An Organocatalytic Asymmetric Approach to Chiral Proline Derived Diketopiperazines Related to the Prenylated Indole Alkaloid Family

Matthew Rees

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School of Chemistry

College of Engineering and Physical Sciences

University of Birmingham

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Abstract

The prenylated indole alkaloids are a large family of natural products that have been isolated from various marine and terrestrial strains of *Penicillium, Aspergillus* and *Malbranchea* fungi. These compounds possess complex polycyclic structures including a characteristic bicyclo[2.2.2]diazaoctane core and have displayed wide-ranging biological activities. Chapter 1 gives an introduction to the prenylated indole alkaloids and important synthetic strategies to the key bicyclic core. Also included in this Chapter is an overview of previous work from our research group towards members of the natural product family as well as more recent work focused on asymmetric organocatalytic reactions of related diketopiperazines and triketopiperazines.

Recent work showed that triketopiperazines will undergo highly enantioselective Michael-additions and Michael addition–ring-closure reactions, efficiently generating compounds possessing the bicyclo[2.2.2]diazaoctane core found in the natural products. Chapter 2 discusses the extension of previous methodology towards a bicyclic triketopiperazine derived from proline including its synthesis and successful implementation in asymmetric Michael additions.

Chapter 3 then explores the Michael addition–ring-closure of the proline derived triketopiperazine which was found to give highly enantioselective and high yielding access to hydroxy diketopiperazines possessing the key bicyclo[2.2.2]diazaoctane. The Chapter also contains further transformations towards the natural product scaffold including a radical Barton-McCombie deoxygenation.

Chapter 4 focusses on a novel Michael–Michael cascade strategy for the synthesis of molecules possessing the bicyclo[2.2.2]diazaoctane core of the prenylated indole alkaloids.

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Glossary of Abbreviations

Ac	Acetyl
acac	Acetylacetonate
ACCN	1,1′-Azobis(cyclohexanecarbonitrile)
AIBN	Azobisisobutyronitrile
Ar	Aryl
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
BOM	Benzyloxymethyl acetal
Bu	Butyl
Bz	Benzoyl
Bzt	Benzotriazole
CAN	Cerium ammonium nitrate
cat	Catalyst
Cbz	Benzyloxycarbonyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisopropyl aluminium hydride
DIPEA	Diisopropyl amine
DKP	Diketopiperazine
DMAP	4-Dimethyl aminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMS	Dimethylsulfide
dr	Diastereomeric ratio
er	Enantiomeric ratio
Et	Ethyl
EWG	Electron withdrawing group
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b] pyridinium 3-oxid hexafluorophosphate
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HPLC	High pressure liquid chromatography
Im	Imidazole
IMDA	Intramolecular Diels–Alder
LDA	Lithium diisopropylamine
mCPBA	meta-Chloroperoxybenzoic acid

Me	Methyl
Ms	Methyl sulfonyl
μwave	Microwave
Napth	Naphthalene
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
[O]	Oxidation/oxidising agent
Ph	Phenyl
PHN	Phenanthryl
PMB	Paramethoxybenzyl
Pr	Propyl
Qd	Quinidine
Qn	Quinine
SEM	2-(Trimethylsilyl)ethoxymethyl
TBAF	Tetrabutylammonum fluoride
TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacid acid/acetate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Toluenesulfonyl
TTMSS	Tris(trimetylsilyl) silane
UV	Ultraviolet

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Chapter One – Introduction to the Prenylated Indole Alkaloids

Isolation and Background

The prenylated indole alkaloids are a large and structurally diverse family of natural products that have been isolated from various marine and terrestrial strains of *Penicillium*, *Aspergillus* and *Malbranchea* fungi.[1] These mycotoxins generally possess a characteristic bicyclo[2.2.2]diazaoctane core, in the form of a bridged diketopiperazine (DKP) or partially reduced variant. The complex polycyclic structures and varied biological activities have been significant in the continued research interest of these compounds.[2] Since the isolation of brevianamide A **1** in 1969 by Birch and co-workers, over 80 members of the prenylated indole alkaloid family have been reported with taichunamide A **9** and peniciherquamide A **10** being recent examples (Figure 1).[3–5]

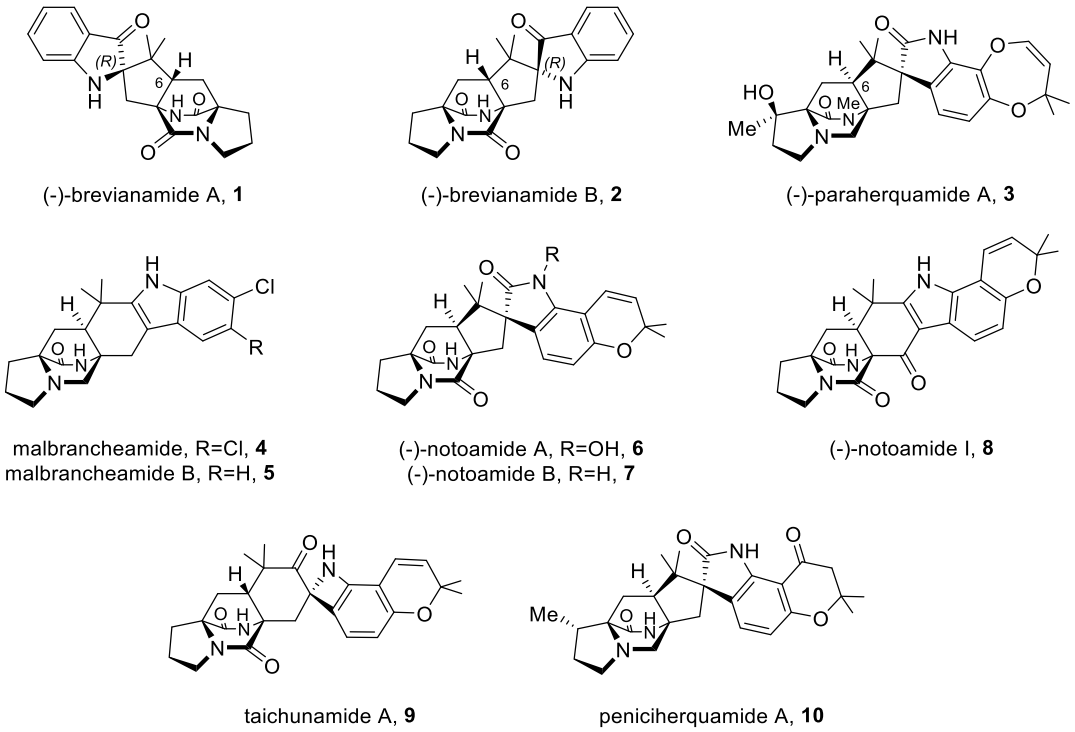


Figure 1 – Examples of prenylated indole alkaloids

Over eight different families of secondary metabolites possessing the bicyclo[2.2.2]diazaoctane core have been reported and members can be more generally grouped as having either spiro or fused skeletons as shown by brevianamide A **1** and malbrancheamide **4** respectively.[1] The prenylated indole alkaloids display complex structural diversity as demonstrated by the examples above, for instance brevianamide A and B (**1** and **2**) are enantiomorphic with respect to the bridged DKP core but the stereochemistry of the spiro-oxindole moieties are consistent. Additionally, other members of the family have been isolated from different fungal strains in either enantiomeric series, such as notoamide B **7**.[6] Other areas of stereocomplexity include C-6 which can be either *syn*- or *anti*- to the pyrrolidine nitrogen, and the presence of functionalised pyrrolidine rings as in paraherquamide A **3**. Modified indoles, or oxindoles, are also found with chlorinated examples such as malbrancheamide and malbrancheamide B (**4** and **5**) or with a pyran or 7-membered ring as in notoamides **6**–**8** and paraherquamide A **3** respectively.[7–9]

Related natural product families include the marcfortines **11**–**12** and chysogenamide A **13**, that bear a piperidine ring derived from pipecolic acid, or methylated piperidine, rather than the usual proline derived pyrrolidine fused structures. Additional related natural products include the asperparilines, **14** and **15**, which possess a spiro-succinimide rather than an indole or oxindole moiety (Figure 2).[10–12]

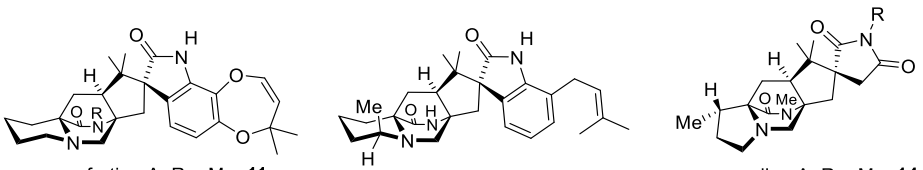


Figure 2 – Prenylated indole alkloids with strucutral differences

The discovery of stephacidin A **16**, avrainvillamide **17** and its dimer stephacidin B **18** spurred further global activity due to the moderate biological activities displayed by these compounds against several cancer cell lines including LNCaP (prostate cancer) and the molecular complexity of stephacidin B **18** (Figure 3).[13]

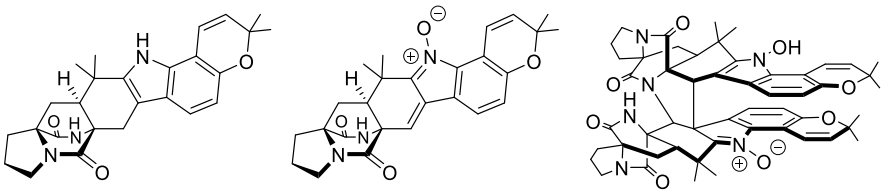
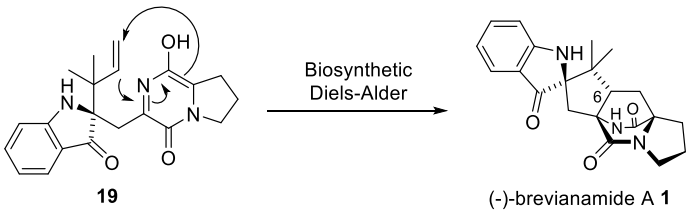


Figure 3 – Stephacidins and avrainvillamide

Despite the structural diversity observed of the compounds shown above, as previously mentioned, they all possess a common bicyclo[2.2.2]diazaoctane core. It has been proposed by the groups of Sammes and Birch that this key bicyclic moiety is formed biosynthetically through a hetero-Diels–Alder reaction (Scheme 1).[14]



Scheme 1 – Proposed biosynthetic Diels–Alder to form the bicyclo[2.2.2]diazaoctane core

Although the reactivity of the unactivated dienophile was initially questioned, significant research has been conducted in support of a biosynthetic Diels–Alder reaction by Williams and co-workers, who have spearheaded research on the prenylated indole alkaloids.

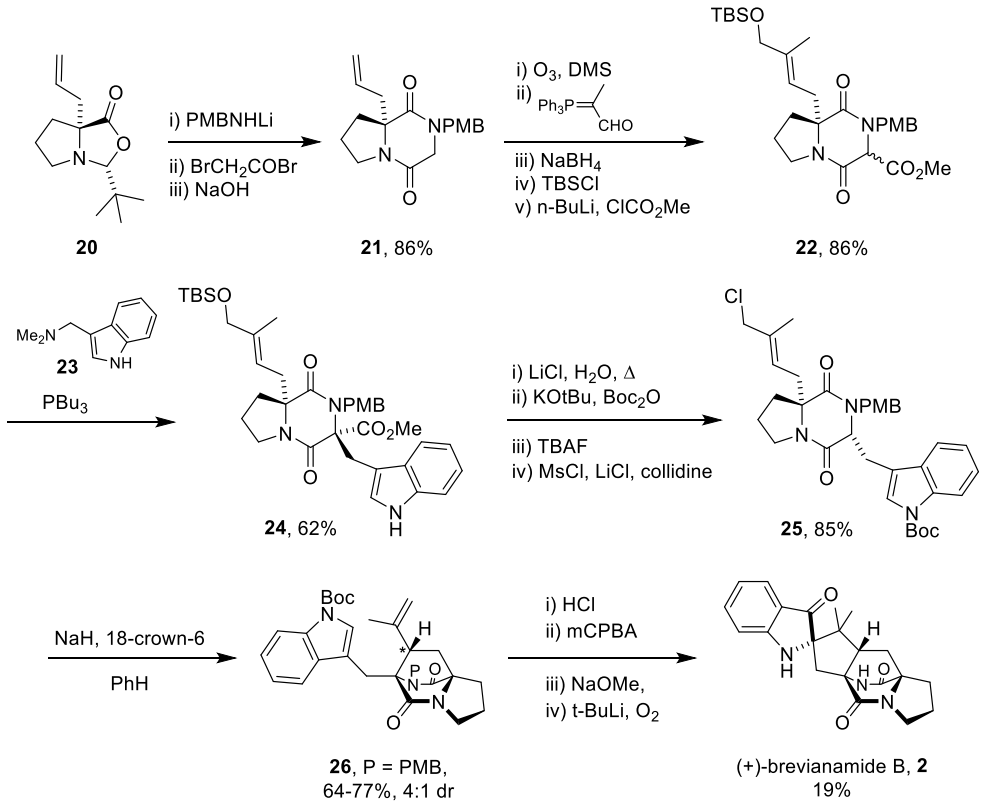
Notable Synthetic Strategies for the Formation of the Bicyclo[2.2.2]diazaoctane Core Towards Members of the Prenylated Indole Alkaloids

Over the past few decades since the first reported synthesis of brevianamide B **2** in 1988, 19 years after its discovery, many syntheses of members of the prenylated indole alkaloids and related compounds bearing the bicyclo[2.2.2]diazaoctane core have been published.[2] Various synthetic strategies have been developed

for the synthesis of the key bicyclic core by multiple research groups including the Simpkins group and a selection of the notable synthetic methods will be discussed in this Chapter.

Intramolecular S_N2' Cyclisation

As mentioned above the Williams research group has spearheaded efforts towards the prenylated indole alkaloids and reported the first synthesis of a member of this natural product family using an intramolecular S_N2' cyclisation to generate brevianamide B **2** (Scheme 2).[15]

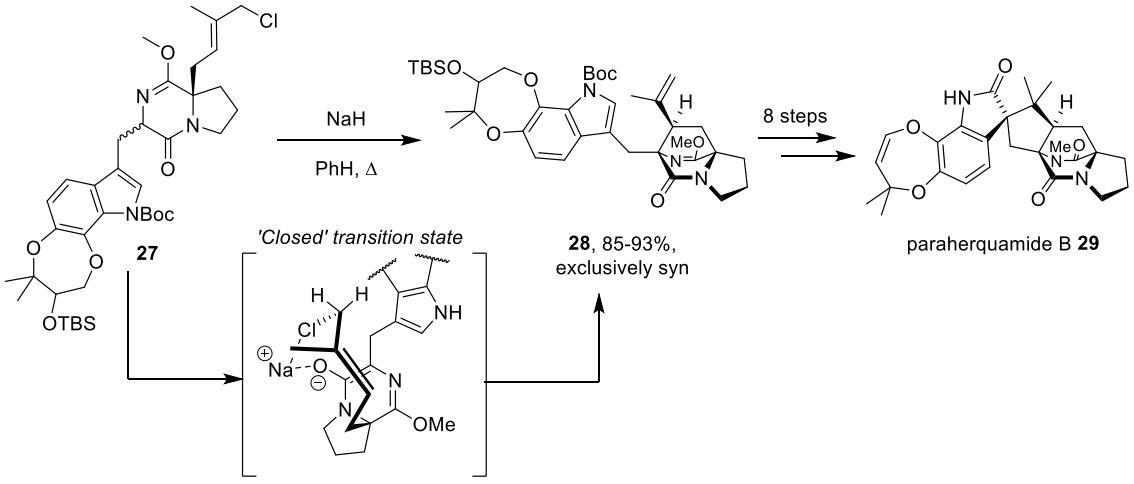


Scheme 2 – Williams total synthesis of brevianamide B using an intramolecular S_N2' cyclisation

Seebach acetal **20** was converted to allylated DKP **21** through nucleophilic ring opening followed by acylation and ring closure. Oxidative cleavage of the alkene using ozone, followed by Wittig olefination, reduction of the aldehyde, TBS protection of the primary alcohol and quenching of the DKP enolate with methyl chloroformate gave adduct **22**. Coupling of adduct **22** with gramine **23**, using tributyl phosphine,

afforded indole adduct **24** before ester removal, Boc protection, TBS removal and chloride displacement gave key intermediate **25**. It was found that the conditions for the S_N2' cyclisation dramatically influenced the reaction outcome; NaH in DMF gave adduct **26** in 62% yield and in a 2:1 dr, whereas NaH in benzene was found to favour the syn-isomer in 82% and 3:97 dr and the best conditions for the anti-isomer were found to be NaH in benzene with 18-crown-6. It was proposed that crown ether stabilisation of the enolate creates an unfavourable steric interaction between the sodium enolate and chloride disfavouring association of the two groups during the transition state. Treatment of cyclised adduct **26** with concentrated HCl resulted in indole deprotection and indole-olefin cyclisation. Oxidation using mCPBA and then treatment with NaOMe generated the spiro-oxindole moiety before removal of the PMB group gave brevianamide B **2**.

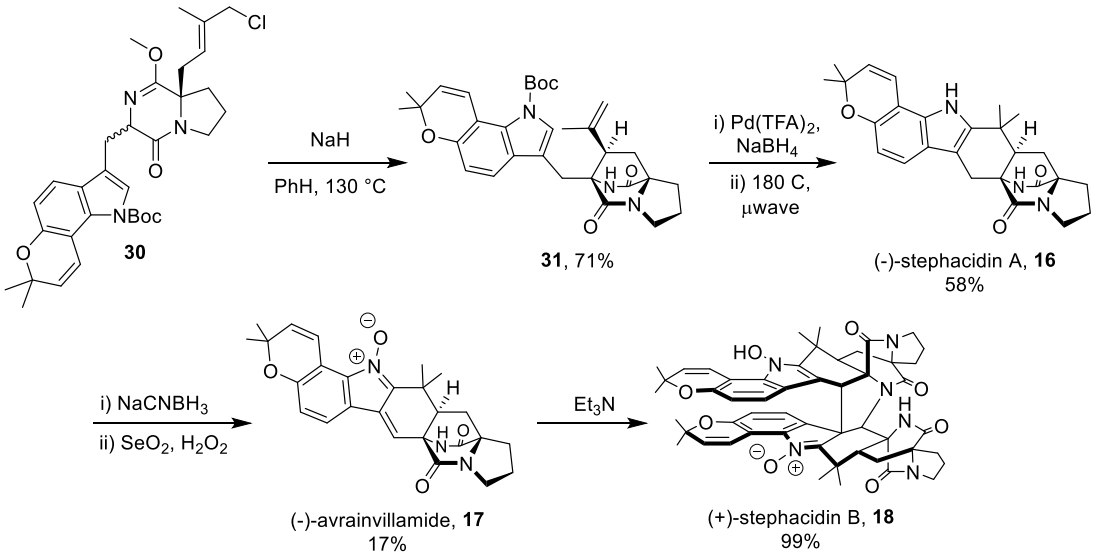
The S_N2' cyclisation strategy was also used to synthesise paraherquamide B **29,** this time using the syn-selective conditions found during the synthesis of brevianamide B **2** (Scheme 3).[16]



Scheme 3 – Williams synthesis of paraherquamide B **29**

Adduct **27** was prepared in a similar method to adduct **25** above and cyclisation through a proposed 'closed' transition state gave compound **28** as a single epimer in excellent yields. Conversion of cyclisation product **28** to paraherquamide B **29** was then completed in 8 steps.

Furthermore, the S_N2' cyclisation strategy was also used to synthesise stephacidin A **16**, avrainvillamide **17** and stephacidin B **18** (Scheme 4).[17]



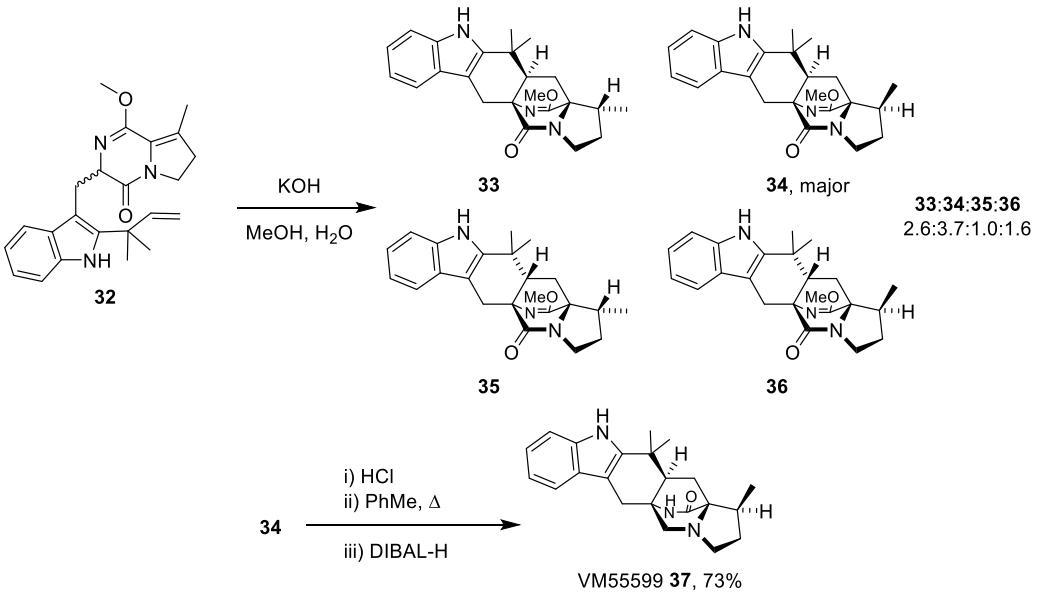
Scheme 4 – Williams synthesis of Stephacidins and avrainvillamide using S_N2' cyclisation

Intramolecular S_N2' cyclisation of allylic chloride **30** gave adduct **31** in good yield with excellent syn selectivity again thought to be due to a 'closed' transition state. Unlike with brevianamide B **2** acidic conditions could not be used for the indole deprotection and cyclisation towards stephacidin A **16** due to the instability of the pyran ring to those conditions. An alternative palladium mediated cyclisation and thermal deprotection of the indole were instead used and afforded stephacidin A **16** in good yield. Avrainvillamide **17** was generated following a previously reported reduction-oxidation procedure and dimerisation using triethylamine gave stephacidin B **18** in excellent yield.

Intramolecular Diels–Alder

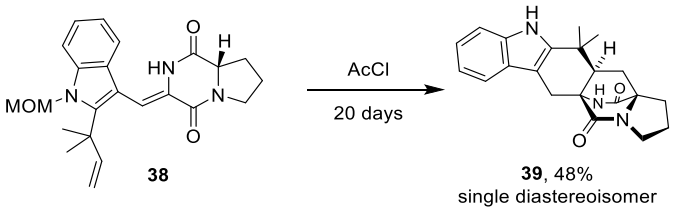
A biomimetic intramolecular Diels–Alder (IMDA) was first employed by Williams and co-workers in the synthesis of brevianamide B **2** and was used soon after for the synthesis of VM55599 **37** (Scheme 5).[18,19] Tautomerisation of adduct **32** to the azadiene is expected under basic conditions allowing the IMDA to

occur. In this case a mixture of all four possible diastereoisomers were obtained with the major product being desired epimer **34** which was converted to VM55599 **37** in good yield.



Scheme 5 – Williams IMDA synthesis of VM55599 **37**

In contrast to the base mediated IMDA, Liebscher and co-workers reported an alternative neutral IMDA cyclisation that displayed excellent diastereocontrol (Scheme 6).[20]



Scheme 6 – Liebscher neutral conditions for IMDA

These neutral conditions where then used by Williams to synthesis VM55599 **37** enantioselectively since the stereochemistry of the β-methyl is retained.[21]

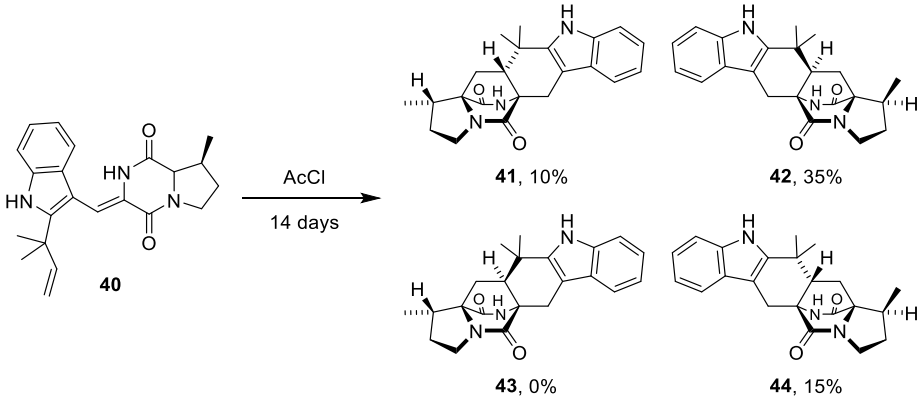
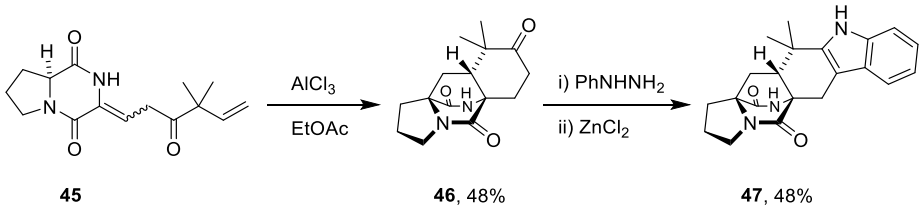


Figure 4 – IMDA under neutral conditions

The IMDA cyclisation of adduct **40** gave a mixture of three of the four possible diastereoisomers and epimer **42** was then reduced using DIBAL-H to give (-)-VM55599 **37** in 68% yield.

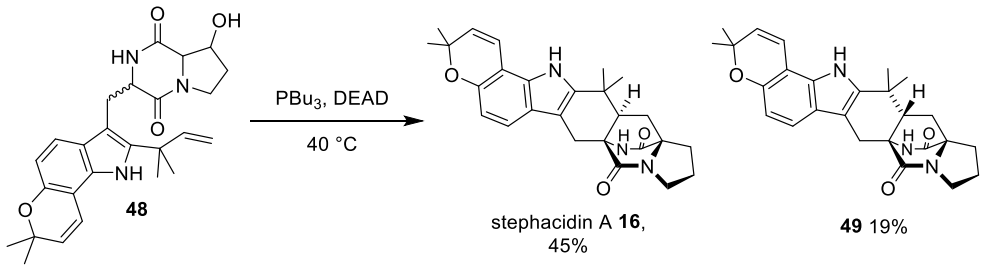
Since the prenylated indole alkaloids share the characteristic bicyclo[2.2.2]diazaoctane core it was envisioned that a common intermediate could be generated to allow divergent access to members of the family. With this in mind ketone **46** was generated using similar methodology to that above and was converted to adduct **47** using phenyl hydrazine and zinc chloride in a Fischer indole synthesis.[22]



Scheme 7 – $AlCl_3$ IMDA and Fischer indole synthesis

Adduct **47** can then be converted to brevianamide B **2** using previously reported oxidative conditions to generate the oxindole moiety. This methodology was found to only give the anti-epimer in contrast to the mixtures of syn- and anti-epimers above, however it was limited by the anti-selectivity and the harsh conditions.

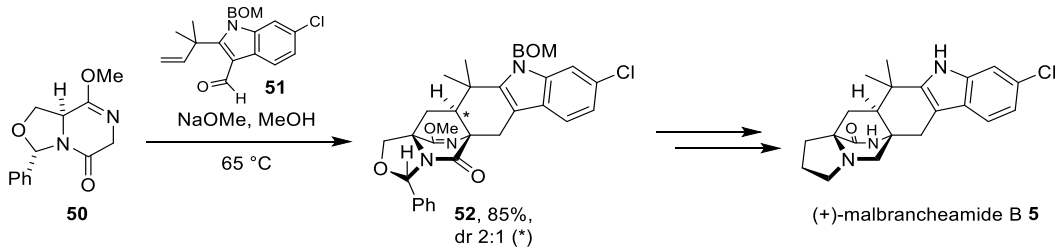
Williams and co-workers additionally found that hydroxy prolines such as **48** were suitable reagents for the IMDA reaction, using excess tributyl phosphine and diethyl azodicarboxylate (DEAD) to form the azadiene through dehydration and tautomerisation.[23]



Scheme 8 – PBu_3/DEAD synthesis of stephacidin A **16**

It was found that both tributyl phosphine and DEAD were required for the IMDA to proceed and a proton chaperone mechanism was proposed.[24]

Scheerer and co-workers have since reported a diastereoselective domino reaction featuring an IMDA by incorporating an endogenous stereocentre in the form of a chiral DKP. This methodology afforded an excellent diastereoselectivity of 95:5 when used on a model system only. Use of this methodology allowed the enantioselective synthesis of (+)-malbrancheamide B **5** however, only moderate diastereocontrol was achieved in the IMDA step (Scheme 9).[25,26]



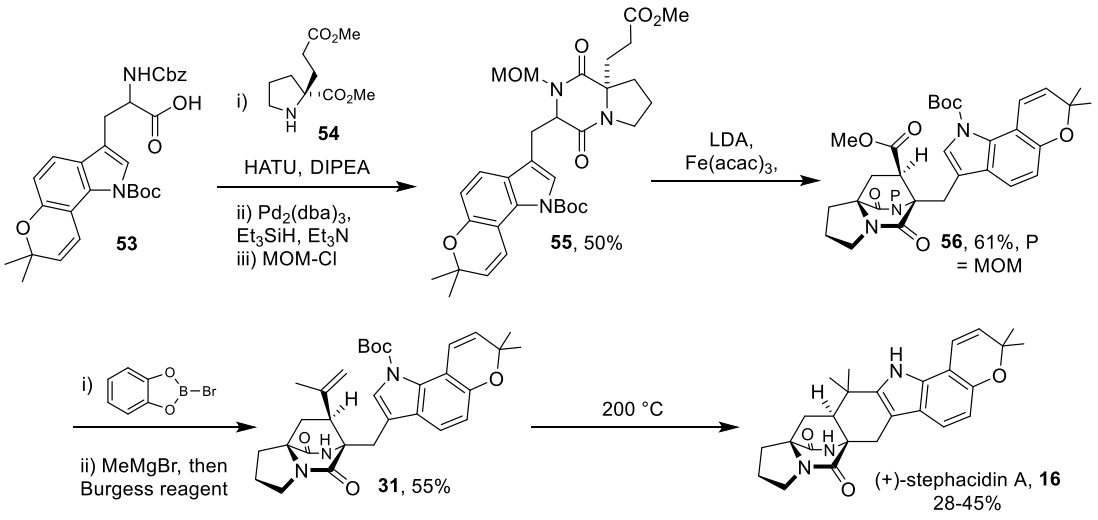
Scheme 9 – Scheerer diastereoselective domino reaction sequence including IMDA to synthesise (+)-malbrancheamide B **5**

Adduct **52** is generated from a domino reaction sequence that consists of an aldol addition and condensation, olefin isomerisation and IMDA cycloaddition. The diastereofacial control of the IMDA

cycloaddition is governed by the chiral aminal directing group which is later reduced to form the pyrrolidine ring.

Oxidative Enolate Coupling

Baran and co-workers developed an oxidative enolate coupling and employed the methodology to form the key bicyclo[2.2.2]diazaoctane core in their synthesis of stephacidin A **16**, avrainvillamide **17** and stephacidin B **18** (Scheme 10).[27–29]

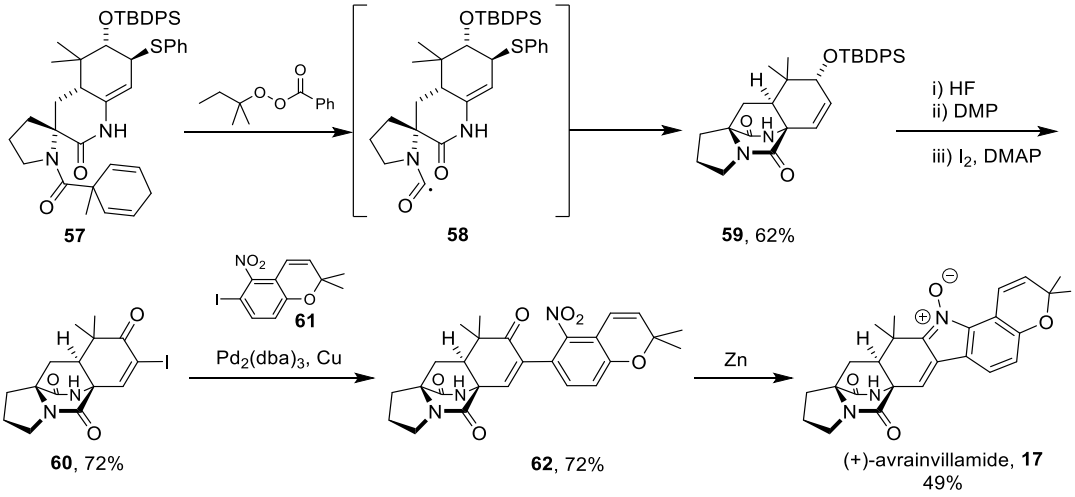


Scheme 10 – Baran oxidative enolate coupling

Key intermediate DKP **55** was generated from the amide coupling of tryptophan derivative **53** with *D*-proline derivative **54** followed by deprotective cyclisation and was then reprotected as the MOM ether. The key ring forming step was achieved using LDA and iron(III) acetylacetonate to affect an oxidative enolate coupling. Removal of the MOM protecting group and conversion of the methyl ester to the disubstituted olefin followed by thermal deprotection of the indole and cyclisation gave stephacidin A **16** from which avrainvillamide **17** and stephacidin B **18** were synthesised.

Radical Cyclisations

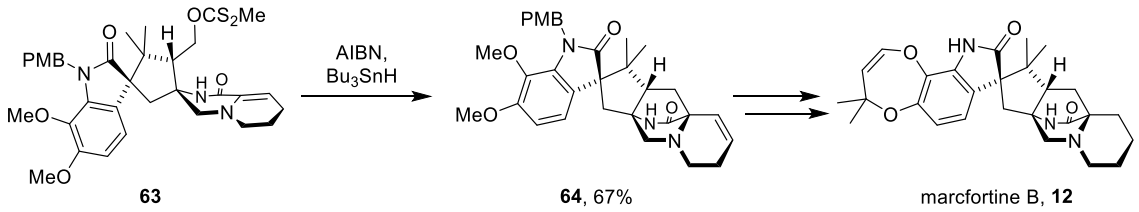
Radical cyclisations have been utilised by multiple research groups to form the characteristic bicyclic core of the prenylated indole alkaloids. In Myers' synthesis of avrainvillamide **17** and stephacidin B **18** the key bicyclo[2.2.2]diazaoctane core was formed through an aminoacyl radical cyclisation (Scheme 11).[30]



Scheme 11 – Myers radical cyclisation

Heating of advanced radical precursor **57** with tert-amyl peroxybenzoate was thought to generate radical **58** which attacks the double bond at the more substituted carbon and expels a phenylthiyl radical thereby generating adduct **59** in good yield. Deprotection, oxidation and iodination afforded adduct **60** which was then reacted with aryliodide **61** using an Ullmann-like coupling to generate **62**. Reduction of the nitro functional group using activated zinc gave avrainvillamide **17** in good yield. Conversion of avrainvillamide **17** into stephacidin B **18** was then achieved using triethylamine as used by Williams in the synthesis previously discussed.

A radical cyclisation was also used to generate the bicyclo[2.2.2]diazaoctane moiety by Trost and co-workers in their synthesis of marcfortine B **12** (Scheme 12).[31]

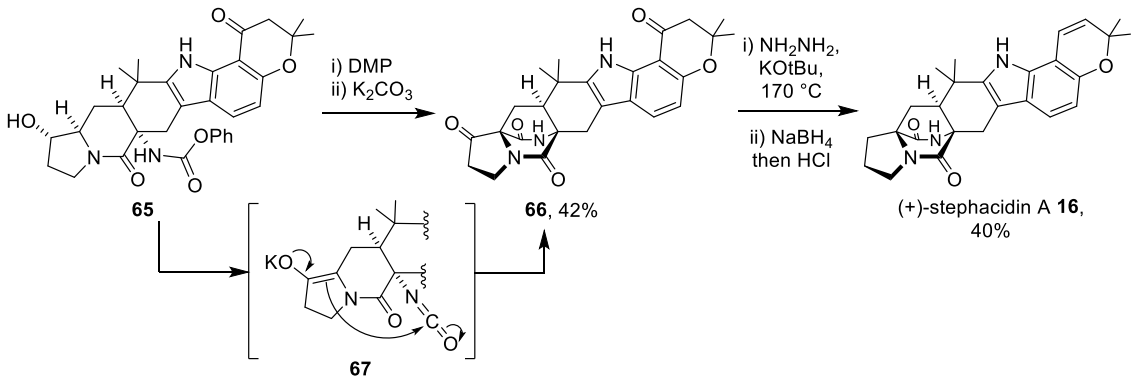


Scheme 12 – Trost synthesis of marcfortine B **12**

Treatment of advanced xanthate **63** with tributyltinhydride and AIBN generated adduct **64** through attack of the enamine by the generated primary radical. The newly formed double bond was proposed to be due to trapping of the secondary radical with AIBN followed by H· abstraction and fragmentation. Transformation of adduct **64** into marcfortine B **12** was then achieved following several subsequent steps to install the 7-membered ring and hydrogenation of the newly formed olefin.

Dieckmann Condensation of an Isocyanate

In recent work from Sarpong and co-workers an enolate-isocyanate Dieckmann condensation was used to synthesise the bicyclo[2.2.2]diazaoctane core and allowed generation of (+)-stephacidin A **16** (Scheme 13).[32]



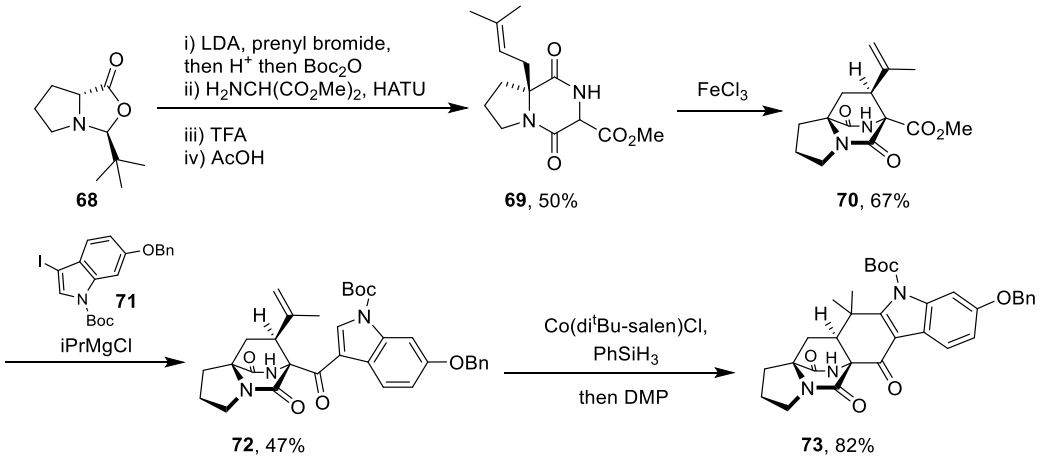
Scheme 13 – Sarpong synthesis of stephacidin A **16**

Oxidation of secondary alcohol **65** and treatment of the resulting ketone with potassium carbonate forms the key bicycle and gave adduct **66** in moderate yield. The simple conditions are proposed to generate

enolate-isocyanate intermediate **67** which can then undergo the aforementioned Dieckmann condensation to forge the bicyclo[2.2.2]diazaoctane core.

Oxidative Aza-Prins Cyclisation

Li and co-workers recently published an elegant oxidative aza-Prins cyclisation route to members of the prenylated indole alkaloid family (Scheme 14).[33]

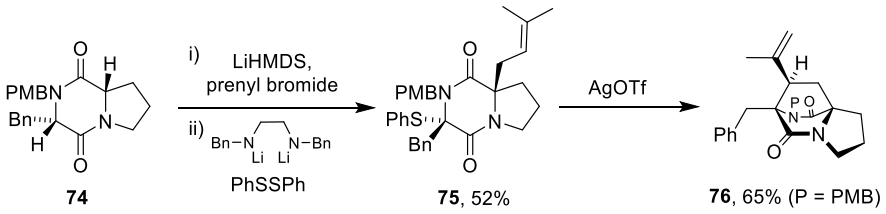


Scheme 14 – Li aza-Prins cyclisation towards notomaide I

Prenylation of Seebach acetal **68** followed by acetal cleavage, Boc protection, amide coupling with dimethyl aminomalonate and acid mediated deprotection-cyclisation gave 1,3-dicarbonyl adduct **69**. Cyclisation of adduct **69** using a $FeCl_3$-mediated oxidative aza-Prins reaction gave tricycle **70** in good yield and as a single diastereoisomer. Grignard addition of modified indole **71** gave ketone **72** before cobalt catalysed cycloisomerisation gave adduct **73** which could be converted in 3 steps to notoamide I **8** which in turn was transformed into 3 other family members.

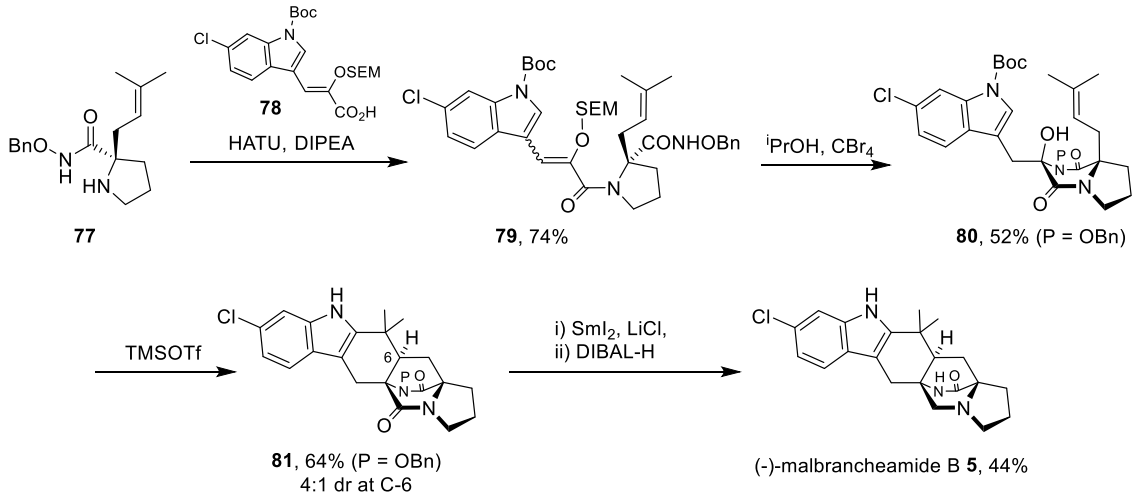
Simpkins Research Group Efforts Towards the Prenylated Indole Alkaloids

The Simpkins research group became interested in the prenylated indole alkaloids following significant work into the deprotonation of DKPs and the reactivity of the resulting enolates.[34,35] Alkylation of proline derived DKPs was found to proceed with initial retention of stereochemistry and further sulfenylation generated adduct **75** which was found to undergo a cationic cyclisation to give adduct **76** (Scheme 15).



Scheme 15 – Simpkins' cationic cyclisation

Attempts to extend this methodology for the synthesis of brevianamide B **2** and the malbrancheamides on mixed proline tryptophan systems were unsuccessful but it was found that a cationic cascade was also possible with hydroxy DKP **80** and generated adduct **81** in good yield (Scheme 16).[36,37]

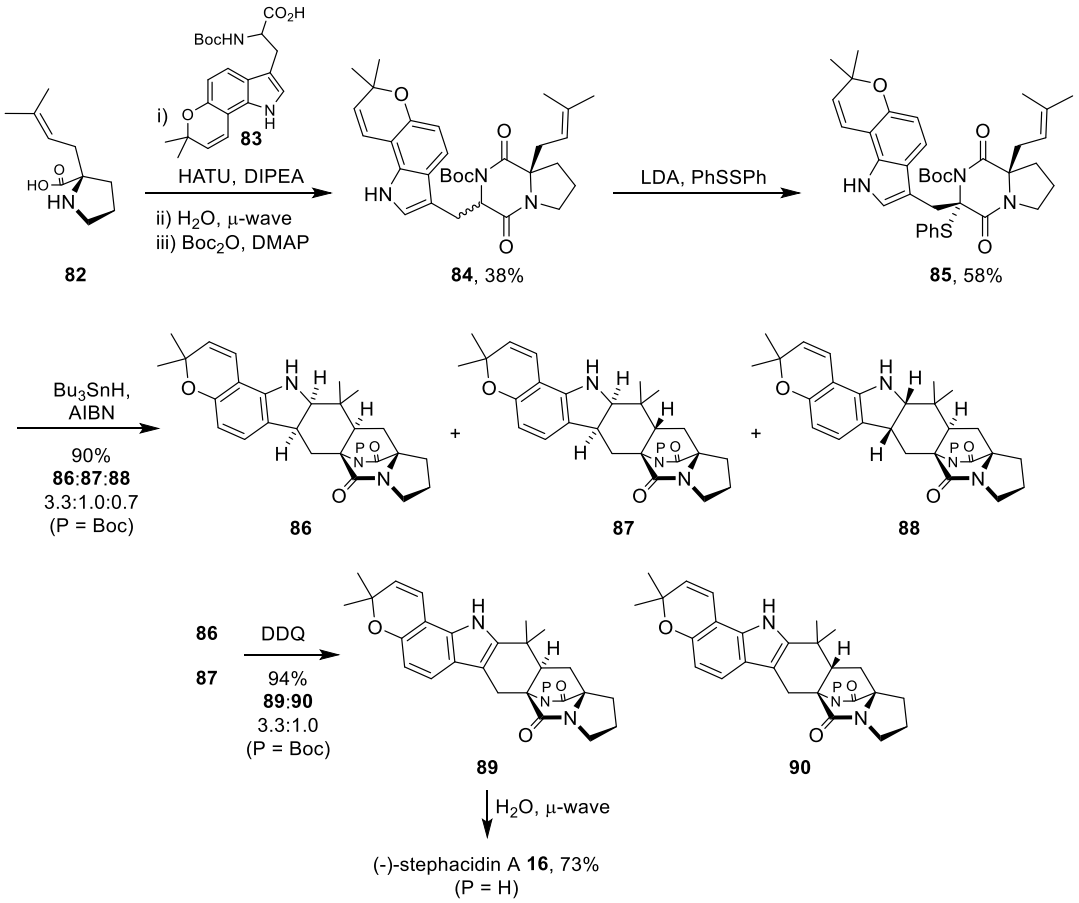


Scheme 16 – Simpkins' cationic cascade synthesis of malbrancheamide B **5**

Key hydroxy-DKP **80** was synthesised from Seebach acetal product **77** through an amide coupling with indole adduct **78** and then acid cyclisation. Treatment of DKP **80** with TMSOTf simultaneously promoted

the cationic cyclisation and deprotected the indole to afford adduct **81** which was then deprotected and reduced to give (-)-malbrancheamide B **5**.

It was later envisioned that this cascade of ring closures could be achieved using radicals and was employed for the synthesis of stephacidin A **16** since the cationic cascade was not suitable due to the instability of the pyran ring to the acidic conditions of the reaction (Scheme 17).[38]



Scheme 17 – Simpkins' radical cascade to stephacidin A **16**

Key thioether **85** was synthesised from prenyl proline derivative **82** and modified tryptophan adduct **83** using an amide coupling, followed by Boc removal and cyclisation, reprotection and then sulfenylation using LDA and phenyl disulfide. The key radical cyclisation was then affected using tributyltinhydride and AIBN and gave a mixture of 3 of the possible 4 diastereoisomers of indoline **86**–**88**. Oxidation of the

mixture of indoline adducts **86** and **87** using DDQ gave indole adducts **89** and **90** and deprotection of adduct **89** gave (-)-stephacidin A **16** in good yield.

Self-Replication of Stereocentres

The previous cascade routes for the synthesis of the prenylated indole alkaloids developed within the Simpkins research group, as have many of the synthesis discussed earlier in the Chapter, relied on Seebach's self-replication of stereocentres (SRS) methodology to access highly stereoenriched alkylated proline derivatives. Seebach and co-workers found that alkylation of pivaldehyde-based oxazolidinone **91a** occurred with retention of stereochemistry using a range of electrophiles (Figure 5).[39]

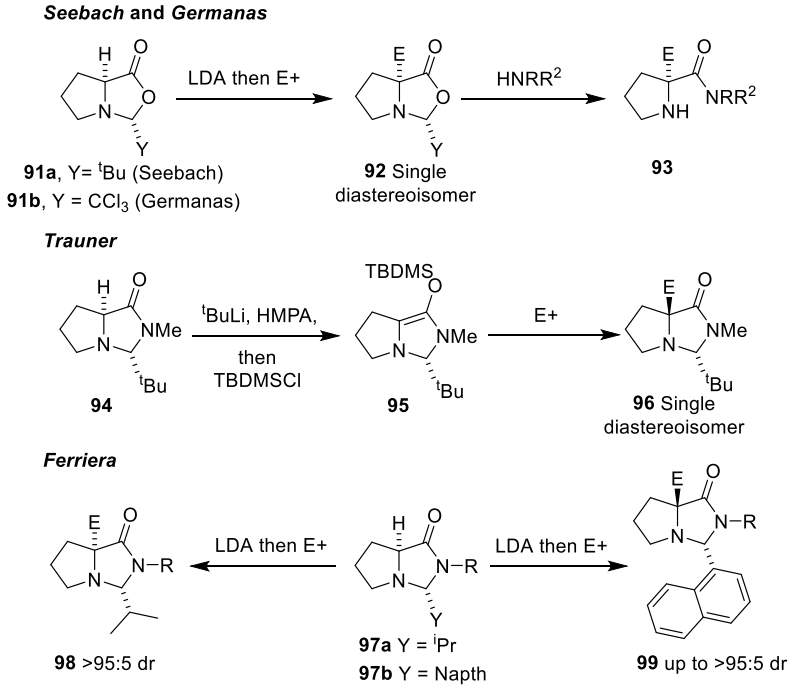


Figure 5 – Advances in Seebach's SRS methodology

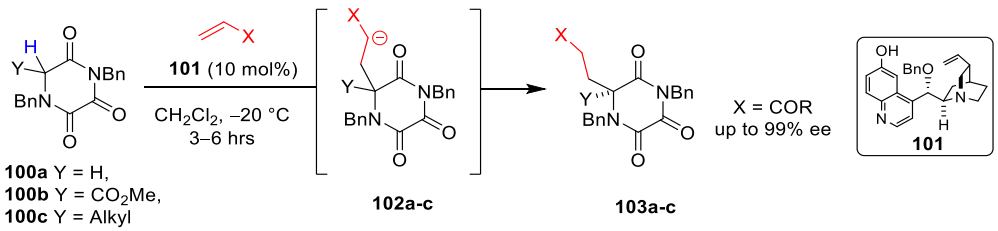
Problems with the stability of **91a** led to the more robust choral-based oxazolidinone **91b** being reported by Germanas and Wang.[40] It has since been found by Trauner that the selectivity can be reversed, giving inversion of stereochemistry, by pregeneration of silyl enol ether **95**.[41] Further to this Ferriera has recently reported that stereocomplementary products can be generated by isobutyraldehyde or 1-naphthaldehyde-

derived imidazolidinones **97a** and **97b**.[42] The single diastereoisomer oxazolidinones and imidazolidinones can then be converted into amino acids or amino amides such as **93** allowing these adducts to be used in further reactions.

Asymmetric Organocatalytic Methodology of Diketopiperazine Derivatives

With the limitation of the SRS methodology requiring strong base and early assignment of the enantiomeric series meant that an organocatalytic methodology to access either enantiomeric series would be highly powerful. To this aim recent work from the Simpkins research group has investigated the Michael addition of DKP derivatives possessing additional activating groups, such as *N*-acyls.[43] Unfortunately it found that the pK_a of the α-proton could not be lowered sufficiently to enable deprotonation by the commonly used cinchona derived asymmetric bifunctional catalysts.

However, it was found that incorporation of the additional activating group within the ring in the form of a triketopiperazine (TKP) successfully allowed highly enantioselective Michael additions to a range of Michael acceptors to give adducts **103a-c**, mediated by cinchona alkaloid derived catalyst **101** (Scheme 18).[43,44]

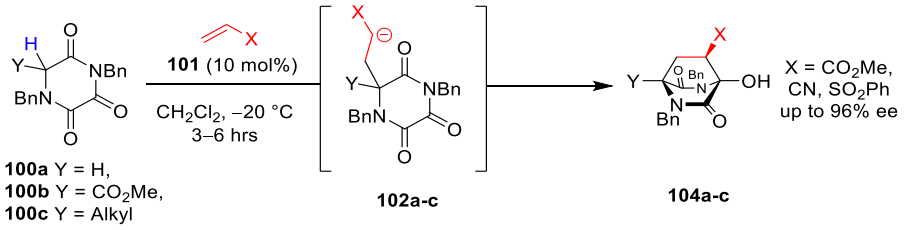


Scheme 18 – Assymetric Michael additions of triketopiperazines

Excellent yields and levels of asymmetric induction were achieved with glycine-derived TKP **100a** and its carboxymethyl analogue **100b** with results up to 99% and 99:1 er. However, when the reaction was performed on alkylated TKPs **100c** (Allyl, Bn or ^{n}Pr) the reactions with Michael acceptors were found to

be much slower than those with TKPs **100a** and **100b** and reduced yields and enantioselectivities were obtained with the best result being 82% and 77:23 er.

In addition to the excellent results obtained for the Michael addition reactions of TKPs **100a** and **100b** a Michael addition–ring-closure process was also reported with certain acceptor classes with the intermediate enolate **102a-c** undergoing an 'aldol'-like ring-closure to afford Michael addition–ring-closure adducts **104a-c** (Scheme 19).



Scheme 19 – Michael addition–ring-closure process of TKPs

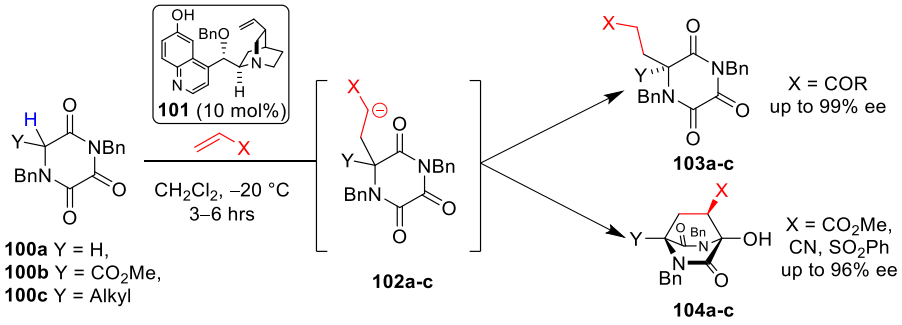
The products generated from this tandem process possess the key bicyclo[2.2.2]diazaoctane core found within the prenylated indole alkaloids, suggesting that this methodology could be a useful strategy for the enantioselective synthesis of members of the natural product family. Since the start of this project further work has been conducted on α-arylated TKPs and also an α-CF_3 TKP and investigations are currently ongoing within the research group.

Chapter Two – Enantioselective Synthesis of Functionalised Proline Derived Triketopiperazines

Aims and Objectives

The development of novel enantioselective approaches to members of the prenylated indole alkaloid family has been a significant area of research within the Simpkins research group as outlined in the introduction. With new members of the family and novel synthetic strategies being reported, the area remains the subject of widespread interest to the scientific community.[32,33,36–38,45]

As discussed earlier, recent work from the Simpkins research group has found that triketopiperazines undergo highly enantioselective Michael additions, mediated by a cinchona alkaloid derived catalyst, to a range of Michael acceptors to give adducts **103a-c** (Scheme 20).[43,44]



Scheme 20 – Overview of previous asymmetric Michael additions of TKPs

A Michael addition–ring-closure process was also reported with certain acceptor classes, generating products **104a-c** which contain the key bicyclo[2.2.2]diazaoctane core found within the prenylated indole alkaloids. Excellent yields and levels of asymmetric induction were achieved with glycine-derived TKP **100a** and its carboxymethyl analogue **100b** (Scheme 20). However, when exploring different α-substituents on the TKP ring it was found that the asymmetric Michael additions of alkylated TKPs **100c**

were noticeably slower and less selective, than **100a** and **100b**, with the best result involving addition to phenyl vinyl ketone, which required 7 days at 0 °C and gave an er of only 77:23.

The aim of this project was to extend the asymmetric Michael addition and Michael addition– ring-closure methodology to a bicyclic triketopiperazine derived from proline, and enable enantioselective Michael additions with or without *in situ* ring closure, to form **106** and **107** respectively (Figure 6).

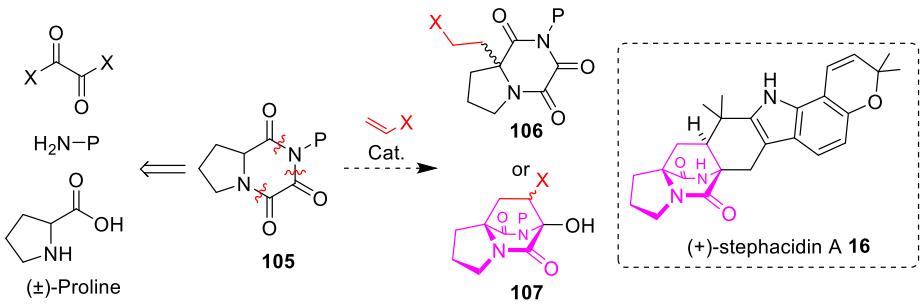


Figure 6 – Overview of proline derived TKP and comparision to stephacidin A

The similarity between tricyclic compound **107** and the tricyclic core of the prenylated indole alkaloids, as highlighted in stephacidin A **16**, is highly evident (Figure 6). This methodology had the potential to give novel access to the pyrrolidine fused bicyclo[2.2.2]diazaoctane core, compared to the stereocontrolled syntheses discussed earlier, since either enantiomeric series should be accessible just by switching catalysts.

A key issue was the potential for proline-derived TKP **105** to react in a similar fashion to the alkylated derivatives **100c**, mentioned above, meaning that the asymmetric Michael additions could have been slow and had lower than desired selectivity. However, considering the fact that proline-derived DKPs have been shown to be more acidic than DKPs derived from other amino acids we had hope that TKP **105** would react more similarly to glycine-derived TKP **100a** than the alkylated analogues.[46,47] Another potential issue regarding proline-derived TKP **105** was the configurational stability of the α-centre (Figure 7).

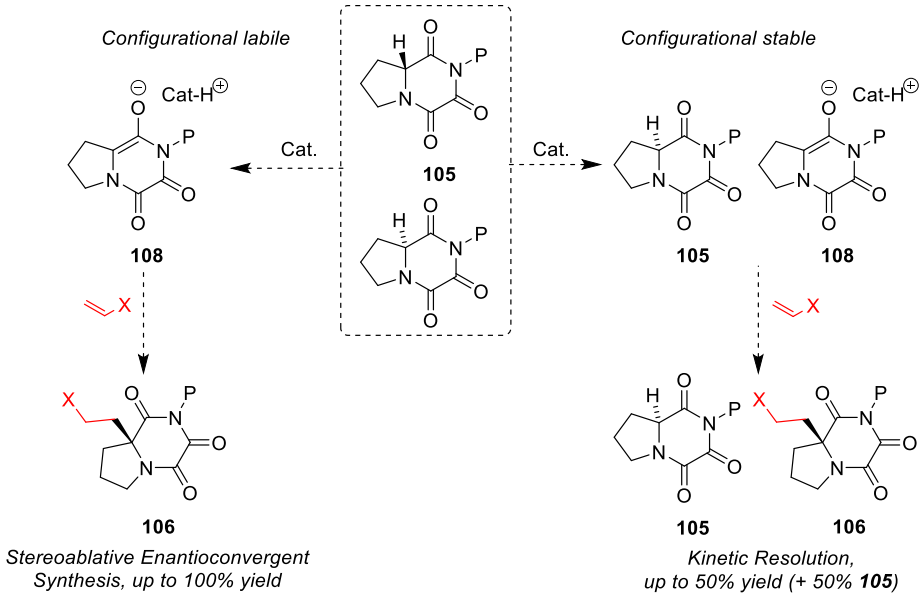


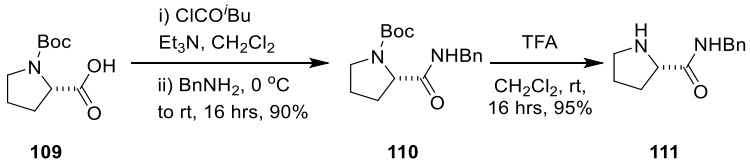
Figure 7 – Consideration on configurational stability

If the proline TKP is configurationally stable under the reaction conditions, it could be envisioned that only one enantiomer of TKP **105** would be deprotonated to generate prochiral enolate **108,** before addition to the Michael acceptor to give adduct **106** along with enantiomerically enriched TKP **105**, in a kinetic resolution. Alternatively a stereoablative enantioconvergent synthesis may be in effect if the TKP is configurationally labile, with prochiral enolate **108** formed from both enantiomers of **105**, allowing adduct **106** to be generated in up to 100% yield.[48,49]

Despite the questions regarding the potential reactivity of the proline TKP the appreciable overlap of the potential Michael addition and Michael addition–ring-closure products with the prenylated indole alkaloids made for an interesting project.

Synthesis of Proline Derived Triketopiperazine

In order to investigate the asymmetric Michael reaction of proline-derived TKP **105** the first priority was the development of a route to the desired TKP. Therefore proline-*N*-benzyl amide **111** was synthesised from commercially available Boc-*L*-proline **109** following a literature procedure (Scheme 21).[50] The benzyl amide was chosen because it had been previously used within our research group on other TKP systems with excellent results.[44]

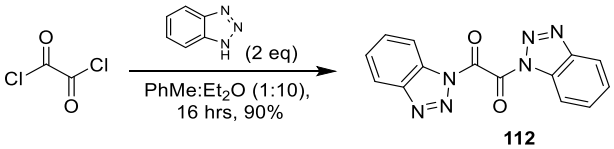


109 **110** **111**

Scheme 21 – Synthesis of proline-*N*-benzyl amide **111**

In the first step Boc-*L*-proline **109** was reacted with *i*-butyl chloroformate, to generate a mixed anhydride and subsequent addition of benzylamine gave amide **110** in good yield, following purification by recrystallisation. Removal of the Boc protecting group using trifluoroacetic acid (TFA), in dichloromethane followed by a basic work-up, gave desired amino amide **111** in excellent yield.

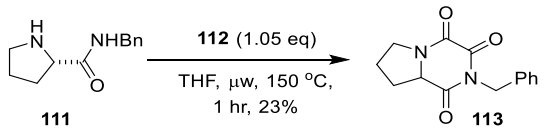
The next step was then the cyclisation of the amino amide using an oxalyl derivative in order to access proline-*N*-benzyl TKP **113**. Previous work within the research group had shown that oxalyl benzotriazole **112** was an effective and easily accessible oxalyl coupling partner for this process and was prepared in excellent yield of 90% (Scheme 22).[44,51]



112

Scheme 22 – Synthesis of oxalyl benzotriazole **112**

The reaction of amino amide **111** with oxalyl benzotriazole **112** was then attempted using a microwave reactor as previously developed within the research group (Scheme 23).[44]



Scheme 23 – Oxalyl benzotriazole cyclisation

The reaction gave desired proline-TKP **113,** but the yield was poor and considerably lower than that for the previous synthesis of glycine-derived TKP **100a** (67%). Attempts to increase the yield by varying the solvent, temperature, reaction time, concentration and equivalents of **112** had no significant effect.

Alternative procedures for the preparation of proline-TKP **113** were then investigated. Diethyl oxalate was successfully used by the groups of Safir, Person and Boa to generate TKPs **115a-e** (Figure 8).[52–55]

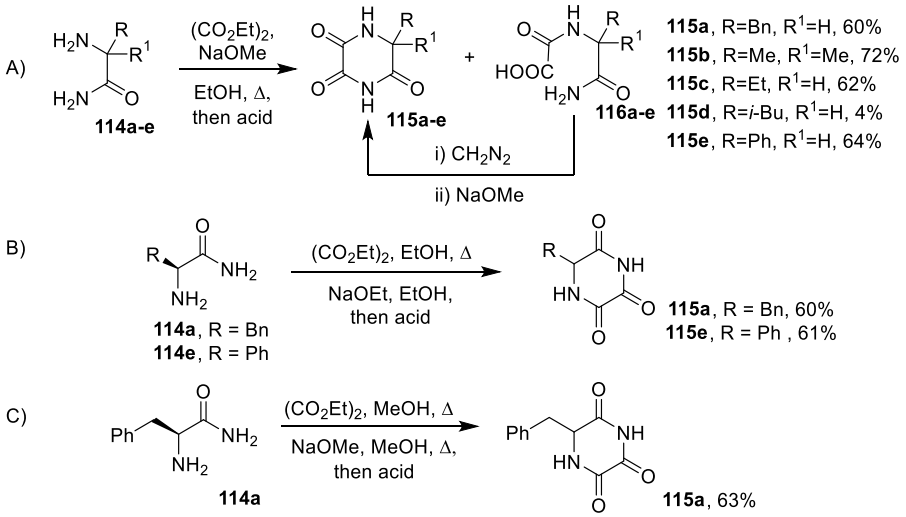


Figure 8 – Previous TKP syntheses using diethyl oxalate

However, the reaction of amino amide **111** under these conditions yielded no desired product, returning only unreacted starting material.

Previous work within the research group had also shown that commercial oxalyl imidazole gave comparable yields to oxalyl benzotriazole.[43] Oxalyl imidazole was also successfully used by the groups of Makino and Overman for the synthesis of proline derived TKP **118** and TKP **120** (Figure 9).[56,57]

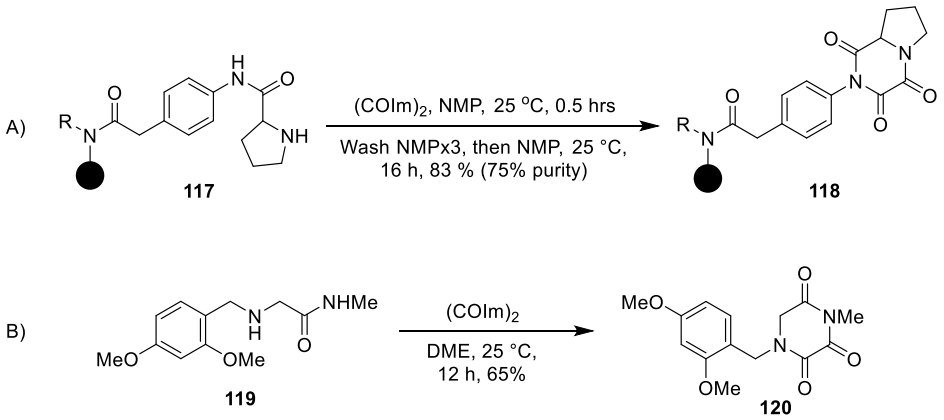
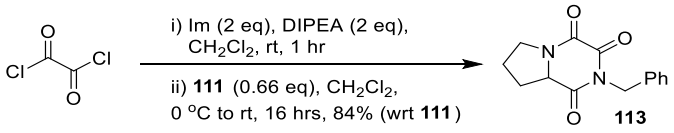


Figure 9 – Makino solid supported TKP synthesis (A) and Overman TKP synthesis (B)

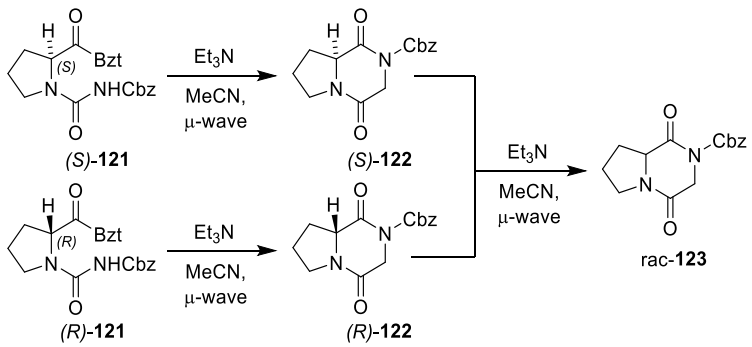
Earlier attempts within the research group to synthesise and isolate oxalyl imidazole, due to its relatively high cost and instability, had proved troublesome and had given poor yields of TKP formation. As an alternative a solution of oxalyl imidazole was prepared *in situ*, following a modified literature procedure, from oxalyl chloride, imidazole and Hünig's base (Scheme 24).[58]



Scheme 24 – Synthesis of proline-TKP using oxalyl imidazole

The addition of amino amide **111** to the solution of oxalyl imidazole followed by overnight stirring yielded proline-TKP **113** in excellent yield. Using oxalyl imidazole showed a considerable improvement in yield over oxalyl benzotriazole (84% ca. 23%), required milder conditions and allowed easier scale-up to multi-gram reactions. Additionally, TKP **113** could be isolated following a simple extraction, washing with 1M HCl and purification by recrystalisation from isopropyl alcohol, further aiding the gram scale synthesis of **113**.

Since TKP **113** was synthesised from *S*-*N*-benzyl prolinamide **111** we expected the isolated product to be the *S*-enantiomer. However, when the optical rotation of proline TKP **113** was measured it was found to be zero, implying that racemisation had occurred ($\alpha_D = 0$). The racemisation of a TKP had been previously reported in the synthesis of phenylalanine derived TKP **115a** by Person and Boa, shown above (Figure 8), although the conditions of sodium alkoxides in refluxing alcohol were harsher than those in the oxalyl imidazole synthesis of **113**. Racemisation has also been reported for related Cbz protected proline DKP **123** (Scheme 25). Katritzky found that when synthesising DKP **123**, using benzotriazole-mediated conditions, only racemic **123** was isolated regardless of starting with either enantiomer of **121**.[59]



Scheme 25 – Racemisation of a proline DKP observed by Katritzky

In hindsight, since Cbz proline DKP **123** underwent racemisation and previous work had shown that TKPs were more acidic than acylated DKPs, it was unsurprising that proline TKP **113** had racemised in the presence of amines.[43]

Attempts to isolate enantiomerically enriched samples of proline TKP **113** under modified reaction conditions or using chiral HPLC were unsuccessful. The compound appeared to racemise on the HPLC column as shown by unresolved and unusually shaped peaks (Figure 10).

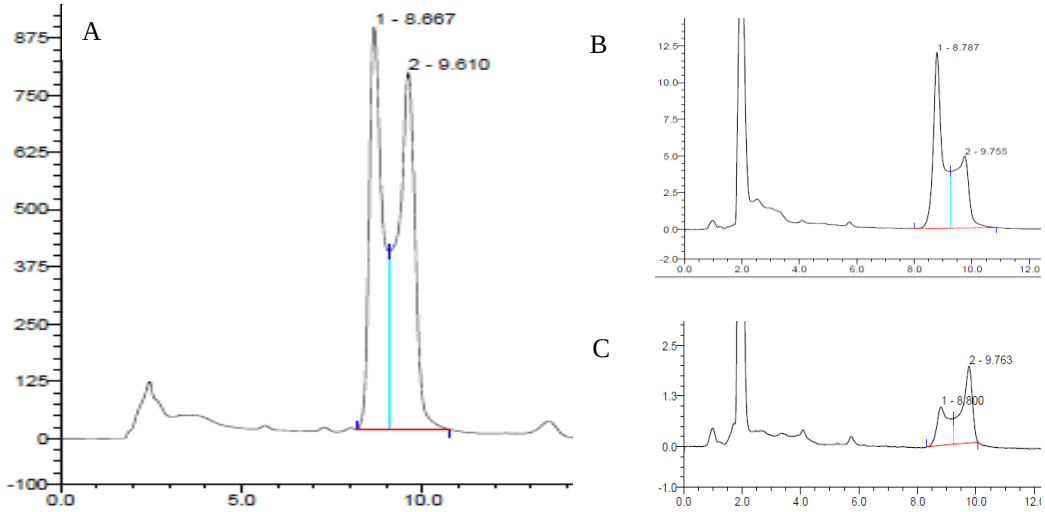
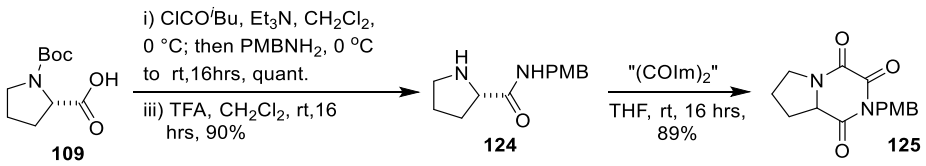


Figure 10 – HPLC traces (A) – racemic sample of Proline TKP **113**, (B) – reinjection of sample from the peak at 8.67 mins, (C) – reinjection of sample from the peak at 9.61 mins

Samples were collected from the middle of both peaks and were reinjected onto the chiral column. The two samples showed peaks for both enantiomers, suggesting that TKP **113** was partially racemised on the column.

The racemisation of **113** demonstrated the activating power of the TKP ring towards enolisation and was encouraging for the desired enantioselective Michael reactions, since the α-proton of the TKP should be readily removed by the basic nitrogen of the chiral catalysts. With the implied configurational lability of TKP **113**, a kinetic resolution during the planned asymmetric Michael reaction was deemed unlikely compared to the stereoablative outcome shown earlier and will be discussed later in the Chapter.

With benzyl protected proline-TKP **113** in hand, 4-methoxybenzyl (PMB) protected TKP **125** was also synthesised. The PMB group has been shown to be a more labile amide protecting group, than the benzyl group, potentially allowing facile removal at a later date (Scheme 26).[60]



Scheme 26 - Synthesis of PMB amide **124** and PMB TKP **125**

Amino amide **124** was synthesised in excellent yield (90% over 2 steps), following the same procedure as for benzyl amide **111**, and was then reacted with oxalyl imidazole to generate PMB protected proline TKP **125** (Scheme 26). Oxalyl imidazole was generated in situ, as described above, and gave TKP **125** in excellent yield as a racemate ($\alpha_D = 0$) matching the prior result with benzyl protected proline TKP **113**.

Synthesis of a Homo-Proline Triketopiperazine

Although the vast majority of the prenylated indole alkaloids possess a fused pyrrolidine ring there is a small proportion of the family that possess a fused piperidine ring, including marcfortines A–C (**11**, **12** and **126**) and chrysogenamide A **13** as mention briefly in Chapter 1(Figure 11).[11,31]

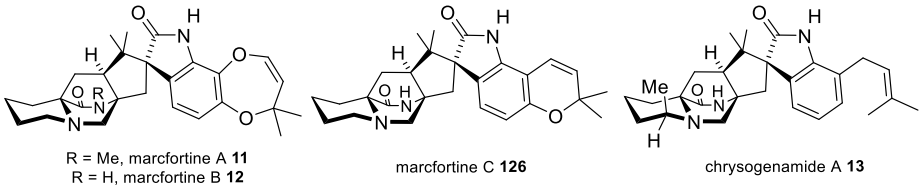
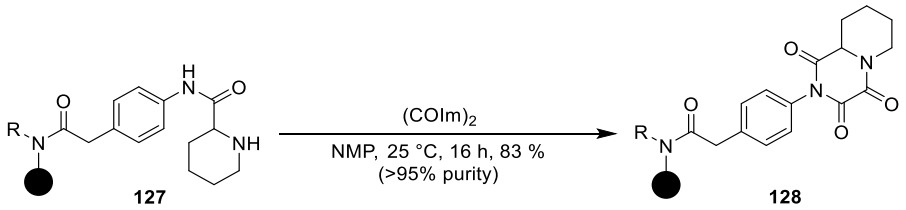


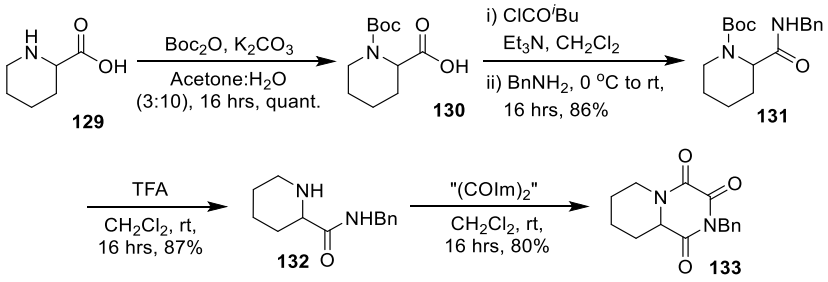
Figure 11 – Examples of prenylated indole alkaloids containing a fused piperidine ring

In this context, it was interesting to synthesis a homo-proline TKP derived from pipecolic acid, in parallel to proline-derived TKP **113**, to investigate the access of adducts related to the natural products shown above. It was hypothesised that a homo-proline-derived TKP would be easier to synthesise than proline TKP **113** since Makino and co-workers had reported that TKPs based on six-membered cyclic amino acids formed in higher yields compared to five-membered cyclic amino acids and required no modification of the method (Scheme 27).[56]



Scheme 27 – Makino solid supported TKP synthesis of piperidine fused system

Benzyl amino amide **132** was synthesised in good yield from commercially available (±)-pipecolic acid **129** in three steps (Scheme 28).



Scheme 28 – Synthesis of homo-proline TKP **133**

Pipecolic acid was protected with Boc anhydride, then coupled with benzylamine, via the mixed anhydride to give adduct **131**. Removal of the Boc group, using TFA, and then cyclisation with a prepared solution of oxalyl imidazole, provided homo-proline TKP **133** in excellent yield.

Enantioselective Michael Additions of Proline Triketopiperazines

With sufficient quantities of proline TKPs **113** and **125** and homo-proline TKP **133** in hand, the next objective was to establish the organocatalytic conjugate addition to Michael acceptors. Previous work had shown that glycine-derived TKP **100a** and carboxymethyl TKP **100b** underwent Michael addition to a number of enones in good yield using triethylamine as the base. Methyl vinyl ketone (MVK) was used to test the reactivity of TKPs **113**, **125** and **133** as Michael donors using triethylamine as base at an initial reaction temperature of –20 °C (Figure 12). Katritzky's Cbz protected proline DKP **123** was also

synthesised and submitted to the reaction conditions, since enolisation had previously been seen using triethylamine, but no Michael adduct was observed.

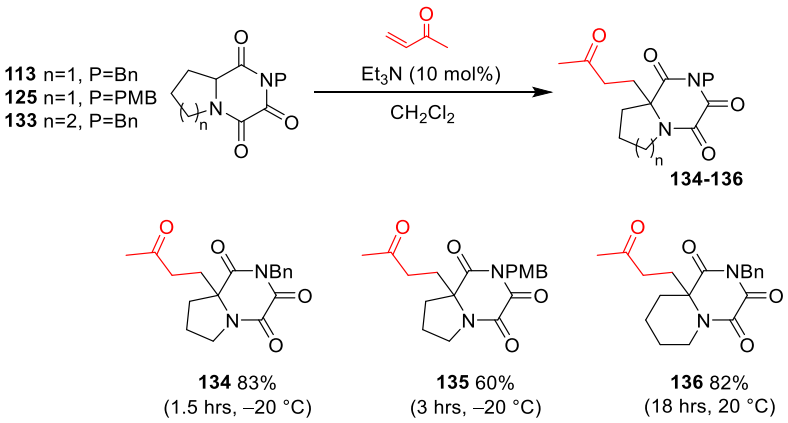


Figure 12 – Michael addition of TKPs **113**, **125** and **133** to methyl vinyl ketone

The reaction of proline TKPs **113** and **125** with MVK proceeded quickly and gave Michael adducts **134** and **135** in moderate to good yields even at –20 °C. This was an excellent result considering alkylated TKPs had previously shown poor reactivity, compared to glycine-derived TKP **100a**, or activated TKP **100b**, and required significantly longer reaction times to reach completion.[43] However, homo-proline TKP **133** showed more similarity to previous alkylated TKPs with less than 5% conversion after reacting overnight at –20 °C. Performing the reaction at room temperature gave compound **136** but the reaction required 18 hours for consumption of the starting material by TLC.

With the alkyl TKPs, the low apparent reactivity and selectivity was attributed to the low basicity of the catalyst and the increased steric hindrance at the reactive centre. Carboxymethyl TKP **100b** overcomes the increased steric hindrance with additional activation from the 1,3-dicarbonyl moiety. Although proline TKP **113** does not have the additional activation through resonance it appeared to be similar in reactivity to glycine and carboxymethyl TKPs **100a** and **100b**.

In DKP systems it has been reported that the α-protons of proline residues are more acidic compared to other amino acid sub-units.[47,59,61,62] In recent work by the O'Donoghue research group, proline residues in

DKPs have been measured to be kinetically more acidic than glycine, alanine and tyrosine residues (Figure 13).

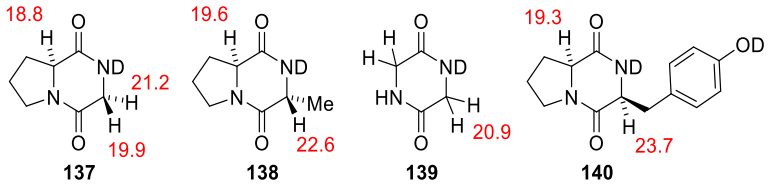


Figure 13 – DKP acidity measurements by O'Donoghue and co-workers

In comparison to non-cyclic DKPs, that assume a planar form, proline-derived DKPs must adopt a boat conformation, due to the constraints of the pyrrolidine ring.[46,63] This difference in conformation places the α-proton into a position with enhanced orbital overlap between σ_{CH} and π^*_{CO} in proline-derived DKPs compared to monocyclic DKPs, lowering the barrier to enolate formation, thereby explaining the difference in acidity (Figure 14).[47]

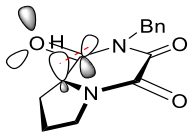


Figure 14 – Orbital overlap

The observed increased reactivity of proline TKP **113** compared to homo-proline TKP **133** was also attributed to this enhanced orbital overlap caused by the strained 5,6-system. Whereas, piperidine fused homo-proline TKP **133** was hypothesised to have reduced stereoelectronic enhancement and there would be increased steric interactions during deprotonation with hydrogens on the pyrimidine ring.

In collaboration the AstraZeneca, pK_a values for several TKPs have been predicted using DFT calculations (B3LYP) with correlation-consistent basic set [cc-pVTZ(+)] in a water SCRF solvent mode.[64] The calculations have a predicted pk_a range of 10.6–11.4, with the pk_as of proline TKP **113** and glycine TKP **100a** predicted to be 10.6. This information supported the observed similar reactivity shown by TKPs **113**

and **100a**. Previous NMR studies in MeCN-d_3 estimated the pk_a of glycine TKP **100a** and carboxymethyl TKP **100b** between 12 and 16.[43] Calculation of the acidity of proline and glycine TKPs **113** and **100a** is currently ongoing in collaboration with the O'Donoghue group. Preliminary results have indicated that proline TKP **113** is more acidic than glycine TKP **100a** which was encouraging for the future asymmetric reactions.

Inspired by the results obtained using triethylamine the asymmetric Michael reaction was then investigated. TKPs **113**, **125** and **133** were reacted with MVK using cinchona derived catalyst **141** and showed promising results (Figure 15).

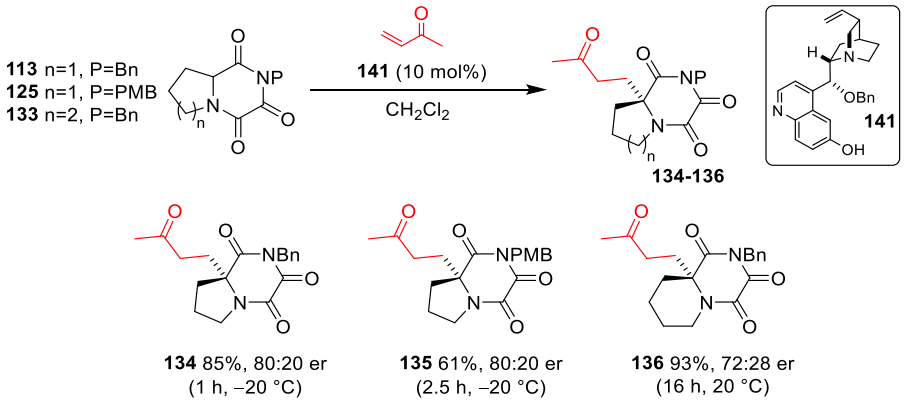


Figure 15 – Initial asymmetric Michael reaction with TKPs

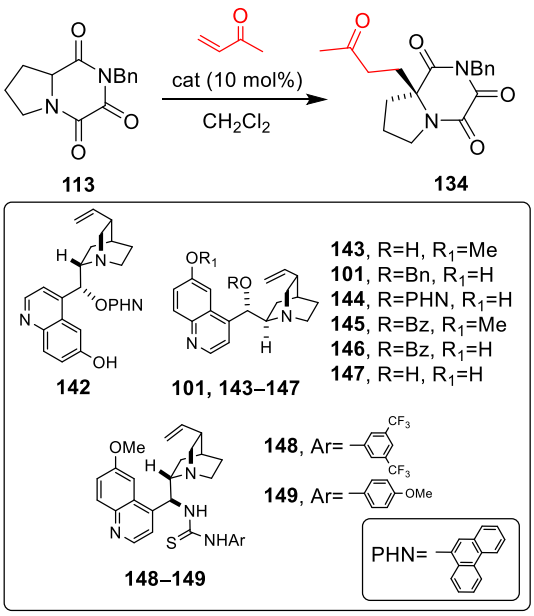
The initial enantioselectivity for the reactions of proline TKPs **113** and **125** were found to be higher than previous results of alkylated TKPs (best result with MVK was 70:30 er). On the proline system, the *N*-benzyl and *N*-PMB adducts had the same measured er as expected due to the similarity of TKPs **113** and **125**. Elevated temperatures were again needed with homo-proline TKP **133**, with less than 10% conversion after 1 day at –20 °C, at room temperature a reduced enantiomeric ratio was measured in comparison the proline adducts **134** and **135** but was similar to the alkylated TKPs results.

The results also showed that the cinchona derived catalyst could interact with both enantiomers of the TKP since yields of greater than 50% were obtained. This is an example of stereoablative enantioconvergent

catalysis since catalyst **141** converts either enantiomer to an achiral intermediate enolate that then undergoes enantioselective conversion to the product.[48]

Katritzky's Cbz protected proline DKP **123** was also submitted to the asymmetric reaction conditions above, in case the bifunctional nature of the catalyst would enable the reaction. However, no Michael adduct was observed, which demonstrates the increased activation of the TKP systems in comparison to acylated DKPs and is in agreement with previous work within the research group.[43,59]

With the promising preliminary results shown with MVK, work then concentrated on screening a number of catalysts in an attempt to increase the enantioselectivity of the reaction. The screen was performed using the addition of benzyl proline TKP **113** to MVK, due to the fast reaction time, moderate yields and established HPLC conditions (Table 1).



Entry	Catalyst	Time (h)	Temp (°C)	Yield (%)[a]	er[b]
1	**143**	3	–20	60	77:23
2	**101**	4	–20	74	19:81
3	**145**	18	–20	60	44:56
4	**146**	2	–20	65	19:81
5	**147**	16	–20	79	28:72
6	**148**	19	–20	63	30:70
7	**149**	23	–20	51	35:65
8	**144**	2.5	–20	42	12:88
9	**144**	22	–30	72	10:90
10	**142**	21	–30	81	78:22

Table 1 – Catalyst screening for the Michael reaction of TKP **113** with MVK [a] – isolated yield, [b] – determined by HPLC

Natural cinchona alkaloid, quinidine **143**, showed moderate enantioselectivity for the same enantiomer as quinine derived catalyst **141**. This switch in selectivity can be attributed to the differing hydrogen bond donors, with **143** having a C9 hydroxyl while **141** has a C6' 'phenol' resulting in a change in the transition state organisation. Catalyst **101** showed equal selectivity to the initial result (80:20 er, Figure 15 vs

entry 2) but in favour of the opposite enantiomer as expected due to the *psuedo*-enantiomeric relationship of catalysts **101** and **141**. Benzoyl catalyst **146** was also tested and showed similar selectivity to benzyl catalysts **101** and **141** (entry 4). Benzoyl protected quinidine **145**, intermediate in the synthesis of benzoyl catalyst **146**, was also tested and as expected showed virtually no enantioselectivity (entry 3). This is due to the lack of a hydrogen bond donor required to effectively organise the transition state.[65] Two thiourea catalysts **148** and **149** were also tested but showed inferior enantioselectivities (entries 6–7). Catalyst **144**, with the larger phenanthryl C9 substituent, showed an improved enantioselectivity compared to benzylated catalyst **101**, however, the rate of reaction was decreased, with only partial conversion after two and a half hours (entry 8). An improved yield and enantioselectivity were obtained for catalyst **144** when the reaction was conducted overnight at a lower temperature (entry 9 *vs.* entry 8). Catalyst **142** gave the enantiocomplementary product although with reduced selectivity (entry 10).

As a result of the catalyst screen the conditions in entry 9 were deemed to be the best for future Michael additions, since they afforded **134** in good yield and with the highest er.

To explore the asymmetric Michael addition further, a number of enones and an unsaturated *N*-acyl oxazolidinone were tested with benzyl proline TKP **113**. Methyl and ethyl vinyl ketones were also tested under the optimised conditions with PMB proline TKP **125** and homo-proline TKP **133** (Figure 16).

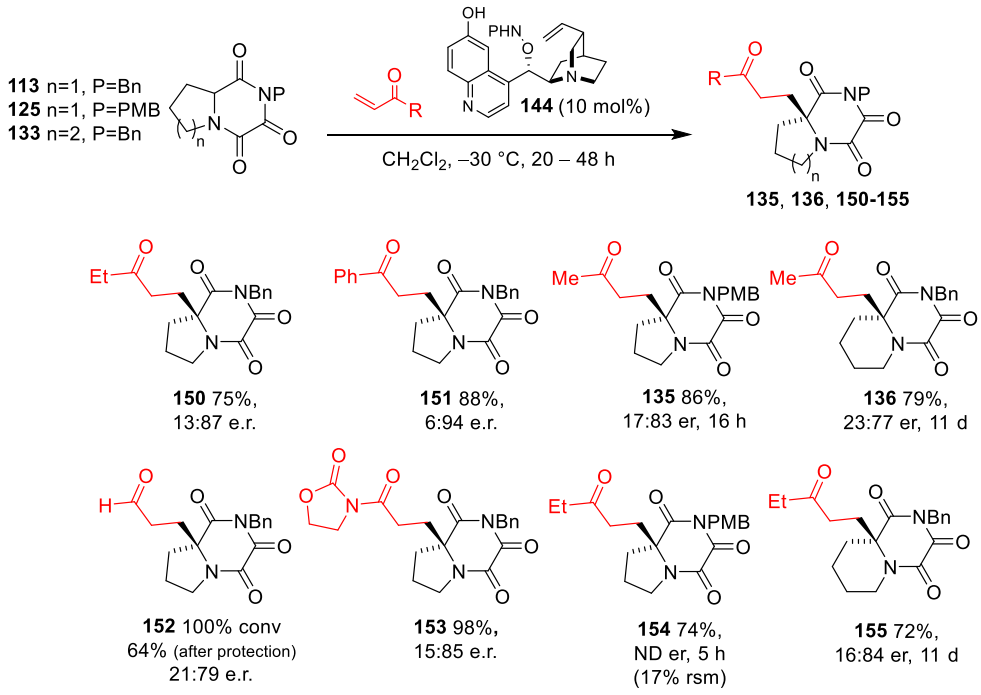


Figure 16 – Scope of Michael addition

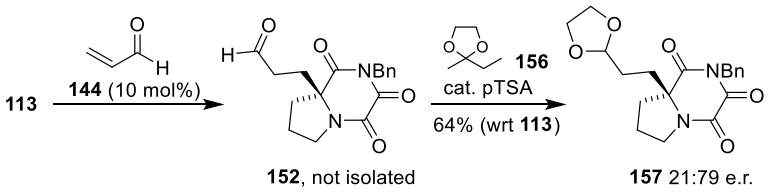
Good levels of enantioselectivity were measured for Michael adducts **135**, **136** and **150**–**155**, with phenyl vinyl ketone adduct giving the best enantiomeric ratio of 6:94. This was also the first time a TKP had been reacted with an oxazolidinone Michael acceptor.

The enantioselectivity for PMB MVK adduct **135** increased slightly over the previous result (17:83 *vs* 80:20) and inverted due to the use of the pseudoenatiomeric catalyst family. Unfortunately, despite trying all available columns, no HPLC conditions were found to split PMB EVK adduct **154**.

For the reactions of homo-proline TKP **133**, the enantioselectivity of MVK adduct **136** was increased (23:77 *vs* 72:28) and the enantiomeric ratio of EVK adduct **155** was found to be good. However, the reactions took 11 days, reducing the practicality of the asymmetric Michael addition with TKP **133** and therefore no further Michael acceptors were tested.

Nonetheless, with proline TKP giving selectivities up to 6:94 er, and homo-proline up to 16:84 er, these were the best results for Michael additions of α-substituted TKPs, other than the doubly-activated carboxymethyl TKP **100b**.

During analysis of the Michael adducts it was found that acrolein adduct **152** required conversion to acetal **157** in order for HPLC analysis to be performed and allow easier purification of the product. Acetal **157** was synthesised in moderate yield from the crude Michael adduct, after evaporation of excess acrolein, using 2-ethyl-2-methyl-1,3-dioxolane **156** as the solvent with a catalytic amount of pTSA (Scheme 29).



Scheme 29 – Conversion of acrolein adduct **152** to acetal **157**

In an attempt to improve the enantiomeric ratio of the Michael adducts an enantioenrichment by crystallisation was attempted.[66,67] Recrystallisation of a sample of MVK adduct **134** (10:90 er) provided crystals of enriched enantiopurity (5:95 er) and subsequent recrystallisation gave an enantiopure sample of **134** (<1:99) (Figure 17).

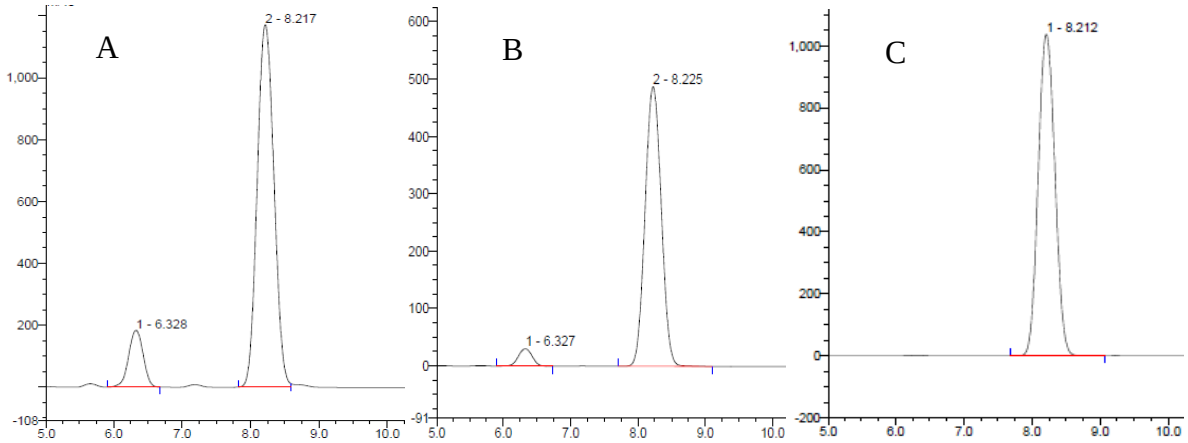


Figure 17 – HPLC traces showing enantioenrichment, A – 10:90 er, B – 5:95 er, C – <1:99 er

In order to confirm the stereochemistry of the Michael adducts, a crystal was grown from a sample of phenyl vinyl ketone adduct **151**, synthesised using catalyst **144**, and the X-ray crystal structure was determined (Figure 18).

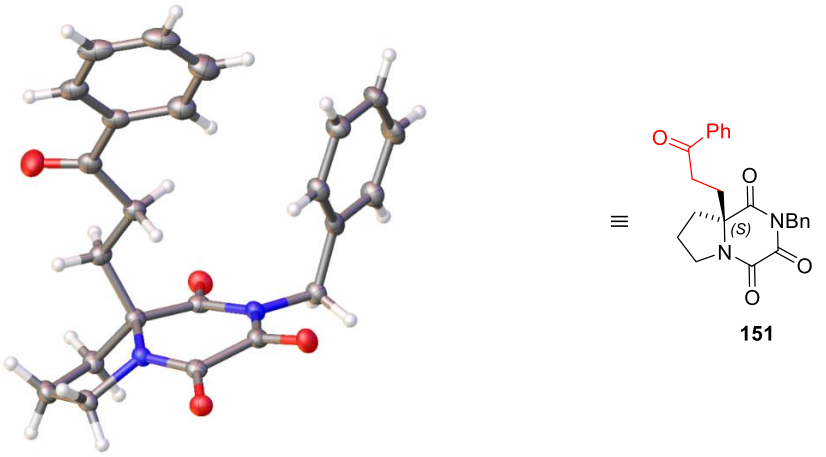


Figure 18 – X-ray structure of **151** with ellipsoids drawn at the 50% probability level

The crystal structure of **151** established the stereogenic centre to be *S* which is in agreement with previous work within the research group.[43,44] The crystal structure also showed the strained conformation of the bicyclic proline TKP and implied that the α-centre of proline TKPs should be readily accessible for the catalyst to deprotonate. The conformation of proline TKP **133** is thought to be main contributing factor for the observed improved rate of reaction for proline TKP **113** over homo-proline TKP **133** and previously mentioned alkyl TKPs.

The assignment of the stereogenic centre was also in agreement with models proposed by Deng and Houk, in which the Michael donor and acceptor are arranged with the catalyst through a network of hydrogen bonds.[68–70] The Deng and Houk models were modified to fit the synthesis of **151**, with the three components arranged as shown in Figure 19.

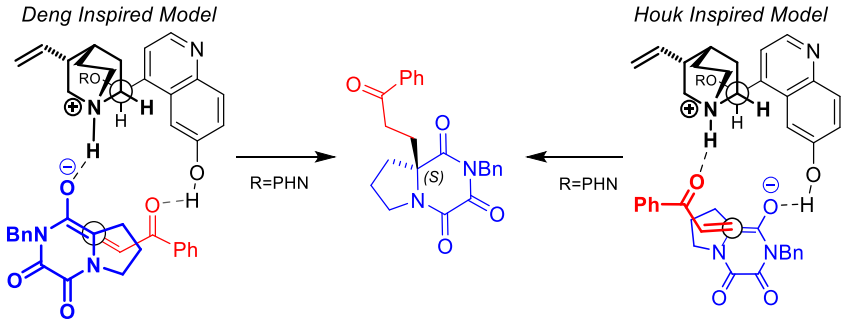
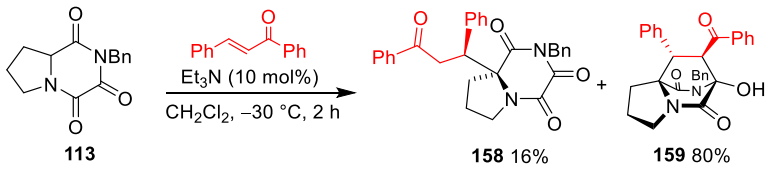


Figure 19 – Models for asymmetric Michael addition

In both models the catalyst can be drawn along the C-8–C-9 bond, resulting in two planes, with the quinuclidine portion above (bold) and hydroxy quinoline portion below. In the Deng inspired model the TKP enolate associates to the protonated quinuclidine and the Michael acceptor associates to the hydroxy quinoline. Whereas, Houk found on related C-9 thiourea catalysts, using DFT calculations, that activation of the acceptor by the protonated quinuclidine and orientation of the nucleophile, after deprotonation by the quinuclidine, by the hydroxy quinoline was the lowest energy transition state.

With good results obtained from simple enones, proline TKP was then reacted with chalcone to further explore the enone class (Scheme 30). Chalcone had previously shown good results, with glycine-derived TKP **100a** undergoing the Michael addition in excellent yield. However, no reaction was seen with activated TKP **100b** or the alkylated TKPs **100c**, presumably due to the increased steric demand of those systems, therefore chalcone was deemed to be a good indicator of reactivity.



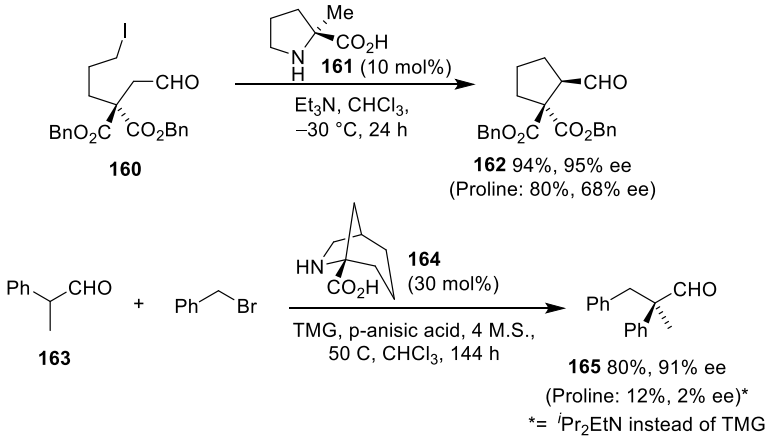
Scheme 30 – Michael addition of proline TKP **113** to chalcone

Surprisingly, two products were isolated, the minor product was found to be the anticipated Michael adduct **158** while the major product was found to be tricyclic Michael addition– ring-closure product **159**.

Hydroxy DKP **159** was isolated as a single diastereoisomer having four contiguous stereocentres and bearing the pyrrolidine fused bicyclo[2.2.2]diazaoctane core found within the prenylated indole alkaloids. This unexpected Michael addition– ring-closure process will be further discussed in Chapter 3.

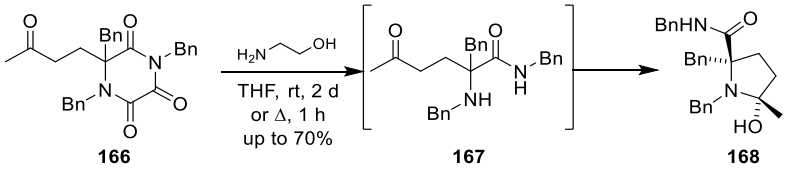
Unveiling of the Aminoamide

With the proline TKP showing successful activation of the amino acid system toward organocatalysed Michael additions, a method of removing the oxalyl functionality of the TKP and unveiling the amino acid derivative would give access to novel fully substituted prolines. Functionalised prolines have been key building blocks in natural product syntheses, including the synthesis of the prenylated indole alkaloids as discussed in the introduction. Quaternary prolines are also valuable in peptidomimetics where they can be incorporated into peptides to induce β-turns or to improve their biological stability.[71,72] Additionally, proline derivatives, including quaternary examples, have played an important role as catalysts in asymmetric enamine organocatalysis reactions as shown in several examples from the List group (Scheme 31).[73,74]



Scheme 31 – List's asymmetric α-alkylation of aldehydes

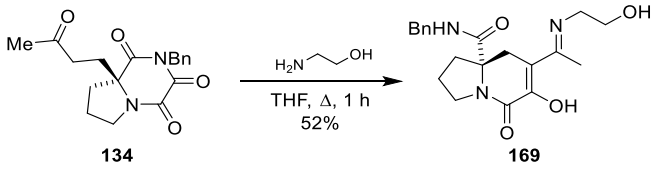
Previous work within our research group showed that the oxalyl moiety could be removed from Michael adducts in moderate yield using ethanolamine (Scheme 32). In the example shown *in situ* cyclisation of the generated amino amide **167** with the pendant ketone gave hemi-aminal **168**.[43]



166 167 168

Scheme 32 – Previous example of oxalyl removal

However, when these reaction conditions were applied to MVK adduct **134**, compound **169** was isolated in moderate yield and none of the desired aminoamide or hemi-aminal were observed (Scheme 33).

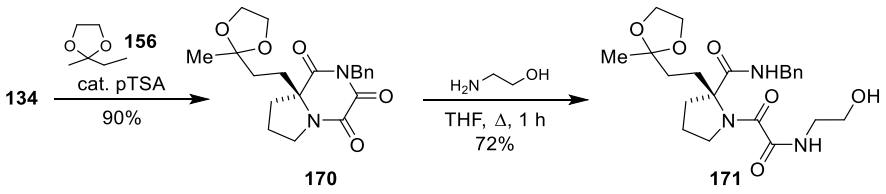


134 169

Scheme 33 – Attempted oxalyl removal

Enamine ring-closure followed by ring-opening of the *N*-acyl hemiaminal and enolisation of the newly formed 1,3-diketone moiety afforded compound **169**. The proline TKP system had shown its susceptibility to undergo ring-closure of the side chain onto the C-3 carbonyl in the result with chalcone (Scheme 30). This type of ring opening had not previously been seen with ethanolamine and will be discussed in more depth in the next Chapter.

In order to prevent the observed ring-closure, protection of the ketone functionality of MVK adduct **134** was proposed. Since conversion of aldehyde **152** to dioxolane **157** had been successful, it was chosen for the protection of Michael adduct **134**. Compound **134** was converted to ketal **170** in good yield, using the same conditions as for the protection of acrolein adduct **152** (Scheme 29 and Scheme 34).



Scheme 34 – Attempted oxalyl removal on protected adduct

Ketal **170** was submitted to the same ethanolamine conditions and cleavage of the imide functionality was found to occur, generating **171** in good yield after heating under reflux for 1 hour, although no desired amino amide was observed (Scheme 34). Ethanolamine addition product **171** was further heated in THF under reflux overnight but no change was observed. Compound **171** was also heated in a microwave reactor, at 125 °C, in THF and then in THF:ethanolamine (5:1), in case another equivalent of bisnucleophile was required, but **171** was returned unchanged in both cases.

With compound **171** seemingly unable to undergo intermolecular cyclisation, to remove the oxalyl functionality, it was hypothesised that using a diamine may enable the intramolecular cyclisation giving access the desired amino amide. Therefore, ketal **170** was reacted with ethylenediamine and *N,N'*-dimethyl ethylenediamine however disappointingly both reagents gave the same result as when ethanolamine was used, with cleavage of the imide but no further reaction.

Unfortunately no method was found to successfully remove the oxalyl moiety, but further research into this area is currently ongoing within the research group.[75]

Summary and Future Work

Bicyclic TKPs derived from proline and pipecolic acid have been successfully synthesised in high yields from the respective amino acids. Despite the use of Boc-*S*-proline, synthesised proline TKPs **113** and **125** were found to be racemic which attests to the activating effect of the TKP ring towards enolisation.

Proline TKPs **113** and **125** were found to undergo Michael additions with simple enones using either triethylamine or cinchona derived catalysts with good rates of reactivity even at low temperatures. Excellent levels of enantioselectivity have been achieved using phenanthryl quinidine derivative **144** (up to 4:96 er) and similar selectivities can be achieved for both the benzyl and PMB protected TKPs.

Homo-proline TKP **133** was found to be less reactive, requiring longer reaction times and when catalyst **144** was used gave moderately lower enantioselectivities (up to 16:84 er). This is in agreement with previous results with alkylated TKPs that found longer reaction times were required, compared to glycine TKP **100a** and its carboxymethyl derivative **100b**, and obtained enantiomeric ratios were lower.

A crystal structure was obtained of Michael adduct **151** and allowed the absolute stereochemistry to be established with quinidine derived catalyst **144** found to generate the *S* enantiomer. This was in agreement with previous work within the research group and with models proposed by Deng and Houk.

Attempts to remove the oxalyl moiety from the Michael adducts using ethanolamine, and other bisnucleophiles, were unsuccessful either undergoing a ring-closure–ring-opening process or stopping after imide cleavage when the ketone was protected.

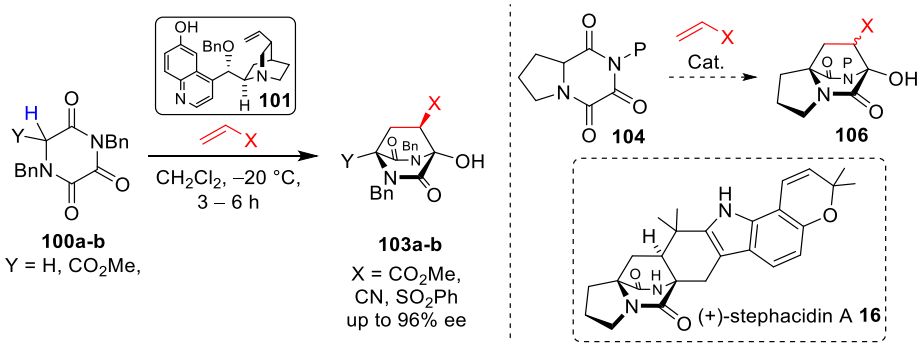
Further studies into the removal of the oxalyl moiety are ongoing within the Simpkins group which will hopefully find a mild and general method applicable to the bicyclic systems. Catalyst development is also required for the homo-proline TKP in order to obtain Michael adducts with excellent enantiomeric ratios

in practical reaction times. The apparent decreased reactivity may require the need for more basic catalysts such as chiral bifunctional guanidines, cyclopropenimines or Dixons iminophosphoranes.[76–78] Ongoing collaborations with the O'Donoghue research group and AstraZeneca interested in the acidity of the TKP systems may aid future catalyst choices. Lastly, a deprotection strategy needs to be further investigated. Previous work in our research group has shown that PMB groups can be removed from proline TKP adducts in moderate yield using cerium ammonium nitrate but optimisation of the result is needed.[79] Additionally DMB and OBn protecting groups have also been used by the research group on DKP and TKP systems but not on the proline TKP system.[5,44]

Chapter Three – Synthesis of Tricyclic Diketopiperazines Possessing the Bicyclo[2.2.2]diazaoctane Core

Aims and Objectives

Over the past decade, the Simpkins research group has developed several cascade methods to synthesise the bicyclo[2.2.2]diazaoctane core of the prenylated indole alkaloids. In recent work, it was shown that a tandem Michael addition–ring-closure process between TKPs and vinyl esters, nitriles and sulfones gave access to cyclic compounds **103**, that possess the core of the natural product family.[43,44] In addition to providing a novel route into the bicyclo[2.2.2]diazaoctane motif, this methodology also gave highly enantioselective access to either enantiomer in excellent yields (Scheme 35).

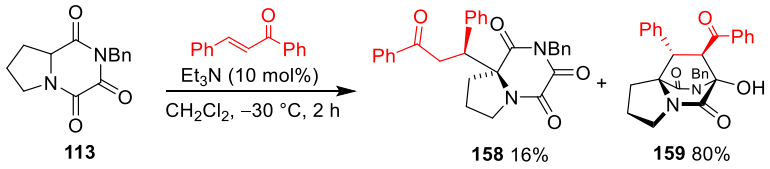


Scheme 35 – Overview of previous TKP Michael-ring closure and extension to proline TKP

This section of the project focussed on the extension of the Michael addition–ring-closure methodology to proline-derived bicyclic TKP **104**. It was envisioned that this process would give novel asymmetric access to tricyclic product **106**, which possesses the pyrrolidine fused bicyclo[2.2.2]diazaoctane core seen in a large majority of the prenylated indole alkaloids, such as stephacidin A **16**. Further transformation could then allow access to derivatives or fragments of this natural product family.

Organocatalysed Tandem Michael Addition–Ring-Closure Methodology: Synthetic Access to Tricyclic Diketopiperazines

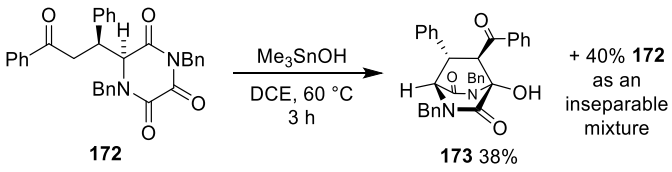
Preliminary exploration of the Michael addition of proline TKP **113** to enones gave promising results in terms of both reactivity and enantioselectivity when using cinchona derived catalysts (Figure 16). Unexpectedly, when proline TKP **113** was reacted with chalcone, to further explore the enone acceptor class, the major product was hydroxy DKP **159** formed by the aforementioned Michael addition–ring-closure process (Scheme 36).



113 **158** 16% **159** 80%

Scheme 36 – Michael addition of TKP **113** with chalcone

Previously, this tandem process had only been seen with vinyl esters, nitriles and sulfones (Scheme 36) with enones only giving 'open' Michael adducts, such as **172**, with alkyl TKPs. Subsequent ring closure of the 'open' adducts could be partially affected in an additional step, using trimethyltinhydroxide, but was only observed with a small number of Michael adducts.[43]

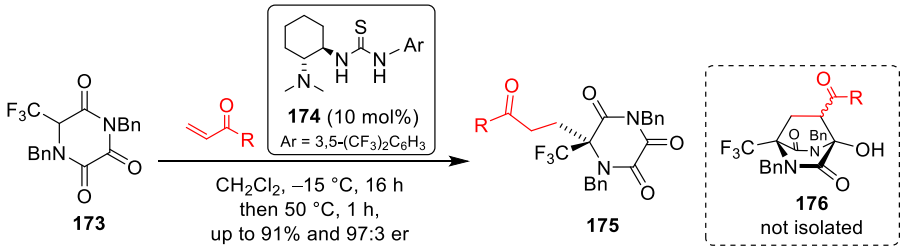


172 **173** 38%

Scheme 37 – Ring closure of chalcone adduct **172**

In contrast, the tandem ring closure was seen with enones in more recent research on the Michael addition of α-CF_3 TKP **173**. The reaction afforded a mixture of desired product **175** and cyclic product **176** when the reaction was quenched at low-temperature. NMR studies showed that closed adduct **176** is initially

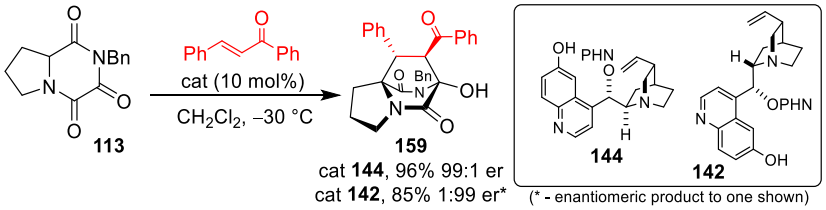
formed and is slowly converted to open adduct **175** over the course of the reaction. Conversion of closed adduct **176** to open Michael adduct **175** was found to occur by heating to 50 °C for 1 hour (Scheme 38).[81]



Scheme 38 – Ring closure with enones on α-CF_3 TKP **173**

In this research Takemoto's catalyst **174** was found to give the best results, with excellent yields and enantiomeric ratios achieved (up to 91% and 97:3 er). Cyclic product **176** was also observed using triethylamine and cinchona alkaloid catalyst **101**, but in reduced yield and enantioselectivity compared to catalyst **174**.

Since α-CF_3 TKP **173** had shown some degree of ring closure in the presence of bifunctional catalysts **101** and **174**, the reaction of proline TKP and chalcone was completed under the previously optimised conditions with catalyst **144** (Scheme 39).



Scheme 39 – Asymmetric reaction of TKP **113** with chalcone

The reaction gave tricycle **159** in excellent yield (96%) and 'open' product **158** was not observed. Not only was the product isolated as a single diastereoisomer in excellent yield but exceptional levels of enantioselectivity were also achieved (99:1 er). This was the first example of an α-substituted TKP undergoing an asymmetric Michael addition with a β-substituted enone. Moreover, use of *pseudo*-

enantiomeric catalyst **142** gave the enantiocomplementary result, with **159** isolated again as a single diastereoisomer in excellent yield and with exceptional enantioselectivity. This result showed the power of this methodology to allow access to either enantiomer of the tricyclic product from a racemic starting material just by switching *pseudo*-enantiomers of the catalyst. Furthermore, four contiguous stereocentres were created with excellent diastereoselectivity and enantioselectivity in a single step from a racemic starting material.

The absolute stereochemistry was established from the X-ray crystal structure of **159** synthesised using catalyst **144** (Figure 20).

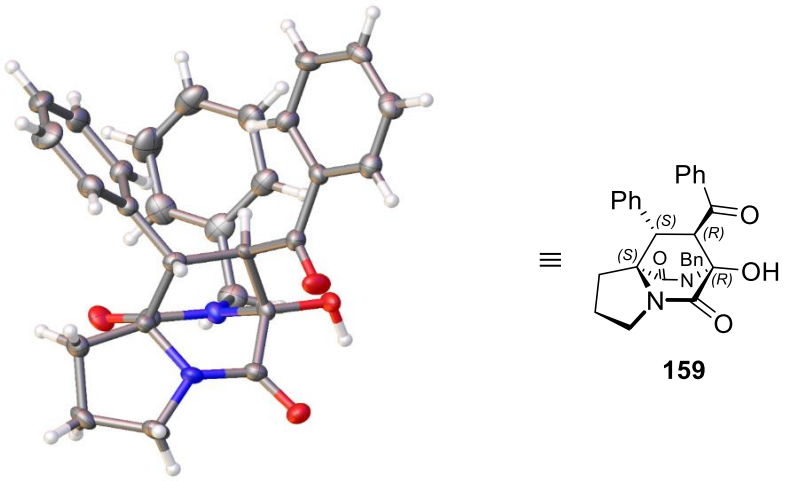


Figure 20 – X-ray structure of tricycle **159** with ellipsoids drawn at the 50% probability level

The structure was found to contain two crystallographically independent molecules of **159**, of which only one is shown for clarity. Both molecules had the same absolute stereochemistry that was determined to be *SSRR*, as shown above, labelled starting from the TKP α-centre (Figure 20). The assignment of the initial stereocentre was in agreement with the previous X-ray data for phenyl vinyl ketone adduct **151** (Figure 18, page 36). The established stereochemistry was also in accordance with models, previously used in Chapter 2, that were adapted from models proposed by Deng and Houk (Figure 21).

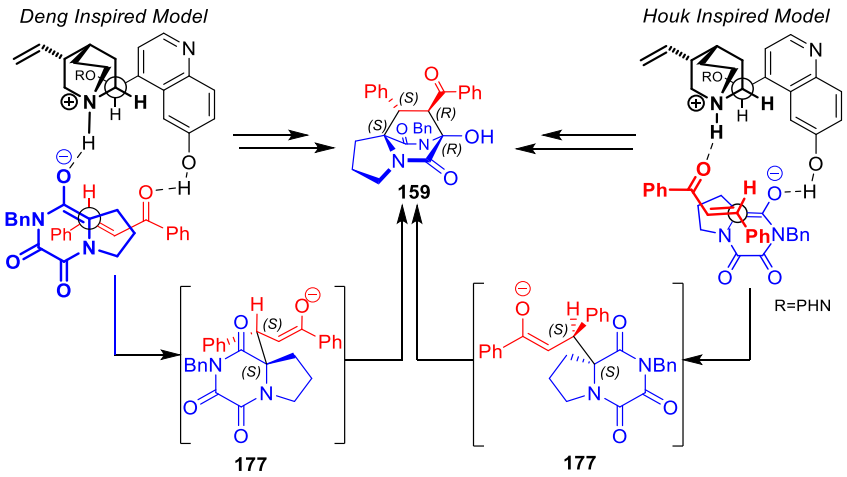


Figure 21 – Models for the synthesis of chalcone adduct **159**

Both models predicted that the addition of the TKP enolate to chalcone should give the first and second stereocentres as *S* in agreement with the X-ray structure. The models required the β-phenyl substituent of chalcone to be positioned *endo* to the TKP, which although it appeared sterically disfavoured should be plausible due to the planar nature of the two groups. Enolate **177** was then expected to minimise steric interactions with the phenyl group, before adding into the reactive C-3 carbonyl, thereby setting the final two stereocentres both as *R*, with the final stereocentre predetermined by the initial facial selectivity of the Michael addition (Figure 21 and Figure 22).

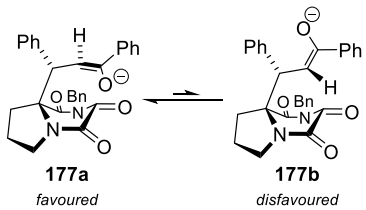


Figure 22 – Reorientation of enolate **177**

It is interesting that the presence of a β-substituent changed the outcome of the Michael addition, with phenyl vinyl ketone affording open adduct **151** whilst the reaction with chalcone gave 'closed' adduct **159**. In addition to the β-substituent, the bicyclic structure of **113** must also have an effect since the reaction of chalcone with glycine TKP **100a** gave 'open' adduct **172** (Figure 23).

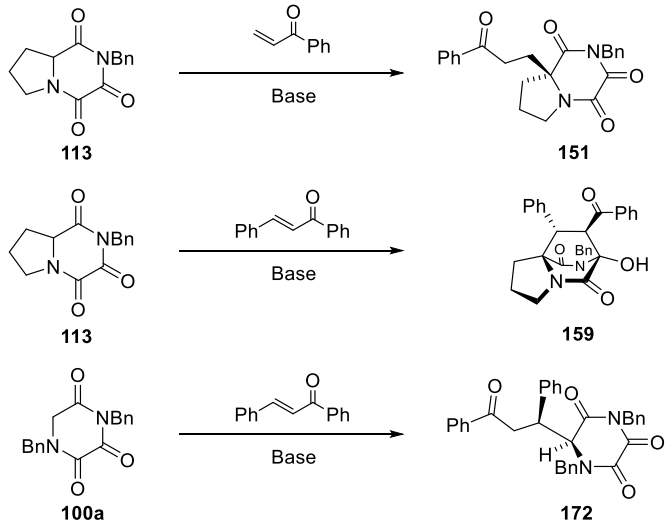


Figure 23 – Different reaction outcomes for TKPs **113** and **100a** with chalcone and phenyl vinyl ketone

This difference in reaction outcome has been previously attributed to a 'buttressing effect' in which the five membered ring has a steric interaction with the β-substituent, which in turn forces the intermediate enolate closer to the reactive C-3 carbonyl promoting ring closer over protonation.[82]

An alternative rational can be sought by considering the different energies for rotation around the newly formed C-C bond of the respective enolates generated from the Michael addition (Figure 24).

The 'open' enolate from addition of proline TKP **113** to phenyl vinyl ketone, **178a**, is expected to be of lower energy than 'closed' enolate **178b**. This is thought to be the case due to the reduced steric interactions from positioning the hydrogens over the TKP and pyrrolidine rings compared to placing the enolate over the TKP ring. The open enolate is also expected to be the lowest energy rotamer for enolate **179** since both the enolate and phenyl ring can be positioned away from the TKP ring. In contrast, the 'open' and 'closed' rotamers of enolate **177** are expected to be of similar energy since they both position one group over either the TKP or pyrrolidine rings. The suspected energy similarity would then allow the enolate to adopt the 'closed' rotamer thereby facilitating attack of the C-3 carbonyl.

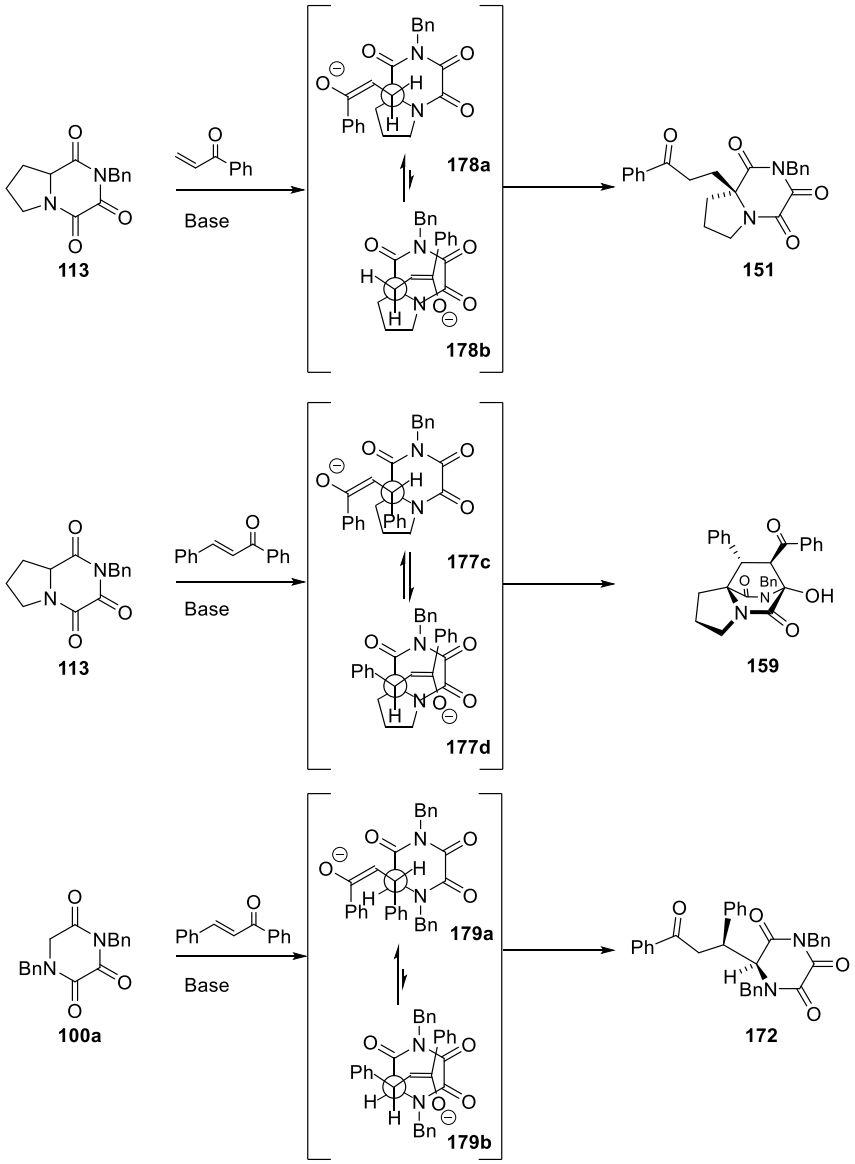
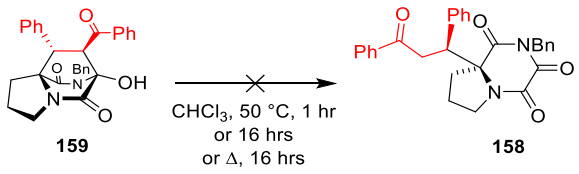


Figure 24 – Energy difference of enolate rotamers following Michael additions, note - the third enolate has been omitted for clarity

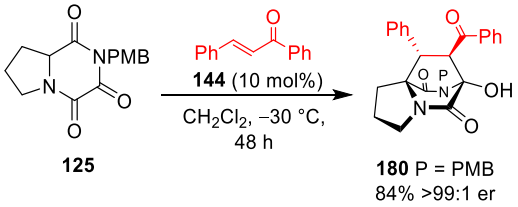
Inspired by previous work with α-CF_3 TKP **173**, in which a retro-'aldol' ring opening of closed adducts could be affected through heating the reaction mixture, the ring opening of chalcone adduct **159** was attempted (Scheme 40).



Scheme 40 – Attempted opening of chalcone adduct **159**

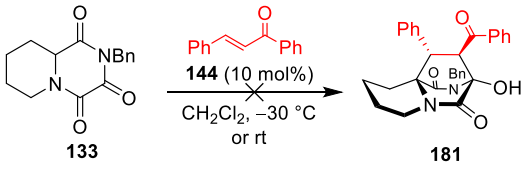
Heating the reaction mixture at 50 °C for 1 hour and for 16 hours was found to return **159** unchanged and no opening was observed even after 16 hours under reflux. Since catalyst **174** was present in the α-CF_3 reaction mixtures, is was suspected that the reaction may be base catalysed therefore the reaction was repeated with triethylamine, which resulted in decomposition, or in the presence of catalyst **144**, which returned the starting material unchanged.

The Michael addition of PMB protected proline TKP **125** was also found to be catalysed by catalyst **144**, giving tricycle **180** as a single diastereoisomer in good yield and in excellent enantiomeric excess (Scheme 41).



Scheme 41 – Michael addition of PMB proline TKP **125** to chalcone

Unfortunately, the reaction of homo-proline TKP **133** was not found to occur with chalcone even when the reaction mixture was allowed to warm to room temperature (Scheme 42).



Scheme 42 – Attempted Michael addition of homo-proline TKP **133** to chalcone

The lack of reaction was attributed to a combination of the lower reactivity of TKP **133**, in comparison to proline-derived TKP **113**, and the increased steric demands of chalcone compared to simple enones, with which TKP **133** had previously reacted. This result was consistent with previous results that had found α-substituted TKPs were unreactive towards chalcone.[43]

Inspired by the excellent result with chalcone, other β-substituted enones and a β-substituted oxazolidinone were then engaged in productive enantioselective Michael addition–ring-closures with proline TKP **113** (Figure 25).

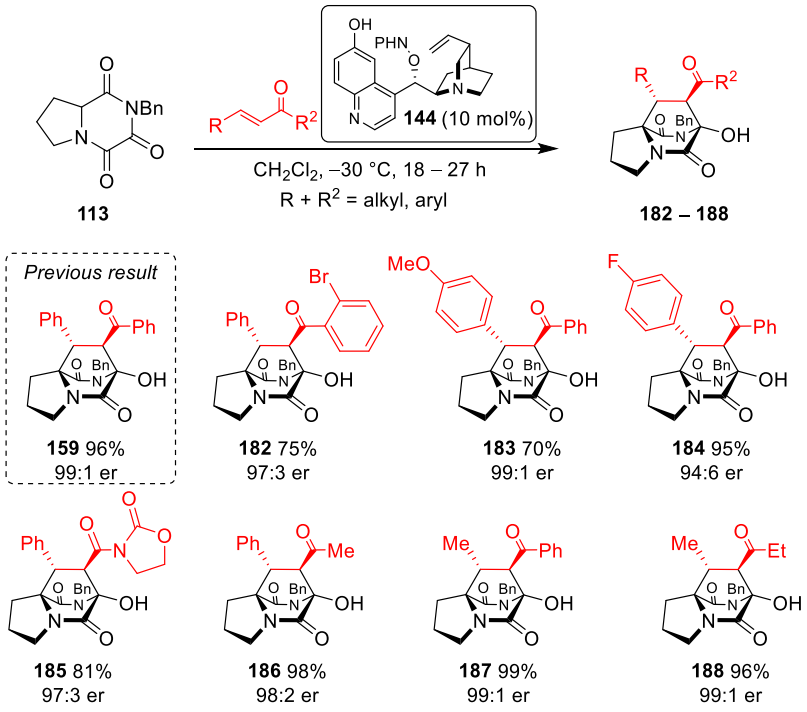
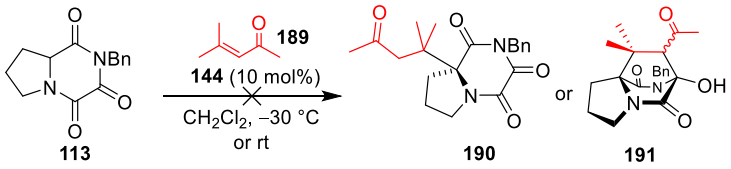


Figure 25 – Scope of Michael addition with β-substituted enones

Pleasingly, the reaction of proline TKP **113** with chalcone variants gave adducts **182-188** with excellent enantioselectivity and were once again isolated as single diastereoisomers in good to excellent yields. Alkyl adducts **186-188** were also generated as single diastereoisomers, in excellent yield and with outstanding enantiomeric ratios, which showed that neither of the aromatic groups were required for ring-

closure to occur, nor for the high diastereoselectivity of the step. Cinnamoyl oxazolidinone adduct **185** was also synthesised in high yield and enantiomeric excess.

Since β-substituted enones had shown excellent results, the Michael addition with mesityl oxide **189**, a β,β-disubstituted enone, was also attempted (Scheme 43).



Scheme 43 – Attempted reaction of proline TKP **113** with mesityl oxide **189**

Unfortunately, the formation of Michael adduct **190** or Michael-ring closure adduct **191** was not observed. Presumably, the additional steric demands imposed by the second β-methyl prevented the Michael addition of TKP **113** occurring.

Following the success of the Michael addition–ring-closure process with β-substituted enones, alternative Michael acceptors were then sought. Previous work had shown that methyl acrylate, acrylonitrile, vinyl sulfones and maleimides were suitable acceptors, reacting with glycine and carboxymethyl TKPs **100a** and **100b** in excellent yields and enantioselectivities.[43,44] The reactions of proline TKP **113** with acrylonitrile and phenyl vinyl sulfone, under the optimised conditions, gave a multitude of products and were not further pursued. On the other hand, methyl acrylate gave clean conversion to tricycle **192** (R = Me), although low and variable yields were obtained following silica-gel chromatography suggesting the instability of tricycle **192** to silica (Figure 26).

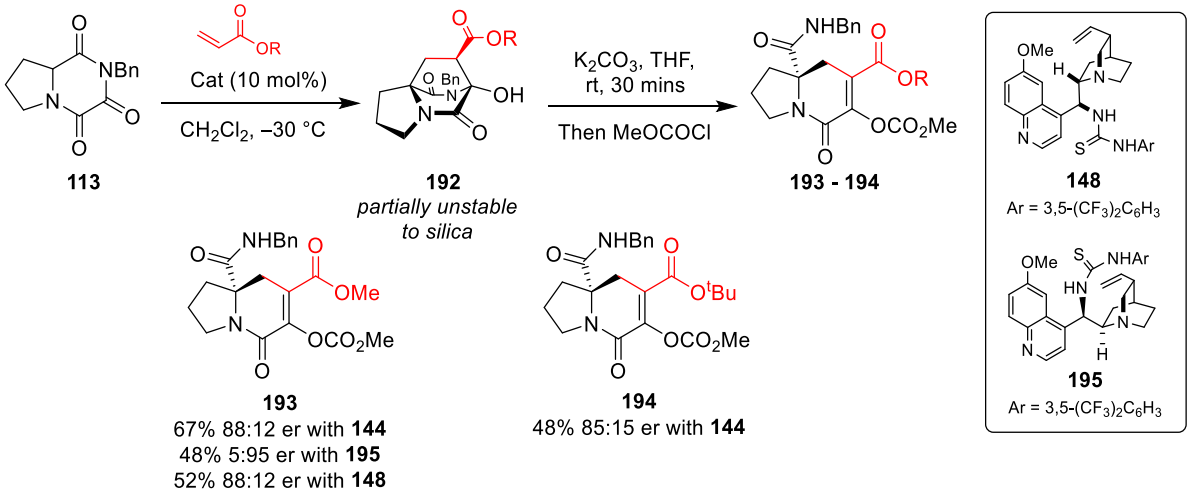


Figure 26 – Michael addition–ring-closure with acrylates

The instability of tricycle **192** was also observed during chiral HPLC analysis with multiple peaks with poor resolution, therefore, tricycle **192** was converted to carbonate **193**. Potassium carbonate was used to effect ring opening of tricycle **192** (R = Me), as seen with ethanolamine in Chapter 2, before acylation with methyl chloroformate to yield carbonate **193** in good yield over 2 steps from TKP **113**. HPLC analysis of carbonate **121** showed a good level of enantioselectivity had been achieved, and a similar result was obtained when the process was repeated with *t*-butyl acrylate to give carbonate **194**.

Thiourea catalysts **148** and **195** had previously shown improved enantiomeric ratios in some Michael addition–ring-closure examples and were therefore tested in the reaction of TKP **113** with methyl acrylate (Figure 26).[43] Quinine derived catalyst **148** was found to give methyl acrylate adduct **193** in an equivalent enantiomeric ratio to catalyst **144**, although an improved enantioselectivity of the opposite enantiomer was obtained when quinidine thiourea **195** was employed in the reaction. The switch in the observed selectivity is due to the different location of the H-bond donor and the inversion of the C-9 centre and was expected from previous work.

The absolute stereochemistry of **192** was assumed from previous work within our research group, which found the electron withdrawing group of the Michael acceptor preferred to be located over the carbonyl

rather than the bulky *N*-benzyl substituent. The stereochemistry was also supported by a crystal structure of a related adduct, which is included and discussed later in this Chapter. The asymmetric reaction generated a single diastereoisomer of tricycle **192**, however, when triethylamine was used as the catalyst an approximate 4:1 mixture of epimers was obtained. Ultimately this was not a concern for the synthesis of carbonates **193**–**194**, due to the removal of the epimeric centre in the products. Since only a single diastereoisomer was observed with the bifunctional catalysts we inferred that the catalyst remains associated with the enolate during the ring closure resulting in the observed diastereocontrol.

The scope of the Michael addition–ring-closure was then expanded to include β-substituted acrylates, which were found to successfully react with TKP **113**, giving adducts **196** and **197** in good to excellent yields (Figure 27).

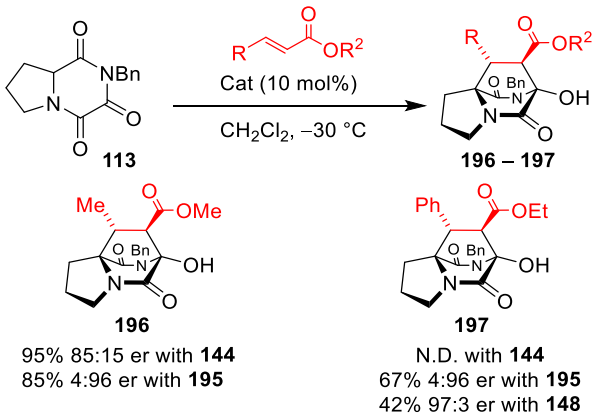


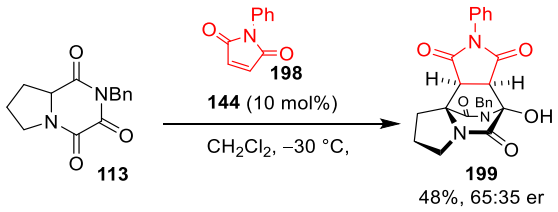
Figure 27 – Michael addition–ring-closure with β-substituted acrylates

In contrast to acrylate adducts **193** and **194**, β-substituted adducts **196** and **197** were found to be stable to silica, which removed the need for conversion into carbonate derivatives. In the reaction with methyl crotonate, compound **196** was generated in an improved enantiomeric ratio of 4:96 when thiourea catalyst **195** was used compared to 85:15 er with phenanthryl catalyst **144**. For this reason, the reaction with ethyl cinnamate was only performed using thiourea catalysts **195** and **148** and gave compound **197** in moderate

yields and excellent enantiomeric ratios. Once again the enantiocomplementary result could be achieved through the use of *pseudo*-enantiomeric catalysts.

Thiourea catalysts **148** and **195** had previously given poor enantiomeric ratios with methyl vinyl ketone (up to 30:70 er, Table 1, page 32) however, the catalysts had given excellent results with acrylates (up to 97:3 er). The justification for this dramatic improvement in enantioselectivity is currently unknown but is consistent with some previous results.[43]

Previous results had shown that maleimides were also suitable Michael acceptors, however in the reaction of *N*-phenyl maleimide **198** with proline TKP **113**, *N*-phenyl maleimide adduct **199** was isolated only in moderate yield and the measured enantiomeric ratio was low (Scheme 44).



Scheme 44 – Michael addition to *N*-phenyl maleimide

The reduced yield was thought to be due to the poor solubility of adduct **199**, which made purification difficult. Alternative maleimides were not tested due to the poor enantioselectivity, which was not expected to significantly increase and for the same reason thiourea catalysts were not tested.

With the excellent results provided by unsaturated esters and oxazolidinones, research then turned to the question of whether α,β-unsaturated amides would be suitable Michael acceptors. Acrylamides are known to be significantly less reactive Michael acceptors in comparison to unsaturated esters or enones.[83] Despite the lower reactivity, asymmetric Michael additions have been reported with a couple of examples shown below (Figure 28).[84,85]

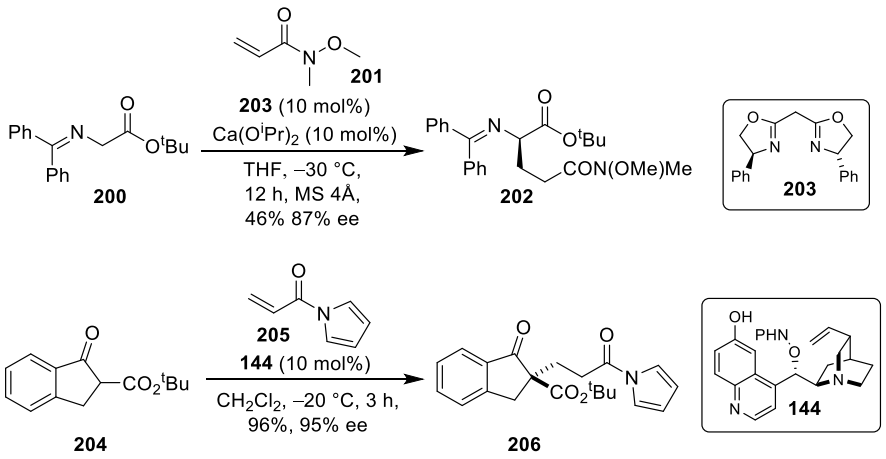


Figure 28 – Examples of asymmetric Michael additions with acrylamides

Kobayashi and co-workers have shown that chiral metal complexes can be used to catalyse the asymmetric Michael addition of adduct **200** to Weinreb acrylamide **201** in moderate yield and good enantiomeric excess. In work more relevant to this project, Dixon and co-workers reported the addition of β-keto ester **204** to *N*-acyl pyrrole **205** using the familiar cinchona derived catalyst **144**. An excellent yield and enantiomeric excess were obtained but the reaction required the use of an activated pyrrole-acrylamide, which is expected to react more like an enone than an acrylamide due to the aromatic nature of pyrrole.

Previous work within our research group had found that TKPs were unreactive towards acrylamides, however since proline TKP had already shown novel reactivity, the reaction with *N*-phenyl acrylamide was attempted (Figure 29). Adduct **207** was isolated in good yield, although an extended reaction time was required in comparison to enones, presumably due to the reduced reactivity of acrylamides. This was thought to be the first example of a cinchona alkaloid catalysed Michael addition to a non-activated acrylamide. In addition to the novel reactivity, the enantioselectivity of adduct **207** was found to be excellent. Spurred on by this result, a range of other acrylamides were tested with TKP **113** (Figure 29).

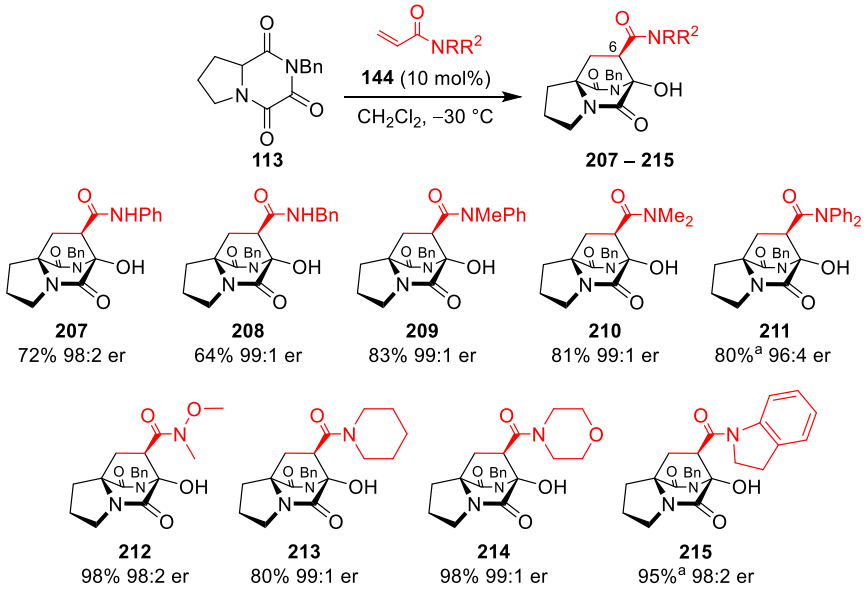


Figure 29 – Scope of Michael addition with acrylamides [(a) – 5–10% of amide epimer observed in crude reaction mixtures]

The Michael addition of TKP **113** was found to be successful with a range of secondary and tertiary acrylamides, including cyclic examples, giving adducts **207**–**215** in good to excellent yields. Exceptional enantiomeric ratios were measured for all adducts with the lowest selectivity (96:4 er) measured for bulky diphenyl adduct **211**. Adducts **207**–**215** were isolated as single diastereoisomers, although approximately 5–10% of the C-6 epimers were observed for diphenyl and indoline adducts **211** and **215** in the crude reaction mixtures. This reduction in diastereoselectivity with adducts **211** and **215** was thought to be due to the bulkiness of the nitrogen substituents which resulted in a reduced catalyst enolate interaction. The generally high diastereocontrol observed with adducts **207**–**215** gave further weight to the hypothesis suggested following the results with acrylates, that the catalyst was involved in the ring-closure step. Further to this, a mixture of epimers at C-6 were observed (approx. 3:1) when triethylamine was used as base for the reaction of TKP **113** with with *N*-phenyl and *N*-benzyl acrylamides, matching the result seen earlier with methyl acrylate. To overcome this issue, the reactions were conducted using a 1:1 mixture of catalysts **142** and **144,** which allowed access to racemic adducts **207**–**215** as single diastereoisomers in good yield and enabled chiral HPLC conditions to be established.

The absolute stereochemistry was determined from an X-ray crystal structure of NMePh adduct **209** (Figure 30).

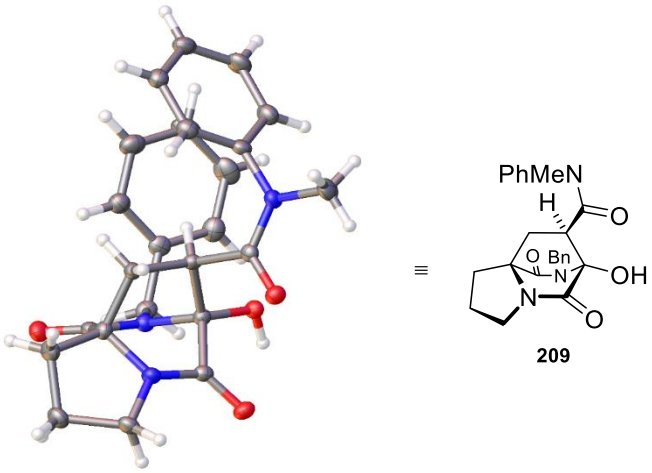
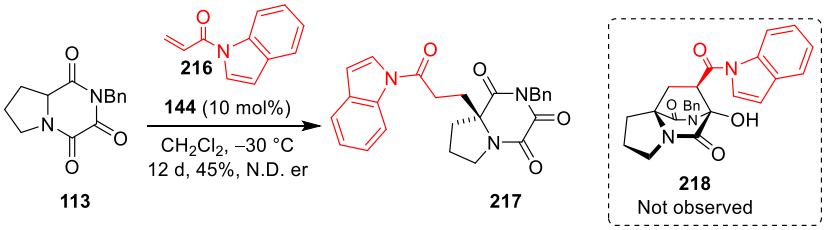


Figure 30 – X-ray structure of NMePh adduct **209** with ellipsoids drawn at the 50% probability level

The solved structure clearly showed the amide group was positioned over the 'front' carbonyl, away from the bulky *N*-benzyl group. This result was in agreement with previous work and was also used to assign the absolute structure of acrylate adducts **192**.

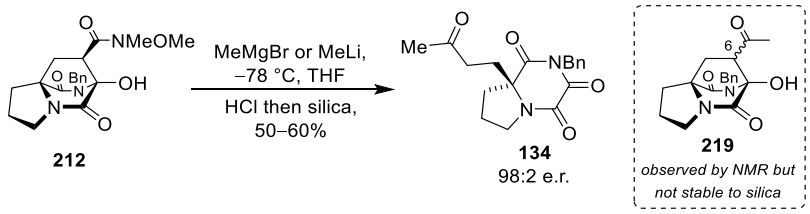
During the screen of acrylamide acceptors, it was found that Michael addition of proline TKP **113** with indole vinyl ketone **216** gave 'open' adduct **217** rather than the expected 'closed' adduct **218** (Scheme 45).



Scheme 45 – Michael addition with indole vinyl ketone **216**.

A plausible explanation for the generation of 'open' adduct **217** is that the acceptor, **216**, is more 'ketone-like' than the other acrylamides above, because of the aromatic indole. The poor solubility of acrylamide **216** and of the product, **217**, was thought to be responsible for the long reaction time and low yield. In light of this result, pyrrole acrylamide **204** was not tested as it was expected to react in the same way.

Determination of the enantiomeric ratio of Weinreb adduct **212** by chiral HPLC could not be achieved with the available columns, due in part to the high polarity of adduct **212**. Consequently, conversion of adduct **212** into a compound suitable for HPLC analysis was required. Weinreb amides are well known for their ability to be converted into ketones through the reaction with Grignard reagents or alkyl lithiums.[86,87] Therefore, Weinreb adduct **212** was treated with methylmagnesiumbromide (Scheme 46).

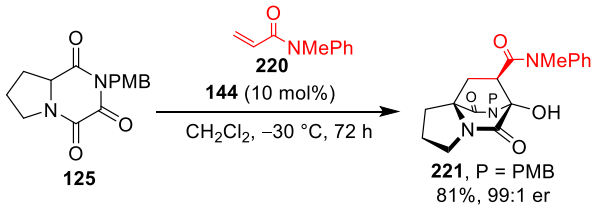


Scheme 46 – Conversion of Weinreb adduct **212**

Grignard addition was found to occur and generated adduct **219**, as a 2.5:1 mixture of epimers at C-6, as seen in the NMR spectrum of the crude reaction mixture, with epimerisation of the C-6 stereocentre adjacent to the amide thought to be caused by the excess Grignard reagent. Surprisingly, when the mixture was purified 'closed' adduct **219** was found to fully convert, presumably *via* a retro-'aldol' ring opening, to adduct **134**. Since HPLC conditions had already been found for methyl vinyl ketone adduct **134**, the enantiomeric ratio of **134** was quickly determined to be 98:2. The enantioselectivity of **214** was confidently inferred from **134** since the initial bond, at the TKP's α-centre, is unaffected by the Grignard addition and subsequent ring opening. The moderate and variable yield of the reaction was attributed to cleavage of the *N*-acyl hemiaminal, which had been previously seen under basic conditions. Attempts to reduce the equivalents of methylmagnesiumbromide used resulted in incomplete reactions and reduced yields. It was found that methyl lithium could also be successfully employed to convert **212** into MVK adduct **134** in similar 50–60% yields. It was envisioned that this methodology could be used to generate a large number of 'open' adducts, through the addition of different Grignard reagents, alkyl lithiums or lithium aluminium hydride to Weinreb adduct **212**. Generation of 'open' compounds in this way would provide them in

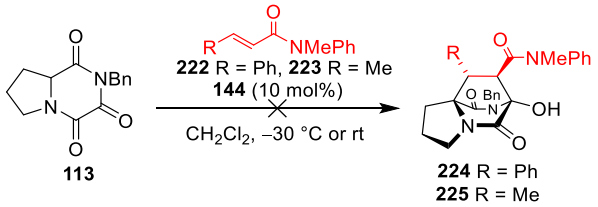
improved enantioselectivity compared to direct synthesis from the respective vinyl ketone/aldehyde, as seen in Chapter 2 (**134** 98:2 er from Weinreb adduct **212** or 90:10 er from the reaction of proline TKP **113** and MVK).

Once again, the observed enantioselectivity was found to be consistent between the *N*-benzyl and *N*-PMB protected TKPs, with adduct **221** synthesised in good yield and with an excellent er.



Scheme 47 – Michael addition of PMB proline TKP **125** with NMePh acrylamide **220**

Since β-substituted enones and acrylates had previously proved successful, β-substituted acrylamides **222** and **223** were also tested with proline TKP **113** (Scheme 48).



Scheme 48 – Attempted Michael addition with cinnamoyl amides **222** and **223**

However, no reaction was observed with either Michael acceptor even when the reaction mixtures were warmed to room temperature. Seemingly, the combination of the increased steric demands and the reduced reactivity of acrylamides meant that β-substituted acrylamides were unsuitable Michael acceptors for this chemistry.

Further Transformations of Michael Addition–Ring Closure Adducts

As shown, the Michael addition–ring-closure process provided a variety of adducts that possess the pyrrolidine fused bicyclo[2.2.2]diazaoctane core that is found within the prenylated indole alkaloids. The tandem process afforded a range of adducts in good to excellent yields and with excellent levels of enantioselectivity and diastereoselectivity (Figure 31). The next stage of the project concentrated on the synthetic transformation of these adducts with the aim to access the aforementioned natural product family.

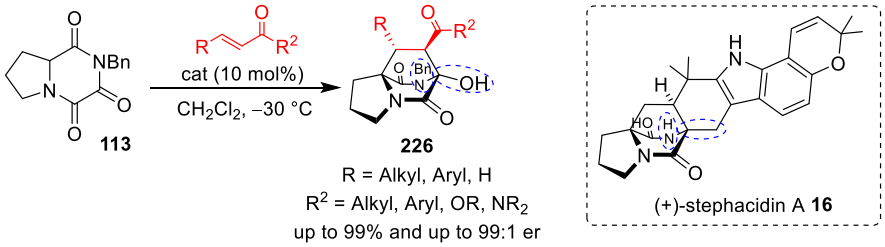
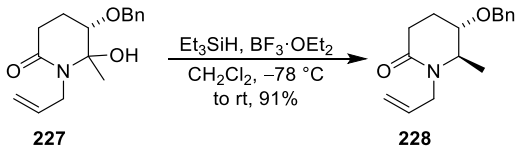


Figure 31 – Overview of Michael addition–ring-closure and the overlap of product **226** with the natural products

It was noted that to increase the potential utility of this methodology for access towards natural product derivatives or fragments, there were two main requirements (Figure 31). Firstly, the Michael addition–ring-closure generated compounds possessing an *N*-acyl hemiaminal. This functionality is not present in the natural product skeleton and had also caused some stability issues, therefore, a strategy was needed for the removal of the bridgehead hydroxyl functionality. Secondly, the natural products have an unprotected, or in some circumstances a methylated, nitrogen so a method for deprotecting the DKP adducts was also sought.

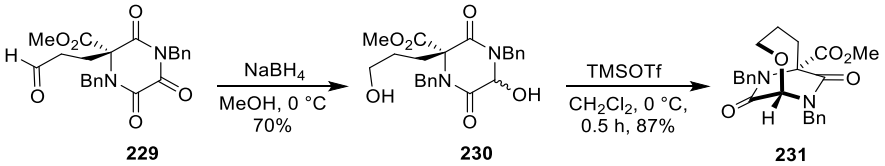
Deoxygenation of Michael-Ring Closure Adducts

Examining the literature showed that *N*-acyl iminium chemistry was a plausible method for the deoxygenation of *N*-acyl hemiaminals, with examples including tertiary hydroxyamides such as the one below (Scheme 49).



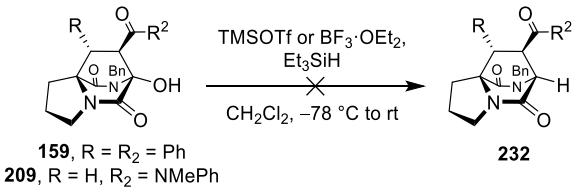
Scheme 49 – Example reduction of N-acyl hemiaminal[88]

In fact, *N*-acyl iminium chemistry had even been used within our research group on a TKP system.[43] Diol **230**, generated from the reduction of the acrolein Michael adduct **229**, using sodium borohydride, was converted to bicycle **231** using TMS triflate in excellent yield (Scheme 50).



Scheme 50 – *N*-acyl iminium ring closure

However, with the tricyclic proline adducts the *N*-acyl hemiaminal is not only tertiary, but also at the bridgehead position, meaning that generation of the intermediate iminium was unlikely to occur. Despite this, two sets of conditions were tested with adducts **159** and **209**, but unsurprisingly no reaction was observed (Scheme 51).



Scheme 51 – Attempted *N*-acyl iminium reduction

Due to the bridgehead position of the hemiaminal a different method was needed for the deoxygenation of the Michael addition–ring-closure products. The Barton–McCombie radical deoxygenation was identified as a potential method, with examples reported for the reduction and alkylation of tertiary bridgehead hydroxyls (Figure 32).

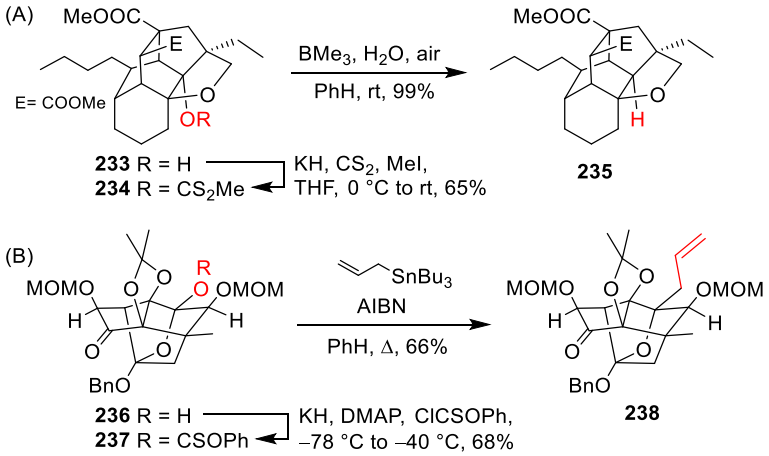


Figure 32 – Examples of radical deoxygenation of tertiary bridgehead hydroxyls[89,90]

Wood and co-workers reported the reduction of alcohol **233**, *via* methyl xanthate **234**, using water and trimethylborane as initiator (Scheme A, Figure 32), whereas Inoue and co-workers generated **238** from alcohol **236**, using a Keck allylation on intermediate thiocarbonate **237** (Scheme B, Figure 32).[89,90]

The literature precedent strongly suggested that reduction of the bridgehead position should be possible using the Barton–McCombie reaction and it gave the possibility for alkylation of the bridgehead position, potentially allowing access towards natural product scaffolds. However, the method required an additional step for the functionalisation of the alcohol to either a xanthate, thiocarbonate or thiocarbamate **240**, in order to achieve deoxygenation. (Figure 33).

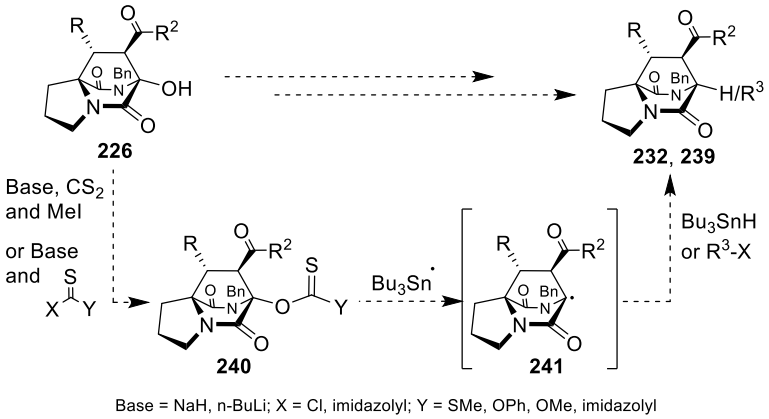
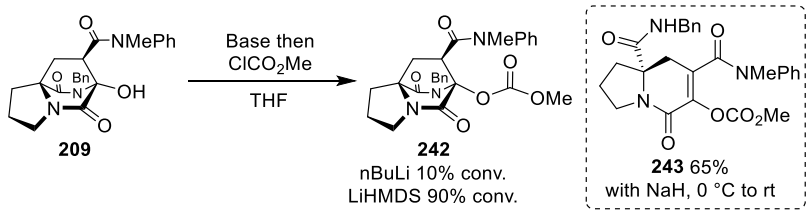


Figure 33 – General Barton–McCombie deoxygenation scheme

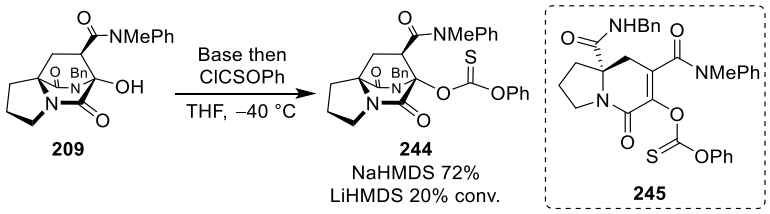
In order to gauge whether functionalisation of the bridgehead hydroxyl was viable, due to the known cleavage of the *N*-acyl hemiaminal under basic conditions, acylation with methyl chloroformate was attempted. Initial studies into the functionalisation of the bridgehead hydroxyl were completed on adduct **209** (Scheme 52).



Scheme 52 – Acylation of bridgehead hydroxyl

Acylation using sodium hydride gave 'opened' product **243** in good yield and attempts to prevent ring opening with colder reaction temperatures were unsuccessful. Substitution of the base to n-butyl lithium was then performed but only partial conversion to product **242** was achieved (approx. 10%), even with 3 equivalents of base. However, when LiHMDS was used the conversion to product was increased to 90%, although **242** could not be isolated cleanly from starting material **209**.

With LiHMDS showing promising results with methyl chloroformate, reaction with O-phenyl chlorothionoformate was then attempted (Scheme 53).

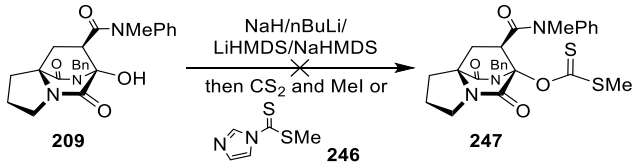


Scheme 53 – Synthesis of thiocarbonate **244**

Reaction of **209** under the previous conditions, using LiHMDS, gave approximately 20% conversion of the starting material and the product was found to be a 4:1 mixture of desired product **244** and 'opened' compound **245**. Swapping the base to NaHMDS was found to give significant improvements, with

thiocarbonate **244** generated in 72% yield. Small quantities of opened thiocarbonate **245** were isolated (up to 10%) but could be separated from the desired product.

Synthesis of methyl xanthate **247** using a range of bases and quenching with carbon disulphide and methyl iodide or imidazolyl dithioester **246** was also attempted (Scheme 54). Unfortunately all attempts were unsuccessful, either returning unreacted **209** or decomposition products in some cases, and consequently xanthate intermediates were not further investigated.



Scheme 54 – Attempted synthesis of xanthate **247**

Concurrently, the acylation and thioacylation reactions were also attempted with chalcone adduct **159** (Figure 34).

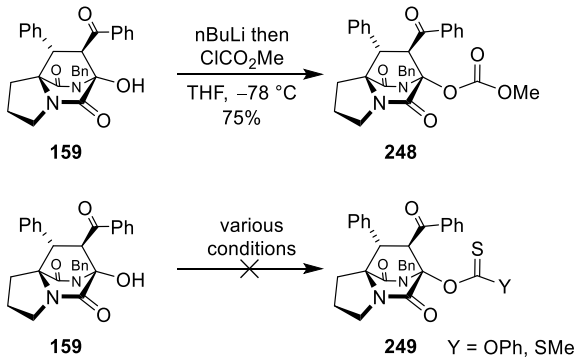
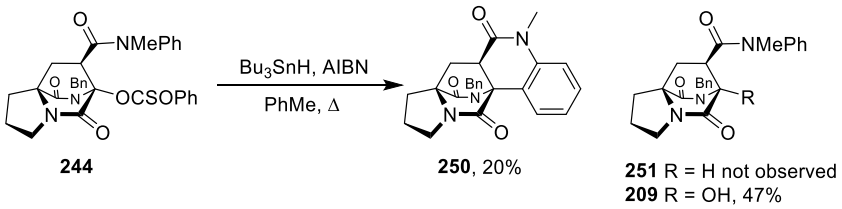


Figure 34 – Functionalisation of chalcone adduct **159**

Acylation of **159** with methyl chloroformate afforded **248** in good yield using n-butyl lithium, but despite trying various conditions the synthesis of thio-derivative **249** was not achieved. Unfortunately compound **159** was not stable under the reaction conditions, with warmer reaction temperatures needed due to the lower reactivity of thionoformate or carbon disulphide compared to methyl chloroformate. Chalcone

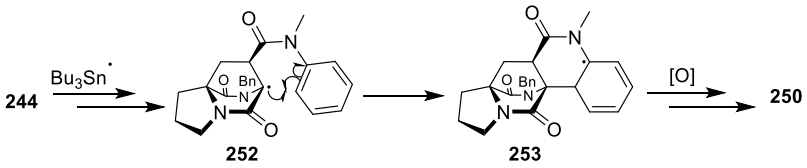
adduct **159** was seen to either undergo cleavage of the *N*-acyl hemiaminal or retro-'aldol' ring opening and therefore synthesis of **249** was not pursued any further.

With thiocarbonate **244** in hand, research then focussed on the radical cleavage of the C-O bond. Tributyl tin hydride and AIBN were found to be the predominant conditions for the Barton–McCombie deoxygenation and were therefore employed on thiocarbonate **244** in toluene (Scheme 55).[91,92]



Scheme 55 – Barton McCombie deoxygenation

Desired product **251** was not observed in the reaction mixture, but instead the reaction generated pentacycle **250** in moderate and variable yields along with significant regeneration of alcohol **209**. Pentacycle **250** is a very interesting compound that was presumably formed by a homolytic aromatic substitution, with addition of the intermediate bridgehead radical into the phenyl ring followed by oxidation (Scheme 56).[93,94]

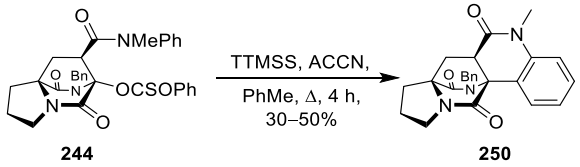


Scheme 56 – Proposed mecahnism for generation of pentacycle **250** through a homolytic aromatic substitution

Regeneration of the alcohol is a common problem of the Barton–McCombie deoxygenation although it is normally only a minor side reaction.[95] Unfortunately, in the case of **244**, alcohol regeneration was found to be the predominant reaction, and was thought to be caused by a formal 1,2-addition of tributyltinhydride to the thiocarbonyl and then degradation to give alcohol **209**. Slow addition of the Bu_3SnH has been shown

to reduced alcohol regeneration but application of this to the reaction of **244** showed no significant change to the result.

Significant work has been completed by the group of Chatgilialoglu into alternative reagents to Bu_3SnH and have reported that tris(trimethylsilyl)silane (TTMSS) is a suitable alternative radical reducing agent.[96,97] Reduction of **244** using TTMSS and AIBN resulted in decomposition of the starting material but swapping the initiator to 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) gave pentacycle **250** in moderate but variable yields but with no alcohol regeneration (Scheme 57).



Scheme 57 – Radical cyclisation of thiocarbonate **244**

It was later found that performing the reaction under air, rather than under nitrogen, resulted in an increased yield of pentacycle **250**, of up to 70%, although the reaction time was extended to 8 hours and additional TTMSS and ACCN had to be added for the reaction to reach completion. The increase in yield was attributed to the improved oxidation of aromatic radical intermediate **253** and the increased reaction times may have been caused by auto-oxidation of the silane to a siloxane and also quenching of radical species by molecular oxygen.[98]

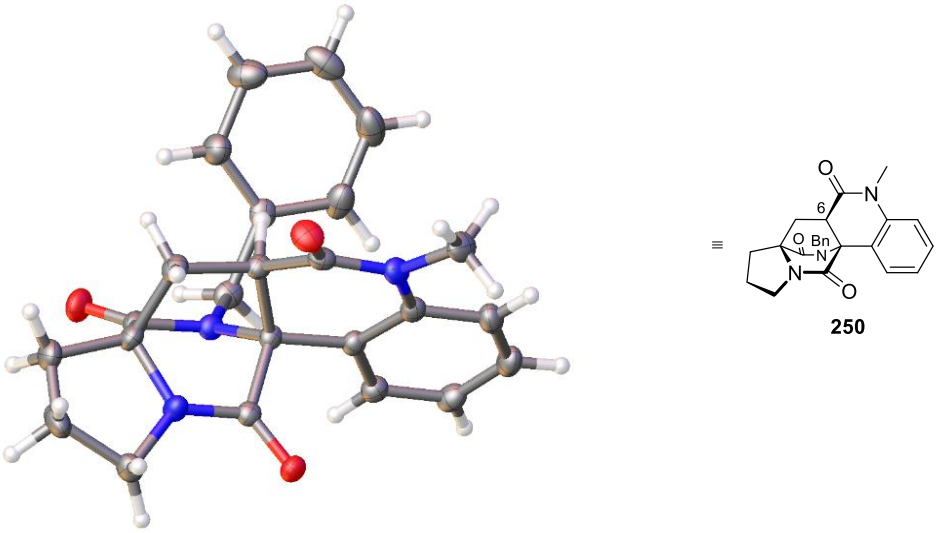
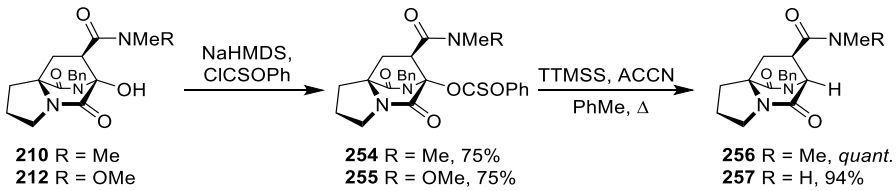


Figure 35 – X-ray structure of pentacycle **250**

The X-ray structure of pentacycle **250** was solved and clearly showed the new bridgehead bond to the phenyl ring (Figure 35). The structure also showed that the C-6 amidic centre had not been epimerised during either the thiocarbonate formation or deoxygenation steps. This was a remarkable result, with pentacycle **250** isolated as a single diastereoisomer in only three steps from TKP **113**. Since amide **209** was synthesised with excellent enantioselectivity, as shown earlier, it was confidently expected that either enantiomer of adduct **209** could be accessed. Furthermore, with the clear similarity of **250** to the natural product family, it demonstrated the utility of the methodology for the access of natural product derivatives.

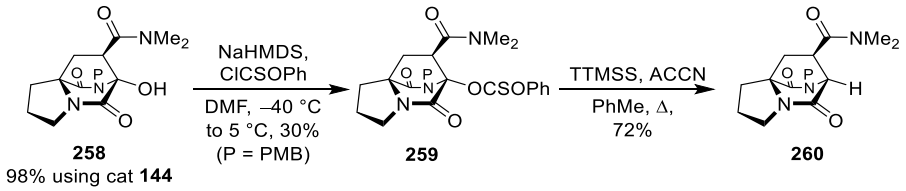
Since aromatic homolytic substitution had occurred with thiocarbonate **244**, related thiocarbonates **254** and **255**, devoid of an aromatic substituent, were synthesised and reduced (Scheme 58).



Scheme 58 – Deoxygenation of non-aromatic amide adducts

Synthesis of dimethyl and Weinreb thiocarbonates **254** and **255** proceeded smoothly and in good yield, with approximately 10% of the open thiocarbonate observed, matching the result with adduct **209**. Initial attempts at the radical reduction of NMe_2 thiocarbonate **254** using the previous conditions, found for **244**, only gave reduced adduct **256** in poor yield (approx. 5%) and completing the reaction with Bu_3SnH resulted in decomposition. However, an excellent yield was obtained when increased quantities of TTMSS (5 equiv.) and ACCN (1.5 equiv.) were used with adduct **256** generated in quantitative yield. Subjecting Weinreb thiocarbonate **255** to the same conditions also resulted in reduction in excellent yield but with concomitant cleavage of the hydroxylamide N–O bond to give secondary amide **257**. Although no reports were found of using Bu_3SnH or TTMSS to effect N–O cleavage, the reductive cleavage of hydroxylamines has been reported for a number of other reducing agents, including Na, Li, SmI_2 and also organic electron donors.[99–101]

With the excellent results obtained for the deoxygenation of adduct **210**, the procedure was repeated on the PMB variant **258**, with the aim of synthesising adduct **260** which could then later be deprotected (Scheme 59).



258
98% using cat **144**

259

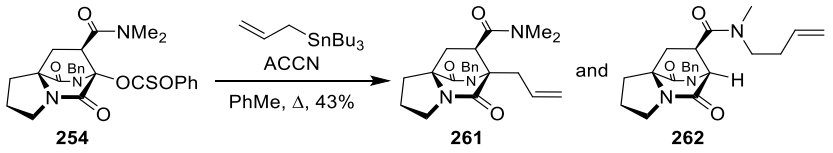
260

Scheme 59 – Deoxygenation of PMB amide adduct **258**

Synthesis of thiocarbonate **259** proved more challenging than for the previous examples above, with significant epimerisation of the amidic stereocentre observed, affording thiocarbonate **259** as a mixture of diastereoisomers. The combination of the diastereomeric mixture and the formation of the usual opened thiocarbonate sideproduct, resulted in the purification of product **259** using preparative HPLC. With

thiocarbonate **259** in hand reduction using TTMSS and ACCN under the previously optimised conditions afforded compound **260** in good yield, ready for deprotection which will be discussed later in this Chapter.

In an effort to extend the radical deoxygenation chemistry, the Keck allylation of thiocarbonate **254** was also attempted (Scheme 60).



Scheme 60 – Keck allylation of NMe_2 thiocarbonate **254**

The reaction was found to proceed but gave a mixture of allylated products which were tentatively assigned as **261** and **262**. Unfortunately, the products could not be separated by silica gel flash chromatography or preparative HPLC so determination of the structure was not achieved. The proposed mechanism for formation of the two isomers is shown below (Figure 36).

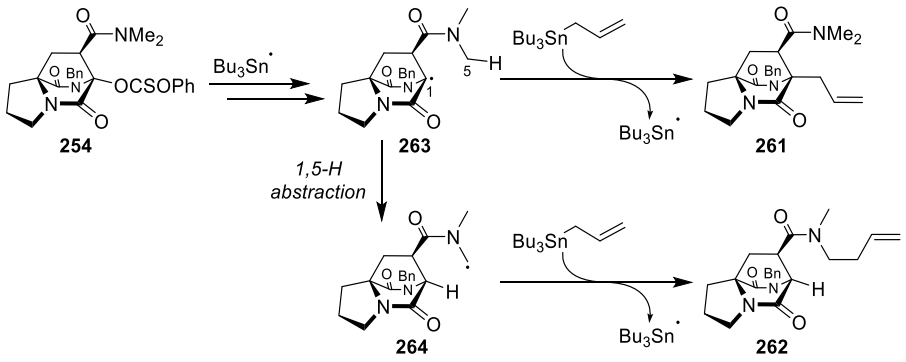
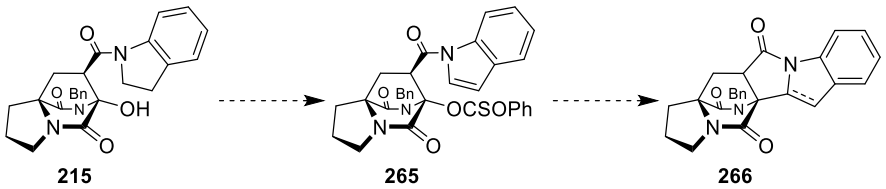


Figure 36 – Proposed mechanism for generation of allylated compounds **261** and **262**

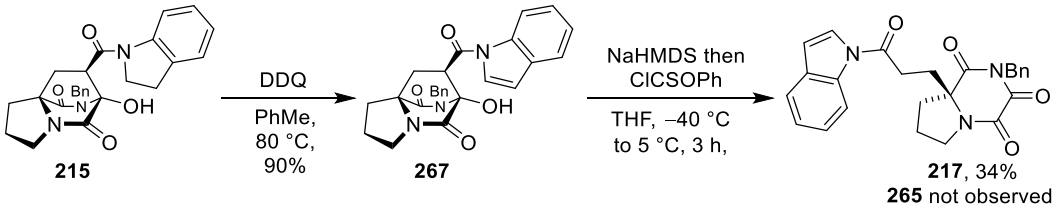
In the presence of Bu_3Sn· thiocarbonate **254** was expected to be converted to bridgehead radical **263** which could then react directly with a molecule of allyl tributyl tin to generate the expected Keck allylation product **261**. Alternatively radical **264** could formed from a 1,5–H abstraction before reaction with allyl tributyl tin that would then generate compound **262** (Figure 36).

Inspired by the homolytic aromatic substitution that generated pentacycle **250**, it was envisioned that a similar cyclisation could occur with indole thiocarbonate **265** (Scheme 61). Incorporation of an indole moiety into the radical adduct was desired to further increase overlap with the natural products, with cyclised product **266** showing significant similarities to several family members.



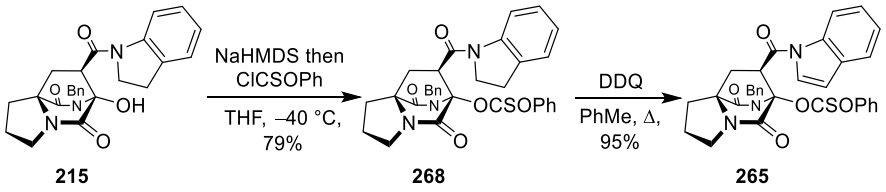
Scheme 61 – Proposed radical cyclisation *via* indole thiocarbonate

Oxidation of indoline adduct **215** with DDQ was achieved in good yield but the conversion of indole **267** to thiocarbonate **265** was unsuccessful, instead affording 'open' indole adduct **217** (Scheme 62).



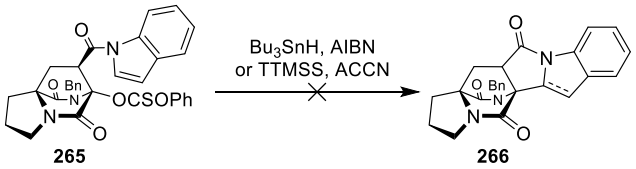
Scheme 62 – Attempted synthesis of indole thiocarbonate **265**

Treatment of indole **267** with base resulted in a retro-'aldol' ring opening giving indole adduct **217**, which was in contrast to the *N*-acyl hemiaminal cleavage seen in the previous thiocarbonate syntheses. This was presumably due to the more ketone-like nature of the acyl indole, compared to the other amides, which made it a better leaving group than the amide. Considering this, the order of the steps was altered and thiocarbonate formation followed by indoline oxidation gave access to indole thiocarbonate **265** in good yield (Scheme 63).



Scheme 63 – Synthesis of indole thiocarbonate **265**

Radical cyclisation of indole thiocarbonate **265** was then attempted but unfortunately compound **266** was not isolated. Various conditions, with both Bu_3SnH and TTMSS, were employed but in all cases no significant products could be identified from the crude reaction mixtures (Scheme 64).



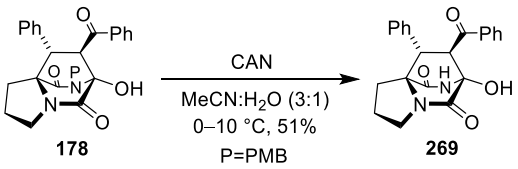
Scheme 64 – Attempted radical cyclisation of indole thiocarbonate **265**

With this result and other attempts to access compounds with an alkylated bridgehead position being unsuccessful, other than generation of pentacycle **250**, research in this area was stopped, however, an alternative approach was undertaken and will be discussed in the next Chapter.

Nitrogen Deprotection

The second desired transformation to increase the structural overlap with the natural product family, was the deprotection of the tricyclic Michael addition–ring-closure adducts. Due to the known difficulty in removing *N*-benzyl groups from amides, the deprotection was only attempted on PMB adducts.[102] Consultation of the literature and based on some preliminary results from our research group, indicated that cerium ammonium nitrate (CAN) should be a suitable oxidant for the removal of the PMB protecting group from Michael addition–ring-closure products.

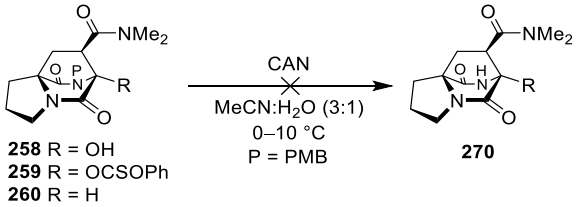
Deprotection of chalcone adduct **179** with an aqueous CAN solution, proceeded in moderate yield although product **269** was found to have poor solubility which made isolation and purification difficult.



Scheme 65 – Deprotection of chalcone adduct **179**

Despite the purification and isolation problems this was an impressive result, especially since removal of the PMB group from similar structures had previously proved troublesome.[45,102] With this promising result the deprotection of other compounds was attempted.

Amide **258**, thiocarbonate **259** and reduced compound **260** were all submitted to the same reaction conditions as used with chalcone adduct **179** (Scheme 66). In all three reactions, anisaldehyde was observed, indicating the progression of the reaction, but no desired compound was isolated.



Scheme 66 – Attempted deprotection of compounds **258**, **259** and **260**

Various modifications were made to the reaction conditions in an attempt to access compound **270**, including shorter reaction times, lower equivalents of CAN and changing the solvent to t-BuOH:CH_2Cl_2 in order to reduce the reaction temperature. However, none of the modifications were found to improve the outcome of the reaction. Unfortunately the deprotection method appeared to only be suitable for chalcone adduct **179** but ongoing research on the removal of a dimethoxy benzyl (DMB) group has given promising results on other TKP systems.

Summary and Future Work

The Michael addition–ring-closure has been observed with a number of acceptors, including β-substituted enones, acrylates and *N*-phenyl maleimide. The tandem process was also found to occur with a wide range of acrylamides, and is believed to be the first example of cinchona alkaloid catalysed Michael addition to unactivated α,β-unsaturated amides. Exceptional levels of enantioselectivity have been recorded across a range of acceptor classes with results up to 99:1 er using cinchona derived catalysts.

As with previous results, the enantioselectivity of the Michael addition appears to be consistent regardless of the use of *N*-benzyl or *N*-PMB protecting groups. The latter of which was oxidatively removed from chalcone adduct **179** in good yield using cerium ammonium nitrate, although attempts at the deprotection of amide adducts were unsuccessful.

To increase structural overlap with the natural product family, deoxygenation of the bridgehead hydroxyl was attempted. No reaction was observed using *N*-acyl iminium chemistry but reduction and cyclisation were found to occur using the Barton–McCombie reaction. Conversion of Michael addition–ring-closure adducts to thiocarbonates was found to proceed in good yield using NaHMDS and *O*-phenyl chloro-thionoformate, although ring opening was observed in low yield (up to 10%). Use of TTMSS and ACCN with NMePh thiocarbonate **244** gave cyclised product **250** in good yield from an aromatic homolytic substitution, whereas the reductions of non-aromatic amides **210** and **212** were achieved using slightly modified conditions in excellent yields. It was also found that reduction of Weinreb adduct **212** occurred with concomitant hydroxylamine cleavage to generate a secondary amide. The deoxygenation of a PMB protected amide adduct was also successful, although lower yields for the formation of thiocarbonate were obtained, due to epimerisation of the centre adjacent to the amide. The Keck allylation of NMe_2 adduct **254** was also attempted but the reaction gave a mixture of allylated products with a side product thought to be caused by 1,5-H abstraction of the bridgehead radical.

Work is currently ongoing within the group on an alternative DMB protecting group which should allow for a milder deprotection of Michael addition–ring-closure and deoxygenation adducts. Previous work on the synthesis of brevianamide B **2** and malbrancheamide B **5** found that an OBn protecting group could be used and later removed using SmI_2.[36] With the observed cleavage of the hydroxylamine in the deoxygenation of Weinreb adduct **212**, there is potential for completing the deoxygenation and deprotection reactions in one step if an OBn or OMe protected proline TKP could be synthesised and taken through the additional steps.

As mentioned earlier, the reaction of Weinreb TKP adduct **212** with Grignard reagents, alkyl lithiums or lithium aluminium hydride should allow access to a number of 'open' adducts all in excellent enantioselectivity which would be set from the initial Michael reaction with Weinreb acrylamide.

Additional work is also needed with acrylonitrile and vinyl sulfones, which gave multiple products under the standard conditions used for the other acceptors. Alternative catalysts and solvents could be screened to see if the expected Michael addition–ring-closure adduct could be established for these acceptor classes, thereby broadening the scope of the reaction. An alternative catalyst such as those mentioned at the end of Chapter 2 may also allow the Michael addition with β-substituted acrylamide and/or with β,β-disubstituted enones and give improved enantioselectivity with the addition to maleimides.

Chapter Four – Accessing the Bicyclo[2.2.2]diazaoctane Core Through a Michael–Michael Cascade

Aims and Objectives

The removal of the problematic bridgehead hydroxyl generated from the Michael-addition–ring-closure process was successfully achieved using a Barton–McCombie radical deoxygenation on a small selection of amide adducts. Attempts to extend this methodology towards the natural products, such as stephacidin A **16**, through inter- or intra-molecular additions were unfortunately not successful. This resulted in a desire to find an alternative cascade process for generating compounds possessing the bicyclo[2.2.2]diazaoctane core without the bridgehead hydroxyl. Our proposed alternative strategy was to replace the reactive carbonyl of the TKPs with an electron deficient alkene to give methylene DKP **272**. It was anticipated that adduct **272** would undergo a Michael addition to give intermediate enolate **273** which would then hopefully close onto the intramolecular Michael acceptor. This Michael–Michael cascade strategy should generate adduct **274**, which possesses the bridgehead C-C bond, as seen in stephacidin A **16**, rather than the problematic *N*-acyl hemiaminal previously generated (Figure 37).

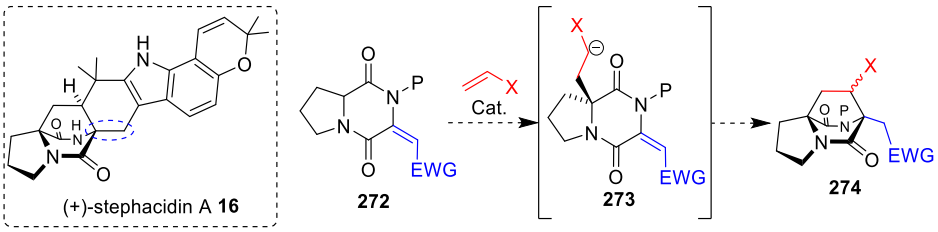


Figure 37 – Proposed Michael–Michael cascade with proline DKP derivative

It was envisioned that methylene DKP **272**, like the previously used TKPs, would also be activated for deprotonation at the α-position, since the electron withdrawing group would withdraw electron density in a similar fashion to the C-3 carbonyl in the TKP system. Although the activation of the extended system

was expected to be less than that seen in the TKP systems, it was hoped that it would be sufficient to allow deprotonation of the α-centre by amine bases, specifically the chiral cinchona alkaloids used for the asymmetric Michael additions with the proline TKPs, enabling the organocatalytic Michael–Michael cascade.

On consultation of the literature it was found that asymmetric Michael–Michael cascades with oxindole derivatives have been previously reported, catalysed by cinchona derived catalysts (Figure 38).[103,104]

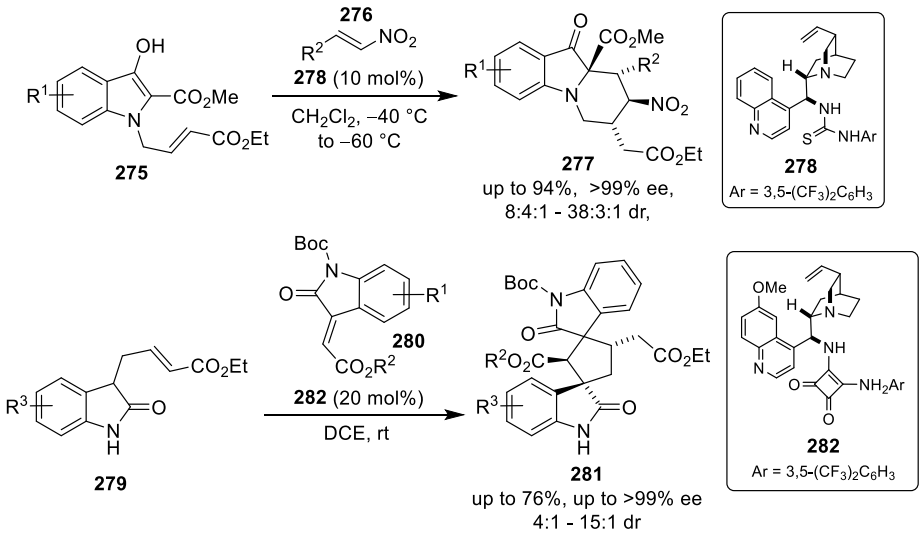


Figure 38 – Examples of Michael–Michael cascades

Xu and co-workers showed that catalyst **277** can deprotonate enol **275** and catalyse the asymmetric Michael addition into nitroolefin **276** before cyclisation of the generated nitronate into the intramolecular acrylate. Wang and co-workers showed that squaramide catalyst **282** can deprotonate oxindole **279** which adds into methylene oxindole **280** followed by cyclisation on to the acrylate moiety of **279** to form spiro-bisoxindole **281**. Both Michael–Michael cascades above were found to be highly enantio- and diastereo-selective, giving products **277** and **281** in good to excellent yields. These results gave confidence for the Michael–Michael strategy towards DKP **274** and the natural product family.

Synthesis of Electron Deficient Methylene Diketopiperazines

The first aim was the synthesis of electron deficient methylene DKPs and examination of the literature showed several potential synthetic routes (Figure 39).[53,105,106]

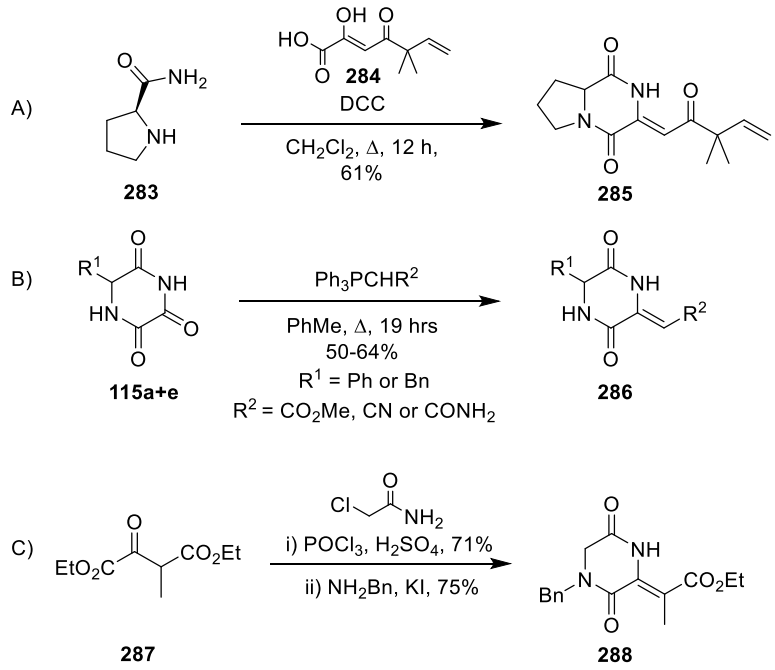
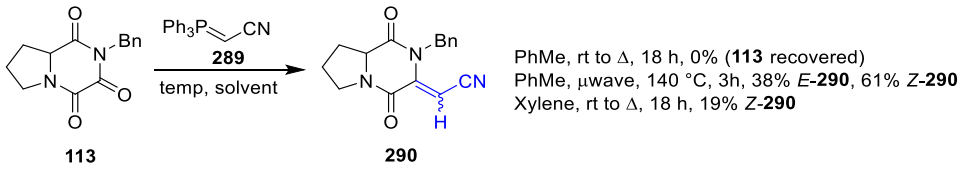


Figure 39 – Examples of the synthesis of electron deficient methylene DKPs

Williams and co-workers synthesised DKP **285** from prolinamide **283** with pyruvic acid derivative **284** through an amide coupling reaction in good yield (A, Figure 39) whilst Person and Le Corre reported the non-classical Wittig reaction of TKPs **115a+e** with several ylides which gave methylene DKP **286** in good yield (B, Figure 39). Finally, Shin and co-workers synthesised DKP **288** from diethyl oxalpropionate **287**, firstly forming the *N*-acyl enamine condensation product before chlorine displacement and then cyclisation using benzylamine (C, Figure 39).

Of the methods shown above, the Wittig reaction was chosen to be investigated first, since this divergent synthesis potentially allowed access to a number of DKPs to be synthesised through varying the choice of ylide.

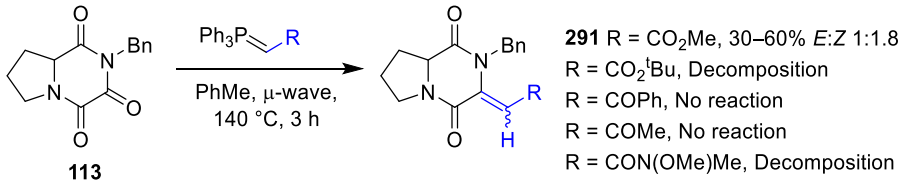
With a significant quantity of benzyl TKP **113** to hand and inspired by the chemistry of Person and Le Corre the reaction with cyano ylide **289**, which was readily prepared following a literature procedure, was investigated (Scheme 67).[107]



Scheme 67 – Conversion of proline TKP to cyano proline DKP

Under the conditions reported by Person and Le Corre no reaction was found to take place, which was thought to be due to the added steric bulk of the *N*-benzyl protecting group compared to the secondary imide in the literature example. As an alternative to conventional reflux conditions and to allow the reaction to be performed at higher temperature, the reaction mixture was heated in a sealed vessel using a microwave reactor at 140 °C for 3 hours. Using these conditions DKP **290** was synthesised in excellent combined yield of 99% as a 1:1.6 mixture of *E* and *Z* isomers which could be separated using silica-gel column chromatography. The minor *E*-isomer was assigned with the newly installed cyano group trans to the *N*-benzyl due to an observed correlation of the alkene CH to the methylene protons of the benzyl group in the NOESY NMR experiment. Considering the limitations of microwave reactors for the synthesis of gram-quantities of cyano-DKP the batch reaction was repeated using xylene to achieve a reaction temperature of 140 °C under reflux, but was found to only give partial conversion to the desired product after 18 hours. Extended reaction times and increased quantities of ylide **289** were investigated, however the reaction yield was found to plateau around 25% and so the microwave conditions were used in multiple batches.

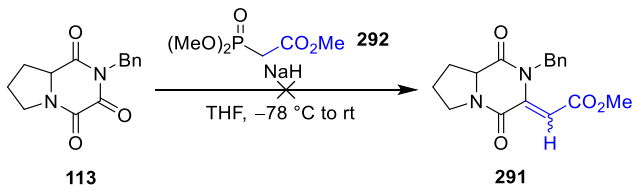
Following the successful synthesis of cyano DKP **290**, a number of other stabilised ylides were tested with proline TKP **113** under the same conditions (Scheme 68).



Scheme 68 – Attempted Wittig reactions

Disappointingly, no reaction or decomposition of **113** was observed for the majority of the ylides, except for methyl (triphenylphosphoranylidene)acetate which afforded carboxymethyl DKP **291** in moderate but highly variable yields. Attempts were made to improve the yield and reproducibility for the synthesis of **291**, including using additives (Et_3N, LiCl and K_2CO_3), changing solvents (xylene and THF) and varying the temperature of the reaction (140–200 °C), however, no significant improvement could be made.

Along with the moderate and variable yield for the synthesis of **291**, isolation of clean product without triphenylphosphine oxide, the by-product from the Wittig reaction, was found to be difficult. In an attempt to remove this purification issue and potentially increase the yield of **291**, a Horner–Wadsworth–Emmons (HWE) reaction was attempted (Scheme 69).



Scheme 69 – Attempted HWE reaction on proline TKP

The benefit of the HWE reaction is that the phosphate by-product is water soluble so can be easily removed from the desired product through an aqueous wash and also the phosphonate carbanion is more reactive than phosphonium ylides. Unfortunately the reaction was unsuccessful, returning TKP **113** along with some minor degradation products. The reaction mixture was observed to turn bright yellow in colour, which was previously found to be indicative of the formation of the TKP enolate, suggesting that the HWE reaction was unsuccessful due to the deprotonation of the acidic α-proton on TKP **113**. Generation of the

TKP enolate was then expected to prevent addition of the phosphonate carbanion into the C-3 carbonyl. This result indicated that phosphonate reagents would not be suitable for the olefination of TKP **113**, due to the high acidity of the α-proton and the increased basicity of phosphonates compared to phosphonium ylides, and therefore were not investigated further.

At the same time cyano ylide **289**, which had shown excellent reactivity with proline TKP **113**, was reacted with a variety of TKPs to investigate the scope of the Wittig reaction (Figure 40).

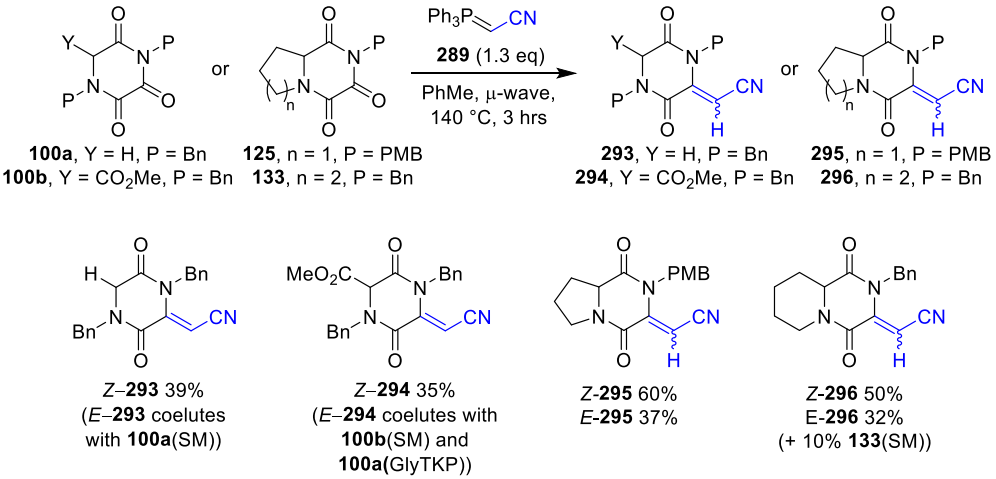
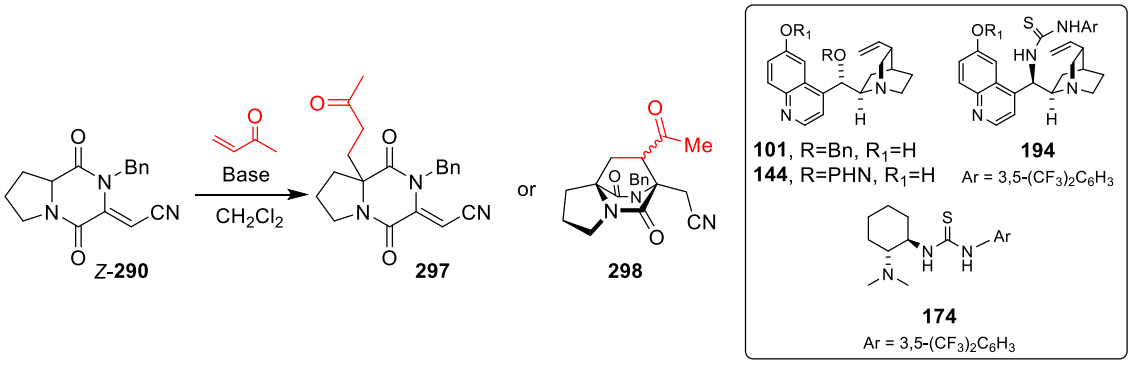


Figure 40 – Scope of the Wittig reaction of cyano ylide with various TKPs

Gratifyingly the reaction was found to be successful with a range of TKPs, with PMB protected DKP **295** and homo-proline adduct **296** generated in good to excellent yields, with *E*:*Z* ratios consistent with the previous result with TKP **113**. The reactions involving glycine and carboxymethyl TKPs **100a** and **100b** were found not to reach completion, irrespective of the equivalents of ylide added. The *Z*-isomers of **293** and **294** could be isolated in moderate yield with the *E*-isomers co-eluting with the unreacted starting materials. In the case of carboxymethyl TKP **100b**, some glycine TKP **100a** also co-eluted with the *E*-isomer, presumably the result of a decarboxylation reaction under the harsh reaction conditions.

Investigation of the Michael–Michael Cascade with Methylene DKPs

With a number of methylene DKPs in hand the next step was to investigate whether they would undergo a Michael–Michael cascade reaction. Initial research was conducted with cyano DKP *Z*-**290** and MVK, as shown below (Table 2).



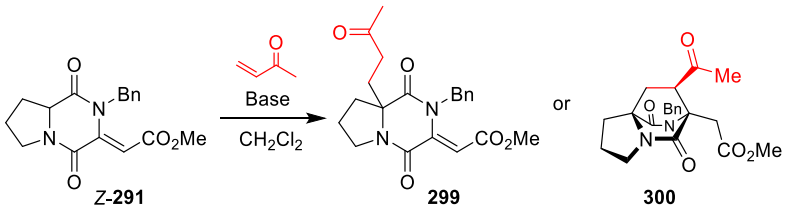
Entry	Catalyst	Temp (°C)	Time (d)	**297** (%)[a]	**298** (%)[a]	er[b]
1	Et_3N	-30	3	10% conv.[c]	0	ND
2	Et_3N	20	3	70	0	ND
3	**144**	20	4	83	0	61:39
4	**101**	2	10	87	0	68:32
5	**194**	2	10	90	0	50:50
6	**174**	2	3	47 (35% rsm)	0	49:51

Table 2 – Asymmetric Michael addition of cyano DKP, [a] – isolated yield, [b] – determined by HPLC, [c] – determined by NMR

The reaction of DKP **290** with MVK was found to be slow when conducted at –30 °C, and the new product was identified as Michael adduct **297** with Michael–Michael adduct **298** unfortunately not observed (entry 1). Michael adduct **297** was isolated in good yield when the reaction was performed at room temperature but again Michael–Michael adduct **298** was not observed (entry 2). The previous optimal catalyst was then employed at room temperature and, as with triethylamine, gave adduct **297** in good yield but the enantiomeric ratio was found to be only moderate (entry 3). Nevertheless this was important progress as it is the first example of this class of Michael donor undergoing an asymmetric Michael addition. It was found that the enantioselectivity could be slightly increased to 68:32 er by using catalyst

101 at 2 °C but the reaction time had to be extended by 6 days to achieve full conversion (entry 4). Thiourea catalyst **194** and Takemoto's catalyst **174** were also tested but afforded product **297** as racemic mixtures (entries 5 and 6). The Michael reaction was also found to proceed with the *E*-isomer of cyano DKP **290** using triethylamine, with a comparable yield of 72%, however, a method for splitting the enantiomers of product *E*-**297** using chiral HPLC could not be established. Therefore, the reaction was not completed using the chiral catalysts since the enantioselectivity could not be determined.

Unfortunately, no Michael–Michael product **298** was observed in any of the reactions above, but inspired by the successful reaction of cyano DKP **290** in the initial Michael addition with MVK, the same reaction was attempted with carboxymethyl DKP *Z*-**291** (Table 3).



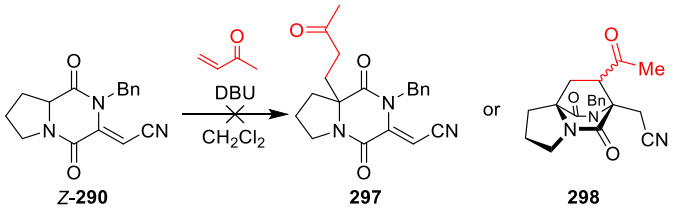
Entry	Base	Temp (°C)	Time (d)	**299** (%)[a]	**300** (%)[a]
1	Et_3N	20	3	No reaction	ND
2	**101**	20	3	No reaction	ND
3	DBU	20	1 (h)	Decomposition	ND
4	DBU	-30	4	30	23
5	DBU	2	4	0	69 (7:1 dr)

Table 3 – Michael–Michael cascade of carboxymethyl DKP, [a] – isolated yield

Disappointingly, no reaction was observed using either triethylamine or catalyst **101** even when conducted at room temperature. This lack of reactivity in comparison to cyano DKP **290** was thought be due to the decreased electron withdrawing nature of the ester group compared to the nitrile, which results in reduced activation of the α-proton. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was then employed as a stronger base in order to deprotonate DKP **291** but was unfortunately found to decompose DKP **291** after 1 hour at room temperature (entry 3). When the reaction was repeated using DBU at –30 °C it was pleasingly

found to give both Michael adduct **299** and also Michael–Michael adduct **300** in 30% and 23% yields respectively (entry 4). Increasing the reaction temperature to 2 °C afforded Michael–Michael adduct **300** as the sole product in a good yield of 69%. Gratifyingly, **300** was also formed in a good diastereomeric ratio, with the major epimer drawn above assigned from correlations in the NOESY NMR and was thought to match the predominate stereochemistry of the desired natural product family. This exceptional result is the first example of a Michael–Michael cascade on a DKP substrate. It also demonstrates that this methodology can be successfully used to access compounds possessing the pyrrolidine fused bicyclo[2.2.2]diazaoctane ring system, with good diastereo-control.

Following the success with the carboxymethyl DKP, the reaction between cyano DKP *Z*-**290** with MVK was repeated using DBU at 2 °C (Scheme 70).



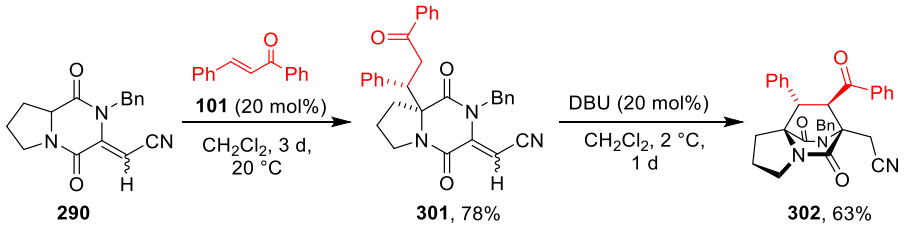
Scheme 70 – Attempted Michael–Michael cascade of cyano DKP

Despite the observation of Michael–Michael product **298** in the NMR spectrum of the crude reaction mixture, neither compound **297** nor **298** could be isolated following purification by silica-gel flash column chromatography. Due to the observed instability of **298** and success of the carboxymethyl system this particular reaction was not investigated further.

Investigating the Scope of the Michael–Michael Cascade

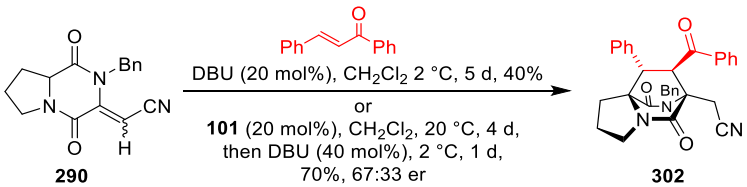
Although the Michael–Michael cascade had been successfully established, the reaction required the use of DBU with the chiral cinchona catalysts showing reduced reactivity. In the asymmetric Michael additions of proline TKP **113**, β-substituted enones were found to undergo a Michael–'aldol' ring closure

in comparison to the Michael reaction observed with simple enones. It was hypothesised that the same reactivity might be seen for the methylene DKP system enabling the Michael–Michael cascade to proceed with β-substituted enones while using the cinchona derived catalysts. Therefore, the reaction of cyano DKP **290** with chalcone using catalyst **101** was investigated (Scheme 71).



Scheme 71 – Reaction of cyano DKP with chalcone

The reaction of DKP **290** with chalcone, using catalyst **101**, was found to afford Michael adduct **301** in good yield and as a single diastereoisomer, with Michael–Michael adduct **302** not observed. Unfortunately, despite the presence of the β-substituent, catalyst **101** could not affect the second Michael addition with protonation of the intermediate enolate instead favoured. Despite this, the reaction is a surprising but notable result as in all previous work only glycine TKP **100a** and proline TKP **113** had reacted with chalcone.[43] Moreover, it was also found that the ring closure of adduct **301** could be successfully affected in a second step using DBU at 2 °C, affording **302** in good yield and impressively as a single diastereoisomer. Racemic Michael–Michael adduct **302** could also be directly generated in one step using DBU in moderate yield (Scheme 72).



Scheme 72 – Michael–Michael cascade of cyano DKP with chalcone

Further to this, it was found that adduct **302** could be synthesised asymmetrically in one-pot using catalyst **101** followed by addition of DBU once full conversion of DKP **290** was observed by TLC. The enantiomeric ratio of the Michael–Michael adduct **302** synthesised using this strategy was measured to be 67:33 er, which is similar to the previous er measured for MVK adduct **297**.

Following the asymmetric Michael addition shown with proline DKP **290** the reaction of DKPs **294** and **293** with MVK were attempted to investigate the scope of the Michael addition and to see if improved enantiomeric ratios could be achieved (Figure 41).

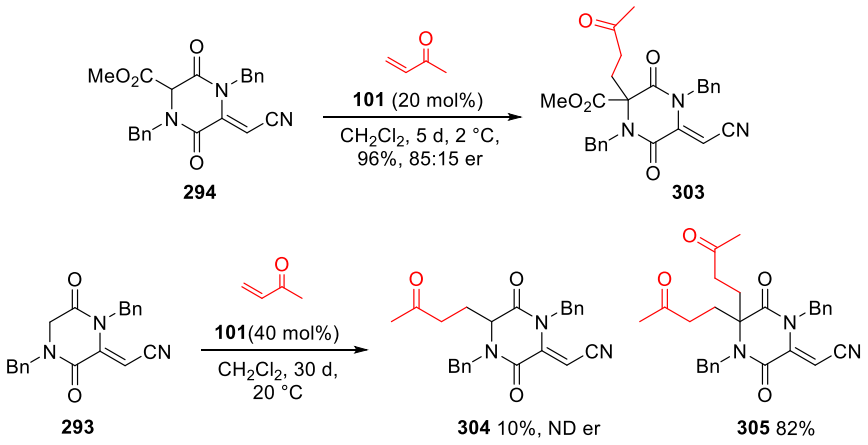
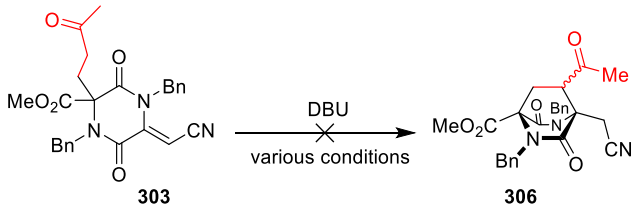


Figure 41 – Exploring the scope of the Michael addition with other cyano DKPs

Carboxymethyl DKP **294** was found to react with MVK, using catalyst **101**, to afford Michael adduct **303** in excellent yield and with a good enantiomeric ratio. The improved enantioselectivity of 85:15 er, in comparison to the 68:32 er result for proline adduct **290**, was thought to be due to the increased acidity of the α-proton in DKP **294** because of the added activation offered by the 1,3-dicarbonyl functionality. On the other hand glycine DKP **293** appeared to be less reactive and required increased catalyst loading, time and temperature with the reaction seeming to not reach completion after 30 days as observed by TLC. However when the reaction mixture was purified, the major product was found to be double Michael adduct **305**, with the minor product being identified as Michael adduct **304**. A small amount of racemic Michael adduct **304** was synthesised using DBU for the development of chiral HPLC conditions to

determine the er of adduct **304**. Unfortunately, a method to separate the enantiomers could not be established with the chiral columns available and therefore the enantiomeric ratio could not be measured. Nonetheless this result is optimistic that DKP **293** underwent not only one but two Michael additions, meaning that this strategy should also work for alkyl methylene DKPs and also allow sequential reactions with two different Michael acceptors to be carried out, as previously established with TKPs.[43] The high er achieved with carboxymethyl DKP **294** also suggests that further Michael adducts should be accessible with good levels of enantio-enrichment however this would require further investigation.

As with the proline derivative, catalyst **101** only achieved the first Michael addition, therefore in an attempt to affect the ring closure, Michael adduct **303** was reacted with DBU (Scheme 73).



Scheme 73 – Attempted Michael ring closure of monocyclic adduct

Various attempts with modifications of the reaction temperature, time and concentration were made to try to generate cyclised compound **306**, however, in all cases only decomposition was observed.

Extension of the Michael–Michael Cascade towards the Prenylated Indole Alkaloid Family

Following the success of the Michael–Michael cascade with the proline DKP, research then focussed on how the cascade process could be extended towards the prenylated indole alkaloid family. The previously generated Michael–Michael adducts demonstrated the utility of the method for generating products possessing the pyrrolidine fused bicyclo[2.2.2]diazaoctane core of the prenylated indole alkaloids.

However, it was hypothesised that the similarity to the skeleton of the natural products could be improved. Comparing the skeleton of members of the natural product family with the products of the Michael–Michael cascade it was noted that adduct **307**, which incorporates the common 2-alkyl indole moiety, shows excellent overlap with the skeleton of stephacidin A **16** for example (Figure 42).

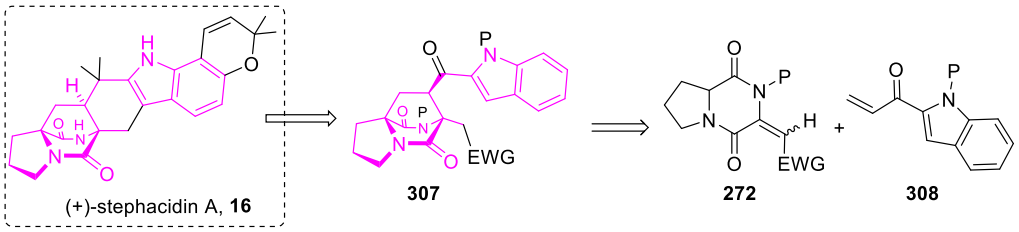
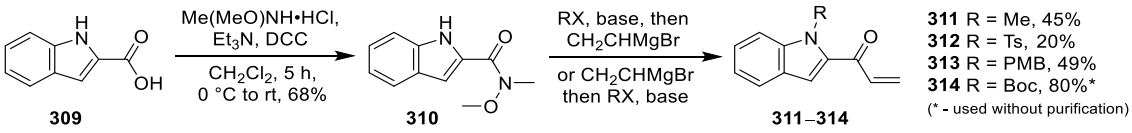


Figure 42 – Proposed extension of Michael–Michael chemistry

It was hypothesised that adduct **307** should be readily accessible from proline DKP **272** and an indole vinyl ketone **308** through the previously established Michael–Michael cascade.

In order to assess whether indole adduct **307** could be accessed, a number of indole vinyl ketones with various protecting groups were synthesised from indole-2-carboxylic acid **309** *via* Weinreb amide **310** inspired by literature precedent of similar substrates (Scheme 74).[108]



Scheme 74 – Generation of indole vinyl ketones

Weinreb amide **310** was synthesised in good yield from an amide coupling reaction before either nitrogen protection followed by Grignard addition (indoles **311**, **312** and **313**) or Grignard addition followed by protection (indole **314**) gave indole vinyl ketones **311**–**314** in variable yields without optimisation. With Michael acceptors **311**–**314** in hand the reaction with cyano proline DKP **290** and its carboxymethyl variant **291** were conducted (Figure 43).

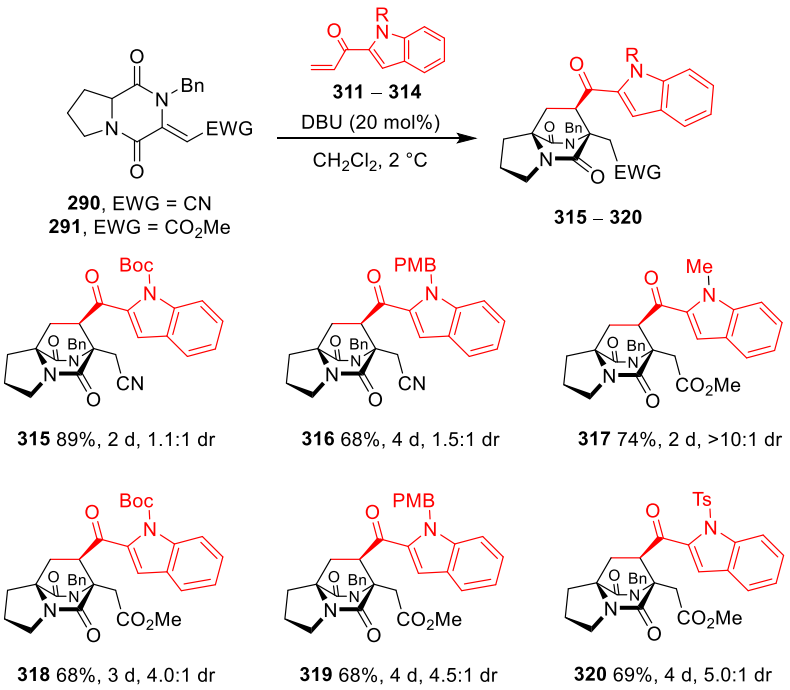


Figure 43 – Exploring scope of Michael–Michael chemistry with indole vinyl ketones

Gratifyingly the reaction was successful with both cyano and carboxymethyl DKPs affording adducts **315**–**320** in good yields. The diastereomeric ratio of the products ranged from very good with methyl indole adduct **317** (>10:1) to 1.1:1 with Boc protected adduct **315**. Interestingly the dr differed depending on the electron withdrawing group, with carboxymethyl derivatives displaying significantly better diastereocontrol. Although the reason behind this is not known, it was found that epimerisation of tosyl adduct **320** occurred when resubmitted to the reaction conditions, with the dr measured dropping from 5.0:1 to 1.5:1 after 1 day, suggesting that DBU was causing epimerisation and a less basic catalyst may be required to obtain products in higher dr. Nevertheless, since the natural product family contains examples of either stereochemistry, the ability to synthesise both epimers of the products increases the utility of this reaction towards the desired natural product derivatives.

Inspired by the interesting results obtained with the proline DKPs the Michael–Michael cascade was also attempted on homo-proline DKP **296** to see if other bicyclic systems would undergo this tandem process.

Three Michael acceptors were utilised; MVK, chalcone and Boc indole vinyl ketone **314**, since these had proved the most successful with the proline DKPs (Figure 44).

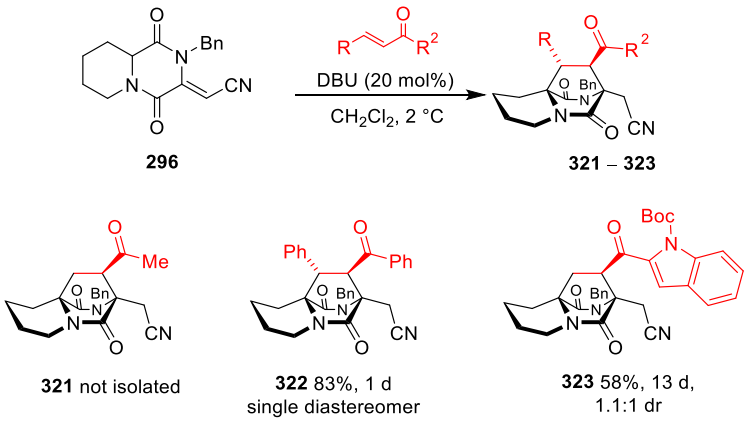


Figure 44 – Michael–Michael reaction with homo-proline cyano DKP

Unfortunately in the reaction with MVK the product could not be isolated, as with cyano proline DKP **290**, despite being observed in the NMR spectrum of the crude reaction mixture. However, the reaction of DKP **296** with chalcone and Boc indole vinyl ketone **314** were pleasingly found to give **322** and **323** in good yields. Chalcone adduct **322** was once again synthesised as a single diastereoisomer whereas indole adduct **323** was generated as a mixture of epimers, matching the result with proline DKP shown earlier. All three reactions were also attempted using cinchona catalyst **101**, however, no reaction was observed in all cases which was presumed to be due to the reduced acidity of DKP **296**, compared to cyano proline DKP **290**, which prevented generation of the DKP enolate.

These excellent results show that the Michael–Michael cascade methodology could also be used to access derivatives of the natural products possessing a piperidine fused bicyclo[2.2.2]diazaoctane core. Additionally it suggested that the methodology could be further extended to other multi-cyclic DKP systems further increasing its potential utility.

Further Transformations of the Michael–Michael Adducts

With the Michael–Michael cascade successfully established giving access to a number of compounds possessing the pyrrolidine and piperidine fused bicyclo[2.2.2]diazaoctane cores, found within the prenylated indole alkaloids. Work then concentrated on further transformations towards the natural product polycyclic scaffold focused on the indole adducts (**315**–**320**) that had previously been targeted because of their appreciable overlap with the natural products (Figure 45).

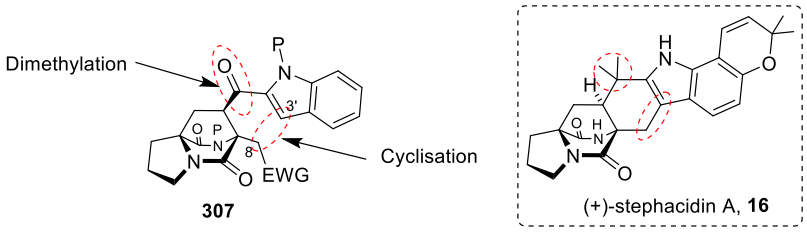
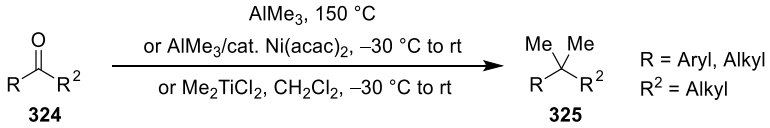


Figure 45 – Comparision of indole adduct

Comparison of indole adduct **307** to stephacidin A **16** identified two key transformations to increase the similarity of derivative **307** with the prenylated indole alkaloids (Figure 45). The two desirable transformations were the conversion of the ketone to a gem-dimethyl group and also the cyclisation between C-8 and C-3' to form a six-membered ring.

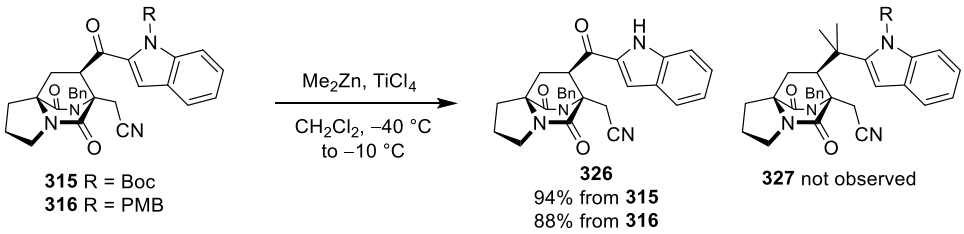
Methodology concerning the geminal disubstitution of carbonyls is dominated by the addition of organometallics into amides and thioamides, as demonstrated in a comprehensive review by Seebach in 2011, occurring through iminium ion intermediates. The transformation of ketones to gem-dimethyls has also been reported but only a handful of times, with the reported examples limited to the three sets of conditions shown below (Scheme 75).[109]



Scheme 75 – Examples of dimethylation chemistry

Meisters and co-workers found that trimethyl aluminium can be used to effect the gem-dimethylation of ketones but high reaction temperatures are required, although further work later found that in the presence of catalytic nickel acetylacetonate the transformation could be completed at low temperature.[110,111] Alternatively, Reetz and co-workers reported that dichloro-dimethyl titanium, which can be synthesised *in situ* from titanium tetrachloride and dimethyl zinc, can also be used for the dimethylation of ketones as well as the trimethylation of acid chlorides at low temperatures.[112–114]

Inspired by the literature examples, Boc indole adduct **315** was initially reacted with Reetz's reagent, generated in situ, in an attempt to generate dimethyl adduct **327** (Scheme 76).

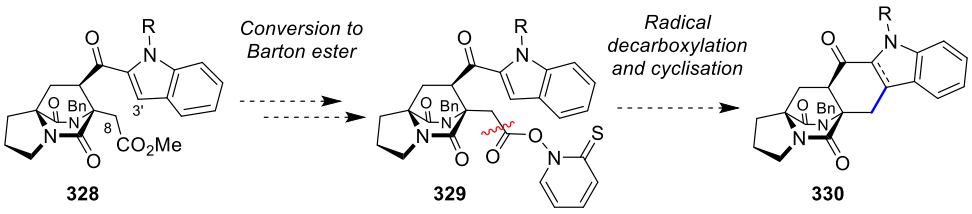


Scheme 76 – Reaction of indole adduct with Reetz reagent

Unfortunately, gem-dimethylation product **327** was not observed, with the reaction conditions instead found to afford deprotected indole adduct **326** in excellent yield. With the known lability of the tert-butoxy carbonyl (Boc) protecting group under Lewis acidic conditions, in hindsight this outcome was not surprising.[31] Repetition of the reaction with PMB protected indole adduct **316**, which was expected to be more stable to the reaction conditions, resulted again in indole deprotection with adduct **326** isolated in good yield. Resubmission of adduct **326** to the reaction conditions returned compound **326** unchanged which suggested that disappointingly the indole adducts are not suitable for the dimethylation chemistry.

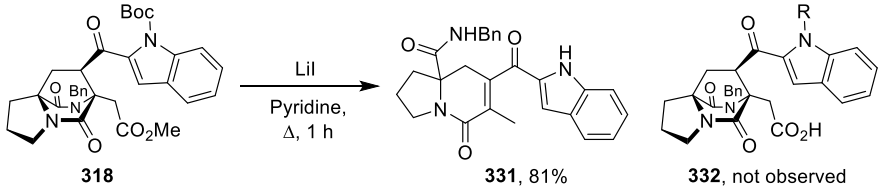
Exploration of the use of trimethyl aluminium to afford dimethylated adduct **327** is proposed for further investigations.

With the attempted gem-dimethylation proving troublesome, work then focussed on the aforementioned cyclisation between the 3-position of indole (C-3') and the carbon adjacent to the electron withdrawing group (C-8) to form the six-membered ring key to accessing the natural product skeleton. Inspired by the successful Barton-McCombie deoxygenation discussed in Chapter 3 it was envisioned that a Barton-McCombie decarboxylation could be used to affect the desired cyclisation, generating cyclised product **330** from carboxymethyl adduct **328** (Scheme 77).



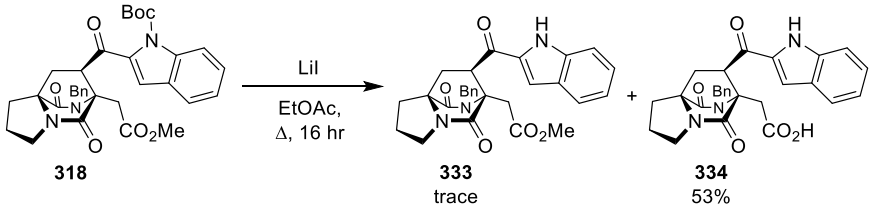
Scheme 77 – Proposed cyclisation *via* Barton-McCombie radical decarboxylation

In order to attempt the radical decarboxylation, the synthesis of Barton ester **329** was first required, which in turn required the conversion of methyl ester **328** to the corresponding carboxylic acid. The saponification of adduct **328** was attempted under standard aqueous lithium hydroxide conditions but the reaction resulted in decomposition of the indole adducts. As an alternative to using basic aqueous solutions a Krapcho demethylation, the first step of the well-known Krapcho decarboxylation reaction sequence, was attempted for the synthesis of carboxylic acid **332** using conditions reported by Magnus and co-workers applied to indole adduct **318** (Scheme 78).[115]



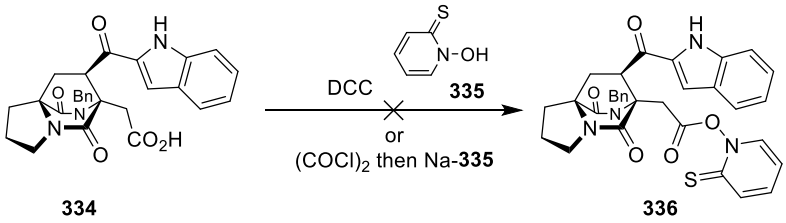
Scheme 78 – Attempted Krapcho demethylation using LiI based on work by Magnus and co-workers[115]

Unfortunately under these conditions adduct **318** underwent a Krapcho decarboxylation along with ring opening of the bridgehead C–N bond and removal of the Boc protecting group to generate adduct **331** in good yield. Using an alternative solvent resulted in conversion of adduct **318** to deprotected adduct **333** after 1 hour with a trace quantity of acid **334**, extending the reaction time to 16 hours allowed the conversion of adduct **318** to acid **334** in a moderate yield of 53% with a trace quantity of adduct **333** remaining (Scheme 79).



Scheme 79 – Krapcho demethylation

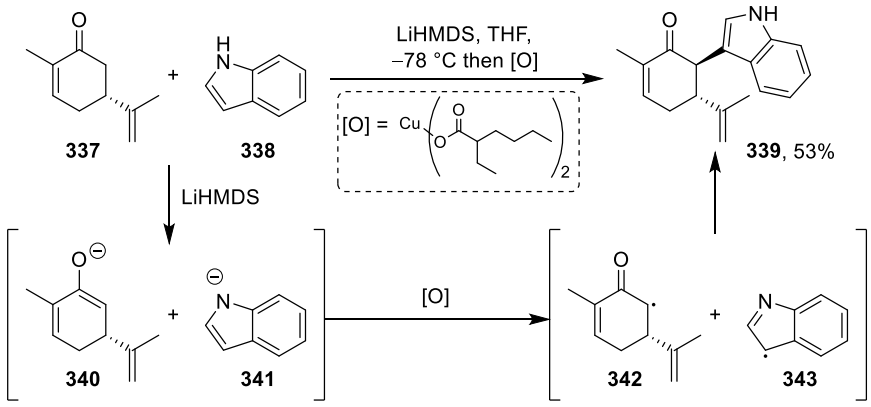
With acid **334** in hand, the coupling reactions with 2-mercaptopyridine *N*-oxide **335** and its sodium salt Na-**335** were then attempted following standard procedures but unfortunately Barton ester **336** could not be isolated (Scheme 80).[116,117]



Scheme 80 – Attempted synthesis of Barton ester

With the moderate yields for the generation of acid **334** and the unsuccessful synthesis of Barton ester **336**, combined with the limited supplies of ester **318**, an alternative approach for forming the desired indole C-3' to C-8 bond was therefore needed.

Baran and co-workers reported the coupling of the 3-position of indole with a range of ketones and esters using LiHMDS and a copper oxidant, successfully using the methodology for the gram-scale synthesis of adduct **339** (Scheme 81).[118]



Scheme 81 – Baran's direct coupling of indole with carbonyl compounds[118]

The reaction is proposed to progress through the deprotonation of both carvone **337** and indole **338** to afford enolate **340** and indole anion **341** that are then oxidised to radicals **342** and **343** to allow diradical coupling to give product **339**.[118]

Inspired by this research an alternative approach towards the polycyclic natural product framework was therefore hypothesised (Figure 46).

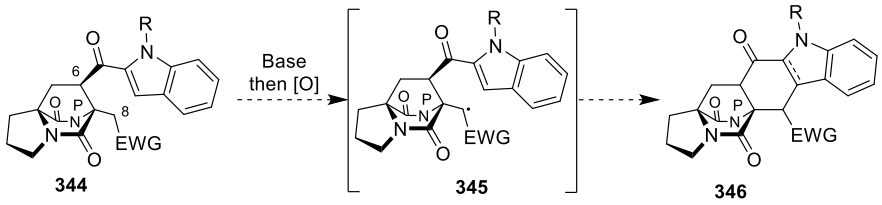


Figure 46 – Proposed radical cyclisation.

It was envisioned that radical **345** could be generated from the deprotonation of indole adduct **344** at C-8 followed by oxidation, which could then undergo radical cyclisation onto the indole moiety or radical coupling (if R = H) to give access to adduct **346**. The reaction of adduct **344** (where R = PMB) under the conditions reported by Baran was attempted but unfortunately resulted in multiple decomposition products thought to arise from a competing deprotonation at C-6 and the resulting ring opening of bridgehead C–N bond.

To prevent this competing deprotonation, an alternative route to radical **345** was envisioned from Michael adduct **347**, through oxidation of the anion that is formed during the Michael–Michael cascade reaction (Figure 47).

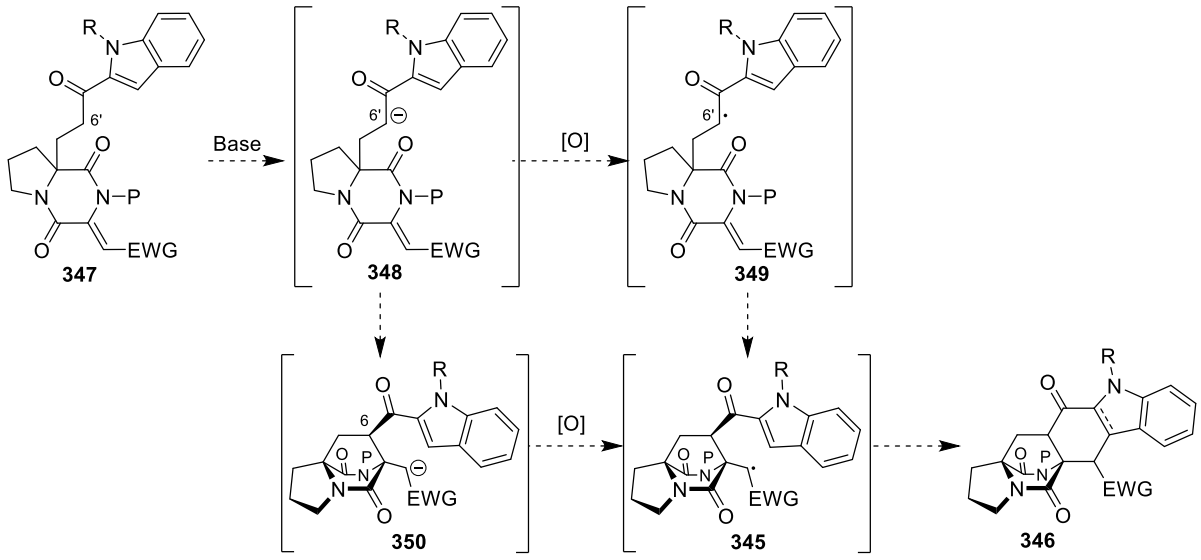
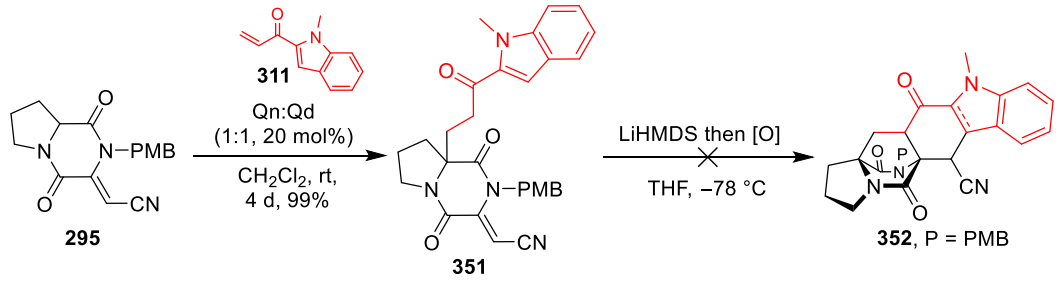


Figure 47 – Proposed oxidative enolate cyclisation

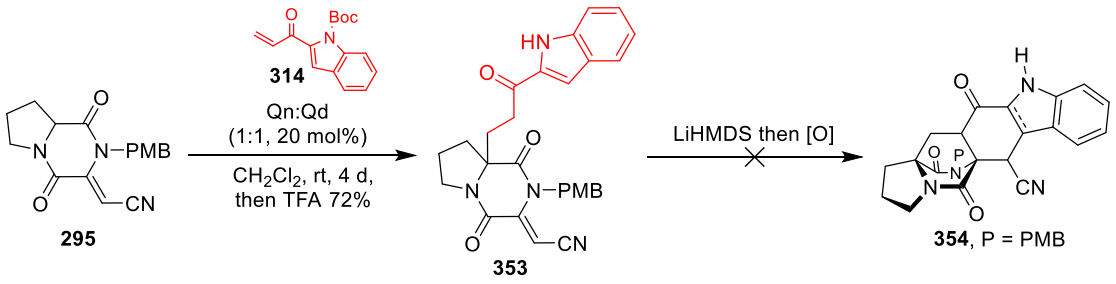
Deprotonation of adduct **347** at C-6' followed by either Michael addition to give anion **350** then oxidation, or by oxidation to give radical **349** that could undergo radical cyclisation, could afford radical **345** which could then generate cyclised adduct **346** as previously discussed. Investigation of this route began with the synthesis of racemic Michael adduct **351** using a 1:1 mixture of quinine (Qn) and quinidine (Qd), and was generated in excellent yield (Scheme 82).



Scheme 82 – Attempted oxidative enolate coupling

Unfortunately the attempted cyclisation of adduct **351** was not successful under the conditions reported by Baran and co-workers. Variations to the reaction temperature and equivalents of base and oxidant were made without success, and alternative oxidants including $FeCp_2PF_6$ and $Fe(acac)_3$ were also attempted. The reactions were mainly found to return starting adduct **351** but as a mixture of *E*- and *Z*-isomers, with no Michael–Michael adduct or cyclised product **352** observed.

The reaction was also attempted with the unprotected indole adduct **353** to investigate a possible bis-radical coupling (Scheme 83).



Scheme 83 – Attempted oxadative enolate coupling with free indole

Adduct **353** was synthesised in good yield, however attempts to affect the radical cyclisation were once again unsuccessful, with adduct **353** again returned as a mixture of *E*- and *Z*-isomers. Variation of the reaction conditions and reagents as with the previous attempted cyclisation also proved unsuccessful. Despite multiple attempted strategies to cyclise both **351** and **353**, the radical cyclisations proved troublesome and were unsuccessful. Further investigation into this ring closure are still required.

Summary and Future Work

A range of electron deficient methylene DKPs were successfully synthesised from several cyclic and non-cyclic TKPs using a Wittig reaction. Multiple DKP products could be synthesised using the cyano Wittig ylide in good to excellent yields of up to 99% whereas proline carboxymethyl DKP **291** could only be generated in variable yields of 30–60%. The Wittig reaction was also attempted with a number of other stabilised ylides however were found to be unsuccessful as was a HWE reaction.

The reaction of cyano proline DKP **291** with MVK using triethylamine and cinchona alkaloid **101** was found not to undergo the expected Michael–Michael cascade, instead affording the product of a single Michael addition. This is the first example of this class of Michael donor undergoing a Michael addition although the enantioselectivity of MVK adduct **297** was found to be only moderate, with the best er measured at 68:32.

Conversely, no reaction was observed between carboxyl methyl proline DKP **291** and MVK using triethylamine or cinchona catalyst **101**, however in the presence of DBU, the Michael–Michael cascade was successfully established in a yield of 69% and in a 7:1 dr. This result is thought to be the first example of a Michael–Michael cascade on a DKP substrate and demonstrated that this strategy could be used to synthesise the pyrrolidine fused bicyclo[2.2.2]diazaoctane ring system found in the prenylated indole alkaloid natural products.

Pleasingly, cyano proline DKP **290** was also found to react with chalcone using cinchona catalyst **101** but the reaction was again found to stop at the Michael product, although cyclisation could be achieved using DBU in a second step. Conducting the reaction with DBU directly gave Michael–Michael adduct **302** and gratifyingly a one-pot asymmetric route to adduct **302** was also established, affording adduct **302** in 70%, 67:33 er and as a single diastereoisomer using catalyst **101** followed by addition of DBU.

An improved enantioselectivity of 85:15 er was achieved for the reaction of doubly activated DKP **294** with MVK suggesting that improved levels of enantio-enrichment of this class of DKP products should be accessible with further investigation. Subsequent ring-closure could be achieved using DBU, but the product could not be isolated due to suspected instability to silica gel column chromatography.

Extension of the Michael–Michael strategy towards the prenylated indole alkaloid family was successfully achieved from the reaction of both cyano DKP **290** and its carboxymethyl derivative **291**, with a variety of protected indole vinyl ketones. Products were obtained in good yields of up to 89% and with diastereomeric ratios ranging from excellent (>10:1) to 1.1:1. However, DBU appeared to cause epimerisation of the products upon resubmission to the reaction conditions, suggesting that further investigation into alternative bases is required and may increase the dr's of the products.

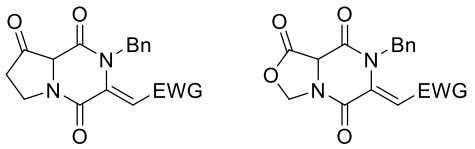
Homo-proline cyano DKP **296** was also successfully shown to undergo the Michael–Michael cascade, with chalcone and Boc indole vinyl ketone in up to 83% yield. This demonstrates that the tandem Michael addition strategy could also be used to generate adducts possessing the piperidine fused bicyclo[2.2.2]diazaoctane core present in some members of the prenylated indole alkaloid family.

Attempts to further functionalise the Michael–Michael adducts towards members of the natural product family through gem-dimethylation and cyclisation were unfortunately unsuccessful with a variety of different radical based cyclisation strategies attempted. Further investigations into both of these steps are needed with the alternative trimethyl aluminium dimethylation conditions one possible area of study.

Additional work is also required to improve the moderate enantioselectivity achieved using cinchona catalyst **101** in the Michael addition step, and alternative chiral bases should be investigated such as chiral bifunctional guanidines, cyclopropenimines or Dixons and co-workers iminophosphoranes.[76–78] These more basic catalysts may also affect the secondary intramolecular Michael addition, which has so far only

been affected using DBU, potentially allowing Michael–Michael adducts to be obtained with improved diastereoselectivity over the current results.

Finally, inspired by the improved enantioselectivity that was achieved with doubly activated DKP **294**, it would be interesting to investigate the reaction of bicyclic DKPs that incorporate additional activating groups, such as oxo-proline DKP **355** and lactone **356** (Figure 48).



355 **356**

Figure 48 – Potentially interesting doubly activated bicyclic DKPs

Chapter Five - Experimental

General Methods

Reactions were carried out under nitrogen using dry solvents. All reagents were used as received from commercial suppliers unless otherwise indicated.

NMR data were recorded on a Bruker AVIII300, or AVIII400 spectrometer in deuterated chloroform (unless otherwise indicated) and spectra were calibrated using residual solvent peaks (^{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) and coupling constants (*J*) are quoted in Hz to one decimal place. Carbon and proton assignments, where reported, were made on the basis of correlations in COSY, HSQC and HMBC spectra as well as PENDANT spectra. Insufficient carbon peaks are quoted for most compounds due to equivalent resonances. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer or a Varian 660-IR, FT-IR spectrometer using Agilent Resolutions Pro software. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

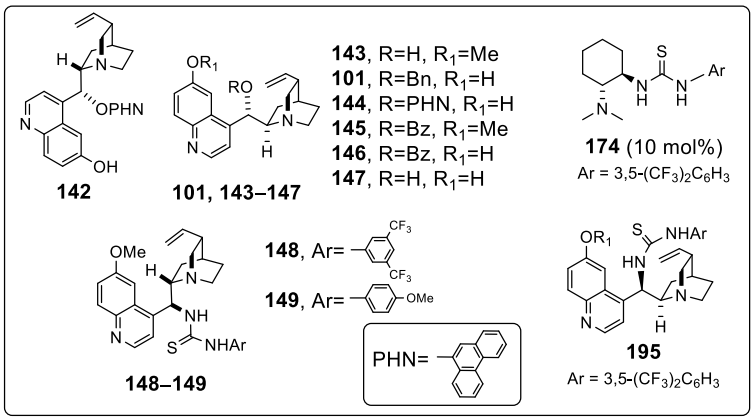
Reaction progress was monitored by thin layer chromatography using Merck silica gel 60 F_{254} plates, which were visualized with UV light and potassium permanganate. Flash column chromatography was carried out using Davisil 60Å or Geduran Si 60 Å (40-63 µm, VWR) silica gel and the indicated solvent systems. Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured using an Optical Activity PolAAr 2001 automatic polarimeter. ESI mass spectra were recorded on either a Micromass LCT time of flight, Waters Xevo G2-XS Tof or Synapt G2-S mass spectrometer.

Microwave reactions were conducted in either a CEM discovery system or a CEM discoveryS system with synergy computer control and monitoring. High performance liquid chromatography (HPLC) analysis was performed using either a P580 Pump from Dionex, Chromeleon Client, version 6.80 SP1 Build 2238, Diacel Chiralcel OD Column (250 × 4.6 mm) or Chiralpak AD Column (250 × 4.6 mm) and Waters 996 Photodiode Array Detector for the UV detection, monitored at 210 or 230 nm, or using a Shimadzu LC–20 Prominence system, Chromeleon client, version 6.80 SR9 Build 2673, Phenomenex Cellulose – 1 (250 × 4.6 mm), Cellulose – 3 (250 × 4.6 mm) or Amylose – 2 (250 × 4.6 mm) columns and Shimadzu SPD–M20A or SPD–20A detectors for the UV detection, monitored at 220, 230 or 254 nm.

Experimental for Chapter 2

Preparation of Catalysts

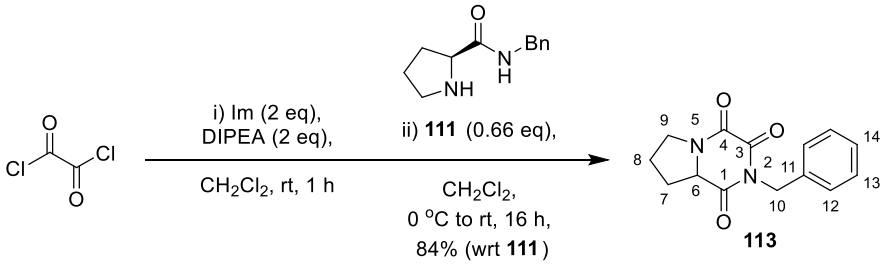
Catalysts **101**, **142**–**149**, and **194** were prepared according to literature procedures.[65,68,119–126]



Catalyst **174** was purchased from Sigma Aldrich.

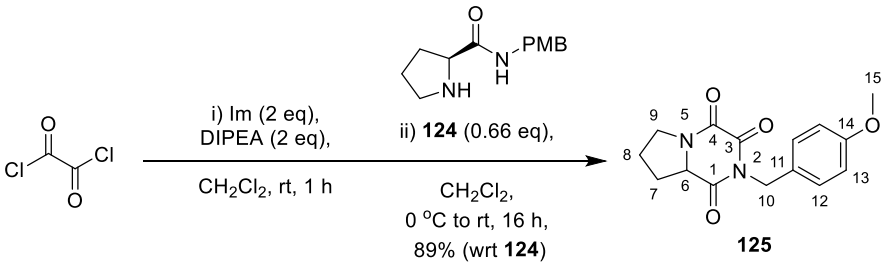
Preparation of Triketopiperazines

Benzyl proline TKP **113**



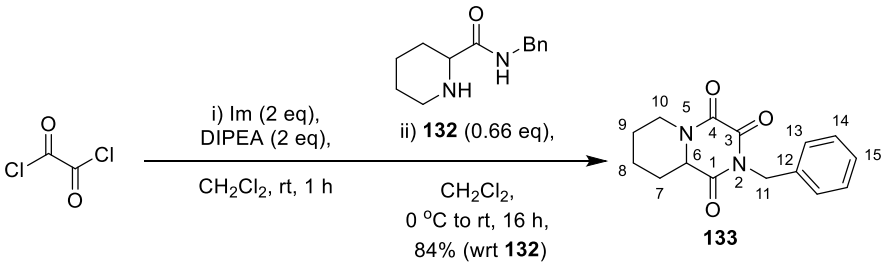
Oxalyl chloride (3.60 mL, 42.6 mmol) in CH_2Cl_2 (40 mL) was added over 10 mins to a stirred solution of imidazole (5.80 g, 85.2 mmol) and diisopropylethylamine (14.8 mL, 85.2 mmol) in CH_2Cl_2 (80 mL). The reaction mixture was stirred for 1 hour at room temperature (rt). The solution was then cooled to 0 °C before *L*-proline-*N*-benzylamine[50] **111** (5.80 g, 28.2 mmol) in CH_2Cl_2 (20 mL) was added over 5 mins. The reaction mixture was stirred and allowed to warm to rt over 16 hours. The reaction was quenched with HCl (1.0 M, aq., 100 mL) and then quickly extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was then recrystallized from hot isopropanol, to give TKP **113** (6.12 g, 23.7 mmol, 84%) as a colourless solid; m.p. 125 – 127 °C; IR (thin film) ν_{max} /cm^{-1}: 2963, 2885, 1744, 1678, 1460, 1434, 1383, 1354, 1318, 1196, 747, 702, 608, 525; δ_H (300 MHz, $CDCl_3$) 7.50 – 7.40 (2 H, m, H-Ar), 7.35 – 7.28 (3 H, m, H-Ar), 5.06 (1 H, d, *J* 13.6, H-10a), 4.99 (1 H, d, *J* 13.6, H-10b), 4.44 (1 H, dd, *J* 10.2, 6.1, H-6), 3.90 – 3.76 (1 H, m, H-9a), 3.75 – 3.61 (1 H, m, H-9b), 2.64 – 2.54 (1 H, m, H-7a), 2.23 – 1.91 (3 H, m, H-7b, H-8); δ_C (101 MHz, $CDCl_3$) 168.0 (C-1), 158.1 (C-3), 151.8 (C-4), 135.4 (C-11), 129.5 (C-13), 128.6 (C-14), 128.16 (C-12), 60.4 (C-6), 45.8 (C-9), 44.2 (C-10), 29.3 (C-7), 21.5 (C-8); m/z (ESI) 259.1 ([MH]$^+$, 100), 281.1 ([MNa]$^+$, 38); HRMS (ESI/[MH]$^+$) Calcd. For $C_{14}H_{15}N_2O_3$: 259.1083, Found 259.1078.

4-Methoxyl benzyl Proline TKP **125**



Oxalyl chloride (2.46 mL, 29.1 mmol) in CH_2Cl_2 (10 mL) was added over 10 mins to a stirred solution of imidazole (3.97 g, 58.3 mmol) and diisopropylethylamine (10.2 mL, 58.3 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 1 hour at rt. The solution was then cooled to 0 °C before *L*-proline-*N*-(4-methoxy)benzylamine **124** (synthesised by the same method as *L*-proline-*N*-benzylamine[2]) (4.55 g, 19.4 mmol) in CH_2Cl_2 (10 mL) was added over 5 mins. The reaction mixture was stirred and allowed to warm to rt over 15 hours. The reaction was quenched with HCl (1.0M, aq., 100 mL) and then quickly extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was then recrystallized from hot isopropanol, giving TKP **125** (4.98 g, 17.3 mmol, 89%) as a colourless solid; m.p. 134 – 136 °C; IR (thin film) ν_{max} /cm^{-1}: 2968, 2889, 1739, 1682, 1450, 1431, 1364, 1311, 1190, 747, 608, 525; δ_H (300 MHz, $CDCl_3$) 7.48 – 7.32 (2 H, m, H-Ar), 6.92 – 6.72 (2 H, m, H-Ar), 5.00 (1 H, d, *J* 13.6, H-10a), 4.92 (1 H, d, *J* 13.6, H-10b), 4.50 – 4.32 (1 H, m, H-6), 3.92 – 3.75 (4 H, m, H-9a, H-15), 3.73 – 3.57 (1 H, m, H-9b), 2.65 – 2.45 (1 H, m, H-7a), 2.24 – 1.84 (3 H, m, H-7b, H-8); δ_C (101 MHz, $CDCl_3$) 167.9 (C-1), 159.5 (C-14), 158.1 (C-3), 151.9 (C-4), 131.1 (C-11), 127.7 (C-13), 113.9 (C-12), 60.4 (C-6), 55.3 (C-15), 45.8 (C-9), 43.7 (C-10), 29.3 (C-7), 21.5 (C-8); m/z (ESI) 577.2 ($[2MH]^+$, 100), 289.1 ($[MH]^+$, 62), 121.0 (58); HRMS (ESI/$[MH]^+$) Calcd. For $C_{15}H_{17}N_2O_4$: 289.1188, Found 289.1192.

Homo-proline TKP **133**



Oxalyl chloride (0.15 mL, 1.72 mmol) in CH_2Cl_2 (2.0 mL) was added over 5 mins to a solution of imidazole (235 mg, 3.45 mmol) and DIPEA (0.62 mL, 3.57 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 hour. The solution was cooled to 0 °C before *N*-benzylpiperidine-2-carboxamide[127] **132** (250 mg, 1.15 mmol) in CH_2Cl_2 (5 mL) was added over 10 mins, and the reaction mixture was stirred for 16 hours. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (silica gel, 80% EtOAC in hexane) followed by trituration in Et_2O to give homo-proline TKP **133** as a colourless solid (250 mg, 0.92 mmol, 80%); m.p. 129–131 °C; IR (thin film) ν_{max} /cm^{-1}: 1742, 1677, 1445, 1384, 1358, 1319, 1253, 1204, 732, 698; δ_H (400 MHz, $CDCl_3$) 7.52 – 7.37 (2 H, m, H-Ar), 7.37 – 7.18 (3 H, m, H-Ar), 5.07 (1 H, d, *J* 13.6, H-11a), 5.00 (1 H, d, *J* 13.6, H-11b), 4.81 – 4.66 (1 H, m, H-6), 4.18 (1 H, dt, *J* 14.9, 7.6, H-10a), 2.67 (1 H, td, *J* 13.1, 3.0, H-7a), 2.46 (1 H, ddd, *J* 7.7, 6.1, 4.5, H-10b), 2.13 – 1.97 (1 H, m, H-9a), 1.91 – 1.77 (1 H, m, H-8a), 1.74 – 1.46 (3 H, m, H-7b, H-8b, H-9b); δ_C (101 MHz, $CDCl_3$) 168.1 (C-1), 156.1 (C-3), 151.1 (C-4), 135.3 (C-12), 129.3 (C-14), 128.6 (C-15), 128.1 (C-13), 60.2 (C-6), 44.0 (C-11), 43.5 (C-10), 32.6 (C-7), 24.8 (C-9), 24.0 (C-8); m/z (ESI) 273.1 ([MH]$^+$, 100), 436.1 (42); HRMS (ESI/[MH]$^+$) Calcd. For $C_{15}H_{17}N_2O_3$: 273.1239, Found 273.1233.

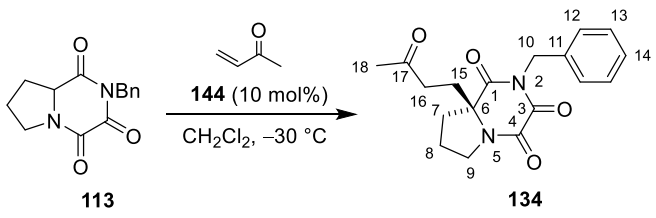
Preparation of Racemic Michael Adducts

Michael acceptor (2.5 eq) was added to a solution of TKP **113**, **125**, or **133** (1 eq) in CH_2Cl_2 at –78 °C, followed by addition of triethylamine (10 mol%) or a 50:50 mixture of **142** and **144** (10 mol%) in CH_2Cl_2. The reaction was then transferred to the freezer and allowed to warm to –30 °C. Reaction progress was monitored by TLC and when the starting material had been consumed the reaction mixture was directly purified by flash chromatography using the indicated solvent system.

Enantioselective Michael Additions of TKPs

General procedure A – Michael acceptor (2.5 eq) was added to a solution of TKP **113**, **125**, or **133** (1.0 eq) in CH_2Cl_2 (0.8 mL) at –78 °C, followed by addition of catalyst **144** (10 mol%) in CH_2Cl_2 (0.2 mL). The reaction was then transferred to the freezer and allowed to warm to –30 °C. Reaction progress was monitored by TLC and when the starting material had been consumed the reaction mixture was directly purified by flash chromatography using the indicated solvent system.

Michael adduct **134**

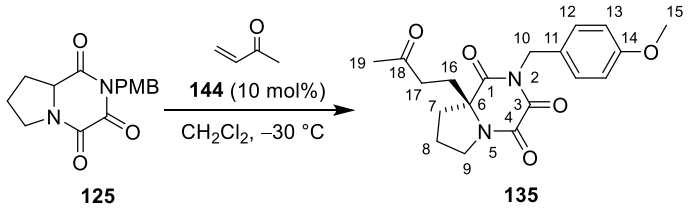


113 134

General procedure A was followed with TKP **113** (100 mg, 0.39 mmol), MVK (68 mg, 79 μL, 0.97 mmol) and **144** (19 mg, 0.040 mmol) as base. Flash chromatography (90% EtOAc in hexane) gave Michael adduct **134** (118 mg, 0.36 mmol, 93%) as a colourless solid in 10:90 er [Amylose-2, MeCN:H_2O 50:50 +0.05%TFA, 0.7 $mLmin^{-1}$, t_1= 10.52 mins, t_2= 12.84 mins or Cellulose-3, MeCN:H_2O 50:50, 1.0 $mLmin^{-1}$, t_1= 6.38 mins, t_2= 8.28 mins]; m.p. 136 – 138 °C; IR (thin film) ν_{max} /cm^{-1}: 2965, 1744, 1714,

1687, 1429, 1356, 1330, 1181, 752; δ_H (300 MHz, $CDCl_3$) 7.52 – 7.43 (2 H, m, H-Ar), 7.38 – 7.28 (3 H, m, H-Ar), 5.04 (1 H, d, *J* 13.5, H-10a), 4.98 (1 H, d, *J* 13.5, H-10b), 3.99 – 3.84 (1 H, m, H-9a), 3.69 – 3.56 (1 H, m, H-9b), 2.32 – 1.96 (8 H, m, H-7, H-8, H-15, H-16), 1.94 (3 H, s, H-18); δ_C (101 MHz, $CDCl_3$) 205.4 (C-17), 170.9 (C-1), 157.9 (C-3), 152.0 (C-4), 135.4 (C-11), 129.7 (C-Ar), 128.7 (C-Ar), 128.3 (C-14), 68.6 (C-6), 45.2 (C-9), 44.3 (C-10), 37.1 (C-15), 34.2 (C-16), 33.1 (C-7), 29.9 (C-18), 19.6 (C-8); m/z (ESI) 351.1 ($[MNa]^+$, 100), 329.2 ($[MH]^+$, 52); HRMS (ESI/$[MH]^+$) Calcd. For $C_{18}H_{21}N_2O_4$: 329.1501, Found 329.1509; $[\alpha]_D^{21} = -32.1$ (*c* 1.01, CH_2Cl_2). Compound **134** can be recrystallized from isopropanol, two successive recrystallisations led to an enhancement of the er up to 99:1 (90:10→95:5→99:1).

Michael adduct **135**

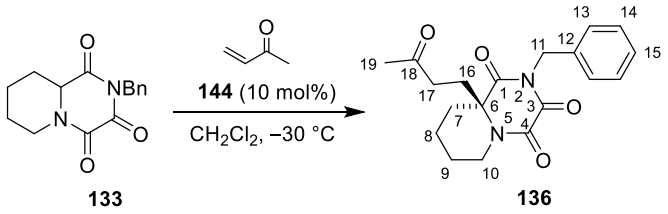


125 **135**

General procedure A was followed with PMB-proline-TKP **125** (30 mg, 0.10 mmol), MVK (21 μL, 0.26 mmol) and **144** (5 mg, 0.010 mmol) as base. Flash chromatography (80% EtOAc in hexane) gave Michael adduct **135** (32 mg, 0.089 mmol, 86%) as a colourless solid in 17:83 er [Cellulose-3, MeCN:H_2O 25:75, 1.0 mLmin^{-1}, t_1= 10.55 mins, t_2= 12.08 mins]; m.p. 138 – 139 °C; IR (thin film) ν_{max} /cm^{-1}: 1741, 1714, 1686, 1612, 1512, 1354, 1248, 1177, 1030; δ_H (300 MHz, $CDCl_3$) 7.46 – 7.35 (2 H, m, H-12), 6.92 – 6.77 (2 H, m, H-13), 4.97 (1 H, d, *J* 13.5, H-10a), 4.91 (1 H, d, *J* 13.5, H-10b), 3.90 (1 H, m, H-9a), 3.74 (3 H, s, H-15), 3.58 (1 H, m, H-9b), 2.32 – 2.14 (2 H, m, H-7a, H-16a), 2.12 – 1.86 (9 H, m, H-7b, H-8, H-16b, H-17, H-19); δ_C (101 MHz, $CDCl_3$) 205.4 (C-18), 170.9 (C-1), 159.6 (C-14), 157.9 (C-3), 152.1 (C-4), 131.2 (C-12), 127.6 (C-11), 113.9 (C-13), 68.5 (C-6), 55.3 (C-15), 45.2 (C-9), 43.7 (C-10), 37.1 (C-16),

34.2 (C-17), 33.2 (C-7), 29.8 (C-19), 19.6 (C-8); m/z (ESI) 381.1 ([MNa]$^+$, 100), 359.2 ([MH]$^+$, 7); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{19}H_{22}N_2O_5Na$: 381.1426, Found 381.1435; $[\alpha]_D^{21} = -70.5$ (*c* 0.93, CH_2Cl_2).

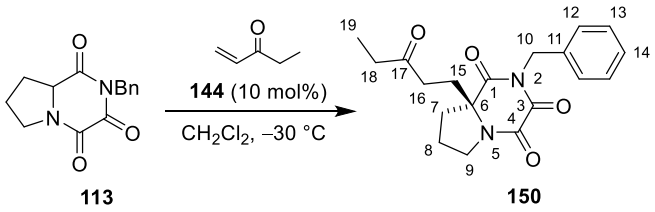
Michael adduct **136**



133 **136**

General procedure A was followed with TKP **133** (30 mg, 0.11 mmol), MVK (23 μL, 0.27 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (75% EtOAc in hexane) gave Michael adduct **136** (32.7 mg, 0.10 mmol, 87%) as a colourless solid in 23:77 er [Cellulose-3, MeCN:H_2O 40:60, 1.0 mLmin^{-1}, t_1= 5.30 mins, t_2= 7.50 mins]; m.p. 142 – 143 °C; IR (thin film) ν_{max} /cm^{-1}: 1740, 1715, 1675, 1428, 1361, 1269, 1218, 1167, 731, 699; δ_H (300 MHz, $CDCl_3$) 7.53 – 7.40 (2 H, m, H-Ar), 7.38 – 7.24 (3 H, m, H-Ar), 5.10 (1 H, d, *J* 13.4, H-11a), 5.01 (1 H, d, *J* 13.4, H-11b), 4.66 (1 H, dd, *J* 13.9, 4.1, H-10a), 2.78 (1 H, app. td, *J* 13.5, 3.0, H-10b), 2.65 – 2.48 (1 H, m, H-7a), 2.39 – 2.21 (1 H, m, H-9a), 2.11 – 1.65 (10 H, m, H-7b, H-8a, H-16, H-17, H-19), 1.59 – 1.37 (1 H, m, H-8b); δ_C (101 MHz, $CDCl_3$) 205.6 (C-18), 171.3 (C-1), 155.8 (C-3), 152.3 (C-4), 135.4 (C-12), 129.5 (C-13), 128.7 (C-14), 128.3 (C-15), 64.4 (C-6), 44.1 (C-11), 38.6 (C-10), 36.7 (C-17), 35.5 (C-16), 29.9 (C-19), 28.7 (C-7), 24.5 (C-9), 19.4 (C-8); m/z (ESI) 365.1 ([MNa]$^+$, 100), 343.2 ([MH]$^+$, 22); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{19}H_{22}N_2O_4Na$: 365.1477, Found 365.1475; $[\alpha]_D^{21} = -31.1$ (*c* 0.81, CH_2Cl_2).

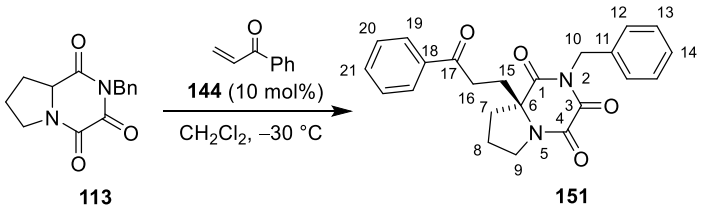
Michael adduct **150**



113 150

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), EVK (25 mg, 30 μL, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (75% EtOAc in hexane) gave Michael adduct **150** (31 mg, 0.09 mmol, 75%) as a colourless solid in 13:87 er [Cellulose-3, MeCN:H_2O 30:70, 1.0 $mLmin^{-1}$, t_1= 9.11 mins, t_2= 10.87 mins]; m.p. 148 – 150 °C; IR (thin film) ν_{max} /cm^{-1}: 2970, 2936, 1740, 1718, 1680, 1431, 1381, 700; δ_H (300 MHz, $CDCl_3$) 7.55 – 7.41 (2 H, m, H-Ar), 7.37 – 7.29 (3 H, m, H-Ar), 5.03 (1 H, d, *J* 13.6, H-10a), 4.97 (1 H, d, *J* 13.5, H-10b), 4.00 – 3.83 (1 H, m, H-9a), 3.70 – 3.54 (1 H, m, H-9b), 2.30 – 1.93 (10 H, m, H-7, H-8, H-15, H-16, H-18), 0.95 (3 H, t, *J* 7.3, H-19); δ_C (101 MHz, $CDCl_3$) 208.3 (C-17), 170.9 (C-1), 157.9 (C-3), 152.0 (C-4), 135.4 (C-11), 129.7 (C-Ar), 128.7 (C-Ar), 128.3 (C-Ar), 68.6 (C-6), 45.2 (C-9), 44.3 (C-10), 35.9 (C-18), 35.9 (C-16), 34.2 (C-7), 33.2 (C-15), 19.6 (C-8), 7.6 (C-19); m/z (ESI) 365.1 ($[MNa]^+$, 100), 343.2 ($[MH]^+$, 27); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{19}H_{22}N_2O_4Na$: 365.1477, Found 365.1491; $[\alpha]_D^{21}$ = –39.4 (*c* 0.94, CH_2Cl_2).

Michael adduct **151**

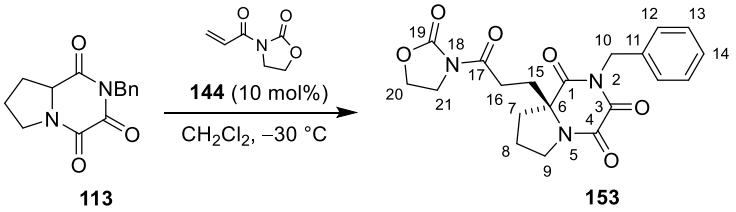


113 151

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), PhVK[3] (41 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (70% EtOAc in hexane) gave Michael adduct

151 (41 mg, 0.105 mmol, 88%) as a colourless solid in 6:94 er [Chiralcel OD, IPA:Hexane 20:80, 1.5 mLmin^{-1}, t_1= 24.92 mins, t_2= 40.65 mins]; m.p. 162 – 164 °C; IR (thin film) ν_{max} /cm^{-1}: 3021, 1744, 1695, 1681, 1368, 1187, 748, 726; δ_H (300 MHz, $CDCl_3$) 7.61 – 7.28 (7 H, m, H-Ar), 7.26 – 7.13 (3 H, m, H-Ar), 5.04 (2 H, s, H-10), 4.02 – 3.88 (1 H, m, H-9a), 3.65 (1 H, ddd, *J* 13.0, 8.2, 4.8, H-9b), 2.63 – 2.39 (2 H, m, H-15), 2.38 – 1.97 (6 H, m, H-7, H-8, H-16); δ_C (101 MHz, $CDCl_3$) 197.0 (C-17), 171.0 (C-1), 157.9 (C-3), 152.0 (C-4), 135.9 (C-18), 135.4 (C-11), 133.5 (C-21), 129.8 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 127.9 (C-Ar), 68.8 (C-6), 45.2 (C-9), 44.3 (C-10), 34.4 (C-16), 33.6 (C-7), 32.3 (C-15), 19.7 (C-8); m/z (ESI) 391.2 ([MH]$^+$, 100), 338.4 (50); HRMS (ESI/[MH]$^+$) Calcd. For $C_{23}H_{23}N_2O_4$: 391.1658, Found 391.1670; $[\alpha]_D^{21}$ = –58.3 (*c* 1.05, CH_2Cl_2).

Michael adduct **153**

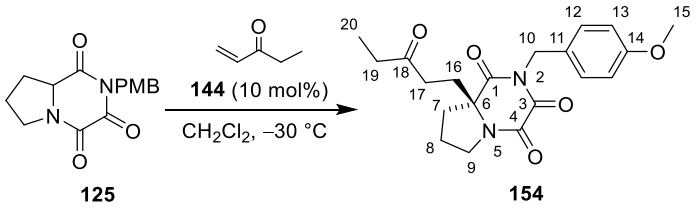


113 **153**

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), acryloyl-2-oxazolidinone[4] (28 mg, 0.20 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (90% EtOAc in hexane) gave Michael adduct **153** (47 mg, 0.12 mmol, 98%) as a colourless gum in 15:85 er [Cellulose-3, MeCN:H_2O 30:70, 0.4 mLmin^{-1}, t_1= 18.03 mins, t_2= 18.97 mins]; IR ν_{max} /cm^{-1}: 2968, 1777, 1741, 1687, 1386, 1359, 1224, 1039, 752, 702; δ_H (300 MHz, $CDCl_3$) 7.49 – 7.36 (2 H, m, H-Ar), 7.34 – 7.25 (3 H, m, H-Ar), 5.08 – 4.90 (2 H, m, H-10), 4.52 – 4.32 (2 H, m, H-20), 4.01 – 3.78 (3 H, m, H-9a, H-21), 3.70 – 3.55 (1 H, m, H-9b), 3.02 – 2.85 (1 H, m, H-16a), 2.76 – 2.60 (1 H, m, H-7a), 2.42 – 1.97 (6 H, m, H-7b, H-8, H-15, H-16b); δ_C (101 MHz, $CDCl_3$) 171.0 (C-17), 170.9 (C-1), 157.7 (C-3), 153.3 (C-4), 152.0 (C-19), 135.4 (C-11), 129.5 (C-Ar), 128.6 (C-Ar), 128.0 (C-Ar), 68.9 (C-6), 62.3 (C-21), 45.3 (C-9), 44.5 (C-10), 42.5 (C-20), 34.2 (C-16), 33.8 (C-7), 29.8 (C-15), 19.7 (C-8); m/z 422.13 ([MNa]$^+$, 100), 400.15

([MH]$^+$, 8); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{20}H_{21}N_3O_6Na$: 422.1328, Found 422.1320; $[\alpha]_D^{21} = -54.1$ (*c* 0.99, CH_2Cl_2).

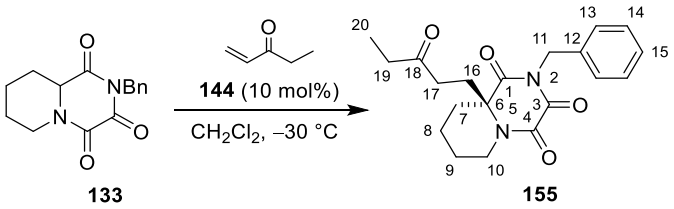
Michael adduct **154**



125 **154**

General procedure A was followed with TKP **125** (29 mg, 0.10 mmol), EVK (21 mg, 25 μL, 0.25 mmol) and **144** (5 mg, 0.010 mmol) as base. Flash chromatography (70% EtOAc in hexane) gave Michael adduct **154** (28 mg, 0.074 mmol, 74%) as a colourless solid; m.p. 134 – 135 °C; IR (thin film) ν_{max} /cm^{-1}: 1741, 1686, 1612, 1512, 1376, 1248, 1178, 1109, 1030; δ_H (400 MHz, $CDCl_3$) 7.33 (2 H, d, *J* 8.8, H-12), 6.75 (2 H, d, *J* 8.8, H-13), 4.88 (1 H, d, *J* 13.5, H-10a), 4.84 (1 H, d, *J* 13.5, H-10b), 3.89 – 3.78 (1 H, m, H-9a), 3.70 (3 H, s, H-15), 3.58 – 3.49 (1 H, m, H-9b), 2.22 – 1.80 (10 H, m, H-7, H-8, H-16, H-17, H-19), 0.87 (3 H, t, *J* 7.3, H-20); δ_C (101 MHz, $CDCl_3$) 208.2 (C-20), 170.9 (C-1), 159.5 (C-14), 157.9 (C-3), 152.1 (C-4), 131.2 (C-12), 127.6 (C-11), 113.9 (C-13), 68.6 (C-6), 55.2 (C-15), 45.2 (C-9), 43.7 (C-10), 35.9 (C-19), 35.8 (C-17), 34.3 (C-7), 33.2 (C-16), 19.6 (C-8), 7.6 (C-20); m/z (ESI) 395.0 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{20}H_{24}N_2O_5Na$: 395.1583, Found 395.1577; $[\alpha]_D^{21} =$ –64.7 (*c* 0.92, CH_2Cl_2).

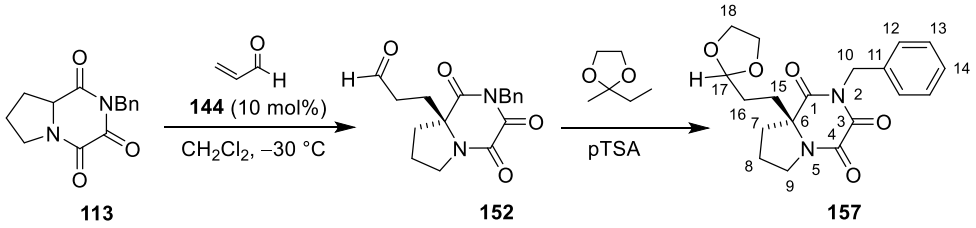
Michael adduct **155**



133 **155**

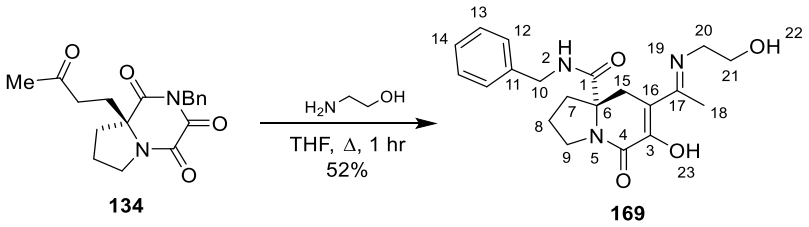
General procedure A was followed with TKP **133** (30 mg, 0.11 mmol), EVK (27 μL, 0.28 mmol) and **144** (5 mg, 0.011 mmol) as base. Flash chromatography (60% EtOAc in hexane) gave Michael adduct **155** (28 mg, 0.079 mmol, 72%) as a colourless solid in 16:84 er [Cellulose-3, MeCN:H_2O 40:60, 1.0 $mLmin^{-1}$, t_1= 6.17 mins, t_2= 8.25 mins]; m.p. 114 – 116 °C; IR (thin film) ν_{max} /cm^{-1}: 2940, 1741, 1713, 1676, 1429, 1363, 1269, 1217, 700; δ_H (400 MHz, $CDCl_3$) 7.46 – 7.40 (2 H, m, H-Ar), 7.33 – 7.26 (3 H, m, H-Ar), 5.10 (1 H, d, *J* 13.4, H-11a), 4.99 (1 H, d, *J* 13.4, H-11b), 4.69 – 4.57 (1 H, m, H-10a), 2.78 (1 H, td, *J* 13.6, 3.0, H-10b), 2.59 (1 H, ddd, *J* 14.1, 10.9, 4.5, H-7a), 2.29 – 2.21 (1 H, m, H-16a), 2.20 – 1.88 (4 H, m, H-16b, H17a, H-19), 1.88 – 1.65 (5 H, m, H-7b, H-8, H-9a, H-17b), 1.55 – 1.39 (1 H, m, H-9b), 0.91 (3 H, t, *J* 7.3, H-20); δ_C (101 MHz, $CDCl_3$) 208.4 (C-18), 171.3 (C-1), 155.8 (C-3), 152.4 (C-4), 135.4 (C-12), 129.5 (C-Ar), 128.6 (C-Ar), 128.3 (C-15), 64.5 (C-6), 44.1 (C-11), 38.6 (C-10), 36.0 (C-19), 35.5 (C-16), 35.4 (C-17), 28.8 (C-7), 24.6 (C-9), 19.4 (C-8), 7.6 (C-20); m/z (ESI) 379.2 ($[MNa]^+$, 25), 357.2 ($[MH]^+$, 100); HRMS (ESI/$[MH]^+$) Calcd. For $C_{20}H_{25}N_2O_4$: 357.1814, Found 357.1822; $[\alpha]_D^{21}$ = –30.5 (*c* 0.87, CH_2Cl_2).

Michael adduct **157**



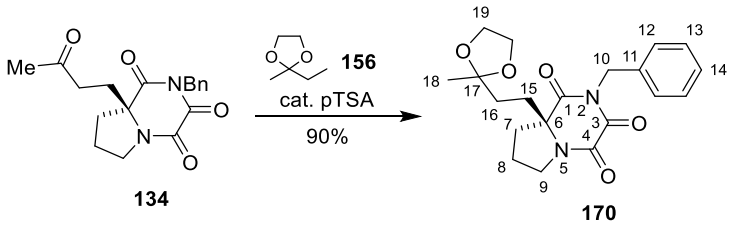
General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), acrolein (17 mg, 20 μL, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Once the reaction was complete by TLC, the volatiles were removed under reduced pressure. The residue was then dissolved in 2-ethyl-2-methyl-1,3-dioxolane (0.5 mL) and *p*-toluenesulfonic acid monohydrate (*p*TSA) (cat., approx. 5 mg) was added and the reaction mixture was stirred for 16 hours. Volatiles were removed under reduced pressure and the residue was purified by flash chromatography (60–70% EtOAc in hexane) and gave Michael adduct **157** (28 mg, 0.077 mmol, 64% w.r.t TKP **113**) as an off-white solid in 21:79 er [Cellulose-3, MeCN:H_2O 40:60, 1.0 mLmin^{-1}, t_1= 4.54 mins, t_2= 7.69 mins]; m.p. 110 – 112 °C; IR (thin film) ν_{max} /cm^{-1}: 2889, 1744, 1683, 1356, 1187, 1134, 1029, 702; δ_H (300 MHz, $CDCl_3$) 7.49 – 7.36 (2 H, m, H-Ar), 7.34 – 7.23 (3 H, m, H-Ar), 4.98 (2 H, s, H-10), 4.68 (1 H, t, *J* 4.2, H-17), 3.92 (1 H, dt, *J* 13.1, 8.4, H-9a), 3.87 – 3.71 (4 H, m, H-18), 3.61 (1 H, ddd, *J* 13.1, 7.2, 5.9, H-9b), 2.33 – 2.12 (2 H, m, H-7a, H-16a), 2.10 – 1.91 (3 H, m, H-8, H16b), 1.77 (1 H, ddd, *J* 14.0, 10.4, 6.1, H-7b), 1.42 – 1.27 (2 H, m, H-15); δ_C (101 MHz, $CDCl_3$) 171.0 (C-1), 158.0 (C-3), 152.1 (C-4), 135.4 (C-11), 129.5 (C-Ar), 128.6 (C-Ar), 128.1 (C-14), 102.6 (C-17), 69.0 (C-6), 65.0 (C-18), 45.0 (C-9), 44.3 (C-10), 34.4 (C-16), 33.5 (C-7), 28.1 (C-15), 19.7 (C-8); m/z 381.1 ([MNa]$^+$, 100), 359.2 ([MH]$^+$, 44), 739.3 ([2MNa]$^+$, 44); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{19}H_{22}N_2O_5Na$: 381.1426, Found 381.1434; $[\alpha]_D^{21}$ = –26.7 (*c* 0.69, CH_2Cl_2).

Ethanolamine enol adduct **169**



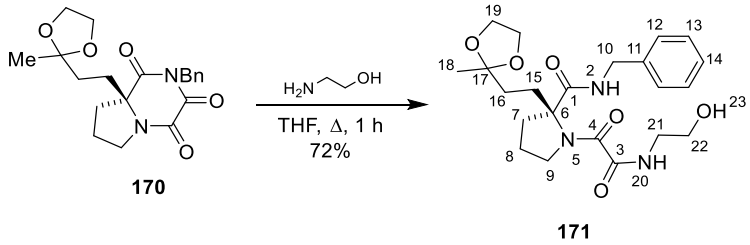
Ethanolamine (19 μL, 0.32 mmol) was added to a solution of Michael adduct **134** (52 mg, 0.16 mmol) in THF (0.5 mL) and the reaction mixture was heated under reflux for 1 hour. Volatiles were removed under reduced pressure and the residue was triturated with THF to give ethanolamine enol adduct **169** (30 mg, 0.082 mmol, 52%) as an off-white solid; m.p. decomp. 210 °C; IR (thin film) ν_{max} /cm^{-1}: 3323 (br), 1765, 1732, 1518, 1421, 1254, 1197, 729, 699; δ_H (400 MHz, DMSO) 12.33 (1 H, t, *J* 5.6, H-22), 8.57 (1 H, t, *J* 6.0, H-2), 7.27 – 7.21 (2 H, m, H-Ar), 7.20 – 7.14 (1 H, m, H-Ar), 7.06 – 7.01 (2 H, m, H-Ar), 5.01 (1 H, s, H-23), 4.29 (1 H, dd, *J* 15.3, 6.0, H-10a), 4.15 (1 H, dd, *J* 15.3, 6.0, H-10b), 3.64 – 3.52 (3 H, m, H-9a, H-21), 3.52 – 3.39 (3 H, m, H-9b, H-20), 3.29 (1 H, d, *J* 14.4, H-15a), 2.53 (1 H, d, *J* 14.4, H-15b), 2.28 – 2.20 (1 H, m, H-7a), 2.01 – 1.85 (5 H, m, H-7b, H-8a, H-18), 1.68 – 1.53 (1 H, m, H-8b); δ_C (101 MHz, DMSO) 175.8 (C-17), 173.1 (C-3), 166.7 (C-1), 161.7 (C-4), 140.0 (C-11), 128.6 (C-Ar), 127.0 (C-Ar), 126.9 (C-14), 97.5 (C-16), 68.9 (C-6), 60.3 (C-21), 46.2 (C-20), 45.8 (C-9), 42.9 (C-10), 38.1 (C-7), 34.4 (C-15), 22.2 (C-8), 15.3 (C-18); m/z (ESI) 394.2 ([MNa]$^+$,100), 765.4 ([2MNa]$^+$, 90).

Ketal adduct **170**



To a solution of Michael adduct **134** (381 mg, 1.16 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (1.0 mL) and CH_2Cl_2 (2.0 mL) was added *p*-toluenesulfonic acid monohydrate (*p*TSA) (cat., 10 mg) the reaction mixture was stirred for 16 hours at room temperature. Volatiles were removed under reduced pressure and the residue was purified by flash chromatography (60–70% EtOAc in hexane) and gave ketal adduct **170** (390 mg, 1.05 mmol, 90%) as a colourless solid; m.p. 130 – 131 °C; IR (thin film) ν_{max} /cm^{-1}: 1743, 1687, 1431, 1379, 1358, 1219, 772, 701; 2:1 mix of rotamers δ_H (400 MHz, $CDCl_3$) 7.49 – 7.41 (2 H, m), 7.36 – 7.23 (3 H, m), 5.07 – 4.93 (2 H, m), 4.02 – 3.69 (4 H, m), 3.67 – 3.57 (1 H, m), 2.34 – 2.14 (2 H, m), 2.12 – 1.95 (3 H, m), 1.95 – 1.92 (1 H, m), 1.36 – 1.18 (2 H, m), 1.10 (2 H, s); δ_C (101 MHz, $CDCl_3$) 205.3, 171.1, 170.9, 158.0, 157.9, 152.1, 152.0, 135.4, 135.4, 129.7, 129.6, 128.7, 128.6, 128.3, 128.1, 108.5, 77.4, 77.0, 76.7, 69.0, 68.5, 64.6, 45.2, 45.0, 44.3, 44.2, 37.1, 34.4, 34.2, 34.1, 33.1, 33.0, 29.8, 23.8, 19.7, 19.6; m/z 395.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{20}H_{24}N_2O_5Na$: 395.1583, Found 395.1584.

Ketal ethanolamine adduct **171**



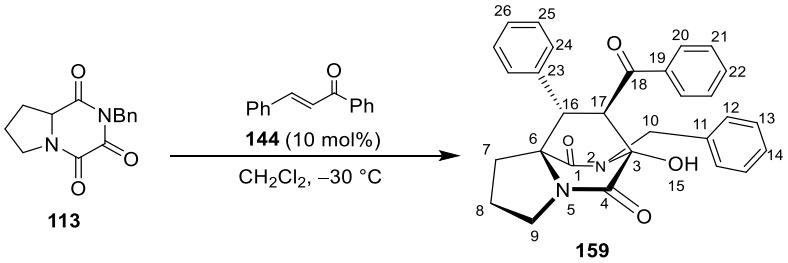
170 **171**

Ethanolamine (0.5 mL) was added to a solution of Michael adduct **170** (51 mg, 0.13 mmol) in THF (0.5 mL) and the reaction mixture was heated under reflux for 1 hour. Volatiles were removed under reduced pressure and the residue was directly purified by flash chromatography (EtOAc) and gave adduct **171** (43 mg, 0.094 mmol, 72%) as a pale yellow oil; IR (thin film) ν_{max} /cm^{-1}: 3332 (br), 2940, 1636, 1527, 1418, 1190, 1061, 749; δ_H (400 MHz, $CDCl_3$) 7.79 (1 H, t, *J* 5.8, H-20), 7.50 (1 H, t, *J* 5.7, H-2), 7.35 – 7.26 (3 H, m, H-Ar), 7.26 – 7.21 (2 H, m, H-Ar), 4.47 (1 H, dd, *J* 15.0, 6.0, H-10a), 4.36 (1 H, dd, *J* 15.0, 5.4, H-10b), 4.19 – 4.06 (1 H, m, H-9a), 3.94 – 3.75 (5 H, m, H-9b, H-19), 3.73 – 3.61 (2 H, m, H-22), 3.48 – 3.30 (2 H, m, H-21), 3.17 (1 H, s, H-23), 2.49 – 2.39 (1 H, m, H-7a), 2.33 (1 H, ddd, *J* 13.6, 9.7, 6.1, H-15a), 2.24 – 2.15 (1 H, m, H-15b), 1.95 – 1.85 (2 H, m, H-8), 1.84 – 1.74 (1 H, m, H-7b), 1.63 – 1.54 (2 H, m, H-16), 1.25 (3 H, s, H-18); δ_C (101 MHz, $CDCl_3$) 172.7 (C-1), 161.7 (C-3), 161.0 (C-4), 138.4 (C-11), 128.6 (C-Ar), 127.5 (C-Ar), 127.3 (C-14), 109.5 (C-17), 73.0 (C-6), 64.7 (C-19), 64.6 (C-19'), 61.3 (C-22), 51.3 (C-9), 43.7 (C-10), 42.1 (C-21), 34.9 (C-7), 33.5 (C-16), 27.9 (C-15), 24.0 (C-8), 23.8 (C-18); m/z 434.2 ([MH]$^+$, 100); HRMS (ESI/[MH]$^+$) Calcd. For $C_{22}H_{32}N_3O_6$: 434.2135, Found 434.2137.

Experimental for Chapter 3

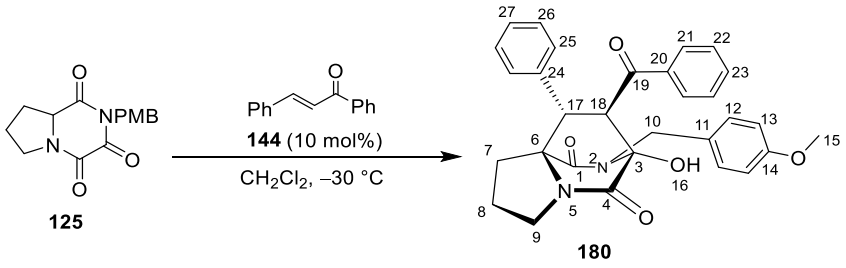
Enantioselective Michael Addition–Ring-Closure Reactions of TKPs

Hydroxy DKP **159**



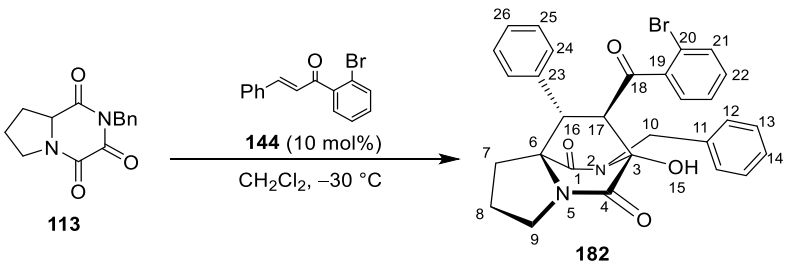
General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), chalcone (60 mg, 0.29 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (40–50% EtOAc in hexane) gave Michael adduct **159** (52 mg, 0.11 mmol, 96%) as a colourless solid in 1:99 er [Cellulose-3, MeCN:H_2O 60:40, 1.0 mLmin^{-1}, t_1= 4.37 mins, t_2= 7.40 mins]; m.p. 93 – 95 °C; IR (thin film) ν_{max} /cm^{-1}: 3323 (br), 3029, 1683, 1449, 1395, 1321, 1216, 1070, 750, 702; δ_H (400 MHz, $CDCl_3$) 7.69 – 7.57 (4 H, m, H-Ar), 7.56 – 7.49 (1 H, m, H-Ar), 7.48 – 7.31 (5 H, m, H-Ar), 7.25 – 7.19 (1 H, m, H-Ar), 7.18 – 7.11 (2 H, m, H-Ar), 6.76 – 6.70 (2 H, m, H-Ar), 5.08 (1 H, s, H-15), 4.91 (1 H, d, *J* 14.2, H-10a), 4.75 (1 H, d, *J* 14.2, H-10b), 4.31 (1 H, d, *J* 6.1, H-17), 3.80 – 3.64 (2 H, m, H-9), 3.45 (1 H, d, *J* 6.1, H-16), 2.52 – 2.43 (1 H, m, H-7a), 2.16 – 1.96 (2 H, m, H-8), 1.83 – 1.73 (1 H, m, H-7b); δ_C (101 MHz, $CDCl_3$) 198.2 (C-18), 168.2 (C-1), 166.2 (C-4), 137.4 (C-11), 137.1 (C-23), 136.7 (C-19), 133.7 (C-Ar), 129.9 (C-Ar), 128.9 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.0 (C-Ar), 84.9 (C-3), 70.8 (C-6), 58.0 (C-17), 52.5 (C-16), 44.8 (C-9), 43.1 (C-10), 28.2 (C-7), 24.6 (C-8); m/z (ESI) 259.1 ([M(–Chalcone)H]$^+$, 100), 467.2 ([MH]$^+$, 42), 933.4 ([2MH]$^+$, 63); HRMS (ESI/[MH]$^+$) Calcd. For $C_{29}H_{27}N_2O_4$: 467.1971, Found 467.1964; $[\alpha]_D^{21}$ = 69.4 (*c* 0.64, CH_2Cl_2).

PMB Hydroxy DKP **180**



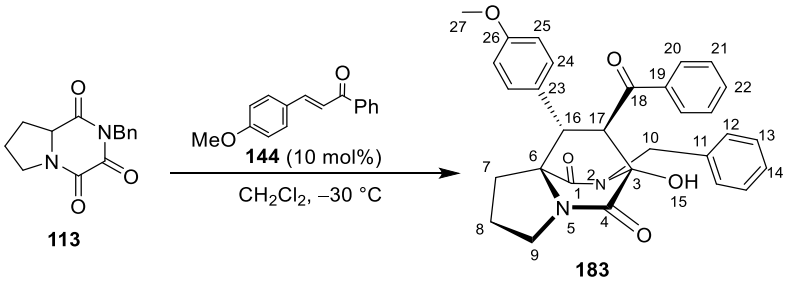
General procedure A was followed with TKP **125** (30 mg, 0.104 mmol), chalcone (60 mg, 0.29 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (50–60% EtOAc in hexane) gave Michael adduct **180** (43 mg, 0.087 mmol, 84%) as a colourless solid in 1:99 er [Cellulose-3, MeCN:H_2O 55:45, 1.0 mLmin^{-1}, t_1= 4.86 mins, t_2= 6.29 mins]; m.p. 150 – 152 °C; IR (thin film) ν_{max} /cm^{-1}: 3334 (br), 3010, 1677, 1611, 1596, 1582, 1511, 1448, 1245, 748, 702; δ_H (400 MHz, $CDCl_3$) 7.62 – 7.54 (4 H, m), 7.50 (1 H, ddt, *J* 8.6, 7.3, 1.3), 7.35 – 7.28 (2 H, m), 7.23 – 7.17 (1 H, m), 7.15 – 7.10 (2 H, m), 6.97 – 6.91 (2 H, m), 6.75 – 6.68 (2 H, m), 5.03 (1 H, s), 4.84 (1 H, d, *J* 14.2), 4.64 (1 H, d, *J* 14.2), 4.28 (1 H, d, *J* 6.1), 3.85 (3 H, s), 3.74 – 3.63 (2 H, m), 3.41 (1 H, d, *J* 6.1), 2.44 (1 H, ddd, *J* 13.3, 7.2, 5.2), 2.14 – 1.93 (2 H, m), 1.74 (1 H, ddd, *J* 13.4, 8.5, 7.3); δ_C (101 MHz, $CDCl_3$) 168.1, 166.2, 159.3, 137.1, 136.7, 133.7, 131.3, 129.7, 128.9, 128.9, 128.5, 128.1, 128.0, 113.9, 84.9, 70.8, 58.1, 55.4, 52.5, 44.8, 42.4, 28.2, 24.5; m/z (ESI) 519.2 ([MNa]$^+$, 100); HRMS (ESI/[MH]$^+$) Calcd. For $C_{30}H_{28}N_2O_5Na$: 519.1896, Found 519.1893; $[\alpha]_D^{21}$ = 41.2 (*c* 1.01, CH_2Cl_2).

Hydroxy DKP **182**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), 2'-bromo chalcone (86 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (40% EtOAc in hexane) gave Michael adduct **182** (49 mg, 0.090 mmol, 75%) as a colourless solid in 97:3 er [Cellulose-3, MeCN:H_2O 45:55, 1.0 mLmin^{-1}, t_1= 10.77 mins, t_2= 15.05 mins]; m.p. 94 – 96 °C; IR (thin film) ν_{max} /cm^{-1}: 3257 (br), 3030, 1685, 1429, 1393, 1319, 1209, 1070, 751, 702; δ_H (300 MHz, $CDCl_3$) 7.55 – 7.44 (3 H, m), 7.40 – 7.07 (10 H, m), 6.79 – 6.67 (2 H, m), 5.11 (1 H, s), 4.86 – 4.71 (2 H, m), 4.29 (1 H, d, *J* 6.0), 3.85 – 3.65 (2 H, m), 3.61 (1 H, d, *J* 6.0), 2.54 – 2.37 (1 H, m), 2.24 – 1.94 (2 H, m), 1.90 – 1.74 (1 H, m); δ_C (101 MHz, $CDCl_3$) 201.3, 168.1, 165.6, 141.1, 137.1, 136.9, 133.7, 132.2, 129.7, 129.4, 128.8, 128.6, 128.2, 127.9, 127.8, 127.2, 119.2, 85.3, 70.8, 61.8, 52.2, 44.8, 43.0, 28.1, 24.6; m/z 259.1 ([M(–2-BrChalcone)H]$^+$, 100), 547.1([MH]$^+$, 38); HRMS (ESI/[MH]$^+$) Calcd. For $C_{29}H_{26}N_2O_4Br$: 547.1055, Found 547.1061; $[\alpha]_D^{21}$= 50.9 (*c* 0.99, CH_2Cl_2).

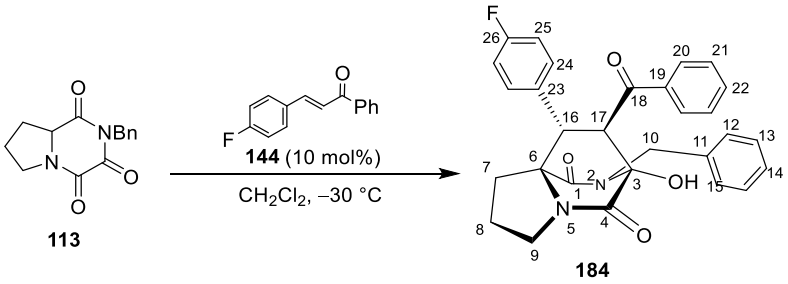
Hydroxy DKP **183**



113 **183**

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), 4-methoxy-chalcone (71 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (40–50% EtOAc in hexane) gave Michael adduct **183** (42 mg, 0.084 mmol, 70%) as a colourless solid in 1:99 er [Cellulose-3, MeCN:H_2O 60:40, 1.0 mLmin^{-1}, t_1= 4.20 mins, t_2= 5.64 mins]; m.p. 92 – 94 °C; IR (thin film) ν_{max} /cm^{-1}: 3312 (br), 3010, 1679, 1514, 1395, 1251, 1181, 1031, 753, 702; δ_H (300 MHz, $CDCl_3$) 7.73 – 7.30 (11 H, m), 6.71 – 6.56 (4 H, m), 5.05 (1 H, s), 4.89 (1 H, d, *J* 14.2), 4.74 (1 H, d, *J* 14.2), 4.27 (1 H, d, *J* 6.1), 3.79 – 3.65 (5 H, m), 3.37 (1 H, d, *J* 6.1), 2.54 – 2.38 (1 H, m), 2.18 – 1.92 (2 H, m), 1.82 – 1.72 (1 H, m); δ_C (101 MHz, $CDCl_3$) 198.3, 168.3, 166.2, 159.2, 137.4, 136.7, 133.7, 129.9, 129.1, 128.9, 128.6, 128.5, 128.0, 114.3, 84.82, 71.0, 58.2, 55.2, 51.8, 44.8, 43.1, 28.2, 24.5; m/z 519.18 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{30}H_{28}N_2O_5Na$: 519.1896, Found 519.1893; $[\alpha]_D^{21}$ = 93.7 (*c* 1.34, CH_2Cl_2).

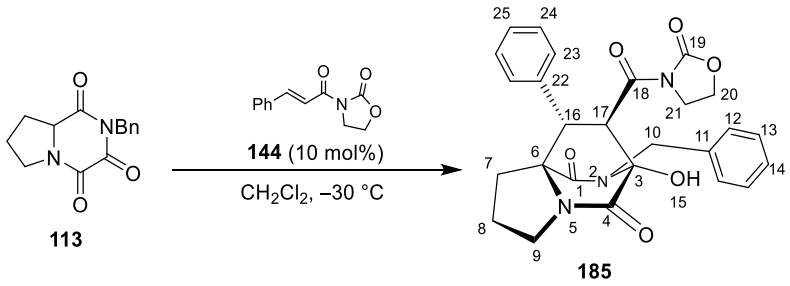
Hydroxy DKP **184**



113 **184**

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), 4-fluoro-chalcone (68 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (50% EtOAc in hexane) gave Michael adduct **184** (55 mg, 0.11 mmol, 95%) as a colourless solid in 6:94 er [Cellulose-3, MeCN:H_2O 50:50, 1.0 $mLmin^{-1}$, t_1= 6.29 mins, t_2= 11.69 mins]; m.p. 150 – 152 °C; IR (thin film) ν_{max} /cm^{-1}: 3312, 3010, 1682, 1511, 1395, 1215, 761, 703; δ_H (300 MHz, $CDCl_3$) 7.70 – 7.52 (5 H, m), 7.51 – 7.31 (5 H, m), 6.87 – 6.75 (2 H, m), 6.71 – 6.59 (2 H, m), 4.98 (1 H, s), 4.89 (1 H, d, *J* 14.2), 4.72 (1 H, d, *J* 14.2), 4.23 (1 H, d, *J* 6.1), 3.78 – 3.67 (2 H, m), 3.43 (1 H, d, *J* 6.1), 2.55 – 2.39 (1 H, m), 2.17 – 1.91 (2 H, m), 1.80 – 1.65 (1 H, m); δ_C (101 MHz, $CDCl_3$) 198.0, 168.0, 166.1, 162.3 (d, *J* 247.6), 137.3, 136.6, 133.9, 132.9 (d, *J* 2.1), 130.0, 129.7 (d, *J* 8.0), 128.9, 128.7, 128.6, 128.1, 115.9 (d, *J* 21.5), 84.9, 70.8, 58.2, 51.7, 44.8, 43.1, 28.2, 24.5; m/z 507.17 ($[MNa]^+$, 100), 485.18 ($[MH]^+$, 5); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{29}H_{25}N_2O_4NaF$: 507.1696, Found 507.1691; $[\alpha]_D^{21}$ = 45.9 (*c* 1.05, CH_2Cl_2).

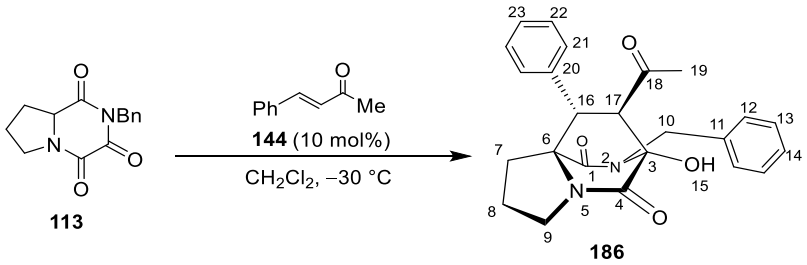
Hydroxy DKP **185**



113 **185**

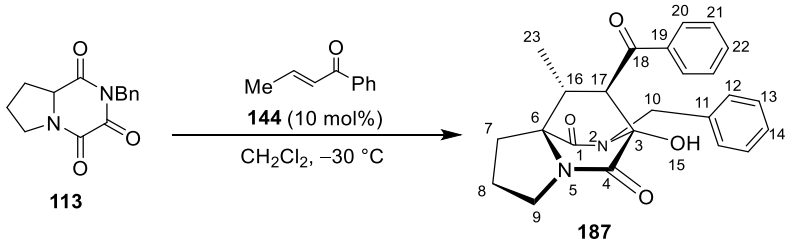
General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), cinnamoyl-2-oxazolidinone (65 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (85% EtOAc in hexane) gave Michael adduct **185** (46 mg, 0.097 mmol, 81%) as a colourless solid in 3:97 er [Cellulose-1, MeCN:H_2O 50:50, 1.0 mLmin^{-1}, t_1= 5.64 mins, t_2= 8.27 mins]; m.p. 166 – 168 °C; IR (thin film) ν_{max} /cm^{-1}: 3332 (br), 3029, 1782, 1688, 1393, 1359, 1203, 1114, 1041, 752, 702; δ_H (300 MHz, $CDCl_3$) 7.52 – 7.43 (2 H, m), 7.43 – 7.29 (3 H, m), 7.26 – 7.12 (3 H, m), 6.86 – 6.73 (2 H, m), 5.39 (1 H, d, *J* 5.7), 4.99 (1 H, s), 4.93 (1 H, d, *J* 14.6), 4.68 (1 H, d, *J* 14.6), 4.48 – 4.21 (2 H, m), 4.18 – 3.85 (2 H, m), 3.76 – 3.63 (2 H, m), 3.56 (1 H, d, *J* 5.8), 2.49 – 2.33 (1 H, m), 2.20 – 1.93 (2 H, m), 1.86 – 1.74 (1 H, m); δ_C (101 MHz, $CDCl_3$) 170.9, 168.1, 165.9, 152.8, 137.1, 136.2, 128.9, 128.8, 128.6, 128.3, 128.1, 127.6, 85.0, 70.8, 61.7, 52.7, 51.8, 44.8, 43.3, 42.8, 28.1, 24.5; m/z (ESI) 476.18 ([MH]$^+$, 100), 498.16 ([MNa]$^+$, 82); HRMS (ESI/[MH]$^+$) Calcd. For $C_{26}H_{26}N_3O_6$: 476.1822, Found 476.1809; $[\alpha]_D^{21}$ = 67.9 (*c* 1.16, CH_2Cl_2).

Hydroxy DKP **186**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), 4-phenyl-3-buten-2-one (44 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (50% EtOAc in hexane) gave Michael adduct **186** (47 mg, 0.12 mmol, 98%) as a colourless solid in 2:98 er [Cellulose-3, MeCN:H_2O 40:60, 1.0 mLmin^{-1}, t_1= 5.76 mins, t_2= 9.47 mins]; m.p. 142 – 144 °C; IR ν_{max} /cm^{-1}: 3309 (br), 3035, 1685, 1495, 1395, 1354, 1189, 1071, 749, 702; δ_H (300 MHz, $CDCl_3$) 7.62 – 7.52 (2 H, m), 7.47 – 7.30 (3 H, m), 7.26 – 7.07 (3 H, m), 6.76 – 6.66 (2 H, m), 4.91 – 4.72 (2 H, m), 3.71 – 3.60 (2 H, m), 3.52 (1 H, d, *J* 5.9), 3.43 (1 H, d, *J* 5.9), 2.48 – 2.35 (1 H, m), 2.20 (3 H, s), 2.13 – 1.93 (2 H, m), 1.81 – 1.63 (1 H, m); δ_C (101 MHz, $CDCl_3$) 206.0, 168.1, 165.7, 137.3, 129.4, 128.9, 128.7, 128.1, 128.0, 127.9, 84.6, 70.7, 63.1, 50.8, 44.7, 43.0, 33.0, 28.0, 24.5; m/z 427.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{24}H_{24}N_2O_4Na$: 427.1634, Found 427.1619; $[\alpha]_D^{21}$ = 2.4 (*c* 1.16, CH_2Cl_2).

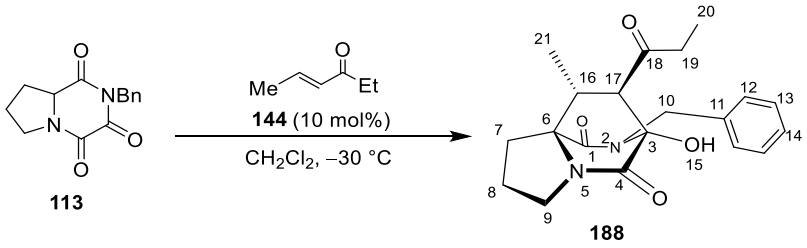
Hydroxy DKP **187**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), phenyl crotonone (45 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (50–55% EtOAc in hexane) gave

Michael adduct **187** (48 mg, 0.12 mmol, 99%) as a colourless solid in 1:99 er [Cellulose-3, MeCN:H_2O 50:50, 1.0 mLmin^{-1}, t_1= 5.39 mins, t_2= 6.77 mins]; m.p. 158 – 159 °C; IR (thin film) ν_{max} /cm^{-1}: 3314 (br), 2970, 1679, 1448, 1395, 1355, 1215, 753, 702; δ_H (300 MHz, $CDCl_3$) 7.72 – 7.47 (5 H, m), 7.49 – 7.32 (5 H, m), 5.00 (1 H, d, *J* 14.2), 4.82 (1 H, s), 4.44 (1 H, d, *J* 14.2), 2.98 – 2.79 (1 H, m), 2.43 – 2.27 (1 H, m), 2.20 – 1.97 (2 H, m), 1.90 – 1.75 (1 H, m), 0.92 (3 H, d, *J* 7.2); δ_C (101 MHz, $CDCl_3$) 198.3, 168.6, 165.7, 138.2, 137.0, 133.7, 129.6, 128.9, 128.6, 128.5, 127.8, 85.0, 70.7, 57.3, 44.5, 42.9, 41.2, 28.3, 24.8, 17.0; m/z 427.16 ([MNa]$^+$, 100), 405.17 ([MH]$^+$, 10); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{24}H_{24}N_2O_5$: 427.1634, Found 427.1632; $[\alpha]_D^{21}$ = 39.1 (*c* 0.92, CH_2Cl_2).

Hydroxy DKP **188**

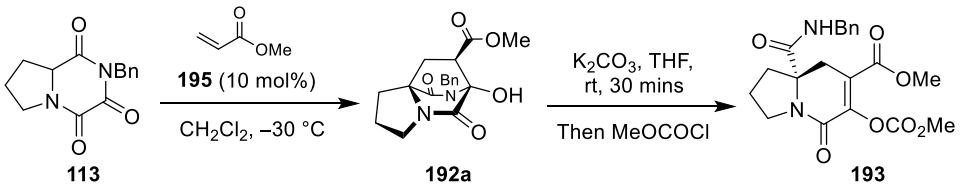


113 **188**

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), 4-hexen-3-one (29 mg, 35 μL, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (40–50% EtOAc in hexane) gave Michael adduct **188** (41 mg, 0.12 mmol, 96%) as a colourless solid in 1:99 er [Cellulose-3, MeCN:H_2O 35:65, 1.0 mLmin^{-1}, t_1= 7.41 mins, t_2= 8.99 mins]; m.p. 110 – 111 °C; IR (thin film) ν_{max} /cm^{-1}: 3243 (br), 2973, 1680, 1456, 1394, 1356, 1187, 702; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.32 (2 H, m), 7.29 – 7.20 (3 H, m), 4.77 (1 H, s), 4.70 (1 H, d, *J* 14.4), 4.46 (1 H, d, *J* 14.4), 3.60 (1 H, ddd, *J* 11.5, 7.8, 3.9), 3.44 (1 H, ddd, *J* 11.3, 8.8, 6.8), 2.76 (1 H, ddd, *J* 13.0, 7.0, 4.1), 2.63 – 2.49 (2 H, m), 2.32 – 2.22 (1 H, m), 2.10 – 2.20 (1 H, m), 2.04 – 1.89 (2 H, m), 1.71 (1 H, ddd, *J* 13.1, 9.5, 7.3), 0.92 (3 H, t, *J* 7.2), 0.81 (3 H, d, *J* 7.2); δ_C (101 MHz, $CDCl_3$) 208.9, 168.5, 165.6, 137.9, 128.9, 128.5, 127.6, 84.6, 70.6, 62.0, 44.4, 42.8,

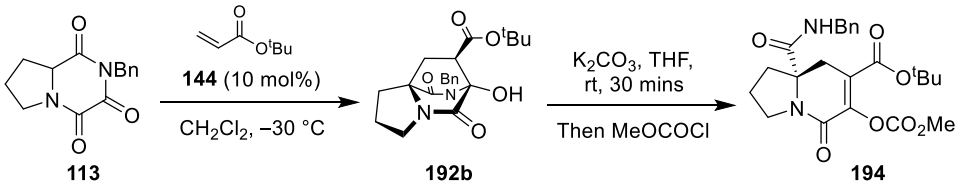
39.9, 38.9, 28.2, 24.7, 17.3, 7.2; m/z 379.2 ([MNa]$^+$, 100), 301.1 ([MH(–C_3H_4O)]$^+$, 75); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{20}H_{24}N_2O_4Na$: 379.1634, Found 379.1636; $[\alpha]_D^{21}$ = –63.2 (*c* 0.88, CH_2Cl_2).

Carbonate adduct **193**



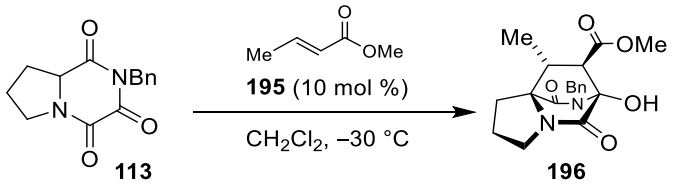
General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), methylacrylate (27 μL, 0.30 mmol) and **195** (7 mg, 0.012 mmol) as base. The volatiles were then removed under reduced pressure and the residue was dissolved in THF (1.0 mL) and K_2CO_3 (20 mg) was then added and the mixture was stirred for 30 mins. Methyl chloroformate (40 μl, 0.50 mmol) was then added and the mixture was stirred for 2 hours. H_2O (5 mL) and EtOAc (10 mL) were then added and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over magnesium sulphate and then purified by flash chromatography (60–70% EtOAc in hexane) gave carbonate adduct **193** (23 mg, 0.058 mmol, 48%) as a colourless solid in 5:95 er [Cellulose-3, MeCN:H_2O 25:75, 1.0 mLmin^{-1}, t_1= 9.38 mins, t_2= 10.56 mins]; m.p. 120 – 122 °C; IR (thin film) ν_{max} /cm^{-1}: 1771, 1721, 1668, 1644, 1518, 1431, 1262, 1189, 731, 699; δ_H (300 MHz, $CDCl_3$) 7.33 – 7.02 (5 H, m), 6.83 (1 H, t, *J* 5.4), 4.50 (1 H, dd, *J* 14.7, 6.8), 4.20 (1 H, dd, *J* 14.7, 5.2), 3.78 (3 H, s), 3.72 (3 H, s), 3.62 (2 H, ddd, *J* 11.9, 6.3, 3.4), 3.53 (1 H, d, *J* 17.1), 2.77 – 2.50 (2 H, m), 2.05 – 1.68 (3 H, m); δ_C (101 MHz, $CDCl_3$) 171.7, 163.9, 158.3, 153.0, 143.7, 137.9, 128.7, 127.8, 127.6, 122.2, 68.3, 56.2, 52.8, 46.2, 44.4, 39.0, 33.9, 29.8, 22.4; m/z 425.1 ([MNa]$^+$, 100), 403.1 ([MH]$^+$, 6); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{23}H_{28}N_2O_7Na$: 425.1427, Found 425.1424 $[\alpha]_D^{21}$ = –152.3 (*c* 0.68, CH_2Cl_2).

Carbonate adduct **194**



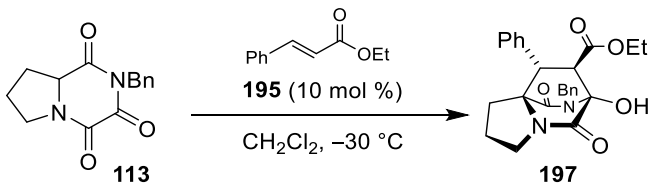
General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), tert-butylacrylate (44 μL, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. The volatiles were then removed under reduced pressure and the residue was dissolved in THF (1 mL) and K_2CO_3 (20 mg) was then added and the mixture was stirred for 30 mins. Methyl chloroformate (40 μl, 0.50 mmol) was then added and the mixture was stirred for 2 hours. H_2O (5 mL) and EtOAc (10 mL) were then added and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over magnesium sulphate and then purified by flash chromatography (60–70% EtOAc in hexane) gave carbonate adduct **194** (26 mg, 0.058 mmol, 48%) as a colourless solid in 15:85 er [Cellulose-3, MeCN:H_2O 40:60, 1.0 mLmin^{-1}, t_1= 14.98 mins, t_2= 18.49 mins]; m.p. 120 – 122 °C; IR (thin film) ν_{max} /cm^{-1}: 1772, 1706, 1665, 1640, 1523, 1440, 1262, 1212, 1142, 732, 698; δ_H (400 MHz, $CDCl_3$) 7.26 – 7.10 (5 H, m), 6.83 (1 H, t, *J* 5.7), 4.47 (1 H, dd, *J* 14.7, 6.6), 4.25 (1 H, dd, *J* 14.7, 5.3), 3.76 (3 H, s), 3.64 – 3.55 (2 H, m), 3.43 (1 H, d, *J* 17.3), 2.72 – 2.66 (1 H, m), 2.63 (1 H, d, *J* 17.3), 1.99 – 1.88 (1 H, m), 1.88 – 1.66 (2 H, m), 1.41 (9 H, s); δ_C (101 MHz, $CDCl_3$) 171.6, 162.4, 158.5, 153.0, 142.3, 137.9, 128.6, 127.7, 127.4, 124.3, 83.1, 68.1, 55.9, 46.0, 44.2, 39.0, 33.9, 28.0, 22.2; m/z 467.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{23}H_{28}N_2O_7Na$: 467.1794, Found 467.1795; $[\alpha]_D^{21}$ = –89.7 (*c* 0.78, CH_2Cl_2).

Ester adduct **196**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), methyl crotonate (32 μL, 0.30 mmol) and **195** (7 mg, 0.012 mmol) as base. Flash chromatography (40–50% EtOAc in hexane) gave Michael adduct **196** (37 mg, 0.10 mmol, 85%) as a colourless solid in 4:96 er [Cellulose-3, MeCN:H_2O 35:65, 1.0 mLmin^{-1}, t_1= 7.75 mins, t_2= 9.74 mins]; m.p. 140 – 142 °C; IR (thin film) ν_{max} /cm^{-1}: 3316 (br), 1739, 1683, 1396, 1358, 199, 702; δ_H (400 MHz, $CDCl_3$) 7.39 – 7.14 (5 H, m), 4.96 (1 H, s), 4.69 (1 H, d, *J* 14.5), 4.53 (1 H, d, *J* 14.5), 3.72 – 3.59 (4 H, m), 3.46 (1 H, ddd, *J* 11.3, 9.1, 6.9), 2.82 (1 H, ddd, *J* 12.9, 6.9, 3.9), 2.50 (1 H, d, *J* 5.0), 2.20 (1 H, dd, *J* 7.2, 5.0), 2.11 – 1.90 (2 H, m), 1.77 – 1.67 (1 H, m), 0.93 (3 H, d, *J* 7.2); δ_C (101 MHz, $CDCl_3$) 171.2, 168.2, 165.9, 137.8, 128.7, 128.6, 127.5, 84.0, 70.6, 56.7, 52.5, 44.5, 42.8, 41.3, 28.3, 24.8, 17.3; m/z 381 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{19}H_{22}N_2O_5Na$: 381.1426, Found 381.1424; $[\alpha]_D^{21}$ = 53.7 (*c* 1.30, CH_2Cl_2).

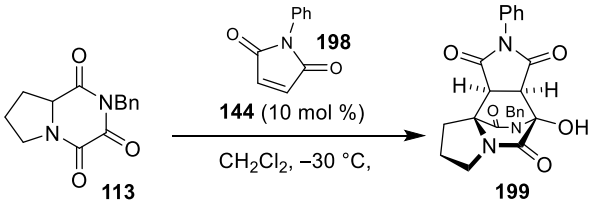
Ester adduct **197**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), ethyl cinnamate (50 μL, 0.30 mmol) and **195** (7 mg, 0.012 mmol) as base. Flash chromatography (50–55% EtOAc in hexane) gave Michael adduct **197** (35 mg, 0.080 mmol, 67%) as a colourless solid in 4:96 er [Cellulose-3, MeCN:H_2O 50:50, 1.0 mLmin^{-1}, t_1= 5.22 mins, t_2= 7.21 mins]; m.p. 140 – 141 °C; IR (thin film) ν_{max} /cm^{-1}: 3309

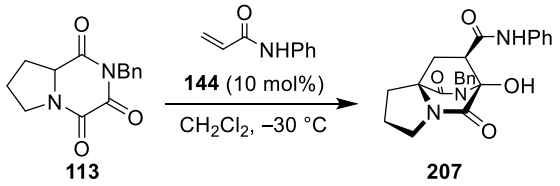
(br),1731, 1681, 1454, 1393, 1302, 1267, 1186, 1070, 732, 701; δ_H (400 MHz, $CDCl_3$) 7.54 – 7.43 (2 H, m), 7.41 – 7.28 (3 H, m), 7.24 – 7.06 (3 H, m), 6.76 – 6.64 (2 H, m), 5.08 (1 H, s), 4.82 (1 H, d, *J* 14.4), 4.71 (1 H, d, *J* 14.4), 4.22 – 4.05 (2 H, m), 3.70 – 3.56 (2 H, m), 3.35 (1 H, d, *J* 5.9), 3.29 (1 H, d, *J* 5.9), 2.41 (1 H, ddd, *J* 13.0, 7.1, 5.2), 2.13 – 1.89 (2 H, m), 1.81 – 1.60 (1 H, m), 1.21 (3 H, t, *J* 7.1); δ_C (101 MHz, $CDCl_3$) 170.7, 167.9, 166.0, 137.2, 136.8, 129.2, 128.9, 128.7, 128.0, 127.7, 84.2, 70.7, 61.7, 57.5, 52.2, 44.7, 43.1, 28.1, 24.5, 14.1; m/z 457.2 ($[MNa]^+$, 100), 435.2 ($[MH]^+$, 12); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{25}H_{26}N_2O_5Na$: 457.1739, Found 457.1742; $[\alpha]_D^{21} = -31.5$ (*c* 0.88, CH_2Cl_2).

Maleimide adduct **199**



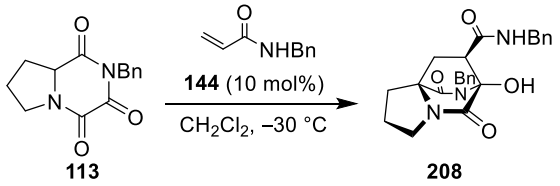
General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), *N*-phenyl maleimide (52 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (50–55% EtOAc in hexane) gave Michael adduct **199** (25 mg, 0.058 mmol, 48%) as a colourless solid in 65:35 er [Cellulose-3, MeCN:H_2O 30:70, 1.0 mLmin^{-1}, t_1= 15.04 mins, t_2= 18.07 mins]; m.p. decomp. 210 – 212 °C; IR (thin film) ν_{max} /cm^{-1}: 3302 (br), 1716, 1697, 1685, 1675, 1498, 1452, 1394, 1195, 967, 772, 729, 692; δ_H (400 MHz, $CDCl_3$) 7.43 – 7.30 (5 H, m), 7.30 – 7.16 (3 H, m), 7.09 – 7.00 (2 H, m), 4.99 (1 H, s), 4.76 (1 H, d, *J* 14.5), 4.53 (1 H, d, *J* 14.5), 3.59 (1 H, ddd, *J* 11.8, 7.9, 4.3), 3.34 – 3.22 (2 H, m), 3.15 (1 H, d, *J* 8.8), 2.93 (1 H, ddd, *J* 13.6, 7.8, 4.5), 2.82 (1 H, ddd, *J* 13.6, 9.1, 7.6), 2.11 – 1.98 (1 H, m), 1.98 – 1.86 (1 H, m); δ_C (101 MHz, $CDCl_3$) 172.2, 170.2, 167.2, 164.7, 137.1, 134.2, 130.9, 129.4, 129.3, 128.8, 128.6, 127.9, 126.3, 126.1, 84.1, 69.3, 50.3, 45.4, 44.4, 44.4, 43.4, 25.5, 24.7; $[\alpha]_D^{21}$ = N.D. (poor solubility).

Amide **207**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), phenyl acrylamide (44 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (70–80% EtOAc in hexane) gave Michael adduct **207** (35 mg, 0.086 mmol, 72%) as a colourless solid in 97:3 er [Cellulose-3, MeCN:H_2O 30:70, 1.0 mLmin^{-1}, t_1= 9.49 mins, t_2= 11.32 mins]; m.p. 134 – 136 °C; IR (thin film) ν_{max} /cm^{-1}: 3316 (br), 1682, 1600, 1548, 1443, 1359, 755, 695; δ_H (400 MHz, $CDCl_3$) 7.60 (1 H, s), 7.48 – 7.39 (2 H, m), 7.39 – 7.25 (7 H, m), 7.18 – 7.04 (1 H, m), 5.36 (1 H, s), 4.82 (1 H, d, *J* 14.8), 4.58 (1 H, d, *J* 14.8), 3.69 – 3.61 (1 H, m), 3.60 – 3.52 (1 H, m), 2.95 – 2.79 (2 H, m), 2.60 (1 H, dd, *J* 13.4, 4.3), 2.21 – 1.87 (4 H, m); δ_C (101 MHz, $CDCl_3$) 169.7, 166.7, 165.0, 137.9, 137.2, 128.9, 128.7, 128.1, 127.6, 124.8, 120.1, 84.9, 66.7, 50.3, 44.6, 43.0, 32.1, 29.2, 24.7; m/z 428.2 ([MNa]$^+$, 100), 406.2 ([MH]$^+$, 12); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{23}H_{23}N_3O_4Na$: 428.1586, Found 428.1587; $[\alpha]_D^{21}$ = 78.7 (*c* 0.94, CH_2Cl_2).

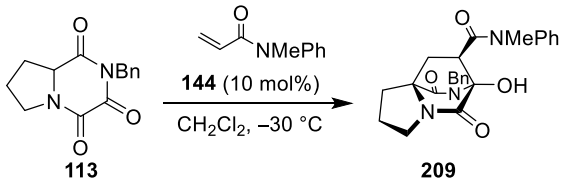
Amide **208**



General procedure A was followed with TKP **113** (30 mg, 0.12 mmol), benzyl acrylamide (47 mg, 0.29 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (80% EtOAc in hexane) gave Michael adduct **208** (31 mg, 0.074 mmol, 64%) as a colourless solid in 99:1 er [Chiralcel OD, IPA:Hexane 20:80, 1.0 mLmin^{-1}, t_1= 13.99 mins, t_2= 23.18 mins]; m.p. 104 – 106 °C; IR (thin film) ν_{max} /cm^{-1}: 3316 (br), 3030,

1674, 1539, 1397, 1357, 1219, 750, 699; δ_H (300 MHz, $CDCl_3$) 7.35 – 7.22 (10 H, m), 6.15 (1 H, s), 5.14 (1 H, s), 4.76 (1 H, d, *J* 14.8), 4.54 (1 H, d, *J* 14.8), 4.40 (2 H, qd, *J* 14.8, 5.7), 3.73 – 3.51 (2 H, m), 2.88 (1 H, dt, *J* 13.2, 6.7), 2.73 (1 H, dd, *J* 10.2, 4.2), 2.55 (1 H, dd, *J* 13.3, 4.3), 2.19 – 1.91 (4 H, m); δ_C (101 MHz, $CDCl_3$) 169.8, 168.5, 165.2, 137.9, 137.7, 128.7, 128.7, 128.0, 127.7, 127.6, 127.5, 84.7, 66.8, 49.5, 44.6, 44.0, 42.9, 32.3, 29.2, 24.7; m/z 442.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{24}H_{25}N_3O_4Na$: 442.1743, Found 442.1746; $[\alpha]_D^{21} = 60.4$ (*c* 1.06, CH_2Cl_2).

Amide **209**



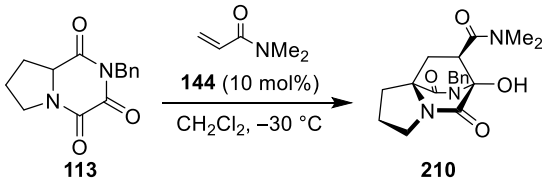
113 **209**

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), methyl phenyl acrylamide (48 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (EtOAc) gave Michael adduct **209** (42 mg, 0.10 mmol, 83%) as a colourless solid in 99:1 er [Cellulose-3, MeCN:H_2O 20:80, 1.0 $mLmin^{-1}$, t_1= 22.38, t_2= 27.33]; m.p. 184 – 186 °C; IR (thin film) ν_{max} /cm^{-1}: 3321 (br), 3005, 1685, 1670, 1455, 1396, 928, 698; δ_H (300 MHz, $CDCl_3$) 7.35 – 7.22 (10 H, m), 6.15 (1 H, s), 5.14 (1 H, s), 4.76 (1 H, d, *J* 14.8), 4.54 (1 H, d, *J* 14.8), 4.40 (2 H, qd, *J* 14.8, 5.7), 3.73 – 3.51 (2 H, m), 2.88 (1 H, dt, *J* 13.2, 6.7), 2.73 (1 H, dd, *J* 10.2, 4.2), 2.55 (1 H, dd, *J* 13.3, 4.3), 2.19 – 1.91 (4 H, m); δ_C (101 MHz, $CDCl_3$) 170.4, 169.5, 166.4, 142.9, 137.7, 129.9, 128.4, 128.1, 127.9, 127.3, 127.1, 85.0, 66.4, 46.2, 44.7, 42.7, 37.6, 34.3, 29.3, 24.7; m/z 442.3 ($[MNa]^+$, 100), 303.1 (8); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{24}H_{25}N_3O_4Na$: 442.1743, Found 442.1734; $[\alpha]_D^{21} = -46.5$ (*c* 0.49, CH_2Cl_2).

Scale up - General procedure A was followed with TKP **113** (500 mg, 1.94 mmol), methyl phenyl acrylamide (468 mg, 2.90 mmol) and **144** (47 mg, 0.097 mmol [5 mol %]) as base. Flash chromatography

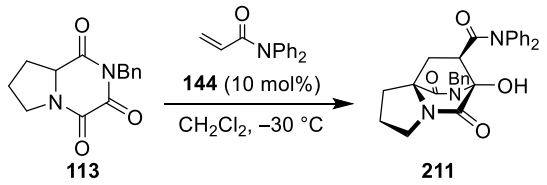
(90–100% EtOAc in hexane) gave Michael adduct **209** (770 mg, 1.62 mmol, 84%) as a colourless solid, with data consistent to that above.

Amide **210**



General procedure A was followed with TKP **113** (30 mg, 0.12 mmol), dimethyl acrylamide (29 mg, 0.29 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (0–10% MeOH in EtOAc) gave Michael adduct **210** (35 mg, 0.097 mmol, 81%) as a colourless gum in 99:1 er [Cellulose-3, MeCN:H_2O 15:85, 1.0 mLmin^{-1}, t_1= 8.13 mins, t_2= 9.85 mins]; IR (thin film) ν_{max} /cm^{-1}: 3278 (br), 2938, 1680, 1641, 1396, 922, 728, 703; δ_H (300 MHz, $CDCl_3$) 7.46 – 7.36 (2 H, m), 7.36 – 7.25 (3 H, m), 5.02 – 4.86 (2 H, m), 4.39 (1 H, d, *J* 14.4), 3.75 – 3.50 (2 H, m), 3.15 (1 H, dt, *J* 8.4, 4.2), 2.98 – 2.79 (4 H, m), 2.74 (3 H, s), 2.26 – 1.79 (5 H, m); δ_C (101 MHz, $CDCl_3$) 169.9, 169.7, 165.6, 138.1, 128.8, 128.6, 127.6, 85.4, 66.6, 45.0, 44.5, 42.9, 37.5, 36.0, 33.8, 29.3, 24.6; m/z 380.2 ([MNa]$^+$, 100), 358.2 ([MH]$^+$, 7); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{19}H_{23}N_3O_4Na$: 380.1586, Found 380.1585; $[\alpha]_D^{21}$ = 31.0 (*c* 0.98, CH_2Cl_2).

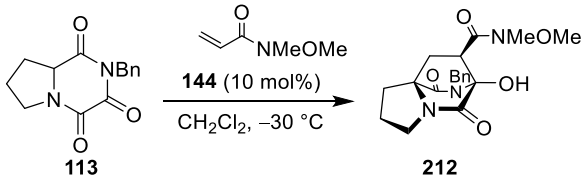
Amide **211**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), diphenyl acrylamide (67 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (50–65% EtOAc in hexane) gave Michael adduct **211** (46 mg, 0.096 mmol, 80%) as a colourless solid in 4:96 er [Cellulose-3, MeCN:H_2O

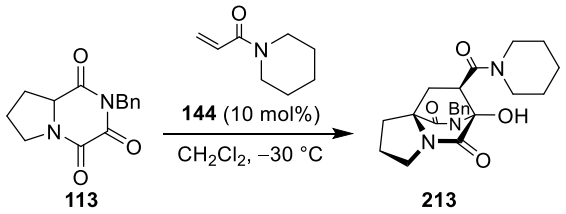
35:65, 1.0 mLmin^{-1}, t_1= 9.14 mins, t_2= 10.21 mins]; m.p. 157 – 158 °C; IR (thin film) ν_{max} /cm^{-1}: 3252 (br), 1676, 1593, 1491, 1387, 1325, 1268, 734, 700; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.24 (6 H, m), 7.19 – 7.08 (9 H, m), 5.21 (1 H, s), 4.54 (1 H, d, *J* 14.7), 4.40 (1 H, d, *J* 14.7), 3.69 – 3.53 (2 H, m), 3.18 (1 H, dd, *J* 10.4, 5.0), 2.81 (1 H, dt, *J* 13.2, 6.4), 2.17 (1 H, dd, *J* 13.0, 5.1), 2.12 – 1.90 (3 H, m), 1.81 (1 H, dt, *J* 13.1, 7.4); δ_C (101 MHz, $CDCl_3$) 170.8, 169.5, 166.2, 142.1, 142.0, 137.6, 129.9, 128.9, 128.5, 128.5, 128.1, 127.9, 127.2, 126.5, 126.3, 85.4, 66.4, 47.2, 44.5, 42.8, 34.5, 29.3, 24.6; m/z 504.2 ([MNa]$^+$, 100), 482.2 ([MH]$^+$, 38); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{29}H_{27}N_3O_4Na$: 504.1899, Found 504.1901; $[\alpha]_D^{21}$ = –123.2 (*c* 0.99, CH_2Cl_2).

Amide **212**



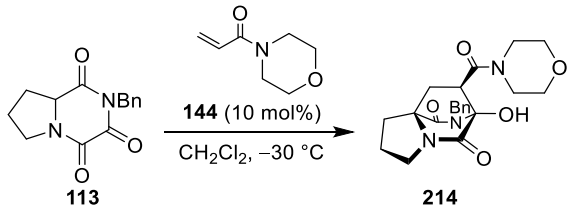
General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), *N*-methoxymethyl acrylamide (35 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (0–5% MeOH in EtOAc) gave Michael adduct **212** (44 mg, 0.12 mmol, 98%) as a colourless gum in 2:98 er [HPLC analysis was performed on **134** formed from the reaction of **212** with MeMgBr (3 eq) in THF followed by purification by flash chromatography; Cellulose-3, MeCN:H_2O 30:70, 1.0 mLmin^{-1}, t_1= 6.09 mins, t_2= 7.58 mins]; IR (thin film) ν_{max} /cm^{-1}: 3319 (br), 1683, 1428, 1394, 1356, 1187, 703; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.33 (2 H, m), 7.32 – 7.21 (3 H, m), 4.96 (1 H, s), 4.89 (1 H, d, *J* 14.5), 4.38 (1 H, d, *J* 14.6), 3.69 – 3.53 (2 H, m), 3.46 (1 H, dd, *J* 10.2, 5.3), 3.38 (3 H, s), 3.10 (3 H, s), 2.86 (1 H, ddd, *J* 13.2, 7.1, 6.1), 2.15 – 1.95 (4 H, m), 1.84 (1 H, dt, *J* 13.1, 7.5); δ_C (101 MHz, $CDCl_3$) 170.9, 169.6, 165.9, 138.1, 128.6, 128.6, 127.4, 84.8, 66.6, 61.4, 44.5, 44.0, 42.9, 33.8, 31.9, 29.3, 24.7; m/z 374.2 ([MH]$^+$, 100); HRMS (ESI/[MH]$^+$) Calcd. For $C_{19}H_{24}N_3O_5$: 374.1716, Found 374.1721; $[\alpha]_D^{21}$ = –14.4 (*c* 0.70, CH_2Cl_2).

Amide **213**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), piperidine acrylamide (42 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (0–5% MeOH in EtOAc) gave Michael adduct **213** (38 mg, 0.096 mmol, 80%) as a colourless gum in 1:99 er [Amylose-2, MeCN:H_2O 40:60, 1.0 mLmin^{-1}, t_1= 6.38 mins, t_2= 9.22 mins]; IR (thin film) ν_{max} /cm^{-1}: 3278 (br), 2937, 2857, 1681, 1633, 1442, 1395, 1248, 750, 703; δ_H (300 MHz, $CDCl_3$) 7.40 – 7.28 (2 H, m), 7.28 – 7.13 (3 H, m), 4.98 (1 H, s), 4.87 (1 H, d, *J* 14.3), 4.28 (1 H, d, *J* 14.3), 3.70 – 3.38 (3 H, m), 3.23 – 3.11 (1 H, m), 3.07 – 2.94 (2 H, m), 2.93 – 2.68 (2 H, m), 2.17 – 1.71 (5 H, m), 1.58 – 1.24 (6 H, m); δ_C (101 MHz, $CDCl_3$) 169.7, 168.1, 165.7, 138.2, 129.0, 128.5, 127.5, 85.3, 66.6, 47.3, 44.5, 44.5, 43.3, 42.9, 34.0, 29.3, 26.5, 25.6, 24.6, 24.4; m/z 420.18 ([MNa]$^+$, 100), 398.19 ([MH]$^+$, 7); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{22}H_{27}N_3O_4Na$: 420.1899, Found 420.1903; $[\alpha]_D^{21}$ = –24.3 (*c* 1.15, CH_2Cl_2).

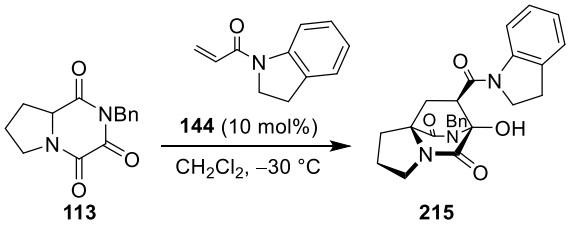
Amide **214**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), morpholine acrylamide (42 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (0.5–1.5% MeOH in EtOAc) gave Michael adduct **214** (47 mg, 0.12 mmol, 98 %) as a colourless gum in 1:99 er [Cellulose-3,

MeCN:H_2O 15:85, 1.0 mLmin^{-1}, t_1= 12.13 mins, t_2= 16.99 mins]; IR (thin film) ν_{max} /cm^{-1}: 3313 (br), 2923, 1679, 1632, 1434, 1364, 1244, 1111, 731, 702; δ_H (300 MHz, $CDCl_3$) 7.42 – 7.35 (2 H, m), 7.33 – 7.21 (3 H, m), 5.08 – 4.93 (2 H, m), 4.28 (1 H, d, *J* 14.3), 3.90 – 3.76 (1 H, m), 3.71 – 3.48 (6 H, m), 3.23 (1 H, ddd, *J* 13.4, 8.0, 3.5), 3.07 – 2.80 (4 H, m), 2.27 (1 H, dd, *J* 13.0, 4.8), 2.17 – 2.00 (2 H, m), 1.95 – 1.82 (2 H, m); δ_C (101 MHz, $CDCl_3$) 169.5, 168.2, 165.2, 138.2, 129.0, 128.5, 127.7, 85.3, 66.8, 66.7, 66.6, 46.5, 44.6, 44.4, 43.0, 42.6, 33.8, 29.3, 24.6; m/z 422.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{21}H_{25}N_3O_5Na$: 422.1692, Found 422.1690; $[\alpha]_D^{21}$ = 9.6 (*c* 0.67, CH_2Cl_2).

Amide **215**

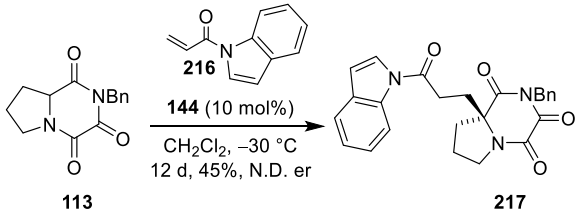


113 215

General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), indoline acrylamide (52 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (60–65% EtOAc in hexane) gave Michael adduct **215** (49 mg, 0.11 mmol, 95%) as a colourless solid in 2:98 er [Cellulose-3, MeCN:H_2O 35:65, 1.0 mLmin^{-1}, t_1= 8.33 mins, t_2= 9.66 mins]; m.p. 164 – 167 °C; IR ν_{max} /cm^{-1}: 3358 (br), 2943, 1680, 1656, 1482, 1418, 1340, 757, 704; δ_H (400 MHz, $CDCl_3$) 8.19 – 8.11 (1 H, m), 7.47 – 7.38 (2 H, m), 7.35 – 7.27 (3 H, m), 7.17 – 7.08 (2 H, m), 6.99 (1 H, td, *J* 7.4, 1.1), 5.16 (1 H, s), 4.97 (1 H, d, *J* 14.4), 4.38 (1 H, d, *J* 14.4), 3.83 (1 H, td, *J* 10.0, 7.1), 3.70 (1 H, dt, *J* 11.3, 7.2), 3.58 (1 H, ddd, *J* 11.4, 7.5, 5.5), 3.49 (1 H, td, *J* 10.1, 6.9), 3.13 – 2.96 (3 H, m), 2.88 (1 H, ddd, *J* 13.2, 7.2, 6.0), 2.32 (1 H, dd, *J* 13.0, 4.9), 2.15 – 1.96 (3 H, m), 1.88 (1 H, dt, *J* 13.1, 7.5); δ_C (101 MHz, $CDCl_3$) 169.6, 167.9, 165.4, 142.4, 138.1, 131.6, 129.0, 128.6, 127.6, 127.4, 124.5, 124.2, 117.6, 85.6, 66.7, 48.3, 48.2, 44.6, 43.0, 33.7, 29.3, 27.6, 24.7;

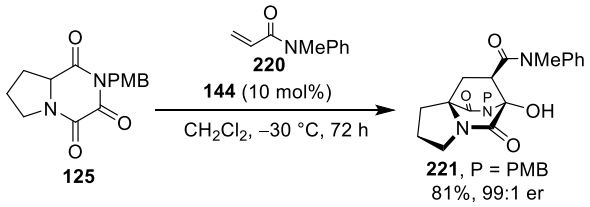
m/z 454.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{25}H_{25}N_3O_4Na$: 454.1743, Found 454.1741; $[\alpha]_D^{21}$ = 20.1 (*c* 0.89, CH_2Cl_2).

Indole amide **217**



General procedure A was followed with TKP **113** (31 mg, 0.12 mmol), indole acrylamide (51 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (40–60% EtOAc in hexane) gave Michael adduct **217** (23 mg, 0.054 mmol, 45%) as a colourless solid [er not determined]; m.p. 188 – 190 °C; IR ν_{max} /cm^{-1}: 2940, 1741, 1694, 1680, 1476, 1312, 754, 725; δ_H (300 MHz, $CDCl_3$) 8.32 (1 H, d, *J* 8.0), 7.61 – 7.55 (1 H, m), 7.54 – 7.48 (2 H, m), 7.39 – 7.28 (3 H, m), 7.27 – 7.23 (1 H, m), 7.18 (1 H, ddd, *J* 7.4, 3.8, 1.2), 6.80 (1 H, d, *J* 3.3), 6.59 (1 H, dd, *J* 3.8, 0.6), 5.09 (1 H, d, *J* 13.5), 5.04 – 4.95 (1 H, m), 3.98 (1 H, dt, *J* 13.1, 8.4), 3.71 (1 H, ddd, *J* 13.0, 7.8, 5.1), 2.51 – 2.31 (4 H, m), 2.31 – 2.09 (4 H, m); δ_C (101 MHz, $CDCl_3$) 170.8, 168.5, 157.8, 135.4, 130.3, 129.7, 128.8, 128.5, 127.6, 125.4, 124.0, 121.0, 116.4, 109.8, 72.6, 68.6, 45.3, 44.4, 34.2, 33.8, 29.7, 22.0, 19.7; m/z 452.2 ([MNa]$^+$, 100), 430.2 ([M]$^+$, 35); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{25}H_{23}N_3O_4Na$: 452.1586, Found 452.1585.

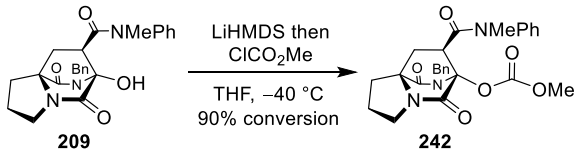
PMB Amide **221**



General procedure A was followed with TKP **125** (35 mg, 0.12 mmol), methyl phenyl acrylamide (48 mg, 0.30 mmol) and **144** (6 mg, 0.012 mmol) as base. Flash chromatography (90% EtOAc in hexane-EtOAc) gave Michael adduct **221** (44 mg, 0.097 mmol, 81%) as a colourless solid in 99:1 er [Cellulose-3, MeCN:H_2O 20:80, 1.0 mLmin^{-1}, t_1= 21.23, t_2= 24.65]; m.p. 174 – 175 °C; IR (thin film) ν_{max} /cm^{-1}: 3323 (br), 3001, 1683, 1671, 1456, 1401, 923, 691; δ_H (300 MHz, $CDCl_3$) 7.63 – 7.22 (9 H, m), 6.11 (1 H, s), 5.18 (1 H, s), 4.71 (1 H, d, *J* 14.6), 4.51 (1 H, d, *J* 14.6), 4.43 (2 H, m), 3.87 (3 H, s), 3.70 – 3.54 (2 H, m), 2.85 (1 H, dt, *J* 13.5, 6.3), 2.75 (1 H, dd, *J* 10.0, 4.5), 2.51 (1 H, dd, *J* 13.5, 4.5), 2.21 – 1.95 (4 H, m); δ_C (101 MHz, $CDCl_3$) 170.7, 168.5, 166.2, 142.5, 137.7, 134.5, 129.9, 128.4, 128.1, 127.5, 127.4, 113.4, 85.4, 66.3, 46.0, 44.8, 42.5, 37.3, 34.0, 29.6, 24.9; m/z 472.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{24}H_{25}N_3O_4Na$: 472.1848, Found 472.1850; $[\alpha]_D^{21}$ = –42.5 (*c* 0.65, CH_2Cl_2).

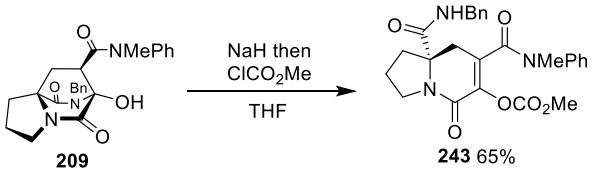
Further Transformations of Michael Addition–Ring-Closure Adducts

Carbonate **242**



LiHMDS (1.0M solution in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred solution of hydroxy DKP **209** (30 mg, 0.072 mmol) in THF (1 mL) at –40 °C and left for 10 minutes before addition of methyl chloroformate (56 μl, 68 mg, 0.72 mmol) in one portion. The reaction mixture was allowed to slowly warm to 5 °C over 2 hours before being quenched with sat. aq. NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with HCl (1.0 M, 10 mL) and brine (10 mL), and then dried over $MgSO_4$ before the solvent was removed under reduced pressure. The residue was then purified by flash chromatography (EtOAc) to give a mixture of carbonate **242** and DKP **209** (approx. 9:1, 90% conversion) as a colourless solid; m.p. 69 – 71 °C; IR (thin film) ν_{max} /cm^{-1}: 2956, 2361, 1775, 1718, 1693, 1657, 1595, 1495, 1430, 1388, 1254, 1204, 1182, 729, 700; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.29 (3 H, m), 7.19 – 7.01 (5 H, m), 6.96 – 6.86 (2 H, m), 5.02 (1 H, d, *J* 15.3), 4.07 (1 H, d, *J* 15.3), 3.95 (3 H, s), 3.82 – 3.70 (1 H, m), 3.62 – 3.50 (1 H, m), 3.22 (3 H, s), 3.04 (1 H, dd, *J* 10.2, 4.4), 2.83 – 2.70 (1 H, m), 2.17 – 1.99 (3 H, m), 1.84 (1 H, ddd, *J* 8.7, 5.9, 3.0), 1.71 (1 H, dd, *J* 12.9, 10.2). δ_C (101 MHz, $CDCl_3$) 169.3, 168.9, 160.9, 152.7, 142.8, 136.7, 129.9, 128.5, 128.1, 127.9, 127.5, 127.5, 90.9, 77.4, 77.1, 76.7, 65.8, 55.9, 45.9, 45.2, 44.4, 38.3, 34.1, 29.4, 24.0; m/z 500.2 ($[MNa]^+$, 100), 478.2 ($[M]^+$, 50); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{26}H_{27}N_3O_6Na$: 500.1798, Found 500.1794.

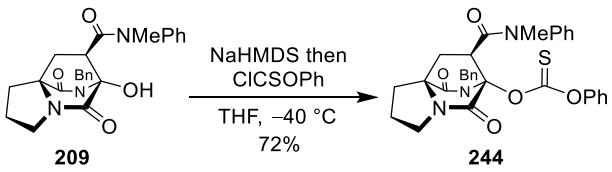
Carbonate **243**



NaH (60% on mineral oil, 9 mg, 0.22 mmol) was added to a solution of amide adduct **209** (30 mg, 0.072 mmol) in THF (1.0 mL) at 0 °C and then was allowed to warm to rt over 30 minutes. Methyl chloroformate (68 mg, 56 μL, 0.72 mmol) was then added and the mixture was stirred at rt for a further 90 minutes. The reaction mixture was quenched with $NaHCO_3$, extracted with DCM and then washed with H_2O. The organic layer was then dried over $MgSO_4$ before the solvent was removed under reduced pressure. Flash chromatography (80% EtOAc in hexane) gave **243** (23 mg, 0.47 mmol, 65%) as a colourless solid; m.p. 160 – 161 °C; IR (thin film) ν_{max} /cm^{-1}: 3365 (br), 2955, 1773, 1645, 1594, 1518, 1495, 1439, 1418, 1383, 1229, 732, 699; δ_H (400 MHz, $CDCl_3$) 7.38 (2 H, t, *J* 7.4), 7.34 – 7.27 (5 H, m), 7.21 (2 H, d, *J* 6.8), 7.14 (2 H, d, *J* 7.4), 6.63 (1 H, s), 4.77 (1 H, dd, *J* 14.6, 7.6), 3.96 (1 H, dd, *J* 14.6, 3.3), 3.75 (3 H, s), 3.63 – 3.50 (2 H, m), 3.46 – 3.32 (4 H, m), 2.76 – 2.49 (2 H, m), 2.02 – 1.82 (2 H, m), 1.77 – 1.62 (1 H, m); δ_C (101 MHz, $CDCl_3$) 171.9, 164.5, 158.0, 152.3, 142.1, 137.7, 136.7, 129.4, 128.7, 127.8, 127.7, 127.5, 127.3, 126.4, 67.9, 55.6, 45.9, 44.3, 39.3, 37.2, 35.0, 22.3; m/z 500.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{26}H_{27}N_3O_6Na$: 500.1798, Found 500.1790.

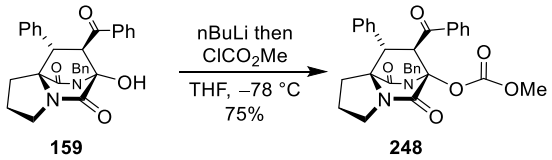
General procedure B – NaHMDS (1.0 M solution in THF) was added dropwise to a stirred solution of hydroxy DKP in THF or DMF at –40 °C and left for 5 mins before addition of *O*-phenyl chlorothionoformate in one portion. The reaction mixture was allowed to slowly warm to 5 °C over 2 hours before being quenched with sat. aq. NH_4Cl. The mixture was extracted with EtOAc (3×) and the combined organic layers were washed with HCl (1.0 M) and brine, and then dried over $MgSO_4$ before the solvent was removed under reduced pressure. The residue was then purified by flash chromatography using the indicated solvent system.

Thiocarbonate **244**



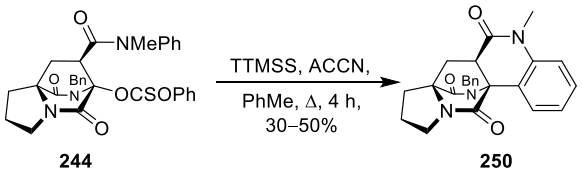
General procedure B was followed with Michael product **209** (192 mg, 0.458 mmol) in THF (5 mL), NaHMDS (1.0 M in THF, 0.92 mL, 0.92 mmol) and *O*-phenyl chlorothionoformate (316 mg, 0.25 mL, 1.83 mmol). Flash chromatography (80–100% EtOAc in hexane) gave thiocarbonate **244** (182 mg, 0.328 mmol, 72%) as a colourless solid; m.p. 192 – 194 °C; IR (thin film) ν_{max} /cm^{-1}: 3060, 1719, 1698, 1657, 1491, 1426, 1385, 1276, 1196, 1142, 1124, 735, 699; δ_H (400 MHz, $CDCl_3$) 7.44 – 7.35 (5 H, m), 7.34 – 7.27 (2 H, m), 7.25 – 7.15 (3 H, m), 7.15 – 7.09 (1 H, m), 7.05 – 6.95 (4 H, m), 4.97 (1 H, d, *J* 15.1), 4.22 (1 H, d, *J* 15.1), 3.84 (1 H, ddd, *J* 11.2, 7.5, 5.6), 3.51 (1 H, dt, *J* 11.3, 7.3), 3.27 (3 H, s), 3.18 (1 H, dd, *J* 10.0, 4.2), 2.74 (1 H, dt, *J* 13.3, 8.0), 2.22 (1 H, dd, *J* 12.9, 4.2), 2.13 – 2.03 (2 H, m), 1.87 (1 H, ddd, *J* 13.0, 7.2, 5.4), 1.68 (1 H, dd, *J* 12.9, 10.0); δ_C (101 MHz, $CDCl_3$) 189.9, 169.5, 168.6, 159.9, 153.6, 142.9, 136.2, 130.0, 129.8, 129.8, 129.6, 129.3, 129.1, 128.7, 128.4, 128.3, 127.9, 127.7, 127.2, 127.1, 127.0, 126.6, 121.6, 94.4, 66.0, 46.1, 46.0, 44.6, 38.6, 33.9, 29.3, 23.8; m/z 578.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{31}H_{29}N_3O_5NaS$: 578.1726, Found 578.1730.

Carbonate **248**



n-BuLi (2.7 M in PhMe, 31 μL, 0.083 mmol) was added to a solution of chalcone adduct **159** (32 mg, 0.069 mmol) in THF (1.0 mL) at -78 °C for 5 minutes before addition of methyl chloroformate (20 mg, 16 μL, 0.21 mmol) and then the mixture was allowed to warm to room temperature over 2 hours. The reaction mixture was quenched with NH_4Cl, extracted with EtOAc and then washed with H_2O. The organic layer was then dried over $MgSO_4$ before the solvent was removed under reduced pressure. Flash chromatography (60% EtOAc in hexane) gave **248** (27 mg, 0.052 mmol, 75%) as a colourless solid; m.p. 174 – 175 °C; IR (thin film) ν_{max} /cm^{-1}: 2955, 1778, 1721, 1693, 1447, 1385, 1260, 1186, 701; δ_H (400 MHz, $CDCl_3$) 7.52 – 7.49 (2 H, m), 7.46 – 7.40 (6 H, m), 7.35 – 7.30 (2 H, m), 7.12 – 7.09 (1 H, m), 7.05 – 7.00 (2 H, m), 6.60 – 6.56 (2 H, m), 5.25 (1 H, d, J 15.0), 4.38 (1 H, d, J 15.0), 4.20 (1 H, d, J 5.9), 3.76 – 3.70 (4 H, m), 3.61 – 3.57 (1 H, m), 3.47 (1 H, d, J 5.9), 2.52 – 2.48 (1 H, m), 2.04 – 1.95 (2 H, m), 1.75 – 1.68 (1 H, m); δ_C (101 MHz, $CDCl_3$) 196.3, 168.3, 160.9, 152.6, 136.8, 136.7, 136.6, 133.7, 130.5, 128.9, 128.8, 128.4, 127.9, 90.4, 70.0, 57.5, 55.9, 52.5, 45.9, 44.5, 28.1, 24.0; m/z 547.2 ($[MNa]^+$, 100), 525.2 ($[MH]^+$, 44); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{31}H_{28}N_2O_6Na$: 547.1845, Found 547.1841.

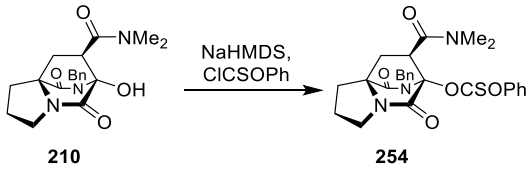
Pentacycle **250**



Tris(trimethylsilyl)silane (TMSS) (29 mg, 35 μl, 0.115 mmol) and 1,1′-Azobis(cyclohexane carbonitrile) (ACCN) (7 mg, 0.029 mmol) were added to a solution of thiocarbonate **244** (32 mg, 0.058 mmol) in dry toluene (2.0 mL, N_2 degassed). The mixture was then degassed by three freeze-thaw cycles before it was heated under reflux for 4 hours. The reaction mixture was then cooled to room temperature and then directly purified by flash chromatography (80% EtOAc in hexane) to give pentacycle **250** (7–12 mg, 0.017–0.029, 30–50%) as a colourless solid; m.p. 199 –200 °C; IR (thin film) ν_{max} /cm^{-1}: 2924, 1684, 1677, 1603, 1455, 1421, 1374, 1267, 1147, 760, 732, 700; δ_H (400 MHz, $CDCl_3$) 7.46 (1 H, ddd, *J* 8.6, 7.4, 1.6), 7.30 (1 H, dd, *J* 7.8, 1.6), 7.24 – 7.16 (3 H, m), 7.16 – 7.05 (2 H, m), 6.98 – 6.86 (2 H, m), 4.98 (1 H, d, *J* 15.3), 4.65 (1 H, d, *J* 15.2), 3.61 – 3.46 (2 H, m), 3.30 (3 H, s), 3.00 – 2.81 (2 H, m), 2.70 (1 H, dd, *J* 13.7, 5.8), 2.15 (1 H, dd, *J* 13.7, 10.5), 2.11 – 1.95 (3 H, m); δ_C (101 MHz, $CDCl_3$) 175.1, 166.6, 164.4, 140.4, 137.2, 130.7, 130.2, 128.8, 127.8, 127.7, 122.5, 119.8, 115.8, 69.1, 66.2, 47.1, 45.0, 44.7, 32.7, 30.4, 29.8, 24.2; m/z 424.2 ($[MNa]^+$, 100), 402.2 ($[MH]^+$, 22); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{24}H_{23}N_3O_3Na$: 424.1637, Found 424.1636.

Nb. Improved yields can be obtained by performing the reaction under air.

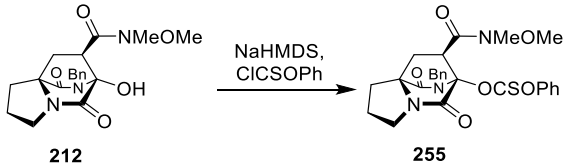
Thiocarbonate **254**



210 **254**

General procedure B was followed with Michael product **210** (280 mg, 0.783 mmol) in DMF (10 mL), NaHMDS (1.0 M in THF, 1.18 mL, 1.18 mmol) and *O*-phenyl chlorothionoformate (405 mg, 0.32 mL, 2.35 mmol). Flash chromatography (EtOAc) gave thiocarbonate **254** (290 mg, 0.588 mmol, 75%) as a colourless solid; m.p. 184 – 186 °C; IR (thin film) ν_{max} /cm^{-1}: 2948, 1717, 1696, 1646, 1489, 1380, 1278, 1197, 1137, 1068, 910, 730, 703, 691; δ_H (400 MHz, $CDCl_3$) 7.56 – 7.50 (2 H, m), 7.49 – 7.43 (2 H, m), 7.43 – 7.27 (6 H, m), 5.66 (1 H, d, *J* 14.8), 4.29 (1 H, d, *J* 14.8), 3.83 (1 H, ddd, *J* 11.3, 7.6, 5.3), 3.48 (1 H, dt, *J* 11.3, 7.4), 3.09 (1 H, dd, *J* 9.8, 4.0), 2.92 (3 H, s), 2.82 (1 H, dt, *J* 13.3, 8.2), 2.44 (1 H, dd, *J* 12.9, 4.0), 2.23 – 2.06 (2 H, m), 1.98 (1 H, ddd, *J* 12.7, 7.2, 5.0), 1.80 – 1.67 (1 H, m); δ_C (101 MHz, $CDCl_3$) 189.7, 169.9, 167.9, 159.3, 153.6, 137.3, 129.7, 129.2, 129.0, 128.5, 127.0, 121.7, 94.5, 66.5, 46.0, 44.9, 44.5, 37.8, 36.4, 33.7, 29.4, 23.7; m/z 516.16 ([MNa]$^+$, 100), 595.30 (30); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{26}H_{27}N_3O_5NaS$: 516.1569, Found 516.1570.

Thiocarbonate **255**



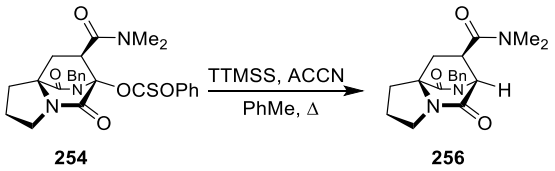
212 **255**

General procedure B was followed with Michael product **212** (246 mg, 0.66 mmol) in DMF (7.0 mL), NaHMDS (1.0 M in THF, 1.0 mL, 1.0 mmol) and *O*-phenyl chlorothionoformate (341 mg, 0.27 mL, 1.98 mmol). Flash chromatography (80–100% EtOAc in hexane) gave thio-carbonate **255** (43 mg, 0.084

mmol, 75%) as a colourless solid; m.p. 187 – 189 °C; IR (thin film) ν_{max} /cm^{-1}: 2979, 1717, 1695, 1659, 1489, 1427, 1381, 1269, 1193, 1141, 734, 699; δ_H (400 MHz, $CDCl_3$) 7.52 – 7.46 (2 H, m), 7.46 – 7.41 (2 H, m), 7.40 – 7.34 (3 H, m), 7.34 – 7.29 (1 H, m), 7.28 – 7.26 (1 H, m), 7.26 – 7.23 (1 H, m), 5.58 (1 H, d, *J* 15.0), 4.31 (1 H, d, *J* 14.9), 3.80 (1 H, dt, *J* 11.3, 6.5), 3.56 – 3.41 (5 H, m), 3.13 (3 H, s), 2.81 (1 H, dt, *J* 13.3, 8.1), 2.18 – 2.03 (3 H, m), 1.94 (1 H, dt, *J* 12.8, 6.2), 1.85 (1 H, dd, *J* 13.0, 10.1); δ_C (101 MHz, $CDCl_3$) 189.9, 169.8, 169.1, 159.6, 153.6, 137.2, 129.7, 129.1, 128.9, 128.3, 127.0, 121.7, 93.9, 66.3, 61.8, 46.1, 44.6, 43.7, 33.9, 32.3, 29.4, 23.8; m/z 532.1 ([MNa]$^+$, 100), 611.29, 40); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{26}H_{27}N_3O_6NaS$: 532.1518, Found 532.1520.

General procedure C – Tris(trimethylsilyl)silane (TTMS) and 1,1′-Azobis(cyclohexane carbonitrile) (ACCN) were added to a solution of thiocarbonate in dry toluene (N_2 degassed). The mixture was then degassed by three freeze-thaw cycles before being heated under reflux for 1 hour. The reaction mixture was then cooled to room temperature and then directly purified by flash chromatography using the indicated solvent system.

Amide DKP **256**

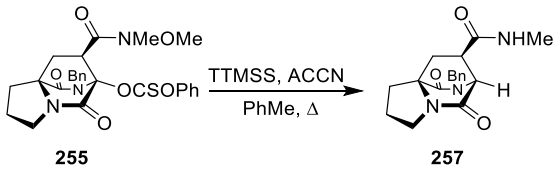


254 **256**

General procedure C was followed with thiocarbonate **254** (30 mg, 0.061 mmol), TTMS (76 mg, 94 μL, 0.30 mmol) and ACCN (22 mg, 0.091 mmol). Flash chromatography (3% MeOH in CH_2Cl_2 then 5% MeOH in 1:1 CH_2Cl_2:EtOAc) gave amide **256** (21 mg, 0.061 mmol, *quant.*) as a colourless solid; m.p. 130 – 131 °C; IR (thin film) ν_{max} /cm^{-1}: 3486 (br), 2926, 1679, 1639, 1495, 1417, 1217, 1145, 733, 702; δ_H (400 MHz, $CDCl_3$) 7.40 – 7.28 (5 H, m), 5.24 (1 H, d, *J* 14.4), 3.95 (1 H, d, *J* 14.4), 3.90 (1 H, d, *J* 3.3), 3.62 – 3.54 (1 H, m), 3.52 – 3.45 (1 H, m), 2.89 (1 H, ddd, *J* 9.8, 4.6, 3.3), 2.85 – 2.76 (4 H, m), 2.48 –

2.39 (4 H, m), 2.13 – 2.00 (2 H, m), 1.99 – 1.87 (2 H, m); δ_C (101 MHz, $CDCl_3$) 171.1, 169.2, 165.1, 136.2, 129.1, 128.9, 128.4, 67.2, 61.5, 48.4, 43.9, 41.4, 36.4, 36.0, 33.8, 29.3, 24.4; m/z 364.16 ($[MNa]^+$, 100; HRMS (ESI/$[MNa]^+$) Calcd. For $C_{19}H_{23}N_3O_3Na$: 364.1637, Found 364.1639.

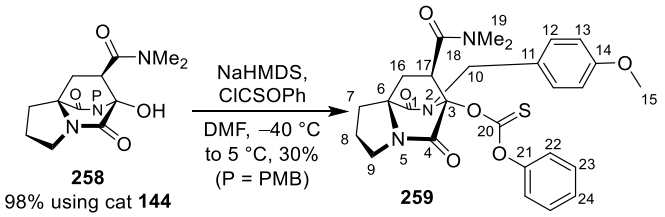
Amide DKP **257**



255 **257**

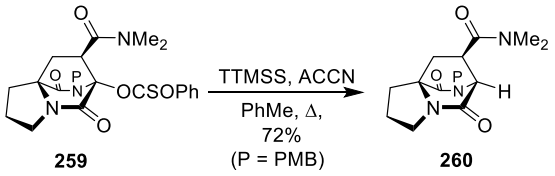
General procedure C was followed with thiocarbonate **255** (25 mg, 0.049 mmol), TTMS (61 mg, 76 μL, 0.245 mmol) and ACCN (18 mg, 0.074 mmol). Flash chromatography (3% MeOH in CH_2Cl_2) gave amide **257** (15 mg, 0.046 mmol, 96%) as a colourless solid; m.p. 67 – 68 °C; IR (thin film) ν_{max} /cm^{-1}: 3315, 2940, 1671, 1555, 1417, 1225, 732, 700; δ_H (400 MHz, $CDCl_3$) 7.40 – 7.28 (3 H, m), 7.26 – 7.20 (2 H, m), 5.60 (1 H, s), 4.86 (1 H, d, *J* 14.7), 4.27 (1 H, d, *J* 14.7), 4.00 (1 H, d, *J* 3.4), 3.58 – 3.44 (2 H, m), 2.80 (1 H, dt, *J* 13.5, 7.0), 2.71 (3 H, d, *J* 4.8), 2.59 (1 H, ddd, *J* 10.2, 4.9, 3.4), 2.28 (1 H, dd, *J* 13.3, 5.0), 2.14 – 1.98 (3 H, m), 1.91 – 1.85 (1 H, m); δ_C (101 MHz, $CDCl_3$) 170.9, 170.1, 165.6, 136.0, 129.1, 128.3, 128.2, 67.1, 62.4, 48.6, 45.0, 44.0, 34.1, 29.3, 26.7, 24.5; m/z 350.2 ($[MNa]^+$, 100), 372.2 (44), 328.2 ($[MH]^+$, 15); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{18}H_{21}N_3O_3Na$: 350.1481, Found 350.1479.

Thiocarbonate **259**



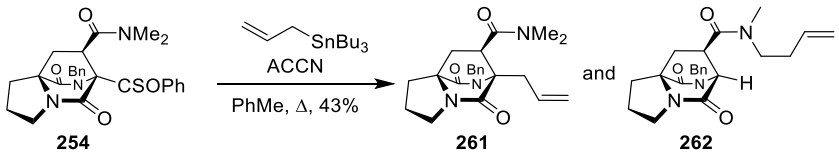
General procedure B was followed with Michael product **258** (144 mg, 0.37 mmol) in DMF (4.0 mL), NaHMDS (1.0 M in THF, 0.48 mL, 0.48 mmol) and *O*-phenyl chlorothionoformate (192 mg, 0.15 mL, 1.11 mmol). Flash chromatography (2–4% MeOH in DCM) followed by preparative HPLC [Phenomenex C-18, H_2O:MeCN gradient 100:0–0:100, 45 minutes] gave **259** (58 mg, 0.11 mmol, 30%) as a colourless solid; m.p. 240 – 242 °C; IR (thin film) ν_{max} /cm^{-1}: 2976, 1721, 1699, 1666, 1595, 1480, 1421, 1276, 732, 699; δ_H (400 MHz, $CDCl_3$) 7.43 – 7.31 (4 H, m, H-12, H-22), 7.27 – 7.17 (3 H, m, H-24, H-23), 6.85 – 6.77 (2 H, m, H-13), 5.50 (1 H, d, *J* 14.9, H-10a), 4.13 (1 H, d, *J* 14.9, H-10b), 3.77 – 3.65 (4 H, m, H-9a, H-15), 3.37 (1 H, dt, *J* 11.3, 7.4, H-9b), 3.05 – 2.98 (1 H, m, H-17), 2.83 (3 H, s, H-19), 2.76 – 2.62 (4 H, m, H-7a, H-19), 2.33 (1 H, dd, *J* 12.9, 4.0, H-16a), 2.12 – 1.94 (2 H, m, H-8), 1.87 (1 H, ddd, *J* 11.8, 8.4, 4.8, H-7b), 1.62 (1 H, dd, *J* 12.9, 9.8, H-16b); δ_C (101 MHz, $CDCl_3$) 189.8 (C-20), 169.8 (C-3), 167.9 (C-18), 159.7 (C-14), 159.4 (C-4), 153.6 (C-21), 130.6 (C-12), 129.7 (C-22), 129.4 (C-11), 127.0 (C-24), 121.7 (C-23), 114.3 (C-13), 94.5 (C-3), 66.5 (C-6), 55.4 (C-15), 45.4 (C-10), 44.9 (C-7), 44.5 (C-9), 38.0 (C-19), 36.4 (C-19), 33.8 (C-16), 29.3 (C-7), 23.7 (C-8); m/z 546.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{27}H_{29}N_3O_6Na$: 546.1675, Found 546.16.77.

PMB amide DKP **260**



General procedure C was followed with thiocarbonate **259** (30 mg, 0.056 mmol), TTMS (70 mg, 87 μL, 0.28 mmol) and ACCN (21 mg, 0.084 mmol). Flash chromatography (4–6% MeOH in 1:1 DCM:EtOAc) gave **260** (15 mg, 0.040 mmol, 72%) as a colourless solid; m.p. 75 – 76 °C; IR (thin film) ν_{max} /cm^{-1}: 2931, 1680, 1634, 1611, 1511, 1413, 1245, 1175, 1030, 731; δ_H (300 MHz, $CDCl_3$) 7.07 – 6.99 (2 H, m), 6.74 – 6.61 (2 H, m), 4.93 (1 H, t, *J* 13.7), 3.76 (2 H, t, *J* 8.8), 3.64 – 3.56 (3 H, m), 3.44 – 3.24 (2 H, m), 2.71 (1 H, ddd, *J* 9.9, 4.7, 3.4), 2.66 – 2.50 (4 H, m), 2.32 (3 H, s), 2.22 (1 H, dd, *J* 12.9, 4.8), 1.95 – 1.66 (4 H, m); δ_C (75 MHz, $CDCl_3$) 171.1, 159.7, 130.1, 128.1, 114.4, 67.1, 61.4, 55.4, 47.8, 43.9, 41.5, 36.5, 36.0, 33.9, 29.3, 24.4; m/z 394.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{20}H_{25}N_3O_4Na$: 394.1743, Found 394.1742.

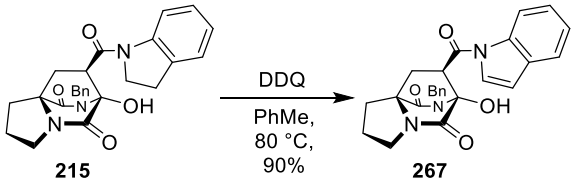
Allylation Adducts **261** and **262**



A solution of thiocarbonate **254** (20 mg, 0.041 mmol), ACCN (15 mg, 0.61 mmol), and allyl tributyltin (134 mg, 126 μL, 0.41 mmol) in toluene (2.0 mL) was freeze-thawed ×2 then heated under reflux for 1 hour. Flash chromatography (2% MeOH in DCM) gave a mixture of **261/262** (7 mg, 0.017 mmol, 43%) as a colourless solid; m.p. 140 – 142 °C; IR (thin film) ν_{max} /cm^{-1}: 2973, 2361, 1687, 1643, 1416, 1216; δ_H (400 MHz, $CDCl_3$) 7.42 – 7.30 (5 H, 5 H, m), 5.69 (1 H, ddt, *J* 17.1, 10.2, 6.9), 5.36 (1 H, ddt, *J* 17.2,

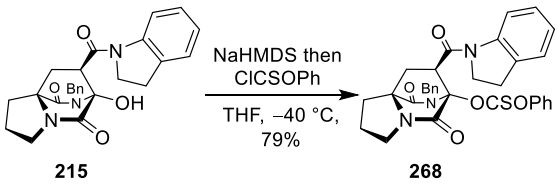
10.2, 7.1), 5.27 (1 H, 1 H, d, *J* 14.4), 5.07 – 4.90 (2 H, 2 H, m), 4.00 – 3.87 (2 H, 2 H, m), 3.62 – 5.57 (1 H, 1 H, m), 3.56 – 3.46 (1 H, 1 H, m), 3.39 (1 H, dt, *J* 13.5, 7.4), 3.27 – 3.18 (1 H, m), 2.91 – 2.77 (4 H, 5 H, m), 2.62 (1 H, dt, *J* 18.6, 5.6), 2.47 – 2.33 (3 H, 2 H, m), 2.21 – 2.18 (2 H, m), 2.12 – 1.86 (5 H, 5 H, m); δ_C (101 MHz, $CDCl_3$) 171.2, 171.1, 169.6, 169.1, 165.3, 165.0, 136.3, 136.2, 135.1, 133.4, 129.2, 129.1, 128.9, 128.8, 128.4, 118.3, 116.8, 67.1, 61.9, 61.5, 48.7, 48.4, 48.4, 48.0, 43.9, 43.9, 41.6, 41.3, 34.8, 34.3, 33.8, 33.8, 32.6, 31.6, 29.4, 24.4, 24.4; m/z 404.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{22}H_{27}N_3O_3Na$: 404.1950, Found 404.1954.

Indole Hydroxy DKP **267**



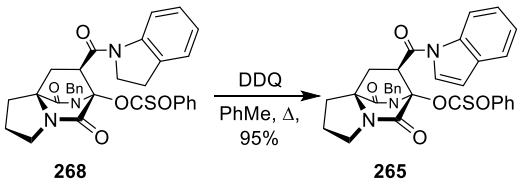
A solution of indoline adduct **215** (50 mg, 0.12 mmol) and DDQ (37 mg, 0.16 mmol) in toluene (2.0 mL) was heated to 80 °C for 2 hours. The solvent was then removed under reduced pressure and the residue taken up in DCM (10 mL) and filtered through celite before evaporating under reduced pressure. Flash chromatography (40–50 EtOAc in hexane) gave **267** (45 mg, 0.10 mmol, 90%) as a colourless solid; m.p. 190 – 192 °C; IR (thin film) ν_{max} /cm^{-1}: 2926 (br), 2361, 2335, 1679, 1452, 1363, 1327, 1206, 747; δ_H (400 MHz, $CDCl_3$) 8.40 (1 H, s), 7.58 – 7.48 (3 H, m), 7.46 – 7.36 (3 H, m), 7.34 – 7.23 (2 H, m), 6.76 (1 H, s), 6.54 (1 H, d, *J* 3.8), 5.12 – 5.00 (2 H, m), 4.42 (1 H, d, *J* 14.3), 3.74 (1 H, dt, *J* 11.4, 7.2), 3.69 – 3.60 (1 H, m), 3.55 (1 H, dd, *J* 10.2, 4.7), 2.99 – 2.90 (1 H, m), 2.40 (1 H, dd, *J* 13.2, 4.8), 2.23 – 2.06 (3 H, m), 1.94 (1 H, dt, *J* 13.3, 7.5); δ_C (101 MHz, $CDCl_3$) 169.3, 168.9, 165.0, 138.0, 135.7, 130.5, 129.1, 128.8, 127.9, 125.3, 125.1, 124.2, 120.8, 117.0, 109.6, 85.3, 66.8, 48.3, 44.7, 43.1, 34.1, 29.3, 24.7; m/z 452.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{25}H_{23}N_3O_4Na$: 452.1586, Found 452.1583.

Indoline thiocarbonate **268**



General procedure B was followed with Michael product **215** (160 mg, 0.37 mmol) in THF (8.0 mL), NaHMDS (1.0M in THF, 0.48 mL, 0.48 mmol) and *O*-phenyl chlorothionoformate (160 mg, 0.13 mL, 0.93 mmol).Flash chromatography (50–80% EtOAc in hexane) gave **268** (166 mg, 0.29 mmol, 79%) as a colourless solid; m.p. 118 – 120 °C; IR (thin film) ν_{max} /cm^{-1}: 2974, 1716, 1694, 1655, 1598, 1481, 1416, 1279, 1194, 1141, 1070, 755, 734, 701; δ_H (400 MHz, $CDCl_3$) 8.06 (1 H, dd, *J* 6.0, 2.7), 7.49 – 7.41 (2 H, m), 7.37 – 7.27 (4 H, m), 7.20 – 7.13 (4 H, m), 7.07 – 7.00 (2 H, m), 6.94 – 6.87 (1 H, m), 5.61 (1 H, d, *J* 14.8), 4.23 (1 H, d, *J* 14.9), 3.85 – 3.67 (2 H, m), 3.51 – 3.34 (1 H, m), 3.12 – 2.91 (3 H, m), 2.90 – 2.72 (2 H, m), 2.38 (1 H, dd, *J* 13.0, 4.2), 2.14 – 1.98 (2 H, m), 1.97 – 1.85 (1 H, m), 1.77 (1 H, dd, *J* 13.0, 9.8); δ_C (101 MHz, $CDCl_3$) 189.1, 169.9, 165.8, 159.1, 153.5, 142.5, 137.4, 131.8, 129.7, 129.3, 129.1, 128.6, 127.3, 127.0, 124.4, 124.3, 121.6, 118.0, 94.5, 66.5, 48.4, 48.1, 46.1, 44.6, 34.0, 29.4, 27.8, 23.8; m/z 590.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{32}H_{29}N_3O_5Na$: 590.1726, Found 590.1728.

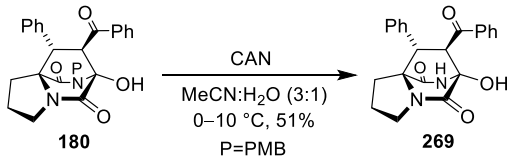
Indole thiocarbonate **265**



A solution of indoline adduct **268** (75 mg, 0.13 mmol) and DDQ (60 mg, 0.26 mmol) in toluene (5.0 mL) was heated to reflux for 4 hours. The solvent was then removed under reduced pressure and the residue

taken up in DCM (10 mL) and filtered through celite before evaporating under reduced pressure. Flash chromatography (30–50% EtOAc in hexane) gave **265** (70 mg, 0.12 mmol, 95%) as a colourless solid; m.p. 114 – 115 °C; IR (thin film) ν_{max} /cm^{-1}: 1718, 1697, 1453, 1281, 1193, 1144; δ_H (400 MHz, $CDCl_3$) 8.30 (1 H, d, *J* 7.6), 7.56 – 7.50 (2 H, m), 7.47 – 7.37 (4 H, m), 7.27 (2 H, dt, *J* 10.5, 2.1), 7.22 – 7.07 (5 H, m), 6.40 (2 H, dd, *J* 12.9, 3.8), 5.64 (1 H, d, *J* 14.8), 4.31 (1 H, d, *J* 14.8), 3.87 – 3.72 (1 H, m), 3.48 (1 H, dt, *J* 11.4, 7.3), 3.38 (1 H, dd, *J* 9.9, 4.2), 2.82 (1 H, dt, *J* 13.4, 7.9), 2.39 (1 H, dd, *J* 13.2, 4.3), 2.16 – 2.04 (2 H, m), 2.00 – 1.82 (2 H, m); δ_C (101 MHz, $CDCl_3$) 189.0, 169.5, 167.1, 159.0, 153.4, 137.4, 135.9, 130.5, 129.6, 129.4, 128.9, 127.0, 125.2, 125.1, 124.3, 121.5, 120.7, 117.2, 109.7, 93.7, 66.5, 48.2, 46.3, 44.7, 34.5, 29.4, 23.9; m/z 588.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{32}H_{27}N_3O_5Na$: 588.1569, Found 588.1556.

Hydroxy amide **269**



Cerium ammonium nitrate (CAN) (356 mg, 0.65 mmol) was added in one portion to a solution of hydroxy DKP **180** (80 mg, 0.16 mmol) in MeCN:H_2O (3:1, 1.2 mL) at 0 °C. The reaction mixture was stirred for 2 hours, warming to 10 °C, before pouring into ice-water (25 mL). The pale yellow precipitate was collected and then washed with chloroform to give deprotected DKP **269** as an off-white solid (31 mg, 0.083 mmol, 51%); m.p. 87 – 88 °C; IR (thin film) ν_{max} /cm^{-1}: 3260 (br), 2926, 1693, 1597, 1449, 1364, 1260, 1214, 751; δ_H (400 MHz, DMSO-d_6) 9.27 (1 H, s), 7.78 – 7.71 (2 H, m), 7.63 – 7.57 (1 H, m), 7.48 – 7.41 (2 H, m), 7.34 – 7.27 (4 H, m), 7.20 (1 H, s), 4.48 (1 H, d, *J* 5.8), 3.57 – 3.42 (3 H, m), 2.09 – 1.98 (2 H, m), 1.82 – 1.65 (2 H, m); δ_C (101 MHz, DMSO-d_6) 198.2, 169.8, 166.3, 138.1, 136.9, 128.7, 128.5,

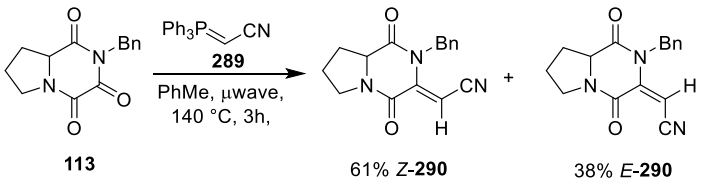
128.2, 127.7, 84.0, 70.3, 58.9, 51.1, 43.9, 40.2, 39.9, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 27.2, 24.0; m/z 399.1 ([MNa]$^+$, 22), 269.0 (100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{22}H_{20}N_2O_4Na$: 399.1321, Found 399.1320.

Experimental for Chapter 4

Synthesis of Methylene DKPs

General procedure D - A microwave vial was charged with TKP, ylide and toluene and then heated in a microwave reactor as stated. Once the solution had cooled the solvent was removed under reduced pressure and the residue was purified by flash chromatography as specified.

Cyano DKP **290**

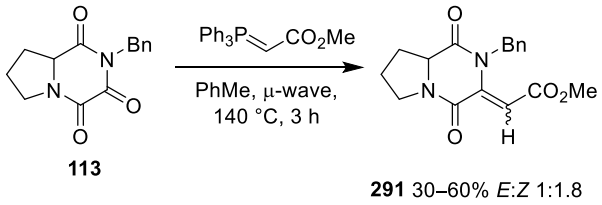


113 61% *Z*-**290** 38% *E*-**290**

General procedure D was followed with TKP **113** (100 mg, 0.39 mmol), ylide **289** (175 mg, 0.58 mmol) and toluene (3.0 mL) and then heated in a microwave reactor at 140 °C for 3 hours. Once the solution had cooled the solvent was removed under reduced pressure and the residue was purified by flash chromatography (2–3% acetone in CH_2Cl_2) to give DKPs Z-**290** (67 mg, 0.24 mmol, 61%) and E-**290** (42 mg, 0.15 mmol, 38%) as colourless solids; Z-**290** - m.p. 117 – 118 °C; IR (thin film) ν_{max} /cm^{-1}: 2976, 2211, 1704, 1677, 1604, 1454, 1442, 1363, 1188, 730, 696; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.08 (5 H, m), 5.90 (1 H, s), 5.56 (1 H, d, *J* 16.2), 5.22 (1 H, d, *J* 16.2), 4.24 (1 H, dt, *J* 6.5, 5.0), 3.73 – 3.50 (2 H, m), 2.54 – 2.36 (1 H, m), 2.14 – 2.01 (2 H, m), 1.98 – 1.81 (1 H, m); δ_C (101 MHz, $CDCl_3$) 166.2, 156.0, 145.1, 134.5, 132.2, 132.0, 128.9, 128.6, 128.5, 128.0, 127.2, 115.9, 84.5, 58.7, 46.5, 46.1, 29.1, 22.0; E-**290** - m.p. 123 – 124 °C; IR (thin film) ν_{max} /cm^{-1}: 2955, 2215, 1700, 1680, 1601, 1455, 1381, 1368,

1214, 730, 698; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.29 (3 H, m), 7.20 – 7.07 (2 H, m), 5.27 (1 H, d, *J* 16.0), 5.11 (1 H, s), 4.69 (1 H, d, *J* 16.0), 4.49 – 4.35 (1 H, m), 3.82 – 3.60 (2 H, m), 2.63 – 2.48 (1 H, m), 2.15 – 2.03 (2 H, m), 2.03 – 1.87 (1 H, m); δ_C (101 MHz, $CDCl_3$) 165.9, 154.3, 147.3, 133.7, 132.9, 132.1, 132.0, 129.3, 128.6, 128.5, 128.3, 126.5, 115.6, 85.9, 58.9, 47.4, 45.9, 29.4, 21.8; m/z 304.1 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{16}H_{15}N_3O_2Na$: 304.1062, Found 304.1065.

Ester DKP **291**

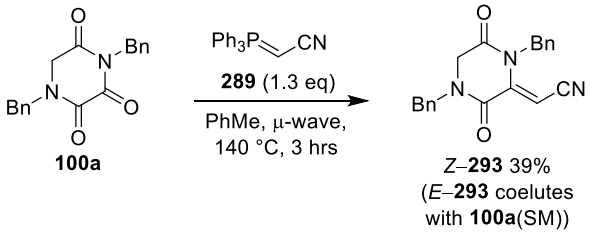


113

291 30–60% *E*:*Z* 1:1.8

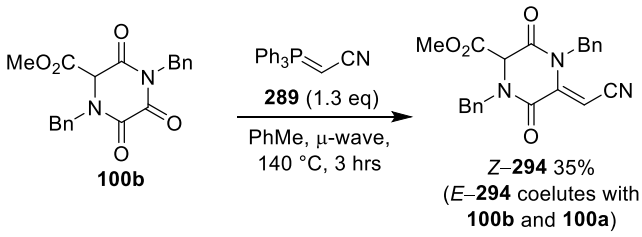
General procedure D was followed with TKP **113** (100 mg, 0.39 mmol), methyl (triphenyl phosphoranylidene)acetate (194 mg, 0.58 mmol) and toluene (2.0 mL) and then heated in a microwave reactor at 140 °C for 3 hours. Once the solution had cooled the solvent was removed under reduced pressure and the residue was purified by flash chromatography (50–100% EtOAc in hexane) to give DKP **291** as a mixture of isomers (30–60% 1:1.8 *E*:*Z*) as a colourless gum; IR (thin film) ν_{max} /cm^{-1}: 2955, 1700, 1674, 1624, 1434, 1369, 1340, 1195, 1170, 733, 700; Z-**291** δ_H (400 MHz, $CDCl_3$) 7.23 – 7.13 (3 H, m), 6.99 – 6.92 (2 H, m), 6.28 (1 H, s), 5.53 (1 H, d, *J* 15.6), 4.73 (1 H, d, *J* 15.6), 4.22 – 4.11 (1 H, m), 3.69 – 3.52 (5 H, m), 2.36 (1 H, dtd, *J* 9.1, 6.8, 2.4), 2.18 – 1.97 (2 H, m), 1.95 – 1.81 (1 H, m); δ_C (101 MHz, $CDCl_3$) 167.3, 165.1, 159.2, 141.2, 135.5, 128.6, 127.6, 127.5, 109.1, 58.6, 52.1, 48.2, 45.6, 28.3, 22.5; m/z 337.1 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{17}H_{18}N_2O_4Na$: 337.1164, Found 337.1168.

Cyano DKP **293**



General procedure D was followed with TKP **100a** (150 mg, 0.49 mmol), ylide **289** (205 mg, 0.68 mmol) and toluene (5.0 mL) and then heated in a microwave reactor at 140 °C for 3 hours. Once the solution had cooled the solvent was removed under reduced pressure and the residue was purified by flash chromatography (35–60% EtOAc in hexane) to give DKP *Z*-**293** (63 mg, 0.19 mmol, 39%) [*E*-**293** coeluted with starting material] as a colourless solid; m.p. 57 – 59 °C; IR (thin film) ν_{max} /cm^{-1}: 3047, 2211, 1703, 1677, 1603, 1495, 1368, 1267, 1176, 730, 700; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.12 (10 H, m), 6.11 (1 H, s), 5.40 (2 H, s), 4.60 (2 H, s), 4.05 (2 H, s); δ_C (101 MHz, $CDCl_3$) 162.6, 156.6, 142.7, 134.2, 134.0, 129.2, 128.9, 128.8, 128.7, 128.6, 128.0, 127.0, 115.9, 85.1, 50.8, 49.0, 46.6; m/z 354.1 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{20}H_{17}N_3O_2Na$: 354.1218, Found 354.1220.

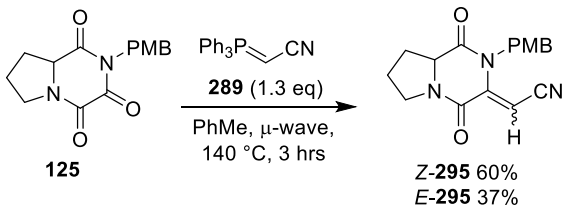
Cyano DKP **294**



General procedure D was followed with TKP **100b** (47 mg, 0.13 mmol), ylide **289** (58 mg, 0.19 mmol) and toluene (2.0 mL) and then heated in a microwave reactor at 140 °C for 3 hours. Once the solution had cooled the solvent was removed under reduced pressure and the residue was purified by flash chromatography (1-3% acetone in CH_2Cl_2) to give DKP *Z*-**294** (17 mg, 0.044 mmol, 35%) [*E*-**294**

coeluted with starting material and glycine TKP **100a**] as a colourless solid; m.p. 144 – 145 °C; IR (thin film) ν_{max} /cm^{-1}: 2957, 2215, 1750, 1704, 1686, 1610, 1496, 1453, 1434, 1366, 1240, 1205, 1174, 731, 699; δ_H (400 MHz, $CDCl_3$) 7.44 – 7.18 (10 H, m), 6.22 (1 H, s), 5.59 (1 H, d, *J* 16.2), 5.32 (1 H, d, *J* 16.2), 4.98 (1 H, d, *J* 14.7), 4.80 (1 H, s), 4.45 (1 H, d, *J* 14.7), 3.71 (3 H, s); δ_C (101 MHz, $CDCl_3$) 165.7, 159.4, 158.3, 143.1, 134.0, 133.5, 129.2, 129.1, 128.9, 128.9, 128.2, 127.0, 115.5, 87.0, 62.9, 54.1, 50.1, 47.2; m/z 412.1 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{22}H_{19}N_3O_4Na$: 412.1273, Found 412.1270.

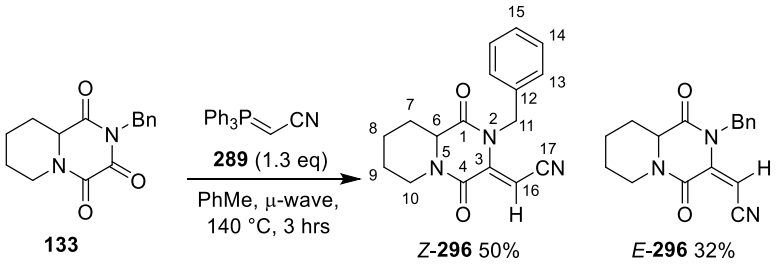
PMB cyano DKP **295**



General procedure D was followed with TKP **125** (200 mg, 0.77 mmol), ylide **289** (303 mg, 1.00 mmol) and toluene (5.0 mL) and then heated in a microwave reactor at 140 °C for 3 hours. Once the solution had cooled the solvent was removed under reduced pressure and the residue was purified by flash chromatography (1–3% acetone in CH_2Cl_2) to give DKPs Z-**295** (130 mg, 0.46 mmol, 60%) and E-**295** (81 mg, 0.28 mmol, 37%) as a colourless solids; Z-**295** - m.p. 122 – 124 °C; IR (thin film) ν_{max} /cm^{-1}: 2961, 2211, 1705, 1678, 1605, 1513, 1444, 1363, 1246, 1**179**, 1028, 734; δ_H (400 MHz, $CDCl_3$) 7.14 – 7.05 (2 H, m), 6.91 – 6.84 (2 H, m), 5.24 – 5.11 (2 H, m), 4.65 (1 H, d, *J* 15.7), 4.47 – 4.35 (1 H, m), 3.84 – 3.74 (4 H, m), 3.72 – 3.60 (1 H, m), 2.57 (1 H, dt, *J* 17.7, 6.5), 2.21 – 1.91 (3 H, m); δ_C (101 MHz, $CDCl_3$) 165.9, 159.5, 154.4, 147.3, 128.1, 125.7, 115.6, 114.7, 85.9, 58.9, 55.4, 47.0, 45.9, 29.4, 21.8; E-**295** - m.p. 128 – 129 °C; IR (thin film) ν_{max} /cm^{-1} :2961, 2214, 1699, 1678, 1600, 1513, 1458, 1373, 1247, 1213, 1**179**, 1030, 733; δ_H (400 MHz, $CDCl_3$) 7.24 – 7.15 (2 H, m), 6.93 – 6.81 (2 H, m), 5.99 (1 H, s), 5.60 (1 H, d, *J* 15.9), 5.21 (1 H, d, *J* 15.9), 4.31 (1 H, dd, *J* 9.7, 6.8), 3.79 (3 H, s), 3.76 – 3.56 (2 H,

m), 2.60 – 2.42 (1 H, m), 2.22 – 2.07 (2 H, m), 2.05 – 1.88 (1 H, m); δ_C (101 MHz, $CDCl_3$) 166.2, 159.3, 156.1, 145.1, 128.9, 126.5, 116.1, 114.2, 84.4, 58.7, 55.3, 46.1, 45.9, 29.1, 22.0; m/z 334.1 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{17}H_{17}N_3O_3Na$: 334.1168, Found 334.1170.

Homo-proline cyano DKP **296**

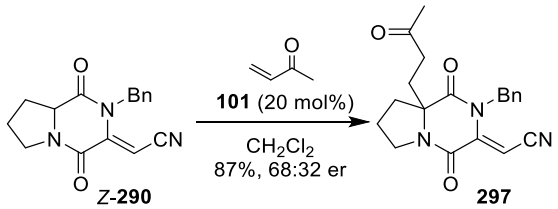


General procedure D was followed with TKP **133** (100 mg, 0.37 mmol), ylide **289** (155 mg, 0.51 mmol) and toluene (3.0 mL) and then heated in a microwave reactor at 140 °C for 3 hours. Once the solution had cooled the solvent was removed under reduced pressure and the residue was purified by flash chromatography (40–60% EtOAc in hexane) to give DKPs *Z*-**296** (54 mg, 0.18 mmol, 50%) and *E*-**296** (35 mg, 0.12 mmol, 32%) as off colourless solids; m.p.155 – 156 °C; IR (thin film) ν_{max} /cm^{-1}: 2942, 2209, 1697, 172, 1601, 1442, 1362, 1271, 1253, 730, 696; *Z*-**296** δ_H (400 MHz, $CDCl_3$) 7.37 – 7.31 (2 H, m, H-Ar), 7.31 – 7.26 (1 H, m, H-Ar), 7.25 – 7.19 (2 H, m, H-Ar), 6.17 (1 H, s, H-16), 5.55 (1 H, d, *J* 16.5, H-11a), 5.49 (1 H, d, *J* 16.4, H-11b), 4.74 – 4.67 (1 H, m, H-10a), 4.16 (1 H, dd, *J* 11.5, 3.0, H-6), 2.68 (1 H, app. td, *J* 13.0, 2.9, H-10b), 2.45 – 2.36 (1 H, m, H-7a), 2.09 – 2.02 (1 H, m, H-8a), 1.84 – 1.76 (1 H, m, H-9a), 1.69 – 1.51 (3 H, m, H-7b, H-8b, H-9b); δ_C (101 MHz, $CDCl_3$) 165.3 (C-1), 154.7 (C-4), 141.6 (C-3), 134.4 (C-12), 128.8 (C-Ar), 127.9 (C-Ar), 126.7 (C-Ar), 116.2 (C-17), 83.5 (C-16), 59.5 (C-6), 46.5 (C-11), 44.1 (C-10), 32.3 (C-7), 24.5 (C-9), 24.1 (C-8); *E*-**296** δ_H (400 MHz, $CDCl_3$) 7.39 – 7.29 (3 H, m), 7.14 – 7.09 (2 H, m), 5.11 (1 H, d, *J* 16.1), 5.08 (1 H, s), 4.90 (1 H, d, *J* 16.0), 4.82 – 4.76 (1 H, m), 4.19 (1 H, dd, *J* 11.5, 3.0), 2.65 (1 H, app. td, *J* 12.9, 3.0), 2.49 – 2.43 (1 H, m), 2.12 – 2.02 (1 H, m), 1.85 – 1.77 (1 H, m), 1.68 – 1.53 (3 H, m); δ_C (101 MHz, $CDCl_3$) 165.4, 153.3, 144.1, 133.1, 129.3, 128.3,

126.3, 116.0, 86.2, 59.4, 47.0, 43.3, 32.6, 24.6, 24.2; m/z 295.2 ([MH]$^+$, 45), 204.1 (87), 91.1 (100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{17}H_{17}N_3O_2$: 295.1321, Found 295.1320.

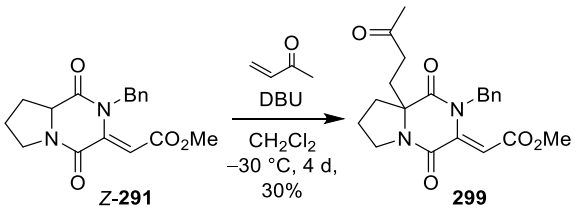
Michael Additions and Michael–Michael Cascade

Michael adduct **297**



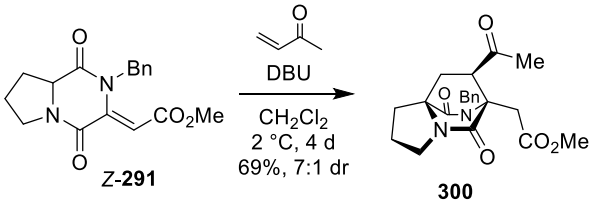
General procedure A was followed with DKP Z-**290** (31 mg, 0.11 mmol), MVK (23 mg, 25 μL, 0.32 mmol) and **101** (8 mg, 0.021 mmol, 20 mol%) as base. Flash chromatography (40–60% EtOAc in hexane) gave **297** (33 mg, 0.095 mmol, 87%) as a colourless solid; m.p. 120 – 122 °C; IR (thin film) ν_{max} /cm^{-1}: 2965, 2211, 1702, 1673, 1605, 1453, 1437, 1353, 1172, 732, 698; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.23 (5 H, m), 6.00 (1 H, s), 5.61 (1 H, d, *J* 16.2), 5.27 (1 H, d, *J* 16.2), 4.85 – 4.78 (1 H, m), 3.70 – 3.62 (1 H, m), 2.50 – 2.35 (2 H, m), 2.30 – 1.95 (9 H, m); δ_C (101 MHz, $CDCl_3$) 205.7, 168.7, 155.9, 144.6, 134.7, 128.8, 128.0, 127.4, 115.9, 84.2, 67.2, 46.7, 45.7, 37.9, 33.4, 32.0, 30.0, 20.1; m/z 374.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{20}H_{21}N_3O_3Na$: 374.1481, Found 374.1483.

Michael adduct **299**



General procedure A was followed with DKP *Z*-**291** (22 mg, 0.070 mmol), MVK (15 mg, 16 μL, 0.21 mmol) and DBU (1 mg, 1 μL, 0.007 mmol) as base. Flash chromatography (55–65% EtOAc in hexanes) gave **299** (8 mg, 0.021 mmol, 30%) as a colourless gum; IR (thin film) ν_{max} /cm^{-1}: 2954, 1713, 1698, 1672, 1626, 1435, 1195, 1171; δ_H (400 MHz, $CDCl_3$) 7.24 – 7.11 (3z H, m), 6.98 – 6.91 (2 H, m), 6.28 (1 H, s), 5.49 (1 H, d, *J* 15.5), 4.72 (1 H, d, *J* 15.5), 3.74 – 3.64 (4 H, m), 3.53 (1 H, ddd, *J* 12.4, 8.5, 4.2), 2.41 (2 H, dt, *J* 11.1, 5.6), 2.23 – 2.10 (1 H, m), 2.09 – 1.85 (7 H, m); δ_C (101 MHz, $CDCl_3$) 206.1, 169.6, 165.0, 158.9, 140.8, 135.6, 128.6, 127.7, 127.5, 108.8, 67.3, 52.1, 48.5, 45.4, 38.3, 33.6, 31.6, 30.0, 20.6; m/z 407.2 ([MNa]$^+$, 100) , 385.2 ([MH]$^+$, 55); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{21}H_{24}N_2O_5Na$: 407.1583, Found 407.1588.

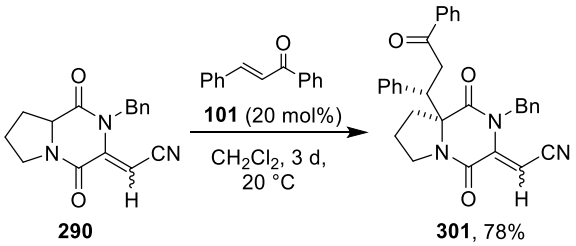
Michael–Michael adduct **300**



General procedure A was followed with DKP **291** (25 mg, 0.080 mmol), MVK (17 mg, 18 μL, 0.24 mmol) and DBU (3 μL, 0.020 mmol). Flash chromatography (80–90% EtOAc in hexane) gave adduct **300** (21 mg, 0.055 mmol, 69%, 7:1 dr) as a colourless solid; m.p. 131 – 133 °C; IR (thin film) ν_{max} /cm^{-1}: 2952, 1731, 1716, 1682, 1435, 1390, 1359, 1198, 1173, 731, 699; δ_H (400 MHz, $CDCl_3$) 7.31 – 7.26 (2

H, m), 7.25 – 7.18 (1 H, m), 7.02 (2 H, d, *J* 7.0), 4.93 (1 H, d, *J* 16.6), 4.45 (1 H, d, *J* 16.6), 4.06 (1 H, dd, *J* 11.3, 5.9), 3.61 – 3.49 (5 H, m), 3.40 (1 H, d, *J* 18.3), 2.96 – 2.84 (2 H, m), 2.43 (1 H, dd, *J* 12.8, 11.4), 2.17 (3 H, s), 2.06 – 1.97 (2 H, m), 1.90 – 1.78 (2 H, m); δ_C (101 MHz, $CDCl_3$) 206.9, 172.0, 171.2, 166.1, 137.4, 128.8, 127.5, 126.2, 126.0, 65.2, 65.1, 52.5, 52.0, 45.4, 44.6, 34.1, 31.9, 30.0, 29.7, 24.3; m/z 407.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{21}H_{24}N_2O_5Na$: 407. 1583, Found 407.1592.

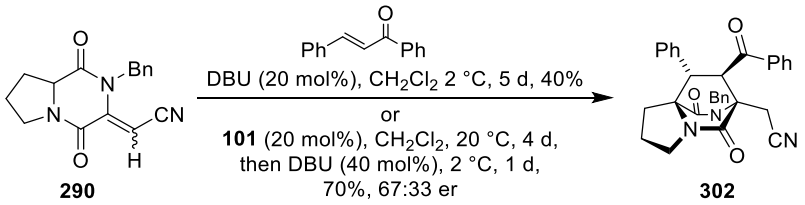
Michael adduct **301**



290 **301**, 78%

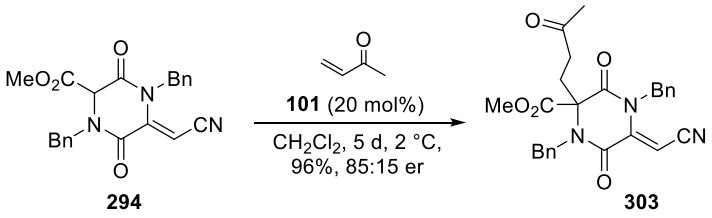
General procedure A was followed with DKP **290** (27 mg, 0.097 mmol), chalcone (51 mg, 0.24 mmol) and **101** (8 mg, 0.02 mmol) as base. Flash chromatography (35–50% EtOAc in hexane) gave **301** (37 mg, 0.076 mmol, 78%) as a colourless solid; m.p. 144 – 145 °C; IR (thin film) ν_{max} /cm^{-1}: 2965, 2211, 1702, 1673, 1605, 1453, 1437, 1353, 1172, 732, 698; δ_H (400 MHz, $CDCl_3$) 7.65 – 7.54 (4 H, m), 7.34 – 7.23 (6 H, m), 7.18 – 7.10 (5 H, m), 6.05 (1 H, s), 5.56 (1 H, d, *J* 15.8), 5.31 (1 H, d, *J* 15.8), 4.85 – 4.78 (1 H, m), 3.70 – 3.62 (1 H, m), 2.50 – 2.35 (2 H, m), 2.30 – 1.95 (5 H, m); δ_C (101 MHz, $CDCl_3$) 198.3, 168.7, 155.9, 144.6, 137.5, 137.1, 136.4, 135.2, 134.7, 128.8, 128.0, 127.4, 126.2 115.9, 84.2, 64.5, 58.3, 54.5, 45.7, 44.8, 29.3, 24.0, 18.0; m/z 512.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{31}H_{27}N_3O_3Na$: 512.1950, Found 512.1951.

Michael–Michael adduct **302**



General procedure A was followed with DKP **290** (21 mg, 0.075 mmol), chalcone (31 mg, 0.15 mmol) and **101** (6 mg, 0.015 mmol, 20 mol%). After 4 days DBU (5 mg, 5 μL, 0.030 mmol) was added and the flask was moved to the fridge for 1 day. Flash chromatography (40–45% EtOAc in hexane) gave **302** (26 mg, 0.053 mmol, 70%) as a colourless solid [Cellulose-3, MeCN:H_2O 45:55, 1.0 mLmin^{-1}, t_1= 8.53 mins, t_2= 11.39 mins]; m.p. 213 – 216 °C; IR (thin film) ν_{max} /cm^{-1}: 2930, 1690, 1673, 1650, 1634, 1594, 1451, 1436, 1391, 1359, 703; δ_H (400 MHz, $CDCl_3$) 7.60 – 7.48 (3 H, m), 7.42 – 7.23 (9 H, m), 7.19 (2 H, d, *J* 7.2), 7.07 (2 H, dt, *J* 7.5, 3.9), 5.75 (1 H, d, *J* 16.5), 4.73 – 4.61 (2 H, m), 3.83 – 3.74 (1 H, m), 3.67 (1 H, dt, *J* 11.4, 7.4), 3.48 (1 H, d, *J* 18.8), 3.17 (1 H, d, *J* 6.4), 2.94 (1 H, d, *J* 18.8), 2.57 – 2.48 (1 H, m), 2.11 – 2.02 (2 H, m), 1.78 (1 H, dt, *J* 13.5, 7.9); δ_C (101 MHz, $CDCl_3$) 198.6, 170.7, 165.4, 136.7, 134.9, 134.4, 129.4, 129.4, 129.1, 128.7, 128.1, 126.3, 116.9, 70.0, 64.2, 58.2, 54.1, 45.1, 45.0, 29.0, 24.3, 18.2; m/z 512.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{31}H_{27}N_3O_3Na$: 512.1950, Found 512.1946.

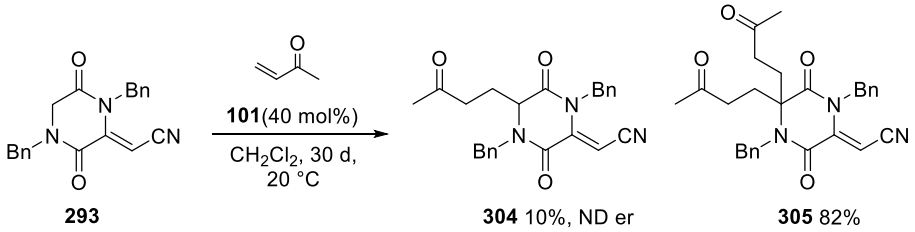
Michael adduct **303**



General procedure A was followed with DKP **294** (35 mg, 0.090 mmol), MVK (19 mg, 22 μL, 0.27 mmol) and **101** (7 mg, 0.018 mmol, 20 mol%) as base. Flash chromatography (25–33% EtOAc in hexane)

gave **303** (40 mg, 0.086 mmol, 96%) as a colourless solid in 85:15 er [Cellulose-3, MeCN:H_2O 45:55, 1.0 mLmin^{-1}, t_1= 11.37 mins, t_2= 12.31 mins]; m.p. 139 – 140 °C; IR (thin film) ν_{max} /cm^{-1}: 3067, 2213, 1758, 1695, 1608, 1437, 1419, 1360, 1264, 1227, 731, 697; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.12 (10 H, m), 6.26 (1 H, s), 5.51 (1 H, d, *J* 16.3), 5.37 (1 H, d, *J* 16.3), 4.64 (1 H, d, *J* 15.2), 4.51 (1 H, d, *J* 15.2), 3.37 (3 H, s), 2.71 – 2.53 (1 H, m), 2.53 – 2.40 (1 H, m), 2.24 – 2.09 (1 H, m), 2.06 – 1.92 (1 H, m), 1.86 (3 H, s); δ_C (101 MHz, $CDCl_3$) 205.3, 166.7, 162.7, 158.2, 141.4, 135.2, 134.2, 129.2, 128.9, 128.7, 128.2, 128.1, 127.0, 126.9, 115.8, 85.2, 77.4, 77.1, 76.7, 71.4, 53.7, 48.3, 47.6, 37.0, 29.7, 27.6; m/z 498.1 ([MK]$^+$, 100), 482.1 ([MNa]$^+$, 60); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{26}H_{25}N_3O_5Na$: 482.1692, Found 482.1693.

Michael adducts **304** and **305**

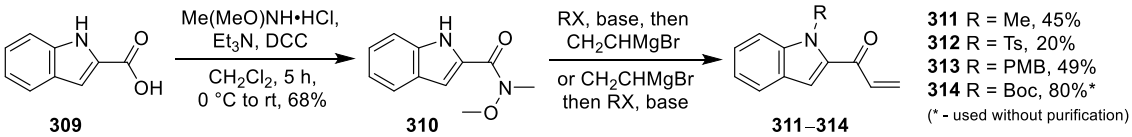


293 **304** 10%, ND er **305** 82%

General procedure A was followed with DKP **293** (15 mg, 0.045 mmol), MVK (8 mg, 9 μL, 0.11 mmol) and **101** (7 mg, 0.018 mmol, 40 mol%) as base . Flash chromatography (0.5–1.5% MeOH in DCM) gave **304** (2 mg, 0.0045 mmol, 10%) as a colourless gum; IR **304** (thin film) ν_{max} /cm^{-1}: 2933, 2212, 1701, 1675, 1606, 1452, 1362, 1260, 1161, 734, 699; δ_H (400 MHz, $CDCl_3$) 7.33 – 7.19 (8 H, m), 7.13 – 7.08 (2 H, m), 6.03 (1 H, s), 5.50 (1 H, d, *J* 16.1), 5.18 (1 H, d, *J* 16.1), 5.16 (1 H, d, *J* 14.7), 4.14 (1 H, d, *J* 14.7), 3.99 (1 H, dd, *J* 10.6, 3.9), 2.56 – 2.35 (2 H, m), 2.29 – 2.18 (1 H, m), 2.07 (3 H, s), 1.75 (1 H, ddt, *J* 14.0, 10.9, 5.5).; δ_C (101 MHz, $CDCl_3$) 206.3, 165.5, 157.5, 143.6, 135.0, 134.4, 129.1, 128.9, 128.5, 128.4, 128.1, 127.1, 115.8, 85.8, 58.5, 48.5, 46.6, 37.8, 30.0, 27.2; m/z 424.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{24}H_{23}N_3O_3Na$: 424.1637, Found 424.1640; and **305** (17 mg, 0.037 mmol, 82%) as a colourless solid; m.p. 116 – 118 °C; IR **305** (thin film) ν_{max} /cm^{-1}: 2968, 2210, 1715, 1696, 1605, 1422,

1361, 1268, 734, 699; δ_H (400 MHz, $CDCl_3$) 7.33 –7.20 (10 H, m), 6.30 (1 H, s), 5.45 (2 H, s), 4.62 (2 H, s), 2.21 – 2.05 (4 H, m), 2.04 – 1.84 (4 H, m), 1.82 (6 H, s); δ_C (101 MHz, $CDCl_3$) 205.4, 166.9, 158.6, 141.9, 136.8, 134.7, 129.1, 129.0, 128.9, 128.5, 128.5, 128.2, 127.4, 116.0, 83.8, 68.6, 47.6, 46.9, 37.5, 32.3, 29.7; m/z 494.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{28}H_{29}N_3O_4Na$: 494.2056, Found 494.2051.

Indole vinyl ketones **311-314**

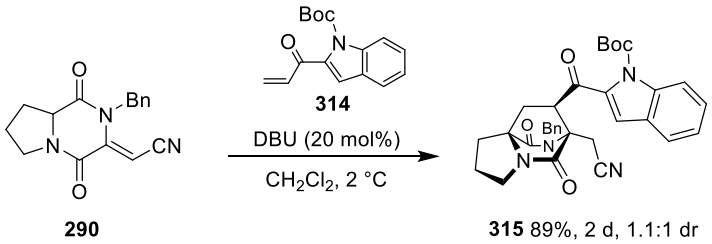


Et_3N (0.87 mL, 628 mg, 6.21 mmol) was added to a suspension of indole-2-carboxylic acid (1.00 g, 6.21 mmol), DCC (1.28 g, 6.21 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (605 mg, 6.21 mmol) in DCM (20 mL) cooled to 0 °C and was stirred for 3 hours and allowed to warm to room temperature. The reaction mixture was then filtered through a plug of celite and then washed with sat. NH_4Cl (20 mL) and brine (20 mL) before being evaporated under reduced pressure. The residue was then dry-loaded onto a silica gel column (10-30% EtOAc in Hex) to give Weinreb adduct **310** (859 mg, 4.21 mmol, 68%) as a colourless solid. The ^1H, ^{13}C and m/z data was consistent with the literature.[128]

Weinreb adduct **310** was then reacted with MeI (2 eq) and NaH (1.5 eq) in DMF followed by vinyl magnesium bromine (4 eq) in THF to give indole vinyl ketone **311** (45% w.r.t **310**). The ^1H, ^{13}C and m/z data was consistent with the literature.[129] Alternatively, reaction of Weinreb adduct **310** with Tosyl chloride (1.2 eq), NaOH (1.8 eq), $BnEt_3NCl$ (0.1 eq) in DCM followed by vinyl magnesium bromine (5 eq) in THF gave indole vinyl ketone **312** (20% w.r.t **310**). The ^1H, ^{13}C and m/z data was consistent with the literature.[129] Reaction of Weinreb adduct **310** with 4-methoxy benzyl chloride (1.5 eq) and NaH (2 eq) in DMF followed by vinyl magnesium bromine (5 eq) in THF gave indole vinyl ketone **313** (49% w.r.t

310). The ^{1}H, ^{13}C and m/z data was consistent with the literature.[129] Finally, reaction of Weinreb adduct **310** with vinyl magnesium bromine (7 eq) in THF followed by Boc_2O (2 eq) and DMAP (0.2 eq) in DCM gave indole vinyl ketone **314** (approx. 80% (crude) w.r.t **310**). The ^{1}H, ^{13}C and m/z data was consistent with the literature.[129]

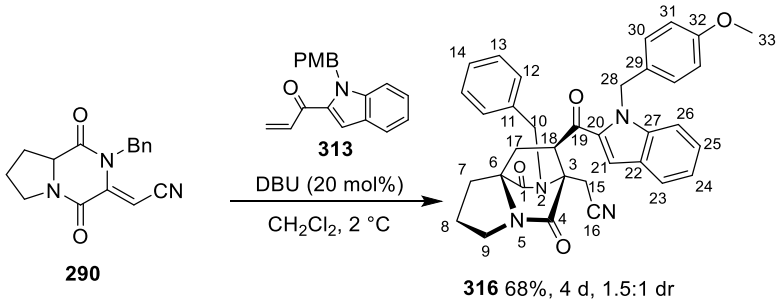
Michael–Michael adduct **315**



General procedure A was followed with DKP **290** (29 mg, 0.10 mmol), **314** (approx.. 85 mg used crude) and DBU (3 μL, 0.020 mmol). Flash chromatography (40–50% EtOAc in hexane) gave adduct **315** (51 mg, 0.091 mmol, 89%, 1.1:1 dr) as colourless gum; IR (thin film) ν_{max} /cm^{-1}: 2980, 1739, 1689, 1386, 1322, 1152, 740; major diastereoisomer δ_H (400 MHz, $CDCl_3$) 7.98 (1 H, dq, *J* 8.4, 0.8), 7.64 (1 H, dt, *J* 7.8, 1.0), 7.46 (1 H, ddd, *J* 8.4, 7.2, 1.3), 7.39 – 7.26 (4 H, m), 7.19 (1 H, d, *J* 0.9), 7.18 – 7.11 (2 H, m), 5.33 (1 H, d, *J* 16.6), 4.67 (1 H, d, *J* 16.6), 4.17 (1 H, dd, *J* 10.9, 5.5), 3.71 – 3.64 (1 H, m), 3.63 – 3.55 (1 H, m), 3.31 (1 H, d, *J* 18.5), 2.94 (1 H, app. dt, *J* 13.1, 6.6), 2.86 (1 H, d, *J* 18.5), 2.48 (1 H, dd, *J* 13.3, 10.9), 2.24 (1 H, dd, *J* 13.4, 5.6), 2.14 – 2.05 (2 H, m), 1.91 (1 H, app. dt, *J* 13.1, 7.5), 1.61 (9 H, s); δ_C (101 MHz, $CDCl_3$) 189.4, 171.9, 164.4, 149.4, 139.0, 137.0, 136.8, 129.3, 128.5, 128.1, 127.1, 126.3, 123.7, 123.1, 117.8, 116.8, 114.9, 85.4, 65.9, 64.5, 51.8, 44.9, 44.7, 35.2, 29.8, 27.9, 27.8, 24.4, 18.4; minor diastereoisomer δ_H (400 MHz, $CDCl_3$) 8.00 (1 H, dd, *J* 8.5, 0.8), 7.64 (1 H, dt, *J* 7.8, 1.0), 7.47 (1 H, ddd, *J* 8.5, 7.2, 1.2), 7.34 – 7.22 (5 H, m), 7.05 (2 H, d, *J* 7.5), 5.53 (1 H, d, *J* 17.0), 4.34 (1 H, d, *J* 16.9), 4.18 (1 H, dd, *J* 10.9, 5.7), 3.64 (2 H, t, *J* 6.8), 3.38 (1 H, d, *J* 15.8), 3.00 – 2.86 (2 H, m), 2.43 (1 H, dd, *J* 13.3, 11.0), 2.27 (1 H, dd, *J* 13.2, 5.7), 2.17 – 2.02 (2 H, m), 1.92 (1 H, dt, *J* 13.3, 7.1), 1.64 (9 H, s); δ_C (101

MHz, $CDCl_3$) 189.5, 170.9, 165.5, 149.4, 139.2, 137.3, 137.0, 129.1, 128.5, 127.7, 127.0, 126.2, 123.7, 123.3, 118.2, 115.7, 114.7, 85.4, 66.1, 64.5, 47.9, 45.7, 44.7, 34.7, 29.8, 28.0, 27.8, 24.5, 24.4, 18.7; m/z 575.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{32}H_{32}N_4O_5Na$: 575.2270, Found 575.2280.

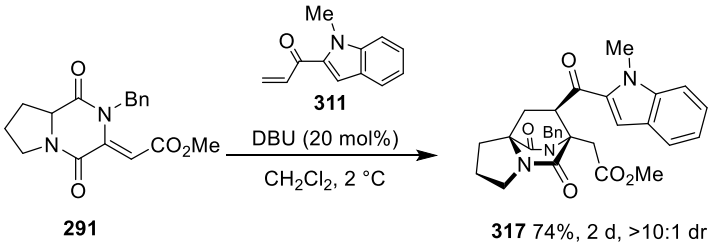
Michael–Michael adduct **316**



General procedure A was followed with DKP **290** (21 mg, 0.075 mmol), **313** (approx.. 50 mg) and DBU (3 μL, 0.015 mmol). Flash chromatography (50–70% EtOAc in hexane) gave adduct **316** (29 mg, 0.051 mmol, 68%, 1.5:1 dr) as a colourless solid; m.p. 123 – 125 °C; IR (thin film) ν_{max} /cm^{-1}: 2961, 1693, 1655, 1613, 1512, 1389, 1249, 1176, 741; Major; minor - δ_H (400 MHz, $CDCl_3$) 7.73 (1 H, d, *J* 8.1, H-Ar), 7.69 (1 H, d, *J* 8.1, H-Ar), 7.48 – 7.27 (11 H, m, H-Ar, H-Ar), 7.25 – 7.11 (6 H, m, H-Ar, H-Ar), 6.97 – 6.84 (5 H, m, H-Ar, H-Ar), 6.83 – 6.77 (2 H, m, H-Ar), 6.77 – 6.71 (2 H, m, H-Ar), 5.82 (1 H, d, *J* 15.7, H-28a), 5.77 – 5.64 (3 H, m, H-28, H-28b), 5.39 (1 H, d, *J* 17.0, H-10a), 5.20 (1 H, d, *J* 16.5, H-10a), 4.77 (1 H, d, *J* 16.5, H-10b), 4.24 – 4.15 (2 H, m, H-19, H-19), 3.83 (1 H, d, *J* 17.0, H-10b), 3.74 (3 H, s, H-33), 3.72 (3 H, s, H-33), 3.69 – 3.53 (4 H, m, H-9, H-9), 3.02 (1 H, d, *J* 18.3, H-15a), 2.94 – 2.83 (2 H, m, H-7a, H-7a), 2.76 (2 H, ABq, *J* 16.0, H-15), 2.64 (1 H, d, *J* 18.3, H-15b), 2.47 – 2.31 (2 H, m, H-18a, H-18a), 2.16 – 1.94 (4 H, m, H-8, H-8), 1.91 – 1.75 (4 H, m, H-7b, H-7b, H-18b, H-18b); δ_C (101 MHz, $CDCl_3$) 190.6 (C-19), 190.3 (C-19), 171.9 (C-1), 170.8 (C-1), 165.5 (C-4), 164.5 (C-4), 159.0 (C-Ar), 158.9 (C-Ar), 141.0 (C-Ar), 137.2 (C-Ar), 137.1 (C-Ar), 133.5 (C-Ar), 133.2 (C-Ar), 130.2 (C-Ar), 130.0 (C-Ar), 129.4 (C-Ar), 129.1 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 126.6

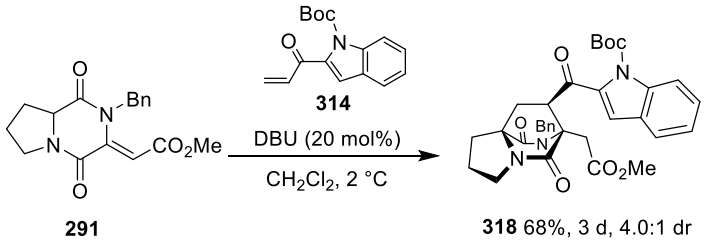
(C-Ar), 126.1 (C-Ar), 125.9 (C-Ar), 123.6 (C-Ar), 123.5 (C-Ar), 121.6 (C-Ar), 116.8 (C-16), 115.6 (C-16), 114.9 (C-Ar), 114.7 (C-Ar), 114.1 (C-Ar), 113.9 (C-Ar), 111.0 (C-Ar), 110.8 (C-Ar), 66.1 (C-6), 65.8 (C-6), 64.7 (C-3), 64.6 (C-3), 55.2 (C-33, C-33), 51.1 (C-19), 47.7 (C-28), 47.5 (C-28), 46.9 (C-19), 45.7(C-10), 44.9 (C-10), 44.6 (C-9, C-9), 36.2 (C-17), 36.0 (C-17), 29.8 (C-7), 29.7 (C-7), 24.5 (C-8), 24.3 (C-8), 18.6 (C-17), 18.3 (C-17); m/z 595.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{35}H_{32}N_4O_4Na$: 595.2321, Found 595.2324.

Michael–Michael adduct **317**



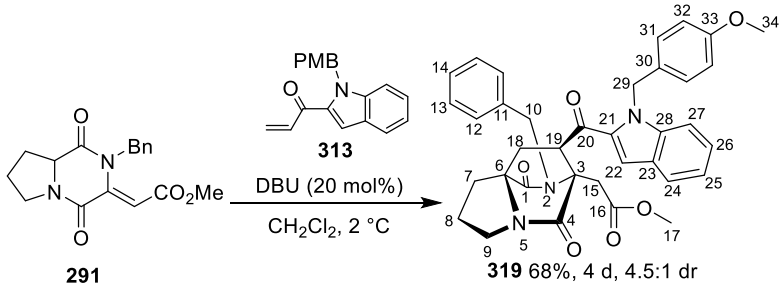
General procedure A was followed with DKP **291** (25 mg, 0.080 mmol), **311** (50 mg, 0.24 mmol) and DBU (2 μL, 0.016 mmol). Flash chromatography (50–70% EtOAc in hexane) gave adduct **317** (33 mg, 0.071 mmol, 74%, >10:1 dr) as a colourless solid; m.p. 168 – 170 °C (decomp); IR (thin film) ν_{max} /cm^{-1}: 2964, 1735, 1690, 1657, 1510, 1392, 1195, 1175, 740; major diastereoisomer δ_H (400 MHz, $CDCl_3$) 7.63 (1 H, d, *J* 8.1), 7.42 – 7.31 (5 H, m), 7.21 – 7.11 (3 H, m), 6.79 (1 H, s), 4.95 (1 H, d, *J* 16.3), 4.87 (1 H, d, *J* 16.3), 4.41 (1 H, dd, *J* 10.8, 5.6), 4.01 (3 H, s), 3.72 – 3.62 (2 H, m), 3.51 (3 H, s), 3.24 (1 H, d, *J* 18.2), 2.93 (1 H, dt, *J* 13.5, 6.9), 2.86 (1 H, d, *J* 18.2), 2.40 (1 H, dd, *J* 13.0, 10.8), 2.07 (3 H, ddt, *J* 10.3, 6.9, 3.6), 1.90 (1 H, dt, *J* 14.4, 7.2); δ_C (101 MHz, $CDCl_3$) 191.6, 172.4, 170.9, 165.7, 140.7, 138.2, 134.0, 129.1, 127.7, 127.1, 126.8, 125.6, 123.2, 121.1, 113.0, 110.5, 66.3, 65.6, 52.0, 50.1, 45.7, 44.6, 36.1, 32.9, 32.4, 29.9, 24.2; m/z 522.2 ($[MNa]^+$, 100), 500.2 ($[MH]^+$, 10); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{29}H_{29}N_3O_5Na$: 522.2005, Found 522.2008.

Michael–Michael adduct **318**



General procedure A was followed with DKP **291** (20 mg, 0.064 mmol), **314** (approx. 85 mg of crude) and DBU (2 μL, 0.016 mmol). Flash chromatography (40–70% EtOAc in hexane) gave adduct **318** (16 mg, 0.027 mmol, 68%, 4.0:1 dr) as a colourless solid; m.p. 155 – 257 °C; IR (thin film) ν_{max} /cm^{-1}: 2979, 1735, 1686, 1390, 1370, 1320, 1158, 1135, 734; major diastereoisomer δ_H (400 MHz, $CDCl_3$) 7.97 (1 H, dd, *J* 8.5, 0.9), 7.61 (1 H, dt, *J* 7.9, 1.1), 7.44 (1 H, ddd, *J* 8.5, 7.2, 1.3), 7.35 – 7.24 (4 H, m), 7.10 – 7.04 (2 H, m), 6.97 (1 H, s), 5.01 (1 H, d, *J* 16.5), 4.64 – 4.52 (2 H, m), 3.68 – 3.57 (2 H, m), 3.35 – 3.25 (4 H, m), 2.97 – 2.85 (2 H, m), 2.39 (1 H, dd, *J* 13.2, 10.8), 2.23 (1 H, dd, *J* 13.2, 5.8), 2.11 – 2.02 (2 H, m), 1.91 (1 H, dt, *J* 13.1, 7.4), 1.61 (9 H, s); δ_C (101 MHz, $CDCl_3$) 190.8, 172.5, 171.0, 165.7, 149.6, 138.5, 137.9, 137.5, 129.0, 127.9, 127.5, 127.2, 126.5, 123.5, 122.8, 116.7, 114.8, 85.3, 65.9, 65.5, 51.7, 50.4, 45.6, 44.6, 35.4, 32.3, 29.9, 27.8, 24.2; minor diastereoisomer - δ_H (400 MHz, $CDCl_3$) 8.02 (1 H, d, *J* 8.5), 7.65 (1 H, app dt, *J* 7.9, 1.1), 7.45 (1 H, ddd, *J* 8.5, 7.2, 1.3), 7.36 – 7.18 (5 H, m), 7.07 (2 H, d, *J* 7.1), 5.40 (1 H, d, *J* 16.9), 4.97 (1 H, dd, *J* 11.2, 5.9), 4.42 (1 H, d, *J* 16.9), 3.62 – 3.57 (2 H, m), 3.54 (3 H, s), 3.25 (1 H, d, *J* 16.0), 2.98 – 2.86 (2 H, m), 2.40 (1 H, dd, *J* 13.1, 11.3), 2.21 (1 H, dd, *J* 13.1, 6.0), 2.13 – 1.99 (2 H, m), 1.88 (1 H, dt, *J* 13.2, 7.2), 1.61 (9 H, s); δ_C (101 MHz, $CDCl_3$) 190.9, 171.3, 170.5, 167.1, 149.4, 139.0, 138.0, 137.6, 128.9, 128.0, 127.2, 127.1, 126.1, 123.5, 123.0, 117.4, 114.6, 114.3, 85.1, 66.0, 65.7, 51.8, 46.9, 46.0, 44.5, 34.7, 31.8, 29.8, 27.9, 24.5; m/z 608.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{33}H_{35}N_3O_7Na$: 608.2373, Found 608.2374.

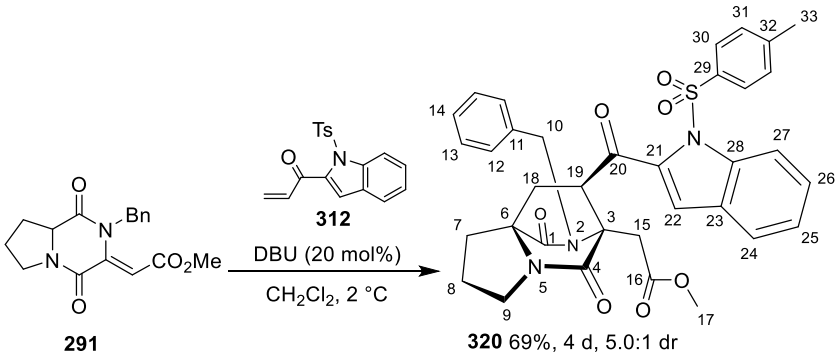
Michael–Michael adduct **319**



General procedure A was followed with DKP **291** (20 mg, 0.064 mmol), **313** (50 mg, 0.24 mmol) and DBU (2 μL, 0.013 mmol). Flash chromatography (50–70% EtOAc in hexane) gave adduct **319** (24 mg, 0.040 mmol, 64%, 4.5:1 dr) as colourless gum; IR (thin film) ν_{max} /cm^{-1}: 2964, 1735, 1690, 1657, 1510, 1392, 1195, 1175, 740; major; minor - δ_H (400 MHz, $CDCl_3$) 7.73 (1 H, d, *J* 8.1, H-Ar), 7.65 (1 H, d, *J* 8.1, H-Ar), 7.48 – 7.23 (10 H, m, H-Ar, H-Ar), 7.22 – 7.12 (6 H, m, H-Ar, H-Ar), 6.98 – 6.85 (6 H, m, H-Ar, H-Ar), 6.80 – 6.68 (4 H, m, H-Ar, H-Ar), 5.80 (1 H, d, *J* 15.7, H-29a), 5.73 – 5.64 (3 H, m, H-29b, H-29), 5.22 (1 H, d, *J* 17.0, H-10a), 4.94 (1 H, dd, *J* 11.0, 5.4, H-19), 4.86 (2 H, s, H-10), 4.43 (1 H, dd, *J* 10.9, 5.6, H-19), 3.81 (1 H, d, *J* 17.0, H-10b), 3.73 (3 H, s, H-34), 3.72 (3 H, s, H-34), 3.62 (2 H, t, *J* 6.9, H-9), 3.59 – 3.52 (5 H, m, H-9, H-17), 3.48 – 3.44 (4 H, m, H-15a, H-17), 3.16 (1 H, d, *J* 18.2, H-15a), 2.93 – 2.83 (2 H, m, H-7a, H-7a), 2.81 – 2.74 (2 H, m, H-15b, H-15b), 2.37 – 2.26 (2 H, m, H-18a, H-18b), 2.10 – 1.92 (4 H, m, H-8, H-8), 1.87 – 1.74 (4 H, m, H-7b, H-7b, H-18b, H-18b); δ_C (101 MHz, $CDCl_3$) 192.5 (C-20), 191.4 (C-20), 172.3 (C-1), 171.4 (C-1), 170.9 (C-16), 170.2 (C-16), 167.0 (C-4), 165.7 (C-4), 158.9 (C-Ar), 158.8 (C-Ar), 140.7 (C-Ar), 140.6 (C-Ar), 138.1 (C-Ar), 138.1 (C-Ar), 134.2 (C-Ar), 133.7 (C-Ar), 130.4 (C-Ar), 130.2 (C-Ar), 129.0 (C-Ar), 128.8 (C-Ar), 128.1 (C-Ar), 127.7 (C-Ar), 127.7 (C-Ar), 127.1 (C-Ar), 127.0 (C-Ar), 126.9 (C-Ar), 126.0 (C-Ar), 125.9 (C-Ar), 123.4 (C-Ar), 123.2 (C-Ar), 121.3 (C-Ar), 114.3 (C-Ar), 114.3 (C-Ar), 114.0 (C-Ar), 113.9 (C-Ar), 113.8 (C-Ar), 111.1 (C-Ar), 110.7 (C-Ar), 66.1 (C-6), 66.1 (C-6), 65.5 (C-3), 55.2 (C-34), 51.9 (C-17), 51.8 (C-17), 50.1 (C-19), 47.5 (C-29), 47.4 (C-29), 46.0 (C-10), 45.9 (C-19), 45.7 (C-10), 44.5 (C-17, C-17), 36.2 (C-18), 35.9

(C-18), 32.7 (C-15), 32.1 (C-15), 29.8 (C-7), 29.7 (C-7), 24.4 (C-8), 24.2 (C-8); m/z 628.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{36}H_{35}N_3O_6Na$: 628.2424, Found 628.2422.

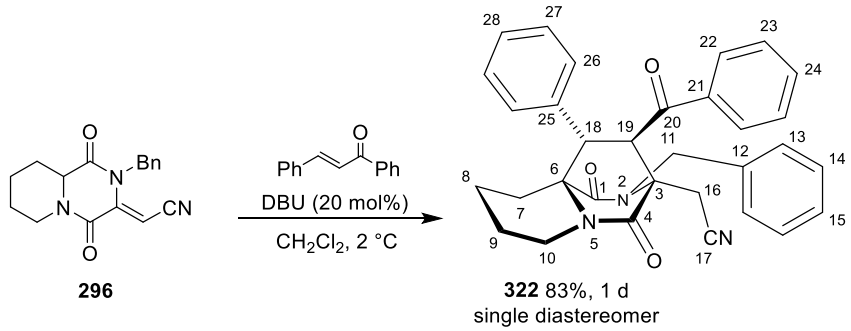
Michael–Michael adduct **320**



General procedure A was followed with DKP **291** (18 mg, 0.057 mmol), **312** (approx. 14 mg) and DBU (2 μL, 0.013 mmol). Flash chromatography (50–67% EtOAc in hexane) gave adduct **320** (24 mg, 0.039 mmol, 69%, 5.0:1 dr) as a colourless solid; m.p. 114 – 116 °C; IR (thin film) ν_{max} /cm^{-1}: 2949, 1737, 1687, 1438, 1394, 1363, 1173, 734, 578; major diastereoisomer - δ_H (400 MHz, $CDCl_3$) 8.17 – 8.11 (1 H, m), 8.02 (1 H, s), 8.00 (1 H, s), 7.63 (1 H, d, *J* 7.8), 7.50 (1 H, ddd, *J* 8.5, 7.3, 1.2), 7.39 – 7.27 (6 H, m), 7.22 (1 H, t, *J* 7.3), 7.09 (2 H, d, *J* 7.2), 5.37 (1 H, d, *J* 17.0), 4.99 (1 H, dd, *J* 10.4, 5.6), 4.32 (1 H, d, *J* 16.9), 3.62 – 3.51 (2 H, m), 3.48 (3 H, s), 3.14 (1 H, d, *J* 16.2), 2.98 – 2.87 (2 H, m), 2.43 (3 H, s), 2.35 – 2.22 (2 H, m), 2.10 – 2.01 (2 H, m), 1.89 (1 H, dt, *J* 13.3, 7.3); δ_C (101 MHz, $CDCl_3$) 191.6 (C-20), 171.6 (C-1), 170.3 (C-16), 166.7 (C-4), 145.1 (C-32), 139.6 (C-Ar), 138.9 (C-Ar), 138.2 (C-11), 136.1 (C-Ar), 129.6 (C-Ar), 128.9 (C-Ar), 128.3 (C-13), 127.7 (C-Ar), 127.6 (C-Ar), 127.2 (C-Ar), 126.3 (C-12), 124.1 (C-Ar), 123.4 (C-Ar), 119.4 (C-Ar), 115.5 (C-Ar), 66.4 (C-6), 66.2 (C-3), 51.8 (C-17), 47.0 (C-19), 46.0 (C-10), 44.5 (C-9), 35.0 (C-18), 32.1 (C-15), 29.8 (C-7), 24.5 (C-8), 21.7 (C-33); minor diastereoisomer - δ_H (400 MHz, $CDCl_3$) 8.07 – 8.00 (1 H, m, H-Ar), 7.82 – 7.76 (2 H, m, H-Ar), 7.54 (1 H, d, *J* 7.8, H-Ar), 7.44 (1 H, ddd, *J* 8.5, 7.3, 1.2, H-Ar), 7.37 – 7.18 (6 H, m, H-Ar), 7.06 – 7.01 (3 H, m, H-Ar), 5.02 (1 H, d, *J* 16.6, H-10a), 4.86 (1 H, dd, *J* 10.6, 5.5, H-19), 4.52 (1 H, d, *J* 16.6, H-10b), 3.74 – 3.67 (1 H, m, H-

9a), 3.66 – 3.60 (1 H, m, H-9b), 3.34 – 3.21 (4 H, m, H-15, H-17), 2.95 – 2.85 (2 H, m, H-7a, H-15b), 2.52 – 2.29 (5 H, m, H-18, H-33), 2.13 – 2.05 (2 H, m, H-8), 2.00 – 1.92 (1 H, m, H-7b); δ_C (101 MHz, $CDCl_3$) 192.8 (C-20), 172.5 (C-1), 170.8 (C-16), 165.6 (C-4), 145.2 (C-32), 139.3 (C-Ar), 138.6 (C-Ar), 137.8 (C-11), 134.4 (C-Ar), 129.6 (C-Ar), 128.9 (C-Ar), 128.4 (C-Ar), 127.8 (C-Ar), 127.7 (C-Ar), 127.5 (C-Ar), 126.3 (C-Ar), 124.5 (C-Ar), 123.0 (C-Ar), 117.9 (C-Ar), 115.6 (C-Ar), 65.9 (C-3), 65.5 (C-6), 51.7 (C-17), 51.7 (C-19), 45.6 (C-10), 44.6 (C-9), 35.2 (C-18), 32.1 (C-15), 29.8 (C-7), 24.2 (C-8), 21.6 (C-33); m/z 640.2 ($[MH]^+$, 100), 662.2 ($[MNa]^+$, 50); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{35}H_{34}N_3O_7S$: 640.2117, Found 640.2119.

Michael–Michael adduct **322**



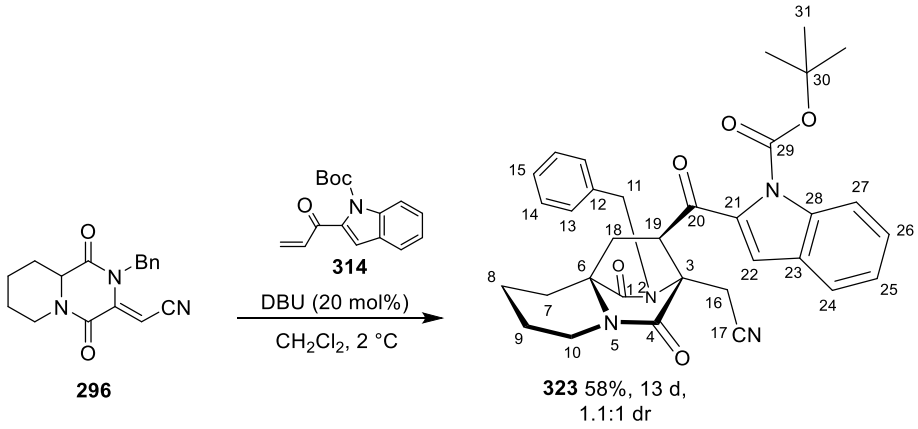
296

322 83%, 1 d
single diastereomer

General procedure A was followed with DKP **296** (22 mg, 0.075 mmol), chalcone (50 mg, 0.024 mmol) and DBU (2 mg, 2 μL, 0.015 mmol). Flash chromatography (30–50% EtOAc in hexane) gave adduct **322** (31 mg, 0.062 mmol, 83%) as a colourless solid; m.p. 181 – 182 °C; IR (thin film) ν_{max} /cm^{-1}: 2950, 1690, 1449, 1383, 1351, 1216, 735, 701; δ_H (400 MHz, $CDCl_3$) 7.54 – 7.45 (3 H, m, H-Ar), 7.39 – 7.27 (6 H, m, H-Ar), 7.26 – 7.17 (4 H, m, H-Ar), 7.04 – 6.96 (2 H, m, H-Ar), 5.77 (1 H, d, *J* 16.6, H-11a), 4.65 (1 H, d, *J* 16.6, H-11b), 4.60 (1 H, d, *J* 6.6, H-19), 3.67 (2 H, app. t, *J* 6.3, H-10), 3.41 (1 H, d, *J* 18.8, H-16a), 3.22 (1 H, d, *J* 6.6, H-18), 2.88 (1 H, d, *J* 18.8, m, H-16b), 2.06 – 1.97 (1 H, m, H-8a), 1.83 – 1.74 (2 H, m, H-9), 1.72 – 1.59 (2 H, m, H-7), 1.48 – 1.37 (1 H, m, H-8b); δ_C (101 MHz, $CDCl_3$) 199.0 (C-20), 170.5 (C-4), 168.4 (C-1), 136.9 (C-25), 136.8 (C-12), 135.1 (C-21), 134.4 (C-Ar), 129.3 (C-Ar), 129.1 (C- Ar),

128.6 (C- Ar), 128.5 (C- Ar), 128.3 (C- Ar), 128.1 (C- Ar), 126.2 (C- Ar), 116.9 (C-17), 62.8 (C-6), 62.6 (C-3), 57.6 (C-19), 54.6 (C-18), 44.9 (C-11), 39.8 (C-10), 25.4 (C-8), 21.4 (C-9), 18.5 (C-16), 17.0 (C-7); m/z 526.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{32}H_{29}N_3O_3Na$: 526.2107, Found 526.2101.

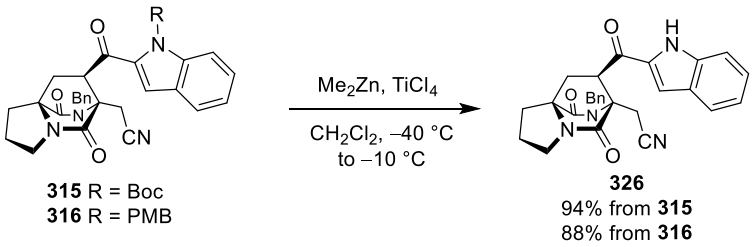
Michael–Michael adduct **323**



General procedure A was followed with DKP **296** (22 mg, 0.075 mmol), **314** (approx. 50 mg used crude) and DBU (2 mg, 2 μL, 0.015 mmol). Flash chromatography (30–50% EtOAc in hexane) gave adduct **323** (25 mg, 0.044 mmol, 58%, 1.1:1 dr) as a colourless solid; m.p. 159 – 161 °C; IR (thin film) ν_{max} /cm^{-1}: 2955, 1739, 1682, 1526, 1444, 1371, 1320, 1265, 1222, 1148, 1130, 732, 699; major diastereoisomer - δ_H (400 MHz, $CDCl_3$) 7.97 (1 H, dd, *J* 8.4, 0.7, H-Ar), 7.63 (1 H, app. dt, *J* 7.9, 0.9, H-Ar), 7.46 (1 H, ddd, *J* 8.5, 7.2, 1.2, H-Ar), 7.38 – 7.26 (4 H, m, H-Ar), 7.19 – 7.13 (3 H, m, H-Ar), 5.34 (1 H, d, *J* 16.6, H-11a), 4.68 (1 H, d, *J* 16.6, H-11b), 4.12 (1 H, dd, *J* 10.9, 5.6, H-19), 3.66 – 3.52 (2 H, m, H-10), 3.29 (1 H, d, *J* 18.4, H-16a), 2.82 (1 H, d, *J* 18.4, H-16b), 2.64 – 2.53 (1 H, m, H-8a), 2.39 (1 H, dd, *J* 13.7, 5.6, H-18a), 2.24 (1 H, dd, *J* 13.7, 10.9, H-18b), 1.88 – 1.64 (5 H, m, H-7, H-8b, H-9), 1.62 (9 H, s, H-31); δ_C (101 MHz, $CDCl_3$) 189.7 (C-20), 171.8 (C-1), 167.8 (C-4), 149.5 (C-29), 139.0 (C-Ar), 137.1 (C-Ar), 137.0 (C-12), 129.3 (C-Ar), 128.5 (C-Ar), 128.0 (C-Ar), 127.1 (C-Ar), 126.4 (C-Ar), 123.7 (C-Ar), 123.1 (C-Ar), 117.7 (C-Ar), 116.8 (C-17), 114.9 (C-Ar), 85.5 (C-30), 63.1 (C-3), 59.0 (C-6), 50.9 (C-19), 44.7 (C-

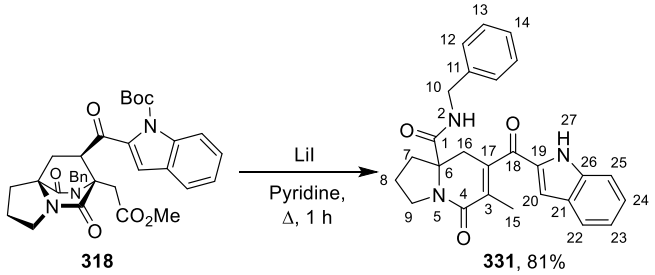
11), 40.4 (C-10), 36.4 (C-18), 27.8 (C-31), 27.1 (C-8), 21.8 (C-9), 18.8 (C-16), 18.0 (C-7); m/z 589.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{33}H_{34}N_4O_5Na$: 589.2427, Found 589.2426.

Indole adduct **326**



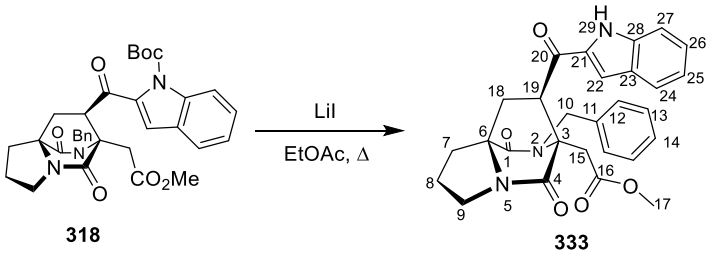
To a solution of $TiCl_4$ (1.0 M, 120 μl, 0.119 mmol) in CH_2Cl_2 (1.0 mL) cooled to –40 °C was added Me_2Zn (1.2 M, 100 μL, 119 mmol) and the mixture was stirred for 20 mins. To this solution was then added a solution of adduct **315** (22 mg, 0.040 mmol) in CH_2Cl_2 (0.5 mL) and the mixture was then allowed to warm to 5 °C over 1.5 hours. The reaction was quenched with water and extracted with EtOAc (3x10 mL) and then washed with brine, dried over $MgSO_4$. The residue was then purified by flash chromatography (50–55% EtOAc in hexane) to give **326** (17 mg, 0.038 mmol, 94%) as a colourless solid; m.p. 130 – 133 °C; IR (thin film) ν_{max} /cm^{-1}: 3313 (br), 2941, 1687, 1649, 1619, 1519, 1497, 1387, 1245, 1141, 732, 699; δ_H (400 MHz, $CDCl_3$) 9.22 (1 H, s), 7.69 (1 H, d, *J* 8.2), 7.49 – 7.31 (5 H, m), 7.23 – 7.12 (3 H, m), 7.06 (1 H, d, *J* 1.6), 5.26 (1 H, d, *J* 16.5), 4.83 (1 H, d, *J* 16.5), 4.21 (1 H, dd, *J* 10.9, 5.3), 3.73 – 3.59 (2 H, m), 3.20 (1 H, d, *J* 18.3), 2.94 (1 H, app. dt, *J* 13.2, 6.7), 2.82 (1 H, d, *J* 18.3), 2.53 (1 H, dd, *J* 13.2, 10.8), 2.16 – 2.03 (3 H, m), 1.97 – 1.85 (1 H, m); δ_C (101 MHz, $CDCl_3$) 189.4, 171.9, 164.4, 138.3, 137.1, 133.7, 129.4, 128.2, 127.7, 127.3, 126.6, 123.5, 121.6, 116.8, 112.5, 111.9, 65.9, 64.6, 49.6, 44.9, 44.7, 35.9, 29.8, 24.4, 18.7; m/z 475.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{27}H_{24}N_4O_3Na$: 475.1746, Found 475.1747.

Indole adduct **331**



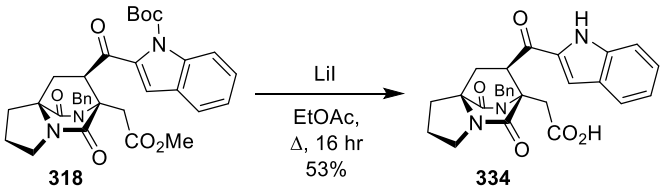
LiI (550 mg) was added to a solution of **318** (40 mg, 0.068 mmol) in pyridine (1.0 mL) and the mixture was heated to reflux for 1 hour. To the cooled solution was added EtOAc (20 mL) and HCl (2M, 10 mL), and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and then purified by flash chromatography (60–100% EtOAc in hexane) in give adduct **331** (18 mg, 0.042 mmol, 61%) as a colourless solid; m.p. 212 – 214 °C; IR (thin film) ν_{max} /cm^{-1}: 3298 (br), 2924, 1651, 1620, 1520, 1432, 1342, 751, 564; δ_H (400 MHz, DMSO) 11.94 (1 H, s, H-27), 8.66 (1 H, t, *J* 6.0, H-2), 7.61 – 7.58 (1 H, m, H-Ar), 7.49 – 7.43 (1 H, m, H-Ar), 7.33 – 7.27 (3 H, m, H-Ar), 7.25 – 7.20 (3 H, m, H-Ar), 7.12 – 7.06 (1 H, m, H-Ar), 7.00 – 6.96 (1 H, m, H-Ar), 4.52 (1 H, dd, *J* 15.2, 6.6, H-10a), 4.19 (1 H, dd, *J* 15.2, 5.3, H-10b), 3.80 – 3.71 (1 H, m, H-9a), 3.62 – 3.51 (1 H, m, H-9b), 3.22 (1 H, d, *J* 16.6, H-16a), 2.91 (1 H, dd, *J* 16.7, 2.8, H-16b), 2.29 (1 H, dd, *J* 11.7, 5.9, H-7a), 2.10 – 1.95 (2 H, m, H-7b, H-8a), 1.77 – 1.60 (4 H, m, H-8b, H-15); δ_C (101 MHz, DMSO) 188.3 (C-18), 173.0 (C-1), 163.8 (C-4), 140.2 (C-Ar), 140.0 (C-3), 139.0 (C-Ar), 134.1 (C-Ar), 130.5 (C-17), 128.6 (C-Ar), 127.3 (C-Ar), 127.1 (C-Ar), 126.7 (C-Ar), 123.5 (C-Ar), 121.0 (C-Ar), 113.3 (C-Ar), 112.3 (C-Ar), 68.0 (C-6), 45.8 (C-9), 43.1 (C-10), 38.9 (C-7), 36.4 (C-16), 22.0 (C-8), 14.2 (C-15); m/z 450.2 ($[MNa]^+$, 100); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{26}H_{25}N_3O_4Na$: 450.1794, Found 450.1795.

Indole adduct **333**



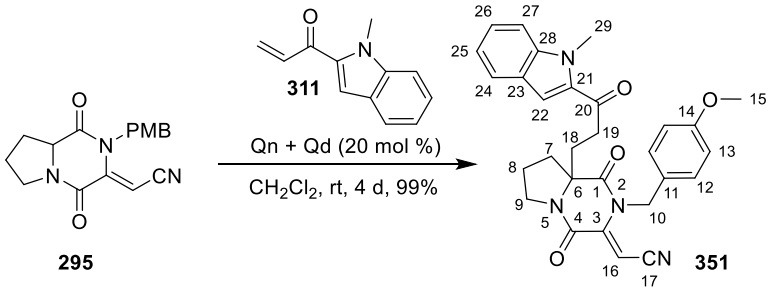
A solution of indole adduct **318** (10 mg, 0.017 mmol) and LiI (60 mg, 0.45 mmol) in EtOAc (1.0 mL) was refluxed for 1 hour. Reaction mixture was diluted with EtOAc (10 mL) and then washed with 1M HCl (aq, 10 mL × 3), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was then purified by flash chromatography (80% EtOAc in hexane to EtOAc) to give indole adduct **333** as a colourless gum; IR (thin film) ν_{max} /cm^{-1}: 3316 (br), 2948, 1738, 1687, 1651, 1518, 1393, 1199, 1174, 1142; δ_H (400 MHz, $CDCl_3$) 8.94 (1 H, s, H-29), 7.68 – 7.62 (1 H, m, H-27), 7.42 – 7.31 (5 H, m, H-13, H-14, H-24), 7.21 – 7.12 (3 H, m, H-12, H-25), 6.74 (1 H, d, *J* 1.8, H-22), 4.96 (1 H, d, *J* 16.3, H-10a), 4.86 (1 H, d, *J* 16.3, H-10b), 4.36 (1 H, dd, *J* 10.6, 5.4, H-19), 3.74 – 3.59 (2 H, m, H-9), 3.53 (3 H, s, H-17), 3.18 (1 H, d, *J* 18.3, H-15a), 2.93 (1 H, app. dt, *J* 13.5, 7.0, H-7a), 2.84 (1 H, d, *J* 18.3, H-15b), 2.39 (1 H, dd, *J* 13.1, 10.7, H-18a), 2.13 – 2.04 (3 H, m, H-8, H-18b), 1.92 – 1.84 (1 H, m, H-7b); δ_C (101 MHz, $CDCl_3$) 190.3 (C-20), 172.3 (C-1), 170.8 (C-16), 165.4 (C-4), 138.1 (C-11), 137.9 (C-23), 134.5 (C-21), 129.1 (C-13), 127.7 (C-Ar), 127.4 (C-Ar), 127.3 (C-Ar), 127.0 (C-12), 123.3 (C-27), 121.4 (C-Ar), 112.3 (C-22), 110.9 (C-24), 66.2 (C-3), 65.6 (C-6), 52.0 (C-17), 48.6 (C-19), 45.7 (C-10), 44.6 (C-9), 35.7 (C-18), 33.0 (C-15), 29.8 (C-7), 24.2 (C-8); m/z 508.2 ($[MNa]^+$, 100), 486.2 ($[MH]^+$, 60); HRMS (ESI/$[MNa]^+$) Calcd. For $C_{28}H_{28}N_3O_5$: 486.2029, Found 486.2032.

Indole acid **334**



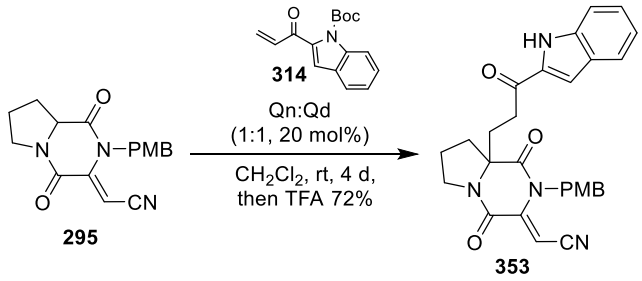
A solution of indole adduct **318** (7 mg, 0.012 mmol) and LiI (60 mg, 0.45 mmol) in EtOAc (0.5 mL) was refluxed for 16 hours. Reaction mixture was diluted with EtOAc (10 mL) and then washed with 1M HCl (aq, 10 mL × 3), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was then purified by flash chromatography (80% EtOAc in hexane to 5% MeOH/0.05% HCOOH in EtOAc) to give indole acid **334** (3 mg, 6.4 μmol, 53%) as a colourless gum; IR (thin film) ν_{max} /cm^{-1}: 3309 (br), 2925, 1730, 1678, 1649, 1519, 1398, 1170, 1140, 733, 699; δ_H (400 MHz, $CDCl_3$) 9.14 (1 H, s), 7.61 – 7.57 (1 H, m), 7.47 – 7.41 (4 H, m), 7.38 – 7.31 (2 H, m), 7.26 – 7.25 (1 H, m), 7.17 – 7.12 (1 H, m), 6.37 (1 H, d, *J* 1.8), 5.31 (1 H, d, *J* 15.8), 4.56 (1 H, d, *J* 15.8), 3.80 (1 H, dd, *J* 10.3, 5.2), 3.74 – 3.66 (1 H, m), 3.65 – 3.58 (1 H, m), 3.07 (1 H, d, *J* 16.5), 2.95 (1 H, dt, *J* 13.5, 6.9), 2.88 (1 H, d, *J* 16.5), 2.28 (1 H, dd, *J* 13.2, 10.4), 2.15 – 2.03 (3 H, m), 2.02 – 1.92 (1 H, m); δ_C (101 MHz, $CDCl_3$) 189.6, 172.0, 170.5, 167.2, 138.3, 138.1, 134.5, 129.2, 128.2, 128.1, 127.7, 127.2, 123.4, 121.5, 112.4, 111.7, 77.3, 77.0, 76.7, 67.2, 66.3, 50.3, 45.2, 45.1, 36.0, 35.3, 29.6, 24.1; m/z (ESI-) 470.2 (M-H, 100); HRMS (ESI/$[M-H]^-$) Calcd. For $C_{27}H_{24}N_3O_5$: 470.1716 found 470.1708.

Indole Michael adduct **351**



General procedure A was followed with DKP **295** (49 mg, 0.16 mmol), **311** (75 mg, 0.44 mmol) and **Qn:Qd** (1:1, 15 mg, 0.031 mmol) as base. Flash chromatography (40–50% EtOAc in hexane) gave Michael adduct **351** (78 mg, 0.16 mmol, 99%) as a colourless solid; m.p. 160 – 162 °C; IR (thin film) ν_{max} / cm^{-1}: 1701, 1664, 1606, 1512, 1440, 1364, 1247, 1176, 910, 728; δ_H (400 MHz, $CDCl_3$) 7.71 (1 H, d, *J* 8.1, H-Ar), 7.46 – 7.34 (2 H, m, H-Ar), 7.25 – 7.20 (2 H, m, H-12), 7.20 – 7.14 (2 H, m, H-22, H-Ar), 6.87 – 6.78 (2 H, m, H-13), 5.91 (1 H, s, H-16), 5.56 (1 H, d, *J* 15.7, H-10a), 5.20 (1 H, d, *J* 15.7, H-10b), 4.06 (3 H, s, H-29), 3.88 – 3.75 (1 H, m, H-9a), 3.69 (4 H, s, H-15, H-9b), 3.02 – 2.83 (2 H, m, H-19), 2.35 – 2.23 (3 H, m, H18a, H-7), 2.21 – 2.02 (3 H, m, H-8, H-18b); δ_C (101 MHz, $CDCl_3$) 190.8 (C-20), 168.8 (C-1), 159.3 (C-14), 156.0 (C-4), 144.7 (C-3), 140.3 (C-28), 133.9 (C-21), 129.1 (C-12), 126.7 (C-11), 126.3 (C-Ar), 125.7 (C-23), 123.1 (C-Ar), 121.0 (C-Ar), 115.9 (C-17), 114.3 (C-13), 111.7 (C-Ar), 110.4 (C-Ar), 84.0 (C-16), 67.5 (C-6), 55.2 (C-15), 46.3 (C-10), 45.7 (C-9), 34.1 (C-19), 33.9 (C-7), 32.7 (C-18), 32.2 (C-29), 20.2 (C-8); m/z (ESI) 497.22 (MH+, 100), 389.16 (25); HRMS (ESI/$[MH]^+$) Calcd. For $C_{29}H_{29}N_4O_4$: 497.2189 found 497.2191.

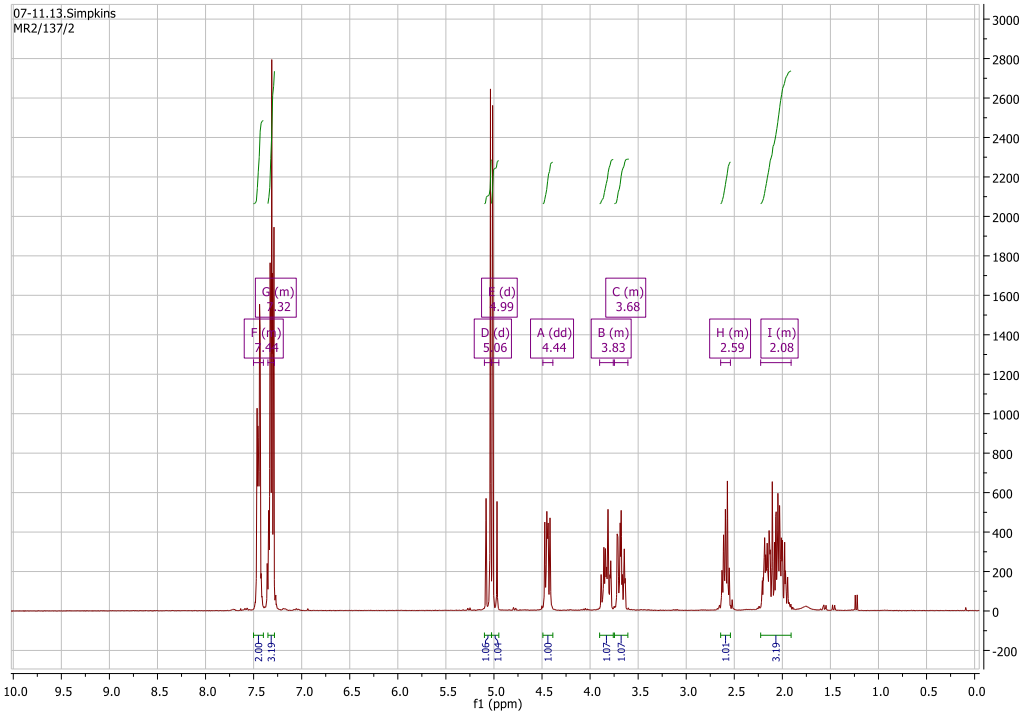
Indole Michael adduct **353**

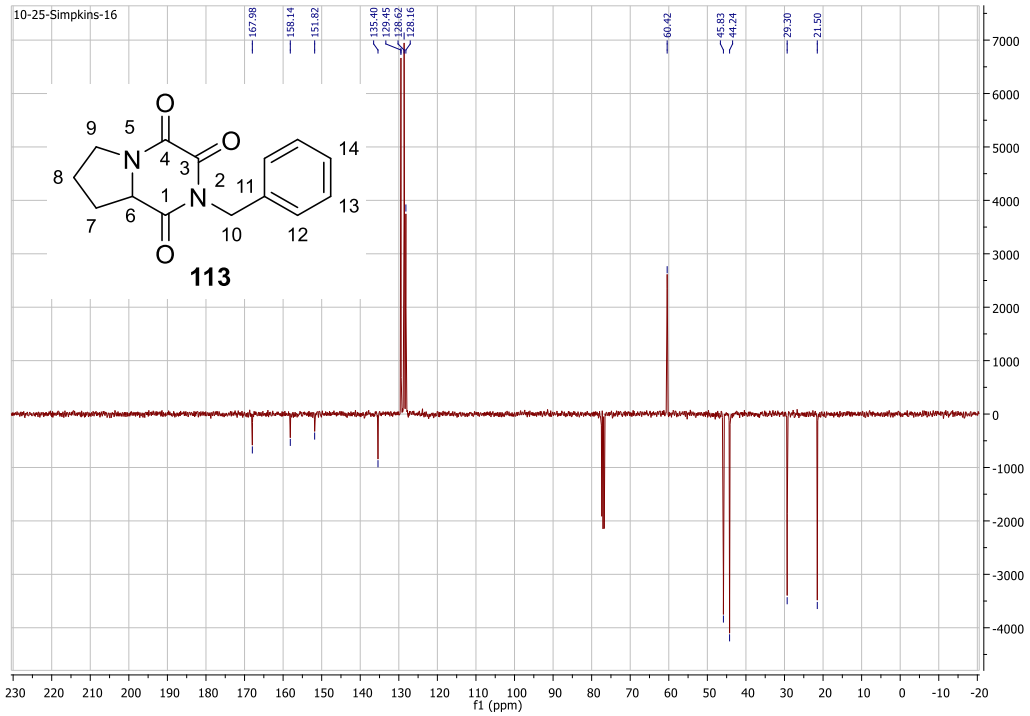


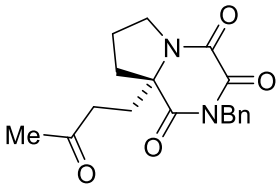
General procedure A was followed with DKP **295** (60 mg, 0.19 mmol), **314** (approx. 131 mg, 0.48 mmol) and **Qn:Qd** (1:1, 15 mg, 0.038 mmol) as base. Once the reaction was complete by TLC, TFA (0.2 mL) was added and the reaction mixture was stirred for 2 hours at room temperature. The solvent was then removed under reduced pressure. Flash chromatography (40–50% EtOAc in hexane) gave deprotected Michael adduct **353** (66 mg, 0.14 mmol, 72%.) as a colourless gum; IR (thin film) ν_{max} /cm^{-1}: 3315 (br), 2965, 2211, 1702, 1673, 1605, 1354, 1175, 735; δ_H (400 MHz, $CDCl_3$) 9.16 (1 H, s), 7.72 – 7.65 (1 H, m), 7.45 – 7.35 (2 H, m), 7.20 – 7.11 (3 H, m), 7.09 – 7.02 (1 H, m), 6.95 – 6.86 (2 H, m), 5.19 (1 H, d, *J* 16.3), 4.78 (1 H, d, *J* 16.3), 4.18 (1 H, dd, *J* 10.8, 5.3), 3.82 (3 H, s), 3.66 (2 H, qt, *J* 7.6, 3.3), 3.18 (1 H, d, *J* 18.3), 2.94 (1 H, dt, *J* 13.3, 6.7), 2.86 (1 H, d, *J* 18.2), 2.50 (1 H, dd, *J* 13.2, 10.9), 2.14 – 2.03 (3 H, m), 1.90 (1 H, dt, *J* 13.3, 7.4), 1.36 – 1.21 (1 H, m); δ_C (101 MHz, $CDCl_3$) 189.5, 172.0, 164.6, 159.6, 138.4, 133.9, 129.1, 128.1, 127.8, 127.5, 123.6, 121.7, 117.0, 114.9, 112.6, 112.0, 66.1, 64.8, 55.5, 49.7, 44.8, 44.6, 36.0, 29.9, 24.5, 18.8; m/z 505.2 ([MNa]$^+$, 100); HRMS (ESI/[MNa]$^+$) Calcd. For $C_{28}H_{26}N_4O_4Na$: 505.1852, Found 505.1851.

Appendix

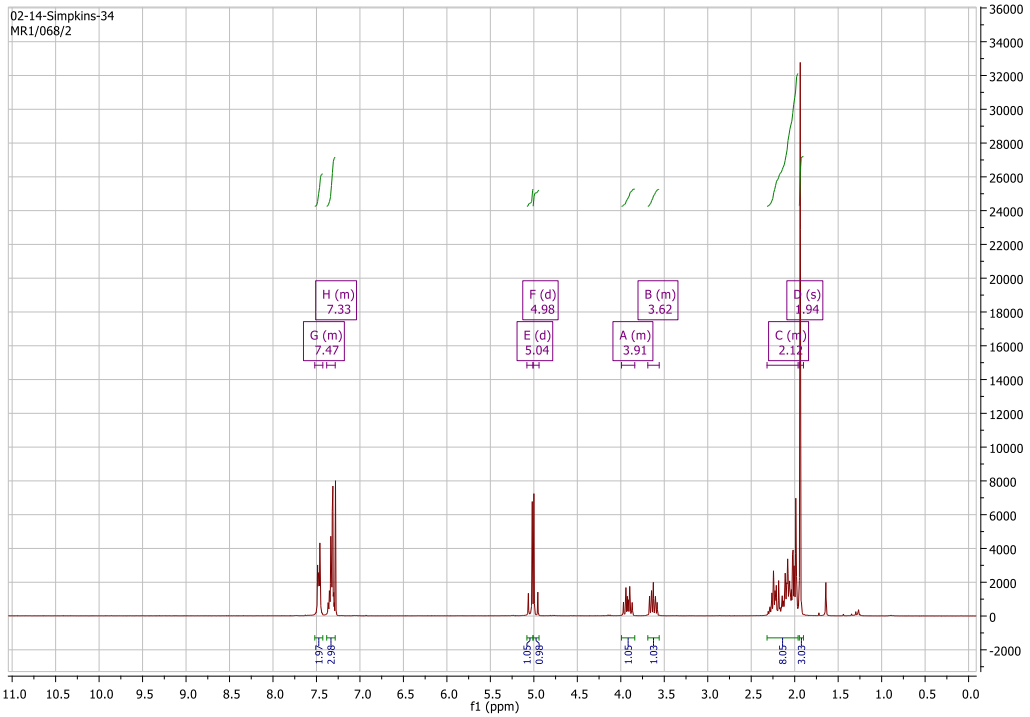
Select NMR Spectra

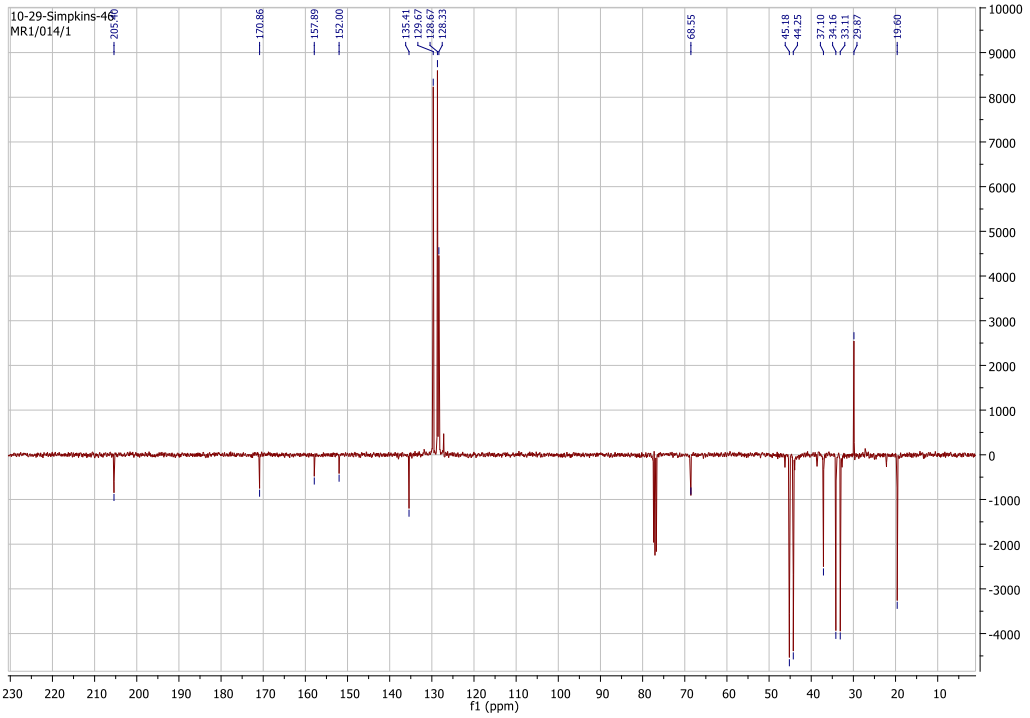


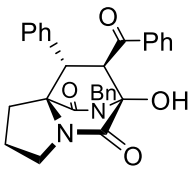



O
N
O
NBn
O
Me
O

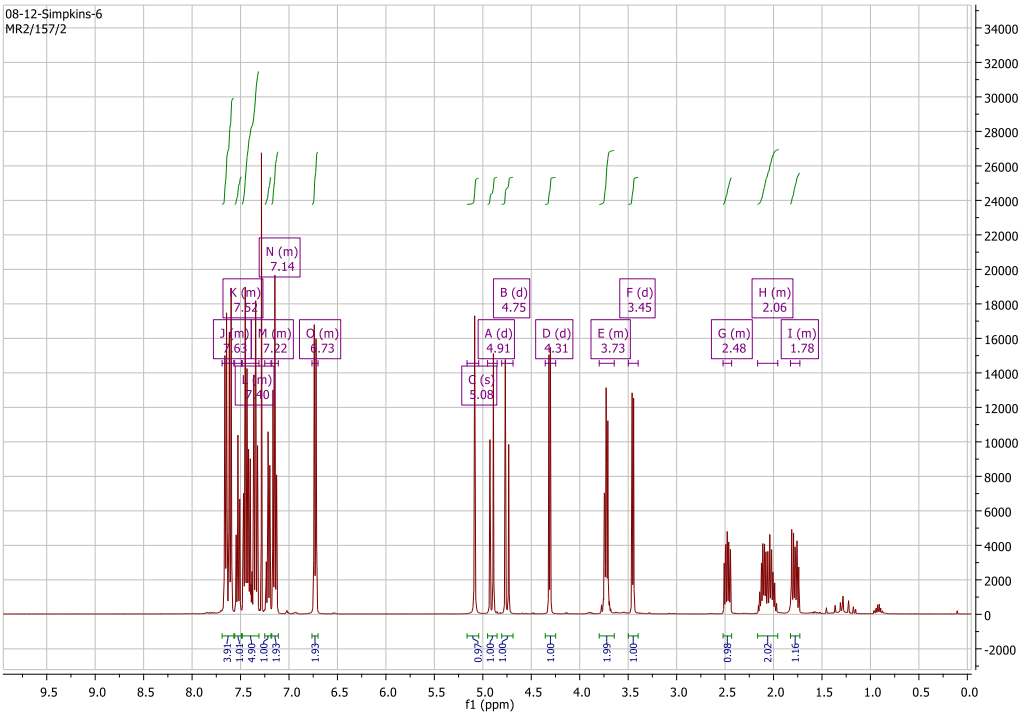
134

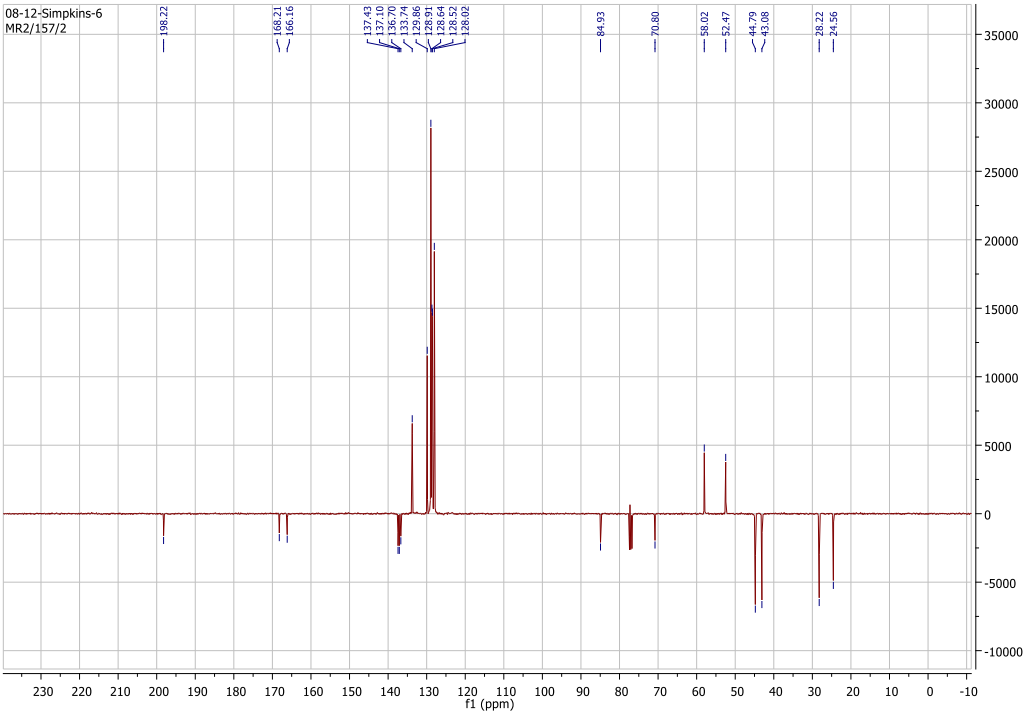

02-14-Simpkins-34
MR1/068/2
H (m) 7.33
G (m) 7.47
F (d) 4.98
E (d) 5.04
B (m) 3.62
A (m) 3.91
D (s) 1.94
C (m) 2.12
f1 (ppm)


10-29-Simpkins-46
MR1/014/1
205.40
170.86
157.89
152.00
135.41
129.67
128.67
128.33
68.55
45.18
44.25
37.10
34.16
33.11
29.87
19.60
f1 (ppm)


Ph
O
Ph
O
Bn
OH
N
N
O

159


08-12-Simpkins-6
MR2/157/2
N (m) 7.14
K (m) 7.52
B (d) 4.75
F (d) 3.45
H (m) 2.06
J (m) 7.63
M (m) 7.22
O (m) 6.73
A (d) 4.91
D (d) 4.31
E (m) 3.73
G (m) 2.48
I (m) 1.78
L (m) 7.40
C (s) 5.08
f1 (ppm)


08-12-Simpkins-6
MR2/157/2
198.22
168.21
166.16
137.43
137.10
136.70
133.74
129.86
128.91
128.64
128.52
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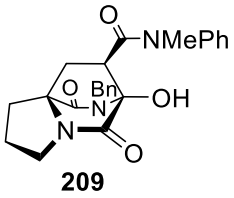
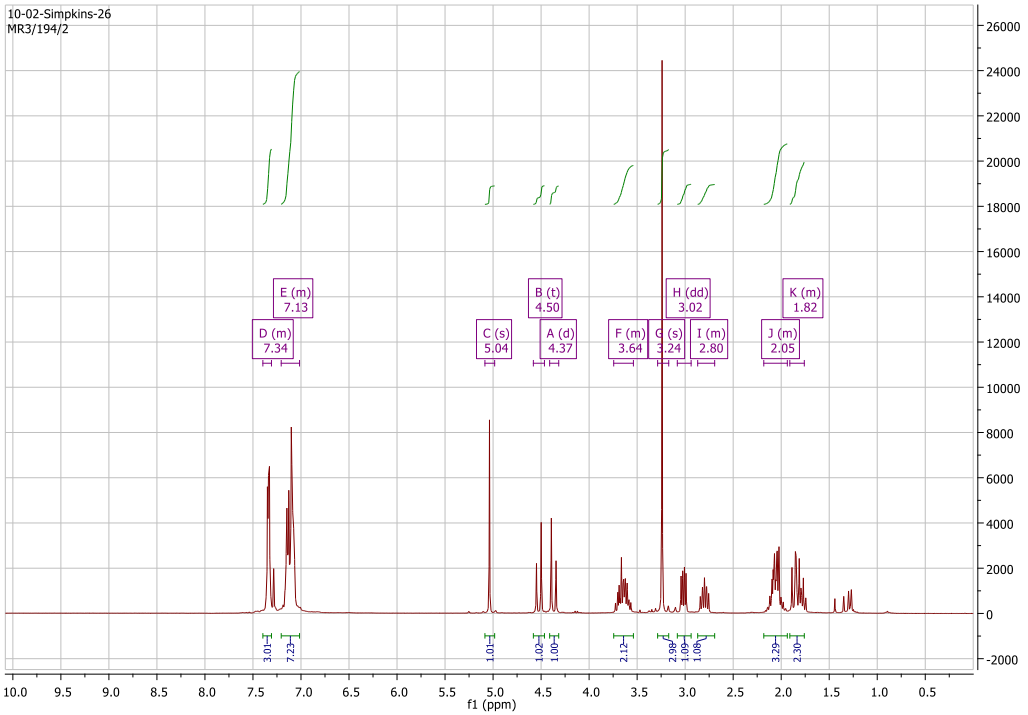
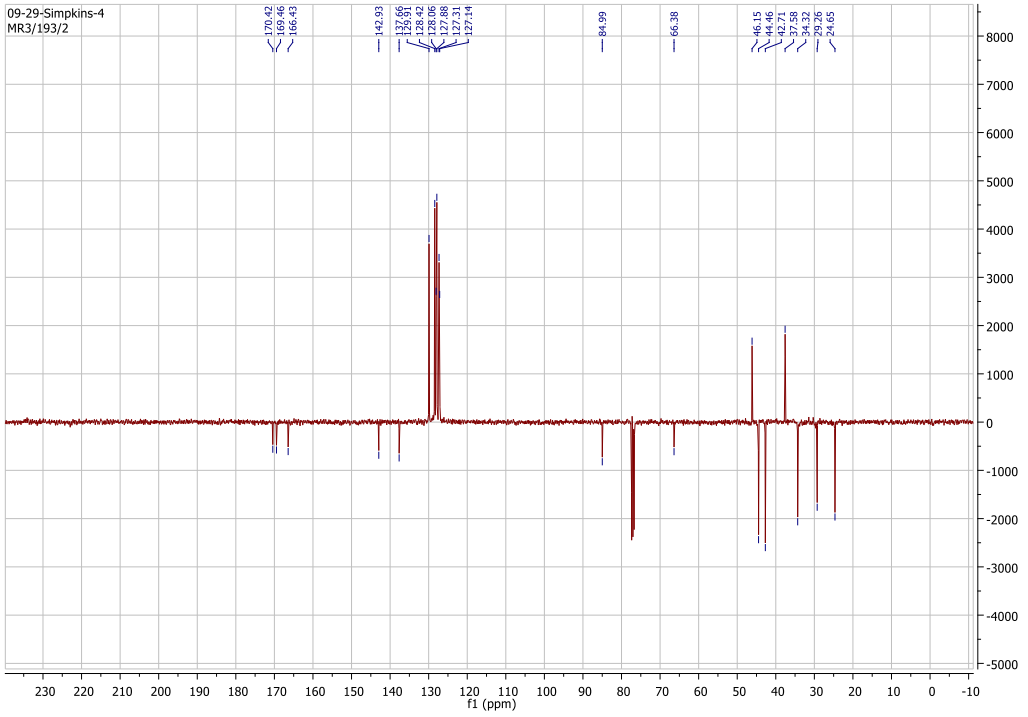
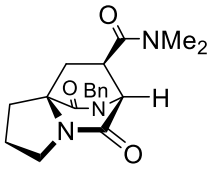
44.79
43.08
28.22
24.56
f1 (ppm)


O
NMePh
O
Bn
OH
N
N
O

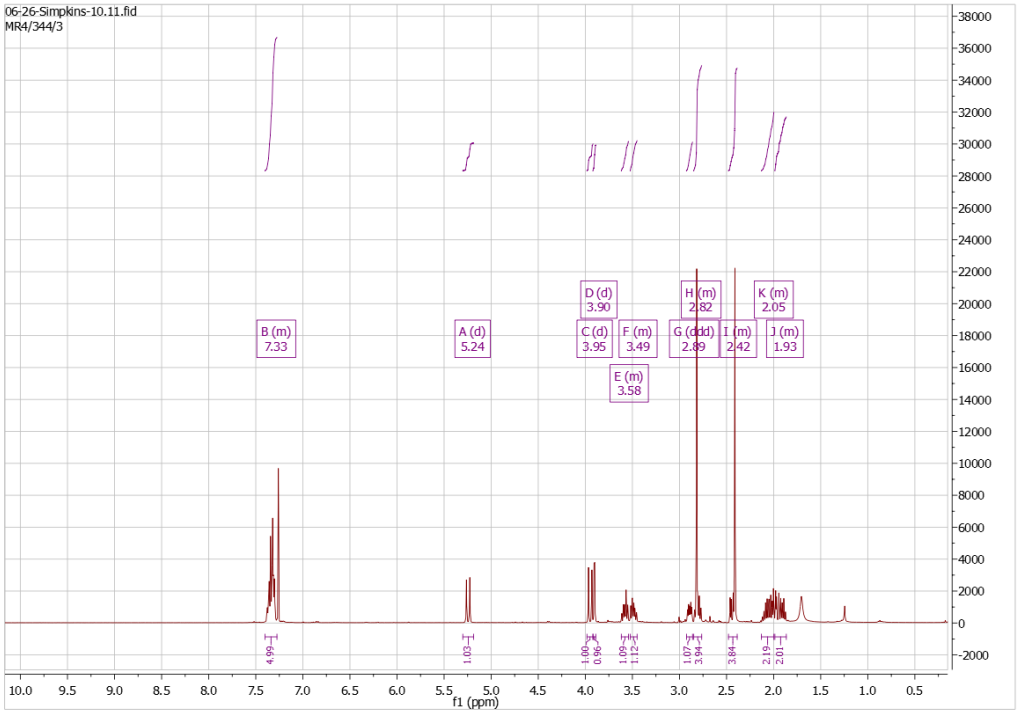
209

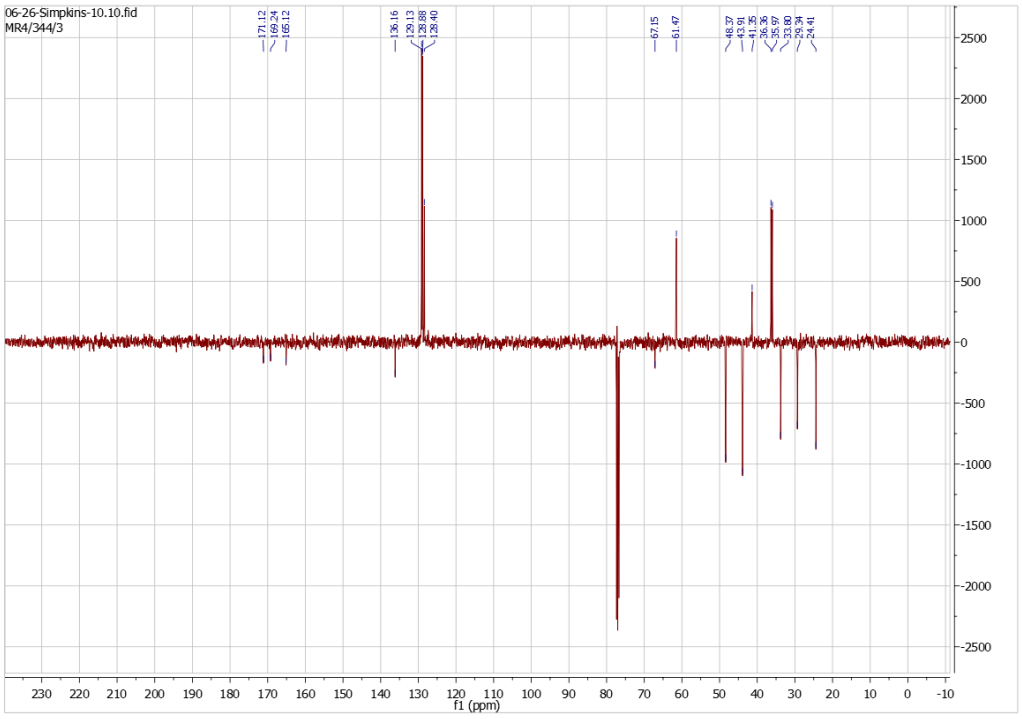

10-02-Simpkins-26
MR3/194/2
E (m) 7.13
D (m) 7.34
C (s) 5.04
B (t) 4.50
A (d) 4.37
F (m) 3.64
G (s) 3.24
H (dd) 3.02
I (m) 2.80
K (m) 1.82
J (m) 2.05
f1 (ppm)


09-29-Simpkins-4
MR3/193/2
170.42
169.46
166.43
142.93
137.66
129.01
128.42
128.06
127.88
127.31
127.14
84.99
66.38
46.15
44.46
42.71
37.58
34.32
29.76
24.65
f1 (ppm)


O
NMe2
O Bn
N
H
N
O

256


06-26-Simpkins-10.11.fid
MR4/344/3
B (m) 7.33
A (d) 5.24
D (d) 3.90
C (d) 3.95
F (m) 3.49
E (m) 3.58
H (m) 2.82
G (ddd) 2.89
I (m) 2.42
K (m) 2.05
J (m) 1.93
f1 (ppm)


06-26-Simpkins-10.10.fid
MR4/344/3
171.12
169.24
165.12
136.16
129.13
128.88
128.40
67.15
61.47
48.37
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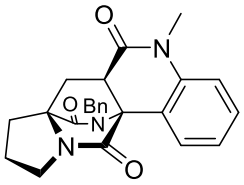
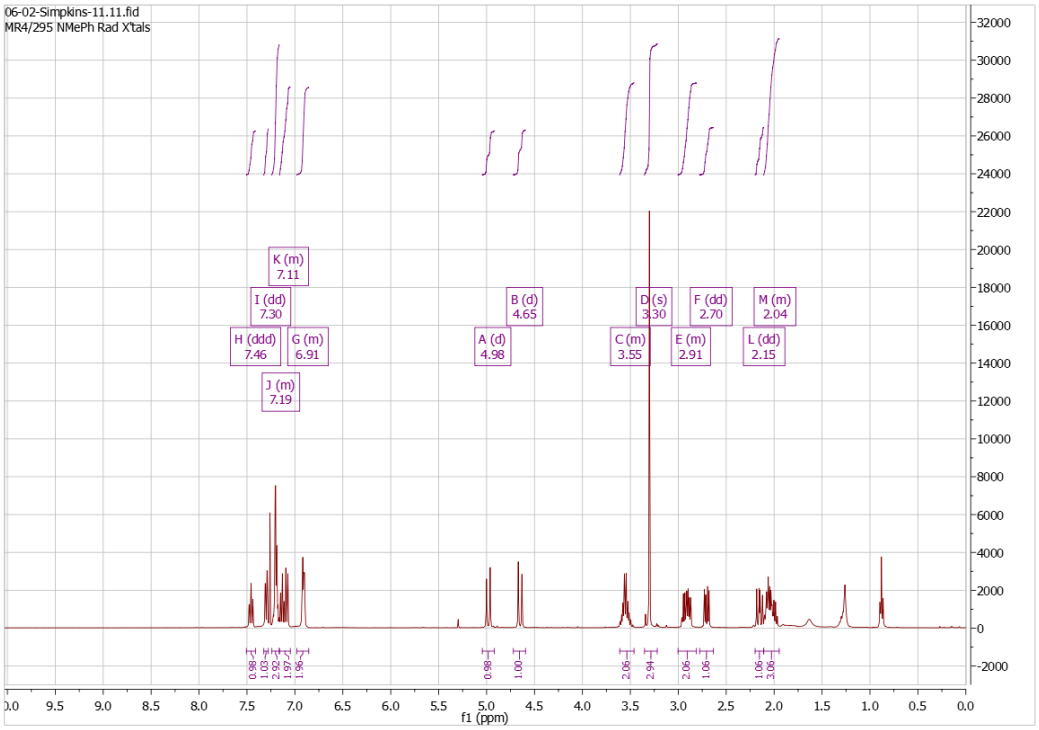
35.97
33.80
29.34
24.41
f1 (ppm)



250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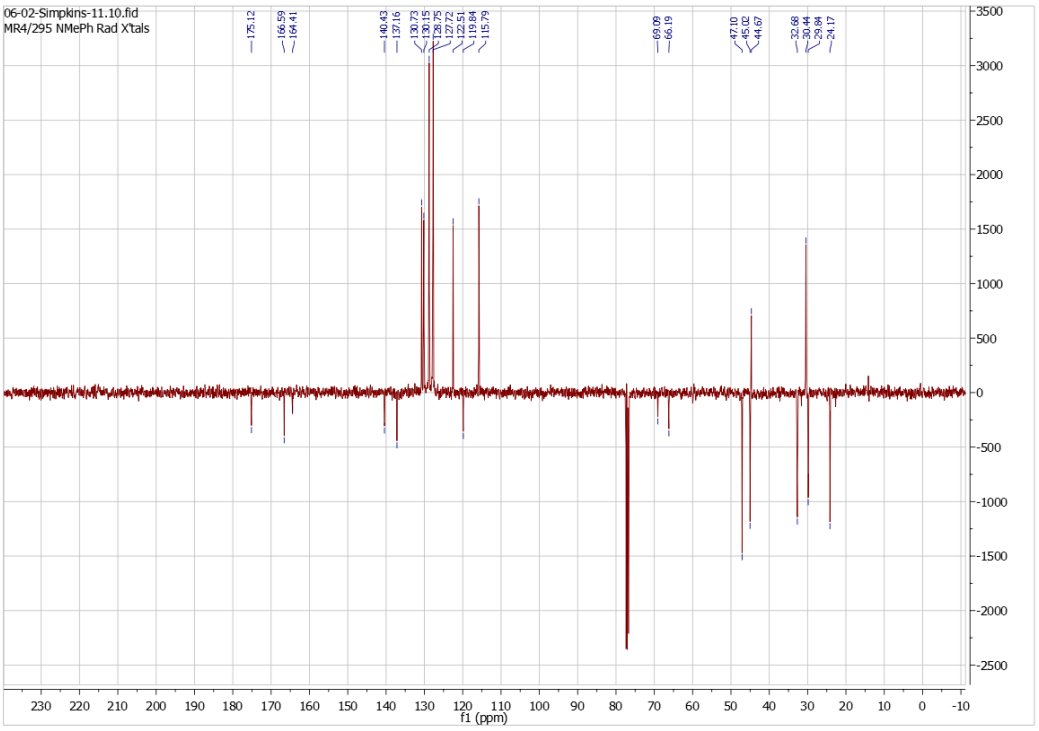
MR4/295 NMePh Rad X'tals
K (m) 7.11
I (dd) 7.30
H (ddd) 7.46
G (m) 6.91
J (m) 7.19
B (d) 4.65
A (d) 4.98
D (s) 3.30
C (m) 3.55
F (dd) 2.70
E (m) 2.91
M (m) 2.04
L (dd) 2.15
f1 (ppm)


06-02-Simpkins-11.10.fid
MR4/295 NMePh Rad X'tals
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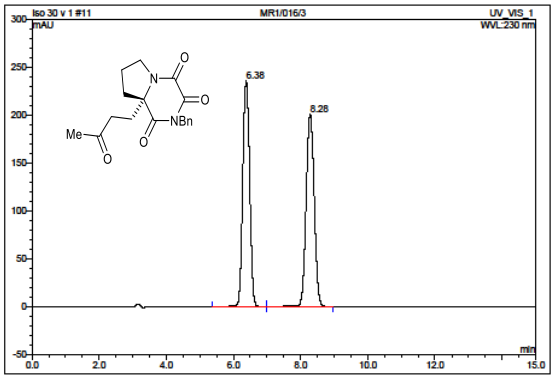
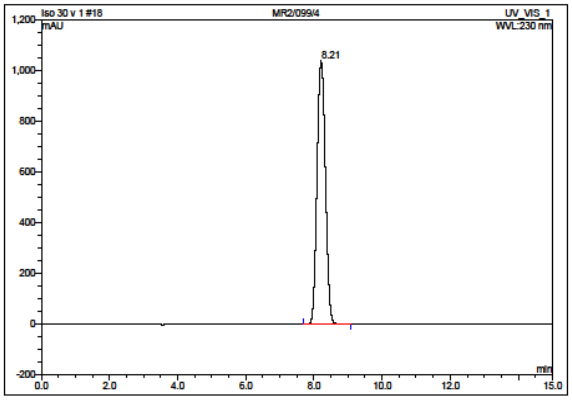
166.59
164.41
140.43
137.16
130.73
130.15
128.35
127.72
122.51
119.84
115.79
69.09
66.19
47.10
45.02
44.62
32.68
30.44
29.94
24.17
f1 (ppm)

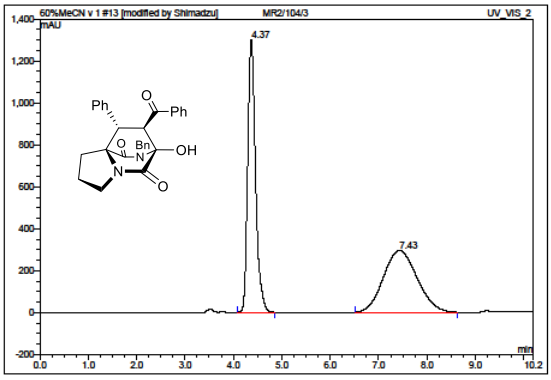
Select HPLC Traces



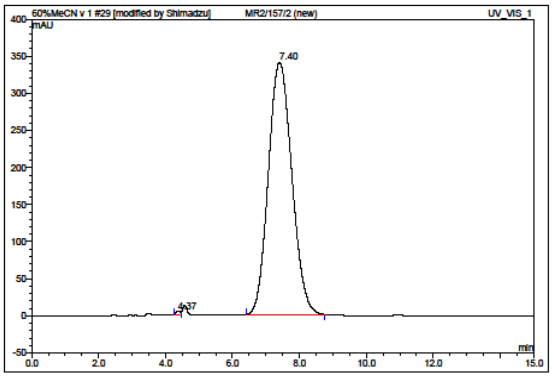
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.38	n.a.	236.101	56.044	49.99	n.a.	BMB
2	8.28	n.a.	200.330	56.066	50.01	n.a.	BMB
Total:			436.431	112.109	100.00	0.000	



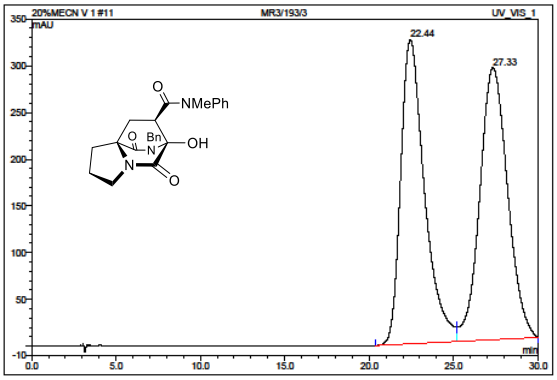
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.21	n.a.	1037.047	294.532	100.00	n.a.	BMB
Total:			1037.047	294.532	100.00	0.000	



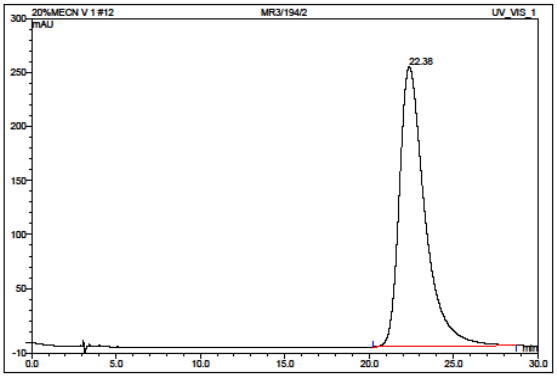
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.37	n.a.	1300.514	243.025	50.58	n.a.	BMB*
2	7.43	n.a.	294.241	237.415	49.42	n.a.	BMB*
Total:			1594.755	480.439	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	4.37	n.a.	4.619	0.608	0.22	n.a.	BM *
2	7.40	n.a.	340.365	275.979	99.78	n.a.	BMB*
Total:			344.984	276.587	100.00	0.000	

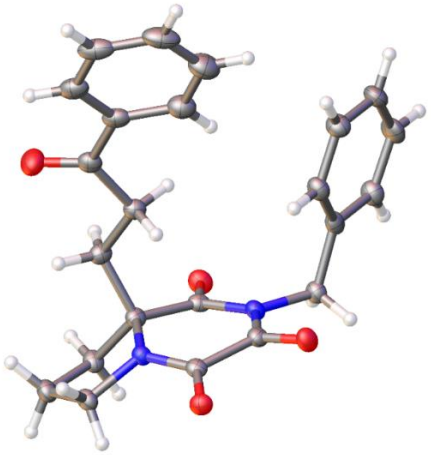


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.44	n.a.	325.715	532.773	48.85	n.a.	BM
2	27.33	n.a.	290.597	557.840	51.15	n.a.	MB
Total:			616.312	1090.613	100.00	0.000	

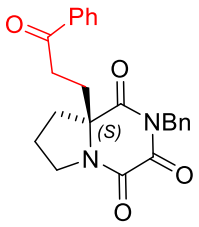


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	22.38	n.a.	259.059	453.236	100.00	n.a.	BMB
Total:			259.059	453.236	100.00	0.000	

X-ray Data



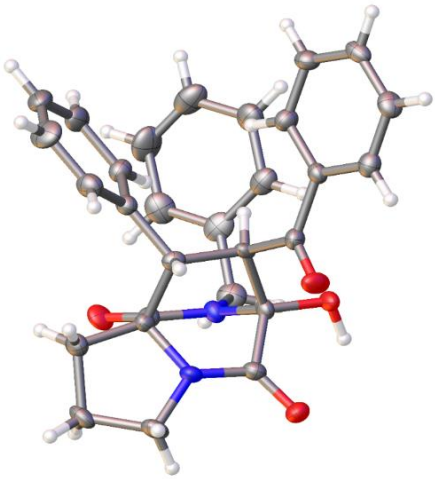
≡



151

Identification code	**151**
Empirical formula	$C_{23}H_{22}N_2O_4$
Formula weight	390.44
Temperature/K	N/A
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.84241(14)
b/Å	13.0771(2)
c/Å	24.8049(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1895.14(7)
Z	4
ρ_{calc}g/cm^3	1.3683
μ/mm^{-1}	0.769
F(000)	826.7
Crystal size/mm^3	0.3385 × 0.0368 × 0.0229
Radiation	Cu Kα (λ = 1.54184)

2Θ range for data collection/°	7.12 to 140.06
Index ranges	$-5 \leq h \leq 6$, $-16 \leq k \leq 16$, $-31 \leq l \leq 30$
Reflections collected	**179**69
Independent reflections	3553 [R_{int} = 0.0489, R_{sigma} = 0.0348]
Data/restraints/parameters	3553/0/261
Goodness-of-fit on F^2	1.114
Final R indexes [I>=2σ (I)]	R_1 = 0.0403, wR_2 = 0.1015
Final R indexes [all data]	R_1 = 0.0470, wR_2 = 0.1038
Largest diff. peak/hole / e $Å^{-3}$	0.34/-0.31
Flack parameter	0.0(2)



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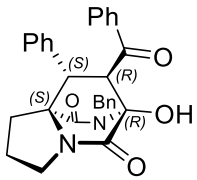
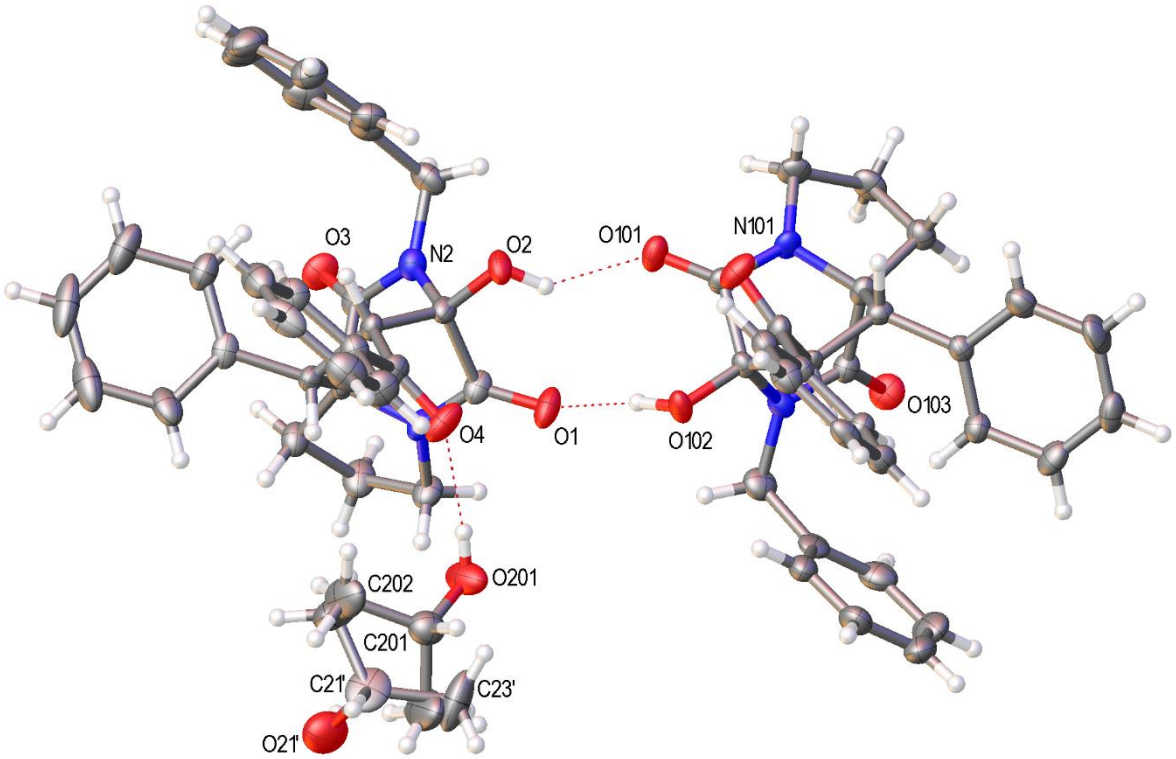
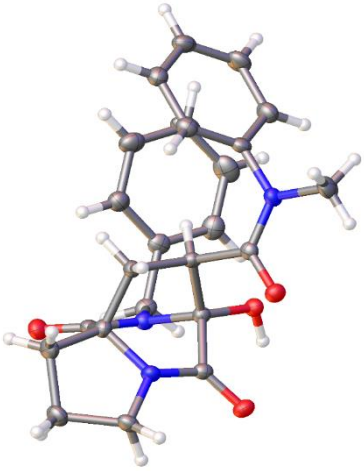


159

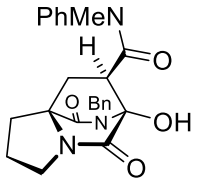


Identification code	**159**
Empirical formula	$C_{30.5}H_{30}N_2O_{4.5}$
Formula weight	496.56
Temperature/K	100.00(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$

a/Å	8.73850(10)
b/Å	8.77985(12)
c/Å	65.4284(6)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	5019.84(10)
Z	8
$\rho_{calc}g/cm^3$	1.314
μ/mm^{-1}	0.713
F(000)	2104.0
Crystal size/mm^3	0.3083 × 0.2449 × 0.1824
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	12.946 to 140.118
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-79 \leq l \leq 79$
Reflections collected	72415
Independent reflections	9525 [R_{int} = 0.0465, R_{sigma} = 0.0234]
Data/restraints/parameters	9525/13/715
Goodness-of-fit on F^2	1.123
Final R indexes [I>=2σ (I)]	R_1 = 0.0490, wR_2 = 0.1100
Final R indexes [all data]	R_1 = 0.0496, wR_2 = 0.1104
Largest diff. peak/hole / e $Å^{-3}$	0.24/-0.24
Flack parameter	0.01(6)



≡



209

Identification code	**209**
Empirical formula	$C_{24}H_{25}N_3O_4$
Formula weight	419.47
Temperature/K	100.01(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	10.50637(13)
b/Å	9.14301(12)
c/Å	11.61629(15)
α/°	90
β/°	110.5829(14)
γ/°	90
Volume/Å^3	1044.63(3)
Z	2
ρ_{calc}g/cm^3	1.334
μ/mm^{-1}	0.748
F(000)	444.0
Crystal size/mm^3	0.2137 × 0.1306 × 0.0679
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	12.648 to 144.19

Index ranges	$-12 \leq h \leq 12$, $-10 \leq k \leq 11$, $-14 \leq l \leq 14$
Reflections collected	36789
Independent reflections	4014 [R_{int} = 0.0302, R_{sigma} = 0.0145]
Data/restraints/parameters	4014/1/289
Goodness-of-fit on F^2	1.103
Final R indexes [I>=2σ (I)]	R_1 = 0.0308, wR_2 = 0.0818
Final R indexes [all data]	R_1 = 0.0321, wR_2 = 0.0829
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.16
Flack parameter	-0.01(5)

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