The Enantioselective Total Synthesis of Sealutomicin C



Stuart Astle

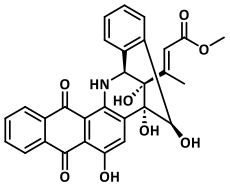
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Abstract

This thesis is divided into six chapters and concerns the successful total synthesis of the natural product sealutomicin C. Chapter 1 provides an overview of anthraquinone-fused enediyne natural products, the sealutomicin natural products, and other related cycloaromatised natural products. Chapter 1 also discusses prior work carried out in the Burton group by previous group member Dr Sean Guggiari towards the synthesis of the natural product unciaphenol, which bears structural similarities to sealutomicin C.



Sealutomicin C

Chapter 2 details work undertaken to prepare lactone-fused chiral dihydroquinolines, using methodology developed by Dr Guggiari to construct the chiral dihydroquinoline scaffold. Chapter 3 discusses the use of these lactone-fused dihydroquinolines as substrates in a key organolithium-mediated cyclisation to construct the core of enantiomeric sealutomicin C. Chapter 3 also discusses efforts to elaborate this core, resulting in the synthesis of *tris*-benzyl protected enantiomeric sealutomicin C.

Chapter 4 concerns the application of the chemistry developed in Chapters 2 and 3 to the synthesis of the correct enantiomer of sealutomicin C, culminating in a successful first-generation synthesis of the target natural product. Chapter 5 presents a shorter and more streamlined second-generation synthesis of sealutomicin C, improving on the work described in Chapters 2 – 4 by employing a more efficient protecting group strategy. Finally, Chapter 6 summarises our achievements and suggests potential strategies to apply the chemistry developed here to the synthesis of the structurally related natural products sealutomicins B and D.

Declaration

The work described in thesis is entirely the work of the author, except where specifically identified, and does not include any collaborative research.

This thesis has not been previously submitted for a degree, diploma, or any other qualification at the University of Oxford or elsewhere.

Stuart Astle

June 2023

Acknowledgements

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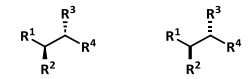
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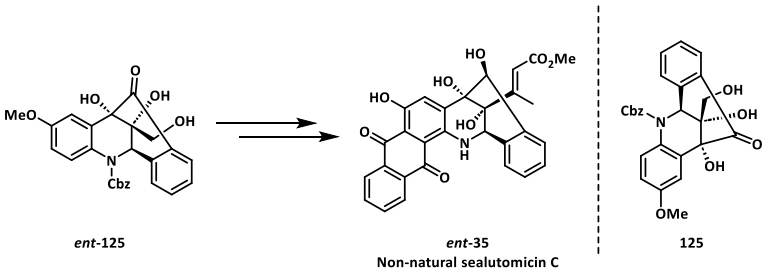
Lastly my family. Thank you to my parents, Sheila and Ian, for encouraging me to follow my interests and to ask questions, for the continuous loving care and for invariably being there for me through good times and bad. Thank you to my sister, Helen, for always being someone to talk to, for the level-headed calmness in times of worry, and for some cracking hiking trips in Scotland. To grow up in such a nurturing family can't be taken for granted and I can't thank you enough.

Notes on Convention

In this thesis, enantiomerically enriched species will be represented with solid and broken wedge bonds. In contrast, solid and broken bold bonds will be used to represent the relative configuration of multiple stereocentres within a racemic sample.



Each compound drawn is given a reference number. Instances of a chiral compound being present as a racemate will be shown by the prefix "*rac*". Where a non-racemic chiral compound is presented, the prefix "*ent*" will be used when the species is related to the preparation of the non-natural enantiomer of a natural product or analogue.



ent-125 | *ent*-35 Non-natural sealutomicin C | 125

Compounds reported in the format "***Author-X***" refer to compounds reported in literature publications where "author" refers to the principal author of the publication and "X" refers to the number assigned to the particular compound in the publication.

Abbreviations

µg	microgram
µM	micromolar
Å	angstrom
ABNO	9-azabicyclonona *N*-oxyl
Ac	acetyl
AFE	anthraquinone-fused enediyne
Alloc	allyloxycarbonyl
aq.	aqueous
Ar	aryl
B	base
BAIB	bis(acetoxy)iodobenzene
BIPY	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzyloxycarbonyl
CD	circular dichroism
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DMB	3,4-dimethoxybenzyl
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EC_{50}	half maximal effective concentration
ee	enantiomeric excess
EI	electron impact
ent	enantiomeric
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
et al.	*et alia*
g	gram
h	hour
hept	heptet
HMBC	heteronuclear multiple bond coupling
HMDS	hexamethyldisilazide

HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
IR	infra-red
J	coupling constant
LDA	lithium diisopropylamide
LLS	longest linear sequence
LRMS	low-resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
m.p.	melting point
m/z	mass/charge ratio
Me	methyl
mg	milligram
MIC	minimum inhibitory concentration
min	minute
mL	millilitre
mmol	millimole
MS	molecular sieve
ng	nanogram
NMI	*N*-methylimidazole
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser spectroscopy
pg	picogram
PG	protecting group
Ph	phenyl
PhMe	toluene
Piv	pivaloyl
PKSE	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
q	quartet

R	generic group
rac	racemic
R_f	retention factor
rOe	rotating-frame Overhauser effect
ROESY	rotating-frame Overhauser enhancement spectroscopy
RT	room temperature
s	singlet
t	triplet
TBAI	tetra-*n*-butylammonium iodide
TE	thioesterase
Temp	temperature
TEMPO	tetramethylpiperidine *N*-oxyl
TES	triethysilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
t_R	retention time
Ts	*para*-toluenesulfonyl
wt.	weight
X	halide

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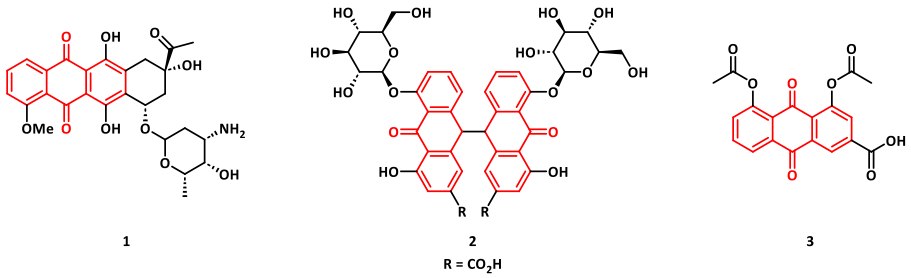
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Chapter 1: Introduction

1.1 Sealutomicin C and Related Natural Products

1.1.1 Anthraquinone-Fused Enediynes

For generations, natural products have played a vital role in the discovery of new drugs across a wide range of therapeutic areas.[1,2] Anthraquinone-fused natural products, bearing an anthracene-9,10-dione motif, have provided numerous medicinally valuable chemical entities which have resulted in the development of many clinically approved drugs.[3] Examples include the chemotherapeutic daunorubicin, the laxative sennoside A and the anti-inflammatory diacerein (**1** – **3**, **Figure 1.1**). Anthraquinone-fused natural products may be divided into three distinct structural categories: monomeric anthraquinoids such as **1**, dimeric mono-linked anthraquinoids such as **2**, and dimeric multi-linked anthraquinoids.



1 2 3

Scheme 1.1: Anthraquinone-fused natural product therapeutics daunorubicin (**1**), sennoside A (**2**) and diacerein (**3**), with the anthracene-9,10-dione motif highlighted in red.

Anthraquinone-fused enediynes (AFEs) are a sub-family of monomeric anthraquinoid natural products, possessing both an anthraquinone unit and a cyclic enediyne core.[4] The first member of this natural product class to be reported, dynemicin A (**4**, **Figure 1.2**), was isolated in 1989 by Konishi *et al.* from the fermentation broth of the bacterium *Micromonospora chersina* M956-1.[5,6] Prior to the discovery of **4**, other natural products bearing enediyne cores had been isolated, such as neocarzinostatin, esperamicin A_1, calicheamicin and C-1027; however, **4** represented the first reported natural product possessing an anthraquinone motif in addition to the enediyne unit.[7–10] AFE **4** was found to display potent antibacterial and antitumour activities, with MIC and IC_{50} values

in the pg/mL to ng/mL range against many bacterial strains and tumour cell lines. Following its enantioselective synthesis by Myers *et al.* in 1995, the absolute configuration of **4** was determined as (2*S*, 3*S*, 4*S*, 7*R*, 8*R*).[11]

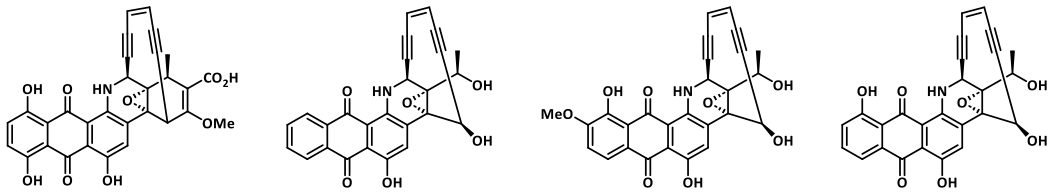
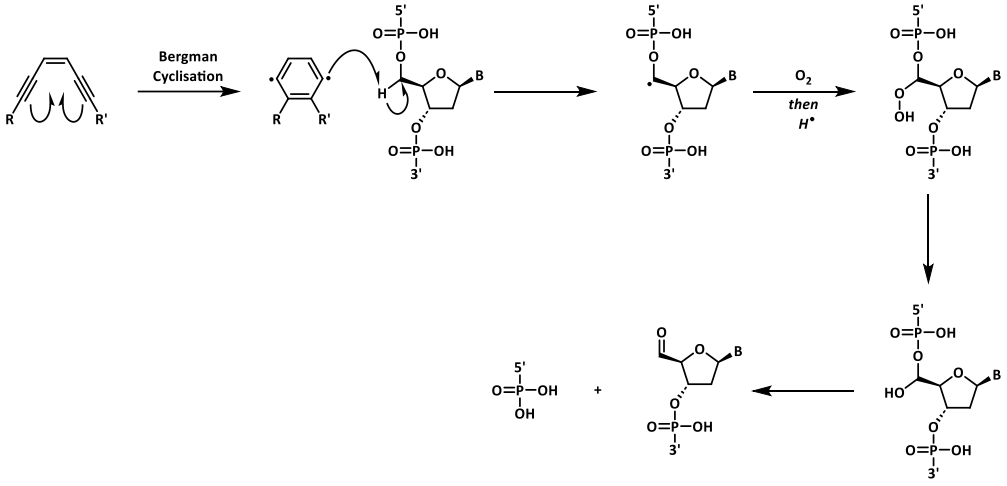


Figure 1.2: Anthraquinone-fused enediynes dynemicin A (**4**), uncialamycin (**5**), tiancimycin A (**6**) and yangpumicin A (**7**).

Since the discovery of **4**, AFEs have received considerable attention from the isolation, synthetic and medicinal chemistry communities, owing to both their potent biological activities (*vide infra*) and intriguing chemical structures. In 2005, Andersen *et al.* isolated uncialamycin (**5**) from cultures of the actinomycete *Streptomyces uncialis* as part of a screening programme to identify natural products that inhibit the growth of *Burkholderia cepacia*.[12] More recently, Shen *et al.* isolated both tiancimycin A (**6**) and yangpumicin A (**7**) using a genome mining approach.[13,14] By analysing all (at the time) ten enediyne biosynthetic gene clusters, the authors were able to identify a set of five genes common to all ten clusters, collectively termed the enediyne polyketide synthase gene cassette. By screening the genomes of nearly 15,000 bacterial strains for this gene cassette, new enediyne-producing strains could be identified, resulting in the isolation and characterisation of tiancimycin A and yangpumicin A from *Streptomyces* sp. CB03234 and *Micromonospora yangpuensis* respectively. Whilst dynemicin A possesses an intact eastern F-ring, the other three AFEs instead bear a hydroxyethyl chain and differ from each other only in their respective oxygenation patterns of the anthraquinone moiety.

Like dynemicin A, uncialamycin, tiancimycin A and yangpumicin A all display potent antitumour properties, with ng/mL IC_{50} values reported against a range of human cancer cell lines.[14] Uncialamycin also showed excellent antibacterial activity against drug resistant strains such as

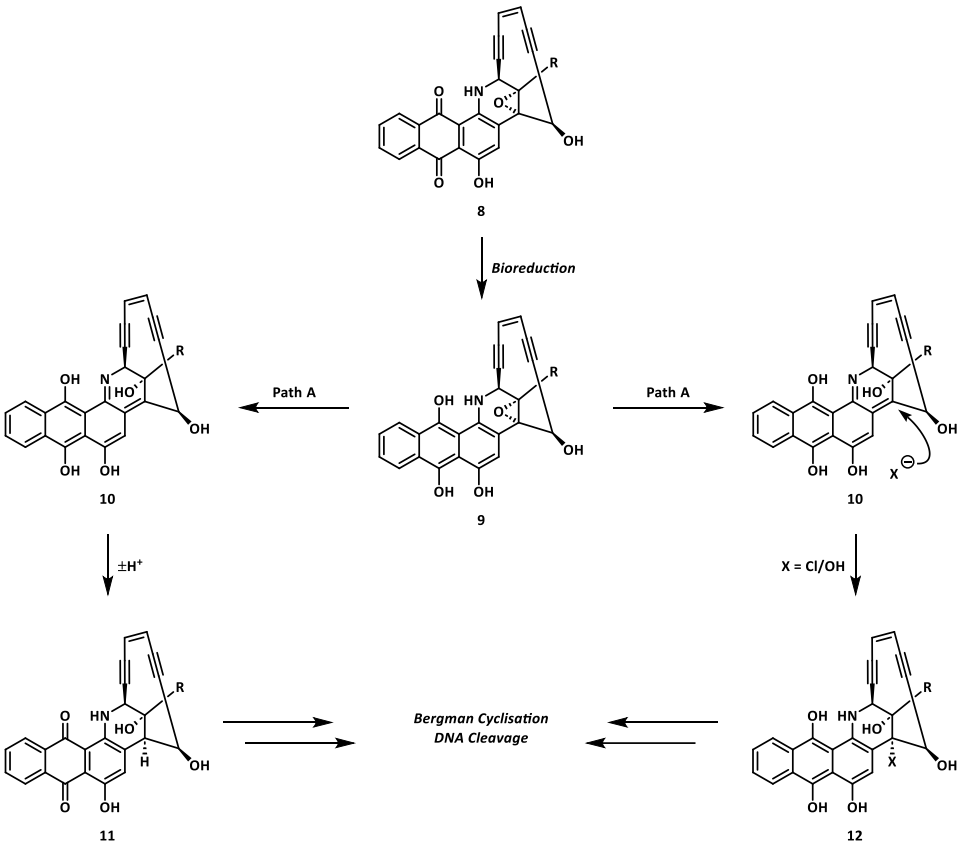
MRSA (MIC = 0.2 ng/mL) and *Burkholderia cepacia* (MIC = 2 ng/mL).[12,15] The cytotoxic activities of AFEs have been extensively studied, revealing considerable insight into their mechanism of action.[16–20] Intercalation of the anthraquinone unit into double-stranded DNA results in the enediyne portion of the molecule being held in the minor groove of the DNA helix, in close proximity to the phosphate-deoxyribose backbone. Bergman cyclisation of the enediyne fragment gives a *para*-benzyne diradical which is capable of hydrogen atom abstraction from the DNA backbone (**Scheme 1.1**). Oxygen atom transfer to the resultant DNA-centred radical from molecular oxygen is followed by DNA fragmentation, triggering DNA cleavage and interstrand cross-linkage, both of which result in cell apoptosis. Cleavage occurs predominantly at the 5' position of A and T residues, as shown in **Scheme 1.1**; however, DNA cleavage may also occur either under anaerobic conditions or at other sites of the DNA backbone.



Scheme 1.1: Bergman cyclisation of an enediyne followed by H-abstraction from DNA and subsequent DNA fragmentation.

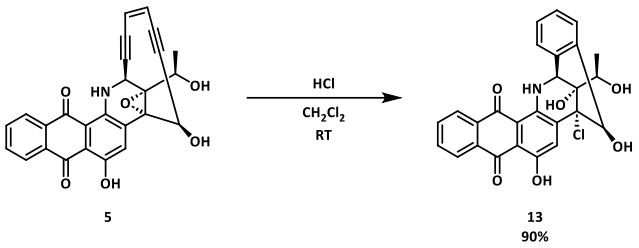
Despite the DNA-cleaving potential of the enediyne warhead, AFEs show high stability both in their pure form and in a range of solutions.[21] The strain arising from the epoxide moiety results in the two alkyne units being held too far apart for cycloaromatisation to readily occur (**Scheme 1.2**). Opening of the epoxide unit relieves this strain, bringing the alkyne units close enough together to trigger cycloaromatisation to the aryne diradical. Under physiological conditions, this epoxide opening is enabled by bioreduction of the anthraquinone core to anthraquinol **9**.[22] The more

electron-rich aromatic system of **9** enables intramolecular epoxide opening to quinone methide **10**, which may in turn either tautomerise to give anthraquinone **11** (**Path A**) or undergo nucleophilic attack to form anthraquinol **12** (**Path B**). In both cases, the alkyne units are brought close enough together to enable enediyne cycloaromatisation and subsequent DNA fragmentation.



Scheme 1.2: Bioreductive epoxide opening and subsequent enediyne cycloaromatisation of AFE **8**.

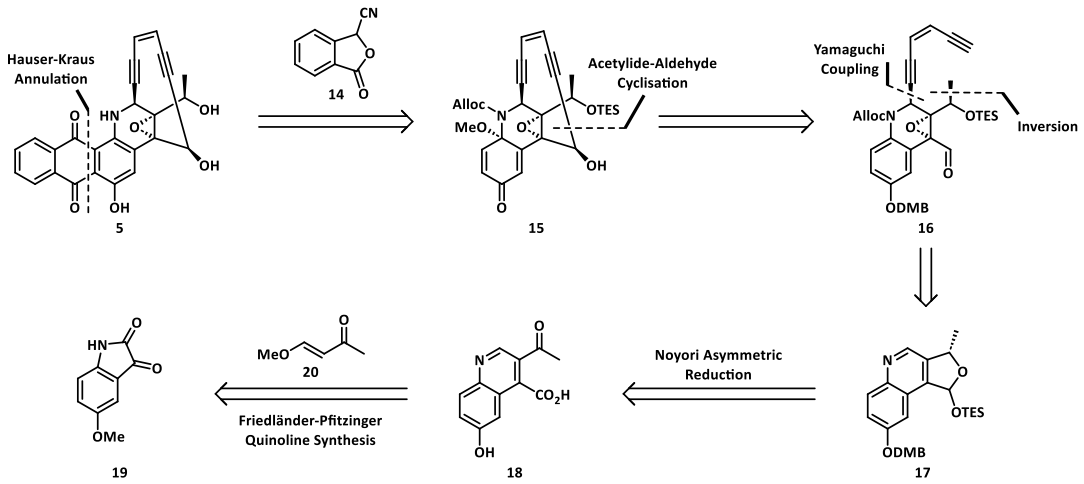
The cycloaromatisation of AFEs may also be triggered by acid-mediated epoxide opening. Nicolaou *et al.* showed that treatment of a solution of uncialamycin (**5**) in dichloromethane with dry HCl resulted in rapid conversion to hexacycle **13** in 90% yield (**Scheme 1.3**). Whilst this acid-mediated cycloaromatisation is unlikely to occur at physiological pH in biological systems, it provides additional evidence for the role of the epoxide unit in controlling the reactivity of the enediyne motif.



Scheme 1.3: Acid-mediated epoxide opening and subsequent cycloaromatisation of uncialamycin (**5**) to hexacycle **13**.

Over the past 20 years, studies towards the total synthesis of AFEs have been spearheaded by K.C. Nicolaou and co-workers, who in 2007 reported the first synthesis of racemic uncialamycin in 22 steps from commercially available starting materials.[21] This work, which enabled the relative configuration of the hydroxyethyl side chain to be determined, was followed a year later by an enantioselective synthesis of **5**, which employed an asymmetric Noyori transfer hydrogenation as the key chirality-installing step.[15] In 2016, the same group published a more streamlined synthesis of **5** and analogues, with a view to trialling the use of these analogues in antibody-drug conjugates for the treatment of cancer.[23] This synthesis, carried out in collaboration with Bristol-Myers Squibb, enabled the preparation of **5** on 100 mg scale in 11% overall yield over 23 steps.

Scheme 1.4 shows the key retrosynthetic disconnections employed during the third synthesis of **5**. A Hauser-Kraus annulation of cyanophthalide **14** with hemiquinone aminal **15** was used to install the anthraquinone unit, whilst the cyclisation of an acetylide onto a pendant aldehyde **16** enabled the closure of the 10-membered enediyne ring. The enediyne fragment was installed *via* a Yamaguchi coupling, whilst an asymmetric Noyori transfer hydrogenation was again employed as the key chirality-installing step, enabling the formation of lactol **17** from ketone **18**. Ketone **18** was in turn prepared using a Friedländer-Pfitzinger quinoline synthesis, enabling the use of cheap, commercially available 5-methoxyisatin **19** as starting material. The late-stage Hauser-Kraus annulation used to install the anthraquinone motif also allowed a variety of analogues of **5** to be prepared *via* the reaction of aminal **15** with substituted derivatives of cyanophthalide **14**. More recently, the same synthetic route was used as a blueprint by Nicolaou *et al.* for the synthesis of tiancimycins A and B, yangpumicin A and additional uncialamycin derivatives.[24]



Scheme 1.4: Key retrosynthetic disconnections employed during Nicolaou's streamlined third-generation total synthesis of uncialamycin.

1.1.2 Cycloaromatised Natural Products

Over the past 35 years, the search for new AFEs and investigations into their syntheses and mechanisms of action have also led to the discovery of many cycloaromatised metabolites derived from AFE biosynthetic precursors. In 1990, Konishi *et al.* reported the isolation of dynemicins M and N (**21** and **22**, **Figure 1.3**) from the same bacterial culture that had produced dynemicin A.[6] The same group reported the isolation of dynemicins O (**23**) and Q (**24**) a year later.[25] These four compounds all possess a bridging aryl ring, derived from Bergman cyclisation of an enediyne precursor, with varying substitution and oxidation patterns around the eastern F-ring. Interestingly, both dynemicins O and Q showed moderately potent antibacterial and antitumour properties, despite lacking a DNA-cleaving enediyne warhead, with MIC and IC_{50} values ranging from 0.1 – 10 μg/mL. In 2016, the Shen group reported the isolation of yangpumicins B – E (**25** – **28**) from *Micromonospora yangpuensis*, all four of which possess the same bridging aryl ring, with either a proton or hydroxyl group at the site of the epoxide opening.[14] More recently, during gene knockout studies designed to probe the biosynthesis of AFE natural products, the same group isolated a variety of cycloaromatised metabolites from genetically modified *Streptomyces* sp. CB03234.[26] These metabolites all possessed either a hydroxybutenolide (**29**) or an α,β-unsaturated ester (**30**) side chain, with a variety of oxygenation patterns observed around the anthraquinone unit and

bridging aryl ring. No data was published by the Shen group regarding the biological activities of the cycloaromatised compounds isolated in these two studies.

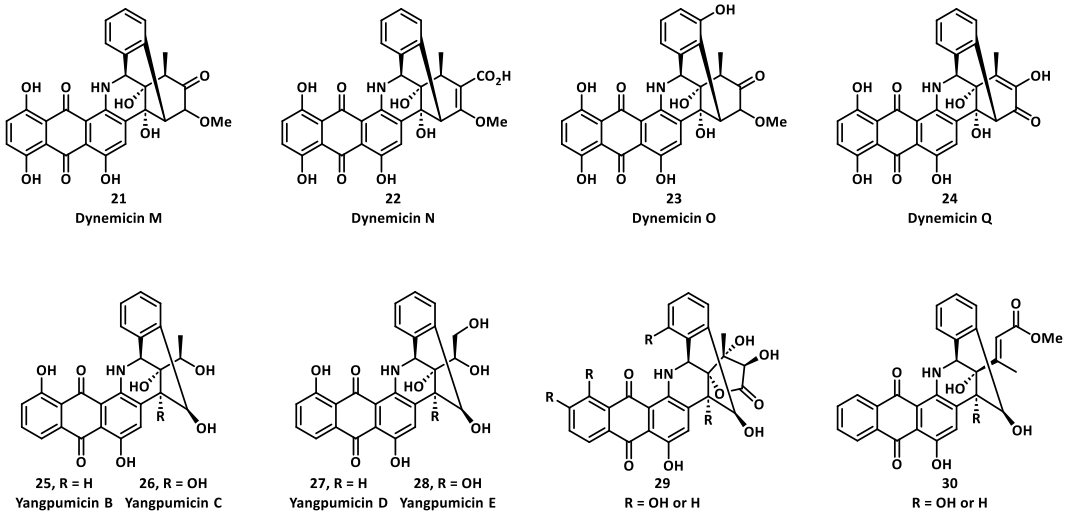
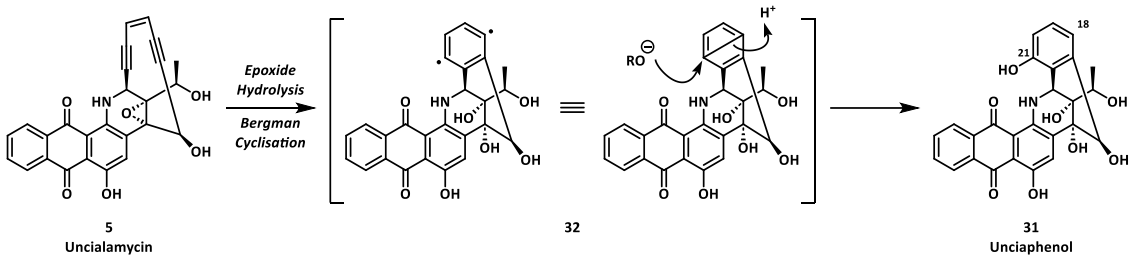


Figure 1.3: Cycloaromatised shunt metabolites isolated alongside AFE natural products.

In 2015, Andersen *et al.* reported the isolation of a new cycloaromatised metabolite, unciaphenol, from cultures of *Streptomyces uncialis* (**31**, **Scheme 1.5**).[27] Like dynemicin O, unciaphenol bears a hydroxyl unit on the bridging aryl ring formed during the Bergman cyclisation of the enediyne unit, albeit in a different position. The authors propose that unciaphenol is made biosynthetically from uncialamycin, with the hydroxyl unit installed *via* attack of an oxygen-based nucleophile on the *para*-benzyne diradical intermediate **32** following enediyne cycloaromatisation. As the Bergman cyclisation of an enediyne produces a singlet diradical, the two singly occupied sp^2 orbitals may interact across the aromatic ring. Molecular orbital calculations have shown that the resulting orbital is antibonding, meaning nucleophilic attack should be facile; thus, the presence of a hydroxyl group at C(21) in unciaphenol and C(18) in dynemicin O may be rationalised by this mechanism.[28–30] This nucleophilic attack could feasibly occur either with or without enzymatic assistance; however, the regioselective O-incorporation observed at C(21) in *Streptomyces uncialis* and at C(18) in *Micromonospora chersina* is consistent with enzymatic involvement. Alternatively, the phenolic hydroxyl groups of **23** and **31** could be installed *via* cytochrome P450 enzymatic oxidation of the benzene ring formed by hydrogen trapping of the *para*-benzyne intermediate.[31]



Scheme 1.5: Unciaphenol (**31**) and proposed biosynthetic formation from uncialamycin (**5**) *via* nucleophilic trapping of *para*-benzyne intermediate **32**.

Unciaphenol was found to inhibit *in vitro* HIV-1 replication without concomitant cytotoxicity to host T-cells (EC_{50} = 9.9 µM). Similar inhibitory effects were observed for T-cells infected with recombinant strains of HIV resistant to the clinically useful antiretroviral therapies indinavir (protease inhibitor, EC_{50} = 14.1 µM), efavirenz (reverse transcriptase inhibitor, EC_{50} = 13.6 µM) and raltegravir (integrase inhibitor, EC_{50} = 6.5 µM). The different mechanisms of action by which these three antiretroviral therapies operate would appear to indicate that unciaphenol inhibits HIV replication by its own distinct mechanism of action. However, since its isolation, no further investigations into the biological activities of this natural product have been carried out. The antiviral activity of unciaphenol, and the antibacterial and antitumour activities displayed by dynemicins O and Q, illustrate that despite the absence of a DNA-fragmenting enediyne warhead, cycloaromatised anthraquinone-fused metabolites display exciting biological activities. At the time of writing, further investigations are required to better understand the mechanisms of action of this class of molecules and to probe their potential therapeutic utility.

1.1.3 Sealutomicins

In 2021, Igarashi *et al.* reported the isolation of four new anthraquinone-fused metabolites from the bacterium *Nonomurea sp.* MM565M-173N2.[32] The first of the four metabolites, sealutomicin A (**33, Figure 1.4**), was identified as a novel anthraquinone-fused enediyne, with a branched side chain containing both a terminal alkene and a methyl ester. The absolute configuration of **33** was assigned by comparison of its circular dichroism spectrum to that of dynemicin A, which was almost identical. By contrast, sealutomicins B – D were all identified as cycloaromatised metabolites,

bearing the same bridging aryl ring previously observed in unciaphenol, dynemicins M – Q and yangpumicins B – E. Sealutomicins B and D both possess a hydroxybutenolide side chain, whereas sealutomicin C possesses an (*E*) α,β-unsaturated ester motif. The authors proposed that **34** – **36** were not generated during the purification process of **33** but were instead produced during the process of bacterial fermentation.

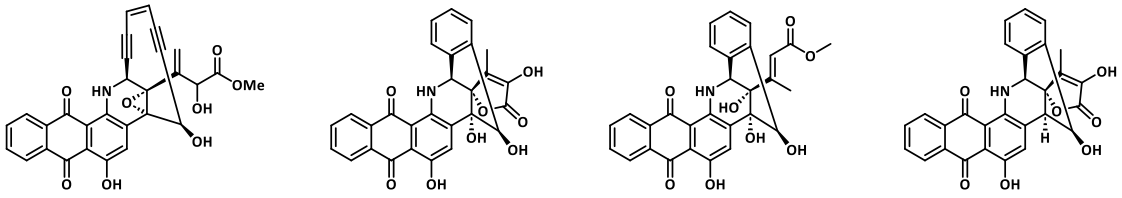


Figure 1.4: Sealutomicins A – D.

The authors propose that sealutomicin C is the same structure as compound ***Shen-14*** reported by Shen *et al.* in their 2018 gene knockout study previously discussed.[26] However, the two studies used different deuterated solvents during their respective NMR analyses of isolated metabolites; Shen *et al.* used acetone-d_6 whereas Igarashi *et al.* used DMSO-d_6. As a result, the proposal that compound ***Shen-14*** is the same structure as sealutomicin C could not be verified.*

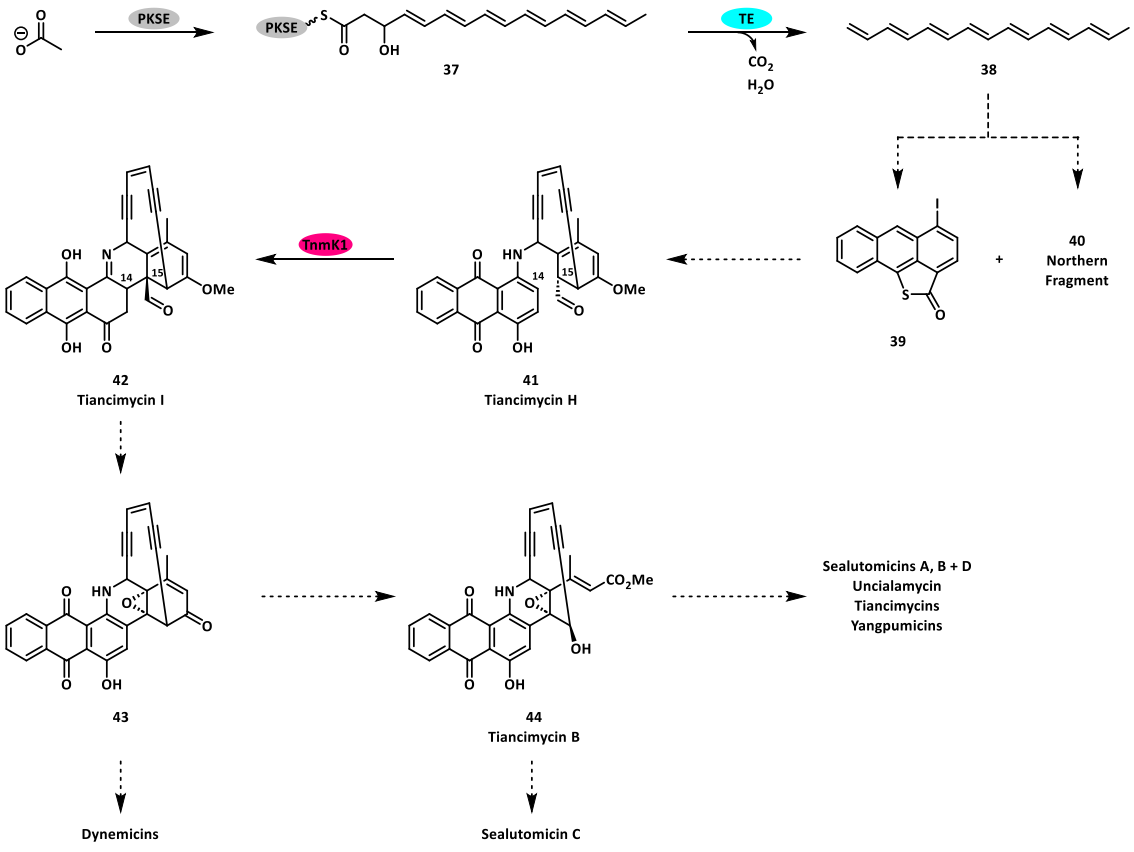
Sealutomicin A was found to display potent *in vitro* antibacterial activity against both Gram-positive and Gram-negative bacteria, with MIC values ranging from 6 – 100 ng/mL. Despite lacking a DNA-fragmenting enediyne unit, sealutomicins B – D all displayed moderate antibacterial activity against Gram-positive bacteria, with MIC values ranging from 0.2 – 3 μg/mL. The authors note that the mechanism of action by which **34** – **36** exert their antibacterial activity is not currently understood and warrants further investigation. They also note that given the anti-HIV activity displayed by the structurally similar cycloaromatised natural product unciaphenol, future efforts to investigate potential antiviral activities of **34** – **36** would be of interest. However, the small quantities of **34** – **36**

* *It should be noted that the tabulated ^{1}H and ^{13}C NMR data reported for compound **Shen-14** by Shen et al. do not match the graphical ^{1}H and ^{13}C NMR spectra reported by Shen et al. for the same compound.*

isolated during the study (1.5 mg, 0.8 mg, and 0.8 mg respectively) would be likely to limit such investigations.

1.1.4 Biosynthesis of AFEs and Related Metabolites

The complex and uniquely functionalised molecular architectures of enediyne-fused natural products have inspired numerous studies seeking to understand their biosynthetic origin. Early feeding studies indicated a polyketide origin for both the enediyne and anthraquinone units of dynemicin A; however, it is only in recent years that much of the current understanding of AFE biosynthesis has come to light.[33–35] **Scheme 1.6** depicts this current view.



Scheme 1.6: Current understanding of biosynthetic pathways to anthraquinone-fused enediynes and derivatives. Solid arrows represent single biosynthetic steps. Dotted arrows represent multiple biosynthetic steps.

Studies by Townsend *et al.* have shown that an iterative type I polyketide synthase (PKSE) is responsible for the formation of a PKSE-tethered β-hydroxyhexaene **37** from acetate building blocks. Subsequent thioester hydrolysis, decarboxylation and hydroxyl elimination are facilitated by

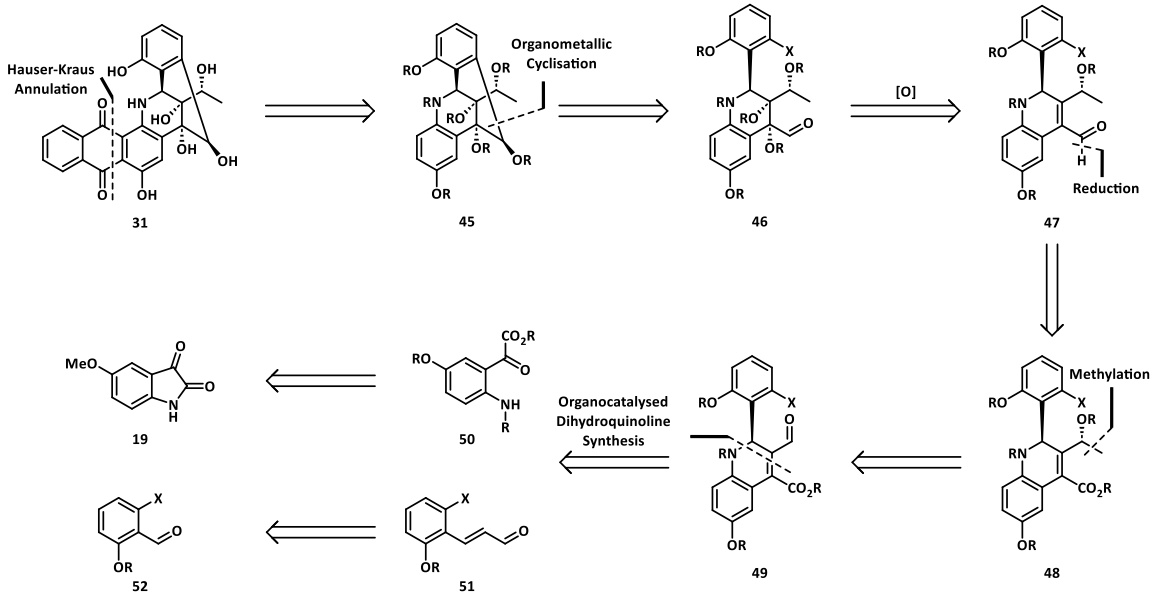
a thioesterase (TE) enzyme to give C_{15}-heptaene **38**.[36,37] Shen *et al.* have recently shown that **38** is an on-pathway intermediate to both the anthraquinone and enediyne portions of the AFE scaffold.[38] Divergent manipulation of **38** results in the formation of γ-thiolactone-fused iodoanthracene **39**, which serves as a precursor to the anthraquinone unit, and an unidentified northern fragment **40** containing the enediyne moiety.[39] Unification of these two components results in the formation of tiancimycin H (**41**), bearing an aldehyde unit. Shen *et al.* recently showed that the enzyme TnmK1, an α,β-hydrolase, catalyses the formation of an enolate from this aldehyde and its subsequent nucleophilic attack onto the adjacent anthraquinone ring, forming the key C(14)-C(15) bond linking the anthraquinone and enediyne scaffolds.[40] Aldehyde removal and epoxidation results in the formation of hexacycle **43**. The dynemicin biosynthetic pathway likely diverges here, requiring both conservation and additional modification of the eastern F-ring.[26] For the biosynthesis of other AFEs, oxidative cleavage of the eastern F-ring of **43** gives tiancimycin B (**44**) bearing an (*E*)-α,β-unsaturated ester side chain. Sealutomicin C is proposed to be the cycloaromatised metabolite derived from **44**. Additional manipulation of this side chain, and C-H oxidation of the anthraquinone unit results in the biosyntheses of uncialamycin, the tiancimycins, the yangpumicins and the remaining sealutomicins.

Whilst the recent studies discussed above have shed considerable light on the biosynthesis of AFEs and related congeners, further investigations are required to fully understand the pathways by which these intriguing natural product scaffolds are prepared. Identifying the structure of northern fragment **40** and understanding both its preparation and subsequent unification with iodoanthracene **39** to give tiancimycin H are of particular interest to the natural product chemistry community. It is hoped that future studies will enable understanding of the full biosynthetic preparation of AFEs from simple metabolic substrates.

1.2 Previous Burton Group Studies Towards Cycloaromatised Natural Products

1.2.1 Proposed Total Synthesis of Unciaphenol

Previous work in the Burton group by former PhD student Dr Sean Guggiari concerned studies towards the enantioselective total synthesis of the natural product unciaphenol (**31**).[41] With its interesting biological profile, intriguing molecular architecture and an absence of previous syntheses, this natural product represented a promising target to the synthetic chemistry community. Guggiari's proposed retrosynthesis of **31** is shown in **Scheme 1.7**.



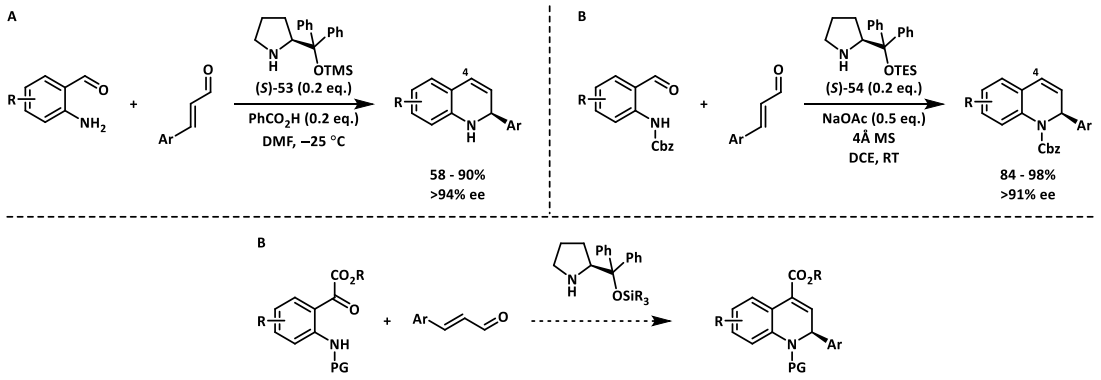
Scheme 1.7: Retrosynthetic analysis of unciaphenol (**31**) by Guggiari.

The anthraquinone unit would be installed using a Hauser-Kraus annulation, as used by Nicolaou *et al.* in their syntheses of uncialamycin. An organometallic-mediated cyclisation of an aryl halide onto a pendant aldehyde **46** would be used to install the bridging bond connecting the aromatic ring of **45** to its adjacent secondary alcohol. Substrate-controlled dihydroxylation of alkene **47** was envisaged to deliver the 1,2-*syn* diol unit, whilst the aldehyde handle would be obtained by reduction of an ester **48**. It was proposed that the secondary allylic alcohol of **48** would be obtained by a diastereoselective methylation of aldehyde **49**. Formation of the chiral dihydroquinoline core of **49** was proposed to take place *via* the enantioselective organocatalysed coupling of an α-keto

ester **50** and a 2,6-disubstituted cinnamaldehyde **51**. These two components could be prepared from 5-methoxyisatin **19** and a 2,6-disubstituted benzaldehyde **52** respectively. As the formation of dihydroquinoline **49** in a high-yielding, enantioselective manner would be crucial to the success of the synthesis, initial work focused on the development of a suitable method to effect this.

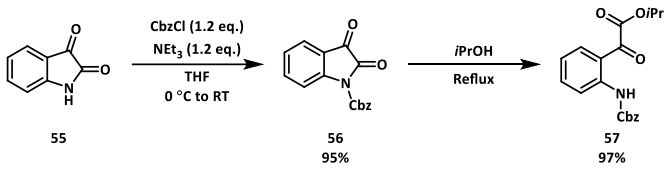
1.2.2 Development of an Enantioselective, Organocatalytic 1,2-Dihydroquinoline Synthesis

Recent years have seen the publication of a variety of methods for the preparation of enantioenriched 1,2-dihydroquinolines. Strategies starting from a pre-formed heterocyclic core include kinetic resolution of racemic 1,2-dihydroquinolines[42,43] and enantioselective organometallic addition[44–49]; however, perhaps the most explored disconnection has been to install the chiral centre during or prior to heterocycle formation. Two early such examples, from the groups of Wang and Córdova, utilised diarylprolinol silyl ether catalysts to effect an aza-Michael/aldol cascade coupling of 2-aminobenzaldehydes with cinnamaldehydes in order to access aryl-substituted 1,2-dihydroquinolines in high yields and >90% *ee* (**Scheme 1.8, A + B**).[50,51] Whilst the dihydroquinolines synthesised in both works lacked substituents at the C(4) position, Guggiari hoped that this methodology could be adapted to the synthesis of the target dihydroquinoline core, by switching the 2-aminobenzaldehyde component for the analogous keto-ester (**Scheme 1.8**, **C**). Such a change would give access to dihydroquinolines bearing a C(4) ester handle, which could subsequently be manipulated during the remainder of the synthesis of unciaphenol.



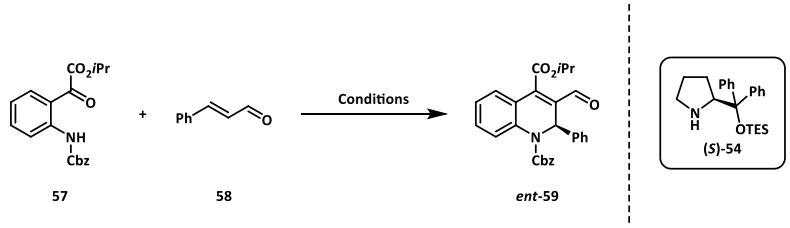
Scheme 1.8: Enantioselective chiral dihydroquinoline synthesis by A) Cordova *et al.* and B) Wang *et al.*; C) Proposed enantioselective dihydroquinoline synthesis by Guggiari.

To investigate the proposed modified organocatalytic cascade, keto-ester **57** was selected as a suitable model substrate. Keto-ester **57** was prepared in almost quantitative yield over two steps from commercially available isatin **55** *via* carbamate protection of the nitrogen unit and subsequent alcoholysis (**Scheme 1.9**).[52]



Scheme 1.9: Guggiari's two-step synthesis of model substrate keto-ester **57**.

Coupling of keto-ester **57** with *trans*-cinnamaldehyde **58** using triethylsilyl prolinol catalyst ***ent*-54** under the conditions reported by Wang gave the desired chiral dihydroquinoline ***ent*-59** in poor yield but excellent enantioselectivity (**Table 1.1**, **entry 1**). Following extensive optimisation of the reaction, Guggiari's improved reaction conditions gave ***ent*-59** in 92% yield and 98% *ee* (**Entry 2**).

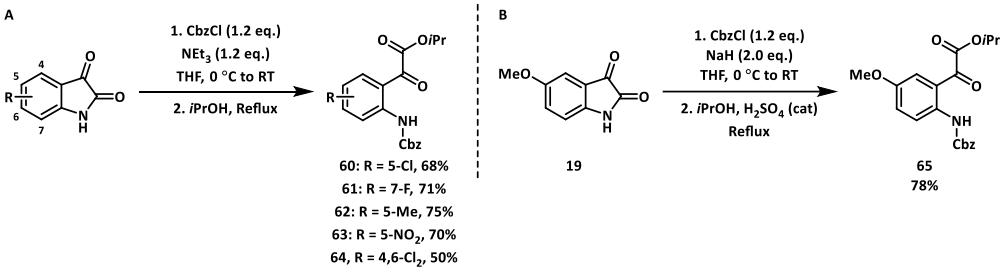


Entry	Conditions	Yield *ent*-59[a]	ee *ent*-59
1	**57 (3.0 eq.), 58 (1.0 eq.) (*S*)-54 (0.2 eq.), NaOAc (0.5 eq.) 4 Å MS, DCE (0.5 M) RT**	**8%**	**98%**
2	**57 (2.0 eq.), 58 (1.0 eq.) (*S*)-54 (0.2 eq.), $PhCO_2H$ (0.5 eq.) 4 Å MS, CH_2Cl_2 (0.5 M) RT**	**92%**	**98%**

Table 1.1: Organocatalysed coupling of keto-ester **57** and cinnamaldehyde **58** to give dihydroquinoline ***ent*-59**. [a] Yield based on aldehyde **58**.

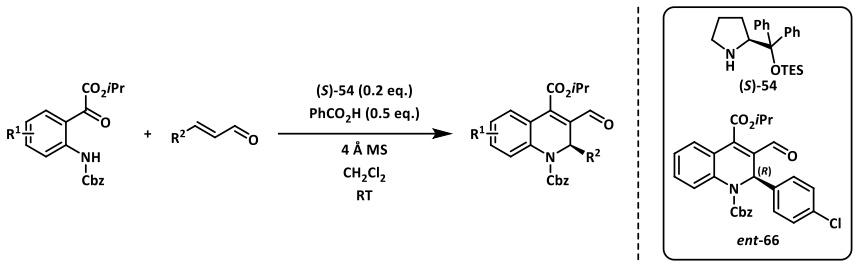
With the optimised conditions established, a series of substrates were trialled by Guggiari to assess the scope of the organocatalytic coupling. In order to carry out the scope, a series of substituted keto-ester substrates were prepared from commercially available isatin starting materials.

Keto-esters **60** – **64** were prepared using the same two step procedure as model substrate **57**, with carbamate protection followed by alcoholysis in isopropanol (**Scheme 1.10**, **A**). 5-Methoxy keto ester **65** was prepared from 5-methoxyisatin (**19**) using slightly modified conditions, with sodium hydride employed as a base during the carbamate protection step, and catalytic sulfuric acid added during the subsequent alcoholysis step (**Scheme 1.10**, **B**).[53]



Scheme 1.10: A) Guggiari's preparation of keto-esters **60** – **64**; B) Guggiari's preparation of keto-ester **65** using modified procedure.

Halogen, methyl, nitro and methoxy substituents were generally well tolerated on the aromatic ring of the isatin-derived keto-ester (**Table 1.2**, **Entries 1 – 5**). The one exception was the 4,6-dichloro keto-ester, which gave a considerably lower *ee* (**Entry 6**). On the aldehyde reactant, a variety of substrates gave dihydroquinolines in excellent enantioselectivity and useable yields, although it was noticeable that electron-donating substituents and sterically demanding *ortho*-substituents resulted in sluggish reactivity and lower yields than electron-withdrawing and *meta*/*para* substituents (**Entries 7 – 13**). No dihydroquinoline product was observed when a cinnamaldehyde bearing a free *ortho*-hydroxyl substituent was subjected to the reaction conditions (**Entry 14**). The absolute configuration of chloro-substituted dihydroquinoline ***ent*-66** was determined to be (*R*) by X-ray crystallography (**Figure 1.5**). The absolute configuration of all other products formed was assigned by analogy to ***ent*-66**.



Entry	R^1	R^2	Yield[a]	ee
1	5-Cl	Ph	92%	98%
2	7-F	Ph	78%	97%
3	5-Me	Ph	94%	98%
4	5-NO_2	Ph	77%	97%
5	5-OMe	Ph	83%	98%
6	4,6-Cl_2	Ph	98%	78%
7	H	4-ClC_6H_4	92%	98%
8	H	3-OMe-4-OAc-C_6H_3	90%	98%
9	H	4-$NO_2C_6H_4$	91%	98%
10	H	2-$NO_2C_6H_4$	70%	96%
11	H	2-$OMeC_6H_4$	39%	91%
12	H	4-$OMeC_6H_4$	74%	93%
13	H	2-BrC_6H_4	40%	95%
14	H	2-OHC_6H_4	0%	n.d.

Table 1.2: Guggiari's substrate scope of enantioselective organocatalytic dihydroquinoline synthesis. [a] Yield based on cinnamaldehyde starting material.

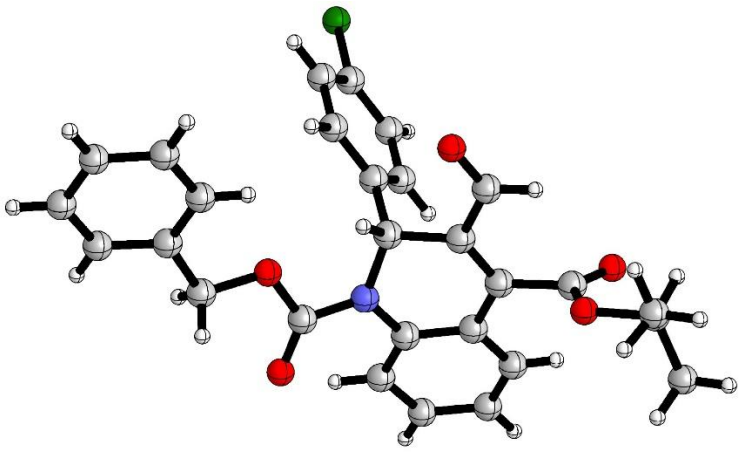
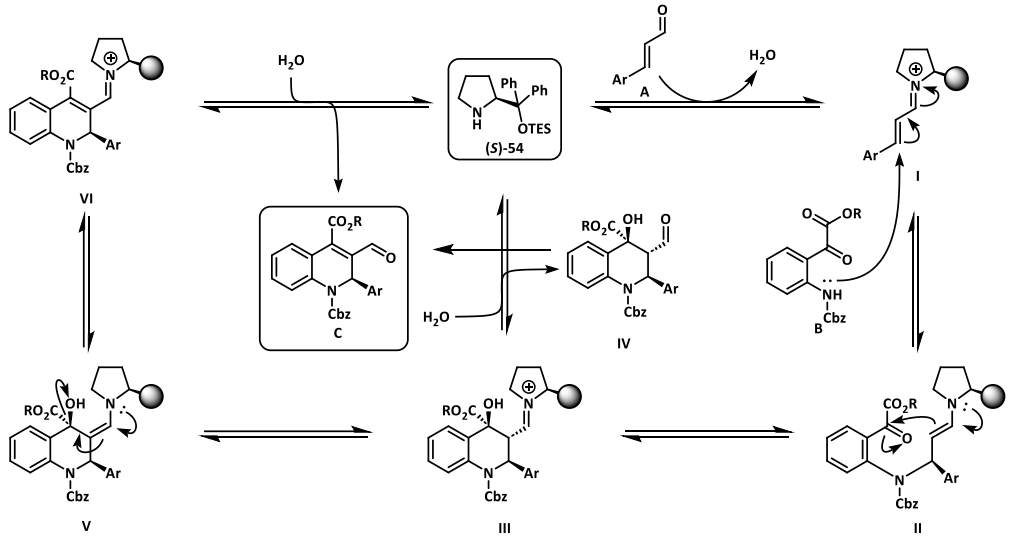


Figure 1.5: X-ray crystal structure of chloro-substituted dihydroquinoline ***ent*-66**.

Guggiari's proposed catalytic cycle for the dihydroquinoline synthesis is shown in **Scheme 1.11**. Condensation of catalyst **(*S*)-54** with cinnamaldehyde **A** gives α,β-unsaturated iminium ion **I**, adopting the s-*trans* conformation as shown to minimise steric clash between the silyl ether side chain and the styrene moiety. The increased electrophilicity of **I**, relative to the cinnamaldehyde starting material, enables Michael addition of the aniline unit of keto-ester **B**, which is directed to the lower face of the β-carbon of **I** by the silyl ether side chain which shields the upper face of the alkene unit. Cyclisation of the resultant enamine **II** onto the pendant ketone electrophile gives catalyst-bound aldol intermediate **III**. Hydrolysis of **III** regenerates the catalyst and gives aldol **IV**, which upon dehydration gives the dihydroquinoline product **C**. Alternatively, deprotonation of intermediate **III** may occur to give enamine **V**, which can in turn eliminate water to give catalyst-bound dihydroquinoline **VI**. Subsequent hydrolysis of **VI** releases the catalyst **(*S*)-54** and gives the dihydroquinoline product **C**. Guggiari noted that **Scheme 1.11** represents the simplest mechanism that rationalises the results observed for this organocatalytic cascade, with a more complex mechanism likely to operate.[54–56]

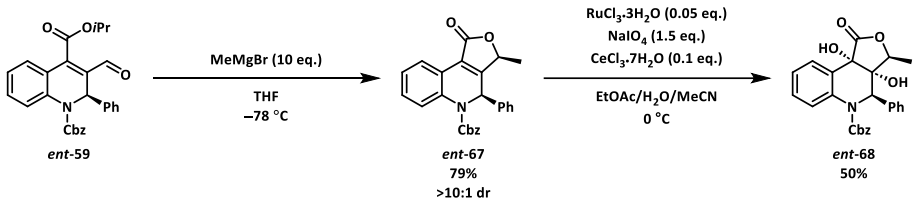


Scheme 1.11: Guggiari's proposed catalytic cycle for enantioselective dihydroquinoline formation.

1.2.3 Studies Towards the Total Synthesis of Unciaphenol

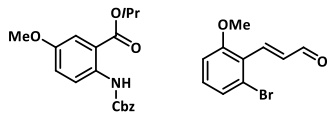
Having developed conditions to enable the synthesis of chiral dihydroquinolines and investigated the substrate scope of this reaction, the remainder of Guggiari's work focused on the application of this organocatalytic reaction to the synthesis of the natural product unciaphenol. Studies conducted by Guggiari were towards the unnatural enantiomer of unciaphenol (***ent*-31**).

Initial work used dihydroquinoline ***ent*-59** as a model system to investigate the proposed methylation and subsequent dihydroxylation steps (**Scheme 1.12**). Addition of ***ent*-59** to a solution of methylmagnesium bromide in THF at low temperature gave lactone ***ent*-67** in 79% yield and high diastereoselectivity. A ruthenium trichloride-catalysed dihydroxylation reported by Plietker *et al.* was used to install the 1,2-*syn* diol motif, giving diol ***ent*-68** as a single diastereomer in 50% yield.[57] Guggiari proposed that the adjacent phenyl ring and methyl group both shield the upper face of the alkene unit of ***ent*-67** , directing the dihydroxylation to the lower face of the alkene.



Scheme 1.12: Methylation and subsequent dihydroxylation of dihydroquinoline ***ent*-59**.

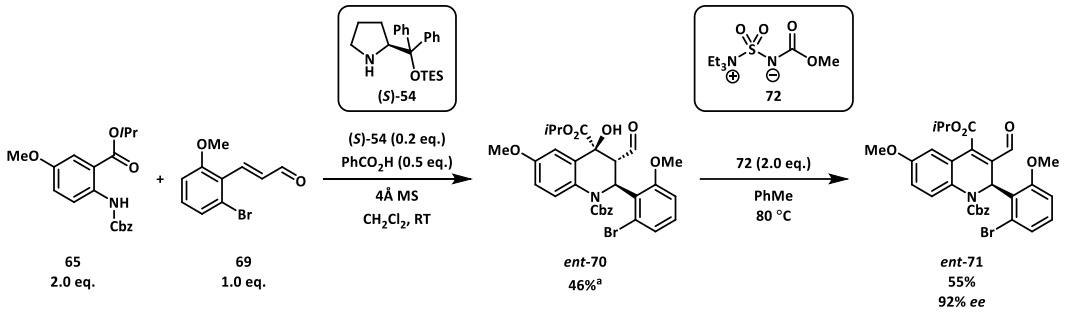
Having established conditions for the aldehyde methylation and facially selective dihydroxylation steps using a model system, Guggiari's attention turned to the synthesis of *ent*-unciaphenol (***ent*-31**). Methoxy keto-ester **65** and disubstituted cinnamaldehyde **69** were selected as the coupling partners to be used in the organocatalytic dihydroquinoline synthesis (**Figure 1.6**). The use of a 2,6-disubstitued cinnamaldehyde was necessary to enable subsequent derivatisation of resultant dihydroquinoline. The halide substituent was needed to provide a handle for the proposed organometallic cyclisation, whilst the methoxy substituent would be necessary to give access to the phenol unit of unciaphenol.



65 69

Figure 1.6: Keto-ester **65** and cinnamaldehyde **69** selected as dihydroquinoline synthesis substrates for the synthesis of unciaphenol.

Unfortunately, using **65** and **69**, the optimised organocatalysis conditions failed to give the target dihydroquinoline ***ent*-71**. Instead, after lengthy reaction times in excess of seven days, aldol intermediate ***ent*-70** was the only product that could be isolated from the reaction (**Scheme 1.13**). Subsequent dehydration of ***ent*-70** required treatment with Burgess reagent (**72**), giving the desired dihydroquinoline ***ent*-71** in just 25% yield over two steps, albeit in high enantioselectivity. Despite extensive efforts to reoptimise the reaction conditions for these substrates, the results in **Scheme 1.13** represent the best yield and *ee* obtained for dihydroquinoline ***ent*-71**. Higher loadings of catalyst **(*S*)-54** resulted in a lower *ee* of dihydroquinoline ***ent*-71** without any notable increase in the yield of aldol intermediate ***ent*-70**. Guggiari proposed that the poor reactivity observed may be due to steric shielding of the cinnamaldehyde β-position by the two *ortho* substituents of the aromatic ring, preventing nucleophilic attack by the keto-ester's aniline unit.



Scheme 1.13: Two-step synthesis of dihydroquinoline ***ent*-71** *via* aldol ***ent*-70**.[a] Yield based on cinnamaldehyde **69**.

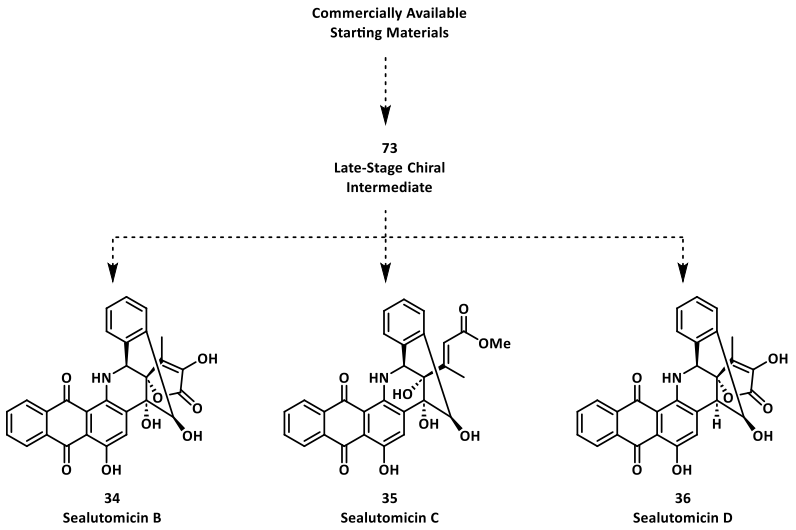
Due to time constraints imposed by his PhD deadline, no further progress was made by Guggiari towards the synthesis of unciaphenol. Unciaphenol remains a synthetic target for the Burton group, with the organocatalytic dihydroquinoline synthesis still considered the optimal method for constructing the core of the natural product. However, work towards the synthesis of unciaphenol

has been paused while the group prioritises the synthesis of other anthraquinone-fused cycloaromatised natural products.

It was postulated that the enantioselective dihydroquinoline synthesis methodology developed by Guggiari could be utilised as part of a synthetic strategy to prepare sealutomicins B – D. These three natural products display interesting antibacterial activities; however, the mechanism by which these activities occur has yet to be determined. Furthermore, the antiviral activity displayed by unciaphenol and the strong structural similarities between unciaphenol and sealutomicins B – D raise the possibility of hitherto unexplored antiviral activities of sealutomicins B – D. A synthetic route giving access to these three natural products would enable investigations into their potential antiviral activities and would also enable the mechanism by which these natural products exert their antibacterial activities to be further explored.

1.3 Project Aims

The overall goal of this project is to develop a divergent synthetic route to the three natural products sealutomicins B – D (**34** – **36**) as single enantiomers (**Scheme 1.14**). Such a synthetic route would allow investigations into the promising biological activities displayed by these natural products. The synthesis of sealutomicin C would also enable verification that sealutomicin C is indeed the same compound as metabolite ***Shen-14*** reported by Shen *et al* during their gene knockout studies of *Streptomyces* sp. CB03234. We anticipated that **34** – **36** may all be prepared *via* differential manipulation of a late stage chiral intermediate **73**, to maximise the efficiency of the synthesis of the three natural products. Ideally, the synthetic route to intermediate **73** would be both short and readily scalable. It was anticipated that the enantioselective organocatalytic dihydroquinoline synthesis methodology developed by Guggiari would then be employed to construct the core of **73**. Whilst the intention was to ultimately synthesise all three natural products, initial attempts focused on the synthesis of sealutomicin C.

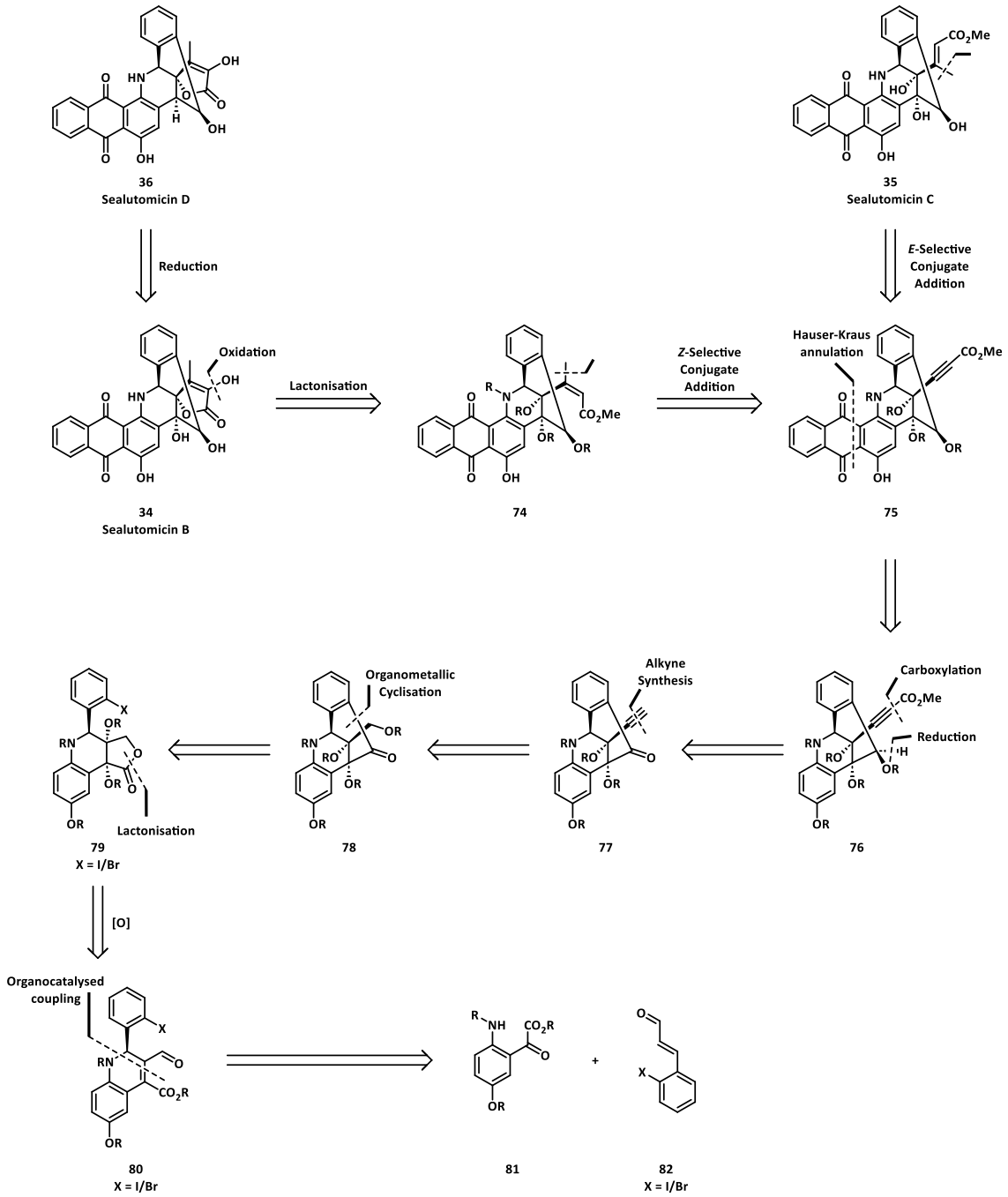


Scheme 1.14: Proposed project goal of synthesising sealutomicins B – D *via* a common late-stage synthetic intermediate.

1.4 Retrosynthetic Analysis

Our retrosynthetic analysis of sealutomicins B – D is shown in **Scheme 1.15**. We envisaged that all three natural products could be prepared from common retrosynthetic intermediate alkyne **75**. Sealutomicin B (**34**) would serve as a retrosynthetic precursor to sealutomicin D (**36**), with reduction of the tertiary alcohol of **34** giving **36**. The lactone side chain of **34** would be obtained by α-oxidation and intramolecular lactonisation of (*Z*)-β-methyl enoate **74**. Enoate **74** could be accessed *via* a *Z*-selective methylation of alkyne **75**, whilst *E*-selective methylation of **75** would give sealutomicin C (**35**). We anticipated that the anthraquinone moiety of **75** could be installed using a Hauser-Kraus annulation, taking inspiration from the synthesis of uncialamycin by Nicolaou *et al*.[15,23] Carboxylation of alkyne **77** would give access to the alkynyl ester motif, while a substrate-controlled reduction of the benzylic ketone of **77** would give the desired epimer of the corresponding secondary alcohol (**76**). Terminal alkyne **77** would be prepared from the derivatisation of a primary alcohol **78**. Formation of the key bridging aryl-ketone bond of **78**, on which the success of the synthesis hinged, was anticipated to occur by means of an organometallic-mediated intramolecular cyclisation of an aryl halide onto a pendant lactone electrophile **79**. This lactone motif would in turn be prepared by simple redox manipulation of a chiral 1,2-dihydroquinoline **80**. The synthesis of **80**

would be achieved by the enantioselective coupling of an *ortho*-halo cinnamaldehyde (**82**) and an α-ketoester (**81**) using the organocatalytic conditions developed by Guggiari.[41]

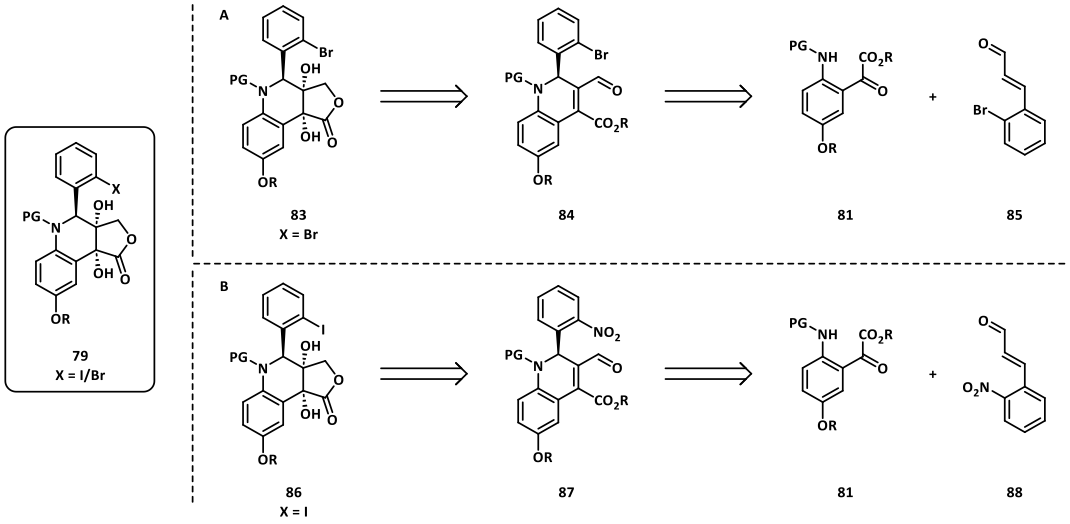


Scheme 1.15: Retrosynthetic disconnections for sealutomicins B – D.

Chapter 2: Synthesis of Organometallic Cyclisation Precursors

2.1 Chapter Introduction

Our first goal was to establish an efficient, scalable route to lactone **79** bearing an aryl halide substituent to participate in the proposed organometallic cyclisation. As discussed in our retrosynthetic analysis (**Chapter 1**), we envisaged that such a lactone would be prepared from a chiral dihydroquinoline, which would in turn be accessed *via* the enantioselective coupling of an *α*-ketoester and an *ortho*-substituted cinnamaldehyde, using the organocatalytic conditions developed by Guggiari.[41] The halide substituent could be installed prior to the dihydroquinoline formation step by using *o*-bromocinnamaldehyde **85** as the aldehyde coupling partner, giving a bromide handle to use during the organometallic cyclisation (**Scheme 2.1, A**). Alternatively, using *o*-nitrocinnamaldehyde (**88**) as the aldehyde coupling partner would install a nitro group handle which could be subsequently manipulated to give access to the aryl iodide (**Scheme 2.1**, **B**).

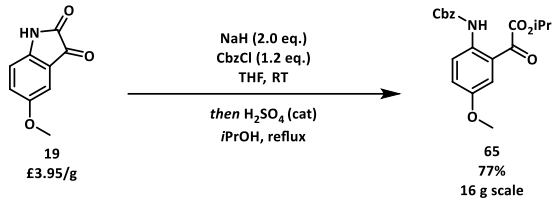


Scheme 2.1: Retrosynthetic analysis of lactones **83** and **86**.

It was decided that both possible routes should be investigated; this would allow identification of the most efficient, scalable lactone synthesis and also enable both iodide and bromide substrates to be trialled in the proposed organometallic cyclisation. This chapter describes our efforts to synthesise iodide **86** and bromide **83**.

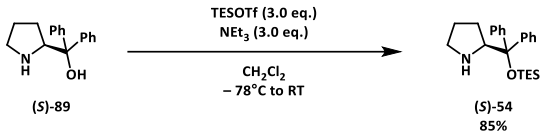
2.2 Keto-Ester and Catalyst Synthesis

Compound **65** was selected as the ketoester coupling partner for the dihydroquinoline synthesis, in the hope that the *para*-methoxy substituent could be manipulated later in the synthesis to facilitate the Hauser-Kraus annulation. Following the procedure of Guggiari, **65** was prepared in a single step from commercially available 5-methoxyisatin (**19**).[41] Carbamate protection of the isatin nitrogen was followed by alcoholysis in acidic isopropanol without intermediate purification, giving the desired ketoester on 16-gram scale (**Scheme 2.2**).



Scheme 2.2: Synthesis of keto-ester **65** from commercially available 5-methoxyisatin **19**.

During our preliminary studies, (*S*)-triethylsilyl prolinol **(*S*)-54** was selected as the catalyst to be used for the enantioselective dihydroquinoline synthesis. Whilst we anticipated that the (*R*) enantiomer of catalyst **54** would be required to access the correct absolute stereochemistry for the natural product, initial studies were carried out using **(*S*)-54** owing to the availability of its prolinol precursor in the Burton group chemical inventory. Catalyst **(*S*)-54** was prepared by silylation of prolinol **(*S*)-89** using triethylsilyl triflate, following the procedure of Shoji *et al.* (**Scheme 2.3**).[58]

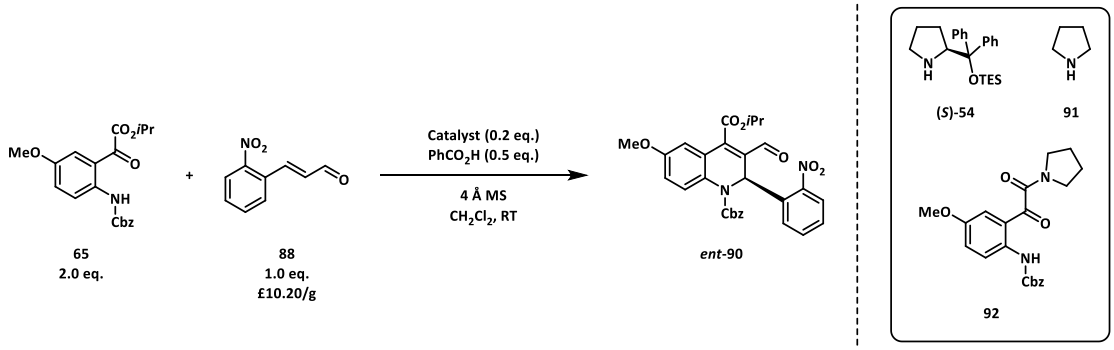


Scheme 2.3: Silylation of prolinol **(*S*)-89** to give catalyst **(*S*)-54**.

2.3 Synthesis of Iodide *ent*-97

2.3.1 Dihydroquinoline Synthesis Using 2-Nitrocinnamaldehyde

Using the organocatalytic conditions established by Guggiari, commercially available 2-nitrocinnamaldehyde **88** was coupled with an excess of ketoester **65** using two different catalysts to give dihydroquinoline ***ent*-90** (**Table 2.1**).[41] One reaction used chiral prolinol catalyst **(*S*)-54** to obtain enantioenriched material, whilst the other employed achiral pyrrolidine **91** to obtain racemic material for HPLC analysis. Chiral catalyst **(*S*)-54** gave the desired dihydroquinoline product ***ent*-90** in 83% yield and 96% ee, as determined by chiral HPLC (**Entry 1**). The absolute configuration of ***ent*-90** was initially assigned by analogy to the dihydroquinoline products prepared by Guggiari. The excess unreacted ketoester **65** could be isolated from the reaction mixture and reused. Achiral pyrrolidine catalyst **91** gave a far lower yield of the dihydroquinoline product ***rac*-90** alongside ketoamide **92**, which was isolated in 47% yield with respect to the pyrrolidine catalyst. (**Entry 2**). Ketoamide **92** is presumably formed by attack of pyrrolidine on the electrophilic ketoester, resulting in a lower effective loading of catalyst to facilitate the dihydroquinoline synthesis and thus a lower yield of ***rac*-90.**

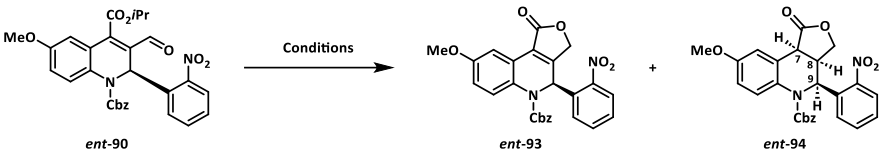


Entry	Catalyst	Yield *ent*-90 [a]	ee *ent*-90
1	(*S*)-54	83%	96%
2	91	10%	0%

Table 2.1: Organocatalysed coupling of ketoester **65** with cinnamaldehyde **88**.[a] Yield based on aldehyde **88**.

2.3.2 Lactonisation and Dihydroxylation

Treatment of aldehyde ***ent*-90** with sodium borohydride in methanol gave a mixture of α,β-unsaturated lactone ***ent*-93** alongside saturated lactone ***ent*-94**, both formed by the alkoxide generated from addition of hydride undergoing *in situ* cyclisation onto the adjacent isopropyl ester (**Table 2.2, entry 1**).[59] The 2D-NOESY spectrum of ***ent*-94** showed strong nOe correlations between protons C(7)**H** and C(8)**H**, protons C(7)**H** and C(9)**H**, and protons C(8)**H** and C(9)**H**, indicating that all three protons lay on the lower face of the tetrahydroquinoline ring. Seeking to preserve the alkene unit, we were pleased to observe that addition of cerium(III) trichloride to the reaction mixture prevented unwanted 1,4-reduction, giving ***ent*-93** as the sole product in 90% yield (**Entry 2**).[60] As shown by Luche *et al.*, the role of the cerium is to catalyse the methanolysis of sodium borohydride.[61] The resultant alkoxyborohydride species is a harder reducing species than the parent borohydride and thus gives a higher 1,2 selectivity.



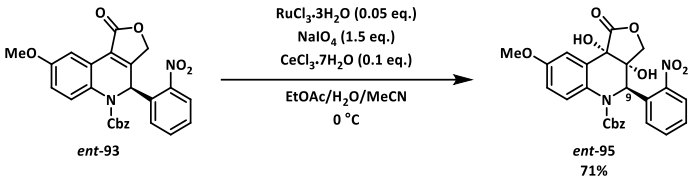
ent-90 *ent*-93 *ent*-94

Entry	Conditions	Yield *ent*-93	Yield *ent*-94
1	$NaBH_4$ (1.1 eq.) MeOH, RT	44%	21%
2	$NaBH_4$ (1.0 eq.), $CeCl_3 \cdot 7H_2O$ (1.0 eq.) MeOH, RT	90%	0%

Table 2.2: Reduction of aldehyde ***ent*-90**.

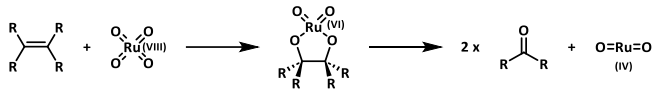
With lactone ***ent*-93** in hand, attention turned to the proposed *syn*-dihydroxylation of the alkene unit. It was hoped that the adjacent aromatic ring of the substrate would shield the upper face of the alkene, directing the oxidation to the lower face. S*yn*-dihydroxylation reactions are often carried out using osmium-based catalysts alongside a stoichiometric oxidant such as *tert*-butyl hydroperoxide[62], potassium ferricyanide(III)[63] or *N*-methylmorpholine *N*-oxide[64]; however, we sought an alternative strategy that would circumvent the use of toxic, expensive osmium reagents. Happily, the ruthenium-based conditions of Plietker *et al.*, previously used by Guggiari, resulted in

complete consumption of lactone ***ent*-93** after just 15 minutes at 0 °C, giving diol ***ent*-95** in good yield as a single diastereomer (**Scheme 2.4**).[57]



Scheme 2.4: Dihydroxylation of alkene ***ent*-93**.

Niggemann *et al*. propose that, during the ruthenium-mediated dihydroxylation reaction, ruthenium tetroxide serves as the active dihydroxylating species. Ruthenium tetroxide-catalysed dihydroxylations often suffer from unwanted oxidative scission of the 1,2-diol product initially formed, giving the unwanted corresponding dicarbonyl (**Scheme 2.5**). The authors propose that the cerium(III) trichloride additive facilitates hydrolysis of the ruthenium(VI) ester intermediate, thereby preventing oxidative scission to the unwanted dicarbonyl and instead favouring the formation of the desired 1,2-*syn* diol.



Scheme 2.5: Oxidative scission of alkenes catalysed by ruthenium tetroxide.

X-ray crystallography analysis of the crystal structure of ***ent*-95** carried out by Owen Smith confirmed that the stereochemical configuration of C(9) was (*R*) and that the two hydroxyl groups lie on the same lower face of the quinoline ring (**Figure 2.1**). Therefore, the absolute configuration of ***ent*-95** was confirmed as that of the structure shown in **Scheme 2.4**.

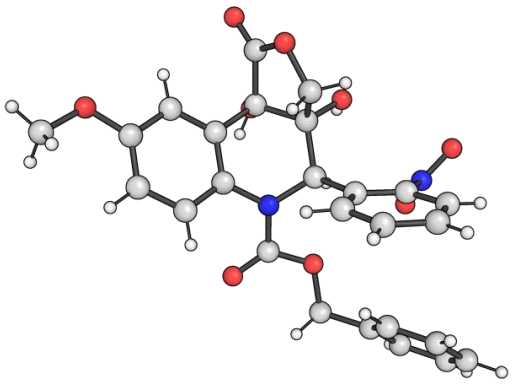
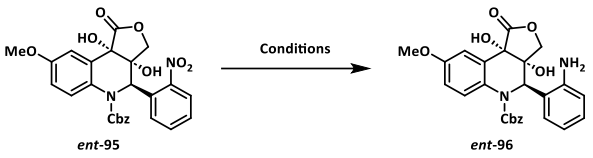


Figure 2.1: X-ray crystal structure of diol ***ent*-95**.

2.3.3 Converting Nitroarene *ent*-95 to Aryl Iodide *ent*-97

We anticipated that the nitroarene unit of ***ent*-95** could be converted to the analogous iodoarene *via* the aniline intermediate. Reduction of ***ent*-95** using tin(II) chloride in ethanol gave aniline ***ent*-96** in poor yield (**Table 2.3, entry 1)**.[65] Switching to an iron-based system with ammonium chloride improved the yield of ***ent*-96**; however, upon scale-up the yield decreased significantly (**Entries 2 – 3**).[66] Addition of acetonitrile to the reaction mixture further improved the yield of ***ent*-96** on small scale, with a smaller drop in yield upon scale-up now observed (**Entries 4 – 5**).[67] Attempts to investigate the reasons for the observed reductions in yield upon scale-up were hampered by the rotameric nature of ***ent*-96**, which resulted in broad, unassignable resonances in the crude NMR spectra of the reactions. No further optimisation of the reaction was carried out at this stage, as sufficient quantities of aniline ***ent*-96** could be accessed to investigate its conversion to the aryl iodide.



ent-95 *ent*-96

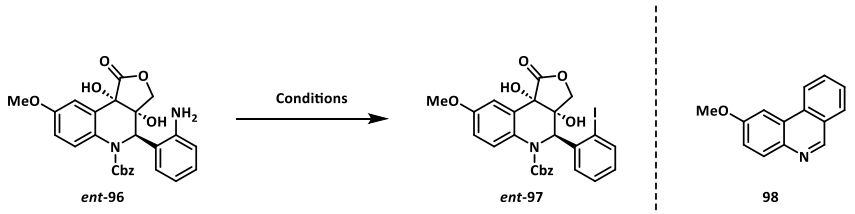
Entry	Scale	Conditions	Yield *ent*-96
1	0.1 mmol	$SnCl_2$ (5.0 eq.) EtOH, Reflux	22%
2	0.1 mmol	Fe (3.0 eq.), NH_4Cl (2.0 eq.) EtOH/H_2O, Reflux	60%
3	0.5 mmol	Fe (3.0 eq.), NH_4Cl (2.0 eq.) EtOH/H_2O, Reflux	32%
4	0.1 mmol	Fe (3.0 eq.), NH_4Cl (2.0 eq.) EtOH/H_2O/MeCN, Reflux	79%
5	0.4 mmol	Fe (3.0 eq.), NH_4Cl (2.0 eq.) EtOH/H_2O/MeCN, Reflux	61%

Table 2.3: Reduction of nitroarene ***ent*-95**.

Since the first report by Sandmeyer in 1884 that aryldiazonium halides undergo copper halide-catalysed decomposition to give aryl halides, a wide range of methods have been reported for the conversion of anilines to their halide counterparts *via* a diazonium intermediate.[68,69] Whilst the traditional Sandmeyer procedure requires isolation and purification of the diazonium salt prior to

conversion to the halide, more recent approaches enable the diazotisation and displacement steps to be carried out in a single reaction, avoiding the need to isolate and handle unstable diazonium salts. Alongside those continuing to employ copper salts[70], many metal-free procedures exist including phase-transfer catalysis[71,72], free-radical halogen abstraction[73] and nucleophilic substitution.[74]

Efforts to convert aniline ***ent*-96** to iodide ***ent*-97** in a single step gave disappointing results (**Table 2.4**). Whilst small quantities of ***ent*-97** were isolated in each case, the various conditions trialled all resulted in many unwanted side products, most of which could not be identified. Interestingly, phenanthridine **98** was isolated from two reactions; its structure was confirmed by comparison to literature data (**Entries 1 + 3**).[75]

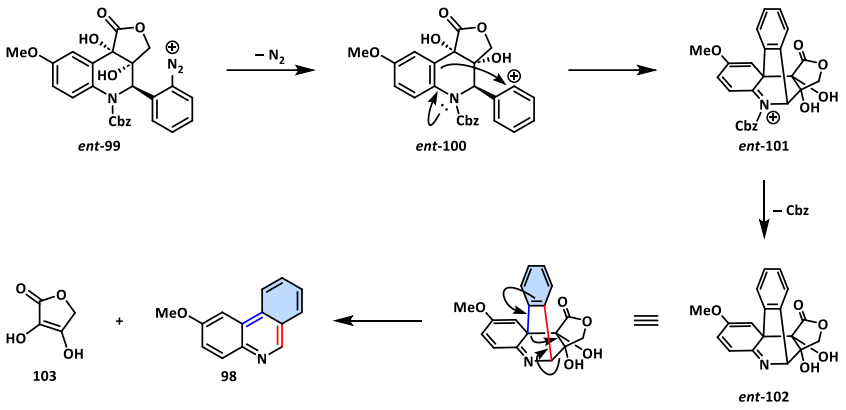


ent-96 *ent*-97 98

Entry	Conditions	Yield *ent*-97	Yield 98
1	$NaNO_2$ (1.1 eq.), HCl, AcOH, 0 °C *then* KI (2.5 eq.), 0 °C to RT	3%	31%
2	$NaNO_2$ (1.1 eq.), HCl, MeOH, 0 °C *then* KI (2.5 eq.), 0 °C to RT	8%	n.d.[a]
3	$NaNO_2$ (5.0 eq.), CH_2I_2 (2.0 eq) H_2O/CH_2Cl_2/AcOH, RT	2%	6%
4	*t*BuONO (4.0 eq.) CH_2I_2, 80 °C	14%	n.d.

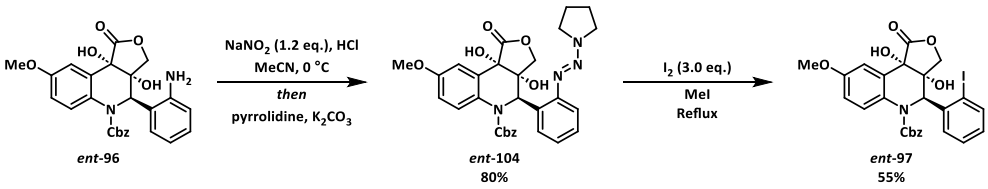
Table 2.4: One-pot conversion of aniline ***ent*-96** to iodide ***ent*-97**. [a] n.d. = not determined

A tentative mechanism for the formation of phenanthridine **98** is shown in **Scheme 2.6**. Diazotisation of the aniline starting material ***ent*-96** gives diazonium ion ***ent*-99**. Loss of nitrogen gas from ***ent*-99** gives vinyl cation ***ent*-100**, which is trapped by the adjacent electron-rich *para*-methoxy aniline ring to give aryl-bridged bicyclic iminium ion ***ent*-101**. Loss of the carbamate protecting group from ***ent*-101**, which may be facilitated by nucleophilic iodide present in the reaction mixture, gives bicyclic imine ***ent*-102**. Imine ***ent*-102** then undergoes a retro-Diels-Alder reaction, eliminating butenolide **103** to form phenanthridine **98**.



Scheme 2.6: Tentative mechanism for the formation of phenanthridine **98** from diazonium ion ***ent*-99**.

The failure to access iodide ***ent*-97** in good yield from aniline ***ent*-96** *via* a one-pot procedure led us to consider a two-step process. Diazotisation of ***ent*-96** with sodium nitrite and trapping of the resultant diazonium salt with pyrrolidine enabled isolation of triazene ***ent*-104**. Triazene ***ent*-104** serves as a stable diazonium equivalent and could be purified before conversion to the aryl halide (**Scheme 2.7**).[76,77] Treatment of ***ent*-104** with molecular iodine in refluxing iodomethane gave the desired iodide in 55% yield, with far fewer unwanted side products.



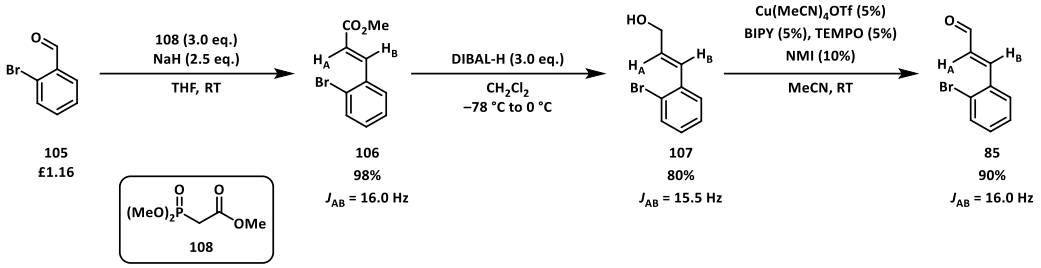
Scheme 2.7: Two-step conversion of aniline ***ent*-96** to iodide ***ent*-97** *via* triazine ***ent*-104**.

2.4 Synthesis of Bromide *ent*-112

2.4.1 Synthesis of 2-Bromocinnamaldehyde 85

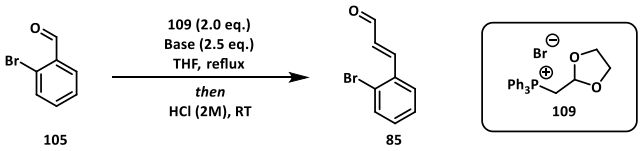
Having synthesised the cyclisation precursor iodide ***ent*-97**, we now turned to the synthesis of its bromide counterpart. Having anticipated installing the bromide unit prior to the organocatalytic dihydroquinoline synthesis, we first required an efficient and scalable means of accessing 2-bromocinnamaldehyde **85**. Cinnamaldehyde **85** was prepared in three steps from commercially available 2-bromobenzaldehyde **105** *via* an olefination/oxidation/reduction sequence (**Scheme 2.8**). Horner-Wadsworth-Emmons reaction of **105** gave α,β-unsaturated ester **106** solely as the (*E*)-

isomer in almost quantitative yield.[78] Reduction of **106** to the allylic alcohol **107** with DIBAL-H was followed by copper-catalysed aerobic oxidation using the conditions of Stahl *et al.* to give cinnamaldehyde **85** in 71% over three steps.[79]



Scheme 2.8: Three-step conversion of benzaldehyde **105** to cinnamaldehyde **85**.

Alternatively, benzaldehyde **105** could be converted to cinnamaldehyde **85** in a single step, with Wittig homologation using masked aldehyde ylide **109** followed by an aqueous acid workup to remove the acetal protecting group (**Table 2.5**).[80] The choice of base proved to be important to the outcome of the reaction, with LiHMDS (**Entry 2**) giving a much greater yield of **85** than potassium *tert*-butoxide (**Entry 1**).



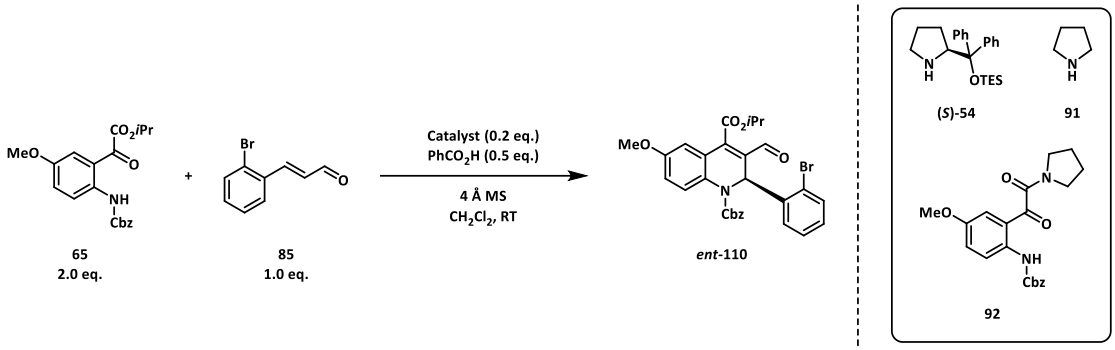
Entry	Base	Yield 85
1	KO*t*Bu	44%
2	LiHMDS	79%

Table 2.5: One-pot conversion of benzaldehyde **105** to cinnamaldehyde **85**.

With both routes giving reliable access to cinnamaldehyde **85** in good yield, the one-pot Wittig procedure was identified as the optimal means of synthesising **85**, owing to its lower step count and higher overall yield. This route would be employed throughout the remainder of the project.

3.4.2 Dihydroquinoline Synthesis Using 2-Bromocinnamaldehyde 85

Coupling of bromocinnamaldehyde **85** with excess ketoester **65** using chiral prolinol catalyst ***ent*-54** gave dihydroquinoline ***ent*-110** in 80% yield (**Table 2.6, Entry 1**).[41] A racemic sample of ***rac*-110** was prepared using catalytic proline **91**, enabling the *ee* of the enantioselective reaction to be determined as 98% by chiral HPLC (**Entry 2**). Ketoamide **92** was again observed in the crude reaction mixture using pyrrolidine **91** but was not isolated.

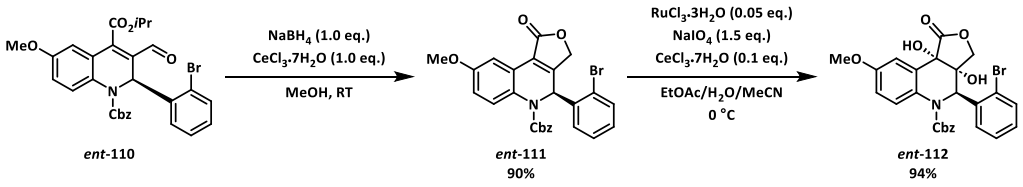


Entry	Catalyst	Yield *ent*-110 [a]	ee *ent*-110
1	**(*S*)-54**	**80%**	**98%**
2	**91**	**16%**	**0%**

Table 2.6: Organocatalysed coupling of ketoester **65** with cinnamaldehyde **85**.[a] Yield based on aldehyde **85**.

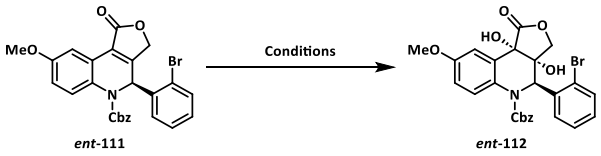
3.4.3 Lactonisation and Dihydroxylation

Subjecting dihydroquinoline ***ent*-110** to the Luche reduction conditions established for the nitro-analogue (*vide supra*) gave α,β-unsaturated lactone ***ent*-111** in 90% yield (**Scheme 2.9**). The ruthenium-catalysed dihydroxylation conditions again gave a single diol diastereomer in 94% yield, which was assigned as ***ent*-112** by analogy to the nitro-diol ***ent*-95**.



Scheme 2.9: Conversion of dihydroquinoline ***ent*-110** to diol ***ent*-112**.

To compare the efficiency of the ruthenium-catalysed dihydroxylation conditions to more commonly used osmium-based procedures, oxidation of alkene ***ent*-111** to diol ***ent*-112** under both Upjohn and racemic Sharpless conditions was trialled.[81,82] Treatment of ***ent*-111** with catalytic osmium tetroxide and stoichiometric *N*-methylmorpholine *N*-oxide (NMO) gave ***ent*-112** in just 15% yield, with the remaining material degrading to a strong baseline spot on the TLC plate of the crude reaction mixture (**Table 2.7, entry 1**). Oxidation using catalytic potassium osmate and stoichiometric potassium ferricyanide resulted in total degradation of the starting material with no sign of ***ent*-112** (**Entry 2**). Given the excellent yield of ***ent*-112** using the ruthenium-catalysed conditions, no further efforts were made to optimise these osmium-based systems.

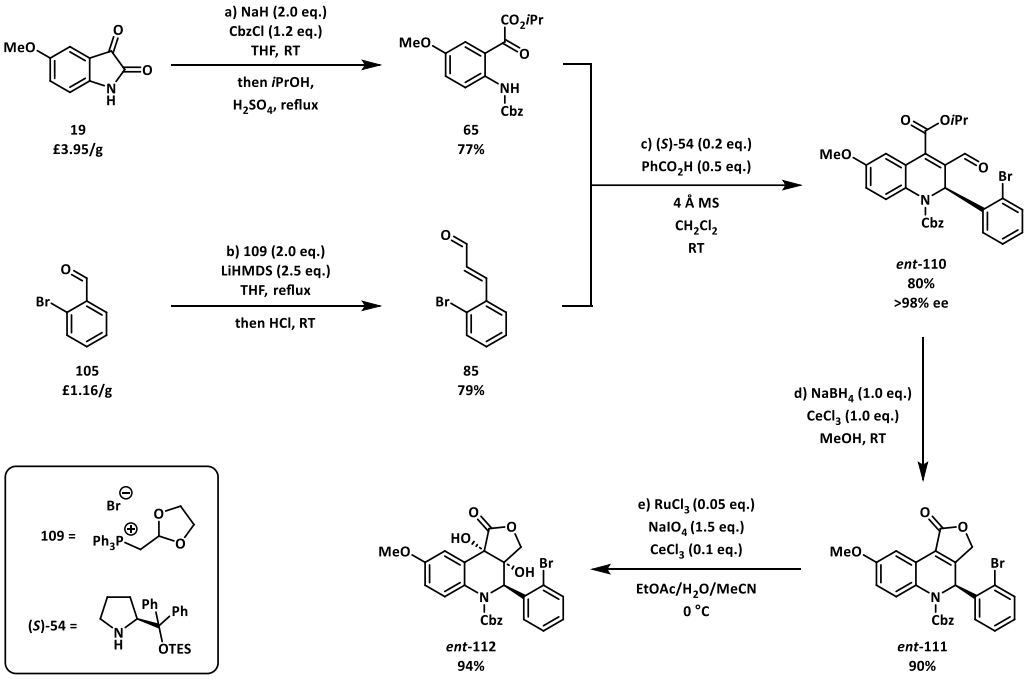


Entry	Conditions	Yield *ent*-112
1	**OsO_4 (5%), NMO (3.0 eq.) THF/H_2O, RT**	**15%**
2	**$K_2OsO_2(OH)_4$ (1%), $K_3Fe(CN)_6$ (3.0 eq.) Quinuclidine (5%), K_2CO_3 (3.0 eq.) *t*BuOH/H_2O, RT**	**0%**

Table 2.7: Osmium-catalysed dihydroxylation of alkene ***ent*-111** to diol ***ent*-112**.

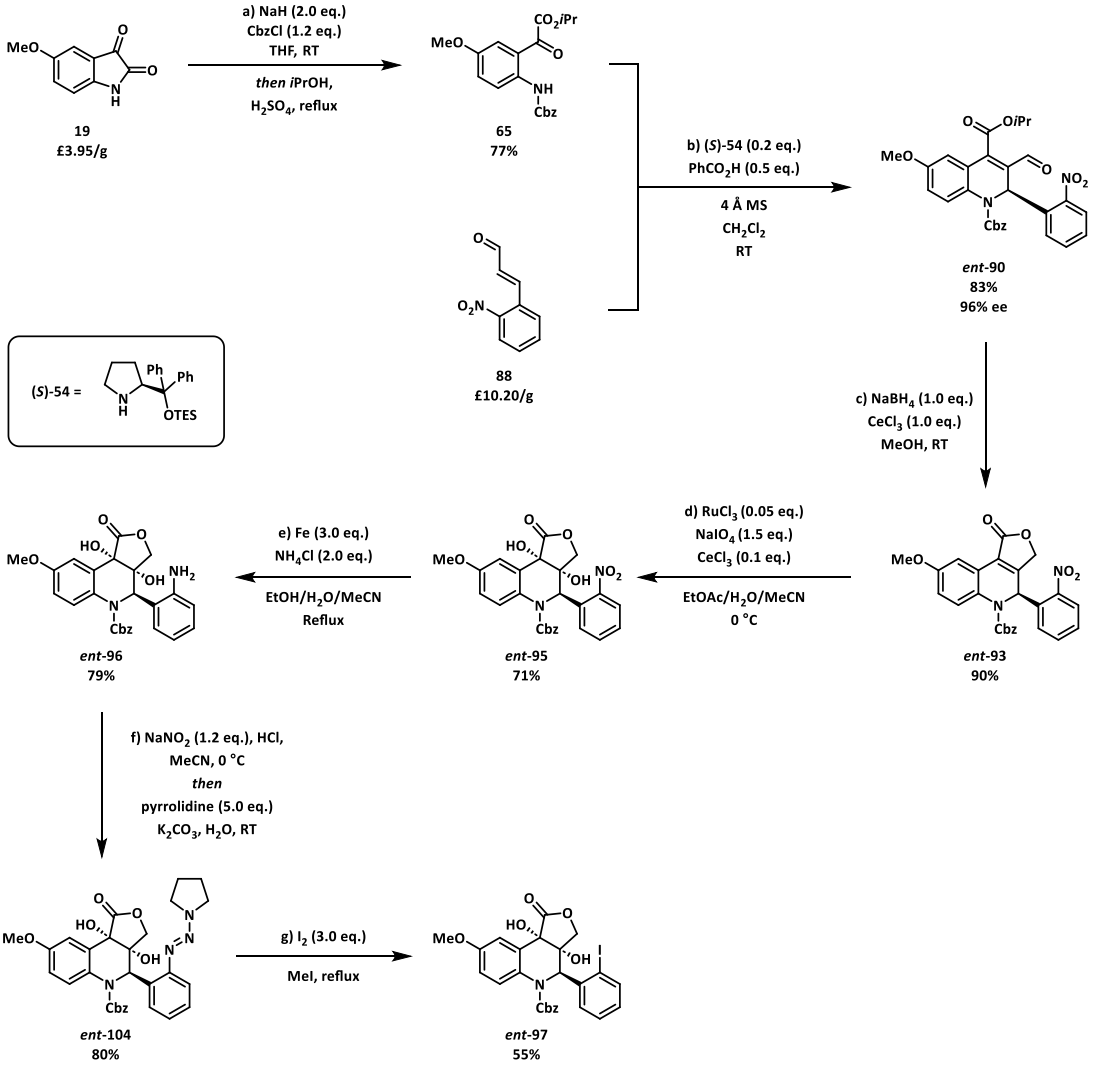
3.5 Chapter Summary

We had successfully developed synthetic routes to aryl iodide ***ent*-97** and aryl bromide ***ent*-112** in order to investigate their suitability as substrates for the proposed organometallic cyclisation. Bromide ***ent*-112** was prepared in four steps from commercially available 2-bromobenzaldehyde **105** in 53.5% overall yield and 98% *ee* (**Scheme 2.10**).



Scheme 2.10: Synthesis of bromide ***ent*-112** in 53.5% yield over four steps from bromocinnamaldehyde **105**.

Iodide ***ent*-97** was prepared in six steps from commercially available 2-nitrocinnamaldehyde **88** in 18.4% overall yield and 96% *ee* (**Scheme 2.11**). Whilst the route to bromide ***ent*-112** was both more efficient and more amenable to scale-up than the route to iodide ***ent*-97**, both halides would be trialled as substrates in the proposed organometallic cyclisation.



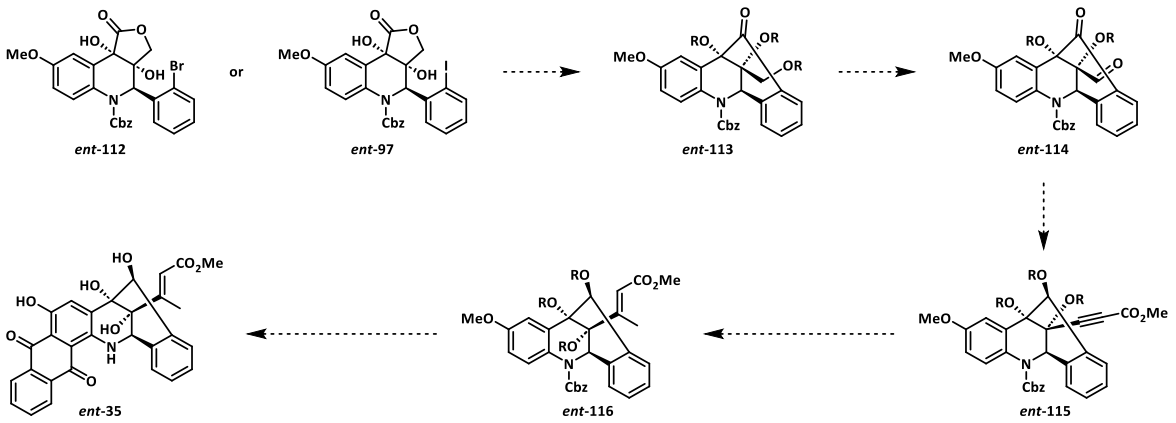
Scheme 2.11: Synthesis of iodide ***ent*-97** in 18.4% yield over six steps from nitrocinnamaldehyde **88**.

Chapter 3: Studies Towards the Synthesis of Enantiomeric Sealutomicin C

3.1 Chapter Introduction

Having successfully synthesised lactones ***ent*-97** and ***ent*-112**, we now sought to develop a synthetic route to enable their conversion to enantiomeric sealutomicin C (***ent*-35**). Whilst we ultimately hoped to synthesise the natural enantiomer of sealutomicin C (**35**), we initially used lactones ***ent*-97** and ***ent*-112** and their derivatives, owing to their immediate availability. This chapter describes our work towards the synthesis of ***ent*-35** from lactones ***ent*-97** and ***ent*-112**. We anticipated that the chemistry established here could then be used towards the synthesis of the correct enantiomer of the natural product (See **Chapter 4** and **Chapter 5**).

Our first task would be to identify conditions to effect the proposed organometallic-mediated cyclisation between the aryl halide and lactone motifs of ***ent*-97** and ***ent*-112**, in order to forge the key bridging aryl-ketone bond of the natural product core (**Scheme 3.1**). Oxidation of the resultant primary alcohol ***ent*-113** would give an aldehyde ***ent*-114** which could in turn be manipulated to give alkynyl ester ***ent*-115**. We envisaged that reduction of the benzylic ketone could be controlled by the substrate to give the correct epimer of the secondary alcohol. Following conversion of the alkynyl ester side chain to the (*E*)-β-methyl enoate ***ent*-116**, a Hauser-Kraus annulation to install the anthraquinone motif and a global deprotection would give enantiomeric sealutomicin C (***ent*-35**).[23]

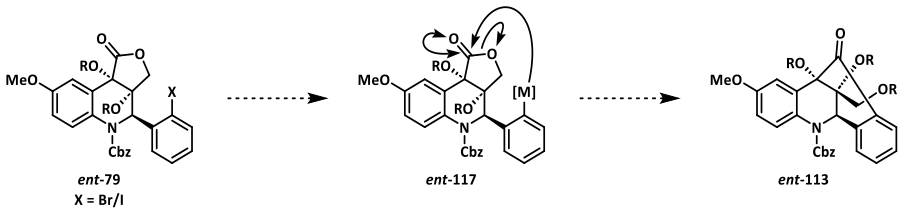


Scheme 3.1: Proposed conversion of lactones ***ent*-97** and ***ent*-112** to enantiomeric sealutomicin C (***ent*-35**).

3.2 Organolithium Cyclisation

3.2.1 Cyclisation of Bromide *ent*-112

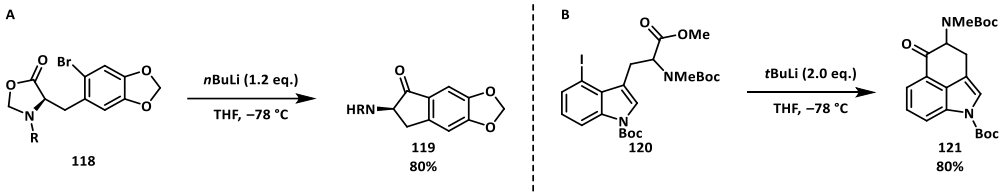
To carry out the proposed cyclisation, we envisaged the formation of an organometallic species ***ent*-117** from our aryl halide starting material. It was postulated that ***ent*-117** would undergo nucleophilic attack onto the adjacent lactone electrophile, with subsequent elimination of a primary alkoxide giving the desired aryl ketone (***ent*-113, Scheme 3.2**). In addition to optimising the conditions required to form the organometallic species ***ent*-117** and enable its nucleophilic attack onto the adjacent lactone, we also needed to identify a suitable protecting group for the 1,2-*syn* diol unit.



Scheme 3.2: Proposed organometallic cyclisation of aryl halide ***ent*-79**.

A search of the literature for similar transformations uncovered two promising reports by Dominguez *et al.* detailing the 5-*exo* trig cyclisation of aryl bromides onto lactone electrophiles, and the application of this chemistry to the synthesis of (+)-ribasine (**Scheme 3.3A**).[83,84] Treatment of aryl bromide **118** with a slight excess of *n*-butyllithium in tetrahydrofuran at −78 °C resulted in lithium-halogen exchange, with attack of the resultant organolithium onto the adjacent lactone followed by the collapse of a tetrahedral intermediate to give the benzylic ketone **119** in 80% yield. Another report by Jia *et al.* employed a similar lithium-halogen exchange strategy for the conversion of aryl iodide **120** to ketone **121** as part of the synthesis of rugulovasine A (**Scheme 3.3B**).[85] Treatment of **120** with *tert*-butyllithium in THF at −78 °C resulted in the formation of an aryl lithium intermediate which, following nucleophilic attack onto a terminal methyl ester, gave **121** in 80% yield. We decided to investigate the application of this lithium-halogen exchange strategy to our

system. Bromide ***ent*-112** was chosen as the initial substrate, owing to its greater availability than iodide ***ent*-97**.



Scheme 3.3: Literature precedent from Dominguez (A) and Jia (B) of the cyclisation of aryl halides onto ester electrophiles *via* lithium-halogen exchange.

We reasoned that the 1,2-*syn* diol unit of bromide ***ent*-112** would require protection to prevent its interference in the lithium-halogen exchange conditions. To gain insight into the conformation of ***ent*-112** and inform our choice of protecting group, we returned to the X-ray crystal structure of nitro-diol ***ent*-95**, which we assumed would adopt a similar conformation to that of ***ent*-112** (**Figure 3.1**). Our analysis of the crystal structure alerted us to the fact that the CH_2 methylene group of the lactone lay directly on the path that the organolithium nucleophile would be required to take in order to attack the carbonyl electrophile. As a result, we hypothesised that a cyclic protecting group which could alter the conformation of the lactone ring and unveil the electrophilic carbonyl may help facilitate the proposed cyclisation.

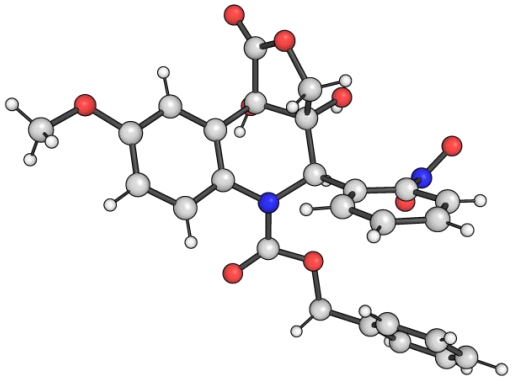
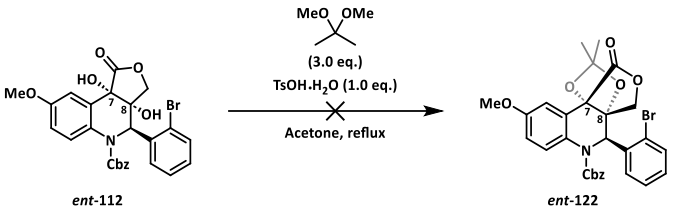


Figure 3.1: X-ray crystal structure of nitro-diol ***ent*-95**.

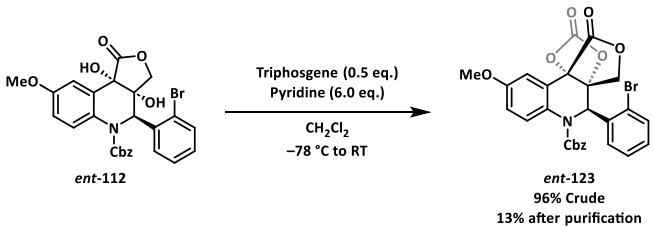
Efforts to convert ***ent*-112** to acetonide ***ent*-122** were unsuccessful; treatment of ***ent*-112** with 2,2-dimethoxypropane under acidic conditions returned only starting material (**Scheme 3.4**).[86] We reasoned that this lack of reactivity could be explained by the reversible nature of acetal formation

and by the gauche arrangement of the C(7)-O and C(8)-O bonds observed in the crystal structure of ***ent*-95**. It is likely that acetal ***ent*-122** would suffer from considerable bond angle strain and thus its formation would be thermodynamically disfavoured.



Scheme 3.4: Failed attempt to convert diol ***ent*-112** to acetal ***ent*-122**.

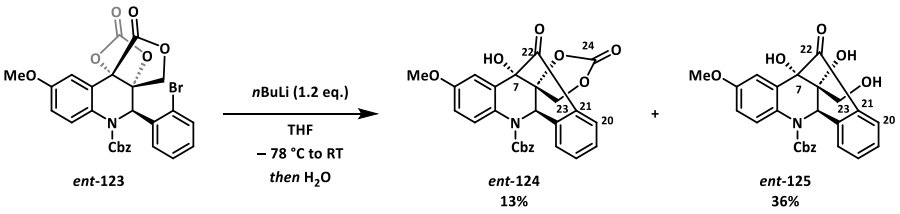
Seeking a cyclic protecting group that could be formed irreversibly under kinetic conditions, we instead considered protecting diol ***ent*-112** as a cyclic carbonate. Treatment of ***ent*-112** with triphosgene and pyridine in dichloromethane gave carbonate ***ent*-123** in almost quantitative crude yield (**Scheme 3.5**).[87] Attempts to purify ***ent*-123** by silica chromatography resulted in a considerable loss in yield, with 2D TLC analysis indicating almost complete degradation on silica; however, ^{1}H NMR analysis of the crude material indicated that the sample was exceptionally clean. Furthermore, the high yield and high level of purity of crude ***ent*-123** could be replicated on multi-gram scale. As a result, we decided to trial the crude sample of ***ent*-123** as a substrate in the proposed organolithium-mediated cyclisation.



Scheme 3.5: Conversion of diol ***ent*-112** to cyclic carbonate ***ent*-123**.

A solution of ***ent*-123** in THF at −78 °C was treated with 1.2 equivalents of *n*-butyllithium and subsequently warmed to room temperature, resulting in complete consumption of starting material. Quenching the reaction with water gave two major products: cyclic carbonate ***ent*-124** and triol ***ent*-125** in 13% yield and 36% yield respectively (**Scheme 3.6**). The ^{1}H/^{13}C HMBC NMR spectra of ***ent*-124** and ***ent*-125** both showed clear correlations between the aryl C(20)**H** proton and

the **C**(22) carbonyl carbon, suggesting that the desired aryl-ketone bond had indeed been formed. In the ^{1}H NMR spectrum of triol ***ent*-125** in DMSO-d_6, the resonances of the two C(23)**H$_2$** protons each appeared as a double doublet due to coupling to the proton of the adjacent free primary alcohol, whilst the resonance of the primary alcohol proton itself also appeared as a double doublet. By contrast, in the ^{1}H NMR spectrum of carbonate ***ent*-124** in DMSO-d_6, the resonances of the two C(23)**H$_2$** protons appeared as doublets, with no coupling to an adjacent alcohol proton. A singlet resonance was observed in the ^{1}H NMR spectra of both compounds, in each case corresponding to the C(7)O**H** tertiary alcohol proton. The ^{1}H/^{13}C HMBC NMR spectrum of ***ent*-124** showed strong correlations between the carbonate **C**(24) carbon and both of the C(23)**H$_2$** protons, which were not observed in the analogous ^{1}H/^{13}C HMBC NMR spectrum of fused carbonate ***ent*-123**. These observations indicated that the carbonate moiety had migrated from its initial fused position in ***ent*-123** to its *spiro* position in ***ent*-124**.



Scheme 3.6: Conversion of carbonate ***ent*-123** to carbonate ***ent*-124** and triol ***ent*-125**.

The structure of triol ***ent*-125** was confirmed by analysis of its X-ray crystal structure by Owen Smith (University of Oxford), giving further evidence that the desired cyclisation to form the bridging aryl-ketone bond had indeed taken place (**Figure 3.2**).

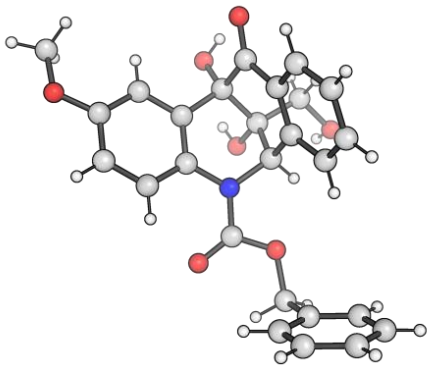
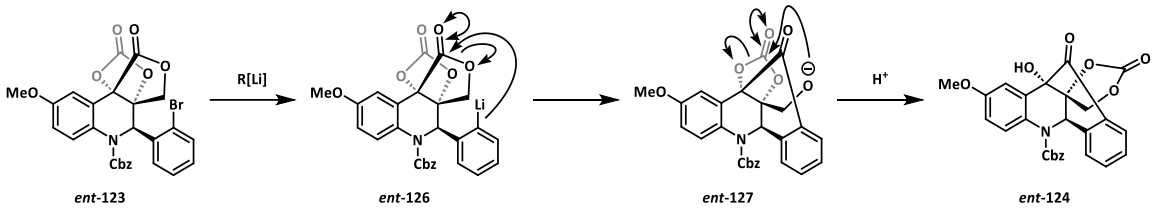


Figure 3.2: X-ray crystal structure of triol ***ent*-125**.

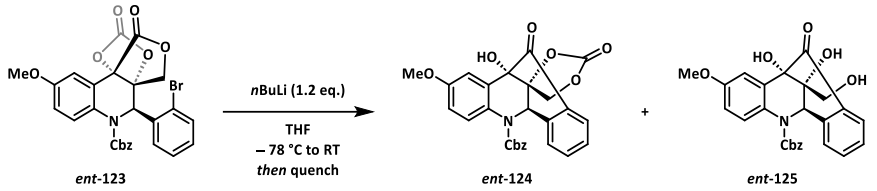
Our proposed mechanism for the formation of ***ent*-124** and ***ent*-125** is given in **Scheme 3.7**. Following lithium-halogen exchange, intramolecular attack of aryl lithium species ***ent*-126** onto the adjacent lactone generates a primary alkoxide ***ent*-127**. The alkoxide in turn attacks the strained fused carbonate ring to form the more stable spiro carbonate motif and a tertiary alkoxide which upon aqueous workup gives the tertiary alcohol group of ***ent*-124**. Subsequent base-mediated hydrolysis of the carbonate group then gives triol ***ent*-125**.



Scheme 3.7: Plausible mechanism for the formation of carbonate ***ent*-124**.

In light of our hypothesis that triol ***ent*-125** is formed by base-mediated hydrolysis of spiro carbonate ***ent*-124**, experiments were conducted to investigate the influence of the reaction quench on the product distribution of ***ent*-124** and ***ent*-125**. Quenching with water gave triol ***ent*-125** as the major product (**Table 3.1, entry 1**), presumably due to the generation of hydroxide following protonation of the tertiary alkoxide. An aqueous acidic quench with saturated ammonium chloride solution gave a 2 : 1 ratio of carbonate : triol (**Entry 2**). Switching to an anhydrous acidic quench with a solution of camphorsulfonic acid in tetrahydrofuran almost fully suppressed formation of triol ***ent*-125** (**Entry 3**). Meanwhile, quenching with water followed by addition of 0.5 M aqueous sodium hydroxide solution resulted in complete hydrolysis of carbonate ***ent*-124** to give only triol ***ent*-125** (**Entry 4**). It was found that these last conditions gave the highest overall yield for the reaction, owing to the easier purification of triol ***ent*-125** than of carbonate ***ent*-124**. Alongside ***ent*-124** and ***ent*-125**, numerous unidentified side products were formed in small quantities during the reaction; however, the high polarity of ***ent*-125** resulted in a much lower retention factor than all other products. As a result, the purification column could initially be flushed with a low-polarity

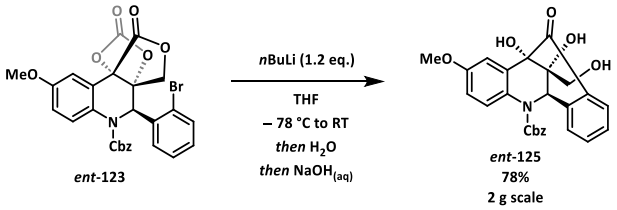
eluent to remove side products before increasing the eluent's polarity to isolate ***ent*-125** in high yield and purity.



Entry	Quench	Crude ratio (*ent*-124 : *ent*-125)[a]	Yield *ent*-124 [b]	Yield *ent*-125[b]
1	H_2O	1 : 3.5	13%	36%
2	$NH_4Cl_{(aq)}$	2 : 1	33%	10%
3	CSA in THF (1.0 M)	5 : 1	42%	6%
4	H_2O then $NaOH_{(aq)}$ (0.5 M)	1 : 20	0%	78%

Table 3.1: Effect of reaction quench on product distribution of carbonate ***ent*-124** and triol ***ent*-125**. [a] Crude ratios determined by NMR. [b] Isolated yields.

We were pleased to observe that the organolithium-mediated cyclisation of ***ent*-123** followed by basic workup to give ***ent*-125** was amenable to scale-up; 2 grams of ***ent*-125** could be prepared in a single reaction under these conditions (**Scheme 3.8**). As a result, no efforts were made to optimise this reaction further.

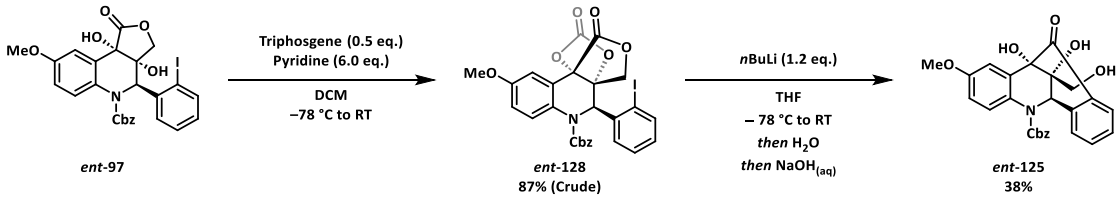


Scheme 3.8: Optimised conditions for cyclisation of ***ent*-3.8**.

3.2.2 Cyclisation of Iodide *ent*-97

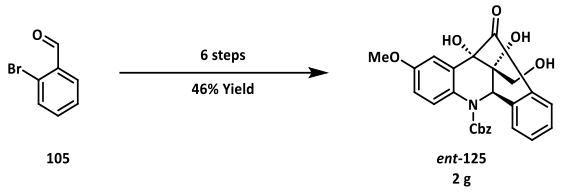
Having optimised conditions for the cyclisation of bromide ***ent*-112**, iodide ***ent*-97** was subjected to the same protection/cyclisation sequence in order to investigate its suitability as an alternative cyclisation substrate. Aryl iodides are known to undergo lithium-halogen exchange more rapidly than their bromide counterparts; as a result, we were hopeful that cyclisation of ***ent*-97** would be equally or more successful than that of bromide ***ent*-112**.[88] Carbonate ***ent*-128** was prepared in 87%

crude yield and used without further purification in the optimised cyclisation reaction, giving triol ***ent*-125** in just 38% yield (**Scheme 3.9**). Full consumption of the iodide starting material was observed; however, analysis of the crude reaction mixture revealed considerable side reactivity to a range of unidentifiable side products.



Scheme 3.9: Carbonate protection and cyclisation of iodide ***ent*-97**.

Given the superior yield obtained from the cyclisation of bromide ***ent*-112** compared to its iodide analogue, combined with its more efficient synthesis from commercially available starting materials, we decided that the bromide route to triol ***ent*-125** would be used for the remainder of our synthesis. This sequence allowed us to construct the full core of *ent*-sealutomicin C in just six steps from 2-bromobenzaldehyde in 46% yield on 2-gram scale (**Scheme 3.10**).



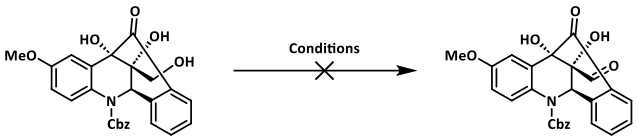
Scheme 3.10: Six-step conversion of 2-bromobenzaldehyde (**105**) to triol ***ent*-125**.

3.3 Alcohol Oxidation

3.3.1 Direct Oxidation Attempts

The next stage of the synthesis required the oxidation of the primary alcohol unit of triol ***ent*-125** to the analogous aldehyde. Initially, we had intended to effect this oxidation in single step, without needing to first protect the two adjacent tertiary alcohol groups. To this end, ***ent*-125** was subjected to the copper-catalysed aerobic conditions reported by Stahl *et al.* (**Table 3.2, entry 1**).[79] Whilst trace amounts of aldehyde ***ent*-129** were observed by LRMS analysis of the reaction mixture, the

reaction appeared to stall quickly, and no aldehyde product could be isolated. The same results were observed using Stahl's modified procedure for electronically and sterically deactivated alcohols, using the less sterically hindered ABNO in place of TEMPO (**Entry 2**).[89] In both cases, the stalling of the reaction coincided with a reaction colour change from brown to light green. The authors report that this colour change indicates the formation of a BIPY-ligated Cu(II) species which signals either completion of the reaction or inhibition of catalyst turnover.[90] We propose that chelation of the Cu(II) species by the two tertiary alcohol groups, which prevents its participation in the oxidation of the primary alcohol and its subsequent reduction to the +1 oxidation state, is responsible for the stalling of the reaction.



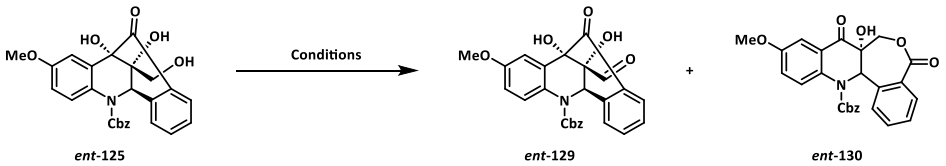
ent-125 *ent*-129

Entry	Conditions	Yield *ent*-129	Result
1	$Cu(MeCN)_4Otf$ (5%) BIPY (5%), TEMPO (5%), NMI (10%) MeCN, RT	0%	Trace reactivity Reaction stalled
2	$Cu(MeCN)_4OTf$ (5%) ^{MeO}BIPY (5%), ABNO (5%), NMI (10%) MeCN, RT	0%	Trace reactivity Reaction stalled
3	DMP (3.0 eq.) $NaCO_3$ (9.0 eq.) CH_2Cl_2, RT	0%	Degradation of SM
4	TEMPO (5%) NaOCl (1.1 eq.) CH_2Cl_2/H_2O, RT	0%	Degradation of SM
5	TPAP (5%) NMO (2.0 eq.) CH_2Cl_2, RT	0%	No reaction

Table 3.2: Failed oxidation of triol ***ent*-125**.

Attempts to oxidise ***ent*-125** using either Dess-Martin periodinane (DMP) or catalytic TEMPO with stoichiometric sodium hypochlorite led only to degradation of the starting material, with no sign of the desired aldehyde ***ent*-129** (**Table 3.2, entries 3 – 4**). Meanwhile, Ley-Griffith conditions using catalytic tetrapropylammonium perruthenate and stoichiometric NMO resulted in no reactivity (**Entry 5**).

Unexpected results were obtained from attempts to oxidise ***ent*-125** using either of the hypervalent iodine reagents bis(acetoxy)iodobenzene (BAIB) or 2-iodoxybenzoic acid (IBX). Treatment of ***ent*-125** with stoichiometric BAIB and catalytic TEMPO resulted in full consumption of starting material; however, aldehyde ***ent*-129** was not observed in the crude reaction mixture and the only product isolated was lactone ***ent*-130** (**Table 3.3, entry 1**).[91] Lactone ***ent*-130** was also isolated following the reaction of ***ent*-125** with excess IBX in either dimethyl sulfoxide or ethyl acetate, this time alongside low yields of desired aldehyde ***ent*-129** (**Entries 2 + 3**).[92,93]



ent-125 *ent*-129 *ent*-130

Entry	Conditions	Yield *ent*-129	Yield *ent*-130
1	**TEMPO (0.1 eq.) BAIB (1.1 eq.) CH_2Cl_2, RT**	**0%**	**33%**
2	**IBX (5.0 eq.) DMSO, RT**	**18%**	**13%**
3	**IBX (5.0 eq.) EtOAc, 80 °C**	**46%**	**11%**

Table 3.3: Conversion of triol ***ent*-125** to aldehyde ***ent*-129** and lactone ***ent*-130**

High-resolution mass spectrometry analysis of ***ent*-130** gave a molecular ion peak with an *m/z* of 460.1391, consistent with a molecular formula of $C_{26}H_{22}NO_7^+$, indicating loss of H_2 from the triol starting material. The ^{13}C NMR spectrum of ***ent*-130** showed a resonance at 170.1 ppm, corresponding to the lactone **C**(22) carbon. The $^{1}H/^{13}C$ HMBC NMR spectrum of ***ent*-130** showed cross peaks between the C(5)**H** aromatic proton and the **C**(7) ketone carbon, the C(23)$\mathbf{H_2}$ protons and the **C**(7) carbon, and the C(23)$\mathbf{H_2}$ protons and the **C**(22) lactone carbon (**Figure 3.3A**). $^{1}H/^{13}C$ HMBC cross peaks were also observed between the C(9)**H** proton and the **C**(7) carbon, and between the C(20)**H** aromatic proton and the **C**(22) carbon (**Figure 3.3B**). As a result of these observations, the structure of ***ent*-130** was assigned as shown in **Table 3.3** and **Figure 3.3**.

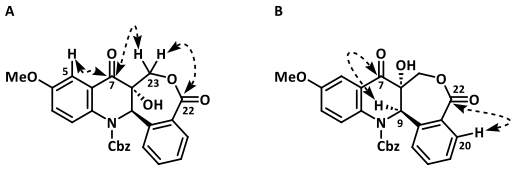
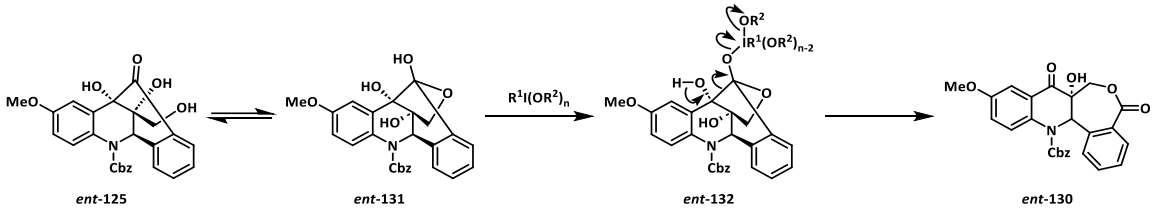


Figure 3.3: Select correlations observed in the $^{1}H/^{13}C$ HMBC spectrum of ***ent*-130**.

Whilst no investigations were made into the mechanism by which lactone ***ent*-130** is formed, a tentative suggestion is shown in **Scheme 3.11**. Tautomerisation of triol ***ent*-125** gives lactol ***ent*-131**, which then undergoes an iodine-triggered oxidative rearrangement to produce the observed lactone product.



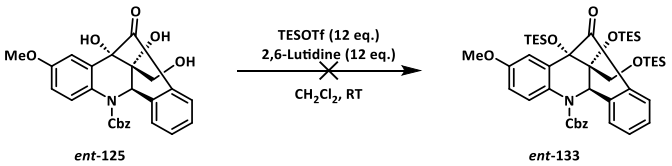
Scheme 3.11: Possible mechanism for the formation of lactone ***ent*-130**.

Whilst the different reaction conditions trialled for the oxidation of ***ent*-125** had produced a range of results, we concluded that the two unprotected tertiary alcohol groups were at least partly responsible for the failure to access acceptable yields of aldehyde ***ent*-129**. Consequently, we decided that protection of these groups would be necessary prior to oxidation of the primary alcohol.

3.3.2 Protecting Group Sequence

In order to protect the two tertiary hydroxyl groups of triol ***ent*-125** whilst leaving the primary alcohol unprotected and free to be oxidised, two possible strategies presented themselves. The first, a two-step sequence, comprised the global protection of all three alcohol groups, followed by selective deprotection of the primary alcohol. Alternatively, selective protection of the primary alcohol followed by protection of the two tertiary hydroxyl groups and subsequent primary alcohol deprotection offered a three-step solution.

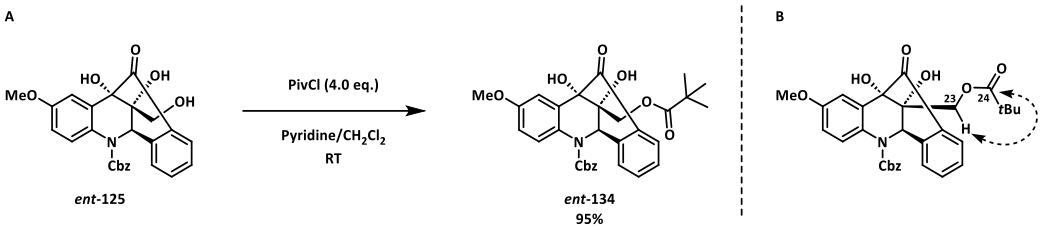
The selective deprotection of silyl ether-protected primary alcohols in the presence of similarly protected secondary or tertiary alcohols is well-established, relying on the less sterically hindered environment surrounding the primary alcohol to facilitate its more rapid deprotection.[94] Attempts were made to access *tris*(triethylsilyl)-protected ***ent*-133**, in the hope that the primary silyl ether group could then be selectively deprotected. Disappointingly, treatment of triol ***ent*-125** with excess triethylsilyltriflate and pyridine resulted in an inseparable mixture of *bis*-protected regioisomers, with no sign of the desired *tris*-protected ***ent*-133** (**Scheme 3.12**). We attributed this failure to the extreme steric crowding that would arise in the desired product, preventing its formation.



ent-125 *ent*-133

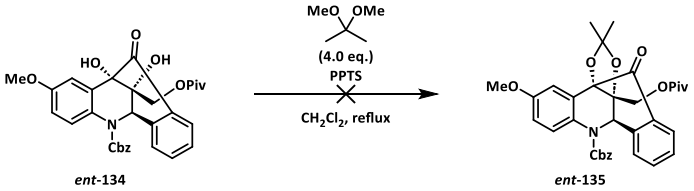
Scheme 3.12: Failure to globally silylate triol ***ent*-125**.

Whilst further attempts could have been made to effect the two-step global protection/selective deprotection sequence, the silylation failure suggested a low likelihood of success for this strategy. Instead, we elected to identify a means of selectively protecting the primary hydroxyl group, which could subsequently be removed after protection of two tertiary hydroxyls. Pivalate esters have served as a popular protecting group in the field of natural product synthesis, owing to their stability towards acidic reagents and straightforward removal under basic conditions.[95–97] Furthermore, the considerable steric bulk of pivalating reagents often renders them highly selective towards primary alcohols in the presence of more hindered hydroxyl units. Treatment of ***ent*-125** with excess pivaloyl chloride in dichloromethane and pyridine proved highly selective for the protection of the primary hydroxyl group, giving pivalate ester ***ent*-134** in almost quantitative yield (**Scheme 3.13**, **A**). The $^{1}H/^{13}C$ HMBC NMR spectrum of ***ent*-134** showed clear cross peaks between the two C(23)**H₂** protons and the **C**(24) ester carbon, confirming that the esterification had been selective for the primary alcohol (**Scheme 3.13**, **B**).



Scheme 3.13: A) Synthesis of pivalate ester ***ent*-134**; B) HMBC correlation between C(23)$\mathbf{H_2}$ protons and **C**(24) carbon of ***ent*-134**.

With ***ent*-134** in hand, we turned our attention to the protection of the two tertiary alcohol groups. Our choice of protecting group was guided by the need for a group which would be stable under the basic conditions required used to remove the pivalate ester and would not undergo migration from the tertiary to the primary alcohol during this deprotection step. Treatment of ***ent*-134** with 2,2-dimethoxypropane under acidic conditions in an attempt to form the dimethyl acetal ***ent*-135** returned only starting material (**Scheme 3.14**). We again attributed this lack of reactivity to the bond angle strain that would arise in the fused 5,6 ring system of the cyclic acetal.

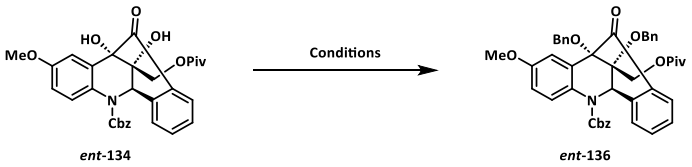


Scheme 3.14: Failed conversion of diol ***ent*-125** to dimethyl acetal ***ent*-135**.

Benzyl ethers are known to be stable under basic conditions and are typically removed either by palladium-catalysed hydrogenolysis or strongly acidic conditions.[98] In addition, they generally display good stability towards mild oxidising reagents, whose use we envisaged later in our synthesis to convert the primary alcohol handle to an aldehyde. These properties led us to seek a method of converting diol ***ent*-134** to its *bis*-benzyl ether.

Deprotonation of a solution of ***ent*-134** with NaHMDS in THF at room temperature followed by addition of benzyl bromide gave no sign of the desired *bis*-benzyl ether ***ent*-136**; subsequent heating to 40 °C led only to degradation of the starting material (**Table 3.4, entry 1**). Addition of tetrabutylammonium iodide (TBAI) as a nucleophilic catalyst gave similar results (**Entry 2**), as did the use of benzyl iodide in place of benzyl bromide as the benzylating reagent (**Entry 3**). Switching

solvent from THF to DMF gave more promising results, with sluggish conversion of ***ent*-134** to ***ent*-136** observed following deprotonation with NaHMDS and treatment with benzyl iodide (**Entry 4**). Despite rapid initial reactivity observed by TLC, the reaction appeared to stall after several hours, which may be due to decomposition of the reactive benzyl iodide. The use of KHMDS alongside a large excess of benzyl bromide and TBAI resulted in a significant increase in the conversion of starting material, giving ***ent*-136** in 63% yield (**Entry 5**). We were pleased to observe that upon scale-up, the same conditions resulted in a further improvement in the reaction yield, giving access to over 2 grams of ***ent*-136** (**Entry 6**). We assume that on smaller scale, quenching of the alkoxide intermediate by adventitious water plays a more significant role on the outcome of the reaction. Whilst further optimisation of this reaction step could likely have been made, time constraints resulting from a loss of lab time due to the COVID-19 pandemic meant we elected to press ahead with the next stage of the synthesis.



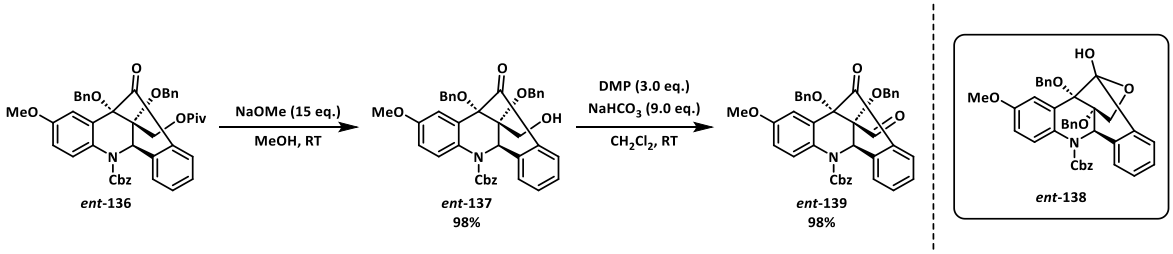
ent-134 *ent*-136

Entry	Scale	Conditions	Yield *ent*-136
1	0.06 mmol	NaHMDS (2.2 eq.) BnBr (4.0 eq.) THF, RT to 40 °C	0%
2	0.06 mmol	NaHMDS (2.2 eq.) BnBr (4.0 eq.), TBAI (1.0 eq.) THF, RT	0%
3	0.06 mmol	NaHMDS (4.0 eq.) BnI (4.0 eq.) THF, RT	0%
4	0.06 mmol	NaHMDS (3.0 eq.) BnI (3.0) DMF, RT	17%
5	0.13 mmol	KHMDS (4.0 eq.) BnBr (10 eq.), TBAI (1.0 eq.) DMF, RT	63%
6	4.27 mmol	KHMDS (4.0 eq.) BnBr (10 eq.), TBAI (1.0 eq.) DMF, RT	74%

Table 3.4: Conversion of diol ***ent*-134** to *bis*-benzyl ether ***ent*-136**.

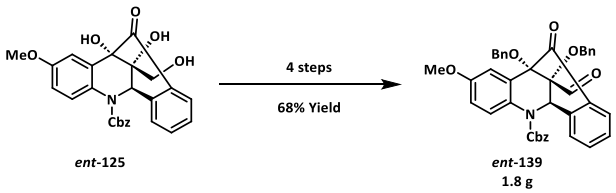
With the two problematic tertiary alcohol groups now protected, attention turned to the deprotection of the primary hydroxyl group and its subsequent oxidation. Treatment of ***ent*-136**

with a freshly prepared solution of sodium methoxide in methanol resulted in efficient depivalation, giving primary alcohol ***ent*-137** in almost quantitative yield (**Scheme 3.15**).[99] Compound ***ent*-137** exists as a 2 : 1 inseparable mixture of the primary alcohol and the corresponding lactol ***ent*-138** in DMSO-d_6. The presence of rotamers resulted in the NMR resonances of ***ent*-138** appearing as broad peaks in the ^{1}H and ^{13}C NMR spectra of the mixture. As a result, only NMR data for the primary alcohol is given in the experimental section of this thesis. Treatment of this mixture with DMP and sodium bicarbonate in dichloromethane resulted in smooth oxidation of both species to aldehyde ***ent*-139**.[100] Aldehyde ***ent*-139** proved to be highly stable and could be stored at room temperature for several weeks without noticeable decomposition.



Scheme 3.15: Two-step conversion of pivalate ester ***ent*-136** to aldehyde ***ent*-139** *via* alcohol ***ent*-139**.

Despite the failure to directly oxidise the primary alcohol of triol ***ent*-125** to its analogous aldehyde, we were pleased that the alternative four-step sequence developed gave aldehyde ***ent*-139** in 68% overall yield and could be replicated easily on large scale (**Scheme 3.16**). Work now turned to the manipulation of this aldehyde handle to access the α,β-unsaturated ester side chain of sealutomicin C.

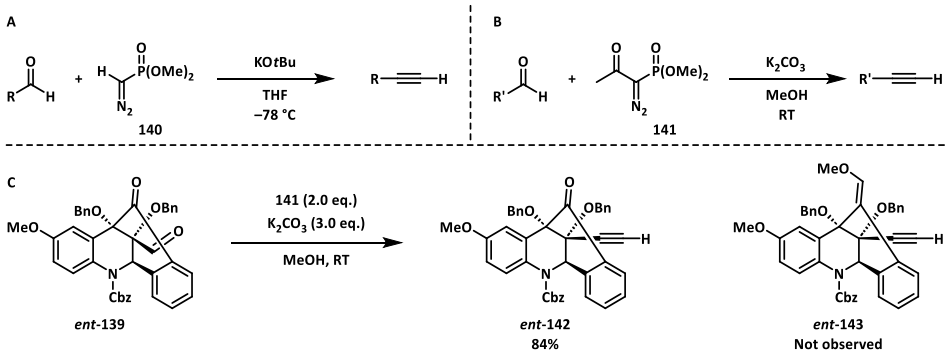


Scheme 3.16: Four-step synthesis of aldehyde ***ent*-139** from triol ***ent*-125**.

3.4 Side Chain Development

3.4.1 Alkyne Homologation and Ketone Reduction

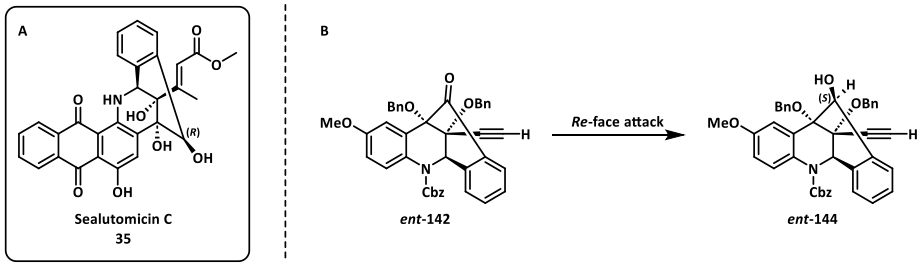
Our proposed synthetic route to complete the side chain of sealutomicin C required the synthesis of an alkynyl ester, which could be used as a Michael acceptor in order to access the required α,β-unsaturated ester motif. The alkynyl ester would be prepared from the carboxylation of a terminal alkyne, which we hoped to access directly from aldehyde ***ent*-139**. The Seyferth-Gilbert homologation enables the conversion of aldehydes to terminal alkynes *via* a base-promoted reaction with dimethyl (diazomethyl)phosphonate (**140, Scheme 3.17A**).[101] The Ohira-Bestmann modification, which utilises dimethyl (1-diazo-2-oxopropyl)phosphonate (**141**), obviates the need for a strong base, enabling the conversion of base-labile substrates (**Scheme 3.17B**).[100] We were concerned that under the Ohira-Bestmann conditions, the benzylic ketone of ***ent*-139** might undergo vinyl carbene formation and subsequent methanolic trapping to give methyl enol ether ***ent*-143**.[102] Fortunately, treatment of ***ent*-139** with the Ohira-Bestmann reagent **141** and potassium carbonate in methanol resulted in smooth conversion to alkyne ***ent*-142** with no sign of ***ent*-143** (**Scheme 3.17C**).



Scheme 3.17: A) Seyferth-Gilbert homologation of aldehydes to terminal alkynes; B) Ohira-Bestmann modification; C) Conversion of aldehyde ***ent*-139** to alkyne ***ent*-142** using Ohira-Bestmann conditions.

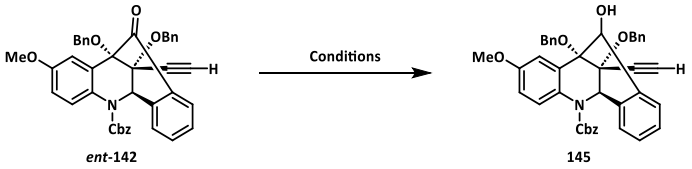
With alkyne ***ent*-142** in hand, we turned to the proposed substrate-controlled reduction of the benzylic ketone moiety of ***ent*-142** to the secondary alcohol motif found in the structure of sealutomicin C. In the isolation paper, this alcohol group of the natural product was determined to

be the (*R*)-epimer (**Scheme 3.18A**); thus, for our present work on the opposite enantiomeric series we would require nucleophilic addition of hydride to the *Re*-face of ketone ***ent*-142** to give the (*S*)-epimer ***ent*-144** (**Scheme 3.18B**). Analysis of 3D-models of ketone ***ent*-142** appeared to suggest that *Si*-face addition of hydride would suffer considerable steric hindrance due to the substrate geometry. Consequently, we felt optimistic that the desired epimer could be accessed without the need for stereoselectivity-controlling reagents. However, if the reduction gave the wrong epimer, inversion of the resultant alcohol using Mitsunobu chemistry could be used to access the correct stereochemical configuration.[103]



Scheme 3.18: A) Stereochemical configuration of secondary benzylic alcohol in sealutomicin C; B) required reduction for opposite enantiomeric series.

When ketone ***ent*-142** was treated with sodium borohydride, no reaction was observed (**Table 3.5, entry 1**).[104] We attributed this lack of reactivity of the ketone to its conjugation with the adjacent benzene ring, raising the C=O π* LUMO and thus reducing the electrophilicity of ***ent*-142**. This conjugation could be observed in the IR spectrum of ***ent*-142**, with the ketone group displaying an IR stretch of 1702 cm^{-1}. Treatment of ***ent*-142** with the more strongly reducing lithium borohydride in tetrahydrofuran resulted in reduction to a single diastereomer **145** (**Entry 2**).[105] Efforts to grow suitable crystals of **145** for X-ray diffraction analysis were unsuccessful and $^{1}H/^{1}H$ NOESY analysis provided no insight into the configuration of the newly formed stereocentre, owing to a lack of other protons in the molecule with which an nOe could be observed. As a result, the configuration of alcohol **145** could not be determined at this time.

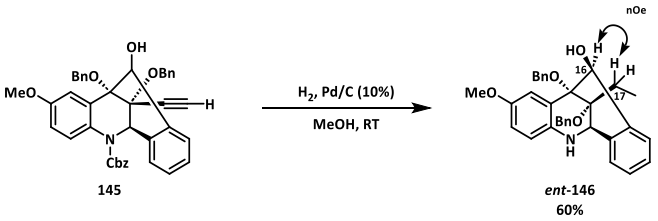


ent-142 145

Entry	Conditions	Yield 145
1	$NaBH_4$ (2.0 eq.) MeOH, RT	0%
2	$LiBH_4$ (5.0 eq.) THF, 0 °C to RT	91%

Table 3.5: Reduction of benzylic ketone ***ent*-142** to alcohol ***ent*-145**.

In order to determine the stereochemical configuration of the newly formed alcohol, the ethynyl chain of **145** was reduced to its ethyl analogue ***ent*-146** (**Scheme 3.19**).[106] Under the hydrogenation conditions used, full cleavage of the carbamate protecting group was also observed. $^1H/^1H$ NOESY analysis of ***ent*-146** showed clear nOe correlations between the C(16)**H** introduced during the borohydride reduction and the newly formed C(17)$\mathbf{H_2}$ methylene group of the ethyl chain. This confirmed unambiguously that alcohol **145** was indeed the desired (*S*) epimer (ie: ***ent*-144**) and that the geometry of ketone ***ent*-142** could be used to control the stereoselectivity of its reduction.



145 *ent*-146 60%

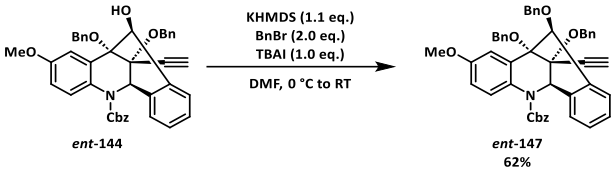
Scheme 3.19: Hydrogenation of alkynyl alcohol **145** to ethyl alcohol ***ent*-146**, with observed nOe correlations.

3.4.2 Alcohol Protection and Alkyne Carboxylation

With the stereochemical configuration of alcohol ***ent*-144** confirmed, we now sought to establish conditions for the protection of the alcohol group and the carboxylation of the alkyne moiety to access an alkynyl ester. In light of the benzyl ether groups already employed for the protection of the two tertiary alcohol units, we intended to also protect the newly formed secondary alcohol as its benzyl ether, in order to simplify the global deprotection that would be required at the end of

the synthesis. Meanwhile, the methyl ester group present in the side chain of sealutomicin C led us to target the methyl ester of alkyne ***ent*-144**, to avoid the need for subsequent transesterification.

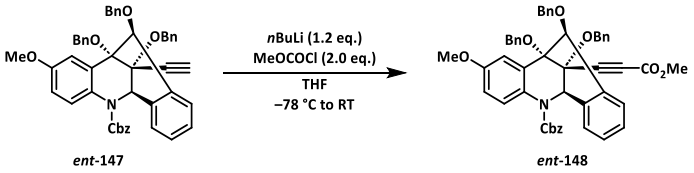
Treatment of a solution of ***ent*-144** in dimethylformamide with a single equivalent of KHMDS followed by addition of benzyl bromide resulted in O-alkylation, giving benzyl ether ***ent*-147** in 62% yield (**Scheme 3.20**). Despite our concerns of possible C-alkylation of the terminal alkyne, no signs of this were detected in the crude reaction mixture; however, some degradation to a baseline TLC spot was observed. No efforts were made to further optimise this reaction at this time.



ent-144 → *ent*-147, 62%

Scheme 3.20: Benzylation of alcohol ***ent*-144**.

Deprotonation of alkyne ***ent*-147** with *n*-butyllithium followed by addition of methyl chloroformate gave alkynyl ester ***ent*-148** in 42% yield alongside a considerable portion of unreacted started material (**Table 3.6, entry 1**).[107] Whilst we initially assumed that this limited reactivity was due to quenching of the acetylide anion intermediate by adventitious water, we were surprised to see that the conversion of starting material and yield of ***ent*-148** both decreased upon scale-up (**Entry 2**). In addition, TLC analysis of the reaction mixture showed signs of starting material degradation, indicating that some portion of the *n*-butyllithium base may be reacting with ***ent*-147** *via* a second, unwanted pathway.

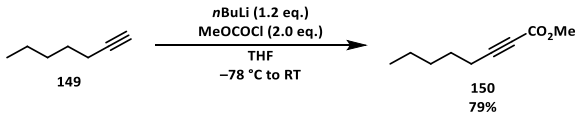


ent-147 → *ent*-148

Entry	Scale	Yield *ent*-148	Recovered *ent*-147
1	0.04 mmol	42%	30%
2	0.14 mmol	31%	34%

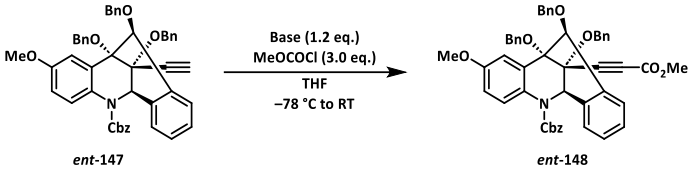
Table 3.6: Conversion of terminal alkyne ***ent*-147** to alkynyl ester ***ent*-148**.

To test the efficiency of our reaction conditions, a simple model system was investigated using *n*-heptyne (**149**). Under the same reaction conditions as described above, smooth conversion to alkynyl ester **150** was observed, with no sign of unreacted starting material nor degradation (**Scheme 3.21**). This confirmed our hypothesis that the poor yields of alkynyl ester ***ent*-148** were due to unwanted side reactivity of the *n*-butyllithium base with our starting material ***ent*-147**. Whilst the exact nature of this side reactivity remained unclear, we concluded that the use of an alternative base to deprotonate our alkyne starting material would be necessary.



Scheme 3.21: Model system for alkyne carboxylation using *n*-heptyne.

A range of bases were screened in order to try and improve the yield of alkynyl ester ***ent*-148** (**Table 3.7**). Deprotonation using freshly prepared lithium diisopropylamide led to degradation of the alkyne starting material, with no sign of the desired product (**Entry 1**); however, moderate successes were achieved using lithium, sodium, and potassium hexamethyldisilazide (**Entries 2 – 4**). In all cases, full consumption of starting material was observed, with NaHMDS giving both the cleanest reaction profile and highest yield of ***ent*-148**. Despite the moderate success of this reaction, we elected to press ahead with the natural product synthesis, as sufficient quantities of ***ent*-148** could be accessed to investigate the conversion of its alkyne unit to the (*E*)-β-methyl enoate side chain of sealutomicin C.



ent-147 *ent*-148

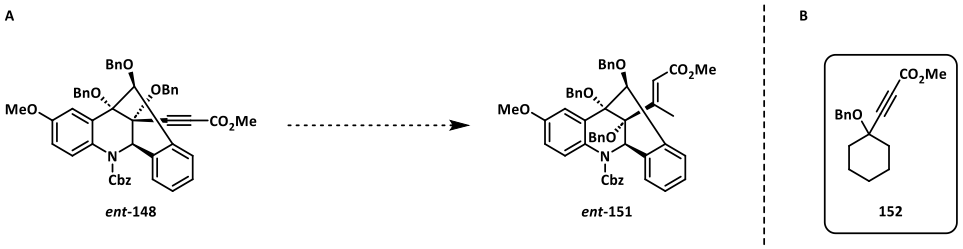
Entry	Base	Yield *ent*-148
1	LDA	0%
2	LiHMDS	44%
3	NaHMDS	58%
4	KHMDS	51%

Table 3.7: Conversion of terminal alkyne ***ent*-147** to alkynyl ester ***ent*-148**.

3.5 (*E*)-β-Methyl Enoate Synthesis

3.5.1 Studies Using a Model System

The completion of the sealutomicin C side chain synthesis required the conversion of the alkynyl ester group of ***ent*-148** to an (*E*)-β-methyl enoate ***ent*-151** (**Scheme 3.22A**). We decided to first investigate this proposed transformation using a model system. We identified compound **152**, possessing an alkynyl ester adjacent to an α-tertiary benzyl ether, as a suitable model substrate (**Scheme 3.22B**).

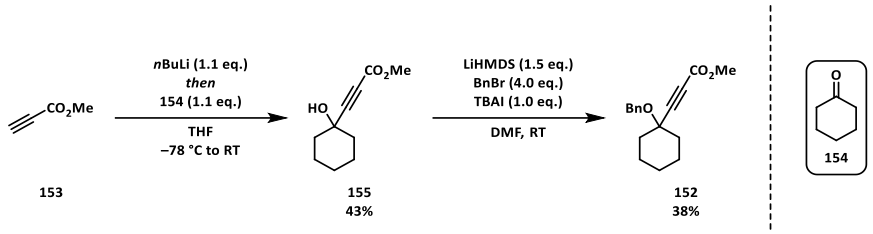


ent-148 *ent*-151 152

Scheme 3.22: A) Proposed transformation of alkynyl ester ***ent*-148** to α,β-unsaturated ester ***ent*-151**; B) proposed model substrate **152** to investigate transformation.

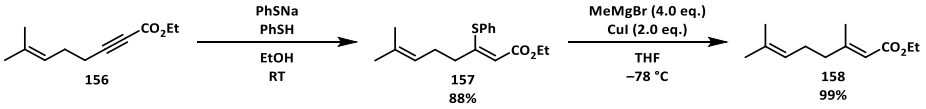
Deprotonation of methyl propiolate (**153**) with *n*-butyllithium followed by addition of cyclohexanone (**154**) gave tertiary alcohol **155** in 43% yield (**Scheme 3.24**).[108] Subsequent benzylation of **155** using LiHMDS and benzyl bromide in THF gave the target model substrate **152**.

No efforts were made to optimise this reaction sequence, as sufficient quantities of **152** could be prepared using the chemistry described.



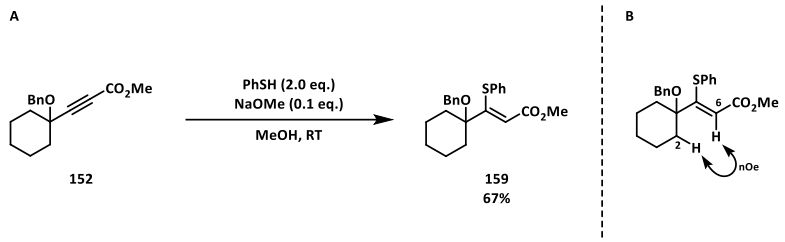
Scheme 3.23: Synthesis of model substrate **152**.

The two-step conversion of alkynyl esters to (*E*)-β-alkyl enoates *via* vinyl sulfides was first reported by Mukaiyama *et al.* in 1973 and subsequently utilised in the stereoselective synthesis of ethyl geranate and insect juvenile hormones.[109–111] Conjugate addition of thiophenolate to alkynyl ester **156** proceeded with complete (*Z*)-selectivity to give vinyl sulfide **157** (**Scheme 3.24**). Subsequent treatment of **157** with the organocuprate derived from methylmagnesium iodide and copper(I) iodide resulted in stereoretentive substitution of the thiophenolate moiety, giving (*E*)-β-methyl enoate **158** in almost quantitative yield with complete stereoselectivity. This methodology has since been utilised in numerous natural product syntheses, including those of ripostatin B and symbiodinolide.[112,113]



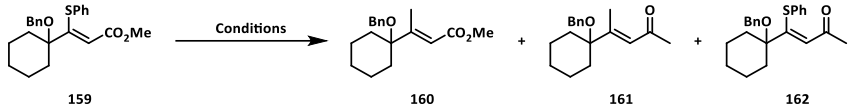
Scheme 3.24: Two-step conversion of alkynyl ester **157** to (*E*)-β-methyl enoate **158** during the synthesis of ethyl geranate by Mukaiyama *et al.*.[110]

In the hope that this chemistry could be applied to our ongoing synthesis, alkynyl ester **152** was treated with thiophenol and catalytic sodium methoxide, giving (*Z*)-vinyl sulfide **159** in 67% yield (**Scheme 3.25A**).[113] The stereochemical configuration of **159** was confirmed by analysis of its $^{1}H/^{1}H$ NOESY spectrum, which showed clear nOe correlations between the vinyl C(6)**H** proton and the C(2)$\mathbf{H_2}$ protons of the cyclohexyl ring (**Scheme 3.25B**).



Scheme 3.25: A) Synthesis of vinyl sulfide **159**; B) nOe correlations of **159** confirming *Z* stereochemistry.

Efforts to convert vinyl sulfide **159** to the desired (*E*)-β-methyl enoate **160** proved unsuccessful (**Table 3.8**). No conversion of starting material **159** was observed under the original conditions reported by Mukaiyama *et al.*, even after raising the reaction temperature from −78 °C to 0°C (**Entry 1**).[109] Switching the copper source from copper(I) iodide to copper(I) cyanide, in the hope that the more reactive "higher order" cyanocuprate might encourage consumption of **159**, also resulted in no reaction (**Entry 2**).[114–117] Attempts to activate the vinyl sulfide starting material by addition of trimethylsilyl chloride also proved fruitless (**Entry 3**).[118] Substituting the Grignard reagent for methyllithium resulted in a complex reaction mixture with no sign of the desired β-methyl enoate **160** (**Entry 4**). Ketones **161** and **162** were isolated in 27% and 19% respectively, appearing to suggest that the vinyl sulfide **159** preferentially undergoes substitution at the carbonyl carbon over the required β-substitution. It is likely that the steric hindrance arising from the tertiary centre adjacent to the alkynyl ester prevents attack on the β-carbon by the organocuprate nucleophile. The lack of success prompted us to discard this two-step approach using vinyl sulfide **159** and instead seek an alternative method for converting alkynyl ester **152** to enoate **160**.

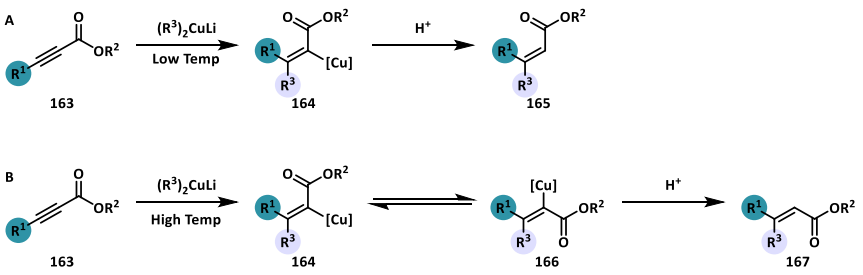


159 160 161 162

Entry	Conditions	Yield 160	Yield 161	Yield 162	Comments
1	MeMgBr (2.3 eq.) CuI (1.2 eq.) THF, −78 °C to 0 °C	0%	0%	0%	No reaction
2	MeMgBr (2.3 eq.) CuCN (1.2 eq.) THF, −78 °C to 0 °C	0%	0%	0%	No reaction
3	MeMgBr (3.9 eq.) CuCN (2.0 eq.), TMSCl (2.0 eq.) THF, −78 °C to 0 °C	0%	0%	0%	No reaction
4	MeLi (3.9 eq.) CuCN (2.0 eq.) THF, −78 °C to 0 °C	0%	27%	19%	-

Table 3.8: Unsuccessful attempts to convert vinyl sulfide **159** to enoate **160**.

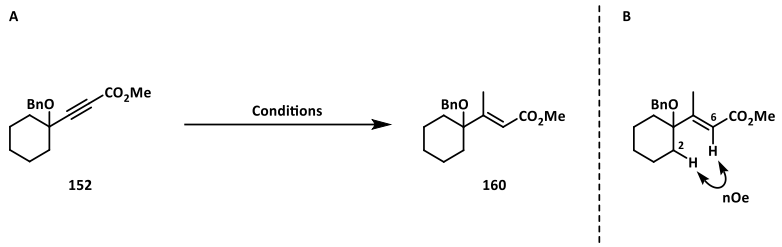
First described by Corey *et al.* in 1969, the conjugate addition of alkylcuprates to alkynyl esters is known to proceed with temperature-dependent stereoselectivity.[119] In all cases, the reaction begins with *syn*-carbocupration of the alkyne triple bond to give vinyl cuprate **164** (**Scheme 3.26**). At low temperatures, typically below −40 °C, no equilibration of **164** occurs. Upon protic workup, stereoretentive protodecupration gives the β-methyl enoate **165** with the newly introduced alkyl group R^3 group *trans* to the ester substituent (**Scheme 3.26A**). At higher temperatures, the vinyl cuprate initially formed may equilibrate with its opposite stereoisomer **166** *via* the corresponding allenoate, in order to reduce allylic strain between the ester group and the original R^1 substituent (**Scheme 3.26B**).[120,121] Subsequent protic workup gives the β-methyl enoate **167** with the newly introduced R^3 group *cis* to the ester substituent.



163 164 165 163 164 166 167

Scheme 3.26: Conjugate addition of alkylcuprates to alkynyl esters: A) low temperature addition with overall *syn*-addition of R^3-H; B high temperature addition with overall *anti*-addition of R^3-H.

Treatment of **152** with one equivalent of the cyanocuprate derived from methylmagnesium bromide and copper(I) cyanide in THF at 0 °C resulted in degradation of starting material, with no sign of the desired enoate **160** (**Table 3.9, entry 1**). The same result was obtained when lowering the reaction temperature to −20 °C (**Entry 2**), whilst at −78 °C no reactivity was observed (**Entry 3**). Switching to the methyllithium-derived cyanocuprate delivered more promising results; addition of alkynyl ester **152** to a solution of the cuprate in THF at −78 °C and allowing the reaction to warm slowly to 0 °C resulted in an inseparable mixture of unreacted starting material and the desired enoate **160** in a 6 : 1 ratio (**Entry 4**). The stereochemical configuration of the alkene **160** was determined by ^{1}H/^{1}H NOESY analysis of the mixture, with clear nOe correlations observed between the vinyl C(6)**H** proton and the C(2)**H$_2$** protons of the cyclohexyl ring. As a result, **160** was confirmed as the desired (*E*) isomer. Switching solvent from THF to diethyl ether resulted in full consumption of starting material, giving **160** in 39% yield with no sign of the unwanted (*E*)-isomer. The fate of the remaining starting material could not be determined, with neither the ^{1}H NMR nor the TLC of the crude reaction mixture showing signs of side product formation. Whilst further optimisation could have been conducted of this reaction using model substrate **152**, we decided instead to investigate the application of the highest-yielding conditions to our real substrate ***ent*-148**.

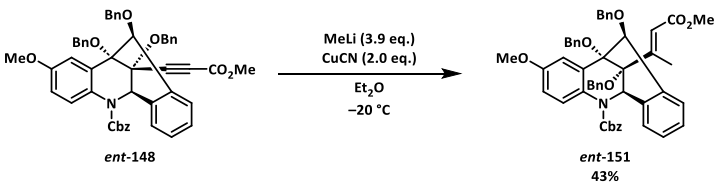


Entry	Conditions	Isolated Yield 160	Comments
1	MeMgBr (1.9 eq.) CuCN (1.0 eq.) THF, 0 °C	0%	Degradation of starting material
2	MeMgBr (2.1 eq.) CuCN (1.0 eq.) THF, −20 °C	0%	Degradation of starting material
3	MeMgBr (10 eq.) CuCN (5.3 eq.) THF, −78 °C	0%	No reaction
4	MeLi (2.3 eq.) CuCN (1.2 eq.) THF, −78 °C to 0 °C	0%	6 : 1 inseparable mixture 152 : 160
5	MeLi (2.9 eq.) CuCN (1.5 eq.) Et_2O, −20 °C	39%	Full consumption of starting material

Table 3.9: A) Conversion of alkynyl ester **152** to (*E*)-β-methyl enoate **160**; B) nOe correlations of **160** confirming desired (*E*)-stereochemistry.

3.5.2 Conjugate Addition Using Natural Product Substrate

Treatment of alkynyl ester ***ent*-148** with two equivalents of the organocuprate derived from methyllithium and copper(I) cyanide under the same reaction conditions described above gave alkenyl ester ***ent*-151** as a single diastereomer in 43% yield (**Scheme 3.27**). The stereochemical configuration of the newly formed alkene unit could not be determined at this stage and so was tentatively assigned as the desired (*E*) isomer by analogy to the model system.

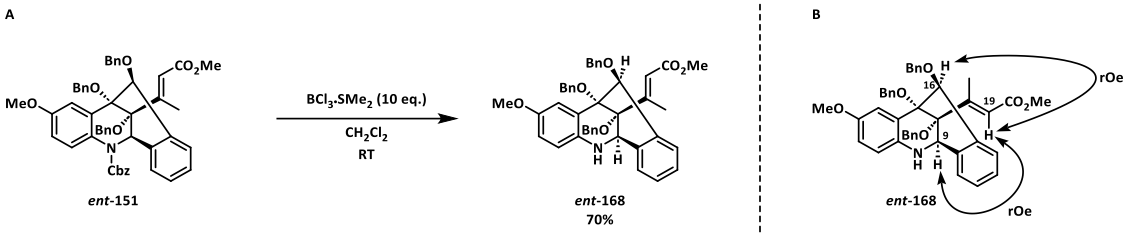


Scheme 3.27: Conversion of alkynyl ester ***ent*-148** to (*E*)-β-methyl enoate ***ent*-151**.

Once again, we were left puzzled by the fate of the remaining material for this conjugate addition reaction. Full consumption of starting material ***ent*-148** was observed, and the mass return of the

crude reaction mixture was good. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture was complicated by peak broadening caused by the presence of rotamers of the carbamate protecting group. Despite this, it was clear that desired product ***ent*-151** was the predominant component of the crude reaction mixture. Given the low yield of ***ent*-151** following chromatographic purification, 2D TLC analysis of ***ent*-151** was conducted to assess its stability on silica; however, no decomposition of ***ent*-151** was observed.

To determine the stereochemical configuration of the newly installed alkenyl ester group, the carbamate protecting group of ***ent*-151** was cleaved, in order to reduce peak broadening caused by the presence of rotamers. Treatment of ***ent*-151** with boron trichloride dimethyl sulfide resulted in selective removal of the carbamate to give aniline ***ent*-168** in 70% yield (**Scheme 3.28A**).[122] Analysis of the ^{1}H/^{1}H ROESY spectrum of ***ent*-168** showed clear correlations between the vinyl C(19)**H** proton and both the C(16)**H** and the C(9)**H** protons, indicated that the alkenyl ester was the desired (*E*) enoate (**Scheme 3.28B**).



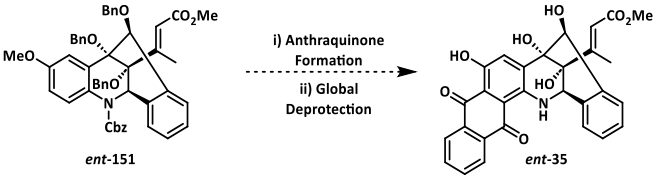
Scheme 3.28: A) Carbamate deprotection of alkenyl ester ***ent*-151** to aniline ***ent*-168**; B) rOe correlations of ***ent*-168** confirmed (*E*) alkene geometry.

Despite the moderate yield of the conjugate addition reaction to give ***ent*-151**, we were pleased to have developed a stereoselective means of accessing the (*E*)-β-methyl enoate side chain of sealutomicin C. Had time permitted, further optimisation of this reaction would have taken place; however, time constraints caused by the COVID-19 pandemic forced us to press ahead with the natural product synthesis.

3.6 Endgame Studies

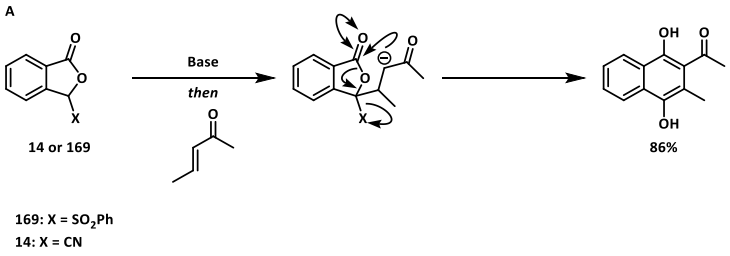
3.6.1 Hauser-Kraus Annulation

With the (*E*)-β-methyl enoate side chain synthesis completed, two further challenges remained in our initial studies towards enantiomeric sealutomicin C (**ent**-**35**). The first concerned the installation of the anthraquinone moiety of the natural product, whilst the second concerned the deprotection of the benzyl protecting groups. We chose to initially focus on the former, in the hope that a subsequent global deprotection step would give **ent**-**35** (**Scheme 3.29**).



Scheme 3.29: Proposed conversion of intermediate ***ent*-151** to enantiomeric sealutomicin C (***ent*-35**).

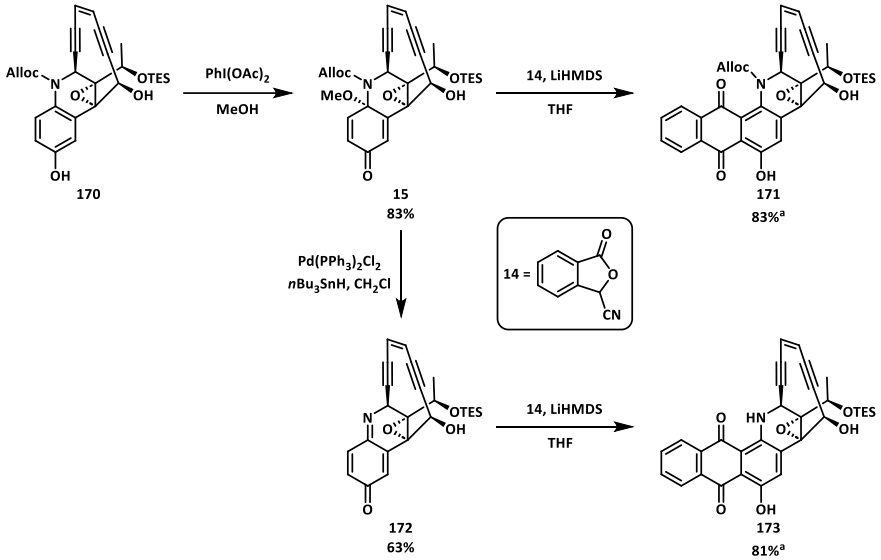
As discussed in **Chapter 1**, we envisaged employing a Hauser-Kraus annulation to install the necessary anthraquinone unit. The reaction begins with conjugate addition of a substituted phthalide nucleophile to a Michael acceptor, with subsequent Claisen condensation and elimination giving the quinone product (**Scheme 3.30**). Whilst Hauser's original publication utilised sulfonylphthalide **169**, Kraus's subsequent modification employed cyanophthalide **14** instead.[123,124] Mal *et al.* showed that the cyano reagent is generally more effective, owing to its reduced steric bulk and greater solubility in the ethereal reaction solvents typically employed.[125]



Scheme 3.30: Hauser and Kraus annulations to prepare substituted quinones.

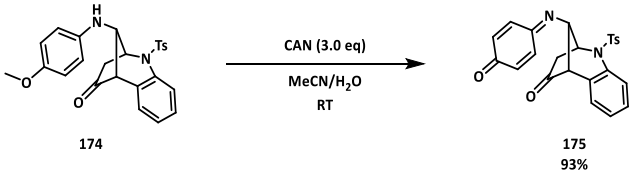
The Hauser-Kraus annulation was employed by Nicolaou *et al.* to install an anthraquinone unit in their syntheses of racemic and enantiopure uncialamycin.[15,21,23] Oxidation of alloc-protected aniline

170 gave hemiquinone aminal **15**, which upon addition to a premixed solution of cyanophthalide **14** and LiHMDS underwent annulation to anthraquinone **171** (**Scheme 3.31**). Alternatively, **15** could be deprotected to give iminoquinone **172**, which also proved to be a suitable electrophile in the annulation to give anthraquinone **173**.



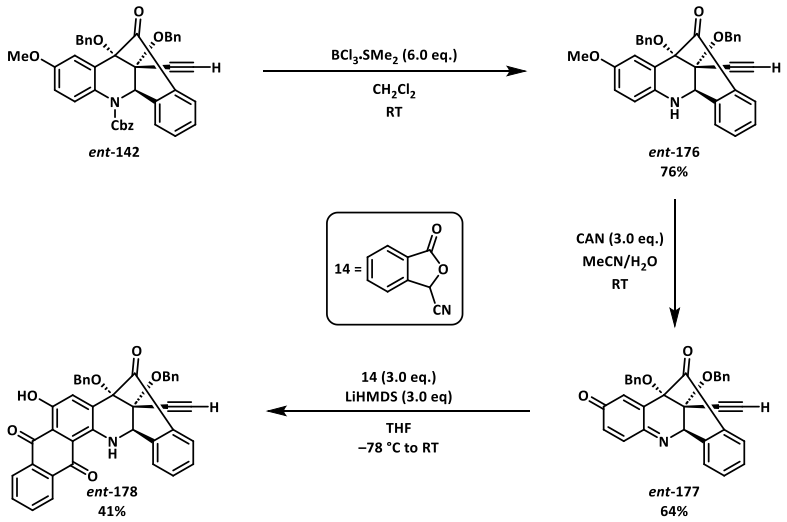
Scheme 3.31: Anthraquinone formation in the total syntheses by Nicolaou *et al.*. [a] Yield based on recovered starting material.

Seeking a method to convert our advanced substrate, aniline ***ent*-168**, to a suitable Hauser-Kraus electrophile, we were intrigued by a report by Leboeuf *et al.*, who demonstrated that *para*-methoxyphenyl amine **174** underwent oxidative demethylation to form *para*-iminoquinone **175** upon treatment with cerium(IV) ammonium nitrate (**Scheme 3.32**).[126] With our advanced substrate ***ent*-168** also possessing a *para*-methoxyphenyl amine motif, we wondered whether this oxidative demethylation reaction could be utilised to access an iminoquinone which could serve as the necessary Hauser-Kraus electrophile.



Scheme 3.32: Conversion of *para*-methoxyphenyl amine **174** to *para*-iminoquinone **175**.[126]

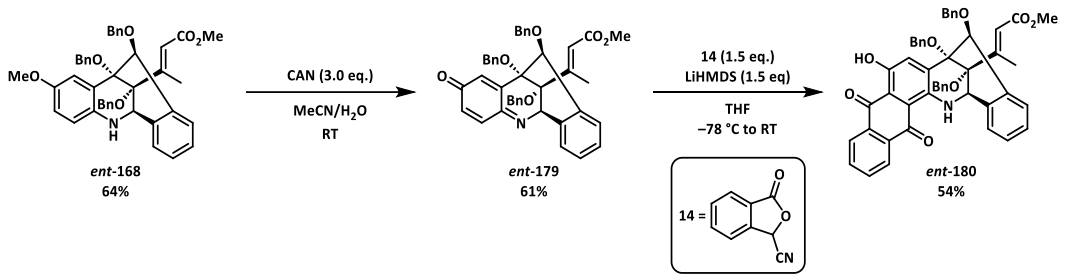
We elected to initially investigate the proposed oxidative demethylation/annulation sequence using alkyne ***ent*-142** as a model substrate. Carbamate deprotection using boron trichloride dimethyl sulfide gave aniline ***ent*-176** in 76% yield, which was then treated with cerium(IV) ammonium nitrate in 3 : 1 acetonitrile : water (**Scheme 3.33**).[122,126] We were pleased to see that oxidative demethylation ensued, giving iminoquinone ***ent*-177** in 64% yield. Iminoquinone ***ent*-177** proved to be stable to purification by flash chromatography and could be stored overnight at −4 °C, with no hydrolysis to the free amine observed. To our delight, addition of ***ent*-177** to a premixed solution of cyanophthalide **14** and LiHMDS at −78 °C before subsequent warming to room temperature resulted in the desired Hauser-Kraus annulation, giving anthraquinone ***ent*-178** in 41% yield.[127] Formation of the anthraquinone unit could be monitored during the reaction by observing the colour change of the reaction mixture from the bright yellow colour of the cyanophthalide anion to the deep purple colour of the anthraquinone product.



Scheme 3.33: Three-step conversion of carbamate ***ent*-142** to anthraquinone ***ent*-178**.

Following the successful synthesis of anthraquinone ***ent*-178**, the same oxidative demethylation/ annulation sequence was investigated using aniline ***ent*-168** (**Scheme 3.34**). Oxidation of ***ent*-168** gave iminoquinone ***ent*-179**, which also proved stable to both flash column chromatography and overnight storage at −4 °C. Reaction of ***ent*-179** with cyanophthalide **14** again resulted in anthraquinone formation, giving ***ent*-180** in 54% yield. No other products were isolated from the

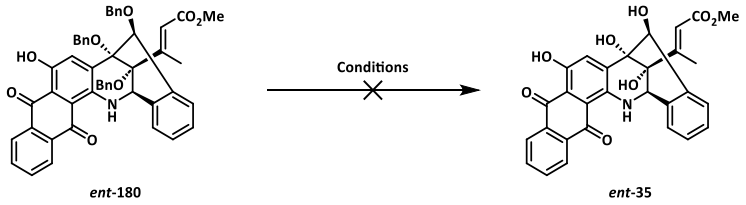
reaction; however, the moderate yield of ***ent*-180** may in part be due to reaction of the cyanophthalide anion with the α,β-unsaturated ester Michael acceptor unit of ***ent*-179**.



Scheme 3.34: Oxidative demethylation and subsequent annulation of aniline ***ent*-168** to give anthraquinone ***ent*-180**.

3.6.2 Deprotection Attempts

Following the success of the oxidative demethylation/annulation sequence, all that remained in order to complete the synthesis of enantiomeric sealutomicin C (***ent*-35**) was the removal of the three benzyl ether protecting groups. Due to the scarcity of material, only two deprotection attempts were made using *tris*-benzyl ether ***ent*-180**. Hydrogenolysis conditions using palladium on carbon resulted in full return of starting material ***ent*-180** (**Table 3.10, entry 1**). No reaction was observed upon treatment of ***ent*-180** with boron trichloride in dichloromethane at −78 °C or upon subsequent warming to −40 °C. Unfortunately, further heating to 0 °C resulted in decomposition of ***ent*-180**, with no sign of the desired natural product enantiomer ***ent*-35** (**Entry 2**).



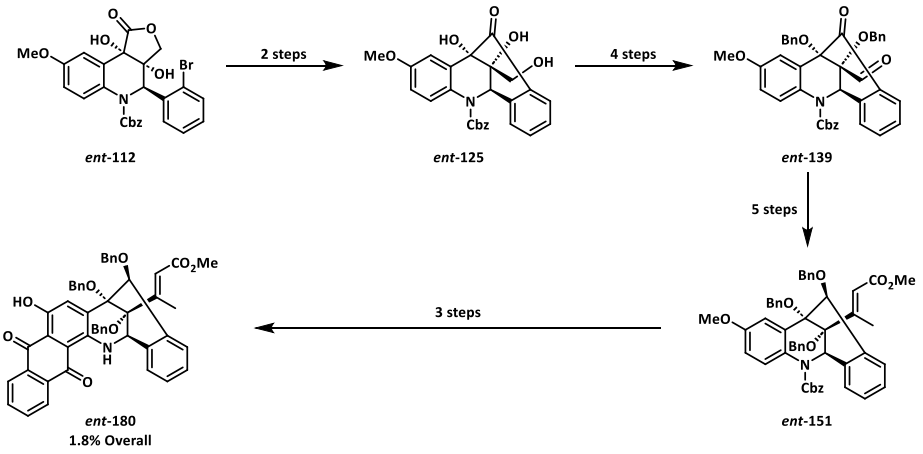
Entry	Conditions	Comments
1	**H_2, Pd/C (0.1 eq.) MeOH, RT**	**No reaction**
2	**BCl_3 (5.0 eq.) CH_2Cl_2 −78 °C to 0°C**	**Below −40 °C no reaction. Above −40 °C decomposition of starting material**

Table 3.10: Failed attempts to deprotect *tris* benzyl ether ***ent*-180** to give enantiomeric sealutomicin C (***ent*-35**).

Whilst the failure to successfully deprotect ***ent*-180** and prepare enantiomeric sealutomicin C (**ent-35**) was highly disappointing, valuable insight into the reactivity of ***ent*-180** had been gained. The instability of anthraquinone ***ent*-180** under Lewis acidic conditions would inform our deprotection strategy for our first-generation synthesis of sealutomicin C (see **Chapter 4**). Meanwhile, the tolerance of the sterically hindered α,β-unsaturated ester unit to hydrogenation conditions would prove invaluable during our second-generation route to the natural product.

3.7 Chapter Summary

We had developed a 14-step sequence enabling the conversion of aryl bromide ***ent*-112** to *tris*-protected enantiomeric sealutomicin C (***ent*-180**) in an overall yield of 1.4% (**Scheme 3.35**). Following an organolithium-mediated cyclisation to complete the synthesis of the natural product core, manipulation of the resultant triol ***ent*-125** gave access to aldehyde ***ent*-139**. Substrate-controlled reduction of the benzylic ketone group was accompanied by stereoselective conversion of the aldehyde handle to the (*E*)-β-methyl enoate side chain to give α,β-unsaturated ester ***ent*-151**. Ester ***ent*-151** was then converted to anthraquinone ***ent*-180** *via* a three-step deprotection/oxidation/annulation sequence. We anticipated that the chemistry developed during this chapter could be applied to the opposite enantiomeric series of compounds in order to synthesise the correct enantiomer of sealutomicin C.

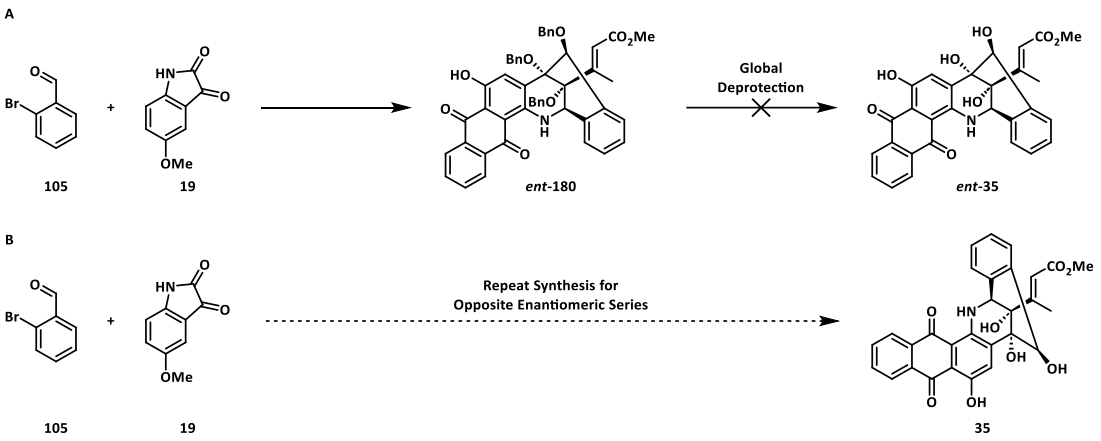


Scheme 3.35: 14-step conversion of aryl bromide ***ent*-112** to anthraquinone ***ent*-180**.

Chapter 4: First-Generation Synthesis of Sealutomicin C

4.1 Chapter Introduction

Chapters 3 and 4 described our efforts to develop a synthetic route towards enantiomeric sealutomicin C (***ent*-35**) from commercially available 2-bromobenzaldehyde and 5-methoxyisatin (**Scheme 4.1A**). Whilst the final deprotection of *tris*-benzyl ether ***ent*-180** to access ***ent*-35** had proven unsuccessful, we were confident that much of the chemistry developed could be applied in a successful synthesis of the natural product. Until now, all research had been carried out on the opposite enantiomeric series to that required for the synthesis of the correct enantiomer of sealutomicin C (**35**). This chapter describes our efforts to repeat this chemistry using the correct enantiomeric series, culminating in a successful first-generation total synthesis of **35** (**Scheme 4.1B**).

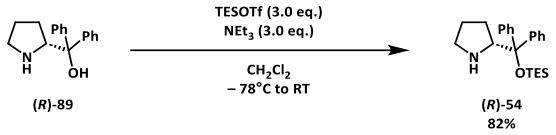


Scheme 4.1: A) Previous work towards *ent*-sealutomicin C (Chapters 3 + 4); B) proposed work towards sealutomicin C.

4.2 Synthesis of Sealutomicin C

4.2.1 Repetition of Route Using Correct Enantiomeric Series

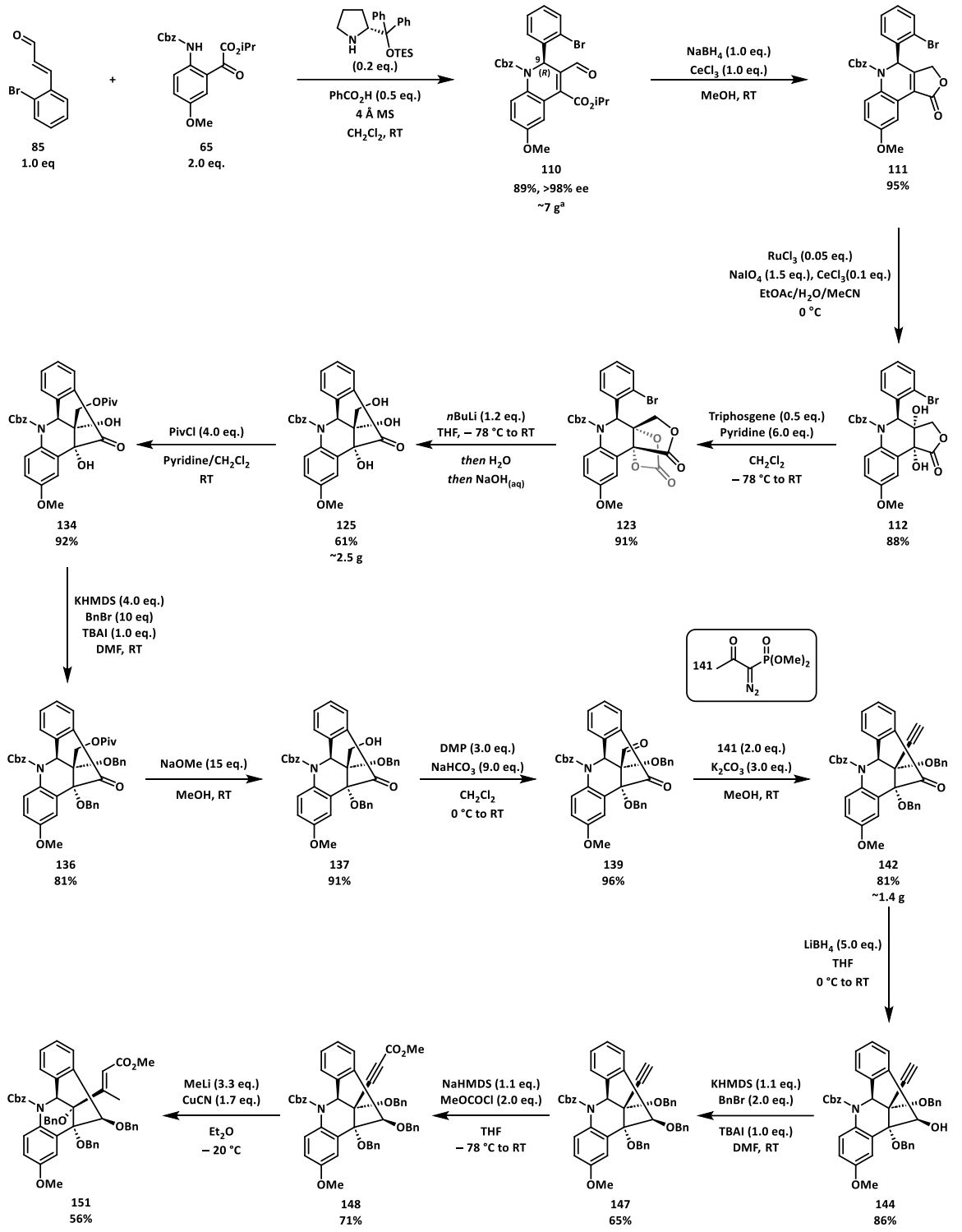
Prolinol **89** was converted to (*R*)-triethylsilyl prolinol **(*R*)-54** using triethylsilyl triflate and triethylamine. The optical rotation of **(*R*)-54** was of a similar magnitude and opposite sign to that previously obtained for catalyst **(*S*)-54**.



Scheme 4.2: Silylation of prolinol **89** to give catalyst **54**.

Enantioselective coupling of bromocinnamaldehyde **85** and ketoester **65** using catalyst **(*R*)-54** under Guggiari's conditions gave dihydroquinoline **110** in good yield on 7-gram scale (**Scheme 4.3**). The *ee* of **110** was determined by chiral HPLC to be greater than 98%, whilst the optical rotation of **110** was of similar magnitude and opposite sign to that of ***ent*-110** which had been previously prepared. Thus, the absolute configuration of **110** was assigned as that shown in **Scheme 4.3**, with the chiral C(9) centre assigned as (*R*). As expected, the chemistry developed in chapters 3 and 4 proved to be robust and repeatable for the correct enantiomeric series. (*E*)-β-methyl enoate **151** was prepared in 14 steps from **85** and **65** in 4.8% overall yield. The compounds synthesised all possessed optical rotations with similar magnitudes and opposite signs to their enantiomeric analogues prepared previously, indicating that no enantioerosion had taken place. Whilst the organolithium cyclisation gave a somewhat lower yield of **125** than that obtained for its enantiomer (61% *vs* 78%), triol **125** could still be synthesised on 2.5 g scale. Despite our failed attempts to remove the benzyl protecting groups in our previous work, we remained confident that a method for their removal could be found. Consequently, we continued to use them throughout the synthesis. Once again, the conjugate addition to alkynyl ester **148** gave only moderate yields of (*E*)-β-methyl enoate **151**; however, we felt that the 130 milligrams of **151** prepared was sufficient to investigate the endgame of the synthesis. Work would now focus on identifying a suitable method for removal of the benzyl

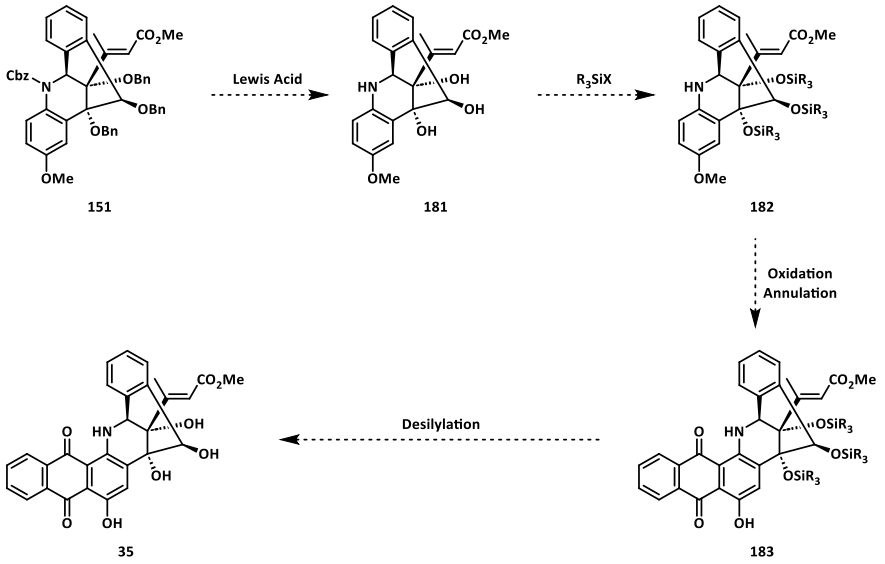
protecting groups and repeating the oxidative demethylation/annulation sequence in order to complete the synthesis of the natural product.



Scheme 4.3: 14-step synthesis of (*E*)-β-methyl enoate **151** from cinnamaldehyde **85** and keto ester **65** in 4.8% overall yield. [a] Yield calculated from cinnamaldehyde **85**.

4.2.2 Deprotection Studies and Endgame

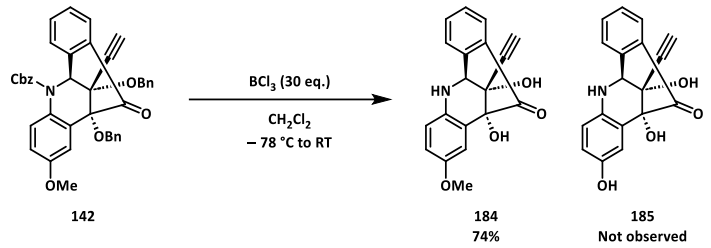
In light of the failure to remove the benzyl ether protecting groups from anthraquinone ***ent*-180**, we sought a method to debenzylate enoate **151** prior to installation of the anthraquinone unit. Our studies using ***ent*-180** indicated that the two tertiary benzyl ether units were resistant to palladium catalysed hydrogenolysis, owing to their sterically hindered environments. Consequently, we elected to investigate their Lewis acid-mediated removal. We anticipated that the benzyl carbamate unit of **151** would be unlikely to survive such conditions. However, we hoped that following the proposed global deprotection, the three alcohol units could be briefly reprotected as silyl ethers, enabling the free aniline to undergo the established oxidative demethylation/annulation sequence (**Scheme 4.4**). Subsequent global desilylation would give sealutomicin C (**35**).



Scheme 4.4: Proposed deprotection and anthraquinone installation.

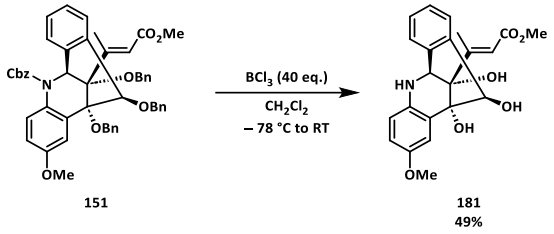
To carry out initial investigations into the Lewis acid-mediated debenzylation, alkyne **142** was selected as a model substrate. A solution of **142** in dichloromethane was cooled to −78 °C and treated with 5 equivalents of boron trichloride; the progress of the reaction was monitored by LRMS.[128] Upon addition of the boron trichloride at −78 °C, rapid loss of the benzyl carbamate was observed; however, no benzyl ether deprotection was observed. Treatment with additional boron trichloride resulted in no further change. Upon warming to 0 °C, monodebenzylation was observed;

however, further warming to room temperature was required to enable full debenzylation, giving diol **184** in 74% yield (**Scheme 4.5**). No demethylation of the anisole unit to the analogous phenol (**185**) was observed.



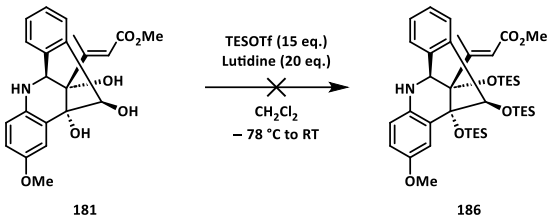
Scheme 4.5: Debenzylation of *bis*-benzyl ether **184** to diol **185**.

Having established conditions for the deprotection of the two tertiary benzyl ether groups of alkyne **142**, we now sought to apply them to the debenzylation of enoate **151**. Treatment of **151** with boron trichloride at −78 °C and subsequent warming to room temperature gave triol **181** in 49% yield. TLC analysis of the crude reaction mixture also showed a strong baseline spot suggesting partial hydrolysis of the methyl ester unit; however, the resultant carboxylic acid could not be isolated. Despite the moderate yield of the reaction, we were pleased to see that the benzyl groups could be successfully removed to give useable quantities of triol **181**.



Scheme 4.6: Global deprotection of *tris*-benzyl ether **151**.

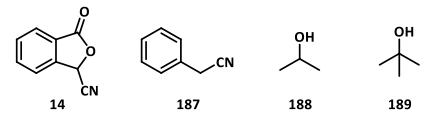
Attempts to reprotect the three hydroxyl groups of **181** as their triethylsilyl ethers proved unsuccessful. Treatment of **181** with a large excess of triethylsilyl triflate and lutidine resulted in incomplete silylation even after warming to room temperature, giving a complex mixture of silyl ether regioisomers, with no sign of the desired *tris*-triethylsilyl ether **186** (**Scheme 4.7**). We attributed this incomplete reactivity to the extreme steric crowding that would arise in **186**.



181 186

Scheme 4.7: Failure to prepare *tris*-silylether **186** from triol **181**.

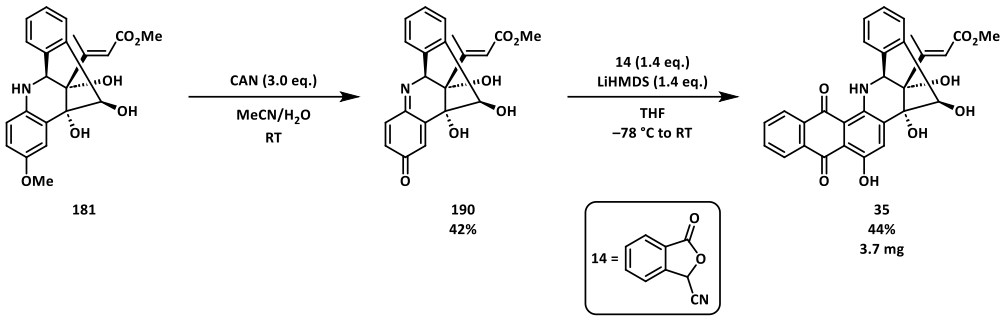
The failure to silylate the hydroxyl units of triol **181** led us to question the need for their reprotection. We had assumed that the protection of these alcohol groups would be necessary to prevent their interference in the anthraquinone-forming Hauser-Kraus annulation by protonating the anionic cyanophthalide intermediate. Whilst the pKa of cyanophthalide **14** has not been reported, the pK_a of structurally related phenylacetonitrile **187** has been measured to be 21.9 in DMSO (**Figure 4.1**).[129] Meanwhile, the pK_a values of isopropanol (**188**) and *tert*-butanol (**189**) in DMSO are 30.3 and 32.2 respectively.[130] We reasoned that the pKa of cyanophthalide **14** would be low enough that the anion derived from **14** would not be protonated by the unprotected hydroxyl groups of our substrate and would instead undergo the desired annulation reaction.



14 pKa = Unknown | 187 pKa = 21.9[a] | 188 pKa = 30.3[a] | 189 pKa = 32.3[a]

Figure 4.1: Relevant pKa values of nitriles **14** + **187** and alcohols **188** + **189**. [a] pKa values measured in DMSO.

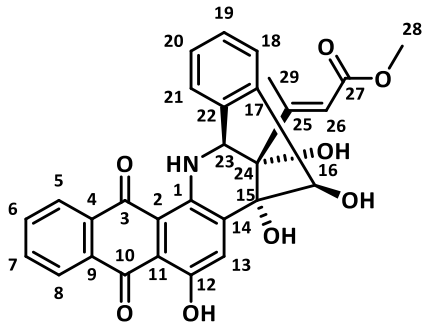
Oxidation of **181** using cerium(IV) ammonium nitrate gave iminoquinone **190** in 42% yield, with some degradation to a baseline spot on the TLC also observed (**Scheme 4.8**). To our delight, addition of **190** to a premixed solution of cyanophthalide **14** and LiHMDS resulted in a deep purple reaction mixture, indicating anthraquinone formation. Purification of the reaction mixture gave 3.7 mg of sealutomicin C **35** in 44% yield. ^{1}H NMR, ^{13}C NMR, HRMS and circular dichroism data of synthetic **35** were entirely in accord with the reported data for the natural product (*vide infra*).



Scheme 4.8: Synthesis of sealutomicin C (**35**) from triol **181**.

4.2.3 Data Comparison for Synthetic and Reported Sealutomicin C

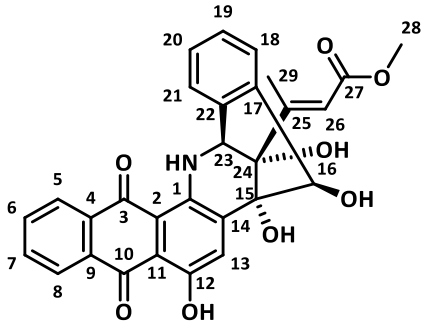
The ^{13}C NMR data for the sample of synthetic sealutomicin C in deuterated DMSO matched those reported in Igarashi's isolation paper, with all resonances consistent to within 0.1 ppm (**Table 4.1**).[32]



Position	δ_C[a] Natural[32]	δ_C[b] Synthetic	Δδ(Natural – Synthetic)
C(1)	143.4 (s)	143.4 (s)	0.0
C(2)	106.1 (s)	106.1 (s)	0.0
C(3)	186.1 (s)	186.1 (s)	0.0
C(4)	132.0 (s)	132.0 (s)	0.0
C(5)	125.9 (d)	125.9 (s)	0.0
C(6)	132.9 (d)	132.8 (s)	0.1
C(7)	134.6 (d)	134.5 (s)	0.1
C(8)	126.3 (d)	126.2 (s)	0.1
C(9)	134.8 (s)	134.8 (s)	0.0
C(10)	180.1 (s)	180.1 (s)	0.0
C(11)	111.9 (s)	111.9 (s)	0.0
C(12)	155.9 (s)	155.9 (s)	0.0
C(13)	130.4 (d)	130.4 (s)	0.0
C(14)	141.7 (s)	141.7 (s)	0.0
C(15)	77.9 (s)	77.9 (s)	0.0
C(16)	74.2 (d)	74.2 (s)	0.0
C(17)	135.9 (s)	135.9 (s)	0.0
C(18)	127.2 (d)	127.2 (s)	0.0
C(19)	127.5 (d)	127.4 (s)	0.1
C(20)	128.4 (d)	128.4 (s)	0.0
C(21)	127.3 (d)	127.3 (s)	0.0
C(22)	137.5 (s)	137.5 (s)	0.0
C(23)	57.8 (d)	57.7 (s)	0.1
C(24)	72.4 (s)	72.4 (s)	0.0
C(25)	158.2 (s)	158.1 (s)	0.1
C(26)	117.4 (d)	117.4 (s)	0.0
C(27)	166.1 (s)	166.1 (s)	0.0
C(28)	50.9 (q)	50.9 (s)	0.0
C(29)	16.9 (q)	16.9 (s)	0.0

Table 4.1: Comparison of ^{13}C NMR data for natural sealutomicin C (reported by Igarashi) and synthetic sealutomicin C (prepared by the author). [a] 150 MHz, DMSO-d_6, proton-coupled; [b] 150 MHz, DMSO-d_6, proton-decoupled

The ^{1}H NMR data for the sample of synthetic sealutomicin C in deuterated DMSO matched those reported by Igarashi, with all resonances equal to within 0.02 ppm (**Table 4.2**).[32]



Position	δ_H[a] Natural[32]	δ_H Synthetic[a]	Δδ(Natural – Synthetic)
C(1)NH	10.82 (d, *J* = 5.4 Hz)	10.83 (d, *J* = 5.5 Hz)	-0.01
C(1)	-	-	
C(2)	-	-	
C(3)	-	-	
C(4)	-	-	
C(5)	8.21 (m)	8.22 (dd, *J* = 7.5, 1.0 Hz)	-0.01
C(6)	7.82 (td, *J* = 7.5, 1.4 Hz)	7.83 (td, *J* = 7.5, 1.0 Hz)	-0.01
C(7)	7.89 (td, *J* = 7.5, 1.4 Hz)	7.90 (td, *J* = 7.5, 1.0)	-0.01
C(8)	8.22 (m)	8.23 (dd, *J* = 7.5, 1.0 Hz)	-0.01
C(9)	-	-	
C(10)	-	-	
C(11)	-	-	
C(12)	-	-	
C(12)OH	13.57 (s)	13.58 (s)	-0.01
C(13)	7.62 (s)	7.63 (s)	-0.01
C(14)	-	-	
C(15)	-	-	
C(15)OH	5.95 (s)	5.95 (s)	0.00
C(16)	4.57 (d, *J* = 5.9 Hz)	4.58 (d, *J* = 6.0 Hz)	-0.01
C(16)OH	6.01 (d, *J* = 5.9 Hz)	6.01 (d, *J* = 6.0 Hz)	0.00
C(17)	-	-	
C(18)	7.33 (d, *J* = 7.5 Hz)	7.34 (d, *J* = 7.5 Hz)	-0.01
C(19)	7.18 (td, *J* = 7.5, 1.3 Hz)	7.19 (t, *J* = 7.5 Hz)	-0.01
C(20)	7.25 (t, *J* = 7.5 Hz)	7.26 (t, *J* = 7.5)	-0.01
C(21)	7.61 (dt *J* = 7.5, 1.3)	7.63 (d, *J* = 7.5 Hz)	-0.02
C(22)	-	-	
C(23)	4.94 (d, *J* = 5.4 Hz)	4.95 (d, *J* = 5.5 Hz)	-0.01
C(24)	-	-	
C(24)OH	5.94 (s)	5.94 (s)	0.00
C(25)	-	-	
C(26)	5.78 (q, *J* = 1.2 Hz)	5.79 (q, *J* = 1.0 Hz)	-0.01
C(27)	-	-	
C(28)	3.51 (s)	3.52 (s)	-0.01
C(29)	2.33 (d, *J* = 1.2 Hz)	2.34 (d, *J* = 1.0 Hz)	-0.01

Table 4.2: Comparison of ^{1}H NMR data for natural sealutomicin C (reported by Igarashi) and synthetic sealutomicin C (prepared by the author). [a] 150 MHz, DMSO-d_6.

The graphical ^{1}H and ^{13}C NMR spectra for the sample of synthetic sealutomicin C in DMSO-d_6 were both in accordance with the analogous spectra reported by Igarashi for natural sealutomicin C in the same solvent (**Figure 4.2** and **Figure 4.3**).

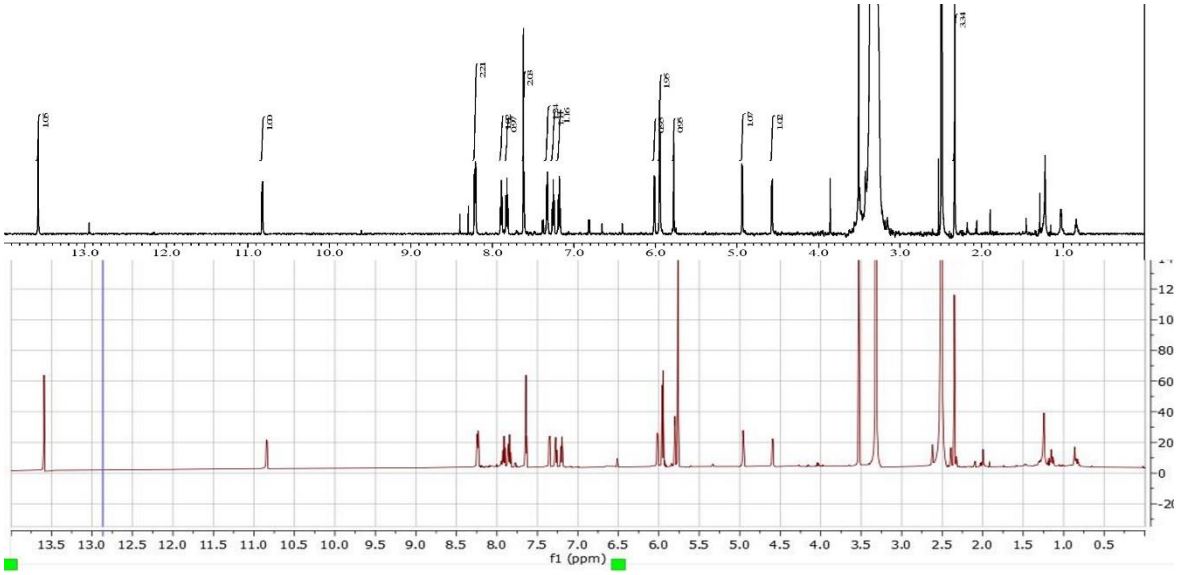


Figure 4.2: Top) ^{1}H NMR spectrum[†] of natural sealutomicin C in DMSO-d_6 reported with Igarashi[32]; bottom) ^{1}H NMR spectrum of synthetic sealutomicin C in DMSO-d_6 prepared by the author.

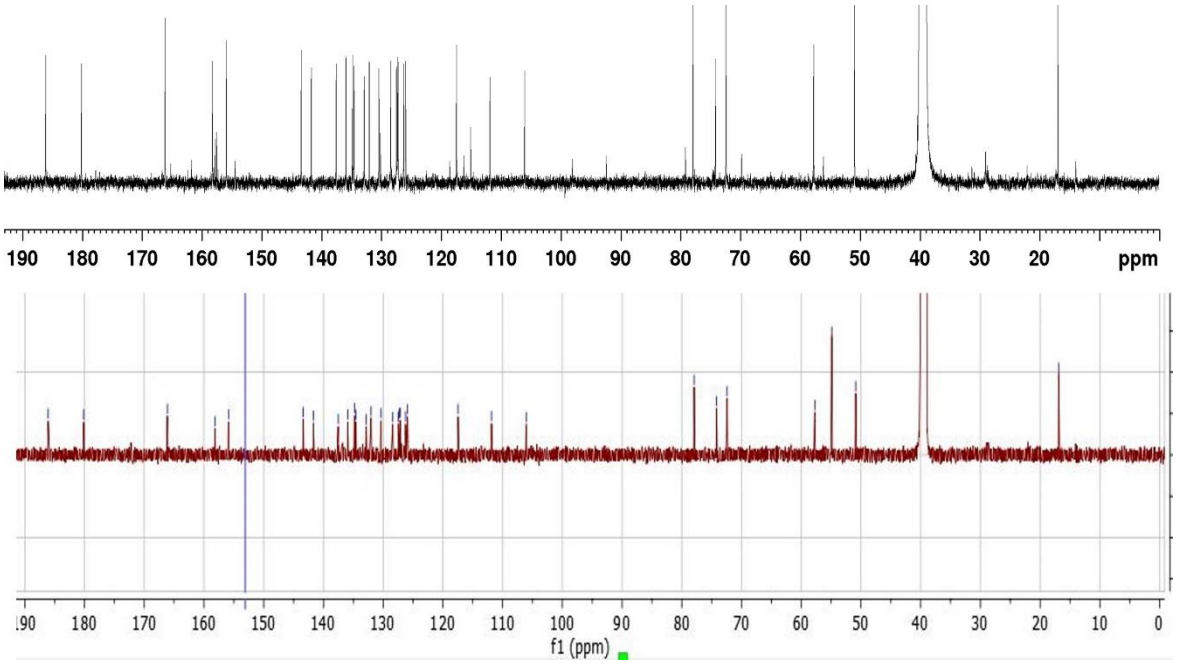


Figure 4.3: Top) ^{13}C NMR[‡] spectrum of natural sealutomicin C in DMSO-d_6 reported with Igarashi[32]; bottom) ^{13}C NMR spectrum of synthetic sealutomicin C in DMSO-d_6 prepared by the author.

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[‡] Reproduced with permission from Springer Nature

Electrospray ionisation high resolution mass spectrometry (ESI HRMS) analysis of the sample of synthetic sealutomicin C gave a molecular ion with a mass-to-charge ratio (m/z) of 514.1490. This matched the ESI HRMS data for natural sealutomicin C, with an *m/z* of 514.1487. Both masses are consistent with the molecular formula $C_{29}H_{24}NO_8^+$, which corresponds to the proton adduct of the proposed structure for sealutomicin C.

Circular dichroism analysis of the sample of synthetic sealutomicin C was carried out by Denis Hartmann (University of Oxford). The CD spectrum of synthetic sealutomicin C (**Figure 4.4 top**) closely matched the CD spectrum of natural sealutomicin C reported by Igarashi (**Figure 4.4 bottom**), indicating that the synthetic sample was the correct enantiomer.[32]

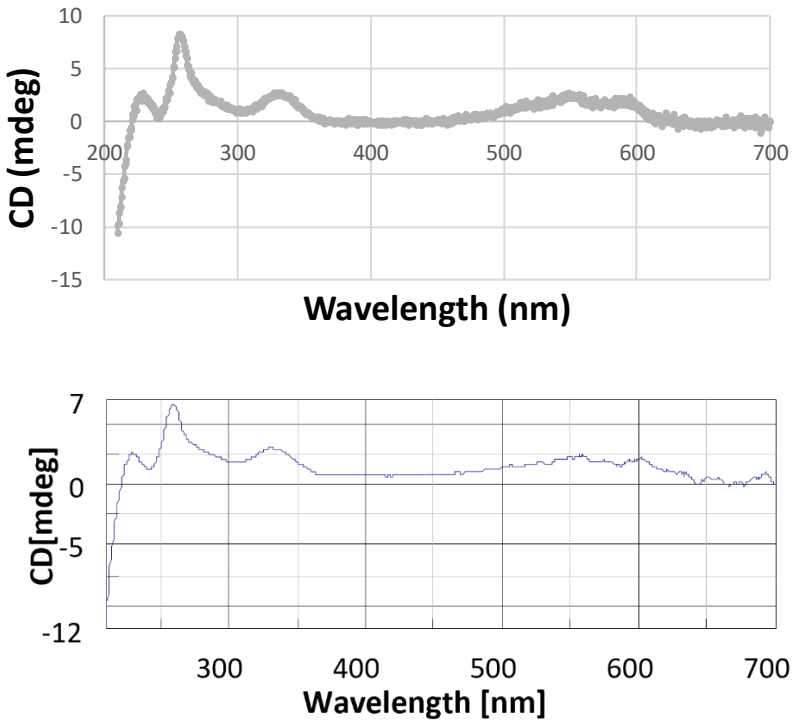


Figure 4.4: Top) circular dichroism spectrum of synthetic sealutomicin C; bottom) circular dichroism spectrum of natural sealutomicin C reported by Igarashi.[§]

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The ^{1}H and ^{13}C NMR data of sealutomicin C were compared to those reported for the compound proposed by Shen to be sealutomicin C (compound ***Shen-14*** of the referenced publication).[26] The graphical ^{1}H NMR spectrum for the sample of synthetic sealutomicin C in acetone-d_6 was in accordance with the graphical ^{1}H NMR spectrum of compound ***Shen-14*** reported by Shen (**Figure 4.5**). The resonances corresponding to the C(1)N**H**, C(12)O**H**, C(15)O**H**, C(16)O**H** and C(24)O**H** protons are visible in the ^{1}H NMR spectrum of natural sealutomicin C; however, they are not observed in the ^{1}H NMR spectrum of synthetic sealutomicin C due to proton exchange in the deuterated NMR solvent.

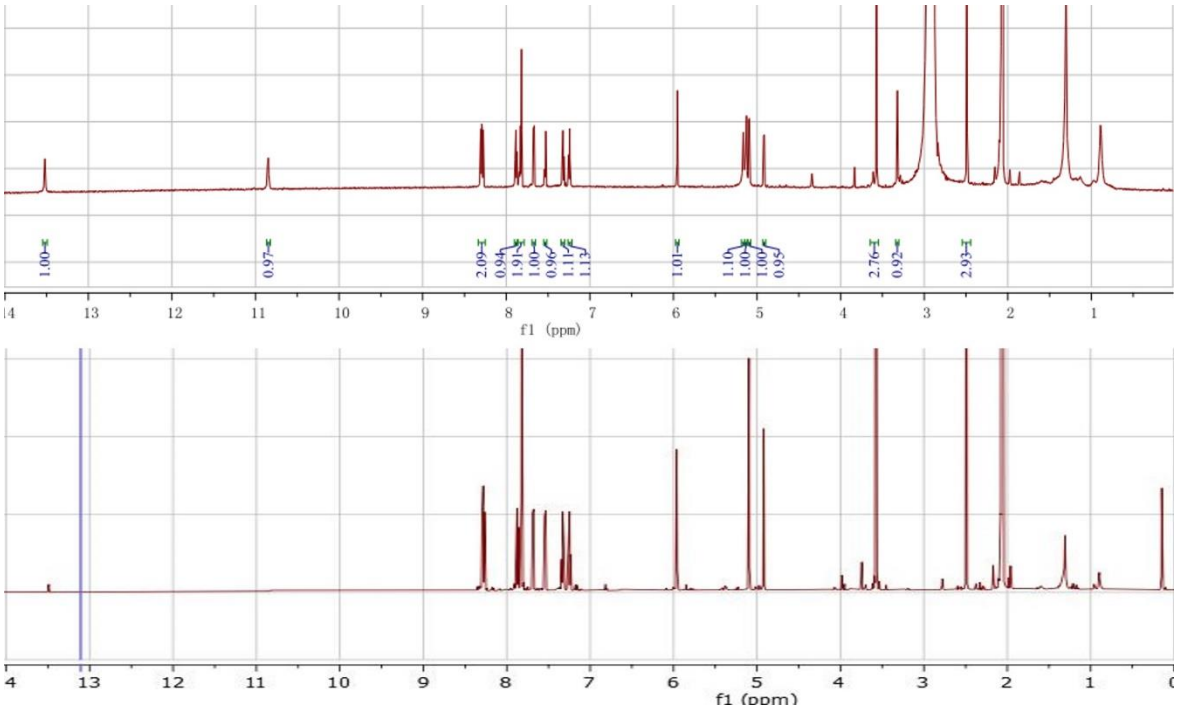


Figure 4.5: Top) ^{1}H NMR** spectrum of natural sealutomicin C in acetone-d_6 reported with Shen[26]; bottom) ^{1}H NMR spectrum of synthetic sealutomicin C in acetone-d_6 prepared by the author.

As previously discussed, the tabulated ^{13}C NMR data of ***Shen-14*** reported by Shen does not match the ^{13}C NMR spectrum of ***Shen-14***. Consequently, the ^{13}C NMR data for the sample of synthetic sealutomicin C in deuterated acetone was compared to the peak-picked resonances shown on the graphical ^{13}C NMR spectrum of compound ***Shen-14*** (**Table 4.3** and **Figure 4.6**) in the same solvent.

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With the exception of the phenolic **C**(12), the ^{13}C NMR resonances of synthetic sealutomicin C were equal to within 0.03 ppm of those reported by Shen for compound ***Shen-14***. We attribute the greater difference observed for the ^{13}C NMR chemical shift of **C**(12) to hydrogen bonding effects of the phenol unit in the deuterated acetone solvent.

The ^{13}C NMR spectrum of ***Shen-14*** reported by Shen shows two resonances at ~ 141 ppm and ~135 ppm which have erroneously not been peak-picked; we propose that these resonances correspond to those observed for **C**(14) and **C**(4) respectively. The ^{13}C NMR resonance of **C**(9) in the sample of synthetic sealutomicin C partially overlaps with the stronger resonance of **C**(7); we propose that this overlap is responsible for the **C**(9) resonance of compound ***Shen-14*** not being reported by Shen.

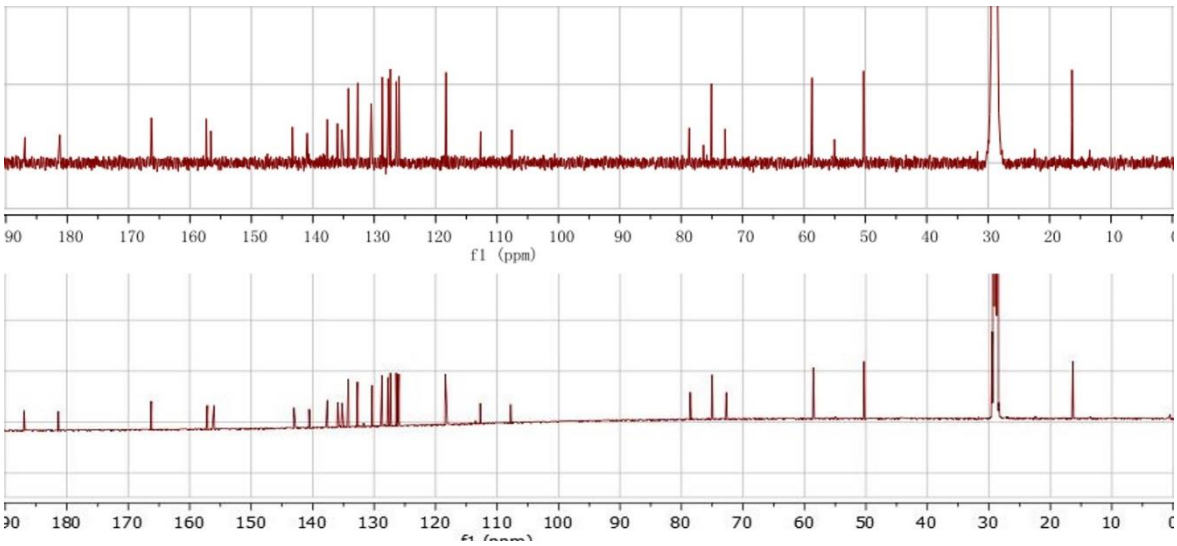
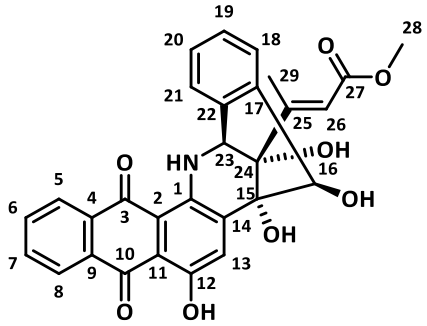


Figure 4.6: Top) ^{13}C NMR spectrum[††] of natural sealutomicin C in acetone-d_6 reported with Shen[26]; bottom) ^{13}C NMR spectrum of synthetic sealutomicin C in acetone-d_6 prepared by the author.

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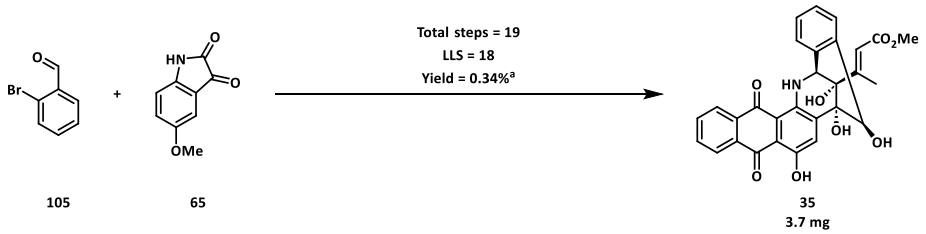
Position	δ_C[a] Natural[26]	δ_C[b] Synthetic	Δδ(Natural – Synthetic)
C(1)	143.3	143.0 (s)	0.3
C(2)	107.6	107.7 (s)	-0.1
C(3)	181.2	181.3 (s)	-0.1
C(4)	-	135.2 (s)	-
C(5)	126.4	126.4 (s)	0.0
C(6)	134.2	134.1 (s)	0.1
C(7)	132.7	132.6 (s)	0.1
C(8)	126.0	125.9 (s)	0.1
C(9)	-	132.7 (s)	-
C(10)	186.9	186.9 (s)	0.0
C(11)	112.7	112.7 (s)	0.0
C(12)	156.6	156.0 (s)	0.6
C(13)	130.5	130.3 (s)	0.2
C(14)	-	140.5 (s)	-
C(15)	78.7	78.5 (s)	0.2
C(16)	75.0	74.9 (s)	0.1
C(17)	136.0	135.9 (s)	0.1
C(18)	127.4	127.3 (s)	0.1
C(19)	128.7	128.7 (s)	0.0
C(20)	127.7	127.7 (s)	0.0
C(21)	127.3	127.3 (s)	0.0
C(22)	137.7	137.6 (s)	0.1
C(23)	58.7	58.5 (s)	0.2
C(24)	72.9	72.6 (s)	0.3
C(25)	157.4	157.1 (s)	0.3
C(26)	118.3	118.4 (s)	-0.1
C(27)	166.3	166.2 (s)	0.1
C(28)	50.3	50.2 (s)	0.1
C(29)	16.4	16.3 (s)	0.1

Table 4.3: Comparison of ^{13}C NMR data for natural sealutomicin C (reported by Shen) and synthetic sealutomicin C (prepared by the author). [a] 176 MHz, Acetone-d_6, peak-picked resonance chemical shifts from graphical NMR spectrum; [b] 150 MHz, Acetone-d_6, proton-decoupled.

The close agreement between the NMR data for our sample of synthetic sealutomicin C and the data reported for compound ***Shen-14*** by Shen enabled us to conclude that the two compounds are indeed the same structure, as proposed by Igarashi.

4.2.4 First Generation Route Analysis

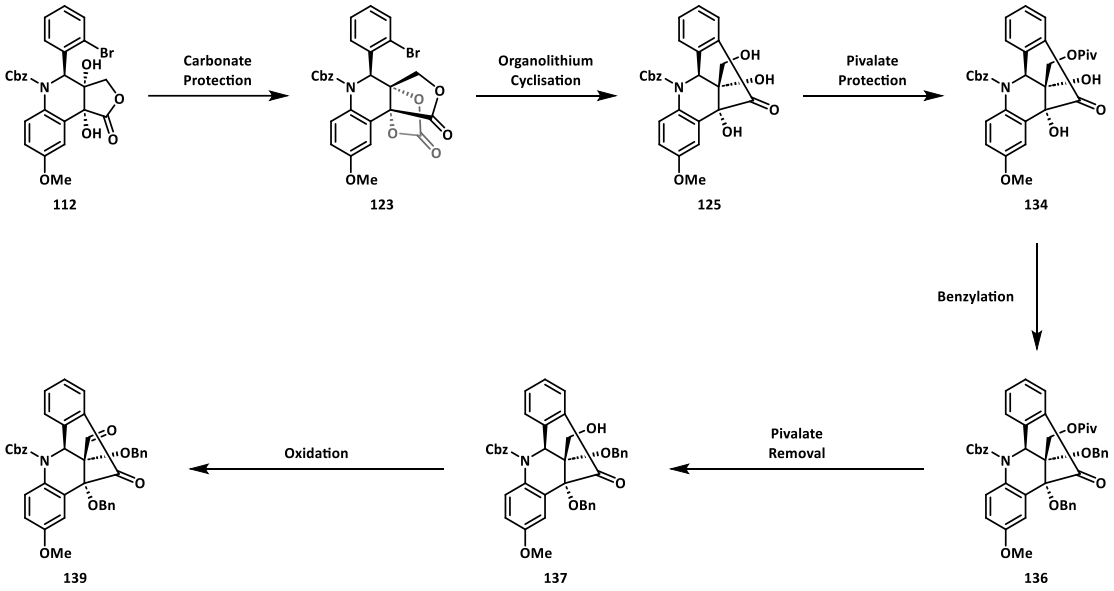
3.7 mg of the natural product sealutomicin C (**35**) had been prepared in 19 total steps from cheap, commercially available 2-bromobenzaldehyde and 5-methoxyisatin (**Scheme 4.9**). The longest linear sequence of the route was 18 steps and the overall yield from 2-bromobenzaldehyde (**105**) was 0.34%. Of the four adjacent chiral centres, only one required the use of stereoselectivity-controlling reagents to install, with the stereochemistry of other three controlled by the geometry of the substrate. Key to the success of the synthesis were the enantioselective organocatalysed dihydroquinoline formation, from which all other stereochemistry during the synthesis was derived, and the organolithium-mediation cyclisation, which enabled the construction of the natural product core.



Scheme 4.9: First-generation synthesis of sealutomicin C from commercially available starting materials.
[a] Yield based upon 2-bromobenzaldehyde (**105**).

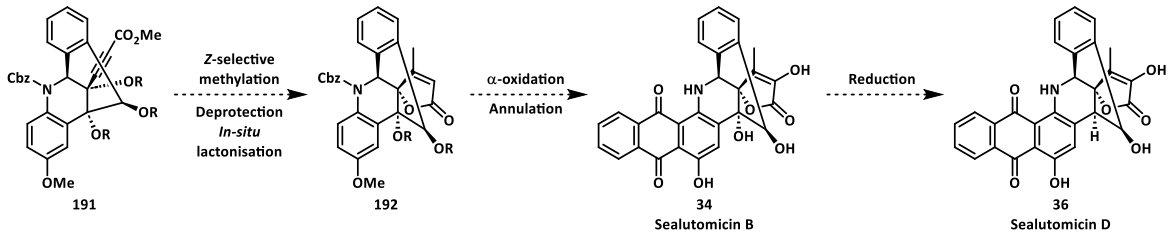
Despite the success of the synthesis, we identified several key issues which we felt merited further attention and improvement. The harsh conditions required for the boron trichloride-mediated debenzylation step resulted in considerable degradation of material and consequently gave a useable but suboptimal low yield. In addition, the need to remove the benzyl ether groups prior to installation of the anthraquinone moiety, and the difficulties encountered in attempting to reprotect the resultant alcohol units, meant it had been necessary to carry the three unprotected hydroxyl groups through both the oxidative demethylation and Hauser-Kraus annulation steps. Given the higher yields that had been obtained for these steps using substrates with protected hydroxyl units (See Chapter 4), we suspected that the presence of these unprotected alcohol groups was at least partly responsible for the low yields of the synthesis endgame.

The step count of the route had suffered because of inefficiencies in our protecting group strategy. Of the six synthetic steps involved in the conversion of diol **112** to aldehyde **139**, four involved only the protection or deprotection of hydroxyl groups (**Scheme 4.10**). In particular, the two tertiary alcohol units were protected twice in quick succession, first as the cyclic carbonate **123** then as the *bis*-benzyl ether **136**. Whilst we accepted that some use of protecting groups was necessary, we questioned whether the existing protecting group strategy could be improved upon.



Scheme 4.10: Six-step conversion of diol **112** to aldehyde **139**, requiring four protection or deprotection steps.

In addition to the issues discussed, we were doubtful of the applicability of the existing synthetic route to sealutomicins B and D. Ultimately, we hoped to be able to synthesise sealutomicins B, C and D *via* a common alkynyl ester intermediate (**191**, **Scheme 4.11**). *Z*-Selective β-methylation of the alkynyl ester followed by selective deprotection of the tertiary alcohol groups could enable lactonisation to occur to give the α,β-unsaturated lactone ring (**192**). α-Oxidation of the lactone and anthraquinone installation would give sealutomicin B, with subsequent tertiary hydroxyl reduction giving sealutomicin D. Such a strategy would hinge on the ability to selectively cleave the protecting groups of the tertiary alcohols whilst leaving the benzyl carbamate intact. We felt that this strategy would be unlikely to succeed with the existing benzyl ether protecting group approach.



Scheme 4.11: Proposed strategy to access sealutomicins B and D from common synthetic intermediate alkynyl ester **191**.

4.3 Chapter Summary

We had successfully developed a first-generation synthetic route to sealutomicin C (**35**). The chemistry developed in chapters 3 and 4 had been applied to the correct enantiomeric series to give **35**, with a method identified to remove the problematic benzyl ether protecting groups in order to access the natural product. Despite this success, we felt that alterations could be made to the route's protecting group strategy, which would improve both the efficiency of the synthesis of **35** and the route's applicability to the synthesis of sealutomicins B and D.

Chapter 5: Second-Generation Synthesis of Sealutomicin C

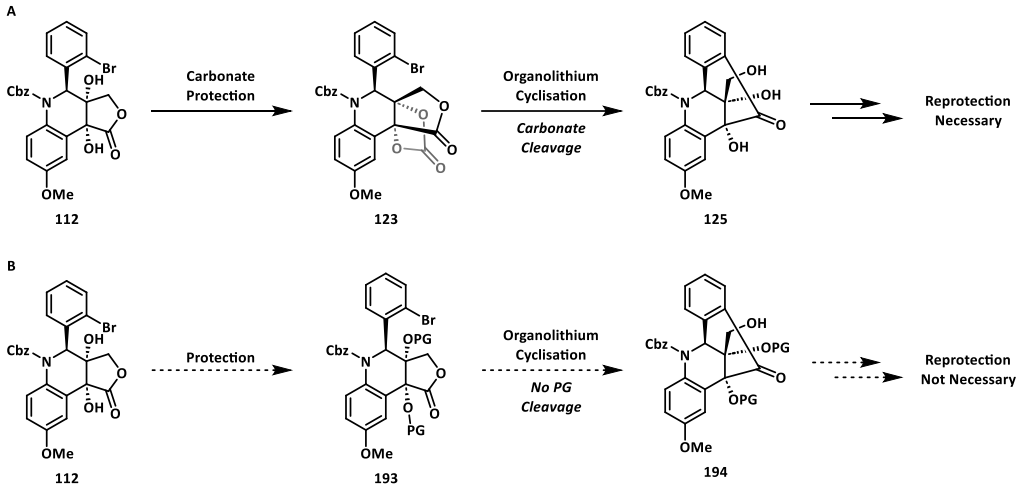
5.1 Chapter Introduction

Chapter 4 described our successful first-generation synthesis of sealutomicin C, building on the chemistry developed in **Chapter 2** and **Chapter 3**. Despite the success of the synthesis, we had identified flaws in our protecting group strategy, which centred around the use of benzyl ether protecting groups. These flaws negatively impacted both the efficiency of the synthetic route and its applicability to future syntheses of sealutomicins B and D. This chapter describes our work to develop an alternative protecting group strategy, culminating in a more efficient second-generation total synthesis of sealutomicin C.

5.2 Second-Generation Synthesis of Sealutomicin C

5.2.1 Alternative Protecting Group Strategy

In our first-generation synthesis, the two tertiary alcohol groups of diol **112** were protected as a cyclic carbonate prior to the organolithium-mediated cyclisation (**Scheme 5.1A**). Whilst this strategy had enabled the key cyclisation to take place, the carbonate had proved to be highly labile under alkaline conditions and so was deliberately cleaved during the workup of the cyclisation reaction, leaving the two tertiary alcohol groups needing to be reprotected. We postulated that an alternative protecting group could be employed which would survive the organolithium cyclisation, obviating the need for reprotection and enabling direct oxidation of the resultant primary alcohol **194** (**Scheme 5.1B**).



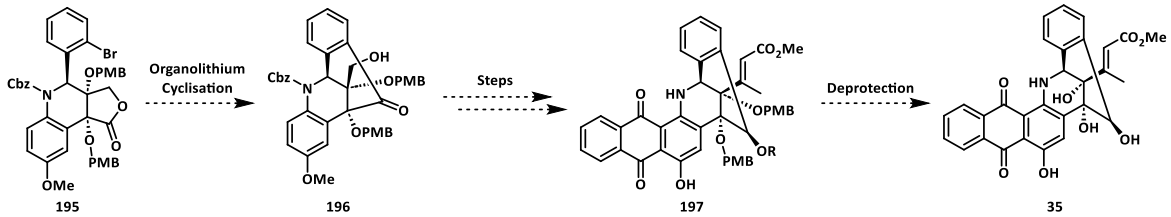
Scheme 5.1: A) Carbonate protection of diol **112** and subsequent need for reprotection after carbonate hydrolysis; B) Proposed alternative strategy with diol protecting group surviving organolithium cyclisation.

Our use of the carbonate protecting group during the first-generation synthesis had been motivated by our hypothesis that the change in the conformation of lactone **112** caused by the installation of a cyclic protecting group was crucial to the success of the organolithium-mediated cyclisation (See **Chapter 3**). Whilst the cyclisation of carbonate **123** had been successful, no efforts had been made to investigate whether the use of a cyclic protecting group was indeed necessary.

The *para*-methoxybenzyl (PMB) group has been used extensively in organic synthesis as a means of protecting alcohol, phenol, and amine units.[98,131] Like their benzyl analogues, PMB ethers are highly stable under basic conditions and do not undergo migration between functional groups. However, the more electron-rich aryl ring of PMB ethers often enables them to be cleaved by less harsh acidic conditions than their benzyl counterparts, and by mild oxidising agents such as cerium(IV) ammonium nitrate and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

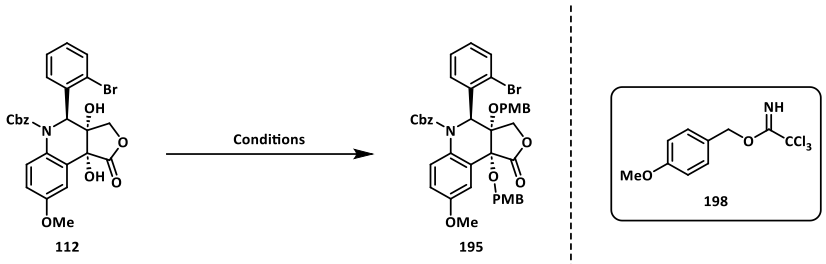
We envisaged a new protecting group strategy whereby *bis*-PMB ether **195** would undergo organolithium-mediated cyclisation with PMB ether retention to give ketone **196** (**Scheme 5.2**). The PMB ether groups could then be carried through subsequent steps of the synthesis without the need for reprotection of the two tertiary alcohol units. We postulated that the milder conditions required for PMB ether deprotection would enable their removal from anthraquinone **197** to give sealutomicin C, allowing the oxidative demethylation and annulation steps to be carried out with

the hydroxyl units still protected. Whilst the strategy hinged on the ability of *bis*-PMB ether **195** to undergo the key organolithium cyclisation, we anticipated that if it were successful, it could improve both the step count of the synthetic route and the yield of the synthesis endgame.



Scheme 5.2: Proposed new protecting group strategy employing PMB ethers.

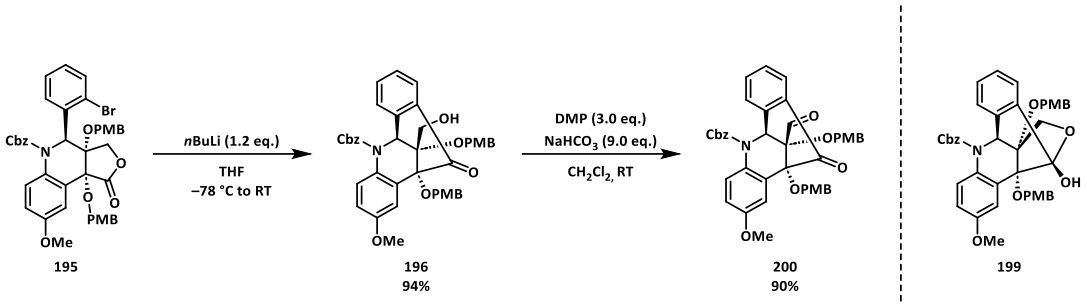
Attempts to convert diol **112** to *bis*-PMB ether **195** using trichloroacetimidate **198** with catalytic triflic acid in either diethyl ether or dichloromethane were unsuccessful, with no conversion of **112** observed (**Table 5.1, entries 1 + 2**).[122] Deprotonation of **112** using sodium hydride followed by addition of *para*-methoxybenzyl chloride (PMBCl) in DMF gave the desired product **195** in just 13% yield. TLC analysis of the crude reaction mixture showed a strong baseline spot, suggesting hydrolysis of the lactone moiety by adventitious water; however, the proposed carboxylic acid was not isolated. Happily, alkylation of **112** with *para*-methoxybenzyl bromide (PMBBr) after deprotonation with NaHMDS gave **195** in 58% on 0.04 mmol scale. As expected, the yield of the reaction improved on scale-up, allowing **195** to be prepared in 76% on 2-gram scale.



Entry	Scale	Conditions	Yield 195	Result
1	0.04 mmol	198 (4.0 eq.) TfOH (0.01 eq.) Et_2O, RT	0%	No reaction
2	0.04 mmol	198 (4.0 eq.) TfOH (0.01 eq.) CH_2Cl_2, RT	0%	No reaction
3	0.04 mmol	NaH (3.0 eq.) PMBCl (5.0 eq.) DMF, RT	13%	Suspected lactone hydrolysis
4	0.04 mmol	NaHMDS (3.0 eq.) PMBBr (5.0 eq.) DMF, RT	58%	-
5	1.85 mmol	NaHMDS (3.0 eq.) PMBBr (5.0 eq.) DMF, RT	76%	-

Table 5.1: Conversion of diol **112** to *bis*-PMB ether **195**.

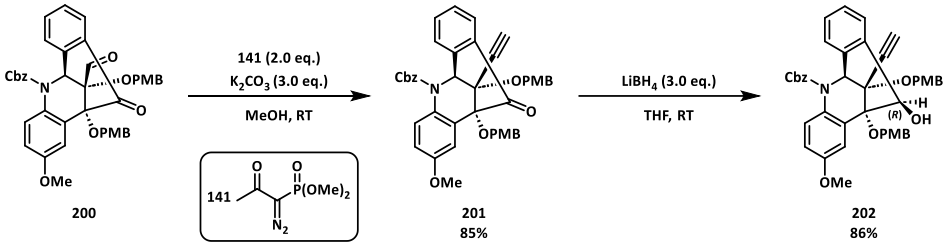
To our delight, treatment of a solution of bromide **195** in THF at −78 °C with 1.2 equivalents of *n*-butyllithium before warming to room temperature resulted in the desired cyclisation, giving ketone **196** in almost quantitative yield (**Scheme 5.3**). Unlike the carbonate protecting group, the PMB ethers showed no sign of either degradation or migration under the reaction conditions. As with its benzyl analogue, ketone **196** exists as a 2 : 1 inseparable mixture of the primary alcohol and its corresponding lactol **199**. The presence of rotamers resulted in the NMR resonances of lactol **199** appearing as broad peaks in the ^{1}H and ^{13}C NMR spectra of the mixture, preventing the assignment of both compounds. Upon heating to 105 °C, the resonances in both the ^{1}H and ^{13}C NMR spectra coalesced, whilst the ratio of primary alcohol to lactol changed to 5 : 1. Only NMR data for primary alcohol **196** taken from the NMR spectra of the mixture at 105 °C is given in the experimental section of this thesis. Oxidation of the mixture of **196** and **199** using Dess-Martin periodinane in dichloromethane gave aldehyde **200** 90% yield, with no oxidative cleavage of the PMB ether groups observed.



Scheme 5.3: Organolithium-mediated cyclisation of aryl bromide **195** to ketone **196** and subsequent oxidation to aldehyde **200**.

5.2.2 Second-Generation Synthesis Completion

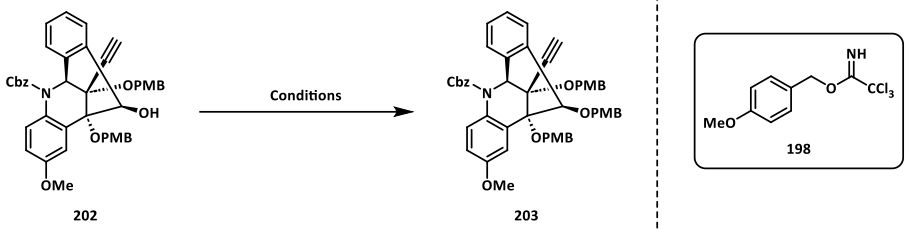
Using the Ohira-Bestmann conditions previously employed, conversion of aldehyde **200** to alkyne **201** proceeded somewhat slower than for its benzyl analogue, with the reaction taking 20 hours to reach completion (**Scheme 5.4**). We reasoned that this sluggish reactivity may be due to the more electron-rich PMB ethers reducing the electrophilicity of the aldehyde moiety. Despite this, alkyne **201** was obtained in good yield, with no unwanted side-reactivity of the ketone group to the methyl enol ether. Reduction of the ketone was again effected using lithium borohydride, giving alcohol **202** as a single diastereomer in 86% yield. The configuration of the newly formed alcohol group was assigned as (*R*) by analogy to the benzyl ether series.



Scheme 5.4: Two-step conversion of aldehyde **200** to benzylic alcohol **201** *via* alkyne **202**.

In light of the PMB ether protecting groups already employed in this second-generation synthesis, we elected to also protect the newly formed benzylic alcohol of **202** as its PMB ether. We hoped that this would enable all three alcohol units to be deprotected simultaneously once the anthraquinone moiety had been installed. Treatment of **202** with trichloroacetimidate **198** and catalytic triflic acid returned only starting material, with no sign of the desired ether **203** (**Table 5.2,**

entry 1).[122] Deprotonation of **202** with KHMDS followed by addition of *para*-methoxybenzyl bromide gave ether **203** in 44% yield as part of a complex reaction mixture (**Entry 2**). Happily, using sodium hydride in place of KHMDS resulted in a much cleaner reaction profile, giving **203** in 87% yield (**Entry 3**).

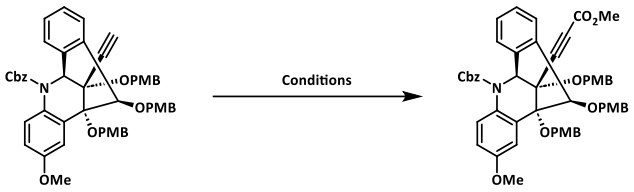


202 203 198

Entry	Conditions	Yield 203
1	198 (1.5 eq.) TfOH (0.05 eq.) Et_2O, RT	0%
2	KHMDS (1.2 eq.) PMBBr (2.0 eq.) DMF, 0 °C to RT	44%
3	NaH (1.2 eq.) PMBBr (2.0 eq.) DMF, 0 °C to RT	87%

Table 5.2: Conversion of benzylic alcohol **202** to PMB ether **203**.

With the secondary alcohol unit successfully protected as its PMB ether, attention turned to the conversion of the terminal alkyne unit of **203** to its alkynyl ester **204** (**Table 5.3**). Deprotonation of **203** with NaHMDS followed by addition of methyl chloroformate, under the conditions employed in the first-generation route, resulted in full consumption of starting material; however, ester **204** was isolated in just 51% yield. Switching the carboxylating reagent to methyl cyanoformate resulted in a drop in the yield of **204** (**Entry 2**).[132] We reasoned that these low yields could be due to the sluggish reactivity of the lithium-coordinated acetylide anion in the reaction mixture. Addition of hexamethylphosphoramide to the reaction mixture, in order to break up organolithium aggregates, and quenching the reaction at −78 °C with pre-cooled methanol resulted in a far cleaner reaction profile and a significant improvement in the yield of ester **204** (**Entry 3**).[133] A further increase in the reaction yield was observed upon scale-up, allowing ester **204** to be prepared in 80% yield on 0.55 mmol scale (**Entry 4**).

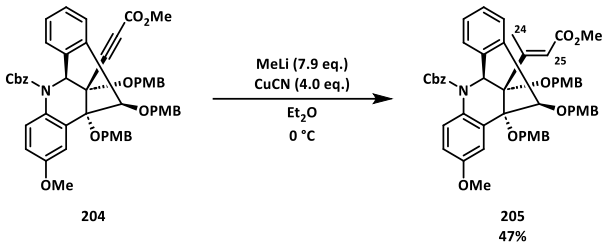


203 204

Entry	Scale	Conditions	Yield 204
1	0.03 mmol	NaHMDS (1.2 eq.) Methyl Chloroformate (2.0 eq.) THF, −78 °C to RT[a]	51%
2	0.03 mmol	LiHMDS (1.5 eq.) Methyl Cyanoformate (3.0 eq.) THF, −78 °C to RT[a]	33%
3	0.03 mmol	LiHMDS (1.2 eq.) Methyl Chloroformate (2.0 eq.) HMPA (5.0 eq.) THF, −78 °C[b]	66%
4	0.55 mmol	LiHMDS (1.2 eq.) Methyl Chloroformate (2.0 eq.) HMPA (5.0 eq.) THF, −78 °C[b]	80%

Table 5.3: Conversion of alkyne **203** to alkynyl ester **204**. [a] Reaction quenched with saturated aqueous ammonium chloride at room temperature; [b] Reaction quenched at −78°C with pre-cooled methanol.

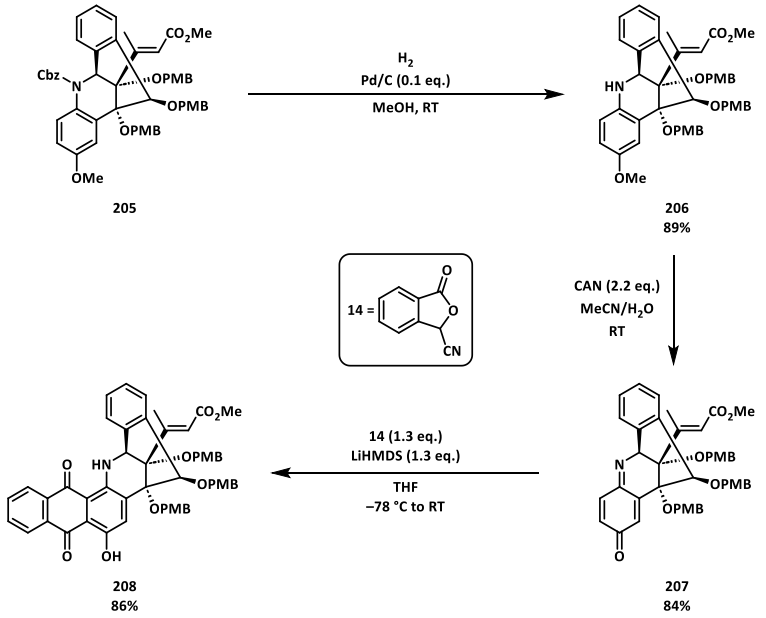
Conversion of the alkynyl ester unit of **204** to the (*E*)-β-methyl enoate side chain of sealutomicin C was carried out using the organocuprate conjugate addition conditions developed in Chapter 4. The desired α,β-unsaturated ester **205** was isolated in moderate yield as a single diastereomer on 100 mg scale (**Scheme 5.5**). The ^{1}H NMR spectrum of **205** showed strong similarities to the spectrum of (*E*)-β-methyl enoate **151** previously prepared. In particular, the chemical shifts and splitting patterns of the C(24)**H$_3$** methyl protons and the C(25)**H** vinyl proton of **205** were almost identical to those observed for **151**. As a result, the stereochemistry of the newly formed alkene unit of **205** was provisionally assigned as the desired (*E*) isomer. Given the lack of success of previous efforts to optimise this reaction during the first-generation synthesis, no further attempts were made to improve the yield of **205**.



204 205 47%

Scheme 5.5: Conversion of alkynyl ester **204** to (*E*)-β-methyl enoate **205**.

Having successfully completed the synthesis of the natural product side chain, we now hoped to install the anthraquinone unit *via* the oxidative demethylation/annulation sequence without inadvertently removing the PMB ether protecting groups. Such a strategy would first require the selective cleavage of the benzyl carbamate from **205**. During the development of the first-generation synthesis discussed in Chapter 4, our unsuccessful efforts to remove the benzyl ether protecting groups from α,β-unsaturated ester ***ent*-180** had demonstrated that the alkene moiety of ***ent*-180** was highly tolerant to hydrogenation conditions, presumably due to its sterically hindered environment. We hoped that hydrogenation of **205** would result in carbamate removal without reducing the alkenyl ester moiety. Happily, treatment of **205** with hydrogen gas and catalytic palladium on carbon in methanol resulted only in carbamate cleavage, giving aniline **206** in 89% yield (**Scheme 5.6**).[134]

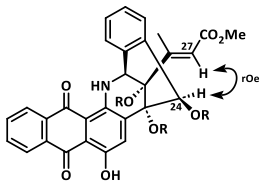


205 206 89% 207 84% 208 86%

Scheme 5.6: Three-step conversion of carbamate **205** to anthraquinone **208**.

We were aware that the proposed oxidative demethylation of aniline **206** to its iminoquinone **207** using cerium(IV) ammonium nitrate posed a risk of concomitant oxidative cleavage of the PMB ether protecting groups. However, we anticipated that the more electron rich *para*-methoxyaniline ring would undergo oxidation more readily than the PMB ether units. Pleasingly, treatment of **206** with a slight excess of cerium(IV) ammonium nitrate gave iminoquinone **207** in good yield, with no sign of PMB ether deprotection (**Scheme 5.6**). Addition of **207** to a pre-mixed solution of cyanophthalide **14** and LiHMDS in THF at −78 °C and subsequent warming to room temperature resulted in the desired Hauser-Kraus annulation, giving anthraquinone **208** in 86% yield. It should be noted that these two key steps gave considerably higher yields than their analogous steps during the first-generation synthesis, presumably due to the protection of the three alcohol units employed here.

^{1}H/^{1}H ROESY analysis of **208** showed a clear rOe correlation between the vinyl C(27)**H** proton and the benzylic C(24)**H** proton (**Figure 5.1**). As a result, the geometry of the β-methyl enoate moiety was confirmed as the desired (*E*) alkene.

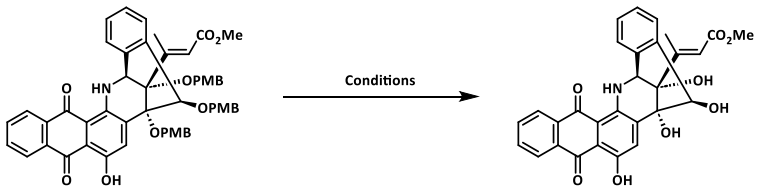


208
R = PMB

Figure 5.1: Observed rOe correlation of **208** confirming (*E*) alkene geometry.

During our development of the first-generation synthesis discussed in Chapter 4, attempts to remove the benzyl ether protecting groups from anthraquinone ***ent*-180** using Lewis acidic conditions had resulted in degradation of the starting material. With this in mind, we elected to seek a means of removing the PMB protecting groups of **208** under oxidative conditions, in order to complete this second-generation synthesis of sealutomicin C.

Addition of cerium(IV) ammonium nitrate to a solution of **208** resulted in rapid decolourisation of the dark purple reaction mixture (**Table 5.4, entry 1**).[135] TLC analysis of the reaction revealed a complex mixture of products, with no sign of the desired product sealutomicin C (**35**). We attributed this colour change to oxidation of the *para*-aminophenol portion of the anthraquinone unit, with degradation of the resultant highly reactive iminoquinone giving a wide range of products. It was not possible to tell from ^{1}H NMR analysis of the crude reaction mixture whether removal of the PMB protecting groups had occurred. Fortunately, treatment of **208** with DDQ resulted only in the desired PMB ether cleavage, leaving the anthraquinone unit unscathed.[136] A large excess of the oxidising agent was required in order to drive the reaction to completion; however, no unwanted side reactivity was observed, giving the natural product sealutomicin C in 70% yield. ^{1}H NMR, ^{13}C NMR and HRMS data for the new synthetic sample of **35** were all in accordance with the synthetic sample of **35** previously prepared.



208 35

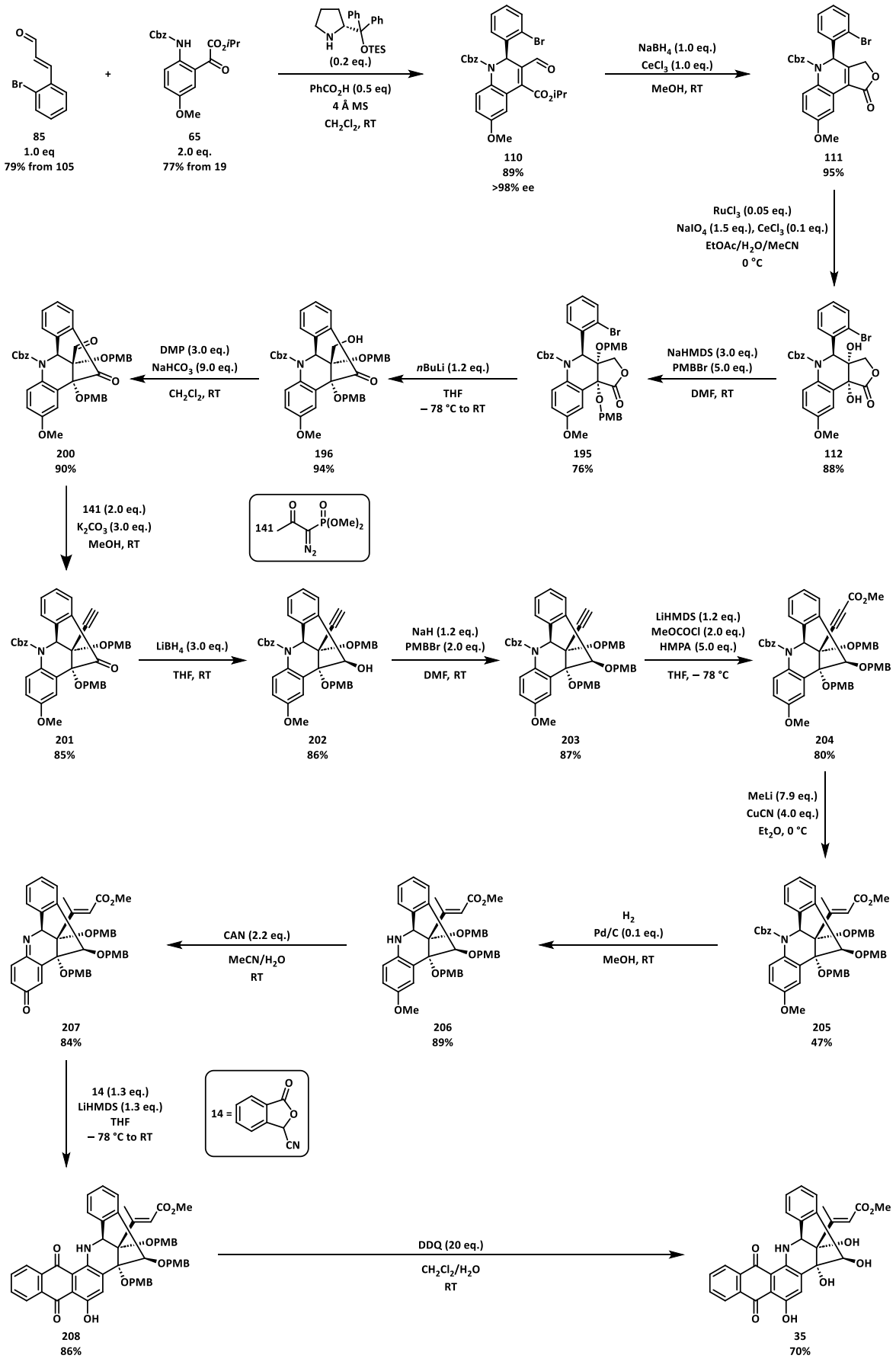
Entry	Conditions	Yield 35	Result
1	**CAN (6.0 eq.) MeCN/H_2O RT**	**0%**	**Anthraquinone degradation**
2	**DDQ (20 eq.) CH_2Cl_2 RT**	**70%**	**Clean deprotection**

Table 5.4: Deprotection of *tris*-PMB ether **208** to sealutomicin C (**35**).

5.2.3 Second Generation Route Analysis

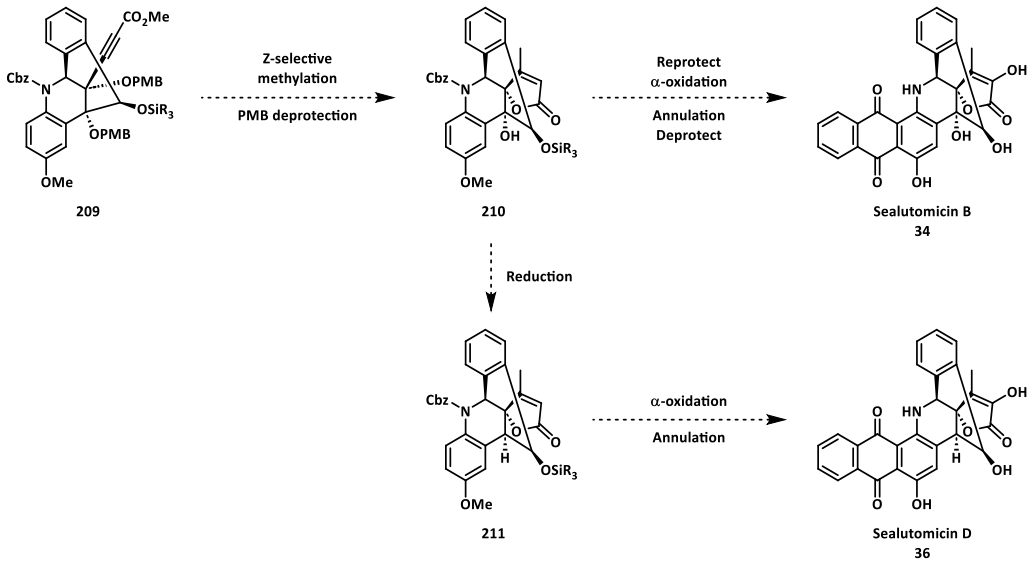
8.3 mg of sealutomicin C (**35**) had been prepared by this second-generation synthetic route in 17 total steps from commercially available 2-bromobenzaldehyde and 5-methoxyisatin (**Scheme 5.7**). The longest linear sequence of the route was 16 steps and the overall yield from 2-bromobenzaldehyde was 3.35%. Whilst much of the chemistry used in the first-generation synthesis had been reapplied to this second synthesis, a new protecting group strategy centred around the use of PMB ethers had been employed. This new strategy had enabled the conversion of diol **112** to aldehyde **200** in just three steps, compared to the six steps required to prepare benzyl analogue **139** during the first-generation synthesis. In contrast to our earlier beliefs, the use of a cyclic protecting group for diol **112** was not necessary to facilitate the key organolithium-mediated cyclisation; indeed, the cyclisation of *bis*-PMB ether **195** was considerably higher yielding than that of its carbonate counterpart **123**.

The ability to remove the PMB protecting groups after the installation of the anthraquinone unit had enabled the oxidative demethylation and Hauser-Kraus annulation steps to be carried out in the absence of any unprotected hydroxyl units, greatly increasing the yield of both steps. In addition, minor modifications to certain reactions such as the carboxylation of alkyne **203** had resulted in higher yields than the analogous steps in the first-generation route. Overall, the development of the second-generation route to sealutomicin C had reduced both the total step count and the longest linear sequence of the natural product's synthesis by two steps and had increased the overall yield of the natural product almost tenfold.



Scheme 5.7: Second-generation synthesis of sealutomicin C (**35**).

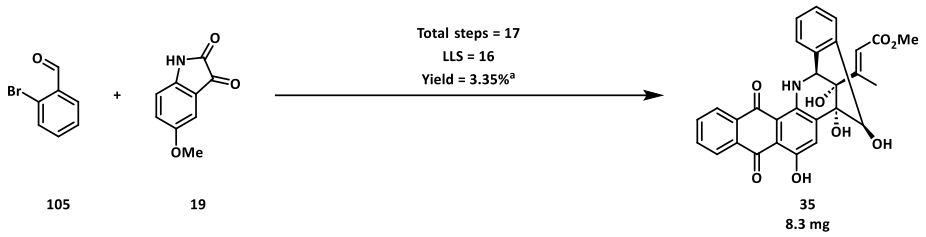
In addition to enabling a far more efficient synthesis of sealutomicin C, the second-generation route should also be far more applicable to the synthesis of sealutomicins B and D, owing to the greater ease with which the PMB protecting groups can be removed. Following reduction of ketone **201**, protection of the resultant secondary benzylic alcohol as a silyl ether should be easily achieved, giving access to alkynyl ester **209** (**Scheme 5.8**). We propose that *Z*-selective methylation of **209** and subsequent oxidative deprotection of the PMB ether units should trigger intramolecular lactonisation to give butenolide **210**, with the secondary alcohol unit still protected. The remaining tertiary alcohol could then be reprotected, with subsequent α-oxidation, annulation and a final global deprotection step giving sealutomicin B. Alternatively, reduction of the alcohol unit of **210** to butenolide **211**, followed by the same α-oxidation, annulation and deprotection sequence would give access to sealutomicin D.



Scheme 5.8: Proposed application of second-generation synthetic route to the synthesis of sealutomicins B and D.

5.3 Chapter Summary

We had successfully developed a second-generation synthetic route to the natural product sealutomicin C, building on our previous work developing a first-generation synthesis described in **Chapters 2 – 4** (**Scheme 5.9**). The second-generation route, featuring a more efficient protecting group strategy, had enabled both the step count and longest linear sequence of the synthesis to be reduced by two steps, and had increased the overall yield of the natural product synthesis by a factor of ten. In addition, we felt that the second synthetic route was more suitable than the first to be used as a means of synthesising sealutomicins B and D, with benzylic alcohol **202** likely to serve as a common synthetic intermediate.

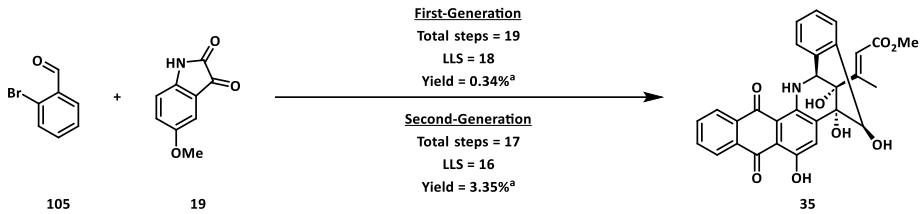


Scheme 5.9: Second-generation synthesis of sealutomicin C from commercially available starting materials. [a] Yield based upon 2-bromobenzaldehyde **105**.

Chapter 6: Conclusions and Future Work

6.1 Conclusion

In summary, we have developed two synthetic routes to the natural product sealutomicin C (**35**). The first-generation route gives **35** as a single enantiomer in 0.34% overall yield over 19 steps from commercially available 2-bromobenzaldehyde and 5-methoxyisatin (**Scheme 6.1**). The improved, second-generation route gives **35** as a single enantiomer in 3.35% overall yield over 17 steps from the same starting materials. To our knowledge, these routes represent the first reported syntheses of sealutomicin C. In addition, we have confirmed that sealutomicin C is the same compound as the metabolite ***Shen-14*** reported by Shen *et al* during their gene knockout studies of *Streptomyces* sp. CB03234.

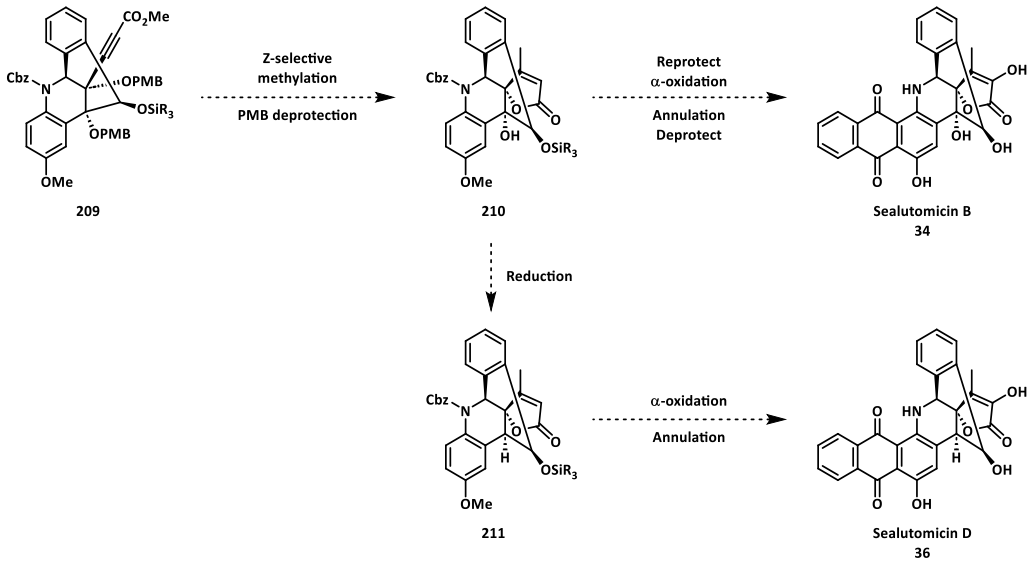


Scheme 6.1: First- and second-generation syntheses of sealutomicin C. [a] Yield based on **105**.

Both synthetic routes to **35** employ a novel, enantioselective, organocatalytic dihydroquinoline synthesis in order to construct the core of the natural product. Meanwhile, an organolithium-mediated cyclisation is used to forge the key bridging bond between the northern aryl ring and the adjacent secondary alcohol unit. The anthraquinone unit is installed using a Hauser-Kraus annulation, whilst the *E*-β-methyl enoate side chain is prepared *via* the stereoselective methylation of an alkynyl ester. The use of PMB ether protecting groups in the second-generation route improves both the overall yield and the step count of this synthesis, relative to the first-generation route, which employs benzyl ether protecting groups instead. No work has been conducted towards the synthesis of either sealutomicins B or D; however, these two natural products remain synthetic targets of interest to the Burton group (*vide infra*).

6.2 Future Work

As discussed in **Chapter 5**, we propose that the second-generation synthetic route to sealutomicin C may also be used to prepare the related natural products sealutomicins B and D (**34** and **36**). We anticipate that alkynyl ester **209** may serve as a common synthetic intermediate to all three natural products, with only a single minor modification to the existing route required to install the silyl ether-protected secondary benzylic alcohol. We anticipate that at low temperatures, the conjugate addition of methyl cuprate to the alkynyl ester unit should give a *Z*-β-methyl enoate motif. Subsequent PMB-ether deprotection should trigger *in situ* lactonisation to butenolide **210**. Oxidation at the α-position of this butenolide, followed by installation of the anthraquinone unit, would give sealutomicin B. Meanwhile, reduction of the tertiary alcohol unit of **210**, before repeating the same α-oxidation and anthraquinone-installation steps, would give sealutomicin D. It remains to be seen whether this synthetic route may also be applied to the total synthesis of other cycloaromatised anthraquinone-fused natural products, such as unciaphenol and yangpumicins B – E.



Scheme 6.2: Proposed future work to synthesise sealutomicins B and D (**34** and **36**) from common synthetic intermediate **209**.

Experimental

General Experimental

Solvents and reagents

All reactions were performed using flame-dried reaction vessels under an atmosphere of argon unless stated otherwise. Anhydrous diethyl ether, acetonitrile, triethylamine and toluene were obtained from solvent dispenser units having been passed through an activated alumina column under argon. Tetrahydrofuran, *N*,*N*-dimethylformamide, dichloromethane, hexamethylphosphoramide and pyridine were dried over 4 Å molecular sieves under argon. Molecular sieves used in dihydroquinoline synthesis reactions were flame dried *in vacuo* immediately before use. Methyl chloroformate was dried using a plug of solid potassium carbonate immediately before use. All other chemical reagents used were commercially available from Alfa Aesar, Fluorochem and Sigma-Aldrich and used as supplied.

The samples of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (***ent*-89**) and (*R*)-diphenyl(pyrrolidin-2-yl)methanol (**89**) used in this work were synthesised by Dr Sean Guggiari during his DPhil studies.

Chromatography

Thin layer chromatography (TLC) was carried out using Merck aluminium-backed TLC Silica Gel 60 F_{254} pre-coated plates (particle size 0.2 mm). Plates were visualised by the quenching of fluorescence under ultraviolet light (λ_{max} = 254 nm) and by staining and heating with potassium permanganate or vanillin. Flash column chromatography was performed using Merck Geduran® 60 silica gel (particle size 40–63 µm) with the solvent system given. All solvents used for chromatography purification were HPLC grade or equivalent and supplied by Sigma Aldrich.

Infrared spectroscopy

Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer as neat samples on the Pike Miracle Attenuated Total Reflectance (ATR) diamond module. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

NMR spectroscopy

Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) spectra were recorded on Bruker AVIII HD 400 nanobay (400/101/377 MHz) and Bruker AVII 500 (500/126/471 MHz) spectrometers in deuterated solvents. Variable temperature proton (^{1}H) and carbon (^{13}C) spectra were recorded on a Bruker AVIII HD 500 with BBF/H Probe spectrometer in deuterated solvent. ^{13}C spectra were recorded with broadband decoupling. Chemical shifts (δ_H, δ_C) are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR and 0.1 ppm for ^{13}C NMR. ^{1}H and ^{13}C NMR spectra were referenced relative to the solvent residual peak ($CDCl_3$, δ 7.26 and 77.16 ppm respectively; DMSO, δ 2.50 and 39.52 ppm respectively; acetone, 2.05 and 29.84 ppm respectively). Peak assignments were made on the basis of chemical shifts, integrations, coupling constants, and comparison to known compounds, using COSY, HSQC, and HMBC experiments where appropriate. Multiplets are described as singlet (s), doublet (d), triplet (t), quartet (q), heptet (hept), multiplet (m), broad (br), or combinations thereof. Coupling constants (*J*) are reported to the nearest 0.5 Hz. Where relevant, **H**H and H**H** refer to diastereotopic atoms.

Optical Rotation

Specific optical rotations were measured on a Perkin Elmer 241 Polarimeter in a cell of path length (l) 1 dm at the sodium D line (589 nm) in $CHCl_3$ at 25 °C and are calculated according to the equation below:

$$[\alpha]_D^{25} = \frac{\alpha}{l \times c}$$

where α is the observed optical rotation, l is the path length in dm and c is the concentration in g/mL. All optical rotation experiments were performed using solutions of between 5 x 10^{-3} g/mL and 10 x 10^{-3} g/mL.

Mass spectrometry

High resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory mass-spec facilities using a Bruker MicroTOF spectrometer. The mass reported is that containing the most abundant isotopes, with each value to 4 decimal places and within 5 ppm of the calculated mass. Mass to charge ratios (*m/z*) are reported in Daltons.

Melting Points

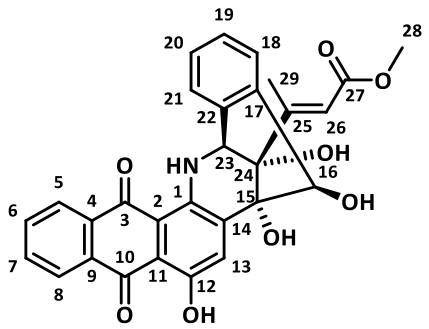
Melting points were determined using a Griffin heated metal block apparatus and are uncorrected. Solids were crystallised from chromatography solvent.

Reporting of compounds

Names written in italics denote compounds previously reported in the literature. Compounds are reported in order their numbering within this thesis. Systematic names were generated by the computer programme ChemDraw according to the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC). However, the numbering on the structures may not correspond to the systematic name. The NMR assignments follow the numbering system shown on the structures for straightforward comparison of data.

Preparations for Compounds and Characterisation Data

Methyl (*E*)-3-((8*S*,9*R*,14*S*,17*S*)-6,8,9,17-tetrahydroxy-5,16-dioxo-5,8,9,14,15,16-hexahydro-8,14-methanoanthra[1,2-b]benzo[*f*]azocin-17-yl)but-2-enoate – Sealutomicin C (35)



Method A: *Prepared according to the procedure of Nicolaou.*[127]

To a solution of 3-cyanophthalide (**14**, 3.6 mg, 0.023 mmol, 1.4 eq.) in tetrahydrofuran (0.4 mL) at –78 °C was added dropwise lithium bis(trimethylsilyl)amide (0.1 M in tetrahydrofuran, 0.23 mL, 0.023 mmol, 1.4 eq.). The resultant bright yellow solution was stirred at –78 °C for 15 min. A solution of methyl (*E*)-3-((6*S*,11*R*,12*S*,13*S*)-11,12,13-trihydroxy-2-oxo-2,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (**190**, 6.2 mg, 0.016 mmol, 1.0 eq.) in tetrahydrofuran (0.4 mL) was added dropwise. The cool bath was removed and the reaction mixture was allowed to warm to RT, during which time the bright yellow solution turned first dark green then dark purple. The reaction was stirred at RT for 15 min then quenched by dropwise addition of sat. aq. ammonium chloride solution (3 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (40% ethyl acetate in pentane) to give the title compound as dark purple oil (3.7 mg, 0.007 mmol, 44%).

Method B: *Prepared according to the procedure of Carreira.*[136]

To a solution of methyl (*E*)-3-((8*S*,9*R*,14*S*,17*S*)-6-hydroxy-8,9,17-tris((4-methoxybenzyl)oxy)-5,16-dioxo-5,8,9,14,15,16-hexahydro-8,14-methanoanthra[1,2-b]benzo[*f*]azocin-17-yl)but-2-enoate (**208**, 20.0 mg, 0.023 mmol, 1.0 eq.) in dichloromethane (2.5 mL) and water (0.25 mL) at RT was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (104.0 mg, 0.46 mmol, 20.0 eq.). The reaction mixture was stirred vigorously at RT for 16 h then cooled to 0 °C and quenched by dropwise addition of sat. aq. sodium bicarbonate (4 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium

sulfate, concentrated *in vacuo* and purified by flash column chromatography (30% to 50% ethyl acetate in pentane) to give the title compound as a dark purple solid (8.3 mg, 0.016 mmol, 70%).

R_f: 0.5 (50% ethyl acetate in petroleum ether).

m.p.: 152.3 – 155 °C.

ν_{max}/cm^{-1} (thin film): 3445 (br, m), 1716 (m), 1617 (m), 1586 (s), 1267 (s), 1243 (s), 1216 (m), 730 (m).

δ_H(600 MHz, DMSO): 13.58 (1H, s, C(12)O**H**), 10.83 (1H, d, *J* = 5.5 Hz, N**H**), 8.23 (1H, dd, *J* = 7.5, 1.0 Hz, C(8)**H**), 8.22 (1H, dd, *J* = 7.5, 1.0 Hz, C(5)**H**), 7.90 (1H, td, *J* = 7.5, 1.0 Hz, C(7)**H**), 7.83 (1H, td, *J* = 7.5, 1.0 Hz, C(6)**H**), 7.63 (1H, s, C(13)**H**), 7.63 (1H, d, *J* = 7.5 Hz, C(21)**H**), 7.34 (1H, d, *J* = 7.5 Hz, C(18)**H**), 7.26 (1H, t, *J* = 7.5 Hz, C(20)**H**), 7.19 (1H, t, *J* = 7.5 Hz, C(19)**H**), 6.01 (1H, d, *J* = 6.0 Hz, C(16)O**H**), 5.95 (1H, s, C(15)O**H**), 5.94 (1H, s, C(24)O**H**), 5.79 (1H, q, *J* = 1.0 Hz, C(26)**H**), 4.95 (1H, d, *J* = 5.5 Hz, C(23)**H**), 4.58 (1H, d, *J* = 6.0 Hz, C(16)**H**), 3.52 (3H, s, C(28)$\mathbf{H_3}$), 2.34 (3H, d, *J* = 1.0 Hz, C(29)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO): 186.1 (**C**(3)), 180.1 (**C**(10)), 166.1 (**C**(27)), 158.1 (**C**(25)), 155.9 (**C**(12)), 143.4 (**C**(1)), 141.7 (**C**(14)), 137.5 (**C**(22)), 135.9 (**C**(17)), 134.8 (**C**(9)), 134.5 (**C**(7)), 132.8 (**C**(6)), 132.0 (**C**(4)), 130.4 (**C**(13)), 128.4 (**C**(20)), 127.4 (**C**(19)), 127.3 (**C**(21)), 127.2 (**C**(18)), 126.2 (**C**(8)), 125.9 (**C**(5)), 117.4 (**C**(26)), 111.9 (**C**(11)), 106.1 (**C**(2)), 77.9 (**C**(15)), 74.2 (**C**(16)), 72.4 (**C**(24)), 57.7 (**C**(23)), 50.9 (**C**(28)), 16.9 (**C**(29)).

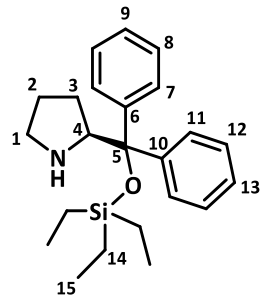
δ_H(600 MHz, Acetone): 8.26 (1H, dd, *J* = 8.0, 1.0 Hz, C(5)**H**), 8.24 (1H, dd, *J* = 8.0, 1.0 Hz, C(8)**H**), 7.85 (1H, td, *J* = 8.0, 1.0 Hz, C(6)**H**), 7.80 (1H, td, *J* = 8.0, 1.0 Hz, C(7)**H**), 7.79 (1H, s, C(13)**H**), 7.66 (1H, dd, *J* = 7.5, 1.5 Hz, C(18)**H**), 7.51 (1H, dt, *J* = 7.5, 1.5 Hz, C(21)**H**), 7.30 (1H, tt, *J* = 7.5, 1.5 Hz, C(19)**H**), 7.22 (1H, td, *J* = 7.5, 1.5 Hz, C(20)**H**), 5.93 (1H, q, *J* = 1.0 Hz, C(26)**H**), 5.07 (1H, s, C(23)**H**), 4.89 (1H, s, C(16)**H**), 3.55 (3H, s, C(28)$\mathbf{H_3}$), 2.46 (3H, d, *J* = 1.0 Hz, C(29)$\mathbf{H_3}$)

δ_C(151 MHz, Acetone): 186.9 (**C**(10)), 181.3 (**C**(3)), 166.2 (**C**(27)), 157.1 (**C**(25)), 156.0 (**C**(12)), 143.0 (**C**(1)), 140.5 (**C**(14)), 137.6 (**C**(22)), 135.9 (**C**(17)), 135.2 (**C**(4)), 134.1 (**C**(6)), 132.7 (**C**(9)), 132.6 (**C**(7)), 130.3 (**C**(13)), 128.7 (**C**(19)), 127.7 (**C**(20)), 127.3 (**C**(18)), 127.3 (**C**(21)), 126.4 (**C**(5)), 125.9 (**C**(8)), 118.4 (**C**(26)), 112.7 (**C**(11)), 107.7 (**C**(2)), 78.5 (**C**(15)), 74.9 (**C**(16)), 72.6 (**C**(24)), 58.5 (**C**(23)), 50.2 (**C**(28)), 16.3 (**C**(29))

m/z HRMS (ESI^+) found 514.1490; $C_{29}H_{24}NO_8^+$ ($M+H^+$) requires 514.1496.

Data in accordance with literature.[32]

(S)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine ((S)-54)



Prepared according to the procedure of Hayashi [58]

To a solution of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (***(S)*-89**, 2.00 g, 7.90 mmol, 1.0 eq.) in dichloromethane (35 mL) at –78 °C was added triethylamine (2.0 mL, 14.2 mmol, 1.8 eq.) and trimethylsilyl triflate (3.2 mL, 14.2 mmol, 1.8 eq.). The resultant solution was warmed to RT and stirred for 4 h then quenched by dropwise addition of sat. aq. sodium bicarbonate (40 mL). The layers were separated and the aqueous layer was washed with dichloromethane (x 3). The combined organic layers were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 60% diethyl ether in pentane) to give the title compound as a colourless oil (2.46 g, 6.72 mmol, 85%).

R_f: 0.3 (60% diethyl ether in pentane).

ν_{max}/cm^{-1} (thin film): 2956 (br, m), 2910 (m), 2876 (m), 1492 (m), 1446 (m), 1071 (m), 739 (m), 701 (s).

δ_H(600 MHz, $CDCl_3$): 7.52 – 7.48 (2H, m, 2 x Ar**H**), 7.41 – 7.36 (2H, m, 2 x Ar**H**), 7.32 – 7.22 (6H, m, 6 x Ar**H**), 4.04 (1H, t, *J* = 7.5 Hz, C(4)**H**), 2.85 (1H, ddd, *J* = 10.0, 7.5, 6.0 Hz, C(1)**H**H'), 2.72 (1H, ddd, *J* = 10.0, 7.5, 6.0 Hz, C(1)H**H'**), 1.76 (1H,br s, N**H**), 1.65 – 1.51 (3H, m, C(2)**HH'**, C(3)**H**H), 1.32 – 1.23 (1H, m, C(3)H**H'**), 0.88 (9H, t, *J* = 8.0 Hz, 3 x C(15)$\mathbf{H_3}$), 0.38 (6H, q, *J* = 8.0 Hz, 3 x C(14)$\mathbf{H_2}$).

δ_C(151 MHz, $CDCl_3$): 146.8 (**Ar**), 145.6 (**Ar**), 129.0 (**Ar**), 128.2 (**Ar**), 127.7 (**Ar**), 127.5 (**Ar**), 127.1 (**Ar**), 127.1 (**Ar**), 83.1 (**C**(5)), 65.8 (**C**(4)), 47.4 (**C**(1)), 27.9 (**C**(3)), 25.3 (**C**(2)), 7.4 (**C**(15)), 6.7 (**C**(14)).

m/z HRMS (ESI^+) found 368.2403; $C_{23}H_{34}NO_9Si^+$ ($M+H^+$) requires 368.2404.

$[\alpha]_D^{25}$ = –30.9

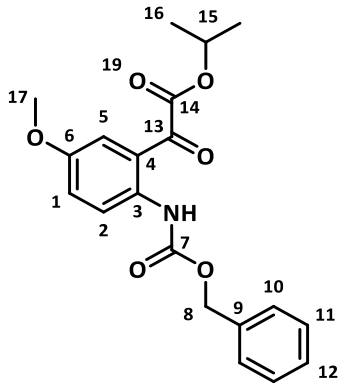
Data in accordance with literature.[58]

A sample of the enantiomer, (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**(*R*)-54**, 2.97 g, 8.09 mmol, 82%), was prepared as above using (*R*)-diphenyl(pyrrolidin-2-yl)methanol (**(*R*)-89**) as starting material.

$[\alpha]_D^{25}$ = +31.1

All other characterisation identical.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methoxyphenyl)-2-oxoacetate (65)



Prepared according to the procedure of Guggiari [41]

To a suspension of sodium hydride (60% in mineral oil, 4.52 g, 113 mmol, 2.0 eq.) in tetrahydrofuran (220 mL) at 0 °C was added 5-methoxyisatin (**19**, 10.0 g, 56.5 mmol, 1.0 eq.) as a single solid portion. The reaction was warmed to RT and stirred for 30 min then benzyl chloroformate (9.50 mL, 6.40 mmol, 1.2 eq.) was added. The reaction was stirred at RT for 3 h then cooled to 0 °C and quenched by dropwise addition of water (200 mL). The tetrahydrofuran was removed *in vacuo* and ethyl acetate (500 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (x 3). The combined organic fractions were dried over magnesium sulfate, concentrated *in vacuo* and redissolved in isopropanol (250 mL). Concentrated sulfuric acid (10 mL) was added and the solution was heated to reflux for 72 h, cooled to RT and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% diethyl ether in petroleum ether) to give the title compound as a yellow solid (16.3 g, 43.8 mmol, 77%).

R_f: 0.2 (20% diethyl ether in petroleum ether).

m.p.: 53.8 – 56.0 °C.

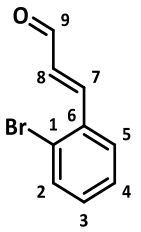
ν_{max}/cm^{-1} (thin film): 1734 (s), 1655 (m), 1588 (m), 1526 (s), 1261 (m), 1207 (s), 1190 (m), 1168 (s).

δ_H(500 MHz, Chloroform-*d*): 10.38 (1H, s, N**H**), 8.46 (1H, d, *J* = 9.5 Hz, Ar**H**), 7.44 – 7.31 (5H, m, 5 x Ar**H**), 7.22 (1H, dd, *J* = 9.5, 3.0 Hz, Ar**H**), 7.15 (1H, d, *J* = 3.0 Hz, Ar**H**), 5.32 (1H, hept, *J* = 6.5 Hz, C(15)**H**), 5.21 (2H, s, C(8)$\mathbf{H_2}$), 3.80 (3H, s, C(17)$\mathbf{H_3}$), 1.41 (6H, d, *J* = 6.5 Hz, 2 x C(16)$\mathbf{H_3}$).

δ_C(126 MHz, Chloroform-*d*): 190.0 (**C**(13)), 163.3 (**C**(14)), 154.0 (**Ar**), 153.7 (**C**(7)), 136.8 (**Ar**), 136.1 (**Ar**), 128.7 (**Ar**), 128.4 (**Ar**), 128.4 (**Ar**), 123.7 (**Ar**), 121.1 (**Ar**), 117.8 (**Ar**), 116.7 (**Ar**), 71.1(**C**(15)), 67.2 (**C**(8)), 55.8 (**C**(17)), 21.8 (**C**(16)).

m/z HRMS (ESI^+) found 372.1441, $C_{20}H_{22}O_6N^+$ ($M+H^+$) requires 372.1442.

(E)-3-(2-Bromophenyl)acrylaldehyde (85)



Method A: *Prepared according to the procedure of Hoover.*[79]

To a solution of (*E*)-3-(2-bromophenyl)prop-2-en-1-ol (**107**, 2.70 g, 12.7 mmol, 1.0 eq.) in acetonitrile (27 mL) at RT was added tetrakisacetonitrile copper(I) triflate (241.2 mg, 0.64 mmol, 0.05 eq.), 2,2-bipyridine (100.0 mg, 0.64 mmol, 0.05 eq.), TEMPO (100.0 mg, 0.64 mmol, 0.05 mmol) and *N*-methylimidazole (101.8 mg, 1.28 mmol, 0.1 eq.), rinsing with 10 mL of acetonitrile after addition of each solid. The resultant brown solution was stirred open to air for 4 h until the solution turned dark green then quenched with water (100 mL). The mixture was extracted with ethyl acetate (x3), dried over sodium sulfate and concentrated *in vacuo* to give the title compound as a white solid (2.41 g, 11.5 mmol, 90%).

Method B: *Prepared according to the procedure of Meisner.*[80]

To a suspension of (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (4.31 g, 10.0 mmol, 2.0 eq.) in tetrahydrofuran (30 mL) at 0 °C was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 12.5 mL, 12.5 mmol, 2.5 eq.). The resultant yellow solution was warmed to RT and stirred for 15 min. A solution of 2-bromobenzaldehyde (919.5 mg, 5.0 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) was added dropwise to the reaction. The reaction was heated to reflux and stirred for 40 h then cooled to room temperature. Aqueous hydrochloric acid solution (2 M, 45 mL) was added and the reaction was stirred at RT for a further 15 h then extracted with ethyl acetate (x 3). The combined organic layers were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (1% to 5% diethyl ether in pentane) to give the title compound as a white solid (832.2 mg, 3.96 mmol, 79%).

R_f: 0.4 (10% diethyl ether in pentane).

m.p.: 66.5 – 68.9 °C.

ν_{max}/cm^{-1} (thin film): 1683 (s), 1619 (m), 1466 (m), 1288 (m), 1134 (s), 1107 (m), 977 (m), 760 (m), 750 (m).

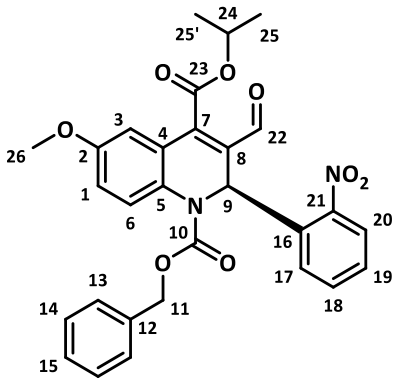
δ_H(600 MHz, $CDCl_3$): 9.77 (1H, d, *J* = 7.5 Hz, C(9)**H**), 7.90 (1H, d, *J* = 16.0 Hz, C(7)**H**), 7.66 (1H, dd, *J* = 8.0, 1.5 Hz, C(2)**H**), 7.65 (1H, dd, *J* = 8.0, 1.5 Hz, C(5)**H**), 7.37 (1H, dddd, *J* = 8.0, 7.5, 1.5, 0.5 Hz, C(4)**H**), 7.28 (1H, ddd, *J* = 8.0, 7.5, 1.5 Hz, C(3)**H**), 6.67 (1H, dd, *J* = 16.0, 7.5 Hz, C(8)**H**).

δ_C(151 MHz, $CDCl_3$): 193.6 (**C**(9)), 150.7 (**C**(7)), 134.0 (**C**(6)), 133.8 (**C**(2)), 132.3 (**C**(3)), 130.9 (**C**(8)), 128.2 (**C**(5)), 128.1 (**C**(4)), 125.9 (**C**(1)).

m/z HRMS (APCI$^+$) found 210.9751; $C_9H_8O^{79}Br^+$ ($M+H^+$) requires 210.9753.

Data in accordance with literature.[78]

1-Benzyl 4-isopropyl (*R*)-3-formyl-6-methoxy-2-(2-nitrophenyl)quinoline-1,4(2*H*)-dicarboxylate (*ent*-90)



Prepared according to the procedure of Guggiari.[41]

To a solution of (*S*)-2-(((triethylsilyl)oxy)diphenylmethyl) pyrrolidine (**(*S*)-54**, 220 mg, 0.600 mmol, 0.2 eq.) in dichloromethane (3.5 mL) was added 2-nitrocinnamaldehyde (532 mg, 3.00 mmol, 1.0 eq.), benzoic acid (183 mg, 1.50 mmol, 0.5 eq), freshly activated 4 Å molecular sieves (1.00 g) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methoxyphenyl)-2-oxoacetate (**65**, 2.23 g, 6.00 mmol, 2.0 eq.). The reaction was stirred at RT for 72 h then filtered through Celite™ and washed with ethyl acetate. The filtrate was washed sequentially with sat. aq. sodium bicarbonate and hydrochloric acid (2 M) and the combined organic fractions were dried over magnesium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 30% ethyl acetate in petroleum ether) to give the title compound as a yellow solid (1.31 g, 2.48 mmol, 83%).

R_f: 0.4 (30% ethyl acetate in petroleum ether).

m.p.: 52.0 – 53.9 °C.

ν_{max}/cm^{-1} (thin film): 1719 (s), 1676 (m), 1568 (m), 1533 (s), 1494 (m), 1360 (m), 1256 (s), 1236 (s), 1213 (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.88 (1H, s, C(22)**H**), 7.67 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.42 – 7.27 (8H, m, 8 x Ar**H**), 7.38 (1H, s, C(9)**H**), 6.98 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 6.90 (2H, m, 2 x Ar**H**), 5.42 (1H, hept, *J* = 6.5 Hz, C(24)**H**), 5.36 (1H, d, *J* = 12.0 Hz, C(11)**H**H), 5.13 (1H, d, *J* = 12.0 Hz, C(11)H**H**), 3.78 (3H, s, C(26)$\mathbf{H_3}$), 1.43 (3H, d, *J* = 6.5 Hz, C(25)$\mathbf{H_3}$), 1.41 (3H, d, *J* = 6.5 Hz, C(25')$\mathbf{H_3}$).

^{13}C NMR (126 MHz, $CDCl_3$, 26 resonances out of 27 observed, 1 x **Ar** resonance not observed): 187.4 (**C**(22)), 164.9(**C**(23)), 156.9 (**Ar**), 153.8 (**C**(10)), 149.4 (**Ar**), 143.6 (**C**(7)), 135.6 (**Ar**), 133.9 (**C**(8)), 132.3 (**Ar**), 130.3 (**Ar**),

129.6 (**Ar**), 129.5 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 127.5 (**Ar**), 124.8 (**Ar**), 124.6 (**Ar**), 118.1 (**Ar**), 110.7 (**Ar**), 71.3 (**C**(24)), 68.8 (**C**(11)), 55.7 (**C**(26)), 48.0 (**C**(9)), 22.0 (**C**(25)), 22.0(**C**(25')).

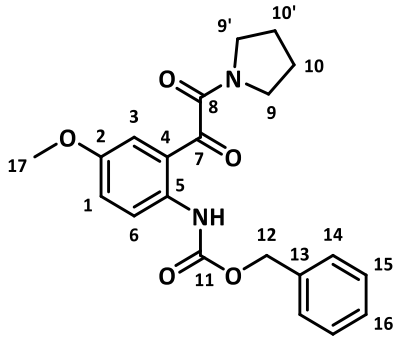
m/z HRMS (ESI$^+$) found 531.1761, $C_{29}H_{27}O_8N_2^+$ (M+H$^+$) requires 531.1762.

ee: 96% (Chiracel AD-H, 10% isopropanol in hexane, flow rate 0.8 mL/min; λ = 254 nm): t_R (major) = 87.5 min, t_R (minor) = 119.6 min.

$[\alpha]_D^{25}$= –193.0

A racemic sample of ***rac*-90** (8.3 mg, 0.02 mmol, 10%) was prepared as described above using catalytic pyrrolidine in place of (*S*)-2-(((triethylsilyl)oxy)diphenylmethyl) pyrrolidine.

Benzyl (4-methoxy-2-(2-oxo-2-(pyrrolidin-1-yl)acetyl)phenyl)carbamate (92)



Isolated as a side product during the preparation of racemic ***rac*****-90** *using catalytic pyrrolidine.*

To a solution of pyrrolidine (12 µL, 0.150 mmol, 1.0 eq.) in dichloromethane (1.5 mL) was added 2-nitrocinnamaldehyde (26.6 mg, 0.150 mmol, 1.0 eq.), benzoic acid (9.2 mg, 0.080 mmol, 0.5 eq), freshly activated 4 Å molecular sieves (50.0 mg) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methoxyphenyl)-2-oxoacetate (**65**, 2.23 g, 6.00 mmol, 2.0 eq.). The reaction was stirred at RT for 48 h then filtered through Celite™ and washed with ethyl acetate. The filtrate was washed sequentially with sat. aq. sodium bicarbonate and hydrochloric acid (2 M) and the combined organic fractions were dried over magnesium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 30% ethyl acetate in petroleum ether) to give the title compound as a pale yellow solid (26.1 mg, 0.070 mmol, 47%).

R_f: 0.1 (30% ethyl acetate in petroleum ether).

m.p.: 110.0 – 111.7 °C

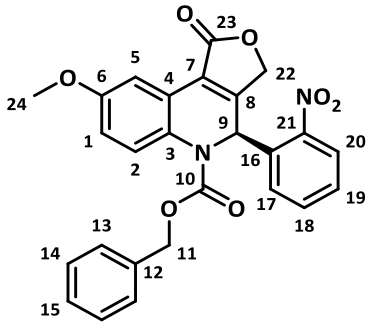
ν_{max}/cm^{-1} (thin film): 1732 (m), 1639 (s), 1587 (m), 1522 (s), 1454 (m), 1418 (m), 1286 (m), 1201 (s), 1167 (m), 1035 (m).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.53 (1H, s, NH), 8.45 (1H, d, *J* = 8.5 Hz Ar**H**), 7.46 – 7.31 (5H, m, 5 x Ar**H**), 7.22 – 7.18 (2H, m, 2 x Ar**H**), 5.22 (2H, s, C(12)**H$_2$**), 3.79 (3H s, C(17)**H$_3$**), 3.64 (2H t, *J* = 6.5 Hz, C(9)**H$_2$**), 3.37 (2H t, *J* = 6.5 Hz, C(9')**H$_2$**), 2.00 – 1.90 (4H, m, C(10)**H$_2$**, C(10')**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.9 (**C**(7)), 164.3 (**C**(8)), 154.2 (**Ar**), 153.7 (**C**(11)), 136.6 (**Ar**), 136.2 (**Ar**), 128.7 (**Ar**), 128.4 (**Ar**), 128.4 (**Ar**), 123.0 (**Ar)**, 121.0 (**Ar**), 118.4 (**Ar**), 117.5 (**Ar**), 67.1 (**C**(12)), 55.9 (**C**(17)), 46.8 (**C**(9)), 45.4 (**C**(9')), 26.0 (**C**(10)), 24.2 (**C**(10')).

m/z HRMS (ESI^+) found 383.1602, $C_{21}H_{23}O_5N_2^+$ ($M+H^+$) requires 383.1601.

Benzyl (*R*)-8-methoxy-4-(2-nitrophenyl)-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (*ent*-93)



Prepared according to the procedure of Janthawornpong.[60]

To a solution of 1-benzyl 4-isopropyl (*R*)-3-formyl-6-methoxy-2-(2-nitrophenyl)quinoline-1,4(2*H*)-dicarboxylate (***ent*-90**, 600 mg, 1.13 mmol, 1.0 eq.) in anhydrous methanol (12 mL) was added cerium(III) trichloride heptahydrate (421 mg, 1.13 mmol, 1.0 eq.) followed by sodium borohydride (42.8 mg, 1.13 mmol, 1.0 eq.). The reaction was stirred at RT for 20 min then quenched with brine (10 mL). The methanol was removed *in vacuo* and ethyl acetate (20 mL) was added. The layers were separated and the aqueous layer was washed with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 20% ethyl acetate in pentane) to give the title compound as a yellow solid (480 mg, 1.02 mmol, 90%).

R_f: 0.5 (30% ethyl acetate in petroleum ether).

m.p.: 71.8 – 75.8 °C.

ν_{max}/cm^{-1} (thin film): 2959 (w), 1762 (s), 1718 (m), 1529 (s), 1499 (m), 1346 (m), 1261 (s), 1243 (s), 1217 (m);

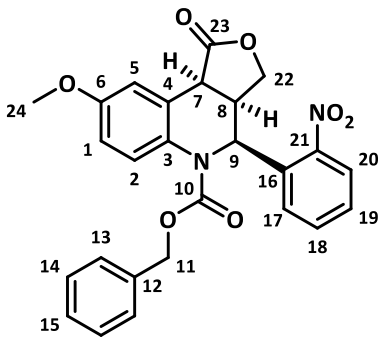
δ_H(500 MHz, $CDCl_3$): 7.95 – 7.91 (1H, m, Ar**H**), 7.81 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.70 (1H, br s, Ar**H**), 7.49 – 7.44 (2H, m, 2 x Ar**H**), 7.36 – 7.31 (4H, m, 4 x Ar**H**), 7.26 – 7.23 (2H, d, 2 x Ar**H**), 7.08 (1H, s, C(9)**H**), 6.93 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 5.21 (1H, d, *J* = 12.0 Hz, C(11)**H**H), 5.13 (1H, d, *J* = 18.5 Hz, C(22)**H**H), 5.10 (1H, d, *J* = 12.0 Hz, C(11)H**H**), 4.77 (1H, d, *J* = 18.5 Hz, C(22)H**H**), 3.88 (3H, s, C(24)**H_3**).

δ_C (126 MHz, $CDCl_3$, 23 resonances out of 24 observed, 1 x **Ar** resonance not observed): 169.7 (**C**(23)), 156.7 (**C**(8)), 154.0 (**C**(10)), 146.8 (**Ar**), 135.2 (**Ar**), 134.8 (**Ar**), 134.6 (**Ar**), 129.9 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 124.9 (**Ar**), 124.6 (**Ar**), 121.4 (**C**(7)), 119.9 (**Ar**), 116.4 (**Ar**), 108.4 (**Ar**), 69.9 (**C**(22)), 68.8 (**C**(11)), 55.8 (**C**(24)), 52.4 (**C**(9)).

m/z HRMS (ESI^+) found 495.1162; $C_{26}H_{20}N_2NaO_7^+$ ($M+Na^+$) requires 495.1163.

$[\alpha]_D^{25}$= –275.0

Benzyl (3a*R*,4*S*,9b*S*)-8-methoxy-4-(2-nitrophenyl)-1-oxo-1,2,3,3a,4,9b-hexahydro-5*H*-cyclopenta[c]quinoline-5-carboxylate (*ent*-94)



Prepared according to the procedure of Venkatesh.[59]

To a solution of 1-benzyl 4-isopropyl (*R*)-3-formyl-6-methoxy-2-(2-nitrophenyl)quinoline-1,4(2*H*)-dicarboxylate (***ent*-90**, 50.0 mg, 0.090 mmol, 1.0 eq) in anhydrous methanol (1.0 mL) was added sodium borohydride (3.7 mg, 0.099 mmol, 1.1 eq.). The resultant solution was stirred at RT for 1 h then quenched with brine (1.0 mL). The methanol was removed *in vacuo* and ethyl acetate (5.0 mL) was added to the resultant aqueous suspension. The layers were separated, the aqueous layer was washed with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 30% ethyl acetate in pentane) to give the title compound as a yellow oil (9.3 mg, 0.020 mmol, 21%).

R_f: 0.3 (30% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 2972 (w), 1773 (m), 1702 (m), 1528 (s), 1504 (s), 1319 (m), 1259 (m), 1229 (m), 733 (s).

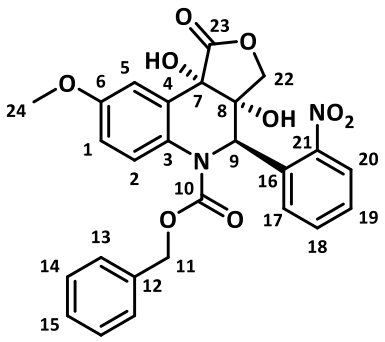
δ_H(500 MHz, $CDCl_3$): 7.92 – 7.87 (1H, m, Ar**H**), 7.66 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.44 – 7.38 (2H, m, 2 x Ar**H**), 7.35 – 7.29 (3H, m, 3 x Ar**H**), 7.19 (1H, d, *J* = 3.5 Hz, Ar**H**), 7.18 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.16 – 7.10 (2H, m, Ar**H**), 6.93 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.38 – 6.32 (1H, m, C(9)**H**), 5.14 (1H, d, *J* = 12.0 Hz, C(11)**H**H), 5.07 (1H, d, *J* = 12.0 Hz, C(11)H**H**), 4.02 – 3.97 (1H, m, C(22)**H**H), 3.94 – 3.82 (3H, m, C(7)**H**, C(8)**H**, C(22)H**H**), 3.85 (3H, s, C(24)**H_3**).

δ_C(126 MHz, $CDCl_3$): 174.9 (**C**(23)), 156.9 (**Ar**), 154.1 (**C**(10)), 149.4 (**Ar**), 135.5 (**Ar**), 134.1 (**Ar**), 133.7 (**Ar**), 129.9 (**Ar**), 129.1 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.0 (**Ar**), 126.0 (**Ar**), 125.0 (**Ar**), 123.4 (**Ar**), 115.3 (**Ar**), 112.7 (**Ar**), 68.4 (**C**(11)), 68.3 (**C**(22)), 55.7 (**C**(24)), 50.2 (**C**(9)), 40.1 (**C**(8)), 38.6 (**C**(7)).

m/z HRMS (ESI^+) found 497.1318; $C_{26}H_{22}N_2NaO_7^+$ ($M+Na^+$) requires 497.1319.

$[\alpha]_D^{25}$ = +127.0

Benzyl (3a*S*,4*R*,9b*S*)-3a,9b-dihydroxy-8-methoxy-4-(2-nitrophenyl)-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (*ent*-95)



Prepared according to the procedure of Niggemann.[57]

A solution of cerium(III) trichloride heptahydrate (93.1 mg, 0.250 mmol, 0.1 eq.) and sodium periodate (815 mg, 3.81, mmol, 1.5 eq.) in water (1.5 mL) was heated to 40 °C for 10 min until the solution turned pale yellow. The solution was cooled to 0 °C and ethyl acetate (1.5 mL) and acetonitrile (4.5 mL) were added. Ruthenium(III) trichloride trihydrate (33.2 mg, 0.13 mmol, 0.05 eq.) was added and the resultant suspension was stirred for 2 min at 0 °C. A solution of benzyl (*R*)-8-methoxy-4-(2-nitrophenyl)-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-93**, 1.20g , 2.54 mmol, 1.0 eq.) in ethyl acetate (3.0 mL) was added and the reaction was stirred at 0 °C for 10 min. Sodium sulfate (1.20 g) was added and the reaction mixture was filtered through Celite™ and washed with ethyl acetate. The filtrate was washed with sat. aq. sodium sulfite, dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by flash column chromatography (20% to 30% ethyl acetate in pentane) to give the title compound as a grey solid (920 mg, 1.82 mmol, 71%).

R_f: 0.6 (50% ethyl acetate in petroleum ether).

m.p.: 215.0 – 219.0 °C.

ν_{max}/cm^{-1} (thin film): 3400 (br,m), 1788 (m), 1699 (m), 1533 (s), 1504 (s), 1271 (m), 1156 (m), 1099 (m), 1020 (s), 729 (s).

δ_H(500 MHz, DMSO): 7.85 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.78 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.61 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.54 (1H, td, *J* = 8.0, 1.5 Hz, Ar**H**), 7.37 (1H, d, *J* = 7.5, Ar**H**), 7.29 – 7.23 (4H, m, 4 x Ar**H**), 7.13 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.11 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.09 (1H, s, C(7)O**H**), 6.74 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.39 (1H, s,

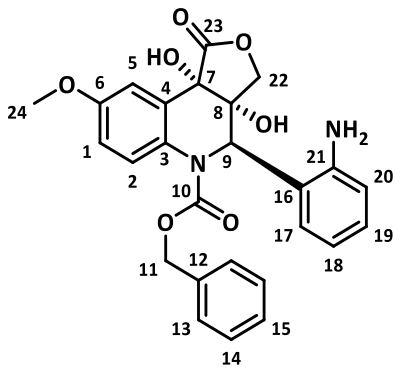
C(8)O**H**), 6.21 (1H, br s, C(9)**H**), 5.11 (1H, d, *J* = 12.5 Hz, C(11)**H**H), 5.08 (1H, d, *J* = 12.5 Hz, C(11)H**H**), 3.75 (3H, s, C(24)**H₃**), 3.41 (1H, br s, C(22)**H**H, 3.14 (1H, d, *J* = 10.0 Hz, C(22)H**H**).

δ_C(126 MHz, DMSO, 23 resonances out of 24 observed, 1 x **Ar** resonance not observed): 174.6 (**C**(23)), 156.2 (**Ar**), 153.6 (**C**(10)), 148.8 (**Ar**), 135.8 (**Ar**), 132.8 (**Ar**), 132.0 (**Ar**), 129.4 (**Ar**), 129.0 (**Ar**), 128.2 (**Ar**), 127.9 (**Ar**), 127.4 (**Ar**), 127.0 (**Ar**), 126.8 (**Ar**), 124.6 (**Ar**), 115.4 (**Ar**), 111.6 (**Ar**), 78.2 (**C**(8)), 75.5 (**C**(7)), 71.4 (**C**(22)), 67.4 (**C**(11)), 56.4 (**C**(9)), 55.4 (**C**(24)).

m/z HRMS (ESI^+) found 529.1215; $C_{26}H_{22}N_2NaO_9^+$ ($M+Na^+$) requires 529.1218.

$[\alpha]_D^{25}$ = –268.0

Benzyl (3a*S*,4*R*,9b*S*)-4-(2-aminophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (*ent*-96)



Prepared by procedure of Fullenkamp.[137]

A suspension of iron powder (33.4 mg, 0.600 mmol, 3.0 eq.) and ammonium chloride (96.0 mg, 1.80 mmol, 9.0 eq.) in ethanol (1.0 mL) and water (0.4 mL) was heated to 45 °C for 20 min until a dark orange colour was observed. Acetonitrile (1.0 mL) was added, followed by benzyl (3a*S*,4*R*,9b*S*)-3a,9b-dihydroxy-8-methoxy-4-(2-nitrophenyl)-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-95**, 100 mg, 0.210 mmol, 1.0 eq.). A reflux condenser was added and the reaction mixture was heated to 80 °C for 1 h then cooled to RT and quenched with sat. aq. sodium bicarbonate (3.0 mL). The layers were separated and the aqueous fraction was extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (50% ethyl acetate in pentane) to give the title compound as a pale yellow solid (75.2 mg, 0.158 mmol, 79%).

*Note: the ^{1}H and ^{13}C NMR spectra of **ent-96** at room temperature display broad, unassignable resonances. Upon heating to 90 °C in DMSO-d_6, the resonances in both the ^{1}H and the ^{13}C NMR spectra coalesce to give clear, defined spectra, indicating the presence of rotamers.*

R_f: 0.3 (70% ethyl acetate in petroleum ether).

m.p.: 100.8 – 107.4 °C.

ν_{max}/cm^{-1} (thin film): 3300 (br, m), 2981 (m), 1763 (s), 1659 (s), 1589 (m), 1503 (s), 1395 (m), 1297 (s), 1250 (s), 1138 (s), 1019 (m), 852 (m), 756 (s).

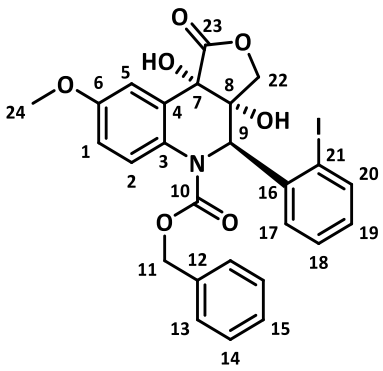
δ_H(600 MHz, DMSO, 363 K): 10.04 (1H, s, N**H**), 7.50 – 7.44 (3H, m, 3 x Ar**H**), 7.42 – 7.37 (2H, m, 2 x Ar**H**), 7.33 (1H, tt, *J* = 7.5, 1.5 Hz, Ar**H**), 7.25 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.13 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, Ar**H**), 7.01 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 6.94 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 6.80 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.71 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.05 (1H, s, C(9)**H**), 5.71 (1H, s, N**H**), 5.31 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.29 (1H, d, *J* = 12.5 Hz, C(11)H**H'**), 4.54 (1H, s, C(7)O**H**), 4.31 (1H, s, C(8)O**H**), 3.68 (3H, s, C(24)**H_3**), 3.67 (1H, d, *J* = 11.5 Hz, C(22)**H**H'), 3.43 (1H, d, *J* = 11.5 Hz, C(22)H**H'**).

δ_C(151 MHz, DMSO, 363 K, 23 resonances out of 24 observed, **C**(23) not observed): 169.4 (**Ar**), 155.6 (**Ar**), 154.2 (**C**(10)), 134.9 (**Ar**), 133.0 (**Ar**), 129.7 (**Ar**), 128.7 (**Ar**), 128.2 (**Ar**), 127.9 (**Ar**), 127.3 (**Ar**), 127.1 (**Ar**), 125.1 (**Ar**), 123.4 (**Ar**), 123.1 (**Ar**), 119.6 (**Ar**), 113.9 (**Ar**), 111.3 (**Ar**), 74.2 (**C**(7)), 69.3 (**C**(8)), 66.7 (**C**(11)), 61.7(**C**(22)), 60.8 (**C**(9)), 54.9 (**C**(24)).

m/z HRMS (ESI$^+$) found 499.1476; $C_{26}H_{24}N_2NaO_7^+$ (M+Na$^+$) requires 499.1476.

$[\alpha]_D^{25}$ = –154.0

Benzyl (3a*S*,4*R*,9b*S*)-3a,9b-dihydroxy-4-(2-iodophenyl)-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (*ent*-97)



Method **A**: *Prepared according to the procedure of Moneypenny.*[77]

A solution of benzyl (3a*S*,4*R*,9b*S*)-4-(2-((*E*)-cyclopentyldiazenyl)phenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-104**, 29.7 mg, 0.053 mmol, 1.0 eq.) and iodine (40.3 mg, 0.160, 3.0 eq.) in iodomethane (1.0 mL) was freeze-pump-thaw degassed. A reflux condenser was attached and the reaction mixture was heated to 80 °C under argon for 1 h then cooled to RT. Sat. aq. sodium sulfite (2 mL) was added and the mixture was extracted with chloroform (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 30% ethyl acetate in pentane) to give the title compound as a clear oil (17.1 mg, 0.029 mmol, 55%).

Method **B**: *Prepared according to the procedure of Ju*.[138]

To a solution of benzyl (3a*S*,4*R*,9b*S*)-4-(2-aminophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-96**, 35.4 mg, 0.074 mmol, 1.0 eq.) in diiodomethane (0.5 mL) was added *tert*-butyl nitrite (36 µL, 0.300 mmol, 4.0 eq.). The reaction was heated to 80 °C for 16 h then cooled to RT, diluted with dichloromethane (2.0 mL) and washed with water. The organic fraction was dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% ethyl acetate in pentane) to give the title compound as a clear oil (5.9 mg, 0.010 mmol, 14%).

R_f: 0.1 (30% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 3396 (br, m), 2971 (w), 1787(m), 1698 (m), 1504 (s), 1395 (m), 1292 (m), 1269 (m), 1149 (m), 1020 (s)

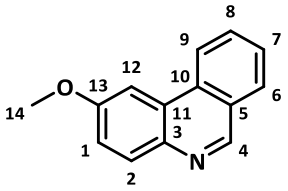
δ_H(500 MHz, $CDCl_3$): 7.87 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.71 (1H, d, *J* = 9.0 H, Ar**H**), 7.30 – 7.23 (3H, m, 3x Ar**H**), 7.21 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.12 – 7.07 (2H, m, 2xAr**H**), 7.02 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 7.00 – 6.93 (3H, m, 3xAr**H**), 5.97 (1H, s, C(9)**H**), 5.16 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.11 (1H, d, *J* = 12.0 Hz, C(11)H**H'**), 3.92 (1H, s, O**H**), 3.80 (3H, s, C(24)**H_3**), 3.68 (1H, d, *J* = 10.0 Hz, C(22)**H**H'), 3.64 (1H, s, O**H**), 3.54 (1H, d, *J* = 10.0 Hz, C(22)H**H'**)

δ_C(126 MHz, $CDCl_3$): 174.5 (**C**(23)), 157.3 (**Ar**), 154.4 (**C**(10)), 141.2 (**Ar**), 140.8 (**Ar**), 135.6 (**Ar**), 130.3 (**Ar**), 130.0 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 127.1 (**Ar**), 126.7 (**Ar**), 125.4 (**Ar**), 117.5 (**Ar**), 111.6 (**Ar**), 99.7 (**Ar**), 79.9 (**C**(8)), 75.6 (**C**(7)), 72.4 (**C**(22)), 68.6 (**C**(11)), 65.5 (**C**(9)), 55.8 (**C**(24))

m/z HRMS (ESI^+) found 588.0512; $C_{26}H_{23}NO_7I^+$ ($M+H^+$) requires 588.0514.

$[\alpha]_D^{25}$ = –27.0

2-Methoxyphenanthridine (98)



Isolated as a side-product during the preparation of iodide ***ent*-97** *according to the procedure of Kennedy*[74]

To a suspension of benzyl (3a*S*,4*R*,9b*S*)-4-(2-aminophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-96**, 33.0 mg, 0.070 mmol, 1.0 eq.) in water (0.4 mL) at RT was added 12 M hydrochloric acid (0.3 mL) and acetic acid (0.1 mL). The suspension was cooled to 0 °C and sodium nitrite (5.3 mg, 0.080 mmol, 1.1 eq.) was added as a single solid portion. The resultant yellow solution was stirred for 20 min at 0 °C. A solution of potassium iodide (28.6 mg, 0.170 mmol, 2.5 eq.) in water was added and the solution was allowed to warm slowly to RT and stirred for 16 h. The reaction mixture was extracted with dichloromethane (x 3) and the combined organic fractions were washed with brine, dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 20% ethyl acetate in pentane) to give the title compound as a clear oil (4.4 mg, 0.020 mmol, 31%).

R_f: 0.4 (30% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 1617 (m), 1524 (m), 1497 (m), 1232 (s), 1220 (m), 1032 (m), 828 (m), 753 (m).

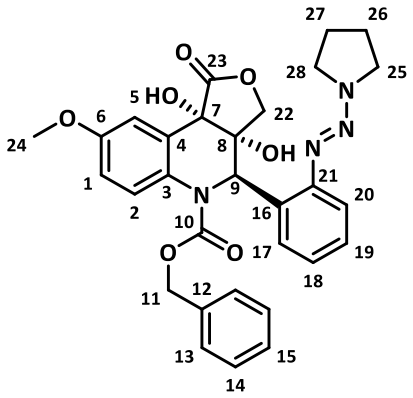
δ_H(500 MHz, $CDCl_3$): 9.18 (1H, s, Ar**H**), 8.56 (1H, d, *J* = 8.0 Hz, Ar**H**), 8.17 (1H, d, *J* = 9.0 Hz), 8.06 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 7.92 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.88 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, Ar**H**), 7.73 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz, Ar**H**), 7.39 (1H, dd, *J* = 9.0, 2.5 Hz, Ar**H**), 4.03 (3H, s, C(14)**H₃**).

δ_C(126 MHz, $CDCl_3$): 158.9 (**Ar**), 150.7 (**Ar**), 139.0 (**Ar**), 132.4 (**Ar**), 131.1 (**Ar**), 131.1 (**Ar**), 129.1 (**Ar**), 127.9 (**Ar**), 126.5 (**Ar**), 125.5 (**Ar**), 122.1 (**Ar**), 118.9 (**Ar**), 103.3 (**Ar**), 55.9 (**C**(14)).

m/z HRMS (ESI^+) found 210.0914; $C_{14}H_{12}NO^+$ ($M+H^+$) requires 210.0913.

Data in accordance with literature.[75]

Benzyl (3a*S*,4*R*,9b*S*)-4-(2-((*E*)-cyclopentyldiazenyl)phenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (*ent*-104)



Prepared according to the procedure of Wu.[76]

To a solution of benzyl (3a*S*,4*R*,9b*S*)-4-(2-aminophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-96**, 200 mg, 0.420 mmol, 1.0 eq.) in acetonitrile (2.0 mL) was added 6M hydrochloric acid (1.6 mL). The solution was cooled to 0 °C and sodium nitrite (34.8 mg, 0.500 mmol, 1.2 eq.) was added. The reaction mixture was stirred for 45 min at 0 °C and was transferred *via* cannula into a solution of pyrrolidine (173 µL, 2.10 mmol, 5.0 eq.) and potassium carbonate (1.65 g, 12.0 mmol) in water (1.0 mL) at 0 °C. The resultant reaction mixture was allowed to warm slowly to room temperature over 30 min whilst stirring. Water (3 mL) was added and the mixture was extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% ethyl acetate in pentane) to give the product as a clear oil (189 mg, 0.340 mmol, 80%).

R_f: 0.4 (50% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 3300 (br, m), 1789 (s), 1707 (s), 1504 (s), 1406 (s), 1314 (s), 1270 (s), 1018 (m), 733 (m).

δ_H(600 MHz, $CDCl_3$, C(7)O**H** not observed): 7.79 (1H, s, Ar**H**), 7.77 (1H, s, Ar**H**), 7.54 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.26 – 7.17 (5H, m, 5 x Ar**H**), 7.12 – 7.05 (2H, m, 2 x Ar**H**), 7.04 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.97 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.23 (1H, s, C(9)**H**), 5.13 (1H, d, *J* = 13.0 Hz, C(11)**H**H'), 5.10 (1H, d, *J* = 13.0 Hz, C(11)H**H'**), 4.07 – 3.99 (2H, m, C(25)$\mathbf{H_2}$), 3.79 (3H, s, C(24)$\mathbf{H_3}$), 3.76 – 3.66 (1H, m, C(28)**H**H'), 3.62 (1H, s, C(8)O**H**), 3.57 – 3.49

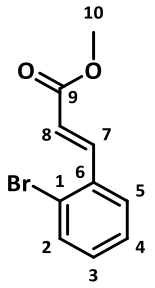
(1H, m, C(28)H**H'**), 3.48 (1H, d, *J* = 10.0 Hz, C(22)**H**H'), 3.44 (1H, d, *J* = 10.0 Hz, C(22)H**H'**), 2.21 – 2.05 (4H, m, C(26)$\mathbf{H_2}$, C(27)$\mathbf{H_2}$).

δ_C(151 MHz, $CDCl_3$): 175.5 (**C**(23)), 157.4 (**Ar**), 154.2 (**C**(10)), 147.4 (**Ar**), 136.1 (**Ar**), 131.8 (**Ar**), 130.4 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 127.5 (**Ar**), 127.3 (**Ar**), 126.3 (**Ar**), 125.8 (**Ar**), 125.1 (**Ar**), 117.4 (**Ar**), 117.4 (**Ar**), 111.8 (**Ar**), 79.6 (**C**(8)), 75.4 (**C**(7)), 74.0 (**C**(22)), 67.9 (**C**(11)), 58.5 (**C**(9)), 55.8 (**C**(24)), 52.4 (**C**(25)), 47.5 (**C**(28)), 23.9 (**C**(26)), 23.9 (**C**(27)).

m/z HRMS (ESI^+) found 559.2184; $C_{30}H_{31}N_4O_7^+$ ($M+H^+$) requires 559.2187.

$[\alpha]_D^{25}$= –418.0

Methyl (E)-3-(2-bromophenyl)acrylate (106)



Prepared according to the procedure of Kim. [78]

To a suspension of sodium hydride (60% in mineral oil, 1.64 g, 40.9 mmol, 2.5 eq.) in tetrahydrofuran (370 mL) at 0 °C was added trimethyl phosphonoacetate (8.94 g, 49.1 mmol, 3.0 eq.) in tetrahydrofuran (30 mL). The reaction mixture was warmed to RT and stirred vigorously for 15 min. A solution of 2-bromobenzaldehyde (3.00 g, 16.8 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) was added dropwise and the reaction was stirred for 1 h then quenched with water (200 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic layers were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (5% ethyl acetate in pentane) to give the title compound as a clear oil (3.84 g, 16.0 mmol, 98%).

R_f: 0.6 (10% ethyl acetate in pentane).

ν_{max}/cm^{-1} (thin film): 1722 (s), 1636 (m), 1467 (m), 1438 (m), 1319 (s), 1287 (m), 1269 (m), 1204 (s), 1176 (s), 761 (s).

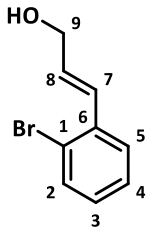
δ_H(600 MHz, $CDCl_3$): 8.06 (1H, d, *J* = 16.0 Hz, C(7)**H**), 7.62 (1H, d, *J* = 8.0 Hz, C(5)**H**), 7.60 (1H, d, *J* = 8.0 Hz, C(2)**H**), 7.33 (1H, t, *J* = 8.0 Hz, C(3)**H**), 7.23 (1H, t, *J* = 8.0 Hz, C(4)**H**), 6.40 (1H, d, *J* = 16.0 Hz, C(8)**H**), 3.83 (3H, s, C(10)$\mathbf{H_3}$).

δ_C(151 MHz, $CDCl_3$): 166.9 (**C**(9)), 143.3 (**C**(7)), 134.6 (**C**(6)), 133.6 (**C**(5)), 131.3 (**C**(1)), 127.9 (**C**(2)), 127.9 (**C**(3)), 125.5 (**C**(4)), 120.8 (**C**(8)), 52.0 (**C**(10)).

m/z HRMS ($APCI^+$) found 240.9855; $C_{10}H_{10}O_2{}^{79}Br^+$ ($M+H^+$) requires 240.9859.

Data in accordance with literature.[78]

(E)-3-(2-Bromophenyl)prop-2-en-1-ol (107)



Prepared according to the procedure of Kim. [78]

To a solution of methyl (*E*)-3-(2-bromophenyl)acrylate (**106**, 3.84 g, 16.0 mmol, 1.0 eq.) in dichloromethane (370 mL) at −78 °C was added diisobutylaluminium hydride (1 M in hexanes, 48.0 mL, 48.0 mmol, 3.0 eq.). The reaction was stirred at −78 °C for 45 min then warmed to 0 °C and quenched by sequential addition of water (1.9 mL), sodium hydroxide (15% wt. in water, 1.9 mL), and water (4.8 mL). The mixture was warmed to RT and stirred for 20 min. Magnesium sulfate was added until the mixture was free-flowing and the reaction was stirred vigorously for 20 min. The mixture was filtered through Celite™, washing with dichloromethane, and the filtrate was concentrated *in vacuo* to give the title compound as a colourless oil (2.70 g, 12.7 mmol, 80%).

R_f: 0.3 (30% diethyl ether in pentane).

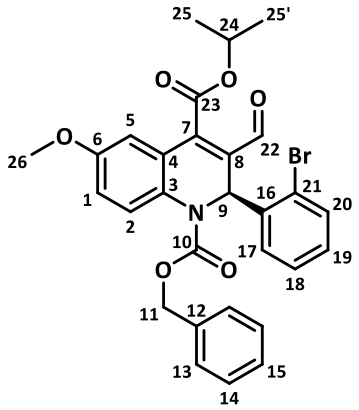
ν_{max}/cm^{-1} (thin film): 3349 (br, m), 1468 (m), 1438 (m), 1096 (m), 1017 (s), 969 (m), 752 (s).

δ_H(600 MHz, $CDCl_3$, 7 out of 8 resonances observed, C(9)O**H** not observed): 7.55 (1H, d, *J* = 8.0 Hz, C(2)**H**), 7.52 (1H, d, *J* = 8.0 Hz, C(5)**H**), 7.27 (1H, t, *J* = 8.0 Hz, C(4)**H**), 7.11 (1H, t, *J* = 8.0 Hz, C(3)**H**), 6.96 (1H, d, *J* = 15.5 Hz, C(7)**H**), 6.32 (1H, dt, *J* = 15.5, 5.5 Hz, C(8)**H**), 4.37 (2H, d, *J* = 5.5 Hz, C(9)$\mathbf{H_2}$).

δ_C(151 MHz, $CDCl_3$): 136.6 (**C**(1)), 133.0 (**C**(2)), 131.6 (**C**(8)), 129.8 (**C**(7)), 129.0 (**C**(3)), 127.5 (**C**(4)), 127.2 (**C**(5)), 123.7 (**C**(6)), 63.6 (**C**(9)).

Data in accordance with literature.[78]

1-Benzyl 4-isopropyl (*S*)-2-(2-bromophenyl)-3-formyl-6-methoxyquinoline-1,4(2*H*)-dicarboxylate (*ent*-110)



Prepared according to the procedure of Guggiari.[41]

To a solution of (*S*)-2-(((triethylsilyl)oxy)diphenylmethyl)pyrrolidine (**(*S*)-54**, 804 mg, 2.19 mmol, 0.2 eq.) in dichloromethane (13 mL) was added 2-bromocinnamaldehyde (**85**, 2.30 g, 10.9 mmol, 1.0 eq.), benzoic acid (614 mg, 5.48 mmol, 0.5 eq), freshly activated 4 Å molecular sieves (4.000 g) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methoxyphenyl)-2-oxoacetate (**65**, 8.13 g, 21.9 mmol, 2.0 eq.). The reaction was stirred at RT for 72 h then filtered through Celite™ and washed with ethyl acetate. The filtrate was washed sequentially with sat. aq sodium bicarbonate and hydrochloric acid (2 M) and the combined organic fractions were dried over magnesium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 30% ethyl acetate in petroleum ether) to give the title compound as a yellow solid (4.92 g, 8.73 mmol, 80%).

R_f: 0.5 (30% ethyl acetate in petroleum ether).

m.p.: 43.8 – 48.4 °C.

ν_{max}/cm^{-1} (thin film): 2982 (w), 1714 (s), 1676 (m), 1493 (m), 1254 (s), 1234 (s), 1212 (s), 1101 (m), 1025 (m).

δ_H(500 MHz, $CDCl_3$): 9.85 (1H, s, C(22)**H**), 7.54 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.47 – 7.29 (6H, m, 6 x Ar**H**), 7.11 (1H, s, C(9)**H**), 7.04 (1H, td, *J* =7.5, 1.5 Hz, Ar**H**), 6.99 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 6.96 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.90 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.80 (1H, dd, *J* = 8.0, 2.0 Hz, Ar**H**), 5.43 (1H, hept, *J* = 6.5 Hz, C(24)**H**), 5.34 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.22 (1H, d, *J* = 12.5 Hz, C(11)H**H'**), 3.80 (3H, s, C(26)$\mathbf{H_3}$), 1.44 (3H, d, *J* = 6.5 Hz, C(25)$\mathbf{H_3}$), 1.42 (3H, d, *J* = 6.5 Hz, C(25')$\mathbf{H_3}$).

δ_C(126 MHz, $CDCl_3$): 187.3 (**C**(22)), 165.0 (**C**(23)), 156.8 (**Ar**), 153.8 (**C**(10)), 143.1 (**C**(7)), 135.8 (**Ar**), 135.4 (**C**(8)), 135.3 (**Ar**), 134.1 (**Ar**), 130.0 (**Ar**), 129.7 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.0 (**Ar**), 127.4 (**Ar**), 125.4 (**Ar**), 123.8 (**Ar**), 117.6 (**Ar**), 110.4 (**Ar**), 71.1 (**C**(24)), 68.4 (**C**(11)), 55.5 (**C**(26)), 51.9 (**C**(9)), 22.0 (**C**(25)), 21.9 (**C**(25')).

m/z HRMS (ESI^+) found 564.1016; $C_{29}H_{27}NO_6{}^{79}Br^+$ ($M+H^+$) requires 564.1016.

ee: 98% (Chiracel OD, 5% isopropanol in hexane, flow rate 0.8 mL/min; λ = 254 nm): t_R (major) = 28.7 min, t_R (minor) = 33.8 min.

$[\alpha]_D^{25}$ = –487.0

A sample of the enantiomer, 1-benzyl 4-isopropyl (*R*)-2-(2-bromophenyl)-3-formyl-6-methoxyquinoline-1,4(2*H*)-dicarboxylate (**110**, 7.17 g, 12.7 mmol, 89%), was prepared as above using (*R*)-2-(((triethylsilyl)oxy)diphenylmethyl) pyrrolidine (**(*R*)-54**) in place of (*S*)-2-(((triethylsilyl)oxy)diphenylmethyl) pyrrolidine (**(*S*)-54**).

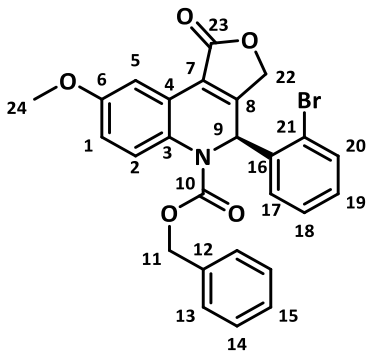
ee: 98% (Chiracel OD, 5% isopropanol in hexane, flow rate 0.8 mL/min; λ = 254 nm): t_R (minor) = 29.5 min, t_R (major) = 33.1 min.

$[\alpha]_D^{25}$ = +336.5

All other characterisation identical.

A racemic sample of ***rac*-110** (22.1 mg, 0.04 mmol, 16%) was prepared as described above using catalytic pyrrolidine in place of (S)-2-(((triethylsilyl)oxy)diphenylmethyl) pyrrolidine.

Benzyl (*S*)-4-(2-bromophenyl)-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (*ent*-111)



Prepared according to the procedure of Janthawornpong.[60]

To a solution of 1-benzyl 4-isopropyl (*S*)-2-(2-bromophenyl)-3-formyl-6-methoxyquinoline-1,4(2*H*)-dicarboxylate (***ent*-110**, 4.91 g, 8.73 mmol, 1.0 eq.) and cerium(III) trichloride heptahydrate (3.25 g, 8.73 mmol, 1.0 eq.) in anhydrous methanol (90 mL) was added sodium borohydride (330 mg, 8.73 mmol, 1.0 eq.) *[Note: sonication is required to fully dissolve the dihydroquinoline starting material]*. The reaction was stirred at RT for 60 min then quenched with brine (50 mL). The methanol was removed *in vacuo* and ethyl acetate (150 mL) was added to the resultant aqueous suspension. The layers were separated, the aqueous layer was washed with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 20% ethyl acetate in pentane) to give the title compound as a yellow solid (3.97 g, 7.86 mmol, 90%).

R_f: 0.6 (30% ethyl acetate in petroleum ether).

m.p.: 50.1 – 55.5 °C.

ν_{max}/cm^{-1} (thin film): 2998 (s), 2886 (m), 1762 (s), 1717 (s), 1382 (s), 1262 (s), 954 (m).

δ_H(500 MHz, $CDCl_3$): 7.75 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.58 – 7.54 (1H, m, Ar**H**), 7.37 – 7.27 (6H, m, 6 x Ar**H**), 7.19 – 7.11 (3H, m, 3 x Ar**H**), 6.99 (1H, s, C(9)**H**), 6.93 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 5.28 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.19 (1H, d, *J* = 12.5 Hz, C(11)H**H'**), 5.04 (1H, d, *J* = 18.0 Hz, C(22)**H**H'), 4.86 (1H, d, *J* = 18.0 Hz, C(22)H**H'**), 3.87 (3H, s, C(24)$\mathbf{H_3}$).

δ_C(126 MHz, $CDCl_3$, 23 resonances out of 24 observed, 1 x Ar resonance not observed): 169.7 (**C**(23)), 157.5 (**C**(8)), 156.7 (**Ar**), 154.4 (**C**(10)), 138.8 (**C**(7)), 135.6 (**Ar**), 133.2 (**Ar**), 130.5 (**Ar**), 129.0 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 127.9 (**Ar**), 120.8 (**Ar**), 120.5 (**Ar**), 116.2 (**Ar**), 108.1 (**Ar**), 69.5 (**C**(22)), 68.7 (**C**(11)), 56.5 (**C**(9)), 55.8 (**C**(24)).

m/z HRMS (ESI^+) found 528.0417; $C_{26}H_{20}NO_5{}^{79}BrNa^+$ ($M+Na^+$) requires 528.0417.

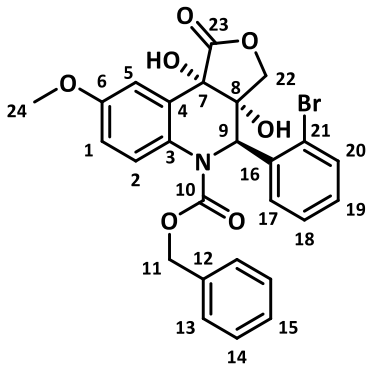
$[\alpha]_D^{25}$ = –572.0

A sample of the enantiomer, benzyl (*R*)-4-(2-bromophenyl)-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (**111**, 7.14 g, 14.1 mmol, 95%), was prepared as above using 1-benzyl 4-isopropyl (*R*)-2-(2-bromophenyl)-3-formyl-6-methoxyquinoline-1,4(2*H*)-dicarboxylate (**110**) as starting material.

$[\alpha]_D^{25}$ = +534.8 (*c* = 1.00, chloroform);

All other characterisation identical.

Benzyl (3a*S*,4*R*,9b*S*)-4-(2-bromophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (*ent*-112)



Prepared according to the procedure of Niggemann.[57]

A solution of cerium(III) trichloride heptahydrate (58.9 mg, 0.16 mmol, 0.1 eq.) and sodium periodate (508.2 mg, 2.38, mmol, 1.5 eq.) in water (1.3 mL) was heated to 35 °C for 10 min until the solution turned pale yellow in colour. The solution was cooled to 0 °C and ethyl acetate (1.5 mL) and acetonitrile (4.0 mL) were added. Ruthenium(III) trichloride trihydrate (20.7 mg, 0.08 mmol, 0.05 eq.) was added as a single solid portion and the suspension was stirred for 2 min. A solution of benzyl (*S*)-4-(2-bromophenyl)-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-111**, 800.0 mg, 1.58 mmol, 1.0 eq.) in ethyl acetate (2.5 mL) and the reaction was stirred at 0 °C for 10 min. Sodium sulfate (2.00 g) was added and the reaction mixture was filtered through Celite™ and washed with ethyl acetate. The filtrate was washed with sat. aq. sodium sulfite, dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by flash column chromatography (20% to 30% ethyl acetate in pentane) to give the title compound as a white solid (804.2 mg, 1.49 mmol, 94%).

R_f: 0.2 (30% ethyl acetate in petroleum ether).

m.p.: 64.1 – 69.0 °C.

ν_{max}/cm^{-1} (thin film): 3407 (br,m), 2964 (m), 1788 (w), 1700 (m), 1504 (s), 1299 (m), 1270 (m), 1150 (m), 1021 (m), 748 (m).

δ_H(600 MHz, $CDCl_3$, C(7)O**H** and C(8)O**H** not observed): 7.74 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.59 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.28 – 7.24 (3H, m, 3 x Ar**H**), 7.18 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.15 (1H, dd, *J* = 7.5, 2.0 Hz, Ar**H**), 7.14 – 7.11 (2H, m, 2 x Ar**H**), 7.04 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 7.03 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.96 (1H, d, *J* = 3.0

Hz, Ar**H**), 6.18 (1H, s, C(9)**H**), 5.15 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.13 (1H, d, *J* = 12.5 Hz, C(11)H**H'**), 3.81 (3H, s, C(24)**H_3**), 3.67 (1H, d, *J* = 10.0 Hz, C(22)**H**H'), 3.60 (1H, d, *J* = 10.0 Hz, C(22)H**H'**).

δ_C(151 MHz, $CDCl_3$): 174.5 (**C**(23)), 157.4 (**Ar**), 154.3 (**C**(10)), 138.1 (**Ar**), 135.6 (**Ar**), 133.9 (**Ar**), 130.5 (**Ar**), 129.8 (**Ar**), 128.6 (**Ar**), 128.3 (**Ar**), 128.1 (**Ar**), 128.0 (**Ar**), 127.4 (**Ar**), 127.2 (**Ar**), 125.6 (**Ar**), 123.7 (**Ar**), 117.6 (**Ar**), 111.5 (**Ar**), 79.8 (**C**(8)), 75.5 (**C**(7)), 72.5 (**C**(22)), 68.5 (**C**(11)), 61.7 (**C**(9)), 55.8 (**C**(24)).

m/z HRMS (ESI^+) found 540.0653; $C_{26}H_{23}NO_7{}^{79}Br^+$ ($M+H^+$) requires 540.0652.

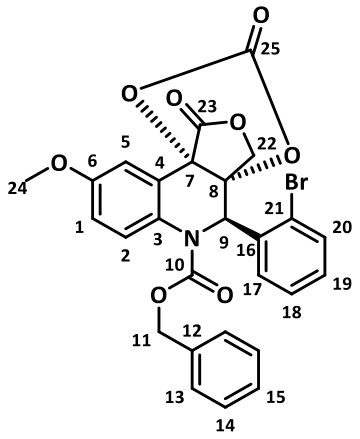
$[\alpha]_D^{25}$ = –65.0

A sample of the enantiomer, benzyl (3a*R*,4*S*,9b*R*)-4-(2-bromophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (**112**, 5.177 g, 9.568 mmol, 88%), was prepared as above using benzyl (*R*)-4-(2-bromophenyl)-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (**111**) as starting material.

$[\alpha]_D^{25}$ = +57.1 (*c* = 1.00, chloroform).

All other characterisation identical.

Benzyl (3a*S*,4*R*,9b*S*)-4-(2-bromophenyl)-8-methoxy-1,11-dioxo-1*H*,3*H*-3a,9b-(epoxymethanooxy)furo[3,4-c]quinoline-5(4*H*)-carboxylate (*ent*-123)



Prepared according to the procedure of Burk.[87]

To a solution of benzyl (3a*S*,4*R*,9b*S*)-4-(2-bromophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-112**, 1.56 g, 2.90 mmol, 1.0 eq.) in dichloromethane (30 mL) was added pyridine (1.4 mL, 17.4 mmol, 6.0 eq.). The solution was cooled to – 78 °C and a solution of triphosgene (430.7 mg, 1.45 mmol, 0.5 eq.) in dichloromethane (10 mL) was added dropwise. The cool bath was removed and the solution was allowed to warm to RT then stirred for a further 20 min. The reaction was cooled to 0 °C, quenched with sat. aq. ammonium chloride (10 mL) and the layers separated. The organic portion was washed sequentially with 2 M HCl and sat. aq. sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo* to give the title compound as a white solid (1.62 g, 2.86 mmol, 98%) which was used without further purification.

Compound ***ent*-123** *is unstable to flash column chromatography and decomposes upon exposure to silica. Characterisation data is given for the crude material.*

R_f: 0.6 (40% ethyl acetate in petroleum ether).

m.p.: 115.6 – 121.8 °C.

ν_{max}/cm^{-1} (thin film): 2926 (m), 1829 (s), 1797 (m), 1715 (m), 1503 (m), 1305 (m), 1256 (m), 1235 (m), 1209 (m), 1028 (m).

δ_H(500 MHz, $CDCl_3$): 7.67 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.64 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 7.38 – 7.27 (6H, m, 6 x Ar**H**), 7.18 (1H, td, *J* = 8.0, 1.5 Hz, Ar**H**), 7.12 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 7.08 (1H, td, *J* = 8.0, 1.5 Hz, Ar**H**),

6.80 (1H, s, C(9)**H**), 6.62 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 5.28 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.21 (1H, d, *J* = 12.5 Hz, C(11)H**H'**), 4.69 (1H, d, *J* = 11.5 Hz, C(22)**H**H'), 4.07 (1H, d, *J* = 11.5 Hz, C(22)H**H'**), 3.89 (3H, s, C(24)**H₃**).

δ_C(126 MHz, $CDCl_3$): δ_C(126 MHz, $CDCl_3$): 167.5 (**C**(23)), 157.5 (**Ar**), 153.9 (**C**(10)), 150.9 (**C**(25)), 135.3 (**Ar**), 134.7 (**Ar**), 134.3 (**Ar**), 131.3 (**Ar**), 131.0 (**Ar**), 128.8 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.1 (**Ar**), 127.5 (**Ar**), 127.4 (**Ar**), 125.1 (**Ar**), 119.7 (**Ar**), 119.6 (**Ar**), 112.9 (**Ar**), 88.9 (**C**(8)), 77.1 (**C**(7)), 71.8 (**C**(22)), 69.1 (**C**(11)), 60.7 (**C**(9)), 55.9 (**C**(24)).

m/z HRMS (ESI^+) found 590.0243; $C_{27}H_{20}NO_8{}^{81}BrNa^+$ ($M+Na^+$) requires 590.0247.

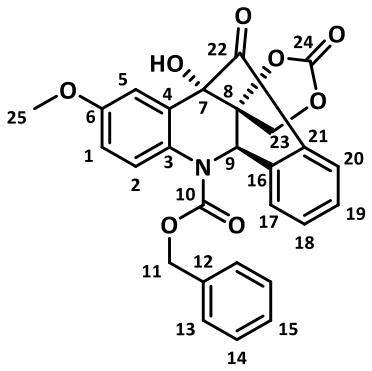
$[\alpha]_D^{25}$= –33.0

A sample of the enantiomer, benzyl (3a*R*,4*S*,9b*R*)-4-(2-bromophenyl)-8-methoxy-1,11-dioxo-1*H*,3*H*-3a,9b-(epoxymethanooxy)furo[3,4-c]quinoline-5(4*H*)-carboxylate (**123**, 4.948 g, 8.726 mmol, 91%), was prepared as above using benzyl (3a*R*,4*S*,9b*R*)-4-(2-bromophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**112**) as starting material.

$[\alpha]_D^{25}$ = +57.1

All other characterisation identical.

Benzyl (4*S*,6'*R*,12'*S*)-12'-hydroxy-2'-methoxy-2,11'-dioxo-11',12'-dihydrospiro[[1,3]dioxolane-4,13'-[6,12]methanodibenzo[*b*,*f*]azocine]-5'(6'*H*)-carboxylate (*ent*-124)



To a solution of benzyl (3a*S*,4*R*,9b*S*)-4-(2-bromophenyl)-8-methoxy-1,11-dioxo-1*H*,3*H*-3a,9b-(epoxymethanooxy)furo[3,4-c]quinoline-5(4*H*)-carboxylate (***ent*-123**, 49.2 mg, 0.09 mmol, 1.0 eq.) in tetrahydrofuran (2.0 mL) at –78 °C was added *n*-butyllithium (1.6 M in hexane, 65 µL, 0.10 mmol, 1.2 eq.). The cool bath was removed and the solution was allowed to warm to room temperature then stirred for a further 20 min. The reaction was cooled to 0 °C, quenched by dropwise addition of camphorsulfonic acid (1 M in tetrahydrofuran, 1 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (40% diethyl ether in pentane) to give the title compound as a pale yellow solid (17.9 mg, 0.04 mmol, 42%).

R_f: 0.3 (40% ethyl acetate in petroleum ether)

m.p.: 64.5 – 67.2 °C.

ν_{max}/cm^{-1} (thin film): 3444 (br, m), 1813 (s), 1697 (s), 1601 (m), 1498 (s), 1391 (m), 1298 (s), 1278 (s), 1238 (s), 1094 (m), 1068 (m), 732 (m).

δ_H(500 MHz, DMSO): 7.84 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.79 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.69 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 7.58 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.54 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 7.51 – 7.48 (2H, m, 2 x Ar**H**), 7.44 (1H, s, C(7)O**H**), 7.44 – 7.39 (2H, m, 2 x Ar**H**), 7.39 – 7.34 (1H, m, Ar**H**), 7.07 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.83 (1H, dd, *J* = 9.5, 3.0 Hz, Ar**H**), 6.60 (1H, s, C(9)**H**), 5.43 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.37 (1H, d,

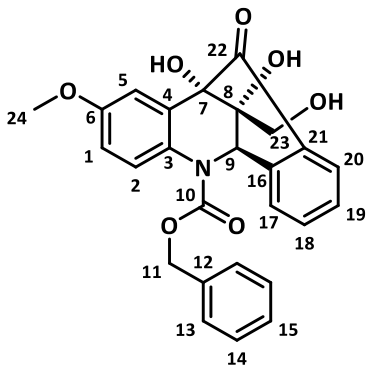
J = 12.5 Hz, C(11)H**H'**), 4.45 (1H, d, *J* = 8.5 Hz, C(23)**H**H'), 4.21 (1H, d, *J* = 8.5 Hz, C(23)H**H'**), 3.69 (3H, s, C(25)$\mathbf{H_3}$).

δ_C(126 MHz, DMSO, 24 resonances out of 25 observed, 1 x Ar resonance not observed): 192.3 (**C**(22)), 155.9 (**Ar**), 153.6 (**C**(10)), 153.1 (**C**(24)), 136.0 (**Ar**), 135.8 (**Ar**), 130.9 (**Ar**), 130.3 (**Ar**), 129.5 (**Ar**), 128.5 (**Ar**), 128.1 (**Ar**), 127.6 (**Ar**), 126.8 (**Ar**), 126.7 (**Ar**), 126.1 (**Ar**), 124.2 (**Ar**), 115.5 (**Ar**), 110.6 (**Ar**), 78.3 (**C**(7)), 77.9 (**C**(8)), 68.0 (**C**(23)), 67.9 (**C**(11)), 58.2 (**C**(9)), 55.3 (**C**(25)).

m/z HRMS (ESI^+) found 510.1161; $C_{27}H_{21}NO_8Na^+$ ($M+Na^+$) requires 510.1159.

$[\alpha]_D^{25}$ = –258.0

Benzyl (6*R*,12*S*,13*S*)-12,13-dihydroxy-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-125)



To a solution of benzyl (3a*S*,4*R*,9b*S*)-4-(2-bromophenyl)-8-methoxy-1,11-dioxo-1*H*,3*H*-3a,9b-(epoxymethanooxy)furo[3,4-c]quinoline-5(4*H*)-carboxylate (***ent*-123**, 3.281 g, 5.81 mmol, 1.0 eq.) in tetrahydrofuran (120 mL) at –78 °C was added *n*-butyllithium (1.6 M in hexane, 4.4 mL, 6.97 mmol, 1.2 eq.). The cool bath was removed and the solution was allowed to warm to room temperature then stirred for a further 20 min. The reaction was cooled to 0 °C and quenched by dropwise addition of water (20 mL). Aqueous sodium hydroxide (0.5 M, 80 mL) was added and the resultant solution was stirred at RT for 90 min then extracted with ethyl acetate (x 5) *[Note: multiple extractions required to ensure full extraction of polar triol]*. The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% to 60% ethyl acetate in pentane) to give the title compound as a pale yellow solid (2.080 g, 4.51 mmol, 78%).

R_f: 0.1 (40% ethyl acetate in petroleum ether).

m.p.: 207 – 210 °C.

ν_{max}/cm^{-1} (thin film): 3447 (br, m), 1692 (s), 1602 (m), 1497 (m), 1457 (m), 1393 (m), 1278 (s), 1175 (m), 1142 (m), 1019 (m), 909 (m), 731 (m).

δ_H(500 MHz, DMSO): 7.73 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.65 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.58 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.54 – 7.49 (3H, m, 3 x Ar**H**), 7.46 – 7.33 (4H, m, 4 x Ar**H**), 7.03 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.72 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.17 (1H, s, C(7)O**H**), 6.05 (1H, s, C(9)**H**), 5.35 (1H, d, *J*=12.5 Hz, C(11)**H**H'), 5.35 (1H, d,

J = 12.5 Hz, C(11)H**H'**), 5.29 (1H, s, C(8)O**H**), 4.84 (1H, dd, *J* = 6.0, 4.5 Hz, C(23)O**H**), 3.69 (1H, dd, *J* = 11.5, 4.5 Hz, C(23)**H**H'), 3.67 (3H, s, C(24)**H_3**), 3.15 (1H, dd, *J* = 11.5, 6.0 Hz, C(23)H**H'**).

δ_C(126 MHz, DMSO): 194.6 (**C**(22)), 155.3 (**Ar**), 154.2 (**C**(10)), 138.4 (**Ar**), 136.4 (**Ar**), 134.8 (**Ar**), 130.6 (**Ar**), 130.0 (**Ar**), 128.8 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 128.0 (**Ar**), 128.0 (**Ar**), 127.7(**Ar**), 125.7 (**Ar**), 123.8 (**Ar**), 114.1 (**Ar**), 111.0 (**Ar**), 79.5 (**C**(7)), 70.0 (**C**(8)), 67.3 (**C**(11)), 62.4 (**C**(23)), 58.3 (**C**(9)), 55.2 (**C**(24)).

m/z HRMS (ESI^+) found 462.1546; $C_{26}H_{24}NO_7^+$ ($M+H^+$) requires 462.1547.

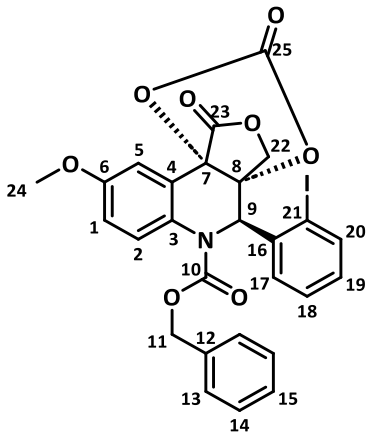
$[\alpha]_D^{25}$ = –233.0

A sample of the enantiomer, benzyl (6*S*,12*R*,13*R*)-12,13-dihydroxy-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**125**, 2.462 g, 5.339 mmol, 61%), was prepared as above using benzyl (3a*R*,4*S*,9b*R*)-4-(2-bromophenyl)-8-methoxy-1,11-dioxo-1*H*,3*H*-3a,9b-(epoxymethanooxy)furo[3,4-c]quinoline-5(4*H*)-carboxylate (**123**) as starting material.

$[\alpha]_D^{25}$ = +330.6

All other characterisation identical.

Benzyl (3a*S*,4*R*,9b*S*)-4-(2-iodophenyl)-8-methoxy-1,11-dioxo-1*H*,3*H*-3a,9b-(epoxymethanooxy)furo[3,4-c]quinoline-5(4*H*)-carboxylate (*ent*-128)



Prepared according to the procedure of Burk.[87]

To a solution of benzyl (3a*S*,4*R*,9b*S*)-3a,9b-dihydroxy-4-(2-iodophenyl)-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (***ent*-97**, 239.8 mg, 0.408 mmol, 1.0 eq.) in dichloromethane (5.0 mL) was added pyridine (0.20 mL, 2.448 mmol, 6 eq.). The solution was cooled to –78 °C and a solution of triphosgene (60.5 mg, 0.204 mmol, 0.5 eq.) in dichloromethane (2.5 mL) was added dropwise. The cool bath was removed and the solution was allowed to warm to RT then stirred for a further 20 min. The reaction was cooled to 0 °C, quenched with sat. aq. ammonium chloride (5 mL) and the layers were separated. The organic portion was washed sequentially with 2 M HCl and sat. aq. sodium bicarbonate, dried over sodium sulfate and concentrated *in vacuo* to give the title compound as a white solid (218.3 g, 0.351 mmol, 87%) which was used without further purification.

*Compound **ent*-128** is unstable to flash column chromatography and decomposes upon exposure to silica. Characterisation data is given for the crude material.*

R_f: 0.6 (40% ethyl acetate in petroleum ether).

m.p.: 81.0 – 84.4 °C.

ν_{max}/cm^{-1} (thin film): 2962 (br, m), 1829 (s), 1797 (m), 1714 (m), 1503 (m), 1305 (m), 1234 (m), 1026 (m).

δ_H(600 MHz, $CDCl_3$): 7.93 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.67 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.65 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.39 – 7.28 (5H, m, 5 x Ar**H**), 7.13 – 7.08 (2H, m, 2 x Ar**H**), 7.00 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 6.61 (1H, s,

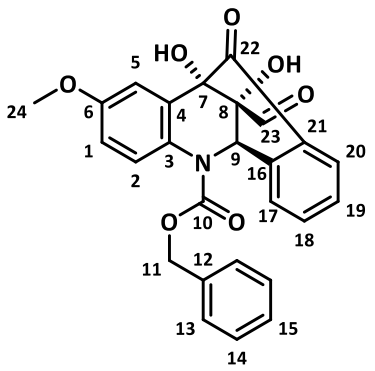
C(9)**H**), 6.56 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 5.28 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.21 (1H, d, *J* = 12.0 Hz, C(11)H**H'**), 4.69 (1H, d, *J* = 11.5 Hz, C(22)**H**H'), 4.09 (1H, d, *J* = 11.5 Hz, C(22)H**H'**), 3.89 (3H, s, C(24)$\mathbf{H_3}$).

δ_C(151 MHz, $CDCl_3$,): 168.1 (**C**(23)), 158.1 (**Ar**), 154.5 (**C**(10)), 151.5 (**C**(25)), 141.9 (**Ar**), 138.4 (**Ar**), 135.9 (**Ar**), 132.0 (**Ar**), 131.7 (**Ar**), 130.2 (**Ar**), 129.4 (**Ar**), 129.3 (**Ar**), 129.0 (**Ar**), 128.1 (**Ar**), 127.5 (**Ar**), 120.4 (**Ar**), 120.2 (**Ar**), 113.5 (**Ar**), 102.1 (**Ar**), 89.3 (**C**(8)), 77.1 (**C**(7)), 72.7 (**C**(22)), 69.8 (**C**(11)), 66.4 (**C**(9)), 56.6 (**C**(24)).

m/z HRMS (ESI^+) found 636.0125; $C_{27}H_{20}INO_8Na^+$ ($M+Na^+$) requires 636.0126.

$[\alpha]_D^{25}$ = –12.9

Benzyl (6*R*,12*S*,13*R*)-13-formyl-12,13-dihydroxy-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-129)



Prepared according to the procedure of More.[92]

A suspension of benzyl (6*R*,12*S*,13*S*)-12,13-dihydroxy-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-125**, 31.0 mg, 0.067 mmol, 1.0 eq.) in ethyl acetate (1 mL) in a microwave vial was heated to 40 °C and stirred for 15 min until the starting material was fully dissolved. 2-Iodoxybenzoic acid (56.5 mg, 0.202 mmol, 3.0 eq.) was added, the microwave vial was sealed and the reaction mixture was heated to 80 °C. After 3.5 h, the reaction mixture was cooled to RT and diluted with ethyl acetate, resulting in the precipitation of a white solid. The mixture was filtered through Celite™ and washed with ethyl acetate. The filtrate was dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% to 40% ethyl acetate in pentane) to give the title compound as a white solid (14.3 mg, 0.031 mmol, 46%).

R_f: 0.3 (50% ethyl acetate in petroleum ether).

m.p.: 120 °C decomposed.

ν_{max}/cm^{-1} (thin film): 3425 (br, m), 1727 (m), 1698 (s), 1498 (s), 1393 (m), 1277 (s), 1239 (m), 1174 (m).

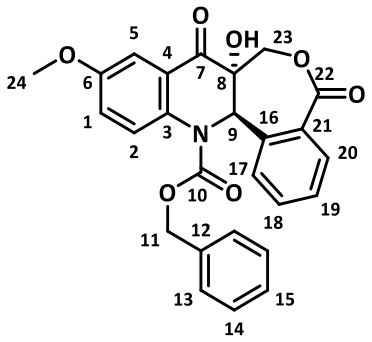
δ_H(500 MHz, $CDCl_3$): 9.60 (1H, s, C(23)**H**), 7.97 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.64 – 7.52 (3H, m, 3 x Ar**H**), 7.49 – 7.32 (6H, m, 6 x Ar**H**), 6.91 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.76 (1H, dd, *J* = 9.1, 3.0 Hz, Ar**H**), 6.15 (1H, s, C(9)**H**), 5.41 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.38 (1H, d, *J*=12.5 Hz, C(11)H**H'**), 4.68 (1H, s), 3.75 (3H, s, C(24)**H_3**), 3.64 (1H, s).

δ_C(126 MHz, $CDCl_3$): 199.0 (**C**(23)), 193.4 (**C**(22)), 156.8 (**Ar**), 154.9 (**C**(10)), 136.1 (**Ar**), 135.8 (**Ar**), 135.7 (**Ar**), 130.5 (**Ar**), 130.3 (**Ar**), 129.9 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 128.2 (**Ar**), 127.7 (**Ar**), 127.3 (**Ar**), 125.8 (**Ar**), 125.4 (**Ar**), 116.5 (**Ar**), 110.0 (**Ar**), 77.8 (**C**(7)), 76.5 (**C**(8)), 68.8 (**C**(11)), 57.1 (**C**(9)), 55.7 (**C**(24)).

m/z HRMS (ESI^+) found 460.1392; $C_{26}H_{22}NO_7^+$ ($M+H^+$) requires 460.1391.

$[\alpha]_D^{25}$–80.6

Benzyl (7a*S*,13a*R*)-7a-hydroxy-10-methoxy-5,8-dioxo-5,7a,8,13a-tetrahydrobenzo[5,6]oxepino[4,3-*b*]quinoline-13(7*H*)-carboxylate (*ent*-130)



Isolated as a side-product during the preparation of aldehyde ***ent*-129** *according to the procedure of More.*[92]

To a solution of benzyl (6*R*,12*S*,13*S*)-12,13-dihydroxy-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-125**, 40.0 mg, 0.087 mmol, 1.0 eq.) in dichloromethane (1 mL) at RT was added (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (1.4 mg, 0.009 mmol, 0.1 eq.) followed by (diacetoxyiodo)benzene (30.8 mg, 0.096 mmol, 1.1 eq.). The resultant solution was stirred for 2 h at RT then quenched with sat. aq. sodium sulfite (2 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% to 40% ethyl acetate in pentane) to give the title compound as a pale yellow oil (13.1 mg, 0.029 mmol, 33%).

R_f: 0.7 (50% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 3411 (br, m), 1717 (s), 1682 (s), 1494 (s), 1307 (s), 1227 (m), 1210 (m), 1023 (m), 732 (m).

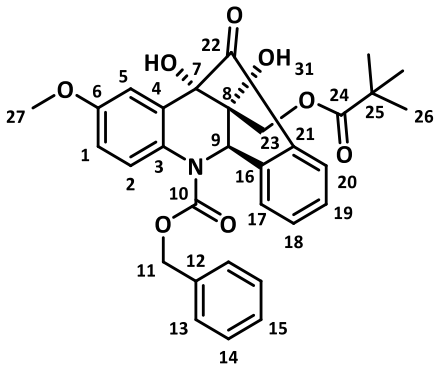
δ_H(500 MHz, $CDCl_3$): 8.06 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.79 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.38 (1H, ddd, *J* = 8.0, 7.5, 1.0 Hz, Ar**H**), 7.35 – 7.21 (8H, m, 8 x Ar**H**), 6.97 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 6.22 (1H, s, C(9)**H**), 5.28 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.20 (1H, d, *J* = 12.5 Hz, C(11)H**H'**), 4.64 (1H, d, *J* = 14.0 Hz, C(23)**H**H'), 4.24 (1H, d, *J* = 14.0 Hz, C(23)H**H'**), 3.82 (3H, s, C(24)**H₃**), 3.62 (1H, s, C(8)O**H**).

δ_C(126 MHz, $CDCl_3$): 190.2 (**C**(7)), 170.1 (**C**(22)), 156.5 (**Ar**), 154.8 (**C**(10)), 136.6 (**Ar**), 135.3 (**Ar**), 134.1 (**Ar**), 133.0 (**Ar**), 131.8 (**Ar**), 129.5 (**Ar**), 129.1 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 125.6 (**Ar**), 125.4 (**Ar**), 125.1 (**Ar**), 123.0 (**Ar**), 109.1 (**Ar**), 76.7 (**C**(8)), 71.9 (**C**(23)), 68.9 (**C**(11)), 63.1 (**C**(9)), 55.8 (**C**(24)).

m/z HRMS (ESI^+) found 460.1391; $C_{26}H_{22}NO_7^+$ ($M+H^+$) requires 460.1391.

$[\alpha]_D^{25}$ = –242.0

Benzyl (6*R*,12*S*,13*S*)-12,13-dihydroxy-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-134)



Prepared according to the procedure of Nicolaou.[139]

To a solution of benzyl (6*R*,12*S*,13*S*)-12,13-dihydroxy-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-125**, 2.064 g, 4.48 mmol, 1.0 eq.) in dichloromethane (35 mL) and pyridine (35 mL) at 0°C was added dropwise pivaloyl chloride (2.2 mL, 17.92 mmol, 4.0 eq.). The reaction mixture was warmed to RT, stirred for 3 h, concentrated *in vacuo* and purified by flash column chromatography (30% ethyl acetate in pentane) to give the title compound as a white solid (2.325 g, 4.265 mmol, 95%).

R_f: 0.6 (50% ethyl acetate in petroleum ether).

m.p.: 180.2 – 181.7 °C.

ν_{max}/cm^{-1} (thin film): 3448 (br, m), 1729 (s), 1695 (s), 1498 (m), 1395 (m), 1282 (s), 1145 (m), 1020 (m).

δ_H(600 MHz, DMSO): 7.78 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.68 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.58 – 7.50 (3H, m, 3 x Ar**H**), 7.48 – 7.40 (3H, m, 3 x Ar**H**), 7.40 – 7.34 (2H, m, 2 x Ar**H**), 7.06 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.76 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.59 (1H, s, C(7)O**H**), 6.04 (1H, s, C(9)**H**), 5.93 (1H, s, C(8)O**H**), 5.33 (1H, d, *J* = 13.0 Hz, C(11)**H**H'), 5.30 (1H, d, *J* = 13.0 Hz, C(11)H**H'**), 4.27 (1H, d, *J* = 12.5 Hz, C(23)**H**H'), 3.71 (1H, d, *J* = 12.5 Hz, C(23)H**H'**), 3.68 (3H, s, C(27)**H₃**), 0.89 (9H, s, 3 x C(26)**H₃**).

δ_C(151 MHz, DMSO, 26 resonances out of 27 observed, 1 x Ar resonance not observed): 194.2 (**C**(22)), 176.9 (**C**(24)), 155.5 (**Ar**), 153.9 (**C**(10)), 137.9 (**Ar**), 136.1 (**Ar**), 135.2 (**Ar**), 130.2 (**Ar**), 129. (**Ar**)7, 129.2 (**Ar**), 128.5 (**Ar**), 128.1 (**Ar**), 128.1 (**Ar**), 128.0 (**Ar**), 127.7 (**Ar**), 126.3 (**Ar**), 114.4 (**Ar**), 110.9 (**Ar**), 79.6 (**C**(7)), 68.9 (**C**(8)), 67.6 (**C**(11)), 65.1 (**C**(23)), 58.1 (**C**(9)), 55.2 (**C**(27)), 38.1 (**C**(25)), 26.5 (**C**(26)).

m/z HRMS (ESI^+) found 568.1941; $C_{31}H_{31}NO_8Na^+$ ($M+Na^+$) requires 568.1942.

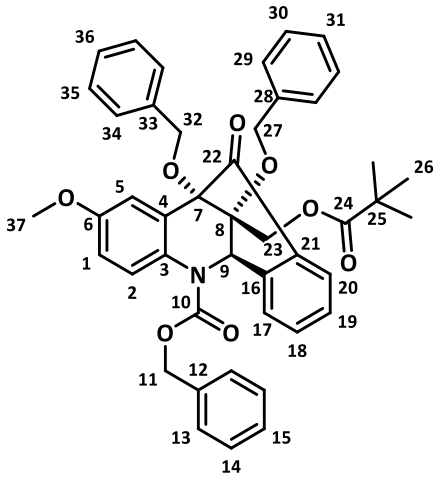
$[\alpha]_D^{25}$ = –332.0

A sample of the enantiomer, benzyl (6*S*,12*R*,13*R*)-12,13-dihydroxy-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**134**, 2.693 g, 4.93 mmol, 92%), was prepared as above using benzyl (6*S*,12*R*,13*R*)-12,13-dihydroxy-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**125**) as starting material.

$[\alpha]_D^{25}$ = +296.3

All other characterisation identical.

Benzyl (6*R*,12*S*,13*S*)-12,13-bis(benzyloxy)-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-136)



To a solution of benzyl (6*R*,12*S*,13*S*)-12,13-dihydroxy-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-134**, 2.325 g, 4.265 mmol, 1.0 eq.) in dimethylformamide (60 mL) at 0 °C was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 34 mL, 17.00 mmol, 4.0 eq.). The reaction mixture was stirred at 0 °C for 10 min then tetrabutylammonium iodide (1.58 g, 4.265 mmol, 1.0 eq.) and benzyl bromide (5.1 mL, 42.65 mmol, 10 eq.) were added. The reaction mixture was warmed to RT and stirred for 78 h. The reaction was then cooled to 0 °C, quenched with sat. aq. ammonium chloride (20 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 30% ethyl acetate in pentane) to give the title compound as a white solid (2.292 g, 3.16 mmol, 74%).

R_f: 0.7 (30% ethyl acetate in petroleum ether).

m.p.: 71.2 – 75.9 °C.

ν_{max}/cm^{-1} (thin film): 1735 (m), 1706 (s), 1497 (s), 1274 (s), 1142 (s), 1020 (m), 736 (m), 697 (m).

δ_H(600 MHz, $CDCl_3$): 8.00 (1H, d, *J* = 8.0 Hz), 7.68 – 7.56 (2H, m), 7.50 – 7.39 (3H, m), 7.39 – 7.31 (7H, m), 7.31 – 7.21 (5H, m), 7.21 – 7.13 (2H, m), 6.96 (1H, d, *J* = 3.0 Hz), 6.74 (1H, s), 6.66 (1H, br s, C(9)**H**), 5.25 (1H, d, *J* = 11.5 Hz, C(11)**H**H'), 5.03 (1H, d, 13.0 Hz, C(32)**H**H'), 4.88 (1H, d, *J* = 13.0 Hz, C(32)H**H'**), 4.85 (1H, br s, C(11)H**H'**), 4.83 (1H, br s, C(27)**H**H'), 4.71 (1H, d, *J* = 13.5 Hz, C(23)**H**H'), 4.59 (1H, br s, C(27)H**H'**), 4.25 (1H, d, *J* = 13.5 Hz, C(23)H**H'**), 3.49 (3H, s, C(37)$\mathbf{H_3}$), 1.10 (9H, s, 3 x C(26)$\mathbf{H_3}$)).

δ_C(151 MHz, $CDCl_3$, 35 resonances out of 37 observed, C(10) and 1 x Ar resonance not observed): 190.5 (**C**(22)), 176.9 (**C**(24)), 156.5 (**Ar**), 140.1 (**Ar**), 137.8 (**Ar**), 136.3 (**Ar**), 135.5 (**Ar**), 134.8 (**Ar**), 131.0 (**Ar**), 129.9 (**Ar**), 129.6 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 127.6 (**Ar**), 127.1 (**Ar**), 127.0 (**Ar**), 126.3 (**Ar**), 123.4 (**Ar**), 117.1 (**Ar**), 109.8 (**Ar**), 85.7 (**C**(7)), 76.3 (**C**(8)), 69.7 (**C**(32)), 68.8 (**C**(11)), 66.2 (**C**(27)), 65.5 (**C**(23)), 55.3 (**C**(37)), 55.2 (**C**(9)), 38.8 (**C**(25)), 27.1 (**C**(26)).

m/z HRMS (ESI^+) found 726.3060; $C_{45}H_{44}NO_8^+$ ($M+H^+$) requires 726.3061.

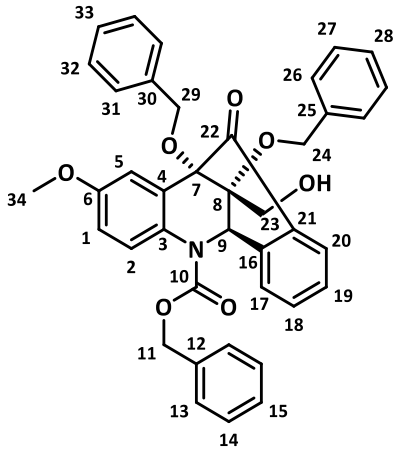
$[\alpha]_D^{25}$ = –204.0

A sample of the enantiomer, benzyl (6*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b,f*]azocine-5(6*H*)-carboxylate (**136**, 2.142 g, 2.953 mmol, 81%), was prepared as above using benzyl (6*S*,12*R*,13*R*)-12,13-dihydroxy-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b,f*]azocine-5(6*H*)-carboxylate (**134**) as starting material.

$[\alpha]_D^{25}$ = +182.6

All other characterisation identical.

Benzyl (6*R*,12*S*,13*S*)-12,13-bis(benzyloxy)-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-137)



Prepared according to the procedure of Khirsariya.[99]

Sodium hydride (60% in mineral oil, 1.840 g, 45.97 mmol, 15.0 eq.) was added portion wise to methanol (75 mL) at 0 °C. The solution was warmed to RT and stirred for 5 min. Benzyl (6*R*,12*S*,13*S*)-12,13-bis(benzyloxy)-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*] azocine-5(6*H*)-carboxylate (**136**, 2.223 g, 3.06 mmol, 1.0 eq.) was added as a single solid portion and the resultant reaction mixture was stirred at RT for 18 h *[Note: the starting material takes around 5 min to fully dissolve]*. The reaction was cooled to 0 °C, quenched with sat. aq. ammonium chloride (40 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% ethyl acetate in pentane) to give the title compound as a white solid (1.934 g, 3.016 mmol, 98%).

*Compound **ent-137** exists as a 2 : 1 inseparable mixture of the primary alcohol (shown) and the corresponding lactol. NMR data is given for the primary alcohol form only, taken from the NMR spectra of the mixture.*

R_f: 0.6 (30% ethyl acetate in petroleum ether).

m.p.: 76.0 – 78.3 °C.

ν_{max}/cm^{-1} (thin film): 2980 (m), 2887 (m), 2361 (m), 2340 (m), 1698 (m), 1686 (m), 1498 (m), 1457 (m), 1393 (m), 1268 (m), 1230 (m), 1147 (m), 953 (m), 630 (m).

δ_H(600 MHz, $CDCl_3$): 7.81 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.72 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 7.68 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.62 – 7.07 (17H, m, 17 x Ar**H**), 6.78 – 6.73 (2H, m, 2 x Ar**H**), 6.61 (1H, s, C(9)**H**), 5.28 (1H, d, *J* = 11.5 Hz, C(11)**H**H'), 5.27 (1H, t, *J* = 4.0 Hz, C(23)O**H**), 5.16 (1H, br s, C(11)H**H'**), 4.99 (1H, d, *J* = 13.0 Hz, C(29)**H**H'), 4.88 (1H, d, *J* = 11.0 Hz, C(24)**H**H'), 4.68 (1H, d, *J* = 11.0 Hz, C(24)H**H'**), 4.59 (1H, d, *J* = 13.0 Hz, C(29)H**H'**), 4.30 (1H, dd, *J* = 13.0, 4.0 Hz, C(23)**H**H'), 3.52 (1H, dd, *J* = 13.0, 4.0 Hz, C(23)H**H'**), 3.46 (3H, s, C(34)**H_3**).

δ_C(151 MHz, DMSO): 190.5 (**C**(22)), 155.5 (**Ar**), 153.9 (**C**(10)), 139.6 (**Ar**), 138.2 (**Ar**), 137.1 (**Ar**), 135.0 (**Ar**), 131.2 (**Ar**), 130.4 (**Ar**), 130.2 (**Ar**), 129.2 (**Ar**), 129.0 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.2(**Ar**), 128.1 (**Ar**) , 127.9 (**Ar**), 127.4 (**Ar**), 127.0 (**Ar**), 126.8(**Ar**), 126.4 (**Ar**) , 126.3 (**Ar**), 123.8 (**Ar**), 115.3 (**Ar**), 110.1 (**Ar**), 84.8 (**C**(7)), 76.4 (**C**(8)), 68.5 (**C**(29)), 67.9 (**C**(11)), 65.8 (**C**(24)), 62.0 (**C**(23)), 54.9 (**C**(34)), 54.8 (**C**(9)).

m/z HRMS (ESI^+) found 664.2302; $C_{40}H_{35}NO_7^+$ ($M+Na^+$) requires 664.2306.

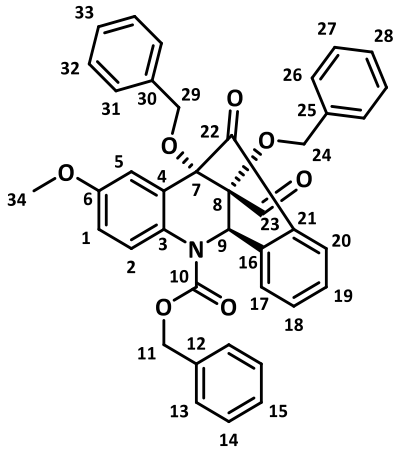
$[\alpha]_D^{25}$ = –117.5

A sample of the enantiomer, benzyl (6*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b,f*]azocine-5(6*H*)-carboxylate (**137**, 1.723 g, 2.687 mmol, 91%), was prepared as above using benzyl (6*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-2-methoxy-11-oxo-13-((pivaloyloxy)methyl)-11,12-dihydro-6,12-methanodibenzo[*b,f*]azocine-5(6*H*)-carboxylate (**136**) as starting material.

$[\alpha]_D^{25}$ = +104.2

All other characterisation identical.

Benzyl (6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-formyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-139)



Prepared according to the procedure of Davies.[140]

To a solution of benzyl (6*R*,12*S*,13*S*)-12,13-bis(benzyloxy)-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-137**, 1.899 g, 2.961 mmol, 1.0 eq.) in dichloromethane (60 mL) at 0 °C was added sodium bicarbonate (2.239 g, 26.650 mmol, 9.0 eq.) followed by Dess-Martin periodinane (3.766 g, 8.880 mmol, 3.0 eq.). The resultant solution was allowed to warm to RT and was stirred for 45 min then diluted with dichloromethane (50 mL) and quenched with sat. aq. sodium bicarbonate (50 mL). Sodium thiosulfate pentahydrate (8 g) was added and the biphasic mixture was stirred vigorously for 10 min. The layers were separated and the aqueous layer was extracted with dichloromethane (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% ethyl acetate in pentane) to give the title compound as a white solid (1.851 g, 2.895 mmol, 98%).

R_f: 0.1 (20% ethyl acetate in petroleum ether).

m.p.: 87.2 – 90.4 °C.

ν_{max}/cm^{-1} (thin film): 3434 (br, m), 1702 (s), 1498 (s), 1455 (m), 1390 (m), 1270 (s), 1232 (s), 1132 (m), 1018 (s), 732 (s).

δ_H(600 MHz, $CDCl_3$): 10.00 (1H, s, C(23)**H**), 7.91 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.65 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.58 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.44 (2H, m, 2 x Ar**H**), 7.42 – 7.30 (8H, m, 8 x Ar**H**), 7.26 – 7.22 (5H, m, 5 x Ar**H**), 7.16 – 7.08 (2H, m, 2 x Ar**H**), 6.95 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.73 (1H, d, *J* = 9.0 Hz, Ar**H**), 6.55 (1H, s, C(9)**H**), 5.28

(1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.21 – 5.06 (2H, m, C(11)H**H'**, C(29)**H**H'), 4.86 (1H, d, *J* = 13.1 Hz, C(29)H**H'**), 4.69 (1H, d, *J* = 10.5 Hz, C(24)**H**H'), 4.51 (1H, d, *J* = 10.5 Hz, C(24)H**H'**), 3.49 (3H, s, C(34)$\mathbf{H_3}$).

δ_C(151 MHz, $CDCl_3$, 33 resonances out of 34 observed, 1 x Ar resonance not observed): 199.3 (**C**(23)), 190.0 (**C**(22)), 156.6 (**Ar**), 154.3 (**C**(10)), 139.7 (**Ar**), 136.9 (**Ar**), 136.7 (**Ar**), 135.5 (**Ar**), 135.1 (**Ar**), 131.3 (**Ar**), 129.9 (**Ar**), 129.5 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.1 (**Ar**), 127.5 (**Ar**), 127.4 (**Ar**), 127.2 (**Ar**), 126.5 (**Ar**), 125.3 (**Ar**), 123.4 (**Ar**), 117.3 (**Ar**), 109.9 (**Ar**), 84.6 (**C**(7)), 80.1 (**C**(8)), 70.2 (**C**(29)), 68.9 (**C**(11)), 67.4 (**C**(24)), 55.4 (**C**(34)), 54.9 (**C**(9)).

m/z HRMS (ESI^+) found 640.2325; $C_{40}H_{34}NO_7^+$ ($M+H^+$) requires 640.2330.

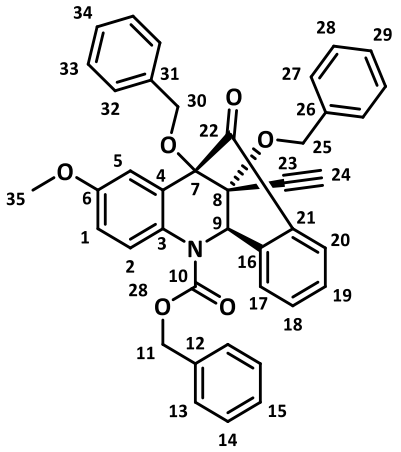
$[\alpha]_D^{25}$ = –188.0

A sample of the enantiomer, benzyl (6*S*,12*R*,13*S*)-12,13-bis(benzyloxy)-13-formyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**139**, 1.659 g, 2.595 mmol, 96%), was prepared as above using benzyl (6*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-13-(hydroxymethyl)-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[b,f]azocine-5(6*H*)-carboxylate (**137**) as starting material.

$[\alpha]_D^{25}$= +168.7

All other characterisation identical.

Benzyl (6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-142)



Prepared according to the procedure of Davies.[140]

To a solution of benzyl (6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-formyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-139**, 1.851 g, 2.895 mmol, 1.0 eq.) in methanol (35 mL) was added potassium carbonate (1.200 g, 8.690 mmol, 3.0 eq.). A solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (**141**, 1.11 g, 5.79 mmol, 2.0 eq.) in methanol (6 mL) was added dropwise to the reaction mixture at RT. The reaction was stirred at RT for 1 h then quenched with sat. aq. sodium bicarbonate (20 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 20% ethyl acetate in pentane) to give the title compound as a pale yellow solid (1.547 g, 2.436 mmol, 84%).

R_f: 0.3 (20% ethyl acetate in petroleum ether).

m.p.: 69.2 – 71.7 °C.

ν_{max}/cm^{-1} (thin film): 3285 (br, m), 2981 (m), 1702 (s), 1498 (s), 1454 (m), 1389 (m), 1269 (s), 1233 (m), 1173 (m), 1017 (m), 733 (m), 697 (m).

δ_H(600 MHz, $CDCl_3$): 7.97 (1H, dt, *J* = 8.0, 1.0 Hz, Ar**H**), 7.71 – 7.61 (1H, m, Ar**H**), 7.58 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.55 – 7.49 (2H, m, 2 x Ar**H**), 7.40 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.33 (7H, dd, *J*=15.0, 7.3 Hz, 7 x Ar**H**), 7.25 – 7.16 (7H, m, 7 x Ar**H**), 6.99 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.67 (1H, s, Ar**H**), 6.47 (1H, s, C(9)**H**), 5.29 – 4.99 (3H, m, C(25)**H**H', C(30)**H**H', C(25)H**H'**), 4.98 – 4.87 (2H, m, C(11)**H**H', C(30)H**H'**), 4.72 (1H, s, C(11)H**H'**), 3.50 (3H, s, C(35)$\mathbf{H_3}$), 2.64 (1H, s, C(24)**H**).

δ_C(151 MHz, $CDCl_3$, 33 resonances out of 35 observed, C(10) and 1 x Ar resonance not observed): 190.8 (**C**(22)), 156.7 (**Ar**), 139.9 (**Ar**), 137.4 (**Ar**), 136.7 (**Ar**), 135.6 (**Ar**), 134.5 (**Ar**), 131.8 (**Ar**), 130.2 (**Ar**), 129.4 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 127.6 (**Ar**), 127.5 (**Ar**), 127.0 (**Ar**), 126.8 (**Ar**), 124.1 (**Ar**), 116.8 (**Ar**), 110.3 (**Ar**), 85.7 (**C**(7)), 81.1 (**C**(24)), 78.8 (**C**(23)), 73.6 (**C**(8)), 69.7 (**C**(30)), 68.7 (**C**(25)), 67.8 (**C**(11)), 59.9 (**C**(9)), 55.4 (**C**(35)).

m/z HRMS (ESI^+) found 636.2377; $C_{41}H_{34}NO_6^+$ ($M+H^+$) requires 636.2381.

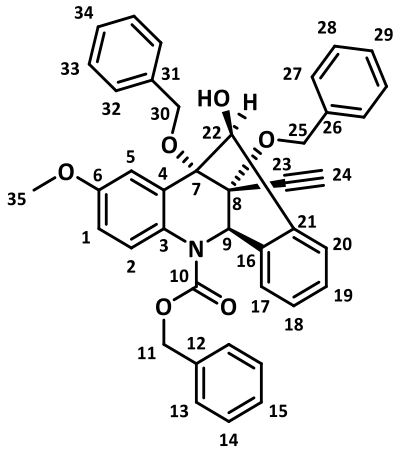
$[\alpha]_D^{25}$ = –345.0

A sample of the enantiomer, benzyl (6*S*,12*R*,13*S*)-12,13-bis(benzyloxy)-13-ethynyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**142**, 1.338 g, 2.106 mmol, 81%), was prepared as above using benzyl (6*S*,12*R*,13*S*)-12,13-bis(benzyloxy)-13-formyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**139**) as starting material.

$[\alpha]_D^{25}$ = +250.7

All other characterisation identical.

Benzyl (6*R*,11*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-11-hydroxy-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-144)



Prepared according to the procedure of Li.[105]

To a solution of benzyl (6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-142**, 500 mg, 0.787 mmol, 1.0 eq.) in tetrahydrofuran (12.0 mL) at 0 °C was added dropwise lithium borohydride solution (2 M in tetrahydrofuran, 2.0 mL, 4.00 mmol, 5.0 eq.). The reaction mixture was warmed to RT and stirred for 8 h then cooled to 0 °C and quenched by dropwise addition of sat. aq. ammonium chloride (10 mL). The reaction mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% ethyl acetate) to give the title compound as a white solid (457.7 mg, 0.718 mmol, 91%).

R_f: 0.2 (20% ethyl acetate in petroleum ether).

m.p.: 79.4 – 83.3 °C.

ν_{max}/cm^{-1} (thin film): 3460 (br, m), 2937 (br, m), 2360 (m), 1688 (s), 1497 (s), 1454 (m), 1316 (m), 1293 (s), 1253 (s), 1125 (m), 1101 (m), 1018 (s), 735 (m), 697 (s).

δ_H(600 MHz, DMSO): 7.55 – 7.31 (12H, m, 12 x Ar**H**), 7.31 – 7.21 (6H, m, 6 x Ar**H**), 7.09 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.09 – 7.04 (2H, m, 2 x Ar**H**), 6.73 – 6.62 (1H, m, Ar**H**), 6.14 (1H, s, C(9)**H**), 6.09 (1H, d, *J* = 6.5 Hz, C(22)O**H**), 5.40 (1H, d, *J* = 6.5 Hz, C(22)**H**), 5.24 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.13 (1H, br s, C(11)H**H'**), 4.94 (1H, d, *J* = 13.0 Hz, C(30)**H**H'), 4.88 (1H, d, *J* = 10.5 Hz, C(25)**H**H'), 4.64 (1H, d, *J* = 13.0 Hz, C(30)H**H'**), 4.52 (1H, d, *J* = 10.5 Hz, C(25)H**H'**), 3.92 (1H, s, C(24)**H**), 3.53 (3H, s, C(35)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO, 34 resonances out of 35 observed, 1 x Ar resonance not observed): 154.1 (**C**(10)), 139.9 (**Ar**), 138.9 (**Ar**), 137.2 (**Ar**), 135.8 (**Ar**), 131.5 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 127.7 (**Ar**), 127.5 (**Ar**), 126.9 (**Ar**), 126.8 (**Ar**), 126.3 (**Ar**), 126.3 (**Ar**), 124.7 (**Ar**), 115.6 (**Ar**), 113.3 (**Ar**), 82.1 (**C**(24)), 80.8 (**C**(7)), 78.9 (**C**(23)), 75.1 (**C**(8)), 74.7 (**C**(22)), 68.3 (**C**(30)), 67.8 (**C**(11)), 66.3 (**C**(25)), 59.9 (**C**(9)), 54.8 (**C**(35)).

m/z HRMS (ESI^+) found 660.2355; $C_{41}H_{35}NO_6Na^+$ ($M+Na^+$) requires 660.2368.

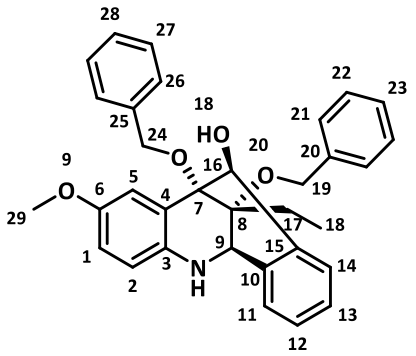
$[\alpha]_D^{25}$ = –18.0

A sample of the enantiomer, benzyl (6*S*,11*R*,12*S*,13*S*)-12,13-bis(benzyloxy)-13-ethynyl-11-hydroxy-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**144**, 433.7 g, 0.681 mmol, 86%), was prepared as above using benzyl (6S,12R,13S)-12,13-bis(benzyloxy)-13-ethynyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[b,f]azocine-5(6H)-carboxylate (**142**) as starting material.

$[\alpha]_D^{25}$ = +25.7 (*c* = 1.00, chloroform);

All other characterisation identical.

(6*R*,11*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-13-ethyl-2-methoxy-5,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-11-ol (*ent*-146)



Prepared according to the procedure of Li.[106]

To a solution of benzyl (6*R*,11*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-11-hydroxy-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-144**, 30.0 mg, 0.050 mmol, 1.0 eq.) in methanol (2 mL) was added palladium on carbon (5% wt. Pd, 10.6 mg, 0.005 mmol, 0.1 eq.). The resulting suspension was degassed with nitrogen for five min. A balloon of hydrogen was added and bubbled with an escape needle for 5 min before the escape needle was removed and the reaction mixture was stirred under positive hydrogen pressure for 4 h. The hydrogen balloon was removed and the suspension was degassed with nitrogen for five min then filtered through Celite™, washing with ethyl acetate. The filtrate was dried over sodium sulfate and concentrated *in vacuo* to give the title compound (15.2 mg, 0.03 mmol, 60%) which was characterised without further purification.

R_f: 0.5 (30% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 3390 (br, m), 1502 (s), 1452 (m), 1273 (m), 1207 (m), 1099 (m), 1056 (m), 1028 (m), 910 (s), 734 (s).

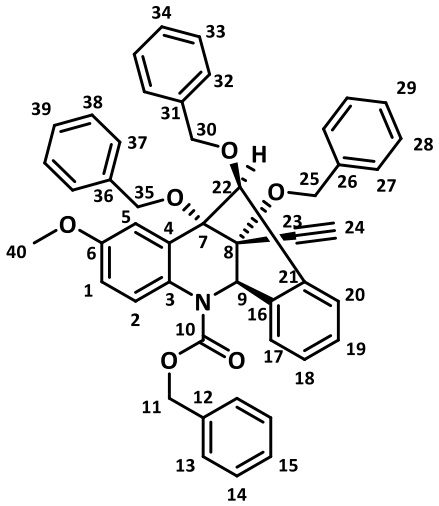
δ_H(500 MHz, DMSO): 7.46 – 7.14 (14H, m, 14 x Ar**H**), 6.86 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.49 (1H, dd, *J* = 8.5, 3.0 Hz, Ar**H**), 6.35 (1H, d, *J* = 8.5 Hz, Ar**H**), 5.81 (1H, d, *J* = 3.0 Hz, C(3)N**H**), 5.56 (1H, d, *J* = 6.5 Hz, C(16)O**H**), 5.04 (1H, d, *J* = 6.5 Hz, C(16)**H**), 4.91 (1H, d, *J* = 13.5 Hz, C(24)**H**H'), 4.89 (1H, d, *J* = 11.0 Hz, C(19)**H**H'), 4.63 (1H, d, *J* = 11.0 Hz, C(19)H**H'**), 4.53 (1H, d, *J* = 13.5 Hz, C(24)H**H'**), 4.50 (1H, d, *J* = 3.0 Hz, C(9)**H**), 3.37 (3H, s, C(29)$\mathbf{H_3}$), 1.96 (1H, dq, *J* = 15.0, 7.5 Hz, C(17)**H**H'), 1.61 (1H, dq, *J* = 15.0, 7.5 Hz, C(17)H**H'**), 1.22 (3H, t, *J* = 7.5 Hz, C(18)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO): 149.6 (**Ar**), 140.8 (**Ar**), 139.6 (**Ar**), 138.6 (**Ar**), 137.4 (**Ar**), 137.3 (**Ar**), 128.6 (**Ar**), 128.1 (**Ar**), 128.0 (**Ar**), 127.5 (**Ar**), 127.0 (**Ar**), 127.0 (**Ar**), 126.8 (**Ar**), 126.5 (**Ar**), 126.5 (**Ar**), 126.4 (**Ar**), 119.5 (**Ar**), 115.8 (**Ar**), 114.3 (**Ar**), 114.1 (**Ar**), 83.2 (**C**(7)), 76.4 (**C**(16)), 76.4 (**C**(8)), 67.5 (**C**(24)), 61.8 (**C**(19)), 57.6 (**C**(9)), 54.8 (**C**(29)), 24.1 (**C**(17)), 8.7 (**C**(18)).

m/z HRMS (ESI$^+$) found 508.2470; $C_{33}H_{34}NO_4^+$ (M+H$^+$) requires 508.2482.

$[\alpha]_D^{25}$ = +208.8

Benzyl (6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-13-ethynyl-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-147)



A solution of benzyl (6*R*,11*S*,12*R*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-11-hydroxy-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-144**, 280.5 mg, 0.440 mmol, 1.0 eq.) in dimethylformamide (9.5 mL) was cooled to 0 °C. Tetrabutylammonium iodide (162.5 mg, 0.440 mmol, 1.0 eq.) was added, followed by potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.97 mL, 0.484 mmol, 1.1 eq.) and then benzyl bromide (104 µL, 0.880 mmol, 2.0 eq.). The reaction was warmed to RT and stirred for 2 h then cooled to 0 °C and quenched by dropwise addition of sat. aq. ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% ethyl acetate in pentane) to give the title compound as a pale yellow solid (198.9 mg, 0.273 mmol, 62%).

R_f: 0.3 (10% ethyl acetate in petroleum ether)

m.p.: 64.0 – 67.4 °C

ν_{max}/cm^{-1} (thin film): 2952 (br, m), 1716 (m), 1689 (m), 1497 (m), 1453 (m), 1391 (m), 1250 (s), 1125 (m), 1102 (m), 1020 (m), 734 (s), 697 (m)

δ_H(600 MHz, DMSO): 7.50 – 7.20 (23H, m, 23 x Ar**H**), 7.17 – 7.06 (2H, m, 2 x Ar**H**), 6.94 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.64 (1H, dd, *J* = 9.5, 3.0 Hz, Ar**H**), 6.16 (1H, s, C(9)**H**), 5.36 (1H, s, C(22)**H**), 5.24 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.16 (1H, d, *J* = 10.5 Hz, C(30)**H**H'), 5.12 (1H, br s, C(11)H**H'**), 5.06 (1H, d, *J* = 10.5 Hz, C(30)H**H'**), 4.97 (1H, d,

J = 12.5 Hz, C(35)**H**H'), 4.93 (1H, d, *J* = 10.5 Hz, C(25)**H**H'), 4.58 (1H, d, *J* = 12.5 Hz, C(35)H**H'**), 4.53 (1H, d, *J* = 10.5 Hz, C(25)H**H'**), 3.99 (1H, s, C(24)**H**), 3.28 (3H, s, C(40)$\mathbf{H_3}$)

δ_C(151 MHz, DMSO, 37 resonances out of 40 observed, C(7) and 2 x Ar resonances not observed): 154.2 (**Ar**), 153.8 (**C**(10)), 139.5 (**Ar**), 138.1 (**Ar**), 137.0 (**Ar**), 136.9 (**Ar**), 135.7 (**Ar**), 131.4 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.4 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 127.6 (**Ar**), 127.2 (**Ar**), 127.0 (**Ar**), 126.9 (**Ar**), 124.1 (**Ar**), 114.7 (**Ar**), 114.2 (**Ar**), 83.7 (**C**(22)), 82.3 (**C**(23)), 78.4 (**C**(24)), 76.2 (**C**(30)), 75.2 (**C**(8)), 69.1 (**C**(35)), 67.9 (**C**(11)), 66.4 (**C**(25)), 59.6 (**C**(9)), 54.4 (**C**(40))

m/z HRMS (ESI$^+$) found 750.2825; $C_{48}H_{41}NO_6Na^+$ (M+Na$^+$) requires 750.2826

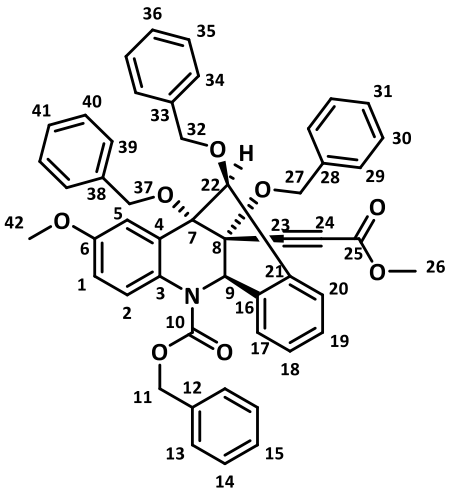
$[\alpha]_D^{25}$ = –56.2 (*c* = 1.00, chloroform)

A sample of the enantiomer, benzyl (6*S*,11*R*,12*S*,13*S*)-11,12,13-tris(benzyloxy)-13-ethynyl-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**147**, 319.9 mg, 0.440 mmol, 65%), was prepared as above using benzyl (6*S*,11*R*,12*S*,13*S*)-12,13-bis(benzyloxy)-13-ethynyl-11-hydroxy-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**144**) as starting material.

$[\alpha]_D^{25}$ = +64.6 (*c* = 1.00, chloroform);

All other characterisation identical.

Benzyl (6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-methoxy-13-(3-methoxy-3-oxoprop-1-yn-1-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-148)



Benzyl (6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-13-ethynyl-2-methoxy-11,12-dihydro-6,12-methano dibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-147**, 34.1 mg, 0.047 mmol, 1.0 eq.) was dissolved in tetrahydrofuran (1 mL) and cooled to –78 °C. Sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 56 µL, 0.056 mmol, 1.2 eq.) was added dropwise and reaction mixture was stirred at –78 °C for 15 min. Methyl chloroformate (11 µL, 0.141 mmol, 3.0 eq.) was added and the reaction was warmed to RT and stirred. After 2 h, the reaction was quenched by dropwise addition of sat. aq. ammonium chloride (1 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 20% ethyl acetate in pentane) to give the title compound as a pale yellow solid (21.4 mg, 0.027 mmol, 58%).

R_f: 0.2 (10% ethyl acetate in petroleum ether).

m.p.: 65.6 – 67.2 °C.

ν_{max}/cm^{-1} (thin film): 1717 (m), 1689 (m), 1497 (m), 1453 (m), 1390 (m), 1250 (s), 1125 (m), 1102 (m), 1020 (m), 735 (s), 698 (s).

δ_H(600 MHz, DMSO): 7.50 – 7.28 (20H, m, 20 x Ar**H**), 7.27 – 7.22 (3H, m, 3 x Ar**H**), 7.11 – 7.06 (2H, m, 2 x Ar**H**), 6.92 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.66 (1H, dd, *J* = 9.5, 3.0 Hz, Ar**H**), 6.28 (1H, s, C(9)**H**), 5.29 (1H, s, C(22)**H**), 5.24 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.15 (1H, d, *J* = 10.5 Hz, C(32)**H**H'), 5.13 (1H, br s, C(11)H**H'**), 5.08 (1H, d,

J = 10.5 Hz, C(32)H**H'**), 4.95 (1H, d, *J* = 12.5 Hz, C(37)**H**H'), 4.85 (1H, d, *J* = 10.5 Hz, C(27)**H**H'), 4.61 (1H, d, *J* = 12.5 Hz, C(37)H**H'**), 4.58 (1H, d, *J* = 10.5 Hz, C(27)H**H'**), 3.75 (3H, s, C(26)$\mathbf{H_3}$), 3.29 (3H, s, C(42)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO, 38 resonances out of 42 observed, 4 x Ar resonances not observed): 154.2 (**Ar**), 153.6 (**C**(10)), 152.3 (**C**(25)), 139.3 (**Ar**), 137.9 (**Ar**), 136.6 (**Ar**), 136.5 (**Ar**), 135.6 (**Ar**), 130.7 (**Ar**), 129.0 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 127.9 (**Ar**), 127.8 (**Ar**), 127.8 (**Ar**), 127.3 (**Ar**), 127.0 (**Ar**), 126.9 (**Ar**), 123.5 (**Ar**), 114.9 (**Ar**), 114.2 (**Ar**), 83.2 (**C**(22)), 82.6 (**C**(7)), 81.6 (**C**(23)), 81.2 (**C**(24)), 76.1 (**C**(32)), 75.6 (**C**(8)), 69.3 (**C**(37)), 68.0 (**C**(11)), 67.1 (**C**(27)), 58.8 (**C**(9)), 54.5 (**C**(42)), 53.4 (**C**(26)).

m/z HRMS (ESI$^+$) found 808.2882; $C_{50}H_{43}NO_8Na^+$ (M+Na$^+$) requires 808.2881.

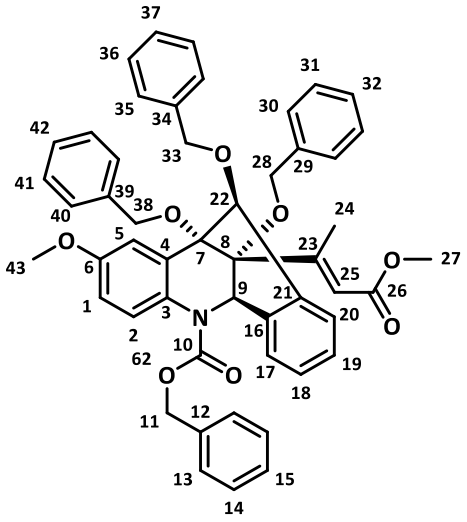
$[\alpha]_D^{25}$ = –49.2

A sample of the enantiomer, benzyl (6*S*,11*R*,12*S*,13*S*)-11,12,13-tris(benzyloxy)-2-methoxy-13-(3-methoxy-3-oxoprop-1-yn-1-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**148**, 240.4 mg, 0.306 mmol, 71%), was prepared as above using benzyl (6*S*,11*R*,12*S*,13*S*)-11,12,13-tris(benzyloxy)-13-ethynyl-2-methoxy-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**147**) as starting material.

$[\alpha]_D^{25}$ = +52.1

All other characterisation identical.

Benzyl (6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-methoxy-13-((E)-4-methoxy-4-oxobut-2-en-2-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (*ent*-151)



Copper(I) cyanide (12.6 mg, 0.078 mmol, 1.8 eq.) was suspended in freeze-pump-thaw degassed diethyl ether (1.6 mL) and cooled to 0 °C. Methyllithium solution (1.7 M in diethyl ether, 0.16 mL, 0.273 mmol, 3.5 eq.) was added dropwise, initially giving a bright yellow suspension which then dissipated over the course of the addition to give a light grey solution. The reaction mixture was cooled to –20 °C and a solution of benzyl (6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-methoxy-13-(3-methoxy-3-oxoprop-1-yn-1-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-148**, 61.5 mg, 0.078 mmol, 1.0 eq.) in diethyl ether (0.5 mL) was added dropwise, giving a pale yellow solution. The reaction was stirred at –20 °C for 14 h then warmed to 0 °C and quenched by dropwise addition of ammonium hydroxide (10% wt. in sat. aq. ammonium chloride, 5 mL). The resultant biphasic mixture was stirred vigorously at RT for 5 min then extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (5% to 12% ethyl acetate in pentane) to give the title compound as a colourless oil (28.7 mg, 0.036 mmol, 43%).

R_f: 0.4 (20% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 1721 (s), 1686 (s), 1499 (s), 1453 (m), 1303 (m), 1252 (m), 1211 (s), 1121 (s), 1025 (m), 736 (m), 697 (m).

δ_H(500 MHz, DMSO): 7.47 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.44 – 7.31 (12H, m, 12 x Ar**H**), 7.31 – 7.11 (12H, m, 12 x Ar**H**), 6.90 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.61 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.32 (1H, s, C(9)**H**), 5.60 (1H, s,

C(25)**H**), 5.24 (1H, d, *J* = 12.0 Hz, C(11)**H**H), 5.17 – 4.98 (2H, m, C(11)H**H'**, C(38)**H**H), 5.04 (1H, d, *J* = 10.5 Hz, C(33)**H**H), 4.95 (1H, d, *J* = 10.5 Hz, C(33)H**H'**), 4.56 (1H, s, C(22)**H**), 4.48 (1H, d, *J* = 12.0 Hz, C(38)H**H'**), 4.46 (1H, d, *J* = 11.0 Hz, C(28)**H**H), 4.28 (1H, d, *J* = 11.0 Hz, C(28)H**H'**), 3.58 (3H, s, C(27)**H₃**), 3.18 (3H, s, C(43)**H₃**), 2.67 (3H, s, C(24)**H₃**).

δ_C(151 MHz, DMSO, 38 resonances out of 43 observed, **C**(23) and 4 x Ar resonances not observed): 165.2 (**C**(26)), 153.9 (**Ar**), 153.5 (**C**(10)), 139.0 (**Ar**), 138.0 (**Ar**), 137.2 (**Ar**), 137.2 (**Ar**), 135.7 (**Ar**), 133.1 (**Ar**), 129.5 (**Ar**), 128.9 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 127.7 (**Ar**), 127.5 (**Ar**), 127.5 (**Ar**), 127.5 (**Ar**), 127.4 (**Ar**), 126.8 (**Ar**), 125.3 (**Ar**), 121.2 (**C**(25)), 115.1 (**Ar**), 114.2 (**Ar**), 84.3 (**C**(7)), 82.1 (**C**(22)), 80.3 (**C**(8)), 76.1 (**C**(33)), 68.9 (**C**(38)), 67.8 (**C**(11)), 64.8 (**C**(28)), 57.2 (**C**(9)), 54.3 (**C**(43)), 51.2 (**C**(27)), 16.1 (**C**(24)).

m/z HRMS (ESI$^+$) found 824.3187; $C_{51}H_{47}NO_8Na^+$ (M+Na$^+$) requires 824.3194.

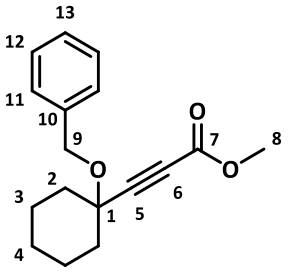
$[\alpha]_D^{25}$ = –70.1

A sample of the enantiomer, benzyl (6*S*,11*R*,12*S*,13*S*)-11,12,13-tris(benzyloxy)-2-methoxy-13-((*E*)-4-methoxy-4-oxobut-2-en-2-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**151**, 135.0 mg, 0.169 mmol, 56%), was prepared as above using benzyl (6*S*,11*R*,12*S*,13*S*)-11,12,13-tris(benzyloxy)-2-methoxy-13-(3-methoxy-3-oxoprop-1-yn-1-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**148**) as starting material.

$[\alpha]_D^{25}$= +166.2

All other characterisation identical.

Methyl 3-(1-(benzyloxy)cyclohexyl)propiolate (152)



To a solution of methyl 3-(1-hydroxycyclohexyl)propiolate (**155**, 703.0 mg, 3.86 mmol, 1.0 eq.) in dimethylformamide (40 mL) at 0 °C was added dropwise lithium bis(trimethylsilyl)amide (1 M in toluene, 5.8 mL, 5.80 mmol, 1.5 eq.). The mixture was stirred at 0 °C for 5 min then benzyl bromide (1.85 mL, 15.44 mmol, 4.0 eq) and tetrabutylammonium iodide (1.43 g, 3.86 mmol, 1.0 eq.) were added. The reaction was warmed to RT and stirred for 18 h then cooled to 0 °C and quenched by dropwise addition of sat. aq. ammonium chloride (30 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (3% diethyl ether in pentane) to give the title compound as a colourless oil (380.1 mg, 1.397 mmol, 38%).

R_f: 0.4 (10% diethyl ether in petroleum ether).

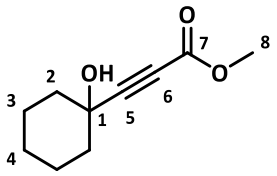
ν_{max}/cm^{-1} (thin film): 1716 (s), 1435 (m), 1290 (s), 1074 (m), 750 (m), 697 (m).

δ_H(600 MHz, $CDCl_3$): 7.41 – 7.32 (4H, m, 4 x Ar**H**), 7.27 (1H, tt, *J* = 7.0, 1.5 Hz, Ar**H**), 4.64 (2H, s, C(9)**H_2**), 3.79 (3H, s, C(8)**H_3**), 2.07 – 1.96 (2H, m, C(2)**H**H'), 1.83 – 1.67 (4H, m, C(2)H**H'**, C(3)**H**H',), 1.61 – 1.48 (3H, m, C(3)H**H'**, C(4)**H**H'), 1.41 – 1.31 (1H, m, C(4)H**H'**).

δ_C(151 MHz, $CDCl_3$): 154.1 (**C**(7)), 138.7 (**Ar**), 128.5 (**Ar**), 127.9 (**Ar**), 127.7 (**Ar**), 89.2 (**C**(5)), 77.8 (**C**(6)), 74.0 (**C**(1)), 66.2(**C**(9)), 52.9 (**C**(8)), 36.7 (**C**(2)), 25.3 (**C**3)), 22.6 (**C**(4)).

m/z HRMS (ESI^+) found 273.1486; $C_{17}H_{21}O_3$ ($M+H^+$) requires 273.1485.

Methyl 3-(1-hydroxycyclohexyl)propiolate (155)



Prepared according to the procedure of Li.[108]

Methyl propiolate (778.5 mg, 9.26 mmol, 1.0 eq.) was dissolved in tetrahydrofuran (18 mL) and cooled to −78 °C. *n*-butyllithium (1.6 M in hexane, 6.4 mL, 10.19 mmol, 1.1 eq.) was added dropwise and the reaction was stirred for 5 min at −78 °C. A solution of cyclohexanone (1.00 g, 10.19 mmol, 1.1 eq.) in tetrahydrofuran (6 mL) was added dropwise. The reaction was warmed to RT and stirred for 3h then cooled to 0 °C and quenched by dropwise addition of sat. aq. ammonium chloride solution (15 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% ethyl acetate in pentane) to give the title compound as a colourless oil (736.5 mg, 4.04 mmol, 43%).

R_f: 0.3 (20% ethyl acetate in petroleum ether).

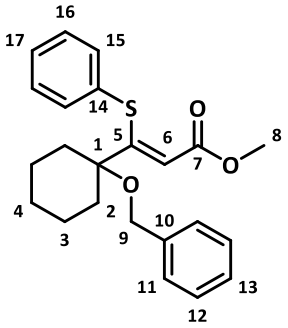
ν_{max}/cm^{-1} (thin film): 3399 (br, m). 2938 (m), 2234 (m), 1716 (s), 1436 (m), 1244 (s), 968 (m), 752 (m).

δ_H(600 MHz, $CDCl_3$, C(1)O**H** not observed): 3.78 (3H, s, C(8)**H₃**), 1.99 – 1.90 (2H, m, C(2)**H**H'), 1.77 – 1.68 (2H, m, C(3)**H**H'), 1.67 – 1.60 (2H, m, C(2)H**H'**), 1.59 – 1.50 (3H, m, C(3)H**H'**, C(4)**H**H'), 1.34 – 1.19 (1H, m, C(4)H**H'**).

δ_C(151 MHz, $CDCl_3$): 154.1 (**C**(7)), 90.8 (**C**(1)), 75.9 (**C**(6))), 68.7 (**C**(5)), 52.9 (**C**(8)), 39.2 (**C**(2)), 25.0 (**C**(4)), 23.0 (**C**(3)).

m/z HRMS (ESI^+) found 205.0837; $C_{10}H_{14}O_3Na^+$ ($M+Na^+$) requires 205.0835.

Methyl (*Z*)-3-(1-(benzyloxy)cyclohexyl)-3-(phenylthio)acrylate (159)



To a solution of thiophenol (0.1 M in methanol, 7.4 mL, 0.735 mmol, 2.0 eq.) at RT was added sodium methoxide (0.1 M in methanol, 0.37 mL, 0.037 mmol, 0.1 eq.). The solution was stirred at RT for 5 min then a solution of methyl 3-(1-(benzyloxy)cyclohexyl)propiolate (**152,** 100 mg, 0.367 mmol, 1.0 eq.) in methanol (1.5 mL) was added dropwise. The reaction was stirred for 90 min at RT then concentrated *in vacuo* and purified by flash column chromatography (4% diethyl ether in pentane) to give the title compound as a colourless oil (93.7 mg, 0.245 mmol, 67%).

R_f: 0.3 (10% diethyl ether in petroleum ether).

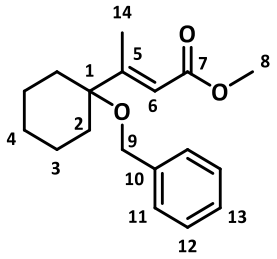
ν_{max}/cm^{-1} (thin film): 2857 (m), 1729 (s), 1439 (m), 1271 (m), 1174 (s), 1066 (m), 1026 (m), 735 (s), 695 (s).

δ_H(600 MHz, $CDCl_3$): 7.44 – 7.40 (2H, m, 2 x Ar**H**), 7.38 – 7.33 (4H, m, 4 x Ar**H**), 7.30 – 7.24 (3H, m, 3 x Ar**H**), 7.17 (1H, tt, *J* = 7.5, 1.0 Hz, Ar**H**), 6.45 (1H, s, C(6)**H**), 4.35 (2H, s, C(9)**H_2**), 3.32 (3H, s, C(8)**H_3**), 2.15 – 2.06 (2H, m, C(2)**H**H'), 1.83 (2H, td, *J* = 13.0, 4.0 Hz, C(2)H**H'**), 1.75 – 1.66 (3H, m, C(3)**H**H', C(4)**H**H'), 1.64 – 1.58 (2H, m, C(3)H**H'**), 1.31 – 1.20 (1H, m, C(4)H**H'**).

δ_C(151 MHz, $CDCl_3$): 166.1 (**C**(7)), 157.0 (**C**(5)), 138.6 (**Ar**), 135.7 (**Ar**), 130.3 (**Ar**), 129.0 (**Ar**), 128.5 (**Ar**), 127.6 (**Ar**), 127.5 (**Ar**), 126.8 (**Ar**), 121.3 (**C**(6)), 80.7 (**C**(1)), 64.0 (**C**(9)), 51.3 (**C**(8)), 34.1 (**C**(2)), 25.5 (**C**(4)), 21.8 (**C**(3)).

m/z HRMS (ESI^+) found 405.1497; $C_{23}H_{26}O_3SNa^+$ ($M+Na^+$) requires 405.1495.

Methyl (*E*)-3-(1-(benzyloxy)cyclohexyl)but-2-enoate (160)



Copper(I) cyanide (49.4 mg, 0.551 mmol, 1.5 eq.) was suspended in freeze-pump-thaw degassed diethyl ether (4 mL) and cooled to 0 °C. Methyllithium solution (1.7 M in diethyl ether, 0.62 mL, 1.064 mmol, 2.9 eq.) was added dropwise, initially giving a bright yellow suspension which then dissipated over the course of the addition to give a light grey solution. The reaction mixture was cooled to –20 °C and a solution of methyl 3-(1-(benzyloxy)cyclohexyl)propiolate (**152**, 100 mg, 0.367 mmol, 1.0 eq.) in diethyl ether (2 mL) was added dropwise, giving a pale yellow solution. The reaction was stirred at –20 °C for 14 h then warmed to 0 °C and quenched by dropwise addition of ammonium hydroxide (10% wt. in sat. aq. ammonium chloride, 5 mL). The resultant biphasic mixture was stirred vigorously at RT for 5 min then extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (4% diethyl ether in pentane) to give the title compound as a colourless oil (41.5 mg, 0.144 mmol, 39%).

R_f: 0.5 (20% diethyl ether in petroleum ether).

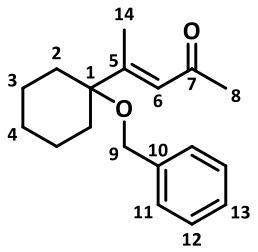
ν_{max}/cm^{-1} (thin film): 1720 (s), 1640 (m), 1435 (m), 1213 (s), 1166 (s), 1143 (s), 1063 (m), 1028 (m), 734 (m), 695 (m).

δ_H(600 MHz, $CDCl_3$): 7.41 – 7.30 (4H, m, 4 x Ar**H**), 7.28 – 7.25 (1H, m, Ar**H**), 5.92 (1H, q, *J* = 1.5 Hz, (C(6)**H**), 4.16 (2H, s, C(9)**H_2**), 3.72 (3H, s, C(8)**H_3**), 2.19 (3H, d, *J* = 1.3 Hz, C(14)**H_3**), 2.03 – 1.96 (2H, m, C(2)**H**H'), 1.74 – 1.65 (3H, m, C(3)**H**H', C(4)**H**H'), 1.59 – 1.54 (2H, m, C(3)H**H'**), 1.48 (2H, td, *J* = 13.0, 4.0 Hz, C(2)H**H'**), 1.27 – 1.18 (1H, m, C(4)H**H'**).

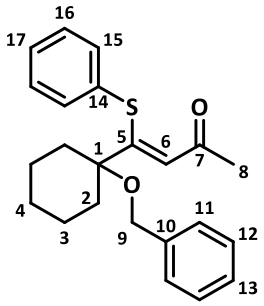
δ_C(151 MHz, $CDCl_3$): 167.5 (**C**(7)), 162.6 (**C**(5)), 139.1 (**Ar**), 128.5 (**Ar**), 127.5 (**Ar**), 127.4 (**Ar**), 116.4 (**C**(6)), 78.9 (**C**(1)), 64.0 (**C**(9)), 51.2 (**C**(8)), 33.2 (**C**(2)), 25.9 (**C**(4)), 21.9 (**C**(3)), 14.4 (**C**(14)).

m/z HRMS (ESI^+) found 311.1617; $C_{18}H_{24}O_3Na^+$ ($M+Na^+$) requires 311.1618.

(*E*)-4-(1-(Benzyloxy)cyclohexyl)pent-3-en-2-one (161) and **(*Z*)-4-(1-(benzyloxy)cyclohexyl)-4-(phenylthio)but-3-en-2-one (162)**



161



162

Copper(I) cyanide (14.1 mg, 0.157 mmol, 2.0 eq.) was suspended in freeze-pump-thaw degassed tetrahydrofuran (1 mL) and cooled to 0 °C. Methyllithium solution (1.7M in diethyl ether, 0.18 mL, 0.314 mmol, 3.9 eq.) was added dropwise, initially giving a bright yellow suspension which then dissipated over the course of the addition to give a light grey solution. The solution was stirred at 0 °C for 5 min then cooled to −78 °C. A solution of methyl (*Z*)-3-(1-(benzyloxy)cyclohexyl)-3-(phenylthio)acrylate (**159**, 30.0 mg, 0.079 mmol, 1.0 eq.) in tetrahydrofuran (0.5 mL) was added dropwise and the reaction was then warmed to RT and stirred for 45 min. The reaction was quenched by dropwise addition of ammonium hydroxide (10% wt. in sat. aq. ammonium chloride, 2 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (4% to 10% diethyl ether in pentane) to give (*Z*)-4-(1-(Benzyloxy)cyclohexyl)-4-(phenylthio)but-3-en-2-one (**162**) as a colourless oil (5.4 mg, 0.015 mmol, 19%) and (*E*)-4-(1-(benzyloxy)cyclohexyl)pent-3-en-2-one (**161**) as a colourless oil (5.8 mg, 0.021 mmol, 27%).

161:

R_f: 0.5 (15% diethyl ether in petroleum ether).

δ_H(600 MHz, $CDCl_3$): 7.37 – 7.30 (5H, m, 5 x Ar**H**), 6.30 (1H, q, *J* = 1.0 Hz, C(6)**H**), 4.16 (2H, s, C(9)**HH'**), 2.23 (3H, s, C(8)$\mathbf{H_3}$), 2.14 (3H, d, *J* = 1.0 Hz, C(14)$\mathbf{H_3}$), 2.01 – 1.94 (2H, m, C(2)**H**H), 1.75 – 1.65 (2H, m, C(3)**H**H), 1.61 – 1.54 (2H, m, C(3)H**H'**), 1.51 – 1.47 (2H, m, C(2)H**H'**), 1.28 – 1.23 (2H, m, C(4)**HH'**).

δ_C(151 MHz, $CDCl_3$): 199.6 (**C**(7)), 160.5 (**C**(5)), 139.1 (**Ar**), 128.5 (**Ar**), 127.5 (**Ar**), 127.4 (**Ar**), 123.8 (**C**(6)), 79.1 (**C**(1)), 64.1 (**C**(9)), 33.3 (**C**(2)), 32.4 (**C**(8)), 29.9 (**C**(4)), 21.8 (**C**(3)), 15.0 (**C**(14)).

m/z HRMS (ESI$^+$) found 295.1671; $C_{18}H_{24}O_2Na^+$ (M+Na$^+$) requires 295.1669.

162

R_f: 0.2 (15% diethyl ether in petroleum ether).

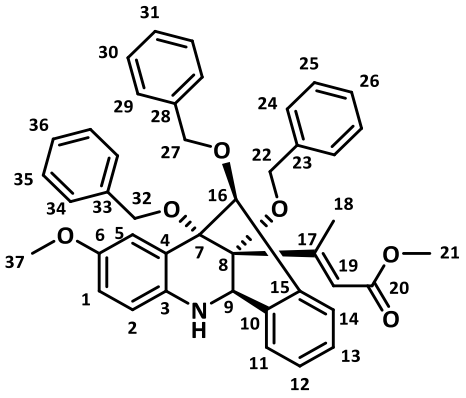
ν_{max}/cm^{-1} (thin film): 3031 (m), 1690 (m), 1582 (m), 1440 (m), 1352 (m), 1149 (m), 1084 (m), 1059 (m), 1026 (m), 741 (s), 698 (m).

δ_H(600 MHz, $CDCl_3$): 7.44 – 7.39 (2H, m, 2 x Ar**H**), 7.38 – 7.33 (2H, m, 2 x Ar**H**), 7.33 – 7.23 (5H, m, 5 x Ar**H**), 7.16 (1H, tt, *J*= 7.0, 1.0 Hz, Ar**H**), 6.68 (1H, s, C(6)**H**), 4.34 (2H, s, C(9)**H$_2$**), 2.11 – 2.08 (2H, m, C(2)**H**H'), 2.06 (3H, s, C(8)**H$_3$**), 1.83 (2H, td, *J* = 13.0, 4.0 Hz, C(2)H**H'**), 1.75 – 1.66 (3H, m, C(3)**H**H**,** C(4)**H**H), 1.61 (2H, dt, *J* = 13.5, 4.0 Hz, C(2)H**H'**), 1.31 – 1.19 (1H, m, C(4)H**H'**).

δ_C(151 MHz, $CDCl_3$): 199.7 (**C**(8)), 153.9 (**C**(5)), 138.6 (**Ar**), 136.2 (**Ar**), 131.1 (**C**(6)), 130.0 (**Ar**), 129.2 (**Ar**), 128.5 (**Ar**), 127.6 (**Ar**), 127.6 (**Ar**), 126.9 (**Ar**), 80.8 (**C**(1)), 64.1 (**C**(9)), 34.1 (**C**(2)), 30.6 (**C**(8)), 25.5 (**C**(4)), 21.8 (**C**(3)).

m/z HRMS (ESI$^+$) found 389.1545; $C_{23}H_{26}O_2SNa^+$ (M+Na$^+$) requires 389.1546.

Methyl (*E*)-3-((6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-methoxy-5,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (*ent*-168)



Prepared according to the procedure of Burton.[122]

To a solution of benzyl (6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-methoxy-13-((E)-4-methoxy-4-oxobut-2-en-2-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-151**, 20.7 mg, 0.026 mmol, 1 eq.) in dichloromethane (0.5 mL) at RT was added boron trichloride methyl sulfide complex (2 M in dichloromethane, 0.13 mL, 0.26 mmol, 10 eq.). The reaction was stirred at RT for 18 h then quenched with water (1 mL) and extracted with dichloromethane (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 15% ethyl acetate in pentane) to give the title compound as a yellow oil (12.1 mg, 0.018 mmol, 70%).

R_f: 0.4 (40% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 1722 (m), 1636 (m), 1502 (s), 1210 (s), 1110 (s), 1094 (s), 770 (m).

δ_H(600 MHz, DMSO): 7.48 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.39 – 7.14 (18H, m, 18 x Ar**H**), 6.76 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.50 (1H, dd, *J* = 8.5, 3.0 Hz, Ar**H**), 6.42 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.09 (1H, d, *J* = 4.0 Hz, C(9)N**H**), 5.64 (1H, s, C(19)**H**), 5.09 (1H, d, *J* = 10.5 Hz, C(27)**H**H), 5.00 (1H, d, *J* = 12.5 Hz, C(32)**H**H), 4.96 (1H, d, *J* = 4.0 Hz, C(9)**H**), 4.93 (1H, d, *J* = 10.5 Hz, C(27)H**H'**), 4.85 (1H, d, *J* = 11.0 Hz, C(22)**H**H), 4.60 (1H, s, C(16)**H**), 4.53 (1H, d, *J* = 12.5 Hz, C(32)H**H'**), 4.24 (1H, d, *J* = 11.0 Hz, C(22)H**H'**), 3.55 (3H, s, C(21)$\mathbf{H_3}$), 3.17 (3H, s, C(37)$\mathbf{H_3}$), 2.58 (3H, s, C(18)$\mathbf{H_3}$).

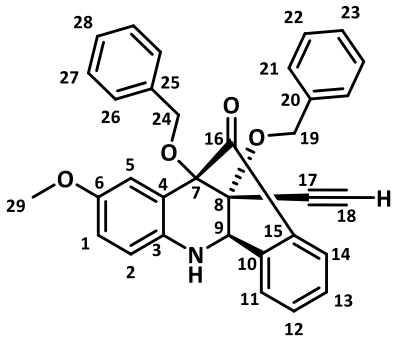
δ_C(151 MHz, DMSO, 34 resonances out of 37 observed, 3 x Ar resonances not observed): 165.7 (**C**(20)), 155.1 (**C**(17)), 149.8 (**Ar**), 139.7 (**Ar**), 138.9 (**Ar**), 138.5 (**Ar**), 138.4 (**Ar**), 137.1 (**Ar**), 135.9 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 127.5 (**Ar**), 127.2 (**Ar**), 127.2 (**Ar**), 127.2 (**Ar**), 127.1 (**Ar**), 126.4 (**Ar**), 120.9 (**C**(19)), 118.8

(**Ar**), 115.8 (**Ar**), 115.2 (**Ar**), 114.7 (**Ar**), 84.4 (**C**(7)), 83.9 (**C**(16)), 80.1 (**C**(8)), 75.9 (**C**(27)), 68.4 (**C**(32)), 63.4 (**C**(22)), 54.9 (**C**(9)), 54.4 (**C**(37)), 51.0 (**C**(21)), 15.8 (**C**(18)).

m/z HRMS (ESI^+) found 668.2996; $C_{43}H_{42}NO_6$ ($M+H^+$) requires 668.3007.

$[\alpha]_D^{25}$= –2.56

(6*R*,12*S*,13*R*)-12,13-Bis(benzyloxy)-13-ethynyl-2-methoxy-5,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocin-11(6*H*)-one (*ent*-176)



Prepared according to the procedure of Burton.[122]

To a solution of benzyl (6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (***ent*-142**, 10.0 mg, 0.016 mmol, 1.0 eq.) in dichloromethane (0.5 mL) at RT was added boron trichloride methyl sulfide complex (2 M in dichloromethane, 48 µL, 0.096 mmol, 6.0 eq.). The reaction mixture was stirred at RT for 14 h then quenched with water (1 mL) and extracted with dichloromethane (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (10% to 25% ethyl acetate in pentane) to give the title compound as a yellow oil (6.0 mg, 0.012 mmol, 76%).

R_f: 0.4 (30% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 1619 (m), 1501 (s), 1270 (m), 1169 (m), 1106 (m).

δ_H(600 MHz, DMSO): 7.91 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.75 (1H, td, *J* = 7.0, 1.5 Hz, Ar**H**), 7.69 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.55 – 7.51 (2H, m, 2 x Ar**H**), 7.44 (1H, ddd, *J* = 8.0, 7.0, 1.5 Hz, Ar**H**), 7.41 – 7.37 (2H, m, 2 x Ar**H**), 7.34 – 7.28 (5H, m, 5 x Ar**H**), 7.28 – 7.23 (1H, m, Ar**H**), 6.77 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.76 (1H, d, *J* = 4.0 Hz, C(3)N**H**), 6.66 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.51 (1H, d, *J* = 9.0 Hz, Ar**H**), 5.20 (1H, d, *J* = 4.0 Hz, C(9)**H**), 5.05 (1H, d, *J* = 12.5 Hz, C(24)**H**H), 4.89 (1H, d, *J* = 12.5 Hz, C(24)H**H'**), 4.86 (2H, s, C(19)**H**H, C(19)H**H'**), 3.74 (1H, s, C(18)**H**), 3.45 (3H, s, C(29)$\mathbf{H_3}$).

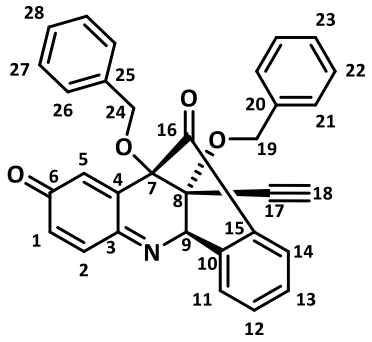
δ_C(151 MHz, DMSO): 190.2 (**C**(16)), 151.5 (**Ar**), 140.6 (**Ar**), 139.6 (**Ar**), 137.9 (**Ar**), 136.2 (**Ar**), 134.6 (**Ar**), 130.3 (**Ar**), 129.9 (**Ar**) , 128.2 (**Ar**)2, 128.2 (**Ar**), 128.1 (**Ar**), 127.7 (**Ar**), 127.5 (**Ar**), 127.1 (**Ar**), 126.8 (**Ar**), 126.3 (**Ar**),

116.9 (**Ar**), 116.1 (**Ar**), 115.6 (**Ar**), 110.4 (**Ar**), 84.5 (**C**(7)), 82.5 (**C**(18)), 80.6 (**C**(17)), 71.5 (**C**(8)), 68.2 (**C**(24)), 65.1 (**C**(19)), 56.1 (**C**(9)), 55.0 (**C**(29)).

m/z HRMS (ESI^+) found 502.2010; $C_{33}H_{28}NO_4^+$ ($M+H^+$) requires 502.2013.

$[\alpha]_D^{25}$ = –233.5

(6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-6,12-methanodibenzo[*b*,*f*]azocine-2,11(6*H*,12*H*)-dione (*ent*-177)



Prepared according to the procedure of Leboeuf.[126]

To a solution of (6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-2-methoxy-5,12-dihydro-6,12-methanodibenzo[*b,f*]azocin-11(6*H*)-one (***ent*-176**, 14.0 mg, 0.028 mmol, 1.0 eq.) in acetonitrile (1.3 mL) and water (0.4 mL) at RT was added cerium(IV) ammonium nitrate (45.9 mg, 0.084 mmol, 3.0 eq.) as a single solid portion. The reaction was stirred for 15 min at RT then diluted with ethyl acetate (3 mL) and water (3 mL). The layers were separated and the aqueous fraction was extracted with ethyl acetate (x 2). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% to 30% ethyl acetate in pentane) to give the title compound as an orange oil (8.9 mg, 0.018 mmol, 64%).

R_f: 0.3 (30% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 1699 (s), 1646 (s), 1630 (m), 1599 (m), 1498 (m), 1455 (m), 736 (s), 697 (m), 668 (s).

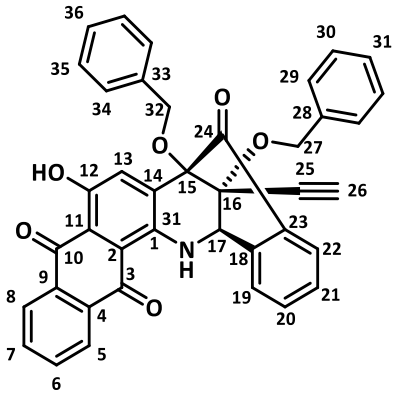
δ_H(600 MHz, $CDCl_3$): 8.11 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.69 – 7.62 (2H, m, 2 x Ar**H**), 7.57 – 7.50 (3H, m, 3 x Ar**H**), 7.39 – 7.34 (2H, m, 2 x Ar**H**), 7.34 – 7.27 (6H, m, 6 x Ar**H**), 7.00 (1H, d, *J* = 10 Hz, C(2)**H**), 6.97 (1H, d, *J* = 2.0 Hz, C(5)**H**), 6.48 (1H, dd, *J* = 10.0, 2.0 Hz, C(1)**H**), 5.88 (1H, s, C(9)**H**), 5.15 (2H, s, C(24)**HH'**), 5.03 (1H, d, *J* = 11.0 Hz, C(19)**H**H'), 4.76 (1H, d, *J* = 11.0 Hz, C(19)H**H'**), 2.67 (1H, s, C(18)**H**).

δ_C(151 MHz, $CDCl_3$): 189.7 (**C**(16)), 186.9 (**C**(6)), 157.6 (**C**(3)), 140.7 (**C**(2)), 140.4 (**Ar**), 138.4 (**Ar**), 137.3 (**Ar**), 136.4 (**C**(4)), 135.4 (**Ar**), 133.1 (**C**(1)), 130.6 (**C**(5)), 129.9 (**Ar**), 129.8 (**Ar**), 128.9 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.0 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 84.6 (**C**(7)), 81.4 (**C**(18)), 79.6 (**C**(17)), 76.7 (**C**(8)) 69.5 (**C**(24)), 68.4 (**C**(9)), 67.4 (**C**(19)).

m/z HRMS (ESI^+) found 486.1699; $C_{32}H_{24}NO_4^+$ ($M+H^+$) requires 486.1700.

$[\alpha]_D^{25}$ = –32.4

(8*S*,14*R*,17*R*)-8,17-Bis(benzyloxy)-17-ethynyl-6-hydroxy-14,15-dihydro-8,14-methanoanthra[1,2-*b*]benzo[*f*]azocine-5,9,16(8*H*)-trione (*ent*-178)



Prepared according to the procedure of Nicolaou.[127]

To a solution of 3-cyanophthalide (**14**, 8.8 mg, 0.055 mmol, 3.0 eq) in tetrahydrofuran (0.5 mL) at –78 °C was added dropwise lithium bis(trimethylsilyl)amide (1 M in toluene, 55 µL, 0.055 mmol, 3.0 eq.). The resultant bright yellow solution was stirred at –78 °C for 15 min. A solution of (6*R*,12*S*,13*R*)-12,13-bis(benzyloxy)-13-ethynyl-6,12-methanodibenzo[*b*,*f*]azocine-2,11(6*H*,12*H*)-dione (***ent*-177**, 8.9 mg, 0.018 mmol, 1.0 eq.) in tetrahydrofuran (0.5 mL) was added dropwise. The cool bath was removed and the reaction mixture was allowed to warm to RT, during which time the bright yellow solution turned first dark green then dark purple. The reaction was stirred at RT for 15 min then quenched by dropwise addition of sat. aq. ammonium chloride solution (2 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (2% ethyl acetate in toluene) to give the title compound as dark purple oil (4.6 mg, 0.007 mmol, 41%).

R_f: 0.4 (5% ethyl acetate in toluene).

ν_{max}/cm^{-1} (thin film): 3266 (br, m), 1793 (m), 1699 (m), 1619 (m), 1587 (s), 1495 (s), 1261 (s), 1173 (m), 1021 (m).

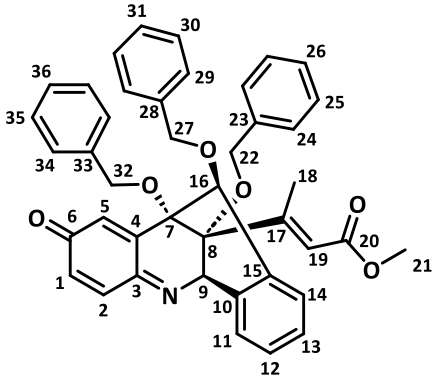
δ_H(600 MHz, $CDCl_3$): 13.20 (1H, s, C(12)O**H**), 10.78 (1H, d, *J* = 5.0 Hz, N**H**), 8.29 – 8.24 (2H, m, 2 x Ar**H**), 8.12 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.78 – 7.74 (2H, m, 2 x Ar**H**), 7.71 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 7.66 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.62 – 7.58 (2H, m, 2 x Ar**H**), 7.53 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.45 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 7.40 – 7.36 (2H, m, Ar**H**), 7.35 – 7.22 (6H, m, 6 x Ar**H**), 5.25 (1H, d, *J* = 11.5 Hz, C(32)**H**H'), 5.13 (1H, d,

J = 11.5 Hz, C(32)H**H'**), 5.09 (1H, d, *J* = 5.0 Hz, C(17)**H**), 5.03 (1H, d, *J* = 11.0 Hz, C(27)**H**H'), 4.92 (1H, d, *J* = 11.0 Hz, C(27)H**H'**), 2.68 (1H, s, C(26)**H**).

δ_C(151 MHz, $CDCl_3$): 189.8 (**C**(24)), 187.3 (**C**(10)), 183.3 (**C**(3)), 157.0 (**Ar**), 140.9 (**Ar**), 140.6 (**Ar**), 138.7 (**Ar**), 137.3 (**Ar**), 135.4 (**Ar**), 134.2 (**Ar**), 133.0 (**Ar**), 132.7 (**Ar**), 131.5 (**Ar**), 130.2 (**Ar**), 129.0 (**Ar**), 129.0 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.4 (**Ar**), 128.2 (**Ar**), 127.9 (**Ar**), 127.8 (**Ar**), 127.8 (**Ar**), 127.6 (**Ar**), 127.5 (**Ar**), 126.6 (**Ar**), 126.5 (**Ar**), 114.4 (**Ar**), 109.6 (**Ar**), 84.9 (**C**(15)), 81.7 (**C**(26)), 79.4 (**C**(25)), 72.3 (**C**(16)), 69.6 (**C**(32)), 66.8 (**C**(27)), 57.3 (**C**(17)).

m/z HRMS (ESI^+) found 618.1907; $C_{40}H_{28}NO_6^+$ ($M+H^+$) requires 618.1911.

Methyl (*E*)-3-((6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-oxo-2,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (*ent*-179)



Prepared according to the procedure of Leboeuf.[126]

To a solution of methyl (*E*)-3-((6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-methoxy-5,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (***ent*-168**, 12.1 mg, 0.018 mmol, 1.0 eq.) in acetonitrile (0.8 mL) and water (0.25 mL) was added cerium(IV) ammonium nitrate (29.8 mg, 0.054 mmol, 3.0 eq.) as a single solid portion. The reaction mixture was stirred for 15 min then diluted with ethyl acetate (2 mL) and water (2 mL). The layers were separated and the aqueous fraction was extracted with ethyl acetate (x 2). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% ethyl acetate in pentane) to give the title compound as an orange oil (7.2 mg, mmol, 61%).

R_f: 0.3 (30% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 1684 (m), 1626 (s), 1436 (m), 1215 (m), 1028 (m), 911 (m), 698 (m), 724 (m).

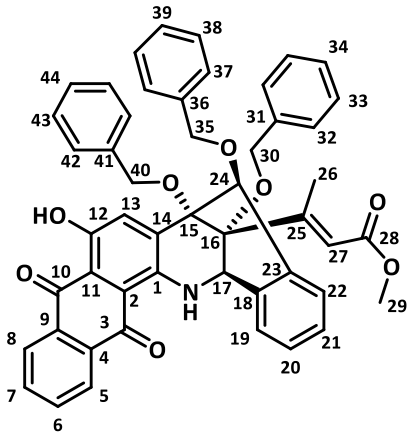
δ_H(600 MHz, DMSO): 7.54 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.43 – 7.26 (16H, m, 16 x Ar**H**), 7.21 (1H, d, *J* = 10.0 Hz, C(2)**H**), 7.19 – 7.16 (2H, m, 2 x Ar**H**), 6.53 (1H, dd, *J* = 10.0, 2.0 Hz, C(1)**H**), 6.43 (1H, d, *J* = 2.0 Hz, C(5)**H**), 6.24 (1H, s, C(9)**H**), 5.82 (1H, q, *J* = 1.5 Hz, C(19)**H**), 5.02 (1H, d, *J* = 12.0 Hz, C(22)**H**H'), 4.97 (1H, d, *J* = 10.5 Hz, C(27)**H**H'), 4.91 (1H, d, *J* = 10.5 Hz, C(27)H**H'**), 4.67 (1H, d, *J* = 12.0 Hz, C(22)H**H'**), 4.59 (1H, s, C(16)**H**), 4.41 (1H, d, *J* = 11.0 Hz, C(32)**H**H'), 4.30 (1H, d, *J* = 11.1 Hz, C(32)H**H'**), 3.57 (3H, s, C(21)$\mathbf{H_3}$), 2.51 (3H, d, *J* = 1.5 Hz, C(18)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO, 34 resonances out of 36 observed, 2 x Ar resonances not observed): 186.4 (**C**(6)), 165.5 (**C**(20)), 160.2 (**C**(3)), 152.7 (**C**(10)), 140.7 (**C**(2)), 138.3 (**Ar**), 137.8 (**Ar**), 137.3 (**Ar**), 136.0 (**C**(4)), 134.5 (**Ar**), 133.8 (**Ar**), 132.4 (**C**(5)), 131.7 (**C**(1)), 128.6 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 127.6 (**Ar**), 127.2 (**Ar**), 122.1 (**C**(19)), 83.9 (**C**(8)), 83.8 (**C**(9)), 79.6 (**C**(16)), 76.2 (**C**(27)), 68.6 (**C**(22)), 64.7 (**C**(32)), 63.9 (**C**(9)), 51.2 (**C**(21)), 15.5 (**C**(18)).

m/z HRMS (ESI$^+$) found 652.2686; $C_{42}H_{38}NO_6^+$ (M+H$^+$) requires 652.2694.

$[\alpha]_D^{25}$-71.4

Methyl (*E*)-3-((8*R*,9*S*,14*R*,17*R*)-8,9,17-tris(benzyloxy)-6-hydroxy-5,16-dioxo-5,8,9,14,15,16-hexahydro-8,14-methanoanthra[1,2-*b*]benzo[*f*]azocin-17-yl)but-2-enoate (*ent*-180)



Prepared according to the procedure of Nicolaou.[127]

To a solution of 3-cyanophthalide (**14**, 2.6 mg, 0.017 mmol, 1.5 eq.) in tetrahydrofuran (0.4 mL) at −78 °C was added dropwise lithium bis(trimethylsilyl)amide (1 M in toluene, 17 µL, 0.017 mmol, 1.5 eq.). The resultant bright yellow solution was stirred at −78 °C for 15 min. A solution of methyl (*E*)-3-((6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-oxo-2,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (***ent*-179**, 7.2 mg, 0.011 mmol, 1.0 eq.) in tetrahydrofuran (0.2 mL) was added dropwise. The cool bath was removed and the reaction mixture was allowed to warm to RT, during which time the bright yellow solution turned first dark green then dark purple. The reaction was stirred at RT for 15 min then quenched by dropwise addition of sat. aq. ammonium chloride solution (2 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (15% to 20% ethyl acetate in pentane) to give the title compound as dark purple oil (4.6 mg, 0.006 mmol, 54%).

R_f: 0.5 (5% ethyl acetate in toluene).

ν_{max}/cm^{-1} (thin film): 1723 (m), 1587 (s), 1497 (m), 1265 (s), 1248 (s), 1210 (s), 1104 (m), 1028 (m), 732 (m), 698 (m).

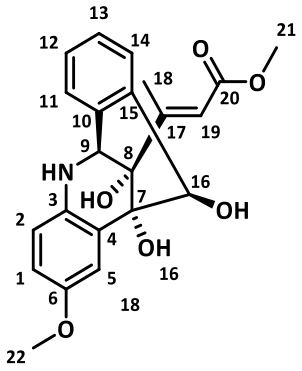
δ_H(600 MHz, DMSO): 13.16 (1H, s, C(12)O**H**), 10.71 (1H, d, *J* = 5.5 Hz, N**H**), 8.22 (1H, dd, *J* = 8.0, 1.5 Hz, C(5)**H**), 8.18 (1H, dd, *J* = 8.0, 1.5 Hz, C(8)**H**), 7.90 (1H, td, *J* = 7.5, 1.5 Hz, C(6)**H**), 7.82 (1H, td, *J* = 7.5, 1.5 Hz, C(7)**H**),

7.64 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.45 – 7.16 (18H, m, 18 x Ar**H**), 7.36 (1H, s, C(13)**H**), 5.70 (1H, d, *J* = 1.5 Hz, C(27)**H**), 5.66 (1H, d, *J* = 5.5 Hz, C(17)**H**), 5.07 (1H, d, *J* = 12.0 Hz, C(40)**H**H'), 5.06 (1H, d, *J* = 10.5 Hz, C(35)**H**H'), 4.96 (1H, d, *J* = 10.5 Hz, C(35)H**H'**), 4.84 (1H, d, *J* = 11.0 Hz, C(30)**H**H'), 4.72 (1H, s, C(24)**H**), 4.46 (1H, d, *J* = 12.0 Hz, C(40)H**H'**), 4.29 (1H, d, *J* = 11.0 Hz, C(30)H**H'**), 3.58 (3H, s, C(29)**H**), 2.62 (3H, d, *J* = 1.5 Hz, C(26)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO): 186.6 (**C**(10)), 181.0 (**C**(3)), 165.4 (**C**(28)), 154.5(**C**(12)), 153.2 (**C**(25)), 144.1 (**C**(14)), 138.4 (**Ar**), 137.9 (**Ar**), 137.7 (**Ar**), 136.1 (**Ar**), 134.7 (**C**(6)), 134.5 (**C**(9)), 134.4 (**Ar**), 133.9 (**C**(1)), 133.1 (**C**(7)), 132.0 (**C**(4)), 130.3 (**C**(13)), 129.2 (**Ar**), 128.6 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 127.9 (**Ar**), 127.8 (**Ar**), 127.7 (**Ar**), 127.6 (**Ar**), 127.5 (**Ar**), 127.4 (**Ar**), 127.0 (**Ar**), 126.3 (**C**(5)), 126.0 (**C**(8)), 121.7 (**C**(27)), 113.1 (**C**(11)), 107.9 (**C**(2)), 84.4 (**C**(15)), 82.6 (**C**(24)), 80.2 (**C**(16)), 76.1 (**C**(35)), 68.9 (**C**(40)), 63.8 (**C**(30)), 53.3 (**C**(17)), 51.2 (**C**(29)), 15.6 (**C**(26)).

m/z HRMS (ESI$^+$) found 784.2903; $C_{50}H_{42}NO_8^+$ (M+H$^+$) requires 784.2905.

Methyl (*E*)-3-((6*S*,11*R*,12*S*,13*S*)-11,12,13-trihydroxy-2-methoxy-5,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (181)



Prepared according to the modified procedure of Janetka.[128]

To a solution of benzyl (6*S*,11*R*,12*S*,13*S*)-11,12,13-tris(benzyloxy)-2-methoxy-13-((*E*)-4-methoxy-4-oxobut-2-en-2-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**151**, 90.0 mg, 0.112 mmol, 1.0 eq.) in dichloromethane (9 mL) at –78 °C was added dropwise boron trichloride (1 M in hexanes, 4.5 mL, 4.50 mmol, 40 eq.). The reaction was stirred at –78 °C for 45 min then warmed to RT and stirred for 36 h. The reaction was then cooled to 0 °C and quenched by dropwise addition of sat. aq. sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (x 3) and the combined layers were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (40% to 50% ethyl acetate in pentane) to give the title compound as a yellow oil (21.7 mg, 0.055 mmol, 49%).

R_f: 0.1 (40% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 3365 (br, m), 2924 (m), 1713 (s), 1637 (m), 1502 (s), 1211 (s), 1038 (m), 735 (m).

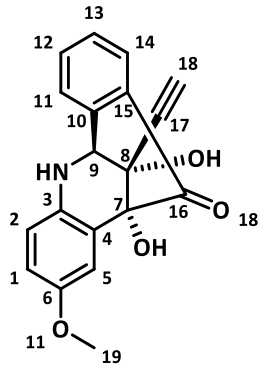
δ_H(600 MHz, DMSO): 7.37 (1H, d, *J* = 7.5 Hz, C(14)**H**), 7.27 (1H, d, *J* = 7.5 Hz, C(11)**H**), 7.23 (1H, t, *J* = 7.5 Hz, C(13)**H**), 7.14 (1H, t, *J* = 7.5, Hz, C(12)**H**), 7.12 (1H, d, *J* = 3.0 Hz, C(2)**H**), 6.51 (1H, dd, *J* = 8.5, 3.0 Hz, C(1)**H**), 6.32 (1H, d, *J* = 8.5 Hz, C(5)**H**), 5.98 (1H, d, *J* = 4.0 Hz, C(16)O**H**), 5.54 (1H, q, *J* = 1.0 Hz, C(19)**H**), 5.50 (1H, d, *J* = 5.5 Hz, N**H**), 5.24 (1H, s, C(7)O**H**), 4.88 (1H, s, C(8)O**H**), 4.47 (1H, d, *J* = 5.5 Hz, C(9)**H**), 4.28 (1H, d, *J* = 4.0 Hz, C(16)**H**), 3.61 (3H, s, C(22)**H₃**), 3.48 (3H, s, C(21)**H₃**), 2.35 (3H, d, *J* = 1.0 Hz, C(18)**H₃**).

δ_C(151 MHz, DMSO): 166.3 (**C**(20)), 159.9 (**C**(17)), 150.7 (**C**(6)), 137.7 (**C**(10)), 137.6 (**C**(15)), 136.0 (**C**(3)), 127.6 (**C**(13)), 127.5 (**C**(14)), 126.8 (**C**(12)), 126.3 (**C**(11)), 126.0 (**C**(4)), 116.7 (**C**(2)), 116.0 (**C**(19)), 114.2 (**C**(5)), 113.7 (**C**(1)), 77.2 (**C**(7)), 75.0 (**C**(9)), 72.3 (**C**(8)), 59.0 (**C**(16)), 55.2 (**C**(22)), 50.7 (**C**(21)), 17.2 (**C**(18)).

m/z HRMS (ESI^+) found 398.1600; $C_{22}H_{24}NO_6^+$ ($M+H^+$) requires 398.1598.

$[\alpha]_D^{25}$ = –100.7

(6*S*,12*R*,13*S*)-13-Ethynyl-12,13-dihydroxy-2-methoxy-5,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocin-11(6*H*)-one (184)



Prepared according to the modified procedure of Janetka.[128]

To a solution of benzyl (6*S*,12*R*,13*S*)-12,13-bis(benzyloxy)-13-ethynyl-2-methoxy-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b,f*]azocine-5(6*H*)-carboxylate (**142**, 10 mg, 0.016 mmol, 1.0 eq.) at – 78 °C was added dropwise boron trichloride (1 M in hexanes, 0.48 mL, 0.48 mmol, 30 eq.). The reaction was stirred at –78 °C for 45 min then warmed to RT and stirred for 14 h. The reaction was cooled to 0 °C and quenched by dropwise addition of sat. aq. sodium bicarbonate (4 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (35% to 45% ethyl acetate in pentane) to give the title compound as a yellow oil (3.8 mg, 0.012 mmol, 74%).

R_f: 0.1 (40% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 3362 (br, m), 1685 (m), 1502 (s), 1281 (m), 1173 (m), 914 (m), 736 (m).

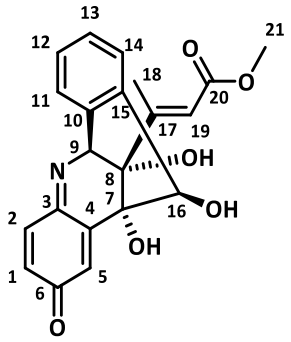
δ_H(600 MHz, DMSO): 7.82 (1H, dd, *J* = 8.0, 1.5 Hz, C(14)**H**), 7.68 (1H, td, *J* = 7.5, 1.5 Hz, C(12)**H**), 7.60 (1H, dd, *J* = 7.5, 1.0 Hz, C(11)**H**), 7.37 (1H, ddd, *J* = 8.0, 7.5, 1.0 Hz, C(13)**H**), 6.93 (1H, d, *J* = 3.0 Hz, C(5)**H**), 6.62 (1H, dd, *J* = 8.5, 3.0 Hz, C(1)**H**), 6.54 (1H, d, *J* = 4.0 Hz, N**H**), 6.38 (1H, d, *J* = 8.5 Hz, C(2)**H**), 6.02 (1H, s, C(7)O**H**), 5.94 (1H, s, C(8)O**H**), 4.54 (1H, d, *J* = 4.0 Hz, C(9)**H**), 3.61 (3H, s, C(19)**H₃**), 3.20 (1H, s, C(18)**H**).

δ_C(151 MHz, DMSO): 193.8, **C**(16), 151.5, (**C**(6)), 142.3 (**C**(15)), 135.1 (**C**(3)), 134.5 (**C**(12)), 129.5 (**C**(10)), 129.5 (**C**(11)), 127.7 (**C**(13)), 126.3 (**C**(14)), 119.0 (**C**(4)), 116.3 (**C**(1)), 115.2 (**C**(2)), 110.9 (**C**(5)), 84.4 (**C**(17)), 80.2 (**C**(7)), 77.5 (**C**(18)), 65.5 (**C**(8)), 59.3 (**C**(9)), 55.3 (**C**(19)).

m/z HRMS (ESI^+) found 322.1074; $C_{19}H_{16}NO_4^+$ ($M+H^+$) requires 322.1074.

$[\alpha]_D^{25}$= +519.4

Methyl (*E*)-3-((6*S*,11*R*,12*S*,13*S*)-11,12,13-trihydroxy-2-oxo-2,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (190)



Prepared according to the modified procedure of Lebouef.[126]

To a solution of methyl (*E*)-3-((6*S*,11*R*,12*S*,13*S*)-11,12,13-trihydroxy-2-methoxy-5,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (**181**, 21.7 mg, 0.055 mmol, 1.0 eq.) in acetonitrile (2.4 mL) and water (0.8 mL) at RT was added cerium(IV) ammonium nitrate (90.5 mg, 0.165 mmol, 3.0 eq.) as a single solid portion. The reaction mixture was stirred for 15 min then diluted with ethyl acetate (5 mL) and water (5 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (x 2). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (70% ethyl acetate in pentane) to give the title compound as an orange oil (8.8 mg, 0.023 mmol, 42%).

R_f: 0.2 (60% ethyl acetate in petroleum ether).

ν_{max}/cm^{-1} (thin film): 3391 (br, m), 1718 (m), 1644 (s), 1624 (m), 1263 (s), 1094 (m), 1037 (m), 736 (s).

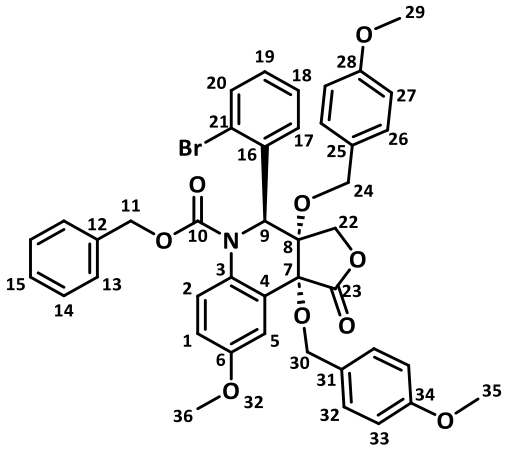
δ_H(600 MHz, DMSO): 7.46 – 7.39 (2H, m, C(11)**H**, C(14)**H**), 7.30 – 7.23 (2H, m, C(12)**H**, C(13)**H**), 7.06 (1H, d, *J* = 10.0 Hz, C(2)**H**), 6.68 (1H, d, *J* = 2.0 Hz, C(5)**H**), 6.45 (1H, dd, *J* = 10.0, 2.0 Hz, C(1)**H**), 5.87 (1H, s, C(7)O**H**), 5.85 (1H, d, *J* = 6.5 Hz, C(16)O**H**), 5.84 (1H, s, C(8)O**H**), 5.81 (1H, q, *J* = 1.5 Hz, C(19)**H**), 5.52 (1H, s, C(9)**H**), 4.45 (1H, d, *J* = 6.5 Hz, C(16)**H**), 3.51 (3H, s, C(21)$\mathbf{H_3}$), 2.27 (3H, d, *J* = 1.5 Hz, C(18)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO): 187.2 (**C**(6)), 166.1 (**C**(20)), 158.3 (**C**(3)), 158.2 (**C**(17)), 143.3 (**C**(4)), 141.0 (**C**(2)), 135.9 (**C**(15)), 135.5 (**C**(10)), 131.2 (**C**(1)), 130.8 (**C**(5)), 128.3 (**C**(11)), 128.0 (**C**(14)), 127.9 (**C**(12)), 127.8 (**C**(13)), 117.3 (**C**(19)), 77.6 (**C**(7)), 76.2 (**C**(8)), 71.7 (**C**(16)), 69.3 (**C**(9)), 50.9 (**C**(21)), 16.8 (**C**(18)).

m/z HRMS (ESI$^+$) found 382.1284; $C_{21}H_{20}NO_6^+$ (M+H$^+$) requires 382.1285.

$[\alpha]_D^{25}$ = –211.2

Benzyl (3a*R*,4*S*,9b*R*)-4-(2-bromophenyl)-8-methoxy-3a,9b-bis((4-methoxybenzyl)oxy)-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (195)



Preparation of 4-methoxybenzyl bromide according to the procedure of Burke.[141]

To a mixture of hydrobromic acid (48% in water, 4.5 mL) and diethyl ether (5 mL) at RT was added a solution of 4-methoxybenzyl alcohol (3.00 g, 21.9 mmol) in diethyl ether (5 mL). The reaction mixture was stirred vigorously for 2 h at RT then diluted with diethyl ether (25 mL) and the layers were separated. The organic layer was washed sequentially with sat. aq. sodium bicarbonate and sat. aq. sodium bromide and then dried over magnesium sulfate and concentrated *in vacuo* at 0 °C to give 4-methoxybenzyl bromide as a colourless oil (3.95 g, 19.7 mmol, 90%). The crude product was used immediately in subsequent procedures without further purification.

Preparation of 195

To a solution of benzyl (3a*R*,4*S*,9b*R*)-4-(2-bromophenyl)-3a,9b-dihydroxy-8-methoxy-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (**112**, 1.00 g, 1.85 mmol, 1.0 eq.) in dimethylformamide (25 mL) at 0 °C was added dropwise sodium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 5.6 mL, 5.60 mmol, 3.0 eq.). The reaction was warmed to RT and stirred for 30 min. 4-methoxybenzyl bromide (1.34 mL, 9.30 mmol, 5.0 eq.) was added dropwise and the reaction was stirred for 12 h at RT. The reaction was then cooled to 0 °C and quenched by dropwise addition of sat. aq. ammonium chloride (20 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (2% to 4% diethyl ether in toluene) to give the title compound as a white solid (1.998 g, 1.411 mmol, 76%).

R_f: 0.8 (10% diethyl ether in toluene).

m.p.: 53.4 – 56.8 °C.

ν_{max}/cm^{-1} (thin film): 1791 (m), 1709 (m), 1613 (m), 1514 (s), 1586 (s), 1302 (m), 1250 (s), 1030 (s)

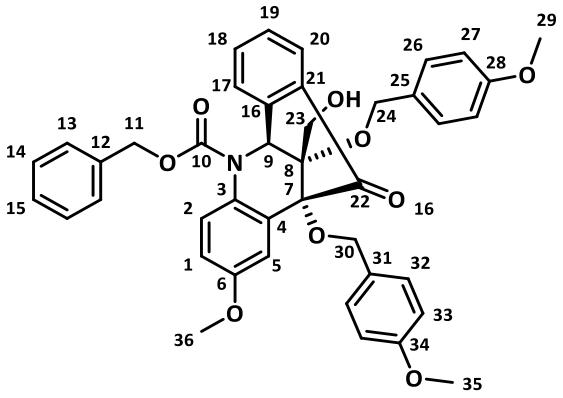
δ_H(600 MHz, $CDCl_3$): 7.69 (1H, d, *J* = 9.0 Hz, Ar**H**), 7.56 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.29 – 7.21 (6H, m, 6 x Ar**H**), 7.18 – 7.13 (2H, m, 2 x Ar**H**), 7.14 – 7.06 (3H, m, 3 x Ar**H**), 7.06 – 7.00 (2H, m, 2 x Ar**H**), 6.87 (1H, dd, *J* = 7.5, 2.0 Hz, Ar**H**), 6.82 – 6.78 (2H, m, 2 x Ar**H**), 6.77 – 6.70 (2H, m, 2 x Ar**H**), 6.73 (1H, s, C(9)**H**), 5.25 (1H, d, *J* = 12.5 Hz, C(11)**H**H'), 5.13 (1H, d, *J* = 12.5 Hz, C(11)H**H'**), 5.03 (1H, d, *J* = 10.0 Hz, C(24)**H**H'), 4.80 (1H, d, *J* = 10.0 Hz, C(24)H**H'**), 4.77 (1H, d, *J* = 10.5 Hz, C(30)**H**H'), 4.32 (1H, d, *J* = 10.5 Hz, C(30)H**H'**), 4.01 (1H, d, *J* = 10.0 Hz, C(22)**H**H'), 3.99 (1H, d, *J* = 10.0 Hz, C(22)H**H'**), 3.84 (3H, s, C(36)$\mathbf{H_3}$), 3.80 and 3.76 (2 x 3H, s, C(29)$\mathbf{H_3}$ and C(35)$\mathbf{H_3}$).

δ_C(151 MHz, $CDCl_3$, 35 resonances out of 36 observed, 1 x **Ar**, resonance not observed): 173.1 (**C**(23)), 159.2 (**Ar**), 157.1 (**Ar**), 154.4 (**C**(10)), 137.4 (**Ar**), 135.8 (**Ar**), 133.9 (**Ar**), 131.9 (**Ar**), 130.2 (**Ar**), 130.0 (**Ar**), 130.0 (**Ar**), 129.6 (**Ar**), 129.4 (**Ar**), 128.6 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 128.0 (**Ar**), 127.4 (**Ar**), 124.5 (**Ar**), 124.2 (**Ar**), 117.5 (**Ar**), 113.8 (**Ar**), 113.7 (**Ar**), 113.2 (**Ar**), 84.8 (**C**(8)), 80.4 (**C**(7)), 71.7 (**C**(22)), 68.4 (**C**(11)), 68.3 (**C**(30)), 67.6 (**C**(24)), 58.3 (**C**(9)), 55.8 (**C**(36)), 55.44 and 55.41 (**C**(29) and **C**(35)).

m/z HRMS (ESI^+) found 802.1617; $C_{42}H_{38}NO_9{}^{79}BrNa^+$ ($M+Na^+$) requires 802.1622.

$[\alpha]_D^{25}$ = –59.7

Benzyl (6*S*,12*R*,13*R*)-13-(hydroxymethyl)-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (196)



To a solution of benzyl (3a*R*,4*S*,9b*R*)-4-(2-bromophenyl)-8-methoxy-3a,9b-bis((4-methoxybenzyl)oxy)-1-oxo-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3*H*)-carboxylate (**195**, 1.096 g, 1.41 mmol, 1.0 eq.) in tetrahydrofuran (27 mL) at –78 °C was added dropwise *n*-butyllithium (1.6 M in hexane, 1.05 mL, 1.688 mmol, 1.2 eq.). The reaction was stirred at –78 °C for 5 min then warmed to RT and stirred for a further 30 min. The reaction was then cooled to 0 °C and quenched by dropwise addition of sat. aq. ammonium chloride solution (20 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (5% to 10% ethyl acetate in toluene) to give the title compound as a white solid (924.1 mg, 1.318 mmol, 94%).

*At room temperature, compound **196** exists as a 2 : 1 inseparable mixture of the primary alcohol (shown) and the corresponding lactol **199**. The ^{1}H and ^{13}C NMR spectra of the mixture at room temperature display broad resonances due to the presence of rotamers. Upon heating to 105 °C in DMSO-d_6, the resonances in both the ^{1}H and the ^{13}C NMR spectra coalesce. At this temperature, the ratio of primary alcohol : lactol is 5 : 1. NMR data is given for the primary alcohol form only, taken from the NMR spectra of the mixture at 105 °C.*

R_f: 0.3 (10% ethyl acetate in toluene).

m.p.: 63.1 – 65.4 °C.

ν_{max}/cm^{-1} (thin film): 1699 (m), 1690 (m), 1515 (s), 1500 (m), 1301 (m), 1250 (s), 1230 (m), 1035 (m).

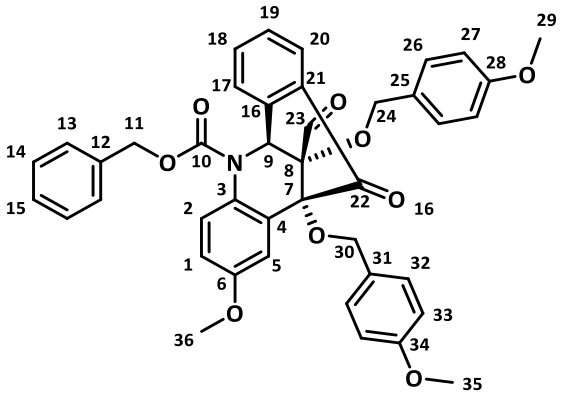
δ_H(500 MHz, DMSO, 378 K): 7.87 – 7.76 (1H, m, Ar**H**), 7.72 – 7.57 (3H, m, 3 x Ar**H**), 7.49 – 7.31 (8H, m, 8 x Ar**H**), 7.12 – 7.07 (2H, m, 2 x Ar**H**), 6.97 – 6.91 (2H, m, 2 x Ar**H**), 6.87 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.81 – 6.78 (2H, m, 2 x Ar**H**), 6.75 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.60 (1H, s, C(9)**H**), 5.34 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.27 (1H, d, *J* = 12.0 Hz, C(11)H**H'**), 4.93 (1H, d, *J* = 12.0 Hz, C(30)**H**H'), 4.87 (1H, t, *J* = 4.5 Hz, C(23)O**H**), 4.85 (1H, d, *J* = 11.0 Hz, C(24)**H**H'), 4.67 (1H, d, *J* = 11.0 Hz, C(24)H**H'**), 4.56 (1H, d, *J* = 12.0 Hz, C(30)H**H'**), 4.26 (1H, dd, *J* = 12.5, 4.5 Hz, C(23)**H**H'), 3.79 and 3.72 (2 x 3H, s, C(29)$\mathbf{H_3}$ and C(35)$\mathbf{H_3}$), 3.60 (1H, dd, *J* = 12.5, 4.5 Hz, C(23)H**H'**), 3.57 (3H, s, C(36)$\mathbf{H_3}$).

δ_C(126 MHz, DMSO, 378K): 190.0 (**C**(22)), 158.3 (**Ar**), 158.3 (**Ar**), 155.1 (**Ar**), 153.4 (**C**(10)), 136.8 (**Ar**), 135.4 (**Ar**), 134.0 (**Ar**), 131.3 (**Ar**), 130.4 (**Ar**), 130.1 (**Ar**), 129.4 (**Ar**), 128.9 (**Ar**), 128.4 (**Ar**), 128.2 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 127.6 (**Ar**), 127.6 (**Ar**), 125.6 (**Ar**), 123.8 (**Ar**), 123.7 (**Ar**), 114.8 (**Ar**), 113.4 (**Ar**), 113.3 (**Ar**), 110.5 (**Ar**), 84.4 (**C**(7)), 76.1 (**C**(8)), 67.9 (**C**(30)), 67.4 (**C**(11)), 64.8 (**C**(24)), 61.7 (**C**(23)), 54.9 (**C**(9)), 54.8 (**C**(36)), 54.7 and 54.6 (**C**(29) and **C**(35)).

m/z HRMS (ESI$^+$) found 724.2513; $C_{42}H_{39}NO_9Na^+$ (M+Na$^+$) requires 724.2517.

$[\alpha]_D^{25}$ = +104.6

Benzyl (6S,12R,13S)-13-formyl-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (200)



Prepared according to the procedure of Davies.[140]

To a solution of benzyl (6*S*,12*R*,13*R*)-13-(hydroxymethyl)-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**196**, 881.9 mg, 1.258 mmol, 1.0 eq.) in dichloromethane (25 mL) at 0 °C was added sodium bicarbonate (951.1 mg, 11.32 mmol, 9.0 eq.) followed by Dess-Martin periodinane (1.60 g, 3.774 mmol, 3.0 eq.). The reaction was warmed to RT and stirred for 1 h then cooled to 0 °C and quenched with sat. aq. sodium bicarbonate (25 mL). Sodium thiosulfate pentahydrate (5 g) was added and the biphasic mixture was stirred rigorously for 10 min. The layers were separated and the aqueous layer was extracted with dichloromethane (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (30% to 50% ethyl acetate in pentane) to give the title compound as a white solid (788.7 mg, 1.128 mmol, 90%).

R_f: 0.2 (30% ethyl acetate in petroleum ether).

m.p.: 74.2 – 77.2 °C.

ν_{max}/cm^{-1} (thin film): 1734 (m), 1706 (m), 1515 (s), 1499 (m), 1302 (m), 1273 (m), 1253 (s), 1235 (m), 912 (m).

δ_H(600 MHz, $CDCl_3$): 9.96 (1H, s, C(23)**H**), 7.90 (1H, dd, *J* = 8.0, 1.5 Hz, Ar**H**), 7.64 (1H, d, *J* = 6.0 Hz, Ar**H**), 7.58 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.43 – 7.38 (2H, m, 2 x Ar**H**), 7.38 – 7.30 (7H, m, 7 x Ar**H**), 7.07 – 7.02 (2H, m, 2 x Ar**H**), 6.96 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.88 – 6.84 (2H, m, 2 x Ar**H**), 6.81 – 6.75 (2H, m, 2 x Ar**H**), 6.74 – 6.72 (1H, m, Ar**H**), 6.53 (1H, s, C(9)**H**), 5.33 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.22 (1H, br s, C(11)H**H'**), 5.04 (1H, d, *J* = 12.5

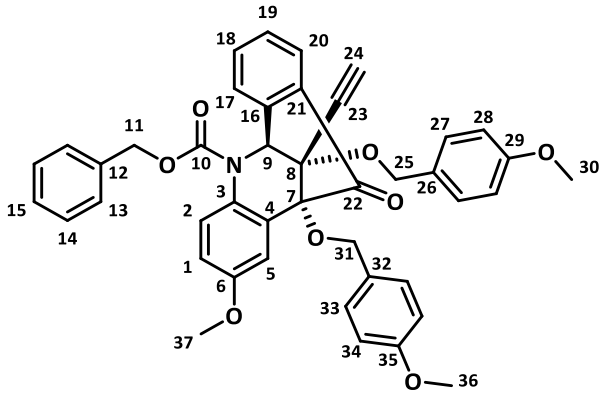
Hz, C(30)**H**H'), 4.75 (1H, d, *J* = 12.5 Hz, C(30)H**H'**), 4.61 (1H, br s, C(24)**H**H'), 4.45 (1H, br s, C(24)H**H'**), 3.81 and 3.76 (2 x 3H, s, C(29)$\mathbf{H_3}$ and C(35)$\mathbf{H_3}$), 3.55 (3H, s, C(36)$\mathbf{H_3}$).

δ_C(151 MHz, $CDCl_3$, 35 out of 36 resonances observed, 1 x Ar resonance not observed): 199.5 (**C**(23)), 190.0 (**C**(22)), 159.5 (**Ar**), 158.9 (**Ar**), 156.6 (**Ar**), 154.4 (**C**(10)), 136.8 (**Ar**), 135.6 (**Ar**), 135.1 (**Ar**), 131.4 (**Ar**), 129.8 (**Ar**), 129.4 (**Ar**), 129.3 (**Ar**), 129.0 (**Ar**), 128.9 (**Ar**), 128.8 (**Ar**), 128.7 (**Ar**), 128.7 (**Ar**), 128.2 (**Ar**), 127.4 (**Ar**), 125.2 (**Ar**), 123.6 (**Ar**), 117.1 (**Ar**), 114.0 (**Ar**), 113.9 (**Ar**), 110.2 (**Ar**), 84.5 (**C**(7)), 80.0 (**C**(8)), 70.0 (**C**(30)), 68.9 (**C**(11)), 67.1 (**C**(24)), 55.51 and 55.49 (**C**(29) and **C**(35)), 55.4 (**C**(36)), 54.9 (**C**(9)).

m/z HRMS (ESI^+) found 722.2355; $C_{42}H_{37}NO_9Na^+$ ($M+Na^+$) requires 722.2361.

$[\alpha]_D^{25}$ = +181.3

Benzyl (6*S*,12*R*,13*S*)-13-ethynyl-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (201)



Prepared according to the procedure of Davies.[140]

To a solution of benzyl (6*S*,12*R*,13*S*)-13-formyl-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**200**, 779.8 mg, 1.115 mmol, 1.0 eq.) in methanol (13 mL) was added potassium carbonate (462.3 mg, 3.345 mmol, 3.0 eq.). Dimethyl (1-diazo-2-oxopropyl)phosphonate (**141**, 428.4 mg, 2.23 mmol, 2.0 eq.) was dissolved in methanol (4 mL) and added dropwise to the reaction mixture at RT. The reaction was stirred at RT for 20 h then quenched with sat. aq. sodium bicarbonate (20 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (2% to 5% diethyl ether in toluene) to give the title compound as a pale yellow solid (661.5 mg, 0.951 mmol, 85%).

R_f: 0.5 (10% diethyl ether in toluene)

$[\alpha]_D^{25}$ = +178.9 (*c* = 1.00, chloroform)

δ_H(600 MHz, DMSO): 7.84 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.74 (1H, td, *J* = 7.5, 7.5 1.5 Hz, Ar**H**), 7.68 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.53 – 7.44 (4H, m, 4 x Ar**H**), 7.43 – 7.34 (5H, m, 5 x Ar**H**), 7.08 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 6.98 – 6.92 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 6.84 – 6.80 (3H, m, 3 x Ar**H**), 6.78 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.39 (1H, s, C(9)**H**), 5.35 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.29 (1H, d, *J*=12.0 Hz, C(11)H**H'**), 4.96 (1H, d, *J* = 11.5 Hz, C(31)**H**H'), 4.84 (1H, d, *J* = 10.0 Hz, C(25)**H**H'), 4.69 (1H, d, *J* = 11.5 Hz, C(31)H**H'**), 4.52 (1H, d, *J* = 10.0 Hz, C(25)H**H'**), 3.98 (1H, s, C(24)**H**), 3.77 and 3.70 (2 x 3H, s, C(30)$\mathbf{H_3}$ and C(36)$\mathbf{H_3}$), 3.56 (3H, s, C(37)$\mathbf{H_3}$)

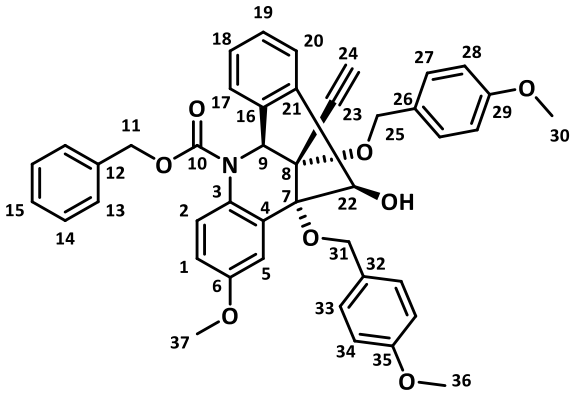
δ_C(151 MHz, DMSO): 190.3 (**C**(22)), 158.9 (**Ar**), 158.6 (**Ar**), 155.7 (**Ar**), 153.8 (**C**(10)), 136.5 (**Ar**), 135.6 (**Ar**), 135.2 (**Ar**), 130.9 (**Ar**), 130.8 (**Ar**), 130.2 (**Ar**), 129.7 (**Ar**), 129.6 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.2 (**Ar**), 127.4 (**Ar**), 124.0 (**Ar**), 115.2 (**Ar**), 113.7 (**Ar**), 113.6 (**Ar**), 110.9 (**Ar**), 84.4 (**C**(24)), 84.3 (**C**(7)), 78.6 (**C**(23)), 72.0 (**C**(8)), 68.3 (**C**(31)), 68.2 (**C**(11)), 66.7 (**C**(25)), 59.2 (**C**(9)), 55.1 (**C**(37)), 55.1 and 55.0 (**C**(30) and **C**(36))

m.p.: 61.4 – 64.2 °C;

m/z HRMS (ESI$^+$) found 718.2394; $C_{43}H_{37}NO_8Na^+$ (M+Na$^+$) requires 718.2411

ν_{max}/cm^{-1} (thin film): 1703 (m), 1613 (m), 1514 (s), 1498 (m), 1300 (m), 1269 (s), 1251 (s), 1234 (m), 1172 (m), 1019 (m)

Benzyl (6*S*,11*R*,12*S*,13*S*)-13-ethynyl-11-hydroxy-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (202)



Prepared according to the procedure of Li.[105]

To a solution of benzyl (6*S*,12*R*,13*S*)-13-ethynyl-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11-oxo-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**201**, 691.7 mg, 0.995 mmol, 1.0 eq.) in tetrahydrofuran (16 mL) at 0 °C was added dropwise lithium borohydride (2 M in tetrahydrofuran, 1.49 mL, 2.985 mmol, 3.0 eq.). The reaction was warmed to RT and stirred for 18 h then cooled to 0 °C and quenched with sat. aq. ammonium chloride (15 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% to 30% ethyl acetate in pentane) to give the title compound as a white solid (596.7 mg, 0.856 mmol, 86%).

R_f: 0.4 (30% ethyl acetate in petroleum ether).

m.p.: 85.7 – 87.1 °C.

ν_{max}/cm^{-1} (thin film): 1697 (m), 1691 (m), 1515 (m), 1498 (m), 1299 (m), 1252 (s), 1035 (m).

δ_H(600 MHz, DMSO): 7.52 – 7.43 (3H, m, 3 x Ar**H**), 7.43 – 7.30 (7H, m, 7 x Ar**H**), 7.29 – 7.24 (2H, m, 2 x Ar**H**), 7.08 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.01 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 6.90 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 6.78 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 6.71 – 6.61 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.12 (1H, s, C(9)**H**), 6.03 (1H, d, *J* = 6.5 Hz, C(22)O**H**), 5.35 (1H, d, *J* = 6.5 Hz, C(22)**H**), 5.28 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.15 – 5.13 (1H, m, C(11)H**H'**), 4.86 (1H, d,

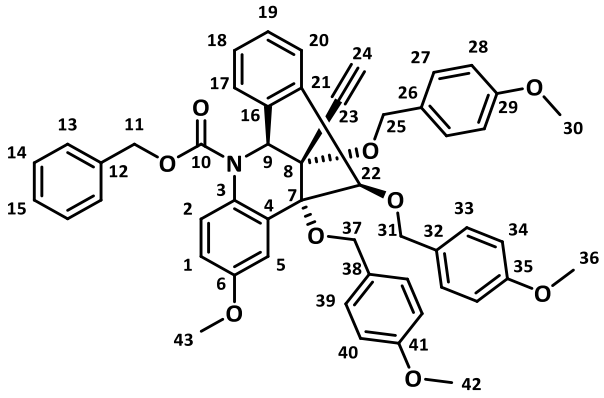
J = 12.0 Hz, C(31)**H**H'), 4.82 (1H, d, *J* = 10.0 Hz, C(25)**H**H'), 4.51 (1H, d, *J* = 12.0 Hz, C(31)H**H'**), 4.44 (1H, d, *J* = 10.0 Hz, C(25)H**H'**), 3.89 (1H, s, C(24)**H**), 3.75 and 3.68 (2 x 3H, s, C(30)$\mathbf{H_3}$ and C(36)$\mathbf{H_3}$), 3.57 (3H, s, C(37)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO, 35 resonances out of 37 observed, 2 x Ar resonances not observed): 158.7 (**Ar**), 158.3 (**Ar**), 154.1 (**Ar**), 153.8 (**C**(10)), 138.9 (**Ar**), 135.8 (**Ar**), 131.7 (**Ar**), 131.5 (**Ar**), 129.4 (**Ar**), 129.1 (**Ar**), 128.7 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 128.0 (**Ar**), 128.0 (**Ar**), 127.9 (**Ar**), 126.9 (**Ar**), 124.9 (**Ar**), 115.7 (**Ar**), 113.6 (**Ar**), 113.5 (**Ar**), 113.1 (**Ar**), 81.9 (**C**(24)), 80.6 (**C**(7)), 79.0 (**C**(23)), 74.9 (**C**(8)), 74.7 (**C**(22)), 68.0 (**C**(31)), 67.8 (**C**(11)), 66.0 (**C**(25)), 59.8 (**C**(9)), 55.03 and 55.02 (**C**(30) and **C**(36)), 54.8 (**C**(37)).

m/z HRMS (ESI$^+$) found 720.2559; $C_{43}H_{39}NO_8Na^+$ (M+Na$^+$) requires 720.2568.

$[\alpha]_D^{25}$ = +26.4

Benzyl (6*S*,11*R*,12*S*,13*S*)-13-ethynyl-2-methoxy-11,12,13-tris((4-methoxybenzyl)oxy)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (203)



To a solution of benzyl (6*S*,11*R*,12*S*,13*S*)-13-ethynyl-11-hydroxy-2-methoxy-12,13-bis((4-methoxybenzyl)oxy)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**202**, 546.2 mg, 0.783 mmol, 1.0 eq.) in dimethyl formamide (15 mL) at 0 °C was added sodium hydride (60% in mineral oil, 37.6 mg, 0.940 mmol, 1.2 eq.) as a single solid portion. The reaction mixture was warmed to RT and stirred for 15 min. 4-Methoxybenzyl bromide (0.25 mL, 1.566 mmol, 2.0 eq.) was added and the reaction was stirred at RT for 14 h then cooled to 0 °C and quenched by dropwise addition of sat. aq. ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (x 3) and the combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (2% to 5% diethyl ether in toluene) to give the title compound as a white solid (556.4 mg, 0.681 mmol, 87%).

R_f: 0.6 (10% diethyl ether in toluene).

m.p.: 65.4 – 67.9 °C.

ν_{max}/cm^{-1} (thin film): 1698 (m), 1614 (m), 1515 (s), 1498 (m), 1394 (m), 1302 (m), 1252 (s), 1035 (m), 736 (m).

δ_H(600 MHz, DMSO): 7.52 – 7.35 (6H, m, 6 x Ar**H**), 7.33 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 7.30 – 7.23 (4H, m, 4 x Ar**H**), 7.23 – 7.19 (2H, m, 2 x Ar**H**), 7.05 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**), 6.97 – 6.95 (2H, m, 2 x Ar**H**), 6.94 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.89 – 6.85 (2H, m, 2 x Ar**H**), 6.82 – 6.77 (2H, m, 2 x Ar**H**), 6.67 – 6.60 (1H, m, Ar**H**), 6.13 (1H, s, C(9)**H**), 5.28 (1H, d, *J* = 11.5 Hz, C(11)**H**H'), 5.27 (1H, s, C(22)**H**), 5.23 – 5.12 (1H, m, C(11)H**H'**), 5.00 (1H, d,

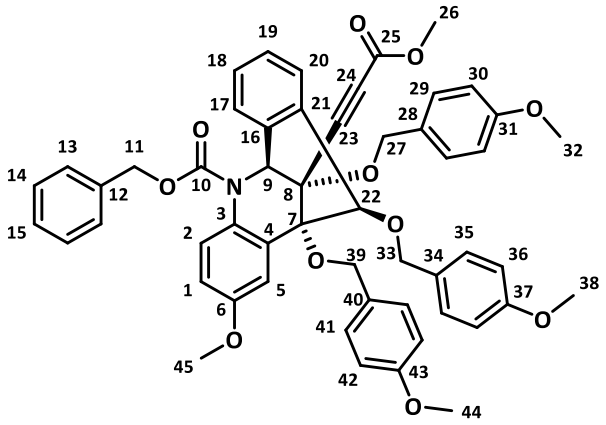
J = 10.0 Hz, C(31)**H**H'), 4.92 (1H, d, *J* = 10.0 Hz, C(31)H**H'**), 4.88 (1H, d, *J* = 11.0 Hz, C(37)**H**H'), 4.86 (1H, d, *J* = 9.5 Hz, C(25)**H**H'), 4.44 (1H, d, *J* = 11.5 Hz, C(37)H**H'**), 4.44 (1H, d, *J* = 9.5 Hz, C(25)H**H'**), 3.94 (1H, s, C(24)**H**), 3.77, 3.74 and 3.68 (3 x 3H, s, C(30)**H₃**, C(36)**H₃** and C(42)**H₃**), 3.36 (3H, s, C(43)**H₃**).

δ_C(151 MHz, DMSO): 158.9 (**Ar**), 158.8 (**Ar**), 158.6 (**Ar**), 154.1 (**Ar**), 153.8 (**C**(10)), 137.1 (**Ar**), 135.8 (**Ar**), 131.5 (**Ar**), 131.5 (**Ar**), 130.2 (**Ar**), 130.1 (**Ar**), 129.5 (**Ar**), 129.0 (**Ar**), 128.9 (**Ar**), 128.8 (**Ar**), 128.6 (**Ar**), 128.5(**Ar**), 128.5 (**Ar**), 128.3 (**Ar**), 128.3 (**Ar**), 128.2 (**Ar**), 126.9 (**Ar**), 125.3 (**Ar**), 124.3 (**Ar**), 114.5 (**Ar**), 114.4 (**Ar**), 113.7 (**Ar**), 113.7 (**Ar**), 113.6 (**Ar**), 83.3 (**C**(22)), 82.1 (**C**(24)), 82.0 (**C**(7)), 78.5 (**C**(23)), 75.6 (**C**(31)), 75.0 (**C**(8)), 68.7 (**C**(37)), 67.9 (**C**(11)), 66.0 (**C**(25)), 59.6 (**C**(9)), 55.1, 55.1 and 55.0 (**C**(30), **C**(36) and **C**(42)), 54.6 (**C**(43)).

m/z HRMS (ESI^+) found 840.3129; $C_{51}H_{47}NO_9Na^+$ ($M+Na^+$) requires 840.3143.

$[\alpha]_D^{25}$= +70.5

Benzyl (6*S*,11*R*,12*S*,13*S*)-2-methoxy-13-(3-methoxy-3-oxoprop-1-yn-1-yl)-11,12,13-tris((4-methoxybenzyl)oxy)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (204)



To a solution of benzyl (6*S*,11*R*,12*S*,13*S*)-13-ethynyl-2-methoxy-11,12,13-tris((4-methoxybenzyl)oxy)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**203**, 556.4 mg, 0.681 mmol, 1.0 eq.) in tetrahydrofuran (14 mL) at – 78 °C was added dropwise lithium bis(trimethylsilyl)amide (1 M in toluene, 0.82 mL, 0.82 mmol, 1.2 eq.) followed by hexamethylphosphoramide (0.59 mL, 3.405 mmol, 5.0 eq.). The reaction mixture was stirred at –78 °C for 15 min. Methyl chloroformate (0.11 mL, 1.362 mmol, 2.0 eq.) was added and the reaction was stirred at –78 °C for 2h then quenched at –78 °C with pre-cooled methanol (5 mL). The mixture was warmed to RT and partitioned between water (30 mL) and ethyl acetate (40 mL). The layers were separated and the aqueous fraction was extracted with ethyl acetate (x 2). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% to 30% ethyl acetate in pentane)to give the title compound as a white solid (477.8 mg, 0.546 mmol, 80%).

R_f: 0.4 (30% ethyl acetate in petroleum ether).

m.p.: 68.6 – 71.0 °C.

ν_{max}/cm^{-1} (thin film): 1718 (m), 1614 (m), 1515 (s), 1498 (m), 1251 (s), 1123 (m), 1102 (m), 760 (m).

δ_H(600 MHz, DMSO): 7.52 – 7.42 (2H, m, 2 x Ar**H**), 7.42 – 7.25 (10H, m, 10 x Ar**H**), 7.25 – 7.20 (2H, m, 2 x Ar**H**), 7.05 (2H, d, *J* = 8.5 Hz, 2 x Ar**H**), 6.99 – 6.94 (2H, m, 2 x Ar**H**), 6.93 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.89 – 6.84 (2H, m, 2 x Ar**H**), 6.83 – 6.77 (2H, m, 2 x Ar**H**), 6.66 (1H, dd, *J* = 9.0, 3.0 Hz, Ar**H**), 6.25 (1H, s, C(9)**H**), 5.29 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.25 – 5.17 (1H, m, C(11)H**H'**), 5.20 (1H, s, C(22)**H**), 4.99 (1H, d, *J* = 10.5 Hz, C(33)**H**H'),

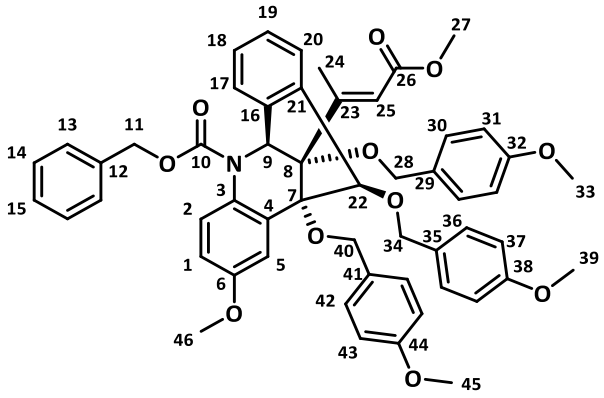
4.95 (1H, d, *J* = 10.5 Hz, C(33)H**H'**), 4.87 (1H, d, *J* = 12.0 Hz, C(39)**H**H'), 4.81 (1H, d, *J* = 10.0 Hz, C(27)**H**H'), 4.50 (1H, d, *J* = 10.0 Hz, C(27)H**H'**), 4.47 (1H, d, *J* = 12.0 Hz, C(39)H**H'**), 3.77, 3.73 and 3.69 (3 x 3H, s, C(32)**H₃**, C(38)**H₃** and C(44)**H₃**), 3.74 (3H, s, C(26)**H₃**), 3.38 (3H, s, C(45)**H₃**).

δ_C(151 MHz, DMSO, 43 resonances out of 45 observed, 2 x Ar resonances not observed): 159.0 (**Ar**), 158.9 (**Ar**), 158.6 (**Ar**), 154.2 (**Ar**), 153.6 (**C**(10)), 152.3 (**C**(25)), 136.7 (**Ar**), 135.7 (**Ar**), 131.2 (**Ar**), 130.8 (**Ar**), 130.3 (**Ar**), 129.9 (**Ar**), 129.6 (**Ar**), 128.9 (**Ar**), 128.9 (**Ar**), 128.7 (**Ar**), 128.6 (**Ar**), 128.6 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 127.0 (**Ar**), 123.7 (**Ar**), 114.7 (**Ar**), 114.4 (**Ar**), 113.8 (**Ar**), 113.7 (**Ar**), 113.6 (**Ar**), 82.7 (**C**(22)), 82.4 (**C**(7)), 81.8 and 81.1 (**C**(23) and **C**(24)), 75.5 (**C**(33)), 75.5 (**C**(8)), 68.9 (**C**(39)), 68.0 (**C**(11)), 66.7 (**C**(27)), 58.8 (**C**(9)), 55.10, 55.08 and 55.0 (**C**(32), **C**(38) and **C**(44)), 54.6 (**C**(45)), 53.3 (**C**(26)).

m/z HRMS (ESI$^+$) found 898.3181; $C_{53}H_{49}NO_{11}Na^+$ (M+Na$^+$) requires 898.3198.

$[\alpha]_D^{25}$= +80.2

Benzyl (6*S*,11*R*,12*S*,13*S*)-2-methoxy-13-((*E*)-4-methoxy-4-oxobut-2-en-2-yl)-11,12,13-tris((4-methoxybenzyl)oxy)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (205)



Copper(I) cyanide (90.0 mg, 1.005 mmol, 4.0 eq.) was suspended in freeze-pump-thaw degassed diethyl ether (4.0 mL) and cooled to 0°C. Methyllithium solution (1.7M in diethyl ether, 1.17 mL, 1.983 mmol, 7.9 eq.) was added dropwise, initially giving a bright yellow solution whose colour dissipated over the course of the addition to give a light grey solution. A solution of benzyl (6*R*,11*S*,12*R*,13*R*)-11,12,13-tris(benzyloxy)-2-methoxy-13-(3-methoxy-3-oxoprop-1-yn-1-yl)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**204**, 61.5 mg, 0.078 mmol, 1.0 eq.) in diethyl ether (3.0 mL) was added dropwise at 0 °C, giving a pale yellow solution. The reaction was stirred at 0 °C for 3 h then quenched by dropwise addition of methanol (3.0 mL). Ammonium hydroxide (10% wt. in sat. aq. ammonium chloride, 10 mL) was added and the resultant biphasic mixture was stirred vigorously at RT for 5 min then extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (2% to 10% diethyl ether in toluene) to give the title compound as a colourless oil (105.5 mg, 0.118 mmol, 47%).

R_f: 0.6 (10% diethyl ether in toluene).

m.p.: 69.4 – 73.2 °C.

ν_{max}/cm^{-1} (thin film): 1719 (m), 1687 (m), 1515 (s), 1303 (m), 1252 (s), 1213 (m), 1121 (m), 1034 (m), 736 (m).

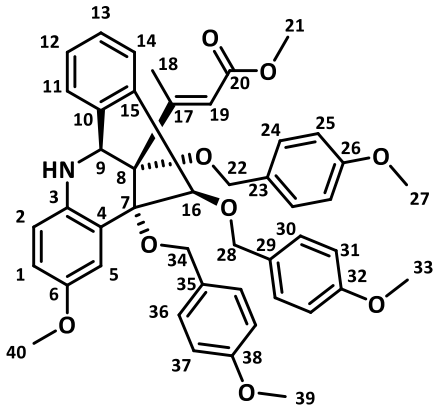
δ_H(600 MHz, DMSO): 7.53 – 7.31 (7H, m, 7 x Ar**H**), 7.32 – 7.25 (3H, m, 3 x Ar**H**), 7.25 – 7.19 (2H, m, 2 x Ar**H**), 7.13 – 7.04 (4H, m, 4 x Ar**H**), 7.00 – 6.96 (2H, m, 2 x Ar**H**), 6.93 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.83 – 6.76 (4H, m, 4 x Ar**H**), 6.62 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.29 (1H, s, C(9)**H**), 5.56 (1H, s, C(25)**H**), 5.29 (1H, d, *J* = 12.0 Hz, C(11)**H**H'), 5.27 – 5.12 (1H, m, C(11)H**H'**), 4.94 (1H, d, *J* = 11.5 Hz, C(40)**H**H'), 4.90 (1H, d, *J* = 10.0 Hz, C(34)**H**H'), 4.81 (1H, d, *J* = 10.0 Hz, C(34)H**H'**), 4.48 (1H, s, C(22)**H**), 4.36 (1H, d, *J* = 11.5 Hz, C(40)H**H'**), 4.36 (1H, d, *J* = 10.5 Hz, C(28)**H**H'), 4.18 (1H, d, *J* = 10.5 Hz, C(28)H**H'**), 3.77, 3.72 and 3.68 (3 x 3H, s, C(33)$\mathbf{H_3}$, C(39)$\mathbf{H_3}$, C(45)$\mathbf{H_3}$), 3.57 (3H, s, C(27)$\mathbf{H_3}$), 3.29 (3H, s, C(46)$\mathbf{H_3}$), 2.67 (3H, s, C(24)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO, 44 resonances out of 46 observed, **C**(23) and 1 x Ar resonance not observed): 165.2 (**C**(26)), 158.9 (**Ar**), 158.8 (**Ar**), 158.7 (**Ar**), 153.5 (**C**(10)), 137.3 (**Ar**), 135.8 (**Ar**), 133.1 (**Ar**), 131.1 (**Ar**), 130.2 (**Ar**), 130.1 (**Ar**), 129.5 (**Ar**), 129.2 (**Ar**), 129.2 (**Ar**), 129.0 (**Ar**), 128.8 (**Ar**), 128.8 (**Ar**), 128.5 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.3 (**Ar**), 127.4 (**Ar**), 126.8 (**Ar**), 125.4 (**Ar**), 121.0 (**C**(25)), 114.8 (**Ar**), 114.5 (**Ar**), 113.8 (**Ar**), 113.7 (**Ar**), 113.5 (**Ar**), 84.2 (**C**(7)), 81.7 (**C**(22)), 80.2 (**C**(8)), 75.6 (**C**(34)), 68.4 (**C**(40)), 67.8 (**C**(11)), 64.4 (**C**(28)), 57.2 (**C**(9)), 55.11, 55.09 and 55.0 (**C**(33), **C**(39) and **C**(45)), 54.4 (**C**(46)), 51.2 (**C**(27)), 16.2 (**C**(24)).

m/z HRMS (ESI^+) found 914.3507; $C_{54}H_{53}NO_{11}Na^+$ ($M+Na^+$) requires 914.3511.

$[\alpha]_D^{25}$= +166.6

Methyl (*E*)-3-((6*S*,11*R*,12*S*,13*S*)-2-methoxy-11,12,13-tris((4-methoxybenzyl)oxy)-5,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (206)



Prepared according to the procedure of Epplin.[134]

To a solution of benzyl (6*S*,11*R*,12*S*,13*S*)-2-methoxy-13-((*E*)-4-methoxy-4-oxobut-2-en-2-yl)-11,12,13-tris((4-methoxybenzyl)oxy)-11,12-dihydro-6,12-methanodibenzo[*b*,*f*]azocine-5(6*H*)-carboxylate (**205**, 109.9 mg, 0.123 mmol, 1.0 eq.) in methanol (13 mL) and ethyl acetate (1 mL) was added palladium on carbon (10% wt. Pd, 13.1 mg, 0.012 mmol, 0.1 eq.). The resulting suspension was degassed with nitrogen for five min. A balloon of hydrogen was added and bubbled with an escape needle for 5 min before the escape needle was removed and the reaction mixture was stirred under positive hydrogen pressure for 3 h. The hydrogen balloon was removed and the suspension was degassed with nitrogen for five min then filtered through Celite™, washing with ethyl acetate. The filtrate was dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (20% to 30% ethyl acetate in pentane) to give the title compound as a pale yellow solid (82.7 mg, 0.109 mmol, 89%).

R_f: 0.3 (30% ethyl acetate in petroleum ether).

m.p.: 89.4 – 91.5 °C.

ν_{max}/cm^{-1} (thin film): 1721 (m), 1614 (m), 1514 (s), 1302 (m), 1252 (s), 1211 (m), 1174 (m), 1038 (s), 764 (m).

δ_H(600 MHz, DMSO): 7.49 – 7.44 (1H, m, Ar**H**), 7.31 – 7.20 (6H, m, 6 x Ar**H**), 7.17 – 7.13 (1H, m, Ar**H**), 7.12 – 7.08 (2H, m, 2 x Ar**H**), 6.97 – 6.94 (2H, m, 2 x Ar**H**), 6.88 – 6.84 (2H, m, 2 x Ar**H**), 6.83 – 6.80 (2H, m, 2 x Ar**H**), 6.79 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.50 (1H, dd, *J* = 8.5, 3.0 Hz, Ar**H**), 6.42 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.05 (1H, d,

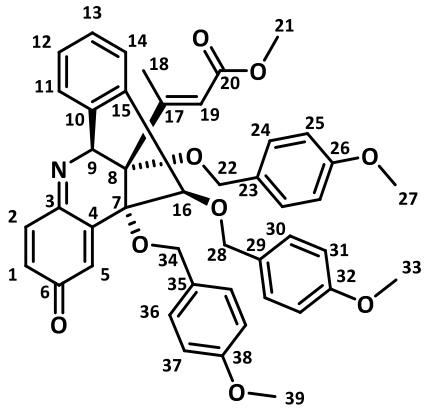
J = 4.0 Hz, N**H**), 5.61 (1H, s, C(19)**H**), 4.93 (1H, d, *J* = 10.0 Hz, C(28)**H**H'), 4.92 (1H, d, *J* = 4.0 Hz, C(9)**H**), 4.88 (1H, d, *J* = 12.0 Hz, C(34)**H**H'), 4.78 (1H, d, *J* = 10.0 Hz, C(28)H**H'**), 4.74 (1H, d, *J* = 10.5 Hz, C(22)**H**H'), 4.51 (1H, s, C(16)**H**), 4.40 (1H, d, *J* = 12.0 Hz, C(34)H**H'**), 4.13 (1H, d, *J* = 10.5 Hz, C(22)H**H'**), 3.76, 3.72 and 3.70 (3 x 3H, s, C(27)$\mathbf{H_3}$, C(33)$\mathbf{H_3}$, C(39)$\mathbf{H_3}$), 3.55 (3H, s, C(21)$\mathbf{H_3}$), 3.29 (3H, s, C(40)$\mathbf{H_3}$), 2.58 (3H, s, C(18)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO, 39 resonances out of 40 observed, 1 x Ar resonance not observed): 165.7 (**C**(20)), 158.8 (**Ar**), 158.6 (**Ar**), 158.5 (**Ar**), 155.4 (**C**(17)), 149.8 (**Ar**), 138.9 (**Ar**), 137.1 (**Ar**), 136.0 (**Ar**), 131.6 (**Ar**), 130.5 (**Ar**), 130.4 (**Ar**), 130.0 (**Ar**), 129.0 (**Ar**), 128.8 (**Ar**), 128.3 (**Ar**), 127.5 (**Ar**), 127.0 (**Ar**), 126.4 (**Ar**), 120.7 (**C**(19)), 119.0 (**Ar**), 115.5 (**Ar**), 115.1 (**Ar**), 113.8 (**Ar**), 113.6 (**Ar**), 113.5 (**Ar**), 84.3 (**C**(7)), 83.5 (**C**(16)), 80.0 (**C**(28)), 75.4 (**C**(34)), 67.9 (**C**(22)), 55.1, 55.04 and 55.01 (**C**(27), **C**(33) and **C**(39)), 54.9 (**C**(8)), 54.8 (**C**(9)), 54.6 (**C**(40)), 51.0 (**C**(21)), 15.9 (**C**(18)).

m/z HRMS (ESI$^+$) found 780.3130; $C_{46}H_{47}NO_9Na^+$ (M+Na$^+$) requires 780.3143.

$[\alpha]_D^{25}$ = +19.7

Methyl (E)-3-((6*S*,11*R*,12*S*,13*S*)-11,12,13-tris((4-methoxybenzyl)oxy)-2-oxo-2,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (207)



Prepared according to the procedure of Lebouef. [126]

To a solution of methyl (*E*)-3-((6*S*,11*R*,12*S*,13*S*)-2-methoxy-11,12,13-tris((4-methoxybenzyl)oxy)-5,6,11,12-tetrahydro-6,12-methanodibenzo[*b*,*f*]azocin-13-yl)but-2-enoate (**206**, 82.7 mg, 0.109 mmol, 1.0 eq.) in acetonitrile (4.0 mL) and water (1.3 mL) was added cerium (IV) ammonium nitrate (131.7 mg, 0.240 mmol, 2.2 eq.) as a single solid portion. The reaction mixture was stirred for 15 min then diluted with ethyl acetate (15 mL) and water (15 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (x 2). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (30% ethyl acetate in pentane) to give the title compound as pale yellow solid (68.2 mg, 0.092 mmol, 84%).

R_f: 0.4 (20% ethyl acetate in petroleum ether).

m.p.: 85.7 – 88.7 °C.

ν_{max}/cm^{-1} (thin film): 1724 (m), 1647 (m), 1614 (m), 1516 (s), 1303 (m), 1254 (s), 1217 (m), 1176 (m), 1061 (m), 1036 (s), 821 (m), 760 (s).

δ_H(600 MHz, DMSO): 7.52 (1H, dd, *J* = 7.5, 1.5 Hz, Ar**H**), 7.33 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.30 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.27 (1H, td, *J* = 7.5, 1.5 Hz, Ar**H**), 7.26 – 7.23 (2H, m, 2 x Ar**H**), 7.22 (1H, d, *J* = 10.0 Hz, C(5)**H**), 7.21 – 7.18 (2H, m, 2 x Ar**H**), 7.11 – 7.07 (2H, m, 2 x Ar**H**), 6.98 – 6.94 (2H, m, 2 x Ar**H**), 6.91 – 6.88 (2H, m, 2 x Ar**H**), 6.87 – 6.82 (2H, m, 2 x Ar**H**), 6.53 (1H, dd, *J* = 10.0, 2.0 Hz, C(1)**H**), 6.44 (1H, d, *J* = 2.0 Hz, C(2)**H**), 6.21 (1H, s,

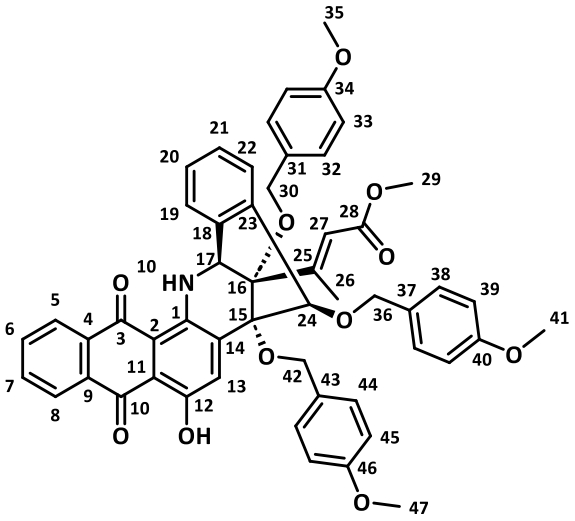
C(9)**H**), 5.79 (1H, q, *J* = 1.5 Hz, C(19)**H**), 4.89 (1H, d, *J* = 11.5 Hz, C(34)**H**H'), 4.83 (1H, d, *J* = 10.0 Hz, C(28)**H**H'), 4.77 (1H, d, *J* = 10.0 Hz, C(28)H**H'**), 4.52 (1H, d, *J* = 11.5 Hz, C(34)H**H'**), 4.49 (1H, s, C(16)**H**), 4.31 (1H, d, *J* = 10.5 Hz, C(22)**H**H'), 4.20 (1H, d, *J* = 10.5 Hz, C(22)H**H'**), 3.76, 3.73 and 3.71 (3 x 3H, s, C(27)**H₃**, C(33)**H₃**, C(39)**H₃**), 3.57 (3H, s, C(21)**H₃**), 2.52 (3H, d, *J* = 1.5 Hz, C(18)**H₃**).

δ_C(151 MHz, DMSO): 186.5 **C**(6), 165.5 **C**(20), 160.2 **C**(3), 158.9 (**Ar**), 158.8 (**Ar**), 158.8 (**Ar**), 153.0 **C**(17), 140.8 (**C**(5)), 136.3 **C**(4), 134.5 (**Ar**), 133.9 (**Ar**), 132.5 (**Ar**), 131.7 (**C**(1)), 130.3 (**C**(2)), 130.1 (**Ar**), 129.8 (**Ar**), 129.4 (**Ar**), 129.2 (**Ar**), 128.9 (**Ar**), 128.5 (**Ar**), 128.4 (**Ar**), 128.2 (**Ar**), 128.1 (**Ar**), 121.9 (**C**(19)), 113.9 (**Ar**), 113.8 (**Ar**), 113.6 (**Ar**), 83.8 (**C**(7)), 83.6 (**C**(8)), 79.1 (**C**(16)), 75.6 (**C**(28)), 68.2 (**C**(34)), 64.3 (**C**(22)), 64.0 (**C**(9)), 55.1, 55.03 and 55.02 (**C**(27), **C**(33) and **C**(39)), 51.2 (**C**(21)), 15.5 (**C**(18)).

m/z HRMS (ESI$^+$) found 764.2824; $C_{45}H_{43}NO_9Na^+$ (M+Na$^+$) requires 764.2830.

$[\alpha]_D^{25}$ = +86.5

Methyl (*E*)-3-((8*S*,9*R*,14*S*,17*S*)-6-hydroxy-8,9,17-tris((4-methoxybenzyl)oxy)-5,16-dioxo-5,8,9,14,15,16-hexahydro-8,14-methanoanthra[1,2-b]benzo[*f*]azocin-17-yl)but-2-enoate (208)



Prepared according to the procedure of Nicolaou.[127]

To a solution of 3-cyanophthalide (**14**, 16.9 mg, 0.110 mmol, 1.3 eq.) in tetrahydrofuran (1.7 mL) at –78 °C was added dropwise lithium bis(trimethylsilyl)amide (1 M in toluene, 0.11 mL, 0.110 mmol, 1.3 eq.). The resultant bright yellow solution was stirred at –78 °C for 15 min. A solution of methyl (*E*)-3-((6*S*,11*R*,12*S*,13*S*)-11,12,13-tris((4-methoxybenzyl)oxy)-2-oxo-2,6,11,12-tetrahydro-6,12-methanodibenzo[b,f]azocin-13-yl)but-2-enoate (**207**, 60.8 mg, 0.082 mmol, 1.0 eq.) in tetrahydrofuran (1.7 mL) was added dropwise. The cool bath was removed and the reaction mixture was allowed to warm to RT, during which time the bright yellow solution turned first dark green then dark purple. The reaction was stirred at RT for 15 min then quenched by dropwise addition of sat. aq. ammonium chloride solution (5 mL) and extracted with ethyl acetate (x 3). The combined organic fractions were dried over sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography (40% ethyl acetate in pentane) to give the title compound as dark purple solid (61.9 mg, 0.071 mmol, 86%).

R_f: 0.5 (10% ethyl acetate in toluene).

m.p.: 115.1 – 118.9 °C.

ν_{max}/cm^{-1} (thin film): 1795 (m), 1732 (m), 1616 (m), 1588 (m), 1515 (s), 1497 (m), 1303 (m), 1251 (s), 1211 (m), 1103 (m), 820 (m), 732 (m).

δ_H(600 MHz, DMSO): 13.21 (1H, s, C(12)O**H**), 10.71 (1H, d, *J* = 5.5 Hz (N**H**)), 8.25 (1H, dd, *J* = 8.0, 1.5 Hz, C(5)**H**), 8.20 (1H, dd, *J* = 8.0, 1.5 Hz, C(8)**H**), 7.92 (1H, td, *J* = 8.0, 1.5 Hz, C(6)**H**), 7.85 (1H, td, *J* = 8.0, 1.5 Hz, C(7)**H**), 7.61 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.37 (1H, s, C(13)**H**), 7.31 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.28 (2H, m, 2 x Ar**H**), 7.26 – 7.23 (1H, m, Ar**H**), 7.19 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.18 (2H, m, 2 x Ar**H**), 7.13 (2H, m, 2 x Ar**H**), 7.01 – 6.97 (2H, m, 2 x Ar**H**), 6.88 – 6.84 (2H, m, 2 x Ar**H**), 6.81 – 6.77 (2H, m, 2 x Ar**H**), 5.67 (1H, q, *J* = 1.5 Hz, C(27)**H**), 5.62 (1H, d, *J* = 5.5 Hz, C(17)**H**), 4.94 (1H, d, *J* = 11.5 Hz, C(42)**H**H'), 4.92 (1H, d, *J* = 10.0 Hz, C(36)**H**H'), 4.82 (1H, d, *J* = 10.0 Hz, C(36)H**H'**), 4.73 (1H, d, *J* = 10.0 Hz, C(30)**H**H'), 4.62 (1H, s, C(24)**H**), 4.32 (1H, d, *J* = 11.5 Hz, C(42)H**H'**), 4.19 (1H, d, *J* = 10.2 Hz, C(30)H**H'**), 3.78, 3.74 and 3.63 (3 x 3H, s, C(35)$\mathbf{H_3}$, C(41)$\mathbf{H_3}$, C(47)$\mathbf{H_3}$), 3.57 (3H, s, C(29)$\mathbf{H_3}$), 2.62 (3H, d, *J* = 1.5 Hz, C(26)$\mathbf{H_3}$).

δ_C(151 MHz, DMSO): 186.6 (**C**(10)), 180.9 (**C**(3)), 165.4 (**C**(28)), 158.9 (**Ar**), 158.9 (**Ar**), 158.7 (**Ar**), 154.6 (**C**(11)), 153.5 (**C**(25)), 144.2 (**C**(14)), 136.1(**Ar**), 134.7 (**C**(6)), 134.7 (**Ar**), 134.5 (**C**(9)), 134.2 (**C**(1)), 133.2 (**C**(7)), 132.1 (**C**(4)), 130.5 (**C**(13)), 130.4 (**Ar**), 130.1 (**Ar**), 129.9 (**Ar**), 129.6 (**Ar**), 129.4 (**Ar**), 129.1 (**Ar**), 129.1 (**Ar**), 127.8 (**Ar**), 127.4 (**Ar**), 127.0 (**Ar**), 126.4 (**C**(5)), 126.0 (**C**(8)), 121.5 (**C**(27)), 114.0 (**Ar**), 113.7 (**Ar**), 113.7 (**Ar**), 113.0 (**C**(12)), 107.8 (**C**(2)), 84.4 (**C**(15)), 82.0 (**C**(24)), 80.1 (**C**(16)), 75.6 (**C**(36)), 68.5 (**C**(42)), 63.4 (**C**(30)), 55.1, 55.0 and 54.9 (**C**(35), **C**(41) and **C**(47)), 53.3 (**C**(17)), 51.2 (**C**(29)), 15.7 (**C**(26)).

m/z HRMS (ESI^+) found 874.3235; $C_{53}H_{48}NO_{11}^+$ ($M+H^+$) requires 874.3222.

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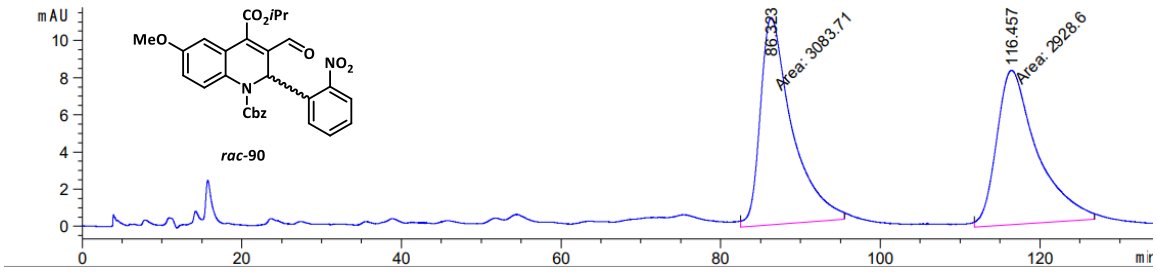
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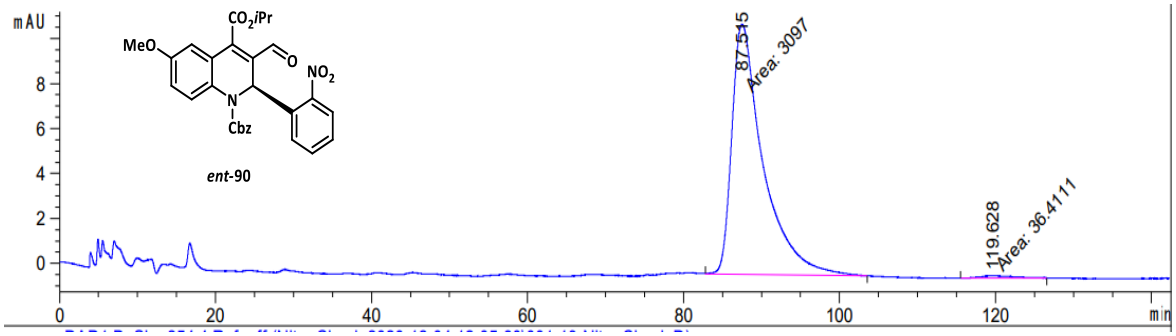
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Appendix

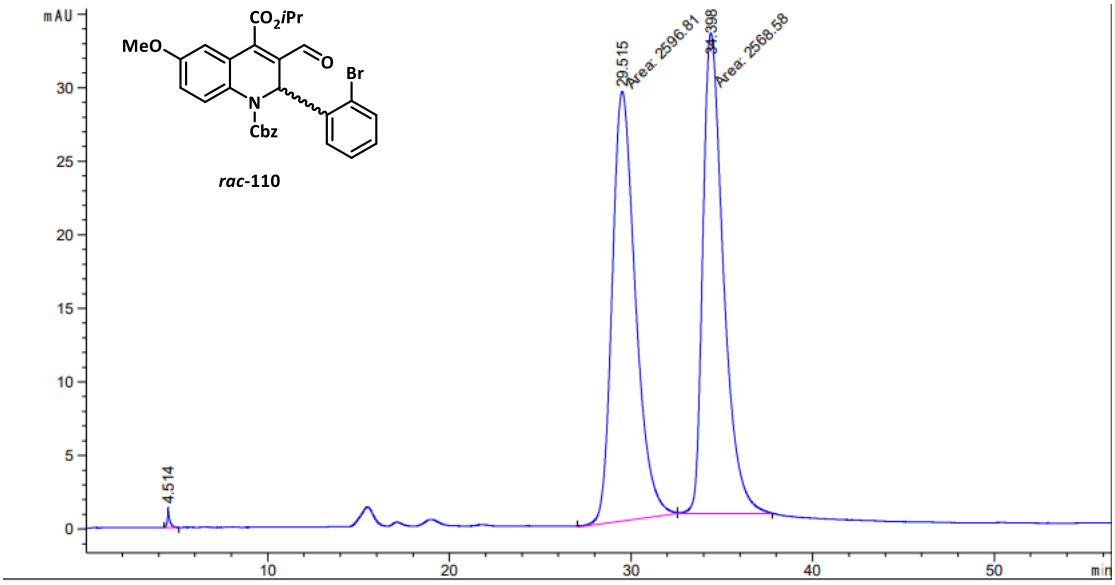
A1: HPLC Traces



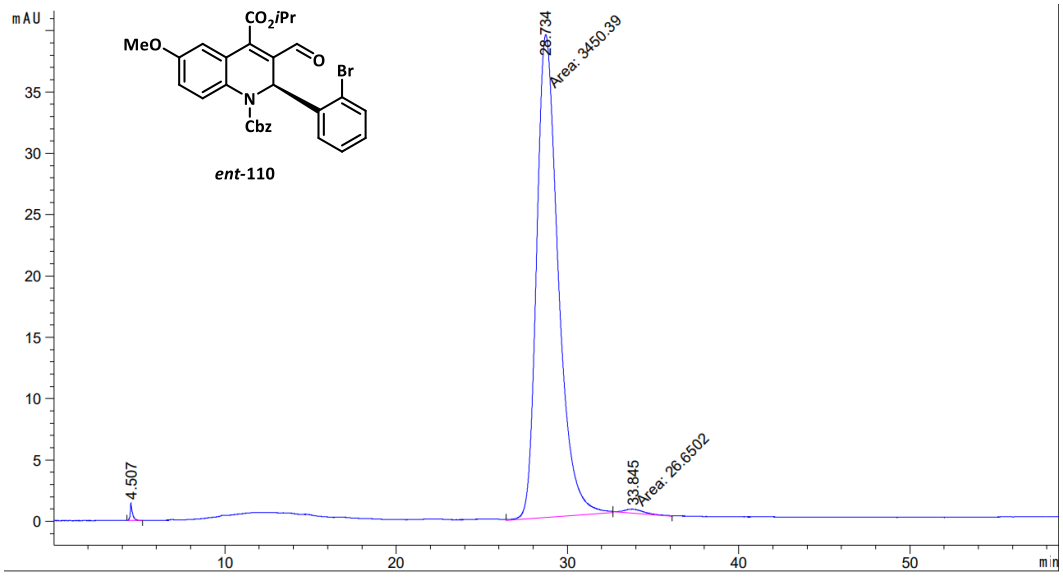
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	86.323	MM	4.6140	3083.70776	11.13901	51.2899
2	116.457	MM	5.8757	2928.60254	8.30714	48.7101



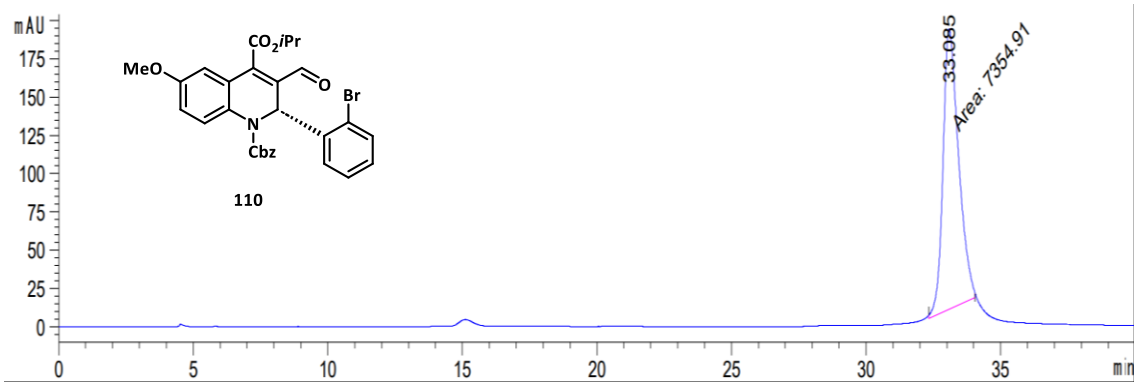
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	87.515	MM	4.6359	3096.99951	11.13412	98.8380
2	119.628	MM	5.3856	36.41108	1.12680e-1	1.1620



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.514	BB	0.1165	11.80692	1.34380	0.2281
2	29.515	MM	1.4833	2596.80713	29.17749	50.1586
3	34.398	MM	1.3113	2568.57715	32.64579	49.6133



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.507	BB	0.1164	12.44926	1.39071	0.3568
2	28.734	MM	1.4609	3450.38574	39.36285	98.8795
3	33.845	MM	1.3311	26.65024	3.33696e-1	0.7637

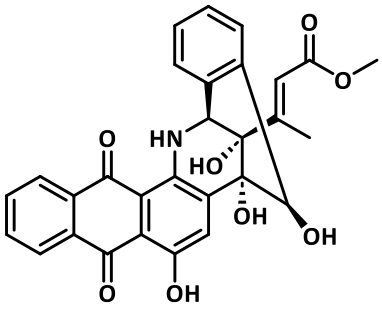


110

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.085	MM	0.6697	7354.91016	183.04808	100.0000

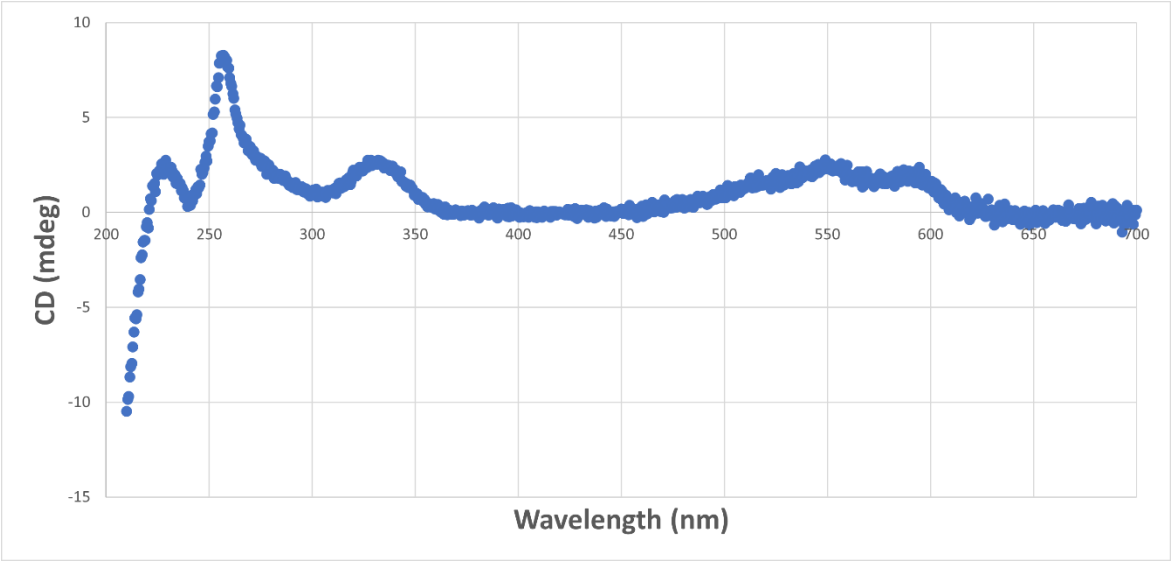
A2: Circular Dichroism

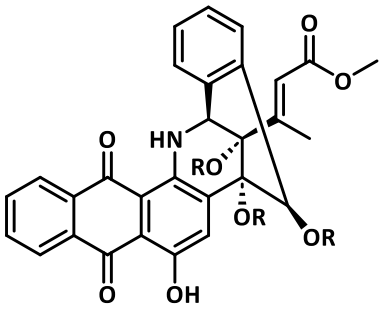
Circular dichroism experiments were carried out by Denis Hartmann (University of Oxford).



35
Sealutomicin C

To a cuvette with 10 mm path length and blackened sides was added a solution of **35** in $CHCl_3$ (0.025 µmol/mL). The sample was then measured on an Applied Photophysics Chirascan™ Spectrophotometer from 210 to 700 nm with a step size of 0.5 nm and a time per point of 1 s. Three successive spectra were recorded, averaged, and smoothed using a Savitzky-Golay filter.





208
R = PMB

Circular Dichroism: To a cuvette with 10 mm path length and blackened sides was added a solution of **208** in $CHCl_3$ (0.062 µmol/mL). The sample was then measured on an Applied Photophysics Chirascan™ Spectrophotometer from 250 to 600 nm with a step size of 0.5 nm and a time per point of 1 s. Three successive spectra were recorded, averaged, and smoothed using a Savitzky-Golay filter.

