **136**.

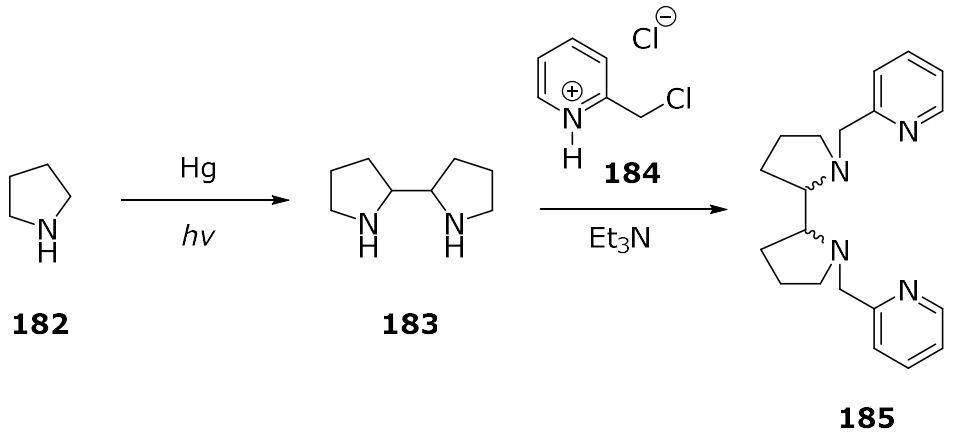


181 **48**

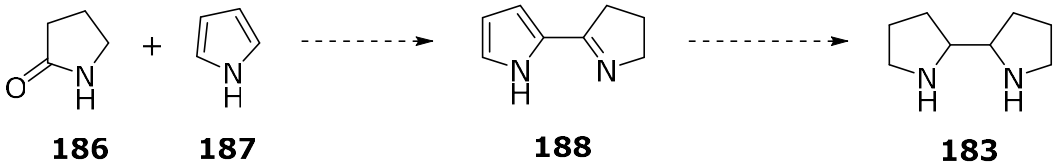
*Scheme 71. The attempted synthesis of **48** from **181** in one step, using periodic acid as the reagent.*

With **180** proving difficult to synthesise selectively without using an Upjohn dihydroxylation, it was proposed that periodic acid could be used to generate **48** directly from **181** (Scheme 71) – a synthetic transformation common in the literature [179]. However, treatment of **181** with periodic acid resulted in decomposition, with starting material fully consumed but no isolation of **48**.

With all attempts unsuccessful in improving the formation of **48** through choice of reagents in the 3 step protocol, efforts were focused towards improving the yield of **48** in the one-pot procedure through the catalyst species used. It was predicted that synthesis of the racemic ligand, which was used in the literature procedure [173], would hopefully increase the yield of **48**. The study contained a substrate scope with a minimum yield of 60%, which would be a reasonable improvement on the current result achieved in this project.



*Scheme 72. The literature procedure for the synthesis of racemic **185** [180].*



*Scheme 73. The plan for an alternative synthesis using a different literature procedure for the formation of **183** [181].*

However, most literature methods detail the synthesis of the racemic ligand **185** through the dimerisation of pyrrolidine, initiated by ultraviolet irradiation with a catalytic amount of elemental mercury (Scheme 72) [180,182]. This procedure was both unsustainable in terms of the use of toxic mercury and also high energy ultraviolet light, as well as the lamp required for the irradiation was unavailable when needed. Therefore, an alternative synthesis of the racemic ligand **185** was devised, using a procedure for the synthesis of **183** documented in the literature (Scheme 73) [181].

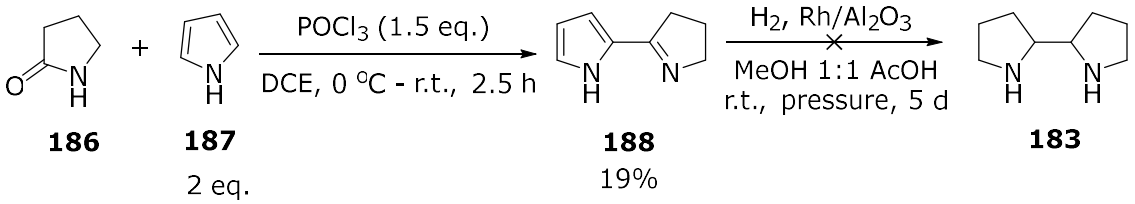
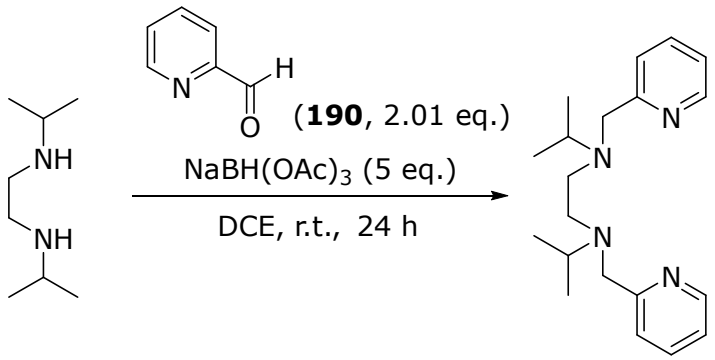


*Table 24. The attempted synthesis of **183** in 2 steps following a literature procedure [181].*

Entry	Pressure	Result
1	Atmospheric	Recovered **188**
2	10 bar	Recovered **188**

The synthesis started with the formation of **188** from pyrrole (**187**) and 2-pyrrolidinone (**186**), mediated by phosphorus(V) oxychloride. This gave **188** in 19% yield after recrystallisation from chloroform – a low yield, but the literature article also experienced a less than average yield value, though not to this degree [181]. However, as the main purpose of this part of the investigation was to synthesise the ligand, this was not optimised further as the material was already in hand. The next step was a global reduction of **188** to form **183**, using dihydrogen with a heterogeneous catalyst of rhodium supported on alumina (Table 24). Initial trials using standard hydrogenation conditions at atmospheric pressure (entry 1) caused no conversion whatsoever, with **188** recovered entirely from the reaction mixture. Under a pressure of 10 bar of hydrogen (entry 2), conversion was also minimal, even though this pressure was higher than that used in the literature synthesis. With these results in hand, it was decided that an alternative ligand system would be trialled for the iron catalyst used in the oxidative cleavage reaction.



189 **191**

67%

*Scheme 74. The literature procedure for the 1-step synthesis of **191** from commercially available **189** [183].*

Other complexes used as iron(II) catalysts include the use of **191** as a ligand. This ligand can be synthesised in one step from commercially available starting materials (Scheme 74). Therefore, it was decided that a selection of these ligands would be prepared, complexed with an iron(II) source and used in a catalyst screen for the 3 step, one pot synthesis of **48** from **11**.

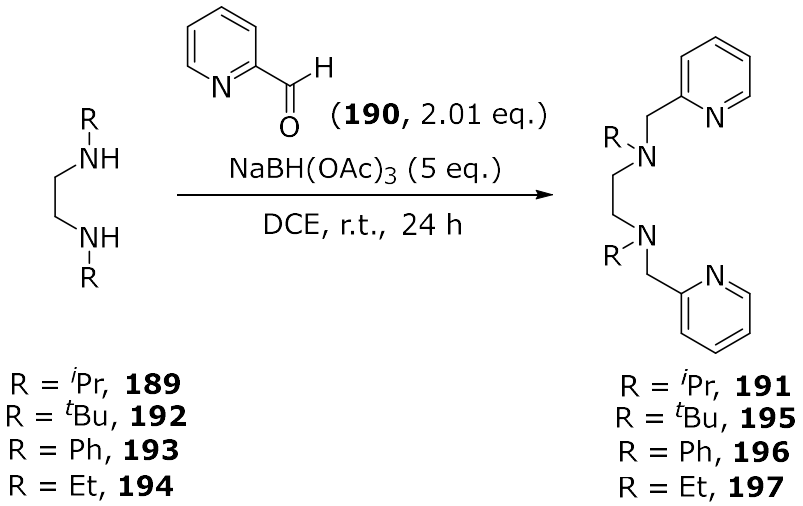


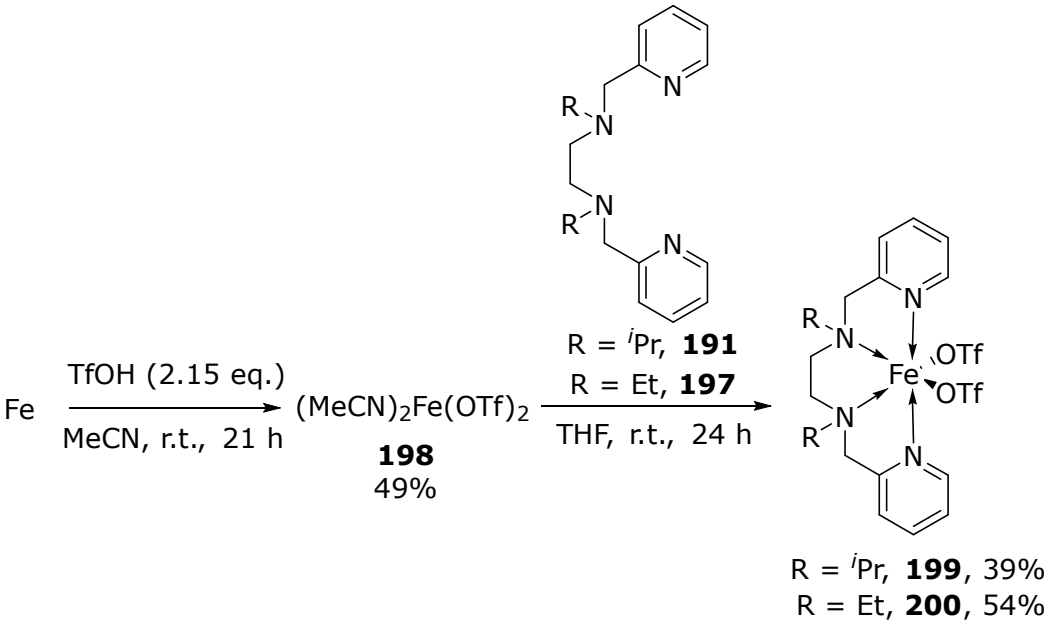
Table 25. The synthesis of a variety of ligands from commercially available N,N'-substituted ethylene diamines using a literature method for double reductive amination [183].

Entry	R =	Result
1	^{i}Pr (**189**)	**191**, 9%
2	^{t}Bu (**192**)	no di-substitution
3	Ph (**193**)	no di-substitution
4	Et (**194**)	**197**, 26%

Four commercially available diamines with varying substituents, in terms of steric demand, were selected (**189, 192** – **194**) and subjected to the reductive amination conditions outlined in the literature (Table 25) [183]. Using the publication example exactly (entry 1), **191** was synthesised in 9% yield. The loss of yield compared to the literature value is most likely due to the purification process – the product, with 4 basic nitrogen atoms, was possible but difficult to purify using column chromatography, even with the mobile phase containing 5-10% triethylamine.

When the *tert*-butyl (entry 2) and phenyl (entry 3) analogues were attempted to be synthesised, double reductive amination was not observed in either case. Some evidence of reaction had occurred, but this was mostly just to the intermediate, with one picolyl group attached to the nitrogen functionalities. This was thought to be due to steric hindrance, therefore these analogues were not

pursued further. However, using the diethyl substituted diamine (entry 4) resulted in the synthesis of **197** in 26% yield.



*Scheme 75. The synthesis of the ligand-iron(II) complexes **199** and **200**.*

With the two ligands prepared, the next step was to synthesise the corresponding iron(II) complexes (Scheme 75). Following the two procedures documented in the literature [183-184], the intermediate bis(acetonitrile) iron(II) triflate (**198**) was synthesised in 49% yield. Upon mixing with the corresponding ligands, the subsequent iron(II) complexes **199** and **200** were then furnished in 54% and 39% yields respectively.

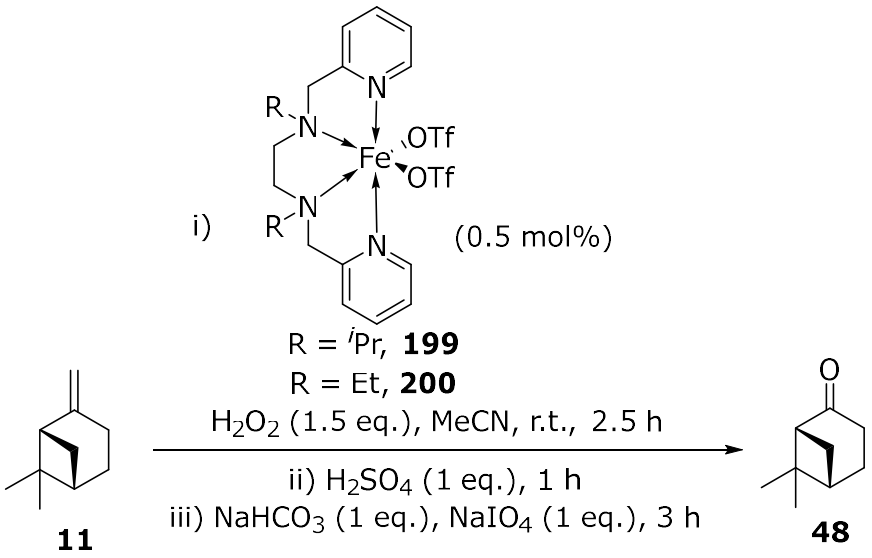


*Table 26. The investigation into changing the iron(II) species as the catalyst in the 3 step, one-pot synthesis of **48** from **11**. Yields of **48** were calculated by ^{1}H NMR using an internal standard (pyrazine).*

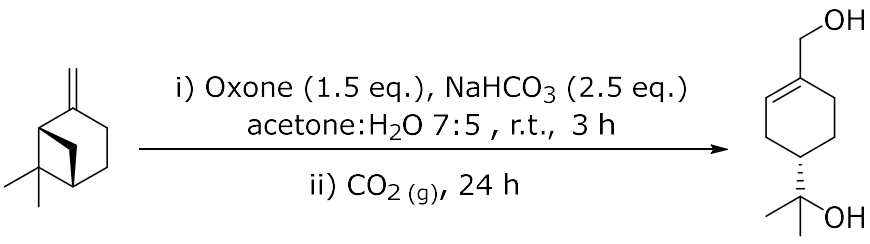
Entry	R =	Yield of **48** (%)
1	Et	3
2	^{i}Pr	2

The iron(II) complexes were then trialled as catalysts in the 3 step, one-pot synthesis of **48** (Table 26). Unfortunately, **48** was only produced in 3% yield when the ethyl-substituted complex **200** was used in the reaction (entry 2). Similarly, another disappointing result of 2% was achieved when **199** was used as the catalyst. The reason for this may be the chiral nature of the substrate **11**, with potential steric clashes that may have been avoided when **176** was used as the catalyst, although further research would be needed to identify the cause fully.

With these results obtained, it was decided that optimisation of the synthesis of **48** would cease at this point. The ozonolysis and Lemieux-Johnson oxidation procedures were reasonably high yielding, but both had drawbacks in terms of safety or toxicity hazards. However, a procedure that achieved a similar yield has so far not been identified. The ruthenium catalysed procedure did at least produce **48** in 41% yield – further optimisation may yet improve this value.

3.5.2.5 Esterification of the side product diol 179

Even though the formation of the side product **179** during the 3 step, one-pot oxidative cleavage of **11** was at the time a drawback, an opportunity was also spotted. One of the hydroxyl groups in the structure of **179** is primary, therefore can be esterified in a facile manner. It was suggested that the acrylate and methacrylate esters of this diol could be synthesised and subsequently polymerised. However in order to make this a viable plan, a more operationally simple synthesis of **179** was first required.



11 **179**
83%, 70% purity
59% by ^{1}H NMR

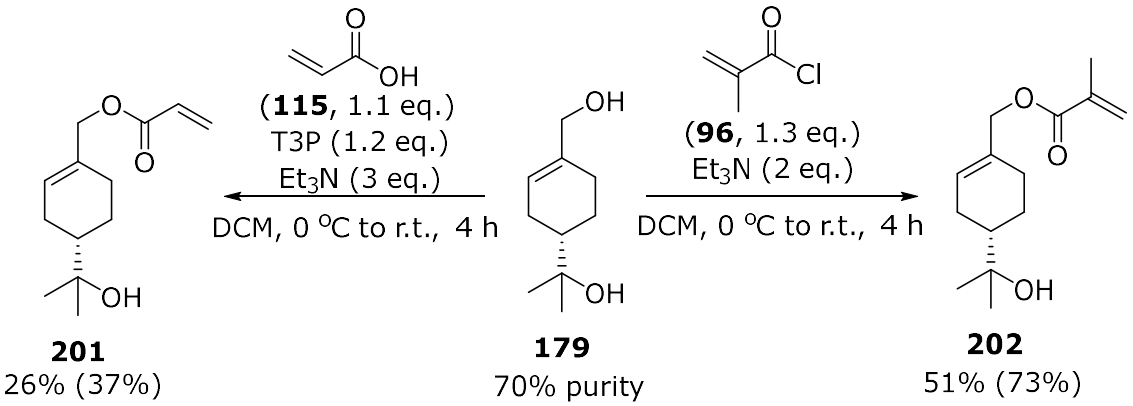
*Scheme 76. The synthesis of the desired diol **179** in a one-pot procedure starting from **11**.*

Taking inspiration from the synthesis of *trans*-sobrerol (**126**) from α-pinene (**10**), documented in the literature [185], **11** was oxidised to generate **181** *in situ* in the reaction mixture (Scheme 76). Subsequent acidification of the reaction mixture using carbon dioxide gas, to achieve a pH value of 4, generated **179** as part of the product, obtained in 83% yield. Analysis of this resulting material showed that **179** was contained within the crude product in approximately 70% purity. A yield value calculated by ^{1}H NMR using pyrazine as an internal standard gave the yield of **179** as 59%.

Further purification of this material by chromatography proved challenging, with a very low mass recovery – **179** was isolated for an analytical sample, but this was in the order of milligrams. This is most likely due to a combination of two reasons – the hydrophilicity of the species, leading to retention of the molecule in the stationary phase, and the acid-labile nature of the product. Acid-mediated

elimination and/or rearrangement of the terpene-based structure may be possible due to the acidic nature of the silica gel used.

With this result, it was decided that the material would be telescoped straight through to the corresponding acrylate and methacrylate esters, which should be much less hydrophilic and therefore easier to isolate by chromatographic means.

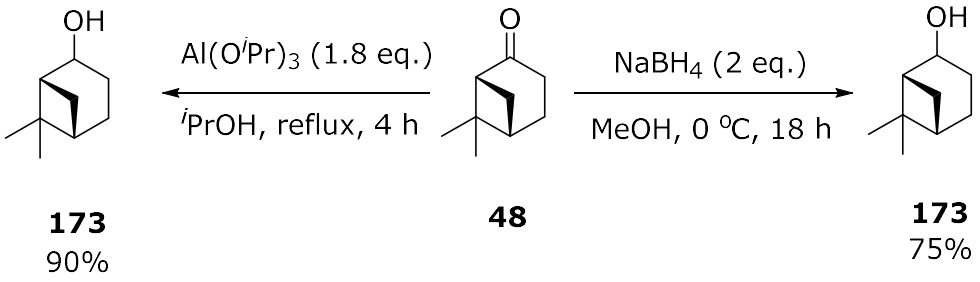


*Scheme 77. The synthesis of the acrylate (**201**) and methacrylate (**202**) species from the corresponding diol **179**.*

The 70% pure diol was submitted to the corresponding esterification conditions for (meth)acryloylation (Scheme 76) to give the acrylate (**201**) and methacrylate (**202**) in 26% and 51% respectively. However, if the purity of the starting material is taken into account, these yield values rise to 37% and 73% respectively.

With the corresponding acrylate and methacrylate monomers now in hand, studies are currently under way to identify suitable polymerisation conditions for production of the respective polymers. These studies are currently in their infancy, but in collaboration with members of the groups of Professors Stockman, Howdle and Irvine, an application will hopefully prove appropriate for these materials once synthesised. With hydroxyl groups present in the backbone, these materials may prove hydrophilic enough for alternative applications to those previously mentioned, although this is possibly just conjecture at this stage of the development process.

3.5.3 Synthesis of nopinol (173)



173
90%

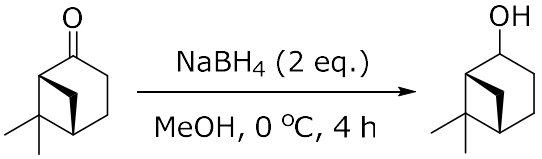
48

173
75%

*Scheme 78. The literature methods for the reduction of the carbonyl functionality in **48** to form **173**.* [186-187]

The next step in the synthesis was to obtain the desired alcohol **173** by reduction of the ketone functionality present in **48** (Scheme 78). Records in the literature show two main methods of this transformation. The first uses sodium borohydride as the reagent [186], while the second is a Meerwein-Ponndorf-Verley reduction using a combination of aluminium *iso*-propoxide and *iso*-propanol [187] – a transformation initially discovered in 1925 [188-190].

The literature also documents the use of lithium aluminium hydride for this transformation [191], but this was deemed not worthy of investigation due to the reactive nature of the reagent which was deemed to be excessive for this particular case. While sodium borohydride is less reactive, it was still shown to be more than capable of effecting this reduction in other literature examples [192].



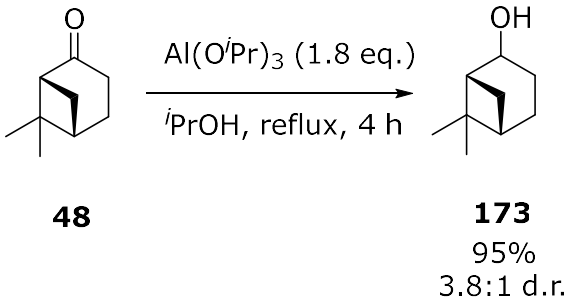
48

173
83%

*Scheme 79. The initial attempt at the reduction of **48** to form **173** using sodium borohydride.*

The initial attempt at using sodium borohydride as the reducing agent to synthesise **173** used the conditions documented in the literature (Scheme 79)

[186]. **173** was produced in 83% yield, and required no further purification as indicated by ^{1}H and ^{13}C NMR. On an additional note, the spectra showed no sign of multiple diastereomers present in the product sample, even without purification – indicating that the transformation was diastereoselective using the conditions outlined (Scheme 79).



48 **173** 95% 3.8:1 d.r.

*Scheme 80. The initial attempt at the synthesis of **173*** via *a Meerwein-Ponndorf-Verley reaction, as documented in the literature [187].*

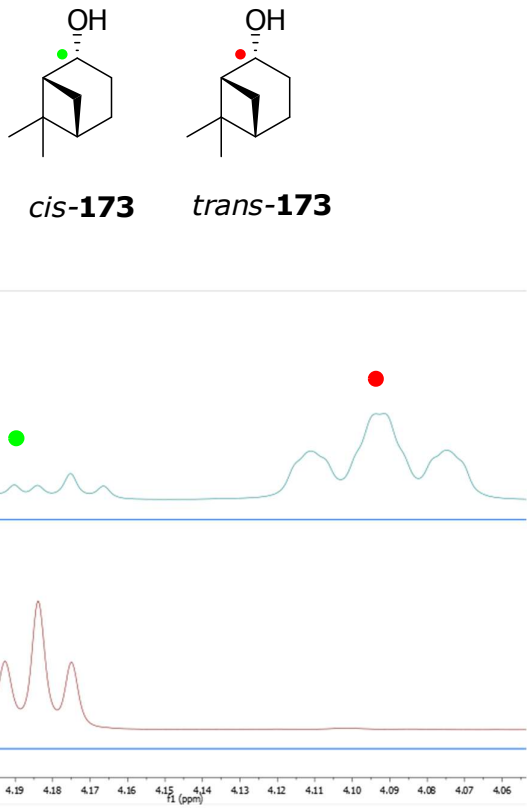
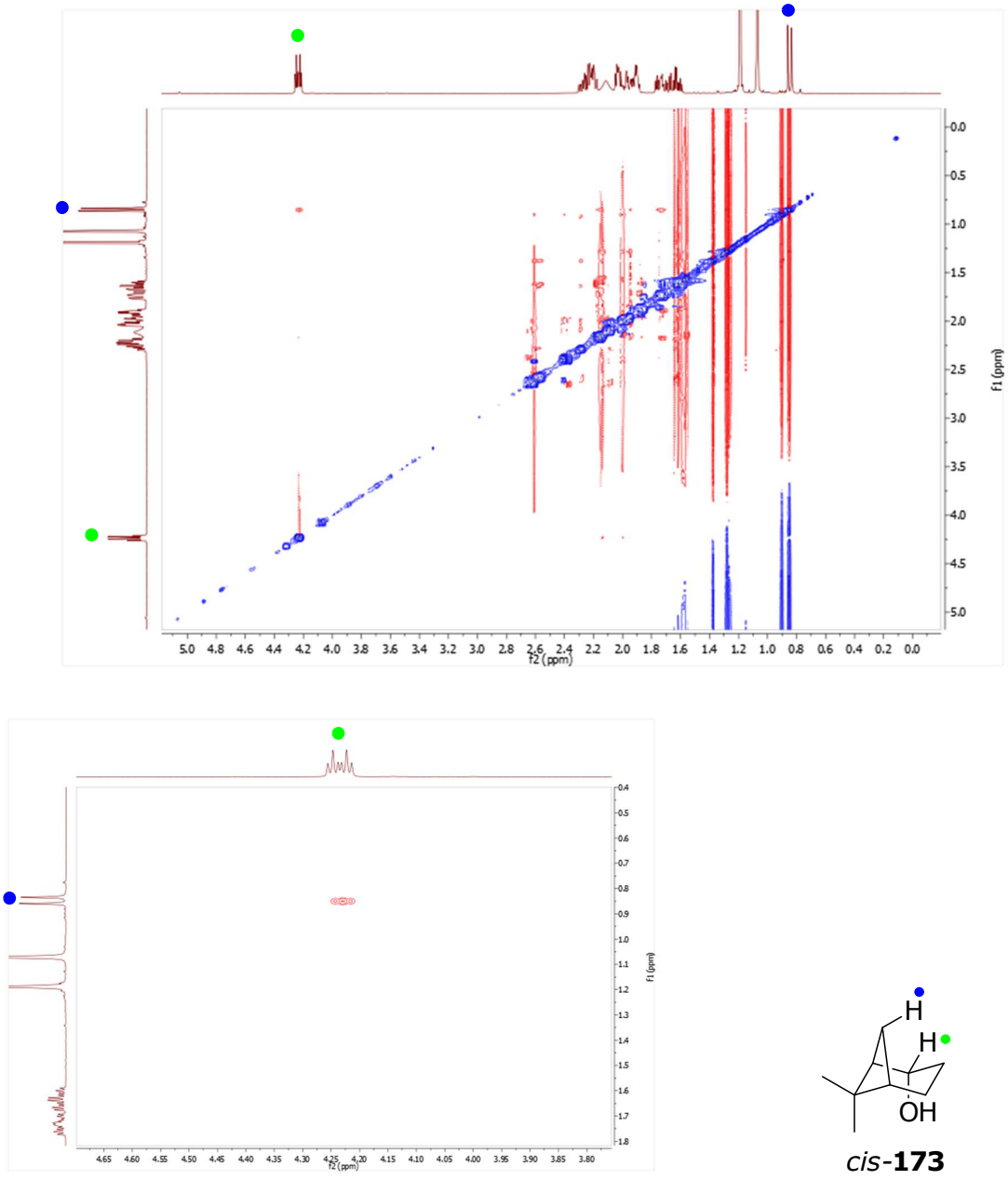


Figure 13. The stacked spectra of the products obtained from the previously mentioned two literature procedures for reduction, borohydride (red, bottom) and Meerwein-Ponndorf-Verley (blue, top), zoomed in to show the alpha-hydrogen to the hydroxyl group.

The Meerwein-Ponndorf-Verley reaction protocol was also attempted, using the conditions outlined in the literature (Scheme 80) [187]. While producing **173** in 95% yield, this procedure was not fully diastereoselective, and a 3.8:1 ratio of products was observed by ^{1}H NMR (Figure 13). However, the spectrum also showed that the major diastereomer was the alternative product of that produced selectively by the reduction using sodium borohydride (Scheme 79).

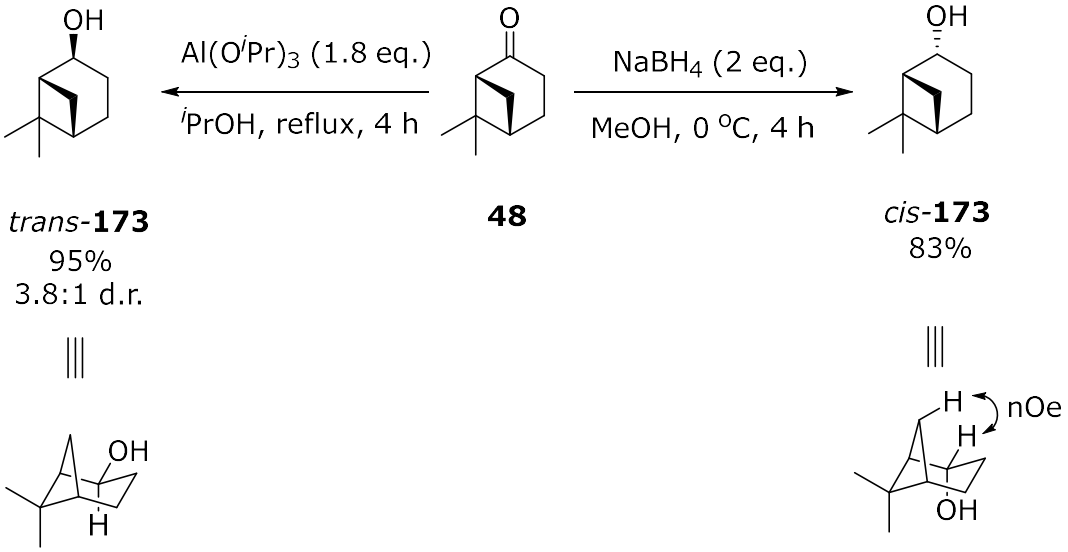


cis-**173**

Figure 14. The full NOESY spectrum (top) with a zoomed focus on the important correlation (bottom) for the product obtained from reduction of ***48*** *with sodium borohydride.*

A NOESY spectrum was also recorded of the product obtained from the reduction with sodium borohydride (Figure 14). This spectrum did indeed show correlations through space between protons in the ^{1}H NMR spectra that allowed for identification of the corresponding product by looking at the protons in the *alpha* position relative to the hydroxyl group in the structure.

It was shown that the hydrogen atom in this position for this diastereo-isomer had a nOe correlation between this proton and one of the hydrogen atoms in the methylene unit of the 4-membered ring.



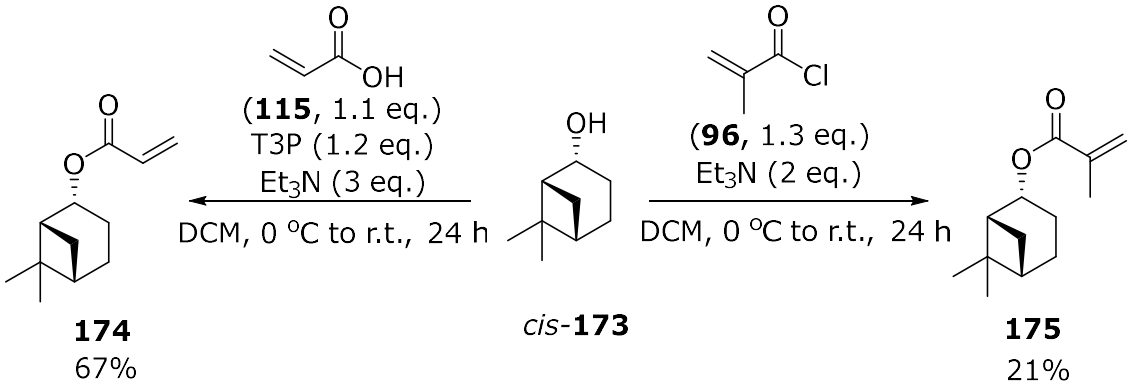
Scheme 81. The corresponding procedures for synthesising cis-***173*** *and* trans-***173*** *respectively, along with the 3-D structures of these compounds.*

Therefore, with this evidence in hand, the structures were assigned as *cis*-**173** and *trans*-**173** respectively, based on nomenclature convention observed in the literature [186]. Furthermore, *trans*-**173** could be isolated by chromatographic purification of the mixture of isomers obtained from the Meerwein-Ponndorf-Verley reduction. The yield of this purification was significantly lower however, due to loss of some of the major isomer as a mixture with the minor component, with only 34% of pure *trans*-**173** isolated.

The 3-D depictions of the two isomers (Scheme 80) give a clear picture of the associated steric factors of the molecules. It was decided that *cis*-**173** would be taken forward in the project, due to the increased steric bulk with the geminal dimethyl group in close proximity to the hydroxyl group. This would give a much more rigid structure in the material made from the polymerisation of the corresponding acrylate or methacrylate ester, which should allow for a higher glass transition temperature of the resulting polymer. Therefore, it was decided that *cis*-**173** would be taken into scale-up procedures.

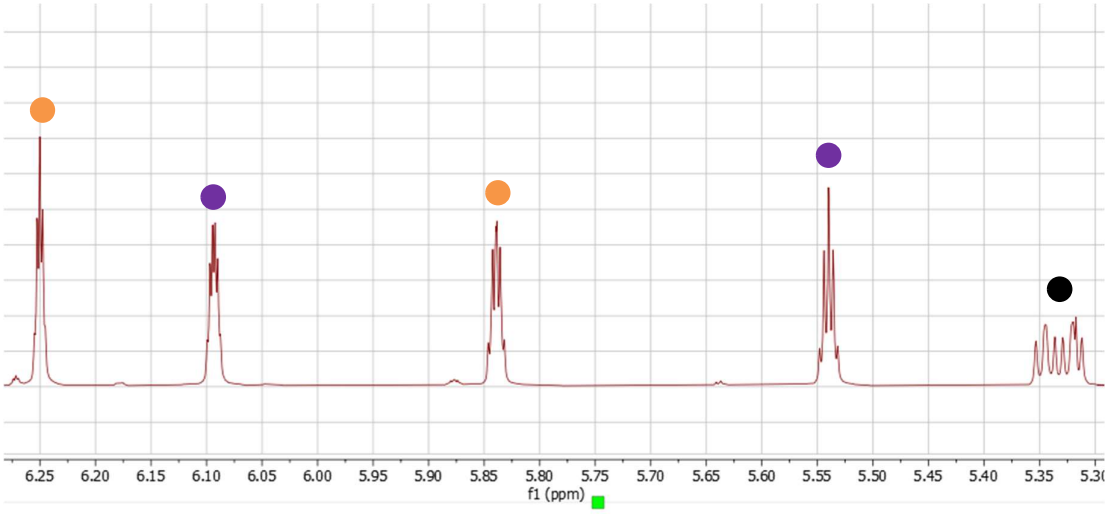
Over the course of the project, the experiment was repeated multiple times to produce the required amounts of *cis*-**173** for monomer synthesis, with reasonably consistent yields ranging from 66% to 86%. Increasing the scale of the reaction from 17.8 mmol to 72.5 mmol also gave essentially unchanged yields for this transformation.

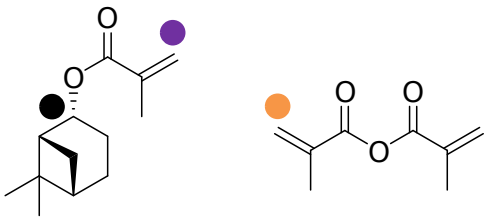
3.5.4 Synthesis of acrylate and methacrylate esters from *cis*-173



*Scheme 82. The initial attempts at the synthesis of **174** and **175** from* cis-***173*** *using esterification conditions outlined in the literature [98].*

With a route to *cis*-**173** now identified, the final step was to perform an esterification reaction to synthesise the desired acrylate (**174**) and methacrylate (**175**) respectively (Scheme 82). The initial attempts at both of these reactions followed the published conditions that were previously established in the Stockman and Howdle group [98]. Using the T3P®/acrylic acid (**115**) esterification conditions gave acrylate **174** in 67% yield, while using methacryloyl chloride (**96**) as the reagent gave the desired methacrylate **175** in only 21% yield. Both of these reactions were conducted on a small to medium scale, using 3.5 mmol of *cis*-**173** as the starting material.





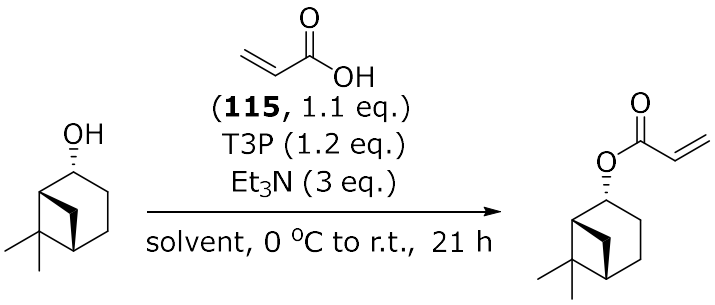
175 **203**

Figure 15. The ^{1}H NMR spectrum of the mixed fraction obtained from chromatographic purification of the crude reaction mixture obtained from the methacryloylation of cis-***173***.

The yield of **175** was so low because the formation of a by-product was observed. The yield of **175** would have been higher, but the by-product contaminated a portion of this as a mixture when collected after column chromatography. Analysis of the ^{1}H NMR spectrum of this mixture showed two extra peaks in the alkene region (Figure 15) and one extra methyl group. Combined with data obtained from the literature [193], it was determined that this by-product was in fact methacrylic anhydride (**203**).

This will have been formed from reaction of **96** with adventitious water in the reaction system to form methacrylic acid (**116**), which then attacks another molecule of **96** to generate **203**. Surprisingly, this occurred even though the reaction glassware was dried thoroughly. Furthermore, the fact that **203** survived the aqueous work-up process, involving both the use of aqueous hydrochloric acid and sodium bicarbonate solutions, was intriguing.

While giving the desired products, the yields of both processes were lower than originally predicted. This is most likely due to the sterically hindered nature of the alcohol functionality in *cis*-**173**, leading to a slow reaction rate. It was thought that optimisation of the reaction conditions would have a great effect on the corresponding yields obtained. With this hypothesis in mind, the procedure for acroylation of *cis*-**173** was subjected to a reaction optimisation protocol.



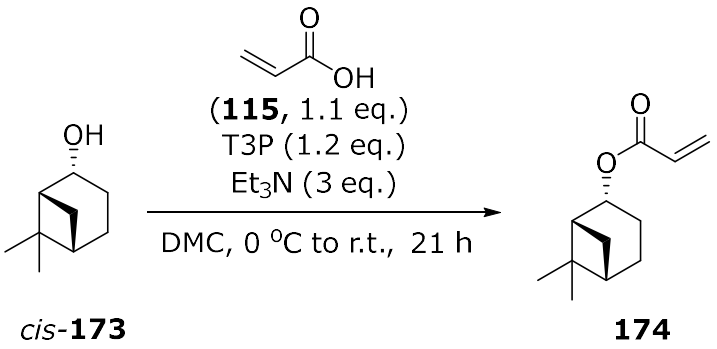
cis-**173** **174**

*Table 27. The optimisation of the reaction solvent in the synthesis of **174** from* cis-***173**. Conversion and yield values were calculated by ^{1}H NMR using an internal standard (pyrazine).*

Entry	Solvent	Conversion (%)	Yield of **174** (%)
1	MeCN	31	7
2	Acetone	61	21
3	EtOAc	90	68
4	Cyclohexane	98	68
5	Et_2O	94	47
6	DMC	84	80

The first reaction parameter investigated was the solvent (Table 27). A range of aprotic solvents were trialled, with a broad spectrum of polarity. Acetonitrile (entry 1) performed poorly, with a low conversion and only 7% of **174** formed. Acetone performed slightly better, doubling conversion and tripling yield (entry 2), but these were still not at optimised levels. Ethyl acetate, cyclohexane and diethyl ether (entries 3-5) all produced a degree of conversion higher than 90%, but the yields of **174** were significantly lower, not breaching 70% in any case. Finally, when dimethyl carbonate (DMC) was used as the reaction solvent (entry

6), conversion was slightly lower at 84%, yet the yield of **174** was 80% - an excellent conversion to yield ratio, showing only a very small degree of side product formation. This was therefore the best candidate as reaction solvent by a reasonable degree.

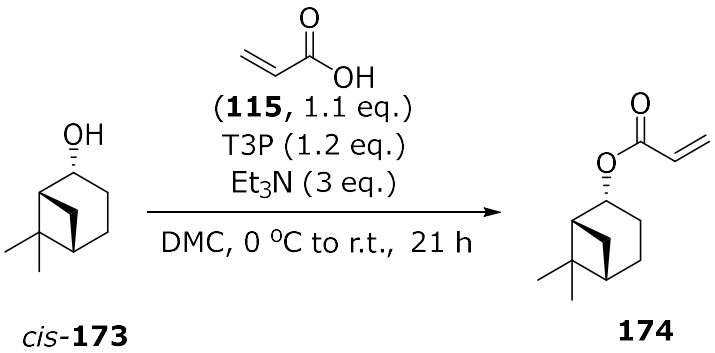


cis-**173** **174**

*Table 28. The optimisation of reaction concentration for the synthesis of **174** from* cis-***173**. Conversion and yield values were calculated by ^{1}H NMR using an internal standard (pyrazine).*

Entry	Concentration (relative to *cis*-**173**)	Conversion (%)	Yield of **174** (%)
1	0.2 M	88	73
2	0.5 M	96	71
3	1 M	95	75
4	2 M	95	77

The next parameter investigated was the reaction concentration, relative to the starting material (*cis*-**173**) (Table 28). With error involved in the process of NMR yield calculations taken into account, the conversion and yield values remained approximately similar as the concentration of the reaction mixture was increased. With no large effect observed, it was decided that a concentration of 2 M would be carried forward, due to the lower costs associated with less reaction solvent and less energy required for mass transport in work-up and purification processes.



cis-**173** **174**

*Table 29. The results of the scale-up of the optimised conditions for the synthesis of **174**. All yields are isolated unless otherwise stated.*

Entry	Scale (mmol of *cis*-**173**)	Yield of **174** (%)
1	3.57	81[a]
2	35.7	80
3	35.7	76

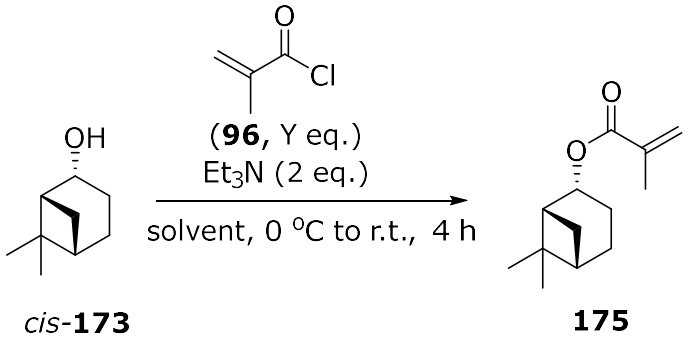
a = calculated by ^{1}H NMR using an internal standard (pyrazine).

With the stoichiometry of most of the reagents at fairly low levels, and the temperature of the reaction more likely to cause product degradation if increased, due to the labile nature of the acrylate functionality, it was decided that further optimisation would not be carried out. Therefore, the conditions were employed in the scale-up of the production of **174** (Table 29). On a small to medium scale (entry 1), **174** was shown to have been formed in 81% yield by ^{1}H NMR analysis. The reaction was then scaled up by a factor of 10 (entries 2 and 3), giving isolated yields after purification by column chromatography of **174** between 76-80%.

Before the optimised conditions were applied to the methacrylate (**175**) synthesis, a procedure to remove any **203** formed in the reaction needed to be identified. It was thought that contact with an aqueous solution of sodium bicarbonate for a matter of hours, rather than minutes, would be enough to cause complete hydrolysis of the anhydride, with a minimal negative effect on the yield of the desired product **175**.

When diethyl ether was used to dissolve the crude reaction mixture, anhydride removal was not complete after stirring with aqueous sodium bicarbonate for 20 hours. However, when the water-miscible solvent, acetone, was used as the

organic component, this procedure did indeed result in total hydrolysis of the unwanted side product. TLC analysis also confirmed that minimal degradation of **175** had occurred, as no *cis*-**173** was present in the resulting product.



cis-**173** **175**

*Table 30. The use of the optimised conditions, with some variations, for the scale-up of the synthesis of **175**. Yields are isolated unless stated otherwise.*

Entry	Scale (mmol of *cis*-**173**)	Y (eq.)	Solvent	Yield of **175** (%)
1	3.57	1.2	DMC	61[a]
2	10.7	1.3	DMC	29
3	10.7	1.3	DMC	41
4	10.7	1.3	DMC	68
5	21.4	1.5	2-MeTHF	42
6	21.9	1.3	DMC	55
7	35.7	1.3	DMC	38
8	35.7	1.3	DMC	46

a = calculated by ^{1}H NMR using an internal standard (pyrazine).

With a method for removing the by-product now identified, the next step was to apply the optimised reaction conditions to the methacroylation of *cis*-**173** to form **175** (Table 30). The initial attempt using these conditions gave a yield of 61% of **175** by ^{1}H NMR (entry 1) – a significant improvement on the first attempt to synthesise **175**. Scaling up the reaction by a factor of 3 was repeated 3 times (entries 2-4), giving a range of yields from 29-68%, even though nothing was different about any of the procedures. The reason for this remains unclear.

Upon approximately doubling the reaction scale again, 2-methyltetrahydrofuran, another renewable solvent option well documented in the literature [194], was

also trialled along with the original solvent choice of DMC (entries 5 and 6). These reactions gave yields of 42% and 55% respectively. Finally, the reaction was scaled up even further to 35.7 mmol and repeated (entries 7 and 8) using the optimised conditions, giving yields of **175** ranging from 38% to 46%.

While better than the original conditions, these yield values are still not great, and this may be due to the increased steric clashing with the bulkier methacryloyl reagent, in combination with the issue of side product formation. It was therefore decided that a transesterification method would be investigated as an alternative strategy for the production of **175**.

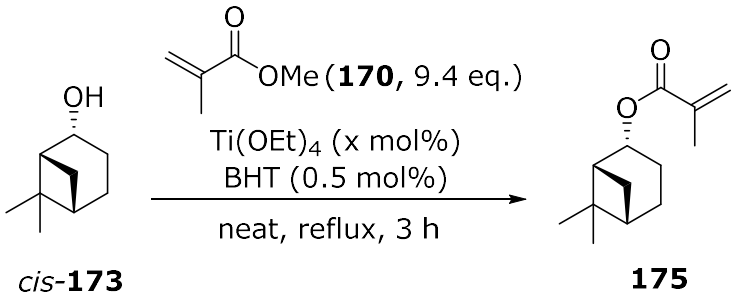


*Table 31. The investigation into varying titanium catalyst loading in the transesterification procedure for the synthesis of **175**. Conversion and yield values were determined by ^{1}H NMR using an internal standard (pyrazine). Yields given in parentheses are isolated values.*

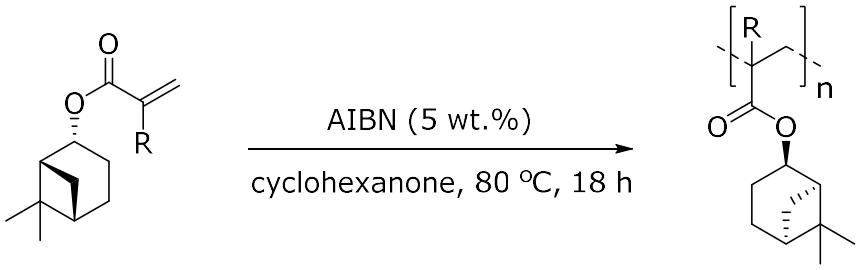
Entry	x (mol%)	Conversion (%)	Yield of **175** (%)
1	2	67	14
2	5	74	55
3	10	94	66 (47)

The loading of the catalyst, titanium(IV) ethoxide, was varied in the transesterification reaction attempts (Table 31). At 2 mol% (entry 1), conversion did not reach high levels and the yield of **175** was poor. Increasing this value to 5 mol% (entry 2) gave a slightly better conversion value, with a much improved yield of 55%. Further increasing the value to 10 mol% (entry 3) gave near complete conversion of starting material, with a 66% yield of **175** by ^{1}H NMR. This sample was then purified using chromatography to give a 47% isolated

yield of **175** – a pleasing result, similar to that achieved by reaction of *cis*-**173** with **96**, albeit on a much smaller scale.

This protocol represents a much more sustainable methacrylate ester synthesis method, as it avoids the use of an acid chloride reagent. The potential for recycling of the methyl methacrylate reagent and solvent is also good. From these results, it may be possible that transesterification becomes the favoured method for methacrylate ester synthesis in the future, with the absence of further ground-breaking research in this area.

3.5.5 Polymerisation and Materials Testing



R = H, **174**
R = Me, **175**

R = H, **204**
R = Me, **205**

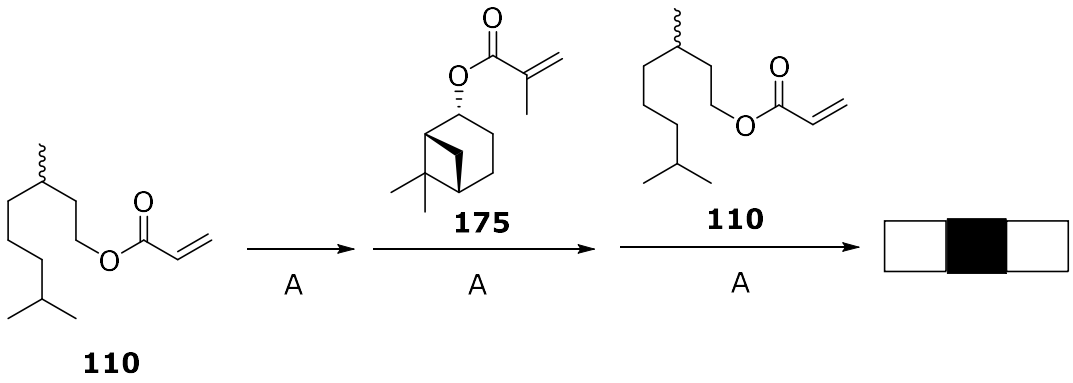
*Table 32. The results of the homopolymerisation of the nopinyl acrylate (**174**) and methacrylate (**175**) monomers. The polymerisation reactions and polymer analyses were carried out by Dr. Olivia Monaghan.*

Entry	R =	Conversion (%)	M_n (g mol^{-1})	M_w (g mol^{-1})	Đ	T_g (°C)
1	H (**174**)	86	72,000	124,000	1.72	63
2	Me (**175**)	91	190,000	301,000	1.56	194

The nopinyl monomers **174** and **175** were then passed to Dr. Olivia Monaghan, and subjected to separate homopolymerisation reactions (Table 32). The resulting polymer materials **204** and **205** were then submitted to analysis by GPC and TGA, in order to discover the properties of the resulting polymers.

Conversion values were also high in both cases, and the polydispersity values were typical of standard free radical polymerisation methods [195]. The acrylate (entry 1) polymerised well, but the methacrylate (entry 2) polymerised extremely well, with the material in excess of 200,000 Da on average. This gives a degree of polymerisation value just shy of 1000 – an excellent result.

As also predicted, the nopinyl polymers had significantly higher glass transition temperature (T_g) values compared to any of the other terpene-based polymers synthesised during the course of the project. With the methacrylate polymer (entry 2) giving a value of 194 °C, this meant it would most likely be suitable for the desired function of becoming a hard-block component in a co-polymer used as a thermoplastic elastomer.



*Scheme 83. The synthesis of a soft-hard-soft tri-block co-polymer using tetrahydrogeranyl acrylate (**110**) as the soft block (white) and **175** as the hard block (black). Performed by Rachel Atkinson, a PhD student in the Howdle group. Conditions: A = AIBN (5 wt.%), cyclohexanone, 80 °C, 18 h.*

The methacrylate was then tested as the hard block in a tri-block, soft-hard-soft co-polymer using tetrahydrogeranyl acrylate (**110**), synthesised by Rachel Atkinson, a PhD student in the group of Prof. Steven Howdle, as the soft block component (Scheme 83). This monomer had also very recently been used as a soft block component in the literature [196]. This investigation proceeded well with promising results, and was passed onto Matthew Elsmore, a PhD student in the Department of Engineering under the supervision of Dr. Davide de Focatiis, for rheology and materials testing. This work is currently progressing well, and a manuscript to detail this work in full is in preparation.

Currently no application has been determined for the acrylate material – however, the polymer fits into a mould easily, and can be shaped to a reasonable degree. This is rare for terpene based monomers, as many of the other materials in the project have been too brittle to work with in this way. Further examination of any potential application for the acrylate material is still ongoing in the Engineering department.

4. Conclusions

In conclusion, a plethora of monomers suitable for either chain-growth or step-growth polymerisation methods have been synthesised from abundant monoterpenes during the course of this research project. All of the synthetic routes developed to these monomers consist of 3 steps or less, and have been optimised with reaction yield, selectivity and sustainability all considered during the process.

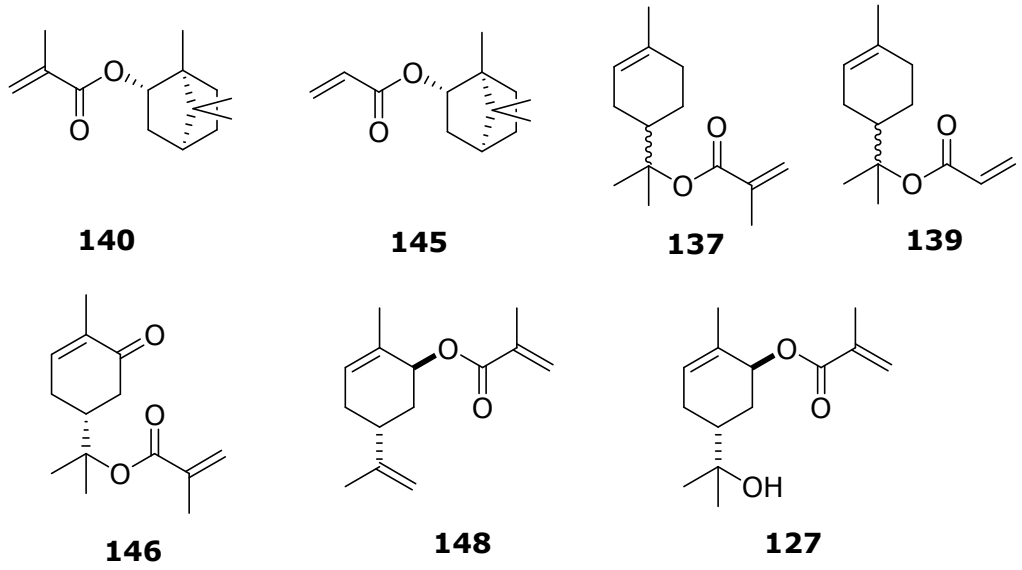
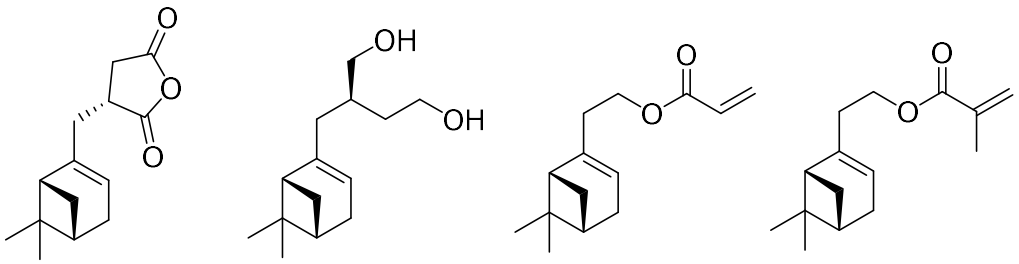


Figure 16. The scope of monomers produced from the optimised (meth)acryloxylation process developed during the investigation.

An acid-catalysed (meth)acryloxylation procedure has been developed, and subsequently optimised to reduce the initial need for chlorinated solvents, and to substitute the costly trifluoromethanesulfonic acid for a cheaper alternative. Heterogeneous catalysis using Amberlyst-15 was also trialled, but was not successful on medium to large reaction scales. The scope of the procedure was then explored to generate 1 more acrylate and 4 more methacrylate monomers (Figure 16).

These materials, alongside other terpene monomers produced from the wider collaborative project, were then tested for anti-attachment properties in the Department of Engineering. This testing found that **137**, a monomer initially produced to prove the structure of **140**, was as effective at preventing adhesion

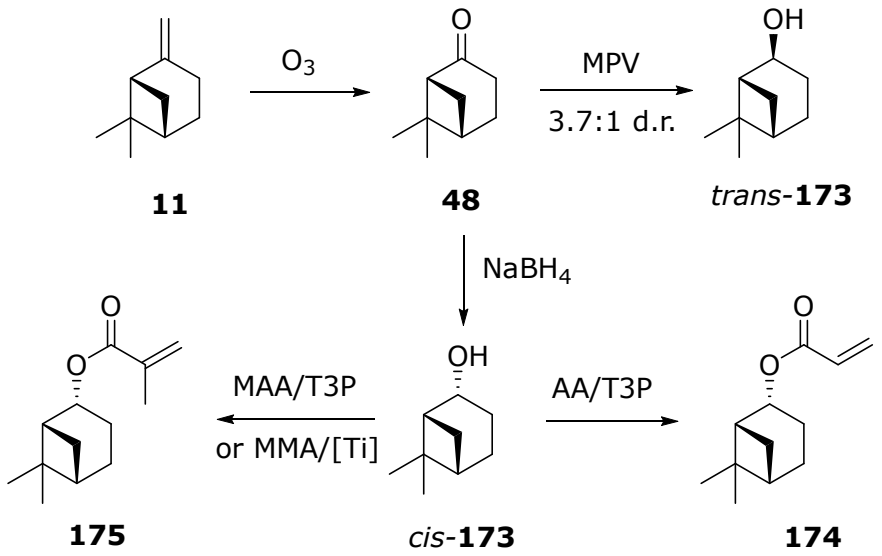
of bacteria to a surface as already established literature examples. This material was then produced on a large scale to satisfy applications testing in the Engineering department, which is currently ongoing.



159 **165** **168** **169**

*Figure 17. The scope of the monomers produced from β-pinene (**11**) using an Alder ene reaction as the key transformation.*

11 is also an excellent substrate for use in the Alder ene reaction, and this was exploited for the generation of two species, **159** and **167**, by reaction of **11** with maleic anhydride and formaldehyde respectively. **159** was then reduced to form diol **165** – both of these species would be applicable for step-growth polymerisation as a di-carboxylic acid equivalent and a diol respectively, which could be suitable for the formation of polyesters. Conversely, **167** was then esterified to form **168** or **169** (Figure 17). These species were proposed to be suitable for chain-growth polymerisation, but unfortunately did not produce homo-polymers efficiently - the reasons for which are still being determined.



*Scheme 84. A summary of the synthesis of monomers **174** and **175** in 3 steps from **11**.*

An acrylate (**174**) and methacrylate (**175**) monomer have also been synthesised in 3 steps from **11** (Scheme 84). Attempts were made to optimise each step of the synthesis, in particular the oxidative cleavage reaction, to attempt to identify a high-yielding yet sustainable transformation. While both ozonolysis and Lemieux-Johnson oxidation procedures gave good yields, their more sustainable variants involving ruthenium or iron catalysis did not match these and returned only moderate yields.

Conditions were identified to obtain either isomer of **173** in excellent yield, with sodium borohydride providing exclusively the *cis*-isomer, and a Meerwein-Ponndorf-Verley reduction yielding *trans*-**173** in a diastereomeric ratio of 3.8:1. Esterification of *cis*-**173** was also shown to proceed with either a stoichiometric amount of coupling reagent, or via a titanium-catalysed transesterification process.

Finally, these monomers were then homo-polymerised by collaborators in the research group of Professor Steven Howdle, with the methacrylate **175** providing polymer **204** with a T_g value of 194 °C. This is currently the highest value observed from any methacrylate ester-based polymer produced during the course of the wider terpenes project. This provided an opportunity for this monomer to be used as a hard-block for a tri-block alternating soft-hard-soft co-

polymer in conjunction with tetrahydrogeranyl acrylate – work which is currently ongoing.

In summary, a total of 15 moieties suitable for various forms of polymerisation have been produced during this research project, of which 7 have not been reported previously for use as a monomer either during the collaborative project, or previously in the literature. Work is currently ongoing in both the Chemistry and Engineering departments to identify polymerisation conditions and potential applications for these species.

5. Experimental Section

5.1 General Remarks

Standard solvents (dichloromethane, ethyl acetate, petroleum ether and others) were purchased from Fisher Scientific and used without further purification unless otherwise stated. Dry tetrahydrofuran and dry diethyl ether were dried by passing through a series of activated alumina columns prior to use. Where other solvents are denoted as dry, this represents a commercially sourced solvent purchased with a purity of at least 99.9%, stored under argon and over molecular sieves. Brine refers to a saturated aqueous solution of sodium chloride. All reactions were conducted under an inert atmosphere of argon unless otherwise stated.

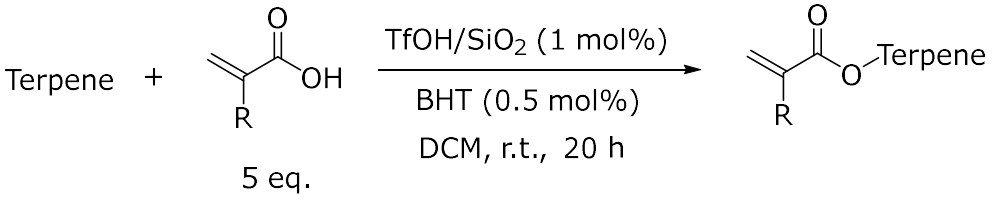
(-)-α-pinene (**10**) and (-)-β-pinene (**11**) were purchased at a purity of 99% with 81% e.e., both from Sigma-Aldrich and were used as received. All other reagents were purchased from either Sigma-Aldrich, Acros Organics, Fisher Scientific or Strem Chemicals, and were used as received unless otherwise stated. *trans*-Sobrerol (**126**) was synthesised by Rhona Savin. Silica gel (60 Å, 40 - 63 micron) was purchased from Sigma-Aldrich. TLC analysis was performed using Merck silica gel 60 F_{254} aluminium backed TLC plates.

NMR spectra were recorded on either a Bruker Avance 400 or a Bruker DPX 400 NMR spectrometer. Chemical shifts are referenced to the solvent peak of $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm). Abbreviations for NMR multiplet analysis were used as follows: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sep = septet, br = broad, app = apparent, m = multiplet.

Mass spectra were recorded on a Bruker microTOF focus II mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 IR spectrometer fitted with an ATR attachment. Optical rotation values were measured on an ADP 440 polarimeter, using a cell with a path length of 0.25 dm. Concentrations are given in grams per 100 mL of solvent. Melting point determinations were performed using a Stuart Scientific SMP3 melting point apparatus, and melting point values are uncorrected.

5.2 Brønsted/Lewis acid catalysed procedures

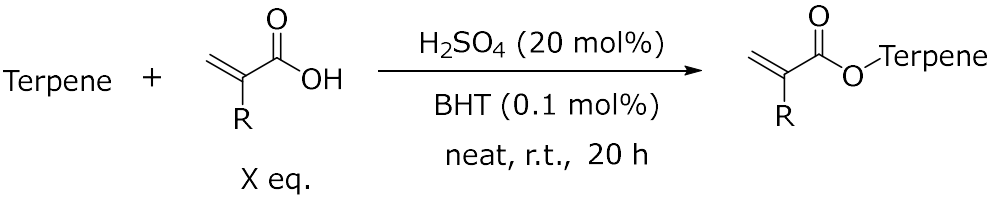
General procedure **A** for trifluoromethanesulfonic acid catalysed (meth)acryloxylation of terpenes



2,6-di-*tert*-butyl-4-methylphenol (0.005 equivalents) was dissolved in dichloromethane at a concentration of [0.4 M] (respective to the terpene) with stirring. The terpene (1.00 equivalent) was added to the solution, followed by (meth)acrylic acid (5.00 equivalents). Silica supported trifluoromethanesulfonic acid (7.5% w/w TfOH, 0.01 equivalents) was then added to the reaction mixture, which was stirred at 20 °C for 20 hours.

The reaction mixture was then filtered under gravity. Organics were washed through with dichloromethane (2 x 1 - 100 mL). The solution was then evaporated to a quarter of the original volume. The mixture was washed with 1 M aqueous sodium hydroxide solution (5 - 500 mL), and then the aqueous layer was washed with dichloromethane (1 - 100 mL). The organic fractions were combined and washed with brine (5 - 500 mL) then dried (Na_2SO_4). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield the crude mixture.

General procedure **B** for solvent-free Brønsted acid catalysed (meth)acryloxylation of terpenes



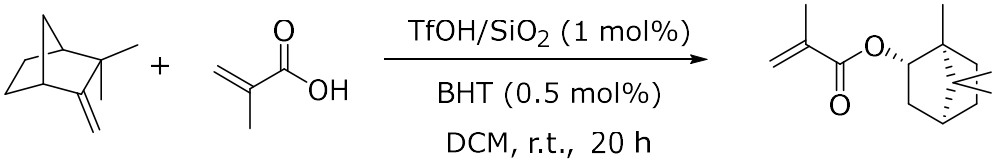
2,6-di-*tert*-butyl-4-methylphenol (0.001 equivalents) was mixed with the terpene (1 equivalent) at room temperature. The (meth)acrylic acid (11.3 – 14.1 equivalents) was added, followed by the slow addition of concentrated sulfuric

acid (20 mol%) with vigorous stirring. The reaction mixture was then stirred at room temperature for 20 hours.

After consumption of starting material was indicated by TLC, the reaction mixture was poured into 1 M aqueous sodium hydroxide (10 – 1000 mL). Organics were extracted into dichloromethane (3 × 5 – 500 mL). The organic fractions were combined and washed with 1 M aqueous sodium hydroxide solution (10 – 1000 mL), saturated aqueous sodium bicarbonate solution (10 – 1000 mL) and brine (10 – 1000 mL), then dried ($MgSO_4$). The mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield the crude mixture.

Synthesis of isobornyl methacrylate (**140**)

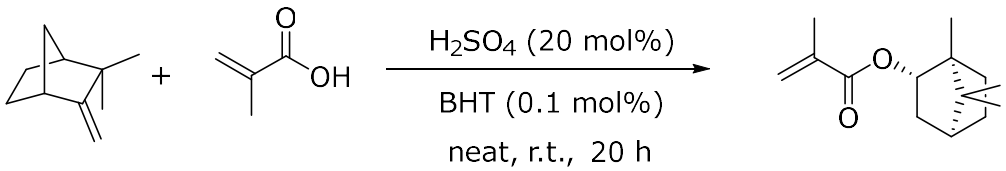
Method 1:



22 **116** 5 eq. **140** 78%

General procedure **A** was followed using camphene (**22**, 1.36 g, 10.0 mmol), methacrylic acid (4.2 mL, 50.0 mmol), silica supported trifluoromethanesulfonic acid (7.5% w/w TfOH, 0.20 g, 0.10 mmol), 2,6-di-*tert*-butyl-4-methylphenol (11 mg, 0.05 mmol) and dichloromethane (25 mL). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 5%) to yield **140** as a pale yellow oil (1.74 g, 78%).

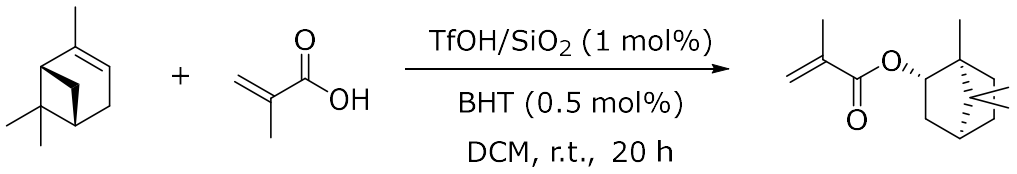
Method 2:



22 **116** 11.3 eq. **140** 83%

General procedure **B** was followed using camphene (**22**, 136 mg, 1.00 mmol), methacrylic acid (1.00 mL, 11.3 mmol) and 98% sulfuric acid (10.8 µL, 0.20 mmol). **140** was obtained as a pale yellow oil (185 mg, 83%) with no further purification required.

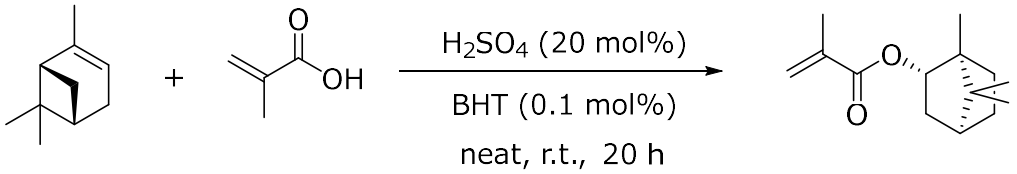
Method 3:



10 **116** 5 eq. **140** 35%

General procedure **A** was followed using (-)-α-pinene (**10**, 16 mL, 100 mmol), methacrylic acid (42 mL, 500 mmol), silica supported trifluoromethanesulfonic acid (7.5% w/w TfOH, 2.00 g, 1.00 mmol), 2,6-di-*tert*-butyl-4-methylphenol (110 mg, 0.50 mmol) and dichloromethane (250 mL). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 5%) to yield **140** as a yellow oil (7.83 g, 35%).

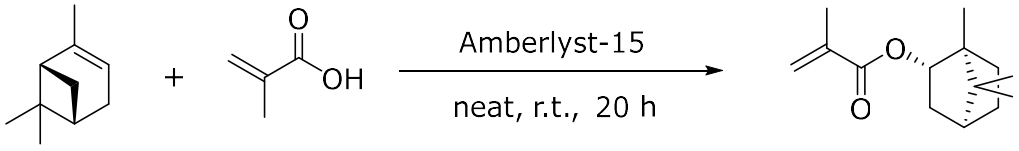
Method 4:



10 **116** 11.3 eq. **140** 22%

General procedure **B** was followed using (-)-α-pinene (**10**, 0.16 mL, 1.00 mmol), methacrylic acid (1.00 mL, 11.3 mmol), and 98% sulfuric acid (10.8 µL, 0.20 mmol). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 20%) to yield **140** as a yellow oil (49 mg, 22%).

Method 5:



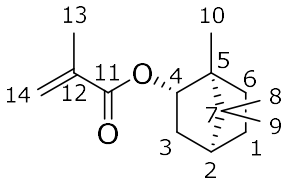
10 **116** 11.3 eq. **140** 41% by ^{1}H NMR

(-)-α-pinene (**10**, 0.16 mL, 1.00 mmol) and methacrylic acid (1.00 mL, 11.3 mmol) were mixed together with stirring. Amberlyst-15 (dry form, 3.0 g) was then added, and the mixture was stirred for 20 hours at room temperature.

The mixture was then filtered under gravity. The filtrate was quenched with saturated aqueous sodium bicarbonate (10 mL). Organics were extracted into dichloromethane (3 × 5 mL). The organic fractions were combined and washed with saturated aqueous sodium bicarbonate (25 mL), brine (25 mL), then dried ($MgSO_4$). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

The yield of **140** was determined by ^{1}H NMR, using pyrazine as an internal standard, to be 41%.

Data collected for (2*S*,4*S*,5*S*)-5,7,7-trimethylbicyclo[2.2.1]heptan-4-yl methacrylate (**140**):



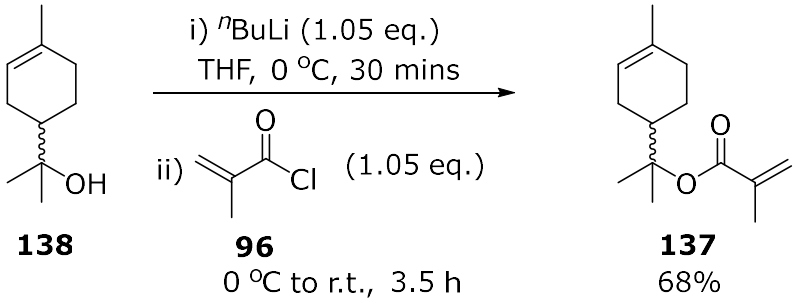
140

R_f (EtOAc:petrol 1:19): 0.29; **$[\alpha]_D^{26.6}$** +6.0° (c 1.86, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2953, 2876, 1714 (C=O), 1453, 1297, 1158, 1082, 974; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.06 (1H, dq, *J* = 1.7, 1.0 Hz, H-14a), 5.52 (1H, dq, *J* = 1.7, 1.6 Hz, H-14b), 4.72 (1H, dd, *J* = 7.4, 3.4 Hz, H-4), 1.93 (3H, dd, *J* = 1.6, 1.0 Hz, H-13), 1.84 – 1.78 (2H, m, H-3a and H-3b), 1.75 (1H, app t, *J* = 4.3 Hz, H-2), 1.70 (1H, app dt, *J* = 11.5, 3.9 Hz, H-1a), 1.57 (1H, app td, *J* = 12.5, 4.3 Hz, H-1b), 1.19 (1H, app td, *J* = 9.4, 3.9 Hz, H-6a), 1.11 (1H, app td, *J* = 10.4,

3.4 Hz, H-6b), 1.02 (3H, s, H-10), 0.86 (3H, s, H-8), 0.85 (3H, s, H-9); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 166.9 (C-11), 136.9 (C-12), 125.0 (C-14), 81.2 (C-4), 48.9 (C-5), 47.0 (C-7), 45.1 (C-2), 38.9 (C-3), 33.8 (C-1), 27.1 (C-6), 20.2 (C-9), 20.0 (C-10), 18.4 (C-13), 11.6 (C-8); **HRMS** (ESI, $[C_{14}H_{22}O_2+Na]^+$): measured 245.1510, theoretical 245.1512.

Spectral data for **140** agrees with the reported values in the literature. [114]

Synthesis of α-terpinyl methacrylate (**137**)



138 **96** **137**

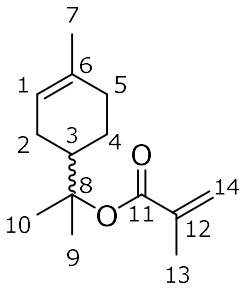
0 °C to r.t., 3.5 h 68%

A dried flask was charged with dry tetrahydrofuran (20 mL) under an inert argon atmosphere. α-terpineol (**138**, 0.83 mL, 5.00 mmol) was added with stirring, and the resulting mixture was cooled to 0 °C (water/ice bath). *n*-Butyllithium (2.366 M in hexanes, 2.22 mL, 5.25 mmol) was added to the mixture over 5 minutes, and the resulting mixture was stirred at 0 °C for 30 minutes. Methacryloyl chloride (0.52 mL, 5.25 mmol) was then added over a period of 5 minutes, and the resulting mixture was stirred at 0 °C for 1 hour. The reaction mixture was then allowed to warm to room temperature, and was stirred for a further 2.5 hours.

After reaction completion had been indicated by TLC, the reaction mixture was quenched (saturated aqueous sodium bicarbonate, 30 mL). Organics were extracted into diethyl ether (3 × 20 mL). The organic fractions were combined and washed with brine (25 mL), then dried ($MgSO_4$). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 0 – 10% ethyl acetate in petroleum ether) to yield the desired product **137** as a pale yellow oil (759 mg, 68%).

Data collected for 2-(4-methylcyclohex-3-en-1-yl)propan-2-yl methacrylate (**137**):

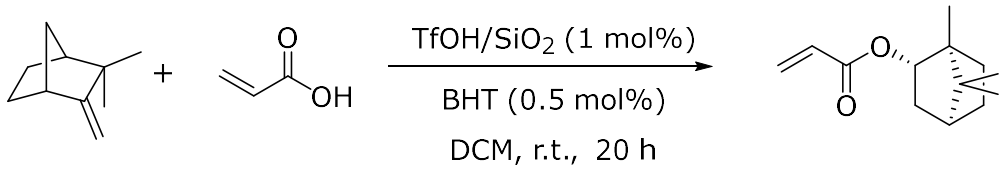


137

R_f (EtOAc:petrol 1:19): 0.37; **$[\alpha]_D^{21.0}$** +10.7° (c 0.39, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2927, 1710 (C=O), 1637, 1400, 1329, 1174, 917, 799; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.00 (1H, dq, *J* = 1.9, 1.0 Hz, H-14a), 5.47 (1H, app qu, *J* = 1.6 Hz, H-14b), 5.41 – 5.35 (1H, m, H-1), 2.09 – 1.95 (4H, m, H-2a, H-2b, H-3 and H-5a), 1.94 – 1.78 (2H, m, H-4a and H-5b), 1.90 (3H, dd, *J* = 1.6, 1.0 Hz, H-13), 1.65 (3H, m, H-7), 1.50 (3H, s, H-10), 1.47 (3H, s, H-9), 1.35 (1H, app qd, *J* = 12.2, 5.6 Hz, H-4b); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 166.6 (C-11), 138.2 (C-12), 133.9 (C-6), 124.2 (C-14), 120.2 (C-1), 84.7 (C-8), 43.1 (C-3), 30.9 (C-2), 26.5 (C-5), 24.1 (C-4), 23.5 (C-7), 23.4 (C-10), 23.3 (C-9), 18.4 (C-13); **HRMS** (ESI, $[C_{14}H_{22}O_2+Na]^+$): measured 245.1500, theoretical 245.1512.

Synthesis of isobornyl acrylate (**145**)

Method 1:

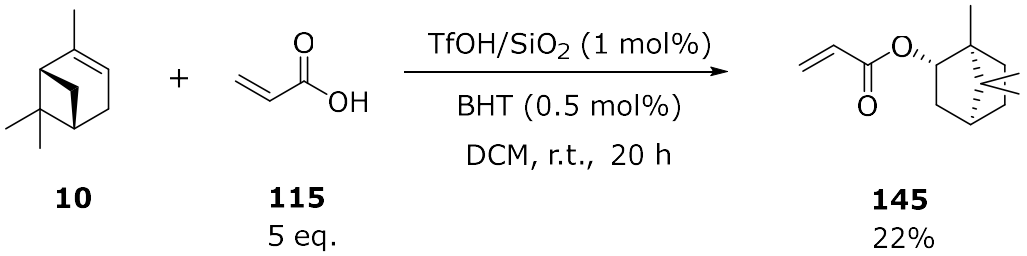


22 **115** 5 eq. **145** 85%

General procedure **A** was followed using camphene (**22**, 1.36 g, 10.0 mmol), acrylic acid (3.4 mL, 50.0 mmol), silica supported trifluoromethanesulfonic acid (7.5% w/w TfOH, 0.20 g, 0.10 mmol), 2,6-di-*tert*-butyl-4-methylphenol (11 mg, 0.05 mmol) and dichloromethane (25 mL). The crude product was purified using

silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 5%) to yield **145** as a pale yellow oil (1.78 g, 85%).

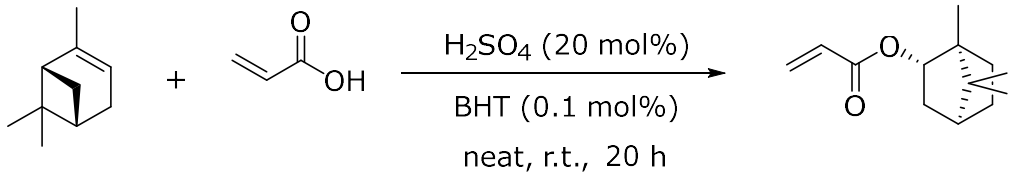
Method 2:



10 **115** 5 eq. **145** 22%

General procedure **A** was followed using (-)-α-pinene (**10**, 1.6 mL, 10.0 mmol), acrylic acid (3.4 mL, 50.0 mmol), silica supported trifluoromethanesulfonic acid (7.5% w/w TfOH, 0.20 g, 0.10 mmol), 2,6-di-*tert*-butyl-4-methylphenol (11 mg, 0.05 mmol) and dichloromethane (25 mL). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 5%) to yield **145** as a yellow oil (497 mg, 22%).

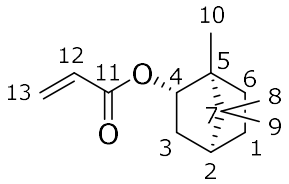
Method 3:



10 **115** 14.1 eq. **145** 11%

General procedure **B** was followed using (-)-α-pinene (**10**, 0.16 mL, 1.00 mmol), acrylic acid (1.00 mL, 14.1 mmol), and 98% sulfuric acid (10.8 µL, 0.20 mmol). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 50%) to yield **145** as a yellow oil (23 mg, 11%).

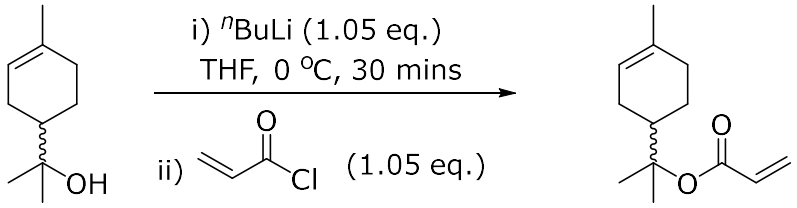
Data collected for (2*S*,4*S*,5*S*)-5,7,7-trimethylbicyclo[2.2.1]heptan-4-yl acrylate (**145**):



145

R_f (EtOAc:petrol 1:19): 0.24; **$[\alpha]_D^{26.6}$** +5.0° (c 0.90, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2953, 2877, 1721 (C=O), 1404, 1267, 1196, 1181, 1082, 809; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.34 (1H, dd, *J* = 17.3, 1.6 Hz, H-13a), 6.10 (1H, dd, *J* = 17.3, 10.5 Hz, H-12), 5.79 (1H, dd, *J* = 10.5, 1.6 Hz, H-13b), 4.75 (1H, dd, *J* = 7.8, 4.0 Hz, H-4), 1.86 – 1.81 (2H, m, H-3a and H-3b), 1.75 (1H, app qu, *J* = 3.7 Hz, H-2), 1.70 (1H, app dq, *J* = 11.7, 3.7 Hz, H-1a), 1.57 (1H, app td, *J* = 12.4, 4.1 Hz, H-6a), 1.16 (1H, dd, *J* = 12.9, 4.1 Hz, H-6b), 1.11 (1H, dd, *J* = 11.6, 3.4 Hz, H-1b), 1.01 (3H, s, H-9), 0.86 (3H, s, H-10), 0.85 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 166.1 (C-11), 130.4 (C-13), 129.6 (C-12), 81.5 (C-4), 49.3 (C-5), 47.4 (C-7), 45.5 (C-2), 39.2 (C-3), 34.1 (C-6), 27.5 (C-1), 20.5 (C-8), 20.3 (C-9), 11.8 (C-10); **HRMS** (ESI, $[C_{13}H_{20}O_2+Na]^+$): measured 231.1357, theoretical 231.1356.

Synthesis of α-terpinyl acrylate (**139**)



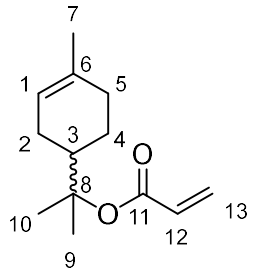
A dried flask was charged with dry tetrahydrofuran (20 mL) under an inert argon atmosphere. α-terpineol (**138**, 0.83 mL, 5.00 mmol) was added with stirring, and the resulting mixture was cooled to 0 °C (water/ice bath). *n*-Butyllithium (2.366 M in hexanes, 2.22 mL, 5.25 mmol) was added to the mixture over 5 minutes, and the resulting mixture was stirred at 0 °C for 30 minutes. Acryloyl chloride (0.43 mL, 5.25 mmol) was then added over a period of 5 minutes, and

the resulting mixture was stirred at 0 °C for 1 hour. The reaction mixture was then allowed to warm to room temperature, and was stirred for a further 2.5 hours.

After reaction completion had been indicated by TLC, the reaction mixture was quenched (saturated aqueous sodium bicarbonate, 30 mL). Organics were extracted into diethyl ether (3 × 20 mL). The organic fractions were combined and washed with brine (25 mL), then dried ($MgSO_4$). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 0 – 10% ethyl acetate in petroleum ether) to yield the desired product **139** as a pale yellow oil (447 mg, 43%).

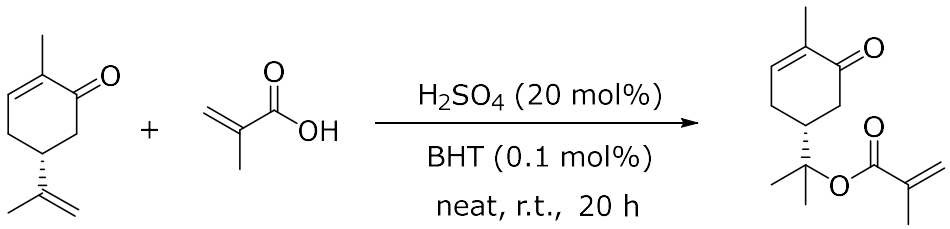
Data collected for 2-(4-methylcyclohex-3-en-1-yl)propan-2-yl acrylate (**139**):



139

R_f (EtOAc:petrol 1:19): 0.33; **$[\alpha]_D^{20.7}$** +9.1° (c 0.26, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2963, 1718 (C=O), 1636, 1401, 1297, 1206, 809; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.28 (1H, dd, *J* = 17.4, 1.6 Hz, H-13a), 6.03 (1H, dd, *J* = 17.6, 10.7 Hz, H-12), 5.72 (1H, dd, *J* = 10.3, 1.7 Hz, H-13b), 5.40 – 5.34 (1H, m, H-1), 2.12 – 1.96 (4H, m, H-2a, H-2b, H-3 and H-5a), 1.90 – 1.78 (2H, m, H-4a and H-5b), 1.64 (3H, m, H-7), 1.49 (3H, s, H-10), 1.46 (3H, s, H-9), 1.32 (1H, app qd, *J* = 12.1, 5.5 Hz, H-4b); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 165.5 (C-11), 134.0 (C-6), 130.5 (C-12), 129.4 (C-13), 120.3 (C-1), 85.3 (C-8), 42.8 (C-3), 30.9 (C-2), 26.5 (C-5), 24.0 (C-4), 23.5 (C-7), 23.4 (C-9), 23.3 (C-10); **HRMS** (ESI, $[C_{13}H_{20}O_2+Na]^+$): measured 231.1348, theoretical 231.1356.

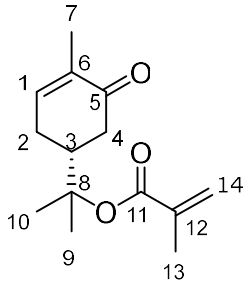
Synthesis of carvone-based methacrylate (**146**)



25 **116** 11.3 eq. **146** 11%

General procedure **B** was followed using (-)-carvone (**25**, 0.16 mL, 1.00 mmol), methacrylic acid (1.00 mL, 11.3 mmol), and 98% sulfuric acid (20 mol%, 10.8 µL, 0.20 mmol). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 100%) to yield **146** as a yellow oil (26 mg, 11%).

Data collected for (*R*)-2-(4-methyl-5-oxocyclohex-3-en-1-yl)propan-2-yl methacrylate (**146**):

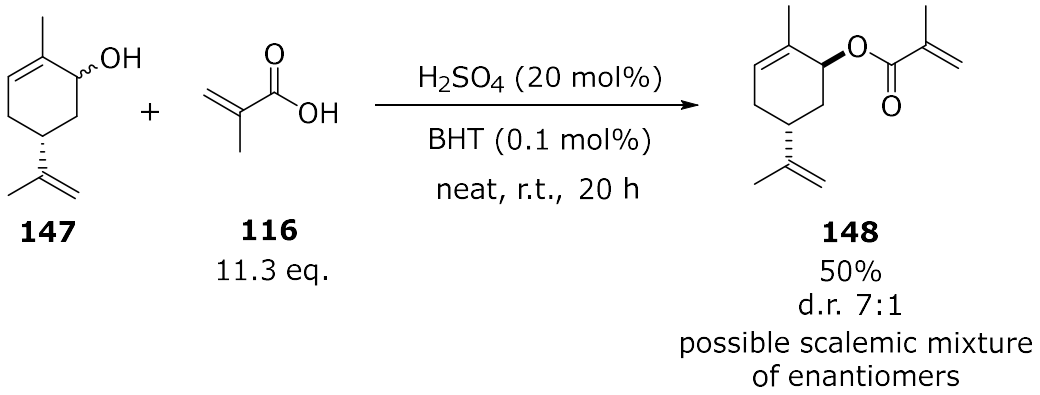


146

R_f (EtOAc:petrol 1:19): 0.21; **$[\alpha]_D^{26.6}$** -95.5° (c 0.37, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2981, 2926, 1710 (C=O), 1672, 1636, 1452, 1302, 1256, 1170, 1130; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.74 (1H, ddd , *J* = 6.0, 2.2, 1.3 Hz, H-1), 5.99 (1H, dq, *J* = 1.6, 1.2 Hz, H-14a), 5.49 (1H, app qu, *J* = 1.6 Hz, H-14b), 2.59 (1H, ddd, *J* = 15.4, 3.6, 1.7 Hz, H-2a), 2.52 (1H, app ddt, *J* = 10.5, 3.7, 1.5 Hz, H-3), 2.41 (1H, app dtt, *J* = 18.1, 4.4, 1.2 Hz, H-4a), 2.30 (1H, m, H-2b), 2.24 (1H, m, H-4b), 1.89 (3H, dd, *J* = 1.6, 1.2 Hz, H-13), 1.77 (3H, app dt, *J* = 2.5, 1.4 Hz, H-7), 1.52 (3H, s, H-9), 1.51 (3H, s, H-10); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 199.6 (C-5), 166.5 (C-11), 144.7 (C-1), 137.7 (C-12), 135.5 (C-6), 125.0 (C-14), 83.0 (C-8), 44.7 (C-3), 39.4 (C-2), 27.2 (C-4), 23.5 (C-9),

18.6 (C-13), 15.7 (C-10); **HRMS** (ESI, $[C_{14}H_{20}O_3+Na]^+$): measured 259.1307, theoretical 259.1305.

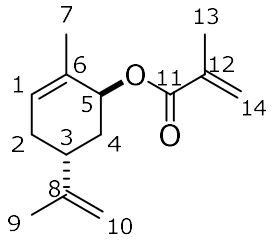
Synthesis of carveol methacrylate (**148**)



147 **116** 11.3 eq. **148** 50% d.r. 7:1 possible scalemic mixture of enantiomers

General procedure **B** was followed using (*R*)-carveol (mix of isomers) (**147**, 0.16 mL, 1.00 mmol), methacrylic acid (1.00 mL, 11.3 mmol), and 98% sulfuric acid (20 mol%, 10.8 µL, 0.20 mmol). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 100%) to yield **148** as a yellow oil (109 mg, 50%, 7:1 d.r., each diastereomer as a scalemic mixture of enantiomers).

Data collected for (3*R*,5*S*)-6-methyl-3-(prop-8-en-3-yl)cyclohex-6-en-5-yl methacrylate (**148**, only major diastereoisomer reported):



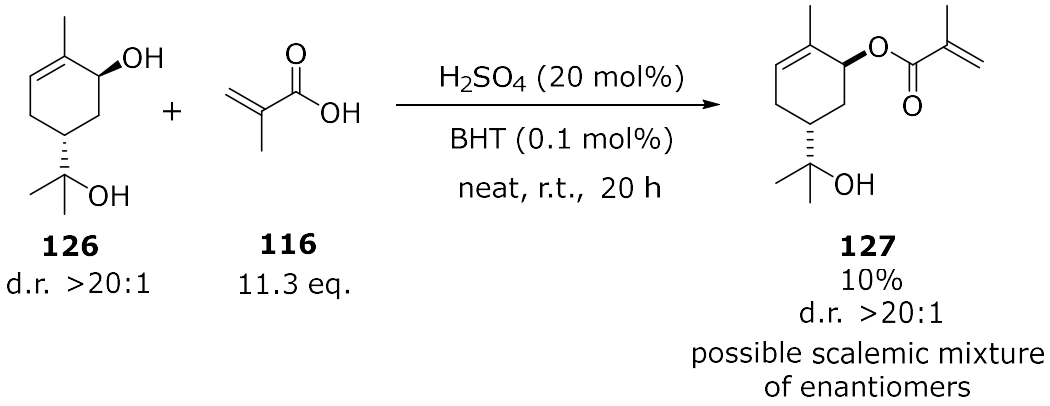
148

R_f (EtOAc:petrol 1:4): 0.71; **$[\alpha]_D^{26.6}$** +13.4° (c 0.86, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3082, 2967, 2918, 1712 (C=O), 1639, 1440, 1304, 1161, 935; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.09 (1H, dq, *J* = 1.1, 0.7 Hz, H-14a), 5.72 (1H, app dt, *J* = 5.4, 1.7 Hz, H-1), 5.53 (1H, app qu, *J* = 1.7 Hz, H-14b), 5.30 (1H, app dt, *J* = 4.1, 1.9 Hz, H-5), 4.71 (2H, app dq, *J* = 14.2, 1.6 Hz, H-10), 2.31 (1H, app tdd, *J* = 13.2, 7.0, 4.1 Hz, H-3), 2.19 (1H, app dtd, *J* = 17.4, 5.2, 1.4

Hz, H-2a), 1.97 (1H, app dq, *J* = 14.2, 2.3 Hz, H-4a), 1.94 (3H, app t, *J* = 1.4 Hz, H-13), 1.86 (1H, app tdd, *J* = 11.9, 4.0, 2.2 Hz, H-2b), 1.71 (3H, app s, H-9), 1.67 (3H, dd, *J* = 2.2, 1.3 Hz, H-7), 1.63 (1H, ddd, *J* = 11.1, 4.0, 1.4 Hz, H-4b); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 167.3 (C-11), 148.8 (C-6), 136.8 (C-12), 131.2 (C-8), 127.8 (C-1), 125.2 (C-14), 109.3 (C-10), 70.9 (C-5), 36.1 (C-3), 33.8 (C-4), 31.0 (C-2), 20.9 (C-9), 20.7 (C-7), 18.3 (C-13); **HRMS** (ESI, $[C_{14}H_{20}O_2+Na]^+$): measured 243.1347, theoretical 243.1356.

Spectral data for **148** agrees with the reported values in the literature. [122]

Synthesis of *trans*-sobrerol methacrylate (**127**)



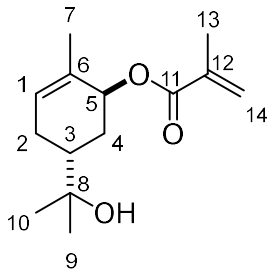
126
d.r. >20:1

116
11.3 eq.

127
10%
d.r. >20:1
possible scalemic mixture of enantiomers

General procedure **B** was followed using *trans*-sobrerol (**126**, 170 mg, 1.00 mmol), methacrylic acid (1.00 mL, 11.3 mmol) and 98% sulfuric acid (20 mol%, 10.8 µL, 0.20 mmol). The crude product was purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 100%) to yield **127** as a pale yellow oil (25 mg, 10%, >20:1 d.r., possible scalemic mixture of enantiomers).

Data collected for (3*R*,5*S*)-3-(8-hydroxypropan-8-yl)-6-methylcyclohex-1-en-5-yl methacrylate (**127**, only major diastereoisomer reported):



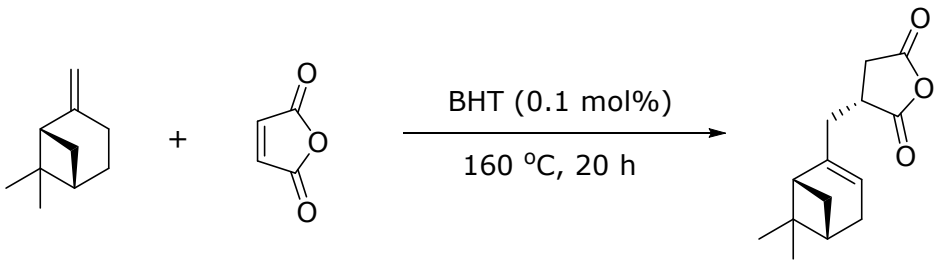
127

R_f (EtOAc:petrol 1:4): 0.50; **$[\alpha]_D^{26.6}$** +58.7° (c 0.36, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3436 (O-H), 2970, 2929, 1711 (C=O), 1636, 1451, 1291, 1026; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.09 (1H, dq , *J* = 1.1, 0.9 Hz, H-14a), 5.72 (1H, ddd, *J* = 5.4, 3.5, 1.7 Hz, H-1), 5.53 (1H, app qu, *J* = 1.6 Hz, H-14b), 5.31 (1H, ddd, *J* = 6.0, 3.8, 1.8 Hz, H-5), 2.19 (1H, app ddt, *J* = 5.9, 3.8, 1.7 Hz, H-2a), 2.02 (1H, app dq, *J* = 14.0, 2.2 Hz, H-4a), 1.94 (3H, dd, *J* = 1.7, 1.4 Hz, H-13), 1.85 (1H, app ddt, *J* = 12.2, 4.7, 1.4 Hz, H-2b), 1.75 (1H, ddd, *J* = 12.3, 3.8, 2.4 Hz, H-3), 1.68 (3H, dd, *J* = 1.7, 1.4 Hz, H-7), 1.47 (1H, dd, *J* = 14.0, 3.8 Hz, H-4b), 1.35 (1H, app dt, *J* = 11.4, 1.5 Hz, *O*-H), 1.18 (3H, s, H-9), 1.17 (3H, s, H-10); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 167.4 (C-11), 136.8 (C-12), 131.2 (C-6), 127.9 (C-1), 125.4 (C-14), 73.9 (C-8), 71.1 (C-5), 39.8 (C-3), 30.5 (C-2), 30.0 (C-4), 27.3 (C-9), 26.9 (C-10), 20.7 (C-7), 18.5 (C-13); **HRMS** (ESI, $[C_{14}H_{22}O_3+Na]^+$): measured 261.1459, theoretical 261.1461.

Spectral data for **127** agrees with the reported values in the literature. [114]

5.3 Ene Reaction Compounds

Synthesis of terpene-based anhydride (**159**) from β-pinene (**11**)

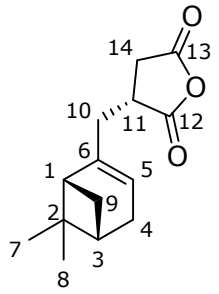


11 **158** 1 eq. **159** 41% 3:1 d.r.

(-)-β-pinene (**11**, 1.60 mL, 10.0 mmol) was dissolved in xylenes (25 mL). 2,6-di-*tert*-butyl-4-methylphenol (2 mg, 0.01 mmol) was added, followed by maleic anhydride (980 mg, 10.0 mmol). A condenser was attached, and the mixture was heated to reflux (160 °C) with stirring for 20 hours.

The mixture was then allowed to cool to room temperature. The solvent was removed under reduced pressure. The residue was then treated with petrol (10 mL) and cooled to 5 °C for 3 hours. The mixture was filtered under vacuum, and the solid was washed with petrol (2 × 10 mL). The solid was then dissolved in ethyl acetate (10 mL) at room temperature. The solution was treated with petrol (10 mL), and the resulting mixture was filtered under gravity. The solvent was then removed from the filtrate under reduced pressure and dried further under high vacuum, yielding **159** as a pale yellow solid with approximately 98% purity by ^{1}H NMR (41%). An analytical sample of **159**, as a single diastereoisomer, was obtained by recrystallising the solid from hot petrol, yielding colourless crystals.

Data collected for 11-(((1*R*,3*S*,11*R*)-2,2-dimethylbicyclo[3.1.1]hept-5-en-6-yl)methyl)dihydrofuran-2,5-dione (**159**, only single diastereoisomer reported):

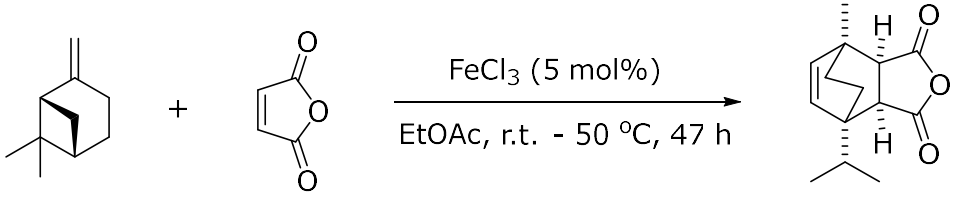


159

R_f (EtOAc:petrol 1:4): 0.58; **$[\alpha]_D^{23.2}$** -37.2° (c 0.86, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2979, 2919, 1769 (C=O), 1702 (C=O), 1685, 1438, 1258, 921; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 5.33 (1H, dd, *J* = 3.0, 2.7 Hz, H-5), 3.13 (1H, app tdd, *J* = 9.7, 5.8, 4.1 Hz, H-11), 2.98 (1H, dd, *J* = 19.0, 9.8 Hz, H-14a), 2.72 (1H, dd, *J* = 19.0, 5.7 Hz, H-14b), 2.62 (1H, app ddt, *J* = 13.9, 4.1, 2.6 Hz, H-4a), 2.40 (1H, app dt, *J* = 8.8, 5.6 Hz, H-9a), 2.33 – 2.31 (1H, m, H-9b), 2.30 – 2.28 (1H, m, H-4b), 2.26 – 2.24 (1H, m, H-10a), 2.10 (1H, app td, *J* = 3.0, 1.2 Hz, H-3), 2.01 (1H, app td, *J* = 5.5, 1.2 Hz, H-1), 1.27 (3H, s, H-7), 1.13 (1H, d, *J* = 8.8 Hz, H-10b), 0.79 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 173.9 (C-13), 170.3 (C-12), 143.3 (C-6), 120.6 (C-5), 45.4 (C-1), 40.5 (C-3), 38.9 (C-11), 38.4 (C-4), 38.0 (C-2), 33.9 (C-14), 31.6 (C-10), 31.3 (C-9), 26.2 (C-7), 21.3 (C-8); **HRMS** (ESI, $[C_{14}H_{18}O_3+Na]^+$): measured 257.1140, theoretical 257.1148.

Spectral data for **159** agrees with the reported values in the literature. [127]

Synthesis of alternative anhydride adduct (**164**)

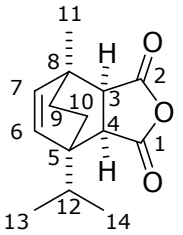


11 **158** 1.1 eq. *rac*-**164** 10%

Maleic anhydride (108 mg, 1.10 mmol) was dissolved in ethyl acetate (2 mL) with stirring. The solution was cooled to 0 °C, and iron(III) chloride (7.2 mg, 0.05 mmol) was added, followed by the slow addition of (-)-β-pinene (**11**, 0.16 mL, 1.00 mmol) over 45 seconds. The solution was stirred and allowed to warm to room temperature, then was stirred for a further 42 hours. The mixture was then heated to 50 °C and stirred for a further 5 hours.

Once reaction completion had been indicated by TLC, the reaction mixture was filtered through a pad of Celite®. Organics were washed through with ethyl acetate (2 × 3 mL). The organic fractions were combined, and the solvent was removed under reduced pressure. The product was then purified using silica gel flash chromatography (eluent mixture of ethyl acetate in petroleum ether, gradient of 0 – 100%) to yield *rac*-**164** as a pale yellow oil (*endo*-adduct, 22.8 mg, 10%).

Data collected for *endo*-5-isopropyl-8-methyl-4a,5,8,8a-tetrahydro-5,8-ethano isobenzofuran-1,2-dione (*rac*-**164**):

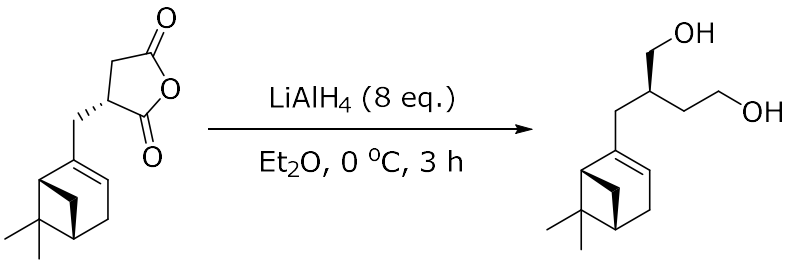


rac-**164**

R_f (EtOAc:petrol 1:2): 0.38; **ν_{max}** (neat, values in cm^{-1}): 2961, 1834 (C=O), 1767 (C=O), 1463, 1258, 1080, 932; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.09 (1H, d, *J* = 8.5 Hz, H-6), 6.01 (1H, d, *J* = 8.5 Hz, H-7), 3.21 (1H, d, *J* = 8.6 Hz, H-3), 2.84 (1H, d, *J* = 8.6 Hz, H-4), 2.55 (1H, app sep, *J* = 6.9 Hz, H-12), 1.49 (3H, s, H-11), 1.46 (1H, dd, *J* = 6.9, 1.6 Hz, H-10a), 1.43 – 1.37 (1H, m, H-10b), 1.34 – 1.28 (2H, m, H-9a and H-9b), 1.08 (3H, d, *J* = 6.8 Hz, H-13), 1.00 (3H, d, *J* = 6.8 Hz, H-14); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 171.6 (C-2), 171.0 (C-1), 137.1 (C-7), 136.4 (C-6), 51.1 (C-4), 47.3 (C-3), 43.6 (C-5), 36.8 (C-8), 33.7 (C-9), 29.4 (C-12), 22.8 (C-10), 22.3 (C-11), 18.4 (C-14), 16.8 (C-13); **HRMS** (ESI, $[C_{14}H_{18}O_3+H]^+$): measured 235.1330, theoretical 235.1329.

Spectral data for *rac*-**164** agrees with the reported values in the literature. [133, 135]

Synthesis of 2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)butane-1,4-diol (**165**)



159

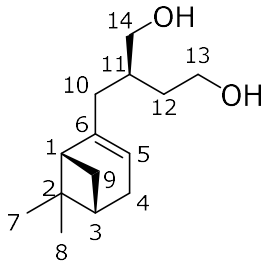
3:1 d.r.

165
98%
3:1 d.r.

In an oven dried round-bottomed flask, the terpene-based anhydride **159** (117 mg, 0.50 mmol) was dissolved in dry Et_2O (5 mL) under an Ar atmosphere. The solution was cooled to 0 °C, and lithium aluminium hydride (152 mg, 4.00 mmol) was added in one portion to the solution. The mixture was then vigorously stirred at 0 °C for 3 hours, and the reaction was monitored by TLC.

After reaction completion had been achieved, the reaction mixture was slowly quenched with H_2O (0.2 mL) over 2 minutes, causing a rapid release of gas. 15% w/v aqueous NaOH (0.2 mL) was then added slowly over 30 seconds. More H_2O (0.6 mL) was added, and the mixture was allowed to warm to room temperature with stirring (15 minutes). The mixture was diluted with Et_2O (5 mL) and then dried ($MgSO_4$). The resulting mixture was filtered under gravity, and washed through with Et_2O (3 × 5 mL). The solvent was removed under reduced pressure to yield **165** as a viscous, colourless oil (109 mg, 98%, 3:1 d.r.). No further purification was required.

Data collected for 2-(((1*R*,3*S*,11*R*)-2,2-dimethylbicyclo[3.1.1]hept-5-en-6-yl)methyl)butane-1.4-diol (**165**, only major diastereoisomer reported):

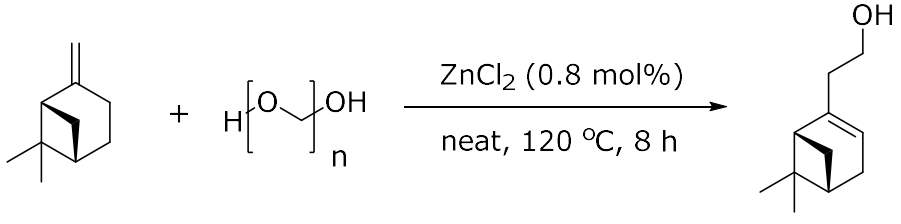


165

R_f (EtOAc:petrol 1:1): 0.11; **$[\alpha]_D^{26.6}$** -13.1° (c 0.45, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3291 (O-H), 3024, 2983, 2877, 2832, 1651, 1467, 1433, 1218, 1039; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 5.20 (1H, app qu , *J* = 1.4 Hz, H-5), 3.74 (1H, ddd, *J* = 11.0, 6.1, 4.5 Hz, H-13a), 3.69 – 3.53 (4H, m, contains 2 × *O*-H, H-13b and H-14a), 3.40 (1H, dd, *J* = 11.0, 7.2 Hz, H-14b), 2.35 (1H, app dt, *J* = 8.8, 5.5 Hz, H-9a), 2.27 – 2.15 (3H, m, contains H-4a, H-4b and H-9b), 2.10 – 2.04 (1H, m, H-3), 2.01 (1H, app td, *J* = 5.4, 1.5 Hz, H-1), 1.95 (1H, ddd, *J* = 13.8, 6.2, 1.1 Hz, H-10a), 1.83 (1H, ddd, *J* = 13.7, 6.5, 1.2 Hz, H-10b), 1.74 – 1.66 (2H, m, contains H-11 and H-12a), 1.53 – 1.49 (1H, m, H-12b), 1.25 (3H, s, H-7), 0.81 (3H, s H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 146.2 (C-6), 118.2 (C-5), 66.5 (C-14), 61.0 (C-13), 45.7 (C-1), 40.8 (C-3), 39.8 (C-10), 37.9 (C-2), 37.3 (C-11), 36.1 (C-12), 31.8 (C-9), 31.3 (C-4), 26.3 (C-7), 21.1 (C-8); **HRMS** (ESI, $[C_{14}H_{24}O_2+Na]^+$): measured 247.1672, theoretical 247.1669.

Spectral data for **165** agrees with the reported values in the literature. [127]

Synthesis of nopol (**167**)



11
1.3 eq.

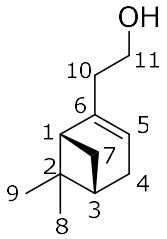
166

167
72%

Para-formaldehyde (1.50 g, 47.5 mmol) and zinc chloride (anhydrous, 50 mg, 36.5 µmol) were mixed as solids. (-)-β-pinene (**11**, 10.4 mL, 61.5 mmol) was then slowly added, and the resulting stirring mixture was heated to 120 °C for 8 hours.

The mixture was then allowed to cool to room temperature with stirring. The desired product was then isolated by silica gel flash chromatography to yield a pale yellow oil (5.65 g, 72%).

Data collected for 2-((1*R*,3*S*)-2,2-dimethylbicyclo[3.1.1]hept-5-en-6-yl)ethanol (**167**):

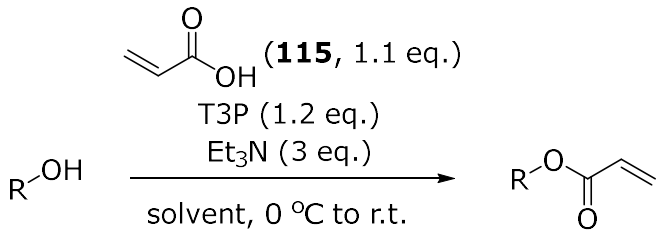


167

R_f (EtOAc:petrol 1:4): 0.37; **$[\alpha]_D^{23.7}$** -37.7° (c 0.36, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3348 (*O*-H), 2915, 2878, 1682, 1466, 1365, 1041, 702; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 5.34 (1H, app ddd, *J* = 5.7, 2.8, 1.5 Hz, H-5), 3.61 (2H, app td, *J* = 6.3, 2.6 Hz, H-11), 2.38 (1H, app dt, *J* = 11.3, 5.5 Hz, H-7a), 2.28 - 2.20 (4H, m, H-4a, H-4b, H-10a and H-10b), 2.13 - 2.08 (1H, m, H-3), 2.04 (1H, app td, *J* = 5.5, 1.5 Hz, H-1), 1.58 - 1.42 (1H, m, *O*-H), 1.28 (3H, s, H-9), 1.14 (1H, d, *J* = 8.6 Hz, H-7b), 0.84 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 144.8 (C-6), 119.6 (C-5), 60.1 (C-11), 45.7 (C-1), 40.8 (C-3), 40.4 (C-10), 38.0 (C-2), 31.9 (C-7), 31.5 (C-4), 26.4 (C-9), 21.3 (C-8); **HRMS** (ESI, $[C_{11}H_{18}O+Na]^+$): measured 189.1239, theoretical 189.1250.

Spectral data for **167** agrees with the reported values in the literature. [197]

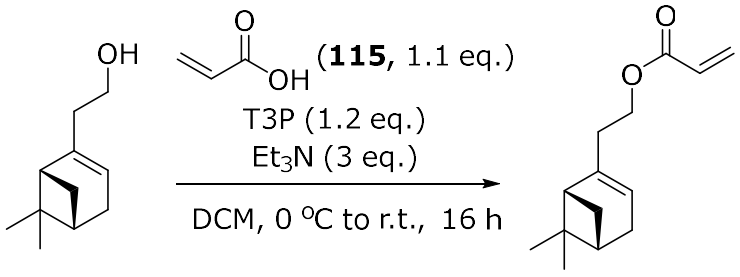
General method **C** for the synthesis of acrylate esters from alcohols using T3P® as a coupling agent



The reaction solvent was charged to a dried flask equipped with a stirrer bar. Triethylamine (3.00 eq.) was added, followed by the alcohol reactant (1.00 eq.) with stirring. The resulting solution was cooled to 0 °C (water/ice bath), then acrylic acid (**115**, 1.10 eq.) was slowly added. After 5 minutes of stirring, T3P® (50% w/w in ethyl acetate, 1.20 eq.) was added over a period of 15 minutes. The resulting mixture was stirred for 15 minutes at 0 °C, then the reaction mixture was allowed to warm to room temperature and stirred for a further 1 – 20 hours until starting material consumption was indicated by TLC.

The reaction was quenched with saturated aqueous ammonium chloride (5 – 100 mL) and stirred for 5 minutes. Organics were then extracted into diethyl ether (3 × 5 – 100 mL). The organic fractions were combined and washed with 1 M hydrochloric acid (10 – 200 mL), saturated aqueous sodium bicarbonate (10 – 200 mL) and brine (10 – 200 mL), then dried ($MgSO_4$). The resulting mixture was filtered under gravity, and then the solvent was removed under reduced pressure to yield the crude product.

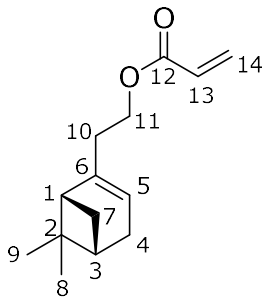
Synthesis of nopyl acrylate (**168**)



167 **168**
63%

General method **C** was followed using nopol (**167**, 2.00 g, 12.0 mmol), acrylic acid (0.91 mL, 13.2 mmol), T3P® (50% w/w in ethyl acetate, 8.61 mL, 14.5 mmol), triethylamine (5.02 mL, 36.1 mmol), and dichloromethane (100 mL), for 16 hours. The crude product was purified using silica gel flash chromatography (eluent mixture of 5 – 10% ethyl acetate in petroleum ether) to yield the desired product **168** as a pale yellow oil (1.68 g, 63%).

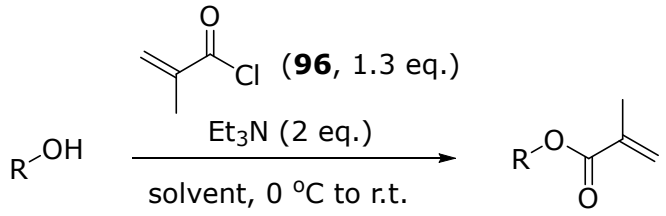
Data collected for 2-((1*R*,3*S*)-2,2-dimethylbicyclo[3.1.1]hept-5-en-6-yl)ethyl acrylate (**168**):



168

R_f (EtOAc:petrol 1:4): 0.71; **$[\alpha]_D^{23.6}$** -18.0° (c 0.1, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2985, 2915, 1724 (C=O), 1406, 1183, 984, 808; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.38 (1H, dd , *J* = 17.4, 1.5 Hz, H-14a), 6.10 (1H, dd, *J* = 17.5, 10.5 Hz, H-13), 5.80 (1H, dd, *J* = 10.5, 1.6 Hz, H-14b), 5.31 (1H, m, H-5), 4.16 (2H, app td, *J* = 7.0, 3.4 Hz, H-11), 2.36 (1H, app dt, *J* = 8.5, 5.6 Hz, H-7a), 2.36 – 2.30 (2H, m, H-10), 2.29 – 2.15 (2H, m, H-4a and H-4b), 2.10 – 2.05 (2H, m, H-1 and H-3), 1.27 (3H, s, H-9), 1.14 (1H, d, *J* = 8.4 Hz, H-7b), 0.82 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 166.3 (C-12), 144.2 (C-6), 130.6 (C-14), 128.7 (C-13), 119.0 (C-5), 63.0 (C-11), 45.8 (C-1), 40.8 (C-3), 38.1 (C-2), 36.0 (C-10), 31.7 (C-7), 31.5 (C-4), 26.4 (C-9), 21.3 (C-8); **HRMS** (ESI, $[C_{14}H_{20}O_2+Na]^+$): measured 243.1348, theoretical 243.1356.

General method **D** for the synthesis of methacrylate esters from alcohols using methacryloyl chloride

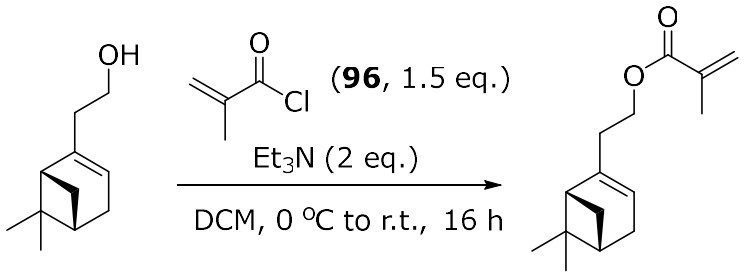


The reaction solvent was charged to a dried flask equipped with a stirrer bar. Triethylamine (2.00 eq.) was added, followed by the alcohol reactant (1.00 eq.) with stirring. The resulting solution was cooled to 0 °C (water/ice bath). After 5 minutes of stirring, methacryloyl chloride (**96**, 1.30 eq.) was added over a period of 15 minutes. The resulting mixture was stirred for 15 minutes at 0 °C, then the reaction mixture was allowed to warm to room temperature and stirred for a further 1 – 20 hours until starting material consumption was indicated by TLC.

The reaction was quenched with water (5 – 100 mL) and stirred for 5 minutes. Organics were then extracted into diethyl ether (3 × 5 – 100 mL). The organic fractions were combined and washed with 1 M $HCl_{(aq.)}$ (10 – 200 mL), saturated $NaHCO_{3\ (aq.)}$ (10 – 200 mL) and brine (10 – 200 mL), then dried ($MgSO_4$). The resulting mixture was filtered under gravity, and then the solvent was removed under reduced pressure to yield the crude product.

Synthesis of nopyl methacrylate (**169**)

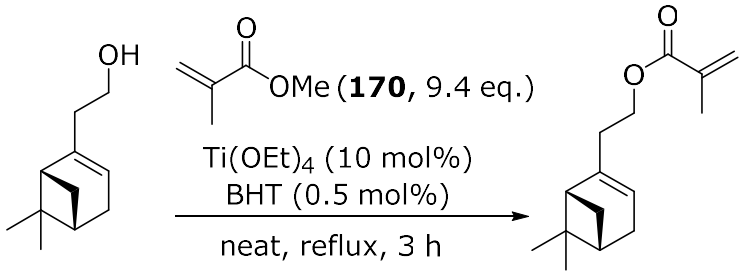
Method 1:



167 **169**
73%

General method **D** was followed using nopol (**167**, 470 mg, 3.0 mmol), methacryloyl chloride (0.42 mL, 4.5 mmol), triethylamine (0.79 mL, 6.0 mmol), and dichloromethane (25 mL). The crude product was purified using silica gel flash chromatography (eluent mixture of 5 – 10% ethyl acetate in petroleum ether) to yield the desired product **169** as a pale yellow oil (482 mg, 73%).

Method 2:

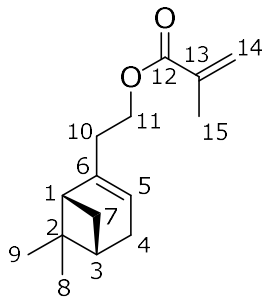


167 **169** 87%

2,6-di-*tert*-butyl-4-methylphenol (1.1 mg, 5.00 µmol) was dissolved in methyl methacrylate (1.00 mL, 9.36 mmol) in a microwave vial with stirring. Nopol (**167**, 0.17 mL, 1.00 mmol) was then added, followed by titanium(IV) ethoxide (21 µL, 0.10 mmol). The vial was then sealed and heated to reflux for 3 hours.

The reaction mixture was then allowed to cool to room temperature. The mixture was filtered through a pad of activated charcoal, then the excess methyl methacrylate was removed under reduced pressure to yield the desired product **169** as a pale yellow oil (203 mg, 87%). No further purification was required.

Data collected for 10-((1*R*,3*S*)-2,2-dimethylbicyclo[3.1.1]hept-5-en-6-yl)ethyl methacrylate (**169**):



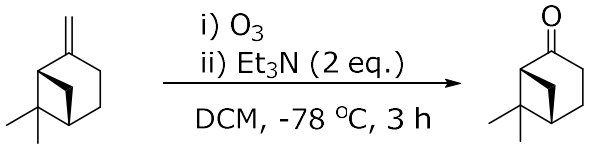
169

R_f (EtOAc:petrol 1:4): 0.74; **$[\alpha]_D^{23.4}$** -41.6° (c 0.1, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2984, 2915, 1718 (C=O), 1638, 1320, 1156, 886, 813; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.08 (1H, dq , *J* = 1.9, 1.1 Hz, H-14a), 5.53 (1H, dq, *J* = 3.0, 1.6 Hz, H-14b), 5.30 (1H, m, H-5), 4.15 (2H, m, H-11), 2.36 (1H, app dt, *J* = 8.7, 5.7 Hz, H-4a), 2.35 – 2.29 (2H, m, H-10), 2.25 – 2.19 (2H, m, H-4b and H-7a), 2.11 – 2.03 (2H, m, H-1 and H-3), 1.93 (3H, dd, *J* = 1.6, 1.0 Hz, H-15), 1.25 (3H, s, H-9), 1.15 (1H, d, *J* = 8.4 Hz, H-7b), 0.82 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 167.6 (C-12), 144.4 (C-6), 136.6 (C-13), 125.3 (C-14), 118.9 (C-5), 63.1 (C-11), 45.8 (C-1), 40.8 (C-3), 38.1 (C-2), 31.8 (C-4), 31.5 (C-7), 26.4 (C-9), 21.2 (C-8), 18.5 (C-15); **HRMS** (ESI, $[C_{15}H_{22}O_2+Na]^+$): measured 257.1507, theoretical 257.1512.

5.4 Hindered (meth)acrylate compounds

Synthesis of nopinone (**48**)

Method 1:



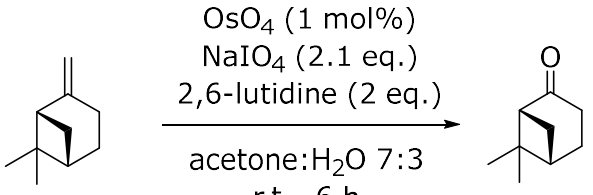
11 **48** 80%

(-)-β-pinene (**11**, 17.4 mL, 110 mmol) was dissolved in dichloromethane (150 mL). The solution was cooled to -78 °C with stirring and then the flask was attached to an ozone generator equipped with an oxygen cylinder. Molecular oxygen was bubbled through the solution for 5 minutes, then the ozone generator was switched on, and the ozone/oxygen mixture was bubbled through the solution maintaining -78 °C for 3 hours. After a persistent metallic blue colour developed, the ozone generator was switched off, and molecular oxygen was bubbled through the reaction mixture for 5 minutes. Triethylamine (30.7 mL, 220 mmol) was then added over a 60 minute period with stirring at -78 °C, turning the mixture deep yellow. The resulting mixture was stirred at -78 °C for a further 2 hours, then was allowed to warm to room temperature and left stirring for a further 18 hours.

The reaction mixture was then washed with 1 M aqueous hydrochloric acid (5 × 100 mL), brine (100 mL) and dried ($MgSO_4$). The resulting mixture was filtered under gravity, then the solvent was removed under reduced pressure to yield a pale yellow oil.

Purification by silica flash gel chromatography (using 0 – 10% ethyl acetate in petrol as the eluent) gave **48** as a pale yellow oil (12.2 g, 80%).

Method 2:



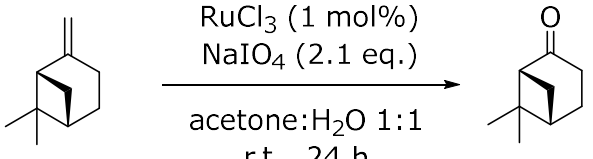
11 **48** 76%

Sodium periodate (4.49 g, 21.0 mmol) was dissolved in water (36 mL) under an inert argon atmosphere. Acetone (84 mL) was added, followed by 2.6-lutidine (2.33 mL, 20.0 mmol). (-)-β-pinene (**11**, 1.56 mL, 10.0 mmol) was then added and the mixture was stirred for 5 minutes at room temperature. Osmium tetroxide (4% in H_2O, 0.64 mL, 0.1 mmol) was then added, and the mixture was stirred for 6 hours.

After starting material consumption had been indicated by TLC, the reaction was quenched with saturated aqueous sodium sulfite (50 mL) and left to stir for 5 minutes. Organics were extracted with diethyl ether (3 × 25 mL). The organic fractions were combined and washed with 1 M aqueous hydrochloric acid (50 mL), saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL), then dried ($MgSO_4$). The mixture was then filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 0 – 20% ethyl acetate in petroleum ether) to yield the desired product **48** as a pale yellow oil (1.05 g, 76%).

Method 3:



11 **48** 41%

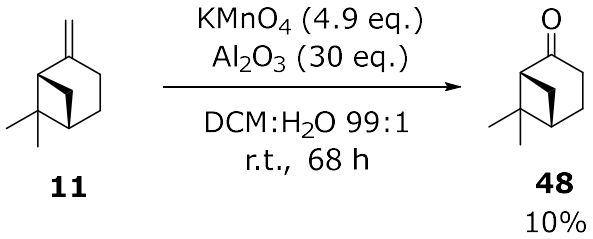
Acetone (60 mL) and water (60 mL) were mixed together at room temperature under an inert argon atmosphere. Sodium periodate (4.49 g, 21.0 mmol) was

added, followed by ruthenium(III) chloride hydrate (25 mg, 0.1 mmol). (-)-β-pinene (**11**, 1.56 mL, 10.0 mmol) was then added slowly to the stirring mixture over a period of 5 minutes. The resulting mixture was left to stir for 24 hours, until starting material consumption had been indicated by TLC.

The reaction mixture was quenched (saturated aqueous sodium sulfite, 50 mL) and left to stir for 15 minutes. Organics were then extracted with diethyl ether (3 × 10 mL). The organic fractions were combined and washed with brine (10 mL), then dried ($MgSO_4$). The resulting mixture was filtered through a pad of Celite® and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 0 – 20% ethyl acetate in petroleum ether) to yield the desired product **48** as a pale yellow oil (570 mg, 41%).

Method 4:



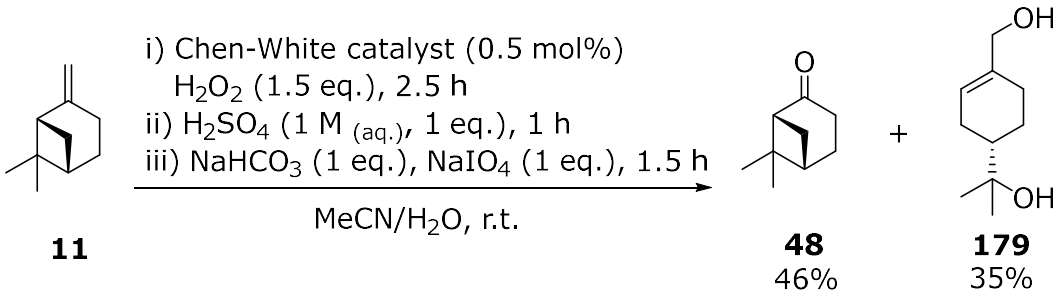
11 **48** 10%

Potassium permanganate (15.5 g, 98.0 mmol) and aluminium oxide (acidic, Brockmann I, 61.2 g, 600 mmol) were mixed together as solids. Water (14.3 mL) was slowly added to the solids with further mixing until a uniform slurry had been achieved. The slurry was then added in portions of approximately 250 mg to a rapidly stirring solution of (-)-β-pinene (**11**, 3.2 mL, 20.0 mmol) in dichloromethane (544 mL). The resulting mixture was then stirred at room temperature for 68 hours.

After starting material consumption had been indicated by TLC, the reaction mixture was filtered under vacuum. Organics were washed through with dichloromethane (2 × 50 mL). The filtrate was then dried ($MgSO_4$) and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 0 – 10% ethyl acetate in petroleum ether) to yield the desired product **48** as a pale yellow oil (262 mg, 10%).

Method 5:



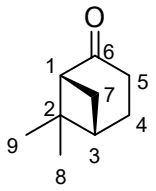
11 **48** 46% **179** 35%

Chen-White catalyst (Fe-(*S*,*S*)-PDP, 3.4 mg, 3.6 μmol) was dissolved in dry acetonitrile (3 mL) under an inert argon atmosphere. (-)-β-pinene (**11**, 0.11 mL, 0.72 mmol) was then added, followed by a solution of hydrogen peroxide (aqueous, 30% w/v, 0.11 mL, 1.08 mmol) in acetonitrile (1 mL). The resulting mixture was left to stir for 2.5 hours at room temperature. A solution of sulfuric acid (98%, 0.04 mL, 0.72 mmol) in water (1 mL) was then added, and the reaction was left to stir at room temperature for a further 1 hour. A solution of sodium bicarbonate (60 mg, 0.72 mmol) and sodium periodate (154 mg, 0.72 mmol) in water (8 mL) was then added to the reaction mixture, which was stirred for a further 1.5 hours.

The reaction mixture was then quenched with saturated aqueous sodium sulfite (5 mL) and left to stir at room temperature for 5 minutes. Organics were then extracted with diethyl ether (3 × 15 mL). The organic fractions were combined and washed with brine (20 mL), then dried ($MgSO_4$). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 0 – 100% ethyl acetate in petroleum ether) to yield the desired product **48** as a pale yellow oil (47 mg, 46%). The side product, ring-opened allylic alcohol **179**, was isolated in the flush fraction (100% ethyl acetate) as a viscous, colourless oil (43 mg, 35%). Data for this compound is outlined later on in this section.

Data calculated for (1*R*,3*S*)-2,2-dimethylbicyclo[3.1.1]heptan-6-one (**48**):

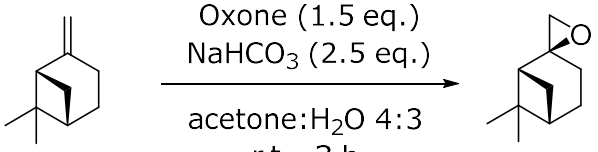


48

R_f (EtOAc:petrol 1:9): 0.32; **$[\alpha]_D^{21.6}$** ($CHCl_3$, c = 0.94): +30.8°; **ν_{max}** (neat, cm^{-1}): 2950, 1706 (C=O), 1459, 1240, 1030; **δ_H** (400 MHz, $CDCl_3$): 2.63 - 2.48 (3H, m, H-1, H-5a and H-7a), 2.34 (1H, ddd, *J* = 19.4, 9.0, 2.1 Hz, H-5b), 2.23 (1H, app tdd, *J* = 6.3, 4.3, 2.1 Hz, H-3), 2.04 (1H, app tdd, *J* = 11.0, 3.9, 2.0 Hz), 1.98 - 1.89 (1H, m, H-4b), 1.57 (1H, d, *J* = 10.6 Hz, H-7b), 1.32 (3H, s, H-8), 0.85 (3H, s, H-9); **δ_C** (100 MHz, $CDCl_3$): 215.2 (C-6), 58.1 (C-1), 41.3 (C-2), 40.5 (C-3), 32.9 (C-5), 26.1 (C-8), 25.3 (C-7), 22.3 (C-9), 21.5 (C-4); **HRMS** (ESI, $[C_9H_{14}O+Na]^+$): measured 161.0944, theoretical 161.0937.

Spectral data for **48** agrees with the reported values in the literature. [198]

Synthesis of β-pinene oxide (**181**)



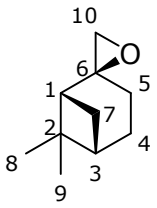
11 **181** 96%

(-)-β-pinene (**11**, 3.12 mL, 20.0 mmol) was dissolved in acetone (80 mL) with stirring. Sodium bicarbonate (4.20 g, 50.0 mmol) was then added to the solution. A solution of Oxone® (9.22 g, 30.0 mmol) in water (60 mL) was then slowly added to the mixture over a period of 30 minutes with rapid stirring. The mixture was then stirred at room temperature for 3 hours, until starting material consumption was indicated by TLC.

The reaction mixture was then quenched (saturated aqueous sodium sulfite, 100 mL) and left to stir for 5 minutes. Organics were then extracted with diethyl ether (3 × 50 mL). The organic fractions were combined and washed with water (50 mL), saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL),

then dried (Na_2SO_4). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield **181** as a colourless oil (2.91 g, 96%). No further purification was required.

Data collected for (1*R*,3*S*,6*S*)-2,2-dimethylspiro[bicyclo[3.1.1]heptane-6,6'-oxirane] (**181**):

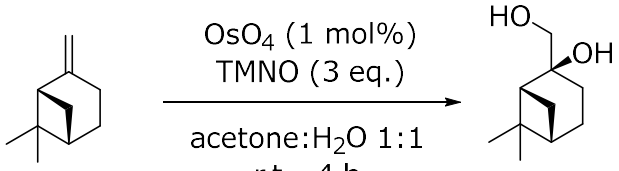


181

R_f (EtOAc:petrol 1:19): 0.61; **$[\alpha]_D^{23.1}$** +0.6° (c 0.99, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 2919, 2869, 1480, 1394, 1196, 908, 824; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 2.77 (1H, d, *J* = 5.0 Hz, H-10a), 2.60 (1H, d, *J* = 5.0 Hz, H-10b), 2.30 – 2.23 (1H, m, H-7a), 2.21 – 2.11 (1H, m, H-5a), 2.01 – 1.96 (1H, m, H-1), 1.93 – 1.76 (2H, m, H-4a and H-4b), 1.71 – 1.64 (1H, ddd, *J* = 15.4, 9.1, 1.9 Hz, H-5b), 1.65 (1H, d, *J* = 10.4 Hz, H-7b), 1.51 (1H, app t, *J* = 5.5 Hz, H-3), 1.24 (3H, s, H-9), 0.91 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 61.6 (C-6), 56.6 (C-10), 49.1 (C-3), 40.8 (C-2), 40.2 (C-1), 26.1 (C-9), 25.2 (C-7), 23.6 (C-5), 22.4 (C-4), 21.2 (C-8); **HRMS** (ESI, $[C_{10}H_{16}O+H]^+$): measured 153.1262, theoretical 153.1274.

Spectral data for **181** agrees with the reported values in the literature. [199]

Synthesis of β-pinene diol (**180**)



11 **180** 46%

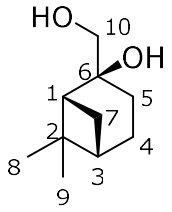
Trimethylamine-N-oxide dihydrate (333 mg, 3.0 mmol) was dissolved in acetone (2.5 mL) and water (2.5 mL) under an argon atmosphere. (-)-β-pinene (**11**, 0.16 mL, 1.0 mmol) was added with stirring, followed by osmium tetroxide (4%

solution in water, 0.06 mL, 10 μmol). The reaction mixture was then stirred at room temperature for 4 hours, until starting material consumption had been indicated by TLC.

The reaction mixture was then quenched (saturated aqueous sodium sulfite, 5 mL) and left to stir for 5 minutes. Organics were extracted into ethyl acetate (3 × 5 mL). The organic fractions were then combined and washed with water (10 mL) and brine (10 mL), then dried (Na_2SO_4). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 20 – 100% ethyl acetate in petroleum ether) to yield the desired product **180** as a white amorphous solid (79 mg, 46%).

Data collected for (1*R*,3*S*,6*S*)-6-(hydroxymethyl)-2,2-dimethylbicyclo [3.1.1]heptan-6-ol (**180**):

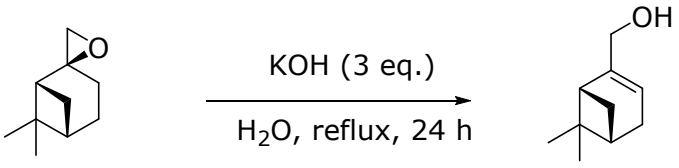


180

R_f (EtOAc:petrol 1:4): 0.05; **m.p.** 82.8 – 84.7 °C; **$[\alpha]_D^{23.0}$** -21.6° (c 0.32, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3309 (O-H), 2988, 2864, 1459, 1215, 1058, 1030, 919; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 3.50 (2H, s, H-10), 2.32 (2H, br s, 2 × *O*-H), 2.23 (1H, dtd, *J* = 10.3, 6.2, 1.2 Hz, H-4a), 2.06 (1H, app t, *J* = 5.1 Hz, H-3), 1.99 – 1.89 (2H, m, H-1 and H-7a), 1.83 – 1.77 (2H, m, H-5a and H-7b), 1.72 (1H, app q, *J* = 10.6 Hz, H-4b), 1.45 (1H, d, *J* = 10.1 Hz, H-5b), 1.24 (3H, s, H-9), 0.92 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 77.2 (C-6), 69.9 (C-10), 48.5 (C-3), 41.3 (C-1), 38.4 (C-2), 27.5 (C-9), 27.4 (C-5), 27.0 (C-4), 24.8 (C-7), 23.5 (C-8); **HRMS** (ESI, $[C_{10}H_{18}O+Na]^+$): measured 193.1202, theoretical 193.1199.

Spectral data for **180** agrees with the reported values in the literature. [200]

Synthesis of myrtenol (**136**)

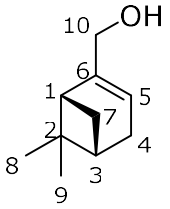


181 **136**
84%

β-pinene oxide (**181**, 152 mg, 1.0 mmol) was suspended in a 1 M aqueous solution of potassium hydroxide (3 mL, 3.0 mmol) with stirring. The vessel was sealed, and heated to 110 °C with stirring for 24 hours.

The reaction mixture was then allowed to cool to room temperature, then quenched with a saturated aqueous solution of ammonium chloride (5 mL). The mixture was then diluted with water (10 mL) and dichloromethane (10 mL). The organic phase was separated, and the aqueous fraction was washed with dichloromethane (5 mL). The organic fractions were combined and washed with brine (10 mL), dried (anhydrous sodium sulfate) and filtered under gravity. The solvent was then removed under reduced pressure to yield **136** as a colourless oil (128 mg, 84%). No further purification was required.

Data collected for ((1*R*,3*S*)-2,2-dimethylbicyclo[3.1.1]hept-5-en-6-yl)methanol (**136**):



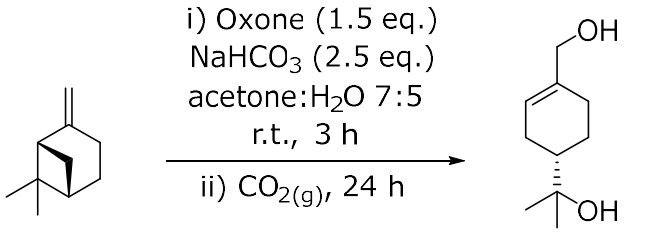
136

R_f (EtOAc:petrol 1:4): 0.58; **$[\alpha]_D^{20.1}$** -46.9° (c 0.60, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3315 (O-H), 2985, 2831, 1431, 1219, 1082, 987, 799; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 5.47 (1H, app sep, *J* = 1.5 Hz, H-5), 3.99 (2H, dd, *J* = 3.4, 1.9 Hz, H-10), 2.41 (1H, app dt, *J* = 8.6, 5.6 Hz, H-7a), 2.36 – 2.20 (2H, m, H-4a and H-4b), 2.17 – 2.08 (2H, m, H-1 and H-3), 1.29 (3H, s, H-8), 1.18 (1H, d, *J* = 9.2 Hz, H-7b), 0.84 (3H, s, H-9); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 147.9 (C-6), 118.0 (C-5), 66.2 (C-10), 43.5 (C-1), 41.1 (C-3), 38.1 (C-

2), 31.8 (C-7), 31.3 (C-4), 26.1 (C-8), 21.3 (C-9); **HRMS** (ESI, $[C_{10}H_{16}O+Na]^+$): measured 175.1081, theoretical 175.1093.

Spectral data for **136** agrees with values reported in the literature [201].

Synthesis of β-pinene-based allylic alcohol (**179**)



11 **179**
83% (crude)

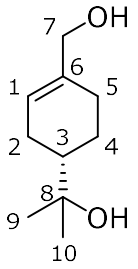
(-)-β-pinene (**11**, 5.73 mL, 36.8 mmol) was dissolved in acetone (140 mL) with stirring. Sodium bicarbonate (7.73 g, 92.0 mmol) was then added to the solution. A solution of Oxone® (16.97 g, 55.2 mmol) in water (100 mL) was then slowly added to the mixture over a period of 60 minutes with rapid stirring. The mixture was then stirred at room temperature for a further 60 minutes, until starting material consumption was indicated by TLC.

Gaseous carbon dioxide was then bubbled through the stirring solution for 4 hours, until the reaction mixture was approximately pH 4. The mixture was then left to stir for 20 hours.

The reaction mixture was quenched (saturated aqueous sodium sulfite, 100 mL) and left to stir for 5 minutes. Organics were then extracted into ethyl acetate (3 × 30 mL). The organic fractions were combined and dried ($MgSO_4$). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure to yield a colourless oil (5.23 g, 83%).

This crude product had a purity of approximately 70%, and was used in subsequent reactions without further purification. An analytical sample was prepared by purification *via* silica gel flash chromatography (eluent of 20 – 100% ethyl acetate in petroleum ether).

Data collected for (*S*)-2-(4-(hydroxymethyl)cyclohex-3-en-1-yl)propan-2-ol (**179**):

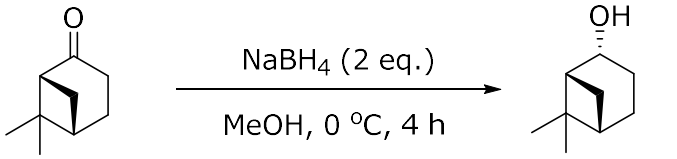


179

R_f (EtOAc:petrol 1:4): 0.08; **$[\alpha]_D^{23.0}$** -77.6° (c 0.38, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3328 (O-H), 2969, 2920, 2839, 1457, 1379, 1219, 1145, 949, 731; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 5.65 – 5.62 (1H, m, H-1), 3.97 – 3.89 (2H, m, H-7), 2.40 – 2.10 (2H, br s, 2 × *O*-H), 2.13 – 2.03 (2H, m, H-2a and H-2b), 1.94 – 1.88 (1H, m, H-5a), 1.85 – 1.75 (1H, m, H-5b), 1.49 (1H, app tdd, *J* = 12.1, 4.5, 2.5 Hz, H-3), 1.27 – 1.16 (2H, m, H-4a and H-4b), 1.15 (3H, s, H-9), 1.13 (3H, s, H-10); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 137.5 (C-6), 122.3 (C-1), 72.7 (C-8), 66.9 (C-7), 45.1 (C-3), 27.3 (C-2), 26.7 (C-9), 26.6 (C-10), 26.3 (C-5), 23.6 (C-4); **HRMS** (ESI, $[C_{10}H_{18}O_2+Na]^+$): measured 193.1193, theoretical 193.1199.

Spectral data for **179** agrees with the reported values in the literature. [202]

Synthesis of *cis*-nopinol (*cis*-**173**)

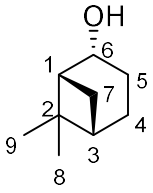


48 → *cis*-**173**, 84%, >20:1 d.r.

Nopinone (**48**, 6.00 g, 43.5 mmol) was dissolved in methanol (300 mL) with stirring. The solution was cooled to 0 °C (water/ice bath), and stirred for 5 minutes. Sodium borohydride (3.29 g, 87.0 mmol) was then added in portions over 15 minutes, and then the mixture was allowed to stir at 0 °C for 4 hours.

After reaction completion had been indicated by TLC, the reaction mixture was carefully quenched with 1 M aqueous hydrochloric acid (200 mL). Organics were then extracted into dichloromethane (3 × 100 mL). The organic fractions were combined and washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), then dried ($MgSO_4$). The mixture was then filtered under gravity, and the solvent was removed under reduced pressure to yield *cis*-**173** a colourless solid (4.88 g, 80%). An analytical sample was obtained by recrystallisation from hot petrol.

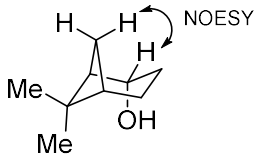
Data calculated for (1*R*,3*S*,6*R*)-2,2-dimethylbicyclo[3.1.1]heptan-6-ol (*cis*-**173**):



cis-**173**

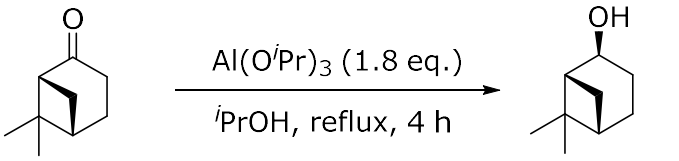
R_f (EtOAc:petrol 1:9): 0.22; **m.p.**: 98.1 – 99.5 °C; **$[\alpha]_D^{26}$** ($CHCl_3$, c = 1.32): -0.4°; **ν_{max}** (neat, cm^{-1}): 3328, 2943, 2865, 1464, , 1335, 1113; **δ_H** (400 MHz, $CDCl_3$): 4.21 (1H, app dt, *J* = 9.7, 3.7 Hz, H-6), 2.25 - 2.17 (2H, m, H-5a and H-7a), 2.09 (1H, br s, *O*-H), 2.01 (1H, m, H-1), 1.97 - 1.86 (2H, m, H-3 and H-4a), 1.75 - 1.67 (1H, m, H-4b), 1.65 - 1.56 (1H, app ddt, *J* = 15.3, 10.4, 3.7 Hz, H-4b), 1.16 (3H, s, H-8), 1.05 (3H, s, H-9), 0.82 (1H, d, *J* = 11.5 Hz, H-7b); **δ_C** (100 MHz, $CDCl_3$): 73.4 (C-6), 48.3 (C-1), 41.0 (C-3), 37.6 (C-2), 28.4 (C-7), 27.5 (C-8), 26.0 (C-5), 24.8 (C-4), 22.7 (C-9); **HRMS** (DIP-EI, calculated for $C_9H_{15}O$ $[M-H]^+$): found 139.1227, calculated 139.1117.

Spectral data for *cis*-**173** agrees with the reported values in the literature. [191]



A NOESY correlation was observed between H-6 and H-7b, confirming the relative configuration of the product.

Synthesis of *trans*-nopinol (*trans*-**173**)



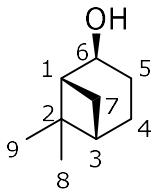
48 *trans*-**173**
95%
3.8:1 d.r.

Aluminium *iso*-propoxide (1.89 g, 9.3 mmol) was dissolved in dry *iso*-propanol (14 mL) in a dried flask under an inert argon atmosphere. Nopinone (**48**, 700 mg, 5.1 mmol) was added to the stirring solution, which was then heated to reflux for 4 hours, until starting material consumption was indicated by TLC.

The reaction mixture was allowed to cool to room temperature, and was then quenched with 1 M aqueous hydrochloric acid (15 mL). The resulting mixture was filtered under vacuum, and organics were washed through with diethyl ether (2 × 10 mL). The layers were separated, and the aqueous fraction was washed with diethyl ether (2 × 10 mL). The organic fractions were combined and washed with 1 M aqueous hydrochloric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (20 mL), then dried ($MgSO_4$). The resulting mixture was then filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product as a colourless oil (676 mg, 95%). Analysis showed this was a 3.8:1 mixture of *trans*-**173** and *cis*-**173**.

A pure sample of *trans*-**173** was obtained using silica gel flash chromatography (eluent of 0 – 20% ethyl acetate in petroleum ether) to yield *trans*-**173** as a colourless oil (242 mg, 34%).

Data collected for (1*R*,3*S*,6*S*)-2,2-dimethylbicyclo[3.1.1]heptan-6-ol (*trans*-**173**):

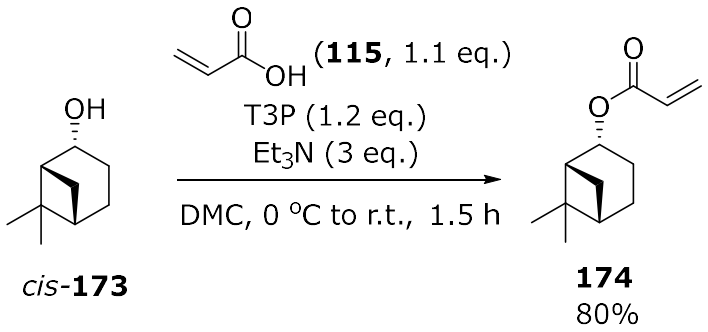


trans-**173**

R_f (EtOAc:petrol 1:4): 0.24; **$[\alpha]_D^{23.0}$** +4.2° (c 0.67, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3300 (O-H), 2946, 2909, 1460, 1366, 1017, 970, 925; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 4.18 (1H, app td, *J* = 8.3, 1.9 Hz, H-6), 2.16 – 2.06 (2H, m, H-5a and H-7a), 1.95 (1H, app td, *J* = 5.2, 2.2 Hz, H-1), 1.92 – 1.88 (1H, m, H-3), 1.86 – 1.78 (1H, m, H-4a), 1.86 – 1.78 (1H, m, H-4b), 1.61 – 1.51 (1H, m, H-7b), 1.51 (1H, d, *J* = 10.4 Hz, H-5b), 1.28 (1H, br d, *J* = 3.4 Hz, *O*-H), 1.23 (3H, s, H-9), 0.80 (3H, s, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 70.1 (C-6), 48.3 (C-1), 40.7 (C-3), 39.7 (C-2), 26.9 (C-9), 26.1 (C-7), 23.4 (C-4), 22.7 (C-5), 20.1 (C-8); **HRMS** (ESI, $[C_9H_{16}O+Na]^+$): measured 163.1093, theoretical 163.1093.

Spectral data for *trans*-**173** agrees with the reported values in the literature. [203]

Synthesis of *cis*-nopinyl acrylate (**174**)

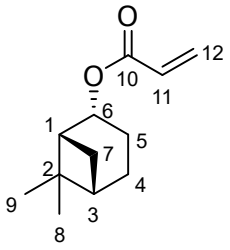


cis-**173**

174
80%

General method **C** was followed using *cis*-nopinol (*cis*-**173**, 5.00 g, 35.7 mmol), acrylic acid (2.70 mL, 39.3 mmol), T3P® (50% w/w solution in ethyl acetate, 25.4 mL, 42.8 mmol), triethylamine (14.9 mL, 107 mmol) and dimethyl carbonate (20 mL). Purification was carried out using silica gel flash chromatography (using 0 – 5% ethyl acetate in petroleum ether as the eluent) to yield **174** as a pale yellow oil (5.28 g, 76%).

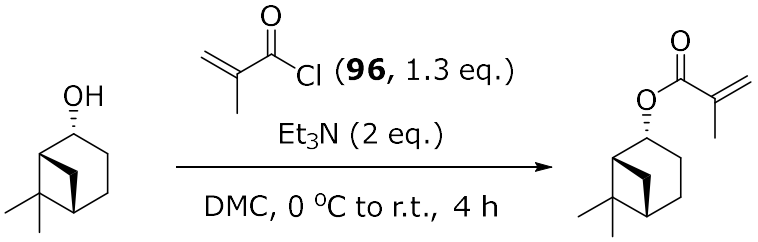
Data collected for (1*R*,3*S*,6*R*)-2,2-dimethylbicyclo[3.1.1]heptan-6-yl acrylate (**174**):



174

R_f (EtOAc:petrol 1:4): 0.62; **$[\alpha]_D^{26.0}$** ($CHCl_3$, c = 1.08): -7.0°; **ν_{max}** (neat, cm^{-1}): 2919, 2870, 1719, 1462, 1209, 930; **δ_H** (400 MHz, $CDCl_3$): 6.35 (1H, dd, *J* = 17.3, 1.5 Hz, H-12a), 6.08 (1H, dd, *J* = 17.3, 10.5 Hz, H-11), 5.78 (1H, dd, *J* = 10.5, 1.5 Hz, H-12b), 5.32 (1H, app dt, *J* = 9.8, 3.4 Hz, H-6), 2.41 – 2.25 (2H, m, H-5a and H-4a), 2.21 – 2.15 (1H, m, H-1), 2.06 – 1.94 (2H, m, H-7a and H-3), 1.85 – 1.75 (1H, m, H-4b), 1.74 – 1.64 (1H, m, H-5b), 1.21 (3H, s, H-9), 1.06 (3H, s, H-8), 1.03 (1H, d, *J* = 10.3 Hz, H-7b); **δ_C** (100 MHz, $CDCl_3$): 166.0 (C-10), 130.0 (C-12), 129.5 (C-11), 75.9 (C-6), 45.3 (C-1), 40.9 (C-3), 37.7 (C-2), 27.7 (C-4), 27.2 (C-9), 24.6 (C-7), 23.0 (C-5), 22.9 (C-8); **HRMS** (ESI, calculated for $C_{12}H_{18}O_2Na$ $[M+Na]^+$): found 217.1196, calculated 217.1199.

Synthesis of *cis*-nopinyl methacrylate (**175**)

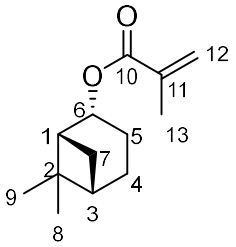


cis-**173**

175
68%

General method **D** was followed using *cis*-nopinol (*cis*-**173**, 1.50 g, 10.7 mmol), methacryloyl chloride (1.36 mL, 13.9 mmol), triethylamine (2.98 mL, 21.4 mmol) and dimethyl carbonate (7.5 mL), with a reaction time of 4 hours. Purification was carried out using silica gel flash chromatography (using 0 – 5% ethyl acetate in petroleum ether as the eluent) to yield **175** as a pale yellow oil (1.51 g, 68%).

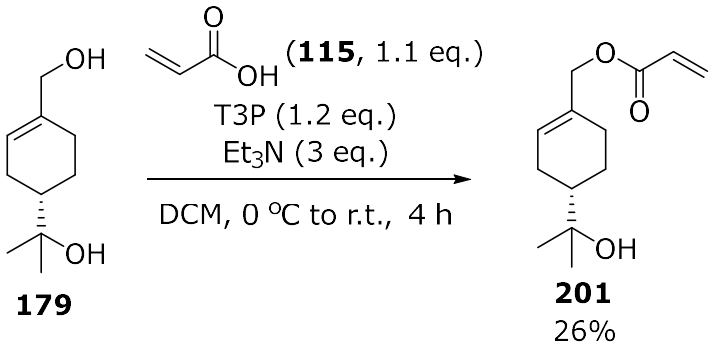
Data collected for (1*R*,3*S*,6*R*)-2,2-dimethylbicyclo[3.1.1]heptan-6-yl methacrylate (**175**):



175

R_f (EtOAc:petrol 1:9): 0.66; **$[\alpha]_D^{26.0}$** ($CHCl_3$, c = 0.98): -8.6°; **ν_{max}** (neat, cm^{-1}): 2921, 2870, 1712, 1637, 1460, 1318, 1171, 1157, 934; **δ_H** (400 MHz, $CDCl_3$): 6.07 (1H, m, H-12a), 5.52 (1H, app qu, *J* = 1.8 Hz, H-12b), 5.31 (1H, app dt, *J* = 9.5, 3.3 Hz, H-6), 2.42 - 2.26 (2H, m, H-5a and H-7a), 2.19 - 2.14 (1H, m, H-1), 2.07 - 1.94 (2H, m, H-4a and H-3), 1.94 - 1.92 (3H, m, H-13), 1.86 - 1.76 (1H, m, H-4b), 1.68 (1H, app ddt, *J* = 15.7, 10.5, 3.3 Hz, H-5b), 1.22 (3H, s, H-9), 1.07 (3H, s, H-8), 1.04 (1H, d, *J* = 10.4 Hz, H-7b); **δ_C** (100 MHz, $CDCl_3$): 167.1 (C-10), 137.2 (C-11), 125.1 (C-12), 76.0 (C-6), 45.3 (C-1), 40.9 (C-3), 37.7 (C-2), 27.7 (C-7), 27.2 (C-9), 24.6 (C-4), 23.1 (C-5), 23.0 (C-8), 18.5 (C-13); **HRMS** (ESI, calculated for $C_{13}H_{20}O_2Na$ $[M+Na]^+$): found 231.1349, calculated 231.1356.

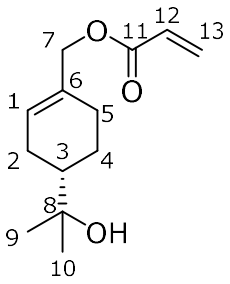
Synthesis of β-pinene based allyl acrylate (**201**)



General method **C** was followed using **179** (1.75 g, 10.3 mmol), acrylic acid (0.77 mL, 11.3 mmol), T3P® (50% w/w in ethyl acetate, 7.35 mL, 12.4 mmol) and triethylamine (4.29 mL, 30.9 mmol) in dichloromethane (35 mL). The crude product was purified using silica gel flash chromatography (eluent of 20 – 50%

ethyl acetate in petroleum ether) to yield the desired product **201** as a pale yellow oil (590 mg, 26%).

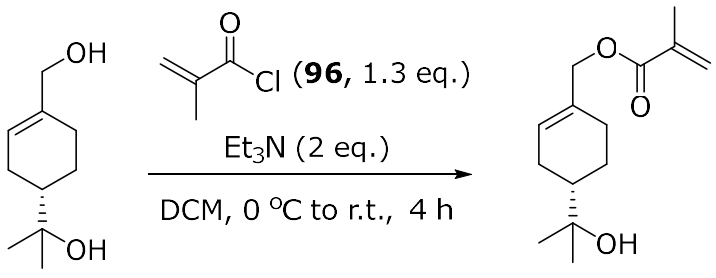
Data collected for (*S*)-(3-(2-hydroxypropan-2-yl)cyclohex-6-en-6-yl)methyl acrylate (**201**):



201

R_f (EtOAc:petrol 1:1): 0.42; **$[\alpha]_D^{20.3}$** -30.9° (c 0.48, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3436, 2970, 2928, 1722 (C=O), 1636, 1407, 1183, 1045, 841; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.41 (1H, dd, *J* = 17.3, 1.5 Hz, H-13a), 6.14 (1H, dd, *J* = 17.3, 10.4 Hz, H-12), 5.83 (1H, dd, *J* = 10.5, 1.5 Hz, H-13b), 5.77 (1H, m, H-1), 4.55 (2H, s, H-7), 2.22 – 2.06 (3H, m, H-2a, H-5a and H-5b), 1.99 – 1.82 (2H, m, H-2b and H-4a), 1.60 (1H, br s, *O*-H), 1.55 (1H, app tdd, *J* = 11.7, 5.2, 2.5 Hz, H-3), 1.36 – 1.22 (1H, m, H-4b), 1.20 (3H, s, H-9), 1.19 (3H, s, H-10); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 166.3 (C-11), 132.9 (C-6), 130.8 (C-13), 128.6 (C-12), 125.9 (C-1), 72.7 (C-8), 68.5 (C-7), 44.9 (C-3), 27.6 (C-9), 27.0 (C-5), 26.8 (C-2), 26.5 (C-10), 23.6 (C-4); **HRMS** (ESI, $[C_{13}H_{20}O_3+H]^+$): measured 225.1489, theoretical 225.1485.

Synthesis of β-pinene based allyl methacrylate (**202**)



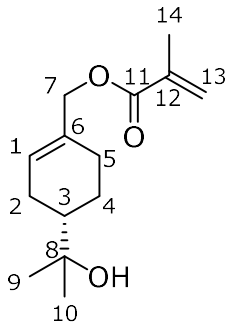
179

202
51%

General method **D** was followed using **179** (1.75 g, 10.3 mmol), methacryloyl chloride (1.31 mL, 13.4 mmol) and triethylamine (2.86 mL, 20.6 mmol) in

dichloromethane (35 mL). The crude product was purified using silica gel flash chromatography (eluent of 20 – 50% ethyl acetate in petroleum ether) to yield the desired product **202** as a pale yellow oil (1.23 g, 51%).

Data collected for (*S*)-(3-(2-hydroxypropan-2-yl)cyclohex-6-en-6-yl)methyl methacrylate (**202**):



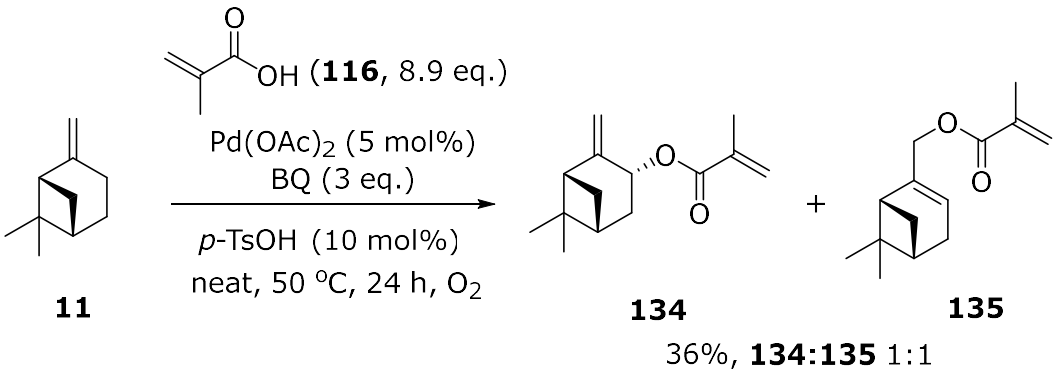
202

R_f (EtOAc:petrol 1:1): 0.47; **$[\alpha]_D^{20.5}$** -31.3° (c 0.50, $CHCl_3$); **ν_{max}** (neat, values in cm^{-1}): 3426, 2969, 2926, 1714 (C=O), 1636, 1453, 1317, 1158, 878, 813; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.11 (1H, dq, *J* = 2.0, 1.1 Hz, H-13a), 5.78 – 5.74 (1H, m, H-1), 5.56 (1H, dq, *J* = 1.6, 1.1 Hz, H-13b), 4.54 (2H, s, H-7), 2.22 – 2.06 (3H, m, H-2a, H-5a and H-5b), 1.99 – 1.82 (2H, m, H-2b and H-4a), 1.95 (3H, dd, *J* = 1.4, 1.1 Hz, H-14), 1.61 – 1.51 (2H, m, *O*-H and H-3), 1.35 – 1.23 (1H, m, H-4b), 1.20 (3H, s, H-9), 1.19 (3H, s, H-10); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 167.6 (C-11), 136.6 (C-12), 132.8 (C-6), 125.6 (C-13), 125.5 (C-1), 72.6 (C-8), 68.5 (C-7), 44.9 (C-3), 27.6 (C-9), 27.0 (C-5), 26.8 (C-2), 26.5 (C-10), 23.6 (C-4), 18.5 (C-14); **HRMS** (ESI, $[C_{14}H_{22}O_3+Na]^+$): measured 261.1472, theoretical 261.1461.

5.5 Miscellaneous compounds

Synthesis of methacrylates **134** and **135** from **11**

Method 1:

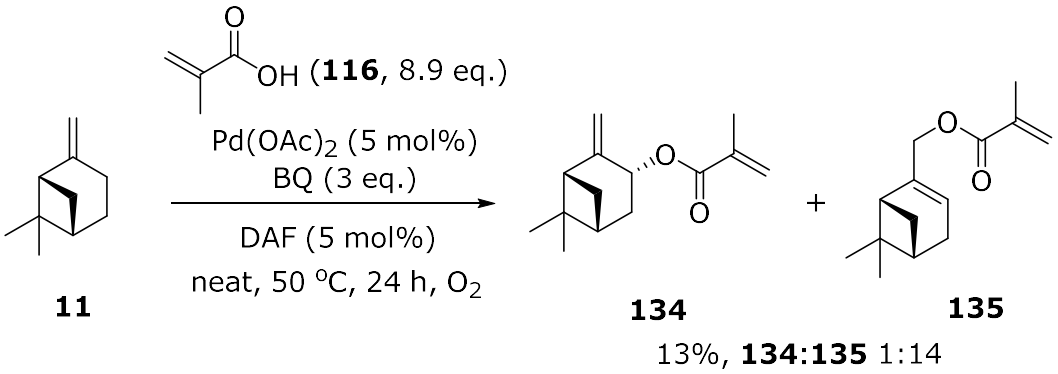


Freshly distilled (-)-β-pinene (**11**, 10.3 mL, 66.0 mmol) was added to a mixture of benzoquinone (21.6 g, 198 mmol), palladium(II) acetate (740 mg, 3.3 mmol), *para*-toluenesulfonic acid monohydrate (608 mg, 6.6 mmol) and methacrylic acid (45 mL, 530 mmol) with stirring. The flask was then equipped with an oxygen atmosphere, and heated to 50 °C for 24 hours.

The reaction mixture was then allowed to cool to room temperature. Dichloromethane (250 mL) was added, and the resulting slurry was filtered under gravity. Organics were washed through with dichloromethane (2 × 500 mL). The organic fractions were combined and washed with water (800 mL), 1 M aqueous sodium hydroxide (800 mL), saturated aqueous sodium carbonate (800 mL), and brine (800 mL), then dried ($MgSO_4$). The resulting mixture was then filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 5 – 10% ethyl acetate in petroleum ether) to yield an inseparable mixture of **134** and **135** as a colourless oil (5.29 g, 36%, **134**:**135** 1:1).

Method 2:

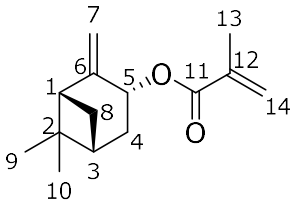


Freshly distilled (-)-β-pinene (**11**, 1.15 mL, 7.4 mmol) was added to a mixture of benzoquinone (2.40 g, 22.2 mmol), palladium(II) acetate (83 mg, 0.37 mmol), 4,5-diazafluoren-9-one (67 mg, 0.37 mmol) and methacrylic acid (5.6 mL, 65.0 mmol) with stirring. The flask was then equipped with an oxygen atmosphere, and heated to 50 °C for 24 hours.

The reaction mixture was then allowed to cool to room temperature. Dichloromethane (50 mL) was added, and the resulting slurry was filtered under gravity. Organics were washed through with dichloromethane (2 × 100 mL). The organic fractions were combined and washed with water (200 mL), 1 M aqueous sodium hydroxide (200 mL), saturated aqueous sodium carbonate (200 mL), and brine (200 mL), then dried ($MgSO_4$). The resulting mixture was then filtered under gravity, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using silica gel flash chromatography (eluent of 5 – 10% ethyl acetate in petroleum ether) to yield an inseparable mixture of **134** and **135** as a colourless oil (220 mg, 13%, **134**:**135** 1:14).

Data collected for (1*R*,3*R*,5*R*)-2,2-dimethyl-6-methylenebicyclo[3.1.1]heptan-5-yl methacrylate (**134**):

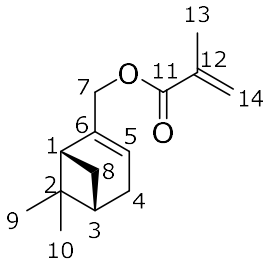


134

R_f (EtOAc:petrol 1:19): 0.54; **ν_{max}** (neat, values in cm^{-1}): 2923, 2869, 1713 (C=O), 1451, 1308, 1162, 917; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.09 (1H, dq, *J* = 1.6, 1.0 Hz, H-14a), 5.62 (1H, dd, *J* = 8.0, 1.0 Hz, H-7a), 5.54 (1H, app qu, *J* = 1.6 Hz, H-14b), 5.08 (1H, m, H-7b), 4.88 (1H, m, H-5), 2.54 (1H, app t, *J* = 5.5 Hz, H-1), 2.44 (1H, app dtd, *J* = 10.0, 5.9, 2.0 Hz, H-8a), 2.39 (1H, app ddt, *J* = 15.1, 8.0, 2.0 Hz, H-4a), 2.00 (1H, app tdd, *J* = 5.9, 4.4, 2.0 Hz, H-3), 1.95 (3H, dd, *J* = 1.6, 1.0 Hz, H-13), 1.83 (1H, ddd, *J* = 15.1, 4.4, 1.0 Hz, H-4b), 1.64 (1H, d, *J* = 10.0 Hz, H-8b), 1.29 (3H, s, H-10), 0.71 (3H, s, H-9); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 167.0 (C-11), 136.9 (C-12), 125.7 (C-14), 114.3 (C-7), 106.1 (C-6), 68.7 (C-5), 51.8 (C-2), 39.5 (C-3), 33.2 (C-4), 28.0 (C-8), 25.8 (C-10), 23.6 (C-1), 21.9 (C-9), 18.7 (C-13); **HRMS** (ESI, $[C_{14}H_{20}O_2+H]^+$): measured 221.1541, theoretical 221.1536.

Spectral data for **134** agrees with the reported values in the literature. [98]

Data collected for (1*R*,3*S*)-2,2-dimethylbicyclo[3.1.1]hept-5-en-6-yl)methyl methacrylate (**135**):

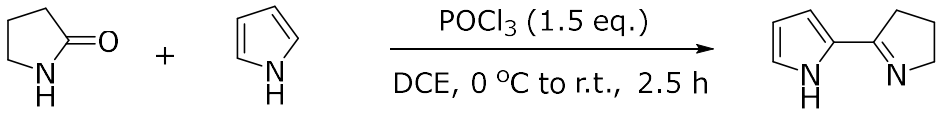


135

R_f (EtOAc:petrol 1:19): 0.54; **ν_{max}** (neat, values in cm^{-1}): 2917, 2832, 1716 (C=O), 1452, 1317, 1154, 938; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 6.12 (1H,

dq, *J* = 1.9, 1.0 Hz, H-14a), 5.60 (1H, app qt, *J* = 2.9, 1.4 Hz, H-5), 5.56 (1H, app qu, *J* = 1.6 Hz, H-14b), 4.51 (2H, app q, *J* = 1.6 Hz, H-7), 2.43 (1H, app dt, *J* = 8.8, 5.6 Hz, H-8a), 2.35 (1H, app dtt, *J* = 17.9, 3.0, 1.8 Hz, H-4a), 2.27 (1H, app dtt, *J* = 17.9, 2.8, 1.7 Hz, H-4b), 2.17 (1H, app td, *J* = 5.8, 1.4 Hz, H-1), 2.14 (1H, app tdd, *J* = 5.7, 2.8, 1.4 Hz, H-3), 1.95 (3H, dd, *J* = 1.6, 1.0 Hz, H-13), 1.31 (3H, s, H-9), 1.22 (1H, app d, *J* = 8.8 Hz, H-8b), 0.86 (3H, s, H-10); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 167.1 (C-11), 143.0 (C-6), 136.4 (C-12), 125.1 (C-14), 121.3 (C-5), 67.1 (C-7), 43.6 (C-1), 40.7 (C-3), 38.0 (C-2), 31.4 (C-8), 31.2 (C-4), 26.1 (C-10), 21.0 (C-9), 18.3 (C-13); **HRMS** (ESI, $[C_{14}H_{20}O_2+Na]^+$): measured 243.1357, theoretical 243.1356.

Synthesis of pyrrolopyrroline (**188**)



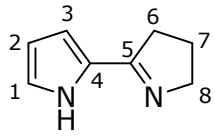
186 **187** 2 eq. **188** 19%

A pre-dried flask was charged with dry 1,2-dichloroethane (30 mL) under an inert argon atmosphere. 2-pyrrolidinone (**186**, 3.79 mL, 50.0 mmol) was added with stirring, followed by pyrrole (6.93 mL, 100 mmol). The resulting mixture was cooled to 0 °C (water/ice bath), and then phosphorus(V) oxychloride (6.99 mL, 75.0 mmol) was added over a period of 30 minutes. The reaction mixture was stirred at 0 °C for a further 30 minutes, then was allowed to warm to room temperature and stirred for a further 2 hours.

The reaction mixture was quenched by pouring over ice. 10 M aqueous sodium hydroxide (50 mL) was then added with stirring, followed by sodium hydroxide pellets until the mixture achieved pH 11. The mixture was stirred for 15 minutes, and then organics were extracted with chloroform (3 × 50 mL). The organic fractions were combined and dried (K_2CO_3). The resulting mixture was filtered, and the solvent was removed under reduced pressure to yield the crude product.

Purification was carried out using recrystallisation from hot chloroform. After 3 iterations, **188** was isolated as a pale orange solid (1.24 g, 19%).

Data collected for 6,7-dihydro-8*H*-2,2'-bipyrrole (**188**):

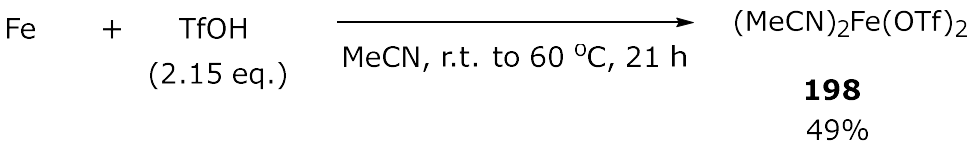


188

R_f (EtOAc:petrol 1:4): 0.05; **m.p.** 130.6 – 131.8 °C; **ν_{max}** (neat, values in cm^{-1}): 3106, 2960, 2862, 1614, 1422, 1112, 723; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 9.89 (1H, br s, *N*-H), 6.93 (1H, dd, *J* = 2.4, 1.5 Hz, H-1), 6.53 (1H, dd, *J* = 3.6, 1.4 Hz, H-3), 6.23 (1H, dd, *J* = 3.5, 2.6 Hz, H-2), 4.01 (2H, app tt, *J* = 7.2, 1.8 Hz, H-8), 2.89 (2H, app tt, *J* = 8.2, 1.7 Hz, H-6), 2.01 (2H, app dqu, *J* = 14.7, 7.5 Hz, H-7); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 166.3 (C-5), 127.8 (C-4), 121.6 (C-1), 112.9 (C-3), 109.4 (C-2), 60.6 (C-8), 34.9 (C-6), 22.8 (C-7); **HRMS** (ESI, $[C_8H_{10}N_2+Na]^+$): measured 157.0732, theoretical 157.0736.

Spectral data for **188** agrees with the reported values in the literature. [181]

Synthesis of bis(acetonitrile)iron(II) trifluoromethanesulfonate (**198**)



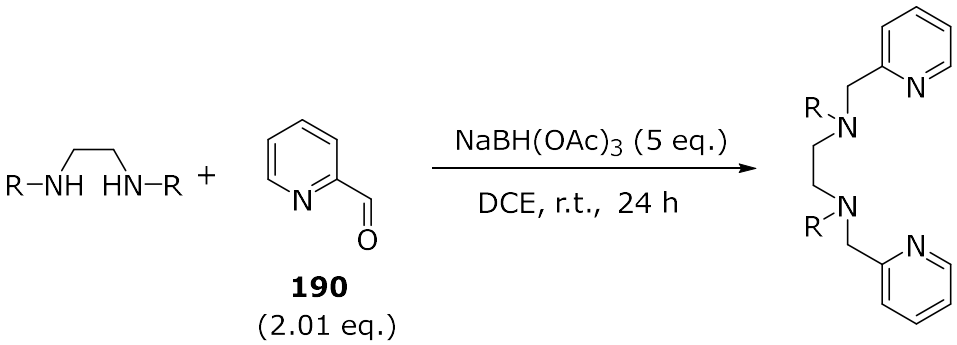
198 was prepared using a method reported in the literature. [184]

A pre-dried flask was charged with iron powder (1.12 g, 20.0 mmol) under an inert argon atmosphere. Dry acetonitrile (20 mL) was added with stirring, followed by trifluoromethanesulfonic acid (3.77 mL, 42.6 mmol) over a period of 10 minutes. The mixture was stirred at room temperature for 1 hour, and then warmed to 60 °C and stirred for a further 20 hours.

Under a positive argon stream, the mixture was filtered under vacuum. The filtrate was reduced to a quarter of the original volume under reduced pressure. Cold, dry diethyl ether (50 mL) was then added, and the mixture was stored at −20 °C for 24 hours. Under a positive argon stream, the mixture was filtered under vacuum. The solid was washed with cold, dry diethyl ether (2 × 25 mL) to

yield the desired product as a pale green solid (4.27 g, 49%). **198** was used without further purification.

General method **E** for the synthesis of bis(*N*-picolyl)-2,2'-bipyrrolidine ligands by double reductive amination



190
(2.01 eq.)

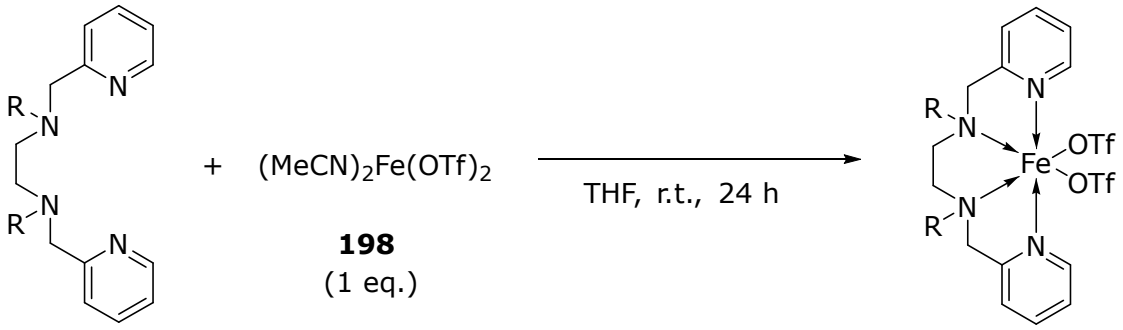
This general method follows a procedure that is reported in the literature. [183]

A pre-dried flask was charged with dry 1,2-dichloroethane (30 mL) under an inert argon atmosphere. The diamine (1.00 eq.) was added to the flask with stirring, followed by 2-pyridinecarboxaldehyde (**190**, 2.01 eq.). The mixture was stirred for 15 minutes at room temperature, and then sodium triacetoxyborohydride (5.00 eq.) was added in one portion. The reaction mixture was then stirred at room temperature for 24 hours.

The reaction mixture was quenched with saturated aqueous sodium bicarbonate (20 mL), and the layers were separated. The aqueous fraction was washed with ethyl acetate (2 × 10 mL). The organic fractions were combined and dried (Na_2SO_4). The resulting mixture was filtered under gravity, and the solvent was removed under reduced pressure. The residue was then dissolved in dry tetrahydrofuran (10 mL) and sodium hydride (60% w/w in mineral oil, 60 mg, 0.75 eq.) was added. The mixture was then stirred for 90 minutes at room temperature.

The solvent was then removed under reduced pressure. Organics were extracted by trituration of the residue with pentane (3 × 10 mL). The pentane fractions were combined, and the solvent was removed under reduced pressure to yield the crude product.

General method **F** for the synthesis of iron(II) complexes from their respective ligands

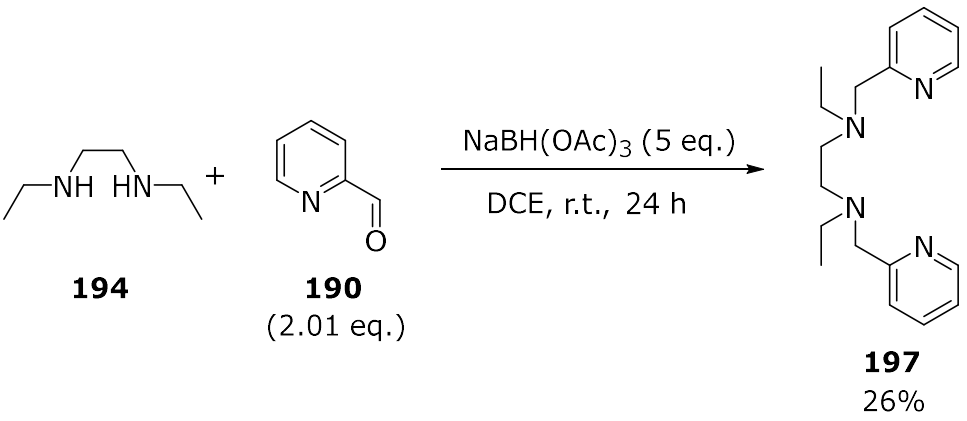


This general method follows a procedure that is reported in the literature. [183]

A pre-dried flask was charged with bis(acetonitrile)-iron(II) trifluoromethanesulfonate (**198**, 1.0 eq.) under an inert argon atmosphere. Dry tetrahydrofuran (9 mL) was added, and the mixture was stirred for 5 minutes at room temperature. A solution of bis(picolyl) ligand (1.0 eq.) in dry tetrahydrofuran (1 mL) was then added, and the mixture was stirred at room temperature for 24 hours.

Under a positive stream of argon, the mixture was then filtered under vacuum. The filtrand was washed with cold, dry diethyl ether (2 × 5 mL) under vacuum to yield the product.

Synthesis of ethyl-substituted ligand (**197**)

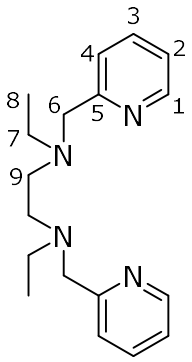


194 **190** (2.01 eq.) **197** 26%

General procedure **E** was followed using *N*,*N*′-diethylethylene diamine (**194**, 0.29 mL, 2.00 mmol), 2-pyridinecarboxaldehyde (0.38 mL, 4.02 mmol) and sodium triacetoxyborohydride (2.12 g, 10.0 mmol). Purification was carried out

using silica gel flash chromatography (eluent of triethylamine : ethyl acetate : petroleum ether, 5 : 20 : 75 to 10 : 40 : 50) to yield the desired product **197** as a pale yellow oil (153 mg, 26%).

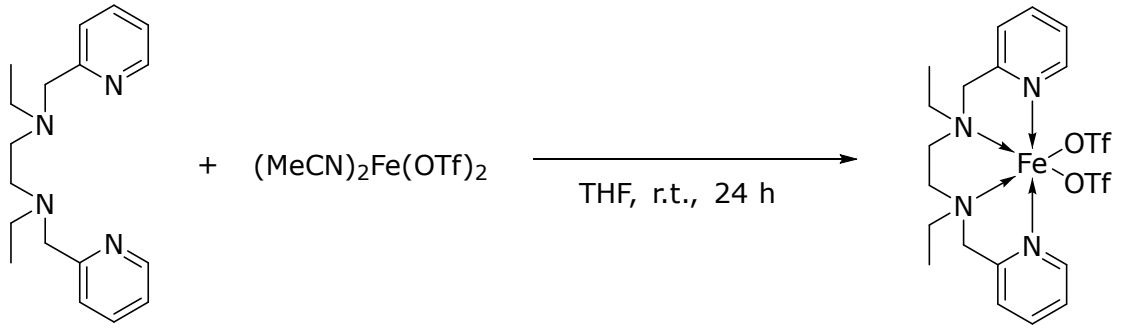
Data collected for *N*,*N'*-diethyl-*N*,*N'*-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (**197**):



197

R_f (Et_3N:EtOAc:petrol 1:4:5) 0.33; **ν_{max}** (neat, values in cm^{-1}): 3008, 2966, 2871, 1589, 1569, 1432, 992, 753; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 8.49 (2H, app dq, *J* = 4.9, 0.9 Hz, H-1), 7.60 (2H, app dt, *J* = 7.8, 1.9 Hz, H-3), 7.43 (2H, d, *J* = 7.9 Hz, H-4), 7.11 (2H, app ddd, *J* = 7.6, 4.9, 1.0 Hz, H-2), 3.72 (4H, s, H-6), 2.63 (4H, s, H-9), 2.55 (4H, q, *J* = 7.3 Hz, H-7), 1.01 (6H, t, *J* = 7.1 Hz, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 160.7 (C-5), 149.0 (C-1), 136.4 (C-3), 122.9 (C-4), 121.8 (C-2), 60.6 (C-6), 51.9 (C-9), 48.6 (C-7), 12.0 (C-8); **HRMS** (ESI, $[C_{18}H_{26}N_4+Na]^+$): measured 321.2067, theoretical 321.2050.

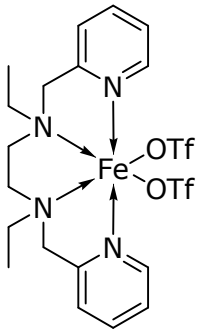
Synthesis of ethyl-substituted ligand-iron(II) complex (**200**)



197 **198** (1 eq.) **200** 54%

General procedure **F** was followed using *N*,*N*′-diethyl-*N*,*N*′-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (**197**, 50 mg, 168 μmol) and bis(acetonitrile)iron(II) trifluoromethanesulfonate (74 mg, 168 μmol). The product **200** was isolated as a dark green powder (59 mg, 54%).

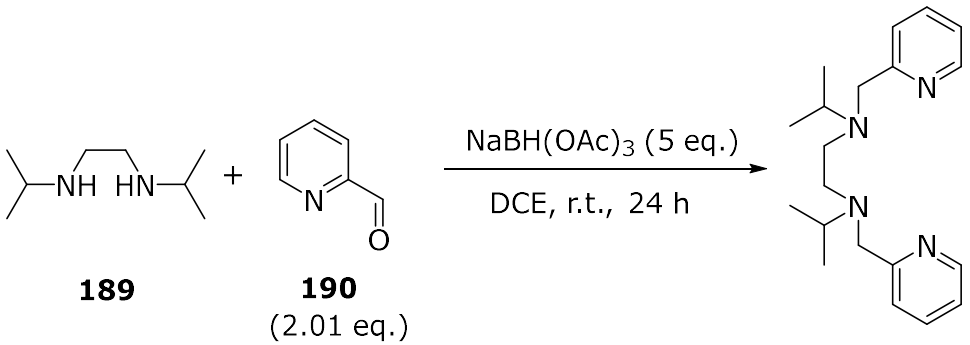
Data collected for (*N*,*N*′-diethyl-*N*,*N*′-bis(pyridin-2-ylmethyl)ethane-1,2-diamine)iron(II) trifluoromethanesulfonate (**200**):



200

ν_{max} (neat, values in cm^{-1}): 2982, 2947, 1608, 1301, 1224, 1025, 631; **HRMS** (ESI, $[C_{20}H_{26}F_6FeN_4O_6S_2+Na]^+$): measured 675.0460, theoretical 675.0440.

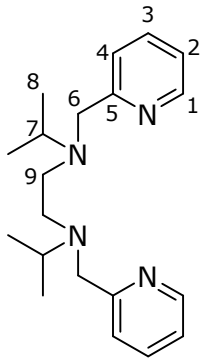
Synthesis of *iso*-propyl-substituted ligand (**191**)



189 **190** (2.01 eq.) **191** 9%

General procedure **E** was followed using *N*,*N*′-di-*iso*-propylethylene diamine (**189**, 0.36 mL, 2.00 mmol), 2-pyridinecarboxaldehyde (0.38 mL, 4.02 mmol) and sodium triacetoxyborohydride (2.12 g, 10.0 mmol). Purification was carried out using silica gel flash chromatography (eluent of triethylamine : ethyl acetate : petroleum ether, 5 : 20 : 75 to 10 : 40 : 50) to yield the desired product **191** as a pale yellow oil (58 mg, 9%).

Data collected for *N*,*N′*-di-*iso*-propyl-*N*,*N′*-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (**191**):

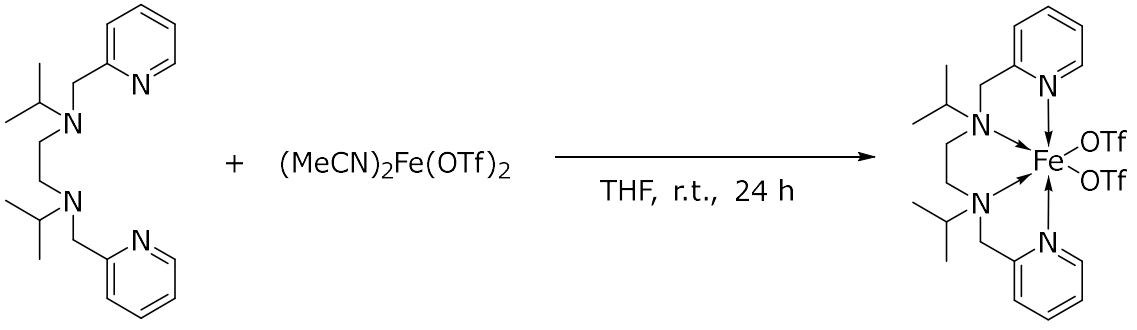


191

R_f (Et_3N:EtOAc:petrol 1:4:5): 0.39; **ν_{max}** (neat, values in cm^{-1}): 3052, 3008, 2929, 1589, 1569, 1431, 1362, 1165, 752; **δ_H** (400 MHz, $CDCl_3$, values in ppm): 8.42 (2H, d, *J* = 4.8 Hz, H-1), 7.55 (2H, app td, *J* = 7.7, 1.9 Hz, H-3), 7.46 (2H, d, *J* = 7.8 Hz, H-4), 7.05 (2H, m, H-2), 3.64 (4H, s, H-6), 2.82 (2H, sep, *J* = 6.6 Hz, H-7), 2.45 (4H, s, H-9), 0.93 (12H, d, *J* = 6.9 Hz, H-8); **δ_C** (100 MHz, $CDCl_3$, values in ppm): 162.0 (C-5), 148.7 (C-1), 136.3 (C-3), 122.5 (C-4), 121.5 (C-2), 56.8 (C-6), 51.2 (C-7), 50.2 (C-9), 18.2 (C-8); **HRMS** (ESI, $[C_{20}H_{30}N_4+Na]^+$): measured 349.2375, theoretical 349.2363.

Spectral data for **191** agrees with the reported values in the literature. [183]

Synthesis of *iso*-propyl-substituted ligand-iron(II) complex (**199**)

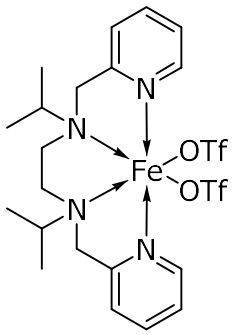


191 **198** (1 eq.) **199** 39%

General procedure **F** was followed using *N*,*N′*-di-*iso*-propyl-*N*,*N′*-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (**191**, 25 mg, 77 μmol) and

bis(acetonitrile)iron(II) trifluoromethanesulfonate (**198**, 34 mg, 77 μmol). The product **199** was isolated as a pale yellow powder (20 mg, 39%).

Data collected for (*N*,*N'*-di-*iso*-propyl-*N*,*N'*-bis(pyridin-2-ylmethyl)ethane-1,2-diamine)iron(II) trifluoromethanesulfonate (**199**):



199

ν_{max} (neat, values in cm^{-1}): 2980, 2952, 1607, 1308, 1214, 1161, 1023, 633; **HRMS** (ESI, $[C_{22}H_{30}F_6FeN_4O_6S_2+Na]^+$): measured 703.0745, theoretical 703.0753.

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