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Developments in

Acyl-Claisen

Rearrangements and

Application to Synthesis

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A thesis submitted in fulfilment of the requirements

for the degree of Doctor of Philosophy in Chemistry.

The University of Auckland

2012
Abstract

The acyl-Claisen rearrangement is a powerful [3,3]-sigmatropic rearrangement of an allylic amine and an acyl chloride derived ketene. The α,β-substituted-γ,δ-olefinic amide 32 derived from this rearrangement has been demonstrated to be a powerful scaffold for elaboration via a number of routes.

This thesis describes the extension of acyl-Claisen rearrangement methodology to produce di-aromatic amides where previously only mono-aromatic amides had been produced. A screen of Lewis acids was carried out in an attempt to optimise rearrangement conditions and a variety of aromatic substrates of varying substitution were utilised. Elaboration of di-aromatic amides was then carried out to produce novel tetraphenyl-tetrahydrofuran 109c and progress was made towards the synthesis of resveratrol dimer tricuspidatol A 109b. Finally the synthesis of magnosalicin 112 was completed via mono-aromatic amide 32m.

The acyl-Claisen rearrangement methodology was further extended in an attempt to produce an asymmetric variant. Preparation of 3-substituted morpholines 181a-g from amino alcohols was carried out and subsequent allylation of these morpholines provided chiral substrates for the acyl-Claisen rearrangement. Rearrangement of many of these chiral allylic morpholines 182a-h/183a-h proved successful and analysis of the pseudoenantiomeric amides produced was carried out by chiral HPLC. Diastereoselectivity ranged from 50:50 to 92:8, although yields also varied widely (14 – 98%). Choosing the most robust rearrangement from this series we carried out a screen of acyl chlorides, establishing a wide range of suitable substituents.
Declaration

This is to certify that:

1) This thesis comprises only the author’s original work.
2) Due acknowledgement to all other material used has been made in the main text of the thesis.

Portions of this work have been previously published as follows:


“You miss 100 percent of the shots you never take” – Wayne ‘The Great One’ Gretzky
Acknowledgements

I am tremendously grateful to my supervisor Dr David Barker for not only all your advice and ideas over the last few years but also for the scholarship that enabled me to work on this Marsden funded project. I have learned a lot and matured significantly as a chemist under your mentorship and certainly could not have gotten where I am without your help.

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>Carbon nuclear magnetic resonance</td>
</tr>
<tr>
<td>$^1$H NMR</td>
<td>Proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>3°</td>
<td>Tertiary</td>
</tr>
<tr>
<td>Å</td>
<td>Ångstrom</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>AcOOH</td>
<td>Peracetic acid</td>
</tr>
<tr>
<td>APCI</td>
<td>Atmospheric pressure chemical ionisation</td>
</tr>
<tr>
<td>amu</td>
<td>Atomic mass units</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic moiety</td>
</tr>
<tr>
<td>ArLi</td>
<td>Generic aryl lithium</td>
</tr>
<tr>
<td>ASTM</td>
<td>American standard test method</td>
</tr>
<tr>
<td>B3LYP</td>
<td>Becke, three-parameter, Lee-Yang-Parr exchange-correlation functional</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BnBr</td>
<td>Benzyl bromide</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>Boc$_2$O</td>
<td>Di-tert-butyldicarbonate</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>conj.</td>
<td>Conjugated</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>Days</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>$N,N'$-Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>ddd</td>
<td>Doublet of doublet of doublets</td>
</tr>
<tr>
<td>ddq</td>
<td>Doublet of doublet of quartets</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DEPTQ</td>
<td>Distortionless enhancement by polarization transfer including the detection of quaternary nuclei experiment</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>$N,N'$-Dimethyl-4-aminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N'$-Dimethylformamide</td>
</tr>
<tr>
<td>dq</td>
<td>Doublet of quartets</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>dt</td>
<td>Doublet of triplets</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>er</td>
<td>Enantiomeric ratio</td>
</tr>
</tbody>
</table>
ESI* Electrospray ionisation
Et Ethyl
et al. Et alii (and others)
Et$_2$O Diethyl ether
EtOAc Ethyl acetate
EtOH Ethanol
FTIR Fourier transform infrared spectroscopy
h Hour(s)
HMBC Heteronuclear multiple bond correlation
HMPA Hexamethylphosphoramide
hNK$_1$ Human natural killer-1
HPLC High-performance liquid chromatography
HSQC Heteronuclear single quantum coherence
$i^\text{Bu}$ Iso-butyl
iefpcm Integral equation formalism polarizable continuum model
$i^\text{Pr}$ Iso-propyl
$i^\text{Pr}_2$NEt Hüning's base
$i^\text{Pr}OH$ Iso-propanol
IR Infrared
$J$ Spin-spin coupling constant
KHMDSD Potassium bis(trimethylsilyl)amide
LA Lewis acid
LDA Lithium diisopropylamide
LDEA Lithium diethylamide
LiHMDS Lithium bis(trimethylsilyl)amide
lit. Literature
m Multiplet
M (scheme) Metal
M.P. Melting point
$m/z$ Mass to charge ratio
Me Methyl
MeCN Acetonitrile
MeI Methyl iodide
MeLi Methyl lithium
MeOH Methanol
$m$- meta
min. Minutes
mol Mole
MOMCl Methyl chloromethyl ether
MOM Methoxymethyl ether
MsCl Methanesulfonyl chloride
$n^\text{BuLi}$ Normal-butyllithium

[xi]
ND  Not determined
NEt₃  Triethylamine
n-hexanes  Normal-hexanes
NMO  N-Methylmorpholine N-oxide
NMR  Nuclear magnetic resonance
nOe  Nuclear Overhauser effect
NPh  N-Phthalyl
^nPr  Normal-propyl
NR  No reaction
φ  Diameter
o-  ortho
o/n  Overnight
OAc  Acetoxy
OBn  Benzyloxy
OMe  Methoxy
OTf  O-Trifluoromethanesulfonate
p-  para
Ph  Phenyl
Ph-H  Benzene
PhMe  Toluene
Phthg  Phthalylglycyl
p-MeOPh  para-methoxyphenyl
ppm  Parts per million
q  Quartet
quant.  Quantitative yield
R, Rⁿ  Alkyl moiety
R_f  Retention factor
RSM  Returned starting material
rt  Room temperature
r_t  Retention time
s  Singlet
s  Seconds
SAMP  (S)-1-Amino-2-methoxymethylpyrrolidine
^Bu  Secondary-butyl
S_N2  Bimolecular nucleophilic substitution
SPh  Thiophenyl
t  Triplet
TBAF  Tetrabutylammonium fluoride
TBAI  Tetrabutylammonium iodide
TBS  tert-Butyldimethylsilyl
TBSCl  tert-Butyldimethylsilyl chloride
^Bu  Tertiary-butyl
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Chemical Name</th>
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<tbody>
<tr>
<td>'BuLi</td>
<td>Tertiary-butyllithium</td>
</tr>
<tr>
<td>'BuOH</td>
<td>Tertiary-butanol</td>
</tr>
<tr>
<td>tert</td>
<td>Tertiary</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>Trimethylsilyltrifluoromethanesulfonate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra violet</td>
</tr>
<tr>
<td>Δ</td>
<td>Reflux</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift (ppm)</td>
</tr>
</tbody>
</table>
Introduction
1.1 The Claisen rearrangement

First reported in 1912 by Ludwig Claisen the Claisen rearrangement is the [3,3]-sigmatropic rearrangement of an allyl-vinyl ether to give a γ,δ-unsaturated carbonyl framework (Scheme 1).² This useful carbon – carbon bond forming reaction is also referred to as the 3-oxa-Cope rearrangement, after the Cope rearrangement, an all carbon variant which was discovered 38 years later.³ The Claisen rearrangement has been thoroughly studied and no fewer than ten derivatives have been developed.⁴-¹³

1.1.1 Naming conventions

The adducts resulting from some Claisen rearrangement variants contain an α,β-substitution pattern (relative to a carbonyl equivalent) resulting in a syn-anti designation. In this work the convention of assigning syn-anti relationships is carried out in an extended chain conformation, although in some cases the more useful depiction is a closed conformation (Figure 1). For example compound 1 would be designated syn- in either depiction. In cases where the original work cited does not follow this convention designations have been translated. Where pendant substituents (R¹ / R²) offer a longer carbon chain extended conformation these have been ignored so as to maintain a meaningful uniformity.

1.1.2 The Claisen rearrangement

The Claisen rearrangement was later found to be common in nature. A key example is the conversion of chorismate 2 into prephenate 3 in the biosynthesis of aromatic amino acids, it is catalysed by the enzyme chorismate mutase (Scheme 2).¹⁴ In its most basic form the Claisen rearrangement requires simply the heating of an allyl vinyl ether at temperatures between 150 – 200 °C to proceed.¹⁵ The Claisen rearrangement tends to proceed via a chair transition state allowing olefin geometry to control, to a large degree, the diastereomeric outcome. This preference can be altered by substituent choice in which case a boat transition state may be preferred.¹⁶-¹⁸

[1]
The rearrangement of aryl-allyl ethers is known as the aromatic Claisen rearrangement (Scheme 3). It proceeds at a higher temperature range (180 – 225 °C) via a chair-like transition state in analogy to the aliphatic Claisen rearrangement.19-20

### 1.1.3 The Ireland-Claisen rearrangement

The Ireland-Claisen rearrangement, reported in 197213 involves the rearrangement of the silyl-enolates of allylic-esters (Scheme 4). An enolate is generated by the addition of base and then trapped as a silyl-ketene acetal. The key advantage of the Ireland-Claisen rearrangement is that it often proceeds at reduced temperatures when compared to the traditional Claisen rearrangement.21 Another cited advantage of the Ireland-Claisen rearrangement is the ability to relatively easily control the stereochemical outcome.22-24 Much like the traditional Claisen rearrangement a chair-like transition state is preferred, given no other steric concerns, plus additional control is gained by the predictable geometry of the enolate (E-enolate – anti-; Z-enolate – syn-), which can be controlled by selecting an appropriate solvent mixture.23 Furthermore work has been done to establish a preference for boat-like transition states through the employment of cyclic-esters.24

### 1.1.4 The simple and chelate enolate Claisen rearrangement

The simple enolate Claisen rearrangement operates, in essence, on the same principles as the Ireland-Claisen rearrangement. In fact, the Ireland-Claisen rearrangement is merely a specialised derivative of a simple enolate Claisen rearrangement utilising a silyl-ether to trap the enolate. The key difference found in the simple enolate Claisen is that the enolate is often not trapped but directly undergoes rearrangement.13,25 The chelate enolate Claisen involves introduction of a chelating substituent to the desired substrate (Figure 2). Thus enolate formation is controlled by the chelation of this substituent to the metal centre. Not only are stereochemical outcomes advantaged by chelation, side reactions are reduced and enolate stability is increased allowing temperature manipulations without trapping (as in the Ireland-Claisen).26-27

---

**Scheme 3**: The aromatic Claisen rearrangement.

**Scheme 4**: The Ireland-Claisen rearrangement.

**Figure 2**: Chelate enolate.
1.1.5 The Claisen-Johnson Orthoester rearrangement

The Claisen-Johnson rearrangement proceeds via condensation of an orthoester with an allylic alcohol to form a ketene acetal (Scheme 5).\textsuperscript{1} Whilst the reaction can proceed at room temperature, the initial mixed orthoester formation is reversible so the reaction is often performed at distillative temperatures to facilitate removal of liberated alcohol, thus driving the equilibrium towards the ketene acetal. The ketene acetal is often poorly defined in stereochemical terms although this can be counteracted with an \(\alpha\)-stereogenic centre. As with many of the Claisen rearrangement derivatives a chair-like transition state is preferred, although this preference can be overcome sterically.\textsuperscript{4,28}

1.1.6 The Meerwein-Eschenmoser-Claisen rearrangement

The Meerwein-Eschenmoser-Claisen rearrangement is very similar to the Claisen-Johnson rearrangement as a ketene acetal is formed with concomitant loss of alcohol.\textsuperscript{5,29-30} In the Meerwein-Eschenmoser derivative an amide-acetal is used in place of the orthoester to effect an acceleration of the sigmatropic process under milder conditions (Scheme 6). As acid is not required in this variant, substrate tolerance is increased for acid-sensitive groups. As with the Claisen-Johnson rearrangement chirality transfer takes place, and similarly to other Claisen rearrangement variants the transition state geometry is highly ordered affording good relative stereocontrol.\textsuperscript{31}

1.1.7 The Carrol rearrangement

The Carrol rearrangement is the sigmatropic rearrangement of an allylic-\(\beta\)-keto ester to a \(\beta\)-keto acid followed by loss of \(\text{CO}_2\) to give a \(\gamma,\delta\)-olefinic ketone (Scheme 7).\textsuperscript{6,32-33} Whilst initial work suggested that the Carrol rearrangement was accelerated by alkaline catalysis it was not established until much later that with two equivalents of base the reaction was greatly
accelerated and proceeded at reduced temperature. The Carrol rearrangement can also be
carried out on aromatic systems by reacting p-quinol 4 with diketene 5 in the presence of
catalytic DMAP to give aryl-acetone systems 6 (Scheme 8).\(^\text{35}\)

\[
\begin{align*}
\text{Scheme 8: An aromatic Carrol rearrangement example.}^{35} \\
\text{Reagents and conditions: i) DMAP (2 mol %), DCM, rt, 72\%.}
\end{align*}
\]

1.1.8 The thio-Claisen rearrangement

The thio-Claisen rearrangement (or 3-thio-Cope) is simply the Claisen rearrangement where
oxygen is replaced with sulfur (Scheme 9).\(^\text{7}\) Although in 1930 the
first thio-Claisen rearrangement was reported, the success of this attempt is disputed.\(^\text{15,36}\) The first confirmed examples of a thio-
Claisen rearrangement involved aromatic substrates, such as
allylphenyl sulfide 7, in a high boiling point amine solvent where the formed
2-allylthiophenol 8 cyclised to eventually give 6,5- and 6,6- ring systems 9 and 10 respectively (Scheme 10).\(^\text{36,37}\)

The first reported isolation of a thio-Claisen rearrangement product (without concomitant
thioetherification) came through work on the aliphatic thio-Claisen rearrangement in 1968.\(^\text{38}\) Thioesters 11 and thioamides were
deprotonated and allyl bromide was added, with many examples rearranging
at room temperature to give desired thiocarbonyl compound 12 (Scheme 11).\(^\text{38}\) As with other Claisen
rearrangement examples the relative stereochemical outcome of the thio-Claisen
rearrangement is governed principally by the highly ordered chair-like transition state.\(^\text{39}\)
1.1.9 The aza-Claisen rearrangement

The aza-Claisen rearrangement (or 3-aza-Cope) is simply the Claisen rearrangement where the oxygen is replaced with nitrogen. Whilst the aza-Claisen rearrangement covers any Claisen variant where nitrogen exists at the 3-position this section will only cover the aza-Claisen rearrangement in a traditional sense with alkyne- and zwitterionic aza-Claisen rearrangements covered separately. Early attempts to perform an aromatic aza-Claisen rearrangement utilising N-allyl aniline 13 failed as the high temperatures required (250 °C) simply resulted in decomposition to aniline 14 and propene 15 (Scheme 12).

Later work demonstrated that the analogous reaction with N-allyl napthylamine 16 proceeded with heating at 280 °C (Scheme 13). The main disadvantage of the aromatic aza-Claisen rearrangement was the required high temperature (200 – 350 °C) often leading to low yields. Typical strategies to decrease the required temperature include protic acid catalysis and Lewis acid catalysis.

Development of the aliphatic aza-Claisen rearrangement occurred a few years later (Scheme 14). It was realised that the spare valence of trivalent nitrogen may offer some advantage over thio- or oxa-Claisen rearrangements as an auxiliary could be attached to direct the stereo-progression. Early work demonstrated that, as expected, the enamine moiety preferred the E- configuration as this supported a chair-like transition state with the bulky substituents in an equatorial position. As with the aromatic aza-Claisen rearrangement, protic acid and Lewis acid catalysis were found to decrease the required temperature.
1.1.10 The amide acetal and amide enolate Claisen rearrangements (aza-Johnson ; aza-Meerwein-Eschenmoser)

The aza-derivatives of the Claisen-Johnson and Meerwein-Eschenmoser-Claisen rearrangements require the usual high temperatures associated with aza-Claisen rearrangements although this can be overcome by tuning the substituents to form an electron donor-acceptor system (Scheme 15). As is typical with other Claisen rearrangements the relative stereochemistry is controlled by the preference for a chair-like transition state, although this preference can be altered by the presence of bulky substituents, especially those attached to the nitrogen atom. In some cases Z-alkenes proceeded through boat-like transition states in order to minimise steric interactions.

1.1.11 The alkyne carbonester aza-Claisen rearrangement

The alkyne carbonester aza-Claisen rearrangement is an example of a zwitterionic aza-Claisen rearrangement, taking advantage of the nucleophilicity of 3°-amines to create a charge separated state. Heating of a tertiary amine such as 17, in the presence of an alkynyl ester 18 induces an addition - rearrangement sequence giving bicycle 19 with syn-selectivity across the bridgehead (Scheme 16).

The substituent at R² played an important role in determining the alkyne addition geometry with bulky substituents causing anti-addition. Acceleration of the initial addition step can be achieved by proton or Lewis acid catalysis enabling the rearrangement to occur at room temperature or below.
1.1.12 The ketene-Claisen (Belluš-Claisen) rearrangement

The ketene Claisen rearrangement was discovered serendipitously when Belluš and co-workers attempted a [2+2] cycloaddition via the combination of ketene 20 and allylic ether 21. Whilst the cycloaddition was successful to a degree, γ,δ-unsaturated ester 22 was identified as a significant by-product resulting from [3,3]-sigmatropic rearrangement. In some cases this ester was the sole product (Scheme 17). Whilst the ketene acetal motif in the ketene-Claisen rearrangement is analogous to that in many of the other Claisen variants, the key advantage is the zwitterionic charge differential between the acetal oxygens. This allows for significant charge acceleration to occur and the rearrangement to proceed at or below room temperature. In the initial communication it was reported that the sulfur and selenium variants of the ketene-Claisen rearrangement were also successful. A nitrogen variant was reported some years later. The latter variant has received much of the attention in recent years as it combines the advantages of the ketene-Claisen variant (fast, low temperature) with the proposed advantages of the aza-Claisen variant (extra valence site, selective enolate formation). This aza-ketene-Claisen rearrangement shall be discussed in the next section.

1.1.13 The aza-ketene-Claisen (aza-Belluš-Claisen; acyl-Claisen) rearrangement

Early work on the aza-ketene-Claisen rearrangement relied on the use of long-lived, electron poor ketenes (Scheme 18). These ketenes were either isolated before use, or generated in situ. Dichloroketene 20 (generated by dehydrohalogenation of dichloroacetyl chloride in the presence of Hünig’s base) was utilised as an electron poor example, rearranging at 2 °C. Several groups have introduced modifications to the aza-ketene-Claisen rearrangement with a view to removing the need for electron-poor ketenes.
Nubbemeyer and co-workers attempted the reaction of N-allyl pyrrolidines 23 with ketenes 24, generated in situ via dehalogenation of α-halogenated acyl chlorides or via dehydrohalogenation of acyl chlorides, without success.\(^\text{63}\) Only ‘von Braun’ type side products 25 and 26 could be recovered (Scheme 19). A modified approach using a two phase system was successful – sequential addition, to a slurry of K\(_2\)CO\(_3\) in DCM at 0 °C, of the allyl-pyrrlidine, acetyl chloride and trimethyl aluminium (10 – 20 mol %) produced the desired rearrangement product.\(^\text{62-63,65}\) Under the latter conditions 0 – 10% of the ‘von Braun’ type side products were still isolated.\(^\text{63}\) In an effort to eliminate the competing ‘von Braun’ process, acyl-fluorides were used. Initial rearrangements without trimethyl aluminium proved unsuccessful however addition of 35 – 100 mol % trimethyl aluminium prompted rearrangement without any evidence of ‘von Braun’ side products (Scheme 20).\(^\text{64}\)

The observed stereochemistry in this work was not as simple as in other Claisen rearrangements as the allylic amines were chiral non-racemic compounds and the authors aimed for a diastereoselective rearrangement. Utilising allyl amine 23a they propose four chair-like transition states the rearrangement could proceed through in order to give the four diastereomeric amides (Scheme 21).\(^\text{65}\) In general the asymmetric induction was stronger in cases where R\(^1\) was larger or more rigid (Table 1).
Interestingly in some examples \((R^1 = \text{Ph}, \text{CH}=\text{CHCH}=\text{CH}_2)\) selectivity was very high for the anti-amide 28a indicating formation of an E-enolate. The stereochemistry of the amides was determined via chemical conversion to \(\gamma\)-butyrolactones 29 and silyl protection of the primary hydroxy group, followed by NMR (nuclear Overhouser effect difference spectroscopic) analysis (Scheme 21).

![Scheme 21: Diastereomeric amides 27a/b, 28a/b derived from the aza-ketene-Claisen rearrangement of allyl amine 23a. Reagents and conditions: i) AlMe3, K2CO3, CHCl3, 0 °C.65](image)

<table>
<thead>
<tr>
<th>R1</th>
<th>Ratio (via each transition state)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27a</td>
</tr>
<tr>
<td>H</td>
<td>60</td>
</tr>
<tr>
<td>CH3</td>
<td>90</td>
</tr>
<tr>
<td>CH2CH2Cl</td>
<td>70</td>
</tr>
<tr>
<td>CH(CH3)2</td>
<td>&gt;97</td>
</tr>
<tr>
<td>CH=CH2</td>
<td>&gt;97</td>
</tr>
<tr>
<td>CH=CHCH=CH2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Ph</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cl</td>
<td>96</td>
</tr>
<tr>
<td>OCH2Ph</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 1: Diastereomeric ratios from the aza-ketene-Claisen rearrangement of allyl amine 23a.

Scheme 22: Preparation of \(\gamma\)-lactone 29 for NMR analysis. Reagents and conditions: i) TFA, MeOH, 65 °C; ii) TBSiCl, base, DCM, rt.
Craig and co-workers later expressed surprise at the formation of an *anti*-amide and postulate that epimerisation may have taken place during the conversion to silyloxy-γ-butyrolactones \(^{29}\). Whilst Nubbemeyer also proposes epimerisation may have occurred in one case \((R^1 = CH_2CH_2Cl)\) there is no explanation for the other cases. Inspection of the experimental details for these cases lends support to the epimerisation hypothesis as reaction times were up to 7 days in the presence of base.\(^{65}\)

Craig and co-workers introduced a ketene-Ireland-Claisen hybrid rearrangement utilising stoichiometric trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a Lewis acid to trap the enolate during rearrangement to an imine followed by loss of the silyl group to yield an amide (Scheme 23).\(^{61}\) A wide variety of allylic amines 30 were screened using ketenes generated *in situ* from propionyl chloride 31a \((R^1 = Me)\) or phenyl acetyl chloride 31b \((R^1 = Ph)\) respectively, giving products 32 that were predominantly *syn*-substituted \((83:17 – 100:0)\) with yields ranging from 30 – 100%.

The observed stereochemistry is rationalised by progression *via* a six-membered chair-like transition state (Figure 3). In some cases \((R^1 = Ph, R^2 = Ph,\) and examples where morpholine 30 was substituted at C1 or C2 (Scheme 23)) the *anti*-diastereomer was also detected. Whilst the authors did not offer an explanation, inspection of the transition state suggests that the *anti*-product could arise either from *Z*-alkene contamination *via in situ* epimerisation of the *E*-alkene, formation of the *E*-enolate or possibly epimerisation of the α-centre during the desilylation step when the imine is present.
MacMillan and co-workers introduced a variant of the aza-ketene-Claisen rearrangement for which they coined the name acyl-Claisen rearrangement.\(^{66}\) Many of the key features of this variant are similar to the work of Nubbemeyer and Craig, an allylic-3°-amine is treated with an acyl chloride in the presence of a Lewis acid and amine base in order to effect a [3,3]-sigmatropic rearrangement. Whilst the principle upon which this variant works is essentially identical to previous work, the development of a methodology geared towards catalytic activation of ketenes is specialised enough that this specific procedure will be referred to as the acyl-Claisen rearrangement, whilst other such procedures will be referred to as aza-ketene-Claisen rearrangements.

### 1.2 The acyl-Claisen rearrangement

MacMillan and co-workers initially attempted to improve the ketene-Claisen (Belluš-Claisen) rearrangement by increasing the scope of available ketenes.\(^ {60}\) Noting that only highly electrophilic ketenes had been used in previous work\(^ {11,54-58,67}\) they hypothesized that utilising Lewis acids would allow less electrophilic ketenes to be employed successfully. Initial attempts using methylketene 24a, with a variety of Lewis acids, proved unsuccessful in effecting Claisen-type rearrangement with cinnamyl methyl ether 33 (Scheme 24). They turned to the aza- equivalent looking for a more nucleophilic ether equivalent to condense with ketene 24a and were rewarded with an efficient room temperature reaction with \(N\)-cinnamyl pyrrolidine 23b to give amide (±)-34, in the presence of several Lewis acids (Scheme 25, Table 2).\(^ {60}\)

![Scheme 24: Attempted ketene-Claisen rearrangement by MacMillan and co-workers.](image)

![Scheme 25: Successful aza-ketene-Claisen rearrangement.](image)

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Mol %</th>
<th>% Yield</th>
<th>Lewis acid</th>
<th>Mol %</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
<td>ZnBr(_2)</td>
<td>100 / 20</td>
<td>89 / 87</td>
</tr>
<tr>
<td>AlCl(_3)</td>
<td>100</td>
<td>90</td>
<td>TiCl(_3)/2THF</td>
<td>100 / 10</td>
<td>83 / 83</td>
</tr>
<tr>
<td>MgBr(_2)</td>
<td>100</td>
<td>80</td>
<td>AlMeCl(_2)</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>Yb(OTf)(_2)</td>
<td>100</td>
<td>90</td>
<td>TiCl(_3)/(O(\text{Pr}))(_2)</td>
<td>20</td>
<td>72</td>
</tr>
</tbody>
</table>

Table 2: Lewis acid catalysed aza-ketene-Claisen rearrangement Lewis acid loading vs. yield.
Stereoselectivity in this reaction was as expected from previous work giving the *syn*-substituted amide (±)-34 (>99:1). The rearrangement proved tolerant to allyl-pyrrolidine substitution proceeding in 68–86% yield, however the need to generate and isolate the ketene was considered a disadvantage and an alternate procedure was investigated – the acyl-Claisen rearrangement (Scheme 26).

In the acyl-Claisen procedure an allylic amine is added to a solution of a Lewis acid in DCM, followed by a tertiary amine base.\(^{60,66}\) An acyl chloride is then added, generating a ketene *in situ* that can condense with the allylic amine and undergo a [3,3]-sigmatropic rearrangement. The prototypical reaction between *N*-cinnamyl pyrrolidine 23 and propionyl chloride 31a proceeded in the presence of 100 mol % dimethylaluminium chloride and Hüning’s base but was not as effective under catalytic conditions, although Yb(OTf)\(_2\) was an exception, proceeding well at 10 mol % loading (Scheme 27, Table 3). The authors next concern was that the amine base could interact with the metal centre and so a screen of amine bases was conducted (with AlMeCl\(_2\), 100 mol %) (Table 4).

Interestingly Hüning’s base proved to be the most effective and basicity was not a strong indicator of efficacy. MacMillan and co-workers looked to the work of Sauer for an

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**Scheme 26: Lewis acid catalysed aza-ketene-Claisen rearrangement allyl substituent tolerance.**

Reagents and conditions: TiCl\(_4\)·2THF (20 mol %), THF, rt, 68–86%.

**Scheme 27: Prototypical acyl-Claisen rearrangement.**

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Mol %</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AlMeCl(_2)</td>
<td>100 / 10</td>
<td>94 / 34</td>
</tr>
<tr>
<td>MgBr(_2)</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Zn(OTf)(_2)</td>
<td>10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>TiCl(_4)·2THF</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Yb(OTf)(_2)</td>
<td>10</td>
<td>84</td>
</tr>
</tbody>
</table>

**Table 3: Prototypical acyl-Claisen rearrangement - Lewis acid loading vs. yield.**

<table>
<thead>
<tr>
<th>Amine base</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPr(_2)NEt</td>
<td>94</td>
</tr>
<tr>
<td>NEt(_3)</td>
<td>44</td>
</tr>
<tr>
<td>Pyridine</td>
<td>&lt;5</td>
</tr>
<tr>
<td>DMAP</td>
<td>5</td>
</tr>
<tr>
<td>DBU</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

**Table 4: Prototypical acyl-Claisen rearrangement - Amine base vs. yield.**
In the presence of alkyl amine bases ketenes are known to dimerize to form β-lactones leading to reduction of yield with some bases (Scheme 28).

Furthermore they hypothesized that the N-cinnamyl pyrrolidine could in fact also catalyse the dimerization process and this was confirmed using real-time IR spectroscopic studies. In order to contend with this unwanted side-reaction a switch to N-allyl morpholines was proposed as the ring oxygen reduces the nucleophilicity and basicity of the amine. They also proposed that the ring oxygen could destabilize the positive charge in the Claisen intermediate and decrease the Lewis basicity of the amide carbonyl thereby increasing the rate of the rearrangement and improving catalyst turnover. N-Crotyl morpholine 30a and propionyl chloride 31a were subjected to a Lewis acid screen in the presence of Hünig’s base (Scheme 29, Table 5).

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Mol %</th>
<th>% conversion</th>
<th>Lewis acid</th>
<th>Mol %</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
<td>Y(OTf)₃</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>10</td>
<td>90</td>
<td>TiCl₃·2THF</td>
<td>10/5</td>
<td>99/92</td>
</tr>
<tr>
<td>MgBr₂·OEt₂</td>
<td>10</td>
<td>39</td>
<td>TiCl₂(O’Pr)₂</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>Yb(OTf)₂</td>
<td>10</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5: acyl-Claisen rearrangement - Lewis acid vs. yield.

TiCl₂·2THF (5 – 10 mol %) proved best in the Lewis acid screen, although AlCl₃ (10 mol %) also fared well. As in previous examples the syn-anti- ratio was >99:1. The acyl-Claisen rearrangement proved tolerant to a variety of substrates condensing propionyl chloride 31a and E-allyl morpholines 30a-d (R₁ = H(b), Me(a), Ph(c), Cl(d) ; R₂ = H, Figure 4) in the
presence of 5 – 10 mol % TiCl₄·2THF and rearranging to give the desired amide in 76 – 95% yield, syn-anti- >99:1.⁶⁰ When Z-allyl morpholine 35a (R¹ = H, R² = Me, Figure 4) was submitted to the same catalytic conditions no rearrangement occurred, however when 100 mol % TiCl₄·2THF was used the reaction proceeded in >95% yield, but the diastereoselectivity was reduced (syn-anti-<5:95).

The authors explained this effect by looking into the two different transition states required by the E- and Z-allyl morpholines (Figure 5). The Z-enolate is favoured⁶⁹ and when condensed with the E-allyl morpholine, transition state 36 places all the bulky substituents in a pseudo-equatorial orientation thus forming a low-energy state and allowing the rearrangement to proceed. In the second case the Z-enolate condenses with the Z-allyl morpholine to form transition state 37 placing the allylic methyl group in a pseudo-axial orientation where it suffers from negative interactions with the metal coordinated enolate oxygen thereby increasing the transition state energy and slowing the rate of reaction. This allows the ketene dimerization process to become more significant. In order to combat this process and perform the rearrangement catalytically with Z-allyl morpholines the authors added propionyl chloride slowly over 10 hours so as to minimize the presence of excess ketene and thus minimise dimerization. This strategy was successful and gave the desired amide in 74% yield (syn-anti- 5:95)(Scheme 30).

An acyl chloride screen was then performed with N-crotyl morpholine 30a and Hünig’s base in the presence of TiCl₄·2THF (5 - 10 mol %)(Scheme 31). The acyl-Claisen rearrangement proved tolerant to a variety of acyl chlorides 31a,c,d (R¹ = H(c), Me(a), iPr(d) ; R² = H) rearranging to give the desired amide in 81 – 93% yield, syn-anti- >99:1 (where applicable). Branched acyl chloride 31e (R¹ = iPr; R² = H) rearranged in a low 28% yield, syn-anti- >99:1 and the more sterically crowded acyl chloride 31f (R¹ = Me ; R² = Me) did not proceed at all.

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Figure 4: Allyl morpholine substrate.

Figure 5: E- and Z-allyl morpholine transition states.

Scheme 30: Accessing the anti-stereochemistry via a Z-alkene.
Heteroatom substituted acyl chlorides were also trialled under the same conditions giving varied results. Acyl chloride 31g ($R^1 = NPh$; $R^2 = H$) gave 77% yield, syn-anti- >99:1 and 31h-i ($R^1 = SP(h), OBn(i)$; $R^2 = H$) rearranged in good yield (81 – 91%) but with syn-anti- 92:8 and 86:14 respectively. MacMillan and co-workers found that this decrease in selectivity was due to a competing un-catalysed background rearrangement. MacMillan and co-workers found that this decrease in selectivity was due to a competing un-catalysed background rearrangement.

Nubbemeyer proposed in his work on the analogous aza-ketene rearrangement that acyl-ammonium intermediate 38 formed prior to enolization to give the Claisen rearrangement precursor 39 (Scheme 32). MacMillan and co-workers investigated this using real-time IR analysis to monitor formation and consumption of the key species (acyl chloride, ketene, acyl-ammonium and amide). They found evidence for a steady concentration of ketene present for much of the reaction time-span indicating an intermediate that is formed and consumed, consistent with a mechanism where a ketene forms and subsequently condenses with the amine species.
1.3 Diastereoselectivity in Claisen rearrangements

Claisen rearrangements in general prefer to adopt chair-like transition states over the boat-like alternative.\textsuperscript{17,23-24,27,31,39,45,47-48,54,61,63,65-66} The simple diastereoselectivity (\textit{syn}-\textit{anti}) is a function of alkene geometry, in the most basic case allyl ether \textit{E,E}-40 proceeds via the chair-like transition states to give \textit{syn}-allyl aldehyde (±)-41 (Figure 6).\textsuperscript{16} In analogy \textit{Z,Z}-42 would proceed via analogous transition states to give the same aldehyde. \textit{Z,E}-43 proceeds in an analogous fashion to furnish \textit{anti}-allyl aldehyde (±)-44, with \textit{E,Z}-45 proceeding likewise. The rearrangement could also take place via a pair of boat-like transition states with \textit{E,E}-40 and \textit{Z,Z}-42 furnishing the \textit{anti}-products and \textit{Z,E}-43 and \textit{E,Z}-45 the \textit{syn}-products. In this case the product ratios (chair vs. boat) reflect the energy difference between transition states.\textsuperscript{16-17}

![Figure 6: Chair-like transition states for simple Claisen rearrangement.]

Whilst in general the chair-like transition state is favoured this preference can be overcome in cases where steric interactions may result in the boat-like transition state having a similar energy. The oxa-Claisen rearrangement is depicted in Figure 6 but this preference is general to both thio- and aza-Claisen rearrangements.\textsuperscript{39,45}

The ketene-acetal family of Claisen rearrangements (Ireland-, enolate-, Johnson-, Meerwein-Eschenmoser-, amide acetal, amide enolate, alkyne carbonester, ketene-, and acyl-) display a similar preference for a chair-like transition state.\textsuperscript{11,23-24,27,31,47-48,54,63,65-66,70} Whilst in the previously mentioned example the diastereoselectivity is a function of a set geometry these variants are dependent on the geometry selected in enolate formation (Figure 7).
When E-46 forms a Z-enolate, rearrangement results in syn-products (±)-48 whereas formation of the E-enolate results in formation of anti-products (±)-47. Thus without control over enolate formation, stereoselectivity is limited. In the Ireland- and related enolate-Claisen rearrangements the crucial enolization step can often be tuned by adjusting base and solvent conditions. For example methyl propionate 49 in THF at -78 °C is deprotonated by LDA to give the Z/E-enolates in 9:91 ratio; by contrast when the solvent system comprises 23% HMPA the Z/E-enolates form in an 84:16 ratio (Scheme 33).

Much work has been done establishing systems and rationale for the selection of an appropriate solvent, base and temperature to predictably favour the desired enolate. The chelate-enolate Claisen rearrangement tackles the issue of enolate geometry by placing an α- or β-heteroatom to form a coordinate bridge between a metal and the carbonyl oxygen (Scheme 34). In these cases either multiple equivalents of base are used or a metal salt (ZnCl₂, MgCl₂, EtAlCl₂, SnCl₂) is added to form the coordinate complex.27,71
In analogous work with enolizable amides the Z-enolate selectivity was found to be even higher than in the oxa-equivalent. Deprotonation with LDA and subsequent rearrangement furnished the amide product in a 99.5:0.5 syn-anti ratio. The increased selectivity is explained by steric influences from the alkylamino group (Figure 8).47

In common with the above work, the aza-Claisen derivative reported by Craig and co-workers displays high levels of diastereoselectivity in many cases, although in some examples as much as 20% of the anti-product is formed (from the reaction of E-alkenes with an expected Z-enolate a syn-product is expected - Figure 7).61 When viewed in relation to the work of MacMillan and co-workers this is surprising as their work was very selective with E-alkenes condensing with Z-enolates to give syn-products.60,66,70 It was noted in the acyl-Claisen rearrangement with α-heteroatomic acyl chlorides that a background rearrangement not involving the Lewis acid could take place and that this process was poorly selective for the syn-product. When stoichiometric Lewis acid was added to compete with this background process the syn-selectivity returned indicating that the Lewis acid contributed in some way to the diastereoselectivity (Scheme 35).60 It is possible therefore that in the work of Craig and co-workers their chosen Lewis acid (TMSOTf) cannot participate in the same way and thus selectivity is compromised.

Scheme 34: Diastereoselectivity in a chelate-enolate Claisen rearrangement.
Reagents and conditions: i) LDA, THF -78 °C; ii) Me$_3$SiCl, -78 °C – rt; iii) H$_2$O, CH$_2$N$_2$, 67% (3 steps), 100:1 (syn-anti).71

Scheme 35: Effect of Lewis acid on acyl-Claisen rearrangement of α-heteroatomic acyl chlorides.
Reagents and conditions: ia) Pr$_2$NEt, DCM, rt, 24%; ib) TiCl$_4$·2THF (100 mol %), Pr$_2$NEt, DCM, rt 83%.

[18]
1.4 Asymmetry in Claisen rearrangements

Whilst the simple diastereoselectivity (syn-anti) discussed in the previous section (1.3) is a feature common to virtually all Claisen variants, enantioselectivity (including its surrogate diastereoselectivity in chiral auxiliary mediated rearrangements) is less easily achieved. Three key strategies have been employed, namely chirality transfer (from a stereocentre present in the starting material), chiral auxiliary strategies and external chiral reagent strategies (i.e. chiral Lewis acids).

1.4.1 Intramolecular chirality transfer

Intramolecular chirality transfer refers to the rearrangement of a chiral substrate to selectively produce a chiral product with gain of a new chiral centre and loss of the old – thus the chiral centre has been transferred.

This technique was used by Takano and co-workers in the synthesis of (+)-latifine.72 Aromatic allyl-ether (S)-50 was submitted to usual aromatic Claisen rearrangement conditions, rearranging to give phenol (R)-51 in 76% yield (Scheme 36). The stereochemical outcome is directed by the stability of the depicted transition state 52 over the alternative chair-like structure that would result in the pendant methylene ether adopting a pseudo-axial position.72

![Scheme 36: Asymmetric aromatic Claisen rearrangement in the synthesis of (+)-latifine. Reagents and conditions: i) N,N-dimethylaniline, Δ, 76%.](attachment:image)

Ireland and co-workers demonstrated a similar reaction with their ester silyl-enolate variant.73 Their investigation into controlling enolate geometry allowed them to control the second stereocentre as well as defining the first through the use of enantiopure starting materials.22-23 Deprotonation of 53 with LDA resulted in an E-enolate that rearranged to give anti-acid 54 in 87% yield with 93:7 dr, on the other hand deprotonation with LiHMDS gave the Z-enolate that rearranged to give syn-acid 55 in 93% yield, 94:6 dr (Scheme 37).73
Heathcock and co-workers demonstrated chirality transfer in Ireland-Claisen rearrangements where the starting material 56 had two stereocentres. An Evan’s asymmetric aldol produced the syn-stereochemistry in substrate 56 which achieved 1,5-asymmetric induction when submitted to Ireland-Claisen rearrangement conditions. Rearrangement of 56 to 57 (86% yield, 95.5:4.5) occurred when LDA was used to form the E-enolate. When 56 was rearranged as the Z-enolate using LDA in HMPA, 58 (80%, 94.5:5.5) was formed instead (Scheme 38).

1.4.2 Chiral auxiliary strategies

Chiral auxiliaries are a common strategy in asymmetric synthesis and have proven successful in many Claisen-variants. Typically the chiral auxiliary uses steric interactions to influence the transition state conformation leading to a particular stereochemical outcome. Whilst both chiral auxiliary and chirality transfer are intramolecular influences on
stereochemical outcome they differ as chirality transfer comes from a stereocentre directly involved in the rearrangement whereas the chiral auxiliary is external to this portion of the framework.

Kallmerten and co-workers demonstrated an Ireland-Claisen rearrangement of allylglycolates using the free alcohol as the attachment point for their chiral auxiliary (Scheme 39).\(^{75}\) Ester 59a (R = Me) rearranged and was trapped with diazomethane to give esters 60a/61a (R = Me) in a 3:1 ratio. Ester 59b (R = Ph) underwent the same rearrangement-trapping sequence to give esters 60b/61b (R = Ph) in a slightly improved 6.1:1 ratio suggesting that a larger substituent may be more successful. Interestingly ester 59c (R = \(\mathrm{iPr}\)) gave esters 60c/61c (R = \(\mathrm{iPr}\)) in 2.4:1 ratio suggesting that factors other than size were involved.\(^{75}\)

![Scheme 39: Asymmetric Ireland-Claisen rearrangement of lactate ethers 59a-c.\(^{75}\)](image)

Reagents and conditions: i) KHMDS, TMSCl, -78 – 0 °C; ii) CH\(_2\)N\(_2\), 0 °C, 60a/61a: 82%; 60b/61b: 77%; 60c/61c: 60%.

Nowaczyk and co-workers developed an asymmetric thio-Claisen rearrangement utilising chiral sulfoxides as the chiral inductor (Scheme 40).\(^{85}\) In one example thioether 62a (R = H) rearranged under standard thermal conditions to give thione 63a (R = H) in 78% yield, 95:5 \(dr\). Thioether 62b (R = Me) rearranged in 76% yield with 100:0 \(dr\) and 62c (R = Br) rearranged in 58% yield with 96:4 \(dr\). Interestingly in all cases if the reaction was run at lower temperature for an extended time diastereoselection suffered.\(^{85}\)
Metz and co-workers utilised a chiral binaphthyl-auxiliary to produce a Meerwein-Eschenmoser-Claisen rearrangement with excellent enantioselectivity (Scheme 41).\textsuperscript{76} Imine 64 rearranged to give amide 65 in 78% yield, 97:3 ee and 97:3 de. A variety of other alkyl substituents rearranged under the same conditions to give similar results.\textsuperscript{76}

Enders and co-workers developed an asymmetric Carrol rearrangement utilising a SAMP hydrazone β-keto ester analogue 66 (Scheme 42).\textsuperscript{77-78} Deprotonation formed dienolate 67 which rearranged and subsequently underwent reduction to give hydrazone 68.

Notable in these examples is the formation of a highly stereocontrolled quaternary centre. Using 2.6 equivalents of LDA formed the dianionic intermediate 67, that the authors posit underwent re – re attack to rearrange forming hydrazone 68 in 48 – 83% yield, 86:9:5:0 – 96:0:4:0 dr for a range of alkyl substituents. The same rearrangement also took place in the
presence of a Lewis acid (TBSOTf) however selectivity was significantly reduced and the major diastereomer (69) was different to that in the dianionic variant. The authors suggest that with formation of silyl ketene acetal 70 the chiral auxiliary is not as involved in stereochemical determination and that some of the rearrangement may proceed via the boat-like transition state. This dienolate rearrangement was successfully used in the synthesis of natural products (-)-malyngolide and (+)-epi-malyngolide.

Kurth and co-workers developed a chiral auxiliary directed aza-Claisen (amide-enolate) rearrangement utilising an amino acid derived oxazoline (Scheme 43). The key factor in the stereochemical outcome of this process was facial selectivity, with si face attack producing an anti- relationship between the auxiliary chiral function (71 X) and α-substituent; and re face attack producing a syn- relationship. The key determinant in this selectivity was the chiral auxiliary with 71a (X = tBu) giving the greatest selectivity (98:2 si:re) and 71b-c (X = Bn, iPr) giving very similar results (94:6 – 97:3 si:re). Notably 71d (X = Ph) gave the poorest result (78:22 si:re), presumably as the net volume of the substituent is smaller and thus could not effect as great an influence.

Tsunoda and co-workers also developed a chiral aza-Claisen rearrangement using chiral amides to induce stereoselectivity (Scheme 44). In nearly every case only the syn-diastereomers were isolated and good selectivity was seen between these two isomers (77:22 – 92:8). Enolization appeared independent of base choice (LDA vs. LiHMDS) and in general better yields and selectivity were achieved when the solvent was toluene.
1.4.3 External chiral reagent strategies

External chiral reagent strategies are essentially an extension of the chiral auxiliary concept, utilising weaker interactions between the chiral reagent and the rearrangement substrate. Whilst in the chiral auxiliary strategy a covalent bond connects the auxiliary and substrate often the chiral reagent in an external strategy will be associated only briefly with the substrate.

Ito and co-workers used a chiral boron bissulfonamide Lewis acid in the asymmetric rearrangement of catechol derivatives to great success. Bidentate coordination of catechol derivative 77 to boron reagent 78 forms a rigid 5-membered intermediate 79, effectively blocking one face of the substrate, thus directing enantioselectivity (Scheme 45). Phenol 80 was formed in 89% yield, 94% ee, and the rearrangement proved efficacious with other similar catechol derivatives.

Corey and co-workers utilised a similar boron reagent 81 for an asymmetric Ireland-Claisen rearrangement, again with great success (Scheme 46). Tuning conditions for selective enolate geometry they formed 82a with 99:1 syn:-anti- selectivity and >97% ee. Acid 83 was
formed with 90:10 *anti*-:*syn* selectivity and 96% ee. A variety of substituents were screened with good selectivity (≥77% ee) including alkyl, aryl and sulfur containing moieties. Reaction time was highly substituent dependent, in some cases requiring up to fourteen days to proceed in moderate yield (65 – 100%).

Hiersemann and co-workers developed a catalytic, chiral Claisen rearrangement using chiral copper(II) bisoxazoline complexes (Scheme 47). Initial work directed at forming a single chiral centre was very successful with 5% catalyst loading giving 96:4 *dr*, 82 - 88% ee and 99 - 100% yield. Catalyst configuration along with substrate geometry combine to determine the absolute configuration of the product (*E*-84 with (S,S)-85 gave (S)-86; *Z*-87 with (S,S)-85 gave (R)-86). The opposite catalyst configuration reversed the selectivity in each case (Scheme 47).

Scheme 47: Asymmetric Claisen rearrangement using a copper complex forming one new stereocentre. Reagents and conditions: DCM, rt, 100%.
Notably substituents on the terminal alkene (e.g. 84/87 C-4 'Pr) were required to gain high levels of enantioselectivity.

Further work directed at forming two chiral centres was also fairly successful with (1Z,5Z)-substrates forming syn-products and (1E,5Z)-substrates forming anti-products. 5% catalyst loading giving 28:72 – 3:97 dr, 72 – 88% ee and 98 – 100% yield (1Z,5E and 1E,5E tended to be less selective). Again catalyst configuration and substrate geometry join to determine the absolute configuration of the product ((1Z,5Z)-88 with (S,S)-85 giving (3R,4S)-89; (1E,5Z)-90 with (S,S)-85 giving (3S,4S)-91)(Scheme 48).

The 'Bu catalyst (Figure 9) was generally less reactive but still provided good selectivity. It was used in the development of a stereochemical model to predict the outcome of this rearrangement (Scheme 49). The 'Bu catalyst confers the reverse selectivity, thus in this case the Z-alkene leads preferentially to formation of (S)-86 due to steric interactions between the ester and the catalyst.
Scheme 49: Stereochemical model for Cu(II)box catalysed Claisen rearrangement.
1.5  Asymmetry in acyl-Claisen rearrangements

1.5.1  First generation asymmetric acyl-Claisen rearrangement (Lewis acid approach)

MacMillan and co-workers developed a first generation asymmetric acyl-Claisen rearrangement shortly following their initial development of the acyl-Claisen procedure.\(^{60, 70}\) They utilised an external chiral reagent strategy, in analogy with the work of Ito,\(^{87}\) Hiersemann\(^{89-90}\) and Corey,\(^{88}\) selecting a chiral Lewis acid complex to infer chirality.

Initial work was performed on the condensation and rearrangement of benzylxoyacetyl chloride 31i and \(N\)-allylmorpholine 30b in the presence of a range of chiral Lewis acids (Scheme 50). The alpha-heteroatomic acyl chloride was chosen as it was hypothesized that a two point coordinate complex could form between the acyl-ammonium species and the Lewis acid, whereas with a non-heteroatomic acyl chloride only single point coordination was possible. Choices of metal-salts were limited to those that were successful in the racemic acyl-Claisen work and chiral ligands were chosen from those that had demonstrated success in generating chiral environments around metal centres.\(^{60}\) Of the ligand architectures studied, salens\(^{91}\), binaphyls\(^{92}\) and bisoxazolines\(^{93}\) a pyridine bisoxazoline (pybox) ligand 93 proved most successful – at 200 mol % loading giving 87% yield, 56% ee – when derived from MgI\(_2\) (Figure 10).

![Scheme 50: Prototypical asymmetric acyl-Claisen rearrangement.](image)

![Figure 10: Chiral ligands tested in the asymmetric acyl-Claisen rearrangement.](image)

Optimisation of ligand architecture was focussed around bidentate bisoxazolines as the additional nitrogen coordination in the pybox ligand was thought to reduce Lewis acidity of the metal centre. A magnesium bisoxazolinybenzene (arbox) complex 94 proved optimal in screening (with the same substrates) at 200 mol % giving 80% yield, 91% ee (Figure 11).
A screen of allyl substrates with Lewis acid 94 and benzyloxyacetyl chloride in the presence of Hünig’s base in DCM at room temperature showed that the rearrangement conditions tolerated a variety of substituents although it was noted that cinnamyl and crotyl morpholines gave predominantly ‘von Braun’ type fragmentation products (see Scheme 19, 1.1.13). The authors proposed that electron donating substituents favoured the ‘von Braun’ pathway, whereas electron withdrawing substituents favoured the acyl-Claisen rearrangement. Attempt to counter this by forming the Lewis acid complex from magnesium salts with less nucleophilic counterion was not altogether successful. Whilst fragmentation was reduced, the overall yield and selectivity were very low and required very high Lewis acid loading (1000 mol %, 21% yield, 73% ee). In all other cases simple diastereoselectivity was retained and enantioselectivity was high (96 – 97% ee) without compromising yield (74 – 95%).

The key drawback of this first generation approach was the requirement for α-heteroatom substitution in the acyl chloride, somewhat limiting substrate scope. Due to the uncatalyzed background rearrangement of these α-heteroatom acyl chlorides any rearrangement in the presence of less than 100 mol % Lewis acid provided limited enantioselectivity.60

1.5.2 Second generation asymmetric acyl-Claisen rearrangement (Lewis acid approach)

MacMillan and co-workers’ second generation approach aimed to use a similar boron bissulfonamide Lewis acid complex to that used by Corey and co-workers in their asymmetric Ireland-Claisen rearrangement (Scheme 46). Whilst complex 81 used in Corey’s work was not a success the toluene sulfonamide derivative 95 proved useful (Figure 12).60 A screen of counterions indicated that ClO₄⁻ gave the best combination of yield and enantioselectivity, whilst not contributing towards formation of ‘von Braun’ fragmentation products.

Figure 11: Arbox Lewis acid.

Figure 12: Boron bissulfonamide complexes.
A substrate screen was carried out utilising propionyl chloride and 200 mol % 31a in the presence of Hünig’s base in chloroform at -30 °C. This second generation approach proved general in terms of substrate scope performing well with alkyl-allyl-, heteroalkyl-allyl- and haloalkyl-allyl morpholines (>99:1 syn:-anti-, 79 – 93% ee). The key exception was carbocation stabilising substituents (e.g. cinnamyl morpholine 30c) where the procedure simply resulted in decomposition of the morpholine substrate.

As these conditions did not require an α-heteroatomic acyl chloride, a variety of acyl chlorides were assessed with mixed success (97:3 – >99:1 syn:-anti-, 10 – 91% ee), the enantioselectivity tending to decrease with steric bulk. The benzyloxyacetyl chloride previously surveyed was, in fact, a poor substrate for these conditions, the increased Lewis acidity causing cleavage of the benzyl ether. Other heteroatomic substituted substrates not susceptible to this fragmentation performed well (although steric bulk again decreased enantioselectivity).

The key drawback of this approach was the requirement for stoichiometric Lewis acid. Rearrangement appeared to suffer from product inhibition and a tendency for chloride ions in solution to exchange with the chlorate counterion forming the less active Lewis acid with chloride counterion.  

1.5.3 Chiral auxiliary approach to an asymmetric acyl-Claisen rearrangement

Raubo and co-workers developed an asymmetric approach to one specific acyl-Claisen rearrangement. 94 In their synthesis of hNK1 receptor antagonist 96 they had intended using an asymmetric Ireland-Claisen rearrangement of allyl ester 97 to form ester 98 (Scheme 51).

![Scheme 51: Asymmetric Ireland-Claisen rearrangement en route to hNK1 antagonist 96. 94](image)

Reagents and conditions: i) LiHMDS, TMSCl, THF; ii) TMSCHN₂, Et₂O, MeOH, 65% (2 steps).
Unfortunately selectivity for 98 favoured an undesired anti-isomer. Thus they turned their attention to the highly syn-selective acyl-Claisen rearrangement. Their chiral auxiliary strategy relied in principle on both the inclusion of a chiral centre in the allylic amine 99 and a chiral centre in the acyl chloride 31j (Scheme 52). Four diastereomers resulted, in the ratio: 100:101:102:103 - 3:18:2:5. The major syn-diastereomer 101 was the desired product and was isolable by column chromatography. Further work on developing this asymmetric acyl-Claisen rearrangement was not conducted.

Scheme 52: Asymmetric acyl-Claisen rearrangement via a chiral auxiliary mediated approach.

1.6 Lignans

Lignans are a widely distributed plant derived class of secondary metabolite natural products produced by the oxidative dimerization of two phenylpropanoid subunits. Classical lignans are those linked in an β-β’ fashion involving six subtypes – dibenzylbutanes, dibenzylbutyrolactones, arylnapthalenes, dibenzocyclooctadienes, 2,6-diarylfurans and substituted tetrahydrofurans – with only the tetrahydrofurans of interest in this work (Figure 13). Additionally lignans where the linkage is other than the β-β’ fashion

Figure 13: Phenylpropane and tetrahydrofuran lignans.
are referred to as neolignans. Another class of compounds that are structurally related, although biogenically different are oligomers of natural stilbenes such as resveratrol 104. These oligomers form what can be thought of as tetra-aromatic tetrahydrofuran lignans (Figure 14). Lignans have a variety of pharmacological activities including anti-tumour, anti-inflammatory, immunosuppression, cardiovascular effects, antioxidant and antiviral. Resveratrol oligomers are known to possess similar activities. It was envisaged that a large number of lignans and resveratrol dimers could be accessible via an acyl-Claisen rearrangement strategy.

1.6.1 Synthesis of tetrahydrofuran lignans via an acyl-Claisen rearrangement strategy

Within our research group an efficient strategy for the synthesis of tetrahydrofuran lignans has been developed. Many lignan targets contain anti- substitution across the C3-C4 bond (Figure 15) and this translates well from the acyl-Claisen amide C2-C3 syn- substitution (extended chain). Our strategy centres around the ability to treat morpholine amides in a similar fashion to Weinreb amides, by nucleophilic attack with carbanion equivalents forming ketone 105. The basic framework is set in place in the first step using the acyl-Claisen rearrangement to establish syn- stereochemistry, followed by addition of a carbanion equivalent to give ketone 105. This ketone is reduced stereoselectively and protected to give alcohol 106, then submitted to a dihydroxylation – oxidative cleavage protocol to yield aldehyde 107. A second
carbanion equivalent is added to the aldehyde giving the final intermediate 108 with all substituents in place. This is activated and undergoes cyclization with concomitant deprotection to furnish the desired tetrahydrofuran 109 (Scheme 53). If the desired configuration of alcohol 108 is not produced by addition of the carbanion equivalent to aldehyde 107, a simple oxidation-stereoselective reduction procedure can epimerise this centre allowing access to other diastereomers of tetrahydrofuran 109.

Using this methodology a variety of racemic natural products and natural product analogues have been prepared starting from N-crotyl morpholine 30a and propionyl chloride 31a or pentanoyl chloride 31k via dialkyl amides 32a-b (Scheme 54).
Scheme 54: Tetrahydrofuran lignans prepared via an acyl-Claisen rearrangement.
With this methodology in place the question of turning the racemic synthesis into an enantioselective synthesis was addressed. It was proposed that enantioselective preparation of amide 110 should allow the remainder of the synthesis to proceed without modification to give chiral products. Known amides \((R,S)-110/(S,R)-111\)^{86} were prepared enantioselectively (9:1 er) \textit{via} a chiral auxiliary mediated aza-Claisen rearrangement, followed by an iodo-lactonization – reductive ring opening to give acid \((R,S)-82\) that was coupled to morpholine using carbodiimide activation to give enantiopure amide \((R,S)-32\) (Scheme 55).

\textbf{Scheme 55: Enantioselective synthesis of (+)-galbelgin 109a.}

\textbf{Reagents and conditions:} i) LiHMDS, PhMe, 140 °C, 72%; ii) I\(_2\), H\(_2\)O/THF (1:1), rt; iii) Zn, AcOH, 60 °C, 74% (2 steps); iv) Morpholine, DCC, DMAP, DCM, 0 °C – rt, 73%; v) MsCl, DCM, 59%.

(+)-Galbelgin 109a was then prepared using the above methodology from amide \((R,S)-32\) (Scheme 55).^{100}
1.7 Objectives

This work intends to extend the above methodology (Scheme 53) to include tetrahydrofuran neolignans and resveratrol oligomers where the C3/C4 substituents are aromatic. This requires an acyl-Claisen rearrangement where either one, or both substituents are aromatic – the latter a substitution pattern that does not appear in MacMillan and co-workers reports (Scheme 56). A variety of interesting targets exist that contain this diaromatic substitution pattern (Figure 16).

Another factor of interest in adapting this methodology is the diastereoselective reduction. Whilst in the case where C3/C4 is methyl the more significant steric effects come from the remainder of the chain, in the case where C3/C4 are aromatic this selectivity may be affected – of particular interest is whether or not this can provide straightforward access to the syn-anti-anti-substitution pattern displayed in Magnosalicin 112 (Figure 16).

Apart from simply extending the substituents available in this methodology we aim to examine a chiral auxiliary approach, analogous to that used in the synthesis of (+)-Galbelgin, in the acyl-Claisen methodology. Our plan is to include a chiral centre on the allyl morpholine and induce diastereoselectivity. The chiral morpholine is to be derived from chiral pool amino acids and the morpholine amide elaborated as in the above methodology (Scheme 57).
Scheme 57: Proposed diastereoselective acyl-Claisen rearrangement and elaboration to a tetrahydrofuran.
Discussion
2.1 Acyl-Claisen rearrangements

MacMillan and co-workers screened a wide variety of substrates in their acyl-Claisen rearrangement development, preparing a variety of α,β-substituted-γ,δ-unsaturated amides (±)-32/(±)-113 (Table 6).60,66

![Diagram of acyl-Claisen rearrangement]

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Table 6: Acyl-Claisen rearrangements screened by MacMillan and co-workers.

Whilst a wide variety of substituents were screened, we noted that in cases where R² is more sterically demanding (R² = Ph), R¹ is undemanding (R¹ = Me) and vice versa (R¹ = OBN, SPh, NPh ; R² = Me). No example combined two sterically demanding moieties. Our work synthesising tetrahydrofuran natural products (1.7) interested us in combinations of acyl chloride and allyl morpholine where both R¹ and R² are aromatic.
2.1.1 Di-aromatic acyl-Claisen rearrangements

Our research group has previously used the acyl-Claisen rearrangement to prepare amide (±)-32a ($R^1 = R^2 = \text{Me}$) for the synthesis of tetrahydrofuran lignans and their analogues following MacMillan and co-worker’s procedure, using AlCl$_3$ (10 mol %) in place of TiCl$_4$·2THF (Scheme 58).$^{99}$

To have a baseline result with which to compare future results and also to prepare material for future work, (E)-crotyl morpholine 30a was prepared via bromination of crotyl alcohol 114 with phosphorous tribromide following the procedure of Haynes et al.$^{104}$ Triethylamine mediated amination of the crude crotyl bromide 115 furnished (E)-crotyl morpholine 30a in 56% yield over two steps. The acyl-Claisen rearrangement took place under typical conditions with crotyl morpholine 30a added to a slurry of aluminium chloride in DCM, followed by Hünig’s base and dropwise addition of propionyl chloride 31a to give amide (±)-32a in 76% yield without evidence of the anti-diastereomers. Spectroscopic data matched the literature values.$^{66}$

Cinnamyl morpholine 30c was prepared by triethylamine mediated amination of commercially available cinnamyl bromide 116, giving morpholine 30c in 89% yield. Attempts to replicate the procedure used in preparation of dimethyl amide (±)-32a using cinnamyl morpholine 30c and phenylacetyl chloride 31b were initially unsuccessful with 10 mol % AlCl$_3$, however upon increasing the AlCl$_3$ loading to 100 mol % the reaction proceeded well giving amide (±)-32c in 94% yield, again without evidence of anti-products (Scheme 59).
Whilst initially the requirement for an increased Lewis acid loading was surprising, review of the literature indicated that in cases where the transition state was expected to be destabilised, increased levels of Lewis acid were required.\textsuperscript{60,66} In MacMillan and co-workers studies involving use of Z-allyl morpholines to form anti- amides they found up to 20 mol \% TiCl\textsubscript{4}·2THF was required (with 100 mol \% producing near quantitative yield), whereas the analogous rearrangement with E-allyl morpholines would proceed with as little as 5 mol \%.

They proposed that 1,3-diaxial strain in transition state 117 due to interaction of the terminal methyl group and metal enolate complex lowered the rate of rearrangement such that competitive fragmentation processes took precedence. Increasing the Lewis acid loading increased the rate of rearrangement. Whilst the same 1,3-diaxial strain is not found in diphenyl transition state 118 we propose some steric congestion is caused by the juxtaposition of the metal ether complex and ketene phenyl ring and rotation out of plane to address this would introduce negative steric reactions with the allyl morpholine chain (Figure 17).

Craig \textit{et al.} had previously prepared both the syn- and anti- diastereomers of amide (±)-32c/(±)-113a allowing comparison of \textsuperscript{1}H NMR data and confirmation that we had produced only the syn-diastereomer. The key differences fall in the resonances of the phenyl rings (δ6.87 – 7.12 syn- cf. δ7.14 – 7.42 anti-), the alkene CH (δ6.06 – 6.23 syn- cf. δ5.81 – 5.86 anti-) and the alkene CH\textsubscript{2} (δ5.02 – 5.18 syn- cf. δ4.67 – 4.85 anti-). Our data (Ph: δ6.92 – 7.12, CH: δ6.16; CH\textsubscript{2}: δ5.06 – 5.15) clearly indicated that only (±)-syn-32c had been produced (refer to Appendix 1 for tabulated values).
With this in mind we decided to investigate further by first preparing amides where only one of the substituents is phenyl ($R^1 = \text{Ph}, R^2 = \text{Me}$ ($\pm$)\text{-}32d; $R^1 = \text{Me}, R^2 = \text{Ph}$ ($\pm$)\text{-}32e) (Scheme 60). When $R^1 = \text{Ph}, R^2 = \text{Me}$ ($\pm$)\text{-}32d, the rearrangement proceeded in a good 85% yield with 10 mol % AlCl$_3$. The opposite configuration ($R^1 = \text{Me}, R^2 = \text{Ph}$ ($\pm$)\text{-}32e) did not proceed at 10 mol % AlCl$_3$ and proceeded only in a modest 26% yield with 100 mol % AlCl$_3$. In the presence of 10 mol % TiCl$_4$·2THF this proceeded to give amide ($\pm$)\text{-}32e in 63% yield, similar to the yield obtained by MacMillan and co-workers. The facility of the first case (to prepare ($\pm$)\text{-}32d) versus the difficulty with ($\pm$)\text{-}32e suggests there is likely more than simply steric congestion at play. MacMillan and co-workers noted that cinnamyl morpholine 30c often performed poorly due to its electron donating effects. It would seem therefore that rearrangements where cinnamyl morpholine 30c is involved may require either more AlCl$_3$ or a stronger Lewis acid (i.e. TiCl$_4$·2THF). In both cases $^1$H NMR spectroscopic data was analogous to that of dimethyl amide ($\pm$)\text{-}32a and diphenyl amide ($\pm$)\text{-}32c in terms of the position of relevant functional group resonances (e.g: ($\pm$)\text{-}32a: CH$_3$: $\delta$1.02, $\delta$1.09; ($\pm$)\text{-}32d: CH$_3$: $\delta$0.78; ($\pm$)\text{-}32e: CH$_3$: $\delta$0.93). Furthermore amide ($\pm$)\text{-}32e was known in the literature and spectroscopic values matched those reported.

We therefore decided to investigate the effect of different Lewis acids on the rearrangement, condensing cinnamyl morpholine 30c and phenylacetyl chloride 31b (Table 7). The Lewis acids we chose to screen were AlCl$_3$ and TiCl$_4$·2THF as we knew they would facilitate the rearrangement. Alongside these we chose AlBr$_3$ and AlI$_3$ as they had not previously been used in an acyl-Claisen rearrangement and we were interested to see if they would perform as well as, or better than, AlCl$_3$. Finally we tested MgBr$_2$·OEt$_2$ as magnesium salts had proven effective in the development of MacMillan’s enantioselective acyl-Claisen rearrangement.
Discussion

The Lewis acid screen revealed that at 100 mol %, AlCl$_3$ and TiCl$_4$·2THF performed most efficiently and there was little difference between the other three (~60% yield). At a 50 mol % loading TiCl$_4$·2THF remained fairly efficient giving amide (±)-32c in 87% yield whilst the others displayed a significant drop in efficiency. The notable exception was AlBr$_3$; whilst efficiency decreased it was not by as large a margin as might be expected. This led us to hypothesize that the level of efficiency at 100 mol % may be lower than optimal due to difficulty in keeping the reagent moisture free. Nonetheless TiCl$_4$·2THF and AlCl$_3$ seemed the best options for this work, with TiCl$_4$·2THF the best option for ‘difficult’ substrates.

Whilst Craig et al. reported the synthesis of diphenyl amide (±)-32c via their ketene-Ireland-Claisen hybrid rearrangement in 90% yield with 88:12 syn/anti- ratio our work represents the first reported diastereoselective synthesis of (±)-syn-32c without any decrease in yield.$^{61,106}$ Thus our methodology is an improvement on the scope of the acyl-Claisen rearrangement potentially allowing selective access to natural product scaffolds previously unavailable via similar methods.

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<th>AlBr$_3$ (Yield %)</th>
<th>All$_3$ (Yield %)</th>
<th>MgBr$_2$·OEt$_2$ (Yield %)</th>
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<td>10</td>
<td>37</td>
<td>80</td>
</tr>
<tr>
<td>100</td>
<td>94</td>
<td>67</td>
<td>59</td>
<td>62</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 7: Screen of Lewis acids in the acyl-Claisen rearrangement of cinnamyl morpholine and phenylacetyl chloride.
Many of the compounds we had interest in preparing had methoxy substituents (often as masked hydroxy functionality in a natural product). Whilst MacMillan and co-workers suggested that electron donating substituents were poor substrates in the acyl-Claisen rearrangement we were interested to investigate the possibility of including electron donating alkoxy groups. Alkoxy substituents are also known to coordinate to Lewis acids\textsuperscript{107} and are often susceptible to cleavage and thus could also be problematic in acyl-Claisen rearrangements.\textsuperscript{108} We therefore decided to investigate the rearrangement of a methoxy substituted acyl chloride with cinnamyl morpholine. para-Methoxyphenylacetyl chloride \textit{31k} was prepared from its parent acid \textit{119} by the method of Drag \textit{et al.},\textsuperscript{109} and reacted with cinnamyl morpholine \textit{30c} using TiCl\textsubscript{4}·2THF in the presence of Hünig’s base and successfully gave amide (±)-\textit{32f} in 73\% yield (Scheme 61).

Pleasingly, despite a stoichiometric loading of TiCl\textsubscript{4}·2THF, no ether cleavage or discrepancies in stereochemistry due to novel coordination of the alkoxy substituent were noted indicating that such substitution should be useable without issue in our intended studies. Analysis of the \textsuperscript{1}H NMR spectrum supported the syn- stereochemistry by analogy with the data for diphenyl amide (±)-\textit{32c} (4-CH: δ6.16; 5-CH\textsubscript{2}: δ5.06 – 5.15; Appendix 1). Most resonances were assigned by analogy with diphenyl amide (±)-\textit{32c} with the key difference found in the para-methoxyphenyl moiety with a pair of doublets (δ6.62, d, J = 8.9 Hz; δ7.08 – 7.13; the second doublet was poorly resolved and hence is reported as a multiplet) characteristic of a para substituted phenyl ring. High resolution mass spectrometry supported our structural assignment with the mass (352.1920 amu) matching that expected.
2.1.2 Di-aromatic acyl-Claisen rearrangements – Tricuspidatol A

With these data in hand we looked towards the preparation of substrates that could be elaborated to tetrahydrofuran natural products (1.7, Figure 16). Our first target was amide (±)-32g en route to resveratrol dimer tricuspidatol A 109b (Scheme 62).\textsuperscript{103}

The first step was synthesis of ester 120, which was achieved quantitatively giving exclusively the E-alkene via Horner-Wadsworth-Emmons olefination of 3,5-dimethoxybenzaldehyde 121 using the method of Skretas et al.\textsuperscript{110} Ester 120 was reduced using 3 equivalents of DIBAL-H to give alcohol 122 in 95% yield. Alcohol 122 was brominated with phosphorous tribromide in DCM and, as bromide 123 proved relatively unstable, immediate addition of morpholine in the presence of triethylamine gave dimethoxycinnamyl morpholine 30e, in 49% yield over two steps (Scheme 63).

Scheme 63: Synthesis of 3,5-dimethoxycinnamyl morpholine 30e.

Reagents and conditions: i) \((\text{EtO})_2\text{P(O)CH}_2\text{CO}_2\text{Et, K}_2\text{CO}_3\), THF, A, quant.; ii) DIBAL-H (1 M, hexanes), DCM, -78 °C, 95%; iii) PBr\textsubscript{3}, DCM, 0 °C – rt; iv) NEt\textsubscript{3}, DCM, 0 °C – rt, 49% (2 steps).

The \textsuperscript{1}H NMR spectrum for morpholine 30e was analysed in analogy with cinnamyl morpholine 30c. As anticipated, the morpholine proton resonances were found in the same regions (30e: δ2.51, t, J = 4.6 Hz, δ3.54 – 3.86, m, cf. 30c: δ2.50, t, J = 4.6 Hz, δ3.74, t, J = 4.6 Hz), as were the 1-CH\textsubscript{2} resonances (30e: δ3.15, dd, J = 1.1, 6.6 Hz, cf. 30c: δ3.15, dd, J =
Discussion

1.3, 6.8 Hz). These resonances were key to determining the structure of morpholine 30e as those remaining were overlaps of methoxy and morpholine protons (δ3.54 – 3.86, 10H) and aromatic and alkene protons (δ6.15 – 6.56, 5H). The latter overlap was expected as it had been seen in precursor alcohol 122. High resolution mass spectrometry provided structural confirmation with the mass found (264.1597 amu) matching that predicted.

With dimethoxycinnamyl morpholine 30e in hand it remained to prepare 3,5-dimethoxyphenylacetic acid 124. Starting from 3,5-dimethoxybenzoic acid 125, reduction using LiAlH₄ according to the method of Kozlowski et al.¹¹¹ gave benzyl alcohol 126 in 85% yield. Bromination was again carried out using phosphorous tribromide, to give benzyl bromide 127 in 92% yield. Bromide 127 was then reacted with sodium cyanide in DMF¹¹¹ to give nitrile 128 in 91% yield, which was used without purification. Nitrile 128 underwent base mediated hydrolysis using the method reported by Winstead et al.¹¹² to give acid 124 quantitatively (Scheme 64). The spectroscopic data for acid 124 matched literature reports.¹¹³

![Scheme 64: Synthesis of 3,5-dimethoxyphenylacetic acid 124. Reagents and conditions: i) LiAlH₄, THF, 0 °C – rt, 85%; ii) PBr₃, DCM, 0 °C – rt, 92%; iii) NaCN, DMF, rt, 91%; iv) NaOH, EtOH/H₂O (2:1), Δ, quant.](image)

With morpholine 30e and acid 124 in hand all that was left was to prepare acyl chloride 31l. This was initially approached using the well used Vilsmeier reagent 129 which was prepared in situ by combination of oxalyl chloride 130 and dimethyl formamide 131. Subsequent addition of a carboxylic acid should then form the desired acyl

![Scheme 65: In situ generation of Vilsmeier reagent 129 in preparation of an acyl chloride.](image)
chloride (Scheme 65).\textsuperscript{114} Unfortunately these conditions proved fruitless, even after several attempts, as assayed by monitoring the presence of the broad O-H absorption band at approximately 3300 cm\textsuperscript{-1} in the FTIR spectrum. Chatterjea \textit{et al.}\textsuperscript{115} have reported the chlorination of acid 124 which was achieved with oxalyl chloride 130, without addition of dimethyl formamide 131. Using these conditions proved successful (monitoring the disappearance of the aforementioned O-H absorption band at approximately 3300 cm\textsuperscript{-1} in the FTIR spectrum) and the crude acyl chloride 31I was used directly in the acyl-Claisen rearrangement with morpholine 30e, furnishing amide (±)-32g in 67\% yield over two steps (Scheme 66).

Scheme 66: Preparation of di-aromatic amide (±)-32g.
Reagents and conditions: i) Oxalyl chloride, PhMe, 10 °C – rt; ii) AlCl\textsubscript{3} (100 mol %), iPr\textsubscript{2}NEt, DCM, rt, 67\% (2 steps).

Analysis of the \textsuperscript{1}H NMR spectrum is simpler than precursor morpholine 30e as the alkene resonances no longer overlap with the aromatic resonances (4-CH: δ6.10; 5-CH\textsubscript{2}: δ5.08 – 5.16). Further to this the 2-CH doublet (δ3.93, d, J = 10.5 Hz) and 3-CH multiplet (δ4.08 – 4.11, m) are separate from the overlapping morpholine and methoxy resonances allowing relatively easy identification. In the \textsuperscript{13}C NMR spectrum the amide quaternary carbon resonance can be seen at δ170.2, and in the FTIR spectrum a band is seen at 1637 cm\textsuperscript{-1} representing the amide carbonyl. Comparing the alkene resonances to the analogous resonances for diphenyl amide (±)-syn-32c at 4-CH: δ6.16 and 5-CH\textsubscript{2}: δ5.06 – 5.15 we determined that novel amide (±)-32g was exclusively the syn- diastereomer (refer to Appendix 1 for tabulated values).
In Figure 17 we saw how two phenyl substituents produced steric congestion in the acyl-Claisen rearrangement transition state and we would expect that in this case, where both aromatic rings are 3,5-disubstituted, steric congestion would be again increased (Figure 18). The decreased yield of amide (±)-32g in comparison to diphenyl amide (±)-32c could be the result of increased steric congestion, although it is difficult to ascertain what role other factors play in this decrease. One assumption in calculating the yield was that acyl chloride 31l formed quantitatively which may not have been the case. The contribution of electronic effects due to additional electron donating groups could also have decreased the yield.

To explore the effect of these additional groups on the reaction we decided to carry out the rearrangements of morpholine 30e with propionyl chloride 31a and phenylacetyl chloride 31b. Using the same conditions as above, amide (±)-32h was prepared in 45% yield (100 mol % AlCl₃) and amide (±)-32i in 40% yield (Scheme 67).

\[
\text{Scheme 67: Preparation of mono-aromatic amides (±)-32h and (±)-32i. Reagents and conditions: i) 32h: AlCl₃ (100 mol %), } \text{Pr₂NEt, DCM, rt, 45%; 32i: AlCl₃ (100 mol %), } \text{Pr₂NEt, DCM, rt, 40%}.
\]

\(^1\)H NMR data for amide (±)-32h was compared to α-methyl amide (±)-32e and the key residues were found within the same ranges (e.g. (±)-32h: 2-CH: δ0.95, d, J = 6.8 Hz; 2-CH: δ2.98 – 3.08, m; 3-CH: δ3.45 – 3.85, m; cf. (±)-32e: 2-CH: δ0.93, d, J = 6.8 Hz; 2-CH: δ3.07, dq, J = 6.8, 9.8 Hz; 3-CH: δ3.48 – 3.72, m). Structural determination was supported by high resolution mass spectrometry with the mass found (320.1855 amu) matching that expected.

\(^1\)H NMR data for amide (±)-32i was compared to diphenyl amide (±)-32c and the key residues were found within the same ranges (e.g. (±)-32i: 2-CH: δ4.00, d, J = 10.5 Hz; 3-CH: δ4.10 – 4.18, m; Ph: δ6.99 – 7.16, m; cf. (±)-32c: 2-CH: δ4.05, d, J = 14.2 Hz; 3-CH: δ4.22,
Discussion

The decreased yield in these cases again suggests that electron rich morpholines such as cinnamyl morpholine 30c and 3,5-dimethoxycinnamyl morpholine 30e perform poorly relative to electron deficient morpholines. We can also see that even with two commercially produced acyl chlorides of high purity the yield when reacted with morpholine 30e is still modest, whether as a result of electronic effects, steric effects or a combination of both.

Finally we added an electron donating substituent to the acyl chloride to investigate what effect this may have on the efficiency of rearrangement. para-Methoxyphenylacetyl chloride 31k was prepared as previously described and reacted, without isolation, with morpholine 30e to give amide (±)-32j in 83% yield (Scheme 68). The rearrangement does not appear to be hindered by either the electronic or steric effects of this substituent. The para-methoxy substitution on acyl chloride 31k may allow greater freedom from steric influence than the case where both rings are 3,5-substituted (Figure 19). For the rearrangement of two components containing substituted aromatic rings this yield is exceptional, being comparable to the yields for diphenyl amide (±)-32c.

Analysis of the $^1$H NMR spectrum showed some overlap between 3,5-dimethoxyphenyl proton resonances and the 4-CH proton resonance ($\delta 6.05 \sim 6.18$). The two doublets characteristic of a para- substituted ring were present at $\delta 6.70$ and $\delta 7.00$. The 5-CH$_2$ resonance ($\delta 5.08 \sim 5.14$) occurred where we would expect for a syn- amide (refer to
Appendix 1 for tabulated values). The 2-CH (δ3.97) and 3-CH (δ4.08 – 4.11) resonances were similar to the analogous resonances for diphenyl amide (±)-32c (2-CH: δ4.05; 3-CH: δ4.22). High resolution mass spectrometry of the product (±)-32j had a mass found (412.2119 amu) matching that expected.

2.1.3 Aromatic acyl-Claisen rearrangements – Magnosalicin
To further investigate the use of highly electron rich morpholines we decided to prepare amide (±)-32k en route to neolignan magnosalicin (±)-112 (Scheme 69). This required use of 2,4,5-trimethoxycinnamyl morpholine 30f which should have an even greater electronic contribution than previous substrates. Preparation of trimethoxycinnamyl morpholine 30f was analogous to the route followed in preparation of dimethoxycinnamyl morpholine 30e. Horner-Wadsworth-Emmons olefination of commercially available 2,4,5-trimethoxybenzaldehyde 132 gave ester 133 exclusively in the E-configuration in quantitative yield. Reduction of 133 with 3 equivalents of DIBAL-H gave alcohol 134 in 77% yield. Bromination using PBr3 was attempted, however bromide 135 was not isolated. Although a variety of conditions were attempted only a complex mixture of products was observed, potentially due to the electron rich aromatic ring facilitating bromination at other sites, or rendering bromide 135 particularly unstable. We therefore turned to an oxidation-reductive amination protocol in place of the bromination-amination sequence we had used for other examples. Manganese dioxide is known to selectively oxidise allylic alcohols to α,β-unsaturated aldehydes without olefin isomerisation. Using 10 equivalents of MnO2 in EtOAc gave aldehyde 136 in 89% yield. Reductive amination using sodium cyanoborohydride and morpholine gave morpholine 30f quantitatively (Scheme 70).
H NMR analysis of morpholine 30f showed many similarities to the spectrum of 3,5-dimethoxycinammyl morpholine 30e. Morpholine proton resonances were almost identical (30f: δ2.52, br s; δ3.75, t,  \( J = 4.6 \) Hz  

\text{cf.} 30e: δ2.51, t,  \( J = 4.6 \) Hz; δ3.54 – 3.86, m) however in this case there was no overlap with methoxy resonances. The 1-CH₂ resonance was also comparable (30f: δ3.17, dd, 1.2, 6.9 Hz  

\text{cf.} 30e: δ3.15, dd,  \( J = 1.1, 6.6 \) Hz) and these two comparisons indicated successful formation of the desired morpholine 30f. Further to this, the alkene protons for morpholine 30f were not obscured (2-CH: δ6.13, dt,  \( J = 6.9, 15.9 \) Hz; 3-CH: δ6.80, dt,  \( J = 1.2, 15.9 \) Hz) allowing analysis of the coupling constant between 2-CH and 3-CH. The coupling constant of 15.9 Hz confirmed the desired \( E \)-configured double bond.¹¹⁷

Morpholine 30f was submitted to the acyl-Claisen rearrangement conditions with propionyl chloride 31a and 100 mol % AlCl₃, but failed to give the desired amide (±)-32k. The only identifiable product was propionamide 137 from ‘von Braun’ type fragmentation (1.1.13, Scheme 71).

Scheme 70: Synthesis of 2,4,5-trimethoxycinammyl morpholine 30f.

Reagents and conditions:  
i) \((\text{EtO})_2\text{P(\text{O})CH}_2\text{CO}_2\text{Et, K}_2\text{CO}_3, \text{THF, } \Delta, \text{ quant.}; \) ii) DIBAL-H (1 M, hexanes), DCM, 0 °C, 77%; iii) MnO₂, EtOAc, rt, 89%; iv) NaBH₃CN, AcOH, MeCN, rt, quant.

Scheme 71: 'Von Braun' type fragmentation of the acyl-ammonium intermediate.
In contrast to previous examples we propose that such highly alkoxy substituted morpholines form transition states (e.g. 138) which are more susceptible to ‘von Braun’ type fragmentation due to their ability to stabilise a carbocation intermediate via formation of quinoid species 139a-b (Scheme 72). Analogous stabilisation is not seen with 3,5-dimethoxyphenyl morpholine 30e due to the lack of ortho/para electron donating substituents on the aromatic ring.

Once formation of quaternary complex 138 has occurred donation of electrons from the trimethoxyphenyl ring allows elimination of amide 137 without nucleophilic attack. Resonance stabilised quinoids 139a-b may then later undergo nucleophilic attack to form allyl chloride 140. The availability of this alternate route to ‘von Braun’ fragmentation products makes fragmentation more facile and may explain why this is the only process seen.

Presumably the other product of fragmentation, allyl chloride 140, was not isolated as it degraded by an analogous mechanism to that seen in our attempts to prepare bromide 135 (Scheme 70). A small screen of Lewis acids was then carried out to see if there were conditions that promoted rearrangement to give amide (±)-32k, without fragmentation (Table 8).
Whilst the rearrangement with morpholine 30f and propionyl chloride 31a did not proceed, our work had shown that rearrangements between an electron rich allyl morpholine and an aromatic acyl chloride proceeded more easily than those where the acyl chloride substituent was alkyl. We therefore attempted the rearrangement condensing morpholine 30f and phenylacetyl chloride 31b in the presence of 100 mol % TiCl₄·2THF and pleasingly rearrangement proceeded in 52% yield (Scheme 73).

<table>
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<tr>
<th>Lewis acid</th>
<th>Mol %</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>AlCl₃</td>
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<td>Amide 137 formed</td>
</tr>
<tr>
<td>MgBr₂·OEt₂</td>
<td>100</td>
<td>Amide 137 formed</td>
</tr>
<tr>
<td>Yn(OTf)₃</td>
<td>100</td>
<td>Amide 137 formed</td>
</tr>
<tr>
<td>TiCl₄·2THF</td>
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<td>Amide 137 formed</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Amide 137 formed</td>
</tr>
</tbody>
</table>

Table 8: Lewis acid screen in the attempted rearrangement of morpholine 30f and propionyl chloride 31a.

Whilst the yield of syn-amide (±)-32l was modest, our expectation that this rearrangement would proceed was fulfilled. What was not expected was that the products (±)-32l and (±)-113b were formed as a 69:31 mixture of syn-anti- diastereomers. This is presumably due either to steric crowding bringing the boat-like transition state closer in energy to the normally favoured chair-like transition state, or due to isomerisation of alkene 30f, or syn-product (±)-32l under the reaction conditions. Formation of the Z-enolate is favoured as nucleophile attack on a ketene occurs preferentially from the less hindered face, whilst for the E-enolate there are negative steric interactions between the ketene and allylic morpholine (Figure 20). Secondary to this effect, if the E-
enolate does form, the transition state requires one of the aromatic substituents to sit in a pseudo-axial position, on topic of any negative steric interactions, assuming the typically energetically favourable chair-like transition state 141a. Due to the potential high energy of a transition state where a substituent is in a pseudo-axial position we must also consider that the boat-like transition state 141b may be of similar or lower energy creating another pathway to the anti-amide (±)-113b (Figure 21).

![Figure 21: Potential transitions states in the formation of amides (±)-32l and (±)-113b.](image)

We propose isomerisation could occur in situ due to a process related to that which in Scheme 72 lead to ‘von Braun’ type fragmentation. In this case formation of a quinoid intermediate could lead to a morpholine anion that recombines with quinoid alkene 139 causing epimerisation (Scheme 74). This process could take place prior to addition of the acyl chloride after which the acyl-Claisen rearrangement becomes the primary process and thus this pathway does not lead to ‘von Braun’ type fragmentation.

![Scheme 74: Possible epimerisation of amine 30f via formation of quinoid intermediate 139.](image)

Analysis of the 1H NMR spectroscopic data first lead us to identify the formation of anti-amide (±)-113b. syn-Amide (±)-32l had key proton residues for 4-CH and 5-CH₂ in the range normally associated with other syn-amides (4-CH: δ6.18, ddd, J = 6.9, 10.0, 17.4 Hz; 5-CH₂:
\[ \delta 5.04 - 5.12, m; \text{Appendix 1}. \] anti-Amide (±)-113b however had the analogous residues in somewhat different ranges (4-CH: \[ \delta 5.85, \text{ ddd, } J = 8.0, 10.5, 17.0 \text{ Hz}; 5-\text{CH}_2: \delta 4.73, \text{ dt, } J = 1.0, 17.0 \text{ Hz}; 5-\text{CH}_3: \delta 4.78, \text{ dt, } J = 1.0, 10.5 \text{ Hz} \] although these are similar to anti-amide (±)-113a prepared by Craig et al. (4-CH: \[ \delta 5.81 - 5.86; 5-\text{CH}_2: \delta 4.67 - 4.85; \text{Appendix 1}).

We also noticed that the unsubstituted phenyl ring proton residues were further upfield for syn-amide (±)-32l (δ6.99 – 7.18) than anti-amide (±)-113b (δ7.21 – 7.42) as in the diphenyl amides (±)-32c and (±)-113b. Analysis of the high resolution mass spectra allowed us to confirm that these two compounds were isomers of the same mass (412.2115 amu), both of which matched the expected mass.

Our previous work indicated that it is the electronics of allyl morpholines, more than steric bulk, that contribute to the lack of rearrangement – as evidenced by the facile rearrangement of phenylacetyl chloride 31b and crotyl morpholine 30a (giving amide (±)-32d in 85% yield – 10 mol % AlCl₃) vs. propionyl chloride 31a and cinnamyl morpholine 30c (giving amide (±)-32e in 26% yield – 100 mol % AlCl₃). Thus we expected that the rearrangement between 2,4,5-trimethoxyphenylacetyl chloride 31m and propionyl chloride 31a should proceed more efficiently.

To test this we first prepared acid 142. Whilst we expected methodology analogous to that used in the preparation of 3,5-dimethoxyphenylacetic acid 124 could have been used for this substrate, we were interested in avoiding the use of sodium cyanide as its toxicity is well known. Turning to the literature we found a relatively esoteric method for preparation of phenylacetic acids from acetophenones via a thiomorpholide intermediate. Firstly the thiomorpholide is formed via a Willgerodt-Kindler reaction where morpholine forms an enamine with an aromatic ketone.\textsuperscript{118-119} Thiation and rearrangement followed by a subsequent hydrolysis step gives the desired carboxylic acid (Scheme 75).
In our case 1,2,4-trimethoxybenzene 143 underwent Friedel-Crafts acylation with acetyl chloride by the method of Hoegberg et al.\textsuperscript{120} to give acetophenone 144 in quantitative yield. Ketone 144 was subjected to the Willgerodt-Kindler, hydrolysis sequence to furnish acid 142 in 20% over two steps (Scheme 76). Whilst the yield was disappointing, mainly due to isolation and purification issues on large scale, it was not optimised as the quantity of acid 142 prepared (1.05 g) was sufficient for all future work.

Chlorination of acid 142 was carried out according to the method of Miller et al.\textsuperscript{121}, in the presence of thionyl chloride, and acyl chloride 31m formation monitored by the disappearance of the O-H band in the FTIR spectrum. Without purification it was transferred into the reaction with crotyle morpholine 30a, TiCl$_4$·2THF (100 mol %) and Hünig’s base giving amide (±)-32m in 82% yield (Scheme 77).
Analysis of the $^1$H NMR spectrum alleviated any concerns that a syn-/anti- mixture of amides had been formed, with only a single diastereomer being observed. The alkene proton resonances (4-CH: δ5.91, ddd, $J = 6.8, 10.5, 17.3$ Hz; 5-CH$_a$: δ5.01, dt, $J = 1.1, 10.5$ Hz; 5-CH$_b$: δ5.10, dt, $J = 1.1, 10.5$ Hz) fell in to the range expected for a syn- amide and there was no sign of any resonances associated with an anti- amide. No doubling was seen of the aromatic proton resonances (δ6.50, s; δ6.98, s) or 3-CH$_3$ proton resonances (δ0.77, d, $J = 7.0$ Hz) as we would expect to see in a syn-/anti- mixture. Comparison of $^1$H NMR data with that from α-phenyl amide (±)-32d allowed structural confirmation as key residues fell within expected ranges ((±)-32m: 2-CH: δ4.06, d, $J = 10.5$ Hz; 3-CH$_3$: δ0.77, d, $J = 7.0$ Hz; 3-CH: δ2.93 – 3.03, m; cf. (±)-32d: 2-CH: δ3.36 – 3.72; 3-CH$_3$: δ0.78, d, $J = 6.8$ Hz; 3-CH: δ3.00 – 3.11, m).

The success of this rearrangement suggests that it was indeed the electronic contributions of the trimethoxyphenyl moiety on allyl morpholine 30f that were proving problematic in the formation of amide (±)-32k.

**Table 9** summarizes the aromatic acyl-Claisen rearrangements we assayed and groups them roughly in order of expected electron donating influence. When R$^2$ is aromatic it appears, in general, that the more electron donating influence present, the poorer the efficiency of acyl-Claisen rearrangement. The caveat to this, however, is that when combined with an aromatic acyl chloride some recovery of efficiency may occur (**Table 9**: Entries 3, 4, 6, 7, 8 and 10). None of the di-aromatic rearrangements could be performed under catalytic Lewis acid conditions.
### 2.1.4 Summary of sterically demanding acyl-Claisen rearrangements

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<th>Entry</th>
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<th>Lewis acid (mol %)</th>
<th>Yield</th>
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Table 9: Summary of aromatic acyl-Claisen rearrangements. *As a 69:31 syn/-anti- mixture.
2.1.5 Quantum chemical investigation of acyl-Claisen rearrangement transition states

The apparent beneficial effect on the yield of a second aromatic moiety in the acyl-Claisen rearrangement was intriguing. The effect appears fairly general and its difference compared to alkyl – aryl systems was seen when trimethoxycinnamyl morpholine 30f would not rearrange with propionyl chloride 31a under any conditions we tested, but gave a 52% yield of amides (±)-32m/(±)-113b when condensed with phenylacetyl chloride 31b (Table 9: Entry 11 vs. 10). We hypothesized that stabilisation, presumably taking place in the transition state to enable these rearrangements to occur, was due to a π – π stacking interaction between the two aromatic rings (Figure 22). We turned to quantum chemical calculations in an attempt to establish theoretically that π-stacking effects may play a role in stabilising rearrangement. Utilising the GAUSSIAN 09 software suite we set up structures juxtaposing cinnamyl morpholine 30c and ketene 24b and performed an energy minimisation (B3LYP, 6-31+G(d,p), iefpcm (DCM), pp. 120).

The output from these calculations showed an unusual deflection of the usual ketene bond angles (180°) and the proximity of the carbonyl carbon to the morpholine nitrogen is approximately the length of a carbon – nitrogen sp³ bond (1.47 Å) reflecting the low energy acyl-Claisen rearrangement transition state (Figure 23). Alongside this observation we can see that the nitrogen – carbon bond of the cinnamyl chain has moved into a position approximating the bond angles around a quaternary nitrogen (Theoretical: 109.5°; Calculated: 110.7°, 108.5°, 112.5° and 110.5°). Our hypothesized π-stacking is not supported by this calculation as analysis of Figure 23 indicates no geometric relationship between the phenyl rings indicative of a stabilised stacking arrangement.
Whilst our hypothesis with regard to π-stacking was not supported by calculations, the deflection seen in the ketene and thus the increased proximity of the carbonyl carbon to the morpholine nitrogen were parameters we thought may be predictive of the facility of a given acyl-Claisen rearrangement. We prepared a calculation juxtaposing crotyl morpholine 30a and ketene 24a derived from propionyl chloride 31a in order to ascertain if the reactive intermediate seen in Figure 23 was general.

**Figure 23:** Results of the density functional theory (DFT) calculation showing proximity of morpholine 30c nitrogen and ketene 24b (NB. Some protons have been omitted for clarity).
The same ketene conformation was predicted by this new data and the proximity of the morpholine nitrogen to the carbonyl centre (1.72 Å) was again close enough to the normal carbon – nitrogen bond length to suggest interaction between the electron clouds in the formation of a reactive intermediate (Figure 24). The nitrogen – carbon bond angles were again as expected for a quaternary nitrogen (110.5°, 108.5°, 112.7° and 110.8°). We then decided to perform an analogous calculation of the rearrangement between 3,5-dimethoxycinnamyl morpholine 30e and ketene 24c derived from 3,5-dimethoxyphenylacetyl chloride 31l as this reaction was known to be lower yielding than the previous two and thus any significant change of distance between nitrogen and carbonyl nuclei may suggest predictability of rearrangement performance (Figure 25).
Again the results appear to suggest that in the expected quaternary reactive intermediate, distance between nitrogen and carbonyl nuclei (1.69 Å) approximates a carbon – nitrogen sp³ bond and the bond angles suggest a quaternary nitrogen species (110.9°, 108.9°, 112.2° and 110.0°). Whilst the morpholine nitrogen and carbonyl distance was similar to the two previous examples and thus not readily correlated to rearrangement facility we hoped that via a comparison of multiple acyl-Claisen rearrangements, from work within our group and in the literature, and their calculated reactive intermediates, a meaningful statistical model could be developed. Unfortunately upon repetition of the calculations for thus far described
experiments we noted variation in both orientation of nuclei and the key bond length we were investigating (Figure 26 1.69 Å cf. Figure 24 1.72 Å).

The initial calculations were performed by Dr Jóhannes Reynisson and upon analysis of our more recent results we once more consulted Dr Reynisson with regard to this variation. We hypothesized that the initial calculations found a local minima and that the variations found were other local minima. Thus he suggested only a significant amount of investigation would enable us to elucidate a global minimum. Unfortunately such an investigation was outside the scope of our work. Whilst our calculations represent local minima, such a significant stabilising effect should surely be present at any energy minimum where the two aryl substituents are reasonably close in space. We are still confident that π – π stacking interactions strong enough to stabilise one of these reactive intermediates are not present.
2.2 Elaboration of acyl-Claisen rearrangement derived amides

As our intent in this work was to prepare tetrahydrofuran natural products from the amides produced in 2.1 we set out to apply the methodology used within our research group (1.7) to achieve this goal. The synthetic plan is identical to that used previously, utilising organometallic reagents to install remaining functionality and minor functional group manipulations to furnish the desired tetrahydrofuran (Scheme 78).

![Scheme 78: Route to generic tetrahydrofuran lignans via an acyl-Claisen rearrangement.](image)

### 2.2.1 Addition of carbanion equivalent to diphenyl amide

Our initial target was a tetra-aromatic natural product analogue based on diphenyl amide (±)-32c used in our methodology studies. As bromoanisole 145 derived lithiate 146 had been used with success within our research group we intended to add this to our amide (Scheme 79). Unfortunately the addition was not facile as anticipated and did not proceed under our standard conditions – lithiation of bromoanisole 145 with "BuLi at -78 °C and addition of diphenyl amide 32c followed by warming to room temperature. No ketone (±)-105a could be isolated and a variety of modifications were attempted without success (Table 10). The standard conditions used were 1.2 equivalents of "BuLi added to a solution of 1.1 equivalents of bromoanisole 145 in THF at -78 °C, followed, after a lithiation time, by addition of amide (±)-32c as a solution in THF and subsequent stirring with the cooling bath removed such that the reaction was able to return to ambient temperature.

![Scheme 79: Attempted lithiate addition to amide (±)-32c.](image)

Reagents and conditions: i) "BuLi, THF, -78 °C; ii) (±)-32c, THF -78 °C – rt NR.
In no case was ketone (±)-$^{105}$a isolated, although we were able to isolate both bromoanisole 145 and anisole 147, indicating that lithiation was taking place. In some cases we also isolated $n$-butyl anisole 148 (Scheme 80).

![Scheme 80: Products recovered from alkylation attempts.](image)

We presumed that appearance of $n$-butylanisole 148 was due to excess $^n$BuLi in the presence of bromoanisole 145. To counteract this, the lithiation was attempted with a great excess (10 eq.) of bromoanisole 145 in the hope that all $^n$BuLi would be consumed. A longer lithiation time was also attempted but unfortunately whilst $n$-butyl anisole 148 was not seen, no ketone was isolated either. Many cases merely returned starting material and a number of unidentifiable by-products. Clayden et al.\textsuperscript{123} reported decomposition of THF in the presence of organolithium bases and we posited this process could be responsible for some of our by-products, in competition with our desired reaction. The reaction when carried out in Et$_2$O in place of THF was again unsuccessful. Another idea to stop production of $n$-butylanisole 148 was to use 'BuLi in place of $^n$BuLi, again whilst successful in preventing formation of $n$-butylanisole 148, no amide was formed. Finally we decided to attempt the addition of different organometallic reagents. CeCl$_3$·7H$_2$O was dried under high vacuum and anisole

<table>
<thead>
<tr>
<th>Organometallic reagent (eq.)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Lithiation time</th>
<th>Reaction time</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^n$BuLi (1.2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>3.5 h</td>
<td></td>
</tr>
<tr>
<td>$^n$BuLi (1.2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>o/n</td>
<td></td>
</tr>
<tr>
<td>$^n$BuLi (1.2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>3.5 h</td>
<td>10 eq. bromoanisole</td>
</tr>
<tr>
<td>$^n$BuLi (1.2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>10 min.</td>
<td>o/n</td>
<td>10 eq. bromoanisole</td>
</tr>
<tr>
<td>$^n$BuLi (1)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>3.5 h</td>
<td>0.9 eq. bromoanisole</td>
</tr>
<tr>
<td>$^n$BuLi (1.2)</td>
<td>-78 - rt</td>
<td>Et$_2$O</td>
<td>5 min.</td>
<td>3.5 h</td>
<td></td>
</tr>
<tr>
<td>$^n$BuLi (1.2)</td>
<td>-78 - rt</td>
<td>Et$_2$O</td>
<td>5 min.</td>
<td>3.5 h</td>
<td>1.2 eq. Bromoanisole</td>
</tr>
<tr>
<td>'BuLi (2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>o/n</td>
<td></td>
</tr>
<tr>
<td>'BuLi (2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>1 min.</td>
<td>o/n</td>
<td></td>
</tr>
<tr>
<td>'BuLi (3)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>3.5 h</td>
<td>3 eq. CeCl$_3$ - organocerium</td>
</tr>
<tr>
<td>PhMgCl (1.1)</td>
<td>-78 - 60</td>
<td>THF</td>
<td>-</td>
<td>6 h</td>
<td>Grignard reagent</td>
</tr>
</tbody>
</table>

Table 10: Attempted alkylations on amide (±)-32c.
lithiate 146 was formed by our standard procedure followed by addition of CeCl₃ and maturation of the organocerium. The amide solution was next added, unfortunately without success. Finally we decided to attempt addition of a commercially available Grignard, again without success.

2.2.2 Addition of carbanion equivalent to monophenyl amide

With this lack of success we were intrigued to explore the lithiation of monophenyl amides (±)-32d and (±)-32e (2.1.1). If the lack of addition to diphenyl amide (±)-32c was purely steric we would expect that 3-phenyl amide (±)-32e should be a better substrate for lithiate addition as steric crowding around the carbonyl centre is significantly reduced. By contrast we would expect 2-phenyl amide (±)-32d to be a poor substrate due to steric crowding. If the lack of addition was due to both steric and electronic factors we could expect that both 2- and 3-phenyl amides (±)-32d, (±)-32e should proceed more easily than diphenyl amide (±)-32c, but still not proceed as easily as the addition to dimethyl amide (±)-32a. Both amides were submitted to the standard conditions and successfully gave ketones (±)-105b (32% yield) and (±)-105c (47% yield) (Scheme 81). Interestingly both amides proved successful substrates for alkylation although the corresponding ketones were only formed in modest yield.

![Scheme 81: Addition of bromoanisole derived lithiate to amide (±)-32d and (±)-32e.](image)

For both ketones identification was facilitated by inspection of the ¹H NMR spectrum. The lack of morpholine proton residues was a good indicator of alkylation, alongside the appearance of two doublets in the aromatic region indicative of a para-substituted aromatic ring ((±)-105b: δ6.87, d, J = 9.0 Hz; δ7.96, d, J = 9.0 Hz; (±)-105c: δ6.96, d J = 8.9 Hz; δ8.00, d, J = 8.9 Hz). The presence of a ketone was confirmed by inspection of the ¹³C NMR spectrum where previously there was an amide carbonyl resonance at δ~170, there was now a ketone carbonyl resonance at δ198.1 ((±)-105b) and δ202.1 ((±)-105c).

Nucleophilic addition of carbanion equivalents to morpholine amides has been considered analogous to addition of carbanion equivalents to Weinreb amides. If we assume the addition occurs via a tetrahedral intermediate as in the addition to a Weinreb amide then we
can see how the steric influence of diphenyl amide (±)-32c compares to that of the two monophenyl amides (Scheme 82). Inspection of the proposed transition states indicates that with either of the monophenyl amides the lack of a second bulky group should allow significantly more freedom in rotation around bonds so as to allow the lithiate to interact at the carbonyl centre, however in the case of diphenyl amide (±)-32c rotation is restricted by negative steric interactions produced by one phenyl ring or the other.

2.2.3 Reduction of diphenyl amide

As attempts to add the desired lithiate to diphenyl amide (±)-32c proved fruitless we investigated alternative routes. The first of these was simply to attempt reduction of amide (±)-32c to give a more reactive aldehyde. Subsequent lithiate addition would give an alcohol which depending on configuration could either continue in our synthesis or undergo an oxidation, stereoselective reduction process to yield the correct configuration. Diphenyl amide (±)-32c was reduced with LiAlH4 at 0 °C and formed diphenyl aldehydes (±)-149 and (±)-150 in 41% yield, alongside amine (±)-151 in 32% yield and alcohol (±)-152 in 27% yield (Scheme 83).

Formation of aldehydes (±)-149/(±)-150 was identified by appearance of downfield 1H NMR residues representative of the aldehyde proton at δ9.59 and δ9.77. Analysis of the remainder [66]
of the spectrum enabled us to confirm epimerisation of the α-phenyl centre. Fortunately anti-aldehyde (±)-150 was known in the literature\textsuperscript{124} enabling full assignment of all proton residues and confirmation of epimerisation.

Identification of alcohol (±)-151 was relatively straightforward as the broad O-H band at 3383 cm\textsuperscript{-1} in the FTIR spectrum indicated presence of an alcohol. This was confirmed by a broad singlet in the \textsuperscript{1}H NMR spectrum at \(\delta 1.48\) representing the alcohol proton. Further to this the presence of residues corresponding to the diastereotopic 1-CH\textsubscript{2} protons confirmed reduction to alcohol (±)-151 (1-CH\textsubscript{a}: \(\delta 3.85\), dd, \(J = 7.8, 11.2\) Hz; 1-CH\textsubscript{b}: \(\delta 3.99\), dd, \(J = 4.8, 11.2\) Hz).

Amine (±)-152 was more challenging to identify as casual inspection of the \textsuperscript{1}H NMR spectrum indicated many similarities to the parent amide (±)-32c. More thorough investigation however indicated many of the resonances were shifted somewhat. The newly formed 1-CH\textsubscript{2} (1-CH\textsubscript{a}: \(\delta 2.53\), dd, \(J = 7.6, 12.8\) Hz; 1-CH\textsubscript{b}: \(\delta 2.79\), dd, \(J = 6.5, 12.8\) Hz) was a key indicator of the reduction, amination sequence taking place, especially as characteristically broad (presumably due to ring flipping) morpholine proton residues were still present (\(\delta 2.24 – 2.42; \delta 3.51 – 3.72\)). Further to this a new residue corresponding to 1-CH\textsubscript{2} was present in the \textsuperscript{13}C NMR spectrum (\(\delta 61.8\)).

In the case of both alcohol (±)-151 and amine (±)-152 we observed no epimerisation. This was determined by comparison of the alkene proton residues with the parent amide (Table 11).

<table>
<thead>
<tr>
<th>Proton</th>
<th>Residue (ppm)</th>
<th>Amide (±)-32c</th>
<th>Alcohol (±)-151</th>
<th>Amine (±)-152</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-CH</td>
<td>6.16, ddd, (J = 6.6, 10.6, 17.2) Hz</td>
<td>6.09, dt, (J = 10.0, 16.9) Hz</td>
<td>6.12, dt, (J = 10.0, 17.0) Hz</td>
<td></td>
</tr>
<tr>
<td>5-CH\textsubscript{2}</td>
<td>5.06 – 5.15, m</td>
<td>5.09, dd (J = 1.5, 10.0) Hz</td>
<td>(J = 1.5, 16.9) Hz</td>
<td>5.03 – 5.14, m</td>
</tr>
</tbody>
</table>

Table 11: Comparison of \textsuperscript{1}H NMR residues for related compounds (±)-32c, (±)-151 and (±)-152.

We were satisfied with this comparison as the \textsuperscript{1}H NMR spectrum for \textit{syn}- aldehyde (±)-149 also showed similarity to amide (±)-32c (Aldehyde (±)-149: 4-CH: \(\delta 6.08\), ddd, \(J = 7.9, 10.4,\)
Discussion

17.2 Hz; 5-CH₂, δ5.13 – 5.20, m) whereas anti- aldehyde (±)-150 did not (Aldehyde (±)-150: 4-CH: δ5.78, ddd, J = 7.7, 10.3, 17.2 Hz; 5-CH₆: δ4.83, dt, J = 1.0, 17.0 Hz; 5-CH₆: δ4.91, dt, J = 1.0, 10.3 Hz) (refer to Appendix 1 for tabulated values).

Formation of amine (±)-152 and alcohol (±)-151 were not unexpected, although we had hoped to avoid their formation by performing the reaction at 0 °C. Whilst the alcohol (±)-151 is simply the result of over-reduction of aldehydes (±)-149/(±)-150, the amine (±)-152 is the result of a reaction temperature high enough to allow lone-pair donation from the nitrogen and elimination of an oxy-aluminium species (Scheme 84).

![Scheme 84: Mechanism of reduction to form amine (±)-152.](image)

Whilst these by-products were relatively easily explained, the presence of epimerised aldehyde (±)-150 was less so. Myers et al.¹²⁵ have reported the aluminium hydride mediated reduction of pseudoephedrine derived amides. In the case where the group α- to the amide carbonyl was phenyl, they also experienced epimerisation of the α-centre. This was proposed to occur via base-mediated enolization of the aldehyde by a pseudoephedrine derived base.¹²⁵ It is conceivable that aldehyde (±)-149 epimerizes by an analogous mechanism with displaced morpholine acting as the base (Scheme 85).

![Scheme 85: Proposed mechanism for epimerisation of aldehyde (±)-149.](image)
We hoped that simply lowering the temperature at which amide (±)-32c was added to LiAlH₄ may enable better control over the products, unfortunately whilst formation of amine (±)-152 was avoided alcohol (±)-151 and aldehydes (±)-149/(±)-150 were still formed.

2.2.4 Addition of carbanion equivalent to diphenyl amide – revised strategy

As we had enjoyed little success with our original strategy, and the modifications made, we developed another approach. Whilst in the previous strategy the amide of the molecule, C-1, had been elaborated first, an alternative is to react the alkene, C4/5, in the initial steps (Scheme 86). Thus our revised strategy would attempt to convert the alkene to an aldehyde and add a carbanion equivalent before functionalising the amide.

![Scheme 86: Revised route to a tetrahydrofuran lignan via an acyl-Claisen rearrangement.](image)

The alkene in amide 32 would be converted via a dihydroxylation – oxidative cleavage protocol to aldehyde 153, followed by addition of a carbanion equivalent and protection of the resultant alcohol. Addition of a second carbanion equivalent to give alcohol 154 followed by activation and cyclization with concomitant deprotection would give tetrastubstituted tetrahydrofuran 109 in analogy with the original strategy. Whilst this strategy still relies on addition to the sterically congested amide carbonyl centre we hoped either conformational change, or electronic change induced by functional group manipulation at the alkene may make this addition more facile.

Diphenyl amide (±)-32c was dihydroxylated using OsO₄ (1 mol %) in the presence of NMO, as in the procedure of Hagiwara et al.,¹²⁶ followed by a sodium periodate mediated oxidative cleavage following the procedure of Wang et al.¹²⁷ to give aldehyde (±)-153a in 77% yield over two steps (Scheme 87). With aldehyde (±)-153a in hand we attempted to add our lithiated reagents. Our first alkylation attempt used commercially available methyllithium to
probe the substrate and pleasingly this reacted well with aldehyde (±)-153a, serendipitously furnishing trisubstituted butyrolactone (±)-155a in 51% yield (Scheme 87).

![Scheme 87: Preparation of trisubstituted butyrolactone (±)-155a from amide (±)-32c. Reagents and Conditions: i) OsO₄, NMO, H₂O/ ᵄBuOH (1:1), 0 °C – rt, quant.; ii) NaIO₄, MeOH/H₂O (3:1), 0 °C – rt, 77%; iii) MeLi, THF -78 °C – rt, 51%.]

Presumably the conformation of the intermediate alcohol (±)-156 is such that intramolecular cyclization is facile and formation of lactone (±)-155a eliminates morpholine (Figure 27). As alcohol (±)-156 was the expected product, analysis of the ¹H NMR spectrum was initially confusing. The disappearance of morpholine proton residues was puzzling, and we had also expected to see the OH proton residue. Once we developed the hypothesis that concomitant cyclization to lactone (±)-155a had occurred the structure was confirmed. Key to this confirmation was the carbonyl stretch at 1769 cm⁻¹ found in the FTIR spectrum consistent with the presence of a gamma lactone.

Whilst the relative configuration across C3-C4 was set in the acyl-Claisen rearrangement we needed to determine the relative stereochemistry formed by addition of methyllithium (C4-C5), especially as the addition appeared diastereoselective (as determined by ¹H NMR spectroscopic analysis). Coupling-constants around 5-membered rings are known to be notoriously poor indicators of stereochemistry due to the many variations in conformation, however Stortz et al.¹²⁸ reported success predicting stereochemistry of γ-lactones using ab initio molecular orbital theory calculations and correlating their results to experimental data. For anti-,anti-lactone 157 \( J_{3-4} = 11.5 \) Hz, approximately 2 Hz larger than the analogous \( J \) values for both the anti- configuration in anti-,syn-lactone 158 and the syn-
configuration in syn-,anti-lactone 159. In lactone 157 $J_{4.5} = 9.5$ Hz, approximately 3 Hz larger than the analogous $J$ value for the anti- configuration in syn-,anti-lactone 159 and approximately 1 Hz larger than the analogous $J$ value for the syn- configuration in anti-,syn-lactone 158 (Figure 28). Thus whilst the two $J$ values when viewed independently may not be altogether significant, when viewed as related may give important structural information. For lactone (±)-155a $J_{3.4} = 12.5$ Hz and $J_{4.5} = 10.0$ Hz, in the range for what we would expect in an anti-,anti-lactone. Furthermore a nOe correlation between 4-CH and 5-CH$_3$ adds further weight to our stereochemical assignment (Figure 29). We presume the diastereoselectivity of this addition is a result of steric influence from the C4 phenyl ring and hoped that this same selectivity would be present in the addition of aromatic carbanion equivalents (Figure 30).

![Figure 29: nOe evidence for relative stereochemistry.](image)

Figure 30: Rationalisation of diastereoselectivity.

This success prompted us to attempt addition of our bromoanisole 145 derived lithiate 146 to establish the superiority of this route over our previous addition attempts. Lithiate 146 was prepared in the general manner (2.2.1) and reacted with diphenyl aldehyde (±)-153a giving the desired triaromatic lactone (±)-155b in 84% yield, again as a single diastereomer (as determined by NMR spectroscopic analysis) (Scheme 88).

![Scheme 88: Preparation of trisubstituted butyrolactone (±)-155b from aldehyde (±)-153a.](image)

Reagents and conditions: i) nBuLi, THF, -78 °C; ii) (±)-153a, THF, -78 °C – rt, 84% (2 steps).
Relative stereochemistry was assigned as \textit{anti-anti} by analogy with lactone (±)-155a as $J_{3,4} = 12.5$ Hz and $J_{4,5} = 10.1$ Hz – which had almost identical corresponding $J$ values.

We then decided to add bromobenzene 160 derived lithiate 161 to aldehyde (±)-153a in order to continue the elaboration and eventually furnish tetraphenyl tetrahydrofuran (±)-109c, a hexa-dehydroxy tricuspidatol A analogue. Lithiate 161 was formed in the presence of tBuLi at low temperature and reaction with aldehyde (±)-153a proceeded as desired to give triphenyl lactone (±)-155c in 69% yield as a single diastereomer (as determined by NMR spectroscopic analysis) (Scheme 89). Relative stereochemistry was assigned as \textit{anti-anti} in analogy with lactone (±)-155a as $J_{3,4} = 12.5$ Hz, and $J_{4,5} = 10.1$ Hz – almost identical to the corresponding $J$ values. Adding further evidence was the lack of nOe interactions between protons around the ring.

\textbf{2.2.5 Further elaboration of diphenyl amide – revised strategy}

As the concomitant alkylation – ring closure appeared quite general we again revised our synthetic strategy to include this modification (Scheme 90).

Scheme 90: Revised route to a tetrahydrofuran lignan via an acyl-Claisen rearrangement.
Having lactone (±)-155c in hand we proceeded on to the second lithiate addition. Lithiate 161 was formed in the presence of tBuLi at low temperature and reaction with lactone (±)-155c furnished hemiacetal (±)-162 in 77% yield as a single diastereomer (as determined by NMR spectroscopic analysis) (Scheme 91).

Relative configuration was predicted to be that resulting from the new phenyl substitutent approaching anti- to the C3 phenyl. As C2 is a quaternary centre there is no proton from which to ascertain coupling interactions. There was coupling between 3-CH and 2-COH ($J = 1.4$ Hz), but no nOe correlation was observed. Using this information we were able to confirm our predicted configuration as the 1.4 Hz coupling between 3-CH and 4-COH results from a long range coupling indicative of a ‘W’ configuration. This configuration was only possible with the hydroxyl group anti- to the 3-CH proton and also would result in no observable nOe correlations (Figure 31).

Reduction of hemiacetal (±)-162 was carried out according to the method of Calzada et al.\textsuperscript{129} adding BF$_3$·OEt$_2$ followed by triethylsilane at low temperature, to effect quantitative reduction to tetraphenyl tetrahydrofuran (±)-109c (Scheme 92). Determination of relative stereochemistry was relatively straightforward via NMR spectroscopic analysis and comparison to tricuspidatol A 109b. Only two resonances are seen as the product is symmetrical, (±)-109c C2/5 at $\delta_{5.43} J = 2.9$, $6.4$ Hz cf. tricuspidatol A 109b C2/5 at $\delta_{5.25} J = 1.5$, $5.0$ Hz, and (±)-109c C3/4 at $\delta_{3.50} J = 2.9$, $6.4$ Hz cf. tricuspidatol A 109b C3/4 at $\delta_{3.50} J = 1.5$, $5.0$ Hz. Therefore in analogy with tricuspidatol A 109b we assigned the relative stereochemistry as anti-,anti-,anti-.
2.2.6 Addition of carbanion equivalent to tricuspiddatol A precursor amide (±)-32g

Concurrently with the work detailed in 2.2.1 - 2.2.5 attempts were made at elaborating di-aromatic amide (±)-32g for the synthesis of tricuspiddatol A 109b. As with diphenyl amide (±)-32c the initial strategy required carbanion equivalent addition to the amide carbonyl and as with diphenyl amide (±)-32c this strategy proved unsuccessful (Scheme 93).

![Scheme 93: Attempted lithiate addition to amide (±)-32g.](image)

Reagents and conditions: i) nBuLi, THF, -78 °C, NR; ii) (±)-32g, THF -78 °C – rt NR.

<table>
<thead>
<tr>
<th>Organometallic reagent (eq.)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Lithiation time</th>
<th>Reaction time</th>
</tr>
</thead>
<tbody>
<tr>
<td>nBuLi (1.1)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>3.5 h</td>
</tr>
<tr>
<td>tBuLi (2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>1 min.</td>
<td>3.5 h</td>
</tr>
</tbody>
</table>

Table 12: Attempted alkylation on amide (±)-32g.

Fewer conditions were attempted as most of the method development work was being done on the diphenyl substrate as material was easier to produce (Table 12). As lithiate additions to amide (±)-32g were unsuccessful we moved on to attempting additions to di-aromatic aldehyde (±)-153b – produced in analogous fashion to diphenyl aldehyde (±)-153a. Di-aromatic amide (±)-32g underwent the dihydroxylation – periodate cleavage procedure giving di-aromatic aldehyde (±)-153b in 56% over two steps (Scheme 94).
Discussion

Unfortunately despite a variety of conditions being attempted addition of bromoanisole 145 derived lithiate 146 was unsuccessful (Table 13). The standard conditions were 1.1 equivalents of "BuLi added to a solution of 1.1 equivalents of bromoanisole 145 in THF at -78 °C, followed, after a lithiation time, by addition of aldehyde (±)-153b as a solution in THF and subsequent stirring with the cooling bath removed such that the reaction was able to return to ambient temperature.

<table>
<thead>
<tr>
<th>Organometallic reagent (eq.)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Lithiation time</th>
<th>Reaction time</th>
<th>Modification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;BuLi (1.1)</td>
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<td>3 h</td>
<td>RSM</td>
<td></td>
</tr>
<tr>
<td>&quot;BuLi (1.1)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>o/n</td>
<td>RSM</td>
<td></td>
</tr>
<tr>
<td>&quot;BuLi (2)</td>
<td>-78 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>3 h</td>
<td>RSM</td>
<td></td>
</tr>
<tr>
<td>&quot;BuLi (2)</td>
<td>0 - rt</td>
<td>THF</td>
<td>5 min.</td>
<td>3 h</td>
<td>RSM</td>
<td></td>
</tr>
<tr>
<td>&quot;BuLi (5)</td>
<td>0 - rt</td>
<td>THF</td>
<td>10 min.</td>
<td>3 h</td>
<td>6 eq. bromoanisole</td>
<td>RSM</td>
</tr>
<tr>
<td>&quot;BuLi (10)</td>
<td>0 - rt</td>
<td>THF</td>
<td>10 min.</td>
<td>3 h</td>
<td>11 eq. bromoanisole</td>
<td>RSM</td>
</tr>
<tr>
<td>PhMgCl (1.1)</td>
<td>0 - rt</td>
<td>THF</td>
<td>-</td>
<td>3 h</td>
<td>Grignard reagent</td>
<td>RSM</td>
</tr>
</tbody>
</table>

Table 13: Attempted alkylation on aldehyde (±)-153b. *RSM indicates return of aldehyde (±)-153b.

In no case was lactone 155d isolated, despite attempts at higher temperature or with large excesses of lithiate. The only product isolated was the quenched lithium species. As a final attempt we explored addition of commercially available phenylmagnesium chloride, however this too gave none of the desired addition product returning only aldehyde (±)-153b.

We expect that these additions are prevented by steric and electronic factors, whether on their own or in combination. Additions to diphenyl aldehyde (±)-153a were very successful, proceeding in good yield however in this case aldehyde (±)-153b has significant steric
hindrance provided by the methoxy substituents which would not allow the rings to sit as close as we expect is possible for the de-methoxy equivalent. We propose that this factor would account for the lack of reaction. Furthermore it is conceivable that methoxy substitution on the aromatic rings renders the protons alpha to these substituents more acidic and this allows quenching of the lithiate, preventing alkylation. Thus a combination of electronic and steric factors may prevent successful formation of lactone (±)-155d.

At this point whilst tricuspidatol A (±)-109b was not achievable, success had been attained in the production of tetraphenyl tetrahydrofuran (±)-109c. Rather than explore other methods to form tricuspidatol A (±)-109b we wished to further develop this methodology by shifting our focus to an alternate lignan, magnosalicin (±)-112 (see 2.1.3, Scheme 69).

### 2.2.7 Elaboration of magnosalicin precursor amide

Whilst di-aromatic amides (±)-32c and (±)-32g required a revised strategy for elaboration, due to the inability to displace the morpholine amide with nucleophiles, magnosalicin (±)-112 should be available from mono-aromatic amide (±)-32m and we expected that we should be able to use the original strategy. A key difference is whilst previously we were investigating production of an anti-,anti-,anti-configuration in this case we require the anti-,anti-,syn-configuration. We were interested to see if this synthesis required extra functional group manipulations to achieve this configuration.

With mono-aromatic amide (±)-32m in hand we commenced our synthesis with addition of commercially available methyllithium. A small excess of methyllithium was added to a solution of amide (±)-32m giving the desired ketone (±)-105d in a modest 50% yield (Scheme 95). As with mono-aromatic amides (±)-32d and (±)-32e success in this substitution is in contrast to di-aromatic amides (±)-32c and (±)-32g adding evidence that steric factors play some part in the unsuccessful attempts.

![Scheme 95: Preparation of alcohol (±)-163 from amide (±)-32m.](image)

Reagents and conditions: i) MeLi, THF, -78 °C – rt, 50%; ii) NaBH₄, MeOH, -78 °C, 92%.
Analysis of the $^1$H NMR spectrum supported the formation of ketone (±)-105d via the disappearance of morpholine proton residues and the appearance of a singlet at δ2.03 representing the methyl ketone protons. Further to this, in the $^{13}$C NMR spectrum the carbonyl was shifted downfield from δ171.9 (amide (±)-32m) to δ208.2 in ketone (±)-105d. Reduction of ketone (±)-105d with NaBH$_4$ at -78 °C gave alcohol (±)-163 in 92% yield, with apparently good diastereoselectivity. Reduction to alcohol (±)-163 resulted in an upfield shift of the new methyl group (δ0.95) and appearance of the 2-CH proton at δ4.13 – 4.21 in the $^1$H NMR spectrum.

This reduction was a key step in development of the desired configuration. In previous work by our group the substituent α- to the ketone carbonyl was always methyl and thus the Felkin-Anh model predicts Si face attack as the ‘R’ group is considered the large substituent (Figure 32). This eventually results in an anti-,anti-,anti-tetrahydrofuran.

In our case however the methyl group is replaced by a trimethoxy phenyl group, which is considered the large substituent such that we should expect hydride attack from the Si face (which is opposite to that in the previous example). Such attack should give the configuration we desire in magnosalicin (±)-112 (Figure 33). Thus we assigned alcohol (±)-163 as the syn-, syn- extended chain conformation.
Alcohol (±)-163 was protected as methoxymethyl ether (±)-106a in 84% yield and submitted to the dihydroxylation – periodate cleavage conditions used previously. Dihydroxylation proceeded in 98% yield, and intermediate diol (±)-164 was used without purification and the oxidation carried out, giving aldehyde (±)-107a in 62% yield over two steps (Scheme 96).

Analysis of the $^1$H NMR spectrum of aldehyde (±)-107a supported the presence of an aldehyde as the distinctive downfield residue (1-CH: $\delta$9.71, d, $J = 3.4$ Hz) was present. The $^{13}$C NMR spectrum also contained a quaternary residue at $\delta$204.6 representing the carbonyl carbon.
With aldehyde (±)-107a in hand we turned our attention to addition of our final fragment – a trimethoxyphenyl group. We intended preparing a suitable substituted bromobenzene followed by lithiation and addition to aldehyde (±)-107a. Bromobenzene 165 was prepared quantitatively by slow addition of bromine to a solution of trimethoxybenzene 166 according to the method of Sutherland et al.\textsuperscript{131} (Scheme 97).

We expected that trimethoxyphenyl lithium 167 could be a relatively unstable lithiate due to the number of electron donating substituents. Thus we turned to the literature for advice on its preparation and reaction. In the work of Johnson et al.\textsuperscript{132} and Burns et al.\textsuperscript{133} lithiate 167 was prepared by addition of $^t$BuLi to bromobenzene 165 at -78 °C in THF followed by addition of their substrate and maintenance of the low temperature throughout the reaction. Recent work in our group had more success using $^t$BuLi with highly substituted aromatic lithiations so we decided to attempt these conditions. Our standard conditions for these attempts used 2.2 equivalents of $^t$BuLi and 1.1 equivalents of bromobenzene 165 in THF at -78 °C with 15 minutes lithiation time followed by addition 1 equivalent of the aldehyde substrate and maintenance of the low temperature (Scheme 98).

**Scheme 97:** Preparation of bromobenzene 165.
Reagents and conditions: i) Br$_2$, DCM, 0 °C, quant.

**Scheme 98:** Attempted preparation of alcohol (±)-108a from aldehyde (±)-107a.
Reagents and conditions: i) $^t$BuLi, THF, -78 °C; ii) (±)-107a, THF, -78 °C, NR.
Discussion

These standard conditions were tried a number of times with little success (Table 14). Lithiation was confirmed by the recovery of debromo-benzene 166 from the reaction mixture however in most cases aldehyde (±)-107a was recovered. The exceptions were cases where it appeared that 'BuLi itself appeared to have added to aldehyde (±)-107a, although these compounds were not isolated. In reactions where lithiation was successful we noted a distinct colour change from colourless to yellow with addition of the BuLi species which faded over time and with addition of our substrate. Transmetallation via addition of a magnesium salt was attempted, however no product was recovered. To combat the hypothesized 'BuLi addition we tried longer lithiation times and excesses of bromobenzene 165. These were unsuccessful at generating the desired product, however appearance of potential butyl addition products was avoided. An attempt to increase the reaction temperature slightly was also met with failure and recovery of debromo-benzene 166. The return of debromo-benzene 166 implied that lithiation was occurring, however addition to our substrate was not occurring at the low temperature. Our attempt to increase the reaction temperature led to discolouration which we took to mean quenching of the lithiate had taken place.

With this failure we decided to turn to a model aldehyde 168 in the hope that we may have some success on a less sterically encumbered substrate and later may be able to translate this success to our desired substrate. We attempted addition of our lithiate 167 to butyraldehyde 168 using our standard conditions, without success (Scheme 99). Further we attempted lithiation at -98 °C, with complete recovery of bromobenzene 165 evidence that lithiation had not taken place; indicating that -78 °C was an appropriate temperature for lithiation but either

<table>
<thead>
<tr>
<th>Organometallic reagent (eq.)</th>
<th>Temp. (°C)</th>
<th>Solvent</th>
<th>Lithiation time</th>
<th>Reaction time</th>
<th>Modification</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBuLi (2.2)</td>
<td>-78</td>
<td>THF</td>
<td>15 min.</td>
<td>3 h</td>
<td></td>
<td>RSM</td>
</tr>
<tr>
<td>tBuLi (2.2)</td>
<td>-78</td>
<td>THF</td>
<td>15 min.</td>
<td>3 h</td>
<td>3 eq. MgBr₂·OEt₂ Grignard</td>
<td>RSM</td>
</tr>
<tr>
<td>tBuLi (2.2)</td>
<td>-78</td>
<td>THF</td>
<td>30 min.</td>
<td>3 h</td>
<td></td>
<td>RSM</td>
</tr>
<tr>
<td>tBuLi (2.2)</td>
<td>-78</td>
<td>THF</td>
<td>30 min.</td>
<td>3 h</td>
<td>10 eq. bromobenzene 165</td>
<td>RSM</td>
</tr>
<tr>
<td>tBuLi (2.2)</td>
<td>-78 - -50</td>
<td>THF</td>
<td>30 min.</td>
<td>3 h</td>
<td>2.9 eq. bromobenzene 165</td>
<td>RSM</td>
</tr>
<tr>
<td>nBuLi (10)</td>
<td>-78</td>
<td>THF</td>
<td>30 min.</td>
<td>3 h</td>
<td>12 eq. bromobenzene 165</td>
<td>RSM</td>
</tr>
</tbody>
</table>

Table 14: Initial conditions attempted in preparation of alcohol (±)-108a from aldehyde (±)-107a. *RSM indicates return of aldehyde (±)-107a, *'Bu indicates addition of the lithiating agent to aldehyde (±)-107a.
not for addition or our lithiate was quenching by some pathway more facile than addition to our desired substrate.

We turned to the literature in an attempt to find an alternative way to complete this synthesis and were fortunate to find the work of Crowther et al.\textsuperscript{134} who had prepared the same lithiate but with different conditions to those previously reported. They had used $^4$BuLi, in diethyl ether as opposed to THF and prepared their lithiate at 0 °C. Given our lack of success we were intrigued by these conditions and elected to try them on our model aldehyde 168. 1 Equivalent of bromobenzene 165 was combined with 1 equivalent of $^4$BuLi at 0 °C followed by addition of 1.1 equivalents of aldehyde 168 giving alcohol 169 in 32% yield. We then investigated addition to aldehyde 170, as the chain length and α-methyl substitution were the same as that seen in our substrate aldehyde (±)-107a. Under the same conditions, addition of lithiate 167 to aldehyde 170 formed alcohol 171 quantitatively (Scheme 100).

We hypothesized that the lack of temperature stability apparent with the earlier conditions was a function of a highly basic lithiate reacting with THF as reported in the work of Clayden et al.,\textsuperscript{123} an issue not apparent when Et$_2$O was the solvent.
With these successes all that remained was for us to apply these same conditions to aldehyde (±)-107a. This reaction proceeded in 76% yield to give alcohol (±)-108a diastereoselectively (Scheme 101). In this case the diastereoselectivity is a function of the bulky lithiate approaching the unhindered face. We can invoke the Felkin-Anh model to show that Re face attack is favoured (Figure 34).

**Scheme 101: Preparation of alcohol (±)-108a from aldehyde (±)-107a.**
Reagents and conditions: i) n-BuLi, Et_2O, 0 °C; ii) (±)-107a, Et_2O, 0 °C – rt, 76%.

**Figure 34: Rationalisation of diastereoselectivity.**

Key to the identification of alcohol (±)-107a was appearance of 1-CHOH, with the 1-CH residue appearing at δ5.51 and the OH residue at δ3.25. Alongside this we found three aromatic proton signals at δ6.53 (integrating for 2H), δ6.85 and δ7.06 and six signals corresponding to methoxy protons where previously there were only three. There was no longer a downfield proton residue representative of the aldehyde proton. Finally there was no sign of a carbonyl residue in the ^13^C NMR spectrum.
The final step in the synthesis of magnosalicin (±)-112 is cyclization to the tetrahydrofuran. Our previous work showed that activation of alcohol (±)-108a with the secondary alcohol protected as a methoxymethyl ether often resulted in concomitant deprotection and cyclization, presumably due to transient production of acid in situ. Alcohol (±)-108a was treated with 1.4 equivalents of methanesulfonyl chloride in the presence of 1.7 equivalents of triethylamine gave (±)-magnosalicin 112 in 62% yield (Scheme 102). Hanessian et al.\textsuperscript{135} performed an analogous cyclization in their work preparing other tetrahydrofuran lignans and proposed rather than a simple $S_N$2 type attack on the mesylate, the mesylate was eliminated by formation of a quinoid type intermediate 173 followed by attack, by the remaining alcohol, on the sp$^2$ carbon reforming the aromatic ring (Scheme 103).

\begin{center}
\includegraphics[width=\textwidth]{scheme102}
\end{center}

**Scheme 102:** Preparation of magnosalicin (±)-112 from alcohol (±)-108a. Reagents and conditions: i) MsCl, NEt$_3$, DCM, rt, 62%.

\begin{center}
\includegraphics[width=\textwidth]{scheme103}
\end{center}

**Scheme 103:** Cyclization mechanism via quinoid intermediate 173.
We proposed that quinoid intermediate (±)-173 should undergo top face attack with the trimethoxyphenyl group ending up anti- to the adjacent methyl to limit negative steric interactions between the trimethoxyphenyl and methyl substituents. This would give the desired stereochemistry for magnosalicin (±)-112. In the work of Hanessian et al.\textsuperscript{135} simple S\textsubscript{N}2 attack would have given the opposite stereochemistry to attack via the quinoid intermediate. In our work, however, S\textsubscript{N}2 attack would give the same stereochemistry and whilst we cannot rule out either pathway both the work of Hanessian and that performed within our group suggest that the quinoid route is typically favoured (Scheme 104)\textsuperscript{99,135}

Our stereochemical prediction is supported by comparison of our NMR data to literature data from isolation\textsuperscript{102} and a biomimetic synthesis (Table 15).\textsuperscript{136} This confirmation of stereochemistry indicated that our prediction of diastereoselectivity at the reduction and lithiate addition stages were correct. The work of Mori et al.\textsuperscript{136} involved a biomimetic synthesis of magnosalicin (±)-112 via a peracetic acid mediated oxidative coupling of α-asarone 174 that produced all four possible diastereomers as racemates (Scheme 105). These isomers were HPLC separated and they reported the data for all four diastereomers.

![Scheme 104: Cyclization mechanism via an S\textsubscript{N}2 mechanism.](image)

![Scheme 105: Mori’s synthesis of magnosalicin (±)-112 and diastereomers (±)-175-177. Reagents and conditions: i) AcOOH, AcOH, 0 °C – rt, 17%.](image)
### Table 15: Comparison of NMR data for magnosalicin (±)-112

<table>
<thead>
<tr>
<th>Residue</th>
<th>Synthetic (±)-112</th>
<th>Isolated (±)-112&lt;sup&gt;112&lt;/sup&gt;</th>
<th>Biomimetic (±)-112&lt;sup&gt;136&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.90 (d, &lt;i&gt;J&lt;/i&gt; = 6.4 Hz)</td>
<td>0.91 (d, &lt;i&gt;J&lt;/i&gt; = 6.5 Hz)</td>
<td>0.90 (d, &lt;i&gt;J&lt;/i&gt; = 6.5 Hz)</td>
</tr>
<tr>
<td>4-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.03 (d, &lt;i&gt;J&lt;/i&gt; = 6.5 Hz)</td>
<td>1.04 (d, &lt;i&gt;J&lt;/i&gt; = 6.5 Hz)</td>
<td>1.04 (d, &lt;i&gt;J&lt;/i&gt; = 6.5 Hz)</td>
</tr>
<tr>
<td>4-CH</td>
<td>2.31 (m)</td>
<td>2.32 (m)</td>
<td>2.31 (ddq, &lt;i&gt;J&lt;/i&gt; = 6.5, 9.0, 10.5 Hz)</td>
</tr>
<tr>
<td>3-CH</td>
<td>3.60 (dd, &lt;i&gt;J&lt;/i&gt; = 8.2, 10.4 Hz)</td>
<td>3.61 (dd, &lt;i&gt;J&lt;/i&gt; = 8.5, 10.5 Hz)</td>
<td>3.6 (dd, &lt;i&gt;J&lt;/i&gt; = 10.5, 8.5 Hz)</td>
</tr>
<tr>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.79 (s)</td>
<td>Not reported</td>
<td>3.79 (s)</td>
</tr>
<tr>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.81 (s)</td>
<td>Not reported</td>
<td>3.81 (s)</td>
</tr>
<tr>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.82 (s)</td>
<td>Not reported</td>
<td>3.82 (s)</td>
</tr>
<tr>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.87 (s)</td>
<td>Not reported</td>
<td>3.87 (s)</td>
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<tr>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.89 (s)</td>
<td>Not reported</td>
<td>3.90 (s)</td>
</tr>
<tr>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.90 (s)</td>
<td>Not reported</td>
<td>3.91 (s)</td>
</tr>
<tr>
<td>2-CH</td>
<td>4.60 (dq, &lt;i&gt;J&lt;/i&gt; = 6.3, 8.2 Hz)</td>
<td>4.61 (m)</td>
<td>4.60 (dq, &lt;i&gt;J&lt;/i&gt; = 6.5, 8.5 Hz)</td>
</tr>
<tr>
<td>5-CH</td>
<td>4.96 (d, &lt;i&gt;J&lt;/i&gt; = 9.1 Hz)</td>
<td>4.98 (d, &lt;i&gt;J&lt;/i&gt; = 9.0 Hz)</td>
<td>4.97 (d, &lt;i&gt;J&lt;/i&gt; = 9.0 Hz)</td>
</tr>
<tr>
<td>Ar-H</td>
<td>6.535 (s)</td>
<td>Not reported</td>
<td>6.535 (s)</td>
</tr>
<tr>
<td>Ar-H</td>
<td>6.54 (s)</td>
<td>Not reported</td>
<td>6.54 (s)</td>
</tr>
<tr>
<td>Ar-H</td>
<td>6.69 (s)</td>
<td>Not reported</td>
<td>6.69 (s)</td>
</tr>
<tr>
<td>Ar-H</td>
<td>7.14 (s)</td>
<td>Not reported</td>
<td>7.14 (s)</td>
</tr>
</tbody>
</table>
2.3 Synthesis of chiral morpholine auxiliaries

As discussed earlier the use of chiral auxiliaries in Claisen rearrangements is a well developed field. Thus far there is only one brief report with regard to the use of chiral auxiliaries in acyl-Claisen rearrangements (Scheme 106). 94

![Scheme 106: Chiral auxiliary mediated asymmetric acyl-Claisen rearrangement from the work of Raubo and co-workers](image)

This report used a proline derived allyl pyrrolidine derivative with some success, however both syn- and anti- diastereomers were formed. MacMillan and co-workers have reported that pyrrolidine performs poorly, in comparison to morpholine, as the tertiary amine in acyl-Claisen rearrangements. 60 We therefore decided to attempt preparation of chiral substituted allyl morpholine substrates and assay their influence on diastereoselectivity in acyl-Claisen rearrangements.

We proposed a short synthesis of these chiral morpholines from commercially available amino alcohols 178, derived from chiral pool amino acids. 137 These amino alcohols would be acylated with chloroacetyl chloride 179, followed by intramolecular alkylation to give morpholinone 180 which could be reduced to the desired substituted morpholine 181. Finally these morpholines would be allylated to give substrates 182/183 desired for acyl-Claisen rearrangement (Scheme 107).
2.3.1 Choice of chiral ‘X’ group

Simple diastereoselectivity in the acyl-Claisen rearrangement is well defined and due to this we can expect rearrangement to proceed through one of two enantiomeric chair-like transition states (Figure 35). The principle behind our modification is that we can introduce a second level of diastereoselectivity, choosing between these two enantiomeric transition states. With the chiral auxiliary in place we could produce two diastereomers which without consideration of the auxiliary chiral centre are enantiomeric. We will refer to these diastereomers as ‘pseudoenantiomeric’, or ‘pseudoenantiomers’ in contrast to simple syn- and anti- diastereomers (Figure 36).

The use of morpholine as a chiral auxiliary creates a relatively complex system. As our auxiliary is mono substituted, formation of each transition state can occur in one of two ways such that each enantiomeric transition state could have the auxiliary in one of two positions allowing two possible pathways to each pseudoenantiomer, one of which may offer a lesser degree of auxiliary participation (Figure 37).
Fortunately we should expect, if the auxiliary is large enough, facial selectivity will occur in the approach of the ketene narrowing the possibilities to two transition states with the auxiliary in a predictable orientation (Figure 38).

The question of whether either transition state 184a or 184b is favoured is also slightly complicated by the possibility of the morpholine ring being in either of two chair or two boat transition states. Working on the assumption that one of the chairs will be favoured over the other, as it will have the auxiliary in an equatorial position, we can eliminate one chair possibility (per transition state). This also suggests that larger auxiliaries may perform better as they will have higher energy demands in switching between the two chair transition states. Whilst normally boat transition states would be eliminated from consideration as well, we acknowledge the possibility that the Lewis acid may coordinate between the morpholine oxygen and the carbonyl oxygen forcing a boat transition state. In any case we can discount the boat where the ring oxygen is pointing away from the carbonyl oxygen (Figure 39).

Inspection of transition states 184a and 184b indicates that 184a may be lower energy. In 184a with the morpholine chair, auxiliary ‘X’ and the metal ether are on opposite sides of the 6-membered transition state, in contrast to 184b where they are on the same side. In both morpholine boats the auxiliary is held away somewhat, however in the case that the auxiliary is big enough it may still have a negative steric effect.
With these possibilities in mind we elected to trial a variety of auxiliaries. There was some indication that bigger may be better, however we felt that too big could raise the energy barrier for rearrangement to the point where no reaction could take place. Whilst net volume may play a major part, another interesting factor may be the placement of that volume. Finally there is potential for another point of coordination if a heteroatom is included in the auxiliary. The auxiliary sidechains and reasoning behind their choice are detailed below (Table 16).

<table>
<thead>
<tr>
<th>Derivative of:</th>
<th>181</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>181a</td>
<td>Small, probe size requirement for selectivity.</td>
</tr>
<tr>
<td>Valine</td>
<td>181b</td>
<td>Aliphatic bulk, close in.</td>
</tr>
<tr>
<td>Leucine</td>
<td>181c</td>
<td>Aliphatic bulk, on pendant.</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>181d</td>
<td>Aliphatic bulk, close in plus ‘reach’.</td>
</tr>
<tr>
<td>Phenylglycine</td>
<td>181e</td>
<td>Aromatic bulk, close in.</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>181f</td>
<td>Aromatic bulk, on pendant.</td>
</tr>
<tr>
<td>Serine</td>
<td>181g</td>
<td>Coordination point, aromatic bulk, on longer pendant.</td>
</tr>
<tr>
<td>Serine</td>
<td>181h</td>
<td>Coordination point, on pendant.</td>
</tr>
</tbody>
</table>

Table 16: Chiral auxiliary sidechain choices and rationale.
2.3.2 Chloroacetylation of amino alcohols (S)-178a-f

The first step in preparing our desired chiral auxiliary morpholines (S)-181a-f ((S)-181g-h will be covered separately) was preparation of chloroacetamides (S)-185a-f via addition of chloroacetyl chloride 179 to amino alcohols (S)-178a-f. Schotten-Baumann conditions were utilised as in the work of Shawe et al.\textsuperscript{138} and gave the desired chloroacetamides (S)-185b-f in good yield (77 – 95%) (Scheme 108).\textsuperscript{139-140} These biphasic conditions appeared to suit examples with large hydrophobic sidechains, with any excess amino alcohol washed out in the aqueous layer along with any quenched chloroacetyl chloride. Unfortunately (S)-178a did not suit these conditions as well, with the yield of (S)-185a highly variable. It was suspected the lack of a significant hydrophobic component in the sidechain may have facilitated product loss into the aqueous layer. Fortunately the conditions of Bedürftig et al.\textsuperscript{141} using triethylamine as the base in monophasic conditions (DCM) worked well and chloroacetamide (S)-185a was isolated in 86% yield after purification by column chromatography (Scheme 108).

Analysis of the \textsuperscript{1}H NMR spectra for chloroacetamides (S)-185a-f provides useful data for structural identification. Whilst the variety of sidechains create obvious differences in each spectrum, the key backbone residues tend to fall within similar regions. The most variable backbone proton is at the chiral centre appearing between \( \delta 3.80 \) – \( \delta 5.13 \) depending on the sidechain. Proton residues for the acetamide are found between \( \delta 4.02 \) and \( \delta 4.14 \). The most difficult assignment is that of the \(-\text{CH}_2\text{OH}\) proton residues as the neighbouring chiral centre causes each of the protons to fall within a distinct region (e.g. 185f: \( \delta 3.64 \), dd, \( J = 4.9 \), 11.1 Hz; \( \delta 3.71 \), dd, \( J = 3.8 \), 11.1 Hz). Analysis of the 2D HSQC NMR allowed assignment by correlation with the carbon residue. These proton residues typically fall between \( \delta 3.58 \) and \( \delta 3.94 \) with each signal appearing as a doublet of doublets. Analysis of optical rotation for each chloroacetamide 185a-f returned non-zero values and, in the cases where a literature precedent was available, matched, indicating preservation of optical purity during this step.
2.3.3 Intramolecular alkylation of chloroacetamides (S)-185a-f

Intramolecular alkylation of chloroacetamides (S)-185b-f was carried out again according to the methods of Shawe et al.\textsuperscript{138} via formation of a sodium alkoxide to give morpholinones (S)-180b-f in modest to excellent yield (53% - quant.). The alanine derivative (S)-185a again proved unresponsive to the standard conditions, however using sodium tert-butoxide in place of sodium hydride proved successful. (Scheme 109).

Structural confirmation of morpholinones (S)-180a-f was performed in analogy with chloroacetamides (S)-185a-f. Identification of the NCHCH\textsubscript{2}O proton residues was simple as in general they appeared as doublets of doublets in an analogous region (δ3.37 – δ4.09) to the equivalent protons in the chloroacetamide precursors. Again analysis of the 2D HSQC NMR was required in order to confirm that the two distinct and separate proton residues were attached to the same carbon. The chiral proton CH-X residues again vary with sidechain, but in general fall between δ3.25 and δ3.81 appearing as a multiplet. Finally the C(O)CH\textsubscript{2}O residues appear as two close doublets in much the same region as in the precursor (δ4.13 – δ4.75). Again analysis of optical rotation returned non-zero values and matched literature values when available, indicating preservation of optical purity.

2.3.4 Reduction of morpholinones (S)-180a-f

Reduction of morpholinones (S)-180a-f was carried our according to the methods of Shawe et al.\textsuperscript{138} in the presence of LiAlH\textsubscript{4} in refluxing THF. We anticipated water solubility to be an issue with isolation and as such developed the procedure to counter this. The LiAlH\textsubscript{4} quench was carried out by dropwise addition of water (0 – 5 °C) in such a way that the majority of the water was consumed in the quench. The reaction mixture was then filtered through a plug of Celite, washing with ethyl acetate and the solvent removed. When necessary the product was further purified by distillation under vacuum, using a short path distillation apparatus. We believe this may be the reason behind some of the lower yields and in practice the purification was often eschewed with product carried through crude to the next step without significant loss of efficiency. Nonetheless the yields

\begin{align*}
\text{Scheme 109: Preparation of morpholinones (S)-180a-f from chloroacetamide (S)-185a-f. Reagents and conditions: i) NaH, THF, 0 °C – rt, (S)-180b: 88% ; (S)-180c: quant.; (S)-180d: quant.; (S)-180e: 57%; 180f: quant. ib) NaO\textsubscript{t}Bu, THF, 0 °C – rt, (S)-180a 53%;}
\end{align*}

\begin{align*}
\text{Scheme 110: Preparation of morpholines (S)-181a-f from morpholinones (S)-180a-f. Reagents and conditions: LiAlH\textsubscript{4}, THF, Δ, (S)-181a: 90%; (S)-181b: 76%; (S)-181c: 63%; (S)-181d: 67%; (S)-181e: quant.; (S)-181f: 53%.}
\end{align*}
of purified product ranged from modest to excellent (53% - quant.) (Scheme 110). The exception to this procedure was again (S)-181a with isolation again proving difficult. In this case the isolation was improved by adding methanolic HCl to the filtered reaction mixture, forming the hydrochloride salt which was used without purification.

Assignment of the $^1$H NMR spectrum was significantly more complicated for the morpholines (S)-181a-f than for morpholinones (S)-180a-f. Similar to the precursors, separation of the two protons on a CH$_2$ between two distinct regions was common, however in this case there were three CH$_2$ groups to contend with and there was significantly more overlap for morpholine proton resonances than observed in the morpholinone. Similarly more variation was encountered presumably due to a variety of factors including sidechain substitution and morpholine ring conformation (chair vs. boat). Key to structural elucidation of these compounds was the use of 2D HSQC and COSY NMR experiments.

Firstly pairing of proton resonances was possible via their HSQC correlations to methylene carbons. Secondly use of the DEPTQ carbon experiment which differentiates between CH, CH$_2$, CH$_3$ and quaternary carbon resonances allowed identification of 3-CH as it was the only ring CH. Identification of the chiral centre allowed easy identification of 2-CH$_2$ via a COSY correlation. The deshielding effect of the ring oxygen was expected to be greater than the nitrogen and thus the two ethereal CH$_2$’s were expected further downfield than the amino CH$_2$ and this coupled with the analogy of 2-CH$_2$ peak locations allowed identification of 6-CH$_2$ resonances and finally this allowed identification of the 5-CH$_2$ (Figure 40). Alongside this came identification of the sidechain resonances. Whilst some resonances were in isolated regions either upfield or downfield of the morpholine ring protons, others overlapped and this introduced another layer of complexity, often relying on COSY interactions between 3-CH and the sidechain protons to allow differentiation.

Analysis of optical rotations returned non-zero values and in the cases where a literature precedent was available the synthesized material matched the reported values.

2.3.5 Morpholines containing oxygenated sidechains

We realised that the preparation of morpholine 181g (and as a derivative, 181h) would require a modified route. Simple reduction of the parent amino acid to amino alcohol 178g (Scheme 111) would lead to a symmetrical diol thereby defeating the purpose of our chiral

![Figure 40: Key interactions in structural elucidation of chiral morpholines (S)-181a-f](image_url)
auxiliary. A protection strategy was therefore required. As serine already contained our desired amino alcohol motif we decided that it would be simple to use serine methyl ester (S)-**186**, protecting the acid function as an ester, and simply follow our usual protocol to form morpholine (R)-**181g-h**. This morpholine would have the opposite configuration at the chiral centre for morpholines (S)-**181a-f** but this would not matter for our methodology study. The proposal was that ester (S)-**186** could be reduced selectively at the morpholinone stage and functionalised as desired prior to reduction to morpholines (R)-**181g-h**.

![Scheme 111: Proposed route to oxygenated auxiliaries.](image)

For acylation with chloroacetyl chloride, serine methyl ester (S)-**186** was submitted to the Schotten-Baumann methodology of Shawe et al.\(^\text{138}\) without success, and we attribute this to either hydrolysis of the ester leading to a water soluble acid or simply that the product (S)-**185g** was polar enough to remain in water. Turning to the non-aqueous method of Bedürftig et al.\(^\text{141}\) using NEt\(_3\) in DCM was successful, furnishing chloroacetamide (S)-**185g** in 91% yield (Scheme 112).

![Scheme 112: Preparation of chloroacetamide (S)-185g from serine ester (S)-186.](image)

Identification of chloroacetamide (S)-**185g** was straightforward by comparison to the chloroacetamides (S)-**185a-f** we had already prepared. The -CH\(_2\)OH residues were found in the same region (δ3.96; δ4.06) and were doublets of doublets as in previous examples. The -CH\(_2\)Cl residue was found at δ4.11 as a singlet and the chiral proton at δ4.68, again in similar regions to previous examples.
Intramolecular alkylation was the next step and as in previous examples we utilised the methodology of Shawe et al.\textsuperscript{138} forming the sodium alkoxide followed by intramolecular alkylation. However we were surprised to find acrylate 187 as the only isolable product (43% yield) (Scheme 113).

Initially the structure of product 187 provided somewhat of a puzzle as the key -CH$_2$O-protons were absent. Closer analysis of the $^1$H and $^{13}$C spectra simplified identification somewhat as the two protons at δ5.96 and δ6.65 in the $^1$H NMR and the single methylene resonance at δ110.0 in the $^{13}$C NMR were indicative of a terminal alkene. From there we proposed acrylate 187 had formed and as it has previously been prepared we were able to compare our data to literature values.\textsuperscript{142}

Review of literature lead us to the work of Goodall \textit{et al.}\textsuperscript{143} who under similar conditions had also experienced β-elimination of serine ester 188 (Scheme 114), indicating that elimination of serine alkoxy groups can be relatively facile.

We hypothesised that the reason such elimination is not seen in our other chloroacetamide systems is that the proton on the chiral carbon is not acidic enough. In this case, the presence of the methyl ester increases the acidity of the α-proton allowing elimination of water (Scheme 115).

- **Scheme 113:** Acrylate formation from chloroacetamide (S)-185g.
  Reagents and conditions: i) NaH, THF, 0 °C – rt, 43%.

- **Scheme 114:** β-elimination to form acrylate 187 in the work of Goodall \textit{et al.}\textsuperscript{143}
  Reagents and conditions: i) DBU or NEt$_3$, heat, 39 – 89%.

- **Scheme 115:** Proposed β-elimination to form acrylate 187.
  Reagents and conditions: i) NaH, THF, 0 °C – rt, 43%.
This unexpected elimination showed that the proposed route using an ester as a surrogate for a protected alcohol was unfeasible and forced re-evaluation of our strategy.

2.3.6 Morpholines containing oxygenated sidechains – revised strategy

With the presence of the ester nullifying our original strategy we decided to remove this moiety. This meant that an alcohol protection strategy with reduction of the ester followed by functionalization was important. Fortunately we came upon the work of Dave et al.\textsuperscript{144} who had prepared a serine derived morpholine by a somewhat different strategy to that we had been investigating (Scheme 116). Whilst the synthesis is longer we felt their route could be modified and would provide a fairly robust synthesis.

Dave et al. used a two step reduction sequence to convert ester (\textit{R})-189 to alcohol (\textit{R})-190, as single step reduction with LiAlH\textsubscript{4} resulted in degradation. We suspected this degradation was caused by loss of their silyl protection during the reduction. We proposed this step could be carried out in a single step by choosing a different protecting group.

We initially wished to prepare \textit{O}-silyl, \textit{N}-Boc protected serine ester (\textit{S})-191 from serine methyl ester (\textit{S})-186, to use as our starting point to evaluate the synthesis. This was accomplished via addition of Boc anhydride in the presence of triethylamine followed by a partial workup and addition of TBSCI and imidazole, giving ester (\textit{S})-191 in 69\% yield over two steps (Scheme 117).
Ester (S)-191 was then reduced using LiBH₄ in THF, proceeding in 98% yield to give deprotected amino alcohol (R)-192a, analogous to the starting point of Dave et al. Following their procedure we alkylated alcohol (R)-192a by stirring with tert-butyl bromoacetate and TBAI in a biphasic aqueous sodium hydroxide, toluene mixture and yielding ester (R)-189b quantitatively (Scheme 118).

Scheme 118: Preparation of 'Bu-ester (R)-189 from diprotected ester (S)-191.
Reagents and conditions: i) LiBH₄, THF, 0 °C - rt, 98%; ii) 30% aq. NaOH, TBAI, PhMe, 0 °C – rt, quant.

The ¹H NMR characterisation of ester (R)-189b was straightforward as the characteristic tert-butyl proton resonances could be assigned by analogy to precursors. Identification of 2-CH was achieved by HSQC correlation to the DEPTQ carbon spectrum identifying the sole CH residue. HMBC correlations between 1-CH₂ and the ester CH₂ allowed differentiation from 3-CH₂ and hence identification. Measurement of the optical rotation returned non-zero values.

Looking ahead in our synthetic plan we realised that at some point we would have to exchange the silyl ether for a benzyl ether as this was one of our desired auxiliaries and would also be a useful protecting group. We proposed that conversion of the silyl ether to a benzyl ether at this stage should allow for a single step reduction and if successful the synthesis could be redesigned to allow benzyl protection from the outset. With this in mind we quantitatively deprotected silyl ether (R)-189b using TBAF in THF and protected the product alcohol (S)-193 with benzyl bromide and TBAI in an aqueous sodium hydroxide - toluene mixture giving benzyl ether (S)-189c in 72% yield (Scheme 119).
Structural analysis was straightforward as benzyl ether \((S)-189c\) is known in the literature.\(^{145}\)

Pleasingly the optical rotation \((\left[\alpha\right]_{22}^D = 13.9)\) was the same as reported \((\left[\alpha\right]_{24}^D = 13.1)\) confirming that no degradation of stereo-purity had occurred during our synthesis.

To prepare benzyl ether \((S)-189c\) had thus far taken four steps, we proposed that this could be shortened to two if we instead started from commercially available \(O\)-benzyl \(N\)-Boc serine \((S)-194\). Therefore serine derivative \((S)-194\) was reduced with \(\text{LiAlH}_4\) in THF and gave alcohol \((R)-192\) in 64\% yield. Alcohol \((R)-192\) was converted to ester \((S)-189c\) in 85\% yield using the same conditions as previously (Scheme 120).

Pleasingly the data for benzyl ether \((S)-189c\) prepared by this new route matched that previously prepared effectively improving the preparation from six steps, 48\% overall yield to two steps 54\% overall yield.
We next attempted our proposed single step reduction using LiAlH$_4$ in THF, rather than the two step process used by Dave et al.,$^{144}$ and pleasingly it furnished alcohol ($S$)-190b in 96% yield. Quantitative O-mesylation was carried out with mesyl chloride and triethylamine in DCM as in the work of Dave et al. $N$-Boc deprotection with TFA in DCM followed, without isolation, by intramolecular alkylation using Hüning’s base in refluxing methanol gave morpholine ($S$)-181g quantitatively (2 steps) (Scheme 121). Thus our desired morpholine ($S$)-181g was prepared in six steps, with 52% overall yield.

![Scheme 121: Preparation of morpholine ($S$)-181g from ester ($S$)-189c.](image)

Reagents and conditions: i) LiAlH$_4$, THF, 0 °C – rt, 96%; ii) MsCl, NEt$_3$, DCM, 0 °C – rt, quant.; iii) TFA, DCM, 0 °C – rt; iv) iPr$_2$NEt, MeOH, Δ, quant. (2steps).

The techniques for structural analysis of morpholine ($S$)-181g were as described previously. Analysis of optical rotation gave a non-zero value, and the high resolution mass spectrum contained a peak indicative of our desired mass (208.1340 amu).

With morpholine ($S$)-181g in hand we considered the preparation of morpholine ($S$)-181h. Our initial plan was to debenzylate and then alkylate, however an extra protection step would be required to avoid $N,O$- double alkylation (Scheme 122). In view of this we elected to forgo making morpholine ($S$)-181h directly and instead deprotect and alkylate after $N$-allylation, thus saving a protection, deprotection sequence.

![Scheme 122: Proposed preparation of morpholine ($S$)-181h from morpholine ($S$)-181g.](image)
2.3.7 N-Allylation of chiral morpholines (S)-181a-g

Initial attempts to allylate chiral morpholine (S)-181f using the same triethylamine mediated conditions as we had used to form allyl morpholines previously (2.1.1 - 2.1.3) proceeded very poorly giving cinnamyl morpholine (S)-183f in only 7% yield. Crotylations using the method of Taylor et al., using Finkelstein conditions, had previously been successful within our research group, so we decided to attempt these. Thus using sodium hydride and catalytic TBAI lead to the formation of desired cinnamyl morpholine (S)-183f in a much improved 81% yield (Scheme 123). The remaining crotyl and cinnamyl morpholines (S)-182a-g/(S)-183a-g were prepared in an analogous fashion. In each case crotyl bromide was prepared as earlier described (2.1.1) and cinnamyl bromide was commercially available (Table 17).

<table>
<thead>
<tr>
<th></th>
<th>Yield (%)</th>
<th></th>
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</tr>
</thead>
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<td>(S)-181</td>
<td>44*</td>
</tr>
<tr>
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<td>30*</td>
<td>(S)-182b</td>
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</tr>
<tr>
<td>(S)-182b</td>
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<td>(S)-182c</td>
<td>65</td>
</tr>
<tr>
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</tr>
<tr>
<td>(S)-182e</td>
<td>81</td>
<td>(S)-182f</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 17: Preparation of allyl morpholines.
Reagents and conditions: 2 eq. NaH, 0.25 eq. TBAI, THF, 0 °C – rt. *3 equivalents of NaH used.
Discussion

$^1$H NMR analysis was performed in the same manner as for assignment of morpholines (S)-181a-g with the added complication of the allylic CH$_2$ residues, often falling in the same region as morpholine ring proton residues. Use of 2D COSY correlations to alkene proton residues alongside 2D HSQC correlations allowing pairing of individual proton residues permitting complete assignment. The key alkene residues for cinnamyl morpholines (S)-183a-g were in all cases well resolved and appeared within a relatively small region (β-CH: δ6.16 – 6.30, ddd; γ-CH: δ6.41 – 6.59, d) with the relevant coupling constant of magnitude consistent with that of E- alkenes ($J$ = 15.8 – 16.2 Hz). The analogous resides for crotyl morpholines (S)-182a-g were not as well resolved however they still appeared within a small region (β-CH: δ5.34 – 5.60; α-CH δ5.55 – 6.74). High resolution mass spectrometry provided mass values matching those predicted.

2.3.8 Elaboration of allyl morpholines (S)-182g and (S)-183g to morpholines (S)-182h and (S)-183h

All that remained was to convert the benzyloxy ether of allyl morpholines 182g and 183g to the methoxy analogue morpholines (S)-182h and (S)-183h. Debenzylation was carried out using BCl$_3$ in order to avoid potential alkene reduction issues anticipated in palladium catalysed hydrogenation which is more commonly used for benzyl deprotection. This proceeded well giving allyl morpholines (S)-182i in 99% yield and (S)-183i in 88% yield. Methylation was achieved using sodium hydride and methyl iodide giving the desired allyl morpholines (S)-182h in 65% yield and (S)-182h quantitatively (Scheme 124).

![Scheme 124](image)

Scheme 124: Preparation of allyl morpholines 182h and 183h from allyl morpholines (S)-182g and (S)-183g.

The $^1$H NMR spectra of these derivatives were analysed as previously described and optical rotation values were non-zero. High resolution mass spectrometry of the pure compounds gave desired masses.

This completed our synthesis of 16 chiral allyl morpholines with 8 different auxiliary sidechains for use in our hypothesized asymmetric acyl-Claisen rearrangement.
2.4 Asymmetric acyl-Claisen rearrangements

With our chiral morpholines in hand we turned our attention to the acyl-Claisen rearrangement of each substrate. As we knew that preparation of both dimethyl amide (±)-32a and diphenyl amide (±)-32c was relatively facile we elected to use these two rearrangements as the basis for our auxiliary screen. The dimethyl examples represent acyl-Claisen rearrangements with little steric bulk supplied by the core amide substitution and the diphenyl examples represent those with significant steric bulk. Our prior work had determined that for substrates with significant steric bulk up to a 100 mol % loading of Lewis acid may be required and thus we decided to standardise the conditions used throughout the screen and decided that 100 mol % Lewis acid loading would be used.

2.4.1 Probing Lewis acid choice

Our previous Lewis acid screen had indicated that either AlCl₃ or TiCl₄·2THF was the most appropriate choice for acyl-Claisen rearrangements where significant steric hindrance may be an issue. As our earlier screen had been performed on diphenyl amide substrates we elected to do the same in this case, with the belief that if rearrangement was facile with the diphenyl substrates, the dimethyl case should be non-problematic. Cinnamyl benzyl morpholine (S)-183f was chosen for our initial experiments. Our first conditions used 100 mol % AlCl₃ and Hünig’s base in DCM with phenyl acetyl chloride 31b and morpholine (S)-183f, however, no rearrangement was seen after twenty-four hours. As high temperature Claisen rearrangements are well known we decided to see if heating of the otherwise identical reaction mixture could promote rearrangement. Gratuitously, moderate heating did result in rearrangement, although in a modest 30% yield. Finally we replaced AlCl₃ with TiCl₄·2THF which gave amides 195a quantitatively, after a room temperature 24 hour reaction (Scheme 125).

![Scheme 125: First attempted asymmetric acyl-Claisen rearrangement. Reagents and conditions: ia) AlCl₃ (100 mol %), iPr₂NEt, DCM, rt, -.; ib) AlCl₃ (100 mol %), iPr₂NEt, DCM, Δ, 30%; ic) TiCl₄·2THF (100 mol %), iPr₂NEt, DCM, rt, 94%.]
2.4.2 \textsuperscript{1}H NMR analysis of pseudoenantiomeric amide 195a

We had expected that \textsuperscript{1}H NMR analysis would allow us to determine a ratio of diastereomers \textit{via} analysis of the ratio of 2-CH and 3-CH proton residues. Unfortunately this was complicated as these residues overlap significantly with the morpholine proton residues and thus meaningful analysis of their relative area was not possible. The only instance in which proton residues are well resolved and not overlapping is the alkene region where the distinctive 4-CH protons can be observed (Figure 41).

![Figure 41: \textsuperscript{1}H NMR spectrum of 195a showing the δ5.30 – 6.30 region containing 4-CH proton resonances.](image)

The two upfield resonances at δ5.38 – 5.48 and δ5.86 – 5.97 are well resolved and on their own appear to indicate the presence of two diastereomers, however closer analysis reveals that the final downfield resonance at δ6.12 – 6.25 is actually an overlap of the same pattern as the other two. All appearances indicate that four different 4-CH protons exist and initially we believed this indicated that we had in fact formed four diastereomers. We considered this a possibility, however believed it was unlikely as it would require formation of either an $E$-enolate or progression \textit{via} a boat-like transition state. Our experience with amides (±)-32m/(±)-113b (see 2.1.3) where we had in fact formed some anti- product meant we could not discount this possibility. Our alternate hypothesis was that these resonances were
instead rotameric in nature resulting from restricted rotation about the amide bond resulting from its partial $sp^2$ character (Figure 42).

![Figure 42: Four possible rotameric conformations of amide 195a.](image)

### 2.4.3 Confirmation of stereochemistry

We proposed a simple experiment that would allow us to distinguish between these two possibilities. Conversion of 2,3-disubstituted amides to the corresponding 2,3-disubstituted acid via formation of an iodolactone and subsequent reductive ring opening had been performed within our research group.\textsuperscript{130} Utilisation of this methodology to form acid (±)-82b from diphenyl amide (±)-32c should give an example of entirely syn- acid. Repetition of this protocol with pseudoenantiomeric amide 195a would give us a diastereomeric mixture of syn- or anti- acids, identifiable by different shifts in the $^1$H NMR spectrum. Alternatively if the above resonances were the result of rotamers we would only see one compound and if it were syn-, the NMR would match the previously prepared acid (±)-82b. Amides (±)-32c and 195a were reacted with iodine in a THF/water mixture in the absence of light to give iodolactone 196 that was immediately refluxed in acetic acid with zinc dust to give acid (±)-82b/82b quantitatively (Scheme 126).
Analysis of the $^1$H NMR spectrum from racemic acid (±)-82b prepared from amide (±)-32c indicated success in formation of the acid. No morpholine proton residues were present and a broad peak at $\delta_{10.24}$ representing the acid OH was present. Comparison of the chemical shifts to both amides (±)-32c/(±)-113a and aldehydes (±)-149/(±)-150 for which data from both syn- and anti- compounds are available supported retention of syn- stereochemistry ((±)-82b: 4-CH: $\delta_{6.03}$, ddd, $J = 7.7, 9.9, 17.4$ Hz; 5-CH$_2$: $\delta_{5.13}$, d, $J = 10.0$ Hz; 5-CH$_2$: $\delta_{5.22}$, d, $J = 17.0$ Hz; cf. (±)-32c: 4-CH: $\delta_{6.16}$; 5-CH$_2$: $\delta_{5.06} - 5.15$; (±)-149: 4-CH: $\delta_{6.08}$; 5-CH$_2$: $\delta_{5.13} - 5.20$). Comparison of the $^1$H NMR spectrum for scalemic acid 82b prepared from pseudoenantiomeric amide 195a indicated that it was identical to racemic acid (±)-82b, thus indicating that the resonances in Figure 41 were the result of rotamers, not diastereomers. The optical rotation for acid 82b prepared from pseudoenantiomeric amides 195a was measured giving a non-zero value of $[\alpha]^20_D = +26.0$ ($c = 0.10$, CHCl$_3$).
Given this success we decided that another simple experiment could provide yet more evidence for rotamers vs. diastereomers. Coupling of morpholine (S)-181f to acid (±)-82b prepared from racemic amide (±)-32c should give a spectrum with rotamers similar to that seen in Figure 41. Pseudoracemic amide (±)-195a was prepared by DCC mediated coupling of acid (±)-82b and morpholine (S)-181f in acetonitrile giving amide (±)-195a in 55% yield (Scheme 127). Analysis of the $^1$H NMR spectrum indicated that the 4-CH resonances were aligned with those in Figure 41 and this provided confirmation that the peaks were the result of rotamers.

![Scheme 127: Preparation of pseudoracemic amide (±)-195a from racemic acid (±)-82b. Reagents and conditions: i) DCC, (S)-181f, MeCN, 0 °C, 55%.

Whilst this issue had been resolved we still required a means of determining the diastereomeric ratio produced in our asymmetric acyl-Claisen. Slight separation of two spots was seen by TLC analysis when the solution was suitably dilute, however attempts to separate the two diastereomers by flash column chromatography was unsuccessful. We turned to HPLC in the hope that we could determine a product ratio. HPLC analysis of pseudoenantiomeric amide 195a was carried out using a 5 µm silica column (Phenomenex LUNA: l = 250 mm, φ = 4.6 mm) however separation was not achieved with a variety of $^i$PrOH/n-hexanes mixtures (Figure 43).
We next attempted separation using a chiral sugar on a 5 µm silica support (Daicel CHIRALPAK IC: l = 250 mm, ø = 4.6 mm) and were pleased to get separation using a 10% iPrOH/n-hexanes mobile phase (Figure 44). This result indicated that formation of pseudoenantiomeric amide 195a occurred with 77:23 selectivity. To confirm that this result was an accurate representation of the diastereomeric ratio we used the same HPLC system and ran a chromatogram of the psuedoracemic amide (±)-195a we had prepared from amide (±)-32c. As expected the peak ratio in this case was 1:1 validating our HPLC method for analysis of these amide products (Figure 45).
Figure 44: HPLC trace for pseudoeantiomeric amide 195a run on a Daicel CHIRALPAK IC normal phase chiral column with 90:10 n-hexanes:iPrOH mobile phase showing separation of amide diastereomers.

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<td>2</td>
<td>23.00</td>
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Figure 45: HPLC trace for pseudoracemic amide (±)-195a (from (±)-32c) run on a Daicel CHIRALPAK IC normal phase chiral column with 90:10 n-hexanes:iPrOH mobile phase showing separation of amide diastereomers.

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<tr>
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<td>50.26</td>
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2.4.4 Asymmetric acyl-Claisen rearrangement of allyl morpholines (S)-182a-h and (S)-183a-h

With a method for analysis of the diastereomeric ratios produced in our asymmetric acyl-Claisen rearrangement we then proceeded to generate a series of di-phenyl amides from allyl morpholines (S)-183a-h and di-methyl amides from allyl morpholines (S)-182a-h. Our standard procedure was followed for the acyl-Claisen rearrangement using 100 mol % TiCl₄·2THF, 1.2 equivalents of the acyl chloride, 1.5 equivalents of Hüning’s base and 1 equivalent of the allyl morpholine in DCM at room temperature for 18 hours. The results of these rearrangements are summarized below (Table 18).

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<th>R¹ / R²</th>
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<th>Amide</th>
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<td>195b</td>
<td>40</td>
<td>ND**</td>
</tr>
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<td>57 : 43</td>
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<td>195i</td>
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<td>-</td>
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<td>195j</td>
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<td>195p</td>
<td>33</td>
<td>50 : 50</td>
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Table 18: Results of asymmetric acyl-Claisen rearrangement auxiliary screen. *As attained by HPLC analysis using a Daicel CHIRALPAK IA normal phase chiral column – peaks in order of elution. **Not determined – refer to text, page 110 for details.
Inspection of these results reveals some obvious trends. ‘X’ groups that are branched at the alpha carbon tend to not proceed when \(R^1 / R^2 = \text{Ph}\) or proceed in low yield when \(R^1 / R^2 = \text{Me}\). Whilst ‘X’ groups that are unbranched at the alpha carbon tend to proceed more efficiently, in general, rearrangements where \(R^1 / R^2 = \text{Me}\) are higher yielding.

Selectivity, in general, appears to increase as steric bulk of both ‘X’ groups and \(R^1 / R^2\) groups increases, as predicted in 2.3.1. Three tiers of selectivity can be identified; those where essentially no, or low, selectivity is seen (Table 18: Entries 2, 3, 5, 13 and 16), those where modest selectivity is seen (Table 18: Entries 6, 11, 12 and 15) and those where high selectivity is seen (Table 18: Entries 9 and 14).

Due to the number of possible transition states it is difficult to specify the exact means by which these different auxiliaries infer diastereoselectivity. If we regard only the cases where \(R^1 / R^2 = \text{Me}\) a pattern emerges whereby selectivity tends to increase as steric bulk and rigidity of the auxiliary increases. This allows us to decouple the effect of the auxiliary bulk from the substituent bulk to some degree. For \(X = ^i\text{Pr}\) (Table 18: Entry 3) and \(X = ^i\text{Bu}\) (Table 18: Entry 5) the selectivity is essentially the same and is low. In contrast when \(X = \text{Ph}\) (Table 18: Entry 9) or \(X = \text{Bn}\) (Table 18: Entry 11) selectivity is modest to high. The key difference between these two sets is the transition from alkyl branched moieties at either the alpha or beta position to phenyl moieties at either the alpha or beta positions. It would appear that the increased rigidity and planarity of a phenyl ring over alkyl substituents is favourable. Indeed when \(X = \text{Ph}\) and \(R^1 / R^2 = \text{Me}\) selectivity is very good. If we compare the corresponding cases where \(R^1 / R^2 = \text{Ph}\) (Table 18: Entries 4 and 6 vs. Table 18: Entries 10 and 12) we see first off that the steric bulk has become too much to overcome for \(X = ^i\text{Pr}\), Ph and the reaction has not proceeded. For \(X = ^i\text{Bu}\) and \(R^1 / R^2 = \text{Ph}\) (Table 18: Entry 6) selectivity has improved greatly and for \(X = \text{Bn}\) and \(R^1 / R^2 = \text{Ph}\) (Table 18: Entry 12) it has remained much the same, at a relatively high level.

Our two oxygenated auxiliaries gave varied results, from zero selectivity to very high selectivity. Unfortunately the yields were relatively poor for all examples (Table 18: Entry 13 - 16). There was no established pattern correlating steric bulk with selectivity and this may indicate involvement of another factor, possible coordination of the oxygen in some cases, although this is difficult to confirm.
Two examples (Table 18: Entry 1 and 7) were not able to be analysed successfully by HPLC. For the first case both peaks co-eluted in solvent systems ranging from 10% \(^{i}\text{PrOH/}n\)-hexanes to 1% \(^{i}\text{PrOH/}n\)-hexanes. Given the low selectivity of the corresponding entry where \(R^1/R^2 = \text{Ph}\) we do not expect high selectivity from this example. The second example was slightly more complicated. Whilst separation was possible more than two peaks appeared, an effect we presume is due to the second chiral centre on the sidechain affecting elution. As this example is very similar to that where \(X = ^{i}\text{Pr}\) we again did not expect a high selectivity.

### 2.4.5 Characterisation of pseudoenantiomeric amides

Further analysis of the \(^1\text{H}\) spectrum for the pseudoenantiomeric amides indicated that full assignment of each resonance would be very difficult if not impossible as the combination of rotamers and diastereomers produced a large amount of overlap (Figure 46). This overlap was compounded by the splitting of morpholine protons as seen in characterisation of morpholines (S)-181a-f. Fortunately high-resolution mass spectrometry was able to provide accurate masses for each amide matching the calculated mass. We used this as confirmation, alongside identification of the distinctive terminal alkene residues in comparison to amides we had prepared previously. FTIR spectroscopy supported the presence of an amide functional group and thus we felt we could definitely account for production of our desired amides.
Figure 46: $^1$H NMR spectrum for amide 195a showing overlapping proton residues.
2.4.6 Acyl chloride screen in the asymmetric acyl-Claisen rearrangement

Having completed our screen of auxiliaries we were interested in carrying out a screen of acyl chlorides to gain an idea of the applicability of this methodology to a variety of functional groups and what effect they have on diastereoselectivity. For the basis of our screen we elected to utilise the auxiliary where $X = \text{Bn}$ 181f. This auxiliary had demonstrated the most consistent yield regardless of $R_1 / R_2$ and whilst selectivity was modest we felt that a more robust reaction was best suited for this screen. We initially attempted the asymmetric rearrangements in which $R_1 = \text{Me}$, $R_2 = \text{Ph}$ and $R_1 = \text{Ph}$, $R_2 = \text{Me}$ (Scheme 128).

We were somewhat surprised to see that the rearrangement where $R_1 = \text{Ph}$, $R_2 = \text{Me}$ did not proceed, whilst the opposite case ($R_1 = \text{Me}$, $R_2 = \text{Ph}$) proceeded in 45% yield. Presumably this is due to unfavourable steric interactions between the $R_1$ phenyl group and the auxiliary benzyl group. These unfavourable interactions are not present when $R_1 = \text{methyl}$ and thus this case rearranges albeit in somewhat reduced yield. As the rearrangement where $R_1 / R_2 = \text{Ph}$ proceeds in very good yield we again see some evidence of di-aromatic stabilisation whether via some electrostatic interactions or the ability to take up a conformation more favourable for rearrangement.

With this result in mind we elected to continue our acyl chloride screen with amine (S)-183f using our standard conditions as previously described (Table 19). We chose to examine a wide range of functional groups in this screen so as to establish a picture of what types of compounds could be targeted using this methodology. Four of these acyl chlorides ($R_1 = \text{SPh}$, Phthg, OBn, $p$-MeOPh) were chosen because they had been used in the work of MacMillan and co-workers and as such there was precedent for their utility in the racemic rearrangement. Thus success with these acyl chlorides would indicate that we were not removing utility from the process. They also provided a variety of heteroatom substitutions (aza, thio and oxy) and a substituted aromatic. Alongside these we chose a branched alkyl substituent ($R_1 = \text{iPr}$), a
simple ether ($R_1 = \text{OMe}$) and an ester ($R_1 = \text{OAc}$) as well as the aforementioned methyl and phenyl substituents.

![Diagram](https://via.placeholder.com/150)

<table>
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<th>$R_1$</th>
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<th>Amide</th>
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<td>195r</td>
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<td>5</td>
<td>195u</td>
<td>83</td>
<td>23 : 8 : 19 : 50</td>
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<td>195x</td>
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<td>9</td>
<td>195y</td>
<td>79</td>
<td>30 : 70</td>
</tr>
</tbody>
</table>

Table 19: Results of asymmetric acyl-Claisen rearrangement acyl chloride screen. *As attained by HPLC analysis using a Daicel CHIRALPAK IA normal phase chiral column – peaks in order of elution. **Phthg = Phthalylglycyl

All of the acyl chlorides rearranged with (S)-183f to form the desired amide generally in good yields. The benchmark for selectivity was amide 195a ($R_1/R_2 = \text{Ph}$; Table 19: Entry 2) with a 21:79 $dr$. For $R_1 = p$-MeOPh (Table 19: Entry 6) we see selectivity is identical (as elution order is not relatable to a specific diastereomer) although the yield is somewhat reduced. The reduction in yield has precedent as the analogous racemic rearrangements also showed a difference in yield ($R_1/R_2 = \text{Ph} – 94\%$ vs. $R_1 = p$-MeOPh / $R_2 = \text{Ph} – 73\%$). The next highest diastereoselectivity (30:70) came from the rearrangement where $R_1 = \text{OAc}$ (Table 19: Entry 9), proceeding in 79\% yield – a pleasing result as we had not previously included ester substitution in an acyl-Claisen rearrangement. The alkyl substituents $R_1 = \text{Me}, \text{'Pr}$ (Table 19: Entries 1 and 7) also rearranged with some degree of diastereoselectivity, 60:40 and 63:37 respectively, indicating that alkyl substituents both branched and unbranched are suitable substrates. Finally the heteroalkyl and heteroaryl substituents proved the least successful in terms of diastereoselectivity. For $R_1 = \text{SPh}, \text{Phthg}$ (Table 19: Entries 3 and 4) diastereoselectivity was essentially 1:1 (56:44 and 43:57) and yields were poor (25\%) to modest (68\%). The rearrangements where $R_1 = \text{OBn}, \text{OMe}$ (Table 19: Entries 5 and 8)
proved to be special cases. Each HPLC trace contained four separate peaks which according to our methodology should indicate four diastereomers. Our conventional wisdom indicated that we would not expect more than two, although we knew more can form in certain cases. We hoped that analysis of the $^1$H NMR spectrum might provide some evidence as although a degree of overlap is seen with two diastereomers we expected that a higher than previously seen number of overlapping peaks should be seen in the case of four diastereomers (with associated rotamers). Previously when dealing with racemic amides we have assigned regions within which the alkene residues fell for syn- and anti- amides. Unfortunately with the rotameric amide mixtures the alkene residues are less indicative. Analysis of the $^1$H NMR spectrum for amide 195u ($R^1 = OBn$) showed that the alkene residues did appear doubled and as such the normal defined splitting pattern was not seen. Analysis of the $^1$H NMR spectrum for amide 195x ($R^1 = OMe$) provided more definite information as the presence of several residues corresponding to the methoxy protons was indicative of more than two diastereomers (and their rotamers). Thus we concluded that in these two cases four diastereomers had formed and that acyl chlorides with an $\alpha$-substituted ether appear to be poor substrates for this methodology.

### 2.4.7 Summary of asymmetric acyl-Claisen rearrangement results

We have established methodology for the successful rearrangement of a variety of substituted allyl morpholines and the analysis of diastereomeric ratios produced therein. In general rigid substituents $\beta$- to the morpholine ring (e.g. Ph) appear most effective at inducing diastereoselectivity although in some cases introduction of substituents $\alpha$- to the morpholine is effective when the amide substituents are small. Introduction of a benzyloxy group $\beta$- to the morpholine ring produces very good selectivity, when amide substituents are bulky, however is detrimental to the yield. A wide variety of substituents can be introduced via acyl chloride substitution although some have detrimental effects on selectivity and yield.

### 2.5 Summary

We have successfully carried out a number of acyl-Claisen rearrangements in which aromatic substitution is present on the acyl chloride, the allyl morpholine or both. A small screen of Lewis acids was carried out to find an optimal catalyst for di-aromatic rearrangements. This determined that TiCl$_4$·2THF was most efficient. Investigation has also been carried out into the apparent stabilisation provided by di-aromatic systems.
Knowledge gained from these studies has been applied to the synthesis of novel compound tetraphenyl tetrahydrofuran (±)-109c and the synthesis of tetrahydrofuran lignan magnosalicin (±)-112.447

Procedures for the synthesis of chiral morpholine auxiliaries 181a-g from amino acids have been established and sixteen chiral allyl morpholines 182a-h and 183a-h have been submitted to acyl-Claisen rearrangement conditions. A method for ascertaining the diastereomeric ratio produced in these rearrangements using HPLC analysis has been developed and applied to all successful asymmetric rearrangements. Further to this work, an acyl chloride screen was completed and these results also submitted to HPLC analysis. Via this work the basis for further research into a chiral auxiliary mediated asymmetric acyl-Claisen rearrangement has been formed which could provide a route to chiral natural product synthesis.

2.6 Future work

2.6.1 Acyl-Claisen rearrangement methodology studies

Whilst much progress was made into elucidation of methodology for preparing di-aromatic amides via the acyl-Claisen rearrangement, we established that these reactions in general appear to require stoichiometric Lewis acid. As this is not entirely desirable a more comprehensive screen of Lewis acids could be performed in order to find one that may allow catalytic rearrangement. This work could then be utilised in the asymmetric acyl-Claisen rearrangement potentially fulfilling the goal of a catalytic enantioselective process.

Further work is required to fully elucidate the apparent stabilisation encountered when carrying out rearrangements to produce di-aromatic amides. A study systematically altering the electron donating and withdrawing substituents on both the acyl chloride and allyl morpholine may provide some insight into the mechanism behind this effect (Scheme 129).

![Scheme 129: Di-aromatic acyl-Claisen rearrangement in which electronics are modulated via the addition of electron donating or withdrawing substituents.](image-url)
Whilst our earlier quantum chemical investigations attempted to simply investigate any obvious electrostatic interactions between phenyl rings, using data from these proposed experiments a more comprehensive investigation could be performed. Key to this would be development of an experimental protocol capable of calculating the effect of the Lewis acid metal centre on surrounding nuclei. From there, investigation of various substituents on both the allyl morpholine and acyl chloride could provide a wide array of data for analysis, hopefully leading to some explanation of the apparent stabilisation.

### 2.6.2 Asymmetric acyl-Claisen rearrangement methodology studies

The studies completed on our asymmetric acyl-Claisen rearrangement give a good basis for further investigation having established procedures for the preparation of starting materials and rearrangement to form a variety of amides. Unfortunately diastereoselectivity is thus far relatively modest or when good is accompanied by a low yield.

For further investigation we propose the use of three more amino acids in synthesis of chiral morpholines. Firstly tyrosine could be used to prepare a $p$-oxygenated analogue of the relatively useful benzyl substituted morpholine ($S$)-181f (Scheme 130). The idea behind this modification is that it may allow coordination of the phenoxy substituent creating a more structured transition state and thus increasing diastereoselectivity. The corollary from this would be that a lack of improvement over the non-oxygenated analogue would give useful data with regard to the participation of heteroatom coordination. As well as using tyrosine, ortho-tyrosine may be investigated in the same way to see if the position of the phenoxy substituent has any effect on the outcome (Scheme 131).

Finally we propose the preparation of a threonine derived morpholine via the route developed for preparation of serine derived morpholines ($S$)-181g and ($S$)-181h (Scheme 132). The premise behind this modification is to investigate if further conformational restriction improves diastereoselectivity. Whilst the best diastereoselectivity came from rearrangement of benzyloxy substituted morpholine ($S$)-183g (Table 18: Entry 14) the other oxygenated
Discussion

examples proved poor (Table 18: Entries 13, 15 and 16). The extra methyl group may be beneficial in these cases.

The isoleucine derived auxiliaries appeared to not proceed due to the methyl group α- to the morpholine ring and whilst we hope that coordination of the oxygen would overcome this issue (S)-181i may also have this issue. In this case we propose that conformation restriction could be achieved by altering the alkoxy substituent. Analogues could be prepared via addition of substituted benzyl bromides adding extra substituents γ- to the morpholine ring (Figure 47).

2.6.3 Natural product synthesis
Through our syntheses of magnosalicin (±)-112 (see Scheme 102, 2.2.7) and tetraphenyl tetrahydrofuran (±)-109c (see Scheme 92, 2.2.5) we established two different approaches to highly substituted tetrahydrofurans derived from acyl-Claisen amides. We propose that these approaches can be applied to the synthesis of complex tetrahydrofuran natural products.

The synthesis of tricuspidatol A 109b (Scheme 133) is already partially complete. Difficulty was met adding a carbanion equivalent to either amide 32g or aldehyde 153b derived from amide 32g. Whilst a comprehensive investigation of the various methods for addition of a carbanion equivalent was beyond the scope of this project, completion of this work would allow efficient synthesis of tricuspidatol A 109b.
We believe that these approaches can be applied to even more complex tetrahydrofuran natural products such as mirabilol A 197 (Scheme 134). Synthesis of such compounds would benefit from future success in development of an asymmetric acyl-Claisen variant allowing stereospecific preparation of these and related natural products.

Scheme 134: Proposed natural product target mirabilol A 197 available from amide 198.
Experimental
General Details

All non-aqueous reactions were carried out under a dry nitrogen atmosphere unless otherwise noted. Solvents were dried either following the methods prescribed by Amarego et al.\textsuperscript{149} – diethyl ether, tetrahydrofuran, toluene and benzene were dried over sodium benzenophenone ketyl and dichloromethane, acetonitrile, Hünig’s base, triethylamine, dimethylformamide were dried over calcium hydride prior to distillation before use; or by adaptation of the methods of Williams et al.\textsuperscript{150} and Burfield\textsuperscript{151} – methanol, dichloromethane, toluene, acetonitrile and dimethyl formamide were dried by up to 72 h exposure to 10\% w/v 3 Å molecular sieves and tetrahydrofuran and diethyl ether were dried and peroxides removed by up to 7 day exposure to 10\% w/v 3 Å molecular sieves and 10\% w/v CoCl\textsubscript{2} (10\%) doped 3 Å molecular sieves. All commercial reagents were used without purification. Flash column chromatography was carried out on a silica gel 60 (40 – 63 µm, 230 – 430 mesh ASTM) solid phase with solvent systems as specified. Thin layer chromatography was carried out using Merck silica gel 60 F\textsubscript{254} aluminium plates pre-coated with silica. Compounds were identified using UV fluorescence and/or staining with either vanillin in ethanolic sulfuric acid (with heating), 3,5-dinitrophenylhydrazine in ethanolic sulfuric acid (with heating), ninhydrin in ethanol/glacial acetic acid (95:5) (with heating) or iodine on silica gel.

Melting points were measured using a Reicher-Kofler block and are uncorrected. High resolution mass spectra were recorded at a nominal resolution of 5000 on a Bruker MicrOTOF-Q II mass spectrometer. Infrared spectra were obtained neat using a Perkin-Elmer Spectrum 1000 series Fourier Transform IR spectrometer with Universal Attenuated Total Reflectance (Diamond) sampling accessory. Absorption maxima are expressed as wave numbers (cm\textsuperscript{-1}). NMR spectra were recorded on either a Bruker Avance AVIII-400 (400 MHz, \textsuperscript{1}H nuclei; 100 MHz, \textsuperscript{13}C nuclei) or a Bruker Avance AV-300 (300 MHz, \textsuperscript{1}H nuclei; 75 MHz, \textsuperscript{13}C nuclei). All chemical shift (\(\delta\)) values are reported in parts per million (ppm) relative to tetramethylsilane (0.0 ppm) as an internal reference. \textsuperscript{1}H NMR data is reported as follows: chemical shift, (relative integral, multiplicity [s – singlet, d – doublet, dd – doublet of doublets, ddd – doublet of doublet of doublets, dt – doublet of triplets, t – triplet, td – triplet of doublets, q – quartet, dq – doublet of quartets, m – multiplet, with br – broad peak as possible modifier], spin – spin coupling constant (\(J\) in Hertz (Hz)), identifier. Optical rotations were determined on the sodium D line (\(\lambda = 589\) nm, 0.1 or 1 dm cell) on a Perkin-Elmer 341 Polarimeter or a Rudolph Research Analytical AUTOPOL IV Automatic
Polarimeter. Absolute values were calculated according to $[a]^T_d = \frac{100}{c} \frac{a}{d}$ where $T =$ temperature in °C, $a =$ observed absorbance, $c =$ concentration in g/100 mL and $l =$ path length in dm or $[a]^T_d = \frac{100}{l} \frac{a}{\rho}$ where $T =$ temperature in °C, $a =$ observed absorbance, $\rho =$ density of the sample in g/mL and $l =$ path length in dm. Diastereomeric ratios were determined by chiral HPLC analysis which was performed on a Shimadzu Instrument (SPD10A detector (D2 lamp) with a LC20At 40 MPa pump). The CHIRALPAK IA analytical column (250 mm × 4.6 mm φ) was manufactured by Daicel Chemical Industries Ltd and reported as: ‘solvent ratio, flow rate, wavelength, sample loop volume, retention times’.

**Quantum chemical calculation methodology**

The molecules were energetically minimized using unrestricted B3LYP with the 6-31+G(d,p) basis set in the GAUSSIAN 09 software suite. The electronic energy calculations were carried out with the larger basis set 6-311+G(2df,p). The zero-point vibrational energies (ZPE) were scaled according to Wong (0.9804). In all cases the normal modes of the molecular vibrations revealed no imaginary frequencies for the calculated structures, which is in support of them representing a minimum on the potential energy surface. The electron affinities (AE) and ionisation potentials (IP) were calculated as described in Foresman and Frisch. The solvent effects of DCM were simulated using the polarised continuum model (iefpcm).
**General Procedures**

**General Procedure A: Bromination of an allylic-alcohol**

To a solution of allylic-alcohol (1 mmol) in DCM or Et₂O (1.1 mL), under an atmosphere of nitrogen at 0 °C, was added phosphorous tribromide (0.047 mL, 0.5 mmol) dropwise. The resulting solution was warmed to room temperature and stirred 18 h. The mixture was poured onto ice and allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with DCM or Et₂O (3 × 0.3 mL). The organic extracts we combined and washed with a 1 M aqueous NaOH solution (1 mL), brine (1 mL) and dried (MgSO₄). The solvent was removed in vacuo to give an allylic bromide that was used in all cases without further purification.

**General Procedure B: acyl-Claisen rearrangement**

To a stirred suspension of a Lewis acid (1 – 100 mol %) in DCM (3 mL), under an atmosphere of nitrogen, was added a solution of an allylic morpholine (1 mmol) in DCM (1 mL) dropwise, followed by iPr₂NEt (0.26 mL, 1.5 mmol) and the resulting mixture was stirred for 15 min. A solution of an acyl chloride (1.2 mmol) in DCM (1 mL) was then added dropwise and the reaction stirred for 24 h. 1 M aqueous NaOH (3 mL) was added, the layers separated and the aqueous layer extracted with DCM (3 × 3 mL). The combined organic extracts were washed with brine (6 mL), dried (MgSO₄) and solvent removed in vacuo. The crude material was purified by flash column chromatography to afford the product.

**General Procedure C: Chloroacetylation of amino-alcohol**

To a solution of amino alcohol (1 mmol) in DCM / 0.5 M aqueous NaOH (1:1, 8 mL) at 0 °C was added chloroacetyl chloride (0.11 mL, 1.4 mmol) dropwise and the reaction stirred vigorously for 3 – 12 h. The layers were separated and the aqueous layer extracted with DCM (3 × 4 mL). The combined organic extracts were dried (MgSO₄) and solvent removed in vacuo. The crude material was purified by flash column chromatography to afford the product.

**General Procedure D: Intramolecular cyclisation to morpholinone**

To a solution of chloroacetamide (1 mmol) in THF (6 mL), under an atmosphere of nitrogen at 0 °C, was added sodium hydride (as a 60% mineral oil dispersion) (0.048 g, 1.2 mmol) and the reaction stirred at room temperature for 1.5 h. Ice was added carefully and the mixture allowed to warm to room temperature. The mixture was extracted with EtOAc (3 × 6 mL),
the combined organic extracts washed with brine (6 mL), dried (MgSO₄) and solvent removed \textit{in vacuo}. The crude material was purified by flash column chromatography to afford the product.

**General Procedure E: Reduction to substituted morpholine**

To a solution of morpholinone (1 mmol) in THF (8 mL), under an atmosphere of nitrogen at 0 °C, was added LiAlH₄ (0.076 g, 2 mmol) and the mixture allowed to come to room temperature, then heated at reflux for 18 h. The reaction was cooled and quenched by the cautious dropwise addition of cold water until gas evolution ceases. EtOAc (8 mL) was added and the mixture stirred for 0.5 h, filtered through a plug of Celite and the plug washed with EtOAc (24 mL), solvent removed \textit{in vacuo} and the product isolated by distillation or used without purification.

**General Procedure F: Alkylation of substituted morpholine**

To a solution of morpholine or substituted morpholine (1 mmol) and TBAI (0.092 g, 0.25 mmol) in THF (4 mL), under an atmosphere of nitrogen at 0 °C, was added sodium hydride (2 - 3 mmol) and the resulting mixture stirred for 30 min. A solution of allylic bromide (1 - 3 mmol) in THF (2 mL) was added dropwise and the reaction stirred at room temperature for 18 h. Ice was added carefully and the mixture allowed to warm to room temperature. The mixture was extracted with EtOAc (3 × 6 mL), the combined organic extracts washed with brine (6 mL), dried (MgSO₄) and solvent removed \textit{in vacuo}. The crude material was purified by flash column chromatography to afford the product.
Synthesis of compounds

(E)-4-(But-2-enyl) morpholine (30a)

The first step was carried out according to general procedure A using (E)-but-2-en-1-ol 114 (4 g, 55 mmol) and phosphorous tribromide (2.68 mL, 27.5 mmol) in Et₂O (60 mL) to furnish the (E)-1-bromobut-2-ene 115 as a colourless oil.

To a solution of (E)-1-bromobut-2-ene 115 (7.43 g, 55 mmol) in DCM (40 mL), under an atmosphere of nitrogen at 0 °C, was added morpholine (5.32 mL, 61 mmol) dropwise. The resulting mixture was stirred at 0 °C for 20 min. Triethylamine (15.2 mL, 110 mmol) was added and the mixture stirred at room temperature for 22 h. Water (50 mL) was added, the layers separated and the aqueous layer further extracted with DCM (3 × 50 mL). The combined organic extracts were washed with 1 M aqueous NaOH (50 mL), dried (MgSO₄) and the solvent removed in vacuo to give the title compound (4.4 g, 56%) as a pale yellow oil.

δH (300 MHz, CDCl₃) 1.62 (3H, dt, J = 6.2, 10.8 Hz, CH₃), 2.35 (4H, t, J = 4.4 Hz, N(CH₂CH₂)₂O), 2.84 (2H d, J = 7.5, CH₂), 3.63 (4H, t, J = 4.4, N(CH₂CH₂)₂O), 5.47 (2H, m, HC=CH).

Spectroscopic data were in accordance with literature values.\textsuperscript{160}
Experimental

\[ \text{\((2R^*,3S^*)-2,3\text{-Dimethyl-1-morpholinopent-4-en-1-one (32a)}\)} \]

The reaction was carried out according to general procedure B with AlCl\(_3\) (0.047 g, 0.35 mmol), (E)-4-(but-2-enyl) morpholine 30a (0.5 g, 3.54 mmol), \(\text{Pr}_2\text{NEt}\) (0.92 mL, 5.31 mmol) and propionyl chloride 31a (0.37 mL, 4.25 mmol). Flash column chromatography (2:1 EtOAc, \(n\)-hexanes gave the *title compound* (0.53 g, 76%) as a pale yellow oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3) 1.02 (3H, d, J = 6.7 \text{ Hz, 3-CH}_3), 1.09 (3H, d, J = 6.7 \text{ Hz, 2-CH}_3), 2.41 – 2.50 (1H, m, 3-CH), 2.58 (1H, dq, J = 6.7, 7.0 \text{ Hz, 2-CH}), 3.49 – 3.66 (8H, m, N(CH\(_2\)CH\(_2\))\text{2O}), 4.91 – 5.04 (2H, m, 5-CH\(_2\)), 5.75 (1H, ddd, J = 7.4, 10.4, 17.6 \text{ Hz, 4-CH}). \]

Spectroscopic data were in accordance with literature values.\(^{66}\)
Experimental

(2S*,3S*)-3-Methyl-1-morpholino-2-phenylpent-4-en-1-one (32d)

The reaction was carried out according to general procedure B with AlCl₃ (0.047 g, 0.35 mmol), (E)-4-(but-2-enyl) morpholine 30a (0.5 g, 3.54 mmol), iPr₂NEt (0.92 mL, 5.31 mmol) and phenylacetyl chloride 31b (0.56 mL, 4.25 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes gave the title compound (0.53 g, 85%) as a white crystalline solid.

δₓ (400 MHz, CDCl₃): 0.78 (3H, d, J = 6.8 Hz, 3-CH₃), 3.00 – 3.11 (1H, m, 3-CH), 3.12 – 3.21 (1H, m, N(CH₂CH₂)₂O), 3.36 – 3.72 (8H, m, 2-CH, N(CH₂CH₂)₂O), 4.97 – 5.14 (2H, m, 5-CH₂), 5.92 (1H, ddd, J = 6.9, 10.5, 17.3 Hz, 4-CH), 7.20 – 7.35 (5H, m, Ar-H).

δₓ (100 MHz, CDCl₃): 17.3 (3-CH₃), 40.2 (C-3), 42.4, 46.2 (N(CH₂CH₂)₂O) 54.3 (C-2), 66.5, 66.8 (N(CH₂CH₂)₂O), 114.0 (C-5), 127.2 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 138.1 (Ar-C), 142.5 (C-4), 171.1 (C-1).

νₓ/ cm⁻¹ 3063 (C-H, aromatic), 2965 (C-H, alkene), 1610 (C=O), 1224 (C-O, aliphatic ether), 753 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 260.1642 C₁₆H₂₂NO₂ requires 260.1645.

M.P. 73 – 76 °C.
Experimental

(2S*,3S*)-1-(4-Methoxyphenyl)-3-methyl-2-phenylpent-4-en-1-one (105b)

To a solution of 4-bromoanisole 145 (0.04 g, 0.21 mmol) in THF (2.5 mL) under an atmosphere of nitrogen at -78 °C, was added a 1.6 M solution of n-BuLi in n-hexanes (0.13 mL, 0.21 mmol) and the resulting solution stirred for 5 min. A solution of amide 32d (0.05 g, 0.19 mmol) in THF (2.5 mL) was added dropwise and the mixture stirred at room temperature for 3 h. Saturated aqueous NH₄Cl (2 mL) was added and the resulting mixture extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (9:1 n-hexanes, EtOAc) gave the title compound (0.017 g, 32%) as a pale yellow oil.

δH (400 MHz, CDCl₃) 0.85 (3H, d, J = 7.0 Hz, 3-CH₃), 3.14 – 3.26 (1H, m, 3-CH), 3.82 (3H, s, OCH₃), 4.37 (1H, d, J = 10.4 Hz, 2-CH), 4.92 – 5.11 (2H, m, 5-CH₂), 5.84 (1H, ddd, J = 7.2, 10.4, 17.4 Hz, 4-CH), 6.87 (2H, d, J = 9.0 Hz, Ar-H), 7.18 – 7.39 (5H, m, Ar-H), 7.96 (2H, d, J = 9.0 Hz).

δC (100 MHz, CDCl₃) 17.7 (3-CH₃), 40.4 (C-3), 55.4 (OCH₃), 58.9 (C-2), 113.7 (2 × Ar-CH) 114.4 (C-4), 127.1, 128.6, 128.7 (5 × Ar-CH) 130.4 (Ar-C) 130.8 (2 × Ar-CH) 138.0 (Ar-C) 163.3 (Ar-C), 198.1 (C-1).

νmax/cm⁻¹ 3063 (CH, aromatic), 1671 (C=O), 1631 (C-H, alkene), 1597 (conj. C-H), 1260 (C-O, aromatic ether).

m/z High Resolution (ESI⁺) found (MH⁺): 281.1540 C₁₉H₂₁O₂ requires 281.1536.
Cinnamyl morpholine (30c)

To a solution of cinnamyl bromide 116 (4.85 g, 24.6 mmol) in DCM (50 mL) under an atmosphere of nitrogen at 0 °C, was added morpholine (2.58 mL, 29.5 mmol) dropwise. The resulting solution was stirred at 0 °C for 20 min. Triethylamine (6.82 mL, 49.2 mmol) was added and the mixture stirred at room temperature for 24 h. Water (50 mL) was added, the layers separated and the aqueous layer further extracted with DCM (3 × 20 mL). The combined organic extracts were washed with 1 M aqueous NaOH (50 mL), dried (MgSO₄) and the solvent removed in vacuo to give the title compound (5.0 g, 89%) as a brown oil.

δH (300 MHz, CDCl₃) 2.50 (4H, t, J = 4.6 Hz, N(CH₂CH₂O), 3.15 (2H, dd, J = 1.3, 6.8 Hz, 1-CH₂), 3.74 (4H, t, J = 4.6 Hz, N(CH₂CH₂O), 6.25 (1H, dt, J = 6.8, 15.9 Hz, 2-CH), 6.56 (1H, d, J = 15.9 Hz, 3-CH), 7.18 – 7.40 (5H, m, Ar-H).

Spectroscopic data were in accordance with literature values.¹⁶¹
Experimental

(2R*,3S*)-2-Methyl-1-morpholino-3-phenylpent-4-en-1-one (32e)

The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.083 g, 0.25 mmol), amine 30c (0.5 g, 2.46 mmol), iPr$_2$NEt (0.48 mL, 3.69 mmol) and propionyl chloride 31a (0.26 mL, 2.95 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.41 g, 63%) as a brown oil.

$\delta$$_H$ (300 MHz, CDCl$_3$) 0.93 (3H, d, $J$ = 6.8 Hz, 2-CH$_3$), 3.07 (1H, dq, $J$ = 6.8, 9.8 Hz, 2-CH), 3.48 – 3.72 (9H, m, N(CH$_2$CH$_2$)$_2$O, 3-CH), 4.96 – 5.06 (2H, m, 5-CH$_2$), 6.02 (1H, ddd, $J$ = 7.8, 10.4, 17.2 Hz, 4-CH) 7.16 – 7.36 (5H, m, Ar-H).

Spectroscopic data were in accordance with literature values.$^{105}$
To a solution of 4-bromoanisole 145 (0.04 g, 0.21 mmol) in THF (2.5 mL) under an atmosphere of nitrogen at -78 °C, was added a 1.6 M solution of n-BuLi in n-hexanes (0.13 mL, 0.21 mmol) and the resulting solution stirred for 5 min. A solution of amide 32e (0.05 g, 0.19 mmol) in THF (2.5 mL) was then added dropwise and the mixture stirred at room temperature for 3 h. Saturated aqueous NH₄Cl (2 mL) was added and the resulting mixture extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (9:1 EtOAc, n-hexanes) gave the title compound (0.025 g, 47%) as a yellow oil.

δ_H (400 MHz, CDCl₃) 0.96 (3H, d, J = 6.7 Hz, 2-CH₃), 3.72 – 3.90 (5H, m, OCH₃, 2-CH, 3-CH), 4.86 – 4.98 (2H, m, 5-CH₂), 5.95 (1H, ddd, J = 7.3, 10.4, 17.4 Hz, 4-CH), 6.96 (2H, d, J = 8.9 Hz, Ar-H), 7.12 - 7.37 (5H, m, Ar-H), 8.00 (2H, d, J = 8.9 Hz, Ar-H).

δ_C (100 MHz, CDCl₃) 17.0 (2-CH₃), 44.5 (C-2), 52.8 (C-3), 55.4 (OCH₃), 113.8 (2 × Ar-CH), 115.4 (C-5), 126.6 (Ar-CH), 128.4 (Ar-CH), 128.6 (Ar-CH), 130.2 (Ar-C), 130.5 (2 × Ar-CH), 139.9 (C-4), 141.8 (Ar-C), 163.5 (Ar-C) 202.1 (C-1).

ν_max/cm⁻¹ 3062 (CH, aromatic), 2874, 2840 (CH), 1670 (C=O), 1598 (conj., C=C).

m/z High Resolution (ESI⁺) found (MK⁺): 319.1099 C₁₉H₂₀KO₂ requires 319.1095.
The reaction was carried out according to general procedure B with AlCl₃ (0.33 g, 2.46 mmol), amine 30c (0.5 g, 2.46 mmol), iPr₂NEt (0.64 mL, 3.69 mmol) and phenylacetyl chloride 31b (0.46 mL, 2.95 mmol). Flash column chromatography (2:1 EtOAc, n-hexanes) gave the title compound (0.75 g, 94%) as a white solid.

δₜ (300 MHz, CDCl₃) 3.06 – 3.81 (8H, m, N(CH₂CH₂)₂O), 4.05 (1H, d, J = 14.2 Hz, 2-CH), 4.22 (1H, dd, J = 10.6, 14.2 Hz, 3-CH), 5.06 – 5.15 (2H, m, 5-CH₂), 6.16 (1H, ddd, J = 6.6, 10.6, 17.2 Hz, 4-CH), 6.92 – 7.12 (10H, m, Ar-H).

M.P. 107 – 109 °C.

Spectroscopic data were in accordance with literature values.⁶¹
(2S*,3S*)-2,3-Diphenylpent-4-enal (149), (2R*,3S*)-2,3-diphenylpent-4-enal (150), (2S*,3S*)-2,3-diphenylpent-4-en-1-ol (151) and 4-((2S*,3S*)-2,3-diphenylpent-4-en-1-yl)morpholine (152)

To a suspension of LiAlH₄ (0.05 g, 1.24 mmol) in THF (6 mL), under an atmosphere of nitrogen at -78 °C, was added a solution of amide 32c (0.2 g, 0.62 mmol) in THF (4 mL) dropwise. The reaction mixture was warmed to 0 °C and monitored by TLC. Formation of a spot (~1h) corresponding to an aldehyde (positive test with 2,4-dinitrophenylhydrazine stain) prompted quenching by gradual addition of a saturated aqueous Rochelle’s salt solution (5 mL). The resulting suspension was filtered through a Celite plug, washed with EtOAc (18 mL), the organic layer collected and the aqueous fraction further washed with EtOAc (2 × 6 mL). Organic extracts were combined, dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (2:1, n-hexanes, EtOAc) gave an inseparable mixture of aldehydes 149 and 150 (1:1.2) (0.06 g, 41%) as an amorphous yellow solid.

Rᵣ = 0.84 (1:1 n-hexanes, EtOAc).

δH (400 MHz, CDCl₃)[* denotes signal from isomer 150] 3.97 (1H, dd, J = 3.3, 10.8 Hz, 2-CH), 4.00 (1H, dd, J = 2.9, 10.5 Hz, 2-CH*), 4.10 – 4.19 (2H, m, 3-CH, 3-CH*), 4.83 (1H, dt, J = 1.0, 17.0 Hz, 5-CH₂*), 4.91 (1H, dt, J = 1.0, 10.3 Hz, 5-CH₃*), 5.13 – 5.20 (2H, m, 5-CH₂), 5.78 (1H, ddd, J = 7.7, 10.3, 17.2 Hz, 4-CH*), 6.08 (1H, ddd, J = 7.9, 10.4, 17.2 Hz, 4-CH), 6.99 – 7.41 (20H, m, Ar-H, Ar-H*), 9.59 (1H, d, J = 2.9 Hz, 1-CHO*), 9.77 (1H, d, J = 3.3 Hz, 1-CHO).
δC (100 MHz, CDCl₃) 50.4 (C-3*), 50.6 (C-3), 63.4 (C-2), 63.9 (C-2*), 116.5 (C-5), 116.8 (C-5*), 126.8 (Ar-CH), 126.9 (Ar-CH*), 127.4 (Ar-CH), 127.8 (Ar-CH*), 128.2 (Ar-CH*), 128.3 (2 × Ar-CH), 128.68 (Ar-CH), 128.7 (Ar-CH*), 129.8 (Ar-CH*), 129.4 (Ar-CH), 129.6 (Ar-CH*), 134.1 (Ar-C), 134.4 (Ar-C*), 140.2 (Ar-C), 141.0 (Ar-C*), 199.0 (C-1*), 199.5 (C-1).

νmax/cm⁻¹ 3061 (C-H, aromatic), 2922 (C-H, alkene), 2922 (C-H, alkyl), 2836, 2733 (C-H, aldehyde), 1710 (C=O), 912 (C-H, alkene), 695 (C-H, aromatic).

m/z High Resolution (APCI) found (MNa⁺): 259.1090 C₁₇H₁₆NaO requires 259.1093.

Spectroscopic data for (2R*,3S*)-150 were in accordance with literature values.¹²⁴

In a separate fraction was obtained alcohol 151 (0.04 g, 27%).

Rf = 0.09 (1:1 n-hexanes, EtOAc).

δH (400 MHz, CDCl₃) 1.48 (1H, br s, OH), 3.19 (1H, ddd, J = 4.8, 7.8, 10.4 Hz, 2-CH), 3.62 (1H, app t, J = 10.0 Hz, 3-CH), 3.85 (1H, dd, J = 7.8, 11.2 Hz, 1-CH₃), 3.99 (1H, dd, J = 4.8, 11.2 Hz, 1-CH₃), 5.09 (1H, dd, J = 1.5, 10.0 Hz, 5-CH₃), 5.19 (1H, dd, J = 1.5, 16.9 Hz, 5-CH₃), 6.09 (1H, dt, J = 10.0, 16.9 Hz 4-CH), 6.96 – 7.18 (10H, m, Ar-H).

δC (100 MHz, CDCl₃) 52.8 (C-2), 53.6 (C-3), 65.7 (C-1), 115.6 (C-5), 126.0 (Ar-CH), 126.5 (Ar-CH), 127.9 (Ar-CH), 128.1 (Ar-CH), 128.2 (Ar-CH), 128.7 (Ar-CH), 140.2 (Ar-C), 140.6 (C-4), 142.2 (Ar-C).

νmax/cm⁻¹ 3383 (O-H), 3061 (C-H, aromatic), 2902 (C-H, alkene), 914 (C-H, alkene), 2926 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MNa⁺): 261.1246 C₁₇H₁₈NaO requires 261.1250.

In a third fraction was obtained amine 152 (0.055 g, 29%).

Rf = 0.03 (1:1 n-hexanes, EtOAc).

δH (400 MHz, CDCl₃) 2.24 – 2.42 (4H, m, N(CH₂CH₂)₂O), 2.53 (1H, dd, J = 7.6, 12.8 Hz, 1-CH₃), 2.79 (1H, dd, J = 6.5, 12.8 Hz, 1-CH₃), 3.19 (1H, dd, J = 7.6, 14.4 Hz, 2-CH), 3.51 – 3.72 (5H, m, N(CH₂CH₂)₂O, 3-CH), 5.03 – 5.14 (2H, m, 5-CH₃), 6.12 (1H, dt, J = 10.0, 17.0 Hz, 4-CH), 6.87 – 6.94 (4H, m, Ar-H), 6.99 – 7.14 (6H m, Ar-H).
\[ \delta_C \ (100 \ \text{MHz, CDCl}_3) \ 48.5 \ (C-2), \ 53.8 \ (N(CH_2CH_2)_2O), \ 54.5 \ (C-3), \ 61.8 \ (C-1), \ 66.9 \ (N(CH_2CH_2)_2O), \ 115.3 \ (C-5), \ 125.9 \ (Ar-CH), \ 126.0 \ (Ar-CH), \ 127.5 \ (Ar-CH), \ 127.8 \ (Ar-CH), \ 128.5 \ (Ar-CH), \ 128.8 \ (Ar-CH) 140.8 \ (C-4), \ 141.7 \ (Ar-C), \ 141.9 \ (Ar-C). \]

\[ \nu_{\text{max}}/\text{cm}^{-1} \ 3061 \ (C-H, \text{aromatic}), \ 2933 \ (C-H, \text{alkene}), \ 1115 \ (C-N), \ 914 \ (C-H, \text{alkene}), \ 697 \ (C-H, \text{aromatic}). \]

\[ m/z \ \text{High Resolution (ESI$^+$/ found (MH$^+$): 308.2012 C}_{21}H_{26}NO \text{ requires 308.2009.} \]
(2S*,3S*)-2,3-Diphenylpent-4-enoic acid (82b)

To a solution of amide 32c (0.90 g, 2.81 mmol) in THF / water (1:1, 16 mL) in the absence of light was added I₂ (1.43 g, 5.63 mmol) and the mixture stirred for 18 h. Diethyl ether was added, the mixture washed with a saturated aqueous Na₂SO₃ (3 × 20 mL) and the solvent removed in vacuo to give iodolactone 196 (1.06 g, quant.) that was used immediately.

To iodolactone 196 (1.06 g, 2.81 mmol) in AcOH (25 mL) added zinc dust (1.31 g, 20 mmol) and stirred the mixture at 70 °C for 18 h. 2 M Aqueous HCl (10 mL) was added slowly and the mixture stirred for 0.25 h, extracted with EtOAc (3 × 15 mL) and solvent removed in vacuo. Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.72 g, quant.) as a white solid.

δ<sub>H</sub> (400 MHz, CDCl₃) 3.95 (1H, d, J = 11.5 Hz, 2-CH), 4.03 (1H, dd, J = 7.7, 11.5 Hz, 3-CH), 5.13 (1H, d, J = 10.0 Hz, 5-CH₃), 5.22 (1H, d, J = 17.0 Hz, 5-CH₃), 6.10 (1H, ddd, J = 7.7, 10.0, 17.0 Hz, 4-CH), 6.97 – 7.23 (10H, m, Ar-H), 10.24 (1H, br s, OH).

δ<sub>C</sub> (100 MHz, CDCl₃) 53.0 (C-3), 56.9 (C-2), 116.3 (C-5), 126.4 (Ar-CH), 127.3 (Ar-CH), 129.7 (Ar-CH), 139.1 (C-4), 140.1 (Ar-C), 178.5 (C-1).

ν<sub>max/cm</sub><sup>⁻¹</sup> 3030 (O-H), 2596 (C-H, alkyl), 1690 (C=O), 1287 (C-O), 923 (C-H, aromatic), 691 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 253.1218 C₁₇H₁₇O₂ requires 253.1223.

M.P. 109 – 111 °C.
(2S,3S)-2,3-Diphenylpent-4-enoic acid (82b’) and (2R,3R)-2,3-diphenylpent-4-enoic acid (82b’’)

To a solution of amide 195a (0.045 g, 0.11 mmol) in THF / water (1:1, 2 mL) in the absence of light was added I₂ (0.061 g, 0.24 mmol) and the mixture stirred for 18 h. Diethyl ether was added, the solution washed with saturated aqueous Na₂SO₃ (3 × 5 mL) and the solvent removed in vacuo to give iodolactone 196 (0.042 g, quant.) that was used immediately.

To iodolactone 196 (0.042 g, 0.11 mmol) in AcOH (0.5 mL) added zinc dust (0.09 g, 1.3 mmol) and stirred the mixture at 70 °C for 18 h. 2 M Aqueous HCl (0.2 mL) was added slowly and the mixture stirred for 0.25 h, extracted with EtOAc (3 × 2 mL) and solvent removed in vacuo. Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compounds (0.023 g, 88%) as a white solid.

Spectroscopic data was in accordance with the previous procedure.

\[ [\alpha]_D^{25} = +26.0 \ (c = 0.10, \text{CHCl}_3) \]
To a stirred solution of amide 32c (0.2 g, 0.62 mmol) in a water / tBuOH (1:1, 8 mL) at 0 °C was added N-methylmorpholine-N-oxide (0.22 g. 1.87 mmol) and an 0.1 M solution of osmium tetroxide in tBuOH (0.06 mL, 0.006 mmol). The reaction mixture was brought to room temperature and stirred for 24 h, quenched by addition of saturated aqueous Na₂SO₃ (10 mL) and stirred for a further 1 h. The aqueous mixture was extracted with EtOAc (3 × 30 mL), the combined organic extracts washed with 1 M aqueous KOH (30 mL), dried (MgSO₄) and solvent removed in vacuo. Gradient elution flash column chromatography (1:1 EtOAc, n-hexanes to 100% EtOAc) gave the title compound (0.218 g, quant.) as a white solid.

δ_H (400 MHz, CDCl₃) 3.17 – 3.30 (2H, m, N(CH₂CH₂)₂O, 5-CH₃) 3.47 – 3.75 (9H, m, N(CH₂CH₂)₂O, 3-CH, 5-CH₃), 4.09 – 4.16 (1H, m, 4-CH), 4.50 (1H, d, J = 10.6 Hz, 2-CH), 6.19 – 7.17 (10H, m, Ar-H).

δ_C (100 MHz, CDCl₃) 42.7, 46.6 (N(CH₂CH₂)₂O), 49.7 (C-2), 51.7 (C-3), 65.9 (C-5), 66.5, 66.8 (N(CH₂CH₂)₂O), 72.5 (C-4), 126.7 (Ar-CH), 126.9 (Ar-CH), 128.0 (Ar-CH), 128.4 (Ar-CH), 128.7 (Ar-CH), 129.8 (Ar-CH), 137.4 (Ar-C), 138.1 (Ar-C), 171.6 (C-1).

ν_max/cm⁻¹ 3418 (O-H), 3324 (O-H), 2925 (C-H, alkyl), 2854 (C-H, alkyl), 1620 (C=O), 1452, 1432 (CH aromatic), 1119 (C-O, ether), 1064 (O-H), 1029 (O-H).

m/z High Resolution (ESI⁺) found (MH⁺): 356.1858 C₂₁H₂₅NO₄ requires 356.1856.

M.P. 157 – 159 °C.
Experimental

(2S*,3S*)-1-Morpholino-1-oxo-2,3-diphenylbutan-4-al (153a)

To a solution of diol 199 (0.15 g, 0.42 mmol) in MeOH / water (3:1, 20 mL) at 0 °C was added sodium periodate (0.11g, 0.51 mmol) and the resulting mixture stirred for 5 h. Brine (5 mL) was added, and the aqueous mixture extracted with EtOAc (4 × 10 mL), the combined organic extracts were dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (2:1 EtOAc, n-hexanes) gave the title compound (0.107 g, 77%) as a pale cream solid.

δH (400 MHz, CDCl₃) 2.99 – 3.77 (8H, m, N(CH₂CH₂)₂O), 4.31 (1H, d, J = 10.6 Hz, 2-CH), 4.57 (1H, d, J = 10.6 Hz, 3-CH), 6.85 – 6.95 (4H, m, Ar-H), 7.07 – 7.13 (3H, m, Ar-H), 7.14 – 7.18 (3H, m, Ar-H), 9.84 (1H, s, 4-CH).

δC (100 MHz, CDCl₃) 42.7, 46.1, (N(CH₂CH₂)₂O), 50.9 (C-2), 62.8 (C-3), 66.2, 66.7 (N(CH₂CH₂)₂O), 127.2 (Ar-CH), 127.7 (Ar-CH), 128.2 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 129.9 (Ar-CH), 132.6 (Ar-C), 136.4 (Ar-C), 170.6 (C-1) 199.5 (C-4).

νmax/cm⁻¹ 3063 (C-H, aromatic), 2954 (C-H alkyl), 2820 (C-H, aldehyde), 1713 (C=O aldehyde), 1621 (C=O amide), 1243 (C-O, ether).

m/z High Resolution (ESI⁺) found (MH⁺): 324.1597 C₂₀H₂₂NO₃ requires 324.1594.

M.P. 99 – 100 °C.
(3S*,4S*,5S*)-5-Methyl-3,4-diphenyldihydrofuran-2(3H)-one (155a)

To a solution of aldehyde 153a (0.1 g, 0.31 mmol) in THF (5 mL), under an atmosphere of nitrogen at -78 °C, was added 1.4 M solution of methyllithium in Et₂O (0.22 mL, 0.31 mmol) and the mixture stirred at room temperature for 3 h. Saturated aqueous NH₄Cl was added (5 mL) and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried (MgSO₄) and solvent remove in vacuo. Flash column chromatography (1:1, EtOAc, n-hexanes) gave the title compound (0.04 g, 51%) as a yellow oil.

δH (400 MHz, CDCl₃) 1.45 (3H, d, J = 6.0 Hz, 5-CH₃), 3.27 (1H, dd, J = 10.0, 12.5 Hz, 4-CH), 4.06 (1H, d, J = 12.5 Hz, 3-CH), 4.63 (1H, dd, J = 6.0, 10.0 Hz, 5-CH), 7.10 – 7.36 (10H, m, Ar-H).

δC (100 MHz, CDCl₃) 18.6 (5-CH₃), 54.9 (C-3), 59.2 (C-4), 80.4 (C-5), 127.7 (Ar-CH), 128.1 (Ar-CH), 128.4 (Ar-CH), 128.8 (Ar-CH), 129.1 (Ar-CH), 135.3 (4-(Ar-C)), 136.2 (3-(Ar-C)), 175.5 (C-2).

νmax/cm⁻¹ 3062, 3032 (C-H, aromatic), 2968 (C-H, alkyl), 1763 (C=O), 1174 (C-O), 696 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 253.1220 C₁₇H₁₇O₂ requires 253.1223.
(3S*,4S*,5R*)-5-(4-Methoxyphenyl)-3,4-diphenyldihydrofuran-2(3H)-one (155b)

To a solution of 4-bromoanisole 145 (0.13 g, 0.68 mmol) in THF (8 mL), under an atmosphere of nitrogen at -78 °C, was added a 1.6 M solution of \textsuperscript{6}BuLi in \textit{n}-hexanes (0.43 mL, 0.68 mmol) and the mixture was stirred for 5 min. A solution of aldehyde 153a (0.2 g, 0.62 mmol) in THF (2 mL) was added dropwise and the reaction was stirred at room temperature for 3 h. Saturated aqueous NH\textsubscript{4}Cl was added (5 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO\textsubscript{4}) and the solvent removed \textit{in vacuo}. Flash column chromatography (2:1 \textit{n}-hexanes, EtOAc) gave the \textit{title compound} (0.097 g, 84%) as a red oil.

\(\delta_H\) (400 MHz, CDCl\textsubscript{3}) 3.66 (1H, dd, \(J = 10.1, 12.5\) Hz, 4-CH), 3.80 (3H, s, OCH\textsubscript{3}), 4.24 (1H, d, \(J = 12.5\) Hz, 3-CH), 5.48 (1H, d, \(J = 10.1\) Hz, 5-CH), 6.75 – 7.40 (14H, m, Ar-H).

\(\delta_C\) (100 MHz, CDCl\textsubscript{3}) 54.8 (C-3), 55.2 (OCH\textsubscript{3}), 59.8 (C-4), 84.9 (C-5), 127.5 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 128.8 (Ar-CH), 128.9 (Ar-CH), 134.9 (2 × Ar-C), 135.6 (Ar-C), 159.9 (Ar-C(OCH\textsubscript{3})), 175.3 (C-2).

\(\nu_{\text{max}}/\text{cm}^{-1}\) 3065 (C-H, aromatic), 2927 (C-H, alkyl), 1777 (C=O), 1250 (C-O, aromatic ether), 1515 (C=C, aromatic), 1154 (C-O, lactone), 831 (C-H, aromatic), 698 (C-H, aromatic).

\(m/z\) High Resolution (ESI\textsuperscript{+}) found (MH\textsuperscript{+}): 345.1484 C\textsubscript{23}H\textsubscript{21}O\textsubscript{3} requires 345.1485.
Experimental

(3S*,4S*,5R*-)3,4,5-Triphenyldihydrofuran-2(3H)-one (155c)\(^{163}\)

![Diagram of the compound](image)

To a solution of bromobenzene 160 (0.14 mL, 1.36 mmol) in THF (15 mL), under an atmosphere of nitrogen at -78 °C, was added a 1.6 M solution of \(^{t}\)BuLi in cyclohexanes (1.63 mL, 2.60 mmol) and the mixture stirred for 15 min. A solution of aldehyde 153a (0.4 g, 1.25 mmol) in THF (2 mL) was added dropwise and the reaction stirred 10 min at -78 °C then allowed to warm to room temperature and stirred for 2 h. Saturated aqueous NH\(_4\)Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL), the combined organic extracts washed with brine (15 mL), dried (MgSO\(_4\)) and solvent removed \textit{in vacuo}. Flash column chromatography (4:1 \textit{n}-hexanes, EtOAc) gave the \textit{title compound} (0.27 g, 69%) as a white solid.

\[\delta_h\] (400 MHz, CDCl\(_3\)) 3.62 (1H, dd, \(J = 10.1, 12.5\) Hz, 4-CH), 4.22 (1H, d, \(J = 12.5\) Hz, 3-CH), 5.52 (1H, d, \(J = 10.1\) Hz, 5-CH), 7.07 – 7.43 (15H, m, Ar-H).

\[\delta_c\] (100 MHz, CDCl\(_3\)) 55.0 (C-4), 60.0 (C-3), 84.9 (C-5), 125.9 (Ar-CH), 127.8 (Ar-CH), 127.9 (Ar-CH), 128.0 (Ar-CH), 128.4 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 129.0 (Ar-CH), 134.8 (Ar-C), 135.7 (Ar-C), 137.1 (Ar-C), 175.2 (C-2).

\(\nu_{\text{max}}/\text{cm}^{-1}\) 3063 (C-H, aromatic), 1769 (C=O), 1151 (C-O), 693 (C-H, aromatic).

\(m/z\) High Resolution (ESI\(^{+}\)) found (MNa\(^{+}\)): 337.1198 C\(_{22}\)H\(_{18}\)NaO\(_2\) requires 337.1199.

M.P. 135 – 140 °C.
To a solution of bromobenzene 160 (0.054 mL, 0.32 mmol) in THF (4 mL), under an atmosphere of nitrogen at -78 °C, was added a 1.6 M solution of tBuLi in cyclohexanes (0.42 mL, 0.67 mmol) and the mixture stirred for 15 min. A solution of lactone 155c (0.1 g, 0.32 mmol) in THF (1 mL) was added dropwise and the reaction stirred for 10 min at -78 °C then allowed to warm to room temperature and stirred for 2 h. Saturated aqueous NH₄Cl (4 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts washed with brine (5 mL), dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (4:1 n-hexanes, EtOAc) gave the title compound (0.11 g, 77%) as a white solid.

δ_H (400 MHz, CDCl₃) 2.95 (1H, d, J = 1.4 Hz, OH), 3.74 (1H, dd, J = 1.4, 12.7 Hz, 3-CH), 4.19 (1H, dd, J = 9.6, 12.7 Hz, 4-CH), 5.36 (1H, d, J = 9.6 Hz, 5-CH), 7.06 – 7.44 (20H, m, Ar-H).

δ_C (100 MHz, CDCl₃) 57.7 (C-4), 64.0 (C-3), 88.3 (C-5), 105.3 (C-2), 126.1 (Ar-CH), 126.7 (Ar-CH), 127.0 (Ar-CH), 127.1 (Ar-CH), 127.7 (Ar-CH), 128.06 (Ar-CH), 128.09 (Ar-CH), 128.29 (Ar-CH), 128.3 (Ar-CH), 128.5 (Ar-CH), 129.9 (Ar-CH), 134.7 (Ar-C), 137.4 (Ar-C), 141.1 (Ar-C), 143.0 (Ar-C).

ν_max/cm⁻¹ 3547 (O-H), 3062 (C-H, aromatic), 2930 (C-H, alkyl), 1450 (C-C, aromatic), 1041 (C-O, alcohol), 1022 (C-O, furan), 695 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MNa⁺): 415.1660 C₂₈H₂₄NaO₂ requires 415.1669.

M.P. 154 – 160 °C.
To a solution of lactol 162 (0.03 g, 0.076 mmol) in DCM (3 mL), under an atmosphere of nitrogen at -78 °C, was added BF$_3$·OEt$_2$ (0.022 mL, 0.18 mmol), triethylsilane (0.036 mL, 0.23 mmol) and the mixture stirred for 1 h, brought to -10 °C and stirred a further 3 h. Saturated aqueous NaHCO$_3$ (3 mL) was added, the organic layer separated and the aqueous layer extracted with DCM (3 × 3 mL). The combined organic extracts were dried (MgSO$_4$) and solvent removed in vacuo. Flash column chromatography gave the title compound (0.029 g, quant.) as a white solid.

$\delta$H (400 MHz, CDCl$_3$) 3.65 (2H, dd, $J = 2.9$, 6.4 Hz, 3-CH, 4-CH), 5.43 (2H, dd, $J = 2.9$, 6.4 Hz, 2-CH, 5-CH), 7.03 – 7.36 (20H, m, Ar-H).

$\delta$C (100 MHz, CDCl$_3$) 63.3 (C-3, C-4), 87.6 (C-2, C-5), 125.8 (Ar-CH), 127.0 (Ar-CH), 128.0 (Ar-CH), 128.3 (Ar-CH), 128.5 (Ar-CH), 137.7 (Ar-C), 138.7 (Ar-C).

$\nu_{\text{max}}$/cm$^{-1}$ 3061 (C-H, aromatic), 2907 (C-H, alkyl), 1450 (C-C, aromatic), 1024 (C-O, furan), 695 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MNa$^+$): 399.1707 C$_{28}$H$_{24}$NaO requires 399.1719.

M.P. 136 – 142 °C.
Experimental

(2S*,3S*)-2-(4-Methoxyphenyl)-1-morpholino-3-phenylpent-4-en-1-one (32f)

To a stirred solution of acid 119 (0.075 g, 0.41 mmol) in toluene (5 mL), under an atmosphere of nitrogen, was added thionyl chloride (0.065 mL, 2.7 mmol) dropwise and the mixture stirred at reflux for 4 h. Solvent was removed in vacuo and the residue taken up in n-hexanes (10 mL), solvent was again removed in vacuo and the resulting acid chloride 31k was placed under an atmosphere of nitrogen and used immediately without purification.

The reaction was then carried out according to general procedure B with TiCl₄·2THF (0.11 g, 0.34 mmol), amine 30c (0.068 g, 0.34 mmol), iPr₂NEt (0.09 mL, 0.51 mmol) and acyl chloride 31k (0.075 mL, 0.41 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.087 g, 73%) as an orange solid.

δH (400 MHz, CDCl₃) 3.12 – 3.22 (1H, m, N(CH₂CH₂)₂O), 3.39 – 3.78 (7H, m, N(CH₂CH₂)₂O), 3.69 (3H, s, OCH₃), 4.01 (1H, d, J = 10.6 Hz, 2-CH), 4.18 (1H, dd, J = 6.7, 10.6 Hz, 3-CH), 5.04 – 5.14 (2H, m, 5-CH₂), 6.15 (1H, ddd, J = 6.7, 10.5, 17.2 Hz, 4-CH), 6.62 (2H, d, J = 8.9 Hz, 2"-CH, 6"-CH), 6.92 – 6.98 (4H, m, 3’-CH, 5’-CH, 3"-CH, 5"-CH), 7.01 – 7.06 (1H, m, 4"-CH), 7.08 – 7.13 (2H, m, 3"-CH, 5"-CH).

δC (100 MHz, CDCl₃) 42.5, 46.2 (N(CH₂CH₂)₂O), 52.3 (C-2), 53.0 (C-3), 55.0 (OCH₃), 66.4, 66.8 (N(CH₂CH₂)₂O), 113.7 (C-2’, C-6’), 115.3 (C-5), 126.2 (C-4’), 128.0 (C-2’, C-6’), 128.8 (C-3’, C-5’), 129.3 (C-1’), 129.5 (C-3”, C-5”), 140.2 (C-4), 141.0 (C-1’), 158.3 (C-4”), 170.9 (C-1).

νmax/cm⁻¹ 3033 (C-H, aromatic), 2966 (C-H, alkene), 2833 (C-H, alkyl), 1623 (C=O), 1249 (C-O, aromatic ether), 1110 (C-O, aliphatic ether), 701 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 352.1920 C₂₂H₂₆NO₃ requires 352.1907.

M.P. 133 – 135 °C.
To a stirred solution of 3,5-dimethoxybenzoic acid 125 (8 g, 40.8 mmol) in THF (200 mL), under an atmosphere of nitrogen, at 0 °C was added portionwise LiAlH₄ (3.1 g, 81.5 mmol) and the resulting mixture stirred overnight at room temperature. The reaction was quenched by the gradual addition of saturated aqueous Rochelle’s salt (50 mL) followed by dilution with water (50 mL). The resulting solution was extracted with EtOAc (3 x 50 mL), the combined organic extracts were dried (MgSO₄) and solvent removed in vacuo to yield the title compound (5.8 g, 85%) as a yellow oil which was used without further purification.

δH (300 MHz, CDCl₃) 2.40 (1H, br s, OH), 3.75 (6H, s, 2 × OCH₃), 4.57 (2H, s, CH₂OH), 6.35 (1H, t, J = 2.4 Hz, 4-CH), 6.48 (2H, d, J = 2.4 Hz, 2-CH, 6-CH).

Spectroscopic data were in accordance with literature values.¹⁶⁴
3,5-Dimethoxybenzyl bromide (127)

To a stirred solution of alcohol 126 (5 g, 29.7 mmol) in DCM (50 mL), under an atmosphere of nitrogen at 0 °C, was added, dropwise, phosphorous tribromide (3.11 mL, 32.7 mmol) and the resulting mixture stirred at room temperature for 1 h. The mixture was poured onto ice, allowed to come to room temperature and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with 1 M aqueous NaOH (20 mL), brine (20 mL), dried (MgSO₄) and solvent removed in vacuo to yield the title compound (6.25 g, 92%) as a gray solid which was used without further purification.

δ_H (300 MHz, CDCl₃) 3.77 (6H, s, 2 × OCH₃), 4.49 (2H, s, CH₂Cl), 6.39 (1H, t, J = 2.1 Hz, 4-CH), 6.51 (2H, d, J = 2.1 Hz, 2-CH, 6-CH).

M.P. 69 – 72 °C [lit. 165 69 – 70 °C].

Spectroscopic data were in accordance with literature values. 166
To a stirred solution of bromide 127 (15.0 g, 64.9 mmol) in DMF (200 mL) was added sodium cyanide (4.80 g, 97.4 mmol) and the resulting mixture stirred at room temperature for 1.5 h. Water (200 mL) was added and the resulting solution extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried (MgSO₄) and solvent removed in vacuo to yield nitrile 128 (10.5 g, 91 %) as a white crystalline solid that was used without further purification.

Cyanide 128 (10 g, 56.4 mmol) was taken up in EtOH / water (1:1, 45 mL), NaOH (0.22 g) was added and the mixture stirred at reflux for 5 h. Approximately 30% of the solvent was removed in vacuo and the residue poured onto ice / 2 M aqueous HCl (20 mL), the resultant precipitate was collected by vacuum filtration and recrystallized from aqueous ethanol to give the title compound (11.1 g, quant.) as a white crystalline solid.

δ_H (300 MHz, CDCl₃) 3.57 (2H, s, CH₂CO₂H), 3.77 (6H, s, 2 × OCH₃), 6.39 (1H, t, J = 2.2 Hz, 4-CH), 6.44 (2H, d, J = 2.2 Hz, 2-CH, 6-CH).

M.P. 95 – 96 °C [lit.¹¹³ 98 – 102 °C].

Spectroscopic data were in accordance with literature values.¹¹³
Experimental

\((E)-\text{Ethyl 3-(3,5-dimethoxyphenyl)acrylate (120)}\)

A solution of triethylphosphonoacetate (9.5 mL, 19.86 mmol) and potassium carbonate (5 g, 32.12 mmol) in THF (30 mL), under an atmosphere of nitrogen, was stirred for 0.5 h then a solution of 3,5-dimethoxybenzaldehyde 121 (3 g, 18.06 mmol) in THF (30 mL) was added. The mixture was stirred at reflux for 20 h, filtered through a plug of Celite that was subsequently washed with EtOAc (20 mL). Solvent was removed in vacuo, the residue was taken up in EtOAc (60 mL), washed with water (30 mL), brine (30 mL), dried (MgSO\(_4\)) and solvent removed in vacuo. Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (4.26 g, quant.) as a white solid.

\(\delta_H\) (400 MHz, CDCl\(_3\)) 1.34 (3H, t, \(J = 5.4\) Hz, OCH\(_2\)CH\(_3\)), 3.82 (6H, s, 2 × OCH\(_3\)), 4.27 (2H, q, \(J = 5.4\) Hz, OCH\(_2\)CH\(_3\)), 6.41 (1H, d, \(J = 15.9\) Hz, ArCHCHCO\(_2\)Et), 6.50 (1H, t, \(J = 2.3\) Hz, 4-CH), 6.67 (2H, d, \(J = 2.3\) Hz, 2-CH, 6-CH), 7.61 (1H, d, \(J = 15.9\) Hz, ArCHCHCO\(_2\)Et).

M.P. 43 – 45 °C [lit.\(^{167}\) 45 – 46 °C].

Spectroscopic data were in accordance with literature values.\(^{167}\)
Experimental

\((E)-3-(3,5-Dimethoxyphenyl)prop-2-en-1-ol\) (122)

To a solution of ester 120 (1.0 g, 4.22 mmol) in DCM (20 mL), under an atmosphere of nitrogen at -78 °C, was added a 1 M solution of DIBAL-H in \(n\)-hexanes (12.66 mL, 12.66 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was quenched by addition of saturated aqueous Rochelle’s salt and stirred at room temperature for 3 h. The resulting solution was diluted with EtOAc (20 mL), filtered through Celite and acidified by addition of 2 M aqueous HCl (20 mL). The organic fraction was separated, dried (MgSO\(_4\)) and solvent removed \textit{in vacuo} to give the crude product. Flash column chromatography (1:1 EtOAc, \(n\)-hexanes) gave the \textit{title compound} (0.78 g, 95%) as a pale yellow oil.

\(\delta\)\(_H\) (300 MHz, CDCl\(_3\)) 3.80 (6H, s, 2 × OCH\(_3\)), 4.32 (2H, d, \(J = 5.4\) Hz CH\(_2\)OH), 6.30 – 6.60 (5H, m, ArCHCHCH\(_2\)OH, 2-CH, 4-CH, 6-CH).

Spectroscopic data were in accordance with literature values.\(^{168}\)
(E)-4-(3-(3,5-Dimethoxyphenyl)allyl)morpholine (30e)

The first step was carried out according to general procedure A using allylic alcohol 122 (0.90 g, 4.63 mmol) and phosphorous tribromide (0.48 mL, 5.10 mmol) in DCM (30 mL) to furnish bromide 123 as a green oil.

To a stirred solution of bromide 123 (1.66 g, 6.46 mmol) in DCM (30 mL), under an atmosphere of nitrogen at 0 °C, was added morpholine (0.44 mL, 5.09 mmol) dropwise and stirred for 0.5 h. Triethylamine (0.77 mL, 5.56 mmol) was added, the reaction was brought to room temperature and stirred overnight. Water was added, the organic layers separated and the aqueous fraction extracted with DCM (3 × 10 mL). The combined organic extracts were washed with 1 M aqueous NaOH (10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed in vacuo. Column chromatography (Al₂O₃, 2:1 EtOAc, n-hexanes) gave the title compound (0.60 g, 49.2 %) as a golden oil.

δ_H (300 MHz, CDCl₃) 2.51 (4H, t, J = 4.6 Hz, N(CH₂CH₂O), 3.15 (2H, dd, J = 1.1, 6.6 Hz, NCH₂CHCHAr), 3.54 – 3.86 (10H, m, 2 × N(CH₂CH₂O), 2 × Ar-OCH₃), 6.15 – 6.56 (5H, m, NCH₂CHCHAr, NCH₂CHCHAr, 3 × Ar-H).

δ_C (100 MHz, CDCl₃) 53.6 (N(CH₂CH₂)₂O), 55.3 (2 × OCH₃), 61.3 (NCH₂CHCHAr), 66.9 (N(CH₂CH₂)₂O), 100.0 (NCH₂CHCHAr), 104.2 (NCH₂CHCHAr), 126.4 (Ar-CH), 133.3 (Ar-CH), 138.7 (Ar-CCH), 160.8 (Ar-COCH₃).

ν_max/cm⁻¹: 2956 (C-H, alkene), 2839 (C-H, alkyl), 1590 (C-C, aromatic), 1203 (C-O, aromatic ether), 1150 (C-O, aliphatic ether) 867 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 264.1597 C₂₅H₃₂NO₆ requires 264.1594.
Experimental

(2R*,3S*)-3-(3,5-Dimethoxyphenyl)-1-morpholino-2-phenylpent-4-en-1-one (32h)

The reaction was carried out according to general procedure B with AlCl₃ (0.051 g, 0.38 mmol), amine 30e (0.1 g, 0.38 mmol), iPr₂NEt (0.099 mL, 0.57 mmol) and propionyl chloride 31a (0.04 mL, 0.46 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.054 g, 45%) as a yellow oil.

δ_H (400 MHz, CDCl₃) 0.95 (3H, d, J = 6.8 Hz, 2-CH₃), 2.98 – 3.08 (1H, m, 2-CH), 3.45 – 3.85 (15H, N(CH₂CH₂)₂O, 3-CH, 2 × OCH₃), 4.99 – 5.02 (1H, m, 5-CH₃), 5.03 – 5.05 (1H, m, 5-CH₆), 5.96 (1H, ddd, J = 7.9, 10.0, 17.6 Hz 4-CH), 6.32 – 6.37 (3H, m, Ar-H).

δ_C (100 MHz, CDCl₃) 16.6 (2-CH₃), 39.7 (C-2), 42.2, 46.2 (N(CH₂CH₂)₂O), 53.6 (C-3), 55.3 (2 × OCH₃), 66.7, 67.1 (N(CH₂CH₂)₂O), 98.1 (Ar-CH), 106.6 (2 × Ar-CH), 115.7 (C-5), 139.4 (C-4), 144.2 (2 × Ar-C), 160.9 (Ar-C), 174.1 (C-1).

ν_max/cm⁻¹ 2963 (C-H, alkene), 2850 (C-H, alkyl), 1634 (C=O), 1234 (C-O, aromatic ether), 1151 (C-N), 1113 (C-O, aliphatic ether).

m/z High Resolution (ESI⁺) found (MH⁺): 320.1855 C₁₈H₂₆NO₄ requires 320.1856.
(2S*,3S*)-3-(3,5-Dimethoxyphenyl)-1-morpholino-2-phenylpent-4-en-1-one (32i)

The reaction was carried out according to general procedure B with AlCl₃ (0.03 g, 0.19 mmol), amine 30e (0.05 g, 0.19 mmol), ⁴Pr₂NEt (0.051 mL, 0.29 mmol) and phenylacetyl chloride 31b (0.03 mL, 0.23 mmol). Flash column chromatography (2:1 EtOAc, n-hexanes) gave the title compound (0.029 g, 40%) as a brown oil.

δₜ (400 MHz, CDCl₃) 3.09 – 3.20 (1H, m, N(CH₂CH₂)O), 3.48 – 3.82 (7H, m, N(CH₂CH₂)₂O), 3.62 (6H, s, 2 × OCH₃), 4.00 (1H, d, J = 10.5 Hz, 2-CH), 4.10 – 4.18 (1H, m, 3-CH), 5.10 – 5.17 (2H, m, 5-CH₂), 6.07 – 6.17 (4H, m, 4-CH, 3 × Ar-H), 6.99 – 7.16 (5H, m, Ar-H).

δₜ (100 MHz, CDCl₃) 40.9, 42.5 (N(CH₂CH₂)₂O), 53.0 (C-2), 53.1 (C-3), 55.2 (2 × OCH₃), 66.4, 66.8 (N(CH₂CH₂)₂O), 98.2 (Ar-CH), 107.9 (Ar-CH), 115.5 (C-5), 126.9 (Ar-CH) 128.4 (Ar-CH), 128.5 (Ar-CH), 137.2 (2-(Ar-C)), 139.6 (C-4), 143.3 (3-(Ar-C)), 160.3 (2 × Ar-C(OCH₃)), 170.6 (C-1).

ν/ cm⁻¹: 3063 (C-H, aromatic), 2962 (C-H, alkene), 2852 (C-H, alkyl), 1634 (C=O, amide), 1202 (C-H, aromatic ether), 1151 (C-H, aliphatic ether), 697 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MNa⁺): 404.1846 C₂₃H₂₇NaNO₄ requires 404.1832.
(2S*,3S*)-2,3-Bis (3,5-dimethoxyphenyl)-1-morpholinopent-4-en-1-one (32g)

To a stirred solution of acid 124 (0.59 g, 3.03 mmol) in toluene (10 mL), under an atmosphere of nitrogen, was added oxalyl chloride 130 (0.59 mL, 6.96 mmol) dropwise and the resulting mixture stirred overnight at room temperature. The solvent was removed in vacuo and the residue taken up in DCM (10 mL), solvent was again removed in vacuo and the resulting acid chloride 311 was placed under an atmosphere of nitrogen and used immediately without purification.

The reaction was carried out according to general procedure B with AlCl₃ (0.30 g, 2.32 mmol), amine 30e (0.62 g, 2.32 mmol), iPr₂NEt (0.44 mL, 3.48 mmol) and acyl chloride 311 (0.65 mL, 2.40 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.68 g, 67%) as a golden oil.

δ_H (400 MHz, CDCl₃) 3.19 – 3.63 (7H, m, N(CH₂CH₂)₂O) 3.64 (12H, s, 4 × OCH₃), 3.68 – 3.76 (1H, N(CH₂CH₂)₂O), 3.93 (1H, d, J = 10.5 Hz, 2-CH), 4.08 – 4.11 (1H, m, 3-CH), 5.08 – 5.16 (2H, m, 5-CH₂), 6.10 (1H, ddd, J = 6.8, 10.7, 17.3 Hz, 4-CH), 6.15 (2H, d, J = 2.2 Hz, 2 × Ar-H), 6.18, 6.19 (2 × 1H, t, J = 2.2 Hz, C-4′, C-4″), 6.24 (2H, d, J = 2.1 Hz, 2 × Ar-H).

δ_C (100 MHz, CDCl₃) 42.5, 46.2 (2 × NCH₂CH₂)₂O), 52.9 (C-2), 53.2 (C-3), 55.2, 55.3 (2 × OCH₃), 66.5, 66.8 (2 × N(CH₂CH₂)₂O) 98.3, 99.3 (C-4′, C-4″), 106.7, 107.0 (C-2′, C-2″, C-6′, C-6″), 115.5 (C-5), 139.4, 140.1 (C-3′, C-3″, C-5′, C-5″), 139.6 (C-4), 160.3 (C-1′, C-1″), 170.2 (C-1).

ν_max/cm⁻¹ 2960 (C-H, alkene), 2838 (C-H alkyl), 1637 (C=O amide), 1456 (C-C aromatic), 1150 (C-O, ether), 726 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 422.2223 C₂₅H₃₂NO₆ requires 422.2224.
Experimental

(2S*,3S*)-2,3-Bis(3,5-dimethoxyphenyl)-4,5-dihydroxy-1-morpholinopentan-1-one (200)

To a stirred solution of amide 32g (0.2 g, 0.62 mmol) in a water / tBuOH (1:1, 8 mL) was added N-methylmorpholine-N-oxide (0.16 g, 1.35 mmol) and an 0.1 M solution of osmium tetroxide in tBuOH (0.06 mL, 0.0045 mmol) at 0 °C. The reaction mixture was brought to room temperature, stirred for 24 h, quenched by addition of saturated aqueous Na₂SO₃ (10 mL) and stirred for a further 1 h. The aqueous mixture was extracted with EtOAc (3 × 30 mL), combined organic fractions washed with 1 M aqueous KOH (30 mL), dried (MgSO₄) and solvent removed in vacuo. Gradient elution flash column chromatography (1:1 EtOAc, n-hexanes, 100% EtOAc) gave the title compound (0.21 g, quant.) as a white solid.

δ_H (400 MHz, CDCl₃) 3.32 (2H, dd, J = 7.3, 11.3 Hz, 5'-CH₂), 3.48 – 3.66 (9H, m, 3-CH, N(CH₂CH₂)₂O), 3.67 (6H, s, 2 × OCH₃), 3.69 (6H, s, 2 × OCH₃), 4.04 – 4.10 (1H, m, 4'-CH, 4"-CH), 4.37 (1H, d, J = 10.5 Hz, 2'-CH), 6.20 (2H, dt, J = 2.3, 13.9 Hz, 4'-CH, 4"-CH), 6.33 (4H, dd, J = 2.3, 9.9 Hz, 2'-CH, 2"-CH, 6'-CH, 6"-CH).

δ_C (100 MHz, CDCl₃) 42.7, 46.6 (N(CH₂CH₂)₂O), 49.7 (C-2), 51.9 (C-3), 55.2 (OCH₃), 55.3 (OCH₃), 65.8 (C-5), 66.5, 66.8 (N(CH₂CH₂)₂O), 72.2 (C-4), 98.5, 99.0 (C-4', C-4"), 107.0, 108.1 (C-2', C-2", C-6', C-6"), 139.5, 140.4 (C-3', C-3", C-5', C-5"), 160.3, 160.5 (C-1', C-1") 171.1 (C-1).

ν_max/cm⁻¹ 3432 (O-H), 2926 (C-H, alkyl), 1594 (C=O), 1260 (C-O, aromatic ether), 1062 (C-O), 1020 (C-O), 800 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 476.2283 C₂₅H₃₄NO₈ requires 476.2279.

M.P. 138 - 140 °C.
Experimental

(2S*,3S*)-2,3-Bis(3,5-dimethoxyphenyl)-4-morpholino-4-oxobutanal (153b)

To a stirred solution of diol 200 (0.21 g, 0.42 mmol) in a 3:1 mixture of MeOH and water (20 mL) at 0 °C was added sodium periodate (0.11 g, 0.53 mmol) and the mixture was stirred for 5h. Brine (5 mL) was added, the solution was extracted with EtOAc (4 × 10 mL), dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.11 g, 56%) as a white solid.

δH (400 MHz, CDCl₃) 3.11 – 3.23 (1H, m, N(CH₂CH₂)₂O), 3.31 – 3.39 (1H, m, N(CH₂CH₂)₂O), 3.49 – 3.63 (4H, m, N(CH₂CH₂)₂O), 3.64 (6H, s, 2 × OCH₃), 3.66 (6H, s, 2 × OCH₃), 3.68 – 3.73 (2H, m, N(CH₂CH₂)₂O), 4.20 (1H, d, J = 10.7 Hz, 2-CH), 4.46 (1H, d, J = 10.6 Hz, 3-CH), 6.07 (2H, d, J = 2.3 Hz, Ar-H), 6.11 (2H, d, J = 2.3 Hz, Ar-H), 6.23 (1H, t, J = 2.3 Hz, Ar-H), 6.28 (1H, t, J = 2.3 Hz, Ar-H), 9.80 (1H, s, 4-CH).

δC (100 MHz, CDCl₃) 42.7, 46.2 (N(CH₂CH₂)₂O), 50.8 (C-2), 55.3 (4 × OCH₃), 62.6 (C-3), 66.3, 66.7 (N(CH₂CH₂)₂O), 99.2, 99.8 (C-4', C-4''), 106.3, 108.0 (C-2', C-2'', C-6', C-6''), 134.7, 138.6 (C-3', C-3'', C-5', C-5''), 160.8, 160.9 (C-1', C-1''), 170.4 (C-1), 198.9 (C-4).

νmax/cm⁻¹ 3020 (C=H, aromatic), 2820 (C=H, aldehyde), 1710 (C=O, aldehyde), 1643 (C=O, amide), 1589 (C=C), 1237 (C=O, aromatic, ether), 1117 (C=O, aliphatic ether), 819 (C=H, aromatic), 692 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 444.2022 C₂₄H₃₀NO₇ requires 444.2017.

M.P. 137 - 142 °C.
Experimental

(2S*,3S*)-3-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-1-morpholinopent-4-en-1-one (32j)

To a stirred solution of acid 119 (0.1 g, 0.6 mmol) in toluene (5 mL), under an atmosphere of nitrogen, was added thionyl chloride (0.087 mL, 1.8 mmol) dropwise and the mixture stirred at reflux for 4 h. Solvent was removed in vacuo and the residue taken up in n-hexanes (10 mL), solvent was again removed in vacuo and the resulting acid chloride 31k was placed under an atmosphere of nitrogen and used immediately, without purification.

The reaction was carried out according to general procedure B with TiCl4·2THF (0.15 g, 0.45 mmol), amine 30e (0.12 g, 0.45 mmol), iPr2NEt (0.12 mL, 0.68 mmol) and acyl chloride 31k (0.1 mL, 0.54 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.16 g, 83%) as a yellow oil.

$\delta^1H$ (400 MHz, CDCl3) 3.13 – 3.22 (1H, m, N(CH2CH2)2O), 3.39 – 3.74 (7H, m, N(CH2CH2)2O), 3.64 (6H, s, 3'-C(OCH3), 5'-C(OCH3)), 3.71 (3H, s, 4''-C(OCH3)), 3.97 (1H, d, J = 10.6 Hz, 2-CH), 4.08 – 4.11 (1H, m, 3-CH), 5.08 – 5.14 (2H, m, 5-CH2), 6.05 – 6.18 (4H, m, 4-CH, 2'-CH, 4'-CH, 6'-CH), 6.70 (2H, d, J = 8.8 Hz, 2''-CH, 6''-CH), 7.00 (2H, d, J = 8.8 Hz, 3''-CH, 5''-CH).

$\delta^1C$ (100 MHz, CDCl3) 42.5, 46.2 (N(CH2CH2)2O), 52.2 (C-2), 53.1 (C-3), 55.1 (4''-C(OCH3)), 55.2 (3'-C(OCH3), 5'-C(OCH3)), 66.5, 66.8 (N(CH2CH2)2O), 98.1 (C-4'), 107.1 (C-2', C-6''), 113.8 (C-2''', C-6''''), 115.5 (C-5), 129.3 (C-1'''), 129.5 (C-3'', C-5''), 139.8 (C-4), 143.5 (C-1'''), 158.5 (C-4'''), 160.9 (C-3', C-5''), 170.9 (C-1).

$\nu_{\text{max}}$/cm$^{-1}$ 2932 (C-H, alkene), 2850 (C-H, alkyl), 1734 (C=O), 1594 (C-C, aromatic), 1203 (C-O, aromatic ether), 1113 (C-O, aliphatic ether), 834 (C-H, aromatic).

$m/z$ High Resolution (ESI+) found (MH+): 412.2119 C24H36NO5 requires 412.2118.
(\textit{E})-Ethyl 3-(2,4,5-trimethoxyphenyl)acrylate (133)

To a solution of triethylphosphonoacetate (4.4 g, 19.6 mmol) in THF (40 mL), under an atmosphere of nitrogen, was added K$_2$CO$_3$ (5.42 g, 39.3 mmol) and the resulting mixture stirred for 0.5 h. A solution of aldehyde 132 (3.5 g, 17.8 mmol) in THF (40 mL) was added and the mixture was stirred at reflux for 24 h, cooled to room temperature and filtered through a plug of Celite that was subsequently washed with EtOAc (20 mL). Solvent was removed \textit{in vacuo} and the residue taken up in EtOAc (50 mL), washed with water (20 mL), brine (20 mL), dried (MgSO$_4$) and solvent again removed \textit{in vacuo}. Flash column chromatography (1:1 EtOAc, \textit{n}-hexanes) gave the \textit{title compound} (4.75 g, quant.) as a white solid.

\[\delta_H (400 \text{ MHz, CDCl}_3)\]
1.34 (3H, t, \(J = 7.1\) Hz, OCH$_2$CH$_3$), 3.86 (3H, s, OCH$_3$), 3.88 (3H, s, OCH$_3$), 3.93 (3H, s, OCH$_3$), 4.26 (2H, q, 7.2 Hz, OCH$_2$CH$_3$), 6.37 (1H, d, \(J = 16.3\) Hz, ArCHCHC(O)OEt), 6.50 (1H, 3-CH), 7.02 (1H, 6-CH), 7.97 (1H, d, \(J = 15.8\) Hz, ArCHCHC(O)OEt).

\[\delta_C (100 \text{ MHz, CDCl}_3)\]
14.4 (OCH$_2$CH$_3$), 56.0 (OCH$_3$), 56.36 (OCH$_3$), 56.4 (OCH$_3$), 60.2 (OCH$_2$CH$_3$), 96.9 (C-3), 110.0 (C-6), 115.0 (C-1), 115.9 (ArCHCHC(O)OEt), 139.4 (ArCHCHC(O)OEt), 143.2, 152.0, 153.8 (C-2, C-4, C-5), 167.7 (C=O).

\(\nu_{\text{max}}/\text{cm}^{-1}\)
2997 (C-H, alkene), 2844 (C-H, alkyl), 1712 (C=O), 1514 (C-C, aromatic), 1207 (C-O, aromatic ether), 1159 (C-O, aliphatic ether), 845 (C-H, aromatic).

\(m/z\) High Resolution (ESI$^+$) found (MH$^+$): 267.1220 C$_{14}$H$_{19}$O$_5$ requires 267.1227.

M.P. 53 – 60 °C.
Experimental

$\text{(E)-3-(2,4,5-Trimethoxyphenyl)prop-2-en-1-ol (134)}$

To a solution of ester 133 (0.95 g, 3.57 mmol) in DCM (20 mL), under an atmosphere of nitrogen at 0 °C, was added a 1 M solution of DIBAL-H in $n$-hexanes (10.7 mL, 10.7 mmol) dropwise and the resulting mixture stirred for 1 h, then quenched by the dropwise addition of 2 M aqueous HCl, until evolution of gas ceased. The mixture was extracted with DCM (3 × 10 mL), dried (MgSO$_4$) and solvent removed in vacuo. Flash column chromatography (1:1 EtOAc $n$-hexanes) gave the title compound (0.67 g, 77%) as a yellow oil.

$\delta_H$ (400 MHz, CDCl$_3$) 1.40 (1H, t, $J = 6.0$ Hz, OH), 3.83 (3H, OCH$_3$), 3.86 (3H, OCH$_3$), 3.90 (3H, OCH$_3$), 4.31 (2H, td, $J = 1.4$, 6.0 Hz, CH$_2$OH), 6.26 (1H, dt, $J = 6.2$, 16.0 Hz, ArCHCHCH$_2$OH), 6.50 (1H, s, 3-CH), 6.87 (1H, dt, $J = 1.4$, 16.0 Hz, ArCH/CHCH$_2$OH), 6.98 (1H, s, 6-CH).

$\delta_C$ (100 MHz, CDCl$_3$) 56.1 (OCH$_3$), 56.5 (OCH$_3$), 56.6 (OCH$_3$), 64.6 (CH$_2$OH), 97.6 (C-3), 109.9 (C-6), 120.6 (C-1), 126.0 (ArCHCHCH$_2$OH), 126.9 (ArCHCHCH$_2$OH), 142.8, 149.2, 151.7 (C-2, C-4, C-5).

$\nu_{\text{max}}$/cm$^{-1}$ 3251 (O-H), 2937 (C-H, alkene), 2831 (C-H, alkyl), 1516 (C-C, aromatic) 1203 (C-O, aromatic ether), 1024 (C-O, alcohol), 855 (C-H aromatic).

$\text{m/z}$ High Resolution (ESI$^+$) found (MNa$^+$): 247.0929 C$_{12}$H$_{16}$NaO$_4$ requires 247.0941.
Experimental

\[(E)-3-(2,4,5-\text{Trimethoxyphenyl})\text{acrylaldehyde (136)}\]

To a slurry of MnO\textsubscript{2} (1.94 g, 22.3 mmol) in EtOAc (30 mL) was added a solution of alcohol 134 (0.5 g, 2.23 mmol) in EtOAc (10 mL). The mixture was stirred for 3 h at room temperature, filtered through a plug of celite and solvent removed in vacuo to give the title compound (0.44 g, 89%) as a white solid that was used without further purification.

\[\delta_H (400 \text{ MHz, } \text{CDCl}_3) \quad 3.88 \text{ (3H, s, OCH}_3), \quad 3.91 \text{ (3H, s, OCH}_3), \quad 3.94 \text{ (3H, s, OCH}_3), \quad 6.52 \text{ (1H, 3-CH), 6.65 (1H, dd, } J = 7.9, 15.9 \text{ Hz, ArCHCHCHO), 7.04 (1H, s, 6-CH), 7.81 (1H, d, } J = 15.9 \text{ Hz, ArCHCHCHO), 9.65 \text{ (1H, d, } J = 7.9 \text{ Hz, ArCHCHCHO).}\]

\[\delta_C (100 \text{ MHz, } \text{CDCl}_3) \quad 56.1 \text{ (OCH}_3), \quad 56.3 \text{ (OCH}_3), \quad 56.5 \text{ (OCH}_3), \quad 97.0 \text{ (C-3), 110.8 \text{ (C-6), 116.0 \text{ (C-1), 126.6 \text{ (ArCHCHCHO), 140.6, 144.0, 145.5 \text{ (C-2, C-4, C-5), 147.4 \text{ (ArCHCHCHO), 204.8 \text{ (ArCHCHCHO).}}}}\]

\[\nu_{\text{max}}/\text{cm}^{-1} \quad 3048 \text{ (C-H, aromatic), 2844 \text{ (C-H, aldehyde), 1655 \text{ (C=O), 1208 \text{ (C-O), 978 \text{ (C-H, alkene).}}}}\]

\[m/z \text{ High Resolution (ESI}^+\text{) found (MNa}^+) : 245.0788 \text{ C}_{12}\text{H}_{14}\text{NaO}_4 \text{ requires 245.0784.}\]

M.P. 135 - 137 °C [lit.\textsuperscript{169} 139 – 140 °C].

Spectroscopic data were in accordance with literature values.\textsuperscript{169}
Experimental

**(E)-4-(3-(2,4,5-Trimethoxyphenyl)allyl)morpholine (30f)**

To a solution of aldehyde 136 (0.2 g, 1.0 mmol), morpholine (0.086 mL, 0.99 mmol) and AcOH (6 drops) in MeCN (8 mL), under an atmosphere of nitrogen, was added NaBH3CN (0.062 g, 0.99 mmol) and the resulting mixture stirred for 18 h. Solvent was removed *in vacuo*, the residue taken up in 1 M aqueous KOH (10 mL), extracted with EtOAc (3 × 10 mL), the combined organic fractions dried (Na2SO4) and solvent removed *in vacuo*. Flash column chromatography (49:1 DCM, MeOH) gave the *title compound* (0.29 g, quant.) as a yellow solid.

δH (400 MHz, CDCl3) 2.52 (4H, br s, N(CH2CH2)2O), 3.17 (2H, dd, J = 1.2, 6.9 Hz, NCH2CHCHAr), 3.75 (4H, t, J = 4.6 Hz, N(CH2CH2)2O)), 3.83 (3H, s, OCH3), 3.85 (3H, s, OCH3), 3.89 (3H, s, OCH3), 6.13 (1H, dt, J = 6.9, 15.9 Hz, NCH2CHCHAr), 6.50 (1H, s, 3-CH), 6.80 (1H, dt, J = 1.2, 15.9 Hz, NCH2CHCHAr), 7.00 (1H, s, 6-CH).

δC (100 MHz, CDCl3) 53.7 (N(CH2CH2)2O), 56.1 (OCH3), 56.4 (OCH3), 56.7 (OCH3), 62.0 (NCH2CHCHAr), 67.0 (N(CH2CH2)2O), 97.8 (C-3), 109.7 (C-6), 117.6 (C-1), 124.2 (NCH2CHCHAr), 127.5 (NCH2CHCHAr), 143.4, 149.5, 151.2 (C-2, C-4, C-5).

νmax/cm⁻¹ 2958 (C-H, alkene), 2860 (C-H, alkyl), 1518 (C-C, aromatic), 1201 (C-O, aromatic ether), 1113 (C-O, aliphatic ether), 855 (C-H, aromatic).

*m/z* High Resolution (ESI⁺) found (MH⁺): 294.1699 C16H24NO4 requires 294.1700.

M.P. 90 - 94 °C.
(2S*,3S*)-1-Morpholino-2-phenyl-3-(2,4,5-trimethoxyphenyl)pent-4-en-1-one (32l) and (2S*,3R*)-1-morpholino-2-phenyl-3-(2,4,5-trimethoxyphenyl)pent-4-en-1-one (113b)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.11 g, 0.34 mmol), amine 30f (0.1 g, 0.34 mmol), iPr₂NEt (0.089 mL, 0.59 mmol) and phenylacetyl chloride (0.063 mL, 0.41 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compounds ((2S*,3S*): 0.051 g, 36%) as a white solid with melting point 137 – 140 °C; ((2S*,3R*): 0.023 g, 16%) as a yellow oil.

(2S*,3S*): δH (400 MHz, CDCl₃) 3.11 – 3.22 (1H, m, N(CH₂CH₂)₂O), 3.41 – 3.63 (7H, N(CH₂CH₂)₂O), 3.64 (3H, s, OCH₃), 3.72 (3H, s, OCH₃), 4.28 (1H, d, J = 10.5 Hz, 2-CH), 4.49 (1H, dd, J = 6.9, 10.5 Hz, 3-CH), 5.04 – 5.12 (2H, m, 5-CH₂), 6.18 (1H, ddd, J = 6.9, 10.0, 17.4 Hz, 4-CH), 6.29 (1H, s, 6'-CH), 6.51 (1H, s, 3'-CH), 6.99 – 7.18 (5H, m, Ar-H).

δC (100 MHz, CDCl₃) 42.5, 46.2 (N(CH₂CH₂)₂O), 48.1 (C-3), 51.4 (C-2), 56.0 (OCH₃), 56.2 (OCH₃), 56.7 (OCH₃), 66.5, 66.9 (N(CH₂CH₂)₂O), 97.7 (C-6'), 114.4 (C-3'), 115.2 (C-5), 121.0 (C-1'), 126.7 (Ar-CH), 128.0 (Ar-CH), 128.5 (Ar-CH), 137.7 (2-C(Ar-C)), 139.7 (C-4), 142.7 (Ar-C), 148.0 (Ar-C), 151.5 (Ar-C), 171.0 (C-1).

(2S*,3R*): δH (400 MHz, CDCl₃) 3.20 – 3.44 (8H, m, N(CH₂CH₂)₂O), 3.84 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 4.26 – 4.34 (1H, m, 3-CH), 4.49 (1H, d, J = 10.6 Hz, 2-CH), 4.73 (1H, dt, J = 1.0, 17.0 Hz, 5-CH₃), 4.78 (1H, dt, J = 1.0, 10.5 Hz, 5-CH₃b), 5.85 (1H, ddd, J = 8.0, 10.5, 17.0 Hz, 4-CH), 6.54 (1H, s, 6'-CH), 6.74 (1H, s, 3'-CH), 7.21 – 7.42 (5H, m, Ar-H).

δC (100 MHz, CDCl₃) 46.2, 46.5 (N(CH₂CH₂)₂O), 50.0 (C-3), 50.8 (C-2), 56.2 (OCH₃), 56.6 (OCH₃), 56.8 (OCH₃), 66.5, 66.8 (N(CH₂CH₂)₂O), 98.5 (C-6'), 114.3 (C-3'), 115.9 (C-5), 148.0 (Ar-C), 151.5 (Ar-C), 171.0 (C-1).
122.5 (C-1’), 128.5 (Ar-CH), 128.8 (Ar-CH), 129.1 (Ar-CH), 138.1 (C-4), 138.2 (2-CH(Ar-C)), 143.0 (Ar-C), 148.3 (Ar-C), 151.4 (Ar-C), 170.8 (C-1).

$\nu_{\text{max}}$/cm$^{-1}$ 2994 (C-H, alkene), 2845 (C-H, alkyl), 1618 (C=O), 1206 (C-O, aromatic ether), 111.5 (C-O, aliphatic ether), 738 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 412.2115 C$_{24}$H$_{30}$NO$_5$ requires 412.2118.
1-(2,4,5-Trimethoxyphenyl)ethanone (144)

To a solution of 2,4,5-trimethoxybenzene 143 (0.5 g, 2.97 mmol) and acetyl chloride 31c (0.23 mL, 3.30 mmol) in DCM (10 mL), under an atmosphere of nitrogen at 5 °C, was added AlCl₃, portionwise, and the resulting mixture stirred at 10 °C for 1 h. 0.5 M Aqueous HCl (13 mL) was added, the organic layer was separated, washed with H₂O (10 mL), dried (Na₂SO₄) and solvent removed under reduced pressure Recrystallization from MeOH gave the title compound (0.62 g, quant.) as a pale pink solid.

δ_H (400 MHz, CDCl₃) 2.60 (3H, s, CH₃), 3.88 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 3.95 (3H, s, OCH₃), 6.51 (CH, s, Ar-H), 7.43 (CH, s, Ar-H).

M.P. 90 - 93 °C [lit.¹⁷⁰ 94 – 95 °C].

Spectroscopic data were in accordance with literature values.¹⁷¹
Experimental

2-(2,4,5-Trimethoxyphenyl)acetic acid (142)

Acetophenone 144 (5.0 g, 23.8 mmol), sulfur (1.92 g, 59.9 mmol) and morpholine (4.14 g, 47.5 mmol) were heated at 160 °C with stirring for 3 h. The resulting mixture was transferred to a conical flask, rinsing with MeOH (6 mL), stood at room temperature for 16 h and the solid (thiomorpholide) collected by vacuum filtration.

The isolated thiomorpholide was dissolved in 15% w/v KOH in EtOH (150 mL), heated at reflux for 14 h, concentrated and the residue taken up in Et₂O / H₂O (1:1, 100 mL), acidified with conc. HCl and the organic fraction separated. The aqueous fraction was extracted with Et₂O (3 × 50 mL), the combined organic fractions dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (1.05 g, 20%) as a white solid.

δ_H (400 MHz, CDCl₃) 3.61 (2H, s, ArCH₂CO₂H), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 6.54 (CH, s, 6-CH), 6.75 (CH, s, 3-CH).

δ_C (100 MHz, CDCl₃) 35.2 (ArCH₂CO₂H), 56.2 (OCH₃), 56.5 (OCH₃), 56.6 (OCH₃), 97.9 (C-6), 113.5 (Ar-C), 114.9 (C-3), 143.2 (Ar-C), 151.8 (Ar-C), 177.3 (C=O).

ν_max/cm⁻¹ 3522 (O-H), 2940, 2838 (C-H, alkyl), 1714 (C=O), 1221 (C-O, aromatic ether).

m/z High Resolution (ESI⁺) found (MNa⁺): 249.0733 C₁₁H₁₄NaO₅ requires 249.0733.

M.P. 78 – 81 °C [lit.172 83 – 85 °C].

Spectroscopic data were in accordance with literature values.172
Experimental

(2S*,3S*)-3-Methyl-1-morpholino-2-(2,4,5-trimethoxyphenyl)pent-4-en-1-one (32m)

To a stirred solution of acid 142 (0.10 g, 0.44 mmol) in benzene (5 mL), under an atmosphere of nitrogen, was added thionyl chloride (0.1 mL, 1.38 mmol) dropwise and the resulting mixture stirred at reflux for 2 h. Solvent was removed in vacuo and the resulting acid chloride 31m was placed under an atmosphere of nitrogen and used immediately without purification.

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.11 g, 0.34 mmol), amine 30a (0.048 g, 0.34 mmol), iPr₂NEt (0.089 mL, 0.51 mmol) and acyl chloride 31m (0.1 mL, 0.41 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.097 g, 82%) as a yellow solid.

δᵣH (400 MHz, CDCl₃) 0.77 (3H, d, J = 7.0 Hz, 3-CH₃), 2.93 – 3.03 (1H, m, 3-CH), 3.12 – 3.20 (1H, m, N(CH₂CH₂)₂O), 3.41 – 3.74 (7H, m, N(CH₂CH₂)₂O), 3.82 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 4.06 (1H, d, J = 10.5 Hz, 2-CH), 5.01 (1H, dt, J = 1.1, 10.5 Hz, 5-CHₐ), 5.10 (1H, dt, J = 1.5, 17.3 Hz, 5-CHₖ), 5.91 (1H, ddd, J = 6.8, 10.5, 17.3 Hz, 4-CH), 6.50 (1H, s, 6'-CH), 6.98 (1H, s, 3'-CH).

δᵣC (100 MHz, CDCl₃) 16.8 (3-CH(CH₃)), 40.2 (C-3), 42.5 (N(CH₂CH₂)₂O), 44.4 (C-2), 45.9 (N(CH₂CH₂)₂O), 56.1 (OCH₃), 56.4 (OCH₃), 56.5 (OCH₃), 66.7, 66.9 (2 × N(CH₂CH₂)₂O), 96.9 (C-6'), 111.4 (C-3'), 113.8 (C-5), 117.9 (C-1'), 142.9 (C-4), 144.0 (Ar-C), 148.6 (Ar-C), 149.9 (Ar-C), 171.9 (C-1).

νₘ/cm⁻¹ 3080 (C-H, aromatic), 2965 (C-H, alkene), 2851 (C-H, alkyl) 1634 (C=O), 1513 (C-C, aromatic), 1203 (C-O, aromatic ether), 1110 (C-O, aliphatic ether), 870 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 350.1954 C₁₉H₂₈NO₅ requires 350.1962.

M.P. 90 – 93 °C.

[164]
(3S*,4S*)-4-Methyl-3-(2,4,5-trimethoxyphenyl)hex-5-en-2-one (105d)

To a 1.6 M solution of methyllithium in Et₂O (1.77 mL, 2.83 mmol) in THF (8 mL), under an atmosphere of nitrogen at -78 °C, a solution of amide 32m (0.9 g, 2.58 mmol) in THF (2 mL) was added dropwise and the mixture stirred at room temperature for 4 h. Saturated aqueous NH₄Cl (5 mL) was added, the mixture extracted with EtOAc (3 × 10 mL), the combined organic fractions were washed with brine (5 mL), dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (2:1 EtOAc, n-hexanes) gave the title compound (0.24 g, 50%) as a yellow oil.

δ_H (400 MHz, CDCl₃) 0.77 (3H, d, J = 7.1 Hz, 4-CH₃), 2.03 (3H, s, 1-CH₃), 2.83 – 2.97 (1H, m, 4-CH), 3.82 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 4.11 (2H, d, J = 10.3 Hz, 3-CH), 4.96 – 5.12 (2H, m, 6-CH₂), 5.91 (1H, ddd, J = 7.0, 10.5, 17.4 Hz, 5-CH), 6.54 (1H, s, 6'-CH), 6.71 (1H, s, 3'-CH).

δ_C (100 MHz, CDCl₃) 17.1 (4-CH(CH₃)), 30.4 (C-1), 38.6 (C-4), 55.5 (C-3), 56.1 (OCH₃), 56.5 (OCH₃), 56.6 (OCH₃), 97.5 (C-6’), 112.0 (C-3’), 114.1 (C-6), 116.5 (C-1’), 142.5 (C-5), 143.4, 148.6, 152.0 (C-2’, C-4’, C-5’), 208.2 (C-2).

ν_{max}/cm⁻¹ 3055 (C-H, alkene), 2960 (C-H, alkene), 2935 (C-H, alkyl), 1709 (C=O) 1508 (C=C, aromatic), 1203 (C-O, aromatic ether).

m/z High Resolution (ESI⁺) found (MNa⁺): 301.1411 C₁₆H₂₂NaO₄ requires 301.1410.
(2R*,3S*,4S*)-4-Methyl-3-(2,4,5-trimethoxyphenyl)hex-5-en-2-ol (163)

To ketone 105d (0.2 g, 0.72 mmol) in MeOH (6 mL), under an atmosphere of nitrogen at -78 °C, was added NaBH₄ (0.11 g, 2.88 mmol). The mixture was stirred at room temperature for 0.5 h, water (3 mL) was added and the volatile components removed in vacuo. The aqueous residue was extracted with EtOAc (3 × 5 mL), the combined organic extracts dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.185 g, 92%) as a pale yellow oil.

δ_H (400 MHz, CDCl₃) 0.79 (3H, d, J = 6.5 Hz, 4-CH₃), 0.95 (3H, d, J = 6.5 Hz, 1-CH₃), 2.68 – 2.72 (2H, m, 3-CH, 4-CH), 3.79 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 4.13 – 4.21 (1H, m, 2-CH), 5.06 (1H, dd, J = 1.9, 10.1 Hz, 6-CH₂), 5.19 (1H, dd, J = 1.9, 17.2 Hz, 6-CH₂), 5.83 (1H, ddd, 8.7, 10.1, 17.2 Hz, 5-CH), 6.53 (1H, m, 6'-CH), 6.86 (1H, br s, 3'-CH).

δ_C (100 MHz, CDCl₃) 19.5 (4-CH(CH₃)), 21.9 (C-1), 38.9, 41.2 (C-3, C-4), 56.0 (OCH₃), 56.6 (OCH₃), 56.7 (OCH₃), 68.0 (C-2), 97.9 (C-6'), 114.2 (C-3', C-6), 119.8 (C-1'), 143.2 (Ar-C), 144.1 (C-5), 147.8 (Ar-C), 152.4 (Ar-C).

ν_max/cm⁻¹ 3483 (O-H), 2965 (C-H, alkene), 2833 (C-H, alkyl), 1509 (C-C, aromatic), 1202 (C-O, aromatic ether), 1031 (C-O, alcohol).

m/z High Resolution (ESI⁺) found (MNa⁺): 303.1568 C₁₆H₂₄NaO₄ requires 303.1567.
Experimental

1,2,4-Trimethoxy-5-((2R*,3S*,4S*)-2-(methoxymethoxy)-4-methylhex-5-en-3-yl)benzene (106a)

To alcohol 163 (0.17 g, 0.62 mmol) in DCM (10 mL), under an atmosphere of nitrogen at 0 °C, was added iPr₂NEt (0.43 mL, 2.48 mmol) and chloromethyl methyl ether (0.12 mL, 1.55 mmol) and the resulting mixture stirred at room temperature for 24 h. Saturated aqueous NH₄Cl (5 mL) was added and the organic layer separated. The aqueous layer was further extracted with DCM (2 × 10 mL), the combined organic layers dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (3:1, n-hexanes, EtOAc) gave the title compound (0.16 g, 84%) as a yellow oil.

δ_H (400 MHz, CDCl₃) 0.74 (3H, d, J = 6.6 Hz, 4-CH₃), 0.96 (3H, d, J = 6.1 Hz, 1-CH₃), 2.63 – 2.74 (1H, m, 4-CH), 2.97 (1H, dd, J = 3.1, 10.7 Hz, 3-CH), 3.32 (3H, s, OCH₂OCH₃), 3.77 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.97 – 4.03 (1H, m, 2-CH), 4.62 (1H, d, J = 6.6 Hz, OCH₃OCH₃), 4.69 (1H, d, J = 6.6 Hz, OCH₃OCH₃), 5.03 (1H, dd, J = 2.0, 10.2 Hz, 6-CH₃), 5.09 (1H, dd, J = 2.0, 17.2 Hz, 6-CH₃), 5.82 (1H, ddd, 8.6, 10.2, 17.2 Hz 5-CH), 6.51 (1H, s, 6’-CH), 7.05 (1H, s, 3’-CH).

δ_C (100 MHz, CDCl₃) 19.2 (4-CH(CH₃), C-1), 40.1 (C-4), 47.0 (C-3), 55.4 (OCH₂OCH₃), 55.9 (OCH₃), 56.5 (OCH₃), 56.9 (OCH₃), 75.0 (C-2), 96.2 (OCH₂OCH₃), 97.4 (C-6’), 114.0 (C-3’, C-6), 120.7 (C-5’), 144.0 (C-5), 143.2, 147.6, 152.6 (C-1’, C-2’, C-4’).

ν_max/cm⁻¹ 2937 (C-H, alkene), 2836 (C-H, alkyl), 1510 (C-C, aromatic), 1203 (C-O, aromatic).

m/z High Resolution (ESI⁺) found (MNa⁺): 347.1832 C₁₈H₂₈NaO₅ requires 347.1829, found (MK⁺): 363.1564 C₁₈H₂₈KO₅ requires 363.1568.
(2*R*,3S*,4R*)-4-(Methoxymethoxy)-2-methyl-3-(2,4,5-trimethoxyphenyl)pentanal

(107a)

To alkene 106a (0.12 g, 0.37 mmol) in a 'BuOH / H₂O (1:1, 5 mL) at 0 °C was added N-methylmorpholine-N-oxide (0.13 g, 1.11 mmol), a 0.1 M solution of osmium tetraoxide in 'BuOH (0.038 mL, 0.0038 mmol). The resulting mixture stirred at room temperature for 18 h saturated aqueous Na₂SO₃ (6 mL) was added, the resulting mixture stirred for 0.5 h and extracted with EtOAc (3 × 5 mL). The combined organic fractions were washed with 1 M aqueous KOH (5 mL), dried (MgSO₄) and solvent removed in vacuo to give the intermediate diol 164 (0.13 g, 98%) that was used without further purification.

To diol 164 (0.12 g, 0.33 mmol) in a MeOH / H₂O (3:1, 12 mL), at 0 °C, was added sodium periodate (0.085 g, 0.4 mmol) and the resulting mixture stirred at room temperature for 18 h. Brine (12 mL) was added, the mixture extracted with EtOAc (3 × 10 mL), dried (MgSO₄) and solvent removed in vacuo to give the title compound (0.69 g, 63%) as a white solid that was used without further purification.

δH (400 MHz, CDCl₃) 0.90 (3H, d, J = 7.4 Hz, 2-CH₃), 1.07 (3H, d, J = 6.4 Hz, C-5), 2.88 – 2.98 (1H, m, 2-CH), 3.32 (3H, s, OCH₂OCH₃)), 3.63 (1H, dd, J = 4.0, 10.0 Hz, 3-CH), 3.80 (3H, s, OCH₃), 3.83 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.92 – 3.98 (1H, m, 4-CH), 4.60 (1H, d, J = 6.9 Hz, OCH₂OCH₃), 4.66 (1H, d, J = 6.9 Hz, OCH₂OCH₃), 6.52 (1H, s, 6’-CH), 6.93 (1H, s, 3'-CH), 9.71 (1H, d, J = 3.4 Hz, 1-CH(O)).

δC (100 MHz, CDCl₃) 12.5 (2-CH₃), 17.6 (5-CH₃), 43.2 (C-3), 47.2 (C-2), 55.5 (OCH₂OCH₃), 56.0 (OCH₃), 56.4 (OCH₃), 56.7 (OCH₃), 74.3 (C-4), 95.2 (OCH₂OCH₃), 87.3 (C-6’), 113.8 (C-3’), 118.2 (C-1’), 142.8, 148.3, 152.4 (C-2’, C-4’, C-5’), 204.6 (C-1).

νmax/cm⁻¹ 3031 (C-H, aromatic), 2934 (C-H, alkyl), 2838 (C-H, aldehyde), 1719 (C=O, aldehyde), 1207 (C=O, aromatic ether), 1134 (C=O, aliphatic ether).

m/z High Resolution (ESI⁺) found (MNa⁺): 349.1617 C₁₄H₂₆NaO₆ requires 349.1622.
M.P. 66 – 68 °C.

1-Bromo-2,3,5-trimethoxybenzene (165)

To a solution of 1,2,4-trimethoxybenzene 166 (1.25 g, 7.43 mmol) in DCM (50 mL), under an atmosphere of nitrogen at 0 °C, was added a solution of bromine (0.40 mL, 7.80 mmol) in DCM (13 mL) dropwise. Upon completion of the bromine addition the reaction mixture was quenched by addition of 10 % aqueous Na$_2$S$_2$O$_3$ (20 mL), the organic layer was separated and washed with saturated aqueous NaHCO$_3$ (10 mL), water (10 mL), dried (MgSO$_4$) and solvent removed in vacuo. Flash column chromatography (9:1 n-hexanes, EtOAc) gave the title compound (1.82 g, quant.) as a white solid.

$\delta_H$ (400 MHz, CDCl$_3$) 3.83 (3H, s, OCH$_3$), 3.87 (3H, s, OCH$_3$), 3.89 (3H, s, OCH$_3$), 6.57 (1H, s, 4-CH), 7.04 (1H, s, 6-CH).

M.P. 53 – 55 °C [lit.$^{173}$ 52 – 54 °C].

Spectroscopic data were in accordance with literature values.$^{173}$
To a solution of bromide 165 (0.1 g, 0.41 mmol) in Et₂O (6 ml), under an atmosphere of nitrogen at 0 °C, was added a 1.4 M solution of "BuLi in cyclohexanes (0.29 mL, 0.41 mmol) dropwise and the mixture stirred for 1 minute. A solution of butyraldehyde 168 (0.041 mL, 0.45 mmol) in Et₂O (2 mL) was then added dropwise and the resulting mixture stirred at room temperature for 1 h. Saturated aqueous NH₄Cl (5 mL) was added, the organic layer separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic fractions were dried (MgSO₄) and solvent removed \textit{in vacuo}. Flash column chromatography (4:1 \textit{n}-hexanes, EtOAc) gave the \textit{title compound} (0.032 g, 32\%) as a white solid.

\[ \delta_H (400 \text{ MHz, CDCl}_3) \]
0.94 (3H, t, \textit{J} = 7.4 Hz, 4-\text{CH}_3), 1.14 – 1.55 (2H, m, 3-\text{CH}_2), 1.62 – 1.85 (2H, m, 2-\text{CH}_2), 2.32 (1H, br d, \textit{J} = 4.6 Hz, OH), 3.83 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 4.87 (1H, br s, 1-\text{CH}), 6.52 (1H, s, 6'-\text{CH}), 6.89 (1H, s, 3'-\text{CH}).

M.P. 79 – 81 °C \textit{[lit.]} 85 – 86 °C.

Spectroscopic data were in accordance with literature values.\textsuperscript{174-175}
Experimental

2-Methyl-1-(2,4,5-trimethoxyphenyl)pentan-1-ol (171)

To a solution of bromide 165 (0.1 g, 0.41 mmol) in Et₂O (6 mL), under an atmosphere of nitrogen at 0 °C, was added a 1.4 M solution of nBuLi in cyclohexanes (0.29 mL, 0.41 mmol) dropwise and the mixture stirred for 1 minute. A solution of 2-methylpentenal 170 (0.041 mL, 0.45 mmol) in Et₂O (2 mL) was then added dropwise and the resulting mixture stirred at room temperature for 1 h. Saturated aqueous NH₄Cl (5 mL) was added, the organic layer separated and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic fractions were dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (4:1 n-hexanes, EtOAc) gave the title compound (0.11 g, quant.), a blue-green oil, as an (60:40) inseperable mixture of diastereomers.

δ_H (400 MHz, CDCl₃) [* denotes signal from the minor diastereomer] 0.74 (3H, d, J = 6.8 Hz, 2-CH₃*), 0.85 (3H, t, J = 7.0 Hz, 5-CH₃), 0.91 (3H, t, J = 7.1 Hz, 5-CH₃*), 0.95 (3H, d, J = 6.8 Hz, 2-CH₃), 0.99 – 1.53, 1.64 – 1.75 (8H, m, 3-CH₂, 3-CH₂*, 4-CH₂, 4-CH₂*), 1.79 – 1.91 (2H, m, 2-CH, 2-CH*), 2.18 (1H, br d, J = 5.0 Hz, OH), 2.29 (1H, br d, J = 5.5 Hz, OH*), 3.809, 3.811 (2 × 3H, s, OCH₃, OCH₃*), 3.845, 3.847 (2 × 3H, s, OCH₃, OCH₃*), 3.89 (6H, s, OCH₃, OCH₃*), 4.57 (1H, br s, 1-CH*), 4.67 (1H, br s, 1-CH), 6.51 (2H, s, 6'-CH, 6'-CH*), 6.84 (1H, s, 3'-CH*), 6.87 (1H, s, 3'-CH).

δ_C (100 MHz, CDCl₃) [* denotes signal from the minor diastereomer] 14.2 (C-5), 14.4 (C-5*), 14.7 (2-CH₃), 16.1 (2-CH₃*), 20.2 (C-4, C-4*), 34.8, 35.7 (C-3, C-3*), 38.7, 39.3 (C-2, C-2*), 56.18, 56.2, 56.6 (3 × OCH₃, 3 × OCH₃*), 74.3 (C-1), 75.0 (C-1*), 97.5 (C-6', C-6*), 111.9 (C-3'), 112.1 (C-3'), 123.4 (Ar-C, Ar-C*).

ν_H cm⁻¹ 3469 (O-H), 2871 (C-H, alkyl), 1508 (C-C, aromatic), 1202 (C-O, aromatic ether), 1032 (C-O, alcohol).

m/z High Resolution (ESI⁺) found (MNa⁺): 291.1560 C₁₅H₂₄NaO₄ requires 291.1567, found (MK⁺): 307.1313 C₁₅H₂₄KO₄ requires 306.1306.

[171]
Experimental

\((1S^*,2R^*,3S^*,4R^*)-4\)-(Methoxymethoxy)-2-methyl-1,3-bis(2,4,5-trimethoxyphenyl)pentan-1-ol (108a)

To a solution of bromide 165 (0.03 g, 0.12 mmol) in Et\(_2\)O (2 ml), under an atmosphere of nitrogen at 0 °C, was added a 1.4 M solution of \(^{6}\)BuLi in cyclohexanes (0.043 mL, 0.06 mmol) dropwise and the mixture stirred for 1 minute. A solution of aldehyde 107a (0.01 g, 0.03 mmol) in Et\(_2\)O (1 mL) was then added dropwise and the resulting mixture stirred at room temperature for 3 h. Saturated aqueous NH\(_4\)Cl (1 mL) was added, the organic layer separated, the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic fractions were dried (MgSO\(_4\)) and solvent removed in vacuo. Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.012 g, 76%),

\[\delta_H (400 \text{ MHz, } \text{CDCl}_3) 0.57 (3\text{H}, \text{d}, J = 6.9 \text{ Hz, } 2\text{-CH}_3), 1.27 (3\text{H}, \text{d}, J = 6.4 \text{ Hz, } 5\text{-CH}_3), 2.36 - 2.46 (1\text{H, m, } 2\text{-CH}), 3.25 (1\text{H, br s, OH}), 3.39 (3\text{H, s, OCH}_2\text{OCH}_3), 3.54 (1\text{H, dd, } J = 3.3, 10.0 \text{ Hz, } 3\text{-CH}), 3.80 (3\text{H, s, OCH}_3), 3.82 (3\text{H, s, OCH}_3), 3.84 (3\text{H, s, OCH}_3), 3.86 (3\text{H, s, OCH}_3), 3.88 (3\text{H, s, OCH}_3), 3.89 (3\text{H, s, OCH}_3), 3.96 - 4.04 (1\text{H, m, } 4\text{-CH}), 4.75 (1\text{H, d, } J = 6.5 \text{ Hz, } \text{OCH}_3\text{OCH}_3), 4.78 (1\text{H, d, } J = 6.5 \text{ Hz, } \text{OCH}_3\text{OCH}_3), 5.51 (1\text{H, br s, } 1\text{-CH}), 6.53 (2\text{H, br s, CH, } 6\text{-CH}, 6\text{-CH}), 6.85 (1\text{H, s, } 3\text{-CH}), 7.06 (1\text{H, s, } 3\text{-CH}).\]

\[\delta_C (100 \text{ MHz, } \text{CDCl}_3) 11.4 (2\text{-CH}_3), 15.7 (C-5), 37.1 (C-2), 44.5 (C-3), 55.4 (\text{OCH}_2\text{OCH}_3), 56.0 (\text{OCH}_3), 56.1 (\text{OCH}_3), 56.2 (\text{OCH}_3), 56.5 (\text{OCH}_3), 56.6 (\text{OCH}_3), 57.0 (\text{OCH}_3), 68.9 (C-1), 76.7 (C-4), 95.7 (\text{OCH}_2\text{OCH}_3), 97.2 (C-6\text{'}), 97.6 (C-6\text{'}), 111.6 (C-3\text{-CH}), 113.9 (C-3\text{-CH}), 121.7 (C-1\text{'}), 123.9 (C-1\text{'}), 142.8, 142.9, 147.9, 148.9, 149.7, 152.2 (C-2\text{'}, C-2\text{''}, C-4\text{'}, C-4\text{''}, C-5\text{'}, C-5\text{''}).\]

\[\nu_{\text{max}}/\text{cm}^{-1} 3484 (\text{O-H}), 2928 (\text{C-H, aromatic}), 2850 (\text{C-H, alkyl}), 1508 (\text{C-C, aromatic}), 1202 (\text{C-O, aromatic ether}), 1029 (\text{C-O, alcohol/aliphatic ether}).\]

\[m/z \text{ High Resolution (ESI')} \text{ found (MNa')}: 517.2394 \text{ C}_{26}\text{H}_{38}\text{NaO}_9 \text{ requires } 517.2408, \text{ found (MK')}: 533.2148 \text{ C}_{26}\text{H}_{38}\text{KO}_9 \text{ requires } 533.2147.\]
Magnosalicin: \((2R^*,3S^*,4R^*,5R^*)-2,4\text{-dimethyl-3,5-bis(2,4,5-trimethoxyphenyl)tetrahydrofuran} (112)\)

To alcohol 108a (5.8 mg, 0.011 mmol) in DCM (1 mL), under an atmosphere of nitrogen, was added triethylamine (2.6 µL, 0.019 mmol) and methanesulfonyl chloride (1.2 µL, 0.015 mmol) and the resulting mixture stirred for 2 h. Saturated aqueous NaHCO₃ (0.5 mL) was added, the organic layer separated and the aqueous layer extracted with DCM (3 × 2 mL). The combined organic extracts were dried (MgSO₄) and solvent removed \textit{in vacuo}. Flash column chromatography (1:1 EtOAc, \(n\)-hexanes) gave the \textit{title compound} (2.8 mg, 62%) as a yellow oil.

\(\delta_{H} (400 \text{ MHz, CDCl}_3)\): 0.90 (3H, d, \(J = 6.4 \text{ Hz, 2-CH}_3\)), 1.03 (3H, d, \(J = 6.5 \text{ Hz, 4-CH}_3\)), 2.31 (1H, m, 4-CH), 3.60 (1H, dd, \(J = 8.2, 10.4 \text{ Hz, 3-CH}\)), 3.79 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 4.60 (1H, dq, \(J = 6.4, 8.2 \text{ Hz, 2-CH}\)), 4.96 (1H, d, \(J = 9.1 \text{ Hz, 5-CH}\)), 6.535 (1H, s, 6ʹ-CH), 6.54 (1H, s, 6ʺ-CH), 6.69 (1H, s, 3ʹ-CH), 7.14 (1H, s, 3ʺ-CH).

\(\delta_{C} (100 \text{ MHz, CDCl}_3)\): 15.0 (4-CH₃), 19.0 (2-CH₃), 44.5 (C-4), 49.4 (C-3), 56.1 (2 × OCH₃), 56.4 (OCH₃), 56.6 (OCH₃), 56.7 (OCH₃), 57.0 (OCH₃), 76.0 (C-2), 80.7 (C-5), 97.5 (C-6), 97.7 (C-6ʺ), 111.3 (C-3ʺ), 113.1 (C-3′), 119.6 (C-1″), 121.6 (C-1″′), 142.7, 143.4, 148.1, 148.9, 151.8, 152.3 (C-2′, C-2″, C-4′, C-4″, C-5′, C-5″).

\(\nu_{\text{max/cm}}^-\): 2960 (C-H, aromatic), 2850 (C-H, alkyl), 1510 (C-C, aromatic), 1204 (C-O, aromatic ether), 1035 (C-O, furan).

\(m/z\) High Resolution (ESI⁺) found (MNa⁺): 455.2035 C₂₄H₃₂NaO₇ requires 455.2037.

Spectroscopic data were in accordance with literature values.¹⁰²,¹³⁶
To (S)-alaninol 178a (1 g, 13.3 mmol) and triethylamine (4.1 mL, 29.3 mmol) in DCM (20 mL), under an atmosphere of nitrogen at -5 °C, was added a solution of chloroacetyl chloride 179 (1.2 mL, 14.6 mmol) in DCM (8 mL) dropwise and the resulting mixture stirred for 1 h, warmed to room temperature and stirred a further 1 h. The mixture was then filtered through a Celite plug with EtOAc (30 mL), and solvent removed in vacuo. Flash column chromatography (2:1 EtOAc, n-hexanes) gave the title compound (1.7 g, 86%) as a yellow oil.

δ_H (400 MHz, CDCl_3) 1.23 (3H, d, J = 6.9 Hz, CH_3), 2.31 (1H, br s, OH), 3.58 (1H, dd, J = 5.6, 10.9 Hz, CH_3OH), 3.71 (1H, dd, J = 3.8, 10.9 Hz, CH_2OH), 4.06 (2H, s, CH_2Cl) 4.07 – 4.15 (1H, m, NHCH), 6.70 (1H, br s, NH).

δ_C (100 MHz, CDCl_3) 16.9 (CH_3), 42.7 (CH_2Cl), 48.0 (NHCH), 66.4 (CH_2OH), 194.1 (C=O).

ν_max/cm⁻¹ 3406 (O-H), 2878 (C-H, alkyl), 1646 (C=O), 1048 (C-O, alcohol), 559 (C-Cl).

m/z High Resolution (ESI⁺) found (MH⁺): 152.0479 C_5H_11Cl^35NO_2 requires 152.0473; found (MH⁺): 154.0452 C_5H_11Cl^37NO_2 requires 154.0444.

[α]_D^25 = -14.7 (c = 1.00, CHCl_3) [lit.][α]_D^19 = -14.7 (c = 13.2, CHCl_3)].

Spectroscopic data were in accordance with literature values.176
Experimental

(S)-5-Methylmorpholin-3-one (180a)\textsuperscript{177}

\[
\begin{array}{c}
\text{Cl} \quad \text{O} \\
\text{HO} \quad \text{NH} \\
\longrightarrow \\
\text{2} \quad \text{3} \quad \text{4} \\
\text{2} \quad \text{6} \\
\text{5} \quad \text{S}
\end{array}
\]

To a slurry of sodium tert-butoxide (0.27 g, 2.3 mmol) in THF (4 mL), under an atmosphere of nitrogen at 0 °C, was added a solution of chloroacetamide \textit{185a} (0.23 g, 1.5 mmol) in THF (2 mL) dropwise and the resulting mixture stirred for 1 h, brought to room temperature and stirred a further 1 h. The mixture was filtered through a Celite plug with THF (10 mL) and solvent removed \textit{in vacuo}. Flash column chromatography (100% EtOAc) gave the \textit{title compound} (0.092 g, 53%) as a pink-red solid.

\[\delta_H (400 \text{ MHz, CDCl}_3) \ 1.19 \ (3\text{H, d, } J = 6.6 \text{ Hz, 5-CH(CH}_3)), \ 3.37 \ (1\text{H, dd, } J = 7.7, 11.5 \text{ Hz, 6-CH}_3), \ 3.67 - 3.78 \ (1\text{H, m, 5-CH}), \ 3.90 \ (1\text{H, dd, } J = 3.6, 11.5 \text{ Hz, 6-CH}_3), \ 4.10 \ (1\text{H, d, } J = 16.9 \text{ Hz, 2-CH}_3), \ 4.20 \ (1\text{H, d, } J = 16.9 \text{ Hz, 2-CH}_3), \ 6.67 \ (1\text{H, br s, NH}).\]

\[\delta_C (100 \text{ MHz, CDCl}_3) \ 18.3 \ (5-\text{CH(CH}_3)), \ 47.4 \ (\text{C-5}), \ 67.5 \ (\text{C-2}), \ 69.3 \ (\text{C-6}), \ 169.1 \ (\text{C-3}).\]

\[\nu_{\text{max/cm}^{-1}} \ 3232 \ (\text{N-H}), \ 2920 \ (\text{C-H, alkyl}), \ 1659 \ (\text{C=O}), \ 1108 \ (\text{C-O, aliphatic ether}).\]

\[m/z \ \text{High Resolution (ESI}^+\text{) found (MH}^+\text{): 116.0708 C}_5\text{H}_{10}\text{NO}_2 \text{ requires 116.0706}.\]

M.P. 51 – 56 °C.

\[\alpha^\circ_0 = +13.6 \ (c = 1.0, \text{MeOH}).\]
(S)-3-Methylmorpholine hydrochloride (181a)\textsuperscript{178}

\[ \text{OCH}_2\text{CH(NH}_2\text{)}\text{Cl}^- \]

To a solution of morpholinone 180a (0.4 g, 3.47 mmol) in THF (40 mL), under an atmosphere of nitrogen at 0 °C, was added LiAlH\textsubscript{4} (0.26 g, 6.95 mmol) portionwise, the reaction mixture was allowed to come to room temperature and then stirred at reflux for 3 h. The mixture was cooled to room temperature and quenched by the cautious addition of MgSO\textsubscript{4}·7H\textsubscript{2}O (1.1 g, 7 mmol) followed by stirring for 1 h. The slurry was filtered through a Celite plug, washing the plug with EtOAc (50 mL) and a 1 M methanolic solution of HCl (25 mL) was added. Removal of solvent \textit{in vacuo} gave the title compound (0.43 g, 90%) as a red solid that was used without further purification.

\[ \begin{align*}
\delta_H (400 \text{ MHz, CDCl}_3) & \quad 1.44 (3\text{H}, d, J = 6.6 \text{ Hz, } 3\text{-CH(CH}_3\text{)}) , 3.05 – 3.18 (1\text{H, m, } 5\text{-CH}_a), 3.29 – 3.44 (2\text{H, m, } 3\text{-CH, } 5\text{-CH}_b), 3.68 (1\text{H, dd, } J = 10.0, 12.6, 2\text{-CH}_a), 3.91 (1\text{H, dd, } J = 3.5, 12.6 \text{ Hz, } 2\text{-CH}_b), 3.95 – 4.00 (2\text{H, m, } 6\text{-CH}_2), 9.89 (1\text{H, br s, NH}), 10.1 (1\text{H, br s, NH}). \\
\delta_C (100 \text{ MHz, CDCl}_3) & \quad 14.3 (3\text{-CH(CH}_3\text{)}), 42.9 (\text{C-5}), 51.1 (\text{C-3}), 63.3 (\text{C-6}), 69.4 (\text{C-2}). \\
\nu_{\text{max}}/\text{cm}^{-1} & \quad 2861 (\text{C-H, alkyl}), 2471 (\text{N-H}), 1106 (\text{C-O, aliphatic ether}). \\
m/z & \quad \text{High Resolution (ESI}^+\text{) found (MH}^+) : 102.0909 \text{ C}_5\text{H}_{12}\text{NO requires } 102.0913. \\
\text{M.P.} & \quad 85 – 87 \degree \text{C}. \\
[a]^{22}_D & \quad +2.6 \ (c = 1.0, \text{MeOH}) \ [\text{lit.}\textsuperscript{178} \ [a]^{10}_D = +3.0 \ (c = 1.0, \text{MeOH})].
\end{align*} \]
Experimental

(S)-4-Cinnamyl-3-methylmorpholine (183a)

The reaction was carried out according to general procedure F with cinnamyl bromide 116 (0.22 g, 2.19 mmol), morpholine hydrochloride 181a (0.10 g, 0.73 mmol), TBAI (0.066, 0.28 mmol) and sodium hydride (0.088 g, 1.10 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.70 g, 44%) as a yellow oil.

\( \delta_H \) (400 MHz, CDCl\(_3\)) 1.04 (3H, d, \( J = 6.3 \) Hz, 3-CH\(_3\)), 2.31 – 2.39 (1H, m, 5-CH\(_3\)), 2.43 – 2.53 (1H, m, 3-CH), 2.80 (1H, dt, \( J = 2.8, 12.0 \) Hz, 5-CH\(_b\)), 2.99 (1H, dd, \( J = 8.1, 13.8 \) Hz, NCH\(_3\)CHCHPh), 3.27 (1H, dd, \( J = 9.0, 11.1 \) Hz, 2-CH\(_a\)), 3.56 – 3.72 (3H, m, 2-CH\(_b\), 6-CH\(_a\), NCH\(_3\)CHCHPh), 3.79 (1H, dt, \( J = 3.0, 11.3 \) Hz, 6-CH\(_b\)), 6.26 (1H, ddd, \( J = 5.5, 8.3, 15.8 \) Hz, NCH\(_2\)CHCHPh), 6.50 (1H, d, \( J = 15.8 \) Hz, NCH\(_2\)CHCHPh), 7.19 – 7.40 (5H, m, Ar-H).

\( \delta_C \) (100 MHz, CDCl\(_3\)) 14.2 (CH\(_3\)), 51.5 (C-5), 55.2 (C-3), 56.4 (NCH\(_3\)CHCHPh), 67.4 (C-6), 72.9 (C-2), 126.1 (NCH\(_2\)CHCHPh), 126.3 (Ar-CH), 127.5 (Ar-CH), 128.6 (Ar-CH), 133.2 (NCH\(_2\)CHCHPh), 136.9 (Ar-C).

\( \nu_{\text{max}}/$\text{cm}^{-1} $) 3025 (C-H, aromatic), 2958 (C-H, alkene), 2850 (C-H, alkyl), 1125 (C-O, aliphatic ether), 691 (C-H, aromatic).

\( m/z \) High Resolution (ESI\(^+\)) found (MH\(^+\)): 218.1526 C\(_{14}\)H\(_{20}\)NO requires 218.1539.

\([\alpha]_D^{23} = +77.0\) (c = 0.10, MeOH).
Experimental

**Experimental**

(S,E)-4-(But-2-en-1-yl)-3-methylmorpholine (182a)

![Structural formula of (S,E)-4-(But-2-en-1-yl)-3-methylmorpholine (182a)]

The reaction was carried out according to general procedure F with crotyl bromide 115 (0.35 g, 2.58 mmol), morpholine hydrochloride 181a (0.18 g, 1.29 mmol), TBAI (0.12, 0.32 mmol) and sodium hydride (0.16 g, 3.87 mmol). Flash column chromatography (2:1 EtOAc, n-hexanes) gave the title compound (0.06 g, 30%) as a yellow oil.

δ_H (400 MHz, CDCl_3) 0.99 (3H, d, J = 6.4 Hz, 3-CH(CH_3)), 1.70 (3H, d, J = 6.2 Hz, NCH_2CHCHCH_3), 2.28 (1H, td, J = 3.2, 11.7 Hz, 5-CH_3), 2.36 – 2.49 (1H, m, 3-CH), 2.71 – 2.83 (2H, m, 5-CH_2, NCH_2CHCHCH_3), 3.25 (1H, t, J = 10.2 Hz, 2-CH_3) 3.37 (1H, dd, J = 5.2, 13.6 Hz, NCH_2CHCHCH_3), 3.59 – 3.70 (2H, m, 2-CH_2, 6-CH_3), 3.80 (1H, d, J = 11.9 Hz, 6-CH_3), 5.45 – 5.55 (1H, m, NCH_2CHCHCH_3), 5.57 – 5.71 (1H, m, NCH_2CHCHCH_3).

δ_C (100 MHz, CDCl_3) 14.1 (3-CH(CH_3)), 17.8 (NCH_2CHCHCH_3), 51.2 (C-5), 55.0 (C-3), 56.4 (NCH_2CHCHCH_3), 67.4 (C-6), 72.9 (C-2), 126.7 (NCH_2CHCHCH_3), 129.4 (NCH_2CHCHCH_3).

ν_max/cm⁻¹ 2955 (C-H, alkene), 2954 (C-H, alkyl), 1074 (C-O, aliphatic ether), 744 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 156.1388 C_9H_{18}NO requires 156.1383.

[a]_D^23 = +65.0 (c = 0.10, MeOH).

[178]
The reaction was carried out according to general procedure C with (S)-valinol 178b (2.0 g, 19.4 mmol) and chloroacetyl chloride 179 (2.17 mL, 27.2 mmol). Flash column chromatography (9:1 DCM, MeOH) gave the title compound (3.3 g, 95%) as a yellow oil.

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 0.96 (3H, d, <i>J</i> = 6.6 Hz, CH(CH<sub>3</sub>)<sub>a</sub>), 0.99 (3H, d, <i>J</i> = 6.6 Hz, CH(CH<sub>3</sub>)<sub>b</sub>), 1.86 – 2.02 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>), 3.04 (1H, br s, OCH), 3.67 – 3.82 (3H, m, NHCH, CH<sub>2</sub>OH), 4.08 – 4.14 (2H, m, CH<sub>2</sub>Cl).

[α]<sub>D</sub><sup>20</sup> = -33.0 (c = 1.00, CH<sub>2</sub>Cl<sub>2</sub>) [lit. 179 [α]<sub>D</sub><sup>20</sup> = -34.1 (c = 1.00, CH<sub>2</sub>Cl<sub>2</sub>)].

Spectroscopic data were in accordance with literature values. 179
(S)-5-Isopropylmorpholin-3-one (180b)

The reaction was carried out according to general procedure D with chloroacetamide 185b (3.2 g, 17.8 mmol) and sodium hydride (0.84 g, 21.4 mmol). Workup gave the title compound (2.3 g, 88%) as a white solid that was used without further purification.

δH (400 MHz, CDCl3) 0.96 (3H, d, J = 6.8 Hz, CH(CH3)a), 1.00 (3H, d, J = 6.7 Hz, CH(CH3)b), 1.74 – 1.86 (1H, m, CH(CH3)2), 3.25 – 3.32 (1H, m, 5-CH), 3.60 (1H, dd, J = 7.0, 11.8 Hz, 6-CHa), 3.90 (1H, dd, J = 4.0, 11.8 Hz, 6-CHb), 4.08 (1H, d, J = 16.5 Hz, 2-CHa), 4.17 (1H, d, J = 16.5 Hz, 2-CHb), 7.02 (1H, br s, NH).

δC (100 MHz, CDCl3) 18.2, 18.3 (2 × CH(CH3)2), 30.6 (CH(CH3)2), 56.9 (C-5), 65.9 (C-6), 67.6 (C-2), 169.6 (C-3).

νmax/cm⁻¹ 3288 (N-H), 2869 (C-H, alkyl), 1659 (C=O), 1114 (C-O, ether), 1097 (C-N).

m/z High Resolution (ESI⁺) found (MH⁺): 144.1013 C7H14NO2 requires 144.1019.

M.P. 65 – 68 °C.

[α]D^20 = -1.96 (c = 1.00, CH2Cl2).
The reaction was carried out according to general procedure E with LiAlH$_4$ (1.2 g, 30.7 mmol), morpholinone 185b (2.2 g, 15.4 mmol). Vacuum distillation (90 °C, 187 mbar) gave the title compound (1.51 g, 76%) as a pale yellow oil

$\delta_H$ (400 MHz, CDCl$_3$) 0.90 (3H, d, $J = 7.0$ Hz, CH(CH$_3$)$_2$), 0.94 (3H, d, $J = 6.5$ Hz, CH(CH$_3$)$_3$), 1.46 – 1.59 (1H, m, CH(CH$_3$)$_2$), 2.49 (1H, t, $J = 8.5$ Hz, 3-CH), 2.87 – 2.99 (2H, m, 5-CH$_2$), 3.22 (1H, t, $J = 10.6$ Hz, 2-CH$_3$), 3.46 (1H, t, $J = 10.6$ Hz, 2-CH$_3$), 3.78 (1H, d, $J = 11.0$ Hz, 6-CH$_3$), 3.88 (1H, dd, $J = 3.0$, 11.0 Hz, 6-CH$_3$).

$\delta_C$ (100 MHz, CDCl$_3$) 18.8, 18.9 (2 × 3-CHCH(CH$_3$)$_2$), 30.2 (3-CHCH(CH$_3$)$_2$), 46.5 (C-5), 60.7 (C-3), 67.5 (C-6), 71.1 (C-2).

$\nu_{\max}/\text{cm}^{-1}$ 3329 (N-H), 2853 (C-H, alkyl), 1104 (C-O, aliphatic ether).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 130.1230 C$_7$H$_{16}$NO requires 130.1226.

[ $\alpha$ ]$_D^{20}$ = -3.0 (neat), [ $\alpha$ ]$_D^{20}$ = -7.2 (c = 1.0, MeOH) is in accordance with data for the $R$-antipode [lit.$^{181}$ [ $\alpha$ ]$_D^{20}$ = +8.7 (neat)].
Experimental

(S)-4-Cinnamyl-3-isopropylmorpholine (183b)

The reaction was carried out according to general procedure F with cinnamyl bromide 116 (0.91 g, 4.6 mmol), morpholine 181b (0.40 g, 3.10 mmol), TBAI (0.29, 0.78 mmol) and sodium hydride (0.15 g, 6.19 mmol). Flash column chromatography (9:1 n-hexanes, EtOAc) gave the title compound (0.47 g, 62%) as a yellow oil.

δH (400 MHz, CDCl3) 0.93 (6H, dd, J = 1.0, 7.0 Hz, 3-CHCH(CH3)2), 2.18 – 2.31 (2H, m, 3-CHCH(CH3)2, 3-CH), 2.39 (1H, td, J = 3.5, 11.7 Hz, 5-CHa), 2.85 (1H, dt, J = 2.5, 11.7 Hz, 5-CHb), 2.96 (1H, dd, J = 8.1, 14.0 Hz, NCH2CHCHPh), 3.40 (1H, t, J = 10.4 Hz, 2-CHa), 3.56 (1H, td, J = 2.5, 11.5 Hz, 6-CHa), 3.63 (1H, ddd, J = 1.5, 5.5, 14.0 Hz, NCH2CHCHPh), 3.72 – 3.82 (2H, m, 2-CHb, 6-CHb), 6.27 (1H, ddd, J = 5.5, 8.0, 15.8 Hz NCH2CHCHPh), 6.52 (1H, d, J = 15.8 Hz, NCH2CHCHPh), 7.19 – 7.41 (5H, m, Ar-H).

δC (100 MHz, CDCl3) 15.8, 19.5 (2 × NCHCH(CH3)2), 25.8 (NCHCH(CH3)2), 52.4 (C-5), 55.3 (NCH2CHCHPh), 64.2 (C-3), 66.5 (C-2), 66.9 (C-6), 126.2 (NCH2CHCHPh), 126.4 (NCH2CHCHPh), 127.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 132.9 (Ar-CH), 137.0 (Ar-C).

νmax/cm⁻¹ 3026 (C-H, aromatic), 2960 (C-H, alkene), 2858 (C-H, alkyl), 1124 (C-O, aliphatic ether), 740 (C-H, alkyl), 691 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 246.1850 C16H24NO requires 246.1852.

[a]D²⁰ = +10.1 (c = 0.10, MeOH).
Experimental

(S,E)-4-(But-2-enyl)-3-isopropylmorpholine (182b)

The reaction was carried out according to general procedure F with crotyl bromide 115 (0.65 g, 4.8 mmol), morpholine 181b (0.42 g, 3.21 mmol), TBAI (0.3, 0.80 mmol) and sodium hydride (0.25 g, 6.42 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.24 g, 41%) as a yellow oil.

δH (400 MHz, CDCl3) 0.91 (6H, t, J = 6.3 Hz, 3-CHCH(CH3)2), 1.70 (3H, d, J = 6.4 Hz, NCH2CHCHCH3), 2.12 - 2.24 (2H, m, 3-CHCH(CH3)2, 3-CH), 2.32 (1H, td, J = 3.5, 11.5 Hz, 5-CHa), 2.73 - 2.84 (2H, m, 5-CHb, NCHaCHCHCH3), 3.30 - 3.42 (2H, m, 2-CHa, NCHbCHCHCH3), 3.55 (1H, td, J = 2.5, 11.5 Hz, 6-CHa), 3.72 - 3.80 (2H, m, 2-CHb, 6-CHb), 5.45 - 5.54 (1H, m, NCH2CHCHCH3), 5.55 - 5.66 (1H, m, NCH2CHCHCH3).

δC (100 MHz, CDCl3) 15.8 (3-CHCH(CH3)a), 17.8 (NCH2CHCHCH3), 19.5 (3-CHCH(CH3)b), 25.6 (3-CHCH(CH3)b), 52.0 (C-5), 54.9 (NCH2CHCHCH3), 64.0 (C-3), 66.5 (C-2), 66.9 (C-6), 126.9 (NCH2CHCHCH3), 129.1 (NCH2CHCHCH3).

νmax/cm⁻¹ 2960 (C-H, alkene), 2856 (C-H, aromatic), 1123 (C-O, aliphatic ether), 967 (C-H, aliphatic).

m/z High Resolution (ESI⁺) found (MH⁺): 184.1700 C11H22NO requires 184.1686.

[α]D²⁰ = +89.5 (c = 0.10, MeOH).
Experimental

(S)-2-Chloro-N-(1-hydroxy-4-methylpentan-2-yl)acetamide (185c)

![Chemical Structure](image)

The reaction was carried out according to general procedure C with (S)-leucinol 178c (1.0 g, 8.50 mmol) and chloroacetyl chloride 179 (0.95 mL, 11.9 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (1.47 g, 87%) as a bronze oil.

δ_H (400 MHz, CDCl_3) 0.95 (6H, t, J = 6.5 Hz, CH_2CH(CH_3)_2), 1.37 – 1.51 (2H, m, CH_2CH(CH_3)_2), 1.58 – 1.70 (1H, m, CH_2CH(CH_3)_2), 2.22 (1H, br s, OH), 3.60 (1H, dd, J = 5.5, 11.0 Hz, CH_aOH), 3.72 (1H, dd, J = 7.5, 11.0 Hz, CH_bOH), 4.02 – 4.13 (3H, m, CH_2Cl, NHCH).

δ_C (100 MHz, CDCl_3) 22.2, 23.0 (2 × CH_2CH(CH_3)_2), 24.9 (CH_2CH(CH_3)_2), 40.0 (CH_2CH(CH_3)_2), 42.8 (CH_2Cl), 50.4 (NHCH), 65.7 (CH_2, CH_2OH), 166.5 (C=O).

ν_max/cm^{-1} 3258 (O-H), 2873 (C-H, alkyl), 1643 C=O), 1073 (C-O, alcohol), 692 (C-Cl).

m/z High Resolution (ESI\(^+\)) found (MH\(^+\)): 194.0941 C_8H_{17}Cl^{35}NO_2 requires 194.0942; found (MH\(^+\)): 196.0913 C_8H_{17}Cl^{37}NO_2 requires 196.0913.

\([\alpha]_D^{25} = -28.4 (c = 1.00, \text{MeOH}) [\text{lit.}\, ^{182} \, [\alpha]_D^{25} = -32.6 (c = 0.52, \text{MeOH})].\)
Experimental

(S)-5-Isobutylmorpholin-3-one (180c)

The reaction was carried out according to general procedure D with chloroacetamide 185c (1.3 g, 6.7 mmol) and sodium hydride (0.32 g, 8.05 mmol). Workup gave the title compound (1.05 g, quant.) as a white solid that was used without further purification.

\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) \]
- 0.95 (6H, dd, \( J = 2.5, 6.5 \text{ Hz} \), \( \text{CH}_2\text{CH(CH}_3)_2 \)), 1.30 – 1.46 (2H, m, \( \text{CH}_2\text{CH(CH}_3)_2 \)), 1.60 – 1.74 (1H, m, \( \text{CH}_2\text{CH(CH}_3)_2 \)), 3.43 (1H, dd, \( J = 4.2, 11.5 \text{ Hz} \), 6-CH), 3.59 – 3.68 (1H, m, 5-CH), 3.90 (1H, dd, \( J = 7.5, 11.5 \text{ Hz} \), 6-CH), 4.11 (1H, d, \( J = 16.5 \text{ Hz} \), 2-CH), 4.21 (1H, d, \( J = 16.5 \text{ Hz} \), 2-CH), 6.80 (1H, br s, NH).

\( \nu_{\text{max}}/\text{cm}^{-1} \)
- 3289 (N-H), 2870 (C-H, alkyl), 1667 (C=O), 1117 (C-O, aliphatic ether).

\( m/z \)
- High Resolution (ESI\(^+\)) found (MH\(^+\)): 158.1178 \( \text{C}_8\text{H}_{16}\text{NO}_2 \) requires 158.1176.

M.P. 60 – 65 °C [lit.\(^{183}\) 70 – 71 °C].

\[ [\alpha]_D^{20} = -9.0 \ (c = 1.00, \text{MeOH}) \ [\text{lit.}\^{183} \ [\alpha]_D^{25} = -3.2 \ (c = 1.00, \text{MeOH})]. \]

Spectroscopic data were in accordance with literature values.\(^{183}\)
Experimental

(S)-3-Isobutylmorpholine (181c)\(^{177}\)

The reaction was carried out according to general procedure E with LiAlH\(_4\) (0.46 g, 12.1 mmol) and morpholinone 180c (0.95 g, 6.04 mmol). Vacuum distillation (58 °C, 4 mbar) gave the title compound (0.55 g, 63%) as a yellow oil.

\(\delta_H\) (400 MHz, CDCl\(_3\)) 0.91 (6H, dd, \(J = 3.5, 9.9\) Hz, CH\(_2\)CH(CH\(_3\))\(_2\)), 1.04 – 1.20 (2H, m, CH\(_2\)CH(CH\(_3\))\(_2\)), 1.49 (1H, br s NH), 1.59 – 1.70 (1H, m, CH\(_2\)CH(CH\(_3\))\(_2\)), 2.79 – 2.90 (2H, m, 5-CH\(_a\), 3-CH), 2.97 (1H, td, \(J = 3.6, 12.0\) Hz, 5-CH\(_b\)), 3.11 (1H, dd, \(J = 10.0, 11.1\) Hz, 2-CH\(_a\)), 3.48 (1H, dt, \(J = 2.5, 11.1\) Hz, 6-CH\(_a\)), 3.72 – 3.82 (2H, m, 2-CH\(_b\), 6-CH\(_b\)).

\(\delta_C\) (100 MHz, CDCl\(_3\)) 22.4, 23.2 (2 × CH\(_2\)CH(CH\(_3\))\(_2\)), 24.1 (CH\(_2\)CH(CH\(_3\))\(_2\)), 41.7 (CH\(_2\)CH(CH\(_3\))\(_2\)), 46.4 (C-5), 52.8 (C-3), 67.8 (C-2), 73.2 (C-6).

\(\nu_{\text{max}}/\text{cm}^{-1}\) 3304 (N-H), 2848 (C-H, alkyl), 1103 (C-O, aliphatic ether).

\(m/z\) High Resolution (ESI\(^+\)) found (MH\(^+\)): 144.1377 C\(_8\)H\(_{18}\)NO requires 144.1383.

\(\alpha = -7.0\ \) (\(c = 1.00,\) MeOH).
Experimental

(S)-4-Cinnamyl-3-isobutylmorpholine (183c)

The reaction was carried out according to general procedure F with cinnamyl bromide 116 (0.12 g, 0.63 mmol), morpholine 181c (0.06 g, 0.42 mmol), TBAI (0.04, 0.10 mmol) and sodium hydride (0.021 g, 0.84 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.094 g, 86%) as a yellow oil.

δ_H (400 MHz, CDCl_3) 0.92 (6H, dd, J = 6.3, 11.9 Hz, 3-CHCH_2CH(CH_3)_2), 1.18 – 1.27 (1H, m, 3-CHCH_2CH(CH_3)_2), 1.44 – 1.53 (1H, m, 3-CHCH_2CHCH(CH_3)_2), 1.53 – 1.64 (1H, m, 3-CHCH_2CH(CH_3)_2), 2.35 – 2.39 (1H, m, 5-CH_a), 2.39 – 2.46 (1H, m, 3-CH), 2.81 (1H, dt, J = 3.1, 12.2 Hz, 5-CH_b), 2.99 (1H, dd, 8.0, 14.0 Hz, NCH_2CHCHPh), 3.35 (1H, dd, J = 8.0, 11.5 Hz, 2-CH_a), 3.59 (1H, ddd, J = 1.5, 5.7, 14.0 Hz, NCH_2CHCHPh), 3.66 (1H, dd, J = 2.6, 9.2 Hz, 6-CH_a), 3.73 – 3.82 (2H, m, 2-CH_b, 6-CH_b), 6.25 (1H, ddd, J = 5.7, 8.0, 15.8 Hz, NCH_2CHCHPh), 6.53 (1H, d, J = 15.8 Hz, NCH_2CHCHPh), 7.21 – 7.40 (5H, m, Ar-H).

δ_C (100 MHz, CDCl_3) 22.2, 23.9 (2 × 3-CHCH_2CH(CH_3)_2), 25.7 (3-CHCH_2CH(CH_3)_2), 36.6 (3-CHCH_2CHCH(CH_3)_2), 51.3 (C-5), 56.3 (NCH_2CHCHPh), 58.1 (C-3), 67.1 (C-6), 71.1 (C-2), 126.2 (NCH_2CHCHPh), 126.5 (Ar-CH), 127.5 (Ar-CH), 128.6 (Ar-CH), 133.3 (NCH_2CHCHPh), 136.9 (Ar-C).

ν_max/cm^-1 3026 (C-H, aromatic), 2954 (C-H, alkene), 2853 (C-H, alkyl), 1126 (C-O, aliphatic ether), 692 (C-H, aromatic).

m/z High Resolution (ESI^+) found (MH^+): 260.1984 C_{17}H_{26}NO requires 260.2009.

[ α ] _D^{20} = +108.0 (c = 0.10, MeOH).

[187]
Experimental

\((S,E)-4-(\text{But-2-en-1-yl})-3\text{-isobutylmorpholine (182c)}\)

The reaction was carried out according to general procedure F with crotyl bromide 115 (0.27 g, 2.02 mmol), morpholine 181c (0.15 g, 1.01 mmol), TBAI (0.09 g, 0.25 mmol) and sodium hydride (0.081 g, 2.02 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.10 g, 50%) as a yellow oil.

\[\begin{align*}
\delta_H \text{ (400 MHz, CDCl}_3\text{) } & \text{ 0.90 (6H, dd, } J = 6.5, 10.5 \text{ Hz, 3-CHCH}_2\text{CH(CH}_3\text{)_2), 1.12} - 1.21 \text{ (1H, m, 3-CHCH}_3\text{CH(CH}_3\text{)_2), 1.39} - 1.47 \text{ (1H, m, 3-CHCH}_5\text{CH(CH}_3\text{)_2), 1.50} - 1.61 \text{ (1H, m, 3-CHCH}_7\text{CH(CH}_3\text{)_2), 1.69} \text{ (3H, d, } J = 7.0 \text{ Hz, NCH}_2\text{CHCHCH}_3\text{), 2.24} - 2.33 \text{ (1H, m, 5-CH}_a\text{), 2.33} - 2.40 \text{ (1H, m, 3-CH), 2.72} - 2.83 \text{ (2H, m, 5-CH}_b\text{, NCH}_3\text{CHCHCH}_3\text{), 3.28} - 3.39 \text{ (2H, m, 2-CH}_a\text{, NCH}_3\text{CHCHCH}_3\text{), 3.59} - 3.68 \text{ (1H, m, 6-CH}_a\text{), 3.73} - 3.80 \text{ (2H, m, 2-CH}_b\text{, 6-CH}_b\text{), 5.43} - 5.53 \text{ (1H, m, NCH}_2\text{CHCHCH}_3\text{), 5.56} - 5.67 \text{ (1H, m, NCH}_2\text{CHCHCH}_3\text{).}
\end{align*}\]

\[\begin{align*}
\delta_C \text{ (100 MHz, CDCl}_3\text{) } & \text{ 17.8 (NCH}_2\text{CHCHCH}_3\text{), 22.1, 23.9 (2 \times 3-CHCH}_2\text{CH(CH}_3\text{)_2), 25.6 (3-CHCH}_2\text{CH(CH}_3\text{)_2), 36.4 (3-CHCH}_2\text{CH(CH}_3\text{)_2), 50.9 (C-5), 55.9 (NCH}_2\text{CHCHCH}_3\text{), 57.8 (C-3), 67.1 (C-6), 71.0 (C-2), 127.1 (NCH}_2\text{CHCHCH}_3\text{), 129.2 (NCH}_2\text{CHCHCH}_3\text{).}
\end{align*}\]

\[\nu_{\text{max/cm}^{-1}} \text{ 2955 (C-H, alkene), 2854 (C-H, alkyl), 1125 (C-O, aliphatic ether), 967 (C-H, alkyl).}\]

\[m/z \text{ High Resolution (ESI}^+\text{) found (MH}^+\text{): 198.1861 C}_{12}\text{H}_{24}\text{NO requires 198.1852.}\]

\[\alpha_0^{25} = +93.7 \text{ (c = 0.10, MeOH).}\]
Experimental

2-Chloro-N-((2S,3S)-1-hydroxy-3-methylpentan-2-yl)acetamide (185d)

The reaction was carried out according to general procedure C with (S)-isoleucinol 178d (1.0 g, 8.50 mmol) and chloroacetyl chloride 179 (0.95 mL, 11.9 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (1.31 g, 77%) as a bronze oil.

δH (400 MHz, CDCl3) 0.93 (3H, t, J = 7.5 Hz, CH(CH3)CH2CH3), 0.97 (3H, d, J = 7.1 Hz, CH(CH3)CH2CH3), 1.11 – 1.24 (1H, m, CH(CH3)CH2CH3), 1.46 – 1.58 (1H, m, CH(CH3)CH2CH3), 1.66 – 1.78 (1H, m, CH(CH3)CH2CH3), 2.13 (1H, br s, OH), 3.68 – 3.80 (2H, m, CH2OH), 3.80 – 3.88 (1H, m, NHCH), 4.10 (2H, s, CH2Cl), 6.75 (1H, br s, NH).

δC (100 MHz, CDCl3) 11.3 (CH(CH3)CH2CH3), 15.6 (CH(CH3)CH2CH3), 25.5 (CH(CH3)CH2CH3), 35.6 (CH(CH3)CH2CH3), 42.8 (CH2Cl), 56.4 (CH, NHCH), 63.4 (CH2, CH2OH) 166.7 (C=O).

νmax/cm⁻¹ 3325 (O-H), 2877 (C-H, alkyl), 1652 (C=O), 1075 (C-O, alcohol), 671 (C-Cl).

m/z High Resolution (ESI⁺) found (MH⁺): 194.0943 C₈H₁₇Cl35NO₂ requires 194.0942; found (MH⁺): 196.0915 C₈H₁₇Cl37NO₂ requires 196.0913.

[α]D²⁰ = -24.1 (c = 0.50, MeOH).

Spectroscopic data were in accordance with literature values.¹⁸⁴
The reaction was carried out according to general procedure D with chloroacetamide 185d (1.2 g, 6.2 mmol) and sodium hydride (0.30 g, 7.40 mmol). Workup gave the title compound (0.97 g, quant.) as a white solid that was used without further purification.

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 0.91 – 0.97 (6H, m, CH(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>), 1.14 – 1.29 (1H, m, CH(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>), 1.46 – 1.63 (2H, m, CH(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>), 3.39 – 3.46 (1H, m, 5-CH), 3.59 (1H, dd, J = 7.5, 12.0 Hz, 6-CH<sub>a</sub>), 3.88 (1H, dd, J = 7.8, 11.9 Hz, 6-CH<sub>b</sub>), 4.09 (1H, d, J = 16.5 Hz, 2-CH<sub>a</sub>), 4.18 (1H, d, J = 16.5 Hz, 2-CH<sub>b</sub>).

ν<sub>max</sub>/cm<sup>-1</sup> 3213 (amide NH), 2956, 2922, 2972 (C–H, alkyl), 1655 (C=O), 1117 (C–O).

m/z High Resolution (ESI<sup>+</sup>) found (MH<sup>+</sup>): 158.1173 C<sub>8</sub>H<sub>16</sub>NO<sub>2</sub> requires 158.1176.

M.P. 104 - 106 °C [lit. 183 112 – 114 °C].

[α]<sup>22</sup> = +8.4 (c = 1.0, MeOH) [lit. 183 [α]<sup>21</sup> = +14.9 (c = 1.0, MeOH)].

Spectroscopic data were in accordance with literature values. 183
(S)-3-((S)-Secbutyl)morpholine (181d)

The reaction was carried out according to general procedure E with LiAlH₄ (0.42 g, 11.1 mmol) and morpholinone 180d (0.87 g, 5.54 mmol). Vacuum distillation (60 °C, 4 mbar) gave the title compound (0.53 g, 67%) as a yellow oil.

δ_H (400 MHz, CDCl₃) 0.85 – 0.93 (6H, m, 3-CHCH(CH₃)CH₂CH₃), 1.08 – 1.25 (1H, m, 3-CHCH(CH₃)CH₂CH₃), 1.27 – 1.39 (1H, m, 3-CHCH(CH₂CH₃)CH₂CH₃), 1.44 – 1.57 (1H, m, 3-CHCH(CH₃)CH₂CH₃), 1.59 (1H, br s, NH), 2.61 (1H, t, J = 8.2 Hz, 3-CH), 2.84 – 3.01 (2H, m, 5-CH₂), 3.24 (1H, dd, J = 11.0, 11.0 Hz, 2-CH₆), 3.46 (1H, td, J = 3.2, 11.0 Hz, 6-CH₆), 3.78 (1H, dd, J = 3.2, 11.0 Hz, 6-CH₆), 3.85 (1H, d, J = 11.0 Hz, 2-CH₆).

δ_C (100 MHz, CDCl₃) 11.0, 14.9 (3-CHCH(CH₃)CH₂CH₃), 25.2 (3-CHCH(CH₂CH₃)CH₂CH₃), 37.2 (3-CHCH(CH₃)CH₂CH₃), 46.8 (C-5), 58.9 (C-3), 70.9 (C-2), 72.9 (C-6).

ν_max/cm⁻¹ 3320 (N-H), 2855 (C-H, alkyl), 1104 (C-O, aliphatic ether).

m/z High Resolution (ESI⁺) found (MH⁺): 144.1380 C₈H₁₈NO requires 144.1383.

[α]_D²⁰ = -23.6 (c = 1.00, MeOH).
Experimental

(S)-3-((S)-Secbutyl)-4-cinnamylmorpholine (183d)

The reaction was carried out according to general procedure F with cinnamyl bromide 116 (0.12 g, 0.63 mmol), morpholine 181d (0.06 g, 0.42 mmol), TBAI (0.04, 0.10 mmol) and sodium hydride (0.021 g, 0.84 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (0.071 g, 65%) as a yellow oil.

$\delta_H$ (400 MHz, CDCl$_3$) 0.92−0.97 (6H, m, 3-CHCH(CH$_3$)CH$_2$CH$_3$), 1.13−1.40 (2H, m, 3-CHCH(CH$_3$)CH$_2$CH$_3$), 1.88−1.99 (1H, m, 3-CHCH(CH$_3$)CH$_2$CH$_3$), 2.33−2.44 (2H, 3-CH, 5-CH$_a$), 2.86 (1H, dt, $J = 2.0, 12.0$ Hz, 5-CH$_b$), 2.96 (1H, dd, $J = 8.4, 13.8$ Hz, NCH$_3$CHPh), 3.39 (1H, t, $J = 10.4$ Hz, 2-CH$_a$), 3.57 (1H, td, $J = 2.4, 11.2$ Hz, 6-CH$_b$), 3.63 (1H, ddd, $J = 1.9, 5.4, 14.0$ Hz, NCH$_3$CHPh), 3.72−3.82 (2H, m, 2-CH$_b$, 6-CH$_b$), 6.28 (1H, ddd, $J = 5.4, 8.1, 15.8$ Hz, NCH$_2$CHPh), 6.52 (1H, d, $J = 15.8$ Hz, NCH$_2$CHCHPh), 7.19−7.41 (5H, m, Ar-H).

$\delta_C$ (100 MHz, CDCl$_3$) 12.7, 13.3 (2 × 3-CHCH(CH$_3$)CH$_2$CH$_3$), 26.8 (3-CHCH(CH$_3$)CH$_2$CH$_3$), 33.1 (3-CHCH(CH$_3$)CH$_2$CH$_3$), 52.6 (C-5), 55.2 (NCH$_2$CHCHPh), 63.1 (C-3), 66.6 (C-2), 67.0 (C-6), 126.2 (Ar-CH), 126.4 (NCH$_2$CHCHPh), 127.4 (Ar-CH), 128.6 (Ar-CH), 132.9 (NCH$_2$CHCHPh), 137.0 (Ar-C).

$\nu_{\text{max}}$ cm$^{-1}$ 3025 (C-H, aromatic), 2959 (C-H, alkene), 2852 (C-H, alkyl), 1123 (C-O, aliphatic ether), 691 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 260.1984 C$_{17}$H$_{26}$NO requires 260.2009.

[α]$_D^{20}$ = +90.1 (c = 0.10, MeOH).
The reaction was carried out according to general procedure F with crotyl bromide 115 (0.27 g, 2.02 mmol), morpholine 181d (0.15 g, 1.01 mmol), TBAI (0.09, 0.25 mmol) and sodium hydride (0.081 g, 2.02 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.11 g, 55%) as a yellow oil.

$\delta_H$ (400 MHz, CDCl$_3$) 0.85 – 0.96 (6H, m, 3-CHCH(CH$_3$)CH$_2$CH$_3$), 1.10 – 1.23 (1H, m, 3-CHCH(CH$_3$)CH$_2$CH$_3$), 1.24 – 1.36 (1H, m, 3-CHCH(CH$_3$)CH$_2$CH$_3$), 1.70 (3H, d, $J = 6.0$ Hz, NCH$_2$CHCHCH$_3$), 1.82 – 1.93 (1H, m, 3-CHCH(CH$_3$)CH$_2$CH$_3$), 2.24 – 3.38 (2H, m, 3-CH, 5-CH$_a$), 2.71 – 2.82 (2H, m, 5-CH$_b$, NCH$_2$CHCHCH$_3$), 3.30 – 3.41 (2H, m, 3-CH, 5-CH$_a$, NCH$_2$CHCHCH$_3$), 3.55 (1H, td, $J = 2.5$, 11.5 Hz, 6-CH$_a$), 3.69 – 3.78 (2H, m, 2-CH$_b$, 6-CH$_b$), 5.45 – 5.54 (1H, m, NCH$_2$CHCHCH$_3$), 5.55 – 5.65 (1H, m, NCH$_2$CHCHCH$_3$).

$\delta_C$ (100 MHz, CDCl$_3$) 12.6, 13.2 (2 $\times$ 3-CHCH(CH$_3$)CH$_2$CH$_3$), 17.8 (NCH$_2$CHCHCH$_3$), 26.8 (3-CHCH(CH$_3$)CH$_2$CH$_3$), 32.9 (3-NCHCH(CH$_3$)CH$_2$CH$_3$), 52.1 (C-5), 54.8 (NCH$_2$CHCHCH$_3$), 62.8 (C-3), 66.6 (C-2), 67.0 (C-6), 126.8 (NCH$_2$CHCHCH$_3$), 129.1 (NCH$_2$CHCHCH$_3$).

$\nu_{max}$/cm$^{-1}$ 2960 (C-H, alkene), 2957 (C-H, alkyl), 1125 (C-O, aliphatic ether), 966 (C-H, alkyl).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 198.1848 C$_{12}$H$_{24}$NO requires 198.1852.

$[\alpha]_D^{25} = +95.2$ (c = 0.10, MeOH).
Experimental

**(S)-2-Chloro-N-(2-hydroxy-1-phenylethyl)acetamide (181e)**

The reaction was carried out according to general procedure C with (S)-phenylglycinol 178e (1.0 g, 7.30 mmol) and chloroacetyl chloride 179 (0.85 mL, 10.2 mmol) and gave the *title compound* (1.40 g, 82%) as a white solid that was used without further purification.

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 3.94 (2H, d, J = 4.8 Hz, CH\textsubscript{2}OH), 4.08 (1H, dd, J = 3.2, 15.4 Hz, CH\textsubscript{3}Cl), 4.14 (1H, dd, J = 3.2, 15.4 Hz, CH\textsubscript{3}Cl), 5.07 – 5.13 (1H, m, NHCH), 7.24 – 7.43 (5H, m, Ar-H).

δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 42.7 (CH\textsubscript{2}Cl), 55.8 (NHCH), 66.2 (CH\textsubscript{2}OH), 126.6 (Ar-CH), 128.2 (Ar-CH), 129.0 (Ar-CH), 141.7 (Ar-C), 169.7 (C=O).

M.P. 106 – 108 °C [lit.\textsuperscript{185} 106 – 108 °C].

[α]\textsubscript{D}\textsuperscript{20} = +36.8 (c = 0.89, CHCl\textsubscript{3}) [lit.\textsuperscript{186} [α]\textsubscript{D}\textsuperscript{20} = +31.8 (c = 0.9, CHCl\textsubscript{3})].

Spectroscopic data were in accordance with literature values.\textsuperscript{186-187}

[194]
The reaction was carried out according to general procedure D with chloroacetamide 185e (1.18 g, 5.5 mmol) and sodium hydride (0.27 g, 6.63 mmol). Flash column chromatography gave the *title compound* (0.56 g, 57%) as a white solid.

$\delta_H$ (400 MHz, CDCl$_3$) 3.56 (1H, dd, $J = 8.4, 11.8$ Hz, 6-CH$_a$), 4.05 (1H, dd, $J = 4.5, 11.8$ Hz, 6-CH$_b$), 4.24 (1H, d, $J = 17.0$ Hz, 2-CH$_a$), 4.33 (1H, d, $J = 17.0$ Hz, 2-CH$_b$), 4.75 (1H, dd, $J = 4.5, 8.4$ Hz, 5-CH), 6.08 (1H, br s, NH), 7.28 – 7.44 (5H, m, Ar-H).

$\delta_C$ (100 MHz, CDCl$_3$) 56.9 (C-5), 67.9 (C-2), 70.4 (C-6), 126.6 (Ar-CH), 128.8 (Ar-CH), 129.1 (Ar-CH) 137.7 (Ar-C), 169.1 (C=O).

$v_{\text{max}}$/cm$^{-1}$ 3182 (N-H), 3068 (C-H, aromatic), 2863 (C-H, alkyl), 1667 (C=O), 1125 (C-O, aliphatic ether), 763 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 178.0846 C$_{10}$H$_{12}$NO$_2$ requires 178.0863.

M.P. 135 – 137 °C.

$[\alpha]_D^{20} = +104.7$ (c = 1.01, CHCl$_3$).
Experimental

(S)-3-Phenylmorpholine (181e)

The reaction was carried out according to general procedure E with LiAlH₄ (0.17 g, 4.52 mmol) and morpholinone 180e (0.40 g, 1.35 mmol) and gave the title compound (0.31 g, quant.) as a white solid that was used without further purification.

δ_H (400 MHz, CDCl₃) 3.0 (1H, dt, J = 1.9, 11.9 Hz, 5-CH₉), 3.14 (1H, td, J = 3.5, 11.9 Hz, 5-CH₉), 3.40 (1H, dd, J = 10.0, 11.0 Hz, 2-CH₈), 3.66 (1H, td, J = 2.5, 11.3 Hz, 6-CH₈), 3.83 (1H, dd, J = 3.0, 11.0 Hz, 2-CH₈), 3.85 – 3.90 (1H, m, 6-CH₉), 3.93 (1H, dd, J = 3.0, 9.9 Hz, 3-CH), 7.25 – 7.42 (5H, m, Ar-H).

δ_C (100 MHz, CDCl₃) 46.6 (C-5), 60.6 (C-3), 67.3 (C-6), 73.7 (C-2), 127.1 (Ar-CH), 127.8 (Ar-CH), 128.5 (Ar-CH), 140.6 (Ar-C).

ν_max/cm⁻¹ 3239 (N-H), 2884 (C-H, aromatic), 2848 (C-H, alkyl), 1102 (C-O, aliphatic ether), 755 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 164.1067 C₁₀H₁₄NO requires 164.1070.

M.P. 58 – 64 °C [lit.181 76 -77 °C].

[α]_D^{20} = +78.7 (c = 1.06, CHCl₃), [α]_D^{20} = +49.5 (c = 1.00, MeOH) is in accordance with data for the R-antipode [lit.181 [α]_D^{20} = -45.8 (c = 1.06, MeOH).
**(S)-4-Cinnamyl-3-phenylmorpholine (183e)**

The reaction was carried out according to general procedure F with cinnamyl bromide 116 (0.47 g, 2.39 mmol), morpholine 181e (0.13 g, 0.80 mmol), TBAI (0.07, 0.20 mmol) and sodium hydride (0.064 g, 1.59 mmol). Flash column chromatography (4:1 *n*-hexanes, EtOAc) gave the title compound (0.15 g, 70%) as a pale yellow solid.

δ_H (400 MHz, CDCl₃) 3.01 (1H, dt, *J* = 1.9, 11.9 Hz, 5-CH₃), 2.67 (1H, dd, *J* = 8.5, 13.9 Hz, NCH₂CHCHPh), 2.40 (1H, td, *J* = 3.5, 11.9 Hz, 5-CH₆), 3.32 – 3.46 (3H, m, 2-CH₃, 3-CH, NCH₂CHCHPh), 3.70 - 3.80 (2H, m, 2-CH₆, 6-CH₃), 3.88 – 3.94 (1H, m, 6-CH₃), 6.16 (1H, ddd, *J* = 4.8, 8.5, 15.9 Hz, NCH₂CHCHPh), 6.41 (1H, d, *J* = 15.9 Hz, NCH₂CHCHPh), 7.18 – 7.43 (10H, m, Ar-H).

δ_C (100 MHz, CDCl₃) 52.1 (C-5), 57.3 (NCH₂CHCHPh), 67.3 (C-6), 67.5 (C-3), 73.4 (C-2), 126.2 (Ar-CH), 126.5 (NCH₂CHCHPh), 127.4 (Ar-CH), 127.8 (Ar-CH), 128.16 (Ar-CH), 128.22 (Ar-CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 132.8 (NCH₂CHCHPh), 137.0 (Ar-C), 139.4 (Ar-C).

ν_max/cm⁻¹ 3027 (C-H, aromatic) 2932 (C-H, alkene), 2844 (C-H, alkyl), 1115 (C-O, aliphatic ether), 704 (C-H, aromatic).

*m/z* High Resolution (ESI⁺) found (MH⁺): 280.1698 C₁₉H₂₂NO requires 280.1696.

M.P. 76 – 80 °C.

[α]_D^23 = +62.5 (c = 0.10, MeOH).
(S,E)-4-(But-2-en-1-yl)-3-phenylmorpholine (182e)

The reaction was carried out according to general procedure F with crotyl bromide 115 (0.25 g, 1.84 mmol), morpholine 181e (0.18 g, 1.29 mmol), TBAI (0.84, 0.23 mmol) and sodium hydride (0.074 g, 1.84 mmol). Flash column chromatography (4:1 EtOAc, n-hexanes) gave the title compound (0.11 g, 53%) as a pale yellow oil.

$\delta^H$ (400 MHz, CDCl$_3$) 1.64 (3H, d, $J = 6.0$ Hz, NHCH$_2$CHCH$_3$), 2.30 (1H, td, $J = 3.5, 11.9$ Hz, 5-CH$_3$), 2.44 (1H, dd, $J = 8.0, 13.4$, NCH$_2$CHCH$_3$), 2.95 (1H, dt, $J = 1.9, 11.9$ Hz, 5-CH$_3$), 3.08 – 3.14 (1H, m, NCH$_2$CHCH$_3$), 3.28 (1H, dd, $J = 3.3, 10.3$ Hz, 3-CH), 3.38 (1H, t, $J = 10.6$ Hz, 2-CH$_3$), 3.67 – 3.78 (2H, m, 2-CH$_3$, 6-CH$_3$), 3.87 – 3.93 (1H, m, 6-CH$_3$), 5.34 – 5.52 (2H, m, NCH$_2$CHCH$_3$), 7.22 – 7.39 (5H, m, Ar-H).

$\delta^C$ (100 MHz, CDCl$_3$) 17.8 (NCH$_2$CHCH$_3$), 51.8 (C-5), 57.0 (NCH$_2$CHCH$_3$), 67.2 (C-6), 67.5 (C-3), 73.4 (C-2), 127.1 (Ar-CH), 127.7 (NCH$_2$CHCH$_3$), 128.1 (Ar-CH), 128.5 (NCH$_2$CHCH$_3$), 129.0 (Ar-CH), 139.5 (Ar-C).

$\nu_{\text{max}}$/cm$^{-1}$ 3025 (C-H, aromatic), 2958 (C-H, alkene), 2851 (C-H, alkyl), 1115 (C-O, aliphatic ether), 700 (C-H aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 218.1543 C$_{14}$H$_{20}$NO requires 218.1539.

$[\alpha]_D^{23} = +133.3$ (c = 0.10, MeOH).
(S)-2-Chloro-N-(1-hydroxy-3-phenylpropan-2-yl)acetamide (185f)

The reaction was carried out according to general procedure C with (S)-phenylalaninol 178f (1.0 g, 6.61 mmol) and chloroacetyl chloride 179 (0.74 mL, 9.25 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (1.37 g, 91%) as a white solid.

$\delta_H$ (400 MHz, CDCl$_3$) 1.60 (1H, br s, OH), 2.86 – 2.97 (2H, m, CH$_2$Ph), 3.64 (1H, dd, $J = 4.9, 11.0$ Hz, CH$_3$OH), 3.71 (1H, dd, $J = 3.8, 11.0$ Hz, CH$_2$OH), 4.02 (2H, d, $J = 6.0$ Hz, CH$_2$Cl), 4.16 – 4.25 (1H, m, NHCH), 6.8 (1H, br s, NH), 7.20 – 7.35 (5H, m, Ar-H).

M.P. 69 – 72 °C [lit. 182 82 – 83 °C].

$[\alpha]^20_D = -29.3$ (c = 1.00, MeOH) [lit. 182 $[\alpha]^20_D = -25.9$ (c = 1.00, MeOH)].

Spectroscopic data were in accordance with literature values. 182,189
The reaction was carried out according to general procedure D with chloroacetamide 185f (7.5 g, 32.9 mmol) and sodium hydride (2.64 g, 65.9 mmol). Workup gave the title compound (6.3 g, quant.) as a white solid. An analytical sample was purified by flash column chromatography (1:1 EtOAc, n-hexanes) and the remainder used without further purification.

\[ \delta_H (400 MHz, CDCl_3) \] 2.70 (1H, dd, \( J = 9.0, 13.4 \) Hz, CH\(_2\)Ph), 2.90 (1H, dd, \( J = 5.8, 13.4 \) Hz, CH\(_2\)Ph), 3.57 (1H, dd, \( J = 6.9, 11.7, 6\)-CH\(_{2}\)), 3.73 – 3.81 (1H, m, 5-CH), 3.93 (1H, dd, \( J = 3.7, 11.7 \) Hz, 6-CH\(_{2}\)), 4.18 (2H, d, \( J = 4.0 \) Hz, 2-CH\(_{2}\)), 7.13 – 7.38 (5H, m, Ar-H).

\( \nu_{max}/cm^{-1} \) 3195 (N-H), 3063 (C-H, aromatic), 2921 (C-H, alkyl), 1666 (C=O), 1125 (C-O, ether), 1089 (C-N), 700 (C-H, aromatic).

\( m/z \) High Resolution (ESI\(^+\)) found (MH\(^+\)): 192.1021 \( C_{11}H_{14}NO_2 \) requires 192.1019.

M.P. 87 – 89 °C [lit.\(^{183}\) 86 – 87 °C].

\([\alpha]_D^{22} = +4.2 \) (c = 1.0, MeOH) [lit.\(^{183}\) \([\alpha]_D^{22} = +3.8 \) (c = 1.00, MeOH)].

Spectroscopic data were in accordance with literature values.\(^{183}\)
Experimental

(S)-3-Benzylmorpholine (181f)

The reaction was carried out according to general procedure E with LiAlH₄ (0.1 g, 2.70 mmol) and morpholinone 180f (0.31 g, 1.35 mmol). Vacuum distillation (140 °C, 4 mbar) gave the title compound (0.128 g, 53%) as a yellow oil.

δH (400 MHz, CDCl₃) 1.70 (1H, br s, NH), 2.48 (1H, dd, J = 9.1, 13.4 Hz, 3-CHCH₃Ph), 2.67 (1H, dd, J = 4.9, 13.4 Hz, CHCH₃Ph), 2.80 – 2.91 (2H, m, 5-CH₂), 2.96 – 3.06 (1H, m, 3-CH), 3.28 (1H, t, J = 10.0 Hz, 2-CH₂), 3.54 (1H, td, J = 3.5, 10.7 Hz, 6-CH₃), 3.76 – 3.85 (2H, m, 2-CH₂, 6-CH₂), 7.14 – 7.35 (5H, m, Ar-H).

[α]D²⁰ = -20.5 (c = 0.05, MeOH) [lit.¹³⁸ [α]D²⁰ = -38.2 (c = 0.0566, MeOH)].

Spectroscopic data were in accordance with literature values.¹³⁸
Experimental

(S)-3-Benzyl-4-cinnamylmorpholine (183f)

The reaction was carried out according to general procedure F with cinnamyl bromide 116 (0.32 g, 1.6 mmol), morpholine 181f (0.19 g, 1.07 mmol), TBAI (0.1, 0.27 mmol) and sodium hydride (0.085 g, 2.13 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.25 g, 81%) as a yellow oil.

δH (400 MHz, CDCl3) 2.45 – 2.53 (1H, m, 5-CHa), 2.61 – 2.70 (1H, m, 3-CH), 2.86 (1H, dt, J = 3.7, 8.5 Hz, 5-CHb), 3.08 (1H, dd, J = 3.3, 12.9 Hz, 3-CHCHaPh), 3.28 (1H, dd, J = 7.7, 13.8 Hz, NCH2CHCHPh), 3.40 (1H, dd, J = 6.4, 11.4 Hz, 2-CHb), 3.55 (1H, dd, J = 3.0, 11.4 Hz, 2-CHb), 3.64 (1H, J = 5.8, 13.8 Hz, NCHbCHCHPh), 3.68 – 3.79 (2H, m, 6-CH2), 6.30 (1H, ddd, J = 5.8, 7.7, 15.8 Hz, NCH2CHCHPh), 6.59 (1H, d, J = 15.8 Hz, NHCH2CHCHPh), 7.13 – 7.42 (10H, m, Ar-H).

δC (100 MHz, CDCl3) 32.5 (3-CHCH2Ph), 50.3 (C-5), 56.8 (NCH2CHCHPh), 60.5 (C-3), 67.2 (C-6), 69.8 (C-2), 126.2 (NCH2CHCHPh), 126.3 (2 × Ar-CH), 127.6 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.2 (2 × Ar-CH), 133.2 (NCH2CHCHPh), 136.9 (Ar-C), 139.0 (Ar-C).

νmax/cm⁻¹ 3025 (C-H, aromatic), 2954 (C-H, alkene), 2852 (C-H, alkyl), 1599 (C-C, aromatic), 1118 (C-O, aliphatic ether), 690 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 294.1859 C20H24NO requires 294.1852.

[α]D²⁰ = +36.0 (c = 0.10, MeOH).
The reaction was carried out according to general procedure F with crotyl bromide 115 (0.57 g, 4.2 mmol), morpholine 182f (0.5 g, 2.82 mmol), TBAI (0.26, 0.71 mmol) and sodium hydride (0.34 g, 8.46 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.34 g, 61%) as a yellow oil.

\[ \delta_H \ (400 \text{ MHz, CDCl}_3) \ 1.74 \ (3H, \text{ dd, } J = 1.0, 6.2 \text{ Hz, NCH}_2\text{CHCHCH}_3), \ 2.37 - 2.46 \ (1H, \text{ m, 5-CH}_a), \ 2.53 - 2.63 \ (1H, \text{ m, 3-CHCHPh}), \ 2.65 - 2.73 \ (1H, \text{ m, 3-CH}), \ 2.75 - 2.82 \ (1H, \text{ m, 5-CH}_b), \ 2.99 - 3.11 \ (2H, \text{ m, 2-CH}_a, NCH}_2\text{CHCHCH}_3), \ 3.33 - 3.44 \ (2H, \text{ m, 2-CH}_a, NCH}_2\text{CHCHCH}_3), \ 3.52 \ (1H, \text{ dd, } J = 3.0, 11.5 \text{ Hz, 2-CH}_b), \ 3.66 - 3.78 \ (2H, \text{ m, 6-CH}_2), \ 5.51 - 5.60 \ (1H, \text{ m, NCH}_2\text{CHCHCH}_3), \ 5.64 - 6.74 \ (1H, \text{ m, NCH}_2\text{CHCHCH}_3), \ 7.11 - 7.21 \ (3H, \text{ m, Ar-H}), \ 7.24 - 7.30 \ (2H, \text{ m, Ar-H}). \]

\[ \delta_C \ (100 \text{ MHz, CDCl}_3) \ 17.9 \ (\text{NCH}_2\text{CHCHCH}_3), \ 32.3 \ (\text{3-CHCH}_2\text{Ph}), \ 50.1 \ (\text{C-5}), \ 56.5 \ (\text{NCH}_2\text{CHCHCH}_3), \ 60.3 \ (\text{C-3}), \ 67.4 \ (\text{C-2}), \ 69.8 \ (\text{C-6}), \ 126.1 \ (\text{NCH}_2\text{CHCHCH}_3), \ 127.0 \ (\text{Ar-CH}), \ 128.4 \ (2 \times \text{Ar-CH}), \ 129.2 \ (2 \times \text{Ar-CH}), \ 129.5 \ (\text{NCH}_2\text{CHCHCH}_3), \ 139.2 \ (\text{Ar-C}). \]

\[ \nu_{\text{max/cm}^{-1}} \ 3025 \ (\text{C-H, aromatic}), \ 2957 \ (\text{C-H, alkene}), \ 2854 \ (\text{C-H, alkyl}), \ 1496 \ (\text{C-C, aromatic}), \ 1119 \ (\text{C-O, aliphatic ether}), \ 699 \ (\text{C-H, aromatic}). \]

\[ m/z \ \text{High Resolution (ESI$^+$) found (MH$^+$): 232.1696 C}_{13}\text{H}_{22}\text{NO requires 232.1696.} \]

\[ [\alpha]_{D}^{20} = +40.3 \ (c = 0.10, \text{ MeOH}). \]
(2S,3S)-1-((S)-3-Benzylmorpholino)-2,3-diphenylpent-4-en-1-one (195a’) and (2R,3R)-1-((S)-3-benzylmorpholino)-2,3-diphenylpent-4-en-1-one (195a’’)

To acid 82b (0.028 g, 0.11 mmol) in MeCN (0.25 mL), under an atmosphere of nitrogen at 0 °C, was added DCC (0.025 g, 0.12 mmol) and the mixture stirred for 1 h. A solution of (S)-3-benzylmorpholine 181f (0.02 g, 0.11 mmol) in MeCN (0.25 mL) was added and the mixture stirred overnight at room temperature. The reaction mixture was filtered through a Celite plug with EtOAc (5 mL), and solvent removed in vacuo. Flash column chromatography (3:1 EtOAc, n-hexanes) gave an inseparable mixture of the title compounds (0.025 g, 55%) as a yellow oil.

$\nu_{\text{max}}/\text{cm}^{-1}$ 3061 (C-H, aromatic), 2961 (C-H, alkene), 1634 (C=O), 1117 (C-O, aliphatic ether), 698 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 412.2261 C$_{28}$H$_{30}$NO$_2$ requires 412.2271.
Experimental

(S)-Methyl 2-(2-chloroacetamido)-3-hydroxypropanoate (185g)

To a solution of (S)-serine methyl ester 186 (2 g, 12.9 mmol) and triethylamine (3.92 mL, 2.2 mmol) in DCM (20 mL), under an atmosphere of nitrogen at \(-5 ^\circ C\), was added a solution of chloroacetyl chloride 179 (1.13 mL, 14.1 mmol) in DCM (4 mL) dropwise and the mixture stirred for 1 h, warmed to room temperature and stirred a further 1 h. The reaction mixture was filtered through a Celite plug with EtOAc (30 mL), and solvent removed \textit{in vacuo}. Flash column chromatography (2:1 EtOAc, \(n\)-hexanes) gave the \textit{title compound} (2.3 g, 91%) as a golden oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3) \begin{align*} 2.55 & (1H, \text{ br s, OH}), \ 3.82 & (3H, \text{ s, OCH}_3), \ 3.96 & (1H, \text{ dd, } J = 3.5, 11.4 \ \text{Hz, 3-CH}_a), \ 4.06 & (1H, \text{ dd, } J = 3.5, 11.4 \ \text{Hz, 3-CH}_b), \ 4.11 & (2H, \text{ s, CH}_2\text{Cl}), \ 4.68 & (1H, \text{ dt, } J = 3.6, 7.5 \ \text{Hz, 2-CH}), \ 7.46 & (1H, \text{ br s, NH}). \end{align*} \]

\[ \delta_C (100 \text{ MHz, CDCl}_3) \begin{align*} 42.4 & (\text{CH}_2\text{Cl}), \ 53.0 & (\text{OCH}_3), \ 54.9 & (C-2), \ 62.9 & (C-3), \ 166.6 & (\text{NHC(O)CH}_2\text{Cl}), \ 170.3 & (C-1). \end{align*} \]

\[ \nu_{\text{max}}/\text{cm}^{-1} \begin{align*} 3347 & (\text{O-H}), \ 2955 & (\text{C-H, alkyl}), \ 1738 & (\text{C=O, ester}), \ 1660 & (\text{C=O, amide}), \ 1532 & (\text{N-H}), \ 1215 & (\text{C-O, ester}) \end{align*} \ 1044 \ (\text{C-O, alcohol}). \]

\[ m/z \ \text{High Resolution (ESI\textsuperscript{+}) found (MNa}\textsuperscript{+}): \ 218.0196 \ \text{C}_6\text{H}_{10}\text{Cl}^{25}\text{NNaO}_4 \text{ requires 218.0191, found (MNa}\textsuperscript{+}): \ 220.0166 \ \text{C}_6\text{H}_{10}\text{Cl}^{37}\text{NNaO}_4 \text{ requires 220.0162.} \]

\[ [\alpha]_D^{22} = +34.1 \ (c = 1.0, \text{CH}_2\text{Cl}_2) \ [\text{lit.}^{141} [\alpha]_D^{22} = +30.8 \ (c = 0.945, \text{CH}_2\text{Cl}_2)]. \]

Spectroscopic data were in accordance with literature values.\textsuperscript{141}

[205]
**Methyl 2-(2-chloroacetamido)acrylate (187)**

The reaction was carried out according to general procedure D with chloroacetamide 185g (0.13 g, 0.66 mmol) and sodium hydride (0.032 g, 0.80 mmol). Flash column chromatography gave the *title compound* (0.05 g, 43%) as a yellow oil.

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 3.88 (3H, OCH\textsubscript{3}), 4.12 (2H, s, CH\textsubscript{2}Cl), 5.96 (1H, d, J = 1.5 Hz, 3-CH\textsubscript{a}), 6.65 (1H, s, 3-CH\textsubscript{b}), 8.85 (1H, br s, NH).

δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 42.7 (CH\textsubscript{2}Cl), 53.1 (OCH\textsubscript{3}), 110.0 (C-3), 130.5 (C-2), 164.6 (NHC(O)CH\textsubscript{2}Cl), 170.7 (C-1).

ν\textsubscript{max}/cm\textsuperscript{-1} 2923 (C-H, alkyl), 1738 (C=O, ester), 1664 (C=O, amide). 1517 (N-H), 1400 (C-O, ester).

Spectroscopic data were in accordance with literature values.\textsuperscript{142}
(S)-Methyl 2-((tert-butoxycarbonyl)amino)-3-((tert-butyldimethylsilyl)oxy)propanoate (191)

To a suspension of ester hydrochloride 186 (3 g, 22 mmol) and triethylamine (3.05 mL, 22 mmol) in DCM (50 mL), under an atmosphere of nitrogen, was added di-tert-butyl dicarbonate (4.8 g, 22 mmol) and the mixture stirred at room temperature for 8 h, washed with 1 M aqueous KH2SO4 (20 mL), 1 M aqueous NaHCO3 (20 mL), brine (20 mL) and dried (MgSO4) to give a solution of the intermediate carbamate in DCM. Imidazole (1.87 g, 27.5 mmol) was added followed by tert-butyldimethylsilyl chloride (3.42 g, 22.7 mmol) and the resulting mixture stirred at room temperature for 24 h. Water was then added (20 mL), the organic layer separated and the aqueous layer further extracted with Et2O (3 × 10 mL). The combined organic layers were dried (MgSO4) and solvent removed in vacuo. Flash column chromatography (9:1, n-hexanes, EtOAc) gave the title compound (5.06 g, 69%) as a colourless oil.

δH (400 MHz, CDCl3) 0.03 (6H, d, J = 5.5 Hz, Si(CH3)2), 0.86 (9H, s, Si(CH3)3), 1.46 (9H, s, OC(CH3)3), 3.82 (1H, dd, J = 3.1, 10.1 Hz, 3-CH3), 4.04 (1H, dd, J = 2.6, 10.1 3-CH3), 4.35 (1H, dt, J = 2.6, 8.6, 2-CH), 5.33 (1H, br d, J = 8.2 Hz, NH).

[α]D^20 = +23.4 (c = 1.55, CHCl3) [lit.190 [α]D^20 = +21.6 (c = 1.39, CHCl3)].

Spectroscopic data were in accordance with literature values.191
(R)-tert-Butyl (1-((tert-butyldimethylsilyl)oxy)-3-hydroxypropan-2-yl)carbamate (192a)

To a solution of ester 191 (2 g, 6.0 mmol) in THF (20 mL), under an atmosphere of nitrogen at 0 °C, was added lithium borohydride (0.42 g, 19.2 mmol) portionwise and the resulting mixture stirred for 18 h, quenched by addition of saturated aqueous NH₄Cl (10 mL) and the mixture extracted with EtOAc (3 × 15 mL) The combined organic extracts were washed with saturated aqueous NH₄Cl (10 mL), saturated aqueous NaHCO₃ (10 mL), brine (10 mL), dried (MgSO₄) and solvent removed in vacuo. Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (1.8 g, 98%) as a yellow oil.

δH (400 MHz, CDCl₃) 0.08 (6H, s, Si(CH₃)₂), 0.90 (9H, s, SiC(CH₃)₃), 1.45 (9H, s, OC(CH₃)₃), 2.67 (1H, br s, OH), 3.62 – 3.73 (2H, m, 3-CH₂), 3.77 – 3.87 (3H, m, 1-CH₂, 2-CH), 5.14 (1H, br s, NH).

[α]D²⁶ = +17.5 (c = 0.75, CHCl₃) [lit.¹⁹² [α]D²⁶ = +17.2 (c = 0.75, CHCl₃)].

Spectroscopic data were in accordance with literature values.¹⁹²
To alcohol 192a (1.83 g, 5.99 mmol) in toluene / 30% aqueous solution NaOH (1:1, 36 mL) at 0 °C was added tert-butyl bromoacetate (1.77 mL, 12.0 mmol), TBAI (1.1 g, 2.99 mmol) and the mixture stirred at room temperature for 3 h. The organic layer was separated and the aqueous layer diluted with water (10 mL), extracted with toluene (3 × 10 mL) and the combined organics extracts were washed with 1 M aqueous HCl (10 mL), dried (Na$_2$SO$_4$) and solvent removed in vacuo. Flash column chromatography (14:1 n-hexanes, EtOAc) gave the title compound (2.51 g, quant.) as a pale yellow oil.

δ$_H$ (400 MHz, CDCl$_3$) 0.06 (6H, s, Si(CH$_3$)$_2$), 0.89 (9H, s, Si(C(CH$_3$)$_3$)), 1.44 (9H, s, OC(CH$_3$)$_3$), 1.48 (9H, s, OC(CH$_3$)$_3$). 3.51 – 3.58 (1H, m, 1-CH$_a$), 3.59 (2H, m, 1-CH$_b$, 3-CH$_a$), 3.70 – 3.80 (2H, m, 2-CH, 3-CH$_b$) 3.96 (2H, d, $J$ = 3.3 Hz, OCH$_2$C(O)OC(CH$_3$)$_3$), 5.05 (1H, br s, NH).

δ$_C$ (100 MHz, CDCl$_3$) -5.5 (2×Si(CH$_3$)$_2$), 18.2 (Si(C(CH$_3$)$_3$) 25.9 (3×Si(C(CH$_3$)$_3$)), 28.1, 28.4 (6×C(CH$_3$)$_3$), 51.1 (C-2), 61.5 (C-1), 69.0 (OCH$_2$C(O)OC(CH$_3$)$_3$), 69.9 (C-3), 79.2, 81.7 (2×OC(CH$_3$)$_3$), 154.6 (NHC(O)OC(CH$_3$)$_3$), 169.2 (OCH$_2$C(O)OC(CH$_3$)$_3$).

ν$_{max}$/cm$^{-1}$ 3453 (N-H), 2858 (C-H, alkyl), 1749 (C=O, ester), 1715 (C=O, carbamate), 1130 (C-O, aliphatic ether), 831 (C-H, alkyl), 776 (C-H, alkyl).

$m/z$ High Resolution (ESI$^+$) found (MK$^+$): 458.2341 C$_{20}$H$_{44}$KNO$_6$Si requires 458.2335.

[$\alpha$]$_D^{19}$ = +6.82 (c = 1.01, CHCl$_3$), [$\alpha$]$_D^{22}$ = +8.50 (c = 1.00, MeOH).
(S)-**tert-Butyl 2-(2-((tert-butoxycarbonyl)amino)-3-hydroxypropoxy)acetate (193)**

To ester 189b (2.18 g, 5.17 mmol) in THF (50 mL), under an atmosphere of nitrogen at 0 °C, was added tetrabutylammonium fluoride (2.70 g, 10.34 mmol) and the reaction stirred for 6 h and quenched by addition of saturated aqueous NH$_4$Cl (25 mL). The mixture was extracted with EtOAc (3 × 50 mL), the combined organic extracts washed with saturated aqueous NaHCO$_3$ (20 mL), brine (20 mL), dried (Na$_2$SO$_4$), and solvent removed in vacuo. Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compound (1.58 g, quant.) as a white solid.

$\delta$H (400 MHz, CDCl$_3$) 1.44 (9H, s, OC(CH$_3$)$_3$), 1.48 (9H, s, OC(CH$_3$)$_3$), 3.32 – 3.42 (1H, br s, OH), 3.54 – 3.61 (1H, m, 1-CH$_a$), 3.63 – 3.74 (2H, m, 1-CH$_b$, 3-CH$_a$), 3.76 – 3.84 (1H, m, 2-CH), 3.86 – 3.93 (1H, m, 3-CH$_b$), 3.96 (2H, d, $J = 5.5$ Hz, OCH$_2$C(O)OC(CH$_3$)$_3$), 5.24 (1H, br s, NH).

$\delta$C (100 MHz, CDCl$_3$) 28.1, 28.4 (6 x (OC(CH$_3$)$_3$), 51.3 (C-2), 63.1 (C-3) 68.2 (C-1), 71.0 (OCH$_2$C(O)OC(CH$_3$)$_3$), 79.5, 82.5 (2 x OC(CH$_3$)$_3$), 156.9 (NHC(O)OC(CH$_3$)$_3$) 170.4 (OCH$_2$C(O)OC(CH$_3$)$_3$).

$\nu$ max/cm$^{-1}$: 3492 (N-H), 3401 (O-H), 2880 (C-H, alkyl), 1732 (C=O, ester), 1671 (C=O, carbamate), 1135 (C-O, aliphatic ether), 1050 (C-O, alcohol).

m/z High Resolution (ESI$^+$) found (MNa$^+$): 328.1732 C$_{14}$H$_{27}$NNaO$_6$ requires 328.1731.

M.P. 61 – 64 °C.

$[\alpha]_D^{20} = -8.93$ (c = 1.00, CH$_2$Cl$_2$).
Experimental

(R)-tert-Butyl (1-(benzylxy)-3-hydroxypropan-2-yl)carbamate (192b)

To acid 194 (1.0 g, 3.39 mmol) in THF (30 mL), under an atmosphere of nitrogen at 0 °C, was added LiAlH₄ (0.39 g, 10.2 mmol) and the resulting mixture stirred at room temperature for 18 h, then quenched by careful addition of water at 0 °C until gas evolution ceased. The resulting slurry was filtered through a Celite plug with hot EtOAc (60 mL) and solvent removed in vacuo to give the title compound (0.61 g, 64%) as a white solid that was used without further purification.

δH (400 MHz, CDCl₃) 1.45 (9H, s, OC(CH₃)₃), 2.57 (1H, br s, OH), 3.58 – 3.85 (5H, m, 1-CH₂, 2-CH, 3-CH₂), 4.52 (2H, s, OCH₂Ph), 5.17 (1H, br s, NH), 7.27 – 7.43 (5H, Ar-H).

M.P. 61 – 63 °C [lit.¹⁹⁴ 62 °C].

[α]₂₂° = +13.9 (c = 1.00, CHCl₃) [lit.¹⁹⁴ [α]₂⁴° = +13.1 (c = 1.00, CHCl₃)].

Spectroscopic data were in accordance with literature values.¹⁹⁴
**Experimental**

(S)-**tert**-Butyl 2-(3-(benzyloxy)-2-((**tert**-butoxycarbonyl)amino)propoxy)acetate (189c)

![Chemical Structure](image)

**Method A:** To alcohol 193 (0.5 g, 1.65 mmol) in toluene / 30% aqueous NaOH (1:1, 10 mL) at 0 °C was added benzyl bromide (0.4 mL, 3.3 mmol) and TBAI (0.24 g, 0.825 mmol). The mixture was stirred at room temperature for 3 h, diluted with water (10 mL) and extracted with toluene (3 × 10 mL). The combined organic extracts were washed with 1 M aqueous HCl (5 mL), brine (5 mL), dried (Na₂SO₄) and solvent removed in vacuo. Flash column chromatography (9:1, n-hexanes, EtOAc) gave the title compound (0.470 g, 72%) as a yellow oil.

δ_H (400 MHz, CDCl₃) 1.44 (9H, s, OC(CH₃)₃), 1.48 (9H, s, OC(CH₃)₃), 3.51 – 3.72 (4H, m, 1-CH₂, 3-CH₂), 3.93 (1H, br s, 2-CH), 3.95 (2H, d, J = 3.3 Hz, OCH₂C(O)OC(CH₃)₃), 4.54 (2H, s, OCH₂Ph), 5.13 (1H, br s, NH).

δ_C (100 MHz, CDCl₃) 28.1 (OC(CH₃)₃), 49.8 (C-2), 68.8 (C-3), 69.0 (OCH₂C(O)C(CH₃)₃), 70.3 (C-1), 73.2 (OCH₂Ph), 79.8, 82.5 (2 × OC(CH₃)₃), 127.6 (Ar-CH), 128.3 (Ar-CH), 138.6 (Ar-C), 155.5 (NHC(O)OC(CH₃)₃), 168.6 (OCH₂C(O)C(CH₃)₃).

[α]_D^23 = +7.35 (c = 1.00, CH₂Cl₂).

Spectroscopic data were in accordance with literature values.¹⁹⁵

![Chemical Structure](image)

**Method B:** To alcohol 192b (0.9 g, 3.20 mmol) in toluene / 30% aqueous NaOH (1:1, 18 mL) at 0 °C was added **tert**-butylbromoacetate (0.95 mL, 6.40 mmol) and TBAI (0.59 g, 1.6 mmol). The mixture was stirred at room temperature for 3 h, diluted with water (15 mL) and extracted with toluene (3 × 20 mL). The combined organic extracts were washed with 1 M aqueous HCl (10 mL), brine (10 mL), dried (Na₂SO₄) and solvent removed in vacuo. Flash column chromatography (9:1 n-hexanes, EtOAc) gave the title compound (1.08 g, 85%) as a yellow oil. Spectroscopic data was in accordance with the previous procedure.
(S)-**tert-**Butyl (1-(benzyloxy)-3-(2-hydroxyethoxy)propan-2-yl)carbamate (190b)

To a solution of ester 189c (0.45 g, 1.13 mmol) in Et2O (15 mL), under an atmosphere of nitrogen at 0 °C, was added LiAlH4 (0.13 g, 3.41 mmol). The mixture was stirred for 6 h, quenched by careful addition of water at 0 °C, until gas evolution ceased, filtered through a Celite plug with EtOAc (30 mL) and solvent removed in vacuo. Flash column chromatography (2:1, n-hexanes, EtOAc) gave the *title compound* (0.35 g, 96%) as a pale yellow oil.

δH (400 MHz, CDCl3) 1.44 (9H, s, OC(CH3)3), 2.13 (1H, br s, OH), 3.48 – 3.66 (6H, m, 1-CH2, 3-CH2, OCH2CH2OH), 3.66 – 3.72 (2H, m, OCH2CH2OH), 3.94 (1H, br s, 2-CH), 4.52 (2H, s, OCH2Ph), 4.94 (1H, br s, NH), 7.27 – 7.39 (5H, m, Ar-H).

δC (100 MHz, CDCl3) 28.4 (OC(CH3)3), 49.7 (C-2), 61.8 (OCH2CH2OH), 68.9, 70.2, 72.3 (C-1, C-3, OCH2CH2OH), 73.3 (OCH2Ph), 79.5 (OC(CH3)3), 127.7 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 138.1 (Ar-C), 156.6 (C=O).

νmax/cm⁻¹ 3340 (O-H), 2975 (C-H, aromatic), 2867 (C-H, alkyl), 1690 (C=O), 1121 (C-O, aliphatic ether), 1057 (C-O, alcohol), 697 (C-H, aromatic).

*m/z* High Resolution (ESI⁺) found (MH⁺): 348.1790 C₁₇H₂₇NNaO₅ requires 348.1781.

[α]D²⁰ = +10.5 (c = 1.00, CH₂Cl₂).
(S)-2-(3-(Benzyloxy)-2-((tert-butoxycarbonyl)amino)propoxy)ethyl methanesulfonate (201)

To alcohol 190b (0.6 g, 1.84 mmol) in DCM (30 mL), under an atmosphere of nitrogen at -30 °C, was added triethylamine (0.77 mL, 5.53 mmol) and mesyl chloride (0.21 mL, 2.77 mmol). The resulting mixture was stirred at room temperature for 2 h, diluted with DCM (30 mL), washed with water (20 mL), 1 M aqueous HCl (10 mL), saturated aqueous NaHCO₃ (10 mL), brine (10 mL), dried (Na₂SO₄) and solvent removed in vacuo. Flash column chromatography (19:1 DCM, EtOAc) gave the title compound (0.74 g, quant.) as a yellow oil.

δₓ (400 MHz, CDCl₃) 1.44 (9H, s, OC(CH₃)₃), 3.00 (3H, s, SCH₃), 3.47 – 3.66 (4H, m, 1-CH₂, 3-CH₂), 3.69 – 3.72 (2H, m, OCH₂CH₂OSO₂CH₃), 3.92 (1H, br s, 2-CH), 4.30 – 4.35 (2H, m, OCH₂CH₂OSO₂CH₃), 4.52 (2H, s, OCH₂Ph), 4.92 (1H, br s, NH), 7.27 – 7.39 (5H, m, Ar-H).

δₓ (100 MHz, CDCl₃) 28.4 (OC(CH₃)₃), 37.6 (SCH₃), 49.7 (C-2), 66.7, 70.1 (C-1, C-3), 66.8 (OCH₂CH₂OSO₂CH₃), 73.2 (OCH₂Ph), 79.5 (OC(CH₃)₃), 127.7 (Ar-CH), 127.8 (Ar-CH), 129.4 (Ar-CH), 138.1 (Ar-C) 155.5 (C=O).

νₓ/cm⁻¹ 3389 (O-H), 2975 (C-H, aromatic), 2870 (C-H, alkyl), 1705 (C=O), 1170 (C-O, aliphatic ether), 917 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MNa⁺): 426.1558 C₁₈H₁₉NNaO₇S requires 426.1557.

[α]₂₃ = +5.87 (c = 1.00, CH₂Cl₂).
(S)-3-((Benzyloxy)methyl)morpholine (181g)

To N-Boc mesylate 201 (0.66 g, 1.6 mmol) in DCM (11 mL) at 0 °C was added TFA (2.54 mL) and the solution stirred at room temperature for 1 h. Solvent was removed in vacuo, saturated aqueous NaHCO₃ (5 mL) was added and the aqueous layer extracted with DCM (3 x 11 mL), dried (Na₂SO₄) and solvent removed under reduced pressure. The crude amine salt (0.5 g, quant.) was used immediately without purification.

To a solution of the mesylate salt (0.5 g, 1.65 mmol) in MeOH (20 mL) was added iPr₂NEt (0.86 mL, 4.94 mmol) and the resulting mixture stirred at 80 °C for 4 h, cooled to room temperature and solvent removed in vacuo. Gradient elution flash column chromatography (100% DCM to 9:1 DCM, MeOH) gave the title compound (0.34 g, quant.) as a yellow oil.

δ_H (400 MHz, CDCl₃) 3.00 – 3.08 (1H, m, 5-CH₃), 3.15 (1H, dt, J = 2.6, 12.6, 5-CH₆), 3.26 – 3.33 (1H, m, 3-CH), 3.50 – 3.60 (3H, m, NHCHCH₂OCH₂Ph, 2-CH₃), 3.65 – 3.67 (1H, m, 6-CH₃), 3.80 – 3.92 (2H, m, 2-CH₂, 6-CH₂), 4.53 (2H, d, J = 2.0 Hz, OCH₂Ph), 7.25 – 7.38 (5H, m, Ar-H).

δ_C (100 MHz, CDCl₃) 44.0 (C-5), 54.1 (C-3), 65.4 (C-6), 67.4 (C-2), 68.1 (3-CHCH₂OCH₂Ph), 73.5 (OCH₂Ph), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.5 (Ar-CH), 137.4 (Ar-C).

υ_max/cm⁻¹ 3422 (N-H), 2860 (C-H, alkyl), 1673 (C-C, aromatic), 1453 (C=C, aromatic), 1041 (C-O).

m/z High Resolution (ESI⁺) found (MH⁺): 208.1340 C₁₂H₁₈NO₂ requires 208.1332.

[α]_D^22 = +6.0 (c = 1.00, CH₂Cl₂) [lit.¹⁹⁶ [α]_D^22 = +5.6 (c = 1.00, CH₂Cl₂)*].

[215]
Brown et al. report a value of \([\alpha]_{D}^{(R)} = 5.6\) for \((R)-\text{181g}\) and a value of \([\alpha]_{D}^{(S)} = -6.0\) for \((S)-\text{181g}\). We believe a transposition of these values has occurred in publication as our value is \([\alpha]_{D}^{(S)} = 6.0\) for \((S)-\text{181g}\) and it would appear unlikely that full inversion of this centre could have taken place in the procedures following the last literature \([\alpha]_{D}\) value.\(^{196}\)
Experimental

\((S)-3-((\text{Benzyloxy})\text{methyl})-4-\text{cinnamylmorpholine (183g)}\)

The reaction was carried out according to general procedure F with cinnamyl bromide 116 (0.14 g, 0.72 mmol), morpholine 181g (0.10 g, 0.48 mmol), TBAI (0.044, 0.12 mmol) and sodium hydride (0.038 g, 0.96 mmol). Flash column chromatography (1:1 EtOAc, n-hexanes) gave the title compound (0.052 g, 34%) as a yellow oil.

\(\delta_H\) (400 MHz, CDCl\(_3\)) 2.37 – 2.45 (1H, m, 5-CH\(_a\)), 2.63 – 2.71 (1H, m, 3-CH), 2.80 (1H, dt, \(J = 3.1, 11.9\) Hz, 5-CH\(_b\)) 3.13 (1H, dd, \(J = 7.9, 14.0\) Hz, NCH\(_2\)CHCHPh), 3.49 – 3.70 (5H, m, NCH\(_b\)CHCHPh, 3-CHCH\(_2\)OCH\(_2\)Ph, 2-CH\(_a\), 6-CH\(_b\)), 3.74 – 3.84 (2H, m, 2-CH\(_b\), 6-CH\(_b\)), 4.52 (2H, d, \(J = 3.0\) Hz, OCH\(_2\)Ph), 6.27 (1H, ddd, \(J = 5.7, 7.7, 15.9\) Hz, NCH\(_2\)CHCHPh), 6.48 (1H, d, \(J = 15.9\) Hz, NCH\(_2\)CHCHPh), 7.20 – 7.39 (10H, m, Ar-H).

\(\delta_C\) (100 MHz, CDCl\(_3\)) 51.2 (C-5), 56.9 (NCH\(_2\)CHCHPh), 59.5 (C-3), 67.1 (C-6), 67.9 (3-CHCH\(_2\)OCH\(_2\)Ph), 69.5 (C-2), 73.4 (OCH\(_2\)Ph), 126.3 (NCH\(_2\)CHCHPh), 127.5 (Ar-CH), 127.7 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 128.6 (Ar-CH), 133.1 (NCH\(_2\)CHCHPh), 136.3 (Ar-C), 137.2 (Ar-C).

\(\nu_{\text{max}}/\text{cm}^{-1}\) 3030 (C-H, aromatic), 2950 (C-H, alkene), 2854 (C-H, alkyl), 1122 (C-O, aliphatic ether), 735 (C-H, aromatic), 693 (C-H, aromatic).

\(m/z\) High Resolution (ESI\(^+\)) found (MH\(^+\)): 324.1963 C\(_{21}\)H\(_{26}\)NO\(_2\) requires 324.1958.

\([\alpha]\)\(_D\) = +54.0 (\(c = 0.10\), MeOH).
Experimental

**(S,E)-4-Cinnamyl-3-(hydroxymethyl)morpholine (183i)**

To a solution of ether 183g (0.16 g, 0.49 mmol) in DCM (20 mL), under an atmosphere of nitrogen at 0 °C, was added a 1 M solution of boron trichloride in DCM (0.99 mL, 0.99 mmol) and the resulting mixture stirred at room temperature for 3 h. Methanol (10 mL) was added and the solvent removed *in vacuo*. The residue was taken up in DCM (20 mL), basified with triethylamine (2 mL) and solvent removed *in vacuo*. Flash column chromatography (100% EtOAc) gave the *title compound* (0.10 g, 88%) as a pale orange solid.

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{) } 2.14 \text{ (1H, br s, OH), 2.49 (1H, ddd, } J = 3.2, 10.2, 12.0 \text{ Hz, 5-CH}_a,\]
\[ 2.54 \text{ – 2.60 (1H, m, 3-CH), 2.92 (1H, dt, } J = 2.8, 12.0 \text{ Hz, 5-CH}_b,\]
\[ 3.11 \text{ (1H, ddd, } J = 0.7, 8.1, 13.7 \text{ Hz, NCH}_a\text{CHCHPh), 3.49 (1H, dd, } J = 2.4, 11.4 \text{ Hz, 3-CHCH}_a\text{OH), 3.56 (3H, m, 2-CH}_a,\]
\[ 6-\text{CH}_a, \text{ NCH}_b\text{CHCHPh), 3.78 \text{ – 3.85 (2H, m, 2-CH}_b, 6-\text{CH}_b,\]
\[ 3.92 (1H, dd, } J = 4.6, 11.4 \text{ Hz, 3-CHCH}_b\text{OH), 6.25 (1H, ddd, } J = 5.5, 8.1, 15.9 \text{ Hz, NCH}_2\text{CHCHPh), 6.56 (1H, d, } J = 15.9 \text{ Hz, NCH}_2\text{CHCHPh), 7.19 \text{ – 7.43 (5H, m, Ar-H).}\]

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{) } 50.7 \text{ (C-5), 56.1 (NCH}_2\text{CHCHPh), 59.1 (3-CHCH}_2\text{OH), 59.6 (C-3),}\]
\[ 66.7 \text{ (C-6), 68.4 (C-2), 125.6 (NCH}_2\text{CHCHPh), 126.3 (Ar-CH), 127.7 (Ar-CH), 128.6 (Ar-CH), 133.6 (NCH}_2\text{CHCHPh), 133.6 (Ar-C).}\]

\[ \nu_{\text{max/cm}}^ {-1} \text{ 3158 (O-H), 2950 (C-H, alkene), 2854 (C-H, alkyl), 1077 (C-O, alcohol), 741 (C-H, aromatic).}\]

\[ m/z \text{ High Resolution (ESI') found (MH')}: 234.1495 \text{ C}_{14}\text{H}_{20}\text{NO}_2 \text{ requires 234.1489.}\]

M.P. 73 – 75 °C.

\[ [\alpha]_D^{23} = +91.2 \text{ (c = 0.10, CHCl}_3\text{).}\]
(S)-4-Cinnamyl-3-(methoxymethyl)morpholine (183h)

To a solution of alcohol 183h (0.08 g, 0.34 mmol) in THF (8 mL) at 0 °C, under an atmosphere of nitrogen, was added NaH (0.028 g, 0.69 mmol) and the mixture stirred for 10 min followed by addition of MeI (0.024 mL, 0.38 mmol) dropwise and the resulting solution stirred at room temperature overnight. Ice (10 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (MgSO₄) and solvent removed under reduced pressure. Flash column chromatography (3:1 EtOAc, n-hexanes) gave the title compound (0.088 g, quant.) as a yellow oil.

δH (400 MHz, CDCl₃) 2.41 (1H, ddd, J = 3.4, 9.7, 12.0 Hz, 5-CH₃), 2.57 – 2.65 (1H, m, 3-CH), 2.82 (1H, dd, 3.0, 12.0 Hz, 5-CH₃), 3.13 (1H, ddd, 0.7, 7.9, 14.0 Hz, NCH₂CHCHPh), 3.34 (3H, s, OCH₃), 3.45 – 3.58 (3H, m, 2-CH₃, 3-CHCH₂OCH₃), 3.60 – 3.69 (2H, m, 6-CH₃, NCH₂CHCHPh), 3.75 – 3.84 (2H, m, 2-CH₃, 6-CH₃), 6.29 (1H, ddd, J = 5.7, 7.8, 15.8 Hz, NCH₂CHCHPh), 6.54 (1H, d, J = 15.8 Hz, NCH₂CHCHPh), 7.20 – 7.40 (5H, m, Ar-H).

δC (100 MHz, CDCl₃) 51.3 (C-5), 56.9 (NCH₂CHCHPh), 59.2 (OCH₃), 59.6 (C-3), 67.1 (C-6), 69.4 (C-2), 70.7 (3-CHCH₂OCH₃), 126.3 (NCH₂CHCHPh, Ar-CH), 127.5 (Ar-CH), 128.6 (Ar-CH), 133.1 (NCH₂CHCHPh), 136.9 (Ar-C).

νmax/cm⁻¹ 3026 (C-H, aromatic), 2956 (C-H, alkene), 2849 (C-H, alkyl), 1121 (C-O, aliphatic ether), 1106 (C-H, aliphatic ether), 693 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MH⁺): 248.1652 C₁₅H₂₂NO₂ requires 248.1645.

[α]D²¹⁰ = +68.0 (c = 0.10, MeOH).
Experimental

\((S,E)-3-(\text{Benzzyloxy)methyl})-4-(\text{but-2-en-1-yl})\text{morpholine (182g)}\)

The reaction was carried out according to general procedure F with crotyl bromide (0.13 g, 0.96 mmol), morpholine 181g (0.10 g, 0.48 mmol), TBAI (0.044, 0.12 mmol) and sodium hydride (0.039 g, 0.12 mmol). Flash column chromatography (1:1 EtOAc, \(n\)-hexanes) gave the title compound (0.11 g, 81%) as a yellow oil.

\(\delta_H\) (400 MHz, CDCl\(_3\)) 1.67 (3H, d, \(J = 5.9\) Hz, NCH\(_2\)CHCHCH\(_3\)), 2.29 – 2.37 (1H, m, 5-CH\(_a\)), 2.56 – 2.64 (1H, m, 3-CH), 2.72 (1H, dt, \(J = 3.2, 11.9\) Hz, 5-CH\(_b\)), 2.90 (1H, dd, \(J = 7.3, 13.5\) Hz, NCH\(_2\)CHCHCH\(_3\)), 3.34 (1H, dd, \(J = 5.7, 13.5\) Hz, NCH\(_2\)CHCHCH\(_3\)), 3.43 – 3.56 (3H, m, 3-CHCH\(_2\)OCH\(_2\)Ph, 2-CH\(_a\)), 3.59 – 3.67 (1H, m, 6-CH\(_a\)), 3.71 – 3.83 (2H, m, 2-CH\(_b\), 6-CH\(_b\)), 4.49 (2H, d, \(J = 4.7\) Hz, OCH\(_2\)Ph), 5.43 – 5.62 (2H, m, NCH\(_2\)CHCHCH\(_3\)), 7.24 – 7.38 (5H, m, Ar-H).

\(\delta_C\) (100 MHz, CDCl\(_3\)) 17.8 (NCH\(_2\)CHCHCH\(_3\)), 50.8 (C-5), 56.5 (NCH\(_2\)CHCHCH\(_3\)), 59.1 (C-3), 67.1 (C-6), 67.8 (3-CHCH\(_2\)OCH\(_2\)Ph), 69.5 (C-2), 73.4 (OCH\(_2\)Ph), 126.9 (NCH\(_2\)CHCHCH\(_3\)), 127.7 (Ar-CH), 128.4 (Ar-CH), 129.4 (NCH\(_2\)CHCHCH\(_3\)), 138.0 (Ar-C).

\(\nu_{\text{max}}/\text{cm}^{-1}\) 3028 (C-H, aromatic), 2956 (C-H, alkene), 2854 (C-H, alkyl), 1122 (C-O, aliphatic ether), 1097 (C-O, aliphatic ether), 697 (C-H, aromatic).

\(m/z\) High Resolution (ESI\(^+\)) found (MH\(^+\)): 262.1809 C\(_{16}\)H\(_{24}\)NO\(_2\) requires 262.1802.

\([\alpha]_D^{23} = +46.1\) (\(c = 0.10,\) MeOH).
To a solution of ether 182g (0.15 g, 0.57 mmol) in DCM (20 mL), under an atmosphere of nitrogen at 0 °C, was added a 1 M solution of boron trichloride in DCM (1.14 mL, 1.14 mmol) and the resulting mixture stirred at room temperature for 3 h. MeOH (10 mL) was added and the solvent removed in vacuo. The residue was taken up in DCM (20 mL), basified with triethylamine (2 mL) and solvent removed in vacuo. Flash column chromatography (100% EtOAc) gave the title compound (0.097 g, 99%) as a yellow oil.

δH (400 MHz, CDCl3) 1.71 (3H, d, J = 6.5 Hz, NCH2CHCH3), 2.37 – 2.45 (1H, m, 5-CHa), 2.46 – 2.52 (1H, m, 3-CH), 2.82 – 2.92 (2H, m, NCH2CHCHCH3, 5-CHb), 3.38 – 3.46 (2H, m, NCHbCHCHCH3, 3-CHCH2OH), 3.52 – 3.65 (2H, m, 2-CHa, 6-CHa), 3.75 – 3.82 (2H, m, 2-CHb, 6-CHb), 3.86 (1H, dd, J = 4.5, 11.5 Hz, 3-CHCH2OH), 5.44 – 5.53 (1H, m, NCH2CHCHCH3), 5.59 – 5.70 (1H, m, NCH2CHCHCH3).

δC (100 MHz, CDCl3) 17.9 (NCH2CHCHCH3), 50.4 (C-5), 55.7 (NCH2CHCHCH3), 59.0 (3-CHCH2OH), 59.3 (C-3), 66.7 (C-6), 68.4 (C-2), 126.6 (NCH2CHCHCH3), 129.8 (NCH2CHCHCH3).

νmax/cm⁻¹ 3368 (O-H), 2955 (C-H, alkene), 2915 (C-H, alkene), 2849 (C-H, alkyl), 1173 (C-O, ether).

m/z High Resolution (ESI⁺) found (MH⁺): 172.1338 C9H18NO2 requires 172.1332.

[α]D²⁰ = +63.2 (c = 0.10, MeOH).
Experimental

(S,E)-4-(But-2-en-1-yl)-3-(methoxymethyl)morpholine (182h)

To a solution of alcohol 182i (0.07 g, 0.41 mmol) in THF (8 mL) at 0 °C, under an atmosphere of nitrogen, was added NaH (0.032 g, 0.81 mmol) and the mixture stirred 10 min followed by addition of MeI (0.028 mL, 0.45 mmol) dropwise) and the resulting solution stirred at room temperature overnight. Ice (8 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (MgSO₄) and solvent removed under reduced pressure. Flash column chromatography (2:1 EtOAc, n-hexanes) gave the title compound (0.05 g, 65%) as a yellow oil.

δ_H (400 MHz, CDCl₃) 1.70 (3H, dd, J = 0.80, 6.0, NCH₂CHCH.CH₃), 2.34 (1H, ddd, J = 3.4, 9.7, 12.0 Hz, 5-CH₃), 2.51 – 2.57 (1H, m, 3-CH), 2.74 (1H, dt, J = 3.0, 12.0 Hz, 5-CH₆), 2.92 (1H, dd, J = 7.5, 13.5 Hz, NCH₆CHCHCH₃), 3.33 (3H, s, OCH₃), 3.38 (1H, ddt, J = 1.3, 5.6, 13.5 Hz, NCH₆CHCHCH₃), 3.44 (2H, d, J = 4.6 Hz, 3-CHCH₂OCH₃), 3.52 (1H, dd, J = 8.9, 11.2 Hz, 2-CH₃), 3.64 (1H, ddd, J = 2.6, 9.8, 12.3 Hz, 6-CH₃), 3.78 (2H, m, 2-CH₆b, 6-CH₆b), 5.47 – 5.56 (1H, m, NCH₂CHCHCH₃), 5.57 – 5.69 (1H, m, NCH₂CHCHCH₃).

δ_C (100 MHz, CDCl₃) 17.8 (NCH₂CHCHCH₃), 50.9 (C-5), 56.4 (NCH₂CHCHCH₃), 59.1 (C-3), 59.2 (OCH₃), 67.1 (C-6), 69.4 (C-2), 70.5 (3-CHCH₂OCH₃), 126.8 (NCH₂CHCHCH₃), 129.4 (NCH₂CHCHCH₃).

ν_max/cm⁻¹ 2923 (C-H, alkene), 2854 (C-H, alkyl), 1121 (C-O, aliphatic ether), 965 (C-H, alkyl).

m/z High Resolution (ESI⁺) found (MH⁺): 186.1495 C₁₀H₂₀NO₂ requires 186.1489.

[a]_D = +66.0 (c = 0.10, MeOH).
**Asymmetric acyl-Claisen derived amides**

Characterisation of pseudoenantiomeric amides is provided below. Due to difficulty assigning residues in the $^1$H and $^{13}$C NMR experiments (with the aid of 2D experiments) brought about by the combination of rotamers and diastereomers these data have been omitted. High resolution mass spectrometry, FTIR spectroscopy and the HPLC retention times (CHIRALPAK IA analytical column (250 mm x 4.6 mm)) have been provided.

$\begin{align*}
(2S,3S)-1-((S)-3\text{-benzylmorpholino})-2,3\text{-diphenylpent-4-en-1-one (195a')} \text{ and } (2R,3R)-1-((S)-3\text{-benzylmorpholino})-2,3\text{-diphenylpent-4-en-1-one (195'')} \\
\end{align*}$

The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.11 g, 0.341 mmol), (S)-3-benzyl-4-cinnamylmorpholine 183f (0.1 g, 0.341 mmol), iPr$_2$NEt (0.089 mL, 0.511 mmol) and phenylacetyl chloride 31b (0.054 mL, 0.409 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the *title compounds* (0.14 g, 98%) as a yellow oil. Further analysis by HPLC determined the ratio to be 21:79.

$\nu_{\text{max}}/\text{cm}^{-1}$ 3061 (C-H, aromatic), 2961 (C-H, alkene), 1634 (C=O), 1117 (C-O, aliphatic ether), 698 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 412.2261 $\text{C}_{28}\text{H}_{30}\text{NO}_2$ requires 412.2271.

HPLC: 9:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; $r_i = 11$ min, 2.88 s; 12 min, 16.2 s.
(2R,3S)-2,3-Dimethyl-1-(((S)-3-methylmorpholino)pent-4-en-1-one (195b’) and (2S,3R)-2,3-dimethyl-1-(((S)-3-methylmorpholino)pent-4-en-1-one (195b”)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.13 g, 0.4 mmol), (S,E)-4-(but-2-en-1-yl)-3-methylmorpholine 182a (0.06 g, 0.4 mmol), iPr₂NEt (0.105 mL, 0.6 mmol) and propionyl chloride 31a (0.042 mL, 0.48 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave the title compounds (0.03 g, 40%) as a yellow oil.

νmax/cm⁻¹: 2970 (C-H, alkene), 1631 (C=O), 1266 (C-H, methyl), 1134 (C-O, aliphatic ether).

m/z High Resolution (ESI⁺) found (MH⁺): 212.1651, C₁₂H₂₂NO₂ requires 212.1645.

These diastereomers were inseparable by HPLC.

HPLC:

9:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; tᵣ = 6 min, 53.88 s.

19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; tᵣ = 9 min, 0.24 s.

19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; tᵣ = 19 min, 47.1s.
Experimental

(2S,3S)-1-((S)-3-Methylmorpholino)-2,3-diphenylpent-4-en-1-one (195c’) and (2R,3R)-1-((S)-3-methylmorpholino)-2,3-diphenylpent-4-en-1-one (195c”)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.13 g, 0.4 mmol), (S)-4-cinnamyl-3-methylmorpholine 183a (0.09 g, 0.4 mmol), iPr₂NEt (0.105 mL, 0.6 mmol) and phenylacetyl chloride 31b (0.063 mL, 0.48 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.028 g, 21%) as a pale cream amorphous solid. Further analysis by HPLC determined the ratio to be 57:43.

ν<sub>max</sub>/cm<sup>-1</sup> 3029 (C-H, aromatic), 2976 (C-H, alkene), 1628 (C=O), 1269 (C-H, methyl), 1129 (C-O, aliphatic ether), 698 (C-H, aromatic).

m/z High Resolution (ESI<sup>+</sup>) found (MK⁺): 374.1531 C₂₂H₂₅KNO₂ requires 374.1517.

HPLC: 9:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; t<sub>i</sub> = 9 min, 0.48 s; 12 min, 21.9 s.
Experimental

(2R,3S)-1-((S)-3-isopropylmorpholino)-2,3-dimethylpent-4-en-1-one (195d’)
and (2S,3R)-1-((S)-3-isopropylmorpholino)-2,3-dimethylpent-4-en-1-one (195d’’)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.13 g, 0.4 mmol), (S,E)-4-(but-2-enyl)-3-isopropylmorpholine 182b (0.073 g, 0.4 mmol), iPr₂NEt (0.105 mL, 0.6 mmol) and propionyl chloride 31a (0.042 mL, 0.48 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) followed by washing with 1 M aqueous HCl (5 mL) gave an inseparable mixture of the title compounds (0.05 g, 47%) as a yellow oil. Further analysis by HPLC determined the ratio to be 34:66.

νmax/cm⁻¹: 2965 (C-H, alkene), 1631 (C=O), 1261 (C-H, methyl), 1127 (C-O, aliphatic ether).

m/z: High Resolution (ESI⁺) found (MH⁺): 240.1957 C₁₄H₂₆NO₂ requires 240.1958.

HPLC: 99:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; rt = 14 min, 8.52 s; 15 min, 39.72 s.
Experimental

\((2R,3S)-1-((S)-3\text{-isobutylmorpholino})-2,3\text{-dimethylpent-4-en-1-one} \ (195') \) and \((2S,3R)-1-((S)-3\text{-isobutylmorpholino})-2,3\text{-dimethylpent-4-en-1-one} \ (195'')\)

The reaction was carried out according to general procedure B with TiCl\(_4\)·2THF (0.13 g, 0.4 mmol), \((S,E)-4\text{-}(\text{but-2-en-1-yl})\text{-3-isobutylmorpholine} \ 182c \ (0.08 \text{ g, 0.4 mmol}), \ \iPr\text{NEt} \ (0.105 \text{ mL, 0.6 mmol}) \) and propionyl chloride \(31a \ (0.042 \text{ mL, 0.48 mmol})\). Flash column chromatography (3:1 \(n\text{-hexanes, EtOAc}\)) gave an inseparable mixture of the \textit{title compounds} (0.08 g, 80\%) as a golden oil. Further analysis by HPLC determined the ratio to be 35:65.

\(\nu_{\max}/\text{cm}^{-1} \ 2959 \ (\text{C-H, alkene}), \ 1633 \ (\text{C}=\text{O}), \ 1266 \ (\text{C-H, methyl}), \ 1136 \ (\text{C-O, aliphatic ether}).\)

\(m/z\) High Resolution (ESI\(^+\)) found (MH\(^+\)) 254.2119 \(\text{C}_{15}\text{H}_{28}\text{NO}_2\) requires 254.2115.

HPLC: 9:1 \(n\text{-hexanes, } \iPrOH; 0.8 \text{ mL/min; 254 nm; 20 } \mu\text{L; } r_t = 5 \text{ min, 43.86 s; 6 min, 9.78 s.} \)
Experimental

(2S,3S)-1-((S)-3-Isobutylmorpholino)-2,3-diphenylpent-4-en-1-one (195g’) and (2R,3R)-
1-((S)-3-isobutylmorpholino)-2,3-diphenylpent-4-en-1-one (195g”)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.13 g, 0.4
mmol), (S)-4-cinnamyl-3-isobutylmorpholine 183c (0.1 g, 0.4 mmol), iPr₂NEt (0.105 mL, 0.6
mmol) and phenylacetyl chloride 31b (0.074 mL, 0.48 mmol). Flash column chromatography
(3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.11 g, 71%) as
a pale yellow oil that partially solidified on standing at 0 °C. Further analysis by HPLC
determined the ratio to be 75:25.

ν_max/cm⁻¹ 3029 (C-H, aromatic), 2959 (C-H, alkene), 1631 (C=O), 1135 (C-O, aliphatic
ether), 697 (C-H, aromatic).


HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 μL; r_t = 12 min, 43.98 s; 14 min,
12.72 s.
Experimental

(2R,3S)-1-((S)-3-((S)-Secbutyl)morpholino)-2,3-dimethylpent-4-en-1-one (195h') and (2S,3R)-1-((S)-3-((S)-secbutyl)morpholino)-2,3-dimethylpent-4-en-1-one (195h'')

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.13 g, 0.4 mmol), (S,E)-4-(but-2-en-1-yl)-3-isobutylmorpholine 182d (0.08 g, 0.4 mmol), iPr₂NEt (0.105 mL, 0.6 mmol) and propionyl chloride 31a (0.042 mL, 0.48 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) followed by washing with 1 M aqueous HCl (5 mL) gave an inseparable mixture of the title compounds (0.024 g, 24%) as a golden oil.

ν_max/cm⁻¹: 2966 (C-H, alkene), 1626 (C=O), 1259 (C-H, methyl), 1110 (C-O, aliphatic ether).

m/z High Resolution (ESI⁺) found (MH⁺): 254.2117 C₁₅H₂₈NO₂ requires 254.2115.

HPLC analysis was inconclusive giving five peaks of ration 13:20:9:9:49.

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; r₁ = 7 min, 15.84 s; 8 min, 2.34 s; 8 min, 42.54 s; 9 min, 7.32 s; 9 min, 52.8 s.
Experimental

(2R,3S)-2,3-Dimethyl-1-((S)-3-phenylmorpholino)pent-4-en-1-one (195j’) and (2S,3R)-2,3-dimethyl-1-((S)-3-phenylmorpholino)pent-4-en-1-one (195j’’)

The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.13 g, 0.4 mmol), (S,E)-4-(but-2-en-1-yl)-3-phenylmorpholine 182e (0.09 g, 0.4 mmol), iPr$_2$NEt (0.105 mL, 0.6 mmol) and propionyl chloride 31a (0.042 mL, 0.48 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.03 g, 26%) as a yellow oil. Further analysis by HPLC determined the ratio to be 11:89.

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 274.1805 C$_{17}$H$_{24}$NO$_2$ requires 274.1802.

$\nu_{\text{max}}$/cm$^{-1}$ 3066 (C-H, aromatic), 2968 (C-H, alkene), 1633 (C=O), 1270 (C-H, methyl), 1119 (C-O, aliphatic ether), 698 (C-H, aromatic).

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; $t_r = 14$ min, 47.04 s; 15 min, 40.38 s.

[230]
Experimental

(2R,3S)-1-((S)-3-Benzylmorpholino)-2,3-dimethylpent-4-en-1-one (195l’) and (2S,3R)-1-
((S)-3-benzylmorpholino)-2,3-dimethylpent-4-en-1-one (195l”)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.13 g, 0.4
mmol), (S,E)-3-benzyl-4-(but-2-en-1-yl) morpholine 182f (0.092 g, 0.4 mmol), iPr₂NEt
(0.105 mL, 0.6 mmol) and propionyl chloride 31a (0.042 mL, 0.48 mmol). Flash column
chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds
(0.11 g, 92%) as a yellow oil. Further analysis by HPLC determined the ratio to be 29:71.

νmax/cm⁻¹ 3070 (C-H, aromatic), 2968 (C-H, alkene), 1630 (C=O), 1267 (C-H, methyl), 1119
(C-O, aliphatic ether), 700 (C-H, aromatic).


HPLC: 9:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; r₁ = 7 min, 27.3 s; 8 min, 40.62 s.
Experimental

\((2R,3S)-1-((S)-3-(\text{benzyloxy)methyl})\text{morpholino})-2,3\text{-dimethylpent-4-en-1-one (195m') and (2S,3R)-1-((S)-3-(\text{benzyloxy)methyl})\text{morpholino})-2,3\text{-dimethylpent-4-en-1-one (195m'')}}\)

The reaction was carried out according to general procedure B with TiCl\(_4\)·2THF (0.13 g, 0.4 mmol), \((S,E)-3-(\text{(benzyloxy)methyl})-4-(\text{but-2-en-1-yl})\text{morpholine 182g (0.1 g, 0.4 mmol), \text{tPr}_2\text{NEt (0.105 mL, 0.6 mmol) and propionyl chloride 31a (0.042 mL, 0.48 mmol). Flash column chromatography (2:1 \text{n-hexanes, EtOAc) gave the title compounds (0.04 g, 29%) as a yellow oil. Further analysis by HPLC determined the ratio to be 41:59.}}\)

\(\nu_{\text{max/cm}^{-1}} 3069 (\text{C-H, aromatic}), 2969 (\text{C-H, alkene}), 2860 (\text{C-H, methylene}), 1637 (\text{C=O}), 1268 (\text{C-H, methyl}), 1119 (\text{C-O, aliphatic ether}), 698 (\text{C-H, aromatic}).\)

\(m/z\) High Resolution (ESI\(^+\)) found (MH\(^+\)): 318.2069 \(C_{19}H_{28}NO_3\) requires 318.2064.

HPLC: 9:1 \text{n-hexanes}, \text{tPrOH; 0.8 mL/min; 254 nm; 20 \mu L; }r_t = 9 \text{ min, 16.08 s; 10 min, 6.18 s.}
Experimental

(2S,3S)-1-((S)-3-((Benzyloxy)methyl)morpholino)-2,3-diphenylpent-4-en-1-one (195n‘)
and (2R,3R)-1-((S)-3-((benzyloxy)methyl)morpholino)-2,3-diphenylpent-4-en-1-one
(195n“)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.07 g, 0.2 mmol),
(S)-3-((benzyloxy)methyl)-4-cinnamylmorpholine 183g (0.064 g, 0.2 mmol), iPr₂NEt
(0.053 mL, 0.3 mmol) and phenylacetyl chloride 31b (0.032 mL, 0.24 mmol). Flash column
chromatography (2:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds
(0.013 g, 14%) as a yellow oil. Further analysis by HPLC determined the ratio to be 92:8.

νmax/cm⁻¹ 3061 (C-H, aromatic), 2923 (C-H, alkene), 2858 (C-H, methylene), 1640 (C=O),
1112 (C-O, aliphatic ether), 697 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MK⁺): 442.2376 C₂₉H₃₂NO₃ requires 442.2377.

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; rt = 13 min, 20.34 s; 16 min,
16.68 s.
Experimental

(2R,3S)-1-((S)-3-(Methoxymethyl)morpholino)-2,3-dimethylpent-4-en-1-one (195o’) and (2S,3R)-1-((S)-3-(methoxymethyl)morpholino)-2,3-dimethylpent-4-en-1-one (195o”)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.07 g, 0.2 mmol), (S,E)-4-(but-2-en-1-yl)-3-(methoxymethyl)morpholine 182h (0.04 g, 0.2 mmol), iPr₂NEt (0.053 mL, 0.3 mmol) and propionyl chloride 31a (0.021 mL, 0.24 mmol). Flash column chromatography (1:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.03 g, 59%) as a yellow oil. Further analysis by HPLC determined the ratio to be 50:50.

ν_max/cm⁻¹ 2965 (C-H, alkene), 2865 (C-H, methylene), 1636 (C=O), 1267 (C-H, methyl), 1121 (C-O, aliphatic ether).

m/z High Resolution (ESI⁺) found (MH⁺): 242.1757 C₁₃H₂₄NO₃ requires 242.1751.

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; t₁ = 10 min, 56.1 s; 11 min, 58.44 s.
Experimental

(2S,3S)-1-((S)-3-(Methoxymethyl)morpholino)-2,3-diphenylpent-4-en-1-one (195p') and (2R,3R)-1-((S)-3-(methoxymethyl)morpholino)-2,3-diphenylpent-4-en-1-one (195p'"

The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.07 g, 0.2 mmol), (S)-4-cinnamyl-3-(methoxymethyl)morpholine $^{183}$h (0.05 g, 0.2 mmol), 'Pr$_2$NEt (0.053 mL, 0.3 mmol) and phenylacetyl chloride $^{31}$b (0.032 mL, 0.24 mmol). Flash column chromatography (2:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.025 g, 33%) as a golden oil. Further analysis by HPLC determined the ratio to be 76:24.

$\nu$$_{\text{max}}$/cm$^{-1}$ 3061 (C-H, aromatic), 2965 (C-H, alkene), 2859 (C-H, methylene), 1638 (C=O), 1265 (C-H, methyl), 1116 (C-O, aliphatic ether), 698 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 366.2072 C$_{23}$H$_{28}$NO$_3$ requires 366.2064.

HPLC: 9:1 n-hexanes, 'PrOH; 0.8 mL/min; 254 nm; 20 µL; $r_t$ = 10 min, 58.4 s; 14 min, 27.06 s.
Experimental

(2R,3S)-1-((S)-3-Benzylmorpholino)-2-methyl-3-phenylpent-4-en-1-one (195r’)
and (2S,3R)-1-((S)-3-benzylmorpholino)-2-methyl-3-phenylpent-4-en-1-one (195r”)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine 182f (0.03 g, 0.1 mmol), iPr₂NEt (0.026 mL, 0.12 mmol) and propionyl chloride 31a (0.010 mL, 0.15 mmol). Flash column chromatography (4:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.015 g, 45%) as a yellow oil. Further analysis by HPLC determined the ratio to be 60:40.

νmax/cm⁻¹ 3061 (C-H, aromatic), 2967 (C-H, alkene), 1633 (C=O), 1262 (C-H, methyl), 1118 (C-O, aliphatic ether), 700 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MNa⁺): 372.1930 C₂₃H₂₇NaNO₂ requires 372.1934.

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; t₁ = 10 min, 12.48 s; 12 min, 35.22 s.
The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine 183f (0.03 g, 0.1 mmol), iPr$_2$NEt (0.026 mL, 0.12 mmol) and phenylthioacetyl chloride (0.019 mL, 0.15 mmol). Flash column chromatography (4:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.011 g, 25%) as a yellow oil. Further analysis by HPLC determined the ratio to be 56:44.

$\nu$$_{\max}$/cm$^{-1}$ 3059 (C-H, aromatic), 2966 (C-H, alkene), 1640 (C=O), 1120 (C-O, aliphatic ether), 700 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MH$^+$): 444.2002 C$_{28}$H$_{30}$NO$_2$S requires 444.1992.

HPLC: 9:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; $r_t$ = 11 min, 6.24 s; 12 min, 36.6 s.
The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine 183f (0.03 g, 0.1 mmol), iPr$_2$NEt (0.026 mL, 0.12 mmol) and phthalglycyl chloride (0.027 g, 0.15 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.033 g, 68%) as a yellow oil. Further analysis by HPLC determined the ratio to be 43:57.

$\nu_{\text{max}}$/cm$^{-1}$ 3062 (C-H, aromatic), 2961 (C-H, alkene), 1713 (C=O), 1654 (C=O), 1116 (C-O, aliphatic ether), 699 (C-H, aromatic).

$m/z$ High Resolution (ESI$^+$) found (MK$^+$): 519.1683 C$_{30}$H$_{29}$KN$_2$O$_4$ requires 519.1681.

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; $t_r$ = 34 min, 48.84 s; 37 min, 16.08 s.
**(2R,3R)-1-((S)-3-Benzylmorpholino)-2-(benzylxy)-3-phenylpent-4-en-1-one (195u’),**
**(2R,3S)-1-((S)-3-benzylmorpholino)-2-(benzylxy)-3-phenylpent-4-en-1-one (195u’’),**
**(2S,3R)-1-((S)-3-benzylmorpholino)-2-(benzylxy)-3-phenylpent-4-en-1-one (195u’’’),**
and **(2S,3S)-1-((S)-3-benzylmorpholino)-2-(benzylxy)-3-phenylpent-4-en-1-one (195u’’’’)**

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine **183f** (0.03 g, 0.1 mmol), iPr₂NEt (0.026 mL, 0.12 mmol) and benzylxyacetyl chloride (0.019 mL, 0.15 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the **title compounds** (0.036 g, 83%) as a yellow oil. Further analysis by HPLC determined the ratio to be 23:8:19:50.

$$\nu_{\text{max}}/\text{cm}^{-1}$$ 3062 (C-H, aromatic), 2964 (C-H, alkene), 1641 (C=O), 1115 (C-O, aliphatic ether), 1082 (C-O, aliphatic ether) 700 (C-H, aromatic).

**m/z** High Resolution (ESI⁺) found (MK⁺): 480.1940 C₂₉H₃₁KNO₃ requires 480.1936.

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 μL; t₁ = 24 min, 25.62 s; 29 min, 44.46 s; 31 min, 47.7 s; 33 min, 54.18 s.
Experimental

(2S,3S)-1-((S)-3-Benzylmorpholino)-2-(4-methoxyphenyl)-3-phenylpent-4-en-1-one (195v’) and (2R,3R)-1-((S)-3-Benzylmorpholino)-2-(4-methoxyphenyl)-3-phenylpent-4-en-1-one (195v’’)

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine 183f (0.03 g, 0.1 mmol), ^3Pr₂NEt (0.026 mL, 0.12 mmol) and 4-methoxyphenylacetyl chloride (0.018 mL, 0.15 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.019 g, 43%) as a yellow oil. Further analysis by HPLC determined the ratio to be 23:77.

ν max/cm⁻¹ 3061 (C-H, aromatic), 2963 (C-H, alkene), 1639 (C=O), 1252 (C-O, aromatic ether) 1118 (C-O, aliphatic ether), 701 (C-H, aromatic).

m/z High Resolution (ESI⁺) found (MK⁺): 480.1935 C₂₉H₃₁KO₃ requires 480.1936.

HPLC: 9:1 n-hexanes, ^3PrOH; 0.8 mL/min; 254 nm; 20 µL; r₁ = 12 min, 35.28 s; 16 min, 36.36 s.
Experimental

(2R,3S)-1-((S)-3-Benzylmorpholino)-2-isopropyl-3-phenylpent-4-en-1-one (195w') and (2S,3R)-1-((S)-3-benzylmorpholino)-2-isopropyl-3-phenylpent-4-en-1-one (195w'')

The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine 183f (0.03 g, 0.1 mmol), iPr$_2$NEt (0.026 mL, 0.12 mmol) and isovaleryl chloride (0.014 mL, 0.15 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.035 g, 92%) as a yellow oil. Further analysis by HPLC determined the ratio to be 62:38.

υ$_{\text{max}}$/cm$^{-1}$ 3063 (C-H, aromatic), 2961 (C-H, alkene), 2865 (C-H, alkyl), 1629 (C=O), 1120 (C-O, aliphatic ether), 700 (C-H, aromatic).

m/z High Resolution (ESI$^+$) found (MH$^+$): 378.2438 C$_{25}$H$_{32}$NO$_2$ requires 378.2428.

HPLC: 9:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; t$_r$ = 8 min, 49.13 s; 18 min, 54.12 s.
Experimental

(2R,3R)-1-((S)-3-Benzylmorpholino)-2-methoxy-3-phenylpent-4-en-1-one (195x'), (2R,3S)-1-((S)-3-benzylmorpholino)-2-methoxy-3-phenylpent-4-en-1-one (195x''), (2S,3R)-1-((S)-3-benzylmorpholino)-2-methoxy-3-phenylpent-4-en-1-one (195x''') and (2S,3S)-1-((S)-3-benzylmorpholino)-2-methoxy-3-phenylpent-4-en-1-one (195x''').

The reaction was carried out according to general procedure B with TiCl₄·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine 183f (0.03 g, 0.1 mmol), iPr₂NEt (0.026 mL, 0.12 mmol) and methoxyacetyl chloride (0.011 mL, 0.15 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.029 g, 79%) as a pale yellow oil. Further analysis by HPLC determined the ratio to be 6:22:35:37.

$\nu_{\text{max}}$/cm⁻¹ 3062 (C-H, aromatic), 2929 (C-H, alkene), 2858 (C-H, alkyl), 1634 (C=O), 1196 (C-O, aliphatic ether), 1116 (C-O, aliphatic ether), 702 (C-H, aromatic).

$m/z$ High Resolution (ESI⁺) found (MH⁺): 366.2063 C₂₃H₂₈NO₃ requires 366.2064.

HPLC: 9:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; $t_r = 9$ min, 37.2 s; 12 min, 41.82 s; 14 min, 48.12 s; 15 min, 52.32 s.
(2R,3R)-1-((S)-3-Benzylmorpholino)-1-oxo-3-phenylpent-4-en-2-yl acetate and (195y')
(2S,3S)-1-((S)-3-benzylmorpholino)-1-oxo-3-phenylpent-4-en-2-yl acetate (195y'')

The reaction was carried out according to general procedure B with TiCl$_4$·2THF (0.03 g, 0.1 mmol), (S)-3-benzyl-4-cinnamylmorpholine 183f (0.03 g, 0.1 mmol), iPr$_2$NEt (0.026 mL, 0.12 mmol) and acetoxyacetyl chloride (0.013 mL, 0.15 mmol). Flash column chromatography (3:1 n-hexanes, EtOAc) gave an inseparable mixture of the title compounds (0.034 g, 86%) as a yellow oil. Further analysis by HPLC determined the ratio to be 30:70.

$\nu_{\text{max}}$/cm$^{-1}$ 3062 (C-H, aromatic), 2961 (C-H, alkene), 2861 (C-H, alkyl), 1743 (C=O, ester), 1629 (C=O), 1228 (C-H, methyl) 1122 (C-O, aliphatic ether), 702 (C-H, aromatic).

m/z High Resolution (ESI$^+$) found (MH$^+$): 394.2010 C$_{24}$H$_{28}$NO$_4$ requires 394.2013.

HPLC: 19:1 n-hexanes, iPrOH; 0.8 mL/min; 254 nm; 20 µL; $t_r$ = 23 min, 27.9 s; 26 min, 38.04 s.
Appendices
**Appendix 1**

Typical $^1$H resonance ranges representing characteristic protons in *syn-* vs. *anti-* acyl-Claisen derived amides and derivatives thereof.

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<td>4-CH</td>
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<td>5-CH$_2$</td>
<td>δ5.00 – 5.20</td>
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<td>4.65 – 4.90</td>
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<td>6.90 – 7.20</td>
<td>R$^1$ or R$^2$ Ar</td>
<td>7.10 – 7.50</td>
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Examples:

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References
References

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