Imperial College London

Towards the Design and Synthesis of Alpha-Helix Mimetics

Thesis submitted in partial fulfilment of a PhD degree

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Declaration of originality

I hereby declare that I have personally prepared this thesis and that the work decribed herein is that of my own and was carried out by myself unless explicity stated otherwise. All sources of information are acknowledged by means of references.

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ABBREVIATIONS

ACM	acetamidomethyl
AcOH	acetic acid
AF-2	activation function-2
AIBN	azobisisobutyronitrile
Ala	alanine
Arg	arginine
Asp	aspartate
Bak	Bcl-2 homologous antagonist killer
Bcl-2	B-cell lymphoma 2
Bim	Bcl-2 like protein 11
Boc	*tert*-butyloxycarbonyl
BOP	(benzotriazol-1-yloxy)*tris*(dimethylamino)phosphonium hexafluorophosphate
BTFFH	*bis*(tetramethylene)fluoroformamidinium hexafluorophosphate
CBI	coactivator binding inhibitor
Cbz	benzyloxycarbonyl
CD	circular dichroism
DA	Diels-Alder
DFT	density functional theory
DHP	dihydropyridine
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
dr	diastereoselectivity
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ER	estrogen receptor
EtOAc	ethyl acetate
EtOH	ethanol
FGI	functional group interconversion
GLP-1	glucagon like peptide-1
GREB1	growth regulation by estrogen in breast cancer
HATU	(1-(bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
HBTU	(2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)

hGH	human growth hormone
HOBt	hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
Ile	isoleucine
K_d	dissociation constant
K_i	inhibitory constant
LBD	ligand binding domain
LCMS	liquid chromatography-mass spectrometry
Leu	leucine
LRH-1	liver receptor homolog-1
LRMS	low resolution mass spectrometry
LUMO	lowest occupied molecular orbital
Lys	lysine
Mcl-1	induced myeloid leukemia cell differentiation protein Mcl-1
m-CPBA	*meta*-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MW	microwave
NIS	*N*-iodosuccinimide
NOESY	nuclear overhauser effect spectroscopy
NR	nuclear receptor
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PPI	Protein-protein interaction
p-TsOH	*para*-toluenesulfonic acid
PyAOP	((7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate)
PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RMS	root mean square difference
ROESY	rotating-frame overhauser effect spectroscopy
RT	room temperature
sec	secondary
SHP	small heterodimer partner

SM	starting material
smMLCK	small muscle myosin light chain kinase
SRC-1	nuclear receptor coactivator 1
T3P	propylphosphonic anhydride
TCBC	2,4,6-trichlorobenzoyl chloride
tert	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIF-2	transcriptional mediators/intermediary factor 2
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TS	transition state
Tyr	tyrosine
Val	valine
VEGF	vascular endothelial growth factor
VT	variable temperature

ABSTRACT

Liver receptor homolog-1 (LRH-1) is a nuclear receptor (NR) that has been implicated to play a critical role in the development of breast cancer owing to its role in the direct regulation of breast cancer cell growth, whereby it acts in concert with the estrogen receptor (ER). Ligand-bound NRs, such as LRH-1, induce their transcriptional activity *via* the recruitment of coactivator proteins. Described herein is research directed at developing small drug-like molecules that can competitively bind to the coactivator binding site on LRH-1 and act as antagonists of the transcriptional activity of LRH-1. Such coactivator binding inhibitors (CBIs) are expected to be complementary to existing NR modulators which competitively bind at the ligand-binding pocket (LBP) of the NR ligand-binding domain (LBD).

Our aim in this work was to develop the synthesis of a non-peptidic α-helix mimetic capable of representing the key α-helical regions of a coactivator protein involved in binding to LRH-1. A majority of the work described in this thesis focusses on the design and synthesis of a bicyclic scaffold capable of reproducing up to five amino acid residues projecting from three different faces of an α-helix.

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INTRODUCTION

1. Protein-Protein Interactions

The human genome contains between 20,000 and 30,000 genes encoding for over 500,000 different types of proteins, and of these proteins over 10,000 can be produced in the cell at any given time.[1] Proteins do not act in isolation, and it is estimated that over 80% of all proteins in cells require interactions with other molecules to achieve function.[1] The formation of a protein-protein complex is principally attributed to van der Waals contacts between nonpolar residues on the protein surfaces (*i.e.* hydrophobic effects). Electrostatic interactions, such as salt bridges, and hydrogen bonding interactions are also essential, as can be the presence of covalent bonds.[2] Interactions between proteins occur at their interfaces through atoms in the amide backbone and functional groups of side-chains present on the two different proteins, sometimes augmented by interactions with other spatially close residues from *e.g.* cofactors (**Figure 1**).

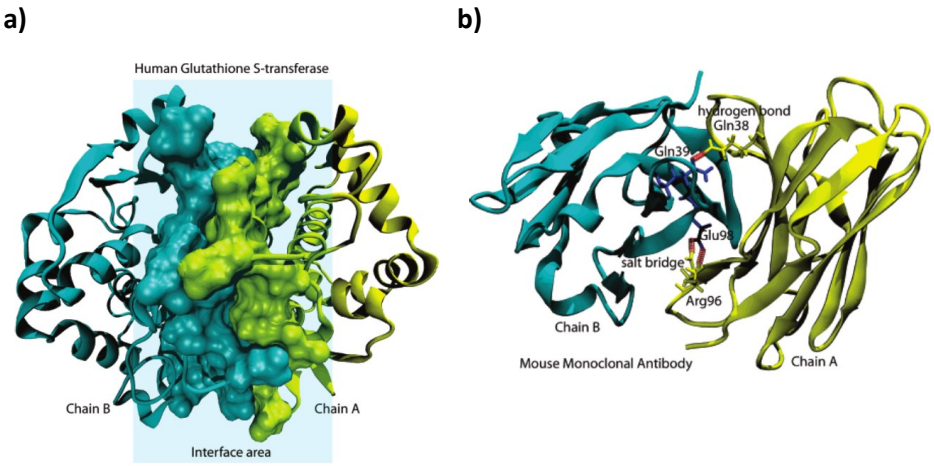


Figure 1 | Illustrations of protein-protein interfaces. a) Two interacting proteins [human glutathione S-transferase, Chains A (yellow) and B (cyan)]. The residues involved in the surface interactions are depicted with surface representation to highlight the complementarity, with the remainder of the protein being shown with ribbons. b) A more detailed dissection of a protein-protein interface [mouse monoclonal antibody, chains A (yellow) and B (cyan)]. Here the hydrogen bond between Gln38 in Chain A and Gln39 in Chain B and the salt bridge between Arg96 in Chain A and Glu98 in Chain B are apparent.[2] (Image taken from Nussinov *et al. Chem. Rev.* 2008).

The direct communication between different proteins, *i.e.* protein-protein interactions (PPIs), plays a vital role in almost all biological processes. PPIs are responsible for holding together the key multi-protein complexes of a cell and play a pivotal role in a wide range of cellular processes, including signal transduction, transcription, replication and membrane transport.[3]

Furthermore, alterations and malfunctions of PPIs are known to be implicated in disease states, including cancer and neurodegenerative diseases.[3] Understanding how one protein interacts with another reveals knowledge of how they come together to construct signalling and

metabolic pathways. Not only does this lead to a more in-depth understanding of systems biology, it also allows us to improve upon our approaches towards medical diagnosis and aids in the development of new therapeutics.[4] Accordingly, there is significant interest in targeting the interfaces in PPIs. However, the complexity associated with such interactions means that this poses an enormous challenge. To put this into perspective, the contact surfaces found in the deep cavities involved in the binding between proteins and small molecules typically lie between ~300 and ~1,000 Å^2 whereas contact surfaces involved in PPIs might be between ~1500 and ~3000 Å^2 and are usually greater than 800 Å^2.[5,6,4] Consequently, for a molecule to achieve competitive binding upon interaction with a protein, it will typically require a high molecular weight to compensate for the distributed free energy associated with a large surface.[7] The inherent dynamicity of proteins together with their intrinsically disordered regions adds further complexity. Another obstacle facing the design of competitive inhibitors of PPIs is that, in contrast to more classical protein targets such as receptors and enzymes, PPIs do not have small-molecule partners in biological systems, and thus we cannot utilize small naturally occurring substrates as a starting point for drug development.[8] Furthermore, whereas interactions between proteins and small molecules often involve small grooves or deep pockets at the key interface, the interactions between proteins usually consist of large and flat contact surfaces.[9]

1.1 Hot Spots

Extensive analysis has shown that although protein contact surfaces are large, the interactions crucial for the affinity of two proteins are not distributed evenly across the surface. Often it is the case that a small subset of residues, or regions of residues, contribute significantly to the binding affinity of a pair of proteins, a feature known as 'hot spots.'[10] A hot spot can be defined as a residue which, when replaced by an alanine residue, results in a substantial decrease in the free binding energy ($\Delta\Delta G_{binding}$ > 1.5 kcal/mol).[11] This was identified by Wells and Clarkson during their seminal investigations into the interaction between human growth hormone (hGH) and its receptor (hGHbp): although approximately 30 side chains from each protein make contact, as evidenced by the X-ray crystal structure of the complex, alanine-scanning mutational analysis revealed that a central hydrophobic region dominated by just two tryptophan residues was responsible for a disproportionately large amount of the binding affinity (greater than three quarters).[11] Interestingly, crystal structures have shown that hot spots are highly complementary to one another. For example, salt bridges and hydrophobic residues on one face slot in small alcoves on the opposite surface,[12] helping to stabilise the PPI. Hot spots are often

found at the centre of the contact interface, constitute less than half of the contact interface in the PPI (**Figure 2**) and are comparable in size to the surface area of a small molecule.[8]

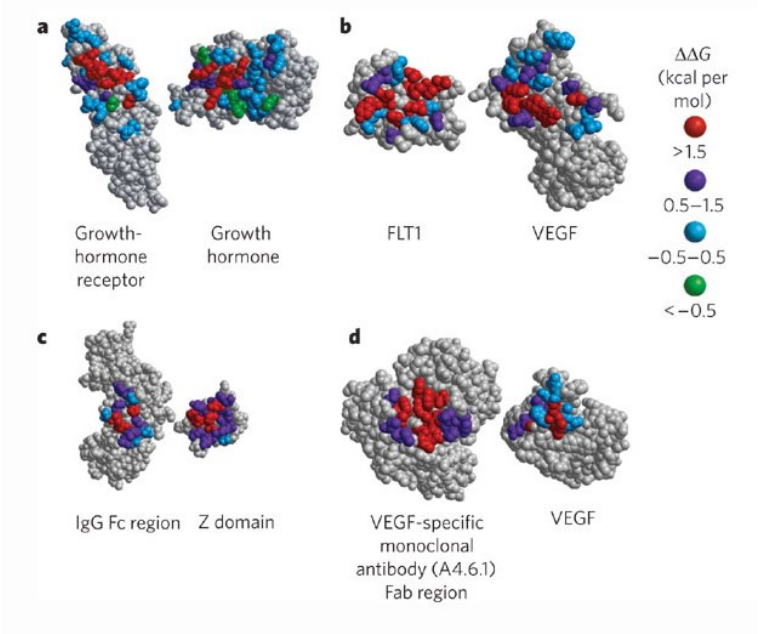


Figure 2 | Examples of protein-protein interface hotspots. Alanine scanning studies were carried out on the contact surfaces of four interacting proteins (a, b, c and d). Changes between the binding free energy (ΔΔG) as compared to interactions with the wild-type protein is indicated by the colour coding amino acid residues: red - most disruptive changes, green - little or no effect.[8] (Image taken from Wells and McClendon, *Nature* 2007).

In essence, although it may be more desirable to replicate a greater surface section of the interface, using small highlighted sections provided by hot spots which are inherently good for ligand binding is widely accepted as an essential strategy for ligand identification.

1.2 Small Molecule Inhibitors of PPIs

Given the characteristics associated with PPIs, such as shallow topological features and large flat surfaces requiring hydrophobic high molecular weight compounds, the notion of attempting to disrupt interactions of this type using exogenous molecules initially drew scepticism: PPIs were widely considered "undruggable."[13] However, the increasing recognition of hot spots and appreciation of the flexibility and adaptivity[14] that exists between two protein surfaces is now recognised to offer realistic prospects that sites on these interfaces can be targeted by small drug-like molecules. Guo *et al.* recently discussed how the characteristics of hot spots could be used to identify druggable pockets and outlined a general strategy for hot spot-based design of PPI inhibitors.[15] More generally, small molecule inhibitors of PPIs have experienced dramatic advances over the last two decades. Indeed, by 2005 there were half a dozen examples of small molecules demonstrating binding affinities, at sites defined by high-resolution structures, which

were comparable to drug leads.[8] Since then the field has propelled into successful territories with many potent inhibitors having been identified for complex proteins and with compounds currently in clinical trials for six targets.[16]

2. Alpha-Helix Mimetics

PPIs can be categorized into groups based on both the structural properties of the globular protein and the characteristics of the relevant peptide chains.[17] We are particularly interested in those which feature secondary structures at the interface. In the last decade there has been a noticeable upsurge in research centred around designing small molecules that emulate elements of the secondary structure at the interface of PPIs.[10] Our focus here is on PPIs involving α-helices at the interface. In excess of 30% of all protein secondary structures constitute α-helices making the α-helix the most dominant secondary structure in natural proteins. Furthermore, designing inhibitors for PPIs which involve an α-helix is generally accepted to be a chemically tractable objective. A typical α-helix[18] has 3.14 residues per turn and a rise of 5.4 Å per turn (**Figure 3a**). Each residue has backbone dihedral angles of Ψ = -50° and Φ = -60° (**Figure 3b**). The spacing of side chains in an α-helix is such that the chains are situated above one another every 3–4 residues (**Figure 3c**). Consequently, the helix can be considered to have three distinct faces if viewed top-down (**Figure 3d**).

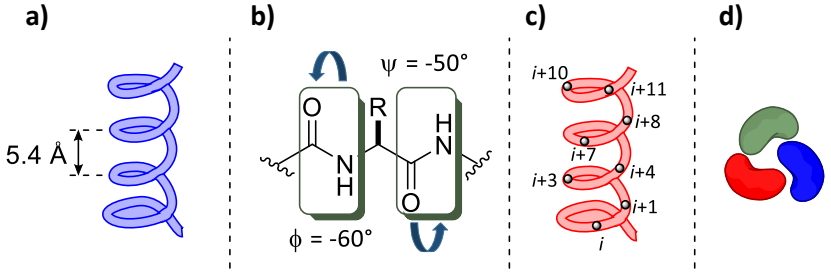


Figure 3 | Illustration of some key structural features of a canonical α-helix. a) Ribbon depiction of an α-helix showing a rise of 5.4 Å per turn. b) Amide backbone showing the dihedral angles. c) Positioning of side chains on a canonical α-helix. d) Top-down view showing three distinct faces of an α-helix.

Given the prevalence of α-helical structures in proteins, it follows that a large proportion of the interactions between proteins should be expected to involve α-helices. Following this hypothesis, designing a template capable of mimicking an α-helix naturally presents a rational approach to the design of low molecular weight inhibitors of PPIs (**Figure 4**).[4]

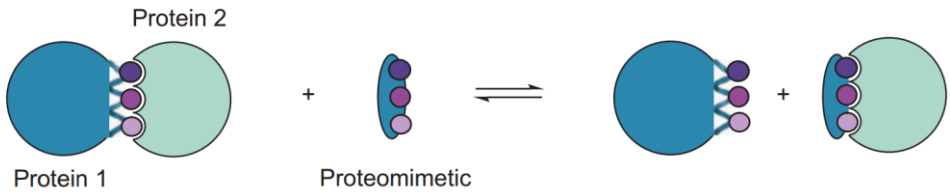


Figure 4 | Schematic representing how a helix mimetic may competitively inhibit a PPI by reproducing key side chains involved in molecular recognition.[4] (Image taken from Wilson *et al. Nat. Chem.* 2013).

α-Helix mimetics typically fall in one of two categories: type I or type III mimetics. Type I mimetics[19] comprises of molecules that themselves adopt a helical structure in close analogy to the natural helix. Type III mimetics[20,21] comprise small molecular scaffolds designed to achieve mimicry by projecting functional groups in similar orientations to those found in the helix in question.

2.1 Type I Mimetics

Type I mimetics encompass classes of compounds that maintain the peptide backbone and serve to bind to a protein by imitating the topography of a structural motif. When developing peptide-based drugs one must take into consideration their susceptibility towards proteolytic degradation and the challenges associated with their poor transport across cell membranes compared to most small molecule inhibitors. The intrinsically conserved nature of peptides imparts an inherent functional complexity that small molecules will struggle to replicate. Additionally, synthetic peptides will not retain their native conformation and will not be as organized in solution as they otherwise would be in their parent protein. For example, they may lose their propensity to adopt a helical structure and may instead exist in random conformations which will likely have an adverse effect on their binding properties to proteins.[22] Several ingenious techniques have been developed, particularly over the last two decades, to favour the solution population of synthetic peptides in a helical conformation. Given the positioning of side chains on an α-helix (*e.g. i*, *i*+4, *i*+7 and *i*+11 – see **Figure 3c**), covalently linking, or 'stapling', two different side chains which are on the same face of the helix presents one method of reducing the conformational freedom accessible to the native molecule. A few of these tethering methods are briefly described below.

One example of inducing α-helicity *via* covalent side chain tethers is the formation of a disulfide bridge. An advantage of this method is its functional group tolerance and the wide variety of

conditions employable to introduce this conformational constraint. In an early example of this, Jackson *et al.* reported the synthesis of a series of short peptides containing a disulfide linkage between residues at the *i* and *i*+7 positions. Using CD to measure ellipticity, they found that when the thiols were protected with an acetamidomethyl (Acm) group, the peptide mainly existed as a random coil whereas the oxidized form containing the disulfide bridge sustained a high degree of α-helicity.[23]

Using a lactam-based tether is another widely employed technique. As an early example, Taylor and Baum used solution NMR data to indicate that the presence of two overlapping side chain lactam bridges on a hexapeptide led to a stable α-helical structure.[24] In a separate noteworthy example, Kim *et al.* used chemical cross-linking and substitution with unnatural helix-favouring amino acids. Cross-linking of two glutamic acid residues at the *i* and *i*+7 positions with an α,ω-diaminoalkane group led to an inhibitor displaying micromolar potency. They successfully stabilized a 14-residue peptide targeting the hydrophobic pocket of HIV-1 gp41 and obtained an X-ray crystal structure of the two bound together which revealed that their peptide was bound to the pocket in a similar helical conformation as the native C-peptide.[25]

Hydrocarbon stapling, *i.e.* the formation of a covalent C-C bond, is arguably the technique that has had the most impact in this field.[26] This non-native linkage has the advantage of avoiding degradation pathways that natural functionalities, such as disulfide- and lactam bridges, can fall victim to.[4] Furthermore, having an all carbon linkage constitutes a structurally minimal motif and is thus appealing from a design perspective. Grubbs and Blackwell were the pioneers in the field of hydrocarbon stapling and devised a stapling technique which involved the construction of a C-C bond *via* ring closing metathesis (RCM).[27] Their seminal work consisted of solution-phase metathesis on model hydrophobic heptapeptides which contained an *O*-allyl serine at the *i* and *i*+4 side chain positions. In this work, the conformation of the parent model peptide already had some degree of α-helicity and the work was a proof-of-concept study which demonstrated that metathesis could be used as a viable tool for the formation of more rigid peptide architectures. An important development in hydrocarbon stapling was realised by the Verdine group who combined RCM of olefin tethers with α,α-disubstitution at the chiral carbon of the side chain residues.[28] Since then, from a synthetic standpoint, hydrocarbon stapling has become very well established for the *i*, *i*+3, i+4 and *i*+7 side chains.[26]

A particularly clever design approach towards constraining peptide conformation was achieved by Alleman *et al.* who devised a way to both stabilize and destabilize the helical motif, thereby controlling protein binding, using an external stimulus. Their work involved an azobenzene tether which was connected *via* two cysteine residues projecting from the same face (*i*, *i*+4, *i*+7 or *i*+11). Irradiation of the system induced reversible isomerization of the double bond – switching the peptides between a random coil like form (*trans*-isomer) and an α-helical form (*cis*-isomer).[29]

Other examples of covalent interactions to maximise helicity involve hydrogen-bonding surrogates,[30] biologically active β-peptides,[31] and mixed α/β-peptides,[32] all of which are described in more detail in an excellent recent review by Wilson and Azzarito.[4] Additionally, several methods incorporating non-covalent interactions to stabilize the α-helical motif have also been investigated, including metal-ligand interactions, salt bridges and cation-π interactions.

2.2 Type III Mimetics

The second major category of α-helix mimetics, called type III mimetics, encompasses *non-peptidic* scaffolds. These so called 'minimalistic mimics' do not involve a peptidic polyamide backbone and, therefore, do not suffer degradation by proteases and ideally exhibit improved cell- and oral-bioavailabilities relative to their peptide counterparts.[33]

Hamilton, one of the pioneers in this field, and his group identified the first true type III α-helix mimetic in which a terphenyl scaffold was proposed to mimic the surface of the helix. Here, the *ortho* substituents on the phenyl ring project in an orientation that reasonably mimics the *i*, *i*+3/4 and *i*+7 residues.[34] Initially, this template was designed to inhibit the interaction between calmodulin and small muscle myosin light chain kinase (smMLCK), but it has subsequently been utilized to target a range of other biologically relevant interactions. Among these other interactions, the potent inhibition of the Bcl-2 family of interactions, which are involved in the regulatory process of the apoptotic pathway, was particularly impressive.[35]

Since Hamilton's first discovery over a decade ago, there have been numerous α-helix mimetic scaffolds which present three side chains. This is largely because synthetic mimicry has focused solely on the hydrophobic face and typically only the *i*, *i*+3/4 and *i*+7 residues have been explored. Notwithstanding a few exceptions however,[36,37] many of the three-residue motifs have failed to show positive biological results and have lacked the required selectivity. Although the

reasons for these observed deficiencies may be due to the issues covered above *i.e.* large protein surface areas, the intrinsically disordered region on the protein surface, protein dynamicity, conformational changes upon ligand binding *etc.*,[4] another possible reason may be that reproducing residues projecting from only one face is not sufficient. More specifically, additional faces of the α-helix should be considered. Arora *et al*.[10] recently carried out an analysis on the full set of helical protein interfaces in the Protein Data Bank in an attempt to understand in detail the location and positioning of hot spots on the helices and contact residues on the partner proteins. Their studies revealed that roughly 40% of the helical interfaces in the data set feature helices with hot spot residues on two or more faces of the helix. Approximately 10% of the interactions require all three faces for the desired interaction with the protein (**Figure 5**).[10]

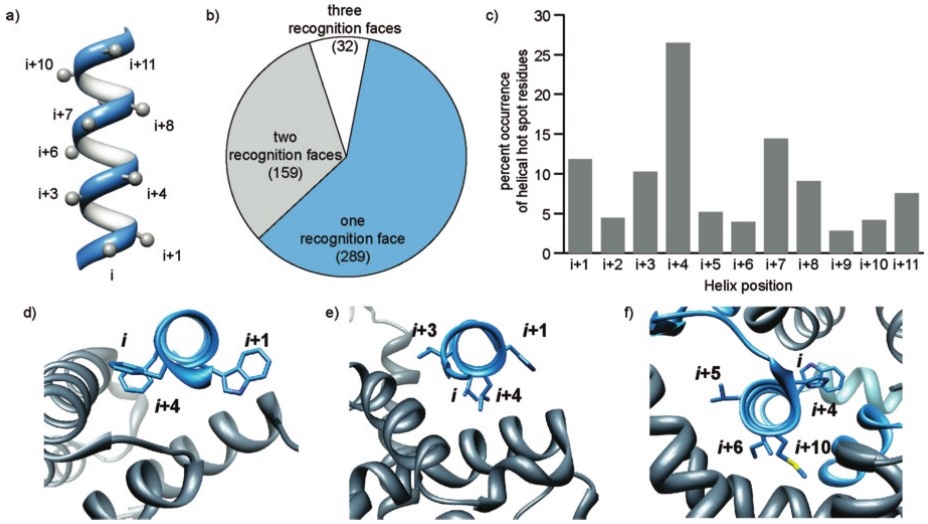


Figure 5 | The energetic contributions of residues found on different faces of interfacial helices. a) Side chain positions on a canonical α-helix. b) Pie-chart illustrating the percent occurrence of hot spot resides on one, two and three faces of an α-helix (the figure in parenthesis shows the total number of helices in each section). c) Bar-graph illustrating the percent occurrence of hot spot residues in regards to its position on the helix. d-f) Depicts examples of PPIs involving an alpha helix with hot spot residues on one, two and three faces of the helix (PDB entries 1xl3, 1xiu, and 1or7). (Image taken from Arora *et al. J. Am. Chem. Soc.* 2011).

Hence, many protein complexes exhibit additional interactions originating from the residues flanking the hydrophobic face of the helix. Furthermore, one should take into account that nearly half of α-helices found in proteins are amphiphilic in nature and possess a hydrophilic surface on the opposite side of a hydrophobic surface. Thus, the so called 'one sided' helix mimetics presenting only three residues will clearly be deficient for mimicking the interactions of these helices. Constructing a scaffold which can project residues on not only one, but two, or perhaps even three faces of an α-helix, should ellicit improvements in binding affinity. These

more involved scaffolds should also enhance the selectivity profile of the inhibitor as they should be more adept at discriminating between protein surfaces through a richer recognition profile.[38]

As our work will focus on mimetics exhibiting five residues and mimicking three faces, readers interested in three residue mimetics are directed to a recent review by Hamilton and Cummings for more information.[21]

2.2.1 Four- and Five-Residue Mimetics

One of the first examples of a mimetic displaying four residues was by Kim and Hamilton in 2006 in their work on diphenylindane-based proteomimetics (**Figure 6**).

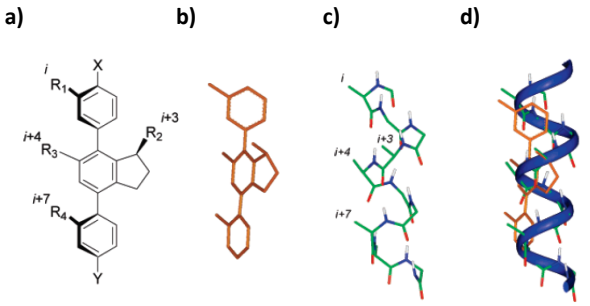


Figure 6 | Hamilton's diphenylindane mimetic. a) 4,7-Diphenyl-1,6-disubstituted indanes. b) Energy minimized (MM2) tetramethyldiphenylindanes. c) Poly-Ala α-helix with *i*, *i*+3, *i*+4 and *i*+7 groups. d) Stereoview of overlay of α-helix with tetramethylphenylindane, Root mean square difference (RMSD): 0.92 Å.[39] (Images adapted and taken from Kim & Hamilton, *Org. Lett.* 2006).

This scaffold stemmed from a combination of their earlier work on the terphenyl system, mimicking the *i*, *i*+4 and *i*+7 residues, and their discovery that a 1,6-disubstituted indane system was able to spatially project adjacent residues (*i.e. i* and *i*+1) on an α helix.[39] Superimposition of the four CH_3-C bonds on the indane with the *i*, *i*+3, *i*+4 and *i*+7 CH_3-C groups on a poly-alanine helix revealed a good match with an RMS difference of 0.92 Å.[39] It is worth mentioning that the synthetic route applied here led to the final compound as a racemate; the low rotational barrier about the aryl-aryl bond meant interconversion of the diastereoisomers at room temperature, consequently allowing an induced fit mode of binding for one of the enantiomers. Nevertheless, an asymmetric approach towards a truly atropisomeric variant of this phenylindane scaffold may increase the effectiveness of this approach further.[40]

Following on from their earlier four residue scaffold, the Hamilton group reported a second scaffold capable of mimicking four residues (*i*, *i*+4, *i*+7 and *i*+11) based on a biphenyl 4,4'-dicarboxamide core (**Figure 7**).[41]

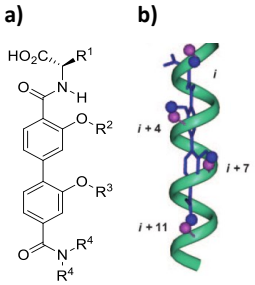


Figure 7 | Hamilton's biphenyl dicarboxamide four residue mimetic. a) Hamilton's biphenyl scaffold. b) Overlay of the biphenyl scaffold (blue) an idealized alanine α-helix mimetic (green with pink methyl groups), RMSD: 1.368 Å.[41] (Image adapted and taken from Hamilton *et al. ChemBioChem* 2009).

This new scaffold combined elements of their earlier works on oligophenyls, which provided the hydrophobic core, and on amide-linked terephthalimides, which improved synthetic accessibility. The α-helix mimicry of this scaffold was explored by targeting the Bcl-xL/Bak protein-helix interface. A focussed library of these biphenyl compounds were prepared and their inhibition constants investigated *in vitro*; the scaffold was shown to inhibit the Bcl-Xl/Bak interaction with their best mimetic giving a K_i value of 1.8 μM (by fluorescence polarization assay) and a K_d of 7.1 μM.[41]

In one of their most recently developed scaffolds Hamilton extended a previously reported benzoylurea system, which was a one sided, three residue α-helix mimetic that showed a 2.4 μM inhibition of the Bcl-xL/Bak interaction. Their new construct represents one of very few examples where five residues have been mimicked and was achieved by replacing the two substituents on the phenyl ring with alkoxy groups and introducing two further alkoxy groups around the ring (**Figure 8**).[42]

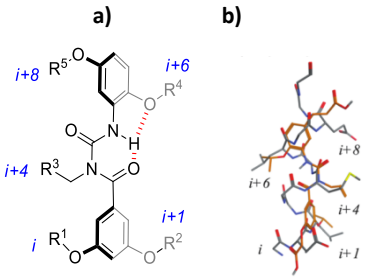


Figure 8 | Hamilton's benzoylurea scaffold. a) Hamilton's benzoylurea scaffold designed to mimic the *i*, *i*+1, *i*+4, *i*+6 and *i*+8 side chains which are present on two faces of an α-helix. b) Superimposition of the lowest energy conformer of the benzoylurea scaffold (orange) with an idealized alanine α-helix (grey).[42] (Image taken from Thompson and Hamilton, *Org. Biomol. Chem.* 2012).

The straightforward alkylation reaction of the phenolic components allowed for the creation of tailored mimetics in which both hydrophobic and hydrophilic substituents could be efficiently introduced. Overlay of their template with a model peptide revealed good overlap with the *i*, *i*+1, *i*+4, *i*+6 and *i*+8 side chain residues which was consistent with their computational studies.

This remains the only example where this selection of amino acids have been mimicked. The existence of the linear scaffold was confirmed by NMR studies which supported the presence of the proposed, and required, intramolecular hydrogen bond (**Figure 8a**).[42]

In 2013, the Fletcher group published their work on amphiphilic α-helix mimetics based on a 1,2-diphenylacetylene scaffold. The presence of a non-rigid intramolecular hydrogen bond between phenyl ring substituents can bias the rotation about the central axis of the 1,2-diphenylacetylene, thus setting up a rigid framework from which they were able to project functional groups at a spatial arrangement similar to the *i*, *i*+2, *i*+5 and *i*+7 residues. Here, the *i*, *i*+7 and *i*+2, *i*+5 residues lie on opposite sides of the helix (**Figure 9**).[43]

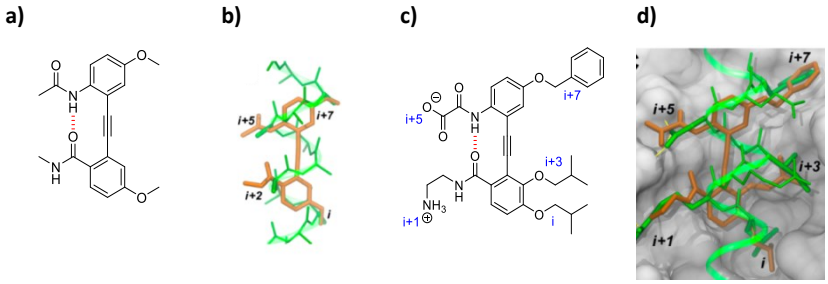


Figure 9 | Fletcher's diphenylacetylene scaffold. a) Fletcher's 'four residue' α-helix mimetic. b) Superimposition of Fletcher's 'four residue' scaffold (orange) on an idealized alanine α-helix (green). c) Fletcher's extended scaffold projecting five residues. d) Superimposition of Fletcher's 'five residue' mimetic (orange) on the Bim-BH_3 α-helix (green).[43] (Image taken from Fletcher *et al. Org. Lett.* 2013).

The Fletcher group went on to accomplish a superior α-helical mimic upon the inclusion of further functionality in the lower phenyl ring of the scaffold (see **Figure 9c**). This new feature allowed for the inclusion of a side chain which would mimic the *i*+3 residue. They were consequently able to develop a novel α-helix mimetic capable of representing five amino acid side chains located across two faces of the helix and within two complete turns.[43]

Very recently, the Fletcher group reported another scaffold which was capable of mimicking two faces of a helix. Here, they demonstrated that a 2,6,9-trisubstituted purine scaffold was capable of disrupting the Mcl-1/Bak-BH3 PPI by mimicking residues present on two different faces of the Bak-BH3 α-helix.[38] Although potent inhibitors have already been developed to disrupt the interaction between the Bak-BH3 α-helix and the Bcl-2 family of proteins, these have been limited to mimicking only three of the four key hydrophobic residues [namely the Leu78 (*i*), Ile81 (*i*+3) and Ile85 (*i*+7) side chains] which are all presented on the same face. Alanine scanning mutagenesis analysis indicated that the Asp83 (*i*+5), found on the opposite face of Bak-BH3, is also important as it binds to Arg139 of Bcl-xL and Arg263 of Mcl-1. Thus, they sought to develop

a purine scaffold that allowed for mimicry of the *i*, *i*+3 and *i*+4 side chains on one face, and the *i*+5 residue on the opposite face (**Figure 10**).

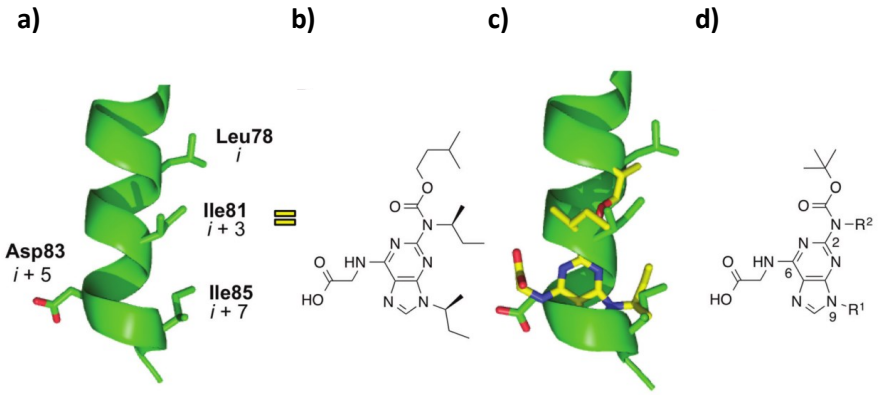


Figure 10 | Fletcher's purine based four residue mimetic. a) Key residues of the Bak-BH3 α-helix. b) Fletcher's purine-based mimetic designed to mimic the Leu78 (*i*), Ile81 (*i*+3), Ile85 (*i*+7) and Asp83 (*i*+5) residues. c) Superimposition of an MM2 energy minimised conformation of molecule in b) together with the Bak-BH3 α-helix. d) Simplified purine-based mimetic design: the *i*+5 residue is fixed as a CH_2COOH, the *i* residue is fixed as a *tert*-butyl, R^1 and R^2 are to imitate *i*+7 and *i*+3 respectively. (Image taken from Fletcher *et al. Org. Biomol. Chem.* 2015).

A small library of compounds was prepared based on the simplified mimetic shown in **Figure 10**, with the most potent compound having R^1 as a 1-naphthylmethyl group and R^2 as a benzyl (estimated IC_{50} = 72 μM). However, it was believed that the *tert*-butyl group, which was incorporated to aid synthetic accessibility and to mimic the Leu78 residue (*i*), may have compromised the mimic potential of this particular scaffold. It is anticipated that a more flexible group might overcome this.[38]

Restorp and Rebek carried out work on a heterocyclic scaffold containing a central piperazine ring functionalized with hydrophobic amino acid side chains with the intention of reproducing the *i*, *i*+4 and *i*+7 residues. Further work then led to an extended class of α-helix mimetics presenting four hydrophobic residues able to project the *i*, *i*+4, *i*+8 and *i*+11 side chains – which overall encompasses three turns of an α-helix (**Figure 11**).[44]

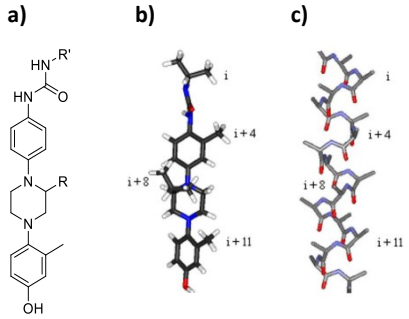


Figure 11 | Restorp and Rebek's piperazine based scaffolds. a) Rebek's heterocyclic piperazine based scaffold. b) Minimized representation of the scaffold. c) An idealized alanine α-helix.[44] (Images adapted and taken from Restorp and Rebek, *Bioorg. Med. Chem. Lett.* 2008).

An attractive feature of this work was the modular synthetic route which allowed for the ready incorporation of different hydrophobic side chains in the scaffold. The mimetic exists in a staggered conformation, much like Hamilton's terphenyl scaffold, which is necessary to allow projection of the side chains in a manner similar to an α-helix.[44]

Ahn *et al.* also constructed a mimetic capable of displaying four residues; they developed a bis-benzamide scaffold which utilized four hydroxyl groups to project functional groups corresponding to the *i*, *i*+2, *i*+5 and *i*+7 amino acid residues (**Figure 12**).[45]

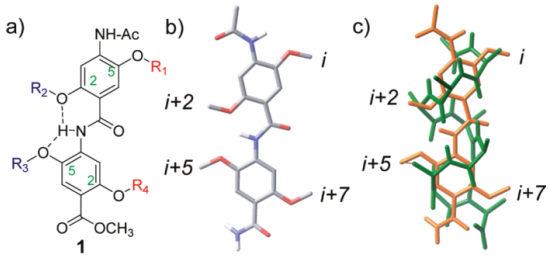


Figure 12 | Ahn *et al's*. bis-benzamide four residue scaffold. a) Ahn's proposed bis-benzamide scaffold. b) The lowest energy conformation. c) Superimposition of the bis-benzamide scaffold (orange) on an idealized α-helix (green).[45] (Image taken from Ahn *et al. Org. Lett.* 2009).

On this scaffold it was the presence of two hydrogen bonds which locked the conformation and allowed for two of the residues to project on one face whilst the two remaining residues projected on the opposite face.[45] To evaluate their α-helix mimicry, three amphiphilic α-helix mimetics were synthesized on the basis of the sequence of α-helical segments in glucagon-like peptide-1 (GLP-1), a hormone which plays a crucial role in glucose homeostatis. Analysis of the X-ray crystal structure confirmed that their bis-benzamide scaffold simultaneously represented both helical faces. The structural analysis also confirmed the presence of two hydrogen bonds (as shown in **Figure 12a**).[45]

In 2014, the Lim group devised a unique mimetic based on a phenyl-piperazine-triazine scaffold to target the Mcl-1/Bim-BH3 PPI. In particular, they were looking to improve the physiochemical properties of some of the traditional mimetics, for example by incorporating heteroatoms to reduce lipophilicity. In this work, the group used a solid-phase approach to develop a diverse library of 36 compounds and discovered a potent inhibitor with their most active compound displaying a K_i of 7.3 μM. In addition, they were able to get selectivity for the Mcl-1 protein over the closely related Bcl-XL, both of which belong to the Bcl-2 family of proteins and contain similar BH3-binding grooves. This work involved mimicking one face of an α-helix but could potentially be extended to incorporate a fourth residue (*i*+5) which would project on the opposite face.[46]

The Lim group have since been exploring a related triazine-piperazine-triazine scaffold (**Figure 13**).[47]

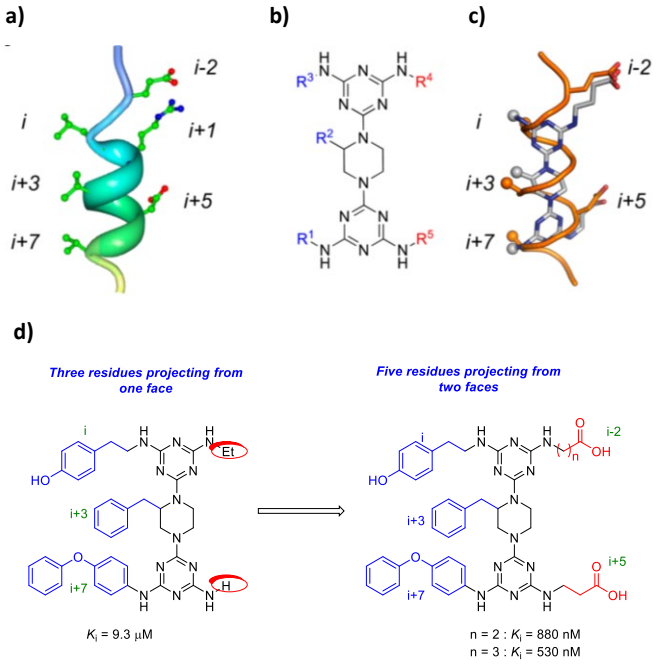


Figure 13 | Lim's triazine based mimetics. a) X-ray crystal structure of Mcl-1 binding helical peptide. b) Lim's triazine-piperazine-triazine scaffold highlighting points for functionalization. c) Superimposition of a minimised triazine-piperazine-triazine scaffold with an idealised α-helix. d) Lim's initial three reside/one face α-helix mimetic (left) and the recently developed five reside/two face α-helic mimetic (right).[48] (Image adapted and taken from Lim *et al. ACS Comb. Sci.* 2015).

After screening a ∼1500-member combinatorial library containing this scaffold, they found a potent inhibitor of the Mcl-1/BH3 interaction. Their initial work focussed on reproducing three hydrophobic residues, designed to mimic the spatial arrangement of the leucine residue at *i*, and the two valine residues at *i*+3 and *i*+7, which all project from one face of the BH3 α-helix. Encouragingly, the synthesis of their scaffold allowed for the ready incorporation of a further two residues (highlighted in red circles in **Figure 13d**). Indeed, this avenue was further explored and the group sought to install hydrophilic functionality at these two positions.[48] When these two positions were replaced with two carboxylic acid containing side chains [**Figure 13d (right)**], there was a significant improvement in antagonistic activity of the Mcl-1/BH3 interaction as compared to the parent three residue mimetic (>11 fold improvement). Thus, they had successfully converted their reasonably potent initial three residue, one face mimetic to a highly potent, amphiphilic, five residue, two face α-helix mimetic. The group are currently in the process of developing a large combinatorial library of related mimetics.[48]

As mentioned previously, we are interested in designing a novel set of α-helix mimetics that are capable of mimicking up to five residues projecting from three different faces. More specifically,

we are hoping for our mimetics to disrupt the PPIs which take place between a nuclear receptor and specific α-helical regions of relevant coactivator proteins. Cofactor proteins serve to regulate a nuclear receptor and can either enhance its transcriptional activity (coactivator) or dampen its transcriptional activity (corepressor).

3. Nuclear Receptors

Nuclear receptors (NRs) are the largest superfamily of ligand-activated transcription factors and are key elements involved in the control of gene expression. In contrast to other transcription factor classes, NR activity can be modulated by binding to small endogenous ligands *i.e.* small lipophilic molecules that can penetrate the nuclear membranes with ease.[49] Apart from their normal physiology, NRs are also known to be involved in many pathological processes, including asthma, cardiovascular disease, inflammation, diabetes, cancer, and rheumatoid arthritis.[49]

The protein structures of NRs can be divided into six separate domains labelled A-F, of which we are most interested in the ligand binding domain (LBD), domain E. This domain is found at the carboxy-terminal end of the protein and can be viewed as a molecular switch: upon ligand binding a conformational change ensues which results in a transcriptionally activate state. NRs can further be grouped into distinct classes depending on their mechanism of action which entails ligand binding, DNA binding, and dimerization (**Figure 14**).[50]

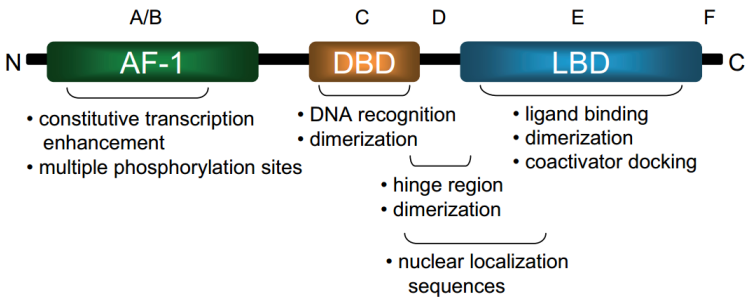


Figure 14 | Schematic illustrating the domain organization of NRs. The basic structural models are written inside the boxes and the general features associated with each module is listed underneath.[51] (Image taken from Pearce *et al. ChemMedChem* 2006).

3.1 Liver Receptor Homolog-1

The NR we are principally interested in is liver receptor homolog-1 (LRH-1). LRH-1 is a member of the steroidogenic factor like subfamily of NRs and is a key component in numerous biological processes, including development, metabolism and steroidogenesis.[52] LRH-1 is predominantly expressed in the liver, pancreas, small intestines and in the adrenal and sex glands, including the

ovaries.[53] For many years LRH-1 was believed to be an orphan receptor, *i.e.* a receptor for which the endogenous ligand has yet to be identified. However, work over the last few years has revealed that bacterial phospholipids present in the LBD of LRH-1 may be acting as endogenous ligands.[53,54,55] Other phospholipids, including sphingosine-1-phosphate[56] and phospholipid dilauroylphosphatidylcholine[57] have also been presented as potential LRH-1 agonists.

LRH-1 has been identified to be involved in the regulation of bile acid production and cholesterol degradation,[58,59,60] however our interest in LRH-1 primarily stems from its highlighted role as a possible target for the treatment of breast cancer.

3.1.1 LRH-1 and Breast Cancer

The hormone estrogen plays a pivotal role in the development and promotion of breast cancer growth. Estrogen is mediated by estrogen receptors with Estrogen receptor-α (ER), a transcription factor which drives cancer cell proliferation, being expressed in the majority of breast cancers. Consequently, the inhibition of ER action is crucial in the treatment of breast cancer and is typically achieved *via* selective estrogen receptor modulators, or anti-estrogens, such as tamoxifen. These act to inhibit ER activity by competing with estrogen for binding to the receptor.[61,62] An alternative method of inhibiting ER activity involves aromatase inhibitors, such as anastrozole and letrozole,[63,64] which act by preventing conversion of androgens into estrogen thereby obstructing the biosynthesis of estrogen.

One of the motivations propelling our research is the resistance observed with inhibitors of ER. Approximately 50% of patients with ERα positive breast cancer do not respond to endocrine therapies and in many cases a relapse is likely. In addition, there are very limited options once such resistance occurs.[61]

LRH-1 is known to play a key role in the development of breast cancer due to its role in the direct regulation of breast cancer cell growth, whereby it acts in concert with the ER.[59,62] Specifically, LRH-1 has been shown to regulate the expression of Growth Regulation by Estrogen in Breast Cancer (GREB1), a well-characterized ERα target gene. The overexpression of LRH-1 results in an increase in levels of GREB1 mRNA whereas knockdown of LRH-1 has the adverse effect of reducing GREB1 expression.[61]

In addition an LRH-1 binding site has been identified in the ER gene promoter *i.e.* ER is an LRH-1 target gene. Synthetic agonists which simulate the activity of LRH-1 increase the levels of ER whereas repression of LRH-1 reduces the expression of ER.[62]

Studies have further revealed that LRH-1 is able to regulate aromatase expression and thereby plays a role in the biosynthesis of estrogen. Due to their structural similarity, LRH-1 and ERα share many binding sites; LRH-1 promotes ERα recruitment and vice versa. This ultimately results in regulation over the expression of estrogen responsive genes and suggests a novel mode of nuclear receptor co-operativity in breast cancer cells (**Figure 15**).[61,65]

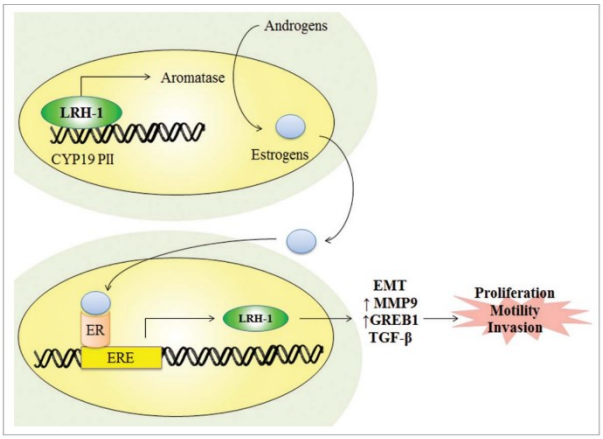


Figure 15 | The action of LRH-1 in breast cancer cells. LRH-1 binds at CYP19 PII resulting in aromatase expression. Aromatase subsequently converts androgens to estrogens that can then bind to ER. ER then interacts with estrogen response elements which leads to the activation of LRH-1. Some of the downstream effects of LRH-1 activation include EMT, up-regulation of MMP9, and GREB1 and TGF-b expression, which ultimately results in cell proliferation, motility, and invasion.[61] (Image taken from Nadolny & Dong, *Cancer Biol. Ther.* 2015).

Targeting LRH-1 therefore represents an important and alternative target for the treatment of breast cancer, especially in endocrine resistance breast cancer.

LRH-1 has been an active area of focus for the Spivey group with previous students directing efforts towards the synthesis of antagonists that bind to the ligand binding pocket of LRH-1.[66,67] In the research described in this thesis, the focus was on developing small drug-like molecules which can competitively bind to the coactivator binding site on LRH-1 and which should therefore be capable of antagonising the transcriptional activity of LRH-1. Switching the mode of therapy to targeting PPIs, such as blocking the interaction between LRH-1 NR and coactivator proteins using coactivator binding inhibitors CBI's, thereby presents an alternative approach to modulating the activity of NRs.

The development of CBIs was pioneered by the group of Katzenellenbogen who were exploring alternative modes at blocking ER action by using molecules which directly disrupt key interactions between the ER and coactivating binding proteins.[68] CBI's serve to block the interaction of NR's with coactivators *via* a direct, competitive mechanism and their mode of action is fundamentally different from traditional agonists.[68,69]

3.1.2 Activation Function 2 and the NR box

The capacity of NRs to switch between their active and inactive states *via* the addition of ligands has led to extensive analysis of biochemical pathways in attempts to better understand their mechanisms. This has ultimately led to knowledge about the mechanism of transcriptional activation by other classes of signal dependent transcription factors.[70] It has been deduced that a short conserved helical sequence within the carboxyl terminus of the LBD, termed the activation function 2 (AF-2), is necessary for ligand dependent activation.[71] Upon binding of agonist ligands a conformational change results which subsequently allows coactivator proteins to bind to the NR.[72] This interaction is an essential requirement for transcriptional activity and one that we hoped our CBI's would interfere with. The interactions between the NR LBD and coactivator proteins are extremely well studied. Upon binding of these two proteins, the helical elements involved in the AF-2 domain, particularly helix 12, in this "transcriptionally active" conformation arranges to form a shallow hydrophobic binding site.[73] Most interactions occurring between this binding site and the NR coactivators occur *via* a conserved α-helical LXXLL (L – leucine, X = any amino acid) signature primary sequence motif on the coactivator protein which has been termed the 'NR box' (**Figure 16**).[74]

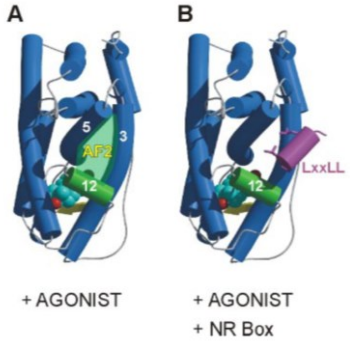


Figure 16 | Schematic representation of the estrogen receptor (ER) bound to the E2 agonist to give a "transcriptionally active" conformation in (A), and the E2/LXXLL NR box in (B). The location of AF-2 domain between helical elements H3-H5 (blue) and H12 (green) is indicated in (A). The LXXLL peptide is shown in (B) with the leucine residues further highlighted by stick representation.[73] (Image taken from Gustafsson *et al. Physiol. Rev.* 2007).

When bound to the NR, the first and third leucine residues point towards the hydrophobic groove. These residues are flanked by two polar residues that are aligned with the intrinsic dipole of the α-helix backbone of the NR peptide, creating a "charge clamp" which 'ties' the coactivator protein in place.[75]

3.1.3 Targeting the AF-2 Domain of LRH-1

LRH-1 appears to be a constitutively active transcription factor and the AF-2 domain of LRH-1 is packed in an active state. Furthermore, the crystal structure of the mouse LRH-1 LBD showed

that, in contrast to many other NRs, there is a sandwich fold of four layers of helices instead of three, and it is this extra layer of the helix fold which stabilizes the canonical LBD, which results in the observed constitutive activity of LRH-1.[76] This feature suggests that one may be able to selectively target the AF-2 binding domain of LRH-1 and hence regulate its transcriptional activity.

It has been identified that LRH-1 can bind to a variety of coactivator proteins, including SRC-1, TIF-2 and PGC1α.[76] Along with regulation by coactivators, LRH-1 has also been shown to be regulated by co-repressor proteins such as the orphan receptor, small heterodimer partner (SHP). The SHP protein contains two functional AF-2 binding domains which bear significant resemblance to the LXXLL motifs found in many NR AF-2 coregulators, including the coactivator proteins mentioned above. It is assumed that SHP employs the same LXXLL-related motifs to interact with LRH-1. Previous studies have revealed however that LRH-1 does not optimally bind to the LXXLL coactivator motif and thus the molecular basis for the LRH-1/SHP is currently not fully understood.[77] Xu *et al*. performed comprehensive structural and biochemical analyses to further understand the interaction between LRH-1 and SHP. Using AlphaScreen assays they demonstrated significant binding between LRH-1 and two SHP LXXLL-related domains, ID1 (SHP-1) and ID2 (SHP-2), which are crucial to the repression of several different NRs. Further, peptide competition experiments revealed that both SHP-1 and SHP-2 bind to LRH-1 (IC_{50} ≈ 0.5μM). Importantly, these binding affinities were comparable to those between LRH-1 and coactivator proteins, SRC-1 and TIF-2 (**Figure 17**).

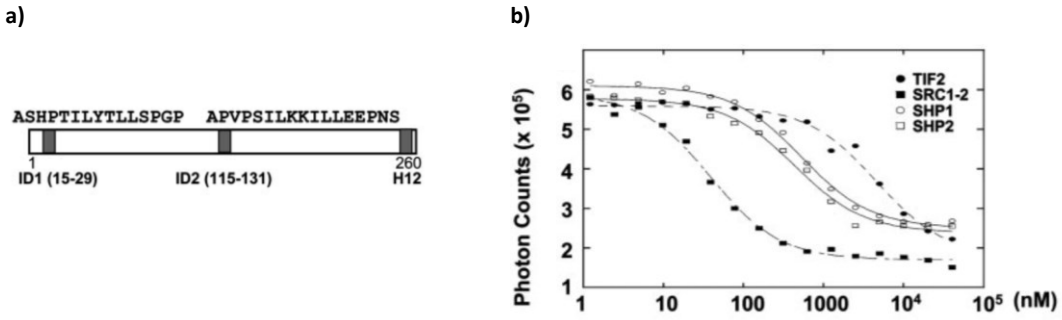


Figure 17 | Co-repression of LRH-1 with the SHP protein. a) A schematic of the SHP protein with the two receptor interaction motifs (ID1 and ID2) highlighted. b) The binding affinity of LRH-1 with SHP ID1, SHP ID2 and two coactivator proteins (SRC-1 and TIF-2) were determined by measuring IC_{50} values determined using peptide competition of the third motif of TIF-2 to LRH-1 – measured by AlphaScreen assays.[76] (Image taken from Xu *et al. Proc. Natl. Acad. Sci.* 2005).

Additionally, SHP-1 and SHP-2 demonstrated preferential binding to LRH-1 over a series of other NRs which it has been reported to repress.[76] Xu *et al.* were also able to crystallize the LRH-1 LBD in complex with SHP ID1. Their structural analysis showed that LRH-1 is folded into an active conformation similar to the apo LRH-1 structure. As alluded to above, it was believed that the

LRH-1 coactivator binding site is not suitable for binding the LXXLL (or related) motif of the coactivator protein, although, this proposal was made based on the apo LRH-1 structure. In contrast, Xu's work revealed that LRH-1 can interact with numerous coactivator motifs. It was discovered that several of the side chains present in the LRH-1 coactivator binding site undergo crucial changes in response to SHP binding which dramatically alters the surface landscape of the binding site on LRH-1, thereby allow binding of the SHP helix.

Alanine scanning mutagenesis studies were used to determine the importance of each residue of the SHP-1 and SHP-2 peptides in binding to LRH-1 (**Figure 18**).

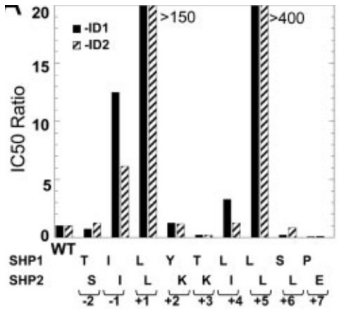


Figure 18 | Alanine scanning mutagenesis analysis of the SHP-1 and SHP-2 binding to LRH-1 as determined by AlphaScreen. IC_{50} ratios were determined between the values of the mutated peptides and the IC_{50} values for the wild-type SHP-1 and SHP-2 domains.[76] (Image taken from Xu *et al. Proc. Natl. Acad. Sci.* 2005).

For both peptide domains, it is clear that replacement of the leucine residues at the *i*+1 and *i*+5 positions with alanine residues have dramatic effects on the binding affinity (>150-fold decrease). This is analogous to the docking mode of coactivator LXXLL-motifs found in other NRs which typically have the *i*+1 and *i*+5 leucine residues orientated towards the central interface of the NR. Interestingly, the *i*-1 isoleucine residue has a significantly greater effect on binding than the *i*+3 polar residues for both SHP-1 and SHP-2. Also of importance are the polar residues at the *i*+2 positions [tyrosine (Y) for SHP-1 and lysine (K) for SHP-2] and the *i*+4 position (leucine for SHP-1 and isoleucine for SHP-2) – see **Table 1**.

Table 1 | Highlighted in red are the key determinants involved in binding of the SHP-1 and SHP-2 α-helical domains with the coactivator binding site of LRH-1.

	***i*-2**	***i*-1**	***i*+1**	***i*+2**	***i*+3**	***i*+4**	***i*+5**	***i*+6**	***i*+7**
SHP-1	T	I	L	Y	T	L	L	S	P
SHP-2	S	I	L	K	K	I	L	L	E

It was therefore planned to replicate the key residues on this highlighted XLXXXL scaffold as the basis of our mimetic design.

4. Project Aim and Previous Work

Our aim in this work was to develop the synthesis of a type III non-peptidic α-helix mimetic that could represent the key residues presented by the α-helical region of a coactivator protein involved in binding to the AF-2 region of the LBD of the NR LRH-1. It was anticipated that such a compound could act to block this PPI and as a consequence behave as an antagonist, potentially with useful biological consequences in the context of breast cancer regulation.

Katzenellenbogen *et al*. recently demonstrated the feasibility of using type III proteomimetics to effectively act as CBI's. They created a small library of symmetric 3,3'-disubstituted biphenyls designed to mimic the binding properties of the NR box on ERα.[75] Their initial results indicated the ability of their compounds to compete for the ERα coactivator binding groove with their most promising candidate exhibiting a K_i of 33 μM in their reporter gene assays.[75]

We were however, specifically interested in developing an α-helix mimetic that would be more sophisticated than the scaffolds containing planar aromatic rings, such as the biphenyl system described above and indeed the terphenyl and related scaffolds discussed earlier. In particular, we planned to develop a mimetic that would be capable of reproducing up to five amino acid residues projecting from three different faces of an α-helix as we anticipated, based on the above described work of Xu *et al.,* that such a design would maximise affinity and selectivity for the targeted PPI.

4.1 α-Helix Mimetic Design

A previous PhD student in the Spivey group, Bayly, had previously conducted studies into the identification of a molecular scaffold capable of representing the five residues discussed above. The scaffold was designed following mapping of the positions of the α-stereogenic carbon atoms (C_α) of the SHP-1 peptide which was chosen as a representative α-helix, based on Xu's work. Analysis of the XLXXLL motif found in SHP-1 revealed distances of approximately 3.8 and 5.3 Å between the α-carbons of the *i*+1 ↔ *i*+2 and the *i*+1 ↔ *i*+3 residues (**Figure 19**).[78]

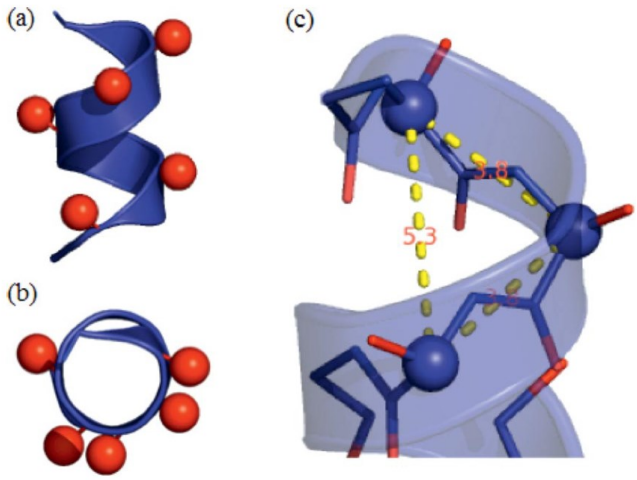


Figure 19 | Analysis of consecutive amino acids in the SHP-1 NR box α-helical domain (PDB: IYUC residues 20-25). a) Canonical α-helix with the *i*-1, *i*+1, *i*+2, *i*+4 and *i*+5 residues indicated with red spheres. b) Top down view showing these residues project from different faces of the helix. c) Distances between the i+1↔i+2, i+2↔i+3 and the i+1↔i+3 C_α's (blue spheres).[78] Image taken from Bayly and Spivey *European J. Org. Chem.* 2013).

Taking into consideration the distances between the C_αs and the intention to project the C_α-C_β bonds with approximately the correct vectors, the molecular design was quickly limited to bicyclic systems. After visual investigation of a series of bicyclic structures, Bayly focussed on the bicyclo[2.2.2] octane scaffold **I** (**Figure 20**).

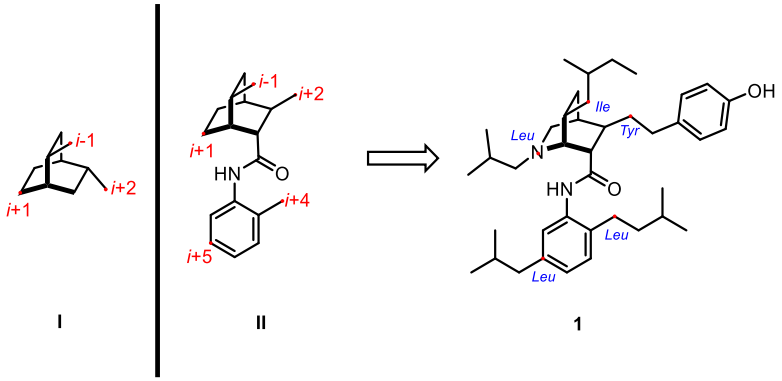


Figure 20 | Using molecular modelling, Bayly arrived at the bicyclo[2.2.2]octane scaffold **I** which projects three of the residues of the SHP-1 peptide (*i*-1, *i*+1 and *i*+2). This was extended to include the *i*+4 and *i*+5 residues upon attachment of the aryl amide to give the complete mimetic, **II**. Replacing the anchor points with the relevant residues found on the SHP-1 peptide gives **1** as a synthetic target.

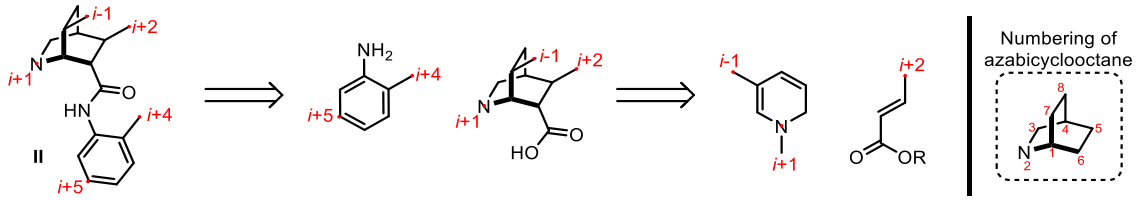
This scaffold matches the geometric constraints set by the SHP α-helix and is capable of projecting three consecutive amino acid side chains, corresponding to the *i*-1, *i*+1 and *i*+2 residues.[67] The remaining vectors of the bicyclic scaffold **I** were further investigated to allow for the incorporation of the final two leucine residues. The original scaffold was subsequently extended to project the *i*+4 and *i*+5 leucine residues *via* the attachment of a disubstituted aryl amide moiety to give the complete scaffold **II** (**Figure 20**). Substitution of the anchor points for

the relevant amino acid side chains present on the SHP-1 peptide leads to a synthetic target such as **1**. The inclusion of the *N* atom at the *i*+1 anchor position, which consequently transforms the core scaffold into an azabicyclo[2.2.2]octane, was designed not only to facilitate synthesis, but it also reduces the lipophilicity of the chosen scaffold.

4.2. Previous Synthetic Work

4.2.1 Development of Core Chemistry

Bayly's initially proposed retrosynthesis involved an amide coupling between a disubstituted aniline and the carboxylic acid of the azabicyclo[2.2.2]octane core (**Scheme 1**).



Scheme 1 | Bayly's retrosynthetic analysis of α-helix mimetic scaffold **II.**

One of the key disconnections involves setting up the biycyclic core, the construction of which was to be achieved *via* the use of a Diels-Alder (DA) reaction using a dihydropyridine (DHP) as the diene (see **section 4.2.2** for a more detailed discussion concerning this step).

To begin with Bayly explored the feasibility of the synthesis on a model scaffold containing methyl groups in place of all side chains (*cf.* five alanine residues). Due to the non-trivial synthesis and instability associated with 5-alkyl-1,2-DHPs[79] (see **section 4.2.2**), required to set up the *i*-1 residue at the C7 position of the azabicyclooctane, it was also decided by Bayly to optimize the synthesis with the significantly more accessible 4-alkyl-1,2-DHP, thus providing an isomer of the desired mimetic (**Figure 21**).

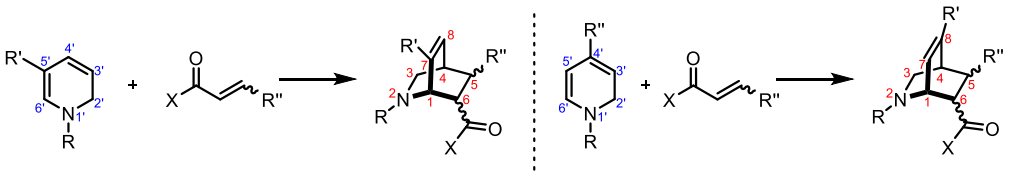
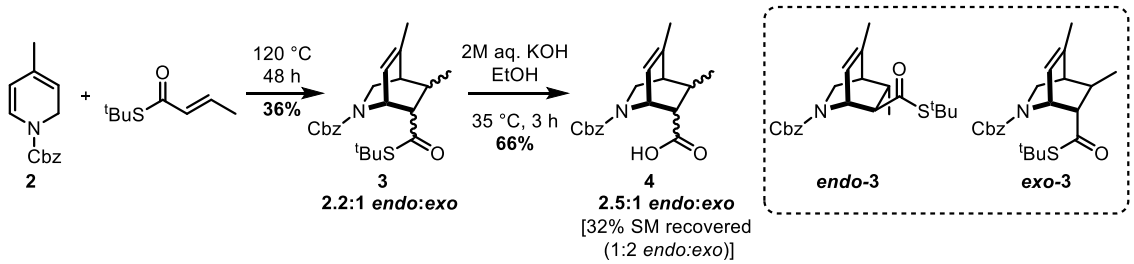


Figure 21 | Synthesis of 5-substituted 1,2-DHP's are non-trivial. Bayly therefore decided to explore the core chemistry on the 4-substituted derivative, which in turn leads to an isomer of the mimetic. The 4' and 5' positions of the DHP translates on to the C8 and C7 positions of the azabicyclooctane respectively.

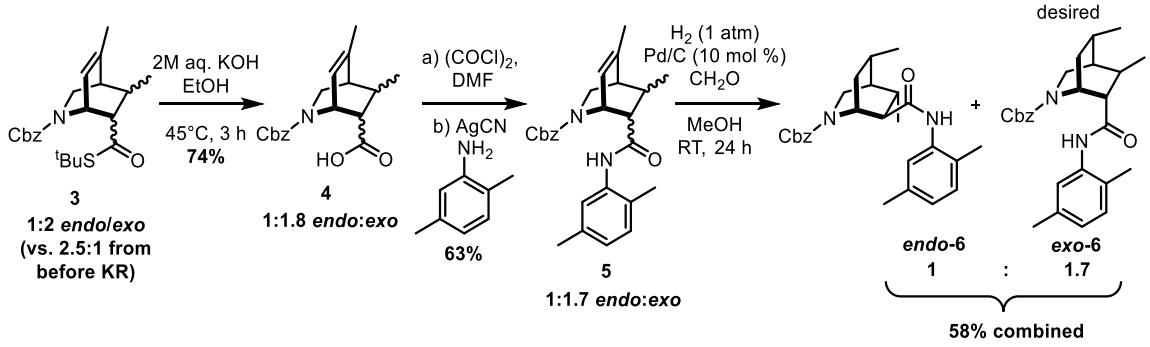
Accordingly, investigations into the DA reactions of 4-methyl-1,2-DHPs and the unsubstituted 1,2-DHP (used as a control to allow evaluation of the impact of the 4-substituent on reactivity) with a wide range of mono-activated dienophiles, including α,β-unsaturated esters, α,β-unsaturated *N*-acyl oxazilidinones and *N*-acyl pyrazoles, and propargyl amides was undertaken.

Despite extensive investigations which involved the use of thermal conditions and Lewis acid promoted conditions, no DA adducts were isolated, with decomposition of the DHP starting material typically being observed. Also explored as dienophiles were *N*-acroyl-2,10-camphorsultams, in combination with group IV Lewis acids, and boronic acid catalysed reactions of acrylic acids; both routes failed to give the desired DA adducts. After many attempts at promoting the DA reactions using Lewis acids, including the use of a variety of Cu, Al and group IV Lewis acids, Bayly concluded such conditions were ultimately not compatible with 1,2-DHP containing compounds, and thus looked to use more reactive dienophiles under thermal conditions. Eventually, some success was achieved with an α,β-unsaturated methyl ketone and an α,β-unsaturated-thioester, with the ketone variant yielding slightly better results. Unfortunately, attempts to convert the methyl ketone to the amide proved problematic. Bayly therefore proceeded with the thioester containing dienophile which gave the azabicyclooctane **3** in 36% yield as an inseparable mixture of the *endo* (undesired) and *exo* (desired) isomers in a 2.2:1 ratio (**Scheme 2**).



Scheme 2 | DA reaction of 4-methyl-*N*-Cbz-1,2-DHP (**2**) with crotonyl thioester and the subsequent hydrolysis reaction.

Hydrolysis of the *endo/exo* mixture of thioester **3** was observed to occur at a greater rate for the undesired *endo* isomer. Using this observation, a partial kinetic resolution allowed for recovery of the starting thioester enriched in the desired *exo* isomer. This *exo*-enriched thioester was then hydrolysed as before and coupled with 2,5-dimethylaniline, *via* the acid chloride, to give an inseparable mixture of *endo*-**5** and *exo*-**5** (**Scheme 3**).



Scheme 3 | Bayly's synthetic route to the model per-methylated mimetic.

Finally, a one-pot, 3-step sequence of reactions to achieve *N*-Cbz hydrogenolysis, reductive-amination with formaldehyde, and diastereoselective alkene hydrogenation was performed yielding a mixture of the two biyclic compounds, *endo*-**6** and *exo*-**6**, which were purified using HPLC. An X-ray crystal structure of the undesired *endo* isomer was obtained which confirmed that the *endo*-adduct was the major product from the initial DA reaction.

4.2.2 Synthesis and Diels-Alder Reactions of 1,2-Dihydropyridines

With the chemistry for this model system established, Bayly next focussed on adapting this route to allow for installation of the correct side chain residues. There was also need to re-investigate the diastereoselectivity in the DA step given the low yield and *dr* in this key step. In addition, a method for installation of the *i*-1 isoleucine residue at the C7 position of the azabicyclooctane core needed to be developed (*cf*. at the C8 position in the model synthesis) – **Figure 22**.

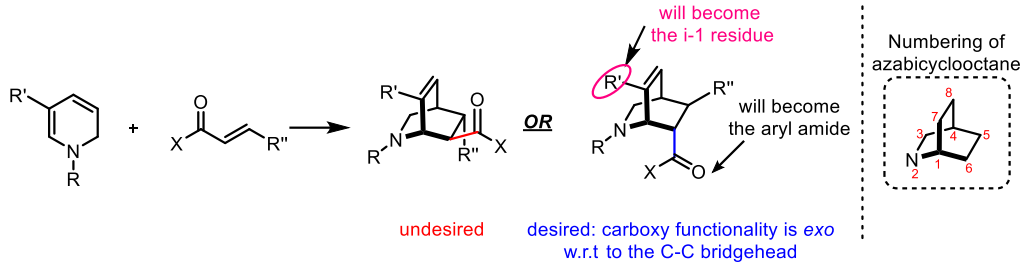
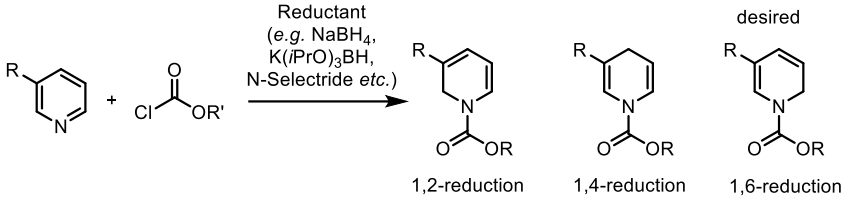


Figure 22 | Key aspects needed to be addressed include the use of a 5-substituted-1,2-DHPs and having the carbonyl group in the *exo* position.

Synthesis of 1,2-Dihydropyridines

Given that the C7 position of the azabicyclic core translates back to the C5 position of the starting 1,2-DHP, understanding the synthesis and reactivity of 5-substituted-1,2-DHPs was necessary. Much of the literature involving the design and use of 1,2-DHPs in synthesis typically have the pyridine *N* atom protected as a carbamate group. This imparts a significant degree of stability onto the DHP, which would otherwise readily oxidise to the corresponding pyridine. The most utilized method for the preparation of such DHPs was developed by Fowler and involves the reduction of an *in-situ* generated *N*-carbalkoxypyridinium ion that is formed upon treatment of a pyridine with a chloroformate ester.[80]

Sundberg *et al.* subsequently analysed how the substituents around the pyridine ring affects the regioselectivity of the reduction step to form the DHP.[81] This included an examination of the reaction of 3-substituted pyridines, which can in principle form 1,2-, 1,4-, and 1,6-reduction products (**Scheme 4**).



Scheme 4 | Reduction of pyridines can lead to three different isomeric 1,2-DHP products.

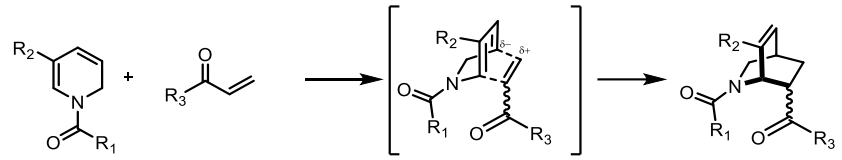
Overall, with sodium borohydride as the reductant, Fowler found that sterically non-demanding donor substituents (*e.g.* alkyl, alkoxy, alkylthio, chloro and bromo groups) greatly favoured 1,2-reduction by a ratio of 9:1 or more relative to the other isomers, while electron withdrawing substituents (*e.g*. CO_2CH_3 and CN groups) gave appreciable amounts of all three isomers. Moreover, using bulky reducing agents did not appear to override the inherent selectivity induced by the donor substituents. The propensity to undergo 1,2-reduction was however weaker for branched substituents such as Me_3Si and *n*-Bu_3Sn, and for these cases the use of bulkier reducing agents could bias the regioselectivity in favour of 1,6-reduction. Although the inclination of pyridines with donor substituents at C3 to be attacked at the C2 carbon (*i.e.* 1,2-reduction) has been well documented, the underlying reason is less understood. Sundberg *et al.* conducted a series of calculations which suggested this regioselectivity is a reflection of the stability of the product. This can be explained using a Huckel model: if one appreciates that a donor substituent, *e.g*. an OMe group, can contribute 2π electrons to the butadiene-resembling π-system of the reduced dihydropyridine, the 1,2-reduction product will resemble a pentadienyl anion π-system. This linearly conjugated π-system will usually be more stable than the corresponding cross conjugated isopentadienyl anion which forms following 1,6-reduction.[81] In contrast to the above proposal based on the stability of the product, it is not unreasonable to suggest that the preference for 1,2-reduction, when there is a donor substituent at the C3 position, might be a consequence of the intrinsic transition state stability.

Given this understanding, installing the alkyl residue on the DHP prior to the DA reaction, particularly *via* the Fowler method, did not seem attractive. Before completely ruling out the this method however, an alternative route to 5-alkyl-1,2-DHP's, developed by Raucher,[79] was attempted by Bayly. However, due to the instability of the resulting DHP and the lengthy synthetic sequence this route was not deemed viable for further development. Clearly, it would be advantageous to develop a route involving a FGI of an appropriate functional group to the desired alkyl side chain *after* the DA reaction.

Diels-Alder Reactions of 1,2-Dihydropyridines

The groups of Sundberg and Krow both explored in detail the role of the substituents on DHP's

in determining the regio- and diastereoselectivity of subsequent DA reactions with a series of dienophiles.[81,82] The regioselectivity of the thermal DA reactions of 1,2-DHPs with mono-activated dienophiles is usually high and leads to the *N* atom of the bicycle being on the same side as the carbon α to the activating group (typically a carbonyl group) (**Scheme 5**).



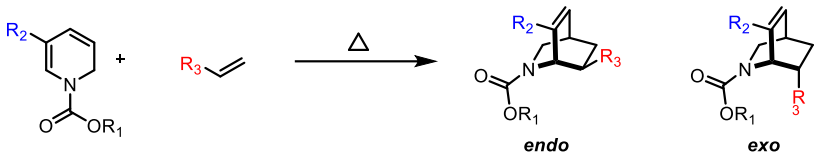
Scheme 5 | Regioselectivity in DA reactions of 1,2-DHPs with monoactivated dienophiles.

By contrast, the diastereoselectivity observed in such reactions is generally poor, leading to mixtures of the *endo* and *exo* isomers. In addition, the outcome with many dienophiles, such as methyl acrylate, methyl vinyl ketone and acrolein, are known to occur under kinetic control.[82]
Before focussing on the substituents around the DHP, it is worth noting that the carbamate protecting group might also exert a slight influence on the outcome of these DA reactions. Krow postulated that there may exist a favourable interaction between the *N* atom of the DHP with the ester carbonyl (of the dienophile), and between the carbonyl of the carbomyl group with the *O* atom of the ester carbonyl, thereby favouring the *exo* isomer. However, this appears to be overcome by the size of the ester group on the dienophile. For example, the reaction between *N*-methoxycarbonyl-1,2-DHP and methyl acrylate in refluxing toluene gives a 1.3:1 *endo/exo* ratio, whereas with benzyl acrylate as the dienophile there is a slightly increased preference for the *endo* isomer (2:1 *endo*/*exo*).[82]
Overall, there does appear to be a greater kinetic preference for the *endo* diastereoisomer in DA reactions with simple monoactivated dienophiles such as those highlighted above. This preference can be rationalised by consideration of secondary orbital interactions between the HOMO of the 1,2-DHP and the LUMO of the dienophile, where the interaction between the carbonyl of the dienophile and the newly forming C=C in the DA adduct favours formation of the *endo* isomer.[83]

Of particular interest to us was the effect that the C5-substituent of the 1,2-DHP might have on the *endo/exo* diastereoselectivity. In the DA reaction between 5-methyl-*N*-methoxycarbonyl-1,2-DHP and styrene, Krow *et al.* observed similar preference for the *endo* isomer (8.1:1 *endo/exo*) as compared to the unsubstituted parent DHP (6.1:1 *endo/exo*) (**Table 2**, entries 1 and 2). [*N.B.* The related unsubstituted *N*-Cbz protected DHP displayed similar *endo/exo* ratios as the methoxycarbonyl derivative]. A comparable propensity for the *endo* isomer to

predominate was also observed in the corresponding DA reaction with methyl vinyl ketone as the dienophile (entry 4, see entry 3 for the unsubstituted DHP).[82]

Table 2 | The stereochemical effect of the 5-substituent on *N*-carboxalkoxy-1,2-DHP's in thermal DA reactions



Entry	R_1	R_2	R_3	*Endo : Exo*	Yield (%)
1	Me	H	Ph	6.1 : 1	32
2	Me	Me	Ph	8.1 : 1	38
3	Me	H	COMe	2.8 : 1	63
4	Me	Me	COMe	9 : 1	22
5	Et	Me_3Si	CO_2Me	1 : 2.4	60

Interestingly, the presence of a Me_3Si group at the C5-position of the DHP appeared to swing the selectivity in favour of the *exo* isomer, giving a 1:2.4 *endo/exo* ratio (entry 5).[81] Presumably the steric bulk of the silyl group clashes with the activating group on the dienophile favouring the *exo* transition state.

In light of this precedent, Bayly hypothesised that the use of a bulky silyl group at C5 could be advantageous for subsequent installation of the *i*-1 residue *via* Hiyama-Denmark type coupling. Not only would the silyl group favour formation of the desired DHP (1,6-reduction favoured over 1,2-reduction) but it would also favour the *exo* DA adduct.

Bayly therefore synthesised 5-dimethylbenzylsilyl-*N*-Cbz-1,2-DHP, envisaging a Hiyama-Denmark type coupling to convert the benzyl silane functionality into the isoleucine residue at a later stage. The thermal DA reaction with crotonyl thioester, the dienophile used to develop the core chemistry above, gave encouraging levels of stereoselectivity (1:2 *endo/exo*), however the yields were very low (12% at 120 °C for 48 h, and 22% at 180 °C in a MW for 4 h). Although similar levels of diastereoselectivity and higher yields were obtained with methyl vinyl ketone (42% at 120 °C for 48 h, and 75% at 180 °C in a MW for 4 h), given the aforementioned challenges associated with converting the methyl ketone to the desired carboxyl functionality, this pathway was abandoned.

4.2.3 Strategy Re-design

At this juncture, a reinvestigation of the structural requirements for α-helix mimicry by Bayly revealed that altering the stereochemistry of the *i*+2 substituent to the *exo* positioned variant would likely maintain the gross mimetic ability of scaffold. The structural analysis also showed

that *i*+5 substituent on the aryl amide could be moved from the *meta* position of the aryl ring to the *ortho* position without apparent detriment to the coordinate overlay (**Figure 23**).

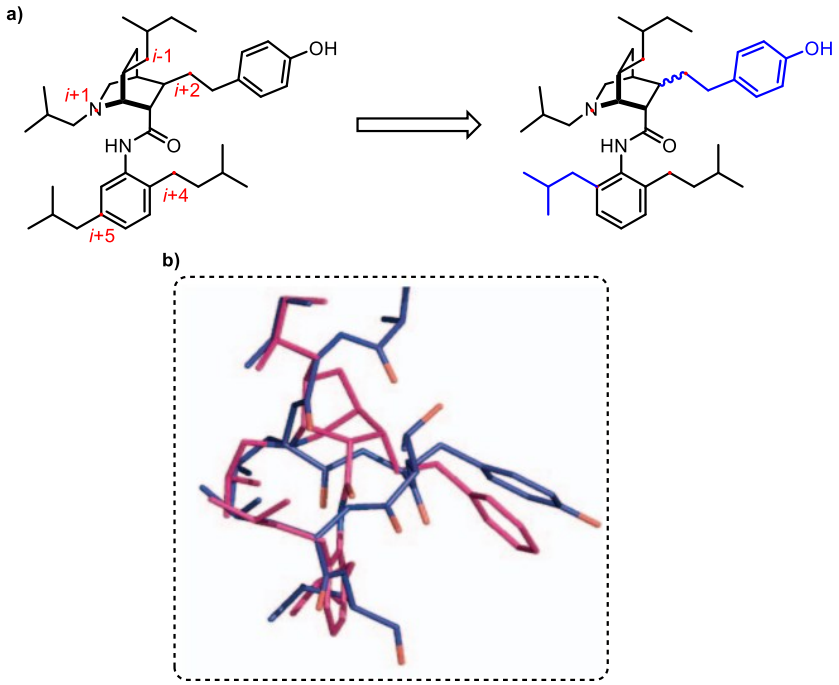
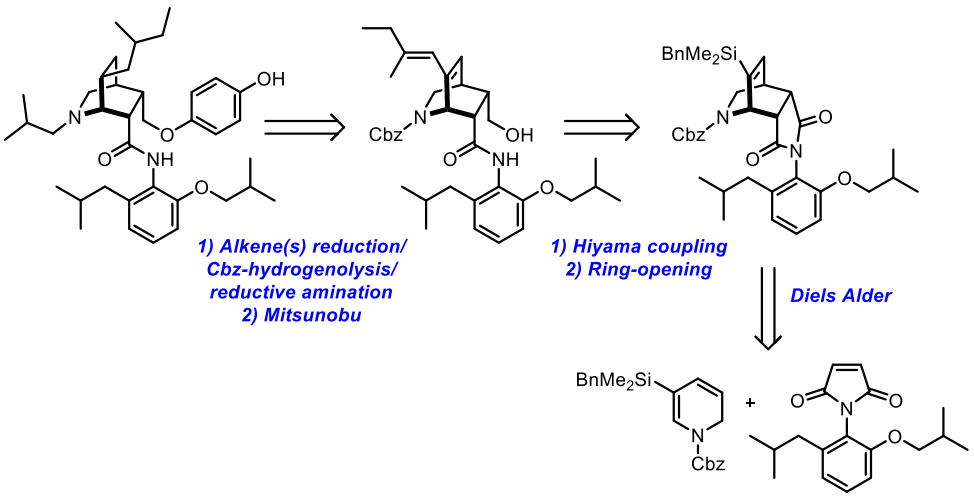


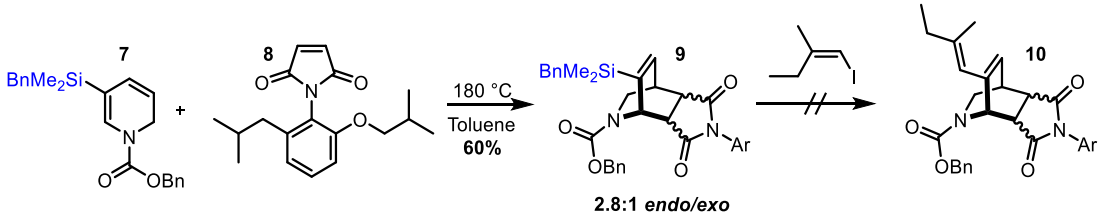
Figure 23 | a) Structural analysis of the mimetic shows that the *i*+2 residue can be in the *exo* position and that the *i*+5 residue can be in the *ortho* position (shown in blue). b) Overlay of this new mimetic (magenta) with SHP-1 (blue) shows good overlay.

The modified geometry of the *i*+2 substituent opens up the possibility of using a *cis*-disubstituted dienophile in the Diels-Alder reaction. Given the markedly increased reactivity of cyclic *cis*-dienophiles in particular, Bayly proposed a synthetic strategy using an *N*-aryl maleimide which already contains the *i*+4 and *i*+5 residues, as the dienophile. The proposed *N*-aryl amide also contains an ether linkage which was not in the original mimetic. This ether was included primarily to aid the synthesis and has the advantage of increasing the number of heteroatoms in the mimetic. Finally, the cyclic dienophile necessitates a regioselective ring-opening reaction and a subsequent Mitsunobu reaction (**Scheme 6**).



Scheme 6 | Overview of Bayly's new synthetic proposal using a diactivated cyclic dienophile.

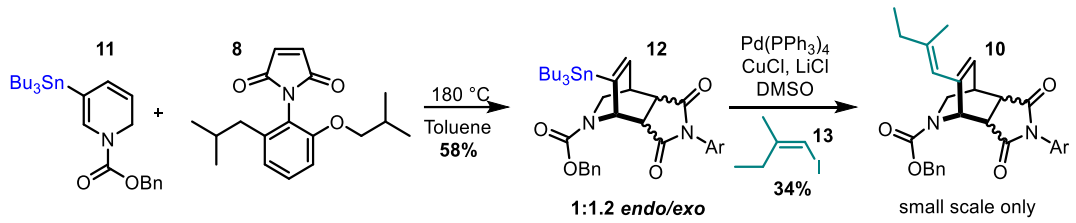
The DA reaction between the C5-silyl substituted DHP (**7**) and *N*-phenylmaleimide gave yields of up to 80%, with equal amounts of the *endo* and *exo* isomers being formed. By contrast, the corresponding DA reaction with the more complex dienophile **8** gave yields up to 60%, with the undesired *endo* isomer of DA adduct **9** predominating (~2.8:1 *endo/exo*) – **Scheme 7**.



Scheme 7| The DA reaction of 5-$BnMe_2Si$-*N*-benzyloxy-1,2-DHP and *N*-aryl amide gave a 2:1 *endo/exo* ratio (N.B: this stereochemical assignment was not fully confirmed). This was to be followed by a Hiyama-Denmark coupling.

The subsequent alkene coupling also proved challenging as under the reaction conditions explored by Bayly, only the desilylated product was obtained, thereby losing the key functional handle at C7.

Finally, Bayly explored having a bulky stannane group in place of the silyl group, with the aim to carry out a Stille coupling to introduce the alkyl chain at C7. The 5-Bu_3Sn–*N*-Cbz-1,2-DHP (**11**) was readily obtained using Fowler's reduction conditions on the 3-substituted pyridine. The following DA reaction with *N*-aryl maleimide **8** occurred in 58% yield, however the diastereoselectivity was poor with the reaction giving a 1:1.2 *endo/exo* ratio (**Scheme 8**).



Scheme 8| The DA reaction of 5-Bu_3Sn-*N*-Cbz-1,2-DHP (**11**) and N-aryl amide **8** gave a 1:1.2 *endo/exo* ratio. The subsequent Hiyama-Denmark coupling reaction proceeded in 34% yield but only on a small scale.

A Stille coupling between the mixture of product isomers **12** and vinyl iodide **13** gave the desired diene **10** in 34% yield, albeit on a very small scale.

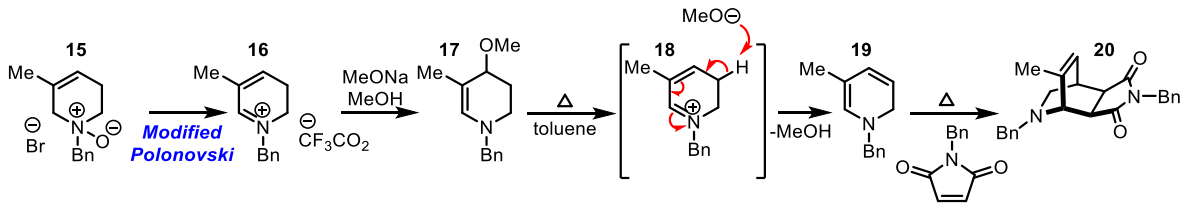
RESULTS AND DISCUSSION

5. Chapter 1 – Cyclic Dienophiles

5.1 Functionalization of the C7 Position (*i*-1 Residue)

At the outset, the plan was to continue with Bayly's synthetic route based on the DA reaction of a maleimide dienophile.

Work initially began towards installation of the alkyl residue at the C7 position of the azabicyclooctane (*i.e. i*-1 residue). Functionalization of a silyl group and a stannane group at this position did not look encouraging and so a new route was sought. Due to the challenges associated with the formation of 5-alkyl-1,2-DHP's *via* Fowler's route, and the lengthy alternative route developed by Raucher, we became interested in a route proposed by Marazano, which involved the *in-situ* formation of the dihydropyridine followed by immediate trapping with a dienophile.[84] Marazano's route requires the formation of *N*-oxide salt **15** which is then converted into dihydropyridinium salt **16** following a modified Polonovski reaction (**Scheme 9**).

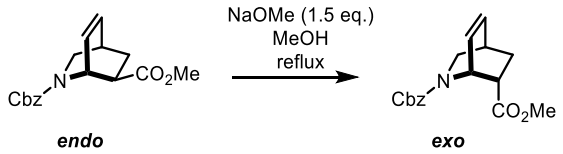


Scheme 9| Marazano's route towards 5-alkyl-1,2-DHP's.[84]

Marazano found that treatment of the *in-situ* generated dihydropyridinium salt with sodium methoxide in methanol gave tetrahydropyridine **17**, which upon heating liberated dihydropyridinium salt **18**. He proposed that this salt reacted with the methoxide anion generated from the previous step to yield the desired 5-alkyl-1,2-DHP **19**. This unstable species was then immediately trapped to prevent decomposition or isomerization to either the 1,4-dihydropyridine or the isomeric 1,2-dihydropyridine. Marazano found that when a reactive dienophile, such as *N*-benzylmaleimide, is present, the corresponding DA-adduct **20** could be isolated in 65% yield with total *endo* selectivity.[84]

The DA reaction of DHPs containing sterically unencumbered *C*-substituents on the DHP ring, such as in the case above, have been noted to give excellent *endo* selectivity when treated with *N*-aryl maleimides. Given the challenges experienced previously in trying to achieve useful levels of diastereoselectivity in this type of DA reaction, we wondered whether this undesired selectivity could be turned to our advantage. In their work on the synthesis of Iboga alkaloid

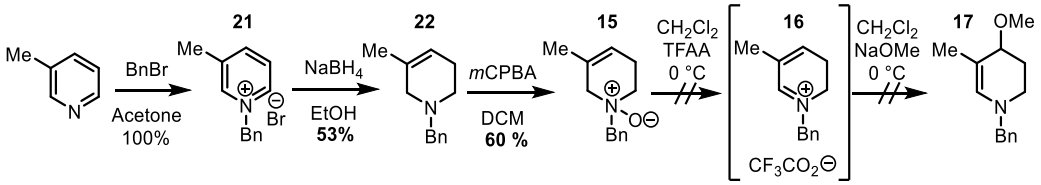
analogues, Sinha *et al.* required an *exo*-ethyl group at the C7 position of an azabicyclooctane which they envisaged to obtain from the corresponding methyl ester. Having isolated mainly the undesired *endo*-isomer, they found they could epimerise this to the desired *exo*-isomer under basic conditions at elevated temperatures, going from the pure *endo*-isomer to a 1:9 *endo/exo* ratio (**Scheme 10**).[85]



Scheme 10| Sinha *et al.*'s epimerisation of an *endo*-isomer to a 1:9 *endo/exo* ratio of isomers upon treatment with base at elevated temperatures.[85]

Inspired by these two findings, we decided to pursue Marazano's dihydropyridine chemistry and cycloaddition reaction, with the aim to epimerise the carboxyl functionality at C7 using Sinha's conditions in the event that the initial selectivity was in favour of the *endo* isomer.

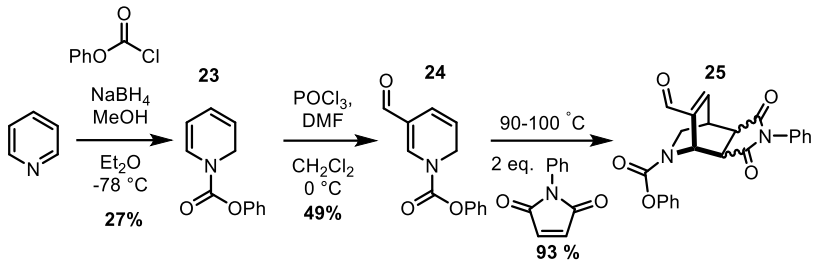
To begin with, we attempted to replicate Marazano's procedure using the same starting materials. Thus, 3-picoline was treated with BnBr to give pyridinium salt **21** in quantitative yield. This was followed by reduction to 3-methyl,1-benzyl,1,2,5,6-tetrahydropyridine (**22**), using $NaBH_4$, which was achieved in moderate yield consistent with literature (**Scheme 11**).[86]



Scheme 11| Attempted synthesis of tetrahydropyridine **17**, the precursor to the corresponding 5-alkyl-1,2-DHP, as developed by Marazano.

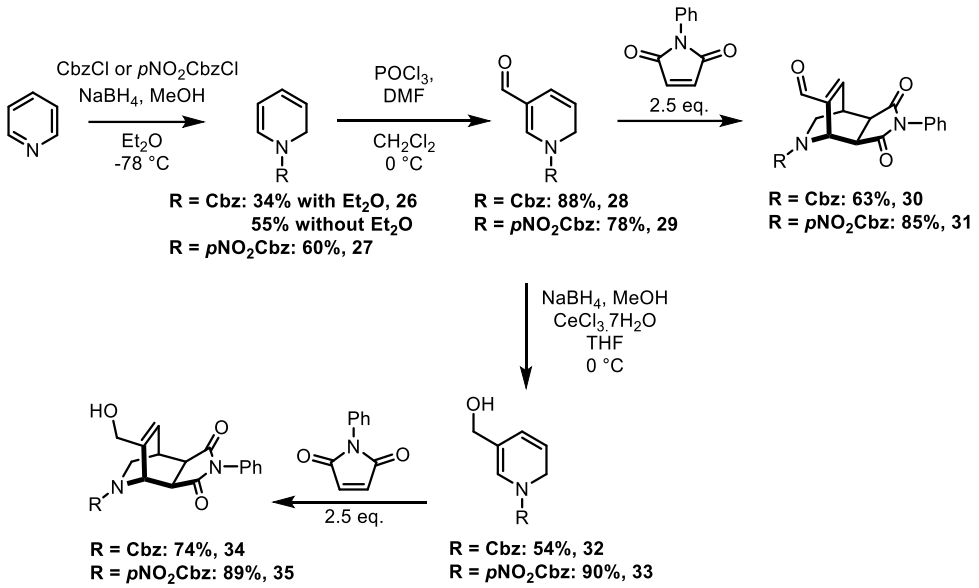
Tetrahydropyridine **22** was treated with *m*CPBA to provide *N*-oxide **15** in 60% yield. Unfortunately, formation of the 4-methoxytetrahydropyridine **17,** which is the precursor to the 1,2-DHP, *via* the modified Polonovski reaction proved to be troublesome. This reaction was attempted repeatedly but no methoxy addition product could be detected. It was hypothesised that the reaction was failing during the first step (*i.e*. the formation of the TFA salt **16**), and thus the reaction was attempted with acetic anhydride in place of TFAA but with no success. Despite our best efforts, which included freshly distilling TFAA three times immediately prior to use and forming the sodium methoxide *in situ*, no positive results were obtained and it was becoming apparent that this protocol was irreproducible. Consequently, we terminated our investigations into this route.

An alternative strategy towards 5-substituted-1,2-DHPs was required and we considered the idea of functionalizing the unsubstituted DHP. Comins had reported selective formylation at the 5 position of an unsubstituted *N*-protected 1,2-DHP, using the phenyloxycarbamate group as the nitrogen protecting group.[87] This chemistry was investigated, initially using the same protecting group as Comins (**Scheme 12**).



Scheme 12 | Synthesis of 5-formyl-1,2-DHP **24** and subsequent DA chemistry.

In regards to the initial formation of the 1,2-DHP it is worth mentioning that prolonged reaction times, elevated temperatures and the use of aprotic solvents such as THF are known to favour the formation of the undesired but more thermodynamically stable 1,4-DHP. Formation of the 1,4-DHP can however be minimized upon maininting the temperature below -70 °C.[81,82] Accordingly, *N*-phenyloxy-1,2-DHP (**23**) was obtained, albeit in poor yield, from pyridine using Fowlers' conditions. As observed by Comins, formylation exclusively at the 5-position occurred to give aldehyde **24.** This crystalline compound was found to be stable to air which presents a clear advantage over other similarly substituted DHP's *e.g.* alkyl, silyl and stannyl substituted derivatives. Heating aldehyde **24** and *N*-phenylmaleimide in the absence of solvent provided a single new spot by TLC analysis with complete consumption of the starting material (SM). The NMR spectra of the isolated compound was complex and appeared to be a mixture of DA adducts. Attempts at hydrolysing the phenylcarbamate using LiOH or KOH to give the free amine compound as a means to simplify the analysis did not prove successful. Given that Bayly had optimised the hydrogenolysis/reductive amination on the *N*-Cbz containing azabicyclooctane, we therefore returned to benzylcarbamate protecting groups; both the Cbz and the *p*NO_2Cbz derivatives were investigated. Podlech examined the effects of adding substituents to the Cbz protecting group and found that the positioning of an electron withdrawing group such as a nitro group or a halogen at the *para* position had the effect of imparting crystallinity into the compounds.[88] The chemistry outlined previously was repeated using these two new protecting groups (**Scheme 13**).



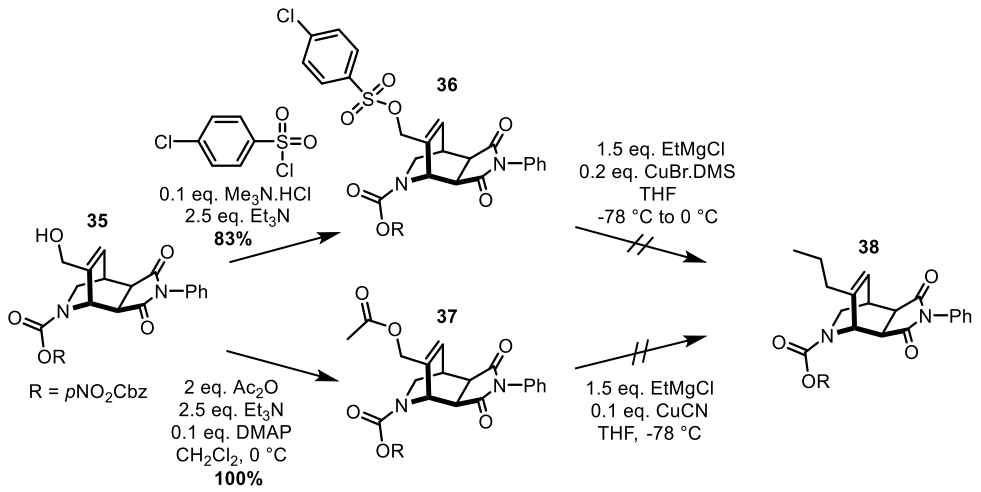
Scheme 13 | Synthesis and DA reactions of 5-formyl-1,2-DHPs containing Cbz and *p*NO_2Cbz protecting groups.

Pleasingly, the formylation reaction on both the Cbz and *p*NO_2Cbz protected 1,2-DHP's proceeded in higher yields than the phenyloxy variant. Aldehydes **28** and **29** were next treated with *N*-phenylmaleimide to give DA adducts **30** and **31** respectively, which as before had complex NMR spectra. Extensive 1D, 2D and VT NMR analysis was then conducted on DA adduct **30** to determine whether the mixture contained two diastereoisomers *i.e. endo*/*exo* isomers, or rotamers about the carbamate bond. The spectroscopic evidence, combined with comparisons with similar compounds in literature, revealed that rotamers (*i.e*. conformational isomers) were responsible for the complexity and that the reaction gave exclusively the *endo*-isomer. Importantly, NOE cross peaks were observed between the *N*-Ph aromatic protons and the aldehyde proton and clear convergence of peaks were observed in the ^{1}H and ^{13}C spectra at higher temperatures.

Attempts at removing the *p*NO_2Cbz protecting group under hydrogenation conditions were unsuccessful. The same was true for the Cbz derivative. Furthermore, attempts to functionalise the aldehyde, for example by reduction using $NaBH_4$ or *via* a Wittig reaction with *sec*-butyltriphenylphosphonium bromide failed. As it was suspected that the unsaturated aldehyde was causing problems with the Cbz cleavage step, it was decided to reduce the 1,2-DHP aldehyde prior to performing the DA reaction. The Luche reduction proved relatively straightforward providing both alcohol **32** and **33** as crystalline solids. As had been the case in previous steps, the yields were markedly higher with the *p*NO_2Cbz protected compound. In addition, the compounds bearing the additional NO_2 group were found to be more stable, for *e.g.* alcohol **34** was found to decompose at room temperature within a few hours whereas compound **35** was

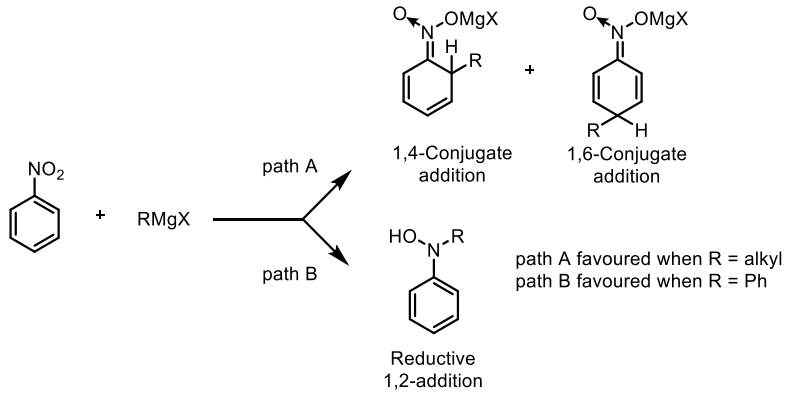
stable**.** The DA reaction proceeded in high yields for both compounds **34** and **35**, again giving total *endo*-selectivity in both cases.

Efforts were then focussed on alkylation at the allylic position *via* a nucleophilic substitution reaction. Initially, the *p*NO_2Cbz protected derivative **35** was investigated. The alcohol was converted into both the parachlorophenylsulfonyl (**36**) and acetylated (**37**) derivatives before exploring the addition of a Grignard reagent (**Scheme 14**).



Scheme 14 | Installation of an alkyl chain at C7.

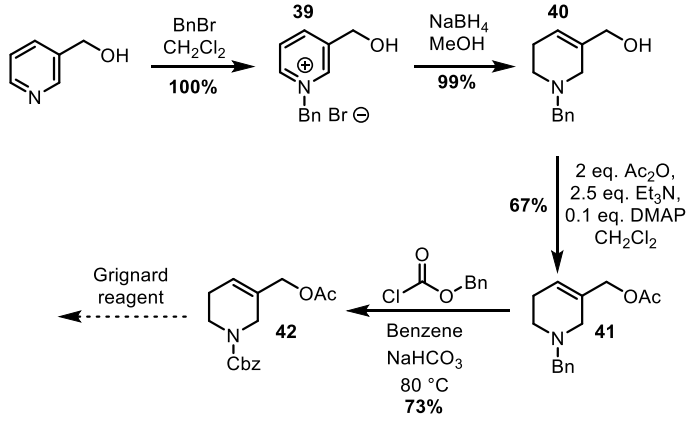
EtMgCl was used for model studies as the use of *sec*-BuMgCl, as required to incorporate the desired isoleucine residue at the *i*-1 position, would introduce a new stereoecentre thereby adding further complexity to the ^{1}H and ^{13}C NMR. After several failed attempts at allylic substitution using both activated alcohol derivatives, it became apparent that the Grignard reagent was interacting preferentially with the *p*NO_2Cbz protecting group. The reaction of Grignard reagents with nitroarenes, though complex, is well known,[89] and in addition to reduction pathways, conjugate addition (path A) and reductive 1,2-addition (path B) of the Grignard onto the aryl ring are both possible – **Scheme 15**.



Scheme 15 | Known modes of reaction of Grignard reagents with nitroarenes.

Nucleophilic substitution using an alkyl metal reagent with the *p*NO_2Cbz derivatives (**36** and **37**) was consequently abandoned. Before exploring the Grignard addition with the Cbz derivative, we decided to explore the allylic alkylation on a model substrate.

There has been significant work over the last few decades in the area of Pd catalysed allylic alkylation, though this has typically involved soft nucleophiles such as malonates.[90,91] These Pd-mediated processed are often hampered by poor regioselectivity (S_N2 *vs*. S_N2') in non-symmetrical allylic substrates and thus were not attractive for us. By contrast, copper has been found to tolerate hard, non-stabilized nucleophiles such as small alkyl organometallic species including organolithium, magnesium and zinc reagents.[92] To explore the copper mediated S_N2 alkylation, allylic acetate **42** was considered an appropriate model for several reasons: the allylic bond is β to the nitrogen atom in a cyclic system; the synthesis makes use of straightforward chemistry commencing from commercially available and cheap pyridine-3-methanol; and finally this route allows for quick variation of the protecting group which we had established is of some importance in this substitution step (**Scheme 16**).



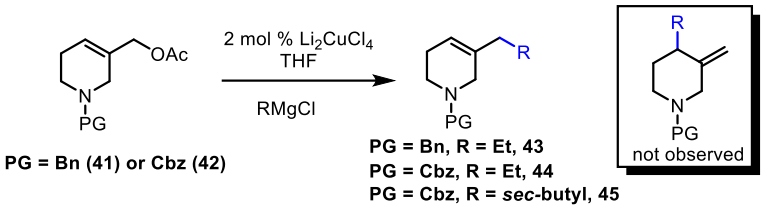
Scheme 16 | Synthesis of model substrates to explore allylic alkylation.

Benzylation of pyridine-3-methanol followed by reduction of the bromonium salt **39** to tetrahydropyridine **40** proceeded in near quantitative yield without the need for purification, after which the alcohol was acetylated in 67% under standard conditions. The allylic alkylation was to be explored on both the Bn protected and Cbz protected compounds. The Cbz protected tetrahydropyridine **42** was synthesised upon treatment of the *N*-Bn compound with benzyl chloroformate under basic conditions.

Bäckvall *et al.* explored in detail the regioselectivity of copper-catalysed Grignard reactions of allylic substrates and demonstrated that it was possible to strongly influence this by varying the reaction conditions in order to control the formation of different active catalytic intermediates.[93] Specifically, considerable efforts were directed towards understanding the behaviour of reactions catalysed by the cheap and readily available commercial compound Li_2CuCl_4. This complex is commonly utilized to promote reactions between Grignard reagents and alkyl halides; its convenience arises from the observation that it is readily soluble in most organic solvents and is quickly reduced to a copper(I) salt by the Grignard reagent at temperatures as low as -78 °C. Thus, the reaction between this copper(I) complex and the Grignard reagent forms an organocopper complex as either a mono- or dialkyl copper species: monoalkylcopper species favour γ-alkylation whereas dialkylcuprates tend to favour α-alkylation, at least with primary allylic acetates. Bäckvall identified four reaction parameters which control the nature of the catalytic species generated: a) Grignard reagent addition time, b) reaction temperature, c) amount of catalyst, and d) the reactivity of the allylic substrate. Overall, the study showed that fast addition of the Grignard reagent (∼2 mins) and a low loading of the Li_2CuCl_4 catalyst (~2 mol%) at low temperatures favours the α-substitution product. Solvent effects, though often pronounced in substitution reactions of allylic acetates with Grignard reagents catalysed by CuCN, were found to be surprisingly unimportant in these reactions.[93]

Inspired by Bäckvall's findings, we began exploring the allylic substitution reactions of model substrates **41** and **42** (**Table 3**).

Table 3 | Investigating substitution reactions on model substrates **41** and **42** using Bäckvall's conditions.



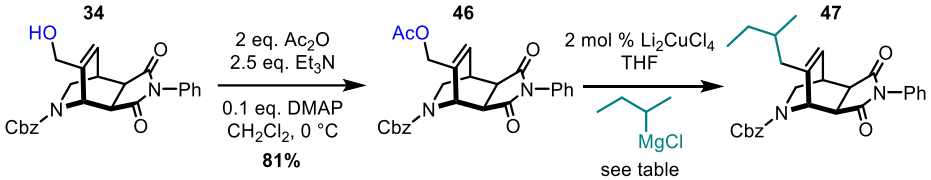
PG = Bn (41) or Cbz (42)

PG = Bn, R = Et, 43
PG = Cbz, R = Et, 44
PG = Cbz, R = *sec*-butyl, 45

Entry	PG	R	Eq. of Grignard	Duration / Temp.	Yield
1	Bn	Et	1.5	1 h / -78 °C	-
2	Bn	Et	1.5	2 h / -30 °C	28%
3	Bn	Et	3	2 h / -30 °C	40%
4	Bn	Et	3	30 mins / 0 °C	49%
5	Cbz	Et	3	30 mins / 0 °C	50%
6	Cbz	*sec*-butyl	3	30 mins / 0 °C	60%

Initially, the reaction was investigated on the benzyl protected derivative **41**. After some optimization of stoichiometry, temperature and time (entries 1-3), we were able to isolate the desired substitution product **43** in 49% (entry 4). Next, using the Cbz protected compound **42**, we were pleased to observe only the desired product **44**, which was isolated in 50% yield (entry 5). The reaction was then attempted using commercial *sec*-butylMgBr which lead to the desired product **45** and in slightly improved yield (entry 6). Given the compatibility of the Cbz protecting group with the Grignard substitution reaction, we were ready to use these optimised conditions on the azabicyclooctane system. Alcohol **34** was first acetylated to give **46** before attempting the substitution reaction (**Table 4**).

Table 4 | Allylic substitution on acetoxy azabicyclooctane **34**.



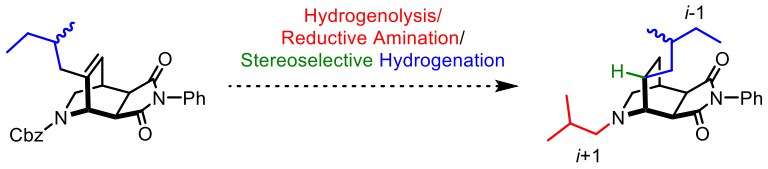
Entry	Eq. of *sec*-butylMgCl	Duration / Temp.	Yield
1	3	2 h / 0 °C	-[a]
2	1	1 h / -78 °C	77%
3	0.85	30 mins / -83 °C	92%

[a]Unidentified by-product formed.

Using excess Grignard reagent at 0 °C however resulted in the formation of an unidentified by-product which lacked the acetate and alkene functionality but did not contain the *sec*-butyl chain. After lowering the temperature and using sub-stoichiometric amounts of the Grignard reagent we were able to isolate the desired product **47** in a 92% yield (entry 3). Installing the alkyl residue at C7 had been a long standing challenge in the synthesis of the core scaffold and we were delighted with the results of this allylic alkylation.

5.2 Installation of the *i*+1 Residue

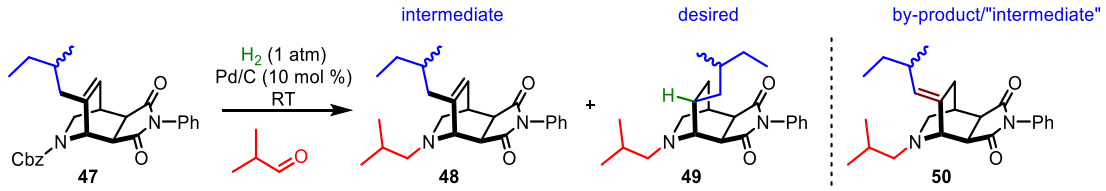
The next step was to effect hydrogenolysis/reductive amination in order to alkylate the *N* atom and install the *i*+1 residue, using conditions we expected would concomitantly reduce the alkene (**Scheme 17**).



Scheme 17 | Proposed hydrogenolysis/reductive amination/ stereoselective hydrogenation reaction.

First we explored the effect that Pd/C and an atmosphere of H_2 had on our system in the absence of aldehyde. We found that the use of a protic solvent was critical as complete consumption of the starting material was observed within 2 h when using EtOH:THF (1:1) compared to very little reaction occurring in EtOAc alone, even after prolonged reaction time. We next introduced isobutyraldehyde into the reaction (**Table 5**).

Table 5 | Attempted hydrogenolysis/reductive amination/stereoselective hydrogenation reaction.



Entry	Solvent	Duration	Yield of 48 (Intm.)	Yield of 49 (Prod.)
1	EtOH:THF (10:1)	45 mins	93%	-
2	MeOH	3 d	22%	21%

H_2 was introduced *via* needle and was bubbled directly into the reaction mixture.

Although the starting material was consumed within 45 mins in EtOH:THF (10:1), only the *N*-alkylated alkene **48** was produced in a yield of 93%; the alkene remained intact (entry 1). Increasing the duration of the reaction did not improve the outcome. Using MeOH as the solvent also saw consumption of the starting material within 45 mins, but once again only the *N*-alkyl alkene **48** was produced. A prolonged reaction time did however lead to the formation of a mixture of the desired alkane **49** (21% yield) and alkene **48** (22% yield). Interestingly, the alkene isomer **50** was also isolated in trace amounts, formed possibly *via* a hydride addition-elimination pathway or a π-allyl metal-1,3 H-shift pathway. The stereochemistry of the product alkane was determined after analysis of the 2D NMR spectra including the NOESY/ROESY spectrum. Specifically, cross-peaks were observed between the newly introduced methine proton (shown in green, **Figure 24**) and both the methylene protons on the isobutyl chain and with the *endocyclic* methylene proton (shown in purple).

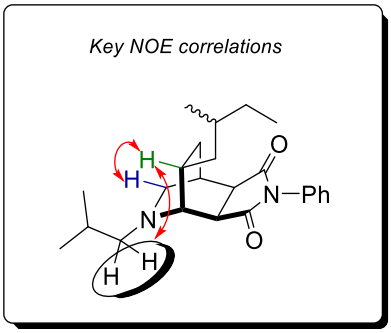


Figure 24 | NOE correlations between newly formed methine proton (green) and other relevant protons confirming desired product.

It was concluded that, as anticipated, the succinimide was effective at blocking one face of the alkene thereby favouring approach of the surface adsorbed hydrogen from the other face (**Figure 25**).

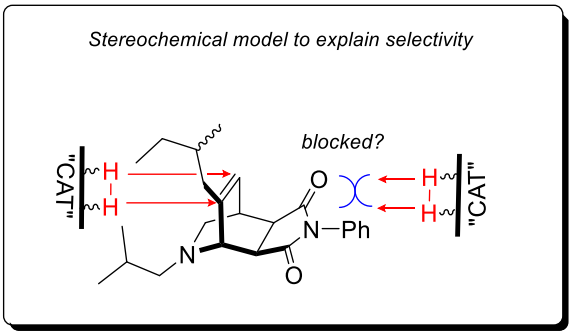
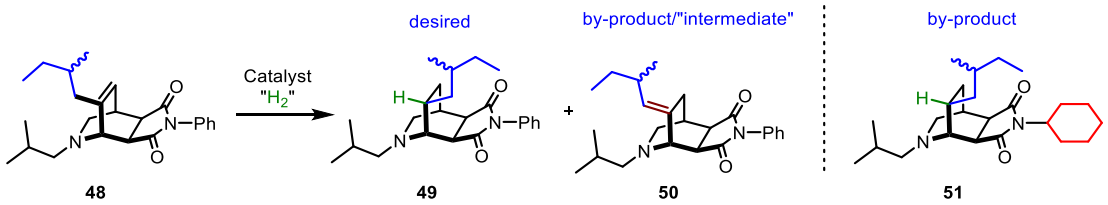


Figure 25 | Model showing anticipated approach of H_2.

To improve the efficiency of this step, a range of conditions were explored for reduction of the sterically congested tri-substituted alkene in compound **48**, which we could form in good yield. Parameters such as solvent, temperature, metal catalyst, H_2 source as well as the presence of additives were explored (**Table 6**).

Table 6 | Hydrogenation of alkene **48.**

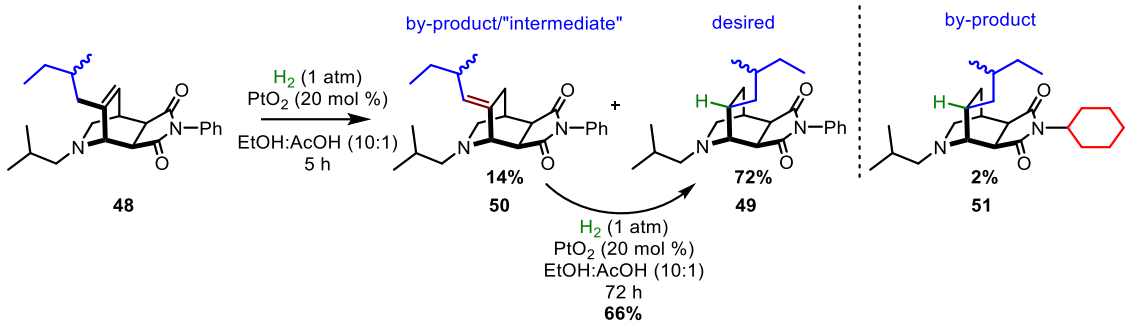


Entry	Catalyst[a]	Solvent	H_2 source	Duration / Temp.	Yield of 49 (Prod.)	Comment
1[b]	Pd/C	EtOH:THF (10:1)	H_2 (1 atm)	24 h / RT	-	Mixture of SM and alkene **50**
2[b]	Pd/C	MeOH	H_2 (1 atm)	3 days / RT	21%	22% SM isolated. Trace amounts of alkene **50** also isolated.
3[b]	PtO_2	EtOH	H_2 (1 atm)	24 h / RT	58% (66% conversion)	10% SM and 12% alkene **50** isolated
4	Pd/C	MeOH	NH_4HCOO	2 h / RT	-	Only SM remaining
5	Pd/C	MeOH	NH_4HCOO	18 h / 60 °C	-	" "
6	Pd/C	EtOH	1,3-cyclohexad-iene	3 h / RT	-	" "
7	Pd/C	EtOH	1,3-cyclohexad-iene	18 h / 65 °C	-	" "
8[b]	$RhCl(PPh_3)_3$	MeOH:THF (1:1)	H_2 (1 atm)	18 h / RT	-	" "
9	PtO_2	EtOH:AcOH (1:1)	H_2 (1 atm)	2 h / RT	30% (59% conversion)	SM completely consumed within 2 h. 16% alkene **50** and trace amounts of cyclohexane **51** isolated.
10	PtO_2	EtOH:AcOH (10:1)	H_2 (1 atm)	5 h / RT	72%	14% of alkene **50** and trace amounts of cyclohexane **51** isolated.

[a]20 mol % of metal catalyst used. [b]H_2 was introduced *via* needle and was bubbled directly into the reaction mixture.

Switching the metal catalyst from Pd/C to Adam's catalyst (PtO_2) greatly accelerated the rate and improved the yield (*cf*. entries 2 and 3), although this did not prevent the formation of the alkene isomer, **50**. Following this result, the one pot hydrogenolysis/reductive amination/hydrogenation reaction was attempted on *N*-Cbz alkene **47** (not shown in table) with PtO_2 and although 31% of the desired alkane **49** was isolated, there still remained some *N*-alkyl alkene **48** after 3 days. Returning to *N*-alkyl alkene **48** as the starting material, transfer-hydrogenation conditions were explored. Unfortunately, neither ammonium formate (entries 4 and 5) nor 1,3-cyclohexadiene (entries 6 and 7) proved useful with the starting material remaining unreacted even after stirring for prolonged reaction times at elevated temperatures. Wilkinson's catalyst [$RhCl(PPh_3)_2$] was explored to see whether a homogenous reaction mixture might give a better result. As with the transfer hydrogenation conditions, only starting material was recovered from the reaction mixture. Returning to the use of Adam's catalyst, AcOH as a 50% v/v co-solvent with EtOH enabled complete consumption of the alkene within 2 h (entry 9).

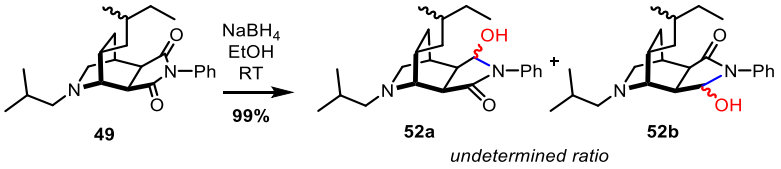
Also observed under these acidic conditions were trace amounts of cyclohexane **51**, formed by reduction of the *N*-phenyl ring. The hydrogenation of aromatic rings when Adam's catalyst is used in conjunction with acid is not uncommon, indeed cyclohexane **51** was never observed in those reactions not involving AcOH. With this in mind, the amount of AcOH was reduced (10:1 EtOH:AcOH, entry 10). Pleasingly, the desired alkane **49** was isolated in 72% with only trace amounts of cyclohexane **51**, although 14% of the alkene isomer **50** was formed. The isolated isomeric alkene could be re-subjected to the hydrogenation conditions, giving the desired alkane **49** (66% yield) along with the cyclohexane by-product **51** (11% yield)**,** after 72 h (**Scheme 18**).



Scheme 18 | Optimized conditions for the hydrogenation of alkene **48** using Adams's catalyst (PtO_2) in EtOH/AcOH.

5.3 Ring-Opening of Cyclic Imide

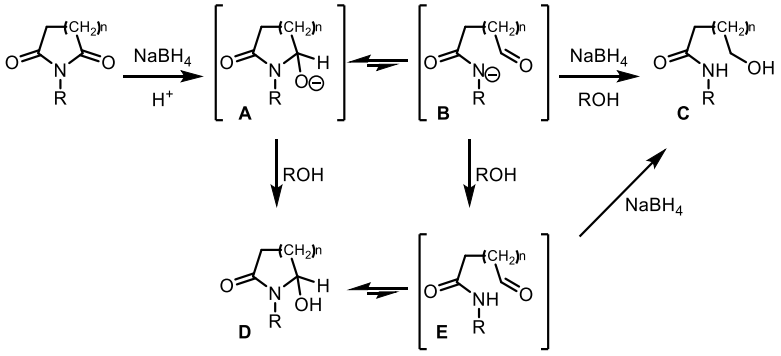
The next stage in our synthetic sequence required the regioselective ring-opening of the cyclic imide **49**. Using a non-azabicyclooctane system, Bayly had discovered that heating an imide in EtOH and $NaBH_4$ in the presence of NaOH resulted in formation of the acyclic product in yields of up to 75%. This reductive ring-opening reaction was carried out on both the *N*-phenyl substituted system and the *N*-(di-*ortho*)-aryl substituted system. Encouraged by these previous findings, cyclic imide **49** was treated with $NaBH_4$ in EtOH gave an inseparable mixture of the regiosomeric lactamols, **52a** and **52b**, in near quantitative yield (**Scheme 19**).



Scheme 19 | Reduction of cyclic imide **49** gave an inseparable mixture of regioisomeric lactamols **52a** and **52b**.

In view of the expectation that the more substituted *N*-aryl imide derivative might display higher intrinsic levels of regioselectivity, it was decided to focus on ring-opening of this mixture of lactamols before addressing regioselectivity issues. Speckamp noted that ring-opening of cyclic imides depends on the ring size of the imide, the nature of the group attached to the nitrogen atom and the presence of ring substituents. Also mentioned was the role of acid, the presence

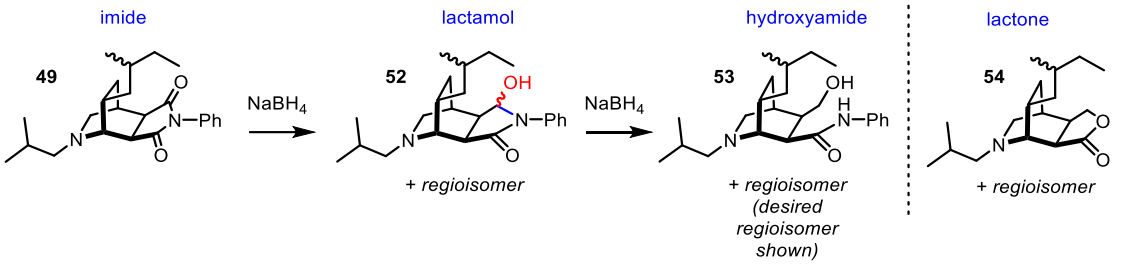
of which appears to shift the equilibrium in favour of the lactamol. By contrast, the presence of base tends to favour the acyclic hydroxyamide. This behaviour is rationalised by recognising that the key step is the ring-cleavage of the oxy-anion **A** to the amide aldehyde **B**, which in turn undergoes reduction *in situ* to form species **C** (**Scheme 20**).[94]



Scheme 20 | Mechanistic considerations in the reduction of cyclic imides. (Scheme adapted from Speckamp *et al. Tetrahedron* 1975).[94]

Speckamp suggested that if species **A** or **B** becomes protonated, forming species **D** or **E** respectively, a tautomeric equilibrium between these two ensues with species **D** apparently being thermodynamically preferred. The presence of acid further favours formation of the lactamol by inhibiting the initial ring-opening (*i.e.* **A** to **B**). Additionally, ring-opening is supressed at lower temperatures. Given these results, the addition of base and conducting the reaction at elevated temperatures might initiate ring-opening of our intermediate lactamol. Consequently, base mediated conditions were investigated on both imide **49** and the mixture of inseparable lactamols, **52a** and **52b** (**Table 7**).

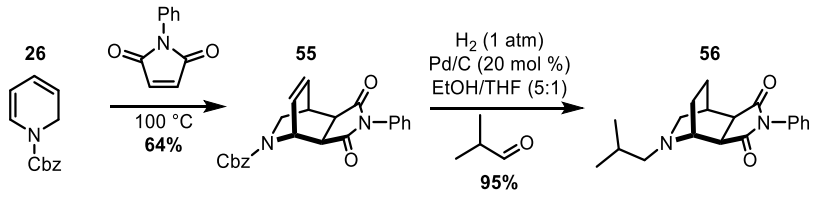
Table 7 | Ring-opening of the cyclic imide (**49**) and the intermediate lactamol (**52a** and **52b**)



Entry	Starting material	Solvent	Duration / Temp.	Base	Outcome
1	Imide **49**	EtOH	1.5 h / RT	-	Inseparable lactamol isomers isolated in 99%.
2	Imide **49**	EtOH:THF (1:1)	2 d / 78 °C	2M NaOH	> 90% lactamol remaining. < 5% of lactone **54** present.
3	Lactamols **52a & 52b**	EtOH	24 h / 78 °C	-	No reaction.
4	Lactamols **52a & 52b**	EtOH:THF (1:1)	24 h / RT	-	No reaction.
5	Lactamols **52a & 52b**	EtOH	3 h / 78 °C	2M NaOH	> 90% lactamol remaining. < 5% of lactone **54** and hydroxyamide **53** present.
6	Lactamols **52a & 52b**	EtOH:THF (1:1)	2 h / 78 °C	2M NaOH	> 90% lactamol remaining. < 5% of lactone **54** and hydroxyamide **53** present.

The lactamol, which could be obtained in almost quantitative yield from the cyclic imide (entry 1), was heated in the presence of excess $NaBH_4$ at 78 °C for 24 h with no change (entry 3). Using THF as a co-solvent appeared to make no difference (entry 4). The presence of 2M NaOH in refluxing EtOH (entry 5) did yield some of the desired ring-opened product **53** but only in small quantities. Also isolated was a small amount of lactone **54**, the formation of which presumably involves deprotonation of the hydroxyamide followed by ring closure with loss of aniline. Analysis of these reactions by ^{1}H NMR was challenging because of the presence of a mixture of regioisomeric lactamols (each of which may exist as separate diastereoisomers) and the diastereotopicity induced by the *sec*-butyl chain. As a result, it was decided to explore the regioselective ring-opening chemistry on a model system.

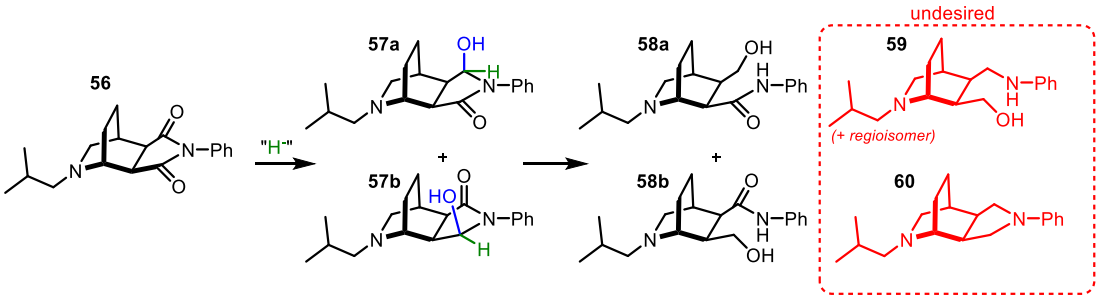
For the model substrate we settled on compound **56** owing to its short and familiar synthesis (**Scheme 21**).



Scheme 21 | Synthesis of model substrate **56.**

In contrast to the trisubstituted alkene **47**, the disubstituted alkene **55** was readily reduced using Pd/C and an atmosphere of H_2 to give the *N*-alkyl cyclic imide **56**. With 2 g of the cyclic imide **56** prepared, its ring-opening was explored (**Table 8**).

Table 8 | Ring-opening of model cyclic imide **56**.



Entry	Solvent	Reducing agent	Duration / Temp.	Yield of lactamols' (57a & 57b)	Yield of hydroxyamides' (58a & 58b)	Comments
1	EtOH	$NaBH_4$	5 h / RT	87%	-	1:1.13 **57a**:**57b**[a]
2	EtOH	$NaBH_4$	3 d / RT	82%	-	5% tertiary amine **60**
3	EtOH:THF (1:1)	$NaBH_4$	3 d / RT	70%	-	7% hydroxyamine **59** 2% tertiary amine **60**
4	THF	$LiBH_4$	5 d / RT	-	-	23% hydroxyamine **59** 70% tertiary amine **60**
5	THF/2M NaOH (5:1)	$LiBH_4$	3 d / 50 °C	~90%[b]	trace	> 90% of crude reaction mixture contains lactamols.
6[b]	THF	$LiBH_4$	24 h / RT	-	-	58% SM, 7% hydroxyamine **59**, 36% tertiary amine **60**.[c]
7	2M NaOH (in EtOH)	$NaBH_4$	30 h / 80 °C	-	-	Significant mass lost after aqueous work-up. ^{1}H NMR of crude shows SM and tertiary amine **60**
8	2M NaOH (in MeOH)	$NaBH_4$	2 d / 80 °C	-	-	All material lost in aqueous work-up

[a]This ratio was determined after several attempts at isolation of each isomer followed by 2D NMR experiments. [b]$FeCl_3$ present. [c]Not isolated yields.

Reduction in the absence of base gave a mixture of two lactamols in good yield (entry 1). It was necessary to determine whether these two compounds were diastereoisomers resulting from hydride addition to one carbonyl from the top and bottom faces respectively, or regioisomeric lactamols resulting from hydride addition to each carbonyl (presumably from one face otherwise four different compounds would result) – **Figure 26**.

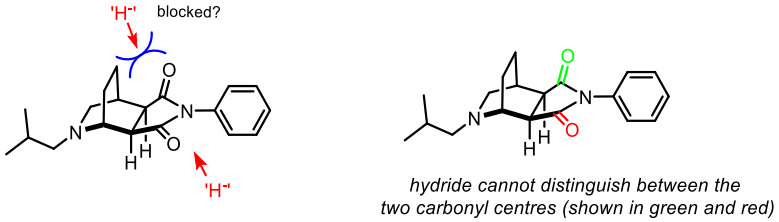
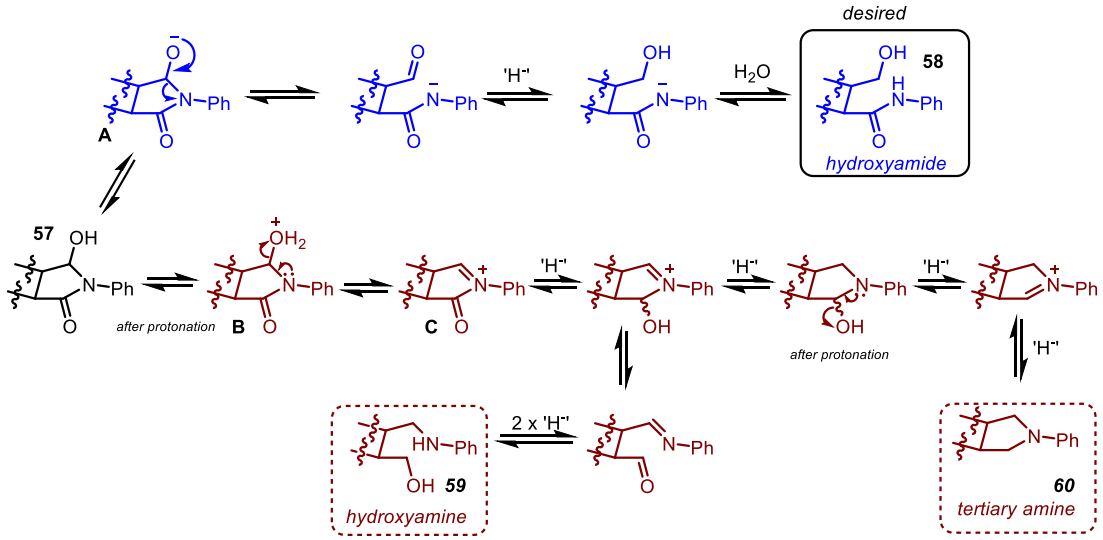


Figure 26 | Potential sites of attack by the hydride reducing agent.

After numerous purification attempts, we were finally able to separate some of each isomer and using 2D NMR correlation experiments both isomers were found to have the new hydrogen atom placed on the bottom face (and the hydroxyl on the top face). Although this might suggest that hydride attack was occurring at both carbons but only from the bottom face, it is likely that the isomers are equilibrating and thus hydride attack from the top face of the imide cannot be ruled out (**Figure 26, left**).

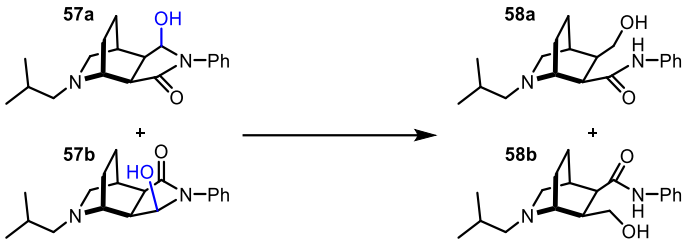
Unfortunately, even after prolonged reaction times these lactamols did not react further to form the hydroxyamides, giving instead the tertiary amine **60** (entry 2). The inclusion of THF as a co-solvent did not improve the outcome, and on this occasion some of the hydroxyamine **59** was also isolated (entry 3). Use of a stronger reducing agent, $LiBH_4$, appeared to accelerate the formation of these undesired by-products (entry 4). Interestingly, heating the imide in the presence of $LiBH_4$ *and* NaOH halted the formation of the undesired by-products **59** and **60**, though the main compound(s) isolated under these conditions were again the lactamols (entry 5). The presence of $FeCl_3$ (entry 6) and the use of an ethanolic solution of NaOH as the solvent (entries 7 and 8) also failed to provide the desired hydroxyamide. A network of pathways leading to each of the observed intermediates is proposed in **Scheme 22**.



Scheme 22 | Proposed pathways from the lactamol to undesired products **59** and **60** (red) and desired product **58** (blue).

It was evident that the presence of NaOH slows the formation of the undesired hydroxyamine **59** and tertiary amine **60.** This is consistent with the mechanism outlined above as both by-products require protonation of the lactamol. We therefore looked at ways to favour the formation of oxy-anion species **A** (pathway in blue) and disfavour the pathway leading to protonated species **B** (**Table 9**).

Table 9 | Ring-opening of the lactamols **57a** and **57b**.



Entry	Solvent	Reducing Agent[a]	Additive	Duration / Temp.	Isolated product	Comments
1	EtOH	$NaBH_4$	-	3 h / RT	-	No reaction
2	EtOH	$NaBH_4$	-	2 d / 78 °C	-	Only SM and trace tertiary amine **60**
3	60% aq. EtOH	$NaBH_4$	-	2 d / 60 °C	-	" "
4	1,4-Dioxane/EtOH (5:1)	$NaBH_4$	-	2 d / 100 °C	-	1:1 SM:hydroxyamine **59**
5	THF/2M NaOH (5:1)	$LiBH_4$ (1 eq.)	-	16 h / RT	-	No reaction
6	THF/2M NaOH (5:1)	$LiBH_4$	-	18 h / 60 °C	-	> 90% of crude reaction mixture containing hydroxyamine **59.**
7	THF	$LiBH_4$	$FeCl_3$	24 h / RT	-	Complex mixture containing lactamol SM, tertiary amine **60** and other unidentified by-products.
8	THF	$LiBH_4$ (1 eq.)	$CoCl_2$	24 h / RT	-	> 90% SM remaining.
9	THF	$LiBH_4$ (2 eq.)	$CoCl_2$	24 h / RT	-	" "
10	THF/EtOH/2M NaOH (1:1:1)	$LiBH_4$ (1 eq.)	$CoCl_2$	24 h / RT	-	" "
11	THF	$LiBH_4$	NaH	6 h / RT		" "
12	2M NaOH (in EtOH)	$NaBH_4$	-	30 h / 80 °C	-	Significant mass lost after aq. work-up.
13	2M NaOH (in EtOH)	$NaBH_4$	-	30 h / 80 °C	-	" "

[a]Typically excess (10 eq.) reducing agent was used unless otherwise specified.

Anticipating that the presence of water might shift the equilibrium towards the desired route by disfavouring the formation of dehydrated species **C**, aqueous EtOH was used as the solvent but with no success (entry 3). Using 1,4-dioxane as the solvent allowed heating of the reaction to 100 °C, but again nothing new occurred (entry 4). Stirring the lactamol with 1 eq. $LiBH_4$ in THF in the presence of NaOH effected no change (entry 5), however, after adding in a large excess of the reducing agent and heating at 60 °C for 18 h the starting material reacted (entry 6), but only to form the undesired hydroxyamine **59**, demonstrating that forcing conditions are required to drive this reaction in the presence of base. We next turned our attention to additives as an alternative means to promote the desired pathway. It was hypothesised that the presence of an azaphilic Lewis acid (LA)[95] might promote the ring-opening step by coordinating to the lone pair of electrons on the nitrogen of the lactamol (**Figure 27**).

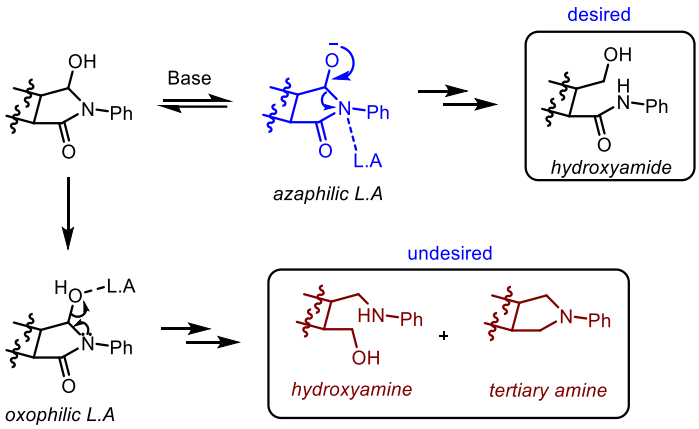
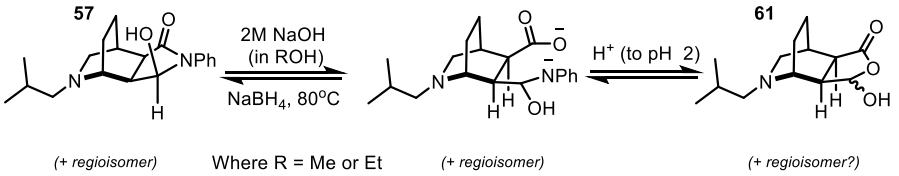


Figure 27 | Proposed role of an azaphilic Lewis acid to potentially promote lactamol ring-opening.

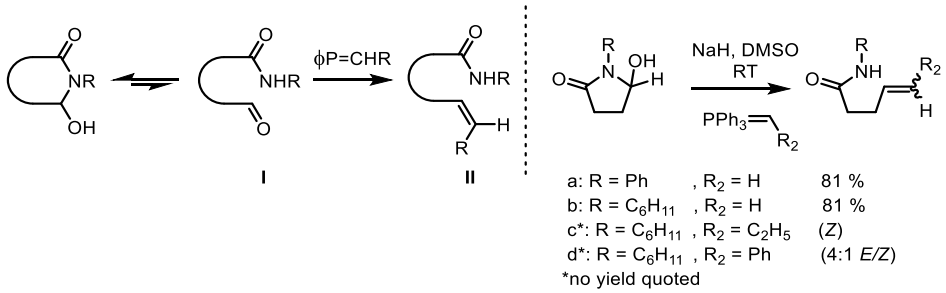
In the event, the presence of the azaphilic LA's $FeCl_3$ or $CoCl_2$ (entries 7 – 10) appeared to accelerate the formation of the undesired tertiary amine **60** (entry 7 – no heating was required to observe this product). As before, the presence of NaOH shut down this pathway (entry 10). Given that the deprotonated lactamol required for the reaction to progress *via* the desired route was clearly in an unfavourable equilibrium with the more stable lactamol, we envisioned that the use of a stronger base might shift the equilibrium in favour of the alkoxide. However, treating the lactamol with NaH followed by $LiBH_4$ saw no reaction (entry 11). Finally, we decided to explore the use of a 2M NaOH solution in alcohol in place of aqueous NaOH as the reaction medium. Accordingly, the lactamol was dissolved in basic ethanolic and methanolic solution before adding $NaBH_4$ and heating the mixture overnight (entries 12 and 13). No SM remained and it was clear that most of the resulting material was soluble in the aqueous phase as very little material was extracted into the organic phase. LCMS analysis suggested the presence of a new species not observed previously, with a mass consistent with the carboxylic acid-amide compound. Curiously, the ratio of the recovered lactamols, after acidification, had changed indicating that the two regioisomeric lactamols reacted at different rates. Also worth nothing is that when the aqueous phase was acidified to pH 2 and extracted, the ^1H NMR spectra of the resulting crude mixture lacked the key lactamol protons (α to hydroxyl group) as well as aromatic protons; further analysis of this material suggested it to be the hydroxylactone species **61** as a single diastereoisomer (**Scheme 23**).



Scheme 23 | Treatment of the lactamol mixture with basic alcohol solution followed by an acidic work-up leads to the formation of a single hydroxylactone compound.

From these results it appears that using a basic solution of alcohol results in the rapid hydrolysis of the imide moiety, preventing any subsequent reduction process from occurring ($NaBH_4$ will not reduce the carboxylate once formed). The addition of acid then favours ring closure, either re-forming the lactamol with loss of H_2O or formation of the hydroxylactone *via* loss of aniline. The decision was made to explore base hydrolysis of the imide in further detail but on a more sophisticated model (see below).

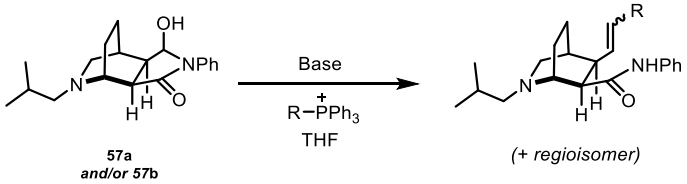
As we had a significant amount of lactamols **57a** and **57b** remaining we also briefly explored ring-opening by alkenylation. Speckamp had reported that lactamols could react with Wittig reagents to give alkenes such as **II** *via* their aldehyde tautomers **I** (**Scheme 24**).[96]



Scheme 24 | Speckamp's alkenylation of lactamols by Wittig reagents (Scheme adapted from Speckamp *et al. Tetrahedron* 1975).[96]

Speckamp used the dimsyl anion to generate his ylides, so we did similarly (**Table 10**):

Table 10 | Attempted ring-opening of lactamol **57** using a Wittig reaction.

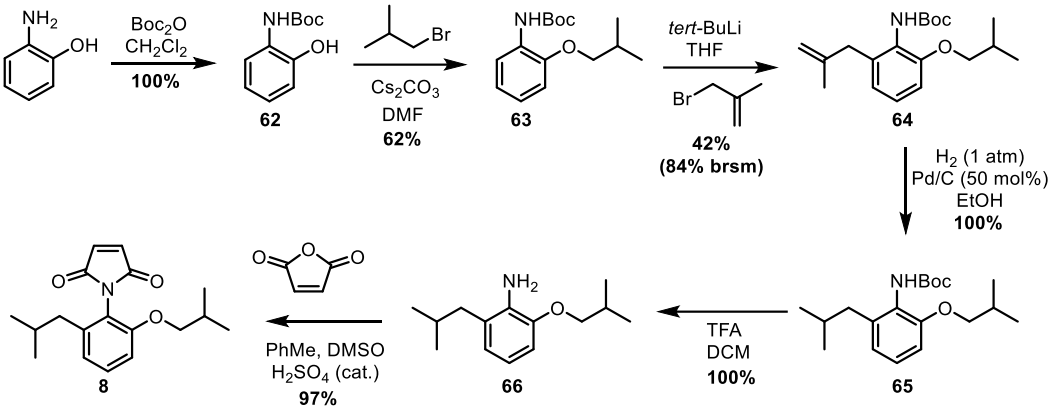


Entry	Starting material	Ylid	Conditions	Product	Comment
1	**57a**	$BnPPh_3^+ Cl^-$	DMSO, NaH, 0 °C – RT, 72 h	-	No reaction
2	**57a**	$BnPPh_3^+ Cl^-$	^{n}BuLi, DMSO, 0 °C – RT, 72 h	-	No reaction
3	**57a** & **57b**	$MePPh_3^+ Br^-$	DMSO, NaH, 0 °C – RT, 18 h	-	No reaction
4	**57a** & **57b**	$MePPh_3^+ Br^-$	^{n}BuLi, DMSO, 0 °C – RT, 18 h	-	No reaction

Both benzyltriphenylphosphonium chloride and methyltriphenylphosphonium bromide were explored using two different bases, but on all occasions no reaction was observed and only the

phosphine oxide was isol ated.

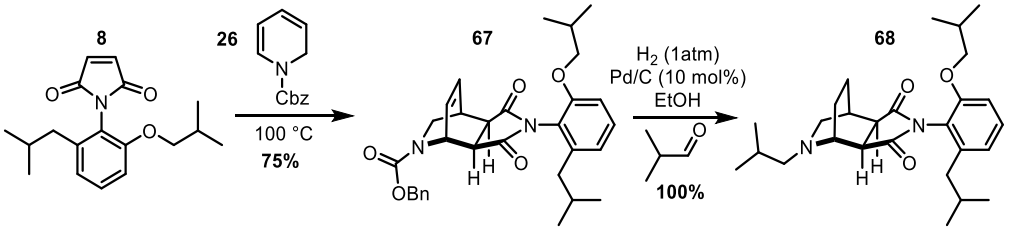
Given our limited success on the model system, we began investigating the ring-opening on a more sophisticated model which contained di-*ortho* substituents on the aryl succinimide moiety. The presence of these relatively bulky side-chains, which are required on the full mimetic, were hoped to favour the ring-opening pathway by relieving steric strain on the azabicyclic structure. To explore this derivative, synthesis of the di-*ortho*-substituted *N*-aryl maleimide **8** was required. This involved repeating a six-step sequence designed and optimized by Bayly from 2-aminophenol (**Scheme 25**).



Scheme 25 | Synthesis of the di-*ortho*-substituted *N*-aryl maleimide **8**.

The synthesis began with Boc protection of 2-aminophenol, then *O*-alkylation with 2-methylpropyl bromide to give ether **63**. *Ortho* lithiation, assisted by the *N*-Boc group, followed by trapping with 2-methyl-prop-1-enyl bromide gave the di-*ortho*-subsituted aryl compound **64** in 42% yield. During this reaction, 50% of the unreacted starting material was typically recovered, which was then re-subjected to the reaction conditions. Hydrogenation of the alkene followed by *N*-Boc deprotection gave aniline **66**, which was then heated with succinic anhydride in the presence of strong acid to give *N*-aryl maleimide **8** in near quantitative yield.

With 3 g of the *N*-aryl maleimide **8**, the thermal DA reaction with unsubstituted *N*-Cbz-1,2-DHP (**26**) was carried out with the aim to extend this to the 5-substituted-1,2-DHP at a later stage. The DA reaction provided two inseparable DA adducts in a combined yield of 75% (**Scheme 26**).



Scheme 26 | Synthesis of DA adduct **67** containing the di-*ortho*-substituted aryl moiety.

At this stage it was necessary to confirm that the two inseparable isomers were atropisomers due to restricted rotation about the *N*-aryl bond (arising from the presence of the two bulky *ortho* substituents) and not *endo/exo* isomers. However, due to the existence of conformational isomerism resulting from restricted rotation about the carbamate bond of the Cbz group, the NMR spectra of the mixture were already complex. We therefore proceeded to the one-pot hydrogenolysis/reductive amination step as this would simplify analysis by removing the Cbz group. The reduction produced two compounds, both corresponding to the reduced *N*-alkylated alkane product in quantitative yield (**Scheme 26**). Analysis of the NMR spectra confirmed each to be the *endo*-DA adduct and that the two compounds were atropisomers due to the restricted rotation about the *N*-aryl bond. Sharp signals were observed in the ^{1}H NMR spectrum of each isomer at room temperature. In addition, no equilibration was observed upon heating both of the isolated isomers in DMSO at 150 °C for 3 days, which further demonstrated that there is very slow interconversion between the two isomers. We were interested to note that the atropisomers were formed in a ∼1:2 **68a**:**68b** ratio and wanted to understand the basis of this preference (**Figure 28**).

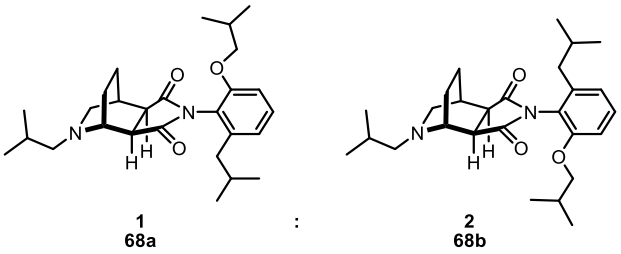


Figure 28 | The presence of the two *ortho* substituents on the aryl ring results in atropisomerism about the N-C_{aryl} bond.

To explore this, compound **68** was modelled using Gaussview. After optimization of the structure at the DFT B3LYP/6-31 G(d,p) level, a dihedral scan about the N-C_{aryl} bond was performed in 18 × 20 degree steps (**Figure 29**).

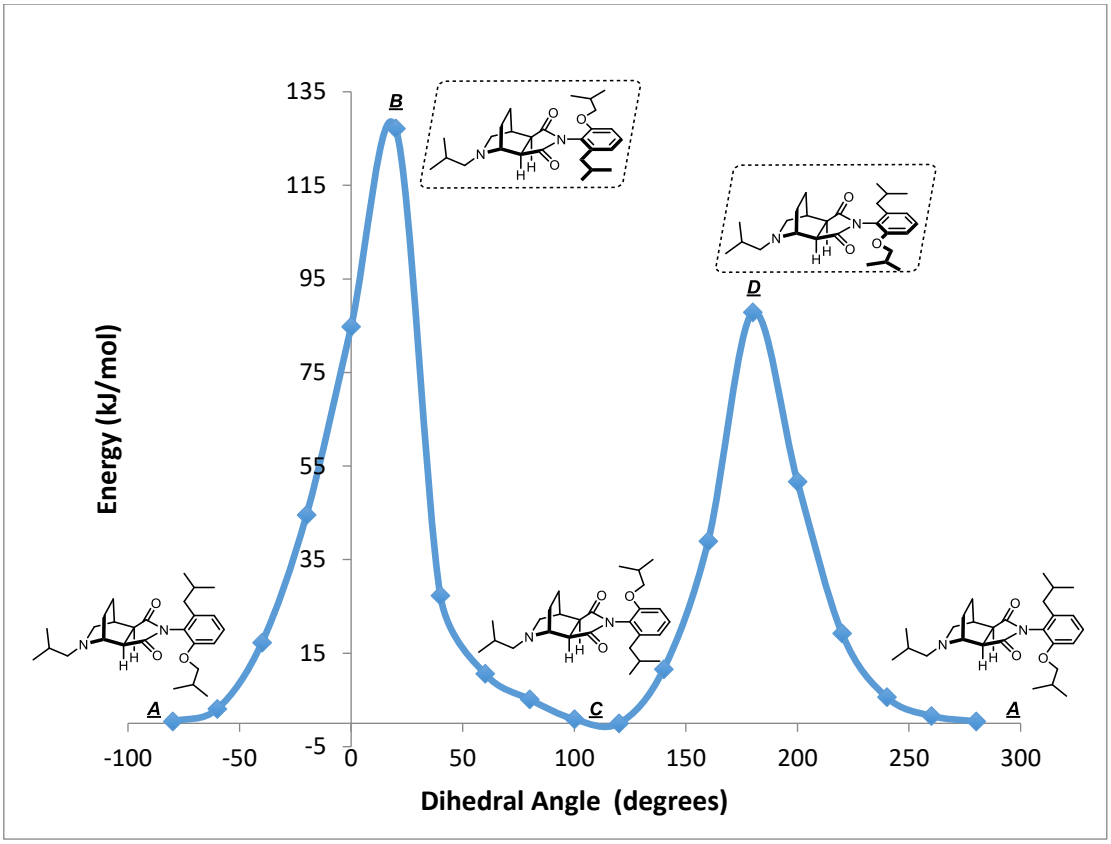


Figure 29 | Energy profile for rotation about the N-C_{aryl} bond.

As expected, the two energy minimized conformations (***A*** and ***C***, **Figure 29**) of compound **68** are computed to be conformationally stable at room temperature and have relatively high barriers to interconversion by rotation (127.1 kJ/mol anticlockwise and 87.8 kJ/mol clockwise, respectively). Also as expected, the two energy minimized conformations correspond to the two situations whereby the aryl moiety is almost perpendicular to the planar imide segment, presumably due to steric/electronic repulsions between the two carbonyls of the imide and the di-*ortho* ring substituents. It is interesting that there is a significant difference between the energies of the two rotational barriers. Examination of the modelled compounds suggests this reflects differences in the interactions between the two different *ortho* aryl ring substituents and the azabicyclooctane ring: the isobutoxy substituent experiences less steric repulsion with the top face of the azabicyclooctane ring as it rotates around in this more sterically congested region as compared to the less flexible isobutyl chain (see **Figure 30**) as the oxygen atom linking the isobutoxy chain to the aromatic ring allows for greater distortion to relieve the strain.

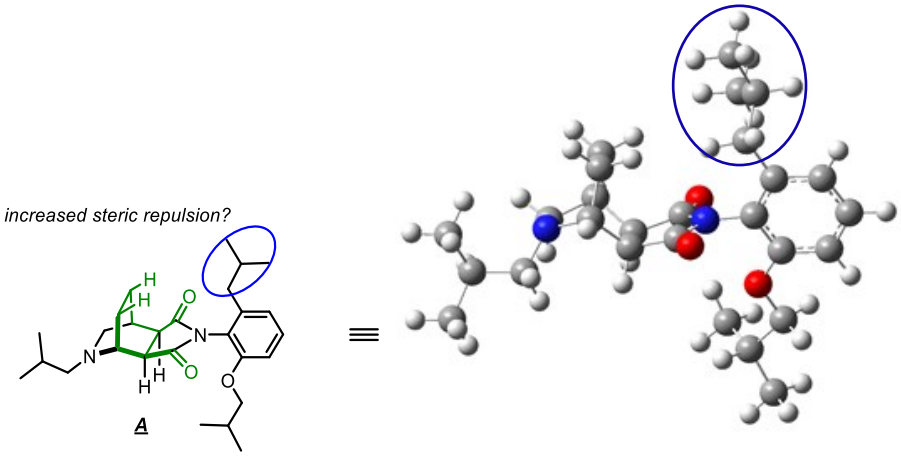
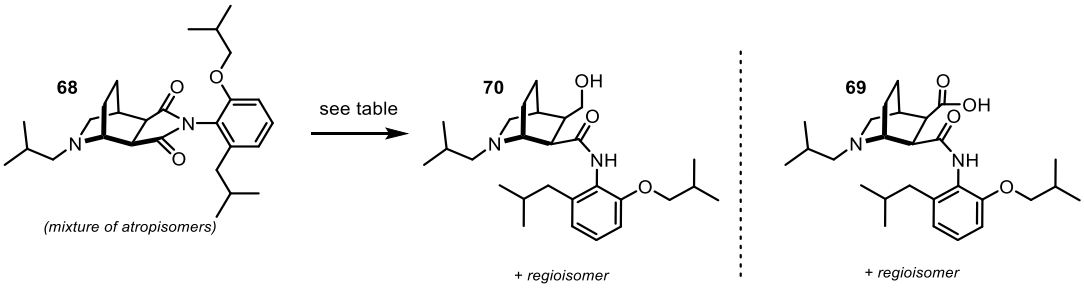


Figure 30 | Model depicting the proposed steric interactions between the isobutyl chain and the 'top' face of the azabicyclooctane ring (shown in green). Only the interactions involved in minimized conformation '**A**' is shown here.

Having confirmed that the DA reaction with the *N*-aryl maleimide, containing the di-*ortho* substituents, proceeded with total *endo* selectivity, we were in a position to explore the ring-opening step. As the atropisomerism observed following the DA reaction was expected to be lost upon ring-opening, a mixture of atropisomers was used for these experiments (**Table 11**).

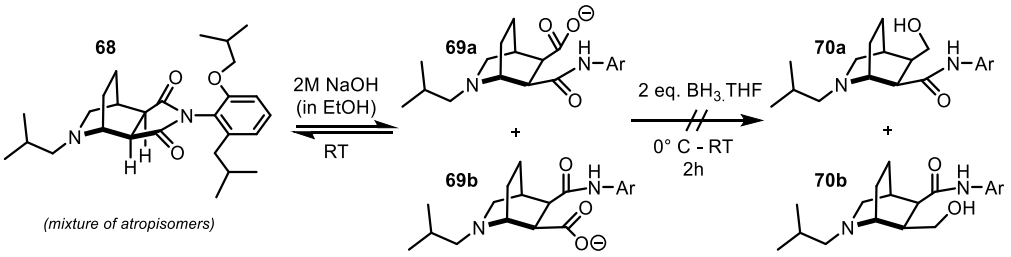
Table 11 | Attempted ring-opening of imide **68**.



Entry	Solvent	Reducing Agent	Duration / Temp.	Comment
1	EtOH	$NaBH_4$	18 h / 78 °C	Ratio of atropisomers changed from 2:1 to 1:1. Only trace amount of lactamols.
2	2M NaOH (in EtOH)	$NaBH_4$	18 h / 78 °C	Regioisomeric mixture of carboxylate salts (94% yield).
3	2M NaOH (in EtOH)	-	6 h / RT	Regioisomeric mixture of carboxylate salt (64% yield). No work-up.

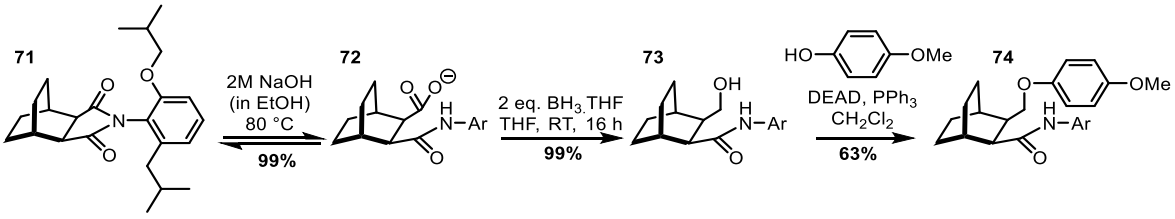
In stark contrast to the reactivity of the *N*-Ph compound **56**, treatment of imide **68** with $NaBH_4$ only resulted in the formation of trace amounts of the lactamol intermediates even after refluxing in ethanol (entry 1). However, when the imide was pre-dissolved in basic ethanolic solution and treated with $NaBH_4$, all of the starting material was consumed producing two new, polar compounds (by TLC analysis). As before, hydrolysis of the imide to the *N*-aryl amide carboxylate salt was believed to have taken place. Unfortunately, due to the polar nature of the

formed compounds it was difficult to isolate them using column chromatography. Furthermore, all attempts to isolate these carboxylic acids after an aqueous work-up by decreasing the pH of the solution, even to neutral pH, shifted the equilibrium in favour of the ring-closed imide and so the starting material reformed. The $NaBH_4$ was found not to be playing a role, as the reaction could be repeated in its absence and the same two polar compounds were observed (entry 3). Unable to isolate the carboxylic acid, the crude carboxylate salt was obtained after a basic work-up after which reduction of the carboxylate was attempted (**Scheme 27**).



Scheme 27 | Hydrolysis of imide **68** followed by attempted reduction using BH_3·THF.

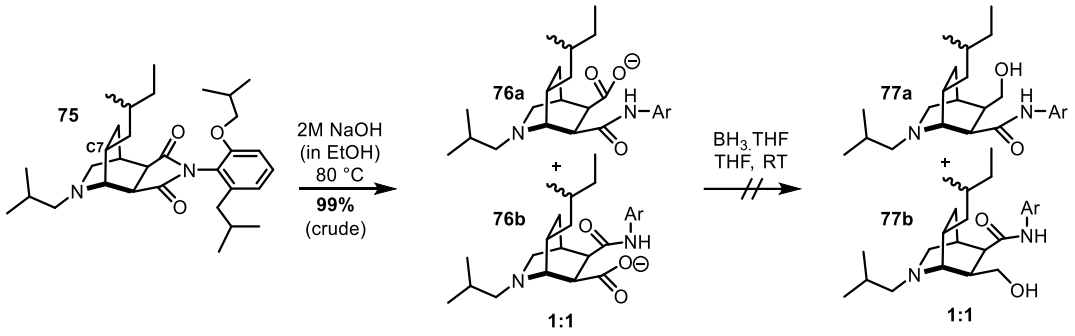
No reaction occurred upon treatment of the carboxylate salt with two equivalents of BH_3·THF at room temperature. In parallel with this work, a post-doctoral researcher in the group, Bodero, was also investigating the ring-opening of an imide on a simpler model system (**Scheme 28**).[97]



Scheme 28 | Bodero's hydrolysis of imide **71** followed by reduction using BH_3·THF and subsequent Mitsunobu etherification.[97]

On this bicyclooctane system (**71**), the hydrolysis and reduction proceeded well. Bodero found that the work-up procedure was critical to success: quenching with methanol was required as treatment with acid or base would result in ring closure to the starting material. Bodero found that the subsequent Mitsunobu coupling to install the tyrosine side chain mimetic group could also be achieved successfully on this model. When Bodero attempted the same hydrolysis/reduction sequence on the azabicyclooctane system **68**, the hydrolysis yielded a 1:1 mixture of the carboxylate amide compounds, **69a** and **69b** and the following hydride reduction, under slightly modified conditions relative to those applied to the all-carbon model (*i.e*. longer duration: 3 days at RT *cf*. 16 h), gave a mixture of two regioisomeric alcohols (**70a** and **70b**) in a

1:1 ratio. Bodero then attempted to perform this sequence of reactions on the complete mimetic **75** (**Scheme 29**).



Scheme 29 | Bodero's attempted imide ring-opening/reduction on complete mimetic **75**.[97]

The hydrolysis with an ethanolic solution of NaOH gave a ∼1:1 mixture of two carboxylate salts, **76a** and **76b**, indicating that the branched alkyl substituent destined to become the *i*-1 side chain (*i.e.* at C7), unfortunately, exerts negligible control over the regioselectivity of this process. Even more disappointingly, the subsequent reduction step proved very challenging: a complex mixture of products was typically obtained, which included the starting material, two hydroxyamides, two amines from amide over-reduction and uncharacterised components in which the aniline and azabicyclooctane core were separated. Unfortunately, the major components were usually the starting material and the over reduced amine. Interestingly four equivalents of BH_3 were required to effect complete consumption of the starting material (*cf*. 2 eq. BH_3 for azabicyclooctane **69** and bicyclooctane **72**), an observation consistent with the competitive formation of over-reduced by-products. It was apparent that the inclusion of the branched alkyl chain at C7 of the azabicyclooctane was having an adverse effect on the carboxylate reduction, presumably by acting as a steric impediment to reduction of the carboxylate functionality and allowing other pathways to dominate. In light of this reductive impasse, the regiorandom proceeding imide ring-opening, not to mention the need to epimerize the amide carbon centre, we decided to abandon work on this route.

6. Chapter 2 – 1,1-Diactivated Dienophiles

6.1 Four-Residue Mimetic

One of the key challenges in the synthesis of the target azabicyclooctane system is that the *N*-aryl-amide moiety is required to be positioned *exo* with respect to the C-C bridgehead. As already demonstrated, whilst the *endo* orientation is relatively easy to obtain, the *exo* stereochemistry is considerably more challenging to introduce as this isomer is often only formed as the minor component of a mixture of the two products of a DA reaction. Published examples of reactions that deliver solely an *exo* substituent at the required position are rare (*vide infra*) but there have been several reports describing methods to prepare compounds which contain a *gem*-dicarboxyl moiety at this position.[86] With this in mind, we became interested in designing a new route to a second generation mimetic in which a *gem*-diamide would be introduced at C6 and the *i*-1 residue at C7 would take the form of an ether substituent (**Figure 31**).

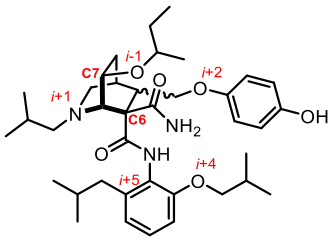
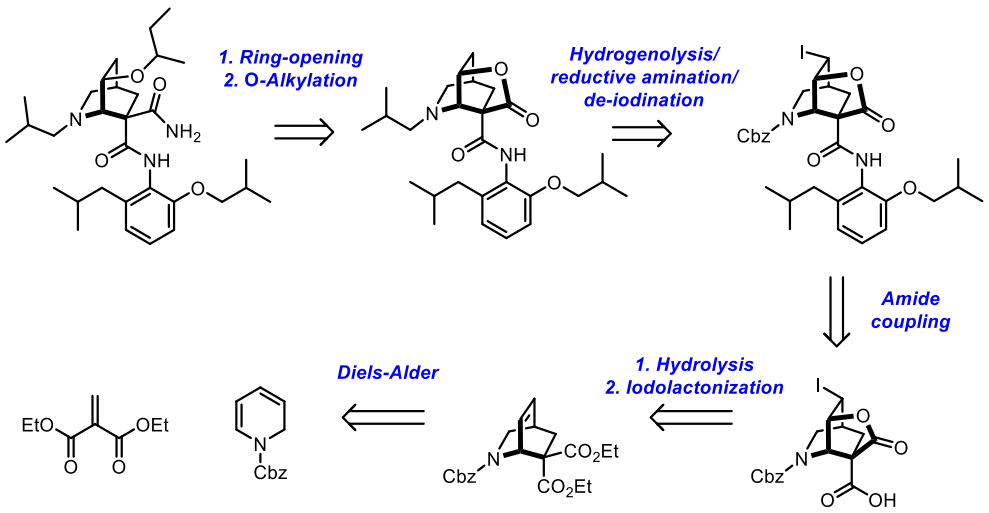


Figure 31 | Second generation target five-residue mimetic.

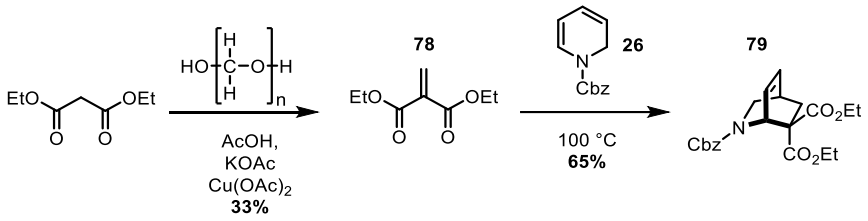
It was envisioned that the additional primary amide group would advantageously increase the hydrophilicity of the mimetic and moreover could be used to direct the introduction of the C7 ether bearing the *i*-1 residue with the correct stereochemistry. A further advantage of this approach was that the diene in the DHP would be simplified: an unsubstituted *N*-Cbz protected 1,2-DHP would be required rather than the 5-substituted one required previously. Initially, the plan was to explore this new chemistry on a four residue mimetic which lacked the *i*+2 residue. A retrosynthetic outline of the new route is depicted in **Scheme 30**.



Scheme 30 | Retrosynthetic route towards a four residue, second generation mimetic which lacks the *i*+2 residue.

The route initially requires a regioselective DA reaction between *N*-Cbz-1,2-DHP and a methylene malonate to set up the azabicyclooctane,[86] followed by hydrolysis of the diester to the dicarboxylic acid. An iodolactonization reaction between the *endo* carboxylic acid and the alkene should then form the γ-lactone, leaving the *exo* carboxylic acid free to undergo an amide coupling with the hindered aniline. The hydrogenolysis/reductive amination conditions previously described should install the *i*+1 residue on the *N* atom whilst simultaneously cleaving the C-I bond. Finally, ring-opening of the lactone with NH_3, followed by alkylation of the resultant alcohol should deliver the target four residue mimetic.

Work commenced with synthesis of methylene diethyl malonate (**78**) by condensation of commercially available diethyl malonate with paraformaldehyde (**Scheme 31**).

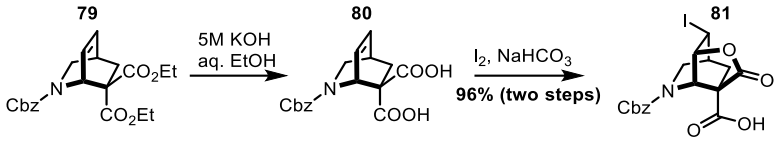


Scheme 31 | Formation of methylene diethyl malonate (**78**) and subsequent DA reaction with *N*-Cbz-1,2-DHP (**26**).

Methylene malonate **78** was formed in 33% yield and proved to be extremely unstable as it is prone to anionic polymerization readily initiated by water.[98] The compound was used immediately after distillation and so was treated with freshly prepared *N*-Cbz-1,2-DHP to effect the DA cycloaddition. After heating at 100 °C for 20 h under an argon atmosphere, the DA adduct **79** was obtained in 65% with 24% of the DHP also recovered. Allowing the reaction to run for

longer (2 days) had an unfavourable effect, lowering the yield to 37% and increasing the amount of by-products formed due to polymerization of the dienophile.

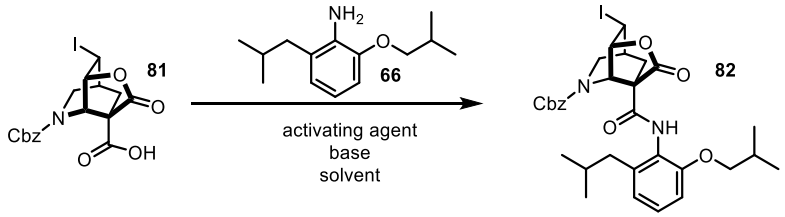
Next, hydrolysis of the diester **79** using KOH gave the diacid **80**, the substrate for the iodolactonization reaction (**Scheme 32**).



Scheme 32 | Synthesis of diacid **80** and subsequent iodolactonization.

Iodolactonization of γ,δ-unsaturated acids can either provide γ-lactones, if carried out under kinetic control (*e.g.* I_2, aq. $NaHCO_3$, or NIS and $CHCl_3$), or δ-lactones, if carried out under thermodynamic control (*i.e.* in the absence of base, *e.g.* I_2 in MeCN).[99] We required the γ-lactone as the alkyl-oxygen bond in this derivative would provide a functional handle at C7 to install the *i*-1 residue. In the event, treatment of dicarboxylic acid **80** with I_2 in aqueous $NaHCO_3$ gave the desired regioisomer and in near quantitative yield over two steps with no purification necessary. Next, coupling of lactone acid **81** with the di-*ortho*-substituted aniline **66** was explored using a variety of standard amide bond forming reaction conditions (**Table 12**).

Table 12 | Optimization of the amide coupling between acid **81** and aniline **66**.



Entry	Eq. of acid	Eq. of anilne	Activating agent	Base	Solvent	Duration / Temp.	Yield of amide (rec. aniline)
1	1.1	1	EDAC	Et_3N	CH_2Cl_2	2 h / RT	30% (30%)
2	1	2	EDAC	Et_3N	CH_2Cl_2	24 h / RT	51% (46%)
3	1.05	1	EDAC	Et_3N	CH_2Cl_2	2 d / RT	48%
4	1	1	EDAC	Et_3N	CH_2Cl_2	60 h / RT	11% (39%)[a]
5	**1**	**1.75**	**EDAC**	**Et_3N**	CH_2Cl_2	**20 h / RT**	**61% (47%)**
6	1.25	1	EDAC	HOBt	DMF	3 d / RT	15%[b]
7	1.25	1	EDAC	HOBt	DMF	3 d / RT	-[c]
8	1.1	1	EDAC	DMAP	CH_2Cl_2	5 h / RT	-
9	1.1	1	HATU	DIPEA	DMA	5 h / RT	20%[b]
10	1.1	1	HATU	DIPEA	DMF	24 h / 60 °C	-
11[c]	1.1	1	$(COCl)_2$ & *cat.* DMF	DIPEA	CH_2Cl_2	2 h / RT	-
12[c]	2	1	TCBC[d]	Et_3N, DMAP	Toluene	18 h / RT	-

Typical coupling conditions involved adding the coupling agent to a solution of the acid and amine, followed by addition of the base. All reactions were conducted under a N_2 atmosphere using dry solvents.

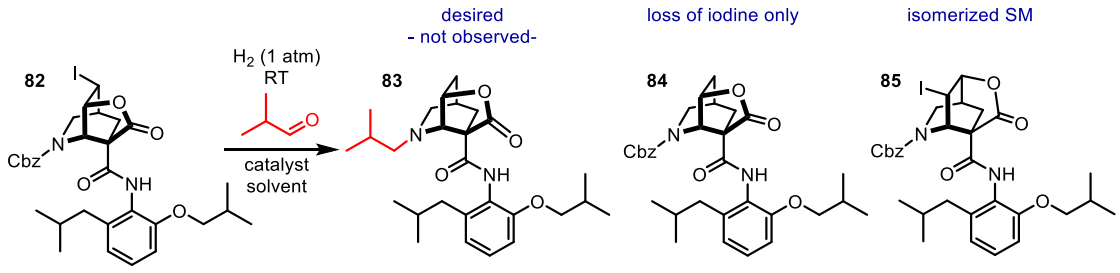
[a]The coupling agent and the carboxylic acid were pre-mixed prior to addition of the aniline. [b]Not isolated yield. Conversion as judged by analysis of ^1H NMR spectra of crude material. [c]Did not use the typical coupling conditions mentioned above.

Abbreviations: EDAC - 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (used as HCl salt); HATU - (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate); HOBt – Hydroxybenzotriazole; TCBC - 2,4,6-trichlorobenzoyl chloride (Yamaguchi reagent).

Use of water soluble EDAC as the activating agent in the presence of Et_3N gave an encouraging 30% isolated yield of the product amide **82**, with 30% recovery of the aniline (entry 1). Variation of the reaction duration and the reactant stoichiometries under these conditions was then explored (entries 1-5). Extending the reaction time appeared to have an adverse effect on the isolated yield (entry 4) suggesting that the product amide may not be stable in the reaction mixture. The best result was obtained using excess aniline - which can easily be recovered if unreacted - stirring at RT for 20 h giving the amide in 61% yield (entry 5). Use of HOBt instead of Et_3N was detrimental to the reaction with only 15% conversion of the aniline observed after 3 days (entry 6). Interestingly, pre-mixing of the acid and the coupling agent appeared to drastically diminish the yield of the reaction with no product observed even after 3 days (entry 7). Using DMAP as the base gave no sign of product after 5 h (entry 8). Changing the coupling agent from EDAC to HATU did not lead to improvements (20% conversion by ^1H NMR analysis of the crude reaction mixture, entry 9) and repeating the reaction at 60 °C for a longer period of time failed to give any product (entry 10). We also looked at forming the acid chloride, but with no success; in the reaction with oxalyl chloride, the aniline appeared to have reacted with the oxalyl chloride instead of the carboxylic acid (entry 11). Use of Yamaguchi's reagent also failed to give the desired product (entry 12). Satisfied with a yield of above 60%, it was decided to move forward with the synthesis.

Focus turned towards installation of the *i*+1 residue using the one pot hydrogenolysis/reductive amination sequence already established for the first generation mimetic. It was anticipated that the conditions applied to effect these transformations would concomitantly effect hydrogenolysis of the C-I bond (**Table 13**).

Table 13 | Attempted hydrogenolysis/reductive amination of iodolactone-amide **82.**



Entry	Catalyst (10 mol %)	Solvent	Duration	Comment
1	Pd/C	EtOH	18 h	No reaction. Poor solubility in EtOH.
2	Pd/C	EtOAc	18 h	59% SM remaining, 15 % des-iodo compound **84**, 21% SM isomer **85**.
3	PtO_2	EtOAc	36 h	> 90% SM remaining with trace amounts of des-iodo compound **84** and SM isomer **85** also present.

Unfortunately, no reaction was observed upon subjection of iodolactone-amide **82** to the standard conditions, most likely due to the poor solubility of the starting material in EtOH. Using EtOAc as the solvent instead, 59% of the staring material was recovered together with 15% of the des-iodo compound **84** and 21% of the isomerised compound **85**. Isomerization of the γ-lactone **82** to the more thermodynamically stable δ-lactone **85** presumably occurs *via* the iodonium salt as indicated in **Figure 32**.

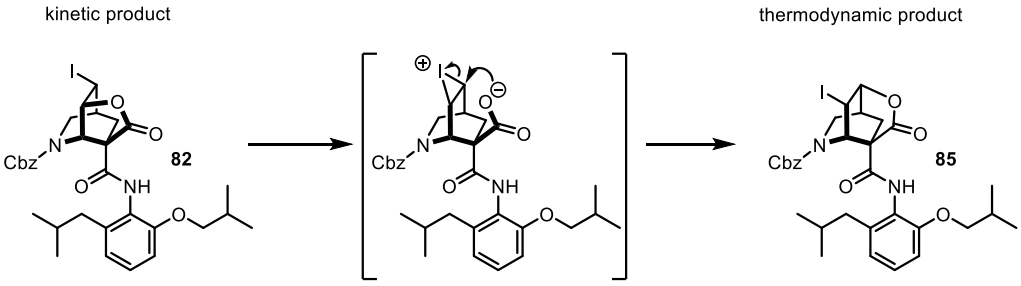
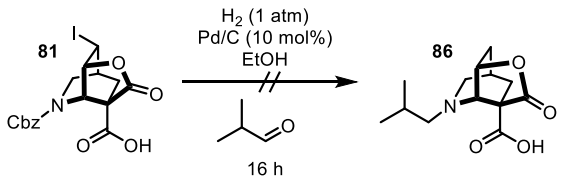


Figure 32 | Isomerization of γ-lactone **82** to the more thermodynamically stable δ-lactone **85.**

Equilibration *via* the iodonium intermediate leads to thermodynamic control over the stereochemistry and appears to take place in the absence of base.[99] Changing the catalyst to PtO_2 did not improve matters, this catalyst proved to be less reactive than the Pd/C resulting in mainly recovery of the starting material (entry 3).

To determine whether the presence of the bulky amide was hindering the reaction, carboxylic acid **81**, which was soluble in ethanol, was subjected to the same conditions (**Scheme 33**).



Scheme 33 | Attempted hydrogenolysis/reductive amination of iodolactone-acid **81.**

No product (**86**) was observed and only starting material was isolated after stirring for 16 h. Given our earlier success with the hydrogenolysis/reductive amination on closely related systems, we were intrigued as to which feature of the iodolactone-amide was inhibiting the removal of the Cbz group. Candidate features were: i) the large iodine atom (*red*), ii) the lactone ring (*green*) or, iii) an interaction between the amide/carboxylic acid proton (*purple*) with the carbamate carbonyl of the Cbz group (**Figure 33**).

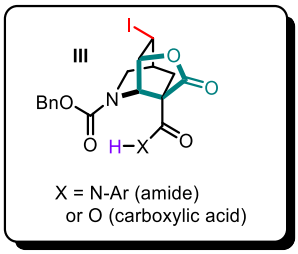
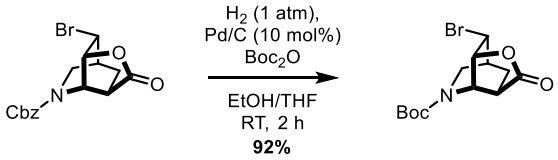


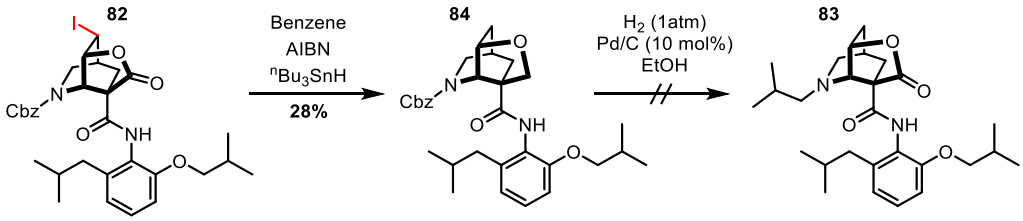
Figure 33 | Three potential features of substrate **III** which could be inhibiting hydrogenolysis.

In their total synthesis of the neuraminidase inhibitor (-)-oseltamivir,[100] Fukuyama's group was able to successfully effect a similar transformation on their azabicyclooctane unit, suggesting that the lactone ring was unlikely to be exerting a detrimental effect on the hydrogenolysis step (**Scheme 34**).



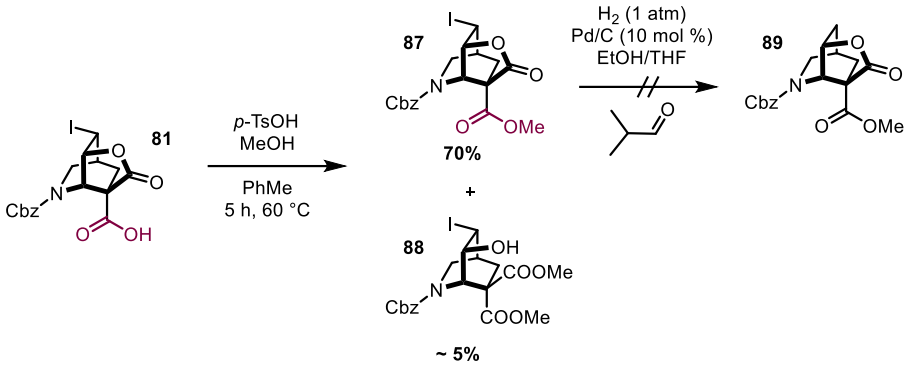
Scheme 34 | Fukayama's successful hydrogenolysis reaction on a tricyclic lactone.[100]

To determine whether the presence of the iodine atom was influential, the des-iodo compound **84** was synthesized after treatment of iodolactone-amide **82** with AIBN and $^{n}Bu_3SnH$ in dry benzene. This reaction provided 28% of the des-iodo compound **84**, together with a 64% recovery of the starting material and 9% of the isomerized starting material **85** (**Scheme 35**).



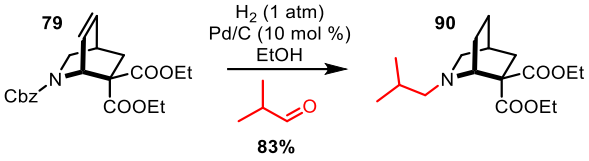
Scheme 35 | Radical deiodination of iodolactone **82** using AIBN/*n*-Bu_3SnH.

However, upon subjection of the des-iodo lactone **84** to the Pd/C catalysed hydrogenolysis conditions, once again the Cbz group remained intact. Our third hypothesis to explain the lack of reaction was that the acidic proton of the carboxylic acid (or amide) was perhaps maintaining the molecule in a conformation that prevented reduction, although this seemed unlikely in a hydroxylic solvent like EtOH. Nevertheless, to test this, the corresponding methyl ester **87** was synthesized in good yield using *p*-TsOH acid and methanol in toluene (**Scheme 36**).



Scheme 36 | Formation of methyl ester **87.**

Subjecting the methyl ester **87** to the hydrogenolysis conditions once again resulted in no reaction after 18 h, with complete recovery of starting material, ruling out the importance of the acidic proton. As a final test, the reducing conditions were explored on the original *gem*-diester DA adduct **79** (**Scheme 37**).



Scheme 37 | Hydrogenolysis/reductive amination of DA adduct *gem*-diester **79.**

Surprisingly, the reaction with *gem*-diester **79** proceeded smoothly and provided the *N*-alkylated alkane **90** in 83% yield. To summarise, of all the substrates subjected to the standard reduction conditions, only the *gem*-diester **79** had reacted (**Figure 34**).

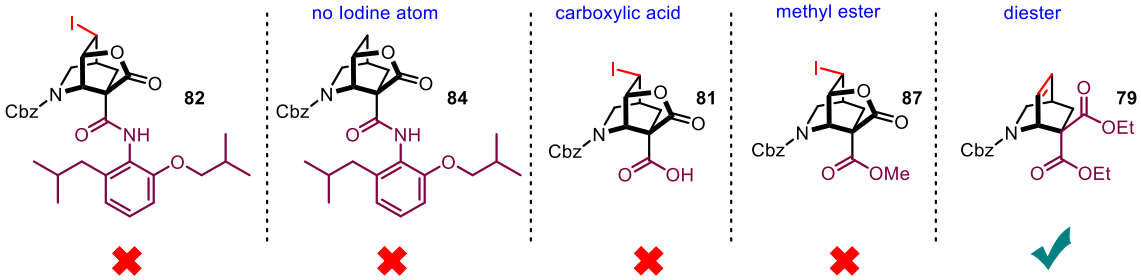
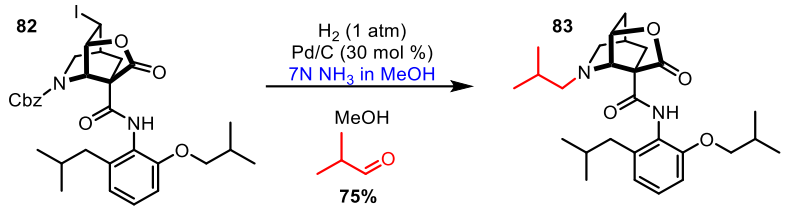


Figure 34 | Summary of the outcome of reactions in which *N*-Cbz-azabicyclooctane derivatives were subjected to H_2 (1 atm)/Pd-C hydrogenolysis/reductive amination conditions.

Unable to explain these results but armed with the knowledge that the presence of base might at least prevent the undesired isomerisation reaction, we began investigating the influence of additives in these reactions. In their work exploring the effect of amines as dopants during benzyl ether hydrogenolysis with H_2-Pd/C, Sajiki *et al.*[101] noted that alkenes, *N*-Cbz groups, benzyl ethers and azides could be readily cleaved in the presence of NH_3. In light of this and

given that in the next step of our proposed synthesis would require opening of the lactone ring with NH_3 to form the primary amide, it was decided to investigate the effect of introducing NH_3 into the hydrogenolysis reaction (**Scheme 38**).

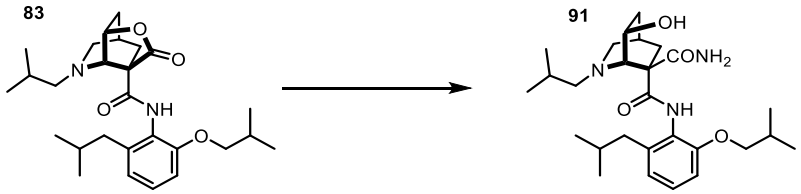


Scheme 38 | Hydrogenolysis/reductive amination of *N*-Cbz-azabicyclooctane **82** in the presence of ammonia.

To our surprise, 75% of the pure *N*-alkyl compound **83** was isolated after stirring for 7 h at ambient temperature. Pleasingly, the reaction was found to be reproducible, although trace amounts of the des-iodo compound **84** were also formed. The presence of NH_3 had clearly allowed for the hydrogenolysis/reductive amination reaction to proceed, but interestingly ring-opening of the lactone did not take place.

Formation of the primary amide **91** *via* lactone ring-opening was subsequently attempted using alternative conditions (**Table 14**).

Table 14 | Attempted ring-opening of the lactone with ammonia (or NH_4OH)**.**



Entry	Reaction Conditions	Outcome
1	*conc. aq.* NH_4OH, 1,4-dioxane, 18 h, RT	No reaction
2	7N NH_3 in MeOH, 4 d, 60 °C, sealed tube	No reaction
3	NH_3 (g), THF/*t*-BuOH, 1.5 h at 0 °C then 1 h at RT	No reaction

Treating lactone **83** with a concentrated solution of aqueous NH_4OH (entry 1) and heating the lactone in neat NH_3 (7N in MeOH) in a sealed tube saw no reaction (entry 2). Bubbling NH_3 gas directly into a solution of the lactone also saw no change (entry 3). We had previously observed some lactone ring-opening during our attempts to form the methyl ester **87** (see **Scheme 36**) and so subjected lactone **83** to the same methanolysis conditions. However, we found only starting material remaining after treatment with *p*-TsOH acid and excess methanol in toluene for 24 h at 65 °C. We speculated that the large aryl amide might be blocking the approach of nucleophiles, even as small as NH_3, from accessing the lactone carbonyl from the front face (as drawn below), and the azabicyclooctane ring protons might be preventing attack from the back face (**Figure 35**) – see page 83-84 for a continuation of this discussion.

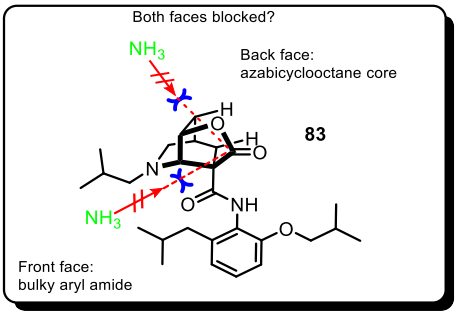
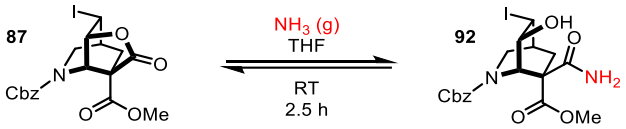


Figure 35 | Proposed rationale for lack of reactivity of lactone **83** with nucleophiles.

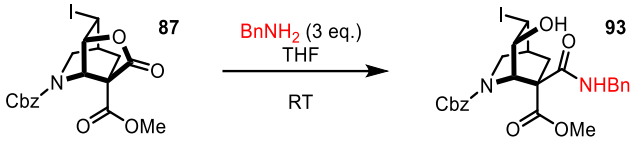
To test this hypothesis we decided to explore the lactone ring-opening on a less sterically hindered system and selected the corresponding methyl ester **87** for this study. After bubbling NH_3 gas for 2.5 h into a solution of the methyl ester in THF at RT, total consumption of the starting material was observed by TLC analysis, however re-analysis of the reaction mixture after standing overnight revealed that the lactone had re-formed (**Scheme 39**).



Scheme 39 | Treatment of methyl ester **87** with NH_3.

The reaction was repeated and purification was carried out immediately to give the desired primary amide **92** in 72% yield. The isolated primary amide was found to undergo spontaneous ring-closure with complete conversion back to the starting γ-lactone **87** being observed after 2 days, neat at RT. The apparent reversibility of this reaction raised some concerns about the following *O*-alkylation step as the presence of base was considered likely to accelerate ring-closure. Consequently, the nucleophile was changed from NH_3 to $BnNH_2$, anticipating that the loss of $BnNH_2$ would be less facile than the loss of NH_3. $BnNH_2$ was also chosen as we envisaged that it might be possible to remove the benzyl group in the hydrogenation/reductive amination conditions that were required later on in the synthesis. The reaction with $BnNH_2$ was initially investigated on a small scale using excess $BnNH_2$, first without an additive and then in the presence of the bifunctional catalyst, 2-OH-pyridine[102] (entries 1 and 2, Table **15**).

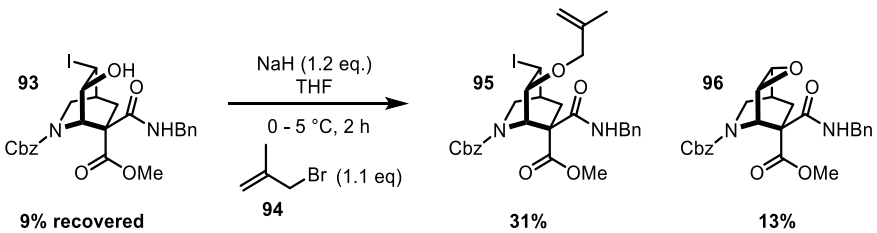
Table 15 | Ring-opening of methyl ester **87** with $BnNH_2$.



Entry	Additive	Scale	Reaction Time	Yield of 93
1	-	20 mg	16 h	92%
2	2-OH-pyridine (0.5 eq.)	20 mg	2 h	68%
3	-	150 mg	2 d	83%

The most promising result was obtained in the absence of the additive (entry 1), so these conditions were repeated on a larger scale (entry 3). After an extended reaction time, the benzylamide alcohol **93** was isolated in 83%. Encouragingly, the benzylamide was found to be markedly more stable than the corresponding primary amide **92**, and only a small degree of ring-closure was observed after standing for 2 days.

Our attention turned to the *O*-alkylation step to install the *i*-1 residue. Features that we considered pertinent to successfully executing this alkylation reaction included: a) the relatively hindered nature of the secondary alcohol would limit its nucleophilicity, b) the formation of an alkoxide adjacent to a C-I bond might lead to formation of an epoxide, and c) the alkoxide might preferentially attack the benzylamide leading to lactone formation. To promote *O*-alkylation, we decided to use a reactive electrophile – the commercially available 3-bromo-2-methylprop-1-ene (**94**). This electrophile, following hydrogenation of the alkene, will furnish a branched alkyl ether that should overlay with the side chain of an isoleucine residue at the *i*-1 position. Although the desired mimetic requires the use of 3-bromo-3-methylpropen-1-ene (which leads to a leucine residue), the instability and need for a regioselective reaction with this electrophile led us to use its isomer to explore the *O*-alkylation. After some initial experiments using excess base (2 eq. of NaH or *tert*-BuOK) which lead to inconclusive results, the reaction was attempted with 1.2 eq. of NaH (**Scheme 40**).

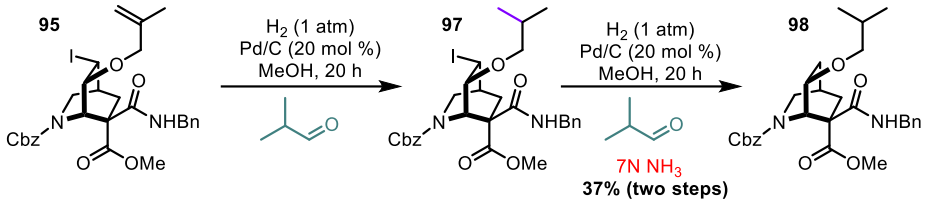


Scheme 40 | *O*-Alkylation of secondary alcohol **93**. The allyl bromide was added to a stirring solution of the alcohol and base.

Under these conditions, the desired *O*-alkylated product **95** was isolated, albeit in just 31% yield. Also isolated was epoxide **96** (13% yield) along with the unreacted starting alcohol (9% yield). In the hope of preventing the undesired epoxidation, the reaction was repeated with the allyl-

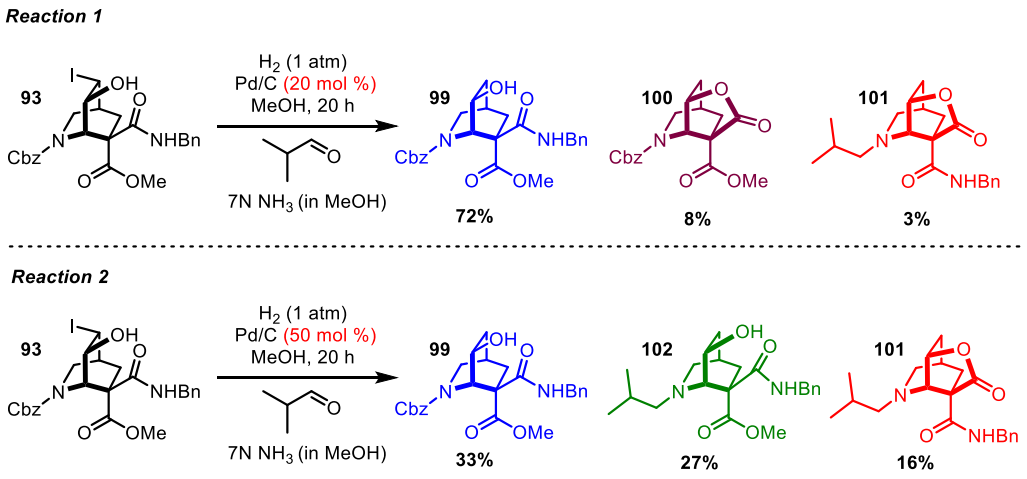
bromide added before the base, but with this order of addition only 30% of the desired product was isolated along with 24% of the epoxide. Although the reaction clearly required further optimization, enough of the *O*-alkylated compound was isolated to investigate the subsequent step.

We hoped that the reducing conditions would result in not only the *N*-Cbz hydrogenolysis/reductive amination, but also the deiodination, alkene reduction and benzyl amide hydrogenolysis. Initially, the reaction was conducted in the absence of methanolic NH_3, after which only the alkene moiety was reduced to give alkane **97** (**Scheme 41**).



Scheme 41 | Proposed order of events in the hydrogenolysis reaction of **95**.

Re-subjecting intermediate **97** to the same conditions in the presence of methanolic NH_3 lead to the isolation of des-iodo compound **98** in 37% overall yield. Once again the Cbz group remained intact despite the presence of methanolic NH_3. This result and our experience of the hydrogenolysis of related compounds indicated that the iodine atom is cleaved prior to the Cbz moiety. In light of this conclusion and taking into account our desire to improve the previous *O*-alkylation step, we explored the hydrogenolysis conditions on hydroxyamide **93** (*i.e.* before *O*-alkylation), in the hope that that removal of the iodine atom might improve the alkylation step by removing the pathway to epoxidation. The hydrogenolysis was performed twice, with the only difference being the loading of the Pd catalyst (increased from 20 mol% to 50 mol %) – **Scheme 42**.



Scheme 42 | Subjecting the hydroxyamide **93** to the standard reduction conditions produced multiple different products.

In both reactions the des-iodo compound **99** was found to be the major compound. In the first reaction, employing 20 mol %. Pd/C, the lactone **100** was formed in 8% yield but it was not formed at all in the second reaction, employing 50 mol % Pd/C, although the desired *N*-alkylated compound **102** which still contained the benzyl protecting group was formed in 27% yield. We were surprised at the divergent outcomes obtained apparently as a result of varying the amount of heterogeneous catalyst used. The formation of the lactone amide **101** in both reactions was also interesting as we had not anticipated its formation. A potential mechanism for its formation *via*-an unusual H-bond assisted amide transfer process is provided below (**Figure 36**), although a related intermolecular $BnNH_2$ mediated trans-acylation reaction of the lactone methyl ester **100** cannot be ruled out.

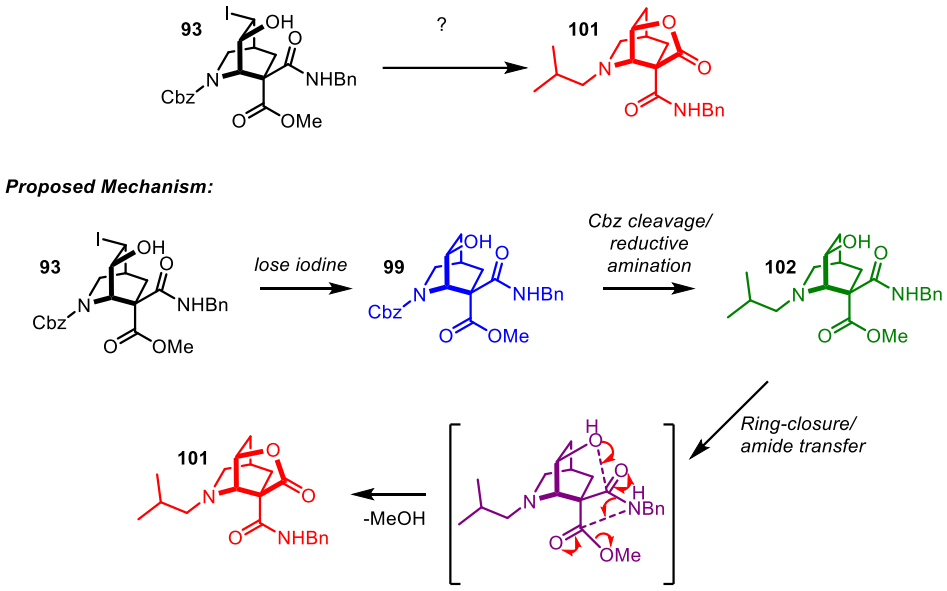
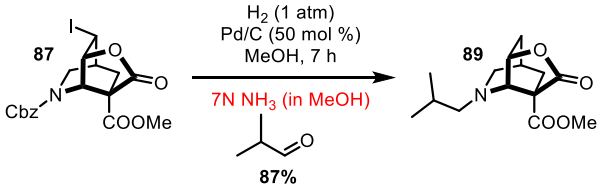


Figure 36 | Proposed pathway and mechanism for the formation of lactone amide **101.**

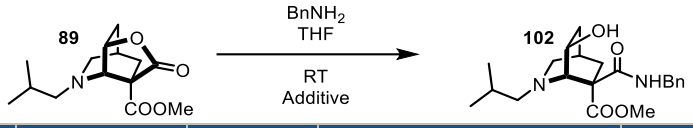
It was clear that use of hydroxyamide **93** as an intermediate was not the way forward. As a result, the hydrogenolysis/reductive amination/deiodination was attempted on γ-lactone **87** *i.e.* prior to ring-opening using $BnNH_2$. Recall that the hydrogenolysis of this compound was attempted previously in the absence of NH_3 as an additive and without success. Pleasingly, in the presence of NH_3 the hydrogenolysis proceeded smoothly and in good yield, and was found to be reproducible (**Scheme 43**).



Scheme 43 | Hydrogenolysis/reductive amination/deiodination of lactone methyl ester **87** with ammonia as the key enabling additive.

Ring-opening of the resulting γ-lactone **89** using $BnNH_2$ was explored next (**Table 16**).

Table 16 | Ring-opening of γ-lactone **89** using $BnNH_2$.



Entry	Eq. of $BnNH_2$	Duration	Additive	Yield of 102
1	5	3 d	-	48%
2	5	2 d	0.5 eq. $ScOTF_3$ (24 h)[a] then 0.5 eq. 2-OH-pyridine (24 h)	57 %
3	10	3 d	5 eq. 2-OH-pyridine	77 %

[a]No reaction was observed, after which 2-OH-pyridine was added.

After some optimization we were able to isolate benzylamide **102** in 77% yield (entry 3). Surprisingly, the reaction of γ-lactone **89** with $BnNH_2$ occurred much more slowly than the corresponding reaction of γ-lactone **87** which contains the *N*-Cbz group and iodine substituent. One proposal for the observed rate difference, based on stereoelectronics, is that the anti-bonding orbital of the C-I bond (*i.e.* $\sigma^*_{C\text{-}I}$) might be interacting with the lone pairs of electrons on the oxygen in the lactone thereby promoting the ring-opening reaction. The electron withdrawing inductive effect (-I) of the *N*-Cbz group increasing the electrophilicity of the carbonyl carbon might also contribute to this reactivity difference (**Figure 37**).

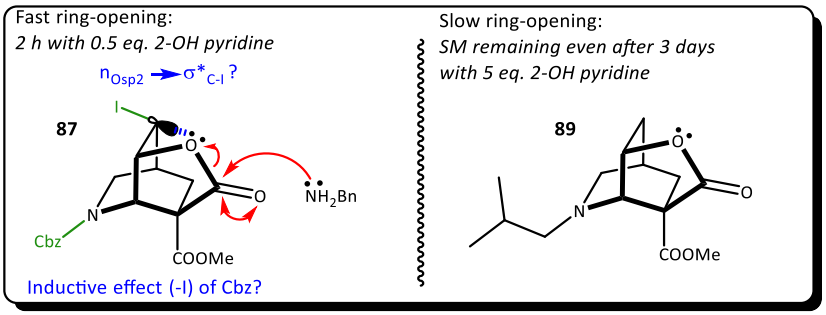
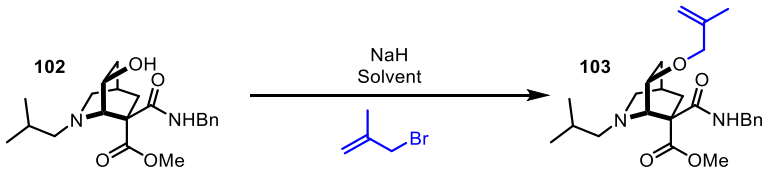


Figure 37 | Proposal for rate difference in ring-opening of γ-lactone **87** *vs*. **89** with $BnNH_2$, based on stereoelectronics.

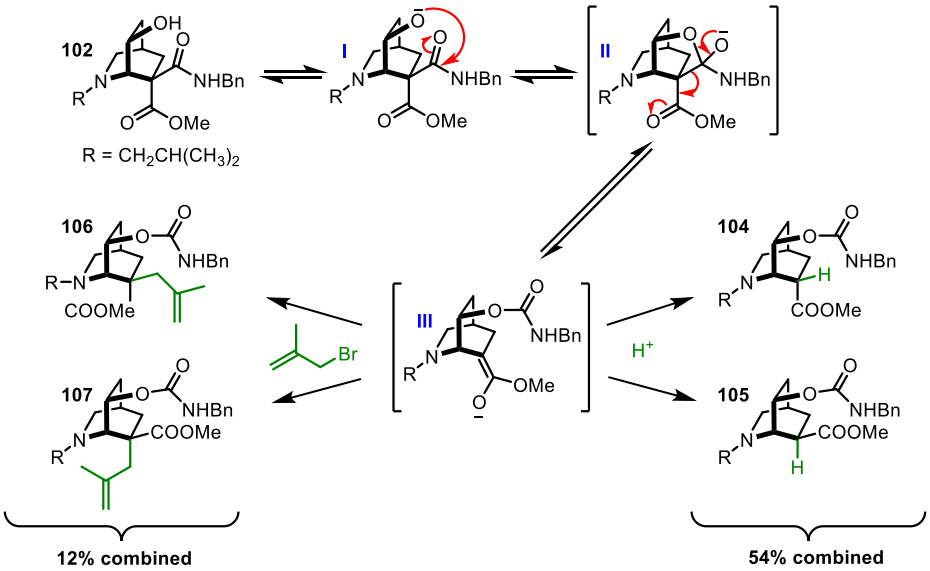
Focus next turned to revisiting the *O*-alkylation step, for which a 31% yield was obtained with alcohol **93** containing the *N*-Cbz group and iodine substituent. The same conditions were applied to alcohol **102** (**Table 17**).

Table 17 | Alkylation of secondary alcohol **102.**



Entry	Eq. of allyl bromide	Eq. of NaH	Solvent	Duration / Temp.	Yield of 103
1	1.1	1.2	THF	2 h / 0°C then 2h / RT	13%
2	1.1	1.2	DMF	3 h / 0°C	70%
3	1.1	2	DMF	45 mins / 0°C	68%
4	2	1.3	DMF	45 mins / 0°C	88%
5	2	1.3	DMF	75 mins / 0°C	87%

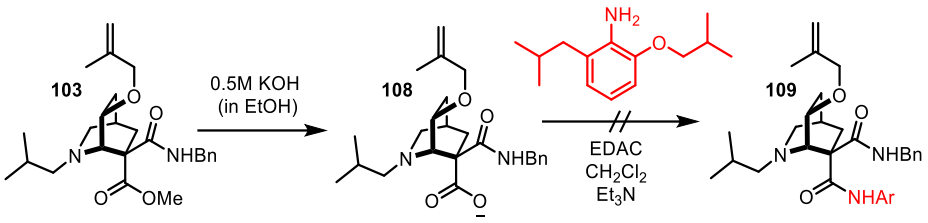
Initially, the reaction was carried out with a slight excess of NaH and allyl bromide in THF; after stirring at 0°C for 2 h, no reaction occurred, the reaction was warmed to RT and stirring for a further 2 h which led to complete consumption of alcohol **102** (entry 1). A complex mixture of five different compounds were formed. After isolation and analysis, these were revealed to be compounds **103**, **104**, **105**, **106** and **107** (see **Scheme 44**).



Scheme 44 | Proposed mechanism for by-products formed during attempted *O*-alkylation of alcohol **102** in THF.

We hypothesised that the hydroxyl group was deprotonated to form an insoluble alkoxide anion **I** that, owing to its appearance as a suspension in THF, did not react with the allyl bromide. Instead, upon warming to RT the anion reacted at the amide carbonyl to form the carbamate enolate (**III**) *via* intermediate **II**, as upon warming to RT the suspension turned into a clear solution. This enolate could then react with the allyl bromide from either face to give compounds **106** and **107**, or similarly with a proton to give compounds **104** and **105**. We concluded that solubilising the initially formed alkoxide anion would be the key to encouraging the desired etherification. The reaction was therefore repeated in DMF and after some further optimisation of the equivalents of base and allyl bromide employed (see entries 2-4), we were ultimately able to increase the yield of the desired *O*-alkylated product to 88% (entry 4). This result was found to be reproducible (entry 5).

The next stage in our design involved introducing the aryl amide moiety. This was to be accomplished either by hydrolysing the methyl ester to the corresponding acid followed by amide coupling using the conditions optimized previously, or by directly coupling the di-*ortho*-substituted aniline to the methyl ester. Having optimized the amide coupling on a related system, hydrolysis to the carboxylic acid was investigated first (**Scheme 45**).

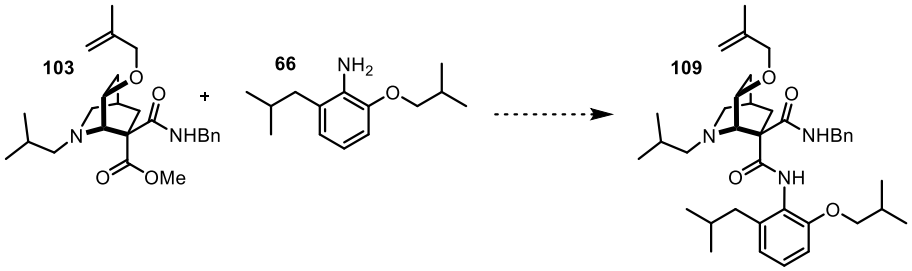


Scheme 45 | Attempted hydrolysis of methyl ester **103** followed by amide coupling.

Hydrolysis of the ester using a solution of KOH in EtOH gave a base line spot by TLC analysis that was tentatively assigned as being the carboxylate salt **108**. Unfortunately, attempts to couple this salt with the aniline using the conditions employed previously proved unsuccessful; complete recovery of the aniline was achieved.

Coupling the aniline directly to the methyl ester was then attempted (**Table 18**).

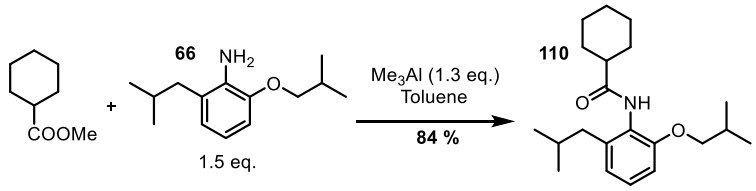
Table 18 | Attempted coupling of methyl ester **103** with aniline **66.**



Entry	Aniline : Methyl ester	Conditions	Outcome
1	1.6 : 1	1.8 eq. LiHMDS, HMPA, THF, 18 h / RT	No reaction Complete SM recovery
2	1 : 1.1	2 eq. Me_3Al, Toluene, 3 h / RT	Consumption of SM within 3 h No sign of product
3	1.5 : 1	1.3 eq. Me_3Al, Toluene, 45 mins / RT	Consumption of SM within 45 mins No sign of product

No reaction was observed when using LiHMDS to form the anilide anion, and after stirring at RT for 18 h both SM's were completely recovered (entry 1). Treatment of the aniline with Me_3Al followed by addition of the ester led to complete consumption of the ester within 3 h at RT. A complex mixture of products resulted with no indication by inspection of the NMR spectra of this mixture that the desired product (**109**) was present (entry 2). Instead it appeared that the Me_3Al had reacted with the carbonyl of either the methyl ester or the benzylamide; inspection of the mass spectrum of the isolated products showed an ion with *m/z* = SM + 16 which was assumed to be due to addition of 'CH_4'. Model studies revealed that the benzylamide group was stable to Me_3Al ruling out interference by the mildly acidic proton of this *sec*-amide. Having the aniline in excess over Me_3Al was next investigated (entry 3). However, although the methyl ester was consumed within 45 mins and one main new spot was observed by TLC analysis, this appeared to be the same unidentified product formed previously. Furthermore, complete

recovery of the aniline again suggested that the Me_3Al was reacting with the methyl ester. Before moving away from the Me_3Al conditions, we wanted to investigate the coupling of the aniline with a simplified methyl ester as we hypothesised that the lack of reaction might be because the aniline was too hindered to react with the Me_3Al and form the unstable Al-complex. Accordingly, using commercial methyl cyclohexanecarboxylate as the model ester and after altering the conditions such that the Me_3Al was no longer in excess, 84% of the cyclohexane amide **110** was isolated (**Scheme 46**).



Scheme 46 | Coupling of methyl cyclohexanecarboxylate with aniline **66.**

Clearly the bulky aniline was able to participate in Me_3Al based coupling. Next we decided to synthesise the benzylamide methyl ester **111** as it presents a closer structural match to our methyl ester (**Figure 38**).

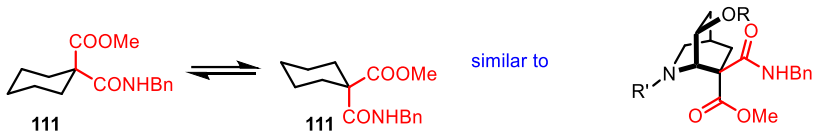
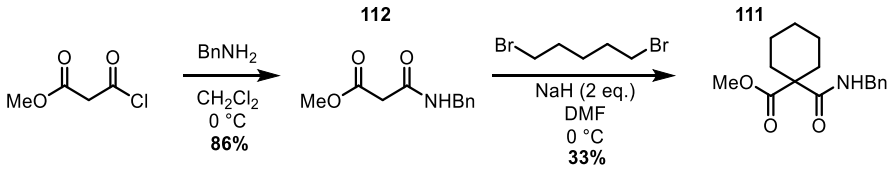


Figure 38 | Structural comparison of model benzylamide methyl ester **111** with the azabicyclooctane methyl ester.

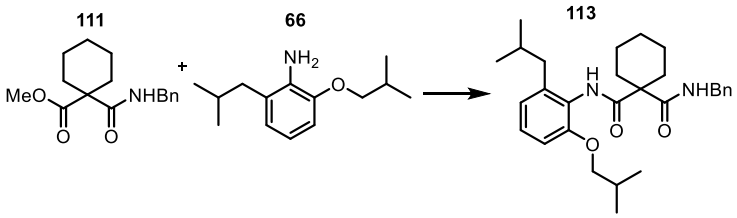
Synthesis of this α-amido ester was achieved *via* a straightforward two step sequence (**Scheme 47**).



Scheme 47 | Synthesis of α-amidoester **111**.

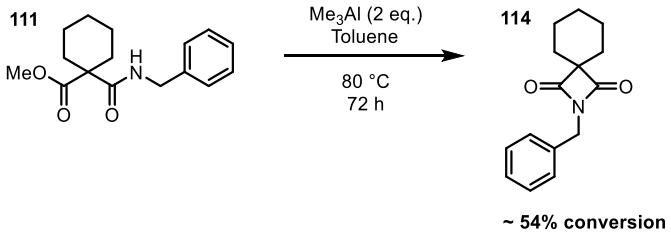
With the α-amido ester and di-*ortho* substituted aniline in hand, a series of known protocols used for coupling anilines to methyl-esters containing a β-carbonyl substituent were evaluated (**Table 19**).

Table 19 | Attempted coupling of di-*ortho* substituted aniline **66** with α-amido ester **111.**



Entry	Methyl ester : Aniline	Conditions	Outcome
1	1 : 2.3	Toluene, 4Å MS, 110 °C / 5 d	-
2	1 : 1.2	$Cu(OAc)_2$, Toluene, 110 °C / 5 d	-
3	1 : 1	NaOMe (3 eq.), MeOH, DMF, 24 h / 95 °C	-
4	1 : 1.1	2-OH-pyridine (5 eq.), Toluene, 24 h / RT	-
5	1 : 1.3	Me_3Al (1.2 eq.), Toluene, 24 h / 70 °C	5% product **113** isolated (not pure) 25% formation of azetidine-dione **114** 20% SM recovered.

Formation of the aryl-amide **113** proved difficult, with no reaction taking place under neat conditions (entry 1), Lewis-acidic conditions (entry 2), basic conditions (entry 3), or in the presence of 2-OH-pyridine which is commonly employed in the aminolysis of esters (entry 4). By contrast, when Me_3Al was used, 5% of the product was isolated together with 25% of the azetidine-dione **114**. The formation of this by-product was unexpected and the decision was made to probe this further as it might reveal why the Me_3Al coupling failed to provide the amide from the azabicyclooctane system. As by-product **114** appeared likely to arise by the starting material reacting with itself, α-amido ester **111** was subjected to 2 equivalents of Me_3Al in toluene. After heating at 80 °C for 72 h, ^1H NMR analysis of the reaction mixture indicated approximately 54% conversion to the azetidine-dione **114** (**Scheme 48**).

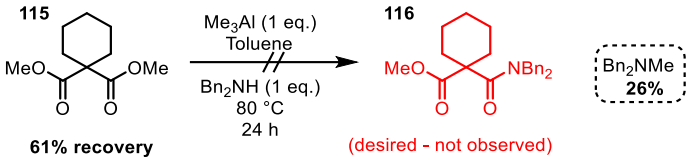


Scheme 48 | Formation of azetidine-dione **114.**

This result and our previous attempts to effect Me_3Al coupling of amines with α-amido/ester-ester compounds indicated that such transformations are difficult. For the α-amido ester substrates we suspected that the acidic amide proton might be culpable, *e.g.* in the above reaction, Me_3Al presumably deprotonates the benzylamide in preference to the aniline proton which subsequently reacts with the methyl ester in an intramolecular fashion. We considered that a similar reaction might occur with the azabicyclooctane **103**. To explore this further, the plan was to remove the acidic proton *via* formation of a tertiary amide. We settled on the

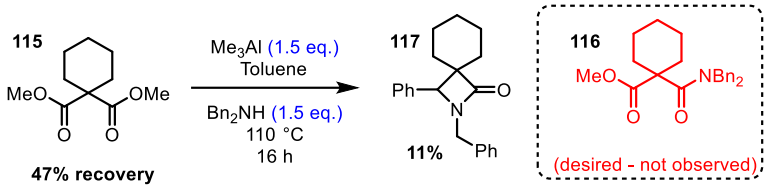
dibenzylamide as this would not necessitate an extra deprotection step should we extend this to our actual system.

To prepare the α-dibenzylamide ester **116**, the cyclohexane dimethyl ester **115** was treated with Me_3Al and Bn_2NH (**Scheme 49**).



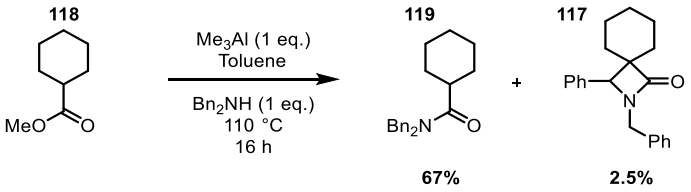
Scheme 49 | Attempted coupling of dimethyl ester **116** and Bn_2Me using Me_3Al.

None of the coupled dibenzylamide ester **116** was observed, instead Bn_2NMe was isolated as a component of an inseparable mixture with the starting dimethyl ester. The reaction was repeated but with pre-mixing of the Me_3Al and Bn_2NH, both of which were in excess, followed by refluxing at 110 °C (**Scheme 50**).



Scheme 50 | Formation of β-lactam **117**.

On this occasion yet another unexpected compound was isolated – the β-lactam **117**. To the best of our knowledge there is no literature precedent for such a transformation using Me_3Al. To determine whether this unexpected transformation could provide a novel and general route to β-lactams, the mechanism for its formation needed to be explored. We decided to investigate whether Me_3Al could effect a similar transformation on a simple amide, or whether the ester component was necessary. Thus, synthesis of cyclohexane dibenzylamide **118** was undertaken (**Scheme 51**).

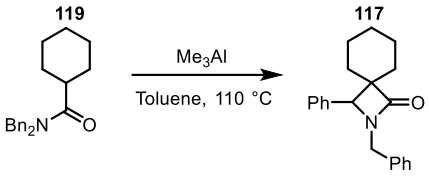


Scheme 51 | Synthesis of cyclohexane dibenzylamide **119.**

Dibenzylamide **119** was isolated in 67% yield as was a small amount of the β-lactam **117**, perhaps suggesting that the dibenzylamide is an intermediate *en route* to the β-lactam. To test this, the

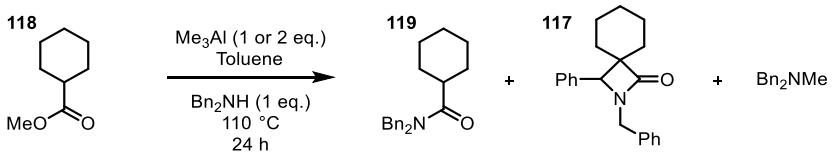
isolated cyclohexane dibenzylamide was subjected to a series of conditions in the presence of Me_3Al and refluxing toluene (**Table 20**).

Table 20 | Reactions of cyclohexane dibenzylamide **119** with Me_3Al.



Entry	Eq. of Me_3Al	Base	Duration	Outcome
1	-	-	3 d	-
2	2	-	3 d	-
3	2	Et_3N (2 eq.)	24 h	-
4	2	Cy_2NH (2 eq.)	24 h	-
5	2	Bn_2NH (2 eq.)	24 h	-

No reaction took place using Me_3Al alone (entry 2) suggesting that a base was necessary to effect the β-lactam formation. Initially Et_3N was used as a base, however again no reaction was observed (entry 3). We then considered using a secondary amine base, as this would react with the Me_3Al to form the unstable amine-Al complex which might be acting as the reactive species. However, the addition of Cy_2NH or Bn_2NH to the reaction made no difference to the outcome (entries 4 and 5). These findings suggests that the cyclohexane dibenzylamide is *not* an intermediate *en route* to the β-lactam. As formation of the β-lactam occurred when cyclohexane methyl ester was subjected to Me_3Al in the presence of Bn_2NH (see **Scheme 51** above) but not when the corresponding cyclohexane dibenzyamide was, we suspected the divergent behaviour to perhaps be due to the higher acidity of the α-proton of the ester (the proposed mechanism in **Figure 39** elaborates on this further). As a final test, we therefore subjected cyclohexane methyl ester to both 1 and 2 equivalents of Me_3Al in the presence of Bn_2NH in refluxing toluene for 24 h (**Scheme 52**).



Scheme 52 | Treatment of cyclohexane methyl ester **118** with varying amounts of Me_3Al.

In both cases, mainly cyclohexane dibenzylamide **119** was observed and only trace amounts of the β-lactam and Bn_2NMe were present. Although the formation of the β-lactam is indeed curious, as we were unable to form this compound in synthetically useful amounts we decided it was time to abandon investigating this chemistry. A speculative mechanism that can account for our observations invokes the initial formation of an unstable amine-Al complex which collapses to give an imine that is subsequently trapped by an enolate formed either *via*

decarboxylation or α-deprotonation of dimethyl ester **115** or methyl ester **118**, respectively (**Figure 39**).

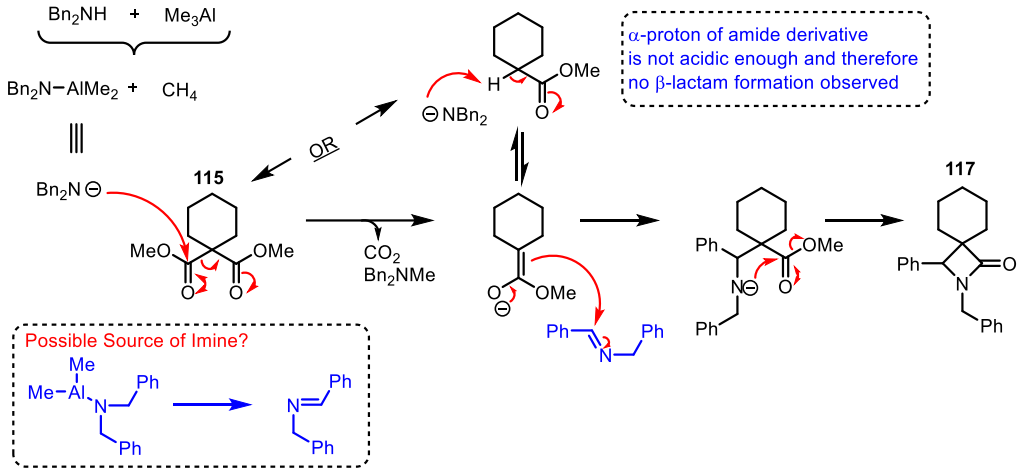
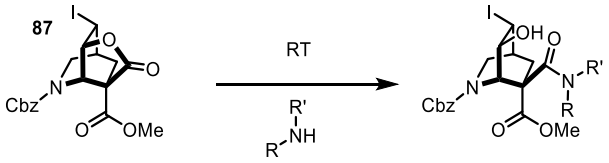


Figure 39 | Proposed mechanism for the formation of the β-lactam **117** and Bn_2NMe.

Whilst these model studies were ongoing, we also began exploring whether nitrogen based nucleophiles other than NH_3 and $BnNH_2$ could initiate ring-opening of the azabicyclic γ-lactone, especially considering our previous difficulties in effecting such a transformation (reversibility issues, differences between NH_3 *vs*. $BnNH_2$, sensitivity to substitution around the azabicyclooctane ring *etc.*). Various reactions were examined (**Table 21**).

Table 21 | Attempted ring-opening of γ-lactone **87** with different nitrogen based nucleophiles.



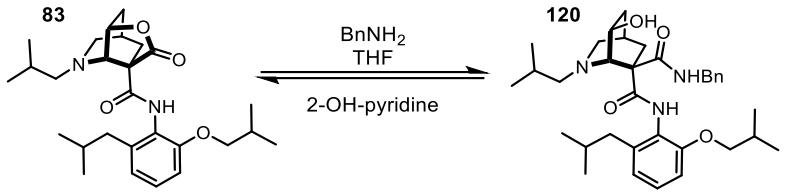
Entry	R	R'	Conditions	Yield of hydroxyamide	Comment
1	H	H	THF, 2.5 h	72%	Reversible
2	H	Bn	2-OH-pyridine, THF, 2 d	83%	
3	Bn	Bn	2-OH-pyridine, THF, 2 d	-	No reaction
4*	H	O-Bn	2-OH-pyridine, THF, 2 d	-	No reaction

*Me_3Al coupling in CH_2Cl_2 was also attempted without success.

Treatment of γ-lactone **87** with Bn_2NH in the presence of 2-OH-pyridine, a bifunctional catalyst commonly employed in the aminolysis of esters, gave no reaction (entry 3), in stark contrast to the behaviour of $BnNH_2$. Steric hindrance offers one explanation for this lack of reactivity but our work on these azabicyclooctane lactones suggests other factors may also be important. No reaction was observed after treatment with *O*-benzyl hydroxylamine either (entry 4), which is similar in size to $BnNH_2$. Having experienced difficulty in attempting to functionalise the methyl ester after the ring-opening of the lactone, and indeed challenges with the ring-opening itself, the decision was made to abandon trying to progress the synthesis *via* the methyl ester

derivative and instead revisit ring-opening of lactone **83**, which already contains the aryl amide. Previously, treatment of this lactone with NH_3 had not resulted in any apparent reaction and this had been attributed to the steric encumbrance of the amide group. However, given that we had subsequently discovered that lactone ring-opening was readily reversible for a closely related system, it was hypothesised that the NH_3 might be attacking the lactone carbonyl but undergoing facile ring-closure. Cognisant that the benzyl amide was significantly more stable than the primary amide on the methyl ester system, lactone **83** was treated with $BnNH_2$ (**Table 22**).

Table 22 | Ring-opening of lactone amide **83** with $BnNH_2$.

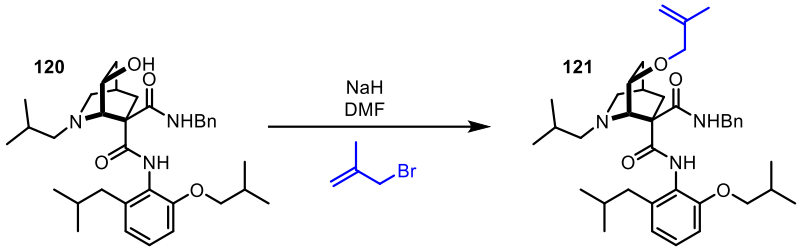


Entry	Eq. of 2-OH-pyridine	Duration	SM recovery	Yield of 120
1	5	36 h	21%	61%
2	5	3 d	48%	32%
3	9	2 d	30%	67%

Although 61% of the ring-opened benzyl amide **120** product was isolated after 36 h, unlike the methyl ester variant, the resulting benzylamide **120** underwent slow ring-closure to the lactone (*i.e.* 11% conversion to lactone after 24 h and 23% conversion after 72 h). Leaving the reaction for a longer period therefore led to a reduced yield (entry 2). However, increasing the equivalents of 2-OH-pyridine did allow for a slight increase in yield (entry 3).

It is not immediately obvious why the rate of reactions with NH_3 and $BnNH_2$ differ so much, or why the lactone amide and lactone methyl ester themselves behave differently in the ring-opening reactions. Perhaps there are conformational effects in play, *e.g.* a favourable 6-membered ring may form as a result of H-bonding with the aryl amide but not the methyl ester. With the secondary alcohol **120** in hand, the *O*-alkylation reaction was explored using conditions optimized on the methyl ester (**Table 23**).

Table 23 | *O*-alkylation of secondary alcohol **120** using previously optimized conditions.

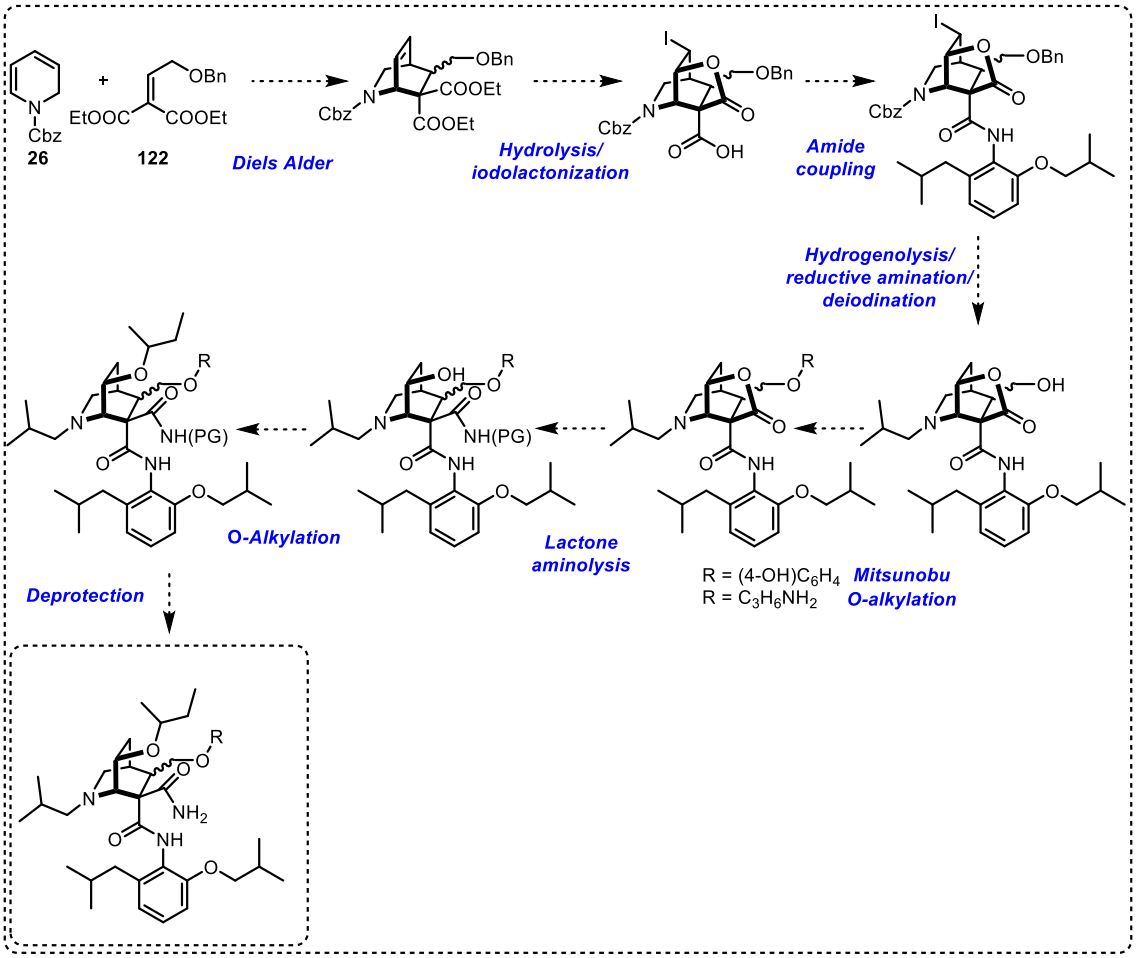


Entry	Eq. of allyl bromide	Eq. of NaH	Additive	Duration / Temp.	Isolated yield of 121
1	2.5	1.3	-	2 h, 0°C	21%
2	3	2.5	0.4 eq. TBAI	7 h, 0°C	16%

The previously optimized conditions did not extend to our new system, and after 2 h there was still a considerable amount of starting material remaining and only 21% of the desired product **121** was isolated as well as a trace amount of lactone **83** (entry 1). Even when allowing for a longer reaction time to 7 h, adding TBAI and increasing the amount of base and allyl bromide, some starting material remained and only 16% of the desired product **121** was isolated. Furthermore, in both reactions, a complex mixture of unidentified by-products was also present. Taking into consideration that the secondary alcohol **120** has a propensity to ring-close, even in the absence of the base, and the low yield in the *O*-alkylation reaction, we hypothesized that the presence of one or both of the acidic protons on the two amides could be impeding the desired reaction. It was considered that substitution of these acidic protons with *e.g.* TMS groups might therefore be advantageous. However, before expending efforts to optimise the *O*-alkylation reaction, which would give a four-residue mimetic after removal of the *N*-benzyl group, it was decided to return to the beginning of the synthesis and incorporate the final residue at the *i*+2 position.[103]

6.2 Five-Residue Mimetic

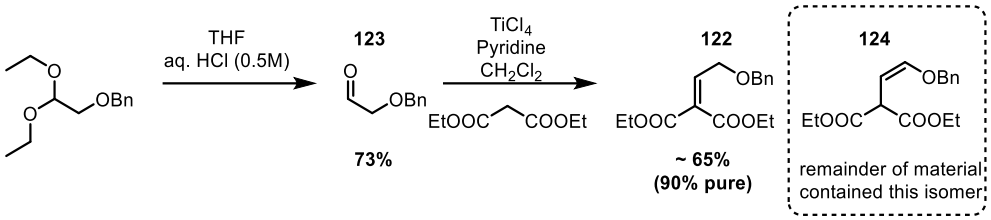
To complete our full five-residue mimetic, we require a functional handle at the C5 carbon of the azabicyclooctane for the *i*+2 residue. To install this final residue, a trisubstituted dienophile was required in the initial DA reaction with *N*-Cbz-1,2-DHP **26**. It was envisioned that following this cycloaddition reaction, the chemistry which was developed for the four residue mimetic would be employed (**Scheme 53**).



Scheme 53 | Proposed synthetic route to the five-residue mimetic.

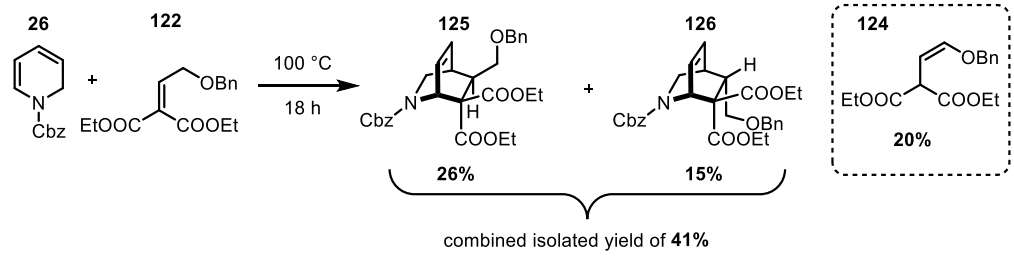
The plan was to develop a mimetic which could reproduce the relevant residue on both the SHP-1 peptide, for which a tyrosine is required at the *i*+2 position, and the SHP-2 peptide, for which a lysine residue is required. Additionally, previous computational calculations revealed that both an *endo* and an *exo* substituted ether group at C5 would overlay acceptably with the tyrosine *i*+2 side chain of the SHP-1 peptide. Achieving diastereocontrol at this position during the DA reaction was therefore not necessary as both diastereoisomers could be taken forward should a mixture ensue. Regarding the choice of the dienophile in the DA reaction, it was initially planned to use *O*-benzyl protected trisubtituted alkene **122** with the aim to reveal the primary alcohol once the core had been constructed and either arylate or alkylate this alcohol to mimic a tyrosine or lysine residue, respectively.

The dienophile **122** was synthesised in two steps from commercially available 2-benzyloxyacetaldehyde diethyl acetal (**Scheme 54**).



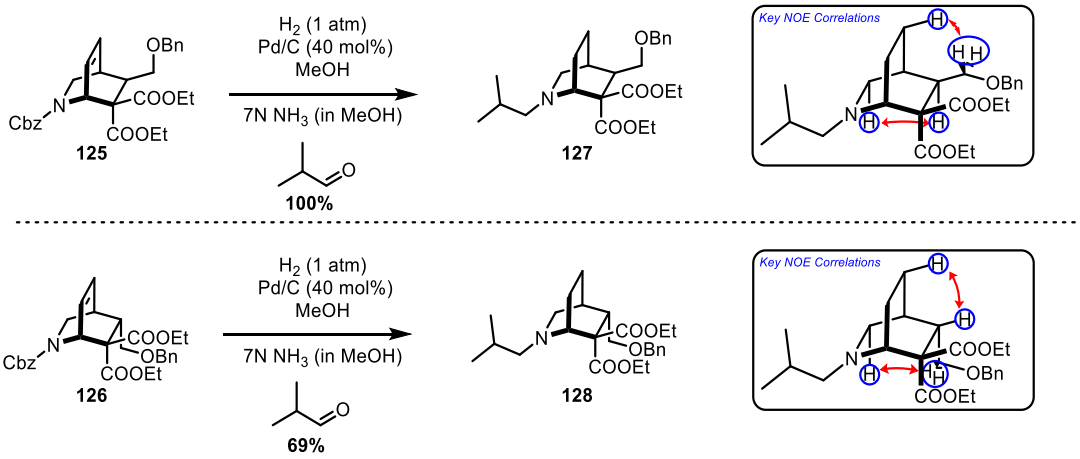
Scheme 54 | Synthesis of dienophile **122**.

Acid hydrolysis of the commercial acetal provided aldehyde **123** in 73% yield. The aldehyde was reacted with diethyl malonate in a Knoevenagel condensation in the presence of $TiCl_4$ and pyridine to give the tri-substituted alkene **122** in 65% overall yield. We found this malonate to be unstable: not only does it polymerise, but it also isomerises to the enol ether **124**. Both processes were found to occur simultaneously even at low temperatures and so its use immediately after preparation was mandated. This dienophile and *N*-Cbz-1,2-DHP **26** were therefore immediately heated at 100 °C for 18 h (**Scheme 55**).



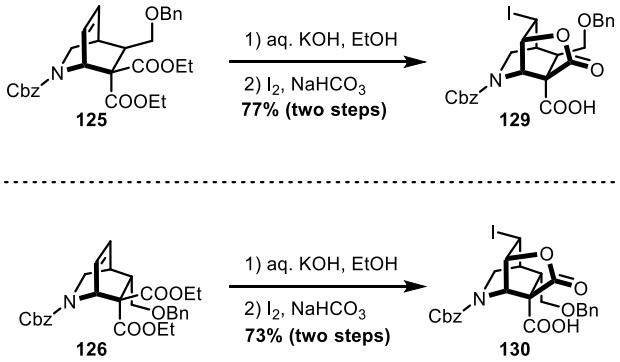
Scheme 55 | Diels-Alder reaction between *N*-Cbz-1,2-DHP **26** and dienophile **122.**

Two DA adducts were isolated in a combined yield of 41% in a 1.7:1 - *endo:exo* ratio. Also isolated was a significant amount of the enol ether **124** and the dimerised alkylidene malonate. The stereochemistry of each diastereoisomer was determined following analysis of their NMR spectra following reduction to *N*-alkylated compounds **127** and **128** (**Scheme 56**).



Scheme 56 | Hydrogenolysis/reductive amination/reduction of DA adducts **125** and **126** to determine their stereochemistry *via* NOE measurements.

Each isomer was then separately carried through to the iodolactonization step (**Scheme 57**).

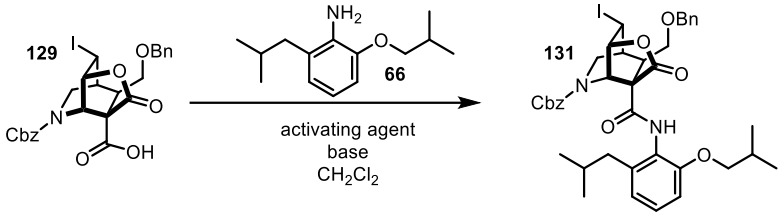


Scheme 57 | Iodolactonization of DA adducts **125** and **126** (carried through separately).

The hydrolysis/iodolactonization reactions proceeded smoothly in both cases providing both carboxylic acids in good yields.

Coupling of di-*ortho* substituted aniline **66** with the newly formed carboxylic acids was first attempted on the *endo* isomer **129** (**Table 24**).

Table 24 | Attempted amide coupling of di-*ortho* substituted aniline **66** and carboxylic acid **129.**



Entry	Eq. of Aniline	Activating agent	Base	Duration / Temp.	Outcome
1	1.8	EDAC	Et_3N	2 d / RT	100% aniline recovery, no desired product, several unidentified side-products.
2	1.8	EDAC	Et_3N	5 d / RT	92% aniline recovery, no desired product, several unidentified side-products.
3	-	$(COCl)_2$ & *cat.* DMF	Et_3N	20 h / RT	No formation of acid chloride.
4	1.3	BTFFH	DIPEA	16 h / 70 °C	~ 95% aniline recovered.
5	3	T3P	DMAP	20 h / RT	50% aniline recovery, trace amounts of desired product **131**, several unidentified by-products.

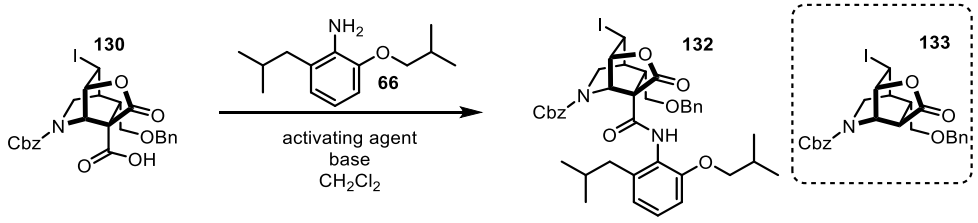
Abbreviations: EDAC - 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (used as HCl salt); BTFFH - bis(tetramethylene)fluoroformamidinium hexafluorophosphate; T3P - propylphosphonic anhydride.

Unfortunately, the conditions which worked smoothly for the four residue system did not appear to translate as we had hoped (entry 1). Not only was the aniline completely recovered, but several by-products had formed. Increasing the reaction time did not improve matters (entry 2). Formation of the amide *via* the acid chloride was also unsuccessful using oxalyl chloride (entry 3). Concerned that the steric environment about the acid was preventing amide formation, we then utilized conditions reported by Ulven *et al.*[104] who had also experienced difficulty in the coupling of sterically hindered acids to electron deficient amines and anilines.

They developed a protocol utilizing the fluorouronium reagent, BTFFH, which forms the acid fluoride *in situ* before coupling with a variety of electron poor amines at elevated temperatures in good to excellent yields. After heating at 70 °C for 16 h in CH_2Cl_2 in a sealed tube most of the aniline remained unreacted with just a trace amount of amide present (entry 4). Use of T3P gave some amide **131**, as evidenced by the characteristic broad amide proton peak at δ = ~9 ppm in the ^{1}H NMR of the crude reaction mixture, however isolation proved extremely challenging (entry 5). Knowing where the product ran by TLC, we decided to run a series of small scale reactions (~5 mg, 0.01 mmol of carboxylic acid **129**) with a variety of different coupling agents: BOP, PyAOP, PyBOP, HBTU, TBTU, T3P, and HATU. All reactions were carried out in DMF using DIPEA as the base and at RT under a N_2 atmosphere – however neither TLC nor ^{1}H NMR analysis of the crude reaction mixtures after mild acidic work-ups looked promising in any of these reactions.

Meanwhile, we were also exploring the amide coupling on *exo*-**130** (**Table 25**).

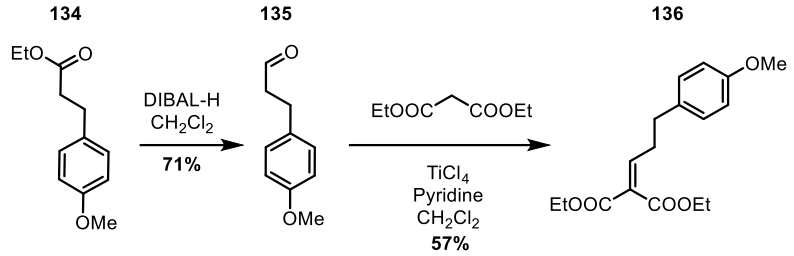
Table 25 | Attempted amide coupling between aniline **66** and carboxylic acid **130.**



Entry	Eq. of Aniline	Activating agent	Base	Duration / Temp.	Outcome
1	1.8	EDAC	Et_3N	2 d / RT	100% aniline recovery, no desired product.
2	1.1	$(COCl)_2$ & *cat.* DMF	Et_3N	20 h / RT	100% aniline recovery, no desired product.
3	3	T3P	Et_3N	40 h / RT	~ 60% aniline recovery, 13% desired product **132**, 55% decarboxylated SM **133**

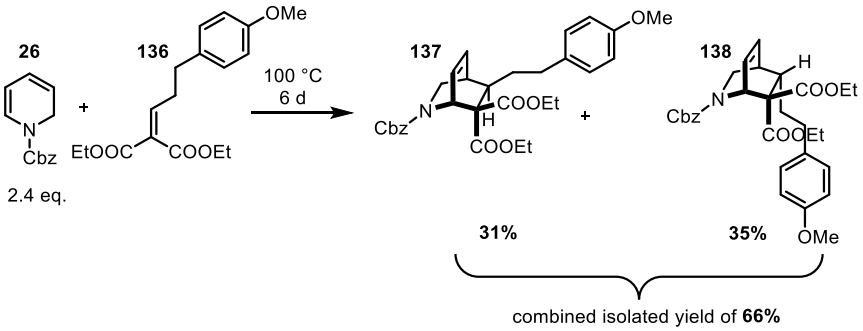
Once again the standard amide coupling conditions yielded none of the desired amide (entries 1 and 2). Use of T3P did result in some of the desired product **132** albeit in just 13% yield, accompanied by 55% of the decarboxylated compound **133** (entry 3).

It was frustrating to realise that the presence of the extra substituent on the azabicyclooctane C5 position had such a profoundly negative influence on the amide coupling reaction. Furthermore, under identical reaction conditions, different by-products were forming for the *endo* and *exo* isomer. It was initially hypothesized that the oxygen atom of the benzyl ether unit was culpable, *e.g.* for the *exo* isomer of the carboxylic acid there may exist a H-bonding between the oxygen atom and the acidic proton *via* a 6-membered ring that might in turn promote decarboxylation. To obtain evidence to support this notion, dienophile **136** was synthesised, which contains an all-carbon chain at the mono-substituted end of the alkene (**Scheme 58**).



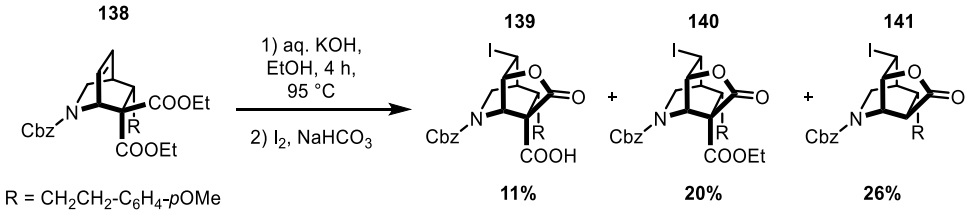
Scheme 58 | Synthesis of dienophile **136.**

Dienophile **136** and *N*-Cbz-1,2-DHP (**26**) were then heated at 100 °C under an argon atmosphere until consumption of the dienophile was observed (**Scheme 59**).



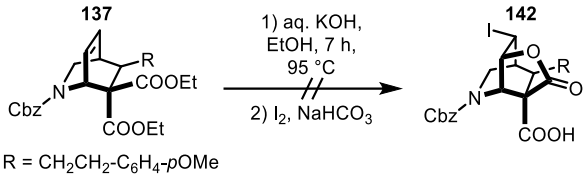
Scheme 59 | DA reaction of dienophile **136** and *N*-Cbz-1,2-DHP.

Two DA adducts were isolated in a combined yield of 66% in a ~ 1:1.1 – *endo*:*exo* ratio. The stereochemistry was assigned based on comparisons with the previous DA adducts. Once again, both diastereoisomers were separately carried through to the iodolactonization step, investigating *exo*-**138** first (**Scheme 60**).



Scheme 60 | Attempted iodolactonization of *exo*-**138.**

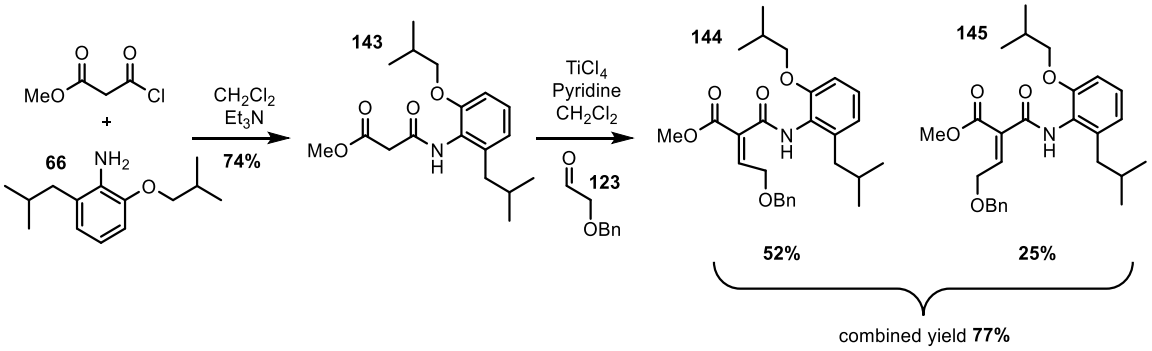
Unfortunately, this did not proceed as smoothly as previous attempts, which typically yielded the desired carboxylic acid in yields of 60-90% with no side products. On this occasion, the desired iodolactone acid **139** was only a minor product. By-products included the ethyl ester **140** and the decarboxylated derivative **141**. Next we explored the iodolactonization on the *endo* isomer (**Scheme 61**).



Scheme 61 | Attempted iodolactonization of *endo*-**137**.

With the *endo* isomer, prolonged heating was required to achieve full hydrolysis of the diester (7 h *cf.* 4 h for its *exo*-congener). The iodolactonization also proved to be problematic: the usual conditions (1 eq. I_2 in aqueous $NaHCO_3$ solution) gave mainly the starting lactone and only a small amount of the desired iodolactone acid **142**. Neither a longer reaction time, nor addition of THF to aid solubility improved matters. We were somewhat baffled by these results given that iodolactonization of all previous compounds had proceeded smoothly and in good yields, but were forced to conclude that replacement of the ether substituent with an alkyl one in the dienophile for the initial DA reaction had not been productive.

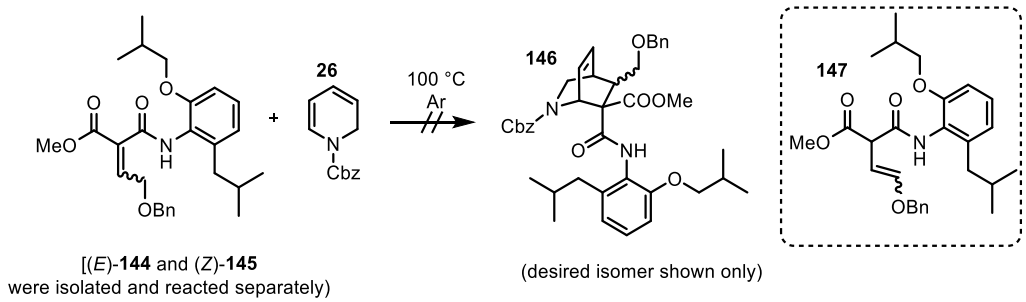
At this stage we decided to change tack and investigate having the aryl amide unit present on the dienophile from the start, *i.e.* employing a mixed amide/ester alkylidene malonate *e.g.* compound **144** or **145** in the initial DA reaction. The immediate questions associated with planning this type of DA reaction were: would they be sufficiently reactive? and what level and sense of *exo/endo* stereoselectivity could be achieved? To answer these questions, the dienophiles needed to be prepared (**Scheme 62**).



Scheme 62 | Synthesis of dienophiles **144** and **145**.

The initial coupling of methyl malonyl chloride and aniline **66** gave α-amido ester **143** in a 74% yield. This was followed by a Knoevenagel condensation which provided the two isomeric alkylidene mixed-malonates in a combined total yield of 77%. The stereochemistry of the two alkenes were determined based on NOE correlations. In this reaction, enol ether **147** was also isolated (*cf.* the isomerization we observed in the case of the alkylidene diethyl malonates,

above). Both dienophiles were then separately treated with *N*-Cbz-1,2-DHP at 100 °C under an argon atmosphere to effect the DA cycloaddition reactions (**Scheme 63**).

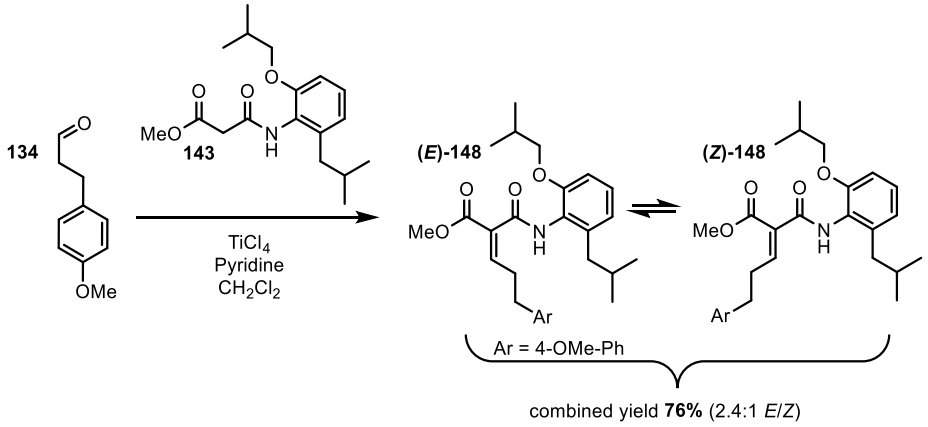


Scheme 63 | DA reaction of alkylidene mixed-malonates **(*E*)-144** and **(*Z*)-145**, and *N*-Cbz-1,2-DHP.

In the case of both isomers, the major component in the reaction mixture was the enol ether **147**. Interestingly, in both reactions some of the free di-*ortho*-substituted aniline **66** was also found. In the case where the (*E*)-isomer was used, although two new spots present on the TLC plate were isolated, both of which might be the DA adducts based on the complex ^{1}H NMR spectra, the total yield based on the mass of these two was approximately 25%. Given the seemingly rapid deconjugation of both dienophiles to the enol ether, which is very likely to be accelerated at elevated temperatures, we decided to modify the dienophile. A literature search revealed that, somewhat surprisingly, there are hardly any examples of β-hydroxy alkylidene malonates. This coupled with the isomerization issues we have experienced points to the presence of the oxygen atom at the β-position being key to the isomerization (*i.e.* the enol ether isomer appears to be more stable than the corresponding alkylidene malonate isomer). The presence of the oxygen atom at that position is not requisite for our final mimetic, the reason for its inclusion was to be able to alter the residue at that position after the benzyl deprotection. Given the apparent issues associated with having the oxygen present, we proposed to alter this such that the trisubstituted alkene not only lacks the oxygen atom, but also already contains the *i*+2 mimic residue. Should this route prove feasible, it would mean that the dienophile for the DA reaction would already include three of the five residues. This would be attractive provided two conditions were met:

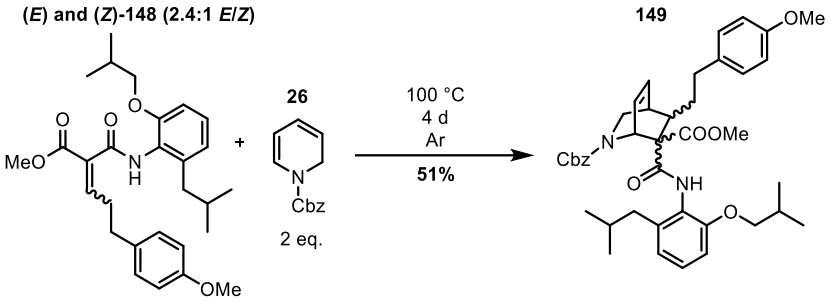
1. the dienophile could be formed in good yield, and,
2. the resulting DA reaction gave good selectivity for the product having the amide moiety *exo* orientated with respect to the bridgehead alkene.

Deciding to focus on the SHP-1 peptide first, a tyrosine residue was required at the *i*+2 position (**Scheme 64**).



Scheme 64 | Synthesis of dienophiles **(*E*)-148** and **(Z)-148**.

Knoevenagel condensation between aldehyde **134** and mixed malonate **143** proceeded in a combined yield of 76%. On this occasion isolation of each alkene was challenging as they were found to interconvert readily on silica gel. The 2.4:1 mixture of two alkenes was treated with *N*-Cbz-1,2-DHP at elevated temperature and under an inert atmosphere (**Scheme 65**).



Scheme 65 | DA reaction of alkylidene mixed-malonates [**(E)-148** and **(Z)-148**] and *N*-Cbz-1,2-DHP.

After heating for 4 d, a single DA adduct **149** was isolated in 51%. NMR studies and a single crystal X-ray structure determination on this product revealed it to be the undesired *exo*-ester isomer (**Figure 40**).

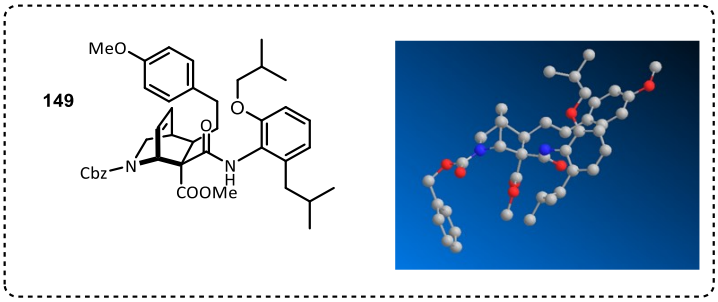


Figure 40 | The structure of the DA adduct **149** as determined by single crystal X-ray structure determination.

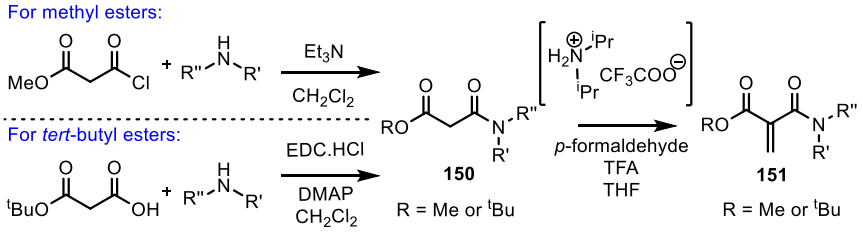
6.3 Diels-Alder Reactions of α-Amido Acrylates[105]

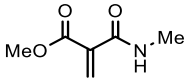
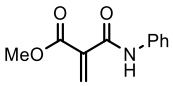
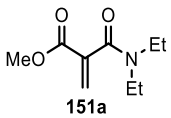
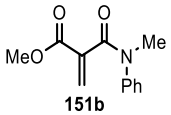
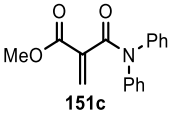
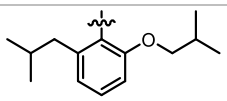
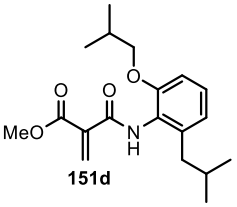
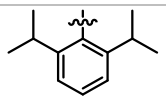
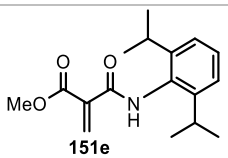
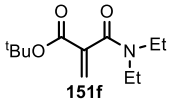
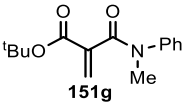
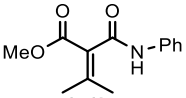
Looking to understand the *exo* selectivity observed above, we were surprised to find only limited literature precedent for the use of *α*-amido acrylates, and β-substituted derivatives thereof in DA reactions. Published reports are limited to cyclic compounds in which the nitrogen is constrained as a lactam,[106,107] part of a quinolone,[108] or part of an oxazine-2,4-dione.[109]

Consequently, we decided to probe the reactivity of acyclic α-amido acrylates as dienophiles in DA reactions to determine the factors influencing their *endo*/*exo* selectivity. In particular, we wanted to investigate the influence of steric and electronic factors in controlling this diastereoselection. To this end, we prepared a suite of β-unsubstituted-α-amido acrylates as test dienophiles. These substrates were chosen for three reasons: firstly, to avoid potential alkene isomerization as we had previously observed, secondly, because only two diastereoisomeric products can form, and thirdly, because they show increased reactivity compared to their β-substituted congeners. The α-amido acrylates were reacted with both *N*-Cbz-1,2-DHP and cyclopentadiene to allow an assessment of the role of the nitrogen substituent in the former dienophiles. We had initially intended to explore 1,3-cyclohexadiene. However our initial control experiments revealed that this did not react efficiently with some of the α-amido acrylates.

The α-amido acrylates (**151a-h**) were synthesized in two steps starting from commercially available methyl malonyl chloride or mono-*tert*-butyl malonate *via* amide bond formation followed by Mannich condensation-elimination (**Table 26**).[110]

Table 26 | Method of synthesis of α-amido acrylates **151.**

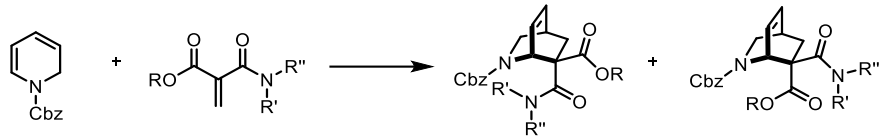


Entry	R	R'	R''	Yield of 150	Yield of 151	Product
1	Me	H	Me	62%[a]	*- polymerized -*	*not isolated*  **151x**
2	Me	H	Ph	99%	*- polymerized -*	*not isolated*  **151y**
3	Me	Et	Et	91%[b]	58%	 **151a**
4	Me	Me	Ph	99%	73%	 **151b**
5	Me	Ph	Ph	43%	93%	 **151c**
6	Me	H		74%[c]	50%	 **151d**
7	Me	H		86%	61%	 **151e**
8	tBu	Et	Et	87%	44%	 **151f**
9	tBu	Me	Ph	93%	56%	 **151g**
10	Me	H	Ph	99%[d]	76%[e]	 **151h**

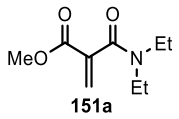
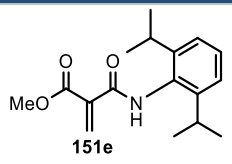
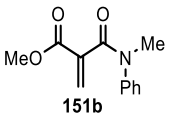
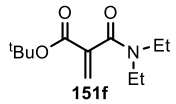
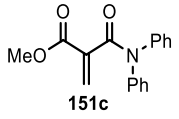
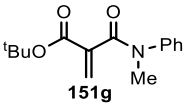
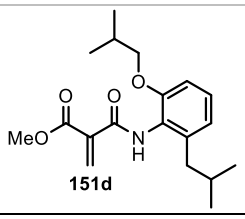
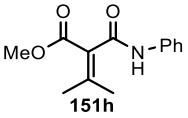
[a]THF as solvent and no Et_3N used. [b]No Et_3N used. [c]See compound **143**. [d]See compound **150x.** [e]Formed *via* a Knoevenagel condensation using acetone, $TiCl_4$, pyridine, CH_2Cl_2.

Rapid polymerization occurred upon attempted isolation of some α-amido methylacrylates containing a secondary amide (entries 1 and 2), whereas no polymerization was apparent with tertiary amides (entries 3-5 and 8-9). Presumably the secondary amides are both adequately nucleophilic and sterically unencumbered to allow for anionic polymerization *via* a 1,4-addition pathway. By contrast, introducing bulky groups on the aryl ring of the secondary amide (entries 6 and 7) or 2,2-dimethyl substitution on the alkene (entry 10) inhibited polymerization allowing the dienophiles to be stored at room temperature for weeks without noticeable decomposition. The thermal DA reactions between the α-amido acrylates and *N*-Cbz-1,2-dihydropyridine were investigated first (**Table 27**).

Table 27 | DA reactions between *N*-Cbz-1-2-DHP and α-amido acrylates **151a-h.**



26 **151** ***endo*-152** ***exo*-152**

Entry	Dienophile	*dr*[a] *Endo : Exo*	Reaction Time	Yield[b]	Entry	Dienophile	*dr*[a] *Endo : Exo*	Reaction Time	Yield[b]
1	 **151a**	1.4 : 1	7 d	50%	5	 **151e**	1 : 4	2.5 h	66%[c]
2	 **151b**	1.6 : 1	3 d	68%	6	 **151f**	3.5 : 1	7 d[d]	37%
3	 **151c**	2.2 : 1	6.5 h	86%	7	 **151g**	15.7 : 1	6 d[d]	48%
4	 **151d**	1 : 3.2	16 h	58%	8	 **151h**	*No reaction*	5 d	-

Reaction conditions unless otherwise specified: dienophile (1 eq.), *N*-Cbz-1,2-dihydropyridine (1.5-2.5 eq.), neat, sealed tube, under Ar, 100 °C. [a]*Endo/exo* ratios were determined by VT 1D and 2D NMR analysis and NOE experiments. [b]Combined isolated yield. [c]Neat for 2 h at 100 °C, then added dry toluene (0.5M) and heated at 100 °C for 30 mins. [d]Unreacted dienophile remaining.

Overall, the diastereoselectivity of DA reactions of 1,2-DHPs with α-amido acrylates appear to be dominated by the relative size of the substituents on the ester and amide. When the size of the groups on the ester and amide are both moderate, such as in dienophiles **151a** and **151b**, there is a slight preference for formation of the *endo*-ester isomer (entries 1 and 2). This intrinsic selectivity may reflect greater secondary orbital interactions between the ester and the diene

due to the lower LUMO energy of an ester as compared to an amide. However, if the amide contains a large substituent, such as the 2,6-diisopropylphenyl group, the formation of the *exo*-ester becomes significantly more favoured (entries 4 and 5). Presumably, the bulky aryl amide group sterically clashes with the *N*-Cbz group in the *endo*-ester transition state (TS) thus favouring the exo-ester-TS (**Figure 41**).

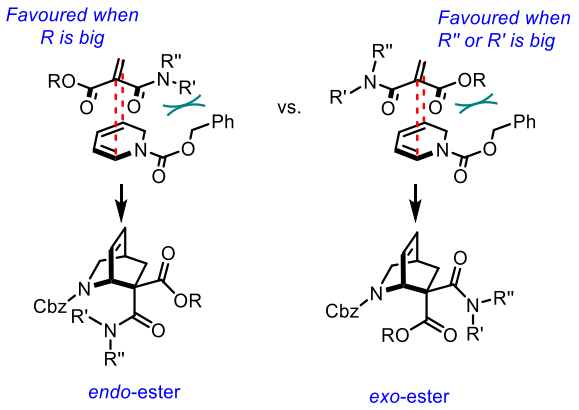


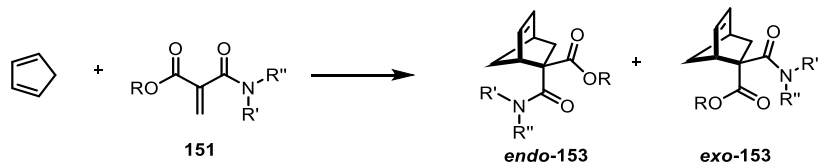
Figure 41 | Proposed rationale for *exo/endo* selectivity in the DA reactions of mixed methylene malonates with 1,2-DHPs.

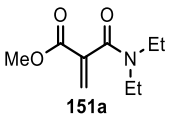
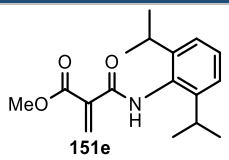
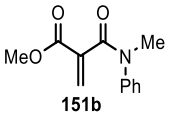
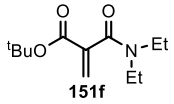
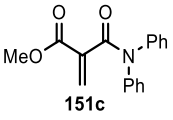
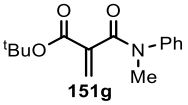
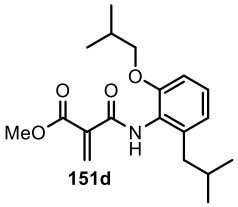
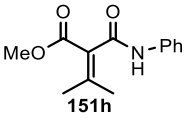
The diphenyl-substituted amide **151c** (entry 3) showed similar levels of *endo*-ester selectivity as amides **151a** and **151b** which contained moderately sized groups, indicating that the two aryl rings do not impose significant steric hindrance. The reactivity of the dienophiles increases considerably when an alkyl group is replaced by an aryl group in the amide, which likely results in the lowering of the LUMO energy (*cf.* reaction times for entries 1 *vs*. 2 *vs*. 3). Replacing the methyl ester with a *tert*-butyl ester tipped the *dr* in favour of the *endo*-ester isomer (*e.g*. **151f** → **151g**, entries 6 and 7) and led to the highest *endo*-ester selectivities. This is consistent with the findings of Krow *et al.,* who noted a greater preference for *endo* azabicyclooctane DA adducts when bulkier groups were present in simple acrylate esters.[111] The *gem*-dimethyl substituted dienophile **151h** was found to be unreactive under the thermal DA conditions (entry 8). To exclude the possibility that *retro*-DA re-addition could be occurring, which would invalidate a TS-based rationalization of the selectivity trends, a mixture of the DA-adducts *endo*-**152e** and *exo*-**152e** was heated in the presence of the diene at 100 °C for 5 days. No equilibration was observed, indicating that the initially observed *exo/endo* ratios reflect kinetic control. This is in agreement with previous studies which have indicated that the stereochemical outcomes for DA reactions between DHPs and acrolein, methyl acrylate, and methyl vinyl ketone have been shown to be of kinetic origin.[111] From a synthetic perspective, the ability to predictably promote either *exo* or *endo* product formation by appropriate choice of ester and amide substituents is attractive. Although the *exo*-ester configuration favoured for the di-*ortho*-

substituted diaryl amides **151d** and **151e** are not useful for our α-helix mimetic targets, the *endo*-ester configuration strongly favoured for the *tert*-butyl esters **151f** and **151g** is potentially valuable for entry to the Iboga alkaloids.[112,113]

For comparison, we next investigated the corresponding thermal DA reactions of cyclopentadiene as the diene (**Table 28**).

Table 28 | DA reactions between cyclopentadiene and α-amido acrylates **151a-h.**



Entry	Dienophile	*dr*[a] *Endo : Exo*	Reaction Time	Yield[b]	Entry	Dienophile	*dr*[a] *Endo : Exo*	Reaction Time	Yield[b]
1	 **151a**	3.5 : 1	24 h	45%	5	 **151e**	3.2 : 1	2.5 h	90%[c]
2	 **151b**	4 : 1	5 h	86%	6	 **151f**	4.9 : 1	48 h	55%
3	 **151c**	2.3 : 1	80 mins	90%	7	 **151g**	4.3 : 1	24 h	67%
4	 **151d**	5.3 : 1	16 h	58%	8	 **151h**	*No reaction*	5 d	-

Reaction conditions unless otherwise specified: dienophile (1 eq.), cyclopentadiene (5 eq.), neat, sealed tube, under Ar, 80 °C. Reactions were stopped once all the dienophile was consumed. [a]*Endo/exo* ratios were determined by VT 1D and 2D NMR analysis and nOe experiments (see SI). [b]Combined isolated yield. [c]Neat for 2 h at 80 °C, then added dry toluene (0.5M) and heated at 80 °C for a further 30 mins.

By contrast to the DA reactions of *N*-Cbz-1,2-DHP, the diastereoselectivities obtained from reactions of cyclopentadiene do not appear to be influenced strongly by the steric demand of the amide and ester groups of the dienophile: all substrates afford the *endo*-ester with fairly high levels of selectivity (entries 1−7). As expected on account of strain relief, cyclopentadiene is more reactive than the 1,2-DHPs as evidenced by shorter reaction times, although the *gem*-dimethyl substituted dienophile **151h** was still unreactive (entry 8). The good levels of *endo/exo* selectivity and insensitivity toward steric congestion displayed in these reactions make them attractive for the synthesis of otherwise difficult to obtain *exo*-amide cyclopentadiene DA adducts.[114,115] The DA adducts *endo*-**153e** and *exo*-**153e** were heated in the presence of

cyclopentadiene at 100 °C for 48 h; there was no observed epimerization after 24 h, although after 48 h traces could be detected (<5%). Given that all but one of the DA reactions (entry 6, 48 h) were complete within 24 h, the observed *endo/exo* ratios were concluded to be those of kinetic control.

Salvatella *et al.* have proposed that electrostatic rather than secondary orbital interactions are responsible for the high *endo* selectivity in the DA reaction between cyclopentadiene and acrolein.[116] They hypothesized that given the greater electronegativity of carbon relative to hydrogen, the δ+ charge on the hydrogen atom of the cyclopentadiene methylene facing the dienophile experiences a coulombic repulsion as it approaches the δ+ charge on the carbonyl carbon thereby destabilizing the *exo*-TS. In our reactions, the lesser δ+ charge on the amide carbonyl carbon as compared to on the ester carbonyl might therefore be expected to give rise to less repulsion and so favour the *endo*-ester TS, as observed (**Figure 42**).

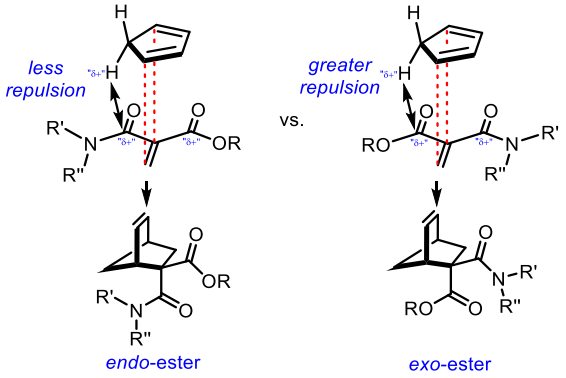
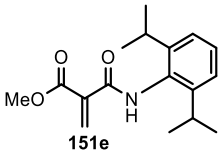
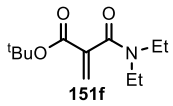


Figure 42 | Proposed rationale for *endo*-ester selectivity, based on the proposals of Salvatella *et al*.[116]

Finally, we investigated whether Lewis acids could be used to perturb the *endo/exo* selectivity of the DA adducts. 1,2-DHPs are unstable in the presence of many Lewis acids and typically require heating to achieve efficient DA reactions.[117,118] Indeed, in our hands, treatment of *N*-Cbz- and *N*-carboxyphenyl-1,2-DHPs with various Lewis acids resulted in rapid formation of a complex mixture of products, as evidenced by ^{1}H NMR. In contrast, cyclopentadiene suffers no such decomposition, and thus we focussed on the influence of Lewis acids on the cyclopentadiene based DA adducts. The effects of three Lewis acids were explored: Et_2AlCl, one of the most frequently utilized Lewis acid in DA reactions;[119] $B(C_6F_5)_3$, a bulky Lewis acid capable of overriding the typically observed endo selectivity in DA reactions of α,β-enals,[120] and TBSOTf, which has been reported to activate acrylamides but not acrylates in DA reactions with cyclopentadiene.[121] Although selective activation of the amide over the ester, or *vice versa*, in an α-amido acrylate was anticipated to be challenging, it was expected that this would be most feasible for sterically and/or electronically differentiated examples. Consequently, each of the three Lewis acids was

reacted with the 2,6-diisopropylphenyl amide/methyl ester dienophile **151e** and the diethyl amide/*tert*-butyl ester dienophile **151f** (**Table 29**).

Table 29 | DA reactions between α-amido acrylates **151e** and **151f** and cyclopentadiene in the presence of Lewis acids.

Entry	Dienophile	Lewis Acid	*dr* *Endo : Exo*	Reaction Time	Yield
1[a]	 **151e**	-	3.2 : 1	2.5 h	90%
2		Et_2AlCl	3.3 : 1	30 mins	77%
3		$B(C_6F_5)_3$	3.2 : 1	30 mins	88%
4		TBSOTf	2.4 : 1	30 mins	75%
5[b]	 **151f**	-	4.9 : 1	48 h	55%
6		Et_2AlCl	7.3 : 1	2 h	66%
7		$B(C_6F_5)_3$	1.1 : 1	30 mins	67%
8		TBSOTf	1 : 1	2.5 h	52%

Reaction conditions unless otherwise specified: dienophile (1 eq.), cyclopentadiene (10 eq.), Lewis acid (1 eq.), under Ar, RT, CH_2Cl_2 (0.1M). [a]Same reaction as **Table 28**, entry 5. [b]Same reaction as **Table 28**, entry 6.

The reactions of the 2,6-diisopropylphenyl amide/methyl ester dienophile **151e** in the presence of 1 equivalent of each of the three Lewis acids resulted in only minor deviations from the *endo/exo* ratio that was observed for the uncatalysed reaction (entries 1-4). The Lewis acid catalysed reactions were however significantly faster (2.5 h → 30 min), suggesting that these Lewis acids are likely either bridging between or at least equally activating the carbonyl groups of the 1,3-dicarbonyl moiety. It would appear therefore that for dienophile **151e**, the bulky aryl amide and methyl ester carbonyls have balanced affinities for the Lewis acids (possibly the higher intrinsic basicity of the amide is counterbalanced by steric factors). By contrast, the diastereoselectivities of reactions of the diethyl amide/*tert*-butyl ester dienophile **151f** were more strongly affected: Et_2AlCl slightly increased the *endo*-ester ratio (entry 6), whereas $B(C_6F_5)_3$ markedly increased the amount of the *exo*-ester formed (entry 7), and TBSOTf similarly increased the amount of the *exo*-ester (entry 8). It would appear therefore that for dienophile **151f** the alkyl amide carbonyl displays stronger affinity than the *tert*-butyl ester carbonyl for the two most bulky Lewis acids (presumably because the bulky *tert*-butyl group limits co-ordination to the ester carbonyl). Finally, TMSOTf was briefly explored as a non-bulky trialkyl silyl triflate, but it was found to be incompatible with our reaction conditions.

Returning to the α-helix mimetics, although the use of 1,1-diactivated dienophiles had provided an entry into a four-residue mimetic, numerous challenges had presented themselves while attempting to extend this to the five-residue scaffold. Consequently, we began looking into the

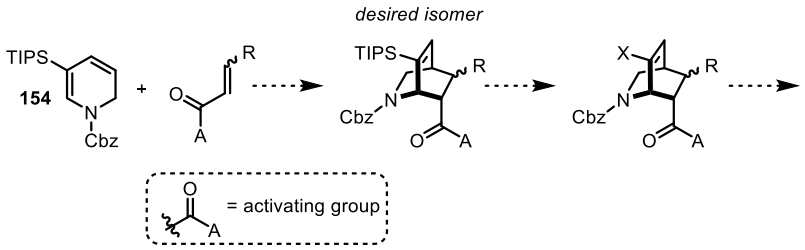
DA reaction of 5-substituted-1,2-DHP's together with monoactivated dienophiles, building on some of Bayly's earlier work. We also commenced work on the DA reaction of *N*-Cbz-1,2-DHP with 1,2-diactivated dienophiles which have been unexplored thus far.

7. Chapter 3 – Monoactivated and 1,2-(*E*)-Diactivated Dienophiles

7.1 – Monoactivated dienophiles

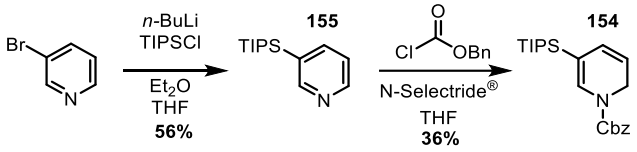
As discussed in **section 4.2.2**, there has been a significant amount of published research into the reaction between 1,2-DHPs and monoactivated dienophiles, with and without Lewis acid promotion.[122,118,82] One feature which is typical of these reactions is that they tend to give predominantly the *endo* isomer, which is undesired in our case. One of the few examples in which the *exo* adduct is favoured was reported by Sundberg *et al*. and involved a 1,2-DHP bearing a Me_3Si group at C5 (see **Table 2**).[81] Bayly had briefly experimented with the idea of having a bulky group at C5 of the 1,2-DHP (which translated to C7 on the azabicyclooctane) to dictate the diastereoselectivity, using $BnMe_2Si$ and Bu_3Sn groups (**Scheme 7** and **Scheme 8**). In both of these cases, a bulky cyclic dienophile was used as the DA partner and only poor or modest selectivities were observed: 2.8:1 *endo/exo* for the $BnMe_2Si$ derivative and 1:1.2 *endo/exo* for the Bu_3Sn derivative. Furthermore, subsequent functionalisation of the $BnMe_2Si$-C bond *via* a Hiyama-Denmark coupling and the Bu_3Sn-C bond *via* a Stille coupling proved problematic.

Deciding that at this juncture it would be worth investigating the reaction of monoactivated dienophiles with a 5-substituted 1,2-DHP, we set about synthesis of *N*-Cbz-5-TIPS-1,2-DHP **154**. The TIPS functional group was chosen not only because of its steric presence, but also because there is precedent for the conversion of a vinyl-TIPS moiety to a vinyl-halogen moiety, giving us an appropriate handle to introduce the *i*+1 residue *via* a transition metal catalysed cross-coupling protocol with an appropriate organometal reagent[123,124] (**Scheme 66**).



Scheme 66 | Proposed reaction of *N*-Cbz-5-TIPS-1,2-DHP with a monoactivated dienophile and subsequent FGI.

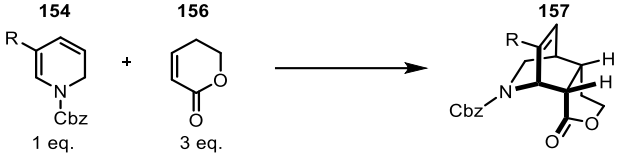
Synthesis of the *N*-Cbz-5-TIPS-1,2-DHP, which has not been isolated before, was achieved using a combination of Wanner's synthesis of 3-silyl pyridines[125] and Sundberg's protocol for the formation of *N*-carboethoxy-5-TMS-1,2-DHP that utilized the bulky reducing reagent, *N*-Selectride® **(Scheme 67).**[81]



Scheme 67 | Synthesis of *N*-Cbz-5-TIPS-1,2-DHP (**154**)**.**

N-Cbz-5-TIPS-1,2-DHP was found to be very unstable, markedly more so than the unsubstituted DHP, with decomposition occurring within 2-3 h of isolation at RT. The DHP was therefore reacted with the dienophile immediately after purification. Initially, the monoactivated dienophile 5,6-dihydro-2*H*-pyran-2-one (**156**) was used as reaction partner as it was envisioned to provide a handle for introducing the *i*+2 residue after ring-opening of the resulting lactone (**Table 30**).

Table 30 | DA reaction using 5,6-dihydro-2H-pyran-2-one (**156**) as the dienophile.



Entry	R	Duration / Temp.	Additive	Outcome
1	TIPS	16 h / 100 °C	-	No reaction
2	TIPS	2 h / 100 °C	$AlCl_3$	1,2-DHP decomposed
3	H	3 d / 100 °C	-	No reaction
4	H	30 mins / RT	$AlCl_3$	1,2-DHP decomposed

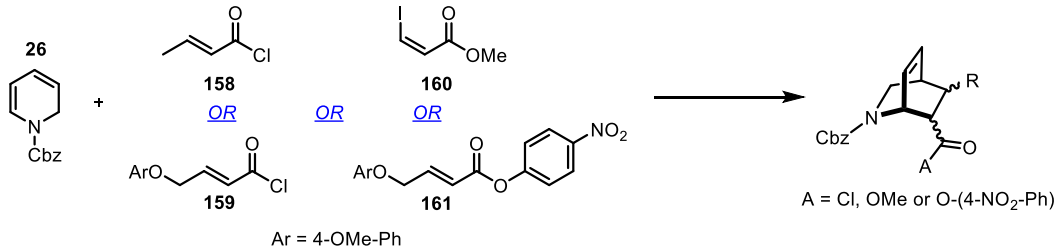
All reactions were carried out in a sealed MW tube and all were purged with Ar prior to sealing.

No reaction took place between the TIPS substituted DHP and the pyran-2-one after heating at 100 °C (entry 1). Given there was no precedent for the use of this DHP as a diene, the pyran-2-one was also treated with the unsubstituted DHP but once again no reaction was observed (entry 3). The group of Onomura were able to promote a DA reaction between *N*-carboethoxy-2-ester-1,2-DHP and *N*-acryloyloxazolidinone with a stoichiometric amount of $AlCl_3$;[126] we therefore set up a reaction with both the substituted and unsubstituted dienes in the presence of $AlCl_3$ (entries 2 and 4). Unfortunately, this lead to rapid decomposition of both DHPs: both reactions turned into a black foam-like solid seconds after $AlCl_3$ addition.

Although the reactivity of 1,2-DHP's with monoactivated dienophiles has been well documented, very few of these dienophiles have substituents at the other end of the alkene (*i.e.* are 1,2-disubstituted alkenes). In fact, other than a methyl substitient,[78,127] examples of 1,2-disubstituted monoactivated dienophiles which react with 1,2-DHPs are limited to those which are tethered on the DHP itself and undergo an intramolecular DA reaction.[128,129] Intrigued by this, we next set about exploring a range of differently functionalised monoactivated dienophiles

containing a substituent at the non-activated end of the alkene. Their reactivity was investigated in thermal DA reactions with *N*-Cbz-1,2-DHP (**Table 31**).

Table 31 | DA reactions of monoactivated dienophiles with *N*-Cbz-1,2-DHP.



Entry	Eq. of *N*-Cbz-1,2-DHP	Dienophile[a]	Reaction conditions[b]	Outcome
1[c]	1	**158**	1 h / 100 °C *then* concentrated and heated in MeOH, 1 h / 50 °C	1,2-DHP decomposed. Trace amounts of methyl ester DA adducts isolated.
2[c]	1	**158**	CH_2Cl_2, 18 h / RT *then* concentrated, and heated in MeOH 1 h / 50 °C	Complex mixture
3[c]	1	**158**	Benzene, 18 h / RT *then* concentrated, and heated in MeOH 1 h / 50 °C	Complex mixture
4	1.3	**158**	2 h / 60 °C	Complex mixture 1,2-DHP decomposed
5	1.3	**158**	3 d / RT	Complex mixture
6	1	**159**	Toluene, 24 h / RT	Complex mixture
7	1	**159**	16 h / 100 °C	Complex mixture 1,2-DHP decomposed
8	1	**159**	CH_2Cl_2, 24 h / RT *then* 18 h / 40 °C	No reaction (after 24 h), complex mixture. 1,2-DHP decomposed
9	1	**159**	MeCN, 24 h / RT *then* concentrated, and heated in MeOH, 3 h / 60 °C	Complex mixture 1,2-DHP decomposed
10	1	**159**	MeCN, 24 h / 40 °C *then* concentrated, and heated in MeOH, 3 h / 60 °C	Complex mixture 1,2-DHP and acid chloride decomposed
11	1	**159**	MeCN, 24 h / 80 °C *then* concentrated, and heated in MeOH, 3 h / 60 °C	Complex mixture 1,2-DHP & acid chloride decomposed
12	1	**160**	24 h / RT	No reaction
13	1	**160**	24 h / 100 °C	2 new spots after a few hours, but disappeared (decomposed) overnight Complex mixture
14	1	**160**	4 h / 80 °C	2 new spots isolated but does not fit with DA adduct(s) Complex mixture
15	3.4	**161**	Benzene, 2 d / 60 °C	No reaction
16	3.4	**161**	Benzene, 2 d / 80 °C	No reaction. Some decomposition of ester. 1,2-DHP remaining
17	3.4	**161**	2 d / 80 °C	Complex mixture. Some decomposition of ester. 1,2-DHP remaining
18	3.4	**161**	2 d / 120 °C	Complex mixture 1,2-DHP and ester decomposed

[a]1 eq. of dienophile used unless stated otherwise. [b]All reactions were carried out in a sealed MW tube and all were purged with Ar prior to sealing. [c]3 eq. dienophile used.

Acid chlorides have been shown to react with 1,2-DHPs,[130] although all examples contain an extra chloride at the activated end and lack a substituent at the non-activated end of the alkene. Nonetheless, we had hoped that the inherently increased reactivity of acid chlorides over *e.g*. ketones and esters, would overcome the reduced reactivity incorporated unto the dienophile by the extra substituent. Treatment of commercial crotonyl chloride (**158**) with the *N*-Cbz-1,2-DHP under a variety of different conditions did not look promising (entries 1-5) and in all cases the reactions were very difficult to follow (smeared TLC plate and broad NMR spectra's). As the isolation of these acid chlorides was problematic, the isolation of the methyl ester derivatives upon treatment with methanol was attempted, but only trace amounts of product were isolated. Acid chloride **159**, which was synthesized in three steps from (*E*)-methyl 4-bromobut-2-enoate, was similarly explored (entry 6 -11). However, as with crotonyl chloride, the reactions were not clean: no DA reaction occurred at RT and decomposition of the DHP and/or the acid chloride was observed upon heating.

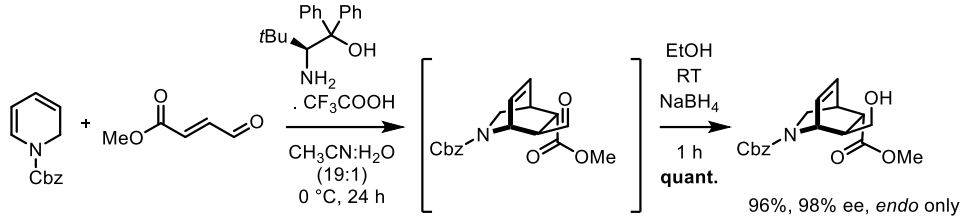
Next, we looked at using β-iodo-α-β-unsaturated methyl ester **160**. We hoped the inclusion of the iodine might increase the reactivity of the dienophile. Furthermore, unlike a carboxyl unit, we anticipated that the inductive effect of the iodide would still render the carbon β to the carbonyl δ+, thereby preserving the regioselectivity of the DA reaction. Methyl ester **160,** which was synthesized after reacting methyl propiolate with NaI and acetic acid, was therefore treated with the DHP. No reaction was observed at RT (entry 12) and a complex mixture and decomposition was observed after heating (entries 13 and 14). Returning to a monoactivated dienophile, the *para*-nitrophenol ester **161** was synthesised from the corresponding acid chloride **159**. As before, either no reaction or decomposition was observed in thermal DA reactions utilizing the *para*-nitrophenol ester **161** as the dienophile (entries 15-18).

Reluctantly, we concluded that the limited reactivity of monoactivated dienophiles containing further functionality at the terminal end was not to be overcome. As we had already developed a viable route towards a four-residue mimetic, which a monoactivated dienophile containing a free alkene would ultimately lead to, we abandoned work on these dienophiles. One class of dienophiles that we had yet to explore however, were 1,2-(*E*)-diactivated dienophiles.

7.2 – 1,2-(*E*)-Diactivated Dienophiles

In **Chapter 1 (Section 5)**, it was found that DA reactions of cyclic 1,2-(*Z*)-diactivated dienophiles with 1,2-DHPs led to *endo*-products exclusively. At the time we had proceeded with the intent to epimerize C6 containing the carboxyl functionality using conditions described by Sinha *et al.,*[85] but owing to issues with the ring-opening, this pathway was abandoned.

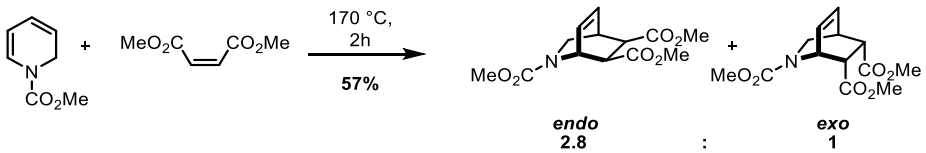
Less established is the DA reaction utilizing 1,2-(*E*)-diactivated dienophiles. The group of Nakano and Mutsuyama have reported the highly enantioselective DA reaction of 1,2-DHP's using a β-amino alcohol organocatalyst (**Scheme 68**).[131]



Scheme 68 | Nakano and Matsuyama's enantioselective DA reaction utilizing a β-amino alcohol catalyst.[131]

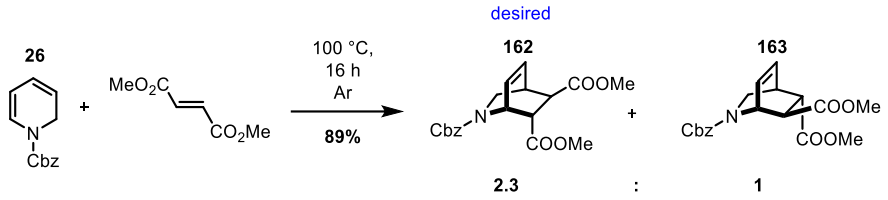
Regioselectivity, and indeed enantioselectivity, was dictated by the formation of an iminium ion intermediate which could then interact with the carbonyl moiety of the 1,2-DHP. Excellent *endo* selectivities were obtained in these DA reactions. However, for this to be of relevance to the synthesis of α-helix mimetics, the stereocentre at C6 would need to be epimerised as previously envisioned.

Next, we considered using a symmetric 1,2-(*E*)-diactivated dienophile, *i.e.* containing the same activating group at both ends of the alkene. Although, the reaction between *N*-methoxycarbonyl-1,2-DHP and dimethyl maleate is known (**Scheme 69**),[132] the corresponding reaction with dimethyl fumarate has not been reported.



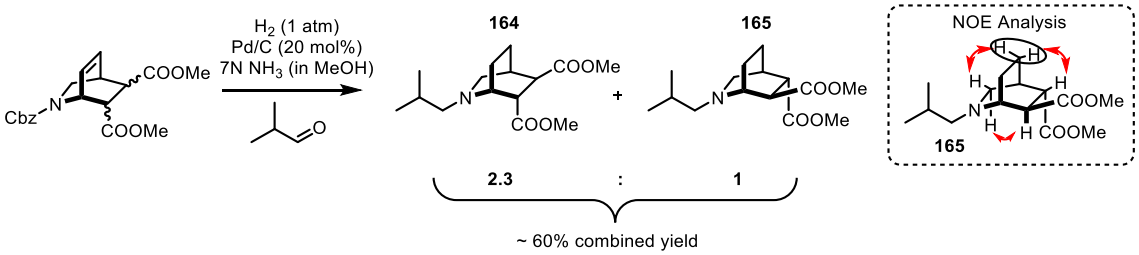
Scheme 69 | Arakawa's DA reaction between N-Moc-1,2-DHP and dimethyl maleate.[132]

Unsurprisingly, the DA reaction with dimethyl maleate afforded the *endo* isomer as the preferred isomer. However, it was not immediately obvious to us what the selectivity would be for dimethyl fumarate. In the event, treatment of dimethyl fumarate with *N*-Cbz-1,2-DHP resulted in an 89% of a mixture of two inseparable DA diastereoisomers (**Scheme 70**).



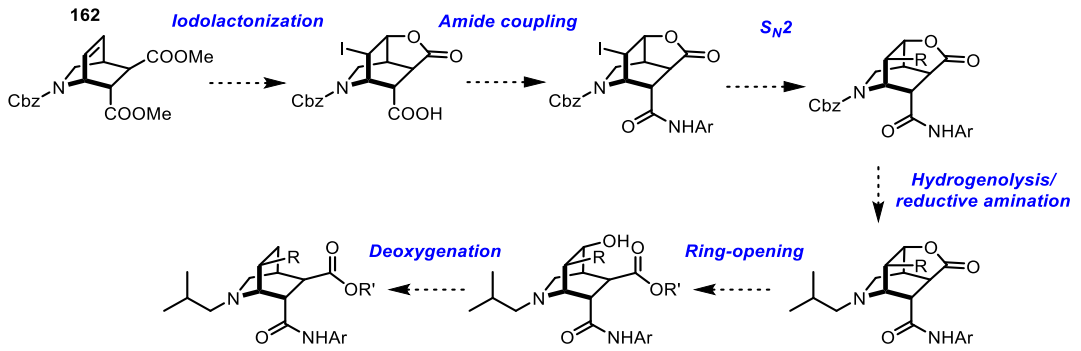
Scheme 70 | DA reaction between *N*-Cbz-1,2-DHP and dimethyl fumarate giving a 2.3:1 selectivity in favour of desired isomer **162**.

We were pleased to note a 2.3:1 ratio in favour of isomer **162**, which has the methyl ester at C6 in the *exo* orientation. Determination of the diastereoselectivity in this reaction was achieved following hydrogenolysis/reductive amination/hydrogenation. This one-pot multistep reaction gave two separable *N*-alkylated alkanes, **164** and **165**, for which relative stereochemistries were established by NOE experiments (**Scheme 71**).



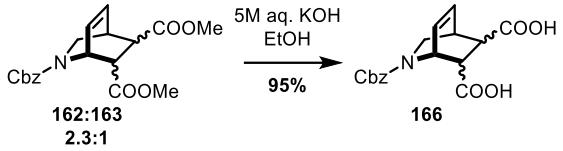
Scheme 71 | Synthesis of *N*-alkyl azabicyclooctanes **164** and **165** for the purpose of determining the *dr* in the preceding DA reaction (*i.e.* as shown in **Scheme 70**).

Using chemistry developed for the four-residue mimetic (**section 6.1**), it was envisaged that iodolactonization of the diacid formed after hydrolysis would tie up the *endo* carboxyl functionality in **162** leaving the *exo*-carboxylic acid free for amide coupling. In contrast to the chemistry described in **chapter 6**, the iodolactonization would place an iodine atom at C7 that we planned to functionalize with the *i*-1 leucine residue mimetic using an S_N2 substitution reaction (**Scheme 72**).



Scheme 72 | Proposed synthetic route to a five-residue mimetic from **162.**

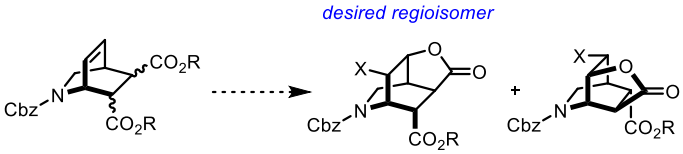
DA adducts **162** and **163**, which were inseparable by column chromatography, were taken through as a mixture with the aim to separate the two isomers at a later stage. Hydrolysis of the adduct mixture proceeded in excellent yield to give a diasteriomeric mixture of diacids **166** in 95% yield (**Scheme 73**).



Scheme 73 | Hydrolysis of diesters **162** and **163**, taken through as a mixture.

Preliminary work on iodo/bromo-lactonization on the mixture of diacids **166** followed (**Table 32**).

Table 32 | Iodo/bromo-lactonization on the diastereoisomeric mixture of diacid **166** and dimethyl ester **(162 & 163).**



Entry	R	X_2	Solvent	Duration / Temp.	Outcome
1	H	I_2	$NaHCO_3$	24 h / RT	Complex mixture
2	H	I_2	THF/H_2O (2:1)	4 d / RT	Complex mixture
3	H	I_2	MeCN	3 d / RT	No reaction
4	H	Br_2	CH_2Cl_2	0 °C to RT / 16 h	No SM; complex mixture
5	H	Br_2	CH_2Cl_2	0 °C / 1 h	No SM; complex mixture
6	Me	I_2	CH_2Cl_2	RT to 45 °C / 5 h	No reaction
7	Me	I_2	MeCN	75 °C / 16 h	< 90% SM
8	Me	ICl	CH_2Cl_2	1 h / RT	No SM; complex mixture

The previously explored iodolactonization conditions (I_2 and $NaHCO_3$) lead to a complex mixture (entry 1). Using a THF/water solvent mixture gave a similar result (entry 2). By contrast, conducting the reaction in acetonitrile led to no reaction, even after 3 days (entry 3). Modifying the halogen source from I_2 to Br_2 also lead to a complex mixture (entries 4 and 5). Iodolactonization was also briefly explored on a mixture of the dimethyl ester derivatives **162** and **163** using I_2 (entries 6 and 7) and also the more reactive reagent, ICl (entry 8), but with no sign of the desired lactone product observable by analysis of the ^1H NMR spectra of the crude reaction mixtures.

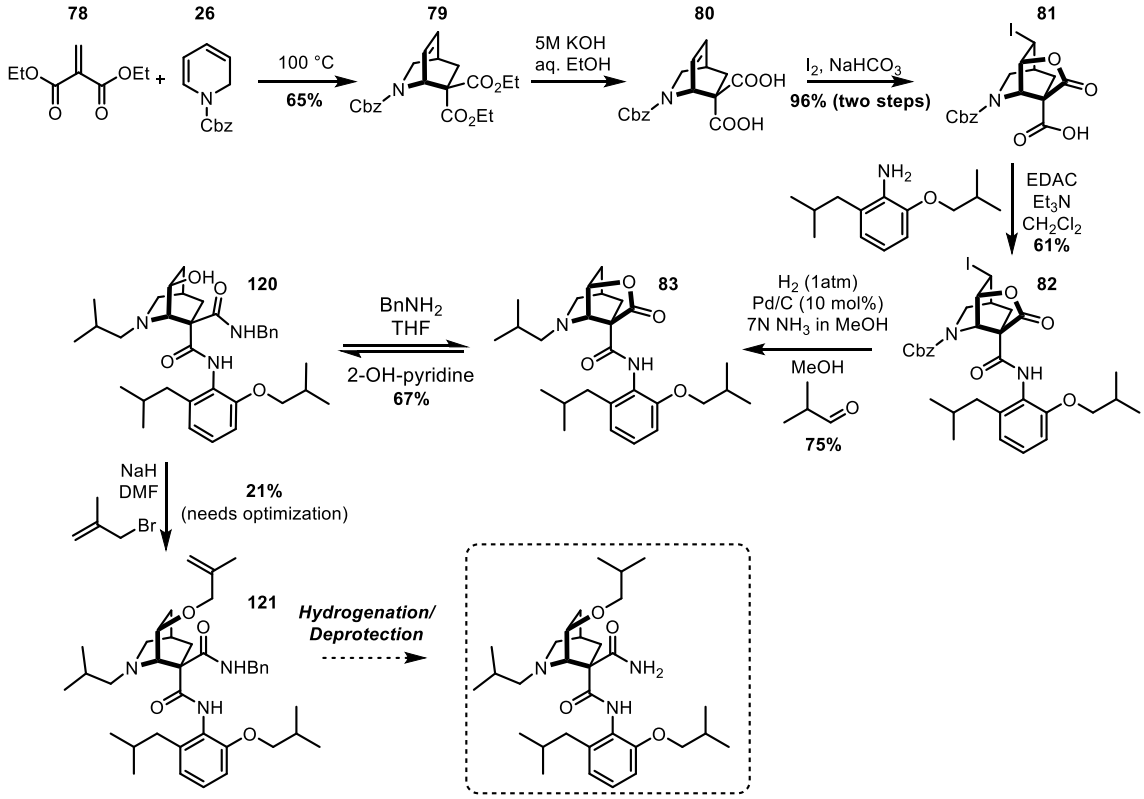
Although these preliminary experiments failed to provide the desired halo-lactone, many additional parameters still require investigation. In addition, it is likely that separating the two diastereoisomers, either immediately following the DA step (*i.e.* diethyl esters **162** and **163**) or

after the hydrolysis step, *e.g.* using silica gel impregnated with metal ions,[133] would simplify analysis of the complex mixtures obtained and aid determination of the course of these reactions. Thus, these early studies are considered inconclusive as to the prospects for future success using 1,2-(*E*)-diactivated dienophiles. Given the favourable diastereoselectivity observed in the initial DA reaction, this route is certainly worth exploring further.

8. Future Work and Conclusions

During this project, a series of activated dienophiles have been investigated in thermal DA reactions with *N*-Cbz-1,2-DHPs. The dienophiles studied have included 1,2-(Z)-diactivated dienophiles, 1,1-diactivated dienophiles, monoactivated dienophiles, and 1,2-(*E*)-diactivated dienophiles. The last category displayed the most promising levels of diastereoselection in the cycloaddition reaction for our target α–helix mimetic.

During these studies, a viable synthetic route towards a four residue mimetic was developed. The order of events was found to be crucial to the successful progression of the route: *e.g.* the amide coupling and the challenging hydrogenolysis/reductive amination/deiodination reaction proved most efficient when carried out prior to the ring-opening of the lactone moiety. A summary of the final route is detailed in **Scheme 74.**

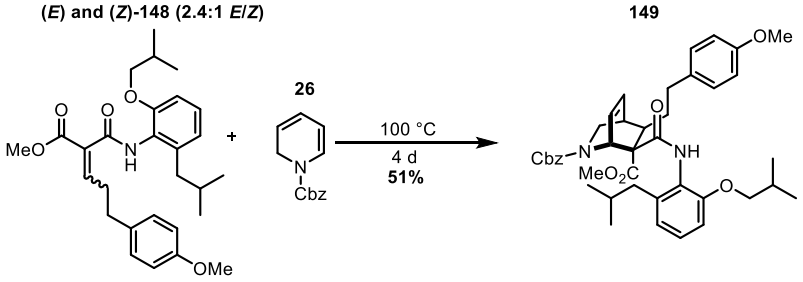


Scheme 74 | Overview of the final route towards a four-residue mimetic.

It is anticipated that this work had laid a strong basis for the successful formation of a series of four-residue mimetics. Once optimization of the *O*-alkylation and the subsequent hydrogenation/deprotection is concluded, it is envisaged that a small library of compounds,

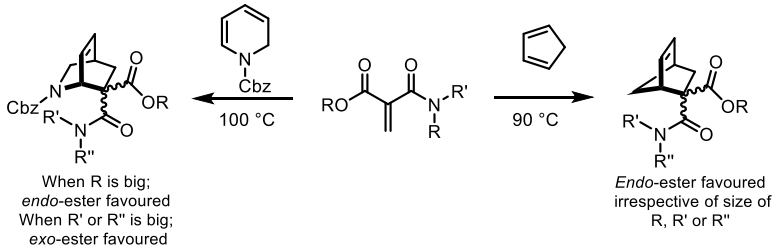
containing different amino acid residues at the anchor points of the mimetic, will be ready for biological testing in the very near future.

Whilst attempting to extend the above route towards a five-residue mimetic, we considered the use of α-amido esters as dienophiles in the DA reaction. We were intrigued with the exclusive *exo*-selectivity (undesired for our mimetic) displayed with the highly functional dienophile **148** when treated with *N*-Cbz-1,2-DHP (**Scheme 75**).



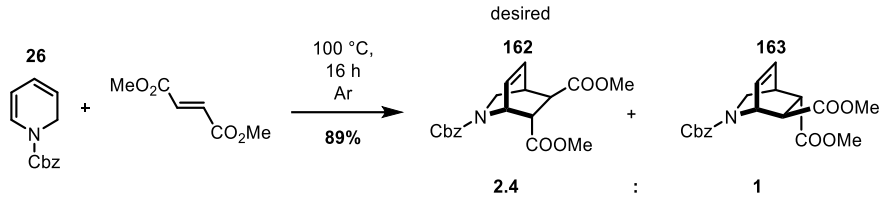
Scheme 75 | DA reaction between tri-substituted alkene **148** and *N*-Cbz-1,2-DHP.

We subsequently became interested in exploring the use of α-amido acrylates as dienophiles in DA reactions with *N*-Cbz-1,2-DHP and cyclopentadiene. We found that the *endo/exo* selectivity in the DA reactions with the DHP is strongly influenced by steric factors, allowing access to good levels of selectivity favouring either isomer. By contrast, when cyclopentadiene is used as the diene, the *endo/exo* selectivity is relatively unaffected by steric factors and electronic factors favour the *endo*-ester product (**Scheme 76**).



Scheme 76 | DA reaction of α-amido acrylates with *N*-Cbz-1,2-DHP and cyclopentadiene.

Towards the latter stages of the project, we explored the use of 1,2-(*E*)-diactivated dienophiles. We were encouraged to find that upon treatment of dimethyl fumarate with *N*-Cbz-1,2-DHP at elevated temperatures, an 89% yield of DA adducts were obtained in a 2.4:1 ratio in preference for isomer **162** which has the methyl ester at C6 in the *exo* orientation (**Scheme 77**).



Scheme 77 | DA reaction between *N*-Cbz-1,2-DHP and dimethyl fumarate giving a 2.4:1 selectivity in favour of desired isomer **162**.

Using the chemistry developed for the four-residue mimetic combined with our understanding of the reactivity of closely related azabicyclooctane systems, it is hoped that DA adduct **162** can be progressed towards the efficient synthesis of a series of five-residue α-helix mimetics.

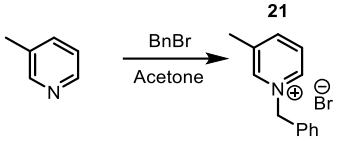
9. Experimental

General Directions

All reactions were performed under nitrogen using oven-dried glassware unless stated otherwise. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogenous materials, unless otherwise indicated. MeCN, CH_2Cl_2, THF, Et_2O, DMF, and toluene were dried and deoxygenated with a Grubbs Pure-Solv 400 solvent purification system. The moisture content of the solvents was monitored by Karl Fischer coulometric titration (Mettler-Toledo DL39). ***Reagents:*** used as purchased from commercial sources, unless otherwise stated, and used according to COSHH regulations. ***Chromatography:*** Flash chromatography (FC) was performed on silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh) unless otherwise stated. ***Melting Points:*** determined on a Stanford Research System OptiMelt. ***Thin Layer Chromatography (TLC):*** performed on Merck aluminium-backed plates pre-coated with silica (0.2 mm, 60 F_{254}) which were visualized either by quenching of ultraviolet fluorescence (λ_{max} = 254 and 366 nm) or staining with; potassium permanganate/Δ, bromoceresol green/Δ or phosphomolybdic acid/Δ TLC dips prepared according to general procedures. ***Infra-red spectra:*** recorded as solids or neat liquids on a Perkin-Elmer FT-IR Spectrum BX, only selected absorbances (ν_{max}) are reported. ***^{1}H NMR spectra:*** recorded on a 400 or 500 MHz Bruker AMX-400/500 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. ***^{13}C NMR spectra:*** recorded at 101 MHz or 125 MHz on a Bruker AMX-400/500 instrument Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. ***NOESY/ROESY spectra:*** recorded on a 500 MHz Bruker AMX-500 instrument. ***Low Resolution*** and ***High Resolution Mass Spectra:*** recorded on either a VG platform II or VG AutoSpec spectrometer, with only molecular ions ($[MH]^+$, $[MNa]^+$, $[MNH_4]^+$, $[MH_2O]^+$, $[MH]^-$) and major peaks being reported.

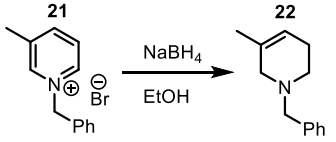
Experimental Procedures

1-Benzyl-3-methylpyridin-1-ium bromide (21)



Adapted from the method of Reding,[86] 3-picoline (2.0 mL, 20.6 mmol) in acetone (2 mL) was cooled to 0 °C. Benzyl bromide (2.44 mL, 20.6 mmol) was added dropwise with stirring overall several minutes. The reaction mixture was stirred at 0 °C for 2 h, allowed to warm to RT and then stirred overnight to give an orange viscous solution. Removal of the solvent under reduced pressure afforded **21** as an off-white solid (5.4 g, 100%); ***mp*** 65 °C; Si gel TLC $\boldsymbol{R_f}$0.00 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 3412, 3030, 1630, 1504, 1498, 1455, 1248, 1204, 1148, 733, 705, 684; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.48 [s, 1H, ArC(2)*H*], 9.38 [d, *J* = 6.1 Hz, 1H, ArC(6)*H*], 8.14 [d, *J* = 7.9 Hz, 1H, ArC(4)*H*], 7.88 [dd, *J* = 8.0, 6.1 Hz, 1H, ArC(5)*H*], 7.69 (m, 2H, Ph), 7.40 – 7.35 (m, 3H, Ph), 6.26 (s, 2H, CH_2Ph), 2.57 (s, 3H, ArCH_3). ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 145.6 [Ar*C*(4)], 144.6 [Ar*C*(2)], 142.2 [Ar*C*(6)], 139.6 [Ar*C*(3)CH_3], 133.0 (Ph), 130.0 (Ph), 129.7 (Ph), 129.6 [Ar*C*(5)], 127.5 (Ph), 63.9 (*C*H_2Ph), 18.8 (Ar*C*H_3); ***HRMS*** *m/z* not found.

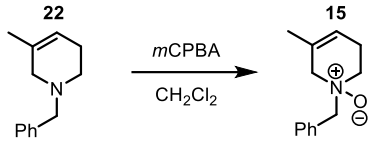
1-Benzyl-3-methyl-1,2,5,6-tetrahydropyridine (22)[134]



Adapted from the method of Reding,[86] benzylpyridinium salt **21** (2.0 g, 7.57 mmol) was dissolved in EtOH (12 mL) and added dropwise *via* an addition funnel to a stirred suspension of $NaBH_4$ in EtOH (20 mL) cooled to 0 °C (H_2 evolved steadily during addition). The mixture was allowed to warm to RT and stirred overnight. The solvent was removed under reduced pressure and the residue was worked up between H_2O and CH_2Cl_2 (3 x 20 mL), brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by Si gel flash chromatography (FC) (*n*-hex/EtOAc 5:1) afforded **22** as a yellow oil (755 mg, 53%); Si gel TLC $\boldsymbol{R_f}$ 0.50 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 2963, 2913, 2797, 1494, 1353, 1343, 1176, 1057, 1028, 975, 829, 738, 698; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.41 – 7.21 (m, 5H, Ar*H*), 5.44 [m, 1H, C=C(4)*H*], 3.59 (s, 2H, PhCH_2), 2.85 [m, 2H, NC(1)H_2], 2.50 [t, *J* = 5.8 Hz, 2H, NC(6)$_2$], 2.12 [m, 2H, C(5)H_2], 1.62 (s, 3H, CH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 138.4 (H_3C-*C*=C), 132.3 (Ar*C*), 129.2 (Ar*C*), 128.2 (Ar*C*), 127.0 (Ar*C*), 119.5 (H_3C-C=*C*), 62.9 (*C*H_2Ph), 57.0 [N*C*(2)H_2], 49.5 [N*C*(6)H_2], 26.0 (NCH_2*C*H_2),

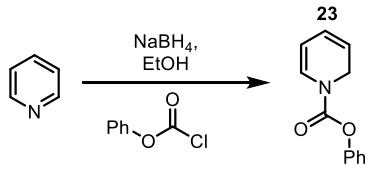
21.1 (*C*H_3); ***LRMS*** *m/z* (Cl^+) 188 [M+H^+]; ***HRMS*** *m/z* (Cl^+) calcd. for $C_{13}H_{18}N$ 188.1431, found 188.1439, Δ = -4.3 ppm. The spectroscopic data were in accordance with the literature.[134]

1-Benzyl-5-methyl-1,2,3,6-tetrahydropyridine 1-oxide (15)[134]



1-Benzyl-3-methyl-1,2,5,6-tetrahydropyridine **22** (520 mg, 2.78 mmol) was dissolved in dry CH_2Cl_2 (11 mL) and treated with *meta*-chloroperbenzoic acid (527 mg, 3.06 mmol) in portions at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 2 h. K_2CO_3 (750 mg) was added to the mixture which was then stirred for a further 1 h. The mixture was suction filtered and the solid was thoroughly washed with CH_2Cl_2. The organic solution was concentrated under reduced pressure and the crude material was purified *via* Si gel FC (CH_2Cl_2/MeOH 1:9 → 1:4) to give *N*-oxide **15** as a light brown oil (340 mg, 60%); Si gel TLC R_f 0.29 (CH_2Cl_2/MeOH 10:1); ***ATR-IR*** ν_{max}/cm^{-1} 3366, 2915, 1659, 1497, 1456, 1013, 922, 768, 737, 726, 702 ; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.61 – 7.52 (m, 2H, Ar*H*), 7.46 – 7.33 (m, 3H, Ar*H*), 5.56 [m, 1H, C(4)*H*], 4.44 (m, 2H, CH_2Ph), 3.78 [d, *J* = 16.1 Hz, 1H, C(2)H_a], 3.47 [d, *J* = 16.1 Hz, 1H, C(2)H_b], 3.32 [t, *J* = 6.1 Hz, 2H, C(6)H_2], 2.67 [m, 1H, C(5)H_a], 2.27 [m, 1H, C(5)H_b], 1.64 (s, 3H, CH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 132.6 (Ph), 129.8 [*C*(3) or C_{quat} Ph], 129.6 (Ph), 128.5 (Ph), 127.9 [*C*(3) or C_{quat} Ph], 118.5 [*C*(4)], 72.1 (*C*H_2Ph), 66.8 [*C*(2)], 60.9 [*C*(6)], 23.0 [*C*(5)], 20.5 (*C*H_3); ***LRMS*** *m/z* (ES^+) 204 [M+H^+]; ***HRMS*** *m/z* calcd. for $C_{13}H_{18}NO$ 204.1388, found 204.1395, Δ = 3.4 ppm. The spectroscopic data were in accordance with the literature.[134]

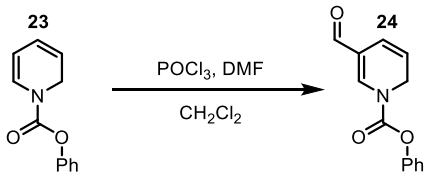
Phenyl pyridine-1(2H)-carboxylate (23)[122]



Adapted from the method of Fowler,[80] pyridine (2 mL, 24.7 mmol) in absolute EtOH (10 mL) was treated with $NaBH_4$ (1.05 g, 27.7 mmol) at -78 °C. Phenylchloroformate (3.1 mL, 24.7 mmol) was then carefully added over a 1 h period *via* a dropping funnel. The reaction mixture was stirred at -78 °C for 2 h, poured into ice-water (a gas presumed to be H_2 was evolved) and extracted with Et_2O (3 x 40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude material as an off-white solid. Recrystallization from EtOH gave **23** as fine white needles (1.35 g, 27%); ***mp*** 64 °C; Si gel TLC R_f 0.31 (*n*-hex/Et_2O 20:1);

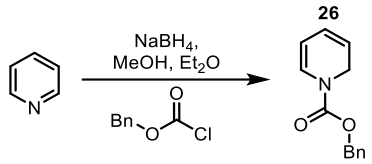
ATR-IR ν_{max}/cm^{-1} 1722, 1654, 1592, 1494, 1360, 1202, 1163, 1075, 749, 690; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.38 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.23 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.14 (d, *J* = 7.8 Hz, 2H, Ar*H*), 6.88 & 6.81 [2 x d, *J* = 7.9 Hz, 1H, C(6)*H*], 5.91 [m, 1H, C(4)*H*], 5.65 – 5.52 [m, 1H, C(3)*H*], 5.32 – 5.21 [m, 1H, C(5)*H*], 4.60 [dd, *J* = 3.9, 2.1 Hz, 1H, NC(2)H_a], 4.46 [dd, *J* = 4.0, 2.1 Hz, 1H, NC(2)H_b]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 151.0 (C=O), 129.4 (Ar*C*), 126.1 [N*C*(6)] , 125.8 (Ar*C*), 125.4 (Ar*C*), 122.3 [*C*(4)], 121.9 (Ar*C*), 121.6 [*C*(3)], 119.5 (Ar*C*), 119.0 (Ar*C*), 106.0 [*C*(5)], 44.3 & 43.9 (NCH_2); **LRMS** *m/z* (Cl^+) 202 [M+H^+]; **HRMS** *m/z* (Cl^+) calcd. for $C_{12}H_{12}NO_2$ 202.0686, found 202.0862, Δ = -3.0 ppm. The spectroscopic data were in accordance with the literature.[122]

Phenyl 5-formylpyridine-1(2H)-carboxylate (24)[87]



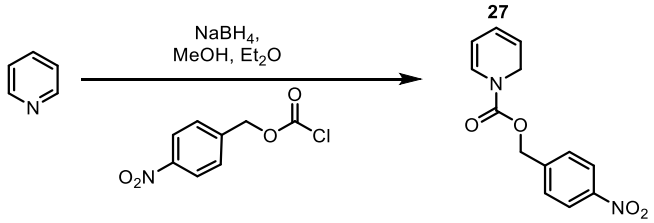
According to the method of Comins,[87] $POCl_3$ (0.25 mL, 2.73 mmol) was added dropwise to DMF (0.48 mL, 6.22 mmol) at 0 °C and stirred for 20 mins. To this was added a solution of 1,2-dihydropyridine **23** (500 mg, 2.48 mmol) in CH_2Cl_2 (2 mL) at 0 °C *via* cannula transfer. The solution was then refluxed at 50 °C for 50 mins; the dark red solution was cooled to 0 °C and treated slowly with KOAc (730 mg) in H_2O (4 mL). After refluxing for a further 20 mins, the mixture was cooled to RT, extracted with CH_2Cl_2 (2 x 25 mL), washed sequentially with H_2O, saturated $NaHCO_3$ solution and brine. The organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material required further aqueous washes with diluted brine to remove remaining amounts of DMF. After drying over $MgSO_4$ and concentrated under reduced pressure once again, the crude material was recrystallized from EtOH to afford aldehyde **24** as fine yellow needles (280 mg, 49%); ***mp*** 94 °C; Si gel TLC R_f 0.30 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 1732, 1651, 1602, 1491, 1344, 1287, 1197, 1156, 978, 751, 697; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.26 (s, 1H, *H*C=O), 7.69 (s, 1H, NC*H*), 7.45 – 7.40 (m, 2H, Ar*H*), 7.33 – 7.27 (m, 1H, Ar*H*), 7.20 – 7.15 (m, 2H, Ar*H*), 6.42 (m, 1H, H_2C-*H*C=C), 5.69 (m, 1H, H_2C-C=C*H*), 4.82 - 4.53 (*br.* m, 2H, NCH_2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 187.5 (H*C*=O), 150.5 (*C*OOPh), 143.0 (N*C*H), 129.8 (Ar*C*), 129.7 (Ar*C*), 126.7 (Ar*C*), 121.4 (Ar*C*), 120.0 (H_2C-C=*C*), 117.1 (H_2C-*C*=C), 46.6 (NCH_2); ***LRMS*** *m/z* (EI^+) 229 $[M]^+$, 230 $[M+H]^+$; ***HRMS*** *m/z* (EI^+) calcd. for $C_{13}H_{11}NO_3$ 229.0739, found 229.0737, Δ = -0.9 ppm. The spectroscopic data were in accordance with the literature.[87]

Benzyl pyridine-1(2H)-carboxylate (26)



Adapted from the method of Fowler,[80] pyridine (6 mL, 74.2 mmol) in MeOH (90 mL) was treated with $NaBH_4$ (2.81 g, 74.2 mmol). The reaction mixture was cooled to -78 °C before carefully adding benzylchloroformate (10.4 mL, 74.2 mmol) over a 1 h period *via* a dropping funnel. The reaction mixture was stirred at -78 °C for 2 h, poured into ice-water (a gas presumed to be H_2 was evolved), and extracted with CH_3Cl (4 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude material as a yellow oil. Si gel FC purification (*n*-hex/Et2O 20:1 → 5:1) afforded **26** as a pale yellow oil (5.49 g, 34%); Si gel TLC $\boldsymbol{R_f}$ 0.40 (*n*-hex/Et_2O 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 3385, 3036, 2924, 2854, 1696, 1497, 1453, 1417, 1310, 1219, 1154, 1118, 1047, 1024, 735, 696; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.41 − 7.32 (m, 5H, Ar*H*), 6.79 & 6.70 [2 x m, 1H, C(6)*H*], 5.87 − 5.80 [m, 1H, C(4)*H*], 5.58 − 5.41 [m, 1H, C(3)*H*], 5.21 − 5.09 [m, 3H : OCH_2Ph & C(5)*H*], 4.40 (*br.* m, 2H, NCH_2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 149.8 (*C*=O), 136.0 (Ar*C*), 128.6 (Ar*C*), 128.3 (Ar*C*), 128.1 (Ar*C*), 125.6 [N-*C*(6)=C], 121.9 [C=*C*(4)], 119.2 [C=*C*(3)], 105.0 [C=*C*(5)], 67.8 (CH_2Ph), 43.6 [N-*C*(2)H_2]; ***LRMS*** *m/z* (Cl^+) 216 $[M+H]^+$; ***HRMS*** *m/z* (Cl^+) calcd. for $C_{13}H_{14}NO_2$ 216.1025 $[M+H]^+$, found 216.1019, Δ = -2.8 ppm. The spectroscopic data were in accordance with the literature.[135]

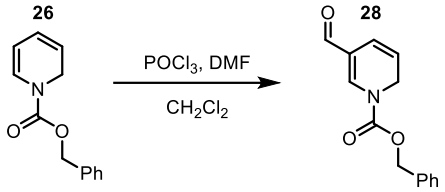
4-Nitrobenzyl pyridine-1(2H)-carboxylate (27)



Adapted from the method of Fowler,[80] pyridine (0.74 mL, 9.18 mmol) in MeOH (3.4 mL) was treated with $NaBH_4$ (350 mg, 9.18 mmol). The reaction mixture was cooled to -78 °C before carefully adding *para*-nitrobenzylchloroformate (1.8 g, 8.35 mmol) in dry Et_2O (2 mL) over a 1 h period *via* a dropping funnel. The reaction mixture was stirred at -78 °C for 3 h, poured into ice-water (a gas presumed to be H_2 was evolved) and extracted with Et_2O (3 x 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Si gel FC purification (pet. Ether/EtOAc 6:1) afforded **27** as a bright yellow solid (1.49 g, 60%); Si gel TLC $\boldsymbol{R_f}$ 0.33 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 3394, 2925, 2855, 1703, 1605, 1517, 1429, 1342,

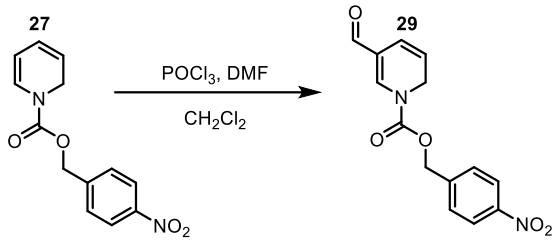
1318, 1260, 1228, 1109, 1013, 846, 736; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.17 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.50 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.68 [m, 1H, C(6)*H*], 5.85 – 5.76 [m, 1H, C(4)*H*], 5.57 – 5.42 [m, 1H, C(3)*H*], 5.26 (s, 2H, OCH_2Ar), 5.20 – 5.09 [m, 1H, C(5)*H*], 4.44 – 4.31 (*br.* m, 2H, NCH_2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 152.5 (*C*=O), 147.7 (Ar*C*, *ortho*-NO_2), 143.4 (d, Ar*C*, *meta*-NO_2), 128.3 (Ar*C*, *para*-NO_2), 128.2 (Ar*C*, *ortho*-NO_2), 125.9 (N-*C*=C), 125.0 (Ar*C*, *meta*-NO_2), 123.8 (Ar*C*, *ipso*-NO_2), 121.8 [C=*C*(4)], 119.4 & 118.7 [C=*C*(3)], 105.6 [d, C=*C*(5)], 66.2 (*C*H_2Ph), 43.9 & 43.7 [N-*C*(2)H_2]; ***LRMS*** *m/z* (ES^+) 277 $[M+NH_4]^+$.

Benzyl 5-formylpyridine-1(2H)-carboxylate (28)



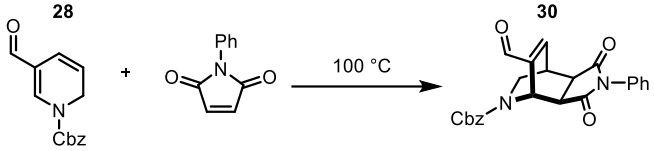
Adapted from the method of Comins,[87] $POCl_3$ (0.58 mL, 6.24 mmol) was added dropwise to DMF (1.10 mL, 14.15 mmol) at 0 °C and stirred for 20 mins. To this was added a solution of 1,2-dihydropyridine **26** (1.22 g, 5.66 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C *via* cannula transfer. The solution was then refluxed at 50 °C for 50 mins; the dark red solution was cooled to 0 °C and treated slowly with KOAc (1.67 g, 16.98 mmol) in H_2O (4 mL). After refluxing for a further 20 mins, the mixture was cooled to RT, extracted with CH_2Cl_2 (2 x 80 mL), washed sequentially with H_2O, saturated $NaHCO_3$ solution and brine. The organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material required further aqueous washes with diluted brine to remove remaining amounts of DMF. After drying over $MgSO_4$ and concentrated under reduced pressure once again, the crude material was purified by AlO FC (*n*-hex/EtOAc 5:1) to afford aldehyde **28** as an orange oil (1.21 g, 88%); Si gel TLC R_f 0.18 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 2922, 1734, 1675, 1661, 1383, 1284, 1264, 1178, 1116, 1024, 1081. ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.16 (s, 1H, *H*C=O), 7.66 – 7.48 (*br.* m, 1H, 1H, NC(6)*H*), 7.44 – 7.37 (m, 5H, Ar*H*), 6.35 [m, 1H, C(3)*H*], 5.60 [m, 1H, C(4)*H*], 5.29 (s, 2H, OCH_2Ph), 4.53 [m, 2H, NC(2)H_2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 187.3 (H*C*=O), 134.8 (Ar*C*), 128.9 (Ar*C*), 128.8 [N*C*(6)H], 128.6 (Ar*C*), 119.7 [*C*(4)], 117.1 [*C*(3)], 69.3 (OCH_2Ph), 46.2 [N*C*(2)H_2]; ***LRMS*** *m/z* (EI^+) 243 $[M]^+$, 244 $[M+H]^+$; ***HRMS*** *m/z* (EI^+)calcd. for $C_{14}H_{13}NO_3$ 243.0895, found 243.0893, Δ = -0.8 ppm.

4-Nitrobenzyl 5-formylpyridine-1(2H)-carboxylate (29)

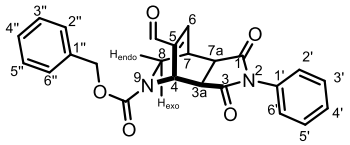


According to the method of Comins,[87] $POCl_3$ (0.55 mL, 5.86 mmol) was added dropwise to DMF (1.00 mL) at 0 °C and stirred for 20 mins. To this was added a solution of the 1,2-dihydropyridine **27** (1.39 g, 5.34 mmol) in CH_2Cl_2 (4.30 mL) at 0 °C *via* cannula transfer. The solution was then refluxed at 50 °C for 50 mins; the dark red solution was cooled to 0 °C and treated slowly with KOAc (1.57 g) in H_2O (9.50 mL). After refluxing for a further 20 mins, the mixture was cooled to room temp., extracted with CH_2Cl_2 (2 x 45 mL), washed sequentially with H_2O, saturated $NaHCO_3$ solution and brine. The organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material required further aqueous washes with diluted brine to remove remaining amounts of DMF. After drying over Na_2SO_4 and concentrated under reduced pressure once again, the crude material was recrystallized from EtOH to afford **29** as a bright yellow solid (1.20 g, 78%); ***mp*** 115–119 °C; Si gel TLC $\boldsymbol{R_f}$ 0.55 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3336, 2925, 2853, 1726, 1668, 1650, 1602, 1519, 1411, 1381, 1344, 1318, 1206, 1158, 1107, 850, 735; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H, *H*C=O), 8.27 (m, 2H, Ar*H*), 7.65 – 7.46 [m, 3H : Ar*H* x 2 & NC(6)*H*], 6.37 [m, 1H, C(4)*H*], 5.63 [m, 1H, C(3)*H*], 5.39 (s, 2H, OCH_2Ar), 4.55 [*br.* s, 2H, NC(2)H_2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 187.3 (H*C*=O), 141.9 (N*C*(6)), 128.9 (Ar*C* x 2), 124.1 (Ar*C* x 2), 118.7 [*C*(3)], 117.1 [*C*(4)], 67.6 (O*C*H_2Ar), 46.3 [N*C*(2)H_2]; **LRMS** *m/z* (ES^+) 289 $[M+H]^+$, 330 $[M+CH_3CN+H]^+$; ***HRMS*** *m/z* (ES^+) calcd. for $C_{14}H_{13}N_2O_5$ 289.0824, found 289.0830, Δ = 2.1 ppm.

(3a*S*,4*R*,7*R*,7a*S*)-Benzyl 5-formyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (30)

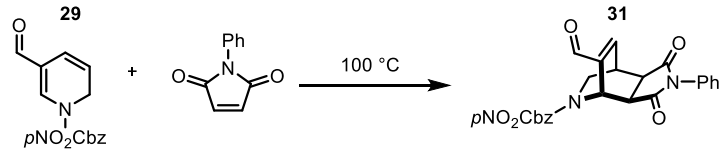


Benzyl 5-formylpyridine-1(2H)-carboxylate (197 mg, 0.81 mmol) and *N*-phenylmaleimide (351 mg, 2.03 mmol) were heated at 100 °C for 18 h under N_2. The reaction mixture was then purified by Si gel FC (*n*-hex/EtOAc 1:1 → 1:2) to provide the Diels-Alder adduct **30** as a yellow fluffy solid (210 mg, 63%); ***mp*** 76-86 °C; Si gel TLC $\boldsymbol{R_f}$ 0.13 (*n*-hex/EtOAc 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 2924, 2853, 1710, 1498, 1455, 1413, 1384, 1345, 1264, 1184, 1106, 754, 698, 616, 574; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

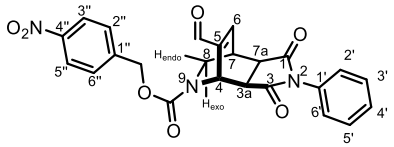


[1]H NMR ($CDCl_3$, 400 MHz) δ 9.54 (*br.* s, 1H, *H*C=O), 7.45 – 7.29 [m, 9H : Ar*H* x 8 & C(6)*H*], 7.07 [d, *J* = 7.4 Hz, 2H : C(2')*H* & C(6')*H*], 5.96 [*br.* m, 1H, C(4)*H*], 5.24 – 5.10 (*br.* m, 2H, OCH_2Ph), 3.83 – 3.71 [*br.* m, 1H, C(7)*H*], 3.64 – 3.48 [m, 2H : C(3a)*H* & C(8)H_{exo}], 3.32 – 3.16 [m, 2H : C(7a)*H* & C(8)H_{endo}]; ***[13]C NMR*** ($CDCl_3$, 101 MHz) δ 185.8 (H*C*=O), 175.4 [*C*(1)], 173.1 [*C*(3)], 154.6 (N*C*=O), 147.0 [*C*(6)], 144.4 [*C*(5)], 129.2 (Ar*C*), 129.0 (Ar*C*), 128.6 (Ar*C*), 128.3 (Ar*C*), 128.2 (ArC), 126.0 (Ar*C*), 67.7 (O*C*H_2), 45.1 – 43.9 [*C*(8) & *C*(4) & C(3a)], 41.0 [*C*(7a)], 34.2 [(*C*7)]; ***LRMS*** m/z (ES^+) 417.14 $[M+H]^+$, 434.16 $[M+NH_4]^+$; ***HRMS*** *m/z* calcd. for $C_{24}H_{21}N_2O_5$ 417.1450, found 417.1438, Δ = -2.9 ppm.

(3a*S*,4*R*,7*R*,7a*S*)-4-Nitrobenzyl 5-formyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (31)



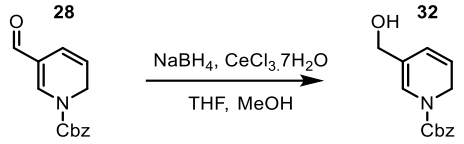
1,2-Dihydropyridine **29** (205 mg, 0.71 mmol) and *N*-phenylmaleimide (308 mg, 1.78 mmol) were heated at 100 °C for 18 h under N_2. The reaction mixture was then purified by Si gel FC (*n*-hex/EtOAc 2:1) to provide the Diels-Alder adduct **31** as an off-white fluffy solid (275 mg, 85%); Si gel TLC R_f 0.29 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3311, 2925, 2854, 1712, 1638, 1521, 1385, 1343, 1265, 1186, 1108, 698, 614, 599, 548; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



[1]H NMR ($CDCl_3$, 400 MHz, 328K) δ 9.52 (*br.* s, 1H, *H*C=O), 8.18 (m, 2H, Ar*H*), 7.51 (m, 2H, Ar*H*), 7.43 – 7.26 [m, 4H : Ar*H* x 3 & C(6)*H*], 7.06 (m, 2H, Ar*H*), 5.92 [m, 1H, C(4)*H*], 5.33 – 5.17 (m, 2H, O*CH*$_2$Ar), 3.75 [m, 1H, C(7)*H*], 3.62 – 3.47 [m, 2H : C(3a)*H* & C(8)H_{exo}], 3.28 [dd, *J* = 8.5, 3.5 Hz, 2H, C(7a)*H*], 3.21 [dd, *J* = 10.5, 1.0 Hz, C(8)H_{endo}]; ***[13]C NMR*** (101 MHz, $CDCl_3$, 328 K) δ 185.9 (H*C*=O), 175.4 [*C*(1)], 173.0 [*C*(3)], 154.1 (N*C*=O), 147.9 [*C*(4'')], 147.0 [*C*(6)], 144.4 [*C*(5)], 143.4 [*C*(1'')], 131.3 [*C*(1')], 129.10 [*C*(3') & *C*(5')], 129.0 [*C*(4')], 128.3 [*C*(2'') & *C*(6'')], 126.0 [*C*(2') & *C*(6')], 123.8 [*C*(3'') & *C*(5'')], 66.1 (O*C*H_2Ar), 45.1 [*C*(8)], 44.8 [*C*(3a)], 44.1 [*C*(4)], 41.0 [*C*(7a)],

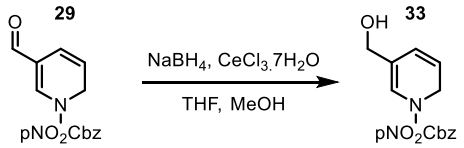
34.2 [*C*(7)]; ***LRMS*** *m/z* (ES^-) 505.11 $[M-H+HCOO]^-$; ***HRMS*** *m/z* calcd. for $C_{25}H_{19}N_3O_9$ 505.1121, found 505.1129, Δ = 1.6 ppm.

Benzyl 5-(hydroxymethyl)pyridine-1(2H)-carboxylate (32)



Adapted from the method of Comins,[87] to a suspension of the aldehyde **28** (1.00 g, 4.12 mmol) in THF (4.50 mL) was added MeOH (12.50 mL) and $CeCl_3.7H_2O$ (1.53 g, 4.12 mmol). The reaction mixture was stirred for 30 mins under N_2 before cooling to 0 °C. $NaBH_4$ (187 mg, 4.94 mmol) was then added portion-wise. The reaction mixture was stirred at 0 °C for 2 h. After H_2O (50 mL) was added to the reaction mixture, the MeOH was removed under reduced pressure before extracting the aqueous with CH_2Cl_2 (4 x 60 mL). The organic solutions were combined, washed with water and brine, and then dried over Na_2SO_4 before concentrating in vacuo to give the crude material as a yellow oil. Si gel FC purification (*n*-hex/EtOAc 1:1) afforded alcohol **32** as a yellow oil (535 mg, 54%); Si gel TLC R_f0.37 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3363, 2925, 2865, 1694, 1453, 1416, 1314, 1261, 1214, 1026, 911, 734, 697; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.40 – 7.30 (m, 5H, ArH), 6.81 – 6.71 [m, 1H, NC(6)*H*], 5.96 [m, 1H, C(4)*H*], 5.60 [m, 1H, C(3)*H*], 5.20 (s, 2H, OCH_2Ph), 4.37 [*br.* s, 2H, NC(2)H_2], 4.09 – 4.02 [m, 2H, CH_2OH]; ***^{13}C NMR*** (101 MHz, $CDCl_3$) δ 135.5 (Ar*C*), 128.6 (d, Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 128.1 (Ar*C*), 123.7 & 123.3 [N*C*(6)], 123.0 [N*C*(4)], 120.2 & 119.7 [N*C*(3)], 68.0 (O*C*H_2Ph), 63.4 & 62.5 (*C*H_2OH), 43.9 [d, NC(2)H_2]; ***LRMS*** *m/z* (ES^+) *m/z*: none found. *N.B.* Compound is unstable as was found to decompose within hours (see ^{13}C NMR spectrum).

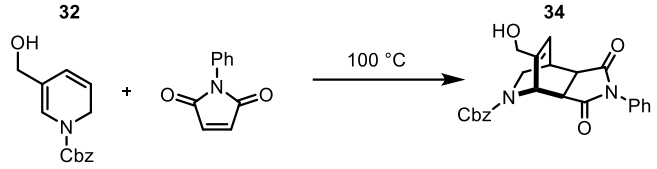
4-Nitrobenzyl 5-(hydroxymethyl)pyridine-1(2H)-carboxylate (33)



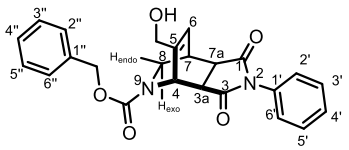
Adapted from the method of Comins,[87] to a suspension of the aldehyde **29** (500 mg, 1.73 mmol) in THF (1.73 mL) was added MeOH (5.30 mL) and $CeCl_3.7H_2O$ (646 mg, 1.73 mmol). The reaction mixture was stirred for 30 mins under N_2 before cooling to 0 °C. $NaBH_4$ (79 mg, 2.08 mmol) was then added portion-wise. The reaction mixture was stirred at 0 °C for 2 h and then at RT for 2 h. After H_2O (30 mL) was added to the reaction mixture, the MeOH was removed under reduced pressure before extracting the aqueous with CH_2Cl_2 (4 x 40 mL). The organic solutions were

combined, washed with water and brine, and then dried over Na_2SO_4. The organic solution was concentrated in vacuo to give the alcohol **33** as an off-white solid (450 mg, 90%); ***mp*** 70-73 °C; Si gel TLC $\boldsymbol{R_f}$0.31 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3375, 2924, 2853, 1707, 1605, 1520, 1401, 1345, 1316, 1275, 1261, 1200, 1106, 764, 750; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.26 – 8.21 (m, 2H, Ar*H ortho*-NO_2), 7.53 (m, 2H, Ar*H meta*-NO_2), 6.79 – 6.73 [m, 1H, NC(6)*H*], 5.99 [m, 1H, C(4)*H*), 5.64 [m, 1H, C(3)*H*], 5.30 (s, 2H, O*C*H_2Ar), 4.40 (m, 2H, NC(2)H_2), 4.10 (s, 2H, *C*H_2OH); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 128.4 (Ar*C*), 128.3 (Ar*C*), 123.9 (m, Ar*C*), {122.8, 122.6 : *C*(4) and N(6)*C*], 120.4 [*C*(3)], 119.7 [*C*(5)], 66.47 (O*C*H_2Ar), 63.3 (*C*H_2OH), 44.0 [N*C*(2)H_2]. ***LRMS*** *m/z* (ES^+) *m/z*: none found.

(3a*S*,4*R*,7*R*,7a*S*)-Benzyl 5-(hydroxymethyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (34)

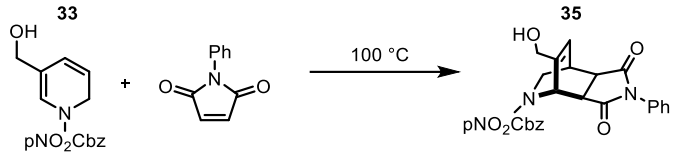


1,2-Dihydropyridine **32** (510 mg, 2.19 mmol) and *N*-phenylmaleimide (901 mg, 5.20 mmol) were heated at 100 °C for 18 h under N_2. The reaction mixture was then purified by Si gel FC (*n*-hex/EtOAc 1:1) to provide the Diels-Alder adduct **34** as an off-white fluffy solid (639 mg, 74 %); ***mp*** 49-53 °C; Si gel TLC $\boldsymbol{R_f}$0.31 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3370, 2925, 2853, 1710, 1607, 1530, 1442, 1260, 1185, 1106, 859, 754; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

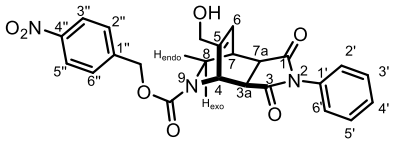


^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 – 7.30 (m, 8H, Ar*H*), 7.14 [m, 2H : C(2')*H* & C(6')H], 6.22 [*app*. dd, *J* = 6.4, 2.0 Hz, 1H, C(6)*H*], 5.38 – 5.09 [m, 3H : O*C*H_2Ph & C(4)*H*], 4.23 – 4.11 (m, 2H, *C*H_2OH), 3.58 – 3.34 [m, 3H : C(7)*H* & C(8)H_{exo} & C(3a)*H*), 3.16 – 3.07 [m, 2H : C(7a)*H* & C(8)H_{endo}]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 176.6 & 176.5 [*C*(1)], 175.1 & 174.9 [*C*(3)], 155.3 & 154.7 (N*C*=O), 145.1 & 144.5 [*C*(5)], 136.3 (Ar*C*), 131.5 (Ar*C*), 129.3 (Ar*C*), 128.9 (Ar*C*), 128.6 (Ar*C*), 128.3 (Ar*C*), 128.3 (Ar*C*), 128.2 (Ar*C*), 128.2 (Ar*C*), 128.1 (Ar*C*), 126.4 (Ar*C*), 124.3 & 124.1 [*C*(6)], 67.5 (O*C*H_2Ph), 62.5 (*C*H_2OH), 48.1 & 47.8 [*C*(4)], 46.5 & 46.1 [*C*(8)], 45.4 & 45.1 [*C*(3a)], 41.6 & 41.6 [*C*(7a)*H*], 33.4 & 33.2 [*C*(7)]; ***LRMS*** *m/z* (ES^+) 419.16 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{24}H_{23}N_2O_5$ 419.1607, found 419.1592, Δ = - 3.6 ppm.

(3a*S*,4*R*,7*R*,7a*S*)-4-Nitrobenzyl 5-(hydroxymethyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (35)

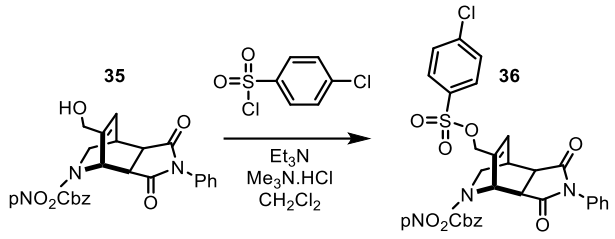


1,2-Dihydropyridine **33** (400 mg, 1.37 mmol) and *N*-phenylmaleimide (656 mg, 3.79 mmol) were heated at 100 °C for 18 h under N_2. The reaction mixture was then purified by Si gel FC (*n*-hex/EtOAc 1:1) to provide the Diels-Alder adduct **35** as an white fluffy solid (570 mg, 89%); ***mp*** 86-92 °C; Si gel TLC R_f 0.25 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3386, 2926, 2853, 1700, 1605, 1520, 1498, 1453, 1387, 1342, 1297, 1152, 1106, 852, 755, 697, 622; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



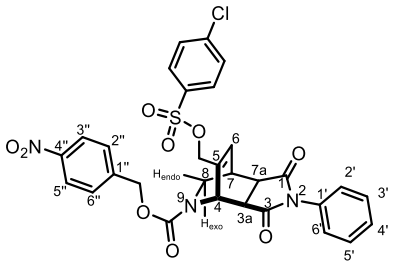
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 [*br.* d, *J* = 8.0 Hz, 2H : C(3'')*H* & C(5'')*H*], 7.60 – 7.36 (m, 5H, Ar*H*), 7.14 [*br* d, *J* = 7.5 Hz, 2H : C(2')*H* & C(6')*H*], 6.29 [*app*. d, *J* = 6.4 Hz, 1H, C(6)*H*], 5.37 – 5.17 [m, 3H : OCH_2Ar & C(4)*H*], 4.26 – 4.15 (m, 2H, CH_2OH), 3.62 – 3.40 [m, 3H : C(7)*H* & C(8)H_{exo} & C(3a)*H*], 3.22 – 3.11 [m, 2H: C(7a)*H* & C(8)H_{endo}]; ***^{13}C NMR*** ($CDCl_3$,101 MHz) δ 176.4 & 176.3 [*C*(1)], 175.0 & 174.7 [*C*(3)], 154.8 & 154.1 (N*C*=O), 147.8 & 147.6 [*C*(4'')], 145.0 & 144.9 [C(5)], 144.3 (Ar*C*), 143.6 & 143.5 [*C*(1'')], 131.4 (Ar*C*), 129.3 (Ar*C*), 129.0 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 126.4 (Ar*C*), 124.93 & 124.25 [*C*(6)], 123.9 [*C*(3'') & *C*(5'')], 66.0 (O*C*H_2Ar), 62.6 (*C*H_2OH), 48.1 & 47.9 [*C*(4)], 46.5 & 46.2 [*C*(8)], 45.5 & 45.1 [*C*(3a)], 41.5 [*C*(7a)], 33.4 & 33.2 [*C*(7)]; ***LRMS*** *m/z* (ES^+) 464.14 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{24}H_{22}N_3O_7$ 464.1458, found 464.1445, Δ = -2.8 ppm.

4-Nitrobenzyl (3a*R*,4*S*,7*S*,7a*R*)-5-((((4-chlorophenyl)sulfonyl)oxy)methyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (36)



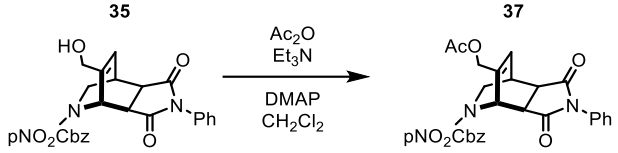
To an ice-cold solution of alcohol **35** (30 mg, 0.065 mmol), Et_3N (18 µL, 0.13) and Me_3N.HCl (1.3 mg, 0.013 mmol) in dry CH_2Cl_2 (0.1 mL) was added a solution of *para*-chlorosulfonyl chloride (16 mg, 0.076 mmol) in dry CH_2Cl_2 (0.1 mL). The reaction mixture was stirred at 0 °C for 1 h. H_2O (2

mL) was added to the mixture which was then extracted with EtOAc (2 x 5 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The crude material was concentrated in vacuo and purified by Si gel FC (*n*-hex/EtOAc 1:1) to give **36** as an off-white semi-solid (34 mg, 83%); Si gel TLC $\boldsymbol{R_f}$ 0.33 (*n*-hex/EtOAc 1:2); (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

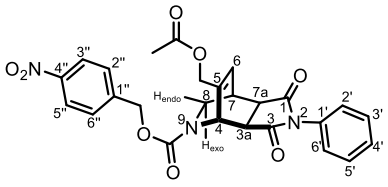


^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 – 8.19 [m, 2H : C(3'')*H* & C(5'')*H*], 7.80 – 7.32 (m, 9H, Ar*H*), 7.16 – 7.03 [m, 2H : C(2')*H* & C(6')*H*], 6.43 [*app*. d, *J* = 19.5, 6.5 Hz, 1H, C(6)*H*], 5.40 – 5.15 [m, 3H : OCH_2Ar & C(4)*H*], 4.58 – 4.54 & 4.09 – 4.06 (m, 2H, CH_2OSO$_2$Ar), 3.59 – 3.38 [m, 3H : C(7)*H* & C(8)H_{exo} & C(3a)*H*], 3.23 – 3.04 [m, 2H: C(7a)*H* & C(8)H_{endo}]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 175.9, 175.8, 174.0, 174.0, 154.6, 154.0, 147.8, 147.8, 143.5, 140.9, 138.3, 137.7, 134.0, 134.0, 131.3, 130.9, 129.8, 129.5, 129.4, 129.3, 129.1, 128.7, 128.6, 128.3, 126.4, 126.4, 126.2, 124.0, 123.9, 68.5, 68.4, 66.2, 66.1, 49.2, 49.0, 48.2, 47.8, 46.2, 46.0, 45.7, 45.2, 45.1, 43.4, 43.2, 41.5, 41.2, 33.3, 29.8; ; ***LRMS*** *m/z* (ES^+) 639.78 $[M+H]^+$.

4-Nitrobenzyl (3a*R*,4*S*,7*S*,7a*R*)-5-(acetoxymethyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (37)

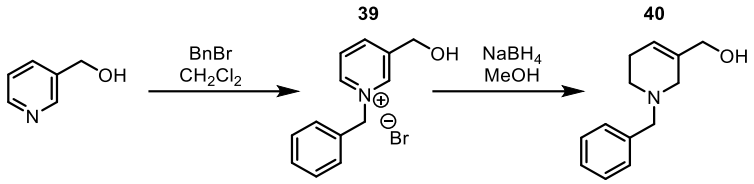


To an ice-cold solution of alcohol **35** (50 mg, 0.11 mmol) in dry CH_2Cl_2 (0.5 mL) was added Ac_2O (20 µL, 0.22 mmol). Et_3N (38 µL, 0.28) and 4-(dimethylamino)pyridine (1.4 mg, 0.01 mmol) were subsequently added to the reaction mixture which was then stirred at 0 °C for 30 mins. A few drops of MeOH was added to quench any excess Ac_2O. H_2O (5 mL) was added to the mixture which was then extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The crude material was concentrated under reduced pressure and purified by Si gel FC (*n*-hex/EtOAc 1:1) to give **36** as an off-white solid (55 mg, 100%) which was immediately taken to the next stage to avoid decomposition; Si gel TLC $\boldsymbol{R_f}$ 0.36 (*n*-hex/EtOAc 1:2); (^{1}H NMR spectrum complicated at RT due to the presence of rotamers)



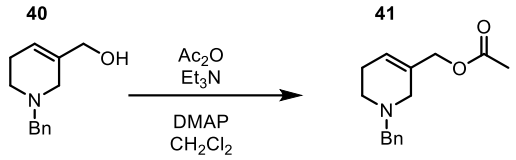
[1]H NMR ($CDCl_3$, 400 MHz) δ 8.24 – 8.19 [m, C(3'')*H* & C(5'')*H*], 7.60 – 7.34 (m, 5H, Ar*H*), 7.19 – 7.11 [m, 2H : C(2')*H* & C(6')*H*], 6.32 [*app*. d, *J* = 17.1, 6.1 Hz, 1H, C(6)*H*], 5.38 – 5.19 [m, 3H : OCH_2Ar & C(4)*H*], 4.78 – 4.46 (m, 2H, CH_2OH), 3.55 – 3.38 [m, 3H : C(7)*H* & C(8)H_{exo} & C(3a)*H*], 3.21 – 3.10 [m, 2H : C(7a)*H* & C(8)H_{endo}], 1.93 – 1.92 (m, 3H, Ac OCH_3); ***LRMS*** *m/z* (ES^+) 506.59 $[M+H]^+$.

(1-Benzyl-1,2,5,6-tetrahydropyridin-3-yl)methanol (40)



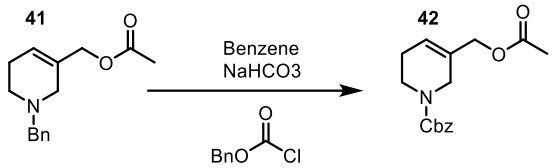
Adapted from the method of Winkler,[136] pyridine-3-methanol (5 mL, 51 mmol) in dry CH_2Cl_2 was treated with benzyl bromide (6.43 mL, 54 mmol) slowly over a 3 h period. The reaction mixture was stirred at RT for 24 h. Removal of the solvent under reduced pressure afforded the benzyl pyridinium salt **39** as viscous orange oil (14.39 g, 99%) which was used crude in the next step without purification. The benzyl pyridinium salt (14.39 g, 51 mmol) was dissolved in MeOH (58 mL) and was cooled to 0 °C. $NaBH_4$ (3.97 g, 105 mmol) was then carefully added portion-wise over 5 h. The reaction mixture was allowed to warm to RT overnight with continued stirring. After removal of the solvent under reduced pressure, saturated $NaHCO_3$ solution was added. After extracting with EtOAc (70 mL x 3), the organic solutions were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford tetrahydropyridine **40** as viscous orange oil (10.50 g, 99%); Si gel TLC R_f 0.1 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3325, 2912, 2808, 1609, 1494, 1450, 1362, 1178, 1128, 1101, 1047, 1012, 731, 699; ***[1]H NMR*** ($CDCl_3$, 400 MHz) δ 7.41 – 7.20 (m, 5H, Ar*H*), 5.62 [m, 1H, C(4)*H*], 3.94 (s, 2H, CH_2OH), 3.60 (s, 2H, ArCH_2), 2.98 [m, 2H, NC(2)H_2], 2.53 [t, *J* = 5.8 Hz, 2H, NC(6)H_2], 2.16 [m, 2H, C(5)H_2]; ***[13]C NMR*** (101 MHz, $CDCl_3$) δ 137.6 (Ar*C*), 136.5 [*C*(3)=C], 129.5 (Ar*C*), 128.3 (Ar*C*), 127.2 (Ar*C*), 121.0 [C=*C*(4)], 65.2 (*C*H_2OH), 62.9 (Ar*C*H_2), 53.1 [N*C*(2)], 49.7 [N*C*(6)], 25.6 [*C*(5)]; ***LRMS*** *m/z* (ES^+) 204.14 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{13}H_{18}NO$ 204.1388, found 204.1378, Δ = -4.9 ppm.

(1-Benzyl-1,2,5,6-tetrahydropyridin-3-yl)methyl acetate (41)



To an ice-cold solution of alcohol **40** (250 mg, 1.23 mmol) in dry CH_2Cl_2 (6 mL) was added Ac_2O (0.23 mL, 2.46 mmol). Et_3N (0.43 mL, 3.08 mmol) and 4-(dimethylamino)pyridine (15 mg, 0.12 mmol) were subsequently added to the reaction mixture which was then stirred at 0 °C for 40 mins. A few drops of MeOH were added to quench any excess Ac_2O. H_2O (5 mL) was added to the mixture which was then extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The crude material was purified by Si gel FC (*n*-hex/EtOAc (1:1) to afford acetate **41** as a pale yellow oil (202 mg, 67%); Si gel TLC $\boldsymbol{R_f}$ 0.29 (*n*-hex/EtOAc 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 3401, 2916, 2801, 1736 (C=O), 1494, 1452, 1367, 1229, 1023, 962, 841, 788, 699; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.40 – 7.24 (m, 5H, Ar*H*), 5.83 [m, 1H, *H*C(4)=C], 4.46 (s, 2H, CH_2OAc), 3.63 (s, 2H, ArCH_2), 3.00 [m, 2H, NC(2)H_2], 2.56 [*app.* t, *J* = 5.8 Hz, 2H, NC(6)H_2], 2.20 [m, 2H, C(5)H_2], 2.05 (s, 3H, Ac OCH_3); ***^{13}C NMR*** (101 MHz, $CDCl_3$) δ 170.9 (*C*=O), 131.5 (Ar*C*), 129.2 (Ar*C*), 128.3(Ar*C*), 127.2 (Ar*C*), 125.2 [*C*(4)=C], 66.8 (*C*H_2OAc), 62.5 (Ar*C*H_2), 53.3 [N*C*(2)H_2], 49.0 [N*C*(6)H_2], 25.6 [NC*C*(5)], 21.0 (O=C*C*H_3); ***LRMS*** *m/z* (ES^+) 246.15 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{15}H_{19}NO_2$ 246.1494, found 246.1489, Δ = -2.0 ppm.

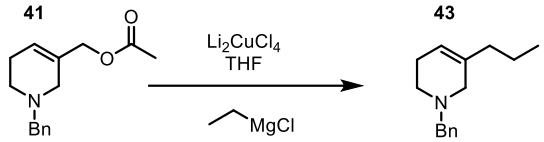
Benzyl 3-(acetoxymethyl)-5,6-dihydropyridine-1(2H)-carboxylate (42)



Adapted from the method of Winkler,[136] to a solution of acetate **41** (500 mg, 2.04 mmol) in benzene (3.1 mL) was added $NaHCO_3$ (86 mg, 1.02 mmol). Benzylchloroformate (0.34 mL, 2.43 mmol) was added slowly over 1 h. The reaction mixture was stirred at RT for 10 mins and then heated to reflux for 40 h under N_2. After cooling to RT the solvent was removed under reduced pressure. The orange oil was dissolved in EtOAc (40 mL) and washed sequentially with H_2O (3 x 30 mL), 0.5M HCl (3 x 30 mL) and brine (3 x 30 mL). The organic solution was dried over $MgSO_4$ and concentrated in vacuo. Purification by Si gel FC (*n*-hex/EtOAc 4:1 → 1:1) gave acetate **42** as an orange oil (430 mg, 73%); Si gel TLC $\boldsymbol{R_f}$ 0.67 (*n*-hex/EtOAc 3:2); ***ATR-IR*** ν_{max}/cm^{-1} 3369, 2924, 2853, 1737 (C=O), 1699 (C=O), 1430, 1361, 1280, 1227, 1105, 1023, 764, 750, 698; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.40 – 7.28 (m, 5H, Ar*H*), 5.90 [*br.* s, 1H, *H*C(4)=C], 5.16 (s, 1H, OCH_2Ph), 4.49 (*br.* s, 2H, CH_2OAc), 3.96 [*br.* s, 2H, NC(2)H_2], 3.55 [*app.* t, *J* = 5.8 Hz, 2H, NC(6)H_2], 2.25 – 2.13

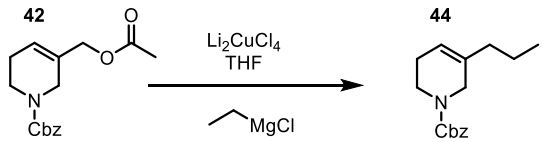
[*br.* s, 2H, C(5)H_2], 2.06 (*br.* s, 3H, Ac OCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.9 (O=$C$$CH_3$), 155.5 (N$C$=O), 128.7 (Ar$C$), 128.6 (Ar$C$), 128.2 (Ar$C$), 128.1 (Ar$C$), 125.7 [$C$(4)=C], 125.0 [C=$C$(3)], 123.7 (Ar$C$), 123.0 (Ar$C$), 67.3 (OC$H_2$Ph), 66.4 ($CH_2$OAc), 44.2 [N$C(2)H_2$], 40.4 [N$C(6)H_2$], 24.7 [$C(5)H_2$], 21.0 (O=C$CH_3$); ***LRMS*** *m/z* ($ES^+$) 290.14 $[M+H]^+$, 312.12 $[M+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{16}H_{20}NO_4$ 290.1387, found 290.1378, Δ = -3.049 ppm. *N.B.* Compound is unstable and was found to decompose upon standing at RT.

1-Benzyl-5-propyl-1,2,3,6-tetrahydropyridine (43)



Adapted from the method of Bäckvall,[93] to a solution of acetate **41** (50 mg, 0.20 mmol) and Li_2CuCl_4 (0.1M in THF, 40 µL, 4 µmol) in dry THF (1 mL) at 0 °C was added EtMgCl (2M in THF, 0.31 mL, 0.61 mmol) drop-wise over 1 min. The reaction mixture was stirred under N_2 at 0 °C for 30 mins. After quenching with saturated NH_4Cl solution, the mixture was extracted with Et_2O (3 x 5 mL). The organic solutions were combined, washed with brine and dried over Na_2SO_4. The crude material was purified by Si gel FC (*n*-hex/EtOAc 6:1) to afford tatrahydropyridine **43** as a colourless oil (21 mg, 49%); Si gel TLC R_f 0.46 (*n*-hex/EtOAc 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 2930, 2857, 1432, 1360, 1281, 1105, 1025, 765; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.42 – 7.22 (m, 5H, ArH), 5.45 [m, 1H, HC(4)=C], 3.60 (s, 2H, ArCH_2), 2.88 [m, 2H, NC(2)H_2], 2.52 [*app.* t, *J* = 5.8 Hz, 2H, NC(6)H_2], 2.14 [m, 2H, C(5)H_2], 1.90 (t, *J* = 7.5 Hz, C$H_2$$CH_2CH_3$), 1.40 (*app.* h, *J* = 7.4 Hz, CH_2C$H_2$$CH_3$), 0.88 (t, *J* = 7.5 Hz, 1H, CH_2CH_3); ***LRMS*** *m/z* (ES^+) 216.17 $[M+H]^+$, ***HRMS*** *m/z* calcd. for $C_{15}H_{22}N$ 216.1752, found 216.1740, Δ = -5.6 ppm. *N.B.* Compound is unstable and was found to decompose upon standing at RT.

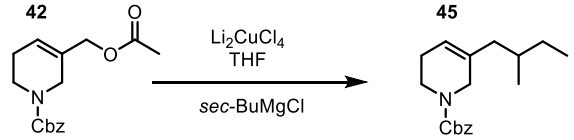
Benzyl 3-propyl-5,6-dihydropyridine-1(2H)-carboxylate (44)



Adapted from the method of Bäckvall,[93] to a solution of acetate **42** (24 mg, 0.083 mmol) and Li_2CuCl_4 (0.1M in THF, 17 µL, 1.7 µmol) in dry THF (0.4 mL) at 0 °C was added EtMgCl (2M in THF, 0.12 mL, 0.25 mmol) drop-wise over 30 seconds. The reaction mixture was stirred under N_2 at 0 ^oC for 40 mins. After quenching with saturated NH_4Cl solution the mixture was extracted with Et_2O (3 x 5 mL). The organic solutions were combined, washed with brine and dried over Na_2SO_4.

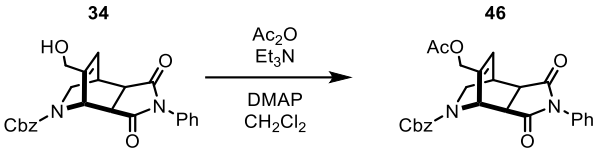
The crude material was purified by Si gel FC (*n*-hex/EtOAc 6:1) to afford compound **44** as a colourless oil (10.5 mg, 50%); Si gel TLC $\boldsymbol{R_f}$ 0.52 (*n*-hex/EtOAc 6:1); ***ATR-IR*** ν_{max}/cm^{-1} 3429, 2958, 2930, 2872, 1701, 1621, 1454, 1427, 1310, 1280, 1209, 1114, 1036, 965, 745, 697; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.35 (m, 5H, Ar*H*), 5.53 [*br.* s, 1H, *H*C(4)=C], 5.15 (s, 2H, OCH_2Ph), 3.84 [*br.* s, 2H, NC(2)H_2], 3.51 [*app* t, *J* = 5.8 Hz, 2H, NC(6)H_2], 2.17 – 2.04 [*br.* s, 2H, C(5)H_2], 1.99 – 1.89 (m, 2H, C$H_2$$CH_2CH_3$), 1.44 (m, 2H, C$H_2CH_3$), 0.89 (t, *J* = 7.3 Hz, 3H, CH_2CH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 155.4 (N*C*=O), 137.0 (Ar*C*), 128.5 (Ar*C*), 127.9 (Ar*C*), 127.9 (Ar*C*), 119.4 (*C*=C), 118.9 (C=*C*), 67.0 (O*C*H_2Ph), 46.0 [N*C*(2)H_2], 40.4 [d, N*C*(6)H_2], 36.9 (*C*$H_2CH_2CH_3$), 25.1 [d, NC*C*(5)H_2], 20.9 (*C*H_2CH_3), 13.8 (*C*H_3); ***LRMS*** *m/z* (ES^+) 260.16 $[M+H]^+$, 282.15 $[M+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{16}H_{22}NO_2$ 260.1645, found 260.1640, Δ = -1.943 ppm.

Benzyl 3-(2-methylbutyl)-5,6-dihydropyridine-1(2H)-carboxylate (45)

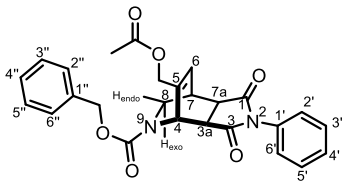


Adapted from the method of Bäckvall,[93] to a solution of acetate **42** (100 mg, 0.35 mmol) and Li_2CuCl_4 (0.1M in THF, 69 µL, 6.9 µmol) in dry THF (2.0 mL) at 0 °C was added *sec*-butylMgCl (25% wt. in THF, 0.59 mL, 1.04 mmol) dropwise over 1 min. The reaction mixture was stirred under N_2 at 0 °C for 30 mins. After quenching with saturated NH_4Cl solution the mixture was extracted with Et_2O (3 x 10 mL). The organic solutions were combined, washed with brine and dried over Na_2SO_4. The crude material was purified by Si gel FC (*n*-hex/EtOAc 6:1 → 4:1) to afford compound **45** as a colourless oil (60 mg, 60%); Si gel TLC $\boldsymbol{R_f}$ 0.33 (*n*-hex/EtOAc 6:1); ***ATR-IR*** ν_{max}/cm^{-1} 2958, 2916, 2873, 1701, 1425, 1360, 1279, 1235, 1198, 1103, 1029, 964, 764, 751, 696; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.43 – 7.27 (m, 5H, Ar*H*), 5.51 [*br.* s, 1H, *H*C(4)=C], 5.16 (s, 2H, OCH_2Ph), 3.82 [*br.* s, 2H, NC(2)H_2], 3.52 [*app.* t, *J* = 5.8 Hz, 2H, NC(6)H_2], 2.20 – 2.08 [*br.* s, 2H, C(5)H_2], 2.02 - 1.93 (*br.* s, 1H, C=CC$H_a$$H_2$), 1.75 (dd, *J* = 13.8, 8.4 Hz, 1H, C=CC$H_b$$H_2$), 1.56 – 1.44 (m, 1H, methine C*H*), 1.35 (m, 1H, C$H_a$$CH_3$), 1.11 (m, 1H, C$H_b$$CH_3$), 0.87 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.83 (d, *J* = 6.7 Hz, 3H, CHCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 158.8 (N*C*=O), 137.0 (Ar*C*), 134.5 (*C*=C), 128.5 (Ar*C*), 127.9 (Ar*C*), 120.8 (C=*C*), 67.0 (O*C*H_2Ph), 46.1 [N*C*(2)H_2], 42.7 (C=C*C*H_2), 40.5 [d, N*C*(6)H_2], 32.6 (methine *C*H), 29.4 (*C*H_2CH_3), 19.0 (CH_2*C*H_3), 11.4 (CH*C*H_3); ***LRMS*** *m/z* (ES^+) 288.20 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{18}H_{26}NO_2$ 288.1964, found 288.1971, Δ = 2.4 ppm.

(3a*S*,4*R*,7*R*,7a*S*)-benzyl 5-(acetoxymethyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (46)

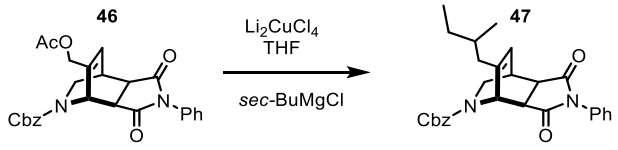


To an ice-cold solution of alcohol **34** (300 mg, 0.72 mmol) in dry CH_2Cl_2 (3.5 mL) was added Ac_2O (0.14 mL, 1.44 mmol). Et_3N (0.25 mL, 1.80 mmol) and 4-(dimethylamino)pyridine (9 mg, 0.072 mmol) were subsequently added to the reaction mixture which was then stirred at 0 °C for 30 mins. A few drops of MeOH were added to quench any excess Ac_2O. H_2O (5 mL) was added to the mixture which was then extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine and dried over Na_2SO_4. The crude material was concentrated in vacuo and purified by Si gel FC (*n*-hex/EtOAc 2:1) to afford acetate **46** as a white fluffy solid (275 mg, 81%)**; *mp*** 43-46 °C; Si gel TLC R_f 0.33 (*n*-hex/EtOAc 1:2); ***ATR-IR*** ν_{max}/cm^{-1} 3033, 2925, 2853, 1738, 1705, 1598, 1498, 1414, 1382, 1344, 1223, 1190, 1102, 1027, 754, 697, 622, 603; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



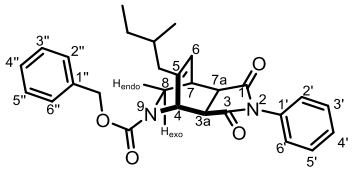
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 - 7.32 (m, 8H, Ar*H*), 7.16 [d, *J* = 7.6 Hz, 2H : C(2')*H* & C(6')*H*], 6.31 [m, 1H, C(6)*H*], 5.42 - 5.23 (m, 1H, C(4)*H*), 5.23 - 5.12 (m, 2H, OCH_2Ph), 4.74 - 4.44 (m, 2H, CH_2OAc), 3.60 - 3.40 [m, 3H : C(7)*H* & C(3a)*H* & C(8)H_{exo}], 3.22 - 3.08 [m, 2H, C(7a)*H* & C(8)H_{endo}], 2.0 – 1.84 (m, 3H, OAc); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 176.5 & 176.4 [*C*(1)], 174.3 & 174.1 [*C*(3)], 170.6 (Ac *C*=*O*), 155.1 & 154.7 (N*C*=O), 140.6 & 140.0 [*C*(5)], 136.4 (Ar*C*), 131.6 (Ar*C*), 129.3 (Ar*C*), 129.0 (Ar*C*), 128.7 (Ar*C*), 128.4 (Ar*C*), 128.2 (Ar*C*), 127.6 [*C*(6)], 126.6 (Ar*C*), 67.7 & 67.6 (OCH_2Ph), 63.3 (CH_2OAc), 48.6 & 48.0 [*C*(4)], 46.1 & 45.8 [*C*(8)], 45.5 & 45.3 [*C*(3a)], 41.5 [*C*(7a)], 33.5 & 33.3 [*C*(7)], 20.6 (O=CCH_3); ***LRMS*** *m/z* (ES^+) 461.17 $[M+H]^+$, 483.15 $[M+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{26}H_{24}N_2O_6Na$ 483.1532, found 483.1541, Δ = 1.9 ppm.

(3a*S*,4*R*,7*R*,7a*S*)-Benzyl 5-(2-methylbutyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (47)



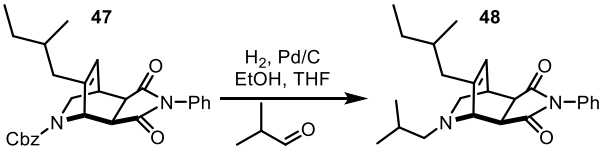
Adapted from the method of Bäckvall,[93] to a solution of acetate **46** (45 mg, 0.098 mmol) and Li_2CuCl_4 (0.1M in THF, 20 µL, 2.0 µmol) in dry THF (0.5 mL) at -82 °C was added *sec*-butylMgCl

(25% wt. in THF, 47 µL, 0.083 mmol) dropwise over 1 min. The reaction mixture was stirred under N_2 at -82 °C for 30 mins. After quenching with saturated NH_4Cl solution, the mixture was extracted with Et_2O (3 x 10 mL). The organic solutions were combined, washed with brine and dried over Na_2SO_4. The crude material was then purified by Si gel FC (*n*-hex/EtOAc 1:1) to give azabicyclooctane **47** as a white fluffy solid (35 mg, 92%); ***mp*** 36-40 °C; Si gel TLC R_f 0.49 (*n*-hex/EtOAc 2:3); ***ATR-IR*** ν_{max}/cm^{-1} 2945, 1709, 1499, 1455, 1414, 1383, 1342, 1258, 1188, 1101, 755, 697, 547; (^{1}H and ^{13}C NMR spectra complicated at RT due to th presence of rotamers *and* diastereoisomers)



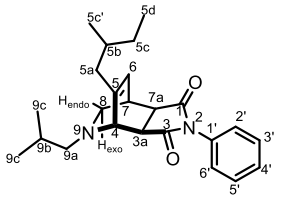
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 – 7.28 (m, 8H, Ar*H*), 7.13 [*app.* t, *J* = 7.2 Hz, 2H : C(2')*H* & C(6')*H*], 5.97 [m, 1H, C(6)*H*], 5.31 – 5.05 [m, 3H : O*CH*$_2$Ph & C(4)*H*], 3.54 – 3.37 [m, 3H : C(7)*H* & C(3a)*H* & C(8)*H*$_{exo}$], 3.18 – 3.05 [m, 2H : C(7a)*H* & C(8)*H*$_{endo}$], 2.25 – 0.61 (m, 13H, 2-MeBu); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 176.9 & 176.8 [*C*(1)], 174.8 & 174.5 [*C*(3)], 154.9 & 154.5 [N*C*=O), 145.3 & 144.6 & 144.5 [*C*(5)], 136.5 (Ar*C*), 136.3 (Ar*C*), 131.6 (Ar*C*), 131.6 (Ar*C*), 129.2 (Ar*C*), 128.9 (Ar*C*), 128.8 (Ar*C*), 128.7 (Ar*C*), 1 28.6 (Ar*C*), 128.5 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 128.2 (Ar*C*), 128.1 (Ar*C*), 127.9 (Ar*C*), 126.3 (Ar*C*), 124.61 & 124.55 & 124.08 & 124.01 [*C*(6)], 67.5 & 67.2 (O*C*H$_2$Ph), 50.3 & 49.8 & 49.6 [*C*(4)], 46.7 & 46.3 [*C*(8)], 45.4 & 45.2 [*C*(3a)], 41.8 & 41.7 & 41.6 (2-MeBu), 41.6 & 41.5 [*C*(7a)], 33.7 & 33.5 [*C*(7)], {32.2, 32.1, 32.0, 31.9, 30.0, 29.7, 28.1, 28.0, 19.5, 19.4, 18.6, 18.5, 11.4, 11.3, 10.9, 10.8 : 2-MeBu}; ***LRMS*** *m/z* (ES$^+$) 459.23 [M+H]$^+$, 500.26 [M+CH_3CN+H]$^+$; ***HRMS*** *m/z* calcd. for $C_{28}H_{31}N_2O_4$ 459.2284, found 459.2304, Δ = 4.4 ppm.

(3a*R*,4*S*,7*S*,7a*R*)-9-Isobutyl-5-(2-methylbutyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3(2H)-dione (48)



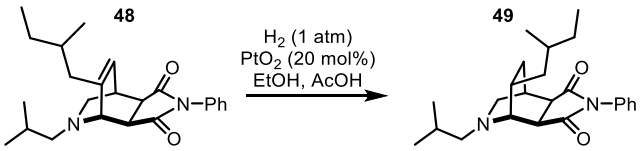
To a solution of *N*-Cbz alkene **47** (50 mg, 0.11 mmol) in EtOH (10 mL) and THF (1 mL) was added isobutyraldehyde (30 µL, 0.33 mmol) followed by Pd/C (10% wt., 23 mg, 0.022 mmol). The reaction mixture was subjected to a H_2 atmosphere for 50 mins. The mixture was then filtered over celite® and washed thoroughly with CH_2Cl_2. The crude material was then purified by Si gel FC (*n*-hex/EtOAc 4:1) to give *N*-alkyl alkene **48** as a white crystalline solid (39 mg, 93%); ***mp*** 72-

75 °C; Si gel TLC R_f 0.46 (*n*-hex/EtOAc 4:1); (^{1}H and ^{13}C NMR spectra complicated due to the presence of diastereoisomers)

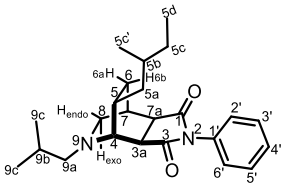


^{1}H NMR ($CDCl_3$, 500 MHz, 323 K) δ 7.45 – 7.40 [m, 2H : C(3')*H* & C(5')*H*], 7.37 – 7.32 [m, 1H, C(4')*H*], 7.18 – 7.14 [m, 2H : C(2')*H* & C(6')*H*], 5.91 [m, 1H, C(6)*H*], 3.75 – 3.69 [m, 1H, C(4)*H*], 3.47 [m, 1H, C(3a)*H*], 3.16 [m, 1H, C(7)*H*], 2.99 [*app.* ddd, *J* = 8.2, 3.2, 1.8 Hz, 1H, C(7a)*H*], 2.94 [m, 1H, C(8)H_{exo}], 2.29 [m, 1H, C(9a)$H_{\underline{a}}$], 2.17 – 1.78 [m, 4H : C(8)H_{endo} & C(9a)$H_{\underline{b}}$ & C(5a)H_2), 1.69 [m, 1H, C(9b)*H*], 1.58 – 1.54 [m, 1H, C(5b)*H*], 1.42 – 0.99 [m, 2H, C(5c)H_2]; 0.93 – 0.81 [m, 12H : C(9c)H_3 x 2 & C(5c')H_3 & C(5d)H_3); ***^{13}C NMR*** ($CDCl_3$, 126 MHz, 323 K) δ 178.0 [*C*(1)], 176.6 [*C*(3)], 144.05 & 143.95 [*C*(5)], 132.3 (Ar*C*), 129.2 (Ar*C*), 128.6 (Ar*C*), 126.6 (Ar*C*), 123.0 & 122.9 [C(6)], 66.4 & 66.3 [C(9a)], 58.9 & 58.7 [C(4)], 54.22 & 54.18 [C(8)], 45.7 & 45.6 [(C(3a)], 43.1 & 42.9 [*C*(5a)], 42.1 [*C*(7a)], 34.11 & 34.06 [*C*(7)], 32.1 [*C*(5b)], 30.1 & 28.9 [*C*(5c)], {27.3, 20.8, 20.7, 19.8, 19.2, 11.4, 11.2 : *C*(9c) & *C*(9c') & *C*(5c') & *C*(5d)]; ***LRMS*** *m/z* (ES^+) 381.25 $[M+H]^+$; **HRMS** *m/z* calcd. for $C_{24}H_{33}N_2O_2$ 381.2542, found 381.2536, Δ = -1.6 ppm.

(3a*R*,4*R*,5*S*,7*S*,7a*R*)-Benzyl 5-(2-methylbutyl)-1,3-dioxo-2-phenyloctahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (49)

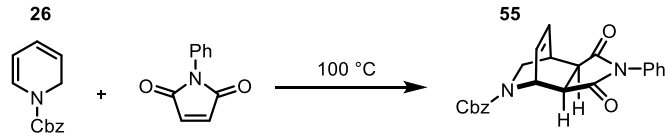


To a solution of alkene **48** (136 mg, 0.36 mmol) in EtOH (1.8 mL) and AcOH (0.18 mL) was added PtO_2 (2 mg, 0.0079 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 5 h. The mixture was then filtered over celite and washed thoroughly with CH_2Cl_2. The crude material was then purified by Si gel FC (*n*-hex/Et_2O 2:1 → 1:2) to give alkane **49** as a white fluffy solid (99 mg, 72%); ***mp*** 70-72 °C; Si gel TLC R_f 0.41 (*n*-hex/Et_2O 1:2); (^{1}H and ^{13}C NMR spectra complicated due to the presence of diastereoisomers)

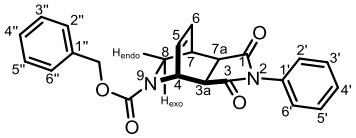


^{1}H NMR (acetone-d_6, 400 MHz) δ 7.50 [m, 2H : C(3')*H* & C(5')*H*], 7.44 – 7.38 [m, 1H, C(4')*H*], 7.36 – 7.30 [m, 2H : C(2')*H* & C(6')*H*], 3.46 – 3.37 [m, 1H, C(3a)*H*], 3.12 [m, 1H, C(7a)*H*], 2.98 [*app.* ddd, *J* = 15.7, 4.3, 2.0 Hz, 1H, C(4)*H*], 2.94 – 2.88 [m, 1H, C(8)H_{exo}], 2.76 [*app.* dt, *J* = 9.9, 1.8 Hz, 1H, C(8)H_{endo}], 2.44 – 2.36 [m, 2H, C(9a)H_2], 2.33 – 2.20 [m, 2H : C(7)*H* & C(5)*H*], 1.92 [m, 1H, C(6a)*H*], 1.79 [m, 1H, C(9b)*H*], 1.45 [m, 1H, C(5b)*H*], 1.36 – 1.20 [m, 2H : C(5a)$H_{\underline{a}}$ & C(5c)$H_{\underline{a}}$], 1.18 – 1.01 [m, 3H : C(5a)$H_{\underline{b}}$ & C(5c)$H_{\underline{b}}$ & C(6b)*H*], 0.93 [*app.* dd, *J* = 6.5, 2.0 Hz, 6H, C(9c)H_3 x 2], 0.85 – 0.77 [m, 6H : C(5d)H_3 & C(5c')H_3]; ***^{13}C NMR*** (acetone-d_6, 101 MHz) δ 179.2 [*C*(1)], 178.0 & 177.9 [*C*(3)], 134.02 & 133.97 [*C*(1')], 129.7 & 129.6 [*C*(3') & C(5')], 129.0 & 128.9 [*C*(4')], 127.52 & 127.45 [*C*(2') & *C*(6')], 65.3 [*C*(9a)], 56.9 & 55.7 [*C*(4)], 55.0 [*C*(8)], 44.0 [*C*(3a)], 43.9 [*C*(7a)], 42.7 & 42.5 [*C*(5a)], 32.9 [*C*(5)], 32.7 [*C*(5b)], {30.7, 30.3, 30.2, 30.1 : *C*(7) & *C*(6) & *C*(5c)}, 27.5 [*C*(9b)], 21.0 & 20.9 [*C*(9c)], {19.31, 19.26 : *C*(5d) & *C*(5c')}, {11.5, 11.4 : *C*(5d) or *C*(5c')}; ***LRMS*** *m/z* (ES^+) 383.28 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{24}H_{35}N_2O_2$ 383.2699, found 383.2719, Δ = 5.2 ppm.

(3a*R*,4*R*,7*S*,7a*R*)-Benzyl 1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (55)



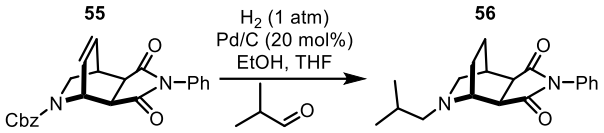
1,2-Dihydropyridine **26** (3.74 g, 17.4 mmol) and *N*-phenylmaleimide (4.70 g, 34.8 mmol) were heated at 100 °C for 18 h under N_2. The reaction mixture was purified by Si gel FC (*n*-hex/EtOAc 2:1) to give Diels-Alder adduct **55** as off-white pinkish fluffy solid (4.32 g, 64%); ***mp*** 54-58 °C; Si gel TLC R_f 0.19 (*n*-hex/EtOAc 2:1); ***ATR-IR*** ν_{max}/cm^{-1} 2924, 2853, 1709, 1497, 1454, 1414, 1384, 1187, 1104, 695; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



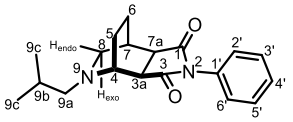
^{1}H NMR (DMSO-d_6, 400 MHz, **298 K**) δ 7.52 – 7.30 (m, 8H), 7.15 – 7.11 (m, 2H), 6.56 – 6.44 (m, 2H), 5.17 – 5.08 (m, 3H), 3.61 – 3.33 (m, 4H), 3.02 – 2.89 (m, 1H); ***^{1}H NMR*** (d-DMSO, 400 MHz, **393 K**) δ 7.49 – 7.30 (m, 8H, Ar*H*), 7.19 – 7.14 [m, 2H : C(2')*H* & C(6')*H*], 6.54 – 6.46 [m, 2H, C(5)*H* & C(6)*H*], 5.15 (s, 2H, OCH_2Ph), 5.12 – 5.06 [m, 1H, C(4)*H*], 3.55 [dd, *J* = 8.0, 4.0 Hz, 1H, C(3a)*H*], 3.48 [dd, *J* = 10.5, 2.1 Hz, 1H, C(8)H_{exo}], 3.38 [m, 1H, C(7)*H*], 3.33 [dd, *J* = 8.0, 3.2 Hz, 1H, C(7a)*H*], 3.03 [dd, *J* = 10.5, 2.7 Hz, 1H, C(8)H_{endo}]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz, **298 K**) δ 176.9, 175.2, 154.4, 153.7, 136.8, 136.7, 133.2, 132.0, 130.9, 130.7, 128.9, 128.5, 128.4, 128.3, 127.94, 127.87, 127.7, 127.6, 126.7, 66.3, 46.3, 45.9, 45.5, 45.2, 45.0, 44.9, 40.2, 40.15, 32.7, 32.5; ***^{13}C NMR***

(DMSO-d_6, 101 MHz, **393 K**) δ 175.8 [*C*(1)], 174.1 [*C*(3)], 153.7 (N*C*=O), 136.3 (Ar*C*), 132.5 [*C*(6)], 131.8 (Ar*C*), 130.2 [*C*(5)], 128.1 (Ar*C*), 127.7 (Ar*C*), 127.6 (Ar*C*), 127.5 (Ar*C*), 127.1 (Ar*C*), 126.8 (Ar*C*), 125.9 (Ar*C*), 65.8 (O*C*H$_2$Ph), 45.9 [*C*(4)], 44.9 [*C*(8)], 44.5 [*C*(3a)], 39.9 [*C*(7a)], 32.2 [*C*(7)]; ***LRMS*** *m/z* (ES$^+$) 389.15 [M+H]$^+$, 406.18 [M+NH$_4$]$^+$; ***HRMS*** *m/z* calcd. for $C_{23}H_{21}N_2O_4$ 389.1501, found 389.1508, Δ = 1.8 ppm.

(3a*R*,4*R*,7*S*,7a*R*)-9-Isobutyl-2-phenylhexahydro-1H-4,7-(epiminomethano)isoindole-1,3(2H)-dione (56)

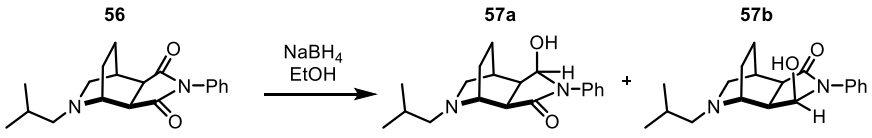


To a solution of alkene **55** (1.1 g, 2.83 mmol) in EtOH (25 mL) and THF (5 mL) was added Pd/C (10% wt., 603 mg, 0.57 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 18 h. The mixture was then filtered over celite and washed thoroughly with CH_2Cl_2. The solvent was removed in vacuo to yield alkane **56** as a white powder (839 mg, 95%); ***mp*** 116–120 °C; Si gel TLC R_f 0.45 (*n*-hex/EtOAc 2:1);



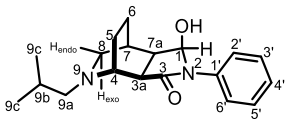
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 – 7.43 [m, 2H : C(3')*H* & C(5')*H*], 7.42 – 7.35 [m, 1H, C(4')*H*], 7.29 – 7.22 [m, 2H : C(2')*H* & C(6')*H*], 3.38 [m, 1H, C(3a)*H*], 3.14 – 3.03 [m, 2H : C(4)*H* & C(7a)*H*)], 2.92 [dd, *J* = 10.2, 2.7 Hz, 1H, C(8)H_{endo}), 2.69 [m, 1H, C(8)H_{exo}], 2.39 – 2.23 [m, 3H : C(7)*H* & C(9a)H_2], 1.99 – 1.87 [m, 1H, C(5)$H_{\underline{a}}$], 1.70 [m, 1H, C(9b)*H*], 1.65 – 1.51 [m, 3H : C(6)H_2 & C(5)$H_{\underline{b}}$], 0.92 – 0.87 [m, 6H, C(9c)H_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 179.1 [*C*(1)], 178.4 [*C*(3)], 132.5 [*C*(1')], 129.7 [*C*(3')], 129.1 [*C*(4')], 126.8 [*C*(2')], 65.6 [*C*(9a)], 56.1 [*C*(8)], 52.1 [*C*(4)], 43.5 [*C*(7a)], 43.0 [*C*(3a)], 28.7 [*C*(7)], 27.1 [*C*(9b)], 22.2 [*C*(5)], 21.1 [*C*(6)], 21.0 [*C*(9c)]; ***LRMS*** *m/z* (ES$^+$) 313.19 [M+H]$^+$; ***HRMS*** *m/z* calcd. for $C_{19}H_{25}N_2O_2$ 313.1916, found 313.1924, Δ = 2.6 ppm.

(1*R*,3a*R*,4*R*,7*S*)-1-Hydroxy-9-isobutyl-2-phenylhexahydro-1H-4,7-(epiminomethano)isoindol-3(2H)-one (57a) & (3*S*,3a*R*,4*R*,7*S*)-3-hydroxy-9-isobutyl-2-phenyloctahydro-1H-4,7-(epiminomethano)isoindol-1-one (57b)



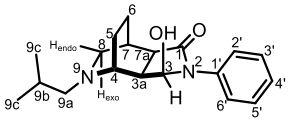
To a solution of imide **56** (520 mg, 1.67 mmol) in EtOH (8.3 mL) was added $NaBH_4$ (63 mg, 1.67 mmol) and the reaction stirred at RT for 10 h. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 x 50 mL). The organics were combined, washed with brine and dried over $MgSO_4$. After removing the solvent under reduced pressure, the crude material was purified using Si gel FC (EtOAc/MeOH 9.5:0.5 → 9:1) to give:

Lactamol **57a** as an white solid (68 mg, 13%); ***mp*** 119-121 °C; ***ATR-IR*** ν_{max}/cm^{-1} 3363, 2950, 2869, 2803, 1673, 1598, 1499, 1413, 1209, 1120, 1071, 732, 692; Si gel TLC R_f 0.42 (EtOAc/MeOH 9:1);



¹H NMR ($CDCl_3$, 400 MHz) δ 7.60 – 7.51 (m, 2H, Ar*H*), 7.40 – 7.32 (m, 2H, Ar*H*), 7.25 – 7.19 (m, 1H, Ar*H*), 5.24 [s, 1H, C(1)*H*], 3.13 [ddd, *J* = 10.2, 4.6, 1.7 Hz, 1H, C(3a)*H*], 2.92 – 2.87 [m, 1H, C(4)*H*], 2.72 [dd, J = 10.1, 2.3 Hz, C(8)H_{endo}] 2.64 [m, 1H, C(8)H_{exo}], 2.35 [m, 1H, C(7a)*H*], 2.25 – 2.11 [m, 2H, C9aH_2), 1.87 – 1.73 [m, 2H : C(7)*H* & C(5)$H_{\underline{a}}$], 1.64 [m, 1H, C(9b)*H*], 1.56 – 1.43 [m, 3H : C(5)$H_{\underline{b}}$ & C(6)H_2], 0.88 – 0.82 [m, 6H, C(9c)H_3 x 2]; ***¹³C NMR*** ($CDCl_3$, 101 MHz) δ 176.0 [*C*(3)], 137.5 (Ar*C*), 129.1 (Ar*C*), 129.1 (Ar*C*), 126.4 (Ar*C*), 123.5 (Ar*C*), 88.7 [*C*(1)], 65.1 [*C*(9a)], 56.0 [*C*(8)], 51.7 [*C*(4)], {43.2, 43.1 : *C*(3a) & *C*(7a)}, 28.5 [*C*(7)], 26.6 [*C*(9b)], {20.8, 20.7, 19.9 : *C*(5) & *C*(6) & C(9c)}; ***LRMS*** *m/z* (ES^+) 315.21 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{19}H_{27}N_2O_2$ 315.2073, found 315.2069, Δ = -1.3 ppm.

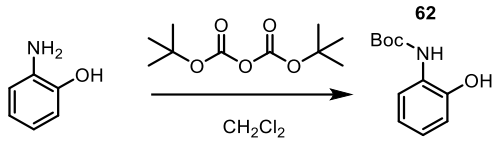
Lactamol **57b** as an off-white solid (59 mg, 11%); ***mp*** 137-139 °C; ***ATR-IR*** ν_{max}/cm^{-1} 3335, 2953, 2926, 2874, 1671, 1599, 1497, 1408, 1069, 733; Si gel TLC R_f 0.40 (EtOAc/MeOH 9:1);



¹H NMR ($CDCl_3$, 400 MHz) δ 7.58 – 7.52 (m, 2H, Ar*H*), 7.44 – 7.36 (m, 2H, Ar*H*), 7.32 – 7.19 (m, 1H, Ar*H*), 5.25 [s, 1H, C(3)*H*], 3.52 (*br* s, 1H, OH), 2.93 – 2.83 [m, 2H : C(7a)*H* & C(8)H_{endo}], 2.77 – 2.71 [m, 1H, C(4)*H*], 2.66 [m, 1H, C(3a)*H*], 2.57 [*app.* dt, *J* = 9.8, 2.4 Hz, 1H, C(8)H_{exo}], 2.30 [m, 2H, C(9a)H_2], 2.12 [m, 1H, C(7)*H*], 1.94 – 1.83 [m, 1H, C(5)*H*], 1.68 [m, 1H, C(9b)*H*], 1.62 – 1.37 [m, 3H : C(5)*H* & C(6)H_2], 0.90 [*app.* dd, *J* = 6.6, 4.1 Hz, 6H, C(9c)H_3 x 2]; ***¹³C NMR*** (101 MHz, $CDCl_3$) δ 175.9 [*C*(1)], 137.3 (Ar*C*), 129.3 (Ar*C*), 126.6 (Ar*C*), 123.8 (Ar*C*), 87.4 [*C*(3)], 65.1 [*C*(9a)], 55.9 [*C*(8)], 51.6 [*C*(4)], 43.0 [*C*(7a)], 41.8 [*C*(3a)], 28.0 [*C*(7)], 26.7 *C*(9b)], {20.8, 20.7, 20.6, 20.3 : *C*(5) & *C*(6) & *C*(9c)]; ***LRMS*** *m/z* (ES^+) 315.21 $[M+H]^+$; ***HRMS*** *m/z*: calcd. for $C_{19}H_{27}N_2O_2$ 315.2073, found 315.2081, Δ = 2.5 ppm.

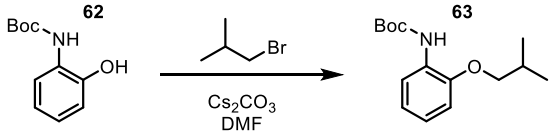
A mixture of lactamol **57a** and lactamol **57b** was also isolated (332 mg, 63%). Total combined yield of reaction: 459 mg, 87%.

Tert-Butyl (2-hydroxyphenyl)carbamate (62)[137]



2-Aminophenol (4.40 g, 40.32 mmol) and boc anhydride (8.80 g, 40.32 mmol) was dissolved in CH_2Cl_2 (15 mL) and stirred at RT overnight. After further diluting in CH_2Cl_2, the organic layer was washed sequentially with H_2O, diluted $NaHCO_3$ solution and brine. The organic layer was then dried over $MgSO_4$ and the solvent removed under reduced pressure to yield *N*-Boc phenol **62** as a pale yellow powder (7.94 g, 100 %); Si gel TLC $\boldsymbol{R_f}$ 0.47 (*n*-hex/EtOAc 3:2); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.17 (*br* s, 1H, N*H*), 7.13 – 6.99 (m, 2H, Ar*H*), 6.96 (dd, *J* = 8.2, 1.6 Hz, 1H, Ar*H*), 6.85 (td, *J* = 7.6, 1.5 Hz, 1H, Ar*H*), 6.68 (*br.* s, 1H, O*H*), 1.53 [s, 9H, (CH_3)$_3$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 155.5 (N*C*=O), 147.8 (Ar*C*), 126.0 (Ar*C*), 125.9 (Ar*C*), 121.8 (Ar*C*), 121.2 (Ar*C*), 119.2 (Ar*C*), 82.5 [O*C*(CH_3)$_3$], 28.7 [OC(*C*H_3)$_3$]; ***LRMS*** *m/z* (ES^+) 251.14 $[M+CH_3CN+H]^+$; ***HRMS*** *m/z calcd.* for $C_{13}H_{19}N_2O_3$ 251.1396, found 251.1404, Δ = 3.2 ppm. The spectroscopic data were in accordance with the literature.[137]

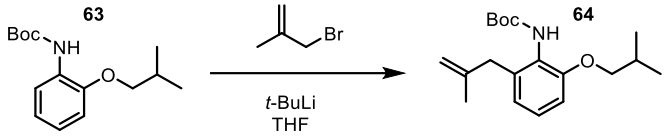
Tert-butyl (2-isobutoxyphenyl)carbamate (63)



According to the method of Bayly,[67] to a solution of phenol **62** in DMF (75 mL) was added Cs_2CO_3 (18.4 g, 56.70 mmol). After stirring the mixture at RT for 30 mins, isobutylbromide (6.16 mL, 56.70 mmol) was added. The reaction mixture was stirred at 60 °C under N_2 for 4 h. H_2O (100 mL) was added and the product was extracted with EtOAc (120 mL). The aqueous was further extracted with EtOAc (2 x 120 mL). The organic solutions were combined, washed with diluted brine (6 x 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by Si gel FC (*n*-hex/EtOAc 14:1 → 9:1) to afford aryl ether **63** as white solid chunks (6.23 g, 62%); ***mp*** 26-28 °C, Si gel TLC $\boldsymbol{R_f}$ 0.60 (*n*-hex/EtOAc 9:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.06 (*br.* s, 1H, N*H*), 7.06 (*br.* s, 1H, Ar*H*), 6.97 – 6.88 (m, 2H, Ar*H*), 6.86 – 6.79 (m, 1H, Ar*H*), 3.78 (d, *J* = 6.7 Hz, 2H, ArOCH_2), 2.15 (dp, *J* = 13.4, 6.7 Hz, 1H, CH_2CH), 1.53 [s, 9H, C(CH_3)$_3$], 1.05

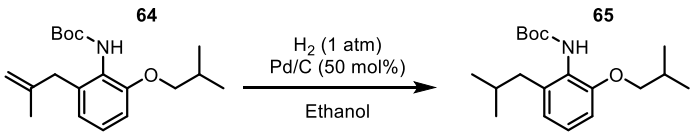
[d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 152.9 (N*C*=O), 147.0 (Ar*C*), 128.3 (Ar*C*), 122.3 (Ar*C*), 120.9 (Ar*C*), 118.1 (Ar*C*), 111.0 (Ar*C*), 80.3 [O*C*(CH$_3$)$_3$], 74.99 (O*C*H$_2$), 28.4 [OC(*C*H$_3$)$_3$], 28.2 (OCH$_2$*C*), 19.4 [CH(*C*H$_3$)$_2$]; ***LRMS*** *m/z* (ES$^+$) 266.14 [M+H]$^+$; ***HRMS*** *m/z* calcd. for $C_{15}H_{24}NO_3$ 266.1756, found 266.1762, Δ = 2.3 ppm.

Tert-butyl (2-isobutoxy-6-(2-methylallyl)phenyl)carbamate (64)



According to the method of Bayly,[67] to a cooled solution of aryl ether **63** (2.20 g, 8.30 mmol) in dry THF (21 mL) at -78 °C was added *tert*-BuLi (1.7M in hexane, 11.7 mL, 19.92 mmol) under N_2. The reaction mixture was stirred at -78 °C for 20 mins and then at -20 °C for 30 mins. 3-Bromo-2-methylpropene (1.84 mL, 18.26 mmol) was then added over a period of 3 mins. The reaction was stirred -20 °C under N_2 for 3 h after which it was quenched with H_2O. Saturated NH_4Cl solution was added and the mixture was extracted with EtOAc (2 x 50 mL). The organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by Si gel FC (*n*-hex/Et_2O 9.5:0.5 → 9:1 → 5:1) to give alkene **64** as a pale pinkish semi-solid (2.47 g, 42%); Si gel TLC R_f 0.32 (*n*-hex/EtOAc 9:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.11 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.80 (dd, *J* = 7.7, 1.3 Hz, 1H, Ar*H*), 6.75 (dd, *J* = 8.1, 1.3 Hz, 1H, Ar*H*), 5.91 (*br.* s, 1H, N*H*), 4.85 – 4.79 (m, 1H, C=C*H*$_a$), 4.71 – 4.64 (m, 1H, C=C*H*$_b$), 3.73 (d, *J* = 6.5 Hz, 2H, OC*H*$_2$), 3.36 (s, 2H, ArC*H*$_2$), 2.09 (*app.* dp, *J* = 13.2, 6.6 Hz, 1H, OCH$_2$C*H*), 1.67 (s, 3H, C(=C)C*H*$_3$), 1.47 [s, 9H, C(C*H*$_3$)$_3$], 1.03 [d, *J* = 7.1 Hz, 6H, CH(C*H*$_3$)$_2$]; ***^{13}C NMR*** (101 MHz, $CDCl_3$) δ 144.6 (Ar*C*), 138.1 (*C*=CH$_2$), 127.0 (Ar*C*), 125.1 (Ar*C*), 121.8 (Ar*C*), 111.9 (C=*C*H$_2$), 110.1 (Ar*C*), 76.7 [O*C*(CH$_3$)$_3$], 74.8 (O*C*H$_2$), 40.3 (Ar*C*H$_2$), 28.4 [OC(*C*H$_3$)$_3$], 28.3 (OCH$_2$*C*), 22.4 (C=C-*C*H$_3$), 19.3 [CH(*C*H$_3$)$_2$]; ***LRMS*** *m/z* (ES$^+$) 320.22 [M+H]$^+$; ***HRMS*** *m/z* calcd. for $C_{19}H_{30}NO_3$ 320.2226, found 320.2230, Δ = 1.2 ppm.

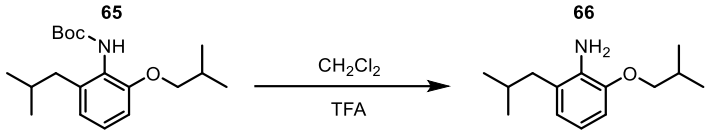
Tert-butyl (2-isobutoxy-6-isobutylphenyl)carbamate (65)



According to the method of Bayly,[67] to a solution of alkene **64** (3.43 g, 10.7 mmol) in EtOH (38 mL) was added Pd/C (10% wt., 570 mg, 0.54 mmol). The reaction was submitted to a H_2 atmosphere for 16 h. The mixture was then filtered over celite® and washed thoroughly with CH_2Cl_2. The crude material was concentrated in vacuo to give alkane **65** as a pale yellow solid (3.45 g, 100%); Si gel TLC R_f 0.33 (*n*-hex/EtOAc 9:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.10 (t, *J* = 8.0

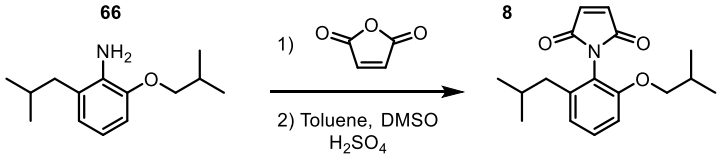
Hz, 1H, Ar*H*), 6.77 (dd, *J* = 7.8, 1.4 Hz, 1H, Ar*H*), 6.72 (dd, *J* = 8.3, 1.3 Hz, 1H, Ar*H*), 5.83 (*br.* s, 1H), 3.71 (d, *J* = 6.4 Hz, 2H, OCH_2), 2.52 (d, *J* = 7.1 Hz, 2H, ArCH_2), 2.09 (*app.* dp, *J* = 13.3, 6.6 Hz, 1H, OCH_2-C*H*), 1.90 (*app.* dp, *J* = 6.8 Hz, 1H, $ArCH_2CH$), 1.47 [*br.* s, 9H, C(CH_3)$_3$], 1.03 [d, *J* = 6.8 Hz, 6H, $OCH_2CH(CH_3)_2$], 0.89 [d, *J* = 6.7 Hz, 6H, $ArCH_2CH(CH_3)_2$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 154.6 (N*C*=O), 140.7 (Ar*C*), 127.0 (Ar*C*), 122.2 (Ar*C*), 109.5 (Ar*C*), 79.6 [O*C*(CH$_3$)$_3$], 74.7 (OCH_2), 41.0 (ArCH_2), {29.2, 28.4, 28.3 : OC(*C*H$_3$)$_3$ & OCH_2*C*H & $ArCH_2$*C*H}, 22.6, [CH(*C*H$_3$)$_2$], 19.3 [ether CH(*C*H$_3$)$_2$]; ***LRMS*** *m/z* (ES$^+$) 322.24 [M+H]$^+$, 385.35 [M+CH_3CN+Na]$^+$; ***HRMS*** *m/z* calcd. for $C_{21}H_{34}N_2O_3Na$ 385.2467, found 385.2474, Δ = 1.8 ppm.

2-Isobutoxy-6-Isobutylaniline (66)



According to the method of Bayly,[67] to a solution of *N*-Boc aniline **65** (3.54 g, 11.02 mmol) in CH_2Cl_2 (27 mL) was added TFA (11 mL). The reaction was stirred at RT for 20 mins. Volatiles were then removed under reduced pressure. The residue was diluted in EtOAc and washed sequentially with saturated $NaHCO_3$ (3 x 100 mL) and brine (3 x 100 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to afford aniline **66** as a dark orange oil (2.44 g, 100%); Si gel TLC ***R$_f$*** 0.61 (*n*-hex/Et_2O 4:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 6.83 – 6.55 (m, 3H, Ar*H*), 3.76 (d, *J* = 6.5 Hz, 2H, OCH_2), 3.59 (*br.* s, 2H, NH_2), 2.40 (d, *J* = 7.2 Hz, 2H, ArCH_2), 2.14 (*app.* dp, *J* = 13.3, 6.7 Hz, 1H, OCH_2C*H*), 1.96 (*app* dp, *J* = 13.6, 6.7 Hz, 1H, $ArCH_2$C*H*), 1.07 [d, *J* = 6.8 Hz, 6H, $OCH_2CH(CH_3)_2$], 0.97 [d, *J* = 6.6 Hz, 6H, $ArCH_2CH(CH_3)_2$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 146.8 (Ar*C*), 134.2 (Ar*C*-NH_2), 126.3 (Ar*C*-CH_2), 122.8 (Ar*C*), 117.4 (Ar*C*), 109.0 (Ar*C*), 74.7 (ArOCH_2), 40.9 (ArCH_2), {28.5, 27.8 : OCH_2*C*H & $ArCH_2$*C*H}, 22.8 [CH(*C*H$_3$)$_2$], 19.4 [ether CH(*C*H$_3$)$_2$]; ***LRMS*** *m/z* (ES$^+$) 222.19 [M+H]$^+$; ***HRMS*** *m/z* calcd. for $C_{14}H_{24}NO$ 222.1858, found 222.1855, Δ = -1.4 ppm.

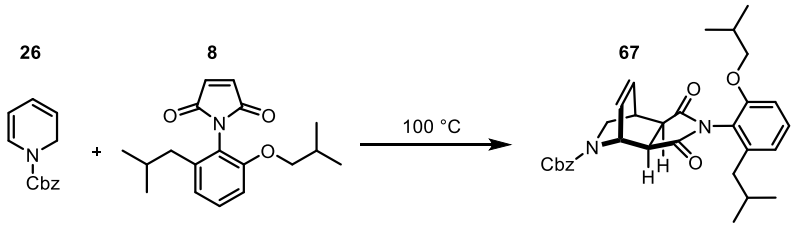
1-(2-Isobutoxy-6-isobutylphenyl)-1H-pyrrole-2,5-dione (8)



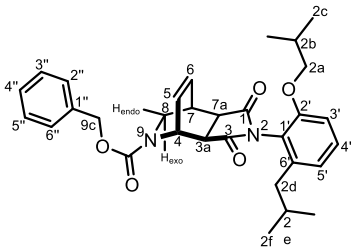
According to the method of Bayly,[67] aniline **66** (2.44 g, 11.04 mmol) and maleic anhydride (1.08 g, 11.04 mmol) were heated at 120 °C for 1 h. Toluene (3.7 mL) and DMSO (0.8 mL) were then added to the reaction flask, followed by concentrated H_2SO_4 solution (62 µL, 1.104 mmol). The brown solution was heated at 135 °C for 16 h after which the reaction was concentrated under

reduced pressure. The crude material was passed through a thick plug of Si and then concentrated under reduced pressure to give maleimide **8** as a brown viscous oil (3.23 g, 97%); Si gel TLC $\boldsymbol{R_f}$ 0.42 (*n*-hex/Et_2O 7:3); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.29 (t, *J* = 8.1 Hz, 1H, Ar*H*), 6.90 – 6.83 (m, 3H : *H*C=C*H* & Ar*H*), 6.79 (dd, *J* = 8.3, 1.1 Hz, 1H, Ar*H*), 3.68 (d, *J* = 6.3 Hz, 2H, OCH_2), 2.33 (d, *J* = 7.2 Hz, 2H, $ArCH_2$), 1.94 (*app.* dt, *J* = 13.2, 6.6 Hz, 1H, OCH_2CH), 1.77 (*app.* dt, *J* = 13.6, 6.8 Hz, 1H, $ArCH_2CH$), 0.92 – 0.85 [m, 6H, $OCH_2CH(CH_3)_2$], 0.85 [d, *J* = 6.5 Hz, 6H, $ArCH_2CH(CH_3)_2$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.5 (*C*=O), 155.1 (Ar*C*), 142.75 (Ar*C*), 134.6 (*C*=*C*), 130.1 (Ar*C*), 122.4 (Ar*C*), 119.2 (Ar*C*), 110.0 (Ar*C*), 74.6 ($ArOCH_2$), 41.1 ($ArCH_2$), {29.3, 28.3 : OCH_2CH & $ArCH_2CH$}, 22.8 [$CH(CH_3)_2$], 19.2 [ether $CH(CH_3)_2$]; ***LRMS*** *m/z* (ES^+) 302.18 $[M+H]^+$, 320.19 $[M+NH_4]^+$; ***HRMS*** *m/z* calcd. for $C_{18}H_{24}NO_3$ 302.1756, found 302.1770, Δ = 4.6 ppm.

Benzyl (3a*R*,4*R*,7*S*,7a*R*)-2-(2-isobutoxy-6-isobutylphenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-4,7-(epiminomethano)isoindole-9-carboxylate (67)



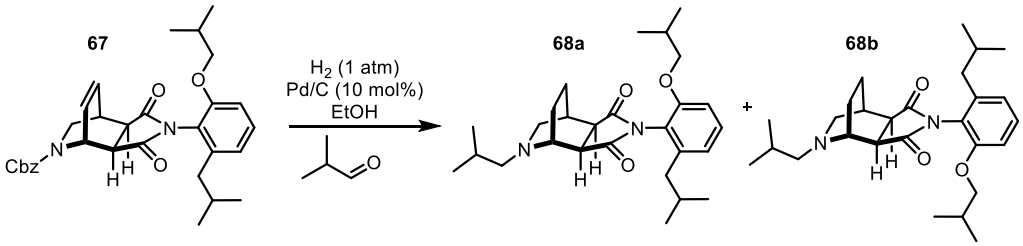
1,2-Dihydropyridine **26** (1.04 g, 3.46 mmol) and *N*-aryl maleimide **8** (1.28 g, 5.94 mmol) were heated at 100 °C for 16 h under N_2. The reaction mixture was purified by Si gel FC (*n*-hex/EtOAc 4:1 → 2:1) to give Diels-Alder adduct **67** as a white foam-like solid (1.28g, 75%); ***mp*** 48-51 °C; Si gel TLC $\boldsymbol{R_f}$ 0.22 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 2959, 2930, 1715, 1468, 1411, 1376, 1336, 1190; [^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers (Cbz) and atropisomers (N-aryl)];



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 – 7.25 (m, 6H, ArH), 6.79 [m, 2H : C(3')*H* & C(5')*H*], 6.63 – 6.36 [m, 2H, C(5)*H* & C(6)*H*], 5.50 – 5.11 [m, 3H : C(9c)H_2 & C(4)*H*], 3.67 [m, 2H, C(2a)H_2], 3.59 – 3.37 [m, 3H : C(7)*H* & C(3a)*H* & C(8)H_{exo}]; 3.22 – 3.07 [m, 2H : C(7a)*H* & C(8)H_{endo}], 2.18 [m, 2H, C(2d)H_2], 1.97 [m, 1H, C(2b)*H*], 1.67 (dp, *J* = 13.2, 6.4 Hz, 1H, C(2e)*H*], 0.98 – 0.89 [m, 6H, C(2c)H_3 x 2], 0.87 – 0.79 [m, 6H, C(2f)H_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 176.9, 176.8, 176.5, 176.3, 175.1, 174.9, 174.7, 174.5, 155.2, 154.8, 154.7, 153.7, 141.5, 140.7, 136.6, 136.5, 136.42, 136.36,

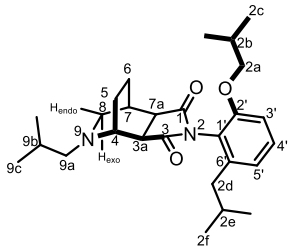
133.3, 133.0, 132.9, 132.6, 132.3, 131.9, 131.7, 131.3, 130.1, 128.7, 128.4, 128.3, 128.1, 127.7, 127.1, 122.4, 122.2, 120.0, 119.3, 110.1, 109.9, 75.0, 74.5, 67.6, 67.4, 46.7, 46.5, 46.3, 46.1, 46.1, 45.9, 41.5, 41.2, 40.6, 33.2, 33.0, 32.9, 32.7, 29.1, 28.7, 28.3, 28.0, 22.8, 22.6, 19.5, 19.3; ***LRMS*** *m/z* (ES^+) 517.27 $[M+H]^+$, 534.28 $[M+NH_4]^+$; ***HRMS*** *m/z* calcd. for $C_{31}H_{37}N_2O_5$ 517.2702, found 517.2708, Δ = 1.2 ppm.

(3a*R*,4*S*,7a*R*)-2-(2-Isobutoxy-6-isobutylphenyl)-9-isobutylhexahydro-1H-4,7-(epiminomethano)isoindole-1,3(2H)-dione (68)



To a solution of alkene **67** (1.28 g, 2.48 mmol) in EtOH (12.5 mL) was added Pd/C (10% wt., 263 mg, 0.25 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 18 h. The mixture was then filtered over celite® and washed thoroughly with CH_2Cl_2. The solvent was removed under reduced pressure and the crude mixture purified by Si gel FC (*n*-hex/EtOAc 7:3 → 1:1) to give:

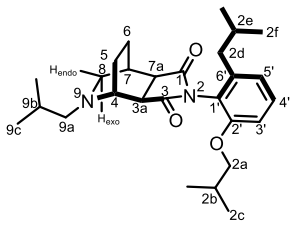
Imide **68a** as an off-white semi-solid (50 mg, 5%); ***ATR-IR*** ν_{max}/cm^{-1} 2952, 2870, 1711, 1582, 1467, 1375, 1273, 1181, 1053;Si gel TLC R_f 0.19 (*n*-hex/Et_2O 7:3);



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 [t, *J* = 8.0 Hz, C(4')], 6.86 [d, *J* = 8.0 Hz, 1H, C(5')*H*], 6.83 [d, *J* = 8.0 Hz, 1H, C(3')*H*], 3.73 [d, *J* = 6.2 Hz, 2H, C(2a)H_2], 3.41 [dd, *J* = 9.9, 4.2 Hz, 1H, C(3a)*H*], 3.18 – 3.03 [m, 2H : C(4)*H* & C(7a)*H*], 2.93 [dd, *J* = 10.2, 2.6 Hz, 1H, C(8)H_{endo}], 2.72 [*br.* m, 1H, C(8)H_{exo}], 2.42 – 2.27 [m, 3H : C(9a)H_2 & C(7)*H*], 2.24 [d, *J* = 7.2 Hz, 2H, C(2d)H_2], 2.03 m, 1H, C(2b)*H*], 1.94 – 1.81 [m, 3H : C(5)H_2 & C(6)H_a], 1.79 – 1.66 [m, 2H : C(9b)*H* & C(2e)*H*], 1.62 – 1.52 [m, 1H, C(6)H_b], 0.96 – 0.82 [m, 18H : C(9c)H_3 x 2 & C(2c)H_3 x 2 C(2f)H_3 x 2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 178.8 [*C*(1)], 178.1 [*C*(3)], 154.95 (Ar*C*), 141.0 (Ar*C*), 129.9 [*C*(4')], 122.3 [*C*(5')], 119.8 (Ar*C*), 110.1 [*C*(3')], 75.3 [*C*(2a)], 65.2 [*C*(9a)], 55.8 [*C*(8)], 51.5 [*C*(4)], {43.6, 43.2 : *C*(3a) & *C*(7a)], 41.1 [*C*(2d)],

28.9 [*C*(9b)], 28.1 [*C*(7)], 27.7 [*C*(2b)], 26.7 [*C*(2e)], 22.8 [*C*(2f)], 21.5 [*C*(5)], 20.6 [*C*(6)], {20.51, 19.48 : *C*(9c) & *C*(2c)]; ***LRMS*** *m/z* (ES^+) 441.31 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{27}H_{41}N_2O_3$ 441.3117, found 441.3130, Δ = 2.9 ppm.

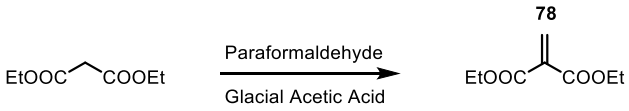
Imide **68b** as an off-white semi-solid (250 mg, 23%); ***ATR-IR*** ν_{max}/cm^{-1} 2953, 2871, 1711, 1586, 1464, 1369, 1270, 1181, 1052; Si gel TLC R_f 0.25 (*n*-hex/Et_2O 7:3);



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 [t, *J* = 8.0 Hz, C(4')], 6.86 [d, *J* = 8.0 Hz, 1H, C(5')*H*], 6.79 [d, *J* = 8.0 Hz, 1H, C(3')*H*], 3.69 [d, *J* = 6.2 Hz, 2H, C(2a)H_2], 3.39 [ddd, *J* = 10.4, 4.2, 1.8 Hz, 1H, C(3a)*H*], 3.14 [*br.* s, 1H, C(4)*H*], 3.08 [dd, *J* = 10.1, 3.8 Hz, 1H, C(7a)*H*], 2.93 [dd, *J* = 10.2, 2.7 Hz, 1H, C(8)H_{endo}], 2.76 [*br.* m, 1H, C(8)H_{exo}], 2.44 – 2.27 [m, 5H : C(2d)H_2 & C(9a)H_2 & C(7)*H*], 2.06 – 1.93 [m, 2H : C(2b)*H* & C(5)$H_{\underline{a}}$], 1.86 – 1.77 [m, 1H, C(9b)*H*] 1.77 – 1.61 [m, 4H : C(6)H_2 & C(5)$H_{\underline{b}}$ & C(2e)*H*], 0.97 – 0.82 [m, 18H : C(9c)H_3 x 2 & C(2c)H_3 x 2 C(2f)H_3 x 2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 179.3 [*C*(1)], 178.5 [*C*(3)], 153.8 (Ar*C*), 141.4 (Ar*C*), 129.8 [*C*(4')], 122.3 [*C*(5')], 120.7 (Ar*C*), 109.9 [*C*(3')], 74.4 [*C*(2a)], 65.2 [*C*(9a)], 55.9 [*C*(8)], 51.4 [*C*(4)], {43.7, 43.5 : *C*(3a) & *C*(7a)], 40.9 [*C*(2d)], 29.0 [*C*(9b)], 28.3 [*C*(2b)], 28.1 [*C*(7)], 26.7 [*C*(2e)], 22.6 [*C*(2f)], 21.6 [*C*(5)], 20.9 [*C*(6)], {20.7, 19.2 : *C*(9c) & *C*(2c)]; ***LRMS*** *m/z* (ES^+) 441.31 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{27}H_{41}N_2O_3$ 441.3117, found 441.3117, Δ = 0.0 ppm.

A mixture of imide **68a** and imide **68b** was also isolated (719 mg, 71%). Total combined yield of reaction: 1.09 g, 100%.

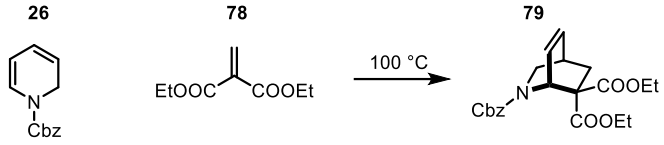
2-Methylenemalonate (78)



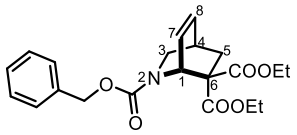
To glacial acid acid (50 mL) was added paraformaldehyde (6.0 g, 0.20 mol), diethyl malonate (15.2 mL, 0.10 mol), copper acetate (1.0 g, 5.50 mmol) and potassium acetate (1.0 g, 10.19 mmol). The reaction was heated at 100 °C for 3 h. Acetic acid was removed under reduced pressure until the contents of flask thickened to a turquoise paste which was subjected to distillation under reduced pressure (80-85 °C, 7 mmHg) to give methylene malonate **78** as a

colourless oil (6.0 g, 33 %); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 6.50 (s, 2H, C=CH_2), 4.27 (q, J = 7.1 Hz, 4H, OCH_2CH3), 1.31 (t, J = 7.1 Hz, 6H, OCH_2CH_3 x 2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 164.0 (*C*=O), 135.2 (*C*=CH_2), 134.0 (C=*C*H_2), 61.5 (O*C*H_2CH), 14.1 (OCH_2CH_3). *N.B.* Compound is unstable with polymerization occurred within minutes; compound should be purged with Ar and used immediately following distillation.

2-Benzyl 6,6-diethyl (1*R*,4*R*)-2-azabicyclo[2.2.2]oct-7-ene-2,6,6-tricarboxylate (79)

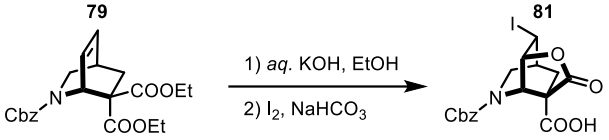


Adapted from the method of Reding,[86] to a dry flask containing freshly distilled diethyl 2-methylenemalonate **78** (5.8 g, 33.7 mmol) was added 1,2-dihydropyridine **26** (1.92 g, 8.92 mmol). The reaction mixture was then stirred at 100 °C under Ar for 20 h after which the mixture was concentrated under reduced pressure. The crude material was then purified by Si gel FC (*n*-hex/EtOAc 4:1 → 7:3) to give Diels-Alder adduct **79** as a viscous colourless oil (2.20 g, 65%); Si gel TLC R_f 0.28 (*n*-hex/Et_2O 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 2978, 1729, 1698, 1410, 1239, 1159, 1112, 1041, 861, 697; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers and the presence of polymerised diester)



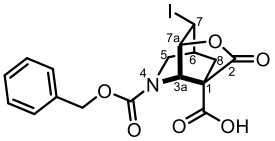
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.27 (m, 5H, Ar*H*), 6.54 – 6.45 [m, 1H, C(7)*H*], 6.44 – 6.35 [m, 1H, C(8)*H*], 5.40 – 5.26 [m, 1H, C(1)*H*], 5.18 – 5.02 (m, 2H, OCH_2Ph) , 4.20 – 4.05 (m, 4H, OCH_2CH_3 x 2), 3.43 – 3.30 [m, 1H, C(3)H_a], 2.98 [m, 1H, C(3)H_b], 2.89 – 2.78 [m, 1H, C(4)*H*], 2.59 [m, 1H, C(5)H_a] 1.82 [m, 1H, C(5)H_b], 1.30 – 1.15 [m, 6H, OCH_2CH_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.4, 170.2, 155.4, 155.0, 134.7, 134.5, 132.2, 131.8, 128.6, 128.5, 128.2, 127.9, 127.7, 67.1, 66.9, 62.3, 62.1, 62.1, 61.9, 61.6, 50.1, 49.5, 46.5, 46.3, 31.8, 31.77, 30.7, 30.4, 14.1, 14.0, 14.0, 14.0; ***LRMS*** *m/z* (ES^+) 388.18 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{21}H_{25}NO_6$ 388.1760, found 388.1761, Δ = 0.3 ppm. *N.B.* This compound typically retains a small amount of polymeric esters.[86]

(3*R*,3a*R*,7a*R*)-4-((Benzyloxy)carbonyl)-7-iodo-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-3(2H)-carboxylic acid (81)



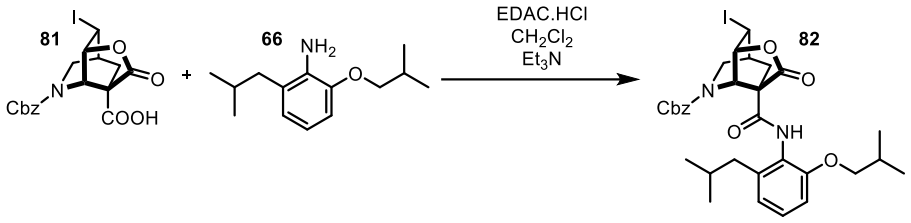
Adapted from the method of Reding,[86] diester **79** (400 mg, 1.03 mmol) was dissolved in absolute EtOH (4 mL). Aqueous 5M KOH (4 mL) was added to give a homogenous yellow solution that grew warm to the touch. This mixture was refluxed under N_2 with stirring for 2 h. The reaction mixture was cooled to RT and diluted with H_2O and then acidified with 4N HCl; the acidification was judged complete when the solution tested below pH 1, and a cloudy mixture was obtained. The mixture was extracted with Et_2O and the layers separated. The aqueous layer was saturated with NaCl, and extracted with Et_2O (5 x 80 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a viscous yellow oil. ^{1}H NMR indicated the presence of the desired diacid, along with appreciable quantities of Et_2O and EtOHl the acid was immediately taken to the next stage.

The crude diacid obtained above was dissolved in saturated $NaHCO_3$ solution (12 mL) to afford a cloudy white solution. Iodine (262 mg, 1.03 mmol) was added and the mixture was stirred vigorously. The iodine slowly dissolved to afford a deep brown solution. After stirring overnight, the mixture was carefully acidified with 4N HCl (caution: vigorous bubbling) until the pH was below 1. The mixture was extracted with Et_2O. The aqueous layer was saturated with NaCl and extracted with Et_2O (5 x 80 mL). The combined organic layers were then decolorized with a small amount of saturated aqueous $Na_2S_2O_3$ solution, and washed with brine. The solution was dried and concentrated in vacuo to give iodolactone **81** as a pale yellow foam-like solid (437 mg, 93%); ***mp*** 183-185 °C; Si gel TLC R_f 0.35 (CH_2Cl_2/MeOH 9:1); ***ATR-IR*** ν_{max}/cm^{-1} 3382, 2924, 1792, 1692, 1425, 1352, 1331, 1309, 1241, 1130, 995; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

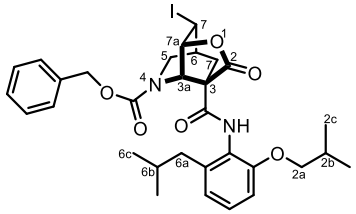


^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 – 7.30 (m, 5H, Ar*H*), 5.47 – 5.03 [m, 5H : OH & OC*H*$_2$Ph & C(3a)*H* & C(7a)*H*], 4.34 [d, *J* = 3.6 Hz, 1H, C(7)*H*], 4.00 [m, 1H, C(5)*H*$_a$], 3.52 – 3.41 [m, 1H, C(5)*H*$_b$], 2.74 [m, 1H, C(8)*H*$_a$], 2.54 – 2.40 [m, 1H, C(6)*H*], 2.25 [m, 1H, C(8)*H*$_b$]; ***^{13}C NMR*** weak spectra ($CDCl_3$, 101 MHz) δ 128.6 (Ar*C*), 128.4 (Ar*C*), 128.0 (Ar*C*), 82.5 [*C*(7a)], 68.4 (O*C*H$_2$Ph), 52.7 [*C*(3a)], 47.5 [*C*(5)], {33.3, 29.7, 23.9 : *C*(6) & *C*(7) & *C*(8)}; ***LRMS*** *m/z* (ES$^+$) 456.00 [M-H]$^-$; ***HRMS*** *m/z* calcd. for $C_{17}H_{15}INO_6$ 455.9944, found 455.9950, Δ = 1.3 ppm.

Benzyl (3*R*,3a*R*,7a*R*)-7-iodo-3-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-4(2H)-carboxylate (82)

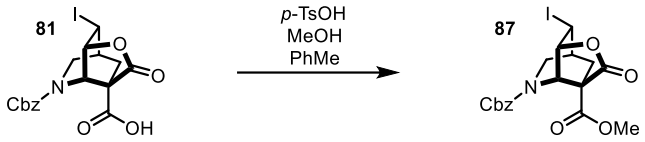


Lactone acid **81** (310 mg, 0.68 mmol) and aniline **66** (265 mg, 1.19 mmol) were transferred to a dry flask and placed on the high vac for 10 mins. After dissolving in dry CH_2Cl_2, EDAC.HCl (169 mg, 0.88 mmol) was added followed by Et_3N (0.14 mL, 1.02 mmol). The reaction mixture was stirred at RT for 20 h under a N_2 atmosphere. 1N HCl was then added and the organic layer separated. The organic solution was further washed with 1N HCl, saturated $NaHCO_3$ solution and brine before drying over $MgSO_4$. The solvent was removed in vacuo and the crude material was then purified by Si gel FC (*n*-hex/EtOAc 10:0 → 9:1 → 4:1) to give amide **82** as an off-white fluffy solid (275 mg, 61%); ***mp*** 137-140 °C; Si gel TLC $\boldsymbol{R_f}$ 0.25 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 3371, 2923, 1647, 783 (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

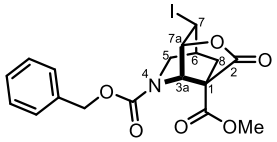


^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 & 8.37 (2 x *br.* s, 1H, N*H*), 7.47 – 7.26 (m, 5H, Ar*H*), 7.15 (m, 1H, Ar*H*), 6.82 – 6.65 (m, 2H, Ar*H*), 5.35 – 4.96 [m, 4H : OCH_2Ph & C(3a)*H* & C(7a)*H*], 4.38 (d, *J* = 3.7 Hz, 1H, C(7)*H*], 4.07 – 3.97 [m, 1H C(5)H_a], 3.77 – 3.50 [m, 3H : C(2a)H_2 & C(5)H_b], 2.67 – 2.22 [m, 5H : C(6a)H_2 & C(6)*H* & C(7)H_2), 2.18 – 1.93 [m, 1H, C(2b)*H*], 1.81 [m, 1H, C(6b)*H*], 1.04 – 0.93 [m, 6H, C(2c)H_3 x 2), 0.90 – 0.80 [m, 6H, C(6c)H_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 175.3, 166.0, 165.9, 155.5, 154.9, 154.1, 153.9, 140.1, 136.4, 136.2, 128.5, 128.1, 128.0, 127.8, 127.6, 123.0, 122.8, 122.3, 122.2, 109.5, 109.3, 82.0, 81.7, 74.6, 74.5, 67.8, 67.6, 52.0, 51.8, 47.5, 47.0, 41.2, 41.1, 33.7, 33.3, 32.8, 29.4, 29.3, 28.4, 23.4, 23.1, 22.6, 22.5, 19.3; ***LRMS*** *m/z* (ES^+) 661.18 $[M+H]^+$, 678.20 $[M+NH_4]^+$, 683.15 $[M+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{31}H_{38}IN_2O_6I$ 661.1775, found 661.1776, Δ = 0.2 ppm.

4-Benzyl 3-methyl (3*R*,3a*R*,7a*R*)-7-iodo-2-oxotetrahydro-3,6-methanofuro[3,2-b]pyridine-3,4(2H,3aH)-dicarboxylate (87)

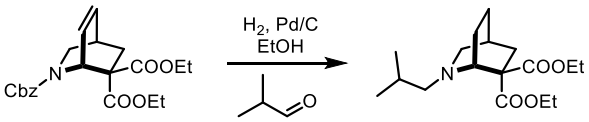


To a solution of iodolactone acid **81** (305 mg, 0.67 mmol) in toluene (1.7 mL) was added MeOH (0.54 mL, 13.4 mmol) and *para*-toluenesulfonic acid (127 mg, 0.67 mmol) and the mixture was stirred at 60 °C for 5 h. Saturated $NaHCO_3$ solution was added to the reaction after which extraction from the aqueous phase was performed using CH_2Cl_2 (4 x 50 mL). The organics were combined and dried over Na_2SO_4. The crude material was purified Si gel FC (*n*-hex/EtOAc 4:1 → 3:2) to give the methyl ester **87** as a sticky white semi-solid (237 mg, 75%); Si gel TLC $\boldsymbol{R_f}$ 0.29 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 2927, 1737, 1373, 1302, 1240, 1099, 1046, 998, 938, 846 (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

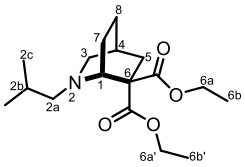


^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 – 7.31 (m, 5H, Ar*H*), 5.37 – 5.01 [m, 4H : OCH_2Ph & C(3a)*H* & C(7a)*H*), 4.33 [d, *J* = 3.7 Hz, 1H, C(7)*H*], 3.99 [*app.* tt, *J* = 11.5, 3.0 Hz, 1H, C(5)H_a], 3.82 & 3.62 (2 x s, 3H, COOCH_3), 3.48 – 3.40 [m, 1H, C(5)H_b], 2.78 [m, 1H, C(8)H_a], 2.52 – 2.41 [m, 1H, C(6)*H*], 2.27 – 2.17 [m, 1H, C(8)H_b]; ***^{13}C NMR*** weak spectra ($CDCl_3$, 101 MHz) δ 153.6, 143.8, 135.9, 128.7, 128.3, 128.1, 127.8, 82.5 , 67.8, 53.7, 53.4, 53.2, 52.7, 47.5, 47.3, 33.3, 33.3, 29.7, 25.0, 24.1, 23.8; ***LRMS*** *m/z* (ES^+) 472.02 $[M+H]^+$, 489.05 $[M+NH_4]^+$, 494.01 $[M+Na]^+$, 535.03 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{18}H_{19}NO_6I$ 472.0257, found 472.0234, Δ = -4.9 ppm.

Diethyl (1*R*,4*S*)-2-isobutyl-2-azabicyclo[2.2.2]octane-6,6-dicarboxylate (90)

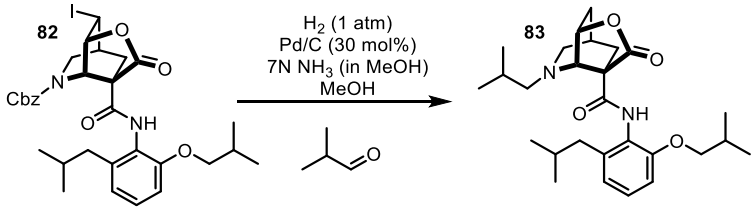


To a solution of *N*-Cbz-alkene **79** (105 mg, 0.27 mmol) in EtOH (1.5 mL) was added isobutyraldehyde (0.074 mL, 0.81 mmol) and Pd/C (10% wt., 29 mg, 0.027 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 24 h. The reaction mixture was then purified by Si gel FC (*n*-hex/Et_2O 4:1 → 3:1) to afford *N*-alkyl alkane **90** as an off-white paste (61 mg, 83%); Si gel TLC $\boldsymbol{R_f}$ 0.72 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 2951, 2869, 1734, 1462, 1365, 1296, 1237, 1196, 1157, 1109, 1068, 1024, 862; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

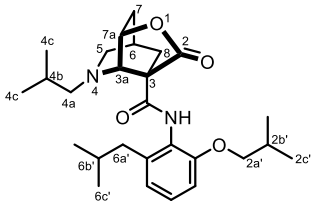


[1]H NMR ($CDCl_3$, 400 MHz) δ 4.35 – 3.90 [m, 4H : C(6a)H_2 & C(6a')H_2], 3.24 [t, *J* = 2.7 Hz, 1H, C(1)*H*], 3.00 [dt, *J* = 9.5, 3.1 Hz, 1H, C(*3*)H_a], 2.61 [dt, *J* = 14.0, 3.0 Hz, 1H, C(5)H_a], 2.30 [dd, *J* = 11.6, 5.4 Hz, 1H, C(2a)H_a], 2.20 – 2.07 [m, 2H : C(2a)H_b & C(3)H_b], 1.90 [m, 2H : C(5)H_b & C(7)H_a], 1.80 – 1.69 [m, 2H : C(4)*H* & C(7)H_b], 1.65 – 1.55 [m, 1H, C(2b)*H*], 1.55 – 1.36 [m, 2H, C(8)H_2), 1.21 [*app.* td, *J* = 7.1, 2.3 Hz, 6H : C(6b)H_3 & C(6b')H_3], 0.77 [*app.* dd, *J* = 9.7, 6.5 Hz, 6H, C(2c)H_3 x 2]; ***[13]C NMR*** ($CDCl_3$, 101 MHz) δ 171.5 (*C*=O), 171.0 (*C*=O), 64.9 [*C*(2a)], {61.2, 61.0 : *C*(6a) & *C*(6a')}, 59.2 [*C*(6)], 55.7 [*C*(1)], 54.4 [*C*(3)], 30.8 [*C*(5)], {26.4, 26.3 : *C*(4) & *C*(2b)], 25.2 [*C*(8)], 20.9 & 20.2 [*C*(2c)], 17.7 [*C*(7)], 14.0 [*C*(6b) & *C*(6b')]; ***LRMS*** *m/z* (ES^+) 312.22 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{17}H_{30}NO_4$ 312.2175, found 312.2169, Δ = -1.9 ppm.

(3*R*,3a*R*,7a*S*)-N-(2-isobutoxy-6-isobutylphenyl)-4-isobutyl-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-3(2H)-carboxamide (83)



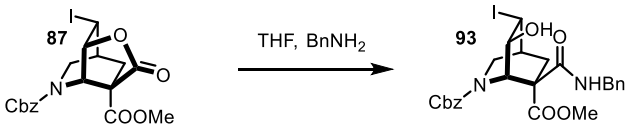
To a solution of *N*-Cbz amide **82** (241 mg, 0.36 mmol) in MeOH (5 mL) was added NH_3 (7N solution in MeOH, 0.16 mL, 1.09 mmol), isobutyraldehyde (0.10 mL, 1.09 mmol) and Pd/C (10% wt., 117 mg, 0.11 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 7 h. The reaction mixture was filtered over celite®, concentrated in vacuo and then purified *via* Si gel FC (*n*-hex/EtOAc 10:1 → 6:1) to afford *N*-alkyl amide **83** as an off-white residue (125 mg, 75%); Si gel TLC R_f 0.44 (*n*-hex/EtOAc 6:1); ***ATR-IR*** ν_{max}/cm^{-1} 3328, 2956, 2928, 2868, 1776, 1684, 1584, 1516, 1464, 1364, 1264, 1164, 1080, 1048;



[1]H NMR ($CDCl_3$, 400 MHz) δ 8.62 (s, 1H, N*H*), 7.12 (t, *J* = 7.9 Hz, 1H, Ar*H*), 6.77 (dd, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 6.73 (dd, *J* = 8.2, 1.3 Hz, 1H, Ar*H*), 4.71 [t, *J* = 6.4 Hz, 1H, C(7a)*H*], 3.71 [dd, *J* = 6.4, 2.1 Hz, 2H, C(2a')H_2], 3.64 [d, *J* = 6.0 Hz, 1H, C(3a)*H*], 3.10 [*app.* dt, *J* = 8.3, 3.4 Hz, 1H, C(5)H_a], 2.82

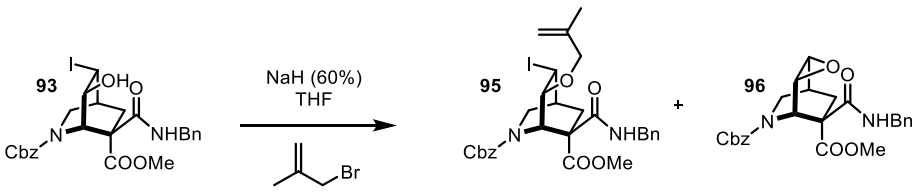
[dd, *J* = 12.8, 5.4 Hz, 1H, C(4a)H_a], 2.72 [dt, *J* = 8.4, 1.8 Hz, 1H, C(5)H_b], 2.51 – 2.39 [m, 3H : C(6a')H_2 & C(4a)H_b], 2.34 [*app.* dt, *J* = 13.7, 2.3 Hz, 1H, C(8)H_a], 2.15 [*br.* s, 1H, C(6)], 2.12 – 2.02 [m, 3H : C(8)H_b & C(2b')*H* & C(7)H_a], 1.93 – 1.79 [m, 2H : C(7)H_b & C(6b')*H*], 1.74 – 1.63 [m, 1H, C(4b)*H*], 1.01 [dd, *J* = 6.7, 3.3 Hz, 6H, C(2c')H_3 x 2], 0.87 [t, *J* = 6.3 Hz, 6H, C(6c')H_3 x 2], 0.82 [t, *J* = 6.6 Hz, 6H, C(4c)H_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 178.3 [*C*(2)], 168.7 (N-*C*=O), 154.1 (Ar*C*), 140.1 (Ar*C*), 127.4 (Ar*C*), 123.7 (Ar*C*), 122.2 (Ar*C*), 109.5 (Ar*C*), 76.1 [*C*(7a)], 74.6 [*C*(2a')], 65.8 [*C*(4a)], 62.0 [*C*(3a)], 54.9 [*C*(5)], 51.0 [*C*(3)], 41.3 [*C*(6a')], 34.2 [*C*(8)], 30.8 [*C*(7)], 28.4 [*C*(2b')], 26.7 [*C*(4b)], 25.9 [*C*(6)], 23.5 [*C*(6b')], 22.7 & 22.5 [*C*(6c)], 20.5 [*C*(4c)], 20.1 & 19.4 [*C*(2c)]; ***LRMS*** *m/z* (ES^+) 457.31 $[M+H]^+$, 520.32 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{27}H_{41}N_2O_4$ 457.3066, found 457.3087, Δ = 4.6 ppm.

2-Benzyl 6-methyl (1*S*,4*S*,6*S*,7*R*,8*R*)-6-(benzylcarbamoyl)-7-hydroxy-8-iodo-2-azabicyclo[2.2.2]octane-2,6-dicarboxylate (93)



To a solution of lactone methyl ester **87** (145 mg, 0.31 mmol) in dry THF (6 mL) was added benzylamine (0.17 mL, 1.55 mmol) and the reaction stirred under N_2 for 44 h. 1N HCl was then added to the reaction mixture and the product extracted with CH_3Cl (3 x 30 mL). The organics were combined, washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded benzylamide alcohol **93** as a fluffy white solid (147 mg, 83%); Si gel TLC R_f 0.26 (*n*-hex/EtOAc 3:2); ***ATR-IR*** ν_{max}/cm^{-1} 3398, 2923, 1729, 1683, 1531, 1450, 1417, 1345, 1294, 1219, 1118, 1079; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers and the chemical shifts were observed to change) ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.43 – 7.15 (m, 10H, Ar*H*), 6.99 & 6.60 (2 x m, 1H, N*H*), 5.34 – 4.98 (m, 2H, NCH_2Ph), 4.90 & 4.71 (2 x m, 1H, I-C*H*), 4.59 – 3.97 (m, 5H), 3.72 (m, 1H), 3.50 – 3.38 (m, 3H, COOCH_3), 3.34 – 3.18 (m, 1H), 2.93 – 2.69 (m, 1H), 2.54 – 2.30 (m, 2H); ***^{13}C NMR*** weak spectra ($CDCl_3$, 101 MHz) δ 168.4, 154.9, 137.7, 136.3, 128.9, 128.7, 128.6, 128.4, 128.3, 128.2, 127.9, 127.7, 127.5, 127.4, 80.6, 80.6, 67.5, 67.4, 55.9, 53.8, 53.6, 53.5, 53.2, 44.4, 44.3, 43.8, 36.7, 36.3, 33.3, 32.8, 31.2, 30.5; ***LRMS*** *m/z* (ES^+) 579.10 $[M+H]^+$, 596.12 $[M+NH_4]^+$, 642.10 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{25}H_{28}N_2O_6I$ 579.0992, found 579.0970, Δ = -3.8 ppm.

2-Benzyl 6-methyl (1*S*,4*S*,6*S*,7*R*,8*R*)-6-(benzylcarbamoyl)-8-iodo-7-((2-methylallyl)oxy)-2-azabicyclo[2.2.2]octane-2,6-dicarboxylate (95) & 6-benzyl 9-methyl (1*S*,2*S*,4*R*,5*S*,9*S*)-9-(benzylcarbamoyl)-3-oxa-6-azatricyclo[3.2.2.02,4]nonane-6,9-dicarboxylate (96)

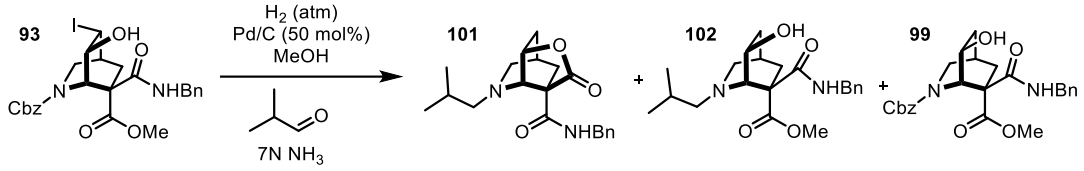


A solution of hydroxy amide **93** (57 mg, 0.099 mmol) in anhydrous THF (0.5 mL) was cooled to 0 °C. NaH (60% dispersion in mineral oil, 4.7 mg, 0.12 mmol) was added and the reaction stirred at 0 °C under N_2 for 1 h. 3-Bromo-2-methylprop-1-ene (10.7 µL, 0.11 mmol) was then added and the reaction stirred at 0 – 5 °C for 1 h. The reaction was quenched with H_2O and extracted with EtOAc (3 x 5 mL). The organics were combined, washed with brine and dried over $MgSO_4$. The crude mixture was purified by Si gel FC (*n*-hex/Et_2O 1:4 → 3:7) to give:

Ether **95** as an off-white paste (19.3 mg, 31%); Si gel TLC R_f 0.50 (*n*-hex/Et_2O 1:4); ***ATR-IR*** ν_{max}/cm^{-1} 3375, 1726, 1690, 1529, 1412, 1342, 1295, 1215, 1019; (^1H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers) ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.46 – 7.26 (m, 8H, Ar*H*), 7.23 – 7.15 (m, 2H, Ar*H*), 6.77 – 6.59 (m, 1H, N*H*), 5.30 – 5.04 (m, 2H), 5.03 – 4.84 (m, 2H), 4.79 – 4.66 (m, 1H), 4.62 – 4.51 (m, 1H), 4.32 – 4.01 (m, 3H), 3.97 – 3.85 (m, 2H), 3.77 – 3.65 (m, 1H), 3.59 – 3.50 (m, 3H), 3.31 – 3.20 (m, 1H), 3.06 – 2.91 (m, 1H), 2.63 – 2.45 (m, 1H), 2.46 – 2.30 (m, 1H), 1.78 – 1.64 (m, 3H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz_3) δ 172.2, 171.9, 166.0, 154.9, 140.8, 137.7, 136.5, 128.7, 128.5, 128.2, 128.1, 127.8, 127.8, 127.6, 113.8, 113.6, 85.1, 85.0, 73.2, 73.2, 67.4, 67.4, 55.9, 53.3, 53.2, 52.5, 51.9, 44.6, 44.4, 36.6, 30.4, 29.6, 29.3, 29.2, 19.5, 19.5; ***LRMS*** *m/z* (ES^+) 633.15 $[M+H]^+$, 650.17 $[M+NH_4]^+$, 696.16 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{29}H_{34}N_2O_6I$ 633.1462, found 633.1460, Δ = -0.3 ppm.

Epoxide **96** as an off-white paste (5.7 mg, 13%); Si gel TLC R_f 0.50 (*n*-hex/Et_2O 1:4); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.43 – 7.20 (m, 10H), 5.76 – 4.94 (m, 4H), 4.57 – 4.35 (m, 2H), 3.67 – 3.59 (m, 1H), 3.59 – 3.36 (m, 3H), 3.36 – 3.20 (m, 2H), 2.64 – 2.45 (m, 2H), 2.26 – 2.08 (m, 1H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.7, 127.7, 127.6, 67.3, 67.1, 58.3, 53.2, 53.1, 52.4, 52.0, 50.3, 50.0, 49.7, 43.9, 43.7, 43.3, 43.2, 29.7, 29.5, 29.1, 28.5; ***LRMS*** *m/z* (ES^+) 451.19 $[M+H]^+$, 468.12 $[M+NH_4]^+$, 473.17 $[M+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{25}H_{27}N_2O_6$ 451.1869, found 451.1867, Δ = -0.4 ppm.

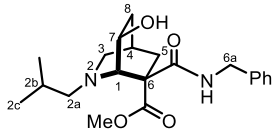
(3*R*,3a*R*,7a*S*)-N-benzyl-4-isobutyl-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-3(2H)-carboxamide (101) & methyl (1*S*,4*R*,6*S*,7*S*)-6-(benzylcarbamoyl)-7-hydroxy-2-isobutyl-2-azabicyclo[2.2.2]octane-6-carboxylate (102) & 2-Benzyl 6-methyl (1*S*,4*R*,6*S*,7*S*)-6-(benzylcarbamoyl)-7-hydroxy-2-azabicyclo[2.2.2]octane-2,6-dicarboxylate (99)



To a solution of *N*-Cbz hydroxy amide **93** (80 mg, 0.14 mmol) in MeOH (1.5 mL) was added NH_3 (7N in MeOH, 40 µL, 0.28 mmol), isobutyraldehyde (38 µL, 0.42 mmol) and Pd/C (10% wt., 74 mg, 0.07 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 20 h. The reaction mixture was then concentrated in vacuo and then purified by Si gel FC (*n*-hex/EtOAc 3:2) to give:

N-Alkyl lactone **101** as an off-white semi-solid (7.6 mg, 16%); Si gel TLC $\boldsymbol{R_f}$0.66 (*n*-hex/EtOAc 3:7); ***ATR-IR*** ν_{max}/cm^{-1}3329, 2956, 2927, 2873, 1774, 1649, 1454, 1332, 1308, 1228, 1164, 1123, 997; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.51 (*br.* s, 1H), 7.36 – 7.26 (m, 10H), 4.66 (t, *J* = 6.4 Hz, 1H), 4.58 – 4.42 (m, 2H), 3.59 (d, *J* = 6.0 Hz, 1H), 3.06 (dt, *J* = 8.7, 3.4 Hz, 1H), 2.81 – 2.70 (m, 2H), 2.42 (dd, *J* = 12.7, 8.9 Hz, 1H), 2.29 (dt, *J* = 13.8, 2.4 Hz, 1H), 2.13 (m, 1H), 2.03 (ddt, *J* = 14.8, 6.9, 2.1 Hz, 1H), 1.95 (dt, *J* = 13.9, 3.2 Hz, 1H), 1.84 (ddd, *J* = 15.0, 4.1, 1.9 Hz, 1H), 1.74 – 1.59 (m, 1H), 0.87 – 0.80 (m, 6H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 169.9, 138.1, 128.7, 127.6, 127.4, 76.0, 65.7, 62.2, 54.9, 50.9, 43.5, 33.6, 30.8, 26.7, 25.8, 20.5, 20.1; ***LRMS*** *m/z* (ES$^+$) 343.2 $[M+H]^+$, 365.2 $[M+Na]^+$, 406.2 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{20}H_{27}N_2O_3$ 343.2022, found 343.2023, Δ = 0.3 ppm.

N-Alkyl alcohol **102** as an off-white semi-solid (14 mg, 27%); Si gel TLC $\boldsymbol{R_f}$0.56 (*n*-hex/EtOAc 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 3328, 2924, 2853, 1784, 1738, 1651, 1532, 1456, 1272, 1227, 1078, 998;

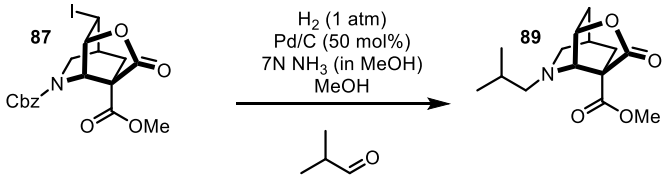


^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 – 7.29 (m, 3H, Ar*H*), 7.24 (m, 2H, Ar*H*), 6.68 – 6.29 (*br.* t, 1H, N*H*), 4.44 [*AB*, 2 x dd, *J* = 14.8, 6.0 Hz, 2H, C(6a)H_2], 4.15 – 4.05 [m, 2H : O*H* & C(7)*H*], 3.75 (s, 3H, OCH_3), 3.48 [d, *J* = 2.8 Hz, 1H, C(1)*H*], 2.91 [*app.* dt *J* = 9.6, 2.4 Hz, 1H, C(3)H_a], 2.69 [*app.* dt, J = 13.6, 2.8 Hz, 1H, C(5)H_a], 2.37 [dd, *J* = 11.7, 5.3 Hz, 1H, C(2a)H_a], 2.21 [dd, *J* = 11.7, 9.4 Hz, 1H, C(2a)H_b], 2.16 – 2.06 [m, 3H : C(3)H_b & C(8)H_a & C(5)H_b], 1.98 – 1.92 [m, 1H, C(4)*H*], 1.62 – 1.56 [m, 1H, C(2b)*H*], 1.42 [m, 1H, C(8)H_b], 0.78 [dd, *J* = 12.1, 6.6 Hz, 6H, C(2c)H_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.1 (O=*C*OMe), 172.2 (O=*C*NBn), 137.6 (Ar*C*), 128.8 (Ar*C*), 127.6 (Ar*C*), 127.5 (Ar*C*), 64.7 [*C*(2a)], 64.0 [*C*(7)], 62.0 [*C*(1)], 59.8 [*C*(6)], 52.9 (O*C*H$_3$), 52.6 [*C*(3)], 44.0 [*C*(6a)], 37.3 [*C*(8)], 30.8 [*C*(5)], 26.7 [*C*(4)], 26.5 [*C*(2b)], 20.8 & 20.1, [*C*(2c)]; ***LRMS*** *m/z* (ES$^+$) 375.23 $[M+H]^+$, 397.21

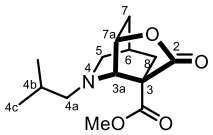
$[M+Na]^+$, 438.24 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{21}H_{31}N_2O_4$ 375.2284, found 375.2299, Δ = 4.0 ppm.

N-Cbz alcohol **99** as an off-white semi-solid (21 mg, 33%); Si gel TLC R_f 0.26 (*n*-hex/EtOAc 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 3359, 2927, 1725, 1690, 1530, 1417, 1294, 1216, 1102; (^1H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers) ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.45 – 7.15 (m, 10H), 6.76 & 6.38 (2 x t, *J* = 5.7 Hz, 1H), 5.29 – 4.94 (m, 3H), 4.55 – 4.27 (m, 2H), 4.19 – 4.07 (m, 1H), 3.48 – 3.42 (m, 3H), 3.30 (*br.* m, 1H), 3.25 – 3.10 (m, 2H), 2.77 – 2.67 (m, 0.5H), 2.54 – 2.44 (m, 1H), 2.25 – 2.11 (m, 1.5H), 2.08 – 1.92 (m, 1H), 1.58 – 1.48 (m, 1H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 172.7, 172.4, 170.7, 169.5, 155.1, 154.9, 137.9, 137.4, 136.6, 136.6, 128.8, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 127.7, 127.5 , 67.2, 67.1, 67.0, 66.9, 56.8, 56.7, 53.2, 53.0, 52.4, 52.6, 46.5, 46.1, 44.1, 35.7, 35.2, 29.7, 29.3, 26.2, 26.1; ***LRMS*** *m/z* (ES^+) 453.2 $[M+H]^+$, 475.2 $[M+Na]^+$, 516.2 $[M+CH_3CN+Na]^+$.

Methyl (3*R*,3a*R*,7a*S*)-4-isobutyl-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-3(2H)-carboxylate (89)



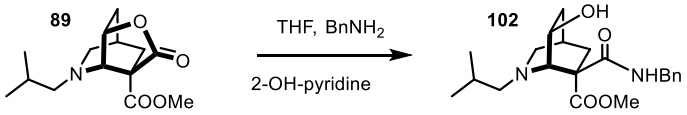
To a solution of *N*-Cbz methyl ester **87** (250 mg, 0.53 mmol) in MeOH (5.3 mL) was added NH_3 (7N in MeOH, 0.23 mL, 1.59 mmol), isobutyraldehyde (0.15 mL, 1.59 mmol) and Pd/C (10% wt., 282 mg, 0.27 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 7 h. The reaction mixture was concentrated in vacuo and then purified by Si gel FC (*n*-hex/Et_2O 6:1 → 3:2) to afford the *N*-alky lactone **89** as an off-white semi-solid (123 mg, 87%); Si gel TLC R_f 0.46 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 2953, 2868, 1784, 1739, 1459, 1437, 1312, 1270, 1227, 1163, 1078, 1056, 998;



^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.74 [t, *J* = 6.4 Hz, 1H, C(7a)*H*], 3.94 [d, *J* = 5.8 Hz, 1H, C(3a)*H*], 3.81 (s, 3H, OCH_3), 2.92 [dt, *J* = 9.3, 3.1 Hz, 1H, C(5)H_a], 2.64 [*app.* dt, *J* = 9.3, 2.1 Hz, 1H, C(5)H_a], 2.54 [*app.* dt, *J* = 14.5, 2.4 Hz, 1H, C(8)H_a], 2.44 – 2.27 [m, 2H, C(4a)H_2], 2.15 – 2.07 [*br.* m, 1H, C(6)*H*], 2.03 – 1.90 [m, 2H : C(8)H_b & C(7)H_a], 1.85 [ddd, *J* = 15.1, 4.0, 2.2 Hz, 1H, C(7)H_b], 1.68 [m, 1H, C(4b)*H*), 0.83 [*app.* dd, *J* = 6.6, 3.7 Hz, 6H, C(4c)H_3 x 2); ***^{13}C NMR*** weak spectra ($CDCl_3$, 101 MHz)

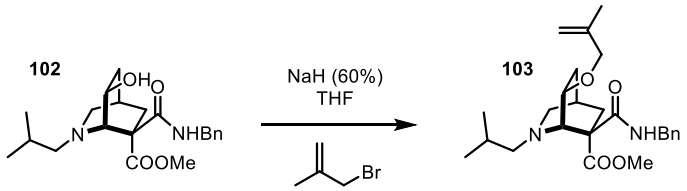
δ {170.7 [*C*(2)] – from HSQC}, 76.3 [*C*(2)], 65.5 [*C*(4a)], 62.8 [*C*(3a)], 55.8 [*C*(5)], 53.0 (OC*H*$_3$), 31.3 [*C*(7)], 30.1 [*C*(8)], 26.5 [*C*(4b)], 25.4 [*C*(6)], 20.3 & 20.0 [*C*(4c)]; ***LRMS*** *m/z* (ES^+) 268.16 $[M+H]^+$, 309.18 $[M+CH_3CN+H]^+$; ***HRMS*** *m/z*: calcd. for $C_{14}H_{22}NO_4$ 268.1549, found 268.1556, Δ = 2.6 ppm.

Methyl (1*S*,4*R*,6*S*,7*S*)-6-(benzylcarbamoyl)-7-hydroxy-2-isobutyl-2-azabicyclo[2.2.2]octane-6-carboxylate (102)

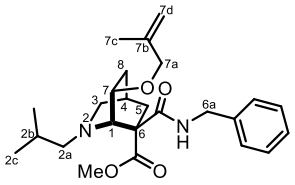


To a solution of lactone methyl ester **89** (31 mg, 0.12 mmol) in dry THF (2.3 mL) was added 2-hydroxypyridine (55mg, 0.58 mmol) and benzylamine (0.13 mL, 1.16 mmol) and the reaction stirred under N_2 for 3 days at RT. The reaction mixture was concentrated in vacuo and then purified by Si gel FC (n-hex/EtOAc 4:1 →1:1) to yield benzyl amide **102** as a yellow solid (33 mg, 77%). See above for spectroscopic data.

Methyl (1*S*,4*R*,6*S*,7*S*)-6-(benzylcarbamoyl)-2-isobutyl-7-((2-methylallyl)oxy)-2-azabicyclo[2.2.2]octane-6-carboxylate (103)



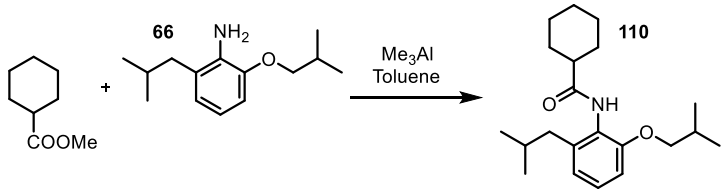
A solution of hydroxy amide **102** (32.5 mg, 0.090 mmol) in anhydrous DMF (0.6 mL) was cooled to 0 °C. NaH (60% dispersion in mineral oil, 4.5 mg, 0.11 mmol) was added and the reaction stirred at 0 °C under N_2 for 1 h. 3-Bromo-2-methylpropene (17 µL, 0.17 mmol) was then added and the reaction stirred at 0 – 5 °C for 40 mins. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 3 mL). The organics were combined, washed with brine and dried over $MgSO_4$. The crude mixture was purified by Si gel FC (*n*-hex/EtOAc 6:1 → 3:2) to afford **103** as an orange semi-solid (32.7 mg, 88%); Si gel TLC R_f 0.48 (*n*-hex/EtOAc 3:2); ***ATR-IR*** ν_{max}/cm^{-1} 3395, 2924, 2847, 1736, 1670, 1520, 1455, 1209, 1077;



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.17 [m, 6H : Ar*H* x 5 & N*H*], 4.94 [*br.* s, 1H, C(7d)H_a], 4.88 [*br.* s, 1H, C(7d)H_a], 4.54 [dd, *J* = 14.8, 6.0 Hz, 1H, C(6a)H_a], 4.24 [dd, *J* = 14.8, 4.7 Hz, 1H, C(6a)H_b],

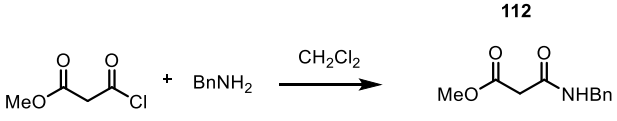
3.85 – 3.75 [m, 3H : C(7)*H* & C(7a)H_2], 3.73 (s, 3H, OCH_3), 3.41 [d, *J* = 2.7 Hz, 1H, C(1)*H*], 2.95 [*app.* dt, *J* = 9.4, 2.7 Hz, 1H, C(3)H_a], 2.58 – 2.45 [m, 2H, C(5)H_2], 2.36 [dd, *J* = 11.5, 5.3 Hz, 1H, C(2a)H_a], 2.20 [dd, *J* = 11.6, 9.2 Hz, 1H, C(2a)H_b], 2.10 [d, *J* = 9.3 Hz, 1H, C(3)H_b], 2.04 – 1.90 [m, 2H : C(8)H_a & C(4)*H*], 1.70 [s, 3H, C(7c)H_3], 1.64 – 1.53 [m, 2H : C(8)H_b & C(2b)*H*], 0.81 [*app.* t, *J* = 6.8 Hz, 6H, C(2c)H_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.0 (O=*C*OMe), 168.8 (O=*C*NBn), 142.2 [*C*(7b)], 138.5 (Ar*C*), 128.6 (Ar*C*), 127.7 (Ar*C*), 127.2 (Ar*C*), 112.2 [*C*(7d)], 72.1 [*C*(7a)], 70.8 [*C*(7)], 64.8 [*C*(2a)], 60.7 [*C*(1)], 59.5 [*C*(6)], 53.2 [*C*(3)], 52.6 (O*C*H_3), 44.2 [*C*(6a)], 33.3 [*C*(8)], 29.0 [*C*(5)], 26.6 [*C*(4)], 26.5 [*C*(2b)], 20.8 & 20.0 [*C*(2c)], 19.5 [*C*(7c)]; ***LRMS*** *m/z* (ES^+) 429.3 $[M+H]^+$.

***N*-(2-Isobutoxy-6-isobutylphenyl)cyclohexanecarboxamide (110)**



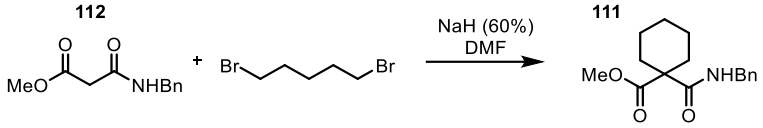
To a solution of aniline **66** (40 mg, 0.18 mmol) in dry toluene (0.3 mL) was added trimethylaluminium (2.0M in hexane, 0.08 mL, 0.16 mmol) at 0 °C. After being stirred for 20 mins at 0 °C, methyl cyclohexanecarboxylate (0.017 mL, 0.12 mmol) was added to the mixture. The reaction mixture was stirred under N_2 for 1 h at RT and then for 16 h at 50 °C. The reaction was quenched with MeOH and then partitioned between saturated $NaHCO_3$ solution and EtOAc (3 x 5 mL). The organics were combined, washed with brine and dried over Na_2SO_4 and evaporated to dryness. The crude material was purified by Si gel FC (*n*-hex/EtOAc 10:1 → 4:1) to provide amide **110** as a white solid (33 mg, 84%); Si gel TLC R_f 0.22 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 3172, 2925, 1650, 1540, 1462, 1280, 1085, 733; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.12 (t, *J* = 7.9 Hz, 1H, Ar*H*), 6.78 (d, *J* = 7.8 Hz, 1H, Ar*H*), 6.76 – 6.68 (m, 2H : ArH & N*H*), 3.70 (d, *J* = 6.4 Hz, 2H), 2.45 (d, *J* = 7.2 Hz, 2H), 2.39 – 2.27 (m, 1H), 2.16 – 1.95 (m, 3H), 1.93 – 1.79 (m, 3H), 1.77 – 1.68 (m, 1H), 1.61 – 1.51 (m, 2H), 1.44 – 1.26 (m, 3H), 1.01 (d, *J* = 6.7 Hz, 6H), 0.86 (d, *J* = 6.6 Hz, 6H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.7, 153.9, 140.5, 127.2, 124.2, 122.3, 109.3, 74.6, 46.0, 41.4, 30.0, 29.2, 28.4, 25.84, 25.83, 22.7, 19.3; ***LRMS*** *m/z* (ES^+) 332.26 $[M+H]^+$, 395.27 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{21}H_{34}NO_2$ 332.2590, found 332.2589, Δ = -0.3 ppm.

Methyl 3-(benzylamino)-3-oxopropanoate (112)[138]



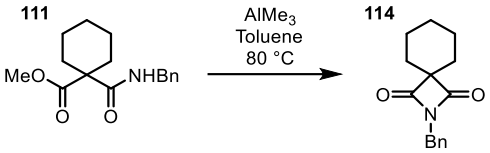
To a stirred solution of methylmalonyl chloride (1.10 mL, 9.95 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, benzylamine (2.17 mL, 19.9 mmol) was added dropwise. After 1.5 h at 0 °C, the reaction was diluted with CH_2Cl_2 (10 mL) and then washed twice with acidic water (0.1N HCl, 10 ml). The organic layers were washed with brine and dried over Na_2SO_4 and the solvent was removed under reduced pressure. After recrystallization from diethyl ether, the α-amido ester **112** was isolated as a pale yellow crystalline solid (1.77g, 86%); Si gel TLC R_f 0.10 (*n*-hex/EtOAc 3:2); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.51 – 7.26 (m, 6H : Ar*H* x 5 *&* N*H*), 4.49 (d, *J* = 5.7 Hz, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 3.38 (s, 2H, COCH_2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.0 (*C*=O), 164.7 (*C*=O), 137.9 (Ar*C*), 128.8 (Ar*C*), 127.7 (Ar*C*), 127.6 (Ar*C*), 52.5 (OCH_3), 43.6 (NCH_2), 40.9 (COCH_2); ***LRMS*** *m/z* (Cl^+) 208.10 $[M+H]^+$, 271.11 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{11}H_{14}NO_3$ 208.0974, found 208.0979, Δ = 2.4 ppm. The spectroscopic data were in accordance with the literature.[138]

Methyl 1-(benzylcarbamoyl)cyclohexane-1-carboxylate (111)



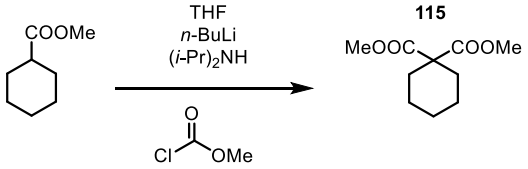
To a solution of α-amido ester **112** (200 mg. 0.97 mmol) in dry DMF (4 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 77 mg, 1.93 mmol) followed by 1,5-dibromopentane (0.13 mL, 0.97 mmol). The reaction was stirred at RT under N_2 for 90 mins after which the mixture was quenched with H_2O. The mixture was extracted with Et_2O and the organic was then washed with diluted brine (x 6) to remove remaining amounts of DMF. The organic solution was dried over Na_2SO_4 and evaporated to dryness. The crude material was purified by Si gel FC (*n*-hex/EtOAc 6:1 → 3:2) to afford α-amido ester **111** as a colourless oil (86 mg, 33%); Si gel TLC R_f 0.47 (*n*-hex/EtOAc 3:2); ***ATR-IR*** ν_{max}/cm^{-1} 3358, 2925, 2855, 1732, 1651, 1525, 1453, 1224, 1137, 1070, 994, 906, 727; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.37 – 7.18 (m, 5H, Ar*H*), 6.22 (*br.* s, 1H, N*H*), 4.43 (d, *J* = 5.8 Hz, 2H, NCH_2Ph), 3.73 (s, 3H, OCH_3), 2.25 – 2.10 (m, 2H, Cy*H*), 1.94 – 1.79 (m, 2H, Cy*H*), 1.74 – 1.60 (m, 2H, Cy*H*), 1.56 – 1.47 (m, 1H, Cy*H*), 1.47 – 1.28 (m, 3H, Cy*H*); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.0 (*C*=O), 170.6 (*C*=O), 138.2 (Ar*C*), 128.7 (Ar*C*), 127.5 (Ar*C*), 55.4 (*C*-COOMe), 52.6 (OCH_3), 43.7 (CH_2Ph), 32.0 (Cy*C*), 25.2 (Cy*C*), 23.2 (Cy*C*); ***LRMS*** *m/z* (ES^+) 276.16 $[M+H]^+$, 298.14 $[M+Na]^+$, 339.17 $[M+CH_3CN+Na)$; ***HRMS*** *m/z* calcd. for $C_{16}H_{22}NO_3$ 276.1600, found 276.1595, Δ = -1.8 ppm.

2-Benzyl-2-azaspiro[3.5]nonane-1,3-dione (114)



α-Amido ester **111** (36 mg, 0.13 mmol) was dissolved in dry toluene (1.3 mL) and cooled to 0 °C. $AlMe_3$ (0.13 mL, 0.26 mmol) was added and the reaction mixture was then heated at 80 °C for 72 h. ^{1}H NMR analysis revealed 54% conversion to azetidinedione **114;** compound **114** was previously isolated as a minor component from a separate reaction as an off-white semi-solid; Si gel TLC $\boldsymbol{R_f}$ 0.65 (*n*-hex/EtOAc 4:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.42 – 7.27 (m, 5H, Ar*H*), 4.43 (s, 2H, NCH_2Ph), 1.89 – 1.76 (m, 4H, Cy*H*), 1.76 – 1.64 (m, 4H, Cy*H*), 1.55 – 1.44 (m, 2H, Cy*H*); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.8 (*C*=O), 135.0 (Ar*C*), 129.0 (Ar*C*), 128.1 (Ar*C*), 128.0 (Ar*C*), 64.6 (O=C*C*C=O), 42.5 (N*C*H_2Ph), 28.0 (Cy*C*), 25.0 (Cy*C*), 22.7 (Cy*C*); ***LRMS*** (Cl^+) *m/z*: not found.

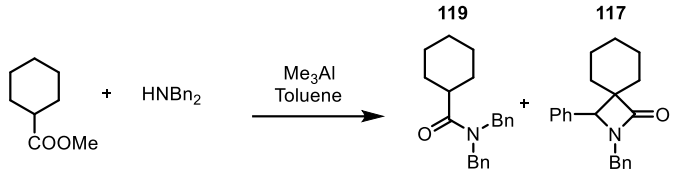
Dimethyl cyclohexane-1,1-dicarboxylate (115)[139]



According to the method of Davis,[139] a three-necked 50-mL round-bottomed flask equipped with a magnetic stir bar, low-temperature thermometer, pressure-equalizing addition funnel and N_2 tee, was charged with dry THF (7.8 mL) and diisopropylamine (1.47 mL, 1.49 mmol). The stirred solution was cooled to approximately -20 °C, to which *n*-BuLi (1.6 M in hexane, 6.55 mL, 1.50 mmol) was added dropwise, maintaining the internal temperature at or below 0 °C. The resultant solution was stirred at 0 °C (internal temperature) for 5 mins and then cooled to -78 °C. A solution of methyl cyclohexancarboxylate (1 mL, 7.00 mmol) in THF (1.8 mL) was then slowly added dropwise *via* the addition funnel, maintaining the temperature below -68 °C. The enolate solution was stirred for an additional hour at -78 °C after which a solution of methyl chloroformate (0.81 mL, 1.50 mmol) in THF (1 mL) was slowly added dropwise, maintaining the temperature below -68 °C. After addition was complete, the solution was allowed to warm to RT (~ 45 mins) with continued stirring under N_2. The reaction mixture was diluted with CH_2Cl_2 and washed consecutively with aqueous NH_4Cl solution and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to dryness. The crude residue was then distilled through a short-path apparatus at reduced pressure. A forerun of $(^iPr)_2NCO_2Me$ amide by-product was collected at bp. 65-75 °C (2.6 mmHg) followed by the desired dimethyl ester **115** which was collected at bp. 83 °C (2.1 mmHg) as a colourless oil (1.01 g, 72%); Si gel TLC $\boldsymbol{R_f}$ 0.41 (*n*-hex/EtOAc 5:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 3.71 (s, 6H, OCH_3 x 2), 2.08 – 1.87 (m, 4H, Cy*H*),

1.57 – 1.37 (m, 6H, Cy*H*); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 172.4 (*C*=O), 55.0 (O=C*C*C=O), 52.5 (O*C*H$_3$), 31.4 (Cy*C*), 25.1 (Cy*C*), 22.8 (Cy*C*); ***LRMS*** *m/z* (Cl^+) 201 $[M+H]^+$, 218 $[M+NH_4]^+$, ***HRMS*** *m/z* calcd. for $C_{10}H_{20}NO_4$ 218.1392, found 218.1399, Δ = 3.2 ppm. The spectroscopic data were in accordance with the literature.[139]

N,N-Dibenzylcyclohexanecarboxamide (119)[140] & 2-Benzyl-3-phenyl-2-azaspiro[3.5]nonan-1-one (117)



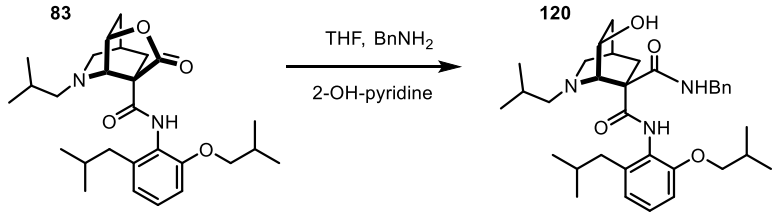
To a solution of dibenzylamine (0.48 mL, 2.50 mmol) in dry toluene (2.5 mL) was added trimethylaluminium (2.0 M in hexane, 1.25 mL, 2.50 mmol) at 0 °C. After being stirred for 1 hr at RT, a solution of methyl cyclohexanecarboxylate (0.36 mL, 2.50 mmol) in dry toluene (2.5 mL) was added to the mixture which was stirred under N_2 at 110 °C for 18 h. The reaction was quenched with MeOH and then partitioned between 1N HCl solution and EtOAc (2 x 50 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude material was purified by Si gel FC (*n*-hex/EtOAc 16:1 → 9:1 → 4:1) to give:

Dibenzylamide **119** as a white powder-like solid (514 mg, 67%); Si gel TLC ***R$_f$*** 0.49 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 2929, 1745, 1453, 1394, 1353, 1072, 946, 700; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.44 – 7.23 (m, 6H, Ar*H*), 7.24 – 7.07 (m, 4H, Ar*H*), 4.58 (s, 2H, NC*H*$_2$Ph), 4.45 (s, 2H, NC*H*$_2$Ph), 2.69 – 2.45 (m, 1H, C*H*CONBn$_2$), 1.91 – 1.55 (m, 7H, Cy*H*), 1.45 – 1.04 (m, 3H, Cy*H*); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 176.9 (*C*=O), 137.7 (Ar*C*), 137.0 (Ar*C*), 128.9 (Ar*C*), 128.6 (Ar*C*), 128.1 (Ar*C*), 127.6 (Ar*C*), 127.3 (Ar*C*), 126.4 (Ar*C*), {49.6, 47.8 : *C*-C=O & NCH$_2$Ph}, 40.9 (Cy*C*), 29.7 (Cy*C*), 25.8 (Cy*C*); ***LRMS*** *m/z* (ES^+) 308.20 $[M+H]^+$, 371.21 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{21}H_{26}NO$ 308.2029, found 308.2014, Δ = 4.9 ppm. The spectroscopic data were in accordance with the literature.[140]

Azetidinone **117** as an off-white semi-solid (19.1 mg, 2.5%); Si gel TLC ***R$_f$*** 0.37 (*n*-hex/EtOAc 4:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.45 – 7.23 (m, 6H, Ar*H*), 7.20 (d, *J* = 7.3 Hz, 2H, Ar*H*), 7.15 (d, *J* = 6.8 Hz, 2H, Ar*H*), 4.92 (d, *J* = 14.9 Hz, 1H, NC*H*$_a$Ph), 4.13 (s, 1H, Cy-C*H*Ph), 3.82 (d, *J* = 14.9 Hz, 1H, NC*H*$_b$Ph), 1.99 – 1.64 (m, 3H, Cy*H*), 1.60 – 1.12 (m, 6H, Cy*H*), 0.98 – 0.78 (m, 1H, Cy*H*); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.0 (*C*=O), 136.0 (Ar*C*), 135.8 (Ar*C*), 128.7 (Ar*C*), 128.5 (Ar*C*), 128.0 (Ar*C*), 127.6.0 (Ar*C*), 127.5 (Ar*C*), 65.8 (Cy-*C*HPh), 60.7 [Cy*C*-CHPh(CO)], 43.7 (NCH$_2$Ph), 32.9 (Cy*C*), 27.2

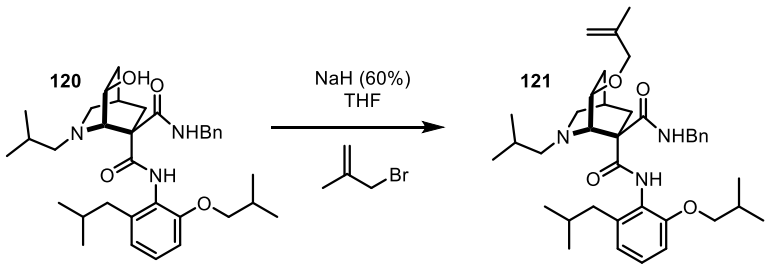
(Cy*C*), 25.2 (Cy*C*), 23.5 (Cy*C*), 22.0 (Cy*C*); ***LRMS*** *m/z* (ES^+) 306.19 $[M+H]^+$, 347.21 $[M+CH_3CN+H]^+$; ***HRMS*** *m/z* calcd. for $C_{21}H_{24}NO$ 306.1858, found 306.1863, Δ = 1.6 ppm.

(1*S*,4*R*,6*S*,7*S*)-N-benzyl-7-hydroxy-N-(2-isobutoxy-6-isobutylphenyl)-2-isobutyl-2-azabicyclo[2.2.2]octane-6,6-dicarboxamide (120)



To a solution of lactone amide **83** (23 mg, 0.094 mmol) in dry THF (1 mL) was added 2-hydroxypyridine (24 mg, 0.25 mmol) and benzylamine (0.055 mL, 0.5 mmol) and the reaction stirred under N_2 for 36 h at RT. The reaction mixture was concentrated in vacuo and then purified by Si gel FC (*n*-hex/EtOAc 9:1 → 3:2) to yield benzylamide **120** as an orange semi-solid (17.4 mg, 61%); Si gel TLC R_f 0.21 (*n*-hex/EtOAc 3:2); ***ATR-IR*** ν_{max}/cm^{-1} 3361, 2926, 1762, 1696, 1680, 1653, 1550, 1520, 1458, 1265; ***^{1}H NMR*** ($CDCl_3$, $CDCl_3$) δ 10.63 (s, 1H, N*H*Ar), 7.35 – 7.27 (m, 4H, Ar*H*), 7.26 – 7.22 (m, 1H, Ar*H*), 7.11 (t, *J* = 7.9 Hz, 1H, Ar*H*), 6.76 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 6.71 (dd, *J* = 7.9, 1.2 Hz, 1H, Ar*H*), 6.41 (t, *J* = 5.6 Hz, 1H, N*H*Bn), 4.55 – 4.40 (m, 2H, NCH_2Ph), 4.28 – 4.16 (*br.* m, 1H, O*H*), 3.69 – 3.55 (m, 2H, OCH_2), 3.46 (d, *J* = 2.8 Hz, 1H), 3.12 (dt, *J* = 10.1, 2.5 Hz, 1H), 2.77 – 2.59 (m, 3H), 2.40 (d, *J* = 7.3 Hz, 2H), 2.38 – 2.27 (m, 2H), 2.22 – 2.03 (m, 3H), 1.97 – 1.89 (m, 1H), 1.87 – 1.78 (m, 1H), 1.77 – 1.63 (m, 2H), 0.94 (*app.* dd, *J* = 6.7, 5.0 Hz, 6H), 0.85 – 0.79 (m, 9H), 0.70 (d, *J* = 6.5 Hz, 3H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.5, 172.9, 154.1, 140.4, 137.6, 128.7, 128.6, 128.0, 127.4, 127.3, 123.8, 122.3, 74.6, 64.4, 64.2, 61.6, 55.8, 52.6, 44.7, 41.5, 35.6, 32.2, 29.7, 28.3, 27.3, 26.5, 22.6, 21.1, 20.2, 19.4; ***LRMS*** *m/z* (ES^+) 563.4 $[M+H]^+$; **HRMS** *m/z* calcd. for $C_{34}H_{50}N_3O_4$ 564.3801, found 564.3801, Δ = 0.0 ppm.

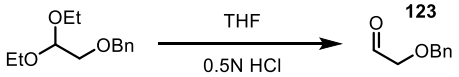
(1*S*,4*R*,6*S*,7*S*)-N-Benzyl-N-(2-isobutoxy-6-isobutylphenyl)-2-isobutyl-7-((2-methylallyl)oxy)-2-azabicyclo[2.2.2]octane-6,6-dicarboxamide (121)



A solution of hydroxy amide **120** (32 mg, 0.057 mmol) in anhydrous DMF (0.6 mL) was cooled to 0 °C. NaH (60% dispersion in mineral oil, 3 mg, 0.074 mmol) was added and the reaction stirred

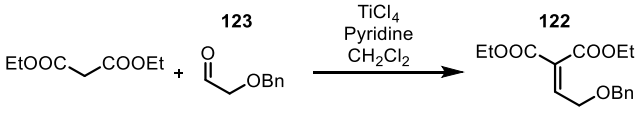
at 0 °C under N_2 for 1 h. 3-Bromo-2-methylpropene (14 µL, 0.14 mmol) was then added and the reaction stirred at 0 – 5 °C for 2 h. The reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 x 5 mL). The organics were combined, washed with brine and dried over $MgSO_4$. The crude mixture was purified by Si gel FC (*n*-hex/EtOAc 20:1 → 4:1 → 1:1) to provide **121** as an orange semi-solid (7.4 mg, 21 %); Si gel TLC $\boldsymbol{R_f}$ 0.38 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 3349, 2924, 2855, 1681, 1509, 1459, 1365, 1249, 1081, 751, 658; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.63 (*br.* s, 1H, N*H*Ar), 7.32 – 7.19 (m, 5H, Ar*H*), 7.10 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.76 (d, *J* = 7.7 Hz, 1H, Ar*H*), 6.69 (d, *J* = 8.1 Hz, 1H, Ar*H*), 5.89 (t, *J* = 5.0 Hz, 1H, N*H*Bn), 4.96 (s, 1H), 4.88 (s, 1H), 4.52 (*AB*, dd, *J* = 14.7, 5.3 Hz, 1H), 4.30 (*AB*, dd, *J* = 14.7, 4.7 Hz, 1H), 3.91 – 3.74 (m, 3H), 3.70 – 3.55 (m, 3H), 3.06 (*app.* dt, *J* = 9.6, 2.6 Hz, 1H), 2.95 – 2.83 (*br.* m, 1H), 2.53 (dd, *J* = 11.7, 5.4 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.36 – 2.22 (m, 2H), 2.13 – 2.03 (m, 2H), 2.02 – 1.90 (m, 2H), 1.88 – 1.77 (m, 1H), 1.72 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 6H), 0.82 – 0.76 (m, 9H), 0.71 (d, *J* = 6.5 Hz, 3H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 172.7, 170.4, 154.0, 142.5, 140.5, 138.2, 128.5, 128.0, 127.2, 127.0, 124.0, 122.3, 111.9, 109.0, 74.5, 72.2, 70.4, 64.4, 59.2, 56.5, 53.1, 44.7, 41.3, 32.3, 30.6, 29.7, 29.3, 28.4, 26.9, 26.4, 22.6, 22.6, 21.1, 20.2, 19.6, 19.4, 19.3; ***LRMS*** *m/z* (ES^+) 618.4 $[M+H]^+$; ***HRMS*** m/z calcd. for $C_{38}H_{56}N_3O_4$ 618.4271, found 618.4276, Δ = 0.8 ppm.

2-(Benzyloxy)acetaldehyde (123)[141]



According to the method of Vasse,[141] 2-benzyloxyacetaldehyde diethylacetal (3 mL, 13.2 mmol) in THF (36 mL) and aqueous HCl (0.5 N, 60 mL) was heated to reflux for 3 h. Water (35 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 75 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. 2-(benzyloxy)acetaldehyde (**123**) was collected after distillation at bp. 105 °C (10 mbar) as a colourless liquid (1.44 g, 73%); Si gel TLC $\boldsymbol{R_f}$ 0.41 (*n*-hex/EtOAc 4:1); ***^{1}H NMR*** (400 MHz, $CDCl_3$) δ 9.73 (s, 1H, *H*C=O), 7.44 – 7.27 (m, 5H, Ar*H*), 4.64 (s, 2H, OCH_2Ph), 4.11 (*br.* s, 2H, CH_2OBn); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 200.5 (*C*=O), 136.9 (Ar*C*), 128.6 (Ar*C*), 128.2 (Ar*C*), 128.1 (Ar*C*), 75.3 (O*C*H_2Ph), 73.7 (*C*H_2OBn). The spectroscopic data were in accordance with the literature.[141]

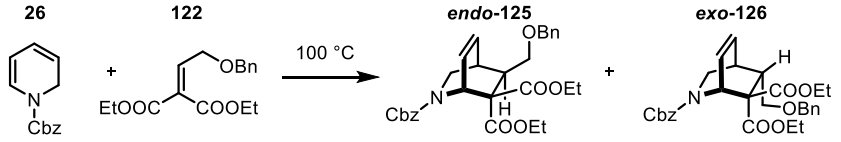
Diethyl 2-(2-(benzyloxy)ethylidene)malonate (122)



A solution of diethyl malonate (1.47 mL, 9.66 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C in an ice bath. To the cooled solution was added $TiCl_4$ by syringe (1.0 M in CH_2Cl_2, 9.66 mL, 9.66 mmol) dropwise over 15 mins. The resulting mixture was stirred with cooling for 30 mins at 0 °C, then 2-(benzyloxy)acetaldehyde (1.45 g, 9.66 mmol) was added (diluted in 2 mL CH_2Cl_2) by syringe. The reaction mixture was stirred for 10 mins at 0 °C after which anhydrous pyridine (1.56 mL, 19.31 mmol) was then added dropwise (caution: exothermic). The reaction was allowed to warm gradually to RT overnight. The reaction mixture was poured over ice and extracted with EtOAc (2 x 60 mL). The organic solution was then washed with brine, dried over $MgSO_4$ and concentrated to dryness. The crude residue was purified by Si gel FC (*n*-hex/EtOAc 10:0 → 6:1 → 4:1) to provide 2.20 g of an off-white free flowing liquid which contains methylene malonate **122** (63% yield) together with the isomerized unconjugated (*Z*)-alkene (*i.e.* allylic ether) in a 4:1 ratio. The mixture was immediately taken through to the next stage to prevent further isomerization.

Methylene malonate (**122**); Si gel TLC R_f 0.34 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 2983, 1730, 1654, 1454, 1371, 1251, 1216, 1097, 1047, 1028, 864, 699; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.43 – 7.27 (m, 5H, Ar*H*), 7.11 (t, *J* = 5.1 Hz, 1H, C=C*H*), 4.53 (s, 2H, OCH_2Ph), 4.37 (d, *J* = 5.0 Hz, 2H, CH_2OBn), 4.28 – 4.19 (m, 4H, OC$H_2$$CH_3$ x 2), 1.33 – 1.24 (m, 6H, OCH_2CH_3 x 2); ***LRMS*** *m/z* (ES^+) 293.14 $[M+H]^+$, 404.16 $[M+K]^+$; ***HRMS*** *m/z* calcd. for $C_{16}H_{21}O_5$ 293.1392, found 293.1389, Δ = 1.0 ppm.

2-Benzyl 6,6-diethyl (1R,4S,5R)-5-((benzyloxy)methyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6,6-tricarboxylate (*endo*-125) & 2-benzyl 6,6-diethyl (1R,4S,5S)-5-((benzyloxy)methyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6,6-tricarboxylate (*exo*-126)



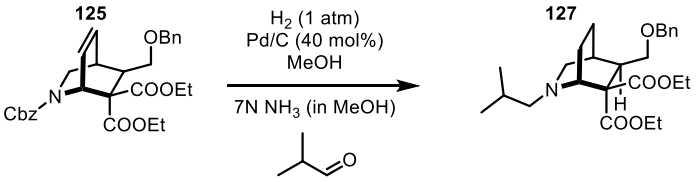
To a dry flask containing freshly prepared diethyl 2-(2-(benzyloxy)ethylidene)malonate **122** (1.76 g, 6.02 mmol) was added 1,2-dihydropyridine **26** (1.43 g, 6.62 mmol). The reaction mixture was then stirred at 100 °C under Ar for 20 h. Volatiles were removed under reduced pressure following which the crude material was purified by Si gel FC (*n*-hex/EtOAc 5:1 → 3:1) to give:

Endo*-125** as a colourless viscous oil (790 mg, 26%); Si gel TLC R_f 0.28 (*n*-hex/EtOAc 4:1); ***ATR-IR ν_{max}/cm^{-1} 2956, 2925, 2852, 1731, 1705, 1455, 1412, 1367, 1335, 1297, 1245, 1204, 1056; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers) ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.42 – 7.23 (m, 10H), 6.66 – 6.51 (m, 1H), 6.34 – 6.20 (m, 1H), 5.33 – 5.18 (m, 1H), 5.17

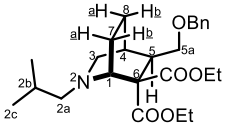
– 4.99 (m, 2H), 4.55 – 4.33 (m, 2H), 4.15 – 3.77 (m, 4H), 3.56 – 3.43 (m, 1H), 3.41 – 3.23 (m, 2H), 3.22 – 3.08 (m, 1H), 3.08 – 2.95 (m, 2H), 1.26 – 0.97 (m, 6H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.1, 169.7, 168.4, 168.2, 155.1, 154.9, 138.1, 138.1, 136.9, 136.6, 132.4, 132.0, 131.9, 131.8, 128.5, 128.4, 128.1, 127.8, 127.7, 127.6, 127.5, 73.0, 70.0, 67.0, 66.7, 63.2, 63.0, 62.1, 61.9, 61.2, 50.9, 50.4, 46.2, 45.9, 41.7, 41.6, 33.2, 33.0, 13.9, 13.8, 13.8; ***LRMS*** *m/z* (ES+) 508.23 $[M+H]^+$, 530.21 $[M+Na]^+$; ***HRMS*** (ES+) *m/z calcd.* for $C_{29}H_{34}NO_7$ 508.2335, found 508.2318, Δ = -3.3 ppm.

Exo*-126** as a colourless viscous oil (450 mg, 15%); Si gel TLC R_f 0.21 (*n*-hex/EtOAc 4:1); ***ATR-IR ν_{max}/cm^{-1} 2952, 2927, 2856, 1733, 1704, 1497, 1454, 1416, 1367, 1334, 1298, 1245, 1200, 1114, 1050; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers) ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.40 – 7.24 (m, 10H), 6.59 – 6.47 (m, 1H), 6.44 – 6.34 (m, 1H), 5.40 – 5.20 (m, 1H), 5.19 – 5.07 (m, 2H), 4.57 – 4.45 (m, 2H), 4.23 – 3.96 (m, 3H), 3.95 – 3.83 (m, 1H), 3.80 – 3.72 (m, 1H), 3.73 – 3.66 (m, 1H), 3.65 – 3.54 (m, 1H), 3.04 – 2.94 (m, 1H), 2.94 – 2.81 (m, 1H), 2.72 – 2.53 (m, 1H), 1.27 – 1.19 (m, 3H), 1.18 – 1.00 (m, 3H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.1, 170.09, 168.65, 168.54, 155.48, 154.92, 138.25, 137.01, 136.90, 136.66, 136.45, 131.02, 130.72, 128.43, 128.39, 127.97, 127.92, 127.80, 127.69, 127.61, 127.50, 77.39, 77.07, 76.75, 73.04, 72.99, 68.15, 66.89, 66.83, 61.62, 61.47, 60.01, 59.88, 50.36, 49.84, 41.09, 40.83, 39.79, 39.24, 32.07, 31.78, 13.98, 13.80. ***LRMS*** *m/z* (ES+) 508.24 $[M+H]^+$, 530.22 $[M+Na]^+$; ***HRMS*** (ES+) *m/z calcd.* for $C_{29}H_{34}NO_7$ 508.2335, found 508.2350, Δ = 3.0 ppm.

Diethyl (1*R*,4*S*,5*R*)-5-((benzyloxy)methyl)-2-isobutyl-2-azabicyclo[2.2.2]octane-6,6-dicarboxylate (127)

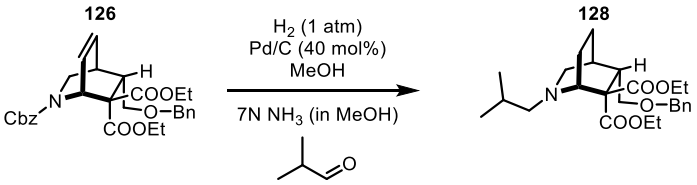


To a solution of *N*-Cbz-alkene **125** (32 mg, 0.063 mmol) in MeOH (1 mL) was added NH_3 (7N in MeOH, 0.03 mL, 0.19 mmol), isobutyraldehyde (0.020 mL, 0.19 mmol) and Pd/C (10% wt., 27 mg, 0.025 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 20 h. The reaction mixture was then purified by Si gel FC (*n*-hex/EtOAc 9:1 → 6:1) to afford alkane **127** as an off-white semi-solid (28 mg, 100%); Si gel TLC R_f 0.54 (*n*-hex/EtOAc 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 2952, 1731, 1457, 1235, 736;

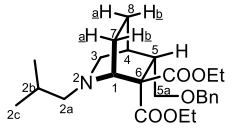


^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 – 7.24 (m, 5H, Ar*H*), 4.53 – 4.44 (*AB*, m, 2H, OC*H*$_2$Ph), 4.32 – 3.94 (m, 4H, OC*H*$_2$CH$_3$ x 2), 3.62 [dd, *J* = 9.2, 4.9 Hz, 1H, C(5a)*H*$_a$], 3.52 [t, *J* = 9.5 Hz, 1H, C(5a)*H*$_b$], 3.24 – 3.20 [m, 1H, C(5)*H*], 3.19 [dd, *J* = 3.4, 2.2 Hz, 1H, C(1)*H*], 3.05 [dt, *J* = 9.7, 3.0 Hz, 1H, C(3)*H*$_{exo}$], 2.35 [dd, *J* = 11.6, 5.2 Hz, 1H, C(2a)*H*$_a$], 2.24 [dd, *J* = 9.7, 2.2 Hz, 1H, C(3)*H*$_{endo}$], 2.14 – 2.03 [m, 2H : C(2a)*H*$_b$ & C(7)*H*$_a$], 1.99 – 1.86 [m, 2H : C(4)*H* & C(7)*H*$_b$], 1.82 – 1.73 [m, 1H, C(8)*H*$_b$], 1.63 – 1.54 [m, 1H, C(2b)*H*], 1.39 – 1.30 [m, 1H, C(8)*H*$_a$], 1.22 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.15 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 0.80 [d, *J* = 6.6 Hz, 3H, C(2c)*H*$_3$], 0.77 [d, *J* = 6.5 Hz, 3H, C(2c)*H*$_3$]; ***^{13}C NMR*** ($CDCl_3$, 126 MHz) δ 172.0 (*C*=O), 169.4 (*C*=O), 138.5 (Ar*C*), 128.3 (Ar*C*), 127.4 (Ar*C*), 72.9 (O*C*H$_2$Ph), 69.4 [*C*(5a)], 64.8 [*C*(2a)], 61.1 & 60.6 (O*C*H$_2$CH$_3$), 61.0 [*C*(6)], 56.6 [*C*(1)], 55.6 [*C*(3)], 37.6 [*C*(5)], 28.7 [*C*(4)], 26.4 [*C*(2b)], 20.9 & 20.2 [*C*(2c)], 19.9 [*C*(8)], 17.4 [*C*(7)], 14.0 & 13.9 (OCH$_2$*C*H$_3$); ***LRMS*** *m/z* (ES^+) 432.27 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{25}H_{38}NO_5$ 432.2750, found 432.2748, Δ = -0.5 ppm.

Diethyl (1*R*,4*S*,5*S*)-5-((benzyloxy)methyl)-2-isobutyl-2-azabicyclo[2.2.2]octane-6,6-dicarboxylate (128)



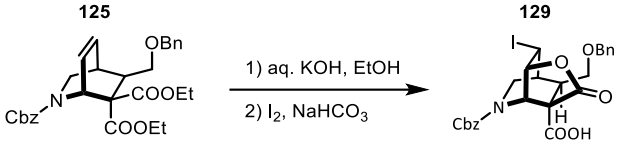
To a solution of *N*-Cbz-alkene **126** (26 mg, 0.050 mmol) in MeOH (0.8 mL) was added NH_3 (7N in MeOH, 0.022 mL, 0.15 mmol), isobutyraldehyde (0.014 mL, 0.15 mmol) and Pd/C (10% *wt*., 22 mg, 0.02 mmol) after which the reaction mixture was subjected to a H_2 atmosphere for 18 h. The reaction mixture was then purified by Si gel FC (*n*-hex/EtOAc 4:1 → 7:3 → 1:1) to afford alkane **128** as an off-white semi-solid (15 mg, 69%); Si gel TLC ***R$_f$*** 0.36 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 2925, 1735, 1460, 1229, 1095, 735, 697



^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 – 7.24 (m, 5H, Ar*H*), 4.61 – 4.44 (AB, m, 2H, OC*H*$_2$Ph), 4.21 – 3.97 (m, 4H, OC*H*$_2$CH$_3$ x 2), 3.90 – 3.77 [m, 2H, C(5a)*H*$_2$], 3.23 – 3.11 [m, 2H : C(1)*H* & C(3)*H*$_{exo}$], 2.65 [m, 1H, C(5)*H*], 2.36 [dd, *J* = 11.5, 5.2 Hz, 1H, C(2a)*H*$_a$], 2.18 [dd, *J* = 11.5, 9.4 Hz, 1H, C(2a)*H*$_b$], 2.10 [*app.* d, *J* = 9.8 Hz, 1H, C(3)*H*$_{endo}$], 2.04 [m, 1H, C(4)*H*], 1.98 – 1.86 [m, 1H, C(7)*H*$_a$], 1.70 – 1.59 [m, 1H, C(2b)*H*], 1.58 – 1.50 [m, 3H : C(8)*H*$_2$ & C(7)*H*$_b$], 1.19 (*app.* dt, *J* = 14.5, 7.1 Hz, 6H, OCH$_2$C*H*$_3$ x 2), 0.81 [*app.* dd, *J* = 8.8, 6.5 Hz, 6H, C(2c)*H*$_3$ x 2]; ***^{13}C NMR*** ($CDCl_3$, 125 MHz) δ 171.0 (*C*=O), 169.5 (*C*=O), 138.8 (Ar*C*), 128.3 (Ar*C*), 127.6 (Ar*C*), 127.4 (Ar*C*), 72.9 (O*C*H$_2$Ph), 70.0 [*C*(5a)],

64.8 [*C*(2a)], 61.2 & 60.5 (O*C*H_2CH_3), 56.7 [*C*(1)], 50.2 [*C*(3)], 40.0 [*C*(5)], 28.2[*C*(4)], 26.4 [*C*(2b)], 25.3 [*C*(8)], 21.0 & 20.3 [*C*(2c)], 18.1 [*C*(7)], 14.0 (OCH_2*C*H_3); ***LRMS*** (MS ES^+) *m/z*: 432.28 $[M+H]^+$; ***HRMS*** *m/z*: *calcd.* for $C_{25}H_{38}NO_5$ 432.2750, found 432.2755, Δ = 1.2 ppm.

(3*R*,3a*R*,7a*R*)-4-((Benzyloxy)carbonyl)-8-((benzyloxy)methyl)-7-iodo-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-3(2H)-carboxylic acid (129)

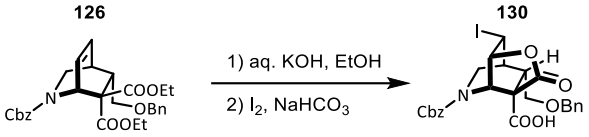


Diester **125** (205 mg, 0.40 mmol) was dissolved in absolute EtOH (1.6 mL). An aqueous KOH solution (5M, 1.6 mL) was added to give a homogenous yellow solution that grew warm to the touch. This mixture was refluxed under N_2 with stirring for 3 h. The reaction mixture was cooled to RT and diluted with water and then acidified with 4N HCl; the acidification was judged complete when the solution tested below pH 1, and a cloudy mixture was obtained. The mixture was extracted with ether and the layers separated. The aqueous layer was saturated with NaCl, and extracted with ether (5 x 30 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a viscous yellow oil. ^{1}H NMR indicated the presence of the desired diacid, along with appreciable quantities of ether and ethanol.

The crude diacid obtained above was dissolved in saturated aqueous $NaHCO_3$ solution (4.5 mL) to afford a cloudy white solution. Iodine (103 mg, 0.40 mmol) was added and the mixture was stirred vigorously. The iodine slowly dissolved to afford a deep brown solution. After stirring overnight, the mixture was carefully acidified with 4N HCl (caution: vigorous bubbling) until the pH was below 1. The mixture was extracted with ether. The aqueous layer was saturated with NaCl and extracted with ether (5 x 30 mL). The combined organic layers were then decolorized with a small amount of saturated aqueous $Na_2S_2O_3$ solution, and washed with brine. The solution was dried and concentrated in vacuo to give iodolactone **129** as a pale yellow gum (179 mg, 77%); Si gel TLC R_f 0.21 (CH_2Cl_2/MeOH 9:1); ***ATR-IR*** ν_{max}/cm^{-1} 2926, 1793, 1728, 1709, 1421, 1318, 1119, 1056, 741, 698; (^{1}H and ^{13}C NMR spectra complicated and very broad at RT due to the presence of rotamers and carboxylic acid) ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.73 – 6.96 (m, 10H), 5.51 – 4.91 (m, 3H), 4.79 – 4.41 (m, 3H), 4.16 – 3.94 (m, 1H), 3.83 – 3.44 (m, 3H), 3.07 – 2.83 (m, 1H), 2.76 – 2.50 (m, 1H), 2.45 – 2.17 (m, 1H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 174.4, 173.4, 156.2, 155.3, 136.4, 128.6, 128.6, 128.6, 128.4, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.0, 81.5, 81.4, 74.7, 72.1, 67.7, 67.4, 65.4, 50.0, 49.7, 38.4, 38.2, 36.7, 36.4, 34.5, 34.5, 32.7, 32.6, 31.9,

30.4, 29.7; ***LRMS*** *m/z* (ES^+) 578.10 $[M+H]^+$, 595.10 $[M+NH_4]^+$; ***HRMS*** *m/z calcd.* for $C_{25}H_{25}INO_7$ 578.0676, found 578.0665, Δ = -1.1 ppm.

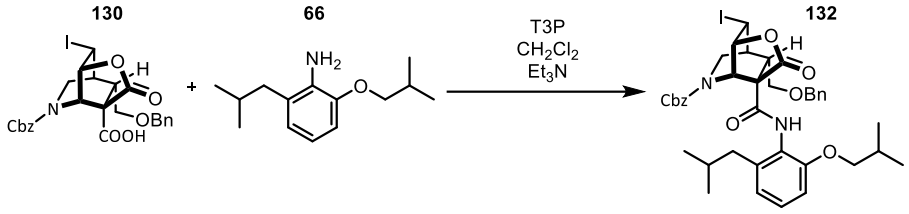
(3*R*,3a*R*,7a*R*)-4-((Benzyloxy)carbonyl)-8-((benzyloxy)methyl)-7-iodo-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-3(2H)-carboxylic acid (130)



Diester **126** (73 mg, 0.14 mmol) was dissolved in absolute EtOH (1.0 mL). An aqueous 5M KOH solution (1.0 mL) was added to give a homogenous yellow solution that grew warm to the touch. This mixture was refluxed under N_2 with stirring for 3 h. The reaction mixture was cooled to RT and diluted with water and then acidified with 4N HCl; the acidification was judged complete when the solution tested below pH 1, and a cloudy mixture was obtained. The mixture was extracted with ether and the layers separated. The aqueous layer was saturated with NaCl, and extracted with ether (x 5). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a viscous yellow oil. ^{1}H NMR indicated the presence of the desired diacid, along with appreciable quantities of ether and ethanol.

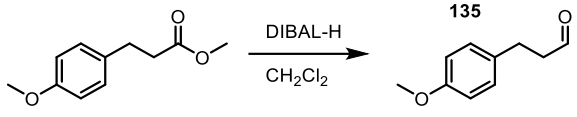
The crude diacid obtained above was dissolved in saturated aqueous $NaHCO_3$ (1.6 mL) to afford a cloudy white solution. Iodine (37 mg, 0.14 mmol) was added and the mixture was stirred vigorously. The iodine slowly dissolved to afford a deep brown solution. After stirring overnight, the mixture was carefully acidified with 4N HCl (caution: vigorous bubbling) until the pH was below 1. The mixture was extracted with ether. The aqueous layer was saturated with NaCl and extracted with ether (5 x 20 mL). The combined organic layers were then decolorized with a small amount of saturated aqueous $Na_2S_2O_3$ solution, and washed with brine. The solution was dried and concentrated in vacuo to give iodolactone **130** as a pale yellow gum (59 mg, 73%); Si gel TLC R_f 0.19 (CH_2Cl_2/MeOH 9:1); ***ATR-IR*** ν_{max}/cm^{-1} 3384, 2960, 2920, 2852, 1800, 1704, 1456, 1424, 1352, 1312, 1108, 1000; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.49 – 7.11 (m, 10H), 5.28 – 4.92 (m, 3H), 4.85 – 4.65 (m, 1H), 4.54 – 4.28 (m, 3H), 3.85 – 3.72 (m, 1H), 3.71 – 3.40 (m, 2H), 2.64 – 2.18 (m, 3H); ***LRMS*** *m/z* (ES^+) 444.01 $[M\text{-}Cbz+H_2]^+$, $[M+H]^+$, 595.10 $[M+NH_4]^+$; ***HRMS*** *m/z calcd.* for $C_{25}H_{25}INO_7$ 578.0676, found 578.0672, Δ = -0.7 ppm.

Benzyl (3*R*,3a*R*,7a*R*)-8-((benzyloxy)methyl)-7-iodo-3-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-2-oxohexahydro-3,6-methanofuro[3,2-b]pyridine-4(2H)-carboxylate (132)



Lactone acid **130** (59 mg, 0.10 mmol) and aniline **66** (52 mg, 0.24 mmol) were transferred to a dry flask and placed on the high vac for 10 mins. After dissolving in dry CH_2Cl_2, and adding Et_3N (50 µL, 0.35 mmol) the flask was cooled to 0 °C before adding propyl phosphonic anhydride (50% wt. in EtOAc, 0.18 mL, 0.31 mmol) was added. The reaction mixture was stirred at RT for 40 h under a N_2 atmosphere. The mixture was then diluted in EtOAc and the organic solution was washed with 1N HCl, saturated $NaHCO_3$ solution and brine before drying over $MgSO_4$. The solvent was removed in vacuo and the crude material was then purified by Si gel FC (*n*-hex/EtOAc 9:1 → 4:1 → 2:1) to give amide **132** as an off-white semi-solid (10 mg, 13%); Si gel TLC $\boldsymbol{R_f}$ 0.61 (*n*-hex/EtOAc 2:1); (^{1}H and ^{13}C NMR spectra complicated at RT due to presence of rotamers) ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.94 & 8.87 (2 x *br.* s, 1H, N*H*), 7.40 – 7.20 (m, 10H : OBn and Cbz Ar*H*), 7.19 – 7.08 (m, 1H, *N*-Ar*H*), 6.78 (d, *J* = 7.8 Hz, 1H, *N*-Ar*H*), 6.72 (d, *J* = 8.3 Hz, 1H, *N*-Ar*H*) 5.24 (t, *J* = 12.0 Hz, 1H), 5.19 – 5.07 (m, 2H), 5.04 & 4.87(2 x d, *J* = 5.7 Hz, 1H), 4.52 – 4.33 (m, 3H), 3.97 – 3.78 (m, 3H), 3.77 – 3.62 (m, 3H), 2.71 – 2.54 (m, 2H), 2.51 – 2.28 (m, 2H), 2.12 – 1.93 (m, 1H), 1.90 – 1.72 (m, 1H), 1.04 – 0.79 (m, 12H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 175.6, 175.5, 163.5, 163.2, 153.7, 140.2, 140.1, 137.6, 137.6, 136.5, 128.7, 128.7, 128.6, 128.2, 128.1, 127.9, 127.8, 127.7, 123.1, 122.4, 122.4, 109.5, 109.3, 82.2, 81.9, 74.7, 74.6, 73.7, 73.5, 68.6, 67.8, 52.2, 41.4, 40.3, 40.3, 40.1, 40.0, 35.2, 35.1, 29.9, 29.2, 29.2, 28.4, 25.1, 24.8, 22.9, 22.7, 19.6, 19.5, 19.4, 19.3; ***LRMS*** *m/z* (ES^+) 781.24 $[M+H]^+$, 798.26 $[M+NH_4]^+$; ***HRMS*** *m/z calcd.* for $C_{39}H_{46}IN_2O_7$ 781.2350, found 781.2355, Δ = 0.6 ppm.

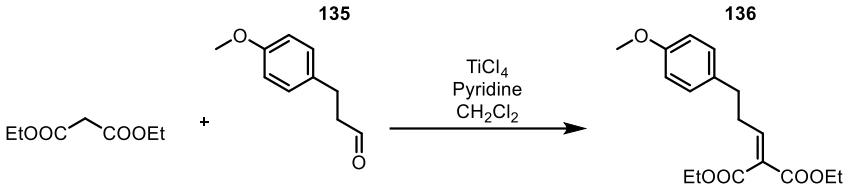
3-(4-Methoxyphenyl)propanal (135)[142]



According the method of Smith,[142] to a stirred solution of methyl 3-(4-methoxyphenyl)propanoate (1.03 g, 5.15 mmol) in anhydrous CH_2Cl_2 (26 mL) at −78 °C under N_2 was added DIBAL-H (1.0 M in hexane, 5.2 mL, 5.20 mmol) dropwise. The reaction was stirred for 1 h before being quenched with saturated NH_4Cl solution. The reaction was allowed to warm to RT, the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 x 80 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced

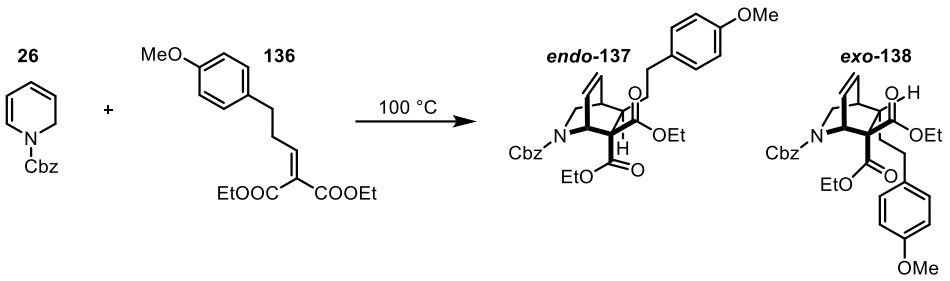
pressure. The residue was purified by Si gel FC (*n*-hex/Et_2O 9:1 → 3:2) to give 3-(4-methoxyphenyl)propanal **135** as colourless oil (600 mg, 71%); Si gel TLC $\boldsymbol{R_f}$ 0.44 (*n*-hex/Et_2O 3:2); ***¹H NMR*** ($CDCl_3$, 400 MHz) δ 9.80 (*br.* t, *J* = 1.5 Hz, 1H, *H*C=O), 7.24 – 7.05 (m, 2H, Ar*H*), 6.95 – 6.72 (m, 2H, Ar*H*), 3.78 (s, 3H, ArOCH_3), 2.90 (t, *J* = 7.5 Hz, 2H, ArCH_2), 2.81 – 2.68 (m, 2H, CH_2CHO); ***¹³C NMR*** ($CDCl_3$, 101 MHz) δ 201.8 (*C*=O), 158.1 (Ar*C*), 132.4 (Ar*C*), 129.3 (Ar*C*), 114.0 (Ar*C*), 55.3 (OCH_3), 45.6 (*C*CHO), 27.3 (ArCH_2). The spectroscopic data were in accordance with the literature.[142]

Diethyl 2-(3-(4-methoxyphenyl)propylidene)malonate (136)



A solution of diethyl malonate (0.41 mL, 2.73 mmol) in CH_2Cl_2 (8 mL) in a round bottom flask was cooled to 0 °C in an ice bath. To the cooled solution, was added $TiCl_4$ by syringe (1.0 M in CH_2Cl_2, 3.0 mL, 3.0 mmol) dropwise over 15 mins. The resulting mixture was stirred with cooling for 30 mins at 0 °C, then 3-(4-methoxyphenyl)propanal **135** (470 mg, 2.86 mmol) was added (diluted in 8 mL CH_2Cl_2) by syringe. The reaction mixture was stirred for 10 mins at 0 °C after which anhydrous pyridine (1.56 mL, 19.31 mmol) was then added dropwise (caution: exothermic). The reaction was allowed to warm gradually to RT overnight. The reaction mixture was poured over ice and extracted with EtOAc (2 x 80 mL). The organic solution was then washed with brine, dried over $MgSO_4$ and concentrated to dryness. The crude residue was purified by Si gel FC (*n*-hex/EtOAc 4:1 → 7:3) to provide 640 mg of a colourless oil which contains the desired alkylidene malonate **136** together with diethyl malonate (in a 7.2:2.8 ratio respectively, *i.e.* 480 mg of **136**, 55% yield); Si gel TLC ***Rf*****:** 0.43 (^{n}Hex:EtOAc, 7:3); ***¹H NMR*** ($CDCl_3$, 400 MHz) δ 7.09 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.01 (t, *J* = 7.7 Hz, 1H, C=C*H*), 6.83 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.34 – 4.16 (m, 4H, COOC$H_2$$CH_3$ x 2), 3.79 (s, 3H, OCH_3), 2.74 (t, *J* = 8.0 Hz, 2H, ArCH_2), 2.64 – 2.55 (m, 2H, C=CCH_2), 1.35 – 1.24 (m, 6H, $COOCH_2CH_3$ x 2). *N.B.* Compound **136** was believed to be unstable and was immediately carried forward to the next step.

2-Benzyl 6,6-diethyl (1*R*,4*S*,5*R*)-5-(4-methoxyphenethyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6,6-tricarboxylate (*endo*-137) & 2-benzyl 6,6-diethyl (1*R*,4*S*,5*S*)-5-(4-methoxyphenethyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6,6-tricarboxylate (*exo*-138)

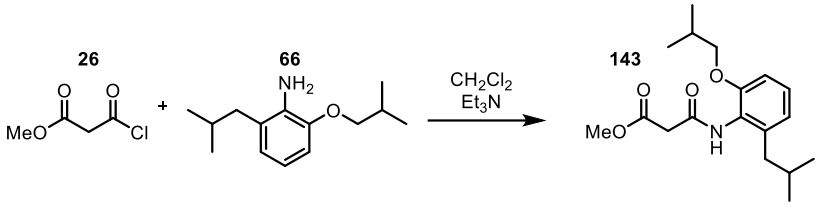


To a dry flask containing recently prepared alkylidene malonate **135** (465mg, 1.52 mmol) was added 1,2-dihydropyridine **26** (800 mg, 3.72 mmol). The reaction mixture was then stirred at 100 °C under Ar for 6 d. Volatiles were removed under reduced pressure following which the crude material was purified by Si gel FC (*n*-hex/EtOAc 4:1 → 3:2) to give:

Endo*-137** as a colourless oil (245 mg, 31%); Si gel TLC R_f 0.43 (*n*-hex/EtOAc 3:2); ***ATR-IR ν_{max}/cm^{-1} 2937, 1728, 1702, 1612, 1512, 1411, 1334, 1298, 1243, 1110, 1035, 750, 699; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.39 – 7.24 (m, 5H : Cbz Ar*H*)), 7.05 (m, 2H, *p*OMe-Ar*H*), 6.81 (m, 2H, *p*OMe-Ar*H*), 6.71 – 6.59 (m, 1H, C=C*H*), 6.32 (m, 1H, C=C*H*), 5.30 – 5.17 (m, 1H, N-C*H*-C=C), 5.16 – 4.98 (m, 2H, OCH_2Ph), 4.22 – 3.80 (m, 4H, OC$H_2$$CH_3$ x 2), 3.78 (s, 3H, OCH_3), 3.44 – 3.19 (m, 1H), 3.15 – 2.87 (m, 3H), 2.75 – 2.62 (m, 1H), 2.60 – 2.49 (m, 1H), 1.70 – 1.60 (m, 1H), 1.30 – 1.20 (m, 1H), 1.20 – 1.03 (m, 6H, OCH_2CH_3 x 2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.7, 170.3, 169.0, 168.8, 157.9, 155.0, 137.0, 136.7, 133.7, 133.1, 132.6, 131.1, 130.8, 129.2, 128.7, 128.6, 128.5, 128.1, 127.9, 127.7, 113.9, 67.1, 66.8, 65.5, 65.3, 62.1, 61.9, 61.2, 55.3, 51.0, 50.4, 46.0, 45.8, 41.7, 34.3, 34.0, 33.3, 33.0, 32.9, 14.1, 13.9; ***LRMS*** *m/z* (ES+) 522.25 $[M+H]^+$, 539.28 $[M+NH_4]^+$, 544.23 $[M+Na]^+$; ***HRMS*** (ES+) *m/z*: *calcd.* for $C_{30}H_{36}NO_7$ 522.2492, found 522.2502, Δ = 1.9 ppm.

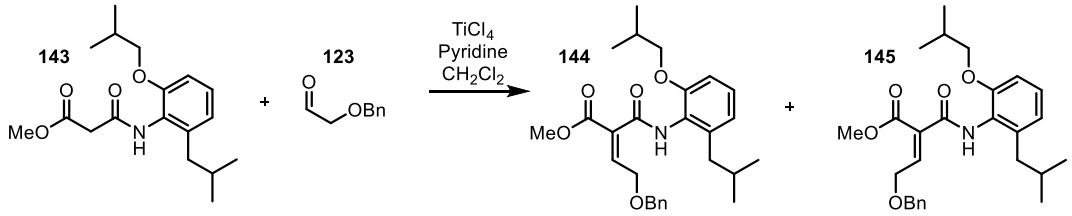
Exo*-138** as a colourless oil (275 mg, 35%); Si gel TLC R_f 0.37 (*n*-hex/EtOAc 3:2); ***ATR-IR ν_{max}/cm^{-1} 2937, 1732, 1703, 1612, 1513, 1417, 1333, 1297, 1245, 1114, 1035, 1039, 751, 699; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.39 – 7.25 (m, 5H : Cbz Ar*H*)), 7.11 – 7.03 (m, 2H, *p*OMe-Ar*H*), 6.84 – 6.79 (m, 2H, *p*OMe-Ar*H*), 6.55 – 6.44 (m, 1H, C=C*H*), 6.40 – 6.25 (m, 1H, C=C*H*), 5.38 – 5.21 (m, 1H, N-C*H*-C=C), 5.19 – 5.04 (m, 2H, OCH_2Ph), 4.19 – 4.00 (m, 4H, OC$H_2$$CH_3$ x 2), 3.78 (s, 3H, OCH_3), 3.65 – 3.59 (m, 1H), 2.93 – 2.82 (m, 1H), 2.81 – 2.72 (m, 1H), 2.68 – 2.59 (m, 1H), 2.55 – 2.42 (m, 2H), 1.98 – 1.74 (m, 2H), 1.25 – 1.03 (m, 6H, OCH_2CH_3 x 2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.7, 169.2, 169.1, 158.0, 137.2, 137.1, 137.0, 136.7, 133.79, 133.77, 131.1, 130.7, 129.3, 128.7, 128.5, 128.04, 127.98, 127.9, 127.9, 114.0, 67.0, 61.7, 61.5, 61.5, 61.3, 55.4, 50.3, 49.8, 40.9, 40.6, 38.7, 38.3, 33.8, 33.8, 33.5, 30.5, 14.1, 14.1; ***LRMS*** *m/z* (ES+) 522.25 $[M+H]^+$, 544.23 $[M+Na]^+$; ***HRMS*** (ES+) *m/z*: *calcd.* for $C_{30}H_{36}NO_7$ 522.2492, found 522.2508, Δ = 3.1 ppm.

Methyl 3-((2-isobutoxy-6-isobutylphenyl)amino)-3-oxopropanoate (143)



To a solution of methyl 3-chloro-3-oxopropionate (0.12 mL, 1.08 mmol) in dry CH_2Cl_2 (6 mL) was added Et_3N (0.15 mL, 1.08 mmol) and the solution was cooled to 0 °C. To this was added a solution of aniline **66** (200 mg, 0.90 mmol) in dry CH_2Cl_2 (3 mL). The reaction mixture was stirred at 0 °C for 30 mins. The solution was washed with a saturated NH_4Cl solution and extracted with CH_2Cl_2 (2 x 40 mL). The organics were combined, washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by Si gel FC (*n*-hex/EtOAc 4:1 → 7:3) to give α-amido ester **143** as a yellow oil (215 mg, 74%); Si gel TLC R_f 0.24 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 3272, 2952, 2868, 1742, 1655, 1531, 1460, 1439, 1348, 1304, 1273, 1226, 1200, 1142, 1058, 727, 767; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.30 (*br.* s, 1H, N*H*), 7.15 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.79 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 6.74 (dd, *J* = 8.2, 1.3 Hz, 1H, Ar*H*), 3.81 (s, 3H, OCH_3), 3.71 (d, *J* = 6.3 Hz, 2H, OCH_2), 3.51 (s, 2H, CH_2COOCH$_3$), 2.45 (d, *J* = 7.2 Hz, 2H, ArCH_2), 2.14 – 2.00 (m, 1H, OCH$_2$C*H*), 1.91 – 1.77 (m, 1H, ArCH$_2$C*H*), 1.00 (d, *J* = 6.7 Hz, 6H, OCH$_2$CHCH_3 x 2), 0.88 (d, *J* = 6.8 Hz, 6H, ArCH$_2$CHCH_3 x 2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.3 (*C*=O), 163.7 (*C*=O), 154.3 (Ar*C*), 140.4 (Ar*C*), 127.8 (Ar*C*), 123.9 (Ar*C*), 122.4 (Ar*C*), 109.8 (Ar*C*), 74.8 (OCH_2), 52.7 (OCH_3), {41.5, 41.3 : H*C*-COOMe & ArCH_2}, {29.4, 28.5 : ArCH$_2$*C*H & ArOCH$_2$*C*H}, 22.7 [ArCHCH$_2$*C*(CH$_3$)$_2$], 19.4 [ArOCHCH$_2$*C*(CH$_3$)$_2$]; ***LRMS*** *m/z* (Cl^+) 322.2 $[M+H]^+$, 385.2 $[M+CH_3CN+Na]^+$; ***HRMS*** *m/z calcd.* for $C_{18}H_{28}NO_4$ 322.2018, found 322.2000, Δ = -5.6 ppm.

Methyl (*E*)-4-(benzyloxy)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)but-2-enoate (144) & methyl (*Z*)-4-(benzyloxy)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)but-2-enoate (145)



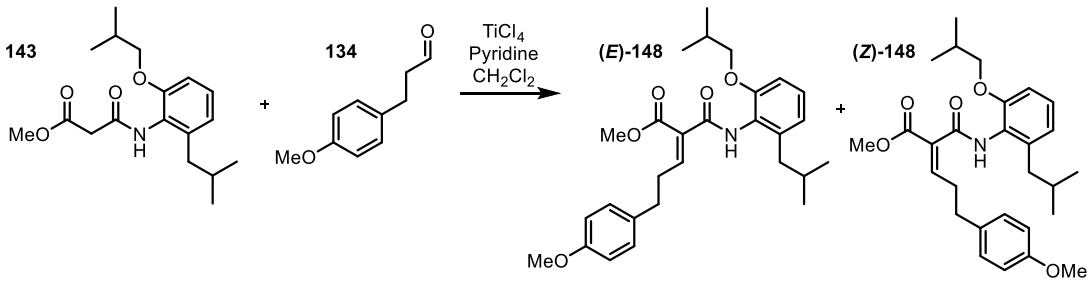
A solution of α-amido ester **143** (177 mg, 0.55 mmol) in dry CH_2Cl_2 (1.4 mL) in a round bottom flask was cooled to 0 °C in an ice bath. To the cooled solution was added $TiCl_4$ by syringe (1.0 M solution in CH_2Cl_2, 0.60 mL, 0.60 mmol) dropwise over 10 mins. The resulting mixture was stirred with cooling for 30 mins at 0 °C, then 2-(benzyloxy)acetaldehyde (**123**, 90 mg, 0.59 mmol) was added (diluted in 1.4 mL CH_2Cl_2) by syringe. The reaction mixture was stirred for 10 mins at 0 °C

after which anhydrous pyridine (0.09 mL, 1.10 mmol) was added dropwise (caution: exothermic). The reaction was allowed to warm gradually to RT overnight. The reaction mixture was poured over ice and extracted with EtOAc (3 x 30 mL). The organic solution was then washed with brine, dried over $MgSO_4$ and concentrated to dryness. The crude residue was purified by Si gel FC (*n*-hex/EtOAc 4:1) to give:

(*E*)-144 as a white semi-solid (61 mg, 25%); Si gel TLC R_f 0.40 (*n*-hex/EtOAc 7:3); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H, N*H*), 7.65 (t, *J* = 4.3 Hz, 1H, C=C*H*), 7.41 – 7.26 (m, 5H, OBn Ar*H*), 7.14 (t, *J* = 8.0 Hz, 1H, *N*-Ar*H*), 6.80 (dd, *J* = 7.6 Hz, 0.8 Hz, *N*-Ar*H*), 6.75 (dd, *J* = 8.2, 1.3 Hz, 1H, *N*-Ar*H*), 4.85 (d, *J* = 4.3 Hz, 2H, C=CCH_2), 4.56 (s, 2H, OCH_2Ph), 3.86 (s, 3H, OCH_3), 3.71 (d, *J* = 6.4 Hz, 2H, ArOCH_2), 2.47 (d, *J* = 7.2 Hz, 2H, ArCH_2), 2.10 – 1.95 [m, 1H, $OCH_2CH(CH_3)_2$], 1.93 – 1.73 [m, 1H, $ArCH_2CH(CH_3)_2$], 0.96 [d, *J* = 6.7 Hz, 6H, $OCH_2CH(CH_3)_2$], 0.88 [d, *J* = 6.6 Hz, 6H, $ArCH_2CH(CH_3)_2$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.8 (O=*C*OMe), 162.0 (O=*C*NH), 158.1 (C=*C*CH_2), 154.2 (Ar*C*), 140.0 (Ar*C*), 137.8 (Ar*C*), 128.5 (Ar*C*), 127.9 (Ar*C*), 127.8 (Ar*C*), 127.4 (Ar*C*), 123.9 (Ar*C*), 122.2 (Ar*C*), 109.7 (Ar*C*), 74.6 (OCH_2C), 73.1 (OCH_2Ph), 70.0 (C=CCH_2), 52.6 (OCH_3), 41.3 (NArCH_2), 29.4 ($ArCH_2C$), 28.4 (OCH_2C), 22.6 [$OCH_2CH(CH_3)_2$], 19.2 [$ArCH_2CH(CH_3)_2$]; ***LRMS*** *m/z* (MS ES$^+$) 454.26 [M+H]$^+$, 476.24 [M+Na]$^+$; ***HRMS*** *m/z* calcd. for $C_{27}H_{36}NO_5$ 454.2593, found 454.2590, Δ = -0.7 ppm.

(*Z*)-145 as a white semi-solid (124 mg, 52%); Si gel TLC R_f 0.36 (*n*-hex/EtOAc 7:3); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.16 (s, 1H, N*H*), 7.88 (t, *J* = 4.7 Hz, 1H, C=C*H*), 7.42 – 7.28 (m, 5H, OBn Ar*H*), 7.15 (t, *J* = 8.0 Hz, 1H, *N*-Ar*H*), 6.80 (d, *J* = 7.7 Hz, 1H, *N*-Ar*H*), 6.75 (d, *J* = 8.1 Hz, 1H, *N*-Ar*H*), 4.59 (2 x s, 4H, C=CCH_2 & OCH_2Ph), 3.86 (s, 3H, OCH_3), 3.71 (d, *J* = 6.3 Hz, 2H, ArOCH_2), 2.46 (d, *J* = 7.1 Hz, 2H, ArCH_2), 2.12 – 1.97 [m, 1H, $OCH_2CH(CH_3)_2$], 1.92 – 1.78 [m, 1H, $ArCH_2CH(CH_3)_2$], 0.98 [d, *J* = 6.8 Hz, 6H, $OCH_2CH(CH_3)_2$], 0.87 [d, *J* = 6.6 Hz, 6H, $ArCH_2CH(CH_3)_2$]; ***^{13}C NMR*** *m/z* ($CDCl_3$, 101 MHz) δ 167.1 (O=*C*OMe), 161.1 (O=*C*NH), 155.2 (C=*C*CH_2), 154.1 (Ar*C*), 140.1 (Ar*C*), 137.6 (Ar*C*), 128.5 (Ar*C*), 127.9 (Ar*C*), 127.8 (Ar*C*), 127.4 (Ar*C*), 125.6 (Ar*C*), 122.2 (Ar*C*), 109.6 (Ar*C*), 74.6 (OCH_2C), 72.9 (OCH_2PH), 69.1 (C=CCH_2), 52.4 (OCH_3), 41.3 (NArCH_2), 29.3 ($ArCH_2C$), 28.4 (OCH_2C), 22.6 [$OCH_2CH(CH_3)_2$], 19.2 [$ArCH_2CH(CH_3)_2$]; ***LRMS*** *m/z* (ES$^+$) 454.26 [M+H]$^+$, 476.25 [M+Na]$^+$; ***HRMS*** *m/z* calcd. for $C_{27}H_{36}NO_5$ 454.2593, found 454.2591, Δ = -0.4 ppm.

Methyl (*E*)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenyl)pent-2-enoate [(*E*)-148)] & methyl (*Z*)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenyl)pent-2-enoate [(*Z*)-148)]



A solution of α-amido ester **143** (180 mg, 0.56 mmol) in CH_2Cl_2 (1.5 mL) in a round bottom flask was cooled to 0 °C in an ice bath. To the cooled solution, was added $TiCl_4$ by syringe (1.0 M in CH_2Cl_2, 0.62 mL, 0.62 mmol) drop-wise over 10 mins. The resulting mixture was stirred with cooling for 30 mins at 0 °C, then 3-(4-methoxyphenyl)propanal (**134**, 101 mg, 0.62 mmol) was added (diluted in 1.5 mL CH_2Cl_2) by syringe. The reaction mixture was stirred for 10 mins at 0 °C after which anhydrous pyridine (0.09 mL, 1.12 mmol) was then added drop-wise (caution: exothermic). The reaction was allowed to warm gradually to RT and stirred for 4 h under N_2. The reaction mixture was poured over ice and extracted with EtOAc (× 3). The organic solution was then washed with brine, dried over $MgSO_4$ and concentrated to dryness. The crude residue was purified by Si gel FC (*n*-hex/EtOAc 7.1 → 8:3) to afford a mixture of *Z*:*E* isomers in a 29:71 ratio (199 mg, 76%). After several further Si gel FC attempts, an appreciable amount of each isomer was isolated for analysis purposes:

(E)*-148:** Si gel TLC R_f 0.18 (*n*-hex/EtOAc 4:1); ***^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.19 – 7.08 (m, 3H), 6.87 – 6.69 (m, 4H), 3.82 (s, 3H), 3.75 (s, 3H), 3.70 (d, *J* = 6.6 Hz, 2H), 3.00 (q, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.48 (d, *J* = 7.2 Hz, 2H), 2.06 – 1.92 (m, 1H), 1.91 – 1.77 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz): δ 162.9, 158.0, 154.2, 153.2, 140.3, 132.7, 129.5, 128.7, 127.5, 122.2, 114.0, 113.8, 109.6, 74.8, 55.2, 52.4, 41.2, 33.9, 31.9, 29.2, 28.3, 22.6, 19.3, 19.2. HRMS (ES) (of *E*:*Z* mixture): *m/z calcd.* for $C_{28}H_{38}NO_5$ 468.2750 $[M+H]^+$, found 468.2744.

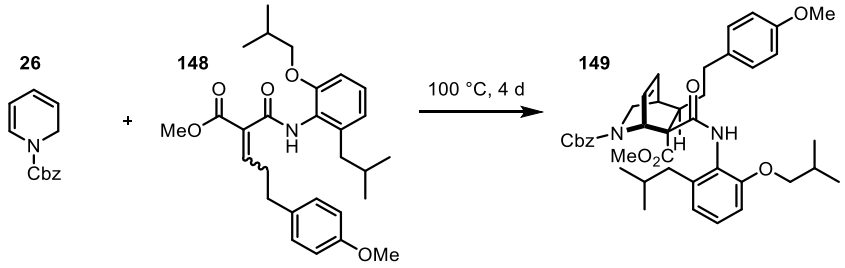
(Z)*-148:** Si gel TLC R_f 0.27 (*n*-hex/EtOAc 4:1); ***^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.03 (s, 1H), 7.64 (t, *J* = 7.1 Hz, 1H), 7.18 – 7.09 (m, 3H), 6.88 – 6.82 (m, 2H), 6.80 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.74 (dd, *J* = 8.3, 1.2 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.71 (d, *J* = 6.3 Hz, 2H), 2.92 – 2.74 (m, 4H), 2.46 (d, *J* = 7.2 Hz, 2H), 2.11 – 1.97 [m, 1H), 1.92 – 1.78 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H); ***^{13}C NMR*** ($CDCl_3$, 101 MHz): δ 168.0, 162.9, 161.9, 158.1, 154.6, 154.2, 154.1, 153.2, 140.1, 132.9, 129.5, 129.3, 128.7, 127.5, 127.3, 126.9, 122.2, 122.2, 114.0, 113.8, 109.6, 74.8, 74.6, 55.3, 55.2, 52.4, 52.2, 41.3, 41.2, 34.0, 33.9, 32.8, 31.9, 29.3, 29.2, 28.4, 28.3, 22.6, 19.3, 19.2.

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*General procedure for DA reactions between α-amido acrylates and N-Cbz-1,2-dihydropyridine (**GP1**):*

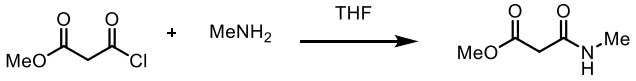
N-Cbz-1,2-dihydropyridine (1.5-2.5 eq.) and α-amido acrylate (1 eq.) were transferred to a Biotage® microwave vial containing a Teflon-coated magnetic stirrer bar which was subsequently thoroughly purged with Ar prior to sealing. The reaction was then heated at 100 °C until consumption of the dienophile was observed by TLC analysis. The reaction mixture was directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

2-Benzyl 6-methyl (1*R*,4*S*,5*R*,6*S*)-6-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenethyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (149)



According to **GP1**, *N*-Cbz-1,2-dihydropyridine (133 mg, 0.62 mmol) and methyl 2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-5-(4-methoxyphenyl)pent-2-enoate **148** (145 mg, 0.31 mmol; as a 29:71 mixture of *Z*:*E* isomers) were heated for 4 d. FC purification (*n*-hex/EtOAc 4:1 → 3:2) afforded *exo*-ester **149** exclusively as an off-white solid (108 mg, 51%); ***mp*** 39 – 40 °C; Si gel TLC R_f 0.24 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 3387, 2954, 2928, 2868, 1740, 1693, 1584, 1512, 1457, 1416, 1366, 1335, 1245, 1179, 1115, 1054, 748; ***^{1}H NMR*** & ***^{13}C NMR***: complex even at 398 K due to rotamers (Cbz) and atropisomerism (*N*-Aryl) – see spectra; ***LRMS*** *m/z* (ES+) 683.37 $[M+H]^+$, 705.35 $[M+Na]^+$; ***HRMS*** (ES) *m/z calcd.* for $C_{41}H_{51}N_2O_7$ 683.3696, found 683.3671. A single crystal X-ray structure determination was performed on this compound to confirm its structure (see Appendix).

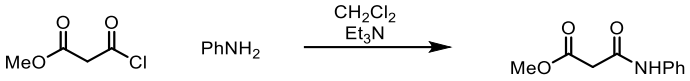
Methyl 3-(methylamino)-3-oxopropanoate (150x)[143]



To a solution of methyl 3-chloro-3-oxopropionate (0.5 mL, 4.52 mmol) in dry THF (9 mL) was added methylamine solution (2.0 M in THF, 4.52 mmol, 9.04 mmol) *via* syringe at 0 °C under N_2. The reaction was stirred for 3 h at 0 – 5 °C after which the solvent was evaporated under reduced pressure. The residue was purified by Si gel FC (*n*-hex/EtOAc 1:6 → 100 % EtOAc) to give the α-amido ester **150x** as a yellow oil (367 mg, 62%); Si gel TLC R_f 0.15 (*n*-hex/EtOAc 1:9); ***^{1}H NMR***

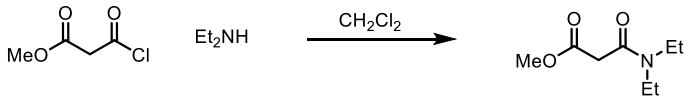
($CDCl_3$, 400 MHz) δ 7.11 (*br.* s, 1H, N*H*), 3.73 (s, 3H, OC*H*$_3$), 3.31 (s, 2H, O=CC*H*$_2$), 2.83 (d, *J* = 4.9 Hz, 3H, NC*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.1 (O=*C*OMe), 165.5 (O=*C*NHMe), 52.4 (O*C*H$_3$), 40.8 (O=C*C*H$_2$), 26.3 (N*C*H$_3$). The spectroscopic data were in accordance with the literature.[143]

Methyl 3-oxo-3-(phenylamino)propanoate (150y)[144]



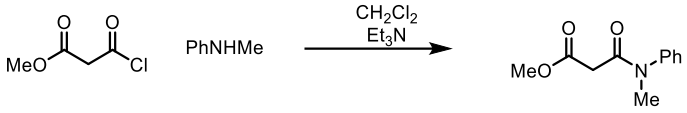
To a solution of methyl 3-chloro-3-oxopropanoate (0.5 mL, 4.52 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C under N_2 was added phenylamine (0.41 mL, 4.52 mmol) after which a suspension resulted. Et_3N (0.73 mL, 5.2 mmol) was then added and after initial white fumes, a clear yellow solution formed. The reaction was stirred at 0 °C for 2 h under N_2. The reaction mixture was concentrated in vacuo, diluted in EtOAc and then sequentially washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by Si gel FC (*n*-hex/EtOAc 4:1 → 3:2) to afford α-amido ester **150y** as a yellow semi-solid (865 mg, 99 %); Si gel TLC ***R$_f$*** 0.15 (*n*-hex/EtOAc 7:3); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.16 (*br.* s, 1H, N*H*), 7.55 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.34 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.13 (t, *J* = 7.4 Hz, 1H, Ar*H*), 3.81 (s, 3H, OC*H*$_3$), 3.49 (s, 2H, O=CC*H*$_2$); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.5 (O=*C*OMe), 162.7 (O=*C*NPh), 137.4 (Ar*C*), 129.0 (Ar*C*), 124.6 (Ar*C*), 120.1 (Ar*C*), 52.7 (O*C*H$_3$), 41.3 (O=C*C*H$_2$). The spectroscopic data were in accordance with the literature.[144]

Methyl 3-(diethylamino)-3-oxopropanoate (150a)[145]



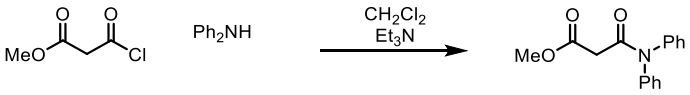
To a solution of methyl 3-chloro-3-oxopropanoate (0.7 mL, 6.53 mmol) in dry CH_2Cl_2 (32 mL) at 0 °C under N_2 was added diethylamine (1.35 mL, 13.05 mmol). The reaction was allowed to warm up to RT and stirred for 3 h. The reaction mixture was further diluted in CH_2Cl_2 and then sequentially washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to provide α-amido ester **150a** as an orange oil (1.03 g, 91 %); Si gel TLC ***R$_f$*** 0.31 (*n*-hex/EtOAc 1:4); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) 3.75 (s, 3H, OC*H*$_3$), 3.44 (s, 2H, O=CC*H*$_2$), 3.40 (q, *J* = 7.4 Hz, 2H, NC*H*$_2$), 3.30 (q, *J* = 7.2 Hz, 2H, NC*H*$_2$), 1.19 (t, *J* = 7.2 Hz, 3H, NCH$_2$C*H*$_3$), 1.14 (t, *J* = 7.1 Hz, 3H, NCH$_2$C*H*$_3$); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 168.3 (*C*=O), 165.1 (*C*=O), 52.4 (O*C*H$_3$), 42.7 (O=C*C*H$_2$), 41.1 & 40.3 (N*C*H$_2$CH$_3$ x 2), 14.2 & 12.8 (NCH$_2$*C*H$_3$ x 2). The spectroscopic data were in accordance with the literature.[145]

Methyl 3-(methyl(phenyl)amino)-3-oxopropanoate (150b)[146]



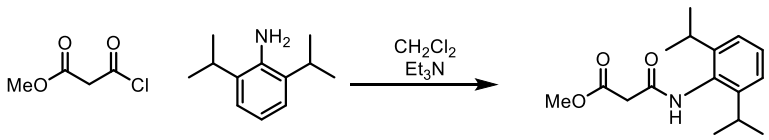
To a solution of methyl 3-chloro-3-oxopropanoate (0.5 mL, 4.52 mmol) in dry CH_2Cl_2 (23 mL) at 0 °C under N_2 was added *N*-methylaniline (0.44 mL, 4.11 mmol) after which a suspension resulted. Et_3N (0.69 mL, 4.93 mmol) was then added and after initial white fumes, a clear yellow solution formed. The reaction was allowed to warm up to RT and stirred for 2 h under N_2. The reaction mixture was concentrated, diluted in EtOAc and then sequentially washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford α-amido ester **150b** as an orange oil (840 mg, 99%); Si gel TLC $\boldsymbol{R_f}$ 0.20 (*n*-hex/EtOAc 4:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.46 – 7.31 (m, 3H, Ar*H*), 7.25 – 7.19 (m, 2H, Ar*H*), 3.67 (s, 3H, OCH_3), 3.30 (s, 3H, NCH_3), 3.22 (s, 2H, O=CCH_2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 168.2 (*C*=O), 165.9 (*C*=O), 143.5 (Ar*C*), 130.0 (Ar*C*), 128.3 (Ar*C*), 127.3 (Ar*C*), 52.3 (OCH_3), 41.3 (O=CCH_2), 37.5 (NCH_3). The spectroscopic data were in accordance with the literature.[146]

Methyl 3-(diphenylamino)-3-oxopropanoate (150c)[147]



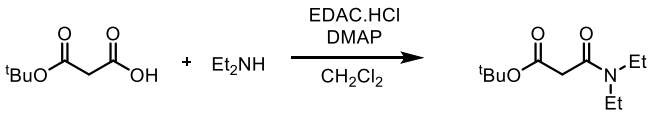
To a solution of methyl 3-chloro-3-oxopropanoate (0.90 mL, 8.40 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C under N_2 was added diphenylamine (1.18 g, 7.0 mmol) followed by Et_3N (1.17 mL, 8.40 mmol). The reaction mixture was slowly allowed to warm up to RT and stirred for 2 h. The reaction mixture was further diluted in CH_2Cl_2 and then sequentially washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was recrystallized (*n*-hex/Et_2O 1:2) to provide α-amido ester **150c** as a pale yellow powder (820 mg, 43%); Si gel TLC $\boldsymbol{R_f}$ 0.23 (*n*-hex/EtOAc 3:2); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.52 – 7.14 (m, 10H, Ar*H*), 3.70 (s, 3H, OCH_3), 3.41 (s, 2H, O=CCH_2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 168.0 (*C*=O), 166.0 (*C*=O), 142.4 (Ar*C*), 130.0 (Ar*C*), 129.0 (Ar*C*), 128.7 (Ar*C*), 128.4 (Ar*C*), 126.5 (Ar*C*), 126.3 (Ar*C*), 52.4 (OCH_3), 42.5 (O=CCH_2); ***LRMS*** *m/z* (ES^+) 270.11 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{16}H_{16}NO_3$ 270.1130, found 270.1143, Δ = 4.8 ppm. The spectroscopic data were in accordance with the literature.[147]

Methyl 3-((2,6-diisopropylphenyl)amino)-3-oxopropanoate (150e)



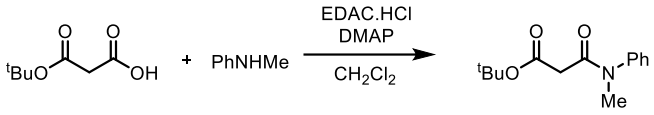
To a solution of methyl 3-chloro-3-oxopropanoate (0.68 mL, 6.40 mmol) in dry CH_2Cl_2 (26 mL) at 0 °C under N_2 was added 2,6-diisopropylaniline (1.0 mL, 5.3 mmol) followed by Et_3N (0.89 mL, 6.4 mmol). The reaction mixture was slowly allowed to warm up to RT and stirred for 3 h. The reaction mixture was further diluted in CH_2Cl_2 and then sequentially washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by Si gel FC (*n*-hex/Et_2O 4:1 → 7:3) to provide α-amido ester **150d** as a fluffy white solid (1.27 g, 86%); ***mp*** 110 – 113 °C; Si gel TLC $\boldsymbol{R_f}$ 0.00 (*n*-hex/Et_2O 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 3235, 2966, 1751, 1648, 1529, 1437, 1337, 1277, 1255, 1155, 796, 745, 709; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.49 (*br.* s, 1H), 7.34 – 7.28 (m, 1H, Ar*H*), 7.23 – 7.16 (m, 2H, Ar*H*), 3.83 (s, 3H, OCH_3), 3.56 (s, 2H, O=CCH_2), 3.04 (h, *J* = 6.9 Hz, 2H, C*H*), 1.20 [d, *J* = 6.9 Hz, 12H, (CH_3)$_2$ x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 170.6 (O=*C*OMe), 164.2 (O=*C*NAr), 145.9 (Ar*C*), 130.8 (Ar*C*), 128.5 (Ar*C*), 123.5 (Ar*C*), 52.7 (*O*CH_3), 40.8 (O=C*C*H_2), 28.9 (Ar*C*H) 23.6 [*br.* m, CH(*C*H_3)$_2$]; ***LRMS*** *m/z* (ES^+) 278.18 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{16}H_{24}NO_3$ 278.1756, found 278.1762, Δ = 2.2 ppm.

Tert-butyl 3-(diethylamino)-3-oxopropanoate (150f)[148]



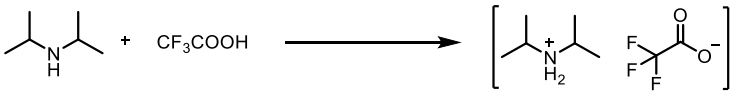
To a solution of DMAP (159 mg, 1.30 mmol) and diethylamine (0.67 mL, 6.49 mmol) in dry CH_2Cl_2 (26 mL) was added 3-(tert-butoxy)-3-oxopropanoic acid (1 mL, 6.49 mmol). The reaction mixture was stirred under N_2 for 2 h. The reaction mixture was then diluted further in CH_2Cl_2 and washed with 1N HCL solution, brine (x 2) and dried over $MgSO_4$. The organic solution was then concentrated under reduced pressure to provide α-amido ester **150f** as a colourless oil (1.21 g, 87%); Si gel TLC $\boldsymbol{R_f}$ 0.20 (*n*-hex/Et_2O 3:2); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 3.39 (q, *J* = 7.1 Hz, 2H, NCH_2), 3.33 (s, 2H, O=CCH_2), 3.28 (q, *J* = 7.1 Hz, 2H, NCH_2), 1.47 [s, 9H, OC(CH_3)$_3$], 1.18 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3), 1.13 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 167.1 (O=*C*), 165.6 (O=*C*), 81.8 [O*C*H(CH_3)$_3$], 42.5 (O=C*C*H_2), 40.1 (N*C*H_2CH_3), 28.0 [OCH(*C*H_3)$_3$], 14.2 & 12.8 (NCH_2CH_3 x 2). The spectroscopic data were in accordance with the literature.[148]

Tert-butyl 3-(methyl(phenyl)amino)-3-oxopropanoate (150g)[146]



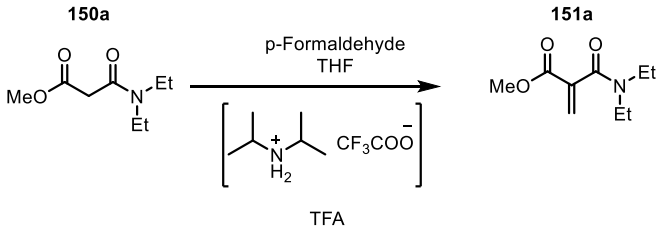
To a solution of DMAP (159 mg, 1.30 mmol) and *N*-methylaniline (0.70 mL, 6.49 mmol) in dry CH_2Cl_2 (26 mL) was added 3-(tert-butoxy)-3-oxopropanoic acid (1 mL, 6.49 mmol). The reaction mixture was stirred under N_2 for 2 h. The reaction mixture was then diluted further in CH_2Cl_2 and washed with 1N HCL solution, brine (x 2) and dried over $MgSO_4$. The organic solution was then concentrated under reduced pressure to provide α-amido ester **150g** as a dark orange oil (1.50 g, 93%); Si gel TLC R_f0.38 (*n*-hex/Et_2O 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 2980, 2936, 1720, 1634, 1478, 1460, 1393, 1368, 131257, 1155, 1117, 850, 734, 701; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.45 – 7.38 (m, 2H, Ar*H*), 7.38 – 7.32 (m, 1H, Ar*H*), 7.25 – 7.21 (m, 2H, Ar*H*), 3.30 (s, 3H, NCH_3), 3.12 (s, 2H, O=CCH_2), 1.42 [s, 9H, OC(CH_3)$_3$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 167.0 (*C*=O), 166.5 (*C*=O), 143.7 (Ar*C*), 129.9 (Ar*C*), 128.2 (Ar*C*), 127.3 (Ar*C*), 81.6 [O*C*H(CH_3)$_3$], 42.7 (O=C*C*H_2), 37.4 (N*C*H_3), 28.0 [OCH(*C*H_3)$_3$]. The spectroscopic data were in accordance with the literature.[146]

Diisopropylammonium 2,2,2-trifluoroacetate[149]



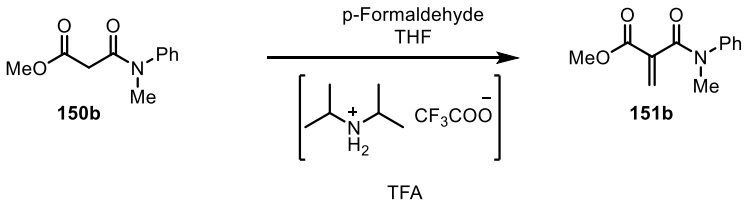
According to the method of Connell,[149] to a stirred mixture of diisopropylamine (7.05 mmol, 50 mmol) in Et_2O (50 mL) at 0 °C was added trifluoroacetic acid dropwise (3.76 mmol, 50 mmol) *via* a dropping funnel. The reaction mixture was stirred at 0 °C for an additional 5 min. The newly formed crystals were filtered and washed with Et_2O (20 mL) and dried under vacuum to afford diisopropylammonium 2,2,2-trifluoroacetate as a white crystalline solid (10.12 g, 95%); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.94 (*br.* s, 2H, NH_2), 3.35 (dh, *J* = 13.3, 6.7 Hz, 2H, NC*H* x 2), 1.32 [d, *J* = 6.5 Hz, 12H, (CH_3)$_2$ x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 161.7 (q, J = 35.1 Hz, *C*=O), 116.5 (q, J = 293.8 Hz, *C*CF_3), 46.8 (N*C*H), 18.8 [NCH(*C*H_3)$_2$]. The spectroscopic data were in accordance with the literature.[149]

Methyl 2-(diethylcarbamoyl)acrylate (151a)



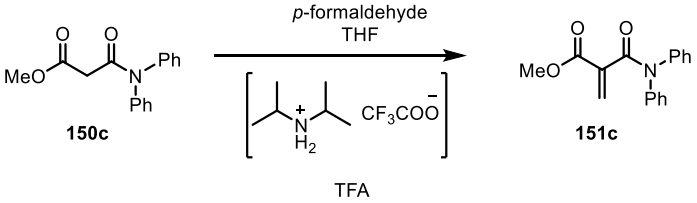
Adapted from the method of Connell,[149] to a solution of α-amido ester **150a** (400 mg, 2.31 mmol), *p*-formaldehyde (208 mg, 6.93 mmol) and $CF_3COONH_2{}^iPr_2$ salt (497 mg, 2.31 mmol) in dry THF (20 mL) was added TFA (18 µL, 0.23 mmol). The reaction mixture was then heated at 60 °C under N_2 for 18 h. The reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl solution (x 2), brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by Si gel FC (*n*-hex/EtOAc 1:4 → 2:3) to give α-amido acrylate **151a** as a pale yellow oil (248 mg, 58%); Si gel TLC $\boldsymbol{R_f}$ 0.39 (*n*-hex/EtOAc 1:4); ***ATR-IR*** ν_{max}/cm^{-1} 1723, 1618, 1486, 1460, 1440, 1326, 1264, 1201, 1173, 1122; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 6.41 (d, *J* = 0.8 Hz, 1H, C=CH_a), 5.83 (d, *J* = 0.8 Hz, 1H, C=CH_b), 3.79 (s, 3H, OCH_3), 3.46 (q, *J* = 7.1 Hz, 2H, NCH_2CH$_3$), 3.23 (q, *J* = 7.2 Hz, 2H, NCH_2CH$_3$), 1.18 (t, *J* = 7.1 Hz, 3H, NCH$_2$CH_3), 1.10 (t, *J* = 7.1 Hz, 3H, NCH$_2$CH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.3 (*C*=O), 164.4 (*C*=O), 138.4 (*C*=CH$_2$), 127.8 (C=*C*H$_2$), 52.5 (O*C*H$_3$), 42.9 & 39.0 (N*C*H$_2$CH$_3$ x 2), 13.8 & 12.6 (NCH$_2$*C*H$_3$ x 2); ***LRMS*** *m/z* (Cl^+) 220.10 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{12}H_{14}NO_3$ 220.0974, found 220.0968, Δ = -2.7 ppm.

Methyl 2-(methyl(phenyl)carbamoyl)acrylate (151b)



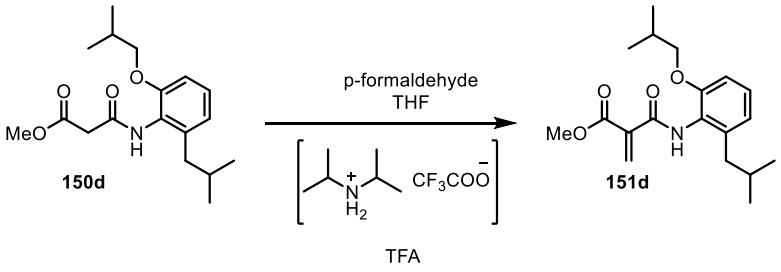
Adapted from the method of Connell,[149] to a solution of α-amido ester **150b** (150 mg, 0.752 mmol), *p*-formaldehyde (65 mg, 2.17 mmol) and $CF_3COONH_2{}^iPr_2$ salt (156 mg, 0.72 mmol) in dry THF (7 mL) was added TFA (6 µL, 0.07 mmol). The reaction mixture was then heated at 60 °C under N_2 for 18 h. The reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl solution (x 2), brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by Si gel FC (*n*-hex/EtOAc 1:1 → 3:2) to give α-amido acrylate **151b** as a pale yellow oil (115 mg, 73%); Si gel TLC $\boldsymbol{R_f}$ 0.52 (*n*-hex/EtOAc 1:4); ***ATR-IR*** ν_{max}/cm^{-1}1725, 1648, 1595, 1496, 1435, 1377, 1264, 1201, 1160, 1112, 772, 699; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.33 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.30 – 7.20 (m, 1H, Ar*H*), 7.13 (d, *J* = 7.7 Hz, 2H, Ar*H*), 6.21 (s, 1H, C=CH_a), 5.85 (s, 1H, C=CH_b), 3.60 (s, 3H, OCH_3), 3.40 (s, 3H, NCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.4 (*C*=O), 164.3 (*C*=O), 143.3 (Ar*C*), 138.6 (*C*=CH$_2$), 130.3 (Ar*C*), 129.4 (Ar*C*), 127.6 (C=*C*H$_2$), 127.2 (Ar*C*), 52.1 (O*C*H$_3$), 37.3 (N*C*H$_3$); ***LRMS*** *m/z* (ES^+) 220.10 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{12}H_{14}NO_3$ 220.0974, found 220.0968, Δ = -2.7 ppm.

Methyl 2-(diphenylcarbamoyl)acrylate (151c)



Adapted from the method of Connell,[149] to a solution of α-amido ester **150c** (800 mg, 2.97 mmol), *p*-formaldehyde (268 mg, 8.91 mmol) and $CF_3COONH_2{}^iPr_2$ salt (640 mg, 2.97 mmol) in dry THF (20 mL) was added TFA (23 µL, 0.29 mmol). The reaction mixture was heated at 60 °C under N_2 for 20 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue purified by Si gel FC (*n*-hex/Et_2O 3:7) to give α-amido acrylate **151c** as a pale yellow oil (780 mg, 93%); Si gel TLC $\boldsymbol{R_f}$ 0.38 (*n*-hex/Et_2O 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 1727, 1662, 1593, 1490, 1399, 1351, 1266, 1201, 1132, 974, 760; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.44 – 7.06 (m, 10H, Ar*H*), 6.31 (s, 1H, C=C$H_{\underline{a}}$), 6.09 (s, 1H, C=C$H_{\underline{b}}$), 3.60 (s, 3H, OCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.2 (*C*=O), 164.2 (*C*=O), 142.2 (Ar*C*), 139.3 (*C*=CH_2), 131.2 (Ar*C*), 129.2 (*C*=CH_2), 128.8 (*br.* Ar*C*), 127.5 (*br.* Ar*C*), 126.5 (*br.* Ar*C*), 52.2 (O*C*H_3); ***LRMS*** *m/z* (ES^+) 282.11 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{17}H_{16}NO_3$ 282.1130, found 282.1142, Δ = 4.3 ppm.

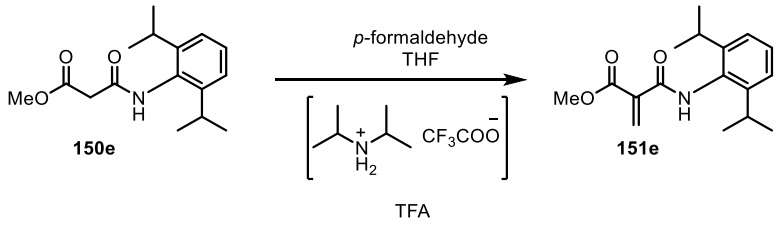
Methyl 2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)acrylate (151d)



Adapted from the method of Connell,[149] to a solution of α-amido ester **150d** (65 mg, 0.20 mmol), *p*-formaldehyde (18 mg, 0.61 mmol) and $CF_3COONH_2{}^iPr_2$ salt (44 mg, 0.20 mmol) in dry THF (2 mL) was added TFA (2 µL, 0.02 mmol). The reaction mixture was heated at 60 °C under N_2 for 18 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue purified by Si gel FC (*n*-hex/Et_2O 1:1) to give α-amido acrylate **151d** as a colourless oil (33 mg, 50%); Si gel TLC $\boldsymbol{R_f}$ 0.38 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 3310, 2953, 2868, 1745, 1733, 1666, 1581, 1516, 1508, 1460, 1266, 1053, 776, 734; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 9.57 (s, 1H, N*H*), 7.21 (d, *J* = 1.6 Hz, 1H, C=C$H_{\underline{a}}$), 7.15 (t, *J* = 7.9 Hz, 1H, Ar*H*), 6.83 (d, *J* = 1.6 Hz, 1H, C=C$H_{\underline{b}}$), 6.80 (dd, *J* = 7.8, 1.3 Hz, 1H, Ar*H*), 6.75 (dd, *J* = 8.2, 1.3 Hz, 1H, Ar*H*), 3.89 (s, 3H, OCH_3), 3.71 (d, *J* = 6.3 Hz, 2H, OCH_2), 2.48 (d, *J* = 7.2 Hz, 2H, ArCH_2), 2.04 (dh, *J* = 13.2, 6.5 Hz, 1H, OCH_2CH), 1.85 (dh, *J* = 13.6, 6.8 Hz, 1H, $ArCH_2CH$), 0.97 (d, *J* = 6.7 Hz, 6H, OCH_2CHCH_3 x 2), 0.87 (d, *J* = 6.6 Hz, 6H, $ArCH_2CHCH_3$ x 2); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.9 (*C*=O), 160.7 (*C*=O), 154.1 (Ar*C*), {140.0,

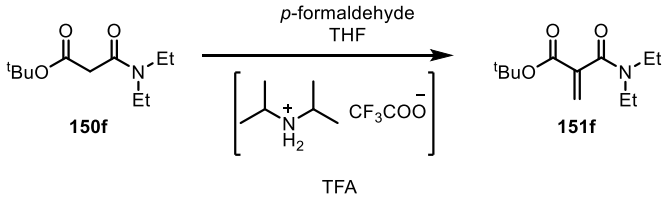
138.7, 132.8, 127.4 : Ar*C*'s & *C*=*C*H$_2$}, 124.2 (Ar*C*), 122.1 (Ar*C*), 109.7 (Ar*C*), 74.6 (O*C*H$_2$), 52.7 (O*C*H$_3$), 41.3 (Ar*C*H$_2$), {29.3, 28.4 : ArCH$_2$*C*H & ArOCH$_2$*C*H}, 22.6 [ArCHCH$_2$*C*(CH$_3$)$_2$], 19.2 [ArOCHCH$_2$*C*(CH$_3$)$_2$]; ***LRMS*** *m/z* (ES$^+$) 334.20 [M+H]$^+$; ***HRMS*** *m/z calcd.* for $C_{19}H_{28}NO_4$ 334.2018, found 334.2208, Δ = 3.0 ppm.

Methyl 2-((2,6-diisopropylphenyl)carbamoyl)acrylate (151e)



Adapted from the method of Connell,[149] to a solution of α-amido ester **150e** (800 mg, 2.88 mmol), *p*-formaldehyde (260 mg, 8.65 mmol) and CF$_3$COONH$_2$^{i}Pr$_2$ salt (620 mg, 2.88 mmol) in dry THF (20 mL) was added TFA (23 µL, 0.29 mmol). The reaction mixture was heated at 60 °C under N_2 for 16 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue purified by Si gel FC (*n*-hex/Et$_2$O 7:3 → 3:7) to give α-amido acrylate **151e** as an off-white fluffy solid (505 mg, 61%); ***mp*** 97-98 °C; Si gel TLC R_f 0.44 (*n*-hex/Et$_2$O 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 3235, 2966, 1751, 1648, 1529, 1437, 1338, 1255, 1214, 1155, 745, 709; ***^{1}H NMR*** (CDCl$_3$, 400 MHz) δ 9.66 (s, 1H, N*H*), 7.33 – 7.26 (m, 2H, Ar*H* & C=C*H*$_a$), 7.23 – 7.17 (m, 2H, Ar*H*), 6.90 (d, *J* = 1.8 Hz, 1H, C=C*H*$_b$), 3.92 (s, 3H, OC*H*$_3$), 3.05 (h, *J* = 6.9 Hz, 2H, ArC*H* x 2), 1.20 [d, *J* = 6.9 Hz, 12H, (C*H*$_3$)$_2$ x 2]; ***^{13}C NMR*** (CDCl$_3$, 101 MHz) δ 167.2 (*C*=O), 161.3 (*C*=O), {145.8, 139.7, 132.3, 131.2, 128.2, 123.4 : Ar*C*'s and *C*=*C*H$_2$}, 52.8 (O*C*H$_3$), 28.9 (Ar*C*H), 23.6 [*br.* M, CH(*C*H$_3$)$_2$]; ***LRMS*** *m/z* (ES$^+$) 290.18 [M+H]$^+$; ***HRMS*** *m/z calcd.* for $C_{17}H_{24}NO_3$ 290.1756, found 290.1758, Δ = 0.2 ppm.

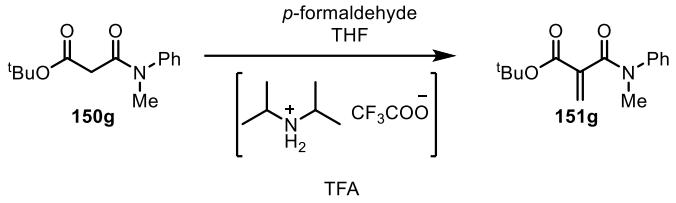
Tert-butyl 2-(diethylcarbamoyl)acrylate (151f)



Adapted from the method of Connell,[149] to a solution of α-amido ester **150f** (1.2g, 5.58 mmol), *p*-formaldehyde (503 mg, 16.7 mmol) and CF$_3$COONH$_2$^{i}Pr$_2$ salt (1.2g, 5.58 mmol) in dry THF (28 mL) was added TFA (43 µL, 0.56 mmol). The reaction mixture was heated at 60 °C under N_2 for 16 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue purified by Si gel FC (*n*-hex/Et$_2$O 3:2) to give α-amido acrylate **151f** as a yellow oil (558 mg, 44%); Si gel TLC R_f 0.27 (*n*-hex/Et$_2$O 1:4); ***ATR-IR*** ν_{max}/cm^{-1} 2977, 2931, 1722, 1640, 1460,

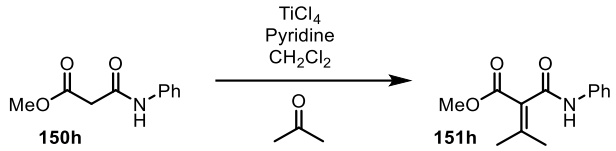
1368, 1258, 1158, 1118, 851; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 6.31 (d, 1H, *J* = 0.8 Hz, C=C*H*$_a$), 5.76 (d, 1H, *J* = 0.8 Hz, C=C*H*$_b$), 3.45 (q, *J* = 7.2 Hz, 2H, NC*H*$_2$), 3.21 (q, *J* = 7.1 Hz, 2H, NC*H*$_2$), 1.49 [s, 9H, OC(C*H*$_3$)$_3$], 1.17 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3), 1.11 (t, *J* = 7.1 Hz, 3H, NCH_2CH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.7 (*C*=O), 162.9 (*C*=O), 140.3 (*C*=CH_2), 126.7 (C=*C*H_2), 82.8 [O*C*H$(CH_3)_3$], 42.6 (N*C*H_2CH_3), 38.7 (O=C*C*H_2), 28.0 [OCH(*C*$H_3)_3$], 13.9 & 12.4 (NCH_2CH_3 x 2); ***LRMS*** *m/z* (ES^+) 228.16 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{12}H_{22}NO_3$ 228.1600, found 228.1602, Δ = 0.9 ppm.

Tert-butyl 2-(methyl(phenyl)carbamoyl)acrylate (151g)



Adapted from the method of Connell,[149] to a solution of α-amido ester **150g** (1.29g, 5.98 mmol), *p*-formaldehyde (540 mg, 17.95 mmol) and $CF_3COONH_2{}^{i}Pr_2$ salt (1.29g, 5.58 mmol) in dry THF (30 mL) was added TFA (46 µL, 0.56 mmol). The reaction mixture was heated at 60 °C under N_2 for 40 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue purified by Si gel FC (*n*-hex/Et_2O 3:2) to give α-amido acrylate **151g** as a yellow oil (873 mg, 56%); Si gel TLC ***R$_f$*** 0.38 (*n*-hex/Et_2O 1:4); ***ATR-IR*** ν_{max}/cm^{-1} 2976, 1715, 1650, 1595, 1496, 1394, 1368, 1272, 1257, 1149, 1110, 849, 768, 699; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.36 – 7.13 (m, 5H, Ar*H*), 6.14 (s, 1H, C=C*H*$_a$), 5.83 (s, 1H, C=C*H*$_b$), 3.39 (s, 3H, NC*H*$_3$), 1.32 [s, 9H, OC(C*H*$_3$)$_3$]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 162.6 (*C*=O), {143.4, 140.7, 129.2, 129.2, 127.2, 127.2 : ArC's & *C*=*C*H_2), 81.8 [O*C*H$(CH_3)_3$], 37.2 (N*C*H_3), 27.8 [OCH(*C*$H_3)_3$]; ***LRMS*** *m/z* (ES^+) 262.14 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{15}H_{20}NO_3$ 262.1443, found 262.1447, Δ = 1.5 ppm.

Methyl 3-methyl-2-(phenylcarbamoyl)but-2-enoate (151h)

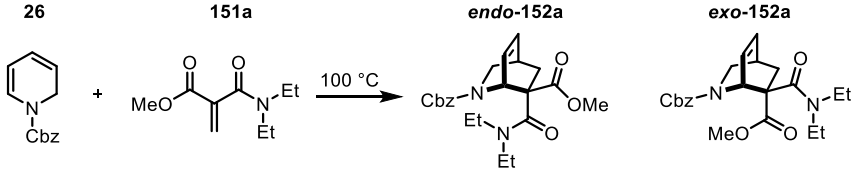


To a solution of α-amido ester **150h** (150 mg, 0.77 mmol) in CH_2Cl_2 (4 mL) in a round bottom flask was cooled to 0 °C in an ice bath. To the cooled solution, was added $TiCl_4$ by syringe (1M in CH_2Cl_2, 0.85 mL, 0.85 mmol) dropwise over 10 mins. The resulting mixture was stirred with cooling for 30 mins at 0 °C, then acetone (0.063 mL, 0.85 mmol) was added. The reaction mixture was stirred for 10 mins at 0 °C after which anhydrous pyridine (0.13 mL, 1.55 mmol) was then added dropwise (caution: exothermic). The reaction was allowed to warm gradually to RT

overnight after which it was poured over ice and extracted with EtOAc (3 x 40 mL). The organic solution was then washed with brine, dried over $MgSO_4$ and concentrated to dryness. The crude residue was purified by Si gel FC (*n*-hex/EtOAc 4:1 → 3:2) to afford tetra-substituted alkene **151h** as a white solid (137 mg, 76%); ***mp*** 137-142 °C; Si gel TLC R_f 0.22 (*n*-hex/EtOAc 3:2); ***ATR-IR*** ν_{max}/cm^{-1} 3240, 1715, 1652, 1547, 1444, 1331, 1258, 1217, 1062, 762; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.73 (*br.* s, 1H, N*H*), 7.58 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.35 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.14 (t, *J* = 7.4 Hz, 1H, Ar*H*), 3.78 (s, 3H, OCH_3), 2.17 (s, 3H, C=CC$_{\underline{a}}H_3$), 2.07 (s, 3H, C=C$_{\underline{b}}$CH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.1 (*C*=O), 164.6 (*C*=O), {155.1, 137.8, 129.1, 127.0, 124.5, 119.9 : Ar*C*'s & *C*=*C*}, 52.0 (O*C*H_3), 24.1 (C=C-*C*$_{\underline{a}}$H$_3$), 22.6 (C=C-*C*$_{\underline{b}}$H$_3$); ***LRMS*** *m/z* (ES^+) 234.11 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{13}H_{16}NO_3$ 234.1130, found 234.1127, Δ = --1.3 ppm.

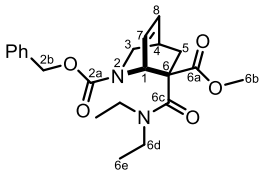
General procedure for DA reactions between α-amido acrylates and N-Cbz-1,2-dihydropyridine (GP1): *N*-Cbz-1,2-dihydropyridine (1.5-2.5 eq.) and α-amido acrylate (1 *eq.*) were transferred to a Biotage® microwave vial containing a Teflon-coated magnetic stirrer bar which was subsequently thoroughly purged with Ar prior to sealing. The reaction was then heated at 100 °C until consumption of the dienophile was observed by TLC analysis. The reaction mixture was directly loaded onto a Si gel column and purified by FC to afford the Diels-Alder adducts.

2-Benzyl 6-methyl (1*R*,4*R*,6*R*)-6-(diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-152a) & 2-Benzyl 6-methyl (1*R*,4*R*,6*S*)-6-(diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-152a).



According to **GP1**, *N*-Cbz-1,2-dihydropyridine (350 mg, 1.63 mmol) and α-amido acrylate **151a** (100 mg, 0.54 mmol) were heated for 7 d. FC purification (*n*-hex:EtOAc 4:1 → 2:3) afforded a mixture of diastereoisomers ***endo*-152a:*exo*-152a** in a 1.4:1 ratio (120 mg, 50%):

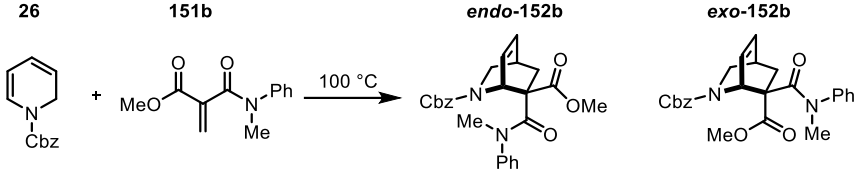
Isolated ***endo*-152a**, colourless paste; Si gel TLC R_f 0.30 (*n*-hex/Et_2O 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 2978, 2957, 1731, 1699, 1638, 1417, 1293, 1245, 1211, 1114, 736, 699; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



1H NMR (DMSO-d_6, 400 MHz, 373 K): δ 7.45 – 7.25 (m, 5H, Ar*H*), 6.48 – 6.36 [m, 2H : C(7)*H* & C(8)*H*], 5.22 – 5.18 [m, 1H, C(1)*H*], 5.11 – 4.97 (*AB*, m, 2H, C(2b)H_2], 3.64 [s, 3H, C(6b)H_3], 3.40 – 3.09 [m, 5H : C(6d)H_2 x 2 & C(3)H_a], 2.91 – 2.82 [m, 2H : C(4)*H* & C(3)H_b], 2.67 [*br.* s, 1H, C(5)H_a], 1.76 [*br.* s, 1H, C(5)H_b], 1.06 – 0.92 [m, 6H, C(6e)H_3 x 2]; ***13C NMR*** (DMSO-d_6, 101 MHz, 373 K): δ 171.3 [*C*(6a)], 166.0 [*C*(6c)], 154.0 (Ar*C*), 136.7 (Ar*C*), {134.1, 130.6 : *C*(7) & *C*(8)}, 127.7 (Ar*C*), 127.0 (Ar*C*), 126.8 (Ar*C*), 65.4 [*C*(2b)], 58.5 [*C*(6)], 51.6 [*C*(6b)], 49.0 [*C*(1)], 45.3 [*C*(3)], 39.8 [*C*(6d)], 32.6 [*C*(5)], 29.8 [*C*(4)], 11.81 [*C*(6e)]; ***LRMS*** *m/z* (ES+) 401.21 $[M+H]^+$, 423.19 $[M+Na]^+$; ***HRMS*** *m/z calcd.* for $C_{22}H_{29}N_2O_5$ 401.2076, found 401.2082, Δ = 1.5 ppm.

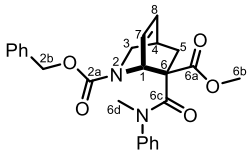
Exo*-152a** not fully separated from ***endo*-152a**, pale yellow paste; Si gel TLC R_f 0.25 (*n*-hex/Et_2O 3:7); distinguishable peaks only: ***1H NMR (DMSO-d_6, 400 MHz, 373 K): δ 6.51 – 6.45 (m, 1H), 6.33 – 6.25 (m, 1H), 5.14 (dd, *J* = 6.0, 0.8 Hz, 1H), 3.52 (s, 3H), 1.45 (dt, *J* = 12.8, 2.7 Hz, 1H), 1.32 – 1.19 (m, 1H); distinguishable peaks only: ***13C NMR*** (DMSO-d_6, 101 MHz, 373 K): δ 171.5, 168.1, 153.7, 136.6, 132.9, 131.5, 127.7, 127.1, 65.6, 59.9, 51.8, 51.0, 30.3, 29.6, 21.3, 13.1.

2-Benzyl 6-methyl (1*R*,4*R*,6*R*)-6-(methyl(phenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-152b) & 2-benzyl 6-methyl (1*R*,4*R*,6*S*)-6-(methyl(phenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-152b)



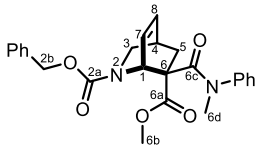
According to **GP1**, *N*-Cbz-1,2-dihydropyridine (135 mg, 0.63 mmol) and α-amido acrylate **151b** (55 mg, 0.25 mmol) were heated for 3 d. FC purification (*n*-hex/Et_2O 1:1 → 1:4) afforded a mixture of diastereoisomers ***endo*-152b:*exo*-152b** in a 1.6:1 ratio (74 mg, 68%):

Isolated ***endo*-152b**, white solid; ***mp*** 83-85 °C; Si gel TLC R_f 0.41 (*n*-hex/Et_2O 1:4); ***ATR-IR*** ν_{max}/cm^{-1} 1737, 1680, 1652, 1638, 1496, 1441, 1417, 1405, 1247, 1215, 1130, 1122, 990, 732; (^1H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



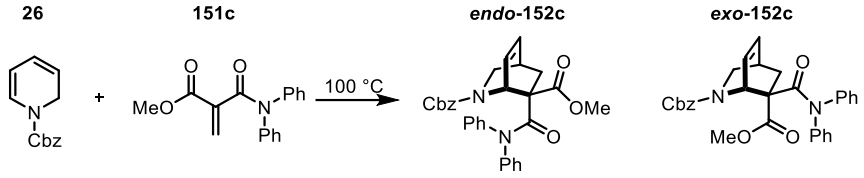
1H NMR (DMSO-d_6, 400 MHz, 398 K): δ 7.43 – 7.22 (m, 10H, ArH), 6.39 – 6.24 [m, 2H : C(7)*H* & C(8)*H*], 5.23 [dd, *J* = 5.8, 1.5 Hz, 1H, C(1)*H*], 5.19 – 5.06 [*AB*, m, 2H, C(2b)H_2], 3.42 [s, 3H, C(6b)H_3], 3.33 [d, *J* = 9.7 Hz, 1H, C(3)H_a], 3.11 [s, 3H, C(6d)H_3], 2.88 [dt, *J* = 9.9, 2.7 Hz, 1H, C(3)H_b], 2.84 – 2.74 [m, 2H : C(4)*H* & C(5)H_a], 1.49 [dt, *J* = 13.2, 2.9 Hz, 1H, C(5)H_b]; ***13C NMR*** (DMSO-d_6, 101 MHz, 398 K): δ 170.2 [*C*(6a)], 167.1 [*C*(6c)], 154.1 (Ar*C*), 142.6 (Ar*C*), 136.5 (Ar*C*), {133.4, 130.5 : *C*(7) & *C*(8)}, 128.4 (Ar*C*), 127.7 (Ar*C*), 127.6 (Ar*C*), 127.0 (Ar*C*), 126.9 (Ar*C*), 126.8 (Ar*C*), 65.5 [*C*(2b)], 59.1 [*C*(6)], 51.1 [*C*(6b)], 49.2 [*C*(1)], 45.2 [*C*(3)], 39.1 [*C*(6d)], 33.1 [*C*(5)], 29.6 [*C*(4)]; ***LRMS*** *m/z* (ES+) 435.19 $[M+H]^+$, 457.18 $[M+Na]^+$; ***HRMS*** *m/z calcd.* for $C_{25}H_{27}N_2O_5$ 435.1920, found 435.1928, Δ = 1.8 ppm.

Isolated ***exo*-152b**, off-white semi-solid; Si gel TLC R_f 0.28 (*n*-hex/Et_2O 1:4); ***ATR-IR*** ν_{max}/cm^{-1} 1739, 1696, 1650, 1593, 1496, 1411, 1363, 1335, 1294, 1276, 1114; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



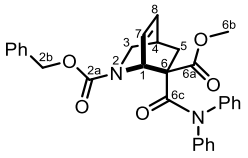
1H NMR (DMSO-d_6, 400 MHz, 378 K): δ 7.43 – 7.25 (m, 8H, Ar*H*), 7.16 – 7.10 (m, 2H, Ar*H*), 6.51 [ddd, *J* = 7.7, 5.9, 1.5 Hz, 1H, C(7)*H*], 6.33 [ddd, *J* = 7.8, 6.5, 1.2 Hz, 1H, C(8)*H*], 5.15 [dd, *J* = 6.0, 1.2 Hz, 1H, C(1)*H*], 5.08 – 4.96 [*AB*, m, 2H, C(2b)*H*], 3.47 [s, 3H, C(6b)H_3], 3.18 – 3.08 [m, 1H, C(3)H_a], 3.07 [s, 3H, C(6d)H_3], 2.86 – 2.75 [m, 2H : C(3)H_b & C(4)*H*], 2.16 [d, *J* = 13.1 Hz, 1H, C(5)H_a], 1.62 [dt, *J* = 13.0, 2.7 Hz, 1H, C(5)H_b]; ***13C NMR*** (DMSO-d_6, 101 MHz, 378 K): δ 170.5 [*C*(6a)], 168.7 [*C*(6c)], 153.6 (Ar*C*), 141.7 (Ar*C*), 136.5 (Ar*C*), {132.5, 131.9 : *C*(7) & *C*(8)}, 128.5 (Ar*C*), 127.7 (Ar*C*), 127.10 (Ar*C*) , 127.06 (Ar*C*), 126.8 (Ar*C*), 124.3 (Ar*C*), 65.5 [*C*(2b)], 60.2 [*C*(6)], 51.5 [*C*(6b)], 51.0 [*C*(1)], 44.7 [*C*(3)], 37.8 [*C*(6d)], 32.9 [*C*(5)], 29.6 [*C*(4)]; ***LRMS*** *m/z* (ES+) 435.19 $[M+H]^+$, 452.22 $[M+NH_4]_+$, 457.18 $[M+Na]^+$; ***HRMS*** *m/z calcd.* for $C_{25}H_{27}N_2O_5$ 435.1920, found 435.1924, Δ = 0.9 ppm.

2-Benzyl 6-methyl (1*R*,4*R*,6*R*)-6-(diphenylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-152c) & 2-benzyl 6-methyl (1*R*,4*R*,6*S*)-6-(diphenylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-152c)



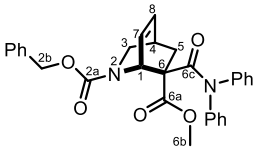
According to **GP1**, *N*-Cbz-1,2-dihydropyridine (467 mg, 2.17 mmol) and α-amido acrylate **151c** (305 mg, 1.09 mmol) were heated for 6.5 h. FC purification (*n*-hex/Et_2O 3:2 → 3:7) afforded a mixture of diastereoisomers ***endo*-152c:*exo*-152c** in a 2.2:1 ratio (465 mg, 86%):

Isolated ***endo*-152c**, white solid; ***mp*** 140-141 °C; Si gel TLC $\boldsymbol{R_f}$ 0.25 (*n*-hex/Et_2O 2:3); ***ATR-IR*** ν_{max}/cm^{-1} 2948, 1719, 1693, 1654, 1491, 1417, 1333, 1275, 1258, 1104, 768, 752, 706; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



^{1}H NMR (DMSO-d_6, 500 MHz, 398 K) δ 7.45 – 7.20 (m, 15H, Ar*H*), 6.37 – 6.30 [m, 1H, C(7)*H*], 6.30 – 6.24 [m, 1H, C(8)*H*], 5.33 [d, *J* = 5.3 Hz, 1H, C(1)*H*], 5.23 – 5.10 (*AB*, *app* q, *J* = 15.5 Hz, 2H, C(2b)H_2], 3.41 [s, 3H, C(6b)H_3], 3.39 – 3.33 [m, 1H, C(3)H_{exo}], 2.93 [dt, *J* = 9.9, 2.6 Hz, 1H, C(3)H_{endo}], 2.88 – 2.78 [m, 2H : C(4)*H* & C(5)H_{exo}], 1.50 – 1.43 [dt, *J* = 16.5, 3.5 Hz, 1H, C(5)H_{endo}]; ***^{13}C NMR*** (DMSO-d_6, 126 MHz, 398 K) δ 169.7 [*C*(6a)], 167.8 [*C*(6c)], 154.4 (Ar*C*), 142.3 (Ar*C*), 136.4 (Ar*C*), {133.3, 130.6 : *C*(7) & *C*(8)}, 128.3 (Ar*C*), 128.0 (Ar*C*), 127.6 (Ar*C*), 127.0 (Ar*C*), 126.8 (Ar*C*), 126.6 (Ar*C*), 65.7 [*C*(2b)], 59.8 [*C*(6)], 51.1 [*C*(6b)], 49.6 [*C*(1)], 45.2 [*C*(3)], 33.4 [*C*(5)], 29.6 [*C*(4)]; ***LRMS*** *m/z* (ES+) 497.21 $[M+H]^+$, 519.19 $[M+Na]^+$; ***HRMS*** *m/z calcd.* for $C_{30}H_{29}N_2O_5$ 497.2076, found 497.2073, Δ = - 0.6 ppm.

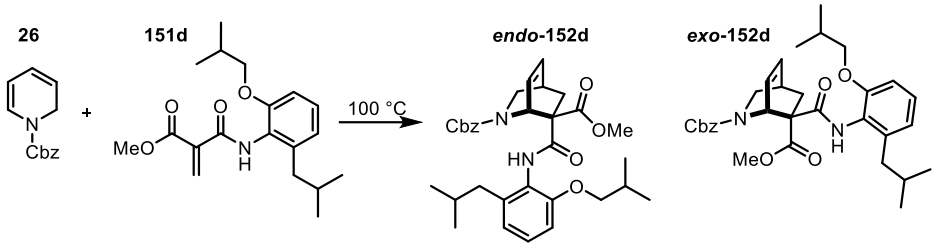
Isolated ***exo*-152c**, white solid; ***mp*** 72-75 °C; Si gel TLC $\boldsymbol{R_f}$ 0.18 (*n*-hex/Et_2O 2:3); ***ATR-IR*** ν_{max}/cm^{-1} 2952, 1740, 1695, 1661, 1491, 1410, 1333, 1292, 1274, 1212, 1107, 753, 693; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 7.43 – 7.18 (m, 15H, Ar*H*), 6.52 [ddd, *J* = 7.7, 5.9, 1.5 Hz, 1H, C(7)*H*], 6.39 [ddd, *J* = 7.9, 6.5, 1.2 Hz, 1H, C(8)*H*], 5.21 [dd, *J* = 5.9, 1.2 Hz, 1H, C(1)*H*], 5.03 (*AB*, *app* q, 2H, *J* = 12.7 Hz, C(2b)H_2], 3.51 [s, 3H, C(6b)H_3], 3.10 [d, *J* = 10.0 Hz, 1H, C(3)H_{exo}], 2.84 – 2.76 [m, 2H : C(3)H_{endo} & C(4)*H*], 2.00 [dd, J = 13.2, 2.9 Hz, 1H, C(5)H_a], 1.82 [dt, *J* = 16.5, 3.5 Hz,

1H, C(5)$H_{\underline{b}}$]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398 K): δ 171.2 [*C*(6a)], 170.0 [*C*(6c)], 154.6 (Ar*C*), 142.6 (Ar*C*), 137.6 (Ar*C*), {133.31, 133.29 : *C*(7) & *C*(8)}, 129.4 (Ar*C*), 129.1 (Ar*C*), 128.7 (Ar*C*), 128.1 (Ar*C*), 127.8 (Ar*C*), 66.6 [*C*(2b)], 62.0 [*C*(6)], 52.5 [*C*(6b)], 52.4 [*C*(1)], 45.6 [*C*(3)], 34.1 [*C*(5)], 30.8; ***LRMS*** *m/z* (ES+) 497.21 $[M+H]^+$, 514.23 $[M+NH_4]^+$; ***HRMS*** *m/z calcd.* for $C_{30}H_{29}N_2O_5$ 497.2076, found 497.2069, Δ = - 1.4 ppm.

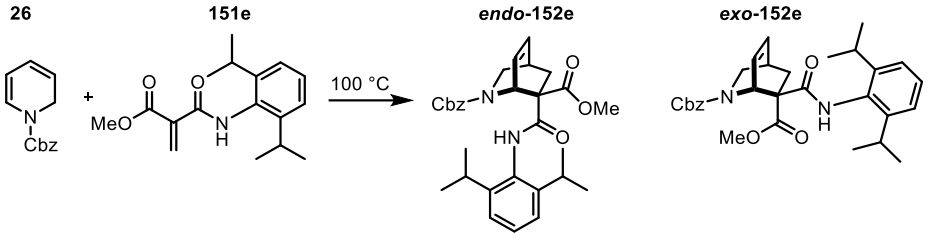
2-Benzyl 6-methyl (1*R*,4*R*,6*R*)-6-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-152d) & 2-benzyl 6-methyl (1*R*,4*R*,6*S*)-6-((2-isobutoxy-6-isobutylphenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-152d)



According to **GP1**, *N*-Cbz-1,2-dihydropyridine (50 mg, 0.23 mmol) and α-amido acrylate **151d** (30 mg, 0.09 mmol) were heated for 16 h. FC purification (*n*-hex/Et_2O 7:3 → 1:1) afforded an inseparable mixture of diastereoisomers ***endo*-152d:*exo*-152d** in a 1:3.2 ratio (29 mg, 58%):

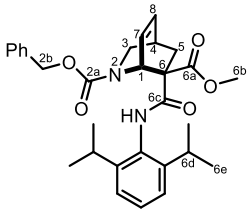
Endo*-152d:*exo*-152d** mixture, off-white semi-solid; Si gel TLC R_f 0.18 (*n*-hex/Et_2O 6:5); ***ATR-IR ν_{max}/cm^{-1} 2955, 2932, 2876, 1736, 1699, 1585, 1499, 1459, 1414, 1248, 1112, 1055, 749, 698; ***^{1}H NMR*** (DMSO-d_6, 400 MHz, 398 K): δ 8.18 (*br.* s, 0.76H), 8.03 (*br.* s, 0.24H), 7.41 – 7.23 (m, 5H), 7.19 – 7.05 (m, 1H), 6.86 – 6.72 (m, 2H), 6.54 – 6.37 (m, 2H), 5.47 – 5.36 (m, 1H), 5.18 – 5.04 (m, 2H), 3.72 – 3.59 (m, 5H), 3.35 – 3.22 (m, 1H), 3.02 – 2.90 (m, 2H), 2.82 – 2.69 (m, 1H), 2.45 – 1.95 (m, 4H), 1.92 – 1.77 (m, 1H), 1.02 – 0.95 (m, 6H), 0.84 (m, 6H); ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398 K): δ 171.7, 170.6, 169.9, 166.9, 154.4, 153.8, 139.9, 136.5, 133.5, 131.0, 130.0, 127.5, 127.5, 126.9, 126.9, 126.6, 126.5, 126.4, 126.4, 124.4, 120.9, 109.7, 109.7, 74.3, 65.7, 65.5, 60.6, 51.7, 51.5, 49.7, 49.2, 46.9, 45.5, 31.0, 30.2, 29.9, 29.7, 29.6, 27.3, 27.2, 27.1, 27.0, 21.7, 21.6, 21.6, 18.3, 18.2; ***LRMS*** *m/z* (ES+) 549.30 $[M+H]^+$, 566.33 $[M+NH_4]^+$; ***HRMS*** *m/z calcd.* for $C_{32}H_{41}N_2O_6$ 549.2965, found 549.2982, Δ = 3.1 ppm.

2-Benzyl 6-methyl (1*R*,4*R*,6*R*)-6-((2,6-diisopropylphenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-152e) & 2-benzyl 6-methyl (1R,4R,6S)-6-((2,6-diisopropylphenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-152e)



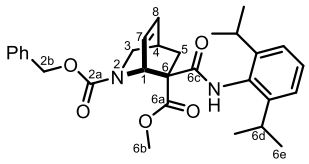
According to **GP1**, *N*-Cbz-1,2-dihydropyridine (349 mg, 1.62 mmol) and α-amido acrylate **151e** (276 mg, 0.96 mmol) were heated for 2 h, after which dry toluene (0.2 mL) was added to aid solubility and the mixture heated at 100 °C for a further 30 mins. FC purification (n-hex/Et_2O 7:3 to *n*-hex/Et_2O 3:7) afforded a mixture of diastereoisomers ***endo*-152e:*exo*-152e** in a 1:4 ratio (319 mg, 66%):

Isolated *endo*-**152e**, colourless paste; Si gel TLC $\boldsymbol{R_f}$ 0.23 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 3371, 2961, 1731, 1695, 1682, 1506, 1496, 1456, 1417, 1334, 1249, 1203, 1120; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



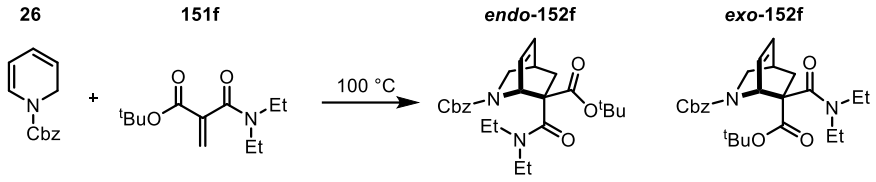
^{1}H NMR (DMSO-d_6, 400 MHz, 398 K) δ 8.64 (*br.* s, 1H, N*H*), 7.35 – 7.25 (m, 6H, Ar*H*) 7.15 – 7.10 (m, 2H, Ar*H*), 6.48 [m, 2H : C(7)*H* & C(8)*H*], 5.50 [dd, *J* = 4.2, 2.9 Hz, 1H : C(1)*H*], 5.12 – 5.05 [m, 2H, C(2b)H_2], 3.70 [s, 3H, C(6b)H_3], 3.28 [dd, *J* = 10.1, 2.1 Hz, 1H, C(3)$H_{\underline{a}}$], 3.07 – 2.92 [m, 4H : C(6d)*H* x 2 & C(3)$H_{\underline{b}}$ & C(4)*H*], 2.55 [dd, *J* = 13.6, 2.5 Hz, 1H, C(5)$H_{\underline{a}}$], 2.15 [dt, *J* = 13.6, 3.1 Hz, 1H, C(5)$H_{\underline{b}}$], 1.10 [*app.* dd, *J* = 6.9, 5.3 Hz, 12H, C(6e)H_3 x 4]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398 K) δ 170.2 [*C*(6a)], 166.8 [*C*(6c)], 154.9 (Ar*C*), 145.8 (Ar*C*), 136.2 (Ar*C*), {134.5, 130.8 : *C*(7) & *C*(8)}, 131.6 (Ar*C*), 127.6 (Ar*C*), 127.2 (Ar*C*), 126.9 (Ar*C*), 126.8 (Ar*C*), 126.6 (Ar*C*), 126.5 (Ar*C*), 125.8 (Ar*C*), 122.1 (Ar*C*), 122.0 (Ar*C*), 65.7 [*C*(2b)], 60.1 [*C*(6)], 51.5 [*C*(6b)], 49.4 [*C*(1)], 46.4 [*C*(3)], 30.5 [*C*(5)], 29.7 [*C*(4)], 27.1 [*C*(6d)], 22.7 & 22.6 [*C*(6d)]; ***LRMS*** *m/z* (ES+) 505.27 $[M+H]^+$, 522.18 $[M+NH_4]^+$, 527.25 $[M+Na]^+$; **HRMS** *m/z calcd.* for $C_{30}H_{37}N_2O_5$ 505.2702, found 505.2706, Δ = 0.8 ppm.

Isolated *exo*-**152e**, colourless paste; Si gel TLC $\boldsymbol{R_f}$ 0.19 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 3323, 2961, 1737, 1692, 1680, 1498, 1415, 1336, 1245, 1114; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



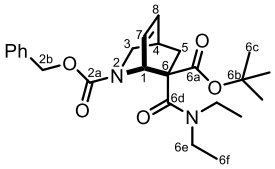
1H NMR (DMSO-d_6, 400 MHz, 398 K): δ 8.72 (*br.* s, 1H, N*H*), 7.43 – 7.29 (m, 5H, Cbz Ar*H*), 7.26 – 7.19 (m, 1H, NAr*H*), 7.15 – 7.07 (m, 2H, NAr*H*), 6.58 – 6.39 [m, 2H : C(7)*H* & C(8)*H*], 5.47 [dd, *J* = 5.7, 1.5 Hz, 1H, C(1)*H*], 5.15 – 5.05 [m, 2H, C(2b)H_2], 3.62 [s, 3H, C(6b)H_3], 3.34 – 3.26 [m, 1H, C(3)H_{exo}], 3.06 – 2.97 [m, 2H, C(6d)*H* x 2), 2.97 – 2.90 [m, 2H : C(3)H_{endo} & C(4)*H*], 2.69 [dd, *J* = 13.5, 2.5 Hz, 1H, C(5)H_{exo}], 2.03 [dt, *J* = 13.5, 2.9 Hz, 1H, C(5)H_{endo}], 1.11 [*app.* dd, *J* = 14.1, 6.9 Hz, 12H, C(6e)H_3 x 4]; ***13C NMR*** (DMSO-d_6, 101 MHz, 398 K): δ 170.5 [*C*(6a)], 167.7 [*C*(6c)], 153.8 (Ar*C*), 145.9 (Ar*C*), 136.6 (Ar*C*), {133.7, 130.9 : *C*(7) & *C*(8)}, 131.7 (Ar*C*), 127.6 (Ar*C*), 126.9 (Ar*C*), 126.8 (Ar*C*), 126.6 (Ar*C*), 122.2 (Ar*C*), 122.0 (Ar*C*), 65.4 [*C*(2b)], 60.7 [*C*(6)], 51.3 [*C*(6b)], 49.4 [*C*(1)], 45.8 [*C*(3)], 31.1 [*C*(5)], 29.7 [*C*(4)], 26.9 [*C*(6d)], 22.6 & 22.5 [*C*(6d)]; ***LRMS*** *m/z* (ES+) 505.27 $[M+H]^+$, 522.30 $[M+NH_4]^+$; ***HRMS*** *m/z calcd.* for $C_{30}H_{37}N_2O_5$ 505.2702, found 505.2727, Δ = 4.9 ppm.

2-Benzyl 6-(tert-butyl) (1*R*,4*R*,6*R*)-6-(diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (endo-152f) & 2-benzyl 6-(tert-butyl) (1R,4R,6S)-6-(diethylcarbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (exo-152f)



According to **GP1**, *N*-Cbz-1,2-dihydropyridine (568 mg, 2.64 mmol) and and α-amido acrylate **151f** (300 mg, 1.31 mmol) were heated for 7 days. FC purification (*n*-hex/EtOAc 4:1 → 2:3) afforded a mixture of diastereoisomers ***endo*-152f:*exo*-152f** in a 3.5:1 ratio (219 mg, 37%):

Isolated ***endo*-152f**, colourless paste; Si gel TLC R_f 0.30 (*n*-hex/EtOAc 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 2972, 2936, 1698, 1638, 1411, 1367, 1332, 1294, 1273, 1250, 1157, 1114, 761, 698; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)

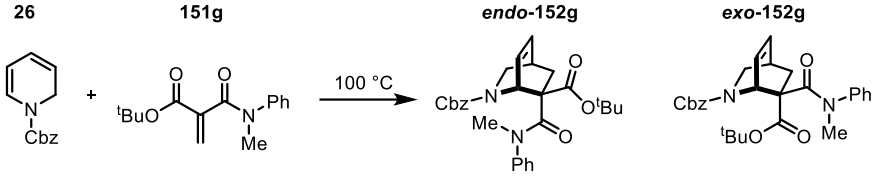


1H NMR (DMSO-d_6, 400 MHz, 398 K) δ 7.42 – 7.24 (m, 5H, ArH), 6.44 – 6.34 [m, 2H, C(7)*H* & C(8)*H*], 5.26 – 5.12 [dd, *J* = 3.2, 3.6 Hz, 1H, C(1)*H*], 5.11 – 5.00 [*AB*, m, 2H, C(2b)H_2], 3.42 – 3.14

[m, 5H : C(6e)H_2 x 2 & C(3)H_a], 2.89 – 2.82 [m, 2H : C(3)H_b & C(4)], 2.49 – 2.44 [m, 1H, C(5)H_a], 1.82 [*br.* d, *J* = 12.7 Hz, 1H, C(5)H_b], 1.40 [s, 9H, C(6c)H_3 x 3], 1.06 [*app.* t, *J* = 7.0 Hz, 6H, C(6f)H_3 x 2]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398K) δ 169.4 [*C*(6a)], 166.6 [*C*(6d)], 154.0 (Ar*C*), 136.7 (Ar*C*), {133.5, 130.6 : *C*(7) & *C*(8)}, 127.5 (Ar*C*), 126.8 (Ar*C*), 126.6 (Ar*C*), 81.0 [*C*(6b)], 65.3 [*C*(2b)], 59.3 [*C*(6)], 49.3 [*C*(1)], 45.5 [*C*(3)], 39.38 [*C*(6e], 32.3 [*C*(5)], 29.9 [*C*(4)], 26.9 [*C*(6c)], 11.7 [*C*(6f)]; ***LRMS*** *m/z* (ES+) 443.26 $[M+H]^+$, 465.23 $[M+Na]^+$; ***HRMS*** *m/z calcd.* for $C_{25}H_{35}N_2O_5$ 443.2546, found 443.2551, Δ = 1.1 ppm.

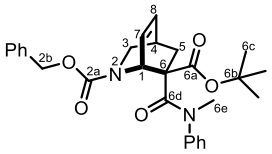
Exo*-152f** not fully separated from ***endo*-152f**, pale yellow paste; distinguishable peaks only: ***^{1}H NMR (DMSO-d_6, 400 MHz, 398 K): δ 6.50 (ddd, *J* = 7.9, 5.9, 1.6 Hz, 1H), 6.30 – 6.24 (m, 1H), 3.15 – 3.04 (m, 2H), 2.95 (dt, *J* = 10.1, 2.7 Hz, 1H), 1.37 (s, 9H); distinguishable peaks only: ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398 K): δ 134.0, 132.3, 130.8, 127.4, 126.8, 126.3, 65.4, 51.1, 45.1, 38.2, 32.2, 29.7, 27.6, 26.6, 25.0, 22.6, 12.5.

2-Benzyl 6-(tert-butyl) (1*R*,4*R*,6*R*)-6-(methyl(phenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*endo*-152g) & 2-benzyl 6-(tert-butyl) (1*R*,4*R*,6*S*)-6-(methyl(phenyl)carbamoyl)-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (*exo*-152g)



According to **GP1**, *N*-Cbz-1,2-dihydropyridine (393 mg, 1.83 mmol) and α0amido acrylate **151g** (321 mg, 1.23 mmol) were heated for 6 days. FC purification (*n*-hex/Et_2O 1:1 → 3:7) afforded a mixture of diastereoisomers ***endo*-152g:*exo*-152g** in a 15.7:1 ratio (280 mg, 48%):

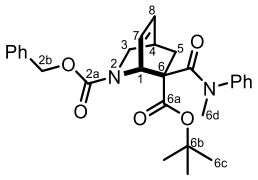
Isolated ***endo*-152g**, colourless paste; Si gel TLC R_f 0.23 (*n*-hex/Et_2O 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 2976, 2936, 1694, 1600, 1495, 1443, 1413, 1367, 1272, 1251, 1153, 1110, 1085, 733, 697; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



^{1}H NMR (DMSO-d_6, 400 MHz, 398K) δ 7.44 – 7.13 (m, 10H, Ar*H*), 6.44 – 6.34 [m, 2H : C(7)*H* & C(8)*H*], 5.35 – 5.28 [m, 1H, C(1)*H*], 5.15 – 5.05 [AB, m, 2H, C(2b)H_2], 3.27 – 3.15 [m, 4H : C(6e)H_3 & C(3)H_a], 2.92 – 2.85 [m, 1H, C(3)H_b], 2.85 – 2.81 [m, 1H, C(4)*H*], 2.67 [*br.* d, *J* = 13.0 Hz, 1H,

C(5)H_a], 1.63 [dt, *J* = 13.2, 2.9 Hz, 1H, C(5)H_b]; 1.41 [s, 9H, C(6c)H_3 x 3]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398K) δ 169.0 [*C*(6a)], 167.5 [*C*(6d)], 154.0 (Ar*C*), 144.0 (Ar*C*), 136.5 (Ar*C*), {133.4, 130.5 : *C*(7) & *C*(8)}, 128.2 (Ar*C*), 127.5 (Ar*C*), 126.9 (Ar*C*), 126.6 (Ar*C*), 126.5 (Ar*C*), 126.0 (Ar*C*), 81.2 [*C*(6b)], 65.5 [*C*(6)], 60.0 [*C*(2b)], 49.0 [*C*(1)], 45.3 [*C*(3)], 38.3 [*C*(6e)], 32.5 [*C*(5)], 29.8 [*C*(4)], 27.0 [*C*(6c)]; ***LRMS*** *m/z* (ES+) 477.24 $[M+H]^+$, 499.22 $[M+Na]^+$; ***HRMS*** *m/z calcd.* for $C_{28}H_{33}N_2O_5$ 477.2389, found 477.2379, Δ = - 2.1 ppm.

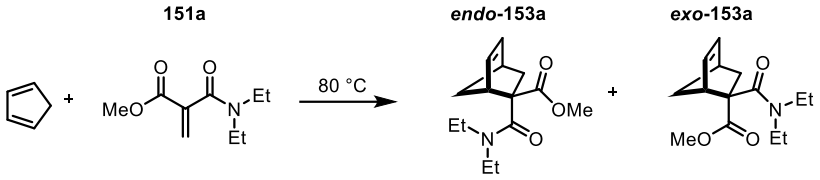
Isolated ***exo*-152g**, pale yellow paste; Si gel TLC R_f 0.15 (*n*-hex/Et_2O 3:7); (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



^{1}H NMR (DMSO-d_6, 400 MHz, 398K) δ 7.39 – 7.26 (m, 8H, Ar*H*), 7.19 – 7.12 (m, 2H, Ar*H*), 6.48 [ddd, *J* = 7.9, 5.8, 1.5 Hz, 1H, C(7)*H*], 6.31 [ddd, *J* = 7.9, 6.5, 1.2 Hz, 1H, C(9)*H*], 5.25 [dd, *J* = 5.8, 1.2 Hz, 1H, C(1)*H*], 5.11 – 4.99 [*AB*, m, 2H, C(2b)H_2], 3.26 – 3.22 [m, 1H, C(3)H_a], 3.11 [s, 3H, C(6d)H_3], 2.92 [dt, *J* = 10.1, 2.7 Hz, 1H, C(3)H_b], 2.85 – 2.80 [m, 1H, C(4)*H*], 2.41 [dd, *J* = 12.9, 3.0 Hz, 1H, C(5)H_a], 1.66 [dt, *J* = 13.0, 2.7 Hz, 1H, C(5)H_b], 1.41 [s, 9H, C(6c)H_3 x 3]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398K) δ {168.9, 168.8 : *C*(6a) & *C*(6d)}, 153.8 (Ar*C*), 143.0 (Ar*C*), 136.2 (Ar*C*), {132.9, 131.5 : *C*(7) & *C*(8)}, 128.1 (Ar*C*), 127.4 (Ar*C*), 126.8 (Ar*C*), 126.6 (Ar*C*), 126.2 (Ar*C*), 125.9 (Ar*C*), 81.5 [*C*(6b)], 65.4 [*C*(6)], 61.0 [*C*(2b)], 51.1 [*C*(1)], 44.8 [*C*(3)], 37.0 [*C*(6e)], 32.2 [*C*(5)], 29.7 [*C*(4)], 26.7 [*C*(6c)]; ***LRMS*** *m/z* (ES+) 477.24 $[M+H]^+$, 494.26 $[M+NH_4]^+$; ***HRMS*** *m/z calcd.* for $C_{28}H_{33}N_2O_5$ 477.2389, found 477.2386, Δ = -0.6 ppm.

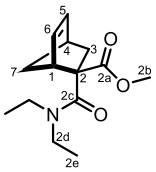
General procedure for DA reactions between α-amido acrylates and cyclopentadiene (GP2): Cyclopentadiene (5 *eq.*) and α-amido acrylate (1 *eq.*) were transferred to a Biotage® microwave vial containing a Teflon-coated magnetic stirrer bar which was subsequently thoroughly purged with Ar prior to sealing. The reaction was then heated at 80 °C until consumption of the dienophile was observed by TLC analysis. The reaction mixture was directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

Methyl (1*R*,2*R*,4*R*)-2-(diethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-153a) & methyl (1*R*,2*S*,4*R*)-2-(diethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-153a)



According to **GP2**, cyclopentadiene (0.23 mL, 2.8 mmol) and α-amido acrylate **151a** (102 mg, 0.55 mmol) were heated for 24 h. FC purification (*n*-hex/Et_2O 2:3) afforded a mixture of diastereoisomers ***endo*-153a:*exo*-153a** in a 3.2:1 ratio (62 mg, 45%):

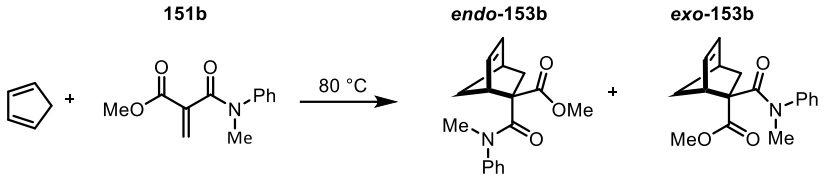
Isolated ***endo*-153a**, colourless paste; Si gel TLC R_f 0.36 (*n*-hex/Et_2O 2:3); ***ATR-IR*** ν_{max}/cm^{-1} 2974, 2941, 1733, 1642, 1456, 1432, 1274, 1251, 1236, 1116, 1059, 711;



^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.29 [dd, *J* = 5.6, 2.9 Hz, 1H, C(5)*H*], 5.82 [dd, *J* = 5.7, 2.9 Hz, 1H, C(6)*H*], 3.57 [s, 3H, C(2b)H_3], 3.46 – 3.41 [m, 1H, C(1)*H*], 3.39 – 3.06 [m, 4H, C(2d)H_2 x 2], 2.92 – 2.79 [m, 1H, C(4)*H*], 2.13 – 1.97 [m, 1H, C(3)H_{endo}], 1.70 [dd, *J* = 11.8, 3.4 Hz, 1H, C(3)H_{exo}], 1.42 – 1.36 [m, 2H, C(7)H_2], 0.98 [t, *J* = 7.0 Hz, 3H, C(2e)H_3], 0.92 [t, *J* = 7.0 Hz, 3H, C(2e)H_3]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 172.7 [*C*(2a)], 169.7 [*C*(2c)], 140.9 [*C*(5)], 132.6 [*C*(6)], 59.1 [*C*(2)], 52.6 [*C*(2b)], 51.7 [*C*(1)], 50.4 [*C*(7)], 42.2 [*C*(4)], 40.5 [*C*(2d)], 36.1 [*C*(3)], 13.4 & 12.6 [*C*(2e)]; ***LRMS*** *m/z* (ES+) 252.16 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{14}H_{22}NO_3$ 252.1600, found 252.1594, Δ = -2.4 ppm.

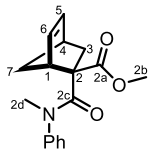
Exo*-153a** not fully separated from ***endo*-153a**, colourless oil; Si gel TLC R_f 0.33 (*n*-hex/Et_2O 2:3); distinguishable peaks only: ***^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.14 (dd, *J* = 5.6, 3.0 Hz, 1H), 6.11 – 6.03 (m, 1H), 3.66 (s, 3H), 2.35 – 2.24 (m, 1H), 1.51 (d, *J* = 8.6 Hz, 1H), 1.31 – 1.26 (m, 1H); distinguishable peaks only: ***^{13}C NMR*** (DMSO-d_6, 101 MHz,) δ 174.6, 168.3, 138.0, 135.9, 61.0, 53.0, 51.0, 47.0, 37.6, 13.7, 12.4.

Methyl (1*R*,2*R*,4*R*)-2-(methyl(phenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-153b) & methyl (1*R*,2*S*,4*R*)-2-(methyl(phenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-153b)



According to **GP2**, cyclopentadiene (0.38 mL, 4.56 mmol) and α-amido acrylate **151b** (200 mg, 0.91 mmol) were heated for 5 h. FC purification (*n*-hex/Et_2O 3:2 → 1:1) afforded a mixture of diastereoisomers ***endo*-153b:*exo*-153b** in a 4:1 ratio (222 mg, 86%):

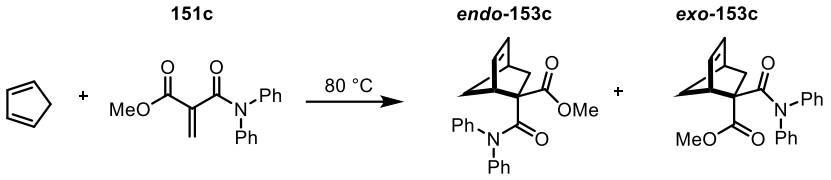
Isolated ***endo*-153a**, yellow solid; ***mp*** 61-63 °C; Si gel TLC R_f0.32 (*n*-hex/Et_2O 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 2974, 1737, 1648, 1595, 1496, 1357, 1251, 1231, 1116, 1057, 705;



^{1}H NMR (DMSO-d_6, 400 MHz, 373K) δ 7.41 – 7.34 (m, 2H, Ar*H*), 7.32 – 7.25 (m, 1H, Ar*H*), 7.21 – 7.13 (m, 2H, Ar*H*), 6.19 [dd, *J* = 5.6, 3.0 Hz, 1H, C(5)*H*], 5.73 [dd, *J* = 5.7, 2.9 Hz, 1H, C(6)*H*], 3.47 [s, 3H, C(2b)H_3], 3.43 – 3.39 [m, 1H, C(1)*H*], 3.16 [s, 3H, C(2d)H_3], 2.88 – 2.82 [m, 1H, C(4)*H*], 1.98 [dd, *J* = 12.0, 3.6 Hz, 1H, C(3)H_{exo}], 1.71 [dd, *J* = 11.9, 3.0 Hz, 1H, C(3)H_{endo}], 1.60 [dt, *J* = 8.5, 1.6 Hz, 1H, C(7)H_{exo}], 1.43 – 1.37 [m, 1H, C(7)H_{endo}]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 373K) δ {170.6, 170.3 : *C*(2a) & *C*(2c)}, 142.6 (Ar*C*), 139.5 [*C*(5)], 131.7 [*C*(6)], 128.4 (Ar*C*), 127.7 (Ar*C*), 126.8 (Ar*C*), 58.7 [*C*(2)], 51.4 [*C*(1)], 51.1 [*C*(2b)], 49.3 [*C*(7)], 41.5 [*C*(4)], 38.3 [*C*(2d)], 35.8 [*C*(3)]; ***LRMS*** *m/z* (ES+) 286.14 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{17}H_{20}NO_3$ 286.1443, found 286.1468, Δ = -1.7 ppm.

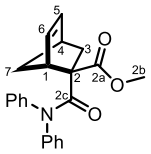
Exo*-153a** not fully separated from ***endo*-153a**, colourless oil; Si gel TLC R_f0.27 (*n*-hex/Et_2O 3:7); distinguishable peaks only: ***^{1}H NMR (DMSO-d_6, 400 MHz, 373K): δ 3.65 (s, 3H), 3.12 (s, 3H), 2.95 – 2.88 (m, 3H), 2.81 – 2.73 (m, 1H), 2.04 (dd, *J* = 12.0, 2.8 Hz, 1H), 1.88 (dd, *J* = 12.0, 3.6 Hz, 1H), 1.49 (d, *J* = 8.8 Hz, 1H), 1.27 – 1.21 (m, 1H); distinguishable peaks only: ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 373K): δ 172.9, 168.1, 137.6, 134.1, 128.5, 127.5, 126.8, 60.5, 51.5, 49.9, 46.6, 40.9, 38.4, 37.2, 30.0; from trace amounts of ***exo*-153a** isolated: ***LRMS*** *m/z* (ES+) 286.15 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{17}H_{20}NO_3$ 286.1443 $[M+H]^+$, found 286.1457.

Methyl (1*R*,2*R*,4*R*)-2-(diphenylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-153c) & methyl (1*R*,2*S*,4*R*)-2-(diphenylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-153c)



According to **GP2**, cyclopentadiene (0.30 mL, 3.56 mmol) and α-amido acrylate **151c** (200 mg, 0.71 mmol) were heated for 80 mins. FC purification (*n*-hex/Et_2O 7:3 → 3:7) afforded a mixture of diastereoisomers ***endo*-153c:*exo*-153c** in a 2.3:1 ratio (221 mg, 90%):

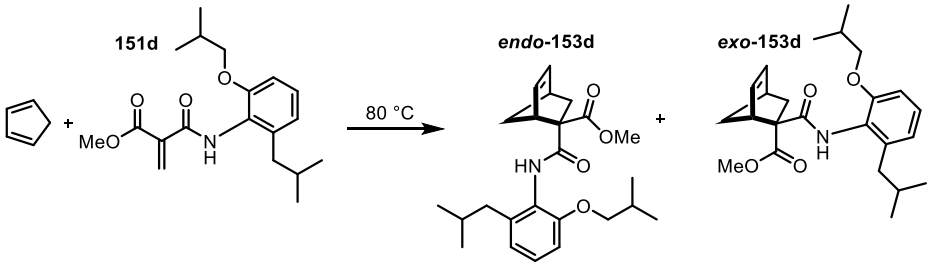
Isolated ***endo*-153c**, colourless paste; Si gel TLC R_f 0.30 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 2980, 2948, 1743, 1714, 1663, 1491, 1333, 1298, 1273, 1255, 1232, 1154, 1116, 756, 700;



^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.46 – 7.16 (m, 10H, Ar*H*), 6.16 [dd, *J* = 5.6, 2.9 Hz, 1H, C(5)*H*], 5.68 [dd, *J* = 5.7, 2.9 Hz, 1H), C(6)*H*], 3.43 [s, 3H, C(2b)H_3], 3.39 – 3.36 [m, 1H, C(1)*H*], 2.90 – 2.78 [m, 1H, C(4)*H*], 2.18 [dd, *J* = 12.0, 3.6 Hz, 1H, C(3)H_{exo}], 1.64 [d, *J* = 8.3 Hz, 1H, C(7)H_{exo}], 1.47 [dd, *J* = 11.9, 2.8 Hz, 1H, C(3)H_{endo}], 1.43 – 1.37 [m, 1H, C(7)H_{endo}]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ {171.7, 171.0 : *C*(2a) & *C*(2c)}, 140.7 [*C*(5)], 132.5 [*C*(6)], 129.5 (Ar*C*), 127.9 (Ar*C*), 59.7 [*C*(2)], 52.8 [*C*(1)], 52.4 [*C*(2b)], 50.5 [*C*(7)], 42.6 [*C*(4)], 37.1 [*C*(3)]; ***LRMS*** *m/z* (ES+) 348.16 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{22}H_{22}NO_3$ 348.1600, found 348.1606, Δ = 1.7 ppm.

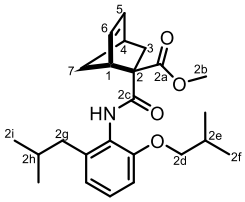
Exo*-153c** not fully separated from ***endo*-153c**, colourless paste; Si gel TLC R_f 0.21 (*n*-hex/Et_2O 1:1); distinguishable peaks only: ***^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.36 (dd, *J* = 5.6, 2.8 Hz, 1H), 6.27 (dd, *J* = 5.6, 2.9 Hz, 1H), 3.69 (s, 3H), 2.80 – 2.70 (m, 2H), 1.72 (dd, *J* = 12.1, 3.5 Hz, 1H); distinguishable peaks only: ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 173.8, 169.2, 139.3, 134.5, 61.7, 52.9, 48.2, 41.8, 38.6; from trace amounts of ***exo*-153c** isolated: ***LRMS*** *m/z* (ES+) 348.16 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{22}H_{22}NO_3$ 348.1600, found 348.1591, Δ = -2.6 ppm.

Methyl (1*R*,2*R*,4*R*)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-153d) & methyl (1*R*,2*S*,4*R*)-2-((2-isobutoxy-6-isobutylphenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-153d)



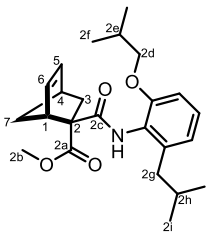
According to **GP2**, cyclopentadiene (0.10 mL, 1.19 mmol) and α-amido acrylate **151d** (30 mg, 0.09 mmol) were heated for 14 h. FC purification (*n*-hex/Et_2O 9:1 → 4:1) afforded a mixture of diastereoisomers ***endo*-153d:*exo*-153d** in a 5.3:1 ratio (28 mg, 58%):

Isolated ***endo*-153d**, white solid; ***mp*** 62.0 °C; Si gel TLC R_f 0.27 (*n*-hex/Et_2O 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 3364, 2955, 2928, 2868, 1732, 1762, 1586, 1498, 1461, 1276, 1260, 1054, 750;



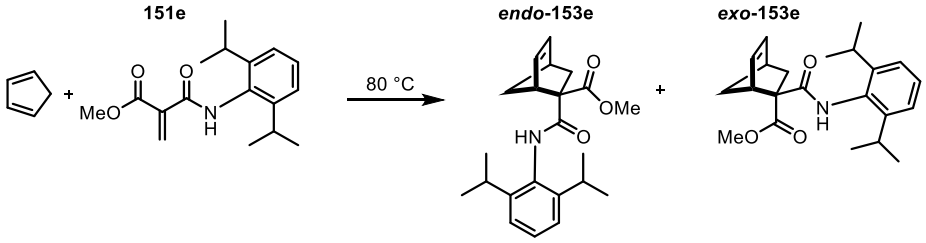
^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.76 (s, 1H, N*H*), 7.14 (t, *J* = 7.9 Hz, 1H, Ar*H*), 6.82 (dd, *J* = 8.3, 1.2 Hz, 1H, Ar*H*), 6.73 (dd, *J* = 7.7, 1.2 Hz, 1H, Ar*H*), 6.29 [dd, *J* = 5.6, 2.9 Hz, 1H, C(5)*H*], 5.99 [dd, *J* = 5.6, 2.8 Hz, 1H, C(6)*H*], 3.65 [d, *J* = 6.4 Hz, 2H, C(2d)H_2], 3.62 [s, 3H, C(2b)CH_3], 3.59 – 3.54 [m, 1H, C(1)*H*], 2.93 – 2.81 [m, 1H, C(4)*H*], 2.36 [dd, *J* = 12.3, 3.7 Hz, 1H, C(3)H_{exo}], 2.33 – 2.23 [m, 2H, C(2g)H_2], 2.00 – 1.86 [m, 2H : C(2e)*H* & C(3)H_{endo}], 1.82 – 1.68 [m, 1H, C(2h)*H*], 1.50 [d, *J* = 8.4 Hz, 1H, C(7)H_{exo}], 1.46 – 1.38 [m, 1H, C(7)H_{endo}], 0.95 (dd, *J* = 6.6, 2.2 Hz, 6H, C(2f)H_3 x 2], 0.80 [dd, *J* = 6.5, 3.9 Hz, 6H, C(2i)H_3 x 2]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 172.3 [*C*(2a)], 169.3 [*C*(2c)], 155.4 (Ar*C*), 141.0 (Ar*C*), 140.4 [*C*(5)], 133.9 [*C*(6)], 127.7 (Ar*C*), 125.2 (Ar*C*), 122.1 (Ar*C*), 110.0 (Ar*C*), 74.4 [*C*(2d)], 62.0 [*C*(2)], 52.6 [*C*(2b)], 49.5 [*C*(1)], 48.9 [*C*(7)], 41.9 [*C*(4)], 41.1 [*C*(2g)], 35.8 [*C*(3)], 28.6 [*C*(2e)], 28.4 [*C*(2h)], 23.0, &22.9 [*C*(2i)], 19.5 [*C*(2f)]; ***LRMS*** *m/z* (ES+) 400.25 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{24}H_{34}NO_4$ 400.2488, found 400.2477, Δ = -2.7 ppm.

Isolated ***exo*-153d**, white solid; ***mp*** 100.3 °C; Si gel TLC R_f 0.20 (*n*-hex/Et_2O 4:1); ***ATR-IR*** ν_{max}/cm^{-1} 3332, 2955, 2928, 2868, 1733, 1704, 1500, 1462, 1276, 1261, 1056, 750;



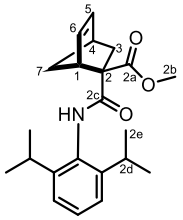
^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.65 (s, 1H, N*H*), 7.12 (t, *J* = 7.9 Hz, 1H, Ar*H*), 6.79 (dd, *J* = 8.5, 1.2 Hz, 1H, Ar*H*), 6.76 – 6.69 (m, 1H, Ar*H*), 6.27 – 6.09 [m, 2H : C(5)*H* & C(6)*H*], 3.70 [s, 3H, C(2b)H_3], 3.68 – 3.58 [m, 3H : C(1)*H* & C(2d)H_2], 2.85 [*br.* s, 1H, C(4)*H*], 2.28 – 2.21 [m, 2H, C(2g)H_2], 2.17 [dd, *J* = 12.5, 3.5 Hz, 1H, C(3)H_{exo}], 2.05 – 1.91 [m, 2H : C(2e)*H* & C(3)H_{endo}], 1.87 – 1.70 [m, 1H : C(2h)*H*], 1.47 – 1.37 [m, 2H, C(7)H_2], 0.96 [dd, *J* = 9.0, 6.6 Hz, 6H, C(2f)H_3 x 2], 0.79 [dd, *J* = 6.4, 1.8 Hz, 6H, C(2i)H_3 x 2]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 172.7 [*C*(2a)], 167.9 [*C*(2c)], 155.3 (Ar*C*), 141.0 (Ar*C*), 139.1 [*C*(5)], 134.6 [*C*(6)], 127.5 (Ar*C*), 125.2 (Ar*C*), 121.9 (Ar*C*), 110.0 (Ar*C*), 74.6 [*C*(2d)], 62.2 [*C*(2)], 52.9 [*C*(2b)], 49.3 [*C*(1)], 48.9 [*C*(7)], 41.9 [*C*(4)], 40.6 [*C*(2g)], 35.7 [*C*(3)], 28.3 [*C*(2e)], 28.2 [*C*(2h)], 23.0 [*C*(2i)], 19.7 [*C*(2f)]; ***LRMS*** *m/z* (ES+) 400.25 $[M+H]^+$; ***HRMS*** (ES+) *m/z*: *calcd.* for $C_{24}H_{34}NO_4$ 400.2488, found 400.2497, Δ = 2.2 ppm.

Methyl (1*R*,2*R*,4*R*)-2-((2,6-diisopropylphenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-153e) & methyl (1R,2S,4R)-2-((2,6-diisopropylphenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-153e)



According to **GP2**, cyclopentadiene (0.20 mL, 2.40 mmol) and α-amido acrylate **151e** (139 mg, 0.48 mmol) were heated for 2 h, after which dry toluene (0.2 mL) was added to aid solubility and the mixture heated at 80 °C for a further 30 mins. FC purification (*n*-hex/Et_2O 4:1 → 3:2) afforded a mixture of diastereoisomers ***endo*-153e:*exo*-153e** in a 3.2:1 ratio (153 mg, 90%):

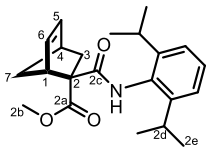
Isolated ***endo*-153e**, white powder; ***mp*** 140-142 °C; Si gel TLC R_f 0.53 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 3311, 2960, 2932, 2868, 1743, 1644, 1501, 1236, 1157, 735;



^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.20 (s, 1H, N*H*), 7.25 (t, *J* = 7.7 Hz, 1H, Ar*H*), 7.17 – 7.09 (m, 2H, Ar*H*), 6.31 [dd, *J* = 5.7, 2.9 Hz, 1H, C(5)*H*], 6.02 [dd, *J* = 5.8, 2.9 Hz, 1H, C(6)*H*], 3.71 – 3.56 [m, 4H : C(2b)H_3 & C(1)*H*], 3.05 – 2.86 [m, 3H : C(2d)*H* x 2 & C(4)*H*], 2.32 [dd, *J* = 12.3, 3.6 Hz, 1H, C(3)H_{exo}], 1.94 [dd, *J* = 12.2, 2.7 Hz, 1H, C(3)H_{endo}], 1.52 – 1.42 [m, 1H, C(7)H_{endo}], 1.43 – 1.33 [m,

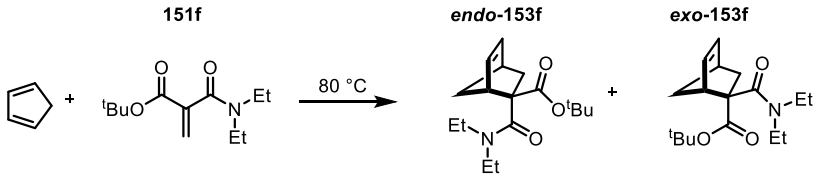
1H, C(7)H_{exo}], 1.24 – 0.94 [m, 12H, C(2e)H_3 x 4]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 172.2 [*C*(2a)], 169.9 [*C*(2c)], 146.6 (Ar*C*), 140.3 [*C*(5)], 133.8 [*C*(6)], 133.1 (Ar*C*), 128.1 (Ar*C*), 123.2 (Ar*C*), 62.1 [*C*(2)], 52.5 [*C*(2b)], 49.3 [*C*(1)], 49.0 [*C*(7)], 42.0 [*C*(4)], 35.8 [*C*(3)], 28.34 & 28.25 [*C*(2d)], 23.9 & 23.8 & 23.7 [*C*(2e)]; ***LRMS*** *m/z* (ES+) 356.22 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{22}H_{30}NO_3$ 356.2226, found 356.2224, Δ = -0.6 ppm.

Isolated ***exo*-153e**, white powder; ***mp*** 165 °C; Si gel TLC R_f 0.45 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 3300, 2957, 2928, 2868, 1738, 1639, 1504, 1236, 736;



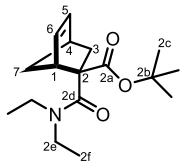
^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.03 (s, 1H, N*H*), 7.23 (t, *J* = 7.6 Hz, 1H, Ar*H*), 7.15 – 7.06 (m, 2H, Ar*H*), 6.30 [dd, *J* = 5.7, 3.0 Hz, 1H, C(5)*H*], 6.09 [dd, *J* = 5.5, 2.9 Hz, 1H, C(5)*H*], 3.71 [s, 3H, C(2b)H_3], 3.67 – 3.61 [m, 1H, C(1)*H*], 3.08 – 2.95 [m, 1H, C(2d)H_a], 2.93 – 2.82 [m, 2H : C(2d)H_b & C(4)*H*], 2.20 [dd, *J* = 12.5, 3.7 Hz, 1H, C(3)H_{exo}], 2.02 [d, *J* = 12.3 Hz, 1H, C(3)H_{endo}], 1.50 – 1.42 [m, 2H, C(7)H_2], 1.21 – 0.96 [m, 12H, C(2e)H_3 x 4]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 173.8 [*C*(2a)], 168.8 [*C*(2c)], 146.8 (Ar*C*), 146.7 (Ar*C*), 139.6 [*C*(5)], 134.3 [*C*(6)], 133.1 (Ar*C*), 128.0 (Ar*C*), 123.2 (Ar*C*), 62.3 [*C*(2)], 52.8 [*C*(2b)], 49.2 [*C*(1)], 49.1 [*C*(7)], 41.9 [*C*(4)], 35.7 [*C*(3)], 28.0 [*C*(2d)], 24.0 & 23.9 [*C*(2e)]; ***LRMS*** *m/z* (ES+) 356.22 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{22}H_{30}NO_3$ 356.2226, found 356.2236, Δ = 2.8 ppm.

Tert-butyl (1*R*,2*R*,4*R*)-2-(diethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-153f) & tert-butyl (1R,2S,4R)-2-(diethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-153f)



According to **GP2**, cyclopentadiene (0.28 mL, 3.30 mmol) and α-amido acrylate **151f** (150 mg, 0.66 mmol) were heated for 48 h. FC purification (*n*-hex/Et_2O 4:1 → 2:3) afforded a mixture of diastereoisomers ***endo*-153f:*exo*-153f** in a 4.9:1 ratio (106 mg, 55%):

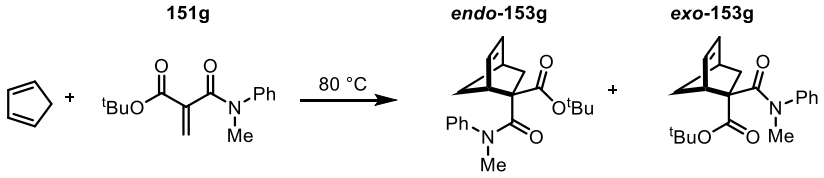
Isolated ***endo*-153f**, white solid; Si gel TLC R_f 0.38 (*n*-hex/Et_2O 3:2); ***ATR-IR*** ν_{max}/cm^{-1} 2976, 2948, 1718, 1635, 1458, 1423, 1367, 1280, 1257, 1139, 1116, 1100, 1052, 845, 709;



^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.29 [dd, *J* = 5.7, 2.9 Hz, 1H, C(5)H], 5.85 [dd, *J* = 5.7, 2.9 Hz, 1H, C(6)H], 3.52 – 3.00 [m, 5H H C(2e)H_2 x 2 & C(1)*H*], 2.83 [*br.* s, 1H, C(4)*H*], 1.95 [dd, *J* = 11.6, 2.1 Hz, 1H, C(3)H_{endo}], 1.67 [dd, *J* = 11.8, 3.6 Hz, 1H, C(3)H_{exo}], 1.43 – 1.28 [m, 11H : C(2c)H_3 x 3 & C(7)H_2], 1.01 [dt, *J* = 17.9, 7.0 Hz, 6H, C(2f)H_3 x 2]; ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 171.0 [*C*(2a)], 170.2 [*C*(2d)], 140.6 [*C*(5)], 132.6 [*C*(6)], 81.0, [*C*(2b)] 60.0 [*C*(2)], 51.85 [*C*(1)], 50.5 [*C*(7)], 42.3 [*C*(4)], 39.1 [*C*(2e)], 35.6 [*C*(3)], 28.0 [*C*(2c)], 13.6 & 12.4 [*C*(2f)]; ***LRMS*** *m/z* (ES+) 294.21 $[M+H]^+$; **HRMS** *m/z calcd.* for $C_{17}H_{28}NO_3$ 294.2069, found 294.2065, Δ = -1.4 ppm.

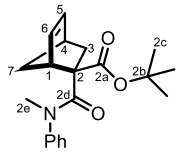
Exo*-153f** not fully separated from ***endo*-153f**, white powder; Si gel TLC R_f 0.37 (*n*-hex/Et_2O 3:2); from trace amounts of ***exo*-6f** isolated: ***ATR-IR ν_{max}/cm^{-1} 2976, 2944, 1718, 1636, 1458, 1421, 1367, 1280, 1257, 1139, 1117, 1099, 1053, 846, 709; distinguishable peaks only: ***^{1}H NMR*** (DMSO-d_6, 400 MHz) δ 6.16 – 6.10 (m, 1H), 6.09 – 6.02 (m, 1H); distinguishable peaks only: ***^{13}C NMR*** (DMSO-d_6, 101 MHz) δ 81.4, 41.9, 37.2, 27.9, 13.9, 12.0; from trace amounts of ***exo*-153f** isolated: ***LRMS*** *m/z* (ES+) 294.21 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{17}H_{28}NO_3$ 294.2069, found 294.2057, Δ = -4.1 ppm.

Tert-butyl (1*R*,2*R*,4*R*)-2-(methyl(phenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*endo*-153g) & tert-butyl (1*R*,2*S*,4*R*)-2-(methyl(phenyl)carbamoyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (*exo*-153g)



According to **GP2**, cyclopentadiene (0.42 mL, 4.94 mmol) and α-amido acrylate **151g** (258 mg, 0.99 mmol) were heated for 24 h. FC purification (*n*-hex/Et_2O 4:1 → 1:1) afforded a mixture of diastereoisomers ***endo*-153g**:***exo*-153g** in a 4.3:1 ratio (217 mg, 67%):

Isolated ***endo*-153g**, off-white powder; ***mp*** 132-136 °C; Si gel TLC R_f 0.32 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 2976, 2932, 1731, 1660, 1494, 1366, 1257, 1154, 1115, 764;



[1]H NMR (DMSO-d_6, 400 MHz) δ 7.39 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.27 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.24 – 7.18 (m, 2H, Ar*H*), 6.40 – 6.20 [*br.* m, 1H, C(5)*H*], 5.85 [*br. m*, 1H, C(6)*H*], 3.44 – 3.38 [m, 1H, C(1)*H*], 3.14 [s, 3H, C(2e)H_3], 2.87 [*br.* s, 1H, C(4)*H*], 2.09 – 1.81 [*br.* m, 2H, C(3)H_2], 1.50 – 1.33 [m, 11H : C(2c)H_3 x 3 & C(7)H_2]; ***[13]C NMR*** (DMSO-d_6, 101 MHz) δ 171.3 [*C*(2a)], 170.5 [*C*(2d)], 140.6 [*C*(5)], 132.4 [*C*(6)], 129.4 (Ar*C*), 127.0 (*br.* m, Ar*C*), 81.3 [*C*(2b)], 60.2 [*C*(2)], 52.0 [*C*(1)], 50.6 [*C*(7)], 42.6 [*C*(4)], 38.7 [*C*(2e)], 35.7 [*C*(3)], 28.1 [*C*(2c)]; ***LRMS*** *m/z* (ES+) 328.19 $[M+H]^+$; ***HRMS*** *m/zcalcd.* for $C_{20}H_{26}NO_3$ 328.1906, found 328.1913, Δ = -2.1 ppm.

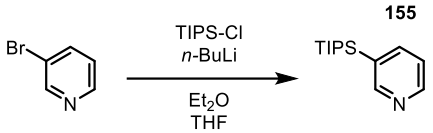
Exo*-153g** not fully separated from ***endo*-153g**, white powder; Si gel TLC R_f 0.3 (*n*-hex/Et_2O 1:1); from trace amounts of ***exo*-153g** isolated: ***ATR-IR ν_{max}/cm^{-1} 2981, 1721, 1658, 1494, 1367, 1247, 1154, 1075, 693; distinguishable peaks only: ***[1]H NMR*** (DMSO-d_6, 400 MHz) δ 6.22 – 6.03 (m, 2H); distinguishable peaks only: ***[13]C NMR*** (DMSO-d_6, 101 MHz) δ 172.8, 129.5, 81.6, 28.0; from trace amounts of ***exo*-153g** isolated: ***LRMS*** *m/z* (ES+) 328.19 $[M+H]^+$; ***HRMS*** *m/z calcd.* for $C_{20}H_{26}NO_3$ 328.1906, found 328.1909, Δ = -1.2 ppm.

***General procedure for DA reactions between α-amido acrylates 4e and 4f and cyclopentadiene in the presence of Et_2AlCl*:** To a solution of α-amido acrylate (**151e** or **151f**, 1 *eq.*) in dry CH_2Cl_2 (0.1M) at 0 °C under Ar was added Et_2AlCl (1 *eq.,* 1M in hexane). The reaction mixture was stirred at RT for 30 mins before cooling back down to 0 °C and adding cyclopentadiene (10 *eq.*), after which the reaction mixture was stirred at RT until consumption of the dienophile was observed by TLC analysis. The reaction mixture was then directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

***General procedure for DA reactions between α-amido acrylates 4e and 4f and cyclopentadiene in the presence of $B(C_6F_5)_3$*:** To a solution $B(C_6F_5)_3$ (1 *eq.*) and 4Å MS in dry CH_2Cl_2 at RT under Ar was added a solution of α-amido acrylate (**151e** or **151f**, 1 *eq.*) in dry CH_2Cl_2 (0.1M). The reaction mixture was stirred at RT for 30 mins before cooling back down to 0 °C and adding cyclopentadiene (10 *eq.*), after which the reaction mixture was stirred at RT until consumption of the dienophile was observed by TLC analysis. The reaction mixture was then directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

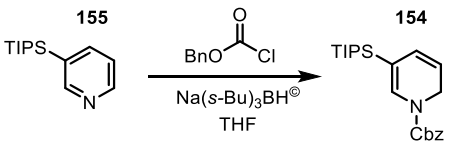
***General procedure for DA reactions between α-amido acrylates 4e and 4f and cyclopentadiene in the presence of TBSOTf*:** To a solution of α-amido acrylate (**151e** or **151f**, 1 *eq.*) in dry CH_2Cl_2 (0.1M) at 0 °C under Ar was added freshly distilled TBSOTf (1 *eq.*). The reaction mixture was stirred at RT for 30 mins before cooling back down to 0 °C and adding cyclopentadiene (10 *eq.*), after which the reaction mixture was stirred until consumption of the dienophile was observed by TLC analysis. The reaction mixture was then directly loaded onto a Si gel column and purified by FC to afford the DA adducts.

3-(Triisopropylsilyl)pyridine (155)[150]



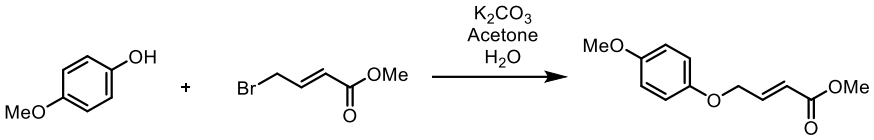
Adapted from the method of Wanner,[125] to a solution of 3-bromopyridine (784 µL, 8.00 mmol) in dry Et_2O (20 mL) under N_2 at -78 °C was added *n*-BuLi (1.6M in hexane, 5.5 mL, 8.8 mmol) dropwise giving 3-lithiopyridine as a yellow precipitate. After 45 mins stirring at -78 °C, triisopropylsilyl chloride (2.03 mL, 8.8 mmol) was added followed by dry THF (15 mL) after which the suspension turned dark green. The reaction mixture was then allowed to warm up to RT and stirred for a further 66 h under N_2 (*N.B.* a bright orange clear solution was observed after an h stirring) before being quenched by the addition of phosphate buffer (1M, pH 7). The reaction mixture was then extracted with CH_2Cl_2 (2 x 100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by Si gel FC (*n*-Hex/EtOAc 9:1 → 4-1 → 3:2) and the fractions containing product were combined and distilled (bp. 110 °C at 4 mbar) to remove any remaining impurities and provide 3-TIPS-pyridine (**155**) as a colourless oil (1.05 g, 56%); Si gel TLC $\boldsymbol{R_f}$0.42 (*n*-hex/EtOAc 3:2); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 8.67 (*br*. s, 1H, Ar*H*), 8.58 (dd, *J* = 4.8, 1.8 Hz, 1H, Ar*H*), 7.77 (dt, *J* = 7.6, 1.9 Hz, 1H, Ar*H*), 7.29 – 7.25 (m, 1H, Ar*H*), 1.52 – 1.35 (m, 3H, TIPS C*H* x 3), 1.08 (d, *J* = 7.5 Hz, 18H, TIPS CH_3 x 3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 155.4 (Ar*C*), 149.7 (Ar*C*), 143.0 (Ar*C*), 130.0 (Ar*C*), 123.1 (Ar*C*), 18.4 (TIPS *C*H_3), 10.6 (TIPS *C*H); ***LRMS*** *m/z* (ES^+) 236.2 $[M+H]^+$. The spectroscopic data were in accordance with the literature.[150]

Benzyl 5-(triisopropylsilyl)pyridine-1(2H)-carboxylate (154)



Adapted from the method of Sundberg,[81] to a solution of 3-TIPS-pyridine (**154**, 300 mg, 1.27 mmol) in dry THF (4 mL) under N_2 at -78 °C was added benzyl chloroformate (0.20 mL, 1.40 mmol) in dry THF (1.4 mL) slowly over the course of 15 mins and the resulting slurry was stirred at -78 °C for 30 mins. To this was added Na(*s*-Bu)$_3$BH (1.0M in THF, 2.67 mL, 2.67 mmol) slowly *via* syringe. The reaction mixture was then stirred at -78 °C for 16 h and then at RT for 6 h. A mixture of 30% H_2O_2 (4 mL) and 10% NaOH (6 mL) was very slowly and carefully added (caution: exothermic). After the addition was complete the mixture was stirred overnight at RT under N_2. The reaction was then poured into ice water and extracted with Et_2O (3 x 50 mL). The ether extracts were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by Si gel FC (n-hex/Et_2O 24:1 → 14:1 → 9:1) to give 1,2-dihydropyridine **154** as a colourless oil (170 mg, 36%); Si gel TLC $\boldsymbol{R_f}$ 0.35 (*n*-hex/EtOAc 9:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.44 – 7.28 (m, 5H, Ar*H*), 6.83 [*app.* d, *J* = 18.8 Hz, 1H, NC(6)*H*], 5.84 [*app* d, *J* = 9.6 Hz, 1H, C(4)*H*], 5.62 – 5.39 [m, 1H, C(3)*H*], 5.22 [*app.* d, *J* = 6.4 Hz, 2H, OCH_2Ph), 4.43 – 4.30 [*br.* m, 2H, NC(2)H_2], 1.23 – 1.11 [m, 3H, TIPS C*H* x 3), 1.06 (d, *J* = 7.0 Hz, 18H, TIPS CH_3 x 6); ***HRMS*** *m/z calcd.* for $C_{22}H_{32}NO_2Si$ 370.2202, found 370.2213, Δ = 3.0 ppm. *N.B.* Compound is very unstable and should be used immediately – decomposition observed in ^{1}H spectrum after only a few hours.

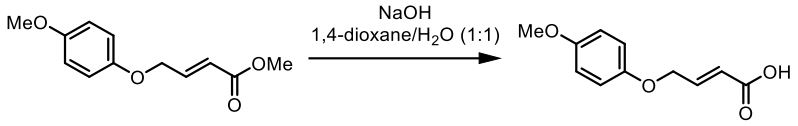
Methyl (*E*)-4-(4-methoxyphenoxy)but-2-enoate[151]



According to the method of Huffman,[151] 4-methoxyphenol (7.92 g, 63.77 mmol) and potassium carbonate (6.17 g, 44.64 mmol) were dissolved in acetone (43 mL) to which 4-methylbromocrotonate (5 mL, 42.51 mmol) was added dropwise over 1 h. The mixture was stirred at RT under N_2 for 20 h and then heated at 50 °C for a further 20 h. The reaction mixture was then concentrated under reduced pressure, diluted in Et2O and washed sequentially with 1M NaOH (x 2) and brine. Th organic solution was concentrated under reduced pressure and the crude material was then purified by Si gel FC (*n*-hex/EtOAc 9:1 → 4:1) to give the corresponding ether as a white solid (7.35 g, 78%); Si gel TLC $\boldsymbol{R_f}$ 0.25 (*n*-hex/EtOAc 4:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.08 (dt, *J* = 15.7, 4.1 Hz, 1H, CH_2CH=C), 6.86 - 6.82 (m, 4, Ar*H*), 6.20 (dt, *J* = 15.8, 2.1 Hz, 1H, CH_2C=C*H*), 4.65 (dd, *J* = 4.1, 2.1 Hz, 2H, OCH_2), 3.77 (s, 3H, ArOCH_3), 3.76 (s, 3H, COOCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 166.6 (*C*=O), 154.2 (Ar*C*), 152.2 (Ar*C*), 143.1 (CH_2C=C), 121.5 (CH_2C=*C*),

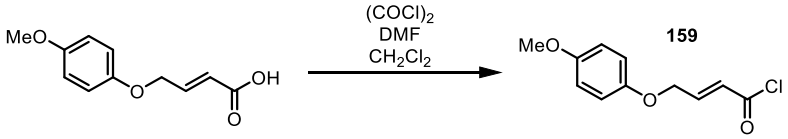
115.7 (Ar*C*), 114.7 (Ar*C*), 67.2 (O*C*H_2), 55.7 (ArO*C*H_3), 51.7 (COO*C*H_3). The spectroscopic data were in accordance with the literature.[151]

(*E*)-4-(4-Methoxyphenoxy)but-2-enoic acid



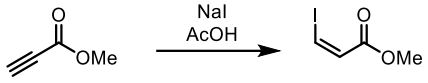
A solution of methyl (*E*)-4-(4-methoxyphenoxy)but-2-enoate (2 g, 8.99 mmol) in 1,4-dioxane/H_2O (1:1, 90mL) was cooled to 0 °C before adding aqueous 5M NaOH solution (9 mL). The reaction was allowed to warm up to RT and stirred for 5 h. The reaction mixture was acidified to pH 1 using 4N HCl to give a white suspension, which was then extracted with Et_2O (200 mL). The organic solution was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the corresponding acid as a white solid (1.75g, 94%); ***mp*** 86 °C; Si gel TLC R_f 0.00 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 3523, 3008, 2956, 2840, 1725, 1699, 1657, 1512, 1245, 1045, 980, 769; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.19 (dt, *J* = 15.7, 3.9 Hz, 1H, CH_2CH=C), 6.87 – 6.82 (m, 4, Ar*H*), 6.22 (dt, *J* = 15.7, 2.1 Hz, 1H, CH_2C=C*H*), 4.68 (dd, *J* = 3.9, 2.1 Hz, 2H, OCH_2), 3.78 (s, 3H, ArOCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 171.2 (*C*=O), 154.3 (Ar*C*), 152.1 (Ar*C*), 145.7 (CH_2C=C), 120.9 (CH_2C=*C*), 115.7 (Ar*C*), 114.8 (Ar*C*), 67.1 (OCH_2), 55.7 (ArOCH_3); ***LRMS*** *m/z* (ES-) 207.0663 $[M-H]^-$; ***HRMS*** *m/z calcd.* for $C_{11}H_{11}O_4$ 207.0657, found 207.0663, Δ = 2.9 ppm.

(*E*)-4-(4-Methoxyphenoxy)but-2-enoyl chloride (159)



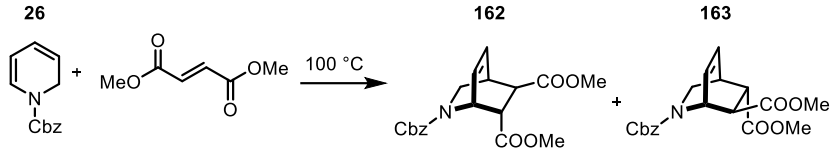
A solution of methyl (*E*)-4-(4-methoxyphenoxy)but-2-enoic acid (400 mg, 1.92 mmol) in CH_2Cl_2 (20mL) was cooled to 0 °C before adding oxalyl chloride (0.18 mL, 2.11 mmol) dropwise followed by 2 drops of DMF. The reaction was allowed to warm up to RT and stirred for 4 h. The reaction mixture was concentrated under reduced pressure to give acid chloride **159** as a brown oil (445 mg, 96%); Si gel TLC R_f 0.35 (*n*-hex/EtOAc 7:3); ***ATR-IR*** ν_{max}/cm^{-1} 3008, 2956, 2839, 1787, 1749, 1652, 1512, 1470, 1245, 779; ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.31 (dt, *J* = 15.3, 3.6 Hz, 1H, CH_2CH=C), 6.90 – 6.81 (m, 4, Ar*H*), 6.48 (dt, *J* = 15.3, 2.2 Hz, 1H, CH_2C=C*H*), 4.73 (dd, *J* = 3.6, 2.2 Hz, 2H, OCH_2), 3.78 (s, 3H, ArOCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 165.8 (*C*=O), 154.7 (Ar*C*), 152.0 (Ar*C*), 150.1 (CH_2C=C), 126.4 (CH_2C=*C*), 115.9 (Ar*C*), 115.0 (Ar*C*), 67.0 (OCH_2), 55.9 (ArOCH_3); ***LRMS*** *m/z* not found.

Methyl (Z)-3-iodoacrylate (160)[152]



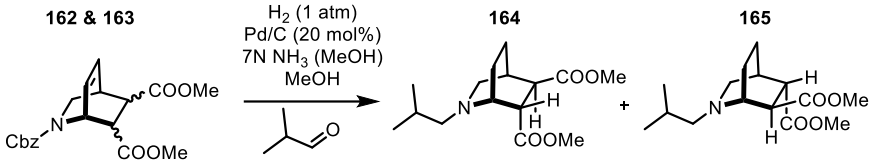
According to the method of Spino,[152] to a solution of methyl propiolate (0.7 mL, 7.87 mmol) in acetic acid (3.9 mL) was added sodium iodide (2.36 g, 15.74 mmol) and the mixture was heated at 70 °C for 40 h. The reaction mixture was diluted in Et_2O and then neutralised with 1N NaOH solution. The aquoues layer was separated and further extracted with Et_2O. The combined organic layers were washed sequentially with saturated Na_2CO_3 solution, saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The organic solution was concentrated under reduced pressure to give vinyl iodide **160** as an orange oil (1.61 g, 96%); Si gel TLC R_f 0.47 (*n*-hex/EtOAc 4:1); ***^{1}H NMR*** ($CDCl_3$, 400 MHz) δ 7.47 (d, *J* = 8.9 Hz, 1H, I-C*H*=C), 6.91 (d, *J* = 8.9 Hz, 1H, I-C=C*H*), 3.78 (s, 3H, OCH_3); ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 165.1 (*C*=O), 129.7 (I-C=*C*), 95.3 (I-*C*=C), 51.8 (O*C*H_3). The spectroscopic data were in accordance with the literature.[152]

2-Benzyl 5,6-dimethyl (1*R*,4*S*,5*R*,6*S*)-2-azabicyclo[2.2.2]oct-7-ene-2,5,6-tricarboxylate (162) & 2-benzyl 5,6-dimethyl (1*R*,4*S*,5*S*,6*R*)-2-azabicyclo[2.2.2]oct-7-ene-2,5,6-tricarboxylate (163)



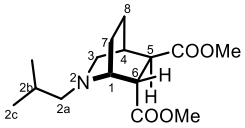
1,2-Dihydropyridine **26** (5.38 g, 25.0 mmol) and dimethyl maleate (7.20 g, 50.0 mmol) were heated at 100 °C for 16 h under N_2. The reaction mixture was purified by Si gel FC (*n*-hex/EtOAc 1:1 → 1:4) to give a white solid which contained an inseparable mixture of diastereoisomers **162**:**163** in a 2.3:1 ratio (8.0g, 89%); ***mp*** 48-50 °C; Si gel TLC R_f 0.30 (*n*-hex/EtOAc 3:7); ***ATR-IR*** ν_{max}/cm^{-1} 2952, 1731, 1695, 1411, 1336, 1296, 1277, 1198, 1178, 1108, 1099, 1033, 730, 697; ^{1}H and ^{13}C NMR spectra complicated at RT due to presence of rotamers ***^{1}H NMR*** (DMSO-d_6, 400 MHz, 398K): δ 7.42 – 7.25 (m, 5H), 6.61 – 6.51 (m, 1H), 6.41 – 6.36 (m, 1H), 5.12 & 5.06 (2 x s, 2H), 5.05 – 4.97 (m, 1H), 3.71- 3.58 (m, 6H), 3.46 (dd, *J* = 5.4, 3.1 Hz, 0.3H), 3.39 – 3.30 (m, 1H), 3.26 – 3.23 (m, 1.4H), 3.18 (m, 0.3H), 2.97 – 2.88 (m, 1.7H), 2.86 – 2.82 (m, 0.3H); ***^{13}C NMR*** (DMSO-d_6, 101 MHz, 398K): δ 171.9, 171.5, 171.1, 170.5, 153.8, 153.6, 136.4, 134.6, 132.3, 131.8, 130.0, 127.6, 127.5, 127.0, 126.9, 126.6, 126.6, 65.6, 65.5, 51.3, 51.2, 51.1, 47.6, 47.3, 46.5, 45.9, 42.2, 41.8, 41.7, 32.7, 32.2; ***LRMS*** *m/z* (ES^+) 360.15 $[M+H]^+$, 377.17 $[M+NH_4]^+$, 382.13 $[M+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{19}H_{22}NO_6$ 360.1447, found 360.1459, Δ = 3.3 ppm.

Dimethyl (1*R*,4*S*,5*R*,6*S*)-2-isobutyl-2-azabicyclo[2.2.2]octane-5,6-dicarboxylate (164) & dimethyl (1*R*,4*S*,5*S*,6*R*)-2-isobutyl-2-azabicyclo[2.2.2]octane-5,6-dicarboxylate (165)



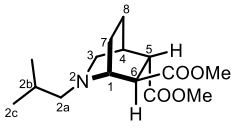
To a solution of a mixture of *N*-Cbz diester (2.3:1, **162:163**) (110 mg, 0.31 mmol) in MeOH (6 mL) was added NH_3 (7N in MeOH, 0.22 mL, 1.55 mmol), isobutyraldehyde (84 µL, 0.93 mmol) and Pd/C (10% *wt*., 65 mg, 61 µmol) after which the reaction mixture was subjected to a H_2 atmosphere for 6 h. The reaction mixture was filtered over celite®, concentrated in vacuo and then purified *via* Si gel FC (*n*-hex/EtOAc 9:1 → 6:1 → 1:1) to afford:

N-alkyl alkane **164** as a colourless oil (39 mg, 45%); Si gel TLC R_f 0.60 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 2953, 1732, 1669, 1599, 1435, 1280, 1227, 1194, 1181, 1033;



^{1}H NMR ($CDCl_3$, 400 MH): δ 3.69 (s, 3H, OCH_3), 3.68 (2, 3H, OCH_3), 3.39 [*app.* dt, *J* = 6.4, 2.0 Hz, 1H, C(5)*H*], 3.12 – 3.02 (m, 3H : C(1)*H* & C(3)H_{exo} & C(6)*H*], 2.26 [dd, *J* = 9.6, 1.9 Hz, 1H, C(3)H_{endo}], 2.20 – 2.10 (m, 3H : C(2a)H_2 & C(4)*H*], 1.97 – 1.86 [m, 1H, C(7)$H_{\underline{a}}$], 1.65 – 1.36 (m, 4H : C(2b)*H* & C(7)$H_{\underline{b}}$ & C(8)H_2], 0.79 & 0.77 [2 x d, *J* = 6.5, 6H, C(2c)H_3 x 2]; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 175.2 (*C*=O), 174.6 (*C*=O), 64.3 [*C*(2a)], 55.6 [*C*(3)], 53.3 [*C*(1)], 52.0 (O*C*H_3), 51.9 (O*C*H_3), 47.0 [*C*(6)], 42.7 [*C*(5)], 29.7 [*C*(4)], 26.5 [*C*(2b)], 21.4 [*C*(8)], 20.9 [*C*(7)], 20.5 & 20.3 [*C*(2c)]; ***LRMS*** *m/z* (ES^+) 284.19 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{15}H_{26}NO_4$ 284.1862, found 284.1877, Δ = 5.3 ppm.

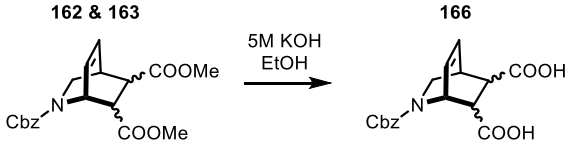
N-alkyl alkane **165** as a colourless oil (9.4 mg, 11%); Si gel TLC R_f 0.45 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 2953, 1731, 1652, 1438, 1198, 1178;



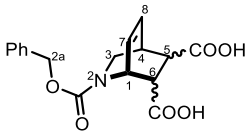
^{1}H NMR ($CDCl_3$, 400 MH): δ 3.70 (s, 3H, OCH_3), 3.69 (2, 3H, OCH_3), 3.47 ([t, *J* = 7.4, 2.4 Hz, 1H, C(6)*H*], 3.15 – 3.07 [m, 1H, C(5)*H*], 2.89 [m, 1H, C(1)*H*], 2.78 [m, 1H, C(3)H_{endo}], 2.34 [m, 1H, C(3)H_{exo}], 2.31 – 2.21 [m, 2H, C(2a)H_2], 2.15 [m, 1H, C(4)*H*], 1.86 – 1.74 [m, 1H, C(7)$H_{\underline{a}}$], 1.69 – 1.59 [m, 3H : C(2b)*H* & C(8)H_2], 1.46 – 1.36 [m, 1H, C(7)$H_{\underline{b}}$], 0.87 [*app.* t, *J* = 7.1, 6H, C(2c)H_3 x 2];

^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.6 (*C*=O), 174.5 (*C*=O), 64.6 [*C*(2a)], 53.2 [*C*(1)], 52.3 [*C*(3)], 52.0 (O*C*H_3 x 2), 43.1 [*C*(5)], 41.7 [*C*(6)], 29.1 [*C*(4)], 26.5 [*C*(2b)], 24.3 [*C*(8)], 22.8 [*C*(7)], 20.7 & 20.6 [*C*(2c)]; ***LRMS*** *m/z* (ES^+) 284.19 $[M+H]^+$; ***HRMS*** *m/z* calcd. for $C_{15}H_{26}NO_4$ 284.1862, found 284.1857, Δ = -1.8 ppm.

(1*R*,4*S*)-2-((Benzyloxy)carbonyl)-2-azabicyclo[2.2.2]oct-7-ene-5,6-dicarboxylic acid (166)



To a solution of a mixture of *N*-Cbz diester (2.3:1, **162:163**) (1 g, 2.78 mmol) dissolved in absolute EtOH (12 mL) was added aqueous 5M KOH (12 mL) to give a homogenous yellow solution that grew warm to the touch. This mixture was refluxed under N_2 with stirring for 3 h. The reaction mixture was cooled to RT and diluted with H_2O and then acidified with 4N HCl; the acidification was judged complete when the solution tested below pH 1, and a cloudy mixture was obtained. The mixture was extracted with Et_2O and the layers separated. The aqueous layer was saturated with NaCl, and extracted with Et_2O (5 x 100 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a colourless gum that consisted of an inseperable mixture of diastereoisomers in a 2.3:1 ratio (880 mg, 95%); Si gel TLC ***R_f*** 0.00 (*n*-hex/Et_2O 1:1); ***ATR-IR*** ν_{max}/cm^{-1} 3407, 1705, 1672, 1425, 1339, 1303, 1277, 1198, 1119; (^{1}H and ^{13}C NMR spectra complicated at RT due to the presence of rotamers)



^{1}H NMR ($CDCl_3$, 400 MH): δ 8.88 – 8.30 (br. s, 2H, COO*H*), 7.39 – 7.20 (m, 5H, Ar*H*), 6.65 – 6.29 [m, 2H : C(7)*H* & C(8)*H*], 5.41 – 4.90 [m, 3H : C(1)*H* & C(2a)H_2], 3.67 – 2.87 [m, 5H : C(3)H_2 & C(4)*H* & C(5)*H* & C(6)*H*] ; ***^{13}C NMR*** ($CDCl_3$, 101 MHz) δ 178.0, 177.9, 177.4, 177.0 176.8, 176.5, 176.3, 175.7, 156.1, 155.4, 155.0, 136.5, 133.3, 133.1, 132.9, 132.8, 131.9, 128.7, 128.6, 128.1, 128.0, 127.9, 127.8, 127.2, 67.6, 67.5, 67.5, 65.5, 58.6, 48.4, 48.2, 48.0, 47.9, 47.2, 46.9, 46.7, 46.6, 43.1, 43.1, 42.7, 42.7, 42.5, 42.4, 33.1, 33.0, 18.3; ***LRMS*** *m/z* (ES^+) 332.11 $[M+H]^+$, 349.14 $[M+NH_4]^+$, 354.09 $[M+Na]^+$; ***HRMS*** *m/z* calcd. for $C_{17}H_{18}NO_6$ 332.1134, found 332.1127, Δ = -2.1 ppm.

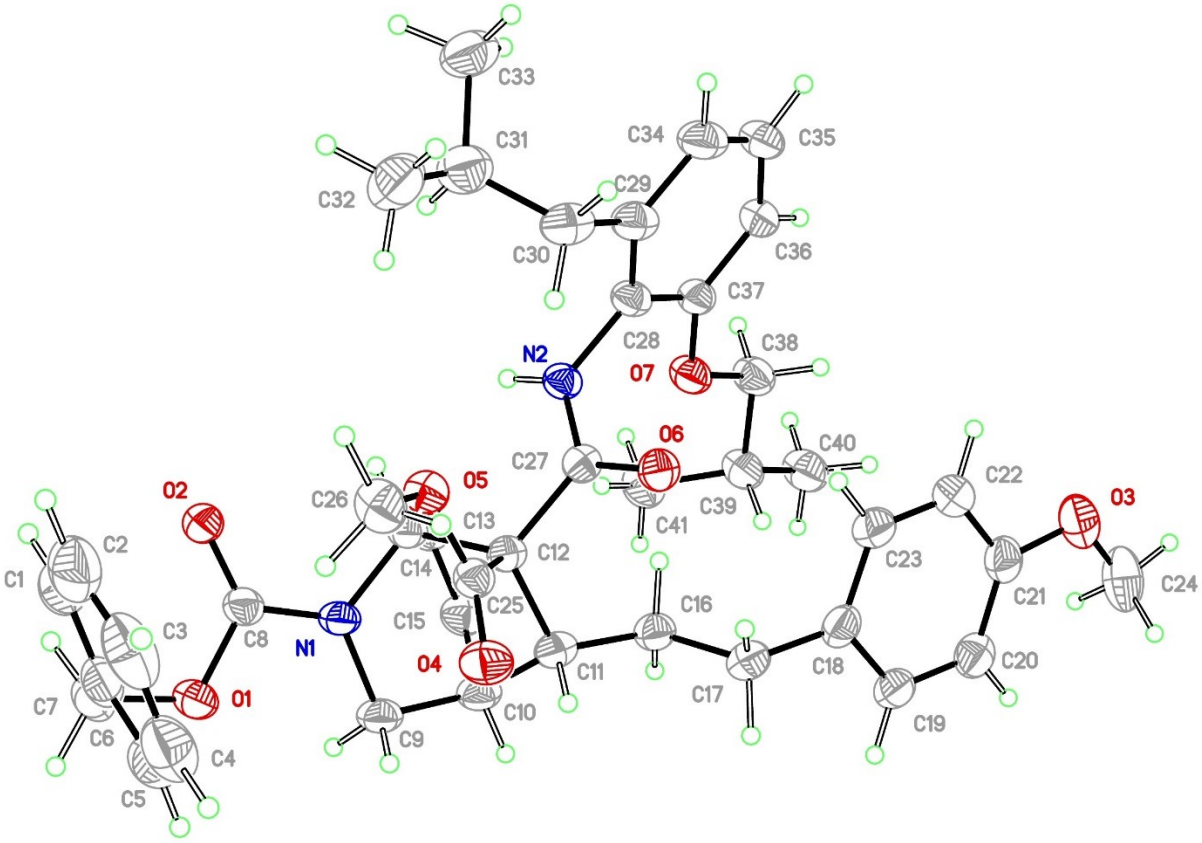
10. Appendix - Single Crystal X-Ray Structure Determination

X-ray structure determination of Compound **149**

Crystal data for **149**: $C_{41}H_{50}N_2O_7$, M_r = 682.83g mol^{-1}, triclinic, space group $P\bar{1}$, a = 11.2573(5)Å, b = 11.5352(5)Å, c = 15.1073(6)Å, α = 76.412(4)°, β = 87.183(4)°, γ = 80.002(4)°, V = 1877.82(14)Å^3, T = 100 K, Z' = 1, Z = 2, ρ = 1.208 g cm^{-3}, Cu$K\alpha$ radiation, λ = 1.54184 Å, μ = 0.660 mm^{-1}, F(000) = 732, crystal size 0.36 x 0.19 x 0.11 mm^3. A total of 30588 reflections were collected of which 7642 were unique, R_{int} = 0.0244, 100% completeness to 0.80Å, wR^2 (all data) = 0.2231, R_1 = 0.0763 for 6380 reflections with $I > 2\sigma(I)$: max/min residual electron density 1.093 and -0.405 e Å^{-3}. CCDC deposition number 1492919.

Colourless crystals of **149** were obtained by vapour diffusion from CH_2Cl_2/*n*-hexane. Data were collected on a Rigaku Oxford Diffraction SuperNova equipped with an Enhance (Cu) X-ray source and an Atlas 2 CCD detector. Low temperature measurements were made using an Oxford Cryosystems Cobra cooler. The non-hydrogen atoms were refined with anisotropic thermal parameters on F^2. Hydrogen atoms attached to heteroatoms were allowed to freely refine whereas those attached to C were generated theoretically at the specific atoms and refined with a riding model. The overall crystal quality was poor and there exists some minor disorder associated with the *iso*-butyl substituent defined by atoms C30-C33 with a maximum peak in the difference electron density map located near to C31 of 1.093 eÅ^{-3}. Unfortunately, the data were not sufficient to be able to sustain a refinement of a disorder model for this substituent. The structure was validated using the IUCr CHECKCIF routine. There were no Type A alerts. There were 3 Type B alerts which have responses contained within the CIF file. The structure was solved with SHELXT and refined using the SHELXL suite of programs.[S1]

S1. Sheldrick, G. M. SHELXTL Version 2014/7. http://shelx.uni-ac.gwdg.de/SHELX/index.php



Ortep diagram of Compound **149**. Thermal ellipsoids are drawn at the 30% probability level for clarity.

11. References

(1) Berggård, T.; Linse, S.; James, P. *Proteomics* **2007**, *7*, 2833.

(2) Keskin, O.; Gursoy, A.; Ma, B.; Nussinov, R. *Chem. Rev.* **2008**, *108*, 1225.

(3) Keskin, O.; Tuncbag, N.; Gursoy, A. *Chem. Rev.* **2016**, *116*, 4884.

(4) Azzarito, V.; Long, K.; Murphy, N. S.; Wilson, A. J. *Nat. Chem.* **2013**, *5*, 161.

(5) Cheng, A. C.; Coleman, R. G.; Smyth, K. T.; Cao, Q.; Soulard, P.; Caffrey, D. R.; Salzberg, A. C.; Huang, E. S. *Nat. Biotechnol.* **2007**, *25*, 71.

(6) Conte, L. Lo; Chothia, C.; Janin, J. *J. Mol. Biol.* **1999**, *285*, 2177.

(7) Smith, M. C.; Gestwicki, J. E. *Expert Rev. Mol. Med.* **2012**, *14*, 1.

(8) Wells, J. A.; McClendon, C. L. *Nature* **2007**, *450*, 1001.

(9) Hopkins, A. L.; Groom, C. R. *Nat. Rev. Drug Discov.* **2002**, *1*, 727.

(10) Bullock, B. N.; Jochim, A. L.; Arora, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 14220.

(11) Clackson, T.; Wells, J. A. *Science* **1995**, *267*, 383.

(12) Arkin, M. R.; Wells, J. A. *Nat. Rev. Drug Discov.* **2004**, *3*, 301.

(13) Moon, H.; Lim, H.-S. *Curr. Opin. Chem. Biol.* **2015**, *24*, 38.

(14) DeLano, W. L.; Ultsch, M. H.; de Vos, A. M.; Wells, J. A. *Science* **2000**, *287*, 1279.

(15) Guo, W.; Wisniewski, J. A.; Ji, H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2546.

(16) Arkin, M. R.; Tang, Y.; Wells, J. A. *Chem. Biol.* **2014**, *21*, 1102.

(17) Scott, D. E.; Bayly, A. R.; Abell, C.; Skidmore, J. *Nat. Rev. Drug Discov.* **2016**, *15*, 533.

(18) Pauling, L.; Corey, R. B.; Branson, H. R. *Proc. Natl. Acad. Sci. U. S. A.* **1951**, *37*, 205.

(19) Henchey, L. K.; Jochim, A. L.; Arora, P. S. *Curr. Opin. Chem. Biol.* **2008**, *12*, 692.

(20) Davis, J. M.; Tsou, L. K.; Hamilton, A. D. *Chem. Soc. Rev.* **2007**, *36*, 326.

(21) Cummings, C. G.; Hamilton, A. D. *Curr. Opin. Chem. Biol.* **2010**, *14*, 341.

(22) Scholtz, J. M.; Baldwin, R. L. *Annu. Rev. Biophys. Biomol. Struct.* **1992**, *21*, 95.

(23) Jackson, D. Y.; King, D. S.; Chmielewski, J.; Singh, S.; Schultz, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 9391.

(24) Bracken, C.; Gulyas, J.; Taylor, J. W.; Baum, J. *J. Am. Chem. Soc.* **1994**, *116*, 6431.

(25) Sia, S. K.; Carr, P. A.; Cochran, A. G.; Malashkevich, V. N.; Kim, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 14664.

(26) Lau, Y. H.; De Andrade, P.; Wu, Y.; Spring, D. R. *Chem. Soc. Rev.* **2015**, *44*, 91.

(27) Blackwell, H. E.; Grubbs, R. H. *Angew. Chemie Int. Ed.* **1998**, *37*, 3281.

(28) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, *122*, 5891.

(29) Wysoczanski, P.; Mart, R. J.; Loveridge, E. J.; Williams, C.; Whittaker, S. B.-M.; Crump, M. P.; Allemann, R. K. *J. Am. Chem. Soc.* **2012**, *134*, 7644.

(30) Cabezas, E.; Satterthwait, A. C. *J. Am. Chem. Soc.* **1999**, *121*, 3862.

(31) Kritzer, J. A.; Lear, J. D.; Hodsdon, M. E.; Schepartz, A. *J. Am. Chem. Soc.* **2004**, *126*, 9468.

(32) Sadowsky, J. D.; Fairlie, W. D.; Hadley, E. B.; Lee, H.-S.; Umezawa, N.; Nikolovska-Coleska, Z.; Wang, S.; Huang, D. C. S.; Tomita, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *129*, 139.

(33) Xin, D.; Ko, E.; Perez, L. M.; Ioerger, T. R.; Burgess, K. *Org. Biomol. Chem.* **2013**, *11*, 7789.

(34) Orner, B. P.; Ernst, J. T.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 5382.

(35) Edwards, T. A.; Wilson, A. J. *Amino Acids* **2011**, *41*, 743.

(36) Kazi, A.; Sun, J.; Doi, K.; Sung, S.-S.; Takahashi, Y.; Yin, H.; Rodriguez, J. M.; Becerril, J.; Berndt, N.; Hamilton, A. D.; Wang, H.-G.; Sebti, S. M. *J. Biol. Chem.* **2011**, *286*, 9382.

(37) Yin, H.; Lee, G.; Park, H. S.; Payne, G. A.; Rodriguez, J. M.; Sebti, S. M.; Hamilton, A. D. *Angew. Chem.* **2005**, *117*, 2764.

(38) Lanning, M. E.; Wilder, P. T.; Bailey, H.; Drennen, B.; Cavalier, M.; Chen, L.; Yap, J. L.; Raje, M.; Fletcher, S. *Org. Biomol. Chem.* **2015**, *13*, 8642.

(39) Kim, I. C.; Hamilton, A. D. *Org. Lett.* **2006**, *8*, 1751.

(40) Jayatunga, M. K. P.; Thompson, S.; Hamilton, A. D. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 717.

(41) Rodriguez, J. M.; Nevola, L.; Ross, N. T.; Lee, G.; Hamilton, A. D. *ChemBioChem* **2009**, *10*, 829.

(42) Thompson, S.; Hamilton, A. D. *Org. Biomol. Chem.* **2012**, *10*, 5780.

(43) Jung, K.-Y.; Vanommeslaeghe, K.; Lanning, M. E.; Yap, J. L.; Gordon, C.; Wilder, P. T.; MacKerell, A. D.; Fletcher, S. *Org. Lett.* **2013**, *15*, 3234.

(44) Restorp, P.; Rebek, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5909.

(45) Marimganti, S.; Cheemala, M. N.; Ahn, J.-M. *Org. Lett.* **2009**, *11*, 4418.

(46) Moon, H.; Lee, W. S.; Oh, M.; Lee, H.; Lee, J. H.; Im, W.; Lim, H.-S. *ACS Comb. Sci.* **2014**, *16*, 695.

(47) Oh, M.; Lee, J. H.; Wang, W.; Lee, H. S.; Lee, W. S.; Burlak, C.; Im, W.; Hoang, Q. Q.; Lim, H.-S. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 11007.

(48) Lee, J. H.; Oh, M.; Kim, H. S.; Lee, H. S.; Im, W.; Lim, H.-S. *ACS Comb. Sci.* **2015**.

(49) Ottow, E.; Weubnabbm, G.; Mannhold, R.; Kubinyi, H.; Folkers, G. *In Nuclear Receptors as Drug Targets*; Wiley, Ed.; Weinheim, **2008**.

(50) Mangelsdorf, D. J.; Thummel, C.; Beato, M.; Herrlich, P.; Schütz, G.; Umesono, K.; Blumberg, B.; Kastner, P.; Mark, M.; Chambon, P.; Evans, R. M. *Cell* **1995**, *83*, 835.

(51) Moore, J. T.; Collins, J. L.; Pearce, K. H. *ChemMedChem* **2006**, *1*, 504.

(52) Fayard, E.; Auwerx, J.; Schoonjans, K. *Trends Cell Biol.* **2004**, *14*, 250.

(53) Ortlund, E. A.; Lee, Y.; Solomon, I. H.; Hager, J. M.; Safi, R.; Choi, Y.; Guan, Z.; Tripathy, A.; Raetz, C. R. H.; McDonnell, D. P.; Moore, D. D.; Redinbo, M. R. *Nat. Struct. Mol. Biol.* **2005**, *12*, 357.

(54) Wang, W.; Zhang, C.; Marimuthu, A.; Krupka, H. I.; Tabrizizad, M.; Shelloe, R.; Mehra, U.; Eng, K.; Nguyen, H.; Settachatgul, C.; Powell, B.; Milburn, M. V; West, B. L. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 7505.

(55) Krylova, I. N.; Sablin, E. P.; Moore, J.; Xu, R. X.; Waitt, G. M.; MacKay, J. A.; Juzumiene, D.; Bynum, J. M.; Madauss, K.; Montana, V.; Lebedeva, L.; Suzawa, M.; Williams, J. D.; Williams, S. P.; Guy, R. K.; Thornton, J. W.; Fletterick, R. J.; Willson, T. M.; Ingraham, H. A. *Cell* **2005**, *120*, 343.

(56) Hadizadeh, S.; King, D. N.; Shah, S.; Sewer, M. B. *Mol. Cell. Endocrinol.* **2008**, *283*, 104.

(57) Lee, J. M.; Lee, Y. K.; Mamrosh, J. L.; Busby, S. A.; Griffin, P. R.; Pathak, M. C.; Ortlund, E. A.; Moore, D. D. *Nature* **2011**, *474*, 506.

(58) Zhou, J.; Suzuki, T.; Kovacic, A.; Saito, R.; Miki, Y.; Ishida, T.; Moriya, T.; Simpson, E. R.; Sasano, H.; Clyne, C. D. *Cancer Res.* **2005**, *65*, 657.

(59) Clyne, C. D.; Speed, C. J.; Zhou, J.; Simpson, E. R. *J. Biol. Chem.* **2002**, *277*, 20591.

(60) Goodwin, B.; Jones, S. A.; Price, R. R.; Watson, M. A.; McKee, D. D.; Moore, L. B.; Galardi, C.; Wilson, J. G.; Lewis, M. C.; Roth, M. E.; Maloney, P. R.; Willson, T. M.; Kliewer, S. A.

Mol. Cell **2000**, *6*, 517.

(61) Nadolny, C.; Dong, X. *Cancer Biol. Ther.* **2015**, *16*, 997.

(62) Thiruchelvam, P. T. R.; Lai, C.-F.; Hua, H.; Thomas, R. S.; Hurtado, A.; Hudson, W.; Bayly, A. R.; Kyle, F. J.; Periyasamy, M.; Photiou, A.; Spivey, A. C.; Ortlund, E. A.; Whitby, R. J.; Carroll, J. S.; Coombes, R. C.; Buluwela, L.; Ali, S. *Breast Cancer Res. Treat.* **2011**, *127*, 385.

(63) Johnston, S. R. D.; Dowsett, M. *Nat. Rev. Cancer* **2003**, *3*, 821.

(64) Chen, S.; Masri, S.; Wang, X.; Phung, S.; Yuan, Y.-C.; Wu, X. *J. Steroid Biochem. Mol. Biol.* **2006**, *102*, 232.

(65) Lai, C.-F.; Flach, K. D.; Alexi, X.; Fox, S. P.; Ottaviani, S.; Thiruchelvam, P. T. R.; Kyle, F. J.; Thomas, R. S.; Launchbury, R.; Hua, H.; Callaghan, H. B.; Carroll, J. S.; Coombes, C. R.; Zwart, W.; Buluwela, L.; Ali, S. *Nucleic Acids Res.* **2013**, *41*, 10228.

(66) Mueller, M. Development of Modulators of LRH-1 as Potential Anti-Cancer Therapeutic Leads, Imperial College London, PhD Thesis, **2013**.

(67) Bayly, A. R. The Design and Synthesis of New Modulators of Liver Receptor Homologue 1 (LRH-1), Imperial College London, PhD Thesis, **2011**.

(68) Sun, A.; Moore, T. W.; Gunther, J. R.; Kim, M. S.; Rhoden, E.; Du, Y.; Fu, H.; Snyder, J. P.; Katzenellenbogen, J. A. *ChemMedChem* **2011**, *6*, 654.

(69) Moore, T. W.; Katzenellenbogen, J. A. *Annu. Rep. Med. Chem.* **2009**, *44*, 443.

(70) Glass, C. K.; Rosenfeld, M. G. *Genes Dev.* **2000**, *14*, 121.

(71) Danielian, P. S.; White, R.; Lees, J. A.; Parker, M. G. *EMBO J.* **1992**, *11*, 1025.

(72) Benecke, A.; Gronemeyer, H. *Gene Ther. Mol. Biol.* **1999**, *3*, 379.

(73) Heldring, N.; Pike, A.; Andersson, S.; Matthews, J.; Cheng, G.; Hartman, J.; Tujague, M.; Ström, A.; Treuter, E.; Warner, M.; Gustafsson, J.-Å. *Physiol. Rev.* **2007**, *87*, 905.

(74) Dubbink, H. J.; Hersmus, R.; Verma, C. S.; van der Korput, H. A. G. M.; Berrevoets, C. A.; van Tol, J.; Ziel-van der Made, A. C. J.; Brinkmann, A. O.; Pike, A. C. W.; Trapman, J. *Mol. Endocrinol.* **2004**, *18*, 2132.

(75) Williams, A. B.; Weiser, P. T.; Hanson, R. N.; Gunther, J. R.; Katzenellenbogen, J. A. *Org. Lett.* **2009**, *11*, 5370.

(76) Li, Y.; Choi, M.; Suino, K.; Kovach, A.; Daugherty, J.; Kliewer, S. A.; Xu, H. E. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 9505.

(77) Sablin, E. P.; Krylova, I. N.; Fletterick, R. J.; Ingraham, H. A. *Mol. Cell* **2003**, *11*, 1575.

(78) Bayly, A. R.; White, A. J. P.; Spivey, A. C. *Eur. J. Org. Chem.* **2013**, 5566.

(79) Lawrence, R. F.; Raucher, S. *Tetrehedron Lett.* **1983**, *24*, 2927.

(80) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.

(81) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51*, 3672.

(82) Krow, G. R.; Huang, Q.; Szczepanski, S. W.; Hausheer, F. H.; Carroll, P. J. *J. Org. Chem.* **2007**, *72*, 3458.

(83) Taylor, C. F.; Houk, I. K. N.; Domelsmithid, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182.

(84) Gil, L.; Gateau-Olesker, A.; Marazano, C.; Das, B, C. *Tetrahedron Lett.* **1995**, *36*, 707.

(85) Paul, S.; Pattanayak, S.; Sinha, S. *Tetrahedron Lett.* **2011**, *52*, 6166.

(86) Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973.

(87) Comins, D. L.; Mantlo, N. B. *J. Org. Chem.* **1986**, *51*, 5456.

(88) Podlech, J. In *Synthesis of Peptides and Peptidomimetics*; Houben-Weyl, Ed.; Thieme Verlag: Stuttgart, **2002**; pp 41–192.

(89) Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalporzo, R.; Ciminale, F. *J. Chem. Soc. Perkin Trans* **1985**, 773.

(90) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.

(91) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

(92) Falciola, C.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765.

(93) Backvall, J.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *48*, 6615.

(94) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(95) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491.

(96) de Boer, J. J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, *16*, 4039.

(97) Bodero, O. Novel Alpha-Helix Mimetics as Anti-Cancer Leads, Imperial College London, Post-Doctoral Report, **2016**.

(98) De Keyser, J.; Altamore, T. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Inc., **2010**; pp 1–4.

(99) Taketomi, T.; Kumobayashi, H.; Takayama, K.; Press, A.; Schwartz, J.; Snyder, W. H.; Prahl,

H.; Lattes, A.; Pu, S.; Ikeda, S.; Katagiri, T.; Tanaka, J.; Watanabe, S. *J. Am. Chem. Soc.* **1978**, *1*, 3950.

(100) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734.

(101) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465.

(102) Whittaker, N.; Openshaw, H, T. *J. Chem Soc* **1969**, *C*, 89.

(103) Work to optimise the *O*-alkylation step and prepare a series of four-residue mimetics using the above described chemistry is currently being continued by a post-doctoral researcher in the Spivey group.

(104) Due-Hansen, M. E.; Pandey, S. K.; Christiansen, E.; Andersen, R.; Hansen, S. V. F.; Ulven, T. *Org. Biomol. Chem.* **2015**, *14*, 430.

(105) Abas, H.; Frampton, C. S.; Spivey, A. C. *J. Org. Chem.* **2016**, *81*, 9947.

(106) Jorge, A.; Bosch, J.; Molins, E.; Roig, A.; Casamitjana, Â.; Lo, V. *Tetrahedron* **2000**, *56*, 4027.

(107) Ohfusa, T.; Nishida, A. *Tetrahedron* **2011**, *67*, 1893.

(108) Fujita, R.; Watanabe, K.; Yoshisuji, T.; Kabuto, C. *Chem. Pharm. Bull.* **2001**, *49*, 893.

(109) N. Katagiri, M. Hirose, M. Sato, C. K. *Chem. Pharm. Bull.* **1989**, *37*, 933.

(110) Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715.

(111) Krow, G. R.; Huang, Q.; Szczepanski, S. W.; Hausheer, F. H.; Carroll, P. J.; V, T. U.; Pennsyl, V. *J. Org. Chem.* **2007**, *72*, 3458.

(112) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.

(113) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028.

(114) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(115) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731.

(116) Garcia, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658.

(117) Seki, C.; Hirama, M.; Hutabarat, N. D. M. R.; Takada, J.; Suttibut, C.; Takahashi, H.; Takaguchi, T.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Yasui, M.; Okuyama, Y.; Takeshita, M.; Matsuyama, H. *Tetrahedron* **2012**, *68*, 1774.

(118) Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron* **2002**, *58*, 8299.

(119) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*, CRC.; Boca Raton:

FL, **1995**.

(120) Zhou, J.-H.; Jiang, B.; Meng, F.-F.; Xu, Y.-H.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 4432.

(121) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219.

(122) Seki, C.; Hirama, M.; Hutabarat, N. D. M. R.; Takada, J.; Suttibut, C.; Takahashi, H.; Takaguchi, T.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Yasui, M.; Okuyama, Y.; Takeshita, M.; Matsuyama, H. *Tetrahedron* **2012**, *68*, 1774.

(123) Sidera, M.; Costa, A. M.; Vilarrasa, J. *Org. Lett.* **2011**, *13*, 4934.

(124) Cottet, P.; Bleschke, C.; Capdevila, M. G.; Tissot, M.; Alexakis, A. *Adv. Synth. Catal.* **2016**, *358*, 417.

(125) Wanner, K. T.; Polborn, K.; Pabel, J.; Hoesl, C. E. *Heterocycles* **2002**, *58*, 383.

(126) Matsumura, Y.; Nakamura, Y.; Maki, T.; Onomura, O. *Tetrahedron Lett.* **2000**, *41*, 7685.

(127) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2013**, *15*, 444.

(128) Comins, D. L.; Clinton A. Brooks; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229.

(129) Cash, B. M.; Prevost, N.; Wagner, F. F.; Comins, D. L. *J. Org. Chem.* **2014**, *79*, 5740.

(130) Szantay, C.; Bolckei, H.; G-Baitz, E. *Tetrahedron* **1990**, *46*, 1711.

(131) Suttibut, C.; Kohari, Y.; Igarashi, K.; Nakano, H.; Hirama, M.; Seki, C.; Matsuyama, H.; Uwai, K.; Takano, N.; Okuyama, Y.; Osone, K.; Takeshita, M.; Kwon, E. *Tetrahedron Lett.* **2011**, *52*, 4745.

(132) Arakawa, Y.; Murakami, T.; Ozawa, F.; Arakawa, Y.; Yoshifuji, S. *Tetrahedron* **2003**, *59*, 7555.

(133) Gocan, S. *J. Chromatogr. Sci.* **2002**, *40*, 1.

(134) Trindade, A. C. L. B.; dos Santos, D. C.; Gil, L.; Marazano, C.; Gil, R. P. de F. *Eur. J. Org. Chem.* **2005**, 1052.

(135) Hutabarat, N. D. M. R.; Seki, C.; Shimizu, T.; Hirama, M.; Kohari, Y.; Nakano, H.; Uwai, K.; Takano, N.; Kwon, E.; Matsuyama, H. *Heterocycles* **2012**, *86*, 203.

(136) Winkler, J. D.; Axten, J.; Hammach, A. H.; Kwak, Y.-S.; Lengweiler, U.; Lucero, M. J.; Houk, K. N. *Tetrahedron* **1998**, *54*, 7045.

(137) Song, A.; Chen, X.; Song, X.; Zhang, X.; Zhang, S.; Wang, W. *Org. Lett.* **2013**, *15*, 2510.

(138) Zhang, Y.; Liao, Y.; Liu, X.; Yao, Q.; Zhou, Y.; Lin, L.; Feng, X. *Chem. Eur. J.* **2016**, *22*, 15119.

(139) Davis, C. R.; Swenson, D. C.; Burton, D. J. *J. Org. Chem* **1993**, *58*, 6843.

(140) Achar, T. K.; Mal, P. *J. Org. Chem.* **2015**, *80*, 666.

(141) Delaye, P.-O.; Vasse, J.-L.; Szymoniak, J. *Org. Biomol. Chem.* **2010**, *8*, 3635.

(142) Smith, A.; Daniels, D. S. B.; Taylor, J. E. *Org. Lett.* **2013**, *15*, 6058.

(143) Schütte, J.; Kilgenstein, F.; Fischer, M.; Koert, U. *Eur. J. Org. Chem.* **2014**, *2014*, 5302.

(144) Chu, G.-H.; Gu, M.; Cassel, J. A.; Belanger, S.; Graczyk, T. M.; DeHaven, R. N.; Conway-James, N.; Koblish, M.; Little, P. J.; DeHaven-Hudkins, D. L.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1951.

(145) Manikowski, A.; Kolarska, Z. *Synth. Commun.* **2009**, *39*, 3621.

(146) Ghosh, S.; De, S.; Kakde, B. N.; Bhunia, S.; Adhikary, A.; Bisai, A. *Org. Lett.* **2012**, *14*, 5864.

(147) Nakajima, M.; Lefebvre, Q.; Rueping, M. *Chem. Commun.* **2014**, *50*, 3619.

(148) Kim, M.-H.; Choi, S.-H.; Lee, Y.-J.; Lee, J.; Nahm, K.; Jeong, B.-S.; Park, H.-G.; Jew, S.-S. *Chem. Commun.* **2009**, 782.

(149) Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715.

(150) Comins, D. L.; Young, Y. C. *J. Org. Chem.* **1990**, *55*, 292.

(151) Huffman, M. A.; Smitrovich, J. H.; Rosen, J. D.; Boice, G. N.; Qu, C.; Nelson, T. D.; McNamara, J. M. *J. Org. Chem.* **2005**, *70*, 4409.

(152) Spino, C.; Rezaei, H.; Dupont-Gaudet, K.; Francis, B. *J. Am. Chem. Soc.* **2004**, *126*, 9926.