Enantioselective Synthesis of Diketopiperazines and Triketopiperazines

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Thesis submitted to the University of Birmingham for the degree of Doctor of Philosophy

August 2015

School of Chemistry

The University of Birmingham

Abstract

The diketopiperazine scaffold can be found in a large number of natural products and commercialised drugs. Conversely, the triketopiperazine one is far less common in Nature and scarce research has been conducted to determine its utility. The project goal was to develop enantioselective organocatalysis on these two frameworks. Chapter 1 gives an introduction on their presence in Nature and the pharmaceutical industry, the most relevant synthetic advances as well as an overview of the organocatalysis tools previously reported.

Although diketopiperazines have been the subject of intense research, no asymmetric methods have been previously reported despite the myriad of available methodologies. Chapter 2 discusses the particular organocatalytic precedents that motivated this project and the initial efforts devoted to develop such methodology. Unfortunately, diketopiperazines showed complete lack of reactivity under a wide range of conditions.

Our interest in developing this enantioselective method in heterocycles related to diketopiperazines made us turn our attention to the triketopiperazine scaffold. The successful application of a cinchona alkaloid derived catalysed Michael addition on this scaffold is described in Chapter 3. Progresses made in the manipulation of the chiral products are also included.

An extension of the previously developed methodology, where selected Michael acceptors afford bicycle[2.2.2]diazaoctane derived products *via* a tandem Michael–ring-closure process, is discussed in Chapter 4.

Acknowledgments

First and foremost, I would like to thank Professor Nigel S. Simpkins for giving me the opportunity to work on this PhD project as well as for his encouragement, advice and inspiration over this period. I would also like to thank Dr Christopher Davies for organising my placement in AstraZeneca, his interest and dedication and for his willingness to assist on my future career.

I am very grateful to the University of Birmingham and AstraZeneca for the financial support of this work. The analytical facilities at both sites have also played a key part in bringing this project to fruition, particularly Dr Chi Tsang and Neil Sumner. I would like to acknowledge Dr Louise Male for acquiring and interpreting the X-ray data sets as well as for helping with the Appendix 2.

I thank every member of the Simpkins group and other labmates I have had the chance of working with –Yang, François, Matt, Mike, Jen, Pete Dale, Jack, Gary, Pete Crick, Ryan and Edgar– for their invaluable help, friendship and all the good times we have had. Special thanks to Dr Sam Butterworth for his sincere commitment, for taking his time to help me expand my chemistry views and for giving me the opportunity to keep growing professionally. It has been great working along side his group too.

Thanks to my friends, Miguel, Fer, Patri, Javi and Gonzalo, for always being there, no matter how far we are. I also want to thank my family for all their support and encouragement.

Last but not least, thanks to Sara, nothing of this would have been possible without you, I love you.

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Glossary of Abbreviations

1,2-DCE	1,2-dichloroethane
1D	one dimensional
2D	two dimensional
Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
AIDS	acquired immune deficiency syndrome
BCRP	breast cancer resistance protein
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CCR5	C-C chemokine receptor type 5
COSY	correlation spectroscopy
DABCO	1,4-diazabicyclo[2.2.2]octane
DABN	1,1′-Bi(2-naphthylamine)

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DHQD	dihydroquinidine
DIAD	Diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DKP	diketopiperazine
DMAP	*N*,*N*'-dimethyl-4-aminopyridine
DME	dimethoxyethane
DMEDA	*N*, *N*'-dimethylethyldiamine
DMF	*N*,*N*'-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPA	diphenylphosphoryl azide
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio
ETPs	epipolythiodioxopiperazines

HIV	human immunodeficiency virus
ESI	electron spray ionisation
GSK	GlaxoSmithKline
HMDS	hexamethyldisilazane/bis(trimethylsilyl)amide
HMPA	hexamethylphosphoric triamide
HOMO	highest occupied molecular orbital
HPLC	high pressure (or performance) liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
IR	infrared spectroscopy
J	coupling constant (in nuclear magnetic resonance spectroscopy)
kcal	kilocalorie
LDA	lithium di*iso*propylamide
LHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
MDR	multi-drug resistant
MAP2	Microtubule-associated protein 2
MOM	Methoxymethyl ether

MS	mass spectrometry
µW	microwaves
NHC	nitrogen heterocyclic carbene
NMP	*N*-Methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectrometry
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OC	Oxytocin
OTf	trifluoromethanesulfonate (triflate)
PK	pharmacokinetics
Ph	phenyl
PHN	9-phenanthryl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PTSA	*para*-toluenesulfonic acid
Py	pyridine
rt	room temperature

R*f*	retardation factor
SAR	structure-activity relationship
SET	single electron transfer
SOMO	singly occupied molecular orbital
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TKP	triketopiperazine
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
UV	ultraviolet spectroscopy

Note: *ee* is used in this document only for the literature values originally reported using this nomenclature. All the enatiomeric data generated within this thesis using chiral HPLC is reported in *er*.

Chapter One

Introduction

1.1 Diketopiperazines

The diketopiperazine framework has gained a privileged status due to the abundance of this motif in natural products and the diverse biological activities they display. Three regioisomers of the diketopiperazine core can be identified: 2,3-diketopiperazines **1**, 2,6-diketopiperazines **2** and 2,5-diketopiperazines **3** (Figure 1.1).

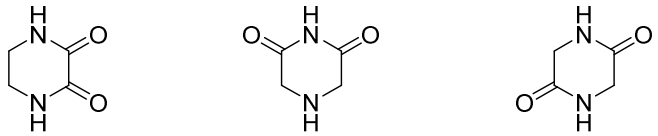


Figure 1.1 Structure of diketopiperazines

Herein we will focus on 2,5-diketopiperazines **3**, also known as 2,5-piperazinediones and abbreviated as DKPs hereafter, which can be understood as constrained cycles formed by the condensation of two α-amino acids.

Despite their apparent simplicity, the rigid scaffold can be substituted in up to four positions, and stereochemistry controlled at both methylene positions. This source of diversity has been the subject of intensive synthetic research for a long period of time. In addition, the

pharmaceutical industry has also showed strong interest in these structures owing to the relevance of amidic groups, as the ones present in DKPs, in the medicinal chemistry context.

Although the first report of a DKP, *cyclo*[Leu-Leu] or "Leucinimide", was in 1849 and the first DKP synthesis,[1] *cyclo*[Gly-Gly], occurred in 1888 from the corresponding glycine ester,[2] it was not until the 20th century that DKPs were acknowledged as a unique class of compounds. In the early 1900s, DKPs were no longer considered mere by-products of polypeptide manipulations. Their abundance in Nature became evident as simple symmetrical and unsymmetrical DKPs were found to exist in polypeptide hydrolysates as well fermentation broths and cultures of yeast, lichens and fungi.[3] From the determination of their physical properties to their use in polypeptide sequence elucidation, synthetic and naturally isolated DKPs were broadly studied by the scientific community.[4]

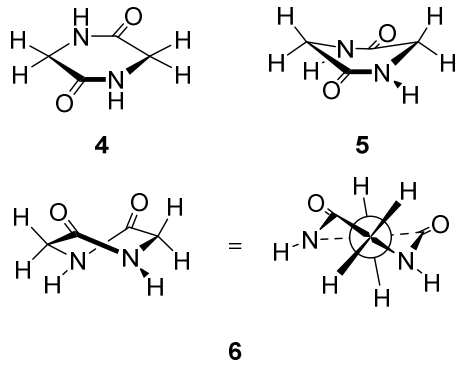


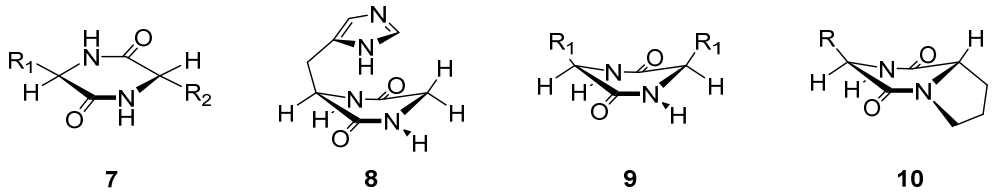
Figure 1.2 Planar (**4**), boat (**5**) and twist-boat (**6**) conformation for DKPs *cyclo*[Gly-Gly]

However, little was known about the precise conformation these molecules adopted in the solid phase. *Cyclo*[Gly-Gly] was shown to be planar (**4**) by the X-ray crystal structure solved by Corey in 1938.[5] This result highlighted the conformational strain the small six membered ring was subjected to in the solid phase. Nonetheless, DKPs were shown to be flexible in solution by NMR studies. Results from these studies suggested that the *cyclo*[Gly-Gly] ring

departs from planarity and its conformation interchanges between two equally populated boat **5** or twist-boat **6** states due to the low energy barrier between conformers (Figure 1.2).[6]

Recent measures of the DKP ring microwave spectrum in the gas phase have confirmed the boat conformation (**5**) to be the prevalent and preferred state.[7] *Ab initio* calculations have also supported this statement although the predicted difference in favour of boat conformer is negligible.[8] These studies conclude that while the boat conformer constitutes the minimum energy, the planar one is a transition state. However, the small energy difference between forms is easily surpassed in the crystal environment and thus, *cyclo*[Gly-Gly] is forced to stack in planar (**4**) and linear hydrogen-bonded tapes.[9]

Substituted DKP conformers vary depending on the nature of the amino acid side chains. If the side chain is an alkyl group, the energy difference between forms becomes unimportant in solution and NMR studies suggest the ring is planar (**7,** R_1=alkyl, R_2=H). Contrarily, when R_1 incorporates an aromatic side chain, such as a histidyl chain, the boat conformation is prevalent by close to 3 kcal/mol. The aromatic ring is suggested to fold over the DKP ring (**8**). This effect is not solvent dependent, which suggests the presence of a strong enough dipole-dipole interaction between the amide groups and the aromatic ring π-electron cloud for dipolar solvents to compete (Figure 1.3).[6a]



7 **8** **9** **10**

Figure 1.3 Substituted DKP conformations

Boat or twisted-boat states become the generally established conformation for the symmetrically *cis*-disubstituted six-membered ring in both solid and solution phase (**9**).[10] Empirical data was confirmed by different X-Ray crystal structures such as *cyclo*[L-Met-L-Met][11] or *cyclo*[L-Glu-L-Glu][12], where the boat geometry is adopted with the side chains folded above the DKP ring. On the contrary, the conformation of *trans*-disubstituted DKPs varies from planar to flattened-chair (**7**, $R_1 = R_2$=alkyl).[9]

DKPs incorporating proline constitute a special case on their own. The additional strain imposed by the fused five-membered ring makes the six-membered one adopt a boat conformation in almost every amino acid DKP combination (**10**).[13]

DKPs are a common scaffold embedded in numerous complex natural products from the fungus, bacteria, plant or animal kingdom. These systems not only constitute a novel and rich biologically active family of compounds but are also a source of new structurally diverse scaffolds for therapeutic applications. In addition, these small heterocycles have been employed as peptide surrogates in many drug discovery projects because they are structurally similar to peptides but allow the potential drug candidates to bypass their undesirable physical and metabolic properties.[14] Owing to the wide diversity of possible chiral amino acids and employing recent advances in solid-phase chemistry, DKPs have been widely used to create libraries of enantioenriched heterocycles valid for combinatorial medicinal chemistry projects. These chiral templates have also been exploited as chiral catalysts and chiral auxiliaries as a result of the reliable methods developed to access a wide variety of derivatives.[15]

1.2 2,5-Diketopiperazines in Nature and drugs

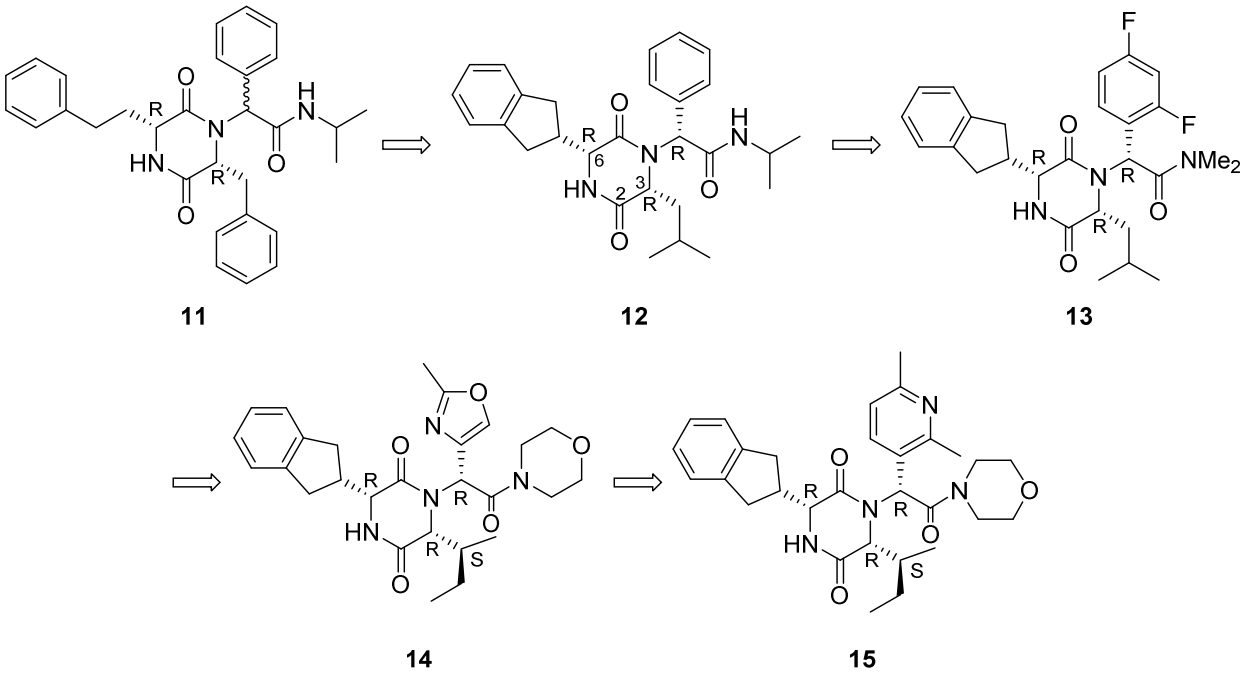
In light of the broad diversity and complexity the DKP subunit can bear, there are an ever-increasing number of structures exhibiting interesting biological activities both isolated from natural sources and synthesised as part of drug discovery projects. The conformationally rigid scaffold enables these molecules not only to incorporate different functional groups with defined stereochemistry but also to bind to multiple biological sites and receptors *via* H-bonds. The drug industry has taken advantage of this motif by: (1) exploring the structure-activity relationship (SAR) to develop pharmaceutical compositions from the hit stage by means of tuning the physicochemical properties in the optimization process, (2) confining linear peptides into rigid and robust scaffolds while maintaining their biological purpose and, (3) using naturally occurring DKPs to both exploit and improve their biological activity.

1.2.1 Medicinal Chemistry

A variety of DKP cores have been found to be excellent examples of how a hit can be transformed and optimised through SAR studies to develop the most potent lead. These studies are designed to understand the key functionalities in the molecule triggering the desired biological effect. Chemical, regiochemical or stereochemical modifications play a key role in tuning the potency of the drug candidate. The following examples of drugs developed by the pharmaceutical industry help to illustrate the process that takes place.

Oxytocin (OC) is a nonpeptidic mammalian neurohypophyasial hormone whose main function is the distension of the cervix and the uterus during labour. Atosiban is an oxytocin antagonist aimed at repressing premature labour. This polypeptidic drug is administrated

intravenously and the pharmaceutical industry has devoted great efforts to find an appropriate non-peptidic oral substituent for it. Researchers at GlaxoSmithKline (GSK) screened numerous compound libraries to detect effective antagonist activity at the OC receptor. DKP **11** (Scheme 1.1) showed promising results as an inhibitor of human OC as an *α*-aryl glyciamide mixture of epimers.[16] Initial SAR studies pointed to DKP **12** where the substituent at C-3 evolved into an isobutyl chain. A four carbon branched alkyl chain was found to be optimal while smaller chains led to decreased antagonist activity. Position C-6 became an indanyl residue as any other aromatic substituent diminished the drug's activity. *R* configuration on the *α*-aryl glyciamide was found optimal in this study. The (3*R*,4'*R*,6*R*) compound was 10-fold more potent than the corresponding (3*R*,4'*R*,6*S*) isomer.



Scheme 1.1 Evolution of nonpeptidic DKP OC antagonist through SAR studies

Initial SAR also highlighted the importance of preserving the DKP *N*-H and carbonyl C-2 unaltered to maximise potency. The aryl group on the *N*-4-glyciamide could not be replaced

by non-aromatic cycles without weakening the potency. By contrast, *para*- and *meta*-substitutions on this aromatic ring, with a variety of different groups, enhanced it. Alkylation of the glyciamide was also tolerated.[17] These led to DKP **13** after optimisation of different pharmacokinetics (PK) properties. Oral exposure, selectivity toward the closely related vasopressin receptors and safety profile improved significantly. Potency, compared to atosiban, was over 60 fold superior *in vitro* at the human OC receptor and comparable in rats.[18]

DKP OC antagonist	**11**	**12**	**13**	**14**	**15**
Potency (pK_i)	6.5	8.4	9.2	9.2	9.9

Table 1.1 Potency values for SAR of nonpeptidic DKP OC antagonist

However, solubility was poor and further transformations were required. Increasing the polarity of both the amide and the aryl substituents did improve solubility albeit with a corresponding worsening of the PK profile. Maintaining the good PK properties of **13** while increasing its solubility was achieved by changing the aryl group for a more polar heterocycle, a 2-methyl-1,3-oxazol. Final tuning included a morpholine amide substituent and a different branching pattern in the C-3 position, which gave rise to DKP **14**, so called retosiban. Despite displaying similar potency levels to DKP **13**, solubility, selectivity over vasopressin receptors and safety profiles were significantly improved. However, poor solubility still posed a significant barrier to overcome and further changes had to be made. Substituting the oxazole by a 2,6-dimethyl-3-pyridyl ring lead to DKP **15**, epelsiban, which not only had the best solubility in the series but also displayed an excellent PK profile and selectivity. Newly

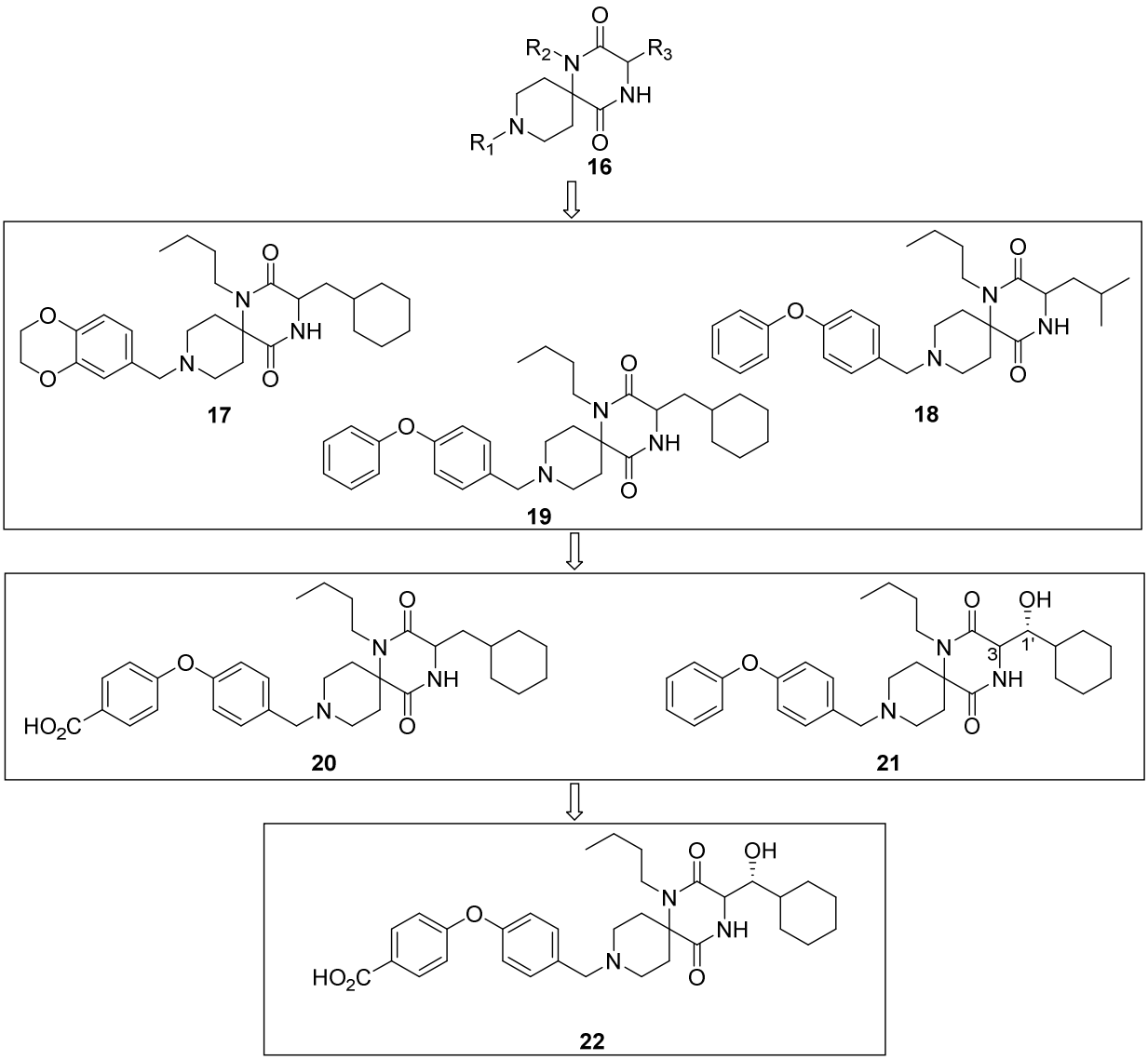
discovered roles of OC antagonist, such as sexual dysfunction or prevention of benign prostate hyperplasia, have motivated further studies and modifications of this drug molecule.[19]

The optimisation of aplaviroc also represents an excellent hit-to-lead development example. This drug is an intended antagonist of the CCR5 chemokine receptor for inhibiting the entry of HIV-1, constituting another approach to the treatment of AIDS.[20] Spiro-DKP scaffold **16** was identified as a lead compound using a combinatorial chemistry approach. This readily available template can be modified in three positions and stereochemistry can be introduced in one of them (Scheme 1.2).

Initial SAR studies suggested the R_1 position to be a *para*-functionalised benzyl for maximum activity. An *n*-alkyl chain was preferred at R_2, an unbranched 4 carbon chain being optimal while a cyclohexamethyl or an isobutyl was the chosen substituent at R_3, leading to the first bioactive DKPs **17**, **18** and **19**.

This generation showed nanomolar activity, high antiviral *in vitro* potency and high affinity for CCR5 compared to related receptors. However, the PK profile was far from optimal, having a high clearance rate in rats and poor solubility.[20] These issues were addressed by either adding a *para* electron-withdrawing substituent to the ether biphenyl chain, such as the acid moiety in **20**, or asymmetrically hydroxylating the R_3 side chain to give spiro-DKP **21**. Antiviral **20** has an improved potency compared to **19** (IC_{50} = 13 nM to 28 nM), whilst significantly overcoming the PK downsides. Oral exposure, bioavailability and solubility were notably improved.[21] Compound **19** was also modified to give the (3*R*, 1′*R*) hydroxylated adduct **21** with the aim of improving the antagonist activity against the CCR5 receptor. Not only was **21** more potent than DKP **19**, but also more selective and soluble. Combining this configuration with the improved PK properties of lead **20** was expected to yield the optimal

CCR5 antagonist. Spiro-DKP **22**, or Aplaviroc, did show potent activity against an array of HIV-1 strains, with excellent selectivity for CCR5 while maintaining a good PK profile.[22] Despite being a suitable HIV-1 antiviral treatment, a small percentage of the patients contracted hepatitis during phase III clinical trial and, therefore, the trials were halted.



Scheme 1.2 Evolution of spiro-DKP **16** towards the final clinical drug **22**

Further examples can be identified where medicinal chemists have employed DKPs as the central core to design drugs for different applications such as cancer inhibitors, antifungal, antibiotic or anxiolytic agents. In addition, DKPs are also used as a template for the preparation of a small range of privileged heterocycles, such as decorated piperazines, through the manipulation of the DKP subunit in the pharmaceutical industry.[23] The excellent properties of DKPs will surely be found suitable in the development of future drug discovery projects. However, as it will be outlined, the stereochemistry displayed around the DKP core is generally introduced by means of the chiral natural and non-natural amino acids constituting the central scaffold prior to the formation of the heterocycle.

1.2.2 Peptidomimetics

Embedding two amino acids in a closed heterocycle allows building constrained peptide analogues of the related linear sequence whilst protecting the amino acids from possible transformations the linear strand would suffer. Bioactive properties are mimicked by displaying the appropriate residues in the same orientation as the corresponding polypeptidic secondary structure. The activities DKP derivatives can mimic range from hormonal regulation to opioid antagonists among others.[24]

1.2.3 Bioactive Natural 2,5-Diketopiperazines

The DKP motif has been identified in numerous isolated natural products. Their distinctive framework, often incorporated into complex structures, has attracted researchers' attention,

not only for the challenge of accomplishing the corresponding total syntheses but also for the intriguing and diverse biological activities these compounds display. Thus, the scientific community has relentlessly pursued more facile and efficient syntheses or biosyntheses to access these DKPs and exploit their medicinal potential.

It was noted in the 1970s and onwards that even the simplest DKP could show interesting bioactive properties. Several studies led to the confirmation that four unsymmetrical DKPs, *cyclo*[His-Pro],[25] *cyclo*[Leu-Gly],[26] *cyclo*[Tyr-Arg],[27] and *cyclo*[Asp-Pro],[28] exhibited varied biological activities in mammals. Later, an increasing number of natural products were discovered with DKP embedded in their structures and structural complexity ranging from symmetrical cyclic peptides, such as fellutanine A **23**, to highly functionalised and decorated scaffolds such as okaramine O **24** or dimers such as ditryptophenaline **25** (Figure 1.4).

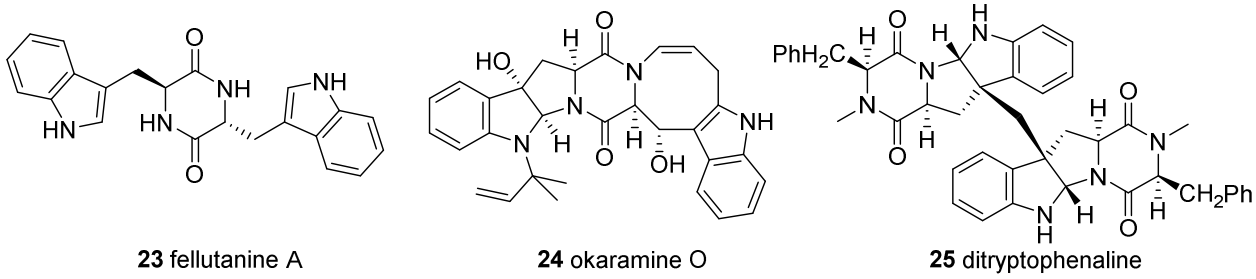
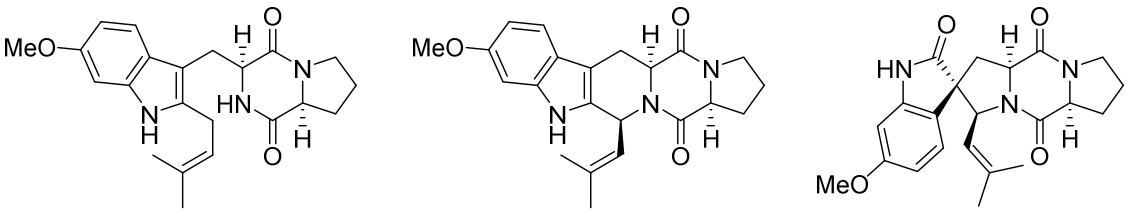


Figure 1.4 Complex DKP structures

Various classes have been categorised depending on their DKP amino acid constituents and numerous families have been reported based on common framework substituents and functionalities. Among all, the *cyclo*[L-Trp-L-Pro] derivatives are a prevalent class of compounds with dauntingly complex structures and promising biological properties. The recurrence of this scaffold can be understood as due to both the predisposition of the proline amino acid about the tertiary amide bond to adopt a *cis*-conformation and, thus, facilitating

the formation of a DKP, and the high nucleophilicity of the indole heterocycle and the vast number of transformations this ring can undergo. Further functionalization often involves the insertion of *iso*prenyl (dimethylallyl) chains and different modes of cyclisation towards the indole ring.



26 tryprostatin A **27** fumitremorgin C **28** spirotryprostatin A

Figure 1.5 Examples of *cyclo*[L-Trp-L-Pro] derived natural products

The bioactive molecules in Figure 1.5 are excellent examples of the diversity and framework complexity these scaffolds can display. This isomeric evolution starts from the annulation of the *iso*prenyl chain in tryprostatin A (**26**) to the DKP amide nitrogen to form the polycyclic derivative **27**, fumitremorgin C. The formation of the spiro moiety, with concomitant oxidation of the indole, represent the highest degree of specialization in this family of compounds rendering extremely intricate molecular architectures, such as spirotryprostatin A (**28**), that exhibit promising biological properties. Among others, tryprostatin A and fumitremorgin C deactivate the multidrug resistance protein (BCRP) responsible for the resistance to chemotherapeutics in breast cancer treatments,[29] whilst tryprostatin A and spirotryprostatin A show cell cycle inhibitory activities at the MAP2, blocking microtubule assembly, and the G2/M phase respectively.[30] Owing to the combination of powerful biological properties with their fascinating framework, numerous research groups have devoted considerable efforts to achieve their syntheses.[31]

1.2.4 Bioactive Bridged 2,5-Diketopiperazines

Bicyclic DKPs are an important and extensive class of compounds that can be divided based on the nature of the bridge across the DKP subunit, either a carbon backbone or a sulfur one.

A prevalent group of naturally occurring bicyclic DKPs are the *cyclo*[L-Trp-L-Pro] with a bicyclo[2.2.2]diazaoctane core embedded within the structure. In addition, they also have at least one *iso*prenyl chain present forming elaborated ring systems.Two groups can be clearly distinguished, simply by categorising the nature of their ring architecture, whether it is a spiro or a fused system. The spiro group is formed of alkaloids such as brevianamide A and B, sclerotamide, versicolamides or paraherquamides while notoamides, aspergamides, avrainvillamide or stephacidin are members of the fused group (Figure 1.6).

These complex molecules, exhibiting intriguing biological properties such as insecticidal, antitumor, anthelmintic, or antibacterial,[32] have represented compelling targets and numerous different approaches have resulted in several total syntheses.[33]

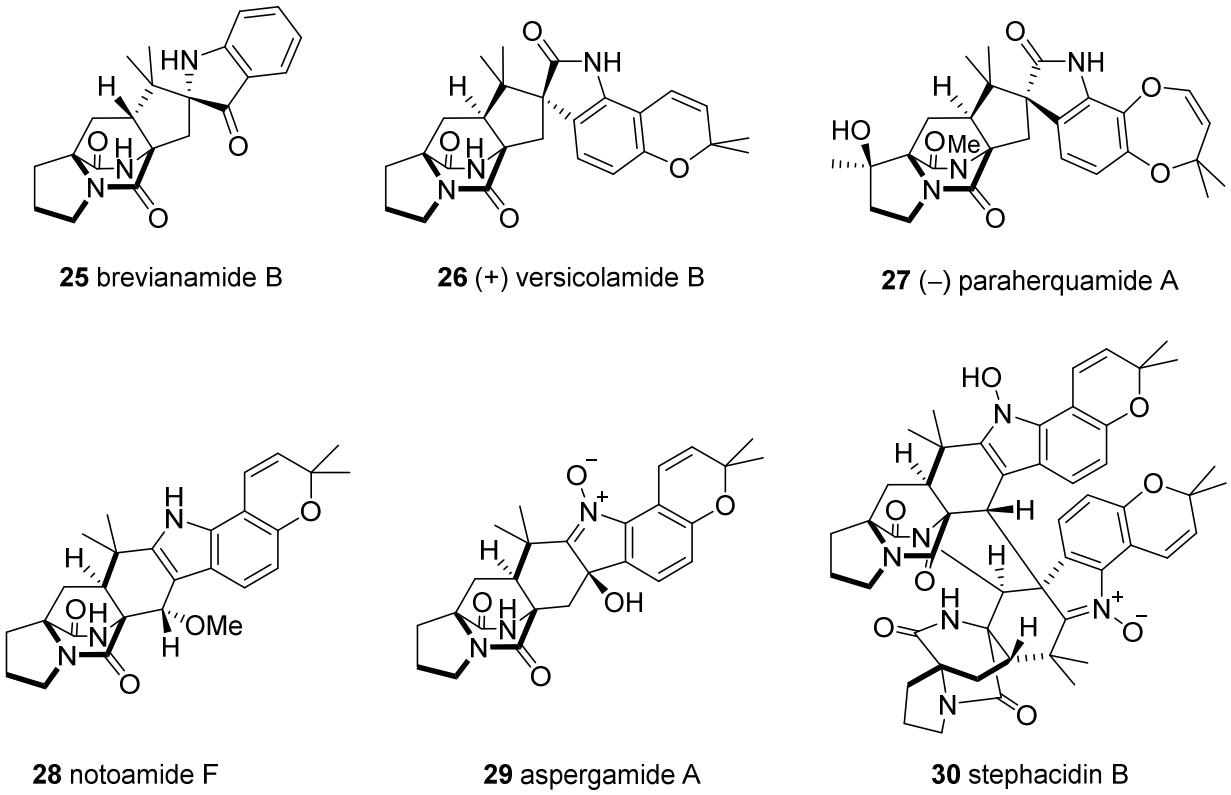
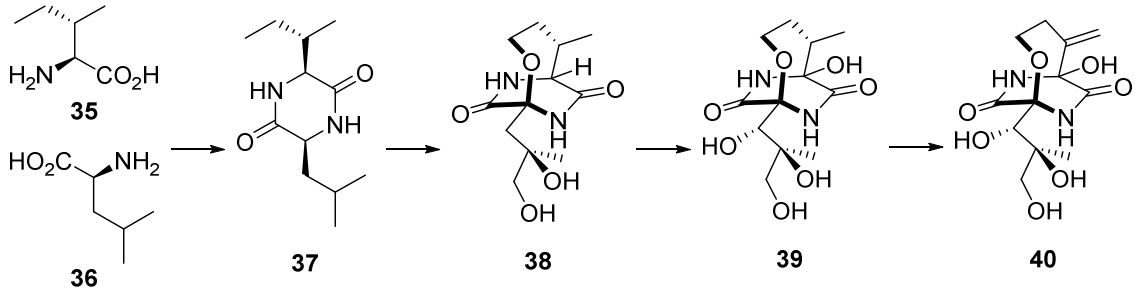


Figure 1.6 Members of the bicyclo[2.2.2]diazaoctane family

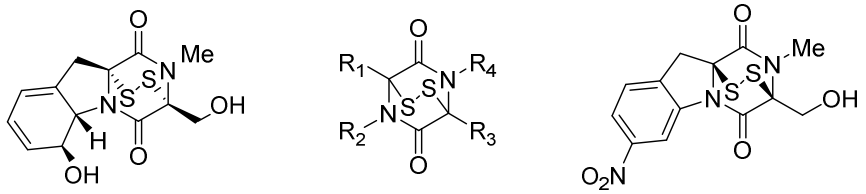
Also noteworthy is the antibacterial agent bicyclomycin **40**, whose molecular structure, relative and absolute stereochemistry were elucidated employing ^{1}H, ^{13}C NMR techniques and X-ray crystal diffraction analysis.[34] Isolated from *Streptomyces sapporonensis*[35] and *Streptomyces aizunensis,*[36] this unique bicyclic DKP is specifically active against a wide array of Gram-negative bacteria by inhibiting the RNA transcription terminator factor rho.[37] This useful characteristic combined with its efficient production from fermentation broth and its low toxicity have helped to market this antibiotic, commonly known as bicozamycin, as a nonspecific diarrhoea treatment in humans and a treatment for bacterial diarrhoea in calves and pigs.[38]



Scheme 1.3 Biosynthesis of bicyclomycin

The intricate bicyclic architecture of bicyclomycin has motivated great efforts in the scientific community. Biosynthetically, bicyclomycin has been shown to originate from the condensation of L-leucine **35** and L-isoleucine **36** to form DKP **37** as shown in Scheme 1.3 which, after sequential oxidations and dehydrogenations, results in bicyclomycin (**40**).[39] Several groups attempted the total synthesis after the structure determination, leading to several synthetic studies of the bicyclomycin core and, eventually, the racemate synthesis by Goto[40] in 1983 and the enantiopure synthesis by Williams in 1984.[41]

Other members of the bridged DKP family are the epipolythiodioxopiperazines (ETPs), natural compounds with a disulfur bridge across the DKP ring. Scaffold **42** in Figure 1.7 represents the common architectural feature of ETPs. Both the number of sulfur atoms and the stereochemistry of the sulfur bridge vary between natural products. Consequently, two distinctive types of structure can be generated, gliotoxin and glionitrin A being two representative members of them.



41 gliotoxin **42** **43** glionitrin A

Figure 1.7 ETP containing DKPs

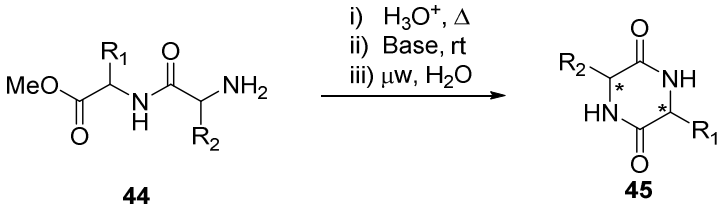
ETPs are secondary metabolites present in fungi and lichens exhibiting a wide array of promising properties. Predominantly, they are known for their cytotoxic effect on tumour cell lines. However, their associated high toxicity has precluded them from usage in clinical trials. The sulfur bridge is directly linked with this high toxicity, as a result of: (1) inactivating protein activity through the formation of mixed disulfide bonds with sulfur dependent enzymes and (2) producing superoxide ions and hydroxyl radicals during redox cycles in cells.[42]

Apart from the already known chemotherapeutic properties of gliotoxin **41**, the most common ETP also exhibits selective immunosuppressive properties and induces apoptosis in certain cells, particularly in the immune system, by breaking DNA strands.[43] Its extensive usage prompted a flurry of synthetic advances that culminated in the enantioselective total synthesis by Kishi.[44]

Sulfur derived DKPs also form open ring systems as metabolites in the same fungi species. The absence of the polysulfur bridge, and its associated *in vivo* side reactions, is the reason for the greatly reduced toxicity exhibited in the bisdethiodi(methylthio)DKP derivatives.[42c]

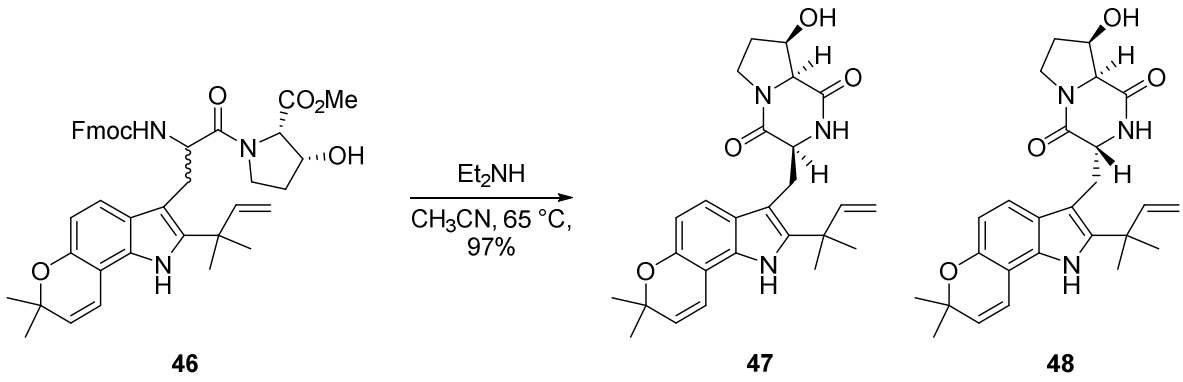
1.2.5 Synthesis and Transformations

DKPs can be synthesised *via* two distinctive methods: (1) amide bond formation, either sequential, by cyclisation of a dipeptide, or direct condensation of two amino acids, or (2) *N*-alkylation. The most common and extensively used strategy, the amide coupling, has proven effective under a varied range of conditions (Scheme 1.4).



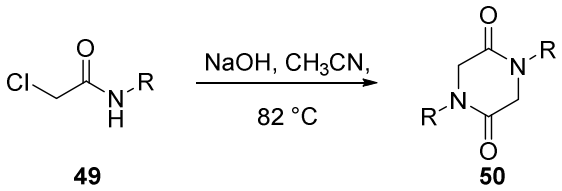
Scheme 1.4 DKP formation *via* amide coupling

Either acid catalysis, often coupled with high temperatures,[45] or basic media,[46] although it has caused racemisation of the DKP product on selected cases, have been found optimal in the synthesis of DKPs. Thermal methods have also been employed to effect this key amide bond formation although microwave assisted cyclisation in aqueous media has recently substituted this approach in light of its simplicity and environmentally friendly characteristics.[47] DKPs embedded in the structure of many natural products have been synthesised through this approach, *e.g.* Williams and co-workers formation of the DKP core as a 1:1 mixture of epimers (**47** and **48**) in the synthesis of versicolamide B (Scheme 1.5).[48]



Scheme 1.5 Formation of DKP in the synthesis of versicolamide B

The second strategy for the synthesis of DKPs takes advantage of the nucleophilic properties of the nitrogen to cyclise onto a range of different electrophiles such as alkyl halides,[49] carbonyls[50] or Michael acceptors (Scheme 1.6).[51]



Scheme 1.6 DKP synthesis *via* alkylation

Either method, under the appropriate reaction conditions, has been demonstrated to deliver enantiomerically pure DKPs. In fact, this is generally the chosen methodology to access non-natural chiral DKPs, as the ones used in the synthesis of Epelsiban or Aplaviroc.[20,52]

Although many transformations around the DKP core have been reported over the years and a vast number of enantioselective methods are currently available, no asymmetric strategies have been described in the literature to date. Therefore, the main aim of this project was to expand and build upon the existing methodology for substituting the DKP ring asymmetrically so a comprehensive review of previous literature was mandatory.

As previously mentioned, DKPs are cyclic dipeptides and hence, they will present usual amide reactivity. Enolate chemistry can be exploited at both the C-3 and C-6 positions with a variety of electrophiles, amidic nitrogens can undergo alkylation and related transformations, and carbonyls can, under specific conditions, be subjected to nucleophilic reactions such as reductions (Figure 1.8).

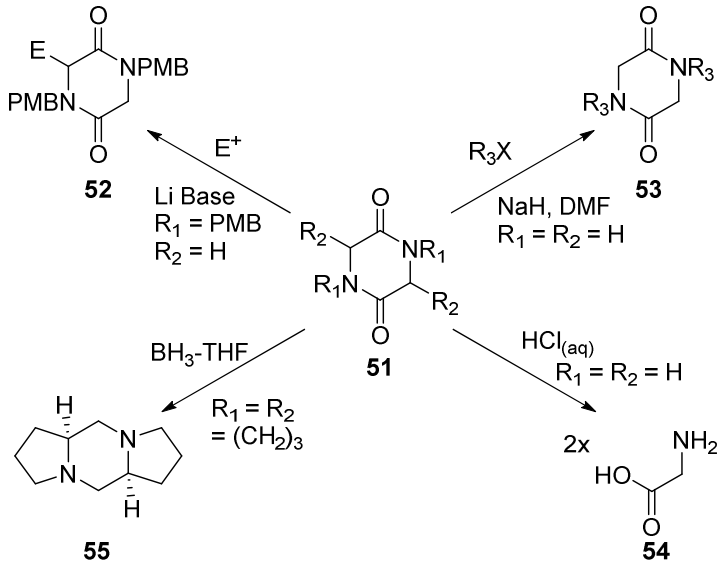
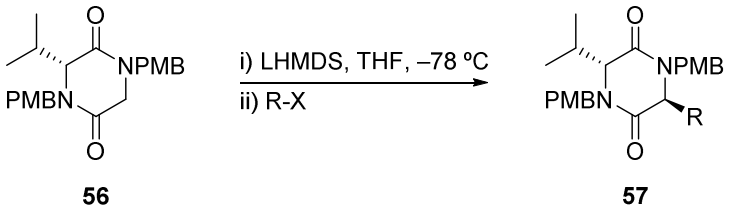


Figure 1.8 General DKP transformations

Using enantioselective methods, prochiral DKP **51** could be conveniently converted into chiral DKP **52**. However, such methodology is not available to date.

Nonetheless, various diastereoselective methods have been published for the DKP core. Davies and co-workers demonstrated that the valine side chain in *cyclo*[Val-Gly] **56** could be used as a chiral auxiliary. DKP **56** can subsequently undergo highly diastereoselective *trans*-alkylations (Scheme 1.7).[53]



Scheme 1.7 Diastereoselective alkylation of **56**

Both bulky protecting groups on the amidic nitrogens (especially PMB) and the minimisation of 1,2-torsional strain in the transition state of the alkylation, which sterically protects the *si* face by the C-3 substituent, were proposed by Davies to play an important role in the diastereomeric outcome of the reaction (Figure 1.9).[53]

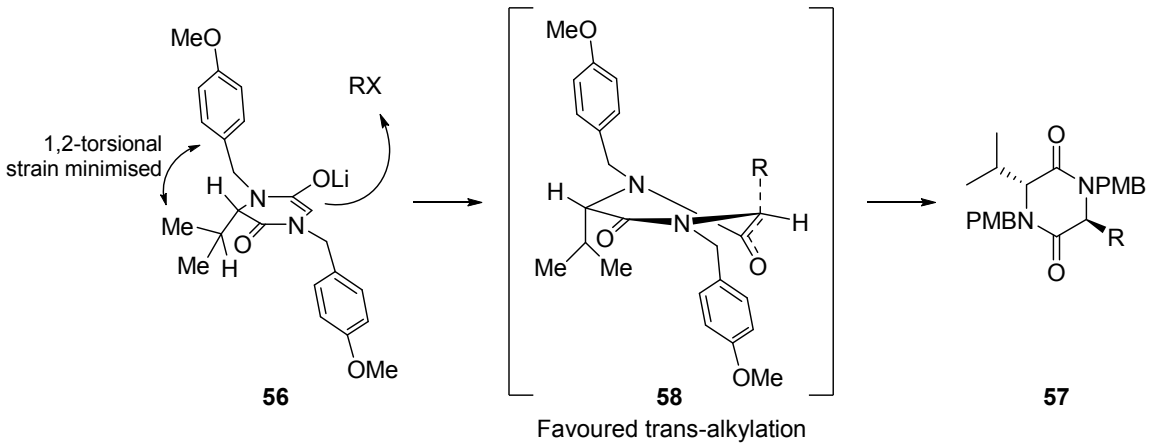
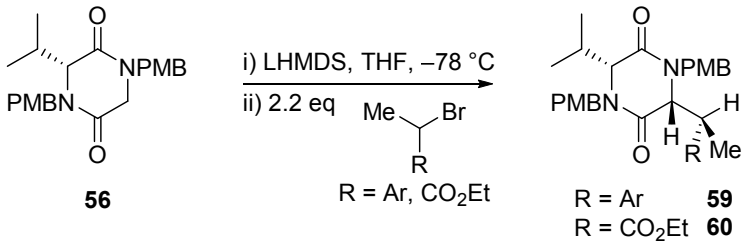


Figure 1.9 Conformation and transition state involved in the *trans*-alkylation of DKPs

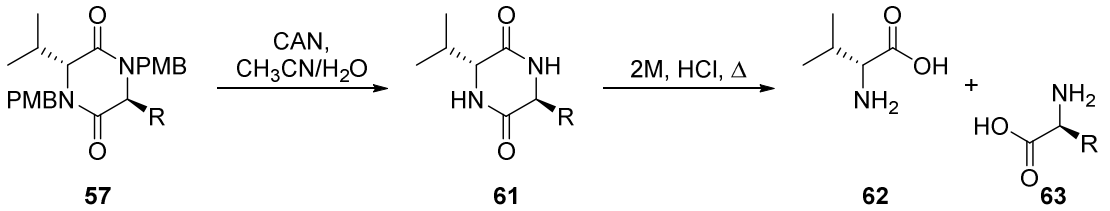
It was later discovered that any alkyl group on the nitrogen would induce the *trans*-alkylation by minimisation of the torsional strain with the *iso*propyl chain.[54] Outstanding diastereomeric ratios were also observed when using a racemic electrophilic source. The DKP enolate was also capable of discriminating between the enantiomers of the electrophile to afford *trans* alkylated products **59** and **60** in high de (up to 97.5:2.5, Scheme 1.8).[55]



56

Scheme 1.8 Diastereoselective alkylation of **56** with racemic electrophiles

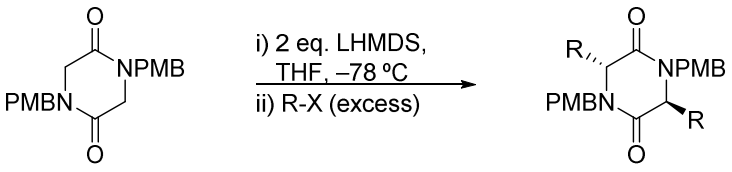
Oxidative conditions to remove the protecting groups followed by acidic treatments were used to unveil the constituent amino acids of the DKPs in high enantiomeric ratio (Scheme 1.9).



57 **61** **62** **63**

Scheme 1.9 Unveiling the chiral aminoacids

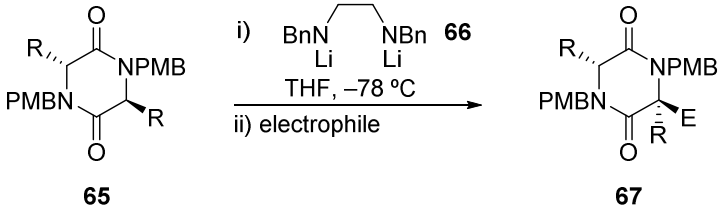
In a similar fashion, Simpkins and co-workers used this concept to synthesise a collection of *trans*-alkylated DKPs **65** from simple PMB-protected glycine anhydride **64**. Using two equivalents of the lithium base and subsequent quench with an excess of alkyl halide furnished the desired *trans*-dialkylated DKPs (Scheme 1.10).[56]



64 **65**

Scheme 1.10 *Trans*-alkylation of PMB-protected glycine anhydride

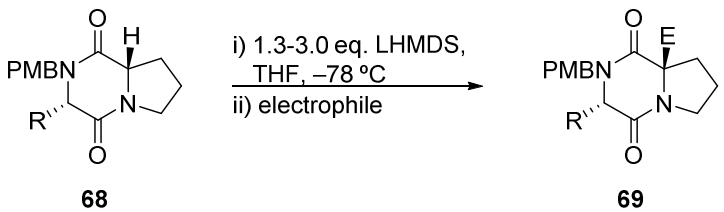
Further alkylation of racemic *trans*-DKPs **65**, albeit problematic with standard lithium bases,[57] did afford the expected product **67** as a single diastereoisomer with the less aggregated base **66** (Scheme 1.11). As Davies predicted,[54] the transition state of both the *trans* and *cis*-DKP in this reaction were the same, due to disposition towards epimerisation of **65** to minimise torsional strains. Therefore, DKP **67** was the only isolated product when either the *cis* or *trans* starting material was employed.



65 **67**

Scheme 1.11 Alkylation of *trans*-DKP with base **66**

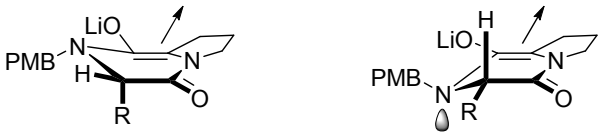
Attemps to conduct this reaction asymmetrically, using chiral lithium amides, only showed very low levels of enantiomeric excess. Synthesising dialkylated-DKPs **65** from corresponding chiral amino acids afforded enantiomerically pure product **67**. This trend was consistent with unsymmetrical proline DKPs **68** and different electrophiles were effectively added into the proline side of the DKP yielding the fully-substituted carbon adducts as single diastereoisomers **69** (Scheme 1.12).



68 **69**

Scheme 1.12 Fully-substituted carbon DKPs *via* alkylation

This report discussed the possibility of complementary conformational arrangements during the alkylation step. Small groups such as R = Me, did not seem to pose enough steric bulk to direct selective alkylation only due to minimisation of torsional strains in the pseudo-axial conformation (**70**). Hence, other factors might play a key role to explain the observed diastereoselectivity. In fact, stereoelectronic effects have been found to direct facial alkylations on various lactam enolates. The alkylation has been shown to be more favoured when the lone pair of electrons on the pyramidilised nitrogen was in anti configuration, as supported by *ab initio* calculations.[58] Hence, an additional transition state (**71**) was proposed (Figure 1.10).



70 **71**

Figure 1.10 Possible transition states involved in the alkylation of DKPs **68**

Nevertheless, these selective alkylations relied on the shape of the DKP and the inherent stereochemistry of the rest of the substituents for the observed selectivity.

Various other attempts to develop stereocontrolled methods and access enantiomerically pure DKPs have been described, such as using chiral inductors on nitrogen,[59] but no truly catalytic method has been described to date. Therefore, the aim for this project was to develop a novel, rapid and stereocontrolled route to access chiral DKPs using recently developed chiral organocatalysts.

1.3. Triketopiperazines

A formal oxidation in one of the methylene positions of a *cyclo*[Gly-Gly] results in the formation of a 2,3,5-triketopipeazine, TKP hereafter (**72**, Figure 1.11). Although we were mainly focused on DKP **3**, the TKP can be regarded as a heterocycle were all three examples of diketopiperazines are incorporated in the same system.

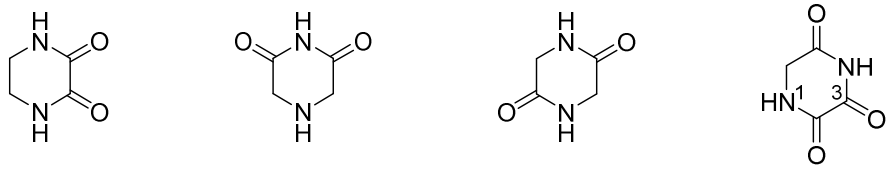


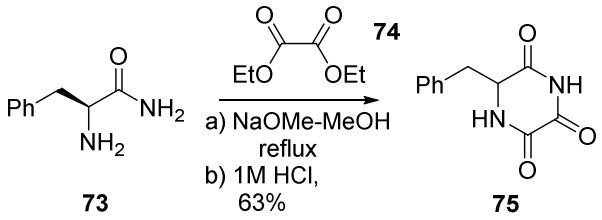
Figure 1.11 TKP structure

Its core, compared to the DKP, can be theoretically accessed *via* a condensation of any amino amide with oxalyl transfer reagents such as oxalyl chloride or dialkoxy oxalates. Owing to this modification, properties and reactivity significantly change.

This heterocycle is far less common than the DKP and is only present in a handful of natural products (see Figure 1.12). However, it can complement the already known reactions DKP can undergo and, hence, expand the knowledge of these small heterocycles. In addition, transformations to convert the TKP core into the more common DKP one can be investigated.

The first isolated TKP dates back to 1917, when Bornwater reported the α-benzyl-TKP after a reaction of racemic phenylalanine amide with oxalyl chloride.[60] The same TKP was obtained by Bergmann and co-workers in 1927 in a seemingly long and inefficient process involving amide couplings and ozonolysis.[61] Both results proved difficult to reproduce and it was not until 1953 when Williams and co-workers reported the first synthesis of a TKP structure from

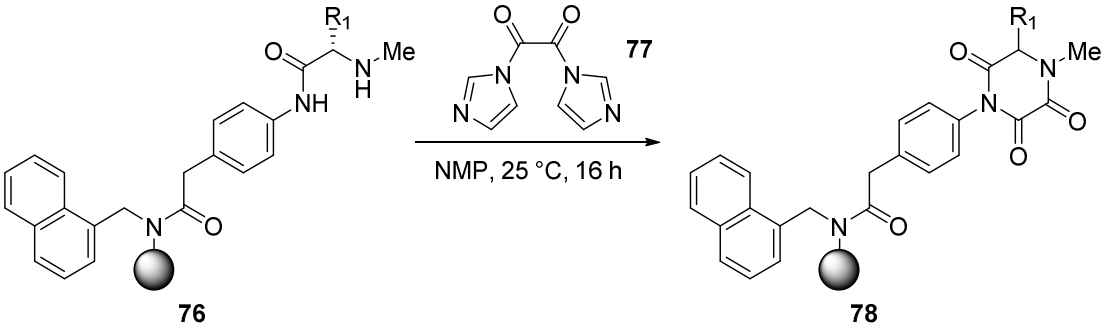
a variation of the barbituric acid skeleton as a result of the effort to find new drugs with related scaffolds. The reaction was performed with different free amino amides and an equimolar amount of ethyl oxalate **74** in sodium methoxide and refluxing ethanol. The desired product was only isolated in moderate yield from the sodium TKP salt.[62] In 2001 Bailey *et al.* used the same procedure with an enantiomerically pure amino amide **73**.[63] Given the reaction conditions, the expected racemisation occurred and product **75** was afforded in a comparable yield (Scheme 1.13).



Scheme 1.13 Formation of TKP

Bailey introduced the first strand of research into TKP manipulation and functionalisation. Nitrogen and enolate alkylations with different halide derivatives were achieved.[63a]

Makino and co-workers reported the first TKP synthesis on solid support using oxalyl diimidazole **77** as a mild cyclising agent.[64] His group accomplished the synthesis of a wide variety of TKPs using enantiomerically pure amino acids as the starting material. Although the mild reaction conditions should allow the products to retain their inherent chirality, as opposed to Williams's and Bailey's TKP syntheses, they did not comment on it in the report. The necessity of alkylating the terminal nitrogen on the amino acid in order to fully accomplish the cyclised product in good yield was highlighted. Hindered and cyclic amino amide precursors underwent the cyclisation successfully and the resulting TKPs were afforded in high yields (Table 1.2).



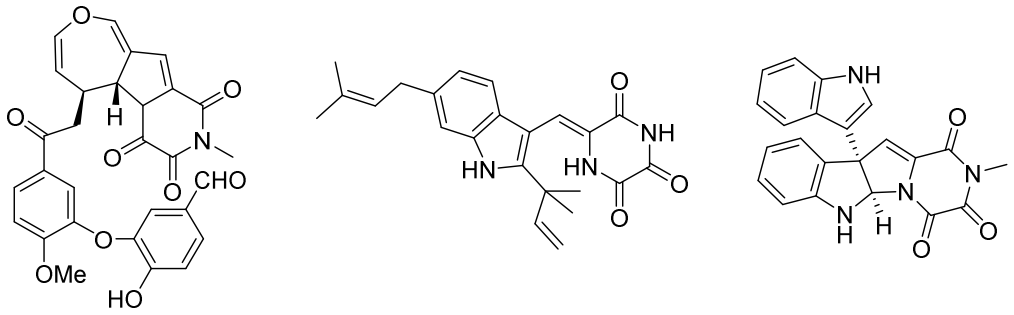
Entry	R_1	Purity (%)	Yield
78a	Bn	89	86
78b	Ph	94	90
78c	*i*Bu	94	81
78d	*i*Pr	87	74

Table 1.2 Solid supported synthesis of several examples of TKPs

1.3.1 Triketopiperazines in Nature

In contrast to the ubiquity of the DKP architecture in nature, the TKP subunit is considerably less abundant. Only a small number have been isolated from fungal sources, usually coexisting with ETP and bisdethiodi(methylthio)DKP derived natural products (Figure 1.12).[65]

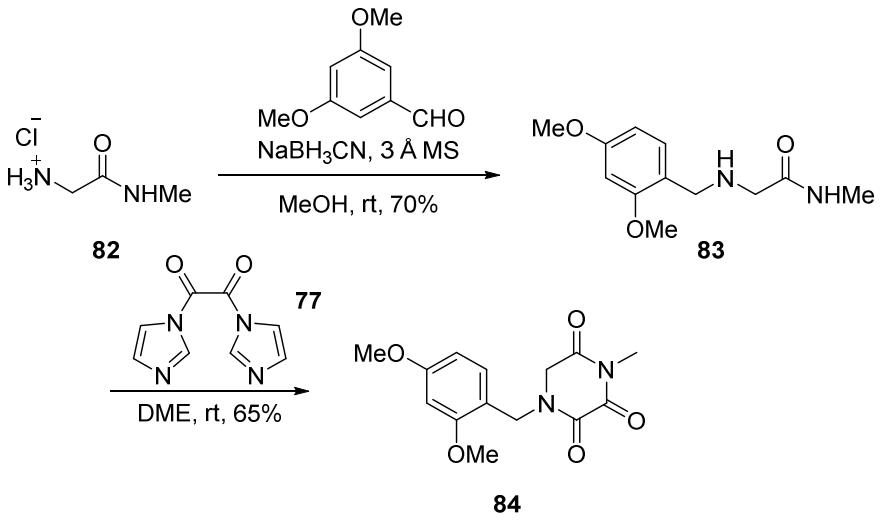
Both dethiosecoemestrin **79** and neoechinulin **80** were isolated from *Emericella striata* and *Aspergillus amstelodami* respectively. Its biological properties have not been extensively studied yet and no total syntheses have been reported to date.



79 dethiosecoemestrin **80** neoechinulin **81** gliocladin C

Figure 1.12 TKP containing natural products

On the other hand, gliocladin C **81** has received more interest from the scientific community. Isolated from a strain of *Gliocladium roseum* by Yoshihide and Usani., together with gliocladin A and B, glioperazine, leptosin D and T988A, (+)-gliocladin C **81** is the only natural product possessing a TKP within its structure whose synthesis has been studied, mainly due to its high cytotoxicity against cultured P388 lymphocytic leukaemia cells.[66] The first synthesis was published in 2007 by Overman *et al.*,[67] and more elegant and direct total syntheses were accomplished by Stephenson, Movassagui and Overman groups independently soon after.[68] Noteworthy was Overman's 2011 synthesis as it represented the first example of the TKP subunit being synthesised under mild conditions in a non-solid-supported approach. While Stephenson and Movassagui introduced the necessary groups and functionalities to build the TKP within the molecule linearly, Overman and co-workers synthesised the TKP separately to include it at a late stage in the sequence in their convergent approach. The cyclisation of the protected amino amide **82** was performed under the same conditions Tsuji's group used on solid support (Table 1.2, *vide infra*, and Scheme 1.14).[68a]



Scheme 1.14 Overman's synthetic pathway towards TKP intermediate.

Since this seminal work, Overman has used protected gliocladin C as a key intermediate to accomplish an array of ETP and bisdethiodi(methylthio)DKP derived natural products total syntheses, showcasing promising reactivity of the TKP framework.[69]

1.4 Organocatalysis

Catalysis is generally understood to be the addition of an external substance, often in a substoichiometric quantity, to a chemical reaction which increases the rate of the process by lowering the energy barrier of the transition state (activation energy), without affecting the overall standard Gibbs energy change. The catalyst is present in the entire reaction and does not get consumed with the reactants.[70] Therefore, the term organocatalysis refers to the addition of an organic compound playing the catalyst's role.

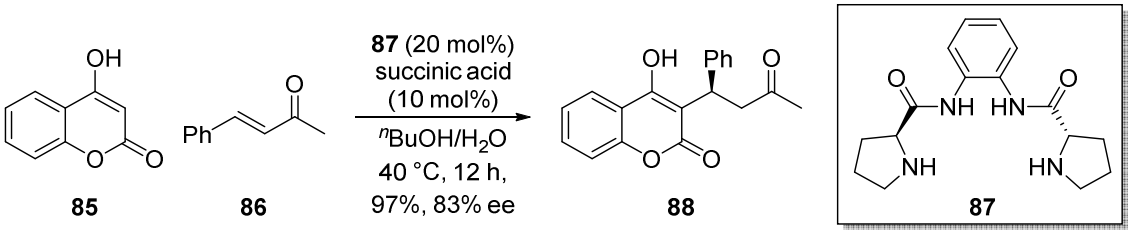
Although the first examples of organocatalysts date back to the 1970s, it was not until the early 2000s that the scientific community has fully appreciated organocatalysis as a powerful tool for the realisation of a wide variety of transformations.

Effective, achiral catalysts, such as DMAP or piperazine in the Knoevenagel condensation, are widely known but organic molecules particularly excel in the realm of enantioselective catalysis.[71]

1.4.1 Enantioselective Organocatalysis

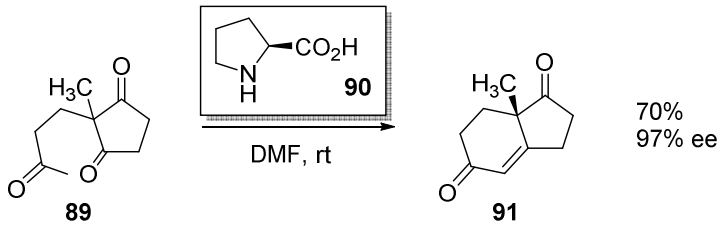
Nowadays organocatalysis is considered an equally important branch in the myriad of available enantioselective reactions, together with enzymatic catalysis and metal-based catalysis. Although metals have undeniable benefits, such as their enormous diversity and reactivity patterns achieved by tuning the ligands, they also have some clear disadvantages over organic catalysis that help us understand the explosion of interest and rapid growth of the field. Often, metal catalysts need to be kept under inert conditions, and metals tend to be toxic and are considerably more expensive. On the other hand, organocatalysis can be run under an oxygen atmosphere and does not need ultra-dried solvents or special experimental measures. The organic precursors, amino acids or natural products, are readily available as single enantiomers in large quantities, and so, easily and cheaply transformed into the active catalysts. Lastly, these organic molecules are generally non-toxic so research can be carried out in a safer environment and the risk of product contamination is greatly reduced. All these factors made this recently defined field very accessible and numerous research groups have quickly adopted it. This high interest helps to explain the exponential growth in the number of publications on the topic during the 2000s.[72] Enantioselective organocatalytic methods have

proved robust and generally applicable and are a convenient approach for medicinal chemists to access enantiomerically enriched drugs, as in the synthesis of anticoagulant warfarin **88** (Scheme 1.15).[73]



Scheme 1.15 Organocatalysis applied to Medicinal Chemistry

Retrospectively, it is surprising how this research area had been overlooked by scientists for so long given the advances in understanding the concepts and reaction profiles of enzymatic transformations in the last century. But it becomes clearer when analysing the first organocatalytic reports, the Hajos-Parrish transformation, in 1974 (Scheme 1.16).

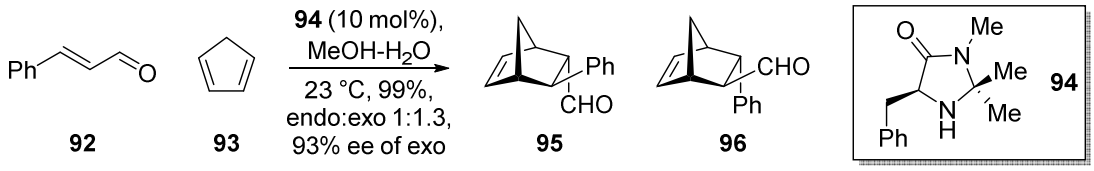


Scheme 1.16 Enantioselective aldol condensation using proline

Even though the similarities of this enantioselective aldol transformation to a simplified biological system where proline acts as an enzyme were pointed out, they failed to underpin the critical concepts around this particular mode of action and hence, expand its applicability.[74] These studies were considered singular and exceptional examples of intramolecular chemistry rather than a discrete part of a new research field, and their overarching benefits were not extrapolated or demonstrated in further reactions.

During the 1980s and 1990s chiral auxiliaries were the cutting-edge and almost unique method for introducing asymmetrically a variety of substitutions.[75] This trend started to shift with the independent studies on organocatalysed epoxidations of alkenes by Yang, Shi and Denmark and their co-workers in 1996, using a combination of chiral ketones and oxone as an enantiomerically pure source of oxirane.[76]

However, it was not until 2000, when MacMillan and co-workers developed the first enantioselective organocatalytic Diels-Alder reaction, that organocatalysis became a concept.[77] In an effort to emulate Lewis acid catalysis, MacMillan suggested the use of secondary amines as a way of activating the LUMO of *α,β*-unsaturated aldehydes by forming the corresponding iminium cation, a very electron-deficient species, better suited to act as a dienophile. In addition, iminium cations are labile enough so as an equilibrium can be established with the aldehyde in aqueous solution, imitating Lewis-acid catalysts turnover. Lastly, using a chiral amine in this process would afford the enantioselective products. A range of aldehydes were used to successfully yield the corresponding bicyclic adducts, albeit in a mixture of *endo*:*exo* products (varying from 1:1 to 35:1). An example can be found in Scheme 1.17.

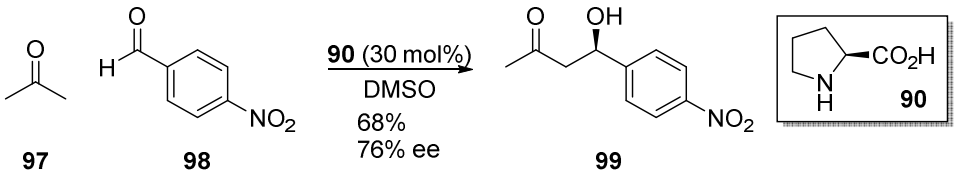


Scheme 1.17 Enantioselective organocatalytic Diels-Alder reaction

The importance of this work lied not only in the discovery of a novel and particular mode of activation for the Diels-Alder reaction, but also the recognition that analogous transformations

using this general activation strategy and effected by chiral organic molecules may be possible.

Contemporaneously, Barbas, Lerner and List demonstrated the general applicability of the intramolecular aldol reaction developed by Hajos *et al.* almost 30 years before.[78] Basing their studies on the mechanism of action of aldolases and aldolase antibodies, powerful catalysts able to resolve aldol products on gram scale through enamine intermediates in both intra and intermolecular transformations,[79] they hypothesised proline should also be capable of performing the aldol reaction intermolecularly. Addition of acetone **97** to a DMSO solution of aldehyde **98** and 30 mol% of catalyst **90** yielded enantioenriched product **99**, as shown in Scheme 1.18.



Scheme 1.18 Enantioselective organocatalytic intermolecular aldol reaction

The authors expressed their initial surprise with respect to the selectivity of the reaction and the absence of side products apart from dehydration. Different aryl aldehydes gave similar outcomes while *iso*butyraldehyde, gave the aldol product in excellent yield and *ee* (97% yield and 96% *ee*). However, more importantly, a metal-free stereocontrolled aldol condensation was proved to take place in the presence of a safe, cheap catalyst readily available in either enantiomeric form. Additionally, it was shown how proline can play a biomimetic role, *via* comparable mechanisms to those used by enzymes. Comprehending the underlying principles of the transformation allowed them to successfully predict the existence of novel and more selective catalysts and their use in a wide range of related reactions.

These two studies initiated a new era for organocatalysis. Improved and unique organocatalysts, as well as sometimes unexpected transformations, were reported with increasing frequency. The scientific community agreed on the identification of generic activation modes, elementary mechanism of catalyst activation, induction and reactivity, to categorise different enantioselective reactions sharing common reactive species (Figure 1.13).[80]

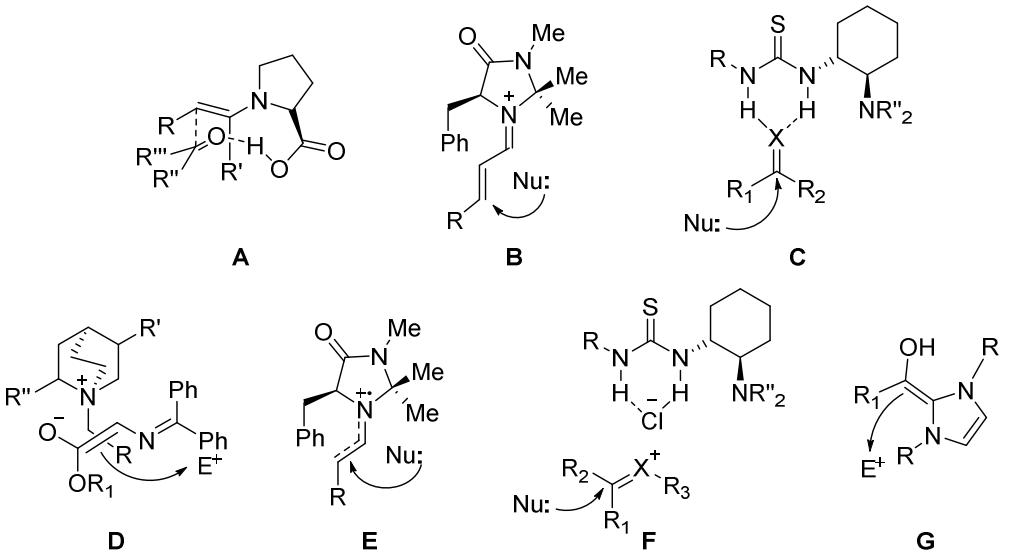


Figure 1.13 General enantioselective organocatalysis modes of activation

Enamine catalysis (**A**): Originally discovered by Hajos's and Eder's groups simultaneously in the 1970s, it was not until 30 years later that the reaction mechanism was determined. The catalyst, typically proline, acts as a bifunctional catalyst forming the enamine of the corresponding carbonyl which interacts with the electrophilic partner electrostatically or by hydrogen bonds. The HOMO energy is increased so it is closer to the LUMO energy of the electrophile.[81]

Iminium catalysis (**B**): Specifically designed as masked Lewis acid catalysis, this chiral catalysis, typically with imidazolidinone derivatives, relies on the formation of *α,β*-

unsaturated iminium derivatives, with lower LUMO energies, to effect several transformations inherently related to Lewis acid catalysis.[82]

Hydrogen-bonding catalysis (**C**): Although there were some early studies in the 1980s suggesting that hydrogen bonding between the organocatalyst and nucleophile in the transition state was responsible for promoting reactions,[83] this mode of action was not completely accepted until Jacobsen's and Corey's research groups published their works on the Strecker reaction.[84] This topic will be covered in depth in the next section.

Phase transfer catalysis (**D**): Originally reported in 1984 and mechanistically established in 1986, the first stereocontrolled version, alkylation of a glycine derivative, dates back to 1989.[85] The catalyst, typically a chiral quaternary ammonium salt, forms a unique ion pair with the deprotonated nucleophile, normally located at the interface constituted by organic/aqueous or solid phases, and diffuses into the organic media to undergo subsequent reaction (*e.g.* alkylation).[86]

SOMO (single-electron occupied molecular orbital) (**E**) and counterion catalysis (**F**): These are novel methods, their modes of action have shown that new reaction pathways and hence, modes of action might be left to discover. In the SOMO catalysis, one-electron oxidation of a proline-enamine yields a highly reactive three π-electron radical which undergoes rapid trapping with a range of "SOMOphiles"-nucleophiles, such as allylsilanes or enolsilanes.[87] On the other hand, electrostatic binding of chlorine with a thiourea catalyst forms a chiral counterion with the electrophile, strong enough to condition the approach of the nucleophile to a unique face of the stabilised cationic species.[88]

NHC (**G**): Although the first examples of nitrogen heterocyclic carbene (NHC) date back to 1943, when a thiazolium salt was discovered to promote the benzoin condensation,[89] the

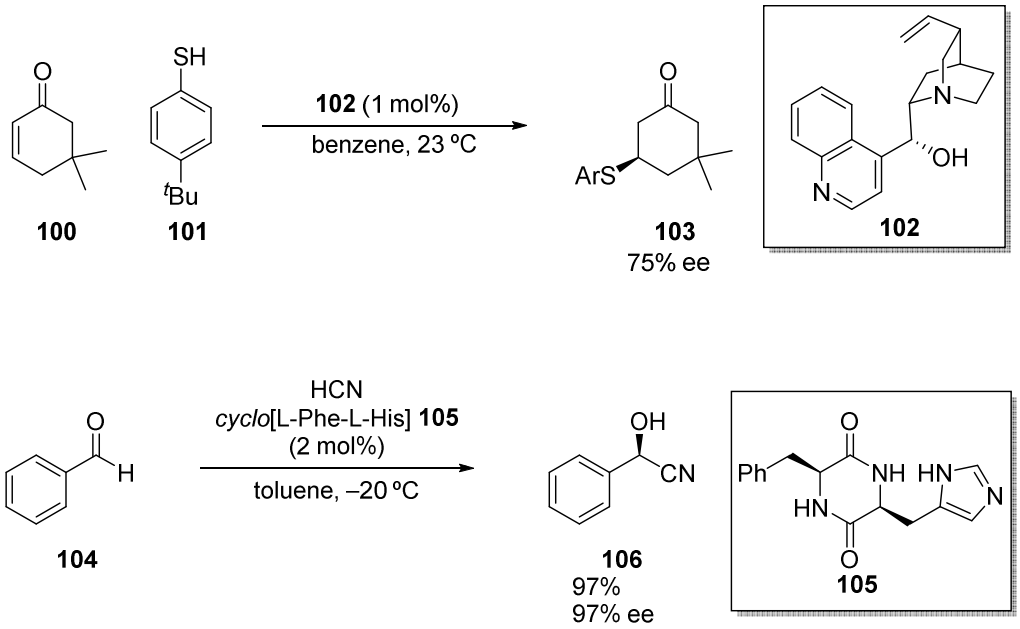
catalytic activity remained unclear until 1958,[90] when the C-2 position of thiazoliums was postulated to hold a carbene. NHCs can be employed as ligands in organometallic chemistry as well as enantioselective organocatalysts when chiral functionalities decorate the framework. A variety of asymmetric transformations have been achieved including the benzoin condensation, Stetter reaction and several cycloadditions.[91]

Organocatalysis is now regarded as a powerful method to construct organic bonds enantioselectively. Research groups have taken advantage of the recognised generic activation modes to develop novel reactions and more selective catalyst families that has helped to understand the field better. However, organocatalysis often complements rather than competes with metal-catalysis, as some fundamental transformations in modern synthetic chemistry, such as C-H activation or photoredox catalysis, are unlikely candidates for organocatalysis. In addition, new reports already show how these rather different methodologies can greatly benefit from each other chemical influence.[92]

1.4.2 Hydrogen-Bonding Catalysis

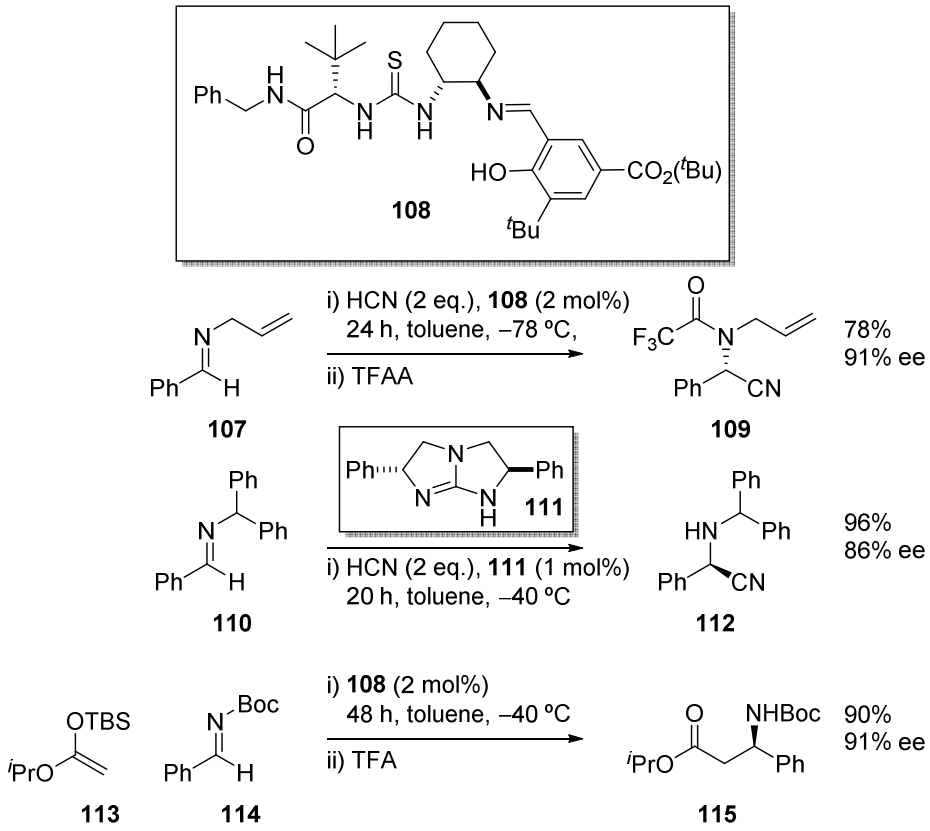
Generally, the aim of enantioselective organocatalysis is to complete the reaction between an electrophile and a nucleophile in a stereocontrolled manner. Thus, activation *via* a chiral acid or a chiral base can be conceived as plausible options to achieve this transformation. Historically, Lewis-acidic metals coupled with chiral ligands or chiral lithium amides were some of the most typical choices to promote such reactions and little was investigated about the possibility of using chiral organic bases instead.[93] As aforementioned, organocatalysis was born as a way to address this underexplored field. Although early reports suggested that

hydrogen-bonds were playing a fundamental role in different reactions such as the asymmetric Michael addition of thiols to *α,β*-unsaturated cycloakenones, catalysed by cinchonidine **102**, or the stereocontrolled cyanohydrin synthesis from benzaldehyde using DKP *cyclo*[L-Phe-L-His] **105** (Scheme 1.19), hydrogen bonding catalysis was not believed to establish strong enough interactions to direct a spatially biased approach.[83,94]



Scheme 1.19 First asymmetric examples of hydrogen-bond catalysis

A few years later a chiral version of the Strecker reaction was independently developed by Jacobsen's and Corey's groups, followed by Jacobsen's *β*-amino acids synthesis (Scheme 1.20), proving the hidden potential of this activation mode.[84,95]



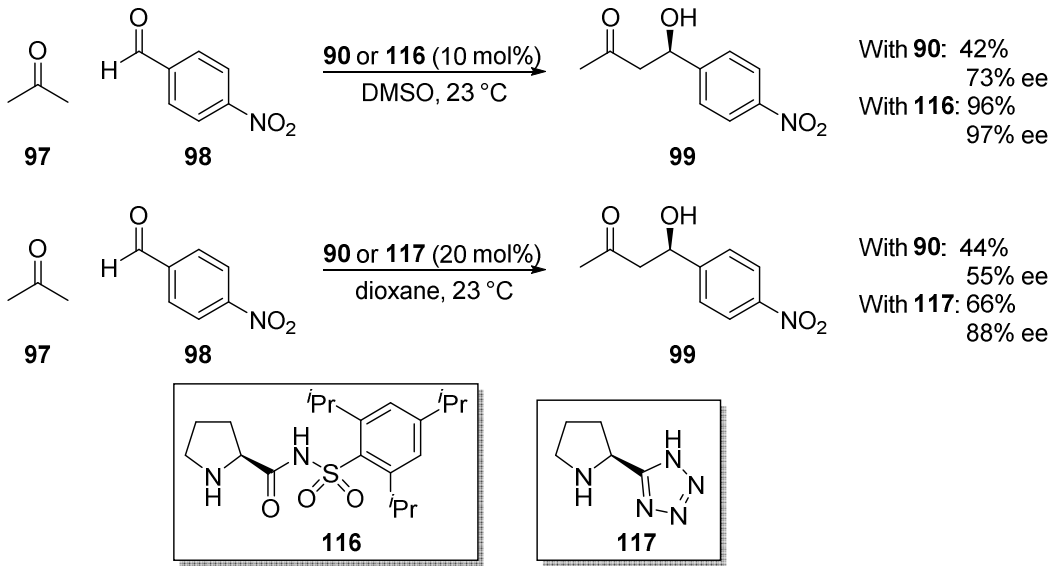
Scheme 1.20 Jacobsen and Corey first hydrogen-bond methodology

Furthermore, the previously mentioned modes of action were also proven to have key hydrogen-bond interactions for the reaction to successfully proceed. Regardless of the type of mechanism, the catalyst is often engaging in specific hydrogen bonds to arrange both reagents in a well-defined three-dimensional transition state before the stereocontrolled reaction happens. Proline, for instance, is not only involved in the formation of the enamine with the secondary amine but the acid is also establishing interactions with the electrophile *via* hydrogen bonding in the transition state prior to the reaction. The contribution of the hydrogen-bond is key to explain the facial selectivity of the newly formed carbon-carbon bond and to delocalise the charge increase in the transition state.[78]

In light of these results, novel bifunctional catalysts based on the proline structure and catalytic mode of action were developed with a wide variety of hydrogen donating components. Additionally, catalysis only based on hydrogen-donor interactions started to be considered viable for an array of transformations. Usually, a typical bifunctional hydrogen-donor catalyst was proposed to display a single or dual acidic hydrogen-bond donor site surrounded by functionalities aimed at secondary interaction with the rest of the reactants, such as weakly basic or acidic moieties, necessary to trigger the desired reaction.[96] The hydrogen-donor is typically a thiourea, phenols or guanidines, with pK_as ranging from 14 to 21, while the flanking sites are normally chiral Brønsted bases.[97] With those characteristics taken into account, different catalysts have been found optimal for enantioselectively promoting transformations, *e.g.* aldol or Michael reaction, and the most distinctive transformations will be briefly discussed, based on the type of electrophiles.

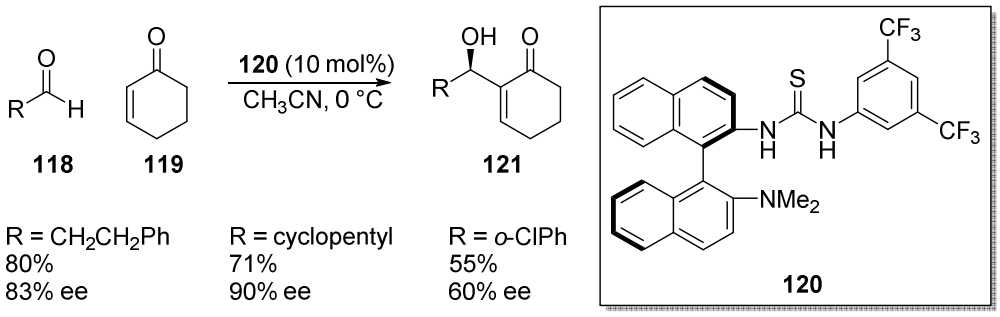
Carbonyl electrophiles

After List, Lerner and Barbas published their studies on the proline catalysed aldol reactions,[78] many research groups shifted their interests towards developing new proline-based catalysts with increased enantio and diastereoselectivity. Despite the proline-catalysed reactivity scope having been expanded since this first example,[81,98] and its clear advantages, *i.e.* enantiopure accessibility of both catalyst isomers,[99] there were also undeniable disadvantages such as poor solubility in organic solvents or low selectivity. The hydrogen-donor site was targeted for subsequent modifications and functionalities, such as acyl sulfonamide or tetrazole, replaced the original acid (Scheme1.21).[100]



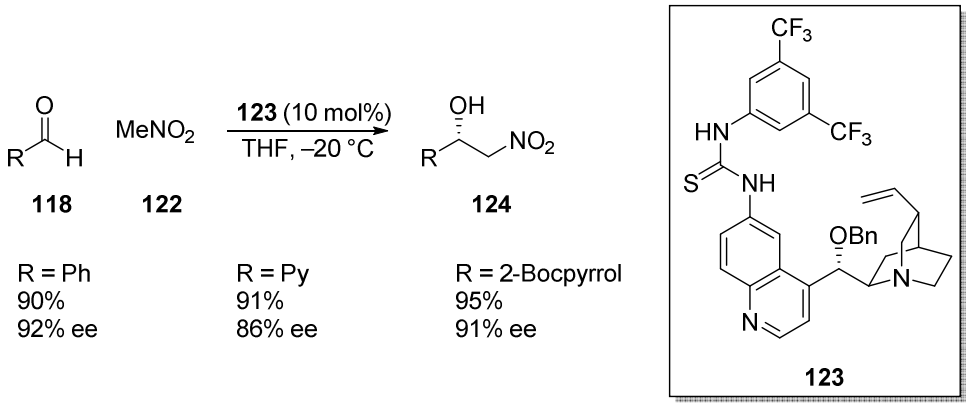
Scheme 1.21 Enantioselective organocatalytic transformations using carbonyl electrophiles

Reversible addition of non-hindered tertiary amines, such as DABCO, to electron-deficient *α,β*-unsaturated carbonyls results in the formation of a nucleophilic enolate capable of reacting with aldehydes. The versatility of the formed *α*-methylene-*β*-hydroxycarbonyl compounds (as in Scheme 1.18) is showcased in the myriad of manipulations these substrates can undergo or the natural products that can be accessed. With the advent of enantioselective organocatalysis this process, known as the Baylis-Hillman reaction, became the focus of considerable attention and asymmetric variants were developed.[101] For instance, development of catalysts based on the axially chiral scaffold of DABN, such as thiourea **120**, has shown remarkable results (Scheme 1.22).[102]



Scheme 1.22 Stereocontrolled Baylis-Hillman organocatalysed reaction

Pro-nucleophile nitromethane can be enantioselectively added to carbonyl groups in a process known as the nitroaldol or Henry reaction. Bifunctional cinchona alkaloid catalyst **123** induces high levels of asymmetry delivering *β*-hydroxynitro compounds (Scheme 1.23).[103] Cyanation of carbonyls can be understood as an analogous reaction, as shown in Scheme 1.19 (*vide supra*).

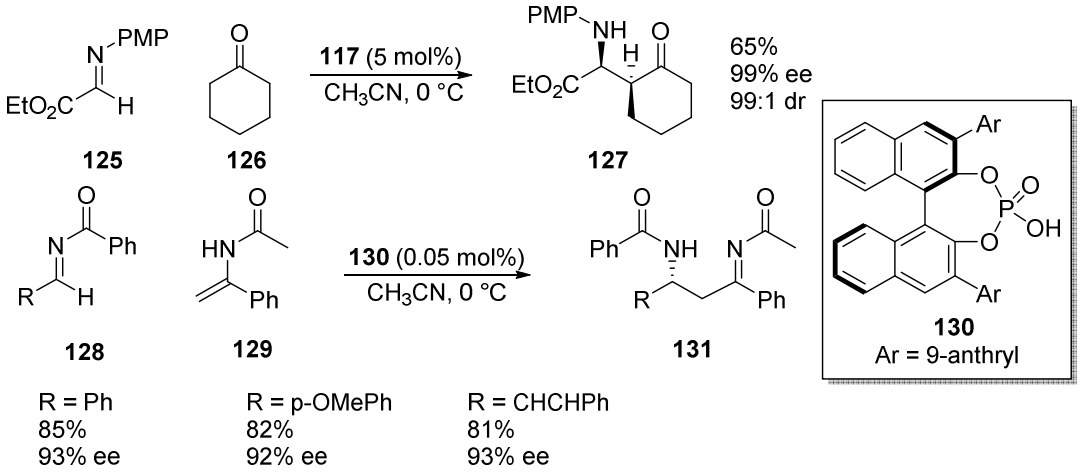


Scheme 1.23 Enantioselective nitroaldol reaction

Imine electrophiles

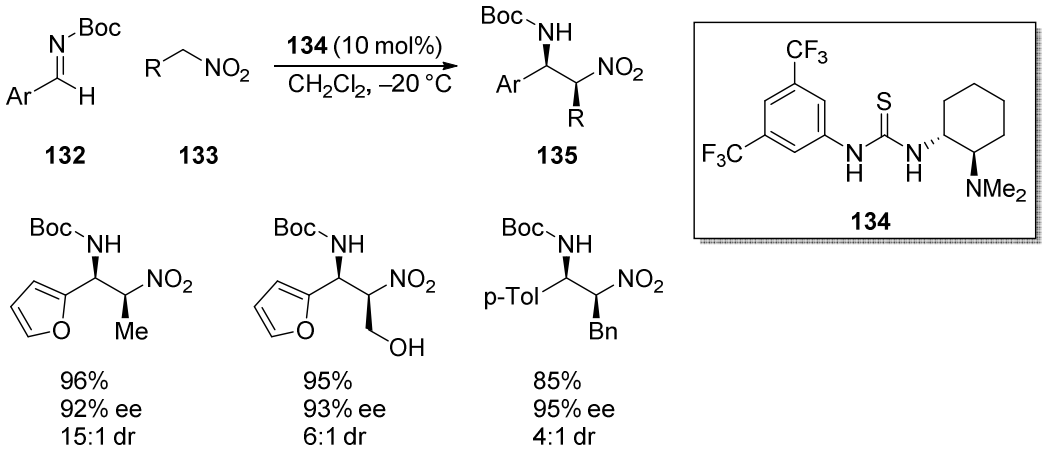
Imines are arguably better electrophiles than carbonyls, owing to their markedly directional hydrogen bond acceptor characteristics. Thus, extensive research has been conducted in this area and a broad range of applications have been reported.

Addition of an enolate, *e.g.* carbonyl, malonate or silyl enol ether, to the imine carbon centre, the Mannich reaction, is a widely employed method in organic synthesis. The stereocontrolled version has become a powerful way of accessing *β*-amino substituted carbon frameworks as in Scheme 1.24.[104]



Scheme 1.24 Asymmetric Mannich examples using hydrogen-bond organocatalysis

Nucleophiles are not just limited to carbonyl enolates, as asymmetric versions of the nitro-Mannich,[105] aza-Baylis-Hillman,[106] Strecker[84] or aza-Friedel-Crafts[107] have also been developed (Scheme 1.25).

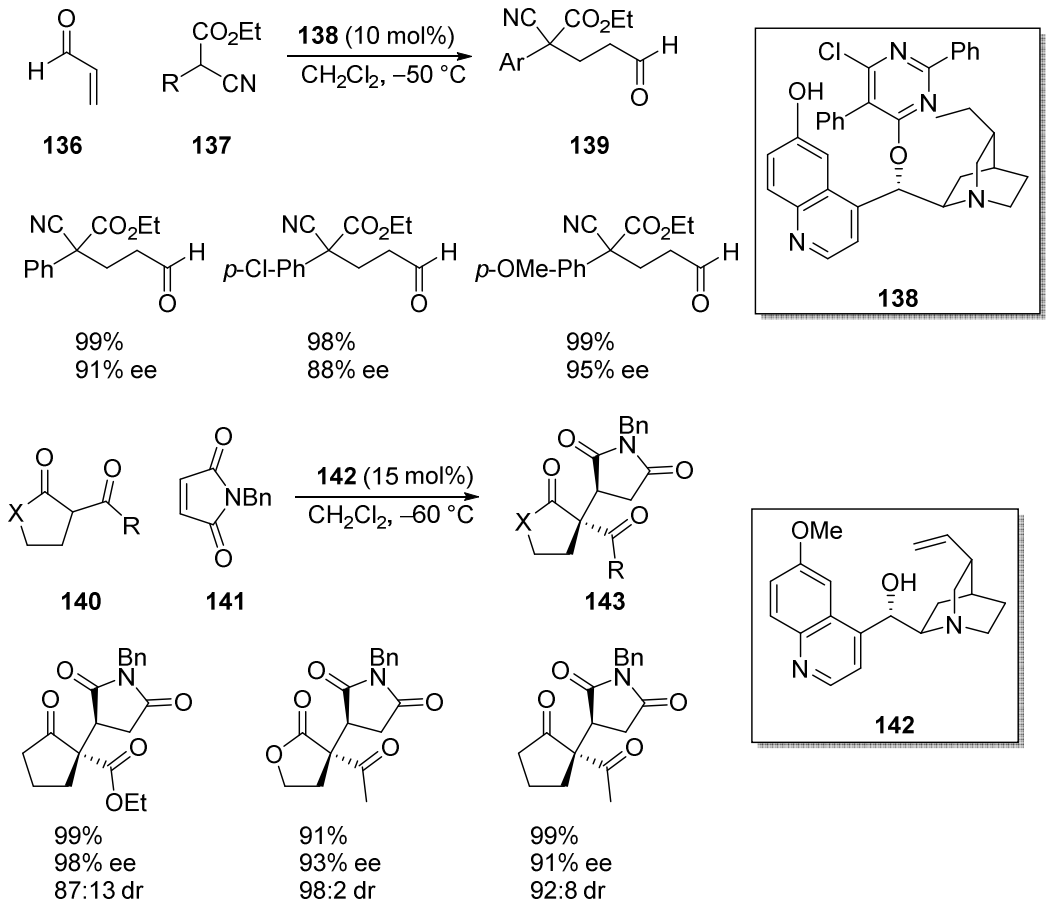


Scheme 1.25 Selected transformations of imine electrophiles

α,β-Unsaturated electrophiles

Addition onto the electrophilic conjugated position of a *α,β*-unsaturated carbonyl adduct of soft nucleophiles constitutes a very important strategy to form new carbon-carbon and carbon-heteroatom bonds. Enantioselective versions of this reaction have been largely explored and cinchona alkaloid derived catalysts have played a prevalent role, demonstrating in numerous cases that their bifunctionality is perfectly suited for performing this particular transformation. An extended discussion in Section 1.4.3 will follow.

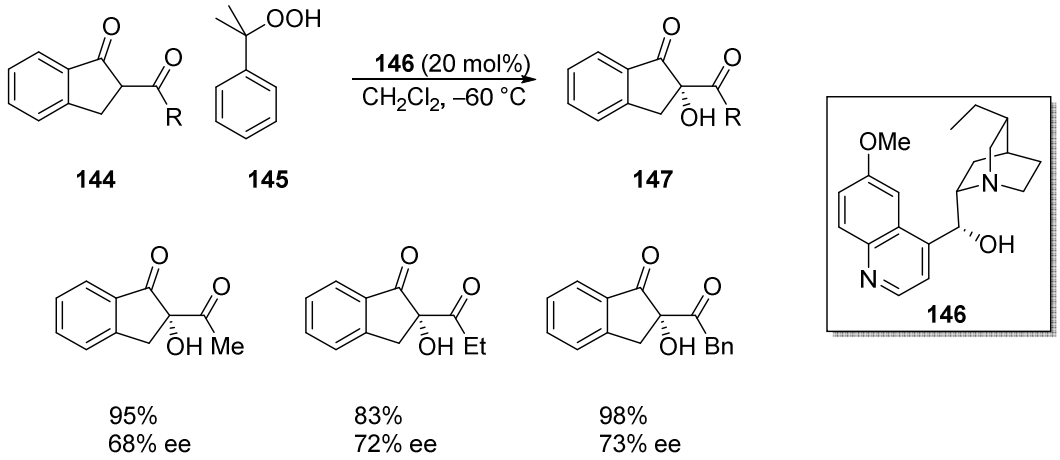
Since the addition of thiol **101** to cyclohexenone **100** catalysed by cinchonidine **102**, first example of an asymmetric Michael addition,[83] a wide range of Michael acceptors have been reported in the literature, such as *α,β*-unsaturated aldehydes,[108] ketones,[109] nitroethylenes[110] or maleimides[111] among others. Some examples are depicted in Scheme 1.26.



Scheme 1.26 Enantioselective Michael additions using hydrogen-donor organocatalysis

Heteroatomic electrophiles

Heteroatoms can be added to a nucleophilic position in a versatile manner using heteroatomic electrophilic sources. Only scarce examples of stereocontrolled reactions with electrophilic sources are available, compared to the volume of published literature around the enantioselective formation of carbon-carbon bonds using organocatalysis. However, a few specific substrates are able to provide electrophilic heteroatoms and oxygenations,[112] aminations,[113] halogenations[114] or oxyamination[115] were achieved using chiral hydrogen-donor Brønsted bases (Scheme 1.27).



Scheme 1.27 Stereocontrolled reactions employing heteroatomic electrophiles

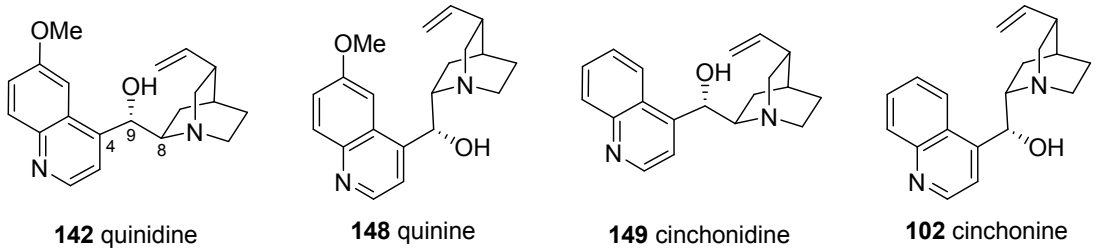
All these catalysts fulfilled the prerequisite aforementioned stating that next to the hydrogen-donor sites there are always flanking functionalities acting as secondary activators helping to prearrange the reagents spatially and electronically to facilitate the enantioselective formation of the new bonds.

1.4.3 The Cinchona Alkaloid Family

Endocyclic basic nitrogen containing molecules isolated from natural sources, excluding amino acids and their derivatives, are commonly known as alkaloids.[70] This extensive group of molecules are all extracted from a variety of animals, plants, fungi or bacteria. The effects these molecules exhibit range from medical (*e.g.* anesthetic, antibacterial or anticancer) to stimulant (*i.e.* psychoactive substances) and even toxic for the human body. Due to the absence of structural resemblance among most alkaloids there is not a uniform classification

of them. However, different families have been categorised based on carbon skeleton similarities or common natural source.

The cinchona family is one of the most prominent and best known alkaloid groups owing to their medicinal properties. Quinine and quinidine, the two most abundant family members, with chemical structures constituting a *pseudo*-enantiomeric pair, have been used for more than 300 years thanks to their respective antimalarial and antiarrhythmic activity (Figure 1.14).[116]



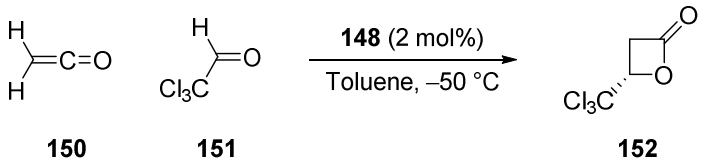
142 quinidine **148** quinine **149** cinchonidine **102** cinchonine

Figure 1.14 Natural members of the cinchona alkaloid family

These alkaloids, together with the myriad of other compounds belonging to this family are isolated from the bark of the cinchona trees, of the *Rubiaceae* family, native to the western part of Amazonas. Despite their formal total syntheses being achieved in 1945 by Woodward and Doering,[117] and more updated total synthesis being published during the last decade,[118] quinine and quinidine are still extracted from the cinchona bark for commercial use. Apart from their therapeutic properties, the cinchona alkaloids have other industrial applications, encompassing the addition of quinine to carbonated water, also known as tonic water, or the use of cinchonine and cinchonidine crystallisation properties for the resolution of racemic mixtures *via* their diastereomeric salts.[119] In the last two decades the cinchona alkaloid family has gained considerable interest across the scientific community due to its chiral inductive

properties, as shown in the extensive literature published on the matter, particularly marked from their use within the asymmetric dihydroxylation catalyst.[120]

Based on the pioneering advances by Bredig and Fiske, who reported the first reaction catalysed by quinine in 1912,[121] Wynberg and co-workers studied several transformations where cinchona alkaloids yielded stereocontrolled products.[83,122] The catalysts were showcasing bifunctional activating properties, making them exceptional candidates for simultaneously activating the nucleophile and the electrophile and, hence, capable of catalysing a wide range of 1,2 and 1,4-additions of nucleophiles. In addition, owing to their constrained scaffolds enantioselectivity could be induced in the reaction products (Scheme 1.28).



150 **151** **152**

Scheme 1.28 Early examples of cinchona alkaloid catalysis

In light of these results, the mechanism of action of cinchona alkaloid catalysed reactions was studied in an attempt to comprehend the close relationship between the alkaloid conformation in the transition state and the induced asymmetry of the reaction products. Initial analysis of the alkaloids reveals that the two rigid subunits are connected within the scaffold by a flexible carbon chain. Torsion of the carbon-carbon bonds involved, the C8-C9 and C4-C9 (Figure 1.14), defines the spatial arrangement between the subunits. Molecular mechanics optimisation carried out by Wynberg and co-workers led to the identification of four minimum energy conformations for the cinchona alkaloid family.[123] They have been

designated based on the different torsional possibilities of the aforementioned carbon-carbon bonds as app-open, app-closed, gauche-open, and gauche-closed (Figure 1.15).[124] App and gauche refers to the torsion angle around the C8-C9 and hence, the relative orientation of H8 and H9, being *anti* in the app confirmation and *syn* in the gauche. The open and closed conformers are related to the C4-C9 rotation and how the quinuclidine bicycle relates to the quinoline heterocycle. The more compact disposition of both subunits corresponds to the closed conformer whereas the open conformer has both substituents far from each other.

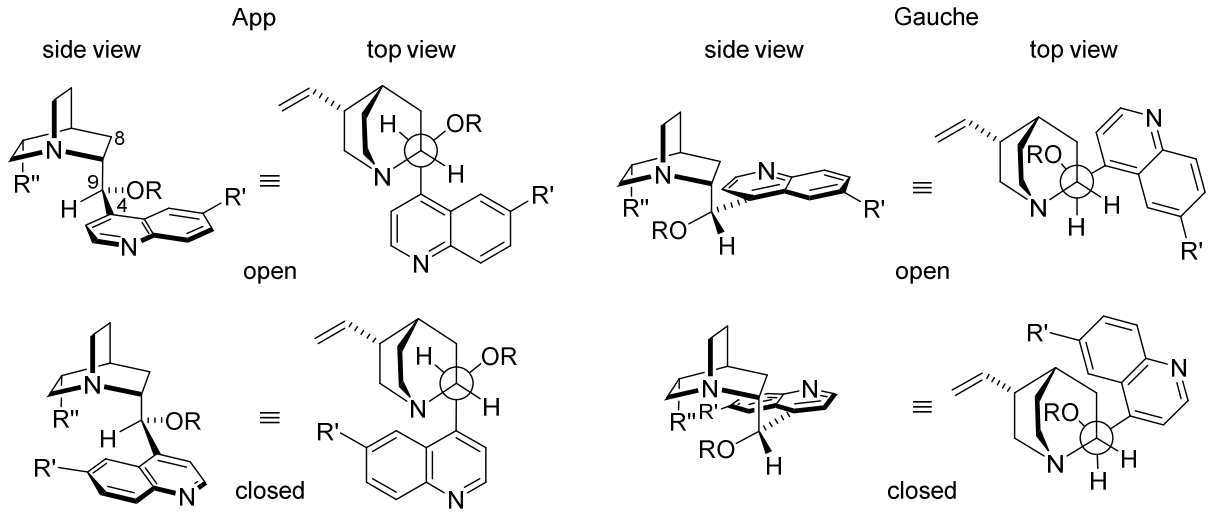


Figure 1.15 Minimum energy conformers of quinidine related cinchona alkaloids members

The substitution pattern on the framework, solvent or additives are all known to alter the preferred conformation of each specific catalyst in solution. nOe experiments were conducted in various solvents with differently functionalised catalysts to determine the solvent dependency of the conformers. For instance, dihydroquinidine (R = variable, R′ = OMe and R″ = Et; DHQD) was chosen to conduct the first complete study for this family.[123b] When bulky substituents (R = *p*-ClBz, $CONMe_2$ or Ac) were placed on O9 the observed conformation was app-closed, as inferred from the nOe correlations between H9 and some

aromatic and quinuclidine protons simultaneously. This was additionally supported by calculations of dihedral angles based on an empirical modification of the Karplus equation.[125] Further analysis using X-Ray diffraction confirmed that these molecules display a closed conformation in the solid state. On the contrary, the natural adduct and methyl ether adduct (R = H or Me) had different nOe correlations and coupling constants from the previous examples, suggesting that an open (gauche-open) conformation was preferred.

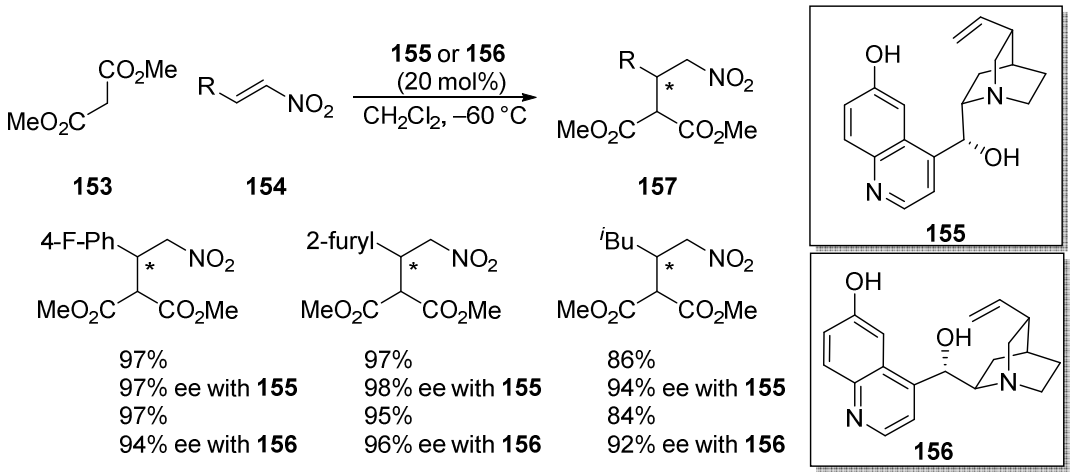
Concurrently, NMR spectra in a range of different solvents were measured from a representative member of each class. While closed conformer (R = *p*-ClBz) remained practically unchanged, only showing some degree of opening in toluene-d_8, open conformer (R = Me) drastically changed its conformation when measured in dichloromethane-d_2 into the closed one. Distinctive nOe correlations and couplings confirmed this change.

Furthermore, additional experiments demonstrated that substrate interaction, *i.e.* acidic media, was responsible for major disruption in the ground state conformations in all cases. When the cinchona alkaloids are used as chiral bases, the basic moiety in the catalyst, the quinuclidine tertiary nitrogen, accepts the proton forming an ion pair with the deprotonated substrate. In the present case, the ^{1}H NMR spectrum of DHQD (R = *p*-ClBz) in trifluoroacetic acid-d_1 revealed that all nearby protons suffered from extensive line broadening coupled with a transition from the coupling constants typical for the closed conformer to those typical for the open conformer.

Similar studies have been subsequently conducted on other cinchona alkaloids members, such as quinine[123a] or cinchonidine derivatives,[126] showing that, regardless of depicting variable

conformations in solution depending on the nature of the solvent or substitution pattern, they all adopt an open-gauche disposition while interacting with acidic substrates.

However, only mediocre levels of asymmetric induction were obtained across a wide range of transformation and the natural members of the cinchona alkaloids were unable to consistently deliver outstanding induced enantioselectivity.[127] Only the previously shown examples by Wynberg and co-workers were reported to give good to excellent enantioselective results. Wynberg suggested that substitution of the C-9 hydroxyl position would negatively influence the asymmetric reaction as the bifunctional properties and thus, the ability to interact with both nucleophile and electrophile and prearrange them before the new bond is formed, would be lost. The versatility of the catalysts to promote further transformations enantioselectively could not be demonstrated due to the difficulties encountered during the catalyst development stage during the 1990s. Simultaneously, the cinchona alkaloids gained tremendous popularity owing to the Sharpless dihydroxylation reaction and similar catalysts also started being used in desymmetrisation and kinetic resolution processes.[128] It was not until Li Deng published his first results on the Michael reaction of malonates to nitroalkenes that a functionalised catalyst was able to yield virtually perfect stereocontrolled results with both catalyst enantiomers (Scheme 1.29). [110a]

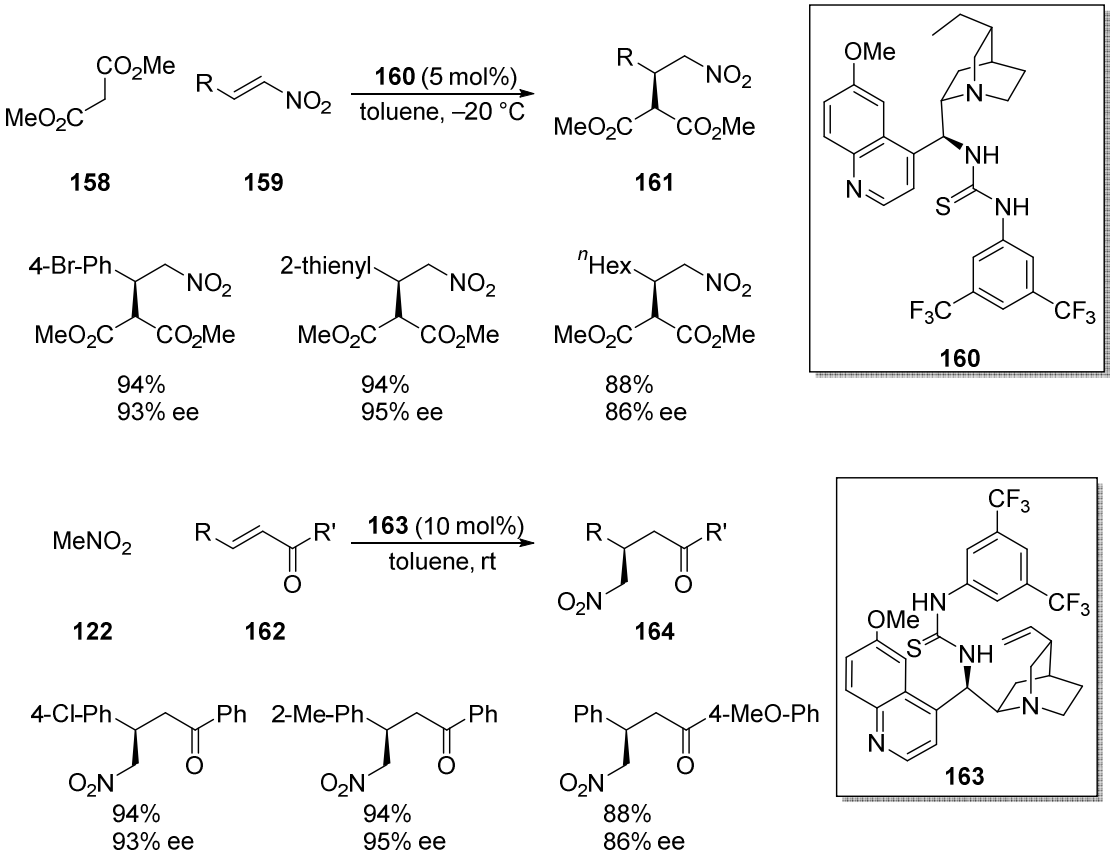


Scheme 1.29 Deng's first reported Michael addition with modified catalysts

Key to the catalyst success was demethylating the aromatic ether to unveil a second electrophilic activator in the catalyst. Not only is a phenolic hydroxyl group more acidic than an aliphatic one, and therefore more prone to establish an H-bond with electrophiles in the transition state, but it also allows functionalisation of the C9 hydroxyl group to force the catalyst to adopt a more reactive conformation. This conclusion was reinforced by consecutive reports from Deng's group, where a bulkier ether substituent was adopted to enhance the open-gauche conformer of the catalyst in the transition state. This change made the catalyst able to deliver outstanding results for increasingly complex substrates.[108,129]

Based on Deng's findings, the members of the cinchona alkaloid family were subjected to major optimisation studies to appropriately suit a wide array of different enantio and diastereoselective transformations. Shortly afterwards, the concept of evolving the electrophilic interaction site on the cinchona alkaloid catalysts coalesced with the possibility of including a thiourea proton donor site, widely used by Jacobsen. The C9 thiourea-substituted cinchona alkaloids were simultaneously reported by the Soós, Connon and Dixon groups to perform Michael additions with nitro alkenes **159** and chalcones **162** respectively

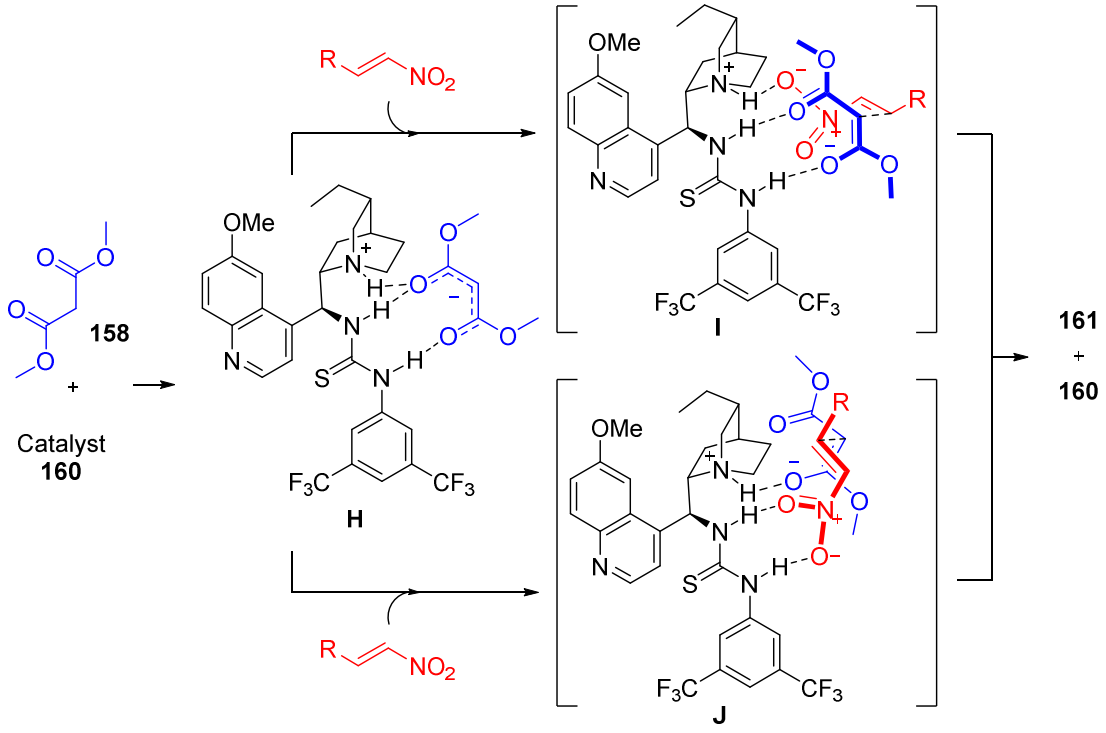
(Scheme 1.30).[130] As part of the synthetic route to afford the desired catalysts, an inversion of the C9 stereochemistry occurs, *via* a Mitsunobu nucleophilic substitution of the hydroxyl for an azide. This non-natural diastereoisomer happened to be more reactive than its natural counterpart when in combination with the thiourea hydrogen donor functionality. Interestingly, and despite this change, Connon observed no inversion in the product configuration when compared to their natural starting alkaloids.



Scheme 1.30 Thiourea based cinchona alkaloids catalysed Michael additions

Mechanistically, the mode of action of this new catalytic approach has been thoroughly studied using computational calculations and Takemoto's proposal regarding thiourea bifunctional catalysts was generally accepted. The induced asymmetry of these chiral

catalysts relies on the double interaction, electrophile with thiourea and deprotonated nucleophile with the protonated tertiary amine forming a ternary complex with an extensive hydrogen-bonding network.[131] Pápai and co-workers set about to theoretically demonstrate this hypothesis by calculating minimum energy conformations for the catalyst, energy involved in the proton transfer and formation of the binary catalyst-nucleophile and the corresponding energies for the reaction transition state.



Scheme 1.31 Theoretically proposed modes of action for a thiourea derived cinchona catalyst

These computational mechanistic studies of the thiourea bifunctional catalysts revealed important features of the reaction pathway (Scheme 1.31):

- The catalyst has a preferred conformation but rotation can freely occur in solution. Substrate binding is often responsible for the structural organization of the catalyst in a more reactive arrangement.
- Binding of any substrates to the thiourea is energetically favored for both the electrophile and the nucleophile. However the definitive reactive conformer is adopted after proton transfer of the nucleophile to the basic centre occurs. The nucleophile forms an ion pair with the catalysts (**E**) where the anionic enolate is stabilised *via* multiple hydrogen bonds involving all three positions.
- Formation of the ternary complex can be accomplished *via* two distinctive pathways. Association of the electrophile either to the protonated quinuclidine (**F**) or to the thiourea (**G**) with concomitant displacement of the enolate. Both complexes have exothermic energies associated and an equivalent energy barrier to yield the stereogenic centre.
- Attempts to calculate the energy of the transition states corresponding to the opposite product stereoisomer resulted in an unfavorable energy difference of about 2.5 kcal/mol. In addition, the transition state with the adequate pre-arranged enantioselectivity has both substrates aligned in a more favorable staggered conformation to minimize steric interactions while the opposite enantiomer corresponding substrates in the transition state are nearly eclipsed, and thus, sterically biased.
- Takemoto's proposed mechanism is, therefore, viable both kinetically and thermodynamically, although imprecise about the first steps in the catalytic cycle.

New hydrogen donor moieties (*e.g.* squaramides) have been incorporated into the library of the cinchona alkaloid catalysts.[132] Updated theoretical data is needed to explain the mechanistic phenomena for each of the reported asymmetric transformations.

The cinchona alkaloid family is an excellent example of how the establishment of multiple, weak hydrogen donor interactions can be powerful enough not only to catalyse a simple electrophile-nucleophile reaction but also to spatially arrange the substrates for the new bond to be formed asymmetrically. These catalysts have become a landmark for any synthetic chemist and their wide applicability allows them to be reliably employed by those in industry similarly to any other enantioselective method known to date. Other aforementioned benefits, *e.g.* inexpensive or robust to atmospheric conditions, are extra reasons to choose this chemistry when possible.

Chapter Two

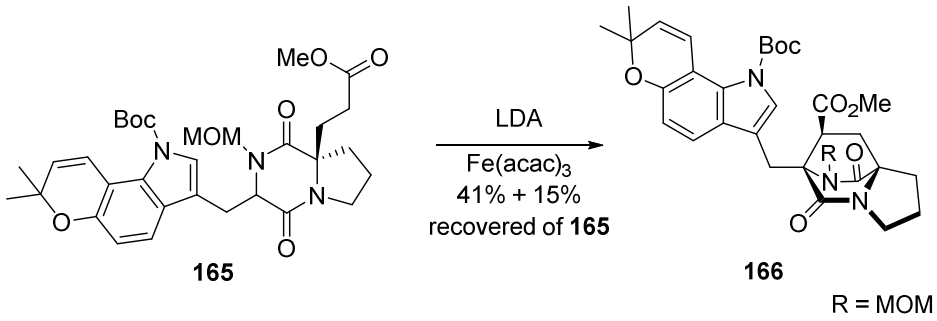
Organocatalysis Chemistry of 2,5-Diketopiperazines

2.1. Aims and Objectives

Numerous total syntheses of natural products incorporating DKPs in their complex structures have been successfully accomplished.[31,133] However, it is worth noting that the heterocyclic ring is often formed in a late stage step, with most of the final target functionalities in place, as previously seen in the total synthesis of versicolamide B by Williams and co-workers (Scheme 1.5).[48]

As far as the total synthesis of bicyclo[2.2.2]diazaoctane natural products is concerned, the formation of the bridge DKP core during the final steps of the synthetic plan often represents the most challenging step in the process. The distinctive strategies adopted to access the alkyl bridge have become prominent landmarks of natural product total syntheses in recent times. The approaches used to trigger the bridge-closing step range from Diels-Alder reactions,[134] enolate couplings[33b,135] to radical[136] or cationic cascades.[33d] For instance, the bridge-forming reaction in Baran's total synthesis of stephacidin A (Scheme 2.1) is an excellent example of how a methodology applied to a unique synthetic challenge prefaced the rebirth of an area of research. Firstly investigated in the 1970s,[137] the access to 1,4-dicarbonyls by means of intra

and intermolecular enolate couplings, using a stoichiometric amount of oxidant (Fe^{III} or Cu^{II}),[138] was expanded owing to the interest motivated by this total synthesis.



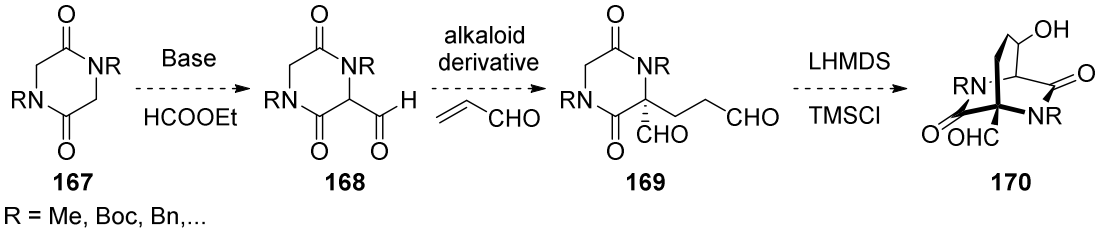
Scheme 2.1 Key bridge-closing step in stephacidin A synthesis

In this particular example, DKP **165** could be envisioned from a hypothetical asymmetric Michael addition between methyl acrylate and the DKP enolate selectively formed at the proline side. However, this chemistry is not available to date and the stereochemistry at this quaternary centre is established by means of Seebach self-reproduction of chirality by α-alkylation of (*S*)-proline in an early stage of the synthesis.[139]

The limited examples on the manipulation of DKPs stereochemistry are the reason why the DKP core is usually formed once the correct substituents, with the desired stereochemistry, have already been introduced. Scarce literature can be found on this topic apart from the well-established diastereoselective alkylation of DKPs using unsymmetrical PMB protected *cyclo*[Val-Gly] DKPs as a chiral auxiliary by Davies and co-workers,[53-55] and the investigations into the synthesis of quaternary streogenic centres of DKPs by Simpkins and co-workers (Schemes 1.7-12).[56]

As mentioned in the introduction, the initial proposal was aimed at developing a rapid, selective and stereocontrolled route to access DKPs, bearing key functionalities within their

frameworks, by applying recently discovered enantioselective organocatalytic methods. We envisioned utilising protected *cyclo*[Gly-Gly] DKPs **167** as prochiral nucleophiles combined with alkaloid derivatives to promote asymmetric transformations with selected electrophiles. These enantiomerically enriched products would be subsequently subjected to bridge-closing conditions to access a wide range of non-natural bicyclic DKPs (Scheme 2.2).

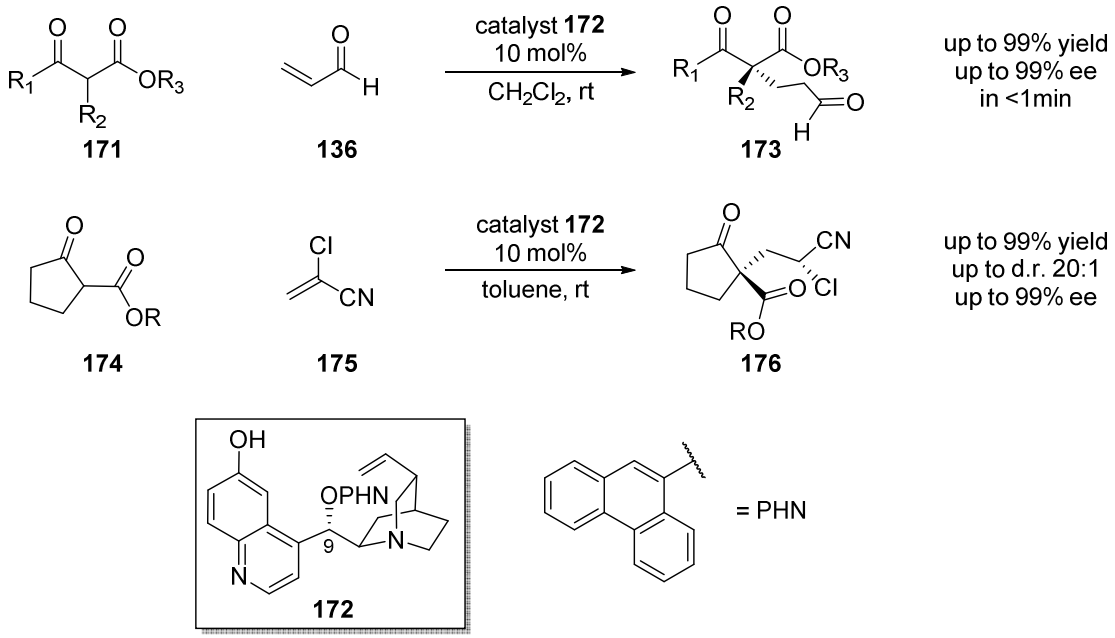


Scheme 2.2 Initial project sequence

Aware of the lack of examples of asymmetric organocatalysed reactions using simple amides as nucleophiles, an additional activating group was concluded to be necessary to facilitate the asymmetric step, for example a formyl group as shown in DKP **168**. Whilst the requirement for an extra carbonyl group may appear to be a disadvantage, this handle could become useful to add key functionalities in a diversity orientated approach for the final DKPs. The electrophilic partner for this reaction was chosen so as to allow subsequent treatment to transform chiral DKP **169** into a bridged product (**170**).

Extensive literature can be found where a wide range of Michael acceptors have been employed in asymmetric Michael additions using countless different types of nucleophiles. Several alkaloid families have been reported to be excellent catalysts to effect asymmetric 1,4-additions. As shown in the introduction, the cinchona alkaloid family is considered a privileged framework in this regard, consistently delivering good results in Michael additions. These catalysts have been quickly adopted by the scientific community due to their

effectiveness, their easy accessibility, cheapness and flexibility towards modification. In fact, selected cinchona alkaloid derivatives have afforded excellent levels of induced asymmetry using 1,3-dicarbonyl nucleophiles and Michael acceptors as shown in Scheme 2.3.[108,129d]

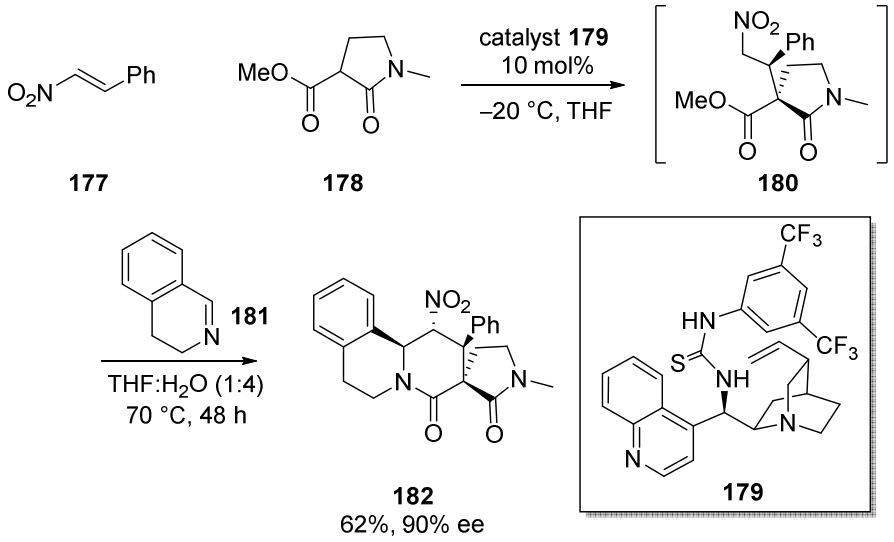


Scheme 2.3 Examples of organocatalysis using Deng´s catalyst

Arylation of the 9-hydroxyl position of quinidine with phenanthroline (PHN) followed by demethylation of the 6-aryl OMe yields the best performing catalyst **172** as demonstrated in many different examples in the literature.[108,129b,129d] As depicted in Scheme 2.3, highly reactive *β*-ketoesters were added into acrolein (**136**) or *α*-chloroacrylonitrile (**175**) in excellent yields, enantio and diastereomeric excesses. We wanted to apply the great potential of this chemistry in the context of DKP modification, which had scarcely been examined previously.

Hence, the key step to determine the viability of this project was recognised to be the asymmetric Michael addition. Only a handful of examples of this transformation in which the 1,3-dicarbonyl group featured an amide function had been reported in the literature. As shown

in Scheme 2.4, Dixon and co-workers subjected ethylcarboxylactam **178** to asymmetric Michael conditions using thiourea catalyst **179**.[140] Once this reaction was completed, imine **181** was added to the reaction mixture and underwent a nitro-Mannich/lactamisation tandem sequence to furnish polycycle **182** in very good *ee*. This strategy was used in the total synthesis of (−)-nakadomarin A to fix, in one step, two out of the four stereogenic centres of the final target.[141]

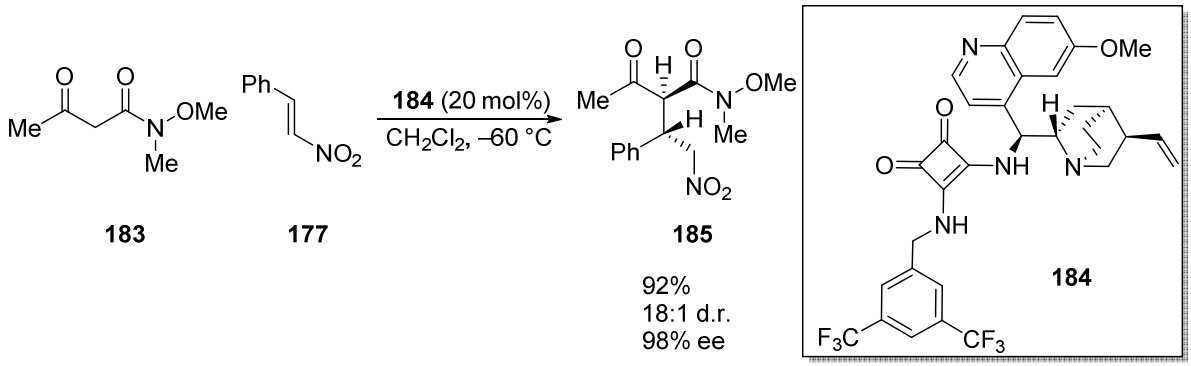


Scheme 2.4 First enantioselective *β*-esterlactam example

This cascade was the first example where an amide, as part of a 1,3-dicarbonyl, was employed for an asymmetric Michael addition using a cinchona alkaloid derived catalyst.

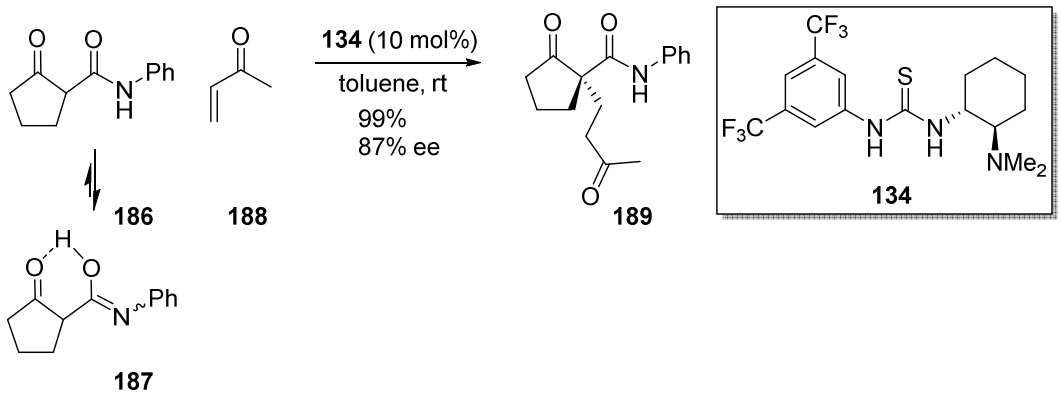
Similarly, the 1,3-ketoamido system **183** has recently been demonstrated to effectively undergo Michael additions using squaramide derived cinchona alkaloid **184** as the organocatalyst (Scheme 2.5). Interestingly, the presence of an amide as part of the nucleophilic partner seemed to suppress the undesirable bias towards racemisation *via* epimerisation of the 1,3-acidic proton at one of the newly created stereogenic centres in **185**,

as opposed to the *β*-ketoester case.[142] The increased acidity of the corresponding *β*-ketoester, expected to be around four orders of magnitude greater (ethyl acetoacetate has a pK_a of 14.2 while *N*,*N*'-dimethylacetoacetamide pK_a is 18.2) was likely to be responsible for this phenomenon.



Scheme 2.5 *β*-ketoamide asymmetric Michael addition

Furthermore, secondary amides have also been reported in the literature as successful Michael donors (Scheme 2.6).[143]

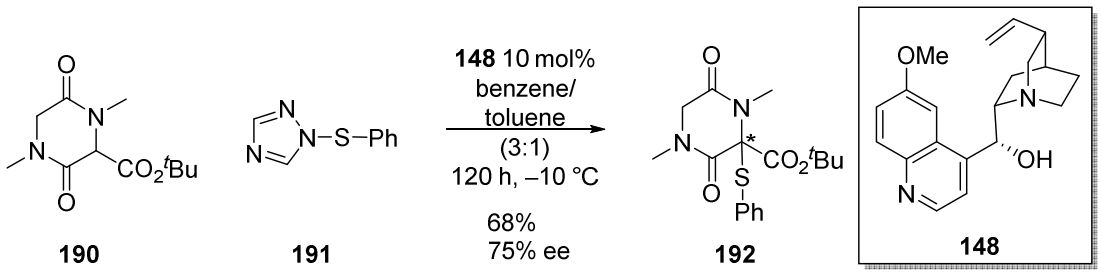


Scheme 2.6 Secondary amide organocatalytic example

The presence of the amidic hydrogen and, in particular, the role of the secondary amide tautomer, in combination with Takemoto´s thiourea catalyst **134**, played a crucial part in the reaction pathway. In fact, the more electron withdrawing the secondary group on the amide was, the greater the contribution of the imidic acid form (**187**) was to the tautomeric

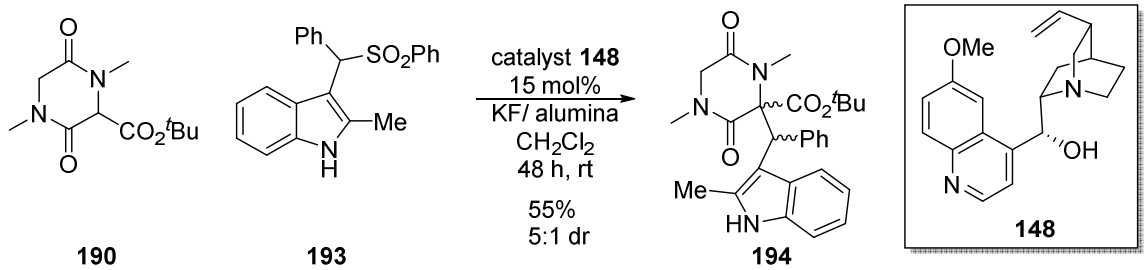
equilibrium and thus, a higher *ee* was recorded for the corresponding product, reaching complete selectivity when using tosyl instead of the phenyl substituent in **186**. Tertiary amides, under the same reaction conditions, did not deliver any Michael product.

As far as organocatalytic chemistry using the DKP framework is concerned, the closest precedent available to date were the investigations carried out by Olenyuk and co-workers, using *α-tert*-butyl ester sarcosine anhydride **190**. The activated DKP was found to undergo *α*-sulfenylation using quinine as organocatalyst.[144] However, only moderate results were obtained across all examples, up to 75% *ee* in the example shown in Scheme 2.7.



Scheme 2.7 Organocatalysed sulfur transfer

The same group also aimed at developing a methodology to rapidly access tryptophan DKP containing natural products (Scheme 2.8).[145]

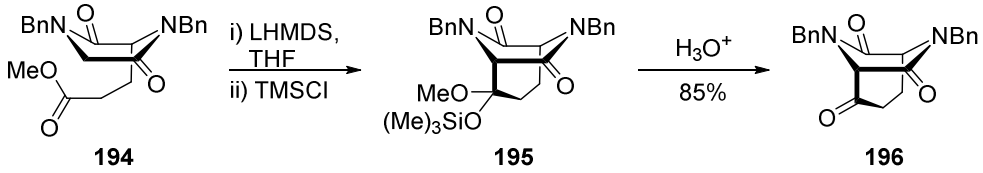


Scheme 2.8 Organocatalysed indole transfer

An organocatalysed nucleophilic substitution of the sulfonyl group in indole **193** by DKP **190** was explored. Despite achieving no degree of enantiocontrol, the desired products were isolated in a modest 5:1 ratio of diastereoisomers.

These few but promising examples utilising DKP structures in asymmetric organocatalysis clearly suggested there was room to expand this research to include different kinds of electrophiles such as Michael acceptors.

Once conditions for the asymmetric Michael addition of DKP **168** were devised, the exocyclic carbonyl functional group would be the perfect handle to explore a broad range of different options to close the bridge on the DKPs. Claisen condensation is a perfectly feasible option, and has previously been reported by Weigl *et al.* (Scheme 2.9).[146]



Scheme 2.9 Dieckmann condensation to bridge-close a DKP

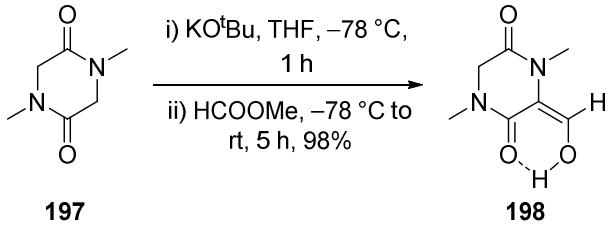
Enantioenriched DKP **194** was accessed from the condensation of (*S*)-glutamate and glycine. Treatment of this DKP with LHMDS triggered Dieckmann condensation with the side-chain ester followed by trimethylchlorosilane quench to yield mixed acetal **195**. Hydrolysis of this compound furnished the desired bicyclo[2.2.3]diazanonane **196**, in good overall yield. This short sequence emphasises how Claisen-type chemistry would be a proven strategy to accomplish the final bridge-closing step in the synthesis of closely related bicyclomycin analogues. In addition, a handful of other approaches have been envisioned to effect similar processes such as radical or cationic reactions. The exocyclic activating carbonyl group could

also be targeted for further functionalisation *via* different strategies, *e.g.* nucleophilic attack by a Grignard reagent.

2.2. Synthesis of 1,3-Dicarbonyl *N,N'*-Alkyl protected DKPs

Although the literature precedents for the proposed key step were somewhat limited, the previously outlined synthetic plan (Scheme 2.3) became the starting point of this project. The first priority was to access a small array of *N*-alkyl protected *β*-carbonyl DKPs for initial tests of the organocatalytic reaction.

Consequently, the synthesis of the *α*-carbaldehyde adduct from commercially available sarcosine anhydride **197** under reported conditions was accomplished (Scheme 2.10).[147] The isolated compound was exclusively the corresponding enolic DKP **198** in 98% yield.

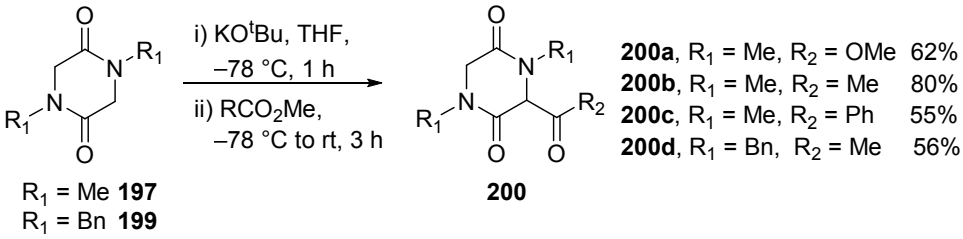


197 **198**

Scheme 2.10 Formylated DKP reaction

Following Olenyuk's protocol, methyl ester **200a**, methyl **200b** and phenyl ketone **200c** substituted DKPs (R_1 = Me) were synthesised in a Claisen type reaction using three equivalents of potassium *tert*-butoxide solution in THF, followed by quenching with the specific electrophile.[144] Benzylated DKP (R_1 = Bn), simply synthesised by treating glycine anhydride with sodium hydride in DMF followed by addition of benzyl chloride,[53] underwent

acylation using the same reaction conditions as before. The desired monoacylated DKPs were afforded as the only product of the reaction in good yields (Scheme 2.11).



Scheme 2.11 Acylated DKP examples

With these four examples of *β*-carbonyl DKPs in hand, a number of popular cinchona alkaloids were synthesised. Starting from natural members quinine, quinidine, cinchonine and dihydroquinine, modified catalysts were synthesised employing reported procedures, and are summarised in Figure 2.1.[110a,130a,148]

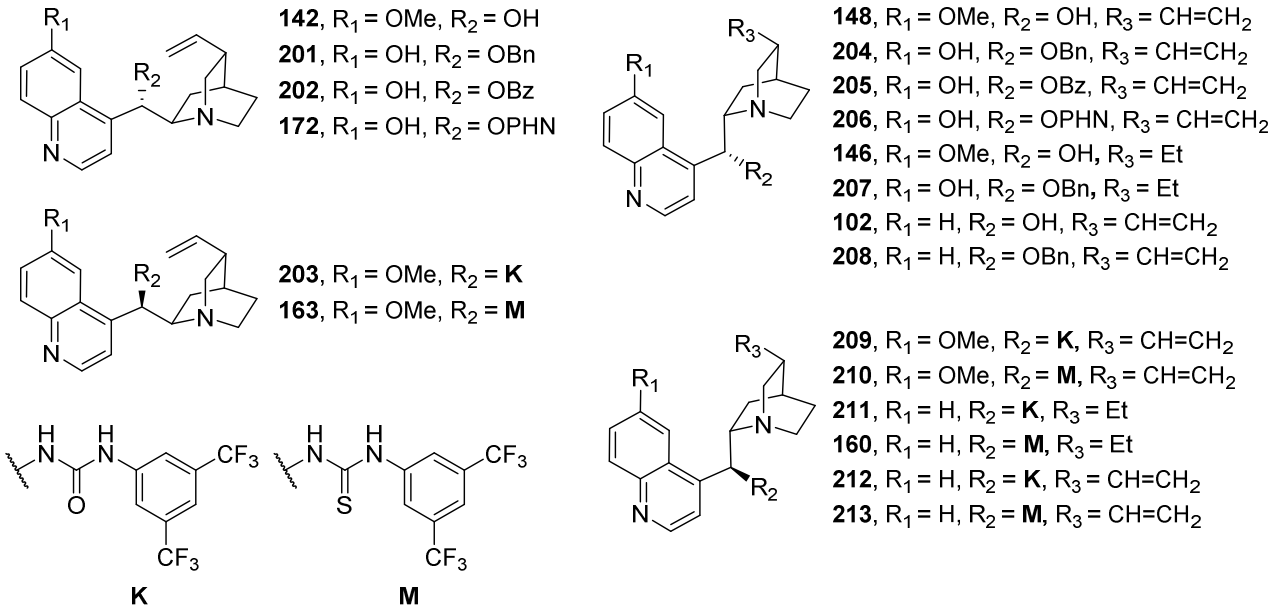
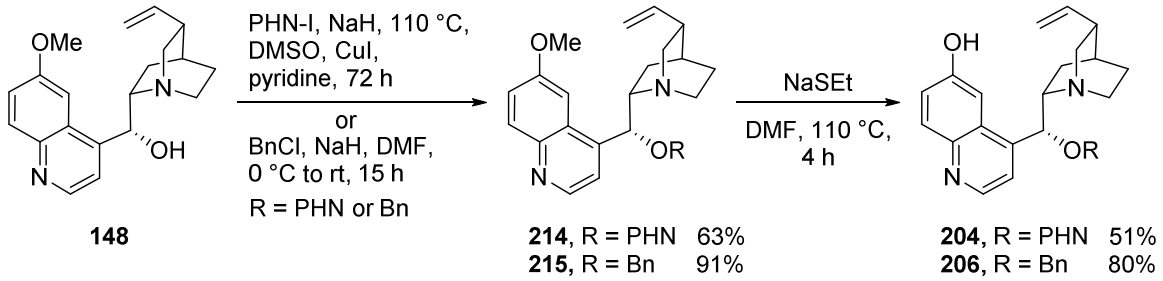


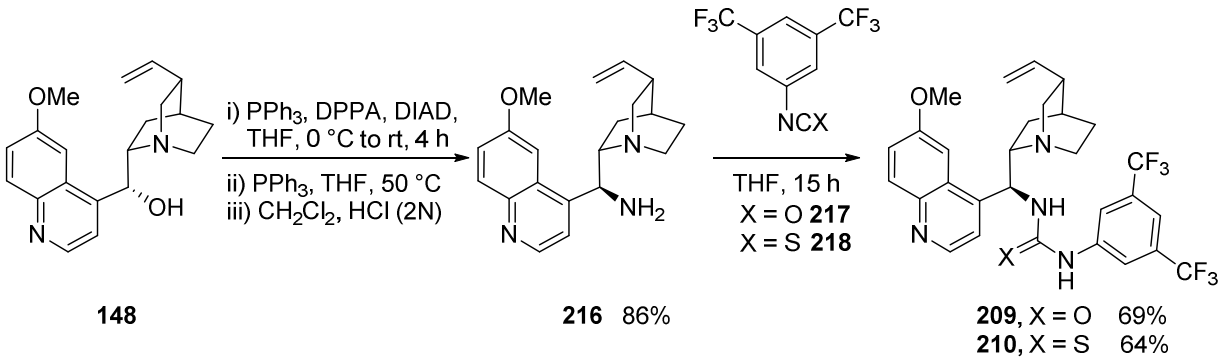
Figure 2.1 Cinchona alkaloids used in the project

Catalyst syntheses could be divided into two distinctive groups, depending on whether the hydroxy group in the aromatic quinoline was unveiled or not. In the first case, synthesis starts with protection of the 9-hydroxy group by either a benzyl or a phenanthryl group, followed by demethylation of the aromatic ether (Scheme 2.12).



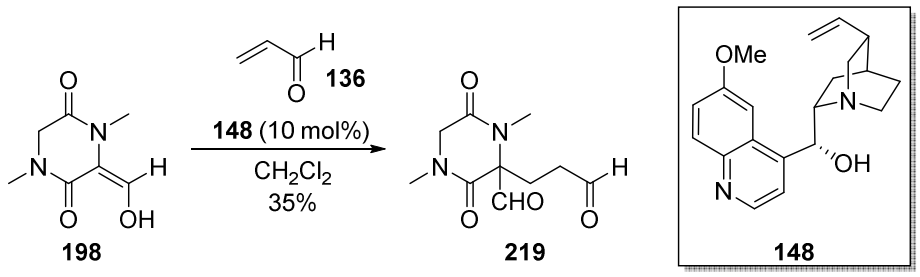
Scheme 2.12 Phenol derived catalyst strategy

In the second case, Mitsunobu reaction of the 9-hydroxyl function in the presence of diphenylphosphoryl azide affords an azide derivative that was *in-situ* reduced to the 9-amino compound. As expected, an inversion of the stereochemistry was observed.[130b] Nucleophilic attack of this amine on either *iso*cyanate **217** or *iso*thiocyanate **218** resulted in the formation of urea and thiourea derived compounds **209** and **210** respectively (Scheme 2.13).



Scheme 2.13 Urea derived catalyst strategy

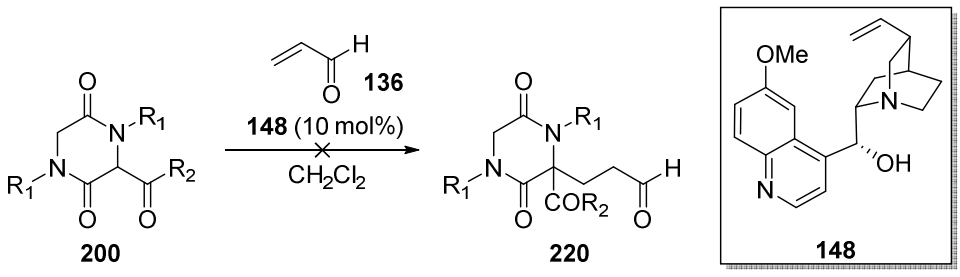
With all materials in hand, the organocatalysed Michael reaction could be attempted. Enolic DKP **198** was reacted under similar conditions to those reported by Deng and co-workers with acrolein as the electrophile.[108] Using a substoichiometric amount (10 mol%) of quinine **148**, the reaction proceeded to give the desired product **219** (Scheme 2.14).



Scheme 2.14 Organocatalysed Michael reaction

However, **219** was judged to be racemic, based on a zero polarimetric reading. Although the catalyst was needed for the completion of the reaction, no product was observed when it was excluded; it was not delivering asymmetric results. No stereoselectivity improvements were noted upon varying the organocatalyst.

The rest of the *β*-carbonyl DKPs were also subjected to these reaction conditions (Scheme 2.15). Unfortunately, none of the desired products were ever observed and only the staring materials and the catalyst were recovered from the reaction mixture.



Scheme 2.15 Organocatalytic Michael reaction on acyl DKPs

These results were in clear contrast to the first Michael adduct formed from DKP **198**. Consequently, the preformed enol was concluded to play a crucial role for the reaction to proceed. In the rest of the cases, the bifunctional catalysts, having a simple tertiary amine, embedded as the quinuclidine bicycle, were presumably not strong enough bases to deprotonate the active site within the 1,3-dicarbonyl in the DKPs.

The low acidity of the alkyl protected DKPs was believed to be responsible for the lack of reactivity towards the cinchona alkaloids derived catalysts. *β*-Ketoesters (pK_a around 15, *vide supra*) were likely to be at the pK_a limit where this type of chemistry was still effective, while the DKP system was known to be less acidic. The synthesis of acyl protected-DKP, by changing the nitrogen protecting groups for carbonyl based ones, *e.g.* Boc, to bring the pK_a of the distal proton down into the reactive range, was the next aim of the project.

2.3. Synthesis of 1,3-Dicarbonyl *N*,*N*'-Carbonyl protected DKPs

The main distinctive feature that makes imide *α*-protons more acidic than those of amides is the possibility of the former to delocalise the lone pair of electrons in the conjugate base over two carbonyl groups instead of one for the latter case. Accordingly, imides have a lower electron density on each carbonyl making them more electrophilic than amides and somewhat similar to ketones in terms of acidity. Theoretical calculations have been conducted to specifically determine pK_a values in acyclic and DKP subunits (Figure 2.3).[149]

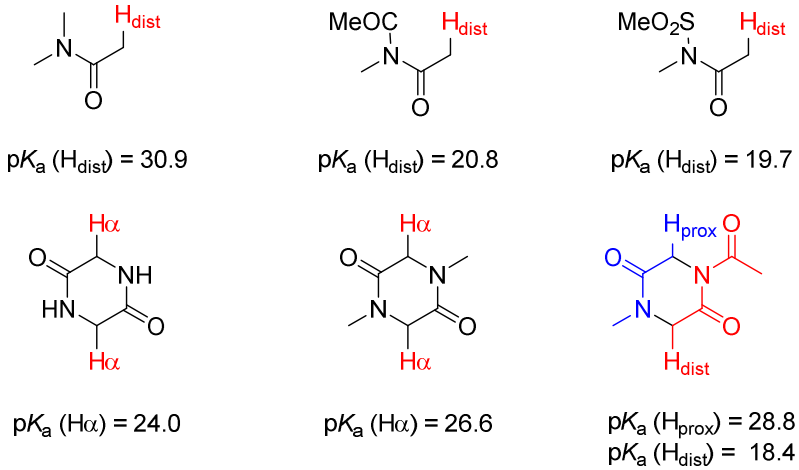
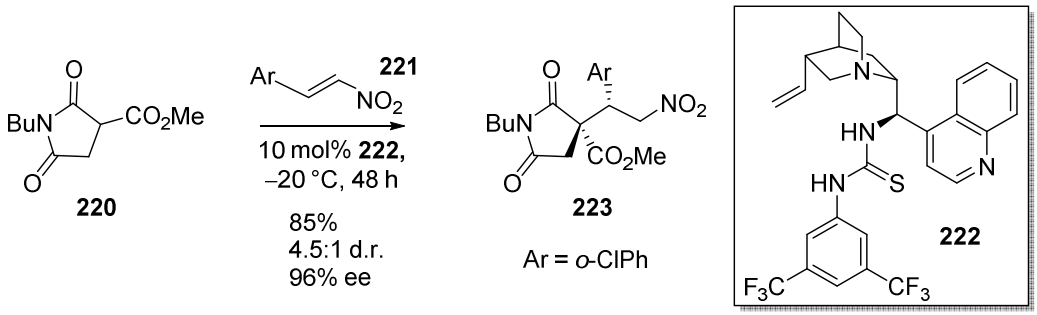


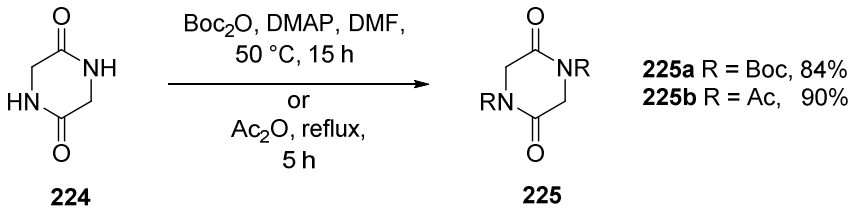
Figure 2.2 Theoretical pK_a of acyclic and cyclic amides and imides, using B3LYP/6-31+G(d) method for the geometries and frequencies in the gas-phase free energy calculations

The pK_a decreases by ten units from acyclic amides to imides. That enormous difference brings the pK_a value of this subunit to the range of a standard acyclic ketone. The same trend is observed within the DKP framework. Although the pK_a of unprotected *cyclo*[Gly-Gly] is substantially lower compared with that of an acyclic amide, and also lower than the sarcosine anhydride DKP, there is a significant difference compared to the acidity of the α-proton, or distal proton, of an imide embedded as part of the protecting group. Thus, acetyl nitrogen protection induces a decrease in the pK_a of the distal proton of five units. Therefore, carbonyl nitrogen protection should bring the pK_a of acyl DKPs to an amenable range for the key asymmetric reaction to work. In addition, *N*-butyl succinimidyl esters had previously been reported in the literature, using typical thiourea catalyst **222** and nitro-styrene **221**, to form the corresponding Michael adducts **223** in very good yield, *ee* and moderate diastereoselectivity (Scheme 2.16).[150]



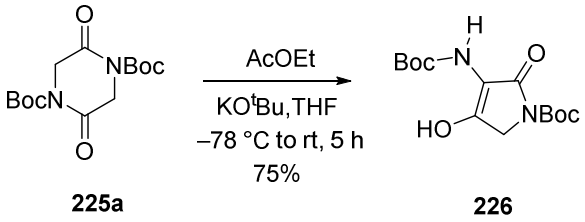
Scheme 2.16 Asymmetric Michael additions of succinimides

In light of this information, *N*,*N*'-diacetyl and *N*,*N*'-diBoc protected DKPs were synthesised. Glycine anhydride **204** was subjected to literature conditions to afford the desired protected DKPs **225a** and **225b** in very good yields (Scheme 2.17).[151]



Scheme 2.17 *N*,*N*'-dicarbonyl protection of DKPs

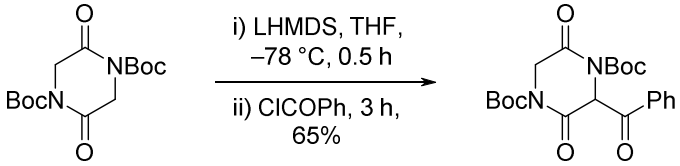
Both DKP products were initially treated under analogous Claisen conditions to those performed on the dialkyl protected DKPs to afford the corresponding acyl DKPs. However, the reaction did not proceed as smoothly as in the latter case due to the increased reactivity of these systems. In the case of *N*,*N*'-diBoc DKP **225a**, the potential intermolecular enolate acylation was overridden by an intramolecular attack of the formed enolate onto the second carbonyl group within the heterocycle, forming transannulated product **226**.[151b,152] No inclusion of the electrophile in **226** or traces of the desired product **227** were observed (Scheme 2.18).



225a **226**

Scheme 2.18 Transannular rearrangement of Boc-DKP

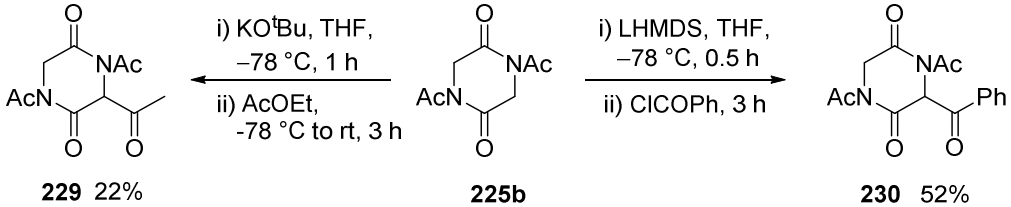
Nevertheless, this problem could be simply overcome by changing the conditions to lithium amide bases, at low temperature combined with highly reactive benzoyl chloride as shown in Scheme 2.19.



225a **228**

Scheme 2.19 Acylation of Boc-DKP

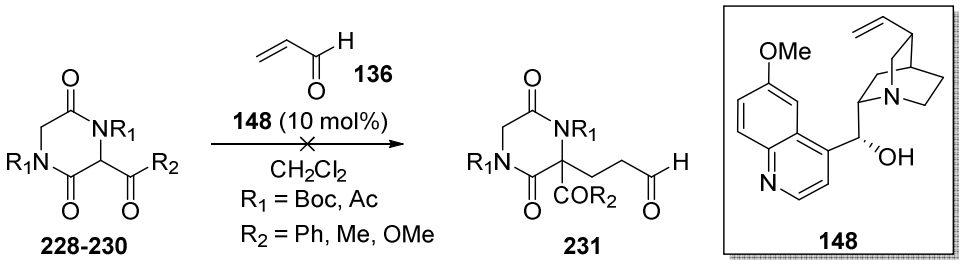
Difficulties were also encountered in the case of the acylation of *N*,*N*'-diacetyl DKP **225b** under classical Claisen conditions. A 22% yield of the final product was the maximum achieved in a very sluggish reaction with numerous undesired by-products, despite attempts at optimisation.[152] A much cleaner reaction with an easier purification process was accomplished by means of LHMDS base, low temperature and an acyl chloride reagent (Scheme 2.20).



229 22% **225b** **230** 52%

Scheme 2.20 Acylation of Acetyl-DKP

With robust routes to access substituted DKPs, the key step was tried prior to building a library of *N*,*N*'-dicarbonyl protected acylated DKPs. To our surprise, all of the tried reactions failed to furnish the desired products. A wide range of conditions were screened, including different catalysts, solvents and Michael acceptors, resulting only in the recovery of starting materials (70-85%, Scheme 2.21).



Scheme 2.21 Michael additions of *N*,*N*'-dicarbonyl DKPs

Disappointingly, the expected increased acidity of the acyl protected systems did not translate into enolate formation by the cinchona alkaloid catalysts action. At this point, the lack of reactivity of DKPs under standard organocatalysed conditions seemed conclusive and no further transformations on the DKP core were pursued to achieve the organocatalysed Michael addition. Devising a reliable route to access the TKP core and determining the optimal conditions for the key 1,4-addition step on this system became the next goal.

2.4. Summary and Future Work

It has been shown how different protected DKPs can undergo acylating chemistry under two different type of conditions, accessing a wide range of 1,3-dicarbonyl DKPs. However, we have been unable so far to successfully manipulate these DKPs under standard

organocatalytic asymmetric Michael conditions. The need for stronger, more basic organocatalysis has become apparent for this chemistry. If these types of catalysts are developed and optimised then reinvestigation of protected acyl DKPs may be fruitful.

Out of current catalysts, it might be recommended to try squaramide based catalysts, which have been shown to be slightly more reactive than Deng´s catalysts. Alternatively, a phase transfer catalytic approach may be more successful.

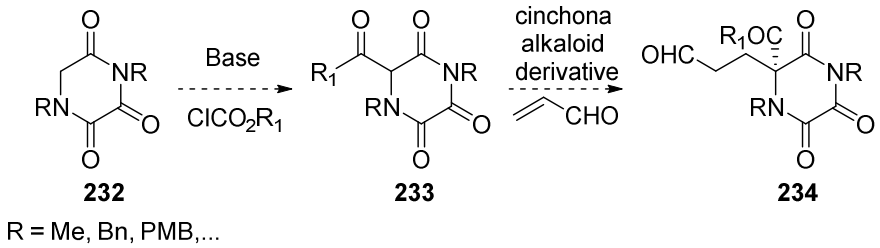
Having seen the asymmetric organocatalytic literature around *β*-ketoamides, how little their pK_a theoretically differs from the synthesised DKPs, and subsequent information generated by this project; it might be worth considering that other factors that will be later discussed might be playing a fundamental role in impeding this chemistry.

Chapter Three

Enantioselective Synthesis of Polyfunctional 2,3,5-Triketopiperazines

3.1. Aims and Objectives

The lack of reactivity exhibited by acylated DKPs, with either alkyl or carbonyl protecting groups on the nitrogen, encouraged us to explore further possibilities where an organocatalysed Michael addition could be performed. The aim was to develop a molecule with an increased acidity of the α-protons by including an imide within the molecular framework, without drifting away from the original goal. The synthesis of the triketopiperazine (TKP) framework addressed all these conditions. We were determined to check whether the key organocatalytic 1,4-addition would now proceed successfully, furnishing the desired enantioenriched products as shown in the proposed synthetic plan (Scheme 3.1).

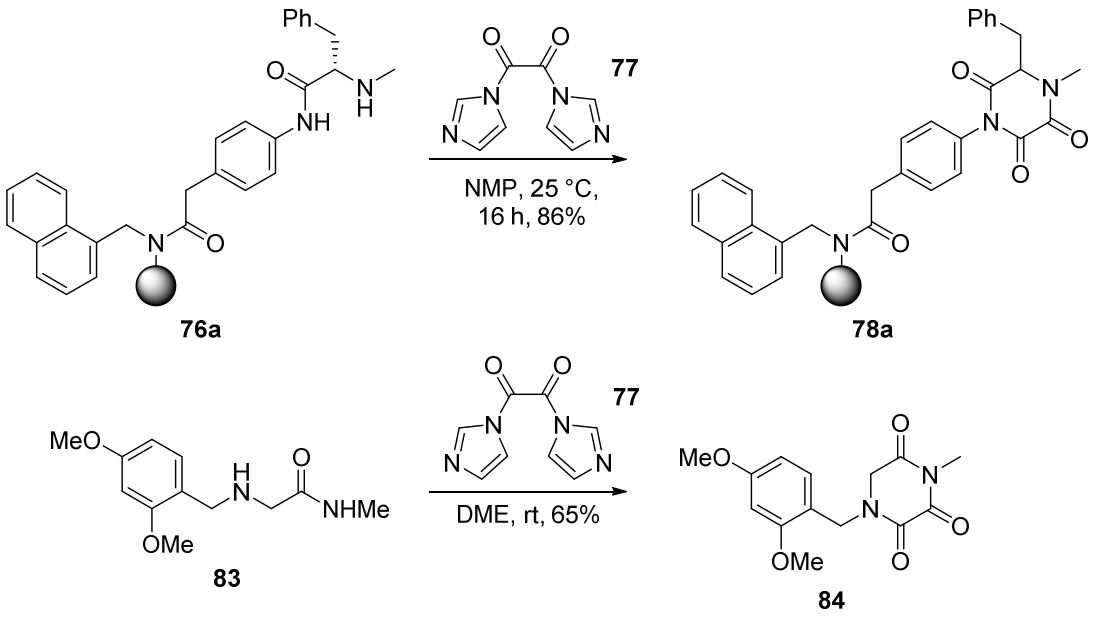


Scheme 3.1 TKP proposed sequence

TKP **232** bears an imide which has been included within the cyclic skeleton of the molecule and so there is only one methylene position available for further functionalisation.

Once the TKP was in hand, the synthetic plan would be analogous to the one devised for the DKPs. The first step would be acylation of the TKP, the extra reactivity provided by the activating group would probably still be necessary, followed by the key step, the stereocontrolled Michael addition, catalysed by cinchona alkaloid derivatives. To the best of our knowledge, the development of organocatalytic methods on this system has not been explored. At this point, different options could be considered, involving either bridge-closing chemistry or carefully selected transformations to afford enantioenriched DKP.

As previously mentioned, there is not much literature available for the synthesis of the TKP framework itself. Hence, the biggest challenge would initially be to develop a streamlined synthesis of the TKP on gram scale. To date, two very similar methods have been reported to synthesise TKPs under mild conditions (Scheme 3.2).[64,68a]

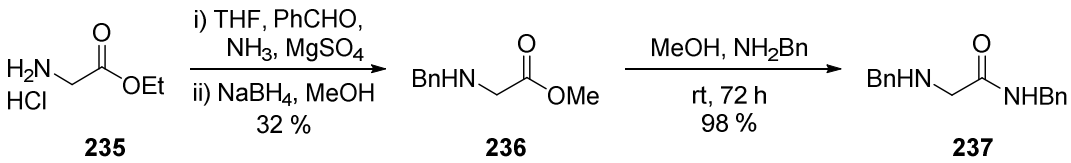


Scheme 3.2 Previous examples of TKP formation

It is worth noting that no oxalyl chloride is used to perform these cyclisations, possibly due to its highly reactive nature which was probably not compatible with either reactants or products. Instead, oxalyl diimidazole **77** was the oxalyl surrogate in the cyclisation step in both cases. Either under solid supported conditions or in solution, this method was very effective at furnishing the desired TKPs. No comments on the stereochemical outcome of the triketopiperazines in the solid supported synthesis were made by the authors in the first example, leaving the experimental assignment incomplete.

3.2. Synthesis of 2,3,5-Triketopiperazines

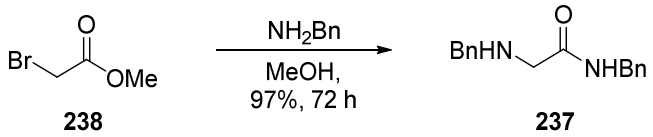
Similarly to the literature procedures, the formation of the TKP system was devised to comprise a di-protected aminoamide, either with the same or different groups on nitrogen, followed by the cyclisation step, using oxalyl diimidazole as described in the literature examples. A fully stepwise approach was developed initially, involving the benzyl protection of the primary amine of glycine ester **235** *via* reductive amination followed by amide formation through long exposure of the aminoester to benzyl amine to finally furnish *N*,*N*'-dibenzyl aminoamide **237** in a 31% yield across the two steps (Scheme 3.3).[153] Although it was a good starting point for the synthesis of aminoamide **237**, the overall synthesis had to be thoroughly optimised were gram quantities of TKP to be produced.



235 **236** **237**

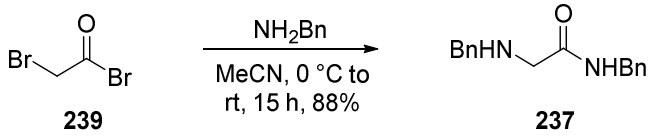
Scheme 3.3 First two steps sequence into aminoamides

One of the main advantages of this first approach was that it would allow us to introduce different protecting groups on each nitrogen and thus reflect that reactivity difference in the final TKP core. However, as a proof of concept a symmetrically protected aminoamide would be equally valid. Consequently, a second generation approach was envisioned to afford compound **237**. Starting from methyl bromoacetate (**238**), a one pot process furnished the desired aminoamide *via* initial nucleophilic substitution of bromine by benzylamine followed by slow ester group interchange to form the final aminoamide using an excess of benzyl amine (Scheme 3.4).



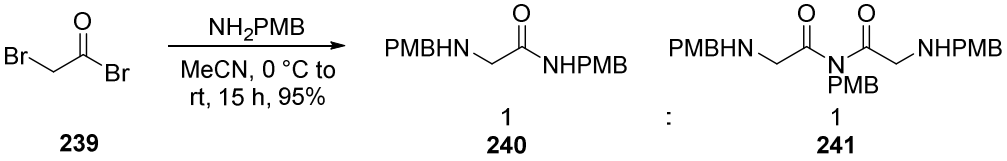
Scheme 3.4 Methyl bromoacetate approach to dibenzyl amino amide

Naturally, the first substitution occurs rapidly, with concomitant formation of one equivalent of the ammonium bromide salt, which remains in the reaction mixture. Although it did not seem to prevent the next transformation from happening, the salt did interfere with the purification process given that the crude material was directly chromatographed when no more ester intermediate could be detected. The large excess of benzylamine was also problematic as it often co-eluted with the desired product. Finally, when applied on large scale, the reaction time for the complete formation of the desired product was unpractically lengthy, sometimes taking weeks. In an attempt to avoid some of these difficulties a third approach was investigated. Highly reactive bromoacetyl bromide (**239**) was employed to form the desired benzyl bromoacetamide at low temperature. Second bromine substitution occurred overnight to yield **237** in twelve hours (Scheme 3.5).[154]



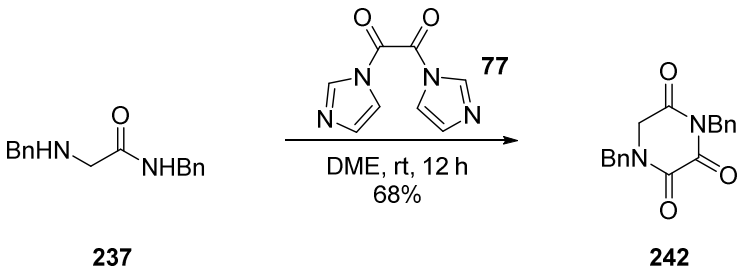
Scheme 3.5 Established method to access dibenzyl amino amide in gram scale

One equivalent of excess amine for each substitution was necessary to neutralise the hydrogen bromide generated in the course of the reaction. In fact, the corresponding salt was precipitated out of the reaction and successfully removed by an aqueous extraction. These reaction conditions enabled us to overcome all difficulties previously encountered: no large excess of amine was needed in the reaction to reach completion, the bromide salt was no longer interfering with the purification and the reaction time was short and reproducible. However, these two steps in a one-pot sequence became inefficient when using other primary amines, such as *para*-methoxy benzyl amine, as different molecular aggregates could be identified from the reaction mixture over a comparable reaction time (Scheme 3.6).



Scheme 3.6 Side product present in PMB amino amide formation

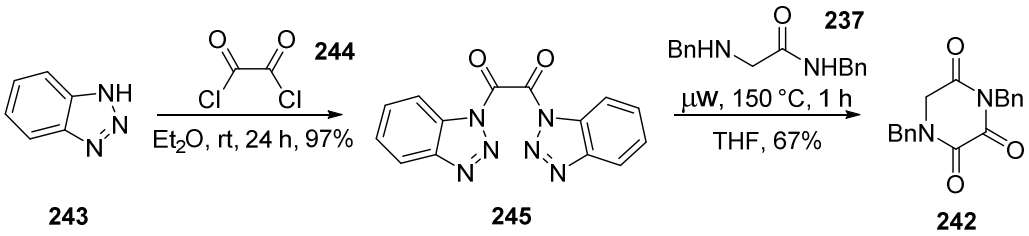
In light of this result, this option was no longer pursued under the present project. With a robust reaction to provide high quantities of aminoamide **237** the synthesis was taken forward to the cyclisation step. The first reaction conditions tried were those published by Overman and co-workers using 1,1'-oxalyldiimidazole.[68a] In this case, reaction of **237** in DME afforded the desired cyclic adduct in 68% (Scheme 3.7).



237 **242**

Scheme 3.7 TKP formation using oxalyl diimidazole

Although the yield of **242** was not outstanding, it was comparable with the results Overman and co-workers observed for the formation of their TKP in solution. Despite being a reliable, robust route to access the TKP scaffold, it was considered that new conditions for this last step needed to be found due to the high cost of the commercial oxalyl reagent. Gram quantities of the desired TKP had to be readily available, and so affordable oxalyl cyclising surrogates were screened. 1,1'-Oxalyldiimidazole synthesis was attempted, using oxalyl chloride, DIPEA and imidazole in various solvents only to see poor conversion into the TKP system, with a maximum yield of 10-15%, upon *in-situ* reaction with aminoamide **237**.[155] Oxalyl 1,1'-dibenzotriazole, developed by Katritsky, was employed next.[156] Originally used for the formation of substituted oxamides using secondary amines, its synthesis was easily accomplished but, treatment of **237** only afforded little amounts of the desired product. It was subsequently found that this was directly linked to the inherent lower reactivity of oxalyl 1,1'-dibenzotriazole compared to the corresponding diimidazole. However, this issue could be easily overcome by subjecting the reaction to harsher conditions, *i.e.* THF at 150 ºC in a microwave reactor, to give comparable yields to the previously developed method (Scheme 3.8).

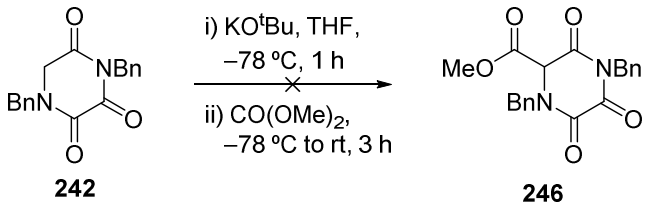


Scheme 3.8 Developed TKP formation using oxalyl dibenzotriazole

At last, an optimised, reliable sequence that was suitable for producing gram quantities of the desired product quickly and in an affordable manner was achieved. This method enable the production of TKP **242** in up to 10 gram batches.

3.2.1. Synthesis of 6-Acyl Triketopiperazines

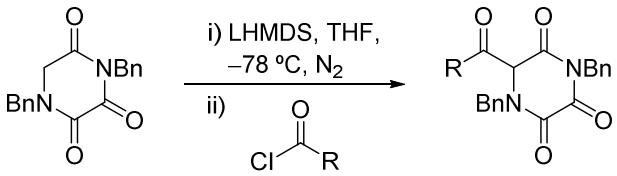
Having established a route to access the TKP core **242**, the project could be continued as outlined in the plan. Introduction of an acyl group was considered essential for the key Michael reaction to be successful. We wished to build several examples of acylated TKPs suitable for undergoing the asymmetric 1,4-addition. Olenyuk's conditions for the acylation of *N*,*N*'-alkyl DKPs were screened first on the TKP system but, unfortunately, no product was recovered from the reaction crude (Scheme 3.9).



Scheme 3.9 First acylation attempt on TKP **242**

The formed enolate was hypothesised to be incompatible with the acylation with dimethyl carbonate as the reaction mixture warmed up to room temperature, and a complex mixture of products was formed that could not be separated or identified.

As explored with the acyl protected DKPs, more reactive electrophiles in combination with LHMDS and lower temperatures were subsequently tried. Several acyl chloride reagents were tested to form the desired TKP derivative (Table 3.1).



242 **246-248**

Entry	R	Eq of ClCOR	Yield (%)
246	OMe	3	23
247	Ph	3	56
248	Me	5	-

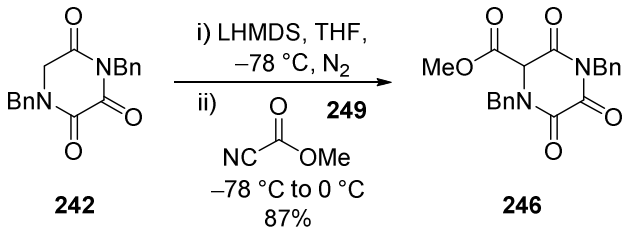
Table 3.1 Acylation results LHMDS and acyl chlorides

Reactions were somewhat sluggish and the final product was isolated in an acceptable yield only with benzoyl chloride (**247**) as the electrophile. In the case of methyl chloroformate, the reaction afforded a mixture of mono and di acylated TKPs together with some *O*-acylated adduct. Separation of this crude mixture was extremely difficult and only a small amount of the desired material (**246**) was successfully recovered. Acetyl chloride mainly furnished the *O*-acylated adduct and no trace of the desired product was observed. It was therefore concluded that this approach was unreliable for the formation of acylated TKPs.

Further exploration of different options was necessary. From our point of view, the perfect acylating agent would have an intermediate electrophilicity between an acyl chloride and an

ester or a carbonate. Thus, we turned our attention to the work developed by Mander and co-workers. Their team synthesised a different kind of electrophile where the leaving group was a cyanide anion instead of the chloride.[157] Their reports included reactions where this reagent was able to furnish the desired acylated products under soft conditions. It was also worth noting that full transformation was accomplished by letting the crude mixture warm up from −78 °C to around 0 °C, thus hinting that the actual transformation needed a higher temperature for completion compared to the acyl chlorides.

Treatment of TKP **242** with Mander's reagent **249** under the previously outlined conditions led to the formation of the desired derivative as the only product in very good yields (Scheme 3.10).

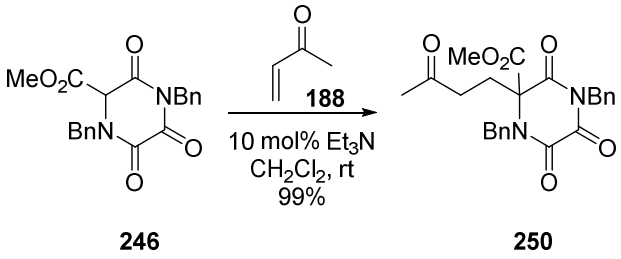


Scheme 3.10 Acylation of TKP **242** using Mander's reagent

Not only could this compound be made using this approach but different acyl groups could be theoretically accessed should the appropriate reagent be in hand. Under these conditions, the proposed Michael donor was finally accessed in a robust and short route with a good overall yield of 57% over three steps linearly from commercially available materials.

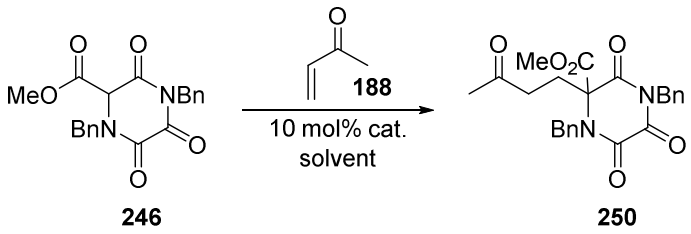
3.3. Enantioselective Michael Reactions on 2,3,5-Triketopiperazines derivatives

With a reliable access to acyl TKPs, the asymmetric organocatalysed 1,4-addition to different Michael acceptors was explored. Firstly it was necessary to check whether the reaction would take place with the TKP substrates. Upon subjecting substrate **246** and vinyl ketone **188** to substoichiometric amounts of triethylamine, in dichloromethane, we were delighted to observe full conversion to Michael adduct **250** in less than one hour at room temperature (Scheme 3.11).



Scheme 3.11 First attempt of a Michael addition using TKPs

The optimisation of the reaction conditions for the asymmetric version of this transformation was targeted next. Some of the cinchona alkaloid bases (Figure 2.1,*vide supra*) in hand were employed in this optimisation study using different solvents and varying temperature with methyl vinyl ketone as the Michael acceptor in all cases. A summary of these results is given in Table 3.1.



Entry	Catalyst	Temp. (°C)	Solvent	time[a]	Yield (%)[b]	*er* (%)[c]
1	**142**	r.t.	CH_2Cl_2	20	94	82:18
2	**148**	r.t.	CH_2Cl_2	20	91	25:75[d]
3	**210**	r.t.	CH_2Cl_2	20	98	31:69[d]
4	**201**	r.t.	CH_2Cl_2	20	99	96:4
5	**201**	r.t.	THF	20	98	95:5
6	**201**	r.t.	toluene	20	98	94:6
7	**201**	r.t.	MeCN	20	99	94:6
8	**201**	0	CH_2Cl_2	60	99	98:2
9	**201**	0	CH_2Cl_2	120	91[e]	97:3
10	**204**	0	CH_2Cl_2	20	82	2:98[d]

[a] Minutes. [b] Isolated yield after chromatography. [c] Determined by HPLC analysis. [d] Enantiomeric product with respect to entry 1. [e] Reaction conducted using 1 mol% catalyst.

Table 3.1 Reaction optimisation

The naturally occurring members of the cinchona alkaloid family, quinine **148** and quinidine **142** furnished the desired product in good chemical yield but, not unexpectedly, the *er* was far from optimal (entry 1 and 2). As expected, this *pseudo*-enantiomeric pair of catalysts afforded enantio-complimentary results of TKP **250**. Surprisingly, although the thiourea derivative **210** furnished the Michael adduct **250** in very good yield, the *er* was disappointing. This is in contrast to the literature examples previously shown, where this catalyst was found to be the most efficient in a wide range of transformations (entry 3). The optimal catalyst for this transformation was found to be benzyl derivative **201** (entry 4). Further conditions screening suggested that dichloromethane was the best solvent in which to run the reaction. Lower temperatures afforded the desired compound in comparable yields and higher *er*. Under these conditions, the catalyst loading could be dropped to 1 mol% without any downside apart from the extended reaction time (entry 9). As expected, benzyl derived quinine derivative **204** yielded the opposite enantiomer of the TKP Michael adduct with equivalent *er* (entry 10).

The scope of the reaction was subsequently explored using differently substituted enones under the previously optimised conditions and results are depicted in Figure 3.1. Catalyst loading was maintained at 10 mol% and the temperature had to be even lower (−20 °C) to guarantee consistently high levels of induced asymmetry across the full set of examples with corresponding longer reaction times.

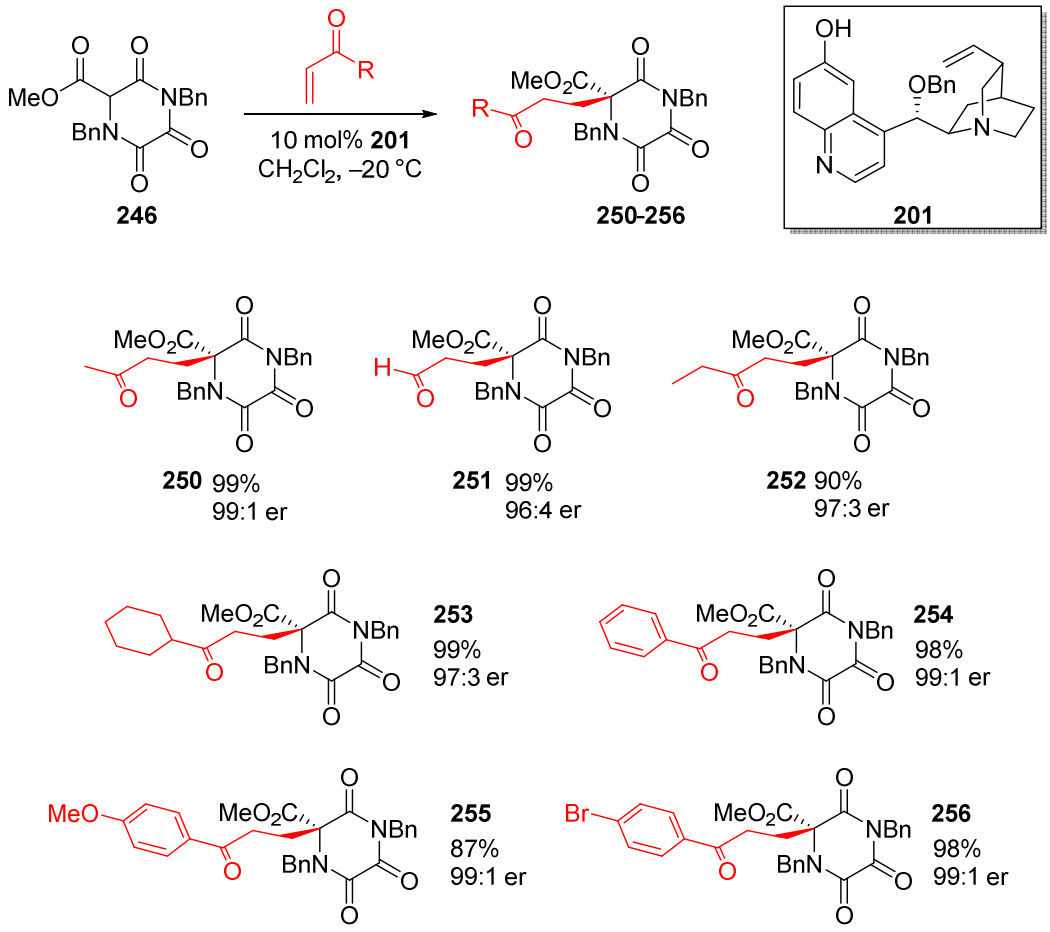
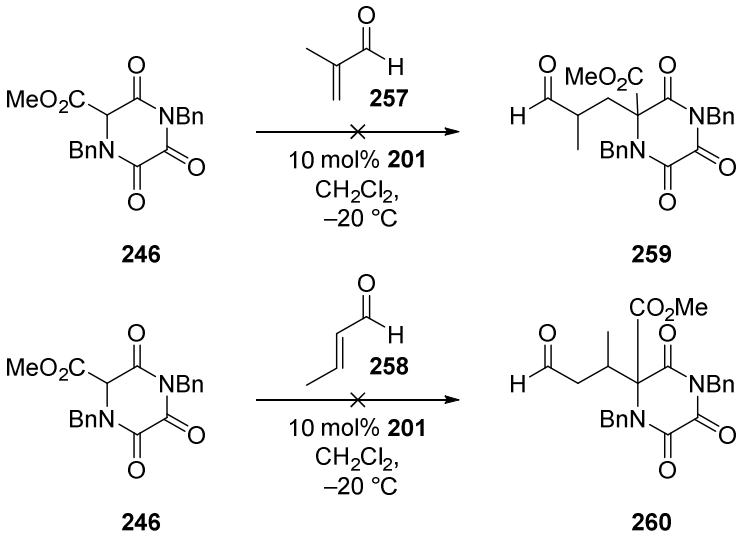


Figure 3.1 Scope of the asymmetric Michael reaction

Very good results, both in terms of yields and levels of induced asymmetry, were observed in all examples. A variety of alkyl or aryl groups, either with electron withdrawing or electron donating properties were placed on the enone. The absolute stereochemistry of all the examples was inferred from the X-ray crystallographic data of a compound appearing later in

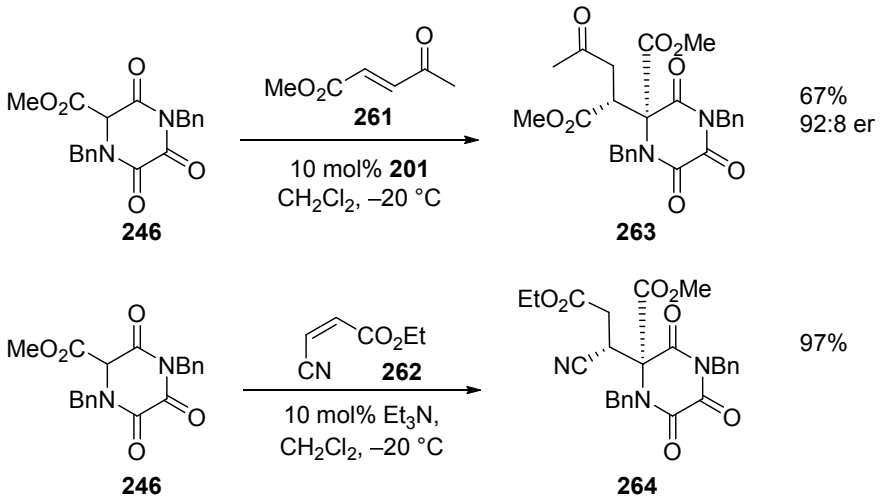
this section. The possibility of incorporating different substitution patterns on the Michael acceptor, either at the α- or β-position on the conjugated alkene was explored next. However, no reaction took place when using the methyl substituted versions of acrolein, methacrolein **257** and crotonaldehyde **258**, under the optimised conditions, and only TKP **246** was recovered from the crude mixture (Scheme 3.12).



Scheme 3.12 Sterically hindered electrophiles showed an absence of reactivity

The increased steric was probably the reason behind this lack of reactivity and it was concluded that when using enones, no alkyl substituent on the alkene was tolerated. However, Michael additions with enones bearing electron withdrawing groups in β-position, which should enhance the electrophilicity of the alkene, might be reactive under the present reaction conditions. Upon subjecting TKP **246** to the optimised conditions in the presence methyl *E*-4-oxo-2-pentanoate **261**, the reaction afforded the desired Michael adduct **263**. Similarly, reacting the same starting material with the doubly activated ethyl *Z*-(β-cyano)acrylate **262** also furnished the desired product **264**, albeit only the racemic product could be formed.

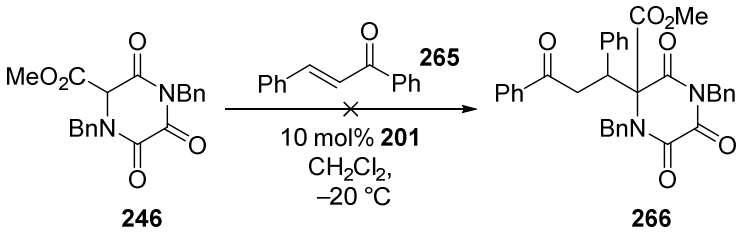
Perhaps, due to the low basicity of the chiral catalyst, compared to trimethylamine, no reactivity was observed in this case (Scheme 3.13).



Scheme 3.13 Doubly activated electrophiles used in Michael additions

Interestingly, only one diastereoisomer was observed from the reaction mixture (see crystal structures data of compounds **263** and **264** in Appendix 2). While it was expected that **261** would react as an activated enone, rather than the opposite way, as an α,β-unsaturated ester, it was pleasing to observe that the cyanoester only formed product **264** resulting from the reaction of the activated unsaturated ester.

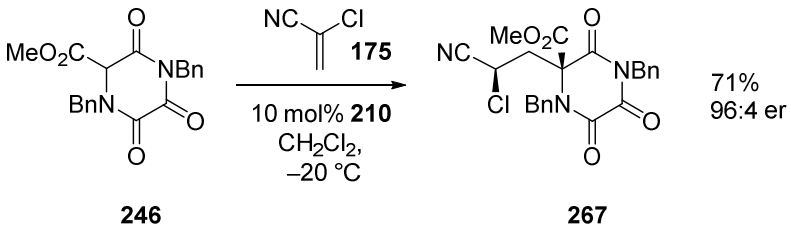
Other types of activation of the β-position of enones were explored next, with weaker electron withdrawing substituents. Chalcone was the selected electrophile as it is commercially available. Disappointingly, no desired product was observed upon reaction of TKP **246** with chalcone **265** under the optimised conditions (Scheme 3.14).



Scheme 3.14 Chalcone Michael addition with TKP **246**

As this reagent was only slightly electronically enhanced, it is probable that the steric hindrance was overriding this factor and impeding the transformation from occurring.

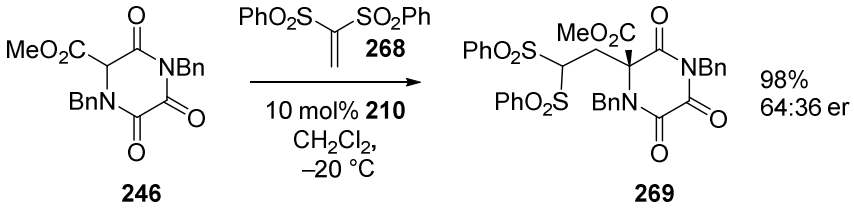
In our desire to increase the number of examples where this catalytic approach could be applied, other Michael acceptors that had been used in previous literature examples were sought. Deng and co-workers reported an organocatalysed reaction using α-chloroacrylonitrile.[129d] Analogously, TKP **246** was treated with this Michael acceptor under the optimised reaction conditions (Scheme 3.15). Interestingly, thiourea catalyst **210** was found optimal for this particular transformation.



Scheme 3.15 Activated acrylonitrile Michael addition

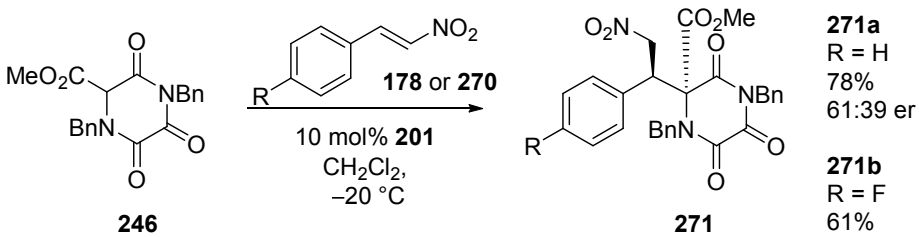
The electron withdrawing properties of the chorine in the α-position of the Michael acceptor are probably contributing to increase the reactivity of **175** equivalent to a ketone adduct. It is also small enough not to hinder the reaction as in the case of methacrolein **257**. Product **267** was afforded in good yield and *er* an only one diastereoisomer was observed (see crystal structures data for compound **267** in Appendix 2). The same group published another paper

employing vinyl sulfones as the Michael acceptor.[158] Likewise, this electrophile could also be applied to the TKP system (Scheme 3.16).



Scheme 3.16 Vinyl disulfone Michael addition

In this case, disulfone TKP **269** was produced in good yield but with poor selectivity. Therefore, although **269** shows the expected stereochemistry from this thiourea **210** organocatalysed reaction, in the absence of the absolute configuration information, we are not completely certain of the predominant stereoisomer. This result suggested that further reaction optimisation was required for this Michael acceptor and reflects the chemical disparity between this α,β-unsaturated derivative and the enones. Nevertheless, showing such a broad reactivity was a great asset for this system to become more useful to the scientific community. Lastly, the widely used nitro olefins were tried on the TKP **246**. Typically nitro styrenes are the most commonly used systems and so two examples to test on the TKP were synthesised. Michael reaction with the TKP system gave the desired products as depicted in Scheme 3.17.



Scheme 3.17 Nitro olefins Michael addition

Both reactions gave the desired products in good yield and only one diastereoisomer could be observed from the crude reaction mixture (although the relative stereochemistry is already known from an X-ray crystal structure data, the sample has not been fully refined to date). However, the present conditions did not induce great levels of asymmetry (61:39 *er*) and the shown isomer in Scheme 3.17 reflects only the expected product in accordance with the relative configuration information obtained in the X-ray and the employed catalyst. Expecting a similar *er* value for the *para*-fluoro nitro TKP derivative, the HPLC value was not determined. Despite showing great potential, thorough optimisation studies will have to be carried out, screening different catalysts, to furnish products with greater levels of enantioselectivity. Although further Michael acceptors were tried for these systems, they will be covered in-depth in the next chapter due to key differences in the reaction outcome.

To gain more insight on the catalyst-substrate interaction before the Michael addition, various NMR studies were performed. Stoichiometric amounts of catalyst **201** and TKP **246** were mixed and their proton NMR spectra recorded and compared against those of pure compounds in deuterated acetonitrile (Figure 3.2). No substantial variations were observed in the mixed spectra. The presence of the α-proton in the lower NMR, as well as the rest of the signals corresponding to the TKP, in the same position suggests that the enolate form of the TKP was not present.

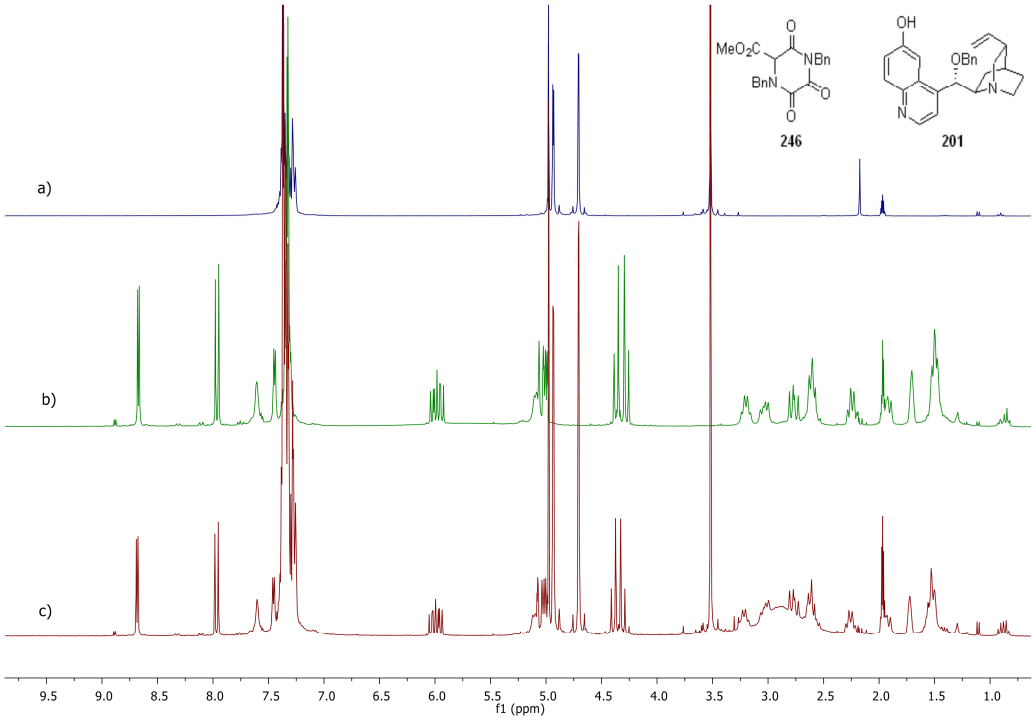


Figure 3.2 ^{1}H NMR spectra of TKP **246** (a), catalyst **201** (b) and mixture (c) in CD_3CN

However, slight variations between the pure catalysts and the one in the mixture were present. Although no direct conclusion can be made, these features might be related to the presence of H-bonds between the TKP and the catalyst. The slight shift (Δ = 0.02 ppm) observed in the signals corresponding to the AB system of the benzyl methylene, as in the left expansion of Figure 3.3, is a clear example. The significant broadening in the NMR region that belongs to the protons surrounding the basic nitrogen (3.3 – 2.5 ppm), in the right expansion, may be related with the likely H-bond created on that centre.

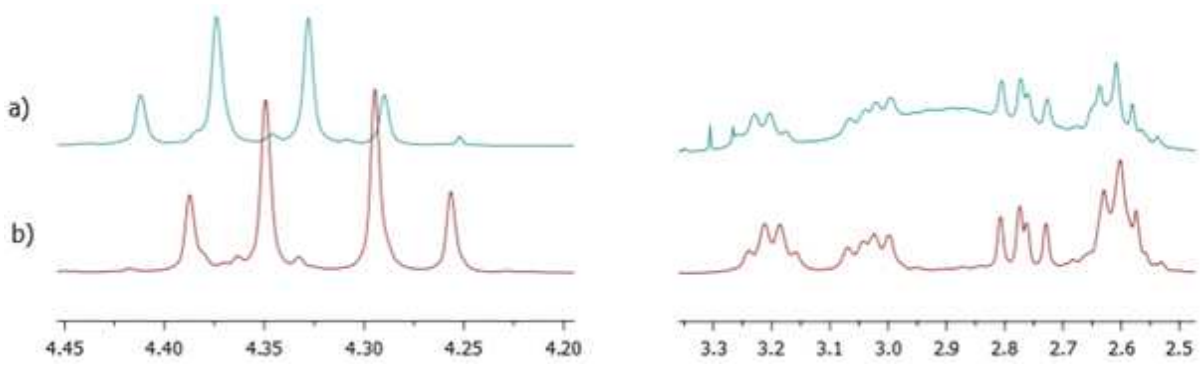


Figure 3.3 Expansions comparing ^{1}H NMR spectra of **201** (a) and mixture with TKP **246** (a)

In order to identify the nature of the enolate by NMR, stoichiometric amounts of TKP **246** and DBU were used in an analogous study (Figure 3.4).

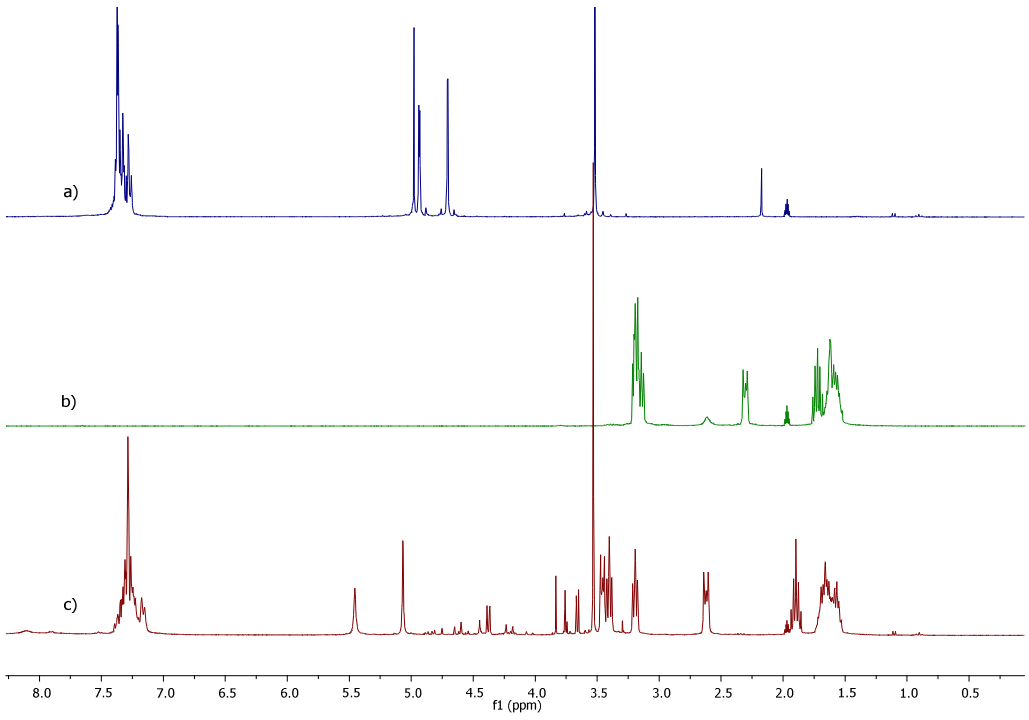


Figure 3.4 ^{1}H NMR spectra of TKP **246** (a), DBU (b) and mixture (c) in CD_3CN

DBU, which is considerably more basic than any cinchona alkaloid catalyst (pK_b of DBU is 12.5 in DMSO while quinuclidine is 9.5[159]) was capable of fully deprotonating **246**. In the left expansion of Figure 3.5 it could be seen how the two benzylic AB systems became broad singlets and were strongly shifted downfield, from 4.93 ppm to 5.46 ppm and 4.70 ppm to 5.06 ppm respectively. Simultaneously, the singlet corresponding to the α-proton disappeared in the presence of DBU. These changes were in accordance with the presence of the enolate form. DBU signals were also drastically changed when mixed with TKP **246**, as seen in the right expansion, indicative of the transformation of the structure upon protonation.[160]

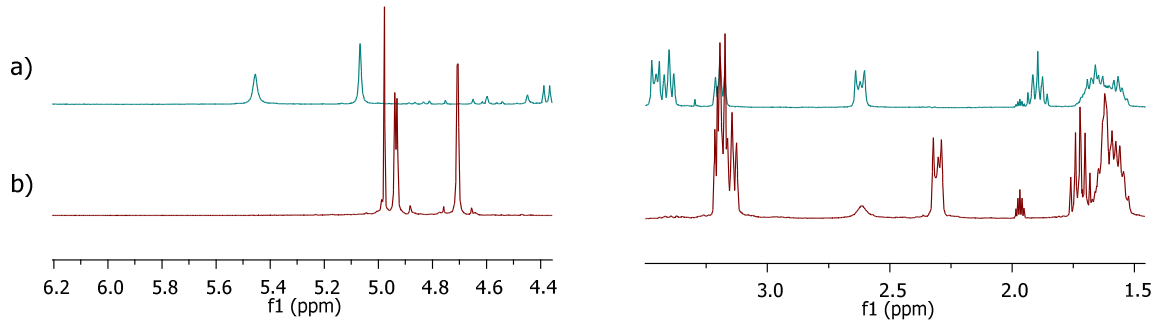


Figure 3.5 Expansions comparing ^{1}H NMR spectra of pure samples signals (b) and mixture (a) of TKP **246** and DBU

In our desire to understand the different reactivity of TKP **246** in comparison with the less acidic parent TKP, the DBU study was extended to compound **242**. In an analogous manner, the NMR spectra of pure TKP, DBU and an equimolar mixture of both were obtained and compared (Figure 3.6). Interestingly, noticeable differences could be observed in contrast with the experiment with carboxymethyl TKP **246**. First, although the integrals for the three methylene positions remain the same, the signal corresponding to the α-position (4.27 ppm) showed significant broadening, indicative of an interaction with the base.

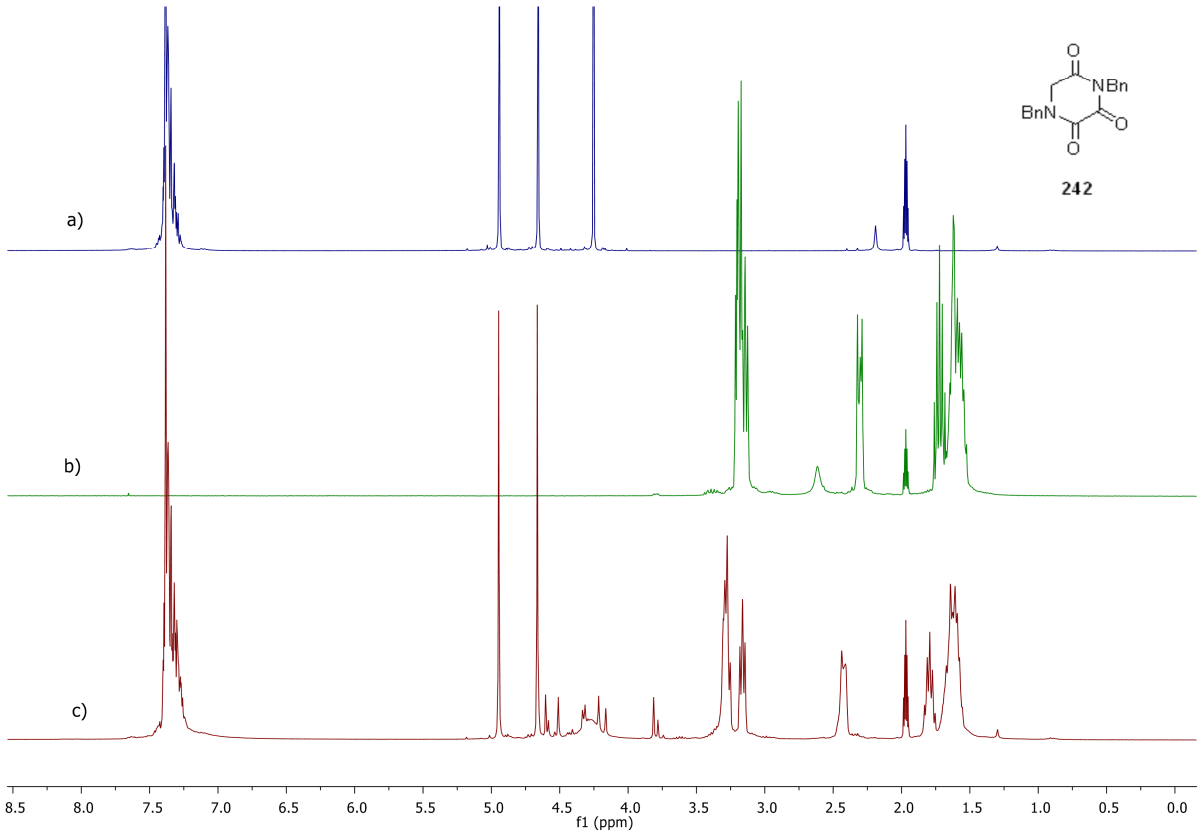


Figure 3.6 ^{1}H NMR spectra of TKP **242** (a), DBU (b) and mixture (c) in CD_3CN

Likewise, the DBU signals in the mixture, albeit generally shifted compared to the signals of pure DBU, were at different ppm values from the ones observed in the previous experiment with TKP **246** (Figure 3.7).

The combination of these two features might indicate that DBU pK_b might not be strong enough, or the α-protons not acidic enough, to fully form the enolate of TKP **242**. Hence, protonated DBU was not observed as in Figure 3.4, and only the interacting acid-base complex is present in the mixed spectrum. Signal shifts, in the case of DBU, and broadening, in the parent TKP, can be associated with the H-bond network that was probably established in the crude mixture.[143b]

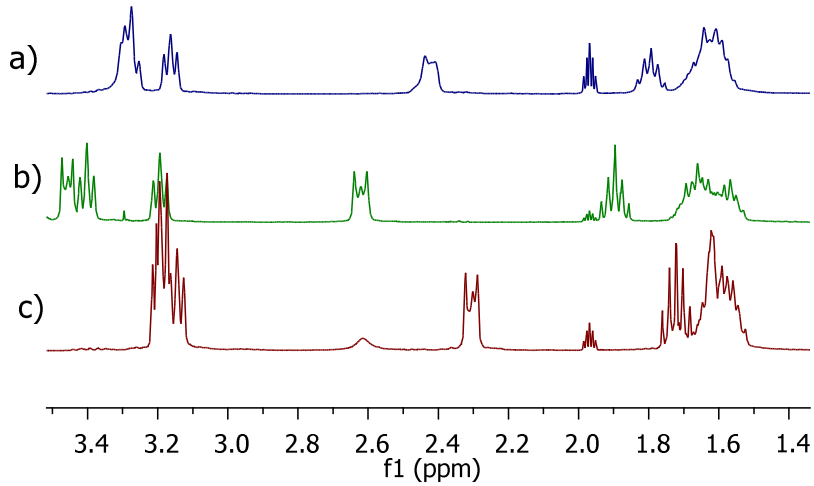
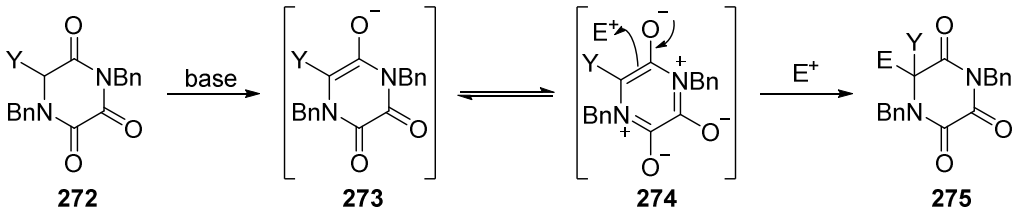


Figure 3.7 Expansion comparing ^{1}H NMR spectra of pure DBU (c), in combination with TKP **246** (b) and **242** (a)

In light of these experiments, it became evident that TKP **242** might display interesting reactivity on its own as a nucleophile due to the unusually low pK_a. Overall, the reactivity and good levels of stereocontrol achieved with the carboxymethyl TKP **246** was remarkable but somehow predictable as it was essentially a 1,3-dicarbonyl system embedded in a cyclic scaffold, similar in pK_a to the system reported in the literature. However, we were curious to explore the limits of the Michael addition's reactivity in the context of the less activated TKP **242**.

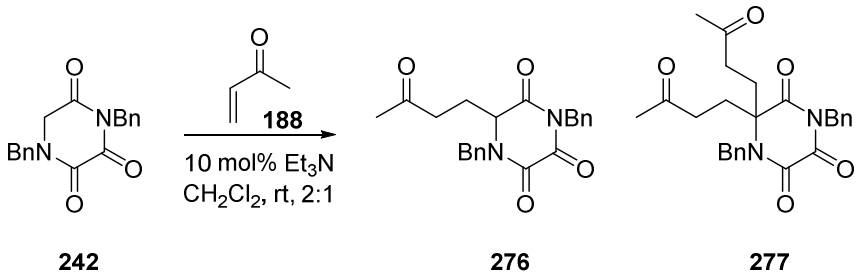
It was clear that TKP system **246**, in sharp contrast with the corresponding DKPs, reacted under literature conditions for the organocatalysed Michael addition very rapidly. Although no direct measure of TKP **246** pK_a has been carried out, and only taking the chemical shift of the α-proton as an approximation of its acidity, this TKP system seemed to be considerably less acidic in comparison with the α-proton of acyl protected DKPs (5.94 ppm of DKP **229**

compared to 4.82 ppm of TKP **246** in chloroform). Although it may appear counterintuitive, this result implies that not only might the acidity of the system be playing a fundamental role in this transformation. It could be hypothesised that a TKP, bearing an extra sp^2 centre within the ring, could form a more stable aromatic intermediate **274**, in equilibrium with the reactive enolate **273**, which, overall, enhances its reactivity towards Michael acceptors (Scheme 3.18).[63b]



Scheme 3.18 Proposed reactive TKP intermediate

Should the proposed intermediate **274** be part of the reaction and bearing in mind the highly reactive system in hand, as shown by the NMR study of TKP **242** with DBU, it was hypothesised whether any extra activating group (Y) was necessary for the Michael addition to occur. TKP **242** might be reactive enough under the present optimised reaction conditions and so, in order to check this premise, it was subjected to the Michael addition reaction with trimethylamine at room temperature (Scheme 3.19).



Scheme 3.19 Initial Michael addition test on parent TKP

In the absence of literature references, the rapid consumption of the starting material to furnish an approximate 2:1 mixture of two products after one hour of reaction, resulting from the mono (**276**) and double Michael addition (**277**) to the parent TKP was surprising. As seen in the ^{1}H NMR spectrum of the reaction mixture in Figure 3.8, both products can be readily identified (see Chapter 5: Experimental Part for a detailed analysis of the mono addition compound).

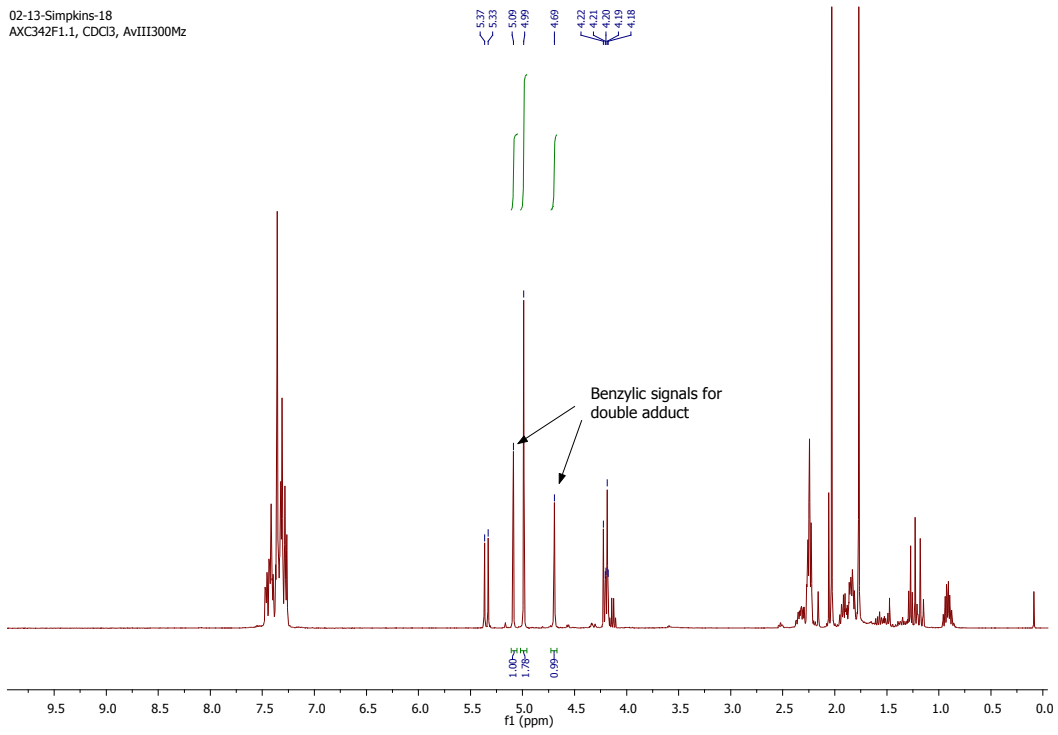
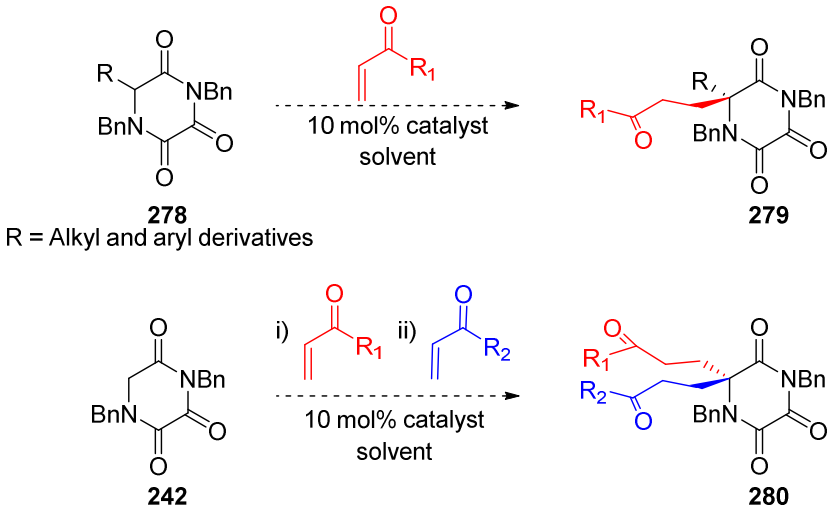


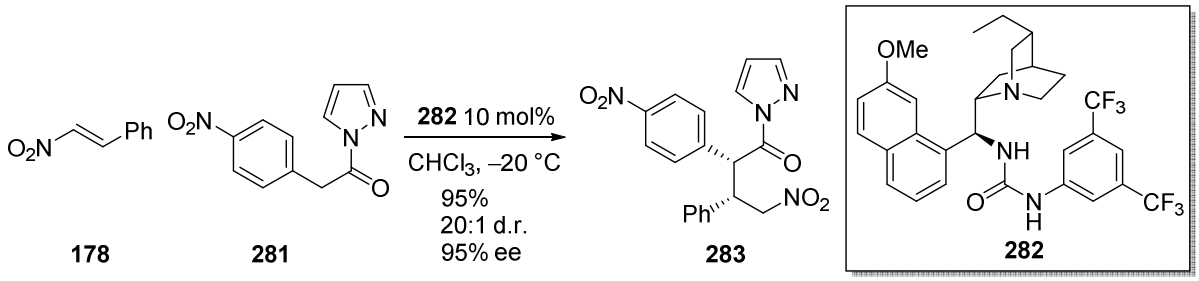
Figure 3.8 ^{1}H NMR spectra of the mixture of mono and double Michael adducts

Not only the activating group was unnecessary for the Michael addition to proceed but the double Michael product observed meant that even α-alkyl TKPs could undergo this reaction. Furthermore, by carefully controlling the stoichiometry and temperature, different tandem 1,4-additions could be sequenced to furnish double-Michael products where two different electrophiles were used (Scheme 3.20).



Scheme 3.20 Proposed reactivity of alkyl-TKP **278** and TKP **242**

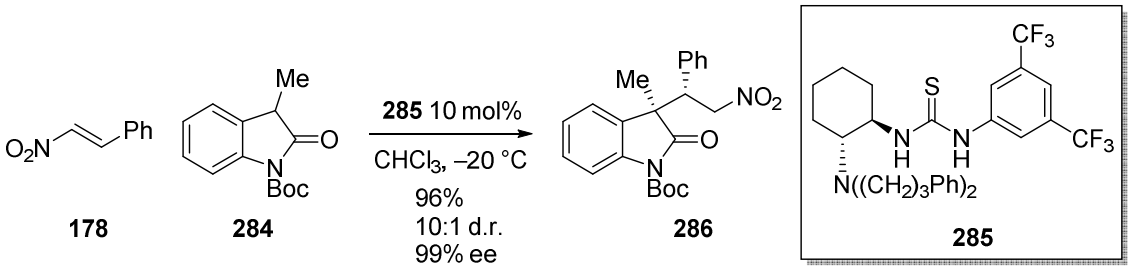
It is also worth noting that this reaction is one of the first examples of asymmetric organocatalysis using a purely mono-activated nucleophile. Only a handful of examples of this type have been described, for example Barbas and co-workers reported an organocatalytic Michael addition of nitro olefins to pyrazoleamide substrates using a urea-based catalyst **282** (Scheme 3.21).[161]



Scheme 3.21 Barbas mono-activated amide surrogate

Although this example constituted the first report on organocatalysis of mono-activated amides, this substrate could not be considered a standard amide. The *N*-pyrazole substituent was likely contributing to bring the pK_a of the α-proton lower than that of a normal amide.

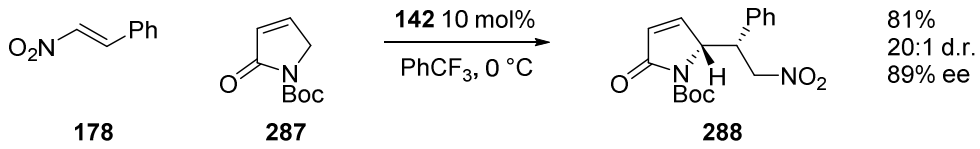
The authors commented on how the ester or the pyrrolidinyl amide showed a complete lack of reactivity under these conditions while the electron-rich pyrrolyl amide showed less enantioselectivity, underlining the importance of the more electron withdrawing characteristics of the pyrazole amide. In addition, the combination with an electron deficient aromatic ring makes this substrate more prone towards deprotonation by typical organocatalysts. Nevertheless, excellent results were obtained across all examples in the paper, reaching high levels of diastereo and enantioselectivity. Also noteworthy is the ability to furnish the desired product in very good *er*. Although the acidic hydrogens in the final product could have been problematic, no *er* erosion or byproducts were reported. The same group published another organocatalysed reaction involving nitro olefins and oxindoles using a newly synthesised thiourea-based catalyst **285** (Scheme 3.22).[162]



Scheme 3.22 Barbas monoactivated imide surrogate

An imide is the sole activating group in this case although reactivity of the system was probably enhanced by both the nature of benzylic position and the aromatic enolate. An alkyl group is tolerated in the α-position and did not seem to interfere with the reaction outcome. Hence, we were confident about the potential of the alkyl TKPs to become valuable substrates for the asymmetric organocatalytic approach. Different simple imides have also been reported in the literature to perform well under typical organocatalytic conditions. γ-Butyrolactam **287**,

in essence an imide surrogate, has also been employed in asymmetric vinylogous Michael additions (Scheme 3.23).[163]



Scheme 3.23 *γ*-Imide Michael addition

N-Boc protection proved of utmost importance to achieve the vinylogous reaction, providing the appropriate imide functionality within the system. Enolate attack has also been explored on this same system, although an activated carbonyl was the electrophile in that case.[164]

With this limited number of precedents the same reaction previously explored with the activated TKP was investigated with the parent compound under analogous conditions (Figure 3.9).

The scope of the reaction was highly reproducible, and good yields were obtained across all substrates. However, enantiomeric excesses were somewhat inconsistent. This was probably due to the presence of a highly acidic proton in the final products which, as seen in the initial experiment, was prone to form the double-Michael adduct. In fact, *er* erosion could be witnessed when **290**, with the enantiomeric ratio of 96:4 already determined, was re-exposed to the same reaction conditions without the electrophile in the mixture. After two hours, the isolated material *er* had been eroded to 89:11. So in this particular transformation, reaction time and low temperature were crucial to avoid *er* erosion and further addition of another electrophile to the TKP core.

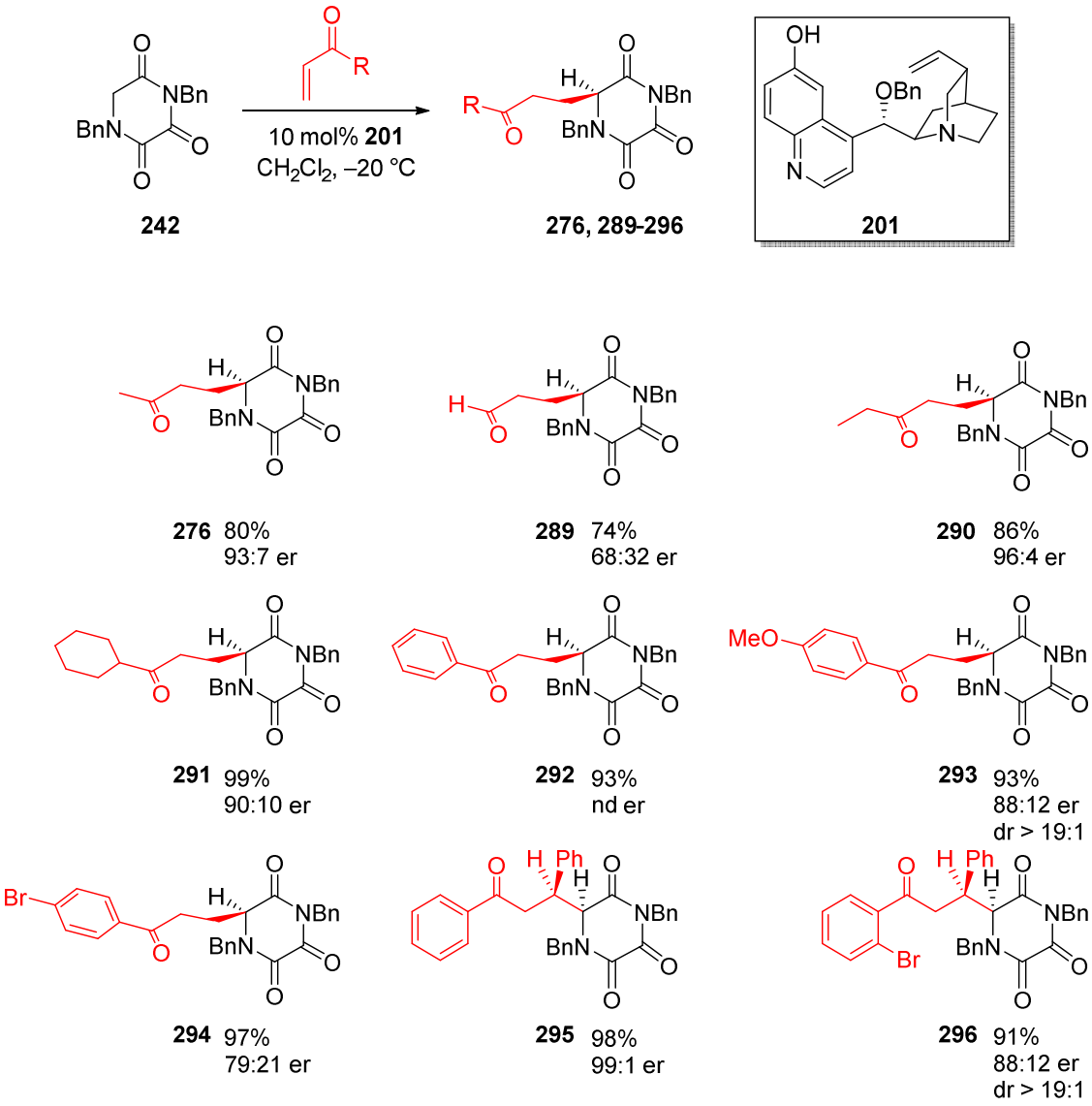


Figure 3.9 Scope of mono-activated Michael addition

In the present study, chalcones were very well tolerated by the nucleophilic substrate, presumably due to the absence of the extra hindrance at the reactive centre. Longer reaction times compared to the non-substituted enones, were necessary, typically five to seven hours. However, it was noteworthy that no overreaction was ever observed in these cases, very likely due to the extra bulkiness around the reactive centre. Products in excellent yields and very good levels of enantioselectivity were afforded in both cases, and only a single diastereoisomer could be detected in the crude reaction mixture.

X-Ray quality crystals were grown from TKP adducts **295** and **296** to help us determine the absolute and relative stereochemistry of the catalysis products. Compound **296** (Flack parameter: -0.027(3)) is depicted in Figure 3.10 and **295** can be found in Appendix 2.

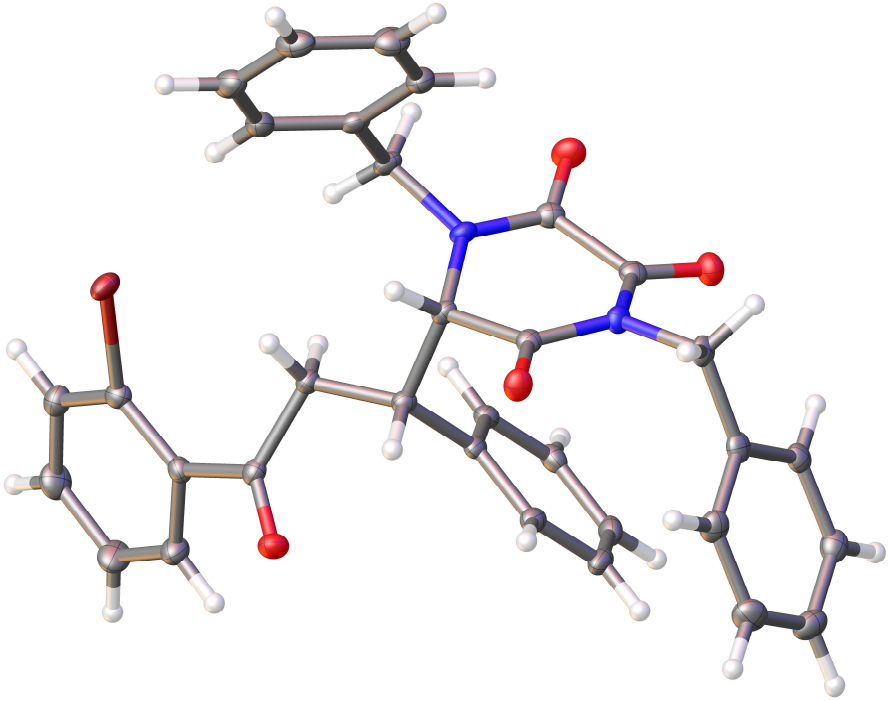


Figure 3.10 TKP **296** crystal structure with 50% of ellipsoid probability

As observed in the X-ray crystal structure, both hydrogens at the reactive centre of the TKP and *β*-position are staggered along the newly created carbon-carbon bond, while the phenyl substituent at the *β*-position and the TKP ring seem to arrange themselves in a gauche conformation. This feature enabled the larger bromophenyl ketone group and the heterocycle adopt an antiperiplanar disposition. This crystal structure helped to propose and rationalise an interaction model that explained the observed stereochemistry. Basing this proposal on Deng's previous reports, a model where the three components of the reaction were arranged was suggested as depicted in Figure 3.11.

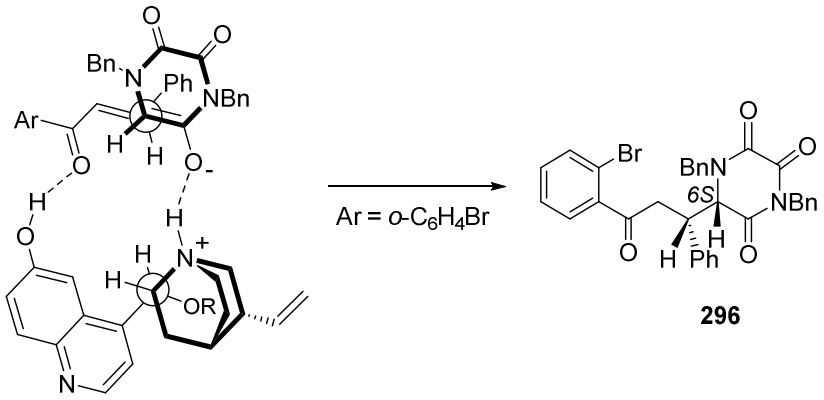


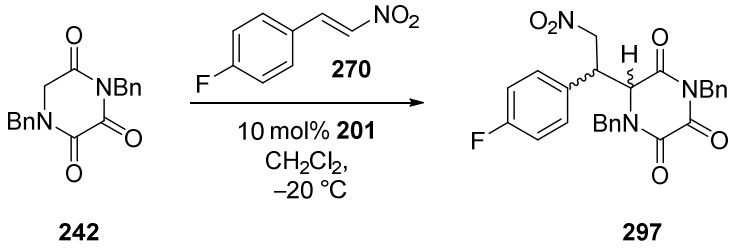
Figure 3.11 Proposed interactions in the transition state of the Michael addition

In this model, the nucleophile and electrophile organised themselves spatially in the required manner for the newly formed carbon-carbon bond to reflect that specific disposition of the substituents in the final product. Although the *endo* arrangement of the *β*-phenyl group from the Michael acceptor with respect to the TKP cycle may appear sterically disfavoured, this stacked conformation is plausible owing to the all-sp^2 planar nature of both rings and explains the disposition observed in the crystal structure. Taking this model into account, the stereochemistry for all previous asymmetric 1,4-additions was confidently expected to remain consistent at the *α*-position of the TKP ring with **296** X-ray.

In an attempt to extend the scope of the reaction, standard alkyl group in either the *α* or *β* position, such as those in methacrolein and crotonaldehyde, on the electrophile were found unable of delivering the desired product under standard conditions. Again, the lack of any form of activation combined with the increase hindrance around the reactive centre was considered responsible for the absence of reactivity.

Conversely, employing activated Michael acceptors, with electron withdrawing groups in either of the two positions of the alkene, such as **261** or **262** dicarbonyl derivatives, *α*-

chloroacrylonitrile or nitro olefins **178** and **270**, as used in the case of TKP **242**, did not furnished a clean product. Instead, the high reactivity of these substrates was hypothesised to be responsible of yielding a mixture of diastereoisomers of both the mono and double Michael products. The separation of this mixture proved daunting and these reactions were concluded to be impractical from a synthetic point of view. However, exclusive mono-substituted TKP, albeit in a complex mixture of inseparable diastereoisomers was isolated when the reaction was interrupted after only 20 minutes of reaction between the parent TKP and nitro olefin **270**, as it was inferred from spectroscopic data analysis (Scheme 3.24).

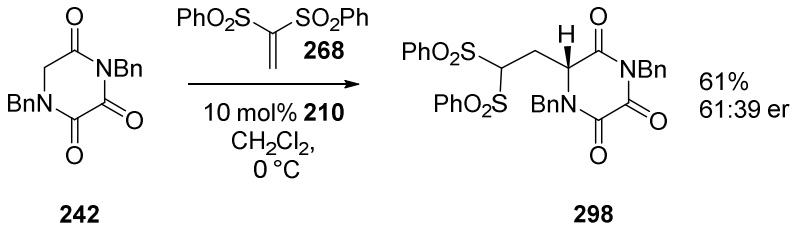


Scheme 3.24 Nitroolefins Michael addition to TKP **242**

In light of these results, the absence of the ester substituent on the TKP was not only reducing the theoretical acidity of the α-proton and, evidently, opening up a second position for further nucleophilic attacks should the conditions be optimal, but it also appears to have a clear impact on the diastereoselectivity, especially when highly reactive electrophiles were employed. When the carboxymethyl TKP **246** was employed, the nucleophilic TKP resembled a 1,3-dicarbonyl moiety. It is conceivable that a more tightly locked catalyst arrangement during the catalyst arrangement, with a higher number of H-bonds, could be responsible for the increased diastereocontrol and faster reaction rate observed with this TKP.

It is also worth mentioning how different reactivity was observed when two very similar electrophiles, such as nitroolefin **178** and chalcone **265** were employed. While the β substitution is the same for both, they differ in the nature of the electron withdrawing carbonyl or nitro group. The nitro group is known to be more electron withdrawing, resulting in a more reactive α,β-unsaturated derivative. However, both Michael acceptors played different, yet revealing, roles in the scope when used in this reaction. Whilst the nitro olefin was reactive enough when TKP **246** was screened, the high reactivity was presumably the origin of the lack of selectivity in the scope of TKP **242**. Conversely, chalcone's lower reactivity did not meet the necessary reactivity requirements in the TKP **246** scope when combined with the high steric clash between the aromatic ring and the methyl ester at the nucleophilic reactive centre. However, in the absence of the ester group in TKP **242**, this Michael acceptor had the perfect reactivity balance to furnish a diastereoselective product of the mono-Michael adduct.

Further electrophiles, such as 1,1'-vinyldisulfone **268**, were employed in this scope. As expected from its lower reactivity compared with other α-activated Michael acceptors and the absence of any diastereoselective challenge, the mono Michael product **298** was the only isolated product from the reaction mixture (Scheme 3.25).

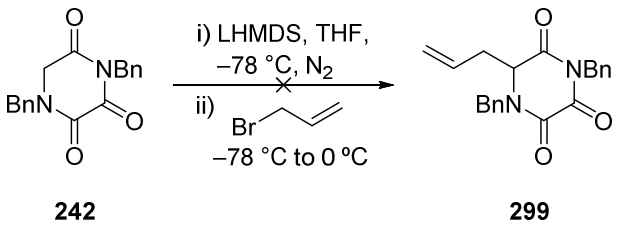


Scheme 3.25 Vinyl disulfone Michael addition

The rather low yield could be associated with the poor solubility of formed TKP **298** and its immediate crystallisation out of the reaction mixture, which could also be linked with the absence of any double Michael product. However, the catalyst did not induce great levels of stereocontrol in this example and TKP **298** represents the expected isomer but we are not absolutely certain about it.

3.4. Synthesis of 6-Alkyl Triketopiperazines

Having established the limits of the asymmetric Michael transformations on the activated TKP **246** and the inactivated parent **242**, we next sought to explore the possibility of effecting these reactions on α-alkylated TKPs. Bearing in mind the possible difficulties, in particular the likely steric clash between the alkyl chain and the electrophile, combined with the absence of further activation and, thus, probable decrease of reactivity, we set about optimising a method that would allow us to introduce different alkyl chains effectively. The first approach consisted of employing LHMDS and allyl bromide (Scheme 3.26)

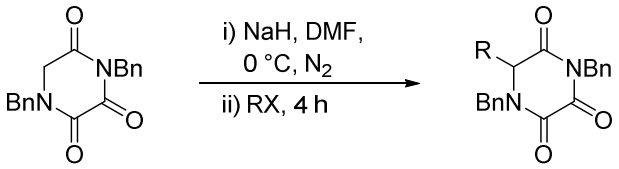


242 **299**

Scheme 3.26 TKP alkylation using lithium bases

Unfortunately, the desired product was never observed, most likely due to the incompatibility of the highly reactive lithium enolate in the temperature ranges where alkyl halides are reactive enough. More typical alkylation conditions using sodium hydride and higher

temperatures were subsequently envisaged. Initially, THF at 0 °C was tried, but optimal yields were achieved using DMF as solvent (Table 3.3)



242 **299-302**

Entry	RX	Yield (%)
299	AllylBr	82
300	BnBr	83
301	^{n}PrI	81
302	MeI	80[a]

[a] Combined yield for the mono and dimethylated TKP

Table 3.3 Alkyl TKP formation

The temperature had to be carefully controlled, especially when smaller electrophiles were employed so as to avoid double alkylation. However, when the methyl iodide was employed, no experimental variations avoided the formation of considerable amounts of **302** together with dialkylated product, in an approximate ratio of 2:1. Apart from this case, three alkylated TKPs were successfully synthesised in very good yields as shown in the previous table.

The organocatalysed asymmetric Michael addition was subsequently tried employing the optimised conditions previously used. Since these substrates could not undergo double addition, all experiments were conducted at 0 °C to accelerate the reaction rate. In spite of this, sluggish transformations with considerably extended reaction times, between five to seven days, were observed across all examples, depending on the nature of the electrophile (Figure 3.12).

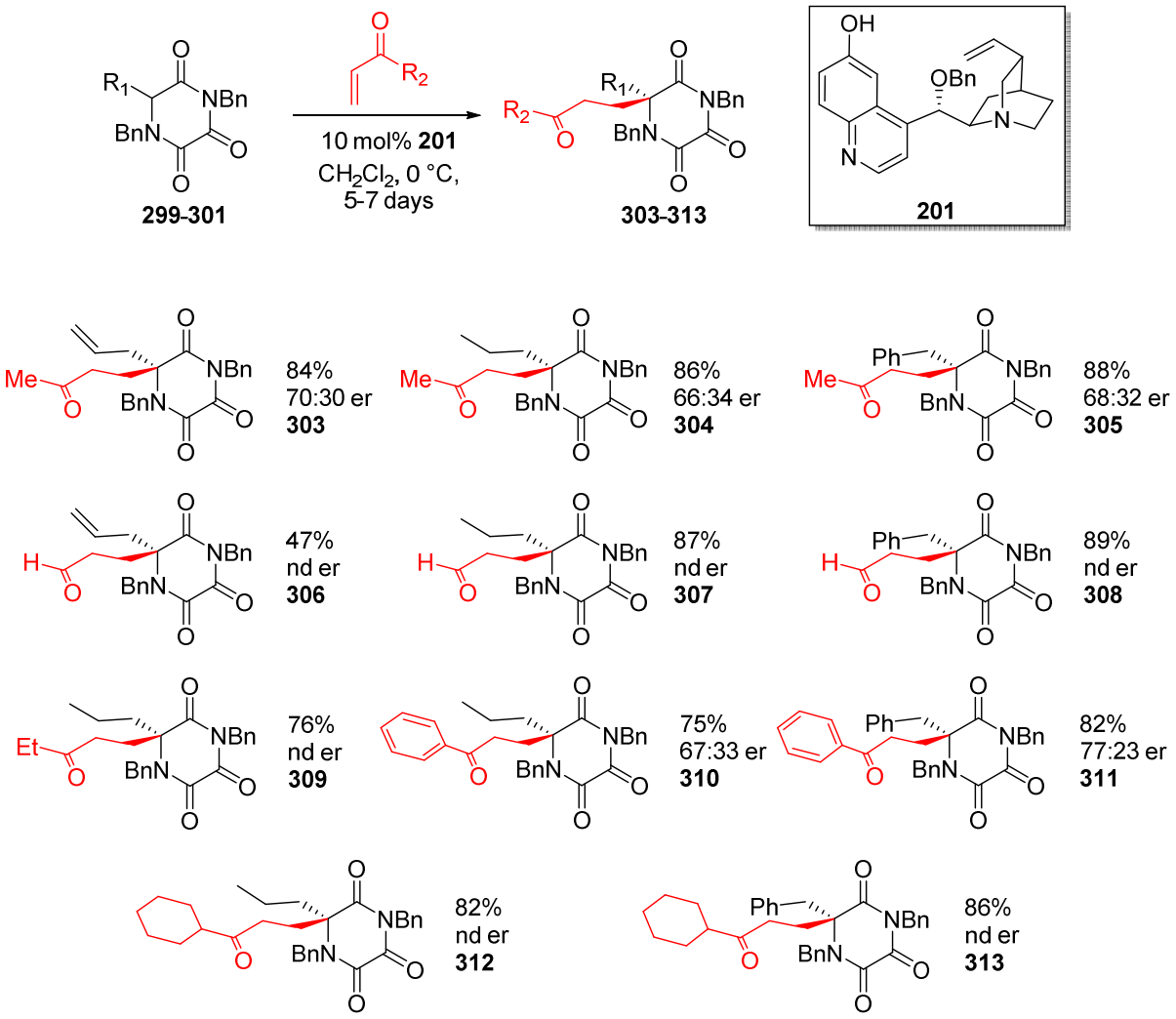
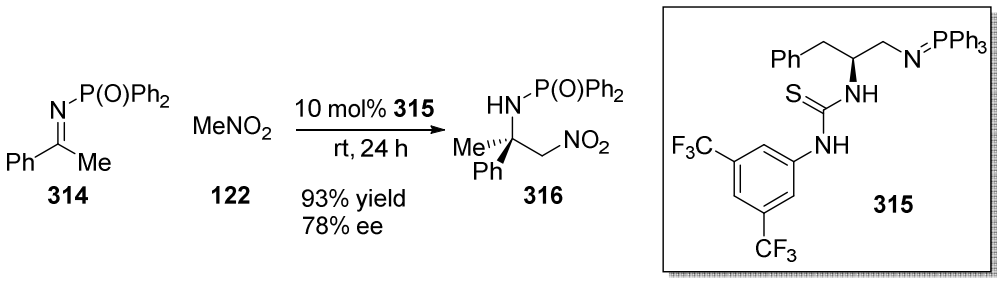


Figure 3.12 Scope of asymmetric Michael additions on alkyl TKPs

The enantiomeric excess was only determined for the methyl vinyl ketone and phenyl vinyl ketone adducts (**303**-**305**, **310** and **311**). A maximum *er* of 77:23 was measured and it was not expected to drastically improve in the rest of the examples. The low basicity of the catalyst, combined with the extra hindrance at the reactive centre was considered responsible for the poor reactivity and selectivity. Nevertheless, this was a remarkable transformation only reported once before in the Barbas example of organocatalysed Michael additions to alkyl oxindoles, a benzylated centre which was inherently more activated than this present example (Scheme 3.22).

It was initially conceived that only one enantiomer of the starting material would react faster than the other in the presence of the cinchona catalyst, *i.e.* a kinetic resolution. However, due to the yield of the reaction being over 50% consistently and the absence of any enantiomeric excess in the unreacted starting material from unfinished experiments that assumption proved to be invalid.

An improvement of the selectivity was pursued and increasing the basicity of the catalyst, in order to have a higher enolate concentration in the reaction, was believed to be crucial. Few examples where stronger bases have been employed in organocatalysis are reported in the literature. We became interested in the triarylamino phosphorane derived catalysts optimised by Dixon and co-workers for the stereocontrolled Henry reaction of nitromethane and substituted *N*-diphenylphosphinoyl ketimines such as **314** (Scheme 3.27).[165]

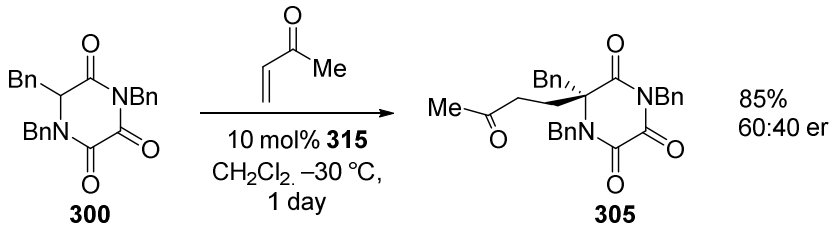


Scheme 3.27 Dixon superbase catalyst example

Typically, tertiary amines have a pK_{BH+} of 18.8 in acetonitrile while these new aminophosphoranes were in the range of 22.7, approximately four orders of magnitude more basic than the commonly used triethylamine. Chiral bifunctional derivative **315** combines this basic moiety with the recurrent thiourea proton donor site in a chiral skeleton, using the corresponding amino acid, phenylalanine in this case, as the starting material. Whilst a standard cinchona alkaloid catalyst showed no reactivity in this study, a range of

enantioselective Henry products such as **316** were isolated when catalyst **315** was employed. More interestingly, asymmetric Michael reactions from Scheme 2.4, previously optimised with cinchona alkaloid derived thiourea catalyst **179** were completed in a matter of hours rather than days with comparable levels of stereocontrol.

Inspired by this result, catalyst **315** was synthesised as reported in this paper to test it on alkyl TKP **300** asymmetric 1,4-additions. Unfortunately, the catalyst failed to deliver the desired results as the level of enantioselectivity achieved was only 60:40 *er*. Nevertheless, reaction time was drastically shortened and the products were formed in only one day at −30 °C (Scheme 3.28).



Scheme 3.28 Dixon base application on alkyl TKPs

In conclusion, although the reaction rate was improved, the spatial layout of the bifunctional catalyst was not probably suit able for substrate **300** in the asymmetric reaction. In comparison with structure of cinchona alkaloids derivatives, this catalyst appears to be much more flexible and different minimum energy conformers might be present in solution. This feature could justify the low level of induced asymmetry as a high bond rotation around the active sites in the catalyst may not be capable of locking the substrates into a fixed arrangement before the carbon-carbon bond was made.

Having both active sites very close together in the catalyst, only separated by a two carbon chain, seemed to be suitable for Dixon's work. However, it is evident that both electrophile and nucleophile involved in this reaction were considerably larger in size than these literature substrates. Thus, optimal interaction in such close proximity might be considerably hindered, and the new bond could not be formed entirely stereoselectively (Figure 3.13).

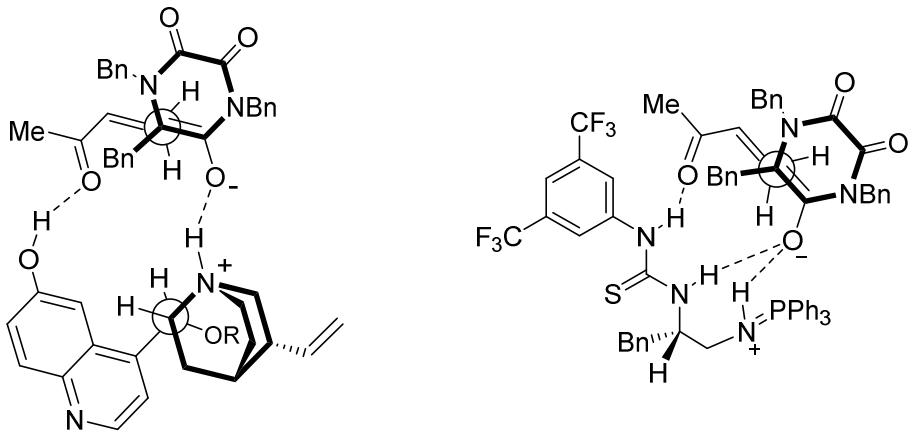
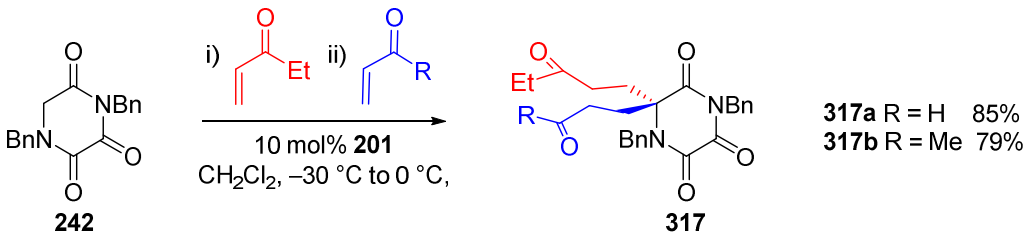


Figure 3.13 Comparison of proposed models leading to TKP **305** with catalysts **201** and **315**

Taking this input into account, *i.e.* in terms of reactivity and conformation, a completely new catalyst could be tailored to meet the specific needs of our reaction system. Although this issue was not cover under the present project, a few proposals will be outlined in the future plans based on the ideas generated from all the gathered information.

Lastly, sequential Michael additions with different electrophiles were explored by controlling temperature and stoichiometry. Essentially, the first Michael could be run as the ones optimised from Figure 3.12, where a low temperature (−20 °C at least) and addition of equimolar amount of the acceptor furnished the mono Michael product. Once the reaction was finished, a superstoichiometric amount of a second acceptor was added. This second reaction

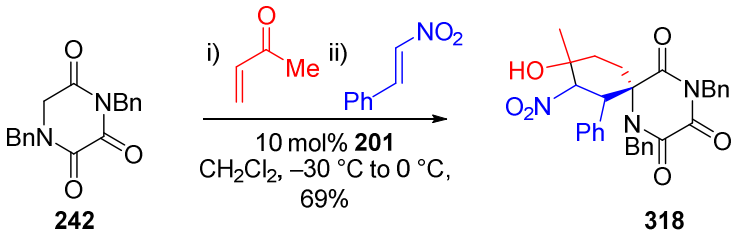
could be treated as an alkyl TKP Michael addition, so the temperature could be raised to 0 °C and the reaction times were extended. The initial tests are depicted in Scheme 3.29.



Scheme 3.29 Sequential Michael addition

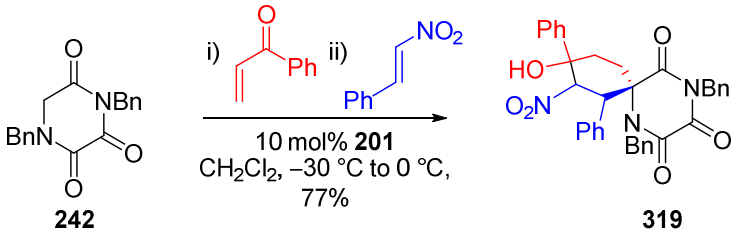
Sequential use of ethyl vinyl ketone, under the same conditions of the mono Michael product, followed by addition of acrolein or methyl vinyl ketone at 0 °C for two days afforded products **317a** and **317b** in good yield. Interestingly, the reaction time of the second addition was shorter if compared with the standard alkyl groups previously tried. Although the reaction was run with a chiral catalyst, no *er* could be determination due to lack of separation of the racemic adducts in any of the chiral columns available.

Further tests, with other electrophiles were pursued. Highly reactive nitro olefins were chosen to take part as the second Michael acceptor. There were some concerns about the reactivity of this class of electrophiles as they feature a fairly bulky group at the reactive centre. The lower reactivity of alkyl TKPs could prevent the second addition of these electrophiles from even occurring. However, we were pleasantly surprised to isolate not the expected product but spiroTKP **318** (Scheme 3.30).



Scheme 3.30 Spiro TKP formation

Product **318** arose from the Henry reaction between the nitro enolate and the electrophilic side chain ketone. This transformation proved to be highly diastereoselective as only one product was observed in a reaction forming four contiguous stereogenic centres. However, the stereochemical assignment could not be completed as the crystallographic data has not been elucidated yet. Lastly, upon subjecting the parent TKP to phenyl vinyl ketone followed by nitrostyrene under the previous reaction conditions, spiroTKP **319** was isolated from the reaction (Scheme 3.31), similarly to the previous example.



Scheme 3.31 Attempt to Spiro-TKP dehydration

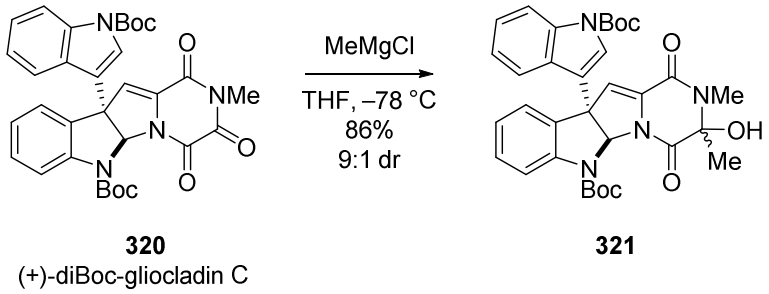
Analogous to spiro TKP **318**, the reaction was highly diastereoselective. No enantiomeric ratios could be determined in these last two examples, as none of the available columns prove effective for any of the spiro-TKPs. Although an optimal catalyst might need to be found for these transformations, the possibility of performing sequential stereoselective Michael additions represents a remarkable and unprecedented feature to date.

3.5. Further Transformations

Having established organocatalytic methods for the enantioselective synthesis of various TKPs, and having set the scene for the synthesis of other TKPs to be optimised in the near future, we became interested in the different chemical alternatives our enantioenriched products could undergo given the key functionalities present within the molecules. Therefore, we focused our efforts on developing routes to access chiral DKPs starting from the TKPs and using chiral TKP systems to form bridged DKPs. Ultimately we aimed to devise a mild method that would enable us to either hydrolyse the TKP ring so the newly formed enantiopure non-natural amino acid could be unveiled or remove the benzyl protecting groups from the nitrogens. Work carried out in these three areas will be subsequently described.

3.5.1. Reduction of the C-3 position

Selective reduction of the carbonyl group belonging to both the imide and the oxalyl moieties, also referred as the C-3 carbonyl, would provide us with a very wide set of tools to access different types of molecules. For instance, complete reduction to the methylene group would furnish the chiral DKP while radical reduction would likely affect this position and the side chain carbonyl group furnishing various bridge-closed structures. Fortunately, the C-3 position has been demonstrated to show distinctive electrophilic properties compared to C-2 and C-5. The possibility of a Grignard reagent to selectively attack this position was shown to be completely selective on this position in the case of unsaturated TKP **320** by Overman and co-workers (Scheme 3.32).[69a]

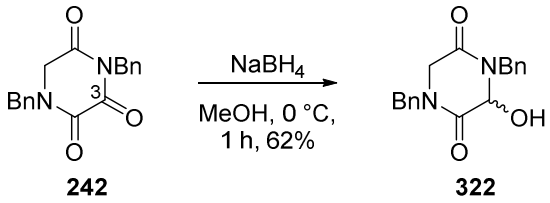


320
(+)-diBoc-gliocladin C

321

Scheme 3.32 First hint of TKP reactivity

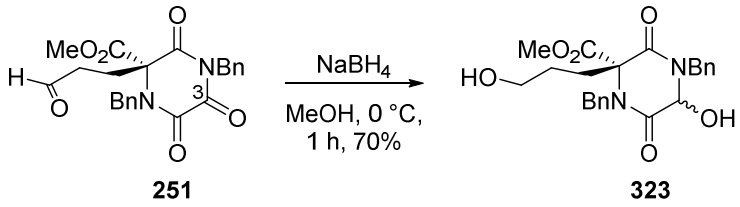
Furthermore, in the same publication, a unified method to access various ETP natural products was described based on the reactivity *α*-hydroxylactam **321** displays, mainly *via* nucleophilic substitutions of the *N*-acyl iminium centre generated under acidic treatment. This approach could be easily adopted should the regioselectivity of any nucleophilic attack be the same for the TKPs. Hence, a simple experiment on the parent TKP in the presence of a simple aldehyde or ketone reductant, such as sodium borohydride, helped us to determine whether or not the attack on the C-3 carbonyl occurred exclusively (Scheme 3.33).



242 **322**

Scheme 3.33 Reduction on a model TKP

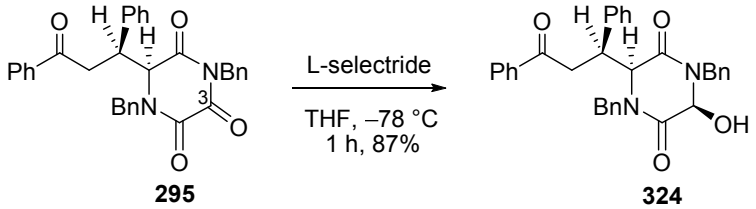
Typical reaction conditions afforded hydroxy-DKP **322** in good yield. The use of the same reductant afforded diol **323** from TKP **251** by reducing the side chain aldehyde witch concomitant attack to the TKP C-3 position exclusively (Scheme 3.34).



Scheme 3.34 Reduction of a chiral TKP

Dihydroxy adduct **323** was isolated in a 1:1 diastereomeric mixture. Many other reducing agents were tried on a range of chiral TKPs to achieve selectivity on the C-3 carbonyl over the diverse side chain groups.

Bulky reducing agents were also screened in a desire to only affect the more rigid and less encumbered region of the molecule. In fact, the reaction of L-selectride with chalcone TKP **295** afforded hydroxy DKP **324** as the only product of the reaction in good yield and only one single diastereoisomer (Scheme 3.35).



Scheme 3.35 Selective reduction of C-3 carbonyl

The steric clash provided by the two phenyl substituents around the side chain ketone was probably hindering the approach of the large reducing agent and preventing any reaction on it. As it can be inferred from product **295**, not only were the side chain substituents obstructing the reduction of the ketone but they were also presumed to impede the approach of the reductant from the top face where the side chain was and thus, explaining why only one diastereoisomer could be observed in the crude reaction mixture. The assignment was also

confirmed by indirect nOe correlation. Whilst no direct H-3/H-6 correlation was detected in a NOESY experiment, there was a correlation between the OH and the sidechain *β*-hydrogen that could only exist in the shown diastereoisomer (Figure 3.14).

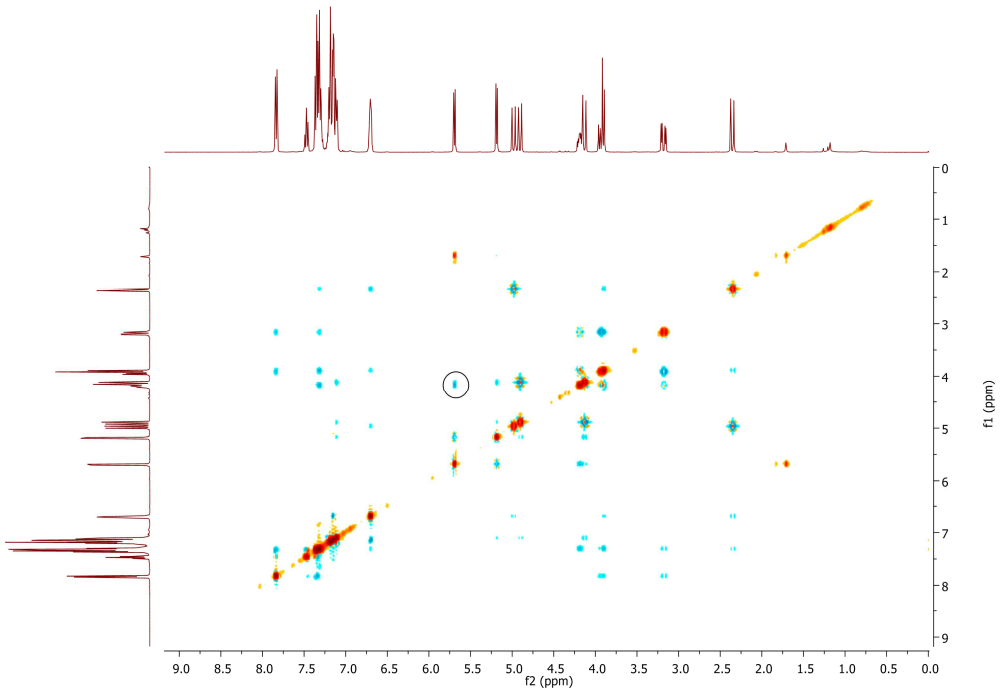
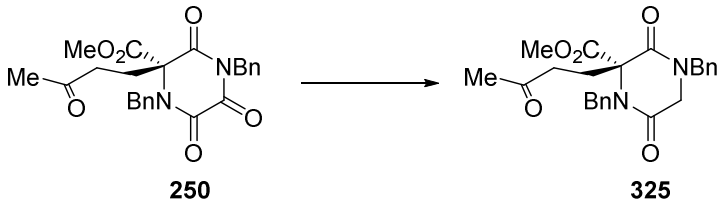


Figure 3.14 NOESY spectra of hydroxyDKP **324**

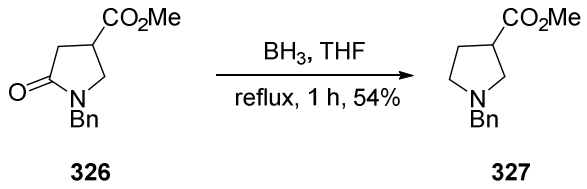
However, this method could not be generally applied to all cases since *β*-substitution proved essential for the selective reaction of the C-3 carbonyl. A mixture of ketone, C-3 and both functionalities reduction were observed from the reaction crude upon subjecting TKP **276** and **292** to these reaction conditions and only very small amounts of the desired products were eventually isolated.

Hence, the aim was to discover a particular set of conditions that allowed the C-3 position of the TKPs to be reduced selectively. Further reducing agents were tried in order to convert the TKP into a DKP as desired (Scheme 3.36)



Scheme 3.36 Desired reduction

Borane is very well known for reducing carbonyl groups such as carboxylic acids or amides, in the presence of esters and sometimes ketones (Scheme 3.37).[166]

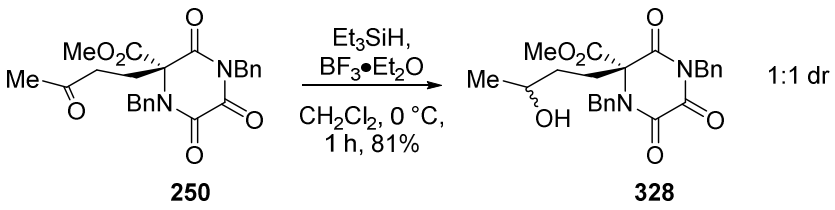


Scheme 3.37 Borane amide reduction

However, upon applying these conditions to the TKP system no reaction took place and only the starting material was recovered from the reaction mixture. It is known that sodium borohydride reduction works *via* hydride addition to the electrophilic centre, and thus, the more electrophilic the carbonyl is, the more facile the reduction. On the other hand, borane is reactive towards amides or acids due to the particularly high electron density these carbonyls have *via* successive coordination of borane molecules empty orbitals to the lone pair of electrons of the oxygen in the carbonyl group. Hence, the more electron density on the carbonyl, the better it would be reduced. In the TKP case, the cyclic carbonyls are not particularly highly charged, as they are imides rather than amides.

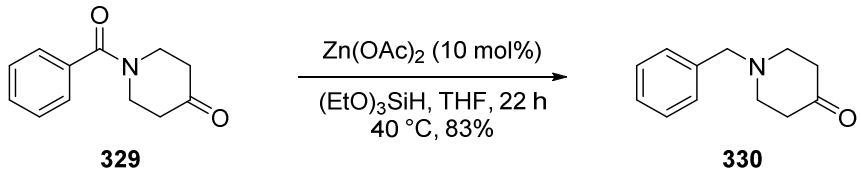
Other amide reduction methods were investigated such as silane hydrides (triethyl silane hydride and triethoxy silane hydride) in the presence of the Lewis acid, boron trifluoride and

TFA. Unfortunately, only the starting materials were recovered after the reaction in all cases but one. The side chain ketone was reduced in the presence of $BF_3 \bullet OEt_2$ and $(Et)_3SiH$ to the alcohol leaving the C-3 position completely untouched and furnishing the product in 81% yield and a 1:1 mixture of diastereoisomers (Scheme 3.38).



Scheme 3.38 Silane reduction of side-chain ketone

Although few catalytic methods are available in the literature for the selective reduction of amides, there have been recent reports by Beller and co-workers where zinc complexes, in the presence of silane hydrides, have been employed to effect such transformations, notably, in the presence of ketones (Scheme 3.39).[167]



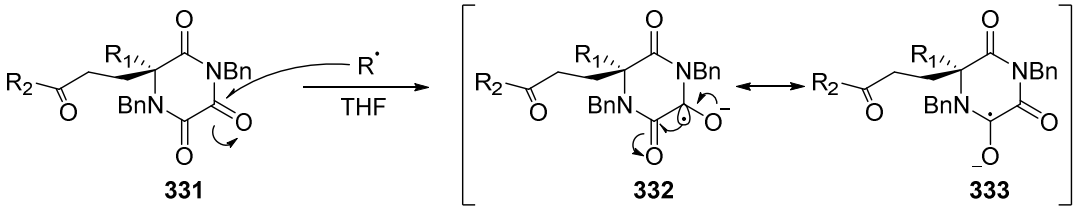
Scheme 3.39 $Zn(OAc)_2$ catalysed amide reduction

Unfortunately, upon treatment of chiral TKP **250** under the same conditions, no reaction took place and the starting materials could be recovered.

Mechanistically, these reaction conditions were proposed to form the reactive complex between the zinc acetate and the silane before it reacts with the carbonyl centre. The hemiaminal silane-ether intermediate was presumed to be formed after the first hydride addition. At this stage, the lone pair of electrons from the nitrogen expelled the oxygen as part

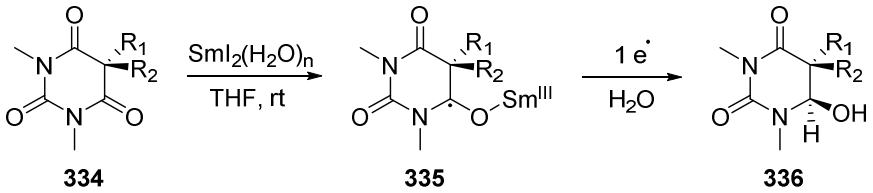
of a zinc-silane aggregate, furnishing the iminium cation intermediate that got subsequently reduced by a second zinc-silane complex. The lone pair of electrons from the amidic nitrogen was reported to play a key role in the amide reduction. In the TKP cases, they are delocalised among more than one centre, forming an imide and an oxalyl amide and, hence, they are not as readily available as this method demands.

Given the low success with hydride type of reductions, we shifted our attention to radical based reducing methods. The TKP system was hypothesised to excel at forming the radical anion intermediate due to both the possibility of delocalising the electron into the contiguous carbonyl and the anomeric stabilisation provided by the imidic nitrogen (Scheme 3.40).



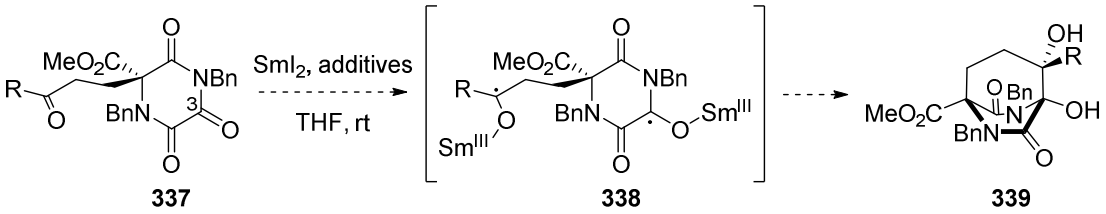
Scheme 3.40 Proposed radical stabilisation on standard TKP system

Typical radical conditions, such as AIBN or light as the radical initiators and tributyltin hydride, tris(trimethylsilyl)silane or bis(tributyltin) were firstly screened in refluxing toluene with no success.[168] Hereafter, we focused our attention on single electron transfer (SET) reagents. Our interest in this type of chemistry was stirred by the work recently published by Procter and co-workers in which they selectively reduce the most electrophilic carbonyl group within the ring of barbituric acid derivatives **334** (Scheme 3.41).[169]



Scheme 3.41 Procter mono-reduction of barbituric acid derivatives

Samarium iodide, in THF with superstoichiometric amounts of water, was employed as the reducing agent in this SET followed by acid quench to furnish hydroxy lactams **336**. The reducing potential of samarium iodide had to be slightly modified so it could reduce the imidic position by forming a more reactive complex with water.[170] Likewise, the same activated imidic position was devised to be readily reduced intheTKPs. The side chain carbonyl group reductive potential would also be within range so it was assumed that two molecules of SmI_2 would be necessary to reduce the Michael adducts. Diradical reaction intermediate **338** would then collapse, forming a new carbon-carbon bond, and furnishing bicyclo[2.2.3]diazanonane structures such as **339**, essentially a bridged DKP, in a formal reductive carbonyl coupling (Scheme 3.42)



Scheme 3.42 Proposed SmI_2 reaction sequence on TKP adducts

With this proposal in mind, trials with Michael adducts in dry THF were firstly carried out to check whether or not these systems were reactive under those conditions, as Procter stated in the barbituric derivatives chemistry. Inthis case, we were delighted to isolate a new compound from the reaction mixture. However, upon thorough spectroscopic analysis, this novel

structure did not match with the proposed reactivity course, but with fused bicyclic compounds **340**-**346**. The reactivity profile was maintained throughout a wide range of different TKP Michael products both asymmetric, such as TKPs **250** and **276**, and racemic, like alkyl TKPs **303**, **304**, **305**, **308** and **309** (Figure 3.15).

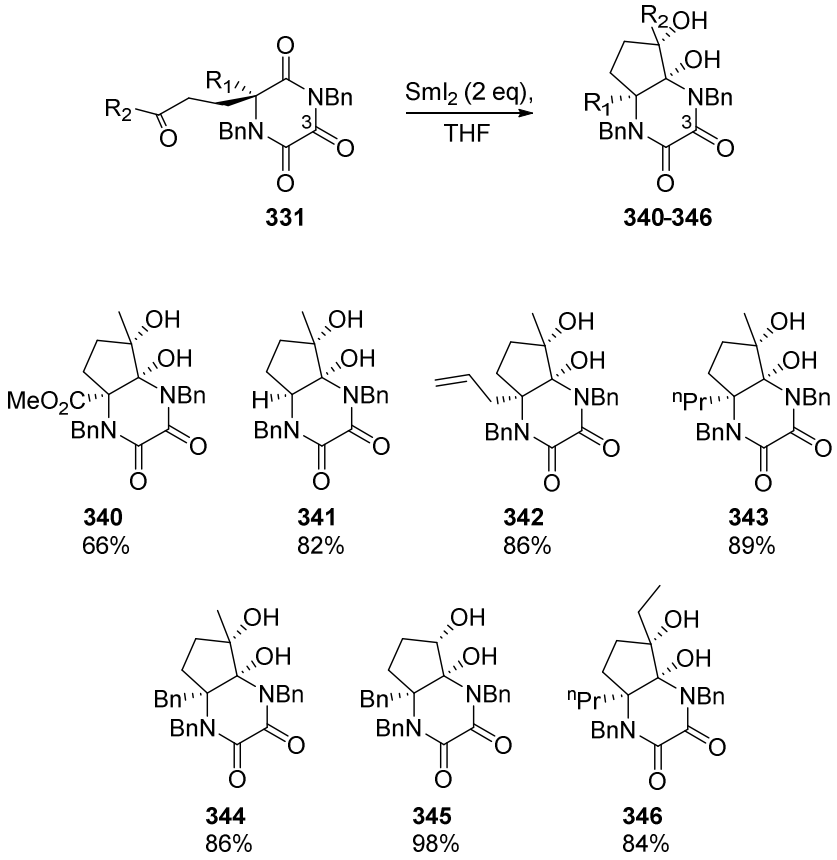


Figure 3.15 Scope of reactions with SmI_2 in THF

The reaction proved highly diastereoselective, as only one single diastereoisomer could be observed in the reaction mixture. X-Ray crystal structure from compound **340** unequivocally demonstrated the structure and absolute stereochemistry (Flack parameter: -0.01(4)) of this product (Figure 3.16).

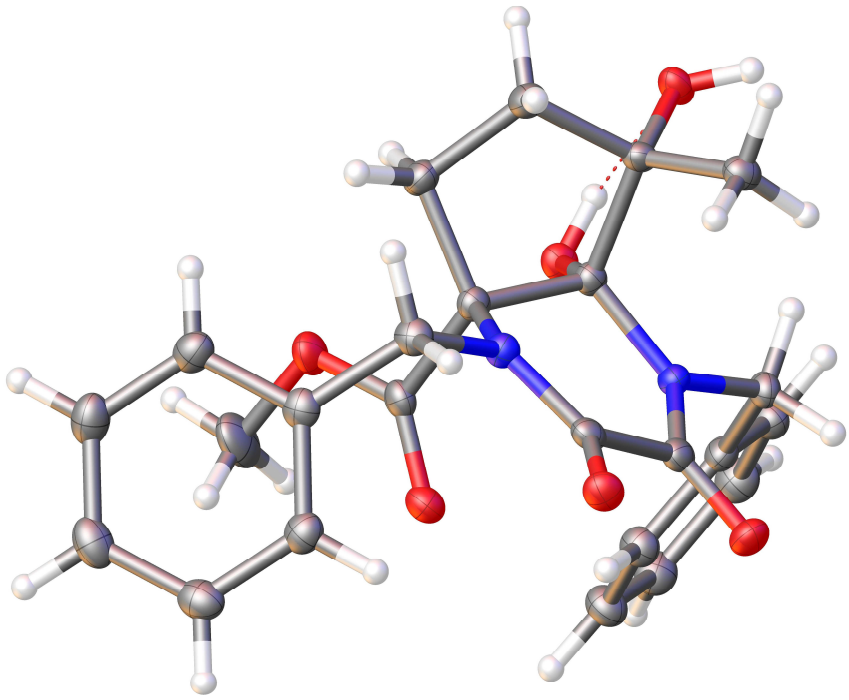


Figure 3.16 Crystal structure of **340** with 50% of ellipsoid probability, d (O-H) = 1.86(3) Å

As it can be seen in the crystal structure, the α-DKP substituent and the two newly generated hydroxy groups are all directed to the back of the molecule.

In order to thoroughly explore this chemistry, the reaction of the same TKP substrates to the conditions first proposed, SmI_2 in THF/water, was also set to check whether the observed reactivity was maintained under a more reactive media and whether the envisioned radical cyclisation was feasible. To our surprise, no traces of the fused DKP systems were observed and the predicted bicyclic systems were solely isolated from the reaction mixture. However, only the more stable alkyl TKPs underwent this transformation and in a lower overall yield compared with the previous examples (Figure 3.17).

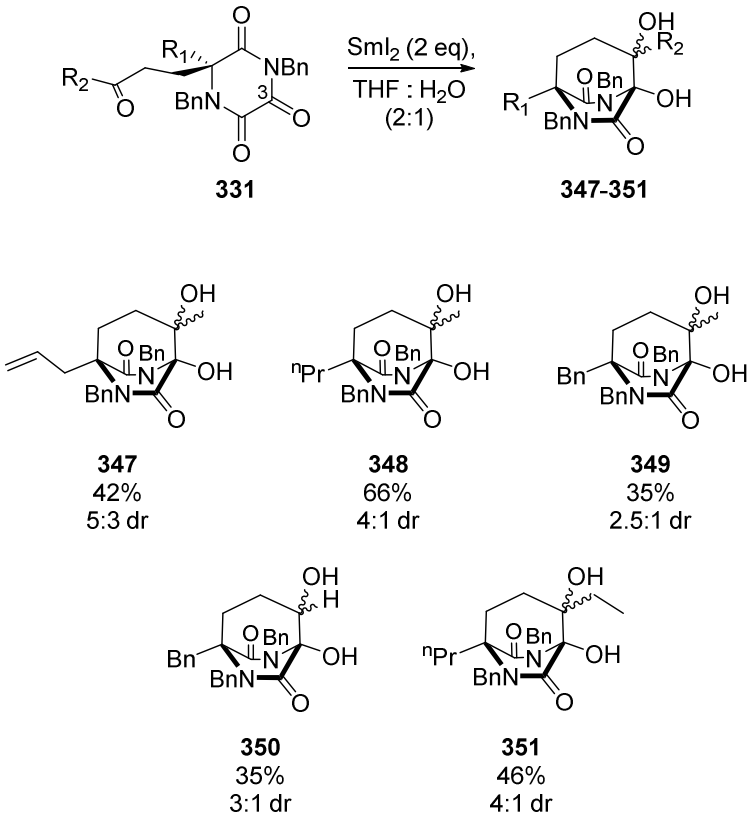


Figure 3.17 Scope of reactions with SmI_2 in THF/H_2O

The reaction was not completely diastereoselective and inseparable mixtures of diastereoisomers, on the bridge fully-substituted carbon, from 2.5:1 to 4:1, were furnished. Likewise, the structural conformation was further checked by X-ray crystallography to confirm the proposed bicyclic DKP from compound **348** (Figure 3.18).

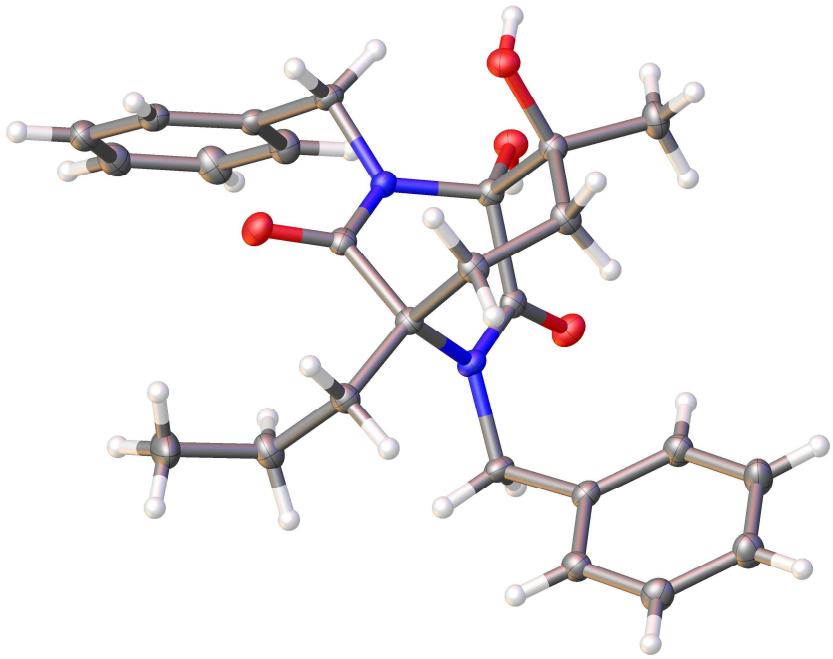
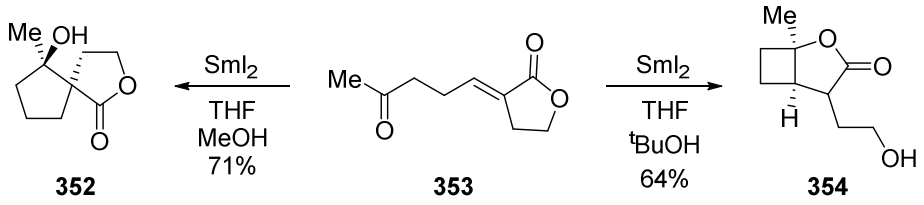


Figure 3.18 Crystal structure of **348** with 50% of ellipsoid probability

The crystal structure of **348** clearly showed the three carbon bridge over the DKP. The structures from both diastereoisomers can be found in the crystal set, the major one being displayed in Figure 3.18. Although the set of results from this last transformation may not appear to be optimal, the possibility of changing the reaction outcome by the simple addition of water is an outstanding feature of these particular TKP Michael products. In the literature, there are only a handful of examples showcasing this interesting property. Procter and co-workers published a samarium iodide mediated transformation where lactone **353** was subjected to radical reducing conditions using two different additives, MeOH and ^{t}BuOH.[171] Interestingly, two set of results could be easily distinguished. MeOH mediated reaction afforded spirolactone **352** while using ^{t}BuOH furnished cyclobutanol derivative **354** (Scheme 3.43).



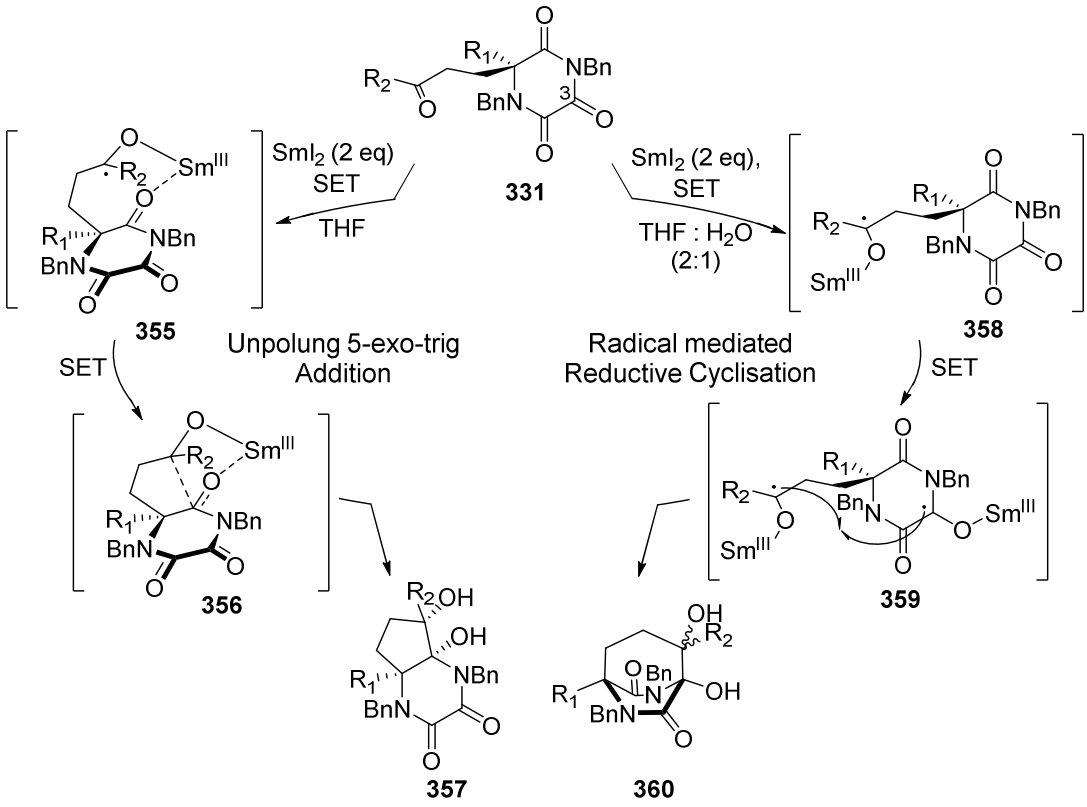
Scheme 3.43 Example of additive dependant SmI_2 reaction

The mechanistic insight behind this phenomenon was based upon the relative rate of proton donation by each of the additives. Fast protonation of the anion generated in the β-position of the unsaturated lactone by MeOH affords the radical enolate of the ester that attacked the ketone electrophilic position after a second electron transfer by samarium affording spiro lactam adduct **352**. On the other hand, if that protonation was slow, as in the ^{t}BuOH case, the anion could live long enough to attack the ketone carbonyl forming the cyclobutanol ring. Second electron donation, followed by relactonisation, furnished product **354**.[172] Two more types of examples by the same group are available where a change of additive swapped the reaction outcome.[173] However, the first comprised a reaction between alkenes and ketones while the last one was essentially an additive promoted transformation after the samarium reduction is over. There are no examples in the literature where an additive is responsible for a change in the reaction regioselectivity involving different carbonyl centres and furnishing two different pinacol outcomes.

Mechanistically, the formation of fused bicyclic framework **357** could be explained by determining which carbonyl was the most susceptible to being reduced. In spite of the C-3 position being a very good radical receptor, as previously stated, the side chain carbonyl still had, in comparison, a more accessible reductive potential. Since the initial potential of the standard SmI_2 in THF solution is not high enough to affect the imidic carbonyl, only the

ketone or aldehyde gets an electron transferred upon treatment with superstoichiometric amounts of the samarium solution. This new species is probably forming an intermediate where Sm (III) is tethered to the closest, less hindered carbonyl group, being the C-5 carbonyl as in **355**. This intermediate presumably exists before the second SET as suggested in the literature.[174] The second electron might be transferred while the new carbon-carbon bond is made in a 5-exo-trig manner to form the fused bicycle. However, this electron can also get transferred before the new bond is formed, as in the previous examples by Procter. Hence, the transformation could be considered a formal unpolung cyclisation of the side chain ketyl carbanion to the C-5 carbonyl position. The high diastereoselectivity could be reasoned due to the proposed tethered transition state where the two oxygen atoms are forced into a *cis* conformation which, as a result, dictates the spatial arrangement of the rest of the groups around the newly created bond (Scheme 3.44, left side).

On the contrary, when there was water present in the reaction mixture the reducing potential was increased. Although the first SET was presumed to occur on the same centre, addition to the carbonyl with the lowest potential energy, donation of a second electron could rapidly occur to the next most electrophilic carbonyl in the molecule given the increased potential of the SmI_2 solution. As previously envisioned, homocoupling of diradical species **359** would form a new carbon-carbon bond furnishing bicyclo[2.2.3]diazanonane type of structures in a formal reductive cyclisation (Scheme 3.44, right side).



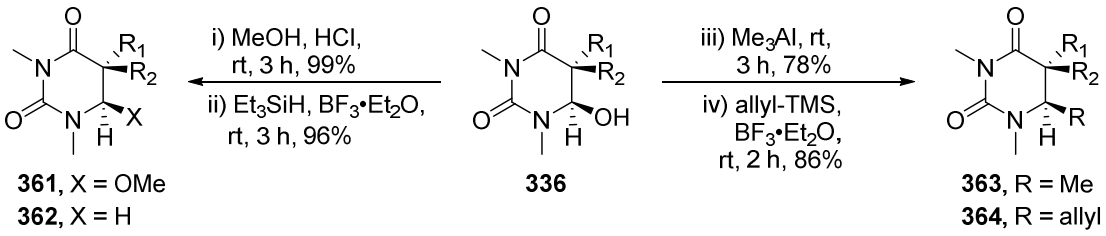
Scheme 3.44 Proposed mechanistic pathways for the SmI_2 reactions

The poor diastereoselectivity was proposed to be due the absence of a tethered intermediate between the di-radical centres which allowed free bond rotation of the side chain radical. If this intermediate could live long enough for the adjacent bond to rotate freely a 1:1 mixture of diastereoisomers would be furnished as a result. The fact that some diastereocontrol was observed could indicate that both these phenomena, the free rotation and the formation of the new bond, are in a similar half-life scale. Changing the additives, such as an alcohol with a slower proton release rate, *e.g.* ^{t}BuOH, may also result in a better diastereoselectivity of this type of bicyclic DKPs. It is also worth noting that no byproducts were the C-3 carbonyl was the only reduced centre was observed in any of the two pathways.

In summary, SmI_2 mediated transformations successfully furnish two different sets of pinacol products depending on the addition of water to the media. Combined with the previously reported reductive approaches, a wide range of transformations, affording very diverse results, could be accomplished for the TKP substrates.

3.5.1.1 Cyclisations *via N*-Acyl Iminium

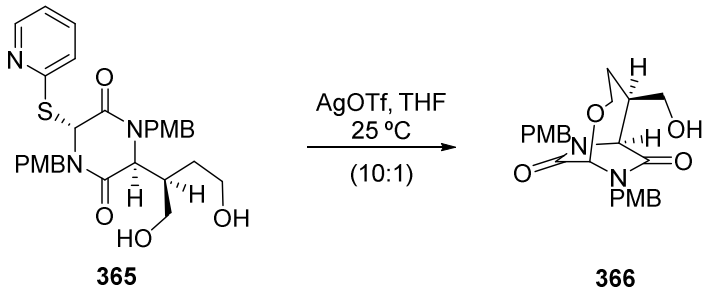
Overman and co-workers employed the hydroxy lactam intermediate **321** to synthesise a myriad of ETP natural products by means of *N*-acyl iminium chemistry. In a similar manner, Procter and co-workers showed how the reduced barbituric adducts **336** could be reacted with very useful nucleophilic building blocks using, once more, *N*-acyl iminium chemistry (Scheme 3.45).



Scheme 3.45 Scope of *N*-acyliminium driven reactions of mono-reduced barbituric acids

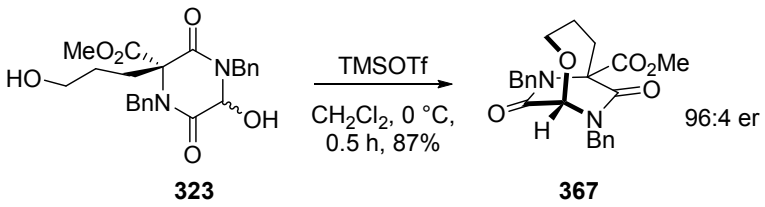
In our desire to build bicyclic DKPs with a clear structural relationship to bicyclomycin **40** we focussed our attention on Williams and co-workers enantioselective total synthesis of this natural product.[41a] With dihydroxy DKP **365** in hand, an intramolecular *N*-acyl iminium cyclisation was triggered upon addition of silver triflate as the Lewis acid. The nitrogen lone pair of electrons expelled the thioaryl group, aided by the Lewis acid, with concomitant nucleophilic attack of this new electrophilic carbon by the side chain hydroxy groups. [2.2.4]

Bicycle **366** was formed in preference to the [2.2.3] option with high diastereoselectivity (Scheme 3.46).



Scheme 3.46 Bridged DKP formation during bicyclomycin synthesis

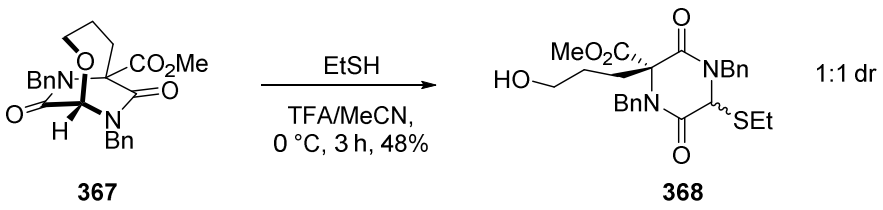
Likewise, dihydroxy adduct **323** , resulting from the reduction of TKP **251**, was envisioned to behave similarly under Williams *N*-acyl iminium conditions. Unfortunately, silver triflate conditions did not prove reactive enough for DKP **323**. However, employing TMS triflate, the desired intermolecular cyclisation was accomplished in less than an hour affording bicyclomycin surrogate **367** in good yield and selectivity (Scheme 3.47).



Scheme 3.47 Bridged DKP formation from TKP adduct **323**

Since aldehydes were not compatible with the available HPLC chiral columns, *er* of TKP adduct **251** was determined using this approach. Bicyclic DKP **367** was a valid substrate for further *N*-acyl iminium reactions and, consequently, it was subjected to a second iteration. In order to determine whether the ether bridge would transmit any stereochemical information, a subsequent nucleophilic addition of a thiol to this position, promoted by TFA, was envisioned

(Scheme 3.48). The aim was to determine if the reaction happened in a concerted way, rather than reacting in a stepwise process where the nucleophile independently attacks the iminium ion.



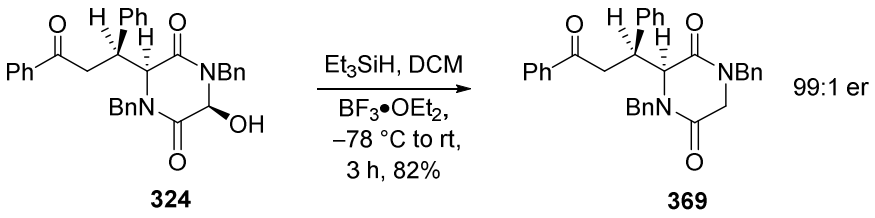
367 **368**

Scheme 3.48 *N*-acyliminium promoted bridge opening

No retention of the stereochemical information was observed and product **368** was isolated as a 1:1 mixture of diastereoisomers as determined by NMR spectroscopy. Hence, it was concluded that further acidic conditions would trigger full formation of the *N*-acyl iminium intermediate on this position prior to the nucleophilic attack. No diastereoselectivity at the C-3 position was enhanced by the fixed stereocentre C-6.

3.5.1.2 Synthesis of Polyfunctional 2,5-Diketopiperazine

As seen in Scheme 3.45, internal cyclisations or attacks *via* chalcogen nucleophilic attacks were not the sole possibilities for this transformation but a wide range of nucleophiles could be used in combination with a Lewis acid to add into the iminium position. Taking Procter's examples into account, hydroxy DKP **324** was subjected to *N*-acyl iminium conditions with BF_3•Et_2O using triethyl silane as the nucleophilic reductant to furnish enantioselective DKP **369** (Scheme 3.49).



Scheme 3.49 DKP formation via *N*-acyl iminium chemistry

This process afforded chiral DKP **369** from the product of a stereocontrolled Michael addition with no erosion of *er* in comparison with original TKP **295** and in an overall yield of 71%.

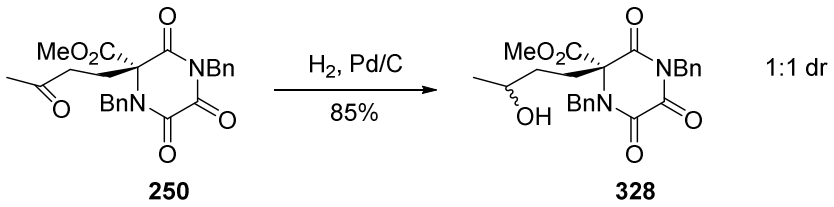
Although DKPs from Michael adducts **276** and **292** were also synthesised, the poor selectivity of the initial reduction step only afforded small quantities of the desired hydroxy DKP intermediate. Not until a selective agent for the exclusive reduction of the C-3 carbonyl is found can this approach become routinely applied for the formation of chiral DKPs from the corresponding TKPs.

3.5.2. TKP Deprotection

TKPs and DKPs present in nature are usually found without substituents on their amidic nitrogens. Thus, we also became interested in devising a set of conditions that would allow us to take the benzyl groups off once the desired transformations around the core were finished. With this proposal in mind different methods to facilitate removal of the benzyl groups were investigated. Although benzyl protecting groups are widely used in organic chemistry, and various deprotection strategies have been optimised, we soon realised that the removal appeared to be a daunting challenge on many occasions in the past for many research groups. For instance, the total synthesis of bicyclomycin had to be fully redone with PMB protecting

groups instead of benzyl ones due to the impossibility of removing them in a late stage of the synthesis without altering the rest of the functional groups.[41b] Likewise, Simpkins and Frebault chose *O*-benzyl hydroxylamine in their total synthesis of *ent*-malbrancheamide B to avoid dealing with the highly resilient standard benzyl group.[33d] Since all the TKP examples had been accomplished with benzyl protecting groups on amides, establishing a method to remove them effectively became highly important.

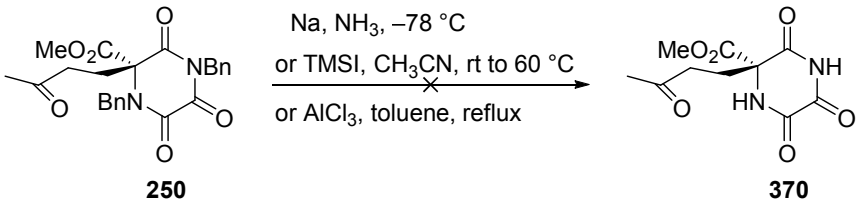
Firstly, hydrogenolysis was investigated as it is the most commonly used method to remove benzyl groups. Typical conditions were applied to TKP **250**, *i.e.* 1 atmosphere of H_2 in the presence of palladium on carbon (Scheme 3.50).



250 **328**

Scheme 3.50 Attempt to remove benzyl protecting groups

Unfortunately, no debenzylation was observed. The only product of the reaction was the reduction of the side chain ketone, affording product **328** as a 1:1 mixture of diastereoisomers as observed in the Et_3SiH reduction. Birch reduction is also a very widely used method to deprotect benzyl groups, although harsher conditions are required.[175] Upon treatment of TKP **250** to the standard sodium in liquid ammonia conditions, no desired product was observed after 30 minutes of reaction and all starting material was fully degraded. The same reaction outcome was observed when other methods, such as TMSI[175] or $AlCl_3$[176] were employed (Scheme 3.51).



250 **370**

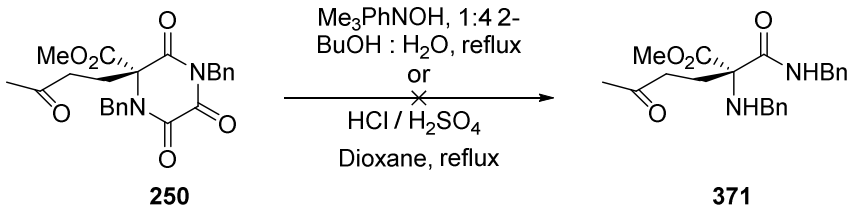
Scheme 3.51 Failed conditions for benzyl group removal

No desired deprotected TKP was ever observed under any of the tried conditions. Should the deprotection became of utmost importance, related TKPs, with similar protecting groups such as PMB, could be synthesised. Owing to their wider and more facile deprotection strategies, and assuming they would display similar reactivity, they would become good candidates to try in the future.

3.5.3. Unveiling the Amino Acid

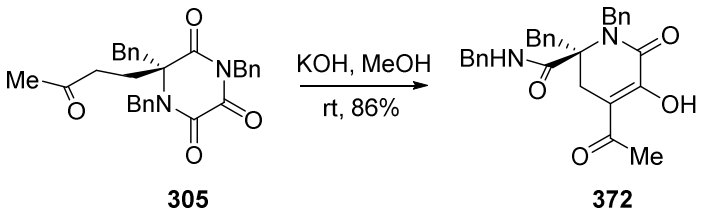
Lastly, we were very interested in developing selective conditions to remove the oxalyl moiety from chiral TKPs. As a result, a non-natural enantioenriched amino amide would be furnished. Developing new methods to synthesise this type of compounds is always one of the highest priorities of organic chemists. Synthetic amino acids can often be found active against particular diseases and its prospective application in the drug discovery process can be of crucial importance. This asymmetric Michael addition was affording masked all-substituted amino acids derivatives, using glycine amide as the starting material. Hence, opening the cyclic system would yield the desired amino acid precursors. Firstly, the TKP systems were hypothesised to behave similarly to the pseudoephedrine and oxazolidinone chiral auxiliaries

during their final deprotection step.[177] Essentially, we envisioned to break similar bonds while preserving the stereochemical information of the newly created stereocentre (Scheme 3.52).



Scheme 3.52 Oxazolidinone and pseudoephedrine deprotection conditions on TKP adduct **250**

Acidic and basic conditions similar to the optimised methods to break both oxazolidinone and pseudoephedrine auxiliaries were employed with TKP substrate **250**. However, application of these conditions did not yield the desired amino amide. Instead, either the starting material was recovered or the TKP was fully degraded in the course of the reaction. It is worth noting that full conversion to compound **372** was observed when subjecting alkyl TKP **305** to basic conditions (Scheme 3.53).



Scheme 3.53 Unexpected reaction of TKP **305**

Surprisingly, product **372** was cleanly furnished as the only product of the reaction. Mechanistically, this compound arose from the enolate attack of the side chain ketone into the C-3 carbonyl of the TKP. Instead of fully dehydrating, impossible due to the bridge-head location of the hydroxy group, and rather than doing a normal retroaldol, the carbonyl was regenerated with concomitant breakage of the C-3/N-4 bond. It seemed that the newly formed

molecule preferred an enol resonance form as confirmed by NMR spectroscopy and X-ray crystallography (Figure 3.19).

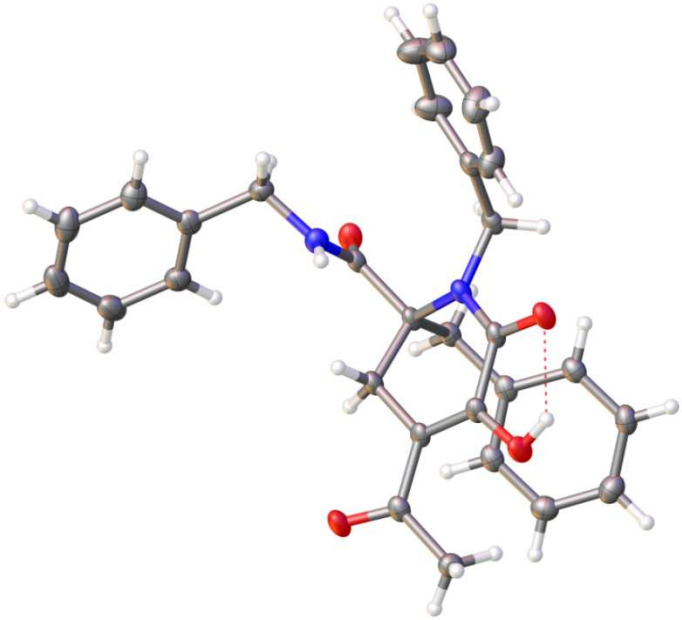
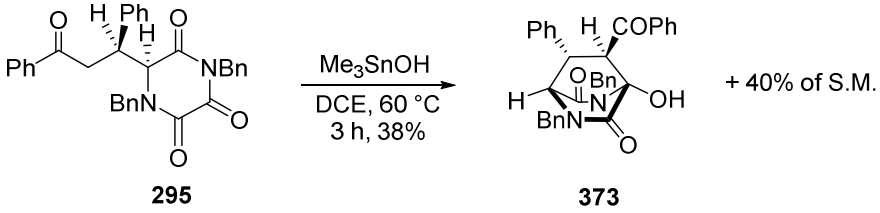


Figure 3.19 Crystal structure of **372** with 50% of ellipsoid probability, d (O-H) = 2.05(3) Å

Although no *er* was determined, the stereochemical information from **305** was presumed to be transferred to **472** as the transformation did not interfere with the first created stereocentre.

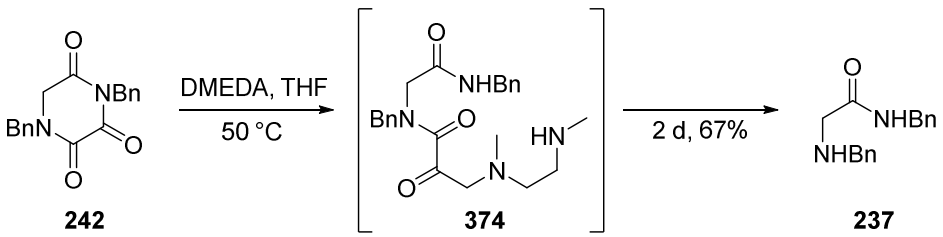
Nicolaou and co-workers found trimethyl tin hydroxide was an excellent reagent to mildly cleave esters and amides bonds when more classical and harsher options failed.[178] Subjecting TKP **295** to these reaction conditions failed to deliver the desired product but an inseparable mixture of starting material and bridged DKP **373** was formed (Scheme 3.54).



Scheme 3.54 Trimethyl tin hydroxide attempt to cleave TKP **295**

No matter how much conditions were altered, with extended reaction times, superstoichiometric amounts of tin and solvent changes, full conversion was never achieved. The tin derivative acted as a Lewis acid, catalysing the aldol reaction of the side chain ketone to the C-3 carbonyl. The desired aminoamide was not detected in the reaction mixture. Interestingly chromatographic purification only furnished 75% of the starting material back, demonstrating the instability of bridged DKP **373**, which was never isolated.

Finally, the possibility of expelling the amino amide by reaction of the TKP systems with a bidentate nucleophile, such as a diamine, was devised. First addition onto the most reactive centre C-3 would yield an acyclic system that would hopefully react *in situ*, driven by the entropic component of the reaction, to form a new cyclic product plus the desired amino amide. It is conceivable that the overall loss of steric clashes would drive the whole process forward under mild conditions. Initial studies with parent TKP **242** and dimethylethylenediamine (DMEDA) were conducted. The starting material was consumed overnight to presumably form intermediate acyclic adduct **374** that was subsequently transformed under slightly more forcing reaction conditions, mild heating and extended reaction times, to the dibenzyl amino amide **237** (Scheme 3.55).

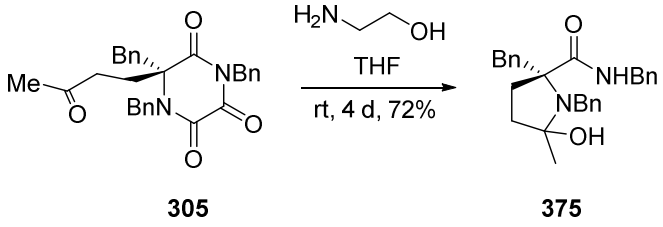


242 **374** **237**

Scheme 3.55 Initial test of proposed TKP cleavage

However, upon subjecting chiral TKPs **250** and **295** to these reaction conditions, the isolation of the starting material was the only observed phenomenon. It was not until alkyl TPK **305**

was exposed to similar reaction conditions over a period of 4 days that no starting material in the reaction mixture was observed. Instead, **375** was the only isolated compound (Scheme 3.56)



305 **375**

Scheme 3.56 Alkyl TKP **305** cleavage

The side chain ketone formed a hemiaminal group with the secondary amine after the aminoamide was extruded from the oxalyl moiety. Although this result is the only example of this type of chemistry we are confident the mild reaction conditions will make the rest of alkyl TKPs undergo the exact same transformation.

3.6. Summary and Future Work

TKPs have been demonstrated to be highly flexible adducts for the asymmetric organocatalysed Michael addition reaction. A wide number of enantioenriched products have been synthesised using TKP **242** and **246** as the nucleophiles and important breakthroughs in the inclusion of alkyl TKPs have been made. Although not all of the examples have been furnished in high *er*, the inclusion of mono-activated and hindered α-alkyl TKPs in this type of catalysis is an extremely remarkable feature in itself that may help to extend organocatalysis to other related substrates. A wide range of subsequent transformations are possible onto the Michael TKP adducts. The samarium iodide chemistry is particularly

noteworthy owing to the unique possibility of varying the reaction outcome by the simple addition of superstoichiometric amounts of water to the media.

Subsequent research in this project will be needed to shed light on some unclear areas. Optimising the catalyst to furnish highly enantioenriched Michael products from alkyl TKPs should be one of the first priorities by either finding the right catalyst in the literature or developing an entirely new one to suit our specific needs based on recent advances in the literature such as the inclusion squaramides in the cinchona alkaloid scaffolds. Studies presented in this chapter should be of great help in the process.

Different TKPs, such as α-arylated ones, can also be synthesised to expand the reaction scope. Likewise, various other electrophiles can be screened, not only carbon based ones, *e.g.* carbonyls or Mannich ones, but also heteroaromatic ones such as dithiols or azadicarboxylates.

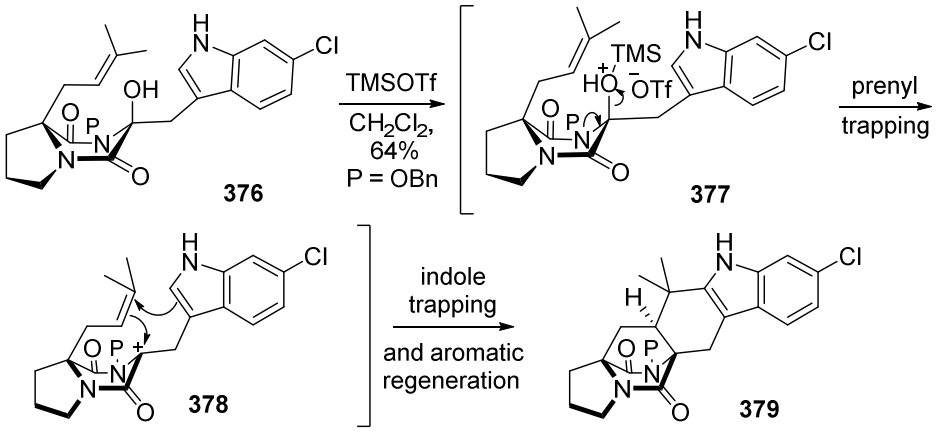
As far as the TKP deprotection is concerned, studies in our laboratory have already demonstrated that PMB can be a suitable protecting group, prone to deprotection and reliably delivering high *er* across many examples. Amino acid unveiling will have to be thoroughly explored but, as aforementioned, the initially developed conditions should prove consistent across all carbon substituted alkyl-TKPs and, possibly, aryl ones in the future.

Chapter Four

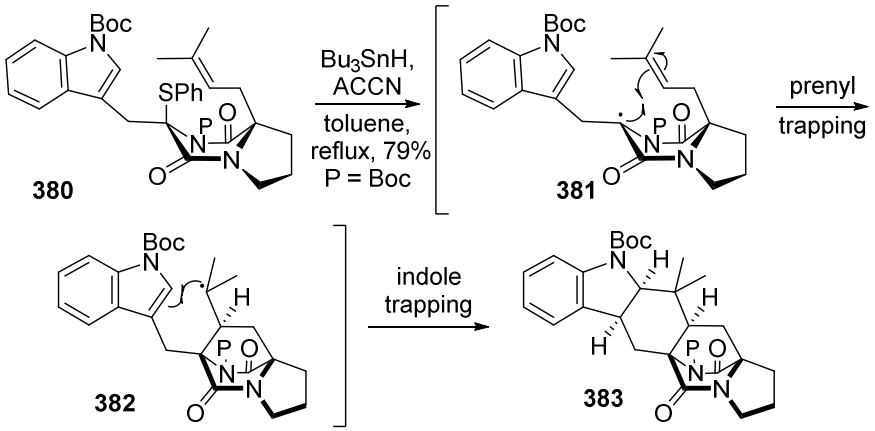
Synthesis of Bridged [2.2.2] Diketopiperazines

4.1. Aims and Objectives

Methodology orientated projects often have the ultimate goal of applying the targeted reaction to the total synthesis of natural products. The Simpkins group in particular has had a longstanding interest in the synthesis of natural products with DKPs embedded in their structure, especially those belonging to the bicyclo[2.2.2]diazaoctane family. Their intricate frameworks, coupled with the potent antitumoural properties they display,[32d] have motivated many research groups worldwide to attempt their total syntheses. Different approaches have been adopted for the cyclisation step, and different cascade processes were developed in our group to tackle the total synthesis of some members of this family (Scheme 4.1, 4.2).[33d,136a]



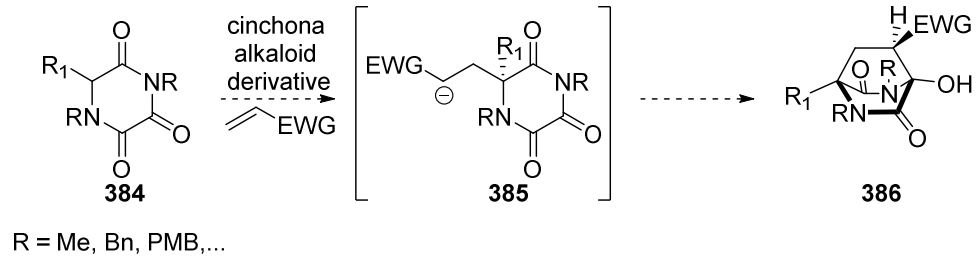
Scheme 4.1 Cationic cascade to form bicyclic DKP core of *ent*-malbrancheamide



Scheme 4.2 Radical cascade to form bicyclic DKP core of stephacidin A

Cationic and radical cascades were optimised to furnish key intermediates in the total syntheses of *ent*-malbrancheamide and stephacidin A in a diastereomeric ratio of 4:1 and 3:1 respectively, favouring the desired epimer at the bridged DKP position. The stereochemical outcome can be explained by minimisation of steric hindrance between the nitrogen protecting group and the *gem*-dimethyl of the prenyl chain in the respective transition states.

Although these reports, in combination with the rest of the bridge closing strategies, are impressive pieces of research, we aimed to apply the TKP methodology to synthesise bicyclo[2.2.2]diazaoctane derivatives. Chiral TKPs were hypothesised to be capable of bridge closing under specific conditions after the Michael addition step as shown in Scheme 4.3. Specifically, the possibility of developing a tandem process where the enolate intermediate from the Michael addition would be reactive enough to attack the proven electrophilic C-3 position was particularly appealing.



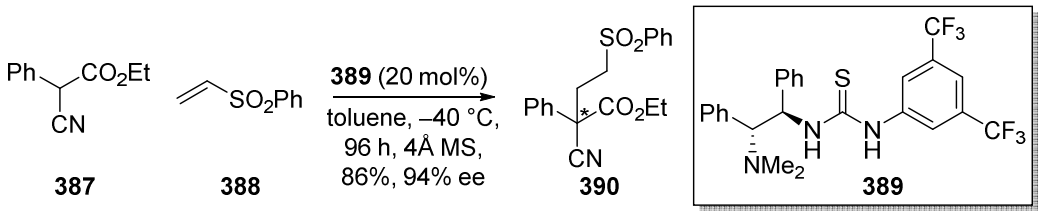
Scheme 4.3 Bicyclic DKP proposed sequence

As outlined in the previous chapter, several conditions such as trimethyltinhydroxide or potassium hydroxide achieved this goal albeit either not to completion or the bicyclic system was cleaved due to the very reactive media. Clearly, the Michael acceptors would have to play a fundamental role for the tandem transformation to be successful. Ketones or aldehydes would not fulfil this role as previously observed. A *α*,*β*-unsaturated carbonyl derivatives whose resulting enolate from the Michael additions could be reactive enough to perform an aldol-type condensation onto the C-3 carbonyl would be needed. For instance, ketone *α*-protons are very labile ($pK_a \leq 20$) and hence, the corresponding enolates are relatively stable and not so reactive, whilst other derivatives, such as nitriles or esters, have less acidic *α*-protons and so their enolates are less stable and more reactive. Therefore, using Michael acceptors that produce highly reactive enolate intermediates might trigger the desired tandem process and furnish the bicyclic structures in a two-step-one-pot sequence.

4.2. Organocatalysed Tandem Michael-Aldol Reaction on Triketopiperazines

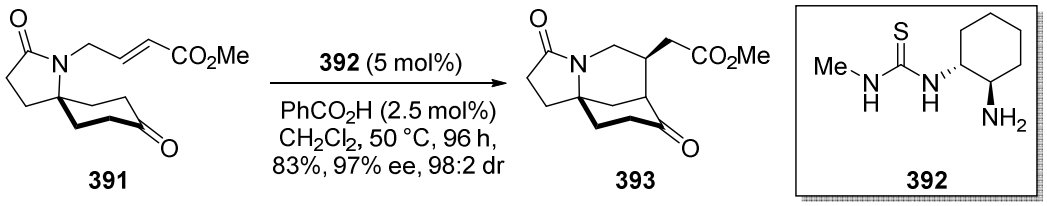
Initially, the literature was examined to find examples of Michael acceptors different from the ones used in the previous chapter and reported to participate in asymmetric organocatalysed Michael additions. Disappointingly, just a handful of publications were

available with different acceptors. For instance, phenyl vinyl sulfone, a fairly stable Michael acceptor, was employed in the 1,4-addition of 1,3-cyanoesters using thiourea derived chiral catalyst **389** (Scheme 4.4).[179]



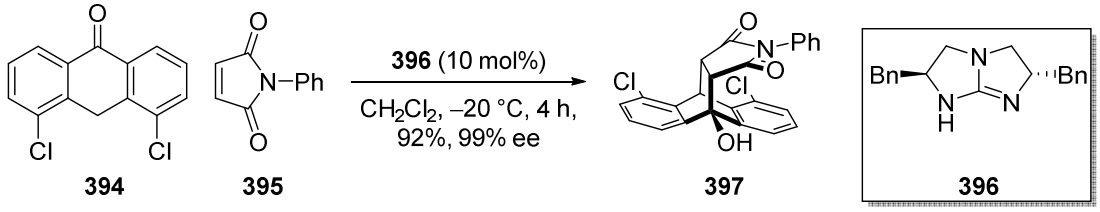
Scheme 4.4 Previous examples with phenyl vinyl sulfone

Good yields and *ee* were obtained, not only using this Michael acceptor but the disulfone analogue too. As far as simple *α,β*-unsaturated esters were concerned, two studies have been recently published where ketone enolates are responsible for the intramolecular attack to furnish chiral cyclic structures, such as **393**, and three stereocentres are generated enantio- and diastereoselectively (Scheme 4.5).[180]



Scheme 4.5 Intramolecular Michael addition of *α,β*-unsaturated ester

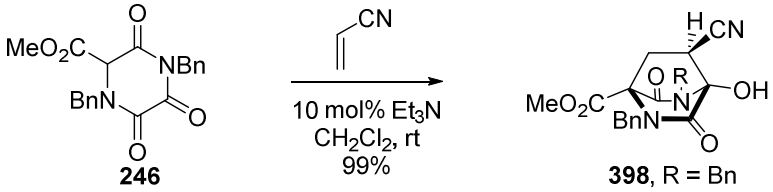
This desymmetrisation was promoted *via* enamine catalysis, similarly to List's proline catalysed aldol reaction. Lastly, the work published by Shen *et al.* showed a similar transformation to the envisioned tandem sequence using guanidine chiral catalyst **396** (Scheme 4.6).[181]



Scheme 4.6 Organocatalysed formal Diels-Alder reaction

Nucleophilic attack of **394** onto the unsaturated position of the *N*-phenyl maleimide, followed by aldol-type condensation furnished bicyclic adduct **397**, in a formal Diels-Alder type reaction. Differently *N*-substituted maleimides were employed in this study, as well various fumarate ester derivatives, such as the ones used in Scheme 3.13. Hence, we were determined to use maleimides as part of the scope to determine whether they would fall under the open TKP category or it would do the tandem sequence.

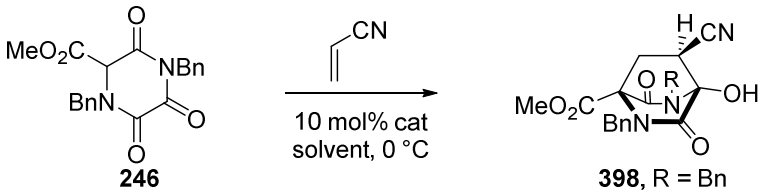
Although literature precedents were scarce, simple Michael acceptors were explored to determine whether they show any reactivity. Typical conditions were used with activated TKP **246** and acrylonitrile as the Michael acceptor to afford achiral DKP **398** (Scheme 4.7).



Scheme 4.7 First attempt to synthesise bicyclic DKP **398** using acrylonitrile

Pleasantly, not only could this Michael adduct promote the desired 1,4-addition, but also the envisioned tandem process was spontaneously triggered in the reaction mixture with no other additives required in a completely diastereoselective process. The greater nucleophilicity of the enolate intermediate was presumed to be playing a fundamental role in the subsequent

bridge closing reaction. The reaction conditions were optimised using this type of electrophile (Table 4.1).



Entry	Catalyst	Solvent	time[a]	Yield (%)[b]	er (%)[c]
1	**142**	CH_2Cl_2	8	99	84:16
2	**148**	CH_2Cl_2	8	98	88:12[d]
3	**201**	CH_2Cl_2	24	80	95:5
4	**207**	CH_2Cl_2	24	82	90:10[d]
5	**204**	CH_2Cl_2	30	82	96:4[d]
6	**210**	CH_2Cl_2	8	88	97:3[d]
7	**210**	THF	8	50	85:15[d]
8	**210**	Toluene	10	80	96:4[d]
9	**210**	MeCN	-	-	-
10	**210**	$CHCl_3$	8	78	95:5[d]

[a] Hours. [b] Isolated yield after chromatography. [c] Determined by HPLC analysis. [d] Enantiomeric product with respect to entry 1. [e] Reaction conducted using 1 mol% catalyst.

Table 4.1 Reaction optimisation

Due to the inherent lower reactivity of the electrophile, all reactions were run at 0 °C in order not to extend the reaction times excessively. Noteworthy, use of the natural catalysts **142** and **148** (entry 1 and 2), as well as thiourea derived catalyst **210** (entry 6), resulted in complete reaction in shorter periods of time compared to previously optimal benzyl derived catalysts **201** and **204** (entry 3, 4 and 5). The distance between the reactive centres in the catalysts seemed to have a clear relationship with this phenomenon, being closer in the first case (**210**),

just a two carbon chain linking both functionalities, while remaining further apart in the latter (**201**, Figure 4.1).

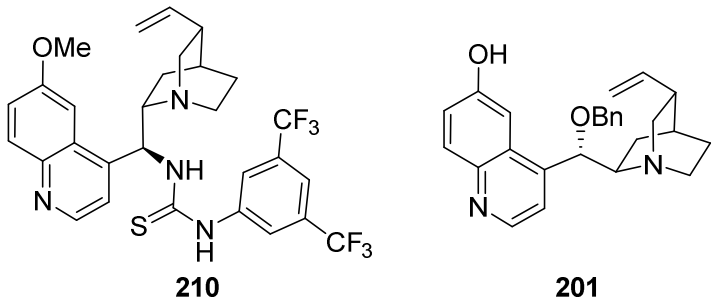
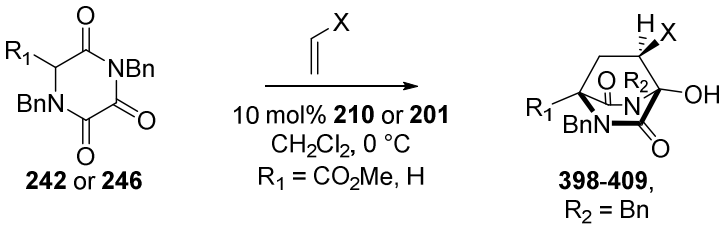


Figure 4.1 Optimal catalysts for tandem Michael-aldol reaction

The effect of this feature might be also linked with increased recorded reaction times, an average of three times longer. Owing to the reduced reaction time, and the greater *er* recorded (entry 6), catalyst **210** was chosen to be optimal for this asymmetric transformation. It was also worth mentioning that certain solvents had a clear negative influence on the reaction outcome. During the reaction optimisation in the previous chapter, the solvent was only witnessed to have a minor effect on the asymmetric reaction. Conversely, in the present case, some solvents made the reaction sluggish, such as THF (entry 7), or prevented it from happening, like acetonitrile (entry 9). Dichloromethane, in combination with catalyst **210**, was found to be the optimal conditions.

With these optimised conditions in hand, other Michael acceptors that could undergo this tandem transformation were screened (Figure 4.2).



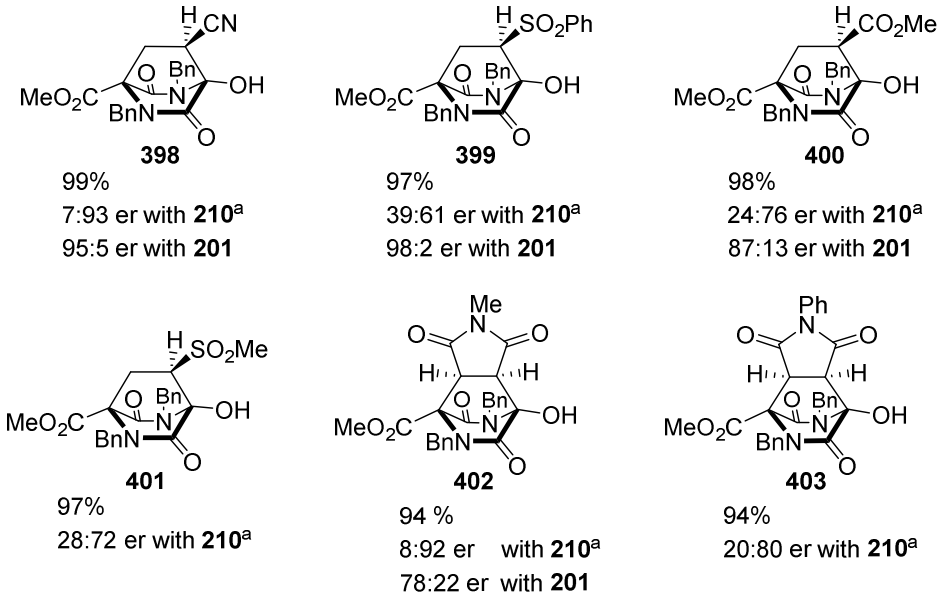


Figure 4.2 Scope of the reaction utilising TKP **246**. [a] Enantiomeric product of displayed compound

Simultaneously, the same optimised conditions were tried on the parent TKP **242** to check whether the reaction outcome was maintained (Figure 4.3).

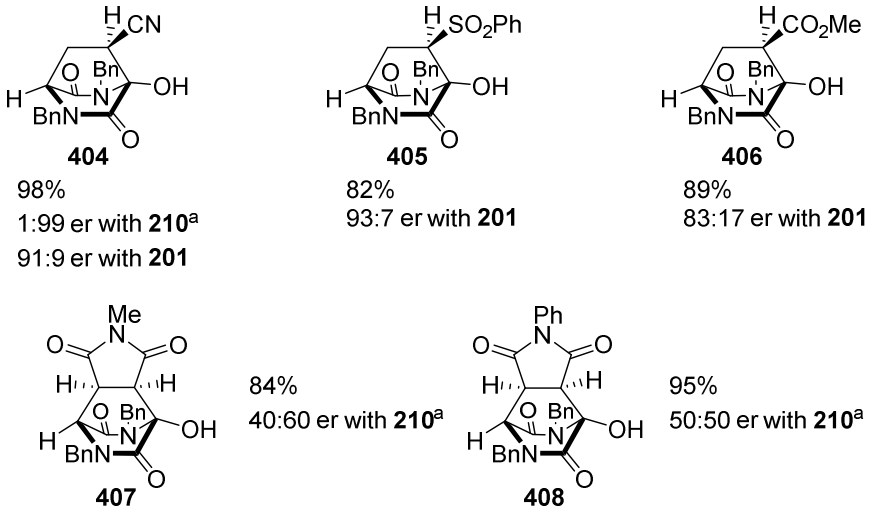


Figure 4.3 Scope of the reaction utilising TKP **242**. [a] Enantiomeric product of displayed compound

This reaction proved to be remarkably diastereoselective as three stereogenic centres were formed, albeit two of them were fixed by initial recognition. Bicyclic structures were afforded

as the only product of the reaction regardless of the TKP starting material used and only one diastereoisomer was isolated in all cases. No special care had to be taken during the asymmetric Michael addition of TKP **242** as the enolate could not be formed using the bridgehead proton and only the mono Michael bicyclic adduct was observed.

Previously optimised conditions did not seem universally applicable to all cases. Every electrophile used in this scope was different from one another, so this lack of homogeneity was not entirely surprising. Employing catalyst **201**, which was also found to deliver great results in this case albeit extended reaction times, gave improved results in some cases. Arguably, it could be inferred that catalyst **210** was optimal when the size of the Michael acceptors remained small (acrylonitrile or maleimides). When larger α,β-unsaturated electrophiles were employed, *e.g.* acrylic esters or vinyl sulfones, the distance between the active sites in the catalyst was reasoned not to be enough for an optimal interaction between nucleophile and electrophile in the transition state.

As far as *er* were concerned, mixed results were observed across the board, and no consistent trend could be easily extrapolated, which was not entirely surprising due to the great disparity among the electrophiles. Pleasingly, maleimides behaved in the same fashion as previously reported by Shen *et al.* although the levels of enantioselectivity were good, using TKP **246**, to poor with TKP **242**. Absolute stereochemistry (Flack parameter: 0.04(8)) was assigned by X-ray crystal determination of structure **406** (Figure 4.4). X-Ray crystal structure from compound **407** was also elucidated and is included in Appendixes 2.

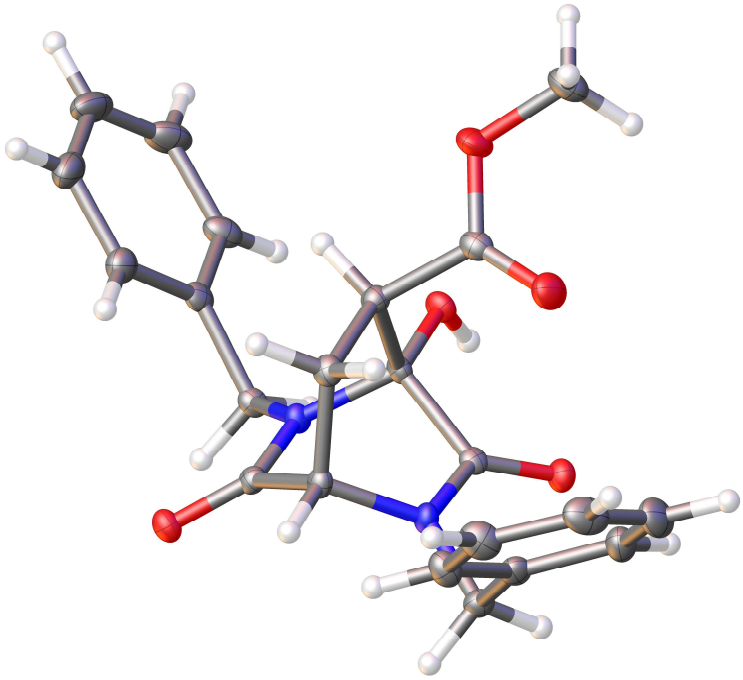
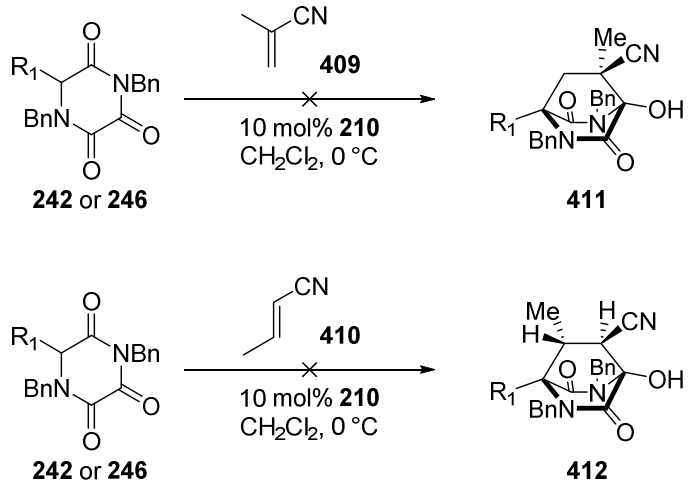


Figure 4.4 X-Ray crystal structure of bicyclic DKP **406** with 50% of ellipsoid probability

As inferred from the crystal structure, the substituent on the bridged chain was located above the less hindering of the two possible functional groups, *i.e.* the carbonyl instead of the benzylated nitrogen selectively. Also noteworthy, this configuration was in accordance with the relative stereochemistry observed in the bicyclo[2.2.2]diazaoctane natural products so a total synthesis using this approach might be accessible once the full potential of this methodology was explored.

The reactivity of these types of electrophiles bearing different substituents in either α or β position was explored next. The scope of this study was limited by the electron withdrawing properties of the substituents in either position of the double bond. Analogous to the previous

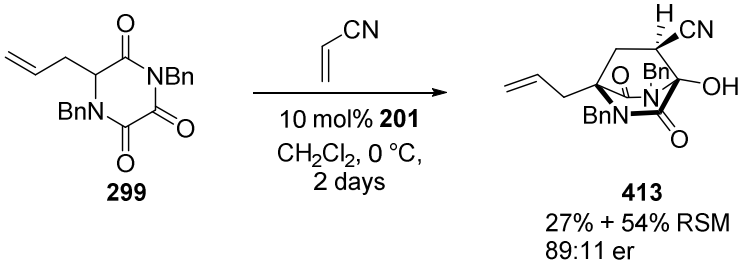
chapter, Michael acceptors having a methyl substituent in either of the positions were tested under the optimal catalytic conditions (Scheme 4.8).



Scheme 4.8 Attempts with both α and β methyl substituted acrylonitrile

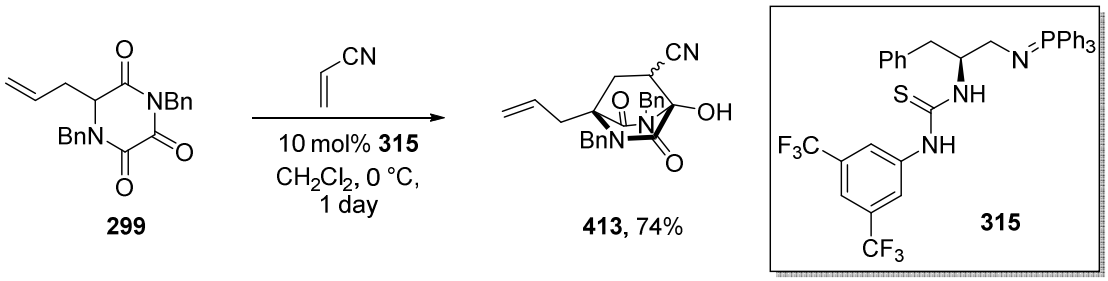
Disappointingly, no reaction took place employing any of the methyl acrylonitrile derivatives in Scheme 4.8. However, this lack of reactivity was expected given the aldehyde counterparts did not give any sign of reactivity either. No more substitution patterns were explored as they were presumed either unreactive or unable to furnish the bicyclic adducts in a tandem process, as it was demonstrated in the previous chapter.

The tandem Michael-aldol type reaction on alkylated TKPs was subsequently investigated. Using TKP **299** and the optimised conditions, product **413** was successfully isolated from the reaction mixture (Scheme 4.9).



Scheme 4.9 Alkyl TKP Michael reaction

Moderate yields of product were isolated albeit in good levels of induced asymmetry and as a single diastereomer. This feature was in sharp contrast with the reaction outcome using the more basic Dixon's triarylamino phosphorane catalyst **315**.[165] Upon subjecting TKP **299** to the same reaction conditions, and only changing the organocatalyst, a separable mixture of diastereoisomers were isolated in a 1:1 ratio, although the reaction time was notably reduced and no starting material was recovered (Scheme 4.10).



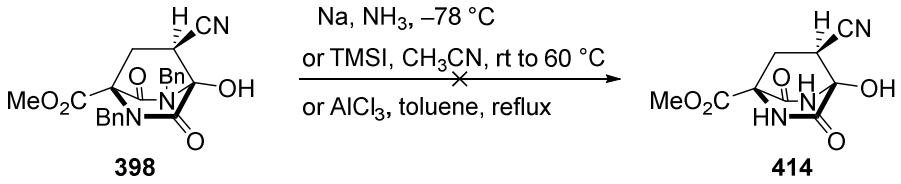
Scheme 4.10 Alkyl TKP Michael reaction

This lack of diastereocontrol could be related to the unrestricted rotation of the catalyst, which might not adopt a fixed conformation during the transition step, affording an epimeric even distribution on the nitrile *α*-position, despite the increased hindrance of the benzyl nitrogen position.

4.3. Further Transformations

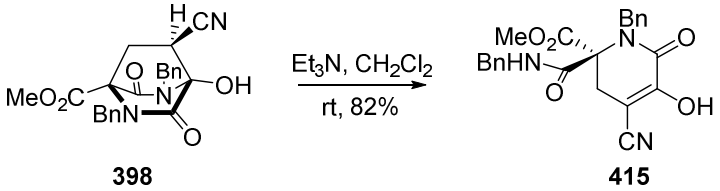
With a set of optimised conditions to afford enantiomerically enriched bridged DKPs in hand, we turned our attention to develop new strategies to make those products more synthetically attractive. For this type of molecule, with a structure clearly related to the DKP core of an extremely important class of natural products, a mild deprotection method was thought to be critically important should the natural product structure ever be attempted.

Similar conditions to the ones applied to the open TKPs were also tried here. The most common benzyl deprotection procedures were used (Scheme 4.11).



Scheme 4.11 Attempts to debenzylated DKP **398**

Unfortunately, and similar to previous results, little success was observed in any of the explored conditions. Once more, amidic benzyl protecting groups proved highly resistant. However, an analogous outcome to the open TKP version was observed when the bicyclic system was subjected to soft basic media (Scheme 4.12).



Scheme 4.12 Bicyclic opening

Deprotonation of C-3 hydroxyl group followed by regeneration of the carbonyl moiety with concomitant TKP ring opening by breaking the adjacent carbon-nitrogen bond and enol formation afforded product **415**. Although no *er* was measured, it was expected to remain unvariable from the starting material **398**.

4.4. Summary and Future Work

An unprecedented tandem asymmetric Michael addition-aldol type transformation, in a formal Diels-Alder manner, was optimised to yield bicyclic DKP adducts equivalent to the core present in the bicyclo[2.2.2]diazaoctane natural product family. An ample range of uncommon electrophiles, scarcely used in the literature, were employed. The different functionalities on the bridge would give enough site selective reactivity for subsequent transformations.

Catalyst optimisation to furnish DKP adducts in better *er* will be necessary for selected electrophiles, such as maleimides, and possibly once this methodology is extended to the alkyl TKPs. In addition, other conditions should be explored in order to access an even wider range of electrophiles that are unreactive under the present conditions, *e.g.* α,β-unsaturated amides.

Further studies on different TKP starting materials as well as on the reactivity of the products will be of utmost importance so as the bicycle[2.2.2]diazaoctane products resemble more closely the natural members were a total synthesis ever attempted. Firstly, this methodology should be applicable to a proline TKP adduct. An ongoing PhD project in the Simpkins laboratory has demonstrated that this system is very capable of doing an analogous

transformation with an even larger number of electrophiles, probably due to the conformation forced by the fused five member ring. Secondly, a mild strategy for the removal of the C-3 hydroxy group should be devised as it is not present in the structure of natural products. This could also be used to introduce further functionalities needed in this position. As this hydroxy lactamic group is located in a bridge head position, no *N*-acyliminium chemistry is likely to work due to the impossibility for this centre to adopt a sp^2 conformation. Hence, other approaches, such as radical chemistry could prove useful in this particular case.

Lastly, a deprotection strategy needs to be optimised. If this chemistry is easily reproduced on the PMB or OBn protected TKPs, it may be recommended to use them instead due to the theoretically more feasible and milder deprotection strategies.

Chapter Five

Experimental part

5.1. General Methods

Reactions were carried out under nitrogen using dry solvents. All reagents were used as received from commercial suppliers unless otherwise indicated. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). NMR data were recorded on a Bruker AVIII300, or AVIII400 spectrometer. Chemical shifts (δ) are quoted in ppm and coupling constants (*J*) are shown in Hz to one decimal place. Spectra were recorded in deuterated chloroform (unless otherwise indicated) and calibrated using residual solvent resonances (^{1}H = 7.26 ppm; ^{13}C = 77.16 ppm). The multiplicities of ^{1}H NMR signals are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Data for ^{1}H NMR spectroscopy is reported as follows: chemical shift (multiplicity, coupling constant, number of protons, assignment); and for ^{13}C NMR spectra: chemical shift (assignment). 2-Dimensional homonuclear (^{1}H-^{1}H) and heteronuclear (^{1}H-^{13}C) NMR experiments, as well as PENDANT spectra, were regularly used for unequivocally assignments. All atoms are labelled to simplify assignments. These numbers do follow IUPAC naming conventions as strictly as possible. The progress of reactions was monitored by thin layer chromatography using Merck silica gel 60 F_{254} plates,

which were visualized with UV light and *p*-anisaldehyde, acidic potassium permanganate or ninhydrin. Flash column chromatography was carried out using Davisil 60Å silica gel and the indicated solvent systems. Optical rotations were measured as dilute solutions in the indicated solvent in a 25 mm glass cell using an Optical Activity PolAAr 2001 automatic polarimetre fitted with a sodium lamp. High performance liquid chromatography (HPLC) analysis was performed using a P580 Pump from Dionex, Chromeleon Client, version 6.80 SP1 Build 2238, Daicel Chiralcel OD Column (250 x 4.6 mm); Daicel Chiralpak AD Column (250 x 4.6 mm); Daicel Chiralpak IB (250 x 4.6 mm); Phenomenex Lux Cellulose-3 (250 x 4.6 mm), and Waters 996 Photodiode Array Detector for the UV detection, monitored at 210 nm, 220 nm or 230 nm.

5.2. Experimental for Chapter 2

Preparation of catalysts

Catalysts **142**, **148**, **149** and **102** were purchased from Aldrich Inc. and Acros Inc.

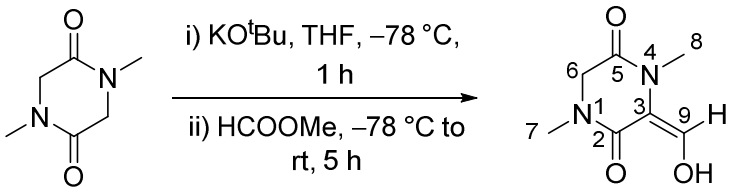
Catalysts **160**, **163**, **172**, **201 – 213** and **315** were prepared according to reported procedures and the spectroscopic data matches the corresponding literature.[130,165,182]

General Procedure A[144]

To a solution of the *N*,*N*'-dialkyl-2,5-DKP in dry THF under an atmosphere of nitrogen at −78 °C, a 1.0 M in THF solution of KO^{t}Bu (2.5 eq) was added. After the mixture was stirred for 5 min, the electrophile (5 eq) was added dropwise *via* syringe and the solution was stirred for 15 min at the same temperature. The reaction was allowed to warm to room temperature and left to stir for 5 hours. When the starting material was consumed the reaction was quenched with

saturated NH_4Cl and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the resulting organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrate under vacuum. The crude was purified by column chromatography on silica gel (CH_2Cl_2/acetone) to afford the product.

Synthesis of (*E*)-3-(hydroxymethylene)-1,4-dimethylpiperazine-2,5-dione **198**[147]

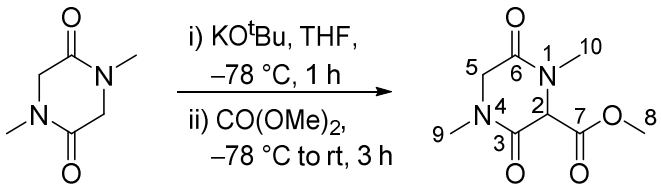


197 **198**

To solution of sarcosine anhydride **197** (250 mg, 1.8 mmol) in dry THF (20 mL) under an atmosphere of nitrogen at −78 °C, a solution of the KO^{t}Bu 1.0 M in THF (4.6 mL, 4.6 mmol) was added. After 5 min ethyl formate (0.528 g, 8.8 mmol, 0.54 mL) was added dropwise *via* syringe. The solution was stirred for further 15 min at the same temperature, allowed to warm to room temperature and left to stir for 5 h. The crude was cooled to 0 °C and the resulting cake was filtered and washed with THF, leaving a yellowish, sticky solid. This solid was subsequently dried under vacuum for 12 h. The dried cake was redisolved in water and acidifies with HCl 1.0 M until pH 3-3.5. The water was evaporated under reduced pressure and the resulting solid was washed with $CHCl_3$. The organic layer was evaporated affording product **198** (295 mg, 97%) as a white solid. m.p. 92 - 95 °C; IR ν_{max} /cm^{-1} 3356, 2951, 1738, 1661, 1424, 1405, 1323, 1255, 1165, 1043, 988, 920, 747, 678; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (d, *J* = 11.2 Hz, 1H, OH), 7.00 (d, *J* = 11.2 Hz, 1H, H-9), 4.05 (s, 2H, H-6), 3.10 (s, 3H,

H-7), 2.99 (s, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (C-5), 159.7 (C-2), 146.0 (C-9), 111.7 (C-3), 51.6 (C-6), 32.7 (C-8), 28.2 (C-7); *m/z* (ES) $C_7H_{11}N_2O_3$ $[MH]^+$ 171.1.

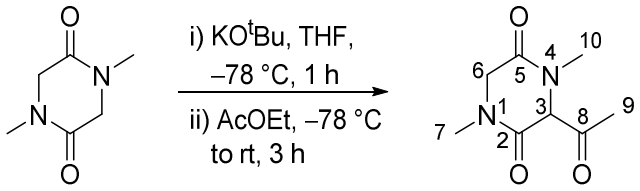
Synthesis of methyl 1,4-dimethyl-3,6-dioxopiperazine-2-carboxylate **200a**



197 **200a**

General procedure A using sarcosine anhydride **197** (500 mg, 3.52 mmol), dimethyl carbonate (1.3 mL, 10.6 mmol), THF (30 mL), 1.0 M solution of KO^{t}Bu in THF (9.2 mL, 9.2 mmol) was followed to synthesise product **200a** (432 mg) as a white solid in 62% yield after being purified by flash column chromatography (gradient: CH_2Cl_2/acetone = (8:2) to (7:3). m.p. 123 - 125 °C; IR ν_{max} /cm^{-1} 2956, 2902, 1733, 1674, 1438, 1402, 1239, 1211 1185, 1039, 1066; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, 1H, H-2), 4.20 (d, *J* = 17.3 Hz, 1H, H-5b), 3.86 (d, *J* = 17.3 Hz , 1H, H-5a), 3.86 (s, 3H, H-8), 3.01 (s, 3H, H-10), 2.97 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (C-7), 164.6 (C-3), 160.1 (C-6), 66.0 (C-2), 53.7 (C-8), 51.7 (C-5), 33.9 (C-9), 32.9 (C-10); *m/z* (ES) $C_8H_{12}N_2O_4$ $[MNa]^+$ 223.1.

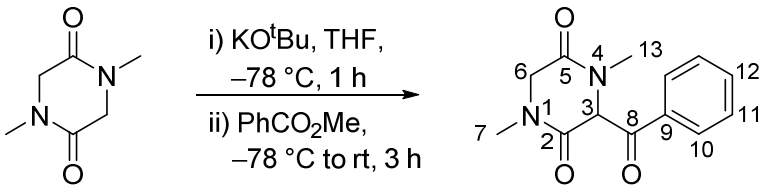
Synthesis of 3-acetyl-1,4-dimethylpiperazine-2,5-dione **200b**



197 **200b**

General procedure A using sarcosine anhydride **197** (1.0 g, 7.05 mmol), EtOAc (3.1 g, 35.2 mmol, 3.2 mL), THF (60 mL), 1.0 M solution of KO^{t}Bu in THF (18.3 mL, 18.3 mmol) was followed to synthesise product **200b** (1.03 g) as a white solid in 80% yield after being purified by flash column chromatography (gradient: CH_2Cl_2/acetone = (8:2) to (7:3). m.p. 134 - 135 °C; IR ν_{max} /cm^{-1} 2986, 2946, 1721, 1658, 1487, 1446, 1405, 1328, 1226, 1170, 1026; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (s, 1H, H-3), 4.01 (d, *J* = 17.3 Hz, 1H, H-6b), 3.78 (d, *J* = 17.3 Hz, 1H, H-6a), 2.94 (s, 3H, H-10), 2.85 (s, 3H, H-7), 2.41 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7 (C-8), 164.8 (C-2), 160.1 (C-5), 73.1 (C-3), 51.7 (C-6), 33.9 (C-7), 33.1 (C-10), 27.9 (C-9); *m/z* (ES) $C_8H_{12}N_2O_3$ $[MNa]^+$ 207.1.

Synthesis of 3-benzoyl-1,4-dimethylpiperazine-2,5-dione **200c**

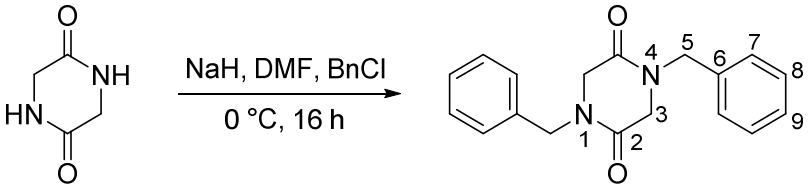


197 **200c**

General procedure A using sarcosine anhydride **197** (250 mg, 1.76 mmol), methyl benzoate (719 mg, 5.28 mmol, 0.66 mL), THF (15 mL), 1.0 M solution of KO^{t}Bu in THF (4.6 mL, 4.6

mmol) was followed to synthesise product **200c** (236 mg) as a white solid in 55% yield after being purified by flash column chromatography (gradient: CH_2Cl_2/acetone = (8:2) to (7:3). m.p. 114 - 116 °C; IR ν_{max} /cm^{-1} 3054, 3008, 2923, 2895, 1675, 1663, 1594, 1482, 1449, 1399, 1262, 1231, 1216, 1020, 960, 688; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dt, *J* = 8.6, 1.7 Hz, 2H, H-10), 7.66 (m, 1H, H-12), 7.52 (m, 2H, H-11), 5.62 (s, 1H, H-3), 4.22 (d, *J* = 17.3 Hz, 1H, H-6b), 3.84 (d, *J* = 17.3 Hz, 1H, H-6a), 2.92 (s, 3H, H-13), 2.87 (s, 3H, H-7). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7 (C-8), 166.1 (C-2), 160.4 (C-5), 134.8 (C-12), 133.9 (C-9), 130.1 (C-Ar), 128.9 (C-Ar), 68.6 (C-3), 52.1 (C-6), 34.0 (C-7), 33.1 (C-13); *m/z* (ES) $C_{13}H_{14}N_2O_3$ $[MNa]^+$ 269.1.

Synthesis of 1,4-dibenzylpiperazine-2,5-dione **199**[183]

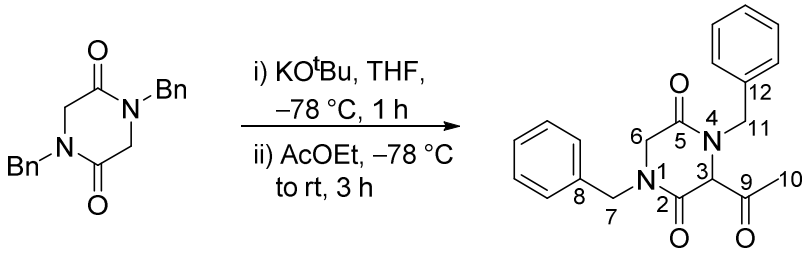


224 **199**

To a suspension of glycine anhydride **224** (570 mg, 5 mmol) in dry DMF (10 mL), NaH (600 mg, 60% suspension in mineral oil, 15 mmol) and benzyl chloride (1.30 g, 1.18 mL, 10.25 mmol) were added sequentially at 0 °C, warmed to room temperature and stirred overnight at room temperature. The reaction was quenched with water (15 mL) and dissolved in EtOAc (12 mL). Both layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with water (2 x 10 mL), brine (10 mL), dried over $MgSO_4$ and condensed under reduced pressure. The crude was purified by recrystallization with EtOAc to afford the title compound **199** (1.05 g, 71%) as a white solid.

m.p. 149 - 151 °C; IR ν_{max} /cm^{-1} 3029, 2936, 1650, 1469, 1455, 1423, 1331, 1274, 1069, 934, 745, 722, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 10H, H-Ar), 4.60 (s, 4H, H-5), 3.95 (s, 4H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (C-2), 134.9 (C-6), 129.0 (C-Ar), 128.6 (C-Ar), 128.2 (C-9), 49.3 (C-3), 49.2 (C-5); *m/z* (ES) $C_{18}H_{18}N_2O_2$, $[MNa]^+$ 317.1.

Synthesis of 3-acetyl-1,4-dibenzylpiperazine-2,5-dione **200d**

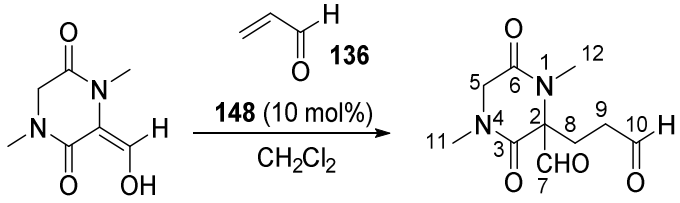


199 **200d**

General procedure A using DKP **199** (294 mg, 1 mmol), EtOAc (440 mg, 0.45 mL, 5.0 mmol), THF (15 mL), 1.0 M solution of KO^{t}Bu in THF (2.6 mL, 2.6 mmol) was followed to synthesise product **200d** (189 mg) as a white solid in 56% yield after being purified by flash column chromatography (gradient: CH_2Cl_2/acetone = (8:2) to (7:3). m.p. 125 - 126 °C; IR ν_{max} /cm^{-1} 3031, 2930, 1729, 1686, 1659, 1494, 1451, 1432, 1356, 1319, 1267, 1229, 1157, 1071, 946, 729, 695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 6H, H-Ar), 7.24 – 7.15 (m, 4H, H-Ar), 4.99 (d, *J* = 14.7 Hz, 1H, H-7b), 4.75 (s, 1H, H-3), 4.63 (d, *J* = 14.6 Hz, 1H, H-11b), 4.48 (d, *J* = 14.6 Hz, 1H, H-11a), 4.11 (d, *J* = 14.7 Hz, 1H, H-7a), 3.97 (d, *J* = 17.2 Hz, 1H, H-6b), 3.82 (d, *J* = 17.2 Hz, 1H, H-6a), 2.23 (s, 3H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0 (C-9), 165.0 (C-2), 160.5 (C-5), 134.7 (C-12), 134.5 (C-8), 129.1 (C-Ar), 129.0 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 69.9 (C-3), 49.8 (C-11), 49.5 (C-6), 48.7 (C-7),

27.8 (C-10); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{20}H_{20}N_2O_3Na$, 359.1374, found $[MNa]^+$ 359.1372.

Synthesis of 1,4-dimethyl-3,6-dioxo-2-(3-oxopropyl)piperazine-2-carbaldehyde **219**



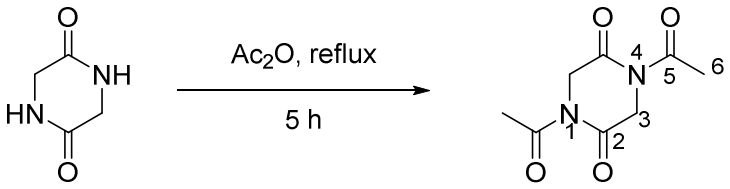
To a solution of DKP **198** (51 mg, 0.3 mmol) in CH_2Cl_2 (0.7 mL) catalyst **148** (9.73 mg, 0.03 mmol) was added. When the mixture became homogeneous acrolein (42 mg, 50 μL, 0.75 mmol) was added dropwise *via* syringe and the reaction was left to stir at room temperature for 24 h. The crude was filtered through a silica pad and washed with EtOAc (5 mL) to remove the catalyst. The reaction was purified by column chromatography on silica gel (CH_2Cl_2/acetone (1:1) to afford compound **219** as a colourless oil (23.7 mg, 35%). IR ν_{max} /cm^{-1} 2921, 1720, 1650, 1452, 1400, 1338, 1249, 1124, 1071, 1016, 734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.0 Hz, 1H, H-10), 9.46 (s, 1H, H-7), 4.06 (m, 2H, H-5), 2.99 (s, 3H, H-12), 2.86 (s, 3H, H-11), 2.77 (m, 1H, H-8b), 2.50 (m, 2H, H-9), 2.21 (m, 1H, H-8a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5 (C-10), 193.1 (C-7), 164.2 (C-3), 161.5 (C-6), 73.9 (C-2), 51.0 (C-5), 37.8 (C-9), 33.9 (C-12), 29.6 (C-11), 23.3 (C-8); *m/z* (ES HRMS) $C_{10}H_{15}N_2O_4$ requires 227.1032, found $[MH]^+$ 227.1024; $[\alpha]_D^{21}$= 0.00 (*c* 1.24, acetone)

Synthesis of di-*tert*-butyl 2,5-dioxopiperazine-1,4-dicarboxylate **225a**

224 **225a**

To a suspension of glycine anhydride **224** (2.00 g, 17.5 mmol) in dry DMF (20 mL), DMAP (0.43 g, 3.5 mmol) and di-*tert*butyl dicarbonate (8.03 g, 36.8 mmol) were added sequentially. The mixture was heated at 50 °C and stirred overnight. The reaction was quenched with water (15 mL) and dissolved in EtOAc (20 mL). Both layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over $MgSO_4$ and condensed under reduced pressure. The crude was purified by column chromatography on silica gel (Petrol/EtOAc (8:2) to afford compound **225a** (4.60 g, 84%) as a white solid. m.p. 125 - 126 °C; IR ν_{max} /cm^{-1} 2976, 1787, 1721, 1674, 1323, 1291, 1185, 1136, 945, 853; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 4H, H-3), 1.52 (s, 18H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C-2), 149.5 (C-5), 85.1 (C-3), 49.5 (C-6), 27.9 (C-7); *m/z* (ES) $C_{14}H_{22}N_2O_6$, $[MNa]^+$ 327.1.

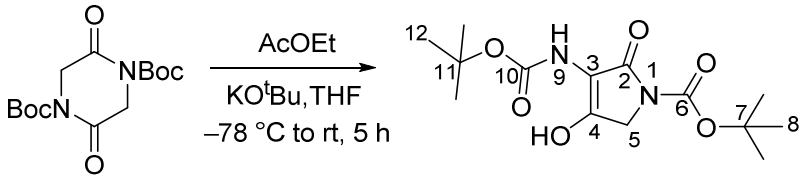
Synthesis of 1,4-Diacetylpiperazine-2,5-dione **225b**



224 **225b**

A suspension of glycine anhydride **224** (1.53 g, 13.4 mmol) in acetic anhydride (8 mL) was refluxed for 5 h. The reaction was allowed to cool down to room temperature, the solvent was azeotropically removed under reduced pressure (MeOH and Toluene) and the resulting brown solid was purified by recrystallization (Et_2O), to afford compound **225b** (2.39 g, 90%) as a white solid. m.p. 97 - 98 °C; IR ν_{max} /cm^{-1} 2926, 1700, 1416, 1358, 1306, 1261, 1225, 1179, 1129, 1078, 1040, 975, 947; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (s, 4H, H-3), 2.59 (s, 6H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C-5), 165.9 (C-2), 47.2 (C-3), 26.7 (C-6), *m/z* (EI) $C_8H_{10}N_2O_4$, $[M]^+$ 198.1.

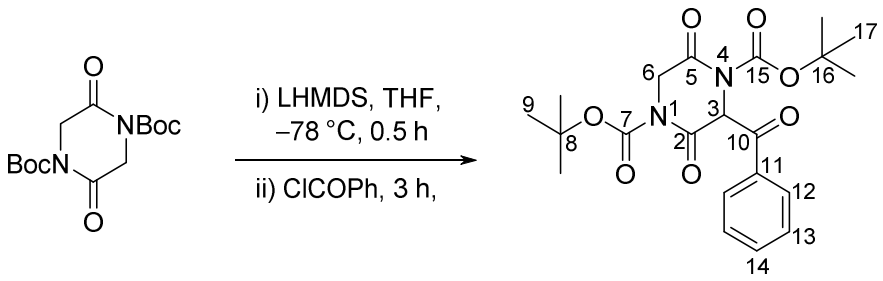
Synthesis of *tert*-butyl 3-((tert-butoxycarbonyl)amino)-4-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate **226**[152]



225a **226**

General procedure A was followed using di-tert-butyl 2,5-dioxopiperazine-1,4-dicarboxylate **225a** (160 mg, 0.48 mmol), EtOAc (220 mg, 0.23 mL, 2.5 mmol), THF (7 mL), 1.0 M solution of KO^{t}Bu in THF (1.3 mL, 1.3 mmol). Compound **226** was obtained (122 mg, 75%) as a white solid. m.p. 64 - 66 °C; IR ν_{max} /cm^{-1} 3333, 2982, 1770, 1710, 1681, 1658, 1532, 1360, 1279, 1257, 1152, 936, 774; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (s, 1H, OH), 6.57 (s, 1H, NH), 4.14 (s, 2H, H-5), 1.55 (s, 9H, H-12), 1.50 (s, 9H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (C-2), 155.7 (C-6), 150.7 (C-4), 148.9 (C-10), 104.0 (C-3), 83.3 (C-11), 83.0 (C-7), 47.0 (C-5), 28.1 (C-12, C-8); (ES) $C_{14}H_{22}N_2O_6$, $[MNa]^+$ 337.1.

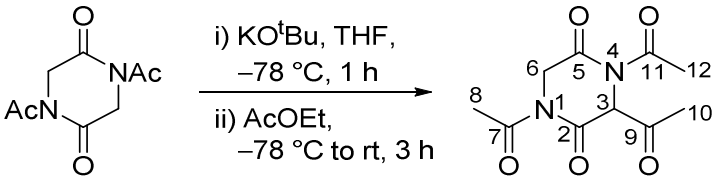
Synthesis of di-*tert*-butyl 3-benzoyl-2,5-dioxopiperazine-1,4-dicarboxylate **228**



225a **228**

To a solution of DKP **225a** (78.3 mg, 0.25 mmol) in dry THF under an atmosphere of nitrogen at −78 °C, a 1.0 M in THF solution of LHMDS (0.26 mL, 0.26 mmol) was added. After the mixture was stirred for 10 min, the electrophile (30.5 µL, 0.26 mmol) was added dropwise *via* syringe and the solution was stirred for 45 min longer at the same temperature. When the starting material was consumed the reaction was quenched with saturated NH_4Cl and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3 x 20 mL) and the resulting organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrate under vacuum. The crude was purified by column chromatography on silica gel (Petrol/EtOAc (8:2) to afford compound **228** (68.1 mg, 65%) as a white solid. m.p. 141 - 143 °C; IR ν_{max} /cm^{-1} 2986, 1780, 1728, 1686, 1451, 1401, 1370, 1296, 1227, 1143, 1083, 978, 723, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (m, 2H, H-12), 7.77 (m, 1H, H-14), 7.55 (t, *J* = 7.8 Hz, 2H, H-13), 6.47 (s, 1H, H-3), 4.73 (d, *J* = 17.9 Hz, 1H, H-6b), 4.26 (d, *J* = 17.9 Hz, 1H, H-6a), 1.52 (s, 9H, H-9), 1.49 (s, 9H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6 (C-10), 164.5 (C-5), 160.6 (C-2), 149.9 (C-15), 149.4 (C-7), 133.1 (C-14), 130.3 (C-11), 129.3 (C-12), 128.9 (C-13), 85.6 (C-8), 85.4 (C-16), 65.8 (C-3), 49.1 (C-6), 27.8 (C-9, C-17); *m/z* (ES HRMS) $C_{21}H_{26}N_2O_7Na$ requires 441.1638, found $[MNa]^+$ 441.1651.

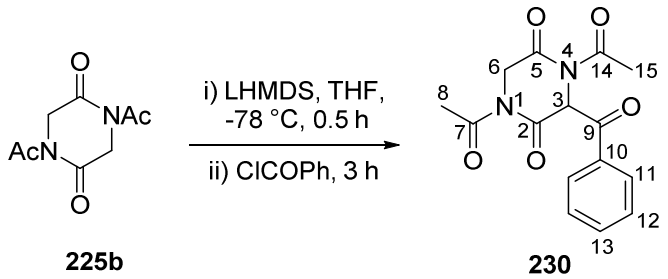
Synthesis of 1,3,4-triacetylpiperazine-2,5-dione **229**[152]



225b **229**

General procedure A was followed using 1,4-diacetylpiperazine-2,5-dione **225b** (100 mg, 0.51 mmol), EtOAc (66.7 mg, 68.5 µL, 0.76 mmol), THF (5 mL), 1.0 M solution of KO^{t}Bu in THF (0.76 mL, 0.76 mmol). Compound **229** was obtained as a colourless oil (25.8 mg, 22%). IR ν_{max} /cm^{-1} 2941, 1682, 1598, 1449, 1369, 1229, 1086, 966, 712, 685; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1H, H-3), 5.04 (d, *J* = 18.1 Hz, 1H, H-6b), 3.90 (d, *J* = 18.1 Hz, 1H, H-6a), 2.63 (s, 3H, H-12), 2.60 (s, 3H, H-8), 2.49 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5 (C-9), 171.2 (C-11), 170.6 (C-7), 165.0 (C-5), 162.3 (C-2), 68.5 (C-3), 46.5 (C-6), 27.4 (C-8), 26.8 (C-10), 26.6 (C-12); *m/z* (ES) $C_{10}H_{12}N_2O_5Na$, $[MNa]^+$ 263.1.

Synthesis of 1,4-diacetyl-3-benzoylpiperazine-2,5-dione **230**



225b **230**

To a solution of DKP **225b** (198.2 mg, 1 mmol) in dry THF under an atmosphere of nitrogen at −78 °C, a 1.0 M in THF solution of LHMDS (1.05 mL, 1.05 mmol) was added. After the mixture was stirred for 10 min, the electrophile (174 µL, 1.5 mmol) was added dropwise *via*

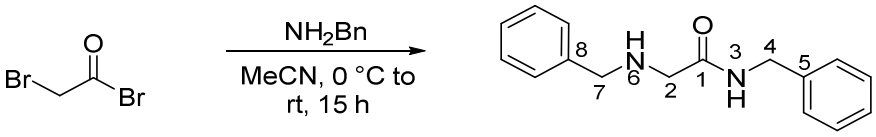
syringe and the solution was stirred for 45 min longer at the same temperature. When the starting material was consumed the reaction was quenched with saturated NH_4Cl and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3 x 30 mL) and the resulting organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrate under vacuum. The crude was purified by column chromatography on silica gel (Petrol/EtOAc (8:2) to (2:1) to afford compound **230** (158 mg, 52%) as a colourless oil. IR ν_{max} /cm^{-1} 1701, 1418, 1366, 1201, 1169, 1089, 1040, 963, 680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (m, 2H, H-11), 7.73 (m, 1H, H-13), 7.58 (m, 2H, H-12), 6.85 (s, 1H, H-3), 5.09 (d, *J* = 18.2 Hz, 1H, H-6b), 4.14 (d, *J* = 18.2 Hz, 1H, H-6a), 2.66 (s, 3H, H-15), 2.55 (s, 3H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0 (C-9), 171.4 (C-14), 170.8 (C-7), 166.0 (C-5), 162.4 (C-2), 135.3 (C-13), 132.9 (C-10), 130.3 (C-11), 129.0 (C-12), 64.0 (C-3), 47.0 (C-6), 27.0 (C-8), 26.6 (C-15); *m/z* (ES HRMS) $C_{15}H_{14}N_2O_5Na$ requires 325.0800, found $[MNa]^+$ 325.0787.

5.3. Experimental for Chapter 3

Preparation of triketopiperazine precursors

1,1'-(1,2-Dioxoethane-1,2-diyl)bis-1*H*-benzotriazole was synthesised according to literature procedures.[156]

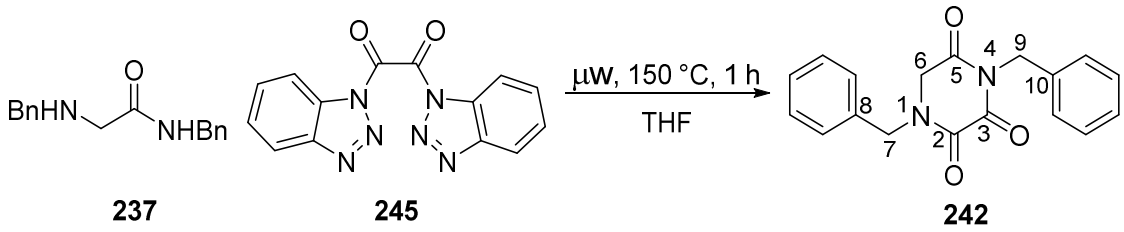
Synthesis of *N*-benzyl-2-(benzylamino)acetamide **237**[154]



239 **237**

To a solution of benzylamine was added (50 mL, 460 mmol)dissolved in dry acetonitrile (500 mL) bromoacetyl bromide (10 mL, 115 mmol) portion wise at 0 °C over a period of 10 minutes under nitrogen. The reaction was left warm to room temperature overnight. After the reaction went to completion, it was quenched with saturated $NaHCO_3$ (100 mL), extracted with EtOAc (3 x 200 mL), the organic layer was washed with brine (1 x 200 mL), dried over $MgSO_4$, filtered an evaporated to afford a colourless oil. The crude product was purified by column chromatography on silica gel (EtOAc/Petrol (1:2) to EtOAc (100%) to afford the desired product **237** (25.8 g, 88%) as a colourless oil. IR ν_{max} /cm^{-1} 3303, 3063, 3030, 2924, 2879, 1650, 1523, 1496, 1454, 1426, 1266, 1028, 910, 731, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H, H-3), 7.44 – 7.19 (m, 10H, H-Ar), 4.48 (d, *J* = 6.0 Hz, 2H, H-4), 3.78 (s, 2H, H-7), 3.38 (s, 2H, H-2), 1.90 (s, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C-1), 139.3 (C-8), 138.4 (C-5), 128.7 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 127.7 (C-Ar), 127.4 (C-Ar), 127.4 (C-Ar), 54.0 (C-7), 52.0 (C-2), 43.0 (C-4); *m/z* (ES HRMS) $C_{16}H_{19}N_2O$ requires 255.1497, found $[MH]^+$ 255.1501.

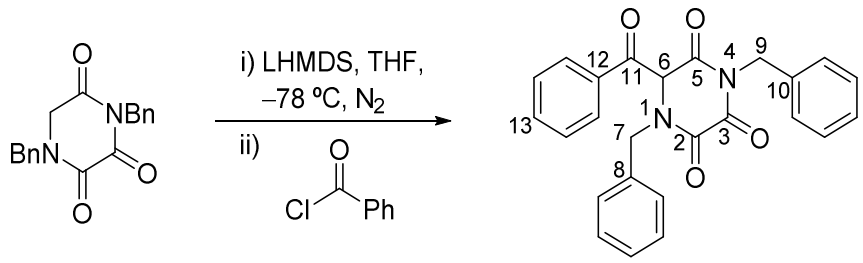
Synthesis of 1,4-dibenzylpiperazine-2,3,5-trione **242**



237 **245** **242**

To a suspension of 1,1'-(1,2-Dioxoethane-1,2-diyl)bis-1*H*-benzotriazole (153.2 mg, 0.53 mmol) in dry THF (1.5 mL) in a microwave vial, *N*-benzyl-2-(benzylamino)acetamide (127.0 mg, 0.50 mmol) was added in one portion. After the vial was closed and the reaction was stirred for 10 min the crude was subjected to the microwave reaction for 1h at 150 °C. The solvent was then evaporated and the residue was purified by column chromatography on silica gel (CH_2Cl_2/acetone (95:5) to afford the desired product **242** (102 mg, 67%) as a yellow solid. m.p. 177 - 180 °C; IR ν_{max} /cm^{-1} 3062, 3036, 2956, 2923, 1748, 1670, 1604, 1425, 1392, 1359, 1341, 1264, 1211, 981, 954, 723, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H, H-Ar), 7.31 – 7.26 (m, 3H, H-Ar), 7.25 – 7.19 (m, 5H, H-Ar), 4.93 (s, 2H, H-9), 4.61 (s, 2H, H-7), 4.12 (s, 2H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (C-5), 156.3 (C-3), 152.1 (C-2), 135.1 (C-10), 133.7 (C-8), 129.7 (C-Ar), 129.2 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 50.5 (C-7), 49.8 (C-6), 44.2 (C-9); *m/z* (ES HRMS) $C_{18}H_{17}N_2O_3$ requires 309.1239, found $[MH]^+$ 309.1231.

Synthesis of 6-benzoyl-1,4-dibenzylpiperazine-2,3,5-trione **247**

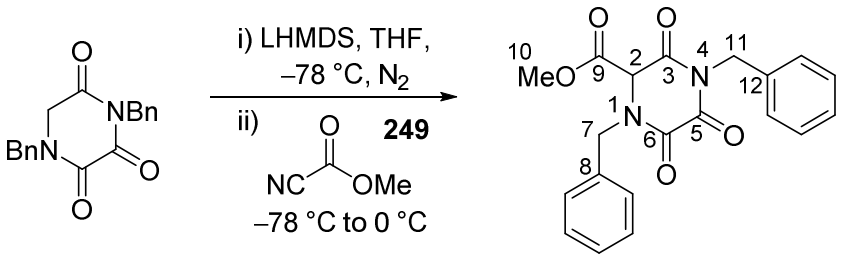


242 **247**

Triketopiperazine **242** (69.3 mg, 0.25 mmol) was dissolved in dry THF (3 mL) and cooled down to −78 °C. LHMDS (1M in THF, 0.26 mmol, 0.26 mL) was subsequently added dropwise and the mixture was left to stir for 45 min. Benzoyl chloride (105 mg, 0.75 mmol, 0.09 mL) was added in one portion and the reaction was further stir at −78 °C for 3h. When the starting material was consumed by TLC the crude was quenched with NH_4Cl (5 mL). Both layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (1 x 15 mL), dried over $MgSO_4$ and condensed under reduced pressure. The crude was purified by column chromatography on silica gel (Petrol/EtOAc (4:1) to Petrol/EtOAc (2:1) to afford **247** (57.1 mg, 56%) as a white solid. m.p. 154 – 155 °C; IR ν_{max} /cm^{-1} 3030, 3012, 1747, 1682, 1437, 1358, 1233, 1182, 933, 919, 731, 697, 683, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H, H-Ar), 7.66 (m, 1H, H-Ar), 7.49 (m, 2H, H-Ar), 7.32 – 7.18 (m, 8H, H-Ar), 7.14 (td, *J* = 7.7, 3.2 Hz, 2H, H-Ar), 5.86 (s, 1H, H-6), 5.08 – 4.95 (m, 2H, H-7b, H-9b), 4.85 (d, *J* = 13.9 Hz, 1H, H-9a), 4.29 (d, *J* = 14.6 Hz, 1H, H-7a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.1 (C-11), 162.6 (C-5), 156.7 (C-3), 154.6 (C-2), 135.3 (C-13), 134.9 (C-10), 132.9 (C-12), 132.7 (C-8), 129.7 (C-Ar), 129.1 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.1 (C-Ar), 65.1 (C-6), 49.7

(C-7), 44.7 (C-9); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{25}H_{20}N_2O_4Na$, 435.1321, found $[MNa]^+$ 435.1322.

Synthesis of methyl 1,4-dibenzyl-3,5,6-trioxopiperazine-2-carboxylate **246**



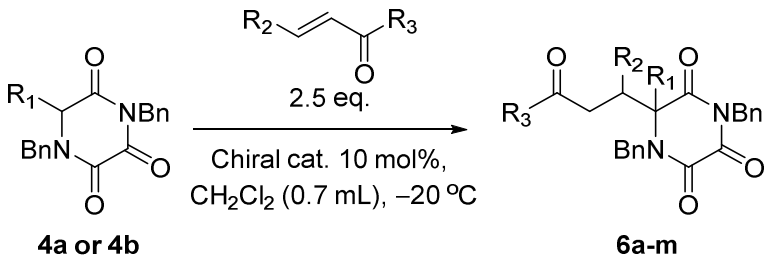
Triketopiperazine **242** (252.4 mg, 0.82 mmol) was dissolved in dry THF (4.5 mL) and cooled down to −78 °C. LHMDS (1M in THF, 0.90 mmol, 0.90 mL) was subsequently added dropwise and the mixture was left to stir for 45 min. Methyl carbonocyanidate (209.2 mg, 2.46 mmol, 0.20 mL) was added in one go and the reaction is left to stir for 20 min at –78 °C and it was let to warm up over 2h to 0 °C. When the starting material was consumed the mixture was quenched with NH_4Cl (5 mL) and EtOAc (5 mL). Both layers were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with brine (1 x 20 mL), dried over $MgSO_4$ and condensed under reduced pressure. The crude was purified by column chromatography on silica gel (Petrol/EtOAc (3:1) to afford **246** (262.5 mg, 87%) as a yellow solid. m.p. 89 – 91 °C; IR ν_{max} /cm^{-1} 2988, 2903, 1748, 1732, 1686, 1435, 1239, 1171, 1059, 731, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.22 (m, 10H, H-Ar), 5.07 – 4.92 (m, 3H, H-7b, H-11), 4.82 (s, 1H, H-2), 4.40 (d, *J* = 14.6 Hz, 1H, H-7a), 3.59 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (C-3), 161.9 (C-9), 155.9 (C-5), 153.0 (C-6), 134.7 (C-12), 133.1 (C-8), 129.5 (C-Ar), 129.1 (C-Ar), 129.0 (C-

Ar), 129.0 (C-Ar), 128.7 (C-Ar), 128.3 (C-Ar), 64.0 (C-2), 54.2 (C-10), 49.9 (C-7), 44.8 (C-11); *m/z* (ES HRMS) $C_{20}H_{18}N_2O_5Na$ requires 389.1113, found $[MNa]^+$ 389.1105.

Preparation of Racemic adducts:

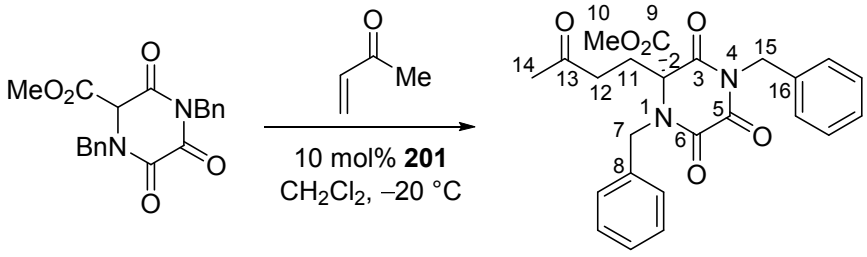
To a solution of triketopiperazine (0.1 mmol) in CH_2Cl_2 (0.7 mL) at −78 °C, triethylamine (10 mol%) was added followed by the Michael acceptor (2.5 eq). The mixture was allowed to warm to −20 °C and left to react until the starting material was consumed. The crude mixture was directly purified by flash chromatography.

General procedure B for enantioselective Michael addition of triketopiperazines to α,β-unsaturated ketones and aldehydes



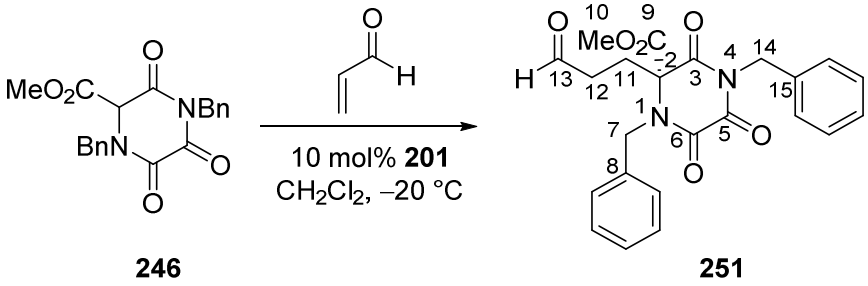
To a mixture of triketopiperazine (0.1 mmol) and chiral catalyst (4.0 mg, 10 mol%) dissolved in CH_2Cl_2 (0.7 mL) at −78 °C, the Michael acceptor was added neat over 1 minute. The reaction mixture was allowed to warm to –20 °C and left to react. After the starting material was completely consumed the crude was directly purified by flash chromatography.

Synthesis of methyl (*S*)-1,4-dibenzyl-3,5,6-trioxo-2-(3-oxobutyl)piperazine-2-carboxylate **250**



General procedure B using triketopiperazine **246** (37.5 mg) was followed to synthesise this product (43.6 mg) as a colourless oil in 99% yield from a reaction catalysed by **201** (10 mol%) at −20 °C for 1.5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **250** with 99:1 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, acetonitrile:water, 40:60, 1 mL/min, λ 210 nm, t(major) = 10.0 min, t(minor) = 11.1 min]. IR ν_{max} /cm^{-1} 2960, 2922, 1768, 1740, 1687, 1415, 1371, 1243, 1079, 705, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 2H, H-Ar); 7.36 – 7.26 (m, 8H, H-Ar); 5.11 (d, *J* = 13.7 Hz, 1H, H-15b); 5.05 (d, *J* = 13.7 Hz, 1H, H-15a); 4.71 (d, *J* = 15.0 Hz, 1H, H-7b); 4.60 (d, *J* = 15.0 Hz, 1H, H-7a); 3.33 (s, 3H, H-10); 2. 61 (m, 2H, H-11); 1.91 (m, 2H, H-12); 1.84 (s, 3H, H-14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9 (C-13), 165.8 (C-9), 165.5 (C-3), 155.2 (C-5), 154.2 (C-6), 134.8 (C-16), 134.8 (C-8), 129.2 (C-Ar), 129.2 (C-Ar), 128.7 (C-Ar), 128.7 (C-Ar), 128.4 (C-Ar), 72.3 (C-2), 53.7 (C-10), 47.7 (C-7), 44.8 (C-15), 36.2 (C-12), 29.6 (C-14), 27.6 (C-11); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{24}H_{24}N_2O_6Na$ requires 459.1532, found $[MNa]^+$ 459.1539; $[\alpha]_D^{21}$ = –25.5 (*c* 1.5, $CHCl_3$).

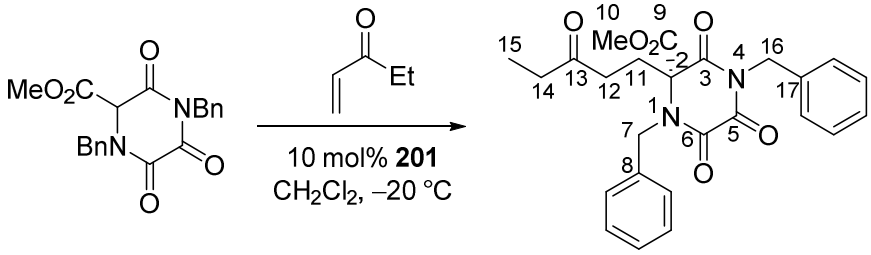
Synthesis of methyl (*S*)-1,4-dibenzyl-3,5,6-trioxo-2-(3-oxopropyl)piperazine-2-carboxylate **251**



246 **251**

General procedure B using triketopiperazine **246** (36.3 mg) was followed to synthesise this product (41.4 mg) as a colourless oil in 99% yield from a reaction catalysed by **201** (10 mol%) at −20 °C for 1 hour. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave product **251**. IR ν_{max} /cm^{-1} 3035, 2956, 1786 1757, 1689, 1440, 1386, 1282, 1008, 702, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H, H-13), 7.47 – 7.14 (m, 10H, H-Ar), 5.10 (d, *J* = 13.7 Hz, 1H, H-14b), 5.05 (d, *J* = 13.7 Hz, 1H, H-14a), 4.70 (d, *J* = 15.0 Hz, 1H, H-7b), 4.64 (d, *J* = 15.0 Hz, 1H, H-7a), 3.35 (s, 3H, H-10), 2.71 (m, 2H, H-11), 2.00 (m, 2H, H-12);^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1 (C-13), 164.8 (C-9), 164.3 (C-3), 154.1 (C-5), 153.2 (C-6), 133.8 (C-15), 133.7 (C-8), 128.1 (C-Ar), 127.7 (C- Ar), 127.7 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 71.3 (C-2), 52.8 (C-10), 46.8 (C-7), 43.9 (C-14), 36.0 (C-12), 24.9 (C-11); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{23}H_{22}N_2O_6Na$, 445.1376, found $[MNa]^+$ 445.1365; $[\alpha]_D^{21}$ = -4.5 (*c* 0.8, $CHCl_3$).

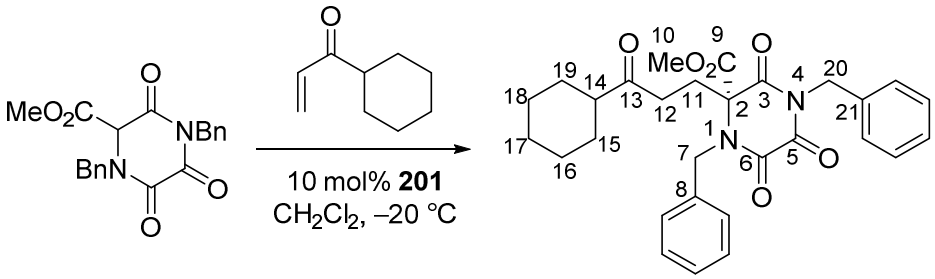
Synthesis of methyl (*S*)-1,4-dibenzyl-3,5,6-trioxo-2-(3-oxopentyl)piperazine-2-carboxylate **252**



246 **252**

General procedure B using triketopiperazine **246** (28.8 mg) was followed to synthesise this product (31.7 mg) as a colourless oil in 90% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 2 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **252** with 97:3 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 80:20, 1.0 mL/min, λ 210 nm, t(major) = 17.4 min, t(minor) = 22.4 min]. IR ν_{max} /cm^{-1} 3034, 2970, 1743, 1685, 1417, 1367, 1231, 1156, 734, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H, H-Ar), 7.36 – 7.25 (m, 8H, H-Ar), 5.11 (d, *J* = 13.7 Hz, 1H, H-16b), 5.05 (d, *J* = 13.7 Hz, 1H, H-16a), 4.73 (d, *J* = 15.0 Hz, 1H, H-7b), 4.59 (d, *J* = 15.0 Hz, 1H, H-7a), 3.33 (s, 3H, H-10), 2.66 (m, 2H, H-11), 2.06 (m, 2H, H-14), 1.90 (m, 2H, H-12), 0.90 (t, *J* = 7.3 Hz, 3H, H-15);^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7 (C-13), 165.9 (C-9), 165.6 (C-3), 155.2 (C-5), 154.2 (C-6), 134.9 (C-17), 134.8 (C-8), 129.2 (C-Ar), 129.2 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 72.4 (C-2), 53.7 (C-10), 47.7 (C-7), 44.8 (C-16), 35.7 (C-14), 34.9 (C-12), 27.7 (C-11), 7.6 (C-15); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ESI) $C_{25}H_{27}N_2O_6$ requires 451.1857, found $[MH]^+$ 451.1869; $[\alpha]_D^{21}$= – 30.9 (*c* 1.3, $CHCl_3$).

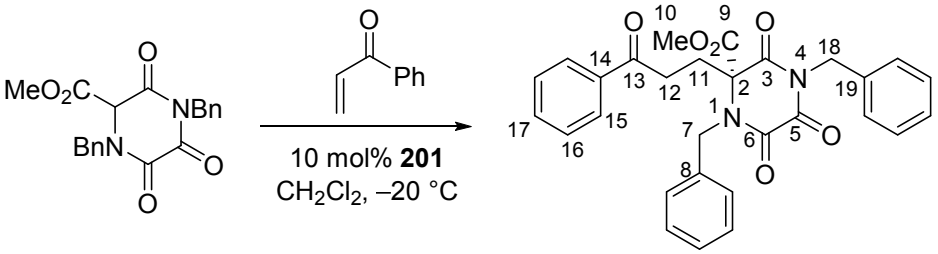
Synthesis of methyl (*S*)-1,4-dibenzyl-2-(3-cyclohexyl-3-oxopropyl)-3,5,6-trioxopiperazine-2-carboxylate **253**



General procedure B using triketopiperazine **246** (34.5 mg) was followed to synthesise this product (48.6 mg) as a colourless oil in 99% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 3 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (19:1) to (4:1) gave **253** with 97:3 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 85:15, 0.7 mL/min, λ 210 nm, t(major) = 30.8 min, t(minor) = 34.7 min]. IR ν_{max} /cm^{-1} 3035, 2931, 2854, 1743, 1685, 1496, 1417, 1367, 1234, 1150, 1030, 733, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H, H-Ar), 7.35 – 7.23 (m, 8H, H-Ar), 5.12 (d, *J* = 13.6 Hz, 1H, H-20b), 5.04 (d, *J* = 13.6 Hz, 1H, H-20a), 4.72 (d, *J* = 15.0 Hz, 1H, H-7b), 4.58 (d, *J* = 15.0 Hz, 1H, H-7a), 3.33 (s, 3H, H-10), 2.65 (m, 2H, H-11), 1.99 – 1.81 (m, 3H, H-12, H-14), 1.75 – 1.67 (m, 2H, H-16b, H-18b), 1.63 (m, 1H, H-17b), 1.56 – 1.44 (m, 2H, H-15b, H19b), 1.23 – 0.99 (m, 5H, H-15a, H-16a, H-17a, H-18a, H-19a);^{13}C NMR (101 MHz, $CDCl_3$) δ 210.3 (C-13), 165.9 (C-9), 165.7 (C-3), 155.2 (C-5), 154.2 (C-6), 134.9 (C-21, C-8), 129.3 (C-Ar), 129.2 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 72.4 (C-2), 53.6 (C-10), 50.6 (C-14), 47.8 (C-7), 44.7 (C-20), 33.1 (C-12), 28.3 (C-15), 28.1 (C-19), 27.9 (C-11), 25.6 (C-16), 25.5 (C-17), 25.4 (C-18); 1 signal in the C-H

aromatic region was not observed due to having equivalent resonances; *m/z* (ESI) $C_{29}H_{33}N_2O_6$ requires 505.2385, found $[MH]^+$ 505.2339; $[\alpha]_D^{21}$= –39.7 (*c* 1.3, $CHCl_3$).

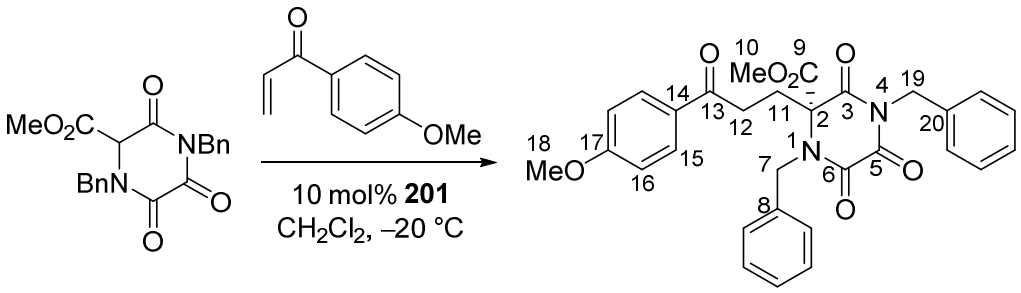
Synthesis of methyl (*S*)-1,4-dibenzyl-3,5,6-trioxo-2-(3-oxo-3-phenylpropyl)piperazine-2-carboxylate **254**



General procedure B using triketopiperazine **246** (34.5 mg) was followed to synthesise this product (46.0 mg) as a colourless oil in 98% yield from a reaction catalysed by **201** (10 mol%) at −20 °C for 1 hour. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (4:1) gave **254** with 99:1 er as determined by HPLC analysis [Daicel Chiralcel OD, hexanes:IPA, 80:20, 1.0 mL/min, λ 210 nm, t(major) = 28.9 min, t(minor) = 40.9 min]. IR ν_{max} /cm^{-1} 3065, 2956, 1763, 1743, 1682, 1599, 1496, 1367, 1222, 1151, 1080, 733, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 3H, H-15, H-17), 7.47 – 7.14 (m, 12H, H-24, H-Ar), 5.15 (d, *J* = 13.6 Hz, 1H, H-18b), 5.09 (d, *J* = 13.6 Hz, 1H, H-18a), 4.86 (d, *J* = 15.0 Hz, 1H, H-7b), 4.57 (d, *J* = 15.0 Hz, 1H, H-7a), 3.32 (s, 3H, H-10), 2.87 (dd, *J* = 9.0, 6.8 Hz, 2H, H-11), 2.56 (m, 1H, H-12b), 2.41 (m, 1H, H-12a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6 (C-13), 165.9 (C-9), 165.7 (C-3), 155.2 (C-5), 154.3 (C-6), 135.9 (C-14), 134.9 (C-19), 134.7 (C-8), 133.4 (C-17), 129.3 (C-Ar), 129.1 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 127.95 (C-Ar), 72.4 (C-2), 53.7 (C-

10), 47.7 (C-7), 44.8 (C-18), 31.5 (C-12), 28.1 (C-11); *m/z* (ESI) $C_{29}H_{27}N_2O_6$ requires 499.1867, found $[MH]^+$ 499.1869; $[\alpha]_D^{21}$= –39.3 (*c* 1.8, $CHCl_3$).

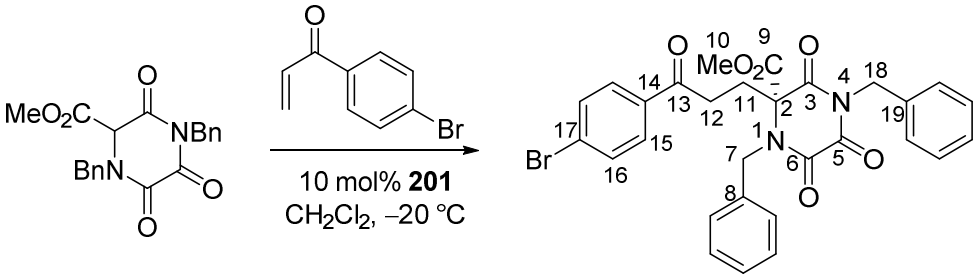
Synthesis of methyl (*S*)-1,4-dibenzyl-2-(3-(4-methoxyphenyl)-3-oxopropyl)-3,5,6-trioxopiperazine-2-carboxylate **255**



General procedure B using triketopiperazine **246** (26.1 mg) was followed to synthesise this product (38.5 mg) as a white solid in 87% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 1.5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **255** with 99:1 er as determined by HPLC analysis [Daicel Chiralcel OD, hexanes:IPA, 80:20, 1.0 mL/min, λ 210 nm, t(major) = 56.1 min, t(minor) = 86.7 min]. m.p. 167 – 168 °C; IR ν_{max} /cm^{-1} 2957, 1763, 1743, 1684, 1600, 1419, 1369, 1259, 1233, 1172, 1028, 735, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H, H-15), 7.42 (m, 2H, H-Ar), 7.34 – 7.12 (m, 8H, H-Ar), 6.84 (m, 2H, H-16), 5.12 (d, *J* = 13.6 Hz, 1H, H-19b), 5.06 (d, *J* = 13.6 Hz, 1H, H-19a), 4.90 (d, *J* = 15.0 Hz, 1H, H-7b), 4.48 (d, *J* = 15.0 Hz, 1H, H-7a), 3.87 (s, 3H, H-18), 3.26 (s, 3H, H-10), 2.83 (m, 2H, H-11), 2.51 (m, 1H, H-12b), 2.35 (m, 1H, H-12a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1 (C-13), 165.9 (C-9), 165.7 (C-3), 163.7 (C-17), 155.3 (C-5), 154.3 (C-6), 135.0 (C-20), 134.7 (C-8), 130.2 (C-15), 129.3 (C-Ar), 129.2 (C-

Ar), 129.0 (C-14), 128.7 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.9 (C-Ar), 113.7 (C-16), 72.4 (C-2), 55.5 (C-18), 53.6 (C-10), 47.6 (C-7), 44.7 (C-19), 31.1 (C-12), 28.3 (C-11); *m/z* (ESI) $C_{30}H_{28}N_2O_7Na$ requires 551.1801, found $[MNa]^+$ 551.1794; $[\alpha]_D^{21} = -28.8$ (*c* 1.3, $CHCl_3$).

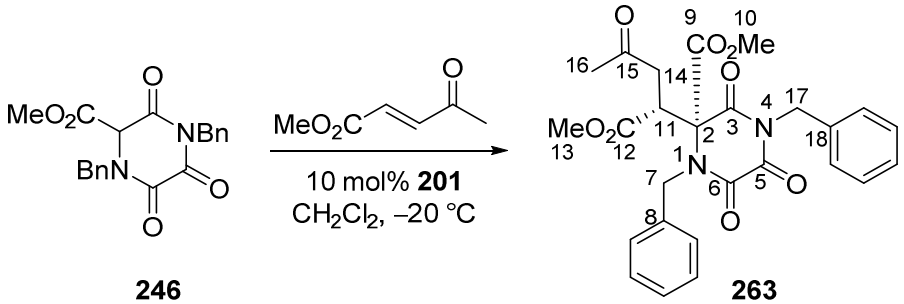
Synthesis of methyl (*S*)-1,4-dibenzyl-2-(3-(4-bromophenyl)-3-oxopropyl)-3,5,6-trioxopiperazine-2-carboxylate **256**



General procedure B using triketopiperazine **246** (32.1 mg) was followed to synthesise this product (56.4 mg) as a white solid in 98% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 1.5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **256** with 99:1 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 80:20, 1.0 mL/min, λ 210 nm, t(major) = 34.0 min, t(minor) = 47.1 min]. m.p. 124 – 127 °C ; IR ν_{max} /cm^{-1} 3052, 2954, 1764, 1743, 1684, 1585, 1496, 1368, 1229, 1071, 1009, 734, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H, H-15), 7.35 (m, 2H, H-Ar), 7.30 (m, 2H, H-16), 7.25 – 7.18 (m, 5H, H-Ar), 7.16 – 7.04 (m, 3H, H-Ar), 5.05 (d, *J* = 13.6 Hz, 1H, H-18b), 4.99 (d, *J* = 13.6 Hz, 1H, H-18a), 4.69 (d, *J* = 15.0 Hz, 1H, H-7b), 4.52 (d, *J* = 15.0 Hz, 1H, H-7a), 3.25 (s, 3H, H-10), 2.75 (m, 2H, H-11), 2.35 (m, 2H, H-12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6 (C-13), 165.9 (C-9), 165.6 (C-3), 155.2 (C-5), 154.3 (C-6),

134.9 (C-19), 134.8 (C-8), 134.6 (C-14), 131.8 (C-16), 129.4 (C-Ar), 129.1 (C-Ar), 128.7 (C-Ar), 128.7 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 72.4 (C-2), 53.7 (C-10), 47.8 (C-7), 44.8 (C-18), 31.5 (C-12), 28.1 (C-11); 2 signals in the C-H aromatic region were not observed due to having equivalent resonances; *m/z* (ESI) $C_{29}H_{26}N_2O_6{}^{79}Br$ requires 577.0968, found $[MH]^+$ 577.0974; $[\alpha]_D^{21}$= –17.4 (*c* 2.0, $CHCl_3$).

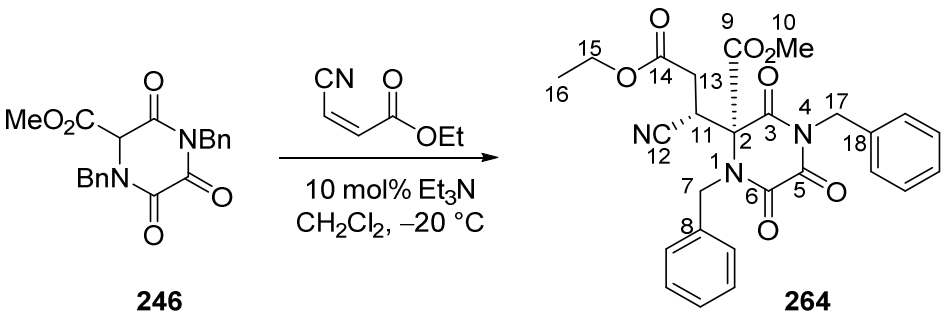
Synthesis of methyl (2*S*)-1,4-dibenzyl-2-((*R*)1-methoxy-1,4-dioxopentan-2-yl)-3,5,6-trioxopiperazine-2-carboxylate **263**



General procedure B using triketopiperazine **246** (32.0 mg) was followed to synthesise this product (27.8 mg) as a white solid in 67% yield from a reaction catalysed by **201** (10 mol%) at 0 °C for 48 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (7:3) gave **263** with 92:8 er as determined by HPLC analysis [Daicel Chiralpak IC, Heptane:Ethanol, 60:40, 2 mL/min, λ 210 nm, t(major) = 7.1 min, t(minor) = 11.8 min]. m.p. 93 – 95 °C; IR ν_{max} /cm^{-1} 3035, 2956, 1741, 1687, 1497, 1434, 1367, 1235, 1172, 1080, 1030, 910, 728, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H, H-Ar), 7.30 – 7.13 (m, 6H, H-Ar), 7.10 (m, 2H, H-Ar), 5.03 (d, *J* = 13.7 Hz, 1H, H-17b), 4.99 (d, *J* = 13.7 Hz, 1H, H-17a), 4.87 (d, *J* = 15.8 Hz, 1H, H-7b), 4.61 (d, *J* = 15.8 Hz, 1H, H-7a), 4.36 (dd, *J* = 10.5, 1.9 Hz, 1H, H-11), 3.46 (s, 3H, H-13), 3.41 (s, 3H, H-10), 2.57 (dd, *J* = 17.3, 10.5 Hz,

1H, H-14b), 2.26 (dd, *J* = 17.3, 1.9 Hz, 1H, H-14a), 1.82 (s, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2 (C-15), 169.9 (C-12), 165.3 (C-9), 164.8 (C-3), 154.7 (C-5), 154.6 (C-6), 134.8 (C-8), 134.6 (C-18), 129.5 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 73.7 (C-2), 53.8 (C-10), 52.9 (C-13), 48.8 (C-7), 45.2 (C-17), 44.9 (C-11), 40.0 (C-14), 29.5 (C-16); *m/z* (ES HRMS) $C_{26}H_{27}N_2O_8$ requires 495.1767, found $[MH]^+$ 495.1770; $[\alpha]_D^{21}$= 11.0 (*c* 1.5, $CHCl_3$).

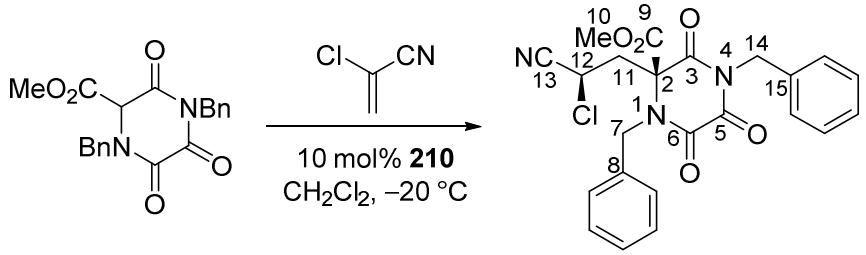
Synthesis of methyl (*S*)-1,4-dibenzyl-2-((*R*)-1-cyano-3-ethoxy-3-oxopropyl)-3,5,6-trioxopiperazine-2-carboxylate **264**



General achiral procedure B using triketopiperazine **246** (35.6 mg) was followed to synthesise this product (22.3 mg) as a white solid in 97% yield from a reaction at 0 °C for 48 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (3:2) gave compound **264**. m.p. 148 – 149 °C; IR ν_{max} /cm^{-1} 2957, 1745, 1690, 1497, 1433, 1373, 1253, 1080, 1009, 734, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H, H-Ar), 7.30 – 7.15 (m, 8H, H-Ar), 5.08 (d, *J* = 13.5 Hz, 1H, H-17b), 5.01 (d, *J* = 13.5 Hz, 1H, H-17a), 4.59 (s, 2H, H-7), 4.00 – 3.91 (m, 3H, H-11, H-15), 3.34 (s, 3H, H-10), 2.19 (dd, *J* = 16.5, 9.4 Hz, 1H, H-13b), 2.01 (dd, *J* = 16.5, 4.7 Hz, 1H, H-13a), 1.12 (t, *J* = 7.2 Hz, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5 (C-14), 163.8 (C-9), 162.8 (C-3), 154.0 (C-5), 153.5 (C-6), 134.1 (C-

18), 133.8 (C-8), 129.5 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 116.1 (C-12), 71.8 (C-2), 62.2 (C-15), 54.4 (C-10), 48.1 (C-7), 45.1 (C-17), 32.3 (C-11), 31.8 (C-13), 13.9 (C-16); *m/z* (ES HRMS) $C_{26}H_{25}N_3O_7Na$ requires 514.1590, found $[MNa]^+$ 514.1599.

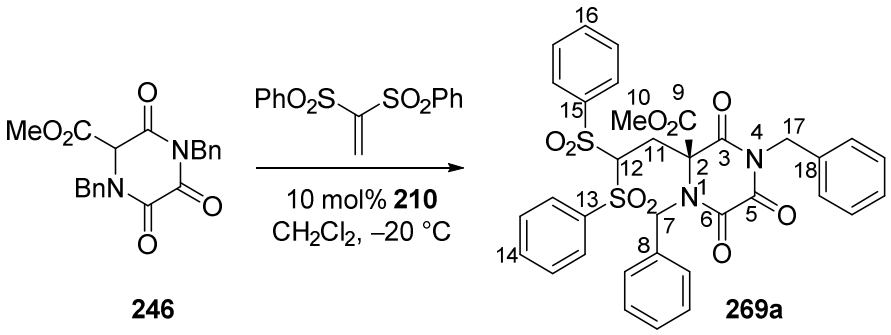
Synthesis of methyl (*R*)-1,4-dibenzyl-2-((*R*)-2-chloro-2-cyanoethyl)-3,5,6-trioxopiperazine-2-carboxylate **267**



General procedure B using triketopiperazine **246** (36.6 mg) was followed to synthesise this product (32.0 mg) as a white solid in 71% yield from a reaction catalysed by **210** (10 mol%) at –20 °C for 0.5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **267** with 96:4 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 85:15, 0.9 mL/min, λ 210 nm, t(minor) = 44.3 min, t(major) = 56.7 min]. m.p. 154 – 155. °C; IR ν_{max} /cm^{-1} 2981, 2954, 1744, 1687, 1498, 1449, 1349, 1232, 1208, 1159, 1074, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 7H, H-Ar), 7.34 – 7.28 (m, 3H, H-Ar), 5.13 (d, *J* = 13.8 Hz, 1H, H-14b), 5.08 (d, *J* = 13.8 Hz, 1H, H-14a), 4.75 (d, *J* = 15.1 Hz, 1H, H-7b), 4.68 (d, *J* = 15.1 Hz, 1H, H-7a), 3.96 (dd, *J* = 8.6, 6.4 Hz, 1H, H-12), 3.32 (dd, *J* = 15.5, 8.6 Hz, 1H, H-11b), 3.32 (s, 3H, H-10), 3.06 (dd, *J* = 15.5, 6.4 Hz, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8 (C-9), 164.1 (C-3), 154.4 (C-5), 153.7 (C-6),

134.3 (C-8), 134.2 (C-15), 129.1 (C-Ar), 129.1 (C-Ar), 129.0 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 115.2 (C-13), 71.0 (C-2), 54.2 (C-10), 48.6 (C-7), 45.3 (C-14), 38.5 (C-11), 36.7 (C-12); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES) $C_{23}H_{20}N_3O_5{}^{35}ClNa$ requires 476.0989 found $[MNa]^+$ 476.0977; $[\alpha]_D^{21}$= 30.2 (*c* 1.2, $CHCl_3$).

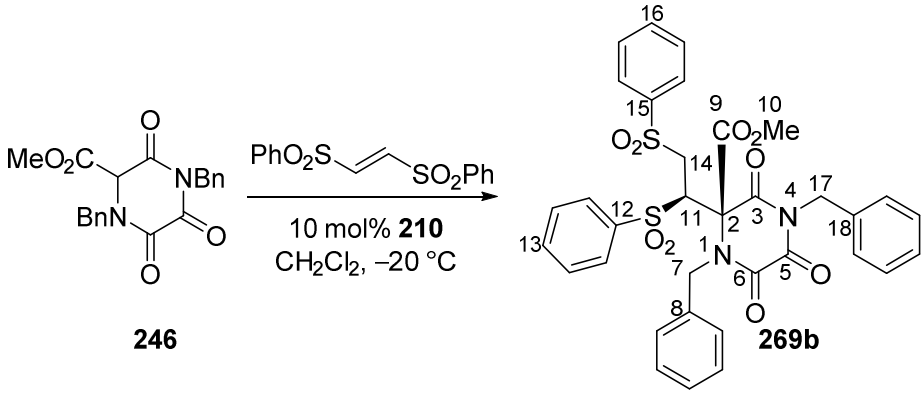
Synthesis of methyl (*R*)-1,4-dibenzyl-2-(2,2-bis(phenylsulfonyl)ethyl)-3,5,6-trioxopiperazine-2-carboxylate **269a**



General procedure B using triketopiperazine **246** (31.5 mg) was followed to synthesise this product (56.0 mg) as a white solid in 97% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 30 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (3:2) gave **269a** with 36:64 er as determined by HPLC analysis [Daicel Chiralpak ID-3, Heptane:Ethanol-Methanol, 70:30, 2 mL/min, λ 220 nm, t(minor) = 11.1 min, t(major) = 15.1 min]. m.p. 158 – 161 °C; IR ν_{max} /cm^{-1} 3070, 2925, 1765, 1744, 1685, 1498, 1446, 1376, 1313, 1226, 1149, 1080, 734, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 3H, H-Ar), 7.88 (dd, *J* = 8.4, 1.1 Hz, 2H, H-Ar), 7.77 (m, 2H, H-Ar), 7.69 – 7.59 (m, 5H, H-Ar), 7.37 (m, 2H, H-Ar), 7.33 – 7.21 (m, 6H, H-Ar), 5.63 (d, *J* = 15.0 Hz, 1H, H-7b), 5.10 (s,

2H, H-17), 4.38 (dd, *J* = 9.4, 2.9 Hz, 1H, H-12), 3.87 – 3.76 (m, 2H, H-7a, H-11b), 3.27 (dd, *J* = 17.0, 9.4 Hz, 1H, H-11a), 2.87 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (C-3), 165.4 (C-9), 154.9 (C-5), 154.3 (C-6), 136.5 (C-13), 136.1 (C-15), 135.3 (C-14), 135.2 (C-16), 134.8 (C-18), 133.8 (C-8), 130.2 (C-Ar), 129.9 (C-Ar), 129.9 (C-Ar), 129.5 (C-Ar), 129.3 (C-Ar), 129.0 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.0 (C-Ar), 79.3 (C-12), 70.0 (C-2), 53.4 (C-10), 47.1 (C-7), 44.9 (C-17), 29.0 (C-11); *m/z* (ES HRMS) $C_{34}H_{31}N_2O_9S_2$ requires 675.1471, found $[MH]^+$ 675.1484; $[\alpha]_D^{21}$ = –2.5 (*c* 1.1, $CHCl_3$).

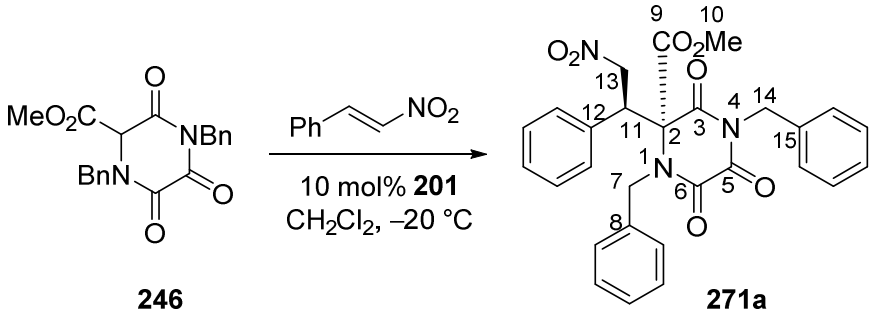
Synthesis of methyl (*R*)-1,4-dibenzyl-2-((*R*)-1,2-bis(phenylsulfonyl)ethyl)-3,5,6-trioxopiperazine-2-carboxylate **269b**



General procedure B using triketopiperazine **246** (36.6 mg) was followed to synthesise this product (35.0 mg) as a white solid in 52% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 20 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (3:2) gave compound **269b**. m.p. 126 – 128 °C; IR ν_{max} /cm^{-1} 3069, 1765, 1745, 1686, 1496, 1448, 1383, 1309, 1226, 1152, 1077, 1023, 910, 741, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H, H-Ar), 7.83 (m, 2H, H-Ar), 7.75 (m, 2H, H-Ar), 7.67 – 7.57 (m, 4H, H-Ar), 7.32 (m, 2H, H-Ar), 7.29 – 7.21 (m, 6H, H-Ar), 7.17 (m, 2H, H-Ar), 5.61 (d, *J* =

15.0 Hz, 1H, H-7b), 5.10 (d, *J* = 14.0 Hz, 1H, H-17b), 5.06 (d, *J* = 14.0 Hz, 1H, H-17a), 4.42 (dd, *J* = 9.4, 2.8 Hz, 1H, H-11), 3.79 (d, *J* = 15.0 Hz, 1H, H-7a), 3.77 (dd, *J* = 17.1, 3.2 Hz, 1H, H-14b), 3.26 (m, 1H, H-14a), 2.85 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (C-3), 165.4 (C-9), 155.0 (C-5), 154.4 (C-6), 136.4 (C-12), 136.0 (C-15), 135.3 (C-13), 135.3 (C-16), 134.8 (C-18), 133.7 (C-8), 130.2 (C-Ar), 129.9 (C-Ar), 129.5 (C-Ar), 129.3 (C-Ar), 129.0 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.0 (C-Ar), 79.1 (C-11), 69.9 (C-2), 53.5 (C-10), 47.1 (C-7), 44.9 (C-17), 28.9 (C-14); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{34}H_{31}N_2O_9S_2$ requires 675.1471, found $[MH]^+$ 675.1487; $[\alpha]_D^{21}$= 8.4 (*c* 1.0, $CHCl_3$).

Synthesis of methyl (*S*)-1,4-dibenzyl-2-((*S*)-2-nitro-1-phenylethyl)-3,5,6-trioxopiperazine-2-carboxylate **271a**

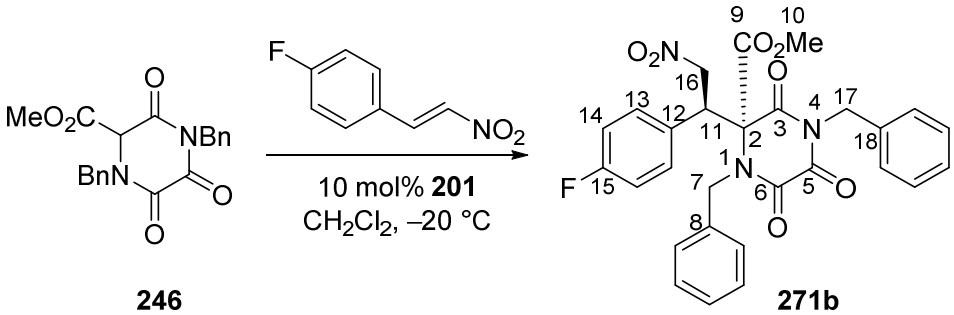


246 **271a**

General procedure B using triketopiperazine **246** (35.2 mg) was followed to synthesise this product (38.1 mg) as a white solid in 78% yield from a reaction catalysed by **201** (10 mol%) at −20 °C for 1.0 hour. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **271a** with 61:39 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, acetonitrile:water, 35:65, 1 mL/min, λ 210 nm, t(minor) =

19.1 min, t(major) = 22.1 min]. m.p. 168 – 169 °C; IR ν_{max} /cm^{-1} 2955, 1749, 1685, 1550, 1496, 1433, 1369, 1242, 1208, 1190, 1079, 1030, 750, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H, H-Ar), 7.48 – 7.42 (m, 3H, H-Ar), 7.36 – 7.28 (m, 3H, H-Ar), 7.27 – 7.20 (m, 3H, H-Ar), 6.99 (t, *J* = 7.3 Hz, 2H, H-Ar), 6.63 (d, *J* = 7.3 Hz, 2H, H-Ar), 5.49 (d, *J* = 15.2 Hz, 1H, H-7b), 5.27 (dd, *J* = 13.6, 2.4 Hz, 1H, H-13b), 5.02 (d, *J* = 13.4 Hz, 1H, H-14b), 4.91 (d, *J* = 13.4 Hz, 1H, H-14a), 4.84 – 4.69 (m, 2H, H-11, H-13a), 4.16 (d, *J* = 15.2 Hz, 1H, H-7a), 3.08 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (C-3, C-9), 154.0 (C-5), 152.6 (C-6), 134.2 (C-8), 133.6 (C-15), 131.2 (C-12), 130.6 (C-Ar), 129.9 (C-Ar), 129.6 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 75.3 (C-13), 73.1 (C-2), 53.4 (C-10), 47.0 (C-7), 46.4 (C-11), 45.1 (C-14); 2 signals in the C-H aromatic region were not observed due to having equivalent resonances*; m/z* (ESI) $C_{28}H_{25}N_3O_7Na$ requires 538.1590, found $[MNa]^+$ 538.1574; $[\alpha]_D^{21}$= 29.9 (*c* 0.9, $CHCl_3$).

Synthesis of methyl (*S*)-1,4-dibenzyl-2-((*S*)-1-(4-fluorophenyl)-2-nitroethyl)-3,5,6-trioxopiperazine-2-carboxylate **271b**

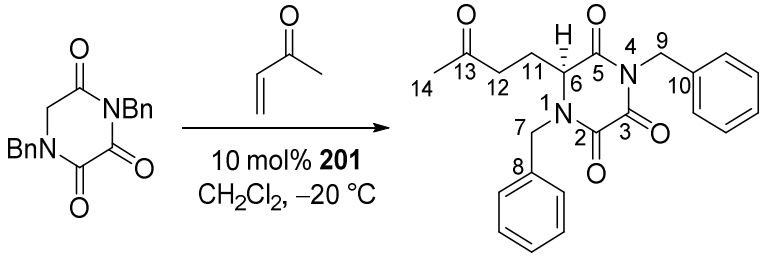


246 **271b**

General procedure B using triketopiperazine **246** (36.6 mg) was followed to synthesise this product (32.4 mg) as a white solid in 61% yield from a reaction catalysed by **201** (10 mol%) at −20 °C for 1.0 hour. Purification by flash column chromatography (gradient: hexane/ethyl

acetate = (9:1) to (3:1) gave compound **271b**. m.p. 139 – 141 °C; IR ν_{max} /cm^{-1} 2962, 1752, 1687, 1606, 1550, 1512, 1431, 1375, 1234, 1207, 1072, 1031, 844, 757, 737, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 2H, H-Ar), 7.51 – 7.44 (m, 3H, H-Ar), 7.37 – 7.29 (m, 3H, H-Ar), 7.25 (m, 2H, H-Ar), 6.62 (t, *J* = 8.5 Hz, 2H, H-Ar), 6.55 (dd, *J* = 8.5 Hz, 5.1, 2H, H-Ar), 5.46 (d, *J* = 15.2 Hz, 1H, H-7b), 5.25 (m, 1H, H-16b), 5.03 (d, *J* = 13.3 Hz, 1H, H-17b), 4.92 (d, *J* = 13.3 Hz, 1H, H-17a), 4.78 – 4.67 (m, 2H, H-11, H-16a), 4.16 (d, *J* = 15.2 Hz, 1H, H-7a), 3.10 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (C-9), 165.1 (C-3), 162.9 (d, *J* = 251.3 Hz, C-15), 153.9 (C-5), 152.6 (C-6), 134.0 (C-8), 133.6 (C-18), 130.7 (C-Ar), 130.1 (d, *J* = 8.4 Hz, C-13), 129.1 (C-Ar), 128.9 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 127.0 (d, *J* = 3.1 Hz, C-12), 116.8 (d, *J* = 21.9 Hz, C-14), 75.4 (C-16), 73.0 (C-2), 53.5 (C-10), 47.0 (C-7), 45.8 (C-11), 45.2 (C-17); *m/z* (ESI) $C_{28}H_{24}N_3O_7NaF$ requires 556.1496, found $[MNa]^+$ 556.1500; $[\alpha]_D^{21}$= 66.8 (*c* 1.3, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-(3-oxobutyl)piperazine-2,3,5-trione **276**

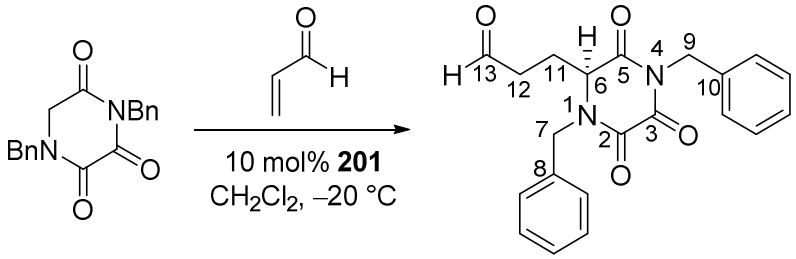


242 **276**

General procedure B using triketopiperazine **242** (29.5 mg) was followed to synthesise this product (28.9 mg) as a colourless oil in 80% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 4 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (1:1) gave **276** with 93:7 er as determined by HPLC analysis

[Daicel Chiralcel OD, hexanes:IPA, 80:20, 2.0 mL/min, λ 210 nm, t(major) = 17.7 min, t(minor) = 44.6 min]. IR ν_{max} /cm^{-1} 3034, 2958, 1743, 1685, 1497, 1429, 1361, 1322, 1261, 1211, 1164, 1077, 1030, 745, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H, H-Ar), 7.39 – 7.35 (m, 5H, H-Ar), 7.34 – 7.29 (m, 3H, H-Ar), 5.35 (d, *J* = 14.5 Hz, 1H, H-7b), 4.99 (s, 2H, H-9), 4.20 (d, *J* = 14.5 Hz, 1H, H-7a) 4.19 (dd, *J* = 8.5 Hz, 3.1 Hz, 1H, H-6) 2.34 (m, 1H, H-11b), 2.24 (t, *J* = 6.7 Hz, 2H, H-12), 2.03 (s, 3H, H-14), 1.91 (m, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0 (C-13), 168.0 (C-5), 156.5 (C-3), 152.9 (C-2), 135.2 (C-10), 134.5 (C-8), 129.4 (C-Ar), 129.1 (C-Ar), 129.0 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 58.6 (C-6), 48.0 (C-7), 44.3 (C-9), 36.8 (C-12), 29.9 (C-14), 27.3 (C-11); *m/z* (ESI) $C_{22}H_{22}N_2O_4Na$ requires 401.1481, found [MNa]$^+$ 401.1477; $[\alpha]_D^{21}$= –157.1 (*c* 1.0, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-(3-oxopropyl)piperazine-2,3,5-trione **289**

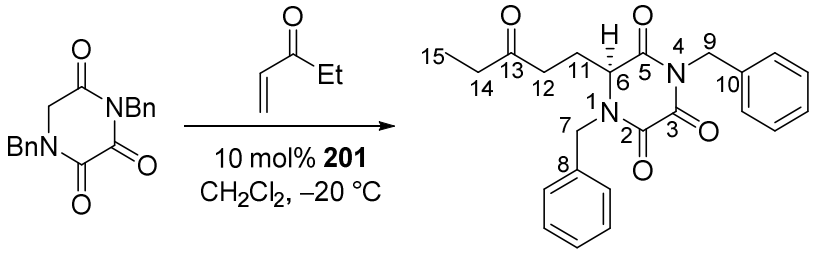


242 **289**

General procedure B using triketopiperazine **242** (30.6 mg) was followed to synthesise this product (26.9 mg) as a colourless oil in 74% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 3 hours. Purification by flash column chromatography (gradient: Hexane/Ethyl acetate = (4:1) to (2:1) gave compound **289**. IR ν_{max} /cm^{-1} 3064, 2927, 2847, 1743, 1721, 1680, 1496, 1431, 1386, 1361, 1322, 1262, 1210, 1161, 1078, 1030, 976, 731, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H, H-13), 7.42 (m, 2H, H-Ar), 7.39 – 7.34 (m,

5H, H-Ar), 7.34 – 7.29 (m, 3H, H-Ar), 5.33 (d, *J* = 14.6 Hz, 1H, H-7b), 4.99 (m, 2H, H-9), 4.28 – 4.19 (m, 2H, H-7a, H-6), 2.47 – 2.33 (m, 3H, H-12, H-11b), 1.95 (m, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (C-13), 167.8 (C-5), 156.4 (C-3), 152.8 (C-2), 135.2 (C-10), 134.4 (C-8), 129.3 (C-Ar), 129.2 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.3 (C-Ar), 58.6 (C-6), 48.1 (C-7), 44.4 (C-9), 37.7 (C-12), 25.8 (C-11); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ESI) $C_{21}H_{21}N_2O_4$ requires 365.1505, found $[MH]^+$ 365.1501; $[\alpha]_D^{21}$= –25.7 (*c* 1.06, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-(3-oxopentyl)piperazine-2,3,5-trione **290**

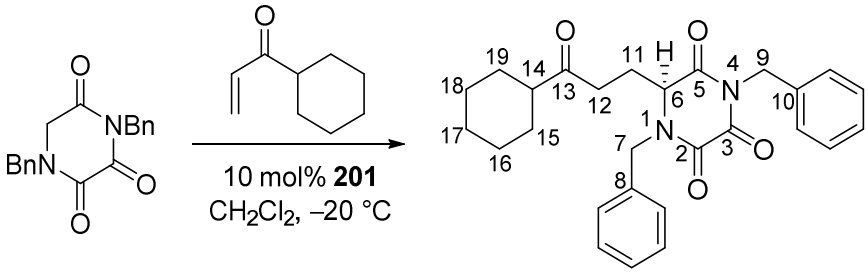


242 **290**

General procedure B using triketopiperazine **242** (30.9 mg) was followed to synthesise this product (34.0 mg) as a colourless oil in 86% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 4 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1) gave **290** with 96:4 er as determined by HPLC analysis [Daicel Chiralcel OD, hexanes:IPA, 80:20, 2.0 mL/min, λ 210 nm, t(major) = 13.3 min, t(minor) = 41.3 min]. IR ν_{max} /cm^{-1} 3065, 3034, 2976, 2940, 1744, 1683, 1497, 1454, 1431, 1361, 1260, 1158, 728, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H, H-Ar), 7.39 – 7.34 (m, 5H, H-Ar), 7.34 – 7.29 (m, 3H, H-Ar), 5.35 (d, *J* = 14.6 Hz, 1H, H-7b), 4.99 (s, 2H, H-9), 4.21 (d, *J* = 14.6 Hz, 1H, H-7a), 4.19 (dd, *J* = 8.3 Hz, 3.2 Hz, 1H, H-6), 2.35 (m, 1H, H-11b),

2.26 (m, 2H, H-14), 2.20 (m, 2H, H-12), 21.96 (m, 1H, H-11a), 1.01 (t, *J* = 7.3 Hz, 3H, H-15);[13]C NMR (101 MHz, $CDCl_3$) δ 208.8 (C-13), 168.0 (C-5), 156.5 (C-3), 152.9 (C-2), 135.3 (C-10), 134.5 (C-8), 129.4 (C-Ar), 129.1 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 58.7 (C-6), 48.0 (C-7), 44.3 (C-9), 36.0 (C-14), 35.4 (C-12), 27.4 (C-11), 7.67 (C-15); *m/z* (ESI) $C_{23}H_{25}N_2O_4$ requires 393.1812, found $[MH]^+$ 393.1814; $[\alpha]_D^{21}$= –77.1 (*c* 1.5, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-(3-cyclohexyl-3-oxopropyl)piperazine-2,3,5-trione **201**

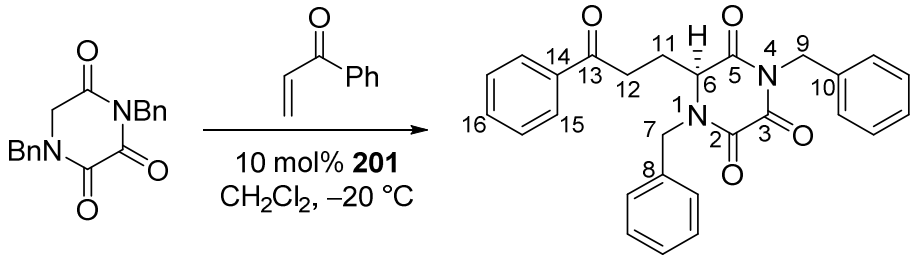


242 **291**

General procedure B using triketopiperazine **242** (29.6 mg) was followed to synthesise this product (42.6 mg) as a white solid in 99% yield from a reaction catalysed by **201** (10 mol%) at −20 °C for 6 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (2:1) gave **291** with 89:11 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, acetonitrile:water, 40:60, 1 mL/min, λ 220 nm, t(minor) = 34.5 min, t(major) = 39.3 min]. m.p. 117 – 119 °C; IR ν_{max} /cm^{-1} 3004, 2928, 2853, 1744, 1675, 1496, 1432, 1363, 1321, 1252, 1209, 1145, 740, 718, 699; [1]H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H, H-Ar), 7.39 – 7.33 (m, 5H, H-Ar), 7.33 – 7.29 (m, 3H, H-Ar), 5.34 (d, *J* = 14.6 Hz, 1H, H-7b), 4.99 (s, 2H, H-9), 4.26 – 4.15 (m, 2H, H-7a, H-6), 2.31 (m, 1H, H-11b), 2.20 (m, 2H, H-12), 2.12 (ddd, *J* = 10.5, 7.4, 2.8 Hz, 1H, H-14), 1.97 (m, 1H, H-11a), 1.83 – 1.72 (m, 2H, H-16b,

H-18b), 1.70 – 1.60 (m, 3H, H-15b, H-17b, H-19b), 1.32 – 1.09 (m, 5H, H-15a, H-16a, H-17a, H-18a, H-19a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (C-13), 168.0 (C-5), 156.5 (C-3), 152.9 (C-2), 135.3 (C-10), 134.5 (C-8), 129.5 (C-Ar), 129.1 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 58.9 (C-6), 50.7 (C-14), 47.9 (C-7), 44.2 (C-9), 33.7 (C-12), 28.4 (C-15), 28.2 (C-19), 27.3 (C-11), 25.7 (C-16), 25.5 (C-17), 25.5 (C-18); *m/z* (ESI) $C_{27}H_{31}N_2O_4$ requires 447.2285, found $[MH]^+$ 447.2284; $[\alpha]_D^{21}$= –76.4 (*c* 0.9, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-(3-oxo-3-phenylpropyl)piperazine-2,3,5-trione **292**

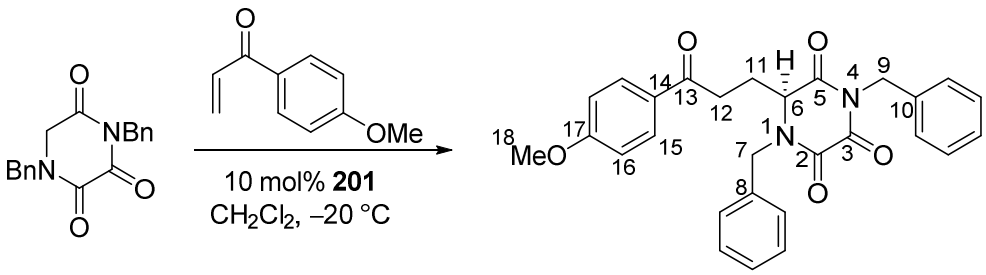


242 **292**

General procedure B using triketopiperazine **242** (36.5 mg) was followed to synthesise this product (34.6 mg) as a white solid in 79% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 2 hours. Purification by flash column chromatography (gradient: Hexane/Ethyl acetate = (4:1) to (2:1) gave compound **292**. m.p. 146 – 148 °C; IR ν_{max} /cm^{-1} 3063, 2921, 2851, 1748, 1673, 1598, 1497, 1435, 1363, 1339, 1324, 1286, 1215, 1161, 1081, 1030, 739, 718, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.3, 1.1 Hz, 2H, H-15), 7.60 (m, 1H, H-16), 7.49 – 7.44 (m, 4H, H-Ar), 7.44 – 7.33 (m, 5H, H-Ar), 7.32 – 7.27 (m, 3H, H-Ar), 5.44 (d, *J* = 14.5 Hz, 1H, H-7b), 5.03 (s, 2H, H-9), 4.31 (dd, *J* = 8.1, 3.3 Hz, 1H, H-6), 4.26 (d, *J* = 14.5 Hz, 1H, H-7a), 2.79 (m, 2H, H-12), 2.54 (dtd, *J* = 11.0, 7.7, 3.3 Hz, 1H, H-11b), 2.18 (m, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5 (C-13), 168.1 (C-5), 156.5 (C-3), 152.9 (C-

2), 136.1 (C-14), 135.3 (C-10), 134.5 (C-8), 133.6 (C-16), 129.5 (C-Ar), 129.1 (C-Ar), 129.0 (C-Ar), 128.7 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 127.9 (C-Ar), 58.8 (C-6), 47.9 (C-7), 44.3 (C-9), 32.0 (C-12), 27.7 (C-11); *m/z* (ESI) $C_{27}H_{25}N_2O_4$ requires 441.1841, found $[MH]^+$ 441.1814; $[\alpha]_D^{21}$= –57.1 (*c* 1.5, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-(3-(4-methoxyphenyl)-3-oxopropyl)piperazine-2,3,5-trione **293**

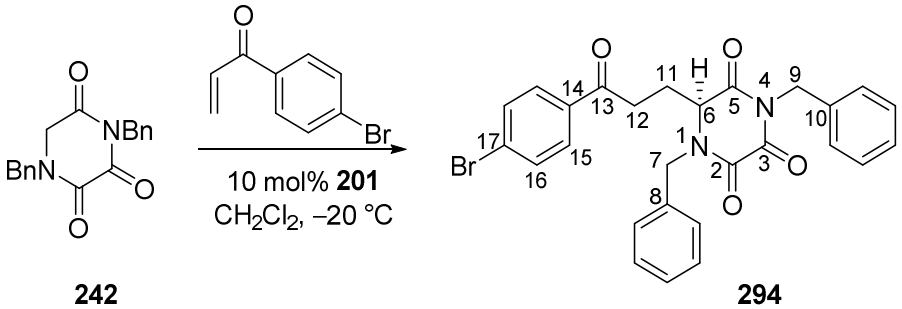


242 **293**

General procedure B using triketopiperazine **242** (30.5 mg) was followed to synthesise this product (43.2 mg) as a white solid in 93% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 2.5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1) gave **293** with 88:12 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 80:20, 1.0 mL/min, λ 210 nm, t(minor) = 43.8 min, t(major) = 49.4 min]. m.p. 153 – 154 °C; IR ν_{max} /cm^{-1} 3018, 2956, 1744, 1672, 1598, 1575, 1455, 1434, 1365, 1318, 1250, 1212, 1172, 1082, 1030, 992, 844, 738, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 2H, H-15), 7.48 (m, 2H, H-Ar), 7.42 – 7.27 (m, 8H, H-Ar), 6.93 (m, 2H, H-16), 5.43 (d, *J* = 14.6 Hz, 1H, H-7b), 5.01 (s, 2H, H-9), 4.30 (dd, *J* = 8.0, 3.2 Hz, 1H, H-6), 4.24 (d, *J* = 14.6 Hz, 1H, H-7a), 3.90 (s, 3H, H-18) 2.72 (m, 2H, H-12), 2.52 (m, 1H, H-11b), 2.18 (m, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9 (C-13), 168.2 (C-5), 163.8 (C-27), 156.6 (C-3),

152.9 (C-2), 135.3 (C-10), 134.5 (C-8), 130.3 (C-15), 129.5 (C-Ar), 129.2 (C-14), 129.1 (C-Ar), 129.0 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 113.8 (C-16), 58.8 (C-6), 55.5 (C-18), 47.8 (C-7), 44.3 (C-9), 31.5 (C-12), 27.8 (C-11); *m/z* (ESI HRMS) $C_{28}H_{26}N_2O_5Na$ requires 493.1730, found $[MNa]^+$ 493.1739; $[\alpha]_D^{21}$= –34.7 (*c* 1.3, $CHCl_3$).

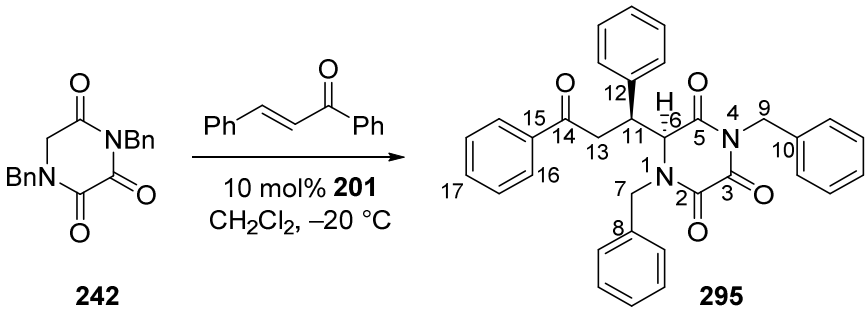
Synthesis of (*S*)-1,4-dibenzyl-6-(3-(4-bromophenyl)-3-oxopropyl)piperazine-2,3,5-trione **294**



General procedure B using triketopiperazine **242** (30.4 mg) was followed to synthesise this product (50.3 mg) as a white solid in 97% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 2 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1) gave **294** with 79:21 er as determined by HPLC analysis [Daicel Chiralcel OD, hexanes:IPA, 91.6:8.4, 0.4 mL/min, λ 210 nm, t(minor) = 179.2 min, t(major) = 192.2 min]. m.p. 173 – 176 °C; IR ν_{max} /cm^{-1} 3006, 1744, 1675, 1586, 1433, 1391, 1368, 1252, 1214, 1199, 1070, 993, 833, 744, 717, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.51 (m, 4H, H-15, H-16), 7.47 (m, 2H, H-Ar), 7.41 – 7.26 (m, 8H, H-Ar), 5.41 (d, *J* = 14.6 Hz, 1H, H-7b), 5.01 (s, 2H, H-9), 4.34 – 4.21 (m, 2H, H-7a, H-6), 2.73 (m, 2H, H-12), 2.51 (m, 1H, H-11b), 2.16 (dt, *J* = 14.3, 7.4 Hz, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4 (C-13), 168.1 (C-5), 156.5 (C-3), 152.9 (C-2), 135.3 (C-10), 134.8 (C-14), 134.5 (C-8), 132.0 (C-16), 129.5 (C-Ar), 129.4 (C-Ar), 129.2 (C-Ar), 129.0 (C-Ar), 128.8 (C-17), 128.7 (C-Ar),

128.7 (C-Ar), 128.4 (C-Ar), 58.7 (C-6), 48.0 (C-7), 44.3 (C-9), 32.0 (C-12), 27.5 (C-11); *m/z* (ESI) $C_{27}H_{23}N_2O_4Na^{79}Br$ requires 541.0739, found $[MNa]^+$ 541.0733; $[\alpha]_D^{21}$= –17.4 (*c* 2.1, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-((*S*)-3-oxo-1,3-diphenylpropyl)piperazine-2,3,5-trione **295**

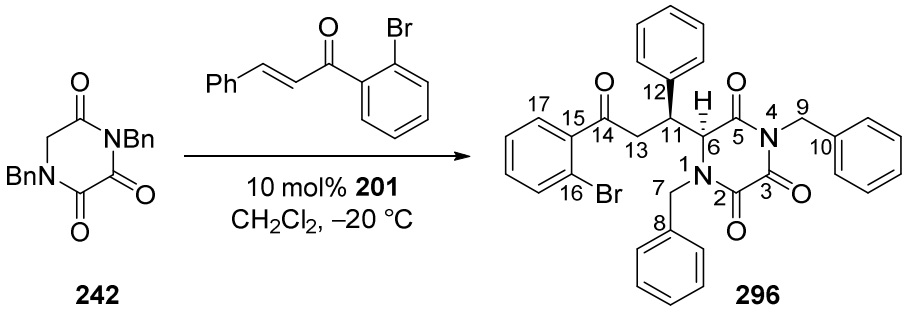


242 **295**

General procedure B using triketopiperazine **242** (28.7 mg) was followed to synthesise this product (47.8 mg) as a white solid in 98% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 6 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **295** with 99:1 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 80:20, 1.0 mL/min, λ 210 nm, t(major) = 32.8 min, t(minor) = 45.4 min]. m.p. 144 – 147 °C; IR ν_{max} /cm^{-1} 3063, 3034, 2955, 1743, 1692, 1682, 1593, 1495, 1449, 1425, 1378, 1356, 1345, 1255, 1215, 1191, 1001, 985, 759, 736, 693; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (m, 2H, H-16), 7.59 (m, 1H, H-17), 7.51 – 7.35 (m, 4H, H-Ar), 7.34 – 7.19 (m, 9H, H-Ar), 7.13 – 7.01 (m, 4H, H-Ar), 5.41 (d, *J* = 14.9 Hz, 1H, H-7b), 4.80 (s, 2H, H-9), 4.54 (d, *J* = 5.6 Hz, 1H, H-6), 3.95 (dd, *J* = 15.2, 5.6 Hz, 1H, H-11), 3.58 (d, *J* = 14.9 Hz, 1H, H-7a), 3.37 (dd, *J* = 17.9, 7.0 Hz, 1H, H-13b), 3.23 (dd, *J* = 17.9, 7.0 Hz, 1H, H-13a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3 (C-14), 167.8 (C-5), 156.5 (C-3), 154.3 (C-2), 137.9 (C-12), 136.1 (C-15), 135.1 (C-10), 134.5 (C-8), 133.6 (C-Ar), 129.7 (C-Ar), 129.3 (C-Ar), 129.2

(C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 128.0 (C-Ar), 64.3 (C-6), 49.8 (C-7), 47.1 (C-11), 44.4 (C-9), 40.1 (C-13); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ESI) $C_{33}H_{28}N_2O_4Na$ requires 539.1968, found $[MNa]^+$ 539.1947; $[\alpha]_D^{21} = -101.3$ (*c* 1.1, $CHCl_3$).

Synthesis of (*S*)-1,4-dibenzyl-6-((*S*)-3-(2-bromophenyl)-3-oxo-1-phenylpropyl)piperazine-2,3,5-trione **296**

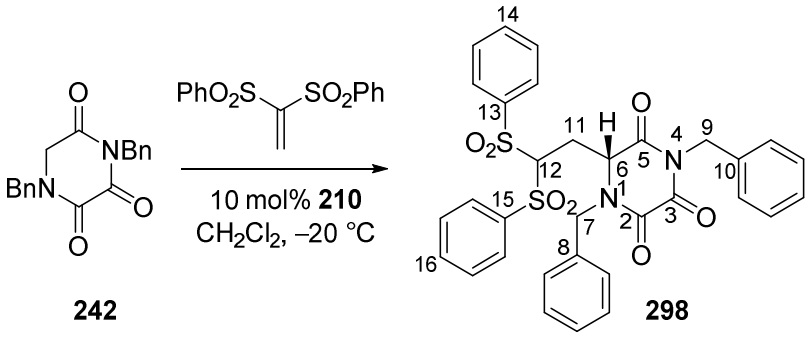


242 **296**

General procedure B using triketopiperazine **242** (30.8 mg) was followed to synthesise this product (53.9 mg) as a white solid in 91% yield from a reaction catalysed by 201 (10 mol%) at –20 °C for 7 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (9:1) to (3:1) gave **296** with 88:12 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 84:16, 0.75 mL/min, λ 210 nm, t(major) = 61.7 min, t(minor) = 69.2 min]. m.p. 124 – 125 °C; IR ν_{max} /cm^{-1} 2971, 2902, 1742, 1680, 1585, 1496, 1408, 1384, 1354, 1294, 1231, 1068, 981, 751, 742, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 1H, H-17), 7.39 (m, 2H, H-Ar), 7.34 – 7.21 (m, 11H, H-Ar), 7.13 (dt, *J* = 4.3, 3.2 Hz, 2H, H-Ar), 7.07 (m, 1H, H-Ar), 6.96 (m, 2H, H-Ar), 5.44 (d, *J* = 14.9 Hz, 1H, H-7b), 4.84 (d, *J* = 13.8 Hz, 1H, H-9b), 4.80 (d, *J* = 13.8 Hz, 1H, H-9a), 4.45 (d, *J* = 5.7 Hz, 1H, H-6), 3.85 (dt, *J* = 8.4, 5.7 Hz, 1H, H-11), 3.56 (d, *J* = 14.9 Hz, 1H, H-7a), 3.41 (dd, *J* = 17.5, 8.4 Hz, 1H, H-

13b), 3.27 (dd, J = 17.5, 5.7 Hz, 1H, H-13a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (C-14), 167.6 (C-5), 156.4 (C-3), 154.2 (C-2), 140.5 (C-12), 136.7 (C-15), 135.0 (C-10), 134.4 (C-8), 133.8 (C-Ar), 132.1 (C-Ar), 129.6 (C-Ar), 129.3 (C-Ar), 129.2 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 127.5 (C-Ar), 118.7 (C-16), 64.4 (C-6), 49.8 (C-7), 47.6 (C-11), 44.5 (C-9), 44.4 (C-13); 2 signals in the C-H aromatic region were not observed due to having equivalent resonances; *m/z* (ESI) $C_{33}H_{28}N_2O_4{}^{79}Br$ requires 595.1245, found $[MH]^+$ 595.1232; $[\alpha]_D^{21}$ = –83.9 (*c* 1.5, $CHCl_3$).

Synthesis of (*R*)-1,4-dibenzyl-6-(2,2-bis(phenylsulfonyl)ethyl)piperazine-2,3,5-trione **298**



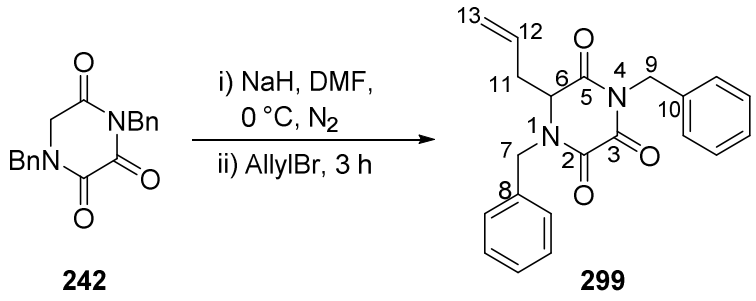
General procedure B using triketopiperazine **242** (31.7 mg) was followed to synthesise this product (50.6 mg) as a white solid in 82% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 20 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (1:2) gave **298** with 61:39 er as determined by HPLC analysis [Daicel Chiralcel OD, heptane:EtOH, 60:40, 2 mL/min, λ 210 nm, t(minor) = 8.2 min, t(major) = 13.7 min]. m.p. 165 – 166 °C; IR ν_{max} /cm^{-1} 3066, 1746, 1687, 1672, 1496, 1447, 1392, 1330, 1182, 1147, 1078, 724, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H, H-Ar), 7.79 (m, 2H, H-Ar), 7.71 (m, 2H, H-Ar), 7.64 – 7.51 (m, 5H, H-Ar), 7.48 – 7.36 (m, 4H, H-Ar), 7.36 – 7.27

(m, 5H, H-Ar), 5.28 – 5.18 (m, 2H, H-12, H-7b), 5.00 (d, *J* = 13.9 Hz, 1H, H-9b), 4.85 (dd, *J* = 11.3, 3.2 Hz, 1H, H-6), 4.67 (d, *J* = 13.9 Hz, 1H, H-9a), 4.32 (dd, *J* = 14.5, 2.2 Hz, 1H, H-7a), 2.96 (ddd, *J* = 15.3, 9.5, 3.2 Hz, 1H, H-11b), 2.57 (m, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C-5), 155.9 (C-3), 152.4 (C-2), 137.8 (C-15), 136.4 (C-13), 135.0 (C-8), 134.9 (C-16), 134.7 (C-14, C-10), 129.8 (C-Ar), 129.3 (C-Ar), 129.3 (C-Ar), 129.2 (C-Ar), 129.2 (C-Ar), 129.1 (C-Ar), 128.7 (C-Ar), 128.7 (C-Ar), 128.3 (C-Ar), 77.9 (C-12), 58.4 (C-6), 48.6 (C-7), 44.7 (C-9), 29.8 (C-11); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{32}H_{29}N_2O_7S_2$, 617.1416, found $[MH]^+$ 617.1413; $[\alpha]_D^{21}$= 8.0 (*c* 0.95, $CHCl_3$).

General procedure C for the alkylation of triketopiperazines

To a suspension of NaH (1.05 eq) in dry DMF (0.25 M) at −10 °C, triketopiperazine **242** (1.0 eq) was added and left to stir for 5 minutes. Alkyl halide (3.0 eq) was subsequently added and the mixture was left to react at that temperature until the starting material was observed to be consumed by TLC. The crude mixture was quenched with water, extracted with AcOEt (3 x 30 mL) and washed with water (4 x 30 mL) and brine (1 x 30 mL), dried over $MgSO_4$ and condensed under reduced pressure. The crude was purified by flash column chromatography.

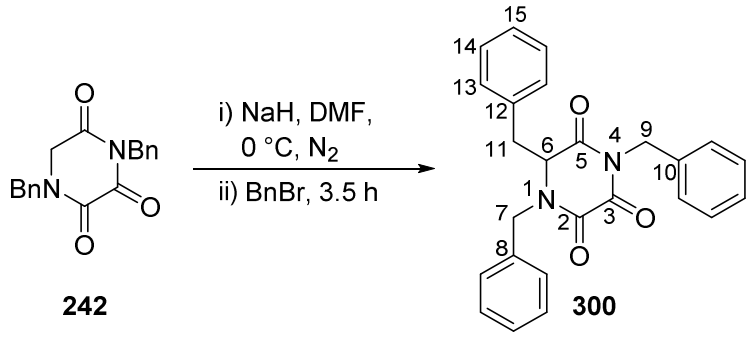
Synthesis of 6-allyl-1,4-dibenzylpiperazine-2,3,5-trione **299**



242 **299**

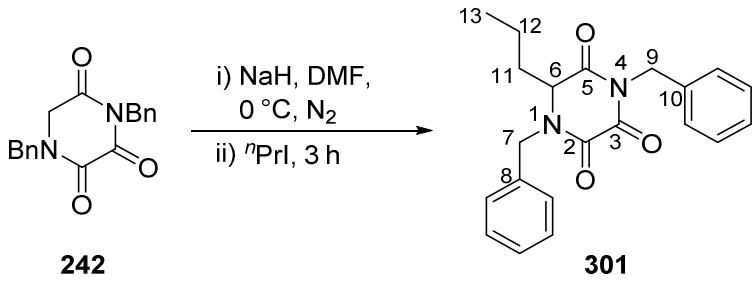
General procedure C using compound **242** (308.4 mg) was followed to synthesise TKP **299** (284.7 mg) in 3 hours as a colourless oil that solidifies on standing in 82% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 73 – 74 °C; IR ν_{max} /cm^{-1} 3033, 2928, 1744, 1682, 1496, 1431, 1385, 1358, 1261, 1192, 1080, 723, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 2H, H-Ar), 7.38 – 7.24 (m, 8H, H-Ar), 5.32 (d, *J* = 14.7 Hz, 1H, H-7b), 5.24 (m, 1H, H-12), 4.98 (dd, *J* = 10.2, 1.3 Hz, 1H, H-13cis), 4.94 (s, 2H, H-9), 4.85 (dd, *J* = 17.0, 1.3 Hz, 1H, H-13trans), 4.28 (dd, *J* = 4.9, 3.6 Hz, 1H, H-6), 4.17 (d, *J* = 14.7 Hz, 1H, H-7a), 2.64 (m, 2H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0 (C-5), 156.7 (C-3), 153.3 (C-2), 135.1 (C-10), 134.3 (C-8), 129.7 (C-Ar), 129.2 (C-Ar), 128.9 (C-Ar), 128.7 (C-12), 128.5 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 122.8 (C-13), 59.6 (C-6), 48.1 (C-7), 44.3 (C-9), 36.6 (C-11); *m/z* (ES HRMS) $C_{21}H_{21}N_2O_3$ requires 349.1552, found $[MH]^+$ 349.1394.

Synthesis of 1,4,6-tribenzylpiperazine-2,3,5-trione **300**



General procedure C using compound **242** (326.0 mg) was followed to synthesise TKP **300** (339.1 mg) in 3.5 hours as an oil that solidifies on standing in 83% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 78 – 81 °C; IR ν_{max} /cm^{-1} 3032, 1743, 1677, 1494, 1455, 1427, 1364, 1321, 1258, 1215, 1176, 979, 743, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.25 (m, 10H, H-Ar), 7.22 (t, *J* = 7.5 Hz, 1H, H-15), 7.09 (t, *J* = 7.5 Hz, 2H, H-14), 6.78 (m, 2H, H-13), 5.59 (d, *J* = 14.6 Hz, 1H, H-7b), 4.75 (d, *J* = 13.5 Hz, 1H, H-9b), 4.71 (d, *J* = 13.5 Hz, 1H, H-9a), 4.49 (dd, *J* = 4.6, 3.6 Hz, 1H, H-6), 4.13 (d, *J* = 14.6 Hz, 1H, H-7a), 3.28 (dd, *J* = 14.0, 4.6 Hz, 1H, H-11b), 3.20 (dd, *J* = 14.0, 3.6 Hz, 1H, H-11a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0 (C-5), 155.8 (C-3), 153.3 (C-2), 134.8 (C-10), 134.1 (C-8), 132.2 (C-12), 130.0 (C-Ar), 129.4 (C-Ar), 129.3 (C-Ar), 129.0 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 128.2 (C-Ar), 60.4 (C-6), 47.9 (C-7), 44.2 (C-9), 38.3 (C-11); *m/z* (ES HRMS) $C_{25}H_{22}N_2O_3Na$ requires 421.1528, found $[MNa]^+$ 421.1522.

Synthesis of 1,4-dibenzyl-6-propylpiperazine-2,3,5-trione **301**



242 **301**

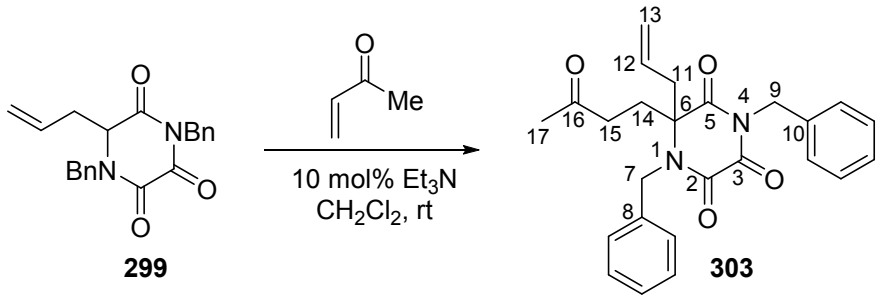
General procedure C using compound **242** (616.0 mg) was followed to synthesise TKP **301** (567.1 mg) in 3 hours as a colourless oil that solidifies on standing in 81% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 75 – 77 °C; IR ν_{max} /cm^{-1} 3032, 2976, 2955, 2872, 1747, 1684, 1671, 1495, 1436, 1375, 1323, 1243, 1190, 1083, 745, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H, H-Ar), 7.40 – 7.34 (m, 3H, H-Ar), 7.34 – 7.27 (m, 5H, H-Ar), 5.35 (d, *J* = 14.7 Hz, 1H, H-7b), 5.04 (d, *J* = 13.6 Hz, 1H, H-9b), 4.99 (d, *J* = 13.6 Hz, 1H, H-9a), 4.21 (dd, *J* = 6.1, 3.3 Hz, 1H, H-6), 4.15 (d, *J* = 14.7 Hz, 1H, H-7a), 1.94 (m, 1H, H-11b), 1.82 (m, 1H, H-11a), 1.15 (m, 1H, H-12b), 0.92 (m, 1H, H-12a), 0.77 (t, *J* = 7.2 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (C-5), 156.7 (C-3), 153.2 (C-2), 135.2 (C-10), 134.3 (C-8), 129.5 (C-Ar), 129.2 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.2 (C-Ar), 59.8 (C-6), 48.0 (C-7), 44.3 (C-9), 34.9 (C-11), 16.5 (C-12), 13.3 (C-13); *m/z* (ES HRMS) $C_{21}H_{22}N_2O_3Na$ requires 373.1528, found $[MNa]^+$ 373.1519.

General procedure D for the preparation of Racemic Alkyl-TKP adducts:

To a solution of alkyl triketopiperazine (0.1 mmol) in CH_2Cl_2 (0.7 mL) at room temperature, triethylamine (10 mol%) was added followed by the Michael acceptor (2.5 eq). The mixture

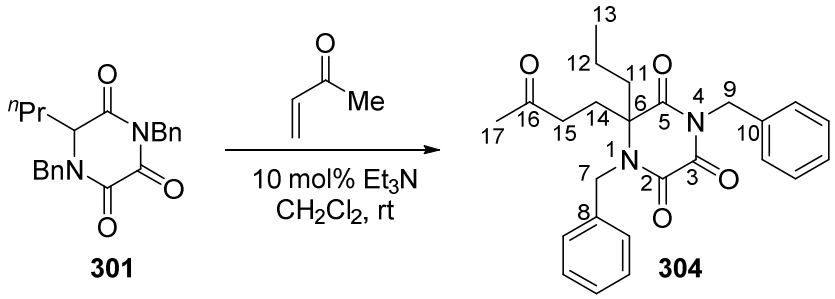
was left to react until the starting material was consumed. The crude mixture was directly purified by flash chromatography.

Synthesis of 6-allyl-1,4-dibenzyl-6-(3-oxobutyl)piperazine-2,3,5-trione **303**



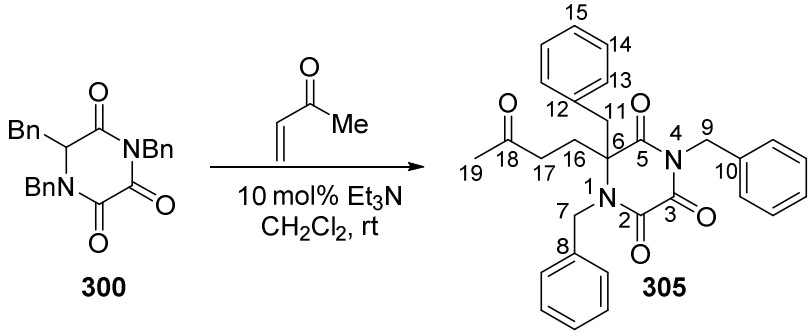
General procedure D using triketopiperazine **299** (35.3 mg) was followed to synthesise **303** (31.1 mg) in 15 hours as a white solid in 73% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 137 – 138 °C; IR ν_{max} /cm^{-1} 3071, 2972, 1738, 1711, 1673, 1496, 1456, 1427, 1356, 1309, 1269, 1257, 1172, 1130, 1080, 934, 756, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.38 (m, 4H, H-Ar), 7.35 – 7.22 (m, 6H, H-Ar), 5.21 (d, *J* = 14.7 Hz, 1H, H-7b), 5.20 (m, 1H, H-12), 5.06 (d, *J* = 13.4 Hz, 1H, H-9b), 5.02 (d, *J* = 13.4 Hz, 1H, H-9a), 4.95 (dd, *J* = 10.2, 1.1 Hz, 1H, H-13cis), 4.85 (dd, *J* = 17.0, 1.1 Hz, 1H, H-13trans), 4.28 (d, *J* = 14.7 Hz, 1H, H-7a), 2.70 (qd, *J* = 14.2, 7.5 Hz, 2H, H-11), 2.33 (m, 1H, H-14b), 2.18 (m, 1H, H-14a), 1.86 (m, 1H, H-15b), 1.73 (m, 1H, H-15a), 1.67 (s, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (C-16), 169.9 (C-5), 155.9 (C-3), 155.2 (C-2), 136.6 (C-8), 135.1 (C-10), 129.7 (C-Ar), 129.0 (C-Ar), 128.9 (C-Ar), 128.6 (C-12), 128.5 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 122.7 (C-13), 70.8 (C-6), 46.5 (C-7), 44.5 (C-9), 43.5 (C-11), 37.1 (C-15), 31.7 (C-14), 29.3 (C-17); *m/z* (ES HRMS) $C_{25}H_{27}N_2O_4$ requires 419.1971, found $[MH]^+$ 419.1955.

Synthesis of 1,4-dibenzyl-6-(3-oxobutyl)-6-propylpiperazine-2,3,5-trione **304**



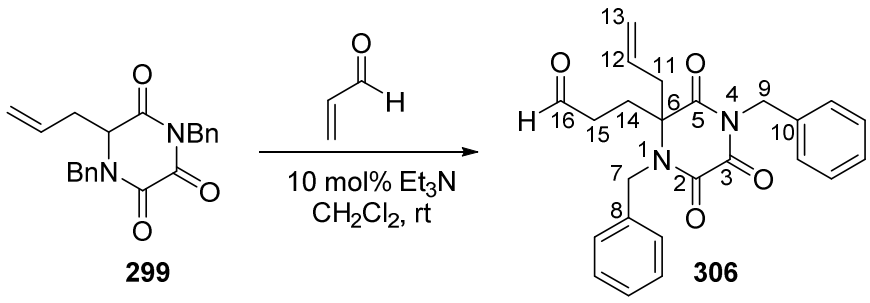
General procedure D using triketopiperazine **301** (35.0 mg) was followed to synthesise **304** (38.1 mg) in 15 hours as a white solid in 89% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 129 – 131 °C; IR ν_{max} /cm^{-1} 2962, 1742, 1708, 1678, 1495, 1455, 1421, 1365, 1316, 1267, 1216, 1173, 1077, 745, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 4H, H-Ar), 7.34 – 7.24 (m, 6H, H-Ar), 5.11 (d, *J* = 13.4 Hz, 1H, H-9b), 5.05 (d, *J* = 13.4 Hz, 1H, H-9a), 4.92 (d, *J* = 14.8 Hz, 1H, H-7b), 4.51 (d, *J* = 14.8 Hz, 1H, H-7a), 2.21 (m, 2H, H-14), 2.00 (m, 1H, H-11b), 1.86 (m, 1H, H-11a), 1.75 (m, 2H, H-15), 1.72 (s, 3H, H-17), 0.93 (m, 1H, H-12b), 0.79 (m, 1H, H-12a), 0.61 (t, *J* = 7.2 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.3 (C-16), 170.5 (C-5), 155.9 (C-3), 155.0 (C-2), 136.6 (C-8), 135.2 (C-10), 129.5 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 71.0 (C-6), 46.3 (C-7), 44.4 (C-9), 41.4 (C-11), 36.9 (C-15), 32.7 (C-14), 29.5 (C-17), 17.1 (C-12), 13.1 (C-13); *m/z* (ES HRMS) $C_{25}H_{29}N_2O_4$ requires 421.2127, found $[MH]^+$ 421.2120.

Synthesis of 1,4,6-tribenzyl-6-(3-oxobutyl)piperazine-2,3,5-trione **305**



General procedure D using triketopiperazine **300** (38.6 mg) was followed to synthesise **305** (42.9 mg) in 15 hours as a white solid in 93% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 171 – 173 °C; IR ν_{max} /cm^{-1} 3062, 2960, 1743, 1703, 1678, 1497, 1455, 1419, 1372, 1326, 1255, 1171, 1079, 736, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H, H-Ar), 7.37 (m, 2H, H-Ar), 7.35 – 7.26 (m, 6H, H-Ar), 7.19 (m, 1H, H-15), 7.05 (t, *J* = 7.7 Hz, 2H, H-14), 6.74 (m, 2H, H-13), 5.63 (d, *J* = 14.7 Hz, 1H, H-7b), 4.86 (d, *J* = 13.4 Hz, 1H, H-9b), 4.75 (d, *J* = 13.4 Hz, 1H, H-9a), 4.16 (d, *J* = 14.7 Hz, 1H, H-7a), 3.34 (d, *J* = 13.9 Hz, 1H, H-11b), 3.22 (d, *J* = 13.9 Hz, 1H, H-11a), 2.53 (ddd, *J* = 14.9, 12.0, 5.4 Hz, 1H, H-16b), 2.31 (ddd, *J* = 14.9, 11.8, 3.0 Hz, 1H, H-16a), 1.84 (ddd, *J* = 17.4, 11.8, 5.4 Hz, 1H, H-17b), 1.59 (m, 1H, H-17a), 1.58 (s, 3H, H-19); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5 (C-18), 170.0 (C-5), 155.3 (C-2), 155.1 (C-3), 136.8 (C-8), 134.8 (C-10), 132.5 (C-12), 130.0 (C-Ar), 129.4 (C-Ar), 129.0 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 128.2 (C-Ar), 72.1 (C-6), 47.0 (C-7), 45.4 (C-11), 44.4 (C-9), 37.3 (C-17), 31.7 (C-16), 29.2 (C-19); 2 signals in the C-H aromatic region were not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{29}H_{28}N_2O_4Na$ requires 491.1947, found $[MNa]^+$ 491.1945.

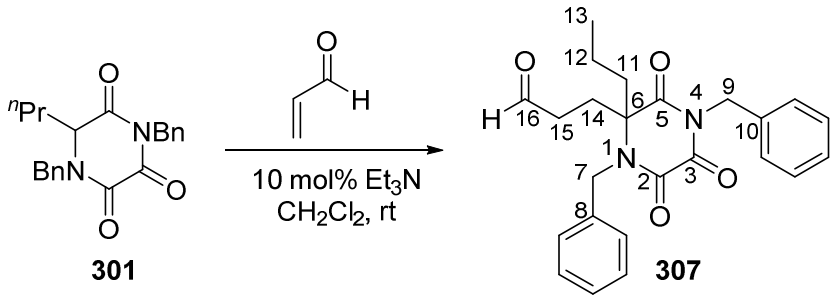
Synthesis of 6-allyl-1,4-dibenzyl-6-(3-oxopropyl)piperazine-2,3,5-trione **306**



299 **306**

General procedure D using triketopiperazine **299** (17.3 mg) was followed to synthesise **306** (20.2 mg) in 25 hours as a colourless oil in 98% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). IR ν_{max} /cm^{-1} 3062, 2960, 1743, 1703, 1678, 1497, 1455, 1419, 1372, 1326, 1255, 1171, 1079, 736, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H, H-16), 7.48 – 7.38 (m, 4H, H-Ar), 7.36 – 7.26 (m, 6H, H-Ar), 5.25 (d, *J* = 14.9 Hz, 1H, H-7b), 5.20 (m, 1H, H-12), 5.07 (d, *J* = 13.4 Hz, 1H, H-9b), 5.01 (d, *J* = 13.4 Hz, 1H, H-9a), 4.97 (dd, *J* = 10.1, 1.0 Hz, 1H, H-13cis), 4.86 (dd, *J* = 17.0, 1.0 Hz, 1H, H-13trans), 4.29 (d, *J* = 14.9 Hz, 1H, H-7a), 2.75 (dd, *J* = 14.2, 7.2 Hz, 1H, H-11b), 2.67 (dd, *J* = 14.2, 7.2 Hz, 1H, H-11a), 2.39 (ddd, *J* = 15.0, 11.3, 5.5 Hz, 1H, H-14b), 2.23 (ddd, *J* = 15.0, 11.1, 3.6 Hz, 1H, H-14a), 1.94 (ddd, *J* = 18.0, 11.1, 5.5 Hz, 1H, H-15b), 1.75 (ddd, *J* = 18.0, 11.3, 3.6 Hz, 1H, H-15a); ^{13}C NMR (101 MHz, CDCl3) δ 198.4 (C-16), 169.8 (C-5), 155.8 (C-3), 155.2 (C-2), 136.5 (C-8), 135.0 (C-10), 129.6 (C-Ar), 128.9 (C-Ar), 128.9 (C-Ar), 128.6 (C-12), 128.5 (C-Ar), 128.3 (C-Ar), 122.9 (C-13), 70.8 (C-6), 46.5 (C-7), 44.5 (C-9), 43.5 (C-11), 38.0 (C-15), 30.0 (C-14); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; m/z (ES HRMS) $C_{24}H_{25}N_2O_4$ requires 405.1814, found $[MH]^+$ 405.1909.

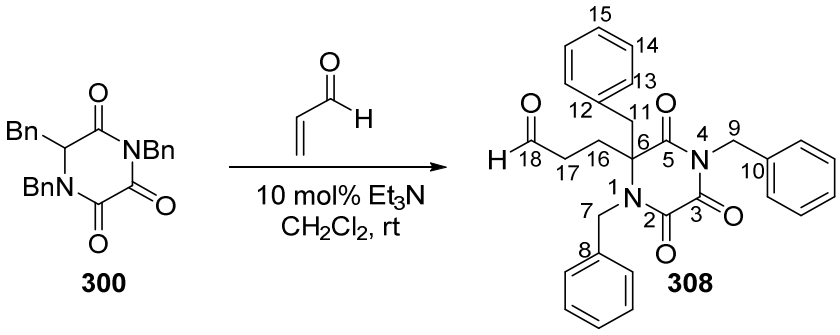
Synthesis of 1,4-dibenzyl-6-(3-oxopropyl)-6-propylpiperazine-2,3,5-trione **307**



301 **307**

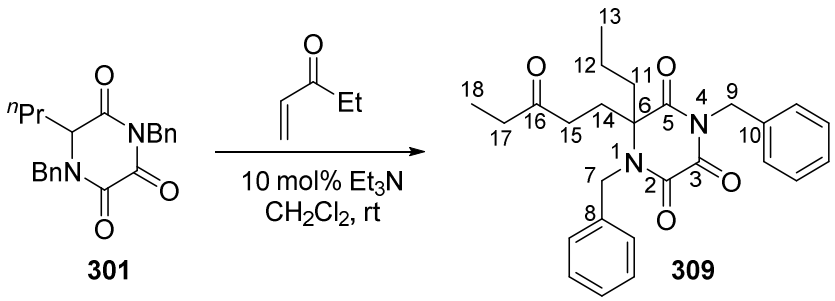
General procedure D using triketopiperazine **301** (33.6 mg) was followed to synthesise **307** (34.5 mg) in 22 hours as a white solid in 85% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 116 – 117 °C; IR ν_{max} /cm^{-1} 2739, 1742, 1718, 1675, 1496, 1455, 1413, 1378, 1360, 1322, 1256, 1221, 1158, 1076, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H, H-16), 7.42 (m, 4H, H-Ar), 7.35 – 7.25 (m, 6H, H-Ar), 5.07 (s, 2H, H-9), 4.98 (d, *J* = 14.9 Hz, 1H, H-7b), 4.49 (d, *J* = 14.9 Hz, 1H, H-7a), 2.33 (m, 1H, H-14b), 2.20 (ddd, *J* = 21.9, 11.1, 5.9 Hz, 1H, H-14a), 2.01 (m, 1H, H-11b), 1.94 – 1.76 (m, 3H, H-11a, H-15), 0.95 (m, 1H, H-12b), 0.79 (m, 1H, H-12a), 0.63 (t, *J* = 7.2 Hz, 3H, H-13);^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (C-16), 170.4 (C-5), 155.8 (C-3), 155.0 (C-2), 136.5 (C-8), 135.1 (C-10), 129.4 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 70.9 (C-6), 46.3 (C-7), 44.5 (C-9), 41.6 (C-11), 37.8 (C-15), 30.9 (C-14), 17.0 (C-12), 13.1 (C-13); *m/z* (ES HRMS) $C_{24}H_{27}N_2O_4$ requires 407.1971, found $[MH]^+$ 407.1975.

Synthesis of 1,4,6-tribenzyl-6-(3-oxopropyl)piperazine-2,3,5-trione **308**



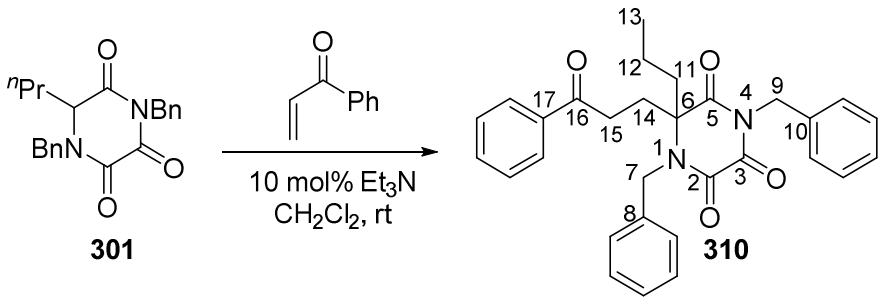
General procedure D using triketopiperazine **300** (41.5 mg) was followed to synthesise **308** (41.4 mg) in 15 hours as a white solid in 93% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 166 – 167 °C; IR ν_{max} /cm^{-1} 3303, 3069, 2977, 2836, 1742, 1705, 1675, 1497, 1454, 1420, 1370, 1326, 1266, 1143, 1079, 982, 737, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H, H-18), 7.42 (dd, *J* = 7.2, 2.0 Hz, 2H, H-Ar), 7.39 – 7.25 (m, 8H, H-Ar), 7.21 (t, *J* = 7.5 Hz, 1H, H-15), 7.07 (t, *J* = 7.5 Hz, 2H, H-14), 6.76 (m, 2H, H-13), 5.66 (d, *J* = 14.7 Hz, 1H, H-7b), 4.86 (d, *J* = 13.4 Hz, 1H, H-9b), 4.73 (d, *J* = 13.4 Hz, 1H, H-9a), 4.19 (d, *J* = 14.7 Hz, 1H, H-7a), 3.37 (d, *J* = 13.9 Hz, 1H, H-11b), 3.22 (d, *J* = 13.9 Hz, 1H, H-11a), 2.57 (ddd, *J* = 15.0, 11.5, 5.4 Hz, 1H, H-16b), 2.37 (ddd, *J* = 15.0, 11.3, 3.3 Hz, 1H, H-16a), 1.91(m, 1H, H-17b), 1.58 (ddd, *J* = 18.3, 11.5, 3.3 Hz, 1H, H-17a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C-18), 169.9 (C-5), 155.3 (C-2), 155.0 (C-3), 136.6 (C-8), 134.7 (C-10), 132.4 (C-12), 129.9 (C-Ar), 129.6 (C-Ar), 129.0 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 72.1 (C-6), 47.1 (C-7), 45.4 (C-11), 44.4 (C-9), 38.2 (C-17), 30.1 (C-16); *m/z* (ES HRMS) $C_{28}H_{26}N_2O_4Na$ requires 477.1790, found $[MNa]^+$ 477.1799.

Synthesis of 1,4-dibenzyl-6-(3-oxopentyl)-6-propylpiperazine-2,3,5-trione **309**



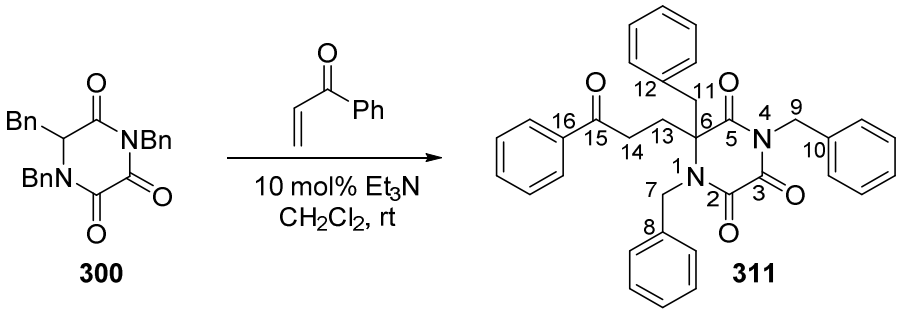
General procedure D using triketopiperazine **301** (250 mg) was followed to synthesise **309** (330 mg) in 15 hours as a white solid in 76% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 147 – 148 °C; IR ν_{max} /cm^{-1} 3069, 2971, 2938, 2876, 1742, 1709, 1671, 1499, 1452, 1420, 1355, 1328, 1265, 1221, 1156, 1080, 979, 723, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 4H, H-Ar), 7.27 – 7.14 (m, 6H, H-Ar), 5.02 (d, *J* = 13.4 Hz, 1H, H-9b), 4.97 (d, *J* = 13.4 Hz, 1H, H-9a), 4.82 (d, *J* = 14.8 Hz, 1H, H-7b), 4.44 (d, *J* = 14.8 Hz, 1H, H-7a), 2.14 (m, 2H, H-14), 1.98 – 1.71 (m, 4H, H-11, H-17), 1.66 (t, *J* = 8.1 Hz, 2H, H-15), 0.83 (m, 2H, H-12), 0.75 (t, *J* = 7.3 Hz, 3H, H-18), 0.52 (t, *J* = 7.2 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1 (C-16), 170.5 (C-5), 156.0 (C-3), 155.0 (C-2), 136.6 (C-8), 135.2 (C-10), 129.5 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 71.1 (C-6), 46.3 (C-7), 44.4 (C-9), 41.5 (C-11), 35.6 (C-15), 35.5 (C-17), 32.7 (C-14), 17.1 (C-12), 13.1 (C-13), 7.6 (C-18); *m/z* (ES HRMS) $C_{26}H_{30}N_2O_4Na$ requires 457.2103, found $[MNa]^+$ 457.2104.

Synthesis of 1,4-dibenzyl-6-(3-oxo-3-phenylpropyl)-6-propylpiperazine-2,3,5-trione **310**



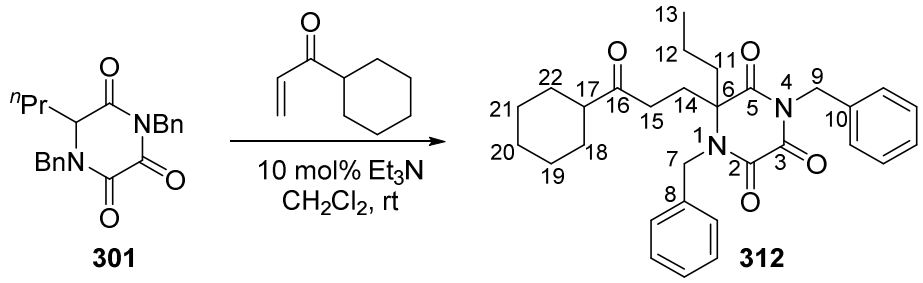
General procedure D using triketopiperazine **301** (35.6 mg) was followed to synthesise **310** (29.7 mg) in 23 hours as a white solid in 61% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 162 – 163 °C; IR ν_{max} /cm^{-1} 2957, 1744, 1675, 1495, 1446, 1416, 1359, 1262, 1148, 1079, 975, 731, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H, H-Ar), 7.51 – 7.44 (m, 4H, H-Ar), 7.44 – 7.33 (m, 4H, H-Ar), 7.32 – 7.23 (m, 3H, H-Ar), 7.17 (t, *J* = 7.4 Hz, 2H, H-Ar), 7.10 (m, 1H, H-Ar), 5.15 (d, *J* = 13.4 Hz, 1H, H-9b), 5.10 (d, *J* = 13.4 Hz, 1H, H-9a), 4.90 (d, *J* = 14.8 Hz, 1H, H-7b), 4.63 (d, *J* = 14.8 Hz, 1H, H-7a), 2.45 (m, 2H, H-14), 2.32 (m, 2H, H-15), 2.07 (ddd, *J* = 14.4, 12.1, 5.1 Hz, 1H, H-11b), 1.90 (m, 1H, H-11a), 0.92 (m, 2H, H-12), 0.63 (t, *J* = 7.2 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C-16), 170.6 (C-5), 156.0 (C-3), 155.0 (C-2), 136.5 (C-17), 135.9 (C-8), 135.3 (C-10), 133.3 (C-Ar), 129.6 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 127.7 (C-Ar), 71.2 (C-6), 46.4 (C-7), 44.4 (C-9), 41.5 (C-11), 33.1 (C-14), 32.1 (C-15), 17.2 (C-12), 13.1 (C-13); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{30}H_{31}N_2O_4$ requires 483.2284, found $[MH]^+$ 483.2282.

Synthesis of 1,4,6-tribenzyl-6-(3-oxo-3-phenylpropyl)piperazine-2,3,5-trione **311**



General procedure D using triketopiperazine **300** (38.0 mg) was followed to synthesise **311** (26.6 mg) in 24 hours as a white solid in 52% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 151 – 153 °C; IR ν_{max}^{-1} /cm^{-}3032, 1742, 1687, 1673, 1662, 1597, 1495, 1450, 1424, 1361, 1304, 1266, 1189, 1085, 968, 742, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 1H, H-Ar), 7.44 – 7.36 (m, 6H, H-Ar), 7.36 – 7.27 (m, 5H, H-Ar), 7.22 (m, 1H, H-Ar), 7.14 – 7.06 (m, 4H, H-Ar), 6.92 (t, *J* = 7.4 Hz, 1H, H-Ar), 6.82 (m, 2H, H-Ar), 5.64 (d, *J* = 14.6 Hz, 1H, H-7b), 4.90 (d, *J* = 13.4 Hz, 1H, H-9b), 4.80 (d, *J* = 13.4 Hz, 1H, H-9a), 4.24 (d, *J* = 14.6 Hz, 1H, H-7a), 3.41 (d, *J* = 13.9 Hz, 1H, H-11b), 3.31 (d, *J* = 13.9 Hz, 1H, H-11a), 2.74 (ddd, *J* = 14.8, 11.7, 5.2 Hz, 1H, H-13b), 2.52 (ddd, *J* = 14.8, 11.5, 3.1 Hz, 1H, H-13a), 2.33 (ddd, *J* = 16.8, 11.5, 5.2 Hz, 1H, H-14b), 2.20 – 2.05 (ddd, *J* = 16.8, 11.7, 3.1 Hz, 1H, H-14a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1 (C-15), 170.1 (C-5), 155.3 (C-2), 155.2 (C-3), 136.5 (C-16), 136.0 (C-8), 135.0 (C-10), 133.0 (C-Ar), 132.6 (C-12), 129.9 (C-Ar), 129.4 (C-Ar), 129.0 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 128.0 (C-Ar), 127.6 (C-Ar), 72.4 (C-6), 47.1 (C-7), 45.5 (C-11), 44.2 (C-9), 32.6 (C-14), 32.2 (C-13); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{34}H_{31}N_2O_4$ requires 531.2284, found $[MH]^+$ 531.2280.

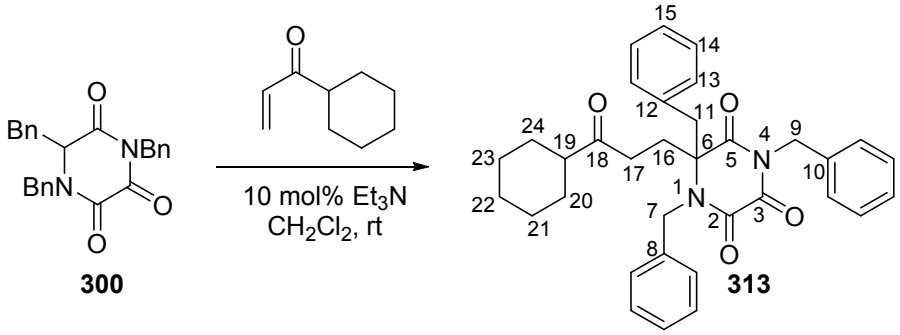
Synthesis of 1,4-dibenzyl-6-(3-cyclohexyl-3-oxopropyl)-6-propylpiperazine-2,3,5-trione **312**



301 **312**

General procedure D using triketopiperazine **301** (33.2 mg) was followed to synthesise **312** (38.1 mg) in 48 hours as a white solid in 82% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 130 – 131 °C; IR ν_{max} /cm^{-1} 2930, 2853 1740, 1705, 1674, 1497, 1447, 1427, 1372, 1319, 1261, 1219, 1149, 1075, 741, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H, H-Ar), 7.40 (m, 2H, H-Ar), 7.35 – 7.22 (m, 6H, H-Ar), 5.13 (d, *J* = 13.4 Hz, 1H, H-9b), 5.05 (d, *J* = 13.4 Hz, 1H, H-9a), 4.89 (d, *J* = 14.8 Hz, 1H, H-7b), 4.52 (d, *J* = 14.8 Hz, 1H, H-7a), 2.19 (m, 2H, H-14), 2.02 (ddd, *J* = 14.4, 12.1, 5.1 Hz, 1H, H-11b), 1.87 (ddd, *J* = 14.4, 12.1, 4.3 Hz, 1H, H-11a), 1.81 – 1.71 (m, 3H, H-15, H-17), 1.71 – 1.65 (m, 2H, H-21b, H-19b), 1.60 (m, 1H, H-20b), 1.49 – 1.35 (m, 2H, H-22b, H-18b), 1.19 – 1.05 (m, 3H, H-21a, H-20a, H-19a), 1.04 – 0.91 (m, 3H, H-12b, H-22a, H-18a), 0.83 (m, 1H, H-12a), 0.62 (t, *J* = 7.2 Hz, 3H, H-13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7 (C-16), 170.6 (C-5), 156.0 (C-3), 155.0 (C-2), 136.6 (C-8), 135.3 (C-10), 129.6 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 71.1 (C-6), 50.5 (C-17), 46.3 (C-7), 44.3 (C-9), 41.4 (C-11), 33.8 (C-15), 32.9 (C-14), 28.4 (C-22), 28.1 (C-18), 25.6 (C-21), 25.5 (C-19), 25.4 (C-20), 17.1 (C-12), 13.1 (C-13); *m/z* (ES HRMS) $C_{30}H_{37}N_2O_4$ requires 489.2753, found $[MH]^+$ 489.2772.

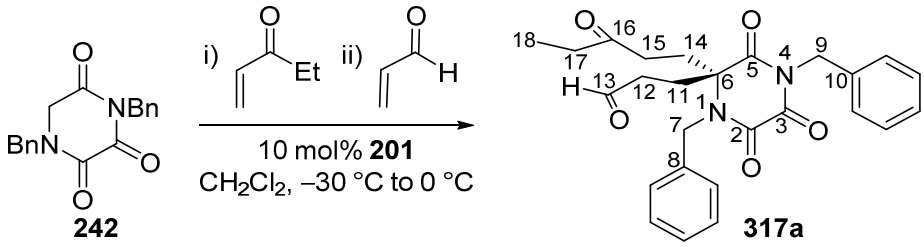
Synthesis of 1,4,6-tribenzyl-6-(3-cyclohexyl-3-oxopropyl)piperazine-2,3,5-trione **313**



General procedure D using triketopiperazine **300** (37.8 mg) was followed to synthesise **313** (44.2 mg) in 40 hours as a white solid in 86% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 168 – 169 °C; IR ν_{max} /cm^{-1} 3065, 2929, 1740, 1671, 1497, 1452, 1427, 1373, 1306, 1253, 1139, 1080, 1031, 741, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H, H-Ar), 7.37 (m, 2H, H-Ar), 7.34 – 7.25 (m, 6H, H-Ar), 7.19 (m, 1H, H-15), 7.08 (t, *J* = 7.6 Hz, 2H, H-14), 6.78 (d, *J* = 7.6 Hz, 1H, H-13), 5.58 (d, *J* = 14.7 Hz, 1H, H-7b), 4.87 (d, *J* = 13.4 Hz, 1H, H-9b), 4.80 (d, *J* = 13.4 Hz, 1H, H-9a), 4.19 (d, *J* = 14.7 Hz, 1H, H-7a), 3.35 (d, *J* = 13.9 Hz, 1H, H-11b), 3.25 (d, *J* = 13.9 Hz, 1H, H-11a), 2.49 (ddd, *J* = 14.9, 12.0, 4.9 Hz, 1H, H-16b), 2.32 (ddd, *J* = 14.9, 11.9, 3.4 Hz, 1H, H-16a), 1.81 (ddd, *J* = 17.1, 11.9, 4.9 Hz, 1H, H-17b), 1.68 – 1.52 (m, 5H, H-17a, H-19, H-23b, H-22b, H-21b), 1.43 (d, *J* = 13.0 Hz, 1H, H-24b), 1.26 (m, 1H, H-20b), 1.16 – 1.02 (m, 3H, H-23a, H-22a, H-21a), 1.00 – 0.80 (m, 2H, H-24a, H-20a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7 (C-18) , 170.1 (C-5), 155.2 (C-3), 155.1 (C-2), 136.7 (C-8), 134.9 (C-10), 132.6 (C-12), 129.9 (C-Ar), 129.4 (C-Ar), 129.0 (C-Ar), 128.9 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 72.3 (C-6), 50.3 (C-19), 47.1 (C-7), 45.3 (C-11), 44.2 (C-9), 34.2 (C-17), 31.9 (C-16), 28.4 (C-24), 28.0 (C-20), 25.6 (C-23), 25.5 (C-21), 25.3 (C-22);

1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{34}H_{37}N_2O_4$ requires 537.2753, found $[MH]^+$ 531.2738.

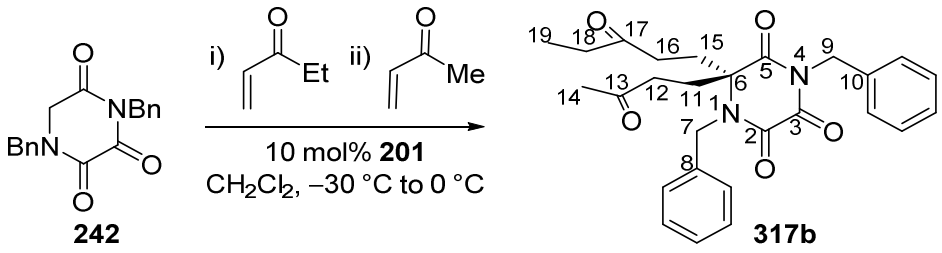
Synthesis of (*R*)-1,4-dibenzyl-6-(3-oxopentyl)-6-(3-oxopropyl)piperazine-2,3,5-trione **317a**



To a mixture of triketopiperazine **242** (0.1 mmol, 30.8 mg) and catalyst **201** (4.0 mg, 10 mol%) dissolved in CH_2Cl_2 (0.7 mL) at –78 °C, ethyl vinyl ketone (0.1 mmol, 10 µL, 1.05 eq) was added neat over 1 minute. The reaction mixture was allowed to warm to –30 °C and left to react. After the starting material was completely consumed, acrolein (33 µL, 0.5 mmol, 5 eq) was added. The temperature was raised to 0 °C and the mixture was left to react until complete consumption of the reactive intermediate, 48 hours. Product **317a** (38.0 mg) was obtained as a white solid in 85% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 127 – 128 °C; IR ν_{max} /cm^{-1} 2976, 2827, 2726, 1725, 1713, 1675, 1493, 1422, 1364, 1314, 1269, 1146, 1080, 1034, 727, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H, H-13), 7.45 (m, 2H, H-Ar), 7.40 (dt, *J* = 5.0, 3.0 Hz, 2H, H-Ar), 7.36 – 7.23 (m, 6H, H-Ar), 5.10 (d, *J* = 13.4 Hz, 1H, H-9b), 5.05 (d, *J* = 13.4 Hz, 1H, H-9a), 4.78 (d, *J* = 14.9 Hz, 1H, H-7b), 4.64 (d, *J* = 14.9 Hz, 1H, H-7a), 2.39 – 2.19 (m, 4H, H-11, H-14), 2.02 (m, 2H, H-17), 1.91 (m, 2H, H-12), 1.80 (m, 2H, H-15), 0.86 (t, *J* = 7.3 Hz, 3H, H-18); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8 (C-16), 198.2 (C-13), 169.8 (C-5), 155.6 (C-3), 154.8 (C-2), 136.4 (C-8), 135.1 (C-10), 129.6 (C-Ar), 129.0 (C-Ar), 128.9 (C-Ar), 128.7

(C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 70.0 (C-6), 46.4 (C-7), 44.5 (C-9), 37.8 (C-12), 35.6 (C-17), 35.6 (C-15), 33.0 (C-14), 31.1 (C-11), 7.6 (C-18); *m/z* (ES HRMS) $C_{26}H_{29}N_2O_5$ requires 449.2076, found $[MH]^+$ 449.2073; $[\alpha]_D^{21} = -3.4$ (*c* 1.2, $CHCl_3$).

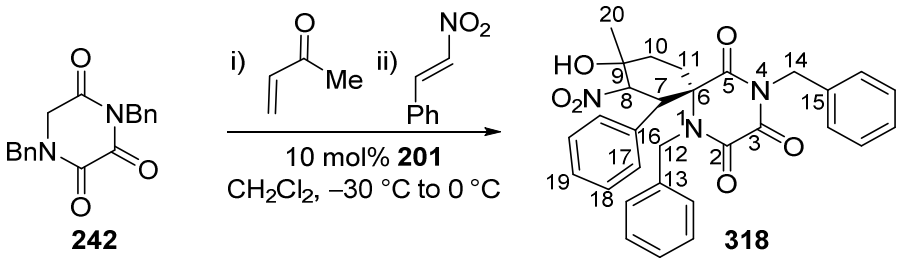
Synthesis of (*R*)-1,4-dibenzyl-6-(3-oxobutyl)-6-(3-oxopentyl)piperazine-2,3,5-trione **317b**



To a mixture of triketopiperazine **242** (0.1 mmol, 30.8 mg) and catalyst **201** (4.0 mg, 10 mol%) dissolved in CH_2Cl_2 (0.7 mL) at –78 °C, ethyl vinyl ketone (0.1 mmol, 10 µL, 1.05 eq) was added neat over 1 minute. The reaction mixture was allowed to warm to –30 °C and left to react. After the starting material was completely consumed, methyl vinyl ketone (35 µL, 0.5 mmol, 5 eq) was added. The temperature was raised to 0 °C and the mixture was left to react until complete consumption of the reactive intermediate, 48 hours. Product **317b** (36.4 mg) was obtained as a white solid in 79% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 139 – 140 °C; IR ν_{max} /cm^{-1} 2951, 1711, 1676, 1496, 1456, 1420, 1363, 1266, 1169, 1143, 1077, 1030, 734, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H, H-Ar), 7.32 (m, 2H, H-Ar), 7.27 – 7.21 (m, 3H, H-Ar), 7.20 – 7.15 (m, 3H, H-Ar), 5.00 (s, 2H, H-9), 4.63 (d, *J* = 14.9 Hz, 1H, H-7b), 4.58 (d, *J* = 14.9 Hz, 1H, H-7a), 2.24 – 2.13 (m, 4H, H-11, H-15), 1.89 (m, 2H, H-18), 1.79 – 1.70 (m, 4H, H-12, H-16), 1.68 (s, 3H, H-14), 0.77 (t, *J* = 7.3 Hz, 3H, H-19); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 207.9 (C-17), 205.1 (C-13), 169.9 (C-5), 155.7 (C-3), 154.9 (C-2), 136.5 (C-8), 135.2 (C-10), 129.7 (C-Ar), 129.0 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 70.0 (C-6), 46.4 (C-7), 44.5 (C-9), 37.0 (C-12), 35.7 (C-16), 35.6 (C-18), 32.8 (C-11, C-15), 29.5 (C-14), 7.5 (C-19); *m/z* (ES HRMS) $C_{27}H_{30}N_2O_5Na$ requires 485.2052, found $[MNa]^+$ 485.2055; $[\alpha]_D^{21}$= 5.0 (*c* 1.0, $CHCl_3$).

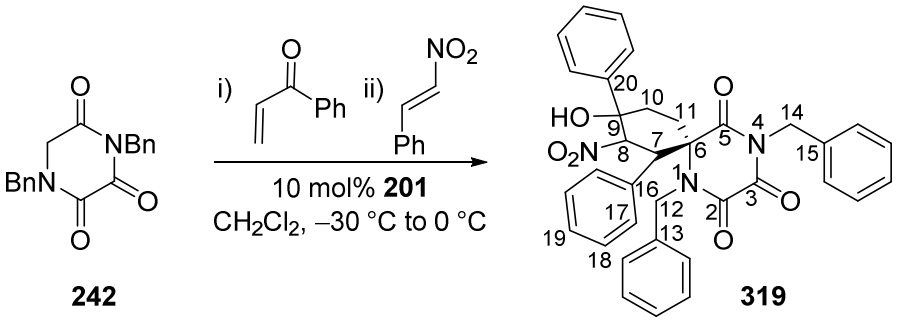
Synthesis of (6*S*,7*R*)-1,4-dibenzyl-9-hydroxy-9-methyl-8-nitro-7-phenyl-1,4-diazaspiro [5.5]undecane-2,3,5-trione **318**



To a mixture of triketopiperazine **242** (0.1 mmol, 30.8 mg) and catalyst **201** (4.0 mg, 10 mol%) dissolved in CH_2Cl_2 (0.7 mL) at −78 °C, methyl vinyl ketone (0.1 mmol, 8 µL, 1.05 eq) was added neat over 1 minute. The reaction mixture was allowed to warm to –30 °C and left to react. After the starting material was completely consumed, nitrostyrene (74.5 mg, 0.5 mmol, 5 eq) was added. The temperature was raised to 0 °C and the mixture was left to react until complete consumption of the reactive intermediate, 72 hours. Product **318** (36.3 mg) was obtained as a white solid in 69% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 184 – 185 °C; IR ν_{max} /cm^{-1} 3401, 2967, 2932, 2879, 1740, 1679, 1548, 1498, 1456, 1423, 1368, 1322, 1301, 1209, 1131, 1030, 990, 752, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 10H, H-Ar), 7.20 (t, *J* = 7.3 Hz, 1H,

H-19), 7.01 (t, *J* = 7.3 Hz, 2H, H-18), 6.87 (d, *J* = 7.3 Hz, 2H, H-17), 5.61 (d, *J* = 12.1 Hz, 1H, H-8), 5.55 (d, *J* = 15.5 Hz, 1H, H-12b), 4.78 (d, *J* = 13.4 Hz, 1H, H-14b), 4.69 (d, *J* = 13.4 Hz, 1H, H-14a), 4.66 (d, *J* = 15.5 Hz, 1H, H-12a), 4.31 (d, *J* = 12.1 Hz, 1H, H-7), 2.82 (d, *J* = 1.9 Hz, 1H, OH), 2.71 – 2.53 (m, 2H, H-11b, H-10b), 1.94 (m, 1H, H-10a), 1.85 (m, 1H, H-11a), 1.45 (s, 3H, H-20); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C-5), 154.2 (C-3), 154.1 (C-2), 136.1 (C-13), 134.4 (C-15), 130.5 (C-16), 130.2 (C-Ar), 129.7 (C-Ar), 129.3 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 126.8 (C-Ar), 91.5 (C-8), 70.1 (C-9), 69.8 (C-6), 47.3 (C-12), 47.1 (C-7), 44.4 (C-14), 34.3 (C-10), 29.3 (C-11), 26.9 (C-20); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ESI HRMS) $C_{30}H_{29}N_3O_6Na$ requires 550.1954, found $[MNa]^+$ 550.1947; $[\alpha]_D^{21}$= –71.7 (*c* 0.8, $CHCl_3$).

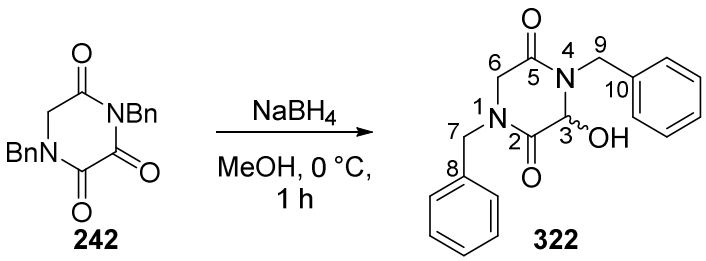
Synthesis of (6*S*,7*R*)-1,4-dibenzyl-9-hydroxy-8-nitro-7,9-diphenyl-1,4-diazaspiro [5.5]undecane-2,3,5-trione **319**



To a mixture of triketopiperazine **242** (0.1 mmol, 30.8 mg) and catalyst **201** (4.0 mg, 10 mol%) dissolved in CH_2Cl_2 (0.7 mL) at –78 °C, phenyl vinyl ketone (0.1 mmol, 13.5 mg, 1.05 eq) was added neat over 1 minute. The reaction mixture was allowed to warm to –30 °C and

left to react. After the starting material was completely consumed, nitrostyrene (74.5 mg, 0.5 mmol, 5 eq) was added. The temperature was raised to 0 °C and the mixture was left to react until complete consumption of the reactive intermediate, 72 hours. Product **319** (45.1 mg) was obtained as a white solid in 77% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 129 – 132 °C; IR ν_{max} /cm^{-1} 3031, 1743, 1677, 1549, 1496, 1448, 1367, 1323, 1203, 1030, 750, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 2H, H-Ar), 7.53 (m, 1H, H-Ar), 7.49 – 7.43 (m, 4H, H-Ar), 7.42 – 7.24 (m, 8H, H-Ar), 7.21 (t, *J* = 7.3 Hz, 1H, H-19), 7.01 (t, *J* = 7.3 Hz, 2H, H-18), 6.95 (d, *J* = 7.3 Hz, 2H, H-17), 6.21 (d, *J* = 12.0 Hz, 1H, H-8), 5.59 (d, *J* = 15.5 Hz, 1H, H-12b), 4.88 (d, *J* = 13.4 Hz, 1H, H-14b), 4.77 (d, *J* = 13.8 Hz, 2H, H-12a, H-14a), 4.46 (d, *J* = 12.0 Hz, 1H, H-7), 3.99 (d, *J* = 2.7 Hz, 1H, OH), 3.00 (m, 1H, H-10b), 2.83 (td, *J* = 13.6, 5.2 Hz, 1H, H-11b), 2.05 – 1.90 (m, 2H, H-11a, H-10a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C-5), 154.2 (C-3), 154.0 (C-2), 141.4 (C-20), 136.0 (C-13), 134.4 (C-15), 133.4 (C-16), 130.2 (C-Ar), 129.9 (C-Ar), 129.3 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 126.8 (C-Ar), 124.4 (C-Ar), 90.7 (C-8), 75.0 (C-9), 69.8 (C-6), 47.8 (C-7), 47.3 (C-12), 44.4 (C-14), 35.6 (C-10), 29.8 (C-11); 2 signals in the C-H aromatic region were not observed due to having equivalent resonances; *m/z* (ESI HRMS) $C_{35}H_{31}N_3O_6Na$ requires 612.2111, found $[MNa]^+$ 612.2109; $[\alpha]_D^{21}$= –33.7 (*c* 1.0, $CHCl_3$).

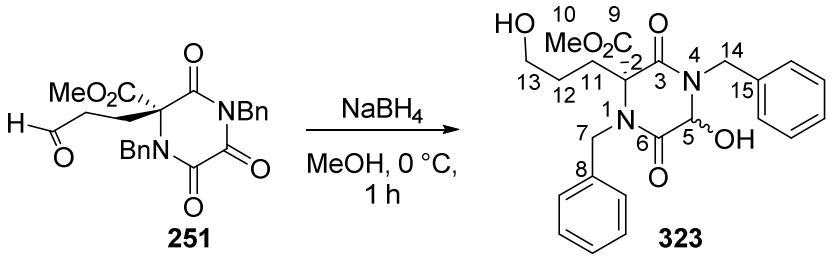
Synthesis of 1,4-dibenzyl-3-hydroxypiperazine-2,5-dione **322**



242 **322**

To a solution of **242** (15.4 mg, 0.05 mmol, 1 eq.) in MeOH (1 mL), $NaBH_4$ (2.4 mg, 0.05 mmol, 1 eq.) was added in one portion at 0 °C. The mixture was left to react at that temperature for 2 h and was then quenched with water (2 mL). The crude was extracted with ethyl acetate (3 x 10 mL) and washed with brine (1 x 15 mL). Compound **322** was obtained as a white solid in 62% yield (9.7 mg) after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to (0:1). m.p. 179 – 181 °C; IR ν_{max} /cm^{-1} 3112, 3032, 2942, 2855, 1639, 1471, 1454, 1310, 1260, 1163, 1104, 1071, 943, 726, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 8H, H-Ar), 7.26 (m, 2H, H-Ar), 5.17 (d, *J* = 14.7 Hz, 1H, H-7b), 5.09 (s, 1H, H-3), 4.70 (d, *J* = 14.6 Hz, 1H, H-9b), 4.48 (d, *J* = 14.6 Hz, 1H, H-9a), 4.27 (d, *J* = 14.7 Hz, 1H, H-7a), 4.09 (d, *J* = 17.6 Hz, 1H, H-6b), 3.86 (d, *J* = 17.6 Hz, 1H, H-6a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (C-5), 164.8 (C-2), 135.6 (C-8), 134.5 (C-10), 129.0 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 128.0 (C-Ar), 77.5 (C-3), 49.5 (C-9), 49.0 (C-6), 46.4 (C-7); *m/z* (ESI) $C_{18}H_{18}N_2O_3Na$ requires 333.1215, found $[MNa]^+$ 333.1231.

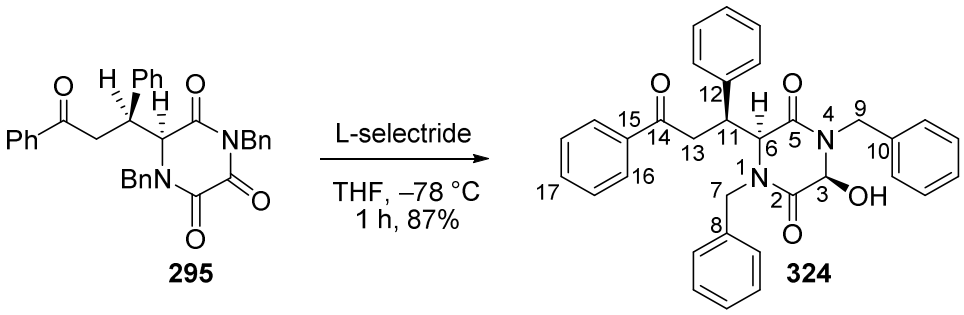
Synthesis of methyl (2*S*)-1,4-dibenzyl-5-hydroxy-2-(3-hydroxypropyl)-3,6-dioxopiperazine-2-carboxylate **323**



To a solution of **251** (105.5 mg, 0.25 mmol, 1 eq.) in MeOH (5 mL), $NaBH_4$ (6.6 mg, 0.18 mmol, 0.70 eq.) was added in one portion at 0 °C. The mixture was left to react at that temperature for 1 h and was then quenched with water (3 mL). The crude was extracted with ethyl acetate (3 x 15 mL) and washed with brine (1 x 15 mL). Compound **323** was obtained as a colourless oil in 71% yield (75.7 mg) as an approximately 1:1 mixture of diastereoisomers after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to (1:2). IR ν_{max} /cm^{-1} 3357, 2953, 1755, 1654, 1496, 1450, 1359, 1233, 1150, 1064, 1030, 986, 731, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 20H, H-Ar), 5.50 – 5.24 (m, 3H, *H-7b*, *H-14b*, H-14b), 5.18 (s, 1H, H-5), 5.14 (s, 1H, *H-5*), 4.71 (d, *J* = 15.2 Hz, 1H, H-7b), 4.51 (d, *J* = 15.2 Hz, 1H, H-7a), 4.31 – 4.17 (m, 3H *H-7a*, *H-14a*, H-14a), 3.66 (dt, *J* = 10.8, 5.4 Hz, 1H, *H-13b*), 3.60 – 3.48 (m, 2H, *H-13a*, H-13b), 3.44 (m, 1H, H-13a), 3.34 (s, 3H, H-10), 3.30 (s, 3H, *H-10*), 2.71 (ddd, *J* = 14.8, 11.0, 6.1 Hz, 1H, *H-11b*), 2.59 – 2.39 (m, 2H, *H-11a*, H-11b), 2.31 (m, 1H, H-11a), 1.50 (m, 1H, H-12b), 1.44 – 1.28 (m, 3H, H-12a, *H-12b*, *H-12a*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (*C-9*), 167.8 (C-9), 166.8 (C-6), 166.3 (*C-6*), 164.0 (*C-3*), 163.8 (C-3), 135.5 (C-8), 135.0 (*C-8*, *C-15*, C-15), 129.4 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 128.0 (C-Ar), 77.2 (*C-5*), 75.6 (C-5), 71.8 (C-2), 70.9 (*C-2*), 61.8 (C-13), 61.6 (*C-13*),

53.9 (*C-10*), 52.9 (C-10), 47.0 (C-7), 46.9 (*C-7*), 46.4 (C-14), 46.1 (*C-14*), 29.3 (C-11), 28.1 (*C-11*), 26.1 (C-12), 25.9 (*C-12*); 3 signals in the C-H aromatic region were not observed due to having equivalent resonances; *m/z* (ESI) $C_{23}H_{26}N_2O_6Na$ requires 449.1689, found $[MNa]^+$ 449.1673.

Synthesis of (3*S*, 6*S*)-1,4-dibenzyl-3-hydroxy-6-((*S*)-3-oxo-1,3-diphenylpropyl)piperazine-2,5-dione **324**

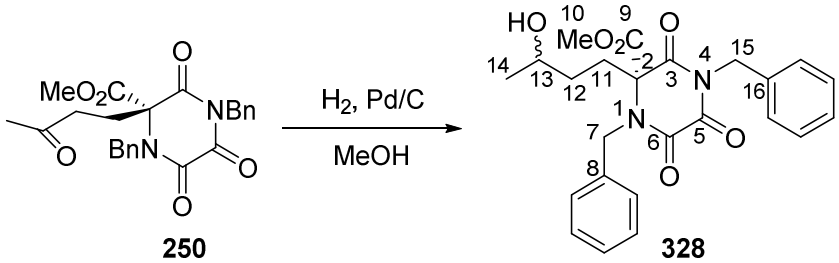


295 **324**

A solution of **295** (99.5 mg, 0.19 mmol, 1.0 eq.) in dry THF (5 mL) was cooled to −78 °C and L-selectride (0.20 mL, 1 M, 1.1 eq.) was added dropwise over 2 minutes. The mixture was left to react at that temperature for 1 h and quenched with saturated NH_4Cl. The crude was extracted with ethyl acetate (3 x 15 mL) and washed with brine (1 x 15 mL). Compound **324** was obtained as a white solid in 87% yield (87.0 mg) after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). m.p. 62 – 65 °C; IR ν_{max}/cm^{-1} 3316, 3063, 3031, 2934, 1658, 1598, 1496, 1464, 1451, 1265, 1233, 1163, 1069, 1030, 987, 729, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H, H-16), 7.47 (m, 1H, H-17), 7.40 – 7.26 (m, 6H, H-Ar), 7.24 – 7.08 (m, 9H, H-Ar), 6.71 (dt, *J* = 4.3, 3.0 Hz, 2H, H-Ar), 5.85 (d, *J* = 6.6 Hz, 1H, OH), 5.19 (d, *J* = 6.6 Hz, 1H, H-3), 4.97 (d, *J* = 15.3 Hz, 1H, H-7b), 4.91 (d, *J* = 15.0 Hz, 1H, H-9b), 4.30 – 4.08 (m, 2H, H-11, H-9a), 3.98 – 3.84 (m, 2H, H-13b, H-6), 3.20

(dd, *J* = 18.5, 5.0 Hz, 1H, H-13a), 2.34 (d, *J* = 15.3 Hz, 1H, H-7a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9 (C-14), 167.7 (C-5), 165.8 (C-2), 141.5 (C-12), 136.4 (C-15), 135.8 (C-8), 135.4 (C-10), 133.5 (C-Ar), 129.4 (C-Ar), 128.8 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 127.9 (C-Ar), 127.7 (C-Ar), 79.4 (C-3), 64.6 (C-6), 48.2 (C-7), 47.4 (C-9), 46.0 (C-11), 42.1 (C-13); *m/z* (ESI) $C_{33}H_{30}N_2O_4Na$ requires 541.2103, found $[MNa]^+$ 541.2099; $[\alpha]_D^{20}$= –85.6 (*c* 2.3, $CHCl_3$).

Synthesis of methyl (2*S*)-1,4-dibenzyl-2-(3-hydroxybutyl)-3,5,6-trioxopiperazine-2-carboxylate **328**



To a solution of **250** (43.6 mg, 0.1 mmol, 1 eq.) in MeOH (4 mL), palladium on carbon (5 mg, 0.1 eq.) was added in one portion. The mixture was flushed with and left under hydrogen atmosphere to react at room temperature for 2 h. After the starting material was consumed, the crude was filtered through celite and the solvent removed under vacuum. Compound **328** was obtained as a colourless oil in 81% yield (35.6 mg) as an approximately 1:1 mixture of diastereoisomers after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to (1:2). IR ν_{max} /cm^{-1} 3482, 2969, 1743, 1686, 1497, 1421, 1369, 1236, 1160, 1081, 732, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 4H, H-Ar), 7.28 – 7.16 (m, 16H, H-Ar), 5.04 (d, *J* = 13.7 Hz, 1H, H-15b), 5.03 (d, *J* = 13.6 Hz, 1H, *H-15b*), 4.96 (d, *J* =

13.6 Hz, 1H, H-15a), 4.95 (d, *J* = 13.7 Hz, 1H, *H-15a*), 4.88 (d, *J* = 15.0 Hz, 1H, H-7b), 4.68 (d, *J* = 15.0 Hz, 1H, *H-7b*), 4.53 (d, *J* = 15.0 Hz, 1H, *H-7a*), 4.42 (d, *J* = 15.0 Hz, 1H, H-7a), 3.43 (m, 1H, H-13), 3.31 (m, 1H, *H-13*), 3.23 (s, 3H, H-10), 3.16 (s, 3H, *H-10*), 2.49 (m, 2H, H-11), 2.35 (m, 1H, *H-11b*), 2.22 (m, 1H, *H-11a*), 0.93 – 0.86 (m, 2H, H-12b, *H-12b*), 0.89 (d, *J* = 6.2 Hz, 3H, H-14), 0.83 (d, *J* = 6.2 Hz, 3H, *H-14*), 0.79 (m, 1H, H-12a), 0.72 (m, 1H, *H-12a*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C-9), 166.1 (*C-9*, C-3), 166.0 (*C-3*), 155.4 (C-5), 155.4 (*C-5*), 154.2 (C-6), 154.2 (*C-6*), 135.1 (*C-8*), 134.9 (C-8), 134.8 (*C-16*), 134.8 (C-16), 129.4 (C-Ar), 129.3 (C-Ar), 129.2 (C-Ar), 129.2 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 73.0 (*C-2*), 72.7 (C-2), 66.8 (C-13, *C-13*), 53.5 (C-10), 53.4 (*C-10*), 47.7 (*C-7*), 47.4 (C-7), 44.7 (C-15), 44.7 (*C-15*), 31.8 (C-12), 31.6 (*C-12*), 30.0 (*C-11*), 30.0 (C-11), 23.7 (C-14), 23.1 (*C-14*); 5 signals in the C-H aromatic region were not observed due to having equivalent resonances; *m/z* (ESI) $C_{24}H_{26}N_2O_6Na$ requires 461.1689, found $[MNa]^+$ 461.1692.

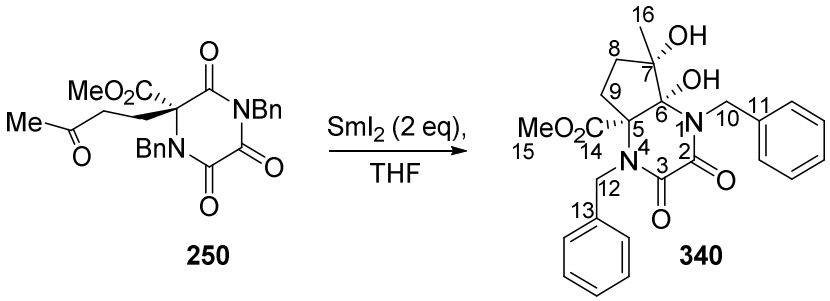
SmI_2 reactions, General procedure E:

To a solution of triketopiperazine **250**, **276**, **303**, **304**, **305**, **308** or **309** (0.05 mmol) in THF (1 mL) at room temperature, SmI_2 solution in THF (2 eq.) was added. The mixture was allowed to react for 2-4 minutes before it was quenched by bubbling air through the solution, followed by HCl (0.1 M, 10 mL). The crude mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (1 x 20 mL), dried over $MgSO_4$, filtered and condensed under reduced pressure. The crude was purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19).

SmI_2 reactions, General procedure F:

To a solution of triketopiperazine **303**, **304**, **305**, **308** or **309** (0.05 mmol) in THF/water (2:1; 1.5 mL) at room temperature, SmI_2 solution in THF (2 eq.) was added. The mixture was allowed to react for 1-5 minutes before it was quenched by bubbling air through the solution, followed by HCl (0.1 M, 10 mL). The crude mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (1 x 20 mL), dried over $MgSO_4$, filtered and condensed under reduced pressure before being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to ethyl acetate (100%).

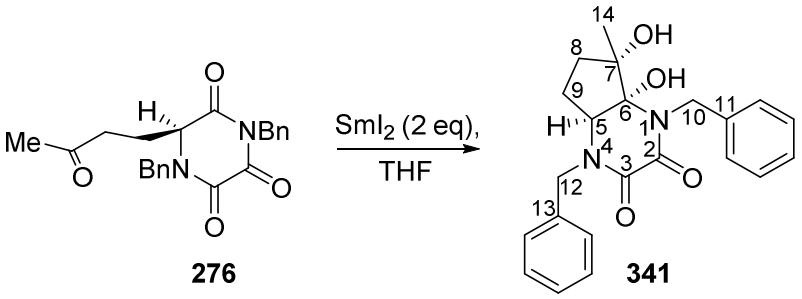
Synthesis of methyl (4a*S*,7*S*,7a*R*)-1,4-dibenzyl-7,7a-dihydroxy-7-methyl-2,3-dioxooctahydro-4a*H*-cyclopenta[b]pyrazine-4a-carboxylate **340**



General procedure E using triketopiperazine **250** (22.1 mg) was followed to synthesise **340** (14.5 mg) in 2 minutes as a white solid in 66% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19). m.p. 195 – 197 °C; IR ν_{max} /cm^{-1} 3304, 2990, 2945, 1731, 1662, 1604, 1497, 1429, 1401, 1362, 1284, 1140, 1078, 962, 889, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H, H-Ar), 7.29 – 7.14 (m, 8H, H-Ar), 4.93 (d, *J* = 14.6 Hz, 1H, H-12b), 4.72 (d, *J* = 14.9 Hz, 1H, H-10b), 4.51

(d, *J* = 14.9 Hz, 1H, H-10a), 4.26 (d, *J* = 14.6 Hz, 1H, H-12a), 3.29 (s, 3H, H-15), 2.67 (ddd, *J* = 14.6, 12.8, 8.5 Hz, 1H, H-9b), 2.22 (m, 1H, H-9a), 1.82(m, 1H, H-8b), 1.54 (m, 1H, H-8a), 1.28 (s, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (C-14), 158.6 (C-2), 155.7 (C-3), 137.5 (C-13), 135.5 (C-11), 128.8 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar), 128.0 (C-Ar), 127.0 (C-Ar), 92.3 (C-6), 81.1 (C-7), 74.3 (C-5), 52.6 (C-15), 47.2 (C-10), 46.2 (C-12), 36.7 (C-8), 27.7 (C-9), 26.7 (C-16); *m/z* (ES HRMS) $C_{24}H_{27}N_2O_6$ requires 439.1869, found $[MH]^+$ 439.1871; $[\alpha]_D^{21}$= 1.5 (*c* 0.8, $CHCl_3$).

Synthesis of (4a*R*,5*S*,7a*S*)-1,4-dibenzyl-4a,5-dihydroxy-5-methylhexahydro-1H-cyclopenta[b]pyrazine-2,3-dione **341**

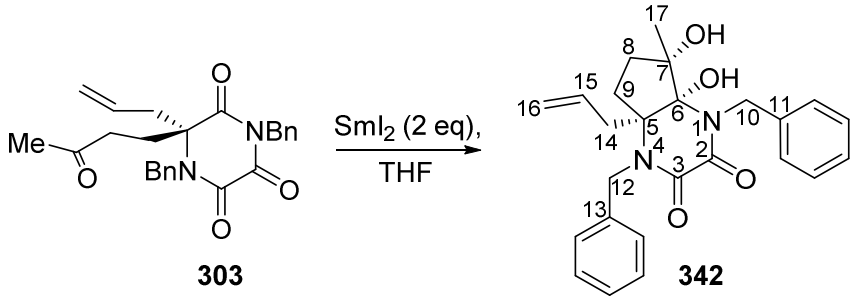


276 **341**

General procedure E using triketopiperazine **276** (18.7 mg) was followed to synthesise **341** (15.2 mg) in 2 minutes as a white solid in 82% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19). m.p. 148 – 150 °C; IR ν_{max} /cm^{-1} 3419, 3025, 2922, 2851, 1675, 1641, 1603, 1494, 1439, 1361, 1257, 1159, 1082, 980, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H, H-Ar), 7.36 – 7.28 (m, 4H, H-Ar), 7.28 – 7.19 (m, 4H, H-Ar), 5.08 (m, 2H, OH, H-12b), 4.89 (d, *J* = 14.7 Hz, 1H, H-10b), 4.76 (d, *J* = 14.7 Hz, 1H, H-10a), 4.32 (d, *J* = 14.8 Hz, 1H, H-12a), 3.96 (dd, *J* = 7.0, 4.2 Hz, 1H, H-5), 2.17 (m, 1H, H-9b), 1.90 – 1.67 (m, 3H, H-8, H-9a), 1.23 (s, 3H, H-14);

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C-2), 155.8 (C-3), 137.7 (C-11), 135.2 (C-13), 128.9 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar), 127.4 (C-Ar), 90.7 (C-6), 82.1 (C-7), 62.6 (C-5), 47.9 (C-12), 46.0 (C-10), 36.2 (C-8), 26.5 (C-9), 24.5 (C-14); *m/z* (ES HRMS) $C_{22}H_{24}N_2O_4Na$ requires 403.1624, found $[MNa]^+$ 403.1634; $[\alpha]_D^{21} = -3.3$ (*c* 0.7, $CHCl_3$).

Synthesis of (4a*R*,5*S*,7a*R*)-7a-allyl-1,4-dibenzyl-4a,5-dihydroxy-5-methylhexahydro-1H-cyclopenta[b]pyrazine-2,3-dione **342**

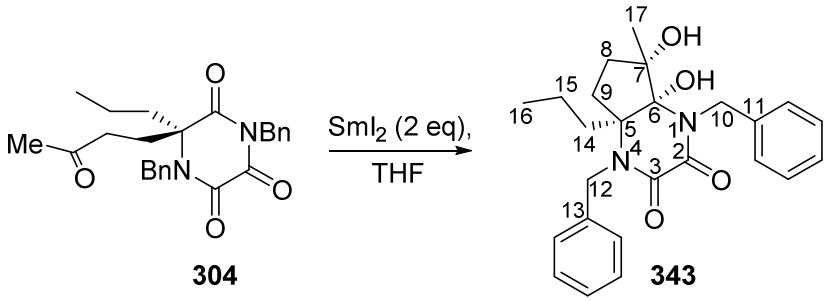


303 **342**

General procedure E using triketopiperazine **303** (20.9 mg) was followed to synthesise **342** (18.4 mg) in 3 minutes as a white solid in 88% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19). m.p. 204 – 206 °C; IR ν_{max} /cm^{-1} 3415, 3332, 3034, 2971, 1650, 1603, 1496, 1453, 1410, 1353, 1260, 1105, 1076, 966, 889, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H, H-Ar), 7.35 (dd, *J* = 7.4, 1.7 Hz, 2H, H-Ar), 7.32 – 7.18 (m, 6H, H-Ar), 5.44 (m, 1H, H-15), 5.16 (d, *J* = 14.9 Hz, 1H, H-12b), 4.89 – 4.83 (m, 2H, H-10b, H-16cis), 4.79 (d, *J* = 17.2 Hz, 1H, H-16trans), 4.30 (d, *J* = 13.9 Hz, 1H, H-10a), 4.05 (d, *J* = 14.9 Hz, 1H, H-12a), 2.65 (dd, *J* = 14.1, 6.3 Hz, 1H, H-14b), 2.34 (dd, *J* = 14.1, 9.1 Hz, 1H, H-14a), 1.96 (m, 2H, H-9), 1.48 (m, 1H, H-8b), 1.11 (s, 3H, H-17), 1.04 (m, 1H, H-8a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C-3), 156.7 (C-

2), 137.7 (C-13), 137.4 (C-11), 131.7 (C-15), 129.8 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.1 (C-Ar), 127.7 (C-Ar), 127.4 (C-Ar), 120.3 (C-16), 92.6 (C-6), 81.4 (C-7), 72.8 (C-5), 47.0 (C-12), 46.2 (C-10), 38.0 (C-14), 36.8 (C-8), 32.4 (C-9), 26.9 (C-17); *m/z* (ES HRMS) $C_{25}H_{28}N_2O_4Na$ requires 443.1947 found $[MNa]^+$ 443.1938.

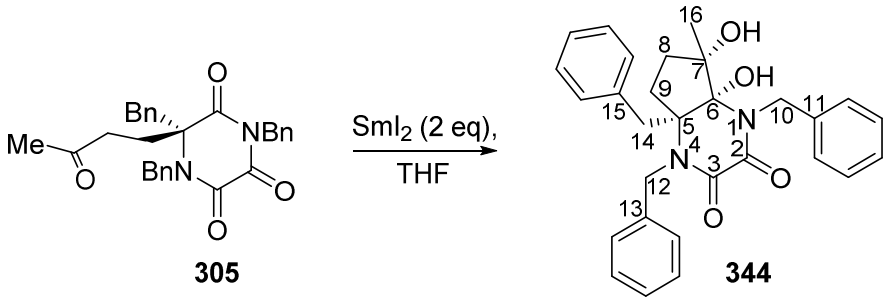
Synthesis of (4a*R*,5*S*,7a*S*)-1,4-dibenzyl-4a,5-dihydroxy-5-methyl-7a-propylhexahydro-1H-cyclopenta[b]pyrazine-2,3-dione **343**



General procedure E using triketopiperazine **304** (21.0 mg) was followed to synthesise **343** (18.8 mg) in 3 minutes as a white solid in 89% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19). m.p. 193 – 195 °C; IR ν_{max} /cm^{-1} 3261, 3066, 2968, 1668, 1643, 1496, 1453, 1409, 1351, 1253, 1154, 1074, 960, 882, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.5, 1.8 Hz, 2H, H-Ar), 7.38 (dd, *J* = 6.1, 3.3 Hz, 2H, H-Ar), 7.32 – 7.23 (m, 6H, H-Ar), 5.79 (s, 1H, OH), 4.99 (d, *J* = 14.8 Hz, 1H, H-12b), 4.79 (d, *J* = 13.8 Hz, 1H, H-10b), 4.70 (d, *J* = 13.8 Hz, 1H, H-10a), 4.31 (d, *J* = 14.8 Hz, 1H, H-12a), 3.41 (s, 1H, OH), 2.05 – 1.87 (m, 3H, H-9, H-14b), 1.56 (m, 1H, H-8b), 1.47 (m, 1H, H-14a), 1.23 – 1.13 (m, 2H, H-8a, H-15b), 1.10 (s, 3H, H-17), 0.90 (m, 1H, H-15a) 0.63 (t, *J* = 7.2 Hz, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C-3), 156.7 (C-2), 137.6 (C-13), 137.4 (C-11), 130.0 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar),

128.4 (C-Ar), 127.7 (C-Ar), 92.5 (C-6), 82.3 (C-7), 72.8 (C-5), 46.6 (C-12), 45.5 (C-10), 36.5 (C-8), 36.1 (C-14), 32.8 (C-9), 27.4 (C-17), 16.8 (C-15), 14.1 (C-16); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{25}H_{31}N_2O_4$ requires 423.2284, found $[MH]^+$ 423.2273.

Synthesis of (4a*R*,5*S*,7a*R*)-1,4,7a-tribenzyl-4a,5-dihydroxy-5-methylhexahydro-1H-cyclopenta[b]pyrazine-2,3-dione **344**

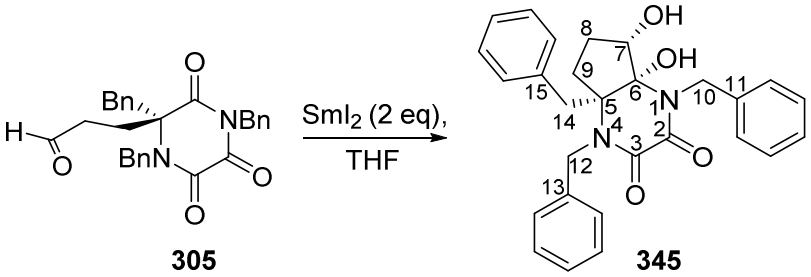


305 **344**

General procedure E using triketopiperazine **305** (24.1 mg) was followed to synthesise **344** (20.7 mg) in 2 minutes as a white solid in 86% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19). m.p. 112 – 113 °C; IR ν_{max} /cm^{-1} 3303, 3064, 2937, 1655, 1604, 1495, 1451, 1401, 1354, 1250, 1133, 1071, 960, 883, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.5, 1.8 Hz, 2H, H-Ar), 7.32 (dd, *J* = 6.5, 2.7 Hz, 2H, H-Ar), 7.25 – 7.15 (m, 9H, H-Ar), 7.02 (dd, *J* = 6.5, 2.9 Hz, 2H, H-Ar), 5.36 (s, 1H, OH), 5.33 (d, *J* = 14.8 Hz, 1H, H-12b), 4.73 (d, *J* = 14.1 Hz, 1H, H-10b), 4.29 (d, *J* = 14.1 Hz, 1H, H-10a), 3.65 (d, *J* = 14.8 Hz, 1H, H-12a), 3.21 (d, *J* = 14.1 Hz, 1H, H-14b), 3.04 (d, *J* = 14.1 Hz, 1H, H-14a), 2.08 (dd, *J* = 10.7, 6.0 Hz, 2H, H-9), 1.32 (dt, *J* = 10.7, 5.8 Hz, 1H, H-8b), 0.78 (m, 1H, H-8a), 0.69 (s, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C-3), 156.0 (C-2), 137.7 (C-13), 137.2 (C-11), 135.0 (C-15), 130.5 (C-Ar),

130.1 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 127.7 (C-Ar), 127.8 (C-Ar), 127.1 (C-Ar), 93.1 (C-6), 81.3 (C-7), 73.3 (C-5), 48.0 (C-12), 45.8 (C-10), 40.1 (C-14), 36.3 (C-8), 32.3 (C-9), 26.8 (C-16); *m/z* (ES HRMS) $C_{29}H_{30}N_2O_4Na$ requires 493.2103, found $[MNa]^+$ 493.2108.

Synthesis of (4a*R*,5*S*,7a*R*)-1,4,7a-tribenzyl-4a,5-dihydroxyhexahydro-1H-cyclopenta[b] pyrazine-2,3-dione **345**

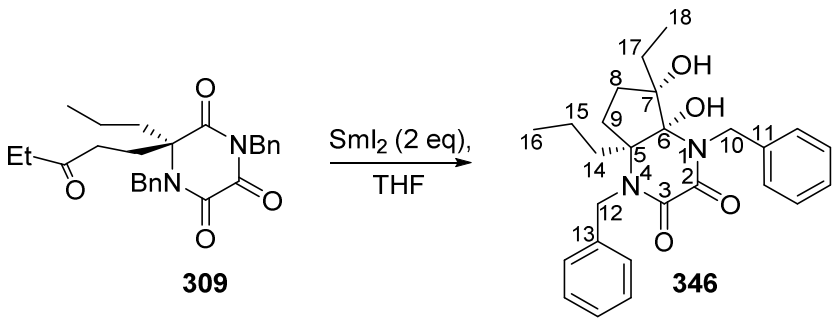


305 **345**

General procedure E using triketopiperazine **305** (22.2 mg) was followed to synthesise **345** (21.9 mg) in 2 minutes as a white solid in 98% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19). m.p. 118 – 119 °C; IR ν_{max} /cm^{-1} 3329, 3031, 2922, 1664, 1604, 1495, 1451, 1421, 1354, 1254, 1145, 1072, 984, 906, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 13H, H-Ar), 7.13 (dd, *J* = 7.6, 1.7 Hz, 2H, H-Ar), 5.45 (d, *J* = 15.1 Hz, 1H, H-12b), 5.03 (d, *J* = 14.7 Hz, 1H, H-10b), 4.60 (s, 1H, OH), 4.27 (d, *J* = 14.7 Hz, 1H, H-10a), 4.03 (m, 1H, H-7), 3.74 (d, *J* = 15.1 Hz, 1H, H-12a), 3.24 (d, *J* = 14.1 Hz, 1H, H-14b), 3.11 (d, *J* = 14.1 Hz, 1H, H-14a), 2.17 (m, 2H, H-9), 1.32 (m, 1H, H-8b), 1.13 (m, 1H, H-8a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (C-3), 154.9 (C-2), 138.3 (C-13), 137.8 (C-11), 134.9 (C-15), 130.3 (C-Ar), 129.3 (C-Ar), 128.7 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar),

90.4 (C-6), 79.6 (C-7), 72.6 (C-5), 47.8 (C-12), 43.8 (C-10), 38.8 (C-14), 33.1 (C-8), 26.9 (C-9); *m/z* (ES HRMS) $C_{28}H_{28}N_2O_4Na$ requires 479.1947, found $[MNa]^+$ 479.1942.

Synthesis of (4a*R*,5*S*,7a*S*)-1,4-dibenzyl-5-ethyl-4a,5-dihydroxy-7a-propylhexahydro-1H-cyclopenta[b]pyrazine-2,3-dione **346**

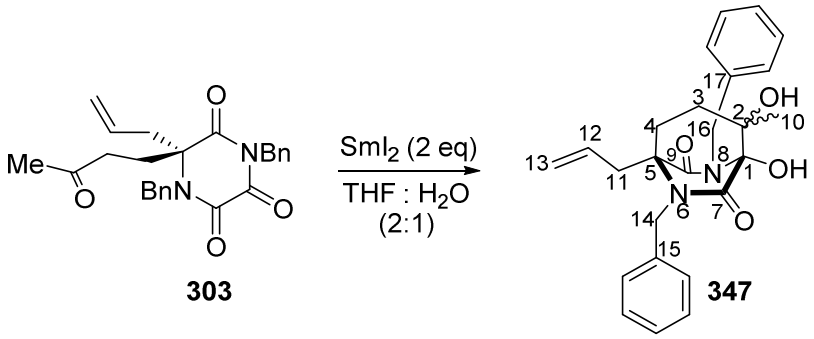


309 **346**

General procedure E using triketopiperazine **309** (21.7 mg) was followed to synthesise **346** (18.4 mg) in 4 minutes as a white solid in 84% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to methanol/ethyl acetate (1:19). m.p. 201 – 203 °C; IR ν_{max} /cm^{-1} 3242, 3285, 2964, 2874, 1680, 1644, 1605, 1495, 1452, 1403, 1359, 1262, 1140, 1075, 952, 875, 695; ^{1}H NMR (400 MHz, $CDCl_3$/MeOD) δ 7.47 (d, *J* = 6.9 Hz, 2H, H-Ar), 7.29 (m, 2H, H-Ar), 7.27 – 7.14 (m, 6H, H-Ar), 5.01 (d, *J* = 14.9 Hz, 1H, H-12b), 4.81 (d, *J* = 13.9 Hz, 1H, H-10b), 4.19 (d, *J* = 13.9 Hz, 1H, H-10a), 4.15 (d, *J* = 14.9 Hz, 1H, H-12a), 1.97 – 1.81 (m, 3H, H-9, H-14b), 1.46 (td, *J* = 14.1, 3.9 Hz, 1H, H-14a), 1.40 – 1.14 (m, 3H, H-8b, H-17), 1.14 – 1.00 (m, 2H, H-8a, H-15b), 0.84 (ddd, *J* = 19.8, 9.7, 6.1 Hz, 1H, H-15a), 0.74 (t, *J* = 7.2 Hz, 3H, H-18), 0.55 (t, *J* = 7.2 Hz, 3H, H-16); ^{13}C NMR (101 MHz, $CDCl_3$/MeOD) δ 159.3 (C-3), 156.6 (C-2), 137.8 (C.13), 137.3 (C-11), 129.6 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 127.9 (C-Ar), 127.6 (C-Ar), 127.2 (C-Ar), 92.7 (C-6), 84.5 (C-7), 72.5 (C-5), 46.5 (C-12), 46.5 (C-10), 36.0 (C-14), 33.2 (C-8), 32.6 (C-9), 32.1 (C-17), 16.8

(C-15), 13.9 (C-16), 7.6 (C-18); *m/z* (ES HRMS) $C_{26}H_{32}N_2O_4Na$ requires 459.2260, found $[MNa]^+$ 459.2258.

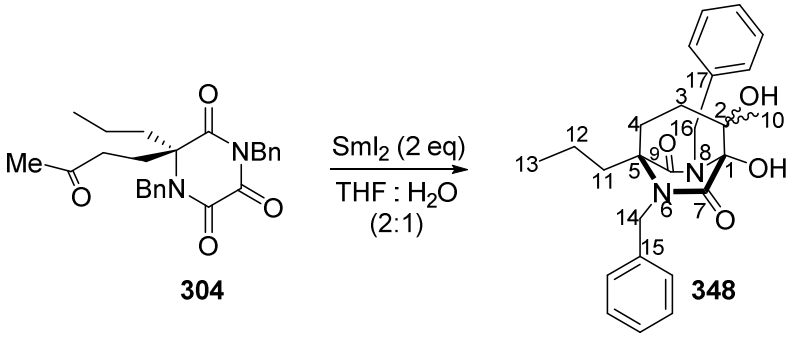
Synthesis of (1*R*,5*R*)-5-allyl-6,8-dibenzyl-1,2-dihydroxy-2-methyl-6,8-diazabicyclo [3.2.2]nonane-7,9-dione **347**



General procedure F using triketopiperazine **303** (20.9 mg) was followed to synthesise **347** (8.9 mg) in 2 minutes as a colourless oil in 42% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to ethyl acetate (100%). IR ν_{max} /cm^{-1} 3393, 2935, 1663, 1496, 1453, 1399, 1353, 1124, 1077, 1028, 704; Major, *minor* (5:3), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 20H, H-Ar), 5.99 – 5.81 (m, 2H, *H-12*, H-12), 5.35 – 5.29 (m, 3H, OH, *OH*, *H-14b*), 5.25 – 5.12 (m, 5H, *H-13*, H-13, H-14b), 5.09 (d, *J* = 14.9, 1H, H-16b), 4.95 (d, *J* = 14.5 Hz, 1H, *H-16b*), 4.69 – 4.56 (m, 3H, H-14a, H-16a, *H-14a*), 4.52 (d, *J* = 14.5 Hz, 1H, *H-16a*), 3.04 – 2.89 (m, 3H, H-11, *H-11b*), 2.81 (dd, *J* = 16.1, 7.2 Hz, 1H, *H-11a*), 2.69 (s, 1H, OH), 2.38 (s, 1H, *OH*), 1.85 – 1.74 (m, 4H, H-3b, *H-4*, H-4b), 1.74 – 1.63 (m, 3H, H-4a, *H-3*), 1.52 (m, 1H, H-3a), 1.27 (s, 3H, *H-10*), 1.13 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C-7, *C-7*), 167.8 (C-9, *C-9*), 138.9 (C-17), 138.4 (*C-17*), 137.0 (C-15, *C-15*), 134.1 (*C-12*), 133.9 (C-12), 128.9 (C-Ar), 128.7 (*C-Ar*), 128.5

(*C-Ar*), 128.4 (C-Ar), 128.3 (C-Ar), 128.1 (*C-Ar*), 128.1 (*C-Ar*), 127.9 (*C-Ar*), 127.6 (C-Ar), 127.6 (C-Ar), 127.2 (*C-Ar*), 126.9 (C-Ar), 118.8 (C-13), 118.5 (*C-13*), 85.6 (*C-1*), 85.5 (C-1), 73.5 (C-2), 73.2 (*C-2*), 66.5 (C-5), 66.1 (*C-5*), 46.3 (C-16), 46.2 (*C-14*), 46.1 (C-14), 45.3 (*C-16*), 38.9 (*C-11*), 38.7 (C-11), 35.4 (C-4, *C-4*), 32.8 (C-3), 31.2 (*C-3*), 24.3 (*C-10*), 22.8 (C-10); *m/z* (ES HRMS) $C_{25}H_{29}N_2O_4$ requires 421.2127, found $[MH]^+$ 421.2122.

Synthesis of (1*R*,5*S*)-6,8-dibenzyl-1,2-dihydroxy-2-methyl-5-propyl-6,8-diazabicyclo [3.2.2]nonane-7,9-dione **348**

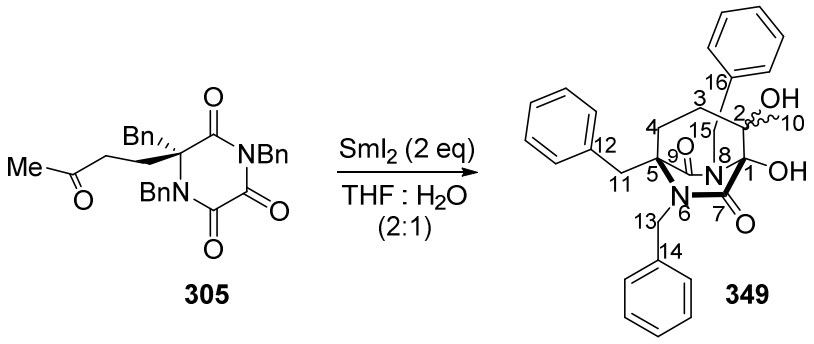


304 **348**

General procedure F using triketopiperazine **304** (21.1 mg) was followed to synthesise **348** (14.0 mg) in 2 minutes as a white solid in 66% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to ethyl acetate (100%). m.p. 130 – 131 °C; IR ν_{max} /cm^{-1} 3391, 3345, 2930, 1648, 1495, 1455, 1416, 1340, 1271, 1126, 1080, 1014, 700; Major, *minor* (4:1), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 4H, H-Ar), 7.39 – 7.21 (m, 16H, H-Ar), 5.35 (d, *J* = 14.7 Hz, 1H, *H-14b*), 5.32 (s, 1H, *OH*), 5.23 (s, 1H, OH), 5.20 (d, *J* = 15.1 Hz, 1H, H-14b), 5.09 (d, *J* = 15.1 Hz, 1H, H-16b), 4.97 (d, *J* = 14.6 Hz, 1H, *H-16b*), 4.59 (d, *J* = 15.1 Hz, 1H, H-16a), 4.47 (d, *J* = 14.6 Hz, 1H, *H-16a*), 4.33 (d, *J* = 15.1 Hz, 1H, H-14a), 4.31 (d, *J* = 14.7 Hz, 1H, *H-14a*), 2.64 (s, 1H, OH), 2.43 (s, 1H, *OH*), 2.29 –

2.17 (m, 2H, H-11b, *H-11b*), 2.04 (m, 1H, H-11a), 1.90 (m, 1H, *H-11a*), 1.77 – 1.65 (m, 10H, H-12, *H-12*, H-3b, *H-3b*, *H-4*, H-4), 1.55 – 1.44 (m, 2H, H-3a, *H-3a*), 1.25 (s, 3H, *H-10*), 1.02 (s, 3H, H-10), 0.99 (t, *J* = 7.4 Hz, 6H, H-13, *H-13*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (*C-7*), 170.7 (C-7), 168.8 (*C-9*), 167.9 (C-9), 139.0 (C-17), 138.5 (*C-17*), 136.9 (*C-15*), 136.8 (C-15), 129.0 (C-Ar), 128.8 (C-Ar), 128.7 (*C-Ar*), 128.6 (*C-Ar*), 128.4 (*C-Ar*), 128.3 (C-Ar), 128.2 (C-Ar), 128.0 (*C-Ar*), 127.4 (C-Ar), 127.3 (*C-Ar*), 127.0 (*C-Ar*), 126.8 (C-Ar), 85.2 (C-1, *C-1*), 73.7 (C-2), 73.2 (*C-2*), 67.8 (C-5), 67.3 (*C-5*), 46.7 (*C-14*), 46.7 (C-14), 46.1 (C-16), 45.1 (*C-16*), 37.3 (C-11), 35.6 (C-4), 35.5 (*C-11*), 32.9 (C-3), 31.4 (*C-4*), 31.0 (*C-3*), 24.0 (*C-10*), 22.8 (C-10), 17.9 (C-12, *C-12*), 14.4 (C-13, *C-13*); *m/z* (ES HRMS) $C_{25}H_{30}N_2O_4Na$ requires 445.2103, found $[MNa]^+$ 445.2096.

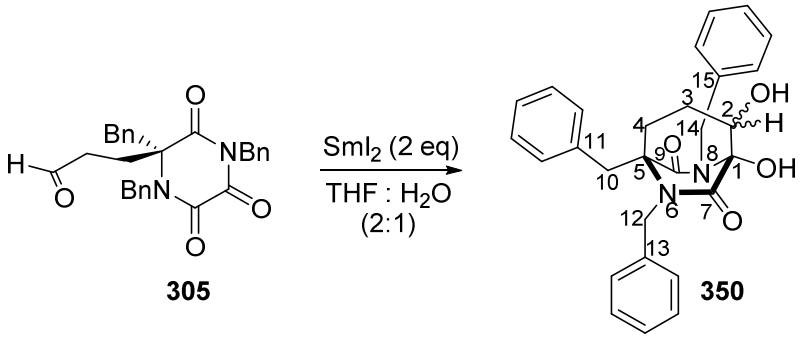
Synthesis of (1*R*,5*R*)-5,6,8-tribenzyl-1,2-dihydroxy-2-methyl-6,8-diazabicyclo[3.2.2]nonane-7,9-dione **349**



General procedure F using triketopiperazine **305** (24.1 mg) was followed to synthesise **349** (8.5 mg) in 2 minutes as a colourless oil in 35% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to ethyl acetate (100%). IR ν_{max} /cm^{-1} 3379, 2934, 1664, 1606, 1496, 1454, 1401, 1352, 1123, 1077, 1028, 699; Major, *minor*

(2.5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.24 (m, 20H, H-Ar), 7.23 – 7.09 (m, 6H, H-Ar), 7.00 (m, 2H, H-Ar), 6.89 (d, *J* = 6.8 Hz, 2H, H-Ar), 5.53 (s, 1H, *OH*), 5.42 (s, 1H, OH), 5.39 (d, *J* = 15.4 Hz, 1H, *H-13b*) 5.19 (d, *J* = 15.1 Hz, 1H, H-13b), 5.14 (d, *J* = 14.7 Hz, 1H, H-15b), 4.96 (d, *J* = 14.1 Hz, 1H, *H-15b*), 4.67 (d, *J* = 14.7 Hz, 1H, H-15a), 4.58 (d, *J* = 14.1 Hz, 1H, *H-15a*), 4.02 (d, *J* = 17.4 Hz, 1H, H-11b), 3.89 (d, *J* = 17.5 Hz, 1H, *H-11b*), 3.87 (d, *J* = 15.1 Hz, 1H, H-13a), 3.82 (d, *J* = 15.4 Hz, 1H, *H-13a*), 3.39 (d, *J* = 17.4 Hz, 1H, H-11a), 3.27 (d, *J* = 17.5 Hz, 1H, *H-11a*), 2.75 (s, 1H, OH), 2.50 (s, 1H, *OH*), 1.89 – 1.70 (m, 5H, H-4, *H-4*, H-3b), 1.64 (m, 2H, *H-3*), 1.50 (m, 1H, H-3a), 1.33 (s, 3H, *H-10*), 1.13 (s, 3H, H-10); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (*C-7*), 170.1 (C-7), 168.5 (*C-9*), 167.7 (C-9), 138.9 (C-16), 138.2 (*C-16*), 137.0 (C-14), 137.0 (*C-14*), 136.5 (*C-12*), 136.3 (C-12), 129.3 (C-Ar), 128.8 (C-Ar), 128.7 (*C-Ar*), 128.7 (C-Ar, *C-Ar*), 128.6 (*C-Ar*), 128.4 (*C-Ar*, C-Ar), 128.3 (C-Ar), 128.1 (*C-Ar*), 128.0 (C-Ar), 128.0 (C-Ar), 127.8 (*C-Ar*), 127.3 (*C-Ar*), 127.0 (C-Ar), 126.4 (C-Ar), 126.3 (*C-Ar*), 85.6 (*C-1*), 85.4 (C-1), 73.9 (C-2), 73.6 (*C-2*), 66.7 (C-5), 66.3 (*C-5*), 46.8 (*C-13*, C-13), 46.2 (C-15), 45.2 (*C-15*), 39.8 (C-11), 39.6 (*C-11*), 35.4 (*C-4*), 35.4 (C-4), 33.5 (C-3), 32.0 (*C-3*), 24.5 (*C-10*), 22.9 (C-10); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{29}H_{30}N_2O_4Na$ requires 493.2103, found $[MNa]^+$ 493.2100.

Synthesis of (1*R*,5*R*)-5,6,8-tribenzyl-1,2-dihydroxy-6,8-diazabicyclo[3.2.2]nonane-7,9-dione **350**

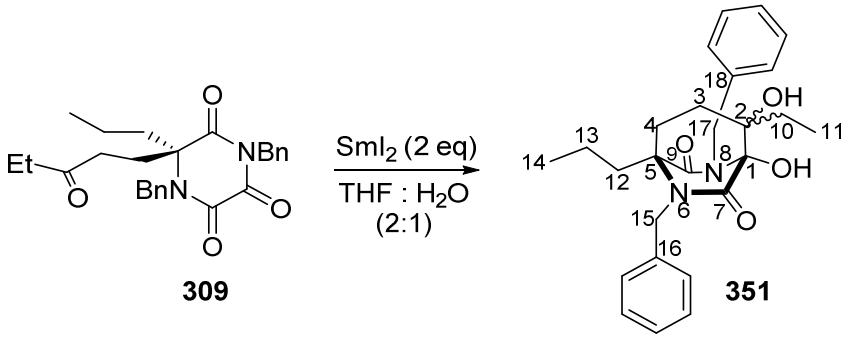


305 **350**

General procedure F using triketopiperazine **305** (22.2 mg) was followed to synthesise **350** (7.8 mg) in 2 minutes as a colourless oil in 35% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to ethyl acetate (100%). IR ν_{max} /cm^{-1} 3386, 2927, 1665, 1605, 1497, 1455, 1397, 1357, 1135, 1077, 1031, 732, 700; Major, *minor* (3:1),^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.5 Hz, 2H, H-Ar), 7.43 – 7.18 (m, 24H, H-Ar), 7.08 (d, *J* = 7.1 Hz, 2H, H-Ar), 7.02 (m, 2H, H-Ar), 5.48 – 5.41 (m, 2H, *OH*, *H-12b*), 5.37 – 5.27 (m, 2H, OH, H-12b), 5.16 (d, *J* = 14.6 Hz, 1H, H-14b), 4.82 (d, *J* = 14.1 Hz, 1H, *H-14b*), 4.76 (d, *J* = 14.1 Hz, 1H, *H-14a*), 4.62 (d, *J* = 14.6 Hz, 1H, H-14a), 3.98 (d, *J* = 17.4 Hz, 1H, H-10b), 3.89 – 3.75 (m, 5H, *H-2*, H-2, *H-12a*, H-12a, *H-10b*), 3.35 – 3.22 (m, 2H, *H-10a*, H-10a), 2.98 (d, *J* = 1.2 Hz, 1H, OH), 2.65 (d, *J* = 1.3 Hz, 1H, *OH*), 1.97 (m, 1H, H-4b), 1.71 – 1.54 (m, 4H, H-4a, *H-4*, H-3b), 1.50 – 1.27 (m, 3H, H-3a, *H-3*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C-7, *C-7*), 167.5 (C-9, *C-9*), 138.6 (C-15), 137.8 (*C-15*), 137.4 (C-13), 137.0 (*C-13*), 136.3 (*C-11*, C-11), 129.1 (*C-Ar*), 129.0 (C-Ar), 128.8 (C-Ar, *C-Ar*), 128.7 (*2x C-Ar*), 128.5 (C-Ar, *C-Ar*), 128.4 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar, *C-Ar*), 127.8 (C-Ar), 127.7 (*C-Ar*), 127.2 (C-Ar, *C-Ar*), 126.5 (C-Ar), 126.4 (*C-Ar*), 84.5 (*C-1*), 83.4 (C-1), 71.1 (C-2), 70.5 (*C-2*), 66.9 (C-5), 66.5 (*C-5*), 46.8 (*C-12*), 46.4 (C-12), 46.3 (C-14), 44.5 (*C-14*), 39.5 (*C-10*,

C-10), 33.3 (C-4), 33.2 (*C-4*), 28.8 (C-3), 27.8 (*C-3*); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{28}H_{28}N_2O_4Na$ requires 479.1947, found $[MNa]^+$ 479.1951.

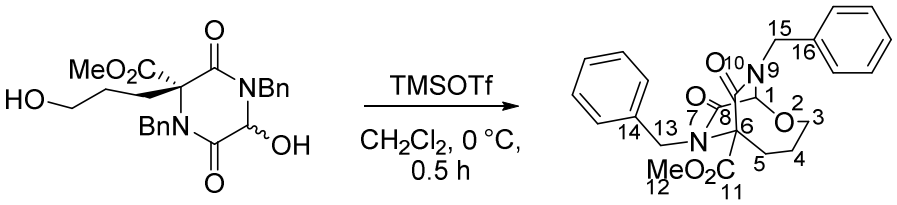
Synthesis of (1*R*,5*S*)-6,8-dibenzyl-2-ethyl-1,2-dihydroxy-5-propyl-6,8-diazabicyclo [3.2.2]nonane-7,9-dione **351**



General procedure F using triketopiperazine **309** (42.6 mg) was followed to synthesise **351** (19.7 mg) in 2 minutes as a colourless oil in 46% yield after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (2:1) to ethyl acetate (100%). IR ν_{max} /cm^{-1} 3397, 3031, 2965, 1662, 1496, 1427, 1400, 1353, 1077, 1028, 733, 701; Major, m*inor* (4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H, H-Ar), 7.41 – 7.36 (m, 3H, H-Ar), 7.35 – 7.20 (m, 15H, H-Ar), 5.32 (d, *J* = 15.3 Hz, 1H, *H-15b*), 5.27 (s, 1H, *OH*), 5.20 (s, 1H, OH), 5.13 (d, *J* = 15.0 Hz, 1H, H-15b), 5.10 (d, *J* = 15.1 Hz, 1H, H-17b), 4.98 (d, *J* = 14.7 Hz, 1H, *H-17b*), 4.60 (d, *J* = 15.1 Hz, 1H, H-17a), 4.45 (d, *J* = 14.7 Hz, 1H, *H-17a*), 4.40 (d, *J* = 15.0 Hz, 1H, H-15a), 4.34 (d, *J* = 15.3 Hz, 1H, *H-15a*), 2.39 (s, 1H, OH), 2.25 – 2.13 (m, 3H, *OH*, H-12b, *H-12b*), 2.05 (m, 1H, H-12a), 1.91 (m, 1H, *H-12a*), 1.84 (dt, *J* = 7.0, 3.9 Hz, 1H, H-3b), 1.75 – 1.67 (m, 2H, *H-3b*, H-4b), 1.65 – 1.53 (m, 5H, *H-3a*, *H-4*, H-3a, H-13b), 1.51 – 1.38

(m, 4H, *H-13*, H-10b, H-4a), 1.32 – 1.20 (m, 3H, *H-10*, H-13a), 1.12 (m, 1H, H-10a), 0.98 (t, *J* = 7.4 Hz, 6H, H-14, *H-14*), 0.92 (t, *J* = 7.5 Hz, 3H, *H-11*), 0.79 (t, *J* = 7.4 Hz, 3H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (*C-7*), 170.8 (C-7), 169.0 (*C-9*), 168.0 (C-9), 139.0 (C-18), 138.5 (*C-18*), 136.9 (*C-16*), 136.8 (C-16), 128.8 (C-Ar), 128.7 (C-Ar, *C-Ar*), 128.6 (*C-Ar*), 128.4 (*C-Ar*), 128.3 (C-Ar), 128.1 (C-Ar), 128.9 (*C-Ar*), 127.4 (C-Ar), 127.2 (*C-Ar*), 127.0 (*C-Ar*), 126.8 (C-Ar), 85.8 (C-1), 85.7 (*C-1*), 75.7 (C-2), 74.7 (*C-2*), 67.7 (C-5), 67.1 (*C-5*), 46.8 (*C-15*, C-15), 46.1 (C-17), 45.5 (*C-17*), 37.4 (*C-12*), 37.2 (C-12), 32.5 (C-4), 31.3 (*C-4*), 31.0 (C-3), 30.3 (*C-3*), 26.4 (*C-10*), 26.2 (C-10), 17.9 (C-13), 17.9 (*C-13*), 14.4 (C-14, *C-14*), 7.0 (C-11), 6.8 (*C-11*); *m/z* (ES HRMS) $C_{26}H_{32}N_2O_4Na$ requires 459.2260, found $[MNa]^+$ 459.2262.

Synthesis of methyl (1*S*,6*S*)-7,9-dibenzyl-8,10-dioxo-2-oxa-7,9-diazabicyclo[4.2.2]decane-6-carboxylate **367**

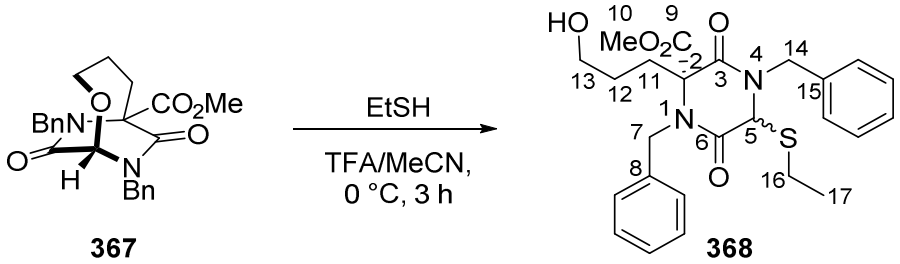


323 **367**

To a solution of **323** (12.0 mg, 0.025 mmol, 1 eq.) in dry CH_2Cl_2 (1.5 mL), TMSOTf (5 µL, 0.028 mmol, 1.1 eq.) was added in one portion at 0 °C. The mixture was left to react at that temperature for 30 min and was quenched with saturated $NaHCO_3$. The crude was extracted with CH_2Cl_2 (3 x 5 mL) and washed with brine (1 x 5 mL). Compound **367** was obtained as a white solid in 87% yield (8.9 mg) after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (2:1) and 96:4 er as determined by HPLC analysis

[Phenomenex Lux Cellulose-3, acetonitrile:water, 35:65, 1 mL/min, λ 210 nm, t(minor) = 28.9 min, t(major) = 35.5 min]. IR ν_{max} /cm^{-1} 2966, 2919, 2872, 2850, 1757, 1668, 1498, 1422, 1360, 1341, 1256, 1233, 1214, 1161, 1099, 1073, 1065, 1040, 945, 890, 741, 716, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.24 (m, 10H, H-Ar), 5.15 (s, 1H, H-1), 5.06 (d, *J* = 14.6 Hz, 1H, H-15b), 4.51 (s, 2H, H-13), 4.18 (d, *J* = 14.6 Hz, 1H, H-15a), 3.81 (dt, *J* = 17.8, 8.9 Hz, 1H, H-3b), 3.49 (s, 3H, H-12), 3.33 (m, 1H, H-3a), 2.42 (m, 1H, H-5b), 2.21 (ddd, *J* = 11.4, 9.1, 4.5 Hz, 1H, H-5a), 1.75 (m, 1H, H-4b), 1.46 (m, 1H, H-4a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (C-10), 167.2 (C-11), 165.6 (C-8), 135.6 (C-14), 134.4 (C-16), 128.9 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 127.9 (C-Ar), 81.5 (C-1), 71.1 (C-6), 63.8 (C-3), 52.8 (C-12), 47.8 (C-15), 47.5 (C-13), 35.6 (C-5), 25.3 (C-4); *m/z* (ESI HRMS) $C_{23}H_{25}N_2O_5$ requires 409.1764, found $[MH]^+$ 409.1763; $[\alpha]_D^{20} = -10.4$ (*c* 0.8, $CHCl_3$).

Synthesis of methyl (2*S*)-1,4-dibenzyl-5-(ethylthio)-2-(3-hydroxypropyl)-3,6-dioxopiperazine-2-carboxylate **368**

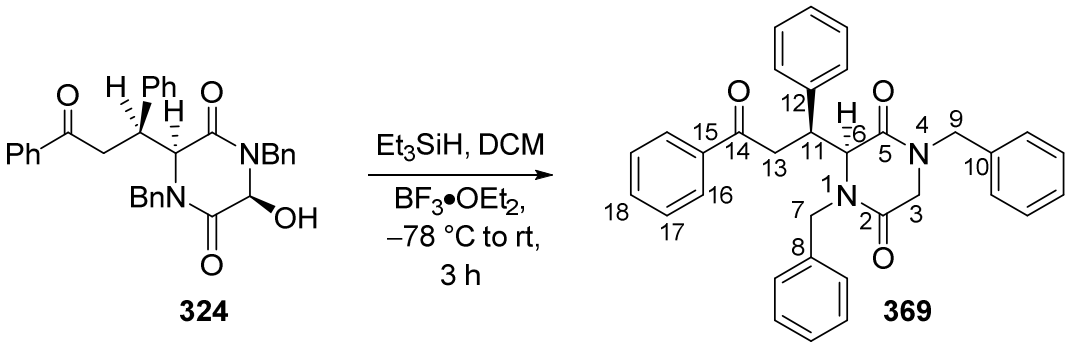


367 **368**

To a solution of **367** (20.4 mg, 0.05 mmol, 1 eq.) in MeCN/TFA (1:1, 2 mL), ethanethiol (30 µL, 0.4 mmol, 8 eq) was added in one portion at room temperature. The mixture was left to react at that temperature for 3 h and was then quenched with Na_2CO_3 (3 mL). The crude was extracted with CH_2Cl_2 (3 x 10 mL) and washed with brine (1 x 15 mL). Compound **368** was

obtained as a colourless oil in 48% yield (11.3 mg) as an approximately 1:1 mixture of diastereoisomers after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1). IR ν_{max} /cm^{-1} 3502, 2926, 1755, 1665, 1497, 1434, 1417, 1355, 1261, 1230, 1168, 1099, 1064, 986, 728, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 20H, H-Ar), 5.49 (d, *J* = 14.8 Hz, 1H, H-7b), 5.46 (d, *J* = 14.6 Hz, 1H, *H-7b*), 4.84 (d, *J* = 15.4 Hz, 1H, H-14b), 4.80 (d, *J* = 15.6 Hz, 1H, *H-14b*), 4.65 (s, 1H, H-5), 4.61 (s, 1H, *H-5*), 4.39 (d, *J* = 15.4 Hz, 1H, H-14a), 4.17 (d, *J* = 14.6 Hz, 1H, *H-7a*), 4.12 (d, *J* = 14.8 Hz, 1H, H-7a), 4.09 (d, *J* = 15.6 Hz, 1H, *H-14a*), 3.44 (s, 3H, H-10), 3.42 – 3.33 (m, 2H, H-13b, *H-13b*), 3.37 (s, 3H, *H-10*), 3.34 – 3.23 (m, 2H, H-13a, *H-13a*), 2.92 (m, 1H, H-16b), 2.84 – 2.69 (m, 3H, H-16a, *H-16*), 2.50 (m, 1H, H-11b), 2.39 (m, 1H, *H-11b*), 2.29 (m, 1H, H-11a), 2.07 (m, 1H, *H-11a*), 1.37 (m, 2H, *H-12*), 1.26 (q, *J* = 7.4 Hz, 6H, H-17, *H-17*), 1.19 (m, 1H, H-12b), 1.13 (m, 1H, H-12a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (C-9), 168.0 (*C-9*), 166.2 (C-3), 165.8 (*C-3*), 163.6 (*C-6*), 163.6 (C-6), 136.5 (*C-15*), 136.2 (C-15), 134.8 (C-8), 134.7 (*C-8*), 129.1 (2x C-Ar), 129.0 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 127.7 (C-Ar), 72.5 (*C-2*), 71.1 (C-2), 62.0 (C-13), 61.7 (*C-13*), 61.1 (C-5), 59.8 (*C-5*), 53.1 (C-10), 53.0 (*C-10*), 47.2 (*C-14*), 46.9 (*C-7*, C-14), 46.5 (C-7), 29.8 (C-11), 29.3 (*C-11*), 28.3 (C-16), 27.7 (*C-16*), 27.0 (*C-12*), 26.1 (C-12), 14.5 (C-17, *C-17*); 4 signals in the C-H aromatic region were not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{25}H_{30}N_2O_5SNa$ requires 493.1773, found $[MNa]^+$ 493.1772.

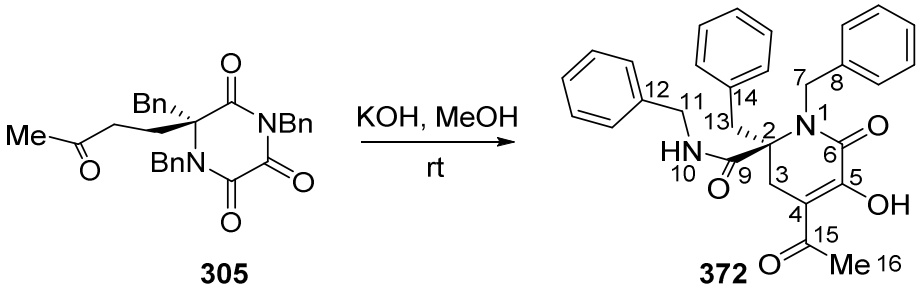
Synthesis of (*S*)-1,4-dibenzyl-3-((*S*)-3-oxo-1,3-diphenylpropyl)piperazine-2,5-dione **369**



To a solution of **324** (54.9 mg, 0.106 mmol, 1 eq.) in dry CH_2Cl_2 (3 mL), triethylsilane (168 µL, 1.06 mmol, 10 eq.) was added in one portion at –78 °C followed by BF_3•Et_2O (65 µL, 0.53 mmol, 5 eq.). The mixture was left to stir at that temperature for 10 min and allowed to warm up to rt over 3h. The reaction was quenched with saturated NH_4Cl and the crude was extracted with CH_2Cl_2 (3 x 5 mL). Compound **369** was obtained as a white solid in 82% yield (43.7 mg) after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (2:1) and 99:1 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 80:20, 1.0 mL/min, λ 210 nm, t(major) = 21.1 min, t(minor) = 33.9 min]. m.p. 54 – 56 °C; IR ν_{max} /cm^{-1} 3062, 3031, 2928, 1663, 1598, 1495, 1452, 1356, 1266, 1233, 1208, 1171, 1073, 1028, 987, 750, 729, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H, H-16), 7.47 (m, 1H, H-18), 7.35 (dd, *J* = 10.5, 4.7 Hz, 2H, H-17), 7.32 – 7.14 (m, 11H, H-Ar), 7.09 (m, 2H, H-Ar), 6.82 (m, 2H, H-Ar), 5.05 (d, *J* = 15.2 Hz, 1H, H-7b), 4.63 (d, *J* = 14.7 Hz, 1H, H-9b), 4.06 (d, *J* = 14.7 Hz, 1H, H-9a), 4.00 – 3.86 (m, 3H, H-3b, H-6, H-11), 3.76 (dd, *J* = 18.0, 7.5 Hz, 1H, H-13b), 3.69 (d, *J* = 17.0 Hz, 1H, H-3a), 3.24 (dd, *J* = 18.0, 5.2 Hz, 1H, H-13a), 2.64 (d, *J* = 15.2 Hz, 1H, H-7a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3 (C-14), 166.4 (C-5), 165.9 (C-2), 140.6 (C-12), 136.7 (C-15), 135.7 (C-8), 135.3 (C-10), 133.3 (C-18), 129.2 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar),

128.0 (C-Ar), 127.9 (C-Ar), 127.7 (C-Ar), 65.0 (C-6), 49.4 (C-9), 49.1 (C-3), 48.6 (C-7), 43.7 (C-11), 41.6 (C-13); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ESI HRMS) $C_{33}H_{31}N_2O_3$ requires 503.2335, found $[MH]^+$ 503.2334; $[\alpha]_D^{20} = -43.2$ (*c* 1.6, $CHCl_3$).

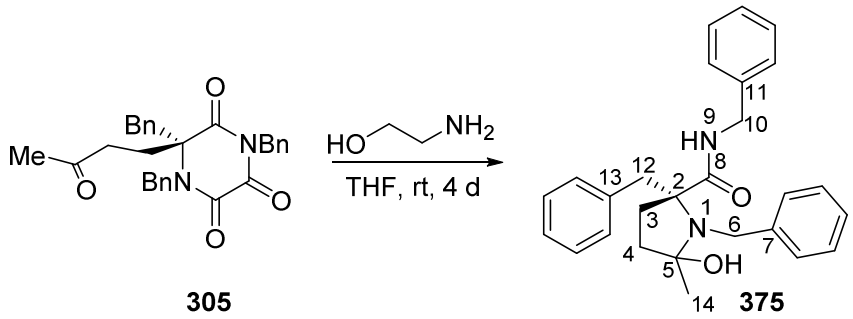
Synthesis of 4-acetyl-*N*,1,2-tribenzyl-5-hydroxy-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxamide **372**



To a solution of **305** (100 mg, 0.31 mmol, 1 eq.) in MeOH (8 mL), potassium hydroxide (30 mg, 0.60 mmol, 2 eq.) was added in one portion at room temperature. The mixture was left to stir at that temperature for 15 min, quenched with saturated NH_4Cl and the crude was extracted with CH_2Cl_2 (3 x 15 mL) and washed with brine (1 x 15 mL). Compound **372** was obtained as a white solid in 86% yield (86.4 mg). m.p. 138 – 140 °C; IR ν_{max} /cm^{-1} 3385, 3319, 3028, 2928, 1664, 1634, 1606, 1534, 1496, 1345, 1256, 1216, 1101, 1078, 1030, 780, 728, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H, OH), 7.36 – 7.17 (m, 11H, H-Ar), 7.03 (m, 2H, H-Ar), 6.96 (m, 2H, H-Ar), 6.04 (s, 1H, NH), 5.03 (d, *J* = 15.9 Hz, 1H, H-7b), 4.72 (d, *J* = 15.9 Hz, 1H, H-7a), 4.29 (dd, *J* = 14.5, 6.3 Hz, 1H, H-11b), 3.91 (dd, *J* = 14.5, 5.0 Hz, 1H, H-11a), 3.46 (d, *J* = 13.8 Hz, 1H, H-13b), 3.13 (d, *J* = 13.8 Hz, 1H, H-13a), 3.00 (d, *J* = 16.8 Hz, 1H, H-3b), 2.83 (d, *J* = 16.8 Hz, 1H, H-3a), 2.24 (s, 3H, H-16); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 199.8 (C-15), 170.5 (C-9), 164.0 (C-6), 150.7 (C-5), 137.9 (C-8), 137.1 (C-12), 135.0 (C-14), 130.3 (C-Ar), 128.9 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 127.9 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 127.2 (C-Ar), 109.5 (C-4), 68.4 (C-2), 49.2 (C-7), 44.0 (C-11), 41.6 (C-13), 31.0 (C-3), 29.4 (C-16); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{29}H_{28}N_2O_4Na$ requires 491.1947, found $[MNa]^+$ 491.1949.

Synthesis of *N*,1,2-tribenzyl-5-hydroxy-5-methylpyrrolidine-2-carboxamide **375**



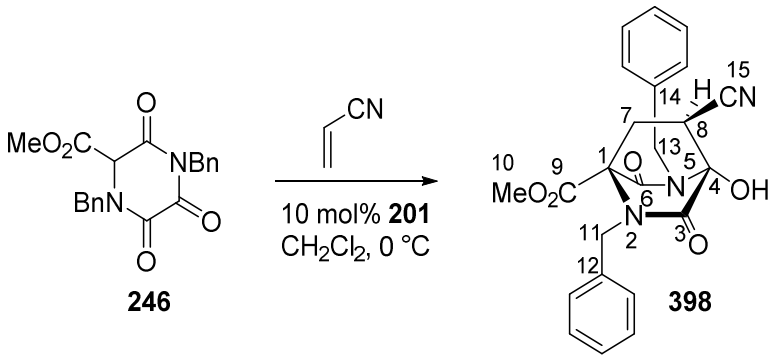
305 **375**

To a solution of **305** (23.4 mg, 0.05 mmol, 1 eq.) in dry THF (3 mL), ethanolamine (36 µL, 0.6 mmol, 10 eq.) was added in one portion at room temperature. The mixture was left to react at that temperature for 2 days until the starting material was consumed. Compound **375** was obtained as a yellowish solid in 72% yield (15.0 mg) after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (1:2). m.p. 49 – 51 °C; IR ν_{max} /cm^{-1} 3385, 3062, 3029, 2924, 1697, 1604, 1495, 1454, 1405, 1290, 1178, 1072, 1029, 732, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H, H-Ar), 7.30 (m, 1H, H-Ar), 7.29 – 7.26 (m, 8H, H-Ar), 7.23 (m, 2H, H-Ar), 4.52 (d, *J* = 15.2 Hz, 1H, H-10b), 4.28 (d, *J* = 15.2 Hz, 1H, H-10a), 3.92 (d, *J* = 15.5 Hz, 1H, H-6b), 3.54 (d, *J* = 15.5 Hz, 1H, H-6a), 3.36 (d, *J* = 15.3 Hz, 1H, H-12b), 3.13 (d, *J* = 15.3 Hz, 1H, H-12a), 1.80 (m, 1H, H-4b), 1.61 (m, 1H, H-3b), 1.42 –

1.29 (m, 2H, H-3a, H-4a), 1.07 (s, 3H, H-14); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1 (C-8), 140.3 (C-7), 138.4 (C-11), 136.8 (C-13), 130.4 (C-Ar), 128.6 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 127.9 (2x C-Ar), 127.5 (C-Ar), 126.6 (C-Ar), 126.3 (C-Ar), 84.4 (C-5), 74.0 (C-2), 46.4 (C-6), 43.7 (C-10), 34.5 (C-4), 32.9 (C-12), 27.9 (C-3), 18.0 (C-14); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS, minus H_2O) $C_{27}H_{29}N_2O$ requires 397.2280, found $[MH]^+$ 397.2278.

5.4. Experimental for Chapter 4

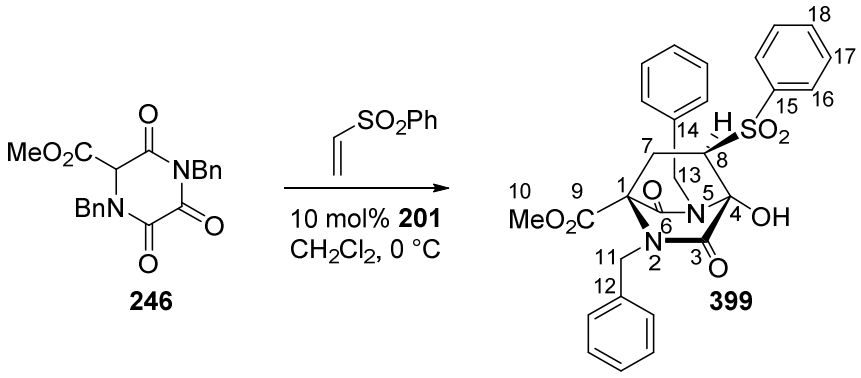
Synthesis of (1*S*,4*S*,8*R*)-methyl 2,5-dibenzyl-8-cyano-4-hydroxy-3,6-dioxo-2,5-diazabicyclo[2.2.2] octane -1-carboxylate **398**



General procedure B using triketopiperazine **246** (28.5 mg) was followed to synthesise this product (32.7 mg) as a white solid in 99% yield from a reaction catalysed by **201** (10 mol%) at 0 °C for 15 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (2:1) gave **398** with 95:5 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, acetonitrile:water, 80:20, 1 mL/min, λ 220 nm, t(minor) = 12.2 min, t(major) = 14.5 min]. m.p. 95 – 98 °C; IR ν_{max} /cm^{-1} 3347, 3034, 2955, 1753, 1687, 1496, 1454, 1390, 1355, 1264, 1180, 1138, 1076, 727, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 8H,

H-Ar), 7.25 (m, 2H, H-Ar), 5.55 (d, *J* = 14.6 Hz, 1H, H-11b), 5.40 (s, 1H, OH), 4.80 (d, *J* = 14.4 Hz, 1H, H-13b), 4.55 (d, *J* = 14.6 Hz, 1H, H-11a), 4.50 (d, *J* = 14.4 Hz, 1H, H-13a), 3.82 (s, 3H, H-10), 2.89 (dd, *J* = 11.0, 4.3 Hz, 1H, H-8), 2.35 (dd, *J* = 14.4, 11.0 Hz, 1H, H-7b), 1.90 (dd, *J* = 14.4, 4.3 Hz, 1H, H-7a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C-3), 164.2 (C-6), 163.5 (C-9), 136.4 (C-14), 134.3 (C-12), 129.1 (C-Ar), 129.0 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.2 (C-Ar), 116.6 (C-15), 82.9 (C-4), 67.5 (C-1), 53.5 (C-10), 47.1 (C-11), 43.6 (C-13), 34.2 (C-8), 32.2 (C-7); *m/z* (ES HRMS) $C_{23}H_{21}N_3O_5Na$ requires 442.1379, found $[MNa]^+$ 442.1377; $[\alpha]_D^{21}$= –60.4 (*c* 1.6, $CHCl_3$).

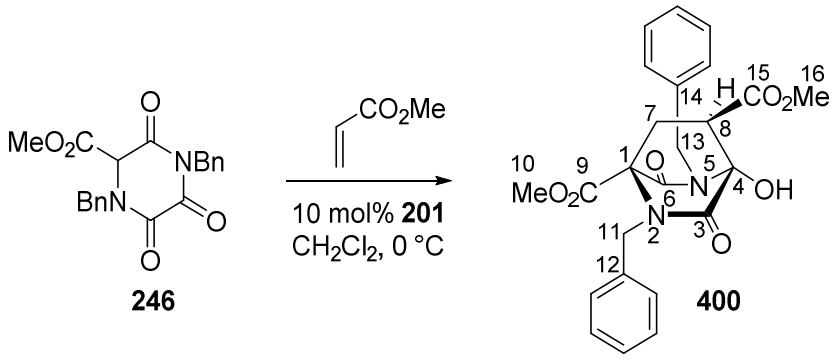
Synthesis of (1*S*,4*S*,8*R*)-methyl 2,5-dibenzyl-4-hydroxy-3,6-dioxo-8-(phenylsulfonyl)-2,5-diazabicyclo [2.2.2]octane-1-carboxylate **399**



General procedure B using triketopiperazine **246** (33.5 mg) was followed to synthesise this product (47.3 mg) as a white solid in 97% yield from a reaction catalysed by **201** (10 mol%) at 0 °C for 20 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (3:2) gave **399** with 98:2 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, acetonitrile:water, 35:65, 1 mL/min, λ 210 nm, t(major) = 24.5 min, t(minor) = 28.7 min]. m.p. 94 – 97 °C; IR ν_{max} /cm^{-1} 3334, 3065, 2954, 1753, 1689, 1496, 1448, 1389,

1355, 1260, 1183, 1147, 1075, 1003, 909, 726, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 3H, H-16, H-18), 7.60 (t, *J* = 7.8 Hz, 2H, H-17), 7.45 (d, *J* = 7.3 Hz, 2H, H-Ar), 7.38 (t, *J* = 7.3 Hz, 2H, H-Ar), 7.31 (m, 2H, H-Ar), 7.23 (m, 2H, H-Ar), 7.17 (m, 2H, H-Ar), 5.52 (d, *J* = 15.0 Hz, 1H, H-11b), 4.75 (d, *J* = 14.3 Hz, 1H, H-13b), 4.61 (d, *J* = 15.0 Hz, 1H, H-11a), 4.28 (d, *J* = 14.3 Hz, 1H, H-13a), 3.69 (s, 3H, H-10), 3.42 (dd, *J* = 11.2, 5.8 Hz, 1H, H-8), 2.67 (dd, *J* = 15.1, 5.8 Hz, 1H, H-7b), 2.45 (dd, *J* = 15.1, 11.2 Hz, 1H, H-7a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C-3), 165.0 (C-6), 163.4 (C-9), 139.4 (C-15), 136.4 (C-14), 134.4 (C-12), 134.0 (C-18), 129.0 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar), 82.1 (C-4), 66.9 (C-1), 63.5 (C-8), 53.3 (C-10), 47.8 (C-11), 43.1 (C-13), 29.3 (C-7); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{28}H_{26}N_2O_7SNa$ requires 557.1358, found $[MNa]^+$ 557.1331; $[\alpha]_D^{21}$= –28.9 (*c* 1.6, $CHCl_3$).

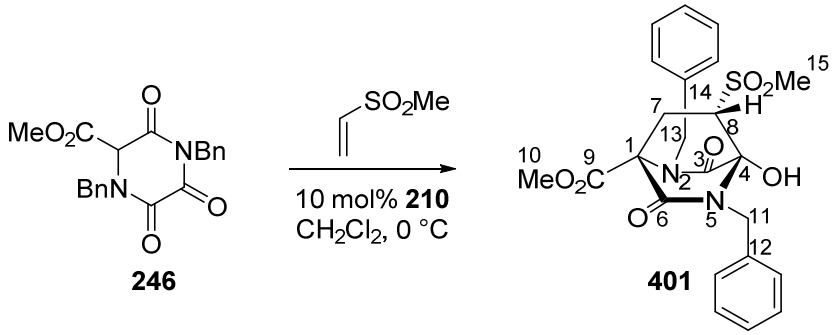
Synthesis of (1*S*,4*S*,8*R*)-dimethyl 2,5-dibenzyl-4-hydroxy-3,6-dioxo-2,5-diazabicyclo [2.2.2]octane-1,8-dicarboxylate **400**



General procedure B using triketopiperazine **246** (27.3 mg) was followed to synthesise this product (33.1 mg) as a white solid in 98% yield from a reaction catalysed by **201** (10 mol%)

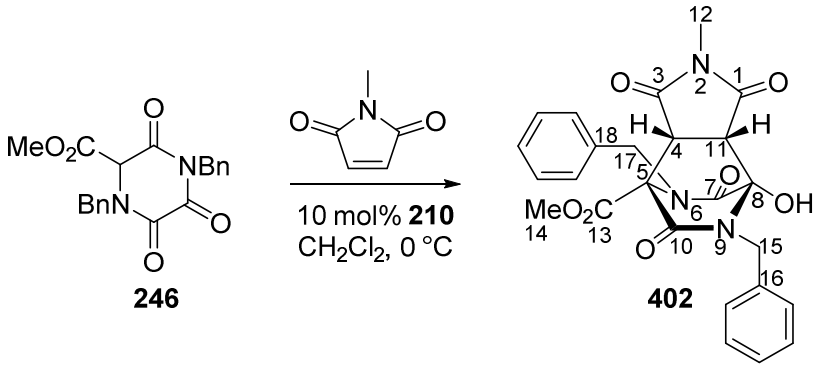
at 0 °C for 18 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = 4:1) to (2:1) gave **400** with 87:13 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 80:20, 1 mL/min, λ 210 nm, t(minor) = 23.8 min, t(major) = 36.9 min]. m.p. 90 – 93 °C; IR ν_{max} /cm^{-1} 3345, 2954, 1744, 1693, 1495, 1436, 1393, 1358, 1266, 1200, 1078, 703; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 10H, H-Ar), 5.43 (d, *J* = 15.0 Hz, 1H, H-11b), 5.09 (s, 1H, OH), 4.71 (d, *J* = 14.6 Hz, 1H, H-13b), 4.59 (m, 2H, H-11a, H-13a), 3.71 (s, 3H, H-16), 3.70 (s, 3H, H-10), 3.01 (dd, *J* = 10.9, 5.2 Hz, 1H, H-8), 2.38 (dd, *J* = 14.2, 10.9 Hz, 1H, H-7b), 2.12 (dd, *J* = 14.2, 5.2 Hz, 1H, H-7a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (C-15), 167.9 (C-3), 165.3 (C-6), 164.2 (C-9), 137.0 (C-14), 135.0 (C-12), 129.0 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 83.4 (C-4), 67.5 (C-1), 53.2 (C-10), 52.6 (C-16), 47.8 (C-8), 47.4 (C-11), 43.2 (C-13), 31.9 (C-7); *m/z* (ES HRMS) $C_{24}H_{24}N_2O_7Na$ requires 475.1481, found $[MNa]^+$ 475.1476; $[\alpha]_D^{21}$= –28.7 (*c* 1.5, $CHCl_3$).

Synthesis of methyl (1*R*,4*R*,8*S*)-2,5-dibenzyl-4-hydroxy-8-(methylsulfonyl)-3,6-dioxo-2,5-diazabicyclo [2.2.2]octane-1-carboxylate **401**



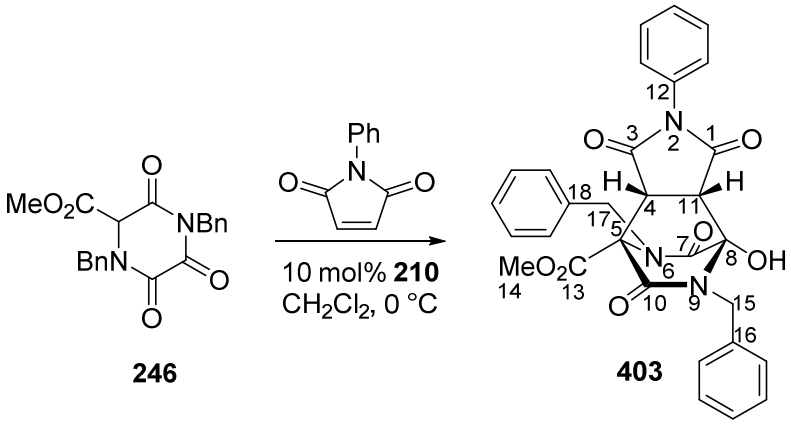
General procedure B using triketopiperazine **246** (32.7 mg) was followed to synthesise this product (28.1 mg) as a colourless oil in 67% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 30 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (3:2) gave **401** with 28:72 er as determined by HPLC analysis [Daicel Chiralcel OD, Heptane:EtOH, 70:30, 2 mL/min, λ 210 nm, t(minor) = 4.6 min, t(minor) = 6.8 min]. IR ν_{max} /cm^{-1} 3335, 3035, 2954, 1754, 1692, 1497, 1455, 1392, 1355, 1263, 1185, 1138, 1077, 1005, 733, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H, H-Ar), 7.30 – 7.16 (m, 7H, H-Ar), 7.08 (m, 1H, H-Ar), 5.58 (s, 1H, OH), 5.42 (d, *J* = 14.9 Hz, 1H, H-11b), 4.83 (d, *J* = 14.4 Hz, 1H, H-13b), 4.48 (d, *J* = 14.9 Hz, 1H, H-11a), 4.37 (d, *J* = 14.3 Hz, 1H, H-13a), 3.60 (s, 3H, H-10), 3.08 (dd, *J* = 11.3, 6.1 Hz, 1H, H-8), 2.93 (s, 3H, H-15), 2.42 (dd, *J* = 15.2, 6.1 Hz, 1H, H-7b), 2.30 (dd, *J* = 15.2, 11.3 Hz, 1H, H-7a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C-3), 165.1 (C-6), 163.3 (C-9), 136.7 (C-14), 134.2 (C-12), 129.1 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.4 (C-Ar), 128.4 (C-Ar), 82.0 (C-4), 66.8 (C-1), 62.7 (C-8), 53.4 (C-10), 47.6 (C-11), 43.3 (C-13), 42.9 (C-15), 28.3 (C-7); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{23}H_{24}N_2O_7SNa$ requires 495.1202, found $[MNa]^+$ 495.1201.

Synthesis of methyl (3a*R*,4*R*,7*S*,7a*S*)-5,8-dibenzyl-7-hydroxy-2-methyl-1,3,6,9-tetraoxooctahydro-4H-7,4-(epiminomethano)pyrrolo[3,4-c]pyridine-4-carboxylate **402**



General procedure B using triketopiperazine **246** (35.9 mg) was followed to synthesise this product (45.0 mg) as a white solid in 96% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 3 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (1:1) gave **402** with 8:92 er as determined by HPLC analysis [Daicel Chiralpak IF, Heptane:EtOH-MeOH, 50:50, 2 mL/min, λ 210 nm, t(minor) = 5.3 min, t(major) = 9.0 min]. m.p. 169 – 171 °C; IR ν_{max} /cm^{-1} 3298, 2979, 1787, 1754, 1688, 1497, 1440, 1386, 1355, 1283, 1205, 1137, 1121, 1063, 1008, 931, 725, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 8H, H-Ar), 7.11 (d, *J* = 3.7 Hz, 2H, H-Ar), 5.11 – 4.95 (m, 2H, H-15b, OH), 4.73 (m, 3H, H-15a, H-17), 4.03 (d, *J* = 9.0 Hz, 1H, H-4), 3.98 (s, 3H, H-14), 3.36 (d, *J* = 9.0 Hz, 1H, H-11), 2.79 (s, 3H, H-12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-3), 170.4 (C-1), 167.4 (C-7), 163.6 (C-10), 163.0 (C-13), 136.5 (C-16), 136.4 (C-18), 128.8 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.0 (C-Ar), 127.5 (C-Ar), 83.0 (C-8), 69.4 (C-5), 53.7 (C-14), 48.8 (C-11), 48.8 (C-15), 45.9 (C-4), 43.6 (C-17), 25.5 (C-12); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{25}H_{24}N_3O_7$ requires 478.1614, found $[MH]^+$ 478.1615; $[\alpha]_D^{21}$= 18.1 (*c* 1.7, $CHCl_3$).

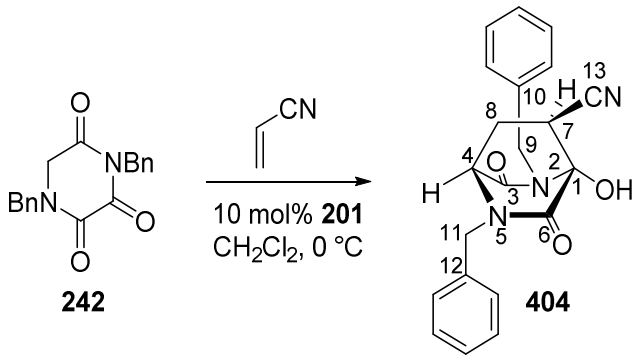
Synthesis of methyl (3a*R*,4*R*,7*S*,7a*S*)-5,8-dibenzyl-7-hydroxy-1,3,6,9-tetraoxo-2-phenyloctahydro-4H-7,4-(epiminomethano)pyrrolo[3,4-c]pyridine-4-carboxylate **403**



General procedure B using triketopiperazine **246** (36.0 mg) was followed to synthesise this product (49.1 mg) as a white solid in 92% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (4:1) to (1:1) gave **403** with 79:21 er as determined by HPLC analysis [Daicel Chiralpak ID2, Heptane:EtOH, 50:50, 2 mL/min, λ 210 nm, t(major) = 4.9 min, t(minor) = 9.4 min]. m.p. 169 – 172 °C; IR ν_{max} /cm^{-1} 3414, 3047, 2958, 1758, 1695, 1496, 1430, 1383, 1297, 1245, 1190, 1075, 1003, 909, 727, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 3H, H-Ar), 7.33 – 7.19 (m, 5H, H-Ar), 7.19 – 7.11 (m, 3H, H-Ar), 7.06 (m, 2H, H-Ar), 6.98 (d, *J* = 3.3 Hz, 2H, H-Ar), 4.90 (d, *J* = 15.5 Hz, 1H, H-15b), 4.71 (m, 2H, H-17), 4.46 (d, *J* = 15.5 Hz, 1H, H-15a), 4.24 (d, *J* = 9.0 Hz, 1H, H-4), 3.84 (s, 3H, H-14), 3.51 (d, *J* = 9.0 Hz, 1H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-3), 170.0 (C-1), 167.7 (C-7), 163.7 (C-10), 163.1 (C-13), 136.5 (C-16), 136.5 (C-18), 130.8 (C-12), 129.3 (C-Ar), 128.7 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 127.8 (C-Ar), 127.0 (C-Ar), 126.4 (C-Ar), 126.1 (C-Ar), 84.0 (C-8), 69.9 (C-5), 53.5 (C-14), 49.6 (C-15), 49.2 (C-11), 46.4 (C-4), 43.4 (C-17); 1 signal in the

C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{30}H_{26}N_3O_7$ requires 540.1771, found $[MH]^+$ 540.1772; $[\alpha]_D^{21}$= –21.6 (*c* 1.5, $CHCl_3$).

Synthesis of (1*S*,4*S*,7*R*)-2,5-dibenzyl-1-hydroxy-3,6-dioxo-2,5-diazabicyclo[2.2.2]octane-7-carbonitrile **404**

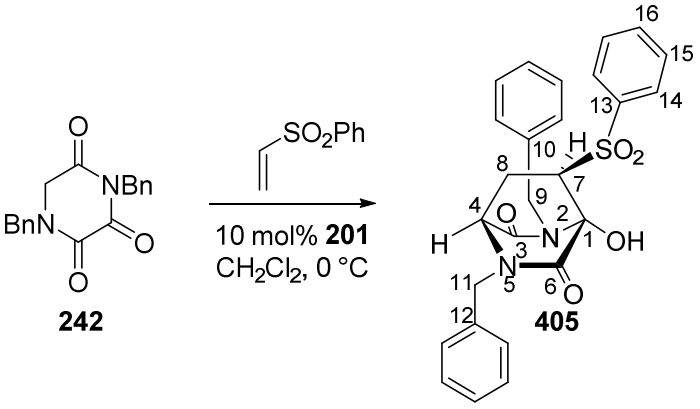


242 **404**

General procedure B using triketopiperazine **242** (29.9 mg) was followed to synthesise this product (37.1 mg) as a white solid in 98% yield from a reaction catalysed by **201** (10 mol%) at –20 °C for 15 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (3:2) gave **404** with 91:9 er as determined by HPLC analysis [Daicel Chiralpak AD, heptanes:IPA, 80:20, 1 mL/min, λ 210 nm, t(major) = 19.5 min, t(minor) = 21.3 min]. m.p. 145 – 147 °C; IR ν_{max} /cm^{-1} 3032, 2943, 1692, 1672, 1496, 1430, 1406, 1352, 1294, 1226, 1130, 1170, 1067, 902, 754, 705, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H, H-Ar), 7.25 – 7.17 (m, 7H, H-Ar), 5.29 (s, 1H, OH), 4.91 (d, *J* = 14.6 Hz, 1H, H-11b), 4.65 (d, *J* = 14.6 Hz, 1H, H-9b), 4.43 (d, *J* = 14.6 Hz, 1H, H-9a), 4.30 (d, *J* = 14.6 Hz, 1H, H-11a), 4.01 (dd, *J* = 3.6, 1.9 Hz, 1H, H-4), 2.86 (dd, *J* = 10.8, 4.3 Hz, 1H, H-7), 2.04 (ddd, *J* = 13.7, 10.8, 1.9 Hz, 1H, H-8b), 1.83 (dt, *J* = 13.7, 4.3 Hz, 1H, H-8a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C-3), 166.2 (C-6), 136.9 (C-10), 134.3 (C-12), 129.3 (C-Ar), 128.8 (C-

Ar), 128.4 (C-Ar), 128.4 (C-Ar), 128.0 (C-Ar), 117.1 (C-13), 83.3 (C-1), 57.8 (C-4), 49.6 (C-11), 42.8 (C-9), 34.2 (C-7), 29.4 (C-8); 1 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{21}H_{19}N_3O_3Na$ requires 384.1324, found $[MNa]^+$ 384.1318; $[\alpha]_D^{21} = -36.1$ (*c* 1.1, $CHCl_3$).

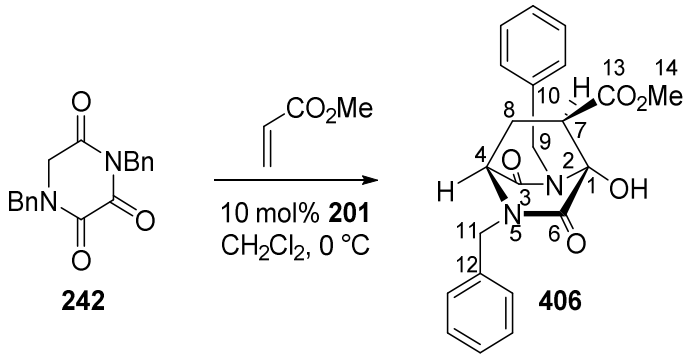
Synthesis of (1*S*,4*S*,7*R*)-2,5-dibenzyl-1-hydroxy-7-(phenylsulfonyl)-2,5-diazabicyclo [2.2.2]octane-3,6-dione **405**



General procedure B using triketopiperazine **242** (30.1 mg) was followed to synthesise this product (38.1 mg) as a white solid in 82% yield from a reaction catalysed by **201** (10 mol%) at 0 °C for 18 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (1:2) gave **405** with 93:7 er as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 80:20, 1 mL/min, λ 210 nm, t(minor) = 26.6 min, t(major) = 31.2 min]. m.p. 150 – 152 °C; IR ν_{max} /cm^{-1} 3318, 3063, 1687, 1496, 1447, 1402, 1356, 1307, 1225, 1146, 1084, 931, 754, 727, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dt, *J* = 8.6, 1.6 Hz, 2H, H-14), 7.62 (m, 1H, H-16), 7.49 (m, 2H, H-15), 7.37 – 7.25 (m, 5H, H-Ar), 7.21 – 7.09 (m, 3H, H-Ar), 7.04 (m, 2H, H-Ar), 4.89 (d, *J* = 14.8 Hz, 1H, H-11b), 4.77 (s, 1H, OH), 4.56

(d, *J* = 14.5 Hz, 1H, H-9b), 4.39 (d, *J* = 14.8 Hz, 1H, H-11a), 4.21 (d, *J* = 14.5 Hz, 1H, H-9a), 3.96 (dd, *J* = 3.6, 2.3 Hz, 1H, H-4), 3.37 (dd, *J* = 11.0, 5.5 Hz, 1H, H-7), 2.39 (ddd, *J* = 14.7, 5.5, 3.6 Hz, 1H, H-8b), 2.03 (ddd, *J* = 14.7, 11.0, 2.3 Hz, 1H, H-8a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (C-3), 166.4 (C-6), 139.4 (C-13), 137.0 (C-10), 134.2 (C-12), 133.9 (C-16), 129.1 (C-Ar), 129.0 (C-Ar), 128.7 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 127.8 (C-Ar), 82.7 (C-1), 63.8 (C-7), 57.0 (C-4), 49.5 (C-11), 42.3 (C-9), 25.9 (C-8); 2 signal in the C-H aromatic region was not observed due to having equivalent resonances; *m/z* (ES HRMS) $C_{26}H_{24}N_2O_5SNa$, 499.1304, found $[MNa]^+$ 499.1300; $[\alpha]_D^{21} = -13.3$ (*c* 0.45, $CHCl_3$).

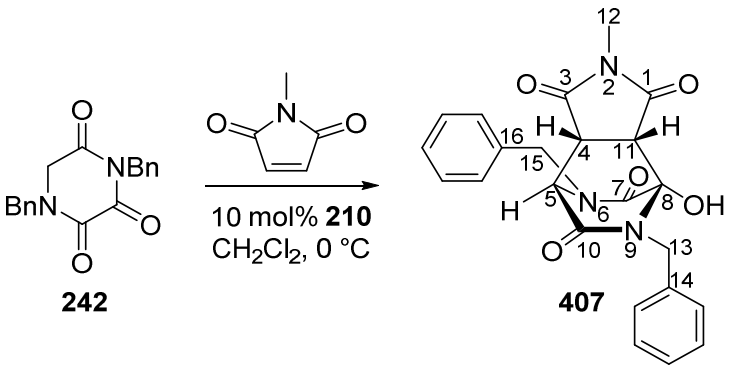
Synthesis of (1*S*,4*S*,7*R*)-methyl 2,5-dibenzyl-1-hydroxy-3,6-dioxo-2,5-diazabicyclo [2.2.2]octane-7-carboxylate **406**



General procedure B using triketopiperazine **242** (31.8 mg) was followed to synthesise this product (35.3 mg) as a white solid in 89% yield from a reaction catalysed by **201** (10 mol%) at 0 °C for 15 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (3:2) gave **406** with 83:17 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, acetonitrile:water, 20:80, 1 mL/min, λ 220 nm, t(major) = 54.5 min, t(minor) = 59.7 min]. m.p. 129 – 131 °C; IR ν_{max} /cm^{-1} 3364, 2953, 1733, 1674, 1655, 1612, 1534,

1496, 1431, 1314, 1222, 1168, 1132, 1028, 909, 736, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H, H-Ar), 7.33 – 7.25 (m, 5H, H-Ar), 4.93 (d, *J* = 14.7 Hz, 1H, H-11b), 4.92 (s, 1H. OH), 4.63 (s, 2H, H-9), 4.48 (d, *J* = 14.7 Hz, 1H, H-11a), 4.03 (dd, *J* = 3.3, 2.4 Hz, 1H, H-4), 3.72 (s, 3H, H-14), 3.06 (dd, *J* = 10.3, 5.5 Hz, 1H, H-7), 2.04 (m, 2H, H-8); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (C-13), 167.7 (C-3), 167.6 (C-6), 137.5 (C-10), 134.8 (C-12), 128.9 (C-Ar), 128.6 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 127.5 (C-Ar), 83.9 (C-1), 57.9 (C-4), 52.5 (C-14), 49.3 (C-11), 48.0 (C-7), 42.4 (C-9), 28.5 (C-8); *m/z* (ESI) $C_{22}H_{22}N_2O_5$ requires 394.1529, found $[M]^+$ 394.1537; $[\alpha]_D^{21}$= 5.1 (*c* 1.1, $CHCl_3$).

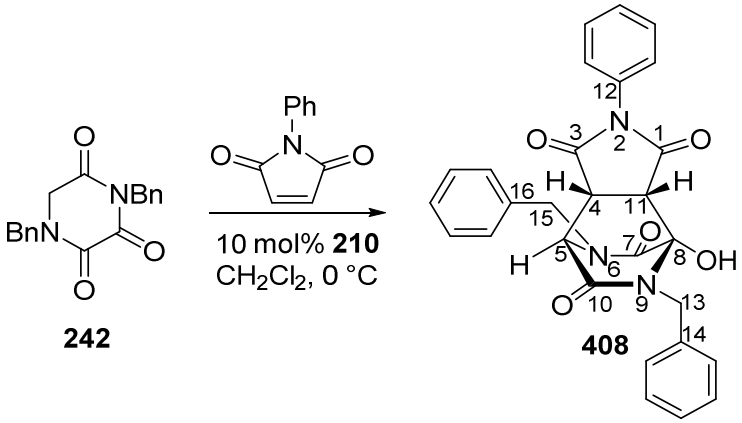
Synthesis of (3a*S*,4*S*,7*R*,7a*R*)-5,8-dibenzyl-4-hydroxy-2-methyltetrahydro-1H-7,4-(epiminomethano) pyrrolo[3,4-c]pyridine-1,3,6,9(2H,3aH)-tetraone **407**



General procedure B using triketopiperazine **242** (28.8 mg) was followed to synthesise this product (33.0 mg) as a white solid in 84% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (1:1) gave **407** with 60:40 er as determined by HPLC analysis [Daicel Chiralpak IF, Heptane:EtOH-MeOH, 50:50, 3 mL/min, λ 210 nm, t(minor) = 1.2 min, t(major) = 1.9 min]. m.p. 158 – 159 °C; IR ν_{max} /cm^{-1} 3149, 3029, 2959, 1787, 1696, 1667,

1495, 1432, 1382, 1283, 1233, 1131, 1079, 913, 737, 698; ^{1}H NMR (400 MHz, MeOD) δ 7.34 – 7.20 (m, 8H, H-Ar), 7.13 (m, 2H, H-Ar), 4.82 (d, *J* = 14.7 Hz, 1H, H-13b), 4.67 (d, *J* = 14.9 Hz, 1H, H-15b), 4.58 (d, *J* = 14.9 Hz, 1H, H-15a), 4.51 (d, *J* = 2.1 Hz, 1H, H-5), 4.11 (d, *J* = 14.7 Hz, 1H, H-13a), 3.44 (dd, *J* = 8.6, 2.1 Hz, 1H, H-4), 3.39 (d, *J* = 8.6 Hz, 1H, H-11), 2.83 (s, 3H, H-12); ^{13}C NMR (101 MHz, MeOD) δ 173.9 (C-3), 172.2 (C-1), 166.7 (C-7, C-10), 137.3 (C-16), 135.2 (C-14), 128.6 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 127.2 (C-Ar), 84,6 (C-8), 59.3 (C-5), 49.6 (C-11), 49.4 (C-13), 43.1 (C-4), 42.1 (C-15), 24.3 (C-12); *m/z* (ES HRMS) $C_{23}H_{21}N_3O_5Na$, 442.1379, found $[MNa]^+$ 442.1381; $[\alpha]_D^{21}$= –6.5 (*c* 0.8, $CHCl_3$).

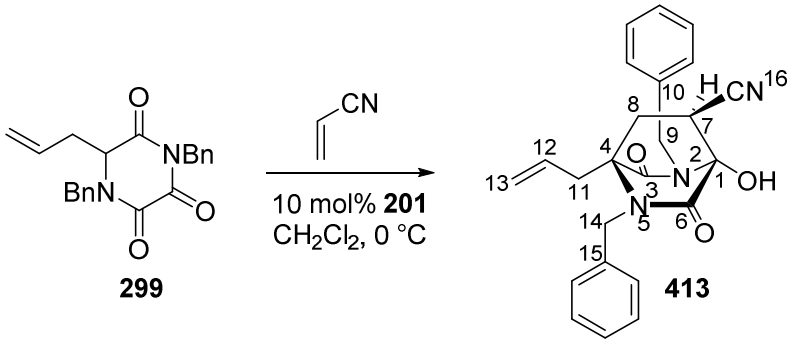
Synthesis of (3a*S*,4*S*,7*R*,7a*R*)-5,8-dibenzyl-4-hydroxy-2-phenyltetrahydro-1H-7,4-(epiminomethano) pyrrolo[3,4-c]pyridine-1,3,6,9(2H,3aH)-tetraone **408**



General procedure B using triketopiperazine **242** (29.0 mg) was followed to synthesise this product (20.1 mg) as a white solid in 41% yield from a reaction catalysed by **210** (10 mol%) at 0 °C for 5 hours. Purification by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (1:1) gave **408** with 50:50 er as determined by HPLC analysis [Daicel

Chiralcel OD, Heptane:EtOH, 60:40, 2 mL/min, λ 210 nm, t(minor) = 5.4 min, t(major) = 10.4 min]. m.p. 186 – 188 °C; IR ν_{max} /cm^{-1} 3021, 1713, 1677, 1496, 1377, 1347, 1221, 1180, 1088, 912, 740, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 3H, H-Ar), 7.30 – 7.19 (m, 8H, H-Ar), 7.08 (m, 4H, H-Ar), 4.99 (d, *J* = 14.6 Hz, 1H, H-13b), 4.69 (d, *J* = 14.7 Hz, 1H, H-15b), 4.61 (d, *J* = 14.7 Hz, 1H, H-15a), 4.55 (d, *J* = 2.8 Hz, 1H, H-5), 4.01 (d, *J* = 14.7 Hz, 1H, H-13a), 3.46 (dd, *J* = 8.9, 2.8 Hz, 1H, H-4), 3.40 (d, *J* = 8.9 Hz, 1H, H-11); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C-3), 170.6 (C-1), 166.5 (C-7), 165.5 (C-10), 137.0 (C-16), 134.0 (C-14), 130.9 (C-12), 129.3 (C-Ar), 129.2 (C-Ar), 129.1 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 127.8 (C-Ar), 126.2 (C-Ar), 84.0 (C-8), 59.4 (C-5), 50.1 (C-13), 49.2 (C-11), 43.0 (C-4), 42.7 (C-15); *m/z* (ES HRMS) $C_{28}H_{23}N_3O_5Na$, 504.1535, found $[MNa]^+$ 504.1540; $[\alpha]_D^{21} = -188.0$ (*c* 0.1, MeOH).

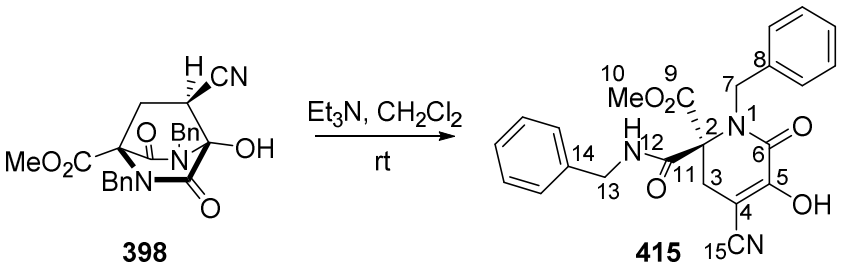
Synthesis of (1*R*,4*S*,7*S*)-4-allyl-2,5-dibenzyl-1-hydroxy-3,6-dioxo-2,5-diazabicyclo [2.2.2]octane-7-carbonitrile **413**



General procedure B using triketopiperazine **242** (32.6 mg) was followed to synthesise this product (10.1 mg) as a colourless oil in 27% yield from a reaction catalysed by **201** (10 mol%) at 0 °C for 48 hours. Purification by flash column chromatography (gradient:

hexane/ethyl acetate = (3:1) to (3:2) gave **413** with 89:11 er as determined by HPLC analysis [Phenomenex Lux Cellulose-3, acetonitrile:water, 35:80, 1 mL/min, λ 220 nm, t(minor) = 19.1 min, t(major) = 21.3 min]. IR ν_{max} /cm^{-1} 3315, 2947, 1693, 1497, 1454, 1431, 1392, 1352, 1171, 1077, 1001, 934, 725, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 8H, H-Ar), 7.16 (m, 2H, H-Ar), 5.96 (m, 1H, H-12), 5.33 (s, 1H, OH), 5.22 (dd, *J* = 10.2, 1.4 Hz, 1H, H-13cis), 5.16 (dd, *J* = 17.1, 1.4 Hz, 1H, H-13trans), 4.95 – 4.88 (d, *J* = 16.0 Hz, 1H, H-14b), 4.79 (d, *J* = 14.5 Hz, 1H, H-9b), 4.77 (d, *J* = 16.0 Hz, 1H, H-14a), 4.59 (d, *J* = 14.5 Hz, 1H, H-9a), 3.06 (dd, *J* = 10.7, 4.8 Hz, 1H, H-7), 3.00 (dd, *J* = 14.5, 5.8 Hz, 1H, H-11b), 2.59 (dd, *J* = 14.5, 8.0 Hz, 1H, H-11a), 2.19 (dd, *J* = 14.3, 10.7 Hz, 1H, H-8b), 2.08 (dd, *J* = 14.3, 4.8 Hz, 1H, H-8a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (C-6), 167.6 (C-3), 137.0 (C-10), 136.3 (C-15), 131.6 (C-12), 129.1 (C-Ar), 128.8 (C-Ar), 128.5 (C-Ar), 128.0 (C-Ar), 127.9 (C-Ar), 126.7 (C-Ar), 120.5 (C-13), 117.3 (C-16), 82.1 (C-1), 63.0 (C-4), 45.7 (C-14), 43.2 (C-9), 34.5 (C-8), 34.4 (C-11), 33.7 (C-7); *m/z* (ES HRMS) $C_{24}H_{24}N_3O_3$ requires 402.1818, found $[MH]^+$ 402.1806; $[\alpha]_D^{21}$= –3.3 (*c* 0.5, $CHCl_3$).

Synthesis of methyl 1-benzyl-2-(benzylcarbamoyl)-4-cyano-5-hydroxy-6-oxo-1,2,3,6-tetrahydro pyridine-2-carboxylate **415**

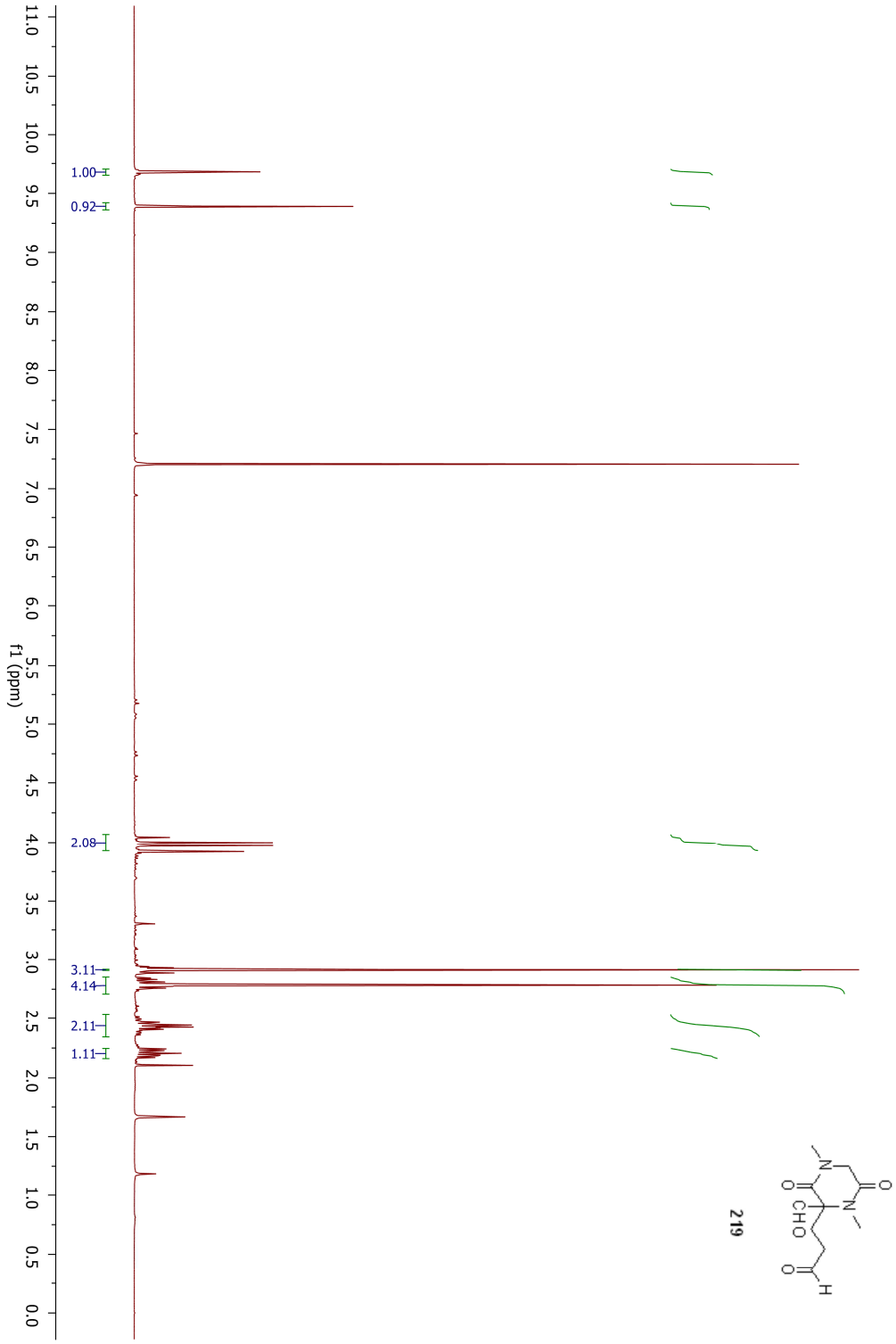


To a solution of **398** (20 mg, 0.05 mmol, 1 eq.) in CH_2Cl_2 (0.8 mL), triethylamine (10 µL, 0.07 mmol, 1.4 eq.) was added in one portion at room temperature. The mixture was left to

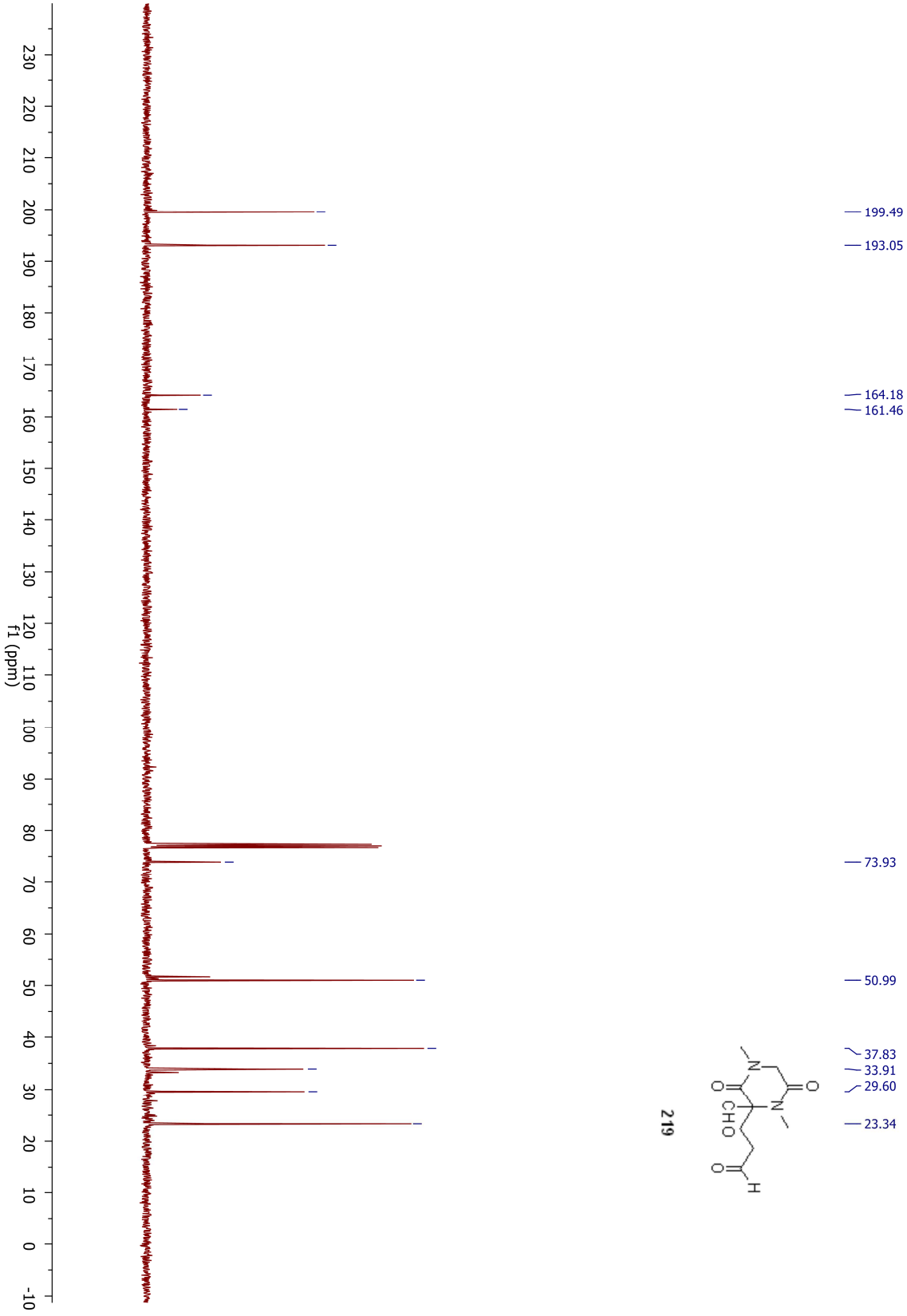
stir at that temperature for 48 h, the solvent was evaporated and compound **415** was obtained as a colourless oil in 82% yield (16.4 mg) after being purified by flash column chromatography (gradient: hexane/ethyl acetate = (3:1) to (1:1). IR ν_{max} /cm^{-1} 3328, 2924, 2218, 1741, 1659, 1524, 1497, 1444, 1345, 14a, 1160, 1080, 1028, 727, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H, OH), 7.39 – 7.27 (m, 6H, H-Ar), 7.24 (m, 2H, H-Ar), 7.16 (m, 2H, H-Ar), 7.08 (s, 1H, NH), 4.76 (d, *J* = 15.5 Hz, 1H, H-7b), 4.71 (d, *J* = 15.5 Hz, 1H, H-7a), 4.48 (dd, *J* = 14.6, 6.0 Hz, 1H, H-13b), 4.25 (dd, *J* = 14.6, 5.1 Hz, 1H, H-13a), 3.64 (s, 3H, H-10), 3.29 (d, *J* = 16.5 Hz, 1H, H-3b), 3.16 (d, *J* = 16.5 Hz, 1H, H-3a); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (C-9), 164.7 (C-11), 162.3 (C-6), 150.7 (C-5), 136.5 (C-14), 135.8 (C-8), 129.0 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 127.8 (C-Ar), 114.1 (C-15), 83.1 (C-4), 72.0 (C-2), 54.1 (C-10), 51.0 (C-7), 44.5 (C-13), 32.6 (C-3); *m/z* (ES HRMS) $C_{23}H_{22}N_3O_5$ requires 420.1559, found $[MH]^+$ 420.1545.

Appendix 1 - NMR Spectra and HPLC Traces

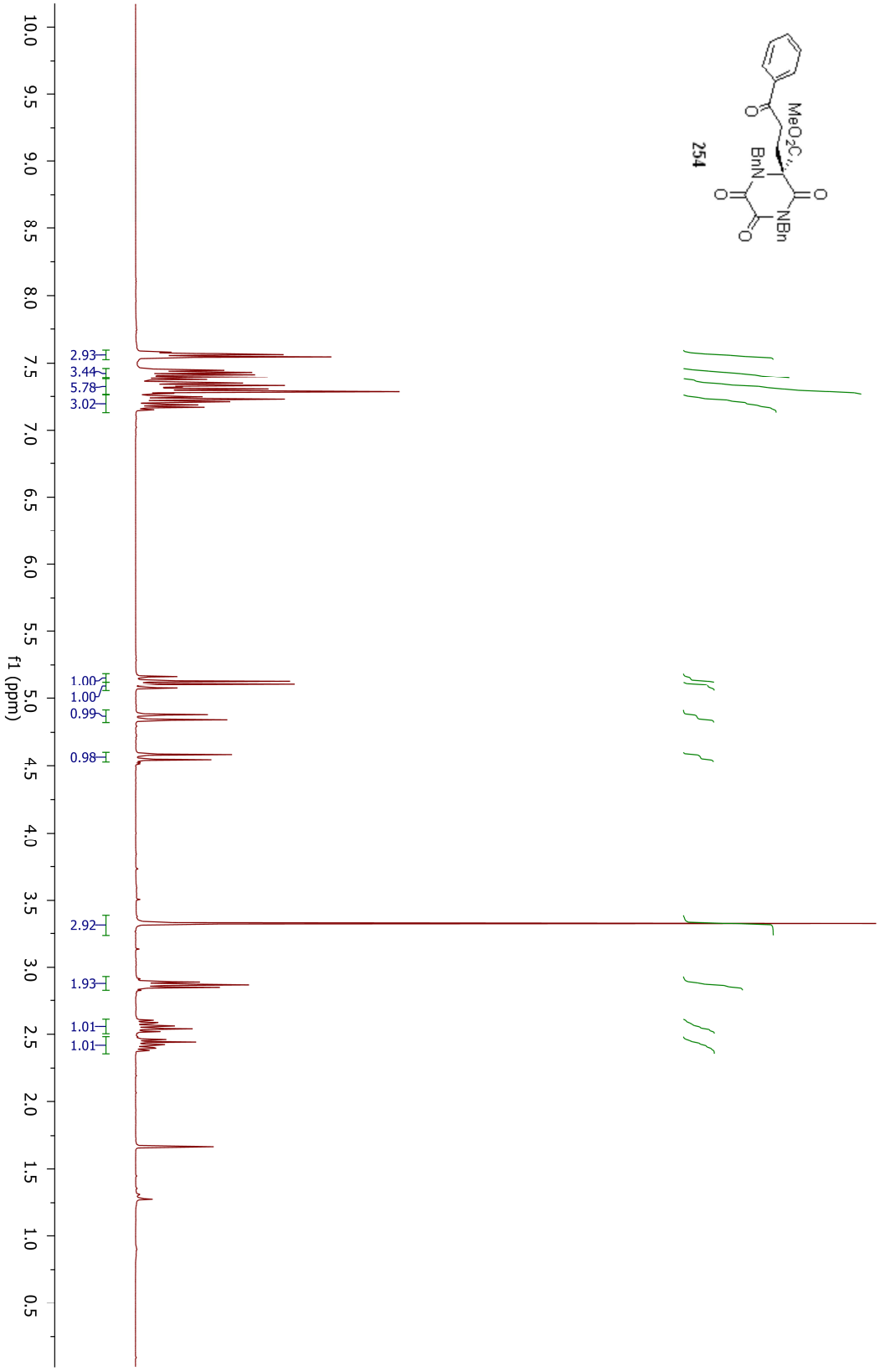
Appendix 1.1 ^{1}H spectrum of **219** (400 MHz, $CDCl_3$)



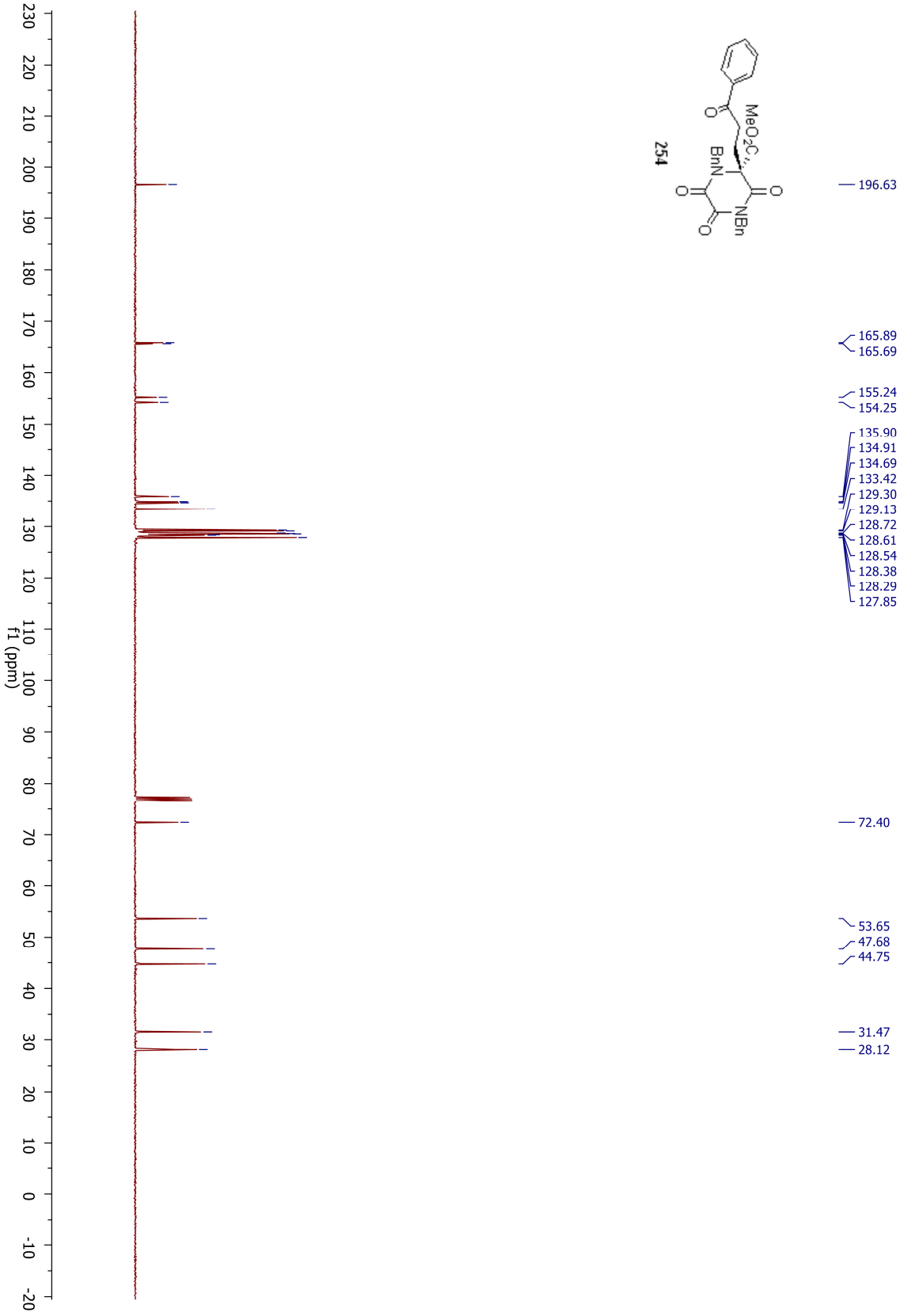
Appendix 1.1 ^{13}C spectrum of **219** (101 MHz, $CDCl_3$)



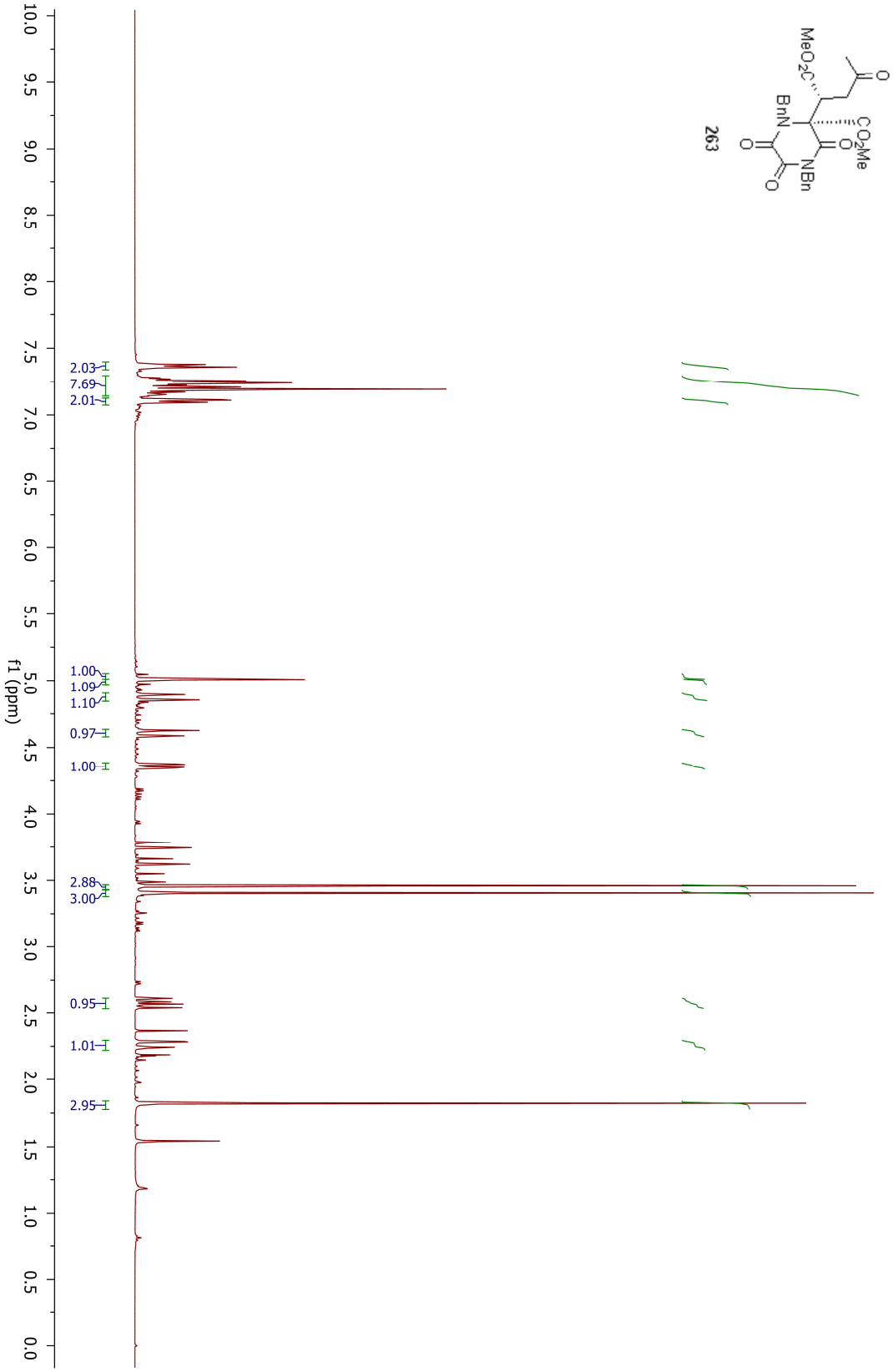
Appendix 1.2 ^{1}H spectrum of **254** (400 MHz, $CDCl_3$)



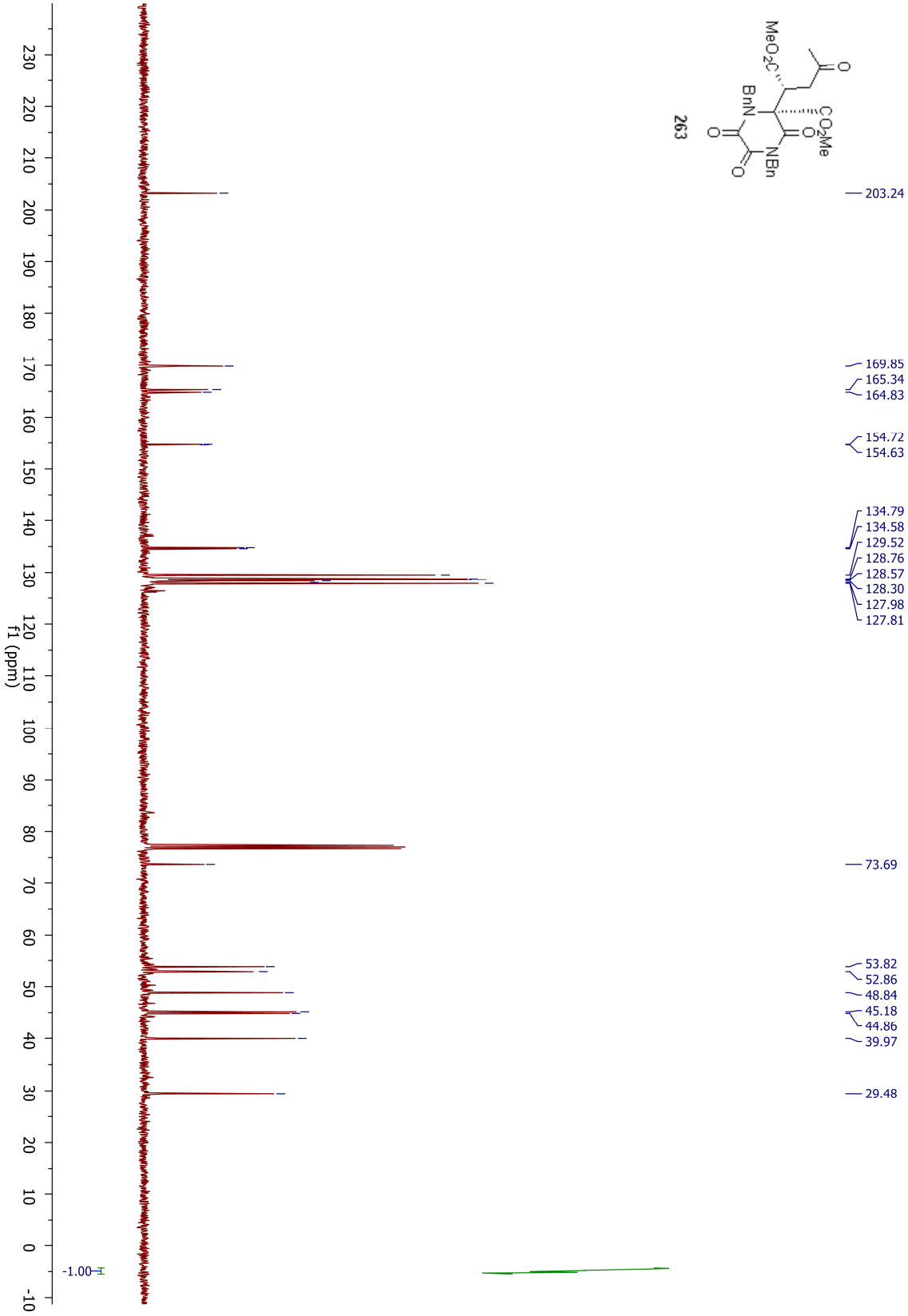
Appendix 1.2 ^{13}C spectrum of **254** (101 MHz, $CDCl_3$)



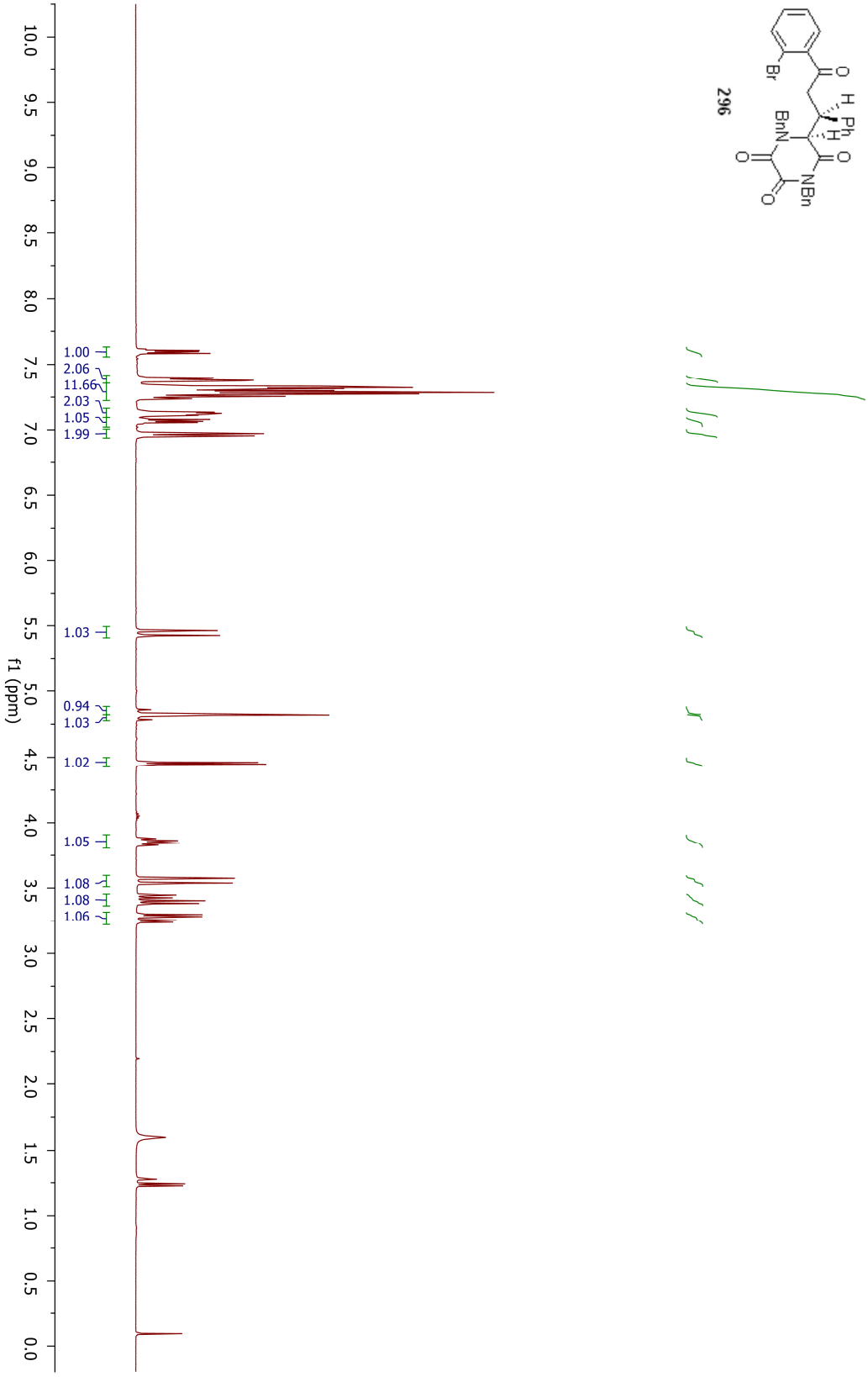
Appendix 1.3 ^{1}H spectrum of **263** (400 MHz, $CDCl_3$)



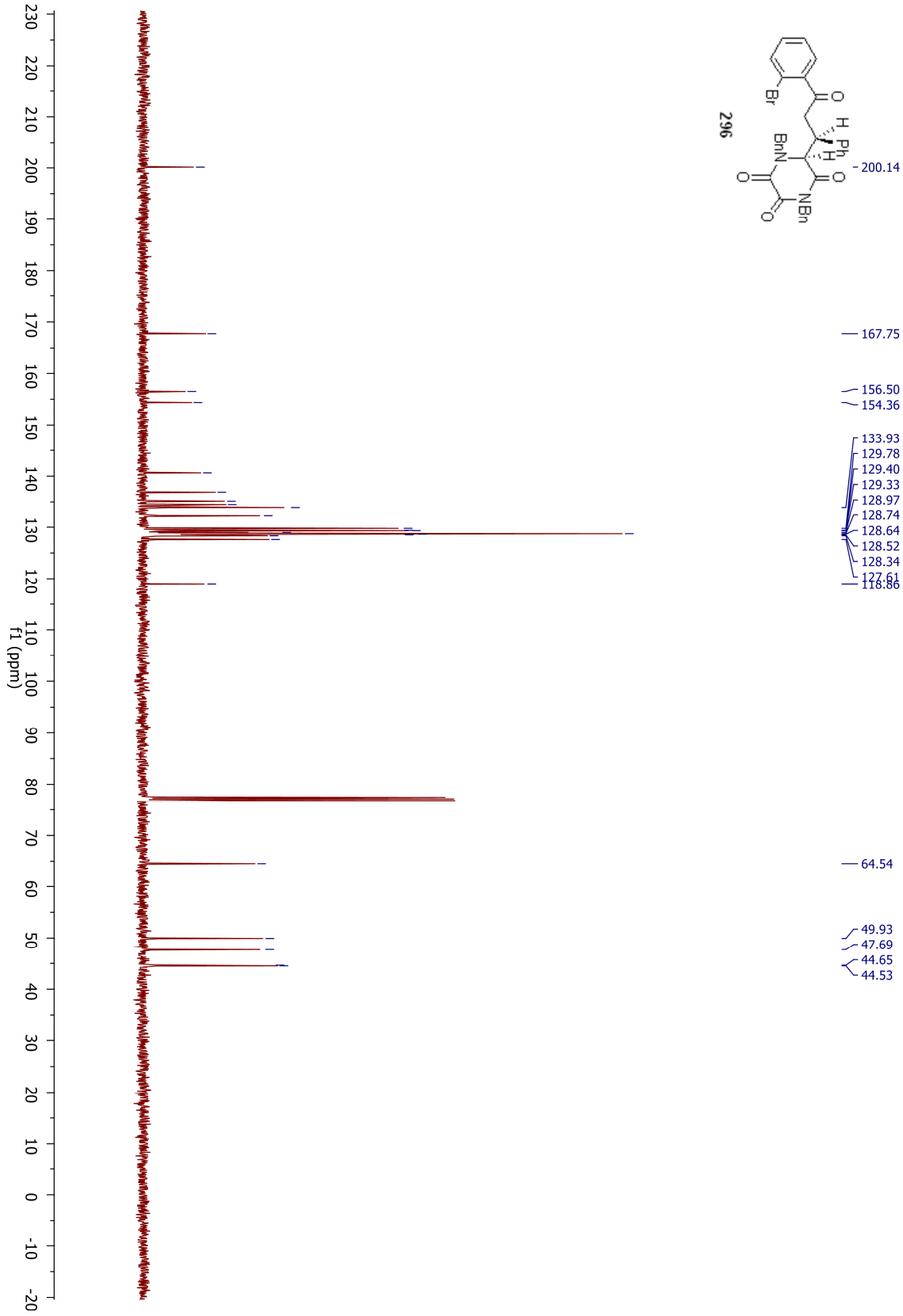
Appendix 1.3 ^{13}C spectrum of **263** (101 MHz, $CDCl_3$)



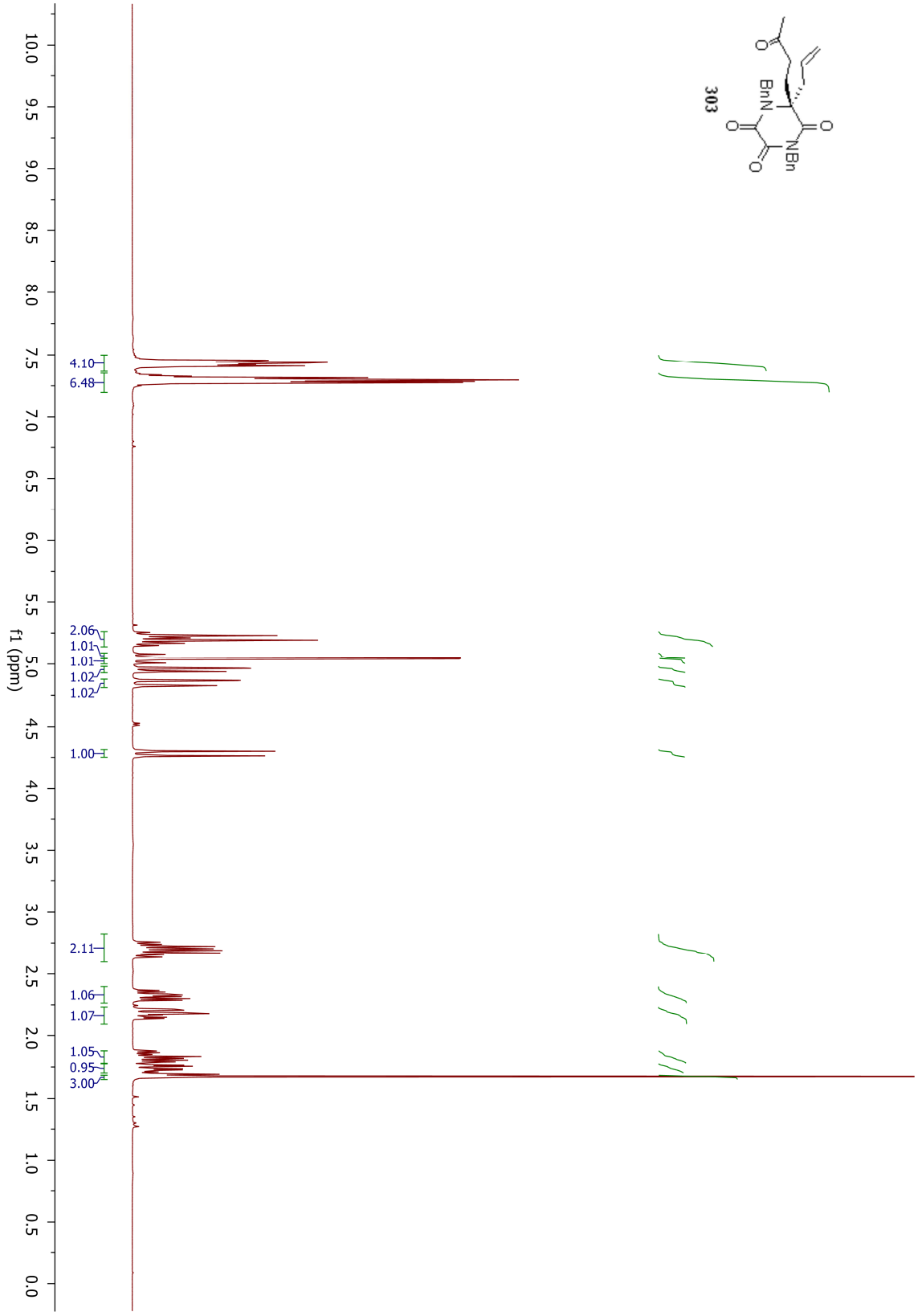
Appendix 1.4 ^{1}H spectrum of **296** (400 MHz, $CDCl_3$)



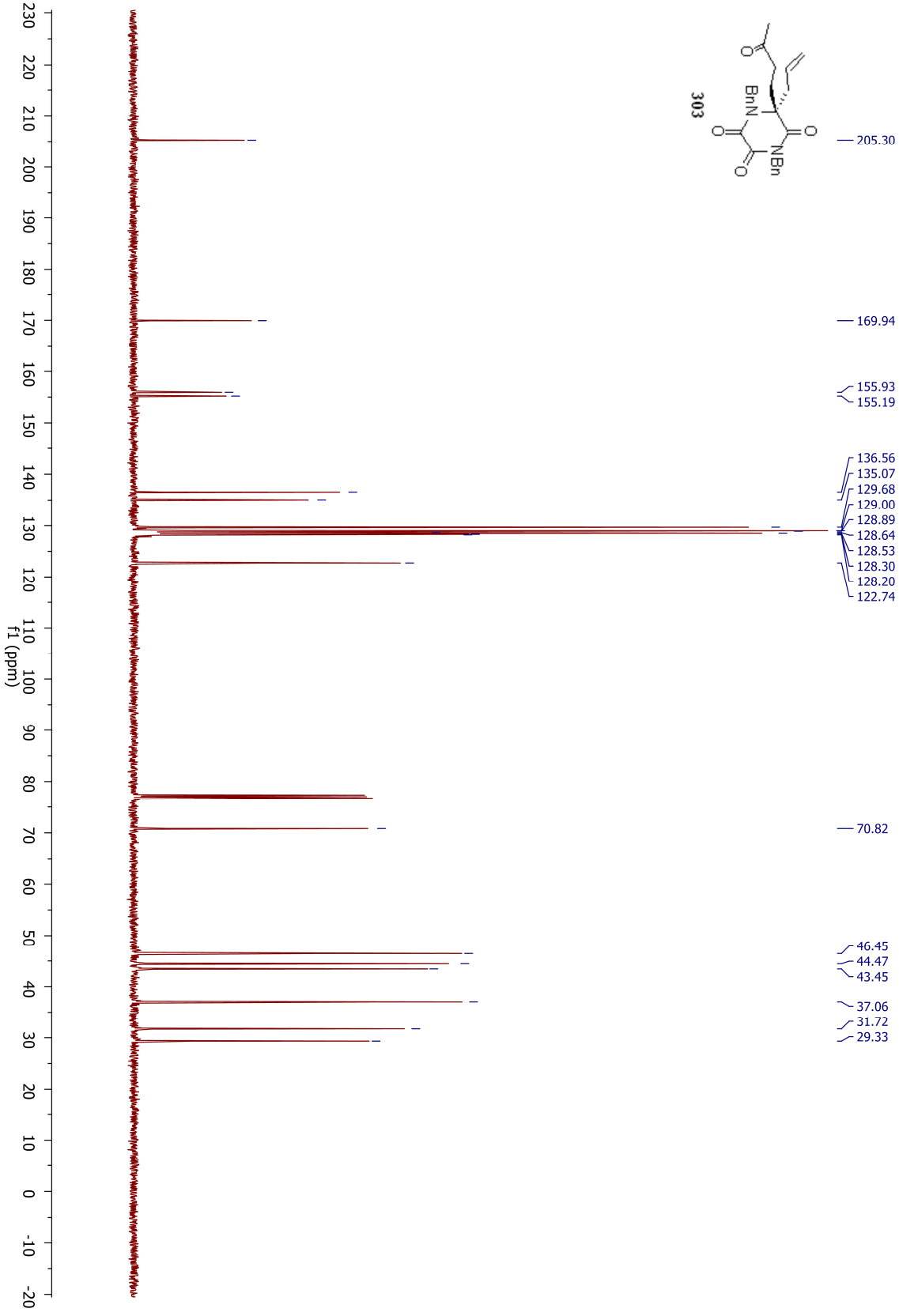
Appendix 1.4 ^{13}C spectrum of **296** (101 MHz, $CDCl_3$)



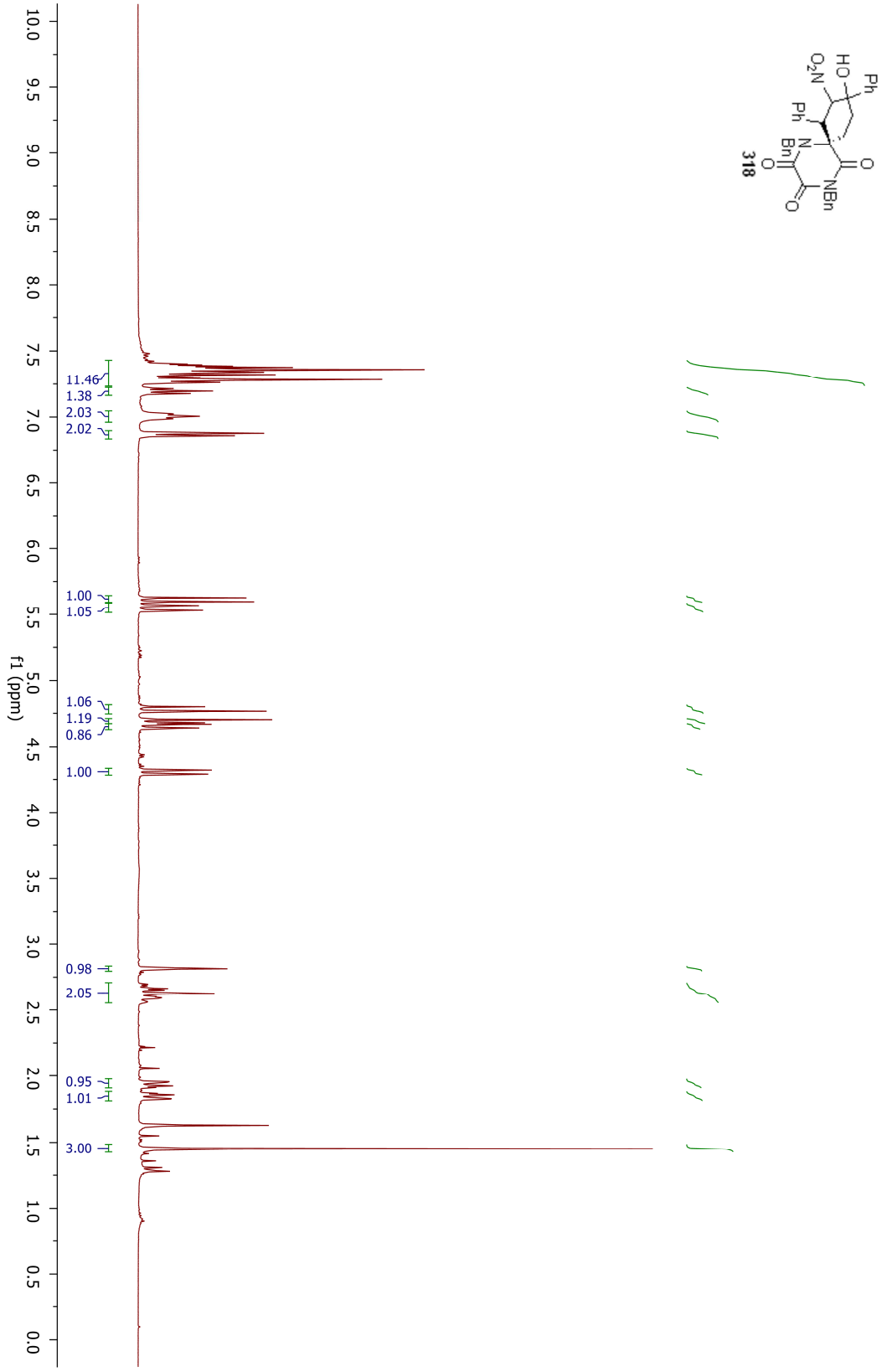
Appendix 1.5 ^{1}H spectrum of **303** (400 MHz, $CDCl_3$)



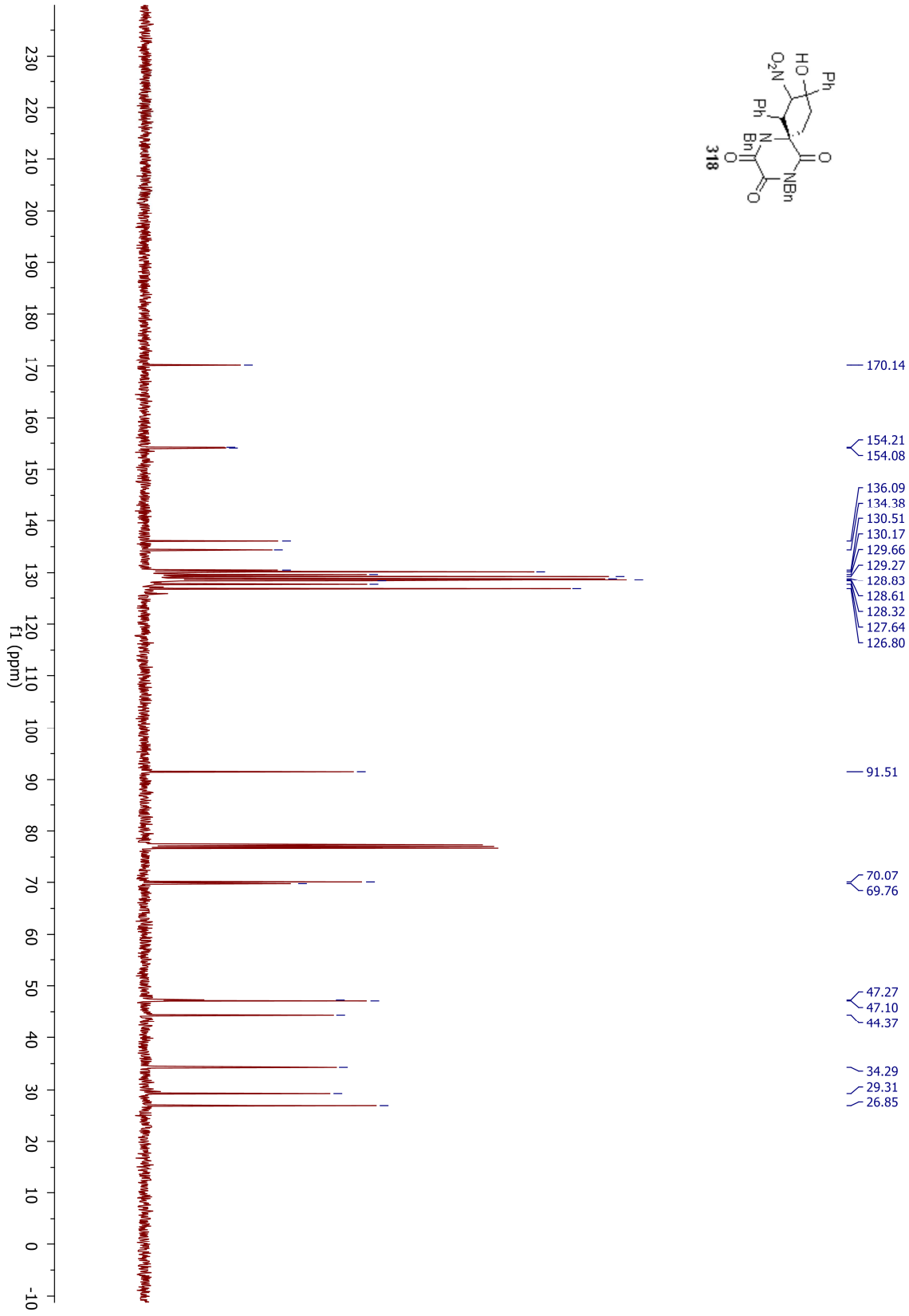
Appendix 1.5 ^{13}C spectrum of **303** (101 MHz, $CDCl_3$)



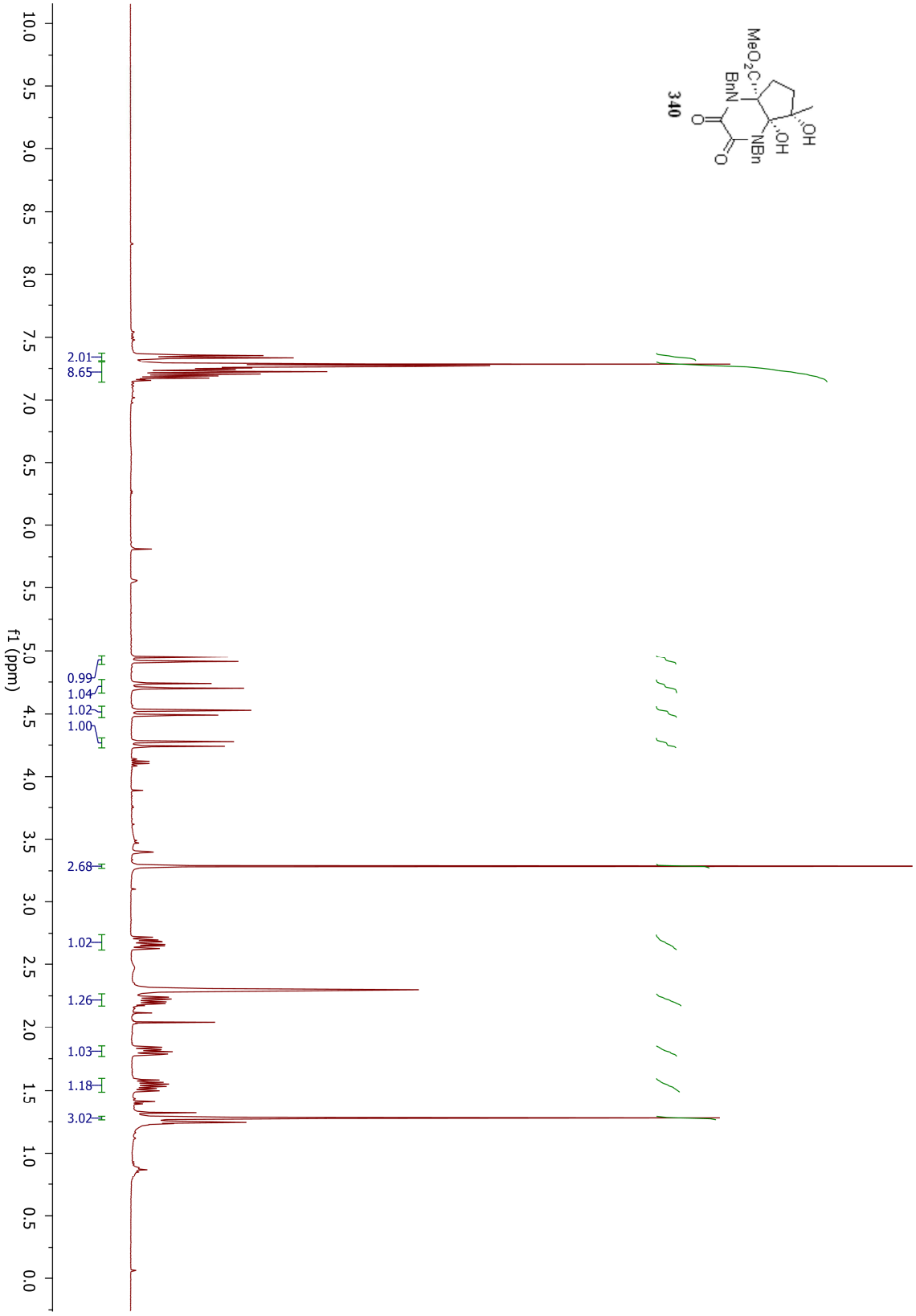
Appendix 1.6 ^{1}H spectrum of **318** (400 MHz, $CDCl_3$)



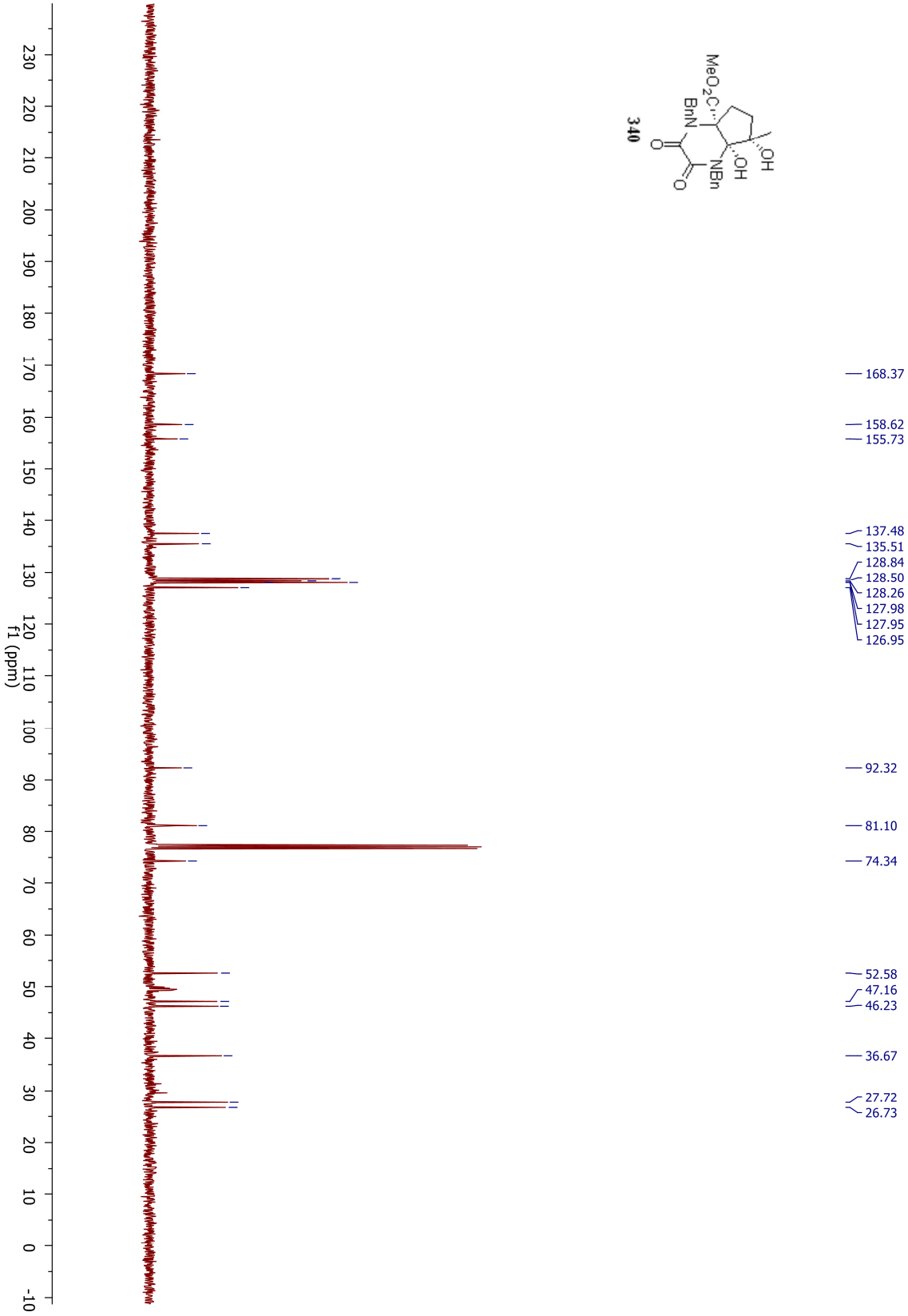
Appendix 1.6 ^{13}C spectrum of **318** (101 MHz, $CDCl_3$)



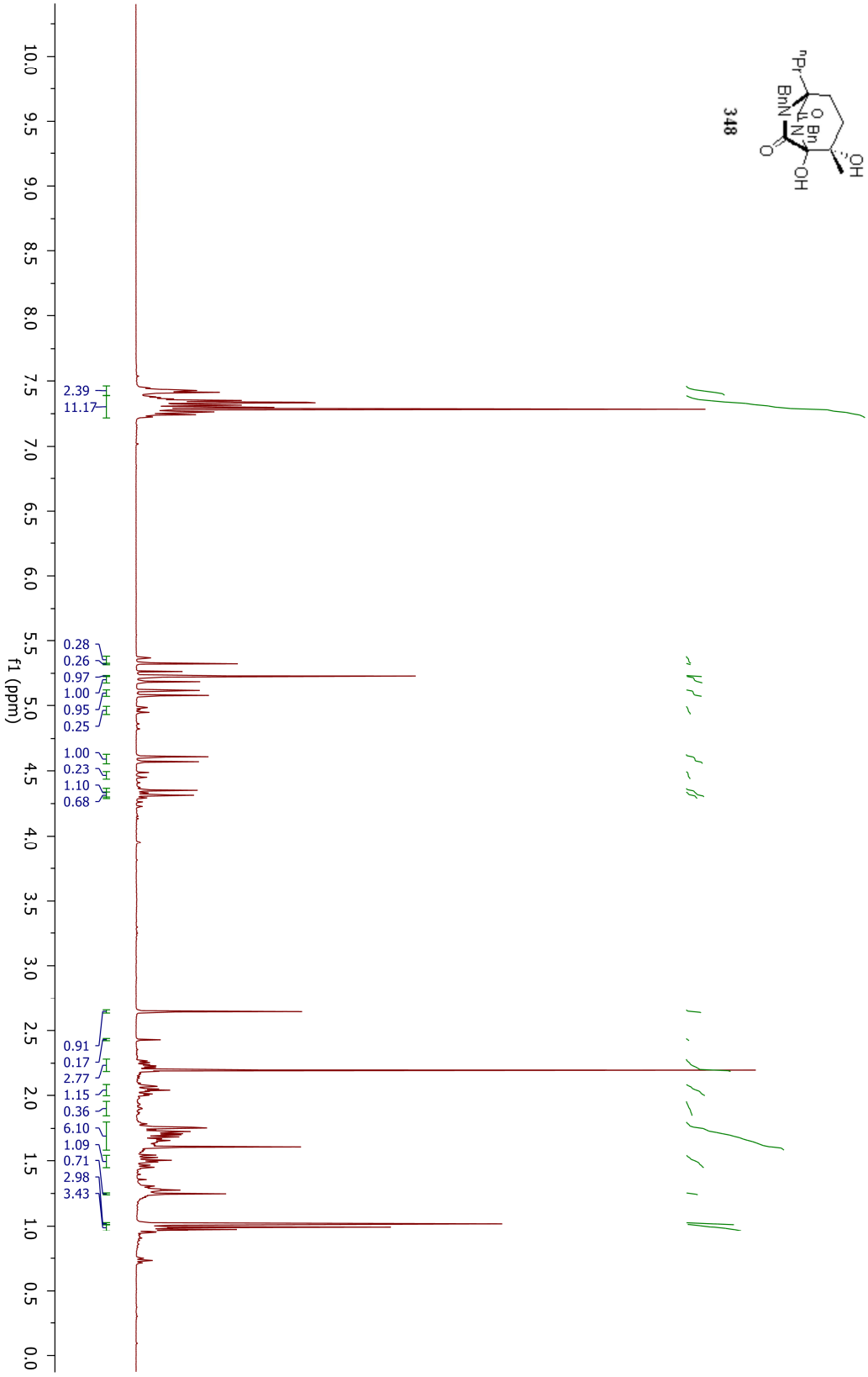
Appendix 1.7 ^{1}H spectrum of **340** (400 MHz, $CDCl_3$)



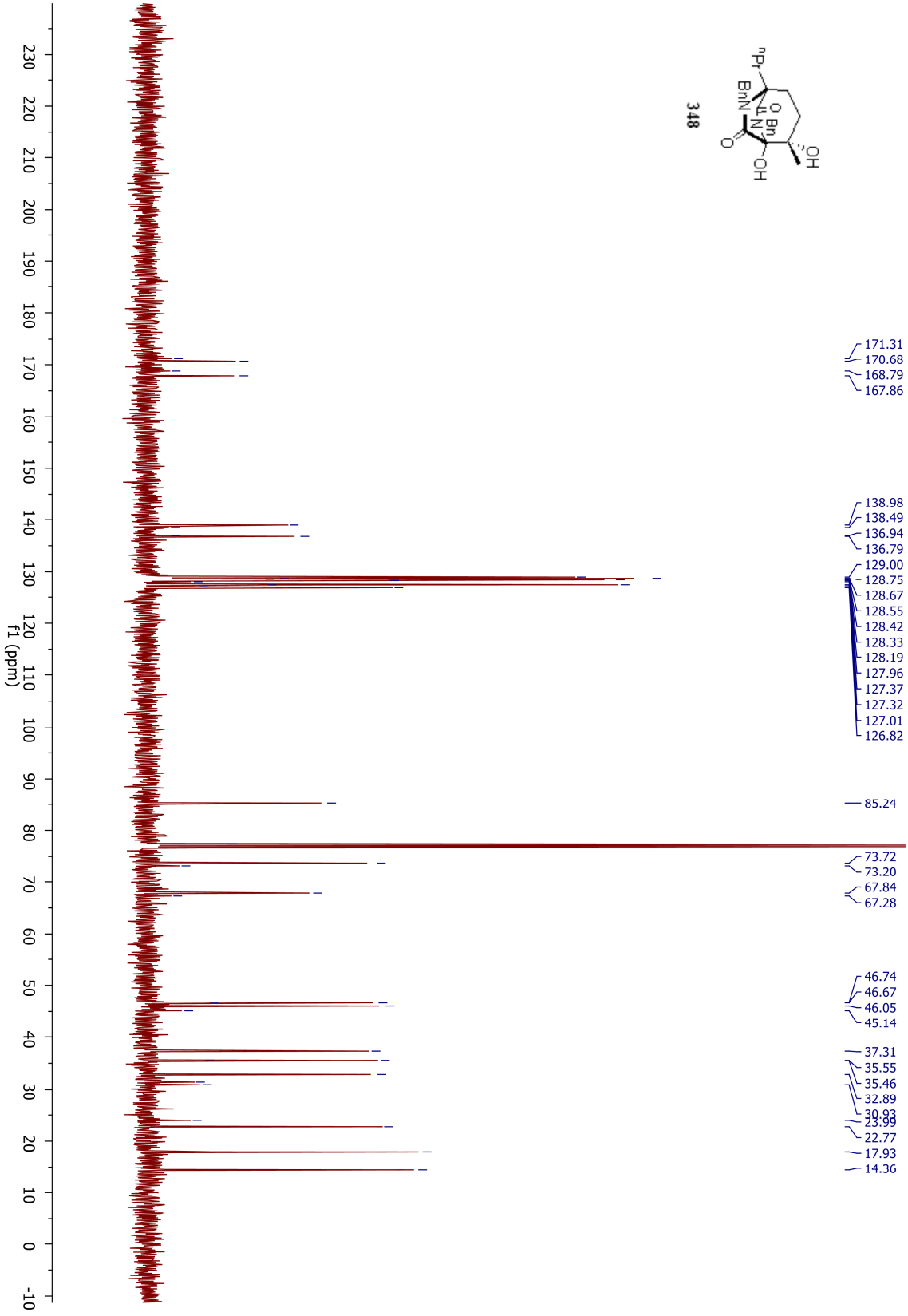
Appendix 1.7 ^{13}C spectrum of **340** (101 MHz, $CDCl_3$)



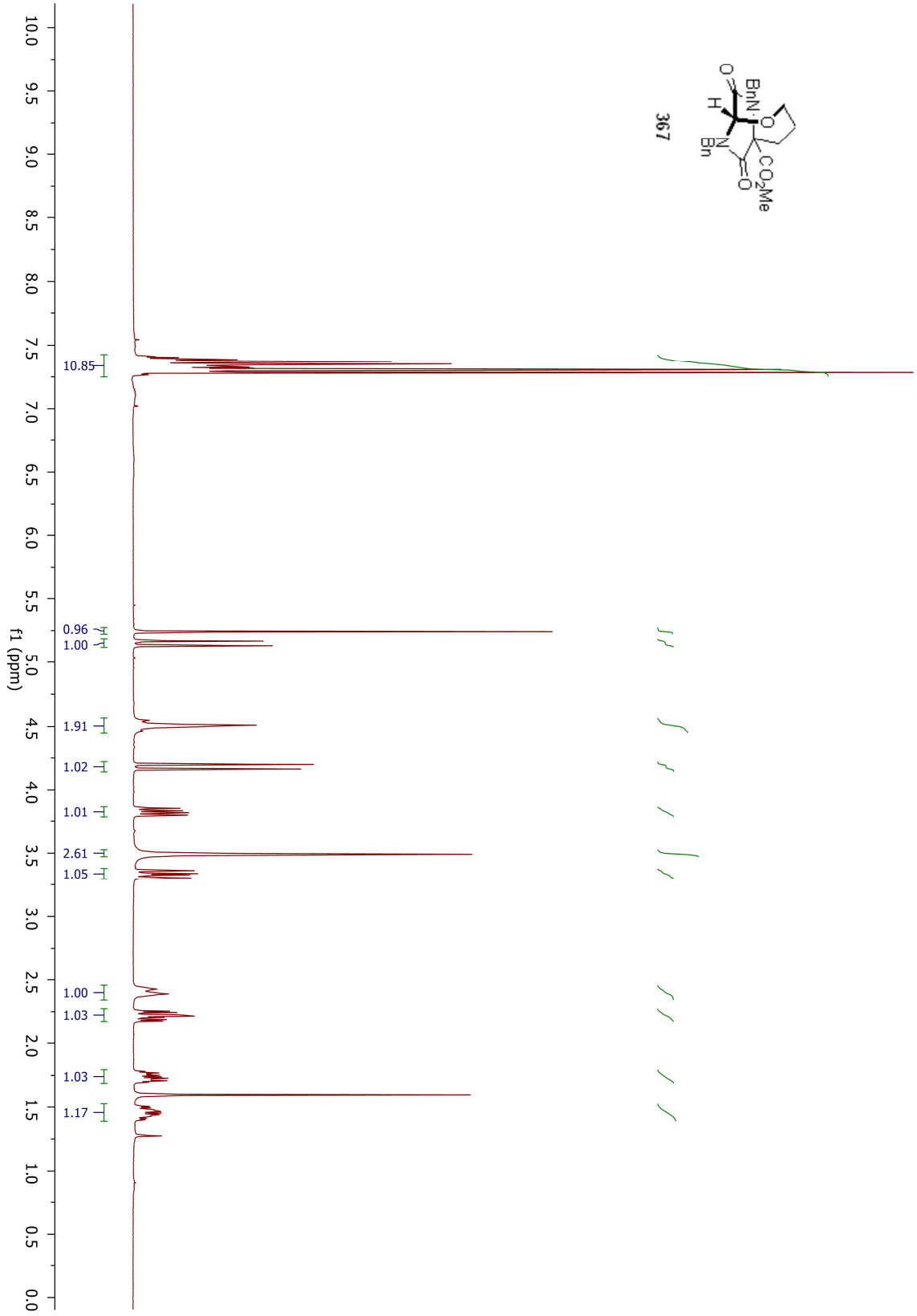
Appendix 1.8 ^{1}H spectrum of **348** (400 MHz, $CDCl_3$)



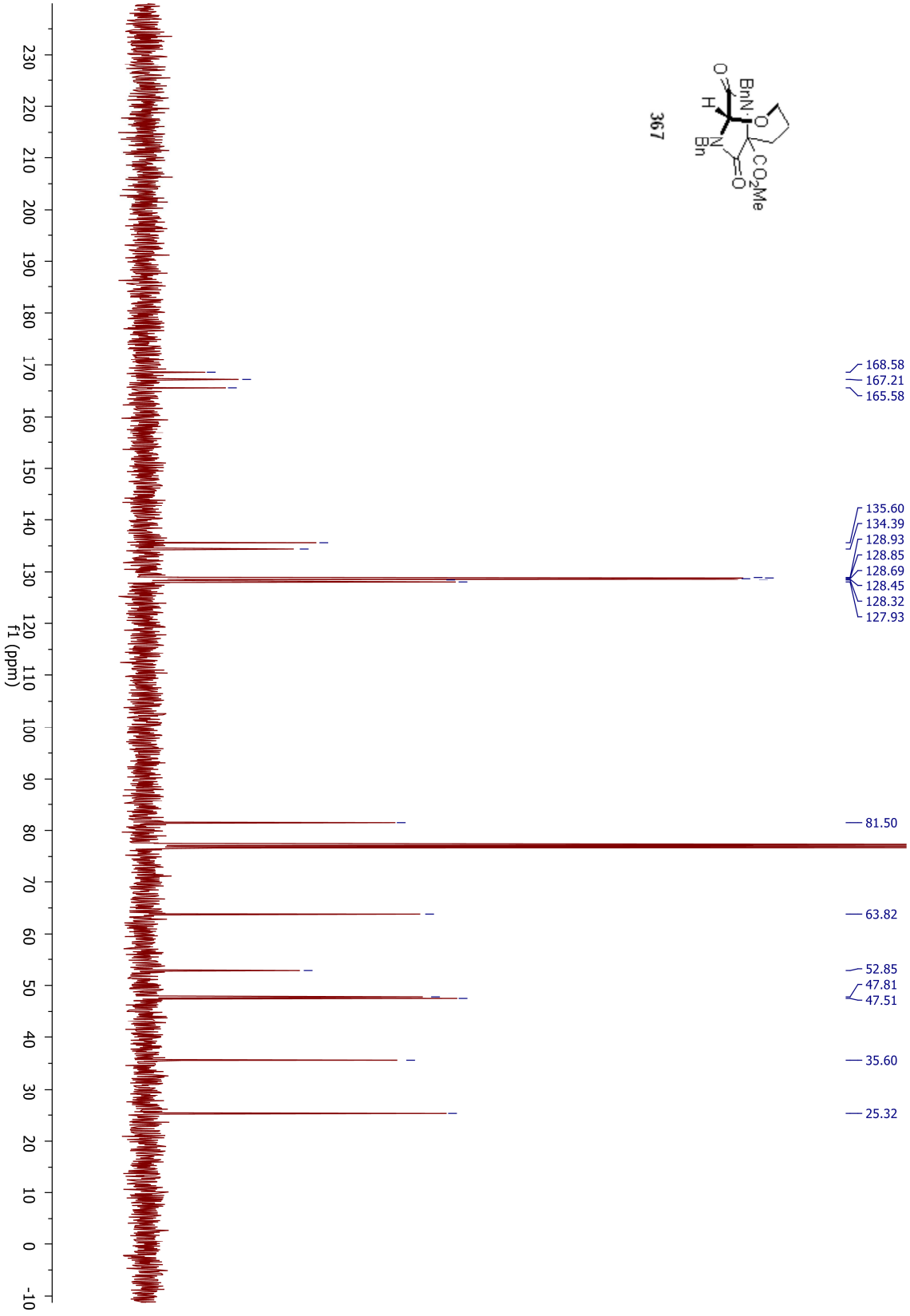
Appendix 1.8 ^{13}C spectrum of **348** (101 MHz, $CDCl_3$)



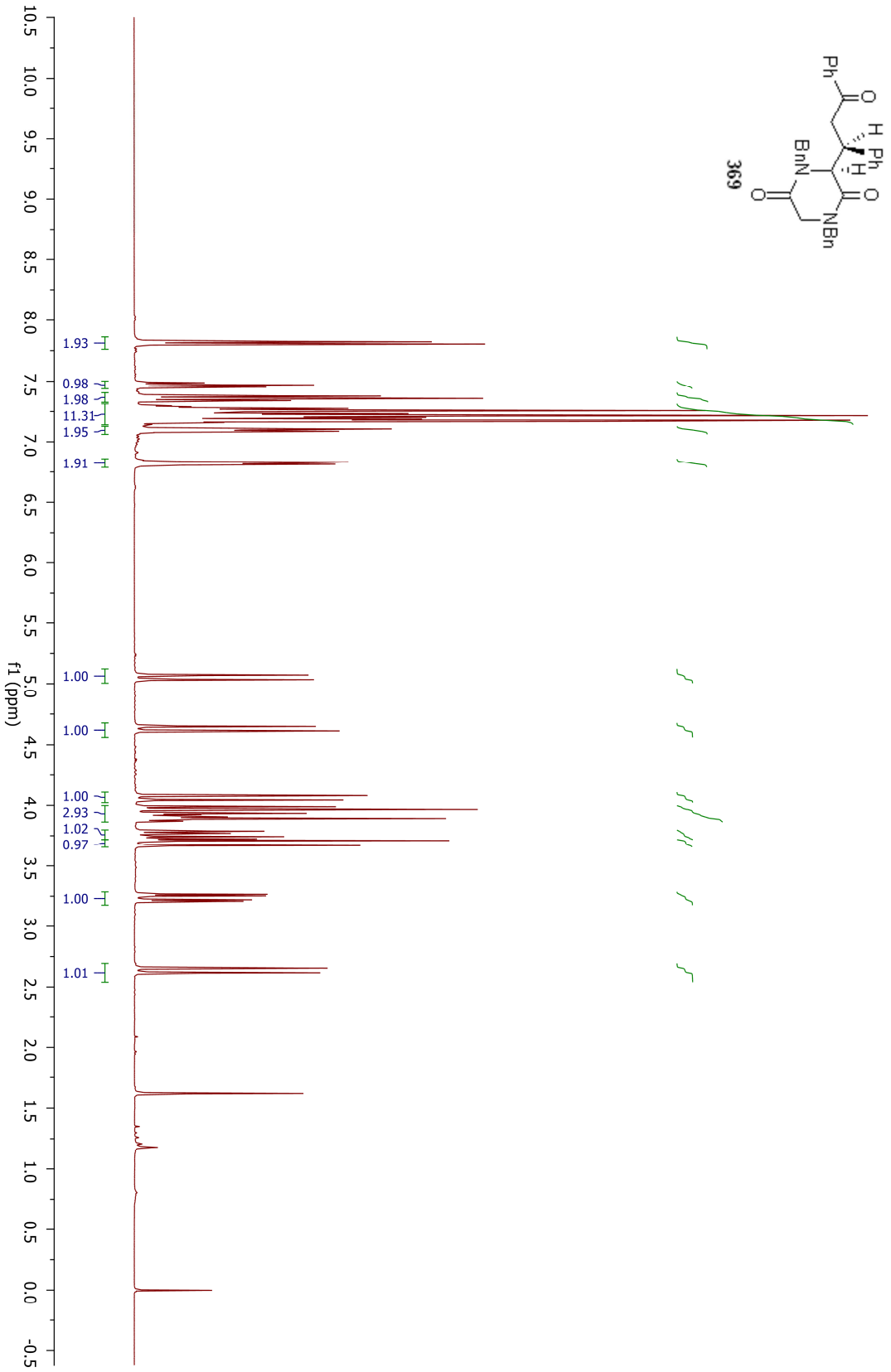
Appendix 1.9 ^{1}H spectrum of **367** (400 MHz, $CDCl_3$)



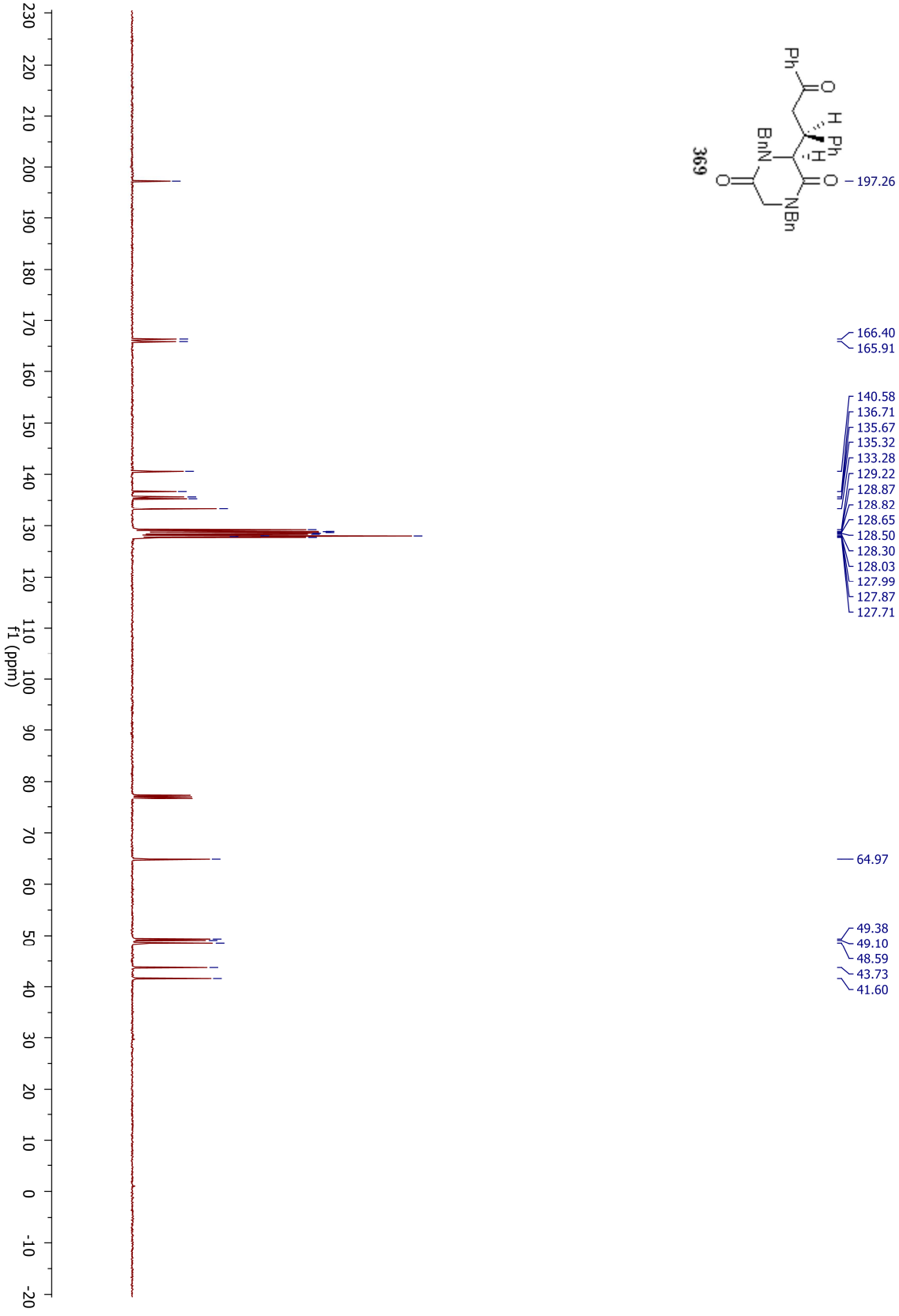
Appendix 1.9 ^{13}C spectrum of **367** (101 MHz, $CDCl_3$)



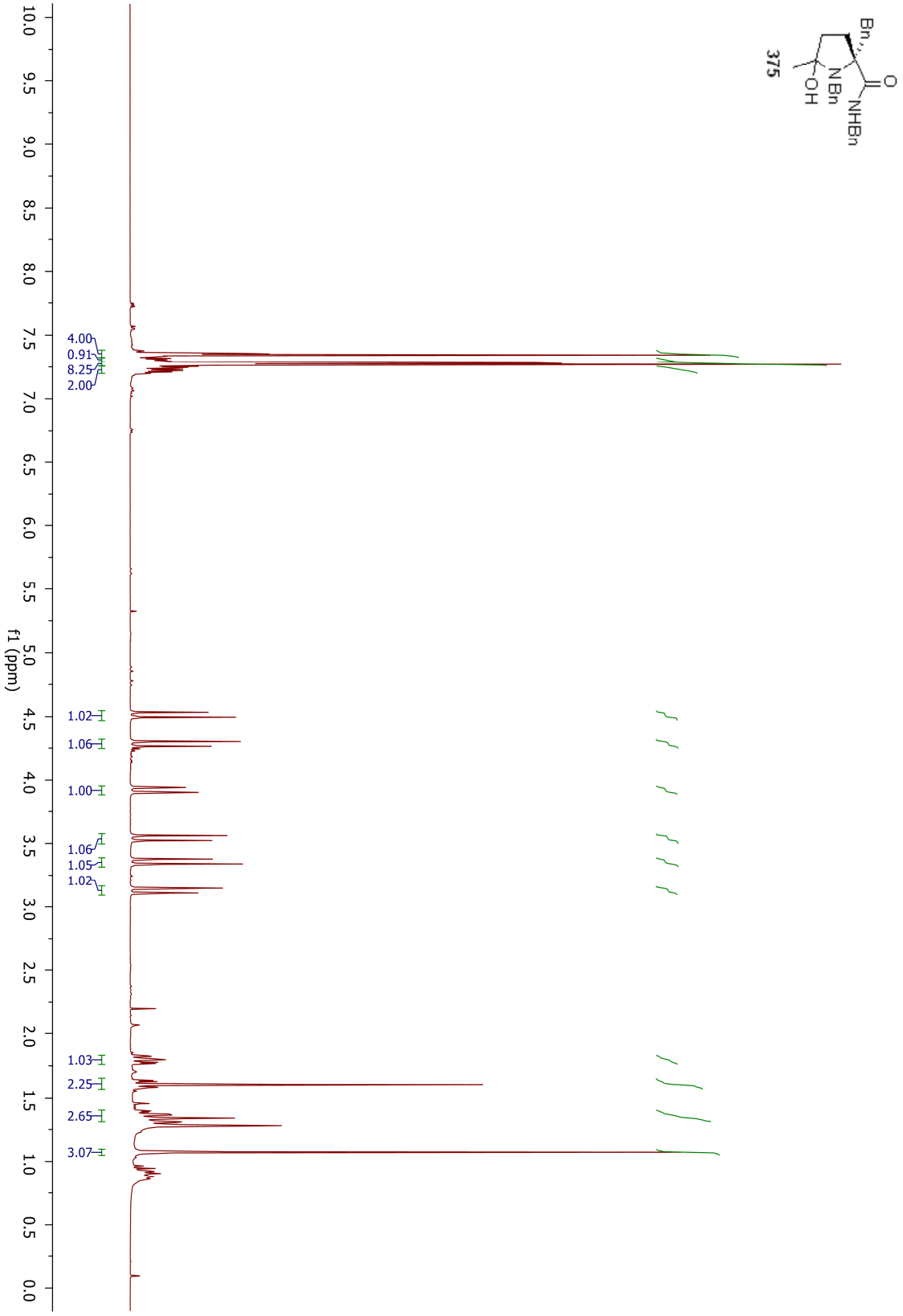
Appendix 1.10 ^{1}H spectrum of **369** (400 MHz, $CDCl_3$)



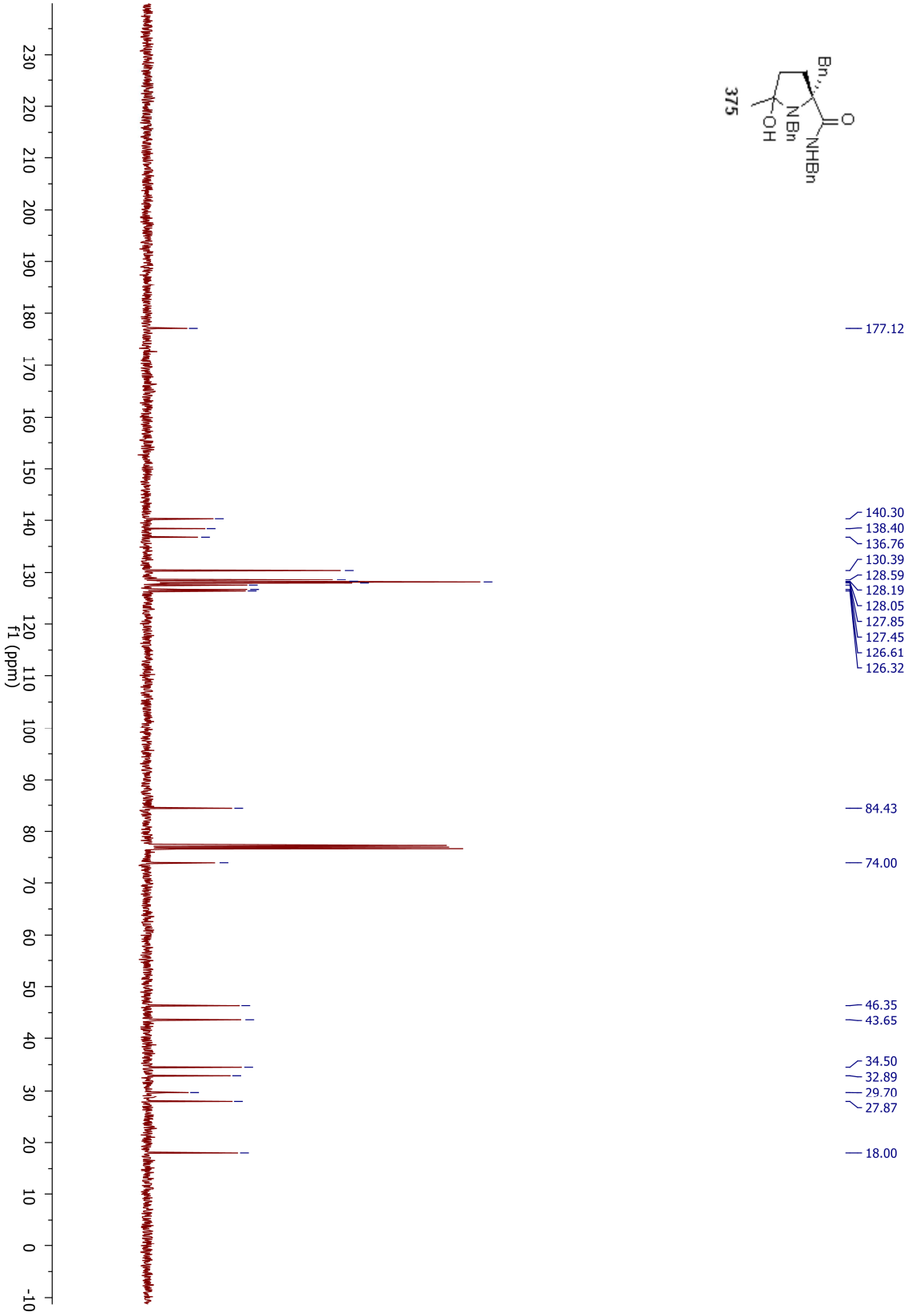
Appendix 1.10 ^{13}C spectrum of **369** (101 MHz, $CDCl_3$)



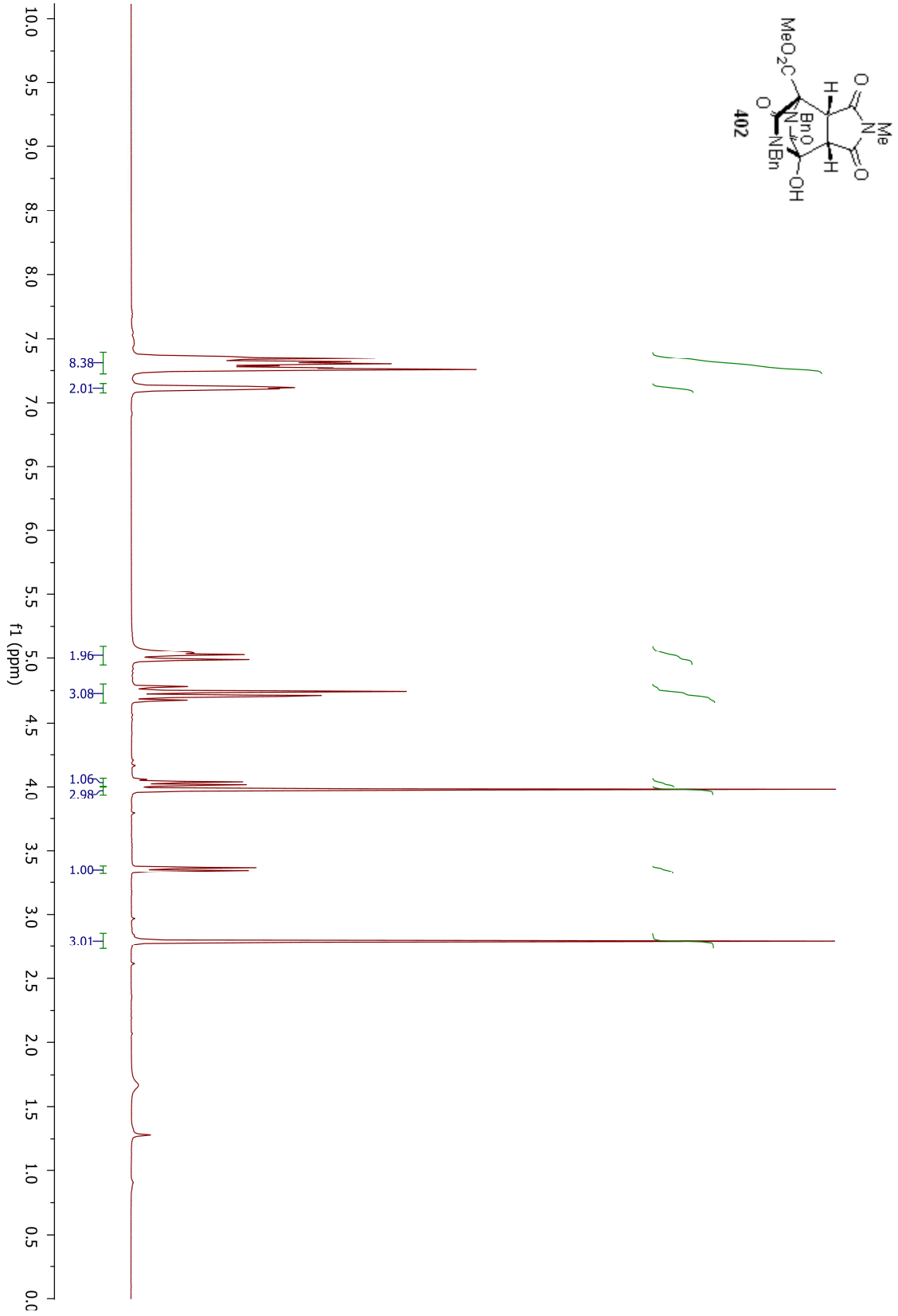
Appendix 1.11 ^{1}H spectrum of **375** (400 MHz, $CDCl_3$)



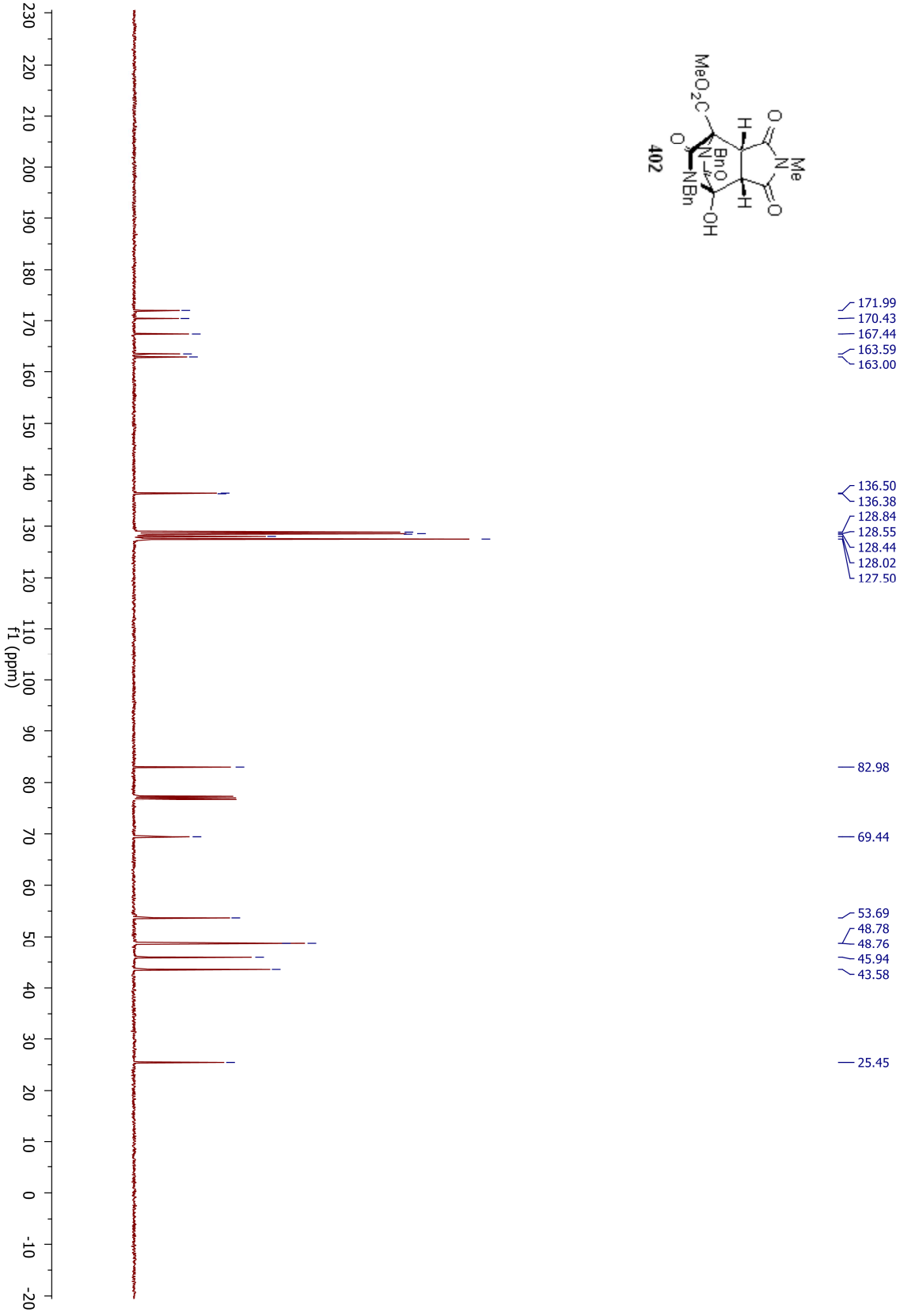
Appendix 1.11 ^{13}C spectrum of **375** (101 MHz, $CDCl_3$)



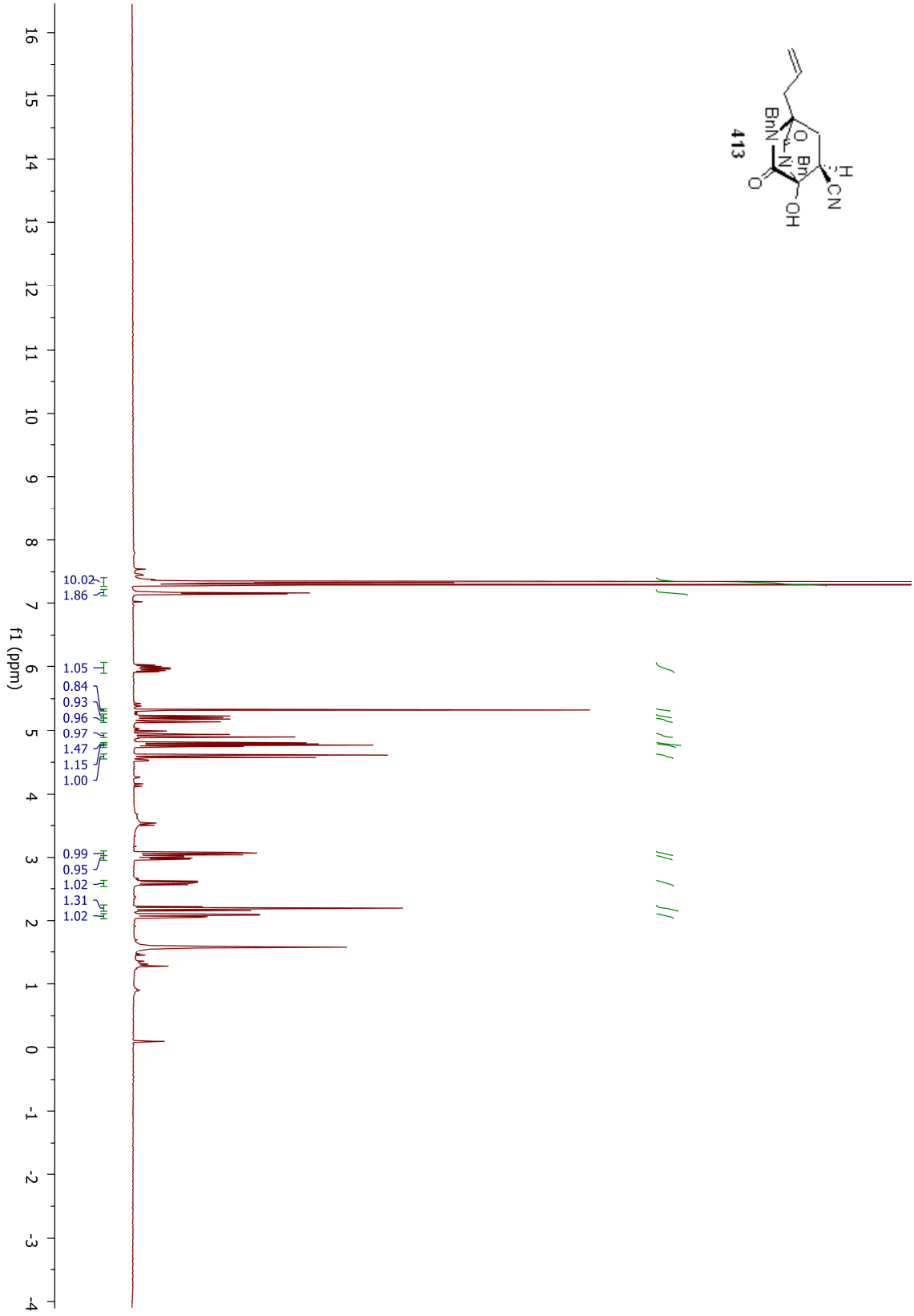
Appendix 1.12 ^{1}H spectrum of **402** (400 MHz, $CDCl_3$)



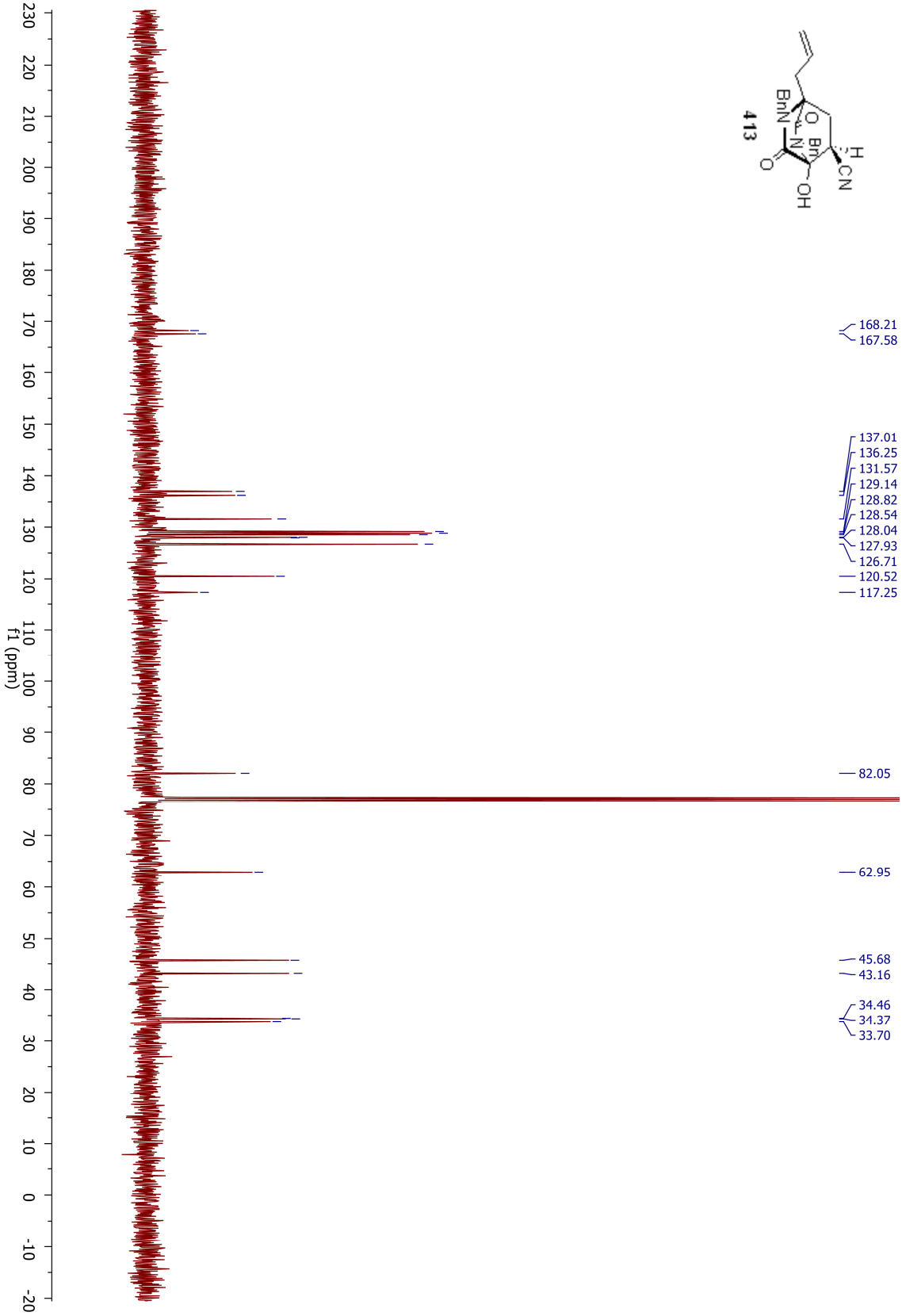
Appendix 1.12 ^{13}C spectrum of **402** (101 MHz, $CDCl_3$)



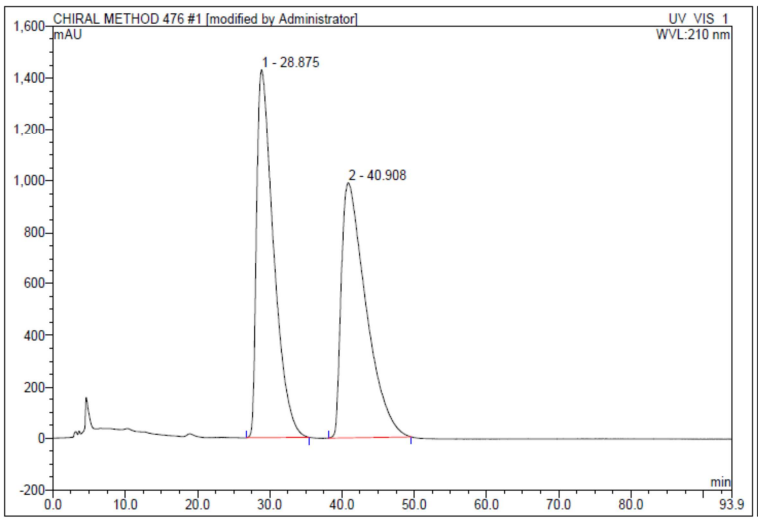
Appendix 1.13 ^{1}H spectrum of **413** (400 MHz, $CDCl_3$)



Appendix 1.13 ^{13}C spectrum of **413** (101 MHz, $CDCl_3$)

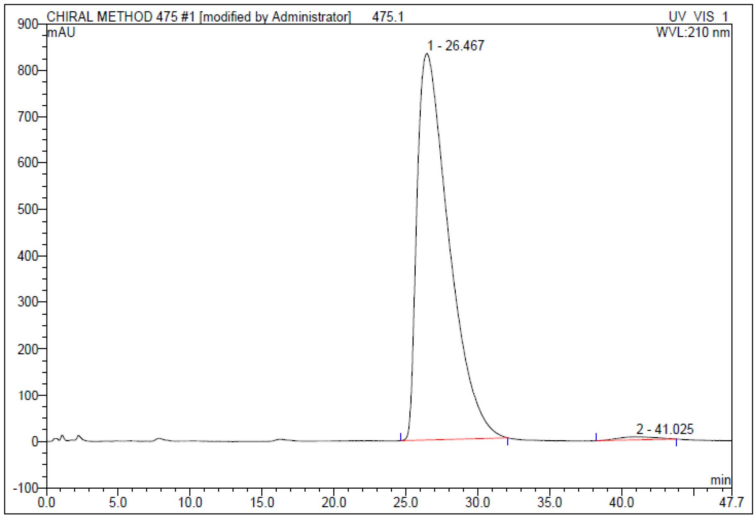


Appendix 1.14 – Example Chiral HPLC chromatograms for **254**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	28.88	n.a.	1431.304	3900.451	49.83	n.a.	BMB
2	40.91	n.a.	991.631	3926.772	50.17	n.a.	BMB
Total:			2422.935	7827.223	100.00	0.000	

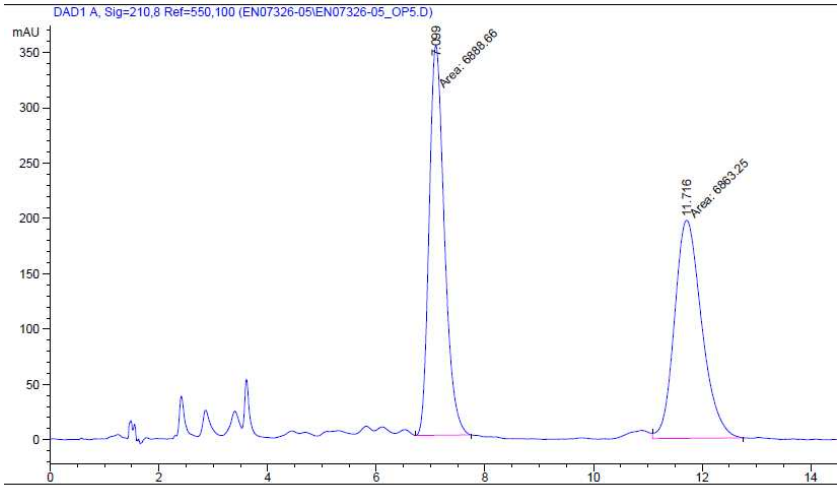
Figure 1 Chiral HPLC Chromatogram of a racemic sample of **254** synthesised using Et_3N. Peak 1 – (–)-**254**, peak 2 – (+)-**254**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.47	n.a.	834.359	2138.952	99.06	n.a.	BMB
2	41.03	n.a.	6.636	20.336	0.94	n.a.	BMB*
Total:			840.995	2159.288	100.00	0.000	

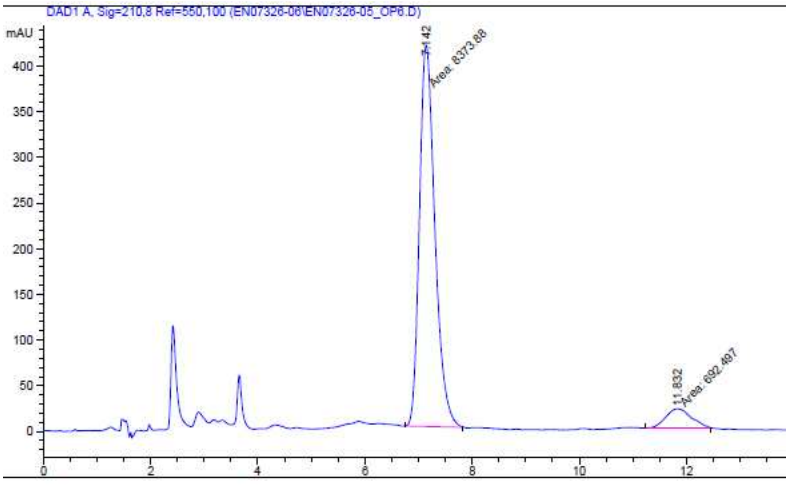
Figure 2 Chiral HPLC Chromatogram of a sample of (–)-**254** with 99:1 *er* synthesised using catalyst **201**. Peak 1 – (–)-**254**, peak 2 – (+)-**254**

Appendix 1.15 – Example Chiral HPLC chromatograms for **263**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.099	MM	0.3255	6888.65869	352.72128	50.0924
2	11.716	FM	0.5797	6863.25146	197.31129	49.9076
Totals :				1.37519e4	550.03258	

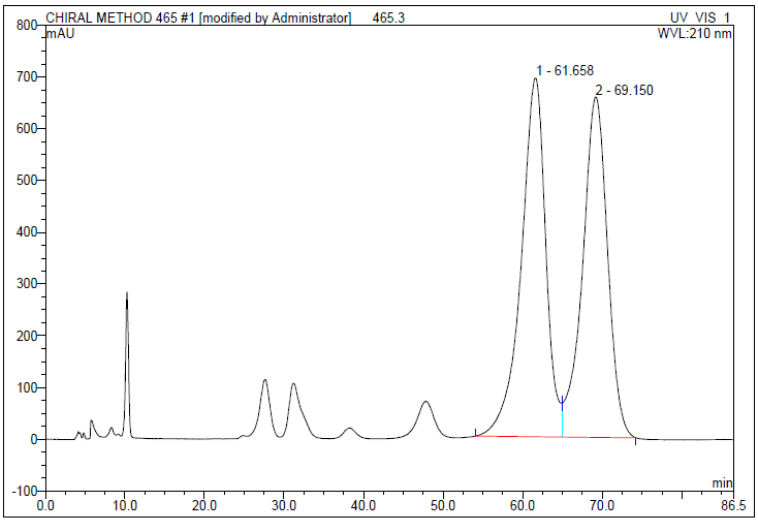
Figure 3 Chiral HPLC Chromatogram of a racemic sample of **263** synthesised using Et_3N. Peak 1 – (+)-**263**, peak 2 – (–)-**263**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.142	MM	0.3343	8373.87793	417.53110	92.3619
2	11.832	MM	0.5536	692.49683	20.84740	7.6381
Totals :				9066.37476	438.37850	

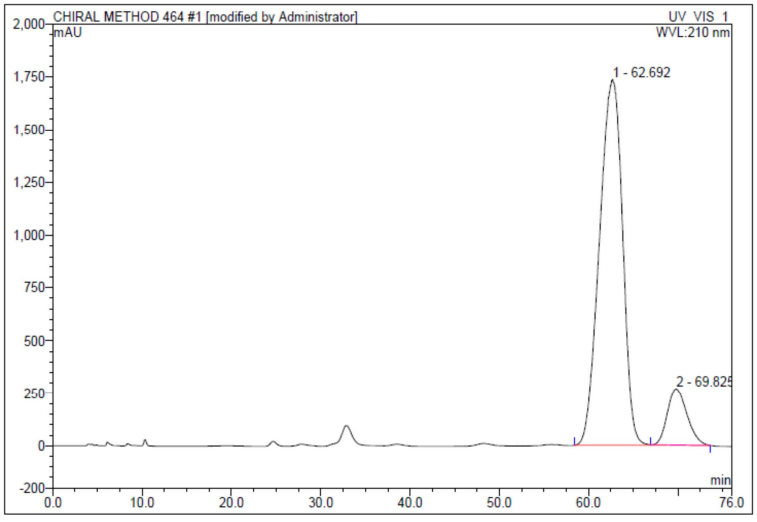
Figure 4 Chiral HPLC Chromatogram of a sample of (+)-**263** with 92:8 *er* synthesised using catalyst **201**. Peak 1 – (+)-**263**, peak 2 – (–)-**263**

Appendix 1.16 – Example Chiral HPLC chromatograms for **296**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	61.66	n.a.	693.236	2472.896	50.72	n.a.	BM
2	69.15	n.a.	657.805	2402.311	49.28	n.a.	MB*
Total:			1351.041	4875.207	100.00	0.000	

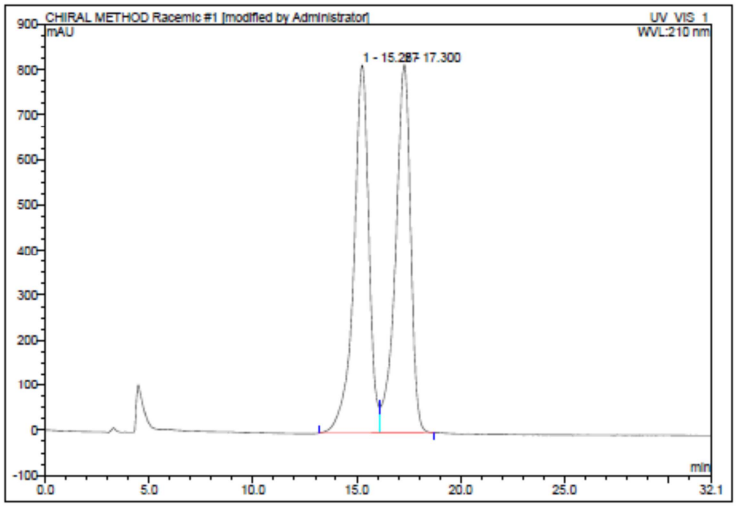
Figure 5 Chiral HPLC Chromatogram of a racemic sample of **296** synthesised using Et_3N. Peak 1 – (–)-**296**, peak 2 – (+)-**296**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	62.69	n.a.	1736.731	5204.523	88.44	n.a.	BMB
2	69.83	n.a.	268.104	680.486	11.56	n.a.	Rd
Total:			2004.835	5885.009	100.00	0.000	

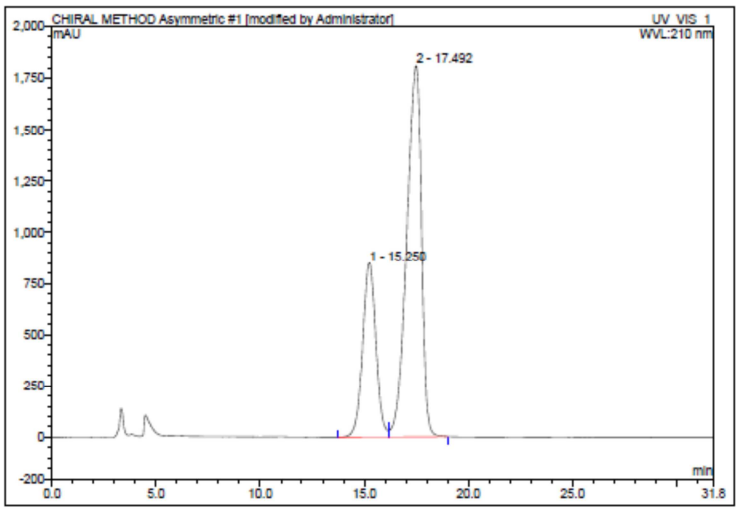
Figure 6 Chiral HPLC Chromatogram of a sample of (–)-**296** with 88:12 *er* synthesised using catalyst **201**. Peak 1 – (–)-**296**, peak 2 – (+)-**296**

Appendix 1.17 – Example Chiral HPLC chromatograms for **303**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.27	n.a.	816.612	688.946	50.04	n.a.	BM
2	17.30	n.a.	817.488	687.965	49.96	n.a.	MB
Total:			1634.100	1376.911	100.00	0.000	

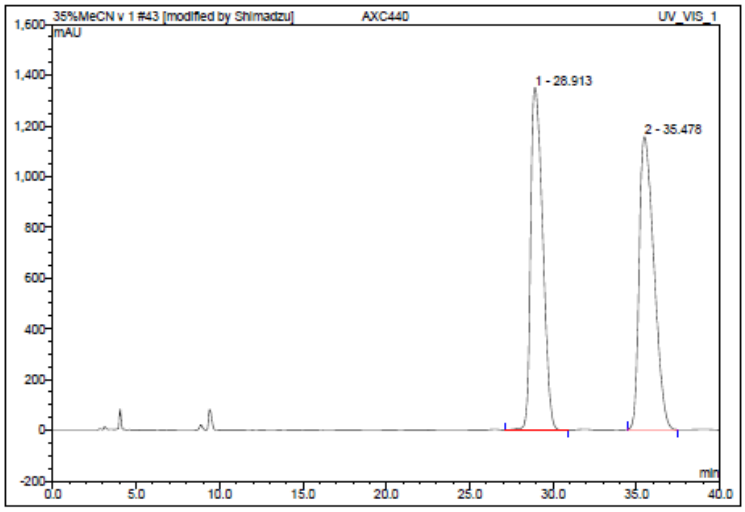
Figure 7 Chiral HPLC Chromatogram of a racemic sample of **303** synthesised using Et_3N. Peak 1 – (–)-**303**, peak 2 – (+)-**303**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.25	n.a.	849.445	627.382	29.67	n.a.	BM
2	17.49	n.a.	1808.131	1487.246	70.33	n.a.	MB
Total:			2657.576	2114.628	100.00	0.000	

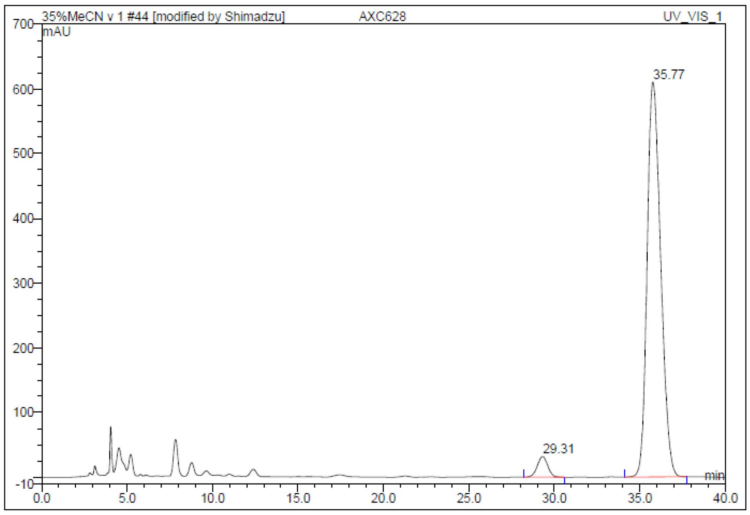
Figure 8 Chiral HPLC Chromatogram of a sample of (–)-**303** with 30:70 *er* synthesised using catalyst **201**. Peak 1 – (–)-**303**, peak 2 – (+)-**303**

Appendix 1.18 – Example Chiral HPLC chromatograms for **367**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	28.91	n.a.	1350.599	1124.992	48.68	n.a.	BMB*
2	35.48	n.a.	1155.243	1185.959	51.32	n.a.	BMB*
Total:			2505.842	2310.950	100.00	0.000	

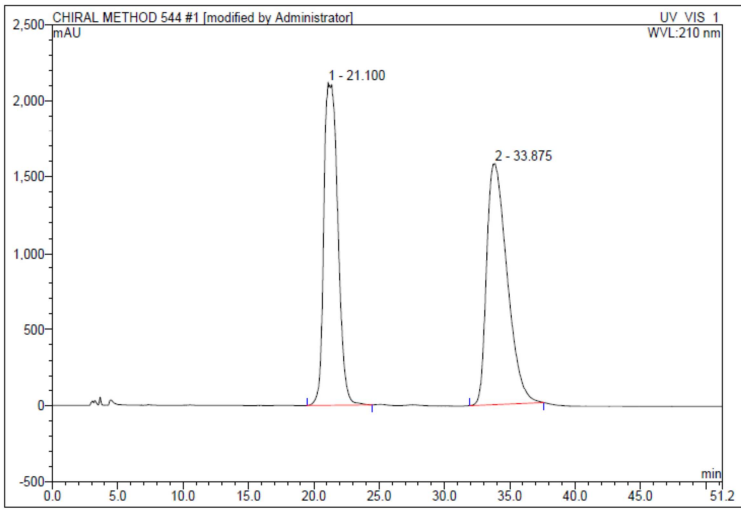
Figure 9 Chiral HPLC Chromatogram of a racemic sample of **367** synthesised using Et_3N. Peak 1 – (+)-**367**, peak 2 – (–)-**367**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.31	n.a.	31.769	22.466	3.85	n.a.	BMB
2	35.77	n.a.	610.469	561.435	96.15	n.a.	BMB
Total:			642.238	583.900	100.00	0.000	

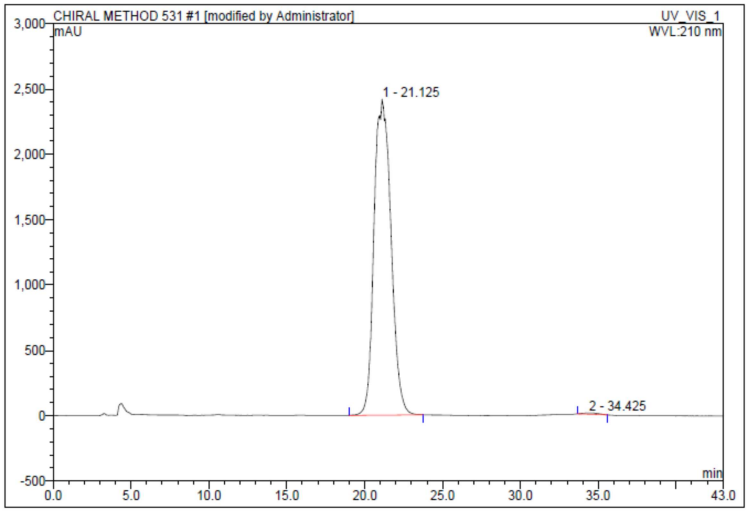
Figure 10 Chiral HPLC Chromatogram of a sample of (–)-**367** with 4:96 *er* synthesised using catalyst **201**. Peak 1 – (+)-**367**, peak 2 – (–)-**367**

Appendix 1.19 – Example Chiral HPLC chromatograms for **369**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.10	n.a.	2124.887	2636.590	47.78	n.a.	BMB*
2	33.88	n.a.	1581.904	2881.312	52.22	n.a.	BMB*
Total:			3706.791	5517.901	100.00	0.000	

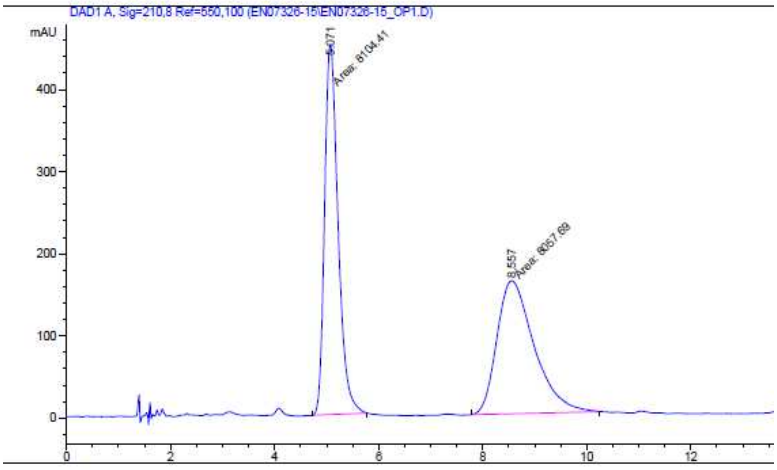
Figure 11 Chiral HPLC Chromatogram of a racemic sample of **369** synthesised using Et_3N. Peak 1 – (–)-**369**, peak 2 – (+)-**369**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.13	n.a.	2420.534	3062.573	99.61	n.a.	BMB*
2	34.43	n.a.	10.642	12.017	0.39	n.a.	BMB
Total:			2431.176	3074.591	100.00	0.000	

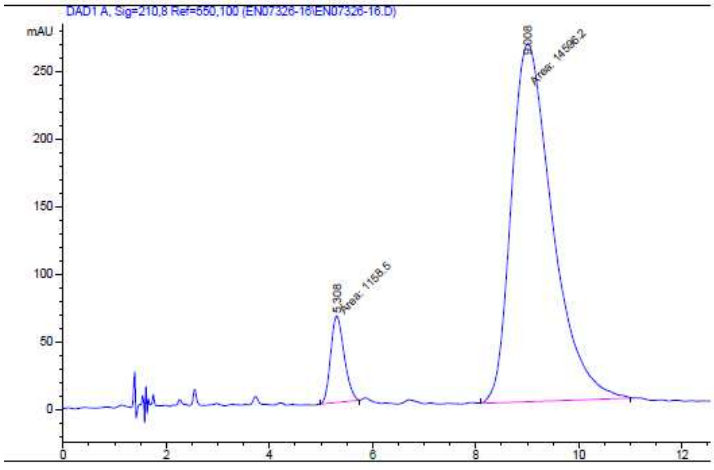
Figure 12 Chiral HPLC Chromatogram of a sample of (–)-**369** with 99:1 *er* synthesised using catalyst **201**. Peak 1 – (–)-**369**, peak 2 – (+)-**369**

Appendix 1.20 – Example Chiral HPLC chromatograms for **402**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.071	MM	0.2998	8104.40527	450.55075	50.1445
2	8.557	MM	0.8286	8057.68555	162.07368	49.8555
Totals :				1.61621e4	612.62444	

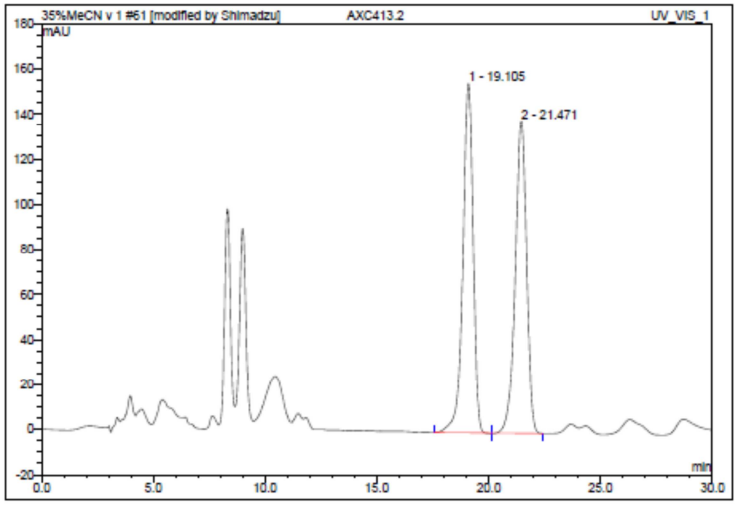
Figure 13 Chiral HPLC Chromatogram of a racemic sample of **402** synthesised using Et_3N. Peak 1 – (–)-**402**, peak 2 – (+)-**402**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.308	MM	0.3026	1158.50488	63.80057	7.3534
2	9.008	MM	0.9204	1.45962e4	264.29977	92.6466
Totals :				1.57547e4	328.10034	

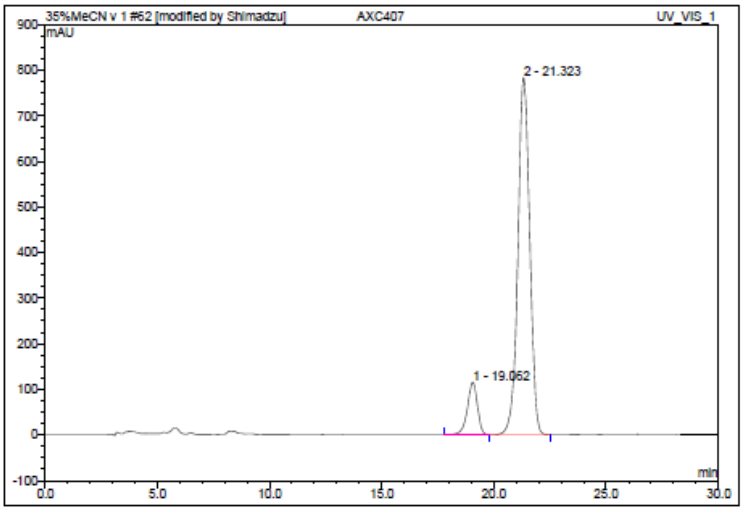
Figure 14 Chiral HPLC Chromatogram of a sample of (+)-**402** with 8:92 *er* synthesised using catalyst **210**. Peak 1 – (–)-**402**, peak 2 – (+)-**402**

Appendix 1.21 – Example Chiral HPLC chromatograms for **413**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.10	n.a.	155.125	82.959	50.40	n.a.	BM
2	21.47	n.a.	138.578	81.645	49.60	n.a.	MB
Total:			293.703	164.604	100.00	0.000	

Figure 15 Chiral HPLC Chromatogram of a racemic sample of **413** synthesised using Et_3N. Peak 1 – (+)-**413**, peak 2 – (–)-**413**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.06	n.a.	114.769	59.629	11.11	n.a.	Ru
2	21.32	n.a.	782.678	476.894	88.89	n.a.	BMB
Total:			897.447	536.524	100.00	0.000	

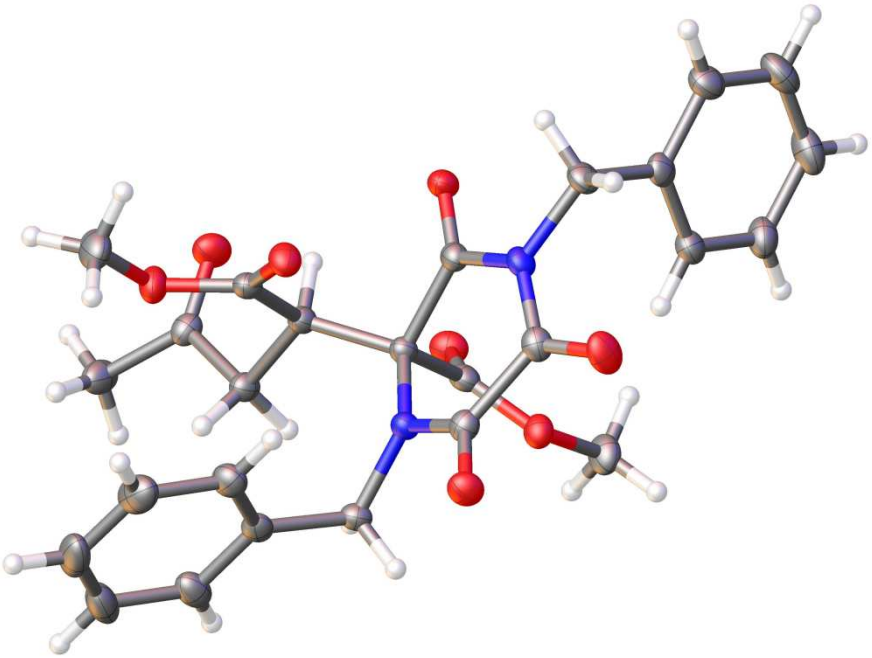
Figure 16 Chiral HPLC Chromatogram of a sample of (–)-**413** with 11:89 *er* synthesised using catalyst **201**. Peak 1 – (+)-**413**, peak 2 – (–)-**413**

Appendix 2 - X-Ray crystal structure data

The datasets for **263**, **264**, **267**, **295**, **296**, **348**, **340**, **372**, **406** and **407** were measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collections were driven and processed and absorption corrections were applied using CrysAlisPro.[184] The structures were solved using ShelXS[185] and refined by a full-matrix least-squares procedure on F^2 in ShelXL.[185] All non-hydrogen atoms were refined with anisotropic displacement parameters. Figures were produced using OLEX2.[186]

All remaining hydrogen atoms in all structures were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

Appendix 2.1 X-Ray Crystal Structure Data for Compound 263



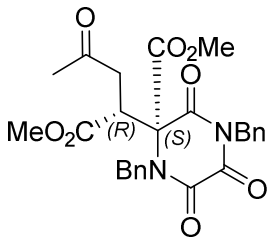


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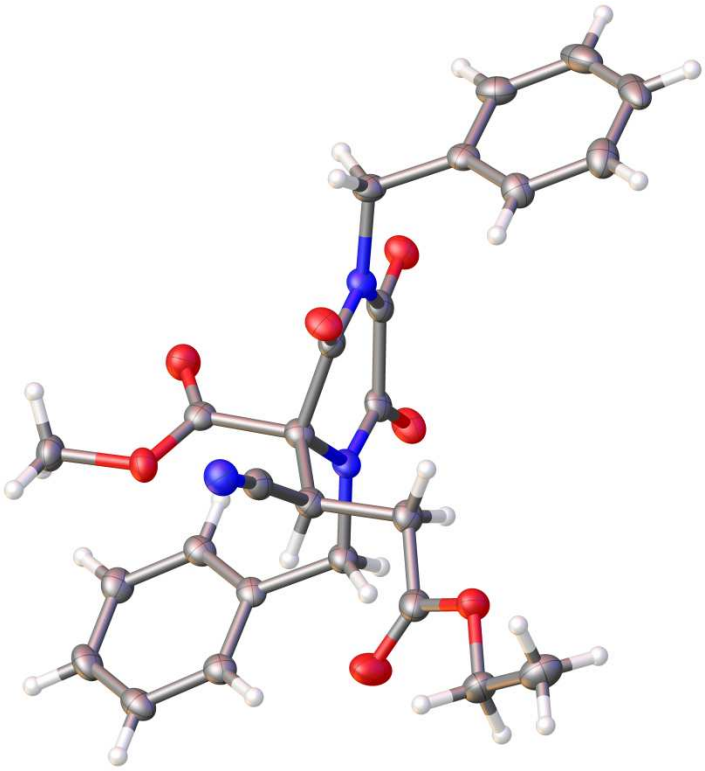
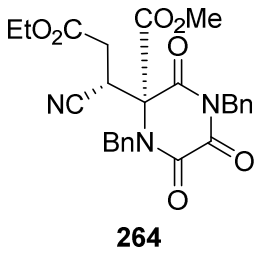
Table 1 Crystal data and structure refinement for **263**

Identification code	**263**
Empirical formula	C26 H26 N2 O8
Formula weight	494.49
Temperature	99.95(17) K
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.99873(6) Å
	b = 15.06796(11) Å
	c = 20.20372(13) Å
Volume	2435.04(3) $Å^3$

Z	4
Density (calculated)	1.349 g/cm^3
Absorption coefficient	0.843 mm^{-1}
Reflections collected	23316
Independent reflections	4908 [R(int) = 0,0284]
Final R indices [I > 2σ(I)]	R1 = 0.0254, wR2 = 0.0649
Flack parameter	-0.03(5)
Ellipsoid probability	50%

Appendix 2.2 X-Ray Crystal Structure Data for Compound 264





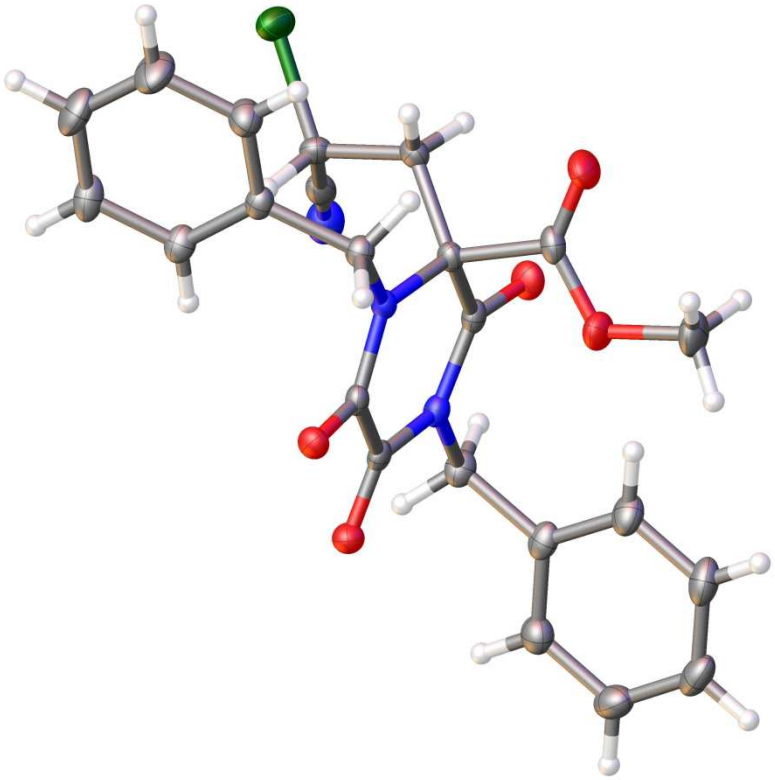
264

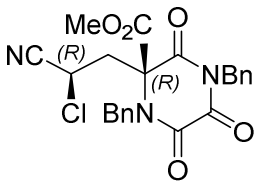
Table 2 Crystal data and structure refinement for **264**

Identification code	**264**	
Empirical formula	C26 H25 N3 O7	
Formula weight	491.49	
Temperature	99.98(13) K	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 8.38756(14) Å	
	b = 27.5099(4) Å	β = 94.2738(13)°

	c = 10.06135(13) Å
Volume	2315.11(6) $Å^3$
Z	4
Density (calculated)	1.410 g/cm^3
Absorption coefficient	0.864 mm^{-1}
Reflections collected	12511
Independent reflections	4156 [R(int) = 0,0215]
Final R indices [I > 2σ(I)]	R1 = 0.0461, wR2 = 0.1212
Ellipsoid probability	50%

Appendix 2.3 X-Ray Crystal Structure Data for Compound 267





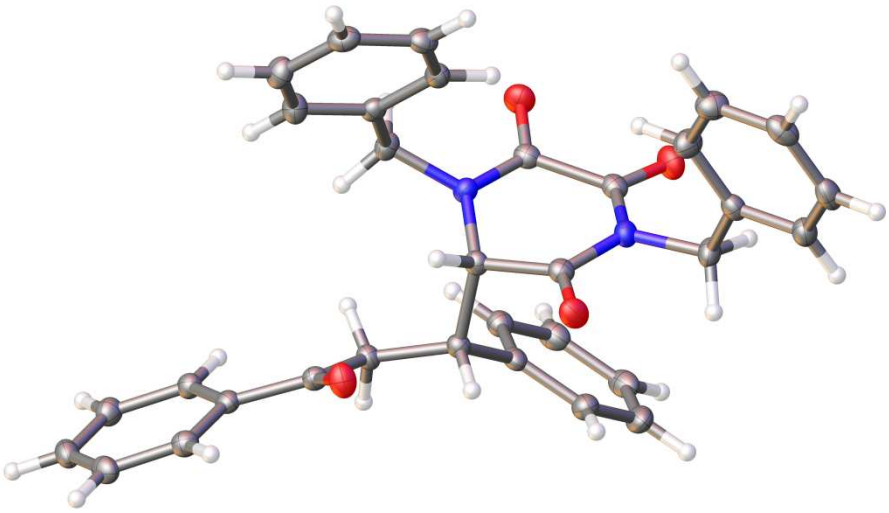
267

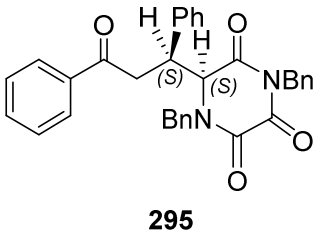
Table 3 Crystal data and structure refinement for **267**

Identification code	**267**
Empirical formula	C23 H20 Cl N3 O5
Formula weight	453.87
Temperature	100.0(2) K
Crystal system	Monoclinic
Space group	I2
Unit cell dimensions	a = 13.6988(3) Å

	b = 7.7497(2) Å	β = 101.8198(19)°
	c = 20.8571(4) Å	
Volume	2167.29(8) $Å^3$	
Z	4	
Density (calculated)	1.391 g/cm^3	
Absorption coefficient	1.912 mm^{-1}	
Reflections collected	18477	
Independent reflections	3833 [R(int) = 0,0405]	
Final R indices [I > 2σ(I)]	R1 = 0.0293, wR2 = 0.0774	
Flack parameter	0.010(8)	
Ellipsoid probability	50%	

Appendix 2.4 X-Ray Crystal Structure Data for Compound 295





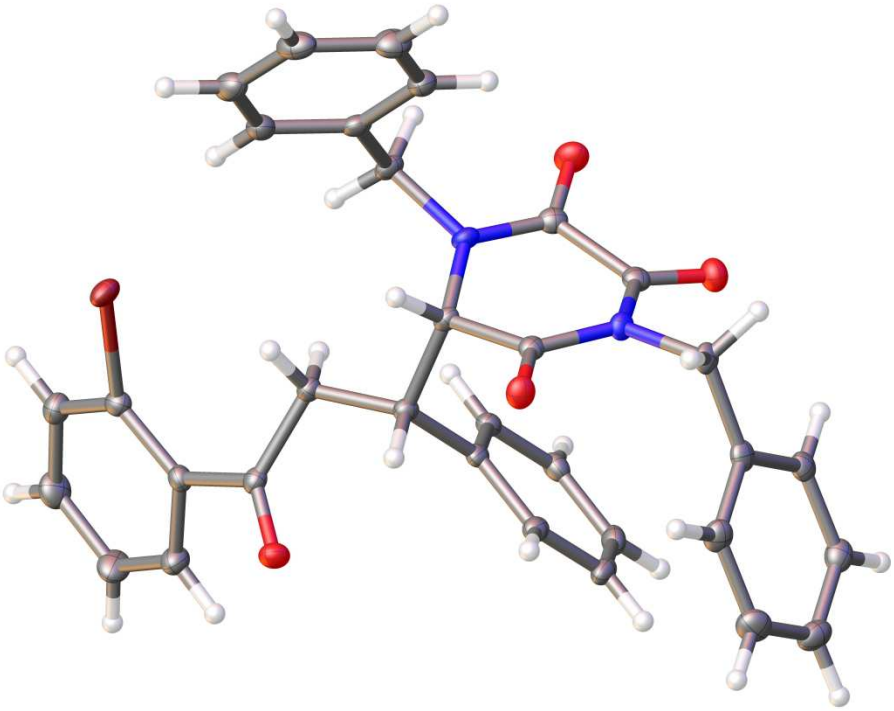
295

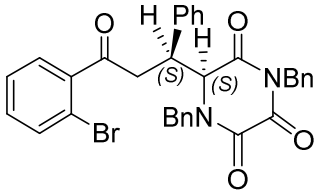
Table 4 Crystal data and structure refinement for **295**

Identification code	**295**
Empirical formula	C33 H28 N2 O4
Formula weight	516.57
Temperature	100.01(10) K
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 12.1648(1) Å
	b = 12.4912(1) Å
	c = 17.1070(2) Å
Volume	2599.46(4) $Å^3$
Z	4
Density (calculated)	1.320 g/cm^3

Absorption coefficient	0.700 mm^{-1}
Reflections collected	24936
Independent reflections	5250 [R(int) = 0,0219]
Final R indices [I > 2σ(I)]	R1 = 0.0243, wR2 = 0.0629
Flack parameter	-0.01(4)
Ellipsoid probability	50%

Appendix 2.5 X-Ray Crystal Structure Data for Compound 296





296

Table 5 Crystal data and structure refinement for **296**

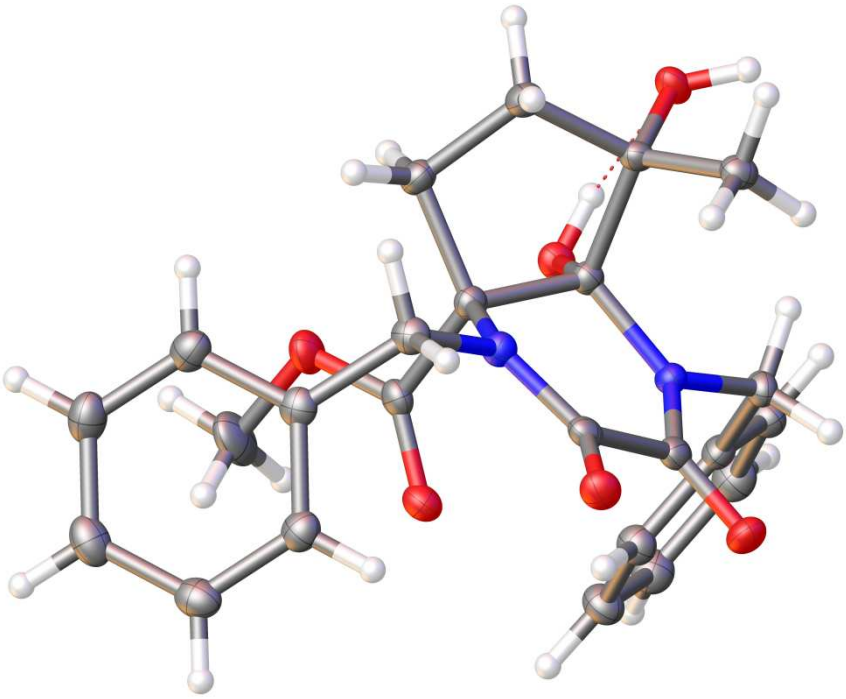
Identification code	**296**	
Empirical formula	C33 H27 Br N2 O4	
Formula weight	595.47	
Temperature	100.01(10) K	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.71430(10) Å	
	b = 22.59340(10) Å	β = 106.7030(10)°
	c = 12.66410(10) Å	
Volume	2662.23(4) $Å^3$	

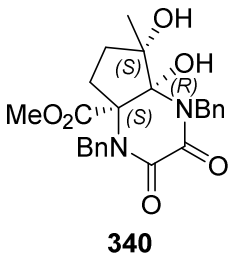
Z	4
Density (calculated)	1.486 g/cm^3
Absorption coefficient	2.456 mm^{-1}
Reflections collected	50958
Independent reflections	10745 [R(int) = 0,0250]
Final R indices [I > 2σ(I)]	R1 = 0.0185, wR2 = 0.0477
Flack parameter	-0.027(3)
Ellipsoid probability	50%

Note:

In **296** there are two crystallographically-independent molecules present.

Appendix 2.6 X-Ray Crystal Structure Data for Compound 340





340

Table 6 Crystal data and structure refinement for **340**

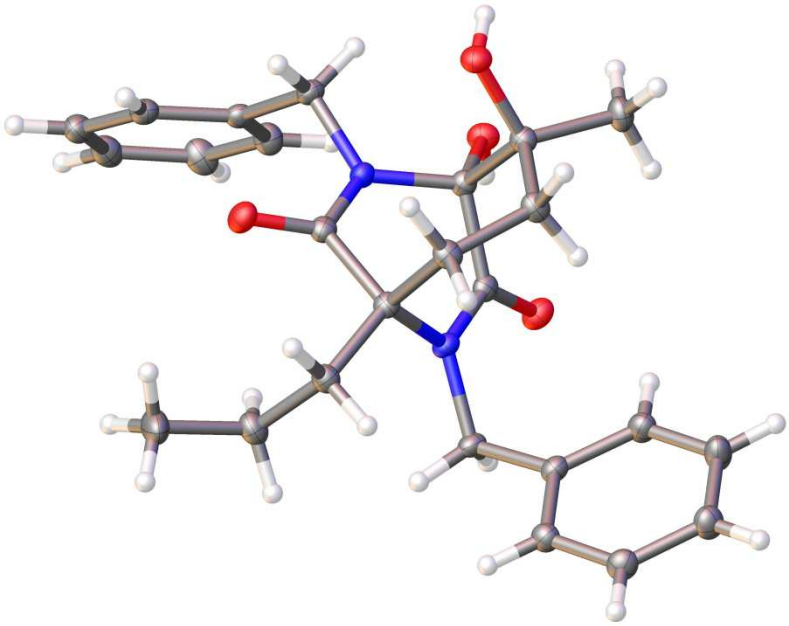
Identification code	**340**	
Empirical formula	C24 H26 N2 O6	
Formula weight	438.47	
Temperature	100.01(10) K	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.97919(10) Å	
	b = 13.10046(15) Å	β = 107.9910(12)°
	c = 9.53352(11) Å	
Volume	1066.61(2) $Å^3$	

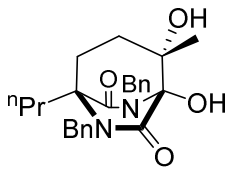
Z	2
Density (calculated)	1.365 g/cm^3
Absorption coefficient	0.815 mm^{-1}
Reflections collected	20053
Independent reflections	4119 [R(int) = 0.0175]
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0242, wR2 = 0.0619
Flack parameter	-0.01(4)
Ellipsoid probability	50%

Note:

In **340** the hydrogen atoms bonded to O(5) and O(24) were located in the electron density and refined freely.

Appendix 2.7 X-Ray Crystal Structure Data for Compound 348





348

Table 7 Crystal data and structure refinement for **348**

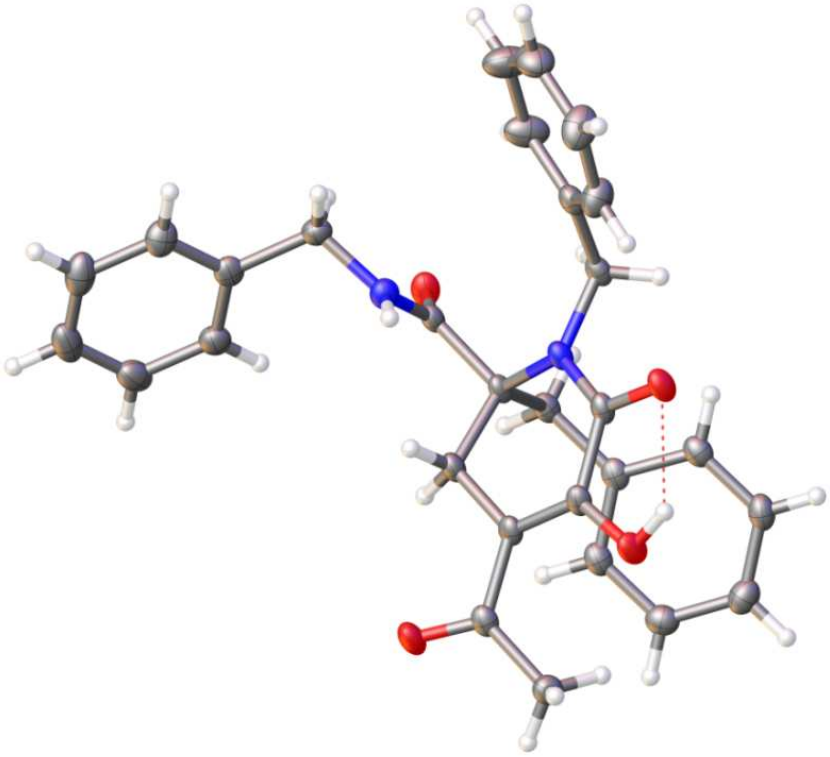
Identification code	**348**	
Empirical formula	C25 H30 N2 O4	
Formula weight	422.51	
Temperature	100.00(10) K	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.28524(10) Å	
	b = 16.44821(13) Å	β = 98.0951(9)°
	c = 10.90880(11) Å	
Volume	2182.38(3) $Å^3$	

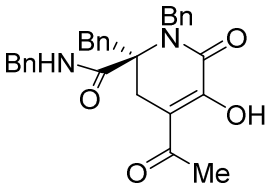
Z	4
Density (calculated)	1.286 g/cm^3
Absorption coefficient	0.702 mm^{-1}
Reflections collected	40678
Independent reflections	4438 [R(int) = 0,0274]
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0346, wR2 = 0.0915
Ellipsoid probability	50%

Note:

In **348** the hydrogen atoms bonded to O(5) and O(24) were located in the electron density and refined freely.

Appendix 2.8 X-Ray Crystal Structure Data for Compound 372





372

Table 8 Crystal data and structure refinement for **372**

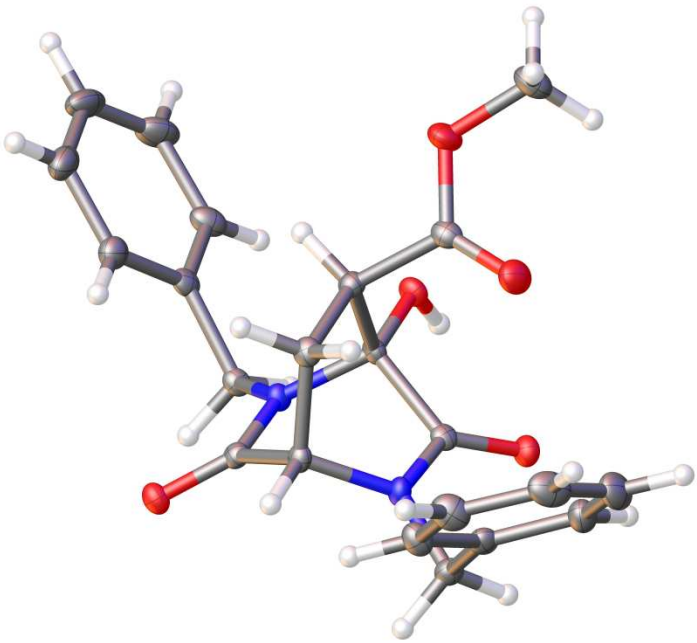
Identification code	**372**	
Empirical formula	C29 H28 N2 O4	
Formula weight	468.53	
Temperature	100.00(10) K	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 12.3676(3) Å	
	b = 23.5052(5) Å	β = 110.221(3)°
	c = 17.6271(4) Å	

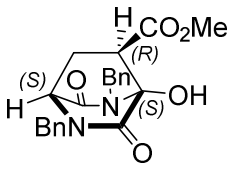
Volume	4808.4(2) $Å^3$
Z	8
Density (calculated)	1.294 g/cm^3
Absorption coefficient	0.697 mm^{-1}
Reflections collected	19259
Independent reflections	8606 [R(int) = 0,0285]
Final R indices [I > 2σ(I)]	R1 = 0.0410, wR2 = 0.1036
Ellipsoid probability	50%

Note:

In **372** the hydrogen atoms bonded to O(5), N(4), O(105), N(104) were located in the electron density and refined freely. There are two crystallographically-independent molecules present.

Appendix 2.9 X-Ray Crystal Structure Data for Compound 406





406

Table 9 Crystal data and structure refinement for **406**

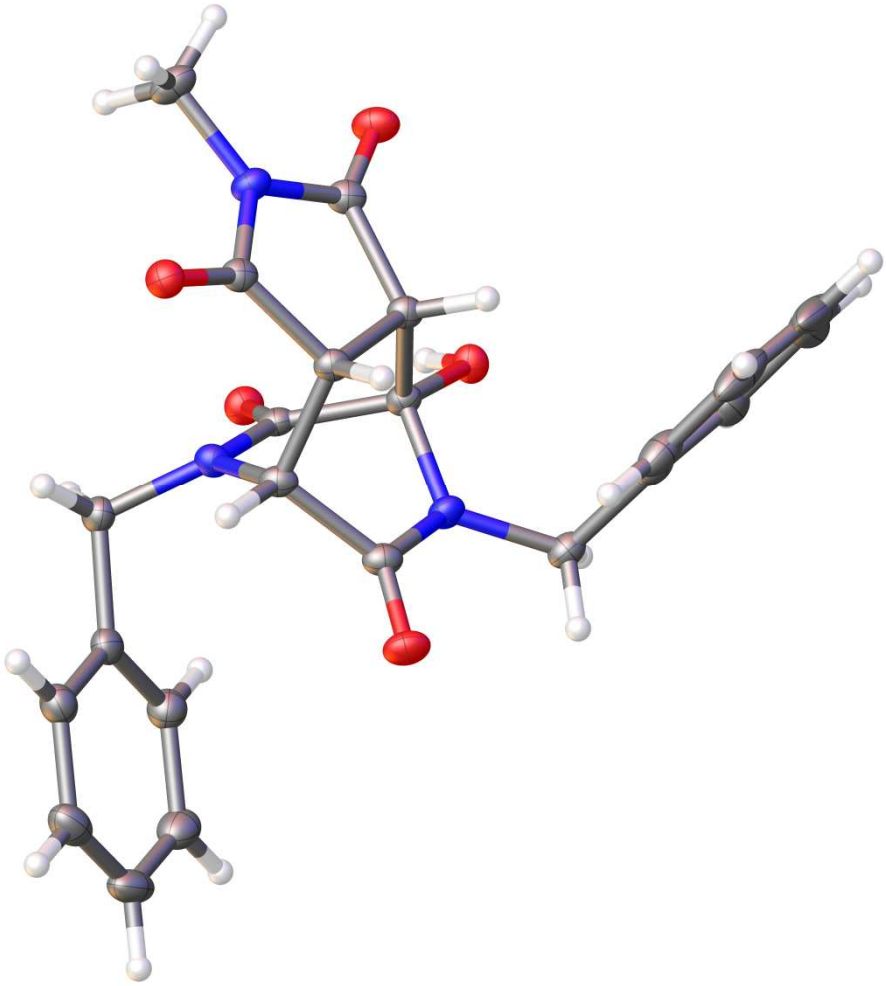
Identification code	**406**	
Empirical formula	C22 H22 N2 O5	
Formula weight	394.41	
Temperature	100.01(13) K	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.14306(17) Å	
	b = 6.28576(7) Å	β = 108.5659(17)°
	c = 13.0165(2) Å	

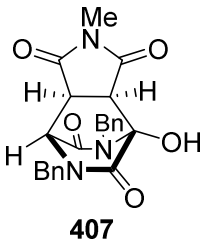
Volume	941.82(2) $Å^3$
Z	2
Density (calculated)	1.391 g/cm^3
Absorption coefficient	0.819 mm^{-1}
Reflections collected	16277
Independent reflections	3748 [R(int) = 0,0386]
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0281, wR2 = 0.0706
Flack parameter	0.04(8)
Ellipsoid probability	50%

Note:

In **406** the hydrogen atom belonging to the hydroxyl group O(2) was located in the electron density and freely refined.

Appendix 2.10 X-Ray Crystal Structure Data for Compound 407





407

Table 10 Crystal data and structure refinement for **407**

Identification code	**407**
Empirical formula	C23 H21 N3 O5
Formula weight	419.43
Temperature	100.00(13) K
Crystal system	Monoclinic

Space group	$P2_1/n$	
Unit cell dimensions	a = 9.9694(2) Å	
	b = 18.7511(2) Å	β = 107.007(2)°
	c = 10.9554(2) Å	
Volume	1958.41(6) $Å^3$	
Z	4	
Density (calculated)	1.423 g/cm^3	
Absorption coefficient	0.842 mm^{-1}	
Reflections collected	12752	
Independent reflections	3677 [R(int) = 0,0300]	
Final R indices [I > 2σ(I)]	R1 = 0.0368, wR2 = 0.0936	
Ellipsoid probability	50%	

Note:

In **407** The hydroxyl hydrogen atom belonging to O(3) was located in the electron density and the position refined freely while the isotropic displacement parameter was based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

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