Derivatisation of Betulin for industrial applications

- Green polymers

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Abstract

Research and development of renewable resources are highly relevant today because of the limited supply of oil and its emission of greenhouse gases. New sustainable material has to be found and the idea of this project is to investigate and create possible conditions for a polymer made of the renewable resource betulin. Betulin is a naturally occurring triterpene in birch bark. A combination of ready access and low cost makes betulin a perfect choice as raw material.

In this study betulin was derivatised into monomers suitable for polymerization. The derivatisation was made on the hydroxyl groups using acrylates, allyls, epoxides and acetates as substituents.

Promising monomers, considering yield of substitution, purity and ease of method, were synthesized using allyls, acryls and acetates. For the epoxide substitution and reaction with two of the acetates poor yield and costly purification was needed. Initial radical polymerization experiment was successfully made of the acrylic monomer.
**List of abbreviations**

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIBN</td>
<td>2,2’-azobis(2-methylpropionitrile)</td>
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<tr>
<td>ADMET</td>
<td>Acyclicdiene metathesis</td>
</tr>
<tr>
<td>ATR-IR</td>
<td>Attenuated Total Reflection-Infra red</td>
</tr>
<tr>
<td>BzO₂</td>
<td>Benzoyl peroxide</td>
</tr>
<tr>
<td>CCl₄</td>
<td>Carbon tetrachloride</td>
</tr>
<tr>
<td>COSY</td>
<td>A 2D ¹H NMR that show the correlation between protons.</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DEPT90</td>
<td>A ¹³C NMR that only displays the carbon bonding to one proton</td>
</tr>
<tr>
<td>DEPT180</td>
<td>A ¹³C NMR that differ CH₂ from CH and CH₃</td>
</tr>
<tr>
<td>DoE</td>
<td>Design of Experiment</td>
</tr>
<tr>
<td>ES-MS</td>
<td>Electrospray-Mass Spectroscopy</td>
</tr>
<tr>
<td>GPC</td>
<td>Gel permeation chromatography</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Correlation</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MMA</td>
<td>Methyl methacrylate</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PHB</td>
<td>Polyhydroxy butyrate</td>
</tr>
<tr>
<td>PLA</td>
<td>Polylactide acid</td>
</tr>
<tr>
<td>PMA</td>
<td>Phosphomolybdic acid</td>
</tr>
<tr>
<td>PP</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>RAFT</td>
<td>Reversible Addition - Fragmentation chain Transfer</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
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1. Introduction

1.1 Processum

Processum Biorefinery Initiative AB is a company focusing on the development of bio- and energy technology, organic and inorganic chemistry as well as sustainable raw materials. Processum has gathered a number of companies to solve common biorefinery matters. The company started in 2003 and is today a leading biorefinery initiative on national as well as international level.¹

1.2 Background

1.2.1 Green polymers and composites

The plastic polymer industry consumes 80% of non-renewable petroleum based raw materials. That is one of many reasons why development of renewable resources for materials is becoming more and more important since the supply of oil is limited and contributes to the greenhouse gas emission. Another reason is the probable characteristics of the renewable products which can be expected less toxic and both biodegradable and biocompatible.²³ Some years ago a renewable composite could be made by simply adding natural waste filler to plastic but the comparison of other commercial materials has led to an increased pressure on research and development of the composites. A lot of research has been made trying to incorporate natural fibres in petrochemical based thermoplastic- and thermoset matrixes. One challenge working with natural fibres is the inconsistency of their properties and characteristics. The compatibility of the fibres and the matrix is sometime also a problem; a modification of the fibre surface can be made to improve the adhesion of the two materials. The most utilized fibres as reinforcements are sugar cane bagasse, bamboo and jute. Even if the incorporation of natural fibres in petrochemical matrixes is a step forward to a sustainable option more has to be done. Research has also been made to composites of bio-based matrixes as PLA (polylactic acid), PHB (polyhydroxy butyrate) and starch. Comparison of PLA, PHB and PP (polypropylene) based composites using the same reinforcement fibre (abaca and jute) has been made. The composite made of the bio-based PLA and PHB matrix both showed better mechanical properties than the PP composite.³ Thermoset matrixes are the most widely used today but the increase in development of thermoplastic matrixes is becoming greater day by day since they are recyclable.³ As raw material for green polymers today plant oils and polysaccharides are the most utilized. Plant oils consist of triglycerides, three linear fatty acids with 8-24 carbon and 0-3 Z double bonds. The fatty acids can also have additional functional groups as hydroxyls and epoxides. The best known and most used (so far today) polymers made of plant oils are alkyd resins (a modified polyester with addition of an unsaturated fatty acid, anhydride or polyols) and epoxy resins. Polymerisation of the plant oils and fatty acids are made in numerous ways since they possess several functional groups. Some examples are ionic reactions of polylols, radical reactions of acrylated soy bean and ADMET polymerisation of castor oil to unsaturated polyesters. The most utilized polysaccharides are starch and cellulose. One application of starch is the fermentation process that give the L- lactic acid that form oligomers by a step-growth condensation and polymerised to the biodegradable PLA by the addition of L–lactide.⁴ Another renewable polymer is PHB, produced by bacterial fermentation.⁵ A sustainable synthesis of furans, which have enormous potential in polymer science, can be made of the sugars xylene and ramnose. The reason furans are promising in polymer science is the ability to create derivatives that can be used in the same manner as petroleum, coal and natural-gas based monomers.² The use of a catalyst can be crucial for failure or success for all polymeric syntheses. An appropriate
catalyst can gain atom economy and/or reduce waste and is therefore always to be considered.

1.2.2 Betulin

Betulin (figure 1) is one of many naturally occurring extractives in birch bark. Betulin is a triterpene that can easily be extracted by organic solvents, thermal sublimation or supercritical carbon dioxide up to 30% of the dry weight. Small amounts of betulinic acid and lupeol is always present in extraction of betulin. The largest source of birch bark is the debarking process in pulp and paper industry which today has no other use and is therefore incinerated to produce energy. Considering the large availability of birch bark and the fact that it’s a renewable resource a betulin-based polymer have great potential for industrial applications. Betulin and its corresponding acid are used in medicine and pharmaceuticals since it has proven anti-inflammatory, anti-viral and anti-tumour properties. Its esters are also used in food and chemical industries as surfactants and plasticizers. Not much research have been devoted to the polymerisation of betulin. Previous work has been focused on polymerisation of betulin as a monomer diol by the use of terephthaloyl-, maleic- and adipic acid derivatives. Reported result of that was a polymer of a molecular weight up to 20000 g mol\(^{-1}\). A recent report describes the polymerization of betulin where the aim is to create a micro porous network which can be used for separation processes, gas storage, catalyst or sorbent. According to the author and to the best of my knowledge there is today no known polymerization utilising the double bond of the betulin molecule.

![Figure 1. Chemical structure of Betulin (Lup-20(29)-ene-3β,28-diol, R = CH\(_2\)OH), betulinic acid (R = COOH) and lupeol (R = CH\(_3\))](image)

1.3 Polymers

There are three common types of polymers; linear, branched and network (figure 2). A linear polymer is a straight chain of monomers while branched polymers has monomer chains attached to some point of another chain. Most linear and branched polymers are soluble in some solvent and able to melt. Responsible for holding the adjacent molecule together is van der Waals force. This week interaction allows the molecules to separate when heated and the polymers are therefore able to melt, so called thermoplastics. The difference between linear/branched- and network polymers is the cross-linking holding the molecules together in the network structure. The cross-linking prevents the molecules to separate and is therefore not possible to melt, so called thermosets. Thermosets are often insoluble and as stated above, they don’t melt. Instead decomposition occurs at some critical temperature when the bonds of the molecule break. Elastomers (rubbers) is a type of network structure but the degree of cross-linkage is low (one cross-link per 500-1000 monomers). This prevents separation of the molecules but still allow the chains to move more freely.
There are two ways of classifying polymer synthesis. The first is related to the reaction mechanism and the second to the way the polymer is growing. The reaction mechanism is divided into addition and condensation polymers. Addition polymers have the same number of atoms as the monomers and therefore, the only product formed is the polymer. Addition polymers are often radical reactions. Condensation polymers have fewer atoms than the monomers because of loss of molecules. The second way of classifying polymers is by their growth, step-growth and chain-growth. If the monomer adds to the end of a growing chain the growing pattern is called chain-growth and if the polymer is formed by randomly addition of di-, trimers and higher species the polymerization is called step-growth. Most step-growth reactions are also condensation processes and equal chain-growth are addition reactions. However there are several exceptions and not true for all reactions.

1.3.1 Radical polymerisation

Most radical reactions need an initiator to start the reaction, but some few only requires heat or uv-light. Radical reactions is divided in three steps; initiation, propagation and termination. Side reactions as chain transfer can occur and terminate the polymer growth and affect the structure of the polymer. Chain transfer occurs in reaction with the solvent, initiator, monomer or another growing chain.

RAFT (reversible addition-fragmentation chain transfer) polymerization is useful when a controlled polymerization process is required. In an ideal radical polymerisation all monomers are initiated and survive the polymerisation without chain transfer or termination. The process also grows at a constant rate. To approach these ideal conditions in real polymerisation reactions a RAFT agent can be used. Common RAFT agents that are used are dithiobenzoates, trithiocarbonates, dithiocarbamates and xanthates which are added to the reaction together with the initiator. The RAFT agent will reversibly deactivate the majority of the living chains (propagated radicals) to so called dormant chains to avoid undesired reactions. The living chains can then react with the dormant chains to gain a controlled reaction.

1.3.2 Initiators

There are four common types of initiators used: peroxides, azo-compounds, redox initiators and photo initiators. To choose an appropriate initiator there is two main factors to consider. The initiator should ideally be soluble in the solvent and the initiator need to have a decomposition temperature that is lower than the boiling point of the solvent.

Peroxides are the most widely used initiator and the most common of them is BzO₂ (Benzoyl peroxide) (figure 3). Since peroxides are thermally unstable they decompose into radicals with different kinetic and temperature depending on its structure. Discolouration of the product is one disadvantage when peroxides are used. The most utilized azo-compounds have a cyano-group attached to the carbon
next to the azo-group, as AIBN (2,2’-azobis(2-methylpropionitrile), figure 3). The formation of \( \text{N}_2 \) is the driving force to produce radicals. Azo-compounds does not stain the sample.\(^{10,15}\) Both peroxides and azo-compounds can beyond heat also often be initiated by \( \text{uv} \)-light. The advantage of \( \text{uv} \)-light is the possibility of running the reaction at lower temperature, which results in a more controllable polymerization process.

\[
\begin{array}{c}
\text{BzO}_2 \\
\end{array}
\]

\[
\begin{array}{c}
\text{AIBN} \\
\end{array}
\]

**Figure 3.** Chemical structure of BzO\(_2\) and AIBN

1.4 **Aim of project**

The aim of this project was to derivatise betulin to make monomers possible for polymerization and to investigate methods to polymerize the monomers.

1.5 **How to solve the problem**

The monomers were synthesized to allow five possible opportunities of polymerisation.

1. **Polyaddition of epoxides.** Betulin was substituted with epichlorohydrin and ionic polymerisation was made by nucleophilic addition of the hydroxyl groups of pure betulin to the epoxide.

2. **Polyaddition by radical reaction of an acrylate.** Betulin was acetylated with acryloyl chloride and polymerised by a radical reaction.

3. **Polycondensation made by nucleophilic addition of a hydroxyl group that replaces a leaving group, e. g. \( \alpha \)-halogenated ester.** Betulin was substituted with bromoacetyl bromide. Polymerisation of the derivatised betulin was made together with a diol (e.g. glycol) as a co-monomer, generating the HBr salt as an easily removed by-product.

4. **Polycondensation made by metathesis.** A non-conjugated double bond was added to betulin for metathesis to be possible.

5. **Polycondensation made by nucleophilic addition of an acid chloride and a hydroxyl group.** Betulin was alkylated with methyl bromoacetate, followed by hydrolysis of the acetate to form the corresponding carboxylic acid which was converted to its acid chloride analogue. The acid chloride can easily be polymerised with the hydroxyl groups of pure betulin.

Determination if a product was substituted was primarily made by \(^1\text{H} \text{NMR analysis (figure 4).}\) The proton attached to the primary (3.19 ppm) and secondary (3.34 and 3.81 ppm) carbon will change in shift dependent of the substituent to the oxygen. The double bond (4.60 and 4.70 ppm) of betulin was used as a reference for determination of the degree of substitution.
1.6 Limitations

Synthetic chemistry being time consuming and labor intense, the greatest limitation of this project is time. Not all ideas can be tested, the ones tested is listed in this paper. Focus on this project is to produce a sustainable green polymer. To avoid emission of SO$_x$ and NO$_x$ when the future material is decomposed or incinerated, reagents that will add sulphur and nitrogen to the product is excluded. The solubility of betulin was poor and therefore the possibilities of analyses were limited. Solvents that could be used were DCM, DCE, THF and 2-methyltetrahydrofuran. Solvents not suitable were acetonitrile, methanol and DMSO. The complete NMR spectrum (e.g. figure 4) of betulin was very complex. A substituted product could therefore be hard to interpret because of overlapping peaks.

**Figure 4.** $^1$H NMR of betulin
2. Results and Discussion

2.1 Monomers

The overall mechanism for the syntheses is an $S_N2$ reaction in the presence of a base (except $2$). All syntheses were followed by some kind of work-up which is not mentioned in this chapter. The primary hydroxyl group is five times more reactive than the secondary. A mono substituted product is therefore assumed to be primary substituted.

![Scheme 1](image1.png)

**Scheme 1.** Overview for the synthetic pathway to $1b$. Four different methods ($1_i$-$1_iv$) were tested.

The synthesis of $1b$ (scheme 1) was attempted using four different synthetic pathways, both in organic solvents and as a phase-transfer reaction. Synthetic pathway $1_i$: Betulin and potassium tert-butoxide was dissolved in THF and epichlorohydrin was added and refluxed at 75 °C. TLC indicated a mixture of betulin, mono- and di-substituted product. The poor solubility of the base could be a possible reason for the incomplete conversion since the concentration affects the reactivity. Even though the crude product was purified by chromatography and analysed by $^1H$ NMR it was not conclusive that the correct product ($1b$) had formed. Another method ($1_{ii}$) was tested using a more soluble base-solvent combination to increase the conversion of betulin. $1_{ii}$: Epichlorohydrin was reacted with betulin and KOH in DMSO at 45 °C. The result of this synthetic pathway also suffered from poor conversion of betulin probably caused by the poor solubility of betulin in DMSO. The crude product was purified by chromatography but $^1H$ NMR was still not convincing for the formation of the desired product ($1b$). Therefore a stronger base and another solvent was tested ($1_{iii}$). Synthetic pathway $1_{iii}$: Epichlorohydrin was reacted with betulin and NaH in DMF. The NaH was not washed to allow easier handling of the reaction but it was also the probable cause of the poor conversion of betulin. $1_{iii}$: The phase transfer reaction was carried out in 2-methyltetrahydrofuran as organic solvent and 50% aqueous NaOH as a base. The coupling between betulin and epichlorohydrin was carried out in the presence of the phase transfer catalyst tetrabutyl ammoniumhydrogensulfate. The reaction was easy to carry out but poor conversion was a recurring problem which couldn’t be solved even by letting the reaction run for days. After work-up further purification was difficult since a wax-like product had formed. The product was analysed by $^1H$ NMR after chromatography purification. From the NMR data, no clear conclusion could be made whether the desired product ($1b$) had been formed or not. Common for all four synthetic pathways was that the conversion of betulin were too low for industrial application even if the correct product were formed, therefore no more time was spent to do further experiments using epichlorohydrin.
Scheme 2. Synthetic pathway to obtain 2b

To obtain monomer 2b (scheme 2) betulin was dissolved in 2-methyltetrahydrofuran, bromoacetyl bromide was added and then heated to 50 °C. The reaction was very simple and according to TLC and ‘H NMR pure di-substituted product (2b) was obtained without any purification needed. Experiments were made by HPLC to investigate if LC-MS analysis was possible for the monomer. Experiments were successfully made by normal phase chromatography but not by reverse phase which was necessary for LC-MS analysis. Monomer 2b was therefore instead investigated by ES-MS. The main result of the ES-MS analysis was adducts (NH$_4^+$, Na$^+$, H$^+$) of the monomer and “dimer”. It was not a true dimer but because of solubility two monomers can be very close appearing to be a dimer. The analysis required extreme parameter settings for ionization of the molecule and because of the poor information this analysis can therefore be excluded for future analysis of polymers made from betulin derivatives.

Scheme 3. Two attempted synthetic pathways to 3b and 4b. Several methods were tested (3i-3ii and 4i-4iii).

Two attempts were made to synthesise 3b (scheme 3). 3i; Betulin and potassium tertbutoxide was dissolved in 2-methyltetrahydrofuran and methyl bromoacetate was added and the reaction was heated to 75 °C. The reaction was followed by TLC and since there was indication of a mixture of betulin, mono- and di-substituted product another method (3ii) was tested to increase the conversion of starting material. To achieve that, a stronger base was chosen. 3ii; In a mixture of betulin and NaH dissolved in NMP, the reagent methyl bromoacetate was added and heated to 50 °C. This reaction was also monitored by TLC indicating a mixture of betulin, mono- and di-substituted product. Purification was made by flash chromatography to obtain the di-substituted product. According to ‘H NMR the same product had formed using both method 3i and 3ii. Except ‘H and $^{13}$C NMR the product was examined by HMQC, HMBC, COSY, DEPT90 and DEPT180. Analysis of the NMR data clearly showed the
monomer formed was $2b$, not the desired $3b$. This synthetic route to $2b$ was more time consuming, more chemicals needed and poorer yield. Also the obtained product was a mixture of betulin, mono- and di- substituted product, therefore purification by chromatography was necessary.

The synthesis of $4b$ (Scheme 3) was made both in organic solvent and as a phase transfer reaction. $4i$ This synthetic pathway was made as a phase transfer reaction using 2-methyltetrahydrofuran as organic solvent and 50% aqueous NaOH as base and inorganic solvent. Betulin was reacted with tert-butyl bromoacetate in the presence of the phase transfer catalyst tetrabutyl ammoniumhydrogensulfate. TLC indicated that betulin was still present together with mono ($4a$)- and di ($4b$)-substituted product. $^1H$ NMR of the crude product could not clarify which product had formed. $4i$; Betulin was reacted with tert-butyl bromoacetate and potassium tertbutoxide in 2-methyltetrahydrofuran and heated to 75 °C. The result was a mixture of betulin, mono ($4a$)- and di ($4b$)-substituted product, so poor that no NMR analysis was made. Instead, another method ($4ii$) using a stronger base was tested. Synthetic pathway $4ii$ was a reaction of tert-butyl bromoacetate and betulin in NMP and NaH. Full conversion of the starting material was not achieved using this method either. $^1H$ NMR of the purified product by chromatography did not indicate formation of correct product ($4b$). All methods resulted in a mixture of betulin, mono- and di-substituted product which therefore required further purification. Considering the degree of conversion and the number of reaction step before the final polymerisable monomer could be formed this process was concluded not suitable for industrial application.

Scheme 4. Synthetic pathway for derivatisation of betulin to $5b$ and $6b$

It was easy to carry out the synthesis of monomer $5b$ (Scheme 4). Pyridine and betulin was dissolved in THF, cooled to 0 °C and allyl chloroformate was added. Even though the reaction was easily performed, it has to be kept in mind that the reaction temperature must be lower than the boiling point of the reagent unless a reflux condenser is used. Full conversion of the starting material was obtained but there was a mixture of mono ($5a$) and di ($5b$) substituted product. No chromatographic purification was done since it is very likely that changes to the reaction condition would lead to that pure di-substituted ($5b$) product could be obtained. $^1H$ NMR indicated correct product formation, which was confirmed by HMQC analysis.

To a mixture of betulin and pyridine in THF at room temperature vinyl chloroformate was added to obtain a pure di-substituted product $6b$ (Scheme 4) without any purification needed. The product of this simple reaction was monitored by TLC and validated by $^1H$ NMR analysis.
Betulin and NaH were refluxed in THF, the reagent allyl bromide was added and the reaction was continued at reflux. The reaction was followed by TLC and stopped when full conversion of the starting material was achieved. The synthesis of 7b (scheme 5) was time consuming but easy to carry out and no purification was required. According to $^1$H NMR pure di-substituted (7b) product was obtained even though TLC indicated presence of mono-substitution (7a). Some unknown impurity was apparent from the NMR data but it was easily filtered off through a silica plug. The coupling between the allyl bromide and betulin was evident from $^{13}$C NMR and DEPT 180.

**Scheme 5.** Synthetic pathway to 7b

To a mixture of betulin and pyridine acryloyl chloride was added. To synthesise the pure di-substituted product 8b (scheme 6), the reagent had to be added in two portions. If not, a mixture of betulin, mono (8a)- and di (8b)-substituted product was formed. A lot of precipitate was formed during the reaction and could potentially be a problem if the reaction mixture is to concentrated. No purification was needed but the work-up is not optimized due to unknown precipitation during extraction and therefore probably accounted for some loss of product. The melting point was determined to 155°C and the structure confirmed by $^1$H and $^{13}$C NMR.

**Scheme 6.** Synthetic pathway to 8b

The reaction conditions for polymerization of a vinyl monomer were examined as a preliminary investigation for the continuing work. The monomer and initiator concentration was taken from organikum$^{18}$ and the reaction temperature according to the Hoffman group$^{19}$. Different solvent (toluene and CCl$_4$) was tested, both with and without degassing.$^{19}$ The confirmation of the reaction conditions for polymerization was successfully made with both solvents, degassed and not degassed. Since the polymerization was possible in both solvents, a third solvent (DCE) was tested for the polymerization of 8b considering solubility, boiling point and toxicity. DCE is less toxic than CCl$_4$ and the solubility of betulin is higher in DCE than toluene. The solubility of 8b still wasn’t high enough to get equal monomer concentration as for...
the controlled conditions even though DCE was used. The monomer was therefore dissolved in a minimum amount of solvent and then used for polymerization.

The result of the initial radical polymerization experiments was a somewhat fragile and insoluble solid product (figure 6). Most likely there is a polymer with a network structure\(^1\) that makes it insoluble. Earlier results\(^6\) from betulin polymerisation shows that a linear polymer, linked by a diester, have gel-like properties and is soluble in e.g. chloroform. Upon evaporation of the solvent, a clear polymer was formed. In our case, the likely reaction of the double bond in betulin with the rest of the polymer gives a higher degree of cross-linking and therefore a less flexible polymer. Because of its insolubility the analysis of the polymer was very difficult. The melting point was determined to see if the product had different physical properties than 8b and the result showed distinctly different properties. The melting point of the product could not be determined. The sample changed colour at 260 °C from colourless to slightly yellow. As the temperature was raised, the colour changed from orange to red. At 350 °C the sample was black and the structure was lost. The solid was analysed by IR spectroscopy to identify any remaining vinyl groups but no conclusions could be made from the spectra. The solid state \(^{13}\)C NMR (figure 5) monitored two ester (carbonyl) peaks, one new (174.41 ppm) and one belonging to \(8b\) (165.29 ppm). The double bond of the acrylate (129.31 ppm) was also still present. The new carbonyl peak indicates formation of a polymer and the presence of the acrylate double bond suggests a heavily branched network with numerous end groups. Since integration was not possible no conclusion could be made if the double bond (C 20-29) of betulin did participate in the reaction or not. The molecular weight of the product was also investigated but without success.\(^{20}\)

*Figure 5. Comparison of the solid state \(^{13}\)C NMR (top) of the polymer product and \(^{13}\)C NMR for the corresponding monomer (bottom)*
The polymerization of 2b and a diol (1, 3-propanediol) was carried out by a phase transfer reaction in 50% NaOH, 2-methyltetrahydrofuran and tertbutyl ammonium hydrogensulfate. Full recovery of betulin occurred and to avoid hydrolysis of the ester another method was considered using dry and inert conditions. The coupling between 2b and the diol was made in NMP and NaH. This polymerisation also resulted in recovery of betulin, using both 1, 3-propanediol and ethylene glycol as diol. Since a larger diol could be a possible steric hindrance for the ester hydrolysis betulin was used as diol but still hydrolysis occurred.

Polymerisation was attempted with oxalyl chloride and betulin in THF. The addition of oxalyl chloride had to be done very carefully to avoid side reactions. Excess oxalyl chloride gave full conversion of betulin and pure di substituted product was obtained. 1H and 13C NMR indicated that it’s more probable that betulin was substituted with oxalalyl chloride on both hydroxyls and then hydrolysed to the corresponding monoesters rather than formation of a polymeric product. 1H and 13C NMR data of the product of equimolar amount of betulin and reagent also indicate a di-substituted product and full conversion of the starting material but still no typically pattern of a polymer. Determination of the molecular weight could clarify what product that had formed. Gel Permeation Chromatography (GPC) was considered but lack of time and reference samples for calibration of the column made the analysis impossible within the limit of this project.

2.3 Evaluation of the polymerization opportunities

The five prospective opportunities for polymerizations had different pros and cons.

For polymerization to occur by polyaddition of epoxides (1b) the monomer has to be at least mono substituted which is an advantage since the purification can be limited or excluded all together. Cons for this method are the risk of polymerisation of the reagent instead of reaction with betulin and that the wax-like product must be purified before further use in continuing syntheses.

Polyaddition by radical polymerisation of an acrylate (8b) was one of the most promising routes since the synthesis of the monomer was simple and only a mono substituted product is required for polymerisation to be possible. A con for this method was that the product assignment needs further work.

Polycondensation made by nucleophilic addition of a hydroxyl group that replaces a leaving group (2b). For this method to be viable, a di-substituted monomer was needed and the simple synthesis of the monomer made this theory very promising, but the recovery of betulin during polymerisation excludes this method for industrial applications. Further work is required to find appropriate reaction conditions, where hydrolysis doesn’t occur.

Catalytic reactions are to prefer for large scale applications. For the polycondensation made by metathesis (5b, 7b) pure di-substituted product was obtained which is
needed to get a polymer of high molecular weight. A by-product is the greenhouse gas ethene and the Grubbs II catalyst used for metathesis is expensive and not sold for industrial use. This method is therefore only considered for industrial application if all others methods is shown impossible.

Polycondensation made by nucleophilic addition of an acid chloride (3b, 4b) and a hydroxyl group was promising since it has been shown that the hydroxyl groups are very suitable for creating coupling with acid chlorides. Cons for this method are the many synthetic steps before the acid chloride-monomer are formed and that the product has to be di-substituted for polymers to gain high molecular weight.
3. Conclusions and prospective work

This work has shown that it is possible to create betulin-based monomers suitable for polymerisation. Radical polymerisation of 8b was successfully accomplished but the product was brittle. A less fragile product could be formed if there is less steric hindrance in the molecule that could be achieved by substitution of the hydroxyl groups of betulin using the green oleic acid (a component in bark). The double bond of oleic acid could then be oxidised to an epoxide and further acetylated to the same functional acrylate as 8b. The successful outcome of the polymerization of 8b is a great reason to believe this prospective polymerization should be possible. But for future esterification of betulin it has to be kept in mind that further addition of a nucleophile in the presence of a base may result in hydrolysis and recovery of betulin. A less brittle product may also be obtained by controlling the polymer growth and structure in the presence of a RAFT agent.

For industrial applications, a relevant prospective research for the known working polymerisation of 8b is investigation of the polymerisation by DoE. This would be helpful in trying to find the mixture where the largest amount of betulin could be mixed with mono- and di-substituted monomers and still obtain a polymer product. For industrial application this is important since less processed material lower the costs. It could also, and almost more important, be examined if the polymer structure is dependent of the degree of substitution of the reaction mixture to obtain a network- or linear/branched structure since they have different physical properties. To increase the information gained from the DoE, some kind of determination of the molecular weight will be necessary (e.g. GPC or MS-techniques).

One more monomer to be considered for prospective work is 2b. Considering polymerisation of 2b for industrial scale, if the appropriate reaction conditions are found to prevent the hydrolysis, the synthesis of 2b should be investigated for a continuous synthesis process. The very simple reaction to produce 2b makes this promising. If conditions proved difficult to be found, hydrolysis of the ester could be prevented by resonance effects of a conjugated substituent, shifting its electrophilic properties.

The outcome of the synthesis of monomer 1b and 4b was not successful enough to do polymerisation experiments. They were not worthy to be tested since there was no expectation of a successful outcome. The synthesis and polymerisation of 1b should nevertheless not be completely excluded for prospective work since literature indicates of polymerisation of epichlorohydrin above 40 °C at certain reaction conditions and also, the epoxide functionality could be obtained by simple oxidation of the double bond of monomer 5b and 7b. The synthesis of 5b and 7b proceeded well but the cons for the metathesis polymerisation make this method only suitable for prospective work if all other fails.
4. Experimental section

4.1 General methods

All NMR samples in solution were analysed by a Bruker Avance, 500 MHz. Solid phase NMR was analysed using a Bruker Avance III, 500 MHz. Fluka analytical, silica gel was used as TLC-cards and the staining solution used was PMA (Phosphomolybdic acid). General Rf for eluent 33% ethyl acetate in heptane: Betulin=0.29, mono-substitution=0.46, di-substitution=0.75. IR was recorded on an ATR-FT-IR Nexus, Thermo Nicolet 470. ES-MS: micromass Quattro microT. Solvent: 10mM ammonium acetate in methanol. The HPLC used was a Waters 2998 Photo Array Detector, 2545 Binary Gradient Module, System Fluid Organiser and 2767 Sample manager. Normal phase: column Sunfire Si 10x50 mm, solvent DCM/10% methanol in DCM. Reverse phase: column Sunfire C18 4.6x75 mm, solvent water/acetonitrile. Before use, NaH was wash with heptane if nothing else stated.

4.2 Experimental procedure

Synthesis of (1):

\textbf{Lup-20(29)}-ene-3,28-bisoxymethyloxirane (1b) \\
\textbf{Lup-20(29)}-ene-28-oxymethyloxirane (1a)

1.1 As a modified version of a literature procedure\textsuperscript{21}, betulin (1.0 g, 0.6 mmol) and KOH (0.32 g, 4.8 mmol) was suspended in DMSO (1.2 ml). Epichlorohydrin (0.56 ml, 7.2 mmol) was added and heated to 45 °C and stirred for 18 hours (overnight). The reaction mixture was filtered and washed with CH\textsubscript{2}Cl\textsubscript{2} (~15 ml). The solution was evaporated to yellow oil. The oil was extracted with diethyl ether (30 + 20 ml) and the organic extracts were washed with brine (10 ml). The solvent was removed under reduced pressure and the product was purified by flash chromatography (7.91 g silica gel, eluent 2-5% MeOH in DCM) to obtain a white solid.

1.2 According to a published procedure\textsuperscript{22}, 50 % NaOH (10 ml), epichlorohydrin (1 ml, 12.78 mmol) and tetrabutyl ammoniumsulfate (0.087 g, 0.2459 mmol) was added to a solution of betulin (0.5 g, 1.129 mmol) dissolved in 2-methyltetrahydrofuran (10 ml). The reaction was stirred for 3 days (over weekend) and followed by TLC (5% MeOH in DCM). The mixture was diluted with ethyl acetate and the phases were separated, the aqueous phase was extracted with ethylacetate (20 + 15 ml) and the combined organic phases were washed with brine). The solvent was removed under reduced pressure and a solid wax-like product was obtained. The solid was purified by flash chromatography (8.66 g silica gel, eluent 10% ethyl acetate in heptane) to give a white solid.

Synthesis of (2):

\textbf{Lup-20(29)}-ene-3,28-bisbromoacetate (2b) \\
\textbf{Lup-20(29)}-ene-28-bromoacetate (2a)

2 were prepared by a modified method of a literature procedure\textsuperscript{23}. Betulin (5 g, 11.3 mmol) was dissolved in 2-methyltetrahydrofuran (70 ml) and bromoacetyl bromide (4.2 ml, 47.8 mmol) was added and stirred at 50 °C for 1.5 h. The mixture was washed
with water twice (50 ml + 30 ml). The organic phase was evaporated, and from the crude residue (a white solid product) was crystallized from isopropanol. 5.54 g product was obtained, yield 70%. \(^1\)H NMR (500 MHz, chloroform-\(d\) 7.27) \(\delta\) ppm 0.80 (d, \(J=9.14\) Hz, 1 H), 0.85-0.91 (m, 12 H), 0.96-1.15 (m, 12 H), 1.21-1.32 (m, 3 H), 1.38-1.46 (m, 6H), 1.51-1.72 (m, 16 H), 1.78-1.88 (m, 2 H), 1.93-2.01 (m, 1 H), 2.44 (td, \(J=10.78, 6.06\) Hz, 1 H), 3.80-3.88 (m, 5 H), 3.95 (d, \(J=11.32\) Hz, 1 H), 4.39 (d, \(J=11.13\) Hz, 1 H), 4.54 (dd, \(J=9.14, 7.15\) Hz, 1 H), 4.61 (s, 1 H) 4.70 (s, 1 H)

**Synthesis of (3):**

**Lup-20(29)-ene-3,28-bisoxymethylacetate (3b)**

**Lup-20(29)-ene-28-oxymethylacetate (3a)**

! None of these syntheses did generate the desired product!

3.1

3 were prepared using a modified method of a literature procedure\(^{24}\). Betulin (0.5 g, 1.13 mmol) was dissolved in dry THF (12.5 ml) and 55% NaH (0.38 g, 4.52 mmol) was added to give a grey suspension. After the dropwise addition of methyl bromoacetate (0.425 ml, 4.52 mmol) the reaction mixture was heated to 50 °C for 4 hours and then allowed to cool to room temperature. The reaction was quenched by the addition of water (20 ml). The mixture was filtered and extracted with ethyl acetate (10 ml). The organic phase was washed with brine and the solvents were removed under reduced pressure. The product was purified by flash chromatography (silica 8.76 g, 100% DCM) to give a white solid.

3.2

According to a literature procedure,\(^{24}\) betulin (0.5 g, 1.1 mmol) was dissolved in 2-methyltetrahydrofuran (25 ml) and potassium tertbutoxide (1.25 g, 11.1 mmol) was added. After the dropwise addition of methyl bromoacetate (1.05 ml, 11.1 mmol) the reaction mixture was heated to 75 °C for 26 hours. The reaction mixture was allowed to cool to room temperature and the reaction was quenched by the addition of water (12 ml). The mixture was separated and the organic phase was washed with brine and then concentrated under reduced pressure. The product was purified by flash chromatography (silica 8.76 g, 100% DCM) to obtain a white solid.

**Synthesis of (4):**

**Lup-20(29)-ene-3,28-bisoxytertbutylacetate (4b)**

**Lup-20(29)-ene-28-oxytertbutylacetate (4a)**

4.1

A modification of a published procedure\(^{24}\) was made. Betulin (0.2 g, 0.45 mmol) was dissolved in dry THF (5 ml) and 55% NaH (0.093 g, 1.8 mmol) was added to give a grey suspension. After the dropwise addition of tert-butyl bromoacetate (0.27 ml, 1.8 mmol) the reaction mixture was heated to 50 °C for 4 hours and then allowed to cool to room temperature. The reaction was quenched by the addition of water (20 ml), filtrated and extracted with ethyl acetate. The solvent was removed under reduced pressure and the resulting yellow oil was recrystallized in 2-propanol. The product was purified by flash chromatography (silica 8.65 g, 33% ethyl acetate in heptane) to obtain a white solid.
According to a combination of two literature procedures, to a solution of betulin (0.5 g, 1.13 mmol) dissolved in 2-methyltetrahydrofuran (10 ml) 50% NaOH (10 ml), tetrabutyl ammoniumsulfate (0.0829 g, 0.25 mmol) and tertbutyl bromoacetate (1.8 ml, 11.5 mmol) were added. The phase transfer reaction was stirred at 40°C overnight. The precipitate was dissolved by addition of water (10 ml) and brine (10 ml) was added to increase the separation. The organic phase was washed with brine (15 + 10 ml). The solvent was removed under reduced pressure and a white solid was obtained which was then recrystallized in 2-propanol.

Synthesis of (5);

Lup-20(29)-ene-3,28-bisallylcarbonate (5b)
Lup-20(29)-ene-28-allylcarbonate (5a)

According to a literature procedure betulin (0.5 g, 1.13 mmol) was dissolved in dry THF (5 ml) and pyridine (0.37 ml, 4.6 mmol) under argon at 0°C. Allylchloroformate (0.48 ml, 4.5 mmol) was added dropwise to form a white suspension. The reaction was stirred for 22 hours (overnight) and monitored by TLC (33% ethyl acetate in heptane). The reaction was quenched by addition of water (2 ml) upon which the precipitate was dissolved. The mixture was extracted with ethyl acetate (2+2 ml) and the organic phase was washed with 2 N HCl (3 ml), NaHCO₃ (aq., sat., 3 ml), brine (5 ml) and dried with Na₂SO₄. The solvent was removed under reduced pressure to obtain a white solid. ¹H NMR (500 MHz, chloroform-d 7.27) δ ppm 0.75-0.80 (m, 1 H), 0.82-0.99 (m, 7 H), 1.02-1.14 (m, 3 H), 1.16-1.33 (m, 3 H), 1.36 - 1.45 (m, 3 H), 1.52 (br. s., 1 H), 1.57-1.76 (m, 6 H), 1.81-1.92 (m, 1 H), 1.95-2.04 (m, 1 H), 2.43 (td, J=10.68, 5.86 Hz, 1 H), 3.93 (d, J=10.73 Hz, 1 H), 4.30-4.37 (m, 1 H), 4.58 - 4.66 (m, 4 H), 4.69 (s, 1 H), 5.25-5.30 (m, 1 H), 5.33 - 5.40 (m, 1 H), 5.91-6.00 (m, 1 H)

Synthesis of (6);

Lup-20(29)-ene-3,28-bisvinylcarbonate (6b)
Lup-20(29)-ene-28-vinylcarbonate (6a)

Betulin (0.5 g, 1.13 mmol) was dissolved in dry THF (5 ml) under argon and vinyl chloroformate (0.31 ml, 3.4 mmol) and pyridine (0.37 ml, 4.5 mmol) were added dropwise. The reaction was monitored by TLC (33% ethyl acetate in heptane) until full conversion (15 minutes). The reaction was quenched by the addition of water (4 ml) and extracted with ethyl acetate (5 ml). The combined organic layers were washed with 1 N HCl (5 ml), NaHCO₃ (aq., sat., 10 ml), brine and dried with Na₂SO₄. A white solid was obtained after evaporation of the solvents. ¹H NMR (500 MHz, chloroform-d 7.27) δ ppm 0.73-0.91 (m, 7 H), 0.93-1.14 (m, 12 H), 1.19-1.33 (m, 3 H), 1.38-1.50 (m, 5 H), 1.54 (br. s., 2 H), 1.57-1.76 (m, 9 H), 1.82-2.02 (m, 3 H), 2.32-2.52 (m, 1 H), 3.99 (d, J=10.73 Hz, 1 H), 4.28-4.47 (m, 2 H), 4.53-4.65 (m, 3 H), 4.70 (s, 1 H), 4.92 (ddd, J=13.91, 8.05, 1.89 Hz, 2 H), 7.05-7.19 (m, 2 H), 13C NMR (126 MHz, chloroform-d 77.00) δ ppm 14.98, 16.22, 16.37, 16.60, 18.30, 19.31, 21.00, 23.75, 25.31, 27.20, 28.09, 29.67, 34.27, 34.56, 37.24, 37.85, 38.28, 38.52, 41.10, 42.94, 46.76, 47.90, 49.00, 50.44, 55.56, 67.58 (C-28), 86.58 (C-3), 97.60( =CH₂), 97.90( =CH₂), 110.30 (C-29), 142.95 (-CH=), 142.99 (-CH=), 150.11 (C-20), 152.99 (C=O), 153.53 (C=O)
Synthesis of (7);

**Lup-20(29)-ene-3,28-bisallylether (7b)**
**Lup-20(29)-ene-28-allylether (7a)**

According to a published procedure, betulin (0.5 g, 1.13 mmol) and 55% NaH (0.20 g, 4.51 mmol) was dissolved in dry THF under argon and refluxed for 24 hours. The reaction mixture was allowed to cool to room temperature and then allyl bromide (0.29 ml, 3.39 mmol) was added dropwise. The reaction mixture was refluxed (115 °C) for 24 more hours, cooled to room temperature and water (5 ml) was added. The organic phase was washed with 1 N HCl (5 ml) + brine (5 ml) and NaHCO₃ (aq., sat., 10 ml). A precipitate formed during the addition of NaHCO₃, the filtrate was purified through a silica plug and the solvent was removed under reduced pressure to obtain a white solid product. 

$^1$H NMR (500 MHz, chloroform-d) $\delta$ ppm 0.68 (d, $J=9.54$ Hz, 2 H), 0.78-0.85 (m, 7 H), 0.88 (d, $J=8.94$ Hz, 1 H), 3.54 (d, $J=9.14$ Hz, 1 H), 3.89 (ddt, $J=12.91$, 5.36, 1.47 Hz, 1 H), 4.58 (d, $J=2.92$ Hz, 1 H), 4.68 (d, $J=2.19$ Hz, 1 H), 5.13 (dq, $J=10.33$, 1.52 Hz, 1 H), 5.19 (dq, $J=10.41$, 1.43 Hz, 1 H), 5.26 (dq, $J=9.54$, 1.72 Hz, 1 H), 5.30 (dq, $J=9.71$, 1.66 Hz, 1 H), 5.88-5.98 (m, 2 H), 13C NMR (126 MHz, chloroform-d) $\delta$ ppm 14.99, 16.27, 16.40, 16.80, 18.48, 19.34, 21.09, 23.35, 25.44, 25.85, 27.42, 28.31, 30.19, 34.44, 35.04, 37.34, 37.68, 38.83, 39.08, 41.20, 42.87, 47.44, 48.22, 49.10, 50.61, 56.05, 68.22, 68.38, 70.90, 72.70, 86.55 (C-3) 109.71 (C-29) 116.18 (=CH₂), 116.91 (=CH₂), 135.67 (-CH=), 136.16 (-CH=), 151.05 (C-20), C\textsuperscript{13}NMR/DEPT180 70.33 (O-CH₂ (-)), 72.37 (O-CH₂ (-))

Synthesis of (8);

**Lup-20(29)-ene-3,28-bisacrylate (8b)**
**Lup-20(29)-ene-28-acrylate (8a)**

Under argon betulin (1 g, 2.25 mmol) was dissolved in dry THF (10 ml) and pyridine (0.8 ml, 9.9 mmol). Acryloyl chloride (0.6 ml, 7.4 mmol) was added dropwise during 15 minutes. The reaction was followed by TLC. After the addition of acryloyl chloride the reaction mixture was stirred for one hour and further acryloyl chloride (0.1 ml, 1.23 mmol) was added and stirred for an additional 30 minutes until the reaction was complete. The reaction was quenched by the addition of water (3 ml) to dissolve the salt. The organic phase was washed with 4 N HCl (5+5 ml), NaHCO₃ (aq., sat., 12+23 ml) and brine (18 ml). A white solid product was obtained after evaporation of the solvents. 

$^1$H NMR (500 MHz, chloroform-d) $\delta$ ppm 0.77-0.92 (m, 8 H), 0.95-1.14 (m, 9 H), 1.18-1.37 (m, 3 H), 1.37-1.46 (m, 4 H), 1.48-1.55 (m, 1 H), 1.65-1.75 (m, 9 H), 1.77-1.91 (m, 2 H), 1.92-2.03 (m, 1 H), 2.48 (td, $J=11.13$, 5.96 Hz, 1 H), 3.94 (d, $J=11.13$ Hz, 1 H), 4.37 (d, $J=9.74$ Hz, 1 H), 4.49-4.65 (m, 2 H), 4.66-4.86 (m, 1 H), 5.82 (ddd, $J=15.50$, 10.43, 1.49 Hz, 2 H), 6.05-6.21 (m, 2 H), 6.40 (td, $J=17.24$, 1.49 Hz, 2 H), 7.31 (s, 2 H), 13C NMR (126 MHz, chloroform-d) $\delta$ ppm 14.99, 16.27, 16.40, 16.80, 18.40, 19.35, 21.04, 23.90, 25.39, 27.30, 28.20, 29.82, 30.02, 34.34, 34.82, 37.31, 37.83, 38.22, 38.60, 41.14, 42.95, 46.73, 47.98, 49.03, 50.51, 55.62, 63.09, 81.31, 110.15 (C-29), 128.87 (=CH₂), 129.39 (=CH₂), 130.33 (CH=), 130.75 (CH=), 150.37 (C-20), 166.31 (C=O), 166.93 (C=O)
Determination of reaction conditions for polymerisation

All these four reactions\textsuperscript{18,19} obtained a product with polymer characteristic properties.

1. MMA (0.2 ml, 1.9 mmol) in CCl\textsubscript{4} (1 ml) AIBN (~0.0025 g, 0.015 mmol) was added and vigorously stirred at 60°C for 24 hours (overnight) in a closed vial.

2. MMA (0.2 ml, 1.9 mmol) in CCl\textsubscript{4} (1 ml) AIBN (~0.0025 g, 0.015 mmol) was added and the mixture was degassed.\textsuperscript{2} The sample was cooled for 2 minutes in liquid nitrogen and then vacuum was added for 3 minutes, the vacuum was closed and the sample was allowed to thaw to room temperature. This was repeated three times. The sample was then vigorously stirred at 60°C for 24 hours (overnight) in a closed vial.

3. MMA (0.2 ml, 1.9 mmol) in toluene (1 ml) AIBN (~0.0025 g, 0.015 mmol) was added and vigorously stirred at 60°C for 24 hours (overnight) in a closed vial.

4. MMA (0.2 ml, 1.9 mmol) in toluene (1 ml) AIBN (~0.0025 g, 0.015 mmol) was added and the mixture was degassed.\textsuperscript{2} The sample was cooled for 2 minutes in liquid nitrogen and then vacuum was added for 3 minutes, the vacuum was closed and the sample was allowed to thaw to room temperature. This was repeated three times. The sample was then vigorously stirred at 60°C for 24 hours (overnight) in a closed vial.

Polymerisation of Lup-20(29)-ene-3,28-bisacrylate (8b)

1. Disubstituted betulinacrylate (8b) (0.113 g, 0.2 mmol) was dissolved in DCE (0.18 ml) and AIBN (~0.0025 g, 0.015 mmol) was added. The reaction mixture was stirred at 60°C for 18 hours. A solid, transparent, insoluble product was obtained. No melting point could be determined; decomposition occurred at ~350°C. \textsuperscript{13}C NMR (solid state) (126 MHz, H2O+D2O) \( \delta \) ppm 16.97, 18.98, 22.02, 25.84, 28.59, 30.40, 35.65, 38.49, 42.22, 43.79, 50.16, 57.07, 63.44, 71.09, 81.73, 94.57, 110.31 (C-29), 118.94, 130.46 (CH= and =CH\textsubscript{2}), 150.95 (C-20), 166.00 (C=O), 175.12 (C=O), IR (ATR) \( \nu/cm^{-1} \) 2945 (C\textsubscript{sp3}-H), 1722 (C=O).

2. Disubstituted betulinacrylate (8b) (0.084 g, 0.15 mmol) was dissolved in DCE (0.15 ml) and a catalytic amount of BzO\textsubscript{2} (cat.) was added. The reaction mixture was stirred at 60°C for 18 hours. A yellow solid, transparent, insoluble product was obtained and no more characterisation was made since lack of time. Because of similarities in physical properties the product were assumed to be the same as for the polymerisation made by AIBN as initiator (experiment above).

Polymersiation of Lup-20(29)-ene-3,28-bisbromoacetate (2b) and a diol

1. An alternative synthesis of the published procedure\textsuperscript{22} was done. 2b (0.5 g, 0.73 mmol) was dissolved in 2-methyltetrahydrofuran (8 ml), 50% NaOH (5 ml), dry 1, 3-propanediol (0.25 ml, 2.9 mmol) and tetrabutyl ammonium sulfate (0.058 g, 0.16 mmol) were added. The mixture was stirred at 40°C and followed by TLC (33% ethyl acetate in heptane). No further work-up was made since betulin was formed according to TLC and NMR.
As described in a literature procedure\(^{27}\), 55\% NaH (0.13 g, 3.1 mmol) and betulin (0.25 g, 0.56 mmol) was dissolved in dry THF (6 ml ) under argon and refluxed at 100 \(^{\circ}\)C for 30 minutes and then allowed to cool to room temperature. \(\text{2b} (0.384\text{ g, 0.56 mmol})\) dissolved in dry THF (5 ml) was added dropwise. The reaction was heated to 100 \(^{\circ}\)C. The reaction was followed by TLC ((33\% ethyl acetate in heptane). No apparent reaction occurred.

A modified version of the procedure of the literature procedure\(^{27}\), ethylene glycol (0.11 ml, 0.29 mmol) and 55\% NaH (0.159 g, 5.88 mmol) was heated in dry NMP (10 ml) to 120 \(^{\circ}\)C under an inert atmosphere and \(\text{2b} (0.5\text{ g, 0.73 mmol})\) dissolved in hot NMP (5 ml, 120 \(^{\circ}\)C) was added. The reaction was kept at 120 \(^{\circ}\)C and followed by TLC (33\% ethyl acetate in heptane) for ten minutes. No further work-up was made since betulin was formed due to ester hydrolysis.

\textbf{Polymerisation of betulin and oxalylchloride}

The polymersiation of betulin through a modified syntesis of the literature procedure\(^{23}\) was made. Betulin (0.4998 g, 1.13 mmol) was dissolved in THF (4.5 ml) under argon and oxalyl chloride (0.0956 ml, 1.13 mmol) was added slowly and dropwise. The reaction was stirred for 30 minutes and followed by TLC (33\% ethyl acetate in heptane), stopped by the addition of water (2 ml) and extracted with ethyl acetate (4+6 ml). The organic phase was washed with brine. A white solid was obtained after evaporation of the solvent. \(^1\text{H NMR (500 MHz, chloroform-d 7.27)}\) \(\delta \text{ ppm} 0.78-1.10 (m, 20 H) 1.12-1.35 (m, 6 H), 1.36-1.62 (m, 7 H), 1.77-1.94 (m, 4 H), 1.98 (m, 1 H), 2.45 (m, 1 H), 4.06 (d, \(J=10.93 \text{ Hz, 1 H})\), 4.46 - 4.51 (m, 1 H), 4.58 - 4.64 (s, 1 H), 4.66 (dd, \(J=11.23, 4.07 \text{ Hz, 1 H})\), 4.71 (s, 1 H), \(^{13}\text{C NMR (126 MHz, chloroform-d 77.00)}\) \(\delta \text{ ppm} 14.17, 14.70, 15.97, 16.13, 16.36, 16.39, 16.41, 18.07, 19.05, 20.74, 21.06, 23.33, 25.02, 26.96, 27.89, 29.41, 29.57, 34.00, 34.36, 34.43, 37.00, 37.64, 37.68, 37.98, 38.01, 38.07, 38.23, 40.84, 42.69, 46.54, 47.67, 48.70, 48.73, 50.17, 55.21, 55.24, 60.48, 65.61, 85.92, 110.13 (C-29) 149.74 (C-20), 157.28 (C=O), 157.83 (C=O), 158.26 (C=O), 158.33 (C=O), 158.38 (C=O), 158.72 (C=O), 158.84 (C=O).
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