Dearomatising Addition of Organolithiums to

2-Aryloxazolines:

A Route to Amino-carbasugar Analogues

A thesis submitted to the University of Manchester for the

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ABSTRACT

DEAROMATISING ADDITION OF ORGANOLITHIUMS TO 2-ARYLOXAZOLINES: A Route to AMINO-CARHASUGAR ANALOGUES

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ACKNOWLEDGEMENTS

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Abstract

Dearomatising Addition of Organolithiums to 2-Aryloxazolines: A Route to Amino-Carbasugar Analogues

A submission for the degree of Doctor of Philosophy at The University of Manchester, James Clayton 2011

2-Aryl-4,5-anti-diphenyloxazolines undergo nucleophilic dearomatising addition to the 2-aryl group when treated with secondary organolithiums at -78 °C in the presence of the deaggregating co-solvent DMPU. Quenching the reaction with methyl iodide gives a highly substituted conjugated diene. Quenching the reaction with a proton source gives a substituted unconjugated 1,4-diene. The stereochemistry of the anti-diphenyl oxazoline controls the diastereoselectivity of the nucleophilic addition; only one diastereoisomeric product is observed. Importantly these conditions allow the dearomatisation of phenyl rings; this moiety has proven resistant to nucleophilic dearomatisation in all but the harshest conditions.

This thesis presents the application of this dearomatising reaction.

First the scope of this method was explored towards the dearomatisation of phenyl rings with fluorine substituents, as precursors for fluorinated carbasugar analogues.

Secondly amino-carbasugar analogues were synthesised. The dearomatisation of a 4-methoxy phenyl ring was used to construct a dearomatised carbocyclic skeleton, which was functionalised through a series of reactions to give fully substituted cyclohexanoid amino-carbasugar analogues. These amino carbasugars were synthesised without the use of protecting groups, in order to do this a number of chemoselective conditions were studied and chemoselective reactions were developed.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Part of this work has been published in the following peer reviewed journals:


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This thesis is dedicated to my Mum and Dad
Janet Clayton and Roger Clayton
Thank you for all your love, guidance, patience and sacrifice.
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A big thank you to my “Study Skills Coach” Helen Stewart. I’m dyslexic (a difficult to spell word that is used to define a group of people that find spelling difficult... Stupid) and Helen’s helped me learn to cope with it better. I think my writing especially has improved, I’ve written a book! Helen has been coaching me for five years, with her guidance I’ve become more able.

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### Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>ATPH</td>
<td>aluminium tris (2,6-diphenylphenoxide)</td>
</tr>
<tr>
<td>BDA</td>
<td>2,5-di(tertiary-butyl)-4-hydroxyanisole</td>
</tr>
<tr>
<td>BHA</td>
<td>2,6-di(tertiary -butyl)-4-methoxyphenyl naphthalenecarboxylate</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1, 1'-Binaphthalene-2,2'-diol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DAIB</td>
<td>Diacetoxyiodobenzene</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIC</td>
<td>N,N-diisopropylcarbodiimide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-dimethyl-N,N'-trimethyleneurea</td>
</tr>
<tr>
<td>Grubbs II</td>
<td>Grubbs’ second-generation ruthenium carbene metathesis catalyst</td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amine</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>IPA</td>
<td>isopropyl alcohol, propan-2-ol</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide.</td>
</tr>
<tr>
<td>LiDBB</td>
<td>lithium 4',4'-ditert-butylbiphenylide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Ms/Mesyl</td>
<td>methane sulfonyl</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazane, sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NBA</td>
<td>N-bromoacetamide</td>
</tr>
<tr>
<td>NMM</td>
<td>N-Methylmorpholine</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PIFA</td>
<td>phenyliodine bis(trifluoroacetate)</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>SAMP</td>
<td>(S)-(+)−1-amino-2-(methoxymethyl)pyrrolidine</td>
</tr>
<tr>
<td>s-Bu</td>
<td>secondary butyl</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>SiPr</td>
<td>1,3-bis(2,6-diisopropyl)phenyl-4,5-dihydroimidazol-2-ylidene</td>
</tr>
<tr>
<td>Sn1</td>
<td>first order nucleophilic substitution</td>
</tr>
<tr>
<td>Sn2</td>
<td>second order nucleophilic substitution</td>
</tr>
<tr>
<td>SnAr</td>
<td>nucleophilic aromatic substitution</td>
</tr>
<tr>
<td>TBD</td>
<td>1,5,7-triazabicyclo[4.4.0]dec-5-ene</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tertiary butyl dimethyl silane</td>
</tr>
<tr>
<td>TBHP</td>
<td>tertiary butyl hydroperoxide</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary butyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethylsulfonyl</td>
</tr>
<tr>
<td>Tf₂O</td>
<td>trifluoromethylsulfonyl anhydride</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoro acetic acid</td>
</tr>
<tr>
<td>TFE</td>
<td>2,2,2-Trifluoroethanol</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMP</td>
<td>2,2,6,6-tetramethylpiperidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts/Tosyl</td>
<td>p-toluenesulfonyl</td>
</tr>
</tbody>
</table>
Aromatic rings are widely available precursors for organic synthesis. They are carried through syntheses as they are relatively unreactive. Due to the stability of aromatic bonding, dearomatising these systems is difficult.

Unlocking the potential of aryl rings as precursors of complex saturated ring systems has been achieved in some cases using a variety of harsh and constraining conditions. Dearomatisation is however a realistic goal for the organic chemist, as it can be achieved using either reductive or oxidative methods in the presence of a variety of functional groups. By unlocking the potential of the aromatic ring, new substituents may be introduced to the unsaturated cyclic core of these molecules with regio- and stereocontrol to yield fully substituted cyclohexane derivatives.
Dearomatisation

Birch reduction

Probably the most commonly known dearomatising reaction is the Birch reduction\(^1\) of benzeneoids 1 and substituted aryl rings. Dissolving Group 1 metals sodium or lithium in liquid ammonia results in a blue solution of solvated electrons. Treatment of benzene in ethanol with this solution results in a 1,4-reduction of benzene (Figure 1) giving an unconjugated cyclohexadiene; the regiochemistry of this reaction can be controlled by the substitution of a phenyl ring. Electron-donating substituents stabilise the intermediate radical at the \(\beta\)-position. Electron-withdrawing substituents stabilise the radical anion at the \(\alpha\)-position (Figure 2).

If the enolate formed after the second electron transfer is in an asymmetric environment then it is possible to achieve a stereoselective quench. The gibberellin synthesis reported by House is a nice example of such a process (Figure 3).\(^2\)
The regiochemistry was shown to be controlled by the stereochemistry of the γ-carboxylic acid so that the new methyl substituent always formed with the carboxylic acids cis. Proline-derived chiral auxiliaries have also been used to control the formation of alkylated Birch products (Scheme 1).\textsuperscript{3}

The simplest function of an oxazoline in synthetic organic chemistry is as a protecting group for a carboxylic acid. Oxazolines are heterocycles; they are cyclic imino esters. Due to the stability associated with five-membered rings and the ring containing electron-withdrawing nitrogen and oxygen atoms, oxazolines possess unique and powerful chemistry (Figure 4).
The oxazoline group is resistant to nucleophiles, bases, radicals and some acids, although it is susceptible to hydrolysis in the presence of a variety of Lewis and Brønsted acids.

Bisoxazoline ligands are utilised in a number of asymmetric catalytic reactions. Most chiral bisoxazoline ligands have C2 symmetry, are bidentate and allow coordination of a Lewis acidic metal ion in an asymmetric environment. Substituents attached to the oxazoline block spatial positions around the metal centre, so reagents may only interact in a certain geometry. By tuning both Lewis acid and chiral pocket, high ee’s can be achieved. Bisoxazoline ligands have been used for asymmetric catalysis in aldol reactions, Diels-Alder reactions, cyclopropanations, Michael reactions and pericyclic reactions amongst others.4

Oxazolines direct ortho lithiation as they utilise both the inductive effect of the electronegative oxygen and nitrogen, and the coordination of an organolithium by the nitrogen lone pair (Scheme – 2). When an ortho substituent is a leaving group e.g. OMe or F, the oxazoline can direct nucleophilic aromatic substitution on the substituted ortho position.6 This reaction was discovered and utilised by Meyers who developed it to form biaryl systems. Using an aryl Grignard reagent or organo-lithium, Meyers was able to carry out nucleophilic aromatic substitution (SNAr) in the presence of an oxazoline and an ortho leaving group.
The Grignard reagent or organo-lithium does not attack the oxazoline nor does it deprotonate it, instead a very useful aryl-aryl bond is formed. This was of great importance as the steric hindrance associated with these bonds made them difficult to synthesise. Chiral oxazoline 16 was used to influence the geometry of the newly formed atropisomeric biaryl bond in the synthesis of enantiomerically enriched biaryl compounds (Scheme 3). This structural motif is found in natural products (Figure 6) and importantly in ligands for asymmetric catalysis such as BINOL and BINAP. Diastereomeric ratios for the asymmetric biaryl synthesis ranged from 1:1 to 25:1 depending on the substituents present on both the aryl Grignard and the aryl oxazoline. If the substituents were 'small' (H, OMe) then racemisation occurred before oxazoline removal. The best diastereomeric ratios were observed when there were three or more ortho substituents present on the aryl starting materials. However following oxazoline removal, all enantiomeric purity was lost, as the heating needed for deprotection overcame the barrier to rotation of the biaryl axis.

Meyers also employed chiral oxazolines in an asymmetric Ullmann coupling, using chiral auxiliaries (oxazolines) on crowded aryl rings to satisfy the steric requirements for atropisomerism (Scheme 4). The coupling proceeded with a diastereoeexcess; the chiral oxazolines were found to be responsible for thermal resolution. The diastereoselectivity improved on prolonged heating. However the reaction also initially proceeded with high $dr$ for coupling, as after only one hour the $dr$ was 63:38 showing a certain
amount of diastereoselectivity for the coupling step. Heating for 40 hours resulted in a thermodynamic resolution increasing the $dr$ to 93:7. The higher barriers to rotation of these molecules allowed for removal of the oxazoline moieties with complete retention of stereochemistry. This biaryl unit was incorporated into an asymmetric synthesis of an ellagitannin 20 (Figure 6).

![Scheme 4 – Meyers’ asymmetric Ullmann coupling](image)

![Figure 6 – ellagitannin](image)

**Meyers’ oxazoline-mediated naphthyl dearomatisation**

Nucleophilic additions to oxazoline substituted naphthyl systems can be achieved by direct introduction of alkyl lithium reagents. Treatment with an alkyl or aryl organolithium, followed by quenching with an electrophile such as an haloalkane, results in the introduction of two new stereogenic centres trans to each other. The nucleophile attacks the 2-position and the electrophilic quench occurs at the 1-position geminal to the oxazoline to give a dihydro naphthalene (Scheme 5). In the presence of a chiral oxazoline the addition can be carried out with a high degree of diastereoselectivity.⁸
Vinyl, isopropenyl and cyclohexyl lithium reagents reacted very slowly with the chiral naphthyl oxazolines. The organolithiums form aggregates that stop addition to the naphthyl ring. To avoid aggregation the organolithium reagents were generated in situ by treating naphthyl oxazoline with tetrakis-substituted-stannane and then methyl lithium. Organolithiums prepared by transmetallation reacted with the naphthyl oxazoline to produce the dihydronaphthalene in good yield (73-79 %) with good diastereoselectivity (9:1). These findings showed that the aggregation state of the organolithium reagent is important. Addition of HMPA to the reaction of n-BuLi with the chiral oxazoline at -78 °C further increased the yield of dearomatised product from 88 % to 92 %; 96 % de was observed in both cases. TMEDA, another deaggregating agent, increased the rate of reaction but did not change the diastereoselectivity.

When the azaenolate formed in the lithiation of naphthyl oxazoline was quenched with a proton, it was initially postulated that the product would be unstable and rearomatise to give an analogous substitution product. Initially, was treated with methyl lithium and quenched with three equivalents of isopropyl alcohol giving a 2:1 mixture of C1 epimeric diastereoisomers and in a 56 % yield. Epimerisation could be controlled if trifluoroacetic acid was used as a quench; where a weak conjugate base is proposed not to promote epimerisation. Quenching the azaenolate of with TFA after treatment with EtLi gave the partially deprotected product as a single diastereoisomer.
The addition of alkyl lithiums was initially observed with achiral oxazolines derived from AMP (β-aminoisobutyl alcohol); these reactions gave mixtures of diastereoisomers. Meyers showed the addition of the organolithium nucleophile was controlled by the substituent at the 4-position. Oxazolines of structure 10 when treated with an alkyl lithium and quenched with methyl iodide gave the product 26. The opposite stereochemistry is observed when chiral oxazoline 27 was used as the chiral auxiliary and the reaction proceeded with a very similar yield (Scheme 7).

The stereochemistry of the substituent in the 4-position of the oxazoline controls the addition of organometallic reagents.

Figure 7 – Stereo and regio control by the substituent in the 4-position of the oxazoline
Nucleophile and quench are always in an *anti* relationship, following the addition of the nucleophile the quench occurs on the opposite face to the nucleophile.

Meyers was also able to use silyl lithium and lithium amide nucleophiles to dearomatise naphthyl rings. Silyl lithums were generated from lithium wire and phenyl dimethyl silyl chloride and were used to dearomatise oxazoline substituted naphthyl rings in good yield. A solvent mixture of 3:1 ether and THF was used as it was necessary to stabilise the aggregation of the freshly prepared silyl lithums to achieve high diastereoselectivity.

Meyers was only able to dearomatise naphthyl rings with cyclic lithium amides in neat HMPA, and only when quenched with methyl iodide (Scheme 9). Quenching the reaction with diethyl carbonate returned starting material which suggested that the addition was reversible.
Transition-metal-mediated dearomatisation reactions

In the presence of 6π electron systems such as benzene or naphthalene, chromium hexacarbonyl forms a half sandwich complex 29 (Scheme 10). These systems also form on substituted aryl rings. A chromium tricarbonyl complex can be considered as an η⁶ Lewis acid. The complex activates the stable aromatic ring towards nucleophilic aromatic substitution and nucleophilic addition as the aromatic n-electrons are further delocalised into the chromium complex, making the aromatic ring more electrophilic. Dearomatising reactions disrupt the aromatic n-system by the addition of a hard nucleophile to the carbon framework, following attack of the nucleophile. The chromium metal centre stabilises a formal negative charge, thus stabilising the intermediate (Scheme 10). Subsequently the chromium metal centre can be alkylated with an alkyl halide; reductive elimination follows, resulting in a trans disubstituted cyclohexadiene 30. Carbon monoxide can also be inserted into the metal-carbon bond of the alkylated chromium. The chromium tricarbonyl metal centre serves as a regiodirecting group as the addition of the nucleophile is exo to the coordinated face of the metal complex, and reductive elimination of the alkylated metal centre installs the new acyl group endo to the chromium tricarbonyl complex 31.

![Scheme 10 – Dearomatising additions to chromium tricarbonyl-bound arenes](image)

The regiodirecting groups are used to control diastereoselective ortho-addition to the complexed arene (Scheme 11). Oxazolines had been shown by Meyers to direct ortho addition to naphthalene and pyridine aromatic systems with carbon nucleophiles. Chiral phenyl oxazolines were synthesised and
complexed to chromium tricarbonyl, so that nucleophilic addition would proceed preferentially at one of the two *ortho* positions.\(^\text{13}\) Meyers had proposed that the lone pair of the nitrogen directed and stabilised an attacking organolithium species in the transition state.\(^\text{4}\) The use of two regiodirecting groups (chromium tricarbonyl and chiral oxazoline) in this method meant that diastereoselective dearomatising addition occurred with excellent *de* and moderate yields. Where a chiral oxazoline was used yields were low, this was because of the steric interaction between the approaching organolithium and the directing group attached to the oxazoline. The organolithium only added *exo* to the face of the arene. The presence of the chromium tricarbonyl unit prevented *endo* addition (Scheme 11). Rotation about the aryl oxazoline bond allowed for two possible rotamers, neither of which was strongly favoured, thus there was only a 50% chance that the oxazoline would be in the correct conformation of the favoured transition state when the organolithium approached. This accounted for the low yields but high *de* as there was only one reaction pathway.

![Scheme 11 – Reaction pathway in the presence of chromium tricarbonyl and chiral oxazoline directing groups](image)

Dearomatised complexes that were subsequently treated with a suitable strong base (NaH) could be deprotonated on the coordinated cyclohexadiene ring, which regenerated the chromiumate complex and allowed a second alkylation when treated with a suitable alkyl halide 32. This sequence of carbonyl insertion, deprotonation and alkylation installed a quaternary centre with stereoselectivity as
the second alkylation also occurred \textit{endo} to the coordinated chromium, and pushed the previous functionalisation into the \textit{exo} position (Scheme 10, 32).

Chiral SAMP hydrazone was investigated as a chiral auxiliary instead of a chiral oxazoline (Figure 8).\textsuperscript{14} These complexes were an improvement on the oxazolines as the hydrazone could be removed in one step by hydrolysis and SAMP hydrazones did not suffer from the same steric interactions as the oxazolines. It is believed that the high diastereoisibility in these reactions is generated by a preference for a Zimmerman-Traxler\textsuperscript{15} chair-like transition state rather than the alternative boat transition state. Decomplexation of the chromium tricarbonyl complexes could be achieved with a number of different oxidising agents, including halogens and ceric ammonium nitrate.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure8.png}
\caption{Chiral SMAP hydrazone as a directing group}
\end{figure}

**Dearomatisation catalysed by palladium**

Palladium catalysis can dearomatise aromatic groups. Electron-rich aromatic groups such as naphthyl,\textsuperscript{16} indole\textsuperscript{17} and phenol\textsuperscript{18} attack electrophilic palladium (II) intramolecularly. The dearomatisations can be considered as an interrupted electrophilic aromatic substitution reaction. In the case of naphthyl and indole, the dearomatisation is stabilised by donation of a nitrogen loan pair. By using a chiral phosphine ligand, asymmetric dearomatisation of the naphthyl system was achieved, whereas an achiral NHC ligand was used for indole dearomatisation. The processes are very similar and the indole dearomatisation may well occur using a chiral phosphine.
Dearomatisation of phenols occurs through a nucleophilic alkylation mechanism (Scheme 13). The electron-rich phenol$^{18}$ 37 attacks electrophilic palladium (II) at the *para* position, the dearomatised intermediate is stabilised by donation of a lone pair from the hydroxyl, subsequent elimination of palladium (0) gives spirocyclic *para*-benzoquinone.

The reaction gave the best results when ligand 39 was used, although the reaction could also be carried out asymmetrically using chiral ligand 40, giving up to 99 % yield and 91 % ee.
Stille couplings are used to form new carbon-carbon single bonds between stannanes and halides, through a palladium-mediated coupling reaction. If simple benzyl chloride is reacted with allyl stannane in the presence of palladium in acetone at room temperature, instead of the expected coupling product being formed, another coupled product formed where the palladium had migrated around the aryl ring (Scheme 14).19

Scheme 14 – Dearomatisation catalysed by palladium

This methodology was extended in a strategy that involved naphthalene derivatives where cinnamyl chloride derivatives 41 were subjected to dearomatising Stille conditions. The cinnamyl system can be considered as a homologated benzyl chloride system capable of forming the η₃ Pd²⁺ complex. This enables the usual palladium coupling cycle to take place, the only difference being that the n allyl complex is able to migrate around the delocalised n system and the new allyl group is installed ortho to the existing alkyl function 42 (Scheme 15).20

Scheme 15 – Palladium catalysed allylative dearomatisation of naphthalene
Dearomatising cyclisations

Schaumann reported the dearomatising cyclisation of a lithiated aziridine onto a tosyl ring in 1991. In this example, an organolithium deprotonated the aziridine which attacked the tosyl protecting group at the ortho position to yield 44. A stabilised anion was formed at the α-position that could be quenched by a number of electrophiles (Scheme 16)

![Scheme 16 – Dearomatising cyclisation onto an aryl sulfonamide by deprotonated aziridine](image)

Chiral tertiary amide 45 was subjected to conditions that would normally give ortho lithiated products 47 and 48 (Scheme 17), however the reaction also resulted in dearomatising cyclisation onto the naphthyl ring 46. A similar reactivity was observed when another tertiary aryl amide 49 was lithiated in the presence of t-BuLi and HMPA, yielding tetrahydroisoindol-1-one 50.

![Scheme 17 – Dearomatising cyclisation of tertiary naphthyl amides](image)
This cyclisation of aryl amides had not been observed before and a stereoselective variation using chiral lithiating reagent $52^{23}$ was developed. Investigations into the regioselectivity of the electrophilic quench, eventually allowed for the synthesis of isodomoic acid C (Scheme 19).$^{24}$

Aryl systems with different substituents that upon lithiation would cyclise gave a greater insight into the mechanism of this cyclisation. $N$-Benzoyl oxazolidine derivative $55$ gave the most detailed insight. The product of this reaction was formed as a single diastereoisomer, a cis tricyclic structure $56$, which on treatment with acid epimerised to the corresponding trans-fused compound $57$ which is the thermodynamic product. The cis-fused rings suggest an electrocyclic mechanism (Figure 9).
**Dearomatising addition in the presence of hindered Lewis acids**

An example of dearomatising addition is the reaction of hindered naphthyl BHA esters 58 with organolithiums. Upon treatment with organolithiums the expected reaction would be for the organolithium to act as a nucleophile and attack the ester or carbonyl to give a tertiary alcohol by 1,2-addition (Figure 10). However in the case of these very hindered electrophiles, nucleophiles such as butyl lithium are unable to add to the carbonyl. Instead conjugate addition to the aromatic framework of the naphthyl ring system at the 2-position occurred, resulting in dearomatisation of one of the two fused aryl rings.\(^{25}\) This reaction was carried out using a BDA ester (Figure 10) which was an excellent 1,4-acceptor, providing dearomatised products in a quantitative yield.

![Figure 9 – Cyclisation of \(N\)-benzoyl oxazolidines](image)

![Figure 10 – Conjugate addition of hindered naphthyl BDA esters](image)

Aluminium tris (2,6-diphenylphenoxide) ATPH, a Lewis acid, complexes with the carbonyl of the ketone and prevents the approach of the nucleophile to the carbonyl,\(^ {26}\) instead of the expected activation of the carbonyl to nucleophilic addition. This reaction was found to work with all common commercially available organolithium reagents: \(n\)-BuLi, \(s\)-BuLi and \(t\)-BuLi. Addition occurs at the 2-position (1,4-addition) after quenching with HCl, or conjugate addition can take place at the 4-position to afford the
1,6-adduct (Figure 10). Reactions are carried out in a mixed solvent system of toluene/THF (50:50). Phenyl dimethyl silyllithium was also shown to be a strong enough nucleophile to dearomatise aromatic carbonyl compounds coordinated to ATPH.\textsuperscript{27} In this case the addition afforded the 1,6-adduct 60.

![Figure 11 - Conjugate addition using aluminium tris (2,6-diphenylphenoxide)](image)

As well as hindered aryl ketones and esters, the conjugate addition rather than nucleophilic attack at the carbonyl group, of hindered tertiary aryl amides, where the nitrogen of the amide is derived from 2,2,6,6-tetramethylpiperidine (TMP) also occurs.\textsuperscript{25} Methyl substituents perform a similar role to the bulky ATPH, allowing conjugate addition of an arene by means of carbolithiation.\textsuperscript{27} Treatment of amide 61 (Scheme 21) with s-BuLi followed by quenches with ammonium chloride and alkyl halides afforded dearomatised products 62. The reactivity of these TMP amides can be attributed to the unusually low barrier to rotation (Figure 12). Conjugation of the nitrogen lone pair to the carbonyl is poor in this system, as the barrier to rotation of this normally rigid amide bond is low (28 kJ mol\textsuperscript{-1}), its rotation can be observed by VT-NMR.

![Figure 12 - Barriers to rotation in aryl amides](image)
The low barrier allows the carbonyl of the TMP amide to conjugate fully to the aromatic system and to provide an electron sink, activating the aryl ring to conjugate addition, while the four methyl groups shield the carbonyl from nucleophilic attack. The unconjugated nitrogen lone pair is not able to coordinate and direct the attack of the organolithium in a way analogous to the mechanism Meyers suggested, as the methyl groups of the TMP prevent this.

**Dearomatising alkylation**

In 1940 R.B. Woodward investigated the formation of quaternary carbon centres in steroidal synthesis. He employed a dearomatisation strategy to alkylate the bicyclic tetrahydro-2-naphthol 63. 63 was treated with aqueous sodium hydroxide and chloroform to produce the para halo alkylated cyclohexadienone 64. This compound was subsequently converted to the reduced methylated compound 65 (Scheme 22) using a rather crude reduction in potassium ethoxide over Lindlar catalyst to give the dehalogenated fully reduced alcohol 65, which was oxidised to form the bicyclic ketone 66.

Under basic conditions methyl aryl ethers with tethered halogenated substituents 67 dearomatise, resulting in *ipso* alkylation 68 (Figure 13). This methodology was initially carried out using a simple brominated tether, proceeding in an analogous manner to the dearomatisation first demonstrated by
Woodward, however this intramolecular example gave fused rings (Figure 13). This reaction did not proceed with a sufficiently high degree of stereochemical control for it to be useful. Using a diazoacetyl as an activating group instead improved the yield of the reaction as diazoacetyl did not suffer from as many steric interactions. Treatment of diazoacetyl tethered bicyclic ether 69 with TFA in CH$_2$Cl$_2$ protonated the diazoacetyl forming α-diazonium-intermediate, which effected ipso alkylation and gave the desired product 70 in a good yield with control of stereochemistry. This reaction and others related to it were shown to be useful tools in the asymmetric synthesis of fused cyclic precursors of diterpenes and gibberellins.

![Figure 13 – Intramolecular ipso alkylation](image)

Larock discovered the dearomatisation of alkynyl-tethered anisole derivatives. Activation of the alkyne toward cyclisation is achieved by iodine monochloride through iodonium ion formation (Scheme 23).

![Scheme 23 – Synthesis of spiro[4.5]trienones](image)

Methoxy substituents are a useful tool in oxidative dearomatisation strategies, as they are electron donating, oxygen lone pairs become delocalised into the post-aromatic system through oxonium ion stabilisation. The methoxy-oxygen rapidly stabilises the dearomatised intermediate, following hydrolysis a substituted spiro-cyclohexadienone system is formed.
These reactions were also investigated using 4-methyl substituted arylamides and it was shown that in certain cases a methyl group is also able to stabilise the cyclohexadiene system. Following dearomatisation, deprotonation of the methyl group leaves a para methylene group 74 (Scheme 24).\textsuperscript{32}

![Scheme 24 – Ipso dearomatising alkylation leaving a para-methylene group](image)

**Organo-catalytic desymmetrisation**

Gaunt desymmetrised the dearomatised halogenated spirocyclic lactam-containing enone 76, which had been synthesised using Larock’s method. An aliphatic aldehyde was used in place of an amide protecting group. A two-step process was devised where first the iodine monochloride initiated dearomatisation. Following purification the second step was an asymmetric 1,4-addition mediated by a proline-derived catalyst. Finally the pendant aldehyde and iodine moieties could be reacted further to give a densely functionalised asymmetric fused ring system.

![Scheme 25 – Desymmetrisation of spirocycles](image)
Oxidative dearomatisation

In 1972 Adler showed that treatment of salicylic alcohols 80 with sodium periodate afforded a dearomatised α-spiro oxirane cyclohexadienone 81 (Figure 14). A similar epoxide-containing dearomatised phenol was used by Corey in the synthesis of ovalicin.

![Figure 14 – Dearomatisation of salicylic alcohols with sodium periodate](image)

Tamura showed that hypervalent iodine compounds could dearomatise phenols and the dearomatised intermediate could be trapped by attack of an alcohol or acid nucleophile, to give a para-benzoquinone monoacetal 83.

![Scheme 26 – Oxidative dearomatisation of phenols to give para-benzoquinone monoacetals](image)

This type of oxidative, nucleophilic dearomatisation was cleverly harnessed in a cascade double annulation strategy by Sorensen to synthesize the core of the cortistatins 85.

![Scheme 27 – Sorensen's dearomatisation cyclisation cascade](image)
Nicolaou and Edmunds used a tethered allyl TMS group 85 as an intramolecular carbo-nucleophile in the synthesis of the core of platensimycin, this is a rare example of a carbon nucleophile in an oxidative dearomatisation of a phenol.\(^\text{37}\)

![Scheme 28](image)

Non-nucleophilic polar solvents such as trifluoroethanol and acetonitrile favour these reactions as they stabilise the polar intermediates of the reactions and do not compete with nucleophiles.

Clive and Fletcher used \textit{para}-benzoquinone monoacetals as intermediates for indirect radical cyclisations onto a benzene ring (Scheme 29). The phenol moieties were restored after cyclisation by rearomatisation under acidic conditions, to give hydroxy substituted aromatic heterocycles.\(^\text{38, 39}\)

![Scheme 29](image)
**Organo-catalytic desymmetrisation of *para*-benzoquinone monoacetals**

Recently two-step oxidative dearomatisation, asymmetric cyclisation strategies have been developed to desymmetrise symmetrical *para*-benzoquinone monoacetals with asymmetric organocatalysts. Again hypervalent iodine oxidants in protic nucleophilic solvents form a *para*-benzoquinone. After the initial oxidation the resultant prochiral *para*-benzoquinone monoacetals rapidly undergo desymmetrising 1,4-addition by tethered moieties, activated by the presence of organocatalysts. These two-step sequences result in highly functionalised enantiomerically enriched fused ring systems (Scheme 30).

**Scheme 30 - Dearomatisation of substituted phenols**

A similar cyclisation catalysed by palladium was reported by Harned, however this cyclisation was racemic (Scheme 31).

**Scheme 31 – Palladium-catalysed cyclisation**
A novel naphthyl dearomatisation strategy was devised by Minard and Feringa, following an asymmetric conjugate addition to the pendant α,β-unsaturated ester (Scheme 32) of compound 104. Addition of copper (II) ethylhexanoate causes a single-electron oxidation to form a radical in the α-position that attacks naphthol in a 5-exo-trig cyclisation. The resultant spirocyclic radical naphthol is then oxidised by a second equivalent of copper (II) ethylhexanoate to give a spirocyclic aryl enone 105. Although the exact enone is yet to be determined, copper probably co-ordinates both the naphthol and enolate. The diastereoselectivity of the cyclisation is controlled by the stereochemistry of conjugate addition.

![Scheme 32 – A conjugate addition, oxidative naphthol dearomatisation](image)

**Dearomatisation of pyridines**

Ziegler and Zeiser first reported that alkyl and aryl lithium compounds add to the α-position of pyridine. The addition of the organolithium had the effect of dearomatising the pyridine nucleus, followed by elimination of lithium hydride to give the corresponding alpha-substituted pyridine 106 (Scheme 33).
However if an oxazoline is present in the 3-position of the pyridine nucleus then an organolithium reagent will add selectively to the 4-position (Figure 15) giving the 3,4-disubstituted 1,4-dihydropyridine (c.f. 108 and 110). This reaction was reported first by Hauck\textsuperscript{46} and then by Meyers.\textsuperscript{47} Meyers carried out this reaction diastereoselectively by using a chiral oxazoline 109 in THF at -78 °C. Arylation and alkylation gave two \textit{dr}s of 92:8 and 97:3 respectively.\textsuperscript{48} Hauck, who’s reactions were racemic, reported that the 1,4-dihydropyridines were stable, and strong oxidising agents were required to rearomatise them, while Meyers reported that a very similar dearomatised pyridyl oxazoline was so unstable that the resulting dihydropyridine had to be trapped with a chloroformate. Both Meyers and Hauck used DDQ to rearomatise the 1,4-dihydropyridine species to the 3,4-substituted pyridine.

Dearomatisation of pyridines can also be achieved in specific cases where there is a methoxy substituent in the 4-position. Reaction with an acylating agent to 'tie up' the lone pair of nitrogen to form an activated pyridinium species, followed by treatment with Grignard reagent and acidic workup gives the dearomatised \textit{N}-acyl-2, 3-dihydro-4-pyridone 112 (Scheme 34).\textsuperscript{49}
The \(N\)-acyl group is not a strong electron-withdrawing group, thus a strong nucleophile is needed to attack the pyridine ring.

Dearomatisation of pyridine can also be achieved by formation of the \(N\)-trifluoromethylsulfonate ester \textbf{113}. The reaction of pyridine with trifluoromethylsulfonyl (triflic) anhydride shows what a unique reagent triflic anhydride is. The reactions of other commonly used sulfonic acid derivatives (ie tosyl chloride and mesyl chloride), are performed in the presence of pyridine. This shows that the presence of the CF\(_3\) moiety and its exceptional electron-withdrawing ability creates an activated pyridinium, a powerful enough electron sink for electron-rich (n basic) aromatic compounds to attack selectively at the 4-position of the pyridinium triflate. This process is followed by rearomatisation of the nucleophile. It can be considered as a reductive dearomatisation. It is a regioselective reaction at the 4-position as the steric bulk of the SO\(_2\)CF\(_3\) group screens the 2- and 6-positions of the ring from nucleophilic attack (Scheme 35).

An intramolecular dearomatisation of a tethered pyridine \textbf{115} was achieved using the precedent set by Corey. The \(N\)-aryl isonicotinamide was treated with triflic anhydride which triggered the intramolecular cyclisation to form the spirocyclic dihydropyridines. The development of this reaction to form these spiro compounds is significant as piperidines spiro linked to other heterocyclic rings are important because of their prevalence in pharmaceutically active molecules. These molecules are
considered privileged structures as components of G-protein coupled receptor ligands that increase release of human growth hormone. After cyclisation the spirocyclic dihydropyridine was functionalised and used in the synthesis of the spirocyclic core of MK-677, a growth hormone receptor surrogate (Scheme 36).

**Scheme 36 – A dearomatising route to MK-677**

**Dearomatisation by cycloaddition**

Electron-deficient nitrobenzenes participate in a dearomatising [3+2] cycloaddition with an \(N\)-alkyl azomethine ylide 117 (Figure 16). The presence of an additional electron-withdrawing group was necessary as nitrobenzene did not participate, whereas methyl 3-nitrobenzoate did. The mechanism of this reaction is yet to be fully understood and there is evidence to support either a single electron transfer or a concerted mechanism.

**Figure 16 – \(N\)-alkyl azomethine ylide & nitrobenzene dearomatising [3+2] cycloaddition**
Summary of dearomatisation

Dearomatisation can be achieved either reductively or oxidatively, often with stoichiometric amounts of reagent. Oxidative pathways often ‘pull’ electrons from a phenolic moiety, the cationic intermediate is often intercepted by a nucleophile, or stabilisation can come from electron-donating substituent to form a quinone type compound (Scheme 37).

Reductive pathways often involve the attack of an organometallic or stabilised anion on an aryl ring. Electrons are then ‘pushed’ on to an electron-withdrawing group before an electrophilic quench.

These dearomatised products possess double bonds that can be further functionalised through desymmetrisations, dihydroxylations and coupling reactions to name but a few. Dearomatised compounds have been used in many total synthesis of natural products, often the least interesting part of a synthesis is the dearomatising step, instead how the revealed functionality is used is the most interesting. Dearomatisation may well be called upon more often in the future as chemists look to design shorter more direct syntheses.

Scheme 37 - Oxidative and reductive dearomatisation
**Carbasugars and cyclitols**

Carbasugars are sugar analogues where the enocyclic oxygen has been replaced by a methylene group. Carbasugars bear close structural resemblance to sugars (Figure 17). A carbasugar is an analogue of a cyclic monosaccharide where the usual ring oxygen atom is replaced by methylene forming a 2,3,4,5-tetrahydroxy-1-(hydroxymethyl)-cyclohexane. Sugar analogues had been synthesised in which ring oxygen atoms were replaced by other atoms, such as sulfur and nitrogen, called thiosugars and iminosugars respectively.

Carbasugars are not lactols, there is no enocyclic oxygen, thus enzymes are unable to ring open and catabolise them. Carbasugars have been investigated as enzyme inhibitors and artificial sweeteners. It is their biological activity that is of most interest, as sugars play such an important role in biological systems. Carbasugars and cyclitols are constituent components of antibiotics. Carbasugars are important because they are mimics of true sugars. Increased understanding of the biological interaction of carbohydrates and glycoconjugates highlights the importance of sugars and saccharides. Processes mediated by these compounds include fertilisation, neuron development, hormonal activity, cell proliferation and organisation, as well as tissue recognition. The adhesion of foreign bacterial and viral cells to eukaryotic membranes is also mediated by saccharide recognition. It is saccharide recognition that is responsible for inducing a protective antibody response; in these circumstances saccharides are used in vaccines to programme an immune response. Thus a modification in the reactivity of sugars may lead to a variety of improvements in the pharmacological properties of many saccharide-based medicinal compounds.

![Figure 17 – Glucose and and Pseudoglucose](image-url)
Methods for the construction of carbasugars and cyclitols

The first conversion of a sugar into a cyclohexane derivative, a cyclitol, was described by Fischer in 1948, when he performed a Henry reaction;\textsuperscript{54} an aldol-type reaction involving a nitro alkane and an aldehyde reacting to give a $\beta$-nitro alcohol. Fischer planned an intramolecular condensation of 6-nitro-6-deoxy-D-glucose 120 and 6-nitro-6-deoxy-D-idose by treating them with barium hydroxide. Fischer did indeed form the cyclohexane backbone 121 and identified the compound by dehydration and creation of the aromatised nitroresorcinol 122 (Scheme 38).\textsuperscript{55}

Scheme 38 – Fischer’s nitro carbasugar synthesis synthesis

It was not until the 1960s that real interest in sugar-like molecules began and the term pseudo-sugar was defined as an analogue of a carbohydrate.

One of the first to be synthesised because of its biological importance was shikimic acid by Daniels and Smissman.\textsuperscript{56} Shikimic acid is a precursor of phenylalanine, tyrosine and tryptophan. The route to shikimic acid used was a Diels-Alder reaction using \textit{trans, trans}-1,4-diacetoxy-1,3-butadiene 123 and methyl acrylate 124, to form the substituted cyclohexene 125 which was dihydroxylated with osmium tetroxide. Thermal decomposition of acetonide 127 eliminated the acetate $\beta$ to the ester and formed 128. Hydrolysis of the ester, acetyl groups and acetonide gave shikimic acid 129 (Scheme 39). A detailed knowledge of the mechanism of these transformations was used to assign the stereochemistry of the intermediates in this reaction sequence. Shikimic acid 129 is now important because it is used as the chiral pool starting material for the anti-influenza drug Tamiflu 130 (Figure 18).\textsuperscript{57}
McCasland, who coined the term carbasugar, synthesised pseudo-talose, also forming the cyclohexene backbone with a Diels-Alder reaction.\(^5\) This time the diene chosen was 2-acetoxyfuran 130 and maleic anhydride 131 was used as the dieneophile. The resultant bridged oxygen \textit{exo-cis} anhydride 132 was dihydroxylated with osmium tetroxide to give 133. This was left in water at room temperature and McCasland then described a remarkable series of reactions, acetyl migration, opening of the bridging ether and finally decarboxylation to give the β-keto acid 134.

Scheme 40) which was then transformed to the penta-acetate by successive treatment with sodium borohydride, methanol-trifluoroacetic acid, and acetic anhydride. This was one of the first syntheses of a pseudo sugar; the exact assignment of all its stereocentres was determined by detailed NMR spectroscopic studies.
An example of carbasugars being synthesised using sugars as starting materials was shown by Nagarajan involving a Claisen rearrangement.\textsuperscript{58, 59} Pyran 135 can be synthesised from glucose, an abundant starting material. The secondary hydroxyl groups were protected with BnCl, the primary hydroxyl group was oxidised to the aldehyde using PDC and olefinated so that the pyran was vinyl substituted. Compound 136 was produced in a 44\% yield over three steps. The Claisen rearrangement was forced by heating in a sealed tube using 1,2-dichlorobenzene as a solvent. The cyclohexene 137 was produced from this reaction in an 86\% yield, but it was unstable and the aldehyde had to be reduced quickly using sodium borohydride. Three carbasugars were synthesised in this way using the cyclohexene 137.
As seen in the aforementioned carbasugar syntheses, unsaturated cyclohexyl backbones are formed and then functionalised using a sequence of oxidative steps: dihydroxylation or epoxidation followed by ring opening. The formation of the individual unsaturated cyclohexyl backbones was often the distinctive aspect of these syntheses.

Jørgensen reported the asymmetric synthesis of carbasugar type molecules (Figure 19). These molecules cannot be called pseudo sugars as they are not actually sugar analogues. They are not sugars with a simple O, CH₂ substitution; they are regioisomeric analogues of ribo-sugars. However their synthesis is still significant in the field, as achiral starting materials are converted into a variety of polyhydroxylated compounds with a high degree of stereoselectivity. Cyclopentadiene was used as a starting material for this process (Scheme 42). Cyclopentadiene was alkylated with benzyl
chloromethyl ether and sodium hydride. It was treated with an asymmetric hydroborating agent, diisopinocampheylborane. Oxidative workup yielded alcohol 143 with 94% ee.

Scheme 42 - Jørgensen's route to sugar analogues

Mehta devised a fragmentative synthesis of a carbasugar from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene 144 and vinyl acetate 145. Formation of tosylate 150 and treatment with sodium methoxide caused a top to bottom Grob-like fragmentation, to deliver an embellished cyclohexanoid 151 with regio- and stereocontrol. 151 was subsequently dihydroxylated and protected in the usual manner (Scheme 43).61

Scheme 43 – Mehta's fragmentive synthesis of carbasugars

A more recent approach to the synthesis of a carbasugar was devised by Cumpstey, where alkene cross metathesis formed the carbocyclic ring towards the end of the synthetic route.62 This synthesis is similar to the one of Nagarajan;59 both use a sugar as a starting material and the extra carbon atom needed to replace the ring oxygen. Nagarajan forced a Claisen rearrangement at high temperature, Cumpstey opted to use intramolecular ring closing metathesis instead (Scheme 44). Hemiacetal 147 was prepared from diacetone glucose by selective deprotection of the primary acetonide. Treatment of hemiacetal 153 with vinyl magnesium chloride formed 148. Forming acetonide 155 allowed the
unprotected hydroxyl group to be oxidised and olefinated, this introduced a methylene metathesis partner for the previously attached vinyl group. Another advantage of this synthesis is that all hydroxyl groups are pre-installed. This is very important as dihydroxylation with osmium tetroxide cannot be used in a viable pharmacological synthesis because it is highly toxic.

**Benzene cis glycol - a biological route to pseudosugars**

Another route to carbasugars and cyclitols is through benzene cis glycols of structure 157. Benzene cis glycol is produced from benzene by a mutant strain of bacteria called *Pseudomonas putida*. These organisms oxidise benzene using it as an energy source. Benzene cis glycol is an intermediate in this process, wild type *Pseudomonas putida* bacteria possess a dehydrogenase capable of rearomatising the diol intermediate to catechol.

![Scheme 44 - Cumpstey's RCM route to 4α-carba-β-d-galactofuranose 156](image)

![Scheme 45 - Enzymatic dihydroxylation of benzene](image)
The strain (39/D) does not possess the dehydrogenase enzyme responsible for rearomatising the cyclohexadiene which stops at the diol stage. The bacteria will tolerate a number of substituted aryl rings. Yields of up to 30g/L of benzoid cis glycols are obtainable using modern techniques of fermentation.

Ley successfully used benzene cis glycols as chiral pool starting materials for the asymmetric synthesis of a carbocyclic analogue of α-glucose 165 (Scheme 46).66

Hudlicky has also successfully performed similar syntheses making more complex enantiomerically pure natural products with benzene cis glycol derivatives (Scheme 47).67

Substituted benzene cis glycol derivatives have been used extensively as starting materials by the synthetic organic community,68 and are still useful structural motifs for total synthesis.
**Amino-carbasugars**

Aminocyclitols and amino-carbasugar analogues are components in a variety of antibiotics and biologically active natural products. At biological pH the amine moiety is protonated and the cationic amino carbasugars mimic transition states in enzymes.

![Chemical structures](image)

Figure 20– The mannostatins and volibose

The mannostatins are a group of naturally occurring glycosidase inhibitors. Points of interest in this family include the incorporation of aminosugars in trehazolin 173 and allosamidin 174 and that the amine moieties of allosamidin 174 are N-acylated. Allosamidin is a naturally occurring protected amino-carbasugar. Interest in these compounds from the pharmaceutical industry has led to the development of volibose 172, an α-glucosidase inhibitor, used for the treatment of diabetes.

The validamycins are a family of amino-carbasugar antibiotics isolated from *Streptomyces hygroscopicus* culture (Figure 21). Structurally they mimic glucose, thus they also display strong glucosidase inhibition.⁶⁹

![Chemical structures](image)

Figure 21 – The validamycins
Synthesis of amino-carbasugars from dearomatised aryl rings

Approaches to aminocyclitols using dearomatised aromatic compounds as starting materials are described in the literature, although there are no examples of amino-carbasugars made in this way.

The Bryce-Smith – Gilbert photoamination dearomatises benzene (Figure 22). Irradiating a 1:1 mixture of benzene and tertiary butylamine gives a mixture of photochemical addition products. The major component is the dearomatised 1,4-cyclohexadiene 178 substituted with tertiary butylamine; conjugated diene 179 is also isolated; however compound 179 aromatises on prolonged exposure to irradiation.

Russell utilised 1,4-cyclohexadiene 178 as a starting material in a synthesis of (±)-conduramine 185. The dearomatised carbocyclic core was effectively brominated without rearomatisation. This bromination not only prevented rearomatisation at a later stage, but also allowed protection as oxazolidine 182. Following bromine elimination by DBU, AD-mix β was used to dihydroxylate selectively the less hindered olefin of diene possessing oxazolidine 183, although this procedure did not resolve the mixture of enantiomers giving an 18 % ee (Scheme 48).
Deprotection of 184 gave enantio-enriched conduramine 185. This synthesis is reasonably concise and uses cheap feed stock chemicals to generate complex biologically active molecules rapidly. Unfortunately the asymmetric dihydroxylation did not serve as a resolution, but there are many more asymmetric processes that may achieve a desymmetrisation of either compound 178 or 180. Resolution of a racemic related compound may also be possible through a method other than the asymmetric dihydroxylation.

Liao’s approach to (−)-conduramine involved a nitroso-Diels Alder reaction using a dearomatised aromatic ring as the diene component. The diene 189 and dieneophile 188 were both generated in situ by oxidation with periodate and bisacetoxy iodobenzene, respectively. The enantio-enriched carbocyclic core 190 was further functionalised in an enantioselective synthesis of (+)-conduramine. Although enantioselective, this synthesis was longer, needing 10 steps to complete the synthesis of (+)-conduramine 192.
Scheme 49 – Synthesis of (+)-conduramine
**Fluorine in organic chemistry**

Introduction of fluorinated groups dramatically changes the physicochemical properties of a molecule; thus fluorinated drugs often have increased biological activity profiles compared to their non-fluorinated counterparts.\(^{73}\)

Fluorine is the most electronegative element; it has the smallest atomic radius of the Period 2 elements, because it has the highest nuclear charge (+9, 9 protons). The high nuclear charge gives an extremely endothermic ionisation energy, -1678.7 kJ mol\(^{-1}\). Fluorine readily accepts an electron having an exothermic 327.6 kJ mol\(^{-1}\) electron affinity.\(^{74}\) The resultant negative charge is stabilised as few electrons shield the proximate nuclear charge. These properties of the nucleus make fluorine intermediate in size between hydrogen and carbon.

When fluorine is used to replace hydrogen in medicinal chemistry there is not much steric impact on the molecule; however electrostatically, this substitution has a huge effect, changing the pK\(_a\) of adjacent functional groups. This effect on pK\(_a\) can be used to tune the bioavailability of a molecule, changing how it is absorbed, distributed and eventually broken down.\(^{73}\)

**The C-F bond**

Replacing an oxygen substituent with fluorine has a less drastic effect on pK\(_a\) as one electronegative group replaces another. The C-F bond is highly polarised; it interacts electrostatically. Exchanging an hydroxyl group with a fluorine substituent keeps electronegativity at that site, whilst at the same time removing a hydrogen bond donor/acceptor.

The carbon fluorine bond is the strongest in organic chemistry (440.99 kJ mol\(^{-1}\)). It has a substantial ionic component and this polarisation is stabilising as C\(^{\delta^+}\) and F\(^{\delta^-}\) attract one another. The bond is highly polarised but not polarisable making fluoride a very poor leaving group. This makes the bond resistant to S\(_{N2}\) reactions; examples of S\(_{N2}\) displacements of F\(^{-}\) are rare.

However fluorine is frequently used as a leaving group in S\(_{NAr}\) reactions where fluorine not only increases the electrophilicity of an aryl ring but also stabilises the negatively charged Meisenheimer intermediate before elimination of fluoride (Scheme 50).
Polar hydrophobicity

Induced dipole interactions (proportional to how polarisable a bond is) have a greater effect on a molecule in aqueous solution than when bound to an enzyme. Reducing the polarisability of a molecule enhances binding. Since C-F bonds are polar but not polarisable, the strategy of replacing polar, polarisable bonds with C-F bonds is called increasing ‘polar hydrophobicity’. This strategy was devised by DiMagno, who synthesised racemic fluorinated sugar analogue 200 (Scheme 51)

200 has an increased transport affinity for the membrane of erythrocytes (red blood cells). Since DiMagno’s publication there has been great interest in the synthesis of fluorinated carbocycles and carbasugars, notably by the groups of Linclau, O’Hagan and Gouverneur. Their synthetic efforts towards fluorinated cyclitols and sugar analogues are summarised in the following sections.
Linclau’s strategy to synthesise fluorinated sugar analogues utilises two reactions, radical addition of halogenated perfluoro halo alkanes and the Sharpless asymmetric dihydroxylation (AD).

When fluorinated alkyl halides like 205 are treated with sodium dithionite in a basic medium, radical initiation occurs, followed by propagation to the most active halide (Br in the case of 203 and I in the case of 205). The perfluorinated alkyl radical then attacks an alkene, these mild conditions were used to construct the carbon backbones of analogues 204[76] and 210[77].

Linclau used the Sharpless asymmetric dihydroxylation to obtain enantio-enriched material. Reactions under standard AD conditions with 207 could take up to 18 days at 4 °C. The loading of catalyst and ligand was increased in order to improve the rate of dihydroxylation, as electron-deficient alkenes react slowly with osmium tetroxide. The improved dihydroxylation conditions using 2 mol % osmium and the (DHQ)₂AQN ligand gave 208 in 78 % ee and 89 % yield. Alkene 201 was also dihydroxylated using AD-mix with an increased catalyst loading, however as the double bond was E and internal the more standard (DHQD)₂PHAL ligand was used to good effect to give 92 % ee and 77 % yield.

Construction of fluorinated carbasugar 204 was rapid as cyclisation occurred after radical addition. Formation of sugar 210 involved formylation of 208 and a subsequent intramolecular attack of an organolithium, generated by lithium halogen exchange on 209 with methyllithium, to give 210 in 84
% yield. Other organometallic reagents such as butyllithium and isopropylmagnesium chloride either caused elimination or attacked the ester.

**O’Hagan**

Linclau’s approach, like DiMagno’s, synthesised fluorinated sugar analogues containing carbons doubly substituted with fluorine. O’Hagan planned to make truer fluorinated sugar analogues by making stereoconservative substitutions, synthesising fluorinated sugar analogues where hydroxyl groups were replaced by fluorine substituents. This removed the ability for hydrogen bond donation, whilst keeping an electronegative group in that position.

![Scheme 53 – O’Hagans stereoconservative synthesis of fluorinated sugar analogues](image-url)
The synthesis started with allylic fluoride 211 which was made in 3 steps from commercially available material. Epoxidation with \textit{m}-CPBA gave an inseparable mixture of diastereoisomers 212. Treatment of this mixture with HF triethylamine salt allowed fluoride to open the epoxide to give a separable mixture of diastereoisomers. The separated diastereoisomers 213 and 214 were treated separately with De-oxofluor®, a fluorodeoxygenation reagent; it gave the \( S_N 2 \) product with inversion of configuration. Following parallel debenzylation, oxidation and cyclisation, fluorinated \( \text{D-glucose} \) analogue 220 and fluorinated \( \text{D-altrose} \) 221 were obtained.80

**Gouverneur**

Gouverneur synthesised a variety of \textit{gem} difluorinated hexosides from key glycal 230, which was synthesised in 7 steps (Scheme 54).81 This synthesis applied a gold-catalysed 6-\textit{endo}-dig cyclisation to form glycal 230 in good yield, using only 1 mol % of catalyst. Luche reduction of 227 gave a 9:1 mixture of diastereoisomers, which could be separated following pivaloylation. Once deprotected, 230 was used as a key intermediate for the synthesis of a variety of fluorinated sugar analogues.
This synthesis only suffers in that it is racemic; if the Reformatsky reaction of 222 and 223 could be made asymmetric the process would be very useful for synthesising a diverse array of deoxy difluoro-hexosides. Also the reduction of 227 is not completely diastereoselective; however the presence of the gem difluoride group probably increases the rate of reduction lowering diastereoselectivity.

Gouverneur has also synthesised a variety of carbocyclic fluorinated inositol analogues using a fluorodesilylation process.\textsuperscript{82} Crucially no carbasugar analogues have been synthesised.

The first example (Scheme 55) shows not only the power of Gouverneur’s fluorodesilylation but again shows the usefulness of the Sharpless asymmetric dihydroxylation in cyclitol synthesis.
TMS-substituted 1,4-cyclohexadiene 235 was desymmetrised using AD, the chiral diol 236 was benzylated to increase the diastereoselectivity of the fluorodesilylation. Fluorodesilylation of 237 gave 238 and a second dihydroxylation gave fluorinated cyclitol derivative 239 in good yield.

Gouverneur has also used the fluorodesilylation reaction in a two-directional approach to fluorinated cyclitols that utilises catalytic alkene metathesis.

Fluorodesilylation of disilylated compound 241 gave a mixture of 3 diastereoisomers, because diastereoselectivity of the fluorodesilylation is poor when the silyl-bearing centre is not stereogenic. The diastereoisomers were partially separated (Scheme 57) to give two samples one containing a 3:1 mixture of 242 and 243, and another that contained a 8:1 mixture of 243 and 244. These mixtures underwent smooth cyclisation when exposed to 5 mol % of Grubbs’ second-generation catalyst.
The acetonide-protected fluorinated cyclohexanes were dihydroxylated under Upjohn dihydroxylation conditions to give three deoxyfluoro-\textit{myo}-inositols.

**Summary of Carbasugar syntheses**

Carbasugars and carbocyclic analogues of sugars can be synthesised through a number of different methods. Most often a carbohydrate or carbohydrate-derived chiral pool starting material is used because these compounds are chiral and have functionality preinstalled.

When enzymatic dearomatisations, Diels Alder reactions and more recently, when carbocycles are constructed using alkene cross metathesis, the Sharpless asymmetric dihydroxylation and racemic Upjohn variants are used again and again to introduce hydroxyl groups.
Chapter 2 - Nucleophilic dearomatisation of 2-aryl oxazolines

Introduction and previous work

Recently Clayden reported the dearomatisation of uncoordinated phenyl rings by secondary and tertiary organo-lithiums.

\[
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{O} \quad \text{N} \\
\text{Ph} \quad \text{Ph} \\
\end{array}
\xrightarrow{1 \text{PrLi, THF, DMPU, } -78^\circ \text{C}}
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{O} \quad \text{N} \quad \text{Li} \\
\text{Ph} \quad \text{Ph} \\
\end{array}
\xrightarrow{2 \text{MeI}}
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{O} \quad \text{N} \\
\text{Ph} \quad \text{Ph} \\
\end{array}
\]

Figure 23 – Dearomatisation of uncoordinated 2-phenyl oxazolines

Meyers pioneered the dearomatising addition of organolithium reagents to aryl rings. The nucleophilic dearomatisation and the regio- and diastereochemical outcome are controlled by a chiral oxazoline substituent. It was found that using the previously unexplored 4,5-anti-diphenyloxazoline in the presence of the deaggregating co-solvent DMPU was crucial to dearomatising a phenyl ring. HMPA also promoted the dearomatising addition in a comparable yield, but DMPU was preferred due to its lower toxicity as HMPA is extremely toxic.

Efforts to extend the dearomatising cyclisation methodology within the Clayden group led to the investigation of the carbolithiation of aziridine 3 (Scheme 58). It was hoped that the cyclisation of this compound would lead to fused ring systems. This aziridine is very similar to the tosyl-protected phenyl substituted aziridine Schaumann reported intramolecularly cyclising onto a tosyl ring resulting in a dearomatised fused tricycle.\(^{21}\) It was hoped that the diphenyl benzoate-protected aziridine would react in a similar manner.
Isolation caused aziridine 3 to rearrange on silica gel giving diphenyl anti-oxazoline 6, submitting this compound to cyclisation conditions; s-BuLi in the presence of DMPU, yielded the dearomatised phenyl oxazoline derivative 7. This dearomatisation was similar to the dearomatising reactions developed by Meyers. Meyers’ methodology was limited to the dearomatisation of naphthyl and pyridyl systems. Personal communication with Meyers confirmed that his group was unable to dearomatise phenyl rings in yields greater than 10%. The anti-diphenyl oxazoline ring system appeared to be uniquely suited for the dearomatisation of phenyl rings.

The dearomatising addition occurred in good yield only in the presence of DMPU which is presumed to alter the aggregation state of the organolithium.84

Scheme 59 – DMPU is necessary for good yields of dearomatised products
To investigate the dearomatisation of phenyl rings under the newly discovered conditions, several other oxazoline derivatives were synthesised, including the corresponding \textit{syn}-diphenyl oxazoline 12 (Figure 24)\cite{85} and Meyers’ oxazoline 13.

It is noteworthy that Meyers methoxy-phenyl oxazoline 13 was dearomatised under the new reaction conditions. This reaction would have almost certainly been carried out in the Meyers laboratory, however it was never reported that it was carried out in the presence of DMPU. Interestingly the newly discovered \textit{anti}-diphenyl oxazoline gave the highest yield of dearomatised 2-oxazoline.

The dearomatising reaction was used in the synthesis of carbasugar analogues (Scheme 60)\cite{86} using \textit{para}-methoxy-substituted aryl oxazoline 8 as starting material. Following subsequent dihydroxylation, oxazoline removal and a second dihydroxylation, carbocyclic altrose analogue 19 containing extra methyl and isopropyl substituents was synthesised.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_60.png}
\caption{Scheme 60 – Parris’ synthesis of carbasugar analogues}
\end{figure}
Results and discussion

The focus of this project was to investigate further the synthetic utility of this reaction, initially how it may be used to dearomatise fluorinated phenyl rings and generate precursors for the synthesis of fluorinated carbasugar analogues (Scheme 61).

Furthermore by altering the existing synthesis and introducing nitrogen-containing moieties to dearomatised compound 9 precursors for amino-carbasugar analogues could be made (Scheme 62).
**Oxazoline synthesis**

Before embarking on this investigation a general route to a series of oxazolines substituted with electron-donating and -withdrawing groups was developed.

There are a variety of methods of synthesising oxazolines with pendant aromatic groups, many of which were developed by Meyers. Methods previously favoured by the Clayden group include rearrangement of an aziridine on silica gel and formation of a β-hydroxyl amide by reacting an α-hydroxylamino alcohol with an aryl acid chloride.

A procedure has been developed by Linclau where a β-hydroxy amide 27 is treated with DIC 26 and heated in a microwave. Copper (II) triflate, a Lewis acid, accelerates S_N2 displacement and forms the oxazoline 29 (Scheme 63).

![Scheme 63 – Linclau’s DIC-activated copper (II) triflate-catalysed cyclisation](image)

The hydroxy amide precursors were difficult to isolate; as they were insoluble in a variety of solvents and adhered to glassware. The hydroxy amides could only be isolated by trituration.

A microwave reactor was used to heat the cyclisation (Table 1, entrys 1-3); however difficulties arose as only small amounts (1-2g) could be cyclised at one time, as this was the largest amount that would fit into the microwave vial. Also reactions where the amide was solvated gave better yields the insolubility of some of the amides caused the copper catalysed DIC activated cyclisation to be unreliable, giving poor yields.
Du had made ligands bearing anti-diphenyl oxazolines using a similar procedure where the hydroxy amide 31 was formed initially from an acyl chloride and an amino alcohol. The procedure differs in the method of activation used to cyclise and form the oxazoline (Scheme 64). Du’s procedure used methane sulfonyl chloride. The mesylate was formed and the oxazolines were subsequently cyclised by refluxing in MeOH and aqueous NaOH. This method was investigated for the synthesis of the desired anti-diphenyl oxazolines.

Yields are based on the amount of (1R,2S)-2-amino-1,2-diphenylethanol starting material used.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Yield of amide</th>
<th>Yield of oxazoline</th>
<th>Cyclisation conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-OMe, 3-F</td>
<td>77 %</td>
<td>48 %</td>
<td>Cu(OTf)$_2$, DIC, THF$^a$</td>
</tr>
<tr>
<td>2</td>
<td>4-F</td>
<td>77 %</td>
<td>24 %</td>
<td>Cu(OTf)$_2$, DIC, THF$^a$</td>
</tr>
<tr>
<td>3</td>
<td>2-F</td>
<td>85 %</td>
<td>33 %</td>
<td>Cu(OTf)$_2$, DIC, THF$^a$</td>
</tr>
<tr>
<td>4</td>
<td>4-F</td>
<td>77 %</td>
<td>72 %</td>
<td>1 MsCl, NEt$_3$, 2 NaOH MeOH $\cdot$</td>
</tr>
<tr>
<td>5</td>
<td>4-F</td>
<td>51 %</td>
<td></td>
<td>TsCl, Py, CH$_2$Cl$_2$$^c$</td>
</tr>
<tr>
<td>6</td>
<td>4-F</td>
<td>62 %</td>
<td></td>
<td>MsCl, 2 equiv NEt$_3$$^d$</td>
</tr>
<tr>
<td>7</td>
<td>4-F</td>
<td>90 %</td>
<td></td>
<td>MsCl, 4 equiv NEt$_3$$^e$</td>
</tr>
<tr>
<td>8</td>
<td>2-F</td>
<td>47 %</td>
<td></td>
<td>MsCl, 4 equiv NEt$_3$$^e$</td>
</tr>
</tbody>
</table>

$^a$ heated in a microwave, $^b$ Du’s 3 step cyclisation conditions, $^c$ cyclisation with Py 1 equiv, TsCl 1.3 equiv. $^d$ one pot, forming amide with 2 equiv NEt$_3$, then MsCl 1.5 equiv. $^e$ one pot, forming amide with 4 equiv NEt$_3$, then MsCl 1.5 equiv.
Following Du’s procedure (Table 1, entry 4) a 72% of oxazoline over 2 steps was obtained, which was a marked improvement on the DIC, Cu(OTf)$_2$ procedure. The mesylated hydroxy amide was far more soluble in organic solvents than the hydroxyamide. Du’s procedure was less successful on the ortho-fluoro hydroxy amide due to the decreased nucleophilicity of the amide, as the electronegative fluorine is in the ortho position.

Cyclisation to form the oxazoline was also attempted using para-toluenesulfonyl chloride (tosyl chloride, TsCl) (Table 1, entry 5). The reaction was monitored in the same way as the reaction activated by mesyl chloride, and required a much longer reaction time of 16 hours to give a 51% yield of oxazoline.

By adding methanesulfonyl chloride to the reaction mixture once all amino alcohol had been consumed, (Table 1, entry 6) both amide formation and mesylation could be carried out in one pot thereby avoiding the difficult isolation of the intermediate hydroxy amide. When the one-pot reaction was carried out in the presence of two equivalents of base, proton NMR spectroscopic analysis of the crude mixture showed that the major component was the oxazoline. Cyclisation had occurred without any reflux step. Clearly mesyl chloride activates the hydroxyl group triggering the intramolecular cyclisation to form the oxazoline.

The procedure was further improved by using 4 equivalents of base (Table 1, entry 7). Repeating the one-pot cyclisation with this modification gave a 90% yield of the desired oxazoline. Coupling and cyclisation of 2-fluoro benzoyl chloride (Table 1, entry 8), gave a 47% yield. Presumably this reduced reactivity is due to the inductive effect of fluorine decreasing the nucleophilicity of the amide C=O bond and reducing the rate of cyclisation. This procedure has been used with a variety of acyl chloride coupling partners bearing a variety of functional groups including both electron-withdrawing and donating groups.
Scheme 65 – One-Pot Synthesis of 2-Aryl-4,5-anti-diphenyloxazolines

Table 2 – One-Pot Synthesis of 2-Aryl-4,5-anti-diphenyloxazolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>Yield</th>
<th>Entry</th>
<th>Structure</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>71 %</td>
<td>8</td>
<td><img src="image2" alt="Structure 8" /></td>
<td>88 %</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Structure 2" /></td>
<td>90 %</td>
<td>9</td>
<td><img src="image4" alt="Structure 9" /></td>
<td>67 %</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Structure 3" /></td>
<td>80 %</td>
<td>10</td>
<td><img src="image6" alt="Structure 10" /></td>
<td>90 %</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Structure 4" /></td>
<td>46 %</td>
<td>11</td>
<td><img src="image8" alt="Structure 11" /></td>
<td>67 %</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Structure 5" /></td>
<td>89 %</td>
<td>12</td>
<td><img src="image10" alt="Structure 12" /></td>
<td>20 %</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Structure 6" /></td>
<td>88 %</td>
<td>13</td>
<td><img src="image12" alt="Structure 13" /></td>
<td>88 %</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Structure 7" /></td>
<td>67 %</td>
<td>14</td>
<td><img src="image14" alt="Structure 14" /></td>
<td>66 %</td>
</tr>
</tbody>
</table>

Yields are based in the amount of (1R,2S)-2-amino-1,2-diphenylethanol starting material used.

* Reaction was carried out on a 10 g scale.

* Where the acid chloride coupling partner was not commercially available, they were made from the corresponding acid.

* Examples provided by Dr R. A. Harvey, and Miss O. Karlubiková, and are characterised in the supporting information of ref. 89.
Extending the methodology dearomatisation to fluorinated phenyl rings

If the dearomatising methodology could be extended to dearomatise phenyl rings bearing fluorine substituents, the dearomatised fluorinated carbocycles could be used as starting materials for the synthesis of fluorinated carbasugar analogues. Starting with the carbon fluorine bond already incorporated in the molecule could be an interesting prospect as the carbon fluorine bond should be robust enough to be carried through a synthesis without destruction or scrambling of stereochemistry.

Fluorinated aryl rings are widely available synthetic precursors and a variety of transition metal-catalysed methods have recently been developed to synthesise fluorinated arenes that were previously unavailable.\(^9\)

Within the Clayden group dearomatisation of 4-fluoro oxazoline had already been achieved in moderate yield.\(^3\) The previous investigation showed aromatic solvents, specifically toluene give higher yields of dearomatised products using sec-butyl lithium in toluene. Again DMPU was necessary to increase the nucleophilicity of secondary alkyl lithiums. No dearomatised products were observed in the absence of DMPU.

Would fluorinated phenyl rings withstand the dearomatising reaction? Then, once dearomatised, could the generated fluorinated carbocycles be converted into fluorinated carbasugar analogues?
Initial results with alkyl quenches

Toluene with 10 equivalents of DMPU was the solvent system chosen for the first attempt to
dearomatise 4-fluoro-substituted aryl oxazoline 20. On addition of isopropyllithium to the cooled (-78
°C) solution, insoluble black salts formed. The reaction was quenched with methyl iodide and TLC
analysis showed only base line material that would not elute (Table 3, entry 1).

Scheme 66 – Dearomatisation of fluorinated aromatic rings quenching with methyl iodide

Cumene has been shown to be a better aromatic solvent to use with organolithium reagents as it will
not deprotonate under the reaction conditions. Upon addition of isopropyllithium to a solution of
cumene and DMPU a colour change was observed; the reaction turned deep green. Colours are
associated with the dearomatised aza-enolate of structure 34. This colour was only temporary and
over the 5 minutes before quenching with methyl iodide the solution became orange/brown. After
quenching and workup TLC revealed a new spot in the reaction mixture. Proton NMR spectroscopic
analysis of this material showed a complex mixture of products and starting material (Table 3, entry
2).

The reaction was repeated, degassing the solvent before the addition of isopropyllithium with the
freeze, pump, and thaw method (Table 3, entry 3). The reaction turned green again, however the
colour started to fade after 5 minutes. The reaction was quenched with methyl iodide after 15 min.
Following workup, proton NMR spectroscopic analysis of this isolated material revealed a mixture of
the dearomatised product 35 and a compound 36 that had rearomatised after the addition of
isopropyllithium.
It was decided that reactions should be quenched before the green colour faded as the dearomatised aza-enolate may be forming quickly and then decomposing. The reaction was repeated six more times, four times in cumene and twice in toluene. Each time the reaction mixtures were freeze, pump, thawed. The reactions always turned deep green on addition of isopropyllithium and then after 5 minutes became dark brown/black. Quenching 2 minutes after addition of isopropyllithium (Table 3, entry 4) gave small amounts (<10 %) of inseparable mixtures of de- and rearomatised compounds, although these reactions were cleaner, as shown by TLC and proton NMR spectroscopic analysis of the crude mixture. Unfortunately separation of the desired product 35 from the rearomatised material 36 was not achieved.

These experiments revealed that the formation of the reactive intermediate, presumably aza-enolate 34 similar to one described by Meyers,⁸ was rapid.

![Chemical structure](image)

Table 3 – optimising the dearomatising addition to 4-fluoro oxazoline 20

<table>
<thead>
<tr>
<th>Entry</th>
<th>Quench</th>
<th>Quench time (min)</th>
<th>Solvent system</th>
<th>Equiv i-PrLi</th>
<th>Outcome of the reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeI</td>
<td>5</td>
<td>Toluene, DMPU</td>
<td>1.5</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>MeI</td>
<td>5</td>
<td>Cumene, DMPU</td>
<td>1.5</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>MeI</td>
<td>15</td>
<td>Cumene⁹, DMPU</td>
<td>1.5</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>MeI</td>
<td>2</td>
<td>Cumene⁹, DMPU</td>
<td>1.5</td>
<td>&lt;10 %&lt;sup&gt;b&lt;/sup&gt;, Cleaner mixture</td>
</tr>
<tr>
<td>5</td>
<td>MeI</td>
<td>2</td>
<td>THF, DMPU</td>
<td>1.5</td>
<td>8 %&lt;sup&gt;c&lt;/sup&gt;, Cleaner mixture</td>
</tr>
<tr>
<td>6</td>
<td>MeI</td>
<td>2</td>
<td>THF, DMPU</td>
<td>3</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>NH₄Cl</td>
<td>2</td>
<td>THF, DMPU</td>
<td>1.5</td>
<td>52 %&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>NH₄Cl</td>
<td>2</td>
<td>THF, DMPU</td>
<td>2</td>
<td>74 %&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>NH₄Cl</td>
<td>2</td>
<td>THF, HMPA</td>
<td>2</td>
<td>73 %&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>¹</sup> Time after addition of isopropyllithium. <sup>²</sup>Yield of dearomatised products based on amount of 20 starting material. <sup>³</sup>Degassed by freeze, pump, and thaw. <sup>⁴</sup>Combined yield of de- & re-aromatised products by proton NMR spectroscopic analysis. <sup>⁵</sup>Combined yield of de- & re-aromatised products.
Due to the difficulties encountered with reactions in aromatic solvents the dearomatising reaction was conducted in THF. When aryl oxazoline 20 was dissolved in THF and DMPU and cooled to −78 °C, addition of isopropyllithium, generation of a deep green colour. The green colour lasted for up to 30 minutes, quenching with methyl iodide shortly after addition of isopropyllithium (2 minutes) gave cleaner products (Table 3, entry 5), but the reaction once again yielded a mixture of inseparable dearomatised and rearomatised compounds.

THF appeared to stabilise the dearomatised aza-enolate longer than toluene did and using THF as a solvent gave homogeneous solutions after quenching with no insoluble salts or biphasic black oils visible afterwards.

Methyl iodide was used to quench the reactions because quenching with this reagent could be used to form methylated products of the 4-methoxy-substituted aryl anti-diphen oxazoline 8 with excellent diastereoselectivity.\textsuperscript{86} However a methyl quench may not be practical for quenching aza-enolate 34 so a protic quench was also investigated. Quenching at −78 °C with saturated aqueous ammonium chloride (Table 3, entry 7) gave the dearomatised unconjugated 1,4-cyclohexadiene 21 in a 52% yield.

Using 2 equivalents of isopropyllithium (Table 3, entry 8) and quenching the reaction with saturated aqueous ammonium chloride after two minutes, was optimal giving dearomatised 1,4-cyclohexadiene 21 in a 74 % yield. Initially removing DMPU was difficult due to its high boiling point, diluting the reaction mixtures with water and extracting with diethyl ether avoided this problem as, like DMF, DMPU is more soluble in water than in diethyl ether.
Ortho lithiation of 3-fluoro phenyl rings

![Ortho lithiation reaction diagram]

Scheme 67 – Attempted dearomatisation of 37

The 4-methoxy, 3-fluoro compound 37 was treated with isopropyllithium under the optimised conditions and this time the reaction turned deep purple. This purple colour was temporary and never lasted more than 5 minutes in THF. After quenching with saturated aqueous ammonium chloride, no dearomatised products were observed; starting material was recovered quantitatively (Scheme 67).

Quenching the reaction with methyl iodide also gave no dearomatised products, instead ortho-lithiation occurred. A small amount of methylated compound 39 was observed by proton NMR spectroscopic analysis of the crude mixture which could be isolated in a 14% yield (Scheme 68). Reactions at different temperatures were carried out to ascertain whether the short-lived aza-enolate was more stable at higher or lower temperatures. Quenching with methyl iodide was conducted at -98 °C and -40 °C, but unfortunately the result was the same at these temperatures, and the ortho-methylated compound was isolated in a similar yield.

![Ortho lithiation of 3-fluoro aryl oxazolines diagram]

Scheme 68 – ortho-lithiation of 3-fluoro aryl oxazolines
The acidity of the proton in the 2-position will be enhanced as it is located between electron-withdrawing fluoro, and oxazoline substituents. Additionally oxazolines coordinate and direct lithiation. Ortho-lithiation is favoured by the structure of compounds 37 and 38. Even under the optimised dearomatisation conditions, isopropyllithium deprotonated the 2-position rather than taking part in a dearomatising addition. To gain further evidence that ortho-lithiation was occurring, the aza-enolates of 3-fluoro aryl oxazolines 37 and 38 were quenched with deuterated methanol.

The ortho-functionalised products were isolated in low yield as the dearomatising conditions break coordination and do not favour ortho-lithiation. Quantitative ortho lithiation was achieved when oxazoline 37 was dissolved in diethyl ether and lithiated with n-butyl lithium (Scheme 69 and Table 4). The reaction was quenched with deuterated methanol and complete incorporation of deuterium was confirmed by proton NMR spectroscopic analysis.

![Scheme 69 - Ortho lithiation of 37](image)

<table>
<thead>
<tr>
<th>R-Li</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Pr</td>
<td>THF, DMPU</td>
<td>45 %</td>
</tr>
<tr>
<td>n-Bu</td>
<td>Et₂O</td>
<td>quant</td>
</tr>
</tbody>
</table>

Table 4 – Ortho lithiation of 37

This labelled material was then resubmitted to the reaction conditions to see if the kinetic isotope effect would favour dearomatisation rather than deprotonation. The reaction was carried out under the optimised reaction conditions, and once again became purple and was quenched after 2 minutes with methyl iodide. No dearomatised products were observed by proton NMR spectroscopic analysis of the crude mixture; but small amounts of ortho-methylated compound 39 were apparent (Scheme 70).

![Scheme 70 - De-deuteration methylation of d-37](image)
Dearomatisation of 2-fluoro phenyl rings

The reaction of the 2-fluoro compound 40 has given the most intriguing and capricious results of all the fluorinated aryl oxazoline derivatives. Meyers used oxazolines to direct organo-metallic reagents (alkyl or aryl) in nucleophilic aromatic substitution reaction of 2-fluoro 2-aryl oxazolines (Scheme 71).6

Scheme 71 – Nucleophilic displacement of ortho-fluoro substituents by organometallic reagents

However when treated with isopropyllithium under optimised dearomatising conditions followed by quenching with ammonium chloride solution (Table 5, entry 1), it was apparent from proton NMR spectroscopic analysis that dearomatised compound 41 and aromatic compound 42 were present in roughly a 2:3 ratio. The dearomatised compound 41 was stable but, preparative HPLC was necessary to separate it from 42.

Scheme 72 – Treatment of 40 with isopropyllithium under the optimised dearomatising conditions
The reaction was repeated at -98 °C to determine whether the $S_N$Ar pathway was disfavoured at lower temperatures (Table 5, entry 2). No dearomatised product was observed at all, only the product of $S_N$Ar. A newly opened bottle of isopropyllithium was used in this reaction.

This reaction was carried out repeatedly at -78 °C, with no success in repeating the initial dearomatisation.

The speed of addition of the isopropyllithium to the reaction mixture may have been playing a role. Organolithiums are strongly basic; the speed of addition has been shown by Beak to influence the outcome of a reaction. The effect can be attributed to local basicity and temperature increase on fast addition. However dearomatised material was not isolated after careful slow additions (over ten minutes) to a rapidly stirred reaction mixture (Table 5, entry 4).

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variable</th>
<th>age of i-Pr Li</th>
<th>Outcome of the reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78 °C</td>
<td>aged bottle</td>
<td>3:2</td>
</tr>
<tr>
<td>2</td>
<td>-98 °C</td>
<td>new bottle</td>
<td>Elimination $S_N$Ar</td>
</tr>
<tr>
<td>3</td>
<td>-42 °C</td>
<td>aged bottle</td>
<td>Elimination $S_N$Ar</td>
</tr>
<tr>
<td>4</td>
<td>Slow addition (10 min)</td>
<td>new bottle</td>
<td>Elimination $S_N$Ar</td>
</tr>
<tr>
<td>5</td>
<td>Quenched with trifluoroacetic acid</td>
<td>aged bottle</td>
<td>Dearomatisation 3:2</td>
</tr>
<tr>
<td>6</td>
<td>Quenched with NH$_4$Cl</td>
<td>aged bottle</td>
<td>Elimination $S_N$Ar</td>
</tr>
<tr>
<td>7</td>
<td>Quenched with trifluoroacetic acid</td>
<td>new bottle</td>
<td>Elimination $S_N$Ar</td>
</tr>
<tr>
<td>8</td>
<td>200 mg scale quenched with TFA</td>
<td>aged bottle</td>
<td>Dearomatisation 11:1</td>
</tr>
</tbody>
</table>
Frustratingly it became apparent that the dearomatisation (Table 5, entry 1) could be repeated under the standard reaction conditions, only when a specific bottle of isopropyllithium was used. It was an older bottle that had been opened, used, sealed and left for approximately a month; titration with N-benzylbenzamideestablished that the concentration was 0.4 M.

It was found that this reaction could be repeated with another bottle of isopropyllithium (that had been similarly opened and sealed for a month), but only when the reaction was carried out on a small scale, using 50 mg of oxazoline, and quenching with trifluoroacetic acid (Table 5, entry 5). After the initial success quenching with trifluoroacetic acid, the reaction was repeated quenching with aqueous ammonium chloride (Table 5, entry 6) and no dearomatised products were observed by proton NMR spectroscopic analysis of the crude mixture of the reaction. A freshly opened bottle of isopropyllithium was used and the reaction was quenched with trifluoroacetic acid (Table 5, entry 7). No dearomatised products were observed by proton NMR spectroscopic analysis of the crude mixture of the reaction, only 42. Quenching the reaction with trifluoroacetic acid did not scale well, increasing the scale of the reaction to 200 mg of oxazoline (Table 5, entry 8), lowered the relative amounts of dearomatised product 41 to the product of SNAr 42, the ratio changed from 3:2 to 11:1 in favour of 42.

The capricious nature of this reaction ment that Dearomatised compound 41 could only be isolated in a 24 % yield and only when 50 mg of oxazoline 40 was treated with isopropyllithium at -78 °C and quenched with trifluoroacetic acid.

For the 2-fluoro aryl oxazoline to undergo dearomatisation the isopropyllithium must attack at the 6-position, as reaction at the 2-position results in SNAr. Following addition of the isopropyllithium to the 6-position there is no feasible mechanism for the elimination of fluoride from the aza-enolate of 2-fluoro aryl oxazoline 40 (Figure 25). Isopropyllithium from the previously opened bottle seems to favour attack at the unsubstituted 6 position rather than at the electron-deficient fluorinated 2-position. However it is not clear what influences the selectivity of this reaction.
Summary

To summarise the oxazoline-promoted diastereoselective nucleophilic dearomatisation of fluorinated aryl rings gives results dependent on substitution pattern.94

1) **Dearomisation:** fluoro substituent in the 4-position promotes dearomisation but only when the reaction is quenched with a proton source.

2) **Lithiation:** with a fluoro substituent at the 3-position cooperatively activates the 2-position towards ortho-lithiation, and 2-alkylated products can be obtained. The acidifying effect of the two directing groups is evidently greater than the dearomatisation-promoting power of the oxazoline.

3) **Substitution:** A fluoro-substituent in the 2-position, dearomisation by attack at the 2- or 6-position is finely balanced: in general the 2-fluoroaryl oxazoline leads to $S_nAr$ substitution of fluoride by isopropyllithium, with the product of a capricious dearomatisation (by attack at the 6-position of the ring) observed only when the reaction was performed on a small scale using an ‘aged’ bottle of isopropyllithium and quenched with trifluoroacetic acid.
**Reasons not to pursue a fluorinated carbasugar analogue**

Dearomatised compound 21 with a vinyl fluoride moiety in the 4-position was investigated as a precursor of fluorinated carbasugar analogues. Carbon fluorine bonds are strong and their asymmetric synthesis is difficult.

![Chemical structures and reactions](image)

Scheme 73 – Functionalisation of 21

Further functionalisations of compound 21 were considered as part of efforts towards a fluorinated carbasugar analogue. First hydroboration of the vinyl fluoride double bond between C3 and C4 could lead to facile installation of hydroxyl functionality. However extensive literature searching revealed that hydroboration of vinyl fluorides and homoallylic trifluoro methyl groups is unachievable and often leads to destruction of the double bond.\(^ {95} \)

An allylic oxidation mediated by selenium dioxide of one of the allylic protons would install a C5 hydroxyl group. Submission of compound 21 to the conditions of Sharpless for catalytic allylic oxidation\(^ {96} \) in the presence of tertiary butyl hydrogen peroxide in wet CH\(_2\)Cl\(_2\) rearomatised the compound.
Dearomatisation of 3-methoxy phenyl ring

After problems with the fluoro-substituted aryl oxazolines, attention was turned to explore the reactivity of 3-methoxy aryl oxazoline. Within the Clayden group oxazoline 44 had been dearomatised with isopropyllithium and sec-butyl lithium, quenching the reaction with methyl iodide to give compounds with similar structure to 45.

![Chemical Structure]

Table 6 – Dearomatisation of 3 methoxy phenyl ring 44

<table>
<thead>
<tr>
<th>Entry</th>
<th>age of i-Pr Li</th>
<th>Outcome of the reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>new bottle</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>2</td>
<td>aged bottle</td>
<td>35 % 45</td>
</tr>
<tr>
<td>3</td>
<td>new bottle</td>
<td>Recovered starting material</td>
</tr>
<tr>
<td>4</td>
<td>10 day ‘old’ bottle</td>
<td>Dearomatisation present by NMR analysis</td>
</tr>
</tbody>
</table>

Compound 44, was dissolved in THF and DMPU, cooled to -78 °C and treated with isopropyllithium, and quenched with methyl iodide after 2 minutes. However proton NMR spectroscopic analysis of the crude revealed that no reaction had taken place (Table 6, entry 1). Neither dearomatised products nor the product of ortho-lithiation were observed and starting material was recovered. Isopropyllithium from a previously unopened bottle had been used and the reaction was repeated one week later and it gave dearomatised product 45 in a 35% yield (Table 6, entry 2). This reaction was repeated with another unopened bottle of isopropyllithium and again no dearomatisation products were observed (Table 6, entry 3). The reaction was repeated over a week later, using exactly the same bottle, and this time dearomatised material 45 was observed by proton NMR spectroscopic analysis of the crude mixture.
This proved to be another capricious reaction observed during the course of the investigation as well as the dearomatisation of ortho-fluoro aryl oxazoline 40.

**Exploring the activity of organolithiums in the presence of additives**

To gain insight into the 'aged' isopropyl lithium, the active isopropyllithium was quenched with deuterated methanol and analyzed. Proton NMR spectroscopic analysis revealed the presence of isopropanol in the pentane solution. This suggested that the isopropyllithium was reacting with oxygen and forming lithium isopropoxide (Scheme 74). The concentration of isopropanol was calculated to be 0.28 mol dm$^{-3}$ (derived from the ratio of isopropanol to pentane 3:1 by proton NMR spectroscopic analysis (Figure 26)). The concentration suggested the isopropyllithium was degrading directly to a lithium alkoxide or peroxide, since the titer of the solution had been establishes as 0.4 mol dm$^{-3}$.

![Scheme 74 – Oxygen degradation of isopropyl lithium](image)

**Figure 26 – Determination of isopropanol in the isopropyllithium solution**

Isopropoxide in the reagent could be responsible for the dearomatisation of the 3-methoxy aryl oxazoline. There are examples in the literature of alkoxides improving the selectivity and yield of organometallic reactions. Trost reported alkoxides from an old bottle of n-butyllithium were responsible
for deprotonation before an asymmetric allylic alkylation\textsuperscript{97} and Fox reported an instance where the ee of a methyl magnesium chloride addition to cyclopropene was improved by the presence of methoxide.\textsuperscript{98} In both of these examples ‘old’ bottles of reagent gave better results than new ones. In Fox’s example the presence of alkoxides in old bottles of methylmagnesium bromide increased both the yield and ee of the asymmetric carbometalation. To make the reaction more reproducible methoxide was generated \textit{in situ} by adding methanol to the reaction mixture. The report by Fox is similar to the oxazoline-mediated dearomatisation as the reaction is a directed carbometalation.

![Scheme 75 – Asymmetric carbometalation of cyclopropenes enhanced by the presence of methoxide](image)

The presence of alkoxides could also be aiding the dearomatising reaction, through acting as a deaggregating additive. In order to test that only alkoxide was promoting the dearomatisation of oxazoline \textbf{44} a dearomatising reaction was carried out in the absence of DMPU, with the ‘active’ bottle of isopropyllithium. No dearomatised products were observed. This reaction reinforced the notion that presence of DMPU was integral to the dearomatisation of 2-aryl oxazolines. DMPU is a cyclic urea and is used to coordinate the lithium cation and increase the nucleophilicity of the organolithium.

Experiments to investigate this hypothesis were devised. Oxazoline \textbf{44} would be used as a probe for reactivity as it appeared to be sensitive to these activated samples of isopropyllithium. To test the hypothesis that impurities in the organolithium reagent could be enabling the dearomatisation of \textbf{44}.

Freshly opened reagent was used under standard conditions, a deep green colour arose on addition, and by proton NMR spectroscopic analysis of the crude mixture revealed that only starting material was present. This reaction confirmed that unopened isopropyllithium did not dearomatise the 3-methoxy aryl oxazoline. Control experiments were conducted alongside reactions with additives to check that the isopropyllithium had not become active.
One equivalent of isopropanol was added to the reaction mixture so lithium isopropoxide was generated \textit{in situ}. Under the usual dearomatising conditions, with isopropanol and an additional equivalent of isopropyllithium added. A deep green colour change occurred as normal, but proton NMR spectroscopic analysis of the crude reaction mixture showed only trace amounts of dearomatised material; starting material was the main constituent (Table 7, entry 3).

Isopropanol and isopropyllithium were also mixed together at -78 °C and 0 °C before addition. The mixture was used as the source of isopropyl lithium and syringed into the reaction mixture; the usual green colour was generated but only starting material was observed by proton NMR spectroscopic analysis of the crude mixture (Table 7, entry 4 and 5). To achieve the same concentration of lithium isopropoxide observed in solution, 0.6 equiv of isopropanol was mixed with 2 equiv of isopropyllithium in pentane. When the solutions were mixed at 0 °C they turned slowly cloudy, their consistency was similar to the ‘old active’ isopropyllithium. Upon mixing, no colour change was observed the solution had lost basicity. Only starting material was present by proton NMR spectroscopic analysis of the crude mixture; no dearomatisation had occurred (Table 7, entry 6).

A solution of new isopropyllithium was mixed with an equal volume of the older isopropyllithium (that would dearomatise the 3-methoxy substrate), at -78 °C separately. On addition of this mixture the solution turned deep blue. After quenching, proton NMR spectroscopic analysis of the crude mixture showed that dearomatisation had occurred (Table 7, entry 7).

A sample of \textit{n}-butyl lithium in hexane from an old bottle was mixed with the fresh inactive sample of isopropyllithium at -78 °C. Treating the 3-methoxy oxazoline with this mixture and quenching the deep green solution with MeI after 2 minutes showed that almost all of the substrate had been dearomatised, with only trace amounts of the starting material by proton NMR spectroscopic analysis of the crude mixture (Table 7, entry 8). It is noteworthy that only the isopropyl nucleophile attacked the phenyl ring.

When the same mixing reactions were undertaken with an old sample of methyllithium in ether no dearomatisation of the starting material was observed (Table 7, entry 9).
Table 7 – The effect of additives on the dearomatisation of 44

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variable</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No DMPU</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>2</td>
<td>i-PrLi from an aged bottle</td>
<td>Dearomised, 35 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>i-PrLi from a fresh bottle, opened that day</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>4</td>
<td>Mixed 1 equiv of IPA with 3.0 equiv i-PrLi at -78 °C</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>5</td>
<td>Mixed 1 equiv of IPA with 3.0 equiv i-PrLi at 0 °C</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>6</td>
<td>0.6 equiv of IPA mixed with 2.6 equiv i-PrLi at 0 °C</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>7</td>
<td>Mixed 1.0 equiv old i-PrLi with 1.0 equiv new i-PrLi at -78 °C</td>
<td>Dearomised</td>
</tr>
<tr>
<td>8</td>
<td>Mixed 1.0 equiv old n-BuLi with 1.0 equiv new i-PrLi at -78 °C</td>
<td>Dearomised&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Mixed 1.0 equiv old MeLi with 1.0 equiv new i-PrLi at -78 °C</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>10</td>
<td>0.6 equiv LiOH mixed with i-PrLi</td>
<td>Dearomised&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Mixed 0.6 equiv of Li&lt;sub&gt;2&lt;/sub&gt;O with 2.0 equiv i-PrLi at -78 °C</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>12</td>
<td>Mixed 0.6 equiv of Li&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; with 2.0 equiv i-PrLi at -78 °C</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>13</td>
<td>Bubbled air through i-PrLi before addition</td>
<td>No dearomatisation</td>
</tr>
<tr>
<td>14</td>
<td>Conducted reaction in a positive pressure of oxygen</td>
<td>No dearomatisation</td>
</tr>
</tbody>
</table>

<sup>a</sup>reactions conducted in THF:DMPU at -78 °C, quenching with MeI after 2 min, <sup>b</sup>determined by NMR analysis of the crude mixture, <sup>c</sup>Yield determined after chromatography, <sup>d</sup>reactions involving BuLi were blue, <sup>e</sup>Dearomatised due to the i-PrLi becoming active.

These results seemed to suggest that there was something in these opened ‘aged’ bottles of isopropyllithium and n-butyl lithium that increased the capacity of the organolithium to dearomatise the phenyl ring. Methyl lithium did not activate the isopropyllithium, which may be because methyl lithium is supplied as a solution in diethyl ether: organolithium decomposition may not occur in the same way in ether which is a more coordinating solvent than pentane.
These experiments established that isopropyllithium could be activated towards the dearomatisation of the harder to dearomatise oxazoline 1 by the presence of n-butyllithium.

Lithium oxide additives were pre-mixed with a newly opened sample of isopropyllithium. Mixing the solution of isopropyllithium with LiOH (0.6 equivalents) appeared to dearomatisate the starting material (Table 7, entry 10), but dearomatisation was also present in the control. The time taken for the isopropyllithium solution to become activated appeared to be short; the bottle became ‘active’ in 7 days. Li₂O and Li₂O₂ were mixed separately with isopropyllithium at -78 °C (Table 7, entry 11 and 12). After addition and workup, proton NMR spectroscopic analysis of the crude mixtures of these reactions showed only starting material and no ortho-lithiated products. The lithium oxides were unable to activate the isopropyllithium solution.

Generating lithium isopropoxide by poisoning/activating the isopropyllithium solution with oxygen in the air was investigated (Table 7, entry 13). A sample of inactive isopropyllithium solution was cooled to 0 °C and air was slowly bubbled through the solution for 5 min. The solution was added to a solution of oxazoline 44 under standard conditions, however the isopropyllithium had been quenched, as no colour change occurred on addition. After workup only the starting material oxazoline 44 was present by proton NMR spectroscopic analysis of the crude mixture.

The reaction was then attempted with short exposure to oxygen. The reaction mixture was prepared as usual under a nitrogen atmosphere at -78 °C (Table 7, entry 14). Just before the addition of the isopropyllithium, a positive pressure of dry oxygen was applied to the reaction mixture. Upon isopropyllithium addition there was a very short-lived flash of green. This reaction served only to show that reactions involving organolithiums should be carried out strictly in the absence of oxygen.

Ultimately the dearomatisation could not be activated by using lithium alkoxide additives. The bottles of isopropyllithium seemed to become active after between 7-10 days of use. For this reason control experiments with no additive were regularly carried out. But the cause of this activity could not be understood.
Previously the dearomatised azaenolate derived from 8 had been quenched with methyl iodide to give a conjugated dearomatised 1,3-cyclohexadiene ring that was disubstituted at the 1-position, possessing methyl and oxazoline moieties. The 2-position was substituted with an isopropyl group. This dearomatised product 9 was transformed into carbasugar analogue 19. Sugars and carbasugars possessing two alkyl groups in these positions are not naturally abundant. Using protic quenches gives an unconjugated 1,4-cyclohexadiene with an isopropyl group in the 2-position 46, as protonation occurs in the 5-position. Could a 1,4-cyclohexadiene such as 46 be converted into a carbasugar analogue possessing fewer alkyl groups?

![Chemical structures and reactions](image)

**Figure 27 - Carbocycles**

The meta-methoxy-substituted aryl oxazoline was chosen as the starting material for these experiments to explore its reactivity further. The reactivity of the para-methoxy-substituted aryl oxazoline was already known, quenching in the 5-position with a protic quench.

**Table 8 – Optimisation of protic quench**

<table>
<thead>
<tr>
<th>Quench</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₄Cl(aq)</td>
<td>Mostly 47 some 48</td>
</tr>
<tr>
<td>AcOH</td>
<td>Unclear mixture</td>
</tr>
<tr>
<td>TFA</td>
<td>Unclear mixture</td>
</tr>
<tr>
<td>MeOH</td>
<td>47 Very clean trace</td>
</tr>
</tbody>
</table>

![Scheme 76 – Protic quench](image)

Experiments varying the protic quench were undertaken: Oxazoline 44 was submitted to the standard dearomatising conditions (~78 °C in THF, DMPU) and quenched with saturated aqueous ammonium
chloride, acetic acid, trifluoroacetic acid and methanol at -78 °C and warmed to room temperature (by proton NMR spectroscopic analysis of the crude mixture). The best protic quench was chosen

Quenching with either acetic acid a trifluoroacetic acid gave very similar mixtures products, mostly rearomatised products with 48 as only the minor component. Methanol however gave a very clear crude NMR containing 47 as major constituent and only small amounts of starting material. Also present was a small amount of epimerised syn diphenyl oxazoline 48. Attempts to isolate 47 chromatographically caused rearomatisation to compound 48 although the starting material and the syn epimer 48 were also isolated.

Dearomatised product 47 was probably acid sensitive as it was unstable on silica and gave mostly rearomatised products, so the crude dearomatised material was carried through to the next step of the synthesis, dihydroxylation. The dihydroxylation was carried using catalytic osmium tetroxide and NMO as the stoichiometric re-oxidant (the Upjohn process). Following workup, proton NMR spectroscopic analysis of the crude mixture showed that the product existed as the hemiketal 49, indicated by the presence of the methoxy group. The α-hydroxy cyclohexenone 50 was isolated in a 20% yield following flash chromatography. The reaction could be carried out reproducibly on crude dearomatised material, however only a 20% yield was obtained. Over-oxidation may have been a competing processes in the reaction mixture, a known side-reaction in the Upjohn process. The Upjohn process
becomes more basic as the reaction progresses. In the presence of excess oxidant it is possible for products of dihydroxylation to be oxidised and rearomatised.

**Summary of oxazoline lithiation investigations**

Capricious results were observed in both the dearomatisation of fluorinated 2-aryl oxazolines and in the dearomatisation of the 3-methoxy oxazoline 44. It did dearomatisate but only when the reaction was carried out on a small scale and the organolithium came from an ‘old active’ bottle (determination of activity was not immediately obvious). It was hoped that by studying the dearomatisation of 3-methoxy 2-aryl oxazoline 44 which appeared to be sensitive to the age of a bottle of organolithium but no additives were discovered that promoted dearomatisation. Reactivity simply became apparent once the bottle had been open for approximately 7 days.

Finally both the fluorinated and non-fluorinated examples of dearomatised 1,4-dienes isolated were not easily functionalised, especially in the case of the case of compound 47 which was not stable to chromatographic purification.
Chapter 3 - Development of routes towards amino carbasugar analogues

The results of the dearomatisation of fluorinated aryl rings showed that dearomatisation would only occur in a few specific cases, and difficulties were encountered with proton-quenched dearomatised non-fluorinated aryl oxazolines. These results led the research to shift from the synthesis of fluoro carbasugar analogues to the synthesis of amino carbasugar analogues. It was proposed the synthesis would be based on the previously reported synthesis of carbasugar analogues.  

Synthesis of amino carbasugar analogues

Attention was turned to the synthesis of amino carbasugar analogues based on the precedent of the carbasugar analogues. The previous route to carbasugar analogues suffered from low yields and many reduction steps. In order to synthesise amino carbasugar analogues a late-stage reductive amination was proposed (Scheme 78).

![Scheme 78 - Comparison between the accomplished route and one proposed for amino-carbasugar analogues](image-url)
Preservation of the ketone moiety on compound 16 is important for this synthesis. The need to keep the ketone would necessitate a change in strategy to increase yields of individual steps, to improve throughput and to achieve chemoselectivity. The previous synthesis involved three reduction steps, two of which are involved in the removal of the oxazoline group to leave an alcohol. The only reducing agent used was sodium borohydride as there were no chemoselectivity issues due to the final product being a poly-ol. As long as each reduction was diastereoselective then over-reduction merely reduced the overall number of steps.

The biggest challenge would be to make the proposed synthesis chemoselective.

**Protecting group free synthesis**

The previous synthesis of carbasugar analogues was accomplished without the use of protecting groups. The oxazoline could be seen as a protecting group for a carboxylic acid, but in this case it is not considered to be a protecting group as it is necessary for dearomatisation; its removal is one of the few functionalisations that does not build a bond present in the target molecule.

The use of an oxazoline is the main reason to keep protections to a minimum, as additional steps required for the installation and removal of protecting groups have a loss of yield associated with them. Protecting group free synthesis requires each reaction to be chemoselective so that functionalisations are carried out in the presence of other reactive moieties, leaving them unchanged. Protecting group free chemoselective synthesis makes syntheses more direct, and therefore higher potentially yielding.
Methods for C3 hydroxyl group installation.

![Chemical Structure]

The electron-rich enol ether 9 was expected to react preferentially with osmium tetroxide, as osmium tetroxide is an electro phalic reagent. Investigations into this reaction were carried out using modified Upjohn conditions using 2 equivalents of NMO with 1 mol % osmium tetroxide in 1:1 tertiary butanol:water. Initial yields for this reaction were poor, between 13 and 18 %. It was found that lowering the catalyst loading to 0.5 mol % increased the yield to between 40 and 60 %, but reactions were slow and yields were inconsistent.

Over-oxidation may have been the problem as a base-line spot appeared on TLC faster than the rate of starting material consumption. NMR spectra of this base-line material revealed loss of the C2 proton indicating over-oxidation. Enolisation followed by deprotonation was occurring as observed by a previous researcher. 103
Oxidation of 16 is caused by the increasing basicity of the reaction, as the concentration of \( N \)-methylmorpholine, a tertiary amine, builds up over the course of the reaction. Unwanted oxidation of diol products can occur at high pH in aqueous media.

An improved Upjohn protocol for dihydroxylation has recently been published by Sharpless and co-workers\textsuperscript{104}, where the reaction is buffered by citric acid. Citric acid also co-ordinates the osmium tetroxide, chelating the metal oxide (Scheme 81) increases the rate at which the complex reacts with double bonds.
When the dihydroxylation of compound 9 was conducted under these conditions, the reaction time was much shorter, starting material was consumed in 2.5 hours on a 0.5 g scale and the product of this reaction was isolated in a 95 % yield.

After the initial success and high yields of compound 16, the reaction became difficult to reproduce. Acidic conditions were causing hydrolysis of the enol ether. Adding the citric acid as the reaction progressed did not change the result of the reaction but did allow for yields of between 10-15% of product 16. The hydrolysed compound 56 co-eluted with 16. It appeared after many attempts at the reaction on varying scales that possibly initial results were anomalous. The appearance of the reaction had also changed; when the reaction was successful, the solutions were clear; however when hydrolysis occurred, the reactions became dark green and eventually black, although none of the parameters had been changed.

The dihydroxylation could be carried out using a pH 7 buffer solution as the aqueous component of the Upjohn dihydroxylation. This unfortunately offered no improvement on the unbuffered system giving a 45-60% yield on a 1 gram scale. Hydrolysed compound 56 was also observed as a minor component by proton NMR spectroscopic analysis of the crude mixture.
rubottom epoxidation

Due to hydrolysis causing problems with the citric acid-buffered dihydroxylation a different approach had to be found in order to introduce the C3 hydroxyl group diastereoselectively. A Rubottom oxidation\textsuperscript{105} is commonly carried out on a silyl enol ether (Scheme 84) but the reaction is analogous for the methyl enol ether present in compound 9. This approach had been explored by a previous researcher with no success.

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] (A) at (0,0) {\textbf{Rubottom epoxidation}};
  \node[anchor=west] (B) at (2,-1) {Due to hydrolysis causing problems with the citric acid-buffered dihydroxylation a different approach had to be found in order to introduce the C3 hydroxyl group diastereoselectively. A Rubottom oxidation\textsuperscript{105} is commonly carried out on a silyl enol ether (Scheme 84) but the reaction is analogous for the methyl enol ether present in compound 9. This approach had been explored by a previous researcher with no success.}
\end{tikzpicture}
\end{center}

Scheme 84 – Rubottom epoxidation

An example from the Myers laboratory\textsuperscript{106} suggested that changing the solvent to methanol and increasing the temperature would not only provide the desired C3 hydroxyl group but also leave a protected ketone in the form of a dimethyl ketal. A protected carbonyl would allow the use of stronger reducing agents for the removal of the oxazoline.

\begin{center}
\begin{tikzpicture}
  \node[anchor=west] (A) at (0,0) {An example from the Myers laboratory\textsuperscript{106} suggested that changing the solvent to methanol and increasing the temperature would not only provide the desired C3 hydroxyl group but also leave a protected ketone in the form of a dimethyl ketal. A protected carbonyl would allow the use of stronger reducing agents for the removal of the oxazoline.}
\end{tikzpicture}
\end{center}

Scheme 85 – Myers’ example of an enol ether Rubottom oxidation

The Rubottom oxidation was carried out in methanol according to the procedure of Myers. Compound 9 was dissolved in MeOH, \textit{m}-CPBA (as supplied by Aldrich) was added and the solution was heated at reflux until all starting material was consumed (1.5 hours). The reaction gave compound 61 in a 59% yield, but this compound was slightly contaminated by the hydrolysis of the enol ether compound 56. \textit{m}-CPBA is supplied 75% pure with impurities including water and \textit{m}-chlorobenzoic acid. The excess \textit{m}-chlorobenzoic acid may be causing the hydrolysis of the enol ether and the acetal of the product, as only the ketone was isolated.
Purifying the \( m \)-CPBA to remove \textit{meta}-chlorobenzoic acid, according to the procedure of Aggarwal and co-workers,\textsuperscript{107} reduced enol ether hydrolysis. Rubottom oxidation of the methyl enol ether \( 9 \) was achieved at room temperature in a 56 % yield. Dearomatised compound \( 9 \) was stirred for 3 days with 1.1 equivalents of purified \( m \)-CPBA in methanol. Following quenching and workup, proton NMR spectroscopic analysis of the crude mixture showed the presence of a dimethyl acetal \( 61 \) as the major component along with the ketone-containing compound \( 16 \) in a ratio of 4:1. Importantly there was no evidence of enol ether hydrolysis. Dimethyl acetal \( 61 \) crystallised on standing in methanol and its crystal structure was obtained (Figure 28). It confirmed the diastereoselectivity of the nucleophilic addition of isopropyl lithium and that the Rubottom oxidation occurred on the less hindered face of the molecule.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme86}
\caption{Scheme 86 – Rubottom oxidation of compound 10}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{crystalstructure61}
\caption{Figure 28 – Crystal structure of 61}
\end{figure}

**Sharpless asymmetric dihydroxylation and Warren racemic dihydroxylation**

The most widely recognised dihydroxylation procedure is the Sharpless asymmetric dihydroxylation. It shows an increased rate of dihydroxylation and is highly reactive for a number of reasons, the reduced Os VI is oxidised to Os VIII by potassium hexacyanoferrate which is a one electron oxidant that does so through a single electron transfer. Oxidant and osmate need not collide in order for oxidation to occur. Using this oxidant also makes the product diols less prone to over oxidation, a common problem with the Upjohn dihydroxylation.
The basic reaction conditions of aqueous potassium carbonate, increases the rate of osmate ester hydrolysis. For internal, branched and lipophilic double bonds, the additive methane sulfonamide is used as it helps solvate hydroxide ions into the organic phase where the osmate ester builds up. These hydroxide ions hydrolyse the osmate ester and ensure catalytic turnover.

The rate of the cycloaddition is accelerated by a Cinchona alkaloid derived ligand (DHQ)$_2$-PHAL or (DHQD)$_2$-PHAL. These ligands increase the rate of osmylation for two reasons. Firstly they change the geometry of OsO$_4$, facilitating cycloadditions. The ligands also create a lipophilic pocket that has
complementary interactions between it and the substrate of dihydroxylation, especially if the double bond has aromatic groups present. This phenomena is known as ligand-accelerated catalysis.\textsuperscript{108}

The Sharpless asymmetric dihydroxylation uses ligands to increase the electron density of the transition metal oxide and decrease the entropy of the system by coordinating both metal oxide and substrate.\textsuperscript{109}

The Sharpless Asymmetric dihydroxylation suffers from reduced yields when the double bond to be dihydroxylated is in a chiral environment and a mis-matched pair effect occurs between the substrate and the chiral ligand. For sterically hindered double bonds the ligands can prevent approach of the osmium tetroxide, and thus no reaction occurs.

A racemic variant of the Sharpless asymmetric dihydroxylation was developed by Warren,\textsuperscript{110, 111} where quinuclidine is used in place of the Cinchona alkaloid-derived ligands (DHQ)\textsubscript{2}-PHAL or (DHQD)\textsubscript{2}-PHAL. Quinuclidine still accelerates the rate of osmylation but not to the same extent as the asymmetric dihydroxylation ligands, however quinuclidine is far less sterically hindered and can be used in the dihydroxylation of sterically encumbered double bonds.

Scheme 88 – Congested double bond dihydroxylation Stoltz

In this example by Stoltz (Scheme 88) the sterically congested double bond of 62 failed to dihydroxylate under more conventional osmium dihydroxylation protocols such as Upjohn and AD. By using modified conditions to those developed by Warren (using DABCO in place of quinuclidine as it performed better),\textsuperscript{112} dihydroxylation and subsequent diol cleavage was achieved in a 70 % yield.
Sharpless has studied the dihydroxylation of both silyl and methyl enol ethers in detail, under asymmetric dihydroxylation conditions. Silyl and methyl enol ethers are stable under the basic conditions, and α-hydroxy ketones were obtained in good to excellent yield 68-95 % and ee 90-97 % (Scheme 89).

Dearomatised compound 9 was submitted to the standard Warren conditions on a 200 mg scale. The reaction was complete within three hours and gave a 90% yield of the α-hydroxy enone 16. This reaction was scaled to 1 g and was essentially quantitative according to proton NMR spectroscopic analysis of the crude mixture. On a 3.75 gram scale the reaction gave a 83% yield; a solution to the difficult dihydroxylation of the enol ether had been found. The crystal structure of 16 revealed that dihydroxylation was diastereoselective, occurring on the less hindered face of the molecule away from the syn oxazoline and isopropyl groups.

**Bromination**

Enol ethers can be halogenated with electrophilic halogen sources. Introducing a bromine in this way to the enol ether would be synthetically useful, new functionally such as an azide may be introduced, as exemplified by Schade (Scheme 91).
Enol ether 9 was brominated in a 70% yield by treatment with NBS in acetonitrile water. The brominated compound 67 was a single diastereoisomer and appeared to have an unusual structure, a hemiacetal bearing an α-bromine.

This initial reaction was carried out on very pure highly crystalline material, repeating this reaction on material that was not crystalline but appeared to be as pure by proton NMR spectroscopic analysis was very difficult. TLC analysis showed that the reaction was not as clean and notably the reaction became yellow within 5 minutes. Buffering the reaction with sodium acetate allowed the reaction to proceed in good yield (76% on a 0.35 g scale), presumably the acidic impurities interfering in bromination were suppressed.

Unfortunately attempts to further functionalise 67 by displacing bromide with sodium azide under phase transfer conditions and in refluxing DMF returned starting material. Hydrolysis of the hemiacetal with aqueous acetic acid also caused hydrolysis of the oxazoline.
Chemoselective hydrolysis of the oxazoline

The proposed synthesis follows the previous synthesis of carbasugar analogues. In the previous synthesis the only substituents required were hydroxyl groups, and as long as functionalising oxidations and reductions were diastereoselective then a sugar analogue would be formed.

However this synthesis requires that there be a carbonyl available for a reductive amination. Previously the oxazoline was removed by Meyers’ alkylation reduction procedure, where methylation with methyl triflate was followed by reduction of the methylated oxazoline (and the carbonyl present on the dearomatised ring) to give an N-methyl oxazolidine.

Chemoselectivity between the reductions of an iminium and a ketone can be achieved with mild reducing agents, such as sodium cyanoborohydride, and sodium triacetoxyborohydride.
However when hydrolysis of acetal $\textbf{61}$ was attempted by stirring in 1:1 MeOH:HCl$_{aq}$(1M), overnight, the oxazoline also hydrolysed, forming compound $\textbf{69}$. This oxazoline hydrolysis had been observed by Meyers$^8$ and within the Clayden group.$^8^5$ This event could be synthetically useful, as a more step economic deprotection could be achieved (Scheme 97) than the previous four step deprotection strategy of alkylation, reduction, hydrolysis and reduction. Acid hydrolysis leaves an ester which can be subjected to methanolysis followed by reduction at a more prudent stage of the synthesis, saving one step. Importantly this partial hydrolysis preserved the ketone moiety, for a late-stage reductive amination.

Unfortunately since purification of compound $\textbf{69}$ led to a complex mixture of products and protection of the free amine was therefore necessary to improve its stability. Selective $N$-acylation was achieved in quantitative yield by treatment with triethylamine and acetic anhydride in CH$_2$Cl$_2$ (Scheme 96). This made the proposed deprotection efficient step economic than Meyers’ deprotection, however it avoids using methyl triflate which is highly toxic.
Compound 70 was purified by passage through a silica plug, washing with 50% ethyl acetate and using ethanol to remove it from the silica.

Compound 70 was subjected to methanolysis with potassium carbonate and methanol, but unfortunately stirring at room temperature with a catalytic amount of potassium carbonate led to 1,4-addition of methoxide to the α,β-unsaturated cyclohexenone moiety 71 as well as transesterification. The α,β-unsaturated cyclohexenone needed to be preserved for future oxidation of both carbons in either a dihydroxylation or a epoxidation. This compound could lead to a deoxy-amino carbasugar. The reaction was repeated using NaOMe; varying reaction times and temperatures led to a combination of starting material and compounds 71 and 72. Methoxide adduct 71 seemed unavoidable, so transesterification was delayed until a later stage of the synthesis when the α,β-unsaturation would not be present as the planned sequence of reactions would remove it with dihydroxylation or epoxidation. The stereoselectivity of the 1,4-addition was unconfirmed.
Enone functionalisation

C5-C6 double bond epoxidation

Enone 70 could potentially be epoxidised and opening of this epoxide with water would give hydroxyl groups in an *anti* relationship. In order to synthesise another amino-carbasugar analogue, epoxidation of enone 70 was investigated. No satisfactory method for the nucleophilic epoxidation of compound 70 was obtained. Reaction with aqueous hydrogen peroxide (Table 10, entries 1-5) led to a 1:1 mixture of epoxide (the stereoselectivity of the epoxidation was unconfirmed) and hydrolysed hydroxy amide 71 (by proton NMR spectroscopic analysis of the crude mixture). Acid 72, the other product of hydrolysis, was not observed presumably as it is hydrophilic. Improving the solubility of 70 by the addition of CH₂Cl₂ resulted in shorter reaction times, but the outcome of the reaction did not change.
Table 10 – epoxidation of 70

<table>
<thead>
<tr>
<th>entry</th>
<th>Conditions</th>
<th>temp</th>
<th>Time</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH, H₂O₂, MeOH&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0 °C-rt</td>
<td>90 min</td>
<td>1:1 mixture of 71 &amp; 73</td>
</tr>
<tr>
<td>2</td>
<td>NaOH, H₂O₂,MeOH, CH₂Cl₂&lt;sup&gt;a*&lt;/sup&gt;</td>
<td>0 °C-rt</td>
<td>60 min</td>
<td>1:1 mixture of 71 &amp; 73</td>
</tr>
<tr>
<td>3</td>
<td>NaOH, H₂O₂,MeOH, CH₂Cl₂&lt;sup&gt;a*&lt;/sup&gt;</td>
<td>0 °C-rt</td>
<td>35 min</td>
<td>1:1 mixture of 70 &amp; 71</td>
</tr>
<tr>
<td>4</td>
<td>NaOH, H₂O₂,MeOH, CH₂Cl₂&lt;sup&gt;a*&lt;/sup&gt;</td>
<td>0 °C</td>
<td>60 min</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃, H₂O₂,MeOH, CH₂Cl₂&lt;sup&gt;b*&lt;/sup&gt;</td>
<td>0 °C-rt</td>
<td>30 min</td>
<td>1:1 mixture of 70 &amp; 71</td>
</tr>
<tr>
<td>6</td>
<td>TBHP, DBU, PhMe&lt;sup&gt;c&lt;/sup&gt;</td>
<td>rt</td>
<td>16 hours</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>TBHP, DBU, PhMe&lt;sup&gt;d&lt;/sup&gt;</td>
<td>rt</td>
<td>16 hours</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>TBHP, DBU, CH₂Cl₂&lt;sup&gt;c&lt;/sup&gt;</td>
<td>rt</td>
<td>16 hours</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

<sup>a</sup>5 equiv H₂O₂, 1 drop NaOH 1M(sol)<sup>b</sup>5 equiv H₂O₂, 1 drop K₂CO₃ 1M(sol), 5:1, MeOH:CH₂Cl₂<sup>c</sup>2 equiv TBHP, 1.2 equiv DBU, 6 equiv TBHP, 1.2 equiv DBU

Keeping the reaction at 0 °C prevented both hydrolysis and epoxidation (Table 10, entry 4). Changing the base to potassium carbonate gave a 1:1 mixture of starting material and product, along with a small amount of the hydrolysis product 71.

Non-aqueous conditions were investigated as hydroxide mediated hydrolysis was a competing pathway. Reaction of 70 with 2 equivalents of TBHP in the presence of 1.2 equivalents of DBU in toluene<sup>115</sup> returned only starting material (Table 10, entry 6). The reaction was repeated with 8 equivalents of TBHP, with a similar result (Table 10, entry 7). The poor reactivity could be due to unfavourable steric interactions between the TBHP and the quaternary C1 position substituted with an ester and methyl group. This interaction may hinder the approach of the TBHP.
C5-C6 double bond dihydroxylation

The enone of compound 70 could also be dihydroxylated with osmium tetroxide; however dihydroxylation of electron-deficient double bonds with transition metal oxides is difficult as both the enone and the transition metal oxide are electron-deficient.

Sharpless Asymmetric Dihydroxylation can be used to dihydroxylate electron deficient double bonds. The mechanism of dihydroxylation is an [3+2] cycloaddition ligands such as quinuclidine, DABCO, DMAP and pyridine are used change the geometry of osmium tetroxide which promotes the cycloaddition and therefore dihydroxylation.

The investigation was directed to the functionalisation of the C5=C6 double bond. First the citric acid buffered, osmium tetroxide-catalysed dihydroxylation conditions developed by Sharpless were investigated. Formation of the osmium citrate complex allows the use of reflux temperatures to increase the rate of dihydroxylation for unreactive double bonds. Compound 70 was dissolved in 1:1 water:tertiary butyl alcohol, and heated under reflux for 45 minutes. This reaction returned starting material, which was surprising as over-oxidation had plagued the dihydroxylation of dearomatised compound 9.

Danishefsky

Danishefsky and co-workers have developed a procedure for the dihydroxylation of α,β-unsaturated cyclohexenones present in steroidal compounds. The procedure was a modification of Upjohn
dihydroxylation where an excess (3 equiv) of DABCO is used as a ligand to activate the osmium tetroxide and a large excess (5 equiv) of the oxidant NMO is necessary. The reaction was conducted in 4:1, THF:water at 40 °C. The elevated temperature is necessary to increase the rate of the reaction. Compound 70 was subjected to the published conditions and after 8 hours the starting material had been consumed. The reaction gave dihydroxylated compound 74b in a 55% yield (Scheme 101), but unfortunately repeating this reaction proved difficult. In subsequent reactions the only new compound was the acylated amino alcohol, the product of ester hydrolysis. The harsh basic conditions used were not compatible with the ester. Water is necessary for osmate ester hydrolysis and under the basic conditions necessary to activate the osmium, the ester group was undergoing hydrolysis. The acid 75 could then be lost in the aqueous phase during workup.

![Scheme 102 – Danishefsky dihydroxylation of compound 70](image)

Recently ruthenium tetroxide has been reported to dihydroxylate electron deficient double bonds efficiently. Lewis acids and Brønsted acids are used to aid ruthenate ester hydrolysis. Plietker’s procedure using cerium (III) chloride to maintain catalytic activity of the ruthenium and avoid over-oxidation of the products was attractive. RuCl₃ is used as a pre-catalyst and sodium periodate as the stoichiometric re-oxidant and the reaction is stirred at 0 °C in a three solvent slurry of ethyl acetate, acetonitrile and water. Fast reaction times are quoted, between 5 and 20 minutes, and products were obtained in good yields. When compound 70 was subjected to these conditions no reaction was observed by TLC or by the limits of proton NMR spectroscopic analysis of the crude mixture. This new dihydroxylation procedure was investigated using 2-cyclohexenone as a model compound. No reaction was observed using the conditions stated in the paper, increasing the amount of RuCl₃ from 0.5 mol% to 20 mol% also gave no products after 1 hour.
Plietker also reported a ruthenium tetroxide catalysed procedure that differed only by the addition of 20 % sulfuric acid\textsuperscript{120} and these conditions can also be used in conjunction with cerium (III) chloride.\textsuperscript{121} The conditions were investigated with the cyclohexenone model compound (Scheme 103). Cyclohexenone was added to stirred slurry of Lewis acid oxidant acetonitrile, sulfuric acid and ethyl acetate at 0 °C. RuCl\textsubscript{3} solution was added to the solution and the progress of the reaction was monitored by TLC. Under these reaction conditions, formation of a new compound occurred rapidly as shown on the TLC plate, although starting material was not consumed at the rate described in the literature (10 min). The reaction was quenched after 3 hours and the dihydroxylated compound \textbf{77} was isolated in a low yield (20 %). Compound \textbf{70} was submitted to the same conditions and the reaction proceeded very quickly with the starting material had been consumed after 6 minutes.

After subjecting Compound \textbf{70} to the sulfuric acid promoted conditions, compound \textbf{74b} was isolated in a 42 % yield (The stereoselectivity of the dihydroxylation was unconfirmed). Over-oxidation may be the cause of these low yields as α-hydroxyl ketones can be cleaved by periodate. Although this process should be slower than the ruthenium-catalysed dihydroxylation it may account for the lower yield.
Reductive amination

With ketone 74b in hand, reductive amination and ester reduction were investigated. These processes could theoretically be carried out at the same time, by forming a stable imine that could be reduced by lithium aluminium hydride or lithium borohydride. This strategy would be difficult as the planned synthesis is protecting group-free and imines that are not substituted at nitrogen hydrolyse easily. Initially the synthesis of a benzyl-protected amine was investigated even though a protected compound would be synthesised.

Ketone 74b was dissolved in CH₂Cl₂ in the presence of dry magnesium sulfate, and benzyl amine. The imine appeared to form very quickly by TLC analysis. Magnesium sulfate was removed by filtration and solvent removed by rotary evaporation, the residue was redissolved in THF and was treated with LiBH₄ at room temperature. Isolation of any products from this reaction was difficult as polar products from this reaction could not be separated from borane-containing residues. Only the acylated amino alcohol 73 could be isolated. Reductive amination of ketone 74b was envisaged by initial formation of an oxime followed by reduction of the oxime to the amine with LiAlH₄. LiAlH₄ would reduce the oxime C=N bond, cleave the N-O bond and reduce the ester to the alcohol. Oximes are more stable than imines and can be formed in aqueous conditions without hydrolysis.
Ketone **74b** was heated in water in the presence of hydroxylamine hydrochloride and sodium acetate. TLC showed two new spots. These fractions were isolated but proton NMR spectroscopic analysis of these fractions was difficult due to the small scale of the reaction. However, the mass spectrum gave the same mass for both fractions. The mass corresponded to the oxime **57**, the two spots could be accounted for by the two geometric isomers of the oxime being formed, as these compounds might have distinctly different polarities.

**Enone functionalisation before oxazoline hydrolysis**

The presence of the ester had become a problem: methanolysis of compound **70** gave oxy-Michael adduct **71**, dihydroxylation of compound **70** gave ketone **74b** that did not readily undergo reductive amination.

Prefunctionalisation of α-hydroxy enone **16** was embarked upon to allow oxazoline deprotection to be carried out afterwards. Dihydroxylation of the enone was attempted first using the Sharpless citric acid buffered Upjohn procedure. The procedure had been shown to be effective for the dihydroxylation of...
electron-deficient double bonds.\textsuperscript{104} Citric acid-complexed osmium tetroxide allows the reaction to be carried out at high temperatures. Within the Clayden group problems had already been experienced with slow dihydroxylations of enones with stoichiometric osmium tetroxide or under standard Upjohn conditions.\textsuperscript{122}

![Scheme 108 – Sedehizadeh’s example of difficult enone dihydroxylation](image)

Due to the high pH of Upjohn conditions conjugated enolate 82 of the fused ring system formed. Dihydroxylation of lactam enolate to provide 83 became an unwanted side reaction.

It was hoped that cyclic enones could be dihydroxylated under the improved acidic new conditions.

A solution of α-hydroxy enone 8 in tertiary butanol/water with NMO, citric acid and catalytic potassium osmate dihydrate was heated at reflux for 5 hours but no new products were apparent by TLC or proton NMR spectroscopic analysis.

![Scheme 109 – Oxidation to quinone type compound 55](image)
Enone dihydroxylation was attempted using the Danishefsky-modified Upjohn procedure, where DABCO is used to activate the electron-deficient osmium tetroxide. The reaction was conducted at 40 °C. After 2 hours the TLC showed that oxidation to the quinone type compound 55 had occurred (Scheme 109); this was confirmed by proton NMR spectroscopic analysis of the crude mixture. The similarity between the literature example and this compound is striking; the large oxazoline must reduce the rate of dihydroxylation by blocking the approach of the ligand bound osmium tetroxide.

Dihydroxylation under the previously successful ruthenium-catalysed conditions was attempted. Running the reaction under the previously optimised conditions rapidly gave a new product (indicated by TLC analysis). Once starting material was consumed the reaction was quenched but after this time only a faint product spot was visible by TLC. Indeed only a small amount (15 mg) of starting material was isolated and an even smaller amount of product (0.4 mg) was isolated. The active dihydroxylating agent ruthenium tetroxide is regenerated with by sodium periodate which is most commonly used to cleave diols. Clearly in this case the rate of dihydroxylation is slower than the rate of diol cleavage. Alternatively the poor yield could be accounted for by the acidic conditions causing a retroaldol reaction. None of these cleavage products could be isolated by stripping the column with ethanol and acetone, as the polyhydroxylated nature of these compounds means the periodate could further degrade them.
Design of a new route involving complete oxazoline removal

After straying from the originally proposed route and discovering that partial hydrolysis of the oxazoline was not a viable strategy, attention was redirected towards a more tried and tested oxazoline deprotection.

In the previous synthesis of carbasugar analogues the oxazoline was successfully removed by an alkylation, reduction, hydrolysis sequence (Scheme 112).\(^8^6\)

Incorporating this deprotection into the route should lead to straightforward oxazoline removal, leaving only the dearomatised carbocyclic core.

Development of a one-pot Meyers deprotection

This deprotection strategy clearly had problems due to the solubility of the hydrolysis products. The more established oxazoline removal strategy was to be used with the α-hydroxy enone containing anti-diphenyloxazoline 16. The oxazoline could be alkylated quantitatively with methyl triflate in \(\text{CH}_2\text{Cl}_2\), to give \(N\)-methyl triflate salt 85 (Scheme 113). This salt had to be reduced to the oxazolidine 51 selectively so that the enone would be preserved for a later stage reductive amination.
Initially weak reducing agents were used to achieve a selective reduction of the iminium salt. Sodium triacetoxyborohydride\textsuperscript{123} was chosen first as this reagent is often used to reduce imines in chlorinated solvents.\textsuperscript{124} This reagent is favoured by the fine chemicals industry as its low reactivity gives it a good safety profile.

Unfortunately reducing the iminium salt in CH$_2$Cl$_2$ at room temperature gave a mixture of desired enone oxazolidine and the two diastereoisomers arising from reducing the enone to the allylic alcohol.

In non-protic solvents such as THF and DCE, reductions with sodium borohydride proceed at much lower rates. In aprotic solvents the rate of reduction is lower and reduced products build up as salts.

In THF at room temperature reduction with sodium borohydride gave a complex mixture of products. Reduction in THF with sodium triacetoxyborohydride at 0 °C gave over-reduction. Reduction with sodium cyanoborohydride in THF at 0 °C appeared to proceed rapidly and cleanly but recovery of the oxazolidine 51, apparently the only product of the reaction, was poor.

Ward developed conditions for a series of chemoselective reductions with sodium borohydride,\textsuperscript{125} where aldehydes are reduced in the presence of ketones,\textsuperscript{126} or ketones are reduced in the presence of enones.\textsuperscript{127} Selective reduction is achieved using sodium borohydride in a CH$_2$Cl$_2$/alcohol mixed solvent system at -78 °C. The nature of the alcohol additive and the amount added control the reduction (Figure 31).
To reduce a ketone in the presence of an enone, a 1:1 mixture of CH\textsubscript{2}Cl\textsubscript{2}:methanol is used with excess sodium borohydride (4.5 equiv) added as a solid, and the reactions are quenched with acetaldehyde.

To reduce an aldehyde in the presence of a ketone, 30% ethanol in CH\textsubscript{2}Cl\textsubscript{2} is used at -78 °C. The amount of alcohol and its bulkiness are used to attenuate the reactivity of sodium borohydride. Quenching these reactions with acetaldehyde was found to be necessary.

Attempting to reduce the iminium salt with sodium borohydride under the methanol/CH\textsubscript{2}Cl\textsubscript{2} conditions at -78 °C gave over-reduction almost instantly.

Hence the ethanol/CH\textsubscript{2}Cl\textsubscript{2} conditions\textsuperscript{126} were used as it was hoped that because these conditions were developed for more sensitive reductions they would perform better. Reducing the iminium salt was performed using only 1 equivalent of sodium borohydride to minimise the chance of over-reduction. The reaction was quenched with distilled acetaldehyde after all iminium salt had been consumed and the reaction was quantitative. Furthermore the system appeared to be very resilient to over-reduction as the reaction could be left for over an hour and TLC showed no sign of over-reduction. The reaction scaled well and was quantitative. As only one equivalent of sodium borohydride was used quenching the reaction with acetaldehyde was not necessary, saturated aqueous ammonium chloride was an adequate quench. The reduction was also selective giving only one diastereoisomer by proton
NMR spectroscopic analysis. Oxazolidine 51 crystallised from petroleum ether and X-ray crystallography confirmed its structure.

The two steps could be carried out in the same reaction vessel by dissolving the oxazoline in the minimum amount of CH₂Cl₂ and adding the alkylating agent. Once alkylation was complete the additional CH₂Cl₂ and ethanol were added, followed by a solution of sodium borohydride in ethanol.

With this difficult reduction accomplished, the deprotection of the oxazolidine was achieved using a procedure developed by Meyers. The oxazolidine residue was dissolved in THF/water, five equivalents of oxalic acid were added and the solution was stirred at 40 °C for 4 days. After purification the aldehyde-containing α-hydroxy enone 86 was reproducibly isolated in a 75 % yield.

A telescoped procedure was developed by performing the alkylation and reduction, then removing the CH₂Cl₂-ethanol and re-dissolving in THF-water adding oxalic acid and heating at 40 °C for 4 days.
A scalable synthesis of aldehyde 86 had been developed; this aldehyde would be used as the carbon skeleton around which functionality would be installed to give a fully substituted amino-carbasugar derivative.

**Chemoselective reduction of aldehyde 86**

The first strategy to give an amino-carbasugar analogue centred on a late-stage reductive amination of the C4 ketone. In order to accomplish a synthesis through this proposed route, a chemoselective reduction of the aldehyde in the presence of the enone was necessary, followed by functionalisation of the enone before the reductive amination.

A chemoselective reduction of the aldehyde 86 was necessary as a global reduction with sodium borohydride would not only reduce the ketone but could potentially also reduce the double bond present in the ring, leading to cyclohexane triol 88. Reduction under Luche conditions would stop the double bond reduction but would still reduce the ketone. Normally over-reduction is not a problem as reduced hydroxyl groups can be reoxidised if protecting groups are in place, but this synthesis uses protecting groups sparingly. A selective oxidation of only the allylic alcohol in the presence of primary and secondary alcohols would be very difficult.
A selection of chemoselective reductions are shown in Scheme 118. Although there is some literature precedent for the chemoselective reduction of aldehydes in the presence of enones they often suffer from the use of specific, obscure toxic reagents and low yields, or both.

![Scheme 118 – Examples of selective resections of aldehydes](image)

Examples of selective reductions are reasonably rare and as such during this investigation only the example by Stork \(^{129}\) was known although later examples by Greaney, \(^{130}\) Stoltz \(^{112}\) and Baran \(^{131}\) emerged. Stoltz and Baran achieved selectivity by using the hindered reducing agent tri-tert-butoxyaluminium hydride. Steric hindrance reduces the availability of the Lewis acidic aluminium centre for coordination and the inductive effect of oxygen in the three coordinated tert-butoxide ligands reduces the nucleophilicity the hydride. \(^{132}\)

Chemoselective reduction of the aldehyde 86 was first attempted using Ward’s procedure as it was used successfully for reduction of the N-methyl iminium salt 85.

Reduction of aldehyde 86 with 1 equivalent of sodium borohydride in 30 % ethanol in CH\(_2\)Cl\(_2\) at -78 °C (Table 11, entry 1), led to over-reduction within 10 minutes and gave a 4:1 mixture of enone 52 and allylic alcohols 87. This result was surprising as the reduction of the N-methyl salt 85 was very selective.

Ward states that the rate of reduction decreases as the substitution of the alcohol additive increases from primary to tertiary (1’>2’>3’). Reductions with methanol were the fastest and reductions with tertiary butanol were the slowest (MeOH>EtOH>IPA>\(t\)-BuOH); although reductions with tertiary...
butanol at -78 °C are not possible as mixtures of tertiary butanol and CH₂Cl₂ freeze at this temperature.¹²⁵

Repeating the reaction on a 50 mg scale using isopropyl alcohol gave much slower reactions (Table 11, entry 2), mainly due to the decreased solubility of sodium borohydride in isopropyl alcohol. Proton NMR spectroscopic analysis of the crude mixture of this reaction showed that only the enone 52 and a trace amount of starting material were present. However the reaction was less selective on a larger scale. TLC analysis showed that, as the reaction progressed, product 52 was reduced further to allylic alcohols 87. On a 100 mg scale the reaction was reasonably selective for the formation of enone 52 which was isolated in a 39 % yield, but allylic alcohols 87 were also isolated as a mixture of diastereoisomers in a 22 % yield. Increasing the scale of this reaction to 400 mg and following the reaction carefully, quenching once all starting material had been consumed gave a 67 % yield of enone 52, and 20 % of allylic alcohols 87.

![Chemical structures](image)

**Table 11 – Attempts at selective reduction of aldehyde 86**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Scale</th>
<th>Time</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄, CH₂Cl₂:EtOH (7:3), -78 °C</td>
<td>50 mg</td>
<td>15 min</td>
<td>4:1 52:87</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄, CH₂Cl₂:IPA (7:3), -78 °C</td>
<td>50 mg</td>
<td>40 min</td>
<td>52, trace 87</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄, CH₂Cl₂:IPA (7:3), -78 °C</td>
<td>100 mg</td>
<td>1 hour 15 min</td>
<td>39 % 52, 22 % 87</td>
</tr>
<tr>
<td>4</td>
<td>NaBH₄, CH₂Cl₂:IPA (7:3), -78 °C</td>
<td>400 mg</td>
<td>35 min</td>
<td>67 % 52, 20 % 87</td>
</tr>
<tr>
<td>5</td>
<td>NaBH(OAc)₃, Toluene:AcOH (95:5)</td>
<td>50 mg</td>
<td>1 hour</td>
<td>over reduction</td>
</tr>
<tr>
<td>6</td>
<td>NaBH₃CN, EtOH:AcOH (98:2)</td>
<td>50 mg</td>
<td>5 min</td>
<td>43 % 52, 19 % 87</td>
</tr>
<tr>
<td>7</td>
<td>NaBH₃CN, EtOH:AcOH (98:2)</td>
<td>400 mg</td>
<td>15 min</td>
<td>82 % 52</td>
</tr>
</tbody>
</table>

2 Acetaldehyde (quench)
A reduction under the conditions of Stork was attempted; toluene was used in place of benzene. Aldehyde 86 was stirred at 0 °C in a solution of toluene:acetic acid (95:5), almost immediately over-reduction was seen by TLC.

Sodium cyanoborohydride is a much weaker reducing agent and Brønsted acids like hydrochloric acid and acetic acid are generally used to increase the electrophilicity of carbonyl compounds and imines, thus reduction of aldehydes can be achieved at low pH.

Aldehyde 86 was dissolved in ethanol and sodium cyanoborohydride was added. The solution was stirred at 0 °C for 1 hour, however no change was observed by TLC so the reaction was allowed to warm to room temperature. Again after 1 hour no change was observed by TLC so the reaction was heated to 40 °C and still only starting material was observed. Acetic acid was added to the reaction mixture as a 2 % co-solvent. This small quantity was chosen as adding larger amounts may have caused over-reduction. (Sodium cyanoborohydride almost exclusively reduces 1,4 before 1,2).

Checking the reaction by TLC at this time showed that the reaction had immediately changed on addition of acid: only one spot was present so the reduction appeared to be selective. The reaction was quenched with sodium hydrogen carbonate, however it transpired that this had not completely quenched the reagent. It was assumed that because the hydride hadn’t been quenched and the reaction had been left too long before purification, over-reduction had occurred.

The reaction was repeated on a larger scale, with 2 % acetic acid co-solvent added from the beginning. The reaction was stirred at room temperature with no change observed by TLC, so the
reaction was heated to 40°C and was complete within 30 min. This proved that both acetic acid and heating were necessary for selective reduction. The reaction was purified immediately after workup, but a lower yield than expected of compound 52 was isolated (43 %), as well as a 19 % yield of the over-reduced allylic alcohols 87 as a mixture of diastereoisomers.

Ward quenched selective reductions using sodium borohydride with freshly distilled acetaldehyde to stop over-reduction. The reaction was repeated on a 100 mg scale and quenched with freshly distilled acetaldehyde once all starting material had been consumed. The yield of product isolated from this reaction increased to 82 % and no over-reduction was observed by TLC or after chromatography.

Using these conditions the aldehyde was successfully selectively reduced on scales ranging from 100 and 500 mg in yields between 70 - 80 %. This represented the second chemoselective reduction achieved during the investigation. The weak reducing agent sodium cyanoborohydride was able to reduce an activated aldehyde by the presence of acetic acid. Enone 52 was crystallised from ethyl acetate and the X-ray crystal structure was obtained.

Enone functionalisation in the absence of the oxazoline

Enone dihydroxylation is well preceded in the literature. A recent example by Irie used a catalytic amount of osmium tetroxide with DABCO as a ligand and N-methyl morpholine N-oxide as the stoichiometric oxidant. 134

Enone functionalisation in the absence of the oxazoline

Enone dihydroxylation is well preceded in the literature. A recent example by Irie used a catalytic amount of osmium tetroxide with DABCO as a ligand and N-methyl morpholine N-oxide as the stoichiometric oxidant. 134
If enone 52 could be dihydroxylated then the resulting poly-hydroxy ketone could have an amino group introduced through reductive amination to make the first amino-carbasugar (Scheme 121).

Scheme 121 – Proposed dihydroxylation reductive amination sequence

The conditions used by Irie are similar to those used by Danishefsky, which were already investigated.

Scheme 122 – Failed Danishefsky dihydroxylation

Danishefsky’s conditions were used initially due to the similarity between enone 52 and the two reported examples. Heating the solution to 40 °C in the presence of DABCO and NMO in THF/water for 24 hours appeared to give a slow conversion of starting material to a more polar product, observed by TLC, but proton NMR spectroscopic analysis of the crude mixture showed a complex mixture of products.

Dihydroxylation under the ruthenium-catalysed conditions returned starting material almost quantitatively (Scheme 123).

Scheme 123 – Failed Ruthenium dihydroxylation

Sodium hydrogen carbonate-buffered Warren RD conditions were used with DABCO as a ligand. These conditions were used because Sharpless had reported the dihydroxylation of enones using the AD system buffered by sodium hydrogen carbonate to suppress retro-aldol reactions of the dihydroxylated products.
After 34 hours under these conditions the enone had not undergone dihydroxylated. Heating at 40 °C for 24 hours did not produce any product either and starting material was recovered in a 50% yield.

This demonstrates the power of the asymmetric dihydroxylation. The (DHQD)$_2$PHAL ligand is responsible for binding osmium and also coordinates alkene substrates through lipophilic interactions. These properties have the net effect of reducing the overall activation barrier of the reaction. Unfortunately the AD ligands are not suitable for use with sterically congested olefins. This example emphasises that simple nucleophilic amines such as DMAP, DABCO and quinuclidine are poor alternatives to the AD ligands.
Stoichiometric dihydroxylations

Stoichiometric amounts of metal oxides such as osmium tetroxide and potassium permanganate are also used to dihydroxylate double bonds, although catalytic versions of these reactions are preferred due to the high toxicity and cost of osmium tetroxide.

Potassium permanganate is used in some cases to dihydroxylate double bonds; however this reaction is not general and can be slow and low-yielding. Despite this, dihydroxylations using potassium permanganate are often preferred by the pharmaceutical industry as manganese is a semi-essential element and biological systems are able to cope with trace residues of this metal. Examples of dihydroxylation with potassium permanganate are most commonly found on steroidal compounds, but examples of carbocycle dihydroxylation also exist in the literature.\textsuperscript{135-137}

![Scheme 125 – Stoichiometric dihydroxylations of carbocycles with potassium permanganate](image1)

Stoichiometric dihydroxylation was attempted using conditions that were successful with enone 52 as shown.

![Scheme 126 – Failed permanganate dihydroxylation](image2)

The enone was stirred in the presence of formic acid and potassium permanganate in acetone and water at -10 °C. The reaction showed no change after one and a half hours, so the solution was...
warmed to 0 °C and stirred for another hour. Finally the reaction was allowed to reach room temperature but no change was observed by TLC. All starting material was recovered from the reaction.

A stoichiometric dihydroxylation with osmium tetroxide and DMAP was chosen as the next possible set of conditions. These conditions were developed by Corey, where DMAP was used as a ligand; it is nucleophilic enough to activate osmium but unlike DABCO and quinuclidine it is less sterically hindered, so that the resultant osmate ester is hydrolysed more easily.

Scheme 127 – Corey’s stoichiometric dihydroxylation osmium tetroxide-DMAP complex

In the previous study investigating the synthesis of carbasugar analogues, the stoichiometric dihydroxylation under the conditions of Donohoe (with TMEDA as a ligand) was used and difficulties arose hydrolysing the resultant osmate ester. The osmium DMAP complex was pre-formed in tertiary butanol and was then added to a solution of enone in tertiary butanol at room temperature, however no new products were observed by TLC analysis.

Poli developed conditions for directed catalytic dihydroxylations. It is proposed that as CH₂Cl₂ is used as solvent reactions can be carried out at higher concentrations. Trimethylamine N-oxide is used under Poli conditions, which is a hydrate and the water present is responsible for hydrolysing the osmate ester and maintaining catalyst turnover.
When dihydroxylation of 52 was attempted under Poli conditions a new more polar spot appeared on the TLC plate after 1.5 hours. After 16 hours however, proton NMR spectroscopic analysis of the crude mixture showed a complex mixture of products. Using CH$_2$Cl$_2$ as a solvent at high concentration clearly gave reactivity. Reducing this reactivity could be achieved by changing the oxidising agent. Trimethylamine $N$-oxide once reduced provides a nucleophilic base that could degrade the poly-ol product or starting material. Changing oxidant to $N$-methyl morpholine $N$-oxide as used in the Upjohn process may reduce degradation as the $N$-methyl morpholine produced after reoxidising osmium is less nucleophilic than trimethylamine.

The Poli conditions were modified using $N$-methyl morpholine $N$-oxide under these conditions, oxidation was much slower. The reaction was stirred at room temperature for 6 days until almost all starting material had been consumed. Lactol 89 was isolated in a 35 % yield. Dihydroxylation had occurred and the release of strain within the molecule had allowed lactolisation to occur, the stereochemistry of lactol 89 was not confirmed.
Dihydroxylation of enone 52 was poor as both the enone olefin and osmium tetroxide are electron-deficient. Steric hindrance could also be playing a part as the methyl and hydroxymethyl groups could be blocking the approach of osmium tetroxide (Scheme 130).

Dihydroxylations of enone 52 were difficult, however lactol 89 was synthesised but the reaction did not scale and routes towards amino-carbasugar analogues using this route were not pursued.
**Enone epoxidation**

Enone **52** was subjected to a standard nucleophilic epoxidation with hydrogen peroxide in methanol with a catalytic amount of sodium hydroxide at 0 °C and allowed to warm to room temperature after 18 hours, proton NMR spectroscopic analysis of the crude mixture of the reaction showed only starting material.

Another set of conditions was discovered in the literature using a similar substrate. The epoxidation used tertiary butyl hydrogen peroxide in THF, with a catalytic amount of benzyltrimethy lammonium hydroxide (Triton B®) as base.\(^{141}\) This lipophilic counter ion may stabilise the enolate intermediate. However this reaction gave back starting material.

![Scheme 131 – Nucleophilic epoxidation of enone 52 with Triton B](image)

Enone **52** was then epoxidised under a different set of nucleophilic epoxidation conditions using tertiary butyl hydrogen peroxide and DBU\(^{115}\). This reaction was difficult to follow by TLC as the epoxide had almost the same R\(_f\) as the starting material. Instead the reaction mixture was analysed by proton NMR spectroscopic analysis analysing aliquots of the reaction mixture. The reaction seemed to proceed quite quickly as indicated by easily visible protons α to the epoxide but the reaction would not progress any further than approximately 50 %. Prolonged exposure to the reaction conditions seemed to degrade the starting material and product and after 16 hours further analysis of the crude reaction mixture showed no discernable peaks.

![Scheme 132 - Taylor’s epoxidation conditions](image)
Taylor has reported some conditions similar to the anhydrous DBU and tertiary butyl hydrogen peroxide conditions, where a sub-stoichiometric amount of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) is used in place of DBU. The conditions were developed for the epoxidation of base-sensitive quinone compounds that rapidly became "unidentified black dyestuff under standard alkaline peroxide conditions". 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) gives good to excellent yields of epoxides in a variety of protic and aprotic solvents.

When the epoxidation of enone 52 was carried out using DBU and tertiary butyl hydrogen peroxide, the reactions became red, the red colour stuck to silica making its separation easy and its isolation difficult. This red colour might represent by-product formation and this could account for low yields. Changing the solvent from CH$_2$Cl$_2$ to acetonitrile reduced the rate of reaction as only small amounts of product were formed after 2 days at room temperature.

<table>
<thead>
<tr>
<th>entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 % H$_2$O$<em>2$, NaOH$</em>{\text{cat}}$, MeOH</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>TBHP, triton B, THP, 0°C</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>TBHP, DBU, CH$_2$Cl$_2$, 0°C</td>
<td>Reactant and product degraded over time</td>
</tr>
<tr>
<td>4</td>
<td>TBHP, DBU, MeCN, 0°C</td>
<td>Very slow reaction trace product after 2 days</td>
</tr>
<tr>
<td>5</td>
<td>TBHP, TBD, CH$_2$Cl$_2$, 0°C</td>
<td>1:1 ratio of starting material and product</td>
</tr>
</tbody>
</table>

Epoxidation under Taylor’s conditions was slow, but unlike reactions with stoichiometric DBU the products and starting material were visible by proton NMR spectroscopic analysis of the crude mixture after 24 hours and did not degrade. However the reaction did not seem to progress further, even after 4 days. Comparison of the product and starting material peaks by proton NMR spectroscopic analysis of the crude mixture indicated that there was a 1:1 ratio of starting material and product, this ratio did not change. A 49 % combined yield of epoxide 90 and starting material 52 (1:1) was isolated from this reaction (Scheme 133). After careful purification by flash chromatography the enone starting material was separated, to give epoxide 90 in a 27 % yield.
NOESY analysis of **90** revealed that the epoxide was located on the more hindered face of the molecule, indicated by a through space coupling between the C1 methyl protons and the epoxide protons.

In order to improve on these slow, low-yielding reactions a metal catalysed epoxidation using VO(acac)$_2$ was attempted although this method is unusual as electrophilic epoxidation of electron deficient olefins is difficult.

Literature president for the epoxidation of enones with t-BuOOH, VO(acac)$_2$ was reported by Markó these epoxidations were directed by an homoallylic alcohol. It was questioned whether the homoallylic alcohol present in **52** could direct epoxidation by VO(acac)$_2$.

Exposure of enone **52** to the reaction conditions, catalytic VO(acac)$_2$ in CH$_2$Cl$_2$ with tertiary butyl hydrogen peroxide as stoichiometric oxidant, gave dione **91**. The wrong type of oxidation had occurred. Interestingly this compound had a different tautomeric structure from the other over-oxidised dione compound **55** observed after dihydroxylation of dearomatised oxazoline **16**.
Oxidising the enone double bond proved difficult: it has two groups present proximal to C1, the methyl and the hydroxymethyl group. These groups may block the approach of the reagents, in the nucleophilic epoxidation of 52 as the reagents undergo a 1,4-addition to form a peroxy-adduct 92. Due to steric repulsions 92 may not be stable and undergoes E1cB elimination, rather than forming epoxide 90.

Scheme 135 – oxidation of 52 by vanadyl acetylacetonate

Scheme 136 – Unfavourable epoxidation of 52
Changing the sequence of the synthesis

Oxidation of the enone before reductive amination was not viable as dihydroxylation of the electron-deficient enone was not easy. By condensing an amine and then carrying out a chemoselective reductive amination to give cyclic allylic amine 94, would lead to a more electron rich electron olefin to take part in dihydroxylation (Scheme 137).

Reductive amination by oxime reduction

The dihydroxylation or epoxidation would have been followed by a reductive amination. Changing the order of transformations to a reductive amination, dihydroxylation sequence would appear more favourable as allylic amines are more electron-rich and make dihydroxylation easier. Provided that initial reductive amination was 1,2-selective and gave an allylic amine, subsequent dihydroxylation should be more straightforward.

Leuckart reaction of the enone was first attempted by refluxing the enone in formic acid in the presence of ammonium acetate as the amine source. Refluxing the reaction mixture for four hours
resulted in quantitative formylation of the two free hydroxyl groups and no imine formation occurred: only diformate 95 could be isolated (Scheme 138).

![Scheme 139– Failed reductive amination](image)

Similarly, conducting a standard reductive amination with ammonium acetate and sodium triacetoxy borohydride under the conditions of Abdel-Magid was also unsuccessful.\(^\text{124}\)

Pre-forming the imine in the presence of molecular sieves or dried magnesium sulfate was not successful, however condensation with hydroxylamine to give oxime 96 was rapid as it is more nucleophilic.

![Scheme 140 – Oxime formation](image)

The oxime 96 could be formed quantitatively by stirring 52 in methanol in the presence of hydroxylamine hydrochloride and sodium acetate (Scheme 140).\(^\text{144}\)

Hydrogenation of the oxime under the conditions developed for stereospecific hydrogenations of oximes with palladium on carbon in the presence of hydrobromic acid 96 gave a complex mixture of products.\(^\text{145}\)

Also reduction of oxime 96 with zinc in acetic acid led to degradation and a complex mixture of products was observed by proton NMR spectroscopic analysis of the crude mixture of the reaction.

Oxime reduction is difficult as the oxime is often deprotonated under the reduction conditions, causing the oxime and hydride to repel each other. Lewis acids reduce this effect for three reasons: they aid reduction through the inductive effect increasing electrophilicity; they accept the negative charge of
the deprotonated oxime; this coordination makes the oxygen of the oxime a better leaving group (Scheme 141).

```
\begin{equation}
\begin{align*}
\text{CO}_2H & \xrightarrow{\text{H}^+} \text{CO}_2^\text{H} \\
\text{CO}_2^\text{H} & \xrightarrow{\text{LA}} \text{CO}_2^- \text{LA} \\
\text{CO}_2^- \text{LA} & \xrightarrow{\text{H}^+} \text{CO}_2^- \\
\text{CO}_2^- & \xrightarrow{\text{H}^+} \text{CO}_2^\text{H} \\
\text{CO}_2^\text{H} & \xrightarrow{\text{LA}} \text{CO}_2^- \text{LA} \\
\end{align*}
\end{equation}
```

Scheme 141 – Oxime reduction with Hydride reagents, added by Lewis acids and sulfonates

Kočovský made oxime mesylates and reduced these with lithium aluminium hydride: as mesylate is a good leaving group better than the corresponding tosylate.\textsuperscript{146} Unfortunately selective mesylation of the oxime under the conditions of Burke failed.\textsuperscript{147}

```
\begin{equation}
\begin{align*}
\text{CO}_2H & \xrightarrow{\text{MsCl}, \text{Py} \quad 0^\circ\text{C} - \rt} \text{CO}_2\text{Ms} \\
\end{align*}
\end{equation}
```

Scheme 142 - Selective mesylation of oxime 96

Various methods for the reduction of this oxime were attempted using borohydride derivatives, activating with different Lewis and Brønsted acids. The conditions are summarised in table 14.
Table 14 – Reduction of oxime 96 with hydride reagents in the presence of Lewis acids

<table>
<thead>
<tr>
<th>entry</th>
<th>Reducing agent/s</th>
<th>Solvent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zinc</td>
<td>AcOH</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>2</td>
<td>NaBH$_3$CN, TiCl$_3$</td>
<td>MeOH</td>
<td>Oxime hydrolysis occurred</td>
</tr>
<tr>
<td>3</td>
<td>NaBH$_4$, TiCl$_3$</td>
<td>EtOH</td>
<td>No reaction recovered SM</td>
</tr>
<tr>
<td>4</td>
<td>NaBH$_4$, TiCl$_4$</td>
<td>Glime</td>
<td>Trace amounts of product</td>
</tr>
<tr>
<td>5</td>
<td>NaBH$_4$, ZrCl$_4$</td>
<td>THF</td>
<td>No reaction recovered SM</td>
</tr>
<tr>
<td>6</td>
<td>NaBH$_4$, LiCl, Amberlyst-15®</td>
<td>THF</td>
<td>No reaction recovered SM</td>
</tr>
<tr>
<td>7</td>
<td>LiAlH$_4$</td>
<td>THF</td>
<td>No reaction recovered SM</td>
</tr>
<tr>
<td>8</td>
<td>LiAlH$_4$ (NOBn oxime ether)</td>
<td>THF</td>
<td>No reaction recovered SM</td>
</tr>
<tr>
<td>9</td>
<td>MoO$_3$, NaBH$_4$</td>
<td>EtOH</td>
<td>Reduction occurred</td>
</tr>
</tbody>
</table>

Attempted reduction of the oxime 96 under the conditions of Leeds with sodium cyanoborohydride was unsuccessful and, over time oxime hydrolysis occurred (Table 14, entry 2).\textsuperscript{148}

Reduction of oxime 96 with borohydride reducing agents in the presence of a variety of Lewis acids also failed but did not hydrolyse the oxime. Reduction in the presence of zirconium tetrachloride failed (Table 14, entry 5).\textsuperscript{149} By proton NMR spectroscopic analysis of the crude mixture titanium tetrachloride\textsuperscript{150} in glyme gave small amounts of product but it could not be isolated by column chromatography (Table 14, entry 4).

Reduction in the presence of Amberlyst 15\textsuperscript{151} (a polymer-supported Brønsted acid) was unsuccessful (Table 14, entry 6).

Due to problems with Lewis acid-activated reductions a protected oxime was synthesised. The O-benzyl ether was synthesised from O-benzyl hydroxylamine hydrochloride and enone 52 with sodium acetate. Reduction of this ether with lithium aluminium hydride was unsuccessful (Table 14, entry 8).\textsuperscript{152}
Overman reported successful reduction of oxime 97 with molybdenum trioxide and sodium borohydride.\textsuperscript{153} Following consultation of the literature reference by Ipaktsch this procedure became even more suitable specifically as examples of selective 1,2-reduction of conjugated oximes were present (Scheme 144).\textsuperscript{154} The literature reference used 1 equivalent of molybdenum trioxide and 4 equivalents of sodium borohydride.

Reduction of 130 mg of oxime 96 under the modified conditions of Overman appeared to consume all starting material by TLC analysis and following workup only 10 mg of crude product was obtained (Scheme 145). Proton NMR spectroscopic analysis of this crude material however showed major a component that was tentatively assigned as allylic amine 94. Mass spectrometry also suggested that allylic amine 94 had formed. Chromatographic purification of this material was difficult; only the minor components of the crude mixture could be isolated. It is presumed that the allylic amine 94, containing many polar functional groups adhered to the silica, this may account for the relatively low mass recovery. Attempts to repeat the reaction and avoid an aqueous workup were completely unsuccessful as partial removal of the solvent led to insoluble black/brown precipitates. Subsequent filtration of remaining solvent carried inorganic materials through the filtration medium. An aqueous workup was clearly necessary. The original manuscript described isolation of the products of the reaction by distillation. The molecule reduced by Overman was reasonably lipophilic with no other polar groups present; this property would have aided recovery.
It is possible that this transformation represents a limitation to synthesis where few protecting groups.

The presence of free hydroxyl groups made recovery of the product difficult due to its affinity with molybdenum-containing by-products of the reaction.

However for this specific transformation, a 1,2-reduction of a conjugated oxime, only molybdenum boride reagents, presumed to be the reactive intermediate in these reactions, have been shown to be effective for this transformation.

**Amino-carbasugars from epoxide 90**

Another route that could stem from aldehyde 86, the dearomatized carbocyclic core, was designed that involved a selective double reduction of the keto-aldehyde and selective 1,2 reduction of the enone to give a compound containing an allylic alcohol 87 that could be epoxidised with \( m \)-CPBA. The epoxide 99 could be opened subsequently with sodium azide and the azide 100 reduced to give an amino carbasugar 101.

**Scheme 147 – diastereoselective Luche reduction**

**Figure 37 – crystal structures of 87a and 87b**
Reduction to give the allylic alcohol was attempted under Luche conditions with 1 equivalent of sodium borohydride in the presence of cerium (III) chloride heptahydrate in methanol.\textsuperscript{155} The reduction was complete in 30 min and gave allylic alcohol diastereoisomers \textit{87a} and \textit{87b} in a 5:1 ratio in an 80 % yield. Using two equivalents of sodium borohydride did not improve the selectivity of the reaction, again a 5:1 ratio of diastereoisomers was isolated and the yield was slightly lower at 76 %. Reducing the temperature to -78 °C and using ethanol (as solvent as it had been successful in other selective reductions in the project), improved the selectivity to 10:1 in favour of diastereoisomer \textit{87a} and gave an 80 % yield.

Diastereoisomers \textit{87a} and \textit{87b} were crystallised from ethyl acetate, and their structures were confirmed by X-ray crystallography (Figure 37).

It is worth noting that on one occasion the reaction was quenched with saturated ammonium chloride solution at -78 °C and aldehyde \textit{102} was isolated in addition to allylic alcohol \textit{87a}. This result is in agreement with the work of Luche\textsuperscript{156} as in the presence of cerium (III) chloride heptahydrate ketones are reduced in the presence of aldehydes.

![Scheme 148 – Isolation of aldehyde 102](image-url)
**Electrophilic epoxidation**

Epoxidation of allylic alcohol 87a was attempted in methanol, using 1 equivalent of \( m \)-CPBA, but unfortunately these conditions did not give the desired product. Proton NMR spectroscopic analysis of the crude mixture showed that the major component was enone 52 and therefore preferential allylic oxidation had occurred.

![Scheme 149 – Allylic oxidation of 87 by \( m \)-CPBA in MeOH](image)

The reaction was repeated using \( CH_2Cl_2 \) as a solvent. The allylic alcohol 87a did not dissolve in \( CH_2Cl_2 \), but the suspension was stirred rapidly at room temperature and on addition of \( m \)-CPBA the reaction began to clear, indicating consumption of starting material. The reaction did not go to completion and only a 50 % yield of epoxide 99 was isolated. As with the epoxidation of dearomatised enol ether containing compound 9, purified \( m \)-CPBA was used for this transformation.

![Scheme 150 – Diastereoselective epoxidation of 99](image)

Adding two equivalents of \( m \)-CPBA gave reactions that went to completion within 30 minutes. The epoxide was obtained in an 80 % yield. Only one diastereoisomer of epoxide was ever observed within the limits of detection by Proton NMR spectroscopic analysis. Epoxide 99 was crystallised from ethyl acetate, and its structure was confirmed by X-ray crystallography (Figure 38). This selectivity could be explained by both the allylic and homoallylic alcohols directing epoxidation to the same face of the double bond (Figure 39).
Opening epoxide 99 with sodium azide

With epoxide 99 in hand, the next step of the synthesis was to incorporate nitrogen into the molecule by opening the epoxide with sodium azide.

Epoxide 99 opened smoothly under mildly acidic conditions: heating under reflux in methanol/aqueous ammonium chloride in the presence of 10 equivalents of sodium azide gave azide 100 in a 62% yield. The azide could be isolated by simple filtration due to its insolubility in CH₂Cl₂. Washing first with CH₂Cl₂ removed any impurities and then a wash with 1:1 CH₂Cl₂:EtOAc gave only azide 100 without the need for chromatography.

Scheme 151 – Proposed opening of epoxide 103 with sodium azide
Ytterbium triflate-mediated epoxide opening

Delgado developed an Ytterbium triflate chelation controlled procedure which allows the alternative opening of the epoxide to occur. Delgado states that hydroxyl groups α to the epoxide aid coordination of Yb$^{3+}$ to the epoxide and assist in the ring opening (Scheme 154).

Epoxide 99 possesses two hydroxyl groups that should cooperatively aid ring opening. Although this system was not tested, two examples of an α-hydroxyl group and an α-hydroxy methane group are both shown to direct ring opening to the same position. These two groups also directed epoxidation.

Epoxide 99 was opened under the conditions of Delgado on a 60 mg scale, using 0.5 equivalents of ytterbium triflate to give a modest 27 % yield of azide 102 in addition to a 36 % yield of azide 100 as the major component. In order to improve reproducibility, it was necessary to modify the conditions. On a 150 mg scale reaction 1.0 equivalent of ytterbium triflate gave epoxide 102 in a 22 % yield after flash chromatography: a small amount of azide 100 was also isolated however it was inseparable from triethylamine. As ytterbium is paramagnetic it makes proton NMR spectroscopic analysis of the crude mixture (isolated after removal of toluene and triethylamine) difficult, so the exact ratio of stereoisomers was not obtained.

Achieving this moderate yield of azide 102 was very rewarding. It was surprising that formation of azide 102 is favoured at all, as a ring flip is necessary in order to obtain an trans di-axial product. A large energy barrier must be overcome in order to cause this ring flip as the isopropyl group would be
pushed axial, in addition to two axial hydroxyl groups. This structure is a high-energy intermediate, although it could be stabilised by chelation (Scheme 155). The resultant tranz di-axial product would have six axial substituents! Thus this conformation is short-lived and the conformation would quickly change to a more equatorial substituted conformation.

Scheme 155 – Ytterbium triflate chelation controlled opening of epoxide 99

The structure of azide 103 was confirmed by NOESY spectroscopy.

Figure 40 – Through-space couplings in 102

Azide Reduction

Scheme 156 – Proposed reduction of azide 100

Azide 100 proved difficult to reduce under standard reduction conditions in methanol under a hydrogen atmosphere with catalytic palladium on carbon. The reaction appeared to be complete within 30 min by TLC analysis, but proton NMR spectroscopic analysis of the crude mixture showed a complex mixture of products. Fortunately an alternative hydrogenation using an H-cube was available. The
manual suggested that very rapid reductions can be tempered by using ethyl acetate as solvent. Hydrogen is less soluble in ethyl acetate than in methanol. The reduction appeared cleaner by TLC analysis when the H-cube was used. A 25 % methanol in ethyl acetate solution was passed through using a small-scale palladium on carbon cartridge, however NMR analysis of the crude mixture was not simple as it contained a mixture of compounds. No starting material was present and there appeared to be two major components. Analysis of the mass spectrum showed only one compound was present that corresponded to the reduced amino carbasugar analogue. The NMR sample was recombined with the crude material and the solvent was removed. This material was re-analysed and the proportions of the two main compounds had changed, but they looked to have done so proportionally.
Figure 41 – Equilibration after reduction of azide 100 to amino-carbasugar analogue 101

The sample had simply been poured back into the round bottomed flask, the NMR tube rinsed with additional methanol and then all solvent removed under reduced pressure. So this was repeated and the sample was checked again with proton NMR spectroscopy, and the proportions of the components had changed so that the peaks that were previously the major components were now the minor components and vice versa. The crude mixtures were redissolved in solvent methanol and removed until only one compound appeared by proton NMR spectroscopy. It took on average 5 to 6 cycles before only one compound was visible. By analysing the mass spectra only the amino carbasugar was
present. Clearly one of the compounds was unstable when warmed under reduced pressure and decomposed; it was most likely a partially reduced azide that decomposes to the amino carbasugar.

On the third attempt at reducing the azide under the same conditions, the reduction was much cleaner but proton NMR spectroscopic analysis of the crude mixture showed it still contained two compounds. Similarly after five cycles of redissolving in methanol followed by removal of this solvent, NMR analysis of the residue revealed only one compound, the amino-carbasugar **101**.

![Scheme 157 – Reduction of azide 100 to amino-carbasugar analogue 101](image1)

Reduction of the regioisomeric azide **102** also proved troublesome. Reductions under the previously successful conditions were unsuccessful as when the azide was passed through the H-cube no products were detected by TLC or proton NMR spectroscopic analysis. This was very disconcerting as the reduction conditions had been difficult with the previous example. So a Staudinger reduction was used as palladium on charcoal had been unsuccessful with azide **100**. Unfortunately TLC analysis of this reaction was very difficult. The azide stained deep blue with PMA and as the reaction progressed, this product diminished but no new spot was detected with a variety of stains.

Reducing the azide with palladium on carbon in ethyl acetate under a hydrogen atmosphere was attempted. After 24 hours no reaction was observed in ethyl acetate by TLC or proton NMR spectroscopy. However changing the solvent to methanol increased the reactivity and starting material had been consumed within 30 minutes. Filtering the reaction mixture with CH$_2$Cl$_2$ showed no products by proton NMR spectroscopy or TLC analysis. The palladium on charcoal was removed by filtering
through a small amount of Celite® on a cotton wool pad. When ethyl acetate:methanol (1:1) was used to flush the filtrate, no products were observed by TLC analysis, but the expected product was observed by proton NMR spectroscopic analysis. Clearly isolation of amino carbasugar 103 was made difficult by solubility issues, when azide 102 was reduced in the H-cube the product amino carbasugar may have dropped out of solution and adhered to the tubing of the H-cube, thus preventing its isolation. But the amino carbasugar could not be detected by staining even by using potassium permanganate. The azide was reduced in a 66 % yield by using palladium on carbon in methanol, and on consumption of starting material filtered immediately through a small Celite® plug on a sintered glass funnel and washed with methanol.

Scheme 159– reduction of azide 102 to amino-carbasugar analogue 103
Other attempts to introduce nitrogen

The following provides a summary of methods used to introduce nitrogen to the dearomatised carbocyclic core before oxazoline removal.

The Overman rearrangement

During the course of the investigation into the selective reduction of iminium salt 85, a reasonable amount of over-reduced oxazolidine-containing diol 17 was isolated. Could over-reduced 17 oxazolidine be selectively reacted with trichloroacetonitrile (Scheme 160), on the less hindered allylic alcohol? Formation of a trichloroacetimidate 104 in this position would be a viable precursor for an Overman rearrangement, which is a robust way of selectively introducing nitrogen into a molecule.\(^\text{158}\)

![Scheme 160 – Proposed selective imidate formation and Overman rearrangement](image)

Oxazolidine 17 was reacted with trichloroacetonitrile in the presence of DBU in CH\(_2\)Cl\(_2\) at 0 °C and the reaction was selective for the allylic alcohol. Reaction with the C3 hydroxyl group is disfavoured due to steric hindrance from the equatorial isopropyl group, the allylic C4 hydroxyl group is more nucleophilic and less sterically hindered. The reaction appears selective for C4 as the double doublet corresponding to the 4′ CH had shifted from 3.58 ppm to 5.26 ppm; all signals integrated and corresponded accordingly. The IR spectrum also showed an imidate C=N at 1655 cm\(^{-1}\).
The Overman rearrangement of \(104\) was attempted in a microwave reactor with catalytic potassium carbonate in xylene,\(^{159}\) but no rearrangement was achieved. \((\text{MeCN})_2\text{PdCl}_2\) was used to catalyse the rearrangement\(^{160}\) at room temperature and at 40 °C but with no success. In order for the rearrangement to proceed a ring flip is required to position the trichloroacetimidate in a position of more favourable orbital overlap (Scheme 161). This ring flip is made difficult due to the proximity of the large oxazolidine and isopropyl group and the ring flip involves these groups moving past each other. However the ring flip would move the equatorial isopropyl group to an axial position. A bulky group in this position would then have a sterically unfavourable interaction with the trichloroacetimidate that reduces favourable orbital overlap.
**Amino hydroxylation**

The Sharpless asymmetric aminohydroxylation (AA) is a progression of the asymmetric dihydroxylation (AD), where an $N$-halo amine derivative is used as both the nitrogen source and stoichiometric oxidant. A catalytic amount of osmium tetroxide is used in the presence of exactly one equivalent of a hydroxide base. Solvents used for this reaction vary; often a 1:1 mixture of tertiary butyl alcohol or isopropyl alcohol, with water is used. The reaction is very sensitive to concentration and substrate slight changes can alter the regioselectivity of aminohydroxylation or can favour dihydroxylation in some cases.

The methyl enol ether in dearomatised oxazoline 9 had already shown good reactivity towards conventional dihydroxylation methods. Sudalai had demonstrated that silyl enol ethers could be amino hydroxylated with excellent enantioselectivities but in moderate yield.\textsuperscript{161}

Aminohydroxylation was therefore attempted on dearomatised enol ether containing compound 9 Under Sharpless conditions using quinuclidine as a ligand (instead of a DHQ derivative) and with $N$-}

\textsuperscript{150}
bromo acetamide as oxidant and nitrogen source. Incorporation of this unit would lead to an $N$-acyl aminocarbasugar analogue, which although protected would be acceptable as amino sugars are often isolated as $N$-acyl derivitives. However $N$-bromo acetamide is also a brominating agent and compound 67 was isolated rather than the aminohydroxylation product.

![Scheme 164](#)

Recently Luxenburger published an improved procedure for the aminohydroxylation where 4-chlorobenzyloxy carbamates are used as the nitrogen source and oxidant. The regioselectivity problems commonly associated with the aminohydroxylation remain, although, importantly the conditions are halide and base free!

![Scheme 165](#)

The oxidant was simply synthesised from commercially available reagents and amino hydroxylation of compound 9 under these simplified conditions gave $\alpha$-hydroxy ketone in a 70 % yield. The selectivity was different from that reported by Sudalai. The nitrogen was delivered to the C4 position and subsequently eliminated. This is probably due to steric rather than electrostatic interactions.
An unfavourable interaction between the isopropyl group and the carboxybenzyl group would occur when the nitrogen is delivered to the C4 Position.
Future work

Generate organolithiums using LiDBB

Broadening the number of nucleophiles for the nucleophilic dearomatisation is clearly the main area for expansion of this methodology. Currently only secondary organolithiums have been shown to dearomatise 2-aryl-4,5-anti-diphenyloxazolines in THF/DMPU at -78 °C.

Meyers dearomatised naphthyl rings predominantly with Grignard reagents. Certain lithium amides and silyl lithiums also dearomatised the naphthyl nucleus but the scope of these reagents was not as broad.

Meyers successfully used lithium 4',4'-ditert-butylbiphenylide (LiDBB)\textsuperscript{164} (Scheme 166) to form particularly hard-to-access organolithiums,\textsuperscript{165} where generation of the nucleophile with well established procedures (i.e., halogen-metal exchange, stannane-lithium exchange) failed. Meyers found reagents made in this way to be "uniformly superior to all other methods thus far employed". Meyers found that the organolithium formed using LiDBB and \(n\)-butyl bromide proceeded to dearomatise 2-aryl oxazolines almost instantly at 0 °C with stereoselectivity comparable to reactions with conventional reagents carried out at -78 °C, but which took much longer (Scheme 167).

\[
\begin{align*}
\text{R}^+X & \xrightarrow{\text{LiDBB}^\ominus} \text{R}^-X & & \text{Li}^- + \text{DBB}^\ominus & \xrightarrow{\text{LiDBB}^\ominus} \text{R}^-\text{Li} & & \text{Li}^- + 2 \text{DBB}
\end{align*}
\]

Scheme 166 – LiDBB mediated organolithium formation and the structure of LiDBB
Organolithium reagents prepared from LiDBB were capable of lithium-halogen exchange with alkyl chlorides. This reaction is usually sluggish using traditional methods. They display remarkable reactivity towards dearomatisation of naphthalene systems. This is most likely as the organolithiums generated in this manner are deaggregated as an equivalent of a lithium halide salt is also created as part of the reaction. The presence of extra lithium cations reduces the aggregation of the organo lithium reagents generated (Scheme 166). The dearomatisation used in this body of work is dependent on the use of DMPU as co-solvent to deaggregate the organolithium nucleophile. Using organolithiums generated with LiDBB in conjunction with our existing conditions may allow new more synthetically interesting/useful nucleophiles to be generated. For instance primary alkyl, aryl and heterocyclic nucleophiles would vastly expand this methodology.

**Nucleophilic addition in the presence of lithium chloride**

We observed that bottles of isopropyllithium became ‘active’ on storage and the reagent from these bottles was able to dearomatise aryl rings when the same reagent from other bottles was not. It was found that bottles of organolithium gradually accumulated lithium alkoxides. Bottles containing lithium alkoxides were not always active and many experiments carried out to determine whether adding or
generating alkoxides in a reaction would increase the nucleophile’s propensity to dearomatisate aryl rings by nucleophilic addition.

With hindsight it is not necessarily the presence of alkoxides but rather the presence of the lithium counter ion that could be causing the difference in reactivity. Over time the presence of an excess of lithium cations changes the aggregation of the organolithium, the need for the organolithium to become active could be explained by a reorganisation in the presence of lithium cations. This could also explain why trying to generate these alkoxides \textit{in situ} had no effect on reactivity. As mentioned Myers was able to show that non-carbon nucleophiles, lithium amides and silyl lithiums also dearomatised naphthyl rings

Knochel has shown that the presence of anhydrous lithium chloride accelerates the rate at which magnesium\textsuperscript{166, 167} and zinc\textsuperscript{168, 169} insert into carbon halogen bonds to form highly reactive deaggregated Grignards and organozinc reagents. These reagents are much simpler to prepare and can be stored at room temperature. Grignards generated using Knochel’s procedure could possibly offer an alternative to LiDBB and for the first time allow organomagnesium reagents to dearomatise an uncoordinated phenyl ring.

The effect of lithium chloride on organolithium aggregation could also be investigated, by carrying out the dearomatising reaction in saturated solutions of lithium chloride (ca. 0.5 M) in THF\textsuperscript{170}.

\textbf{Protecting groups}

Two amino carbasugar sugars were synthesised using a protecting group-free synthetic route and the lack of protection has caused difficulties. The most prominent of these was observed in the reductive amination of oxime \textsuperscript{96} where isolation of allylic amine \textsuperscript{94} was very difficult. Protecting specifically for this step is justifiable as it is at a late stage in the synthesis and would greatly enhance the likelihood of completing the synthesis of an amino-carbasugar analogue. The presence of protecting groups may favour incorporation into an oligosaccharide.
Summary of significant results

One-pot synthesis of 2-Aryl-4,5-anti-diphenyloxazolines

A one-pot synthesis of 2-aryl-4,5-anti-diphenyloxazolines was developed. An amino alcohol was coupled with a benzoyl chloride in the presence of excess triethylamine to produce a β-hydroxyamide. Direct treatment of the β-hydroxyamide in situ with methanesulfonyl chloride formed the oxazoline in good yields. This procedure tolerated a variety of functional groups, and was scalable, regularly being carried out in the laboratory on a 10 g scale, and it was carried out twice in an industrial reactor on a 30 and 40 g scale.
Lithiation of fluorinated 2-aryloxazolines

To summarise the oxazoline-promoted diastereoselective nucleophilic dearomatisation of fluorinated aryl rings gives results dependent on substitution pattern.

1) **Dearomatisation**: A fluoro substituent in the 4-position promotes dearomatisation but only when the reaction is quenched with a proton source.

![Dearomatisation Diagram]

2) **Lithiation**: A fluoro substituent in the 3-position cooperatively activates the 2-position towards ortho-lithiation, and 2-alkylated products can be obtained. The acidifying effect of the two directing groups is evidently greater than the dearomatisation-promoting power of the oxazoline.

![Lithiation Diagram]

3) **Substitution**: With a fluoro-substituent in the 2-position, dearomatisation by attack at the 2- or 6-position is finely balanced: in general the 2-fluoroaryl oxazoline leads to $S_{N}Ar$ substitution of fluoride by isopropyllithium, with the product of a capricious dearomatisation (by attack at the 6-position of the ring) observed only when the reaction was performed on a small scale using an ‘aged’ bottle of isopropyllithium and quenched with trifluoroacetic acid.

![Substitution Diagram]
Successful route to amino-carbasugar analogues

The dearomatising nucleophilic addition could be carried out on 5 g batches of 4-methoxyphenyl-2-aryl-4,5-anti-diphenyloxazoline 8, to give dearomatised compound 9. The enol ether in the dearomatised carbocyclic core of 9 was then selectively dihydroxylated using RD conditions developed by Warren.\textsuperscript{111}

Removal of the oxazoline moiety from 16 was achieved through an alkylation, reduction and hydrolysis sequence. Conditions developed by Ward were used whereby reduction with sodium borohydride\textsuperscript{125} was selective, leaving the enone in 16 untouched. Following alkylation and reduction, oxazolidine 85 could be isolated in a quantitative yield. Oxazolidine 85 was hydrolysed to aldehyde 86 in good yield using oxalic acid in THF and water. The deprotection could be telescoped avoiding purification of intermediates, without significant loss in yield.
Aldehyde 52 was used as a carbocyclic skeleton from which two amino carbasugars were synthesised. Luche reduction in ethanol at -78 °C selectively reduced both the enone-carbonyl and the aldehyde in 86 with 10:1 dr. Allylic alcohol-containing carbocycle 90 was epoxidised with m-CPBA to give epoxide 99. Epoxide 99 could be opened under different conditions to give two different azides: acidic polar protic conditions gave azide 100, whereas basic aprotic non-polar conditions in the presence of a Lewis acid gave azide 102. Both azides were hydrogenated to give amino carbasugar analogues 101 and 103. The amino carbasugar analogues were synthesised without using protecting groups.

The enone in aldehyde 86 was preserved so that a reductive amination to introduce nitrogen could occur, following removal of the oxazoline. The preserved enone was not utilised in the synthesis of the amino carbasugar analogues, however whilst developing a route involving the proposed reductive amination a selective reduction was developed that used sodium cyanoborohydride in the presence of acetic acid, and reduced the aldehyde in the presence of the enone. Subsequent functionalisation of enone 52 proved difficult. This poor reactivity is attributed to steric hindrance from the methyl and hydroxymethyl groups blocking the approach of reagents.
Unsuccessful route to amino-carbasugar analogues

The successful route previously described was developed as a result of a route followed where the oxazoline was partially hydrolysed following dearomatisation and enol ether oxidation. This route also involved the incorporation of an $N$-acyl protecting group after hydrolysis of the oxazoline to avoid rearrangement to the isomeric amide. The route was ultimately not pursued as the ester in compound 74 was prone to cleavage under the conditions of reductive amination and unfortunately isolation of the highly soluble acid (the product of cleavage) was not possible.
Chapter 4 - The Experimental Section

General Information

NMR spectra were recorded on a Bruker Ultrashield 400 or 500 spectrometer. The chemical shifts ($\delta$) are reported in ppm downfield of tetramethylsilane and coupling constants ($J$) reported in hertz and rounded to 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), septet (sept), octet (oct), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standards when assigning NMR spectra ($\delta$H: CDCl$_3$ 7.27 ppm; $\delta$C: CDCl$_3$ 77.0 ppm DMSO-$d_6$ 2.50 ppm; $\delta$C: DMSO-$d_6$ 39.4 ppm). $J$ values were calculated using ACD Labs 1D NMR processor 11.01 software.

Low and high resolution mass spectra were recorded by staff at the University of Manchester. EI and CI spectra were recorded on a Micromass Trio 2000; ES and APCI spectra were recorded on a Micromass Platform II; high resolution mass spectra (HRMS, EI and ES) were recorded on a Thermo Finnigan MAT95XP mass spectrometer. Infrared spectra were recorded on a Perkin Elmer Spectrum RX I FTIR spectrometer as a film on a sodium chloride plate. Only absorption maxima of interest are reported and are quoted as wavenumbers (cm$^{-1}$). Melting points (mp) were determined on a Gallenkamp apparatus and are uncorrected. Thin layer chromatography (TLC) was performed using commercially available precoated plates (Macherey-Nagel POLYGRAM Sil G/UV$_{254}$) and visualised with UV light at 254 nm. Flash chromatography was carried out using Fluorochem Davisil 40-63u 60 Å.

All reactions were conducted under an atmosphere of dry nitrogen in flame-dried glassware. Tetrahydrofuran (THF) was distilled under nitrogen from sodium using benzophenone as an indicator. Dichloromethane (CH$_2$Cl$_2$) and toluene & cumene were obtained by distillation from calcium hydride under nitrogen. Petrol refers to the fraction of light petroleum ether boiling between 40-65 °C. Anhydrous dimethylhexahydro-2-pyrimidinone (DMPU) was used as supplied by Aldrich/Fluka. All other solvents and commercially obtained reagents were used as received or purified using standard procedures.
• Isopropyl lithium was obtained as a solution in pentane. We have observed the concentration of isopropyl lithium solution to change once opened (~5 days). Unless a new bottle was opened and used, isopropylithium solution was titrated prior to use against a cooled (−40 °C) 1 M solution of benzyl benzamide in dry THF, according to the method of Chong:


• m-CPBA (meta-Chloroperoxybenzoic acid) was purified according to the procedure of Aggarwal:


• Oxazolines were made according to our ‘one-pot’ procedure:


**Atom labelling** – All compounds characterised have two general structures
Synthesis of (4R,5R)-4,5-dihydro-2-(phenyl)-4,5-diphenyloxazole: [6]

Benzoyl chloride (0.59 mL, 1.1 equiv) was added drop-wise over a period of 5 minutes to a stirred solution of the amine (1R,2S)-2-amino-1,2-diphenylethanol (1.00 g, 4.69 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (70.00 mL) and Et$_3$N (2.60 mL, 4 equiv) at 0 °C under a nitrogen atmosphere. The solution was stirred for 16 hours. The white precipitate was cooled to 0 °C and methane sulfonyl chloride (0.54 mL, 1.5 eq) was added drop-wise over 5 minutes. The solution cleared as the oxazoline formed. The reaction was monitored by TLC and quenched with aqueous NH$_4$Cl (40 mL) after all the amide had been consumed. The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (40 mL). The combined organic phases were washed with aqueous NaHCO$_3$ (20 mL) and then brine (20 mL). The solution was dried with MgSO$_4$ and the solvent was partly removed under reduced pressure, leaving approximately 5 mL solvent to load the crude reaction mixture onto silica gel. Flash chromatography (EtOAc in petroleum ether 10 %) gave the title compound (0.97g, 71 %) as a colourless solid.

$[\alpha]_D^{22}$: $-17.6$ (c. 1.0, CHCl$_3$); $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ 8.07 (d, $J$ 8 Hz, 2H, C6', C2', H), 7.50-7.10 (m, 13H, Ar), 5.35 (d, $J$ 8 Hz, 1H, C5 H), 5.17 (d, $J$ 8 Hz, 1H, C4 H); $^{13}$C-NMR (CDCl$_3$, 75.5 MHz) $\delta$ 164.1, 142.0, 140.5, 131.8, 2 X 128.9, 128.9, 128.7, 2 X 128.5, 2 X 128.4, 127.8, 127.5, 2 X 126.8, 2 X 125.7, 89.0, 78.9.

Synthesis of (4R,5R)-4,5-dihydro-2-(3-methoxyphenyl)-4,5-diphenyloxazole: [44]

3-Methoxy benzoyl chloride (0.70 mL, 1.1 equiv) was added drop-wise over a period of 5 minutes to a stirred solution of (1R,2S)-2-amino-1,2-diphenylethanol (1.00 g, 4.69 mmol, 1.0 equiv) in CH₂Cl₂ (70.00 mL) and Et₃N (2.60 mL, 4.0 equiv) at 0 °C under a nitrogen atmosphere. The solution was stirred for 16 hours. The white precipitate was cooled to 0 °C and methane sulfonyl chloride (0.54 mL, 1.5 eq) was added drop-wise over 5 minutes. The solution cleared as the oxazoline formed. The reaction was monitored by TLC and quenched with saturated aqueous NH₄Cl (40 mL) once all the amide had been consumed. The solution was extracted with CH₂Cl₂ (40 mL). The combined organic phases were washed with aqueous NaHCO₃ (20 mL) and then brine (20 mL). The solution was dried with MgSO₄, the solvent was partly removed under reduced pressure, leaving approximately 5 mL solvent to load the crude reaction mixture onto silica gel. Flash chromatography (EtOAc in petroleum ether 20 %) gave the title compound (1.14 g, 88 %) as a colourless solid.

Rf: 0.14 (10 %, Petrol:EtOAc); Mpt: 92-94 °C; [α]²²D: +4 (c. 1.0, CHCl₃); MS m/z (ES+) 352 (100 %, (M+Na)⁺); HRMS: found 330.1491, (M+H)⁺, C₂₂H₂₀N₂O₂ requires 330.1489; ν max (film)/cm⁻¹ 3030 (C-H), 1650 (C=N); ¹H-NMR (CDCl₃, 400 MHz) δ 7.65 (d, J 8 Hz, 1H, CH C4”), 7.60 (s, 1H, CH C2”), 7.39-7.18 (m, 11H, Ar), 7.02 (dd, J 8 ,4 Hz, 1H, CH C6”), 5.34 (d, J 8 Hz, 1H, CH C5), 5.15 (d, J 8 Hz, 1H, CH C4), 3.80 (s, J 8 Hz, 3H, OMe); ¹³C-NMR (CDCl₃, 100 MHz) δ 164.0 (C=N), 159.6 (C3’), 141.9 (Ar), 140.5 (Ar), 129.6 (Ar), 128.9 (Ar), 2 X 128.9 (Ar), 128.7 (Ar), 127.5 (Ar), 127.8 (Ar), 2 X 126.8 (Ar), 2 X 125.7 (Ar), 121.1 (C2’), 118.6 (C6’), 112.8 (C4’), 89.1 (C5), 79.1 (C4 ), 55.5 (OMe).
Synthesis of (4R,5R)-4,5-dihydro-2-(4-methoxyphenyl)-4,5-diphenyloxazole: [8]

4-Methoxy benzoyl chloride (7.15 mL, 1.1 equiv) was added drop-wise over a period of 20 minutes to a stirred solution of (1R,2S)-2-amino-1,2-diphenylethanol (10.00 g, 46.89 mmol, 1.0 equiv) in CH₂Cl₂ (1.00 L) and Et₃N (26.00 mL, 4.0 equiv) at 0 °C under a nitrogen atmosphere. A precipitate formed, the reaction was warmed to room temperature, stirring was continued for 5 hours until the starting material had been completely consumed. The colourless emulsion was cooled to 0 °C and methane sulfonyl chloride (5.40 mL, 1.5 eq) was added drop-wise over 40 minutes. The solution cleared as the oxazoline formed. The reaction was monitored by TLC. Once all amide had been consumed the reaction was quenched with aqueous NH₄Cl (150 mL). The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (200 mL). The combined organic phases were washed with aqueous NaHCO₃ (200 mL) and then brine (150 mL). The solution was dried with MgSO₄ the solvent was partly removed under reduced pressure, leaving approximately 5 mL solvent to load the crude reaction mixture onto silica gel. Flash chromatography (EtOAc in petroleum ether 10 %) gave compound 8 (13.71 g, 89 %) as a colourless solid.

Rᶠ: 0.39 (20 %, EtOAc in Petroleum ether); Mpt: 89-91 °C; [α]⁰²⁰⁺ : -36 (c. 1.0, CHCl₃); MS m/z (ES⁺) 330.4 (100 %, (M+H)⁺); HRMS: found 330.1485, (M+H)⁺; C₂₂H₂₀NO₂ requires 330.1489;

Microanalysis found: C (79.88 %), H (5.89 %), N (4.25 %), C₂₂H₁₉NO₂ requires: C (80.22 %), H (5.81 %), N (3.90 %); ν max(film)/cm⁻¹ 3030 (C-H), 1647 (C=N); ¹H-NMR (CDCl₃, 400 MHz) δ 7.99 (d, J 9 Hz, 2H, CH C₂', C₆'), 7.19-7.34 (m, 10H, Ar), 6.89 (d, J 9 Hz, 2H, CH C₃', C₅'), 5.29 (d, J 7 Hz, 1H, CH 5), 5.11 (d, J 7 Hz, 1H, CH 4), 3.78 (s, 3H, OMe); ¹³C-NMR (CDCl₃, 100 MHz) δ 162.8 (C=N),
4-Fluorobenzoyl chloride (0.30 mL, 1.1 equiv) was added drop-wise over a period of 5 minutes to a stirred solution of (1R,2S)-2-amino-1,2-diphenylethanol (0.50 g, 2.34 mmol, 1.0 equiv) in CH₂Cl₂ (40.00 mL) and Et₃N (1.28 mL 4.0 equiv) at 0 °C. The solution was allowed to reach room temperature and stirred for 16 hours. The resultant white emulsion was cooled to 0 °C and methane sulfonyl chloride (0.26 mL, 1.5 equiv) was added drop-wise over 5 minutes. The solution cleared as the oxazoline formed. The reaction was monitored by TLC and quenched with saturated aqueous NH₄Cl (20 mL) once all the amide had been consumed. The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (20 mL). The organic layers were washed with saturated aqueous NaHCO₃ (10 mL), brine (10 mL) and, the solution was dried with MgSO₄. The solvent was partly removed under reduced pressure, leaving approximately 5 mL solvent to load the crude reaction mixture onto a silica gel column. Flash chromatography (5 % EtOAC in petroleum ether) gave compound 20 (0.66 g, 90 %) as a clear oil that solidified on standing.

Rf: 0.30 (10 % EtOAc in petroleum ether);  Mpt: 89-92 °C; [α]22D: +2 (c. 1.0, CHCl₃);  MS m/z (ES+) 318.1 (100 %, (M+H)+); HRMS: found 318.1294, (M+H)+, C₂₁H₁₇FNO requires 318.1289;

νmax (film)/cm⁻¹ 1651 (C=N), 3030 (C-H); ¹H-NMR (CDCl₃, 500 MHz) δ 8.06 (dd, J=9, J=5 Hz, 2H, CH 6·&2'), 7.40-7.15 (m, 10H, Ar), 7.08 (t, J=8.5 Hz, 2H, CH 3·&5'), 5.34 (d, J=7.5 Hz, 1H, CH 5), 5.15 (d, J=7.5 Hz, 1H, CH 4); ¹³C-NMR (CDCl₃, 125 MHz) δ 163.9 (d, J= 250 Hz), 162.1, 140.8, 139.3,
129.9 (d, $J^F$ 8 Hz), 2 x 127.9 (d, $J^F$ 7 Hz), 127.5, 126.8, 2 x 125.7, 2 x 124.7, 122.7, 2 x 114.6 (d, $J^F$ 21 Hz), 114.5, 88.2, 77.9.

**Synthesis of (4R,5R)-1-(2-Fluorophenyl)-4,5-dihydro-4,5-diphenyloxazole: [40]**

2-Fluorobenzoyl chloride (0.61 mL, 1.1 equiv) was added drop-wise over a period of 5 minutes to a stirred solution of (1R,2S)-2-amino-1,2-diphenylethanol (1.00 g, 4.69 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (5 mL/mmol) and Et$_3$N (2.60 mL, 4 equiv). After addition the solution was allowed to reach room temperature and stirred for 16 hours. The white precipitate was cooled to 0 °C and methane sulfonyl chloride (0.52 mL, 1.5 equiv) was added drop-wise over 5 minutes. The solution cleared as the oxazoline was formed. The reaction was monitored by TLC and quenched with saturated aqueous NH$_4$Cl (40 mL) once all the amide had been consumed. The phases were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (40 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ (20 mL), brine (20 mL) and was dried with MgSO$_4$. The solvent was partly removed under reduced pressure, leaving approximately 5 mL solvent to load the crude reaction mixture onto silica gel. Purification with flash chromatography (10 % EtOAc in petroleum ether) gave compound 8 (1.10 g, 76 %) as a clear oil that solidified on standing.

**R$_f$:** 0.23 (25 % EtOAc petroleum ether); **Mpt:** 82-84 °C; **$[\alpha]_D^{22}$:** −3.6 (c. 1.0, CHCl$_3$); **MS m/z (ES+):** 318 (100 %, (M+H)$^+$); **HRMS:** found 318.1287, (M+H)$^+$, C$_{21}$H$_{17}$FNO requires 318.1289; **$V_{\text{max}}$(film)/cm$^{-1}$:** 1640 (C=N), 3030 (Ar C-H); **$^1$H-NMR (CDCl$_3$, 500 MHz) δ:** 7.44 (dt, $J 7.5, J^F$ 2 Hz, 1H, CH 6′), 7.48-7.10 (m, 1H), 7.36 (m, 12, Ar), 5.33 (d, $J$ 8 Hz, 1H, CH 5), 5.19 (d, $J$ 8 Hz, 1H, CH 4); **$^{13}$C-NMR (CDCl$_3$, 125 MHz) δ:** 160.4 (d, $J^F$ 258 Hz), 159.8, 147.7, 139.3, 132.2, 130.4, 127.9, 2 x 127.8, 127.5, 126.8, 2 x 125.7, 2 x 124.6, 123.1, 123.0, 115.8 (d, $J^F$ 21 Hz), 114.9, 87.5, 78.0.
Synthesis of (4R,5R)-1-(3-Fluoro-4-methoxyphenyl)-4,5-dihydro-4,5-diphenyloxazole:

3-Fluoro-4-methoxybenzoic acid (2.00 g, 11.76 mmol, 1.0 equiv) was stirred in thionyl chloride and CH\(_2\)Cl\(_2\) (1:1, 10.00 mL). Six drops of DMF were carefully added by syringe and the reaction was heated to 80 °C until IR analysis indicated complete consumption of the carboxylic acid. The solvent and excess thionyl chloride were removed under reduced pressure to afford the benzoyl chloride which was used without further purification.

(1R,2S)-2-Amino-1,2-diphenylethanol (1.00 g, 4.69 mmol, 1.0 equiv) and Et\(_3\)N (2.60 mL, 4 equiv) were stirred at 0 °C in CH\(_2\)Cl\(_2\) (100 mL). A solution of the crude benzoyl chloride (0.96 g, 1.1 equiv) in CH\(_2\)Cl\(_2\) (2.50 mL) was added to the reaction mixture. The reaction mixture was stirred at 0 °C for 1 hour after which the reaction was allowed warm to room temperature and then stirred until complete by TLC. The resultant white emulsion was re-cooled to 0 °C and methane sulfonyl chloride (0.54 mL, 1.5 equiv) was added drop-wise over 3 minutes. The solution cleared as the oxazoline formed. The reaction was monitored by TLC. Once all the amide had been consumed the reaction was quenched with saturated aqueous NH\(_4\)Cl (40 mL). The phases were separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (40 mL). The organic layers were washed with saturated aqueous NaHCO\(_3\) (20 mL) and then brine (20 mL). The organic layer was dried with MgSO\(_4\). The solvent was removed under reduced pressure and the product was purified by flash chromatography (50 % EtOAc in petroleum ether) to give the title compound 37 (1.44 g, 88 %) as a clear oil that crystallised on standing.
$R_f$: 0.30 (25 % EtOAc:petroleum ether); **Mpt**: 80-82 °C; \([\alpha]_D^{22}: -22\) (c. 1.0, CHCl$_3$); **MS m/z** (ES+) 348.0 (100 %, (M+H)$^+$); **HRMS**: found 348.1402, (M+H)$^+$, C$_{22}$H$_{19}$FNO$_2$ requires 348.1394; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1651 (C=N), 3030 (C-H); ¹H-NMR (CDCl$_3$, 500 MHz) δ 7.81 (dd, $J$ 8.5, 1.5 Hz, 1H, C6' H), 7.78 (dd, $J$ 9.5, 2.0 Hz, 1H,C2' H), 7.40-7.17 (m, 10H, Ar), 6.95 (dd, $J$ 8.5, $J^F$ 8.5 Hz, 1H, CH 5'), 5.32 (d, $J$ 8 Hz, 1H, CH 5), 5.12 (d, $J$ 8 Hz, 1H, CH 4), 3.88 (s, 3H, OMe); ¹³C-NMR δ 151.8, 150.8 (d, $J^F$ 247 Hz), 149.6, (d, $J^F$ 11 Hz), 139.3, 127.9, 127.8, 127.5, 126.5, 125.7, 124.6, 124.2 (d, $J^F$ 7.5 Hz), 119.3, 119.2, 115.3 (d, $J^F$ 20 Hz), 111.6 (d, $J^F$ 2 Hz), 88.1, 77.9, 55.2.

**Synthesis of (4'R,5'R)-1-(3-Fluorophenyl)-4,5-dihydro-4,5-diphenyloxazole: [38]**

3-Fluorobenzoyl chloride (0.61 mL, 1.1 equiv) was added drop-wise over a period of 5 minutes to a stirred solution of (1R,2S)-2-amino-1,2-diphenylethanol (1.00 g, 4.69 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (5 cm$^3$/mmol) and Et$_3$N (2.60 mL, 4 equiv) at 0 °C under a nitrogen atmosphere. After addition the solution was allowed to reach room temperature and stirred for 16 hours. The resultant white emulsion was cooled to 0 °C and methane sulfonyl chloride (0.54 mL, 1.50 equiv) was added drop-wise over 5 minutes. The solution cleared as the oxazoline formed. The reaction was monitored by TLC and quenched with saturated aqueous NH$_4$Cl (40 mL) after all the amide had been consumed. The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (40 mL). The organic layers were washed with saturated aqueous NaHCO$_3$ (20 mL) and brine (20 mL). The solution was dried with MgSO$_4$ and the solvent was partly removed under reduced pressure, leaving approximately 5 mL solvent to load the crude reaction mixture onto silica gel. flash chromatography (10 % EtOAc in petroleum ether) gave compound 38 (1.17 g, 80 %) as a clear oil that crystallised on standing.
Rf: 0.34 (20% EtOAc in petroleum ether); Mpt: 60-62 °C; \([\alpha]_D^{22} = -2.8\) (c. 1.0, CHCl₃); MS m/z (ES⁺) 318.2 (100%, (M+H)⁺); HRMS: found 138.1282, (M+H)⁺, C₂₁H₁₇FNO requires 138.1289;  

V_{\text{max(film)}}/\text{cm}^{-1} 3030 (\text{C-H}), 1635 (\text{C=N}); ^1H-NMR (CDCl₃, 500 MHz) δ 7.86 (d, J 7.5 Hz, 1H, CH 6'), 7.76 (td, J 9.5, J^F 1.5 Hz, 1H, CH 5'), 7.41-7.12 (m, 12H, Ar), 5.35 (d, J 4.5 Hz, 1H, CH 5), 5.17 (d, J 4.5 Hz, 1H, CH 4);  

\(^{13}C\)-NMR (CDCl₃, 125 MHz) δ 162.6 (d, J^F 245 Hz), 163.1 (d, J^F 2 Hz), 161.7, 141.6, 140.1, 130.1 (d, J^F 8 Hz), 129.5 (d, J^F 8 Hz), 129.0, 128.9, 128.6, 127.9, 126.7, 125.7, 124.4 (d, J^F 3 Hz), 118.8 (d, J^F 20 Hz), 115.7 (d, J^F 24 Hz), 89.3, 78.8.

Synthesis of (4\text{R},5\text{R})-1-(2-Deutero-3-fluoro-4-methoxyphenyl)-4,5-dihydro-4,5-diphenyloxazole: [d-37]

\begin{center}
\[ \text{Oxazoline 37 (0.10 g, 0.28 mmol, 1.0 equiv) was dissolved in dry THF (3 mL), DMPU (0.34 mL, 10 equiv) was added and the solution was cooled to -78 °C. Isopropyl lithium solution (0.80 mL, 0.7 M in pentane, 2.0 equiv) was added and the reaction turned deep purple. After 2 minutes, deuterated methanol (0.5 mL) was added and the flask was allowed to warm to room temperature. The reaction mixture was partitioned between ether (10 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was then washed with water (2 X 5 mL) to remove DMPU, washed with brine (10 mL) and dried with MgSO₄. The solvent was removed under reduced pressure before purification. Flash chromatography (20% EtOAc in petroleum ether) gave the title compound \textit{d-37} (0.46 g, 45%) as a colourless clear oil.} \]
\end{center}

Rf: 0.3 (20% EtOAc in petroleum ether); \([\alpha]_D^{22} = -23.2\) (c. 1.0, CHCl₃); MS m/z (ES⁺) 349 (100%, (M+H)⁺); HRMS: found 349.1457, (M+H)⁺, C₂₂H₁₈DFNO₂ requires 349.1458; V_{\text{max(film)}}/\text{cm}^{-1} 2932 170
(C-H), 1649 (C=N); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.81 (d, \(J\) 9 Hz, 1H, C6' H), 7.35 - 7.15 (m, 10H, Ar), 6.95 (dd, \(J\) 8.5, \(J^F\) 8.5 Hz, 1H, C5' H), 5.31 (d, \(J\) 8 Hz, 1H, C5 H), 5.12 (d, \(J\) 8 Hz, 1H, C4 H), 3.86 (s, 3H, OMe); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) 163.0, 153.1, 151.7 (d, \(J^F\) 246 Hz), 150.6, 141.9, 140.3, 2 x 128.9, 128.5, 127.8, 2 x 126.8, 2 x 125.7, 125.4, 125.3, 120.4, 120.3, 120.2, 116.5, (d, \(J^F\) 25 Hz) 116.4, 112.7, 89.2, 78.9, 56.3.

**Synthesis of (4\(R,5R\))-1-(2-Deutero-3-Fluorophenyl)-4,5-dihydro-4,5-diphenyloxazole: [\(d\)-38]**

![Diagram](image)

Oxazoline 38 (0.10 g, 0.32 mmol, 1 equiv) was dissolved in THF (3.00 mL), DMPU (0.38 mL, 10 equiv) and the solution was cooled to -78 °C. Isopropyl lithium solution (0.90 mL, 0.7 M in pentane, 2.0 equiv) was added and the reaction turned deep green. After 2 minutes, deuterated methanol (0.50 mL) was added and the flask was warmed to room temperature. The reaction mixture was partitioned between ether (10 mL) and saturated aqueous NH\(_4\)Cl (10 mL). The organic layer was then washed with water (2 x 5 mL) to remove DMPU, washed with brine (10 mL) and dried with MgSO\(_4\). The solvent was removed under reduced pressure before purification with flash chromatography (20 % EtOAc in petroleum ether) to give compound \(d\)-38 (0.45 g, 44 %) as a colourless clear oil.

**R\(_f\):** 0.34 (20 %, EtOAc in petroleum ether); [\(\alpha\)]\(_D\)\(^{22}\) : -3.2 (c. 1.0, CHCl\(_3\)); **MS m/z** (ES+) 319 (80 %, (M+H)+), 341 (60 %, (M+Na)+); **HRMS:** found, M+H\(^+\) 319.1357, C\(_{21}\)H\(_{16}\)DFNO requires 319.1352; **\(V_{max}(\text{film})/\text{cm}^{-1}\)** 1649 (C=N); \(^1\)H-NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.84 (d, \(J\) 8 Hz, 1H, C6' H), 7.10-7.45 (m, 12H, Ar), 5.35 (d, \(J\) 8 Hz, 1H, C5 H), 5.16 (d, \(J\) 8 Hz, 1H, C4 H); \(^{13}\)C-NMR (CDCl\(_3\), 100 MHz) \(\delta\) 162.5 (d, \(J^F\) 245 Hz), 163.1 (d, \(J^F\) 2 Hz), 140.6, 139.1, 129.1, 129.1, 128.5, 128.4, 2 X 127.9, 127.8, 127.5, 126.9, 2 x 125.7, 2 x 124.7, 123.3, 117.7 (d, \(J^F\) 20 Hz), 114.6 (d, \(J^F\) 25 Hz), 88.2 77.9.
Synthesis of (4R,5R)-1-(3-Fluoro-4-methoxy-2-methylphenyl)-4,5-diphenyl-4,5-dihydrooxazole: [39]

Oxazoline 37 (100 mg, 0.28 mmol, 1.0 equiv) was dissolved THF (3.00 mL), DMPU (0.34 mL, 10.0 equiv) was added and the solution was cooled to -78 °C. Isopropyl lithium solution (0.80 mL, 0.7 M in pentane, 2.0 equiv) was added to the stirred solution and the reaction turned deep purple. After 2 minutes, methyl iodide was added (0.20 ml, 11.6 equiv) and the solution became orange/brown. The flask was allowed to warm to room temperature. The reaction mixture was partitioned between ether (10 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was then washed with water to remove DMPU (2 X 5 mL) and dried with MgSO₄. The solvent was removed under reduced pressure before purification with flash chromatography (10 % EtOAc in petroleum ether) to give compound 39 (153 mg, 14 %) as a colourless clear oil.

Rᶠ: 0.35 (20 %, EtOAc in petroleum ether); [a]ᶠ²⁰⁰: + 51.6 (c. 1.0, CHCl₃); MS m/z (ES+) 362 (100 %, (M+H)+), 384 (90 %, (M+Na)+); HRMS: found 362.1548, M+H⁺, C₂₃H₂₀FNO₂ requires 362.1551; νᶠ max (film)/cm⁻¹1642 (C=N); ¹H-NMR (CDCl₃, 400 MHz) δ 7.72 (dd, J₉, 2 Hz, 1H, C₆″ H), 7.39-7.19 (m, 10H, Ar), 6.78 (dd, J₉, J₈ 8.5 1H, C₅′ H), 5.24 (d, J₉ 7.5 Hz, 1H, C₅ H), 5.18 (d, J₉ 7.5 Hz, 1H, C₄ H), 3.86 (s, 3H, OMe), 2.58 (d, J₉ 3 Hz, 3H, C₂′ Me); ¹³C-NMR (CDCl₃, 100 MHz) δ 163.6, 151.0 (d, J₂⁺ 245 Hz), 149.9, 142.2, 140.6, 129.0, 2 x 128.9, 128.5, 127.8, 127.6, 126.6, 2 x 126.3 (d, J₂⁺ 11 Hz), 126.2, 2 x 125.8, 120.1 (d, J₂⁺ 4 Hz), 109.5 (d, J₂⁺ 2 Hz), 89.2, 88.1, 56.2, 12.6 (d, J₂⁺ 7.5 Hz).
Synthesis of \((4\,R,5\,R)-1-(4\text{-}Fluoro\text{-}2\text{-}isopropylphenyl)\text{-}4,5\text{-}diphenyl\text{-}4,5\text{-}dihydrooxazole:\) [36]

\[
\begin{align*}
\text{SeO}_2 \text{ (22.00 mg, 0.5 equiv) was added to undried bench CH}_2\text{Cl}_2 \text{ (2.00 mL) and a solution of TBHP (0.18 mL, 5.5 M decane,) was added. The suspension was stirred for 15 minutes and compound 21 ((4\,R,5\,R)-2-((R)-4-fluoro-6-isopropylcyclohexa-1,4-dienyl)-4,5-dihydro-4,5-diphenyloxazole) (140 mg, 0.38 mmol, 1.0 equiv) was added as a solution in undried bench CH}_2\text{Cl}_2 \text{ (2.00 mL). The solution was stirred at room temperature (3 days) until all of compound 21 was consumed as indicated by TLC. The reaction mixture was diluted with CH}_2\text{Cl}_2 \text{ (10 mL), saturated aqueous NH}_4\text{Cl was added. The aqueous layer was extracted with CH}_2\text{Cl}_2 \text{ (20 mL) and the combined organic layers were washed with brine and dried with MgSO}_4. The solvent was removed under reduced pressure before purification with flash chromatography (2.5 % EtOAc in petroleum ether) to give the title compound 36 (138.00 mg, 99 %) as an opaque oil.}
\end{align*}
\]

\(R_f\): 0.60 (10 %, EtOAc in petroleum ether); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3030 (Ar C-H), 1641 (C=N); \(^1\text{H-NMR}\) (CDCl\(_3\), 400 MHz) \(\delta\) 7.84 (dd, \(J^F\) 6 Hz, 1H, C6' H), 7.38-7.21 (m, 10H, Ar), 7.07 (dd, \(J^F\) 10, J 3 Hz, 1H, C3' H), 6.88 (ddd, \(J^F\) 8.5, J 8, 3 Hz, C5` H ), 5.27 (d, J 8 Hz, C5 H), 5.20 (d, J 8 Hz, C4 H), 4.09 (dsept, 4 Hz, J 7, 1H, i-Pr C-H), 1.12 (d, J 7 Hz, 6H, both i-Pr Me ); \(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz) \(\delta\) 163.9, 150.9 (d, \(J^F\) 244 Hz) 142.0, 140.4, 132.6 (d, \(J^F\) 8 Hz), 132.5 (d, \(J^F\) 10 Hz), 129.0, 128.9, 2 x 128.6, 128.5, 127.8, 2 x 126.6, 2 x 125.8, 113.8 (d, \(J^F\) 20 Hz), 112.6 (d, \(J^F\) 22 Hz), 88.4, 79.3, 29.6, 26.7, 23.9, 14.1.
Synthesis of (4R,5R)-1-((R)-4-Fluoro-6-isopropylcyclohexa-1,4-dienyl)-4,5-dihydro-4,5-
diphenyloxazole: [21]

Oxazoline 20 (0.18 g, 0.57 mmol, 1.0 equiv) was in dissolved in THF, DMPU (0.70 mL, 10 equiv) was added and the solution was cooled to -78 °C. Isopropyl lithium solution (2.28 mL, 0.5 M in pentane, 2 equiv) was added and the reaction turned deep green. After 2 minutes, saturated aqueous NH₄Cl solution (1.00 mL) was added. The flask was warmed to room temperature before addition of methanol (1.00 mL). The reaction mixture was partitioned between ether (10 mL) and saturated aqueous NH₄Cl (10 mL). The organic layer was then washed with water (2 X 5 mL) to remove DMPU, washed with brine (10 mL) and dried with MgSO₄. The solvent was removed under reduced pressure, flash chromatography (3 % EtOAc in petroleum ether) gave the title compound 14 (0.153 g, 74 %) as an opaque oil.

Rf: 0.62 (20 % EtOAc in petroleum ether); [α]D²⁰ +1.6 (c. 1.0, CHCl₃); MS m/z (ES+) 362.2 (100 %, (M+H)+); HRMS: found 362.1910, (M+H)+, C₂₄H₂₅FNO requires 362.1915; νmax(film)/cm⁻¹ 2959 (C-H), 1717 (C=C), 1619 (C=N); ¹H-NMR (CDCl₃, 500 MHz) δ 7.43-7.10 (m, 10H, Ar), 6.80 (ddd, J² 7.5, J4.5, 3 Hz, 1H, C6’ CH), 5.24 (ddd, J² 17.5, J 5, 2 Hz, 1H, C3’ CH), 5.14 (d, J 7 Hz, 1H, C5 CH), 5.03 (d, J 7 Hz, 1H, C4 CH), 3.54-3.49 (m, 1H, C2” CH), 3.01 (ddd, J² 23, J 6, 3 Hz, 1H, C5” CH) 2.89 (ddd, J² 23, J 9, 5 Hz, 1H, C5” CH), 2.43-2.33 (m, 1H, i-Pr H), 0.93 (d, J 7 Hz, 3H, i-Pr Me), 0.71 (d, J 7 Hz, 3H, i-Pr Me); ¹³C-NMR (CDCl₃, 125 MHz) δ 163.4 (d, J² 2 Hz), 157.19 (d, J² 254 Hz), 141.9, 140.6, 131.3 (d, J² 11 Hz), 2 x 128.9 (d, J² 11 Hz), 128.5, 128.4, 127.8, 2 x 126.7, 2 x 125.8, 125.7, 100.3 (d, J² 14 Hz), 88.3, 79.1, 42.3 (d, J² 6.5 Hz), 31.0, 27.9 (d, J² 29 Hz), 20.6, 16.3.
Synthesis of (4R,5R)-4,5-Dihydro-1-(2-isopropylphenyl)-4,5-diphenyloxazole: [42]

Oxazoline 40 (50.00 mg, 0.16 mmol, 1 equiv) was dissolved in THF (5.00 mL), DMPU (0.22 mL, 10.0 equiv) was added and the solution was cooled to –78 °C. Isopropyl lithium solution (0.66 mL, 2 equiv, 0.45 M in pentane) was added and the reaction turned deep green. After 2 minutes, the reaction was quenched with TFA (0.50 mL). The reaction mixture was taken out of the dry ice bath and allowed to warm to room temperature before addition of methanol (1.00 mL). The reaction mixture was partitioned between ether (10 mL) and saturated aqueous NaHCO₃ (10 mL). The organic layer was washed with water (2 X 5 mL) to remove DMPU, washed with brine (10 mL) and dried with MgSO₄. The solvent was removed under reduced pressure before purification using preparative HPLC. (2 % EtOAc in petroleum ether) to give compound 42 (18.00 mg, 34 %) as a colourless clear oil.

Rₐ: 0.5 (20 % EtOAc in petroleum ether); MS m/z (ES+) 342.2 (100 %, (M+H)+); HRMS: found 342.1860, (M+H)+, C₂₄H₂₄NO requires 342.1852; νmax(film)/cm⁻¹ 3029 (Ar C-H), 1643 (C=N); ¹H-NMR (CDCl₃, 500 MHz) δ 7.81 (d, J 7 Hz, 6H, ), 7.40-7.16 (m, J 7 Hz, 1H, Ar), 5.29 (d, J 8 Hz, 1H, ), 5.21 (d, 1H, ), 4.00 (sept, J 7 Hz, 1H, CH i-Pr), 1.23 (d, J 7.5 Hz, 6H, both i-PrMe); ¹³C-NMR (CDCl₃, 125 MHz) δ 163.9, 148.4, 141.1, 139.4, 130.0, 129.2, 2 x 127.9, 127.8, 127.4, 126.7, 2 x 125.6, 125.4, 125.0, 2 x 124.8, 124.5, 87.3, 78.2, 28.5, 21.6, 21.3.
Synthesis of (4\textit{R},5\textit{R})-1-((\textit{R})-2-Fluoro-6-isopropylcyclohexa-1,4-dienyl)-4,5-dihydro-4,5-
diphenyloxazole: [41]

Oxazoline 40 (50.00 mg, 0.16 mmol, 1 equiv) was dissolved in THF (5.00 mL), DMPU (0.22 mL, 10.0
equiv) was added and the solution was cooled to –78 °C. Isopropyl lithium solution (0.66 mL 0.45 M
in pentane, 2 equiv) was added to the stirred solution and the reaction mixture turned deep green.
After 2 minutes, the reaction was quenched with TFA (0.50 mL). The reaction mixture was allowed to
warm to room temperature before addition of methanol (1.00 mL). The reaction mixture was
partitioned between ether (10 mL) and saturated aqueous NaHCO$_3$ (10 mL). The organic layer was
washed with water to remove DMPU (2 X 5 mL), washed with brine (10 mL) and dried with MgSO$_4$.
The solvent was removed under reduced pressure before purification using preparative HPLC (2 %
EtOAc in petroleum ether), to give compound 41 (12.00 mg, 24 %) as a colourless clear oil.

$R_f$: 0.4 (20 %, EtOAc in petroleum ether); **MS m/z** (ES+) 362.2 (100 %, (M+H)$^+$); **HRMS**: found
362.1926, (M+H)$^+$, $C_{24}H_{25}FNO$ requires 362.1915; $\nu_{\text{max}}$(film)/cm$^{-1}$ 2959 (C-H), 1679 (C=N); **$^1$H-
NMR** (CDCl$_3$, 400 MHz) $\delta$ 7.35-7.13 (m, 10H, Ar), 5.77-7.64 (m, 2H, C3' + C4' CH), 5.72 (d, $J$ 7.5 Hz,
1H, C5 H), 5.43 (d, $J$ 7.5 Hz, 1H, C4 H), 3.51-3.43 (m, 1H, C2' H), 3.04-2.83 (m, 2H, C5' CH$_2$), 2.14 (d
sept, $J^\text{sept}$ 7, $J$ 3.5 Hz, 1H, i-Pr CH), 0.97 (d, $J$ 7 Hz, 3H, i-Pr Me), 0.79 (d, $J$ 7 Hz, 3H, i-Pr Me); **$^{13}$C-
NMR** (CDCl$_3$, 100 MHz) $\delta$ 160.6, 140.2 (d, $J^\text{C}$ 144 Hz), 127.8, 2 x 127.7 (d, $J^\text{C}$ 8 Hz), 127.3, 126.7, 2 x
125.7, 2 x 124.6, 124.5 (d, $J^\text{C}$ 2 Hz), 121.3 (d, $J^\text{C}$ 10 Hz), 105.0, 87.3, 77.4, 43.2, 30.2 (d, $J^\text{C}$ 14 Hz),
27.7(d, $J^\text{C}$ 25 Hz), 19.5, 15.6.
Synthesis of (4\text{R},5\text{R})-4,5-dihydro-2-((1\text{S},6\text{S})-6-isopropyl-5-methoxy-1-methylcyclohexa-
4',6'-dienyl)-4,5-diphenyloxazole: [45]

(4\text{R},5\text{R})-4,5-Dihydro-2-(3-methoxyphenyl)-4,5-diphenyloxazole 44 (1.00 g, 3.04 mmol, 1.0 equiv) was
dissolved THF (50 mL). DMPU (4.3 mL, 12.0 equiv) was added and the solution was cooled to −78 °C.
Isopropyl lithium solution (10 mL, 2 equiv) was added and the reaction turned deep green. After 30
minutes, methyl iodide (0.22 mL, 1.2 equiv) was added and the reaction mixture was warmed to room
temperature before addition of methanol (3.00 mL). The reaction mixture was partitioned between
ether (40 mL) and saturated aqueous ammonium chloride (40 mL). The organic layer was then
washed with water to remove DMPU (2 X 5 mL), washed with brine (20 mL) and dried with MgSO₄.
The solvent was removed under reduced pressure before purification with flash chromatography
(EtOAc in petroleum ether 5 %) to give compound 45 (0.72 g, 60 %) as a colourless solid.

\textbf{R} f: 0.24 (9:1, Petrol:EtOAc); \textbf{Mpt}: 129-131 °C; $[\alpha]_{\text{D}}^{22}$: +110.4 (c. 1, CHCl₃); \textbf{MS m/z (ES+)} 388.3 (98
\%, (M+H)+), 410.0 (100 \%, (M+Na)+); \textbf{HRMS}: found 388.2268, (M+H)+, C_{26}H_{30}NO₂ requires 388.227;
\textbf{V}_{\text{max}}(\text{film/cm}^{-1}) 2962 (C-H), 1659 (C=N); \textbf{¹H-NMR (CDCl₃, 400 MHz)} δ 7.10-7.35 (m, 10H, Ar), 5.93
(d, J 10 Hz, 1H, C6' H), 5.75 (dd, J 9, 6 Hz, 1H, C5' H), 5.13 (d, J 9 Hz, 1H, C5 H), 4.97-5.02 (m, 2H,
C4 H & C4'), 3.53 (s, 3H, OMe), 2.27 (brd, J 3 Hz, 1H, C2' H), 1.97 (dsept, J 3, 7 Hz, 1H, \text{-Pr CH},
1.45 (s, 3H, C1' Me), 0.99 (d, J 7 Hz, 3H, \text{-Pr Me}), 0.91 (d, J 7 Hz, 3H, \text{-Pr Me}); \textbf{¹³C-NMR (CDCl₃,}
100 MHz) δ 171.4 (C=N), 157.3 (C3'), 142.0 (Ar), 140.0 (Ar), 2 X 128.9 (Ar), 2 X 128.8 (Ar), 128.4
(Ar), 127.6 (Ar), 2 X 126.7, 2 X 125.8, 125.1 (C6'), 122.1 (C5'), 93.1 (C4'), 88.9 (C5), 78.8 (C4), 54.3
(OMe), 43.7, 30.8 (\text{-Pr CH}, 25.1 (Me), 23.7 (\text{-Pr Me}), 17.9 (\text{-Pr Me}).
Synthesis of (4R,5R)-4,5-dihydro-2-((1S,6S)-6-isopropyl-4-methoxy-1-methylcyclohexa-2,4-dienyl)-4,5 diphenyloxazole: [9]

(4R,5R)-4,5-Dihydro-2-(4-methoxyphenyl)-4,5-diphenyloxazole 8 (5.00 g, 15.18 mmol, 1.0 equiv) was placed in a dry three-necked round-bottomed flask equipped with stirrer bar, and low temperature thermometer was sealed and flushed with N₂. Dry THF (50.00 mL) was added and the oxazoline was dissolved. DMPU (16.60 mL, 9.0 eq) was added and the solution was cooled to -78 °C over 15 minutes. Isopropyl lithium solution (39.00 mL, 1.3 equiv, 0.5 M) was added to the stirred solution slowly over 15 minutes and the reaction turned deep green. After 20 minutes, methyl iodide (1.40 mL, 1.5 equiv) was added and the reaction mixture turned orange. The round-bottomed flask was taken out of the dry ice bath and allowed to warm to room temperature before addition of methanol (10 mL). The reaction mixture was partitioned between ether (100 mL) and aqueous ammonium chloride (40 mL). The organic layer was then washed four times with water (5 mL) to remove DMPU and dried with MgSO₄. The solvent was removed under reduced pressure before purification with flash chromatography (5 % EtOAc in petroleum ether) to compound 9 (4.06 g, 70 %) as a colourless solid.

δ: 0.34 (20 %, Petrol:EtOAc); Mpt: 120 °C; [α] D²⁰: -136 (c. 1, CHCl₃); MS m/z (ES+) 388, (M+H)+, 410, (M+Na)+; HRMS: found 388.2284, (M+H)+, C₂₆H₃₀NO₂ requires 388.2271; Microanalysis found: C (80.95 %), H (7.54 %), N (3.61 %), C₂₆H₃₀NO₂ requires: C (80.26 %), H (8.14 %), N (3.35 %);

ν max (film)/cm⁻¹ 2956 (C-H Ar), 1662 (C=N); ¹H-NMR (CDCl₃, 400 MHz) δ 7.11 - 7.36 (m, 10H, Ar), 6.34 (d, J 10 Hz, 1H, C6' H), 5.65 (dd, J 10, 2 Hz, 1H, C5' H), 5.14 (d, J 9 Hz, 1H, 5 H), 4.98 (d, J 9 Hz, 1H, 4 H), 4.44 (dd, J 6, 2 Hz, 1H, C3' H), 3.54 (s, 3H, OMe), 2.50 (dd, J 6.5, 3.5 Hz, 1H, C2' H),
1.93 (sept, 1H, i-Pr H), 1.48 (s, 3H, Me), 0.91 (d, J 7 Hz, 3H, i-Pr Me), 0.87 (d, J 7 Hz, 3H, i-Pr Me);

$^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 171.2 (C=N), 153.1 (C4'), 141.9 (Ar), 140.4 (Ar), 135.0 (C5'), 2 X 128.9 (Ar), 2 X 128.8 (Ar), 128.4 (Ar), 2 X 126.8 (Ar), 2 X 125.8 (Ar), 125.6, 121.7 (C6'), 89.1 (C5), 88.5 (C3'), 88.1, 78.9 (C4), 54.3 (OMe), 46.9 (C2'), 42.0 (C1'), 29.8 (i-Pr CH), 25.8 (C1 Me), 19.4 (i-Pr Me), 17.0 (i-Pr Me).

**Synthesis of (4S)-4-((4R,5R)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)-2-hydroxy-3-isopropyl-4-methyl-cyclohexa-2,5-dien-1-one: [55]**

(4R,5R)-4,5-Dihydro-2-((1S,6S)-6-isopropyl-5-methoxy-1-methylcyclohexa-2,4-dienyl)-4,5-diphenyloxazole 16 (40.00 mg, 0.10 mmol, 1.0 equiv) was dissolved in a mixture of water (0.2 mL) and THF (0.80 mL). $N$-methyl morpholine $N$-oxide (60.00 mg, 5 equiv), DABCO (35.00 mg, 3 equiv) and OsO$_4$ solution (0.08 M, t-BuOH, 0.016 mL, 0.01 equiv) were added and the reaction was stirred at 40 °C for two days and was quenched with 5 % solution of sodium metabisulfate (10 mL). The reaction mixture was extracted with EtOAc (20 mL). The organic layer was washed with brine (10 mL) and dried with MgSO$_4$ before purification with flash chromatography (7 % EtOAc in petroleum ether), to give compound 55 (16.00 mg, 40 %) as a colourless clear oil.

$R_f$: 0.26 (20 %, EtOAc in petrol); $[\alpha]_{D}^{22}$: +227.6 (c. 1, CHCl$_3$); MS m/z (ES+) 388.2 (100 %, (M+H)$^+$); HRMS: found 388.1914, (M+H)$^+$, $C_{25}H_{26}NO_3$ requires 388.1907; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3393 (OH), 2932 (CH), 1646 (C=O); $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 7.10-7.35 (m, 10H, Ar), 6.96 (d, J 10 Hz, 1H, C5' H), 5.56 (s, 1H, OH), 6.41 (d, J 10 Hz, 1H, C6' H), 5.14 (d, J 8.5 Hz, 1H, C5 H), 5.10 (d, J 8.5 Hz, 1H, C4 H), 2.53 (sept, J 7.5 Hz, 1H, i-Pr CH), 1.66 (s, 3H, C1' Me), 1.25 (d, J 7 Hz, 3H, i-Pr-Me), 1.20 (d, J 7 Hz, 3H, i-Pr-Me); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 181.1 (C4' C=O), 167.1 (C2 C=N), 152.9
(C3'), 145.2 (Ar), 141.2 (Ar), 138.8 (Ar), 136.1 (Ar), 2 X 129.0 (Ar), 2 X 128.9 (Ar), 127.9 (Ar), 2 X 126.6 (Ar), 2 X 126.6 (C5), 125.6 (C4), 90.32 (C5'), 77.65 (C6'), 46.98 (C1'), 30.49 (i-PrCH), 22.92 (C1' Me), 19.96 (i-Pr Me), 19.47 (i-Pr Me).

**Synthesis of (4R,5R)-4,5-dihydro-2-((S)-6-isopropyl-5-methoxycyclohexa-1,4-dienyl)-4,5-diphenyloxazole: [47]**

![Chemical structure](image)

(4R,5R)-4,5-Dihydro-2-((1S,6S)-6-isopropyl-5-methoxy-1-methylcyclohexa-2,4-dienyl)-4,5-diphenyloxazole 44 (50.00 mg, 0.15 mmol, 1.0 equiv) was dissolved THF (5.00 mL), DMPU (0.22 mL, 12.0 equiv) was added and the solution was cooled to -78 °C. Isopropyl lithium solution (0.65 mL, 2 equiv) was added and reaction turned deep green. After 5 minutes, the reaction was quenched with methanol (1 mL) and warmed to room temperature before addition of NH₄Cl (1 mL). The reaction mixture was partitioned between ether (10 mL) and water (10 mL). The organic layer was then washed with water (2 X 5 mL) to remove DMPU the combined organic layers were washed with brine and dried with MgSO₄. Compound 47 was unstable toward flash chromatography, thus this material was used without purification (57.00 mg crude mass).

**¹H-NMR** (CDCl₃, 400 MHz) δ 7.12-7.36 (m, Ar), 6.89 (s, 1H, C6' H), 5.13 (d, J 7.5 Hz, 1H, C5 H), 5.03 (d, J 7.5 Hz, 1H, C4 H), 4.68 (s, 1H, C4' H), 3.48 (s, 3H, OMe), 3.42 (m, 1H, C2' H), 2.86 (m, 2H, CS' CH₂), 2.16 (d sept, J7, 3 Hz, 1H, i-Pr CH), 0.99 (d, J7 Hz, 3H, i-Pr Me), 0.80 (d, J7 Hz, 3H, i-Pr Me).
Synthesis of (2S)-3-((4R,5R)-4,5-dihydro-4,5-diphenyloxazol-2-yl)-6-hydroxy-2-isopropylcyclohex-3-enone: [50]

A yellow oil containing (4R,5R)-4,5-dihydro-2-((S)-6-isopropyl-5-methoxycyclohexa-1,4-dienyl)-4,5-diphenyloxazole 47 was dissolved in a 4:1 mixture of tertiary butanol and water (6 mL). N-methylmorpholine N-oxide (36.00 mg, 2.00 equiv) and osmium tetroxide (0.34 mL, 0.01 equiv, 0.08 M in t-BuOH) were added. The reaction was monitored by TLC. Upon complete consumption of starting material, the reaction was quenched with a 5 % solution of sodium metabisulphite (3 mL). The organic layer was extracted with ethyl acetate (20 mL), washed with brine (10 mL) and dried with MgSO₄. The solvent was removed under reduced pressure before purification with flash chromatography (10 % EtOAc in petroleum ether) to give compound 50 as a yellow oil (0.013 g, 23 %).

R_f: 0.19 (20 %, Petrol:EtOAc); MS m/z (ES+) 376.3 ((M+H)+, 100 %); HRMS: found 376.1903, (M+H)+, C₂₄H₂₆NO₃ requires 376.1907; ¹H-NMR (CDCl₃, 400 MHz) δ 7.38-7.10 (m, 10H, Ar), 6.79 (q, J 3 Hz, 1H, C6’ H), 5.17 (d, J 8 Hz, 1H, C5’H), 5.05 (d, J 7.5 Hz, 1H, C4 H), 4.44 (dt, J 9, 3.5 Hz, 1H, C4’ H), 3.76 (d, J 4 Hz, 1H, OH), 3.56 (dd, J 6, 2 Hz, 1H, C2’ H), 3.18 (ddd, J 19, 9, 5.5 Hz, 1H, C5’ Ha), 2.56 (sept, 1H, i-Pr-H), 2.38 (dd, J 19, 9.5 Hz, 1H, C5’ Hb), 0.99 (d, J 7 Hz, 3H, i-Pr-Me), 0.91 (d, J 7 Hz, 3H, i-Pr-Me); ¹³C-NMR (CDCl₃, 100 MHz) δ 209.9 (C=O), 162.6 (C2 C=N), 114.6 (Ar), 140.2 (Ar), 132.9 (C6’), 129.0 (Ar), 128.9 (Ar), 128.6 (Ar), 128.2 (Ar), 127.9 (Ar), 2 X 126.6 (Ar), 126.0 (Ar), 2 X 125.6 (Ar), 88.5 (C5), 78.9 (C4), 71.7 (C4’), 54.7 (C2’), 36.1 (C5’), 30.8 (i-Pr C2’), 29.72, 20.9 (i-Pr Me), 19.3 (i-Pr Me).
Synthesis of (4S,5S,6R)-4-((4R,5R)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)-6-hydroxy-5-isopropyl-4-methylcyclohex-2-enone: [16]

(4R,5R)-4,5-Dihydro-2-((1S,6S)-6-isopropyl-4-methoxy-1-methylcyclohexa-2,4-dienyl)-4,5-diphenyloxazole 9 (3.76 g, 9.70 mmol, 1.0 equiv) and methane sulfonamide (0.92, 1.0 equiv) were dissolved in tertiary butanol (80.00 mL). Water (80.00 mL) was added and the solutes precipitated. Quinuclidine (0.16 g, 0.15 equiv), potassium ferricyanide (9.54 g, 3.0 equiv) and K$_2$CO$_3$ (4.00 g, 3.0 equiv) were added to the stirred solution. OsCl$_3$$\cdot$H$_2$O (0.24 g, 0.07 equiv) was added and the orange solution became green. The reaction was stirred at room temperature, after 3 hours TLC analysis showed complete consumption of starting material. The reaction was extracted with EtOAc, (60 mL) the organic extracts were washed with 1M HCl (10 mL), 10 % aqueous sodium metabisulfite (20 mL), brine (10 mL) and dried with MgSO$_4$. The solvent was removed under reduced pressure before purification with flash chromatography (20 % EtOAc in petroleum ether) to give the compound 16 as a clear crystalline solid (3.15 g, 83 %).

R: 0.50 (20 %, EtOAc in petrol); Mpt: 121 - 123 °C (Petrol:EtOAc); [α]$^D_{22}$: +192 (c. 1, CHCl$_3$); MS m/z (ES+) 390.3 ((M+H)$^+$, 100 %); HRMS: found 390.2064, (M+H)$^+$, C$_{25}$H$_{28}$NO$_3$ requires 390.2065;

Microanalysis found: C (77.09 %), H (6.99 %), N (3.60 %), C$_{25}$H$_{27}$NO$_3$ requires: C (76.97 %), H (7.25 %), N (3.29 %); V$_{max}$(film)/cm$^{-1}$ 3475 (OH), 2934 (CH Ar), 1686 (C=O), 1647 (C=N); $^1$H-NMR (CDCl$_3$, 400 MHz) δ 7.10 - 7.36 (m, 10H, Ar), 6.70 (d, J 10 Hz, 1H, C5'H), 6.11 (d, J 10 Hz, 1H, C6'H), 5.15 (d, J 10 Hz, 1H, 5 CH), 5.03 (d, J 10 Hz, 1H, 4 CH), 4.61 (d, J 13 Hz, 1H, C3' CH), 3.50 (bs, 1H, C3' OH), 2.33 (sept, J 1 Hz, 1H, i-Pr-H), 1.91 (d, J 13 Hz, 1H, C3' H), 1.55 (s, 3H, C1' Me), 1.10 (d, J 7 Hz, 3H, i-Pr-Me), 1.08 (d, J 7 Hz, 3H, i-Pr-Me); $^{13}$C-NMR (CDCl$_3$, 100 MHz) δ 201.7 (C5'), 167.5 (C2 C=N), 153.9 (C=O), 140.5 (Ar), 138.5 (Ar), 2 X 129.0 (Ar), 2 X 128.9 (Ar), 128.8 (Ar), 127.9 182
(Ar), 2 X 126.7 (Ar), 2 X 126.2 (Ar), 124.8 (C6'), 90.2 (C5), 77.8 (C4), 72.1 (C3'), 55.2 (C2'), 44.1 (C1'), 27.1 (i-Pr C H), 25.9 (i-Pr-Me), 25.6 (C1 Me), 17.4 (i-Pr-Me).

**Synthesis of (4S,5S)-4-((4R,5R)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one: [56]**

(4R,5R)-4,5-Dihydro-2-((1S,6S)-6-isopropyl-4-methoxy-1-methylcyclohexa-2,4-dienyl)-4,5-diphenyloxazole 9 (0.38 g, 0.98 mmol, 1.0 equiv) was dissolved in a t-BuOH (10.00 mL) and water (10.00 mL). Citric acid (0.27 g, 0.75 equiv) and NMO (0.13 g, 1.1 equiv) were added. The solution was sealed and osmium tetroxide solution (0.24 mL, 0.02 equiv 0.08 M in t-BuOH) was added. After 2 hours the reaction became black and was quenched with a 5 % solution of sodium metabisulfate (10 mL) and the organic layers were extracted with ethyl acetate (20 mL), dried with MgSO₄ and the products were purified with flash chromatography (10 % EtOAc in petroleum ether) to give compound **56** oil (0.19 g, 43 %). Starting material compound 9 (51.00 mg, 13 %) was also isolated.

**Rf:** 0.30 (20 %, EtOAc in petrol); [α]D²²: +121.6 (c. 1, CHCl₃); **MS m/z (ES+)** 396 (100 %, (M+Na)+);

**HRMS:** found 374.2113, (M+H)+, C₂₅H₂₈NO₂ requires 374.2115; V_max(film)/cm⁻¹ 2958 (Ar CH), 2359, 1678 (enone), 1657 (C=N); **¹H-NMR** (CDCl₃, 400 MHz) δ 7.34-7.16 (m, 8H, Ar), 7.12-7.07 (m, 2H, Ar), 7.02 (d, J 10 Hz, 1H, C5' H), 5.96 (d, J 10 Hz, 1H, C6' H), 5.12 (d, J 9 Hz, 1H, C5 H), 4.99 (d, J 9 Hz, 1H, C4 H), 2.63 (dd, J 8, 17 Hz, 1H, C3' Ha), 2.47 (dd, J 5, 17 Hz, 1H, C3' Hb), 2.19-2.09 (m, 2H, i-Pr H & C2' H), 1.56 (s, 3H, C1' Me), 0.92 (d, J 7 Hz, 3H, i-Pr Me), 0.81 (d, J 7 Hz, 3H, i-Pr Me); **¹³C-NMR** (CDCl₃, 100 MHz) δ 199.6 (C5'), 168.6 (C2 C=N), 153.1 (C4'), 141.1 (Ar), 139.4 (Ar), 2 X 129.0 (Ar), 2 X 128.9 (Ar), 128.7 (Ar), 128.2 (Ar), 127.9 (C6), 2 X 126.6 (Ar), 2 X 126.0 (Ar), 89.6
(C5), 78.3 (C4), 48.4 (C2'), 42.4 (C1'), 34.6 (C3'), 28.6 (C i-Pr H), 25.7 (C1' Me), 23.2 (i-Pr Me), 18.6 (i-Pr Me).

**Synthesis of (1R,5S,6S)-5-((4R,5R)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)-6-isopropyl-2,2-dimethoxy-5-methylcyclohex-3-enol: [61]**

![Chemical Structure](image)

(4R,5R)-4,5-Dihydro-2-((1S,6S)-6-isopropyl-4-methoxy-1-methylcyclohexa-2,4-dienyl)-4,5-diphenyloxazole 9 (0.71 g, 1.83 mmol, 1 equiv) was dissolved in methanol (10.00 mL) with stirring. m-CPBA (0.34 g, 1.1 equiv) was added in one portion to the stirred solution the reaction turned a clear bright yellow, the heat was removed and the solution was left to stir for 16 hours. The solution was carefully neutralised with aqueous NaHCO₃ solution. The aqueous layer was separated and was extracted twice with ethylacetate (10 mL) the organic layer was dried with MgSO₄. Solvent was removed under reduced pressure. Products purified using flash chromatography (15 % EtOAc in Petroleum ether). Compounds were isolated as a 4:1 mixture of acetal 61 and ketone 16 (0.46 g, 55 %).

**Rf:** 0.18 (20 %, Petrol:EtOAc); **Mpt:** 90-93 °C (CH₂Cl₂); **[α]**²⁰⁺ : +174 (c. 1, CHCl₃); **MS m/z (ES+)** 436.3 (100 %, (M+H)+); **HRMS:** found 458.2290, (M+H)+, C₂₇H₃₄NO₄ requires 458.2302; **νₓ max (film)/cm⁻¹** 1645 (C=N), 3547 (OH); **¹H-NMR (CDCl₃, 400 MHz)** δ 7.10 - 7.35 (m, 10H, Ar), 5.76 (s, 2H, C 5” and 6” H), 5.11 (d, J 10.0 Hz, 1H, C5 H), 4.97 (d, J 10.0 Hz, 1H, C4 H), 4.33 (t, J 11.0 Hz, 1H, C3’ H), 3.34 (s, 3H, OMe), 3.32 (s, 3H, OMe), 2.40 (d, J 10 Hz, 1H, C3’ OH), 2.20 (sept, J 7 Hz, 1H, i-Pr H), 1.68 (d, J 12 Hz, 1H, C2’ H), 1.42 (s, 3H, C1’ Me), 1.09 (d, J 7 Hz, 3H, i-Pr Me), 0.96 (d, J 7 Hz, 3H, i-Pr Me); **¹³C-NMR (CDCl₃, 100 MHz)** δ 169.4 (C2 C=N), 141.1, 138.9, 137.7 (C5), 128.9 (Ar), 128.8 (Ar), 128.7 (Ar), 127.9 (Ar), 126.7 (Ar), 126.2 (Ar), 125.3 (C6’), 97.9 (C4’), 90.1
(C5), 77.9 (C4), 70.7 (C3'), 52.1 (C2'), 51.4 (OMe), 49.8 (OMe), 43.6 (C1'), 26.8 (iPr Me), 25.9 (C1'Me), 17.4 (iPr Me).

Synthesis of (1S,5R,6S)-((1R,2R)-2-acetamido-1,2-diphenylethyl) 5-hydroxy-6-isopropyl-1-methyl-4-oxocyclohex-2-enecarboxylate: [70]

(4R,5R)-4,5-Dihydro-2-((1S,6S)-6-isopropyl-4-methoxy-1-methylcyclohexa-2,4-dienyl)-4,5-diphenyloxazole (0.78 g, 2.00 mmol, 1.0 equiv) was dissolved in methanol (10.00 mL) and HCl (1M, 10.00 mL) and was stirred for 16 hours. The solution was neutralised with saturated NaHCO$_3$ solution, EtOAc (20.00 mL) was added and the organic layer was isolated. The aqueous layer was extracted twice with EtOAc (5.00 mL). The organic layer was dried with sodium sulfate, filtered and the solvent was removed under reduced pressure. Hydrolysis of the oxazoline was confirmed by NMR of this crude material. Acylation was performed on this crude material, the compound was dissolved in CH$_2$Cl$_2$ (5.00 mL) with stirring and cooled to 0 °C. Triethylamine (0.48 mL, 2.0 equiv) was added followed by acetic anhydride (0.49 mL, 3.0 equiv). The reaction was taken out of the ice bath after 5 minutes and left stirring at room temperature. On consumption of starting material as determined by TLC analysis the reaction was quenched saturated aqueous with NH$_4$Cl (5 mL). The aqueous layer was extracted with EtOAc (20 mL) and organic layers combined and dried with magnesium sulfate. The reaction was purified using a silica plug. 50 % EtOAc in petroleum ether (60 mL) to remove impurities, EtOH (30 mL) removed the title compound from the silica. The ethanol fraction was evaporated under reduced pressure to give compound 70 (0.71 g, 90 %) as a yellow oil.
$R_f$: 0.36 (70 %, EtOAc in petrol); $[\alpha]_D^{22} : +75.2$ (c. 1, CHCl$_3$); **MS m/z** (ES+) 472.3 (100 %, (M+H)$^+$);

**HRMS**: found 472.2095, (M+H)$^+$, C$_{27}$H$_{32}$NO$_5$ requires 472.2094; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 1655 (amide), 1682 (cyclohexeneone), 1723 (ester); **$^1$H-NMR** (CDCl$_3$, 400 MHz) $\delta$ 7.21-6.95 (m, 10H, Ar), 6.45 (d, J 10 Hz, 1H, C5), 6.10 (d, J 10 Hz, 1H, C6), 6.00 (d, J 9 Hz, 1H, NH), 5.95 (d, J 8 Hz, 1H, C5' H), 5.41 (t, J 8 Hz, 1H, C4' H), 4.38 (d, J 13 Hz, 1H, C3 H), 3.44 (s, 1H, C3OH), 1.89 (s, 3H, Ac Me), 1.88 (sept, 1H, i-Pr H), 1.76 (d, J 13 Hz, 1H, C2 H), 1.33 (s, 3H, C1 Me), 0.95 (d, J 7 Hz, 3H, i-Pr Me), 0.62 (d, J 7 Hz, 3H, i-Pr Me); **$^{13}$C-NMR** (CDCl$_3$, 100 MHz) $\delta$ 201.4 (C5'), 171.3 (Ar), 169.2 (Ar), 152.2 (Ar), 137.4 (Ar), 136.3 (Ar), 128.7 (Ar), 128.6 (Ar), 128.4 (Ar), 128.1 (Ar), 127.2 (Ar), 127.0 (Ar), 125.7 (C6), 79.7 (C5), 71.5 (C3), 57.3 (C4'), 55.4 (C2), 49.8 (C1), 26.7, 25.8 (i-Pr Me), 24.4 (C1 Me), 23.4 (NMe), 16.4 (i-Pr Me).
Synthesis of (1R,2S,3S,5R,6S)-((1R,2R)-2-acetamido-1,2-diphenylethyl) 2,3,5-trihydroxy-6-isopropyl-1-methyl-4-oxocyclohexanecarboxylate: [74b]

CeCl₃ (8.00 mg, 0.1 equiv) and sodium periodate (0.07 g, 1.5 equiv) were dissolved in water (0.20 mL) with stirring and gently heated with a heat gun until the solution became yellow. Acetonitrile was added and the slurry was cooled to 0 °C. A solution of ester (1S,5R,6S)-((1R,2R)-2-acetamido-1,2-diphenylethyl) 5-hydroxy-6-isopropyl-1-methyl-4-oxocyclohex-2-enecarboxylate 70 in EtOAc (0.1 g, 0.22 mmol, in 0.6 mL) and sulfuric acid (0.014 mL, 0.2 equiv, 3M) were added to the vigorously stirred solution RuCl₃ solution (10 μL, 0.1 M, 0.005 equiv) was added. After 30 minutes sodium sulfate and EtOAc (10 mL) was added to quench the reaction. The slurry was filtered and solvent removed under reduced pressure. Crude material was re-dissolved in CH₂Cl₂ and loaded on to silica gel. Purified with flash chromatography (65 % EtOAc in pet ether) give compound 74 (0.045 g, 42 %) as a colourless oil.

Rf: 0.34 (EtOAc); [a]D²² : –29.6 (c. 1, CHCl₃); MS m/z (ES+) 482 (100 %, (M-H)+), 506 (100 %, (M+Na)+); HRMS: found 506.2163, (M+Na)+, C₂₇H₃₃NO₇Na requires 506.2149; νmax(film)/cm⁻¹ 1656 (Acyl amide), 1721 (ketone and ester); ¹H-NMR (CDCl₃, 400 MHz) δ 7.26-7.00 (m, 10H, Ar), 6.08 (s, 1H, AcNH), 6.07 (d, J 8 Hz, 1H, BnHO), 5.47 (t, J 9 Hz, 1H, BnHN), 4.68 (bs, 1H, C5 H), 4.62 (bd, J 11 Hz, 1H, C3 H), 3.29 (bd, J 3 Hz, 1H, C6 H), 3.67 (bs, 1H, C3 OH), 3.23 (bs, 1H, C5 OH), 3.05 (bd, J 11 Hz, 1H, C6 OH), 1.93 (s, 3H, NAc), 1.79 (d, J 11 Hz, 1H, C2 H), 1.73 (sept, J 7 Hz, 1H, i-Pr H), 1.42 (s, 1H, C1 Me), 0.91 (d, J 7 Hz, 3H, i-Pr Me), 0.70 (d, J 7 Hz, 3H, i-Pr Me); ¹³C-NMR (CDCl₃, 100 MHz) δ 211.2, 173.5, 169.6, 137.5, 136.1, 128.8, 128.7, 128.5, 128.1, 127.2, 127.1, 78.5, 78.0,
74.1, 73.4, 57.4 (C3), 53.3 (C2), 50.8 (C1), 27.6 (C1), 26.3 (i-Pr Me), 23.4 (NMe), 20.6 (C1 Me), 17.6 (i-Pr Me).

**Synthesis of (1R,2S,3R,6R)-methyl 3-hydroxy-2-isopropyl-6-methoxy-1-methyl-4-oxocyclohexanecarboxylate: [71]**

![Chemical Structure](image)

(1S,5S,6S)-((1R,2R)-2-acetamido-1,2-diphenylethyl) 5-hydroxy-6-isopropyl-1-methyl-4-oxocyclohex-2-ene carboxylate 74 (70.00 mg, 0.16 mmol, 1 equiv) was dissolved in MeOH (1 mL), K₂CO₃ (5.00 mg) was added and the solution was stirred for 16 hours at room temperature. The solution was quenched with saturated ammonium chloride solution (5 mL) and extracted with EtOAc (5 mL). The organic layer was dried with MgSO₄. The solvent was removed under reduced pressure and the products were purified with flash chromatography (40 % EtOAc in petroleum ether) to give compound 71 (17.00 mg, 42 %) as a clear oil.

- **Rᵣ**: 0.40 (50 %, EtOAc in petrol); [α]$_{D}^{22}$: -72.8 (c. 1, CHCl₃); **MS m/z** (ES+) 281 (75 %, (M+Na)$^+$), 313 (100 %, (M+MeOH+Na)$^+$); **HRMS**: found 281.1371, (M+Na)$^+$, C₁₃H₂₂O₅Na requires 281.1359;
- **V$_{max}$(film)/cm$^{-1}$**: 3482 (OH), 2958 (CH), 1752 (C=O); **¹H-NMR** (CDCl₃, 400 MHz) δ 3.69 (bd, $J$ 7 Hz, 1H, C₃ H), 3.43 (s, 3H, CO$_₂$ Me), 3.31 (s, 3H, C₆ OMe), 3.21 (dd, $J$ 4, 10 Hz, 1H, C₆ H), 2.28 (ddd, $J$ 2, 9.5, 14 Hz, 1H, C₃ OH), 2.10 (dd, $J$ 3.5, 5 Hz, 2H, C₅ H₂), 2.06 (dd, $J$ 3.5, 14 Hz, 1H, C₂ H), 1.92 (dsept, $J$ 4, 7 Hz, 1H, i-Pr H), 1.17 (s, 3H, C₂ Me), 0.95 (d, $J$ 7 Hz, 3H, i-Pr Me), 0.71 (d, $J$ 7 Hz, 3H, i-Pr Me); **¹³C-NMR** (CDCl₃, 100 MHz) δ 174.6 (CO$_₂$Me), 105.0 (C₄), 78.5 (C₃), 68.3 (C₆), 57.9 (OMe), 50.8 (CO$_₂$Me), 47.3 (C₁), 44.2 (C₂), 29.5 (C₅), 27.0 (i-Pr CH), 21.4 (i-Pr Me), 15.9 (i-Pr Me), 15.2 (C₁ Me).
Synthesis of \((4S,5S,6R)-6\text{-bromo}-4\)-(\((4R,5R)-4,5\text{-diphenyl}-4,5\text{-dihydrooxazol}-2\text{-yl})-5\text{-isopropyl}-1\text{-methoxy}-4\text{-methyl-cyclohex-2-en-1-ol}: [67]\)

\((4R,5R)-4,5\text{-Dihydro-2-((1S,6S)-6\text{-isopropyl}-4\text{-methoxy}-1\text{-methylcyclohexa-2,4-dienyl})-4,5\text{diphenyloxazole 16}\) (0.35 g, 0.92 mmol, 1 equiv) was dissolved in acetonitrile (8.00 mL) at room temperature, water (0.40 mL) and NaOAc (0.11 g, 1.5 equiv) was added. The solution was cooled to 0 °C, NBS (0.25 g, 1.5 equiv) was added in one portion. The reaction mixture cleared and became slightly yellow, it was stirred at 0 °C for 20 minutes the reaction was warmed to room temperature over 40 minutes. The reaction mixture was extracted with EtOAc (20 mL), combined organic extracts were washed with a 10 % solution of sodium metabisulfite (10 mL). The organic layer was washed with saturated brine (10 mL) and dried with MgSO₄. The solvent was removed under reduced pressure. Purification by flash chromatography (5 % to 20 % gradient EtOAc in petroleum ether) gave compound 67 (0.319, 76 %) as an opaque oil.

\(R_f\): 0.41 (25 %, EtOAc in petrol); \([\alpha]^2_{D}\)\(^2\): +24.8 (c. 1, CHCl₃); MS \text{m/z (ES+)} 506 (85%), 508 (100%); HRMS: found 506.1313, (M+Na)\(^+\), \(C_{26}H_{30}^{79}\text{BrNO}_3\) requires 506.1301; \(\nu\text{max (film)/cm}^{-1}\) 3439 (OH), 2955 (CH), 1661 (C=N); \(^1\text{H-NMR}\) (CDCl₃, 400 MHz) \(\delta 7.44\) (d, \(J 7\) Hz, 2H, Ar), 7.31-7.13 (m, 8H, Ar), 6.32 (d, \(J 8\) Hz, 1H, C5'), 6.10 (d, \(J 8\) Hz, 1H, C6'), 5.75 (br d, \(J 7.5\) Hz, 1H, C5 H), 5.00 (d, \(J 8\) Hz, 1H, C4 H), 4.34 (br s, 1H, C4' OH), 3.73 (br d, \(J 4.5\) Hz, 1H, C3' H), 3.67 (s, 3H, C4' OMe), 2.04 (ap t, \(J 4\) Hz, 1H, C2' H), 1.96 (m, 1H, \(\text{i-Pr H}\)), 1.35 (s, C1' Me), 0.91 (d, \(J 7\) Hz, 3H, \(\text{i-Pr Me}\)), 0.11 (d, \(J 7\) Hz, 3H, \(\text{i-Pr Me}\)); \(^{13}\text{C-NMR}\) (CDCl₃, 100 MHz) \(\delta 175.5\) (C=N), 142.2 (C5'), 138.7 (Ar), 138.1 (Ar), 129.9 (Ar), 129.6 (Ar), 128.2 (Ar), 127.5 (Ar), 126.9 (Ar), 92.9 (C4'), 74.4 (C5), 63.6 (C4), 57.6 (C2'), 55.5 (OMe), 52.5 (C3'), 49.6 (C1'), 27.4 (\(\text{i-Pr C H}\)), 23.7 (\(\text{i-Pr Me}\)), 16.6 (C1' Me), 15.2 (\(\text{i-Pr Me}\)).
Synthesis of (4S,5S,6R)-6-hydroxy-5-isopropyl-4-methyl-4-((2R,4R,5R)-3-methyl-4,5-diphenyl-oxazolidin-2-yl)cyclohex-2-en-1-one: [51]

N-methyl triflate salt 85 (2.00 g, 4.94 mmol, 1.0 equiv) was dissolved in CH\textsubscript{2}Cl\textsubscript{2}:ethanol (100 mL, 7:2) and cooled to -78 °C for 20 minutes. A solution of NaBH\textsubscript{4} in ethanol (0.14 g, 1.0 equiv, in 10 mL) was added to the cooled solution of the triflate salt. After 25 minutes the reaction was quenched with of saturated NH\textsubscript{4}Cl (40 mL) and allowed to reach room temperature. The phases were separated and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (20 mL). The combined organic layers were washed with brine (10 mL) and dried with MgSO\textsubscript{4}. Solvent was removed under reduced pressure; the solid was redissolved in MeOH and evaporated to dryness to remove boron containing residues. The oxazolidine 51 was an off white solid (1.46 g, 100 %) and was used without further purification.

**R**\textsubscript{f}: 0.39 (20 %, EtOAc in petrol); **Mpt**: 138-140 °C (Petroleum ether); **[α]**\textsubscript{D<sup>22</sup>}: +260 (c. 1, CHCl\textsubscript{3}); **MS**

m/z (ES+) 428 (100 %, (M+Na)<sup>+</sup>); **HRMS**: found 428.2181, (M+Na)<sup>+</sup>, C\textsubscript{26}H\textsubscript{31}NO\textsubscript{3}Na requires 428.2196; **Microanalysis** found: C (77.01 %), H (7.71 %), N (3.45 %), C\textsubscript{26}H\textsubscript{31}NO\textsubscript{3} requires: C (77.02 %), H (8.05 %), N (3.40 %); **ν<sub>max</sub>(film)/cm\textsuperscript{-1}** 3489 (OH), 2954 (CH), 1679 (C=O); **¹H-NMR** (CDCl\textsubscript{3}, 400 MHz) δ 7.14 -7.26 (m, 8H, Ar), 7.11-7.07 (m, 2H, Ar), 6.95-6.91 (m, 2H, Ar), 6.14 (d, J\textsubscript{10} Hz, 1H, C5′ H), 4.78 (dd, J 13, 2 Hz, 1H, C3′ H), 4.74 (s, 1H, C2 H), 4.54 (d, J 9 Hz, 1H, C5 H), 3.34 (d, J 2 Hz, 1H, C3′ OH), 3.30 (d, J 9 Hz, 1H, C4 H), 2.37 (t, 3H, NMe), 2.18 (sept, J 7 Hz, 1H, i-Pr H), 1.76 (d, J 13 Hz, 1H, C2 H), 1.31 (s, 3H, Me), 1.29 (d, J 7 Hz, 3H, i-Pr Me), 1.13 (d, J 7 Hz, 3H, i-Pr Me); **¹³C-NMR** (CDCl\textsubscript{3}, 100 MHz) δ 202.9 (C4′), 157.7, 137.8 (Ar), 136.9 (Ar), 128.9 (Ar), 128.5 (Ar), 128.1 (Ar), 128.1 (Ar), 127.9 (Ar), 126.5 (C6′), 126.3, 100.6 (C2), 86.6 (C5), 72.2 (C4), 56.6 (C3′), 53.5 (C2′), 49.3 (C1′), 41.7 (NMe), 26.7 (i-Pr CH), 26.5 (i-Pr Me), 24.2 (C1 Me), 17.6 (i-Pr Me).
Synthesis of (1R,2R,5S,6S)-6-isopropyl-5-methyl-5-((2R,4R,5R)-3-methyl-4,5-diphenyl-oxazolidin-2-yl)cyclohex-3-ene-1,2-diol: [17]

(4S,5S,6R)-4-((4R,5R)-4,5-Diphenyl-4,5-dihydrooxazol-2-yl)-6-hydroxy-5-isopropyl-4-methylcyclohex-2-enone (1.43 g, 3.53 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (10.00 mL) at room temperature, freshly opened MeOTf (0.44 mL, 1.1 equiv) was added and the solution was stirred at room temperature for three hours until formation of the N-methyl triflate salt was complete as indicated by TLC analysis and the off white salt crashing out of solution. MeOH (30.00 mL) was added, and the reaction mixture was cooled to 0 °C. NaBH₄ (0.29 g, 2.0 equiv) was added as a solid, the solution cleared and became yellow. The reaction mixture was allowed to reach room temperature over 40 minutes and was concentrated by half under reduced pressure. EtOAc (20 mL) was added and the solution was washed with saturated NH₄Cl (10 mL), and brine before drying with MgSO₄. The solvent was removed under reduced pressure and the residue purified with flash chromatography (5 % to 30 % gradient EtOAc in petroleum ether) to give compound 17 (0.64 g, 42 %) and compound 51 (0.68 g, 45 %) as a clear oils.

R₂: 0.29 (40 %, EtOAc in petrol); [α]_D^{22} : +120.8 (c. 1, CHCl₃); MS m/z (ES-) 406 ((M-H)^-, 100 %); HRMS: found 408.2532, (M+H)^+ requires 408.2534; ν_{max}^{film}/cm⁻¹ 3389 (strong OH), 2950 (CH); ^1H-NMR (CDCl₃, 400 MHz) δ 7.23-7.09 (m, 10H, Ar), 6.97-6.92 (m, 2H, Ar), 5.96 (dd, J₂, 10 Hz, 1H, C6’ H), 5.55 (dd, J₂, 10 Hz, 1H, C5’ H), 4.66 (d, J9 Hz, 1H, C5 H), 4.46 (s, 1H, C2 H), 4.05 (dd, J7, 12 Hz, 1H, C3’ H), 3.85 (m, 1H, C4’ H), 3.21 (d, J9 Hz, 1H, C4 H ), 2.42 (br s, 2H, OH x 2), 2.08 (sept, J7 Hz, 1H, i-Pr H), 1.39 (d, J12 Hz, 1H, C2’ H), 1.21 (d, J7 Hz, 3H, i-Pr Me), 1.11 (d, J7 Hz, 3H, i-Pr Me), 1.09 (s, 3H, C1’ Me); ^13C-NMR (CDCl₃, 100 MHz) δ 138.6 (Ar), 138.4 (Ar), 134.4 (C5’), 128.6 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.8 (Ar), 2 X
126.3 (Ar), 100.0 (C2), 85.6 (C5), 79.6 (C4), 75.9 (C4'), 75.8, 73.8 (C3'), 54.1 (C2'), 48.6 (C1'), 41.9 (NMe), 27.4 (iPr Me), 25.9 (i-PrC H), 24.7 (C1' Me), 17.9 (i-Pr Me).

Synthesis of [(1R,4S,5S,6R)-6-hydroxy-5-isopropyl-4-methyl-4-[(2R,4R,5R)-3-methyl-4,5-diphenyl-oxazolidin-2-yl]cyclohex-2-en-1-yl] 2,2,2-trichloroethanimidate: [104]

(1R,2R,5S,6S)-6-Isopropyl-5-methyl-5-((2R,4R,5R)-3-methyl-4,5-diphenyl-oxazolidin-2-yl)cyclohex-3-ene-1,2-diol 17 (0.23 g, 0.56 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (6 mL) and stirred at 0 °C, DBU (0.10 mL, 1.3 equiv) was added the solution was stirred for five minutes. Trichloroacetonitrile (0.06 mL, 1.5 equiv) was added, TLC analysis indicated complete consumption of starting material after 15 minutes. The reaction was quenched with saturated NH₄Cl (5 mL), extracted with CH₂Cl₂ (10 mL) washed with Brine (5 mL) and dried with Na₂SO₄. Solvent was removed under reduced pressure before purification with flash chromatography (5 % to 40 % gradient EtOAc in petroleum ether) to give compound 104 (0.19 g, 61 %) as a colourless oil.

Rf: 0.64 (35 %, EtOAc in petrol); [α]D²²: +214 (c. 1, CHCl₃); Vmax(film)/cm⁻¹ 3345 (OH), 1655 (CH), 1655 (C=O); ¹H-NMR (CDCl₃, 400 MHz) δ 8.24 (s, 1H, NH), 7.26-6.09 (m, 10H, Ar), 6.33 (dd, J 2,10 Hz, 1H, C5' H), 5.82 (dd, J 10, 3 Hz, 1H, C6' H), 5.26 (m, 1H, C4' H), 4.84 (d, J 9 Hz, 1H, C5 H), 4.63 (s, 1H, C2 H), 4.60 (dd, J 12, 5.5, 2 Hz, 1H, C3' H), 4.41 (d, J 2 Hz, 1H, C3' OH), 3.40 (d, J 9 Hz, 1H, C4 H), 2.45 (s, 3H, NMe), 2.25 (sept, J 7 Hz, 1H, i-Pr H), 1.67 (d, J 12 Hz, 1H, C2' H), 1.35 (d, J 7.5 Hz, 3H, i-Pr Me), 1.31 (s, 3H, C1' Me), 1.26 (d, J 7.5 Hz, 3H, i-Pr Me); ¹³C-NMR (CDCl₃, 100 MHz) δ 164.4 (C2 C=O), 138.6 (Ar), 137.8 (C5'), 128.4 (Ar), 128.3 (Ar), 138.1 (Ar), 127.9 (Ar), 192
127.8 (Ar), 127.6 (Ar), 126.8 (Ar), 126.6 (Ar), 123.8 (C2), 86.1 (C4'), 85.9 (C5), 79.4 (C4), 71.3 (C3'), 54.6 (C2'), 47.6 (C1'), 41.9 (NMe), 27.2 (iPr Me), 26.2 (iPr CH), 24.5 (C1' Me), 17.6 (iPr Me).

**Synthesis of (1S,5R,6S)-5-hydroxy-6-isopropyl-1-methyl-4-oxo-cyclohex-2-ene-1-carbaldehyde: [86]**

(4S,5S,6R)-4-((4R,5R)-4,5-Diphenyl-4,5-dihydrooxazol-2-yl)-6-hydroxy-5-isopropyl-4-methylcyclohex-2-enone 16 (3.90 g, 10.01 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (40.00 mL), MeOTf (1.22 mL, 1.1 equiv) was added and the solution was stirred for 16 hours at room temperature. EtOH (50 mL) and CH₂Cl₂ (100 mL) were added, and the solution was cooled to -78 °C. NaBH₄ (0.37 g, 1.0 equiv, in 10.00 mL of ethanol) was added over a period of 2 minutes. After 30 minutes TLC analysis indicated complete consumption of starting material. The reaction was quenched with saturated NH₄Cl (40 mL), removed from the cooling bath and allowed to reach room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (100 mL). The combined organic layers were washed with brine (20 mL) and dried with MgSO₄. The solvent was removed under reduced pressure; the solid was redissolved in MeOH and evaporated to dryness. This solid was dissolved in THF (60.00 mL), water (30.00 mL) and oxalic acid (7.00 g, 7.7 equiv) were added and the solution was heated at 40 °C for 4 days. The solution was extracted with EtOAc (100 mL), the combined organic layers were washed with saturated NaHCO₃ (10 mL), brine (20 mL) and dried with MgSO₄. Purification with flash chromatography (5 % to 25 % gradient EtOAc in petroleum ether) to give aldehyde 86 (1.44 g, 73 %) as an oil that crystallized on standing. Oxazolidine 51 (0.27 g, 7 %) was also isolated.
Rf: 0.33 (20 %, EtOAc in petrol); Mpt: 87-89 °C (MeOH); [α]D: +458 (c. 1, CHCl3); MS m/z (ES+): 196 (100 %, M); HRMS: found 195.1032, (M+ - H) requires 195.1026; Microanalysis found: C (67.47 %), H (8.60 %), C11H16O3 requires: C (67.32 %), H (8.22 %); Vmax(film)/cm⁻¹ 3488 (O-H), 2958 (C-H), 1717 (C=O aldehyde), 1672 (C=O enone); ¹H-NMR (CDCl3, 400 MHz) δ 9.74 (s, 1H, aldehyde), 6.35 (d, J 10 Hz, 1H, C5 H), 6.22 (d, J 10 Hz, 1H, C6 H), 4.33 (d, J 13 Hz, 1H, C3 H), 3.57 (s, 1H, C3 OH), 2.09 (sept, J 7 Hz, 1H, i-Pr H), 1.97 (d, J 13 Hz, 1H, C2 H), 1.36 (s, 3H, C1 Me), 1.08 (d, J 7 Hz, 3H, i-Pr Me), 1.02 (d, J 7 Hz, 3H, i-Pr Me); ¹³C-NMR (CDCl3, 100 MHz) δ 200.2 (C4), 199.9 (C2'), 151.5 (C6), 127.9 (C5), 71.6 (C3), 56.8 (C2), 55.7 (C1), 26.6 (C i-Pr H), 25.6 (i-Pr Me), 21.1 (C1 Me), 17.9 (i-Pr Me).

**Synthesis of (4S,5S,6R)-6-hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one: [52]**

(1S,5R,6S)-5-Hydroxy-6-isopropyl-1-methyl-4-oxo-cyclohex-2-ene-1-carbaldehyde 86 (0.40 g, 2.04 mmol, 1.0 equiv) was dissolved in EtOH (15.00 mL) at room temperature with stirring. AcOH (0.40 mL) was added and the solution was heated to 40 °C. NaBH₃CN (0.13 g, 1.0 equiv) was added and the reaction mixture was stirred for 15 minutes and the reaction was quenched with acetaldehyde (2.00 mL), heating was removed and stirring continued for 10 minutes. Saturated aqueous NaHCO₃ (5 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (10 mL) and CH₂Cl₂:EtOAc (1:1, 20 mL). The combined organic extracts were washed with brine (10 mL) and dried with MgSO₄ before purification with flash chromatography (5 % to 20 % gradient EtOAc in petroleum ether) to give compound 52 (0.33 g, 82 %) as clear oil that crystallised on standing.
**Rf:** 0.23 (30 %, EtOAc in petrol) visualised with PMA;  
**Mpt:** 49-50 °C (MeOH);  
**[α]_{D}^{22}** : +54.4 (c. 1, CHCl3);  
**MS m/z** (ES+) 221 (100 %, (M+Na)^+);  
**HRMS:** found 221.1149, (M+Na)^+, C_{11}H_{18}O_{3}Na requires 221.1148;  
\[\nu_{\text{max}}\text{(film)}/\text{cm}^{-1}\] 3493 OH, 3448 OH, 2963 (CH), 1660 (enone C=O);  
**¹H-NMR** (CDCl3, 400 MHz) δ 6.57 (d, J 10 Hz, 1H, C5 H), 6.08 (d, J 10 Hz, 1H, C6 H), 4.62 (d, J 13 Hz, 1H, C3 H), 3.85 (d, J 11 Hz, 1H, C2' H), 3.44 (s, 1H, C3OH), 1.96 (sept, J 7 Hz, i-Pr H), 1.74 (d, J 13 Hz, C2 H), 1.49 (brs, 1H, C2' OH), 1.14 (d, J 7 Hz, 3H, i-Pr Me), 1.08 (d, J 7 Hz, 3H, i-Pr Me), 1.04 (s, 3H, C1 Me);  
**¹³C-NMR** (CDCl3, 100 MHz) δ 202.5 (C4), 157.6 (C5), 126.1 (C6), 72.1 (C3), 66.2 (C2'), 54.7 (C2), 44.6 (C1 Me), 30.9 (i-PrCH), 26.8 (i-Pr Me), 23.8 (C1 Me), 17.3 (i-Pr Me).

**Synthesis of (1S,3R,4S,5S,6S)-3-hydroxy-5-(hydroxymethyl)-4-isopropyl-5-methyl-7-oxabicyclo[4.1.0]heptan-2-one:** [90]

(4S,5S,6R)-6-Hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one 52 (93.00 mg, 0.47 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (2.00 ml), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (20.00 mg, 0.3 equiv) and t-BuOOH (0.46 mL, 5.5 equiv, 5.5 M in decane) were added sequentially. The solution was stirred at room temperature for 7 days. The reaction was loaded directly on to a column of silica gel and purified with flash chromatography (30 % EtOAc in petroleum ether) the material isolated from this column was not pure by NMR. Impurities were removed by a second purification (10 % MTBE in CH₂Cl₂) to give compound 90 (26.00 mg, 27 %) as a clear oil.

**Rf:** 0.31 (60 %, EtOAc in petrol);  
**[α]_{D}^{22}** : +46.8 (c. 1, CHCl3);  
**MS m/z** (ES+) 237.11 (100 %, (M+Na)^+);  
**HRMS:** found 237.11, (M+Na)^+, C_{11}H_{18}O_{4}Na requires 237.10;  
\[\nu_{\text{max}}\text{(film)}/\text{cm}^{-1}\] 3436 (OH), 2965 (CH), 1718 (C=O);  
**¹H-NMR** (CDCl3, 400 MHz) δ 4.59 (d, J 12 Hz, 1H, C3 H), 3.99 (d, J 11 Hz, 1H, C6 H), 3.99 (d, J 11 Hz,
1H, C2' H), 3.64 (d, J 11 Hz, 1H, C2' H), 3.53 (d, J 4 Hz, 1H, C5 H), 3.41 (d, J 4 Hz, C6 H), 1.84 (sept, J 7 Hz, 1H, i-Pr H), 1.46 (d, J 12 Hz, 1H, C2 H), 1.14 (s, 3H, C1 Me), 1.06 (d, J 7 Hz, 3H, i-Pr Me), 1.00 (d, J 7 Hz, 3H, i-Pr Me); \(^{13}\text{C-NMR}\) (CDCl\(_3\), 100 MHz) \(\delta\) 208.9 (C4), 70.3 (C3), 66.9 (C6), 65.6 (C2'), 60.1 (C2), 55.0 (C5), 40.0 (C1), 27.8 (i-Pr H), 26.5 (i-Pr Me), 21.7 (C1 Me), 17.6 (i-Pr Me).

**Synthesis of ((1S,5R,6S)-5-formyloxy-6-isopropyl-1-methyl-4-oxo-cyclohex-2-en-1-yl) methyl formate:** [95]

\[\text{H} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{CO} \quad \text{H}\]

(4S,5S,6R)-6-Hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one \(52\) (30.00 mg, 0.15 mmol, 1 equiv) was dissolved in Formic acid (5.00 mL), NH\(_4\)OAc (110.00 mg, 10.0 equiv) was added and the solution was heated at reflux for 3 hours. The reaction was neutralized with saturated aqueous NaHCO\(_3\), and extracted with EtOAc. The organic layer was dried with Na\(_2\)SO\(_4\) and the solvent was removed under reduced pressure. To give the title compound (39.00 mg, 100 %) as a clear oil.

\(^{1}\text{H-NMR}\) (CDCl\(_3\), 400 MHz) \(\delta\) 8.26 (s, 1H, COH), 8.07 (s, 1H, COH), 6.56 (d, J 10 Hz, 1H, C5 H), 6.08 (d, J 10 Hz, 1H, C6 H), 5.83 (d, J 12 Hz, 1H, C3 H), 4.34 (d, J 12 Hz, 1H, C2' H), 4.15 (d, J 12 Hz, 1H, C2' H), 2.23 (d, J 13.5 Hz, 1H, C2 H), 2.07 (sept, J 7 Hz, 1H, i-Pr H), 1.25 (s, 3H, C1 Me), 1.14 (d, J 7 Hz, 3H, i-Pr Me), 0.97 (d, J 7 Hz, 3H, i-Pr Me).
(5S,6S)-5-(hydroxymethyl)-6-isopropyl-5-methyl-cyclohex-3-ene-1,2-dione: [91]

(4S,5S,6R)-6-Hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one 52 (0.10 g, 0.50 mmol, 1.0 equiv) was dissolved in CH$_2$Cl$_2$, VO(acac)$_2$ (8.00 mg, 0.06 equiv) was added and the solution was stirred at room temperature for 2 minutes before t-BuOOH (0.10 mL, 5.5 M in decane, 1.1 equiv) was added the solution became deep red. The reaction was stirred at room temperature for 3 hours. Saturated NH$_4$Cl (5 mL) was added and the reaction mixture was extracted with CH$_2$Cl$_2$ (10 mL). The combined organic extracts were washed with brine (5 mL) and dried with Na$_2$SO$_4$. The solvent was removed under reduced pressure before purification with flash chromatography (0 – 15 % gradient EtOAc in petroleum ether) to give compound 91 (0.097 g, 95 %) as an oil.

$R_f$: 0.7 (60 %, EtOAc in petrol) visualized with PMA; $[\alpha]_{D}^{22}$: +95.6 (c. 1, CHCl$_3$); MS m/z (ES+) 219 (100 %, (M+Na)$^+$); HRMS: found 219.0966, (M+Na)$^+$, C$_{11}$H$_{16}$O$_3$Na requires 219.0992; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3441 (OH), 2960 (CH), 1691 (C=O); $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 7.30 (d, $J$ 9 Hz, 1H, C$_5$ H), 6.18 (d, $J$ 9 Hz, 1H, C$_6$ H), 4.89 (s, 1H, C$_1'$ OH), 4.10 (d, $J$ 8 Hz, 1H, C$_2'$ H), 3.42 (d, $J$ 8 Hz, 1H, C$_2'$ H), 2.16 (dsept, $J$ 2, 7.5 Hz, 1H, i-Pr H), 1.73 (d, $J$ 2 Hz, 1H, C$_2$ H), 1.39 (s, 3H, C$_1$ Me), 1.22 (d, $J$ 7 Hz, 3H, i-Pr Me), 1.19 (d, $J$ 7 Hz, 3H, i-Pr Me); $^{13}$C-NMR (CDCl$_3$, 100 MHz) $\delta$ 194.8 (C4), 165.9 (C3), 124.6 (C6), 106.1 (C5), 73.2 (C$_1'$ Me), 58.9 (C2), 49.7 (C i-Pr H), 26.6 (C1), 22.0 (i-Pr Me), 19.4 (i-Pr Me), 17.6 (C$_1$ Me).
Synthesis of \((1S,2S,3S,4S,5R,6S)-6\text{-isopropyl-8-oxabicyclo[2.2.2]octane-2,3,4,5-tetrol}\):

(4S,5S,6R)-6-Hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one 52 (50.00 mg, 0.25 mmol, 1.0 equiv) and NMO hydrate (60.00 mg, 2.0 equiv), were dissolved in CH$_2$Cl$_2$ (2.00 ml). OsO$_4$ solution (0.16 mL, 0.05 equiv, 0.08 M in t-BuOH) was added. The solution was stirred at room temperature for five days. The crude reaction mixture was purified by flash chromatography (70 – 100 % gradient EtOAc in petroleum ether), to give compound 89 (20 mg, 35 %) as a colourless solid.

R$_f$: 0.3 (EtOAc) visualised with KMnO$_4$; [a]$_D^{22}$: −3.4 (c. 1, MeOH); MS m/z (ES+) 255 (100 %, (M+Na)$^+$); HRMS: found 255.1201, (M+Na)$^+$, C$_{11}$H$_{20}$O$_5$Na requires 255.1203; $\nu_{\text{max}}$(film)/cm$^{-1}$ 3227 (OH), 2953 (CH); $^1$H-NMR (CD$_3$OD, 400 MHz) $\delta$ 3.94 (d, $J$ 9 Hz, 1H, C5 H), 3.70 (dd, $J$ 9, 1 Hz, 1H, C1' H), 3.59 (d, 1H, C3 H), 3.54 (dd, $J$ 11, 2 Hz, 1H, C1' H), 3.41 (dd, $J$ 9, 2 Hz, 1H, C6 H), 2.02 (d sept, $J$ 7, 3 Hz, 1H, i-Pr H), 1.14 (m, 1H, C2 H), 0.97 (d, $J$ 5 Hz, 3H, i-Pr Me), 0.95 (d, $J$ 5 Hz, 3H, i-Pr Me), 0.78 (s, 3H, C1 Me); $^{13}$C-NMR (CD$_3$OD, 400 MHz) $\delta$ 97.2 (C4), 72.9 (C6), 70.8 (C3), 67.4 (C2'), 66.5 (C5), 52.5 (C4), 39.7 (C1), 28.5 (i-Pr CH), 23.9 (i-Pr Me), 18.8 (i-Pr Me), 16.0 (C1 Me).
Synthesis of (4S,5S)-6-hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one oxime: [96]

(4S,5S,6R)-6-Hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one 52 (0.13 g, 0.66 mmol, 1.0 equiv) was dissolved in MeOH (6.00 mL) NH₂OH·HCl (0.23 g, 5.0 equiv) and NaOAc (0.27, 5.0 equiv) were added the reaction was stirred at room temperature for 1 hour. Water (2.00 mL) was added and the solution was extracted with EtOAc (20 mL). The organic extracts were washed with brine (10 mL) and the solvent was removed under reduced pressure to give (4S,5S)-6-hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one oxime (0.13 g, 89 %) as a 2:3 mixture of oximes 96, as an orange oil.

**MS m/z** (ES+) 236 (100 %, (M+Na)⁺); Major ^1H-NMR (CDCl₃, 400 MHz) δ 6.81 (d, J 10 Hz, 1H, C5 H), 5.94 (d, J 10 Hz, 1H, C6 H), 5.32 (br s, 1H, NOH), 4.90 (d, J 12 Hz, 1H, C3 H), 3.73 (d, J 11 Hz, 1H, C2' H), 3.38 (d, J 11 Hz, 1H, C2' H), 2.01 (sept, J 7 Hz, 1H, i-Pr C H), 1.61 (d, J 12 Hz, 1H, C 2H), 1.19-1.14 (m, 6H, i-Pr Me X2), 1.05 (s, 3H, C1 Me), minor ^1H-NMR (CDCl₃, 400 MHz), 6.18 (d, J 10 Hz, 1H, C5 H), 5.97 (d, J 10 Hz, 1H, C6 H), 5.32 (br s, 1H, NOH), 5.12 (d, J 10 Hz, 1H, C3 H), 3.60 (d, J 11 Hz, 1H, C2' H), 3.32 (d, J 11 Hz, 1H, C2' H), 2.10 (sept, J 7 Hz, 1H, i-Pr C H), 1.69 (d, J 10 Hz, 1H, C 2H), 1.19-1.14 (m, 6H, i-Pr Me X2), 1.10 (s, 3H, C1 Me).
Synthesis of (1R,5S,6S)-2-benzoylimino-5-(hydroxymethyl)-6-isopropyl-5-methyl-cyclohex-3-en-1-ol

(4S,5S,6R)-6-Hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one 52 was dissolved (40.00 mg, 0.20 mmol, 1.0 equiv) in MeOH (3.00 mL). NaOAc (25.00 mg, 1.5 equiv) and O-benzylhydroxylamine hydrochloride (40.00 mg, 1.5 equiv) were added and the solution was stirred for 16 hours at room temperature. Water (5 mL) was added and the reaction mixture was extracted with EtOAc (10 mL). The organic layer was washed with brine (5 mL) and dried with Na$_2$SO$_4$. The solvent was removed under reduced pressure to give (1R,5S,6S)-2-benzoylimino-5-(hydroxymethyl)-6-isopropyl-5-methyl-cyclohex-3-en-1-ol (37.00 mg, 60 %) as a 13:1 mixture of isomers.

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ 7.31-7.19 (m, 5H, Ph), 6.66 (d, $J$ 10 Hz, 1H, C5 H), 5.82 (d, $J$ 10 Hz, 1H, C6 H), 5.04 (d, $J$ 3 Hz, 2H, OCH$_2$Ph), 4.73 (d, $J$ 12 Hz, 1H, C3 H), 3.63 (d, $J$ 11 Hz, 1H, C2' H), 3.27 (d, $J$ 11 Hz, 1H, C2' H), 1.91 (sept, $J$ 7 Hz, 1H, iPr CH), 1.55 (d, $J$ 12 Hz, 1H, C2 H), 1.10 (d, $J$ 7 Hz, 3H, iPr Me), 1.08 (d, $J$ 7 Hz, 3H, iPr Me), 0.95 (sept, 3H, C1 Me).
Synthesis of (1R,5S,6S)-2-amino-5-(hydroxymethyl)-6-isopropyl-5-methyl-cyclohex-3-en-1-ol \[94\]

(4S,5S)-6-Hydroxy-4-(hydroxymethyl)-5-isopropyl-4-methyl-cyclohex-2-en-1-one oxime (0.14 g, 0.65 mmol, 1 equiv) was dissolved in Ethanol (10 mL) and heated to 40 °C. Molybdenum trioxide (0.14 g, 1.5 equiv) was added and finely ground Sodium borohydride (0.10, 4 equiv) was added in portions with fizzing. The Black solution was stirred at 40 °C for 16 hours. The reaction was quenched with 1M potassium hydroxide solution (3 mL). The reaction mixture was filtered through a pad of celite, the filtrate was extracted with ethyl acetate (20 mL). The organic extract was dried with Na$_2$SO$_4$, and evaporated under reduced pressure. NMR analysis of this crude material showed major a component that was tentatively assigned as allylic amine \[94\], mass spectrometry also suggested that allylic amine \[94\] had formed.

**MS m/z** (ES+) 200 (100 %, (M+H)$^+$); **HRMS**: found 200.1650, (M+H)$^+$, C$_{11}$H$_{22}$NO$_2$ requires 200.1645; **$^1$H-NMR** (CDCl$_3$, 400 MHz) $\delta$ 5.57 (d, $J$ 10 Hz, 1H, C6 H), 5.26 (dd, $J$ 10, 2 Hz, C5 H), 3.53 (d, $J$ 11 Hz, 1 H, C2" H), 3.15 (d, $J$ 11 Hz, 1 H, C2’ H), 1.89 (sept, $J$ 7 Hz, 1H, $\text{Pr}$ CH), 1.41 (d, $J$ 7H, 6H, $\text{Pr}$Me X2), 0.88 (s, 3H, C1 Me).
Synthesis of \((1R,2R,5S,6S)-5\text{-}(\text{hydroxymethyl})-6\text{-}\text{isopropyl}-5\text{-}\text{methyl}\text{-}\text{cyclohex-3-ene-1,2-diol}:: \text{[90a]}\)

\((1S,5R,6S)-5\text{-}\text{Hydroxy}-6\text{-}\text{isopropyl}-1\text{-}\text{methyl}-4\text{-}\text{oxo}\text{-}\text{cyclohex-2-ene-1-carbaldehyde} \text{ 86 (0.20 g, 1.01 mmol, 1.0 equiv)} \text{ was dissolved in EtOH 5.00 mL, CeCl}_7\text{H}_2\text{O (0.37 g, 1.0 equiv) was added} \text{ and the solution was cooled to -78 °C. A solution of NaBH}_4 \text{ (0.04 g, 1.0 equiv, in EtOH 1 mL) was added, the reaction was stirred for 30 minutes and allowed to reach room temperature. IMPORTANT once at ROOM TEMPERATURE the reaction was quenched with saturated aqueous NH}_4\text{Cl solution (5 mL). The reaction was extracted with CH}_2\text{Cl}_2:\text{EtOAc (1:1, 20 mL) the combined organic extracts were washed with brine (5 mL) and dried with Na}_2\text{SO}_4. The solvent was removed under reduced pressure and flash chromatography (5 % to 20 % gradient EtOAc in petroleum ether) gave compound 90a (0.16 g, 80 %).}

R: 0.14 (60 %, EtOAc in petrol) visualised with PMA; Mpt: 131-134 °C (MeOH); [α]_{D}^{22} : +18.8 (c. 1, CHCl₃); MS m/z (ES+) 199 (100 %, (M-H)⁺); \(V_{\text{max}}\text{(film)}/\text{cm}^{-1}\) 3392 (OH), 2930 (CH), 1672 (C=C);

\(^{1}\text{H-NMR} \text{(CD}_3\text{OD, 400 MHz) δ 5.46 (d, J 10, 2 Hz, 1H, C6 H), 5.30 (d, J 10, 2 Hz, 1H, C5 H), 3.83 (m, 1H, C4 H), 3.76 (dd, J 7, 11 Hz, 1H, C3 H), 3.45 (d, J 11 Hz, 1H, C H COH), 3.24 (d, J 5 Hz, 1H, C H COH), 1.89 (sept, J 7 Hz, 1H, iPr H), 1.34 (d, J 12 Hz, 1H, C2 H), 1.05 (d, J 7 Hz, 6H, iPr Me), 0.86 (s, 3H, C1 Me);^{13}\text{C-NMR} \text{(CD}_3\text{OD, 400 MHz) δ 136.8 (C5), 129.4 (C6), 76.3 (C4), 74.1 (C3), 67.7 (C2'), 53.7 (C1), 45.0 (C2), 27.6 (iPr CH), 27.5 (iPr Me), 24.7 (C1 Me), 18.1 (iPr Me).}}\)
(1S,4R,5R,6S)-4,5-dihydroxy-6-isopropyl-1-methyl-cyclohex-2-ene-1-carbaldehyde: [102]

When the reduction of (1S,5R,6S)-5-hydroxy-6-isopropyl-1-methyl-4-oxo-cyclohex-2-ene-1-carbaldehyde 86 was quenched with NH₄Cl whilst still at -78 °C this aldehyde 102 was observed by NMR analysis of the crude mixture as a minor component in a 5:2 ratio with (1R,2R,5S,6S)-5-(hydroxymethyl)-6-isopropyl-5-methyl-cyclohex-3-ene-1,2-diol.

¹H-NMR (CDCl₃, 400 MHz) δ 9.58 (s, 1H, COH), 5.76 (dd, J 10, 2 Hz, 1H, C₅H), 4.99 (dd, J 10, 2 Hz, 1H, C₆H), 3.96 (d, J 2, Hz, 1H, C₄H), 3.79 (d, J 12 Hz, 1H, C₃H), 1.84 (sept, J 7 Hz, 1H, iPr CH), 1.55 (d, J 12 Hz, 1H, C₂H), 1.07 (s, 3H, C₁ Me), 1.03 (d, J 7 Hz, 3H, iPr Me), 0.92 (d, J 7 Hz, 3H, iPr Me).
Synthesis of \( (1R,2S,5S,6S)-5-\text{(hydroxymethyl)}-6\text{-isopropyl}-5\text{-methyl-cyclohex-3-ene-1,2-diol} \): [90b]

\[
\begin{align*}
&\text{(1S,5R,6S)-5-Hydroxy-6-isopropyl-1-methyl-4-oxo-cyclohex-2-ene-1-carbaldehyde} \quad 86 \quad (0.18 \; \text{g}, \; 0.91 \; \text{mmol}, \; 1.0 \; \text{equiv}) \; \text{was dissolved in MeOH} \; 5.00 \; \text{mL}, \; \text{CeCl}_7\text{(H}_2\text{O)} \; (0.68 \; \text{g}, \; 2.0 \; \text{equiv}) \; \text{was added and the solution was cooled to 0 °C with stirring. Finley powered NaBH}_4 \; (0.07 \; \text{g}, \; 2.0 \; \text{equiv}) \; \text{was dissolved was added to the reaction mixture. The solution was stirred at 0 °C for 30 minutes and allowed warm to room temperature. Once at room temperature the reaction was quenched with saturated aqueous NH}_4\text{Cl solution} \; (5 \; \text{mL}). \; \text{The reaction was extracted with CH}_2\text{Cl}_2\text{:EtOAc} \; (1:1, \; 20 \; \text{mL}) \; \text{the combined organic extracts were washed with brine} \; (5 \; \text{mL}) \; \text{and dried with Na}_2\text{SO}_4, \; \text{the solvent was removed under reduced pressure before purification with flash chromatography (5 % to 20 % gradient EtOAc in petroleum ether) to give compounds 90a} \; (0.12 \; \text{g}, \; 76 \; \%) \; \text{and 90b} \; (23.00 \; \text{mg}, \; 12 \; \%) \; \text{as colourless solids.}
\end{align*}
\]

\( \text{Rf: 0.09 (60 \; \%, \; EtOAc in petrol) visualised with PMA; } \quad [\alpha]^{22}_D : +70.8 \; (\text{c. 1, CHCl}_3); \text{ MS m/z (ES-)} \; 199 \; (100 \; \%, \; \text{M-H}^-); \text{ HRMS: found 199.1350, (M-H)^-}; C_{11}H_{19}O_3 \text{ requires 199.1339; V}_{\text{max (film)}}/\text{cm}^{-1} \; 3355 \; (\text{OH}), \; 2949 \; (\text{CH}), \; 1650 \; (\text{C=C}); \text{ H-NMR} \; (\text{CDCl}_3, \; 400 \; \text{MHz}) \; \delta \; 5.94 \; (\text{dd, } J 10, \; 5 \; \text{Hz, 1H, C5 H}), \; 5.50 \; (\text{d, } J 10 \; \text{Hz, 1H, C6 H}), \; 4.20 \; (\text{d, } J 4.5 \; \text{Hz, 1H, C4 H}), \; 4.01 \; (\text{apt t, } J 5 \; \text{Hz, 1H, C3 H}), \; 3.60 \; (\text{d, } J 11 \; \text{Hz, 1H, C2' H}), \; 3.22 \; (\text{d, } J 11 \; \text{Hz, 1H, C2' H}), \; 1.92 \; (\text{sept, } J 7 \; \text{Hz, 1H, } \text{i-Pr H}), \; 1.75 \; (\text{br s, 3H, OH}), \; 1.45 \; (\text{d, } J 12 \; \text{Hz, 1H, C2 H}), \; 1.12 \; (\text{d, } J 7 \; \text{Hz, 3H, } \text{i-Pr Me}), \; 1.09 \; (\text{d, } J 7 \; \text{Hz, 3H, } \text{i-Pr Me}), \; 0.92 \; (\text{s, 3H, C1 Me}); \text{ C-NMR} \; (\text{CDCl}_3, \; 100 \; \text{MHz}) \; \delta \; 139.3 \; (\text{C6}), \; 127.4 \; (\text{C5}), \; 69.0 \; (\text{C4}), \; 66.6 \; (\text{C3}), \; 66.5 \; (\text{C2'}), \; 48.4 \; (\text{C2}), \; 44.5 \; (\text{C1}), \; 27.2 \; (\text{i-Pr Me}), \; 26.0 \; (\text{C } \text{i-Pr H}), \; 24.3 \; (\text{C1 Me}), \; 17.3 \; (\text{i-Pr Me}).}
Synthesis of \((1S,2S,3R,4S,5S,6R)-5\text{-}(\text{hydroxymethyl})\text{-}4\text{-isopropyl}\text{-}5\text{-methyl}\text{-}7\text{-oxabicyclo}(4.1.0)\text{heptane-2,3-diol: [99]}

\((1R,2R,5S,6S)-5\text{-}(\text{hydroxymethyl})\text{-}6\text{-isopropyl}\text{-}5\text{-methyl}\text{-}\text{cyclohex-3-ene-1,2-diol 90a (0.14 g, 0.70 mmol, 1.0 equiv) was stirred as a suspension in CH}_2\text{Cl}_2 (4.00 mL) and to 0 °C. m-CPBA (0.24, 2.0 equiv) was added and reaction was stirred at 0 °C for 30 minutes, during this time reaction cleared. The reaction was warmed to room temperature. The reaction mixture was concentrated by half under reduced pressure, before purification with flash chromatography (40 % to 80 % gradient EtOAc in petroleum ether) to give compound 99 (0.12, 84 %) as a colourless solid.}

\textbf{R}_f: 0.26 (EtOAc) visualised with PMA; \textbf{Mpt:} 122-124 °C (EtOAc); \textbf{[a]}^{22}_D: +16.6 (c. 1, MeOH); \textbf{MS m/z} (ES+) 239 (100 %, (M+H)\textsuperscript{+}); \textbf{HRMS:} found 239.1253, (M+H)\textsuperscript{+}, \text{C}_{11}\text{H}_{21}\text{O}_4 requires 239.1254; \textbf{ν}_{\text{max}}(\text{film})/\text{cm}^{-1} 3291 (\text{OH}); \textbf{¹H-NMR} (CD\textsubscript{3}OD, 400 MHz) δ 3.68 (d, \textit{J} 10 Hz, 1H, C2’ OH), 3.57 (dd, \textit{J} 2, 6 Hz, 1H, C4 H), 3.49 (dd, \textit{J} 8, 11.5 Hz, 1H, C3 H), 3.36 (d, \textit{J} 10 Hz, 1H, C2’ OH), 3.25 (t, \textit{J} 4 Hz, 1H, C5 H), 2.91 (d, \textit{J} 4 Hz, 1H, C6 H), 1.78 (sept, \textit{J} 7.6 Hz, 1H, \textit{i-Pr} H), 1.10 (d, \textit{J} 11.5 Hz, 1H, C2 H), 1.06 (s, 3H, C1 Me), 0.99 (d, \textit{J} 7 Hz, 3H, \textit{i-Pr} Me), 0.91 (d, \textit{J} 7 Hz, 3H, \textit{i-Pr} Me); \textbf{¹³C-NMR} (CD\textsubscript{3}OD, 100 MHz) δ 76.8 (C4), 70.9 (C3), 65.4 (C2’), 61.9 (C6), 58.9 (C5), 54.5 (C2), 41.6 (C1), 28.1 (C \textit{i-Pr} H), 27.3 (\textit{i-Pr} Me), 22.4 (C1 Me), 18.4 (\textit{i-Pr} Me).
Synthesis of (1R,2R,3R,4S,5R,6S)-6-azido-5-(hydroxymethyl)-5-methylcyclohexane-1,2,3,4-tetraol: [100]

(1S,2S,3R,4S,5S,6R)-5-(hydroxymethyl)-4-Isopropyl-5-methyl-7-oxabicyclo(4.1.0)heptane-2,3-diol 99 (0.05 g, 0.23 mmol, 1.0 equiv) was dissolved in MeOH (3.20 mL), NaN₃ (0.17 g, 10 equiv) was added, aqueous NH₄Cl (0.80 mL, 1.2 M) was added as a co-solvent. The solution was stirred at room temperature for 10 minutes and the solution was heated at reflux for 16 hours. The solvent was removed under reduced pressure; toluene (7.00 mL) was added and removed under reduced pressure twice, to remove water. CH₂Cl₂ (7.00 mL) was added, all solids were agitated with a micro-spatula and the heterogeneous mixture was filtered through a cotton wool plug in a glass Pasteur pipette, CH₂Cl₂ (10 mL) was pushed through the filtrate and collected. Followed by a mixture of EtOAc and CH₂Cl₂ (1:1, 15.00 mL) which was pushed through and collected; TLC analysis showed that the EtOAc:CH₂Cl₂ contained only one spot. The solvent was evaporated under reduced pressure, MeOH was added to the solid and evaporated under reduced pressure to remove EtOAc. Azide 100 (0.03 g, 62 %) was isolated as a colourless solid that was used without further purification.

Rf: 0.34 (EtOAc) visualised with PMA; [α]D²²: +32.4 (c. 1, MeOH); MS m/z (ES+) 282 (100 %, (M+Na)+); HRMS: found 282.1428, (M+Na)+, C₁₁H₂₁N₃O₄Na requires 282.14; Vmax(film)/cm⁻¹ 3170 (OH), 2914 (CH), 2103 (N=); ¹H-NMR (CD₃OD, 400 MHz) δ 3.95 (t, J 3.5 Hz, 1H, C5 H), 3.88 (d, J 11 Hz, 1H, C2' H), 3.73 (dd, J 11, 9 Hz, 1H, C3 H), 3.72 (d, J 3.5 Hz, 1H, C6 H), 3.44 (dd, J 9.5, 4 Hz, 1H, C4 H), 3.28 (d, J 11 Hz, 1H, C2' H), 1.88 (sept, J 7 Hz, 1H, 3Pr H), 1.32 (d, J 11 Hz, 1H, C2 H), 1.01 (d, J 7 Hz, 3H, 3Pr Me), 0.98 (d, J 7 Hz, 3H, 3Pr Me), 0.97 (s, 3H, C1 Me); ¹³C-NMR (CD₃OD, 100 MHz) δ 74.8 (C4), 73.3 (C5), 70.8 (C6), 70.7 (C4), 66.6 (C2'), 51.3 (C2), 46.2 (C1), 27.5 (C1 Me), 27.1 (C 3Pr H), 23.4 (3Pr Me), 18.6 (3Pr Me).
Synthesis of \((1R,2R,3S,4S,5R,6S)\)-6-azido-4-(hydroxymethyl)-4-methylcyclohexane-1,2,3,5-tetraol: [102]

\[(1S,2S,3R,4S,5S,6R)\] -5-(hydroxymethyl)-4-Isopropyl-5-methyl-7-oxabicyclo(4.1.0)heptane-2,3-diol (0.15 g, 0.69 mmol, 1.0 equiv) was dissolved in toluene with the aid of gentle heating from a Heat Gun. The solution was then stirred at room temperature, Yb(OTf)₃ (0.436 g, 1.0 equiv was added) and NaN₃ (0.45 g, 10 equiv) were added and the solution was stirred vigorously so all solids in the toluene were moving fluidly. Triethylamine (1.47 mL, 15 equiv, freshly distilled from CaH₂) was added and the heterogeneous slurry was heated to 80 °C for 14 hours. The solvent was removed under reduced pressure a 9:1 mixture of CH₂Cl₂:EtOAc (7.00 mL) was added, all solids were agitated with a microspatula and the heterogeneous mixture was loaded on to a column of silica gel and purified with flash chromatography (30 % to 60 % gradient EtOAc in petroleum ether) to give compound 102 (40.5 mg, 22 %) as a colourless oil that solidified on standing compound 100 was isolated as a minor component in Et₃N·TfOH. Due to the presence of Ytterbium, determination of diastereotopic ratio by NMR analysis could not be carried out.

\(R_f\): 0.66 (EtOAc) visualised with PMA; \([\alpha]_{22}^{22}\): +0.2 (c. 1, MeOH); \textbf{MS} \text{ m/z} (ES+) 282 (100 %, (M+Na)+); \textbf{HRMS}: found 282.1432, (M+Na)+, \(C_{11}H_{21}N_3O_4Na\) requires 282.1424; \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\) 3360 (OH), 2971 (CH), 2111 (N=N); \(\textbf{1H-NMR (CD}_3\text{OD), 400 MHz}\) \(\delta\) 3.84 (dd, \(J = 11, 9\) Hz, 1H, C3 H), 3.75 (t, \(J = 10\) Hz, 1H, C5 H), 3.56 (d, \(J = 11\) Hz, 1H, C2' H), 3.46 (d, \(J = 11\) Hz, 1H, C2' H), 3.00 (d, \(J = 10.5\) Hz, 1H, C6 H), 2.96 (dd, \(J = 10, 9\) Hz, 1H, C4 H), 1.90 (sept, \(J = 7\) Hz, 1H, \(i\text{-Pr}\) H), 1.03 (d, \(J = 4\) Hz, 3H, \(i\text{-Pr}\) Me), 1.01 (d, \(J = 4\) Hz, 3H, \(i\text{-Pr}\) Me), 1.00 (d, \(J = 8\) Hz, 1H, C2 H), 0.88 (s, 3H, C1 Me); \(\textbf{13C-NMR (CD}_3\text{OD, 100 MHz}\) \(\delta\) 80.1 (C6), 78.8 (C4), 73.4 (C3), 69.7 (C5), 63.6 (C2'), 53.5 (C2), 45.1 (C1), 27.4 (\(i\text{-Pr}\) Me), 27.2 (C \(i\text{-Pr}\) H), 22.7 (C1 Me), 18.4 (\(i\text{-Pr}\) Me).
Synthesis of $(1R,2S,3R,4S,5R,6S)$-4-amino-5-(hydroxymethyl)-6-isopropyl-5-methyl-cyclohexane-1,2,3-triol: [101]

Azide 100 (20.00 mg, 0.08 mmol, 1.0 equiv) was dissolved in 25 % MeOH in EtOAc (15.00 ml) and the solution was hydrogenated using an H-Cube containing a small scale 5 % Pd/C cartridge set to full H mode. The solution was pumped through at a rate of 0.5 mL/minutes at room temperature. The hydrogenated material was collected and the solvent was removed under reduced pressure. This material contained two compounds that equilibrated to the title compound on repeated dissolving in and evaporation of MeOH (17.8 mg, 98 %) as a colourless oil.

$R_f$: 0.28 (EtOAc, ); $[\alpha]_{D}^{22}$: −19.2 (c. 1, MeOH); MS m/z (ES-) 258 (100 %, (M-H)); HRMS: found 232.1564, (M-H)$^-$ requires 232.1554; $V_{\text{max}}$ (film)/cm$^{-1}$ 3336 (OH), 2947 (CH), 2359 (NH), 2340 (NH);

$^1$H-NMR (CD$_3$OD, 400 MHz) δ 3.83 (dd, $J$ 12, 9 Hz, 1H, C3 H), 3.80 (t, $J$ 3 Hz, 1H, C5 H), 3.79 (dd, $J$ 11 Hz, 1H, C2' H), 3.50 (dd, $J$ 9, 4 Hz, 1H, C4 H), 3.25 (d, $J$ 11 Hz, 1H, C2' H), 2.96 (d, $J$ 3 Hz, 1H, C6 H), 1.83 (sept, $J$ 7 Hz, 1H, i-Pr H), 1.45 (d, $J$ 11 Hz, 1H, C2 H), 1.05 (d, $J$ 3 Hz, 3H, i-Pr Me), 1.03 (d, $J$ 3 Hz, 3H, i-Pr Me), 0.88 (s, 3H, C1 Me); $^{13}$C-NMR (CD$_3$OD, 100 MHz) δ 75.9 (C5), 74.7 (C4), 71.3 (C3), 68.3 (C2'), 59.6 (C6), 50.6 (C2), 45.1 (C1), 27.7 (i-Pr C H), 27.3 (i-Pr Me), 23.0 (C1 Me), 18.5 (i-Pr Me).
Synthesis of (1R,2R,3S,4R,5S,6S)-3-amino-5-(hydroxymethyl)-6-isopropyl-5-methyl-cyclohexane-1,2,4-triol: [102]

Azide 102 (18.70 mg, 0.07 mmol, 1.0 equiv) was dissolved in MeOH (2.00 mL), and was transferred to a flask containing 10 % Pd/C (5 mg). The suspension was stirred for 4 hours at room temperature under an atmosphere of H₂ (balloon). The reaction was diluted with methanol and the reaction was filtered through celite on a sintered glass funnel. The solution was cooled with an ice bath and filtered through a small plug of cotton wool and silica in a glass Pasteur pipette. The solvent was removed under reduced pressure to give (10.8 mg, 66 %) as a colourless oil.

Rf: 0.3 (EtOAc); [α]D²²: −3.2 (c. 1, CHCl₃); MS m/z (ES+) 234 (100 %, M-H⁺); HRMS: found 234.1696, (M-H)⁺ C₁₁H₂₄NO₄ requires 234.1700; V_max (film)/cm⁻¹ 3248 (OH), 2916 (CH); ¹H-NMR (D₂O, 400 MHz) δ 3.71 (d, J 12 Hz, 1H, C₁’ H), 3.67 (dd, J 11.5, 8.5 Hz, 1H, C3), 3.57 (d, J 12 Hz, 1H, C₁’ H), 3.11 - 2.97 (m, 3H, C4, 5 & 6 H), 2.00 (sept, J 7 Hz, 1H, i-Pr H), 1.15 (d, J 11.5 Hz, 1H, C₂ H), 1.04 (s, 3H, C₁ Me), 1.00 (d, J 7 Hz, 3H, i-Pr Me), 0.94 (d, J 7 Hz, 3H, i-Pr Me); ¹³C-NMR (D₂O, 100 MHz) δ 79.4 (C4), 77.8 (C5), 72.1 (C3), 63.1 (C1’), 51.4 (C5), 50.6 (C2), 43.0 (C1), 26.2 (i-Pr C H), 25.3 (i-Pr Me), 20.9 (C₁ Me), 17.6 (i-Pr Me).
Crystallography data

Oxazoline containing α-hydroxy enone [16]

Table 1. Crystal data and structure refinement for s3134m.

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<td>Temperature</td>
<td>100(2) K</td>
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<td>Wavelength</td>
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</tr>
<tr>
<td>Crystal system, space group</td>
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<td>Unit cell dimensions</td>
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<tr>
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<td>b = 12.5073(11) Å, beta = 90 deg.</td>
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<tr>
<td></td>
<td>c = 21.7999(19) Å, gamma = 90 deg.</td>
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<tr>
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<td>F(000)</td>
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<td>Crystal size</td>
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<td>Theta range for data collection</td>
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<td>Limiting indices</td>
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<td>Reflections collected / unique</td>
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<tr>
<td>Completeness to theta = 26.42</td>
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<td>Absorption correction</td>
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<td>Refinement method</td>
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<td>Data / restraints / parameters</td>
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Table 1. Crystal data and structure refinement for s3148m.

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<th>Description</th>
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<tr>
<td>Empirical formula</td>
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<td>Wavelength</td>
<td>0.71073 Å</td>
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<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic, P2(1)2(1)2(1)</td>
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<tr>
<td>Unit cell dimensions</td>
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<td>Theta range for data collection</td>
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<td>Limiting indices</td>
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<td>Reflections collected / unique</td>
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<td>Absorption correction</td>
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<td>Max. and min. transmission</td>
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$N$-methyl oxazolidine containing α-hydroxy enone [85]

![Chemical structure of $N$-methyl oxazolidine containing α-hydroxy enone]

Table 1. Crystal data and structure refinement for s3422m.

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<td>100(2) K</td>
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<tr>
<td>Wavelength</td>
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<td>Crystal system, space group</td>
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**α-hydroxy enone containing aldehyde [86]**

![Chemical structure](image)

Table 1. Crystal data and structure refinement for s3346m.

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<td>Wavelength</td>
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<td>Crystal system, space group</td>
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<td>Largest diff. peak and hole</td>
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α-hydroxy enone [52]

Table 1. Crystal data and structure refinement for s3350m.

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<tr>
<td>Formula weight</td>
<td>198.25</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.9091(8) Å, alpha = 90 deg.</td>
</tr>
<tr>
<td></td>
<td>b = 12.0174(12) Å, beta = 101.894(2) deg.</td>
</tr>
<tr>
<td></td>
<td>c = 11.6054(12) Å, gamma = 90 deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>4.1220 Mg/m^3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.087 mm^-1</td>
</tr>
<tr>
<td>F(000)</td>
<td>432</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.35 x 0.20 x 0.05 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.47 to 28.27 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-10&lt;=h&lt;=10, -15&lt;=k&lt;=15, -14&lt;=l&lt;=14</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>9456 / 2682 [R(int) = 0.0455]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00</td>
<td>99.8%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9957 and 0.9701</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2682 / 1 / 263</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
<td>1.157</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0430, wR2 = 0.0793</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0473, wR2 = 0.0808</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.7(11)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.295 and -0.173 e.A^-3</td>
</tr>
</tbody>
</table>
Table 1. Crystal data and structure refinement for s3420n.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>s3420n</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C22 H42 O7</td>
</tr>
<tr>
<td>Formula weight</td>
<td>418.56</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Triclinic, P1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.0020(17) Å, alpha = 91.054(4) deg.</td>
</tr>
<tr>
<td></td>
<td>b = 7.0450(17) Å, beta = 99.221(4) deg.</td>
</tr>
<tr>
<td></td>
<td>c = 12.695(3) Å, gamma = 112.153(4) deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>570.4(2) Å³</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>1, 1.219 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.089 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>230</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.25 x 0.20 x 0.04 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.63 to 28.31 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-9&lt;=h&lt;=9, -9&lt;=k&lt;=9, -16&lt;=l&lt;=16</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>4893 / 2566 [R(int) = 0.0703]</td>
</tr>
<tr>
<td>Completeness to theta</td>
<td>= 25.00 98.5 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9965 and 0.9781</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2566 / 3 / 282</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>0.930</td>
</tr>
<tr>
<td>Final R indices [1&gt;2sigma(I)]</td>
<td>R1 = 0.0570, wR2 = 0.1071</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0963, wR2 = 0.1474</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-2(2)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.259 and -0.274 e.A⁻³</td>
</tr>
</tbody>
</table>
Allylic alcohol [87b]

Table 1. Crystal data and structure refinement for s3469ba.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>s3469ba</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C11 H20 O3</td>
</tr>
<tr>
<td>Formula weight</td>
<td>200.27</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 11.879(11) Å, alpha = 90 deg.</td>
</tr>
<tr>
<td></td>
<td>b = 10.806(10) Å, beta = 99.886(18) deg.</td>
</tr>
<tr>
<td></td>
<td>c = 9.456(9) Å, gamma = 90 deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>1195.8(19) Å³</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4, 1.112 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.079 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>440</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.70 x 0.50 x 0.50 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.57 to 23.25 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-13&lt;=h&lt;=10, -11&lt;=k&lt;=12, -7&lt;=l&lt;=10</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>4461 / 1709 [R(int) = 0.0511]</td>
</tr>
<tr>
<td>Completeness to theta</td>
<td>99.8 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.000 and 0.615</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1709 / 203 / 142</td>
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<tr>
<td>Goodness-of-fit on F²</td>
<td>1.372</td>
</tr>
<tr>
<td>Final R indices [1&gt;2sigma(I)]</td>
<td>R1 = 0.0954, wR2 = 0.1980</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1141, wR2 = 0.2056</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.300 and -0.274 e.A⁻³</td>
</tr>
</tbody>
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### Table 1. Crystal data and structure refinement for s3423m.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Identification code</td>
<td>s3423m</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C22 H40 O9</td>
</tr>
<tr>
<td>Formula weight</td>
<td>448.54</td>
</tr>
<tr>
<td>Temperature</td>
<td>180(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>Orthorhombic, P2(1)2(1)2(1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.394(5) Å alpha = 90 deg.</td>
</tr>
<tr>
<td></td>
<td>b = 11.463(8) Å beta = 90 deg.</td>
</tr>
<tr>
<td></td>
<td>c = 27.013(19) Å gamma = 90 deg.</td>
</tr>
<tr>
<td>Volume</td>
<td>2289(3) Å^3</td>
</tr>
<tr>
<td>Z, Calculated density</td>
<td>4, 1.301 Mg/m^3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.100 mm^-1</td>
</tr>
<tr>
<td>F(000)</td>
<td>976</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.30 x 0.20 x 0.03 mm</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.51 to 25.31 deg.</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-8 &lt;= h &lt;= 8, -13 &lt;= k &lt;= 13, -30 &lt;= l &lt;= 32</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>16052 / 4100 [R(int) = 0.1905]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9970 and 0.9707</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4100 / 62 / 292</td>
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<tr>
<td>Goodness-of-fit on F^2</td>
<td>0.994</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.1251, wR2 = 0.2650</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.2071, wR2 = 0.3185</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-3(4)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.538 and -0.520 e.A^-3</td>
</tr>
</tbody>
</table>
133. C. F. Lane, Synthesis, 1975, 135-146.