Towards an Automated Alpha Amino Acid Synthesis and Selective Removal of Sensitizers from Natural Product Extracts: Feverfew (Tanacetum parthenium)
Automated Alpha Amino Acid Synthesis

and

Selective Removal of Sensitizers from Natural Product Extracts: Feverfew (Tanacetum parthenium)

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Preamble

This thesis took over five years to actually do all the experiments (many times on evenings and weekends). It took over a year to write and edit. In the end, these past few years have resulted in the absorption of a lot of chemistry, the engagement to my wife-to-be Crystal, and a slew of students learning from me (both at the university and at The Academy).

It is said that in order to obtain a Ph.D., one needs to contribute to the field in which one studies. I have learned a lot of chemistry, and there’s some really neat stuff in here. It is my naïve hope that someone can learn from this work.

There were many chemistry people who I would like to thank: James Jaquith, Matt Lalonde, Chris Vanderwal, Jay Cadieux, and of course Tony Durst.

I dedicate this thesis to my grandfather. Polska Wolna, Wolna Polska.

Karol Gajewski

Ottawa, Ontario, Canada

26 April 2004
Abstract: Part 1

In an effort to synthesize α-amino acids via automated methods, the DKR reaction had to be adapted to work on a polymeric support. (R)-pantolactone was derivatized so that it could be incorporated into a polymer. The new derivative was also evaluated in some DKR reactions to make sure none of the efficacy was lost.

The thesis describes the conversion of (R)-pantolactone into a number of N-aryl substituted γ-lactams. Enantiomerically pure (R)-3-hydroxy-1-(4-methoxyphenyl)-4,4-dimethylpyrrolidin-2-one (19) was obtained via a seven step sequence in an overall yield of 27%. Racemic versions of several of these compounds (most notably the para methoxy 19 and unsubstituted 26) were produced in a one pot procedure. Compound 19 was acylated with several different α-bromo acids and evaluated as a chiral auxiliary in DKR reactions with a number of primary and secondary amines. The diastereomer ratios obtained were comparable or better than those observed in similar reactions when (R)-pantolactone was used as the auxiliary.

The compound 26 was transformed via a series of reactions into 70 for polymerization using Grubbs ROMP approach. The polymer (75) obtained had molecular weights of 7000, 10,000 and 35,000 depending on the catalyst loading; with the latter showing a PDI of 1.09. These polymers were soluble in chloroform and thus easy to characterize by NMR. Removal of the TBDMS group afforded a highly insoluble polymer that proved difficult to acylate with α-bromoacids that were required to attempt the DKR reaction on a polymer supported chiral auxiliary. A modified version of the polymer 75 may be necessary to complete the original goal of this thesis.
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Part 2

Selective Removal of Sensitizers from Natural Product Extracts:
Feverfew (Tanacetum parthenium)
Abstract

Feverfew is a recognized herbal medicine that shows effectiveness as a prophylactic in the treatment of migraines. The question of whether α-methylene γ-lactone sesquiterpene, parthenolide 2.1, is a key active ingredient, or simply the cause of allergic reactions suffered by a significant number of users requires that parthenolide be selectively removed from the mixture of compounds that are present in the feverfew extracts. The second part of the thesis describes the almost complete removal of parthenolide from feverfew extracts using a polymer supported sulfinate reagent developed for this purpose. The effective removal of only parthenolide, as evidenced by HPLC traces, is described.
Part 2: Selective Removal of Sensitizers from Natural Product Extracts:

Feverfew (Tanacetum parthenium)

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4.0 Feverfew Background

Feverfew is a plant, *Tanacetum parthenium* (L) (*synonym: Chrysanthemum parthenium* (B)) (*family Asteraceae or Compositae*), whose medicinal properties of pain relief have been cited at least as far back as the 16th century\(^1\). Indeed, there is mention of feverfew as far back\(^2\) as the 10th century as “feferfuige”. While the folk medicine is mostly used for the prophylactic treatment of migraines\(^3\), the proof of its clinical efficacy is still under development (more on the clinical trials below.) One of the problems with folk remedies is that because of the lack of a formal clinical trial system, the exact modes of action, as well as the active ingredients are often still not fully accepted. What follows is a roadmap of the pertinent literature, which will demonstrate the importance of carrying out this project.

One of the key difficulties with the use of a plant is determining which parts of the plant are needed, in what quantity, and in some cases which subspecies may also be used. Due to the varying weather and soil conditions around the world, a given plant species may not be able to grow everywhere that it is needed. Feverfew grows in Europe, North Africa, China, Japan, and parts of North America as well as in Australia. In fact, due to the potential for benefit for the public good, both Canada and the US have government or university initiatives to investigate the feasibility of feverfew as a crop and its general hardiness. In Canada, this work was undertaken by the Alberta Agriculture Research Farm in Fairview, Alberta. The research\(^4\) showed overall good hardiness and high yield. In the United States, the work\(^5\) was carried out as part of the
Chapter 1  Dynamic Kinetic Resolution and Alpha Amino Acids

1.0  α-Amino Acids

Alpha amino acids are known to be part of the building blocks of life since they are the key structural components of peptide chains that make up proteins. Nature uses only twenty α-amino acids to synthesize the vast array of proteins crucial to the functioning of most life forms. In addition to these twenty, almost another one thousand naturally occurring α-amino acids have been identified (these are also known as nonprotein amino acids and result from modification of the existing 20 amino acids.) These rare ones only occur in a variety of other biologically active compounds, such as hemisteralin (isolated from the sponge Siphonochalina sp as well as from Auletta sp), alliin (constituent of garlic), and L-DOPS (L-threo-3-(3,4-dihydroxyphenyl)serine, a drug used for the treatment of Parkinson’s disease).
Given the diversity of naturally occurring amino acids, it is desirable to be able to
synthesize not only the ones that do occur in nature, but also a wider variety of amino
acids, with even greater flexibility in terms of structure and chirality. To that end, it is
necessary to be able to generate not only the $\alpha$-amino acid functional group in a variety
of substrates but also the appropriate chirality in a controlled manner.

Other biologically active molecules also bear the $\alpha$-amino acid (or ester) moiety,
and the ability to introduce such a functional group would allow for the synthesis of
analogs, ones with more precisely tuned effects. All the amino acids used to make
proteins in the human body have the same (S) chirality at the amino-bearing carbon.

What effect does that have upon these biologically active molecules? The underlying
importance of chirality is emphasized by thalidomide:

![Thalidomide](image)

The chirality at the $\alpha$-amino moiety in thalidomide is the deciding factor between
the molecule being a morning sickness drug and a tetratogen$^1$. This disparity between the

\[ \text{Figure 1: Examples of natural products that contain rare amino acids} \]

\[ \text{Figure 2: Thalidomide} \]
modes of activity between enantiomers of a given molecule also occurs with other biologically active compounds:

- ketoprofen’s two enantiomers are both active. One has anti-inflammatory activity, and the other prevents bone deterioration in teeth
- ibuprofen’s two enantiomers only differ in the speed of their effectiveness: 12 minutes versus 38 minutes for their anti-inflammatory activity

1.1 On the Construction of α Amino Acids

The α-amino acid functional group can be created in a number of different ways, given that it’s made up of its two constituents: an amino group and a carboxylic acid group. When considering the assembly of this combined functionality, a choice has to be made with respect to sequence in which bonds are to be made and how they will be attached.

An efficient synthesis of amino acids which creates a number of bonds in one pot is the Ugi reaction. The synthetic usefulness of the Ugi reaction is that it is able to create a peptide bond, as well as introduce a chiral centre (marked with a star in the diagram below)
However, the Ugi reaction does not tolerate a large variety of functional groups on the substrates due to the presence of a basic and an acidic component. Moreover, it also suffers from characteristically low yields. This is not a reaction that allows for maximum flexibility.

The development of other approaches to α-amino acids are driven by the necessity for greater diversity and to further improve both yields as well as enantioselectivities.

The more reliable methods for the synthesis of α-amino acids require a different approach, as summarized in the figure below.
a) alkylation route
b) amination route (this work)
c) carboxylation route
d) hydrogenation

Figure 4: Amino Acid Disconnections
1.2 General Approaches to Enantiomerically Pure \( \alpha \)-Amino Acids

Within the wide scope of organic synthesis, the construction of enantiomerically pure \( \alpha \)-amino acids has been studied since the earliest days of chemistry. Not surprisingly, more efficient and more elaborate methods have been devised as our knowledge of chemistry continues to grow.

The general approaches are as follows:

- **Classical Resolution.** The separation of a racemic compound (or one with a low enantiomeric enrichment) into its two enantiomeric constituents.

- **Enzymatic Resolution.** A preferential reaction between one enantiomer of a substrate and an enzyme. The other enantiomer is left largely unreacted.

- **Catalytic Hydrogenation.** The use of an organometallic species that catalytically delivers hydrogen gas upon a prochiral substrate to generate a chiral centre.

- **Chiral Auxiliaries.** This is a very large area of research, comprising of chiral auxiliaries that are attached via the carboxylic acid moiety (as an amide, for instance the work of Prof. Dave Evans), attached via the nitrogen (as in the many examples of the Strecker synthesis), or elsewhere in the starting material (cyclic derivatives, *et al*). The point is the same: derivatization of the substrate with small chiral molecules attached in hopes of inducing chirality elsewhere in the molecule.

- **Dynamic Kinetic Resolution.** The application of the Curtin-Hammett Principle by generating fast and slow reacting diastereomers which can
interconvert under the reaction conditions. In ideal cases, this leads to the potential of converting a diastereomeric mixture into an enantiomerically pure compound in 100% yield.

1.2.1 Classical Resolution

The basic for classical resolution is that upon crystallization, enantiomers will preferentially crystallize with enantiomers of like chirality. A triage allows for the isolation of the enantiomer of interest. This methodology is the least efficient, since by definition it is limited to a 50% yield due to the racemic mixture that one starts with. An early account\(^4\) describes the process, which is tedious at best and has been superceded by the other methods described below. The key to this is the formation of conglomerates\(^5\), which occur for some of the common amino acids and their simple derivatives, such as histidine hydrochloride. However, others are not as cooperative: alanine, leucine and tryptophan crystallize as racemic compounds.

Derivatization by formation of the appropriate salt is still commonplace, since it allows for a last stage purification in pharmaceutical preparations. As with the histidine example, above, the choice of salt allows for enantiomeric crystallization, so a compound can be pure not only with respect to byproducts but also optical purity.

While not strictly considered classical resolution, it is possible to use a second optically pure compound to help preferentially crystallize out one enantiomer. Natural products are often used, since they can be obtained in optically pure form. The 12\(^{th}\) Edition Merck Index\(^6\) lists one of the uses of brucine in analytical chemistry for
separating racemic mixtures. Brucine is an alkaloid with a trialkyl-substituted nitrogen atom that allows for the formation of an ion pair with a sufficiently acidic centre. The basis for this kind of resolution is a “match – match” or “match – mismatch” system. The chiral nature of brucine would either allow it form a salt (match – match) and crystallize out of solution, or form a salt (match – mismatch) that stays in solution. In the case of compounds that have basic centers, for example, amines, one can use a chiral acid such as tartaric or camphoric acid in the same manner. While not as popular as the other methods, this method is still used when the others fail. One very good example is the large scale manufacture of Ibuprofen. The commercial synthesis of this important anti-inflammatory drug still involves a classical resolution. The reason for the resolution is that it is an inexpensive procedure since the resolving agent can be recycled, and racemization of the leftover material can be achieved by refluxing in a basic medium. While it is true that the maximum yield for a single step is only 50%, successive iterations allow for higher yields. After the third crop is isolated, the maximum yield is 87.5%, and the rest can be saved for the next big batch.

1.2.2 Enzymatic Resolution

This methodology is based upon differences of rates of reaction of enzymes with the two enantiomers of a chiral organic substrate. In the case of enzymatic resolution via acetate hydrolysis one of the enantiomers of a racemic mixture of acetates is hydrolyzed preferentially by an enzyme. In this case, the type of enzyme would be a lipase. Interestingly enough, a lipase is also used to preferentially acylate one of the enantiomeric hydroxyl groups of a racemic mixture of alcohols. The active site in the
enzyme will determine the extent of enantiodifferentiation. Ideally, at 50% conversion, the difference in reactivities of the two enantiomers will be large enough so that only one enantiomer has been converted and the other remains as the free hydroxyl in solution. Separation via flash chromatography yields one enantiomer as the alcohol and the other enantiomer as the acetate. Much like classical resolution, this also suffers from a maximum yield of 50%, unless the process is repeated (in this case, after a suitable racemization step). For example, let us consider a racemic mixture of acetates:

![Chemical diagram showing enantiodifferentiation](image)

**Figure 5**: Enzyme catalyzed acylation

It should be noted that the chiral centre need not rest in the alcohol. A specific example\(^8\) from the Department of Biochemistry of the University of Ottawa shows that this method can also be applied to the resolution of racemic acids via hydrolysis of their esters.

\[ \text{H-Lys-OEt} \xrightarrow{\text{trypsin}} (\text{L}) \text{H-Lys-OH} \]
\[ (\text{D}) \text{H-Lys-OEt} \]

\[ \text{H-Arg-OEt} \xrightarrow{\text{trypsin}} (\text{L}) \text{H-Arg-OH} \]
\[ (\text{D}) \text{H-Arg-OEt} \]
The interesting conclusion from this study was that the enzyme was not as selective with respect to the free amino acids as compared to N-acetyl or N-benzoyl derivatives, but the ratio of the rate constants for the two enantiomers is still quite good (108 for lysine and 632 for arginine). Finally, the major drawback here is that there is a lack of generality. For instance, it is not possible to predict how well the enzyme would perform on a new substrate (i.e. which enantiomer will be hydrolyzed) if it will work at all.

The 50% of the undesired material, after suitable racemization, can then be resubjected to the reaction conditions, and after isolation, yield a total of 75% of the desired product. After another iteration, the yield increases to 87.5% and so on. However, this is misleading, since the intermediate steps, by virtue of the fact that there are transfers involved, will likely lead to a loss of product. Moreover, the “suitable racemization” must be a relatively innocuous process that does not have any other products or side reactions.

However, other kinds\(^9\) of enzymatic resolutions are possible: dehydrogenases (such as baker’s yeast) that convert 2-oxo acids to the corresponding 2-hydroxy acids, and oxynitrilases which convert ketones and aldehydes to 2-hydroxy acids (ketones yield tertiary alcohols, and aldehydes yield secondary alcohols.) Here the yield can be quantitative since a chiral center is created from an achiral precursor.

Enzymes have been studied for a long time, and in a select few cases, it has been possible to couple two enzymatic systems in order to obtain more than 50% yield of the desired enantiomer. Lipases, as mentioned above, are used to hydrolyze or acylate alcohols. This does not have a built-in racemization process, but in the case of enzymes
that participate in redox reactions, this is possible. The enzymes that do this are called oxidoreductases, and the key to their utility is the generation of a stereogenic centre. Baker’s yeast, as well as dehydrogenases are able\textsuperscript{10} to generate chiral alcohols from precursor ketones. Their activity depends heavily on the functionality present in the substrate, as well as the steric environment of the prochiral center.

A far more intriguing use of enzymes has been to apply them to the Dynamic Kinetic Resolution method in hopes of eliminating the 50\% maximum yield for the well known lipase enzymes. Since there is a difference in the reactivity of the substrates with respect to the enzyme, the proportion of products could be altered if the racemization could be done \textit{in situ} rather than after a workup. The product could therefore be optically pure if two conditions are satisfied: that the difference in reactivity between the two enantiomers with respect to the enzyme is large enough, and that the rate of racemization is much faster than the rate of reaction with the undesired enantiomer. However, since this approach more properly falls under the category of Dynamic Kinetic Resolution, it will not be covered here.

1.2.3 Catalytic Hydrogenation

Catalytic hydrogenation has been recognized by the Nobel committee in 2001. Half of the Prize was awarded for “work on chirally catalyzed hydrogenation reactions” and was shared between Ryoji Noyori and William S. Knowles. Their respective accounts of research\textsuperscript{11} show how it is possible to synthesize \(\alpha\)-amino acids by catalytic asymmetric hydrogenation of a suitable enamine. The Monsanto L-DOPA process is outlined below\textsuperscript{12}: 
Figure 6: The Monsanto process of making L-DOPA

The key step in this process is the reaction that generates the stereogenic centre. Due to the high reactivity of the catalytic complex, mole ratios were on the order of 20,000 : 1 of substrate to catalyst. The asymmetric hydrogenation was not perfect, however, and yielded the L-isomer in 88% enantiomeric excess. Classical resolution needed to be used in order to obtain optically pure L-isomer.

Whenever systems such as catalytic hydrogenation are cited, the erroneous “man-made catalyst” term is used, which implies that the chirality is created de novo, but this is not strictly true. The CAMP ligand (methylocyclohexyl-o-anisylphosphine), has a chiral centre that is ultimately derived from menthol\textsuperscript{13}.

The key reason why the Monsanto process works is that the enamine forms exclusively in the Z configuration. This underlines the particular nuance that this kind of reaction exhibits, that the alkene forms only that isomer, and that isomer is sufficiently reactive for the rhodium reducing agent. If the double bond in the reduction substrate (top right structure in figure 6) contained a second carboxylic acid moiety the enantioselectivity drops down to zero.
The key advantage of this reaction, within the scope of alpha amino acid synthesis, is its application to the hydrogenation of imines and enamines. As long as it is possible to stereoselectively create the appropriate C=C and C=N bonds, amino acids of high optical purity can be obtained.

While not an example that is directly related amino acid synthesis, but in contrast to the Monsanto process, imines derived from aryl ketones have been reduced\textsuperscript{14} in good to excellent yield with good to excellent enantioselectivity to yield 2-aryl amines. This example is shown here to show that the catalytic hydrogenation of imine systems is also as effective as the catalytic hydrogenation of the enamine systems.

![Figure 7: Simple catalytic hydrogenation of imines](image)

1.2.4 Chiral Auxiliaries

One of the more reliable ways of inducing chirality is to temporarily shield one side of a reactive centre so that only the other side is available for bond formation. The concept is simple: place a chiral centre as close as possible to the reaction centre, have a large bulky group present to shield one side, make sure it is orthogonal\textsuperscript{15} to the reaction conditions, and remove it after the reaction is done. Within the scope of the synthesis of $\alpha$-amino acids, the most obvious choice would be to make an ester or amide that can be easily removed after the chirality has been installed. Work done by the group of David
A. Evans at Harvard\textsuperscript{16} and John C. Vederas at the University of Alberta\textsuperscript{17} has established the use of oxazolidinones as chiral auxiliaries. The two most commonly used auxiliaries, which yield products of opposing stereochemistry are shown below; they are referred to by the natural products from which they derive their chirality.

\[
\begin{align*}
\text{(S)-Valinol} \\
\text{derived chiral auxiliary}
\end{align*}
\]

\[
\begin{align*}
\text{(1S, 2R)-Norephedine} \\
\text{derived chiral auxiliary}
\end{align*}
\]

Figure 8: Popular chiral auxiliaries for α-amino acid synthesis

The nitrogen in the chiral auxiliary above is acylated with the carboxylic acid that will become the amino acid, and the imide is treated with a lithium or sodium amide base. The chiral induction is based upon preferential formation of the (Z) enolate, concomitant with chelation of the carbonyls by the metal centre. The chiral centres present in the auxiliaries serve to position a group that effectively shields one side of the enolate, thereby preventing attack from that side.

\[
\begin{align*}
\text{1. Acylation} \\
\text{2. MNR}_2 \\
\text{(Z) enolate}
\end{align*}
\]

Figure 9: Use of the oxazolidinone chiral auxiliary

It should be noted that there is some flexibility with respect to the conditions, as many refinements have been published since the early 1980's. Instead of using an amide
base, dialkyl boron triflates have been used in conjunction with tertiary amine bases in order to generate the same (Z) enolate with the highest possible purity. Introduction of the amino functionality has been carried out directly by using di-tert-butyl azodicarboxylate (DBAD), or trisyl azide as the electrophile. Alternatively, NBS can be used, introducing a bromine, which is subsequently displaced by sodium azide or tetramethylguanidinium azide.

1.2.5 The Dynamic Kinetic Resolution Approach to α-Amino Acids

Dynamic Kinetic Resolution (DKR), is a concept that has received profound interest in the area of asymmetric synthesis\textsuperscript{18}. The idea that DKR is based on is the Curtin-Hammett Principle, and it would allow for the synthesis of (theoretically) a single diastereomer from a racemic starting material. This has the advantage over classical resolutions in that the maximum yield approaches quantitative in one operation instead of the 50% limit imposed by classical resolutions.

The Curtin-Hammett Principle\textsuperscript{19} states that for a reaction that has two possible routes\textsuperscript{20}, with two different activation energies, the ratio of the products will be determined by the difference in the activation energies. The DKR process builds on that idea, by using reaction conditions that interconvert the two diastereomers or enantiomers of a substrate much more rapidly than the rates of reaction giving rise to the products. Thus the faster reacting diastereomer will be generated from the remaining slower reacting diastereomer (see figure 24). For instance, given a reaction between an amine as a nucleophile and an α-bromo ester that can exist as a mixture of diastereomers, the
energetic profile of the reaction would be as follows (E₁ through E₆ are Gibbs free energy values, B, D and F are transition states):

![Energy profile diagram](image)

Figure 10: Energy profile for a DKR reaction

This idea that there can be an equilibration of two substrates in solution that will react at different rates has been exploited by a number of different groups. The simplest example of this was observed in 1858 by Louis Pasteur, who noticed a difference in solubility between the levorotary and dextrorotary enantiomers of tartrates in supersaturated solutions of a racemic mixture of the tartrate salts. Equilibration between the substrates has most often been exploited by interconverting the substrates via an intermediate D (see figure 10) by way of *in situ* racemization, complexation or a reversible addition. The intermediate may be a planar intermediate or contain the characteristics of inversion of a chiral centre. However, D needs to exist in order to
differentiate this process from a simple kinetic resolution. Some examples, adapted from Noyori’s review of DKR, are given below.

![Chemical structures](image)

Figure 11: DKR reactions involving in situ racemization

In the above examples, the formation of an enantiomERICALLY pure or highly enriched product involves rapid interconversion of the enantiomers of the substrate as compared to the rate of reaction to generate the product. In the first example, as well as in the second, there is a key tautomerization which allows for the interconversion of the enantiomers (see figure, below)

![Chemical structures](image)

Figure 12: Facile racemization of thiazolidene carboxylic acid

There are also other zwitterionic structures that could theoretically be invoked, but they are improbable. While not a formal keto-enol tautomerization, it is based on the
same principle. The chiral differentiation occurs at the enzyme, which has an active site that is three dimensional, and therefore will preferentially bind one of the two enantiomers, meaning that the enantiomer that binds better will react faster.

In the beta keto ester (see middle reaction in figure 11), there is a formal keto-enol tautomerization that equilibrates the populations of the two enantiomers, only one of which reacts preferentially with the metal centre (or enzyme, as the case may be.) The key to this reaction is that since there are two chiral centres that are generated, the formation of only one of four products is quite desirable from a synthetic point of view.

![Diagram of chiral β hydroxy ester formation](image)

Figure 13: DKR route to a chiral β hydroxy ester

Depending on the system used (metal mediated or enzymatic), the reaction can yield a specific compound (i.e. only I or only J), or simply the desired relative
stereochemistry (i.e. syn I/L vs anti J/K). From the figure above, it is more readily apparent that the facile tautomerization of the enantiomers of the starting material is key to the DKR process. Similarly to the previous example, a planar intermediate is key to allowing the interconversion between the two enantiomers.

The specifics behind the third example that was listed in Figure 11 will be covered later, since it follows a similar idea to the work previously done by Durst and Koh (see ref. 26). For sake of brevity, the rapid equilibration is achieved by having the bromide anion in solution which rapidly undergoes a nucleophilic attack on the α-bromo ester. One of the two enantiomers reacts faster than the other with the substrate.

DKR reactions need not involve strict bond breaking and bond reforming steps in the rapid equilibration process of the enantiomers (see figure below).

![Diagram of DKR reaction involving complexation](image)

Figure 14: A DKR reaction involving complexation

By use of the chirality in the naturally occurring sparteine, and an “umbrella inversion” of the anion at the carbon centre, the anion can be informally considered a chiral one, which allows one enatiomer to preferentially attack the electrophile. The obvious drawback here is that due to the sparteine, the synthesis is limited to generating only one enantiomer due to the lack of a sparteine of opposite chirality.
Strict conformational control need not be the only way in which the energies of the transition states can be differentiated. The following example uses polarized light to favour the formation of one product over another. The exact details on why one of the helical isomers is favoured over another is not explicitly mentioned, but a connection to the conjugated system is assumed.

\[ \text{Figure 15: DKR reaction involving reversible addition} \]

The intermediates and mechanism of isomer interconversion are shown below.

\[ \text{Figure 16: Interconversion of atropisomers via iodine radical addition} \]

The bold bond in the radical intermediate is the key to the whole scheme. Upon addition of an iodine radical (resulting from the homolytic bond cleavage of the iodine
when exposed to light), the double bond is broken and it is now possible to rotate around the C-C bond and interconvert the isomers. The right circularly polarized light provides the necessary means by which the two transition states leading to the different helical isomers are differentiated. The enantiomeric excess of one of the helical isomers that results upon elimination of the iodide radical is not as pronounced as in the other cases, but is a novel application of the DKR idea.

Recent papers have expanded on the DKR concept and applied it to the synthesis of axially chiral molecules (atropisomers). This particular application involves large aromatic systems, not unlike the one pictured in figure 15, but the synthesis of axially chiral compounds allows for not only natural product synthesis, but also chiral ligands for organometallics\textsuperscript{23} (see figure 17, below.) Therefore, the importance of the DKR reaction lies not only in generating chiral centers when making target molecules, but also making chiral molecules that will then generate other chiral centers.

Figure 17: A recent Application of DKR for Atropisomers
The *in situ* racemization seen in the earlier examples (figure 11, for instance) need not take place at a strictly acidic centre. Two of the more interesting examples are imine-enamine tautomerization\(^\text{24}\) as a route to chiral piperidines, and ruthenium-catalyzed alcohol isomerization combined with enzymatic kinetic resolution as a route to \(\delta\)-hydroxy esters\(^\text{25}\) (this is akin to Figure 13, but without the \(R_2\) substituent, and leads to two products, not four) which seems to be a battle between two groups: one in Sweden and one in Korea (see ref. 25).

![Figure 18: Kinetic resolution using a metal and an enzyme](image)

1.2.5.1 Previous Dynamic Kinetic Resolution work done in the Durst lab

An early communication by Durst and Koh\(^\text{26}\) indicated that a potentially viable route to \(\alpha\)-amino acids exists via quenching of an \(\alpha\)-halo ketene with an optically active alcohol. (see Figure 19) This approach allows for quite a bit of flexibility due to the fact that the starting material (an \(\alpha\)-bromo acid) can be readily generated from a carboxylic acid.\(^\text{27}\) Other groups\(^\text{28}\) found this to be a useful route to \(\alpha\)-amino-, \(\alpha\)-hydroxy- and \(\alpha\)-
thiocarboxylic acid derivatives by using other nucleophiles (amino, alkoxy, etc) in the reaction.

![Chemical structure (Figure 19: Published DKR Synthesis)](image)

The figure above does not tell the whole story, but first some background needs to be explained. The first step, where the alkylhaloketene reacts with the chiral alcohol, is based on Larsen and Corley’s work on arylmethylketenes. The key to the reaction was the planar ketene that would be attacked by the chiral alcohol. One of the benefits of using a compound of known chirality was that the chirality that would be generated was predictable: (R)-pantolactone would yield the (S) configuration preferentially over the (R) configuration. In the diagram above, the ketene is an alkyl halo ketene, but the reaction, both in terms of yield and diastereoselectivity works almost as well as the arylmethylketenes. The diastereoselectivities were not as impressive as the ones in Larsen and Corley’s work, but that was attributed to the smaller size of the halide as compared to the methyl group in the arylmethylketenes. In fact, if the R group in Figure 19, above, is large enough, the diastereoselectivity does increase to very acceptable levels (de’s ranged from 75 to over 95.)

This work was carried out in the Durst lab by Kevin Koh and Rob Ben, and the second step took place with predictable inversion of stereochemistry if sodium azide was used. A surprising result was obtained when the nucleophile benzylamine acted upon the doubly halogenated substrate in the figure below.
Figure 20: Genesis of DKR in the Durst lab

The starting material had the S configuration at the \( \alpha \)-carbon and a diastereomeric ratio (S,R) to (R,R) of 6:1. The product had a diastereomeric ratio of 5:1, but more importantly the major isomer also had the S configuration at the \( \alpha \)-carbon signifying retention of configuration at the reacting center. Since one is dealing with an \( S_n2 \) process, this result suggested a double inversion sequence. In order to make sure that this is what was happening, the same reaction was carried out with a 1:1 diastereomeric mixture. This gave a product with a better diastereomeric ratio of 7:1 in favour of the (S,R) isomer. The key here is the iodide. Once the reaction starts, iodide ions are liberated, which can then epimerize the alpha position in true DKR fashion. While bromide ions are also present and also epimerize the alpha position, the iodide accomplishes this task at a faster rate due to its greater nucleophilicity and leaving group ability.

This reaction was found to be relatively general and could be used to generate cyclic (five and six membered rings) as well as acyclic \( \alpha \)-amino esters. Moreover, the use of a quaternary ammonium iodide salt facilitated the racemization at a rate much faster than the rate of product formation.

Subsequent work by Rob Ben in his doctoral studies was aimed at improving the diastereomeric excess of the DKR reaction. The use of other chiral alcohols as chiral auxiliaries failed to improve the diastereomeric excess, the alcohols evaluated included:
(S)-methyl mandelate, (S)-methyl lactate, trans-2-phenyl-cyclohexanol, (R)-diacetone-glucose, as well as others depicted below:

![Chemical structures](image)

Figure 21: Other chiral auxiliaries evaluated by Rob Ben

Of the alcohols depicted above, none were better, and only the oxazolidinone matched (R)-pantolactone’s diastereoselectivity. The authors proposed that the conformation of the pantolactone ester of an α-bromo acid is strongly favoured as shown in figure 22.

![Chemical structures](image)

Figure 22: Conformations of pantolactone esters

A partial explanation of why the pantolactone was so good has to do with the carbonyl’s ability hydrogen bond with the amino nucleophile thereby helping to deliver the substrate from one (less hindered) side of the molecule over another. Based on the performance of the different auxiliaries and the solvent system used for the reaction, it is thought\textsuperscript{32} that hydrogen bonding between the nucleophile and the carbonyl serves to selectively deliver the nucleophile on one side of the substrate over another. To that end, a one-time synthesis of a lactam chiral auxiliary (see next page) yielded a slightly better
result than the lactone. The reasoning behind this is the increased basicity of the carbonyl oxygen in a lactam over that of one in a lactone.

Figure 23: One time lactam DKR experiment

Key issues that remained unresolved were that there was still a possibility of competing elimination in substrates where there is a β-hydrogen and the nucleophile is quite basic, additionally there is the matter of low diastereoselectivity in cases where the nucleophile is sufficiently small to be unaffected by the chiral auxiliary, or too basic to allow for effective hydrogen bonding with the carbonyl oxygen of the chiral auxiliary (see above).

The issue of size-dependent diastereoselectivity was solved with a slight modification to the nitrogen nucleophile. In the case of the generation of simple amino
esters, the size of the nucleophile could be increased temporarily by using benzylamine, dibenzylamine or diphenylmethanamine. Increasing the size of the nucleophile improves the diastereoselectivity. In fact, dibenzylamine yielded a single diastereomer when used with α-bromophenylacetic acid as the DKR partner\(^{33}\), which is a very encouraging result since the benzyl groups can be removed via palladium reduction conditions. However, the increased size of the nucleophile does lead to higher basicity, which may contribute to the formation of the elimination product in the case of substrates with β-hydrogens. Another alternative to larger nucleophiles is the use of diphenylmethanamine, which could also be removed with reducing conditions as before, but has the advantage in that it is a monosubstituted amine, and therefore would not generate as much of the elimination product as the dibenzylamine due to its lower basicity.

Chirality in the nucleophile does not affect the outcome of the DKR reaction. Methylbenzylamines of opposing chirality were used with equal efficacy, which discounts any possibility of a match/mismatch between the substrates.

This background information is sufficient to allow for the design of an automated system where α-amino acids of novel structure and high optical purity could be manufactured. The general process is outlined below.
The resin would start out as a chiral-auxiliary terminated polymer.

The resin would be esterified with an $\alpha$-halo acid to yield an $\alpha$-haloester.

Under DKR conditions, the $\alpha$-halo ester is converted to an $\alpha$-amino ester. If the amine attacks the ester carbonyl carbon, then the amide is cleaved from the resin (thereby retaining product purity).

Once the ester linkage is hydrolyzed, the $\alpha$-amino acid is isolated, allowing the resin to be reused. The key feature is that this does not require any further purification.

Table 1: The automated amino acid synthesizer using the DKR process

The process outlined above could be automated, and with a parallel synthesizer could be used to manufacture a combinatorial library where the first point of diversity would be the R group on the acid, and additional points of diversity on the nitrogen (R’ and R’’). In the case of amino acids that require the highest possible optical purity, the process could be modified to include a reduction step. Ben reported during his doctoral studies that the use of a dibenzylamine nucleophile gave rise to a single diastereomer. Treatment of the product with palladium on carbon in a methanol / acetic acid solution would be effective in removing the benzyl protecting group. It may only be a matter of semantics, but the 1993 Tetrahedron Letters paper (see last paper in ref. 26) describes a reduction of the reduced N-benzyl amino alcohol, not the N-benzyl amino ester. Given the breadth of background in the synthetic work of amino acids, especially on solid
supports, the extension of this methodology to a polymer support should be trivial\textsuperscript{34}. Specifically, removal of the benzyl protecting group prior to the removal of the chiral auxiliary is possible. However, due to increased product stability in protected form, it is usually more desirable to retain the protecting group. One key additional benefit of keeping the substrate attached to the polymer is that it is possible to elaborate the structure by further synthetic manipulation. In the context of combinatorial chemistry, this means adding on another point of diversity (i.e. cross-coupling in the case of aryl groups with appropriate functionality). In the strict context of \( \alpha \)-amino acid synthesis, this could mean removing the benzyl protecting group and following that with derivatization by attaching another amino acid, or different alkyl group.

1.2.5.2 Kinetic Considerations for DKR reactions

It is important to take into consideration the kinetics that are at the heart of the DKR process. By having an adequate understanding, it will be possible to appreciate why certain reactions are going to work, and why other reactions are best suited to other approaches. In order to facilitate the explanation of the kinetics behind the DKR process, the following figures are presented:
Figure 24: An example of a DKR reactions and associated rate constants

The anomalous compound labeling in the figure above is to allow the reader to discern between the product and substrate; it also corresponds to figure 10. The rate constants (k₁ through k₈) in figure 24 are related to the energies in figure 10 via the following set of equations:

\[
E_1 = RT \ln k_7 \\
E_2 = RT \ln k_8 \\
e^{\frac{E_2}{RT}} - e^{\frac{E_1}{RT}} = k_3
\]

Applying the Curtin-Hammett principle, the product ratio of A and G is decided by the relative magnitudes of E₁ and E₂. The key to this reaction is the racemization of the substrate rapidly enough such that there is enough of the faster reacting substrate for the nucleophile to react with. The racemization is most easily achieved by addition of an iodide tertiary ammonium salt (in effect, lowering E₃ and E₄ in figure 10). The choice of an iodide tertiary ammonium salt is twofold: it is soluble in tetrahydrofuran (the solvent of choice for the DKR reaction) and the iodide counter ion is a very good nucleophile and a very good leaving group. The iodide should be able to rapidly react with the α-bromo ester to yield the α-ido ester in situ. Since the iodide is a better leaving group
than bromide, the α-iodo ester should be faster reacting than the corresponding α-bromo ester in the racemization reaction. In effect, this means that there are four potential substrates that could react with the nucleophile, giving rise to two products.

Using figure 24, the concept can be more easily explained in terms of relative rate constants. The constants \( k_1 \) and \( k_2 \) are relative rate constants, taking into account the forward as well as the backward reaction. In order for the dynamic kinetic resolution to work, the magnitude of \( k_1 \) must necessarily be larger than either \( k_5 \) or \( k_6 \) or both. Similarly, the magnitude of \( k_2 \) must necessarily be larger than either \( k_7 \) or \( k_8 \), or both. It is not a necessary condition for the rate constants \( k_1, k_5 \) and \( k_6 \) to be comparable to \( k_2, k_7 \) and \( k_8 \) as long as \( k_4 \) and/or \( k_3 \) is larger than \( k_5 \) and \( k_6 \) if \( k_1 \) is smaller than \( k_2 \).

The nucleophilicity of the iodide ion over the bromide ion is solvent dependent\(^{36}\) but the reactivity of alkyl iodides versus alkyl bromides is more dramatic. In effect, a given alkyl bromide is slower to react with any nucleophile when compared to the corresponding alkyl iodide, which means that the alkyl bromide is slower to racemize than the alkyl iodide but also slower to react with a nitrogen nucleophile. This means that \( k_2 \) (see figure 24) will be larger than \( k_1 \), and \( k_3 \) and \( k_4 \) will be larger than \( k_1 \). Additionally, \( k_3 \) and \( k_4 \) will be larger than \( k_5 \) and \( k_6 \) as long as the nucleophile used is less nucleophilic than the iodide. Figure 24, then, becomes more simplified:
Compounds 1 and 2 are still present in solution and will still give rise to products A and G, but not of significance if the nucleophile is less nucleophilic than iodide. Physically, this is interpreted as $k_8$ being larger than $k_5$ (or $k_7$ being greater than $k_6$).

A diastereomeric excess of one compound (for instance A) requires that necessarily ($k_7 > k_8$) and ($k_2 > k_8$). The key point here is that as long as $k_3$ and $k_4$ are greater than $k_5$, then $k_5$ can be ignored. Interestingly, $k_1$ still plays a minor role in that instead of both $k_3$ and $k_4$ being greater than $k_5$, only one of them needs to be significantly greater than $k_5$ if $k_1$ is greater than $k_5$.

A possible route for a given diastereomer is as follows: compound 1 is in solution and has a choice of reacting with the nucleophile to yield G (via $k_5$), reacting with iodide to yield 3 (via $k_4$), or reacting with bromide to yield 2 (via $k_1$). Necessarily, $k_4$ is greater than $k_1$ due to the greater nucleophilicity of iodide (see above), which means that there is a greater likelihood of the formation of 3 over 2. Similarly, if the nucleophile is less nucleophilic than iodide, then $k_4$ will be greater than $k_5$, giving rise to a greater likelihood of the formation of 3 over G. With 3, it is only possible to form 4 (via $k_2$) or A (via $k_7$). If $k_2$ is relatively large, then the product distribution between products G and A will be determined solely on the ratio of $k_7$ and $k_8$. This, in turn, is dictated by the activation energies for those two processes.
The DKR reaction relies on the use of a chiral auxiliary, which (in the earlier published materials) is discarded after the reaction. Industrial, as well as academic perspectives\textsuperscript{37} frown upon “disposable” atoms, citing inefficiency of the synthetic design leading to environmental concerns. There are drives to render reactions to a catalytic nature, as well as a minimal use of auxiliary molecules. However, classical peptide syntheses usually rely on solid-supported reactions\textsuperscript{38}, which are necessarily two phase systems and suffer from kinetic drawbacks. An acceptable medium would be to be able to synthesize α-amino acids, and eventually even polypeptides, by use of the chiral auxiliary supported on a soluble resin (see § 3.1). Using this approach, the molecule which is normally disposed of can be used for further reactions. This has the added benefit of becoming a moot point with continued recycling of the polymer, since the auxiliary may be continued to be used as long as the polymer does not degrade. As opposed to classical solid supports, solution phase polymers do not have to have the kind of mechanical stability that are required of their solid phase kin.

1.3 Industrial Perspectives

The combinatorial chemistry industry\textsuperscript{39} is defined by companies who make libraries of compounds. This is different than more traditional synthetic chemistry, which is target oriented and consists of synthetic steps that either build upon a skeleton or have protection and deprotection steps. Combinatorial chemistry is focused on diversity oriented synthesis, where the synthetic steps are concerned with introducing a variety of
substituents, as well as the common protection and deprotection steps. Automated processes facilitate this by using a pool of reagents for the introduction of substituents, usually guided by intuition or QSAR\textsuperscript{40}.

The synthesis of $\alpha$-amino acids on solid support is rare enough that it has not appeared in the literature, presumably owing to the commercial nature of this kind of undertaking. There are numerous conference proceedings, which can be found by searching for “automated amino acid synthesis” on an academic search engine such as SciFinder\textsuperscript{TM}\textsuperscript{41}, but a distinct lack of papers is apparent. The few papers that do appear, are from companies. The Chiron Corporation, a publically traded company, has published some papers about their automated synthesizer\textsuperscript{42}.

The flip side of this kind of chemistry would be the means by which the process is automated. To that end, there are numerous companies which market automated synthesizers. One such company\textsuperscript{43}, Argonaut Technologies is representative of this niche market. They manufacture three different automated synthesizers, in their product lines: The Nautilus\textsuperscript{TM}, Trident\textsuperscript{TM}, and Advantage\textsuperscript{TM}. All of them are billed as synthesizers, and their application notes are the best compromise between proprietary information of the companies who use them and the ability of the machines. In all cases, it is possible to use a variety of temperatures and conditions, but formal synthesis of amino acids via the disconnection used in this thesis is markedly absent. Indeed, in reviewing all the application notes of all the systems listed in reference 43, the only amino acid synthesis that is advertised is coupling of amino acid residues.

Given the flexibility of these machines to accept and deal with both solid and solution phase chemistry, Dynamic Kinetic Resolution is an attractive possibility,
especially when one considers the unique advantage of the approach described in section §3.2. Specifically, the only applications involving solid supports where the substrate is immobilized, involve the "traditional" Rink and Merrifield resins. No applications involving ROMP spheres or ROMP gels are known (resins are discussed in chapter 3).
Chapter 2  How to Design a Polymer-Supported Chiral Auxiliary?

Immobilizing the chiral auxiliary on a solid support can be achieved in a number of different ways. The preferred method would be to build upon the idea of the (R)-pantolactone chiral auxiliary and use a modified version that would be as, or more efficient in terms of generating the appropriate diastereomer, and that would also have a means by which it could be attached to a solid support. From a structural perspective, the region where the attachment would be least obtrusive to the DKR reaction would be at the ester oxygen. Changing the oxygen to a different atom with a higher valence would allow for the addition of other substituents that could then be attached to a polymer.

![Chemical Structure](image)

Figure 26: Focus of this phase of the project

2.1 Stereospecific approaches to the synthesis of the chiral auxiliary

(R)-pantolactone is an inexpensive source of chirality for the synthesis of the lactam. The general concept would be to convert the pantolactone to a solid-supported
lactam (the concept depicted in figure 26, above.) This led to the following general scheme:

Scheme 1: General approach to a chiral pantolactam

The key considerations in this scheme are that the integrity of the chiral centre is preserved. This prevents the use of any excessively basic conditions. Luckily, the basicity of neutral amines is insufficient to deprotonate a proton that is geminal with an oxygen and alpha to an ester. It does prevent, however, the use of anionic (i.e. amide salts) reagents. This means that introduction of the nitrogen (replacing the oxygen in pantolactone) must be done with a neutral amine.

2.1.1 THP ethers and neopentyl alcohols

Scheme 2: THP approach
The commercially available (R)-pantolactone was protected as a tetrahydropyran ether and the lactam ring was opened with benzylamine. The resulting alcohol 9a resisted mesylation and tosylation. Based on NMR spectra and careful flash chromatography, it was deduced that the neopentyl alcohol was slower to react with the sulfonyl chlorides than the amide nitrogen. This was supported by the isolation of N-tosyl-benzylamine from one of the reaction runs. Presumably, the following sequence applies:

![Chemical Structures](image)

Figure 27: Proposal of tosylation side reaction

The reason that the protected pantolactone is not isolated is due to the deprotection by the HCl present (from the tosyl chloride). (R)-Pantolactone is quite water soluble and therefore washed away in an aqueous layer upon workup.
This route to the desired lactam was still salvageable if it were possible to oxidize the alcohol 9 to the aldehyde 14 and close the ring via reductive amination followed by competitive nucleophilic attack (in the figure below, the nitrogen with the $R_3$ substituent would attack the carbonyl carbon, and the subsequent ejection of the $R_1$, $R_2$ substituted amine would yield the lactam).

\[
\begin{align*}
R_1 & \quad N \quad R_2 \\
\text{RO} & \quad \text{O} & \quad \text{RH} \\
9a & \quad \text{R = THP} & \quad 14 & \quad 15 & \quad 11 \nonumber
\end{align*}
\]

Figure 28: Steps required to salvage the “ring opened” route

However, oxidation of 9 (with a THP or MOM protecting group) resulted in complex mixtures that could not be effectively separated into its components by flash chromatography. The only identifiable product that was isolated after several runs was a succinimide (see figure 29). The formation of this unusual compound was puzzling, since it was formed even when stoichiometric oxidation conditions were used (i.e. PCC, PDC, Swern).

\[
\begin{align*}
\text{MOMO} & \quad \text{N} \quad \text{Ph} & \quad \text{OH} & \quad [O] & \quad \text{MOMO} & \quad \text{N} \quad \text{Ph} & \quad \text{OH} & \quad \text{MOMO} & \quad \text{N} \quad \text{Ph} & \quad \text{O} \\
9 & \quad 16 & \quad 17 \nonumber
\end{align*}
\]

Figure 29: Unusual oxidation product
While it's not entirely clear how two equivalents of hydrogen can be eliminated with only one equivalent of oxidizing agent, it is possible that the common amidol intermediate, structure 16 above, oxidizes rapidly in air. This would explain why the same product was obtained whether Swern conditions were used or chromate oxidizing agents. No starting alcohol 9 was recovered in these oxidation reactions.

The structure 17 is supported by NMR and MS. Deprotection and subsequent use (see below) also support this conclusion. The key feature in the $^1$H NMR (see figure below) is the lack of the CH$_2$ AB quartet that should appear upon ring closure. Not only is this AB quartet missing, but the two protons which correspond to that methylene group are not found in the spectrum.

![MOMO](image)

Figure 30: Compound 17. Succinimide derivative of chiral auxiliary
The peaks are assigned as follows: multiplet at 7.3-7.2 ppm is from the aryl group, the two doublets (one at 5 ppm, the other at 4.7 ppm) are from the methylene group of the MOM protecting group, 4.6 ppm is the methylene group from the benzylic group, 4.2 ppm is the methine hydrogen geminal to the oxygen in the ring, 3.4 ppm is the methyl group of the MOM protecting group, and the two diastereomeric geminal methyl groups are at 1.3 and 1.1 ppm. These assignments were based on analogous compounds made throughout this work (i.e. for the methylene peaks due to the MOM group, see the $^1$H NMR spectrum of compound 18, figure 36).

This compound deserved scrutiny in terms of its effectiveness as a potential chiral auxiliary. It was used for a simple DKR reaction, but the resulting amino ester was not stable on silica and the NMR spectrum was not suitable for determination of the diastereomeric excess. Thus a new approach needed to be taken.

One of the side products from the oxidation of 9a was a diol resulting from the loss of the THP protecting group, but a more robust protecting group (the MOM protected derivative 9b) was not the solution we were looking for. A number of oxidations were attempted on 9b, once again yielding complex mixtures of compounds. The product mixture resembled somewhat the products obtained from the oxidation of the THP ethers. This indicated that the problem was not with the protecting group, but elsewhere in the molecule. Under the premise that the secondary amide was responsible for the problems encountered in the oxidation, the tertiary amide 9c was prepared.
The preparation of compound 9c proved to be the important break, since it allowed not only the preparation of the aldehyde 14, but also its purification. The spectrum of 9c is of note. The –CH$_2$– responsible for the AB system in the pantolactone spectrum (see § 2.1.2), now appears as a set of two doublets (approximately 3.2 ppm and 3.8 ppm), whereas the geminal dimethyl groups have almost coalesced into a single peak below 1 ppm.
Figure 32: $^1$H NMR spectrum of compound $9c$

A simple generalization can be made for this kind of system. In ring opened products, the geminal dimethyl groups typically appear to be almost a singlet and have a
shift below 1 ppm, whereas in closed ring compounds the shift for these methyls is above 1 ppm and gives two distinct peaks.

Scheme 3: Reductive amination approach

Below is shown the spectrum of aldehyde 14. The diastereotopic geminal dimethyl groups are slightly distinct (0.02 ppm difference), and the aldehyde peak is clearly visible at 9.8 ppm. This spectrum represents a highly simplified version of the system, since the AB system is not present. The two singlets due to the MOM group and the two multiplets for the pyrrolidine ring are found a $\delta = 4.59$ and 4.29 ppm. A small amount of impurity as evidenced by the additional peaks, especially at $\delta = 9.75$ ppm was present. This was carried through the subsequent steps without interference and was presumably removed during flash chromatography.
The most effective amine for the reductive amination step in scheme 3 (above) turned out to be para-methoxyaniline, presumably due to the increased stability of the imine. The reductive amination could be achieved most simply by combining the necessary aniline, the aldehyde and ethanol in order to facilitate the formation of the imine, and stirring this mixture with 10% palladium on carbon in an atmosphere of hydrogen gas.

Immediately following is the spectrum of the imine. Except for the additional aromatic peaks (and the new methoxy peak), the spectrum is relatively unchanged from that of the aldehyde, which supports the proposed product. The imine hydrogen is found at $\delta = 8$ ppm. The $-\text{CH}_2-$ of the MOM protecting group shows slight splitting, indicating that these two diastereotropic hydrogens are in somewhat different magnetic environments.
It should be pointed out that the imine spectrum was obtained on a crude product, and no attempt was made to purify the imine. This is common practice when the stability of the imine in unknown, and indeed the imine does undergo fairly rapid hydrolysis in the course of a chromatographic separation.

Figure 34: $^1$H NMR spectrum of the imine

The cyclization of 15 was achieved after several attempts at finding the required conditions. Simple heating of the amine with a substoichiometric (0.9 equiv) amount of acetic acid was found to yield the best results. This was a tricky set of conditions because a stoichiometric amount would simply yield the salt, and a catalytic amount would be too sluggish. The effectiveness of this method was explained thus: the acetic acid serves to protonate the pyrrolidine during the formation of the tetrahedral intermediate but is removed in a salt form by virtue of the increased basicity of pyrrolidine as compared to
aniline, which is why with substoichiometric quantities of acetic acid, the formation of the salt between the aniline and the acetic acid is negligible, thereby allowing the reaction to proceed. In order to discuss the cyclization in any depth, and be able to convincingly show that indeed it took place, the spectrum of the amine (15) as well as the proposed cyclized product are included in the next two pages. The two things to note between the spectra of the imine (previous page) versus that of the amine (following page) is that the AB system next to the geminal dimethyl group is once again visible (around 3 ppm) and the shifts of the geminal dimethyl group itself are again near 1 ppm.

There are a number of key features in the spectrum of compound 18 that are immediately obvious: the pyrrolidine ring is no longer present, the geminal dimethyl groups are now once again diastereotopic, the AB system next to the geminal dimethyl groups is showing a quartet (overlapping with the MOM group’s terminal –CH₃ group) and the –CH₂– of the MOM protecting group also shows up as an AB quartet.

These changes are consistent with a closed lactam ring (also supported by IR: the product has a peak in the IR at 1688 cm⁻¹ as expected for a 5-membered lactam, while the open chain amide has an IR band at 1635 cm⁻¹). The subtle change of a nitrogen for an oxygen has resulted in the AB system of the ring to shift from 3.9 ppm to 3.4 ppm. (the spectrum of pantolactone is included in § 2.1.2) Mass spectra (specifically HRMS) also support the formation of 18 (see Experimental Section for details).
Figure 35: $^1$H NMR spectrum of amine 15
Figure 36: $^1$H NMR spectrum of protected lactam 18
In terms of the cyclization, mineral acids were ineffective at converting the starting material to product. Finally, R. B. Woodward's protocol of using triflic acid in dichloromethane was used to deprotect the MOM ether according to literature precedent.

The stereospecific synthesis of the lactam 19 was accomplished in seven steps in 27-30% overall yield (varying yields according to the scale, which provided several grams of the chiral auxiliary). The individual steps were readily amenable to scaleup, which allowed for the evaluation of the lactam as a chiral auxiliary as compared to the lactone parent compound. Given that the diastereoselectivity for the DKR reaction was similar to that of the lactone (those results are presented in section §2.4), the results were considered to be encouraging. It was now necessary to expand on the work, and see how the lactam could be attached to a polymer. For this purpose, a different reaction was developed in order to generate larger quantities of racemic pantolactam, bearing substituents on the nitrogen that could prove useful for the attachment to a polymeric system.

2.1.2 NMR of (R)-pantolactone

The compounds from the preceding section deserved come closer scrutiny due to the fact that they are novel and some have not yet been reported in the literature. The one spectrum that is in the literature is that of the starting material, pantolactone. The most interesting aspect of the spectra on both the lactam and lactone ring systems is the AB system that is next to the geminal dimethyl group. In the spectrum of pantolactone, the
chiral centre causes the geminal dimethyl groups and the hydrogens of the methylene

group to be diastereotopic, and one can easily see two distinct \(-\text{CH}_3\) signals and an \(\text{AB}\)

quartet.

![Diagram](image)

Figure 37: ¹H NMR spectrum of (R)-pantolactone, 7

2.2 The usefulness of racemic chiral auxiliaries

This section describes a one-pot synthesis of \(N\)-substituted pantolactams.

Unfortunately, in this simple procedure the chirality is lost. A racemic version of the \(N\)-

substituted pantolactam is still useful for the determination of the efficiency of the chiral
auxiliary as a whole, since the usefulness of the chiral auxiliary lies in its ability to generate one diastereomer over another. For instance, a racemic mixture of chiral auxiliaries is coupled to a racemic mixture of α-bromo esters. The NMR spectrum will show two compounds instead of four because the homochiral diastereomers will have the same NMR (i.e. the (S,S) and the (R,R) isomers) spectra. Schematically, this is as follows:

![Homochiral esters have same NMR spectra](image1)

![Heterochiral have same NMR spectra](image2)

**Figure 38 : Homochiral and heterochiral α-bromo esters**

The analogous case can be made for the DKR products arising from the above compounds due to the fact that the homochiral products will also have the same NMR spectra. Therefore, if we consider the case above, with a racemic mixture of α-bromo esters (racemic from the point of view of the chiral auxiliary as well as the α-bromo acid), and once the DKR reaction is carried out, it will favour the reaction of one pair of diastereomers over the other pair (the ones called “homochiral” above, and 21 – (S,R) and 21 – (R,S) in the figure below). Thus the faster reacting diastereomers will give rise to an enriched composition of “heterochiral” products (22 – (R,R) and 22 – (S,S) in the figure below). In both cases the enrichment will be the same (by symmetry arguments)
and since the NMR spectra of 22 - (R,R) and 22 - (S,S) are identical, the ratio of the diagnostic peaks will be a true indication of the diastereoselectivity of the reaction.

Figure 39: Rationale for the use of racemic chiral auxiliaries in diastereoselectivity determination

2.3 One step synthesis of a racemic chiral pantolactam auxiliary

A serendipitous discovery was made as part of the work involving the synthesis of the ring opened lactam 9a. The heater/stirrer apparatus was not in proper working condition and occasionally the temperature fluctuated. The reaction with the primary amine required heating at 60°C for at least 18 hours. Such an extended heating period
involved an overnight stint. During one of these experiments, the temperature control on the heater failed and heating occurred in excess of 150°C. Workup of this particular reaction mixture gave the N-benzyl lactam 23 as a major product. Spectral properties are provided in the Experimental Section. An important observation was that 23 was obtained in racemic form. The high reaction temperature and the basic amine were sufficient to cause racemization of the chiral center α to the carbonyl group.

![Reaction scheme](image)

Figure 40: Formation of 23 from (R)-pantolactone

Upon further study, the yield of the lactam could be increased by increasing the temperature: yields were still quite poor, sometimes 0, more typically in the 50% range, when the temperature was varied from 100°C to 230°C. Yields were not improved when excess benzylamine was employed. The reaction time was established to be 6 to 8 hours, beyond which the yields dropped off significantly. Equivalents of benzylamine were initially thought to be important, but it turned out that higher equivalents of benzylamine only resulted in higher yields because benzylamine was decomposing over time. A summary chart would be of little use to the reader, since the highest yield ever achieved for a lactam product with benzylamine as the amine was 50% (approximately 230°C, 8 hours, 2 equivalents of benzylamine). The balance of the mass could not be identified as any previously synthesized product and is believed to consist of decomposition products.

The thermal one-pot reaction was revisited upon completion of the synthesis of the enantiomerically pure (para-methoxy)-N-phenylpantolactam 19. Based on the
information that the p-methoxyaniline was useful in the synthesis of a stable imine, it was concluded that aniline itself might be a useful substrate in this reaction. Indeed, it was found that the reaction between aniline and pantolactone yielded only the lactam 26 when they were heated together\textsuperscript{45}. The structure of the product was readily apparent. This was a puzzling result since no ring opened amide 24 was ever obtained, even when the reaction was carried out at lower temperatures. The mechanism for the formation of 26 must, therefore, follow a different mechanism (b in Scheme 4) than the mechanism that gives rise to the ring opened lactam when using aliphatic amines (a in the following mechanism).

Scheme 4 : Pathways of ring opening of pantolactone

First, it is important to explain these modes of reactivity. One of the ideas that could help explain this reactivity is the nucleophilic nature of aniline. Aniline is not as good a nucleophile as an aliphatic amine due to the participation of its lone pair of electrons in resonance with the aryl ring. Aniline is also a better leaving group than an aliphatic amine, thus 24 could rapidly return to pantolactone under the reaction conditions via a tetrahedral intermediate. It is only at significantly higher temperatures
(150-180°C) that the reaction takes place, and in that case, it is only the lactam 26 that is isolated. Therefore it is proposed that at the higher temperature, the alternate mode of attack is now at the sp³ carbon attached to the alkyl oxygen with the carboxylate becoming the leaving group. Lactones are known to open with some very powerful nucleophiles (however, these are usually thiolates) at the sp³ carbon with the displacement of a carboxylate. Following that mode of reactivity, initial attack at the sp³ carbon is followed by proton transfer to yield the γ-amino acid 25. The intermediate γ-amino acid 25, is not isolated. It condenses to the lactam 26, similar to the synthesis of amides by heating amines and acids at high temperatures. The yield of 26 in this one pot transformation was typically near quantitative.

Moreover, given that compound 24 is never isolated, it either does not form, or quickly undergoes a reverse reaction back to starting materials. In comparison, formation of 25 is irreversible and it still has a very good nucleophile that can then attack the carbonyl, do a proton transfer to the hydroxyl and dehydrate to the lactam. Examples in the literature of conversions of compounds of the type 25 to compounds of type 26 are the backbone of classical peptide synthesis. However, the astute reader will question the possibility of 24 converting to 26 directly. This is not as likely as the case of 25 converting to 26. In the conversion of 24 to 26, the weakly nucleophilic amide nitrogen would have to serve as the nucleophile, and the hydroxyl group would have to serve as the leaving group. This combination is not likely to lead to a reaction despite the high temperatures.

It is important to note that in the above reaction between pantolactone and aniline, greater care was taken to exclude air (degassing) than in the earlier reaction between
pantolactone and benzylamine, which meant that there was no opportunity to obtain overoxidized products. In fact, in contrast to the reactions with benzylamine, once air and moisture were carefully controlled, there were no side products. In a sealed tube reaction, the reaction was done at intervals of temperatures and the reaction was analyzed by NMR. The reaction does not seem to start until close to 180°C, and then it directly converts to 26, in up to quantitative yield. This is in stark contrast to the results when benzylamine is used instead of aniline because at every temperature step of the way above 60°C, there is a ring-opened product 27, (scheme 5, following page) immediately, and a multitude of other products are formed along with the ring opened product, until the temperature increases to some value over 150°C, where a considerable portion of the products decompose, and small amounts of the lactam are left over. A result like this casts a doubtful shadow over the reaction pathway “a” in scheme 4, above.

Further investigations into this reaction have yielded interesting results. The aniline (different anilines could be used) could be combined neat with pantolactone in a pressure tube, which gave rise to a clear orange-yellow solution. This solution often contained air bubbles, which were removed with low pressure. The tube was pressurized with nitrogen, sealed, and placed in a common household microwave to be heated for just over six hours at maximum power (successive iterations of 99 minutes and 99 seconds). This procedure allowed for stark simplicity (an acceptably small aliquot could be removed to monitor reaction progress via NMR) in the experimental procedure since the lactam was the only product, and would consume all the starting material. A slight excess of starting material could be effectively removed by a slightly acidic aqueous
wash (pantolactone is readily water soluble, and any aniline would be washed away as a protonated salt).

While the secret to this transformation is the temperature, there was also very limited success with benzylamine (see scheme below).

![Scheme 5: One step benzylamine route to the pantolactam 23](image)

One further note regarding these ring opened products 27 and 24 needs to be addressed. The aliphatic amide derived ring opened product 27 which does form, can be subjected to higher temperature heating to yield a mixture of pantolactone and the lactam 23 (albeit in low yield)\(^{47}\). This proves that the formation of 27 is reversible, and that over time pathway “b” wins out by virtue of the fact that it’s irreversible (see scheme 5, above). Included below are some of the compounds accessible via this approach.

The one step lactam formation from (R)-pantolactone was also studied with the aromatic and benzylic amines which we felt had potential for the preparation of polymer supported chiral auxiliaries. The amines employed were:

- p-methoxyaniline and p-hydroxyaniline
- p-bromo- and p-iodoaniline
- p-aminobenzoic acid
- benzyl and α-methylbenzylamine

The results are summarized in Table 2.

The reaction of pantolactone with p-methoxyaniline was equally good as with aniline itself (and the lactam 19 was obtained in quantitative yield.) The increased nucleophilicity of p-methoxyaniline allowed this conversion to occur at a lower temperature (150-160°C.) Unfortunately, the use of p-hydroxyaniline resulted in complex mixtures containing no substantial amounts of the desired lactam. Surprisingly, protection of the phenol via an allyl group did not prevent this complex mixture formation.

Halogenated anilines were found to be relatively sensitive to the reaction conditions. p-Bromoaniline yielded the p-bromolactam 29 in 30-60% yield, the dehalogenated lactam 26 in 10-30% yield, as well as unidentifiable oxidation products. Careful deoxygenation of the reaction mixture prior to heating improved the yield of 29. p-Iodoaniline did not yield any product that resembled the expected products.

The p-amino benzoic acid decomposed rapidly under the reaction conditions, even before the mixture reached the desired temperature.

Benzylation and pantolactone yielded the ring opened product 27 exclusively at temperatures up to and including 180°C. Beyond that temperature, a mixture of 27 and 23 were obtained. The isolation of 27 is consistent with its greater stability as compared to the aniline analogue 24. This reaction requires chromatography owing to the presence
of byproducts resulting from decomposition of the benzylamine as well as removal of 27, the yield of 23 was moderate at best (50%).

It is also possible to use optically pure α-methylbenzylamine in to obtain diastereomeric lactams (chirality in the lactone is not preserved, presumably due to the acidity of the proton alpha to the carbonyl and the basicity of the amine) which provides a diastereomeric mixture, which shows up as two spots by TLC, and is presumed to be chromatographically separable. Hydrogenolysis of a given diastereomer would yield an enantiomerically pure lactam without a substituent on the nitrogen (see scheme following page)

![Scheme 6: Possible routes to enantiomers of 31]

Overall, this was not a preferred route, since the yield of the diastereomeric mixture is 39%.
Table 2: Summary of single step pantolactam synthesis

<table>
<thead>
<tr>
<th>Lactams prepared with high reproducibility</th>
<th>Lactams prepared with limited reproducibility</th>
<th>Lactams that could not be prepared due to decomposition of the aniline starting material</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 19" /> quant. yield</td>
<td><img src="image" alt="Structure 29" /> 30-60% byproduct is dehalogenated lactam</td>
<td><img src="image" alt="Structure 32" /></td>
</tr>
<tr>
<td><img src="image" alt="Structure 26" /> quant. yield</td>
<td><img src="image" alt="Structure 30" /> low yields (39%)</td>
<td><img src="image" alt="Structure 33" /></td>
</tr>
<tr>
<td><img src="image" alt="Structure 23" /> moderate yields (50%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With the exception of compound 30, HRMS spectral data accompanies the NMR data and is provided in the experimental section. Compound 30 was only analyzed by NMR, and was found to have similar spectral properties to 23.

In short, this procedure allows for a reliable one step synthesis of pantolactams. Unfortunately, racemization is observed under the high temperature conditions. The
tranformation is not general. Iodinated anilines decompose near 110°C, and p-aminobenzoic acid yielded a complex mixture which did not contain a lactam. The reaction involving bromoaniline is quite sensitive, requiring careful degassing prior to heating.

Derivatization of 26 or 29 should allow for functionalization that would not be accessible via direct combination of appropriately functionalized starting materials, as shown below (32 is not obtainable from direct combination of pantolactone and p-cyanoaniline, and 29 gives mixed results. The chemistry for 29, 32, and 33 is described in detail in sections §3.3.2 and 3.4).

![Chemical structures showing derivatization scheme of 26](image)

As mentioned above, there is a key drawback to this one-step reaction for making 26. The chirality present in the (R)-pantolactone starting material is annihilated due to the basic reagents and the high temperatures.
2.4 The effectiveness of the pantolactam chiral auxiliary 19 in DKR reactions

A number of different α-bromo acids were coupled to the p-methoxy chiral auxiliary 19 and reacted with a series of amines. These reactions were carried out analogously to previous DKR reactions in the Durst lab, in order to be able to compare objectively the results. The reactions were all carried out using dry distilled THF as the organic solvent, tetrabutylammonium iodide as the iodide source, and a 1% molar excess of amine nucleophile. The reactions were all carried out at room temperature, and monitored by thin layer chromatography. Due to a lack of combinatorial chemistry equipment, a modified setup was created in order to facilitate parallel synthesis. A 20 cm x 20 cm x 5 cm piece of styrofoam was used, with six places melted out to accommodate six 25 mL round bottom flasks. This setup was the right size to fit on a stirring plate, and DKR experiments were started every 8 or 16 hours. This allowed enough time to work up experiments that were completed while others continued. In addition, for the bulk of the DKR products (with the exception to reactions that involved pyrrolidine), the isolation of the crude could be done by a simple two step process. The reaction mixture was first diluted with more THF, and filtered to remove the triethylamine hydrobromide and the tetrabutylammonium iodide salts. Ether was then added, and any precipitate formed was filtered off. The residue, after solvent removal, was usually pure enough for diastereomer determination by 1H NMR. In a few cases, the amino ester was the precipitate, and was analyzed directly. It should be noted that in all cases the product was isolated by chromatography and characterized appropriately (see Experimental Section).
The products all had key diagnostic peaks in the $^1$H NMR spectrum that were used to determine the diastereomeric ratios. The following figure shows the hydrogens corresponding to the peaks and their typical shift ranges.

![Diagram of molecular structure](image)

**Figure 41**: Diagnostic peaks used to determine the diastereoselectivity

The methine hydrogen geminal to the new amino group is not a very useful proton for diagnostic purposes because it will have a different multiplicity depending on the nature of the R group. (see Table later in this Section). The biggest drawback to using that hydrogen is that it occurs in the 3 - 4 ppm region, and often overlaps with many other peaks.

The peaks present in the chiral auxiliary due to the methine hydrogen and the geminal methyl groups have the advantage of not varying quite as much, and being in regions of the spectrum where there are generally no other peaks. The diastereomeric ratio, as determined by the two peaks at around $\delta = 5.5$ ppm due to the hydrogen $\alpha$ to the amide carbonyl group for the two diastereomers, agreed well when compared to the ratio using the diastereotopic methyl peaks near 1 ppm. If the ratio of products is 1 : 10, then there are two peaks around 5.5 ppm, with relative areas of 1 and 10, and a total area corresponding to one hydrogen. The region near 1 ppm will have four peaks (because there are two diastereotopic methyl groups) with relative areas of $3 : 3 : 30 : 30$. 
Figure 42: $^1$H NMR of DKR product 19a

In the 500 MHz $^1$H NMR of 19a, the peaks due to the minor diastereomer are annotated by a star (*). In this case, due to the overlap with the much larger peak due to the major diastereomer, the peak at 5.34 ppm is not very useful. However the singlet methyl groups at 1.2 and 1.0 ppm are useful, since they are well separated from other peaks, and helped determine the 30:1 diastereomeric ratio of products.

On the following page, a $^1$H NMR spectrum is given of DKR product 19b, with an expansion of the key region around $\delta = 4.4-4.5$ ppm. The diastereomeric ratio of 7:1 is easy to obtain by comparing the peaks at 5.475 and 5.469 ppm.
Figure 43: $^1$H NMR of DKR product 19b

The matrix below outlines the results for the DKR reactions. Only a few of the compounds have been prepared previously. In several cases, the analogous reactions with (R)-pantolactone as a chiral auxiliary were also carried out.
Table 3: DKR results for chiral auxiliary 19

<table>
<thead>
<tr>
<th>Diastereomer ratio (yield)</th>
<th>Br</th>
<th>Br</th>
<th>Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>BnNH₂</td>
<td>8 : 1&lt;sup&gt;a&lt;/sup&gt; (quant.)</td>
<td>9 : 1&lt;sup&gt;b&lt;/sup&gt; (68%)</td>
<td>15 : 1 (95%)</td>
</tr>
<tr>
<td>Adamantylamine</td>
<td>16 : 1 (62%)</td>
<td>26 : 1 (72%)</td>
<td>30 : 1 (52%)</td>
</tr>
<tr>
<td>AdNH₂</td>
<td>7 : 1&lt;sup&gt;e&lt;/sup&gt; (quant.)</td>
<td>14 : 1&lt;sup&gt;f&lt;/sup&gt; (quant.)</td>
<td>&gt; 99 : 1 (65%)</td>
</tr>
<tr>
<td>BnNMe</td>
<td>4 : 1&lt;sup&gt;d&lt;/sup&gt; (quant.)</td>
<td>Inseparable Mixture&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 : 1&lt;sup&gt;c&lt;/sup&gt; (73%)</td>
</tr>
<tr>
<td>Pyrrolidine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>: A single reaction, run by M. Jung, used a similar chiral auxiliary, but with a methyl substituent on the nitrogen, gave a 64% yield of a 9:1 mixture of diastereomers. Rob Ben’s reaction with (R)-pantolactone gave a 70% yield of a 7:1 mixture of diastereomers.

<sup>b</sup>: compare with a 84% yield of a 10:1 mixture of diastereomers.

<sup>c</sup>: compare with a 87% yield of a 4:1 mixture of diastereomers. A second trial, using the aniline-derived chiral auxiliary, with 15% of Bu₄NI gave a 4:1 diastereomeric ratio.

<sup>d</sup>: in this case, elimination effectively competes with the DKR reaction, and the product mixture is inseparable by flash chromatography, or HPLC.

<sup>e</sup>: the comparison experiment was run by me, to get an idea of how this nucleophile performs with (R)-pantolactone, and was found to have a diastereoselectivity of 20:1 by 500 MHz ¹H NMR. The reaction with (R)-pantolactone gave a disappointing yield of 44%, the mass balance was the nucleophilic displacement of the chiral auxiliary (see below).

<sup>f</sup>: the comparison experiment was also carried out by me, and was found to have a diastereoselectivity of 5:1 with (R)-pantolactone, and a yield of 96%.

**Conclusion:** As can be seen from the Table above, the lactam chiral auxiliary functions as least as well and often somewhat better than the (R)-pantolactone chiral auxiliary. One of the main key benefits was the increased yield, since it was possible to
simply add ether to precipitate out the salts and recover the amino esters in relatively pure form.

2.4.1 The effectiveness of the pantolactam chiral auxiliary in anionic carbon-carbon bond forming reactions

In addition to the aminations, we investigated several other reactions with the hope of expanding the scope of the utility of this new chiral auxiliary. The first one that we focused on was a carbon-carbon bond forming reaction. This is simply an extension of the original DKR reaction. There is concern, however, of the implications of using a strongly basic carbon-centred negative charged nucleophile, since there are two somewhat acidic protons in the α-bromo ester starting material. Racemization of the chiral centre in the chiral auxiliary, as well as racemization of the product are both possible unwanted side reactions. The substrates chosen for potential stereoselective C-C bond formation were the active methylene compounds 34, a β-ketosulfone, diethyl malonate 35 and malononitrile 36. In each of these compounds the acidity of the methylene hydrogens (pKa 10-13) is such that the anion is expected to act only as a potential nucleophile and not as a base in the presence of 21a or 21b.

![Figure 44: Substrates used in potential anionic DKR reactions](image-url)

Figure 44: Substrates used in potential anionic DKR reactions
The sulfone 34 was unreactive towards 21a and 21b when triethylamine was used as a base. When the sodium salt of the sulfone was used, a complex mixture of compounds was obtained. Flash chromatography of the reaction mixture provided products that corresponded to the starting materials, in 60-80% yield. Similar results were obtained with diethyl malonate 35: no reaction was observed when the sodium and lithium salts of diethyl malonate (generated from sodium and lithium hydride, respectively, and diethyl malonate) were stirred with either 21a or 21b for 24 hours in THF at room temperature. These two substrates 34, and 35 may be too sterically demanding to undergo this reaction, but a smaller substrate such as malononitrile 36 might be successful.

The $^1$H NMR of the crude reaction mixture of the reaction between malononitrile 36 and α-bromo ester (21b) in the presence of triethylamine was consistent with the formation of approximately 3:2 diastereomeric ratio of triethylammonium salts of the expected DKR product shown below.

![Chemical structure](image)

**Figure 45**: Salt formation in the anionic DKR reaction

Silica gel chromatography, using 2:1 hexanes to ethyl acetate provided a yellow amorphous powder in yields varying from 64% to nearly quantitative yield. The $^1$H NMR of this product, 38 which eluted off the column was consistent with the assigned structure as a 2:1 diastereomeric product mixture.
The ratio is based on the relative size of the two sets of diastereotopic methyl peaks at $\delta = 1.30, 1.12$ ppm and $1.18, 0.76$ ppm. The diastereomeric ratio in a series of runs, even with slightly lower temperatures (-10°C) did not change from 3 : 2 for the salt. Interestingly, the methine hydrogen of the chiral auxiliary has the same chemical shift ($\delta = 5.46$ ppm) in both diastereomers.

A change in the diastereomer ratio appears to have occurred during chromatography, this may be due to the rather high acidity of key hydrogens in the product. Deuterium exchange studies confirm the high acidity (triethylamine is sufficiently basic to cause the exchange of the hydrogen between the nitrile groups, and somewhat surprisingly, also the benzylic hydrogen.)

![Figure 46 : Malononitrile DKR product](image)

In a follow up experiment; allylbromide was added to the malononitrile reaction mixture after 2 hours. Based on the deuterium exchange results discussed above, we envisaged the possible formation of either or both 39 and 40. In the event, only 39 was isolated in 97% yield.
The \(^1\)H NMR (see Experimental Section) clearly indicated the presence of an allyl group ($\delta = 5.5–5.7$ (2H), and $5.8–6.1$ (1H), and the diastereoselectivity can still be measured by the diastereomeric peaks at $\delta 4.2$ ppm. Unfortunately, the diastereomeric ratio is $2:1$.

2.4.2 The effectiveness of the lactam chiral auxiliary in radical reactions

In Porter's paper\(^{48}\) on the origins of stereoselectivity in radical additions, he uses a number of different chiral auxiliaries to investigate how much selectivity can be expected in radical reactions. Specifically, the following reaction warranted closer inspection:

\[
\text{Scheme 8 : Radical substitution with a chiral auxiliary}
\]
The only difference between the esters that are investigated in this study and the ones in the DKR reaction is that in Porter’s case, he is starting with the alpha-iodo esters. The reactions we carried out were modified with respect to the previous DKR reactions, and also differently than Porter’s example. Due to the nature of the reaction, the reaction was run in a quartz tube, with benzene as the degassed solvent, this was achieved by bubbling nitrogen into solution for half an hour. In contrast to Porter’s heating of the AIBN, the solution was stirred at room temperature with a UV light (254 nm) for 8 to 16 hours (monitored by TLC) in the presence of 10% molar equivalent AIBN as well as the DKR requisite quaternary ammonium salt. Unfortunately, as with the anionic DKR, the diastereoselectivity for the allylated product 41 was a paltry 2 : 1, and a modest yield of 69%.

![Figure 48: Radical induced allylation under DKR conditions](image)

2.5 A different chiral auxiliary

In the course of other studies conducted in the Durst lab, the following compound 42 was made. It was thought that it might also function as a good chiral auxiliary for our DKR studies. Compound 42 appeared to share many of the key features with the pantolactam auxiliaries prepared in this thesis. These include the α-hydroxyamide structure with the hydroxyl group in a chiral environment. If positive results were
obtained for the solution phase studies, the auxiliary should be easily attached to a solid support via the nitrogen substituent

\[ \text{HO-} \text{N-} \text{42} \]

The synthesis\textsuperscript{49} of this compound starts with isatin \textbf{43}, and is pictured below.

\[ \text{O-} \text{NH} \text{43} \xrightarrow{\text{NaH Mel}} \text{O-} \text{N-} \text{44} \xrightarrow{\text{Na}_2\text{S}_2\text{O}_4} \text{HO-} \text{N-} \text{42} \]

Scheme 9: Synthesis of the isatin-derived chiral auxiliary \textbf{42}

The reaction scheme above is used directly as performed by a former fellow Durst lab member, Gordana Babic. The use of sodium hydride either as a 60\% suspension in oil or a pure powder did not appreciably change the results of the initial alkylation. The product was the same (i.e. orange-red solid) with similar yields (75 – 85\%). The only change made to the experimental conditions was the purification of the final product, which was found to be soluble in chloroform and relatively insoluble in ether. The spectrum of the product is shown below.
Figure 49: 300 MHz $^1$H NMR spectrum of compound 42

By altering the alkylating group at the first step, it would be possible to attach the chiral auxiliary to a polymer support. Thus 43 could be attached to a linear polyvinyl benzyl chloride or the monomethyl ether of polyethylene glycol, both of which are discussed in the next chapter.

It should be noted that the reduction for a polymer supported chiral auxiliary (i.e. a compound analogous to 44) would be carried out in a different manner. The reduction of 44 to 42 leads to a racemate. There is however a literature precedent$^{50}$ for a chiral
reduction of 44 using a metal complex, and one using a reductase from *Candida parapsilosis*.

The coupling of 42 with α-bromo propanoic acid was carried out with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) as the coupling reagent. The TLC of the reaction product showed a single spot and the $^1$H NMR spectra indicated the formation of the desired compound 45 as a set of diastereomers. However, it showed a second set of peaks, which indicated another set of compounds. The TLC showed only a single spot.

![Chemical reaction](image)

Figure 50: Use of DMC to couple chiral auxiliary 42 to 2-bromopropanoic acid

Upon inspection of the mass spectra, it was determined that this was due to displacement of bromide by chloride, leading to the diastereomeric α-chloro ester 48. Indeed, the formation of the α-chloro ester was found to be temperature dependent. When the esterification reaction was carried out at higher temperatures, the product obtained was almost exclusively the α-chloro ester 48. In each case the diastereomeric ratio for 45 and 48 was near 1:1. The assignment was based on the mass spectrum of the mixture which showed molecular ion peaks at 297 and 299 (1:1 ratio) for the bromine-containing 45 and at 253 and 255 (3:1 ratio) for the chlorine-containing 48.
Figure 51: Mysterious second set of diastereomers revealed

Disappointingly, a DCC coupling was not successful due to the side reaction pictured below. Even modified conditions, using HOBT as an additive were not enough to prevent the side reaction from happening. Apparently, the nucleophilic strength of 42 is comparable to dicyclohexylurea (DCU) and the latter, rather than 42, becomes acylated. This was evidenced by the large cyclohexyl peaks in the NMR and the isolation of the starting 42 from the reaction mixture.

Figure 52: A different unwanted side product

While the formation of 48 was a setback, it should not affect the DKR reaction since the use of the quartenary ammonium iodide salt will hopefully convert both the α-chloro ester and the α-bromo ester to the same α-iodo ester mixtures in situ and allow the reaction to progress in the usual manner.
DKR reactions were carried out to 50% and full conversion. At 50% conversion, the reaction was worked up and the crude products were separated by column chromatography. The presence of both the α-bromo 45 and α-iodo ester were confirmed by mass spectroscopy and $^1$H NMR. Unfortunately, an attempt to carry the reaction to completion did not allow us to isolate pure samples of the desired N-benzyl amino ester. A sample containing mostly 45 and very little 48 was analyzed by $^1$H NMR. The region used to determine the diastereomer product ratios was the area around δ = 6 ppm, and it indicated a possible 1:1:1 mixture. Moreover, flash chromatography appeared to lead to the decomposition of the product. This was highly disappointing and work on this chiral auxiliary was abandoned.

Figure 53: $^1$H NMR spectrum of an α-bromo ester 45 with the new chiral auxiliary
Chapter 3  Potential Supports for the DKR Reaction

3.1  Polymer Supported Reactions and their Application to α-Amino Acid Synthesis

There is a concern over the change in kinetics that a classical solid support will instill upon the DKR reaction. Traditional solid supported reactions have one significant disadvantage: time. Given that the reactions have changed from a solution phase reaction to a solid/liquid reaction, the kinetics change. The result of this change is that the reactions on solid supports tend to take longer than the corresponding solution phase reactions. This could be a potential concern since our solution-phase DKR reaction (an SN₂ process) requires a modest amount of time. Slowing down a slow reaction could make the process painstakingly slow. Work by Janda (specifically his work on the now commercially available Janda/Jels™) has yielded a potential solution: by using supports which have selective properties such that it is possible to keep the polymer support in solution for the duration of the reaction and, upon addition of an appropriate additional solvent, the support would precipitate out, facilitating the purification of the product.

This is generally referred to as SPSS: Solution Phase Supported Synthesis. Resins that are readily amenable to such applications are principally polyethylene glycol (PEG) resins and linear polystyrene resins (LPS) resins; other options also exist. Functionalization for the purpose of connecting the chiral auxiliary to the resin is somewhat more facile with a hydroxyl-terminated PEG resin, since a simple nucleophilic
displacement (after conversion of the hydroxyl to a suitable leaving group) allows for a strong permanent linkage. Commercial LPS resins can be purchased with carboxyl termini, but also easily functionalized via lithiation of the phenyl ring\textsuperscript{54}.

When considering a polymer-supported reaction, the same design process that occurred for solid phase reactions needs to occur for solution phase reactions, but different criteria enter the picture. The following are a few of the more important considerations for solid phase polymer-supported reactions and they are compared to solution phase polymer-supported reactions:

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Solid Phase Polymer-Supported Reaction</th>
<th>Solution Phase Polymer-Supported Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical stability</td>
<td>Important due to the stress that the polymer might encounter while undergoing the reaction (stirring)</td>
<td>Not really an issue during the reaction, just during the filtering process</td>
</tr>
<tr>
<td>Solvent Swelling</td>
<td>Important, since it determines the ease at which the reactant is able to encounter the supported substrate</td>
<td>Since the polymer is already in solution, its ease of reactivity is determined by diffusion.</td>
</tr>
</tbody>
</table>

Polymer supports can be rendered soluble if there are enough moieties present in the backbone which can interact with the solvent. In the case of the Janda/いえる\textsuperscript{TM}, they become more soluble with increased crosslinking with an alkyl-tethered p-vinyl phenol\textsuperscript{55}; shown below.
Figure 54: Components of a Janda/Jel™

The Janda/Jel™ polymer forms a microgel in solution suitable for organic synthesis. This is due to the oxygens and the saturated carbons in the crosslinker. There are a number of other papers by Janda that feature the synthesis of solid phase polymer supports having better swelling properties rather than forming microgels. Therefore, a polymer support should be chosen so that it will have a favourable combination of properties.

There is also an often overlooked property of polymers, especially when they are used for reactions. Since they function as a scaffold, it will have a limited number of functional groups per unit mass. All of the above approaches to polymer supported reactions (using linear polystyrene (LPS), polyethylene (PEG), methoxy polyethylene (MPEG) as well as the crosslinked Janda/Jel™) have a loading capacity highly dependent on the molecular weight of the polymer. In the following table, loading capacities are given in mmol per gram, and average molecular weights in brackets and assumes that there is a single point of attachment.
<table>
<thead>
<tr>
<th>Number of monomers</th>
<th>Carboxy terminated LPS resin</th>
<th>MPEG resin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.96 (252)</td>
<td>3.09 (323)</td>
</tr>
<tr>
<td>10</td>
<td>0.77 (1,290)</td>
<td>1.39 (719)</td>
</tr>
<tr>
<td>50</td>
<td>0.18 (5,455)</td>
<td>0.40 (2,479)</td>
</tr>
<tr>
<td>∞</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The reason why polymers with larger molecular weights are still made despite their low loading capacity is because as the molecular weight increases, the polymer becomes more solid (some of the lower molecular weight polymers are viscous liquids) which is favourable in terms of handling, since the polymer can be filtered and washed. However, as the molecular weight increases, the quantity of substrate that can be loaded on the polymer decreases drastically, which requires large quantities of the prepared polymer in order to have usable quantities of product.

From a design perspective, the problem with the above approaches is that the chiral auxiliary would be attached to the termini of the polymer. This can be obviated by having the chiral auxiliary throughout the polymer, as if it was part of the monomer. Potential problems arise, depending on the kind of polymer used. Solvent swelling, which will affect the accessibility of reagents to the supported substrate, will depend heavily on the type of polymer support used and the solvent. By minimizing the size of the polymer backbone, the solvent swelling properties approach those of the chiral auxiliary itself, rather than that of the polymer support. Finally, the increased proportion of sp³ hybridized carbons with respect to sp² hybridized carbons imparts a better solubility profile for the polymer.

The question of how to make the polymer is also important. A polymer which needs to have the chiral auxiliary grafted onto the terminal groups is easier to make than
one where the chiral auxiliary must be grafted onto the individual monomer units, because of the aforementioned solvent effects. Innovation has brought forth a new alternative: polymerization that uses the chiral auxiliary as an integral part of the monomer.

This approach is not traditionally seen as a good one, since even more variables have to be taken into account. The polymerization mechanism would have to be considered, since polymerization of something as common as polystyrene can give rise to syndiotactic, or even atactic polymers.

![Diagram of polymerization process](image)

Figure 55: Potential problems with styrene polymerization

These arrangements would have unforeseen consequences upon the DKR reaction because it would impart steric or conformational effects which would alter diastereomeric ratios. The precise conditions for the polymerization mechanism must also be fully compatible with the various functional groups present in the chiral auxiliary monomer. Moreover, control over the molecular weight must be kept in check, since a narrow polydispersity gives rise to more finely defined properties. This is increasingly important with polymers of a molecular weight range where a large polydispersity might lead to a polymer that is a viscous oil rather than a solid.
3.1.1 A Corollary by the Calmès and Camps groups.

While the previous work by the Durst group has been published, it took the work of two groups approximately ten years\textsuperscript{56} and twenty students to achieve a similar output to this work. However, while their work does focus on pantolactone and a pantolactam on a polymer support, the work has never involved a DKR reaction on a polymer support, nor have they used a ROMP polymer in any of their work. Their approaches to amino acid synthesis center around the 1992 through 1994 papers by Durst (see ref. 26), where the key to the synthesis is the attack of the pantolactone upon a ketene.

The polymer support used was a Rink amide resin and is shown below (with chiral auxiliary attached) for reference. It should be noted that it is an insoluble resin, and therefore does not contain the benefits that the ROMP resin does (high loading capacity, solubility, etc).

![Chemical structure](image)

Figure 56: The Rink resin used by Calmès, et al.

The reason that the bulk of this work went unnoticed by us is that the journals that the work was published in were not indexed by the abstracts services we have available at
the university (*Tetrahedron Asymmetry* being the key one). It is fortuitous that their work has not overlapped with ours in our main objectives.

Unfortunately, the Camps group did very recently publish\(^{37}\) one reaction that I carried out independently: the conversion of compound 7 to 26 (see §2.3) by heating under microwave irradiation. Our experimental procedures are quite similar, but not the same. Our experimental conditions call for no additives, and the use of a common household microwave. The product obtained, if necessary, only requires an aqueous wash to remove the excess starting materials. Their use of other additives (TsOH·H₂O) or other conditions (MeOH solution in a pressure reactor instead of microwaves) requires column chromatography.

3.2 ROMP – a strategy that allows for a simple entry into functional polymers

ROMP – Ring Opening Metathesis Polymerization\(^{58}\), is a transition metal catalyzed approach to polymerization. The advances made in this field have made it possible to polymerize molecules that bear a variety of functional groups that a few years ago would have seemed incompatible with polymerization processes. The widespread synthesis and use of polymer-supported reagents is not new, but generating these reagents from appropriate monomers is a relatively new idea\(^{59}\). Generating a polymer with chiral auxiliaries from a monomer carrying a chiral auxiliary, and keeping the chiral centre intact is a new idea. This approach is superior to attaching the chiral auxiliary to a polymer, since the degree of functionalization does not change as drastically with
increased molecular weights as with the LPS and PEG polymers. The maximum loading capacity will be the reciprocal of the molecular weight of the monomer.

The suitability of this approach can be explained by the mechanism\textsuperscript{60}. The heart of the ROMP reaction is the Ruthenium catalyst.

\begin{center}
\begin{tikzpicture}
    % Add the diagram here
\end{tikzpicture}
\end{center}

\textbf{Figure 57:} The catalytic cycle for a ROMP reaction.

I was fortunate to witness\textsuperscript{61} Prof. Robert Grubbs explaining why this works as well as it does, he offered the following chart in part of the explanation:
Table 4: Prof. Grubbs Table of Metal Reactivity

<table>
<thead>
<tr>
<th></th>
<th>Ti</th>
<th>W</th>
<th>Mn</th>
<th>Ru</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acids</td>
<td>Acids</td>
<td>Acids</td>
<td>Olefins</td>
<td></td>
</tr>
<tr>
<td>Alcohols</td>
<td>Alcohols</td>
<td>Alcohols</td>
<td>Acids</td>
<td></td>
</tr>
<tr>
<td>Aldehydes</td>
<td>Aldehydes</td>
<td>Aldehydes</td>
<td>Alcohols</td>
<td></td>
</tr>
<tr>
<td>Ketones</td>
<td>Ketones</td>
<td>Olefins</td>
<td>Aldehydes</td>
<td></td>
</tr>
<tr>
<td>Esters</td>
<td>Olefins</td>
<td>Ketones</td>
<td>Ketones</td>
<td></td>
</tr>
<tr>
<td>Olefins</td>
<td>Esters</td>
<td>Esters</td>
<td>Esters</td>
<td></td>
</tr>
</tbody>
</table>

The table is ordered in terms of reactivity of the metals in the top row to the functional groups below, in decreasing degrees of reactivity. For instance, titanium is more reactive towards acids than alcohols. From this Table, it can readily be seen that for ruthenium, a double bond is the most reactive moiety, more reactive than carbons attached via π-bonds to heteroatoms. Several examples showing the preference of reactivity are shown below; these barely scratch the surface of this rich and diverse field of research.
Figure 58: ROMP examples showing Ru specificity

This means that if there was a double bond introduced somewhere in the chiral auxiliary, it could be used as the handle by which the polymer could be made. It should be noted that the functional group of choice containing the double bond is the bicyclo[2.2.1]heptene ring. The reason for this choice is that it is a strained system and the relief of ring strain helps drive the reaction. Ruthenium catalysts for olefin metathesis reactions are also able to undergo other metathesis reactions such as cross metathesis, but these reactions are secondary to ring opening metathesis polymerization when a bicyclo[2.2.1]heptene substrate is involved.

The issue of tacticity could be solved if an appropriately symmetric linker is used. Since ROMP with a ruthenium catalyst will use a double bond as the site of polymerization, the remaining atoms of the chiral auxiliary can be attached to a ring with an odd number of atoms that contains the double bond, thereby solving the quandry of symmetry.
As can be seen from figure 59, both problems are solved if the chiral auxiliary is attached via a ring which contains an odd number of atoms, and the linking site is incapable of (R) and (S) chirality. Isomerism with respect to the geometry around the double bond is not really an issue since the catalyst prefers to generate the more thermodynamically stable trans double bonds.

The last major issue with regards to polymerization is that of kinetics. Since ROMP is a living polymerization, every metal centre is reacting as fast as all the other ones assuming that there is no localized concentration of monomer. This means that all other factors being equal, every polymer "strand" should be just as long as every other one, giving rise to the ideal polydispersity index of nearly 1.0.

3.3 On the Synthesis of a Polymer-compatible Chiral Auxiliary

Various methods are available for the attachment of novel molecules to polymer supports. Organometallic couplings as well as nucleophilic displacements are the most common. Given that the currently synthesized chiral auxiliaries (e.g. 26) have an aryl group farthest away from the chiral centre, an investigation into the feasibility of a metal-mediated coupling onto a polymeric support was first pursued, given that such reactions
have ample precedent and are high-yielding. This meant that the chiral auxiliary would need to have a synthetic handle in order to participate in these couplings, for example a p-bromo substituent as found in 29.

3.3.1 One step or two steps

The one step synthesis of 29 by heating of pantolactone with p-bromoaniline was described earlier. However, the formation of 29 was accompanied by dehalogenation to 26. Since separation was not trivial, this meant that this was not a good route to large amounts of 29. Another way in which one could obtain p-bromo chiral auxiliary 29 was by an electrophilic aromatic substitution.

![Scheme 10: Bromination of 26](image)

The $^1$H NMR of 29 showed an interesting coupling pattern which appeared to be similar to an AB quartet, but upon magnification, it appeared to be an AB quartet of triplets, which in aromatic system is denoted as AA'BB'. This is typical of a para substituted aromatic molecule. No evidence for the formation of any ortho brominated
product was seen in the $^1$H NMR of the crude bromination product. The electrospray ionization mass spectroscopy (EIMS) spectrum showed the expected 1 : 1 set of peaks at 283 and 285.

The success of the bromination reaction was a good thing, since it promised to open the door to various palladium couplings such as the Heck reaction. Such couplings tend to work more smoothly with iodinated rather than brominated aromatics thus an attempt was made to prepare the iodo analog of 29. The synthesis of this compound was not possible by the one step approach (see §2.3) due to the instability of p-iodo aniline at high temperatures and unfortunately the analogous electrophilic iodination reaction of 26, shown in Scheme 10 (substituting I$_2$ for Br$_2$) (above) yielded unidentifiable mixtures of products.

The reason for the failure of the one step reaction (see § 2.3) was initially attributed to radical decomposition of either the starting material or the product. In hopes of preventing the dehalogenation in the one step reaction, 2,5-ditertbutylphenol was added, but failed to help yield the p-iodo product or increase the yield of the p-bromo product.

The quantitative yield of 29 from 26 in the electrophilic aromatic substitution in Scheme 10, in addition to the quantitative yield of 26 from pantolactone made this route the preferred one for obtaining 29 in sufficiently large quantities in order to investigate the possibility of attaching 29 directly to a polymer. This approach was envisaged before the idea of the ROMP approach, and appeared to be facile in execution (see §3.1). The SPSS work carried out by Janda’s group is characterized by attaching molecules of interest to PEG polymers via palladium couplings or direct displacement. In order to
discover what kinds of conditions might be successful for direct attachment of the chiral auxiliary to a polymer, a model system that would contain a bromobenzene and an allyl ether was investigated. The idea was that the polymer would be an allylated PEG resin, which is easily prepared on a massively large scale by simply mixing allyl bromide with PEG and triethylamine.

Model reactions did indeed provide the appropriate Heck coupled products. The reactions were followed by TLC and required extensive amounts of reaction time: approximately 80% conversion at 48 hours and complete at approximately 60 hours. The yields were fair to excellent as shown in Figure 60. However, the allylated PEG resin did not behave as well as its small molecule counterpart, despite the use of a number of other conditions, more reactive catalysts and forcing conditions (see Table 5, following Figure 60.)

![Chemical structures](image)

**Figure 60**: Successful Heck couplings of model compounds

It should be noted that the chiral auxiliary with a bromine at the para position (29, A in the figure below) did not participate as expected in the Heck reaction. Products
isolated were either the starting material, or a mixture of starting material along with some dehalogenated chiral auxiliary 26, which indicates that it is possible that the metal did in fact insert into the carbon-halogen bond. Other conditions and their results are summarized below:

Aryl Halides

![Aryl Halides](image)

Olefins

![Olefins](image)
Table 5: Results of Attempted Heck Couplings

<table>
<thead>
<tr>
<th>Aryl halide</th>
<th>Olefin</th>
<th>Pd source</th>
<th>Phosphorus source</th>
<th>Base / Additive</th>
<th>Solvent</th>
<th>Product isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>CH₂CN</td>
<td>S.M.</td>
</tr>
<tr>
<td>A</td>
<td>E</td>
<td>PdCl₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>CH₂CN</td>
<td>S.M.</td>
</tr>
<tr>
<td>A</td>
<td>F</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>CH₂CN</td>
<td>S.M.</td>
</tr>
<tr>
<td>B</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃ / TBAI</td>
<td>CH₂CN</td>
<td>S.M.</td>
</tr>
<tr>
<td>B</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>S.M.</td>
</tr>
<tr>
<td>D</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>None</td>
<td>NEt₃</td>
<td>CH₂CN</td>
<td>S.M.</td>
</tr>
<tr>
<td>A</td>
<td>E</td>
<td>Pd(PhCN)₂Cl₂</td>
<td>P⁴Bu₃ (2 eq)</td>
<td>Ne⁵Pr₃ / CuI</td>
<td>Dioxane</td>
<td>S.M.</td>
</tr>
<tr>
<td>D</td>
<td>F</td>
<td>Pd(OAc)₂</td>
<td>None</td>
<td>NEt₃</td>
<td>CH₂CN</td>
<td>S.M.</td>
</tr>
<tr>
<td>D</td>
<td>G</td>
<td>Pd(OAc)₂</td>
<td>None</td>
<td>NEt₃</td>
<td>CH₂CN</td>
<td>S.M.</td>
</tr>
<tr>
<td>D</td>
<td>G</td>
<td>Pd(OAc)₂</td>
<td>None</td>
<td>NEt₃</td>
<td>DMF</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>G</td>
<td>Pd(OAc)₂</td>
<td>None</td>
<td>NEt₃</td>
<td>DMSO</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>H</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>Yes</td>
</tr>
<tr>
<td>D</td>
<td>H</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>TMEDA</td>
<td>DMF</td>
<td>S.M.</td>
</tr>
<tr>
<td>C</td>
<td>H</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>Yes</td>
</tr>
<tr>
<td>C</td>
<td>H</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMSO</td>
<td>Yes</td>
</tr>
<tr>
<td>A</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>E</td>
<td>Pd(PPh)₃</td>
<td>None</td>
<td>K₂CO₃</td>
<td>DMF / EtOH</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>H</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>*</td>
</tr>
<tr>
<td>B</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>S.M.</td>
</tr>
<tr>
<td>B</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>S.M.</td>
</tr>
<tr>
<td>A</td>
<td>F</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>G</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>*</td>
</tr>
<tr>
<td>D</td>
<td>E</td>
<td>Pd(OAc)₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃</td>
<td>DMF</td>
<td>S.M.</td>
</tr>
<tr>
<td>A</td>
<td>E</td>
<td>PdCl₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃ / CuI</td>
<td>DMF</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>E</td>
<td>PdCl₂</td>
<td>None</td>
<td>NEt₃ / CuI</td>
<td>DMF</td>
<td>*</td>
</tr>
<tr>
<td>A</td>
<td>E</td>
<td>PdCl₂</td>
<td>PPh₃ (4 eq)</td>
<td>NEt₃ / KI</td>
<td>DMF</td>
<td>*</td>
</tr>
</tbody>
</table>

S.M. refers to the starting material. * refers to a mixture of starting material and the dehalogenated product.

Despite the encouraging result with allyl phenyl ether, it is possible that part of the reason that this did not work is that the palladium may in fact coordinate with the allyl group, displacing an alkoxide, forming a π-allylpalladium intermediate via η³ coordination. This kind of chemistry has been exploited by Oppolzer⁶³, and is the first
step in his work on polyfused ring systems. Simpler examples can be seen in section 12.5.C of Michael Smith’s “Organic Synthesis”.

![Chemical structure diagram]

**Loss of acetate in Oppolzer's ring formation reaction**

![Chemical structure diagram]

**Possible side reaction in my work**

**Figure 61**: Possible side reaction with PEG-480

### 3.3.2 A pendant amino group

A brominated aryl ring is still useful, since it contains a suitably useful functional group that is orthogonal (in terms of reactivity) to other functional groups present in the molecule. A cyanobenzene lactam (see below) was prepared$^{64}$, in hopes of generating a primary amine, which could then be used to perform a nucleophilic displacement upon a mesylated PEG resin$^{65}$.

![Chemical structure diagram]

**Figure 62**: Derivatization of compound **29**

82% yield
The $^1$H NMR for 32 was quite easy to compare to that of 29. In 29, the aromatic system showed an AA'BB' system, which appeared to be an AB quartet of triplets. Compound 32 had a much simpler system where the aromatic peaks appeared as two sets of doublets, at $\delta = 7.77$ and 7.65 ppm. The HRMS confirmed the identity of 32.

It should be noted that compound 32 could not be prepared by refluxing para cyanoaniline and pantolactone (i.e. by a one step method) together in a sealed tube, since the two starting materials are recovered intact even when the sealed tube is heated to 210°C. This means that the aniline used for the one step reaction (see §2.3) cannot have electron withdrawing groups on it.

The synthesis of 32 raised several interesting new problems, some of which were solved. The reduction of the cyano group would have to be achieved without affecting the amide linkage in order to retain the ability to induce chirality in the DKR reaction. This was ultimately achieved by use of a cobaltous boride (Co$_2$B) reagent, which as seen by thin layer chromatography seemed to go to completion. However, the product, which now possessed a primary amine as well as an alcohol, was far too water soluble in order to be isolated in anything other than trace amounts.

Figure 63: Cobaltous boride reduction

The traces of product that were isolated did give some limited spectral data, but the spectral data also contains other compounds. HRMS data, however, did show the
appropriate peak (and M+1 peak) at 234.1349 (calc'd 234.1368). Additional spectral details are in the experimental section.

Other than the isolation problem, there were also two other contributing factors for abandoning this approach. The route now contains a lot of steps (generation of the N-phenyl lactam 26, bromination to 29, conversion to the cyano derivative 32, and reduction to 58) even before the chiral auxiliary is resolved or attached to a polymer. Long syntheses are not likely to carry over well into large scale work due to high costs resulting from time commitments and multiple reagents. The other reason that this approach was abandoned was that if 58 was attached to a polymer, it was most probably going to retain its aliphatic nitrogen (depending on how it is attached to the polymer), which may complicate the DKR reaction since one of the byproducts of the DKR reaction is a halo acid (HBr and/or HI) which is usually removed with triethylamine. A rogue basic amine elsewhere could cause the polymer to precipitate out of solution and unfavourably alter the kinetics of the reaction.

3.4 A Less Basic Nitrogen

Second year organic chemistry stresses the idea that the basicity of an amine can be lowered by having the nitrogen bonded to functional groups in which the lone pairs on the nitrogen can participate in resonance. This means that the problem suggested above can be obviated by having an aniline in place of the aliphatic amine.

Once again using introductory organic chemistry as a guide, the N-phenyl lactam was reacted with an excess of nitric acid in sulfuric acid. Surprisingly, this resulted in not
only oxidation of the alcohol to the ketone, but also in a double nitration of the aryl ring (see figure below). Careful addition of a stoichiometric amount of nitric acid in sulfuric acid at low temperature without any solvent resulted in a modest amount of mononitrated product, albeit in a 2:1 ratio of para to ortho substitution. The mixture of ortho and para products was completely unexpected based on the clean introduction of Br into 26 to form only the para electrophilic aromatic substitution product 29 when Br₂/FeCl₃ was used. Switching to a different source of nitronium electrophile (NO₂BF₄) did not appreciably change the ratio between the ortho and para nitrated products. The use of copper(II)nitrate, however, was able to affect the same product (in the same isomer ratio) without the harsh conditions. Fortunately, the two isomers could be easily separated by column chromatography and the formation of the ketone could be suppressed by protecting the alcohol as a TBDMS ether. (see scheme below)
Scheme 11: Derivation of the chiral auxiliary 26

Reduction of 33 to the aniline 63 was initially achieved by the use of zinc in acetic acid, but the previously used reduction using cobaltous boride was more efficient on larger scales. The \(^1\)H NMR spectra of 33, 60, and 62 were the main diagnostic means by which their identity was elucidated. The \(^1\)H NMR spectrum of 33 shows a typical \textit{para} substitution peak pattern of two sets of doublets. Compound 62 showed a doublet, a triplet, and what is presumed to be an overlapping doublet and triplet. This pattern is consistent with \textit{ortho} disubstituted aryl rings. The formation of the oxidized products 60 and 61 can be explained by the fact that nitric acid is also a well known oxidizing agent. The identity of 60 (both isomers, as they were inseperable by flash chromatography) was
confirmed by the presence of a second C=O band in the IR, as well as mass spectroscopy and NMR. The $^1$H NMR of 60 was greatly simplified when it was compared to 61. In compound 60 the geminal dimethyl groups are now equivalent and appear as one peak at $\delta = 1.4$ ppm. The methylene group in the ring (which appears as an AB quartet in (R)-pantolactone) has coalesced into a singlet. Following the reduction references in §2.5, compound 60 has potential as it could be reduced to give an optically active product (64, see below).

Compound 61 is characterized by the further shift of the aryl peaks to $\delta = 8.7$ ppm due to the electron withdrawing nature of the two nitro groups, and the area of the aryl peaks integrates for a total of three protons.

While 63 was not reactive enough to do a nucleophilic displacement on a mesylated PEG backbone, it had a very useful moiety that could be exploited in a ROMP strategy. Moreover, it was quite simple to prepare compared to the aliphatic amine 58. “Simple” here refers to the experimental ease: high yielding reactions requiring minimal column chromatography.

![Figure 64: Potential chiral auxiliaries and their problems](image)

It should be duly noted that 63 (see previous page) is a protected version of 64.
3.5 ROMP Precursors

In order to be able to do the ROMP reaction, the substrate must have a double bond as part of a strained ring. The most often used substrates for this reaction are norbornene (65) derivatives, because they are readily available from Diels-Alder chemistry.

![Figure 65: Simple ROMP example](image)

The example above uses ethylene as a substrate only in the most formal sense. Practical Diels-Alder reactions have an electron withdrawing group on the dienophile, and based on that idea, the following compound was thought to make a good analogue for ethylene in the above figure.

![Figure 66: Diels Alder dienophile](image)

Compound 67 above was prepared by combining the aniline 63, acryloyl chloride and triethylamine at 0°C. The $^1$H NMR spectrum showed the characteristic acrylamide peaks, with a doublet of doublets at $\delta = 6.63$-$6.37$ ppm, another doublet of doublets at $\delta =$
6.29-6.20 ppm, and a doublet of doublets at δ = 5.73-5.69 ppm, all of which are from the vinyl group.

Compound 67 was thought to be a very good candidate for the Diels-Alder reaction, since the classic Diels-Alder reaction requires an electron rich diene and an electron poor dienophile. Much to our surprise, the amide carbonyl did not make the double bond electrophilic enough to react with cyclopentadiene (a well known and reactive Diels-Alder diene.) No reaction was seen between 67 and cyclopentadiene despite the use of Lewis Acid additives (EtAlCl2, AlCl3) and in the presence of microwaves.

As an alternative approach, we expected that 68 (which we felt could be prepared from 59 and acryloyl chloride) would react more readily with Diels-Alder dienes. Attempts at attaching the acryloyl moiety directly to 59 via Friedel-Crafts or radical methods were not successful. It seems that the aryl ring is activated, but the Lewis Acids also competitively deprotect the alcohol.

![Figure 67: Unsuccessful acrylation attempts](image-url)
A different polymerization "handle" was therefore needed, and efforts were put into making compound 69 in the figure below.

![Figure 68: ROMP precursors](image)

Reaction of maleic anhydride with the TBDMS-protected aniline 63 did not yield 69. Instead a Michael addition reaction occurred to give 71. This reaction (shown in the figure below) proceeds quite rapidly at room temperature, and the adduct 71 precipitates quite readily from solution, forming yellowish needles. $^1$H NMR data showed peaks ($\delta = 4.14, 3.33, 3.08$ ppm) that integrated for a total area of three hydrogens, which indicated that 71 was formed instead of 69. No alkene hydrogen absorption, indicative of the desired 69 was noted.
Figure 69: Michael addition of 63 to maleic anhydride

To that end, it was necessary to approach the synthesis of 70 from another angle\(^6\). If there is a difficulty with the Diels-Alder reaction, don’t do it the difficult way. Maleic anhydride itself reacts quite readily with cyclopentadiene and yields a very well known endo adduct. The resulting tricyclic anhydride reacted with the protected chiral auxiliary to provide a maleimide derivative 70.

Given the published results by Grubbs and others\(^7\), we were led to believe that it would be possible to discover a certain combination of additives and an appropriate metal catalyst that would in fact allow for the polymerization of this substrate. Unfortunately, there is still debate as to whether both endo and exo adducts are polymerizable\(^8\), with some articles specifically not mentioning the relative stereochemistry of their substrates nor a preparation method. Preliminary results with the endo substrate (see table below) did not show promising results.
Table 6: ROMP polymerization results for the endo isomer

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Additive</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grubbs I</td>
<td>CH₂Cl₂</td>
<td>None</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Grubbs I</td>
<td>CH₂Cl₂</td>
<td>PPh₃ (2 eq)</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Grubbs I</td>
<td>CH₂Cl₂ / Benzene</td>
<td>None</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Grubbs I</td>
<td>Benzene</td>
<td>None</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Grubbs I</td>
<td>(ClCH₂)₂ / MeOH</td>
<td>None</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Grubbs I</td>
<td>(ClCH₂)₂ / MeOH / H₂O</td>
<td>None</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>Grubbs I</td>
<td>(ClCH₂)₂ / MeOH</td>
<td>Bu₄NI</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>RuCl₃ / Grubbs I</td>
<td>(ClCH₂)₂ / MeOH</td>
<td>None</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>RuCl₃ / Grubbs I</td>
<td>(ClCH₂)₂ / MeOH</td>
<td>Bu₄NI</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>RuCl₃ / Grubbs I</td>
<td>CH₂Cl₂</td>
<td>PPh₃ (2 eq)</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>RuCl₃</td>
<td>CH₂Cl₂</td>
<td>Bu₄NI</td>
<td>*</td>
</tr>
</tbody>
</table>
* by NMR, there seemed to be approximately 5-10% conversion after 24 hours, but this could correspond to an inactive species with a Ru centre and a single incorporated monomer.

Using the published method⁶⁹, the initial endo Diels-Alder adduct of maleic anhydride and cyclopentadiene was thermally isomerized and recrystallized for isolation.

![Diagram](image)

Figure 70: Preparation of exo-72

The endo and exo isomers were characterized by their melting points as per ref 66, endo-72 having a melting point of 165°C, and exo-72 having a melting point of 143°C. There were also slight differences in the ¹H NMR spectra as well: coupling differences (the methine hydrogens will couple according to the Karplus curve) as well as
shielding from the distant pi system in the double bond. Characterization data is provided in the Experimental section.

The difference in reactivity between the endo and exo adducts was apparent in that the endo adduct simply needed to be heated with aniline 63 in order to form the maleimide 70. The exo adduct furnished the amic acid 73 and refused to dehydrate to the maleimide (see below).

![Diagram of chemical reactions]

Figure 71: Preparation of endo and exo ROMP precursors 70
This was remedied by the addition of thionyl chloride to the neat amic acid 73. A basic workup yields the pure exo maleimide 70. However, due to time constraints (as well as other concerns, see below), it was not tested under the ROMP conditions.

The simple problem that is encountered, and only occasionally mentioned in the literature is that the Ru centre still retains some degree of electrophilic character. This means that the presence of any unusually polar groups will continue to hinder the polymerization reaction. Polar groups may hinder the reaction by the formation of two important compounds which prevent the metal centre from participating in the catalytic cycle. The key to this is the endo configuration. Due to the three dimensional shape, any substituents on the five membered ring are in close proximity to the double bond, which also creates steric congestion.

3.6 Coordination chemistry to lend a helping hand

If it is possible to interrupt this coordination between the ruthenium and the oxygen, the ROMP reaction might proceed to completion. The question was how to do it. Getting rid of the oxygens might be possible via a reduction with LiAlH₄, but that would add more steps. Preemptively removing the oxygens by reducing the cyclopentadiene / maleic anhydride adduct to the diol, mesylating the hydroxyls, and hoping the aniline would affect the double displacement seemed to be a lot of wishful thinking. The aniline nitrogen was already known to not be a good nucleophile, and would probably require prolonged heating, which might result in mixtures where the
nitrogen might displace the leaving groups on different monomers rather than cyclize on one.

Diels-Alder chemistry has taught us the importance of additives. Perhaps an additive might serve well. Titanium tetraisopropoxide was chosen due to the fact that it was on hand and would serve well as a benchmark. It is a strong Lewis Acid, and therefore would do well to coordinate to the oxygen and hopefully prevent coordination to the ruthenium. However, necessarily, it would have to be used in a stoichiometric quantity.

In order to not waste the precious quantity of monomer made, a simpler system was synthesized, which contained the problematic carbonyls:

![Image of a simple ROMP precursor with carbonyls](image)

Figure 72: A simple ROMP precursor with carbonyls

This model system was made the same way as the chiral version. Additionally, the same efforts were taken to make some of the exo isomer, which were successful. In the process of making this compound, a few references\textsuperscript{70} came to light, which contained the necessary information regarding the polymerization of “problematic” monomers. Indeed, a degassed dichloromethane solution of the monomer in the presence of two\textsuperscript{71} equivalents of Ti(O'Pr)\textsubscript{4}, as well as the first generation Grubb’s catalyst provided a somewhat viscous mixture after 24 - 48 hours. Taking a cue from classical polymer chemistry, the workup consisted of adding ethyl vinyl ether, stirring, followed by precipitation of the polymer with methanol. This provided the polymer in sufficiently pure form.
The same conditions\textsuperscript{72}, applied to the chiral auxiliary, provided the ROMP-ed chiral auxiliary 75. Interestingly enough, there was no difference in the TLC spots despite the increased molecular weight of the polymer. This means that in order to properly monitor this reaction, aliquots would have to be removed and analyzed by NMR.

![Diagram of molecular structures]

Figure 73: The ROMP approach in practice

Characterization of low molecular weight polymers is difficult, but still possible. Since the polymers made were of a relatively low molecular weight (i.e. less than 100,000 atomic weight), NMR spectra are still quite usable. Typical of polymers, the spectrum experienced line broadening. This line broadening has to do with the fact that the constituent functional groups, which were present in the monomer, are now slightly different in the polymer. A methine group that is closer to the end of the polymer behaves slightly different than one that is in the middle of the polymer. Moreover, the distribution of such nuclei is also dependent on the polydispersity of the polymer, since a longer polymer will still have all the peaks that a shorter polymer has. The restricted degrees of freedom of a nucleus closer to the middle of the polymer has a direct influence upon the ability of that nucleus' dipole to relax, thereby affecting the $T_1$ of a given nucleus. This, coupled with the slightly different electronic environment, leads to line
broadening and can make spectra difficult to interpret. However, the most important information could still be seen. Mainly, the disappearance of the strained olefin peak at \( \delta = 6.3 \) ppm, and the appearance of the olefinic peak at \( \delta = 5.7 \) ppm. This is consistent with the ring opening of the norbornene skeleton. This is also the means by which a ROMP reaction can be monitored.

In the \(^1\text{H\ NMR}\) spectrum of the polymer obtained by polymerization of the chiral auxiliary, there are still a number of singlets, and their appearance as slightly broadened singlets means that the polydispersity is relatively low, but it also means that the polymer is not very long, since there aren’t a lot of spectroscopically “different” nuclei.

![Figure 74: \(^1\text{H\ NMR of polymer 75}\)](image)

3.7 Help from the Grubbs group
Fortuitously, my supervisor (Prof. Tony Durst) met Dr. T.L. Chan who carried out his Ph.D. under the supervision of Prof. Robert Grubbs and now has a postdoctoral appointment in the laboratory of Prof. Jean Frechet. Dr. Chan was provided with a sample of my monomer, that he then polymerized with a new and more reactive catalyst\textsuperscript{73}.

Since this experiment was run in the Frechet laboratories at U. C. Berkeley, it was possible to do more extensive characterization than what was available in Ottawa for the polymers that I had made. In particular, GPC (Gel Permeation Chromatography) analysis allowed for a more detailed analysis, yielding not only average molecular weight of the polymer but also the polydispersity\textsuperscript{74}.

The polymer made at Berkeley, despite different polymerization conditions, had very similar physical properties, including being a white powder that was soluble in CHCl\textsubscript{3}, as the one that I had made with my modified conditions. The use of more reactive catalysts allows for less “harsh” reaction conditions. Specifically, it is possible to avoid the use of strong Lewis Acids such as Ti(O\textsuperscript{Pr})\textsubscript{4}. These more reactive catalysts have increased the electronic density around the ruthenium centre, rendering them less oxophilic. It should be noted that despite the fact that alkenes will react before alcohols and carbonyls (see table 4, p. 86), oxygen atoms in the monomer will still coordinate to the ruthenium centre, and it is this coordination that leads to catalyst inactivity. Increasing the electron density at the ruthenium centre increases the overall stability of the complex, making coordination towards oxygen atoms less favourable.

The tradeoff is that while the catalyst increases in complexity, so does its cost. This increase in complexity has led to increased stability as the decreased dependence on
phosphine ligands has bestowed air and moisture resistance. The figure below shows the catalysts, early at the left, most recent on the right.

Figure 75: Ruthenium catalysts for ring opening metathesis polymerization

3.8 Learning to work with polymers

The protected polymer (75) was freely soluble in chloroform. Deprotection was attempted with TFA in chloroform, but was incomplete by $^1$H NMR. The sample was resubmitted to the deprotection conditions but the deprotection never progressed beyond 10-20% (determined by $^1$H NMR). The inability to complete the deprotection was thought to be due to the TFA. Switching to the use of TBAF in THF caused immediate precipitation of the polymer, but $^1$H NMR analysis of the product again indicated incomplete deprotection. The progress of the deprotection could easily be evaluated by noting the disappearance of the three peaks with the lowest ppm shift on the spectrum (at 0.9 ppm, 0.2 ppm and 0.1 ppm) due to the TBDMS group.

The hurdle that was preventing the completion of the deprotection was puzzling. Examination of related literature and a discussion with Prof. Robert Ben indicated that
the use of DMSO and DMF were likely to lead to success. Indeed the combination of DMSO and TBAF led to complete deprotection as judged by the disappearance of the peaks due to the TBDMS protecting group.

Figure 76: Deprotection of the polymer-supported chiral auxiliary

Unfortunately, the resulting polymer was no longer soluble in chloroform. Characterization became more difficult, since DMSO-d$_6$ was the only readily available solvent that we had on hand in which the deprotected polymer was somewhat soluble. The sample could be recovered by addition of water. The characterization difficulty lies with DMSO's perpensity to attract water. Water in the NMR solvent resulted in not only unwanted peaks in the $^1$H NMR spectrum, but also a further broadening of the already broad peaks due to the partial insolubility imparted by the increased water content.

3.8.1 Deprotection easy, Acetylation not so easy
The deprotected polymer (76) was no longer soluble in chloroform. It was therefore decided to carry out the acylation in DMSO or DMF. Unfortunately, DMSO would be an unsuitable solvent for the esterification reaction, since alcohols are known to oxidize in this solvent when in the presence of carbodiimides. The esterification reactions, therefore, were carried out in DMF.

Figure 77: Attempted esterification of deprotected polymer 76

α-Bromophenylacetic acid was chosen as the acid partner since it is unable to undergo the unwanted β-elimination side reaction upon reaction of the acylated polymer with benzylamine. Furthermore the acylated polymer was not expected to yield a complicated $^1$H NMR spectrum. Under ideal conditions, the polymer would be analyzed by $^1$H NMR (possibly using the more costly DMF-d$_7$ solvent in hopes of avoiding the partial insolubility that occurs with the water present in the DMSO-d$_6$ solvent.) Ideally, we would be able to determine not only the degree of loading but also the diastereomer ratio in both the initially acylated polymer and the diastereomer ratio after the DKR reaction with benzylamine before the amino acid is cleaved from the resin.

Owing to the small quantities of polymer available, as well the increasingly dominating time constraints, there was only enough time to attempt two esterification
reactions. The coupling agents of choice that were evaluated were DCC and CDI (see below.)

![Chemical Reaction]

Figure 78: Esterification conditions attempted on the polymer

The DCC conditions seemed the most promising, since the aryl region (7.5 – 7.0 ppm) showed an increase in area, indicating approximately 20% loading. Unfortunately, upon reexposure of the sample to the same acylating conditions no further ‘loading’ was observed.

The CDI conditions were not successful at all, and the polymer that was isolated has the same NMR spectrum as it did before the reaction. It is unknown why it would not react, since evolution of CO₂ was observed at the beginning of the reaction, indicating activation of the CDI reagent.

It therefore becomes apparent that a more detailed study needs to be undertaken in order to determine the exact conditions necessary to achieve the coupling of the carboxylic acids to the resin. These include, but are not limited to, use of acyl chlorides, and other coupling reagents (i.e. EDC, DMC, mixed anhydrides, etc)
The conclusions that can be drawn from this work, is that it is possible to attach a chiral lactam auxiliary to a support. Additionally, the model studies described in this thesis indicated that DKR reactions with such lactams auxiliaries work as well as they do with pantolactone.

Future Work

A number of aspects of this work took much more time than anticipated and thus it is clear that more work is required to consider this project “finished.”

In particular, at the end of this work we were disappointed by the change in solubility in going from the TBDMS protected polymer to the polymer carrying the necessary hydroxyl group. This polymer did not appear to swell when placed in CHCl₃ or THF thus making the loading of the polymer with α-bromo acids more difficult. Time did not permit further experimentation. Specifically, precise protocols have to be developed in order to determine the optimum means by which the α-halo acid must be attached to the polymer. Given the results from section §2.5, the use of an acyl chloride might not be the best route and a mixed anhydride might have to be used.

We anticipate that the acylated polymer might again be soluble in chloroform or THF. This is important not only for the ease of working with the system but more importantly, we expect that it will be crucial that the DKR reactions occur in solution rather than at the solid liquid interface. We are confident that the diastereomer ratios will translate from the small molecule lactam chiral auxiliary to the related polymer system.
Logically, it follows that a protocol must also be developed for the actual polymer supported DKR reaction. While this may not necessitate another Ph.D. thesis, a series of reactions have to be carried out with varying concentrations, equivalents of amine, etc. The issue of equivalents of nucleophile is an important one since an excess of nucleophile is traditionally used in polymer supported reactions in order to facilitate rapid reaction completion but in this case may cause premature cleavage from the resin, lowering the overall yield.

The issue of characterization must also be addressed. Due to the limited instrumentation on hand, the characterization has been done from the point of view of small molecule synthesis. Luckily, with the aid of other groups, we were able to carry out a minimal amount of characterization on one of our polymers. *In situ* characterization would be ideal, since it would allow for the determination of completion of the loading of the polymer as well as the completion of the DKR reaction.

The most important aspect of future work is to address that the issue of chirality. Due to ease of procurement, racemic pantolactams were used to synthesize monomers. In order to be effective in any synthesis, a chiral version (again, ideally a separate synthesis of both enantiomers) would have to be made. There is, potentially, a simple solution to this problem: the use of a chiral protecting group for the hydroxyl group. Separation of the two resulting diastereomers could be carried out at any later point in the synthetic sequence, allowing for serendipitous discovery of experimentally facile conditions (i.e. one diastereomer would preferentially crystallize out of a common solvent such as benzene or ether). Alternatively, one could consider asymmetric
reduction of an appropriate α-keto lactam, such as 60 (obtained as a byproduct in the one of the nitration attempts.)

Finally, other polymer systems might be considered in order to achieve the desired solubility characteristics. One approach might be to consider preparing a copolymer consisting of either endo or exo 70 and endo or exo 74. By varying the ratio of the two monomers, polymers with different loadings of the hydroxyl carrying chiral auxiliary would be produced. This should affect the solubility of the final polymer.

Alternatively other monomers such as the ones below could be prepared and subjected to polymerization in order to generate polymers with the desired properties.

\[
\text{NH}_2 \quad \text{O} \quad \text{PO} \quad \text{PO}
\]

\[
\text{O} \quad \text{N} \quad \text{PO} \quad \text{PO}
\]

\[
\text{O} \quad \text{N} \quad \text{PO} \quad \text{PO}
\]

\[
\text{P} = \text{TBDMS}
\]

\[
\text{Figure 79: A simpler monomer based on 63}
\]

The monomer could more easily be generated from compound 63, and the completion of the polymerization could be monitored by the loss of ethylene gas from solution. This would also have the advantage of having an even greater loading capacity than the polymer described in this work.
Experimental

General procedures

Tetrahydrofuran, and benzene were distilled over sodium-benzophenone ketyl immediately prior to use. Dichloromethane was distilled over calcium hydride immediately prior to use. DMF, DMSO and acetonitrile were distilled over activated molecular sieves and stored over molecular sieves. All over solvents were distilled or were of reagent grade quality. Unless stated otherwise, all non-aqueous reactions were performed under an atmosphere of dry nitrogen.

Flash chromatography refers to silica gel chromatography using 230-400 mesh silica under nitrogen pressure using the specified eluant mixture. Thin layer chromatography (TLC) was performed on Merck 60F 254 precoated silica gel plates.

Infrared spectra were obtained as thin films using a Mobem FT-IR model MB-100 using sodium chloride plates unless specified otherwise. Mass spectra were recorded on KRATOS Concept IH or Concept IIH mass spectrometers. Peak intensities are given as percentage of the base peak intensity.

Unless otherwise indicated, all NMR spectra were recorded in chloroform-\textit{d}, using a Varian Gemini-200 spectrometer, operating at 200 MHz for proton and 50 MHz for carbon spectra, or a Varian XL-300 spectrometer, operating at 300 MHz for proton and 75 MHZ for carbon spectra. The coupling patterns are described as (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (dd) doublet of doublets, (dt) doublet of triplets, (etc), or (br) broadened.
Compound 8b: The MOM-protected (R)-pantolactone

\[
\begin{array}{c}
\text{MOMO} \\
\text{(R)-dihydro-3-(methoxymethoxy)-4,4-dimethylfuran-2(3H)-one}} \\
\text{8b}
\end{array}
\]

A 200 mL round-bottomed flask was charged with 10.0 g (76.7 mmol) of (R)-pantolactone, dry THF (30-50 mL) a magnetic stirrer, and cooled to 0°C. Triethylamine 11.8 mL (84.26 mmol, 1.1 eq) was added via a syringe and the system was sealed except for a nitrogen line. After 30 minutes of stirring with the triethylamine, chloromethyl methyl ether 17.55 mL (229.9 mmol, 3 eq) was added via a syringe dropwise over a 30 minute time period.

The reaction with chloromethyl methyl ether required overnight stirring. The initial reaction provided a white precipitate, while the reaction flask, upon completion of the reaction, had a biphasic solution, the top phase of which was clear, and the bottom phase was yellow and oily.

In order to prevent loss of product, the sample was dried down before performing an aqueous extraction. This removed the top phase, giving the product as a yellow oil in 77 to 92% yield, depending on scale.

\[^1\text{H NMR}\ (\text{CDCl}_3, 500\text{MHz}) \delta 4.96-4.94, (dd, J = 1.0, 6.8 \text{ Hz}, 1\text{H}), 4.67-4.65 \text{ (dd, } J = 1.0, 6.8 \text{ Hz, } 1\text{H}), 4.01 \text{ (s, } 1\text{H}), 3.94-3.86 \text{ (AB q, } J = 8.9, 34.9 \text{ Hz, } 2\text{H}), 3.38 \text{ (s, } 3\text{H}), 1.15 \text{ (s, } 3\text{H}), 1.05 \text{ (s, } 3\text{H}).
\]

\[^{13}\text{C NMR}\ (\text{CDCl}_3, 125\text{MHz}) \delta 175.00, 96.00, 78.30, 76.02, 55.80, 22.98, 19.32.\]

\textbf{EI-MS} \text{ m/z (\%): 173 (2), 159 (4), 143 (21), 99 (47), 45 (base).}

\textbf{HRMS} \text{ calc'd for C}_{8}\text{H}_{14}\text{O}_4 : 174.0892, \text{ found: 174.0848.}

\textbf{IR (cm}^{-1})\text{: 2959, 2921, 2852, 2828, 1782, 1463, 1375, 1150, 1118, 1012, 993, 918.}
Compound 9c: The ring-opened, protected pantolactone

\[
\text{(R)-4-hydroxy-2-(methoxymethoxy)-3,3-dimethyl-1-(pyrrolidin-1-yl) butan-1-one}
\]

To a stirred solution of 3-methoxymethoxy-4,4-dimethyl-dihydro-furan-2-one (8b) (310 mg, 1.78 mmol) pyrrolidine (0.164 mL, 1.96 mmol) was added with a stirring bar. No solvent was used, and the solution was stirred overnight. The progress of the reaction was monitored by thin layer chromatography using 3:1 hexanes:ethyl acetate as the eluant. Upon satisfactory completion, the resulting solution was yellowish and was taken up in approximately 20 mL methylene chloride, and an aqueous extraction was performed (no acid). The two phases changed colour to a milky-cloudly colour for the aqueous phase, and a yellow opaque cloudy phase for the organic. The organic phase was dried with MgSO\textsubscript{4} and rotoevaporated to furnish a yellow oil with a pungent stench. Attempts at recrystallization with ether-hexanes provided the product as a yellow oil.

Yields ranged from 86% to quantitative, depending on scale.

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500MHz) \delta 4.58 (s, 2H), 4.10 (s, 1H), 3.68 (m, 3H), 3.50 (m, 3H), 3.34 (s, 3H), 1.95 (m, 2H), 1.82 (m, 2H), 0.98 (s, 3H), 0.97 (s, 3H).}\]

\[\text{EI-MS m/z (%): 143 (11), 114 (18), 99 (61), 71 (33), 45 (100), 28 (85).}\]

\[\text{HRMS (FAB) calc'd for C\textsubscript{12}H\textsubscript{24}NO\textsubscript{4}: 246.1706, found 246.1995.}\]

\[\text{IR (cm}^{-1}\text{): 3403 (broad), 1629, 1453, 1356, 1337, 1145, 1108, 1044, 916.}\]
Compound 14: Aldehyde of compound 9c

(R)-3-((methoxymethoxy)-2,2-dimethyl-4-oxo-4-(pyrrolidin-1-yl)butanal

Method 1: PCC Oxidation.
A small sample of the alcohol (4-hydroxy-2-methoxymethoxy-3,3-dimethyl-1-
pyrrolidin-1-yl-butan-1-one) (270 mg, 1.10 mmol) was added to a 25 mL round bottom
flask, charged with a magnetic stirrer, dry dichloromethane (approx 5 mL) and 10 mg of
NaHCO₃. PCC (262 mg, 1.212 mmol) was added slowly and the solution was left to stir
for several hours. The reaction monitored by TLC (reaction compared to the starting
material using 3:1 hexanes:ethyl acetate as the eluant). The Rf value of the product (0.6)
was higher than that of the starting material (0.3).

Upon completion of the reaction, diethyl ether was added to the flask and the
supernatant was immediately placed on a very short silica gel column (pure ether) and
250 mL of diethyl ether was used to elute the aldehyde which was isolated by
rotoevaporation of the ether.

Method 2: Swern Oxidation
On a larger scale, the aldehyde was prepared by using the Swern oxidation.

Oxalyl chloride (0.203 mL, 1.25 eq) was combined with dimethyl sulfoxide
(0.331 mL, 2.5 eq) in dichloromethane in a 25 mL flask charged with a stirrer and cooled
to −78°C. The mixture was allowed to stir for 30 minutes to allow the complex to form.
The alcohol (4-hydroxy-2-methoxymethoxy-3,3-dimethyl-1-pyrrolidin-1-yl-butan-1-one)
(455 mg, 1.868 mmol) in a separate 10 mL flask with 5 mL of dichlormethane, was
cannulated slowly into the reaction mixture and was allowed to stir for 30 minutes.
Triethylamine (1.30 mL, 5 eq) was added and the flask was brought to room temperature
by removing the cold bath.

The contents of the reaction flask were poured into a separatory funnel containing
saturated ammonium chloride solution, and vigorously shaken. The organic phase was
dried down, taken up in ether and a subsequent aqueous extraction provided the aldehyde
in near-quantitative yield.

The sample was usually sufficiently pure for further reactions, but if the ¹H NMR
spectrum showed impurities, the sample was chromatographed with the same solvent
system used for TLC monitoring.

¹H NMR (CDCl₃, 500MHz) δ 9.74 (s, 1H), 4.60 (s, 2H), 4.31 (s, 1H), 3.70 (m, 1H), 3.45
(m, 3H), 3.32 (s, 3H), 1.93 (m, 2H), 1.82 (m, 2H), 1.12 (s, 3H), 1.10 (s, 3H).
$^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 203.87, 168.55, 95.85, 78.85, 55.92, 48.61, 47.10, 46.11, 26.19, 24.02, 19.62, 17.87.

**EI-MS** m/z (%): 243 (0.2), 212 (7), 154 (47), 113 (30), 98 (100), 83 (23), 70 (24), 55 (81), 45 (78).

**FAB-MS** m/z (%): 244 (90), 212 (92), 154 (50), 132 (100), 98 (50), 83 (44), 69 (46).

**IR (cm$^{-1}$):** 2784, 2733, 1719, 1638.
Compound 15: The alkylarylamine

\[
\text{MOMO} \quad \text{15} \\
\text{HN} \quad \text{OMe}
\]

(R)-4-(4-methoxyphenylamino)-2-(methoxymethoxy)-3,3-dimethyl-1-(pyrrolidin-1-yl)butan-1-one

Compound 14 (500 mg, 1.38 mmol) was combined with p-anisidine (188 mg, 1.52 mmol) in a 25mL round bottom flask with a magnetic stirrer and 95% ethanol (15 mL). A 10% mass equivalent to 14 of 10% Pd on carbon was added (50 mg, effectively 1% catalyst) and the mixture was allowed to stir under an atmosphere of hydrogen gas supplied by a rubber balloon. The reaction was monitored by thin layer chromatography (either 3:1 Hexanes:Ethyl Acetate or 2:1 Hexanes:Ethyl Acetate) until all the starting material had disappeared. In the case of prolonged reaction times (reaction incomplete after 48 hours) more catalyst was added.

In all the reaction runs, the product was sufficiently pure after filtering and rotary evaporation to continue on to the next step without flash chromatography.

\(^1\text{H NMR}\ (\text{CDCl}_3, 500\text{MHz}) \delta 6.70-6.68 (d, J = 8.9 \text{ Hz}, 2H), 6.54-6.52 (d, J = 8.9 \text{ Hz}, 2H), 4.55 (s, 2H), 4.20 (s, 1H), 3.67 (s, 3H), 3.63-3.34 (m, 4H), 3.29 (s, 3H), 3.05-2.96 (AB q, J = 12.4, 31.5 \text{ Hz}, 2H), 1.86-1.66 (m, 4H), 1.06 (s, 3H), 1.05 (s, 3H).

\(^{13}\text{C NMR}\ (\text{CDCl}_3, 125\text{MHz}) \delta 169.19, 151.72, 143.33, 114.77, 114.06, 95.82, 78.67, 55.84, 55.36, 53.18, 46.96, 45.92, 38.86, 26.24, 23.89, 22.88, 22.38.

**EI-MS** m/z (%): 350 (47), 204 (11), 154 (100), 136 (64), 128 (35).

**HRMS (FAB)** calc’d for C_{19}H_{30}N_{2}O_{4}: 350.2206, found 350.2178.

**IR (cm\(^{-1}\)):** 3374, 1635, 913, 817, 727.
Compound 18: The protected lactam

\[
\text{MO MO} \quad \text{N} \quad \text{OMe} \\
(R)-3-(methoxymethoxy)-1-(4-methoxyphenyl)-4,4-dimethylpyrrolidin-2-one
\]

Compound 15 (132 mg, 0.39 mmol) was combined with toluene (5mL) and a substoichiometric quantity of acetic acid (0.6 – 0.7 molar equivalent) and refluxed. TLC’s (2:1 Hexanes:Ethyl Acetate) were analyzed every three hours until the reaction was deemed complete. The organic layer was washed with 10% HCl solution, and after rotary evaporation, the product was usually sufficiently pure for the next step. Flash column chromatography was used with the same solvent system as the TLC’s to purify the material from batches that contained impurities.

\(^1\text{H NMR} \ (\text{CDCl}_3, \ 500\text{MHz}) \ \delta \ 7.49-7.45 \ (d, \ J = 9.1 \text{ Hz}, \ 2\text{H}), \ 6.88-6.85 \ (d, \ J = 9.1 \text{ Hz}, \ 2\text{H}), \ 5.08-5.07 \ (d, \ J = 6.7 \text{ Hz}, \ 1\text{H}), \ 4.76-4.74 \ (d, \ J = 6.7 \text{ Hz}, \ 1\text{H}), \ 4.03 \ (s, \ 1\text{H}), \ 3.76 \ (s, \ 3\text{H}), \ 3.44 \ (s, \ 3\text{H}), \ 3.47-3.37 \ (\text{AB q, } J = 7.7, \ 37.8 \text{ Hz}, \ 2\text{H}), \ 1.26 \ (s, \ 3\text{H}), \ 1.12 \ (s, \ 3\text{H}).
\]

\(^13\text{C NMR} \ (\text{CDCl}_3, \ 125\text{MHz}) \ \delta \ 171.42, \ 156.61, \ 132.61, \ 121.20, \ 114.06, \ 96.47, \ 93.11, \ 91.29, \ 81.75, \ 58.07, \ 55.8, \ 55.43, \ 37.95, \ 24.80, \ 20.69.
\]

\text{EI-MS} \ m/z \ (\%) \ 279 (14), \ 204 (50), \ 69 (20), \ 45 (32), \ 30 (100).

\text{HRMS} \ \text{calc'd for } \text{C}_{15}\text{H}_{21}\text{NO}_4 : 279.1471, \ \text{found: } 279.1460.

\text{IR} \ (\text{cm}^{-1}): \ 1688 \ (\text{C}=\text{O})

\text{Melting Point}: \ \text{Melting point was found to be } 73.5 - 75.0^\circ\text{C (uncorrected).}
Compound 19: (R)-n-(p-methoxyphenyl)-pantolactam

\[
\text{(R)-3-hydroxy-1-(4-methoxyphenyl)-4,4-dimethylpyrrolidin-2-one}
\]

To a solution of the protected lactam 18 (151 mg, 0.54 mmol) in dichloromethane (5 mL), a few drops of trifluoroacetic acid were added. The solution was allowed to sit for a period of no less than 6 hours. If the TLC showed that the reaction wasn’t complete, more drops of TFA were added.

Once the deprotection was deemed complete by TLC (1:1 Hexanes:Ethyl Acetate), the reaction mixture was poured into a separatory funnel with water, and the organic phase was isolated, dried down and analyzed by NMR. The purity of the product was good, but occasionally the product needed recrystallization by dissolving in dichloromethane (or ether) and slowly adding hexanes. The yield was generally very good (81 - 99%) even on larger scales.

\[\text{H NMR (CDCl}_3, 500\text{MHz}) \delta 7.48-7.43 \text{ (d, } J = 9.2 \text{ Hz, } 2\text{H}), 6.89-6.87 \text{ (d, } J = 9.2 \text{ Hz, } 2\text{H}), 4.86-4.84^* \text{ (d, } J = 3.7 \text{ Hz, } 1\text{ OH}), 4.09-4.07 \text{ (d, } J = 3.7 \text{ Hz, } 1\text{H}), 3.78 \text{ (s, } 3\text{H}), 3.50-3.28 \text{ (AB q, } J = 9.5, 22.7 \text{ Hz, } 2\text{H}), 1.22 \text{ (s, } 3\text{H}), 1.05 \text{ (s, } 3\text{H}).\]

\[\text{C NMR (CDCl}_3, 125\text{MHz}) \delta 173.40, 156.82, 132.35, 121.33, 114.17, 78.33, 58.19, 55.47, 38.58, 24.56, 19.96.\]

\[\text{EI-MS m/z (\%)} 235 (43), 149 (100), 135 (39), 120 (26), 69 (20), 56 (83), 40 (58).\]

\[\text{HRMS calc'd for C}_{13}\text{H}_{17}\text{NO}_3: 235.1209, \text{found 235.1203.}\]

\[\text{IR (cm}^{-1}) 3408 (\text{OH}), 1693 (\text{C=O}).\]

**Optical Rotation:** -37.5° [c = 2.0, CH\(_2\)Cl\(_2\)]

* It should be noted that this is not always visible, and is highly dependent on the quality of the sample, as well as the quality of the deuterated chloroform. The position, as with all hydroxyl peaks, varies. At δ 4.46 / 4.45, it is still visible, but broadens considerably if the center of the peak moves further to the right, to such a degree that the coupling constant is not measurable.
Compound 19: Racemic preparation of aryl substituted and aryl unsubstituted lactams

Equimolar amounts of racemic pantolactone (1g, 76.8 mmol) and p-anisidine (0.95g, 76.8 mmol) were combined in a high pressure tube. This tube was evacuated under low pressure to remove gases and bubbles from the clear amber mixture. It was sealed and placed inside a common household microwave specially adapted for such a purpose. The tube was heated in successive iterations of 99 minutes and 99 seconds at high power until it had been heated for no less than 6 hours total. The tube was allowed to cool, and a small sample was removed to be analyzed by $^1$H NMR, monitoring for the disappearance of the AB quartet from $\sim 3.9$ ppm and the appearance of a new AB quartet at $\sim 3.4$ ppm.

Upon satisfactory conversion, methylene chloride was added, and washed with 1% HCl solution, dried with magnesium sulfate and dried down. Spectroscopic analyses, with the exception of optical rotation, were identical with the chiral compound.
Compound 21: Alpha bromo esters of the lactam auxiliary

DCC method - Representative preparation

The chiral auxiliary (19, 235.6 mg, 1 mmol) was dissolved in distilled acetonitrile, and 1.25 molar equivalents of DCC (dicyclohexylcarbodiimide, 273.4 mg, 1.25 mmol) was added and the mixture was stirred until it was clear. DMAP (dimethylaminopyridine, 10 mg) was added to catalyze the esterification. Finally, the acid was added (equimolar amount corresponding to the chiral auxiliary). The mixture was allowed to stir for no less than 4 hours, and monitored by TLC (usually 1:1 Hexanes: Ethyl Acetate). Upon completion, the mixture was diluted with diethyl ether, filtered, and the solvent was evaporated to give a product suitable for further reactions. If the reaction was not complete after 8 hours, 0.1 molar equivalents of DCC was added, and the reaction was further monitored for completion.

DMC method – Representative preparation

The chiral auxiliary (1 mmol) was dissolved in distilled dichloromethane (5 – 10 mL), along with an equimolar amount of the acid (1 mmol) and freshly prepared DMC (1 mmol). The flask was cooled to 0°C, and two molar equivalents of pyridine (2 mmol) were added dropwise via syringe. The reaction was monitored by TLC after 15 minutes, and was usually complete by that time. In cases when it wasn’t complete, the reaction was allowed to stir for up to four hours before more DMC and pyridine was added. Upon completion, the reaction mixture was diluted with more dichloromethane (5 – 10 mL), and washed successively with 1% HCl, saturated bicarbonate solution, and brine. After drying with MgSO₄, the solvent was removed by rotary evaporation under low pressure to provide the product in sufficient purity for further reactions.
Ester obtained from alpha-bromo phenylacetic acid and the p-methoxy-lactam chiral auxiliary.

This compound was prepared using the DCC method starting with 215 mg (1 mmol) of α-bromophenylacetic acid and 235 mg (1 mmol) of the chiral auxiliary 19. Yield after chromatography was 60% (30% starting material was also recovered), 86% based on conversion.

The key diastereomeric peaks are both alpha to a carbonyl moiety and appear at δ 5.55 / 5.51 ppm and δ 5.40 / 5.39 ppm. The integration of the first set of peaks indicates a diastereomeric ratio of 1.3 : 1. This was the same ratio of the integration of the peaks at δ 0.879 ppm and δ 1.307 ppm, which are part of the geminal dimethyl system in the lactam ring (note the change in magnitude of the upfield peak versus the downfield peak).

\[ \text{H NMR (CDCl}_3, 200\text{MHz) } \delta \text{ 7.63-7.33 (m, 7H), 6.90-6.86 (d, } J = 9.0 \text{ Hz, 2H), 5.55 (s, 0.5H), 5.51 (s, 0.5H), 5.40 (s, 0.5H) 5.39 (s, 0.5H), 3.77 (s, 3H), 3.60-3.55 (d, } J = 9.3 \text{ Hz, 0.5H), 3.55-3.51 (d, } J = 9.2 \text{ Hz, 0.5H), 3.47-3.43 (d, } J = 9.7 \text{ Hz, 0.5H), 3.41-3.36 (d, } J = 9.7 \text{ Hz, 0.5H), 1.31 (s, 1.5H), 1.17 (s, 3H), 0.88 (s, 1.5H)} \]

The explanation for the seemingly confusing fractions above can be explained via the presence of the diastereomers, the AB coupling system of the methylene system in the lactam ring, and overlapping of some of the peaks. No attempt was made to isolate one of the diastereomers over another due to the lack of separation of the spots on a TLC plate.

Since these compounds were obtained as mixtures and processed further in the DKR reactions, they were not further characterized.
Ester obtained from alpha-bromo butyric acid and the p-methoxy-lactam chiral auxiliary.

This compound was prepared using the DCC method starting with 107 μL (1 mmol) of α-bromobutyric acid and 235 mg (1 mmol) of the chiral auxiliary 19. Yield after chromatography was 376.6 mg (98%).

The key diastereomeric peaks are at δ 5.36 / 5.34 ppm. The integration of the peaks indicates a diastereomeric ratio of 1.3 : 1.

\[ ^1H \text{NMR (CDCl}_3, \text{ 200MHz)} \delta \ 7.49-7.43 \ (d, J = 8.6 \text{ Hz, 2H}), \ 6.86-6.82 \ (d, J = 9.0 \text{ Hz, 2H}), \ 5.36 \ (s, 0.5H), \ 5.34 \ (s, 0.5H), \ 4.34-4.22 \ (m, 1H), \ 3.73 \ (s, 3H), \ 3.57-3.52 \ (d, J = 9.7 \text{ Hz, 1H}), \ 3.45-3.39 \ (d, J = 9.5 \text{ Hz, 1H}), \ 2.25-1.93 \ (m, 2H), \ 1.26 \ (s, 1.5H), \ 1.25 \ (s, 1.5H), \ 1.14 \ (s, 1.5H), \ 1.13 \ (s, 1.5H), \ 1.09-1.01 \ (t, J = 7.3 \text{ Hz, 1.5H}), \ 1.08-1.00 \ (t, J = 7.3 \text{ Hz, 1.5Hz}) \]

The explanation for the seemingly confusing fractions above can be explained via the presence of the diastereomers, the AB coupling system of the methylene system in the lactam ring, and overlapping of some of the peaks. No attempt was made to isolate one of the diastereomers over another due to the lack of separation of the spots on a TLC plate.
Ester obtained from alpha-bromo propanoic acid and the p-methoxy-lactam chiral auxiliary

This compound was prepared using the DCC method starting with 81 μL (0.9 mmol) of α-bromopropionic acid and 212 mg (0.9 mmol) of the chiral auxiliary 19. Yield after chromatography was 280 mg (84%).

The key diastereomeric peaks are at δ 5.40 / 5.37 ppm. Approximate ratio of diastereomers was 1 : 1.

\[ ^1H \text{NMR (CDCl}_3, 200MHz) \delta 7.49-7.43 \text{ (d, } J = 8.8 \text{ Hz, 2H), 6.90-6.86 \text{ (d, } J = 9.0 \text{ Hz, 2H), 5.40 \text{ (s, 0.5H), 5.37 \text{ (s, 0.5H), 4.60-4.40 \text{ (m, 1H), 3.78 \text{ (s, 3H), 3.62-3.57 \text{ (d, } J = 9.7 \text{ Hz, 1H), 3.49-3.43 \text{ (d, } J = 9.5 \text{ Hz, 1H), 1.93-1.89 \text{ 1.88-1.84 \text{ (diastereomeric d, } J = 7 \text{ Hz, 3H), 1.31 \text{ (s, 3H), 1.19 \text{ (s, 3H).}}}} \]

The explanation for the seemingly confusing fractions above can be explained via the presence of the diastereomers, the AB coupling system of the methylene system in the lactam ring, and overlapping of some of the peaks. No attempt was made to isolate one of the diastereomers over another due to the lack of separation of the spots on a TLC plate.
4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 2-bromo-2-phenylacetate

**Ester prepared from alpha-bromo phenylacetic acid and chiral auxiliary 26**

This compound was prepared using the DMC coupling method starting with 2.516 g (11.7 mmol) of α-bromophenylacetic acid and 2.400 g (11.7 mmol) of the chiral auxiliary 26. Yield after aqueous workup was 4.660 g (99%).

The key diastereomeric peaks are at δ 5.55 / 5.47 ppm. Approximate ratio of diastereomers was 1 : 1.

**1H NMR** (CDCl₃, 300MHz) δ 7.64-7.11 (m, 10H), 5.55 (s, 1H), 5.41 (s, 1H), 3.64-3.41 (m, 2H), 1.32 (s, 1.5H), 1.16 (s, 3H), 0.86 (s, 1.5H)

**13C NMR** (CDCl₃, 75MHz) δ 168.02, 167.93, 167.86, 167.43, 138.72, 138.69, 135.83, 134.84, 131.79, 129.27, 128.97, 128.84, 128.67, 128.56, 128.38, 128.08, 124.94, 119.37, 79.63, 79.42, 65.70, 57.45, 57.42, 50.50, 47.12, 46.98, 45.08, 37.68, 37.55, 24.67, 24.53, 20.84, 20.58, 15.14.

Once again, the DMC coupling gave rise to alpha-chloro and alpha-bromo compounds, doubling the number of expected peaks in the spectrum.
Ester prepared from alpha-bromo butanoic acid and chiral auxiliary 26

This compound was prepared via the DMC starting with 1.0 mL (9.8 mmol) of α-bromobutanoic acid and 2.0 g (9.8 mmol) of the chiral auxiliary 26. Yield after aqueous workup (chromatography was unnecessary with DMC) was 3.45g (quantitative, taking into consideration the presence of the α-chloro ester).

This compound could not be prepared via the DCC coupling method. Owing to faster workup (no chromatography), the DCC coupling method was abandoned. This also means that when other reactions needed to be run again, they were prepared using the DMC method in favour of the DCC method. However, this lead to alpha chloro compounds as well as alpha bromo compounds.

The key diastereomeric peaks are at δ 5.40 / 5.37 ppm. Approximate ratio of diastereomers was 1 : 1.

$^1$H NMR (CDCl₃, 300MHz) δ 7.61-7.58 (d, J = 8.1 Hz, 2H), 7.38-7.33 (t, J = 7.4, 8.1 Hz, 2H), 7.18-7.13 (t, J = 7.4 Hz, 1H), 5.41 (s, 3H), 4.41-4.26 (m, 1H), 3.63-3.60 (d, J = 9.3 Hz, 1H), 3.53-3.49 (d, J = 9.9 Hz, 1H), 2.26-1.97 (m, 2H), 1.31 & 1.30 (diastereomeric s, 3H), 1.18-1.15 (diastereomeric d, 3H), 1.17-1.05 (diastereomeric t, 3H).

$^{13}$C NMR (CDCl₃, 75MHz) δ 169.46, 168.86, 168.23, 138.87, 138.86, 138.84, 138.83, 128.94, 128.92, 125.00, 124.96, 119.43, 119.40, 119.38, 79.19, 79.14, 79.03, 79.00, 59.01, 58.30, 57.69, 57.66, 57.60, 47.62, 46.86, 37.75, 37.52, 37.47, 28.58, 28.54, 28.20, 28.05, 24.74, 24.72, 21.04, 21.01, 20.97, 20.94, 11.82, 11.76, 10.43, 10.41.

(the spectrum includes both the alpha chloro and alpha bromo compounds, as well as diastereomers for each compound)

EI-MS m/z (%) 41 (100), 105 (59), 172 (69), 204 (78), 309 (Cl, 35), 311 (Cl, 12), 353 (Br, 25), 355 (Br, 25).

HRMS calc'd for C₁₆H₂₇NO₃Br: 353.0627, found 353.0648.
for heavier isotope: 355.0606, found 355.0627.
HRMS calc'd for C₁₆H₂₇NO₃Cl: 309.1132, found 309.1103.
For heavier isotope: 311.1102, found 311.1107.
Compound 22: Products of the DKR reaction.

General Procedure:

A 25 mL round-bottomed flask, equipped with a stir bar and a nitrogen line was charged with the α-bromo ester (1.0 mmol), triethylamine (1.05 mmol), tetrabutylammonium iodide (0.2 mmol) and the nucleophile (1.01 mmol) in 10 mL of freshly distilled THF. The resulting mixture was stirred at room temperature for at least 6 hours, and monitored by TLC (usually 1:1 hexanes:ethyl acetate) until it was deemed complete.

The solution was then diluted with diethyl ether and filtered to provide the crude product which was analyzed by $^1$H NMR to give the crude diastereomeric ratio of products. Column chromatography yielded the α-amino ester in good to excellent yield (50% - quantitative) and was characterized.
Acid: alpha-Bromo phenylacetic acid

Nucleophile: Benzylamine

Diastereoselectivity was judged from the peaks at δ 4.59 ppm and 4.57 ppm, with relative areas of 14.837 and 1.0, respectively. The isolated yield was 95%.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.47-7.43 (m, 4H), 7.36-7.28 (m, 7H), 7.25-7.21 (m, 1H), 6.88-6.87 (d, J = 9.1 Hz, 2H), 5.40 (s, 1H), 4.59 (s, 1H), 3.78-3.77 (m, 5H), 3.48-3.47, (AB d, J = 9.5 Hz, 1H), 3.31-3.29 (AB d, J = 9.5 Hz, 1H), 2.30 (br s, 1H), 1.03 (s, 3H), 0.66 (s, 3H).

FAB-MS m/z (%) 94 (56), 186 (100), 278 (25), 370 (11), 459 (21).

HRMS calc'd for C$_{28}$H$_{31}$N$_2$O$_4$: 459.2284, found 459.2306.
Acid: alpha-Bromo butanoic acid                     Nucleophile: Benzylamine

Diastereoselectivity was judged from the peaks at δ 5.48 ppm and 5.45 ppm, with relative areas of 8 and 1, respectively. The isolated yield was quantitative.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.51-7.49 (d, J = 9.1 Hz, 2H), 7.37-7.36 (d, J = 7.3 Hz, 2H), 7.31-7.28 (t, J = 7.3 Hz, 2H), 7.23-7.20 (t, J = 7.3 Hz, 1H), 6.90-6.88 (d, J = 9.1 Hz, 2H), 5.48 (s, 1H), 3.92-3.90 (AB d, J = 12.9 Hz, 1H), 3.78 (s, 3H), 3.73-3.70 (AB d, J = 12.9 Hz, 1H), 3.61-3.59 (AB d, J = 9.5 Hz, 1H), 3.47-3.45 (AB d, J = 9.5 Hz, 1H), 3.42-3.40 (t, J = 5.5 Hz, 1H), 2.20 (br s, 1H), 1.84-1.70 (m, 2H), 1.28 (s, 3H), 1.13 (s, 3H), 1.01-0.98 (t, J = 7.5 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 174.73, 168.27, 156.85, 139.91, 132.23, 128.29, 126.93, 121.23, 114.13, 78.31, 61.92, 58.18, 55.44, 51.95, 37.38, 26.60, 24.80, 21.26, 10.11.

FAB-MS no satisfactory spectrum could be obtained.
Acid: alpha-Bromo propanoic acid  Nucleophile: Benzylamine

Diastereoselectivity was judged from the peaks at δ 5.43 ppm and 5.41 ppm, with relative areas of 8.7 and 1, respectively. The isolated yield was 68%.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.51-7.49 (d, J = 9.1 Hz, 2H), 7.36-7.35 (d, J = 7.5 Hz, 2H), 7.31-7.28 (t, J = 7.3, 7.7 Hz, 2H), 7.23-7.20 (t, J = 7.3 Hz, 1H), 6.90-6.88 (d, J = 9.1 Hz, 2H), 5.43 (s, 1H), 3.91-3.88 (d, J = 12.8 Hz, 1H), 3.78 (s, 3H), 3.76-3.73 (d, J = 12.8 Hz, 1H), 3.60-3.56 (m, 2H), 3.47-3.45 (d, J = 9.5 Hz, 1H), 1.90 (br s, 1H), 1.41-1.39 (d, J = 7 Hz, 3H), 1.28 (s, 3H), 1.13 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 175.06, 168.22, 156.92, 139.79, 132.25, 128.33, 128.29, 126.95, 121.27, 114.17, 78.40, 58.30, 55.85, 55.43, 51.80, 37.34, 24.88, 21.15, 19.28

FAB-MS m/z (%) 91 (49), 134 (32), 236 (51), 397 (100).

HRMS calc'd for C$_{23}$H$_{29}$N$_2$O$_4$: 397.2127, found 397.2040.

In the $^1$H NMR, the system at δ 3.60-3.56 ppm contains the other half of the AB system seen at δ 3.47-3.45 ppm as well as the proton alpha to the carbonyl that bears the nitrogen.
Acid: alpha-Bromo propanoic acid
Nucleophile: 1-Adamantamine

Diastereoselectivity was judged from the peaks at δ 5.35 ppm and 5.34 ppm, with relative areas of 25.9 and 1, respectively. The isolated yield was 72%.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.47-7.45 (d, J = 9.2 Hz, 2H), 6.86-6.84 (d, J = 9.2 Hz, 2H), 5.35 (s, 1H), 3.74 (s, 3H), 3.72-3.68 (q, J = 7.1 Hz, 1H), 3.54-3.52 (d, J = 9.5 Hz, 1H), 3.43-3.41 (d, J = 9.5 Hz, 1H), 2.00 (br s, 3H), 1.95 (br s, 1H), 1.63-1.54 (br m, 12H), 1.32-1.31 (d, J = 7.1 Hz, 3H), 1.23 (s, 3H), 1.10 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 177.12, 168.26, 156.76, 132.17, 121.17, 114.04, 78.18, 58.11, 55.35, 50.92, 48.55, 42.88, 37.41, 36.44, 29.45, 24.77, 22.48, 21.09.

EI-MS m/z (%) 135 (58), 136 (78), 178 (64), 204 (100), 235 (85), 279 (31), 309 (7), 440 (1).

HRMS calc'd for C$_{26}$H$_{36}$N$_2$O$_4$: 440.2675, found 440.2680.
Acid: alpha-bromo propanoic acid          Nucleophile: N-methylbenzylamine

Diastereoselectivity was judged from the peaks at δ 5.45 ppm and 5.44 ppm, with relative areas of 14.4 and 1, respectively. The isolated yield was 96%.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.51-7.50 (d, J = 9.3 Hz, 2H), 7.36-7.34 (d, J = 7.5 Hz, 2H), 7.30-7.27 (t, J = 7.2, 7.6 Hz, 2H), 7.22-7.19 (t, J = 7.2 Hz, 1H), 6.90-6.88 (d, J = 9.2 Hz, 2H), 5.45 (s, 1H), 3.85-3.83 (d, J = 13.5 Hz, 1H), 3.78 (s, 3H), 3.76-3.73 (d, J = 13.6 Hz, 1H), 3.65-3.60 (q J = 7.1Hz, 1H), 3.59-3.57 (d, J = 9.5 Hz, 1H), 3.48-3.47 (d, J = 9.5 Hz, 1H), 2.37 (s, 3H), 1.41-1.40 (d, J = 7.1 Hz, 3H), 1.27 (s, 3H), 1.14 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 172.43, 168.44, 156.83, 139.55, 132.27, 129.77, 128.82, 128.14, 126.83, 121.25, 114.13, 78.04, 60.23, 58.17, 55.44, 37.73, 37.26, 24.81, 21.38, 19.73.

FAB-MS m/z (%) 91 (49), 134 (32), 236 (51), 397 (100).

HRMS calc'd for C$_{24}$H$_{31}$N$_2$O$_4$: 411.2284, found 411.2443.
Acid: alpha-bromo butanoic acid  
Nucleophile: N-methylbenzylamine

Diastereoselectivity was judged from the peaks at $\delta$ 5.47 ppm and 5.46 ppm, with relative areas of 7.37 and 1, respectively. The isolated yield was quantitative.

$^1$H NMR (CDCl$_3$, 500MHz) $\delta$ 7.52-7.50 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 6.9 Hz, 2H), 7.29-7.26 (t, J = 7.1, 7.7 Hz, 2H), 7.21-7.18 (t, J = 7.3 Hz, 1H), 6.89-6.87 (d, J = 9.0 Hz, 2H), 5.47 (s, 1H), 3.89-3.86 (d, J = 13.8 Hz, 1H), 3.76 (s, 3H), 3.58-3.56 (d, J = 9.5 Hz, 1H), 3.47-3.45 (d, J = 9.5 Hz, 1H), 3.37-3.34 (t, J = 7.5, 7.7 Hz, 1H), 2.36 (s, 3H), 1.91-1.71 (m, 2H), 1.26 (s, 3H), 1.14 (s, 3H), 1.01-0.98 (t, J = 7.3, 7.5 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 171.65, 168.46, 156.84, 139.74, 132.33, 128.78, 128.09, 126.77, 121.25, 114.14, 78.01, 66.99, 58.35, 58.20, 55.42, 37.69, 37.20, 24.73, 23.23, 21.47, 10.87.

EI-MS m/z (%) 91(91), 120 (48), 162 (100), 204 (36), 305 (12), 424 (4).

HRMS calc'd for C$_{25}$H$_{32}$N$_2$O$_4$: 424.2362, found 424.2376.
Acid: alpha-bromo butanoic acid  
Nucleophile: 1-adamantamine

Diastereoselectivity was judged from the peaks at $\delta$ 5.39 ppm and 5.38 ppm, with relative areas of 16.2 and 1, respectively. The isolated yield was 62%.

$^1$H NMR (CDCl$_3$, 500MHz) $\delta$ 7.48-7.46 (d, $J = 9.1$ Hz, 2H), 6.87-6.85 (d, $J = 9.1$ Hz, 2H), 5.39 (s, 1H), 3.75 (s, 3H), 3.56-3.54 (d, $J = 9.5$ Hz, 1H), 3.51-3.49 (dd, $J = 5.5$, 7.3 Hz, 1H), 3.43-3.41 (d, $J = 9.5$ Hz, 1H), 2.01 (br s, 4H), 1.74-1.54 (br m, 12H), 1.25 (s, 3H), 1.13 (s, 3H), 0.98-0.95 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 176.71, 168.36, 156.80, 132.26, 121.23, 114.10, 78.13, 58.09, 55.41, 54.47, 50.84, 43.01, 37.51, 36.52, 29.61, 28.98, 24.82, 21.24, 10.35.

EI-MS m/z (%) 135 (100), 192 (99), 234 (37), 303 (13).

HRMS the spectrum did not contain any suitable M+ peak.

An M+ corresponding to the starting material was not observed, and the following disconnections are proposed for the mass peaks:
Acid: α-bromo butanoic acid

Nucleophile: pyrrolidine

Diastereoselectivity was judged from the peaks at δ 5.45 ppm and 5.43 ppm, with relative areas of 4.3 and 1, respectively. The isolated yield was quantitative.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.47-7.46 (d, J = 9.2 Hz, 2H), 6.86-6.84 (d, J = 9.2 Hz, 2H), 5.45 (s, 1H), 3.75 (s, 3H), 3.56-3.54 (d, J = 9.5 Hz, 1H), 3.45-3.42 (d, J = 9.7 Hz, 1H), 3.27-3.24 (dd, J = 5.6, 8.8 Hz, 1H), 2.74-2.69 (m, 4H), 1.87-1.74 (m, 6H), 1.24 (s, 3H), 1.11 (s, 3H), 0.98-0.95 (t, J = 7.5 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 172.25, 168.36, 156.78, 132.25, 121.19, 114.03, 77.87, 67.53, 58.13, 55.39, 50.26, 37.24, 24.81, 23.49, 21.33, 10.42.

EI-MS m/z (%) 112 (100), 156 (21), 204 (31), 235 (7), 279 (6), 305 (10), 374(5).

HRMS calc'd for C$_{21}$H$_{30}$N$_2$O$_4$: 374.2206, found 374.2181.
Acid: α-bromo phenylacetic acid  
Nucleophile: N-methylbenzylamine

Diastereoselectivity was judged from the peaks at δ 5.65 ppm and 5.48 ppm, with relative areas of 1 and 100, respectively. The isolated yield was 65%.

$^1\text{H NMR}$ (CDCl$_3$, 500MHz) δ 7.54-7.52 (d, J = 7.3 Hz, 2H), 7.50-7.48 (d, J = 9.0 Hz, 2H), 7.37-7.34 (t, J = 7.1, 7.3 Hz, 4H), 7.31-7.27 (q, J = 6.7, 7.7 Hz, 3H), 7.23-7.20 (t, J = 7.3 Hz, 1H), 6.89-6.88 (d, J = 9.2 Hz, 2H), 5.48 (s, 1H), 4.50 (s, 1H), 3.78 (s, 3H), 3.72-3.69 (d, J = 13.3 Hz, 1H), 3.65-3.62 (d, J = 13.3 Hz, 1H), 3.54-3.52 (d, J = 9.7 Hz, 1H), 3.38-3.36 (d, J = 9.5 Hz, 1H), 2.27 (s, 3H), 1.12 (s, 3H), 0.84 (s, 3H).

$^{13}\text{C NMR}$ (CDCl$_3$, 125MHz) δ 171.16, 168.30, 156.84, 138.90, 136.87, 132.27, 128.92, 128.84, 128.49, 128.20, 128.13. 126.90, 121.22, 114.12, 78.13, 71.62, 58.51, 58.15, 55.43, 39.08, 37.51, 24.67, 20.84.

**FAB-MS** m/z (%) 91 (50), 137 (100), 246 (32), 338 (11), 473 (89).

**HRMS** calc'd for C$_{29}$H$_{33}$N$_2$O$_4$: 473.2440, found 473.2450.
Acid: α-bromo phenylacetic acid  Nucleophile: 1-adamantamine

Diastereoselectivity was judged from the peaks at δ 4.77 ppm and 4.75 ppm, with relative areas of 30 and 1, respectively. The peak at 5.349 ppm seems to have a shoulder peak to one side at 5.343 ppm, which is why it is not used in the determination of diastereoselectivity.

The isolated yield was 52%.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.47-7.46 (d, J = 9.2 Hz, 2H), 7.43-7.41 (d, J = 7.1 Hz, 2H), 7.30-7.27 (t, J = 7.1 Hz, 2H), 7.24-7.21 (t, J = 7.3 Hz, 1H), 6.88-6.86 (d, J = 9.2 Hz, 2H), 5.35 (s, 1H) 4.77 (s, 1H), 3.77 (s, 3H), 3.47-3.45 (d, J = 9.5 Hz, 1H), 3.30-3.28 (d, J = 9.5 Hz, 1H), 2.02 (br s, 5H), 1.68-1.58 (br m, 12H), 0.98 (s, 3H), 0.63 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 174.53, 168.31, 156.82, 141.40, 132.23, 128.51, 127.59, 127.52, 121.21, 114.10, 78.41, 58.06, 57.60, 55.43, 51.40, 43.09, 337.66, 36.50, 29.55, 24.52, 20.40.

EI-MS m/z (%): 135 (89), 240 (100), 284 (7), 502 (1).

HRMS calc'd for C$_{31}$H$_{38}$N$_2$O$_4$: 502.2832, found 502.2845.
Acid: alpha-bromo phenylacetic acid  

Nucleophile: pyrrolidine

Diastereoselectivity was judged from the crude 200 MHz spectrum, from peaks at δ 5.37 and 5.30 ppm, with relative areas of 4.3 and 1, respectively. Upon column chromatography the compound obtained was a more equal mixture of the two diastereomers, and there are peaks at δ 5.37 and 5.32 ppm with relative areas of 3 and 1, respectively.

The isolated yield was 73%.

\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 500MHz) δ 7.54-7.43 (m, 5H), 7.33-7.26 (m, 2H), 6.87-6.83 (m, 2H), 5.37 (s, 1H), 4.21 (s, 1H), 3.49-3.45 (2 d, J = 9.5 Hz, 1H), 3.36-3.35 (d, J = 9.7 Hz, 0.5 H), 3.29-3.27 (d, J = 9.7 Hz, 0.5 H), 2.74-2.52 (m, 4H), 1.90-1.76 (br m, 6H), 1.27 (s, 1.5H), 1.06 (s, 1.5H), 0.99 (s, 1.5H), 0.65 (s, 1.5H).

\textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 125MHz) δ 173.45, 170.85, 168.30, 156.79, 137.10, 132.33, 132.19, 130.30, 128.96, 128.59, 128.45, 121.21, 114.13, 78.27, 78.14, 73.16, 72.57, 58.18, 55.41, 52.37, 52.07, 38.49, 37.64, 24.91, 24.51, 23.36, 20.41, 19.94.

\textbf{FAB-MS} m/z (%) 75 (100), 186 (47), 278 (9), 423 (4).

\textbf{HRMS} calc'd for C\textsubscript{26}H\textsubscript{30}N\textsubscript{2}O\textsubscript{4}: 423.2283, found 423.2263.

It should be noted that even the \textsuperscript{13}C NMR spectrum is complicated with the presence of diastereomeric peaks, giving rise to a higher number of peaks than expected.
Acid: α-bromo butanoic acid  
Nucleophile: N-methylbenzylamine

Diastereoselectivity was judged from the peaks at δ 5.44 and 5.40 ppm, with relative areas of 17 and 1, respectively (200 MHz) and 5.443 and 5.40 ppm, with relative areas of 20 and 1, respectively (500 MHz).

The isolated yield was 44%.

$^1$H NMR (CDCl₃, 500MHz) δ 7.34-7.33 (d, J = 7.5 Hz, 2H), 7.30-7.27 (t, J = 7.3, 7.9 Hz, 2H), 7.23-7.20 (t, J = 6.9, 7.7 Hz, 1H), 5.44 (s, 1H), 4.07-4.02 (q, J = 9.0, 14.8 Hz, 2H), 3.86-3.83 (d, J = 13.5 Hz, 1H), 3.69-3.66 (d, J = 13.7 Hz, 1H), 3.35-3.32 (dd, J = 7.5, 7.9 Hz, 1H), 2.33 (s, 3H), 1.86-1.72 (p, J = 7.3 Hz, 2H), 1.20 (s, 3H), 1.12 (s, 3H), 0.99-0.96 (t, J = 7.3, 7.5 Hz, 3H)

$^{13}$C NMR (CDCl₃, 125MHz) δ 172.15, 171.22, 139.44, 128.72, 128.14, 126.87, 76.13, 74.75, 66.71, 39.99, 37.50, 23.06, 22.93, 20.17, 10.75.

EI-MS m/z (%): 91 (97), 129 (19), 162 (100), 211 (65).

No satisfactory HRMS could be obtained due to the lack of an M+ peak. Of the MS peaks above, the 162 peak is key, since it corresponds to the amine and the C₃ fragment of the side chain, indicating the formation of the C-N bond. The lack of a peak at 310, which would correspond to the amide (2 eq of amine, one displacing the halogen, one displacing the chiral auxiliary) eliminates the presence of the side product.
Acid: α-bromo propanoic acid  
Nucleophile: N-methylbenzylamine

Diastereoselectivity was judged from the peaks at δ 5.42 and 5.41 ppm, with relative areas of 5.3 and 1. The isolated yield was 96%.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.34-7.33 (d, J = 6.9 Hz, 2H), 7.31-7.27 (t, J = 7.3, 7.5 Hz, 2H), 7.23-7.20 (t, J = 7.3, 7.1 Hz, 1H), 5.42 (s, 1H), 4.06-4.01 (q, J = 9.0, 15.0 Hz, 2H), 3.82-3.79 (d, J = 13.5 Hz, 1H), 3.71-3.68 (d, J = 13.5 Hz, 1H), 3.63-3.58 (q, J = 7.1 Hz, 1H), 2.34 (s, 3H), 1.39-1.37 (d, J = 7.1 Hz, 3H), 1.19 (s, 3H), 1.12 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 172.16, 171.98, 139.28, 128.72, 128.20, 126.95, 76.14, 74.83, 60.01, 58.23, 40.04, 37.59, 22.97, 20.10, 15.55.

EI-MS m/z (%) 91 (100), 148 (93), 197 (4), 305 (3).

HRMS calc'd for C$_{17}$H$_{23}$NO$_4$: 305.1627, found 305.1640.
Compound 23: The N-benzyl lactam

![Chemical Structure](image)

1-benzyl-3-hydroxy-4,4-dimethylpyrrolidin-2-one

This compound was prepared by the same method used for the racemic preparation of compound 19. No attempts were made to prepare it in optically active form.

Initial experiments were carried out on a 100 mg (0.768 mmol) of pantolactone scale, using 84 μL (0.768 mmol, 1 eq) and 168 μL (1.536 mmol, 2 eq) of benzylamine. Ideal conditions required 1 equivalent of benzylamine, 220°C and yielded 194 mg (88%) of 23.

On higher scales (approx 1 g of pantolactone), quantitative yields could be obtained.

$^1$H NMR (CDCl$_3$, 200MHz) δ 7.32-7.18 (m, 5H), 4.53-4.46 (d, J = 14.5Hz, 1H), 4.38-4.31 (d, J = 14.5 Hz, 1H), 4.00 (s, 1H), 2.97-2.92 (d, J = 9.7 Hz, 1H), 2.84-2.79 (d, J = 9.7 Hz, 1H), 1.15 (s, 3H), 0.93 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 50MHz) δ 174.37, 135.68, 128.74, 128.25, 127.79, 77.86, 56.23, 46.87, 24.71, 19.97

IR (cm$^{-1}$): 3370, 1668, 1491, 1450, 1250, 1122, 1079, 910.

EI-MS m/z (%) 91 (100), 186 (96), 219 (65).

HRMS calc'd for C$_{13}$H$_{17}$NO$_2$: 219.1259, found 219.1256.
Compound 26: The N-phenyl lactam

This compound was prepared by the same method used for the racemic preparation of compound 19. No attempts were made to prepare it in optically active form.

Initial experiments were carried out on a 100 mg (0.768 mmol) of pantolactone scale, using 71.5 mg (0.768 mmol, 1 eq) of aniline. Ideal conditions (microwave) yielded 158 mg (>99%) of 26.

This reaction was successfully carried out on large scale (approx 5 – 10 g of pantolactone) with the same (quantitative) yields.

$^1$H NMR (CDCl$_3$, 300MHz) $\delta$ 7.61-7.58 (d, J = 8.7 Hz, 2H), 7.38-7.33 (t, J = 7.4, 8.1 Hz, 2H), 7.17-7.12 (t, J = 7.4 Hz, 1H), 4.11 (s, 1H), 3.55-2.52 (d, J = 9.3 Hz, 1H), 3.45-3.42 (d, J = 9.5 Hz, 1H), 1.31 (s, 3H), 1.08 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 75MHz) $\delta$ 174.41, 139.47, 129.36, 125.27, 119.91, 78.79, 58.10, 38.80, 24.97, 20.35.

IR (cm$^{-1}$): 3350, 1686, 1599, 1500, 1418, 1382, 1305, 1274, 1125, 759, 687.

EI-MS m/z (%) 77 (72), 106 (82), 119 (100), 205 (58).

HRMS calc'd for C$_{12}$H$_{13}$NO$_2$: 205.1103, found 205.1039.

In the multiple times that this compound has been made, careful precipitation has allowed for the identification of the broad OH peak at $\delta$ 4.5 ppm.
Compound 29: A Brominated Chiral Auxiliary

\[
\text{HO-} \begin{array}{c}
\text{N} \\
\text{Br}
\end{array} \text{N-} \begin{array}{c}
\text{O}
\end{array} \text{Cyclopentanone}
\]

5-(4-Bromo-phenyl)-2-hydroxy-3,3-dimethyl-cyclopentanone

Method 1: A heating experiment (see compound 19 for general procedure) at 200°C for 6 hours with 0.615 g (4.7 mmol) of pantolactone and 0.812 g (4.7 mmol) of p-bromoaniline furnished 1.205 g of product, of which 28% (0.264 g, 1.288 mmol) was 26, and 72% (0.941 g, 3.3 mmol) was 29. This represents a total 98% yield, but an effective 70% yield of 29.

Method 2 (more reliable) Iron (III) Chloride (three granules, catalytic) was combined with 100 mg of 26 (0.49 mmol) in dichloromethane (8 mL) in a round bottom flask previously charged with a stirring bar and stirred. Bromine (25 µL, 0.5 mmol) was added dropwise and the mixture was allowed to stir overnight. An aqueous / organic workup provides the chiral auxiliary in quantitative yield. The \(^1\)H NMR indicated only para substitution.

\(^1\)H NMR (CDCl₃, 500MHz) δ 7.51-7.48 (AA'BB', J = 9.0, 2.4 Hz, 2H), 7.46-7.43 (AA'BB', J = 9.2, 2.2 Hz, 2H), 4.09 (s, 1H), 3.53 (s, 1 OH), 3.50-3.48 (d, J = 9.5 Hz, 1H), 3.40-3.39 (d, J = 9.5 Hz, 1H), 1.30 (s, 3H), 1.07 (s, 3H).

\(^13\)C NMR (CDCl₃, 125MHz) δ 173.95, 138.17, 131.89, 120.83, 117.62, 78.30, 57.54, 38.29, 24.51, 19.91.

EI-MS m/z (%) 106 (51), 184 (100), 186 (94), 205 (49), 283 (77), 285 (76).

HRMS calc'd for C₁₂H₁₄NO₂Br: 283.0208, found 283.0179.
Compound 30: The N-(α-methyl)benzyl lactam

![Chemical Structure](image)

3-hydroxy-4,4-dimethyl-1-(1-phenylethyl)pyrrolidin-2-one

This compound was prepared by the same method used for the racemic preparation of compound 19 requiring 200°C for 12 hours, on a 100mg (0.768 mmol) scale, furnishing 69.4 mg (39% yield, 0.297 mmol) of 30 after column chromatography. No attempts were made to prepare it in optically active form. Characterization was limited to spectral analysis, since we were only interested in seeing if the diastereomers were visible by NMR.

The diastereomers are denoted 1 and 2, but their relative and absolute configurations are unknown.

**^1^H NMR** (CDCl₃, 200MHz) δ 7.38-7.20 (m, 5H), 5.46-5.38 (overlapping q, J = 4 Hz, 1H), 4.02 (s diastereomer 1, 0.5H), 3.96 (s, diastereomer 2, 0.5H), 2.98-2.91 (d of AB system of diastereomer 1, J = 6 Hz, 0.5H), 2.91-2.88 (d of AB system of diastereomer 2, J = 6 Hz, 0.5H), 2.61-2.58 (d both diastereomers, J = 6, 1H), 1.52-1.50 (d, diastereomer 1, J = 4Hz, 1.5H), 1.50-1.48 (d, diastereomer 1, J = 4Hz, 1.5H), 1.14 (s, diastereomer 1, 1.5H), 1.10 (s, diastereomer 2, 1.5H), 1.01 (s, diastereomer 2, 1.5H), 0.74 (s, diastereomer 1, 1.5H).

**^1^C NMR** (CDCl₃, 50MHz) δ 174.10, 139.44, 128.58, 127.66, 127.22, 78.02 (#1), 77.64 (#2), 52.32 (#1), 51.84 (#2), 49.22 (#1), 49.01 (#2), 24.69 (#1), 24.53 (#2), 19.91 (#1), 19.36 (#2), 15.86 (#1), 15.60 (#2).
Compound 32: para-cyano chiral auxiliary

\[
\text{OH} \quad \text{N} \quad \text{CN} \\
\text{32}
\]

4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzonitrile

Compound 29 (1.5475g, 5.44 mmol) was dissolved in DMF (approx 40 mL) in a 100 mL round-bottom flask that was charged with a magnetic stirrer. Copper (I) cyanide (2.0g, 21.8 mmol) was added and the mixture was stirred and heated at reflux for 8 hours. The mixture was analyzed by TLC and if the starting material was not consumed, the reflux was allowed to continue. Upon satisfactory completion, the mixture was taken up in diethyl ether, and washed with brine. Flash column chromatography provided the product in low to good yield (40% up to 82%).

\(^1\text{H NMR}\) (CDCl\textsubscript{3}, 300MHz) \(\delta\) 7.77-7.75 (d, \(J = 12\text{Hz}, 2\text{H}\)), 7.65-7.63 (d, \(J = 12\text{Hz}, 2\text{H}\)), 4.14 (s, 1H), 3.54-3.44 (AB q, \(J = 5.0, 14.4\text{ Hz}, 2\text{H}\)), 1.32 (s, 3H), 1.07 (s, 3H).

\(^{13}\text{C NMR}\) (CDCl\textsubscript{3}, 75MHz) \(\delta\) 174.67, 142.75, 133.10, 120.83, 118.96, 107.58, 78.30, 57.14, 38.17, 24.46, 19.92.

\(\text{HRMS (EIMS) calc'd for C}_{13}\text{H}_{14}\text{N}_{2}\text{O}_{2}: 230.1055, \text{found 230.1067.}\)
Compounds 33 and 62: TBDMS-protected nitro lactam

![Chemical Structure](image)

3-(tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-1-(4-nitro-phenyl)-pyrrolidin-2-one and 3-(tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-1-(2-nitro-phenyl)-pyrrolidin-2-one

The TBDMS protected lactam 59 (7.597g, 23.78mmol) was dissolved in acetic anhydride (100mL, solvent), and stirred with the aid of a magnetic stirrer. Crystals of cuprous (II) nitrate (2.8206g, 12.13 mmol, 0.51 eq) were added slowly, furnishing a green-blue solution. This solution was allowed to stir at room temperature and the progress of the reaction was monitored by thin layer chromatography using a 5:1 mixture of Hexanes to Ethyl Acetate. Upon satisfactory conversion of the starting material, a saturated solution of sodium bicarbonate was added and the nitrated product was recovered by dichloromethane extraction from the resulting slurry, yielding a yellowish solid upon evaporation of the solvent. The two isomers were separable by flash column chromatography, using the same solvent system as for the thin layer chromatography, again yielding yellow solids.

Alternatively, the isomers could be separated by fractional recrystallization, using toluene and hexanes, ether/hexanes or ethyl acetate/hexanes.

Based on 100% conversion, the ratio of isomers is 1:2, favouring the unwanted ortho isomer.

**Ortho isomer:**

**$^1$H NMR (CDCl₃, 200MHz)** \( \delta \) 7.95-7.90 (dd, \( J = 7.8, 1.2 \) Hz, 1H), 7.63-7.56 (td, \( J = 7.4, 1.4 \) Hz, 1H), 7.41-7.30 (td, \( J = 7.6, 1.4 \) Hz, 1H), 7.32-7.28 (dd, \( J = 8.0, 1.0 \) Hz, 1H), 3.98 (s, 1H), 3.56-3.42 (AB q, \( J = 9.2, 17.8 \) Hz, 2H), 1.23 (s, 3H), 1.16 (s, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H).

**Para isomer:**

**$^1$H NMR (CDCl₃, 300MHz)** \( \delta \) 8.22-8.19 (AA'BB', \( J = 9.3, 1.2, 0.6 \) Hz, 2H), 7.85-7.81 (AA'BB', \( J = 9.3, 1.2, 0.6 \) Hz, 2H), 4.06 (s, 1H), 3.50 (s, 2H), 1.24 (s, 3H), 1.07 (s, 3H), 0.94 (s, 9H), 0.21 (s, 3H), 0.13 (s, 3H).

**$^{13}$C NMR (CDCl₃, 125MHz)** \( \delta \) 173.76, 145.02, 124.75, 118.33, 79.62, 56.81, 38.07, 25.73, 25.71, 25.64, 24.60, 20.38, 18.37, 7.33, -4.17, -5.28.

**EI-MS** m/z (%): 349 (4.2), 307 (100), 261 (20), 162 (43), 100 (59).

**IR (cm$^{-1}$):** 1732 (C=O), 1503 (aryl-NO$_2$), 1330 (aryl-NO$_2$), 851 (para disubstituted benzene).

**HRMS** the spectrum did not contain any suitable M+ peak. (EI and CI methods were used)
Anionic DKR products:

The reaction conditions were the same as those for the amine-related DKR products (see general procedure for compound 22: 1 eq of α-bromo ester, 1.05 eq triethylamine, 0.2 eq tetrabutylammonium iodide, and 1.01 eq nucleophile, in freshly distilled THF.)
Compound 38

![Chemical Structure]

Acid: alpha-bromo phenylacetic acid  
Nucleophile: malononitrile (36)

The reaction was run on a 176 mg (0.437 mmol) scale, with an isolated yield of 108 mg (64%).

Given the disappointing $^1$H NMR spectrum, the only other characterization obtained was a mass spectrum. Please note that the chiral auxiliary used is the unsubstituted aryl ring (as opposed to the para-methoxy variant used the other DKR reactions), and the field strength of the spectrometer.

$^1$H NMR (CDCl$_3$, 200MHz) $\delta$ 7.60-7.10 (m, 10 H), 5.44 (s, 1H), 4.56-4.36 (m, 2H), 3.62-3.38 (m, 2H), 1.34 (s, CH$_3$), 1.18 (s, CH$_3$), 1.14 (s, CH$_3$), 0.78 (s, CH$_3$).

EI-MS m/z (%) 77 (33), 105 (29), 119 (20), 172 (24), 204 (31), 387 (100)

HRMS calc'd for C$_{23}$H$_{21}$N$_3$O$_3$: 387.1583, found 387.1587.

For the last four peaks, the ones at $\delta$ 1.34 and 1.18 add up to 3 protons, and the last two also add up to 3 protons. The ones at $\delta$ 1.34 and 1.14 ppm are from one diastereomer, and the ones at 1.18 and 0.78 are from the other diastereomer.

This NMR analysis is in good agreement with the other DKR products. The high resolution mass spectrum is surprisingly good. A deuteration study simplified the multiplet at $\delta$ 4.56-4.36 into a singlet.
Acid: alpha-bromo butyric acid  Nucleophile: malononitrile (36)

The reaction was run on a 105 mg (0.29 mmol) scale, with an isolated yield of 98.4 mg (quantitative).

The diastereomeric peaks were present at $\delta$ 5.47 and 5.41 ppm with relative areas of 1.08 and 1, respectively.

$^1$H NMR (CDCl$_3$, 200MHz) $\delta$ 7.61-7.10 (m, 5H), 5.47 and 5.41 (s, 1H), 4.22-4.03 (m, 2H), 3.70-3.39 (m, 2H), 2.20-2.00 (m, 2H), 1.20-1.00 (m, 9H).
Compound 39: Allylation of compound 38

\[
\begin{align*}
&\text{4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3,3-dicyano-2-phenylhex-5-enoate} \\
\end{align*}
\]

The reaction was run as a double DKR reaction in that the α-bromo ester (325.3 mg, 0.81 mmol) was combined in a round-bottom flask with the malononitrile (53.5 mg, 0.81 mmol), allyl bromide (70 μL, 0.81 mmol), triethylamine (118 μL, 0.85 mmol), and the quaternary ammonium iodide salt (TBAI, 60mg, 0.162 mmol). The solvent used was THF (15 mL), and the workup consisted of a simple aqueous workup, with dichlormethane as the organic phase. Crude product yield was 337 mg (97%).

The diastereomeric peaks were at 4.21 and 4.17, with relative areas of 1.96 and 1, respectively.

\[^1\text{H NMR}\] (CDCl\textsubscript{3}, 200MHz) δ 7.60-7.10 (m, 10 H), 6.05-5.83 (m, 1H), 5.51-5.41 (m, 3H), 4.21 and 4.17 (s, 1H), 3.64-3.38 (m, 2H), 2.92-2.80 (m, 2H), 1.32 (s, CH\textsubscript{3}), 1.22 (s, CH\textsubscript{3}), 1.18 (s, CH\textsubscript{3}), 0.77 (s, CH\textsubscript{3}).

It should be noted that the multiplet at 3.64-3.38 ppm is the normal AB quartet in the lactam ring, but an underlying quartet prevents a more detailed characterization. For the last four peaks, the ones at δ 1.32 and 1.18 add up to 3 protons, and the ones at 1.22 and 0.77 add up to 3 protons. The ones at δ 1.32 and 1.22 ppm are from one diastereomer, and the ones at 1.18 and 0.77 are from the other diastereomer.
Compound 41: The radical DKR product

Acid: alpha-bromo phenylacetic acid

Radical partner: allyl tributyl tin

The α-bromo ester (713 mg, 1.77 mmol) was combined with allyltributyl tin (0.825 mL, 2.66 mmol, 1.5 eq) and tetrabutyl ammonium iodide (131 mg, 0.354 mmol, 0.2 eq) in a quartz tube. The flask was then charged with dry benzene and degassed. AIBN (29 mg, 0.177 mmol, 0.1 eq) was then added and the flask degassed again. It was then exposed to UV light of ν 254 nm for 8 hours, at which point the progress of the reaction was determined by TLC. If the starting material was not consumed, the reaction was allowed to continue, and more benzene was added if necessary.

The diastereomeric peaks are at 4.22 and 4.18 ppm, with relative areas of 1.96 and 1, respectively. The isolated yield was 69%.

$^1$H NMR (CDCl$_3$, 500MHz) δ 7.57-7.51 (m, 4H), 7.44-7.41 (m, 3H), 7.37-7.31 (m, 2H), 7.17-7.14 (m, 1H), 6.00-5.84 (m, 1H), 5.52-5.41 (m, 3H), 4.22 and 4.18 (s, 1H), 3.58-3.36 (m, 2H), 2.84-2.79 (m, 2H), 1.30 (s, CH$_3$), 1.19 (s, CH$_3$), 1.14 (s, CH$_3$), 0.74 (s, CH$_3$).

$^{13}$C NMR (CDCl$_3$, 125MHz) δ 167.69, 167.53, 138.60, 130.79, 129.84, 129.27, 129.15, 128.84, 127.88, 124.97, 124.05, 119.34, 113.86, 113.64, 79.97, 79.35, 57.27, 55.49, 54.54, 40.45, 40.00, 37.43, 24.29, 21.30, 20.45.

EI-MS m/z (%) 68 (85), 106 (37), 177 (47), 253 (66), 289 (40), 315 (13), 363 (2).

HRMS calc'd for C$_{23}$H$_{26}$NO$_3$: 363.1834, found 363.1836.
Compound 42: A different chiral auxiliary

\[
\text{HO-N}^\text{42}
\]

3-hydroxy-1-methyldolin-2-one

This compound was previously prepared by Gordana Babic during her graduate studies, and the experimental procedure is the same as the one in her thesis (M.Sc. Gordana Babic, 2003, p114), with the following difference: the final product was found to be relatively insoluble in ether, and so the workup involved an aqueous/organic extraction with water and chloroform. The final product was recrystallized from ether. The following characterization data is different from that in Godana Babic’s thesis (CDCl₃ rather than DMSO). The product is soluble in deuterated chloroform to the point where a perfect crystal will show its OH peak.

The scale used started with 5.0 g of isatin. Similar yields were obtained (66-80%).

\textbf{¹H NMR} (CDCl₃, 300MHz) \(\delta\) 7.46-7.43 (d, \(J = 7.3\) Hz, 1H), 7.33-7.27 (tt, \(J = 1.1, 7.7\) Hz, 1H), 7.11-7.05 (td, \(J = 1.1, 7.4\) Hz, 1H), 6.81-6.78 (d, \(J = 7.8\) Hz, 1H), 5.11 (s, 1H), 4.93 (s, OH), 3.15 (s, 3H).

\textbf{¹³C NMR} (CDCl₃, 75MHz) \(\delta\) 177.51, 143.62, 129.60, 127.15, 125.06, 123.22, 108.40, 69.72, 26.20.

\textbf{mp} 150-151°C

Compound 44: The ketoamide

\[
\text{O=NO}^\text{44}
\]

1-methyldoline-2,3-dione

The spectral data as well as the experimental details are the same as those in Godana’s thesis ((M.Sc. Gordana Babic, 2003, p113).
Compounds 45 and 48: Alpha halo esters with the new auxiliary

1-methyl-2-oxoindolin-3-yl 2-bromopropanoate  1-methyl-2-oxoindolin-3-yl 2-chloropropanoate

**Ester prepared from α-bromo propanoic acid and chiral auxiliary 42**

This compound was prepared using the DMC coupling method (see compound 21) starting with 1.5 g (10 mmol) of 42, 0.9 mL of α-bromo propionic acid (10 mmol). Using the $^1$H NMR as a guide, the ratio of α-chloro to α-bromo could be calculated. A 50/50 mixture could be obtained when the reaction was run at room temperature with the flask in a water bath (the reaction is exothermic). The isolated yield was 71% (this is taking into account the lower molecular weight chloro compound).

$^1$H NMR (CDCl$_3$, 300 MHz), δ 7.38-7.31 (t and d, J = 7.6 Hz (d), 2H), 7.09-7.04 (t, J = 7.6 Hz, 1H), 6.84-6.82 (d, J = 7.7 Hz, 1H), 6.02, 6.01, 5.89, 5.83 (diastereomeric singlets of the two halo compounds, 1H), 4.55-4.42 (m, 1H), 3.22 (s, 3H), 1.89-1.81 (diastereomeric doublets of one compound, 1.78H), 1.76-1.69 (diastereomeric doublets of one compound, 1.2H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 171.05, 169.62, 169.33, 144.49, 130.67, 130.62, 130.57, 125.59, 125.33, 125.21, 123.46, 123.32, 123.29, 123.23, 108.62, 71.07, 70.98, 70.64, 70.49, 51.99, 51.79, 39.14, 38.93, 26.42, 21.36.

IR (cm$^{-1}$): 1739 (C=O), 1726 (C=O), 1614 (C=O).

EI-MS (%): 162 (100), 253 (16), 255 (6), 297 (8), 299 (8).

HRMS (EI-MS)
calc’d for C$_{12}$H$_{12}$NO$_3$Br: 297.0001, found 297.0012.
calc’d for C$_{12}$H$_{12}$NO$_3$Br: 298.9980, found 298.9954.
calc’d for C$_{12}$H$_{12}$NO$_3$Cl: 253.0506, found 253.0564.
calc’d for C$_{12}$H$_{12}$NO$_3$Cl: 255.0476, found 255.0559.
Compounds 46

![Chemical Structure](image)

1-methyl-2-oxindolin-3-yl 2-bromobutanoate
and
1-methyl-2-oxindolin-3-yl 2-chlorobutanoate

**Ester prepared from alpha-bromo butanoic acid and chiral auxiliary 42**

This compound was prepared using the DMC coupling method (see compound 21) starting with 1.5 g (10 mmol) of 42, 1.1 mL of α-bromo butanoic acid (10 mmol). Using the $^1$H NMR as a guide, the ratio of α-chloro to α-bromo could be calculated. A 30/70 mixture could be obtained when the reaction was run at room temperature with the flask in a water bath (the reaction is exothermic). The yield was 78% (this is taking into account the lower molecular weight chloro compound).

$^1$H NMR (CDCl$_3$, 300 MHz), δ 7.37-7.32 (t and d, J = 7.5 Hz, 2H), 7.08-7.03 (t, J = 7.6 Hz, 1H), 6.84-6.81 (d, J = 7.9 Hz, 1H), 6.01 6.00, 5.89, 5.84 (diastereomeric singlets of the two halo compounds, 1H), 4.29-4.22 (m, 1H), 3.21 (s, 3H), 2.19-1.97 (m, 2H), 1.09-1.00 (overlapping triplets, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 171.47, 169.32, 168.90, 144.48, 130.56, 130.53, 125.50, 125.34, 125.33, 123.46, 123.37, 123.24, 123.16, 108.59, 70.89, 70.62, 70.50, 58.30, 58.17, 46.72, 46.59, 28.32, 28.27, 28.20, 26.40, 11.77, 1.73, 10.37, 10.28.

EI-MS (%) 162 (100), 267 (12), 269 (4), 311 (35), 313 (31).

HRMS (EI MS)
calc’d for C$_{13}$H$_{14}$NO$_3$Br : 313.0137, found 313.0188.
calc’d for C$_{13}$H$_{14}$NO$_3$Br : 311.0157, found 311.0144.
calc’d for C$_{13}$H$_{14}$NO$_3$Cl : 269.0633, found 269.0599.
calc’d for C$_{13}$H$_{14}$NO$_3$Cl : 267.0662, found 267.0645.
Compounds 47

1-methyl-2-oxindolin-3-yl 2-bromo-2-phenylacetate
and
1-methyl-2-oxindolin-3-yl 2-chloro-2-phenylacetate

Ester prepared from alpha-bromo phenylacetic acid and chiral auxiliary 42

This compound was prepared using the DMC coupling method (see compound 21) starting with 1.5 g (10 mmol) of 42, 810 mg of α-bromo phenylacetic acid (10 mmol). Using the $^1$H NMR and mass spectrum as a guide, the ratio of α-chloro to α-bromo could be calculated. A >10:1 mixture could be obtained when the reaction was run at room temperature with the flask in a water bath (the reaction is exothermic). It should be noted that the α-chloro is formed preferentially to the α-bromo, as evidenced by the lack of the appropriate peak in the mass spectrum. The yield was 46%.

$^1$H NMR (CDCl$_3$, 300 MHz) δ 7.49-7.45 (m, 2H), 7.38-7.28 (m, 4H), 7.15-7.11 (d, J = 7.6 Hz, 1H), 7.01-6.94 (t, J = 7.8 Hz, 1H), 6.80-6.76 (d, J = 7.9 Hz, 1H), 5.99, 5.95, 5.88 (diastereomeric singlets of the two halo compounds, 1H), 5.49, 5.45 (diastereomeric singlets of the two halo compounds, 1H), 3.18 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) δ 171.17, 167.92, 144.47, 135.18, 130.60, 129.45, 128.95, 127.98, 125.34, 123.26, 123.16, 108.60, 71.15, 58.62, 26.42.

HRMS (EIMS) calc’d for C$_{17}$H$_{14}$NO$_3$Cl: 315.0662, found 315.0681.
Attempted DKR reactions of compounds 45, 46, 47, 48

The reaction conditions were the same as those for the amine-related DKR products (see general procedure for compound 22: 1 eq of α-bromo ester, 1.05 eq triethylamine, 0.2 eq tetrabutylammonium iodide, and 1.01 eq nucleophile, in freshly distilled THF.)

The main reason why these reactions failed to be characterized was that the $^1$H NMR of the product changed drastically from the crude taken before column chromatography and after. The appearance of new peaks suggests a rearrangement. The use of 1% triethylamine when packing the chromatography column (in hopes of reducing the acidity of the column) did not improve the purity of the compounds coming off the column.

The same series of amine nucleophiles were used as for the evaluation for chiral auxiliary 19.
Compound 58: *para*-methyleneamino chiral auxiliary

\[
\begin{align*}
\text{HO} & \text{N-} \text{NH}_2 \\
\text{1-(4-(aminomethyl)phenyl)-3-hydroxy-4,4-dimethylpyrrolidin-2-one}
\end{align*}
\]

Compound 32 (30 mg, 0.13 mmol) was combined with methanol (2 mL) in a round bottom flask charged with a large, strong magnetic stirrer. Cobalt (II) chloride (0.1 molar equivalent) was added, followed by four portions of sodium borohydride (2 molar equivalents with respect to the boron, excess) over a period of four hours. Cobaltous boride (CoB) could be seen precipitating in the flask as a black solid. The reaction was assumed to be complete when the TLC showed no more starting material. The reaction was quenched by the addition of saturated ammonium chloride until the addition of more ammonium chloride did not cause the reaction mixture to bubble. The pH was adjusted with solid sodium bicarbonate and the mixture was extracted with two portions of 5 mL of diethyl ether to provide the product in low yields (4 mg, 13% yield) as a yellow solid.

\[^{1}H\text{ NMR (CDCl}_3, 200\text{MHz)} \delta 7.63-7.56 (d, J = 14 \text{ Hz}, 2H), 7.35-7.32 (d, J = 14 \text{ Hz}, 2H) 4.09 (s, 1H), 3.76 (br s, 2H), 3.56-3.39 (AB q, J = 7, 23 \text{ Hz}, 2H), 2.30 (br s, 2H), 1.31 (s, 1H), 1.06 (s, 3H).\]

\[^{13}C\text{ NMR (CDCl}_3, 75\text{MHz)} \delta 173.53, 138.07, 131.95, 129.00, 119.57, 119.24, 78.38, 57.64, 52.17, 38.55, 24.56, 19.93.\]

HRMS (EIMS) calc’d for C_{13}H_{18}N_{2}O_{2}: 234.1368, found 234.1349.
Compound 59 : TBDMS-protected lactam

\[
\text{TBDMSO} \quad \text{N} \quad \text{59}
\]

2-(tert-butyldimethylsilanyloxy)-3,3-dimethyl-5-phenylcyclopentanone

The alcohol (compound 26, 17.64 g, 86 mmol) was combined with TBDMSCl (27 g, 86 mmol) and imidazole (6.4 g, 94 mmol, 1.1 molar equivalents) in a round bottom flask that had previously been charged with a magnetic stirrer and dichloromethane (200 mL). The mixture was allowed to stir overnight, and the progress of the reaction was monitored by TLC (2:1 Hexanes : Ethyl Acetate). When the starting material was consumed, the reaction was worked up. A sodim bicarbonate wash, followed by a brine solution wash, removed the byproducts. The organic phase was dried to provide the protected alcohol in quantitative yield. It is a thick, viscous clear brown liquid, but also possible as a long clear brown crystal.

\[
^1H \text{ NMR (CDCl}_3, 300 MHz) \delta 7.63-7.59 (AA'B'B'C dt, J = 1.0, 8.0 Hz, 2H), 7.36-7.31 (AA'B'B'C tt, J = 2.0, 7.4 Hz, 2H), 7.13-7.11 (AA'B'B'C tt, J = 7.4 Hz, 1H), 4.02 (s, 1H), 3.45-3.40 (AB q, J = 5.0, 14.4 Hz, 2H), 1.21 (s, 3H), 1.06 (s, 3H), 0.94 (s, 3H), 0.22 (s, 3H), 0.13 (s, 3H).
\]

\[
^{13}C \text{ NMR (CDCl}_3, 75 MHz) \delta 172.74, 139.57, 128.79, 124.31, 119.27, 79.81, 57.00, 38.21, 25.79, 25.66, 26.62, 25.00, 20.38, 18.40, -4.09, -5.33.
\]

IR (cm\(^{-1}\)) : 3064, 3048, 1716, 1598, 1501, 1405, 1149.

EI-MS m/z (%) 309 (47), 204 (82), 106 (100), 77 (61).

HRMS the spectrum did not contain any suitable M+ peak. (EI and CI methods were used).
Compound 60: Oxidized mononitrated lactams

![Chemical structures](Images)

Compound 26 (65.8 mg, 0.321 mmol) was placed without solvent in a round bottom flask. An equimolar mixture of nitric acid and sulfuric acid (35 µL, 0.321 mmol) that had been prepared previously and held in a glass stoppered vial was added in a dropwise fashion. Care was taken to ensure that the drops were added slowly and that the liquid acid had a chance to come into contact with all the substrate. The resulting product mixture was a darker orange solid.

The spectrum has both compounds. The peaks at 3.96 and 3.91 ppm are two singlets, one belonging to each compound. The same case can be made for the peaks at 1.40 and 1.38 ppm. The geminal dimethyl groups are now equivalent, due to the adjacent ketone, but would have slightly different shifts in the two compounds. The last missing peak for the ortho substituted compound is in the 8.05-8.01 range.

**$^1H$ NMR** (CDCl$_3$, 300MHz) δ 8.33-8.28 (d, $J = 12$ Hz, 1H), 8.05-8.01 (d, $J = 12$ Hz, 1H), 7.76-7.70 (t, $J = 8$ Hz, 1H), 7.58-7.52 (t, $J = 8$ Hz, 1H), 7.42-7.38 (d, $J = 8$ Hz, 1H), 3.96 (s, 1H), 3.91 (s, 1H), 1.40 (s, 2 CH$_3$), 1.38 (s, 2 CH$_3$).

**$^{13}$C NMR** (CDCl$_3$, 75MHz) δ 143.68, 134.35, 129.33, 126.98, 126.00, 124.93, 118.92, 58.59, 56.51, 41.07, 39.92, 23.81, 23.49.

**IR** (cm$^{-1}$): 1765 (C=O), 1721 (C=O), 913, 854, 753, 732.

**EI-MS** m/z (%) 56 (100), 83 (35), 151 (21), 164 (9), 202 (6), 234 (16), 248 (133).

**HRMS** calc’d for C$_{12}$H$_{12}$N$_2$O$_4$: 248.0797, found 248.0787.
Compound 61: Dinitrated lactams

![Chemical Structures](image)

Compound 26 (784.8 mg, 3.828 mmol) was placed without solvent in a round bottom flask. An equimolar mixture of nitric acid and sulfuric acid that had been prepared previously and held in a glass stoppered vial was added (0.77 mL, 7.656 mmol) in a dropwise fashion, until two molar equivalents had been added. Care was taken to ensure that the drops were added slowly and that the liquid acid had a chance to come into contact with all the substrate. The resulting product mixture was a darker orange solid. An aqueous / organic extraction with the aid of dichloromethane provided the product in quantitative yield, albeit a 1:1 mixture of isomers.

**$^1H$ NMR** (CDCl$_3$, 200MHz) $\delta$ 8.70-8.69 (d, J = 2.6 Hz, 1H), 8.46-8.41 (dd, J = 2.6, 8.9 Hz, 1H), 7.51-7.46 (d, J = 9 Hz, 1H), 4.09 (s, 1H), 3.75-3.71 (d, J = 9 Hz, 1H), 3.55-3.51 (d, J = 9.2 Hz, 1H), 1.30 (s, 3H), 1.08 (s, 3H).

**$^1H$ NMR** (CDCl$_3$, 200MHz) $\delta$ 8.74-8.72 (d, J = 2.6 Hz, 1H), 8.49-8.44 (dd, J = 2.6, 8.9 Hz, 1H), 7.52-7.48 (d, J = 9 Hz, 1H), 5.42 (s, 1H), 3.87-3.83 (d, J = 9.4 Hz, 1H), 3.65-3.61 (d, J = 9.2 Hz, 1H), 1.40 (s, 3H), 1.26 (s, 3H).

The isomers require careful chromatographic separation, as they are quite close together. I did not determine which isomer corresponds to which spectrum.
Compound 63: TBDMS-protected aniline lactam

3-((tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-1-(4-amino-phenyl)-pyrrolidin-2-one

The nitro lactam (33, 10g, 27.4 mmol) was combined with dichloromethane in a round bottom flask charged with a large, strong magnetic stirrer. Cobalt (II) chloride (3.6 g, 27.4 mmol) was added, followed by four portions of sodium borohydride (4 g, 54.8 mmol, excess) over a period of four hours. Cobaltous boride (Co₂B) could be seen precipitating in the flask as a black solid.

An acid/base workup with diethyl ether as the organic phase provided not only the product, but any remaining starting material was resubjected to the reaction conditions to give the product in 97% isolated yield. The product was sufficiently pure to proceed to the next step.

Alternatively, the reduction could also be carried out with zinc and acetic acid, following literature precedent. However, this procedure occasionally called for heating to 45-50°C, and was not routinely used for batches for fear of deprotecting the alcohol.

¹H NMR (CDCl₃, 300MHz) δ 7.33-7.30 (d, J = 8.9 Hz, 2H), 6.63-6.60 (d, J = 8.9 Hz, 2H), 3.98 (s, 1H), 3.60 (br s, 2H), 3.40-3.37 (d, J = 9.4 Hz, 1H), 3.33-3.30 (d, J = 9.4 Hz, 1H), 1.17 (s, 3H), 1.03 (s, 3H), 0.92 (s, 9H), 0.20 (s, 3H), 0.11 (s, 3H).

¹³C NMR (CDCl₃, 50MHz) δ 172.02, 143.41, 131.02, 121.13, 115.11, 79.72, 57.56, 38.23, 25.76, 24.69, 20.38, 18.34, -4.13, -5.36.

EI-MS m/z (%): 75 (52), 162 (24), 185 (9), 259 (52), 277 (100), 303 (4), 334 (1).

IR (cm⁻¹): 3445, 3359, 3226, 1694 (C=O), 1635, 1515, 1005, 922, 870, 836, 779, 667.

HRMS calc'd for C₁₈H₃₀N₂O₂Si: 334.2077, found 334.2059.
Compound 64: N-aminophenyl lactam

\[
\begin{array}{c}
\text{HO} \\
\text{O} \\
\text{N} \\
\text{64} \\
\text{NH}_2 \\
\end{array}
\]

1-(4-aminophenyl)-3-hydroxy-4,4-dimethylpyrrolidin-2-one

Compound 60 (\textit{ortho} isomer, 110.9 mg, 0.45 mmol) was added to a round bottom flask containing a magnetic stirrer, methanol (solvent, 15 mL) and acetic acid (1 mL, excess). Zinc metal (ground particles, 150 mg, 2.3 mmol, 5 equivalents) was added and the mixture was stirred at reflux overnight. A basic solution (1M NaOH, approx 20 mL) was added and the flask was put on the rotary evaporator until the bulk of the methanol was removed (resulting in oily drops on the surface). The basic aqueous / ether workup provided the product in low yield (40%).

\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 200MHz) \(\delta\) 7.35-7.32 (d, \(J = 8.7\) Hz, 2H), 6.68-6.65 (d, \(J = 8.7\) Hz, 2H), 4.05 (s, 1H), 3.60 (br s, 2H), 3.49-3.47 (d, \(J = 9.6\) Hz, 1H), 3.35-3.32 (d, \(J = 9.6\) Hz, 1H), 1.29 (s, 3H), 1.06 (s, 3H).

\textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 75MHz) \(\delta\) 172.94, 143.77, 130.56, 121.14, 115.27, 78.31, 58.20, 38.67, 24.59, 19.96.

Closer inspection of the aromatic peaks in the \textsuperscript{1}H spectrum reveals that they are in fact doublets triplets, representing a AA’XX’ system, with the other coupling constant equal to 1.5 Hz. However, a detailed simulation was not carried out to verify this observation.
Compound 67: TBDMS-protected crotylamide lactam (Diels Alder dienophile)

3-(tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-1-(4-acrylamido-phenyl)-pyrrolidin-2-one
or
N-(4-(3-(tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl)phenyl)acrylamide

Compound 63 (770 mg, 2.3 mmol) was dissolved in dichloromethane (20 mL) in a round bottom flask. The flask was then cooled to 0°C, and triethylamine (320 µL, 2.3 mmol) was added, followed by acryloyl chloride (186µL, 2.3 mmol). The mixture was allowed to stir under a nitrogen atmosphere for four hours, then was monitored by TLC until the starting material was consumed. Standard acid/base workup furnished the product in acceptable quality and 84% yield.

$^{1}H$ NMR (CDCl$_3$, 300MHz) δ 7.73 (br s, 1H), 7.59 (br s, 4H), 6.63-6.37 (dd, J = 1.5, 17 Hz, 1H), 6.29-6.20 (dd, J = 10, 17 Hz, 1H), 5.73-5.69 (dd, J = 1.5, 10 Hz, 1H), 4.02 (s, 1H), 3.46-3.38 (AB q, J = 9.6, 17.1 Hz, 2H), 1.21 (s, 3H), 1.05 (s, 3H), 0.93 (s, 9H), 0.21 (s, 3H), 0.12 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 75MHz) δ 172.81, 163.51, 135.86, 134.38, 131.09, 127.72, 120.51, 120.19, 120.16, 79.75, 57.31, 38.35, 25.76, 24.69, 20.42, 18.39, -4.13, -5.36.

EI-MS m/z (%) 75 (18), 185 (11), 259 (40), 331 (100), 385 (9).

HRMS the spectrum did not contain any suitable M+ peak.
Compound 70: ROMP precursor

Compound 63 (592.3 g, 1.8 mmol) was dissolved in dichloromethane (15 mL) in a round bottom flask. To that flask was added the Diels-Alder adduct (endo 72, 290.3 mg, 1.77 mmol), and the mixture was allowed to stir with the aid of a magnetic stirrer. The mixture was then heated to boiling (~45°C) for an hour. The mixture was then cooled, a molar equivalent of thionyl chloride (130 μL, 1.77 mmol) was added, and the mixture was heated to boiling again. Upon basic workup, the maleimide is furnished as a white fluffy solid in near quantitative yield.

(* Alternatively, this could be done with the exo adduct with no other changes to the procedure.)

$^1$H NMR (CDCl₃, 300MHz) δ 7.72-7.67 (d, J = 8.7 Hz, 2H), 7.12-7.08 (d, J = 8.9 Hz, 2H), 6.23 (s, 2H), 4.00 (s, 1H), 3.48-3.39 (m, 6H), 1.78-1.75 (br d, J = 8.8 Hz, 1H), 1.60-1.56 (br d, J = 9.4 Hz, 1H), 1.20 (s, 3H), 1.03 (s, 3H), 0.93 (s, 9H), 0.20 (s, 3H), 0.12 (s, 3H).

$^{13}$C NMR (CDCl₃, 75MHz) δ 176.82, 172.85, 139.64, 135.45, 134.53, 127.49, 127.03, 119.36, 79.67, 56.86, 52.17, 46.98, 46.22, 46.02, 45.70, 38.11, 25.73, 24.56, 20.24, 18.33, -4.17, -5.37.

EI-MS m/z (%) 162 (4), 283 (8), 357 (100), 399 (4), 423 (14).

HRMS the spectrum did not contain any suitable M+ peak. However, the peak fragments support the proposed structure:

\[
\text{calc'd for } C_{23}H_{27}N_7O_4Si_1: \ 423.1740, \text{ found } 423.1761.
\]

\[
\text{calc'd for } C_{9}H_{8}NO_2: \ 162.0555, \text{ found } 161.9860
\]
Compound 72: Diels Alder adducts of maleic anhydride and cyclopentadiene

Commercial cyclopentadiene dimer was thermally cracked by boiling (an oil bath at 160-180°C was used as the heat source) and the cyclopentadiene was distilled off and into a flask containing neat maleic anhydride. Excess cyclopentadiene was washed off with hexanes to provide endo-72 as a white powder in quantitative yield.

Endo-72 was converted to a 50/50 mixture of endo-72 and exo-72 by heating it with a butane torch neat until it just begins to bubble. Chlorobeneze was added and the mixture was recrystallized to furnish white crystals of exo-72.

**Endo-72**

$^1$H NMR (CDCl$_3$, 300MHz) δ 6.30-6.29 (t, J = 1.8 Hz, 2H), 3.57-3.47 (m, 4H), 1.78-1.74 (dt, J = 9.0, 1.6 Hz, 1H), 1.57-1.53 (dt, J = 9.0, 1.4 Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 75MHz) δ 171.27, 135.53, 52.73, 47.04, 46.09.

**Melting Point** (uncorrected) 165°C

**Exo-72**

$^1$H NMR (CDCl$_3$, 300MHz) δ 6.34-6.33 (s, 2H), 3.44 (s, 2H), 3.00 (s, 2H) 1.69-1.64 (dt, J = 9.0, 1H), 1.47-1.42 (dt, J = 9.0, 1H).

$^{13}$C NMR (CDCl$_3$, 75MHz) δ 171.55, 137.93, 48.73, 46.84, 44.09

**Melting Point** (uncorrected) 143°C
Compound 74: ROMP precursor

\[
\begin{align*}
\text{p-Methoxy aniline}^* \text{ (p-anisidine, 0.9111g, 7.4 mmol) was dissolved in dichloromethane} \\
\text{in a round bottom flask. To that flask was added an equimolar amount of the} \\
\text{Diels-Alder adduct}^{**} \text{ 72 (end o isomer, 1.2133 g, 7.4 mmol), and the mixture was allowed to stir} \\
\text{with the aid of a magnetic stirrer. The mixture was then heated to boiling (~45°C) for an hour.} \\
\text{The mixture was then cooled, and thionyl chloride (0.42 mL, 7.4 mmol) was added, and} \\
\text{the mixture was heated to boiling again. Upon basic workup, the ROMP precursor is} \\
\text{furnished as a brownish solid in near quantitative yield (98%).} \\
\text{(* Alternatively, other anilines could be used to furnish similar ROMP precursors) } \\
\text{(** Also, the exo adduct could be used with no other changes to the procedure)}
\end{align*}
\]

\textit{endo}

\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 300MHz) \(\delta\) 7.03-7.00 (d, J = 9 Hz, 2H), 6.92-6.89 (d, J = 9 Hz, 2H),
6.23 (s, 2H), 3.77 (s, 3H), 3.47-3.38 (m, 4H), 1.77-1.74 (d, J = 8.9 Hz, 1H), 1.59-1.56 (d, J = 8.9 Hz, 1H).

\textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 75MHz) \(\delta\) 177.13, 159.44, 135.50, 134.55, 127.81, 124.40, 114.39, 55.44, 47.02, 46.07, 45.68, 45.41.

\textbf{EI-MS} m/z (%): 66 (46), 91 (13), 188 (13), 203 (100), 269 (17).

\textbf{HRMS} calc’d for \(\text{C}_{16}\text{H}_{15}\text{N}_{1}\text{O}_{3}\): 269.1052, found 260.1037.

For completeness, the \textit{exo} isomer:

\textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 200MHz) \(\delta\) 7.17-7.14 (d, J = 8 Hz, 2H), 6.92-6.89 (d, J = 8 Hz, 2H),
6.32 (s, 2H), 3.78 (s, 3H), 3.38 (m, 2H) 2.81 (m, 2H), 1.62-1.57 (d, J = 9 Hz, 1H), 1.47-1.42 (d, J = 9 Hz, 1H).
Compound 75: Polymer-supported chiral auxiliary, protected

\[
\text{TBDMSO} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{O} \\
\text{75} \quad \text{Ph}
\]

Compound* 70 (1.2160 g, 2.53 mmol) is dissolved in dichloromethane (25 mL). The solution is then degassed, and titanium tetraisopropoxide (2.3 mL, 7.6 mmol, 3 equivalents) is added. The solution is allowed to stir for a half hour and an appropriate quantity of Grubbs catalyst I is added (the exact quantity required is based on the desired molecular weight, in this experiment, a 5000 MW polymer was desired and 208.2 mg, 0.253 mmol was used), and the mixture is left to stir. After a period of 16 hours, an aliquot is removed and analyzed by NMR. If there are no more peaks at ~6 ppm, then the polymer can be isolated. A couple of drops of phenyl vinyl ether are added.

The polymer is most readily isolated by precipitating it out with methanol, or other simple alcohols. This was done twice so as to remove the bulk of the titanium metal.

The cis/trans isomer ratio in the polymer was not determined.

(*Other substrates, such as 74, could be substituted with no other change in procedure)

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300MHz)} \delta 7.68 \text{ (br s, 2H)}, 7.20 \text{ (br s, 2H)}, 5.6 \text{ (br s, 2H)}, 3.99 \text{ (br s, 1 H)}, 3.35 \text{ (br s, 4H)}, 2.98 \text{ (br s, 2H)}, 2.00-1.4 \text{ (br s, 2H)}, 1.18 \text{ (br s, 3H)}, 1.00 \text{ (br s, 3H)}, 0.92 \text{ (br s, 9H)}, 0.19 \text{ (br s, 3H)}, 0.11 \text{ (br s, 3H)}.\]

\[\text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75MHz)} \delta 175.56, 172.71, 139.44, 129.32, 128.30, 127.58, 126.94, 126.77, 126.25, 119.20, 79.60, 60.23, 56.74, 48.81, 45.30, 40.45, 38.01, 34.50, 29.53, 26.76, 26.07, 24.48, 20.19, 18.25, 14.00, -4.20, -5.41.\]

\textbf{EI ESI-MS (MeOH)} m/z 1703, 1453, 1313, 1176, 1096, 1051, 1006, 912 (base), 808.

\textbf{PDI}: 1.09
Compound 76: Polymer-supported chiral auxiliary, deprotected

The polymer (35 mg, 74 μmol) was dissolved in DMSO (DMF could also be used) and an excess of TBAF solution was added (1.0 mL of a 1.0M solution in THF, 1mmol). The yellowish solution turned slightly orange. This solution was allowed to sit overnight (16 hours) in order to allow for complete deprotection.

The polymer is most readily isolated by precipitating it out with methanol, or other simple alcohols. This provided the polymer as a white precipitate in solution, but when it was dried the colour was a faint beige colour.

The polymer was not soluble in chloroform or THF.

$^{1}H$ NMR (CDCl$_3$, 300MHz) δ 7.68 (br s, 2H), 7.20 (br s, 2H), 5.60 (br s, 2H), 3.99 (br s, 1 H), 3.35 (br s, 4H), 2.98 (br s, 2H), 2.00-1.40 (br s, 2H), 1.18 (br s, 3H), 1.00 (br s, 3H).

IR (DMSO) cm$^{-1}$ 3400 (OH), 1700-1625 (C=O).
References


2 CHM 4123: Medicinal Chemistry, Jan-April 1998, given by Prof. Tony Durst.


12 Adapted from Knowles’ Nobel lecture.

13 See above reference.

Orthogonality refers to the ability of a functional group to remain inert under a set of conditions (usually applied when one talks about combinations of protecting groups).


These two routes should be interconvertible, either directly as in this work, or indirectly as in the example of the generation of atropisomers that follows in the examples.


27 Carboxylic acids can, in turn, be generated from a wide variety of other functional groups either directly or indirectly: Larock, R. C., Comprehensive Organic Transformations, Wiley-VCH, New York, NY, 1999, 1623-1995.


29 Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J., J. Am. Chem. Soc., 1989, 111(19), 7650. Larsen and Corley do point out that this is not the first example of a chiral alcohol being added to a ketene, rather this is the first example of a reaction that yields a product of such high diastereoselectivity.

References 4, 5 and 6 in the paper provide ample evidence to this.

30 See reference 25, above

31 see ref 25, the 1992 paper


33 (R)-pantolactone is assumed.

34 A cursory examination of Greene and Wuts Protecting Groups in Organic Chemistry shows that the hydrogen source is not limited to H2 gas, indeed cyclohexene can be used. The Pd source can be a nanoparticle suspension in order to aid in the process.

35 By solvent of choice, it is understood that this is the solvent that provides the greatest diastereoselectivity in the product. It is incidental that this solvent is compatible with polymer supports (see later sections)


The first credited with this innovation was Merrifield, who has a resin named after him. Other resins were developed by Rink, and Wang.

While not specifically related to this sentence, the following reference was instrumental in the background research for this section: Bunin, B. A., The Combinatorial Index, Academic Press, San Diego, CA, 1998. The associated website was also useful: www.combinatorial.com

QSAR: quantitative structure activity relationships. This requires some kind of screening process in conjunction with the synthesis.

Registered trademark of the Chemical Abstracts Service of the American Chemical Society.

These papers appear in the International Journal of Peptide and Protein Research. The scientist to look for is Dr. Ronald N. Zuckermann. A good lead paper is Zuckermann, R. N.; Kerr, J. M.; Siani, M. A.; Banville, S. C., Int. J. Peptide Protein Res., 1992, 40, 497. There are several semi-automated methods referenced, and the fully automated ones are simple amino acid linkings and subsequent attachments. Therefore, they are all (including the Zuckermann paper) strictly peptide synthesizers, and not amino acid synthesizers.

The example used is Argonaut Technologies, but others that also sell such instruments include, but are not limited to are: Beckman-Coulter (ORCA® robots), Mettler-Toledo Autochem (Discoverer Synthesizers™, Miniblock™ series of instruments, as well as the MultiMax™ series of instruments), Charbydis Technologies (Iliad™ PS2 Personal Synthesis Systems), Chemspeed Inc. (USA) Chemspeed UK Ltd. Chemstspeed Ltd. (Switzerland) (Accelerator™ series of synthesizers, as well as the SmartStart™ synthesizer). There are other examples, but are omitted for sake of brevity.

Initial nucleophilic ring opening of the lactone was done with benzylamine.

It should also be noted that due to the high temperatures and the presence of the aniline resulted in complete racemization of the product. As a result, racemic pantolactone was used in favour of its optically active enantiomer. The consequences of this decision are dealt with later on.

Due to the resulting racemization under the reaction conditions, racemic pantolactone was used, which was less expensive.

However, this experiment was performed before the discovery of the improved sealed tube procedure.


Made by carrying out the acylation reaction at 0°C.


One common approach seems to be a two step process of bromination followed by halogen-metal exchange. See Bengalia, M.; Puglisi, A.; Cozzi, F., *Chem. Rev.*, 2003, 103(9), 3401 and references cited therein.


61 Prof. Grubbs gave a seminar at the 2002 CSC Conference in Vancouver.


64 Via coupling with CuCN, a reaction learned in second year organic chemistry.

65 It should be noted that this the most common way in which other molecules are attached to polymeric supports, including the Janda/els, see ref 53.

66 This was fortuitous, since there are a number of reports which state that while it is possible to make resins from such substrates, the mechanisms of their formation are not yet as well developed as the ROMP mechanism which would mean that there isn't that much control over smaller molecular weight polymers. See refs 1-6,19-21 in Sung, C. S. P.; Phelan, J. C., Macromolecules, 1997, 30(22), 6837.

Numerous discussions with Prof. Fogg as well as her research group were also integral in deciding how to proceed with this kind of substrate.


Two equivalents since there are two carbonyls per monomer unit.

In this case, three equivalents of titanium (IV) tetraisopropoxide were used, since there is another carbonyl in the lactam.

Unfortunately, I never got to communicate with the person who did this work, and as such I do not have any experimental details.

The polymer made, albeit only a small quantity, had an average molecular weight of 35,000.
Section 4  Feverfew and Parthenolide. Which is best?

4.0  Feverfew Background

Feverfew is a plant, *Tanacetum parthenium* (L) (synonym: *Chrysanthemum parthenium* (B)) (family *Asteraceae* or *Compositae*), whose medicinal properties of pain relief have been cited at least as far back as the 16th century. Indeed, there is mention of feverfew as far back as the 10th century as "feferfuige". While the folk medicine is mostly used for the prophylactic treatment of migraines, the proof of its clinical efficacy is still under development (more on the clinical trials below.) One of the problems with folk remedies is that because of the lack of a formal clinical trial system, the exact modes of action, as well as the active ingredients are often still not fully accepted. What follows is a roadmap of the pertinent literature, which will demonstrate the importance of carrying out this project.

One of the key difficulties with the use of a plant is determining which parts of the plant are needed, in what quantity, and in some cases which subspecies may also be used. Due to the varying weather and soil conditions around the world, a given plant species may not be able to grow everywhere that it is needed. Feverfew grows in Europe, North Africa, China, Japan, and parts of North America as well as in Australia. In fact, due to the potential for benefit for the public good, both Canada and the US have government or university initiatives to investigate the feasibility of feverfew as a crop and its general hardiness. In Canada, this work was undertaken by the Alberta Agriculture Research Farm in Fairview, Alberta. The research showed overall good hardiness and high yield. In the United States, the work was carried out as part of the
Nutraceuticals Program at the Clemson Public Service Experiment Station, which is a joint plan of work with Clemson University. The main focus was to use feverfew as a replacement crop for tobacco. However, not all growers share this benevolent disposition for the public good. Herbal suppliers in Britain eager to get this plant to market have been supplied with *Matricaria recutita* as well as *Tanacetum vulgare* instead, it is unknown whether these plants were supplied because they are also believed to work as well as *T. parthenium* or whether they were supplied by enterprising growers eager to cash in on the lack of concrete evidence surrounding the exact activity of this plant. To complicate this a little further, the plant is also sometimes referred to as Bachelor’s Button, and has the name *Chrysanthemum parthenium*.

It is generally accepted that the bulk of the active ingredients are in the leaf of the plant. However, some herbal suppliers are using the whole dried plant, which causes a decrease in activity because the leaf does not make up the bulk of the mass of the dried material. The flower, stalk as well as other parts of the plant do not contain as much of the active ingredient(s), which results in a dilution effect, decreasing the potency and preventing effective clinical trials. Until the exact combination of compounds resulting in the formulation of the active ingredients is known, the efficacy of the products on the market will vary to the extent that some brands of feverfew extract will not have the desired properties.

4.1 Clinical Trials of Feverfew

The chronology of the clinical trials is as follows: the earliest one is from 1983 in a journal called *MIMS Magazine*, which is an adjunct to the British Pharmacopeia. The second trial was published in 1985 in the *British Medical Journal*, (notably, it features amongst its
authors the author of the 1983 paper. The final trial was reported in 1988 in the highly respected medical journal *The Lancet*\textsuperscript{11}. The last two featured a double blind clinical trial, and the last one also had a randomized crossover of the two groups. Given the general\textsuperscript{12} acceptance of these clinical trials, it should come as no surprise that the unregulated nature of this extract has resulted in a rather large torrent of eager suppliers\textsuperscript{13}. The results of the trials are summarized individually, given that the techniques and processes sufficiently differed between them.

4.1.1 The 1983 Clinical Trial

This clinical trial used 270 migraine sufferers over a span of 2.5 years, "... in which 70 % of those who drank tea made from feverfew daily for extended periods of time concluded that the herb decreased the frequency of attacks, caused them to be less painful, or both. Many of these patients had previously failed to respond to a wide range of more orthodox pharmacologic approaches." It should be duly noted that no mention is made of parthenolide, active ingredients, just that the three small leaves or one large leaf was consumed daily. The other key point is that no mention is made of the mode of activity of feverfew, just that it works.

One interesting note by the director of the clinical study is that one third of the patients "... had no further migraine attacks after initial use of the herb." The extent of this was not fully appreciated until after the end of the study, when 80 % of those for whom the herb worked started to experience migraines 2-3 weeks after cessation of leaf ingestion. Moreover, once treatment was reinstated, the migraines went away again.
4.1.2 The 1985 Clinical Trial

While not as large as the previous clinical trial, this one was quite important. It was carried out at the City of London Migraine Clinic and used 17 patients in a double-blind study. A double blind study is important since even the doctors who prescribe the drugs do not know whether or not they are prescribing a placebo. The relative benefit of such a study is directly related to its impact in terms of how seriously it considered by people who are suspicious of who carries out such studies, since it eliminates personal bias on the part of the doctor.

One of the key issues with migraines is its ability to incapacitate a percentage of the people who suffer from them. In this case, two people dropped out of the study because of the recurrence of severe migraines, it turned out that these people were being treated with the placebo, which further supports the data from the previous study where the cessation of treatment causes the migraines to return with full force. Along with the ability to incapacitate its sufferers, migraines also have additional effect of causing nausea and vomiting. The use of feverfew decreased the occurrence of vomiting from 79% in the placebo group to 42% in the active treatment.

The obvious shortcoming of this clinical study is that it sampled a very small number of people. In today’s market, this would be accepted as a Stage II clinical trial. The other shortcoming is that other prophylactic measures that were started by the patients were allowed to be used during the clinical trial. These other prophylactic measures were not specified, and therefore it is unknown what effects they may have not only on the patient but also on the feverfew.
Finally, this was the first study where parthenolide was mentioned. The authors noted “... that the plant is rich in sesquiterpene lactones, the principal one of which is parthenolide.”

4.1.3 The 1988 Clinical Trial

The third clinical trial was larger in scope than the second but not as big as the first, with 76 patients. This study was also carried out in a double blind fashion and, additionally, also featured a crossover period after four months. This means that a patient who was receiving the placebo for four months would then receive the feverfew extract for four months and vice versa.

As seen in the previous study, not everyone finished the study: 16 people dropped out. The same kinds of results were seen as with the previous study (fewer migraines, milder migraines, and considerably less nausea and vomiting.)

More importantly, however, is that the investigators in the study actually suggested a mode of action (see below) and attributed it directly to the sesquiterpene lactones, of which parthenolide is the most abundant. It should be pointed out that this is merely a suggestion, as there has been a number of different modes of action suggested which are responsible for feverfew’s prophylactic effects.

4.2 Parthenolide and the Mode(s) of Action of Feverfew

Parthenolide (see figure, below) is a sesquiterpene lactone, and contains a α-methylene γ-lactone moiety.
Figure 1: Parthenolide

The debate with respect to whether this is the active ingredient or not takes on a number of different facets. From a chemical perspective, the molecule can undergo a number of different reactions, the most probable ones involve nucleophilic attack. The epoxide, ester carbonyl and alpha methylene moieties are all subject to attack by nucleophiles, both hard and soft.

In the human body, very reactive molecules are generally not well tolerated. $\alpha$-methylene $\gamma$-lactones, such as parthenolide, have been implicated in allergic eczematous contact dermatitis$^{14}$. However, the dermatitis condition was "...not considered prohibitory for therapeutic use..." It causes apoptosis and cell necrosis$^{15}$, which is not necessarily a bad thing, since it allows for the regulation of the cell cycle, and as such is considered as a potential cancer and tumor active compound$^{16}$.

Recent research$^{17}$ has shown that parthenolide and other $\alpha$-methylene $\gamma$-lactones act directly and specifically on NF-$\kappa$B$^{18}$, which is a transcription factor, and an important mediator in the inflammatory process. The connection between parthenolide's anti-inflammatory activity (specifically relieving arthritic pain) and its prophylactic use against migraines has been noted previously$^{19}$. Indeed, the mechanism of action of inflammation in general might be somehow connected to migraines via inhibition of prostaglandin synthesis$^{20}$. This particular mode of action is shared with the anti-inflammatory and headache mode of action of acetylsalicylic acid and other non steroidal anti-inflammatory drugs (NSAIDs). However, as has been shown with new drugs such as Vioxx®, it may just be that it is a question of selectivity, and as such remains
a tenuous link at best. Moreover, parthenolide-containing extracts have\textsuperscript{21} been used for the treatment of inflammation.

The key question then becomes whether the biological activity is a result of the parthenolide or some of the other approximately 50 other compounds\textsuperscript{22} present in the feverfew extract, some of which are also sesquiterpene lactones (they are shown in the following section) and of those only half contain the reactive $\alpha$-methylene $\gamma$-lactone moiety. Given that this functionality is known to be a sensitizer and cause of contact dermatitis, it would help to settle these arguments by simply removing the parthenolide from the extract and subjecting it to a clinical trial.

An insightful account of the mechanism of action of parthenolide has been brought forth by Arnason \textit{et al.}\textsuperscript{23}, and is directly related to the efficacy of the extract's migraine prophylactic activity. The certainty introduced by the word "directly" in the previous sentence is due to the ongoing\textsuperscript{24} studies, and revolve around 5-HT receptors. 5-HT is the short form of 5-hydroxytryptamine, which is another name for serotonin. The Arnason paper details the mode of action as the inhibition of serotonin release, as assayed in bovine platelets. This is an important and rapid step forward, since abnormal serotonergic function is part and parcel of a migraine attack. In cases of so-called "classic migraines\textsuperscript{25}, in the period immediately preceding an attack (the aura phase), the serotonin plasma levels increase, but then drastically fall off and remain low during the attack\textsuperscript{26}. From that, it can be inferred that the low level is either due to the tissues and platelets taking up the serotonin, or that it is excreted. Indeed it is the latter, as 5-HT and some of its metabolites are found in the urine during attacks. This means that if one can stop the platelets, tissues and such, from releasing the serotonin, one has a better chance of preventing a
migraine attack. The proof that the serotonin release is partially responsible is simple: exposure
to agents that cause serotonin release (i.e. reserpine, fenfluramine, etc) induce migraine attacks.

Preventing (inhibiting) serotonin release lies at the heart of migraine prophylaxis. The
only problem is that there are a number of serotonin receptors against which affinities can be
studied: 5-HT_{1D} is a good candidate, since agonists of that receptor are effective in the acute
treatment of migraines. In the 5-HT_{2} receptor subtypes, there is a range of effects, and so from a
neuroscience point of view further studies are needed on their own.

To summarize the relationship from the bioassay standpoint (q.v. ref 23), the bioactivity
is closely correlated ($r = 0.95$) to the parthenolide content. Other sesquiterpenes also contribute
to 5-HT release inhibition, and as such also need to be accounted for when the extract is
formulated$^{27}$. The IC$_{50}$ of parthenolide for 5-HT release inhibition is 3.03 $\mu$M and is at least a
couple of orders of magnitude better$^{28}$ than two of the most widely used migraine prophylactic
drugs: verapamil hydrochloride (IC$_{50} = 577.5$ $\mu$M) and propranolol hydrochloride (IC$_{50} = >939.8$
$\mu$M).

4.3 Hypothesis behind the project.

Despite the above line of evidence, there is still no definitive proof that parthenolide in
the active ingredient in feverfew. Indeed some researchers$^{29}$ suggest that parthenolide may
actually only cause the undesired allergy causing side effect.

Is parthenolide the “true” active ingredient in feverfew? If it is then a parthenolide free
extract should not be effective. If it is not, and it is not an effective synergist for the other
compounds in feverfew, then its removal should create an extract of feverfew that is not allergy causing (hypoallergenic).

While the exact mechanism of action of feverfew extract with or without parthenolide is beyond the scope of this thesis, a key issue must be addressed. It can be argued that carrying out a clinical trial on pure parthenolide could solve the question of parthenolide as an active ingredient\(^{30}\). This would be ideal, but such an approval is extremely costly since it would fall into the requirements for clinical trials for single entity drugs and require long term animal toxicity studies to prove its safety before the necessary human phase I and phase II trials could begin.

4.4 Removing a needle from a haystack

The extract of feverfew contains a large number of compounds (q.v. ref. 22), and in order to be able to remove one compound, or one class of compound, is no simple feat. Luckily, the crux of the problem is the reactive \(\alpha\)-methylene \(\gamma\)-lactone moiety. The approach, therefore, can selectively target that moiety, since it is so reactive. The following figure shows those compounds that not only have anti-secretory activity but also contain an \(\alpha\)-methylene \(\gamma\)-butyrolactone unit as part of their sesquiterpenoid skeleton.
Figure 2: Sesquiterpenes from *Tanacetum parthenium*

The figures above are adapted from the article in *Phytochemistry* (q.v. ref. 22) and are arranged in the order of their abundance, with the amount in milligrams in brackets. While the relative amount of each of them is significantly less than that of parthenolide (200 : 10), they would also be removed because they all feature the reactive $\alpha$-methylene $\gamma$-butyrolactone unit.

Since the parthenolide concentration is by far the largest on feverfew, its removal should be key, unless one or more of the the other constituents shown in Fig. 2 is more active than the parthenolide. The quantity is based on an extract of the aerial parts of the plant (2.5 kg). A number of other compounds are also present, mostly comprised of other terpenoids (i.e. pinene derivatives, farnesene, etc.)

Ample precedent for the removal of related sensitizers has been shown by Prof. Jean Fréchet when he was a professor at the University of Ottawa\textsuperscript{31}. The basic approach to his work is the same as that which we wanted to take, except that there were two issues that needed to be
addressed first. A number of the resins that Fréchet used had powerful nucleophiles, some of which were “hard” nucleophiles (see figure below).

![Nucleophiles](image)

*Figure 3: Nucleophiles used by Fréchet et al.*

The above nucleophiles would not suit our case, as we have both the methylene lactone carbonyl group and an epoxide that can also be attacked by a hard nucleophile. It is true that these functional groups can remain intact in the presence of such nucleophiles, but it is also true that they decompose rapidly under Lewis Acid catalytic conditions. The extract may contain compounds that can function as Lewis Acids, which would then facilitate the attack of the nucleophiles upon the epoxide.

Therefore, the sulfinate group was chosen. It is acknowledged to be a soft nucleophile that adds in a Michael [1,4] fashion rather than [1,2] addition to an α,β-unsaturated carbonyl compounds. The sulfinate bearing resin functions well on its own on acid-containing substrates, but may need acetic acid to work with neutral substrates\(^{32}\).
4.4.1 Model study

The addition of the sodium salt of benzenesulfinic acid to parthenolide occurs readily in ethanol, but only if a stoichiometric amount of acetic acid is used. This may be due to the reversible nature of the sulfinate addition.

![Chemical Diagram](image)

Figure 4: Addition of sodium benzenesulfinate to parthenolide

The reaction was sluggish at room temperature, but proceeded to completion upon heating to 40-45°C\(^\text{33}\). The acetic acid is necessary as a proton source. The reaction could be monitored by TLC and HPLC. The latter is preferable, since it is the means by which the parthenolide is quantified in the extract.

There is a bit of a difficulty with monitoring the reaction by NMR due to the necessity\(^\text{34}\) of having to run the NMR with a mixture of CDCl\(_3\) and sufficient deuterated DMSO to make that parthenolide soluble. This solvent has a high affinity for water, and there is usually a signal\(^\text{35}\) due to water (\(\delta 3.33\) ppm) obscuring some peaks, and it may be of such great intensity with respect to the sample that the sample peaks are hidden under it.
However, a magnification of the aromatic and methylene area of the spectrum (approximately 8ppm to 5ppm) allowed us to monitor the reaction.

Figure 5: Expansion of the 8 - 5 ppm region in the NMR of the benzene sulfinate and parthenolide reaction

The spectra require some explanation. The top trace is that of parthenolide, with (a) and (b) being the individual methylene protons. The lower trace is that of parthenolide after the reaction with a slight excess of benzenesulfinic acid (the reaction was run in ethanol with acetic acid as the proton source). Peaks labeled (d) and (c) are the aryl hydrogens of the benzene ring (specifically (d) are the ortho hydrogens, and (c) are the meta and para hydrogens.) The little doublets to the left of the (d) peak as well as the (e) peak are the excess benzenesulfinic acid. More importantly, however, is that the methylene peaks have disappeared.

The methylene hydrogens, which are adjacent to an SO₂ functional group, move to ~2.6-2.8 ppm by analogy to CH₃SO₂CH₃, and as such are now obscured by the big DMSO peak.
4.4.2 Polymer supports

In an effort to make everything "in house", it was hoped that a polystyrene resin could be functionalized in order to meet our needs. The standard\textsuperscript{36} approach of lithiation followed by quenching the anion with sulfur dioxide would allow for the flexible introduction of a range of degrees of functionalization. However, this approach was not very successful. In our hands, only a low incorporation of sulfur could be achieved. To this end, a different approach was used, whereby a sulfonyl chloride functionality would be introduced and then reduced to the desired sulfinate. This can be achieved by exposing the polymer to chlorosulfonic acid (see figure below.)

![Figure 6: Chlorosulfonylation of a styrene polymer](image-url)
Reduction of the resulting sulfonyl chloride can be achieved with a number of different reducing agents, which are detailed along with the different polymer backbones used below.

4.4.2.1 1% crosslinked polymer functionalized by chlorosulfonylation

In hopes of having the most effective polymer possible, a stock unfunctionalized polymer (polystyrene, 1% crosslinked with divinylbenzene) was functionalized in this way to yield a polymer, which had sulfur on 91-94% of the phenyl groups (by elemental analysis). It was then reduced with sodium borohydride. However, this material was ineffective and unable to remove any significant amounts of parthenolide, presumably due to the highly polar (and therefore insoluble) nature of the polymer.

4.4.2.2 20% crosslinked polymer functionalized by chlorosulfonylation

A macropore polystyrene resin with 20% crosslinking with divinylbenzene allows for a greater flexibility in terms of choice of solvents for the extract. This is important, since not every solvent can be used, some will likely remain. Only a few organic solvents are plausible if the product is destined for human use. Using the above chlorosulfonic acid procedure, followed by a sodium borohydride reduction in THF, a polymer functionalized with sodium sulfinate units was prepared. The presence of these units was verified by IR bands at 1024 and 960 cm\(^{-1}\). This polymer was able to remove 3.7 mg to 6.3 mg of parthenolide per gram of polymer as evidenced by HPLC traces of feverfew extract solutions (in ethanol and ethyl acetate, respectively).
4.4.2.3 Commercial chlorosulfonylated polymer

A commercial crosslinked polystyrene resin\textsuperscript{37} was investigated next since it had a known degree of incorporation of sulfur, and could be transformed into the required sulfinate via reduction of the sulfonyl chloride moiety. This is in contrast to the above polymers where the number of functional units is dependent on two reactions: the first to incorporate the sulfonyl chloride moiety and then the reduction of sulfonyl chloride units. It is important to reduce all of the sulfonyl chloride units since their presence may cause removal of alcohol containing constituents of parthenolide as sulfonates.

\begin{center}
\begin{align*}
\text{Cl} & \quad \rightarrow \quad \text{OR} + \text{HCl} \\
\text{O=S=O} & \quad \text{O=S=O}
\end{align*}
\end{center}

\textit{Figure 7: Reaction of the chlorosulfonylated polymer with alcohols}

Initial studies with a sodium dithionate slurry in water did not achieve fully the desired transformation, but the polymer was still able to remove small amounts of parthenolide. It is thought that since the slurry contained water, it would prevent desired polymer solubility. The reduction of all of the sulfonyl chloride units was incomplete since the ‘reduced’ polymers had large peaks at 1592 and 1172 cm\textsuperscript{-1}, indicating unreacted sulfonyl chloride units in addition to a peak at 1130 cm\textsuperscript{-1} suggesting sulfonate units). A sodium dithionate reduced polymer was able to remove 1.9 to 3.5 mg of parthenolide per gram of polymer as evidenced by HPLC traces of the standardized parthenolide solutions in ethanol.
4.4.2.4 Other methods for the reduction of chlorosulfonylated polymers

![Reduction of a chlorosulfonylated polymer](image)

**Figure 8**: Reduction of a chlorosulfonylated polymer

The next reducing agent of choice was sodium borohydride. This had the obvious advantage of using THF as the solvent of choice, which is known to be a good solvent for LPS polymers. Indeed, by analyzing the polymer by IR spectroscopy, the bands at 1376 and 1172 cm\(^{-1}\) disappeared, and a band at 959 cm\(^{-1}\) appeared, indicating conversion of the sulfonyl chloride to sodium sulfinate. The performance of the polymer reduced in this fashion was not as good as expected. There wasn’t much improvement over the polymer that was obtained by sodium dithionate, with a removal capacity of 1.3 mg of parthenolide per gram of polymer in an ethanolic parthenolide solution. The polymer obtained by reduction with a dithionate slurry also removed the same order of parthenolide (1.9 to 3.5 mg) despite having fewer sulfinate units. Could the hypothesis be wrong in assuming that the sulfinate unit was the best nucleophile for this reaction? The thought did occur, but a major aspect of polymer chemistry had been overlooked. The polymer was solubilized quite well in THF, and therefore a THF extract of feverfew would be more compatible with the polymer. To that end, a THF feverfew extract was prepared and the polymer was then used to remove the parthenolide. The performance was noticeably improved with a removal capacity of 7.2 mg of parthenolide per gram of polymer.
from one batch, and 10.6 mg of parthenolide per gram of polymer in a second batch of the polymer prepared using the exact same procedure. There are a number of possible explanations that could account for this difference in activity. Polar solvents such as ethanol might hydrogen bond with the sulfinate group, thereby preventing it from reacting with the parthenolide in solution. It is evident that the solvent may create a high desolvation barrier that prevents the polymer from removing parthenolide in polar protic solvents.

One cannot ignore the fact that sodium borohydride has a relatively poor solubility in organic solvents, and in order to ensure that the reduction step goes to completion, a different reducing agent, possibly lithium borohydride or DIBAL-H, with a better solubility should be used. A reducing agent that is soluble in THF should be a better reducing agent simply because it would be able to react more easily with more functional groups. The difference between the reductions carried out with a sodium diithionate slurry in water and a reduction carried out with sodium borohydride in THF could easily be seen when one compares the IR spectra of the polymers (the borohydride reduction did not have bands that corresponded to any remaining sulfonyl chloride functional groups).

To that end, DIBAL-H (diisobutyl aluminum hydride) was used since it satisfied the THF solubility criteria. The enhanced reactivity did mean that a stoichiometric amount had to be used in order to prevent overreduction. This was not necessary with sodium borohydride since there was no overreduction as long as the reaction was carried out at 0°C. However, the polymer prepared by a DIBAL-H reduction was not significantly better than the one prepared by a borohydride reduction, as evidenced by IR. The starting material bands (see chart below) disappeared, but the desired sulfinate
<table>
<thead>
<tr>
<th>Polymer-bound SO₂Cl</th>
<th>1592</th>
<th>1376, 1172</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer-bound SO₂Na</td>
<td>1180</td>
<td>959</td>
</tr>
<tr>
<td>Polymer-bound SO₃Na</td>
<td>1200</td>
<td>1130</td>
</tr>
</tbody>
</table>

Table 1: IR bands of sulfur-containing polymers

bands were not as strong as with the polymer prepared via borohydride reduction. This is attributed to possible difficulties with hydrolysis of the sulfinate from the dialkylaluminum reagent. The polymer obtained by DIBAL-H reduction was able to remove 2.2 to 2.5 mg of parthenolide per gram of polymer from an ethyl acetate feverfew extract (compared to 7 to 10 mg per gram of polymer with the borohydride-reduced polymer).

Linear polystyrene polymers generally are not well known to intercalate significant amounts of polar molecules such as water and alcohols (this is analogous to the case on the previous page where feverfew extracts in different solvents were used). The reason why the intercalation of alcohols is important in this case is that an alcohol is needed to quench the aluminum sulfinate.

\[
\text{Figure 9: Reduction of the P-SO₂Cl polymer with DIBAL-H}
\]
4.4.3 HPLC traces showing the progress of parthenolide removal

The following are the HPLC traces which show the decrease in the concentration of parthenolide, and a concomitant increase in a new peak. This new peak is the sulfinate adduct (top right structure in figure 3), since this was a model experiment using the sodium salt of benzenesulfinic acid.

![HPLC traces](image)

Figure 10: Feverfew extract before and after treatment with 2.2

The key feature of these images is that the shape and area of the other peaks does not change appreciably after the treatment. This is important because the other compounds have been retained in order for the further (clinical) evaluation of the extract to be effective. The concentration of the parthenolide in the left hand trace is 483 μg/mL, and in the right hand trace...
is 73.4 µg / mL, a removal of 85% of the parthenolide in the extract. The new peak (due to compound 2.2) would not be present if the extract was treated with the polymer (see below), but here serves to validate that the area lost due to parthenolide will create a new area due to the adduct.

The other series of HPLC traces (see below) that are of interest are the ones where the parthenolide has been completely removed. In this case, there is no new peak that appears because the polymer was used to remove the parthenolide, and therefore there is no new peak that appears. In this case, the concentration of parthenolide was reduced from 818.4 µg/mL to 13.5 µg/mL, a removal of 98% of the parthenolide present.

Figure 11: HPLC traces of polymeric removal of parthenolide
These HPLC traces show the effectiveness of the sulfinate approach to the selective removal of parthenolide. To show the difference against a different strategy, the following are two gas-liquid chromatograms from an early Fréchet paper in *Can. J. Chem.* The polymer used was one with an amine functionality (P-CH₂CH₂NH₂). The extract was crude costus essential oil, which also contains significant amounts of sesquiterpenes related to parthenolide (the region with the bracket underneath). The focus of that paper was the removal of DHC:

![Figure 12: DHC – dehydrocostuslactone (left) and costunolide (right)](image)

The key features of these figures is that in this approach, there is a noticeable quantity of other related compounds that are also removed. These other compounds were also
sesquiterpenes bearing the $\alpha$-methylene $\gamma$-lactone functionality. This removal procedure also irreversibly destroys one of the main components of costus essential oil: costunolide. It should be noted that of the compounds that were identified in the mixture, none of them had particularly sensitive functional groups, which allowed the use of the amine-functionalized polymer. In the case of feverfew, it was desirable to be able to retain the parthenolide in case it does turn out to be the main active ingredient. This might lead to an improved isolation procedure for parthenolide, but is outside the scope of this thesis.

4.4.4 Solvents for extraction

In terms of extractions, solvent swelling is an issue more from the Connely Surface (the solvent-accessible volume) which means not only the size of the solvent molecule, but also the polarity. The easiest example of why this is important from the point of view of the substrate to be picked up is that the solvation and desolvation may be energetically prohibitive. In the case of feverfew the solvents we used and tested were: ethanol, DMF, THF and ethyl acetate. The two solvents that were most compatible with the polymer were ethyl acetate and THF. A simple set of experiments, which used a known amount of parthenolide in solution, were used to see how much a given polymer could remove in a 16-24 hour period at 40-45°C.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Amount of Parthenolide Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Acetate</td>
<td>11.3 mg parthenolide / gram of polymer</td>
</tr>
<tr>
<td>THF</td>
<td>10.6 mg parthenolide / gram of polymer</td>
</tr>
<tr>
<td>EtOH</td>
<td>1.3 mg parthenolide / gram of polymer</td>
</tr>
</tbody>
</table>
The choice of solvent is important for a number of different reasons. From a preparative chemistry standpoint, a solvent that was compatible with the polymer support was needed, and both THF and ethyl acetate fit that requirement since they allow the polymer to remove approximately ten times more parthenolide than if the feverfew was extracted with ethanol.

A different standpoint, that of safety, helps us make the choice between THF and ethyl acetate. United States federal regulations require that THF can be used in conjunction with food, drugs and cosmetics as long as the residual amount does not exceed 1.5% (this is with regards to the packaging). Alternatively, ethyl acetate is used as a pharmaceutical aid as a flavouring agent and is used as an artificial fruit essence. While not completely safe (ethyl acetate has an LD₅₀ of 11.3 mL/kg in rats), it is preferred to THF.

4.4.5 Recycling

The recyclability of a polymer is always an important question. Upon recycling, a second run would reveal how reversible the addition would be and ultimately how industrially viable the whole process would be. Luckily, the elimination that regenerates the α-methylene moiety proceeds quite readily with sodium hydroxide in THF at room temperature (see next page). The polymer mentioned in the previous section, which was able to remove 11.3 mg of parthenolide per gram of polymer was recycled in this fashion and was able to remove 12.1 mg of parthenolide per gram of polymer in a second run, indicating that the polymer is robust enough to be able to be recycled. In order to determine the durability of the polymer, it was exposed to an excess of feverfew extract, in order to make sure that the polymer was fully loaded with parthenolide. It was then recycled and its IR spectrum was compared to the IR spectrum of the
polymer before it was exposed to parthenolide. The new spectrum revealed that the polymer does indeed oxidize to the sulfonylic acid (i.e. R-SO$_2$Na$^+$ $\rightarrow$ R-SO$_3$Na$^+$)

The key concern in this case was the oxidation of the polymer and degradation of the functional groups. Indeed, certain conditions lead to the destruction of the requisite functionality, such as washing with acetone (presumably due to nucleophilic attack upon the carbonyl, but this addition is reversible). Washings with saturated sodium bicarbonate also led to the destruction of the sulfinate groups, as evidenced by IR. Sodium bicarbonate is not, by its chemical nature, an oxidizing medium, but the handling of the polymer (involving many transfers in air, especially during filtering and drying) is thought to be the reason why the polymer oxidizes. Prevention of polymer oxidation could not be wholly achieved, but handling the polymer under nitrogen whenever possible was effective in preventing the appearance of IR bands corresponding to R-SO$_3$Na$^+$. The key time when the polymer is believed to be oxidized is when it is undergoing drying.

Figure 14: Regeneration of parthenolide after capture
4.4.6 Maximum loading capacity

The removal of parthenolide was experimentally carried out first in standardized solutions containing only the solvent, parthenolide and the polymer. The idea that there might be problems when one switched to the feverfew extract resulted in some additional experiments. The difference in parthenolide uptake was evident when a batch of polymer was split into two batches: one lot was used with feverfew extracts and one lot was used with a standard solution of parthenolide.

The difference in time was immediately obvious: removal of parthenolide from the standard solution was complete overnight (i.e. up to 16 hours). Reaction of the polymer with the feverfew extract took somewhat longer, and required approximately 40 hours. The reason for the uncertainty is because the preferred method of analysis (thin layer chromatography) yields a new spot at the same R$_f$, but that is not parthenolide (as assayed by HPLC). A small aliquot was analyzed by HPLC at 16 hours and still contained parthenolide. In other words, it is possible that the removal took less than 40 hours, but thin layer chromatography was no effective in determining when the removal is complete.

The difference in loading capacity of a polymer in a standardized parthenolide solution versus a feverfew extract was noticeable. A maximum uptake experiment using a polymer in a standardized THF solution with parthenolide showed that the polymer was able to remove 37 mg of parthenolide per gram of polymer, and 17 mg of parthenolide per gram of polymer after recycling$^{41}$. This is in comparison to the 10-15 mg that was seen when the polymer was used with feverfew extracts.
The maximum loading capacity allows for a more effective means by which the "quality" of the polymer can be measured. Quality, in this case, is defined as the degree to which the polymer can rapidly, and selectively, capture parthenolide from solution. It became immediately obvious that the performance of the polymer in a standard solution with only parthenolide as compared to a feverfew extract was quite different.

A statistical screening effect was immediately recognized. In a single match system, it can easily be explained with the following diagram:

\[ A \rightarrow A' \quad A \rightarrow A' \quad A' \rightarrow B' \quad B' \rightarrow C' \quad C' \rightarrow D' \quad D' \rightarrow E' \quad E' \rightarrow A' \]

Case 1: parthenolide only  
Case 2: feverfew extract

Figure 15: Statistical screening

In order for a reagent and substrate to react, they must meet a set of criteria, including collision. In the first case, the probability of the sulfinate colliding with the parthenolide, upon adequate diffusion, is 50%. This is made up of four cases of collisions, but only two types: A collides with A (same as A' collides with A', which is unproductive) and the other type is A collides with A' (or vice versa).

However, in the second case, there are a number of other compounds in solution. These compounds can have a variety of effects: they can react directly with the sulfinate functional groups or otherwise outright degrade the polymer, they can prevent the sulfinate groups from reacting, or not have any noticeable effect. A little bit more explanation is necessary when mentioning that the sulfinate groups are prevented from reacting. The feverfew extract contains compounds, some of which have yet to be identified, which could directly react with the sulfinate
group. Acidic compounds could protonate the sulfinic group, making it less nucleophilic. The sulfinate group could also do a Michael addition upon other compounds.
Experimental Section

General Comments

Determination of polymer loading: mass increase method.

This method, while not very accurate, is still quite often used due to its stark simplicity and rapid results. The method relies upon a dry sample, which is weighed after the reaction. In the case of the reaction below, the following mathematical sequence is used:

\[
\begin{align*}
\text{MW} & \quad 104 \\
\text{Mass} & \quad A \\
\text{Moles} & \quad n_A \\
\end{align*}
\hspace{1cm}
\begin{align*}
202.5 & \quad 104 \\
B & \quad n_H \\
n_{\text{Cl}} & \quad n_{\text{Cl}}
\end{align*}
\]

Since \( 104 + A = n_A = n_H + n_{\text{Cl}} \),

and \( n_H(202.5) + n_{\text{Cl}}(104) = B \)

the system can be solved knowing only the starting mass A and the final mass B. While it is possible that end caps (the functional groups at either end of the polymer) may deviate these numbers somewhat, that degree of error is smaller than the error involved with the masses of A and B.
Determination of polymer loading: elemental analysis method.

Samples were submitted to Guelph Chemical Laboratories Ltd for analysis. The results had a percentage for carbon, hydrogen, sulphur and chlorine (the analysis was done on the sulfonyl chloride polymer) Again, the scheme is the same (see below). From the % mass numbers, it is possible to get molar ratios of the elements. The ratio of sulfur to chloride is important to note, since it gives an idea of the extent of accidental hydrolysis of the polymer. It should be near 1.0

Determination of polymer loading: comments

The key point to mention here is that of the degree of crosslinking with divinylbenzene. The effect of crosslinking is ignored, since it is effectively negligible. In the first part, the difference would be the lower molecular mass of the individual units, by 2 amu. However, this loss of mass is ~1% of the mass of the monomer unit (MW 202), and the degree of crosslinking is 20% or less, which leads to a deviation of 0.2%, and therefore ignored. In the elemental analysis calculations, the calculations rely on carbon and sulfur exclusively, and crosslinking can be ignored.

5.0 Characterization of sulfur-containing compounds: IR bands.

S=O stretching occurs from 1050 – 1210 cm⁻¹. Electronegative substituents raise the frequency.

SO₂ has two strong bands: 960(±10) cm⁻¹ and 1110 – 1200 cm⁻¹.

C-SO₂-Cl has two bands: ~1380(±10) cm⁻¹ and ~1180(±10) cm⁻¹.

Sulfonate salts (R-SO₃⁻): strong band in 1280 – 1160 cm⁻¹, medium band in 1120 – 1090 cm⁻¹.

Sulfinic acids: 1090 – 990 cm⁻¹ and 810 – 850 cm⁻¹.
5.1.1 Polymer purchased from NovaBiochem (P-SO₂Cl)

The spectrum below is that of the polymer as received from NovaBiochem. The key peaks have been marked as 1084 (S=O), 1173 (SO₂), and 1378 cm⁻¹ (C-SO₂-Cl).

5.1.2 Sodium borohydride reduction of P-SO₂Cl polymer

The polymer beads (2.000 g) were swollen with THF, and cooled to 0°C. Sodium borohydride (1.316g, 12 molar equivalents based on 2.2 mmol/g functionalization of polymer) was added and the mixture was stirred at 0°C for 6 hours. The mixture was then allowed to warm to room temperature and was left stirring overnight. The mixture was once again cooled to 0°C and a saturated solution of ammonium chloride was added dropwise until the further additions did not result in bubbling, indicating complete quenching of the borohydride. The polymer was then filtered off and washed with successive quantities of water until the water had a pH of approximately 7 (multicoloured litmus paper). The polymer was then dissolved in THF
(25 mL) and 25 mL of 1M NaOH was added and left to stir for 2 hours. The polymer was then filtered off and washed with successive quantities of water until the water had a pH of approximately 7 (multicoloured litmus paper). The polymer was finally washed with a 1:1 THF:water mixture and then dried under vacuum. The polymer beads were visually unchanged. The weight was 1.8911g. From the spectrum below, it can be seen that the SO$_2$Cl peak at 1378 cm$^{-1}$ is gone, and new peaks at 830, 1011 cm$^{-1}$ due to the sulfinate are now present. The peaks at 963, 1184 cm$^{-1}$ are due to SO$_2$.

![P-SO$_2$Na$^+$ polymer](image)

5.1.3 DIBAL-H reduction of P-SO$_2$Cl polymer

The polymer (1.000g, 2.9mmol/gram) was swollen in THF (25mL) and cooled to 0°C. A 1M solution of DIBAL-H in THF was added (6.8mL, 1mmol excess) dropwise. The mixture was allowed to stir for 3 hours. Upon warming to room temperature, the THF was decanted and new THF was added (20mL), followed by 20mL of 1M NaOH. This mixture was allowed to stir overnight (approx 16 hours). The liquid was decanted, and aliquots of distilled water were added
until the pH of was rinsing was 7. A 1:1 THF : water solution was added and the mixture was allowed to stir for up to an hour. The liquid was then decanted. A new aliquot of distilled water was added, and decanted. The next aliquot for washing was a 1:1 water:ethanol solution, followed by ethanol. After the last washing, the polymer was filtered, and dried under vacuum overnight to yield a solid (1.0322g). As per the previous compound, the 1378 cm⁻¹ SO₂Cl peak is gone, and a new peak at 1007 cm⁻¹ (due to the sulfinate) has appeared. 959 (SO₂) and 1180 (SO₂) are also present.

5.1.4 Chlorosulfenylation of a crosslinked polystyrene polymer

A commercial polystyrene polymer (3.03 g, 29.1 mmol, based on styryl group) was dissolved in chloroform (90 mL), and chlorosulfonic acid was added (10mL, excess). The mixture was then refluxed for eight hours. Upon cooling, the excess chlorosulfonic acid is decanted, quenched and discarded. The polymer was washed with chloroform four times (4x10mL) (sufficient volume to completely cover the polymer surface), then washed with
acetonitrile, and then washed with successive amounts of water until the pH of the water is 7. The polymer was washed a final time with acetone, and then dried to yield a solid (2.1497g). 1175 (SO$_2$) and 1368 (C-SO$_2$-Cl) cm$^{-1}$ are the key bands, which confirm the necessary functionality.

![P-SO$_2$-Cl polymer](image)

The polymers used for this step were 1% crosslinked polymers and 20% crosslinked polymers (macropore resin) from Aldrich. The macropore resin was the one more often used due to ease of use.

5.1.5 Recycling of the polymer

The polymer beads were dissolved in THF (~25mL per 0.1 gram of polymer) and 10mL of 1M NaOH solution was added. The mixture was left to stir for 16-24 hours, and then the polymer was filtered and washed as in the reduction reactions (§2.3.2 and §2.3.3). Upon drying, the polymer was analyzed by FTIR to ensure that it had been regenerated was then used for further reactions.
5.1.6 Removal of parthenolide

The polymer (as prepared previously) was added to the feverfew extract (as prepared previously) and one molar equivalent of acetic acid (1 mol equivalent based on polymer loading) and the mixture was left to stir for 24 to 48 hours at 40 - 45°C. The polymer was filtered off and the mixture analyzed by HPLC to determine the loss of parthenolide. Key peak 1780 cm⁻¹ (lactone carbonyl in parthenolide), 830, 1011 cm⁻¹ (unreacted sulfinate), 968, 1184 cm⁻¹ (SO₂).

5.2 Detection and analysis of parthenolide:

TLC method: This method used Silica Gel 60 F₂₅₄ plates developed with and Ethyl Acetate:
Hexane ratio of 1 : 2. Parthenolide has an Rₜ of 0.5 in this system.

HPLC method⁴²: Dried samples are ground to a fine powder, using a La Minerva grinder (Bologna, Italy) and a 40 mesh screen. A portion of each powdered sample (~ 1.0 gram) is
extracted with 20 mL of an organic solvent (as per the solvent studies), for 15 minutes at 60°C, followed by centrifugation and collection of the supernatant. The extract volume is adjusted to 20 mL, if necessary. Samples (1.5 mL) are filtered through a 0.22 μm PTFE membrane (Chromatographic Specialties, Brockville, Canada) prior to injection of 5 μL into the HPLC system.

5.3 HPLC Equipment & Conditions

Instrumentation: Beckman HPLC system consisting of an autosampler (Module 502 with 5μL loop), solvent delivery system (Module 126), photo diode array detector (Module 168), and System Gold software (version 8.10).

Columns: 5 μm LiChrospher® 100 RP-18, 125 x 4.6 mm analytical cartridge & 5 μm LiChrospher® 100 RP-18, 4 x 4.6 mm guard cartridge (E. Merck / BDH Inc., Toronto, Canada) Chromatographic Conditions: mobile phases were water and acetonitrile, with a flow rate of 1.1 mL / min, and isocratic elution using 45% acetonitrile in 16 minutes. The detection wavelength used was 210nm.

Injection of parthenolide (Aldrich, St. Louis43) produces a single peak eluting at ~5.3 minutes. Peak identity in samples was confirmed by relative retention time, and by spectral analysis versus the standard. Based on injection of a known amount of this standard, its response factor is calculated and stated as μg / mL / area unit, when measured at 210nm.

Key HPLC traces are shown in the discussion.
6.0 Conclusion

The work detailed within this thesis fulfills the criteria set forth at the outset of the project. Specifically, a solid state method was developed for the removal of parthenolide from feverfew extracts.

However, this project is part of a larger project involving a company and potentially a new product for human consumption. This potentially hypoallergenic feverfew extract will still need to undergo testing on human subjects in order to determine whether the removal of parthenolide has resulted in a decrease in allergenic reactions.

It will then be up to the market to determine whether a hypoallergenic feverfew product can be economically viable, especially considering the % of people who suffer from the side effects and the general customer acceptance of feverfew as a migraine prophylactic.
A Google search of “buy feverfew extract (cap OR capsule)” resulted in about 3,000 hits, the bulk of which were verified to be online marketplaces. By including “(cap OR capsule)”, this eliminated approximately 41,000 hits, which involved journal articles, as well as anecdotal mentions.


18 NF-κB is an acronym for “Nuclear Factor - κB” This is a transcription factor, and is usually activated by oxidants, or by an inflammation via a signalling pathway. The exact details of these mechanisms are outside the scope of this thesis, but remain remarkably comprehensible for the average organic chemist who has an interest in medicinal chemistry.


25 Those are the ones that are also known as “migraines with aura.” The City of London Migraine Clinic is a leading center for headach research and has broken down migraines into two groups: “classic” and “common”. Common migraines are ones without aura, and the classical are migraines with aura.

26 Sommerville, B. N.; *Neurology*, 1976, 26, p41.
27 A DIN – Drug Identification Number does exist for the feverfew extract and extracts bearing a DIN must have a minimum quantity of parthenolide.

28 A chapter, edited by Prof. Arnason, for an upcoming book: Chapter 13 Sesquiterpene Lactones Revisited, p333-364, *Phytochemistry of Medicinal Plants*, J. T. Arnason et al eds, Plenum Press, New York, 1995, details a number of other compounds. However, there are only two other compounds which have a better IC_{50} than parthenolide, but not significantly so (IC_{50} of Ursiniolide A is 1.78 μM, and for Cinerenin acetate it is 2.04 μM). Neither occurs in feverfew.


30 Even this is a strictly theoretical case, since parthenolide decomposes quite readily on standing when it is in its pure form. Commercial parthenolide requires storage in a freezer to prevent decomposition.


33 A range is specified since it is quite difficult to maintain a temperature in a lab whose air circulation changes along with day and night air conditioning. Luckily it wasn’t as bad as in the previous case with the lactam synthesis.

34 The high polarity of the sesquiterpene lactones may be the cause of the insolubility in CDCl₃, (see ref 22) The sesquiterpene lactones were chromatographed on silica using ether and increasing methanol (up to 10%) mixtures.

35 Additionally, there is also an intermolecular exchange, resulting in a peak for HDO at δ 3.30 ppm as a 1:1:1 triplet with J = 1Hz.


37 CN-Calbiochem-Novabiochem product #01-64-0430, batch A26184. Substitution 2.9 mmole/g according to certificate of analysis, determined by elemental analysis of nitrogen after coupling with benzylamine.


39 *Fed. Reg.*, 1962, 27, p3919. This is the April 25th issue.

The drop in activity is attributed to impurities the the THF, which was evidenced by the IR spectra, which showed oxidation of the sulfinate groups.

HPLC method was developed by John Livsey from the Arnason group in Biology, who also ran the analyses.

Sample kindly provided by Leiner Health Products, but once that was used up, successive samples of parthenolide were purchased from Aldrich.