TOWARDS THE TOTAL SYNTHESIS OF CALYCIPHYLLINE A-TYPE *DAPHNIPHYLLUM* ALKALOIDS



A thesis submitted in partial fulfilment of the requirement for the

degree of Doctor of Philosophy (DPhil)

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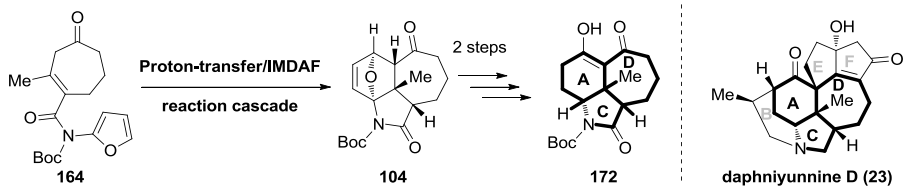
Abstract

Towards the total synthesis of calyciphylline A-type *Daphniphyllum* alkaloids

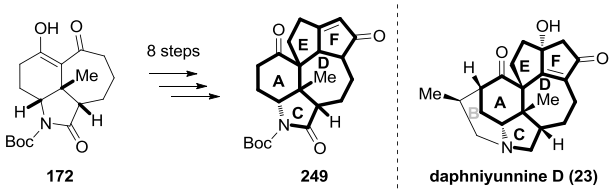
Iacovos N. Michaelides St. Hugh's College DPhil Trinity term 2014

This thesis details the studies towards the total synthesis of the calyciphylline A-type *Daphniphyllum* alkaloids, with a particular focus on daphniyunnine D (**23**).

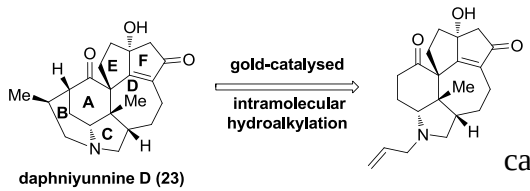
Chapter 1 introduces these biologically and synthetically interesting polycyclic natural products and describes our designed approach towards their synthesis. Separate studies targeting the construction of two tricyclic ring systems have been developed. These provide rapid entry to synthetically versatile intermediates, allowing for the potential synthesis of numerous members of the alkaloid family.



Chapter 2 describes the first study which focuses on the construction of the main tricyclic [6–5–7] ACD core **172** *via* a proton-transfer/IMDAF reaction cascade as the main step. Large scale synthesis of the precursor to this cascade **164** has allowed for the successful investigation of an asymmetric variant giving rise to an enantioenriched adduct **104**.



Chapter 3 describes a novel design for the construction of the [7–5–5] DEF tricycle common to 100+ *Daphniphyllum* alkaloids. An IMPKR, double-bond migration, allylic oxygenation protocol was first validated on a model system and later applied in combination with the synthetic route developed in chapter 2 to achieve the construction of the [6–5–7–5–5] ACDEF pentacycle **249**.



Chapter 4 focuses on the construction of the piperidine ring B *via* an intramolecular gold-catalysed 6-*exo*-*trig* hydroalkylation. During the development of the route to daphniyunnine D, various intermediates were afforded which were further elaborated to provide appropriate cyclisation substrates for this study. Their synthesis combined with proof of principle experiments for the desired cyclisation conclude this dissertation work.

Declarations and copyright

I declare that thesis has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree at this or any other university or institute of learning. Any work done in collaboration with a research colleague has been fully acknowledged and referenced within the text. All compounds in the experimental chapter 5 were synthesised and characterised by myself unless otherwise stated.

I was admitted as a probationary research student in October 2010 and as a candidate for the degree of Doctor of Philosophy in October 2011; the higher study for which this is a record was carried out in the University of Oxford between 2010 and 2014.

Iacovos N. Michaelides

Date Signature of candidate:

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Acknowledgements

First and foremost I would like to thank Darren, for giving me the opportunity to work in his research group and for being such an enthusiastic supervisor these past years. Convincing me to take on the "Daphny" project at the end of my undergraduate degree is something that I will always be grateful to him for.

Working in the Dixon group has been one of the most interesting working environments I've ever experienced. Thank you all for making it such an interesting if not enjoyable place to work in!

To my laboratory mentor, Dr. Benjamin Darses, I owe my deepest gratitude. His patience, enthusiasm and support has been inspirational. I would also like to thank the other members of the Daphny-crew: Filippo, Bal, Pando and Pavol for all their help and advice during the course of this project. My gratitude also goes to Yusuke Ogura, whose enthusiasm for total synthesis can convince anyone that anything and everything is possible in one year. Thanks also for your insight in life's most important "thing". Your friendship these last 2 years has been a great bonus to working in G5.

Eddy, Andrew and Dave; you were greatly missed these last two years. From counterstrike, to road trips in the Bayous, to football games in Scotland, to deep fried pizzas, its been educational. CONFIDEMUS

Jin and Matt, thank you for spending hours booking, running and solving my crystal structures!

A BIG BIG thank you to all my proof readers: Bal, Yusuke, Matt, Allegra, Daniel, Joanna. Thanks for your constructive criticism and for selflessly setting aside a significant amount of time to help me out; much obliged. Joanna, thanks for your patience and understanding these past few months.

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Thank you to the viras, for their alternative way of supporting me during these past 4 years.

Finally, I would like to thank my father and mother to whom I owe everything, including this thesis. You have been unconditionally supportive of all my choices and for that I am forever grateful. Thank you for all your encouragement during the years, especially during the difficult moments.

Abbreviations

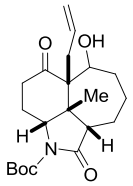
°C	Degrees Celsius
Å	Ångström
Ac	Acetyl
Acac	acetylacetonato
AcOH	Acetic acid
AIBN	2,2′-Azobis(2-methylpropionitrile)
Aq	Aqueous
App	Apparent
Ar	Aryl
atm	atmosphere
9-BBN	9-Borabicyclo[3.3.1]nonane
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	2,2'-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1´-binaphtalene-2,2´-diol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bp	Boiling point
br	Broad
brsm	Based on recovered starting material
n-Bu	*n*-Butyl
CAN	Ceric ammonium nitrate
Cbz	carboxybenzyl
Cod	1,5-cyclooctadiene
Conc	Concentration
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
DA	Diels–Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
DEPT	Distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPP	Diphenylphosphate
dppe	1,2-Bis(diphenylphosphino)ethane
dq	Doublet of quartets
dr	Diastereoisomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron impact
equiv	equivalents
ES	ElectroSpray Ionisation
Et	Ethyl
EDG	Electron donating group
EWG	Electron withdrawing group
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
fcc	Flash column chromatography
FI	Field ionisation
G	Gram
H	Hour(s)
HOMO	Highest occupied molecular orbital
HMBC	Heteronuclear multiple-bond correlation experiment
HPLC	High performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear single-quantum coherence experiment
Hz	Hertz
IEDDA	Inverse-electron-demand Diels–Alder
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
IMDAF	Intramolecular Diels–Alder of furan
IMPKR	Intramolecular Pauson–Khand reaction
IPA	*Iso*-propylalcohol
IPr	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
J	Coupling constant
JohnPhos	Au[P(*t*-Bu)$_2$(*o*-biphenyl)]
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide

LUMO	Lowest unoccupied molecular orbital
[M]	Metal complex
M	Molar concentration
m	Multiplet
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Mega hertz
Min	Minute(s)
mL	Millilitre
µL	Microlitre
mmol	Millimole
mM	millimolar
MO	Molecular orbital
Mol	mole
MOM	methoxymethyl
mp	Melting point
MS	Molecular sieves
MS	Low resolution mass spectrometry
Ms	Methanesulfonyl
m/z	Mass to charge ratio
NBD	norbornadiene
NMR	Nuclear Magnetic Resonance
NMO	4-Methylmorpholine *N*-oxide
Ns	*Para*-nitrobenzenesulfonyl
nOe	Nuclear Overhauser Effect
Nu	nucleophile
o	Ortho
OH	Hydroxy
OTf	Trifluoromethanesulfonate
p	*para*
PE	Petroleum ether bp 30-40 °C
PG	Protecting group
Ph	Phenyl
PKTR	Pauson–Khand type reaction
PKR	Pauson–Khand reaction
PMB	*Para*-methoxybenzyl
PMP	*Para*-methoxyphenyl
ppm	Parts per million
Pr	propyl
q	Quartet
R	Generic substituent
rac	Racemic
R_f	Retardation factor
Rochelle salt	*L*-(+)-tartaric acid potassium sodium salt
r.r.	Regioisomeric ratio
quint	Quintet
RCM	Ring-closing metathesis
rt	Room temperature
s	Singlet
sxt	Sextet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBAB	Tetrabutylammonium bromide
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
Temp	temperature
t/*tert*	*tertiary*
Tf	triflate
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMANO	Trimethylamine N-oxide
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
t_R	Retention time (HPLC)
Ts	*Para*-toluenesulfonyl
TS	Transition state
p-TsCl	*Para*-toluenesulfonyl chloride
p-TsOH	*Para*-toluenesulfonic acid
UV	ultraviolet

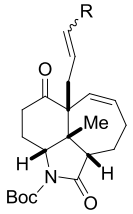
Stereochemistry

Stereochemistry is drawn as proposed by Maehr.[i]

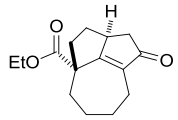
Normal bond thickness indicates racemic compounds (if only one stereocentre is present) or connectivity where the relative or absolute configuration is unknown (if more than one stereocentre is present) (a). A wavy bond indicates connectivity leading to a mixture of diastereoisomers (or enantiomers if it is the only stereocentre) (b). Solid and broken lines indicate diastereopure or diastereoenriched racemic compounds where the relative configuration is known (c). Solid and broken wedges indicate enantiopure or enantioenriched compounds where the absolute configuration is known (d). Furthermore, known absolute stereochemistry (i.e. known rotation of plane-polarised light) is designated by use of the symbols (–), (+), (±); (e).

(a) 

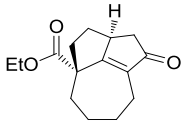
Relative configuration of the diastereoisomeric C-OH bond is unknown.

(b) 

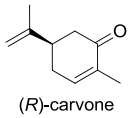
A mixture of *Z* and *E* diastereoisomers exist.

(c) 

Diastereopure or diastereoenriched racemic compound with known relative configuration.

(d) 

Enantiopure or enantioencriched compound with known absolute configuration.

(e) 

(*R*)-carvone indicates the drawn absolute configuration. The name (–)-carvone indicates that the absolute stereochemistry is also known.

[i] H. Maehr, *J. Chem. Educ*. **1985**, *62*, 114.

Chapter 1: Introduction

1.1 The Daphniphyllum alkaloids

The *Daphniphyllum* alkaloids are a family of over 250 natural products isolated from 15 species of the genus *Daphniphyllum*, a genus of dioecious evergreen trees and shrubs endemic to Asia (Japan, New Guinea, India, central China and Taiwan).[1] Although the first isolation was reported in 1909 by Yagi,[2] it was not until 1966 that Hirata and Yamamura accomplished the first structural elucidation of an alkaloid of this family which they appropriately named daphniphylline.[3] Since their seminal report, hundreds of *Daphniphyllum* alkaloids consisting of unique and stereochemically complex structures have been isolated, with new reports in the literature dating up to and including 2014.[4] Owing to the large number of family members, these alkaloids have been classified into 14 types based on the architectural design of their comprising polycyclic structural motifs (daphniphylline, secodaphniphylline, yuzurimine, daphnilactone A, daphnilactone B, yuzurine, bukittinggine, daphnezomines, daphnicyclidins, daphmanidins, daphniglaucins, calyciphyllines, paxdaphnine A, daphlongeranines). Demonstrating the variation in structural complexity, Figure 1 represents the polycyclic skeletons common to eight of these sub-types of the *Daphniphyllum* alkaloid family.

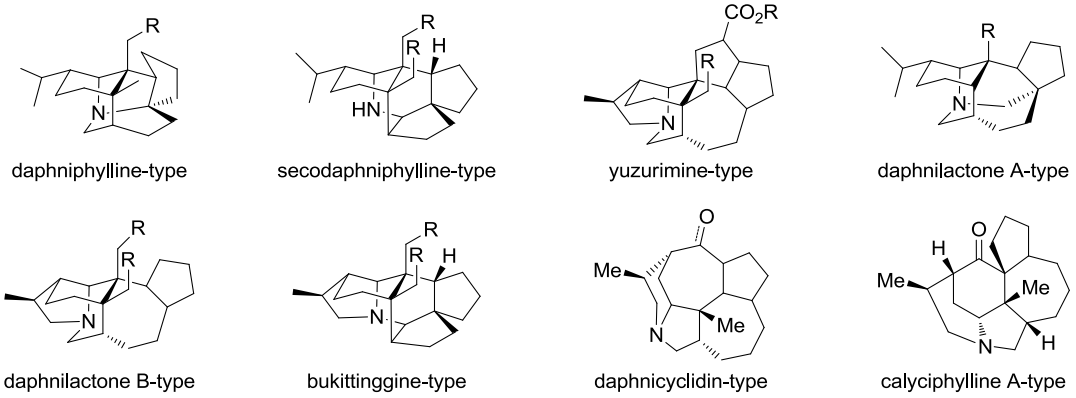


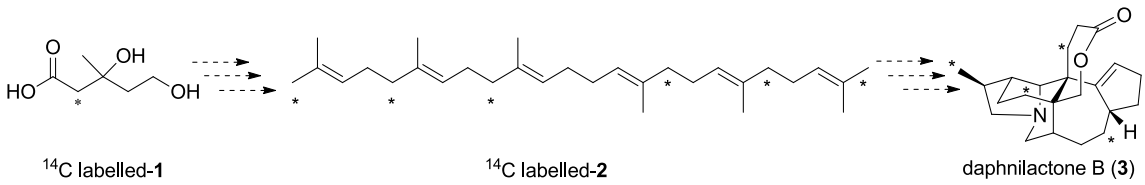
Figure 1: Representative skeletons of 8 types of *Daphniphyllum* alkaloids.

Because of their structural complexity, combined with the intriguing biological activities exhibited in some cases (antioxidant, anti-HIV,[4] elevation of nerve growth factor, antiplatelet activating factor, vasorelaxant, anti-tumour, pesticide and insecticide activities),[1] these alkaloids have received significant interest from the synthetic community.[5]

1.2 Biosynthetic studies

The *Daphniphyllum* alkaloids can be further described as pseudoalkaloids, cryptoalkaloids or terpenoid-alkaloids.[6] These alternative descriptions stem from their biosynthetic origin. In the biosynthesis of "true alkaloids", Nature implements amino acids for the construction of their skeleton as well as for the incorporation of their characteristic nitrogen atom.[6] As the name suggests, much like terpenes, the carbon backbone of terpenoid-alkaloids is constructed from prenyl units. Furthermore, the nitrogen source for these alkaloids is thought to be primary amines like methylamine, pyridoxamine,[7] ethylamine and 2-aminoethanol.

In 1973, Suzuki and Yamamura confirmed the terpenoid origin of the *Daphniphyllum* alkaloids by conducting feeding experiments on the leaves of *D. macropodum* and the fruits of *D. teijsmanni* using ^{14}C labelled (*RS*)-mevalonic acid (**1**) and ^{14}C labelled squalene (**2**).[8] Degradation studies on the isolated alkaloidal components led them to conclude that the natural products daphniphylline and codaphniphylline were biosynthesised *via* a squalene-like intermediate from six equivalents of **1**, whereas four equivalents were incorporated in daphnilactone B (**3**) (Scheme 1).



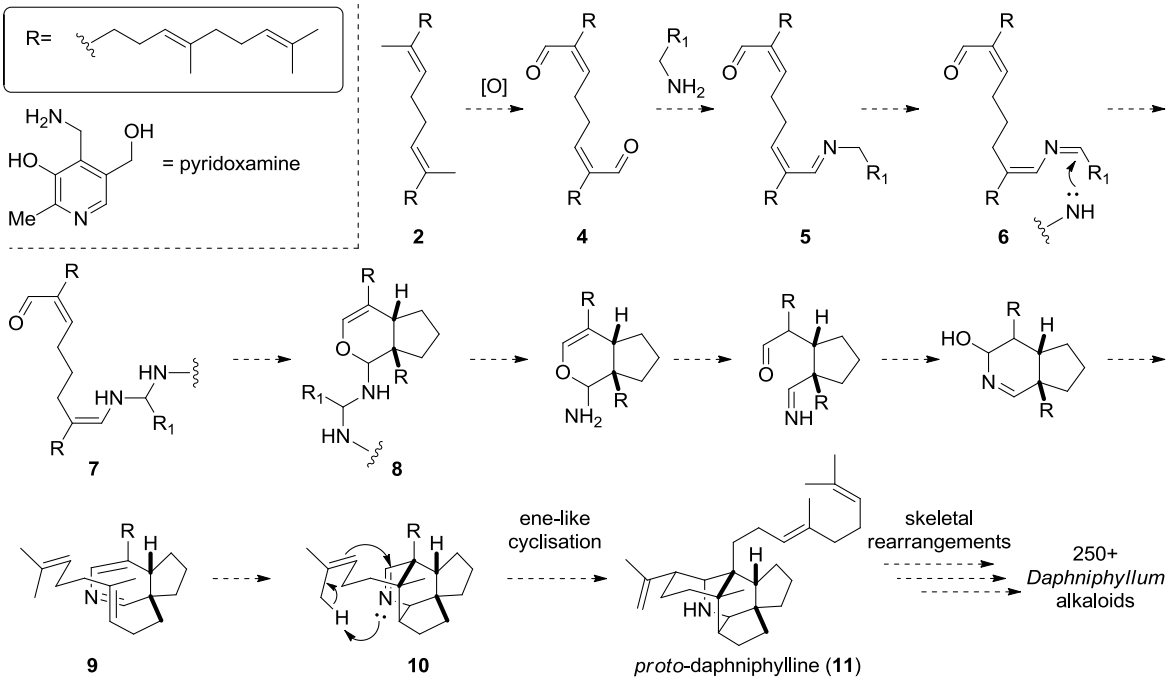
Scheme 1: Incorporation of (*RS*)-mevalonic acid (1) in daphnilactone B (3). Asterisks indicate ^{14}C labelling.

Although insightful, these experiments were not designed to ascertain the manner in which the nitrogen atom is introduced in these complex natural products. This missing link in their biosynthesis has been thoroughly studied by the Heathcock group. In an overview of the group's studies titled: "*Nature knows best: an amazing reaction cascade is uncovered by design and discovery*",[9] Heathcock points out the importance of investigating biosynthetic pathways. Furthermore he describes how insight into "Nature's design" can assist the synthetic chemist to construct complex polycyclic targets in a rapid and elegant manner.

As outlined in Heathcock's proposed biosynthesis shown in Scheme 2, the first step towards the formation of these terpenoid-alkaloids is the oxidation of squalene (**2**) to the dialdehyde **4**.[9,10] Subsequently, a primary amine (amino acid or pyridoxamine)[7] could react with one of the aldehydes to form imine **5** which could undergo a prototropic rearrangement to give enimine **6**. As enimine double bonds are not particularly nucleophilic, they then proposed that a nucleophilic species could add to the imine double bond and form enamine **7**. Subsequently, an enamine/enal can undergo an overall [4+2] cycloaddition[11] to give rise to the dihydropyran **8**.[i] Following its formation, a series of addition/elimination processes can form the dihydropyridine **9** which is then perfectly poised to undergo a Diels–Alder cycloaddition to give tetracycle **10**. A final ene-like cyclisation then affords the "*primordial*" *proto*-daphniphylline (**11**). It is widely accepted

[i] No details of the mechanism are made in reference 11, nor in Heathcock's publications. A true hetero Diels–Alder could be envisaged as well as a tandem Michael addition/cyclisation cascade.

that subsequent skeletal rearrangements of this pentacycle afford the scaffolds found in all 250+ related *Daphniphyllum* alkaloids.[1]



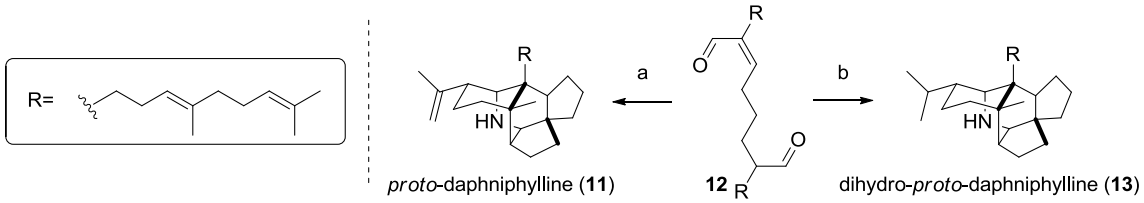
Scheme 2: Heathcock's proposed biosynthesis for the *Daphniphyllum* alkaloids.

1.3 Biomimetic synthesis

By synthesising building blocks similar in structure to the intermediates proposed in their biosynthetic pathway, Heathcock and co-workers were able to achieve the biomimetic synthesis of numerous *Daphniphyllum* alkaloids; thus confirming many of their postulations.

Perhaps the most impressive testament to their biomimetic approach is the synthesis of *proto*-daphniphylline (**11**) *via* a single step pentacyclisation. Treating the dihydrosqualene dialdehyde **12** with ammonia and warm acetic acid afforded the product in a reasonably high 15% yield; considering the complexity of the transformation (Scheme 3a). Moreover, replacing ammonia with methylamine, they accomplished the diastereoselective synthesis

of its reduced form, dihydro-*proto*-daphniphylline (**13**) in an impressive 65% yield, constructing five rings in a single step (Scheme 3b).

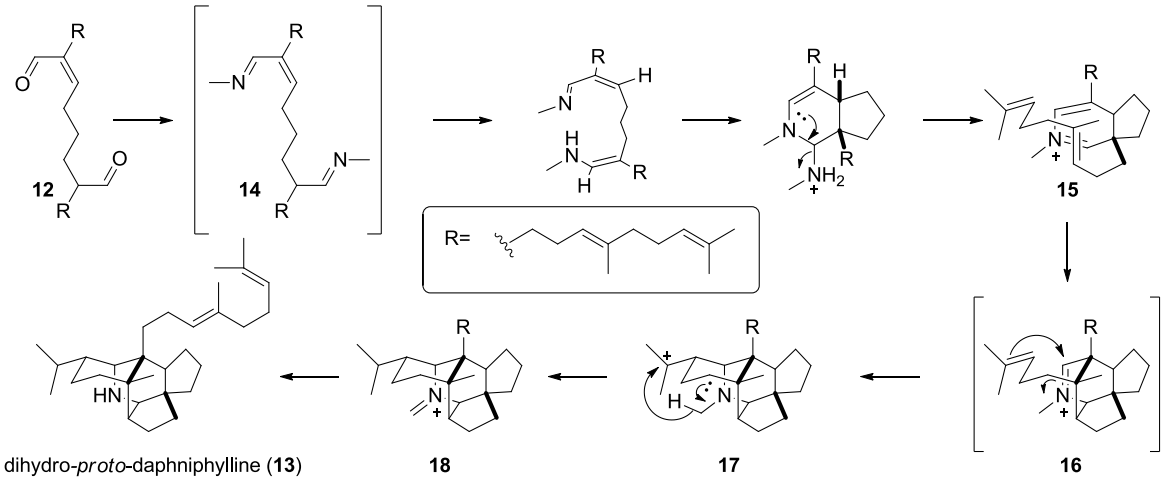


Scheme 3: Heathcock's one-pot biomimetic pentacyclisation. Reaction conditions: (a) NH_3, NEt_3·HCl, CH_2Cl_2, rt, 16 h, then NH_4OAc, AcOH, 80 °C, 3 h, 15%; (b) $MeNH_2$, NEt_3, CH_2Cl_2/DMSO, rt, 2 h, then AcOH, 80 °C, 11 h, 65% (including the yield for the formation of the dialdehyde *via* a Swern oxidation).

In their proposed mechanism, the methylamine condenses onto the aldehyde to form the bisimine intermediate **14** which was in fact isolated and characterised in a separate experiment (Scheme 4). Subsequently, a formal cycloaddition presumably takes place to provide the dihydropyridinium ion **15** after an elimination of a methylamine.[i] At this point it is believed that a concerted inverse electron demand Diels–Alder cycloaddition[12] takes place to provide the *N*-methyliminium **16**. This intermediate has also been isolated and characterised, presumably as the acetate salt. A final Prins-like cyclisation gives rise to the pentacycle **17**. A 1,5-hydride shift[ii] then occurs providing the iminium **18** which is hydrolysed on work-up to obtain dihydro-*proto*-daphniphylline (**13**). Noteworthy are the different mechanisms ammonia and methylamine induce in the final stages of this transformation. Ammonia presumably promotes an ene-type cyclisation to give rise to *proto*-daphniphylline (**11**) as proposed in the biosynthesis (Scheme 2).

[i] This formal [4+2] cycloaddition is somewhat different from their biosynthetic proposal as one double bond of the squalene has been reduced, meaning that a sufficiently nucleophilic enamine rather than an enimine can be formed. However, no details as to whether a dihydropyran is formed prior to the dihydropyridinium ion have been provided.

[ii] Perhaps the Prins-like cyclisation and the 1,5-hydride shift also take place in a concerted fashion.



Scheme 4: Proposed mechanism for the biomimetic synthesis of dihydro-*proto*-daphniphylline (13**).**

1.4 Introduction to the calyciphylline A-type alkaloids—specific focus in daphniyunnine D

Given their unique structural features, of particular interest to the Dixon group are the calyciphylline A-type *Daphniphyllum* alkaloids. Representative examples of this subclass, named after the first isolated alkaloid **19**,[13] are shown in Figure 2.

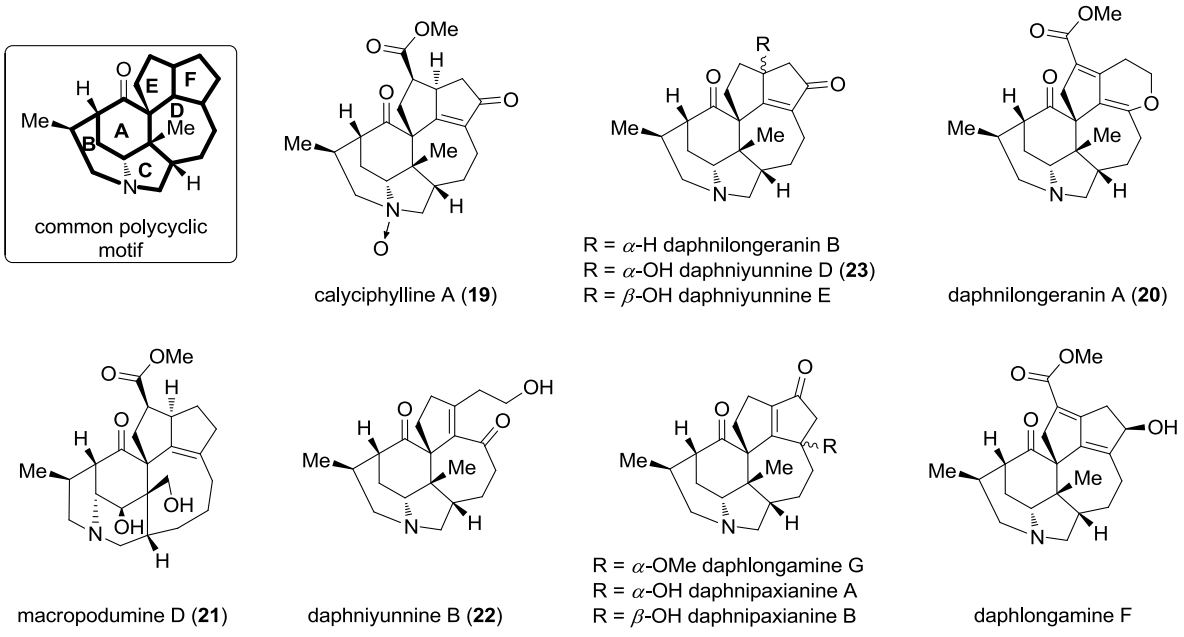


Figure 2: Representative examples of the calyciphylline A-type alkaloid subclass.

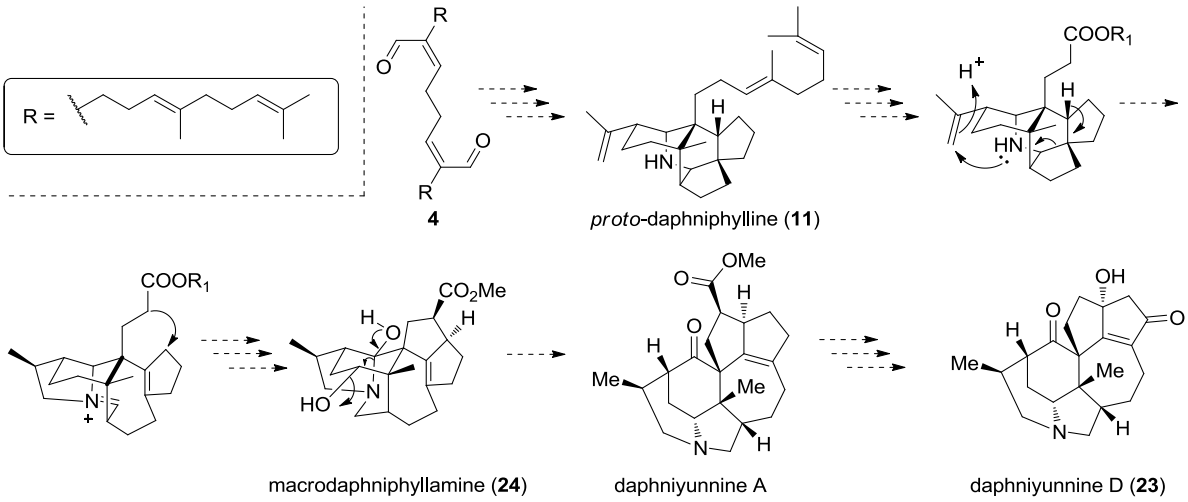
One appealing characteristic of this subclass is the ABCDEF hexacyclic structural motif that the majority of the 24 calyciphylline A-type alkaloids have in common (exceptions

include daphnilongeranin A (**20**), macropodumine D (**21**) and daphniyunnine B (**22**)). Combined with the fact that there are no reports of their total synthesis in the literature, we believed that investigation into the synthesis of this subclass of alkaloids could provide an excellent platform for novel reaction discovery.

It was desirable to develop a broad synthetic approach towards their synthesis in order to allow for the construction of numerous members as well as their derivatives. This would allow for the in-depth investigation of their biological activities. For the purposes of this project however, we needed a specific focus in order to guide our efforts, therefore daphniyunnine D (**23**) was selected as our initial target.

This alkaloid was first isolated in 2006 by Yue and co-workers from the stems and leaves of *D. yunnanense*, a shrub endemic to China.[14] Not only does it contain the common pentacyclic motif mentioned earlier, it is also one of the isolated alkaloids known to exhibit significant biological activity (cytotoxic activity against two tumour cell lines, P-388 and A-549 with IC_{50} values of 3.0 and 0.6 μM, respectively). Its architectural design consists of seven carbon-centred stereocentres, two of which are contiguous quaternary, moulding the molecule into a bowl-shaped framework typical to the sub-family's members.

In terms of its biosynthetic origin, daphniyunnine D (**23**) is thought to be generated from enzymatic manipulations of the yuzurimine-type alkaloids (e.g. macrodaphniphyllamine (**24**)) (Scheme 5).[14] In turn, these are biosynthesised *via* the primordial *proto*-daphniphylline (**11**) as proposed by Heathcock (*vide supra*).



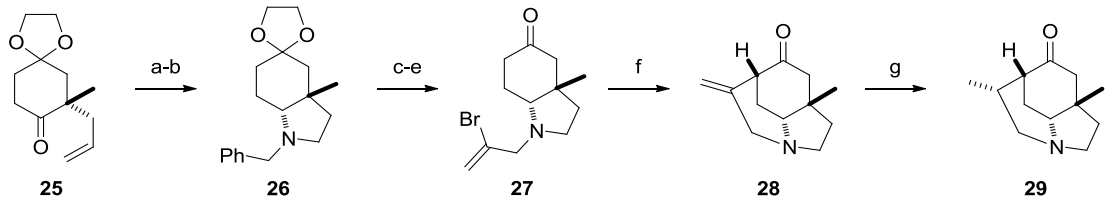
Scheme 5: Plausible biosynthesis of daphniyunnine D (23**).**

1.5 Synthetic studies towards the total synthesis of calyciphylline A-type alkaloids

1.5.1 Model studies towards the construction of calyciphylline A-type related scaffolds

To date, no total synthesis of the calyciphylline A-type alkaloids has been accomplished. Recently however, a significant number of synthetic studies towards the cores of these complex natural products have been reported.[15] These include investigations into the construction of the sub-family's: AC bicycle;[16] ABC,[17] ACD,[18] ADE,[19] BCD,[20] DEF[21] tricycles; and ABCD tetracycle.[22]

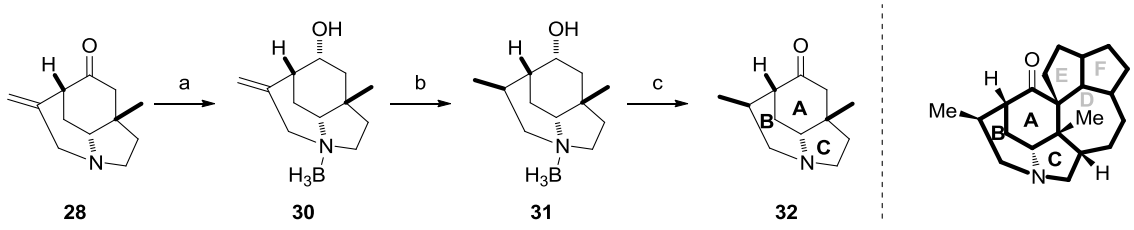
In 2005, a seminal study targeting the construction of the ABC tricyclic framework of these alkaloids was reported by the Bonjoch group.[17a] Using the monoprotected substrate **25**, they demonstrated that an ozonolysis followed by a double reductive amination using benzylamine can achieve the construction of the AC bicycle **26** in 59% yield (Scheme 6). After attaching a vinylbromide moiety on the deprotected nitrogen and subsequently removing the acetal functionality, a Pd-catalysed intramolecular coupling to the α-position of the ketone **27** was accomplished. This key step gave rise to the targeted ABC ring system **28** in 45% yield.



Scheme 6: Pd-catalysed intramolecular coupling strategy for the construction of the ABC tricyclic framework. Reaction conditions: (a) O_3, CH_2Cl_2, –78 °C; (b) $BnNH_2$.HCl, $NaBH_3CN$, MeOH, rt, 59% (two steps); (c) H_2 (1 atm), $Pd(OH)_2$, EtOAc, 88%; (d) 2,3-dibromopropene, K_2CO_3, LiI, MeCN, 55 °C, 55%; (e) HCl (10% aq), THF, rt, 95%; (f) PhOK, $Pd(PPh_3)_4$, THF, reflux, 45%; (g) Pd/C, H_2 (1 atm), MeOH, rt, 80%.

As expected however, a subsequent heterogeneous hydrogenation of the afforded *exo*-olefin in **28** avoided the hindered concave face of the tricycle. This led to the formation of the undesired epimer **29** of the ABC tricycle of the calyciphylline A-type alkaloids (Scheme 6g).

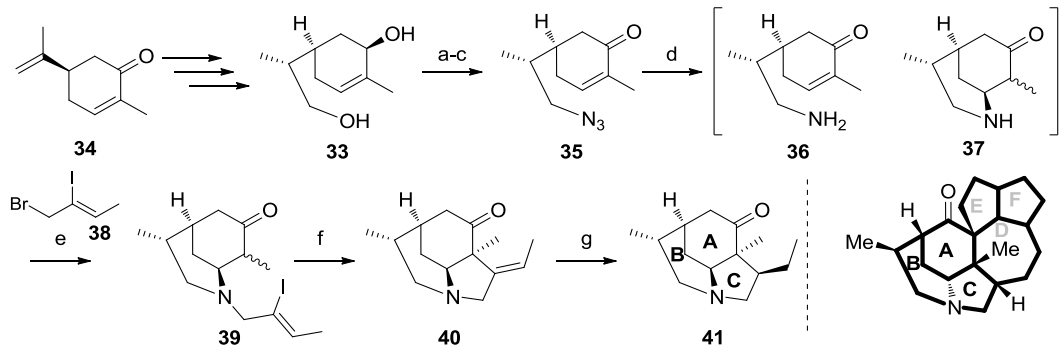
To circumvent this problem, they designed an alternative substrate-directed hydrogenation of **28** (Scheme 7). Diastereoselective reduction of the ketone afforded alcohol **30** as the amine-borane complex.[i] Subsequently, this alcohol directed the Rh-catalysed hydrogenation of the *exo*-olefin from the desired hindered face of the tricycle, providing **31** in 56% yield (its epimer was also isolated in 16%). A final Swern oxidation afforded the [6–6–5] ABC tricyclic ketone **32** with the desired relative stereochemistry with respect to the natural products.



Scheme 7: Substrate-directed hydrogenation of the *exo*-olefin of 28**. Reaction conditions: (a) $NaBH_4/CeCl_3$, MeOH, –78 °C, 62%, 4:1 dr (major shown); (b) $[Rh(NBD)(DIPHOS\text{-}4)]BF_4$, H_2 (400 psi), NaH, THF, 56% of desired** 31 **and 16% of its epimer; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78 °C to rt; then HCl (2 M), reflux, 50% (over two steps).**

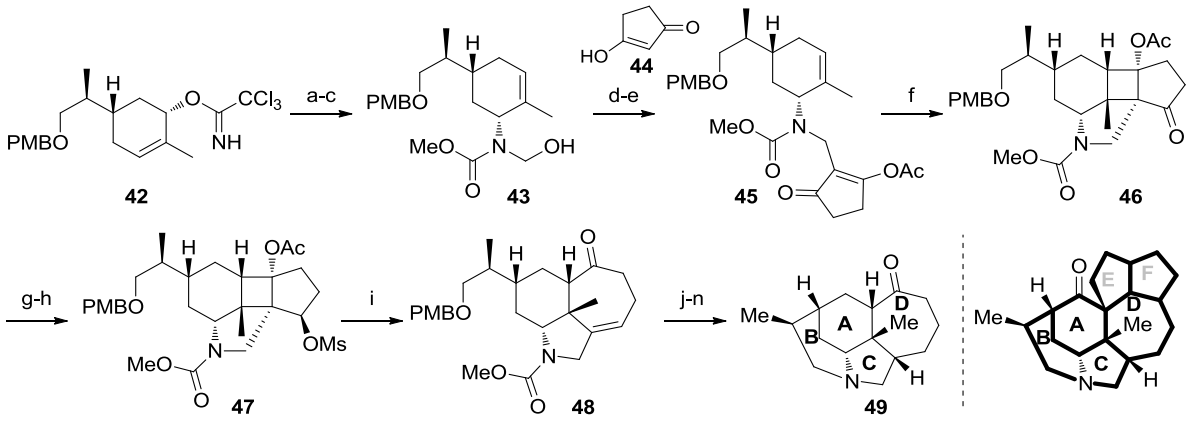
[i] This acts as a protecting group for the nucleophilic nitrogen and thus inhibits any potential nitrogen-directed hydrogenations.

Liang and co-worker achieved the asymmetric formation of this ABC tricycle using an alternative approach.[17b] In their design, the key steps involved an *aza*-Michael and a Pd-catalysed enolate *α*-vinylation (Scheme 8). The diol substrate **33** was prepared *via* an established protocol reported by Overman,[23] starting from (*R*)-carvone (**34**). Subsequently an azide functionality was introduced on the primary alcohol and the secondary alcohol was oxidised to ketone **35**. A Staudinger reaction on the azide then provided a mixture of the *aza*-Michael substrate **36** and the cyclised product **37**. Avoiding their separation, this mixture was treated directly with the crotyl bromide **38** in basic conditions, affording the cyclised *N*-allylated **39** as a mixture of diastereoisomers. Following this, a Pd-catalysed enolate *α*-vinylation scrambled the diastereoisomeric centre and provided the tricycle **40** as a single diastereoisomer in 84% yield. Unlike in Bonjoch's design (*vide supra*), the *exo*-olefin in this tricycle necessitated hydrogenation on the convex face. This was successfully achieved using Pd/C to provide the model [6–6–5] ABC tricycle **41** in 97% yield with complete stereocontrol.



Scheme 8: Liang's asymmetric synthesis of the ABC tricycle *via* an *aza*-Michael, Pd-catalysed *α*-vinylation strategy. Reaction conditions: (a) TsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 76%; (b) NaN_3, DMF, 90 °C, 95%; (c) PCC, CH_2Cl_2, rt, 91%; (d) PPh_3, THF:H_2O, rt; then (e) (*Z*)-1-bromo-2-iodobut-2-ene, K_2CO_3, THF, reflux, 89% (over two steps); (f) $Pd(PPh_3)_4$, *t*-BuOK, THF, reflux, 84%; (g) Pd/C, H_2 (balloon), MeOH, 97%.

The enantiomer of diol **33**, was also used by the Wang group in three core studies of the calyciphylline A-type alkaloids.[18a,18c,22a] In their most elaborate study they achieved the asymmetric construction of the ABCD tetracycle using an Overman rearrangement,[24] a [2+2] photocycloaddition and a Grob fragmentation[25] as key steps (Scheme 9).[22a]



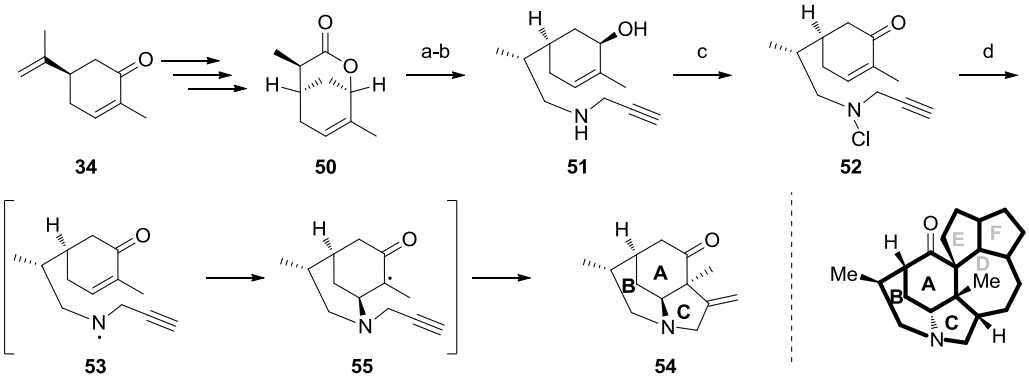
Scheme 9: Wang's asymmetric synthesis of the ABCD tetracycle. Reaction conditions: (a) xylene, reflux, 50% (from previous step); (b) (i) *p*-TsOH, $HC(OMe)_3$, MeOH, DMF, reflux; then (ii) trichloroacetamide substrate, Na_2CO_3, 150 °C (sealed tube), 82%; (c) $(HCHO)_n$, *t*-BuOK, *t*-BuOH, rt, 54%; (d) $Sn(NTf_2)_4$, 44, MeCN, rt, 77%; (e) AcCl, NEt_3, CH_2Cl_2, 0 °C, 95%; (f) *hv* (254 nm), MeCN, 0 °C, 50%; (g) $NaBH_4$, MeOH, 0 °C, 95%; (h) DMAP, MsCl, pyridine, rt; (i) K_2CO_3, MeOH, rt, 82%; (j) CAN, MeCN, H_2O, 0 °C, 99%; (k) MsCl, NEt_3, 0 °C to rt, 95%; (l) TMSI, CH_2Cl_2, rt; then (m) NEt_3, CH_2Cl_2, rt, 80% (over two steps); (n) PtO_2/C, H_2 (1 atm), MeOH, rt, 94%.

From the enantiomer of diol **33**, imidate **42** which was poised to undergo the Overman rearrangement, was afforded. Heating this in xylene and reacting the rearranged product (not shown) with trimethylorthoformate followed by paraformaldehyde, the *N*-acyl iminium precursor **43** was obtained. This successfully underwent an intermolecular Mannich condensation[26] with $Sn(NTf_2)_4$ and hydroxyenone **44** followed by acetylation of the product to provide the [2+2] photocycloaddition substrate **45**. The key step was then performed using UV-light to provide the cyclobutane-containing tetracycle **46** in 50% yield.[i] In order to prepare the tetracycle for the anticipated Grob fragmentation, the ketone was diastereoselectively transformed to the mesylated alcohol **47**. A base-mediated fragmentation subsequently provided the multifunctionalised **48** which represents a model of the ACD tricycle of the calyciphylline A-type alkaloids. The PMB alcohol in **48** was then transformed to the primary mesyl alcohol and the carbamate was removed to provide the corresponding pyrrolidine (not shown). This allowed for a cyclisation *via* an

[i] Owing to the strain within the cyclobutane ring, a related tricycle was also afforded in 29% yield *via* a retro-aldol fragmentation.

intramolecular nucleophilic substitution under basic conditions (Scheme 9m). A final heterogeneous Pt-catalysed hydrogenation of the olefin from the convex face of the afforded tetracycle gave rise to the elaborate [6–6–5–7] ABCD framework **49** as a single enantiomer, with the matching relative stereochemisty found in the targeted alkaloids.

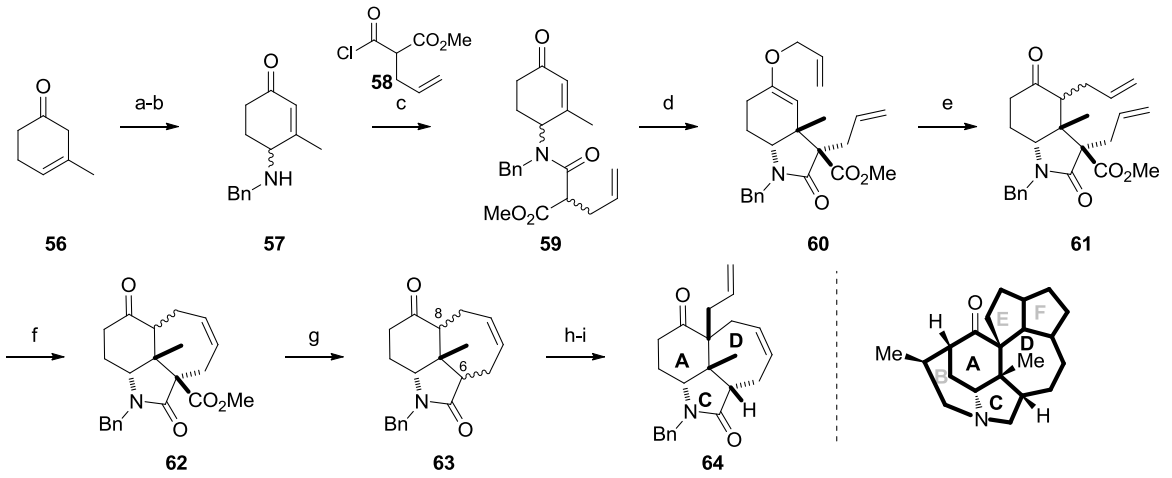
To investigate a radical cyclisation approach,[17c] the Stockdill group also took advantage of established elaborations of (*R*)-carvone (**34**)[23a] to provide the bicyclic lactone **50** (Scheme 10). A subsequent DIBAL-H reduction afforded the corresponding lactol which was reductively aminated with propargylamine to provide the secondary amine **51**.



Scheme 10: Stockdill's tandem radical cyclisation for the construction of the ABC tricycle. Reaction conditions: (a) DIBAL-H, THF, –78 °C, 95%; (b) propargylamine, THF, rt; then $NaBH_4$, MeOH, rt, 91%; (c) NCS, CH_2Cl_2, –78 °C to rt; then DMP, 0 °C to rt, 96%; (d) $SnBu_3H$, AIBN, toluene, reflux, 76%.

Reaction with NCS at a low temperature achieved the nitrogen's chlorination and a final oxidation afforded the radical cyclisation substrate **52** in 96% yield over two steps. Treatment of this substrate with AIBN and $SnBu_3H$ mediated the homolytic N-Cl bond cleavage to provide the *N*-centred radical **53** *in situ*. This underwent the designed cyclisation cascade to afford tricycle **54**. Presumably the radical undergoes a cyclisation onto the enone to provide a stabilised radical on the *α*-position of the ketone **55** which is in turn trapped by the pendant alkyne. A final hydrogen atom abstraction from the afforded vinyl radical gives rise to the [6–6–5] ABC tricycle of the alkaloids.

The Dixon group has also been successful in synthesising a calyciphylline A-type alkaloid skeleton *via* a Michael addition[27] strategy whilst investigating the total synthesis of daphniyunnine B (**22**) (Scheme 11).[18b]



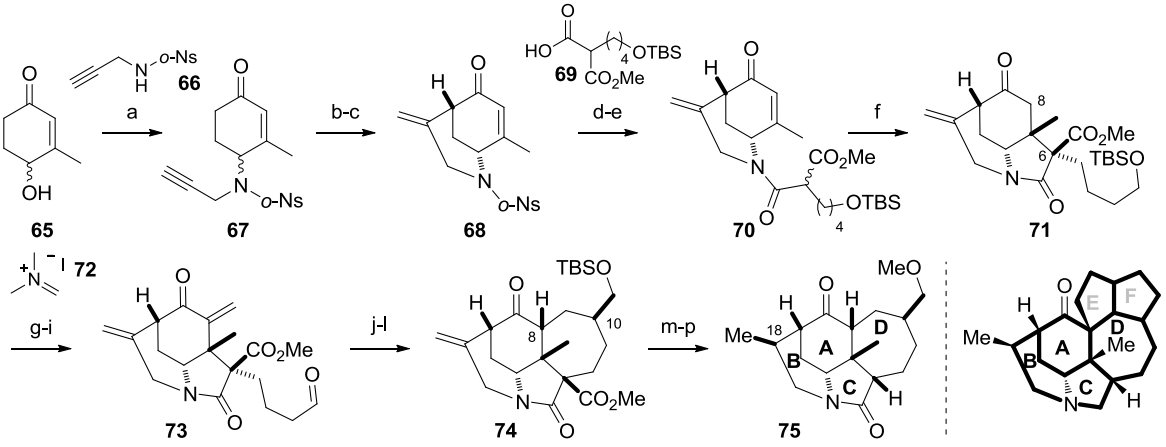
Scheme 11: Dixon's Michael addition strategy to the synthesis of the ACD tricycle. Reaction conditions: (a) LHMDS, THF, –78 °C; then I_2, –78 °C; then (b) $BnNH_2$, DMSO, rt, 56% (over three steps); (c) NEt_3, 58, CH_2Cl_2, 0 °C 76-91%; (d) KHMDS, THF, 0 °C to rt then allyl *p*-toluenesulfonate, 18-crown-6, 78%; (e) mesitylene, reflux, 63%, 6:1 dr; (f) Grubbs I, CH_2Cl_2, reflux, 98%, 6:1 dr; (g) LiCl, H_2O, DMSO, 170 °C, 73%, mixture of four diastereoisomers; (h) KHMDS, THF, rt; then allyl *p*-toluenesulfonate, 18-crown-6, 89%, 3.2:1 dr; (i) mesitylene, reflux, 58%.

Starting from ketone **56** representing ring A of the natural product, a γ-enolate formation, iodination, substitution protocol afforded the benzylamine **57** in 56% overall yield. Subsequent acylation of the nitrogen using acid chloride **58** provided the Michael addition precursor **59** as an inseparable mixture of diastereoisomers. After optimising the reaction conditions it was discovered that using KHMDS, a Michael addition followed by a tandem enolate allylation can provide enol ether **60** with complete stereocontrol. **60** was perfectly poised to undergo a Claisen rearrangement to afford bicycle **61** in 63% yield and 6:1 dr. Subsequently, a ring-closing metathesis (RCM) with the Grubbs I catalyst gave rise to the [6–5–7] ACD tricycle **62** in 98% yield and 6:1 dr.

Removal of the methyl ester functionality *via* a Krapcho dealkoxycarbonylation[28] afforded tricycle **63** as a mixture of four diastereoisomers at C6 and C8. In order to further elaborate the core, the ketone was allylated once more to provide the corresponding enol ether (not

shown) in 89% yield and 3.2:1 dr (at C6) with absolute regiocontrol. A second Claisen rearrangement provided a mixture of three diastereoisomers, from which the major component **64**, was isolated in 58% yield. Overall, this strategy selectively installs four stereocentres, including the two contiguous quaternary ones, providing a model synthesis of the [6–5–7] ACD tricycle found in the calyciphylline A-type alkaloids.

Li and co-workers also took advantage of the aforementioned Michael addition strategy for their studies.[22b] In combination with a Toste–Conia–ene gold-catalysed cyclisation,[29] the [6–6–5–7] ABCD tetracycle of the calyciphylline A-type alkaloids was synthesised (Scheme 12). Starting from the readily available building block **65**, a Mitsunobu reaction with the *o*-nosylamine **66** provided the gold cyclisation substrate **67**. Through a prior activation to the corresponding silyl enol ether, a mild Au-catalysed cyclisation using $Au(PPh_3)NTf_2$ afforded the [6–6] bicycle **68**. After deprotection of the nosyl group, the corresponding piperidine was coupled to the acid **69** to give rise to the Michael addition substrate **70**.



Scheme 12: Li's synthesis of the ABCD tetracycle. Reaction conditions: (a) 66**, PPh_3, DIAD, THF, 0 °C, 84%; (b) TBDPSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 10 min; then (c) $Au(PPh_3)NTf_2$, toluene:MeOH (10:1), rt, 76% (over two steps); (d)** ***p*****-toluenethiol, K_2CO_3, DMF, 22 °C; then (e)** 69**, HOBt, EDC·HCl, NEt_3, CH_2Cl_2, rt, 78% (over two steps); (f) K_2CO_3, MeCN, 100 °C, 82%; (g)** 72**, DBU, CH_2Cl_2, 55 °C, 64%; (h) HF·py:THF (1:5), 0 °C; then (i) DMP, CH_2Cl_2, rt, 81% (over two steps); (j) NEt_3, CH_2Cl_2, 60 °C; then** ***t*****-BuOK,** ***t*****-BuOH, 0 °C, 45%; (k) $LiAlH(O\mathit{t}\text{-}Bu)_3$, CH_2Cl_2, –40 °C; then (l) TBSOTf, NEt_3, CH_2Cl_2, –78 °C, 67% (over two steps); (m) Crabtree's cat., H_2 (balloon), CH_2Cl_2, 22 °C, 82%; (n) HF·py:THF (1:4), 0 °C; then (o) MeOTf, 2,6-di-*tert*-butylpyridine, 22 °C; then (p) $LiCl{\cdot}H_2O$, DMSO, 170 °C, 42% (over three steps).**

This amide was subjected to basic conditions (K_2CO_3 in MeCN) at 100 °C to mediate the desirable transformation in 82% yield and 8:1 dr in favour of the drawn isomer **71** (diastereoisomeric at C6). **71** was then homologated at C8 using Eschenmoser's salt (**72**) (Scheme 12g). Transformation of the primary TBS-protected alcohol to aldehyde **73** allowed for the second intramolecular Michael addition to take place. This was accomplished using NEt_3 and *t*-BuOK[i] in CH_2Cl_2 at 60 °C to provide the corresponding tetracycle (not shown) in 45% yield. A reduction of its aldehyde was followed by a TBS protection of the primary alcohol to provide the highly functionalised tetracycle **74**.

To establish whether this could constitute an appropriate model for the targeted alkaloids, a hydrogenation of the *exo*-cyclic olefin as well as a dealkyloxycarbonylation of the methyl ester were necessary. To this end, they demonstrated that although Pd/C provided the exclusive formation of the undesired diastereoisomer, Crabtree's catalyst[ii] afforded the desired epimer at C18 in 82% yield (Scheme 12m). This result is of great importance because it complements Bonjoch's studies[17a] and demonstrates that the *exo*-cyclic olefin can be stereoselectively hydrogenated under homogeneous catalysis.[iii] This allows for facile access to the desired *exo*-methyl diastereoisomer without the need for substrate-directed transformations.

Subsequent removal of the TBS protection of the alcohol followed by its methylation, allowed for the removal of the methyl ester *via* Krapcho conditions. This provided the tetracycle **75** representing an advanced model of the calyciphylline A-type alkaloids. Confirming Dixon's finds, the Li group also demonstrated that a Claisen rearrangement

[i] *t*-BuOK was used after the NEt_3-promoted intramolecular Michael addition to allow for the epimerisation of the undesired minor diastereoisomer; epimeric at C10.

[ii] Crabtree's catalyst= $[Ir(cod)(PCy_3)(py)]PF_6$.

[iii] It should be noted that when Bonjoch and co-workers used Crabtree's catalyst for the hydrogenation of their analogous olefin, the *exo*-cyclic double bond migrated to an *endo* position without being hydrogenated.

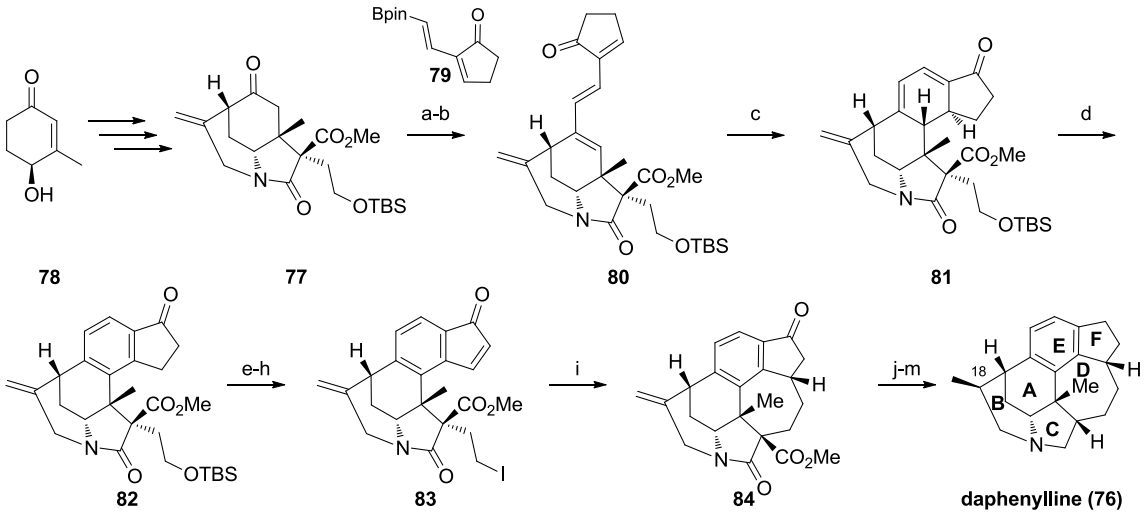
strategy can also be employed on substrate **74** to quarternarise the C8 position with the desired relative stereochemistry (transformation not shown).

1.5.2 Total synthesis of daphenylline

As already mentioned, to the best of our knowledge, no synthesis of the calyciphylline A-type alkaloids has been accomplished. However, Li and co-workers have recently published the total synthesis of the structurally related,[i] daphenylline (**76**) (Scheme 13).[5n] Isolated in 2009, this structurally unique natural product is the only known *Daphniphyllum* alkaloid to contain a benzene ring moiety.[30] Model studies detailing the incorporation of its rare arene motif have recently been reported by the She group.[31] As this functionality is not present in the calyciphylline A-type alkaloids, these approaches have not been included in the introduction of this thesis. Notable however is Li's concise asymmetric synthesis of the natural product (Scheme 13),[5n] relevant to the work in the Dixon group.

Using chemistry reported in their model study to the calyciphylline A-type alkaloids (*vide supra*), tricycle **77** was synthesised as a single enantiomer in six steps from hydroxyenone **78** (98% ee). For the construction of the arene motif, they transformed the ketone to a vinyl triflate (not shown). This allowed for the Suzuki coupling with boronate **79** to afford the anticipated triene **80**. Subsequently a photoinduced olefin isomerisation/6π-cyclisation cascade was achieved under irradiation with a Hg lamp-500 W (exclusion of O_2 was crucial for this step) to give pentacycle **81** in 71% yield.

[i] The clear classification of daphenylline is not yet established. Throughout this thesis it will be considered as structurally related to calyciphylline A-type alkaloids.



Scheme 13: Li's total synthesis of daphenylline (76**). Reaction conditions: (a) KHMDS, $PhNTf_2$, THF, –78 °C; (b)** 79**, $Pd(PPh_3)_4$, K_2CO_3, DME, rt to 60 °C, 73% (over two steps); (c)** ***hν*** **(Hg lamp 500 W), benzene, 0 °C, 71%; (d) air, DBU, 60 °C, 67%; (e) TMSOTf, NEt_3, CH_2Cl_2, –78 °C; then (f) $Pd(OAc)_2$, MeCN, rt, 81% (over two steps); (g) HF·pyr, THF, 0 °C; then (h) I_2, PPh_3, imidazole, CH_2Cl_2, rt, 93% (over two steps); (i) $(TMS)_3SiH$, AIBN, CH_2Cl_2, rt to 75 °C, 98%; (j) H_2, Crabtree's catalyst, CH_2Cl_2; then (k) $LiCl·H_2O$, DMSO, 160 °C, 86% (over two steps); (l) Pd/C, H_2, MeOH, rt; (m) $LiAlH_4$, Et_2O, rt to 40 °C, 66% (over two steps).**

Recognising the inherent acidity of the hydrogen on the *ε*-position of the enone, they stirred pentacycle **81** in DBU under air at 60 °C to afford the oxidised arene scaffold **82** in 67% yield. Subsequent transformations including a Saegusa–Ito oxidation[32] gave enone **83**, poised to undergo a radical cyclisation. Treatment with AIBN and $(TMS)_3SiH$ in toluene at 75 °C achieved the construction of the final ring D in hexacycle **84**. After four subsequent steps including a Crabtree-catalysed hydrogenation[i] and a Krapcho dealkyloxycarbonylation (Scheme 13j-k) the synthesis of (–)-daphenylline (**76**) was accomplished in a total of 25 steps.

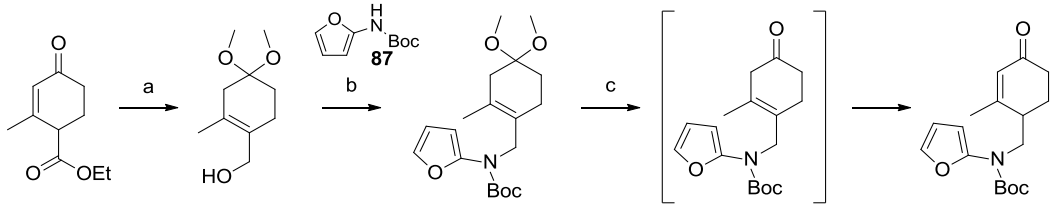
[i] The desired epimer at C18 was the major diastereoisomer of the hydrogenation in >30:1 dr.

1.6 Preliminary work leading to this project

1.6.1 Studies towards the total synthesis of daphniyunnine B

Apart from developing a Michael addition strategy (*vide supra*), our group has also been successful in achieving the construction of the [6–5–7] ACD tricycle *via* an alternative approach. John Ward[i] investigated the total synthesis of daphniyunnine B (**22**) (Figure 2) and developed a route to its ACD core by employing an intramolecular furan Diels–Alder reaction (IMDAF)[ii] as a key step.

In Ward's model study, the commercially available Hagemann's ester (**85**) was employed as the foundation of ring D in daphniyunnine B (**22**) (Scheme 14). The enone functionality of this six-membered ring represented the dienophile of the designed intramolecular cycloaddition. An acetal protection of the ketone allowed for the reduction of the ester affording alcohol **86**. Subsequently, a one-pot reaction for the introduction of the diene/furan cycloaddition partner was developed. Tosylation of the primary alcohol followed by its substitution using the potassium salt of the *N*-Boc 2-aminofuran (**87**) afforded the amido furan **88** in 72% yield.



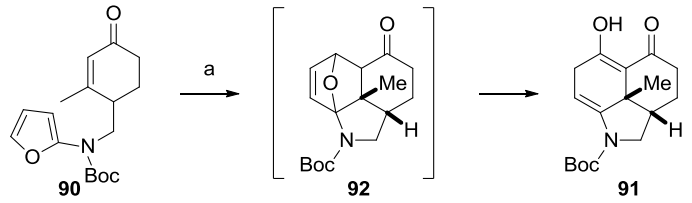
Scheme 14: Preparation of amido furan 90**. Reaction conditions: (a) (i) $CH(OMe)_3$, *p*-TsOH, MeOH, rt; then (ii) $LiAlH_4$, THF, 0 °C, 64% (over two steps); (b) *n*-BuLi, TsCl,** 87**, KHMDS, THF, –78 °C to rt, 72%; (c) (i) 0.1 M HCl:THF, rt; then (ii) K_2CO_3, MeOH, rt, 88% (over two steps).**

[i] PhD student; thesis submission 2010.

[ii] In the literature, the intramolecular Diels–Alder reaction of furans is abbreviated as IMDAF and will be abbreviated as such throughout the thesis regardless of the syntax of the sentence. For example "then the intramolecular furan Diels–Alder reaction was investigated", will be abbreviated "then the IMDAF reaction was investigated".

The acetal functionality was removed under acidic conditions to form **89** which was then subjected to catalytic basic conditions, re-conjugating the double bond with the ketone. This two-step process gave access to the enone **90** in an overall 88% yield. The IMDAF cycloaddition was first investigated on this 6-membered dienophile, as opposed to its 7-membered ring analogue in order to establish a proof of principle for the designed retrosynthesis of the [6–5–7] ACD core of daphniyunnine B (**22**).

It was discovered that heating **90** to reflux in toluene in the presence of an antioxidant (BHT), can afford the desired [6–5–6] model tricycle **91** following a fragmentation of the IMDAF adduct **92** (Scheme 15).[i]



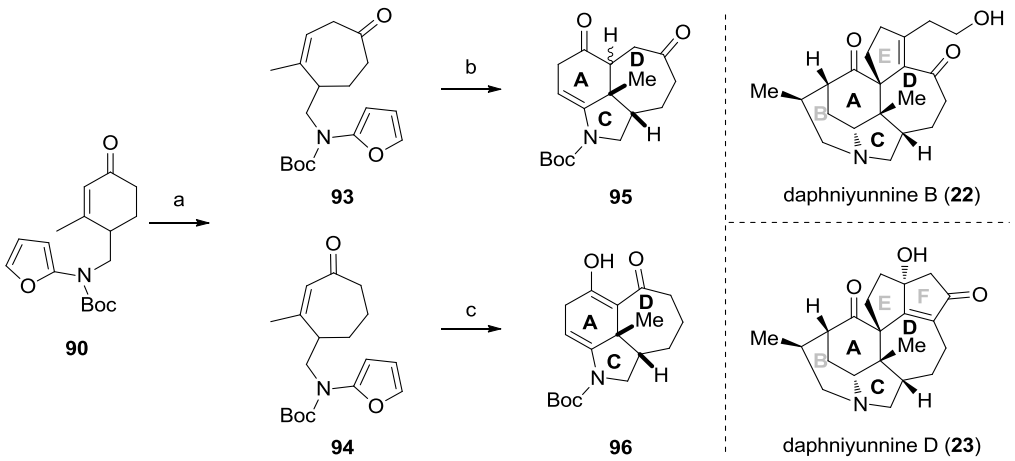
90 **92** **91**

Scheme 15: Synthesis of the [6–5–6] model tricycle 91 ***via*** **an IMDAF approach. Reaction conditions: (a) BHT, toluene, reflux, 80%, enol:keto >20:1.**

Tricycle **91** was isolated in 80% yield as a single diastereoisomer and its relative stereochemistry was established by nOe experiments. Having confirmed the feasibility of this approach, Ward set out to apply it to the analogous 7-membered ring dienophile.

Reaction of the 6-membered ring enone **90** in the presence of $AlMe_3$ gave rise to the homologated **93** in a poor 27% yield alongside the undesired regioisomer **94** in 9% (Scheme 16a).

[i] Details of the mechanism of this reaction will be provided in the following chapter (see Scheme 20 on page 28).



Scheme 16: Synthesis of two ACD tricycles relevant to the calyciphylline A-type alkaloids. Reaction conditions: (a) (i) $AlMe_3$, $TMSCHN_2$, CH_2Cl_2, –78 °C to rt, then (ii) 1 M HCl:THF (1:1), rt, 27% of 93 **and 9% of** 94**; (b) BHT, toluene, reflux, 77%, 2:1 dr; (c) BHT, toluene, reflux, 60%, enol:keto 5:1.**

Nevertheless, substrate **93** was subjected to the optimised IMDAF reaction conditions and pleasingly afforded the targeted ACD core **95** of daphniyunnine B (**22**) in 77% yield and 2:1 dr. The relative stereochemistry was tentatively assigned based on the selectivity of the reaction of the analogous 6-membered ring dienophile **90**.

Moreover, heating the regioisomer **94** in toluene provided a secondary [6–5–7] tricycle **96** in 60% yield as a single diastereoisomer.

Unfortunately, the low yields of the one-carbon homologation reaction rendered this route incompatible for large scale synthesis. However, these early investigations provided evidence that the IMDAF strategy was a viable and rapid method for accessing complex tricyclic skeletons in a single operation. Although the secondary tricycle **96** was undesired for the purposes of Ward's project, it was in fact this side product that inspired the work described in this thesis; the investigation of the total synthesis of daphniyunnine D (**23**).

1.6.2 Studies towards the total synthesis of daphniyunnine D

Inspired by Ward's investigations, Dr. Benjamin Darses[i] commenced a study towards the total synthesis of daphniyunnine D using an IMDAF cycloaddition as the key step. Because the investigations reported in this thesis are directly related to that of Dr. Darses, his contribution is included and reported in the subsequent chapters in parallel. As it is often difficult to draw a distinction, the reader is kindly asked to refer to the experimental chapter 5. This chapter describes reactions that were either: (a) developed during the course of this project or (b) optimised from Darses' initial work.

1.7 Dixon and co-workers' retrosynthetic analysis of daphniyunnine D

By chance, Ward provided a proof of principle that the IMDAF reaction was a realistic as well as rapid entry to the tricyclic [6–5–7] ACD core of daphniyunnine D (Scheme 16c). Inspired by this result, we designed a route where the ACD tricycle would act as the foundation of the molecule, on which the remaining cycles and functionalities would be constructed in a controlled and stereoselective manner.

In our retrosynthetic analysis, the precursor **97** to the IMDAF adduct would be synthesised *via* an amide coupling reaction starting from the relatively simple precursors **98** and the aminofuran **99** (Figure 3). Upon validation of the key IMDAF step, a more detailed investigation was also planned to discover whether an asymmetric organocatalytic variant would be possible; giving rise to attractive diastereo- and enantioselectivities. Subsequently a ring-opening/fragmentation of the IMDAF adduct **100** followed by the hydrogenation of the afforded enamide (not shown) would provide the ACD tricycle **101**.

[i] Post-doctoral researcher in the Dixon group 2009-2011.

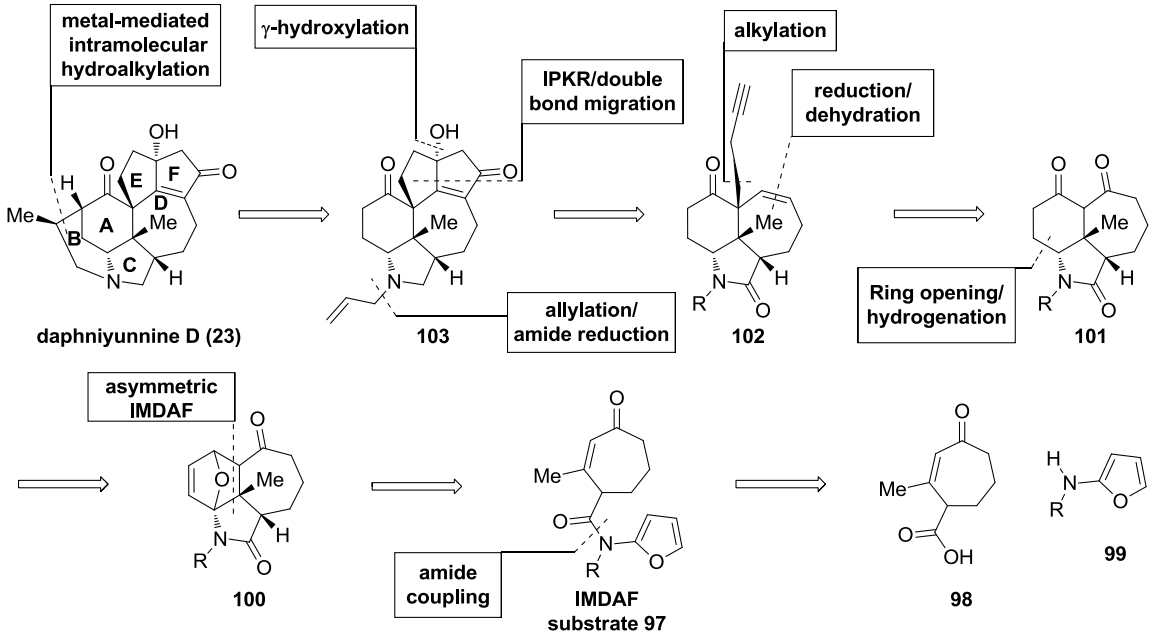


Figure 3: Dixon and co-workers' retrosynthetic analysis of daphniyunnine D (23**).**

Simple synthetic manipulations would give rise to the deoxygenated and alkyne-decorated tricycle **102**. An intramolecular Pauson–Khand reaction (IMPKR), double-bond migration, γ-hydroxylation protocol was then envisaged to obtain the ACDEF pentacycle of the natural product (not shown). The final objective was to complete the synthesis of daphniyunnine D *via* a metal-catalysed intramolecular hydroalkylation reaction of the allylated IMPKR adduct **103**.

1.8 Thesis objectives

The overall objective of this thesis was to implement the designed retrosynthetic route in a short, elegant and stereoselective manner in order to achieve the first asymmetric total synthesis of daphniyunnine D. Where possible, we wanted to construct versatile polycyclic intermediates which would also allow for the total synthesis of other members of the *Daphniphyllum* alkaloid family.

The primary aim was to synthesise sufficient quantities of advanced intermediates using the unpublished work of Dr. Darses. This would allow the improvement, optimisation and further development of the route with the final aim of synthesising the target molecule.

The following chapters detail the synthetic efforts towards this goal. A more focused retrosynthetic analysis will be presented at the start of each chapter which will be discussed as follows:

1) An intramolecular furan Diels–Alder reaction approach for the synthesis of the main [6–5–7] tricyclic core (ACD rings) of daphniyunnine D;

2) An intramolecular Pauson–Khand reaction approach for the synthesis of the ACDEF pentacycle of daphniyunnine D;

3) An intramolecular hydroalkylation approach for the synthesis of ring B of daphniyunnine D.

Chapter 2: An intramolecular furan Diels–Alder reaction approach for the synthesis of the main [6–5–7] tricyclic core (ACD rings) of daphniyunnine D

2.1 Introduction

Basing the investigations on Ward's results and his serendipitous access to the ACD tricyclic core of daphniyunnine D (**23**) en route to daphniyunnine B (**22**), a new approach was initiated towards the total synthesis of the former. Construction of the 7-membered ring scaffold (ring D) was to be designed in a direct manner, avoiding the low yielding one carbon-homologation implemented by Ward (see section **1.6.1**).

2.2 Aims and retrosynthetic analysis

Access to the racemic ACD tricyclic core **104** of daphniyunnine D (**23**) was achieved prior to the start of this thesis project *via* a key furan intramolecular Diels–Alder (IMDAF) reaction. Therefore, the initial aim of this chapter was the large scale synthesis of the key IMDAF precursor **105** using the unpublished route. This would allow for its improvement, by addressing key issues encountered during its development (Figure 4). Secondly, we envisioned introducing asymmetry in the ACD tricyclic core **104** through the development of an organocatalytic asymmetric variant of the IMDAF reaction.

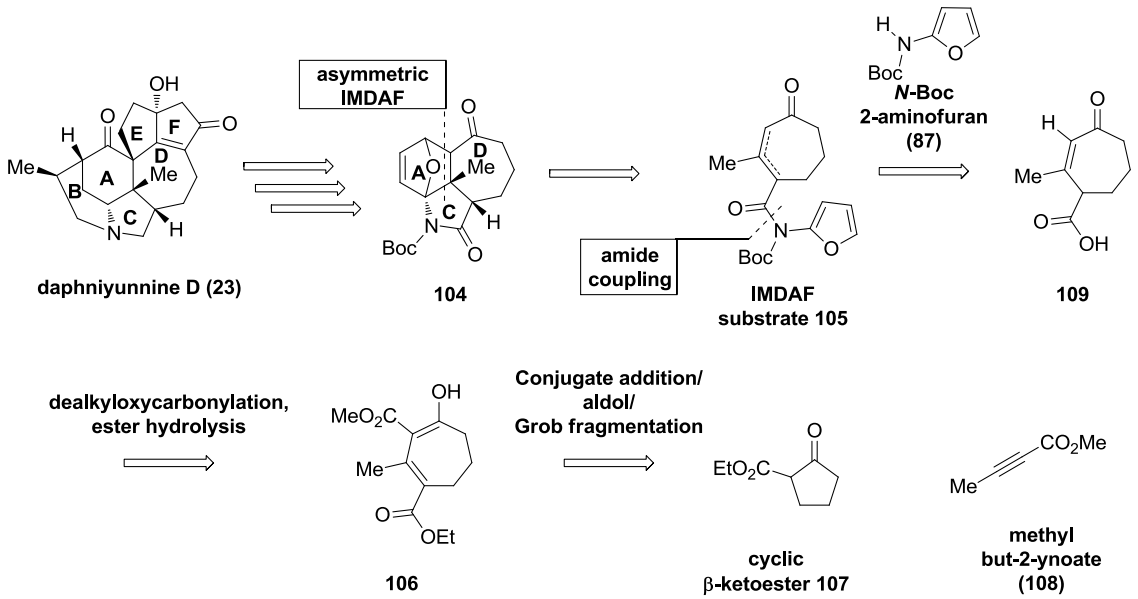


Figure 4: Retrosynthetic analysis of daphniyunnine D, an IMDAF reaction focus.

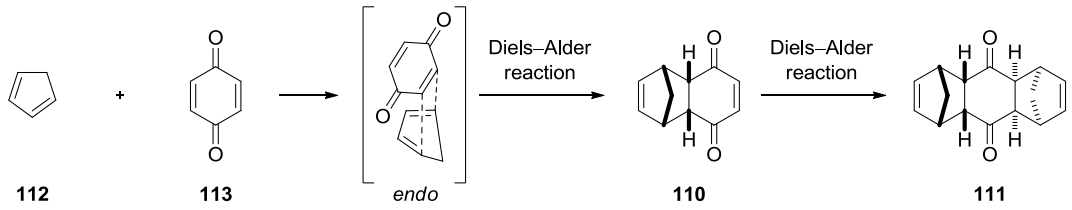
In order to avoid the low yielding one-carbon homologation used by Ward, synthesis of the 7-membered ring **106** would be achieved in a one-step ring-expansion *via* a conjugate addition/aldol/Grob fragmentation reaction cascade (*vide infra*)[33] from simple and commercially available starting materials **107** and **108** (Figure 4). This cyclic ketodiester **106** would then be converted to the amide coupling precursor, acid **109**, through an initial dealkyloxycarbonylation followed by an ester hydrolysis. An amide coupling with **87** would provide access to the IMDAF substrate **105** allowing for the detailed investigation of the asymmetric variant of the key cycloaddition.

Before discussing our work in this area, the relevant Diels–Alder reaction and recent advances in its asymmetric variant are introduced in the following sections.

2.3 The Diels–Alder reaction

After identifying bicycle **110** and tricycle **111** as arising from the [4+2] cycloaddition reaction of cyclopentadiene (**112**) with quinone (**113**) (Scheme 17), Diels and Alder wrote in their 1928 landmark paper:[34] "*Thus it appears to us that the possibility of synthesis of*

complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps even alkaloids, has been moved to the near prospect".



Scheme 17: The discovery of the Diels–Alder reaction in 1928 leading to the Nobel prize award in Chemistry in 1950 to Professor O. Diels and his student K. Alder.

Over time, this reaction has revolutionised the field of organic chemistry making it one of the most powerful tools available to the modern organic chemist. This atom economic pericyclic process involving a conjugated diene (e.g. **112**) and a dienophile (e.g. **113**) can lead to molecules of great complexity, generating a six-membered ring containing a substituted double bond with two newly formed single bonds with up to four contiguous stereocentres in a single step. The regioselectivity of the bond forming events is directed by the favourable molecular orbital overlap of the reacting partners.[i,35] Marking the centenary of Alder's birth, in 2002 the group of Nicolaou compiled a review demonstrating the power of this simple yet elegant one-step transformation in total synthesis.[36]

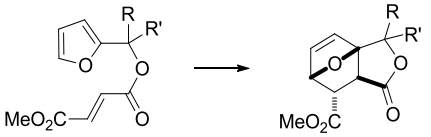
2.4 The Diels–Alder reaction of furans

Aromatic 4π-dienes such as furans, thiophenes and pyrroles can also undergo the Diels–Alder reaction with a variety of alkenes, alkynes and allenes, despite their aromatic nature leading to a lower reactivity.[37] In fact, the Diels–Alder reaction of furans was one of the first reactions studied by the discoverers of the transformation.[38] Besides the lower reactivity of furans, a further drawback of this version of the [4+2] cycloaddition is its propensity to undergo a retro Diels–Alder leading to no net outcome.[39] Several groups

[i] Rationale for the regioselectivity in the Diels–Alder is often provided using frontier molecular orbital (FMO) theory.[35]

have focused their efforts in order to address both these limitations. In order to overcome the loss of the aromatic character of the furan as well as the build up of steric strain in the afforded oxabicyclic adduct, Lewis-acid catalysis and high pressure methods have been employed when thermally unstable reactants are used; a comprehensive review details these investigations.[37]

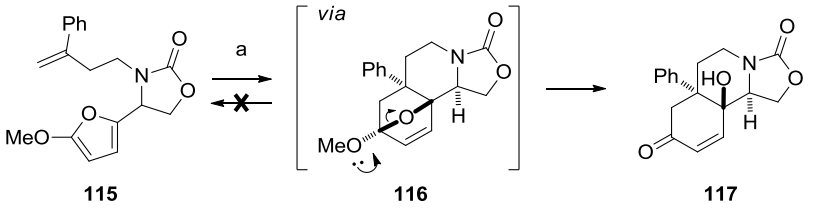
An alternative to the organisation offered by the high pressure in the intermolecular furan Diels–Alder reactions is attaching the furan to the dienophile in the intramolecular variant, thus reducing the kinetic barrier of bringing the two reactive partners in close proximity.[37] A further rate acceleration can also be observed with molecules containing a geminal dialkylsubstitution on the tether of the furan (i.e. **114** in Scheme 18). This *gem-dialkyl effect* can be attributed to the *Thorpe-Ingold effect*[40] lowering the kinetic barrier to cycloaddition *via* a bond-angle compression resulting from steric repulsion. This acceleration can also be credited to the *reactive rotamer effect*, where the geminal substitution leads to an enrichment of "productive" rotamers in the ground state.[41]



114

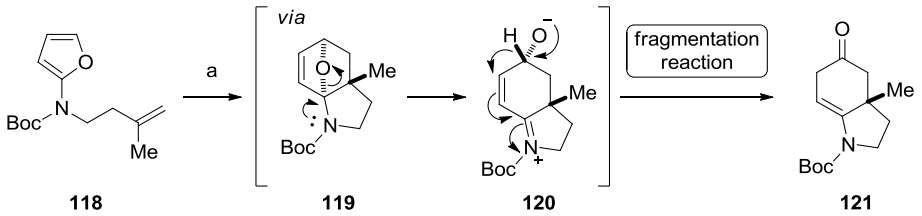
Scheme 18: The "*gem-dialkyl effect*", leading to the rate acceleration of the cycloaddition.

Although kinetic barriers can be overcome by the aforementioned methods, the thermodynamic disadvantage of losing the aromatic character of the furan still leads to the retro Diels–Alder taking place in certain systems. A method of intercepting the cycloreversion is to perform an irreversible step after the cycloaddition. In 1995, Hudlicky achieved this by including a labile acetal functionality on **115** poised to cause the cleavage of the cycloadduct **116** and thus intercept the retro Diels–Alder to afford **117** after hydrolysis, albeit in a low 13% yield (Scheme 19). It is noteworthy that substituting the methoxy functionality with a hydrogen atom led to no net outcome.[42]



Scheme 19: Hudlicky's protocol for intercepting the retro Diels–Alder. Reaction conditions: (a) sealed tube, toluene 250 °C, 13% plus degradation products.

Padwa and co-workers, whose work is directly related to this thesis, demonstrated that the energy of the HOMO of the furan and thus its reactivity can be increased by introducing an electron-donating group on the 2-position.[43] After demonstrating the application of this activation in the intermolecular cycloaddition, a great effort has since been undertaken in the intramolecular variant (IMDAF), giving rise to oxo-hexahydroindole scaffolds present in many alkaloids including daphniyunnine D.[44] The concept of the activation of the diene was further combined with an irreversible step conceptually similar to Hudlicky's (Scheme 20).

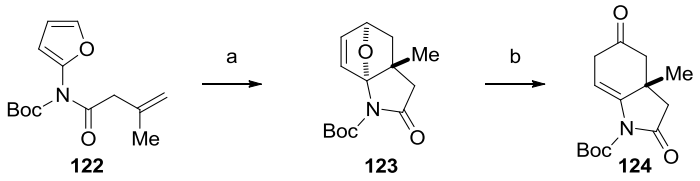


Scheme 20: Padwa's protocol for intercepting the retro Diels–Alder *via* a fragmentation of the oxabicyclic adduct. Reaction conditions: (a) sealed tube, benzene, 165 °C, 71%.

In their design, 2-amidofuran **118** affords the cycloadduct **119**, which undergoes a rapid ring-opening driven by the electron-donating nature of the nitrogen's lone pair; **119** was never isolated. Subsequently, a hydrogen-shift of the attained zwitterion **120** gives rise to the oxo-hexahydroindole **121** (this cascade will be termed as a "fragmentation" of the oxabicyclic adduct from this point onwards).[i]

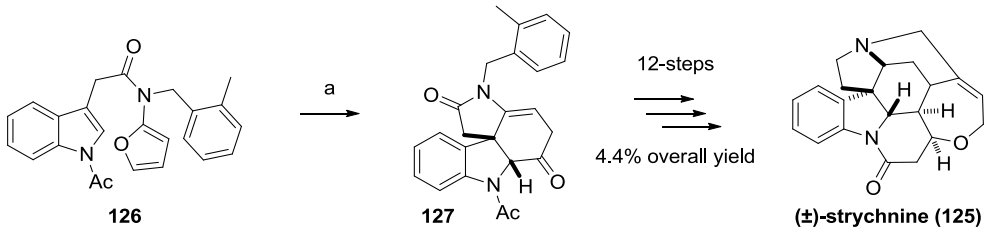
[i] If the methyl group is replaced by a hydrogen atom, the indoline analogue is formed *via* an initial ring opening followed by a subsequent dehydration leading to aromatisation.

Padwa and co-workers soon discovered that the analogous reaction of 2-imidofuran **122**,[45] with an extra carbonyl in conjugation with the nitrogen, could be performed at rt[i] and in some cases isolation of the initially formed *aza*-oxabicyclo adduct **123** was possible (Scheme 21). The dramatic rate enhancement was attributed to the restricted rotation about the C-N bond forcing the molecule in a more reactive conformation.[46] Isolation of the *aza*-oxabicyclic adducts was credited to the lower reaction temperatures employed and to the reduction of the extent of ring fragmentation due to the extra carbonyl reducing the nucleophilicity of the conjugated nitrogen. Under more forcing conditions i.e. higher temperatures, the molecules fragmented as expected to furnish the dioxo-hexahydroindole **124**.



Scheme 21: Dramatic rate enhancement observed by Padwa using a 2-imidofuran. Reaction conditions: (a) spontaneous cycloaddition at 25 °C following the synthesis of 122 ***via*** **an amide coupling, 56% (over two steps); (b) sealed tube, toluene, 140 °C, 92%.**

The versatility of the methodology developed by Padwa was demonstrated in its application towards natural product synthesis,[47] an example of which was the stereocontrolled synthesis of (±)-strychnine (**125**).[48] An IMDAF/fragmentation reaction cascade of **126** in toluene at 150 °C (microwave reactor) with a catalytic amount of MgI_2 gave rise to **127** in 95% yield (Scheme 22).



Scheme 22: Padwa's synthesis of (±)-strychnine. Reaction conditions: (a) MgI_2, toluene, 150 °C, 95%.

[i] The [4+2] cycloaddition occurred whilst synthesising the precursor **122.**

2.5 Asymmetric Diels–Alder reaction

2.5.1 Introduction

The real power of the Diels–Alder reaction becomes apparent when carried out under catalytic asymmetric conditions. Extensive investigation of the asymmetric variant using chiral Lewis-acids has been carried out by many researchers. Corey, being a significant contributor to the field, published a review in 2002 with the state of the art catalysts.[49]

In relation to the work reported in this thesis, although the asymmetric Lewis-acid catalysed Diels–Alder reaction of furans has been accomplished,[49,50] the organocatalytic variant is less established (see section **2.5.3**). The organocatalytic conventional Diels–Alder reaction on the other hand has recently received great attention, especially after MacMillan's contributions to the field[51c] reigniting interest from the synthetic community (see section **2.5.2.1**).[51]

Organocatalysis avoids the use of toxic metals and is thus becoming an appealing and burgeoning field.[52] Furthermore, organocatalysts are operationally easy to handle, without the need for rigorously dry or deoxygenated conditions.

2.5.2 Enantioselective organocatalytic Diels–Alder reaction

Despite recent interest, the field of the enantioselective organocatalytic Diels–Alder reaction is still in its early development. Many forms of catalysis have been investigated including iminium, enamine,[i,53,54] Brønsted acid, Brønsted base and bifunctional catalyst approaches. However, with the exception of the more developed iminium catalysis, little is

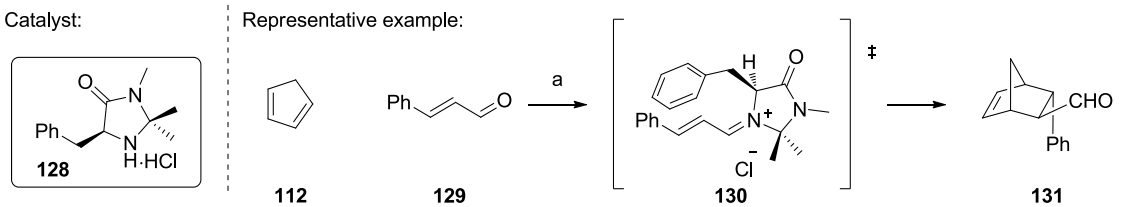
[i] Enamine catalysis has been used to catalyse the inverse-electron-demand Diels–Alder reaction (IEDDA),[53] however, as it is not relevant to the work of this thesis it will not be discussed. The group of Jørgensen has been particularly prolific in this field. For selected examples see reference 54.

known about the true mechanistic pathways of the other forms of catalysis, although different postulations exist.

The following sections provide leading examples for each type of organocatalysis, accompanied by a rationale for the enantioinduction. Selected relevant examples for each of the reports is given, demonstrating the type of catalysis without discussing its scope and limitations.

2.5.2.1 Iminium catalysis

In 2000, MacMillan and co-workers published the "*first general enantioselective organocatalytic Diels–Alder reaction*",[55] which emulated the LUMO-lowering activation of dienophiles, associated with Lewis-acid catalysis. This was achieved *via* the reversible formation of iminium ions from *α,β*-unsaturated aldehydes using a chiral imidazolidinone catalyst **128** derived from (*S*)-phenyl alanine. In their report, the asymmetric induction between cyclopentadiene (**112**) and (*E*)-cinnamaldehyde (**129**) was attributed to: (a) the selective formation of the (*E*)-iminium isomer **130** in order to avoid the non-bonding interactions between the dienophile and the geminal methyl substituents of the catalyst, as well as (b) the shielding of the *Re*-face[i] of the substrate by the catalyst's benzyl group, exposing the *Si*-face to attack by the diene **112**. In a selected example, the cycloadduct **131** was afforded in 99% yield and 93% ee for both *exo* and *endo* isomers (Scheme 23).



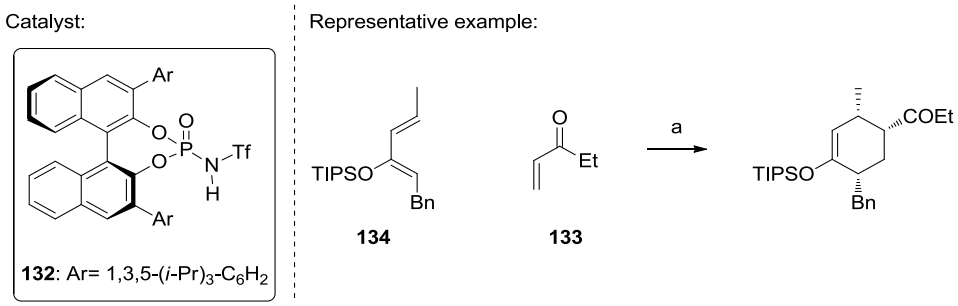
Scheme 23: MacMillan's "*first general enantioselective organocatalytic Diels–Alder reaction*". Reaction conditions: (a) 128 **(5 mol %), MeOH/H_2O, 23 °C, 99%, 1.3:1 *exo*:*endo*, 93% *exo* ee.**

[i] The "*Re*-face" designation refers to the sp^2 carbon-centre on the *β*-position of the iminium ion.

This report helped revive the field of asymmetric Diels–Alder organocatalysis, especially after its application to the less reactive *α,β*-unsaturated ketones[56] as well as the total synthesis of relevant natural products.[57] Since then, numerous iminium catalysts have been reported, employing chiral primary as well as secondary amines,[58] hydrazines, aziridines and solid supported analogues.[51b,c]

2.5.2.2 Brønsted acid catalysis

In a similar fashion, chiral Brønsted acids (also known as hydrogen-bonding or H-bonding catalysts) can activate the dienophile carbonyl *via* hydrogen-bonding thus lowering its LUMO whilst at the same time directing the approach of the reacting partners in an ordered chiral transition state. The group of Yamamoto has shown that (*S*)-BINOL derived *N*-triflyl phosphoramidate **132** can catalyse the asymmetric Diels–Alder between *α,β*-unsaturated ketone **133** and electron-rich dienes (e.g. **134**) to give moderate yields and high enantioselectivities, albeit with a relatively narrow substrate scope (Scheme 24).[59]



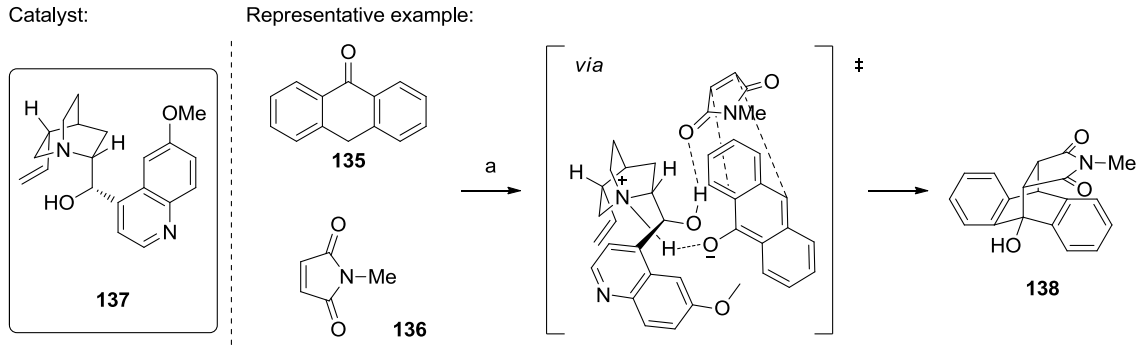
Scheme 24: Yamamoto's Brønsted acid catalysed Diels–Alder reaction. Reaction conditions: (a) 132 **(5 mol %), toluene, –78 °C, 99%, 85% ee.**

Other groups have also developed this mode of asymmetric Diels–Alder catalysis using chiral phosphoric acid,[60] thiourea,[61] tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)[62] and amidinium derived catalysts.[63]

2.5.2.3 Brønsted base and bifunctional catalysis

Unlike the aforementioned types of catalysis, base catalysed Diels–Alder reactions work through the activation of the diene by raising its HOMO energy as opposed to lowering the LUMO energy of the dienophile. Brønsted base catalysis is often used in combination with bifunctional catalysis and both will therefore be discussed in parallel.

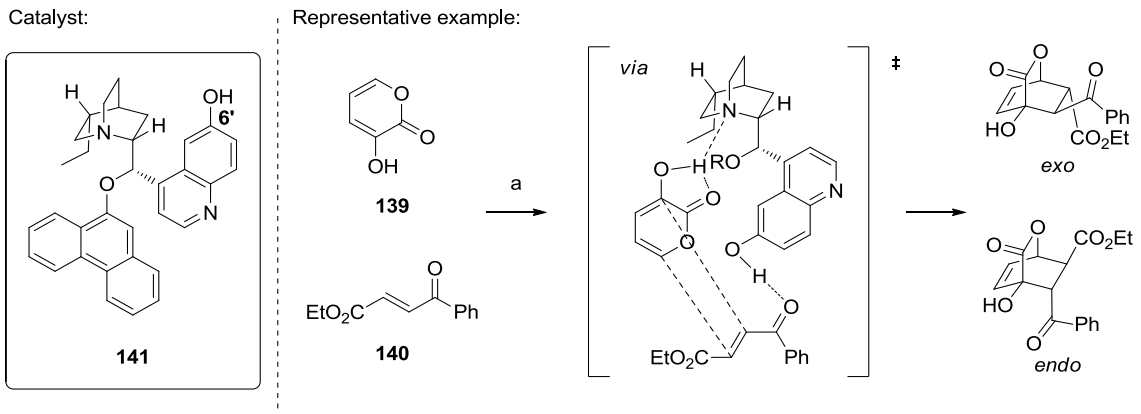
In 1989 Riant and Kagan attempted to introduce asymmetry in the base catalysed reaction[64] between anthrone (**135**) and *N*-methyl maleimide (**136**) using various alkaloid bases, prolinol and *N*-methylephedrine as organocatalysts. Using a catalytic amount of quinidine (**137**) they obtained the cycloadduct **138** in an excellent 97% yield with a moderate selectivity of 61% ee (Scheme 25).[65] They postulated that the conjugate acid of the chiral quinidine introduces asymmetry to the system in a bifunctional manner by: (a) associating as the counter ion of the achiral dienolate of **135**, whilst at the same time (b) H-bonding to **136**.



Scheme 25: Quinidine catalysed Diels–Alder reaction. Reaction conditions: Reagents and conditions: (a) 137 **(10 mol %), $CHCl_3$, –50 ° C, 97%, 61% ee.**

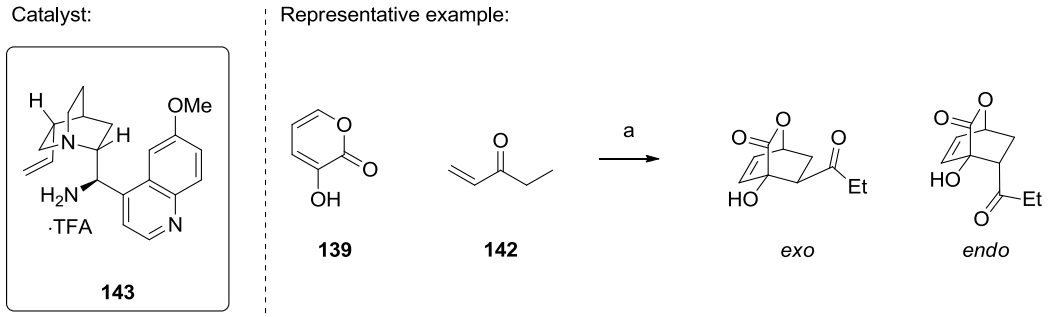
In an elegant demonstration of bifunctional organocatalysis, in 2007 Deng reported the highly selective asymmetric Diels–Alder reaction of 2-pyrone **139** with active, electron-poor dienophiles (e.g. *α,β*-unsaturated ester **140**) using bifunctional organocatalyst **141** (Scheme 26).[66] Deng reasoned that: (a) the catalyst's quinuclidine functionality raises the HOMO of **139** by partial enolate formation and (b) the 6'-hydroxyquinoline

functionality lowers the LUMO of the dienophile by H-bonding to it whilst directing the incoming entities in an enantioselective manner.



Scheme 26: Deng's Diels–Alder reaction of 139 **with activated dienophiles *via* asymmetric bifunctional organocatalysis. Reaction conditions: (a)** 141 **(5 mol %), Et_2O, rt, 87%, 97:3 *exo*:*endo*, 94% *exo* ee.**

However, when Deng used this methodology to catalyse the Diels–Alder reaction of 2-pyrone **139** with simple, non-activated α,β-unsaturated ketones (e.g. **142**), the catalyst proved ineffective. After testing various H-bond donors and acceptors with no success, a different strategy was adopted.



Scheme 27: Deng's Diels–Alder reaction of 2-pyrone with non-activated dienophiles *via* asymmetric bifunctional organocatalysis. Reaction conditions: (a) 143 **(5 mol %), 20 mol % TFA, CH_2Cl_2, –20 °C, 99%, 97:3 *exo*:*endo*, 99% *exo* ee.**

Similar to MacMillan, Deng achieved the lowering of the LUMO of the unreactive dienophile **142** by forming a chiral iminium ion using the TFA salt of epi-amino-quinidine **143**.[67] In parallel, the quinuclidine functionality in **143** raised the HOMO of the diene similarly to the aforementioned example, giving rise to excellent yields, diastereo- and enantioselectivities (Scheme 27).[68]

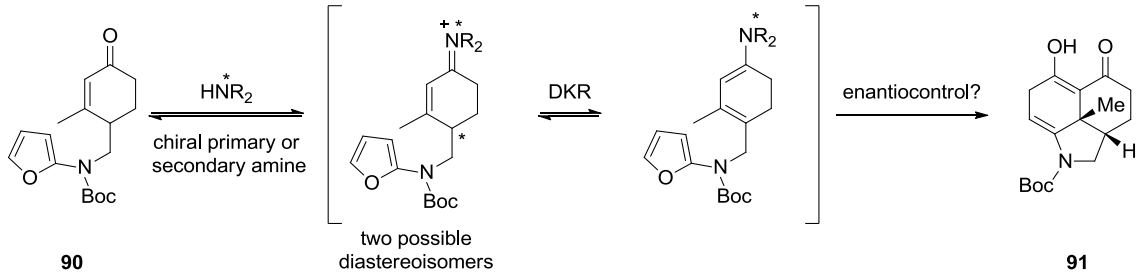
2.5.3 Organocatalytic enantioselective Diels–Alder reaction of furans

Asymmetric induction in the intermolecular Diels–Alder reaction of furans as well as the IMDAF reaction has mostly been achieved through substrate control or Lewis-acid catalysis.[37,49,50] The organocatalytic variant is an attractive yet unprecedented alternative.[69]

2.5.3.1 Organocatalytic enantioselective IMDAF reaction

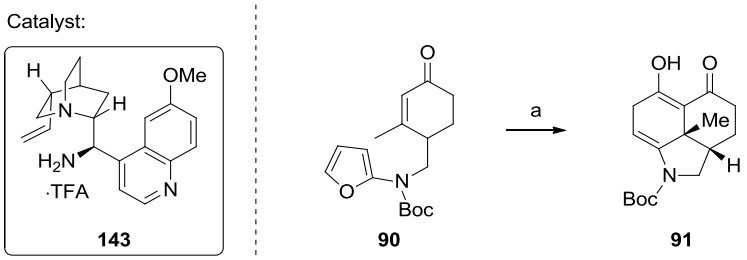
As mentioned in section **1.6.1**, Ward achieved the construction of the ACD tricyclic cores of both daphniyunnine B (**22**) and D (**23**) *via* a one-carbon homologation followed by an IMDAF cycloaddition. Because the one-carbon homologation was low yielding, Ward begun a preliminary investigation of the enantioselective variant of the IMDAF using the easily accessible non-homologated 6-membered ring analogue **90**. Already establishing that the IMDAF/fragmentation reaction could be promoted under thermal conditions to give rise to the racemic [6–5–6] tricyclic model **91**, attempts were made to introduce enantioselectivity *via* organocatalysis.

Since primary and secondary amines can: (a) activate dienophiles *via* iminium catalysis[51] and (b) racemise the γ-position of enones *via* the formation of dienamine intermediates,[70] a dynamic kinetic resolution (DKR)[71] was envisaged to occur between the diastereoisomeric iminium and dienamine forms of **90**, derived by reacting it with a chiral amine. During this rapid equilibrium, one diastereoisomer of the two possible iminium ions would undergo an IMDAF reaction at a faster rate, thus giving rise to an enantioenriched tricycle **91** (Scheme 28).



Scheme 28: Ward's proposal for enantiocontrol in the IMDAF/fragmentation reaction.

The results of this investigation were only preliminary, however, Ward discovered that chiral secondary amine catalysts such as MacMillan's imidazolidinone **128**, (*S*)-proline and other proline derived catalysts proved ineffective towards the IMDAF reaction. It was postulated that these catalysts form a stable enamine, making the dienophile unavailable for cycloaddition. However, when the TFA salt of epi-amino-quinidine **143** was used, an 81% ee for the model tricyclic [6–5–6] adduct **91** was achieved, albeit in low yield and using a high catalyst loading (Scheme 29).



Scheme 29: Proof of principle for Ward's asymmetric IMDAF reaction. Reaction conditions: (a) 143 **(40 mol %), TFA (40 mol %), THF, 50 °C, 25%, 81% ee.**

This transformation provided a proof of principle for the induction of asymmetry in the IMDAF reaction, however it did not afford the desired [6–5–7] tricycle of the calyciphylline A-type subclass of the *Daphniphyllum* alkaloids. Attempts towards the asymmetric construction of this tricycle were not carried out.

2.6 An intramolecular furan Diels–Alder reaction approach for the synthesis of the main [6–5–7] tricyclic core (ACD rings) of daphniyunnine D: results and discussion

2.6.1 Introduction

The remainder of this chapter focuses on our efforts towards the [6–5–7] enantioenriched tricyclic ACD core of daphniyunnine D (**23**). The unpublished work of Dr. Darses had already set a foundation for the route to the racemic core; however certain issues regarding low yields and irreproducibility had to be addressed. Furthermore, sufficient quantities of the IMDAF precursor needed to be synthesised in order to ensure the thorough and effective study of the asymmetric variant of this cycloaddition, crucial to the success of the project.

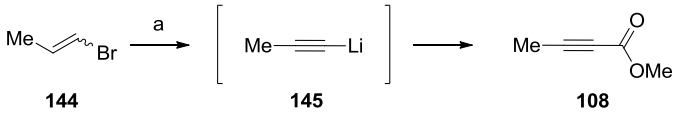
2.6.2 Construction of the 7-membered ring dienophile

2.6.2.1 Synthesis of 7-membered ring D via a 5 to 7 ring-expansion reaction cascade

It was discovered that rapid entry to the 7-membered ring of the natural product could be accessed following a modification of a previously published 5 to 7 ring-expansion reaction[33] using oxocyclopentanecarboxylate (**107**) and methyl but-2-ynoate (**108**). Although the internal alkynoate **108** is commercially available, its high price[i] encouraged us to develop a scalable and reproducible procedure for its synthesis. Our protocol[72] is based on a method previously reported for the preparation of propargylic secondary alcohols and ketones.[73] We make use of the cheap and commercially available mixture of *Z* and *E* isomers of 1-bromo-1-propene (**144**) by treating it with *n*-BuLi at −78 °C to generate

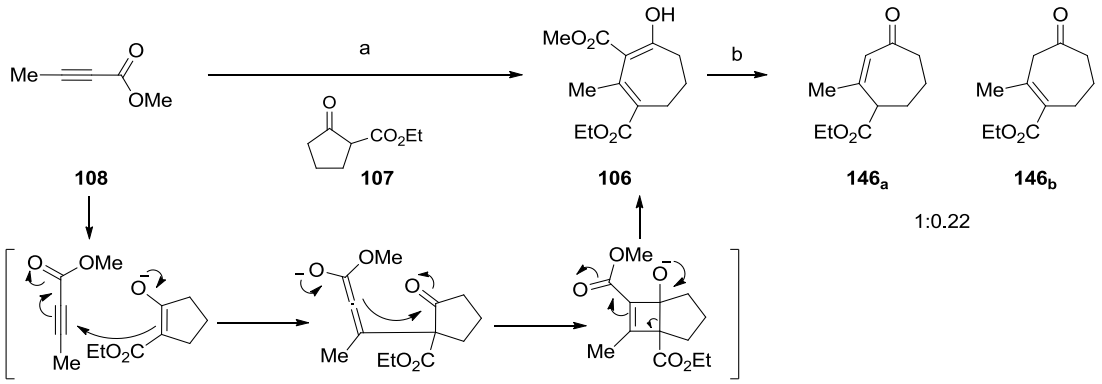
[i] £288.86 per 25 g (Acros Organics).

the propynyllithium (**145**) *in situ*.[i] This nucleophile is then reacted with methyl chloroformate to afford the desired alkynoate **108** in 77% yield (Scheme 30).[ii] The procedure can give rise to multigram quantities of this synthetically useful reagent[74] essential to our synthesis.



Scheme 30: Facile multigram synthesis of methyl but-2-ynoate (108**). Reaction conditions: (a) *n*-BuLi (2.1 equiv), methyl chloroformate, THF, –78 °C to rt, 77%.**

Subsequently, the methyl but-2-ynoate (**108**) was reacted with the sodium salt of the commercially available ethyl 2-oxocyclopentanecarboxylate (**107**) in refluxing THF, to form the ring-expanded **106** in 72% yield (Scheme 31a).[33] This one-pot transformation combines a tandem intermolecular Michael addition[27] to the electron-poor triple bond followed by an intramolecular cyclisation to the ketone, with a final Grob-type fragmentation[25] providing direct access to the multifunctional 7-membered ring **106**.



Scheme 31: Synthesis of 7-membered ring ketoester 146**. Reaction conditions: (a) NaH, ethyl 2-oxocyclopentanecarboxylate (**107**), THF, reflux, 72%; (b) LiCl, HCl (aq), DMSO, 120 °C, 75%.**

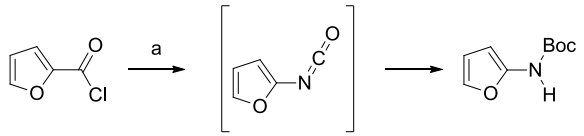
Subjecting **106** to Krapcho dealkyloxycarbonylation[28] using LiCl in wet DMSO allowed for the chemoselective removal of the more labile methyl ester functionality affording the

[i] There is uncertainty as to whether this is formed *via* a carbene mechanism or not; especially as a mixture of *Z* and *E* isomers of 1-bromo-1-propene is used.

[ii] This scalable and reproducible reaction was also performed on a 952 mmol scale (115 g of **144**) to afford the alkynoate **108** in 80% yield (experiment conducted by Dr. Darses).

7-membered ring ketoester **146** in 75% yield as an inseparable mixture of regioisomers (1:0.22).[i,74d]

To allow for the IMDAF cycloaddition, introduction of the 4π-electron furan functionality to the dienophile ketoester **146** was required. With a large scale preparation report of the *N*-Boc amino furan **87** from Padwa,[75] and with prior experience in the Dixon group in handling this electron-rich furan, we synthesized **87** on a multigram scale (50 g of **147**) *via* a Curtius rearrangement[76] using 2-furoyl chloride (**147**) and sodium azide in *t*-BuOH (Scheme 32).



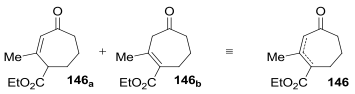
147 **87**

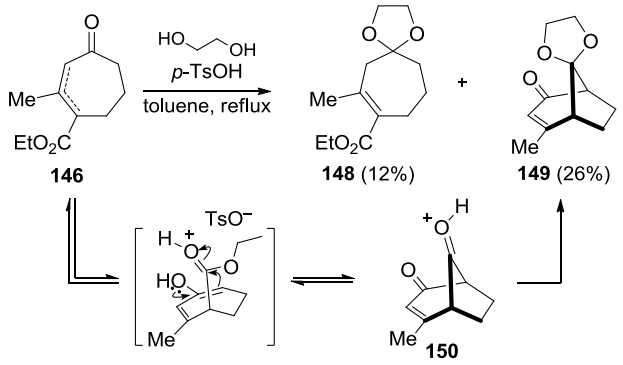
Scheme 32: Large scale synthesis of *N*-Boc amino furan (87**). Reaction conditions: (a) NaN_3, *t*-BuOH, rt for 15 h then reflux for 10 h, 79%.**

2.6.2.2 A serendipitous discovery of an acid-catalysed synthesis of bicyclo[3.n.1]alkenediones

In an attempt to protect the ketone functionality in ketoester **146** prior to the introduction of the diene, Dr. Darses noted that using ethylene glycol with catalytic *p*-TsOH, afforded only 12% of the desired acetal **148**. The major product, isolated in 26% yield was the unexpected monoprotected bicyclo[3.2.1]alkenedione **149** (Scheme 33). Formation of this major side-product was attributed to an acid-catalysed Dieckmann-type reaction[77,78] of the enol form of the cyclic enone **146** onto the activated ester moiety, followed by an *in situ* protection of the afforded ketone **150**.

[i] For the purposes of simplicity, the 7-membered ring ketoesters $\mathbf{146}_a$ and $\mathbf{146}_b$ will be drawn as shown in the remainder of this thesis.





Scheme 33: Proposed mechanistic pathway for the unexpected formation of monoprotected bicyclo[3.2.1]alkenedione 149**.**

Although undesirable in our synthesis of daphniyunnine D, this intriguing motif is present in numerous biologically active and synthetically challenging polyphenol and phloroglucinol derivatives.[79] Examples of these natural products are vitisinol D (**151**) (radical scavenger),[80] garsubelin A (**152**) (potential anti-Alzheimer agent)[81] and welwistatin (anticancer activity) (**153**) (Figure 5).[82] We believed that our acid-mediated cyclisation may constitute a unique entry into scaffolds related to these natural products; therefore, an investigation was carried out to test the generality of the transformation. This research occurred prior to the DPhil work presented in this thesis,[i] but has been included in this chapter for completeness.

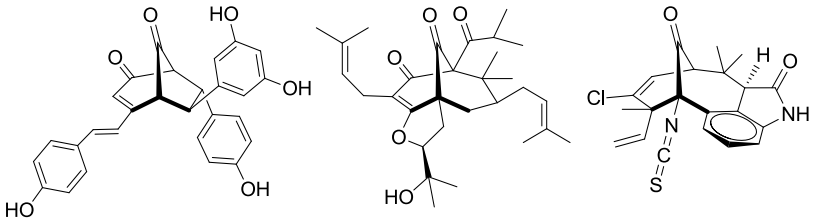


Figure 5: Naturally occurring bicyclo[*m*.*n*.1]alkanone frameworks.

It was discovered that under optimised conditions, a catalytic amount of *p*-TsOH in the absence of ethylene glycol in *m*-xylene reflux can give rise to a range of bicyclo[3.*n*.1]alkenediones in good yield (Figure 6).[74d] Substrates for this acid-catalysed

[i] The development of this project took place in the academic year 2009-2010 (Part II/Master thesis project: Iacovos N. Michaelides), independent from the work documented in this thesis.

cyclisation were synthesised using the ring-expansion, dealkyloxycarbonylation protocol developed en route to daphniyunnine D.

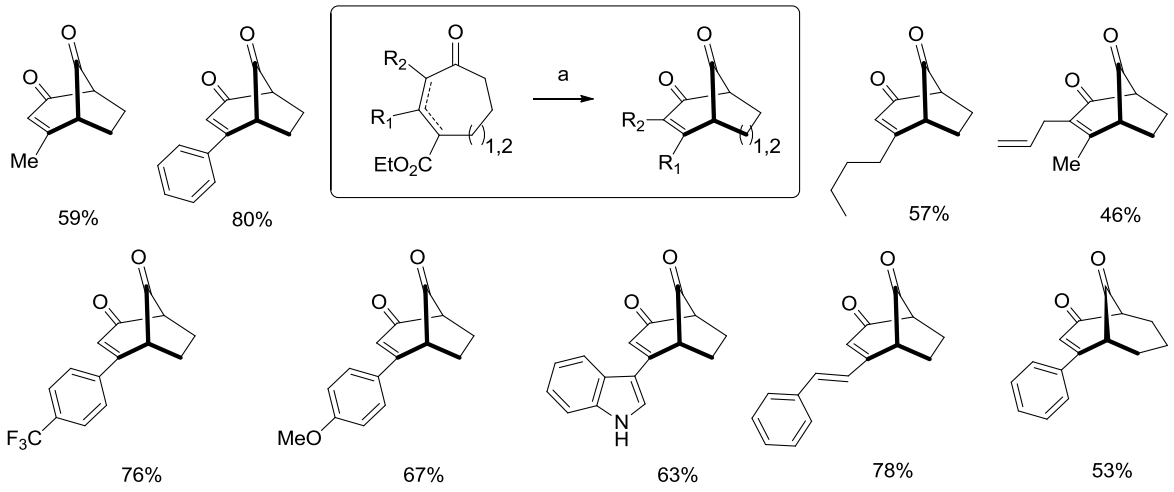
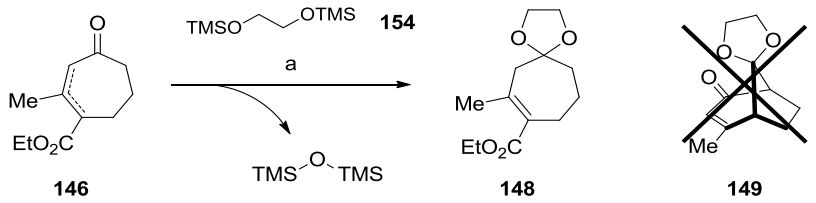


Figure 6: Scope of acid-catalysed synthesis of bicyclo[3.*n*.1]alkenediones. Reaction conditions: (a) *p*-TsOH (10 mol %), *m*-xylene, reflux.

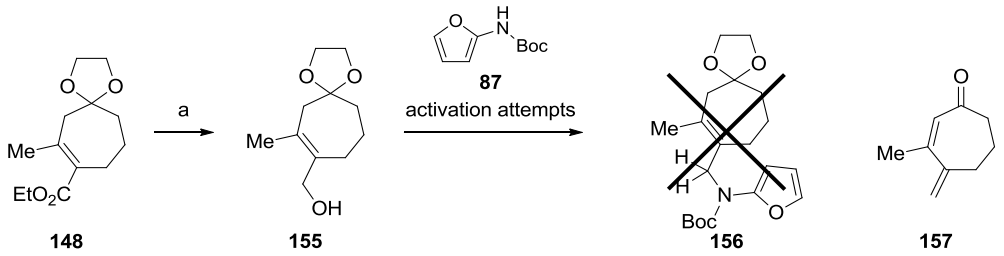
2.6.2.3 Furan moiety introduction to the 7-membered ring core

An alternative aprotic protection[83] using 1,2-bis-(trimethylsiloxy)ethane (**154**) with a catalytic amount of TMSOTf in CH_2Cl_2 gave rise to the desired acetal **148** in 90% yield, with no isolation of products associated with the aforementioned Dieckmann-type reaction. The equilibrium in this acetalisation is driven by the formation of the stable hexamethylsiloxane, allowing for the protection at lower temperatures thus avoiding the formation of the bicyclo[3.2.1]alkenedione **149** (Scheme 34). These mild conditions are known to inhibit double-bond isomerisation processes.[84]



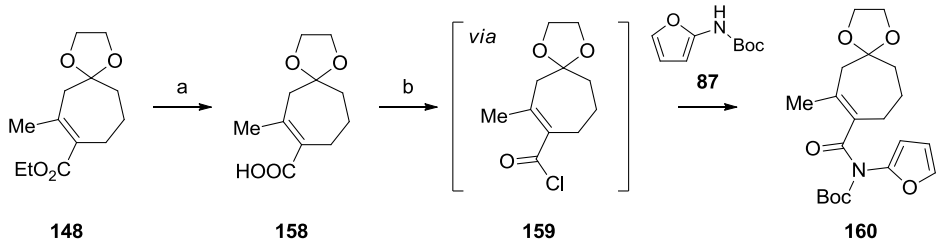
Scheme 34: Aprotic acetal protection. Reaction conditions: (a) TMSOTf, 1,2-bis-(trimethylsiloxy)ethane, CH_2Cl_2, rt, 90%.

Following Ward's protocol (see section **1.6.1**), Dr. Darses successfully reduced the ethyl ester moiety to the alcohol **155** in 82% yield using $LiAlH_4$. However, tosylation of the alcohol followed by a nucleophilic substitution with the potassium salt of **87** was unsuccessful in forming **156**, as complex mixtures containing the deprotected diene **157** were afforded (Scheme 35).



Scheme 35: Synthesis of alcohol 155 **following Ward's protocol. Reaction conditions: (a) $LiAlH_4$, THF, 0 °C, 82%.**

A change of strategy was sought and rather than introducing **87** *via* a nucleophilic substitution, an amide coupling to the hydrolysed ester of **148** was envisaged. To this effect a basic ester hydrolysis afforded the amide coupling substrate **158** in 95% yield which was subsequently activated to the acid chloride **159** using oxalyl chloride with a catalytic amount of DMF. Reaction of the activated acid with the sodium salt of **87**[i] afforded the desired amide coupled product **160** in 63% yield (Scheme 36).



Scheme 36: Synthesis of 160**. Reaction conditions: (a) KOH (aq), THF/MeOH, 60 °C, 95%; (b) (i) NaH, DMF, oxalyl chloride, THF, 0 °C then (ii) NaH,** 87**, THF, 0 °C, 63%.**

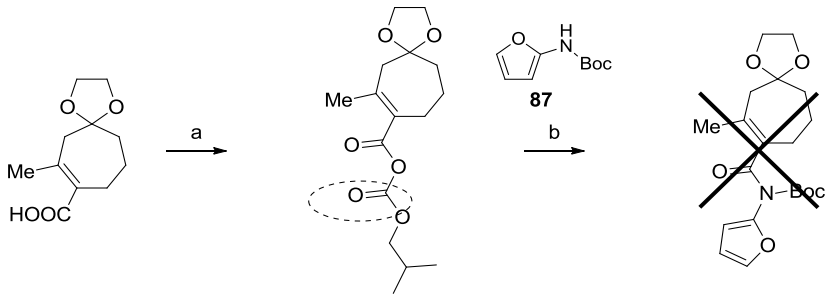
However, the yield of this amide coupling was unsatisfactory for a reaction at this early stage in the synthesis. Moreover, the reaction proved unreliable especially when performed

[i] The nitrogen's nucleophilicity in **87** is somewhat diminished due to the conjugated Boc group, therefore the formation of its anionic form prior to nucleophilic attack is necessary. See reference 75.

on large scale. To this end, multigram quantities of its precursor **158** were synthesised to allow for its investigation.

2.6.2.4 Alternative amide coupling methods

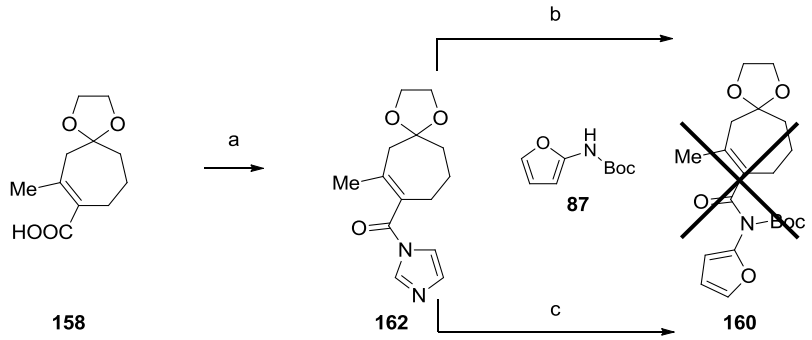
Alternative approaches for the activation of acid **158** were sought using isobutyl chloroformate[85] and carbonyldiimidazole (CDI).[86] A one-pot attempt to couple the mixed anhydride **161** (formed *in situ*) with the sodium salt of **87** failed to afford the desired product. As the presumed mixed anhydride appeared to be stable on TLC, we successfully isolated this "activated" form of the acid in 77% yield by fcc and confirmed its structure by NMR analysis (Scheme 37). Unfortunately, coupling the nucleophile **87** to the freshly purified anhydride **161** also failed to provide the product and slow hydrolysis back to the acid **158** was observed. We suspect that the nucleophile may attack the undesired carbonyl of the anhydride leading to hydrolysis.



Scheme 37: Coupling attempt using a mixed anhydride. Reaction conditions: (a) NaH, isobutyl chloroformate, THF, 0 °C to rt, 77%; (b) NaH, 87**, THF, 0 °C, no product formation.**

Reacting acid **158** with CDI, we successfully synthesised and isolated the acyl imidazole **162** in 81% yield (Scheme 38). Unfortunately, this mode of activation was also unsuccessful in providing the coupled product, even after heating the imidazoyl **162** with the nucleophile to reflux in toluene (Scheme 38c).

These "activated" acid equivalents, **161** and **162**, were deemed unreactive towards attack by the bulky *N*-Boc amino furan **87**, either because of steric clashes with the nucleophile or because of lack of electrophilicity at their carbonyl centres.



Scheme 38: Coupling attempt using CDI activation. Reaction conditions: (a) CDI, THF, 0 °C to rt, 81%; (b) NaH, 87**, THF, 0 °C to reflux, no product formation; (c) NaH,** 87**, toluene, 0 °C to reflux, no product formation.**

Having failed to identify better candidates for the amide coupling, we decided to revisit the acid chloride activation with the intention of optimising it to a scalable route.

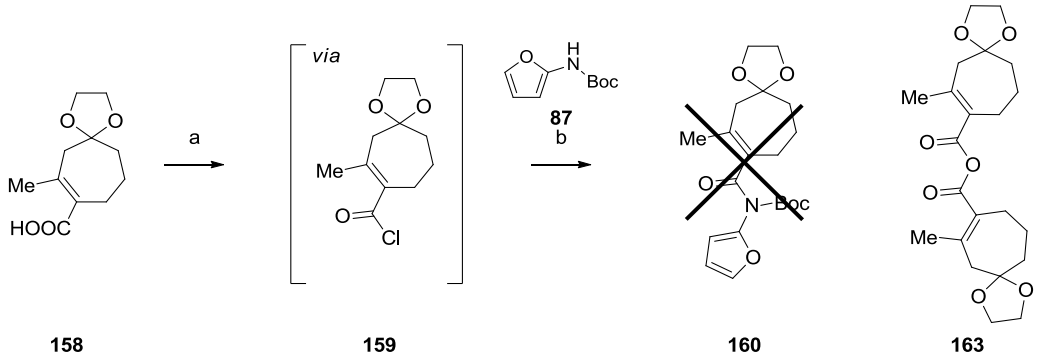
2.6.2.5 Optimisation of the amide coupling—acid chloride activation

One possible reason for the irreproducibility observed in the acid chloride activation may be due to the acid labile acetal present in the amide coupling substrate **158**. Any HCl evolution during the formation of the acid chloride from oxalyl chloride may affect an acid catalysed deprotection of both the acid **158** and acid chloride **159** which could possibly lead to further side-reactions. For this reason, both the sodium salt of the acid **158** as well as the incoming nucleophile **87** have to be preformed.[i] By doing so, a proton source in the reaction mixture can be eliminated and instead of HCl, benign NaCl precipitates out of the reaction which can be removed during work-up.[87] Another potential problem is the introduction of moisture during the handling of the reactive acid chloride **159**. Moisture

[i] Attempting the reaction without using NaH for the formation of the sodium salts, complex reaction mixtures were obtained.

would reform **158** from the acid chloride **159** and at the same time form HCl which would again jeopardise the integrity of the acetal.

In preliminary experiments, reduced pressure was used to remove the large excess of the electrophilic oxalyl chloride before the coupling took place. As a dark colour evolution was noted during the concentration of the yellow acid chloride oil when low yielding reactions were performed, a one-pot protocol avoiding the handling of the sensitive acid chloride **159** was attempted. Employing fewer equivalents of oxalyl chloride, no evaporation was thought necessary prior to the introduction of the nucleophile **87**.

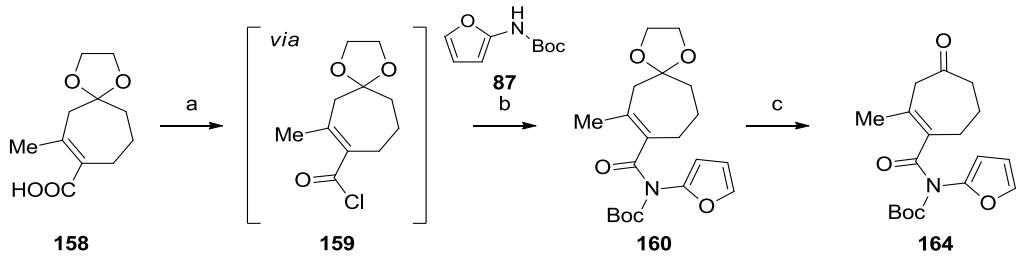


158 **159** **160** **163**

Scheme 39: Undesired anhydride 163 **formation. Reaction conditions: (a) NaH, DMF, oxalyl chloride, THF, 0 °C to rt; (b) NaH,** 87**, THF, 0 °C, 51% of** 163**.**

This reaction did not provide any of the coupled product **160**, however, the dimerised acid **163** was isolated in 51% yield (Scheme 39). This led us to consider that if the acid chloride formation rate is slow enough it would allow for any unreacted acid to attack the nascent acid chloride leading to the anhydride **163**. Although this may itself be reactive towards nucleophilic attack, it would inevitably always lead to a stoichiometric evolution of the unactivated acid **158**, so its formation needed to be avoided. Studying the crude NMR spectra of previous unsuccessful coupling attempts, we noted that this anhydride **163** was the main impurity often overlooked due to nearly identical peaks with the acid precursor in the ^{1}H NMR spectra. This discovery was key to solving this challenging step.

After significant optimisation,[i] a reliable and reproducible synthesis was established amenable to scale-up, giving rise to **160** in a significantly improved 81% yield (Scheme 40).[ii] It was discovered that for the acid chloride to compete successfully with the anhydride formation, a large excess of oxalyl chloride was necessary combined with a higher temperature (25 °C rather than 0 °C). In order to remove any moisture, molecular sieves were included in the reaction mixture and to avoid the handling of the acid chloride a stream of nitrogen was used to evaporate the THF and excess oxalyl chloride; use of a rotary evaporator led to inconsistent results. After re-diluting the crude acid chloride in THF, the preformed sodium salt of **87** was added as a suspension in THF at 0 °C to give rise to **160** after only 10 min; this part of the reaction was instantaneous.



Scheme 40: Optimised amide coupling reaction and synthesis of IMDAF reaction substrate 164**. Reaction conditions: (a) NaH, 3Å MS, DMF, oxalyl chloride, THF, 0 °C; then (b) NaH,** 87**, THF, 0 °C, 81%; (c) *p*-TsOH (10 mol %), acetone, rt, 78%.**

Having optimised this capricious amide coupling step, an acetal deprotection using catalytic *p*-TsOH in acetone at rt gave rise to the IMDAF substrate **164** in 78% yield (Scheme 40). With sufficient material in hand, our focus now turned to the investigation of the key organocatalytic enantioselective IMDAF reaction.

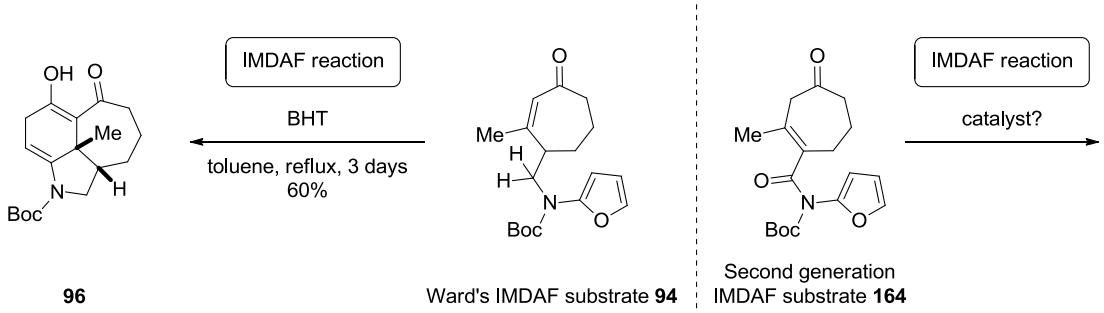
[i] Variations in temperature, reaction period, solvent, concentration, equivalents as well as rates of addition of reagents were investigated.

[ii] Largest scale attempted was with 6.0 g of the acid **158**. Refer to chapter 5 for details of the meticulous experimental method, including a photograph of the experimental setup.

2.6.3 IMDAF reaction investigation

2.6.3.1 Synthesis of the racemic IMDAF adduct

In Ward's investigations, the double-bond of both the 6- as well as the 7-membered ring IMDAF substrates **90** and **94** was in conjugation with the ketone, poised to undergo the cycloaddition upon heating to reflux in toluene (see Scheme 16). Furthermore, introduction of asymmetry in his 6-membered ring-system **90** was achieved by epimerising the γ-position of the ketone *via* iminium-enamine catalysis (see section **2.5.3.1** and Scheme 28).

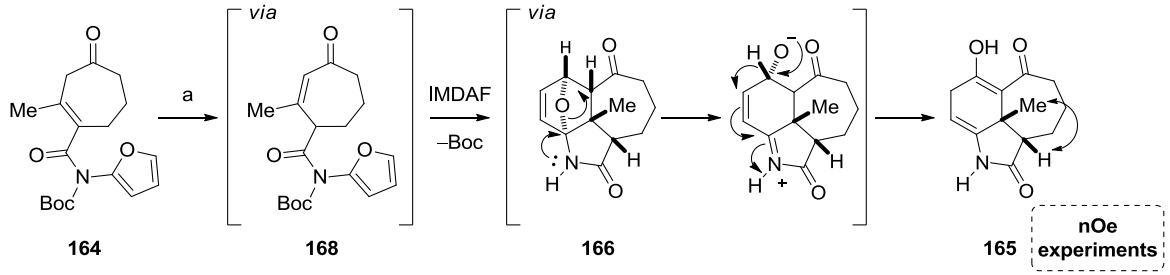


Scheme 41: Direct comparison between Ward's amido-IMDAF substrate 94 **and the second generation's imido-IMDAF substrate** 164**.**

In our second generation synthesis, replacing the methylene unit adjacent to the nitrogen, with a carbonyl, led to the double-bond in the analogous imido-IMDAF substrate **164** to be in conjugation with the amide as opposed to the ketone (Scheme 41).

Aware that 2-imidofurans undergo the cycloaddition unassisted even at rt (Scheme 21),[45,46] if any asymmetry is to be introduced in our system it would be prior to the double-bond coming into conjugation with the ketone. Making the assumption that the IMDAF reaction would occur in tandem right after the dienophile formation, different conditions were tested to probe the reactivity of our substrate **164** towards this cascade.

In a preliminary experiment,[i] using acidic conditions to migrate the double bond i.e. catalytic *p*-TsOH in refluxing toluene, did not afford the desired adduct **104** (Figure 4 on page 25). Instead, the ring-opened **165** was isolated in 10% yield (Scheme 42). We concluded that these conditions not only promoted the cascade, leading to the formation of the adduct **104**, they also led to the deprotection of the Boc group.[ii] This enabled the lone pairs of the nitrogen in **166** to fragment the oxabicyclic adduct, giving rise to hydroxyenone **165** as a single diastereoisomer after enolisation[iii]. Lowering the temperature to 85 °C did not lead to any reaction nor did refluxing the starting material in toluene in the absence of *p*-TsOH.



Scheme 42: Acid-catalysed IMDAF reaction. Reaction conditions: (a) *p*-TsOH (20 mol %), toluene, reflux, 10%.

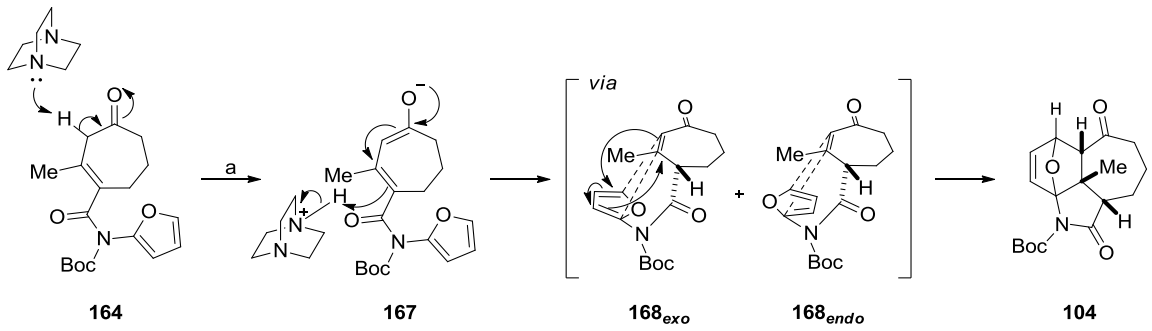
Although the anticipated product was not afforded, this reaction proved that not only can the IMDAF cycloaddition take place in our system, it can also undergo the fragmentation of the adduct giving rise to a [6–5–7] tricycle **165** in a highly diastereoselective manner. Confirmation of its relative stereochemistry by nOe experiments gave us confidence that this sequence of reactions could constitute a unique entry into the targeted calyciphylline A-type *Daphniphyllum* alkaloid scaffolds.

A short screen of conditions[i] revealed that a catalytic amount of DABCO in toluene at 85 °C can give rise to the IMDAF adduct **104** in 96% yield and 86:14 dr without

[i] Experiment conducted by Dr. Darses.
[ii] The opposite sequence of events is also possible.
[iii] No diketone peaks were observed in the NMR spectra.

undergoing the fragmentation (Scheme 43). As the diastereoisomers could not be separated by fcc, their relative stereochemistry was not determined at this point. Since the relative stereochemistry of the resultant tricycle **165** from the aforementioned fragmentation had already been established, it was assumed that the two diastereoisomers were a consequence of an *exo* and an *endo* cycloaddition pathway giving rise to opposite orientations of the oxido bridge in the afforded adduct.

As the reaction does not occur in the absence of a catalyst, even when refluxing in toluene, it is postulated that the DABCO initially deprotonates the α-position of the ketone leading to the extended enolate **167** (Scheme 43). This enolate then undergoes a γ-protonation from the conjugate acid of DABCO giving rise to the reactive dienophile **168**; an overall proton-transfer from the α- to the γ-position of the ketone. A tandem IMDAF reaction (*exo* or *endo*) then occurs spontaneously to afford the desired adduct **104**. From this point onwards, this reaction will be referred to as a "proton-transfer/IMDAF reaction cascade".



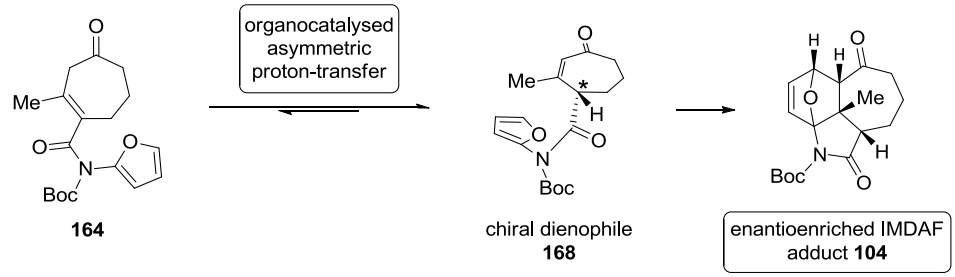
Scheme 43: Postulated reaction mechanism for the novel proton-transfer/IMDAF reaction cascade. Reaction conditions: (a) DABCO (10 mol %), toluene, 85 °C, 96%, 86:14 dr.

2.6.3.2 Organocatalytic enantioselective synthesis of the IMDAF adduct

2.6.3.2.1 Establishing conditions for the asymmetric variant of the proton-transfer/IMDAF reaction cascade

The successful access to the racemic adduct set the scene for the investigation of the asymmetric variant of this novel proton-transfer/IMDAF reaction cascade. If the

proton-transfer could be performed in an enantiocontrolled manner, the IMDAF would trap the transient chiral dienophile **168** to give rise to an enantioenriched adduct **104** (Scheme 44).



Scheme 44: Introduction of asymmetry in the proton-transfer/IMDAF reaction cascade.

Unfortunately the moderate diastereoselectivity of the reaction hindered these efforts as initial attempts to separate the diastereoisomers on the HPLC were unsuccessful. To circumvent this problem, different temperatures were tested for the cascade in order to improve the diastereoselectivity.

It was discovered that the reaction takes place at 50 °C to give rise to a quantitative yield of the adduct with a significantly improved 95:5 dr in only 18 hours.[i,ii] We also noted that the cascade occurs at rt, however 6 days are necessary and the adduct is afforded with the same dr. A variety of solvents were also screened (see appendix), however toluene was superior to these in terms of yield and diastereoselectivity.

The improved diastereoselectivity not only facilitated the analysis of the racemate on the HPLC, it also allowed us to determine the relative configuration of the major IMDAF adduct by nOe experiments. Consistent with Padwa's reports[45] the *exo*-adduct is the major diastereoisomer, therefore the product of the cycloaddition will be depicted as such in the remainder of this thesis. This result is attributed to the minimising of steric clashes in the

[i] A 3.5 day reaction is described in the experimental chapter 5. It was later discovered that prolonged reaction periods were not necessary to drive the reaction to completion.

[ii] Using NEt_3 instead of DABCO resulted in a slower reaction even though both have a very similar pK_a in DMSO (9.0 and 8.9 respectively).

transition state by formation of the oxido bridge *anti* to the substituents on the bridgehead carbon. As we have not isolated the minor diastereoiosmer form this reaction, we have only tentatively assigned it as the *endo*-adduct. Higher temperatures seem to favour its formation, raising questions as to whether the cycloaddition stage of the cascade is in fact reversible.[i]

Having optimised the conditions for the racemic cascade, investigation into the asymmetric variant was initiated. As some chiral catalysts (*vide infra*) proved sluggish even at 50 °C, a loading of 20 mol % and a long reaction period of 11 days was employed for the catalyst screen. This ensured some product formation for HPLC analysis.

2.6.3.2.2 Catalyst screen for the asymmetric proton-transfer/IMDAF reaction cascade

Postulating that the asymmetric cascade could occur *via* a combination of enamine and iminium catalysis (see section **2.5.3.1** on page 35), (*S*)-*α*-methylbenzylamine was used with benzoic acid as co-catalyst to promote the reaction (Figure 7). Although **164** appeared stable to the benzoic acid, only traces of product were afforded even after 7 days at 50 °C. When the bifunctional epi-amino-quinine derived primary amine **catalyst 13**[ii] was employed (the TFA salt of its pseudoenantiomer **143**[iii] used by Ward to induce an 81% ee in his system), a significant 37% ee was afforded for the IMDAF adduct.[iv] Furthermore, when quinidine (**catalyst 9**) was used, a catalyst unable to perform iminium catalysis due to the absence of a primary amine, a low yet noteworthy ee of 13% was observed. This led

[i] Performing the reaction at 105 °C gave rise to the product in 89% yield and a significantly lower 62:38 dr in favour of the *exo* product.

[ii] The catalyst numbering follows the numbering reported in the appendix, which includes all the asymmetric reaction attempts.

[iii] *Cinchona* alkaloids exist as diastereoisomeric pairs in nature (e.g. cinchonine/cinchonidine and quinidine/quinine). Although they are not enantiomeric pairs they do give rise to opposite enantiomers in asymmetric catalysis, therefore these alkaloid pairs are often termed pseudoenantiomers in the literature (*vide infra* Figure 8).

[iv] The + and – signs preceding the ee's of the adducts in Figure 7 and the remaining chapter have been included to demonstrate the relative enrichment of one enantiomer over another. Moreover, they correlate to the corresponding optical rotation signs of the adduct.

us to conclude that iminium catalysis is not a requirement for reactivity nor asymmetric induction.

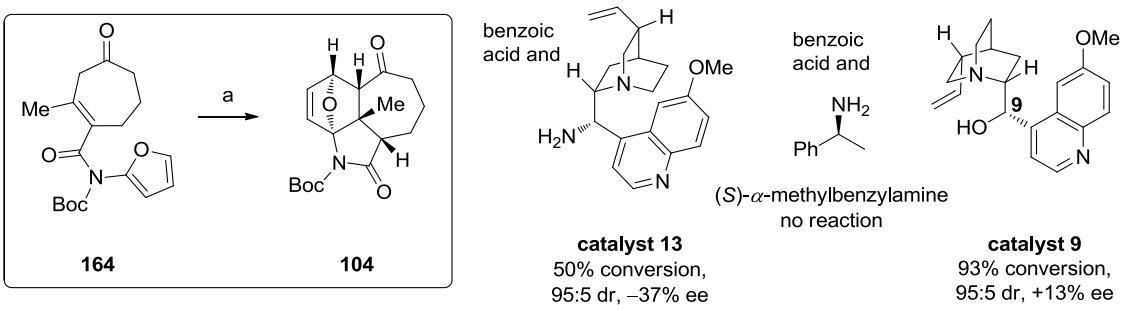


Figure 7: Attempts to validate the iminium catalysis hypothesis. Reaction conditions: catalyst (20 mol %), toluene, 50 °C.

These primary results led us to reconsider Ward's hypothesis concerning a DKR between the iminium[i] and enamine[ii] forms of the dienophile (see section **2.5.3.1**). It is important to note that compared to Ward's system, not only is the double bond not conjugated to the ketone in **164**, a 7- rather than a 6-membered ring contains the dienophile. It wouldn't be unreasonable therefore for two distinct catalytic pathways to occur in these related systems.

Encouraged by the aforementioned results using *cinchona* alkaloid catalysts, a different hypothesis was put forward. Since they contain a quinuclidine core related to DABCO in both structure and pK_a (Figure 8),[iii,88] these chiral alkaloids may perform the transformation in a similar fashion to DABCO (Scheme 43). The induction of enantioselectivity could be a consequence of the chirality of the alkaloid and its conjugate acid directing the proton-transfer steps of deprotonation and protonation respectively, whilst simultaneously H-bonding[89] to the substrate leading to enantiocontrol; similar to Deng's approach (see

[i] MacMillan-type catalysts based on imidazolidinone scaffolds were investigated prior to the work in this thesis and were met with little success as they were unable to give significant ee's.

[ii] Proline and proline-derived catalysts, known to perform well under enamine catalysis were tested. However, they did not afford the IMDAF adduct.

[iii] pK_a values for quinuclidine and DABCO in DMSO= 9.8 and 8.9 respectively (see reference 88).

section **2.5.2.3**).[66] Some further ordering may be possible *via* π-stacking between the catalyst's quinoline functionality and the furan of **164**.

Subsequently, a significant *cinchona*-derived bifunctional organocatalyst screen using our in-house library took place. The natural pseudoenantiomeric *cinchona* alkaloids are represented in Figure 8 for clarity. In the remainder of this section only the key findings which led to our best results will be reported, with particular focus on the enantioselectivity of the reaction rather than the conversion. Tables with conversions, diastereoselectivities and enantioselectivities of all our attempts have been included in the appendix for completeness.

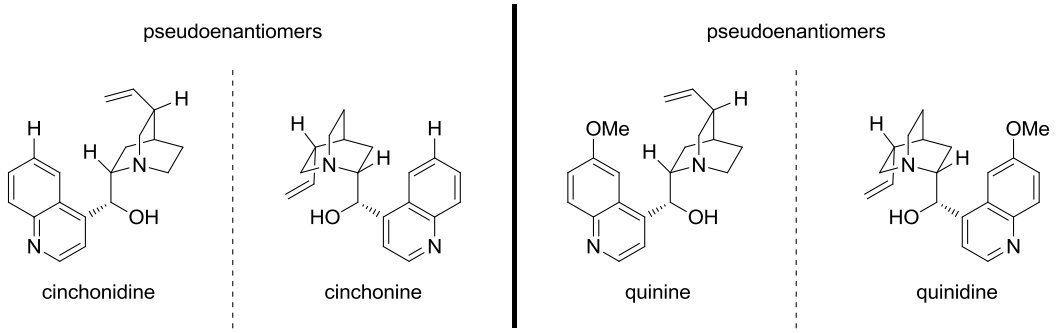


Figure 8: The natural *cinchona* alkaloids.

Inspired by Deng who demonstrated that *cinchona*-derived bifunctional catalysts containing a 6'-hydroxyquinoline can activate dienophiles *via* H-bonding (see section **2.5.2.3**), **catalyst 11** and **12** were used in our system. Although **catalyst 11** afforded a poor 7% ee, **catalyst 12** gave rise to the adduct in an improved 44% (Figure 9).

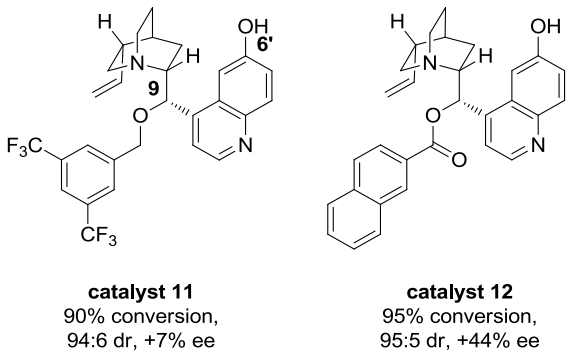
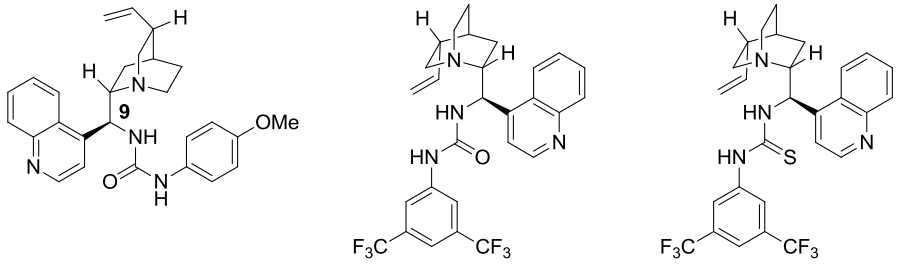


Figure 9: *Cinchona* alkaloid derived H-bond donor catalysts.

This encouraged us to investigate stronger H-bond donor catalysts, i.e. *cinchona*-derived ureas and thioureas (Figure 10).[89,90] Although these bidentate H-bond donors did not offer any improvement, the fluctuation in ee between different ureas (29-38%) and thioureas (6-36%) gave us confidence that varying the functionality at the C9 position of the *cinchona* scaffolds may lead to improvements in enantioselectivity (representative examples: Figure 10).



catalyst 1
80% conversion,
96:4 dr, –38% ee

catalyst 3
57% conversion,
94:6 dr, +32% ee

catalyst 26
31% conversion
(stopped after 48 h),
94:6 dr, +28% ee

Figure 10: *Cinchona* alkaloid derived urea and thiourea catalysts.

The real breakthrough in terms of selectivity and understanding of our catalytic system was achieved when the monodentate H-bond donors bearing a secondary amide functionality on the C9 position of the *cinchona* scaffold were employed.[90] Screening a family of benzoylamide derived *cinchona* catalysts we noted a significant improvement in enantiocontrol with ee's of the afforded adducts exceeding 50% in most cases (Figure 11). A relative inversion in ee was also observed when compared to their urea and thiourea analogues (e.g. **catalyst 1** *vs* **15**). An explanation for this is provided in section **2.6.3.2.3**.

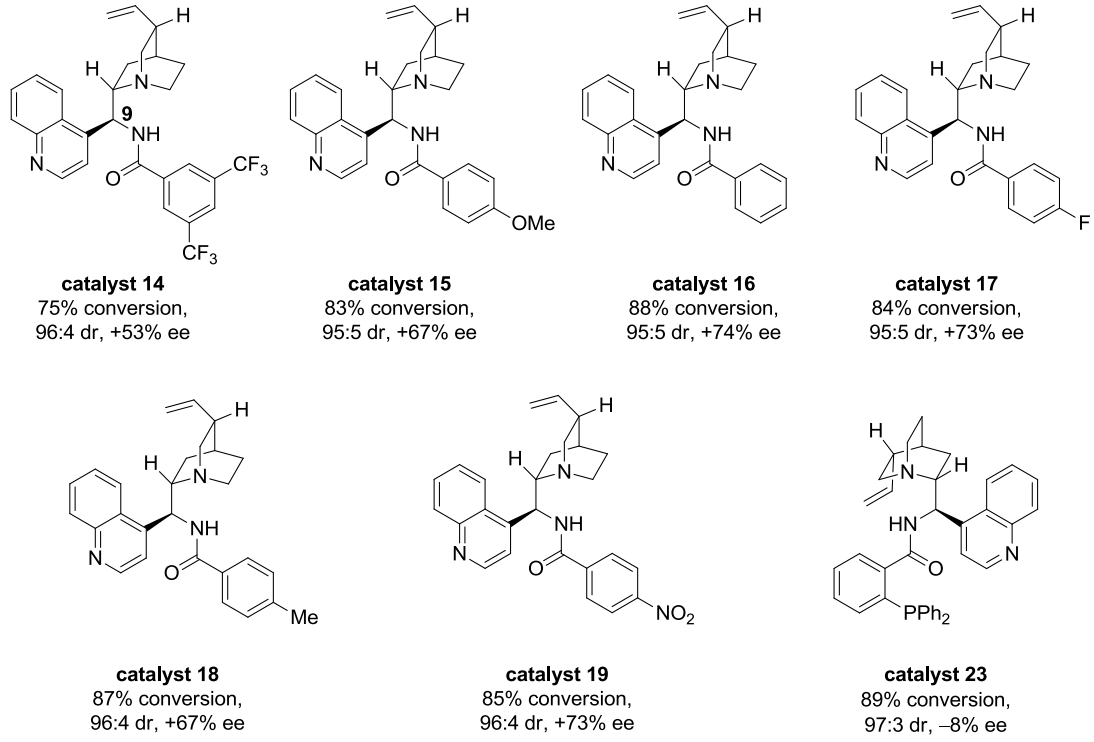


Figure 11: Cinchonine and cinchonidine derived benzoylamides.

The enantiocontrol did not appear to follow any trend correlating to the electron-rich or electron-poor character of the aromatic ring, which should affect the H-bond donor acidity and thus its enantiocontrol.[89] Instead, the fluctuation in ee seemed to originate from the varying bulk of the benzoylamide catalyst; a dramatic drop to 8% ee was observed using bulky **catalyst 23**. **Catalysts 16** and **17** bear testimony to both these facts as they are effectively isosteres of each other with electronically different aromatic rings, yet have near to identical ee's.

From this screen we eventually concluded that the cinchonidine derived *p*-nitrophenyl **catalyst 19** gave a very promising ee of 73%.[i] Directly comparing it to its quinine derived homologue **catalyst 22**, a minor drop to 69% ee was noted. Unfortunately, in an attempt to attain a corresponding enrichment in the opposite enantiomer of the adduct, an unexpected drop to 44% ee was observed when using the pseudoenantiomer (**catalyst 20**) of **catalyst**

[i] **Catalyst 16** gave a 74% ee; however, as **catalyst 19** and its analogues were available in larger quantities from our group's database, investigations relating to the latter catalyst took place.

19. This dramatic change in ee may lead to problems in the synthesis of daphniyunnine D as we have not determined the absolute stereochemistry of the adduct, nor do we know the absolute stereochemistry of the natural product.

Comparing **catalyst 20** and **21** we further concluded that reduction of the olefin functionality has only a subtle influence in the asymmetry of the reaction, although a higher conversion was observed (Figure 12).

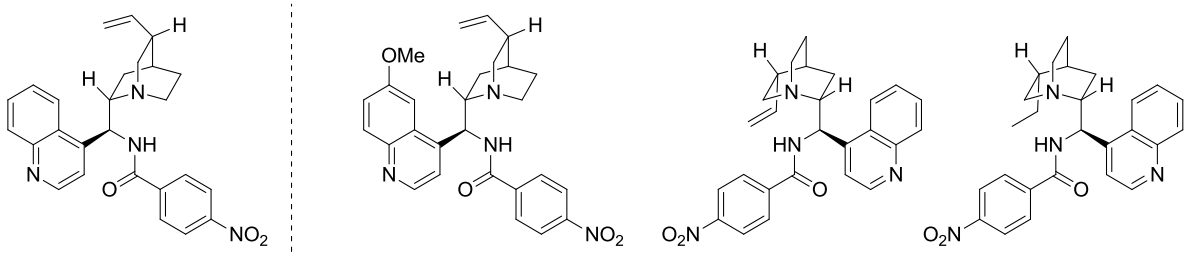


Figure 12: *p*-nitro benzoylamide derived *cinchona* catalysts.

Having identified our optimal H-bond donor, the bifunctional Takemoto-type scaffold[91] **catalyst 24** and Dixon's bifunctional iminophosphorane (BIMP)[92] scaffold **catalyst 25** were also tested; however, no improvements in ee were observed (Figure 13).

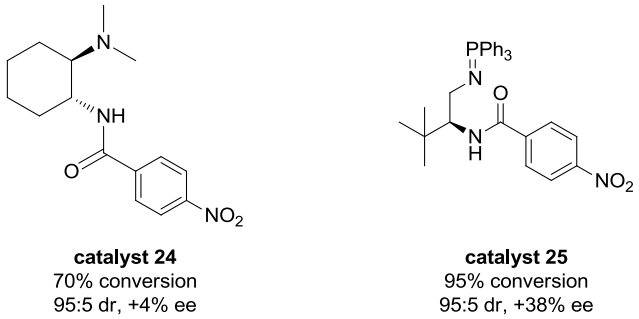


Figure 13: Takemoto-type and BIMP scaffolds.

The temperature variation for the reaction was not investigated with our optimal catalyst. However, using the quinidine-derived **catalyst 22** (69% ee at 50 °C) we noted that no

reaction occurred at rt after 4 days and moreover, increasing the temperature to 75 °C the adduct was afforded in a lower 46% ee.[i]

Therefore, using the *p*-nitro benzoylamide derived **catalyst 19**, we subsequently performed a solvent and concentration screen at 50 °C to further improve the enantiocontrol (see appendix). In conclusion, our best result was achieved when heating **catalyst 19** in *m*-xylene (0.06 M) at 50 °C to give the IMDAF adduct in quantitative yield, 96:4 dr and 76% ee.

2.6.3.2.3 Mechanism and origin of asymmetry

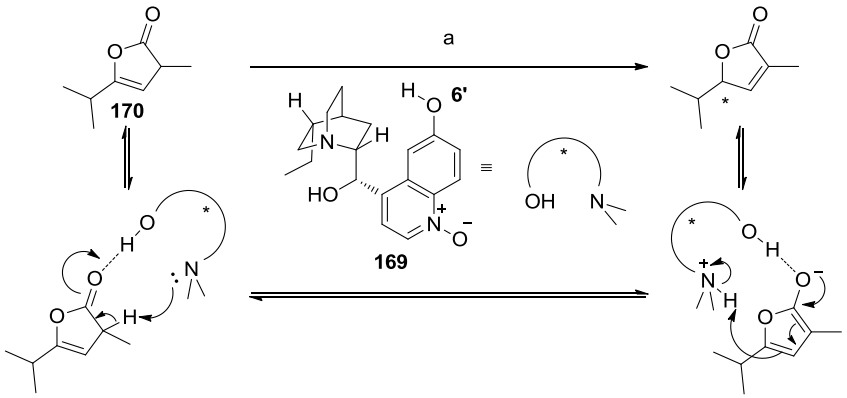
In the symmetric reaction, we believe the role of DABCO begins and ends with the proton-transfer stage of the cascade. As soon as the dienophile is formed, the IMDAF reaction occurs rapidly and irreversibly at 50 °C. In order to prove this, several attempts were made to intercept the cascade and isolate the *in situ* formed dienophile **168** before it undergoes the cycloaddition. This would allow us to investigate whether the IMDAF reaction can take place uncatalysed, at rt. Unfortunately, these reactions either led to degradation of the substrate **164**, to its recovery or to the isolation of the adduct **104**. Perhaps the second part of the cascade is indeed rapid, trapping the dienophile as soon as it forms, preventing us from isolating it.

With regards to the chiral bifunctional catalysts, we believe that they too are solely responsible for the primary proton-transfer stage of the cascade and not the cycloaddition. Whether a DKR at the proton-transfer stage alone is responsible for the induction of asymmetry has not been determined as the dienophile could never be isolated to measure its ee at different conversions. However, to support our claim of the irreversibility of the cascade at 50 °C, DABCO was added to a solution of an enantioenriched adduct (74% ee)

[i] The yield for this reaction (48%) is not representative as several aliquots were taken to monitor its progression.

in toluene at 50 °C. After 2 days, the adduct was re-isolated with an unchanged dr and ee concluding that the cascade at this temperature is indeed irreversible. This supports the claim that a DKR cannot take place after the cycloaddition stage of the cascade. However, a DKR at the proton-transfer stage cannot be disregarded.[i]

During the investigation of this transformation, Deng's group published a paper describing the "*asymmetric olefin isomerisation of butenolides via proton-transfer catalysis by an organic molecule*".[93] In this biomimetic transformation, they reported the asymmetric isomerisation of a range of butenolides by the *cinchona*-derived catalyst **169** giving rise to excellent yields and enantioselectivities. In their proposed catalytic cycle, deprotonation of the *β,γ*-butenolide **170** occurs after H-bonding to the catalyst. This association subsequently directs the asymmetric rate-determining *γ*-protonation from the protonated quinuclidine (or the 6'-OH) of the catalyst (Scheme 45).[94]



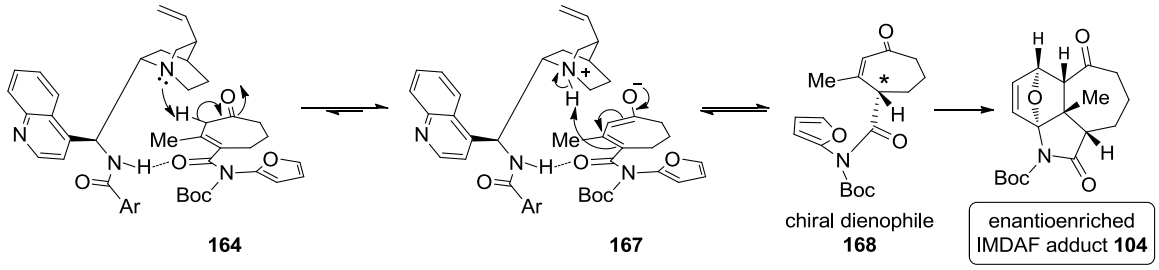
Scheme 45: Deng's asymmetric isomerisation of butenolides *via* proton-transfer catalysis. Reaction conditions: (a) 169 **(0.5 mol %), CH_2Cl_2, rt, 95%, 94% ee.**

We believe that a related induction of asymmetry is also operating in the proton-transfer stage of our system. We postulate that the benzoylamide H-bonds to the amide of the substrate **164**[ii] prior to deprotonation of the *α*-proton by the quinuclidine functionality of

[i] Furthermore in an experiment performed by Dr. Pavol Jakubec, we noted that the ee of an adduct from a reaction stopped before its full conversion is identical to the ee after full conversion to the product.

[ii] The carbonyl of the substrate's amide should be more nucleophilic than the ketone; however, this may not necessarily be true considering the high functionality surrounding this specific amide.

the catalyst (Scheme 46). The protonated quinuclidine is then responsible for the enantiocontrolled proton-transfer to the substrate's *γ*-position giving rise to the dienophile **168**, which then spontaneously undergoes the IMDAF reaction unassisted.



Scheme 46: Postulated organisation of the chiral transition state in the organocatalytic asymmetric proton-transfer/IMDAF reaction cascade.

We believe that the benzoylamide's moderate ability to H-bond is essential to the high enantioselectivity, as it allows for both the protonation of the quinuclidine and the deprotonation of its conjugate acid, all whilst it's loosely H-bonded/associated to the substrate. It might be possible that the drop in ee observed with the urea and thiourea catalysts may be because these stronger/bidentate H-bond donors disallow the aforementioned loose association and thus lead to lower enantioselectivities. The drop in ee from 32% to 28% when comparing the thiourea **catalyst 26** with the weaker H-bond donor, the urea **catalyst 3**, also supports this theory (Figure 10). Additionally, their strong association could potentially give rise to a different pathway altogether, leading to a proton-transfer on the opposite side of the substrate compared to when using the benzoylamides. This may explain why enantioenrichment of the antipode is observed when directly comparing the ee of the adducts afforded from a benzoylamide *vs* a urea/thiourea derived cinchonidine (compare **catalyst 15** with **catalyst 1**).

2.6.4 Elaboration of the cascade's adduct to give rise to the ACD tricyclic core of daphniyunnine D

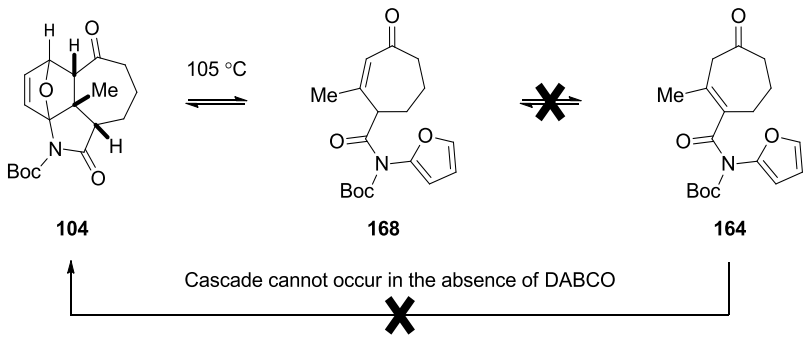
The final section of chapter 2 focuses on the elaboration of the IMDAF adduct **104** leading to the formation of the ACD tricyclic core of daphniyunnine D (**23**). In the absence of a finalised route to the natural product, further work to improve the enantioselectivity was not deemed necessary. Therefore the remaining investigations in this thesis focus on the racemic route towards the natural product.[i]

2.6.4.1 Controlled fragmentation of the IMDAF adduct

To avoid the deprotection of the Boc group (seen using catalytic *p*-TsOH), we attempted promoting the ring-opening of the IMDAF adduct under forcing conditions using *m*-xylene in a sealed tube at 160 °C. Unfortunately, this only led to a complex reaction mixture, possibly a consequence of the thermal Boc removal.

Lowering the temperature to 110 °C in toluene-d_8 and monitoring the reaction by ^{1}H NMR, we concluded that there was no product formation. However, after heating at this temperature for 2 days we noted that the dr of the IMDAF adduct switched from 96:4 to 27:73. Initially considered irreversible in our system (at least at 50 °C), it appears that at this temperature, the retro-cycloaddition is made possible allowing for an equilibrium to be established between the adduct **104** and the ring-opened cycloaddition precursor **168** (Scheme 47). Although slow, this reversible reaction presumably leads to the formation of the thermodynamic diastereoisomer of the IMDAF adduct. Unfortunately, after prolonged heating we were unable to isolate this isomer as degradation of the inseparable diastereoisomeric adducts occurred at a faster rate relative to their isomerisation.

[i] Investigation of the asymmetric reaction was taken over by Dr. Pavol Jakubec.



Scheme 47: Equilibrium established between the forward and retro IMDAF cycloaddition.

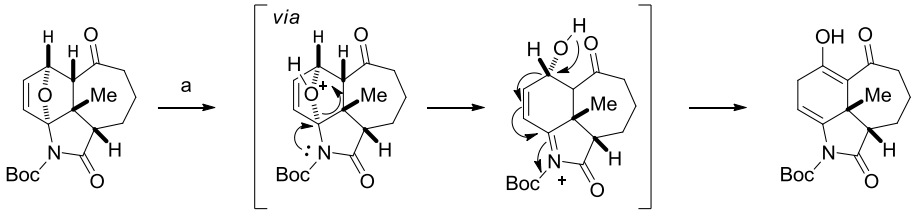
As the proton-transfer/IMDAF cascade cannot occur in the absence of DABCO even when refluxing in toluene (see section **2.6.3.1** and Scheme 47) evidence of the formation of **164** would prove that the proton-transfer is also reversible/significant at this temperature. Since no precursor was isolated, we concluded that the equilibrium established is only between the adduct **104** and the cycloaddition precursor **168**. Perhaps the rate of the IMDAF and the retro reaction is much higher than that of proton-transfer. This was a crucial result because if both steps proved to be reversible at equal rates, the undesired racemisation of our enantioenriched adduct would take place at these high temperatures.[i]

It was eventually discovered that the fragmented IMDAF adduct can be attained with the Boc group left intact if a substoichiometric amount of dichloroacetic acid is injected to a refluxing solution of a diastereoisomeric mixture of **104** (96:4 dr) in toluene (Scheme 48). After an optimal time of 5 min, the reaction is quickly diluted and then quenched; prolonged reaction periods lead to the deprotection of the Boc group. Although sensitive, this reaction is amenable to large scale preparation, with a 7 g reaction giving rise to the fragmented **171** in 86% yield as a single diastereoisomer.[ii] We believe that the acid protonates the oxygen of the dihydrofuran thus making it easier for the electrons on the nitrogen to break the C-O single bond under these forcing conditions. A subsequent

[i] Racemisation at 50 °C does not occur, see section **2.6.3.2.3**.

[ii] Although we are unsure of the structure of the minor diastereoisomer of the IMDAF adduct, we assume that it also gives rise to the fragmented tricycle **171**.

rearrangement as reported by Padwa[44] gives rise to the hydroxyenone **171** after enolisation (Scheme 48). The diketone functionality is not detected in the ^{1}H nor the ^{13}C NMR spectra perhaps owing to the stability of the intramolecular H-bond between the two oxygens in its keto-enol form. A similar observation was made by Ward in his related [6–5–6] and [6–5–7] tricyclic ring systems (see section **1.6.1**).



Scheme 48: Fragmentation of IMDAF adduct 104 **providing the Boc-protected** 171**. Reaction conditions: (a) dichloroacetic acid (80 mol %), toluene, reflux, 86%.**

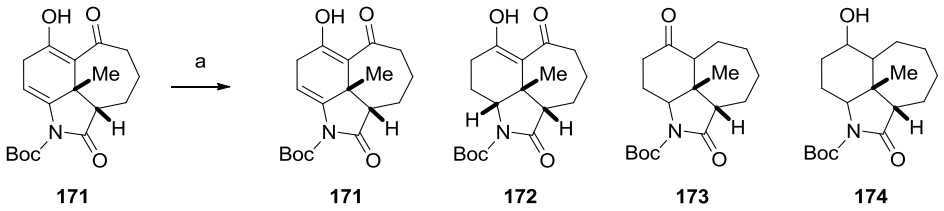
Although the fragmentation was finally accomplished in our system, we needed to confirm that these harsh conditions would not lead to the erosion of ee in the enantioenriched adducts. Pleasingly, reacting 10 mg of **104** at 46% ee, provided the fragmented product **171** with identical ee, albeit in a low 40% yield.[i] This confirmed our assumption that even if the retro-cycloaddition becomes significant in the timescale of this high temperature reaction, the proton-transfer is either irreversible or slow, thus avoiding loss of asymmetry.

2.6.4.2 Hydrogenation of enamide to provide the ACD tricyclic core of daphniyunnine D

At this point, the enamide in the tricycle **171** needed to be reduced in a stereoselective manner to provide the relevant cyclohexanone functionality present in daphniyunnine D (**23**). Considering the tricycle's likely three dimensional structure, we were confident that heterogeneous hydrogenation would deliver a hydrogen molecule on the more exposed convex face of the tricycle **171**.[95]

[i] The low yield is attributed to the small scale of the reaction. This result was confirmed by Dr. P. Jakubec: 485 mg of an enantioenriched adduct **104** provided the fragmented tricycle **171** in identical ee and 81% yield.

Initial attempts to hydrogenate this double bond using Pearlman's catalyst ($Pd(OH)_2$) in MeOH under an atmosphere of hydrogen, gave rise to complex mixtures and occasionally led to incomplete reactions even after 48 hours. Alongside the hydrogenated tricycle **172**, on two separate occasions we were able to isolate small quantities of the major contaminants: the over-reduced products ketone **173** and alcohol **174** (Scheme 49).



Scheme 49: Hydrogenation in the absence of water leads to the over-reduction. Reaction conditions: (a) $Pd(OH)_2$ (7 mol %), MeOH, H_2 (balloon), rt, mixture of products.

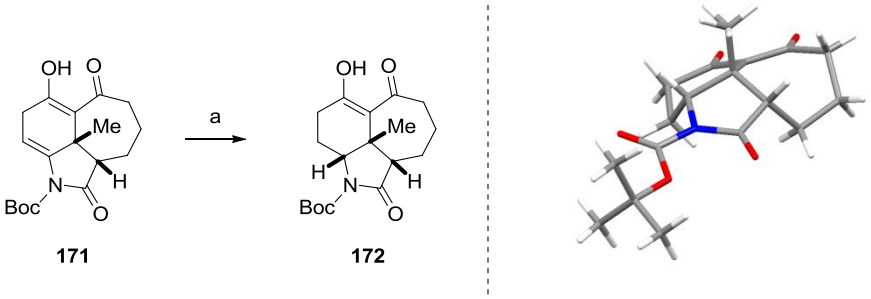
The mechanism of this unexpected over-reduction is unknown; however, it may arise from a *haptophilic effect*[96] of the hydroxyenone functionality of tricycle **171** to the palladium catalyst. This anchoring of the catalyst to the tricycle could assist the reduction of the hydroxyenone[97] giving rise to ketone **173** and alcohol **174** after subsequent hydrogenations, whilst at the same time inhibiting the desired transformation.

As different solvents are known to affect the *haptophilic* substrate interactions by binding to the active site of the palladium catalyst,[96b] we considered using water in our methanolic hydrogenation to disrupt these over-reduction pathways. In fact, using Pearlman's catalyst[i] in MeOH in the presence of water (25:4) at rt led to a faster and chemoselective hydrogenation, providing tricycle **172** as a single diastereoisomer in 88% yield after only 24 hours (Scheme 50). Furthermore, nOe experiments provided encouraging results concerning the stereochemistry of the product. Subsequent single X-ray crystallography unambiguously confirmed that the afforded tricycle contained the analogous relative

[i] $Pd(OH)_2$ purchased from Alfa-Aesar was necessary for this transformation (#42578). Catalysts from different suppliers gave inconsistent results.

stereochemistry found in the ACD rings of daphniyunnine D and the remaining calyciphylline A-type alkaloids.

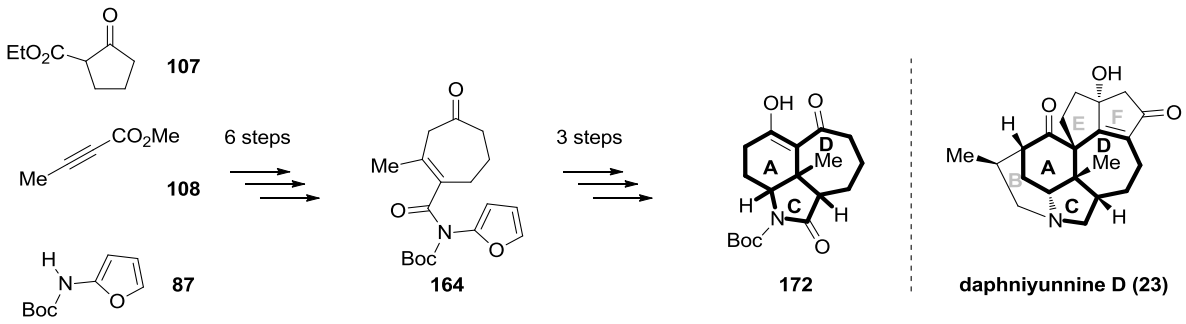
The diastereoselectivity of this reduction was key to validating our initially proposed IMDAF approach for the synthesis of these alkaloids. In our designed retrosynthesis of daphniyunnine D, this all carbon [6–5–7] tricyclic ACD ring system, behaves as the foundation of the synthesis onto which the remaining ring systems will be constructed.



Scheme 50: Heterogeneous hydrogenation of 171 **and crystal structure of tricyclic ACD core** 172 **of daphniyunnine D. Reaction conditions: (a) $Pd(OH)_2$ (7 mol %), MeOH:H_2O (25:4), H_2 (balloon), rt, 88%.**

2.7 Summary and conclusion of chapter 2

From simple and commercially available starting materials we demonstrated that the main all carbon [6–5–7] tricyclic ACD ring system **172** present in daphniyunnine D (**23**) can be constructed in a rapid and highly diastereoselective manner in just 9 steps (Scheme 51). The key reactions include a ring-expansion, a proton-transfer/IMDAF cascade followed by a stereoselective fragmentation and hydrogenation of the afforded adduct. Investigations into the asymmetric variant of the proton-transfer/IMDAF reaction cascade have shown that the tricycle can also be constructed in an enantioselective manner, although optimisation is necessary for the application of this organocatalytic transformation to the asymmetric total synthesis of our target.



Scheme 51: Summary of our approach to the tricyclic core 172 **of daphniyunnine D.**

The elaboration of the tricycle to allow for the two ensuing key disconnections, the intramolecular Pauson-Khand and the intramolecular hydroalkylation reaction will be the focus of chapters 3 and 4 respectively.

Chapter 3: An intramolecular Pauson–Khand reaction approach for the synthesis of the ACDEF pentacycle of daphniyunnine D

3.1 Introduction

With the tricyclic ACD core accessed using our novel proton transfer/IMDAF reaction cascade, focus was shifted to the design of the [7–5–5] all-carbon DEF tricycle present in our synthetic target. Variations of this structural motif are present in most of the calyciphylline A-type subclass and in over 100 alkaloids of the whole *Daphniphyllum* alkaloid family. Representative examples are shown in Figure 14.

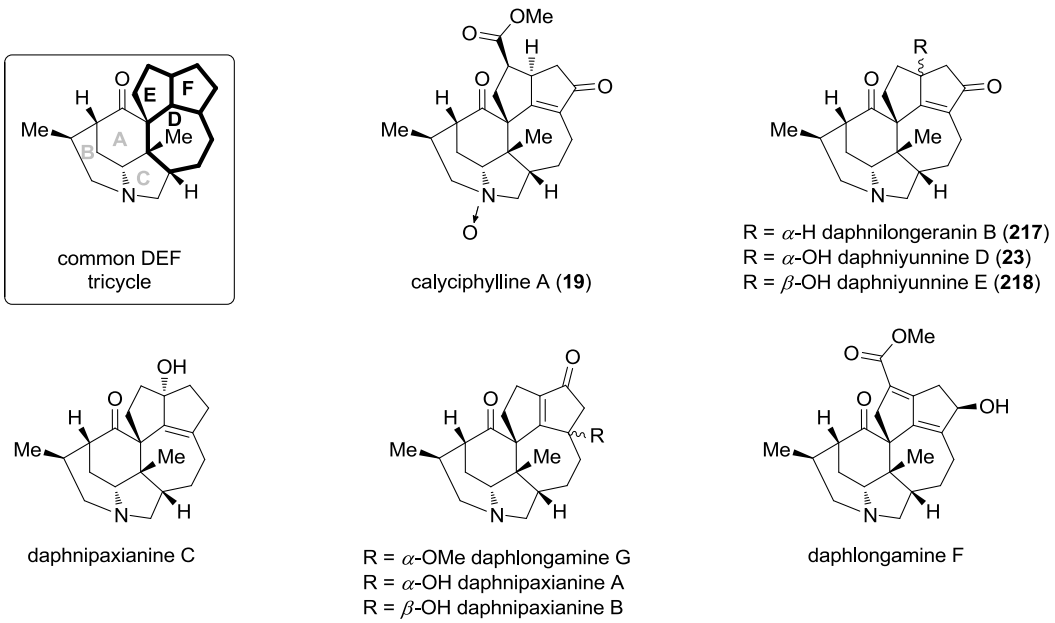


Figure 14: Calyciphylline A-type *Daphniphyllum* alkaloids bearing the [7–5–5] all-carbon DEF tricycle.

At the commencement of this project no specific investigation into the synthesis of this tricycle had been reported. However, two examples of its construction *via* an intramolecular aldol reaction have since been described by the groups of Carreira and Smith in their synthesis of (+)-daphmanidin E[5m] and (–)-calyciphylline N[5o] respectively.

In order to complete the synthesis of daphniyunnine D (**23**), a practical and efficient route to the DEF tricycle needed to be developed which we hoped would be applicable to the construction of related alkaloids.

3.2 Aims and retrosynthetic analysis

Cycloaddition reactions, as demonstrated in chapter 2, can provide rapid access to complex ring systems especially if performed intramolecularly. Similar to our IMDAF approach, we envisioned that the [7–5–5] all-carbon DEF tricycle may be constructed through the use of another cycloaddition, the intramolecular variant of the Pauson–Khand reaction (IMPKR). We believed that manipulation of the ACD tricyclic core **172**, obtained *via* the protocol reported in chapter 2, could give rise to a substrate, itself able to undergo the intramolecular cycloaddition to afford the ACDEF pentacycle **175** (Figure 15).

In order to synthesise this pentacycle with a correctly positioned cyclopentenone double-bond in the all-carbon DEF skeleton, a [2+2+1] cycloaddition between a pendant alkene, a cycloheptyne functionality and a CO molecule is required. However, the necessary inclusion of the cycloheptyne functionality (e.g. in **176**) in the structurally rigid/strained tricycle **172** (see crystal structure in Scheme 50) was not considered a viable option.[i,98,99]

We hypothesised that this problem could be circumvented by exchanging the cycloaddition partners. A less strained 7-membered alkene **102** could undergo a cycloaddition with a pendant alkyne, to give rise to an alternative pentacycle **177** (Figure 15). This route would place the double-bond in the wrong position in the cyclopentenone ring F. However, a subsequent double-bond migration from the trisubstituted to the thermodynamically favoured fully-substituted position would afford the desired pentacycle **175**.

[i] The half-life of isolated cycloheptyne is approximately 1 hour at –76 °C, owing to the strain imposed on the sp-hybridised carbons.[98] Complexation with $Co_2(CO)_8$ however, relieves this strain. For an example of an IMPKR with Co-cycloheptyne complexes, see reference 99.

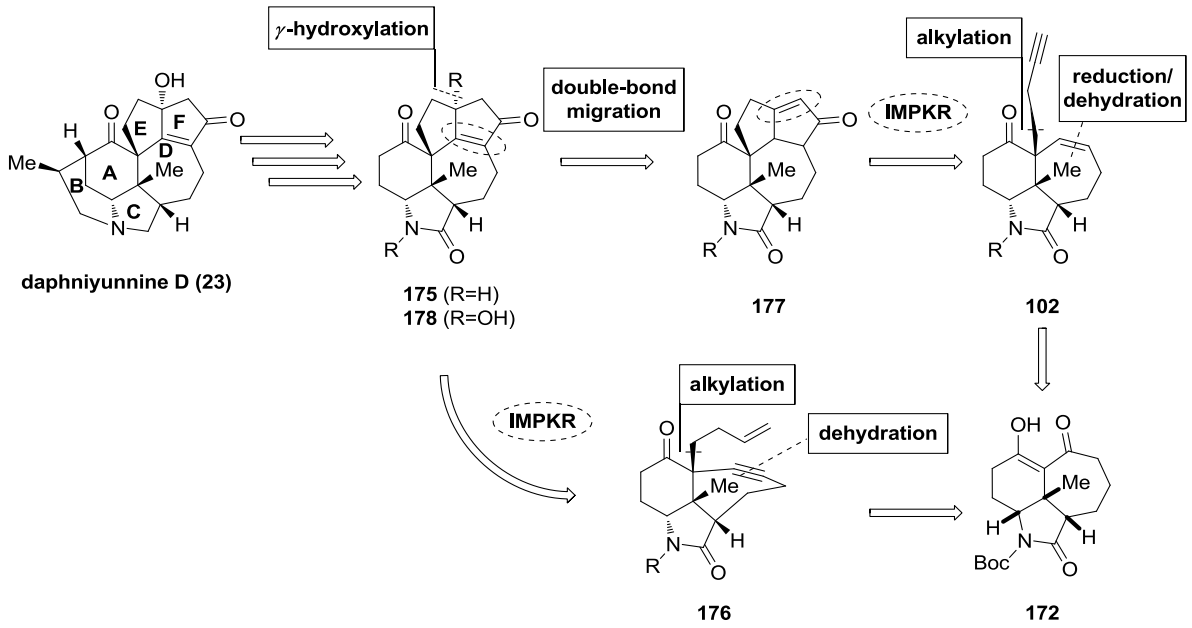


Figure 15: Retrosynthetic analysis of daphniyunnine D, a comparative IMPKR focus between cycloheptyne substrate 176 **and cycloheptene substrate** 102**.**

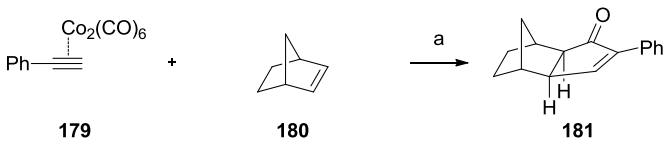
Late stage oxygenation on the γ-position of the derived enone **175** would yield the pentacyclic skeleton **178** of daphniyunnine D (**23**), with the synthesis of the final 6-membered ring B remaining to complete our synthetic target.

Before discussing our work in this area, the relevant Pauson–Khand reaction (PKR) is introduced.

3.3 The Pauson–Khand reaction

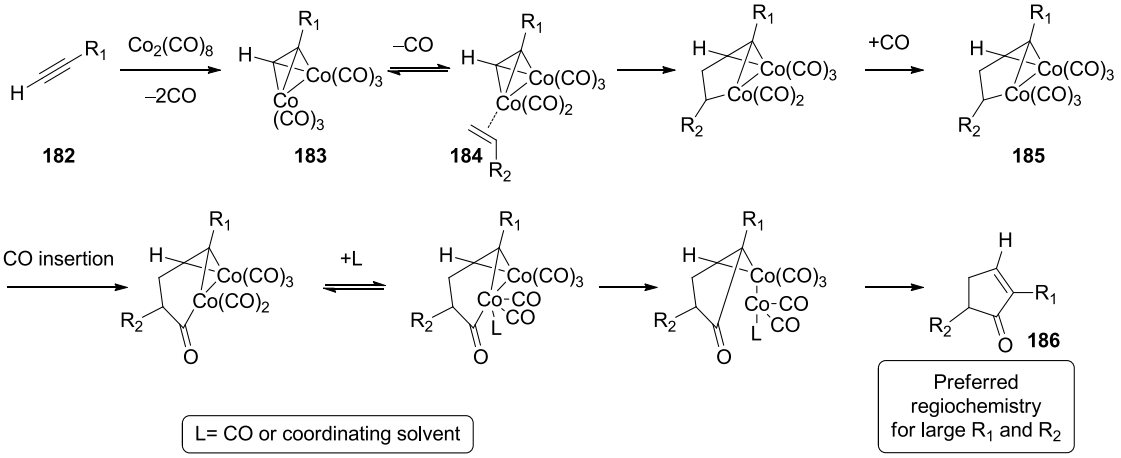
3.3.1 Discovery and mechanism

First discovered in 1971, the Pauson–Khand reaction (PKR) consists of a formal [2+2+1] cycloaddition of an alkyne, alkene and a carbon monoxide molecule mediated by dicobalt octacarbonyl $Co_2(CO)_8$.[100] In their seminal report, Pauson and co-workers discovered that heating a range of preformed Co-alkyne complexes (e.g. **179**) in aromatic solvents in the presence of norbornene (**180**) gave rise to cyclopentenone scaffolds after incorporation of a CO molecule (e.g. **181** in Scheme 52).



Scheme 52: Seminal report of the PKR. Reaction conditions: (a) mesitylene, 60-70 °C, 59%.

Whilst the mechanism for this cycloaddition remains elusive, the most widely accepted pathway for the reaction is described below (Scheme 53). In the postulation, reaction of $Co_2(CO)_8$ with a generic alkyne **182** gives rise to the stable and isolable alkyne-$Co_2(CO)_6$ complex **183** which then undergoes dissociation of a CO ligand from one cobalt centre, allowing for the coordination of an olefin (e.g. **184**). This step is reversible and is commonly regarded as rate-determining. Various groups have investigated ways of promoting/accelerating this dissociation and this will be discussed in the following section.



Scheme 53: Postulated mechanism for the PKR.

Following its coordination, the olefin undergoes an insertion into the Co-C bond to give rise to cobaltacycle **185** after a CO ligation. It is believed that the reason strained olefins, like norbornene, demonstrate good reactivity in the PKR is due to the release of strain at this stage. This carbon-carbon bond forming step determines the regioselectivity of the reaction as unsymmetrical alkynes and alkenes react on the least hindered sp and sp^2 carbons respectively (see position of phenyl group in Scheme 52). It is worth mentioning that this prediction is normally obeyed by the alkyne component, however unsymmetrical

olefins tend to give mixtures of regioisomers. Subsequent CO insertion into **185** followed by two consecutive reductive eliminations affords the cyclopentenone **186**. Interestingly, regioselectivity is higher and easier predicted in the intramolecular variant which will be discussed in section **3.3.3.3**.

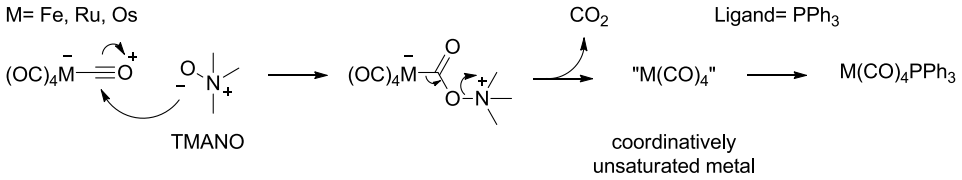
3.3.2 Promoters of the Pauson–Khand reaction

In the early reports,[100a,b,c] the dissociation of the CO ligand and the subsequent formation of the cobaltacycle was promoted by heating the Co-alkyne complex in the presence of the alkene. The harsh conditions (60-120 °C) and long reaction periods required for this promotion (6 hours to 4 days) often led to low conversions and were the reason for the initial limited scope of the reaction. Since its discovery, various groups have attempted to accelerate the rate-determining CO dissociation step in order to promote the PKR at lower temperatures, thus making the reaction more general.

Conditions reported to promote/accelerate the PKR include the use of ultrasound (sonication)[101] as well as the dry-state adsorption of the preformed Co-alkyne complex onto silica,[102] alumina and zeolites.[103] Highly polar solvents such as DMSO[104] and NH_4Cl(aq) in dioxane[105] also accelerate the PKR, as does the use of additives such as phosphine oxides,[101] sulfides[106,107] and amines.[108] All the aforementioned reaction conditions, postulated to involve the labilisation of a CO ligand from the cobalt centre, demonstrate accelerated, higher yielding and often milder alternatives to the thermal promotion of the PKR. To this day, little is known about the precise mechanism of their promotion as isolation of intermediates in the PKR, with the exception of the initial Co-alkyne, is very rare.[109]

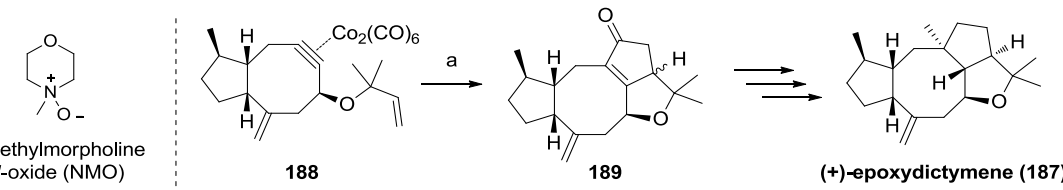
The real breakthrough in promoting the PKR, through the use of amine *N*-oxides, was discovered independently by Schreiber[110] and Jeong[111] in 1990 and 1991 respectively.

Inspired by the ability of trimethylamine *N*-oxide (TMANO) to oxidatively remove CO ligands from metals, allowing for their subsequent complexation (e.g. by PPh_3), they hypothesised that similar reagents could also be used to promote the PKR (Scheme 54).[112]



Scheme 54: Oxidative removal of a CO ligand from a metal centre using TMANO followed by its complexation, e.g. by PPh_3.

Similarly, a molecule of *N*-oxide can attack a CO ligand of the Co-alkyne complex **183** (Scheme 53), producing CO_2(g), thus allowing for the coordination of the olefin to the vacant site of the cobalt centre. By assisting this rate-limiting step, a large rate acceleration is observed, allowing the reaction to be performed at lower temperatures. Investigating the synthesis of (+)-epoxydictymene[113] (**187**) Schreiber and co-workers demonstrated that although a slightly lower yield was observed compared to when the IMPKR of **188** was thermally promoted (75% yield, 4:1 dr), impressive diastereocontrol was possible when 4-methylmorpholine *N*-oxide (NMO) was used as a promoter in CH_2Cl_2 at rt. This provided the desired adduct **189** in 68% yield and 11:1 dr (Table 1, entry 1). A year later, Jeong and co-workers reported a similar rate acceleration using TMANO, allowing for both the inter- as well as intramolecular PKR to be carried out between temperatures of 0 °C to rt.



Entry	Conditions (a)	Yield (%)	dr
1	NMO, CH_2Cl_2, rt	68	11:1
2	MeCN, 82 °C	75	4:1
3	MeCN, ultrasound 45 °C	45	3:1

Table 1: Use of NMO in Schreiber's amine *N*-oxide promoted IMPKR.

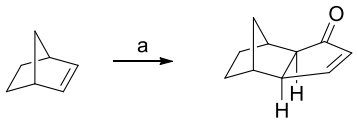
Many improvements in the promotion of the PKR have been reported since its discovery in 1971. However, as most still require a source of heat, no promoter matches the generality, mildness and effectiveness of the amine *N*-oxide activation.

3.3.3 Advances of the Pauson–Khand reaction

3.3.3.1 Cobalt catalysed PKR

An improvement of the PKR has been its execution with catalytic amounts of metal, avoiding the use of large quantities of toxic reagents. This requires the catalyst to be regenerated by replacing the lost CO ligand, necessitating a CO atmosphere for catalytic turnover.

The earliest report was as early as 1973 by Pauson and co-workers,[100c] where the strained and thus reactive norbornene (**180**) was treated with a continuous flow of a 1:1 mixture of acetylene and CO(g) in *iso*-octane at 60-70 °C. A $Co_2(CO)_8$ loading as low as 2.4 mol % was implemented to provide **190** in 62% yield (Scheme 55).

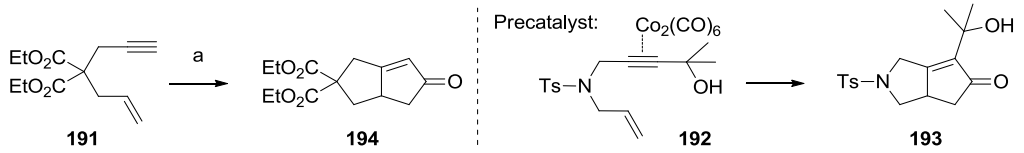


180 **190**

Scheme 55: First catalytic example of the PKR. Reaction conditions: (a) acetylene/carbon monoxide (1:1), $Co_2(CO)_8$ (2.4 mol %), *iso*-octane, 60-70 °C, 62%.

Formation of inactive metal clusters[114] in the catalytic PKR is considered one of the main problems regarding the efficient turnover of $Co_2(CO)_8$ (*vide infra* section **3.4.1**). To this end, Jeong and co-workers demonstrated a significant yield increase from 4 to 82% when $P(OPh)_3$ was included in the catalytic IMPKR of **191** as a potential Co-stabilising ligand (Table 2, entry 1 *vs* 2).[115] In 1999 Krafft and co-workers took advantage of the bench-stable Co-alkyne complex **192**,[116] avoiding the use of poor quality $Co_2(CO)_8$ in their catalytic system.[117] In their protocol, as soon as this pre-catalyst undergoes an IMPKR to

193, an atmosphere of CO ensures the *in situ* formation of active $Co_2(CO)_8$ for the desired IMPKR of **191**. The relative difference in polarity between the adduct **193** generated from the $Co_2(CO)_8$ surrogate **192** and the desired adduct **194** allows for the facile separation of the product by fcc (Table 2, entry 3).



191 **194** **192** **193**

Entry	Author	Catalyst (loading)	Solvent, temp	CO pressure (atm)	Time (h)	Yield (%)
1	Jeong	$Co_2(CO)_8$ (1 mol %)	1,2-DME, 120 °C	3	24	4
2	Jeong	$Co_2(CO)_8$ (3 mol %) $P(OPh)_3$ (10 mol %)	1,2-DME, 120 °C	3	24	82
3	Krafft	**192** (10 mol %)	1,2-DME, 70 °C	1	2	78

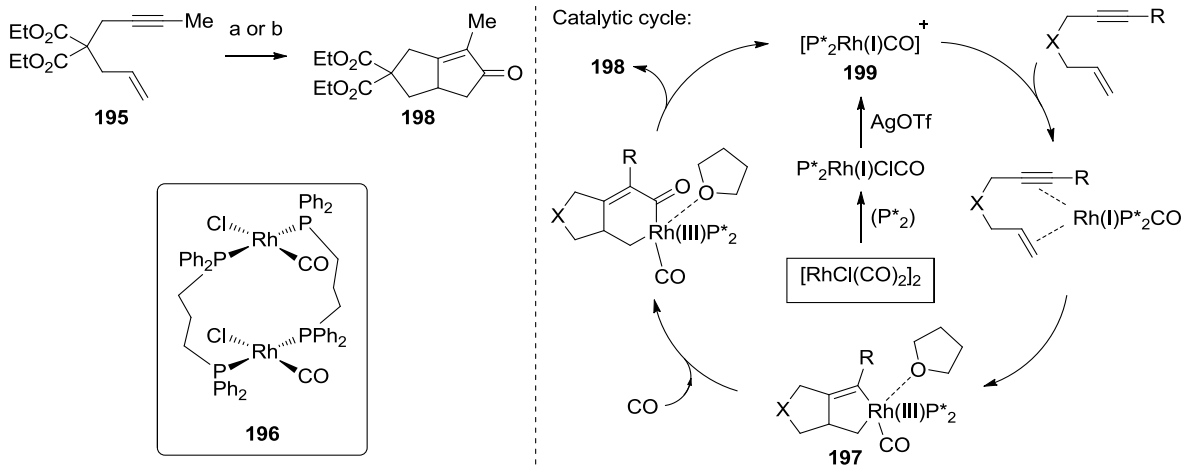
Table 2: Catalytic IMPKR of a representative substrate 191 **using different conditions.**

3.3.3.2 Catalysis beyond cobalt

Whilst the PKR refers to the use of cobalt to mediate the formal [2+2+1] cycloaddition, other transition metals have been reported to perform the reaction. The stoichiometric use of $Fe(CO)_4$(acetone),[118] $W(CO)_5$(THF),[119] $Cp_2Mo_2(CO)_4$,[120] and $Mo(CO)_6$[121] can mediate the Pauson–Khand type reaction (PKTR) although none of these metal carbonyl mediated methodologies seem to have been successful in replacing the use of the classic $Co_2(CO)_8$. The use of these alternative metals however, inspired research groups to search for catalytic systems beyond cobalt.

Seminal reports by Buchwald and co-workers demonstrated the first PKTR where titanocene complexes were used to catalyse the formal cycloaddition of alkenes and alkynes in the presence of a CO atmosphere.[122] Since Buchwald's reports, many research groups have published catalytic systems for the PKTR using different metals including iridium, ruthenium, nickel, palladium and rhodium under a CO atmosphere.[100i] Perhaps the catalytic system that stands out the most as being a very promising candidate in replacing $Co_2(CO)_8$, is the one using rhodium metal.[123] In 1998 Jeong and co-workers reported the

impressive rhodium catalysed PKTR of **195** using the binuclear Rh-catalyst **196** under an atmosphere of CO (Scheme 56, conditions a).[124,125]



Scheme 56: Jeong's development of a catalytic PKTR. Reaction conditions: (a) 196 **(2.5 mol %), CO (1 atm), toluene, 110 °C, 95%; (b) $[RhCl(CO)_2]_2$ (3 mol %), (*S*)-BINAP (6 mol %), AgOTf (9-12 mol %), CO (1 atm), THF, 90 °C, 95%, 70% ee.**

With this proof of principle in hand, the methodology was developed further by successfully using the chiral ligand (*S*)-BINAP (P^*_2) with $[RhCl(CO)_2]_2$ and the additive AgOTf, inducing high enantiocontrol in their systems (Scheme 56, conditions b).[126]

In their proposed catalytic cycle, a molecule of THF assists the formation of the octahedral metallacyclopentene Rh(III) intermediate **197**. A subsequent insertion of a CO molecule followed by a reductive elimination forms the desired product **198** and regenerates the catalytically active cationic Rh(I)-carbonyl species **199**.

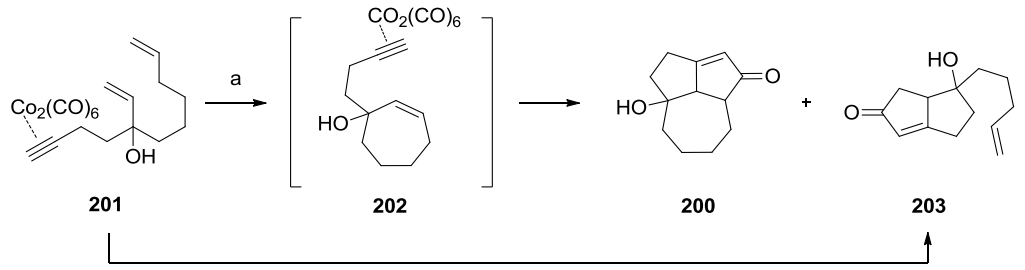
Subsequently, even milder methods for the asymmetric PKTR have been reported, increasing the substrate scope, enantioselectivities and yields, making rhodium catalysis a promising alternative to the classic use of cobalt.[127] Furthermore, the ability of rhodium species to catalyse the decarbonylation of aldehydes to give rise to catalytically active Rh-carbonyls, has led to the development of the "CO free" PKTR.[128,100h]

3.3.3.3 Higher selectivity, reactivity and complexity afforded in the IMPKR

Although the intermolecular PKR can lead to synthetically useful cyclopentenones, its regioselectivity is difficult to predict, especially with respect to the olefin partner. The fact that high temperatures are necessary in this intermolecular reaction also leads to further erosion of yield and regioselectivity. Furthermore, strained olefins are often necessary to achieve good reactivity with alkynes. In addition, olefins containing electron-withdrawing groups are also often notoriously bad coupling partners although recent advancements have circumvented these problems.[129,130] In 1981 Schore and co-workers addressed the issues of regioselectivity and low yield and furthermore showed that strained olefins were not a requirement in the analogous intramolecular variant of the Pauson–Khand reaction (IMPKR).[131]

The IMPKR provides a very powerful method for constructing polycyclic molecules when performed on a cyclic substrate. Relevant to this thesis, methodologies for the construction of oxygen, nitrogen and sulfur containing [5–5–5],[132] [6–5–5],[133] [7–5–5],[134] [8–5–5][134c] fused tricyclic ring systems have been reported. However, the construction of an all-carbon tricyclic skeleton, which is directly related to this thesis and the synthesis of daphniyunnine D (**23**), is less prevalent in the literature.

In 2003 Pérez-Castells and co-workers demonstrated that an elegant one-pot tandem ring-closing metathesis (RCM)-IMPKR could be implemented in order to access tricyclic fused ring systems containing oxygen and nitrogen tethers.[134b] Five years later, they expanded this methodology to the construction of an all-carbon [7–5–5] tricycle **200** (Scheme 57).[135] In this report, Co-alkyne complex **201** underwent a Ru-catalysed olefin RCM followed by an IMPKR with the nascent cycloheptene **202**.



Scheme 57: Pérez-Castells' approach to the all-carbon [7–5–5] tricyclic ring system. Reaction conditions: (a) (i) [$(Cy_3P)_2Cl_2Ru$=CHPh] (5 mol %), toluene, rt then (ii) NMO, 40 °C, 35%, mixture of products 200**:**203 **(3:2).**

The problem with this reaction is that the IMPKR can take place prior to the RCM if the reagents are not added in tandem. This pathway led to the formation of **203** in the aforementioned example, which was inseparable from the desired tricycle **200**.[i] Nevertheless, this report represents a relevant approach to the total synthesis of daphniyunnine D (**23**) proving that a cycloheptene with a pendant terminal butynyl can undergo the IMPKR, albeit in low yield.[ii]

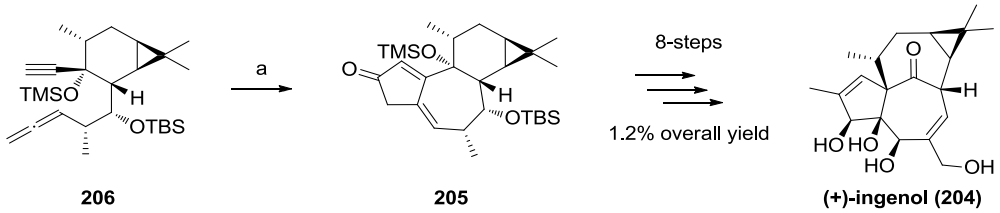
3.3.3.4 The application of the IMPKR in the total synthesis of natural products

The true power of the IMPKR is demonstrated in its application towards the total synthesis of polycyclic natural products where great complexity in the targets can often be achieved with impressive stereoselectivity (e.g. Schreiber's application of the IMPKR in the total synthesis of (+)-epoxydictymene[113] (**187**) in Table 1).

Recently, in the concise total synthesis of (+)-ingenol (**204**),[136] the Baran group used a Rh-catalysed allenic intramolecular PKTR[137] to provide the key tetracyclic intermediate **205** from allene **206**, on a 1.5 g scale (Scheme 58). Previous syntheses of the natural product were between 37-45 steps long compared to Baran's 14-step synthesis. Combined with other efficient transformations, the application of the catalysed PKTR in the rapid

[i] Although this was not reported in this specific example, presumably by monitoring the completion of the RCM before the addition of NMO, the formation of **203** can be avoided altogether.
[ii] For a relevant [7–5–5] all-carbon tricycle construction from a non-terminal alkyne, see reference 134c.

construction of this challenging and sterically congested natural product pays testament to the power of the reaction in providing complex polycyclic molecules in a single transformation.[138]



Scheme 58: Baran's application of the allenic IMPKR for the total synthesis of (+)-ingenol. Reaction conditions: (a) [RhCl(CO)$_2$]$_2$ (10 mol %), CO (1 atm), *p*-xylene, 140 °C, 72%.

3.4 An IMPKR approach for the synthesis of the [7–5–5] tricycle (DEF rings) of daphniyunnine D: results and discussion

This section of the chapter focuses on the construction of the DEF tricycle of the natural product *via* the proposed IMPKR, double-bond migration, allylic oxygenation protocol. The first part describes the design, optimisation and further elaboration of a model study, first initiated by Dr. Darses, to validate our approach. In this study, **207** was used to mimic the tricyclic IMPKR substrate **102** in our retrosynthesis of daphniyunnine D (**23**) (Figure 15). The second part demonstrates the application of this study in combination with the work reported in chapter 2, for the synthesis of a [6–5–7–5–5] pentacycle (ACDEF rings) of daphniyunnine D; structurally related to **178** (Figure 16).

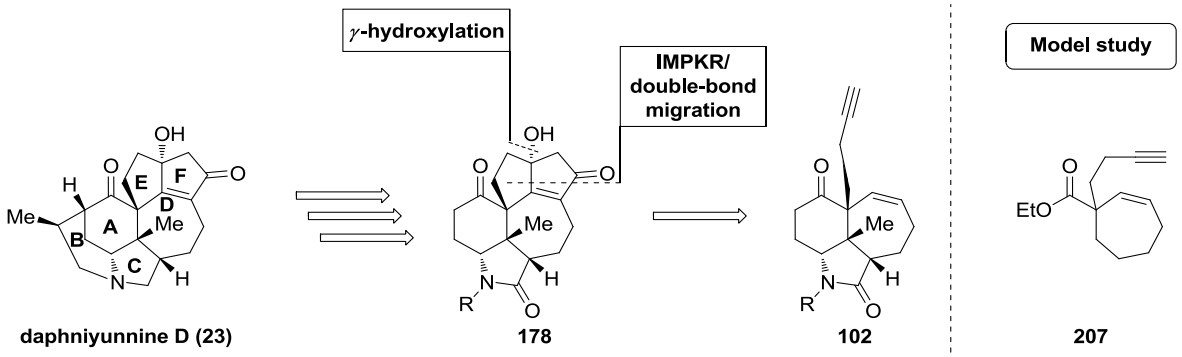


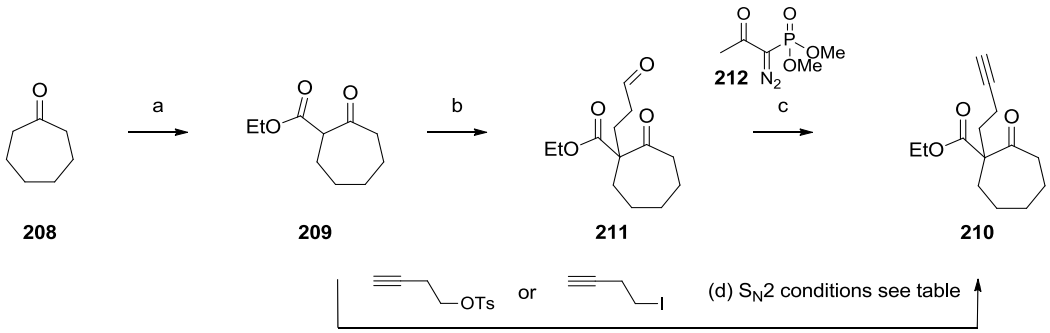
Figure 16: Model substrate 207 **representing ring D in the retrosynthetic analysis of daphniyunnine D.**

3.4.1 Synthesis of the [7–5–5] tricycle (DEF rings) of daphniyunnine D—a model study

3.4.1.1 Synthesis of the all-carbon tricyclic skeleton via an IMPKR

Before applying our proposed approach (see section **3.2**) to the total synthesis of the natural product, investigations on a model system began. We wanted to assess our protocol in an expedient manner making use of cheap and commercially available starting materials. We therefore chose cycloheptanone (**208**) as a starting point for this study, representing the 7-membered ring D of the natural product.

We were confident that simple elaborations of this ring would allow for a substrate similar in structure and functionality to that in daphniyunnine D (**23**). To mimic the carbonyl on ring A, **208** was esterified to ketoester **209** in 98% yield using NaH and diethylcarbonate (see scheme in Table 3). Subsequently, the necessary alkynyl appendage for the IMPKR needed to be introduced, therefore different conditions known to promote the S_N2 reaction of both 1-but-3-ynyl tosylate and 4-iodobut-1-yne were tested to afford the desired alkyne **210** in a direct manner (Table 3d). Unfortunately the reaction was not efficient, with yields ranging between 14-27%, thus forcing us to adopt an alternative two-step pathway. Taking advantage of the reactivity of acrolein towards Michael additions, we were able to synthesise aldehyde **211** in a high 85% yield using NEt_3 in DMF. Subsequently, the aldehyde was homologated to the desired alkyne **210**, *via* the Ohira–Bestmann modification[139] of the Seyferth–Gilbert homologation[140] in 85% yield and a 72% overall yield from ketoester **209**. Use of ethanol as solvent in the homologation with K_2CO_3 and the diazophosphonate **212**, avoided the undesired transesterification of the ethyl ester in **211**.

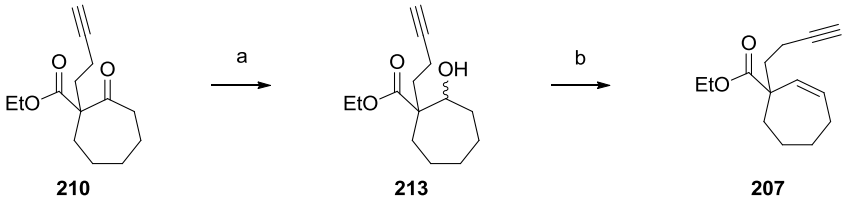


Entry	Conditions (d)	Yield (%)
1	NaH, 1-but-3-ynyl tosylate, NaI, DMF, 0 °C→rt→50 °C →95 °C	No reaction
2	NaH, 4-iodobut-1-yne, THF, reflux	No reaction
3	NaH, 4-iodobut-1-yne, DMF, 0 °→rt	27
4	NaH, 4-iodobut-1-yne, DMF, rt→50 °C	18
5	Cs_2CO_3, TBAB, 4-iodobut-1-yne, toluene:chloroform (9:1), rt	No reaction
6	KOH, TBAB, 4-iodobut-1-yne, CH_2Cl_2, rt	16
7	$CsOH·H_2O$, TBAB, 4-iodobut-1-yne, CH_2Cl_2, rt	14

Table 3: Synthesis of alkyne 210**. Reaction conditions: (a) NaH, diethyl carbonate, toluene, 100 °C, 98%; (b) NEt_3, acrolein, DMF, rt, 85%; (c) K_2CO_3,** 212**, EtOH, 0 °C to rt, 85%; (d) see table.**

Next, we focused our attention on the dehydration of the cycloheptanone in **210** for the introduction of the alkene functionality necessary for the IMPKR. Attempting to do this directly using the Shapiro reaction[141] unfortunately only led to complex reaction mixtures.[i] A stepwise route was therefore considered by first reducing the ketone to the secondary alcohol and subsequently eliminating it to afford the desired cycloheptene **207** (Scheme 59). The optimal conditions for reduction proved to be the mild Luche conditions[142] using $CeCl_3·7H_2O$ and $NaBH_4$ in MeOH. These gave the target alcohol **213** in 78% yield and 1:0.4 dr; lower yields were observed in the absence of $CeCl_3·7H_2O$. Moreover, a one-step protocol including the mesylation of the alcohol in pyridine at rt and its subsequent elimination at reflux afforded the dehydrated IMPKR precursor **207** in 72% yield.

[i] Experiment conducted by Dr. Darses.

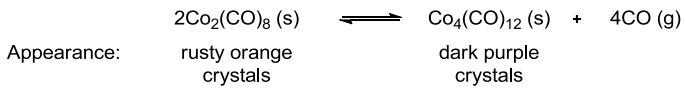


210 **213** **207**

Scheme 59: Synthesis of the IMPKR substrate. Reaction conditions: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 78%, 1:0.4 dr; (b) MsCl, pyridine, rt (6.5 h) then reflux (21 h), 72%.

With the substrate **207** in hand, we were ready to investigate the crucial key step of our proposal for the synthesis of the tricycle *via* an IMPKR. Since the stoichiometric use of $Co_2(CO)_8$ seems to be the "gold standard" reagent for the PKR, we decided to use these conditions to achieve the cycloaddition in our system.

The synthesis of Co-alkyne complexes from alkynes is a fast, efficient and very clean process, however the quality of the $Co_2(CO)_8$ is key to the success of the reaction. Research papers often mention that "*new bottles*" or "*freshly sublimed*" reagent is required for the reproducibility of their reactions, however the reason for this is rarely given. We too experienced issues with the quality of this widely used reagent. $Co_2(CO)_8$ is normally sold as a rusty orange coloured crystal moistened with hexane (1-10%). However, at rt $Co_2(CO)_6$ is formed by the loss of two CO ligands. This then dimerises to form the purple $Co_4(CO)_{12}$ which is catalytically inactive (Scheme 60).[i,143] Once opened, commercial bottles of this reagent are destined to decompose if not stored under an atmosphere of CO, even if stored at –20 °C under an atmosphere of argon (in our hands).



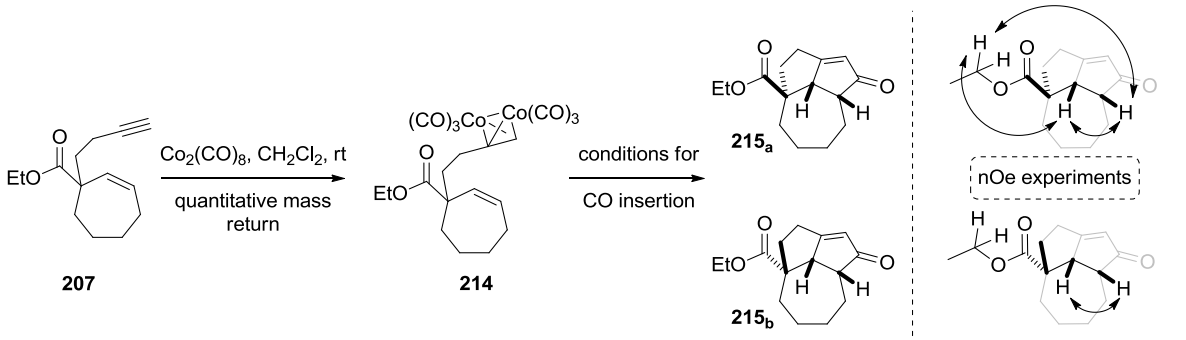
Scheme 60: The equilibrium reaction between $Co_2(CO)_8$ and $Co_4(CO)_{12}$.

We believe that this unreactive cobalt species is the main cause for most of the inefficiencies and irreproducibilities of reports in the literature. Nevertheless, although the

[i] This cobalt species was actually reported to promote the PKR by Chung and co-workers, however the active catalyst in this reaction is still $Co_2(CO)_8$ which is regenerated *in situ* at 150 °C under a high pressure of CO (10 atm).[143]

decomposition upon storage is evident, if $Co_2(CO)_8$ of good quality is used to form a Co-alkyne complex, no issues relating to its decomposition during the time-scale of the complexation were apparent in our system; the reaction is indeed very fast and clean.

Having addressed the issues with the synthesis of the Co-alkyne complex **214** of our IMPKR substrate **207** investigation into the promotion of the stoichiometric cycloaddition could be undertaken (Table 4).



Entry	Solvent	Promoter (equiv)	T (°C)	Time (h)	Yield % (dr $\mathbf{215_a}$:$\mathbf{215_b}$)
1[a]	MeCN	heat	reflux	24	43 (4.0:1.0)
2	CH_2Cl_2	DMSO (6)	rt	24	0 (N/A)
3	CH_2Cl_2	PhSMe (6)	rt	24	0 (N/A)
4	CH_2Cl_2	$CyNH_2$ (6)	rt	24	0 (N/A)
5	1,4-dioxane	NH_4Cl (aq 2 M)	100	1	complex mixture (N/A)
6	CH_2Cl_2	TMANO (9)	rt	24	39 (3.4:1.0)
7	CH_2Cl_2	NMO (9[b])	rt	24	44 (4.0:1.0)
8[c]	**CH_2Cl_2**	**NMO (9)**	**rt**	**22**	**58 (3.7:1.0)**

Table 4: Optimisation of the IMPKR. [a] CH_2Cl_2 from the initial step was removed under reduced pressure, and to the resultant dark coloured oil was added MeCN. [b] An initial 6 equiv were added, followed by a further 3 equiv after 18 h. [c] The Co-alkyne complex formed in the initial step was purified by fcc before subjecting it to the stated conditions.

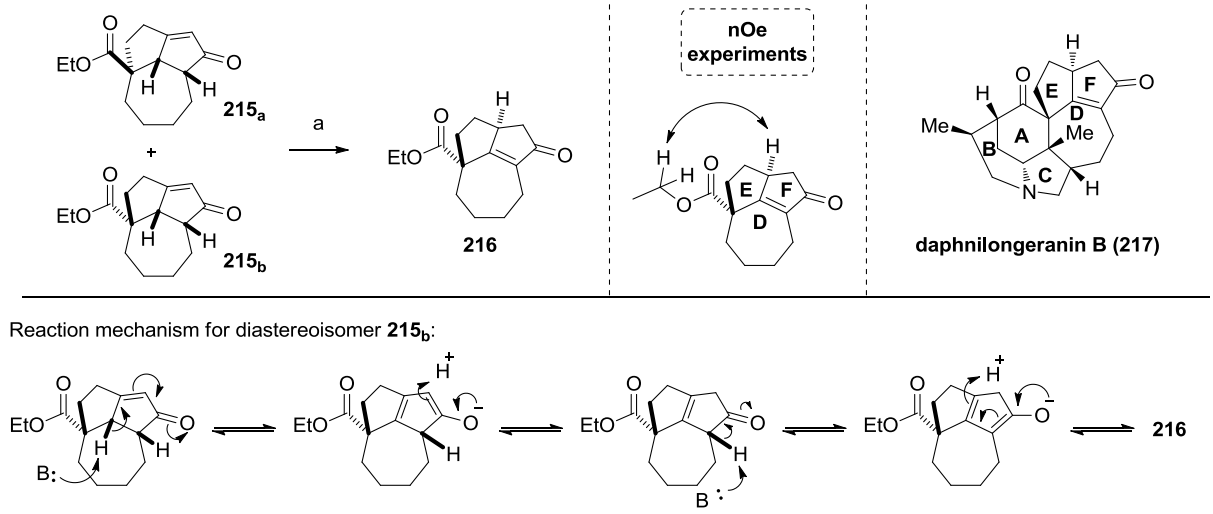
Our first attempt was the thermal promotion of the IMPKR. Boiling the complex **214** in MeCN, in the absence of a promoter, gratifyingly afforded the desired adduct **215** in an encouraging 43% yield and a 4:1 dr (Table 4, entry 1). Attempts to promote the reaction using additives reported in the literature[100d-i] e.g. DMSO, PhSMe, and $CyNH_2$ unfortunately only resulted in the gradual degradation of **214** at rt[i] and no evidence of product formation was witnessed (Table 4, entries 2-4). Promotion using a biphasic system with aqueous NH_4Cl and 1,4-dioxane at 100 °C[105] only led to a complex reaction mixture

[i] Heating these reaction mixtures was not attempted in order to avoid further decomposition.

(Table 4, entry 5). The use of TMANO gave a 39% yield (Table 4, entry 6), whereas employing NMO proved to be more effective providing the desired product **215** in 44% yield (Table 4, entry 7). Promoting the IMPKR with NMO immediately after purification by fcc led to a further improvement and **215** was afforded in 58% yield as a *ca*. 4:1 mixture of diastereoisomers in favour of $\mathbf{215_a}$ (Table 4, entry 8). The stereochemistry of both diastereoisomers was determined by nOe experiments.

Although we proved we could synthesise the IMPKR adduct **215** in this model system, validation of our approach necessitated the migration of the double-bond in our diastereoisomeric mixture, setting it in the correct position in relation to the natural product. For the promotion of this crucial migration, different bases were used to mediate the necessary tautomeric steps. Whilst BEMP and DBU in CH_2Cl_2[i] only afforded traces and a 52% yield of **216** respectively, K_2CO_3 in ethanol smoothly achieved the transformation in a high 92% yield (Scheme 61). Although subtle, we believe this transformation is a consequence of the thermodynamic benefit of migrating the double-bond from a triply to a fully substituted position in the tricycle **216**.[144] From the ethanolic solution of our diasteromeric mixture, only one diastereoisomer of the product **216** was afforded. This possessed the relative stereochemistry matched to that present in the DEF rings of daphnilongeranin B (**217**); stereochemistry determined by nOe experiments. This natural product is another member of the calyciphylline A-type subclass of the *Daphniphyllum* alkaloid family which differs to daphniyunnine D (**23**) only in the γ-position of the enone on the DEF tricycle where a hydrogen atom, not a hydroxyl group is located.

[i] Experiments conducted by Dr. Darses.

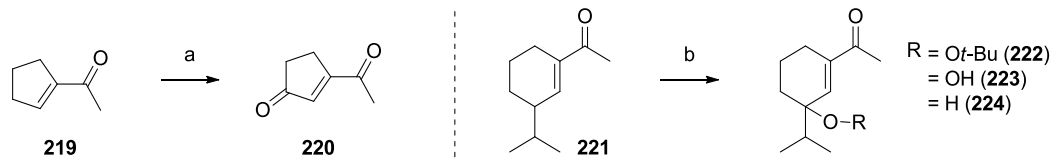


Scheme 61: Base mediated double-bond migration of the IMPKR adduct 215 **(3.7:1). Reaction conditions: (a) K_2CO_3, EtOH, rt, 92%. Reaction mechanism shown using diastereoisomer** 215_b**.**

3.4.1.2 Allylic oxygenation of the all-carbon tricyclic skeleton

To complete the synthesis of the model of daphniyunnine D (**23**) and possibly its related epimer daphniyunnine E (**218**) (Figure 14), a late stage allylic oxygenation of the enone in tricycle **216** was necessary.[145]

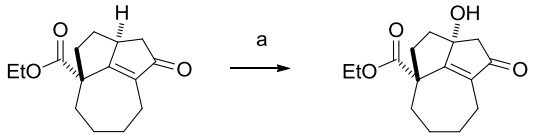
For achieving this transformation we firstly chose to implement Corey's method for the: "*mild, catalytic and highly selective method for the oxidation of α,β-enones to 1,4-enediones*" using Pearlman's catalyst ($Pd(OH)_2$).[146] Normally associated with reductive conditions, this catalyst, in combination with *tert*-butylhydroperoxide (TBHP) and K_2CO_3 achieves the mild and selective oxidation of the γ-position of various enones (e.g. **219**) to the corresponding dienones (e.g. **220**) (Scheme 62).



Scheme 62: Corey's palladium catalysed oxidation of *α,β*-enones. Reaction conditions: (a) $Pd(OH)_2$ (5 mol %), *t*-BuOOH, K_2CO_3, CH_2Cl_2, 24 °C, 81%; (b) $Pd(OH)_2$ (5 mol %), *t*-BuOOH, K_2CO_3, CH_2Cl_2, 24 °C, 60%, 20%, 4% for 222**,** 223 **and** 224 **respectively.**

This reaction is thought to occur *via* a radical-chain mechanism initiated by the *tert*-butylperoxy radical generated in these conditions.[i,147] Notably, when only one hydrogen was present on the *γ*-position of the enone (i.e. in **221**), the authors reported a high yielding reaction affording peroxides **222** and **223** as well as the *γ*-hydroxyenone **224** in 60%, 20% and 4% yield respectively. Therefore, we thought this method could be used for the formation of the desirable C-O *σ*-bond in our tricyclic ring system **216**.

In fact, using a stoichiometric amount of $Pd(OH)_2$, the desired *γ*-hydroxyenone tricycle **225** was isolated from the reaction mixture in a low yet promising 20% yield (50% based on recovered starting material).

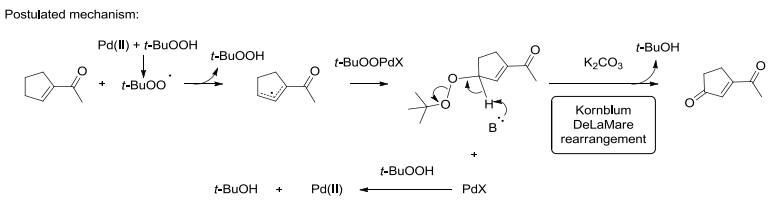


216 **225**

Scheme 63: Allylic oxygenation of the tricyclic model 216 **using Corey's protocol. Reaction conditions: $Pd(OH)_2$ (106 mol %), *t*-BuOOH, K_2CO_3, CH_2Cl_2, 0 °C to rt, 20% (50% brsm).**

Next we employed Watt's radical oxygenation conditions whereby TBHP in the presence of AIBN[ii] and O_2(g) is used to achieve the *γ*-peroxidation of enones (Scheme 64a).[148] In this protocol, a reductive work-up using $SnCl_2$(aq) is used to subsequently cleave[iii,149] the O-O *σ*-bond of the peroxides (Scheme 64b). Overall this method represents a two-step protocol for the formal *γ*-hydroxylation of enones.[150]

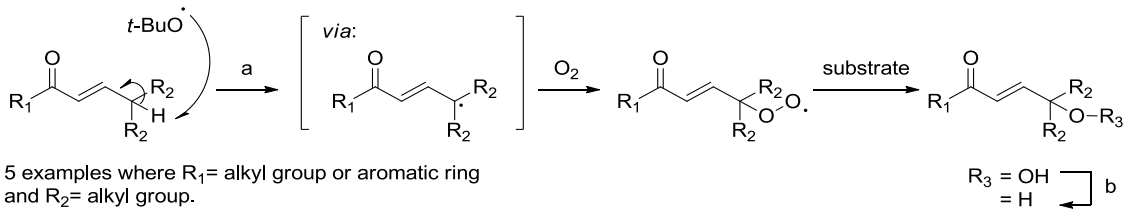
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i 

For the Kornblum DeLaMare rearrangement see reference 147.

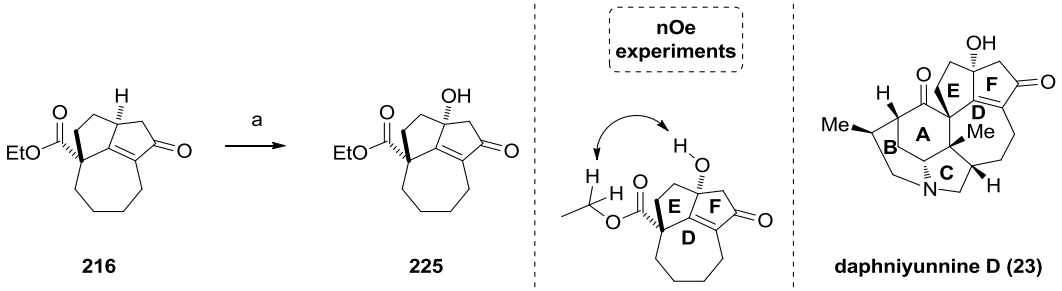
ii Although the *γ*-peroxidation can also occur in the absence of AIBN, lower yields were observed in Watt's report.[148]

iii Alternative reagents/conditions including Pd/C with H_2, Mg/MeOH, Zn/HOAc and triphenyl phosphine are known for the reductive cleavage of the O-O bond.[149]



Scheme 64: Watt's free radical hydroxylation of simple acyclic enones. Reaction conditions: (a) TBHP (aq) (70% w/w), AIBN, O_2(g), 60 °C; then (b) $SnCl_2$ (1 M solution made up using a 2 M HCl (aq)), 28-66% (over two steps).

Its application to our model tricycle **216** gratifyingly afforded the desired oxygenated tricycle **225**, in an acceptable 34% yield. Furthermore, nOe experiments allowed for the assignment of the relative stereochemistry which matches that of daphniyunnine D (Scheme 65).



Scheme 65: Allylic oxygenation of the tricyclic model 216 **using Watt's protocol. Reaction conditions: (a) AIBN (22 mol %), *t*-BuOOH, O_2(g), 60 °C; then $SnCl_2$ (1 M solution made up using a 2 M HCl (aq)), 34% (over two steps).**

As no other regio- or stereoisomers were observed, the low yield is perhaps a consequence of the decomposition of the starting material and/or product under the oxidative conditions. Furthermore, repeated attempts of purification *via* fcc also led to low mass returns. Although the yields for this final transformation are low, they demonstrate the possibility of this desirable late stage stereoselective functionalisation of our DEF tricycle.

Overall, a synthetic route providing access to the substitution patterns present in two calyciphylline A-type alkaloids, daphnilongeranin B (**217**) and daphniyunnine D (**23**) was successfully developed *via* this model study. Next, the key transformations: IMPKR, double-bond migration, allylic oxygenation needed to be applied towards the total synthesis of daphniyunnine D (**23**).

3.4.2 Application of the model study towards the synthesis of daphniyunnine D

This section focuses on the elaboration of the tricyclic [6–5–7] core **172** discussed in chapter 2, for the application of our protocol in the construction of the ACDEF pentacycle of daphniyunnine D (**23**). To allow this, a pendant terminal butynyl needed to be introduced to the tricycle (i.e. in **226**) and furthermore the 7-membered ring ketone had to be transformed into an olefin to provide an advanced tricycle **102** able to undergo the IMPKR (Figure 17).

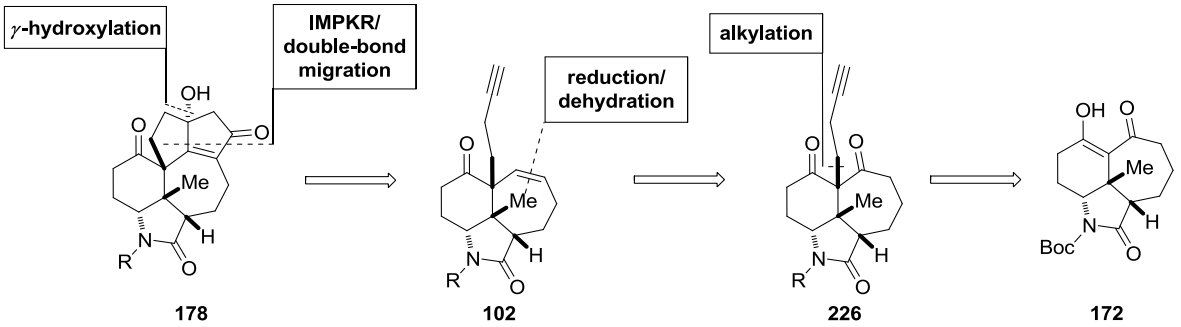


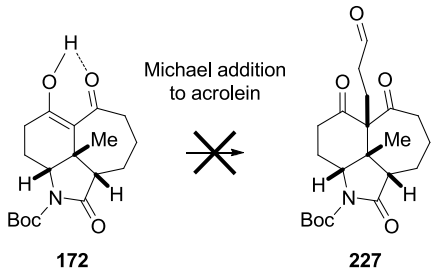
Figure 17: Assignment of the disconnections used in the model study to the retrosynthesis of daphniyunnine D.

Although undesired, modifications and detours of the protocols developed in the model system were required when applied to the multifunctional ACD tricycle **172**. These will be the focus of the remaining sections of chapter 3.

3.4.2.1 Side chain introduction on the tricyclic core towards the synthesis of an IMPKR substrate

The stable masked diketone (hydroxyenone functionality) of tricycle **172** is the main reason why alternative approaches to its functionalisation were necessary when compared to cycloheptanone (**208**) in the model study. Trying to parallel the synthetic approach used for the model system, early attempts by Dr. Darses to functionalise the central carbon atom between the two ketones *via* a Michael addition were unsuccessful in providing **227**

(Scheme 66). This is perhaps due to the H-bonded hydroxyenone functionality effectively behaving as a protecting group for this central targeted carbon atom.

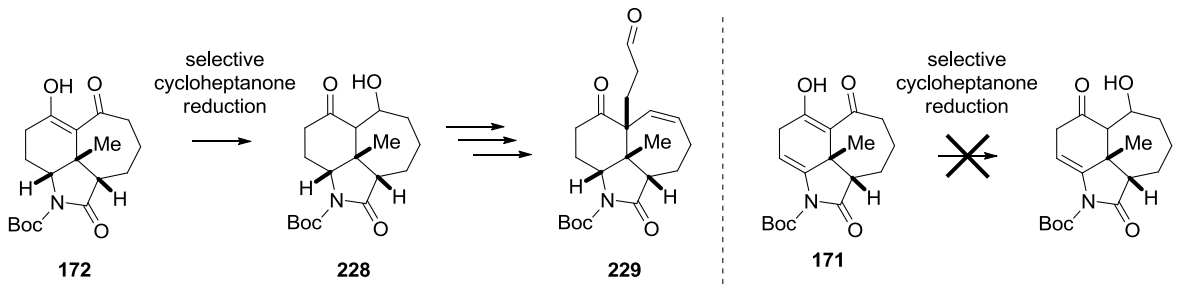


172 227

Scheme 66: Dr. Darses' attempts to achieve the Michael addition of tricycle 172 **to acrolein.**

It was hypothesised at the time that if the cycloheptanone functionality were to be reduced to alcohol **228** and then eliminated, the Michael addition approach could be re-investigated to afford tricyclic aldehyde **229** (Scheme 67). However, this transformation was not endeavoured at this stage in the synthesis. It was assumed that the chemoselective reduction of the cycloheptanone would prove challenging in the presence of the 6-membered ring enol; which is effectively a masked carbonyl functionality.[151]

An early attempt to reduce the hydroxyenone functionality in the enamide **171** using $NaBH_4$ was unsuccessful, perhaps owing to the stability of the functionality. Stronger reducing agents (e.g. $LiAlH_4$) were used on a related *N*-allylated tricycle; however, complex inseparable mixtures were afforded (*vide infra* section **4.4.3.1**). To circumvent these problems, an alternative approach to reducing the cycloheptanone functionality combined with the elimination of the nascent alcohol was developed, however these results will be discussed in chapter 4 (*vide infra* Scheme 97).

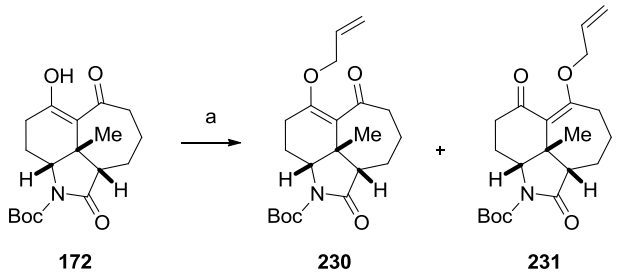


Scheme 67: Considerations for the chemoselective reduction of the cycloheptanone functionality in afforded ACD tricyclic ring systems.

Although the hydroxyenone caused problems relating to its reduction and to the Michael addition to acrolein, we considered taking advantage of this "frozen enol" functionality. We envisioned an alternative two-step access to the functionalisation of the central carbon in **172** *via* a Claisen rearrangement.[152] It was anticipated that the intramolecular nature of the rearrangement would increase our chances of forming the desired *C*-*C* bond. A subsequent hydroboration of the double-bond in the product, followed by an oxidation would lead to the formation of the desired pendant aldehyde **227**.

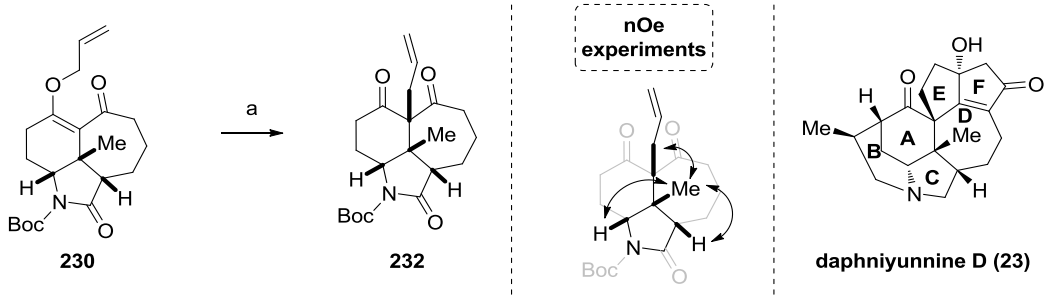
To this end, allylation of the tricyclic hydroxyenone **172** with allyl bromide, mediated by K_2CO_3 resulted in the allylated enol **230** in 79% yield (Scheme 68). In the crude ^{1}H-NMR spectrum a 10% impurity was observed which was attributed to the allylated isomeric product **231**.[i] This is the result of the regioselectivity in the allylation of the delocalised enolate, created *in situ* in the basic and high temperature reaction conditions. It is worth noting that only the 6-membered ring enol is observed in the $CDCl_3$ ^{1}H- and ^{13}C-NMR spectra of tricycle **172**.

[i] This result was confirmed in a separate experiment, where the desired **230** was isolated in 76% yield alongside the regioisomer **231** in 17% yield. The structure of **231** was subsequently confirmed by full analysis.



Scheme 68: Allylation of tricyclic hydroxyenone 172**. Reaction conditions: (a) K_2CO_3, allyl bromide, acetone, reflux, 79% of** 230 **and 10% of** 231**.**

Having functionalised tricycle **172**, we wanted to determine whether a Claisen rearrangement would achieve the allylation of the central carbon atom. Indeed, refluxing the *O*-allylated compound **230** in toluene overnight, afforded the desired rearranged product **232** as a single diastereoisomer, albeit in only 57% yield (Scheme 69).[i] Importantly, nOe experiments revealed that the allyl group was present on the convex face of the tricycle as required for the synthesis of daphniyunnine D. Although encouraged by the diastereoselectivity of the reaction, a possible improvement in the yield and its viability to scale-up were still to be determined.

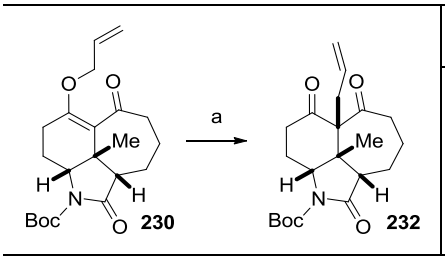


Scheme 69: Access to the desired *C*-allylated tricycle 232**. Reaction conditions: (a) toluene, reflux, 57%.**

In a test reaction prior to the scale-up of this rearrangement, we noted the intensification of polar and baseline spots in our TLC analysis during the course of the reaction. Although *N*-Boc groups are generally stable at these temperatures (toluene reflux= 110-111 °C)[153] interactions with acidic components in the glassware combined with long reaction periods were thought to be responsible for its possible deprotection in our system. To test this

[i] This unoptimised experiment was conducted by Dr. Darses.

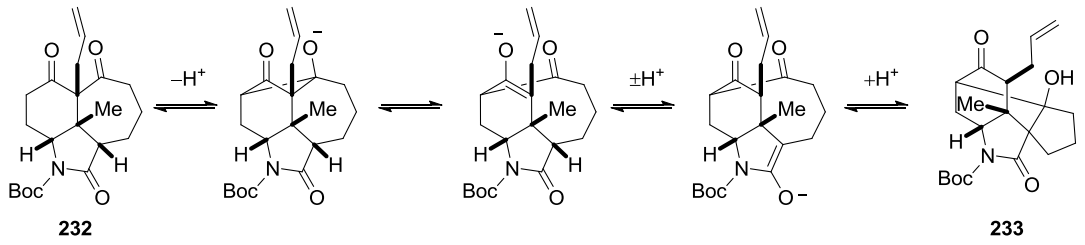
hypothesis the glassware was base-washed using a solution of concentrated KOH and the toluene was passed through anhydrous K_2CO_3; unfortunately this led to an even lower 50% yield (Table 5, entry 2). With a similar rationale we attempted buffering our toluene solution using an innocent basic additive. Gratifyingly, adding 5 equivalents of the non-nucleophilic Hünig's base to our toluene solution, led to the rearranged product **232** in an improved 86% yield (Table 5, entry 3).[i]



Entry	Solvent, temp	Additional conditions (a)	Yield (%)
1	Toluene, reflux	N/A	57
2	Toluene, reflux	Base washed solvent and glassware	50
3	Toluene, reflux	5 equiv of *N*,*N*-diisopropylethylamine	86

Table 5: Investigation into the Claisen rearrangement of the *O*-allylated tricycle 230**.**

From Dr. Darses' work, we knew that diketone **232** was incompatible to the basic conditions necessary for the hydroboration of the double-bond. In his attempts, not only did 9-BBN not react with this terminal olefin, the basic conditions used in the work-up led to a base induced fragmentation to provide the unexpected and structurally complex tetracycle **233** (Scheme 70).



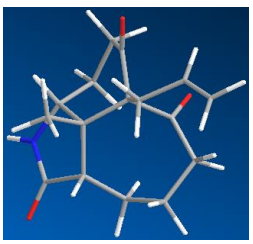
Scheme 70: Base mediated fragmentation of 232**.**

Furthermore, when the selective reduction of the cycloheptanone in **232** was attempted with DIBAL-H, no reaction was observed whilst the use of L-Selectride® led to complex reaction mixtures. In fact, as the route appeared to have reached a dead-end at this point, this project was abandoned and alternative routes were designed.

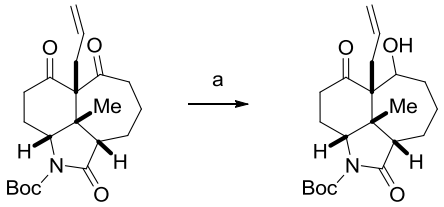
[i] Unfortunately, the regioisomer **231** did not behave in the same way. Employing the conditions for the rearrangement only led to its decomposition.

However, noting the synthetic potential of this multifunctional tricycle **232** and its relevance to the total synthesis of daphniyunnine D (**23**), it seemed prudent to reassess its reactivity. It was believed that the 6- and 7-membered ring ketones in **232** would exhibit different reactivities due to a combination of electronic and steric effects. If the cycloheptanone proved to be more reactive/electrophilic we could potentially selectively reduce this ketone under forcing conditions. Furthermore, if the opposite scenario was the case, we could mask the cyclohexanone carbonyl with a suitable protecting group, allowing for appropriate transformations on the remaining ketone.

At the early stages of this reassessment we were pleased to note that addition of $NaBH_4$ to a methanolic solution of **232** led to the clean formation of just one molecule. After NMR analysis we concluded that the hydride led to the fortuitous reduction of the 7-membered ring over the cyclohexanone functionality, giving a single diastereoisomer of **234** in 74% yield (Scheme 71); no other diastereoisomers were isolated. This is contrary to what would normally be expected when comparing the reactivity of the two cyclic ketones independently, in a non-polycyclic environment.[i,154] Impressed by the selectivity of this reaction, further investigation into this route was rekindled.



Minimised molecular model of **232** using ChemBio3D



232 **234**

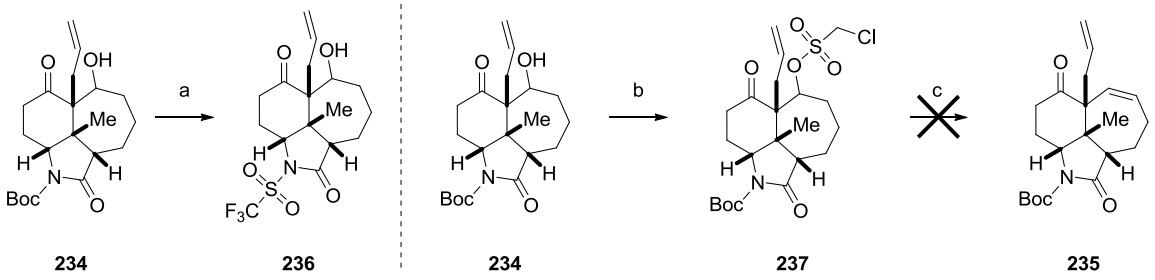
Scheme 71: Chemo- and diastereoselective reduction of 232 **using $NaBH_4$. Reaction conditions: (a) $NaBH_4$, MeOH, –20 °C, 74%.**

[i] In a solvent mixture of MeOH:CH_2Cl_2 (1:1) with an excess of $NaBH_4$ at –78 °C, cyclohexanone is reduced in 1 hour whereas 14 hours are necessary for cycloheptanone.[154]

NOe experiments were carried out to better understand the selectivity of the reaction; however these remain inconclusive, with no clear data supporting one diastereoisomer of the alcohol over the other. Based on simple molecular modelling, the chemoselectivity is attributed to the fact that the cyclohexanone in the diketone **232** is already locked in a strained boat conformation (Scheme 71). Having an sp^2 centred ketone is perhaps more favourable than forming a tetrahedral sp^3 centre which would add to both the overall torsional and transannular strain of the tricycle. The 7-membered ring on the other hand is less prone to be affected by its conformation. Although it too is locked in the polycyclic molecule, its larger size allows more flexibility in the system and thus results in a reduced energy difference between the sp^2 ketone and the sp^3 alcohol.

With the alcohol in hand we were hoping that we could follow the model's mesylation/elimination protocol to afford the desired olefin **235**. To our disappointment however, mesylation of the alcohol using a range of conditions reported in the literature did not lead to any reaction. Its unreactive nature is possibly a consequence of its proximity to the allyl bearing quaternary carbon of the sterically congested tricycle **234**.

In an attempt to increase the reactivity of the sulfonyl group of the electrophile, we used triflic anhydride which led to a complex mixture from which sulfonamide **236** was isolated in 27% yield. It is likely that residual triflic acid in the commercial bottle of the anhydride may have caused the *N*-Boc deprotection of our substrate which then reacted with the anhydride *in situ* (Scheme 72a).

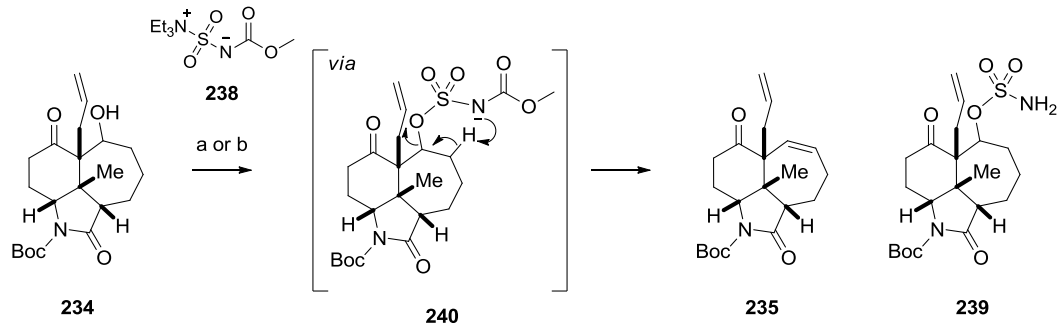


Scheme 72: Neopentyl alcohol activation. Reaction conditions: (a) KHMDS, Tf_2O, CH_2Cl_2, rt, 27%; (b) McCl, pyridine, 50 °C, 54%; (c) DBU, toluene, 50 to 130 °C (sealed tube), no reaction.

Some success was achieved when the chloromethanesulfonate (McCl) was used for activation.[155] McCl transforms alcohols into excellent leaving groups and is regarded as superior to the methylsulfonate owing to its enhanced electrophilicity and also to trifluoromethylsulfonate in terms of its stability. Although formation of the desired C-O bond was achieved on the neopentyl alcohol in 54% yield, attempting to eliminate this activated alcohol **237** using DBU in toluene in a sealed vial gave no product even at 150 °C. Interestingly not only was **237** unreactive towards elimination, absolutely no degradation was observed in these harsh conditions, confirming the increased stability of this activating group (Scheme 72).

Subsequently, different protocols were sought avoiding the use of sulfonyl groups for the activation of the alcohol. To our disappointment, employing the Grieco elimination[156] conditions by first substituting the alcohol with a selenide also led to no reaction. Baran and co-workers reported the elimination of a neopentyl alcohol using Mitsunobu conditions (DEAD, PPh_3)[157] for its activation in their synthesis of (±)-steviol.[158] In our hands a complex reaction mixture was observed upon activation and this method was also abandoned.

Discouraged with the lack of progress regarding the elimination of the alcohol, even after its successful activation using McCl, we turned our attention to the use of commercially available dehydrating agents. Employing Martin's sulfurane[159] to assist the dehydration did not affect the alcohol, even after heating in a sealed vial at 130 °C. However, heating a solution of the alcohol in toluene with Burgess reagent (**238**)[160] at 80 °C for 3 days provided the olefin **235** for the first time, albeit in a low 18% yield (Scheme 73a).



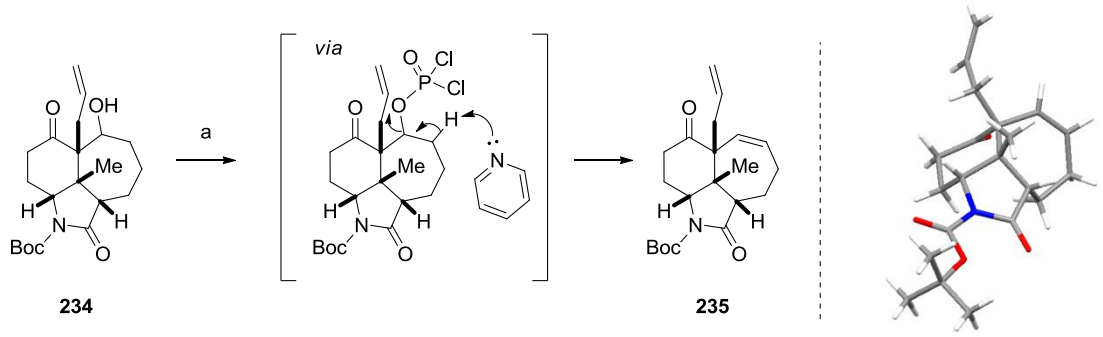
Scheme 73: Dehydration of 234 **using Burgess reagent. Reaction conditions: (a)** 238**, toluene, 80 °C, 3 d, 18% of** 235 **and 35% of** 239**; (b)** 238**, toluene, reflux, 5 h, 56% of** 235 **and 16% of** 239**.**

Tricyclic sulfamate **239** derived from the deacetylation of the methoxycarbonylsulfamate intermediate **240** was also isolated in a 35% yield.[i,161] Dropwise addition of a solution of **238** in toluene to a solution of **234** at reflux improved the yield to 56%; however, the formation of the side product **239** in 16% yield could not be avoided (Scheme 73b). Whilst these reactions proved that the elimination of the neopentyl alcohol in **234** was indeed possible, the low yields necessitated its further investigation.

Activation of the alcohol using phosphoryl chloride ($POCl_3$) in pyridine at rt was unsuccessful. However, heating the reaction mixture to 85 °C afforded a 53% yield of the dehydrated **235**. Even with a low yield, the practical simplicity as well as the reasonably clean crude ^{1}H-NMR spectrum of this one-pot reaction encouraged us to continue its investigation. In fact, with some optimisation we discovered that a dropwise addition of $POCl_3$ to a solution of **234** in refluxing pyridine combined with a reasonably short reaction time of 45 min, afforded the desired molecule in 72% yield.[ii] Although we were confident no stereocentres were epimerised, the relative stereochemistry of **235** was unambiguously confirmed using single X-ray crystallography (Scheme 74).

[i] Similar side products are known to eliminate under basic conditions and high temperatures[161] however these attempts were unsuccessful in our hands.

[ii] No other products, e.g. the chlorinated tricycle, were isolated from the reaction mixture.

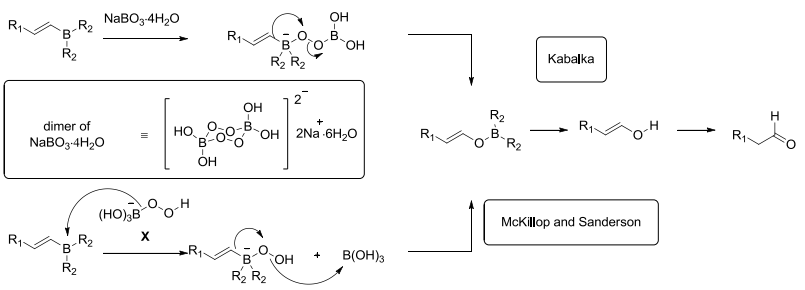


Scheme 74: Dehydration of alcohol 234 **using $POCl_3$ and crystal structure of** 235**. Reaction conditions: $POCl_3$, pyridine, reflux, 72%.**

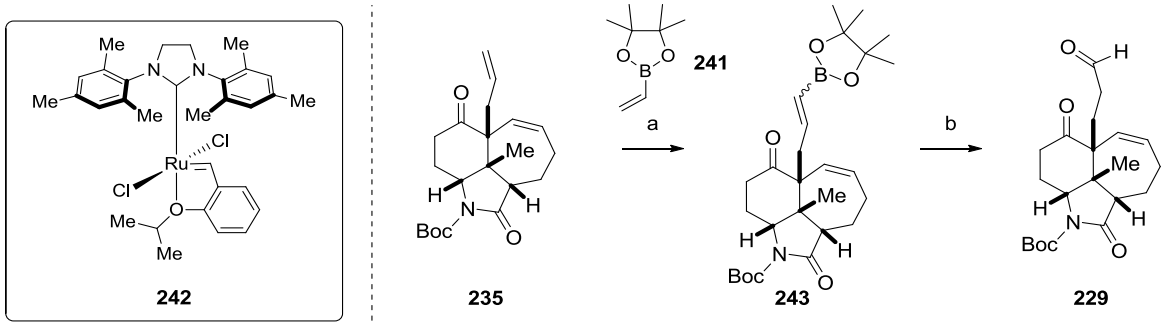
Satisfied with the dehydration reaction, we focused our attention to the transformation of the allyl group to the aldehyde which would then allow its homologation to the terminal alkyne. With the cycloheptanone functionality removed, we believed that the basic conditions required for the hydroboration work-up would not lead to any base mediated fragmentations related to those observed by Dr. Darses (Scheme 70). However, using 9-BBN to achieve the selective hydroboration of the terminal olefin of the allyl group in the presence of the cycloheptene functionality, led to no reaction; as did the use of BH_3.

Disappointed with the lack of reactivity of tricycle **235** towards hydroboration, an alternative strategy was employed using a vinyl boronate cross-metathesis, oxidation protocol as reported by Danishefsky and co-workers.[162] Pleasingly, the cross-metathesis of **235** to vinyl pinacol boronate **241**[163] using Hoveyda-Grubbs 2nd generation catalyst (**242**) provided **243** as a 1:1.4 mixture of *Z* and *E* isomers in 82% yield (Scheme 75a). This was subsequently oxidised using sodium perborate ($NaBO_3{\cdot}4H_2O$),[164] affording the desired aldehyde **229** in 44% overall yield over two steps.[i] Whilst TMANO in refluxing THF can

[i]Although sodium perborate is often regarded as the salt form of hydrogen peroxide, it is unlikely that it exists as a mixture of sodium borate and peroxide in aqueous solution and it is still unknown which active boron species is responsible for the mild



also be used to achieve the boronate oxidation, in our hands no product was isolated and instead decomposition of **243** was observed.



Scheme 75: Application of Danishefsky's cross-metathesis/oxidation protocol for the transformation of terminal olefins to aldehydes. Reaction conditions: (a) 241**,** 242 **(10 mol %), CH_2Cl_2, reflux; then (b) $NaBO_3 \cdot 4H_2O$, THF:H_2O (1:1), rt, 44% (over two steps).**

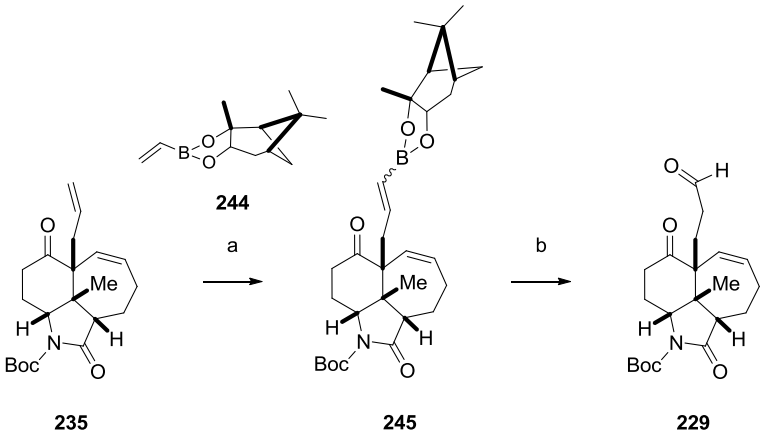
Although this alternative two-step protocol gave access to the desired aldehyde **229** for the first time, problems arose when larger scale reactions were carried out. During the optimisation of the reaction to provide consistent results we discovered the possible reasons for its sensitivity. One problem was the incomplete removal of the ruthenium species (even after fcc or the use of Quadrasil® metal scavengers) which led to inconsistent mass returns in the first step and more importantly a detrimental effect on the yield of the oxidation step. Another problem could be the possible formation of polar side-products in the second step, e.g. hydrates of the aldehyde **229** or hydrolysed forms of the vinyl boronate **243**, although none of these were isolated. The most important reason for the inconsistent results is attributed to the sensitivity of the pinacol boronate to hydrolysis especially on silica gel (performing a two-dimensional TLC of the isolated boronate **243** we noted its significant decomposition). This explained why longer exposure to silica gel,

oxidative properties of this reagent. Kabalka and co-workers presumed that these are a consequence of having borate as a leaving group compared to the commonly used highly alkaline/hydrogen peroxide solution oxidative work-ups.[164b] McKillop and Sanderson established, using NMR and Raman spectroscopy, that in dilute aqueous solutions (<0.1 M), peroxoborate anions exist which may be responsible for the delivery of a hydrogen peroxide anion at a lower pH to those necessary when using hydrogen peroxide alone.[164c] Furthermore, they suggested that the ability of $B(OH)_3$ to accept a hydroxyl anion from the hydrogen peroxide leaving group may assist the O-O bond cleavage. In more alkaline solutions they attribute the oxidising activity to either hydrogen peroxide or its anion.

either when purifying larger reactions or when carrying out multiple purifications by fcc in an attempt to remove the Ru-species led to lower overall yields. Unfortunately, attempting the oxidation on the crude reaction mixture of **243**, avoiding its exposure to silica, only led to complex reaction mixtures with limited product isolation.

As the thermodynamic stability of B-O bonds is very similar in boronic acids and esters (boronates), hindered cyclic boronates have been designed in order to prevent their facile hydrolysis.[165] Whilst pinacol boronates are often the reagents of choice for Suzuki cross-couplings due to their relative stability as well as their low cost, the pinacol boronate of our substrate **243** clearly lacked this stability and thus alternatives were explored.

Pinanediol boronates are considered as one of the species most resistant to hydrolysis, transesterification and ligand exchange due to the rigidity and spatial orientation of the diol. Furthermore, although more expensive, (+)-vinyl pinanediol boronate (**244**) is also commercially available. During our failed attempts to optimise the cross-metathesis reaction with the vinyl pinacol boronate, we noted that we could accomplish the reaction mildly at rt using a reduced pressure (16 mbar). This assists the removal of the stoichiometric ethylene gas by-product, which often causes catalyst sequestration during low temperature metathesis reactions.[166] When we replaced **241** with the (+)-vinyl pinanediol boronate (**244**) we were pleased to see that the new boronate **245** could be afforded in high purity, as a mixture of 4 diastereoisomers in a 91% yield, after fcc (Scheme 76). Although we noted some degradation on TLC, this was negligible compared to the pinacol analogue **243**.



Scheme 76: Cross-metathesis using (+)-vinyl pinanediol boronate and the subsequent oxidation to 229**. Reaction conditions: (a)** 244**,** 242 **(20 mol %), mesitylene, rt, 16 mbar, 91%; (b) $NaBO_3.4H_2O$, THF:H_2O (10:1), rt, 68% (62% over two steps).**

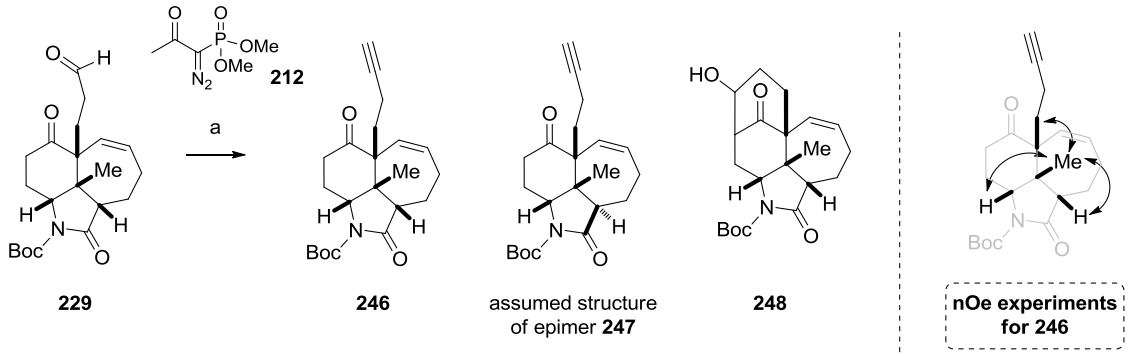
Gratifyingly, sodium perborate could also oxidise this more stable boronate **245** however the yields, although generally higher, were still somewhat inconsistent. We soon discovered that by reducing the amount of water in the reaction mixture and by avoiding a final aqueous work-up,[i] consistent results were possible giving an overall yield of 62% over the two steps. A high concentration of water in the solution may lead to the formation of hydrolysed forms of the boronate and/or the aldehyde.

One step away from testing out the key IMPKR on our real system, we now needed to homologate our aldehyde **229** to afford the necessary pendant alkyne functionality. Avoiding unnecessary deviation from our model study, we subjected our aldehyde **229** to identical reaction conditions with K_2CO_3 and the Ohira–Bestmann reagent (**212**) at 0 °C to mediate the transformation (Scheme 77). A complete and relatively clean reaction was noted, with both a more lipophilic as well as a more polar spot evident by TLC analysis.

Upon their isolation, we noted that the top-spot comprised of two very close running ones. One of the two was isolated in relatively high purity and full NMR analysis on a small quantity revealed that it was the alkyne **246** with the desired relative stereochemistry (see

[i] The H_2O present in the reaction was removed by addition of large amounts of anhydrous sodium sulfate which was subsequently filtered off alongside the reaction's precipitates.

nOe in Scheme 77). Unable to separate the second compound, we tentatively assigned it as the epimer **247**; NMR analysis of the mixture of molecules revealed similar chemical shifts to **246** in both the ^{1}H and ^{13}C NMR spectra. Although we have no conclusive data supporting this, we believe the epimeric position giving rise to **247** is the α-position of the γ-lactam. Perhaps the electron-withdrawing Boc group causes a somewhat ketonic character on the carbonyl increasing the acidity of the hydrogen atom on this position. An undesired intramolecular aldol reaction from the acidic α-position of the ketone to the electrophilic aldehyde gave rise to the third isolated product **248** (polar spot). In conclusion, the homologation provided the desired alkyne **246** in 29% yield, a mixture of epimers in 19% and the aldol product **248** in 13% (Scheme 77).

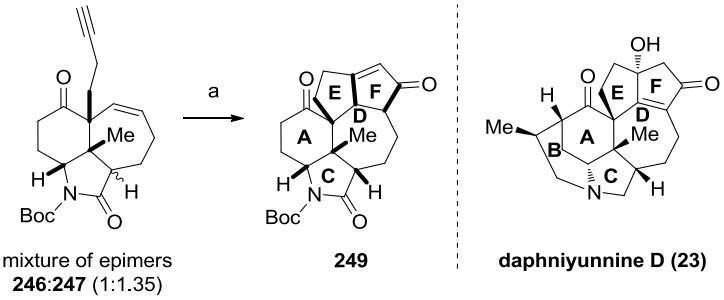


Scheme 77: Homologation of 229 **using the Ohira–Bestmann reagent. Reaction conditions: K_2CO_3,** 212**, EtOH, 0 °C to rt, 29% of** 246**, 19% of a mixture of** 246 **and** 247 **(1:0.55), 13% of** 248**.**

3.4.2.2 Formation of the [6–5–7–5–5] pentacycle (ACDEF rings) of daphniyunnine D via an IMPKR

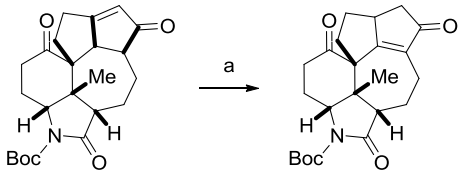
With only 2 mg of a mixture of alkyne epimers (1:1.35 of **246**:**247**) we wanted to attempt the crucial IMPKR on our substrate using $Co_2(CO)_8$ and NMO for its promotion (Scheme 78). Due to the small scale of the cycloaddition experiment, less than 1 mg of product was isolated after fcc. However, we were pleased to see the correct mass peaks in the mass spectrum, indicating the clear incorporation of a molecule of CO in our tricyclic ring system. Although contaminated with either impurities or diastereoisomers, the

characteristic enone functionality was present in our NMR analysis and thus the synthesis of pentacycle **249** was confirmed in 36% yield. Since a mixture of epimeric alkynes was added to this reaction we are unsure as to which diastereoisomer of **249** was isolated (the desired diastereoisomer is drawn for clarity). NOe experiments were not attempted as these would be inconclusive and weak owing to both the contamination of the sample as well as its minute quantity.



Scheme 78: Synthesis of the ACDEF pentacycle 249 **of daphniyunnine D *via* an IMPKR. Reaction conditions: (a) $Co_2(CO)_8$, CH_2Cl_2, rt, assumed quantitative; then (b) addition of NMO at rt, 36%.**

A small scale IMPKR was also attempted on a sample of pure alkyne **246** (stereochemistry determined by nOe experiments). However, although the ^{1}H NMR spectrum of the isolated product contained the chemical shifts consistent with the first experiment, it was heavily contaminated with impurities, making us unable yet again to confirm the relative stereochemistry of the adduct. Considering the efficiency with which the double-bond migration occurred in our model, we hoped that this would be paralleled in the real system to provide **250**. With a pure sample of **250** we would be able to confirm the relative stereochemistry of the pentacycle, however, due to the small scale of the experiment (<1 mg) we were unable to isolate the desired product after reacting **249** with K_2CO_3 in EtOH and no clear conclusions were drawn.



249 **250**

Scheme 79: A single unsuccessful attempt at the double-bond migration of pentacycle 249**. Reaction conditions: (a) K_2CO_3, EtOH, no product isolation.**

Although the relative stereochemistry of the IMPKR adduct **249** remains unknown, the important thing to note is that the cycloaddition approach towards the synthesis of daphniyunnine D is indeed possible. Optimisation of the homologation as well as further investigations into the key IMPKR are necessary to fully validate this approach and make it amenable to scale-up.

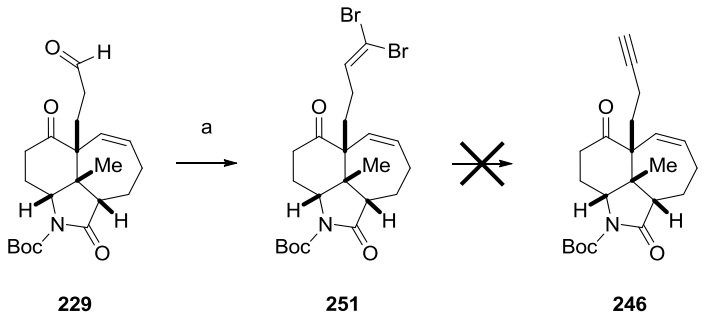
3.4.2.3 Alternative homologation of aldehyde 229 via a Corey-Fuchs reaction

As the basic conditions of the Ohira–Bestmann modification for the homologation led to low yields and epimers of **246** as well as the aldol side product **248**, we wanted to reassess our retrosynthetic approach for daphniyunnine D.

Having demonstrated that the synthesis of the pentacycle **249** is possible *via* an IMPKR, one option would be to leave this cycloaddition for the final stages of the synthesis. If ring B could be synthesised prior to the IMPKR, the undesired enolate formation may not occur due to the steric constraints of the polycyclic ring system, thus preventing the formation of the aldol side product during the homologation of the aldehyde.

The second option would be the investigation of the alternative homologation of the aldehyde **229** *via* the Corey–Fuchs reaction.[167] This requires the transformation of the aldehyde to a dibromoolefin which is subsequently treated with a strong base to afford the terminal alkyne. Testing this second proposal was faster and easier, therefore we chose to transform **229** to the dibromoolefin **251** using standard conditions (i.e. CBr_4 and PPh_3 in

CH_2Cl_2). Although the first stage of the reaction was successful in providing **251** in a 93% yield (Scheme 80), its transformation to the alkyne **246** was met with challenges of its own.



229 **251** **246**

Scheme 80: The Corey-Fuchs reaction on aldehyde 229**. Reaction conditions: (a) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 93%.**

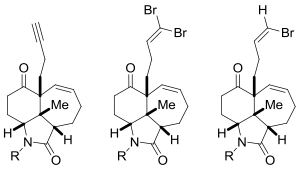
Even though we are confident that using *n*-BuLi to affect the second stage of the Corey–Fuchs reaction provided the desired alkyne,[i] various inseparable side products were also formed. Although no aldol reaction is possible, these basic conditions could still cause a similar epimerisation to that observed in **247**. Furthermore, they could also cause the base mediated *N*-Boc deprotection of our *γ*-lactam. Both these reasons, combined with the possible enolate formation at the *α*-position of the ketone in **251**, made calculating the equivalents of *n*-BuLi necessary for the reaction challenging. In fact all our attempts in optimising the formation of the alkyne **246** were met with little success and inseparable complex reaction mixtures were afforded in all cases.[ii]

Disappointed with the capricious nature of the alkyne transformation, we considered using the dibromo functionality as a means of protecting our reactive aldehyde **229**, allowing for

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[i] This was confirmed by matching NMR spectra to those of **246**, isolated from the homologation of the aldehyde **229** using the Ohira–Bestmann reagent.

[ii] Basing our conclusion on NMR and mass spectra run on two groups of molecules isolated by fcc, the shown *N*-Boc protected tricycles and their deprotected analogues are believed to form in this reaction (epimers are also possible). Unfortunately these have not been confirmed or isolated pure due to the identical polarities of the compounds in each group. Use of the bulkier base *t*-BuLi did not provide a cleaner reaction and instead led to a similar outcome.



Group A: R= Boc

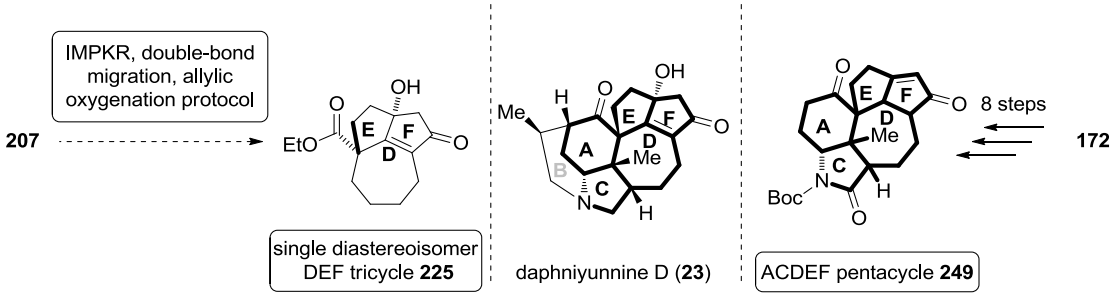
Group B: R= H

the transformations necessary for the synthesis of ring B. These investigations, alongside different approaches towards the synthesis of ring B are discussed in chapter 4.

3.5 Summary and conclusion of chapter 3

A model system was used to validate our synthetic approach towards the construction of the DEF tricycle present in the calyciphylline A-type *Daphniphyllum* alkaloids. An IMPKR, double-bond migration protocol was employed to give rise to the stereoselective formation of the tricycle **216** present in daphnilongeranin B (**217**). A subsequent late stage regio- and stereoselective allylic oxygenation provided **225** with matching substitution patterns present in our target molecule, daphniyunnine D (**23**).

Using an IMPKR, the synthesis of the [6–5–7–5–5] ACDEF pentacycle **249** found in daphniyunnine D (**23**) was made possible by elaborating the ACD tricycle core **172** (Scheme 81). Optimisation and further investigation of the final homologation and IMPKR are now necessary to allow for the validation of the subsequent double-bond migration, allylic oxygenation protocol in our real system.



Scheme 81: Summary of the application of our model study for the synthesis of the ACDEF pentacycle 249 **of daphniyunnine D.**

Although the IMPKR approach has proved possible for the total synthesis of the targeted natural product, having encountered low yields for the Ohira–Bestmann homologation as well as for the IMPKR, an investigation into the synthesis of ring B was initiated. If ring B could be synthesised prior to the DEF tricycle in high yield, then the IMPKR, double-bond

migration, allylic oxygenation protocol could be applied in the final stages of the synthesis of daphniyunnine D. The investigation into the synthesis of ring **B**, with the final aim of combining the strategies developed in chapters 2 and 3 for the synthesis of the natural product, is the focus of the final chapter 4.

Chapter 4: An intramolecular hydroalkylation approach for the synthesis of ring B of daphniyunnine D

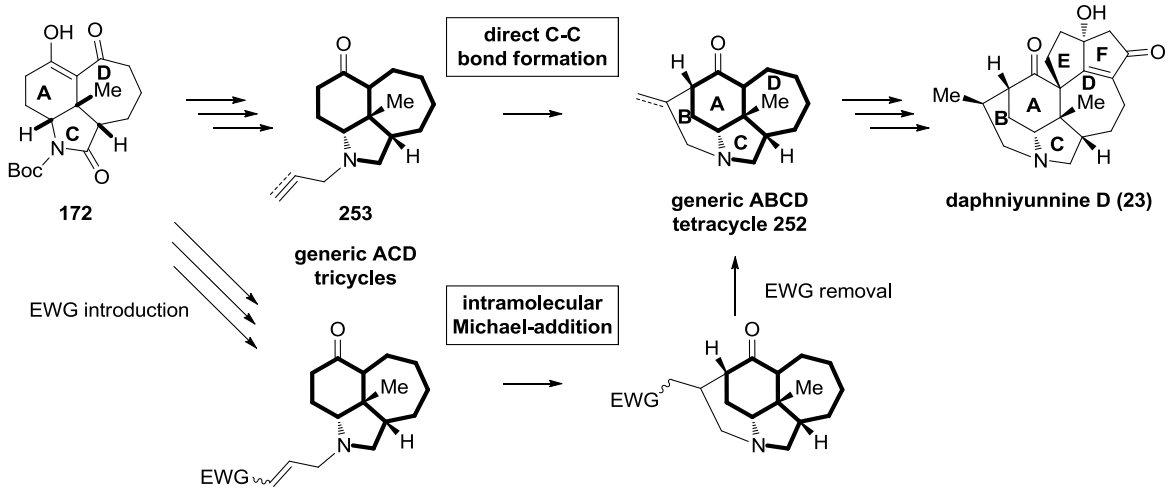
4.1 Introduction

This chapter discusses the investigations into the construction of the 6-membered ring B of daphniyunnine D. Combined with the asymmetric IMDAF and IMPKR approaches of the preceding chapters, the formation of this ring will allow for the total synthesis of our target.

4.2 Aims and retrosynthetic analysis

The synthesis of the 6-membered ring B in the calyciphylline A-type *Daphniphyllum* alkaloids is arguably one of the most challenging and least explored transformations towards their total synthesis. With the IMDAF approach establishing a facile route to the *N*-Boc protected ACD tricyclic core **172** of daphniyunnine D (**23**), we wanted to explore the possibility of introducing ring B in a facile and stereocontrolled fashion (Scheme 82).

For the construction of the ABCD tetracycle, a generic structure of which **252** is representative (Scheme 82), we envisaged a direct C-C bond formation between the α-position of the 6-membered ring ketone and an unactivated double or triple bond[168] attached to the nitrogen of the ACD tricycle **253**. This transformation would avoid the need to introduce and subsequently remove electron-withdrawing activating groups (EWG) on the pendant olefin; which would be necessary if an intramolecular Michael addition[27] strategy is to be implemented (Scheme 82).

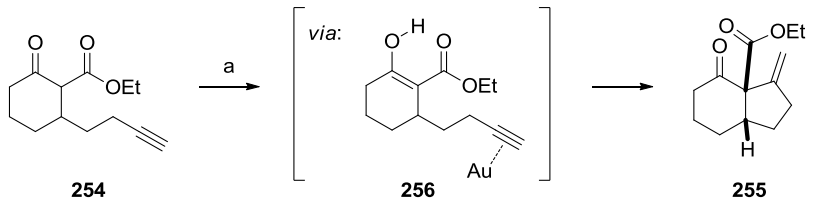


Scheme 82: Direct C-C bond formation for the synthesis of ring B compared to an indirect Michael-addition approach.

4.3 Intramolecular hydroalkylation reactions

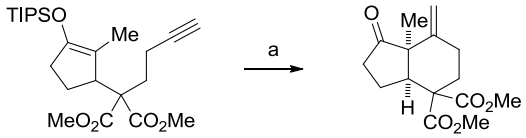
4.3.1 Toste-Conia-ene reaction (intramolecular hydroalkylation of triple bonds)

In a significantly improved variant of the thermal Conia–ene reaction,[169] Toste and co-workers demonstrated that a cyclisation between a series of *β*-ketoesters (e.g. **254**) onto pendant alkynes can take place at rt using only catalytic amounts of $AuPPh_3Cl$ combined with co-catalyst AgOTf (Scheme 83); the halophilic silver additive ensures the formation of the active Au(I) cationic species.[29] Avoiding the use of high temperatures needed in the classic Conia-ene reaction,[169] this methodology provides a mild alternative, giving rise to the diastereoselective and high yielding formation of cyclic and bicyclic systems (e.g. **255**), an example of which is given in Scheme 83. Deuterium labelling experiments supported their mechanistic proposal of an intramolecular nucleophilic attack of the enol form of the ketoester to the Au(I)-alkyne complex **256** in an *exo-dig* fashion.



Scheme 83: The Toste–Conia–ene reaction. Reaction conditions: (a) $AuPPh_3Cl$ (1 mol %), AgOTf (1 mol %), CH_2Cl_2, rt, 90%.

Acknowledging the limitation of necessitating a highly enolisable methylene unit as a nucleophile, Toste and co-workers developed the reaction further to allow silyl enol ethers (e.g. **257**) to act as reactive partners (Scheme 84).[170] By prior formation of these so called "*frozen enol equivalents*" simple ketones can formally undergo this Au-catalysed *exo-dig* cyclisation using only slightly elevated temperatures of 40 °C. As the enol hydrogen atom is replaced with a silyl group, a proton source (e.g. MeOH or water) is necessary to ensure catalyst turnover. Of particular interest to the synthesis of the calyciphylline A-type *Daphniphyllum* alkaloids is an isolated highly diastereoselective 6-*exo-dig* cyclisation affording the *exo*-methylene bicycle **258** in 94% yield (Scheme 84).



257 **258**

Scheme 84: Toste's Au(I)-catalysed carbocyclisation of silyl enol ethers and alkynes. Reaction conditions: (a) $AuPPh_3Cl$ (10 mol %), $AgBF_4$ (10 mol %), CH_2Cl_2/H_2O (10:1), 40 °C, 94%.

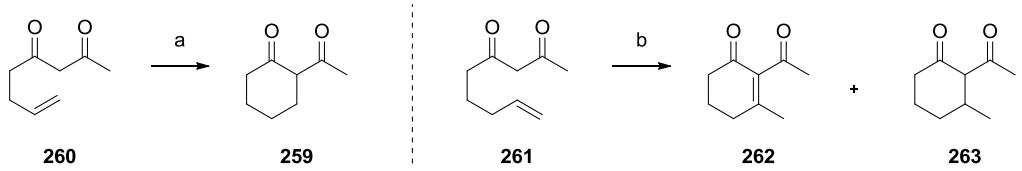
If this reaction is to be applied to the total synthesis of daphniyunnine D, a stereoselective reduction of the product olefin is necessary. As we were unsure of how this *exo*-double bond would behave under hydrogenation conditions, we were cautious of identifying this disconnection as a viable approach. In fact in a model study,[17a] the group of Bonjoch demonstrated that the wrong diastereoisomer with regards to the calyciphylline A-type alkaloids would be afforded if this double bond were to be hydrogenated using Pd/C (see Scheme 6g on page 9). Recently however, Li and co-workers demonstrated that replacing palladium with Crabtree's catalyst for the hydrogenation (see Scheme 13j on page 17), indeed provides the correct diastereoisomer needed for the synthesis of ring B in the related natural product daphenylline (**76**).[5n] In the absence of this key result at the beginning of this project, we proposed performing a hydroalkylation reaction on an alkene

as opposed to an alkyne in order to circumvent any problems that may arise from this necessary transformation.

4.3.2 Intramolecular hydroalkylation of unactivated alkenes

4.3.2.1 Palladium catalysed hydroalkylation of unactivated alkenes

In 2001, Widenhoefer and co-workers demonstrated the first transition-metal catalysed intramolecular hydroalkylation of unactivated double bonds with 3-butenyl *β*-dicarbonyls.[171] In a representative example, using a catalytic amount of $PdCl_2(MeCN)_2$ in dioxane at rt, 6-membered ring **259** was afforded from diketone **260** *via* a 6-*endo-trig* pathway (Scheme 85a).

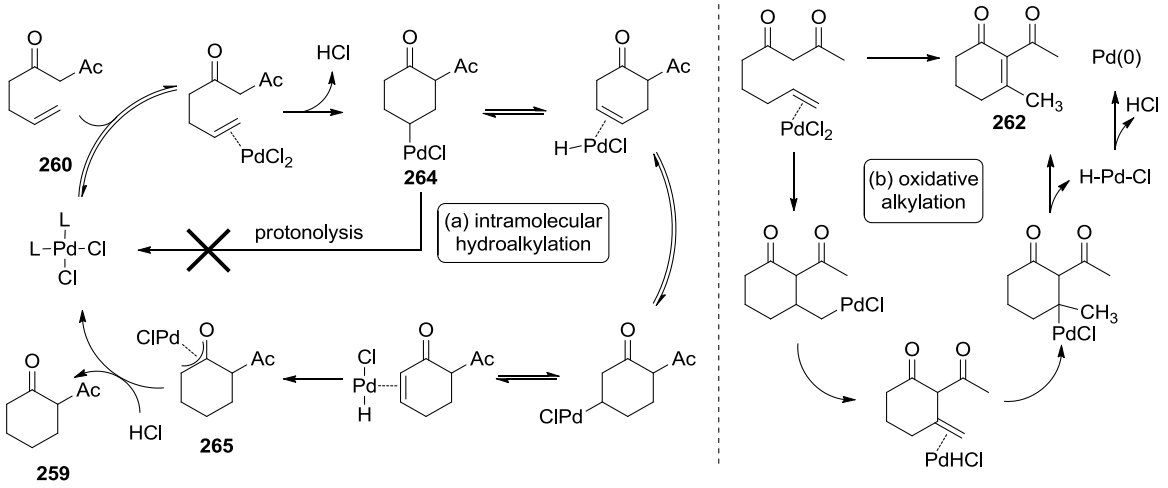


Scheme 85: Pd(II)-catalysed intramolecular hydroalkylation. Reaction conditions: (a) $PdCl_2(MeCN)_2$ (10 mol %), dioxane, rt, 81%; (b) $PdCl_2(MeCN)_2$ (1 equiv), dioxane, rt, 85% yield (8:1 mixture of products 262**:**263**).**

Attempting to expand their methodology to 4-pentenyl *β*-dicarbonyls (e.g. **261**) they noted that a full equivalent of the catalyst was necessary for complete conversion (Scheme 85b). In this analogous reaction, a competitive oxidative alkylation occurred giving rise to an 8:1 mixture of the cyclohexenone **262** and its corresponding cyclohexanone **263** in a combined 85% yield.[172]

Investigating the mechanisms of these reactions using deuterium labelling,[173] they concluded that when using 3-butenyl *β*-dicarbonyls, the cyclohexanone product **259** is not afforded *via* the expected protonolysis of the derived Pd-alkyl complex **264** (Scheme 86a). Instead, a series of fast *β*-hydride elimination/addition reactions take place to eventually give rise to the Pd-enolate complex **265**. In fact, this is the species which subsequently

undergoes protonolysis to give rise to the observed product **259** whilst regenerating the catalytically active Pd(II) species; an overall redox neutral cycle.[173]



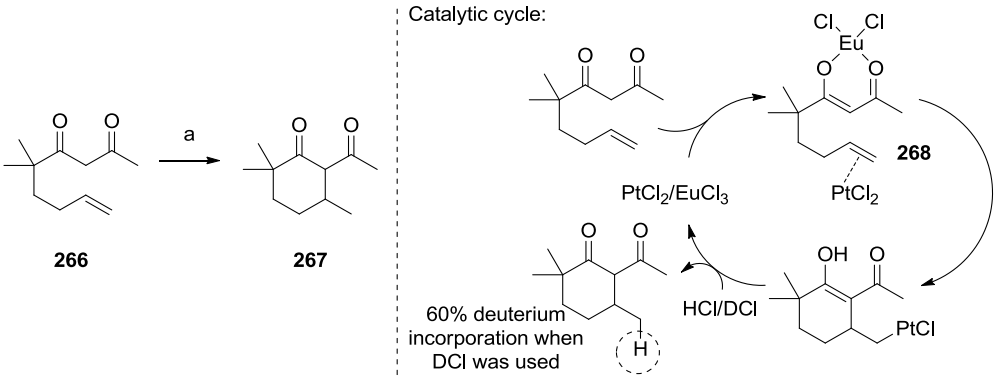
Scheme 86: (a) Pd(II)-catalysed intramolecular hydroalkylation catalytic cycle; (b) an alternative pathway in the Pd(II)-catalysed oxidative alkylation.

Although no rationale was provided, when using 4-pentenyl *β*-dicarbonyls, the necessary elimination/addition reactions for the formation of the Pd-enolate complex are less efficient. Instead, an alternative Pd-mediated pathway isomerises the double bond to afford the oxidised cyclohexenone **262**. A final *β*-hydride elimination as opposed to a protonolysis takes place (Scheme 86b). The nascent H-Pd-Cl then undergoes a reductive elimination to give rise to Pd(0) which is not an active species in this process. The Widenhoefer group however, took advantage of this reaction and by adding an oxidant (e.g. $CuCl_2$) they achieved the catalytic turnover of the Pd(II) catalyst to give rise to a range of substituted cyclohexenone compounds.[172]

4.3.2.2 Platinum catalysed hydroalkylation of unactivated alkenes

For *β*-hydride elimination to take place in organometallic reactions, a vacant coordination site on the metal centre is necessary.[174] Owing perhaps to the stronger bonds in platinum species,[175] lower reactivity of Pt(II)-alkyl complexes is observed compared to Pd(II) analogues with respect to *β*-hydride elimination.[176] Taking advantage of their further

ability to (a) activate alkenes towards nucleophilic attack as well as (b) readily undergo protonolysis,[176] the Widenhoefer group also achieved the true hydroalkylation reaction of 4-pentenyl *β*-dicarbonyls (e.g. **266**) to give rise to a range of methyl substituted cyclohexanones[i] (e.g. **267**) using $[PtCl_2(CH_2{=}CH_2)]_2$ as catalyst (Scheme 87).[177] During the optimisation of the reaction they discovered that catalytic amounts of $EuCl_3$ improved the yield, presumably due to the formation of the nucleophilic Eu-enolate **268**. Using deuterium labelling they demonstrated that a true direct protonolysis occurs in this reaction as opposed to the analogous reaction with Pd(II), thus confirming their proposed catalytic cycle shown in Scheme 87.



Scheme 87: Widenhoefer's Pt(II)/Eu(III) catalysed intramolecular hydroalkylation. Reaction conditions: (a) $[PtCl_2(CH_2{=}CH_2)]_2$ (1 mol %), $EuCl_3$ (2 mol %), HCl (1 equiv), dioxane, 90 °C, 85%, keto:enol 1:1.[i]

Although this methodology provides the *exo*-methyl substitution pattern present in the calyciphylline A-type alkaloids, it appears to be limited to 1,3-dicarbonyls. Enabling this transformation on our afforded ACD tricycle of daphniyunnine D would thus necessitate additional steps in our synthesis.

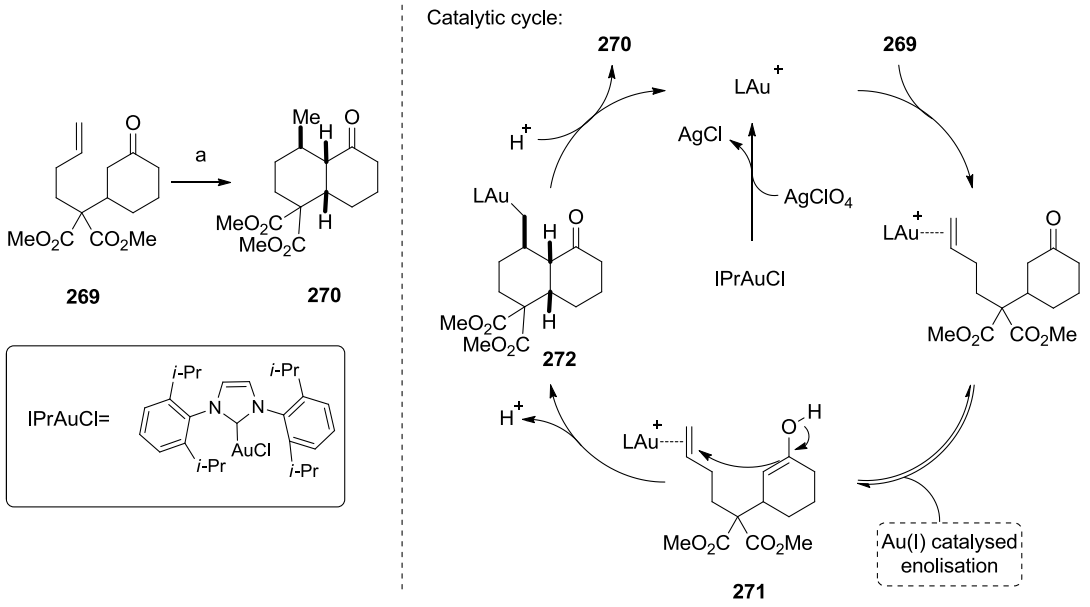
[i] No comment about diastereoselectivity was made in this report. Each product was isolated as a mixture of keto:enol tautomers. Data for the keto tautomer can be found in the supporting information, however no dr is provided.

4.3.2.3 Gold-catalysed hydroalkylation of unactivated alkenes

The activation of alkenes towards nucleophilic attack by *C*-centred nucleophiles appears to be heavily limited to activated/enolisable methylene units like 1,3-diketones (*vide supra*) and 1,3-ketoesters.[178,179] A few examples of the synthesis of 6-membered rings *via* (a) 6-*exo*-*trig* direct hydroalkylation using unactivated α-aryl ketones and (b) 6-*endo*-*trig* pathway using α-aryl and alkyl ketones have been reported by the group of Widenhoefer.[180] However, these necessitate additives like TMSCl and HCl to promote the sluggish enolisation of the ketone, crucial for reactivity.

Recognising the ability of gold complexes to activate double bonds towards inter- and intramolecular nucleophilic attack by oxygen, nitrogen and activated *C*-centred nucleophiles (1,3-dicarbonyls),[181,178,179] the group of Che set out to investigate whether simple ketones could also be used.[182] As gold complexes have been reported to enolise the α-position of ketones,[183] they proposed a catalytic hydroalkylation whereby no additive would be necessary to augment their nucleophilicity.

In fact using an IPrAuCl/$AgClO_4$ catalytic system in a solution of toluene at 90-110 °C, a range of substrates giving rise to 5- and 6-membered rings were afforded in high yields (71-99%) and diastereoselectivities (up to 10.3:1) *via* an *exo*-*trig* cyclisation pathway. The relevance of this cyclisation to our synthetic target is clearly demonstrated in Scheme 88, whereby olefin **269** undergoes a 6-*exo*-*trig* cyclisation to give rise to bicycle **270** in a high 90% yield and 9.5:1 dr. It is important to note that in this example, the major diastereoisomer (shown) contains a very similar substitution pattern to daphniyunnine D, where the hydrogen on the α-position and the methyl on the β-position of the ketone are both on the same side of the product [6–6] bicycle **270**.



Scheme 88: Che's intramolecular *exo-trig* hydroalkylation reaction of unactivated alkenes and ketones. Reaction conditions: (a) IPrAuCl (5 mol %), $AgClO_4$ (5 mol %), toluene, 90 °C, 90%, 9.5:1 dr.

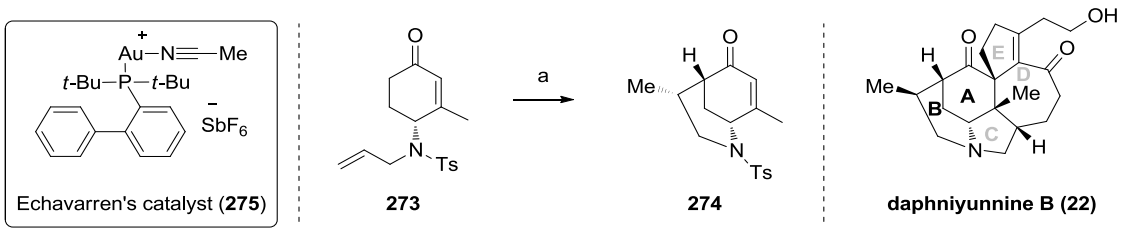
In their proposed mechanism, the Au-catalyst activates the double bond towards nucleophilic attack by the enol form **271** of the ketone **269** to give rise to the Au-alkyl intermediate **272** (Scheme 88). A subsequent protodeauration affords the final product **270** and regenerates the catalytically active Au(I) species.

Variable yields and diastereoselectivities were observed when different Au-catalysts, Ag-additives, solvents as well as concentrations were employed. Therefore, we identified this Au-catalysed *exo-trig* cyclisation as a potentially versatile and promising candidate for the stereoselective synthesis of daphniyunnine D's ring B.

4.3.2.4 A gold-catalysed intramolecular hydroalkylation en route to the total synthesis of daphniyunnine B—Dixon preliminary results

During the course of this project, an investigation targeting the total synthesis of the related daphniyunnine B (**22**) (Figure 2 on page 6) was also ongoing in the Dixon group. The construction of ring B in this project occurs at an earlier stage starting from the

6-membered ring *N*-allylamine **273** (Scheme 89).[i] Its enol form was envisaged to undergo an intramolecular hydroalkylation onto its unactivated alkene *via* a 6-*exo*-*trig* pathway. This would give rise to bicycle **274**, representing the AB ring system in daphniyunnine B (**22**). It was in fact discovered that heating a toluene solution at reflux with a 10 mol % loading of Echavarren's catalyst (**275**)[ii] gives rise to the product in a relatively high 81% yield and 9:1 dr (Scheme 89); a selectivity similar to that reported by Che.[182]



Scheme 89: Au-catalysed cyclisation en route to daphniyunnine B. Reaction conditions: Echavarren's catalyst (275**) (10 mol %), toluene, 110 °C, 81%, 9:1 dr.**

Contrary to Che's reports however, the undesired epimer (shown) in relation to the construction of the natural product was afforded. An azabicyclo[3.3.1]nonene **274** as opposed to a *cis*-decalin **270** (Scheme 88) is formed in this reaction. It is possible that different ring constraints are at play during the bond forming and breaking events of the cyclisation, giving rise to an inversion in diastereoselectivity.

Subsequently, attempts to invert the diastereoselectivity were undertaken. It was discovered that conversions and selectivities are affected by changes in the temperature, solvent, Au-catalyst[iii] as well as Ag-additive employed. Unfortunately however, the diastereoselectivity was never inverted and therefore this route towards the synthesis of daphniyunnine B (**22**) was abandoned.

[i] This project was investigated by Dr. O. P. Morejon and Dr. B. Kang.

[ii] Echavarren's catalyst is already an active cationic Au(I)-species due to the weak coordination of the antimonate anion. Therefore, Ag-additives are not necessary for its activation.

[iii] IPrAuCl, $AuPPh_3Cl$, $(p\text{-CF3-Ph})_3AuCl$ were all active.

4.4 An intramolecular hydroalkylation approach for the synthesis of the 6-membered ring B of daphniyunnine D: results and discussion

4.4.1 Introduction

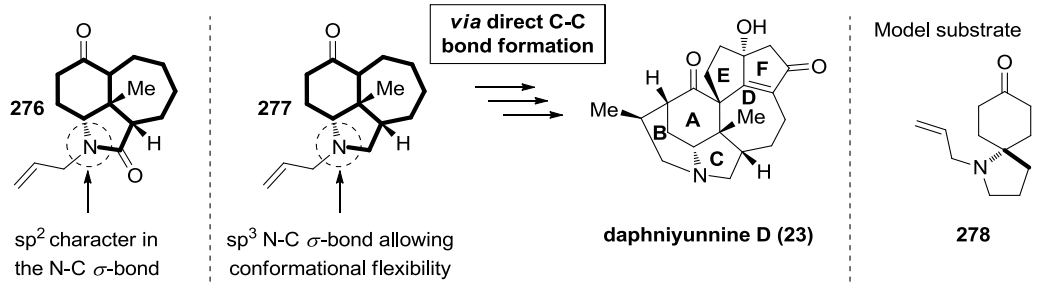
As outlined in our retrosynthetic plan, a 6-*exo*-*trig* intramolecular hydroalkylation strategy using an unactivated olefin would provide direct access to the targeted ring B of daphniyunnine D. At various stages during the development of our synthetic route, model substrates allowing for the investigation of its construction were prepared.

The preliminary results relating to the synthesis of daphniyunnine B (*vide supra* section **4.3.2.4**) gave us confidence that this disconnection was a realistic approach to our target, as reactivity had already been established. Furthermore, it was hypothesised that if performed on a late stage intermediate, with the ACD tricycle of the natural product already in place, a higher diastereoselectivity may be attained. Due to the steric constraints of the ACD tricycles described in the preceding chapters, we were confident that the major diastereoisomer of the reaction would result from the positioning of the *exo*-methyl group on ring B on the convex face of the afforded tetracycle. This would avoid the build up of steric clashes within the concave face (see retrosynthesis in Scheme 82 and crystal structure of tricycle **235** in Scheme 74 on page 95).

4.4.2 Proof of principle

Considering the sp^2 character of the γ-lactam's C-N σ-bond in the afforded ACD tricycles described in chapters 2 and 3, we anticipated that a pendant allyl group on the nitrogen may be unable to come into close proximity with the α-position of the ketone in order to react (e.g. in generic tricycle **276**, Scheme 90). We therefore considered that this functionality would have to be reduced to an sp^3 amine (e.g. generic tricycle **277**) to allow the necessary conformational flexibility in the system. However, amines are known to

poison Au-catalysts by ligating to the electrophilic gold centre.[184] For this reason introduction of an electron-withdrawing group on the nitrogen (e.g. amide, nosyl, Cbz or tosyl) is often used to reduce its nucleophilicity and allow for turnover of the catalyst (e.g. section **4.3.2.4**).[179a,182,185] As a tertiary amine is already present in the tricyclic **277**, introduction of a deactivating group is not possible and thus an alternative approach needed to be considered.



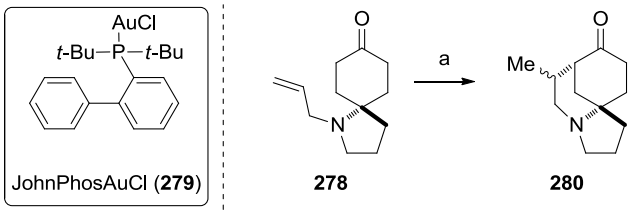
Scheme 90: A comparative study between a *N*-allyl *γ*-lactam and a *N*-allyl pyrrolidine containing generic ACD tricycle.

During the course of this thesis project, an independent study in the Dixon group, targeting scaffolds found in the *Strychnos* alkaloids[186] afforded the spiro *N*-allylamine **278** (Scheme 90). Although not directly related to our target, we believed that this tertiary amine could constitute an appropriate model for investigation of the desired hydroalkylation reaction. If a Au-catalysed cyclisation could be achieved in this less sterically demanding spiro tertiary amine **278**, this would increase our confidence of its feasibility in the real system.

Although the report by Che used the *N*-heterocyclic carbene IPrAuCl catalyst, we wanted to use another bulky catalyst which would potentially shield the gold centre and furthermore allow us to carry out the reaction at high temperatures. As our group was successful in achieving the high temperature cyclisation of the *N*-tosyl allylamine **273** using Echavarren's catalyst (**275**) (*vide supra* Scheme 89), we chose to use the related Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl/JohnPhosAuCl (**279**) catalyst in combination with AgOTf for its activation. This catalytic system has also been used to perform the *exo-trig*

hydroalkylation of simple alkenes by activated methylene compounds in a related publication by the Che group.[179a]

As a first attempt, heating the spiro compound **278** at 90 °C in toluene with a 20 mol % loading of our Au-catalyst and AgOTf additive did not promote the desired transformation. However, after increasing the temperature to reflux, a change in the reaction mixture indicated by TLC analysis, became apparent. In fact, although the crude ^{1}H NMR spectrum of the reaction corresponded mainly to the starting material, two doublet peaks in the region of 1.00 ppm suggested that the *exo*-methyl of the expected tricyclic product **280** may have been produced (Scheme 91).



Scheme 91: Au-catalysed cyclisation using a spiro *N*-allylamine—proof of principle. Reaction conditions: (a) JohnPhosAuCl (279**) (60 mol %), AgOTf (60 mol %), *p*-TsOH (1.1 equiv), toluene, 90 °C, 1:0.3 dr. Isolated 33% yield of the major diastereoisomer.**

When nitrogen- or sulfur-containing bifunctional H-bonding organocatalysts (e.g. amines, ureas, thioureas) are used in combination with Au-catalysis, reduced reactivity is often observed due to sequestration of the catalyst.[184] Strong Brønsted acids have been reported to assist catalyst turnover in these systems by protonating these nucleophilic atoms and thus regenerating the catalytically active gold species.[184,185] Therefore, in our second attempt for the intramolecular hydroalkylation, we used 1.1 equivalents of *p*-TsOH to determine whether we could drive the reaction to completion (Scheme 91). In fact using a higher loading of our catalytic system (60 mol %) at 90 °C we noted the complete consumption of the starting material by TLC analysis. Isolation of the polar compounds derived from the amine starting material **278** proved challenging, however from a 15 mg reaction, 5 mg of one of the major products could be isolated allowing for NMR analysis.

The ^{1}H NMR spectrum of this product contained a distinctive doublet at 0.87 ppm (J = 7.0 Hz) characteristic of the *exo*-methyl adjacent to a C-H position in the expected tricycle (Figure 18). Full NMR analysis confirmed the synthesis of the desired product.

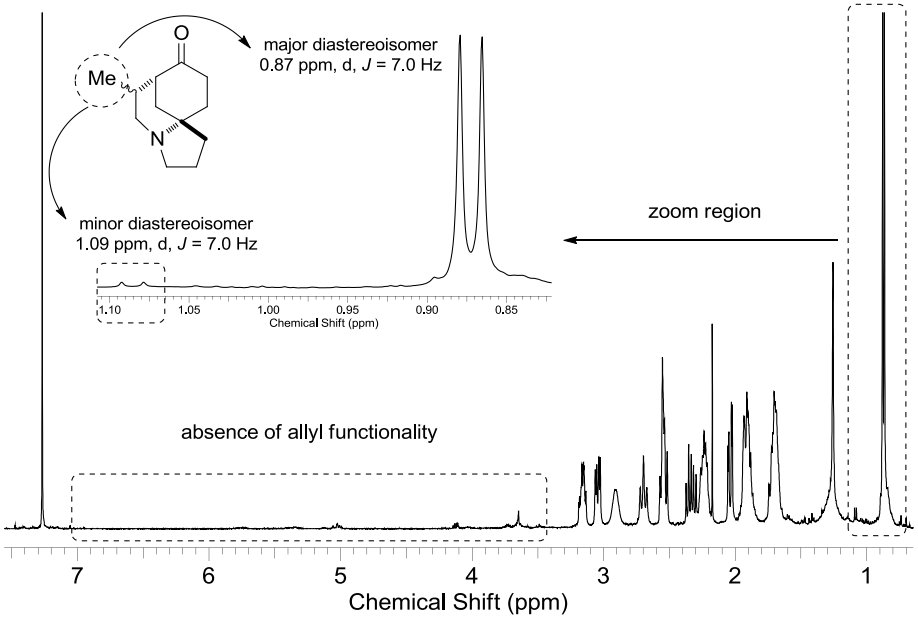


Figure 18: ^{1}H NMR spectrum of the isolated major diastereoisomer of tricycle 280 **with traces of the minor.**

Inspecting the crude ^{1}H NMR spectrum and assuming that a doublet at 1.09 ppm (J = 7.0 Hz) represented the minor diastereoisomer of the reaction, we concluded that a *ca.* 1:0.3 dr of the desired tricycle **280** was produced. As the stereochemistry of the spiro compound **278** is unrelated to that of our [6–5–7] ACD tricycle, we did not pursue determining the relative stereochemistry of the cyclised products. However, the observed reactivity established that a tertiary amine substrate can undergo the desired 6-*exo*-*trig* intramolecular Au-catalysed hydroalkylation in the presence of a Brønsted acid.

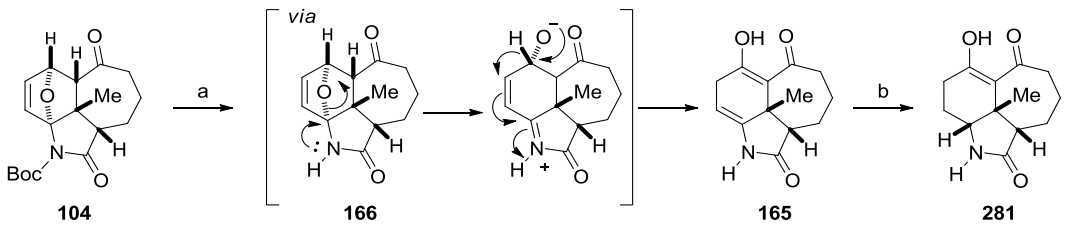
4.4.3 Application of the gold-catalysed intramolecular 6-exo-trig hydroalkylation for the synthesis of ring B of daphniyunnine D

4.4.3.1 Intramolecular hydroalkylation in the presence of the hydroxyenone functionality of the [6–5–7] ACD tricycle

With a proof of principle established, we set out to test this crucial cyclisation on several structural variations of the ACD tricycle prepared using the chemistry described in the preceding chapters. If successful, we would thereby achieve the construction of the [6–6–5–7] ABCD tetracycle of daphniyunnine D.

As previously described in chapter 2, whilst trying to promote the proton-transfer/IMDAF reaction cascade, it was discovered that catalytic *p*-TsOH in toluene at reflux led to both the desired cascade as well as fragmentation of the adduct **104** *via* the acid catalysed *N*-Boc deprotection (see Scheme 42 on page 48). Although the deprotection was undesired at this stage in the synthesis, we wanted to take advantage of this mode of fragmenting the IMDAF adduct for the purposes of studying the intramolecular hydroalkylation reaction. With the Boc group removed, an allyl group could be introduced to the tricycle allowing for its investigation.

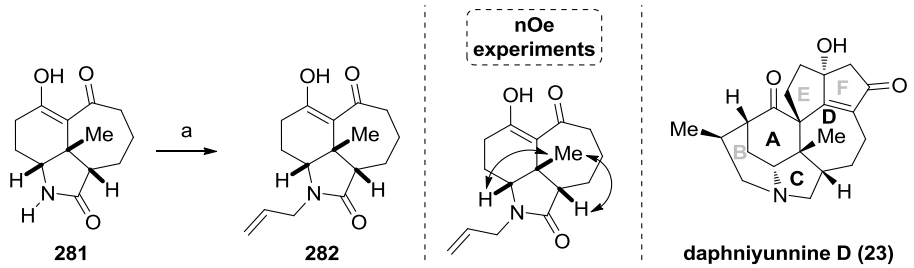
We therefore attempted the fragmentation of the IMDAF adduct (96:4 dr) **104** by removing the Boc group in a controlled fashion (Scheme 92). Pleasingly, using TFA in CH_2Cl_2 at rt led to its removal as well as the tandem fragmentation of **166**, giving rise to tricycle **165** as a single diastereoisomer. It appears that even at this temperature, the nucleophilicity of the deprotected nitrogen is sufficient to mediate the fragmentation of the adduct (Scheme 92a).



Scheme 92: Deprotection, fragmentation and stereoselective hydrogenation of the IMDAF adduct 104**. Reaction conditions: (a) TFA, CH_2Cl_2, rt; then (b) $Pd(OH)_2$ (20 mol %), MeOH, H_2 (balloon), rt, 67% (over two steps).**

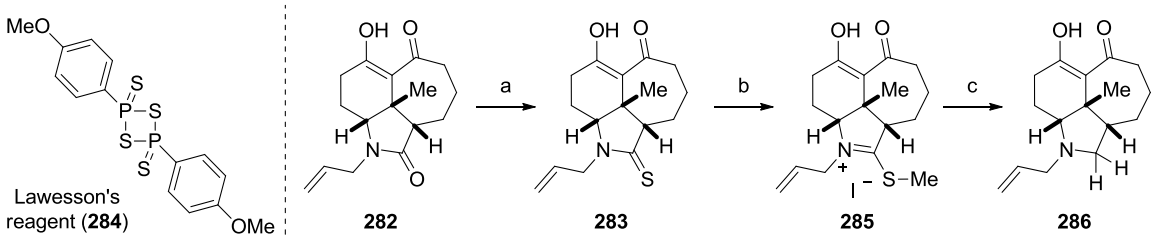
Prior to the introduction of the allyl group, the enamide functionality in tricycle **165** needed to be stereoselectively hydrogenated. Using Pearlman's catalyst in MeOH under a hydrogen atmosphere, afforded tricycle **281** as a single diasteroisomer (Scheme 92b). As the *N*-Boc deprotected enamide **165** proved to be unstable at rt, the hydrogenation was performed on the crude reaction mixture to provide the stereoselective formation of the product in a 67% yield over two steps (Scheme 92). Unfortunately, the yield of this two-step reaction was inconsistent (50-84%) owing to difficulties regarding the isolation of the polar product by fcc. However, it is important to note that no products derived from the reduction of the hydroxyenone functionality in this system were observed (cf Scheme 49 on page 63).

A subsequent S_N2 reaction in *t*-BuOH using *t*-BuOK as base and allyl bromide as the electrophile afforded the desired *N*-allyl tricycle **282** in 82% yield; relative stereochemistry confirmed by nOe experiments (Scheme 93). Pleasingly, no allylation of the hydroxyenone functionality was observed, possibly due to the lower temperature employed when compared to the allylation of **172** described in section **3.4.2.1** (acetone reflux). This *N*-allyl tricycle provided the first substrate for the investigation of the intramolecular Au-catalysed hydroalkylation.



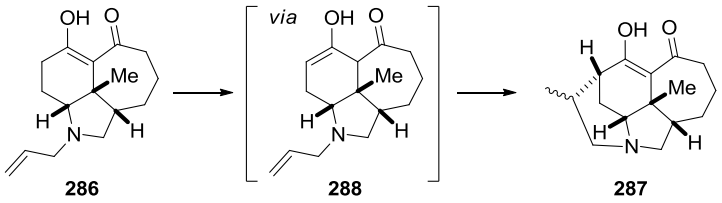
Scheme 93: Chemoselective allylation of the lactam 281**. Reaction conditions: (a) *t*-BuOK, allyl bromide, *t*-BuOH, 30 °C, 82%.**

As previously mentioned, we were unsure as to whether the allylated amide would allow the tricycle to adopt the necessary conformation for cyclisation. Two attempts using loadings of up to 20 mol % of the catalytic systems: (a) IPrAuCl with $AgClO_4$ (Che's conditions) and (b) JohnPhosAuCl (**279**) with AgOTf ("proof of principle" conditions) were unsuccessful in providing the cyclised product even when heated to reflux in toluene. Assuming the unreactive nature of the substrate was due to its rigid conformation, we sought to reduce the allylated amide functionality. For this reduction, DIBAL-H was used to chemoselectively reduce the electron-rich amide over the hydroxyenone functionality. Unfortunately, no reaction was observed even when allowed to reach rt and we thus moved on to $LiAlH_4$ for its reduction. As this reaction also proved unsuccessful with the formation of complex mixtures, we eventually chose to employ Sundberg's protocol for amide reduction.[187] Thus we transformed the lactam to thiolactam **283** using Lawesson's reagent (**284**)[188] in toluene at 50 °C (Scheme 94). This low temperature allowed for selective formation of the desired thiolactam in 59% yield without affecting the hydroxyenone/diketone functionality. Subsequently, the nucleophilic thiolactam was methylated using MeI in MeCN to provide sulfonium salt **285**. This transformation activated the thiolactam towards reduction and was thus rapidly reacted with the mild reducing agent $NaBH_3CN$ in MeOH to provide the desired tertiary amine **286** in 57% yield over two steps (Scheme 94).



Scheme 94: Reduction of the amide *via* the Sundberg protocol. Reaction conditions: (a) 284**, toluene, 50 °C, 59%; (b) MeI, MeCN, rt to 50 °C; then (c) $NaBH_3CN$, MeOH, 0 °C to rt, 57% (over two steps).**

With tertiary *N*-allylamine **286** in hand, we next explored the key cyclisation. Reacting **286** with JohnPhosAuCl (**279**) and AgOTf (60 mol %) in the absence of *p*-TsOH did not provide any product even when heated to reflux in toluene (*vide infra* Table 6, entry 1). Using 1.1 equivalents of *p*-TsOH in an attempt to avoid the potential poisoning of the catalyst did not seem to offer much improvement, as the starting material still dominated our TLC analysis (Table 6, entry 3). However, upon recovering **286** from the reaction mixture, a second compound was isolated with promising peaks detected in the ^{1}H NMR spectrum relating to the desired tetracycle **287** (Scheme 95).



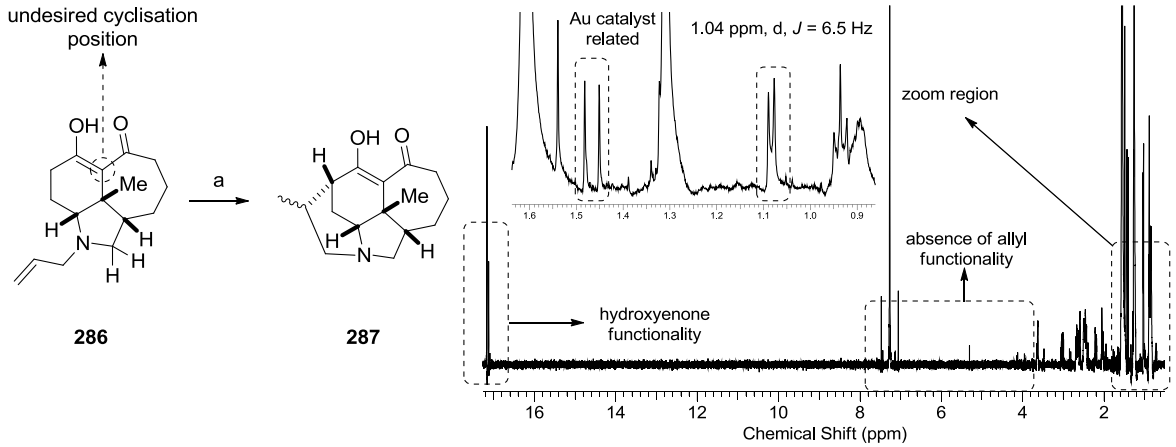
Entry	Au-catalyst/Ag-additive (mol %)	Acid (equiv)	Temp/toluene (°C)	Yield (% (dr))
1	JohnPhosAuCl/AgOTf (60)	-	50 to reflux	No product isolation
2	IPrAuCl/$AgClO_4$ (30)	-	80 to reflux	No product isolation
3	**JohnPhosAuCl/AgOTf (60)**	***p*-TsOH (1.1)**	**50 to reflux**	***ca.* 20 (1:0.4)**
4	JohnPhosAuCl/AgOTf (60)	*p*-TsOH (3.3)	50 to reflux	No product isolation
5	JohnPhosAuCl/AgOTf (60)	DPP (1.2)	50 to reflux	No product isolation
6	JohnPhosAuCl/$AgClO_4$ (60)	DPP (1.2)	50 to reflux	No product isolation

Table 6: Summary of Au-catalysed cyclisation attempts on the tricyclic *N*-allyl amine 286 **(toluene used in all experiments). DPP= diphenyl phosphate.**

As the experiment was performed on a small scale (4 mg), the aforementioned compound was only afforded in <1 mg and its NMR spectra were heavily contaminated with impurities, preventing us from confirming its structure.[i] However, the NMR analysis demonstrated the clear disappearance of the allyl functionality. Furthermore, a doublet was

[i] The experimental for **287** has not been included in chapter 5. All the relevant data from our analysis has been included here.

detected in the ^{1}H NMR spectrum at 1.04 ppm (J = 6.5 Hz), reminiscent of the one observed in our "proof of principle" experiment using the spiro *N*-allylamine **278** (Scheme 91).



Scheme 95: Au-catalysed cyclisation of tricyclic *N*-allyl amine 286**. Reaction conditions: (a) *p*-TsOH (1 equiv), JohnPhosAuCl (**279**) (60 mol %), AgOTf (60 mol %), toluene, 50 °C to reflux, <1 mg of potential tetracycle** 287 **isolated.**

The hydroxyenone was left intact as two peaks at around 17.0 ppm, characteristic of this functionality, were also present (1:0.4 dr). This eliminated the possibility of the cyclisation occurring *via* the undesired 6-membered ring enol position of the tricycle (Scheme 95). This cyclisation would be even more challenging as the allyl group is not in close proximity to this position. The mass spectrum of this impure product also contained peaks corresponding to tetracycle **287**.[i] Several reactions with slightly modified conditions were also attempted in order to improve and thus confirm this result, unfortunately however these trials were unsuccessful (Table 6).

No further investigation into the cyclisation of the *N*-allylamine substrate **286** was carried out because of the insufficient quantity of material available at this late stage. We had no conclusive data supporting the formation of the desired tetracycle in our single semi-

[i] The molecular weight of the starting material **286** and the product **287** are identical. However, the differences in: (a) their R_f values in the TLC analysis and (b) their NMR spectra, indicate different compounds.

successful experiment (Table 6, entry 3). Furthermore, given the poor reactivity of this substrate, alternative hydroalkylation precursors were considered.

We attribute the lack of reactivity in this substrate to the stability of the hydroxyenone functionality, preventing the efficient and necessary enolisation to **288** (see scheme in Table 6). Moreover, this functionality (similar in structure to the classic acetylacetonato ligand (acac)) may effectively chelate the gold species in the reaction mixture thus inhibiting the desired catalysis.[189] Therefore, when considering the synthesis of alternative cyclisation substrates, we turned our attention to the construction of *N*-allylamines lacking this deactivating functionality.

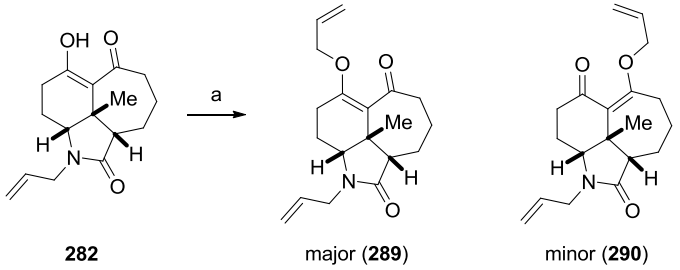
4.4.3.2 Intramolecular hydroalkylation in the absence of the hydroxyenone functionality in the [6–5–7] ACD tricycle

4.4.3.2.1 Intramolecular hydroalkylation—a model substrate investigation

Considering the possible detrimental effect which the stable hydroxyenone functionality may have on the Au-catalysed cyclisation, we explored several methods for its removal. Whilst attempting to functionalise the central carbon atom between the hydroxyenone functionality using an *O*-allylation, Claisen rearrangement protocol (see section **3.4.2.1**), we believed that a similar transformation may be suitable for investigation of the intramolecular hydroalkylation.

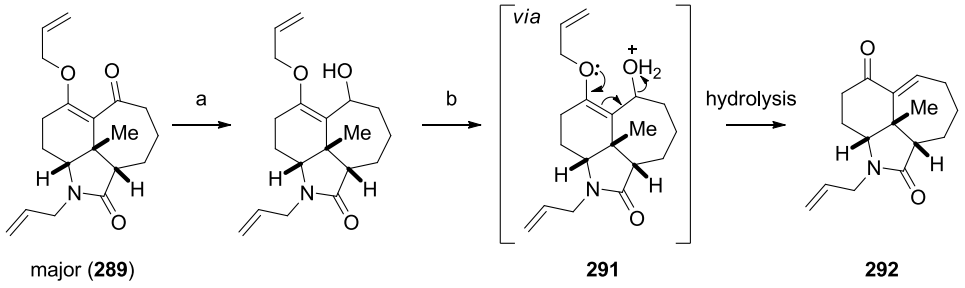
A selective *O*-allylation of the 6-membered ring enol in the *N*-allyl tricycle **282** would provide an unconventional method for protecting this tautomeric form of the cyclohexanone functionality (Scheme 96). This would subsequently allow for a reductant to be employed and selectively reduce the non-allylated 7-membered ring ketone. To this effect we discovered that under optimal conditions, the tricyclic hydroxyenone **282** can be allylated in THF using KHMDS and allyl tosylate to afford the desired product **289** in 62%

yield along with its undesired isomer **290** in 21%; a catalytic amount of 18-crown-6 ensured *O*-allylation as opposed to *C*-allylation (Scheme 96).



Scheme 96: *O*-allylation of tricyclic hydroxyenone 282**. Reaction conditions: (a) KHMDS, allyl tosylate, 18-crown-6 (30 mol %), THF, rt to 60 °C, 62% of** 289 **and 21% of** 290**.**

We subsequently observed that by adding $LiAlH_4$ to a solution of the desired *O*-allylated tricycle **289** in THF at –60 °C, the cycloheptanone functionality can indeed be selectively reduced (Scheme 97). Furthermore, by quenching the reaction mixture with MeOH and then adding HCl(aq), an E1 mechanism[i] mediates the elimination of the protonated heptanol **291** to provide the enone tricycle **292** in quantitative yield after a concomitant hydrolysis of the afforded oxonium ion. The relative stereochemistry was confirmed by nOe experiments.

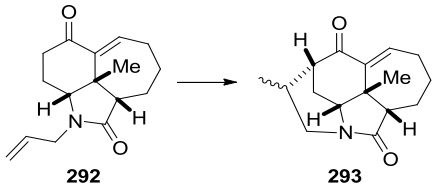


Scheme 97: Reduction and subsequent dehydration of the *O*-allylated tricycle 289**. Reaction conditions: (a) $LiAlH_4$, THF, –60 °C; then (b) HCl (1 M), MeOH, rt, 100% (over two steps).**

We believed that this *N*-allyl enone may provide a good model substrate able to enolise the necessary α-position of the ketone under the conditions of the Au-catalysed cyclisation. Furthermore, as amides are tolerated in Au-catalysis,[179a] we chose to determine the reactivity of **292** towards cyclisation, prior to considering the reduction of the lactam to the

[i] This mechanism is facilitated by the stabilisation of the carbocation by the allyl enol ether.

more flexible tertiary amine. For promoting this transformation, different conditions were explored, examples of which are provided in Table 7.



Entry	Au-catalyst/Ag-additive (mol %)	Temp/toluene (°C)	Yield (%)
1	Echavarren's (10)	reflux	No product isolation
2	IPrAuCl/$AgClO_4$ (20)	reflux	No product isolation
3	**JohnPhosAuCl/AgOTf (5)**	**100**	Possible product formation
4	**JohnPhosAuCl/AgOTf (100)**	**60**	Possible product formation
5	$AuPPh_3Cl$/AgOTf (10)	90	No product isolation
6	Au(*p*-CF_3-Ph)$_3$Cl/AgOTf (10)	80 to 100	No product isolation

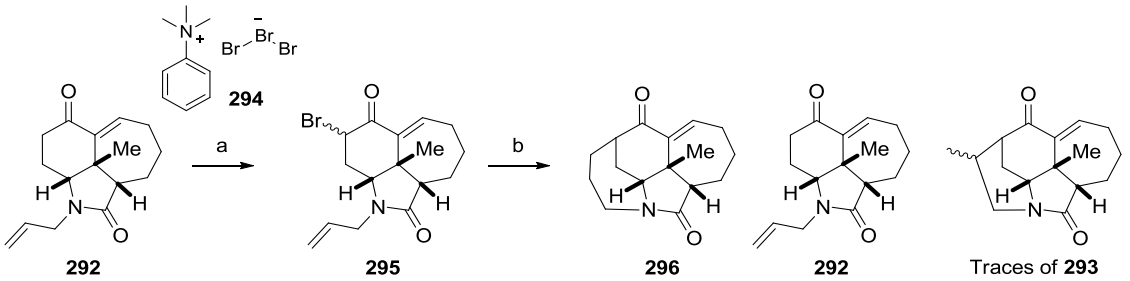
Table 7: Selected Au-catalysed cyclisation attempts on the tricyclic *N*-allyl amide enone 292 **(toluene used in all experiments).**

Unfortunately this *N*-allyl enone substrate **292** also proved to be unreactive to the cyclisation conditions. Long reaction periods between 24-48 h were employed to promote the potential product formation, however in most cases the starting material was recovered unaffected; although complete mass returns were not observed. In one attempt, using a 5 mol % loading of our catalytic system, after a 48 h reaction we noted possible peaks relating to the desired tetracycle **293** in the ^{1}H NMR spectrum of the recovered starting material (Table 7, entry 3). Using a full equivalent of the Au-catalyst and lowering the temperature to 60 °C for 3 days, to avoid the decomposition of **292**, did not provide any improvement (Table 7, entry 4). Moreover, due to the high catalyst loading, recovery of **292** and the possible cyclised product was untenable and no further conclusions were drawn. Even if the desired tetracycle was formed, minute quantities were afforded, leading us to conclude that this substrate was unsuitable for the required transformation using Au-catalysis.

Before reducing the amide functionality we wanted to employ an alternative approach in order to gain some insight into the potential reactivity of the substrate **292**. If a *C*-centred

radical could be afforded on the *α*-position of the ketone, then a 6-*exo-trig* or a 7-*endo-trig* cyclisation onto the allyl group may be possible.

To investigate this proposal, tricyclic enone **292** was reacted for 30 min with trimethylphenylammonium tribromide (**294**) in THF at rt to provide the *α*-brominated tricycle **295** in 91% yield and 2.4:1 dr (Scheme 98a); prolonged reaction periods led to the dibromination of this position.



Scheme 98: A radical approach to effect the desired cyclisation. Reaction conditions: (a) 294**, THF, rt, 91%, 2.4:1 dr; (b) HSnBu$_3$, AIBN, benzene, 80 °C, 27% of** 296**, 34% of** 292 **(with traces of** 293**).**

Subsequently, the brominated tricycle was reacted with tributyltin hydride in benzene at 80 °C in the presence of AIBN to form a stabilised radical on the *α*-position of the ketone (Scheme 98b). From the reaction mixture we isolated the undesired [6–7–5–7] tetracycle **296** in 27% yield, confirming that the amide tricycle may be too rigid to allow for the necessary 6-*exo-trig* cyclisation. Reaction onto the terminal position of the allyl in a 7-*endo-trig* fashion is evidently more easily achieved. The debrominated tricycle **292**, derived from the hydrogen abstraction by the radical, was also isolated in 34% yield. Upon close inspection of the ^{1}H NMR spectrum, this product also contained peaks relating to the desired tetracycle **293**, as observed in the recovered starting material of the Au-catalysed reaction (*vide supra* Table 7). Figure 19 shows the spectrum of a mixed fraction isolated after fcc, containing all the aforementioned products of the reaction mixture. Notable is the doublet at 1.05 ppm (J = 7.0 Hz), possibly relating to the *exo*-methyl in tetracycle **293**.

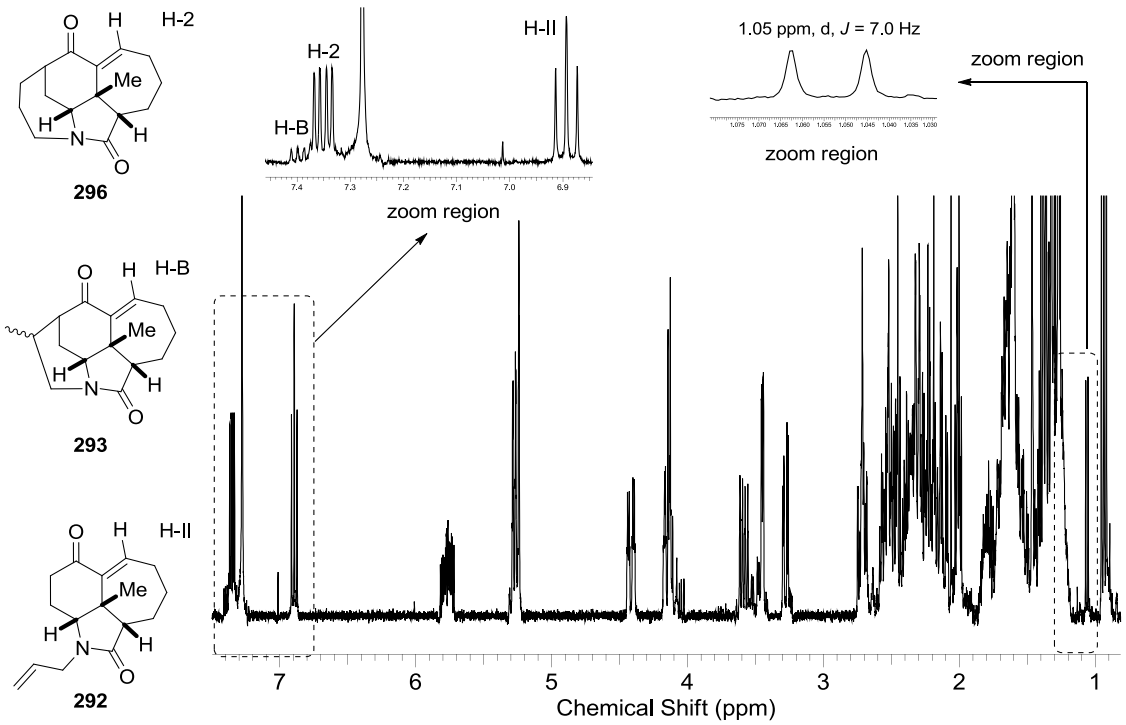
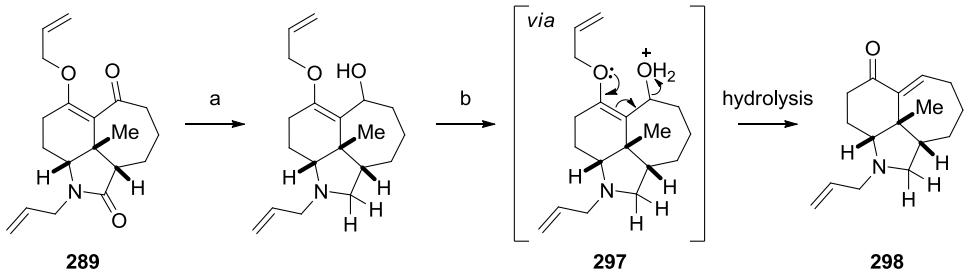


Figure 19: ^{1}H NMR containing all the products isolated from the radical cyclisation of the brominated tricycle 295**.**

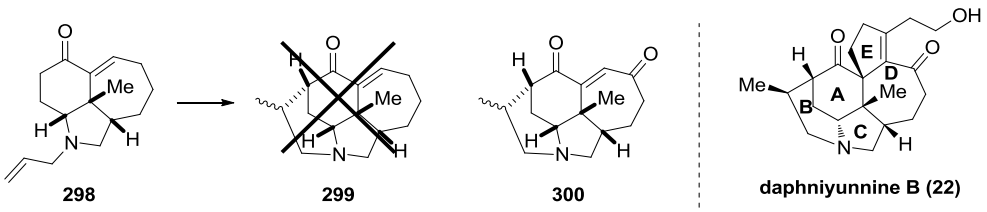
The possibility of this 6-*exo*-*trig* cyclisation was not ruled out completely, as some evidence of the desired tetracycle **293** was observed in both the radical as well as the Au-catalysed reactions. However, as the reactivity was poor, we decided to abandon studies on these rigid amide-containing substrates.

Transformation of the amide to the analogous amine would hopefully allow the necessary flexibility in order for the 6-*exo*-*trig* cyclisation to be favoured in our system. Once more, we took advantage of the *O*-allyl protection of our 6-membered ring enol (*vide supra* Scheme 97). Dropwise addition of a THF solution of $LiAlH_4$ to a solution of **289** allowed for the reduction of both the amide as well as the cycloheptanone functionality when performed at a higher temperature of 25 °C (rt) (Scheme 99). Similarly a subsequent MeOH quench, followed by the addition of HCl(aq), promoted the elimination of the nascent protonated alcohol **297** and afforded the tricyclic *N*-allyl amine **298** in 61% yield.



Scheme 99: Reduction and subsequent dehydration of the *O*-allylated tricycle 289**. Reaction conditions: (a) $LiAlH_4$, THF, rt; then (b) HCl (1 M), MeOH, rt, 61% (over two steps).**

Next we sought to explore the Au-catalysed cyclisation of the product amine **298**. Executing the reaction in the absence of a Brønsted acid confirmed the need for a proton source to prevent catalyst poisoning, as no reactivity was observed (Table 8, entry 1). When an equivalent of *p*-TsOH was added to the reaction mixture, a new spot appeared on our TLC analysis (Table 8, entry 2).



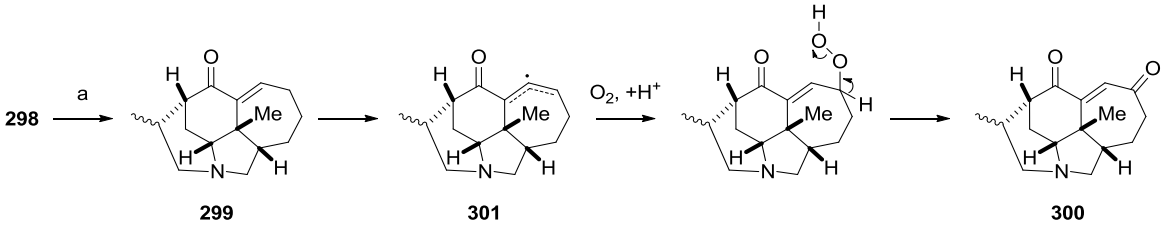
Entry	Au-catalyst/Ag-additive (mol %)	Acid (equiv)	Temp/toluene (°C)	Yield (% (dr))
1	JohnPhosAuCl/AgOTf (60)	-	60 to 90	No product isolation
2	JohnPhosAuCl/AgOTf (60)	*p*-TsOH (1.1)	50 to 90	10 (2.1:1)
3	**JohnPhosAuCl/AgOTf (60)**	**CSA (±) (1.1)**	**50 to 90**	**10 (4.5:1)**

Table 8: Au-catalysed cyclisation attempts on the tricyclic allyl amine enone 298 (toluene used in all experiments).

After multiple purifications by fcc, a compound was isolated with features in its NMR spectra corresponding to the desired tetracycle **299**; formed *via* a 6-*exo*-*trig* pathway. Unfortunately however, the mass spectra did not correspond to the desired product **299**. After further analysis, it was concluded that the isolated compound constituted of an inseparable diastereoisomeric mixture of the unexpected oxidised tetracycle **300**; isolated in a 10% yield and 2.1:1 dr.

The mechanism for this reaction is unknown, however it is possible that it follows a similar pathway to that observed in Corey's method for the γ-oxidation of enones using $Pd(OH)_2$ (Scheme 62 on page 83).[146] Perhaps the Au-catalyst, in combination with the Ag-additive

and the high temperature of the reaction mixture, promotes the desired cyclisation to **299** and then leads to the formation of an enone radical **301** (Scheme 100).[i,190] This could then react with residual oxygen present in the reaction flask to give rise to the observed product **300** following a Kornblum DeLaMare rearrangement.[147,191]



Scheme 100: Formation of the oxidised tetracycle 300**. Reaction conditions: (a) JohnPhosAuCl (60 mol %), AgOTf (60 mol %), *p*-TsOH (1.1 equiv), 50 to 90 °C, 10% (2.1:1 dr).**

Although undesired, this oxidised tetracycle could serve as a synthetically useful intermediate for the synthesis of the related daphniyunnine B (**22**), which contains the additional carbonyl on the 7-membered ring. Using (±)-CSA instead of *p*-TsOH provided a similar result with the product isolated in 10% yield and an enhanced 4.5:1 dr after two purification attempts (Table 8, entry 3). We believe the difference in the dr is a consequence of an enhancement upon purification and not a result of the different acids employed.[ii] The relative stereochemistry of the tetracycles could not be determined by nOe experiments due to the heavy peak overlap of the two diastereoisomers in the ^{1}H NMR spectrum of the inseparable mixture.

No other compounds were identified in these reactions, however **298** was observed in the crude ^{1}H NMR spectrum, suggesting that they did not proceed to completion. Unfortunately, owing to the polarity of the amine starting material as well as the afforded amine tetracycles, their isolation proved very challenging. Although the isolated yield of

[i] The enone radical formation may be independent of the Au-catalyst/Ag-additive system. For the use of gold as an oxidant see reference 190.

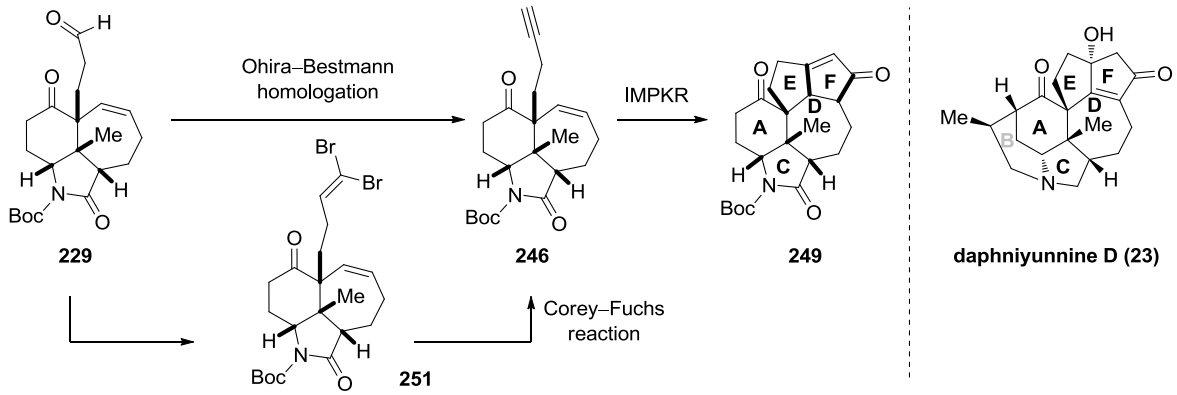
[ii] The crude ^{1}H NMR spectrum contains catalyst related peaks at the enone region, preventing us from readily determining the true dr of the reaction mixture.

the reaction is low, we believe this can be improved by (a) optimising the reaction and driving it to completion as well as (b) improving our method of purification.

4.4.3.2.2 Intramolecular hydroalkylation—application to the real system

Although the desired 6-*exo*-*trig* Au-catalysed cyclisation reaction occurred with concomitant oxidation on the model system, we demonstrated that it is indeed a realistic disconnection for the synthesis of ring B of daphniyunnine D. Even though the reaction was low yielding, reactivity had been established and we therefore sought to apply and subsequently optimise the cyclisation on the real system.

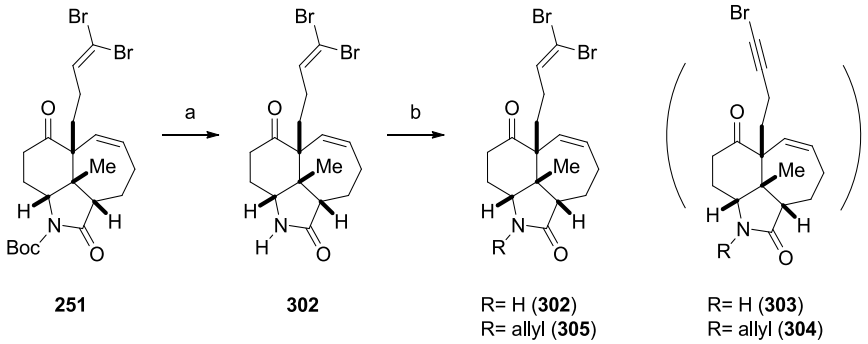
As previously discussed in chapter 3, homologation of the pendant aldehyde **229** to the alkyne **246** *via* the Ohira–Bestmann protocol[139] prior to the IMPKR proved challenging. Moreover, although its conversion to the dibromoolefin **251** was high yielding, its subsequent transformation to the pendant butyne *via* the Corey–Fuchs reaction did not provide an efficient access to the IMPKR precursor **246** (see section **3.4.2.3** and Scheme 101). Instead we considered using the dibromoolefin functionality as a protecting group for the electrophilic aldehyde **229**, to allow for the transformations necessary for the investigation of the Au-catalysed cyclisation.



Scheme 101: Approaches towards the synthesis of the vital pendant alkyne precursor to the IMPKR 246**.**

As per our previous manipulations of *N*-Boc protected substrates, addition of TFA to a solution of the dibromoolefin **251** afforded the deprotected tricycle **302** in quantitative

yield (Scheme 102). Following this, allylation of the crude reaction mixture was achieved using KHMDS and allyl bromide in a solution of THF. Under our optimised conditions, a dropwise addition of KHMDS at –78 °C is followed by the addition of allyl bromide. In order to avoid the monobromo elimination compounds **303** and **304**,[i] which are inseparable from the starting material **302** and product **305** respectively, a gradual increase in temperature is necessary. If the reaction is allowed to rise from –78 °C to rt overnight, the formation of these impurities can be minimised. In a representative reaction, the desired *N*-allylated dibromoolefin **305** was isolated in 67% yield alongside 13% of the recovered unreacted starting material **302**.

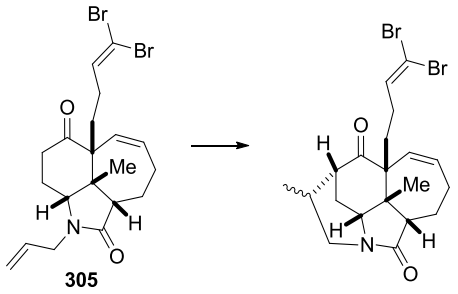


251 **302**

Scheme 102: Transformation of *N*-Boc protected 251 to *N*-allyl tricycle 305**. Reaction conditions: (a) TFA, CH_2Cl_2, rt, quantitative; (b) KHMDS, allyl bromide, THF, –78 °C to rt, 67%; 77% based on recovered** 302 **(over two steps).**

Once again, we wanted to test the Au-catalysed cyclisation using this *N*-allyl amide **305**, prior to its reduction to the amine which may cause catalyst deactivation. The conditions attempted are summarised in Table 9.

[i] These elimination products were detected in the mass spectra. Confirmation of their structure by NMR analysis proved challenging as these were small inseparable impurities in both the isolated starting material **302** and product **305**.



305

Entry	Au-catalyst/Ag-additive (mol %)	Solvent	Temp (°C)	Yield (%)
1	JohnPhosAuCl/AgOTf (100)	Toluene	90 to reflux	No product isolation (63% rsm)
2	Echavarren's (50)	Toluene	reflux	No product isolation
3	Echavarren's (60)	Mesitylene	190 (oil-bath temp; sealed vial used)	No product isolation
4	Echavarren's (60)	Toluene and D_2O	reflux	No product isolation (66% rsm)
5	IPrAuCl/$AgClO_4$ (60)	Toluene	reflux	No product isolation (47% rsm)

Table 9: Au-catalysed cyclisation attempts on the tricyclic dibromo *N*-allyl amide 305**. rsm= recovery of starting material.**

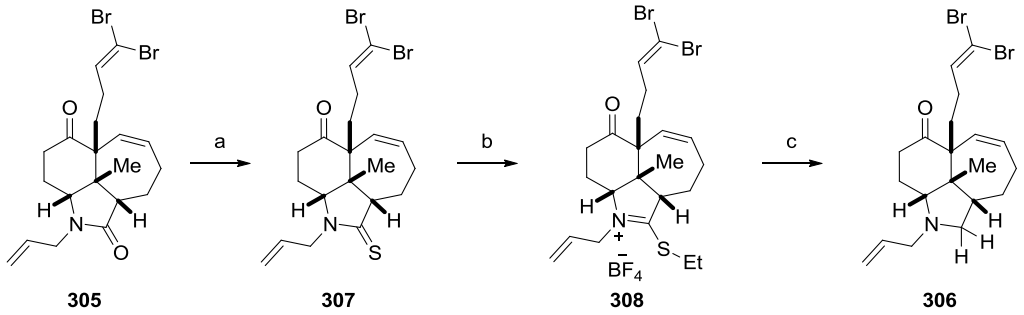
Disappointingly, none of these conditions led to the desired transformation, even when a full equivalent of the catalytic system was used (Table 9, entry 1). Subjecting the substrate to a higher temperature of 190 °C (oil-bath temp) also failed to affect any cyclisation (Table 9, entry 3). Furthermore, in cases where the recovery of **305** was endeavoured, mass returns were not quantitative as its separation from the Au-catalysts proved challenging (Table 9, entries 1, 4 and 5).

At the beginning of these investigations we were not confident of the compatibility of the dibromoolefin functionality with the halophilic silver co-catalysts and the high temperatures necessary. Although these reactions did not establish whether reactivity is possible, they did demonstrate that this functionality is somewhat tolerant of these conditions, as its recovery was possible even after 24-48 h reaction periods.

Before reducing the amide in order to investigate the cyclisation on the analogous amine, we first sought to determine whether the Au-mediated enolisation of the α-ketone of **305** is in fact possible. Similar to the method of Che,[182] we added D_2O to the reaction and heated the mixture to reflux in toluene overnight with Echavarren's catalyst (60 mol %) (Table 9,

entry 4). Unfortunately the ^{1}H NMR spectra of both the crude reaction mixture as well as the recovered starting material were inconclusive, as integration of the peaks of interest was challenging due to overlap with irrelevant peaks. Deuteration of **305** was also hard to discern in the mass spectra as these were complicated due to the two isotopic bromine atoms.

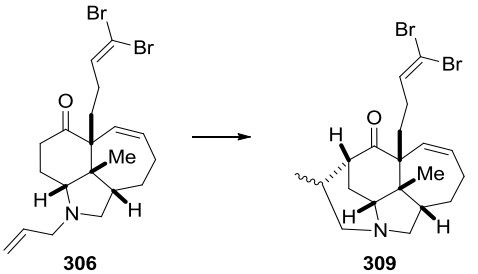
To prepare the analogous *N*-allylamine **306**, once again we chose to form the thioamide **307** using Lawesson's reagent (**284**) in order to selectively activate lactam **305** towards reduction (Scheme 103).



Scheme 103: Reduction of the amide *via* the Raucher protocol. Reaction conditions: (a) 284**, toluene, 60 °C, 63%; (b) Et_3OBF_4, CH_2Cl_2, 0 °C to rt; then (c) $NaBH_3CN$, MeOH, 0 °C to rt, 86% (over two steps).**

After isolating thiolactam **307** in 63% yield, we established that the Raucher protocol[192] could be used for its efficient activation using triethyl tetrafluoroborate (Et_3OBF_4) to form the sulfonium salt **308**. A subsequent mild reduction of the crude salt using $NaBH_3CN$ in MeOH, afforded the desired amine **306** in 86% over two steps, without reducing the ketone functionality (Scheme 103). Various conditions for the Au-catalysed cyclisation were subsequently tested (Table 10).

Firstly, the catalytic system which promoted the cyclisation of the model substrate was employed (Table 10, entry 1). Unfortunately, these conditions did not provide any trace of product **309** and instead **306** was recovered in 75% yield. Subsequently, we explored the use of Echavarren's catalyst (**275**) as it had proved optimal in the cyclisation of *N*-tosyl amine **273** to provide the [6–6] AB bicycle of daphniyunnine B (**22**) (see section **4.3.2.4**).



306 309

Entry	Au-catalyst/Ag-additive (mol %)	Acid (equiv)	Temp/toluene (°C)	Yield (%)
1	JohnPhosAuCl/AgOTf (60)	(±)-CSA (1.1)	50 to reflux	No product isolation (75% rsm)
2	Echavarren's (60)	-	80	No product isolation
3	Echavarren's (50)	(±)-CSA (1.5)	50 to reflux	No product isolation
4	Echavarren's (60)	DPP (4)	rt to reflux	No product isolation (78% rsm)
5	Echavarren's (400)	DPP (4)	rt to reflux	No product isolation

Table 10: Au-catalysed cyclisation attempts on the tricyclic dibromo *N*-allyl amine 306**. rsm= recovery of starting material.**

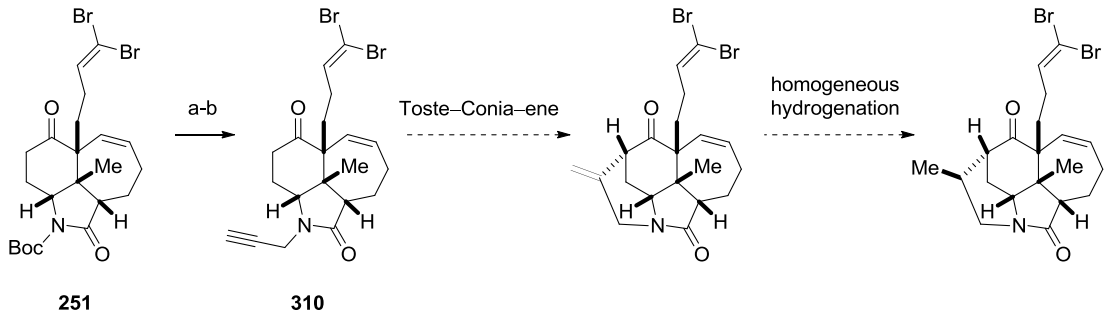
As expected, in our control experiment, no cyclisation products were afforded in the absence of a Brønsted acid (Table 10, entry 2). Next we tried using 1.5 equivalents of (±)-CSA to assist the catalyst turnover, however, this reaction was also unsuccessful in providing the desired product (Table 10, entry 3).

In a report by our group, diphenyl phosphate (DPP) was shown to promote the catalytic turnover of Au-catalysts when used in combination with tertiary amine bifunctional organocatalysts.[185] Similarly, we sought to establish whether DPP may accomplish this in our system; however, once again no cyclised products were isolated (Table 10, entry 4). To determine whether the Au-catalyst is indeed sequestered by the tertiary amine present in our substrate, 4 equivalents were employed in another experiment (Table 10, entry 5). Unfortunately, even under these super-stoichiometric conditions, no cyclisation was observed. This led us to conclude that at least in our hands, JohnPhosAuCl and Echavarren's catalyst do not seem to promote the desired intramolecular hydroalkylation under these conditions.

No further investigation into alternative Au-catalysts was pursued due to insufficient material at this stage in the project. From these preliminary experiments, we concluded that

although the dibromoolefin functionality appears to be relatively stable to the conditions necessary for Au-catalysis, the promotion of the desired transformation has proven challenging.

With a reliable route to the dibromoolefin tricycle **251** established, synthesis of sufficient material for the rigorous investigation of this key cyclisation is now necessary. As the Toste–Conia–ene reaction[29,170] has been successfully employed in combination with a homogeneous hydrogenation to afford ring B of the related alkaloid daphenylline,[5n] perhaps a similar approach could be used in our system. To this effect, propargyl amide **310** was synthesised in 79% yield over two steps from **251**. However investigation of Toste–Conia–ene reaction and the required subsequent hydrogenation is pending (Scheme 104).



251 **310**

Scheme 104: Synthesis of *N*-propargyl amide 310 **and its potential application to the synthesis of ring B. Reaction conditions: (a) TFA, CH_2Cl_2, rt, quantitative; (b) KHMDS, propargyl bromide, THF, –78 °C to rt, 79% (over two steps).**

4.5 Summary and conclusion of chapter 4

In our studies towards the total synthesis of daphniyunnine D, we have demonstrated that a Au-mediated 6-*exo*-*trig* hydroalkylation is a viable approach to the synthesis of ring B in the calyciphylline A-type alkaloids.

However, in the cases where the cyclisation has been successful, high catalyst loadings were necessary and poor yields were obtained making us unable to determine whether these reactions are indeed catalytic. Furthermore, the relative stereochemistry of the

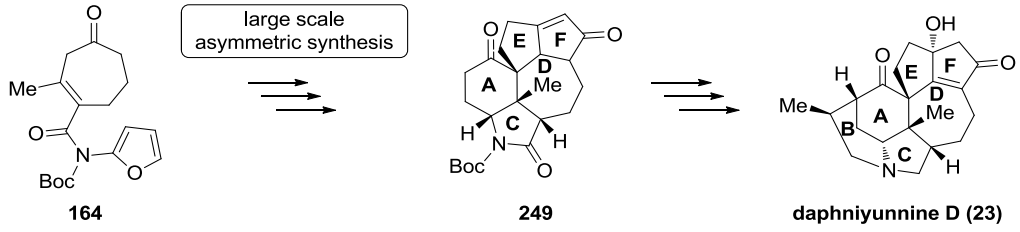
afforded ABCD tetracycles has not been established. In conclusion, although possible, it appears that this disconnection may not be ideal for the synthesis of ring B of the natural product and therefore different approaches need to be considered.

The alternative radical cyclisation has been attempted on a *N*-allylamide substrate **292** and shown to favour a 7-*endo-trig* pathway. As traces of the desired tetracycle have been observed in this alternative approach, perhaps the radical reaction will favour the 6-*exo-trig* cyclisation if performed on a more conformationally flexible tricyclic amine. This would allow the allyl group to come into closer proximity to the α-position of the cyclohexanone functionality.

4.6 Outlook and future work

The synthesis of the advanced [6–5–7–5–5] ACDEF pentacycle **249** found in daphniyunnine D (**23**) has been achieved *via* a proton-transfer/IMDAF reaction cascade and an IMPKR as key steps.

In order to achieve the total synthesis of daphniyunnine D, **249** needs to be synthesised asymmetrically and on large scale by implementing the organocatalytic asymmetric variant of the proton-transfer/IMDAF reaction cascade described in section **2.6.3.2**. A large scale synthesis of the advanced enantiopure **249** is necessary to allow for: (a) the optimisation of developed steps in the route (with particular focus on the homologation of aldehyde **229**) as well as (b) investigation into the double-bond, allylic oxygenation protocol necessary for the completion of the DEF tricyclic motif found in the natural product (Scheme 105).



Scheme 105: Future work for the total synthesis of daphniyunnine D (23**).**

Following the aforementioned elaborations, investigation into the construction of the piperidine ring B needs to be resumed. Although a Au-catalysed intramolecular hydroalkylation on an unactivated olefin provides direct access to this ring, perhaps alternative approaches will be necessary to ensure the robust and reproducible synthesis of the targeted daphniyunnine D (**23**).

Our overall aim set out at the beginning of this project was to synthesise daphniyunnine D (**23**) using synthetically versatile intermediates throughout our route, allowing for access to other natural products. If we are successful in completing the synthesis of the final ring B in an expedient manner, syntheses for other *Daphniphyllum* alkaloids will be proposed, based on our asymmetric proton-transfer/IMDAF reaction cascade and IMPKR protocols. The final objective of this long term project will be the synthesis of sufficient quantities of these alkaloids, allowing for their rigorous biological evaluation.

Chapter 5: Experimental

5.1 General experimental

5.1.1 General techniques

Reactions were carried out under a nitrogen atmosphere in oven-dried glassware at room temperature (rt= 20-25 °C) unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Temperatures of 0 °C and −78 °C were obtained using an ice-bath and a dry-ice/acetone bath respectively. Reflux conditions were obtained using an oil-bath equipped with a thermometer. When reaction temperatures are quoted, these refer to the temperature of the oil-bath.

5.1.2 Compound naming

Compound names are those generated by ACD LABS 12.0 following IUPAC nomenclature. The NMR assignment numbering is arbitrary and does not follow any particular IUPAC convention relating to the naming of the drawn molecules. Where possible this numbering is consistent between molecules in the synthetic route.

5.1.3 Solvent & reagents

Anhydrous toluene, tetrahydrofuran and dichloromethane were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58Å, basic, Sigma-Aldrich) columns. Other solvents were used directly as received from commercial suppliers. Petroleum ether (PE) refers to distilled light petroleum of fraction (30-40 °C). Bulk solutions were evaporated under reduced pressure using a rotary evaporator (water-bath temperature= 40 °C). Brine refers to a saturated aqueous solution of NaCl. Reagents used

were obtained from commercial suppliers and used without purification. Na_2SO_4 refers to anhydrous sodium sulphate.

5.1.4 Chromatography

Flash column chromatography was carried out on Merck Kieselgel (230-400 mesh). All reactions were followed by thin-layer chromatography (TLC) where practical, using Merck aluminium backed sheets coated with Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica, which were visualised under UV light (λ_{max}= 254 or 365 nm). The sheets were developed using potassium permanganate or vanillin stains. HPLC separation was performed on Agilent Technologies 1200 series machine fitted with the appropriate chiral column and stated solvent system.

5.1.5 Spectroscopy

All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 500 MHz and Bruker 400 MHz spectrometers and are quoted in ppm for measurement against a tetramethylsilane (TMS) or residual solvent peaks as internal standards. Unless otherwise stated all experiments were carried out using $CDCl_3$ as solvent. Chemical shifts (δ) are given in parts per million (ppm ± 0.01), and coupling constants (J) are given in Hertz (Hz ± 0.5 Hz).

The ^{1}H NMR spectra are reported as follows: δ/ppm (multiplicity, number of protons, assignment, coupling constant J/Hz (where appropriate). Multiplicity is abbreviated as follows: app = apparent,[i] s = singlet, br s = broad singlet, d = doublet, br d = broad doublet,

[i] The labelling "apparent" is used to provide further information and explain why coupling constants in certain cases do not match the coupling constants of the corresponding peaks of interest. For example, app dt describes a peak that looks like a dt but is in fact an undefined ddd. The three fold coupling in this case is observed in the COSY spectrum of the molecule of interest. The lack of definition is a consequence of the sensitivity of the instrument used. It is important to note that in certain cases it is possible that identical

dd = doublet of doublets, t = triplet, dt = doublet of triplet, q = quartet, dq = doublet of quartet, quint = quintet, m = multiplet,[i] app s = apparent singlet, app d = apparent doublet, app t = apparent triplet, app q = apparent quartet. The ^{13}C NMR spectra are reported in δ/ppm. Two-dimensional (COSY, HSQC, HMBC) NMR spectroscopy were used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer deposited as a thin film (either on a NaCl plate or on the diamante ATR module). Only selected maximum absorbances ($\mathbf{\nu_{max}}$) of significant or diagnostic peaks are reported (in wavenumbers/cm^{-1}).

Low resolution mass spectra were recorded on a Waters LCT premier XE Micromass spectrometer (ESI). High resolution mass spectra (ESI) were recorded on a Bruker MicroTof mass spectrometer. High resolution mass spectra (field ionisation, FI) were recorded on a Bruker FT-ICR Apex III spectrometer.

Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

5.1.6 Polarimetry

Optical rotations were recorded using an Optical Activity polarimeter (Perkin Elmer 241 polarimeter); specific rotations ($[\alpha]_D$)[ii] are reported in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are quoted in g/100 mL of solution; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius (°C).

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coupling constants between two protons cause the formation of a "true" dt. However, in the majority of cases, a mismatch in the coupling constants of the corresponding peaks disproves this.

[i] If a multiplet integrating for 1H is 95% symmetric, the shift for the mean point is given in ppm. If it is distorted by impurities or is overlaid with large solvent or grease peaks, a range is given in ppm.

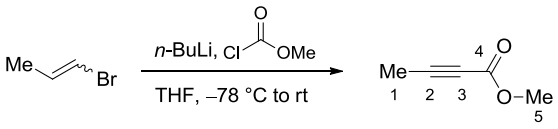
[ii] $[\alpha]_D^{20} = \alpha \cdot 100 / l \cdot c$. Where: α= measured rotation (°) c= concentration (1 g/100 mL); l= length of path (dm).

5.1.7 X-ray crystallography

Single crystal X-ray diffraction data were collected at 150 °K using an Enraf-Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer. The crystal structures were solved with SIR92 and refined with CRYSTALS (software package) by J. Yang (DJD group) and M. Rattley (DJD group) under the guidance of Dr. A. L. Thompson of the University of Oxford Chemical Crystallography department.

5.2 Experimental Chapter 2

5.2.1 Synthesis and characterisation of methyl but-2-ynoate (108):



To an oven-dried round-bottomed flask equipped with an electronic thermometer was added (*Z/E*)-1-bromo-1-propene (10.0 mL, 117 mmol) followed by anhydrous THF (125 mL) and the reaction mixture was maintained under a nitrogen atmosphere. The flask was cooled to –78 °C, and after 10 min *n*-BuLi (2.5 M solution in hexanes, 98.0 mL, 245 mmol) was added dropwise, maintaining the temp below –60 °C. Following the end of the addition, the off-white mixture was stirred for 1 h 30 min at –78 °C and then methyl chloroformate (12.0 mL, 155 mmol) was added dropwise over 40 min maintaining the temp between –70 °C and –60 °C. The mixture was stirred for 2 h at –78 °C and then the cooling bath was removed, allowing the mixture to warm to rt over 1and 30 min. 60 mL of water were added and the organic layer was decanted. The aqueous fraction was extracted with Et_2O (2×50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure (40 °C, 100 mbar) to afford an orange brown liquid. Purification by distillation through a 5 cm long Vigreux column (bp = 64-67 °C, 60 mbar) provided methyl but-2-ynoate as a colourless oil (8.80 g, 77% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2957 (C-H), 2247 (C≡C), 1714 (C=O), 1436, 1263, 1075.

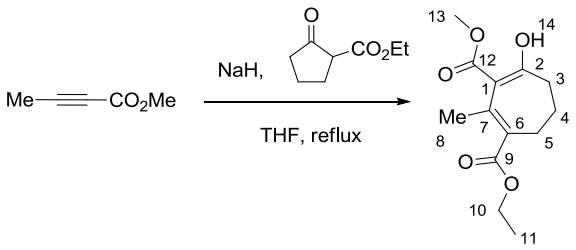
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 3.76 (s, 3H, H-5), 1.99 (s, 3H, H-1).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 154.1 (C-4), 85.7 (C-2), 72.1 (C-3), 52.5 (C-5), 3.7 (C-1).

Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.16%. Found: C, 61.12; H, 6.00%.

Data is in accordance with the literature.[72,74]

5.2.2 Synthesis and characterisation of 1-ethyl 3-methyl 4-hydroxy-2-methylcyclohepta-1,3-diene-1,3-dicarboxylate (106):



To a suspension of NaH (60% dispersion in mineral oil, 27.0 g, 675 mmol) in anhydrous THF (1 L) at reflux under a nitrogen atmosphere, was added ethyl 2-oxocyclopentanecarboxylate (**107**) **(**104 mL, 702 mmol) dropwise. After stirring for 10 min, a clear yellow solution was formed, to which methyl 2-butynoate (**108**) (50.0 mL, 500 mmol) was added dropwise. The reaction mixture was allowed to stir at reflux for 3 h. The reaction was cooled to rt, quenched with aqueous HCl (1 M, 800 mL) and extracted using EtOAc (3×800 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [97:3]) to provide **106** as a white solid (91.4 g, 72% yield).

mp 44-48 °C

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2930 (C-H), 2865 (C-H), 1710 (C=O), 1645 (C=O), 1587 (C=C), 1241.

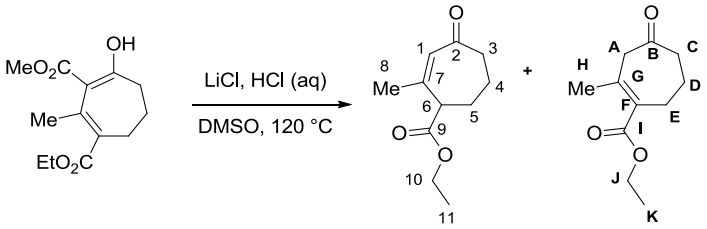
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 12.85 (s, 1H, H-14), 4.20 (q, 2H, H-10, J = 7.0 Hz), 3.77 (s, 3H, H-13), 2.21-2.36 (br s, 4H, H-3 & H-4 or H-5), 2.21-2.15 (m, 2H, H-4 or H-5), 2.14 (s, 3H, H-8), 1.30 (t, 3H, H-11, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 178.7 (C-2), 171.6 (C-12), 168.6 (C-9), 143.6 (C-7), 129.2 (C-6), 103.8 (C-1), 60.1 (C-10), 51.5 (C-13), 32.8 (C-4 or C-5), 31.2 (C-3), 27.3 (C-4 or C-5), 20.8 (C-8), 14.3 (C-11).

m/z (ES+) 277 ([M+Na]$^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{18}NaO_5^+$) requires ***m/z*** 277.1046, found ***m/z*** 277.1043.

5.2.3 Synthesis and characterisation of ethyl 2-methyl-4-oxocyclohept-1-ene-1-carboxylate and ethyl 2-methyl-4-oxocyclohept-2-ene-1-carboxylate (146):



To a mixture of ketodiester **106** (97.0 g, 381 mmol) and LiCl (80.8 g, 1.91 mol) in DMSO (1.45 L) at rt under a nitrogen atmosphere, was added aqueous HCl (1 M, 150 mL). The reaction was heated at 120 °C (oil-bath temp) for 5 h. The reaction was cooled to rt, and diluted to half its original concentration using Et_2O. The diluted reaction mixture was then washed with brine (3×) and the combined aqueous layers were back-extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15]) to provide an inseparable isomeric mixture (**146$_a$**:**146$_b$**, 1:0.22) as a colourless oil (56.3 g, 75% yield). For ease of interpretation, the integrations below are indicated as if each isomer was isolated in 100% purity.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2980 (C-H), 2939 (C-H), 2871 (C-H), 1730 (C=O), 1709 (C=O), 1665 (C=O).

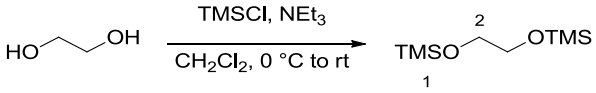
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.95 (s, 1H, H-1), 4.20-4.09 (m, 4H, H-10 & H-**J**), 3.40 (dd, 1H, H-6, J = 7.0, 4.0 Hz), 3.21 (s, 2H, H-**A**), 2.63-2.50 (m, 5H, H-3$_a$ & H-**C** & H-**E**), 2.44 (app dt, 1H, H-3$_b$, J = 15.5, 6.0 Hz), 2.22 (app ddt, 1H, H-5$_a$, J = 14.0, 7.0, 5.5 Hz), 2.05 (s, 3H, H-**H**), 2.01-1.88 (m, 6H, H-5$_b$ & H-**D** & H-8), 1.88-1.79 (m, 1H, H-4$_a$), 1.79-1.69 (m, 1H, H-4$_b$), 1.28-1.20 (t, 3H, H-**K**, J = 7.0 Hz), 1.23 (t, 3H, H-11, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 206.6 (C-**B**), 202.5 (C-2), 171.8 (C-9), 168.6 (C-**I**), 151.7 (C-7), 140.9 (C-**F** or C-**G**), 131.4 (C-1), 129.7 (C-**F** or C-**G**), 61.1 (C-10), 60.3 (C-**J**), 51.4 (C-**A**), 50.5 (C-6), 43.5 (C-**C** or C-**E**), 42.1 (C-3), 28.3 (C-5), 28.1 (C-**C** or C-**E**), 26.3 (C-8), 25.4 (C-**D**), 23.0 (C-**H**), 19.4 (C-4), 14.1 (C-**K**), 13.9 (C-11).

m/z (ES+) 219 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{16}NaO_3^+$) requires ***m/z*** 219.0992, found ***m/z*** 219.0991.

5.2.4 Synthesis and characterisation of 2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (154):

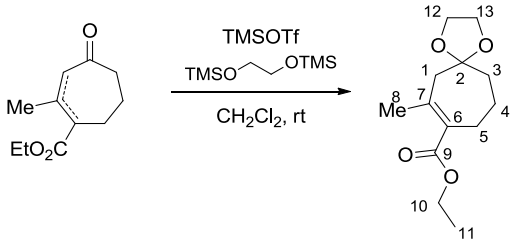


To a solution of ethylene glycol (50.0 mL, 897 mmol) in anhydrous CH_2Cl_2 (2.5 L) at rt under a nitrogen atmosphere, was added NEt_3 (287 mL, 2.06 mol). The reaction was cooled to 0 °C and then TMSCl (250 mL, 1.97 mol) was added dropwise over 30 min. Upon addition of the TMSCl, the ice-bath was removed and the thick white suspension was allowed to warm to rt over 2 h whereupon it turned pink. The reaction was filtered through a pad of Celite® and washed with PE. The filtrate was concentrated and PE was added to precipitate out a white solid, which was then filtered. This process was repeated twice more, and the filtrate was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford a dark yellow oil. Purification by distillation (bp = 93 °C, 96 mbar) provided 2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane as a colourless oil (145.2 g, 78% yield). Data is consistent with the literature.[193]

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 3.63 (s, 4H, H-2), 0.11 (s, 18H, H-1).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 63.9 (C-2), –0.5 (C-1).

5.2.5 Synthesis and characterisation of ethyl 7-methyl-1,4-dioxaspiro[4.6]undec-6-ene-8-carboxylate (148):



To a solution of **146** (45.0 g, 229 mmol) in freshly distilled CH_2Cl_2 (2.0 L) under a nitrogen atmosphere at rt, was added 2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (225 mL, 918 mmol) followed by TMSOTf (1.7 mL, 9.39 mmol) dropwise. The mixture gradually changed from yellow to dark red. After 14 h the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×600 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The concentrate was dissolved in a minimal amount of pentane and then cooled to –20 °C. Upon crystallization, the crystals were filtered off and washed with cold pentane. This process was repeated 8 times to provide **148** as transparent pink crystals (49.5 g, 90% yield).

mp 35-37 °C

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2938 (C-H), 1707 (C=O), 1641 (C=C).

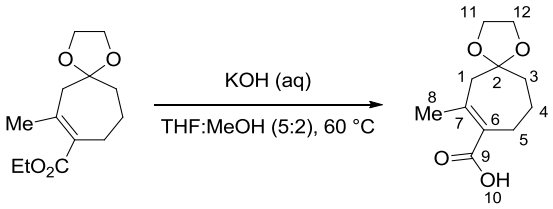
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 4.18 (q, 2H, H-10, J = 7.0 Hz), 4.00-3.90 (m, 4H, H-12 & H-13), 2.58 (s, 2H, H-1), 2.47-2.41 (m, 2H, H-5), 2.08 (s, 3H, H-8), 1.93-1.84 (m, 2H, H-3), 1.71-1.61 (m, 2H, H-4), 1.29 (t, 3H, H-11, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 169.4 (C-9), 144.2 (C-7), 130.6 (C-6), 107.1 (C-2), 64.6 (C-12 & C-13), 60.2 (C-10), 46.0 (C-1), 40.7 (C-3), 28.7 (C-5), 24.5 (C-8), 23.5 (C-4), 14.3 (C-11).

m/z (ES+) 263 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{20}NaO_4^+$) requires ***m/z*** 263.1254, found ***m/z*** 263.1254.

5.2.6 Synthesis and characterisation of 7-methyl-1,4-dioxaspiro[4.6]undec-7-ene-8-carboxylic acid (158):



To a solution of **148** (20.0 g, 83.2 mmol) in MeOH (60 mL) and THF (150 mL) at rt, was added aqueous KOH (2 M, 150 mL). The reaction mixture was heated at 60 °C (oil-bath temp) for 24 h and then cooled to rt, quenched with aqueous HCl (2 M, 150 mL) and extracted using EtOAc (3×200 mL). The combined organic extracts were dried over Na_2SO_4,[i] filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc:AcOH [88:10:2]) to provide **158** as a white solid (16.8 g, 95% yield).

mp 82-84 °C

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3444 (O-H), 2939 (C-H), 1676 (C=O).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 12.10 (br s, 1H, H-10), 4.01-3.91 (m, 4H, H-11 & H-12), 2.64 (s, 2H, H-1), 2.54-2.49 (m, 2H, H-5), 2.19 (s, 3H, H-8), 1.93-1.87 (m, 2H, H-3), 1.70-1.62 (m, 2H, H-4).

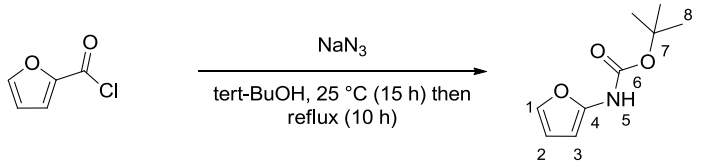
^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 174.5 (C-9), 149.2 (C-7), 129.6 (C-6), 107.0 (C-2), 64.6 (C-11 & C-12), 46.9 (C-1), 40.7 (C-3), 28.2 (C-5), 25.1 (C-8), 23.3 (C-4).

m/z (ES+) 235 ($[M+Na]^+$, 100%)

[i] Great care must be taken to completely dry the organic extracts, as any acidic aqueous phase will lead to decarboxylation of the acid when concentrated at 40 °C under reduced pressure.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{16}NaO_4^+$) requires ***m/z*** 235.0941, found ***m/z*** 235.0943.

5.2.7 Synthesis and characterisation of tert-butyl 2-furylcarbamate (87):



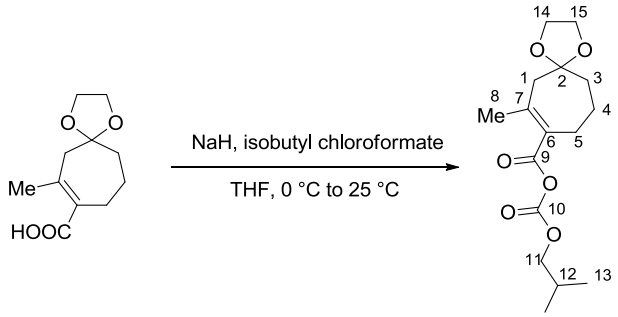
To a solution of 2-furoyl chloride (38.0 mL, 385 mmol) in *t*-BuOH (400 mL) at rt under a nitrogen atmosphere, was added sodium azide (27.6 g, 425 mmol) portion-wise over 10 min. The reaction was left stirring at 25 °C for 15 h and then heated at reflux for a further 10 h behind a protective/blast shield. The reaction was cooled to rt, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [95:5→90:10]) to provide **87** as a white solid[i] (56.0 g, 79% yield). Data is consistent with the literature.[194]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.05-7.07 (dd, 1H, H-1, J = 2.0, 1.0 Hz), 6.74 (br s, 1H, H-5), 6.33 (dd, 1H, H-2, J = 3.0, 2.0 Hz), 6.03 (br s, 1H, H-3), 1.51 (s, 9H, H-8).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 151.9 (C-6), 145.4 (C-4), 136.0 (C-1), 111.2 (C-2), 95.1 (C-3), 81.3 (C-7), 28.2 (C-8).

[i] Upon transferring this white solid to a storage bottle, it changed to a light purple colour and stored for more than 5 months in this form. The NMR spectra and the reactivity of the different coloured compounds are identical.

5.2.8 Synthesis and characterisation of isobutyl (7-methyl-1,4-dioxaspiro[4.6]undec-7-en-8-yl)carbonyl carbonate (161):



To a suspension of NaH (60% dispersion in mineral oil, 10.4 mg, 0.260 mmol) in anhydrous THF (0.5 mL) was added a solution of acid **158** (50.0 mg, 0.236 mmol) in anhydrous THF (0.5 mL) at 0 ^{o}C followed by isobutyl chloroformate (32.0 μL, 0.247 mmol). The reaction was left to warm to rt and subsequently the reaction mixture was filtered through a pad of Celite®. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [90:10]) to provide **161** as a colourless oil (53.4 mg, 77% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2959 (C-H), 2879 (C-H), 1795 (C=O), 1734 (C=O), 1147, 1067.

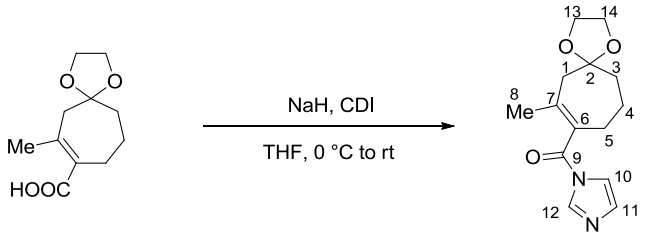
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 4.05 (dd, 2H, H-11, J = 6.5, 0.5 Hz), 3.99-3.91 (m, 4H, H-14 & H-15), 2.65 (s, 2H, H-1), 2.54-2.46 (m, 2H, H-5), 2.17 (s, 3H, H-8), 2.04 (app dquin, 1H, H-12, J = 13.5, 6.5 Hz), 1.92-1.86 (m, 2H, H-3), 1.71-1.63 (m, 2H, H-4), 0.97 (app br dd, 6H, H-13, J = 7.0, 1.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 162.7 (C-9 or C-10), 152.5 (C-9 or C-10), 150.0 (C-7), 128.1 (C-6), 106.8 (C-2), 75.4 (C-11), 64.6 (C-14 & C-15), 47.0 (C-1), 40.7 (C-3), 28.2 (C-5), 27.6 (C-12), 25.2 (C-8), 23.2 (C-4), 18.8 (C-13).

m/z (ES+) 335 ([M+Na]$^{+}$, 100%)

HRMS (ES+) exact mass calculated for [M+Na]$^{+}$ ($C_{16}H_{24}NaO_6^{+}$) requires ***m/z*** 335.1465, found ***m/z*** 335.1466.

5.2.9 Synthesis and characterisation of 1H-imidazol-1-yl(7-methyl-1,4-dioxaspiro[4.6]undec-7-en-8-yl)methanone (162):



To a solution of **158** (50.0 mg, 0.236 mmol) in anhydrous THF (0.5 mL) was added CDI (38.2 mg, 0.236 mmol) as a solution in THF (1 mL) at 0 ^{o}C. The reaction was allowed to warm to rt overnight and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc:AcOH [60:40:1]) to provide **162** as a colourless oil (50.0 mg, 81% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2941 (C-H), 2885 (C-H), 1719 (C=O), 1370, 1227.

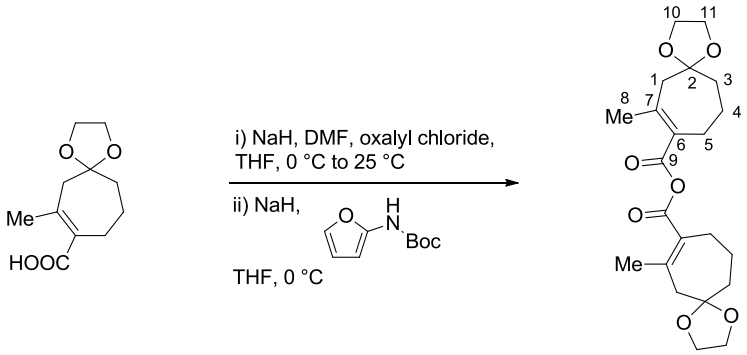
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 8.22 (s, 1H, H-11), 7.54 (s, 1H, H-10 or H-12), 7.10 (s, 1H, H-10 or H-12), 3.97 (s, 4H, H-13 & H-14), 2.58 (s, 2H, H-1), 2.46-2.40 (m, 2H, H-5), 1.97-1.91 (m, 2H, H-3), 1.74-1.68 (m, 2H, H-4), 1.66 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 169.0 (C-9), 139.5 (C-6 or C-7), 138.2 (C-11), 131.3 (C-10 or C-12), 130.9 (C-6 or C-7) , 116.2 (C-10 or C-12), 107.3 (C-2), 64.7 (C-13 & C-14), 44.3 (C-1), 40.6 (C-3), 30.1 (C-5), 24.7 (C-8), 22.8 (C-4).

m/z (ES+) 285 ([M+Na]$^{+}$, 100%)

HRMS (ES+) exact mass calculated for [M+Na]$^{+}$ ($C_{14}H_{18}N_2NaO_3^{+}$) requires ***m/z*** 285.1210, found ***m/z*** 285.1216.

5.2.10 Synthesis and characterisation of 7-methyl-1,4-dioxaspiro[4.6]undec-7-ene-8-carboxylic anhydride (163):



To a suspension of NaH (60% dispersion in mineral oil, 22.6 mg, 0.565 mmol) in anhydrous THF (5 mL) at 0 ^{o}C under a nitrogen atmosphere, was added a solution of acid **158** (100 mg, 0.471 mmol) in anhydrous THF (4 mL, a total of 1 mL of anhydrous THF used for washings) dropwise. DMF (2.0 µL, 0.026 mmol) was then added followed by oxalyl chloride (48.0 µL, 0.567 mmol) dropwise. The reaction was heated at rt for 20 min and then concentrated under reduced pressure to afford the acid chloride intermediate.

To a suspension of NaH (60% dispersion in mineral oil, 22.6 mg, 0.565 mmol) in anhydrous THF (5 mL) at 0 ^{o}C under a nitrogen atmosphere, was added a solution of the *N*-Boc 2-aminofuran **87** (103.6 mg, 0.565 mmol) in anhydrous THF (4 mL, a total of 1 mL of anhydrous THF used for washings) dropwise. After 20 min this *N*-Boc 2-aminofuran salt was added dropwise at 0 ^{o}C to the preformed acid chloride. After 1 h, water was added to the reaction mixture and extracted using EtOAc (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [70:30]) to provide only the undesired anhydride (**163**) as a dark purple oil (49.0 mg, 51% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2935 (C-H), 2861 (C-H), 1771 (C=O), 1710 (C=O), 1680, 1628, 1062.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.99-3.90 (m, 8H, H-10 & H-11), 2.63 (s, 4H, H-1), 2.49-2.44 (m, 4H, H-5), 2.15 (s, 6H, H-8), 1.91-1.86 (m, 4H, H-3), 1.69-1.62 (m, 4H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 164.4 (C-9), 150.8 (C-7), 129.4 (C-6), 106.8 (C-2), 64.5 (C-10 & C-11), 46.8 (C-1), 40.6 (C-3), 28.2 (C-5), 24.9 (C-8), 23.2 (C-4).

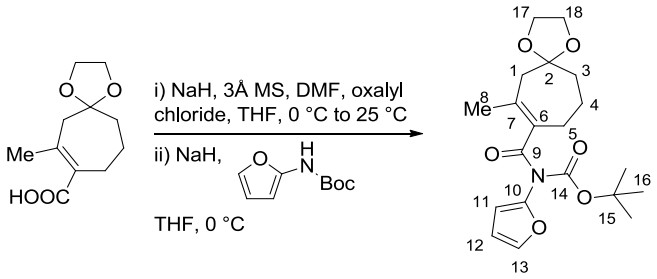
m/z (ES+) 835 ($[2M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{30}NaO_7^+$) requires ***m/z*** 429.1884, found ***m/z*** 429.1881.

5.2.11 Synthesis and characterisation of tert-butyl 2-furyl[(7-methyl-1,4-dioxaspiro[4.6]undec-7-en-8-yl)carbonyl]carbamate (160):



Experimental setup



To a suspension of NaH (60% dispersion in mineral oil, 621.9 mg, 15.55 mmol) in anhydrous THF (30 mL) at 0 ^oC under a nitrogen atmosphere, was added a solution of acid **158** (3.000 g, 14.13 mmol) in anhydrous THF (15 mL, a total of 15 mL of anhydrous THF used for washings) dropwise. The reaction was then heated at 25 ^oC for 20 min. Meanwhile, to a purged 250 mL three-necked flask fitted with 2 two-way taps (one connected to a Schlenck line and the other connected to an outlet tube) and equipped with 3.0 g MS 3Å (oven-dried activation), was added anhydrous THF (30 mL), anhydrous DMF (120.0 µL, 1.550 mmol) and then oxalyl chloride (4200 µL, 49.63 mmol) dropwise at 25 ^oC. After 5 min, the preformed acid salt suspension was added dropwise over 10 min (2×7.5 mL of anhydrous THF used for washings). After stirring for 1 h at 25 ^oC, a nitrogen flow was used to stream off the solvent and oxalyl chloride. The reaction was concentrated

to a thick light brown oil which was then put under vacuum and cooled to 0 ^{o}C, and then the *N*-Boc 2-aminofuran salt formation began.

To a suspension of NaH (60% dispersion in mineral oil, 1.131 g, 28.28 mmol) in anhydrous THF (30 mL) at 0 ^{o}C under a nitrogen atmosphere, was added a solution of the *N*-Boc 2-aminofuran **87** (5.179 g, 28.27 mmol) in anhydrous THF (15 mL) dropwise (a total of 7.5 mL of anhydrous THF used for washings) . After 20 min the *N*-Boc 2-aminofuran salt was added dropwise over 10 min at 0 ^{o}C to a solution of the preformed chloride in THF (60 mL) (a total of 7.5 mL of anhydrous THF used for washings). After 15 min at 0 ^{o}C, water (100 mL) was added to the reaction, and extracted using EtOAc (3×100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide **160** as a yellow oil (4.346 g, 81% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2980 (C-H), 2940 (C-H), 2886 (C-H), 1746 (C=O), 1698 (C=O).

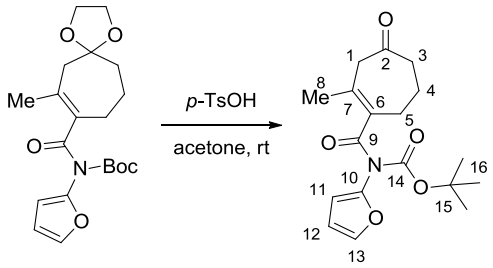
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.31 (dd, 1H, H-13, *J* = 2.0, 1.0 Hz), 6.40 (dd, 1H, H-12, *J* = 3.0, 2.0 Hz), 6.16 (dd, 1H, H-11, *J* = 3.0, 1.0 Hz), 3.95-3.83 (m, 4H, H-17 & H-18), 2.45 (s, 2H, H-1), 2.32-2.29 (m, 2H, H-5), 1.90 (s, 3H, H-8), 1.85-1.81 (m, 2H, H-3), 1.65-1.59 (m, 2H, H-4), 1.46-1.43 (m, 9H, H-16).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 172.2 (C-9), 151.2 (C-14), 143.8 (C-10), 140.5 (C-13), 136.2 (C-7), 133.8 (C-6), 111.2 (C-12), 107.3 (C-2), 105.9 (C-11), 83.6 (C-15), 64.4 (C-17 & C-18), 44.5 (C-1), 40.3 (C-3), 30.0 (C-5), 27.7 (C-16), 23.7 (C-8), 22.9 (C-4).

m/z (ES+) 400 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{27}NNaO_6^+$) requires ***m/z*** 400.1731, found ***m/z*** 400.1725.

5.2.12 Synthesis and characterisation of tert-butyl 2-furyl[(2-methyl-4-oxocyclohept-1-en-1-yl)carbonyl]carbamate (164):



To a solution of **160** (5.887 g, 15.60 mmol) in acetone (156 mL) at rt under a nitrogen atmosphere, was added *p*-TsOH (269.0 mg, 1.562 mmol). After 5 days reaction was complete by mass spectrometry. The reaction was quenched with brine (75 mL) and a saturated aqueous solution of $NaHCO_3$ (75 mL) and extracted using EtOAc (3×150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:Et_2O [60:40]) to provide **164** as a yellow solid (4.044 g, 78% yield).

mp 44-47 °C

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2981 (C-H), 2939 (C-H), 1748 (C=O), 1706 (C=O), 1609 (C=C).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.32 (dd, 1H, H-13, *J* = 2.0, 1.0 Hz), 6.42 (dd, 1H, H-12, *J* = 3.5, 2.0 Hz), 6.18 (dd, 1H, H-11, *J* = 3.5, 1.0 Hz), 3.18 (s, 2H, H-1), 2.55-2.48 (m, 4H, H-3 & H-5), 2.01-1.94 (m, 2H, H-4), 1.90 (s, 3H, H-8), 1.45-1.41 (s, 9H, H-16).

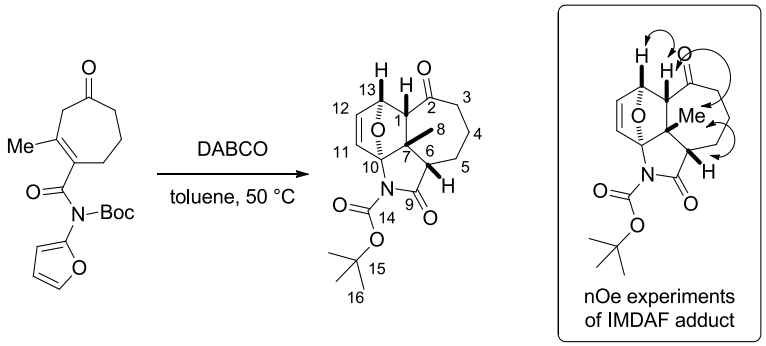
^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 207.3 (C-2), 172.0 (C-9), 150.8 (C-14), 143.4 (C-10), 140.7 (C-13), 133.0 (C-6), 130.6 (C-7), 111.3 (C-12), 105.9 (C-11), 84.0 (C-15), 49.4 (C-1), 43.0 (C-3), 29.9 (C-5), 27.7 (C-16), 23.7 (C-4), 22.7 (C-8).

m/z (ES+) 400 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{23}NNaO_5^+$) requires ***m/z*** 356.1468, found ***m/z*** 356.1467.

5.2.13 Synthesis and characterisation of racemic tert-butyl (2aS,6aR,9aR,9bR)-9b-methyl-2,6-dioxo-2a,3,4,5,6,6a,7,9b-octahydro-7, 9a-epoxycyclohepta[cd]indole-1(2H)-carboxylate (104):

5.2.13.1 Racemic



To a solution of **164** (2.000 g, 5.999 mmol) in anhydrous toluene (80 mL) at rt under a nitrogen atmosphere, was added DABCO (0.067 g, 0.597 mmol) in one portion. The reaction was then heated to 50 °C (oil-bath temp) for 3.5 days. The reaction was cooled to rt and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [60:40]) to provide **104** as a chromatographically inseparable mixture of diastereoisomers as an off-white solid (2.000 g, 100% yield, dr 95:5).

mp 137-140 °C

IR (film)/cm^{-1} ν_{max} 2980 (C-H), 2872 (C-H), 1791 (C=O), 1766 (C=O), 1705 (C=O).

NMR data for minor diastereoisomer (observable peaks):

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.61 (d, 1H, J = 6.0 Hz), 6.51 (dd, 1H, J = 6.0, 2.0 Hz), 6.47 (br d, 1H, J = 2.0 Hz), 2.30 (s, 1H), 1.51 (s, 9H), 1.17 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) 208.1, 173.5, 149.3, 133.9, 102.1, 84.0, 76.2, 61.6, 52.8, 46.0, 43.1, 27.2, 21.0, 19.9.

NMR data for major diastereoisomer:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.55 (d, 1H, H-11, J = 6.0 Hz), 6.47 (dd, 1H, H-12, J = 6.0, 2.0 Hz), 5.44 (br d, 1H, H-13, J = 2.0 Hz), 2.62-2.42 (m, 3H, H-3 & H-6), 2.27 (s, 1H, H-1), 2.08-1.94 (m, 2H, H-4_a & H-5_a), 1.92-1.78 (m, 2H, H-4_b & H-5_b), 1.52 (s, 9H, H-16), 1.29 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 207.9 (C-2), 176.8 (C-9), 149.0 (C-14), 134.4 (C-11), 134.1 (C-12), 104.0 (C-10), 84.3 (C-15), 76.5 (C-13), 64.9 (C-1), 54.6 (C-6), 45.4 (C-7), 39.5 (C-3), 27.9 (C-8 & C-16), 27.8 (C-4 or C-5), 24.5 (C-4 or C-5).

m/z (ES+) 689 ($[2M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{23}NNaO_5^+$) requires ***m/z*** 356.1468, found ***m/z*** 356.1465.

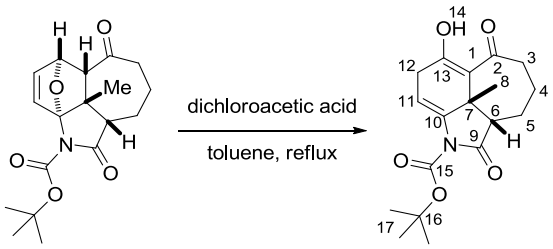
5.2.13.2 Asymmetric

To a solution of **164** (20 mg, 0.056 mmol) in *m*-xylene (1 mL) at rt under a nitrogen atmosphere, was added **catalyst 19** (5.5 mg, 0.012 mmol) in one portion. The reaction was then heated to 50 °C (oil-bath temp) for 11 days. The reaction was cooled to rt and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [60:40]) to provide **104** as a chromatographically inseparable mixture of diastereoisomers as an off-white film (20 mg, 100% yield, dr 96:4, +76% ee).

Data for enantioenriched 104**:** ***vide supra.*** $[\alpha]_D^{25}$ = +1.1 (*c* 1.7, $CHCl_3$).

5.2.14 Synthesis and characterisation of racemic tert-butyl (2aS,9bS)-7-hydroxy-9b-methyl-2,6-dioxo-2,2a,3,4,5,6,8,9b-octahydro-1H-cyclohepta[cd]indole-1-carboxylate (171):

5.2.14.1 Racemic



To a refluxing solution of **104** (7.30 g, 21.9 mmol) in anhydrous toluene (225 mL, oil-bath temp= 130 °C) under a nitrogen atmosphere, was added dichloroacetic acid (1.40 mL, 17.0 mmol) in one portion *via* syringe. After 5 min[i] the reaction was diluted with EtOAc (200 mL), quenched with a saturated aqueous solution of $NaHCO_3$ (640 mL) and extracted with EtOAc (3×200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide **171** as a white solid (6.30 g, 86% yield).

mp 139-143 °C

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$[ii] 2932 (C-H), 1761 (C=O), 1736 (C=O), 1611 (β-diketone; enol form), 1289, 1250, 1145.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 16.56 (s, 1H, H-14), 6.03 (dd, 1H, H-11, J = 6.5, 2.0 Hz), 3.19 (dd, 1H, H-12$_a$, J = 22.0, 2.0 Hz), 3.04 (dd, 1H, H-12$_b$, J = 22.0, 6.5 Hz), 2.55 (app td, 1H, H-3$_a$, J = 12.5, 8.5 Hz), 2.45-2.36 (m, 2H, H-6 & H-3$_b$), 2.04-1.97 (m, 1H, H-5$_a$), 1.94-1.86 (m, 2H, H-4), 1.64-1.55 (m, 10H, H-5$_b$ & H-17), 1.37 (s, 3H, H-8).

[i] If the reaction is left for longer than 5 min the yield drops significantly. This is assumed to be due to the formation of the *N*-deprotected analogue of the both the starting material and the product.
[ii] No O-H peak observed.

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 194.8 (C-2), 186.8 (C-13), 175.6 (C-9), 149.3 (C-15), 141.8 (C-10), 110.5 (C-1), 101.8 (C-11), 84.6 (C-16), 52.6 (C-6), 41.5 (C-7), 35.6 (C-3), 32.0 (C-12), 28.0 (C-17), 27.7 (C-8), 25.2 (C-5), 22.3 (C-4).

m/z (ES+) 356 ($[M+Na]^+$, 100%)

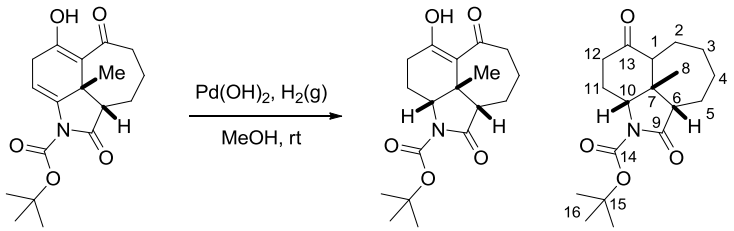
HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{23}NNaO_5^+$) requires ***m/z*** 356.1468, found ***m/z*** 356.1468.

5.2.14.2 Using enantioenriched starting material

To a refluxing solution of **104** (9.5 mg, 0.028 mmol) in anhydrous toluene (0.5 mL, oil-bath temp= 130 °C) under a nitrogen atmosphere, was added dichloroacetic acid (2 μL, 0.024 mmol) in one portion *via* syringe. After 5 min the reaction was diluted with EtOAc (5 mL), quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide **171** as a yellow amorphous solid (6.3 mg, 66% yield, 46% ee).

Data for enantioenriched 171**:** ***vide supra*****.** $[\alpha]_D^{20}$ = –2.7 (*c* 0.315, $CHCl_3$).

5.2.15 Synthesis and characterisation of racemic tert-butyl (2aS,9aR,9bS)-7-hydroxy-9b-methyl-2,6-dioxo-2,2a,3,4,5,6,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (172) & tert-butyl (2aS,9aR,9bR)-9b-methyl-2,7-dioxododecahydro-1H-cyclohepta[cd]indole-1-carboxylate (173):



To a suspension of $Pd(OH)_2$[i] (25 mg, 0.018 mmol, 20% on carbon, nominally 50% water) in MeOH (3 mL) at rt was added **171** (30 mg, 0.090 mmol) in one portion. The reaction was degassed using a vacuum at 85 mbar and then charged with H_2 (this operation was repeated 5 times).[ii] After 56 h the reaction was filtered through a pad of Celite® and washed multiple times with EtOAc. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15]) to provide **172** as a white amorphous solid (19 mg, 63% yield)[iii] alongside **173** as a pale yellow oil (4.6 mg, 16%).

Data for pure 172**:** ***vide infra*** **section** 5.2.17**.**

Data for 173**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2929 (C-H), 2855 (C-H), 1781 (C=O), 1749 (C=O), 1716 (C=O), 1328, 1152.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 4.03 (dd, 1H, H-10, J = 12.5, 4.5 Hz), 2.84 (dddd, 1H, H-11_a, J = 12.5, 8.0, 4.5, 1.5 Hz), 2.56 (ddd, 1H, H-12_a, J = 16.5, 1.5 Hz), 2.45 (app br d, 1H, H-1, J = 9.0 Hz), 2.43-2.30 (m, 1H, H-12_b), 2.26-2.20 (m, 1H, H-3_a), 2.16 (dd, 1H, H-6, J = 12.5, 2.0 Hz), 2.11-2.04 (m, 1H, H-4_a or H-5_a), 1.98-1.86 (m, 3H, H-2 & H-11_b & H-4 or

[i] $Pd(OH)_2$ purchased from Alfa-Aesar.

[ii] H_2 was charged using a double-skinned balloon (one balloon inside another) purchased from Aldrich Chemical Company, Inc. Model number: Z154997 (wall thickness 15 mm).

[iii] This was in fact contaminated with the over-reduced **173**.

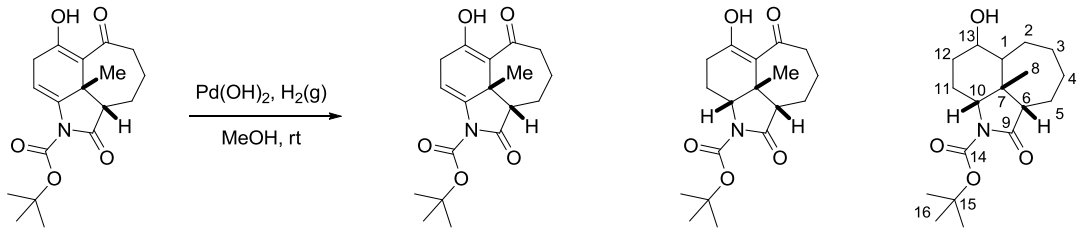
H-5), 1.69-1.52 (m, 10H, H-4_b or H-5_b & H-16), 1.34-1.26 (m, 1H, H-4_b or H-5_b), 1.21-1.14 (m, 2H, H-2_b & H-3_b), 0.92 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 208.4 (C-13), 172.2 (C-9), 150.6 (C-14), 83.5 (C-15), 62.8 (C-10), 58.9 (C-1), 57.3 (C-6), 43.4 (C-7), 38.1 (C-12), 30.6 (C-4 or C-5), 29.6 (C-2), 28.1 (C-16), 25.9 (C-4 or C-5), 24.2 (C-11), 21.6 (C-3), 18.7 (C-8).

m/z (ES+) 344 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{27}NNaO_4^+$) requires ***m/z*** 344.1832, found ***m/z*** 344.1821.

5.2.16 Synthesis and characterisation of racemic tert-butyl (2aS,9aR,9bS)-7-hydroxy-9b-methyl-2,6-dioxo-2,2a,3,4,5,6,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (172) & tert-butyl (2aS,9aR,9bR)-7-hydroxy-9b-methyl-2-oxododecahydro-1H-cyclohepta[cd]indole-1-carboxylate (174):



To a suspension of $Pd(OH)_2$[i] (84.5 mg, 0.0602 mmol, 20% on carbon, nominally 50% water) in MeOH (30 mL) at rt was added **171** (300 mg, 0.900 mmol) in one portion. The reaction was degassed using a vacuum at 85 mbar and then charged with H_2 (this operation was repeated 5 times).[ii] After 42 h 30 min the reaction was filtered through a pad of Celite® and washed multiple times with MeOH. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15]) to provide the recovered **171** as a white solid (81.8 mg, 27% yield). A

[i] $Pd(OH)_2$ purchased from Alfa-Aesar.

[ii] H_2 was charged using a double-skinned balloon (one balloon inside another). Balloons were purchased from Aldrich Chemical Company, Inc. Model number: Z154997 (wall thickness 15 mm).

second purification by flash column chromatography (eluted with benzene:acetone [96:4]) provided **172** as a white amorphous solid (92.1 mg, 31%) and **174** as a yellow oil (11.6 mg, 4%).

Data for 171**:** ***vide supra*** **section** 5.2.14**.**

Data for 172**:** ***vide infra*** **section** 5.2.17**.**

Data for 174**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3511 (broad; O-H), 2927 (C-H), 2869 (C-H), 1775 (C=O), 1719 (C=O), 1291, 1155.

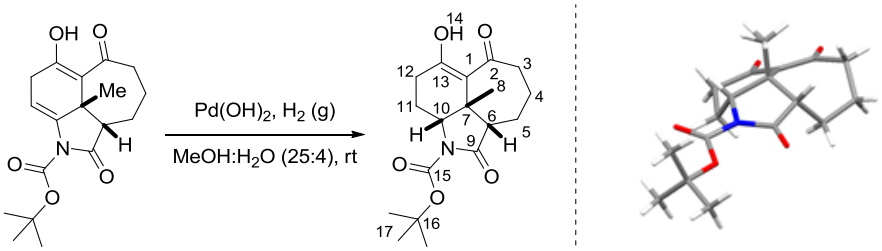
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 3.80 (app br q, 1H, H-13, J = 3.0 Hz), 3.61 (app t, 1H, H-10, J = 3.5 Hz), 2.34 (app dq, 1H, H-11_a or H-12_a, J = 15.0, 3.5 Hz), 2.20 (t, 1H, H-6, J = 6.0 Hz), 2.13-2.01 (m, 2H, H-5_a & H-11_b or H-12_b), 1.95 (app ddt, 1H, H-2_a, J = 15.0, 12.0, 7.5 Hz), 1.77-1.69 (m, 1H, H-5_b), 1.66-1.47 (m, 17H, H-1 & H-2_b & H-11 or H-12 & H-3 & H-4 & H-16), 1.36 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 176.6 (C-9), 150.9 (C-14), 82.8 (C-15), 71.8 (C-13), 63.8 (C-10), 55.8 (C-6), 42.0 (C-7), 38.2 (C-1), 28.1 (C-16), 27.6 (C-2), 27.10 (C-11 or C-12), 27.08 (C-3 or C-4 or C-8), 26.1 (C-5), 22.0 (C-3 or C-4 or C-8), 21.9 (C-3 or C-4 or C-8), 16.4 (C-11 or C-12).

m/z (ES+) 346 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{29}NNaO_4^+$) requires ***m/z*** 346.1989, found ***m/z*** 346.1978.

5.2.17 Synthesis and characterisation of racemic tert-butyl (2aS,9aR,9bS)-7-hydroxy-9b-methyl-2,6-dioxo-2,2a,3,4,5,6,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (172):



To **171** (3.00 g, 9.00 mmol) and $Pd(OH)_2$[i] (885 mg, 0.630 mmol, 20% on carbon, nominally 50% water) at rt, was added MeOH (300 mL) and H_2O (48 mL). The reaction was degassed using a vacuum at 85 mbar and then charged with H_2 (this operation was repeated 5 times).[ii] After 24 h the reaction was filtered through a pad of Celite® and washed multiple times with MeOH. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide **172** as a white amorphous solid (2.67 g, 88% yield). Recrystallised from Et_2O and CH_2Cl_2 to provide **172** as a colourless crystalline solid.

mp 105-107 °C.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3457 (broad; O-H), 2975 (C-H), 2936 (C-H), 2869 (C-H), 1781 (C=O), 1743 (C=O), 1717 (C=O), 1603 (*β*-diketone; enol form), 1306, 1155.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 16.43 (s, 1H, H-14), 3.83 (dd, 1H, H-10, *J* = 12.0, 4.0 Hz), 2.62 (app dt, 1H, H-3_a, *J* = 13.0, 8.0 Hz), 2.45-2.29 (m, 5H, H-3_b & H-6 & H-11_a & H-12), 2.21 (app ddt, 1H, H-5_a, *J* = 14.0, 7.0, 2.0 Hz), 1.89-1.77 (m, 2H, H-4), 1.70-1.59 (m, 1H, H-5_b), 1.57 (s, 9H, H-17), 1.46-1.36 (m, 4H, H-11_b & H-8).

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[i] $Pd(OH)_2$ purchased from Alfa-Aesar was necessary (#42578). Catalysts from different suppliers gave inconsistent results.

[ii] H_2 was charged using a double-skinned balloon (one balloon inside another). Balloons were purchased from Aldrich Chemical Company, Inc. Model number: Z154997 (wall thickness 15 mm).

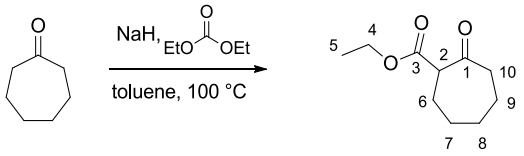
^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 199.1 (C-2), 185.2 (C-13), 175.0 (C-9), 149.9 (C-15), 111.1 (C-1), 83.7 (C-16), 66.1 (C-10), 53.7 (C-6), 38.8 (C-7), 36.9 (C-3), 31.7 (C-8), 29.8 (C-12), 28.0 (C-17), 26.7 (C-5), 26.3 (C-11), 22.2 (C-4).

m/z (ES+) 358 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{25}NNaO_5^+$) requires ***m/z*** 358.1625, found ***m/z*** 358.1624.

5.3 Experimental Chapter 3–model study

5.3.1 Synthesis and characterisation of ethyl 2-oxocycloheptanecarboxylate (209):



To a degassed flask containing NaH (60% dispersion in mineral oil, 14.2 g, 355 mmol) under a nitrogen atmosphere at rt, was added anhydrous toluene (280 mL) and then diethyl carbonate (31.0 mL, 256 mmol). This mixture was heated at 100 °C (oil-bath temp) and then cycloheptanone (15.0 mL, 127 mmol) was added over 2 h using a syringe pump. After 2h 30 min the yellow suspension was cooled to rt and diluted with EtOAc (200 mL). 100 mL of water were added followed by aqueous HCl (3 M) (500 mL) to dissolve the salt. The organic layer was extracted with EtOAc (3×200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [90:10]) to provide **209** as a pale yellow oil (22.9 g, 98% yield). **209** exists in equilibrium with its enol form; keto:enol, 1:0.23. Data is consistent with the literature.[195] Only selected/clear proton peaks of the enol tautomer have been included.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2931 (C-H), 2857 (C-H), 1738 (C=O ester), 1704 (C=O ketone).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 12.72 (s, 1H, C-O**H** of *enol form*), 4.21-4.09 (m, 2H, H-4),[i] 3.50 (dd, 1H, H-2, J = 10.5, 4.0 Hz), 2.63-2.50 (m, 2H, H-10), 2.11-2.02 (m, 1H, H-6_a), 1.95-1.74 (m, 4H, H-6_b & H-7_a & H-8_a & H-9_a), 1.63-1.51 (m, 1H, H-9_b), 1.48-1.37 (m, 2H, H-7_b & H-8_b), 1.27 (t, 3H, H-5 of *enol form*, J = 7.0 Hz), 1.23 (t, 3H, H-5, J = 7.0 Hz).

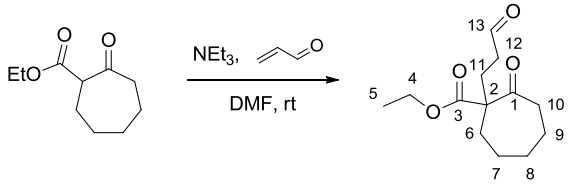
[i] Multiplet is observed with some symmetry, however it is overlaid with the H-4 peaks of the enol form.

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.1 (C-1), 170.5 (C-3), 60.9 (C-4), 58.8 (C-2), 43.0 (C-10), 29.5 (C-8), 27.9 (C-7), 27.5 (C-6), 24.3 (C-9), 14.0 (C-5).

m/z (ES+) 391 ($[2M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{16}NaO_3^+$) requires ***m/z*** 207.0992, found ***m/z*** 207.0991.

5.3.2 Synthesis and characterisation of racemic ethyl 2-oxo-1-(3-oxopropyl)cycloheptanecarboxylate (211):



To a solution of **209** (4.94 g, 26.8 mmol) in anhydrous DMF (12.5 mL) under a nitrogen atmosphere at rt, was added anhydrous NEt_3 (560 µL, 4.02 mmol) and then acrolein (2.70 mL, 40.4 mmol). After 18 h the reaction was diluted with Et_2O (40 mL) and then washed with brine (2×25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide **211** as a colourless oil (5.50 g, 85% yield).[i]

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2934 (C-H), 2861 (C-H), 1707 (C=O).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 9.72 (s, 1H, H-13), 4.22-4.12 (m, 2H, H-4), 2.68-2.61 (m, 1H, H-10_a), 2.61-2.53 (m, 1H, H-12_a), 2.52-2.38 (m, 2H, H-10_b & H-12_b), 2.24 (m, 1H, H-11_a), 2.11 (app dd, 1H, H-6_a, J = 14.0, 8.5 Hz), 1.91 (m, 1H, H-11_b), 1.81-1.58 (m, 5H, H-6_b & H-7_a & H-8_a & H-9), 1.58-1.49 (m, 1H, H-8_b), 1.49-1.40 (m, 1H, H-7_b), 1.25 (td, 3H, H-5, J = 7.0, 1.0 Hz).

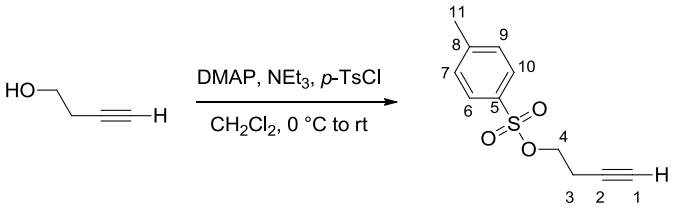
[i] **211** should be used fresh for the reproducibility of the next step for the synthesis of **210**.

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.3 (C-1), 201.2 (C-13), 172.2 (C-3), 61.6 (C-2), 61.3 (C-4), 42.2 (C-10), 39.7 (C-12), 33.8 (C-6), 29.7 (C-8), 27.6 (C-11), 25.4 (C-9), 24.8 (C-7), 14.0 (C-5).

m/z (ES+) 295 ($[M+MeOH+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+MeOH+Na]^+$ ($C_{14}H_{24}NaO_5^+$) requires ***m/z*** 295.1516, found ***m/z*** 295.1517.

5.3.3 Synthesis and characterisation of but-3-yn-1-yl 4-methylbenzenesulfonate:

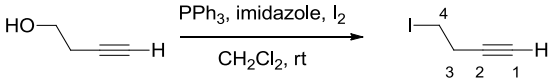


To a degassed flask purged with nitrogen, containing 3-butyn-1-ol (1.50 mL, 19.8 mmol) and DMAP (121 mg, 0.990 mmol) was added anhydrous CH_2Cl_2 (28.0 mL) at rt. The reaction was cooled to 0 °C and subsequently NEt_3 (3.00 mL, 21.5 mmol) was added followed by a solution of *p*-TsCl (3.97 g, 20.8 mmol) in CH_2Cl_2 (7 mL). The reaction was left stirring overnight, diluted with water, quenched with aqueous HCl (1 M) and extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [90:10→80:20]) to provide the title compound as a pale yellow oil (3.54 g, 80% yield). Data is consistent with the literature.[196]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.80 (d, 2H, 2×H-Ar, J = 8.0 Hz), 7.35 (d, 2H, 2×H-Ar, J = 8.0 Hz), 4.20-3.99 (m, 2H, H-4), 2.58-2.52 (m, 2H, H-3), 2.45 (s, 3H, H-11), 1.97 (t, 1H, H-1, J = 3.0 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 145.0 (C-5 or C-8), 132.7 (C-5 or C-8), 129.8 (2×C-Ar), 127.9 (2×C-Ar), 78.3 (C-2), 70.7 (C-1), 67.4 (C-4), 21.6 (C-11), 19.4 (C-3).

5.3.4 Synthesis and characterisation of 4-iodobut-1-yne:[197]



To a flask containing anhydrous CH_2Cl_2 (50 mL) at rt under a nitrogen atmosphere, was added PPh_3 (22.5 g, 85.8 mmol) followed by imidazole (5.85 g, 85.9 mmol). Iodine (21.8 g, 85.9 mmol) was then added and the resulting mixture was stirred at rt for 10 min.[i] Subsequently 3-butyn-1-ol (5.00 mL, 66.1 mmol) was added as a solution in anhydrous CH_2Cl_2 (60 mL) via a cannula and stirred at rt for 3 h (the reaction mixture was protected from light).[ii] The reaction was then concentrated under a stream of nitrogen to around 10 mL. To the concentrated solution was added PE to precipitate a solid (phosphine oxide) which was filtered through a pad of Celite®. To the filtrate was added PE to further precipitate this solid which was subsequently filtered again. The filtrate was concentrated under a stream of nitrogen and subsequently the crude product was purified by flash column chromatography (eluted with PE) to provide the title compound as a pale orange oil (8.5 g, 72% yield).[iii]

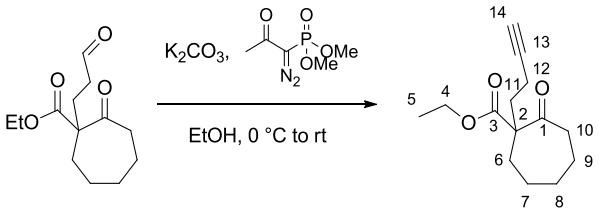
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.34-3.13 (m, 2H, H-4), 2.83-2.68 (m, 2H, H-3), 2.15 (app br d, 1H, H-1, J = 1.5 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 82.6 (C-2), 70.2 (C-1), 23.6 (C-3), 1.0 (C-4).

HRMS (FI^+) exact mass calculated for $[M]^{\cdot+}$ ($C_4H_5I^{\cdot+}$) requires ***m/z*** 179.9430, found ***m/z*** 179.9437.[iv]

[i] Upon addition of each of these reagents, sufficient time was afforded to achieve their complete dissolution in CH_2Cl_2.
[ii] The flask was covered with aluminium foil.
[iii] Filtration of this oil on alumina, leads to a lighter yellow colouration.
[iv] FI refers to "field ionisation".

5.3.5 Synthesis and characterisation of racemic ethyl 1-(but-3-yn-1-yl)-2-oxocycloheptanecarboxylate (210):



To a solution of freshly purified **211**[i] (5.16 g, 21.5 mmol) in EtOH (450 mL) under a nitrogen atmosphere at 0 °C, was added anhydrous K_2CO_3 (5.94 g, 43.0 mmol) in one portion. The diazophosphonate (**212**= Ohira–Bestmann reagent)[ii] (4.95 g, 25.8 mmol) was added dropwise as a solution in EtOH (10 mL). A further 10 mL of EtOH were used for thorough washes of the syringe. The mixture was allowed to gradually warm to rt over 24 h. The reaction was concentrated under reduced pressure, diluted with EtOAc (350 mL) and then quenched with a saturated aqueous solution of $NaHCO_3$ (350 mL). The organic layer was extracted with EtOAc (2×200 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15]) to provide **210** as a colourless oil (4.30 g, 85% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3285 (C≡C-H), 2935 (C-H), 2861 (C-H), 1708 (C=O), 1446.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 4.25-4.14 (m, 2H, H-4), 2.65 (ddd, 1H, H-10$_a$, J = 12.5, 9.5, 3.5 Hz), 2.48 (ddd, 1H, H-10$_b$, J = 12.5, 8.5, 3.5 Hz), 2.29-2.21 (m, 2H, H-11$_a$ & H-12$_a$), 2.20-2.09 (m, 2H, H-6$_a$ & H-12$_b$), 1.94 (t, 1H, H-14, J = 2.5 Hz), 1.90-1.82 (m, 1H, H-11$_b$), 1.80-1.51 (m, 6H, H-6$_b$ & H-7$_a$ & H-8 & H-9), 1.47-1.36 (m, 1H, H-7$_b$), 1.26 (t, 3H, H-5, J = 7.0 Hz).

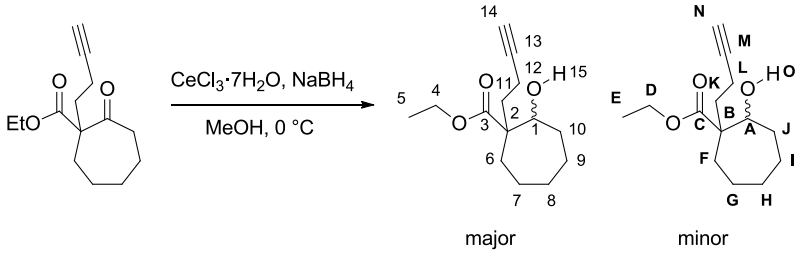
[i] **211** should be used fresh and in high purity for the reproducibility of **210**.
[ii] Synthesized by Dr. B. Darses.

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 208.9 (C-1), 171.9 (C-3), 83.8 (C-13), 68.5 (C-14), 62.0 (C-2), 61.3 (C-4), 42.0 (C-10), 34.3 (C-11), 33.0 (C-6), 29.7 (C-8 or C-9), 25.5 (C-8 or C-9), 24.8 (C-7), 14.3 (C-12), 14.0 (C-5).

m/z (ES+) 259 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_3^+$) requires ***m/z*** 259.1305, found ***m/z*** 259.1305.

5.3.6 Synthesis and characterisation of racemic ethyl 1-(but-3-yn-1-yl)-2-hydroxycycloheptanecarboxylate (213):



To a solution of **210** (1.00 g, 4.23 mmol) in MeOH (24.0 mL) under a nitrogen atmosphere at rt, was added $CeCl_3 \cdot 7H_2O$ (1.83 g, 4.91 mmol). Upon complete dissolution of the cerium salt, the flask was cooled to 0 °C and then $NaBH_4$ (192 mg, 5.08 mmol) was added portion-wise, maintaining the temp between 0-12 °C. After 1 h 30 min at 0 °C the reaction was quenched with a saturated aqueous solution of NH_4Cl (70 mL) and then extracted with EtOAc (3×100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [95:5]) to provide **213** as a pale yellow oil (783 mg, 78% yield, 1:0.4 dr). For ease of interpretation, the integrations below are indicated as if each isomer was isolated in 100% purity.

NMR spectra of **213** were complicated by the presence of 2 diastereoisomeric species and therefore **213** has not been fully characterised. The connectivity was further confirmed by

spectroscopic data and by full assignment of the dehydrated product, **207**, obtained in the following step.

IR (film)/cm-1 ν_{max} 3531 (broad; O-H), 3306 (alkyne C-H), 2930 (C-H), 2864 (C-H), 1718 (C=O), 1182.

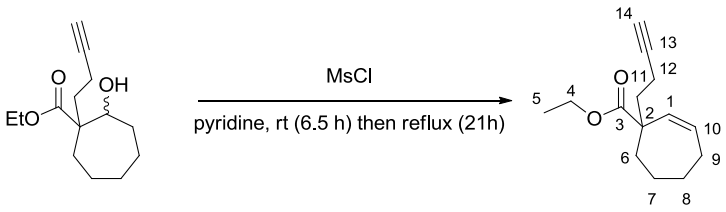
^{1}H NMR ($CDCl_3$, 300 MHz) (Mixture of diastereoisomers) δH 4.22-4.12 (m, 4H, H-4 & H-**D**), 4.07-4.00 (m, 1H, H-1), 3.59 (app td, 1H, H-**A**, J = 9.0, 3.0 Hz), 3.08 (d, 1H, H-**O** , J = 9.5 Hz), 2.65 (d, 1H, H-15, J = 3.0 Hz), 2.30-1.15 (m, 36H).

^{13}C NMR ($CDCl_3$, 75 MHz) (Mixture of diastereoisomers, observed peaks) δC 177.0 (C-3), 176.4 (C-**C**), 84.3 (C-13), 84.2 (C-**M**), 76.6 (C-**A**), 74.9 (C-1), 68.3 (C-14), 68.3 (C-**N**), 60.8 (C-4), 60.6 (C-**D**), 53.5 (C-**B**), 52.9 (C-2), 36.8, 33.7, 32.7, 32.3, 31.8, 31.7, 28.6, 27.4, 24.4, 23.0, 22.5, 22.3, 14.2 (C-5 or C-**E**), 14.1 (C-5 or C-**E**).

m/z (ES+) 261 ([M+Na]+, 100%).

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{22}NaO_3^+$) requires ***m/z*** 261.1461, found ***m/z*** 261.1455.

5.3.7 Synthesis and characterisation of racemic ethyl 1-(but-3-yn-1-yl)cyclohept-2-ene-1-carboxylate (207):



To a solution of the mixture of diastereoisomers (1:0.4) of **213** (770 mg, 3.23 mmol) in pyridine (10 mL) under a nitrogen atmosphere at rt, was added MsCl (1.30 mL, 16.8 mmol) dropwise to yield a yellow solution. The reaction was left stirring for 6 h 30 min and then was heated at reflux (oil-bath temp= 140 °C) for 21 h. The dark reaction was cooled to rt and quenched with a saturated aqueous solution of $NaHCO_3$ (40 mL) and extracted with EtOAc (4×50 mL). The combined organic extracts were dried over Na_2SO_4,

filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [100:0→99:1→98:2]) to provide **207** as a yellow oil (516 mg, 72% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3301 (C≡C-H), 2929 (C-H), 2863 (C-H), 1726 (C=O), 1448.

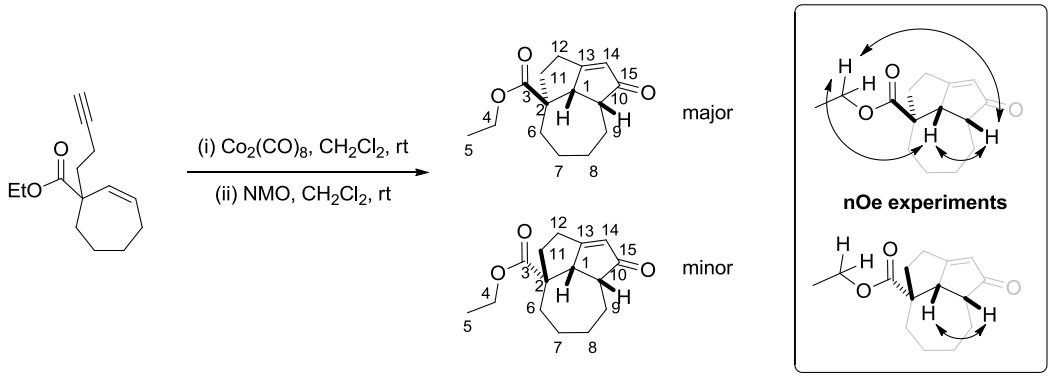
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.85 (dt, 1H, H-10, J = 12.0, 6.0 Hz), 5.61 (d, 1H, H-1, J = 12.0 Hz), 4.15 (q, 2H, H-4, J = 7.0 Hz), 2.25-2.06 (m, 4H, H-9 & H-12), 1.98-1.90 (m, 4H, H-6_a & H-11 & H-14), 1.79-1.67 (m, 3H, H-6_b & H-7), 1.59-1.49 (m, 2H, H-8), 1.26 (t, 3H, H-5, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 175.4 (C-3), 132.8 (C-10), 132.7 (C-1), 84.1 (C-13), 68.3 (C-14), 60.6 (C-4), 51.8 (C-2), 38.5 (C-11), 34.8 (C-6), 27.9 (C-9), 26.9 (C-8), 25.5 (C-7), 14.2 (C-5 & C-12).

m/z (ES+) 243 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_2^+$) requires ***m/z*** 243.1356, found ***m/z*** 243.1356.

5.3.8 Synthesis and characterisation of racemic ethyl (4aS,8aR,8bS)-1-oxo-3,4,5,6,7,8,8a,8b-octahydrocyclopenta[cd]azulene-4a(1H)-carboxylate (215$_a$) & ethyl (4aR,8aR,8bS)-1-oxo-3,4,5,6,7,8,8a,8b-octahydrocyclopenta[cd]azulene-4a(1H)-carboxylate (215$_b$):



To a degassed flask containing $Co_2(CO)_8$ (186 mg, 0.544 mmol) was added anhydrous CH_2Cl_2 (5 mL) under an argon[i] atmosphere at rt. To this dark brown solution was added **207** (100 mg, 0.454 mmol) as a solution in anhydrous CH_2Cl_2 (5 mL) dropwise (a total of a further 5 mL of anhydrous CH_2Cl_2 used for washings). After 1 h 30 min the solvent was removed under reduced pressure to provide a dark viscous oil. This oil was purified by rapid flash column chromatography (eluted with CH_2Cl_2). To a solution of the resultant purified Co–alkyne complex in anhydrous CH_2Cl_2 (15 mL), under an argon atmosphere at rt, was added NMO (479 mg, 4.09 mmol) in one portion. The reaction was stirred overnight (11 h 30 min) and then it was opened to the atmosphere. After a further 10 h 30 min, the resulting violet heterogeneous reaction was filtered through a pad of Celite® and washed with CH_2Cl_2. The filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15]) to provide the major diastereoisomer **215$_a$** as a yellow oil (51.3 mg, 46% yield) and then the minor diastereoisomer **215$_b$** as a pale yellow oil (14.0 mg, 12% yield) giving an overall 58% yield.

[i] This argon atmosphere is essential in providing reproducible results.

Data for major diastereoisomer 215_a**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2855 (C-H), 1723 (C=O), 1698 (C=O), 1635 (C=C).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.03-6.01 (br m, 1H, H-14), 4.23 (q, 2H, H-4, J = 7.5 Hz), 3.64 (m, 1H, H-1), 2.79-2.74 (m, 1H, H-10), 2.74-2.60 (m, 2H, H-12), 2.37-2.23 (m, 2H, H-9_a & H-11_a), 2.02 (ddd, 1H, H-11_b, J = 13.0, 8.0, 2.0 Hz), 1.98-1.91 (m, 1H, H-6_a), 1.75-1.56 (m, 3H, H-7_a & H-8_a & H-9_b), 1.30 (t, 3H, H-5, J = 7.5 Hz), 1.24 (app td, 1H, H-6_b, J = 13.5, 2.0 Hz), 1.14-1.04 (m, 1H, H-7_b), 0.90 (app br q, 1H, H-8_b, J = 13.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 213.4 (C-15), 188.2 (C-13), 175.6 (C-3), 126.6 (C-14), 60.8 (C-4), 56.1 (C-1), 55.0 (C-2), 48.6 (C-10), 39.4 (C-11), 34.6 (C-6), 29.2 (C-9), 27.2 (C-7), 26.6 (C-8), 24.9 (C-12), 14.3 (C-5).

m/z (ES+) 271 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}NaO_3^+$) requires ***m/z*** 271.1305, found ***m/z*** 271.1301.

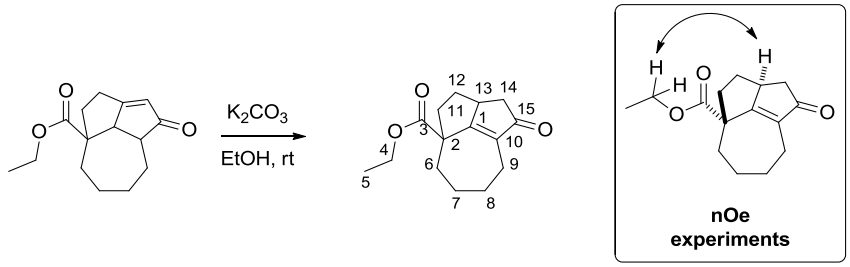
Data for minor diastereoisomer 215_b**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2930 (C-H), 2854 (C-H) 1727 (C=O), 1700 (C=O), 1631 (C=C).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.89-5.86 (br m, 1H, H-14), 4.14-3.98 (m, 2H, H-4), 2.97 (app br dt, 1H, H-1, J = 7.5, 1.0 Hz) 2.74 (app dd, 1H, H-12_a, J = 18.5, 11.0 Hz), 2.66-2.58 (m, 1H, H-10), 2.52 (m, 1H, H-12_b), 2.47-2.42 (m, 1H, C-**H**), 2.30 (ddd, 1H, H-11_a, J = 13.0, 8.0, 1.5 Hz), 2.20 (dt, 1H, C-**H**, J = 13.0, 7.0 Hz), 2.06-1.96 (m, 3H, 3×C-**H**), 1.92-1.83 (m, 1H, C-**H**), 1.40-1.22 (m, 3H, 3×C-**H**), 1.18 (t, 3H, H-5, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 211.2 (C-15), 182.8 (C-13), 174.7 (C-3), 125.8 (C-14), 60.3 (C-4), 59.8 (C-1), 54.2 (C-2), 48.9 (C-10), 39.1 (C-11), 38.3 (**C**H_2), 28.2 (**C**H_2), 27.6 (**C**H_2), 26.2 (**C**H_2), 25.8 (C-12), 14.0 (C-5).

5.3.9 Synthesis and characterisation of racemic ethyl (2aS,4aR)-1-oxo-2,2a,3,4,5,6,7,8-octahydrocyclopenta[cd]azulene-4a(1H)-carboxylate (216):



To a solution of the mixture of diastereoisomers (*ca.* 4:1) of **215** (155 mg, 0.624 mmol) in EtOH (6 mL) was added anhydrous K_2CO_3 (119 mg, 0.861 mmol) in one portion at rt. After 20 h brine was added and the reaction was then extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15]) to provide **216** as a yellow oil, which solidified to a yellow solid on standing (142 mg, 92% yield).

mp 29-32 °C.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2930 (C-H), 2855 (C-H), 1727 (C=O), 1705 (C=O), 1668 (C=C), 1447.

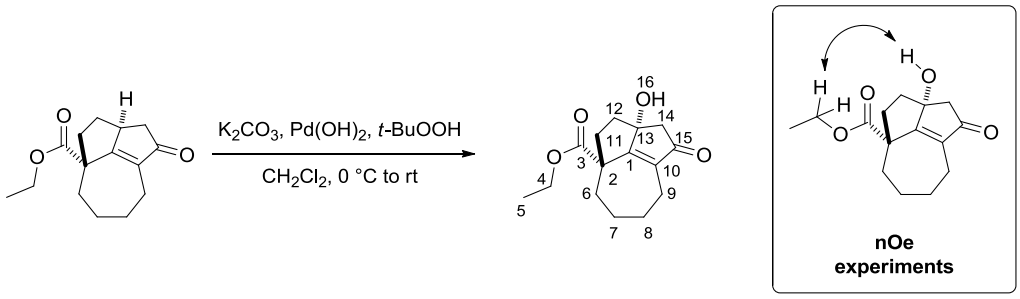
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 4.27-4.13 (m, 2H, H-4), 3.02 (app ddt, 1H, H-13, J = 12.5, 6.5, 3.0 Hz), 2.65 (dd, 1H, H-14$_a$, J = 18.0, 6.0 Hz), 2.53 (ddd, 1H, H-9$_a$, J = 15.5, 5.0, 3.0 Hz), 2.39-2.28 (m, 2H, H-6$_a$ & H-11$_a$), 2.14-2.04 (m, 3H, H-9$_b$ & 12$_a$ & 14$_b$), 2.01 (dd, 1H, H-11$_b$, J = 14.0, 8.0 Hz), 1.95-1.89 (m, 1H, H-7$_a$), 1.83-1.78 (m, 1H, H-8$_a$), 1.64 (m, 1H, H-7$_b$), 1.47 (ddd, 1H, H-6$_b$, J = 13.5, 12.5, 2.5 Hz), 1.27 (t, 3H, H-5, J = 7.0 Hz), 1.24-1.14 (m, 2H, H-8$_b$ & H-12$_b$).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.6 (C-15), 184.3 (C-1), 174.3 (C-3), 139.0 (C-10), 61.1 (C-4), 54.1 (C-2), 45.1 (C-13), 41.6 (C-14), 40.8 (C-11), 38.1 (C-6), 30.1 (C-12), 27.5 (C-7), 26.6 (C-8), 23.3 (C-9), 14.2 (C-5).

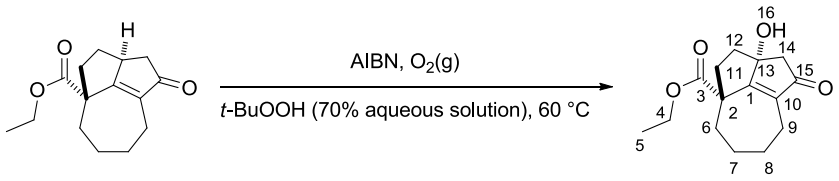
m/z (ES+) 519 ([2M+Na]$^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}NaO_3^+$) requires ***m/z*** 271.1305, found ***m/z*** 271.1304.

5.3.10 Synthesis and characterisation of racemic ethyl (2aR,4aR)-2a-hydroxy-1-oxo-2,2a,3,4,5,6,7,8-octahydrocyclopenta[cd]azulene-4a(1H)-carboxylate (225):



Corey's method: To a 2 mL glass vial equipped with a stirrer bar, **216** (12 mg, 0.049 mmol), K_2CO_3 (3.5 mg, 0.025 mmol) and $Pd(OH)_2$ (73 mg, 0.052 mmol) was added *t*-BuOOH (6M in decane) (41 μL, 0.25 mmol) at 0 °C followed by 0.20 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred at rt for 48 h and then filtered through a pad of Celite®. It was then concentrated under a stream of nitrogen. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide the recovered **216** (7.0 mg) and **225** as a white solid (2.7 mg, 20% or 50% yield based on recovered starting material [brsm]).



Watt's method: To a 2 mL glass vial equipped with a stirrer bar, **216** (19 mg, 0.077 mmol) and AIBN (2.8 mg, 0.017 mmol) was added 0.42 mL of *t*-BuOOH (70% aqueous solution). The reaction mixture was heated at 60 °C under an oxygen atmosphere. After 48 h the reaction mixture was cooled to rt and diluted with Et_2O (16 mL). The organic layer was then washed with freshly prepared $SnCl_2$ (1 M) [made up using aqueous HCl (2 M)]

(2×5 mL)[i] followed by water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified twice by flash column chromatography (eluted with pentane:Et_2O [20:80]) to provide **225** as a white solid (6.9 mg, 34% yield).

mp 80-83 °C.

IR (film)/cm-1 ν_{max} 3447 (broad; O-H), 2928 (C-H), 1712 (C=O), 1674 (C=O).

^{1}H NMR (CD_2Cl_2, 500 MHz) δH 4.23 (qd, 2H, H-4, *J* = 7.0, 1.0 Hz), 3.10 (s, 1H, H-16), 2.64-2.54 (m, 2H, H-11_a & H-14_a), 2.50-2.42 (m, 2H, H-9_a & H-14_b), 2.37 (ddd, 1H, H-6_a, *J* = 14.0, 5.5, 2.5 Hz), 2.18 (dd, 1H, H-12_a, *J* = 13.0, 7.5 Hz), 2.08 (ddd, 1H, H-9_b, *J* = 15.5, 12.0, 3.5 Hz), 1.97 (app dd, 1H, H-11_b, *J* = 13.5, 8.5 Hz), 1.94-1.88 (m, 1H, H-7_a), 1.84-1.75 (m, 1H, H-8_a), 1.71-1.56 (m, 2H, H-7_b & H-12_b), 1.49 (ddd, 1H, H-6_b, *J* = 13.5, 12.0, 3.0 Hz), 1.29 (app t, 4H, H-5 & H-8_b, *J* = 7.0 Hz).

^{13}C NMR (CD_2Cl_2, 125 MHz) δC 207.7 (C-15), 179.1 (C-1), 175.9 (C-3), 141.4 (C-10), 83.6 (C-13), 62.3 (C-4), 54.3 (C-2), 49.2 (C-14), 40.2 (C-11), 38.4 (C-6), 36.7 (C-12), 27.8 (C-7), 26.8 (C-8), 23.7 (C-9), 14.5 (C-5).

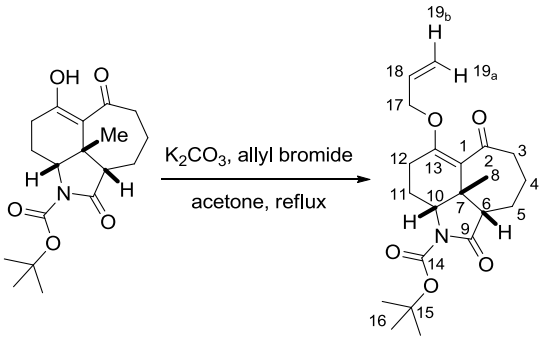
m/z (ES+) 551 ([2M+Na]+, 100%).

HRMS (ES+) exact mass calculated for [M+Na]+ ($C_{15}H_{20}NaO_4^+$) requires m/z 287.1254, found m/z 287.1255.

[i] When the solution was prepared, a fine insoluble white powder was observed. This powder was filtered on Celite® and then the clear solution was used as stated above.

5.4 Experimental Chapter 3–real system

5.4.1 Synthesis and characterisation of racemic tert-butyl (2aS,9aR,9bS)-9b-methyl-2,6-dioxo-7-(prop-2-en-1-yloxy)-2,2a,3,4,5,6,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (230):



To a solution of **172** (1.250 g, 3.727 mmol) in acetone (56 mL) at rt under a nitrogen atmosphere, was added anhydrous K_2CO_3 (2.576 g, 18.64 mmol) in one portion and allyl bromide (8000 μL, 92.45 mmol) in one portion (a total of 29 mL of acetone used for washings). The reaction was then placed in a preheated oil-bath at 85 °C for 30 h. The reaction was cooled to rt, filtered on a pad of Celite® and washed multiple times with acetone. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with PE:Et_2O [60:40]) to provide **230** as a pale yellow oil (1.104 g, 79% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2977 (C-H), 2934 (C-H), 2871 (C-H), 1781 (C=O), 1746 (C=O), 1716 (C=O), 1670 (C=C), 1455, 1293, 1156.

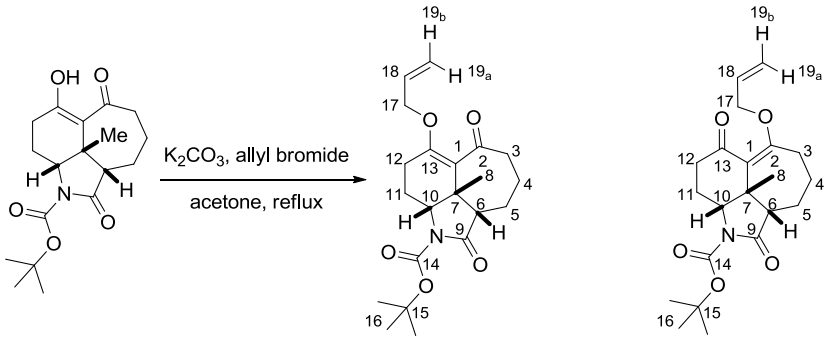
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.85 (app br ddt, 1H, H-18, J = 17.0, 10.5, 5.5), 5.26 (dd, 1H, H-19_a, J = 17.0, 1.0 Hz), 5.19 (dd, 1H, H-19_b, J = 10.5, 1.0 Hz), 4.30-4.19 (m, 2H, H-17), 3.79 (dd, 1H, H-10, J = 7.0, 3.0 Hz), 2.63 (app dt, 1H, H-3_a, J = 15.0, 6.5 Hz), 2.42 (ddd, 1H, H-3_b, J = 15.0, 9.0, 5.5 Hz), 2.36 (dd, 1H, H-6, J = 8.0, 2.5 Hz), 2.23-2.01 (m, 5H, H-5_a & H-11 & H-12), 1.91 (app td, 1H, H-4_a, J = 15.0, 8.0 Hz), 1.82-1.74 (m, 1H, 5_b), 1.69-1.58 (m, 1H, 4_b), 1.55 (s, 9H, H-16), 1.28 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.2 (C-2), 174.6 (C-9), 150.2 (C-13 or C-14), 150.1 (C-13 or C-14), 133.4 (C-18), 122.1 (C-1), 117.5 (C-19), 83.3 (C-15), 68.9 (C-17), 62.3 (C-10), 55.6 (C-6), 44.5 (C-3), 39.0 (C-7), 28.0 (C-16), 26.8 (C-8), 26.2 (C-5), 24.3 (C-11), 22.0 (C-4), 20.7 (C-12).

m/z (ES+) 398 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{29}NNaO_5^+$) requires ***m/z*** 398.1938, found ***m/z*** 398.1938.

5.4.2 Synthesis and characterisation of racemic tert-butyl (2aS,9aR,9bS)-9b-methyl-2,6-dioxo-7-(prop-2-en-1-yloxy)-2,2a,3,4,5,6,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (230) and tert-butyl (2aS,9aR,9bS)-9b-methyl-2,7-dioxo-6-(prop-2-en-1-yloxy)-2,2a,3,4,5,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (231):



To a solution of **172** (66.0 mg, 0.197 mmol) in acetone (3 mL) at rt under a nitrogen atmosphere, was added K_2CO_3 (136 mg, 0.984 mmol) in one portion and allyl bromide (420 μL, 4.85 mmol) in one portion (a total of 1.5 mL of acetone used for washings). The reaction was then placed in a preheated oil-bath at 85 °C for 30 h. The reaction was cooled to rt, filtered on a pad of Celite® and washed multiple times with acetone. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with PE:Et_2O [80:20→60:40]) to provide **230** as a pale yellow oil (56 mg, 76% yield) and **231** as a pale yellow oil (12.5 mg, 17%).

Data for major regioisomer 230 ***vide supra*** **section** 5.4.1**.**

Data for minor regioisomer 231**:**

IR (film)/cm^{-1} ν_{max} 2931 (C-H), 1782 (C=O), 1744 (C=O), 1716 (C=O), 1675 (C=C-OR), 1303, 1155.

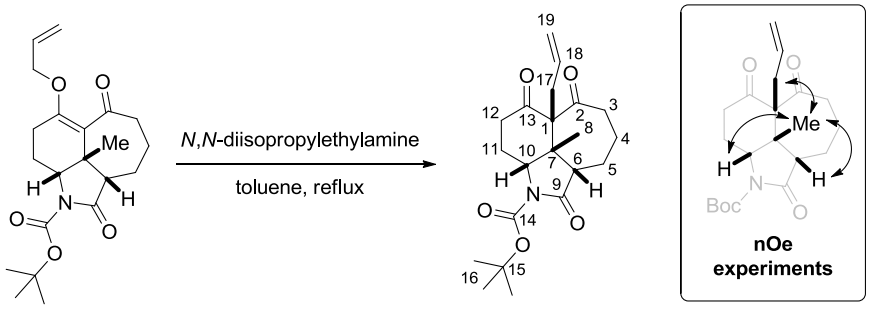
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.84-5.98 (m, 1H, H-18), 5.37 (dd, 1H, H-19$_a$, J = 17.0, 1.0 Hz), 5.24 (dd, 1H, H-19$_b$, J = 10.5, 1.0 Hz), 4.27-4.45 (m, 2H, H-17), 3.71 (dd, 1H, H-10, J = 12.5, 3.0 Hz), 2.45-2.60 (m, 1H, H-12$_a$), 2.37-2.45 (m, 1H, 1 × CH_2), 2.14-2.33 (m, 4H, H-6 & 3 × C$\underline{H}_a$H$_b$), 1.69-1.93 (m, 3H, 3 × CH$_a\underline{H}_b$), 1.55 (s, 9H, H-16), 1.34 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 201.1 (C-13), 175.6 (C-9), 161.0 (C-2), 149.7 (C-14), 133.1 (C-18), 120.9 (C-1), 117.7 (C-19), 83.7 (C-15), 70.5 (C-17), 66.2 (C-10), 53.7 (C-6), 41.0 (C-7), 36.7 (C-12), 29.4 (C-8), 28.0 (C-16), 27.3 (CH_2), 26.7 (CH_2), 22.4 (CH_2).

m/z (ES+) 398 ([M+Na]$^+$, 100%)

HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{21}H_{29}NNaO_5^+$) requires ***m/z*** 398.1938, found ***m/z*** 398.1927.

5.4.3 Synthesis and characterisation of racemic tert-butyl (2aS,6aS,9aR,9bS)-9b-methyl-2,6,7-trioxo-6a-(prop-2-en-1-yl)dodecahydro-1H-cyclohepta[cd]indole-1-carboxylate (232):



To a solution of **230** (1.10 g, 2.93 mmol) in anhydrous toluene (75 mL) at rt under a nitrogen atmosphere, was added *N*,*N*-diisopropylethylamine (2.60 mL, 14.9 mmol) in one portion *via* syringe. The reaction was then placed in a preheated oil-bath at 120 °C for 12 h. The reaction was cooled to rt and concentrated under reduced pressure. The crude

product was purified by flash column chromatography (eluted with PE:Et_2O [60:40]) to provide **232** as a white solid (949 mg, 86% yield).

mp 136-140 °C

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2978 (C-H), 2940 (C-H), 1782 (C=O), 1747 (C=O), 1711 (C=O), 1348, 1220.

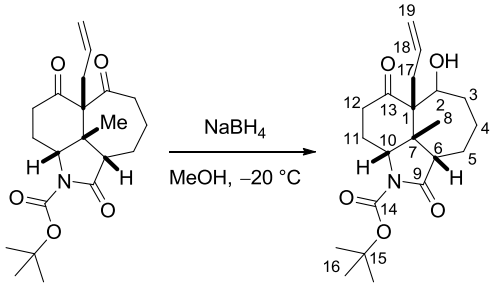
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.32 (app dtd, 1H, H-18, *J* = 17.0, 9.5, 5.0 Hz), 5.04-4.95 (m, 2H, H-19), 4.15 (dd, 1H, H-10, *J* = 10.0, 6.0 Hz), 3.55-3.41 (m, 2H, H-3_a & H-17_a), 2.64 (app dq, 1H, H-11_a, *J* = 14.0, 5.5 Hz), 2.53-2.40 (m, 3H, H-3_b & H-12), 2.25 (app br d, 1H, H-5_a, *J* = 14.5 Hz), 2.12 (dd, 1H, H-17_b, *J* = 13.5, 9.5 Hz), 2.08-1.98 (m, 2H, H-4_a & H-6), 1.89 (app dq, 1H, H-11_b, *J* = 14.0, 9.5 Hz), 1.70 (app dtd, 1H, H-5_b, *J* = 14.5, 12.5, 2.0 Hz), 1.57 (s, 9H, H-16), 1.49 (m, 1H, H-4_b), 1.21 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 208.0 (C-13), 207.0 (C-2), 174.3 (C-9), 149.8 (C-14), 132.6 (C-18), 117.9 (C-19), 83.9 (C-15), 68.3 (C-1), 61.5 (C-10), 59.6 (C-6), 43.4 (C-7), 41.2 (C-3), 37.9 (C-17), 36.6 (C-12), 28.1 (C-11), 28.04 (C-16), 27.99 (C-5), 26.8 (C-4), 25.4 (C-8).

m/z (ES+) 398 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{29}NNaO_5^+$) requires ***m/z*** 398.1938, found ***m/z*** 398.1939.

5.4.4 Synthesis and characterisation of racemic tert-butyl (2aS,6aS,9aR,9bS)-6-hydroxy-9b-methyl-2,7-dioxo-6a-(prop-2-en-1-yl)dodecahydro-1H-cyclohepta[cd]indole-1-carboxylate (234):



To a solution of **232** (946 mg, 2.52 mmol) in MeOH (93 mL) at –20 °C under a nitrogen atmosphere, was added $NaBH_4$ (1.33 g, 35.2 mmol) portion-wise. After 1 h 30 min the reaction was diluted with CH_2Cl_2 (110 mL), quenched with brine (110 mL) and extracted with CH_2Cl_2 (3×110 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:Et_2O [50:50]) to provide **234** as a white foam (708 mg, 74% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3503 (broad; O-H), 2977 (C-H), 2931 (C-H), 1775 (C=O), 1703 (C=O), 1299, 1151.

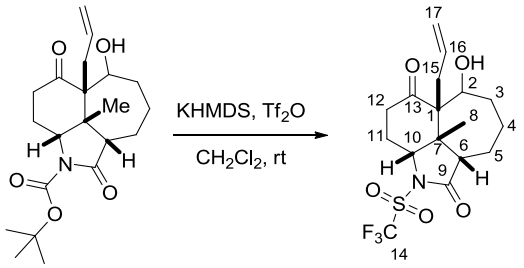
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.51 (app ddt, 1H, H-18, J = 17.0, 10.0, 7.5 Hz), 5.18-5.09 (m, 2H, H-19), 4.44 (br dd, 1H, H-2, J = 5.0, 2.0 Hz), 4.06 (dd, 1H, H-10, J = 11.0, 6.0 Hz), 3.07 (dd, 1H, H-17_a, J = 14.0, 7.5 Hz), 2.56 (app dtd, 1H, H-11_a, J = 13.5, 5.5, 3.5 Hz), 2.52-2.42 (m, 2H, H-6 & H-12_a), 2.40-2.30 (m, 3H, H-3_a & H-12_b & H-17_b), 2.15-2.08 (m, 1H, H-5_a), 1.83-1.71 (m, 3H, H-3_b & H-4_a & H-11_b), 1.69-1.57 (m, 1H, H-4_b), 1.56 (s, 9H, H-16), 1.51 (s, 3H, H-8), 1.46-1.27 (m, 1H, H-5_b).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 210.1 (C-13), 176.2 (C-9), 150.2 (C-14), 132.5 (C-18), 119.3 (C-19), 83.4 (C-15), 72.8 (C-2), 63.6 (C-10), 59.4 (C-6), 58.7 (C-1), 47.2 (C-7), 39.6 (C-17), 36.7 (C-12), 32.3 (C-3), 29.5 (C-5), 28.2 (C-11), 28.1 (C-16), 27.9 (C-8), 24.8 (C-4).

m/z (ES+) 400 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{31}NNaO_5^+$) requires ***m/z*** 400.2094, found ***m/z*** 400.2078.

5.4.5 Synthesis and characterisation of racemic (2aS,6aS,9aR,9bS)-6-hydroxy-9b-methyl-6a-(prop-2-en-1-yl)-1-[(trifluoromethyl)sulfonyl]decahydro-1H-cyclohepta[cd]indole-2,7-dione (236):



To a solution of **234** (12 mg, 0.032 mmol) in anhydrous CH_2Cl_2 (3.2 mL) at rt under a nitrogen atmosphere, was added KHMDS (0.5 M solution in toluene, 71 μL, 0.035 mmol) dropwise. After 10 min Tf_2O (16 μL, 0.095 mmol) was added dropwise. After 30 min the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and then extracted with Et_2O (3×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:Et_2OAc [70:30→50:50]) to provide **236** as a yellow film (3.5 mg, 27% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3561 (broad; O-H), 2918 (C-H), 2867 (C-H), 1767 (C=O), 1702 (C=O), 1408, 1209, 1140.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.49 (app ddt, 1H, H-16, J = 17.0, 10.0, 7.5 Hz), 5.19-5.13 (m, 2H, H-17), 4.46 (app br d, 1H, H-2, J = 4.0 Hz), 4.22 (dd, 1H, H-10, J = 12.0, 6.0 Hz), 3.07 (dd, 1H, H-15_a, J = 14.0, 7.5 Hz), 2.68-2.60 (m, 2H, H-6 & H-11_a), 2.51 (app td, 1H, H-12_a, J = 15.0, 5.5 Hz), 2.40 (app dt, 1H, H-12_b, J = 15.0, 3.5 Hz), 2.39-2.35 (m, 1H, H-3_a), 2.34 (dd, 1H, H-15_b, J = 14.0, 7.5 Hz), 2.12 (m, 1H, H-5_a), 2.02 (dddd, 1H, H-11_b, J =

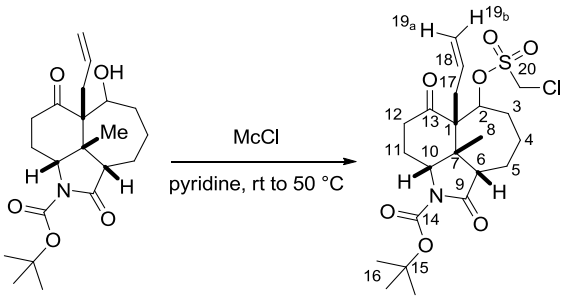
15.5, 14.0, 12.0, 4.0 Hz), 1.83-1.74 (m, 2H, H-3_b & H-4_a), 1.68 (m, 1H, H-4_b), 1.59 (s, 3H, H-8), 1.46 (m, 1H, H-5_b).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 208.3 (C-13), 175.2 (C-9), 131.8 (C-16), 119.9 (C-17), 119.3 (q, C-14, J_{CF} = 321.0 Hz) 72.8 (C-2), 67.0 (C-10), 58.8 (C-1), 58.4 (C-6), 48.7 (C-7), 39.6 (C-15), 36.4 (C-12), 32.1 (C-3), 29.7 (C-5 or C-11), 29.5 (C-5 or C-11), 27.5 (C-8), 24.9 (C-4).

m/z (ES+) 432 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}F_3NNaO_5S^+$) requires ***m/z*** 432.1063, found ***m/z*** 432.1067.

5.4.6 Synthesis and characterisation of racemic tert-butyl (2aS,6aS,9aR,9bS)-6-{[(chloromethyl)sulfonyl]oxy}-9b-methyl-2,7-dioxo-6a-(prop-2-en-1-yl)dodecahydro-1H-cyclohepta[cd]indole-1-carboxylate (237):



To a solution of **234** (10 mg, 0.026 mmol) in pyridine (1 mL) at rt under a nitrogen atmosphere, was added McCl (10 μL, 0.11 mmol) dropwise and after 1 h the reaction was heated to 50 °C (oil-bath temp). A further portion of McCl (10 μL, 0.11 mmol) was added dropwise and after 2h 15 min the reaction was cooled to rt and diluted with EtOAc (12 mL) before being washed with a saturated aqueous solution of $CuSO_4$ (1×5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with toluene:acetone [96:4 →60:40]) to provide **237** as an orange oil (7.0 mg, 54% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2930 (C-H), 1779 (C=O), 1741 (C=O), 1706 (C=O), 1458, 1369, 1155.

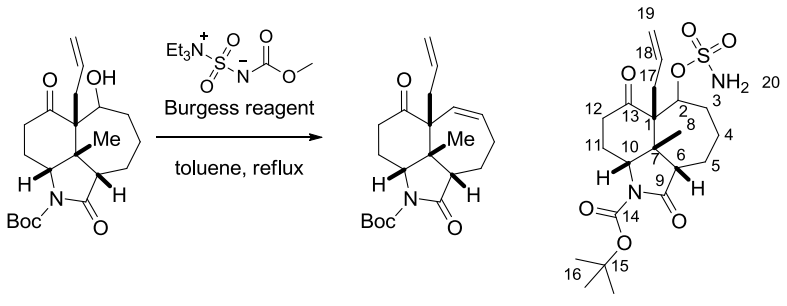
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 5.56-5.43 (m, 2H, H-2 & H-18), 5.30 (dd, 1H, H-19_a, J = 17.0, 1.0 Hz), 5.23 (dd, 1H, H-19_b, J = 10.0, 1.0 Hz), 4.64 (d, 1H, H-20_a, J = 12.0 Hz), 4.60 (d, 1H, H-20_b, J = 12.0 Hz), 4.08 (dd, 1H, H-10, J = 12.0, 5.5 Hz), 2.94 (dd, 1H, H-17_a, J = 14.5, 7.5 Hz), 2.61 (app dtd, 1H, H-11_a, J = 14.0, 5.5, 3.0 Hz), 2.53-2.34 (m, 6H, H-4_a or H-5_a & H-6 & H-12 & H-17_b), 2.26-2.15 (m, 2H, H-3), 1.93-1.82 (m, 1H, H-4_b or H-5_b), 1.82-1.75 (m, 1H, H-11_b), 1.70-1.58 (m, 1H, H-4_b or H-5_b), 1.57 (s, 9H, H-16), 1.46 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 208.0 (C-13), 175.1 (C-9), 150.0 (C-14), 130.4 (C-18), 121.3 (C-19), 87.2 (C-2), 83.8 (C-15), 63.4 (C-10), 59.5 (C-6), 58.9 (C-1), 54.6 (C-20), 47.5 (C-7), 39.5 (C-17), 36.6 (C-12), 30.0 (C-4 or C-5), 29.5 (C-3), 28.05 (C-16), 27.96 (C-11), 27.5 (C-8), 25.1 (C-4 or C-5).

m/z (ES+) 512 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{32}ClNNaO_7S^+$) requires ***m/z*** 512.1480, found ***m/z*** 512.1464.

5.4.7 Synthesis and characterisation of racemic tert-butyl (2aS,6aR,9aR,9bS)-9b-methyl-2,7-dioxo-6a-(prop-2-en-1-yl)-2,2a,3,4,6a,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (235) & racemic tert-butyl (2aS,6aS,9aR,9bS)-9b-methyl-2,7-dioxo-6a-(prop-2-en-1-yl)-6-(sulfamoyloxy)dodecahydro-1H-cyclohepta[cd]indole-1-carboxylate (239):



To a refluxing solution of **234** (30 mg, 0.079 mmol) in anhydrous toluene (1.2 mL, oil-bath temp= 120 °C) under a nitrogen atmosphere, was added Burgess reagent (40 mg, 0.17

mmol) as a solution[i] in anhydrous toluene (2 mL) dropwise *via* syringe. After 5 h 15 min the reaction was cooled to rt and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15→0:100]) to provide as a white foam (16 mg, 56% yield) followed by **239** as a pale yellow oil (5.7 mg, 16%).

Data for 235**:** ***vide infra*** **section** 5.4.8.

Data for 239**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3340 & 3259 (NH_2), 2935 (C-H), 1775 (C=O), 1703 (C=O), 1371, 1155.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.54 (app ddt, 1H, H-18, *J* = 17.0, 10.0, 7.0 Hz), 5.28-5.15 (m, 3H, H-2 & H-19), 5.11 (s, 2H, H-20), 4.07 (dd, 1H, H-10, *J* = 11.5, 5.5 Hz), 2.97 (dd, 1H, H-17_a, *J* = 14.0, 7.0 Hz), 2.58 (app dtd, 1H, H-11_a, *J* = 14.0, 5.5, 3.5 Hz), 2.47-2.42 (m, 2H, H-6 & H-12_a), 2.41-2.31 (m, 4H, H-4 & H-12_b & H-17_b), 2.17 (app br dd, 1H, H-5_a, *J* = 14.5, 4.5 Hz), 1.87-1.76 (m, 2H, H-3_a & H-11_b), 1.71-1.66 (m, 1H, H-3_b), 1.56 (s, 9H, H-16), 1.47 (s, 3H, H-8), 1.46-1.37 (m, 1H, H-5_b).

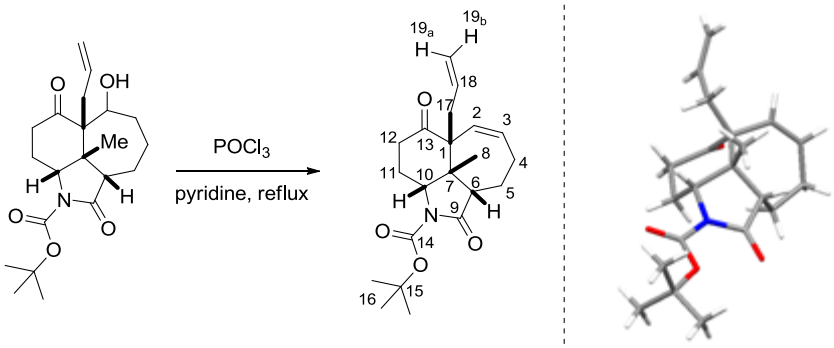
^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 208.2 (C-13), 175.7 (C-9), 150.0 (C-14), 131.1 (C-18), 120.5 (C-19), 85.7 (C-2), 83.8 (C-15), 63.5 (C-10), 59.4 (C-6), 59.1 (C-1), 47.5 (C-7), 39.5 (C-17), 36.7 (C-12), 29.7 (C-5), 29.1 (C-4), 28.1 (C-16), 27.9 (C-11), 27.5 (C-8), 25.0 (C-3).

m/z (ES+) 479 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{32}N_2NaO_7S^+$) requires ***m/z*** 479.1822, found ***m/z*** 479.1818.

[i] The Burgess reagent/inner-salt is not completely solvated in toluene.

5.4.8 Synthesis and characterisation of racemic tert-butyl (2aS,6aR,9aR,9bS)-9b-methyl-2,7-dioxo-6a-(prop-2-en-1-yl)-2,2a,3,4,6a,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (235):



To a solution of **234** (236 mg, 0.625 mmol) in pyridine (12 mL) at reflux under a nitrogen atmosphere, was added $POCl_3$ (290 μL, 3.11 mmol) dropwise. After 45 min the reaction was cooled, diluted with CH_2Cl_2 (12 mL), quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide **235** as a white foam (161 mg, 72% yield). Recrystallised from Et_2O and CH_2Cl_2 to provide **235** as a white crystalline solid.

mp 153-156 °C.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2924 (C-H), 2853 (C-H), 1780 (C=O), 1745 (C=O), 1715 (C=O), 1463, 1306, 1152.

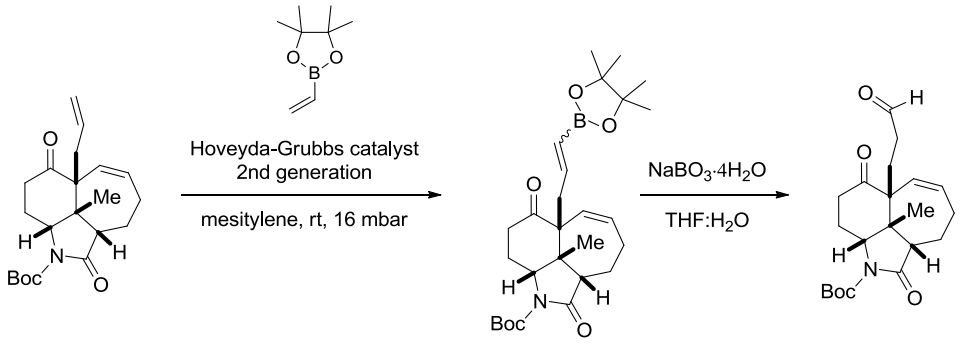
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.84 (ddd, 1H, H-3, J = 12.0, 5.5, 2.5 Hz), 5.51 (dddd, 1H, H-18, J = 17.0, 10.0, 8.0, 6.5 Hz), 5.25 (ddd, 1H, H-2, J = 12.0, 2.5, 1.5 Hz), 5.15 (dd, 1H, H-19_a, J = 17.0, 1.0 Hz), 5.10 (app d, 1H, H-19_b, J = 10.0 Hz), 4.20 (dd, 1H, H-10, J = 10.5, 6.5 Hz), 2.73 (app dtd, 1H, H-11_a, J = 14.0, 6.5, 3.5 Hz), 2.61 (app td, 1H, H-12_a, J = 15.0, 6.5 Hz), 2.57-2.35 (m, 4H, H-4_a & H-12_b & H-17), 2.31-2.20 (m, 1H, H-4_b), 2.15 (app d, 1H, H-6, J = 11.0 Hz) 1.99 (app dd, 1H, H-5_a, J = 14.5, 6.5 Hz), 1.91-1.74 (m, 2H, H-5_b & H-11_b), 1.56 (s, 9H, H-16), 1.30 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.3 (C-13), 175.6 (C-9), 150.0 (C-14), 133.3 (C-3), 131.4 (C-18), 127.5 (C-2), 119.1 (C-19), 83.0 (C-15), 60.6 (C-10), 56.4 (C-1), 55.8 (C-6), 49.3 (C-7), 42.4 (C-17), 35.4 (C-12), 30.4 (C-4), 29.8 (C-11), 28.1 (C-16), 26.1 (C-8), 24.6 (C-5).

m/z (ES+) 382 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{29}NNaO_4^+$) requires ***m/z*** 382.1989, found ***m/z*** 382.1986.

5.4.9 Synthesis and characterisation of racemic tert-butyl (2aS,6aR,9aR,9bS)-9b-methyl-2,7-dioxo-6a-(3-oxopropyl)-2,2a,3,4,6a,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (229):



To a round bottomed flask containing **235** (67.0 mg, 0.186 mmol) at rt, was added sequentially: vinylboronic acid pinacol ester (48.0 μL, 0.283 mmol), Hoveyda-Grubbs catalyst 2nd generation (11.7 mg, 0.0187 mmol) and anhydrous CH_2Cl_2 (4 mL). The reaction was flushed with nitrogen and then placed in a preheated oil-bath at 40 °C for 24 h. The reaction was cooled to rt and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with C_6H_6:EtOAc [84:16]) to provide **243** as a 1:1.4 mixture of *Z* and *E* isomers as a dark brown oil (74.6 mg, 82%

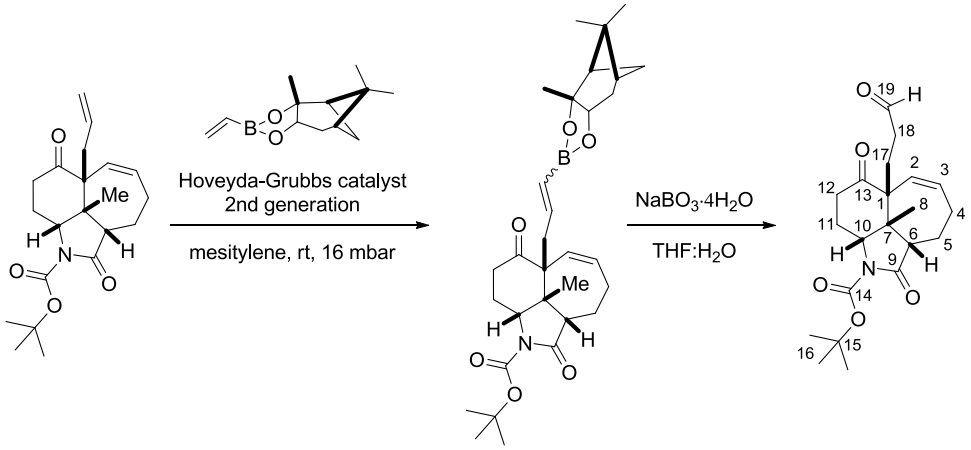
yield).[i] NMR spectra of **243** were complicated by the presence of the diastereoisomeric species. The connectivity in **243** was confirmed by spectroscopic data and by full assignment of the oxidised product, **229**, obtained in the following step.

To a solution of the mixture of diastereoisomers of **243** (74.6 mg, 0.154 mmol) in anhydrous THF (6.2 mL) at rt, was added H_2O (6.2 mL) and then $NaBO_3 \cdot 4H_2O$ (142 mg, 0.923 mmol) portion-wise. After 1 h of vigorous stirring, brine (5 mL) and H_2O (5 mL) were added sequentially. The reaction was then extracted with Et_2O (3×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with C_6H_6:EtOAc [80:20]) to provide **229** as a white foam (30.5 mg, 53% yield or 44% over two steps).

Data for 229**:** ***vide infra*** **section** 5.4.10**.**

[i] This yield is not representative as Ru-species were clearly present in the isolated product because of the dark colouration.

5.4.10 Synthesis and characterisation of racemic tert-butyl (2aS,6aR,9aR,9bS)-9b-methyl-2,7-dioxo-6a-(3-oxopropyl)-2,2a,3,4,6a,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (229):



To a round bottomed flask containing **235** (100.0 mg, 0.2782 mmol) at rt, was added Hoveyda-Grubbs catalyst 2nd generation (34.90 mg, 0.05570 mmol) and then (+)-vinylboronic acid pinanediol ester (97.5 mg, 0.4731 mmol) as a solution in mesitylene (10 mL). A further 10 mL of mesitylene was added to the reaction mixture before the flask was sealed with a rubber septum and subsequently subjected to a reduced pressure of 16 mbar (a needle connected to a vacuum line was used to attain this pressure). After 21 h the reaction was directly purified by flash column chromatography (eluted with CH_2Cl_2[i] followed by C_6H_6:Et_2O [90:10→80:20→0:100]) to provide **245** as a mixture of 4 inseparable diastereoisomers as an off-white foam (135.5 mg, 91% yield).

NMR spectra of **245** were complicated by the presence of diastereoisomeric species. The connectivity in **245** was confirmed by spectroscopic data and by full assignment of the oxidised product, **229**, obtained in the following step.

To a solution of the mixture of diastereoisomers of **245** (133.0 mg, 0.2474 mmol) in anhydrous THF (23 mL) at rt, was added $NaBO_3 \cdot 4H_2O$ (228.4 mg, 1.484 mmol) in one

[i] CH_2Cl_2 was used to remove the mesitylene as well as the Hoveyda-Grubbs catalyst 2nd generation.

portion and then H_2O (2300 μL) dropwise. After 1 h 30 min of vigorous stirring Na_2SO_4 (31.5 g) was added portion-wise. After 5 min the insoluble precipitates were filtered off and washed multiple times with EtOAc. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with PE:Et_2O [60:40→40:60]) to provide **229** as a white foam (63.30 mg, 68% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2970 (C-H), 2932 (C-H), 2852 (C-H), 1777 (C=O), 1743 (C=O), 1713 (C=O), 1150.

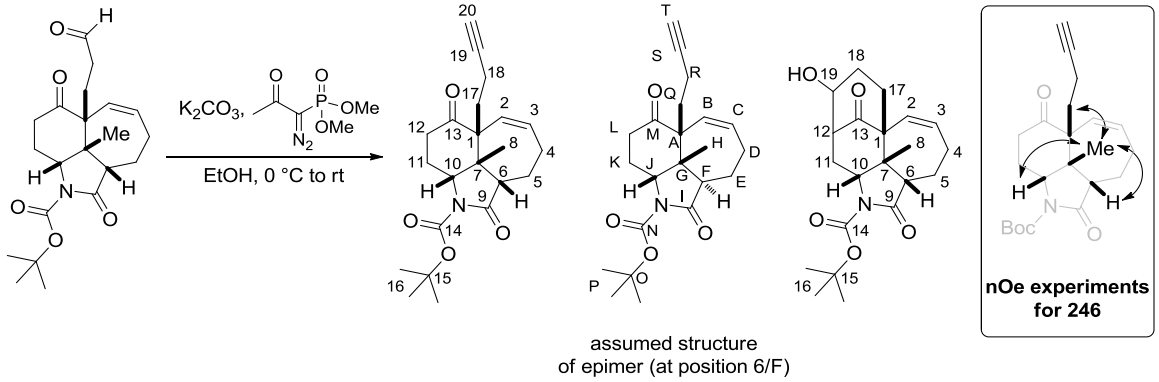
^{1}H NMR (C_6D_6, 500 MHz) δ_H 9.10 (s, 1H, H-19), 5.39 (ddd, 1H, H-3, *J* = 12.0, 5.5, 2.5 Hz), 4.54 (ddd, 1H, H-2, *J* = 12.0, 3.0, 1.5 Hz), 3.98 (dd, 1H, H-10, *J* = 10.0, 6.5 Hz), 2.48 (app dtd, 1H, H-11_a, *J* = 14.0, 6.5, 4.0 Hz), 2.06 (app br ddtd, 1H, H-4_a, *J* = 19.0, 5.5, 3.0, 1.5 Hz), 1.93-1.84 (m, 3H, H-5_a & H-6 & H-12_a), 1.83-1.67 (m, 3H, H-4_b & H-12_b & H-18_a), 1.65-1.57 (m, 1H, H-5_b), 1.56-1.44 (m, 11H, H-11_b & H-16 & H-18_b), 1.37-1.29 (m, 2H, H-17), 0.80 (s, 3H, H-8).

^{13}C NMR (C_6D_6, 125 MHz) δ_C 208.6 (C-13), 199.5 (C-19), 174.1 (C-9), 151.6 (C-14), 133.5 (C-3), 128.5 (C-2), 83.0 (C-15), 60.6 (C-10), 56.5 (C-6), 55.5 (C-1), 49.2 (C-7), 39.0 (C-18), 35.3 (C-12), 30.6 (C-4), 29.7 (C-11), 29.3 (C-17), 28.5 (C-16), 26.1 (C-8), 25.2 (C-5).

m/z (ES+) 430 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{33}NNaO_6^+$) requires ***m/z*** 430.2200, found ***m/z*** 430.2197.

5.4.11 Synthesis and characterisation of racemic tert-butyl (2aS,6aR,9aR,9bS)-6a-(but-3-yn-1-yl)-9b-methyl-2,7-dioxo-2,2a,3,4,6a,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (246) and tert-butyl (2aR,6aR,9aR,9bS)-6a-(but-3-yn-1-yl)-9b-methyl-2,7-dioxo-2,2a,3,4,6a,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (247) and tert-butyl (2aS,6aR,11aR,11bS)-9-hydroxy-11b-methyl-2,12-dioxo-2a,3,4,7,8,9,10,11,11a,11b-decahydro-6a,10-methano-1-azacycloocta[cd]azulene-1(2H)-carboxylate (248):[i]



To a solution of **229** (13.7 mg, 0.036 mmol) and diazophosphonate **212** (8.40 mg, 0.044 mmol) in EtOH (1.8 mL) at 0 °C under a nitrogen atmosphere, was added anhydrous K_2CO_3 (10.0 mg, 0.072 mmol) in one portion. After 5 h the mixture was concentrated under reduced pressure, diluted with EtOAc (5 mL) and then quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). After extraction with EtOAc (2×10 mL) the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20]) to provide an assumed mixture of alkyne epimers (**246**:**247**, 1:0.55) as a colourless oil (2.60 mg, 19% yield), the desired product **246** as a colourless oil (3.90 mg, 29% yield) and the undesired aldol product **248** as a colourless oil (1.80 mg, 13% yield).

[i] With the exception of the desired product, there is ambiguity regarding the naming of the molecules as the relative stereochemistry was not concluded.

Data for single isomer 246**:**

IR (film)/cm^{-1} ν_{max} 3263 (C≡C-H), 2980 (C-H) , 2966 (C-H), 1780 (C=O), 1746 (C=O), 1713 (C=O), 1327, 1305, 1150.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.85 (ddd, 1H, H-3, *J* = 11.5, 5.5, 2.5 Hz), 5.15 (app br dt, 1H, H-2, *J* = 11.5, 2.5 Hz), 4.20 (dd, 1H, H-10, *J* = 9.5, 6.5 Hz), 2.76-2.61 (m, 2H, H-11_a & H-12_a), 2.50-2.43 (m, 1H, H-12_b), 2.41-2.33 (m, 1H, H-4_a), 2.30-2.20 (m, 1H, H-4_b), 2.17-1.96 (m, 6H, H-5_a & H-6 & H-17 & H-18_a & H-20), 1.94-1.83 (m, 1H, H-11_b), 1.82-1.71 (m, 2H, H-5_b & H-18_b), 1.56 (s, 9H, H-16), 1.30 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.6 (C-13), 175.5 (C-9), 149.9 (C-14), 133.8 (C-3), 127.0 (C-2), 83.5 (C-15), 82.9 (C-19), 69.3 (C-20), 60.6 (C-10), 55.8 (C-1 or C-6), 55.7 (C-1 or C-6), 49.3 (C-7), 36.9 (C-17), 35.3 (C-12), 30.1 (C-4), 29.5 (C-11), 28.1 (C-16), 26.1 (C-8), 24.5 (C-5), 13.5 (C-18).

m/z (ES+) 394 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{29}NNaO_4^+$) requires ***m/z*** 394.1989 found ***m/z*** 394.1984.

NMR data for mixture of assumed isomers 246 **&** 247 **(for ease of interpretation, the integrations below are indicated as if each isomer was isolated in 100% purity):**

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.04 (ddd, 1H, H-**C**, *J* = 12.5, 9.0, 3.5 Hz), 5.85 (ddd, 1H, H-3, *J* = 11.5, 5.5, 2.5 Hz), 5.21-5.13 (m, 2H, H-2 & H-**B**), 4.26-4.16 (m, 2H, H-10 & H-**J**), 2.75-2.61 (m, 4H, H-11_a & H-$\mathbf{K_a}$ & H-12_a & H-$\mathbf{L_a}$), 2.52-1.70 (m, 21H, H-4 & H-D & H-5 & H-$\mathbf{E_a}$ & H-6 & H-**F** & H-11_b & H-$\mathbf{K_b}$ & H-12_b & H-$\mathbf{L_b}$ & H-17 & H-**Q** & H-18 & H-**R**), 1.57-1.55 (m, 18H, H-16 & H-**P**), 1.30 (s, 3H, H-8), 1.16 (s, 3H, H-**H**).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.6 (C-13 & C-**M**), 175.5 (C-9), 172.6 (C-**I**), 150.1 (C-**N**), 149.9 (C-14), 133.8 (C-3), 133.7 (C-**C**), 128.7 (C-**B**), 127.0 (C-2), 83.5 (C-15 & C-**O**), 82.9 (C-19), 82.7 (C-**S**), 69.5 (C-**T**), 69.3 (C-20), 60.6 (C-10), 59.6 (C-**A**), 59.2 (C-**J**), 55.8

(C-1 or C-6), 55.7 (C-1 or C-6), 53.2 (C-**F**), 49.3 (C-7), 47.4 (C-**G**), 36.9 (C-17), 35.7 (C-**L**), 35.3 (C-12), 34.8 (C-**Q**), 30.1 (C-4), 29.5 (C-11), 28.1 (C-16 & C-**P**), 27.5 (C-**D**), 27.2 (C-**K**), 26.1 (C-8), 24.5 (C-5), 20.7 (C-**E**), 19.4 (C-**H**), 13.8 (C-**R**), 13.5 (C-18).

Data for undesired aldol product 248**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3486 (broad; O-H), 2963 (C-H), 2917 (C-H), 2850 (C-H), 1776 (C=O), 1747 (C=O), 1714 (C=O), 1301, 1150.

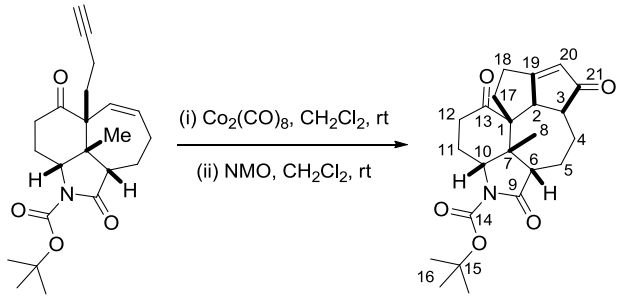
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.82 (ddd, 1H, H-3, *J* = 11.5, 6.0, 3.0 Hz), 4.96 (ddd, 1H, H-2, *J* = 11.5, 2.5, 1.5 Hz), 4.38 (dd, 1H, H-10, *J* = 11.0, 7.5 Hz), 4.16 (app dt, 1H, H-19, *J* = 11.5, 6.0 Hz), 3.20 (ddd, 1H, H-11_a, *J* = 14.5, 7.5, 2.0 Hz), 2.93 (app td, 1H, H-12, *J* = 5.0, 2.0 Hz), 2.47-2.38 (m, 1H, H-4_a), 2.33-2.20 (m, 2H, H-4_b & H-17_a), 2.16-2.08 (m, 2H, H-6 & H-18_a), 1.98 (app dd, 1H, H-5_a, *J* = 14.5, 7.5 Hz), 1.86-1.73 (m, 3H, H-5_b & H-11_b & H-18_b), 1.56 (s, 9H, H-16), 1.44 (app td, 1H, H-17_b, *J* = 15.0, 5.0 Hz), 1.32 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 211.2 (C-13), 175.3 (C-9), 149.9 (C-14), 133.1 (C-3), 127.8 (C-2), 83.6 (C-15), 72.8 (C-19), 60.8 (C-10), 56.1 (C-6), 53.4 (C-1 or C-12), 53.3 (C-1 or C-12), 49.3 (C-7), 35.2 (C-17), 30.3 (C-4 or C-11 or C-18), 30.2 (C-4 or C-11 or C-18), 30.0 (C-4 or C-11 or C-18), 28.0 (C-16), 25.6 (C-8), 24.7 (C-5).

m/z (ES+) 398 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{29}NNaO_5^+$) requires ***m/z*** 398.1938 found ***m/z*** 398.1926.

5.4.12 Synthesis and characterisation of racemic tert-butyl (3aR,5aS,7aS,9bR,11aR,11bS)-11b-methyl-1,5,8-trioxo-2,3,3a,5a,6,7,7a,8,9b,10,11,11b-dodecahydro-1H-cyclopenta[1,8]azuleno[5,4,3a-cd]indole-4(5H)-carboxylate (249):[i]



To a solution of mixture of epimers **246**:**247** (1:1.35)[ii] (2.3 mg, 6.2 μmol) in anhydrous CH_2Cl_2 (0.8 mL) at rt under an argon atmosphere, was added $Co_2(CO)_8$ (2.5 mg, 7.3 μmol) in one portion. After 2 h 20 min NMO (6.5 mg, 55 μmol) was added in one portion. After 1 h 20 min the resulting violet heterogeneous reaction was filtered on a pad of Celite® and washed multiple times with CH_2Cl_2. The filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [30:70]) to provide **249**[iii] as a yellow film (900 μg, 36% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ the acquired spectrum was too weak to detect any significant peaks over the baseline's noise.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.93 (br s, 1H, H-20), 4.07 (dd, 1H, H-10, J = 7.0, 2.5 Hz), 3.13 (m, 1H, H-2), 2.89-2.81 (m, 1H, H-18_a), 2.65-1.99 (m, 11H, H-3 & H-4_a & H-5_a & H-

[i] There is ambiguity regarding the naming of **249** as the relative stereochemistry was not concluded.

[ii] This experiment was repeated with the purified alkyne **246** (stereochemistry confirmed by nOe experiments). Although the same peaks were detected in the product's ^{1}H NMR spectrum, it was heavily contaminated by unknown inseparable impurities. The less successful outcome of this second attempt was attributed to the bad quality of the reagents having a deleterious effect on the small scale reaction, and not the starting material **246**.

[iii] This was contaminated with unknown inseparable impurities one of which could be a diastereoisomer of **249**. However, due to the small scale of the experiment and the failure to separate/purify the products, this remains unconfirmed.

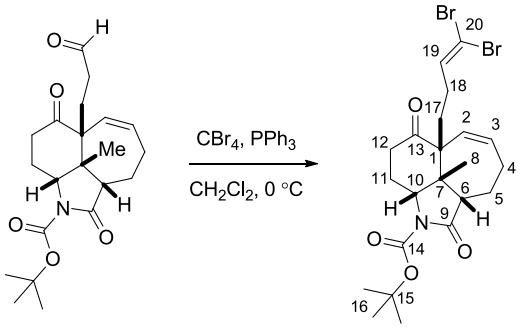
6 & H-11 & H-12 & H-17 & H-18$_b$), 1.56 (s, 9H, H-16), 1.46-1.35 (m, 1H, H-4$_b$), 1.25 (s, 3H, H-8), 1.19-1.08 (m, 1H. H-5$_b$).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 210.5 (C-13 or C-21), 210.0 (C-13 or C-21), 181.8 (C-19), 171.8 (C-9), 150.4 (C-14), 124.5 (C-20), 83.5 (C-15), 59.9 (C-1), 58.7 (C-10), 54.9 (C-6), 54.4 (C-2), 48.5 (C-3),44.4 (C-7), 34.8 (C-12), 30.3 (C-17), 28.1 (C-16), 25.5 (C-5 or C-11 or C-18), 25.4 (C-5 or C-11 or C-18), 25.3 (C-5 or C-11 or C-18), 21.8 (C-4), 16.0 (C-8).

m/z (ES+) 422 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{23}H_{29}NNaO_5^+$) requires ***m/z*** 422.1938 found ***m/z*** 422.1921.

5.4.13 Synthesis and characterisation of racemic tert-butyl (2aS,6aR,9aR,9bS)-6a-(4,4-dibromobut-3-en-1-yl)-9b-methyl-2,7-dioxo-2,2a,3,4,6a,7,8,9,9a,9b-decahydro-1H-cyclohepta[cd]indole-1-carboxylate (251):



To a solution of CBr_4 (508.8 mg, 1.534 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C under a nitrogen atmosphere, was added PPh_3 (804.8 mg, 3.068 mmol) as a solution in anhydrous CH_2Cl_2 (2 mL) dropwise (a total of 2 mL of anhydrous CH_2Cl_2 used for washings). After 30 min **229** (80.00 mg, 0.2131 mmol) was added as a solution in anhydrous CH_2Cl_2 (2 mL) dropwise (a total of 2 mL of anhydrous CH_2Cl_2 used for washings). After 40 min the reaction was quenched with a saturated solution of $NaHCO_3$ (24 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and

concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:Et_2O [60:40]) to provide **251** as a white foam (104.8 mg, 93% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2966 (C-H), 1779 (C=O), 1744 (C=O), 1713 (C=O), 1305, 1150.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.41 (t, 1H, H-19, J = 7.5 Hz), 5.86 (ddd, 1H, H-3, J = 12.0, 5.5, 2.5 Hz), 5.18 (br ddd, 1H, H-2, J = 12.0, 2.5, 1.5 Hz), 4.18 (dd, 1H, H-10, J = 10.0, 6.5 Hz), 2.78-2.61 (m, 2H, H-11_a & H-12_a), 2.53-2.44 (m, 1H, H-12_b), 2.44-2.35 (m, 1H, H-4_a), 2.32-2.20 (m, 1H, H-4_b), 2.15 (app br d, 1H, H-6, J = 11.5 Hz), 2.04-1.93 (m, 2H, H-5_a & H-18_a), 1.93-1.83 (m, 2H, H-11_b & H-17_a), 1.83-1.63 (m, 3H, H-5_b & H-17_b & H-18_b), 1.56 (s, 9H, H-16), 1.28 (s, 3H, H-8).

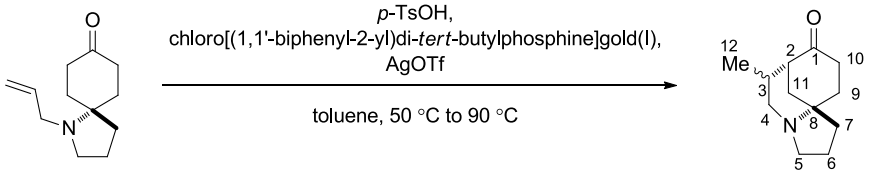
^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.7 (C-13), 175.5 (C-9), 149.9 (C-14), 136.4 (C-19), 133.8 (C-3), 127.3 (C-2), 90.8 (C-20), 83.6 (C-15), 60.6 (C-10), 55.8 (C-1 or C-6), 55.7 (C-1 or C-6), 49.4 (C-7), 35.4 (C-17), 35.2 (C-12), 30.1 (C-4), 29.6 (C-11), 28.1 (C-16), 27.7 (C-18), 26.1 (C-8), 24.5 (C-5).

m/z (ES+) 554 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{29}Br_2NNaO_4^+$) requires ***m/z*** 552.0356, 554.0337 & 556.0316 found ***m/z*** 552.0358, 554.0339 & 556.0326.

5.5 Experimental Chapter 4

5.5.1 Synthesis and characterisation of racemic (6S,7R,10aS)-6-methylhexahydro-1H-7,10a-methanopyrrolo[1,2-a]azocin-8(5H)-one (280):[i]



To a solution of **278** (15.0 mg, 0.0776 mmol)[ii] in anhydrous toluene (1.2 mL) at 50 °C (oil-bath temp) under a nitrogen atmosphere, was added *p*-TsOH (15.0 mg, 0.0871 mmol) in one portion. After 30 min chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I) (24.7 mg, 0.0465 mmol) and AgOTf (12.0 mg, 0.0467 mmol) were added sequentially followed by toluene (0.8 mL) for washing the sides of the flask. The temp of the oil-bath was then set to 90 °C. After 23 h the reaction was concentrated under reduced pressure. The crude product was purified twice by flash column chromatography (eluted with EtOAc:acetone [90:10→100:0] followed by CH_2Cl_2:MeOH [70:30]) to provide **280** as a pale yellow film (5.00 mg, 33% yield).[iii]

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2921 (C-H), 2850 (C-H), 1709 (C=O), 1279, 1030.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 3.20-3.13 (m, 1H, H-5_a), 3.05 (dd, 1H, H-4_a, J = 13.0, 5.5 Hz), 2.91 (br s, 1H, H-5_b), 2.70 (app t, 1H, H-4_b, J = 12.5 Hz), 2.59-2.50 (m, 2H, H-2 & H-10_a), 2.38-2.29 (m, 1H, H-10_b), 2.28-2.19 (m, 2H, H-3 & H-7_a), 2.04 (dd, 1H, H-11_a, J = 13.0, 3.5 Hz), 1.97-1.84 (m, 3H, H-6 & H-11_b), 1.76-1.63 (m, H-7_b & H-9), 0.87 (d, 3H, H-12, J = 7.0 Hz).

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[i] IUPAC name for one (the desired) of the possible diastereoisomers.

[ii] Provided by A. Y. Gammack.

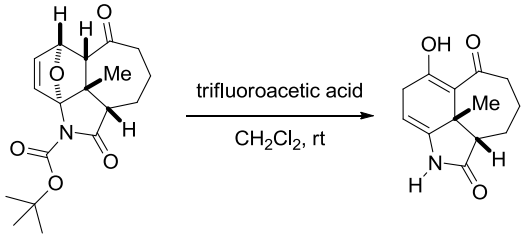
[iii] Mixed fractions including the second diastereoisomer were also isolated; overall 4.8 mg, 32% yield. However, this second diastereoisomer has not been confirmed.

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 212.7 (C-1), 57.6 (C-8), 52.5 (C-4), 51.2 (C-2), 50.3 (C-5), 39.6 (C-10), 37.9 (C-9), 36.2 (C-11), 30.8 (C-3), 29.4 (C-7), 20.2 (C-6), 16.5 (C-12).

m/z (ES+) 194 ($[M+H]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{20}NO^+$) requires ***m/z*** 194.1539, found ***m/z*** 194.1537.

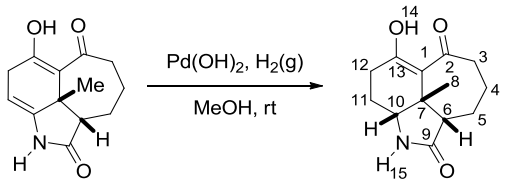
5.5.2 Synthesis of racemic (2aS,9bS)-7-hydroxy-9b-methyl-2a,3,4,5,8,9b-hexahydro-1H-cyclohepta[cd]indole-2,6-dione (165):



To a solution of **104** (2.913 g, 8.738 mmol) in anhydrous CH_2Cl_2 (130 mL) at rt under a nitrogen atmosphere with light protection,[i] was added trifluoroacetic acid (3300 μL, 43.10 mmol) dropwise. After 2 h 30 min the reaction was quenched with a saturated solution of $NaHCO_3$ (110 mL), diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3×80 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide a yellow oil. The crude product was used in the next step without further purification.

[i] The flask was covered with aluminium foil. The lactam is unstable to light and was thus used directly in the next step.

5.5.3 Synthesis and characterisation of racemic (2aS,9aR,9bS)-7-hydroxy-9b-methyl-2a,3,4,5,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,6-dione (281):



To a solution of **165** (assumed quantitative from previous step, 8.738 mmol) in MeOH (43 mL) at rt, was added $Pd(OH)_2$ (2.457 g, 1.750 mmol, 20% on carbon, nominally 50% water). The reaction was degassed using a vacuum at 85 mbar and then charged with H_2 (this operation was repeated 5 times).[i] After 24 h the reaction was filtered through a pad of Celite® and washed multiple times with MeOH. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with EtOAc:acetone [85:15])[ii] to provide **281** as a white solid (1.378 g, 67% yield).

mp 149-152 °C.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3220 (broad; N-H & O-H), 2950 (C-H), 2866 (C-H), 1691 (C=O), 1593 (β-diketone; enol form), 1452.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 15.99 (s, 1H, H-14), 6.80 (br s, 1H, H-15), 3.40 (dd, 1H, H-10, J = 11.0, 4.0 Hz), 2.68 (app dt, 1H, H-3_a, J = 13.5, 10.0 Hz), 2.46-2.39 (m, 2H, H-3_b & H-12_a), 2.30 (ddd, 1H, H-12_b, J = 17.5, 12.5, 4.5 Hz), 2.22-2.15 (m, 2H, H-5_a & H-6), 2.03 (app dq, 1H, H-11_a, J = 13.0, 4.5 Hz), 1.86-1.78 (m, 2H, H-4), 1.63-1.54 (m, 1H, H-5_b), 1.51-1.41 (m, 4H, H-11_b & H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 199.2 (C-2), 185.7 (C-13), 178.5 (C-9), 111.21 (C-1), 62.2 (C-10), 52.1 (C-6), 42.3 (C-7), 37.0 (C-3), 31.5 (C-8), 29.6 (C-12), 28.5 (C-11), 26.3 (C-5), 22.1 (C-4).

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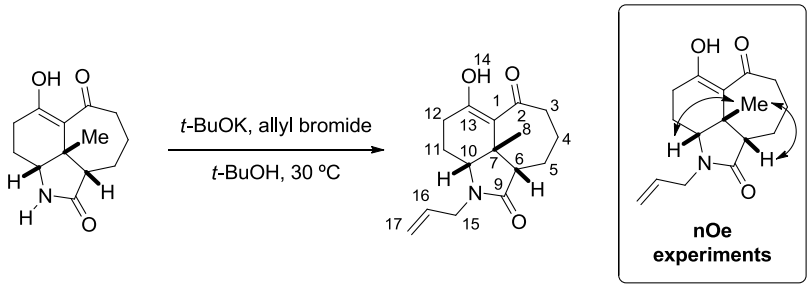
[i] H_2 was charged using a double-skinned balloon (one balloon inside another). Balloons were purchased from Aldrich Chemical Company, Inc. Model number: Z154997 (wall thickness 15 mm).

[ii] As **281** is very insoluble in organic solvents, the yields vary (50-84%) due to the purification method used (e.g. dry loading the column, loading with CH_2Cl_2, loading with EtOAc). The above procedure is a representative example.

m/z (ES+) 258 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{17}NNaO_3^+$) requires ***m/z*** 258.1101, found ***m/z*** 258.1099.

5.5.4 Synthesis and characterisation of racemic (2aS,9aR,9bS)-7-hydroxy-9b-methyl-1-(prop-2-en-1-yl)-2a,3,4,5,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,6-dione (282):



To a suspension of **281** (300 mg, 1.28 mmol) in *t*-BuOH (6 mL) at 30 °C under a nitrogen atmosphere, was added *t*-BuOK (472 mg, 4.21 mmol) in one portion. After 45 min allyl bromide[i] (360 μL, 4.16 mmol) was added dropwise. After 18 h the reaction was diluted with EtOAc (10 mL) and quenched with aqueous HCl (1 M, 12 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [50:50]) to provide **282** as a dark pink solid[ii] (288 mg, 82% yield).

mp 68-71 °C.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3473 (broad; O-H), 2952 (C-H), 2866 (C-H), 1683 (C=O), 1595 (*β*-diketone; enol form), 1454, 1262.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 16.57 (s, 1H, H-14), 5.75 (dddd, 1H, H-16, J = 17.5, 10.0, 8.0, 4.5 Hz), 5.21-5.29 (m, 2H, H-17), 4.43 (br ddt, 1H, H-15_a, J = 15.5, 4.5, 1.5 Hz), 3.54

[i] Allyl iodide can also be used; however allyl bromide gave more consistent results.
[ii] Often isolated as a dark yellow amorphous solid. Colouration depends on the extent of purity.

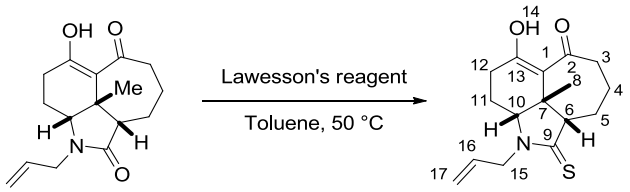
(dd, 1H, H-15$_b$, *J* = 15.5, 8.0 Hz), 3.28 (dd, 1H, H-10, *J* = 12.0, 5.0 Hz), 2.67 (app td, 1H, H-3$_a$, *J* = 12.5, 8.5 Hz), 2.36-2.46 (m, 2H, H-3$_b$ & H-12$_a$), 2.13-2.32 (m, 4H, H-5$_a$ & H-6 & H-11$_a$ & H-12$_b$), 1.75-1.90 (m, 2H, H-4), 1.46-1.57 (m, 2H, H-5$_b$), 1.38 (s, 3H, H-8), 1.23 (app qd, 1H, H-11$_b$, *J* = 12.5, 3.5 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 199.0 (C-2), 185.8 (C-13), 174.6 (C-9), 132.3 (C-16), 118.5 (C-17), 111.4 (C-1), 66.0 (C-10), 52.6 (C-6), 43.3 (C-15), 40.0 (C-7), 36.7 (C-3), 31.9 (C-8), 29.7 (C-12), 26.5 (C-5), 26.0 (C-11), 22.2 (C-4).

m/z (ES+) 298 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}NNaO_3^+$) requires ***m/z*** 298.1414, found ***m/z*** 298.1416.

5.5.5 Synthesis and characterisation of racemic (2aS,9aR,9bS)-7-hydroxy-9b-methyl-1-(prop-2-en-1-yl)-2-thioxo-1,2,2a,3,4,5,8,9,9a,9b-decahydro-6H-cyclohepta[cd]indol-6-one (283):



To a solution of **282** (16.0 mg, 0.058 mmol) in anhydrous toluene (1.2 mL) at 50 °C (oil-bath temp) under a nitrogen atmosphere was added Lawesson's reagent (30.6 mg, 0.076 mmol) in one portion. After 16 h 30 min the reaction was concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [85:15]) to provide **283** as a brown oil (10.0 mg, 59% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2952 (C-H), 2925 (C-H), 2863 (C-H), 1595 (*β*-diketone; enol form), 1499, 1267.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 16.46 (s, 1H, H-14), 5.85 (app ddq, 1H, H-16, *J* = 17.0, 7.5, 5.0 Hz), 5.35-5.30 (m, 2H, H-17), 5.02 (ddt, 1H, H-15$_a$, *J* = 5.0, 5.0, 1.5 Hz), 3.96-3.87

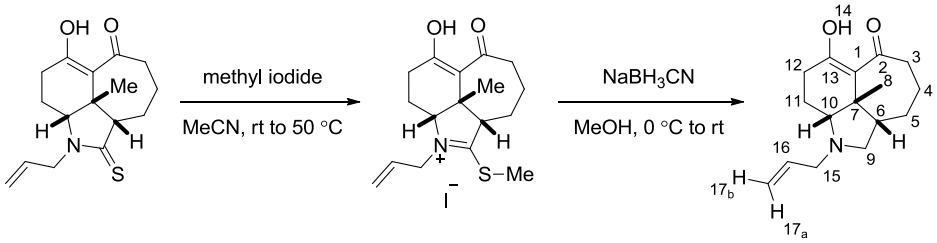
(m, 1H, H-15$_b$), 3.60 (dd, 1H, H-10, *J* = 12.5, 4.5 Hz), 2.78 (dd, 1H, H-6, *J* = 12.0, 1.5 Hz), 2.64 (app td, 1H, H-3$_a$, *J* = 13.0, 8.0 Hz), 2.53 (app dd, 1H, H-5$_a$, *J* = 14.0, 8.0 Hz), 2.49-2.39 (m, 2H, H-3$_b$ & H-12$_a$), 2.34-2.19 (m, 2H, H-11$_a$ & H-12$_b$), 2.00-1.90 (m, 1H, H-4$_a$), 1.87-1.78 (m, 1H, H-4$_b$), 1.59 (app dtd, 1H, H-5$_b$, *J* = 14.0, 12.0, 7.0 Hz), 1.39-1.30 (m, 4H, H-8 & H-11$_b$).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 203.6 (C-9), 199.1 (C-2), 184.8 (C-13), 130.3 (C-16), 119.7 (C-17), 111.3 (C-1), 73.7 (C-10), 64.5 (C-6), 49.0 (C-15), 41.8 (C-7), 36.7 (C-3), 31.6 (C-8), 29.9 (C-5), 29.7 (C-12), 25.6 (C-11), 22.5 (C-4).

m/z (ES+) 314 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}NNaO_2S^+$) requires ***m/z*** 314.1185, found ***m/z*** 314.1178.

5.5.6 Synthesis and characterisation of racemic (2aS,9aR,9bS)-7-hydroxy-9b-methyl-1-(prop-2-en-1-yl)-1,2,2a,3,4,5,8,9,9a,9b-decahydro-6H-cyclohepta[cd]indol-6-one (286):



To a solution of **283** (80.0 mg, 0.275 mmol) in MeCN (2.8 mL) under a nitrogen atmosphere was added methyl iodide (21.0 μL, 0.337 mmol) dropwise at rt. After 15 min the reaction was put in a preheated oil-bath at 50 °C. After 2 h 30 min a further portion of methyl iodide (64.0 μL, 1.03 mmol) was added dropwise. After 2 h the reaction was concentrated under reduced pressure.

The salt **285** was dissolved in MeOH (2.6 mL) and to this solution was added $NaBH_3CN$ (34.5 mg, 0.549 mmol) in one portion at rt. After 1 h 45 min a further portion of $NaBH_3CN$ (27.2 mg, 0.433 mmol) was added in one portion. After 45 min the reaction was quenched

with a saturated solution of $NaHCO_3$ (12.5 mL) and extracted with CH_2Cl_2 (5×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified twice by flash column chromatography (eluted with CH_2Cl_2:MeOH [99:1]) to provide **286** as a pale yellow oil (28.5+12.3= 40.8 mg, 57% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2928 (C-H), 2865 (C-H), 2785 (C-H), 1593 (β-diketone; enol form), 1455, 1410.

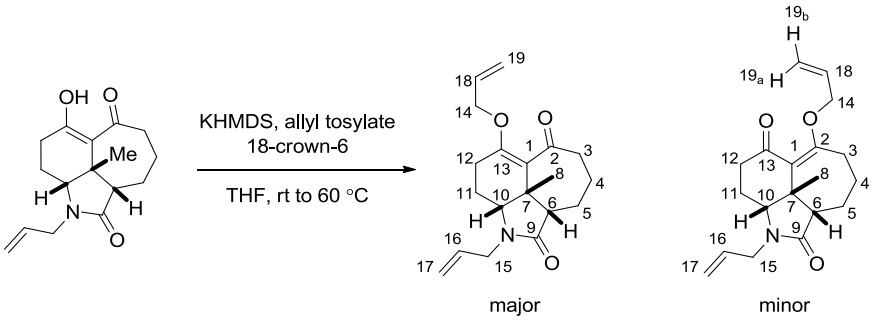
^{1}H NMR (C_6D_6, 500 MHz) δ_H 17.79 (s, 1H, H-14), 5.80 (dddd, 1H, H-16, J = 17.0, 10.0, 7.5, 5.0 Hz), 5.12 (app dq, 1H, H-17_a, J = 17.0, 2.0 Hz), 5.01 (app br dt, 1H, H-17_b, J = 10.0, 2.5 Hz), 3.08 (ddt, 1H, H-15_a, J = 14.0, 5.0, 2.0 Hz), 2.55-2.40 (m, 4H, H-3_a & H-9_a & H-12_a & H-15_b), 2.34-2.25 (m, 2H, H-3_b & H-9_b), 2.02-1.93 (m, 2H, H-10 & H-12_b), 1.52-1.13 (m, 7H, H-4 & H-5 & H-6 & H-11), 1.04 (s, 3H, H-8).

^{13}C NMR (C_6D_6, 125 MHz) δ_C 200.3 (C-2), 187.0 (C-13), 137.0 (C-16), 116.5 (C-17), 112.7 (C-1), 72.6 (C-10), 60.1 (C-9), 56.3 (C-15), 46.8 (C-6), 45.4 (C-7), 38.0 (C-3), 30.9 (C-4 or C-5 or C-11), 29.8 (C-8), 28.8 (C-12), 21.9 (C-4 or C-5 or C-11), 20.5 (C-4 or C-5 or C-11).

m/z (ES+) 262 ($[M+H]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}NO_2^+$) requires ***m/z*** 262.1802, found ***m/z*** 262.1798.

5.5.7 Synthesis and characterisation of racemic (2aS,9aR,9bS)-9b-methyl-1-(prop-2-en-1-yl)-7-(prop-2-en-1-yloxy)-2a,3,4,5,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,6-dione (289) and racemic (2aS,9aR,9bS)-9b-methyl-1-(prop-2-en-1-yl)-6-(prop-2-en-1-yloxy)-2a,3,4,5,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,7-dione (290):



To a solution of **282** (224 mg, 0.814 mmol) in anhydrous THF (7 mL) at rt under a nitrogen atmosphere, was added KHMDS (0.5 M solution in toluene, 1.80 mL, 0.900 mmol) dropwise. After 10 min allyl tosylate (230 μL, 1.28 mmol) was added dropwise followed by 18-crown-6 (65.0 mg, 0.246 mmol) and the reaction was then placed in a preheated oil-bath at 60 °C for 2 h 20 min. The reaction was filtered on a pad of Celite® and washed multiple times with EtOAc. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (eluted with PE:EtOAc [55:45→0:100]) to provide **289** as a pale yellow oil (160 mg, 62% yield) followed by **290** as a thick yellow oil (54.0 mg, 21% yield).[i]

Data for major product 289**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2927 (C-H), 1687 (C=O), 1597, 1450, 1416.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 5.84 (app ddt, 1H, H-18, *J* = 17.0, 10.5, 5.5 Hz), 5.73 (dddd, 1H, H-16, *J* = 17.5, 10.0, 8.0, 5.0 Hz), 5.28-5.15 (m, 4H, H-17 & H-19), 4.46 (ddt, 1H, H-15_a, *J* = 15.5, 5.0, 1.5 Hz), 4.2 (dt, 2H, H-14, *J* = 5.5, 1.5 Hz), 3.45 (app dd, 1H, H-15_b, *J* = 15.5, 7.5 Hz), 3.35 (dd, 1H, H-10, *J* = 6.0, 3.5 Hz), 2.63 (app dt, 1H, H-3_a, *J* =

[i] **290** is unstable to acidic conditions. NMR was initially taken in $CDCl_3$ but this slowly reconverts to the starting material therefore C_6D_6 was used as an alternative NMR solvent.

15.5, 5.5 Hz), 2.40 (ddd, 1H, H-3_b, *J* = 15.0, 9.5, 5.5 Hz), 2.32 (app dd, 1H, H-6, *J* = 6.5, 3.0 Hz), 2.21-2.08 (m, 3H, H-5_a & H-12), 1.94-1.84 (m, 2H, H-11), 2.32 (app dd, 1H, H-4_a, *J* = 6.5, 3.0 Hz), 1.74-1.63 (m, 2H, H-4_b & H-5_b), 1.25 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 209.9 (C-2), 175.0 (C-9), 149.1 (C-13), 133.5 (C-18), 132.4 (C-16), 122.6 (C-1), 118.3 (C-17), 117.4 (C-19), 68.8 (C-14), 60.9 (C-10), 54.7 (C-6), 44.6 (C-3), 43.2 (C-15), 40.6 (C-7), 26.3 (C-8), 25.6 (C-5), 22.5 (C-11), 21.4 (C-4), 20.2 (C-12).

m/z (ES+) 338 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{25}NNaO_3^+$) requires ***m/z*** 338.1727, found ***m/z*** 338.1722.

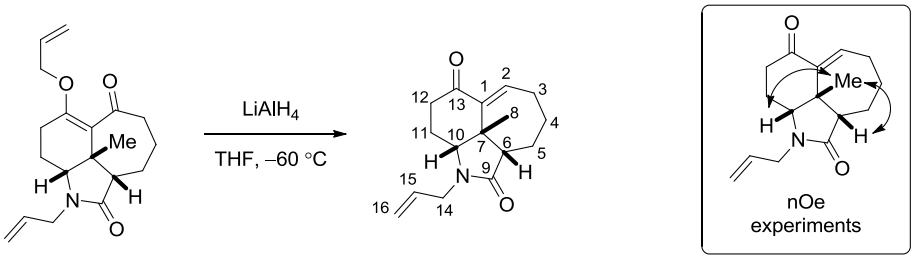
Data for minor product 290**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2941 (C-H), 1685 (C=O), 1449, 922.

^{1}H NMR (C_6D_6, 500 MHz) δ_H 5.79 (app ddt, 1H, H-18, *J* = 17.0, 10.5, 5.0 Hz), 5.54 (dddd, 1H, H-16, *J* = 17.0, 10.0, 7.0, 5.0 Hz), 5.29 (app dq, 1H, H-19_a, *J* = 17.0, 1.5 Hz), 5.01 (app dq, 1H, H-19_b, *J* = 10.5, 1.5 Hz), 4.98-4.92 (m, 2H, H-17), 4.26 (ddt, 1H, H-15_a, *J* = 15.0, 5.0, 1.5 Hz), 4.16 (ddt, 1H, H-14_a, *J* = 13.0, 5.0, 1.5 Hz), 3.98 (ddt, 1H, H-14_b, *J* = 13.0, 5.0, 1.5 Hz), 3.23 (dd, 1H, H-15_b, *J* = 15.5, 7.5 Hz), 2.67 (dd, 1H, H-10, *J* = 13.0, 3.5 Hz), 2.27 (app dd, 1H, H-5_a, *J* = 13.5, 7.5 Hz), 2.09 (ddd, 1H, H-12_a, *J* = 19.0, 5.0, 2.0 Hz), 1.91 (dd, 1H, H-6, *J* = 12.0, 1.5 Hz), 1.85-1.80 (m, 2H, H-3), 1.72 (ddd, 1H, H-12_b, *J* = 19.0, 14.0, 5.0 Hz), 1.52 (app dtd, 1H, H-5_b, *J* = 13.5, 12.0, 7.5 Hz), 1.46-1.33 (m, 2H, H-4_a & H-11_a), 1.28-1.19 (m, 1H, H-4_b), 1.19-1.08 (m, 1H, H-11_b), 0.96 (s, 3H, H-8).

^{13}C NMR (C_6D_6, 125 MHz) δ_C 200.3 (C-13), 174.6 (C-9), 161.3 (C-2), 134.6 (C-18), 133.8 (C-16), 122.4 (C-1), 117.9 (C-17), 117.1 (C-19), 71.7 (C-14), 66.4 (C-10), 52.5 (C-6), 43.6 (C-15), 42.7 (C-7), 36.9 (C-12), 29.6 (C-8), 28.0 (C-3), 27.7 (C-5), 26.2 (C-11), 22.8 (C-4).

5.5.8 Synthesis and characterisation of racemic (2aS,9aR,9bS)-9b-methyl-1-(prop-2-en-1-yl)-2a,3,4,5,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,7-dione (292):



To a solution of **289** (128 mg, 0.406 mmol) in anhydrous THF (6.5 mL) at –60 °C (cryoprobe used with an acetone bath) under a nitrogen atmosphere, was added $LiAlH_4$ (1 M solution in THF, 450 μL, 0.450 mmol) dropwise. After 2 h the reaction was quenched with MeOH (9.5 mL) and after 1 h 30 min the ice-bath was removed. After 1 h aqueous HCl (1 M, 9.5 mL) was added and after a further 30 min a saturated solution of Rochelle's salt (6.2 mL) was added. After 1 h the reaction was extracted with EtOAc (4×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [55:45] to provide **292** as a white solid (110 mg, 100% yield).

mp 75-78 °C.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2930 (C-H), 2862 (C-H), 1681 (C=O), 1610 (enone C=C), 1455, 1267.

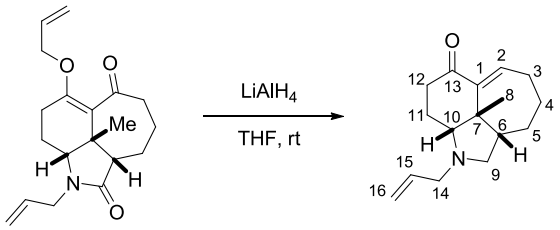
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.89 (app t, 1H, H-2, J = 8.0 Hz), 5.76 (dddd, 1H, H-15, J = 17.0, 10.0, 7.5, 5.0 Hz), 5.29-5.22 (m, 2H, H-16), 4.41 (app br ddt, 1H, H-14_a, J = 15.5, 5.0, 1.5 Hz), 3.58 (dd, 1H, H-14_b, J = 15.5, 7.5 Hz), 3.27 (dd, 1H, H-10, J = 12.5, 3.5 Hz), 2.59-2.50 (m, 1H, H-12_a), 2.35-2.12 (m, 6H, H-3 & H-5_a & H-6 & H-11_a & H-12_b), 1.88-1.74 (m, 1H, H-4_a), 1.67 (app td, 1H, H-4_b, J = 12.5, 6.5 Hz), 1.62-1.44 (m, 2H, H-5_b & H-11_b), 1.32 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 200.4 (C-13), 175.3 (C-9), 142.1 (C-1), 139.6 (C-2), 132.4 (C-15), 118.5 (C-16), 65.7 (C-10), 51.8 (C-6), 43.3 (C-14), 42.9 (C-7), 35.4 (C-12), 29.3 (C-8), 27.3 (C-5), 25.7 (C-11), 24.0 (C-3), 22.2 (C-4).

m/z (ES+) 282 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}NNaO_2^+$) requires ***m/z*** 282.1465, found ***m/z*** 282.1453.

5.5.9 Synthesis and characterisation of racemic (2aS,9aR,9bS)-9b-methyl-1-(prop-2-en-1-yl)-1,2,2a,3,4,5,8,9,9a,9b-decahydro-7H-cyclohepta[cd]indol-7-one (298):



To a solution of **289** (138 mg, 0.438 mmol) in anhydrous THF (14 mL) at rt under a nitrogen atmosphere, was added $LiAlH_4$ (1 M solution in THF, 1.80 mL, 1.80 mmol) dropwise at rt. After 4 h the reaction was cooled to 0 °C and quenched with MeOH (1 mL). After 15 min the ice-bath was removed and after a further 15 min aqueous HCl (1 M, 10 mL) was added in one portion. After 2 h a saturated solution of Rochelle's salt (10 mL) was added and the reaction was left stirring for a further 14 h before being extracted with EtOAc (3×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [80:20] to provide **298** as a yellow oil (66.0 mg, 61% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2926 (C-H), 2861 (C-H), 2796 (C-H), 1687 (C=O), 1609 (enone C=C), 1456, 1256.

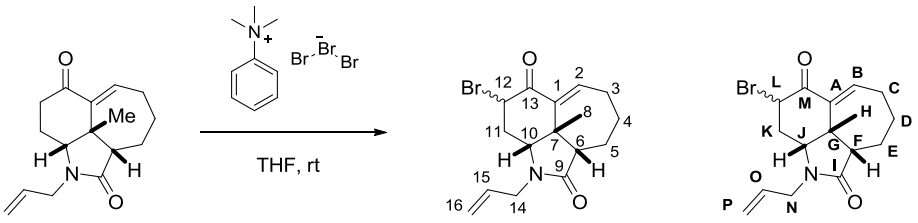
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.94 (dd, 1H, H-2, *J* = 8.5, 6.5 Hz), 5.90 (dddd, 1H, H-15, *J* = 17.0, 10.0, 7.5, 5.5 Hz), 5.25-5.08 (m, 2H, H-16), 3.45-3.37 (m, 1H, H-14_a), 2.98-2.88 (m, 1H, H-14_b), 2.87-2.78 (m, 1H, H-9_a), 2.65 (app t, 1H, H-9_b, *J* = 7.5 Hz), 2.55 (ddd, 1H, H-12_a, *J* = 17.5, 8.0, 5.0 Hz), 2.44-2.38 (m, 1H, H-10), 2.38-2.27 (m, 2H, H-3), 2.19 (ddd, 1H, H-12_a, *J* = 17.5, 9.0, 4.5 Hz), 2.07-2.00 (m, 1H, H-11_a), 2.00-1.92 (m, 1H, H-6), 1.80-1.51 (m, 5H, H-4 & H-5 & H-11_b), 1.23 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 201.9 (C-13), 142.7 (C-1), 139.0 (C-2), 135.7 (C-15), 116.8 (C-16), 71.2 (C-10), 58.3 (C-9), 56.4 (C-14), 49.1 (C-7), 45.8 (C-6), 34.1 (C-12), 29.8 (C-5), 27.8 (C-8), 25.4 (C-3), 23.0 (C-11), 21.6 (C-4).

m/z (ES+) 246 ($[M+H]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}NO^+$) requires ***m/z*** 246.1852, found ***m/z*** 246.1845.

5.5.10 Synthesis and characterisation of racemic (2aS,9aR,9bS)-8-bromo-9b-methyl-1-(prop-2-en-1-yl)-2a,3,4,5,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,7-dione (295):



To a solution of **292** (27.8 mg, 0.107 mmol) in anhydrous THF (1 mL) at rt under a nitrogen atmosphere was added trimethylphenylammonium tribromide (42.3 mg, 0.113 mmol) in one portion. After 30 min[i] the reaction was quenched with a saturated aqueous solution of sodium thiosulfate (2 mL) and after a further 10 min extracted with EtOAc

[i] Longer reaction times lead to dibromination on the α-position.

(3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:EtOAc [60:40]) to provide **295** as a dark yellow oil[i] (33.1 mg, 91% yield, 2.4:1 dr). Data provided for mixture of diastereoisomers.

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2924 (C-H), 2860 (C-H), 1685 (C=O), 1604 (enone C=C), 1452, 1302.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.10 (app t, 1H, H-2, J = 8.0 Hz), 7.03 (app t, 1H, H-**B**, J = 8.0 Hz), 5.82-5.70 (m, 2H, H-15 & H-**O**), 5.32-5.26 (m, 4H, H-16 & H-**P**), 4.54 (app t, 1H, H-12, J = 3.5 Hz), 4.45-4.33 (m, 3H, H-**L** & H-14$_a$ & H-**N$_a$**), 3.92 (dd, 1H, H-10, J = 11.5, 4.0 Hz), 3.58 (app dd, 1H, H-14$_b$, J = 15.0, 7.5 Hz), 3.57 (app dd, 1H, H-**N$_b$**, J = 15.5, 7.5 Hz), 3.32 (dd, 1H, H-**J**, J = 12.5, 3.5 Hz), 2.75 (app dt, 1H, H-**K$_a$**, J = 13.0, 4.0 Hz), 2.53 (app dt, 1H, H-11$_a$, J = 14.5, 3.5 Hz), 2.40-2.24 (m, 6H, H-3 & H-**C** & H-6 & H-**F**), 2.22-2.14 (m, 2H, H-5$_a$ & H-**E$_a$**), 1.98 (m, 1H, H-**K$_b$**), 1.93-1.78 (m, 3H, H-4$_a$ & H-**D$_a$** & H-11$_b$), 1.74-1.61 (m, 2H, H-4$_b$ & H-**D$_b$**), 1.56-1.39 (m, 5H, H-5$_b$ & H-**E$_b$** & H-8), 1.33 (s, 3H, H-**H**).

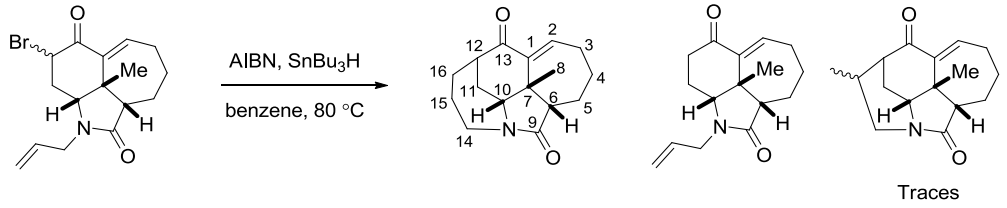
^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 194.1 (C-13), 192.9 (C-**M**), 175.3 (C-9), 175.1(C-**I**), 144.4 (C-2), 142.9 (C-**B**), 140.0 (C-**A**), 139.5 (C-1), 132.0 (C-15 & C-**O**), 119.1 (C-16 & C-**P**), 64.9 (C-**J**), 61.3 (C-10), 51.8 (C-6), 51.5 (C-**F**), 45.9 (C-**L**), 45.3 (C-12), 43.5 (C-14), 43.4 (C-**N**), 42.9 (C-**G**), 42.5 (C-7), 37.8 (C-**K**), 33.5 (C-11), 29.4 (C-**H**), 29.0 (C-8), 27.2 (C-5 & C-**E**), 24.4 (C-3), 24.1 (C-**C**), 22.2 (C-4), 22.1 (C-**D**).

m/z (ES+) 360 & 362 ([M+Na]$^+$, 100%)

HRMS (ES+) exact mass calculated for [M+Na]$^+$ ($C_{16}H_{20}NNaO_2^+$) requires ***m/z*** 360.0570 & 362.0550, found ***m/z*** 360.0569 & 362.0560.

[i] The dark colouration intensifies significantly upon standing.

5.5.11 Synthesis and characterisation of racemic (2S,7aS,12aS,12bR)-12a-methyl-2,3,4,5,7a,8,9,10,12a,12b-decahydro-2,12-methanocyclohepta[3,4]pyrrolo[1,2-a]azepine-7,13(1H)-dione (296):



To a solution of **295** (16.3 mg, 0.048 mmol) in benzene (5 mL) at rt under a nitrogen atmosphere, was added tributyltin hydride (14.0 μL, 0.052 mmol) followed by AIBN (1.20 mg, 7.31 μmol). The reaction was degassed using a vacuum and then charged with nitrogen (this operation was repeated 5 times) and then placed in a preheated oil-bath at 80 °C for 2 h 30 min. The reaction was cooled to rt and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with CH_2Cl_2:acetone [95:5]) to provide **296** as a pale yellow film (4.40 mg, 27% yield) and the debrominated product **292** (4.2 mg, 34% yield).[i]

Data for 296**:**

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2929 (C-H), 2852 (C-H), 1689 (C=O), 1599 (enone C=C), 1418.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.34 (m, 1H, H-2), 4.17-4.11 (m, 1H, H-14_a), 3.44 (dd, 1H, H-10, J = 5.0, 1.5 Hz), 2.74-2.67 (m, 2H, H-14_b & H-12), 2.57-2.42 (m, 3H, H-3_a & H-6 & H-11_a), 2.41-2.30 (m, 2H, H-3_b & H-16_a), 2.11 (dd, 1H, H-11_b, J = 15.5, 5.0 Hz), 2.03-1.97 (m, 2H, H-5), 1.82-1.73 (m, 1H, H-4_a), 1.73-1.54 (m, 2H, H-4_b & H-15_a), 1.46 (s, 3H, H-8), 1.42-1.35 (m, 1H, H-16_b), 1.27 (m, 1H, H-15_b).

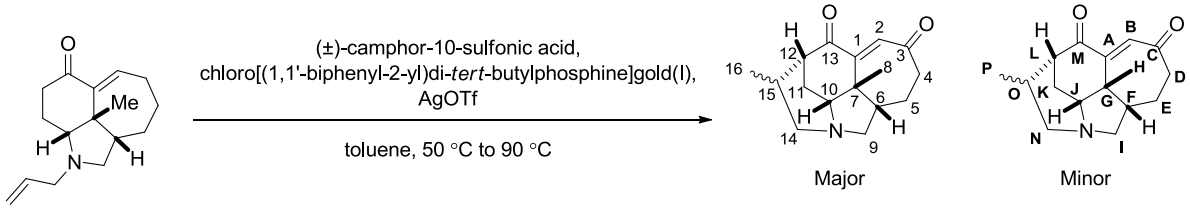
[i] The ^{1}H-NMR spectrum of **292** possibly contains traces of the desired 6-membered ring product **293** at 1.05 ppm (d, J = 7.0 Hz). This was inseparable from the major component and thus unconfirmed. This trace was also observed in experiments shown in Table 7, entry 3 & 4 on page 125.

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 200.1 (C-13), 174.9 (C-9), 147.9 (C-2), 138.3 (C-1), 62.3 (C-10), 51.7 (C-6), 49.3 (C-7), 41.6 (C-12), 39.5 (C-14), 33.4 (C-16), 28.1 (C-3), 27.3 (C-15), 25.6 (C-11), 25.3 (C-5), 21.0 (C-8), 20.5 (C-4).

m/z (ES+) 282 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}NNaO_2^+$) requires ***m/z*** 282.1465, found ***m/z*** 282.1455.

5.5.12 Synthesis and characterisation of racemic (2R,6aS,11aS,11bR)-3,11a-dimethyl-1,3,4,6,6a,7,8,9,11a,11b-decahydro-2H-2,11-methanocyclohepta[a]indolizin-12-one (300):



To a solution of **298** (25.5 mg, 0.104 mmol) in anhydrous toluene (2.6 mL) at 50 °C (oil-bath temp) under a nitrogen atmosphere, was added (±)-camphor-10-sulfonic acid (26.6 mg, 0.115 mmol) in one portion. After 30 min chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I) (33.1 mg, 0.062 mmol) and AgOTf (16.0 mg, 0.062 mmol) were added sequentially followed by toluene (0.8 mL) for washing the sides of the flask. The temp of the oil-bath was then set to 90 °C. After 26 h the reaction was concentrated under reduced pressure. The crude product was purified twice by flash column chromatography (eluted with EtOAc followed by CH_2Cl_2:MeOH [95:5]) to provide **300** as a yellow film (2.60 mg, 10% yield, 4.5:1 dr).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2927 (C-H), 2851 (C-H), 1686 (C=O), 1674 (C=O), 1589, 1458.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 6.86 (s, 1H, H-**B**), 6.78 (s, 1H, H-2), 3.56-3.44 (m, 2H, H-9_a & H-$\mathbf{I_a}$), 3.00-2.91 (m, 3H, H-14_a & H-10 & H-**J**), 2.78 (d, 1H, H-$\mathbf{N_a}$, J = 3.5 Hz), 2.71-

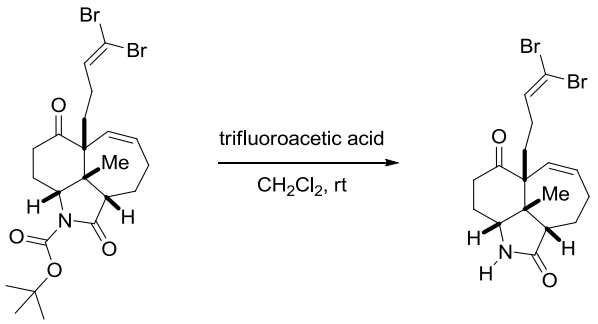
2.61 (m, 3H, H-4_a & H-**D_a** & H-12), 2.61-2.39 (m, 8H, H-4_b & H-**D_b** & H-6 & H-**F** & H-9_b & H-**I_b** H-**K_a** & H-**L**), 2.38-2.13 (m, 6H, H-5_a & H-**E_a** & H-11 & H-14_b & H-15), 2.13-2.06 (m, 1H, H-**O**), 2.06-1.83 (m, 3H, H- 5_b & H-**E_b** & H-**K_b**), 1.33 (s, 3H, H-**H**), 1.32 (s, 3H, H-8), 1.30 (d, 3H, H-**P**, J = 7.5 Hz), 0.89 (d, 3H, H-16, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 206.4 (C-**C**), 206.2 (C-3), 201.9 (C-**M**), 200.7 (C-13), 148.5 (C-1), 147.3 (C-**A**), 132.8 (C-**B**), 131.6 (C-2), 65.3 (C-**J**), 65.1 (C-10), 60.3 (C-**I**), 60.3 (C-9), 55.1 (C-14), 52.2 (C-**N**), 51.7 (C-6), 50.8 (C-**F**), 49.6 (C-7), 49.2 (C-**G**), 47.3 (C-12), 46.4 (C-**L**), 40.6 (C-4), 40.5 (C-**D**), 34.7 (C-15), 31.9 (C-8 & C-**H**), 31.8 (C-**O**), 30.2 (C-5), 25.4 (C-11), 18.7 (C-**K**), 17.6 (C-**P**), 17.0 (C-16).

m/z (ES+) 260 ($[M+H]^+$, 100%)

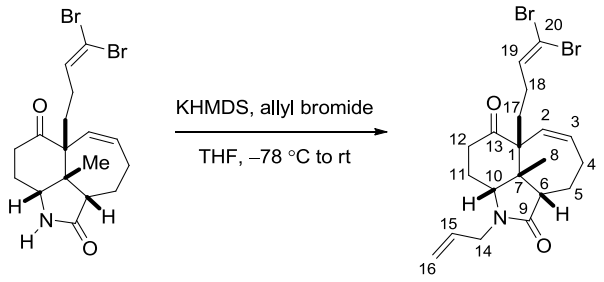
HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}NO_2^+$) requires ***m/z*** 260.1645, found ***m/z*** 260.1651.

5.5.13 Synthesis of racemic (2aS,6aR,9aR,9bS)-6a-(4,4-dibromobut-3-en-1-yl)-9b-methyl-2a,3,4,6a,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,7-dione (302):



To a solution of **251** (21.1 mg, 0.0397 mmol) in anhydrous CH_2Cl_2 (4.3 mL) under a nitrogen atmosphere at rt, was added trifluoroacetic acid (43.0 μL, 0.562 mmol) dropwise. After 1 h 30 min the reaction was quenched with a saturated solution of $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide an off-white foam. The crude product was carried on to the next step without further purification.

5.5.14 Synthesis and characterisation of racemic (2aS,6aR,9aR,9bS)-6a-(4,4-dibromobut-3-en-1-yl)-9b-methyl-1-(prop-2-en-1-yl)-2a,3,4,6a,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,7-dione (305):



To a solution of **302** in anhydrous THF (2.1 mL) at –78 °C under a nitrogen atmosphere, was added KHMDS (0.5 M solution in toluene, 119 μL, 0.0595 mmol) dropwise. After 30 min allyl bromide (10.0 μL, 0.116 mmol) was added dropwise and the reaction was allowed to reach rt gradually over 19 h.[i] The reaction was quenched with a saturated solution of NH_4Cl (2 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:Et_2O [20:80→0:100] followed by EtOAc:acetone [90:10→80:20]) to provide **305** as a pale yellow foam (12.6 mg, 67% yield) followed by recovered starting material **302** (2.30 mg, 13% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2962 (C-H), 1707 (C=O), 1682 (C=O), 1682 (C=O), 1449.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.39 (t, 1H, H-19, *J* = 7.0 Hz), 5.82 (ddd, 1H, H-3, *J* = 12.0, 5.0, 3.0 Hz), 5.74 (m, 1H, H-15), 5.30-5.22 (m, 2H, H-16), 5.19 (app dt, 1H, H-2, *J* = 12.0, 2.0 Hz), 4.41 (ddt, 1H, H-14_a, *J* = 15.0, 5.0, 1.5 Hz), 3.57 (app t, 1H, H-10, *J* = 7.0 Hz), 3.50 (dd, 1H, H-14_b, *J* = 15.0, 8.0 Hz), 2.61-2.41 (m, 2H, H-12), 2.41-2.16 (m, 3H, H-4 & H-11_a), 2.12 (dd, 1H, H-6, *J* = 12.0, 1.0 Hz), 2.06-1.95 (m, 2H, H-5_a & H-18_a), 1.94-

[i] The temperature increase needs to be gradual in order to avoid the elimination of the dibromo functionality.

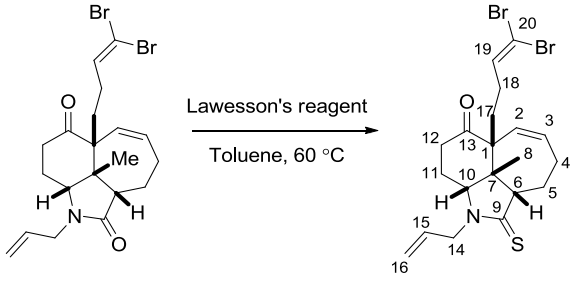
1.79 (m, 2H, H-11_b & H-17_a), 1.79-1.57 (m, 3H, H-5_b & H-17_b & H-18_b), 1.25 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 210.7 (C-13), 175.1 (C-9), 136.8 (C-19), 133.4 (C-3), 132.4 (C-15), 128.1 (C-2), 118.9 (C-16), 90.5 (C-20), 60.7 (C-10), 56.1 (C-1), 54.9 (C-6), 49.6 (C-7), 43.4 (C-14), 35.6 (C-17), 34.6 (C-12), 30.2 (C-4), 28.1 (C-18), 26.9 (C-8), 26.5 (C-11), 24.5 (C-5).

m/z (ES+) 472 ($[M+H]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{25}Br_2NNaO_2^+$) requires ***m/z*** 492.0144, 494.0125 & 496.0104 found ***m/z*** 492.0152, 494.0132 & 496.0122.

5.5.15 Synthesis and characterisation of racemic (2aS,6aR,9aR,9bS)-6a-(4,4-dibromobut-3-en-1-yl)-9b-methyl-1-(prop-2-en-1-yl)-2-thioxo-1,2,2a,3,4,6a,8,9,9a,9b-decahydro-7H-cyclohepta[cd]indol-7-one (307):



To a solution of **305** (28.6 mg, 0.061 mmol) in anhydrous toluene (2.3 mL) at 60 °C (oil-bath temp) under a nitrogen atmosphere was added Lawesson's reagent (22.1 mg, 0.055 mmol) in one portion. After 4.5 h the reaction was concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with CH_2Cl_2[i] followed by PE:Et_2O [70:30→60:40]) to provide **307** as a colourless film (18.7 mg, 63% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3013 (C-H), 2963 (C-H), 2918 (C-H), 1711 (C=O), 1488, 1306.

[i] CH_2Cl_2 was used to remove Lawesson's reagent's lipophilic side products.

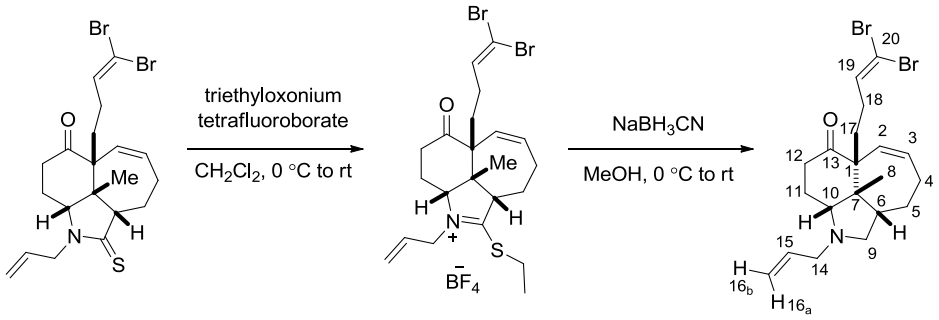
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.39 (t, 1H, H-19, J = 7.5 Hz), 5.91-5.78 (m, 2H, H-3 & H-15), 5.40-5.29 (m, 2H, H-16), 5.16 (app dt, 1H, H-2, J = 12.0, 2.0 Hz), 5.01 (app ddt, 1H, H-14_a, J = 15.0, 5.0, 1.5 Hz), 3.91-3.80 (m, 2H, H-10 & H-14_b), 2.67-2.53 (m, 2H, H-6 & H-12_a), 2.53-2.40 (m, 2H, H-11_a & H-12_b), 2.40-2.25 (m, 3H, H-4 & H-5_a), 2.05-1.83 (m, 2H, H-11_b & H-18_a), 1.83-1.61 (m, 4H, H-5_b & H-17 & H-18_b), 1.21 (s, 3H, H-8).

^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 209.6 (C-13), 204.3 (C-9), 136.5 (C-19), 133.9 (C-3), 130.4 (C-15), 127.2 (C-2), 120.2 (C-16), 90.7 (C-20), 67.4 (C-10), 66.4 (C-6), 55.7 (C-1 or C-7), 51.7 (C-1 or C-7), 49.3 (C-14), 36.0 (C-17), 34.7 (C-12), 30.1 (C-4), 27.9 (C-18), 27.4 (C-11), 27.2 (C-5), 26.0 (C-8).

m/z (ES+) 488 ($[M+H]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}Br_2NOS^+$) requires ***m/z*** 486.0096, 488.0076 & 490.0055 found ***m/z*** 486.0102, 488.0080 & 490.0058.

5.5.16 Synthesis and characterisation of racemic (2aS,6aR,9aR,9bS)-6a-(4,4-dibromobut-3-en-1-yl)-9b-methyl-1-(prop-2-en-1-yl)-1,2,2a,3,4,6a,8,9,9a,9b-decahydro-7H-cyclohepta[cd]indol-7-one (306):



To a solution of **307** (19.0 mg, 0.039 mmol) in anhydrous CH_2Cl_2 (3 mL) under a nitrogen atmosphere was added triethyloxonium tetrafluoroborate (0.9 M solution[i] in CH_2Cl_2, 87.0 µL, 0.078 mmol) dropwise at 0 °C. After 15 min the reaction was removed from the ice-

[i] This was freshly prepared using anhydrous CH_2Cl_2.

bath and allowed to reach rt over 3.5 h at which point the reaction was concentrated under reduced pressure.

The salt **308** was dissolved in MeOH (2 mL) and cooled to 0 °C. To this solution was added $NaBH_3CN$ (36.5 mg, 0.581 mmol) as a solution in MeOH (1 mL) dropwise (a total of 1 mL of MeOH used for washings). After 15 min the reaction was removed from the ice-bath and allowed to reach rt over 3 h at which point the reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (4×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with C_6H_6:Et_2O [90:10]) to provide **306** as a colourless oil (15.3 mg, 86% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 2924 (C-H), 2853 (C-H), 2795 (C-H) 1707 (C=O), 1457.

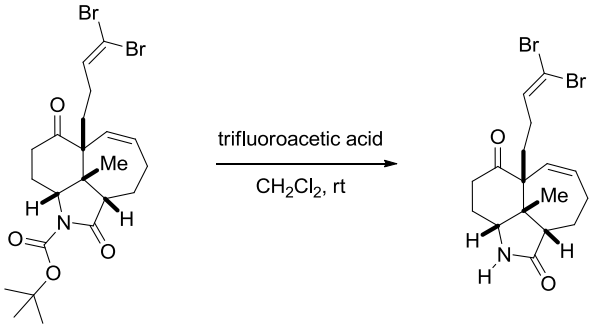
^{1}H NMR (C_6D_6, 500 MHz) δ_H 6.05 (t, 1H, H-19, J = 7.5 Hz), 5.84 (dddd, 1H, H-15, J = 17.0, 10.0, 7.5, 5.0 Hz), 5.62 (ddd, 1H, H-3, J = 12.0, 6.0, 2.5 Hz), 5.17 (app br dq, 1H, H-16_a, J = 17.0, 2.0 Hz), 5.05 (app br d, 1H, H-16_b, J = 10.0 Hz), 4.98 (m, 1H, H-2), 3.12 (app ddt, 1H, H-14_a, J = 14.0, 5.0, 2.0 Hz), 2.61 (app dd, 1H, H-14_b, J = 14.0, 7.5 Hz), 2.53-2.44 (m, 2H, H-9_a & H-12_a), 2.41-2.32 (m, 2H, H-5_a & H-9_b), 2.18-2.14 (m, 1H, H-10), 2.05 (ddd, 1H, H-12_b, J = 18.0, 9.0, 6.0 Hz), 2.00-1.93 (m, 1H, H-18_a), 1.90-1.81 (m, 2H, H-4_a & H-5_b), 1.81-1.74 (m, 1H, H-18_b), 1.74-1.67 (m, 1H, H-4_b), 1.67-1.58 (m, 2H, H-11_a & H-17_a), 1.56-1.47 (m, 2H, H-11_b & H-6), 1.28-1.25 (m, 1H, H-17_b), 0.92 (s, 3H, H-8).

^{13}C NMR (C_6D_6, 125 MHz) δ_C 210.6 (C-13), 139.1 (C-19), 137.3 (C-15), 133.3 (C-3), 130.0 (C-2), 116.5 (C-16), 90.0 (C-20), 68.9 (C-10), 59.3 (C-9), 57.9 (C-1 or C-7), 56.6 (C-14), 54.7 (C-1 or C-7), 48.7 (C-6), 35.4 (C-17), 35.1 (C-12), 30.6 (C-5), 30.2 (C-4), 29.7 (C-18), 28.6 (C-8), 22.8 (C-11).

m/z (ES+) 458 ($[M+H]^+$, 100%)

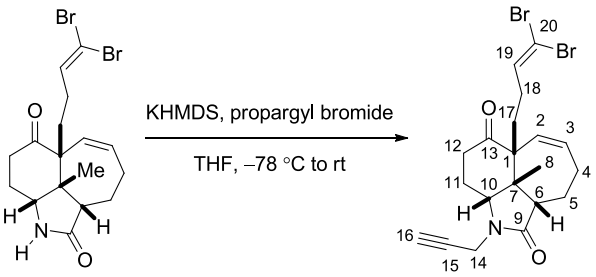
HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{28}Br_2NO^+$) requires ***m/z*** 456.0532, 458.0512 & 460.04912 found ***m/z*** 456.0525, 458.0503 & 460.0482.

5.5.17 Synthesis of racemic (2aS,6aR,9aR,9bS)-6a-(4,4-dibromobut-3-en-1-yl)-9b-methyl-2a,3,4,6a,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,7-dione (302):



To a solution of **251** (20.7 mg, 0.0390 mmol) in anhydrous CH_2Cl_2 (4.2 mL) under a nitrogen atmosphere at rt, was added trifluoroacetic acid (42.0 μL, 0.548 mmol) dropwise. After 1 h 30 min the reaction was quenched with a saturated solution of $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide an off-white foam. The crude product was carried on to the next step without further purification.

5.5.18 Synthesis and characterisation of racemic (2aS,6aR,9aR,9bS)-6a-(4,4-dibromobut-3-en-1-yl)-9b-methyl-1-(prop-2-yn-1-yl)-2a,3,4,6a,8,9,9a,9b-octahydro-1H-cyclohepta[cd]indole-2,7-dione (310):



To a solution of **302** (assumed quantitative from previous step, 0.0390 mmol) in anhydrous THF (2 mL) at –78 °C under a nitrogen atmosphere, was added KHMDS (0.5 M solution in toluene, 117 μL, 0.0585 mmol) dropwise. After 30 min propargyl bromide (13.0 μL,

0.117 mmol of 80 wt. % in toluene) was added dropwise and the reaction was allowed to reach rt gradually over 21 h. The reaction was quenched with a saturated solution of NH_4Cl (2 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluted with PE:Et_2O [30:70] to provide **310** as a white foam (14.5 mg, 79% yield).

IR (film)/cm^{-1} $\boldsymbol{\nu_{max}}$ 3300 (C≡C-H), 3252 (C≡C-H), 2962 (C-H), 2937 (C-H), 1683 (C=O), 1444.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 6.41 (t, 1H, H-19, *J* = 7.0 Hz), 5.82 (ddd, 1H, H-3, *J* = 12.0, 5.0, 3.5 Hz), 5.20 (app dt, 1H, H-2, *J* = 12.0, 2.0 Hz), 4.57 (dd, 1H, H-14$_a$, *J* = 17.5, 2.5 Hz), 3.83-3.72 (m, 2H, H-10 & H-14$_b$), 2.64-2.53 (m, 1H, H-12$_a$), 2.53-2.32 (m, 3H, H-4$_a$ & H-11$_a$ & H-12$_b$), 2.27 (t, 1H, H-16, *J* = 2.5 Hz), 2.26-2.17 (m, 1H, H-4$_b$), 2.13 (dd, 1H, H-6, *J* = 12.0, 1.5 Hz), 2.07-1.57 (m, 7H, H-5 & H-11$_b$ & H-17 & H-18), 1.27 (s, 3H, H-8).

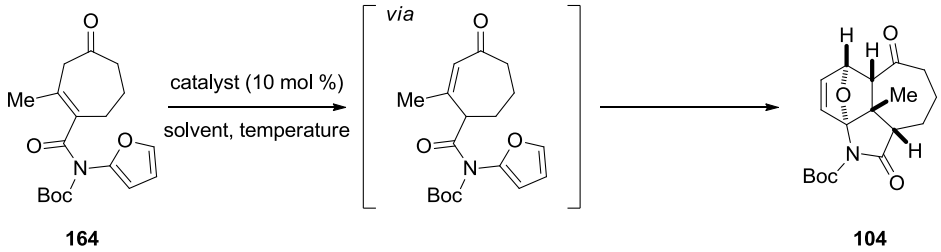
^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 210.6 (C-13), 174.8 (C-9), 136.7 (C-19), 133.3 (C-3), 128.2 (C-2), 90.6 (C-20), 77.2 (C-15), 72.7 (C-16), 60.9 (C-10), 56.0 (C-1), 54.7 (C-6), 49.5 (C-7), 35.6 (C-17), 34.5 (C-12), 30.4 (C-14), 30.2 (C-4), 28.1 (C-18), 26.7 (C-8), 26.2 (C-11), 24.4 (C-5).

m/z (ES+) 492 ($[M+Na]^+$, 100%)

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{23}Br_2NNaO_2^+$) requires ***m/z*** 489.9988, 491.9967 & 493.9947 found ***m/z*** 489.9988, 491.9966 & 493.9945.

Appendix

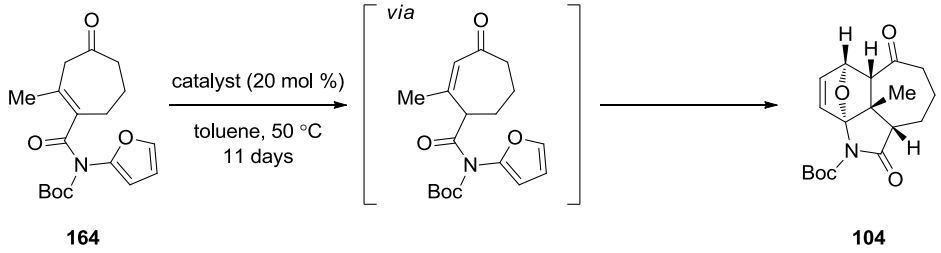
6.1 Racemic IMDAF reaction investigation



Entry	Catalyst	Solvent	Temperature	Yield (%)	dr
1	no catalyst	Toluene	50 °C	-	N/A
2	DABCO	Toluene	50 °C	100%	96:4
3[i]	DABCO	Toluene	85 °C	96%	86:14
4	DABCO	1,2-DCE	50 °C	64%	98:2
5	DABCO	DMF	50 °C	34%	96:4
6	DABCO	MeCN	50 °C	89%	96:4
7	DABCO	THF	50 °C	84%	94:6
8	DABCO	Dioxane	50 °C	100%	96:4

A solvent screen was conducted on 50 mg of substrate **164** using DABCO (10 mol %) in 2 mL of solvent.

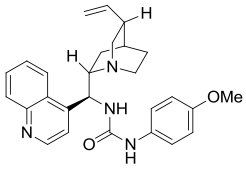
6.2 IMDAF reaction investigation using bifunctional organocatalysts



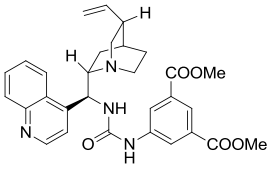
A catalyst screen was conducted on 20 mg of substrate **164** using catalyst (20 mol %) in 1 mL of anhydrous toluene at 50 °C. All conversions (starter and product %) were determined by ^{1}H NMR using mesitylene as a standard.

[i] Experiment conducted by Dr. B. Darses.

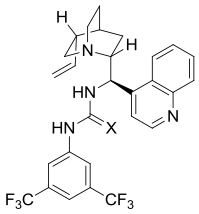
6.2.1 Cinchonine/cinchonidine derived ureas and thioureas



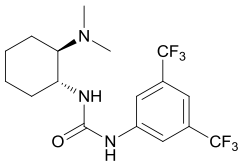
catalyst 1



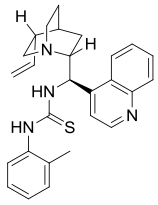
catalyst 2



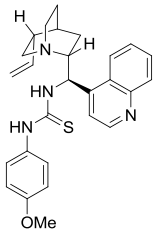
catalyst 3; X= O
catalyst 26; X= S



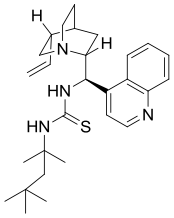
catalyst 4



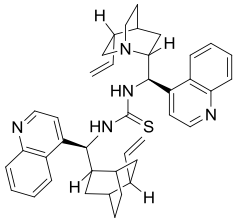
catalyst 5



catalyst 6



catalyst 7

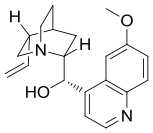


catalyst 8

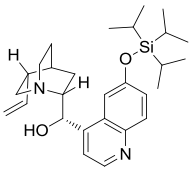
Entry	Catalyst	Starter (%)	Product (%)	dr	ee (%)
1	1	0	80	96:4	–38
2	2	2.5	80	95:5	–29
3	3		57[i]	94:6	+32
4	26		31[i]	94:6	+28
5	4	5	80	95:5	+20
6	5	61	38	94:6	+24
7	6		100[i]	95:5	+36
8	7	23	56	94:6	+26
9	8	50	50	94:6	+6

[i] Refers to % yield (not conversion).

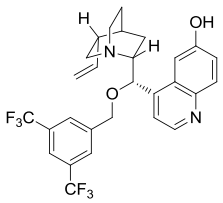
6.2.2 Quinidine derived alcohols/ethers/esters and epi-amino quinine



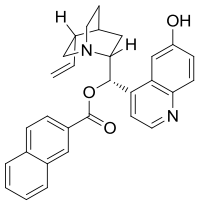
catalyst 9



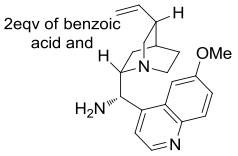
catalyst 10



catalyst 11



catalyst 12

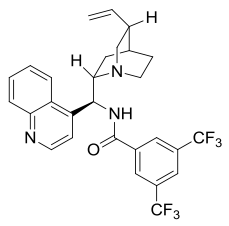


catalyst 13

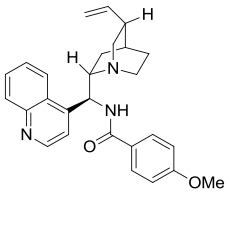
Entry	Catalyst	Starter (%)	Product (%)	dr	ee (%)
10	9	0	93	95:5	+13
11	10	0	91	95:5	+16
12	11	0	90	94:6	+7
13	12	0	95	95:5	+44
14	13	0	50[i]	95:5	–37

[i] Refers to % yield (not conversion).

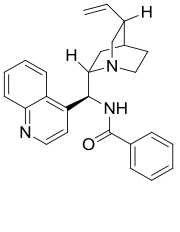
6.2.3 Cinchonine/cinchonidine/quinine derived amides



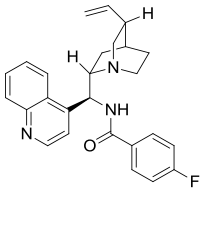
catalyst 14



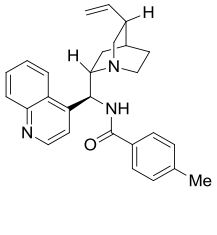
catalyst 15



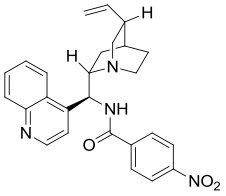
catalyst 16



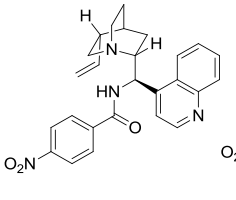
catalyst 17



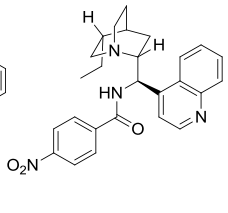
catalyst 18



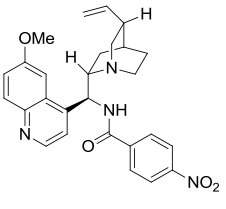
catalyst 19



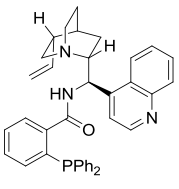
catalyst 20



catalyst 21



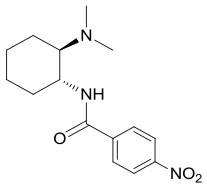
catalyst 22



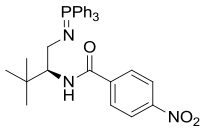
catalyst 23

Entry	Catalyst	Starter (%)	Product (%)	dr	ee (%)
15	14	13	75	96:4	+53
16	15	3	83	95:5	+67
17	16	4	88	95:5	+74
18	17	4	84	95:5	+73
19	18	0	87	96:4	+67
20	19	15	85	96:4	+73
21	20	43	45	96:4	–44
22	21	28	72	97:3	–41
23[i]	22	7	84	96:4	+69
24	23	0	89	97:3	–8

6.2.4 p-nitrophenyl derived Takemoto-type and BIMP scaffolds



catalyst 24



catalyst 25

Entry	Catalyst	Starter (%)	Product (%)	dr	ee (%)
25	24		70[ii]	95:5	+4
26	25		95[ii]	95:5	+38

[i] This experiment was also performed at 75 °C to provide the adduct **104** in a lower +46% ee.
[ii] Refers to % yield (not conversion).

*6.2.5 **Conditions screening for** catalyst 19*

Entry	Catalyst	Solvent	Conc (M)	Starter (%)	Product (%)	dr	ee (%)
27	19	Toluene	0.060	15	85	96:4	+73
28	19	Toluene	0.120	7	86	96:4	+55
29	19	Toluene	0.006	83	16	95:5	+73
30	19	Benzene	0.060	49	48	97:3	-63
31	**19**	***m*-Xylene**	**0.060**	**0**	**100**	**96:4**	**+76**[i]
32	19	Mesitylene	0.060	5	77	95:5	+74
33	19	PhCl	0.060	50	50	96:4	+66
34	19	EtOAc	0.060	43	57	96:4	+49
35	19	$CHCl_3$	0.060	74	25	98:2	+26
36	19	Cyclohexane	0.060	3	87	95:5	+47
37	19	MeCN	0.060	36	64	98:2	*rac*
38	19	1, 4-Dioxane	0.060	5	85	95:5	+68
39	19	THF	0.060	4	83	97:3	+41

Conclusions: (a) the cinchonidine derived amides yield the highest ees with **catalyst 19** in *m*-xylene with a 0.060 M concentration offering the highest ee (+76%) (b) unfortunately the pseudoenantiomer, **catalyst 20**, does not provide an equal ee for the antipode of the adduct **104**.

[i] $[\alpha]_D^{25}$ = + 1.1 (*c* 1.7, $CHCl_3$).

6.3 Publications

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