

Studies Towards the Total Synthesis of an Anti-HIV Natural Product

Sean Guggiari

Merton College, University of Oxford

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Abstract

This thesis primarily concerns progress made towards the total synthesis of the natural product unciaphenol. The first half of Chapter 1 serves as an introduction to the target molecule and closely related enediyne natural products. This includes biological activity, proposed biosynthetic pathways, and previous synthetic efforts on the most closely related natural product to unciaphenol. The second half of Chapter 1 offers a brief historical perspective on the development of iminium ion and enamine organocatalysis. The use of such methods in the preparation of structural motifs similar to the core of unciaphenol is discussed.

Chapter 2 details the proposed strategy for the total synthesis of unciaphenol, including an amine catalysed coupling of an isatin-derived α-keto ester with an α,β-unsaturated aldehyde.

A general protocol for the preparation of such α-keto esters is presented in Chapter 3.

The development of the proposed organocatalysed cyclisation is detailed in Chapter 4. This begins with optimisation of the reaction conditions and is followed by investigation of the substrate scope. A putative mechanism and elucidation of product stereochemistry is offered.

Chapter 5 concerns the use of a model system to probe the proposed route to unciaphenol following the organocatalysed coupling.

Finally, Chapter 6 presents progress made on the total synthesis of unciaphenol using fully functionalised substrates. Included are the preparation of α,β-unsaturated aldehydes for the organocatalysed cyclisation and transformations subsequent to this coupling.

Full experimental details for all compounds prepared are offered further within the thesis.

Declaration

The work described in this thesis is entirely the work of the author and does not include any collaborative work, with the following exception:

All DFT calculations discussed in section 5.1 were performed by Thomas Sheridan.

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

Sean Guggiari

September 2019

Acknowledgements

It's strange. Though the past four years have held nothing but interesting times, few words now come to mind. If you are here seeking eloquence, none will be found. The words below are true and heartfelt, and so perhaps that will suffice. Also humour. There's hopefully some of that here, too.

When I moved to Oxford, I had little idea of where I was going. So a huge thanks to Prof. Jonathan Burton for giving me the chance to work in this group. Your continuous guidance and support have taught me much and served me motivation on numerous occasions. The relentless optimism, however…

In a somewhat similar vein, I would thank David Klauber, my industrial mentor. Your advice throughout has been valuable, as was your hosting of me at AstraZeneca last summer. Indeed, thanks are owed to everyone who aided me during that placement, with particular mention to Mairi Littleson for ensuring I never got sick of it.

Thanks of course must go to the SBM CDT, along with the EPSRC and all industrial sponsors, for providing my funding over the past four years. This has been a fantastic opportunity and I am grateful to Prof. Martin Smith, Prof. Darren Dixon, Lara Laurenço Venda, Maitaine Fernandez Chento, and Laura Thomas for all of the behind the scenes organisation.

Much less would have been accomplished were it not for the contributions of the CRL staff, with particular thanks to the NMR and X-ray crystallography services.

Where would this thesis be without proof-readers? I'd like to say in the same place, but that's assuredly incorrect. So, thanks to Prof. Jonathan Burton, Sam Chan, Jack Sutro, Dan Brown,

and Tom Sheridan for taking the time and effort to help improve this work. And thank you for accordingly taking all blame for any residual spelling or grammatical errors: I can't risk turnishing my own reputation.

In fact, the Burton group as a whole has been a wonderful experience both within and without the lab. In this, I feel I found what I was looking for and have learnt more of the world than I ever could have expected. To name but a few group members for their individual contributions to the past four years: Kilian Garrec, Manjeet Kumar, Nada Kurdi, Tom Sheridan, Dan Brown, Jack Sutro, Joe Mason, Sam Chan, Sandra Ainsua Martinez, Owen Smith, Bruno Sousa, and Erin Shepherd. By and large, all members not listed here, including Part II, visiting, and SBM rotation students have all contributed to the fantastic group atmosphere. Long may this continue.

Finally, as is tradition, I would thank my family. Through the highs and lows, you have always offered comfort and support. Without you, I would not be where I am now. Thank you.

Abbreviations

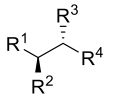
Ac	acetyl
ADC	antibody-drug conjugate
Alloc	allyloxycarbonyl
Am	amyl
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	aryl
B	base
Bn	benzyl
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting material
Bu	butyl
cat.	catalyst
Cbz	benzyloxycarbonyl
CI	chemical ionisation
cod	1,5-cyclooctadiene
conc.	concentration
COSY	correlation spectroscopy
CSA	camphor-10-sulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-*para*-benzoquinone
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMFDMA	*N*,*N*-dimethylformamide dimethyl acetal
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
dsDNA	double-stranded deoxyribonucleic acid
E	electrophile
EC_{50}	half maximal effective concentration
ee	enantiomeric excess

EI	electron ionisation
ent	enantiomeric
equiv	equivalents
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation spectroscopy
HMDS	bis(trimethylsilyl)amide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
HWE	Horner-Wadsworth-Emmons
i	iso
IC_{50}	half maximal inhibitory concentration
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
LDA	lithium diisopropylamide
lit.	literature
LUMO	lowest unoccupied molecular orbital
µw	microwave
m.p.	melting point
m/z	mass/charge ratio
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MIC	minimum inhibitory concentration
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonyl
MVK	3-buten-2-one
n	*normal*
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	*para*-nitrobenzenesulfonyl
Nu	nucleophile
PCC	pyridinium chlorochromate

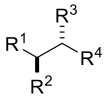
Ph	phenyl	TBS	*tert*-butyldimethylsilyl
PKS	polyketide synthase	temp	temperature
ppm	parts per million	TES	triethylsilyl
PPTS	pyridinium	Tf	trifluoromethanesulfonyl
	para-toluenesulfonate	TFA	trifluoroacetic acid
Pr	propyl	TFAA	trifluoroacetic anhydride
quant.	quantitative	THF	tetrahydrofuran
R	generic group	TIPS	triisopropylsilyl
rac	racemic	TLC	thin layer chromatography
R_f	retention factor	TMS	trimethylsilyl
rsm	recovered starting material	TPAP	tetrapropylammonium
rt	room temperature		perrhuthenate
sat.	saturated	Ts	*para*-toluenesulfonyl
t	*tert*	X	halide

Notes on convention

Within 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.[i]



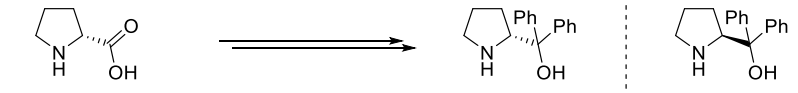
enantioenriched



racemic

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 separately in both enantioenriched forms, the prefix *ent*- will be used when:

1) the species is prepared by direct modification of the non-natural enantiomer of a natural product.

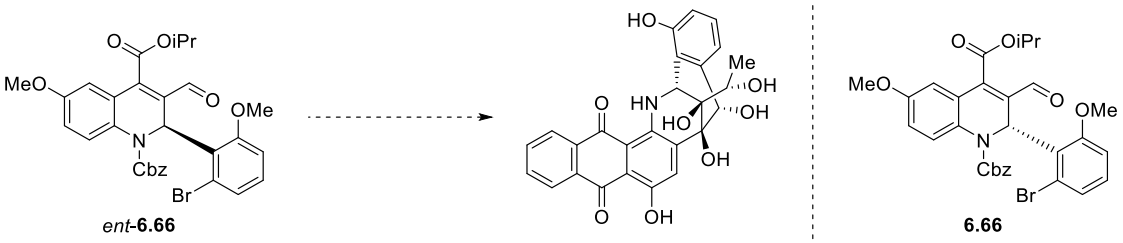


non-natural proline
ent-**1.81**

ent-**4.4**

4.4

2) the species is related to the preparation of the non-natural enantiomer of a natural product or analogue.



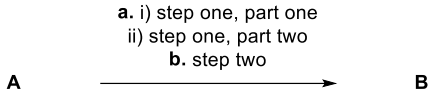
ent-**6.66**

non-natural unciaphenol
ent-**1.1**

6.66

[i] H. Maehr, *J. Chem. Educ.*, 2009, **62**, 114.

In reaction schemes, steps labelled as **a.**, **b.** etc. indicate a work-up and/or purification. Within these, sub-steps labelled as i), ii) etc. indicate isolation occurring only after the final sub-step.



*two isolations: after **a.** ii) and **b.***

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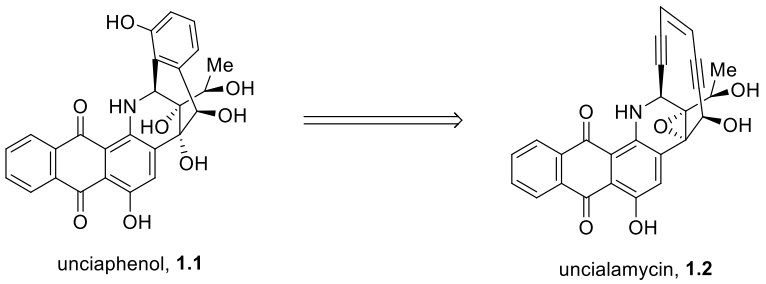
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1 Introduction

1.1 Unciaphenol and related natural products

1.1.1 Isolation of unciaphenol (1.1)

While lichens are an underexplored source of natural products, secondary metabolites isolated from associated organisms can display a wide range of biological activities.[1,2] One such example is the anthraquinone unciaphenol (**1.1**) (Scheme 1.1).[3] This compound was isolated by Andersen and co-workers from cultures of *Streptomyces uncialis*, extracted from the surface of the lichen *Cladonia uncialis*. Its structural features bear a strong resemblance to uncialamycin (**1.2**), which was isolated from the same cultures a decade prior.[4] This has led to the proposal that **1.2** is the biosynthetic precursor to **1.1** *via* Bergman cyclisation and oxygenation of the resultant arene (see section 1.1.3 for a more detailed discussion).



Scheme 1.1: Unciaphenol (**1.1**) and its proposed biosynthetic precursor uncialamycin (**1.2**).

Uncialamycin (**1.2**) itself belongs to the family of anthraquinone-fused enediyne natural products, of which there are four parent members (Figure 1.1). Dynemicin A (**1.3**) was the first to be isolated and contains the most elaborate northern fragment.[5] Tiancimycin A (**1.4**)[6] and yangpumicin A (**1.5**)[7] were isolated more recently by Shen and co-workers using a genome mining approach. This consisted of identifying five genes common to (at the time) all ten

known enediyne gene clusters, collectively termed the enediyne polyketide synthase (PKS) gene cassette. High-throughput screening of bacterial genomes for this PKS gene cassette signalled enediyne-producing strains, from which **1.4** and **1.5** were isolated. Unlike with dynemicin A (**1.3**), the three other anthraquinone enediynes bear an identical northern fragment, differing only in the oxygenation of the anthraquinone itself.

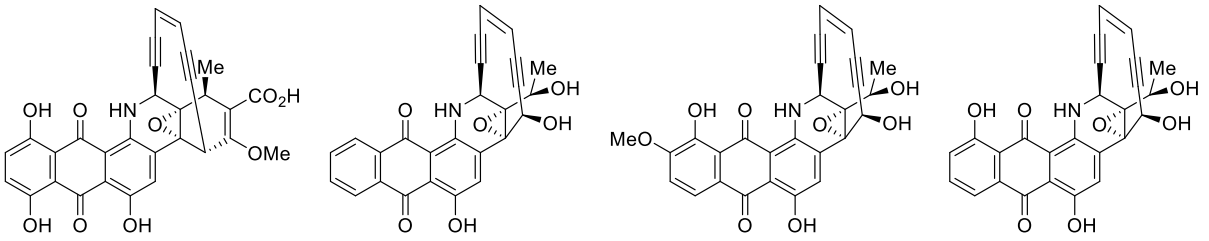


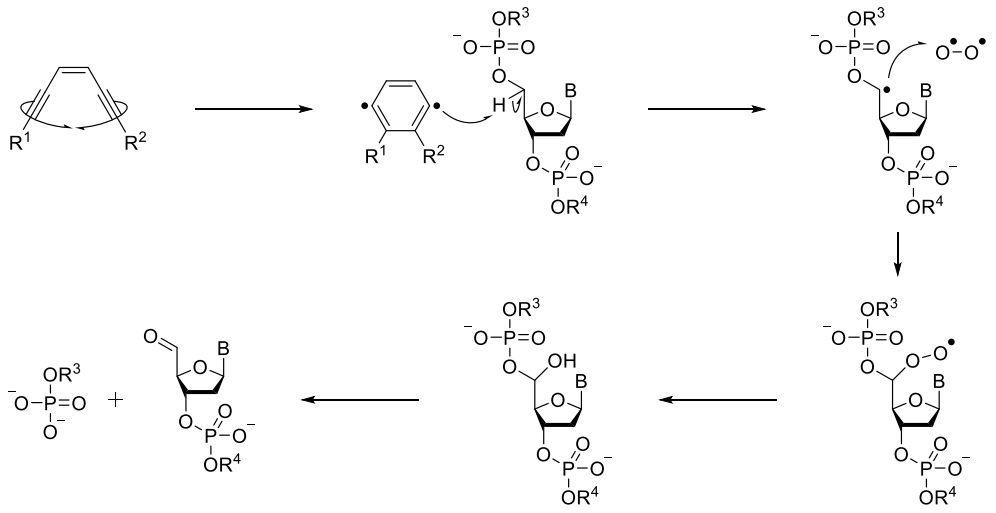
Figure 1.1: Anthraquinone-fused enediyne natural products.

1.1.2 Biological activity of unciaphenol (1.1) and related enediynes

In their isolation study, Andersen and co-workers screened unciaphenol (**1.1**) for biological activity in a range of assays.[3] From this, they report that **1.1** shows *in vitro* inhibition of HIV-1 replication (EC_{50} = 9.9 μM) with negligible cytotoxicity towards the host T-cell line. More interesting is that unciaphenol (**1.1**) demonstrated similar activity against strains resistant to three marketed anti-retroviral drugs: indinavir-resistant (14.1 μM), efavirenz-resistant (13.6 μM), and raltegravir-resistant (6.5 μM). These three treatments have different mechanisms of action: protease inhibition, non-nucleoside reverse transcriptase inhibition, and integrase inhibition respectively. That unciaphenol (**1.1**) appears relatively unaffected by the evolved resistances suggests a distinct mechanism of action in combating HIV. Elucidation of the relevant interactions, however, was hindered by the low quantity of **1.1** isolated.

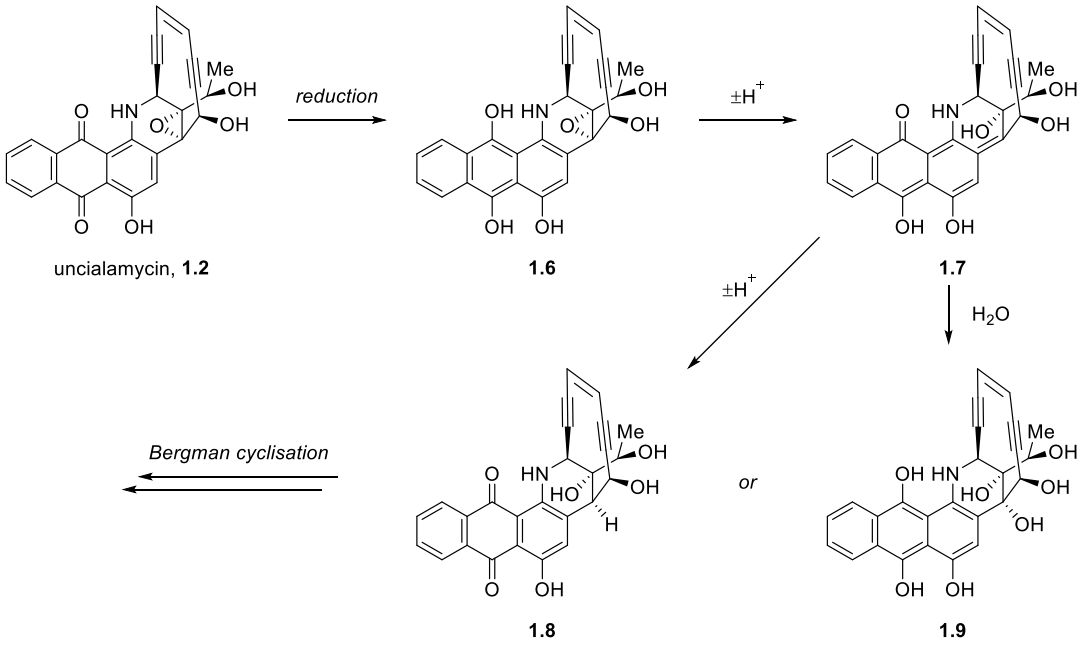
In contrast, the related enediynes in Figure 1.1 all show similarly potent cytotoxicity, both against bacterial strains and cancer cell lines. Several studies have demonstrated minimum inhibitory concentrations (MIC's) frequently below 1 ng.mL^{-1} against a range of gram-positive bacteria.[4,5,8] While the anthraquinone enediynes are often less effective against gram-negative strains, MIC values are still typically below 0.1 μg.mL^{-1}. Against various cancer cell lines, IC_{50} values on the order of 1 nM are frequently reported.[6–8]

The anthraquinone portion of the enediynes in Figure 1.1 is believed to intercalate into B-DNA, holding the remainder of the molecule in the minor groove.[9,10] The cytotoxicity then arises from the enediyne itself, *via* Bergman cyclisation to the corresponding *para*-benzyne diradical (Scheme 1.2).[11] When intercalated into DNA, these aryl radicals are held in close proximity to the deoxyribose units, leading to hydrogen abstraction from the DNA itself. Under aerobic conditions, the resulting carbon-centred radical can undergo quenching by triplet oxygen followed by subsequent fragmentation. An example involving C5′ abstraction is shown below.[12] Anaerobic conditions lead to alternative degradation pathways.[13] Both have been shown to cause dsDNA cleavage and interstrand crosslinks, ultimately leading to apoptosis.[14]



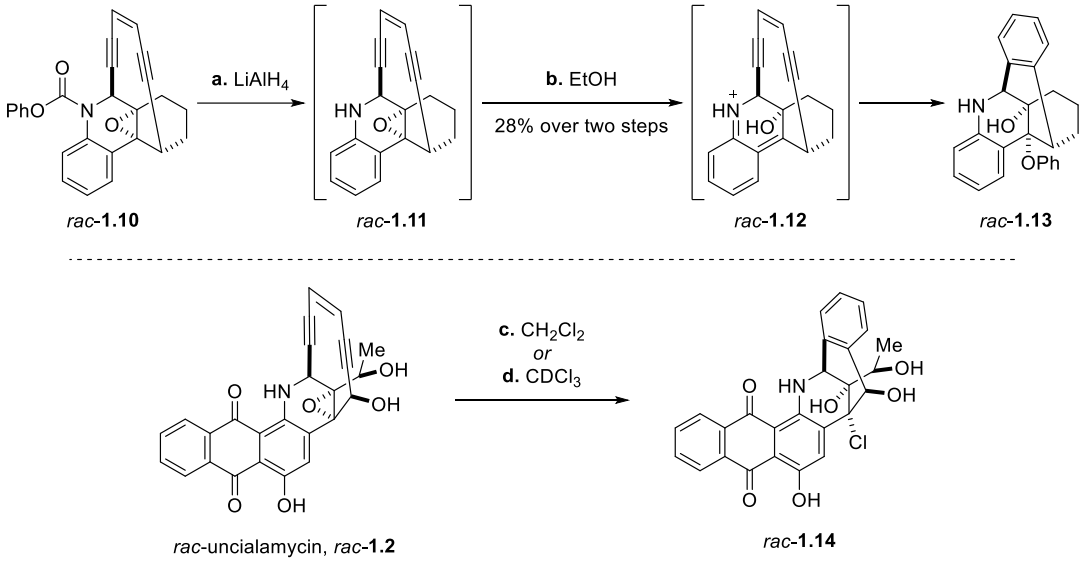
Scheme 1.2: Enediyne-induced degradation of DNA *via* C5′ hydrogen abstraction.

The isolated enediyne structures in Figure 1.1, however, have been described as stable both in pure form and in a variety of solutions.[15] This comes from the strain introduced by the epoxide moiety, which holds the reacting ends of the alkynes too far apart for significant interaction (3.60 Å in the X-ray crystal structure of **1.2**).[15] Opening of this epoxide relieves this strain and permits a rapid Bergman cycloaromatisation. Although this proceeds rapidly with acid catalysis (*vide infra*),[15] it is less facile under more physiologically relevant conditions.[8] Acceleration of the Bergman cycloaromatisation in the presence of thiols supports a mechanism beginning with reduction of the anthraquinone (Scheme 1.3).[8,9,12] Two electron reduction (or sequential one electron reductions) of uncialamycin (**1.2**) would produce anthraquinol **1.6**. This conjugated aromatic system is considerably more electron rich and so can better stabilise the open form of the epoxide, **1.7**. Tautomerisation of this quinone methide gives **1.8**, restoring the quinone system. Alternatively, nucleophilic attack (with water producing **1.9**) retains the reduced form of the arene. The strain induced by the epoxide is no longer present in either **1.8** or **1.9**, leading to facile Bergman cyclisation and DNA degradation.



Scheme 1.3: Proposed epoxide opening in a biological setting to allow Bergman cycloaromatisation.

Additional work by Nicolaou and co-workers has shown that initial reduction may not be required, depending on the substrate and the exact conditions. An analogue lacking the anthraquinone, *rac*-**1.11**, formed *in situ* from carbamate *rac*-**1.10**, was found to readily undergo cycloaromatisation to *rac*-**1.13** (Scheme 1.4).[16] Assistance from the nitrogen lone pair *via* iminoquinone methide *rac*-**1.12** was proposed to explain the lower stability of *rac*-**1.11** with respect to dynemicin A (**1.3**). This suggests that the electron withdrawing anthraquinone serves to temper the reactivity of the nitrogen lone pair to prevent premature epoxide opening. Meanwhile, the facile formation of *rac*-**1.14** from racemic uncialamycin (*rac*-**1.2**) in either HPLC grade CH_2Cl_2 or NMR grade $CDCl_3$, likely due to trace HCl or DCl catalysis, was postulated to involve a similar intermediate.[17]

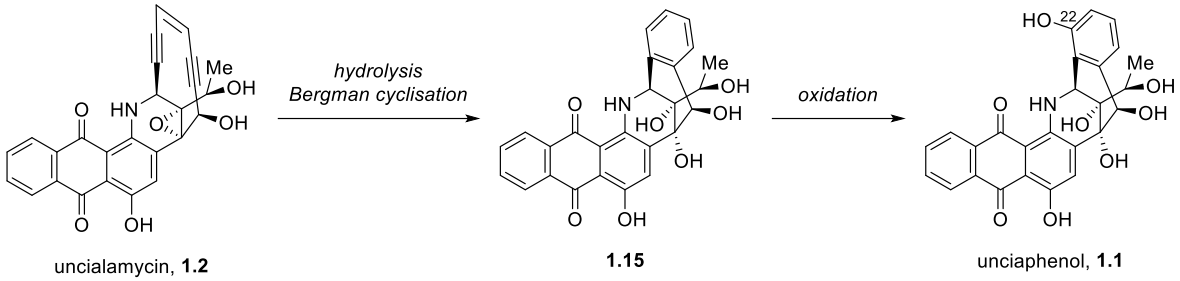


Scheme 1.4: Top: facile epoxide opening and Bergman cyclisation on an enediyne lacking the anthraquinone;[16] bottom: epoxide opening under trace acid catalysis.[17] Reagents and conditions: (a) $LiAlH_4$ (2.5 equiv), THF, 0 °C, 30 min; (b) EtOH, rt, 5 h, 28% over two steps; (c) CH_2Cl_2, rt, 12 h; (d) $CDCl_3$, rt, 30 min.

1.1.3 Biosynthesis of unciaphenol (1.1)

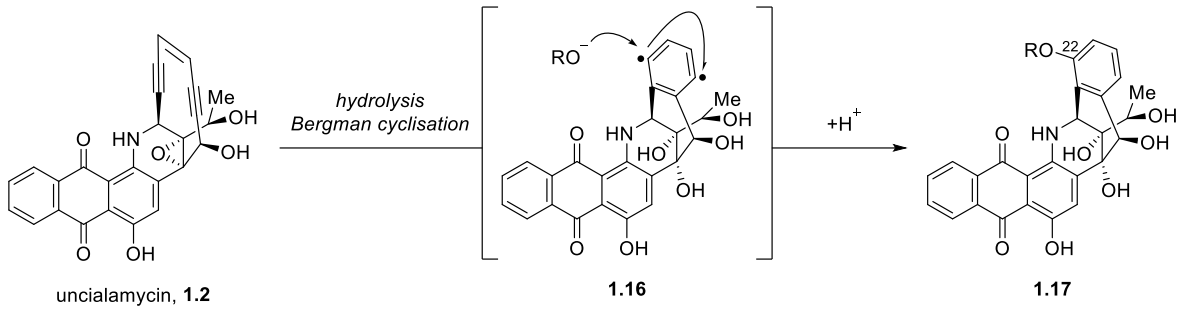
The mechanism of action discussed in the previous section would appear to also serve as the biosynthetic route from uncialamycin (**1.2**) to unciaphenol (**1.1**). Unlike the pathway shown to

1.9 (Scheme 1.3), however, no net redox of the anthraquinone moiety occurs. This may indicate epoxide hydrolysis more analogous to the acid catalysed reaction to *rac*-**1.14**, although reoxidation of an anthraquinol species could follow a reductive epoxide hydrolysis pathway. Another interesting aspect of **1.1** is the oxygen incorporation at C22. One possibility for this is *via* cytochrome P450 oxidation of the unfunctionalised arene of **1.15**, formed from Bergman cyclisation and hydrogen abstraction (Scheme 1.5).[18]



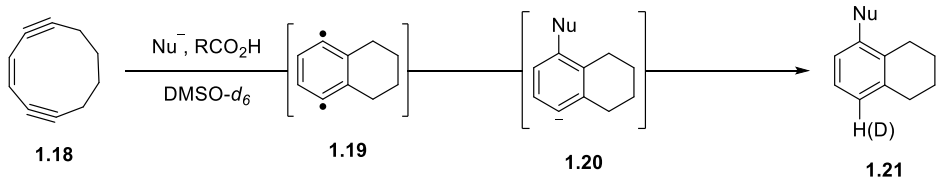
Scheme 1.5: Oxygenation at C22 of unciaphenol (**1.1**) may proceed *via* a cytochrome P450 oxidation following Bergman cyclisation and hydrogen abstraction.

In their isolation report, Andersen and co-workers suggested an alternative mechanism for this oxygen incorporation: regioselective addition of an oxygen-based nucleophile to the *para*-benzyne intermediate, **1.16**, with subsequent protonation of the resultant aryl anion (Scheme 1.6).[3] As the Bergman cycloaromatisation produces a singlet diradical species, the singly occupied sp^2 orbitals are able to interact across the ring. Molecular orbital calculations show that this interaction is actually antibonding,[19] and so (ignoring desolvation energies) addition of an anionic nucleophile is a barrierless transformation.[20] The highly basic resultant aryl anion would be rapidly protonated to produce **1.17**. Depending on the nature of the nucleophile, this could give **1.1** directly or require further modification.



Scheme 1.6: Oxygenation at C22 of unciaphenol (**1.1**) may proceed *via* addition of an oxygen-based nucleophile to the *para*-benzyne diradical intermediate, with subsequent protonation of the resultant aryl anion.

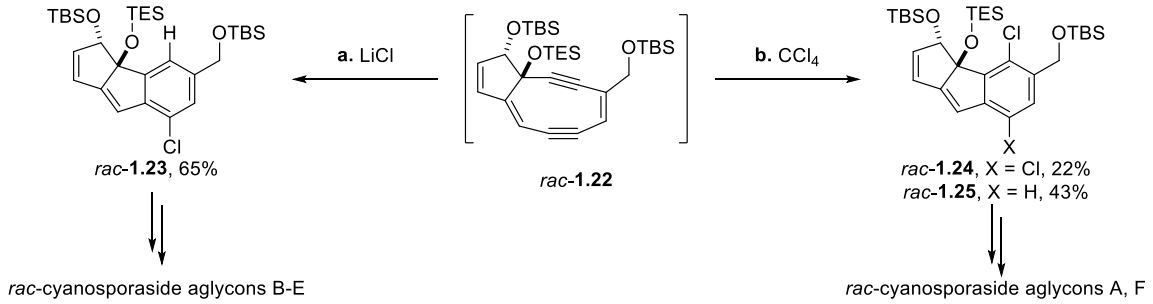
Such a transformation has been experimentally investigated by Perrin and co-workers on the simpler enediyne substrate **1.18** (Scheme 1.7).[21] Heating in DMSO-d_6 triggered cycloaromatisation to **1.19**, which was measured to be the rate-determining step. Addition of a variety of nucleophiles was possible, giving **1.20**. This anion would readily deprotonate (dedeuterate) the solvent, likely due to its greater abundance than the added acid, to provide the monofunctionalised product, **1.21**. In nucleophile competition experiments, the ratio of **1.21** was found to strongly correlate with the nucleophiles' desolvation energies.



Scheme 1.7: Perrin and co-workers' demonstration of nucleophilic addition to *para*-benzyne. Nu = I, Br, Cl, SCN, N_3, CN, OAc.

Such a reaction of *para*-benzynes has been proposed as the biosynthetic pathway to the sporolide[22] and cyanosporaside[23] natural products, with Hirama and co-workers using the technique in a synthesis of the latter aglycons (Scheme 1.8).[24] *In situ* formation of enediyne *rac*-**1.22** gave regiodivergent chlorination with different chlorine sources. Ionic chloride gave *rac*-**1.23** as the only product, presumably by nucleophilic addition to the diradical. To access

the other isomer, *rac*-**1.25**, a radical chlorination was used, which also generated dichlorinated species *rac*-**1.24**.



Scheme 1.8: Hirama and co-workers' regiodivergent reactivity of *para*-benzyne *en route* to cyanosporaside aglycons.[24] Reagents and conditions: (a) KO*t*-Bu (85 equiv), LiCl (0.7 M), DMSO, rt, 12 h, 65%; (b) KO*t*-Bu (85 equiv), Et_2O, CCl_4, rt, 15 h, 22% *rac*-**1.24**, 43% *rac*-**1.25**.

The sporolides and cyanosporasides are isolated as mixtures of chlorination regioisomers, potentially arising from addition to either *para*-benzyne radical site. In contrast, unciaphenol (**1.1**) was reported as a single isomer, as was the similar compound dynemicin O (**1.26**) (Figure 1.2).[25] This could indicate an enzymatically assisted Bergman cyclisation, although the isolation of a single regioisomer in Scheme 1.8 supports the possibility of simple substrate control for **1.1** and **1.26**.

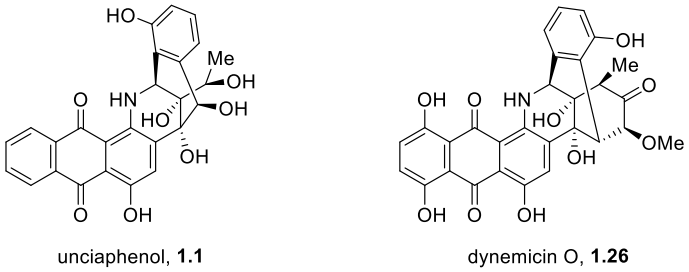
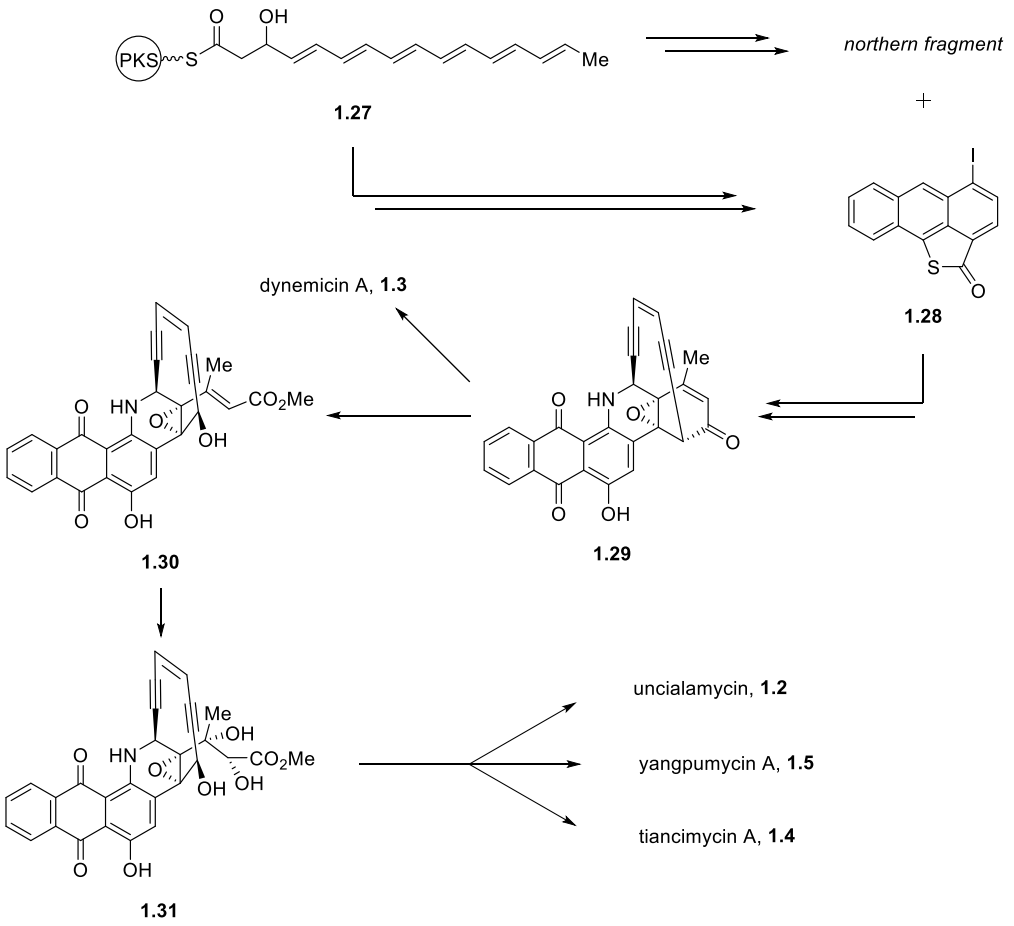


Figure 1.2: Unciaphenol (**1.1**) and similar natural product dynemicin O (**1.26**).

1.1.4 Biosynthesis of anthraquinone enediynes

Elucidation of the biosynthetic pathways to anthraquinone enediyne natural products includes contributions from several groups, although the full details are still not understood.

The current view is depicted in Scheme 1.9. Iwasaki and co-workers began investigations by determining the origin of dynemicin A's carbon skeleton through isotopic labelling studies.[26] This showed that both the northern, enediyne fragment and southern, anthraquinone fragment were of polyketide origin, consisting of heptaketide chains. It was later shown that the enediyne portion of all known enediyne-containing natural products originates from the same octaketide, **1.27**.[27,28] The vast differences in their structures originate downstream of this intermediate. More recently, Townsend and co-workers have shown that **1.27** is also an intermediate on the pathway to the anthraquinone fragment of dynemicin A (**1.3**), with all oxygenation on the southern portion derived from molecular oxygen.[29] Anthracenyl iodide **1.28** was subsequently identified through gene knockout studies and appeared to be essential to the production of dynemicin A (**1.3**).[30] The unexpected presence of the aryl iodide likely indicates its direct involvement in coupling to a suitable northern fragment. Although the precise identity of the latter is unknown, cyclisation and nitrogen incorporation are presumed to have taken place on **1.27** before this coupling. Shen and co-workers have also performed gene knockout studies, this time on tiancimycin producing bacteria, to study the biosynthetic pathways.[31] Through the isolation of numerous products, they propose enediyne **1.29** as an intermediate common to the biosynthesis of all anthraquinone enediynes. Tailoring steps would then convert **1.29** to the four known groups of the natural products. The dynemicins likely branch here, as they require addition to the northern fragment. The other three groups, however, are proposed to share a common oxidative cleavage *via* **1.30** and **1.31**. Although unciaphenol appears to be an intermediate on the pathway to the tiancimycins, it is suggested that some of the anthraquinone oxidations occur before the full tailoring of the northern fragment from **1.31**. They do not offer any evidence as to whether the yangpumicins are directly biosynthesised from uncialamycin (**1.2**).



Scheme 1.9: Current understanding of the biosynthesis of anthraquinone enediyne natural products.

In their gene knockout studies, Shen and co-workers identify the production of several shunt products that have undergone a Bergman cyclisation. Within these, there are three that possess oxygenation of this arene, all in the same position as for unciaphenol (Figure 1.3). This perhaps lends support for a non-enzymatic conversion of **1.2** to **1.1**.

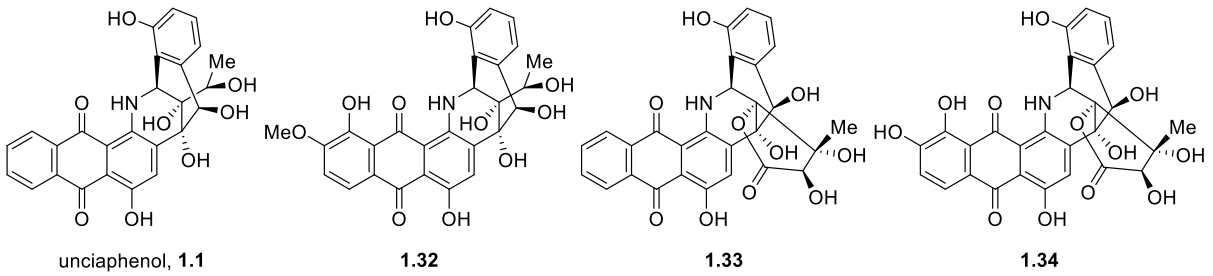
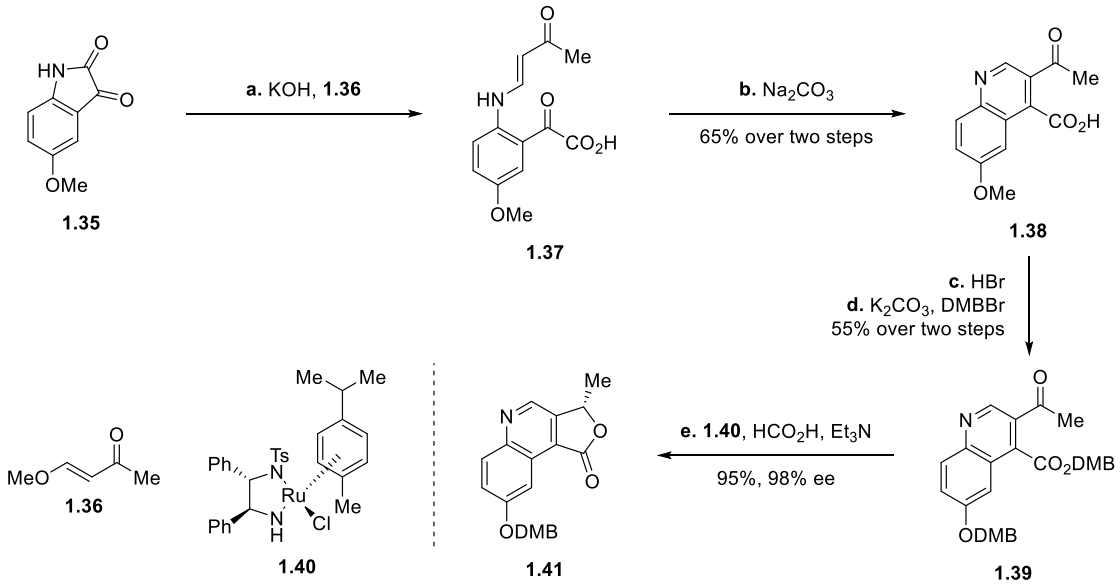


Figure 1.3: Unciaphenol (**1.1**) with Bergman cyclisation oxygenation shunt products from gene knockouts in tiancimycin biosynthesis.

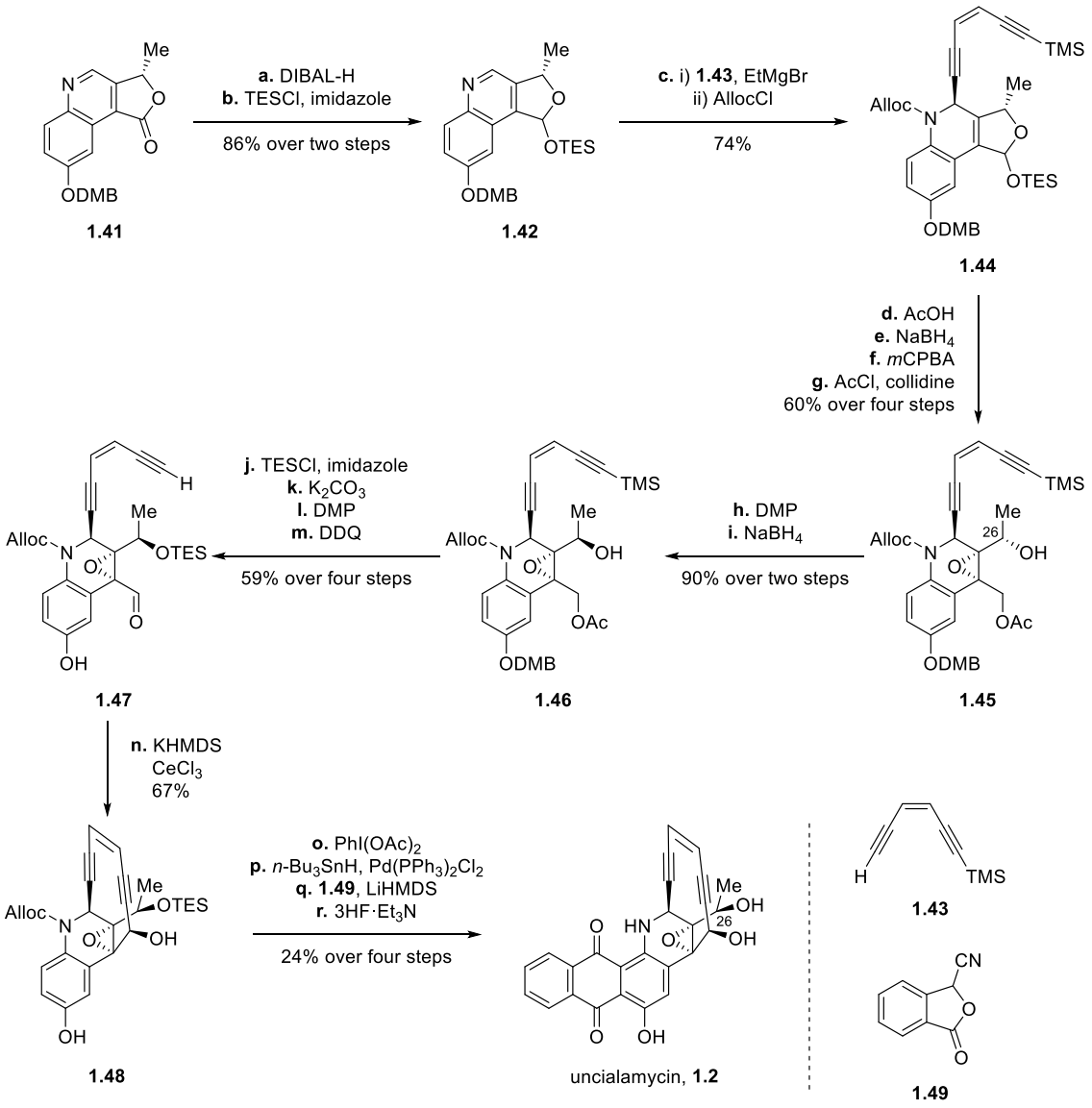
1.1.5 Total synthesis of uncialamycin (1.2)

To date, there are no reports beyond the isolation paper that deal with unciaphenol (**1.1**). Uncialamycin (**1.2**), however, has been the subject of several articles, with two groups targeting its total synthesis. Of these, only Nicolaou and co-workers have published a completed route. Their first effort was to *rac*-**1.2** and the C26 epimer, to determine the relative configuration at this stereocentre.[15] This was modified shortly after to access an enantioselective route, the beginning of which is shown in Scheme 1.10.[8] The synthesis begins with a two-step Pfitzinger reaction of 5-methoxyisatin (**1.35**) with **1.36** to generate quinoline **1.38**.[32] The methoxy group was here converted to the more easily cleavable 3,4-dimethoxybenzyl (DMB) ether, as cleavage of the methyl ether at a later stage was found to occur with erosion of enantiomeric excess (ee). Esterification also took place in step (d), providing **1.39**. This was subjected to Noyori asymmetric transfer hydrogenation of the ketone using (*S*,*S*)-catalyst complex **1.40**[33] to set the configuration at what becomes C26 of uncialamycin (**1.2**). *In situ* lactonisation provided **1.41** in good ee, which could be further improved through recrystallisation. This is the major modification from the original racemic route, which instead utilised a sodium borohydride reduction of the sodium salt of **1.38**. From **1.41**, completion of the total synthesis of **1.2** followed the previously published racemic route (Scheme 1.11). Conversion of lactone **1.41** to protected lactol **1.42** allowed Yamaguchi addition of enediyne **1.43** into the quinoline, trapping with allyl chloroformate to give **1.44**.[34] The facial selectivity of this addition is proposed to be sterically controlled by the previously installed stereocentre to give the enediyne *anti* to the methyl group. Four-step conversion to epoxide **1.45** revealed the free secondary alcohol, which required inversion of configuration to access the natural C26 epimer of unciaphenol (**1.2**). Oxidation with Dess-Martin

periodinane followed by sodium borohydride reduction generated the desired epimer, **1.46**, with over 96% selectivity. Preparation of the unnatural C26 epimer of unciaphenol simply omitted steps (h) and (i). Species **1.46** was then subjected to protecting group adjustments and oxidation to aldehyde **1.47**. The DMB ether was cleaved here to avoid issues with its instability in the following reaction. In cyclisation of the enediyne onto the aldehyde, a mixture of secondary alcohol epimers was formed. It was found that, while the undesired epimer of **1.48** was favoured with LiHMDS, inversion of the diastereocontrol could be achieved by use of KHMDS as the base. Pre-mixing **1.47** with cerium(III) chloride further improved both the yield and diastereomeric ratio (5:1) of **1.48**. Finally, oxidation to an iminoquinone with deprotection of the nitrogen allowed a Hauser-Kraus annulation with cyanophthalide **1.49**.[35,36] Removal of the silyl protecting group provided uncialamycin (**1.2**) in around 1% yield over 23 steps from **1.35**.



Scheme 1.10: Nicolaou and co-workers' enantioselective route to key intermediate **1.41** in their total synthesis of uncialamycin (**1.2**). Reagents and conditions: (a) KOH (1.0 equiv), **1.36** (1.5 equiv), H_2O, rt, 20 min; (b) sat. aq. $NaHCO_3$, 80 °C, 30 min, 65% over two steps; (c) *n*-Bu_4NBr (0.1 equiv), HBr (48% aq.), 110 °C, 40 h; (d) K_2CO_3 (8.0 equiv), *n*-Bu_4NI (0.15 equiv), DMBBr (3.0 equiv), DMF, rt, 3 h, 55% over two steps; (e) **1.40** (5 mol %), HCO_2H (4.3 equiv), Et_3N (2.5 equiv), CH_2Cl_2, 0 °C, 36 h, 95%, 98% ee.



Scheme 1.11: The completion of Nicolaou and co-workers' enantioselective total synthesis of uncialamycin (**1.2**).[8,15] Reagents and conditions:[i] (a) DIBAL-H (1.1 equiv), CH_2Cl_2, –78 °C to rt, 1 h; (b) TESCl (1.3 equiv), imidazole (2.6 equiv), DMF, rt, 20 min, 86% over two steps; (c) i) **1.43** (1.8 equiv), EtMgBr (1.9 equiv), rt, 30 min, ii) AllocCl (1.6 equiv), rt, 5 min, 74%; (d) 2:4:1 AcOH:MeCN:H_2O, rt, 5 h, 91%; (e) $NaBH_4$ (1.0 equiv), MeOH, rt, 10 min; (f) *m*CPBA (1.4 equiv), CH_2Cl_2, 0 °C, 3 h, 80% over two steps; (g) AcCl (1.1 equiv), collidine (3.0 equiv), 0 °C to rt, 12.5 h, 82%; (h) DMP (2.0 equiv), CH_2Cl_2, rt, 90 min, 92%; (i) $NaBH_4$ (1.0 equiv), MeOH, rt, 10 min, 98%; (j) TESCl (1.5 equiv), imidazole (3.0 equiv), DMF, 0 °C, 10 min; (k) K_2CO_3 (2.0 equiv), 2:1 THF:MeOH, 0 °C, 20 min, 78% over two steps; (l) DMP (2.0 equiv), CH_2Cl_2, rt, 3 h, 87%; (m) DDQ (4.0 equiv), 10:1 CH_2Cl_2:H_2O, rt, 12 h, 87%; (n) KHMDS (5.0 equiv), $CeCl_3$ (4.0 equiv), THF, –78 °C to –40 °C, 1 h, 67%; (o) $PhI(OAc)_2$ (1.1 equiv), MeOH, rt, 10 min, 80%; (p) *n*-Bu_3SnH (1.1 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol %), H_2O (4.0 equiv), CH_2Cl_2, rt, 20 min, 52%; (q) **1.49** (3.0 equiv), LiHMDS (3.0 equiv), THF, –78 °C to rt, 1 h, 63%; (r) 3HF·Et_3N (100 equiv), THF, rt, 1 h, 92%.

[i] Nicolaou and co-workers' 2008 publication[8] provided no experimental details for the conversion of **1.41** to uncialamycin (**1.2**) beyond reference to their previous racemic route.[15] Hence, the yields presented here for steps (a) – (i) are those from the racemic synthesis. In their 2007 publication, no yields were provided for the transformation of *rac*-**1.46** to *rac*-**1.2**. The yields presented here for steps (j) – (r) instead belong to the analogous reactions of *rac*-**1.45** to produce the C26 epimer of *rac*-**1.2**.

More recently, the above synthetic route has, in collaboration with Bristol-Myers Squibb, been refined for more efficient larger scale preparation of **1.2** and analogues.[17,37] This has primarily consisted of additional conditions screening for a number of transformations and adjusting the protecting group strategy. The end goal is the use of uncialamycin analogues in antibody-drug conjugates (ADCs) for the treatment of cancer.[10] A major advantage of uncialamycin (**1.2**) as a starting point for ADCs is that the anthraquinone moiety can readily be modified without loss of potency. This allows inclusion of a linker attachment point in the final step of the synthetic sequence by use of an alternative cyanophthalide to **1.49**. One such compound reported is shown in Figure 1.4. The ADCs that contained protease-cleavable linkers, **1.50**, showed highly potent (IC_{50} < 1 nM) and selective cytotoxicity against two cell lines tested.

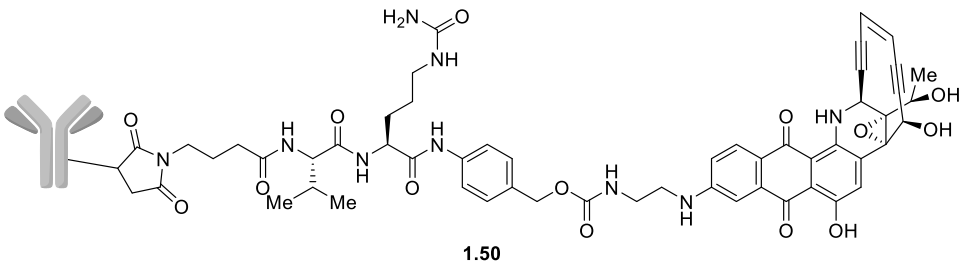
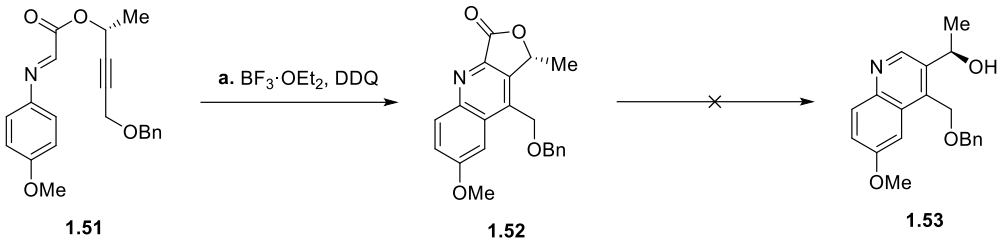


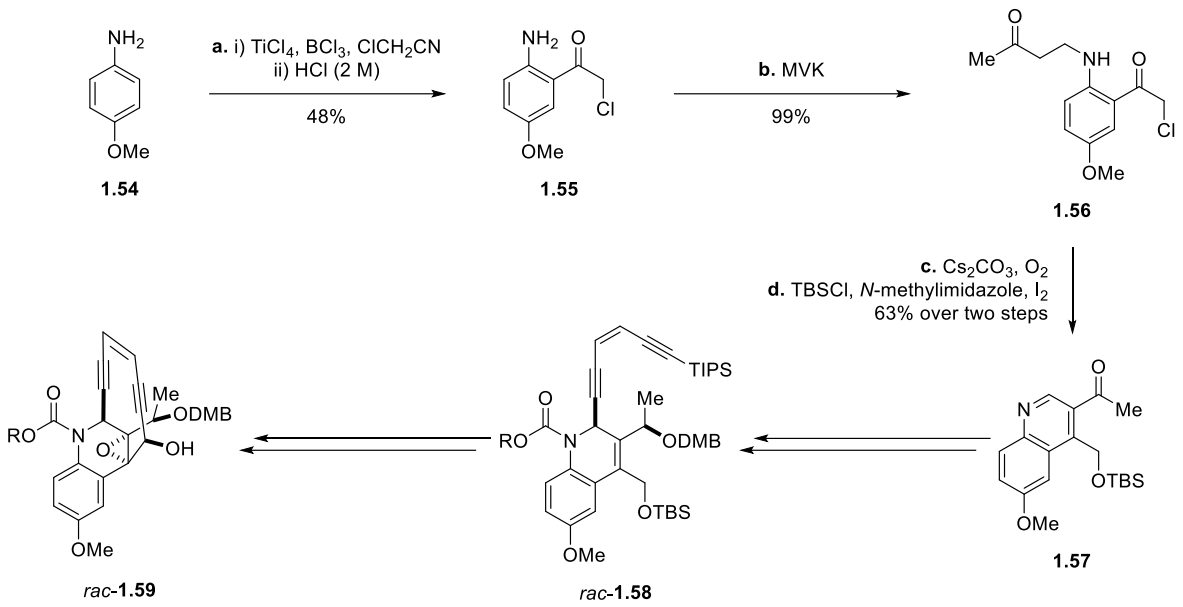
Figure 1.4: One of the ADC designs using an uncialamycin analogue tested by Chowdari and co-workers.[10]

Uncialamycin (**1.2**) has also been targeted by van de Weghe and co-workers, with two publications detailing progress. The first, from 2009, describes the development of a Lewis acid promoted Povarov reaction.[38] Included in the paper is the preparation of a quinoline with the C26 stereocentre of uncialamycin installed, **1.52**, (Scheme 1.12). Their second publication, however, begins by stating that they were unable to hydrolyse the lactone and decarboxylate to transform **1.52** to **1.53** as required for uncialamycin.



Scheme 1.12: Initial attempt towards uncialamycin from van de Weghe and co-workers.[38] Reagents and conditions: (a) $BF_3{\cdot}OEt_2$ (1.0 equiv), DDQ (1.0 equiv), CH_2Cl_2, rt, 1 h.

The second report from van de Weghe and co-workers in 2011 was more focused on the total synthesis of uncialamycin (**1.2**), although ultimately fell short due to a number of factors.[39] The route commenced with acylation of *para*-anisidine (**1.54**) to give **1.55**. Alkylation of the nitrogen then provided **1.56**. This was transformed into quinoline **1.57** *via* a Robinson annulation with an oxygen atmosphere facilitating oxidation of the dihydroquinoline intermediate. From this point, the synthesis bears relatively strong resemblance to that from Nicolaou and co-workers (*vide supra*). However, van de Weghe and co-workers struggled to reduce ketone **1.57** with useful levels of enantioselectivity, the highest reported being 48% ee. Hence, they conducted subsequent investigations on racemic material. In addition of the enediyne moiety into the quinoline, they reported only moderate levels of stereoinduction from the secondary alcohol stereocentre, typically around 3:2 in favour of the desired *cis* isomer, *rac*-**1.58**. These epimers were also found to be inseparable for certain *N*-protecting groups. Closing the enediyne ring to *rac*-**1.59** presented similar issues of poor diastereocontrol and complex mixtures of isomers. The paper concludes by acknowledging that the approach requires modification and/or further experimental effort.



Scheme 1.13: Second attempt towards uncialamycin from van de Weghe and co-workers.[39] Reagents and conditions: (a) i) $TiCl_4$ (1.0 equiv), BCl_3 (1.1 equiv), $ClCH_2CN$ (4.8 equiv), CH_2Cl_2, PhMe, 120 °C, 5 h, ii) HCl (2 M), reflux, 1 h, 48%; (b) MVK (2.0 equiv), THF, 65 °C, 24 h, 99%; (c) $CsCO_3$ (3.0 equiv), MeOH, O_2 atmosphere, reflux, 3 h; (d) TBSCl (1.0 equiv), *N*-methylimidazole (3.0 equiv), CH_2Cl_2, rt, 5 h, 63% over two steps.

1.2 Enantioselective organocatalysis and cascade reactions

The topic of organocatalysis is extremely broad, referring to the use of a (typically) small, solely organic species to catalyse a reaction.[40] Despite early beginnings,[41] its development lagged behind that of biological and metal catalysis. Within recent decades, however, several new modes of organocatalysis have been developed, using a wide range of catalysts (Figure 1.5). Examples include *N*-heterocyclic carbenes (**1.60**),[42] Brønsted acids (**1.61**),[43,44] sulfides (**1.62**),[45] ammonium salts (**1.63**),[46] and even simple aldehydes (**1.64**).[47] Since the work in this report primarily involves amine catalysis *via* covalently bound intermediates, the following introduction will focus on such catalysts. The term cascade, undefined by IUPAC, will be used to refer to a sequence of more than one reaction occurring without any external change of conditions. The first reaction must be essential for a subsequent transformation to occur.

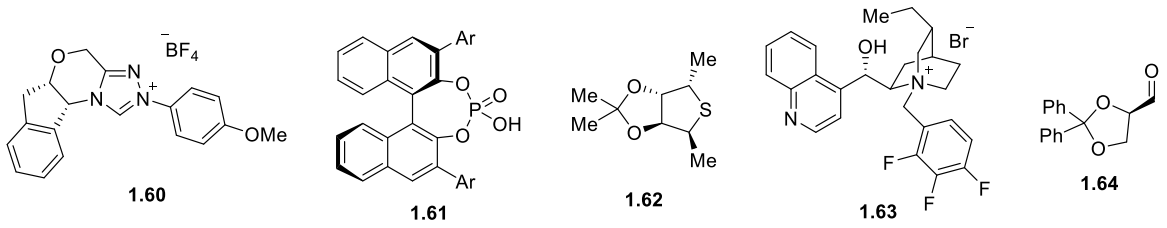
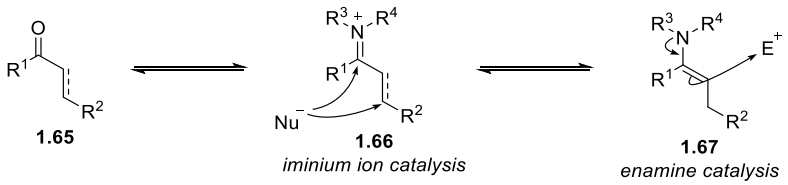


Figure 1.5: Selected examples of organocatalysts used for enantioselective reactions.

1.2.1 Early amine organocatalysis

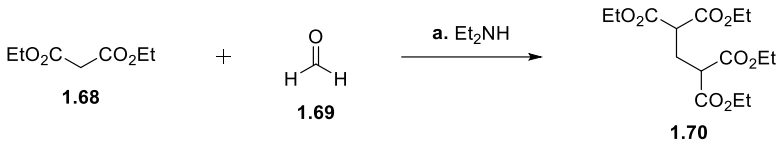
Amines can catalyse reactions of aldehydes and ketones *via* several modes of action, with two discussed here in more detail (Scheme 1.14). Firstly, the iminium ion initially formed from condensation provides a more electrophilic analogue of the carbonyl, lowering the LUMO of the system. Reaction will often involve either direct addition to the iminium ion or reaction at the β-carbon of an α,β-unsaturated system, although other transformations are possible. This is termed 'iminium ion catalysis'. The lowering of the C=X π* orbital energy increases the acidity of any α-C–H bonds, allowing deprotonation to the enamine more readily than for the corresponding enolate formation. This nucleophilic species gives rise to the second reactivity mode, termed 'enamine catalysis', in which the enamine participates in addition or substitution reactions with electrophiles. Both iminium ion and enamine catalysis have been identified in enzymatic processes,[48,49] although these will not be discussed in this thesis.



Scheme 1.14: Common reactivity modes in amine catalysis.

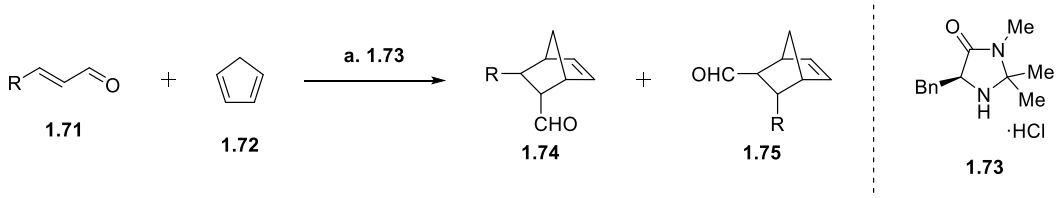
The first report of iminium ion catalysis was from Knoevenagel in 1894, where secondary amines were used in the condensation of diethyl malonate (**1.68**) with formaldehyde (**1.69**)

(Scheme 1.15).[50] Evidence for the involvement of iminium ion catalysis rather than simply base catalysis came much later.[51]



Scheme 1.15: Knoevenagel's report of secondary amine catalysis.[50] Reagents and conditions: (a) Et_2NH, H_2O, rt, 12 h.

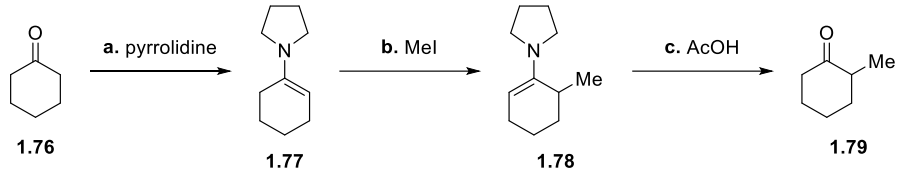
Several reports of iminium ion catalysis followed Knoevenagel's, including in Michael additions[52,53] and the use of proline for stereoinduction.[54] However, it wasn't until MacMillan and co-workers' seminal paper in 2000 that the field of asymmetric iminium ion catalysis flourished (Scheme 1.16).[55] Setting out to catalyse Diels-Alder reactions of α,β-unsaturated aldehydes by a LUMO lowering strategy, imidazolidinone **1.73** was found to offer good yields, ee's, and rate enhancements.



Scheme 1.16: MacMillan and co-workers' development of a secondary amine catalyst for asymmetric Diels-Alder reactions.[55] Reagents and conditions: (a) **1.73** (5 mol %), 19:1 MeOH:H_2O, rt.

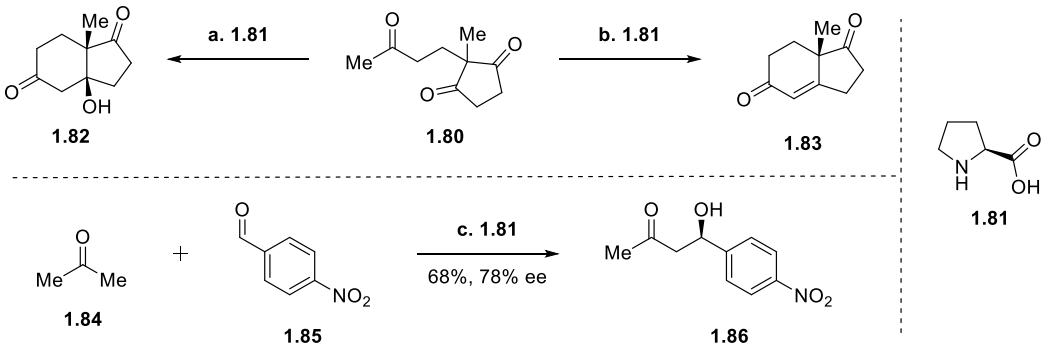
Enamine catalysis initially took longer to develop than its iminium ion counterpart. Although there had been scattered examples of enamine catalysis prior,[56,57] Stork and co-workers gave some of the first detailed reports on the use of enamines for the α-functionalisation of aldehydes and ketones (Scheme 1.17).[58,59] These reactions were carried out over three steps, involving stoichiometric generation and isolation of the enamine, **1.77**; reaction with an electrophile, and finally hydrolysis to reveal the monosubstituted carbonyl product, **1.79**. With this method came solutions to some of the issues encountered at the time in

α-functionalisation of carbonyl groups, namely chemo- and regioselectivity of α-substituted substrates.



Scheme 1.17: Stork and co-workers' early work on enamines.[58] Reagents and conditions: (a) pyrrolidine, benzene, reflux; (b) MeI, MeOH, reflux; (c) AcOH, H_2O, reflux.

A key advancement came in the Hajos-Parrish-Eder-Sauer-Wiechert reaction, with contributions from two groups (Scheme 1.18).[60,61] Both involved the treatment of racemic triketones such as **1.80** with substoichiometric amounts of proline (**1.81**) to access fused bicyclic diketones of the forms **1.82** and **1.83**. The products were isolated in good yields and optical purities. Although this laid the groundwork for asymmetric enamine catalysis, few major advances were seen until an intermolecular analogue of the Hajos-Parrish-Eder-Sauer-Wiechert reaction was reported by List and co-workers in 2000 (Scheme 1.18).[62]



Scheme 1.18: Top: asymmetric enamine catalysis developed by Hajos and Parrish (a)[61] and by Eder, Sauer, and Wiechert (b);[60] bottom: List and co-workers' early development work in asymmetric enamine catalysis.[62] Reagents and conditions: (a) **1.81** (3 mol %), DMF, rt, 20 h, 93% optical purity; (b) **1.81** (50 mol %), $HClO_4$ (1 M), MeCN, reflux, 22 h, 84% optical purity; (c) **1.81** (30 mol %), DMSO, rt, 4 h, 68%, 78% ee.

1.2.2 Families of amine organocatalyst and explanation of stereoinduction

Since the early 2000's, the field of asymmetric amine organocatalysis has grown significantly. Numerous new catalyst designs have been developed and applied to existing and novel transformations. A brief survey of organocatalysts is shown in Figure 1.6. In general, these amines can be used for both iminium ion and enamine catalysis, although performance can vary. Proline (**1.81**) has continued to find use, while isosteres such as tetrazole **1.87** can offer improvements through greater solubility in organic solvents.[63] Modification of the carboxylic acid of proline (**1.81**) to form diarylprolinol **1.88** was developed independently by the groups of Hayashi[64] and Jørgensen[65] and has many variants. Macmillan and co-workers' initial imidazolidinone, **1.73**, has also given rise to numerous catalysts based on the same core. Primary amines, such as **1.89**[66] and **1.90**,[67] are less commonly used, with anilines (**1.91**) even less common.[68] They require acidic conditions for iminium ion catalysis but can offer advantages with sterically congested substrates. Finally, achiral amines have been used with chiral counteranions (**1.92**) to effect asymmetric transformations.[69] This relies on the potential for close ion pairing with the cationic iminium ion intermediate, depending on the precise conditions and substrates.[70] Of the catalysts displayed in Figure 1.6, variations on the structures of **1.88** and **1.73** are the most commonly encountered.

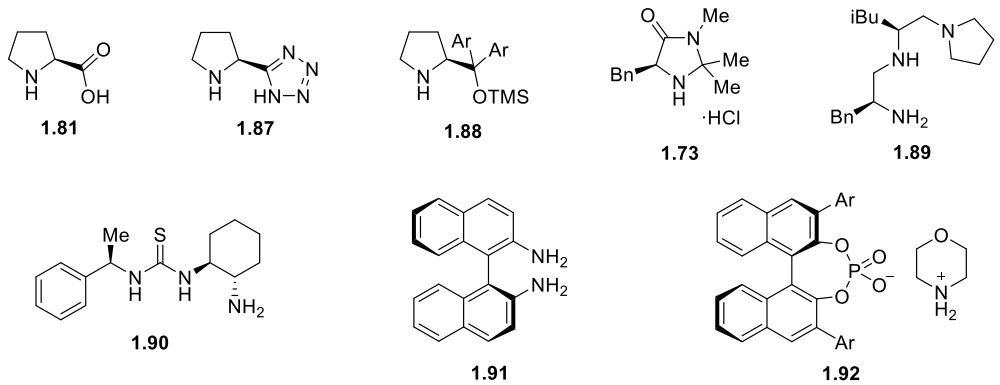


Figure 1.6: Examples of amine organocatalyst designs for enantioselective synthesis.

Despite the variation in structure, amine organocatalysts can typically be grouped into two categories to explain their stereoinduction (Figure 1.7). Initial condensation with an aldehyde or ketone will produce the most thermodynamically favourable iminium ion or enamine. The sterically largest substituents across the C–N and any C=C bonds (if tautomerisation is permitted) will tend to favour the *trans*-geometry, with s-*trans* conformations between adjacent π-bonds. From here, catalysts such as **1.88** and **1.73** will sterically shield one face of the π-system, favouring reaction on the opposite face of the π-system. Catalysts such as **1.81**, **1.87**, **1.89**, **1.90**, and **1.91** can instead coordinate to a reagent through hydrogen bonding or ion pairing, guiding reaction to the same face of the π-system. Note that while Figure 1.7 shows reaction with only nucleophiles and electrophiles, this model will generally apply to any reactant used, such as dienes in MacMillan and co-workers' Diels-Alder reactions (Scheme 1.16). Additionally, this model can also explain stereocontrol where the iminium ions and enamines have more or fewer alkenes, although the stereoinduction from the catalyst weakens the further from the catalyst the reacting centre becomes. Jørgensen and co-workers have reported dienamines existing in a 1:2 *E*:*Z* equilibrium ratio at the γ,δ-alkene, which could directly affect the stereochemistry formed in reaction at the δ-C.[71]

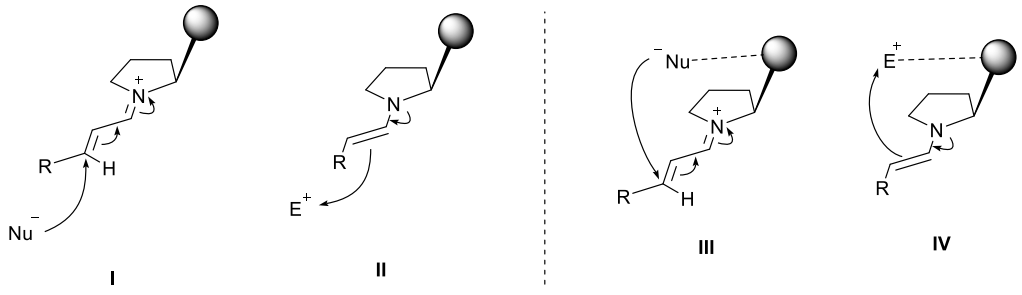
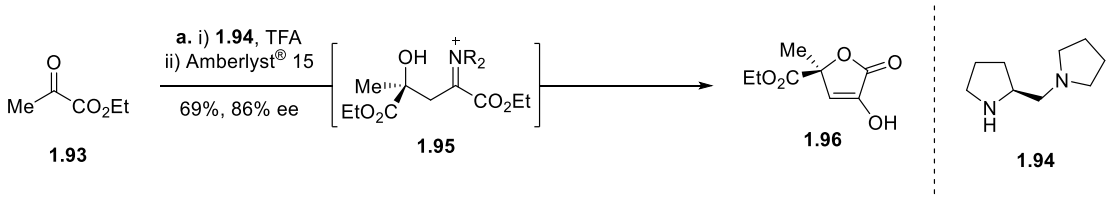


Figure 1.7: Simple stereoinduction model for amine organocatalysts. Upon adopting the lowest energy geometry of all rotatable bonds, either: left: steric shielding directs reaction to the opposite face; right: coordination directs reaction to the same face.

Although the above model allows prediction and rationalisation of stereochemical outcomes, other factors can influence the stereoselectivity of the reaction. Enhancement or erosion of enantiomeric excess from the initial reaction may occur and can provide drastically different results for otherwise small changes in the catalyst, substrates, or solvent. This becomes a consideration when equilibration can occur between intermediates following the stereogenic bond forming step. Blackmond and co-workers have coined the term 'downstream species' to describe such intermediates that directly affect the stereochemical outcome.[72,73]

1.2.3 α-Keto esters in amine organocatalysis

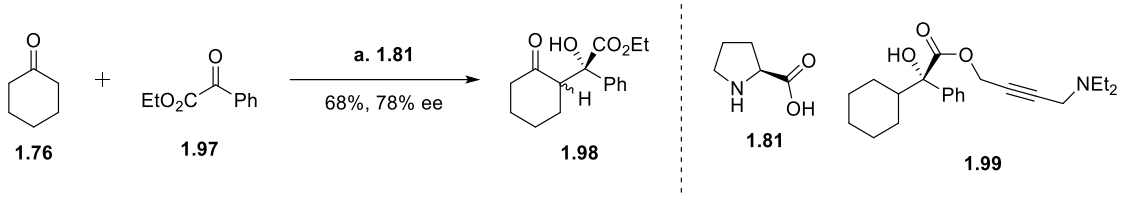
α-Keto esters are a relatively uncommon functional motif in synthetic organic chemistry, despite their importance in primary metabolism. As such, it is unsurprising that there are relatively few reports of their participation in amine organocatalysis. One such example from Dondoni and co-workers involves the amine (**1.94**) catalysed dimerisation of ethyl pyruvate (**1.93**) to give isotetronic acid **1.96** (Scheme 1.19).[74] This reaction presumably involves formation of intermediate **1.95** by enamine catalysis, followed by lactonisation and hydrolysis.



Scheme 1.19: Dondoni and co-workers' example of enamine catalysis using an α-keto ester.[74] Reagents and conditions: (a) i) **1.94** (30 mol %), TFA (30 mol %), iPrOH, rt, 16 h, ii) Amberlyst® 15, CH_2Cl_2, rt, 3 h, 69% **1.96** as a mixture of keto and enol forms, 86% ee measured after silylation.

Other reports show the use of α-keto esters as electrophiles in L-proline (**1.81**) catalysed aldol reactions (Scheme 1.20).[75,76] These cases tend to use non-enolisable α-keto esters such as **1.97**, accessing the corresponding aldol products, **1.98**. The example below is taken from

Maruoka and co-workers' asymmetric formal synthesis of the muscarinic receptor antagonist oxybutynin (**1.99**).[76]

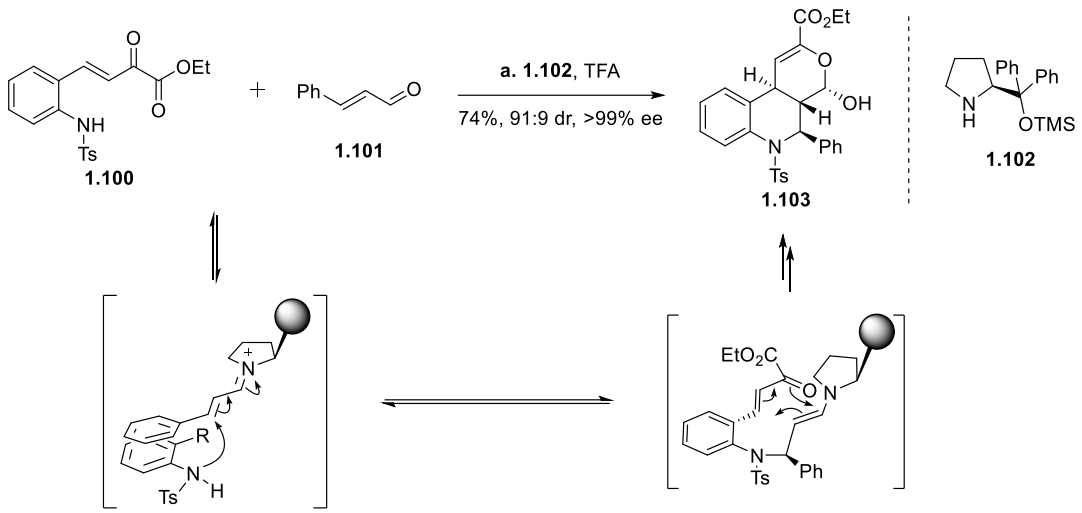


Scheme 1.20: Maruoka and co-workers' example of enamine catalysis with an α-keto ester electrophile.[76] Reagents and conditions: (a) **1.81** (30 mol %), DMSO, rt, 72 h, 89%, 98% ee.

Participation of α-keto ester substrates in cascade reactions featuring more than one amine organocatalysed step will be included in the next section.

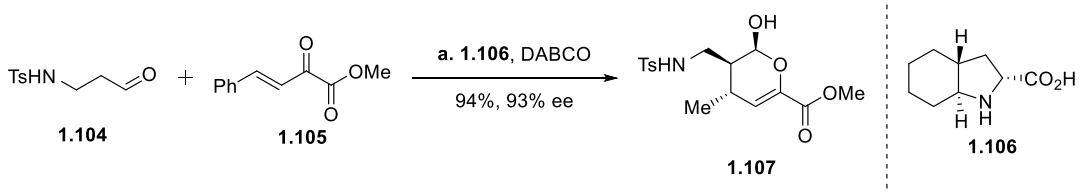
1.2.4 Cascades involving amine organocatalysis

As mentioned above, amine organocatalysts can often be used for both iminium ion and enamine catalytic cycles. These functional groups are closely related, however, and will often both be generated during a particular reaction. An example is shown below, in Zeng, Zhong, and co-workers' synthesis of tetrahydropyranoquinolines using Hayashi-Jørgensen catalyst **1.102** (Scheme 1.21).[77] Michael addition of **1.100** to the α,β-unsaturated iminium ion formed between **1.101** and **1.102** generates a chiral enamine. Cyclisation of this onto the α,β-unsaturated keto ester moiety can then occur, either in a stepwise fashion or *via* a hetero Diels-Alder to give, after hydrolysis, **1.103**. This organocatalysed cascade utilises both iminium ion and enamine catalysis, forming three new bonds and four stereocentres in good yield and both diastereo- and enantioselectivity.



Scheme 1.21: Zeng, Zhong and co-workers' organocatalysed cascade with α,β-unsaturated keto ester substrates.[77] Reagents and conditions: (a) **1.101** (1.5 equiv), **1.102** (10 mol %), TFA (10 mol %), 1,4-dioxane, rt, 24 h, 74%, 91:9 dr, >99% ee.

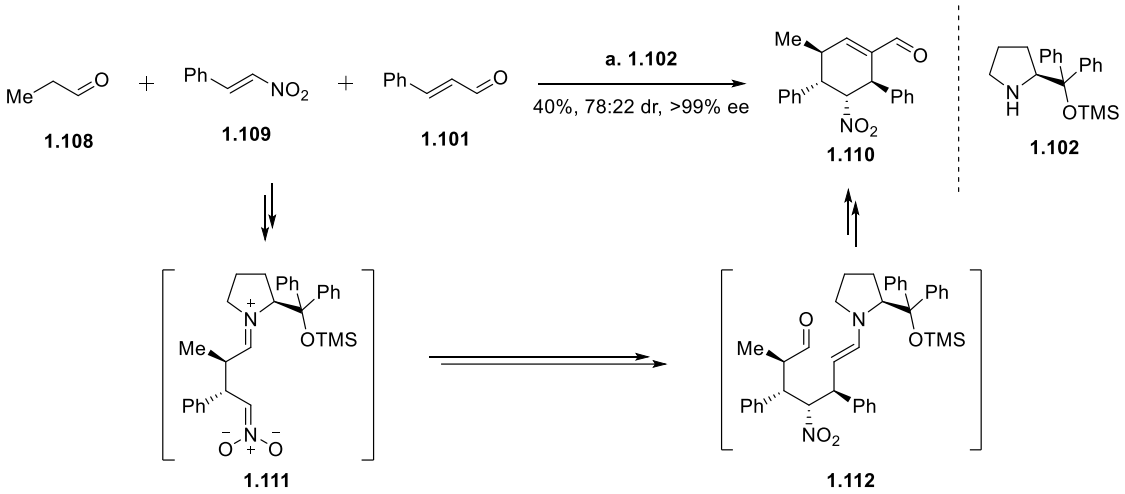
Cascade reactions can also be initiated by enamine catalysis, such as with Zhang and co-workers' dihydropyran synthesis (Scheme 1.22).[78] In this cascade sequence, catalyst **1.106** first forms the enamine of **1.104**. This can then undergo Michael addition onto α,β-unsaturated α-keto ester **1.105** to provide **1.107** after hydrolysis in good yield and ee.



Scheme 1.22: Zhang and co-workers' enamine-initiated organocatalysed cascade reaction of α-keto esters.[78] Reagents and conditions: (a) **1.104** (2.0 equiv), **1.106** (10 mol %), DABCO (20 mol %), *n*-BuOH, rt, 24 h, 94%, 93% ee.

Multicomponent reactions, in which more than two reactants are combined, are also possible. An early demonstration of such a process by Enders and co-workers is shown below (Scheme 1.23).[79] Condensation of catalyst **1.102** with **1.108** produces an enamine, which can undergo Michael addition to nitroolefin **1.109**, initially giving zwitterion **1.111**. Iminium ion formation by condensation of **1.102** with the α,β-unsaturated ester, **1.101**, then facilitates a second Michael addition to give **1.112**. This in turn produces an enamine, which can cyclise

and dehydrate to give the cyclohexene product, **1.110**. Although the yield and diastereoselectivity are perhaps lower than desired, the use of amine catalyst **1.102** effects a significant increase in complexity that would be challenging to produce otherwise.



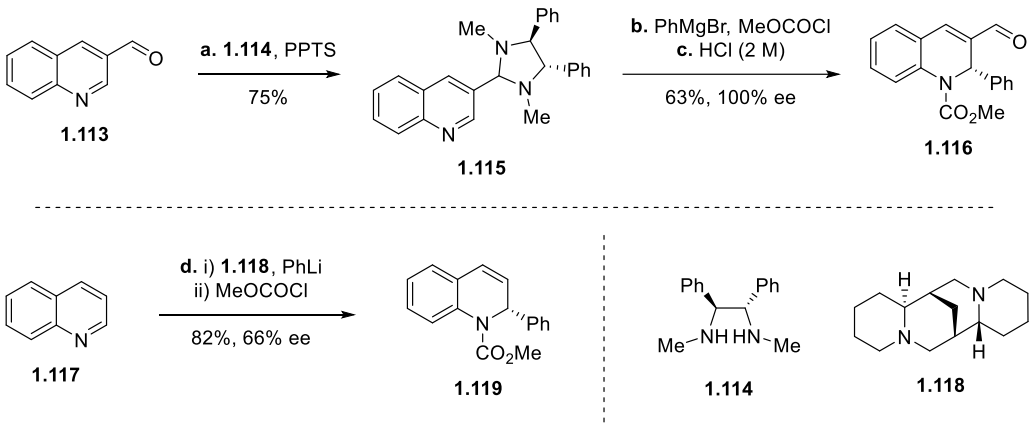
Scheme 1.23: Enders and co-workers' multicomponent organocatalysed cascade reaction.[79] Reagents and conditions: (a) **1.108** (1.20 equiv), **1.101** (1.05 equiv), **1.102** (0.20 equiv), PhMe, rt, 16 h, 40% **1.110**, 78:22 dr, >99% ee.

1.2.5 Synthesis of enantioenriched 2-aryl-1,2-dihydroquinolines

1,2-Dihydroquinolines are a useful motif found in bioactive molecules as well as ligand scaffolds.[80,81] The ease of further manipulation of the alkene also offers facile access to a wide variety of useful tetrahydroquinoline structures, including those present in the anthraquinone enediyne natural products (Figure 1.1).[82] As such, there has been considerable interest in methods to prepare 1,2-dihydroquinolines enantioselectively without resorting to chiral resolution.[83] The discussion here will focus on 1,2-dihydroquinolines bearing a 2-aryl substituent.

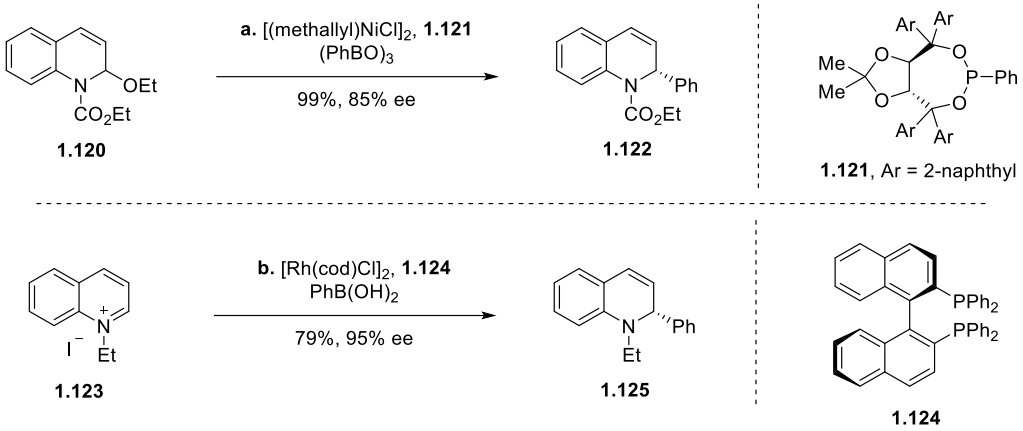
Perhaps the most obvious route to 1,2-dihydroquinolines would be from the corresponding quinoline structures. While monoreduction in a regio- and enantioselective manner is not well-developed, with reduction to the tetrahydroquinoline more common,[84,85] there are

several methods to add the aromatic group to a quinoline starting material with concomitant dearomatisation. Alexakis and co-workers have reported two such enantioselective methods (Scheme 1.24).[86–88] The first requires additional functionality on the starting quinoline, **1.113**, to incorporate a chiral auxiliary, **1.114**. The diamine of **1.115** can then direct addition of the Grignard reagent through coordination to magnesium ions, providing **1.116** with high levels of stereocontrol. The second method instead uses chiral ligands such as (–)-sparteine (**1.118**) with organolithium reagents. While this no longer requires an aldehyde, the ee of **1.119** is considerably lower.



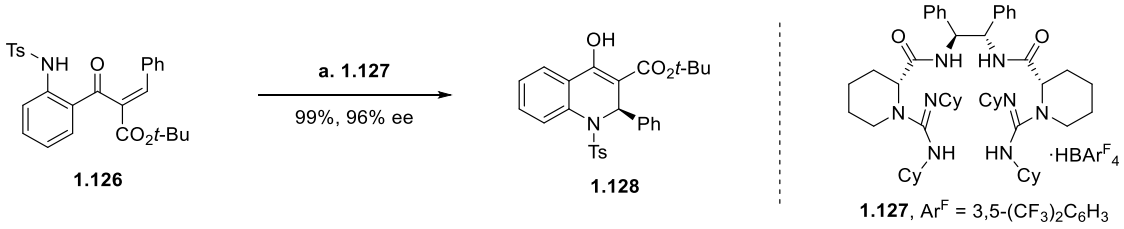
Scheme 1.24: Two methods from Alexakis and co-workers for the regio- and enantioselective addition of organometallic reagents to quinolines.[86–88] Reagents and conditions: (a) **1.114**, PPTS (10 mol %), PhMe, reflux, 75%; (b) PhMgBr, THF, rt, 63%; (c) HCl (2 M), rt, 100% ee based on dr before hydrolysis; (d) i) PhI (1.2 equiv), *n*-BuLi (1.2 equiv), **1.118** (1.0 equiv), PhMe, –78 °C, 1 h, ii) MeOCOCl (1.2 equiv), –78 °C, 10 min, 82%, 66% ee.

More recently, transition metal catalysts have been used to produce similar products to those above (Scheme 1.25). Doyle and co-workers developed a nickel catalysed cross-coupling with masked *N*-acylquinolinium ions, **1.120**.[89–91] Later, adoption of phosphine ligand **1.121** enabled **1.122** to be produced in good enantiomeric excess. Wang, Wei, and co-workers have since reported a similar rhodium catalysed process on *N*-alkylquinolinium salts, **1.123**, providing 1,2-dihydroquinolines, **1.125**, typically with higher ee's than in Doyle and co-workers' report.[92]



Scheme 1.25: Top: Doyle and co-workers' nickel catalysed methodology for the enantioselective synthesis of 1,2-dihydroquinolines;[91] bottom: Wang, Wei, and co-workers' rhodium catalysed preparation of enantioenriched 1,2-dihydroquinolines.[92] Reagents and conditions: (a) [(methallyl)NiCl]$_2$ (5 mol %), **1.121** (15 mol %), (PhBO)$_3$ (0.75 equiv), NaOPh·3H$_2$O (15 mol %), 47:3 dioxane:*t*-AmOH, rt, 24 h, 99%, 85% ee; (b) [Rh(cod)Cl]$_2$ (2.5 mol %), **1.124** (7 mol %), PhB(OH)$_2$ (2.0 equiv), AgBF$_4$ (10 mol %), K$_3$PO$_4$·3H$_2$O (1.5 equiv), PhMe, 45 °C, 12 h, 79%, 95% ee.

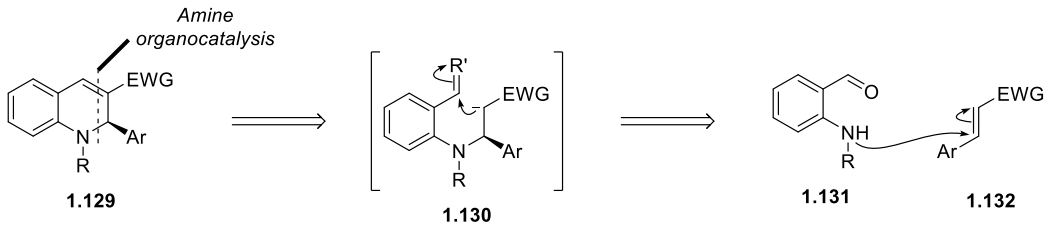
Several groups have published Brønsted acid catalysed syntheses of 1,2-dihydroquinolines, utilising chiral counteranions to impart enantioselectivity. Cyclisation steps include a Pictet-Spengler reaction,[93] allylic substitution,[94] and Michael addition (Scheme 1.26).[95] The latter of these actually uses an achiral acid and a bisguanidine to produce chiral salt **1.127**, which offers slightly improved enantiomeric excess of **1.128** over the bisguanidine alone.



Scheme 1.26: Feng, Liu, and co-workers' Brønsted acid catalysed synthesis of enantioenriched 1,2-dihydroquinolines.[95] Reagents and conditions: (a) **1.127** (5 mol %), CH$_2$Cl$_2$, –60 °C, 10 h, 99%, 96% ee.

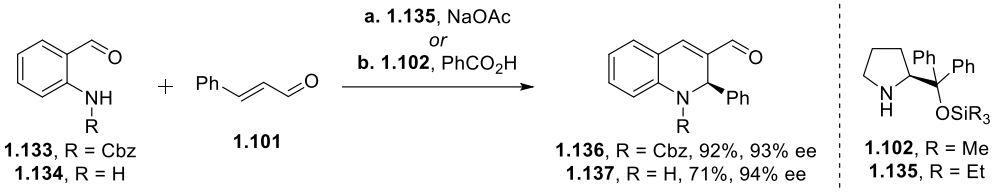
Cascade amine organocatalysis has been viewed as an attractive route for the preparation of 1,2-dihydroquinolines, with numerous examples published. The predominant disconnection made is as shown in Scheme 1.27, with Michael addition of aniline **1.131** onto **1.132** followed

by cyclisation onto the aldehyde. Although this restricts the structure of **1.129** to containing an electron withdrawing substituent at C3, the starting materials are often simple to prepare.



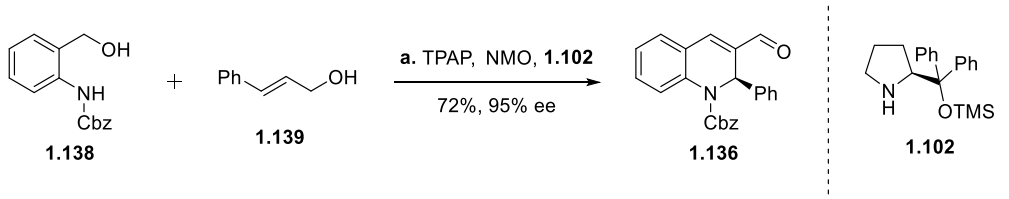
Scheme 1.27: General strategy for amine organocatalysed synthesis of 1,2-dihydroquinolines.

The first such examples were published in 2007 by the Wang and Córdova groups.[96,97] Both used cinnamaldehyde substrates with a Hayashi-Jørgensen catalyst, **1.102** or **1.135**, (Scheme 1.28), with Córdova and co-workers initially reporting a racemic version using pyrrolidine as catalyst.[98] While Córdova and co-workers used a low excess of unprotected aniline, **1.134**, the necessity of long reaction times at low temperature makes this methodology less practical than that of Wang and co-workers. When conducted at room temperature, a higher yield and faster reaction were observed at the expense of enantioselectivity (85% ee). The mechanism is proposed to begin with formation of the α,β-unsaturated iminium ion from **1.101** and the catalyst. Enantiodetermining Michael addition generates an enamine (*vide supra*), which can undergo the 6-*exo*-*trig* cyclisation, followed by $E1_{cB}$ dehydration. It is also possible that activation of the benzaldehyde occurs *via* iminium ion formation, although no evidence has been provided for this.



Scheme 1.28: Organocatalysed 1,2-dihydroquinoline syntheses from Wang and co-workers, (a),[96] and Córdova and co-workers, (b).[97] Reagents and conditions: (a) **1.133** (3.0 equiv), **1.135** (20 mol %), NaOAc (50 mol %), activated 4 Å MS (ground) (75 mg), $ClCH_2CH_2Cl$, rt, 60 h, 92% **1.136**, 93% ee; (b) **1.134** (1.2 equiv), **1.102** (20 mol %), $PhCO_2H$ (20 mol %), DMF, –25 °C, 47 h, 71% **1.137**, 94% ee.

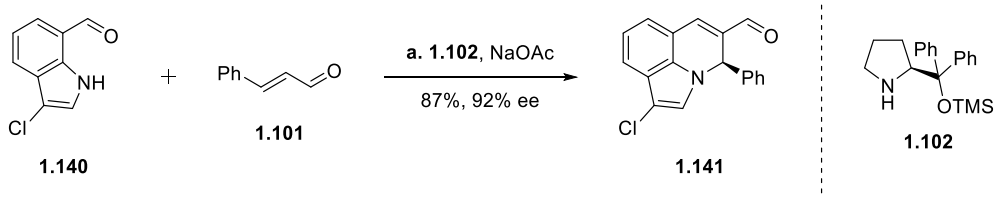
Rueping and co-workers have extended the above cascade by the *in situ* generation of both **1.133** and **1.101** from their corresponding alcohols, **1.138** and **1.139** respectively (Scheme 1.29).[99] The presence of the transition metal catalysis had little effect on the organocatalysis, albeit offering slightly lower yields of **1.136**, demonstrating the potential for combinations of other catalytic cycles.[100] As the benzaldehyde and cinnamaldehyde substrates are often prepared *via* the alcohols, this cascade could increase the efficiency of preparing structures such as **1.136**. Additionally, avoiding isolation of the aldehyde starting materials should improve reproducibility: trace carboxylic acid impurities, formed *via* aerobic oxidation of the corresponding cinnamaldehydes, have been shown to affect optimisation conditions in amine organocatalysis.[101]



Scheme 1.29: Rueping and co-workers' incorporation of ruthenium catalysed oxidation into organocatalysed 1,2-dihydroquinoline synthesis.[99] Reagents and conditions: (a) **1.138** (2.0 equiv), TPAP (7 mol %), NMO (3.5 equiv), **1.102** (20 mol %), 4 Å MS, CH_2Cl_2, rt, 48 h, 72%, 95% ee.

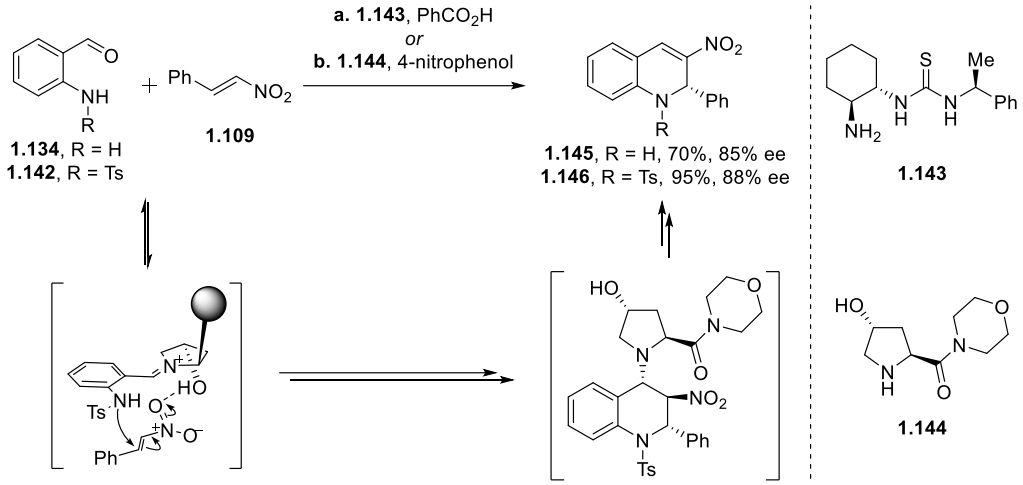
More recently, modifications have been made to the above cascade. Xiang, Yang, and co-workers have replaced the cinnamaldehydes with cyclic α,β-unsaturated ketones, using a proline catalyst.[102] Moreau, Coeffard, and co-workers instead demonstrated the use of

3-substituted indoles for the preparation of fused tricyclic products such as **1.141** (Scheme 1.30). The necessity of an electron withdrawing substituent at C3 of the indole may be to increase the acidity of the nitrogen, leading to a more nucleophilic *N*-anion, as no reaction was observed for C3–H.



Scheme 1.30: Moreau, Coeffard, and co-workers' organocatalysed cascade for the preparation of enantioenriched 1,7-annulated indoles.[103] Reagents and conditions: (a) **1.101** (1.5 equiv), **1.102** (15 mol %), NaOAc (1.1 equiv), $CHCl_3$, 55 °C, 40 h, 87%, 92% ee.

α,β-Unsaturated aldehydes are not the only electrophiles possible in these reactions, however. Despite their inability to condense with the amine catalysts, nitroolefins such as **1.109** have found use in similar cascade reactions, with the groups of both Xu and Yin reporting comparable sets of conditions (Scheme 1.31).[104,105] In these cases, it is proposed that the catalyst forms an iminium ion from the benzaldehyde, with hydrogen bonding to the nitro group both activating it toward nucleophilic attack and controlling the facial selectivity of Michael addition. The *in situ* generated nitronate undergoes 6-*exo*-*trig* cyclisation onto the iminium ion, likely releasing the catalyst *via* an $E1_{cB}$ mechanism. Similar to the reactions in Scheme 1.28, there is the possibility of using an unprotected aniline, albeit providing a slightly lower yield of the 1,2-dihydroquinoline product.



Scheme 1.31: Organocatalysed synthesis of 1,2-dihydroquinolines using nitroolefins from Xu and co-workers, (a),[104] and Yin and co-workers, (b).[105] Reagents and conditions: (a) **1.134** (1.0 equiv), **1.143** (20 mol %), $PhCO_2H$ (20 mol %), 4 Å MS, iPrOH, rt, 48 h, 70% **1.145**, 85% ee; (b) **1.109** (2.0 equiv), **1.144** (20 mol %), 4-nitrophenol (20 mol %), 4 Å MS, $CHCl_3$, rt, 72 h, 95% **1.146**, 88% ee.

So, while the use of amine organocatalysis requires particular types of functionality for the preparation of 1,2-dihydroquinolines, there is some flexibility. The products' C3 substituents potentially also allow further elaboration of the structures. Combined with the easy access to starting materials and mild reaction conditions, this area remains an attractive synthetic strategy.

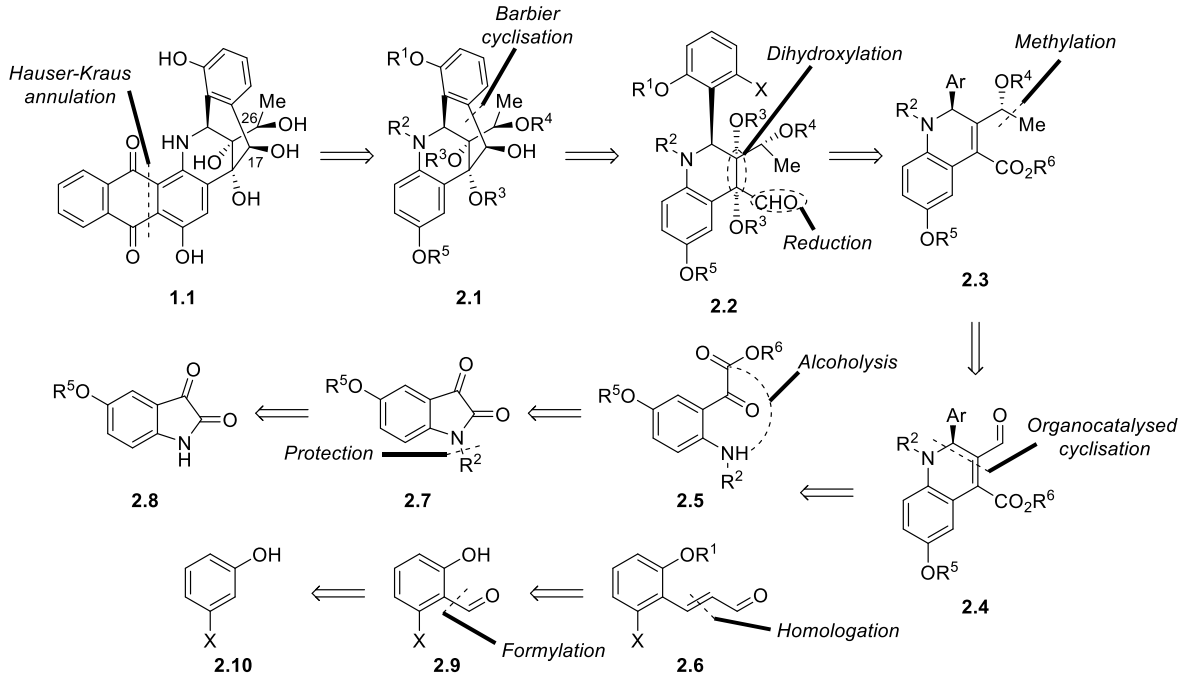
1.3 Aims of project

The primary goal of this project is to design and execute an enantioselective total synthesis of the natural product unciaphenol (**1.1**).[3] Ideally, the route should be short, efficient, and readily scalable. Once this has been accomplished, biological testing further to that performed in the isolation report would be targeted to better understand its anti-HIV activity and potential as a lead compound for treatment of HIV. As such, a modular synthetic route that permits easy access to analogues of unciaphenol (**1.1**) would also be beneficial. It is believed that an organocatalysed cascade could assist greatly with both complexity generation and stereochemical control early in the synthesis. The development of this transformation could

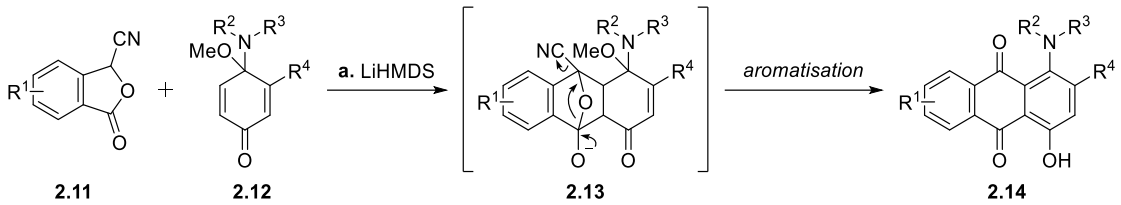
permit access to a novel heterocyclic substructure possessing several areas for further elaboration. Hence, optimisation and understanding of this organocatalysed cascade will be a secondary objective for the project.

2 Retrosynthetic analysis

The retrosynthetic analysis for the planned total synthesis of unciaphenol (**1.1**) is shown in Scheme 2.1. The first disconnection would be formation of the anthraquinone moiety using a Hauser-Kraus annulation on the semiquinone aminal of **2.1** (Scheme 2.2). While both namesake reactions were originally developed using α,β-unsaturated carbonyl compounds as the second coupling partner,[35,36,106] the extension to iminoquinones[107] and semiquinone aminals[108,109] has extended the scope and offered improved selectivity. Deprotonation of phthalide **2.11** allows Michael addition to the semiquinone aminal, **2.12**, followed by cyclisation of the resultant enolate onto the lactone. Fragmentation of bridged intermediate **2.13**, followed by aromatisation, produces anthraquinone product **2.14**.



Scheme 2.1: Retrosynthetic analysis for the planned total synthesis of unciaphenol.



Scheme 2.2: Nicolaou and co-workers' improvement on the Hauser-Kraus annulation.[109] Reagents and conditions: (a) LiHMDS (1.2 equiv), THF, –78 °C to rt, 1 h.

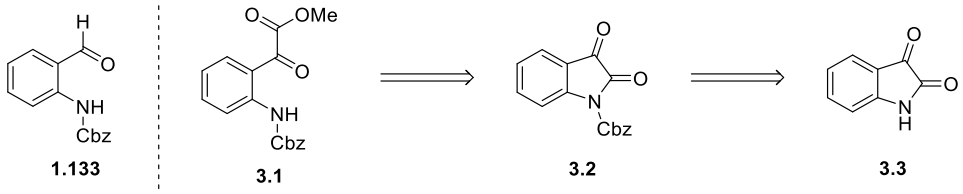
Following the Hauser-Kraus disconnection, the bridging ring of **2.1** would be formed *via* metalation of a suitable C–X bond (X = (pseudo)halide) in **2.2**. This would enable a Barbier-type coupling with the aldehyde to generate the secondary alcohol at C17.[110–116] The inherent stereocontrol for this transformation is difficult to predict, though an oxidation-reduction sequence should allow for epimeric enrichment if required. Although Nicolaou and co-workers overcame a similar challenge in their synthesis of uncialamycin (**1.2**) (see section 1.1.5),[15] the difference between the cyclisation modes is too great to rely on similar solutions. In the proposed system, the extent to which there will be restricted rotation around the C–aryl bond of **2.2** is not known; this may pose issues if the C–X bond is preferably oriented away from the aldehyde. The *syn*-diol of **2.2** would arise from dihydroxylation of α,β-unsaturated ester **2.3**, followed by reduction to the aldehyde. It is anticipated that the aryl group will impart the desired facial selectivity of this oxidation, primarily through steric effects. Diastereoselective methylation of aldehyde **2.4** would give rise to the stereogenic alcohol at C26, with again the possibility of an oxidation-reduction sequence should substrate or reagent control prove insufficient.[117] Enantioselective routes to 1,2-dihydroquinolines such as **2.4**, possessing substitution at C4 of the quinoline (the ester), are not well reported in the literature. Nevertheless, the synthesis of key intermediate **2.4** is expected to take place through an organocatalysed coupling of **2.5** and **2.6**. Involving an iminium ion/enamine cascade, this step was inspired by the literature reports discussed in section 1.2.5, exchanging the benzaldehyde

moiety for the α-keto ester of **2.5**.[96–99,103] This novel substrate should be readily accessible *via* N-protection (**2.7**) and alcoholysis of a suitably functionalised isatin, **2.8**. The other coupling partner, cinnamaldehyde **2.6**, will be prepared from formylation (**2.9**) and homologation of a simpler aromatic precursor, **2.10**.

3 Synthesis of isatin-derived α-keto esters

3.1 Route development

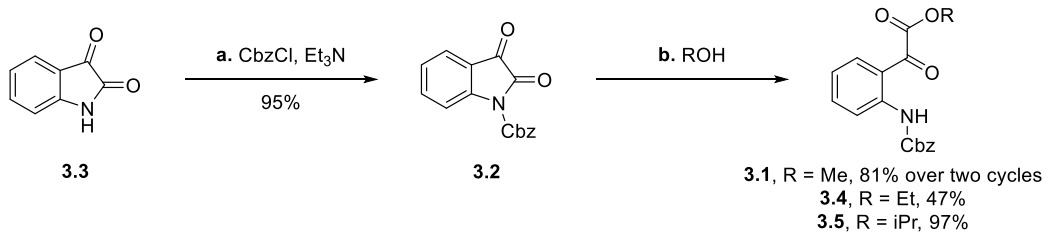
The first aim of the project was the preparation of isatin-derived α-keto esters. Taking Wang and co-workers' substrate, **1.133**,[96] as a guide, analogously protected α-keto ester **3.1** was targeted as a model system (Scheme 3.1). Although Córdova and co-workers have reported a similar transformation with unprotected anilines (see section 1.2.5),[97,98] it was felt that a free secondary amine would pose problems further into the total synthesis. With isatin (**3.3**) as an inexpensive starting material, Cbz-protection of the nitrogen would give **3.2**. Subsequent alcoholysis should provide **3.1** in a rapid manner.



Scheme 3.1: Left: Wang and co-workers' optimisation substrate;[96] right: synthetic plan to the targeted model substrate.

Although isatin (**3.3**) is known to exist as the NH and OH tautomers,[118] reaction with electrophiles under basic conditions is predominantly through the nitrogen.[119] Partial alkylation at the adjacent oxygen has been observed for certain electrophiles, as well as in methylation of the silver salt of isatin.[120] Cbz-protection was found to proceed with complete regioselectivity, following the procedure of Suzuki and co-workers (Scheme 3.2).[121] While **3.2** is unstable to silica, it can be cleanly filtered from the reaction mixture, washing with water, such that recrystallisation was deemed unnecessary. While the reaction of N-protected isatins with nucleophiles to open the heterocycle is fairly well-documented, the majority of examples utilise *N*-acyl substrates.[122–125] The reported procedures for alcoholysis of carbamate-

protected variants typically involve the use of strong bases or a two-step hydrolysis-coupling procedure.[126,127] Initial attempts at a simpler route took inspiration from the Pfitzinger reaction, in which isatin (**3.3**) is rapidly hydrolysed in a hydroxide solution.[32] However, exposure of **3.2** to methanolic sodium methoxide produced a complex mixture of products, including loss of the Cbz group and a hydrolysis product, most likely formed in the work-up. To avoid such complications with base-sensitivity, neutral solvolysis conditions were tried. Unlike with *N*-acyl derivatives,[122] stirring in methanol at room temperature showed little to no conversion, but heating to reflux pleasingly effected clean formation of ester **3.1**. Conversion plateaued at around 1:5 (**3.2**:**3.1**) regardless of which was taken as the starting material, signalling equilibration. Although both **3.2** and **3.1** show significant instability on silica, the keto ester could be crystallised from the reaction mixture on cooling, allowing a facile purification.



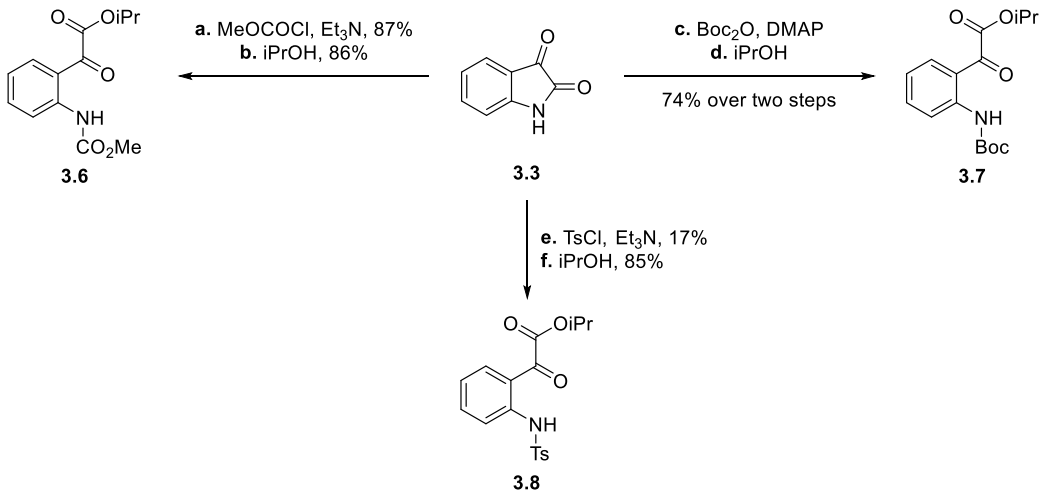
Scheme 3.2: Synthetic route to isatin-derived α-keto esters. Reagents and conditions: (a) CbzCl (1.2 equiv), Et_3N (1.2 equiv), THF, 0 °C to rt, 90 min, 95%; (b) (**3.1**): MeOH, reflux, 90 min, 81% over two cycles; (b) (**3.4**): EtOH, reflux, 2 h, 47%; (b) (**3.5**): iPrOH, reflux, 6 h, 97%.

The corresponding ethyl and isopropyl esters, **3.4** and **3.5** respectively, could be made by an analogous route, albeit requiring longer reaction times for high conversion. While ethyl ester **3.4** displayed somewhat increased stability, silica gel chromatography was not feasible. Its purification was additionally complicated by difficulty in triggering crystallisation, resulting in a lower isolated yield. Isopropyl ester **3.5** displayed similar properties, with crystallisation of a pure sample often taking days under vacuum or in the freezer. However, isopropyl alcohol

enabled complete conversion of **3.2**, with product **3.5** proving stable enough to purify by column chromatography. While the use of sulfuric acid as a catalyst offered shorter solvolysis reaction times, slightly decreased yields of **3.5** were isolated. Hence, the uncatalysed alcoholysis conditions were retained.

3.2 Substrate scope of isatin-derived α-keto ester synthesis

With this operationally simple two-step sequence developed for the synthesis of isatin-derived α-keto esters, the scope of the procedure was investigated. In all of the cases below, the isopropyl ester was chosen for its improved stability over the ethyl and methyl esters and hence simpler purification. Variation of the *N*-protecting group was investigated first (Scheme 3.3).

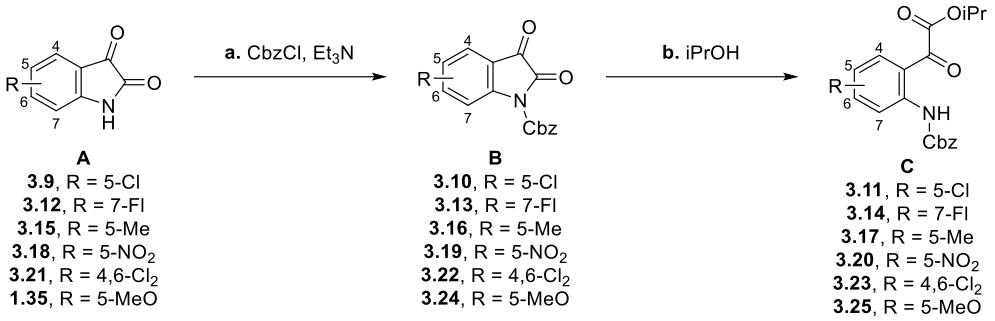


Scheme 3.3: Variation of the *N*-protecting group of isatin-derived α-keto esters. Reagents and conditions: (a) MeOCOCl (1.2 equiv), Et_3N (1.2 equiv), THF, 0 °C to rt, 60 min, 87%; (b) iPrOH, reflux, 6.5 h, 86%; (c) Boc_2O (1.2 equiv), DMAP (0.1 equiv), THF, 0 °C to rt, 4 h; (d) iPrOH, reflux, 7 h, 74% over two steps; (e) TsCl (1.0 equiv), Et_3N (1.0 equiv), PhMe, 90 °C, 3 h, 17%; (f) 1:1 iPrOH:THF, reflux, 67 h, 85%.

While other chloroformate reagents could be subjected to equivalent protection conditions, Boc_2O required the inclusion of nucleophilic catalyst DMAP.[128,129] Purification of the *N*-Boc-isatin intermediate was found to be unnecessary, as residual DMAP and Boc_2O could

be more readily removed after solvolysis. Tosylation proved more difficult, with much poorer conversion observed than has been previously reported.[130] Regardless, the solvolysis of all three N-protected intermediates proceeded in high yield to produce **3.6**, **3.7**, and **3.8**.

While there are numerous literature methods for the preparation of substituted isatins,[131] the set of commercially available structures was considered broad enough to suffice for this study (Table 3.1). In general, the nature of the substituents had little effect on either the N-protection or the solvolysis (Table 3.1, entries 1-5). As before, intermediate **B** is simply filtered from the reaction mixture, washing with water. This procedure did appear insufficient in the purification of **3.19** and **3.22** (Table 3.1, entries 4-5), although subjection of the impure material to solvolysis produced similar yields over two steps to the other substrates. Of the keto esters displayed below, only **3.23** (Table 3.1, entry 5) displayed notable instability to silica, with the lower yield due to partial degradation during purification. Unexpectedly, 5-MeO-isatin (**1.35**) seemed to be incompatible with the N-protection conditions, with a complex mixture formed in which none of the desired intermediate, **3.24**, could be observed. Heating this complex mixture to reflux in iPrOH showed no formation of keto ester **3.25**. As this substrate possesses the oxygenation pattern required for the planned total synthesis of unciaphenol (**1.1**), alternative protection conditions were sought. Sodium hydride was used to generate the anion of **1.35** stoichiometrically, to which was added CbzCl (Table 3.1, entry 6).[132,133] An aqueous quench allowed isolation of a mixture of **3.24** and the corresponding keto acid. Esterification of this mixture proved sluggish under neutral conditions, but the presence of sulfuric acid as a catalyst converged both species to **3.25** in high yield over two steps.



entry	substrate	yield(B)[a]	time(b)/h	yield(C)[a]
1	**3.9**	93%	7	73%
2	**3.12**	84%	7	84%
3	**3.15**	85%	23	88%
4	**3.18**	n.d.[b]	15	70%[c]
5	**3.21**	n.d.[b]	6	50%[c]
6[d]	**1.35**	n.d.[b]	-	78%[c]

Table 3.1: Scope for the synthesis of substituted isatin-derived α-keto esters. Reagents and conditions: (a) CbzCl (1.2 equiv), Et_3N (1.2 equiv), THF, 0 °C to rt, 1.5 h; (b) iPrOH, reflux. [a] Isolated yield; [b] n.d. = not determined, **B** not obtained pure and used directly in the following step; [c] yield over two steps; [d] alternative conditions used: (c) CbzCl (1.2 equiv), NaH (2.0 equiv), 0 °C to rt, 3.5 h; (d) H_2SO_4 (cat.), iPrOH, reflux, 61 h.

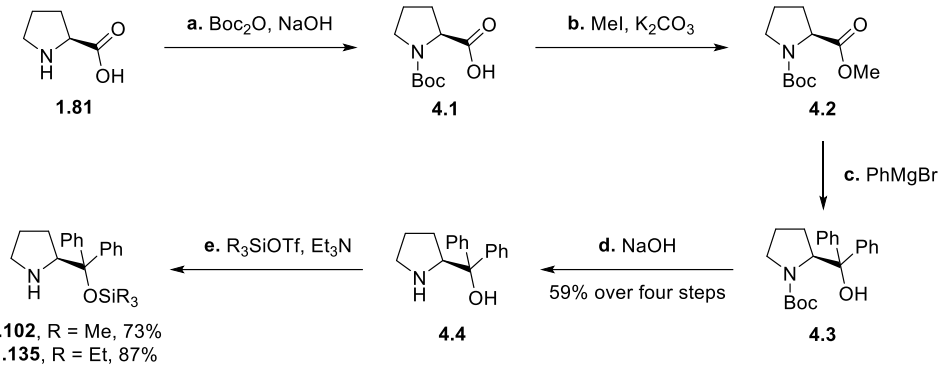
With a range of suitable bifunctional substrates in hand, the next focus was on trialling their compatibility in the planned organocatalysed coupling with cinnamaldehydes.

4 Organocatalysed cyclisation development

4.1 Catalyst synthesis

While there are numerous chiral amine organocatalysts used to effect enantioselective preparation of 1,2-dihydroquinolines,[96,97,99,102–105] the superficial similarity between the coupling planned for the synthesis of unciaphenol (**1.1**) and that reported by Wang and co-workers suggested first a simple exchange of substrates should be tried.[96] This has an added advantage of the accessibility of diphenylprolinol catalyst **1.135**, in comparison with some more specialised designs.

The synthesis of catalyst **1.135** began with the N-protection of L-proline (**1.81**) to provide *N*-Boc-L-proline (**4.1**) (Scheme 4.1), according to the procedure of Wersin and co-workers.[134] The remainder of the synthesis then follows that reported by Boeckman and co-workers.[135] Formation of the methyl ester, **4.2**, allows double addition of phenylmagnesium bromide to produce tertiary alcohol **4.3**. Deprotection of the Boc group provides diphenylprolinol, **4.4**, on which silylation of the alcohol can give the desired catalyst structures **1.102** and **1.135**. While it was hoped that the use of an achiral secondary amine would allow access to the equivalent racemic reaction, it was expected that the enantiomeric catalyst, *ent*-**1.135**, would be required for the natural enantiomer of unciaphenol (**1.1**). This was prepared using an identical route from D-proline (*ent*-**1.81**) (see section 8.3). Although a shorter sequence to *ent*-**4.4** has been reported, its use of stoichiometric (–)-sparteine rendered it a less attractive proposition.[136]

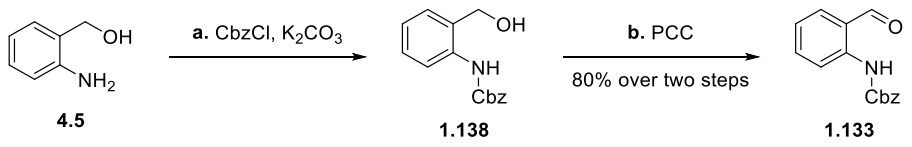


Scheme 4.1: Preparation of Hayashi-Jørgensen catalysts, following procedures of Wersin and co-workers[134] and Boeckman and co-workers.[135] Reagents and conditions: (a) Boc_2O (1.0 equiv), NaOH (1.1 equiv), 2:3 *t*-BuOH:H_2O, rt, 18 h; (b) MeI (2.2 equiv), K_2CO_3 (1.1 equiv), DMF, rt, 24 h; (c) PhMgBr (2.5 equiv), THF, rt, 4 h; (d) NaOH (10.0 equiv), EtOH, reflux, 105 min, 59% over four steps; (e) (**1.102**) TMSOTf (1.4 equiv), Et_3N (1.4 equiv), CH_2Cl_2, –78 °C to rt, 4 h, 73%; (e) (**1.135**) TESOTf (1.8 equiv), Et_3N (1.8 equiv), CH_2Cl_2, –78 °C, 5.5 h, 87%.

4.2 Optimisation of α-keto ester substrates in the organocatalysed cyclisation

4.2.1 Validation of Wang and co-workers' conditions

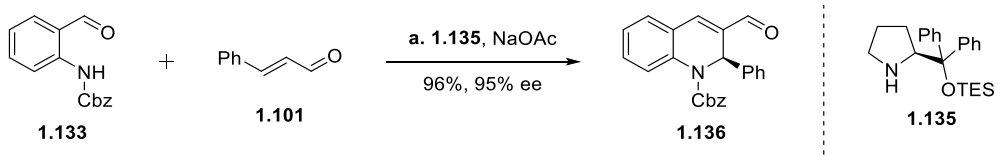
To confirm the activity of the prepared catalysts (*vide supra*) and probe the reproducibility of Wang and co-workers' cyclisation,[96] 2-aminobenzaldehyde **1.133** was prepared by the procedure of Lin and co-workers (Scheme 4.2).[137] N-Protection of aniline **4.5** followed by oxidation of **1.138** rapidly provided the necessary structure, **1.133**.



Scheme 4.2: Synthesis of Wang and co-workers' cyclisation substrate, according to the procedure of Lin and co-workers.[137] Reagents and conditions: (a) CbzCl (1.1 equiv), K_2CO_3 (10 equiv), THF, rt, 16 h; (b) PCC (1.2 equiv), CH_2Cl_2, rt, 6.5 h, 80% over two steps.

Subjecting **1.133** to the literature conditions (at 1.5 × scale for practical simplicity) with *trans*-cinnamaldehyde (**1.101**) produced the expected 1,2-dihydroquinoline, **1.136**, in similar yield to that reported (Scheme 4.3).[96] A racemic sample, *rac*-**1.136**, was prepared in an equivalent reaction, simply replacing **1.135** with an equal quantity of pyrrolidine. This allowed

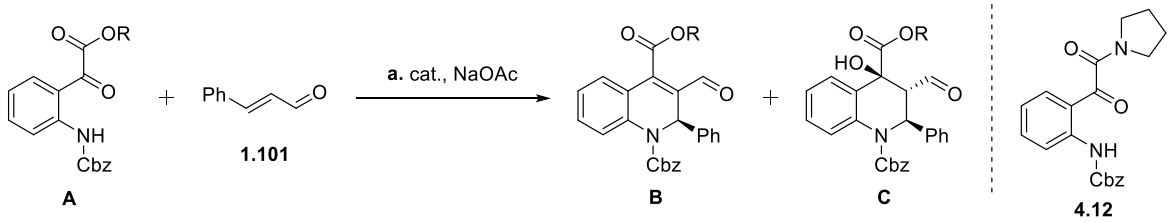
measurement of the enantiomeric excess by chiral HPLC, which showed the selectivity was similar to, if slightly higher than, that reported (95% ee vs. 93% ee).



Scheme 4.3: Reproduction of Wang and co-workers' cyclisation conditions.[96] Reagents and conditions: reaction run on 0.15 mmol **1.101**; (a) **1.133** (3.0 equiv), **1.135** (20 mol %), NaOAc (50 mol %), activated 4 Å MS (ground) (75 mg), $ClCH_2CH_2Cl$, rt, 70 h, 96%, 95% ee.

4.2.2 Initial subjection of α-keto esters to organocatalysed cyclisation

Confident that the prepared batch of catalyst was satisfactory, and the reaction was robust, it was repeated replacing aldehyde **1.133** with keto ester **3.1** while keeping all other factors constant (Table 3.1). After stirring at room temperature for a similar length of time, the crude ^{1}H NMR spectrum showed very little consumption of either starting material. Following purification by column chromatography, trace quantities of desired 1,2-dihydroquinoline *ent*-**4.6** and aldol product *ent*-**4.7** could be observed (Table 4.1, entry 1). For a discussion of the absolute and relative stereochemical assignment of these two structures, see section 4.4. When an equivalent amount of pyrrolidine was used in place of **1.135**, neither of these products were observed (Table 4.1, entry 2). This was likely due to more rapid reaction of the amine catalyst with the keto ester, **3.1**, to give keto amide **4.12**. An analogous keto amide formed with **1.135** was never observed. Instead, the majority of **1.135** could be recovered through column chromatography and showed no reduction in activity when subjected to the reaction in Scheme 4.3.



entry	R/#(A)	cat.	time/h	#(B)	yield(B)[a]	#(C)	yield(C)[a]	yield(4.12)[a,b]
1	Me/**3.1**	**1.135**	63	*ent*-**4.6**	<5%	*ent*-**4.7**	<5%	N/A[c]
2	Me/**3.1**	pyrrolidine	65	*rac*-**4.6**	n.d.[d]	*rac*-**4.7**	n.d.[d]	86%
3	Et/**3.4**	**1.135**	69	*ent*-**4.8**	25%	*ent*-**4.9**	7%	N/A[c]
4	Et/**3.4**	pyrrolidine	69	*rac*-**4.8**	13%	*rac*-**4.9**	21%	75%
5	iPr/**3.5**	**1.135**	137	*ent*-**4.10**	8%	*ent*-**4.11**	10%	N/A[c]
6	iPr/**3.5**	pyrrolidine	137	*rac*-**4.10**	<5%	*rac*-**4.11**	25%	76%

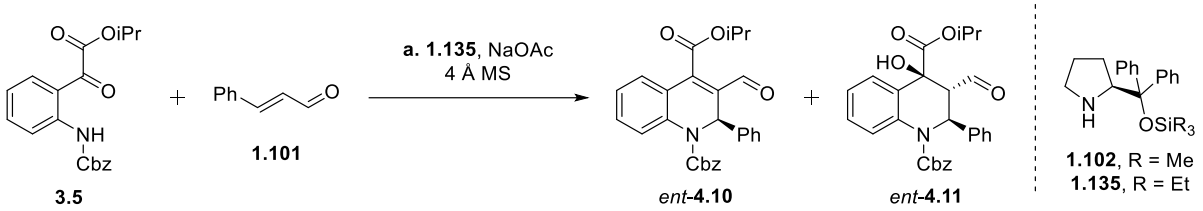
Table 4.1: Initial results using keto esters in the organocatalysed cyclisation. Reagents and conditions: all reactions run on 0.15 mmol **1.101**; (a) **A** (3.0 equiv), **1.135** or pyrrolidine (20 mol %), NaOAc (50 mol %), activated 4 Å MS (ground) (75 mg), $ClCH_2CH_2Cl$, rt. [a] Isolated yield; [b] yield based on pyrrolidine; [c] N/A = not applicable; [d] n.d. = not determined.

Although it was unclear why chiral catalyst **1.135** showed poor reactivity, the achiral variant suggested that the methyl ester was perhaps too reactive. To investigate this, the ethyl and isopropyl esters, **3.4** and **3.5** respectively, were subjected to the same pair of reactions (Table 4.1, entries 3-6). Indeed, both substrates performed better than **3.1**. While both returned similar quantities of keto amide **4.12**, the desired cyclisation appeared more competitive. The yields of 1,2-dihydroquinoline and aldol product were still low, but in all cases higher than with methyl ester **3.1**. Despite the higher yields for the ethyl ester, **3.4**, subsequent optimisation was conducted on the isopropyl ester, **3.5**, due to the more difficult purification of substrate **3.4** (see section 3.1).

4.2.3 Optimisation of reaction conditions

A brief conditions screen was carried out using isopropyl ester **3.5** (Table 4.2). Increasing the catalyst loading resulted in a similar increase in the combined yield of *ent*-**4.10** and *ent*-**4.11**

(Table 4.2, entries 1-3), suggesting that the issue lay with low turnover of the catalyst. These experiments allowed the isolation of sufficient material to measure the enantiomeric excess of the isolated 1,2-dihydroquinoline. While aldol product *ent*-**4.11** could not be made to produce a clean trace on chiral HPLC, a measurement of ee for *ent*-**4.10** was feasible. Pleasingly, the ee was high and showed no change, within error, under different catalyst loadings. Since the less sterically bulky keto ester **3.4** displayed increased conversion (*vide supra*) a less sterically demanding catalyst, **1.102**, was tried (Table 4.2, entry 4). However, this offered only minor increases in the yields of *ent*-**4.10** and *ent*-**4.11**, while causing a notable drop in enantiomeric excess of *ent*-**4.10**. Heating the reaction in an attempt to overcome a potentially higher activation barrier offered similar results (Table 4.2, entry 5). Suspecting that hydrolysis of the catalyst from an intermediate-bound species may be turnover limiting, molecular sieves were omitted (Table 4.2, entry 6). This more than doubled the combined yield of products, albeit at a reduced ratio of *ent*-**4.10**:*ent*-**4.11**. Two additional products were isolated from the column in similar amounts to *ent*-**4.11**, although their identities could not be determined. One of these products, after 2 weeks standing in $CDCl_3$, produced a ^1H NMR spectrum that showed similar quantities of **3.5**, **1.101**, *ent*-**4.11**, and a triethylsilyl species, suggesting a reversibly formed intermediate. Running the reaction with no additive gave little change to the original conditions (Table 4.2, entry 7). The breakthrough came when switching to an acidic additive, $PhCO_2H$, with this seemingly offering a complete solution to the problems faced (Table 4.2, entry 8). One new issue was that *ent*-**4.10** from this reaction would streak during column chromatography. Up to this point, each reaction had been directly subjected to silica chromatography. Pleasingly, insertion of a work-up procedure, consisting of a base wash and an acid wash, prior to purification solved the issue of streaking and allowed an accurate yield to be determined (Table 4.2, entry 9).

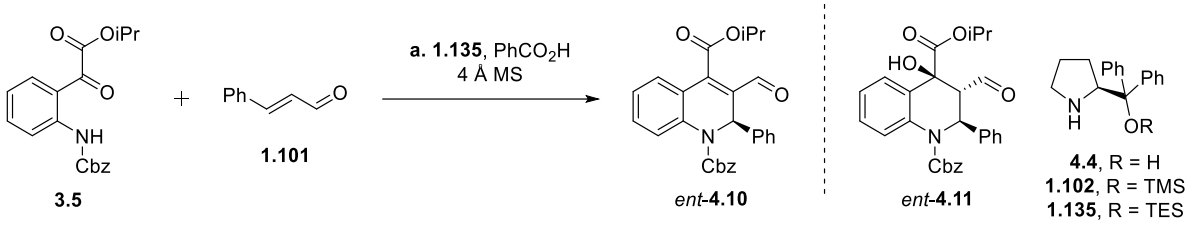


entry	change to conditions	time/h	yield(*ent*-4.10)[a]	% ee(*ent*-4.10)	yield(*ent*-4.11)[a]
1	-	89	8%	98	10%
2	50 mol % **1.135**	91	18%	98	24%
3	100 mol % **1.135**	95	37%	98	53%
4	**1.102** in place of **1.135**	89	12%	88	13%
5	run at 40 °C	94	13%	83	8%
6	4 Å MS omitted	92	10%	94	31%
7	NaOAc omitted	98	9%	96	6%
8	$PhCO_2H$ in place of NaOAc	90	>90%	96	0%
9[b]	$PhCO_2H$ in place of NaOAc	92	95%[c]	96[c]	0%[c]

Table 4.2: Initial screen of conditions for optimisation of the cyclisation with keto ester substrates. Reagents and conditions: all reactions run on 0.15 mmol **1.101**; (a) **3.5** (3.0 equiv), **1.135** (20 mol %), NaOAc (50 mol %), activated 4 Å MS (ground) (75 mg), $ClCH_2CH_2Cl$, rt. [a] Isolated yield; [b] work-up performed prior to purification; [c] average of two runs.

With the yield of the reaction now significantly improved, a more thorough optimisation screen was run using Table 4.2, entry 9 as a starting point (Table 4.3). Lower yields here are generally the result of lower conversion rather than side-product formation. It was quickly found that the new conditions required a shorter reaction time to reach full conversion (Table 4.3, entries 1-2). The molecular sieves were found to be important to both the conversion of starting reactants and dehydration of *ent*-**4.11** to *ent*-**4.10** (Table 4.3, entry 3). This is somewhat different to the NaOAc conditions (*vide supra*), where their absence appeared to improve turnover of the catalyst. While unactivated molecular sieves helped effect complete conversion of *ent*-**4.11** to *ent*-**4.10**, the yield was notably lower than with freshly dried molecular sieves (Table 4.3, entry 4). Reducing the loading of the excess reactant,

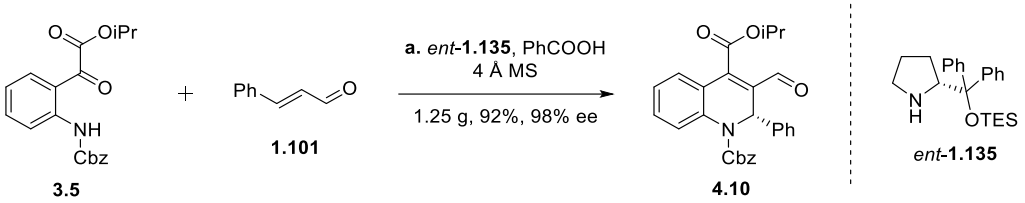
3.5, and catalyst, **1.135**, was possible without significantly lowering the yield or ee of *ent*-**4.10** (Table 4.3, entries 5-7), with entry 5 considered the optimal balance of efficiency and reaction rate. In stark contrast to the use of NaOAc, less sterically demanding catalyst **1.102** performed similarly well to **1.135**, although with a slightly messier crude reaction mixture (Table 4.3, entry 8). Omission of the silyl group using catalyst **4.4**, however, resulted in complete lack of conversion (Table 4.3, entry 9). Buffering the pH of the reaction through a 1:1 mixture of $PhCO_2H$ and $PhCO_2Na$ offered little change in outcome (Table 4.3, entry 10). When varying reaction solvent, there is a general trend towards higher yields for less polar solvents, with the exception of acetonitrile (Table 4.3, entries 11-18). Explanation for this observation will not be provided here, as the mechanism will contain numerous reaction steps and intermediate species, and so the effect of solvent on the reaction outcome will undoubtedly be rather complex. Chlorinated solvents and toluene all performed similarly well with regards to rate and yield of *ent*-**4.10**. All but acetonitrile and THF showed no accumulation of aldol intermediate *ent*-**4.11**. Of these solvents, CH_2Cl_2 was chosen as it provided the optimal yield and enantioselectivity, albeit with the downside of higher solvent volatility. This could be alleviated by addition of more solvent partway through the reaction. Finally, the amount of molecular sieves could be reduced somewhat without significantly lengthening the reaction (Table 4.3, entries 19-20). Interestingly, the enantiomeric excess of *ent*-**4.10** remained high (>96%) across all sets of conditions reported in Table 4.3.



entry	3.5/equiv	additional change to conditions	solvent	time/h	yield[a]	% ee
1	3.0	-	$ClCH_2CH_2Cl$	43	98%	97
2	3.0	-	$ClCH_2CH_2Cl$	19	78% (8%)	98
3	3.0	4 Å MS omitted	$ClCH_2CH_2Cl$	68	23% (42%)	99
4	3.0	4 Å MS not activated	$ClCH_2CH_2Cl$	46	70%	98
5	2.0	-	$ClCH_2CH_2Cl$	46	91%	97
6	1.0	-	$ClCH_2CH_2Cl$	72	76%	98
7	2.0	10 mol % **1.135**	$ClCH_2CH_2Cl$	168	80%	98
8	2.0	**1.102** in place of **1.135**	$ClCH_2CH_2Cl$	48	83%	99
9	2.0	**4.4** in place of **1.135**	$ClCH_2CH_2Cl$	69	<5%	n.d.[b]
10	2.0	$PhCO_2Na$ (50 mol %) added	$ClCH_2CH_2Cl$	46	92%	97
11	2.0	-	CH_2Cl_2	48[c]	98%	99
12	2.0	-	$CHCl_3$	46	95%	98
13	2.0	-	DMSO	47	<5%	n.d.[b]
14	2.0	-	PhMe	47	97%	98
15	2.0	-	DMF	48	15%	96
16	2.0	-	MeCN	48	78% (9%)	97
17	2.0	-	THF	49	43% (24%)	98
18	2.0	-	Et_2O	47[c]	85%	99
19	2.0	4 Å MS (50 mg)	CH_2Cl_2	49[c]	88%	98
20	2.0	4 Å MS (25 mg)	CH_2Cl_2	48[c]	56%	98

Table 4.3: Full optimisation of the organocatalysed cyclisation with benzoic acid as an additive. Reagents and conditions: all reactions run on 0.15 mmol **1.101**; (a) **3.5**, **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (75 mg), solvent, rt. [a] Isolated yield, numbers in parentheses refer to *ent*-**4.11**; [b] n.d. = not determined; [c] additional solvent added after 24 h to compensate for solvent loss.

While scale-up necessitated a slightly increased reaction time, there was little decrease in yield. Altogether, this offered the optimised reaction conditions for the enantioselective organocatalysed coupling of **3.5** and **1.101**, this time performed with enantiomeric catalyst *ent*-**1.135** to generate **4.10** (Scheme 4.4).

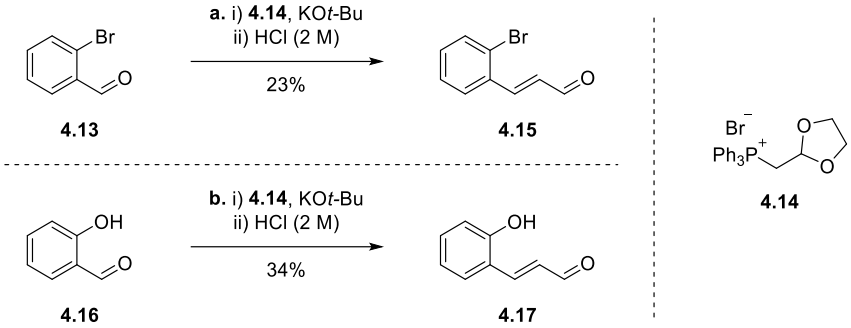


Scheme 4.4: Optimised organocatalysed cyclisation on gram-scale. Reagents and conditions: reaction run on 3.0 mmol **1.101**; **3.5** (2.0 equiv), *ent*-**1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (beads) (1.0 g), CH_2Cl_2, rt, 71 h, 92%, 98% ee.

4.3 Investigating the substrate scope of the cyclisation

4.3.1 Cinnamaldehyde synthesis

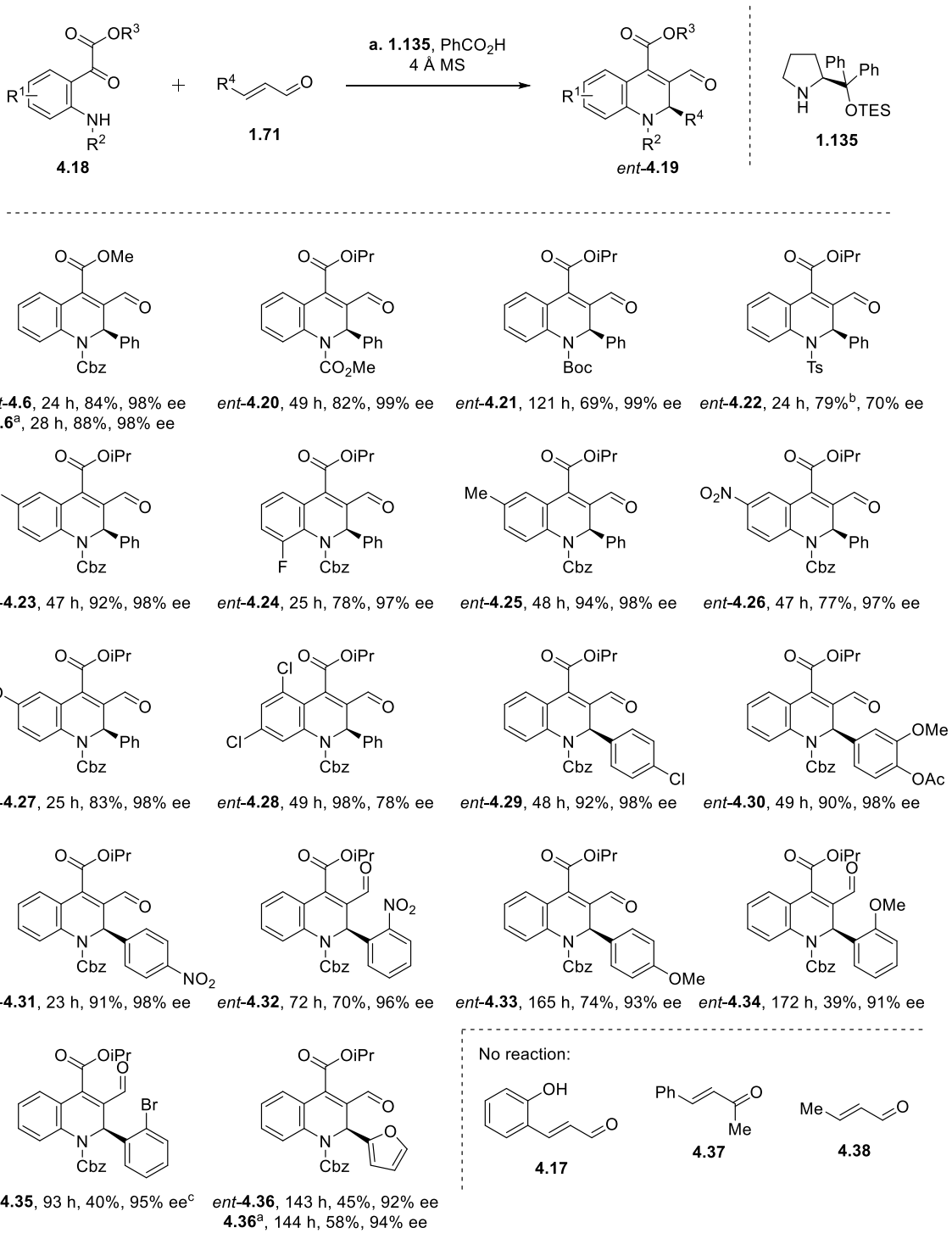
While there is a wide range of commercially available α,β-unsaturated aldehydes, it was necessary to make two that possessed functionality of interest for the proposed total synthesis. These were prepared through Wittig homologation of the corresponding benzaldehydes (Scheme 4.5). Treatment of benzaldehydes **4.13** and **4.16** with the ylide of **4.14**, followed by hydrolysis, provided access to cinnamaldehydes **4.15** and **4.17** in synthetically useful yields.[138] These homologation conditions were at this stage unoptimised, and so the yields could undoubtedly be improved (see section 6.1 for a discussion of the homologation conditions).



Scheme 4.5: Synthesis of two cinnamaldehyde substrates. Reagents and conditions: (a) i) **4.14** (2.0 equiv), KO*t*-Bu (1.1 equiv), THF, reflux, 26 h, ii) HCl (2 M), rt, 16 h, 23%; (b) i) **4.14** (1.2 equiv), KO*t*-Bu (2.2 equiv), THF, reflux, 22 h, ii) HCl (2 M), rt, 30 min, 34%.

4.3.2 Substrate scope of the organocatalysed cyclisation

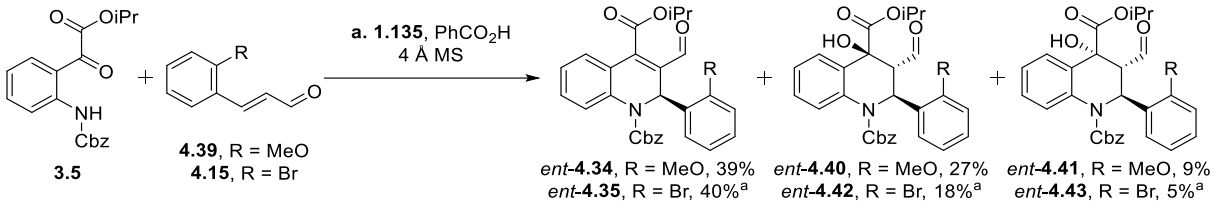
To further investigate the cyclisation from Scheme 4.5, a range of differently functionalised keto esters, **4.18**, and α,β-unsaturated aldehydes, **1.71**, were subjected to the optimised reaction conditions (Scheme 4.6). No further optimisation was undertaken at this stage. In order to measure the ee of the 1,2-dihydroquinoline products, *ent*-**4.19**, by chiral HPLC, each reaction was also run with 1.0 equivalent of pyrrolidine in place of chiral catalyst **1.135**. The yields of these racemic versions typically suffered due to reaction of pyrrolidine with **4.18** to form the corresponding keto amide, analogous to **4.12**. Sufficient racemic material was, however, isolated for each substrate pair with the exception of *rac*-**4.6** and *rac*-**4.36**. The increased reactivity of the former's keto ester, **3.1**, and the latter's lower rate of desired cyclisation necessitated preparation of a racemate by mixing with the enantiomeric products, **4.6** and **4.36**. These were synthesised by an equivalent reaction using enantiomeric catalyst *ent*-**1.135** in place of **1.135**.



Scheme 4.6: Scope for the developed organocatalysed coupling of isatin-derived α-keto esters and α,β-unsaturated aldehydes. All isolated yields unless otherwise specified. Reagents and conditions: reactions run on 0.15 mmol **1.71**; (a) **4.18** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt. [a] Reaction run using enantiomeric catalyst *ent*-**1.135** to obtain the opposite enantiomer, **4.19**; [b] NMR yield due to inseparable starting material **3.8**; [c] average of two runs.

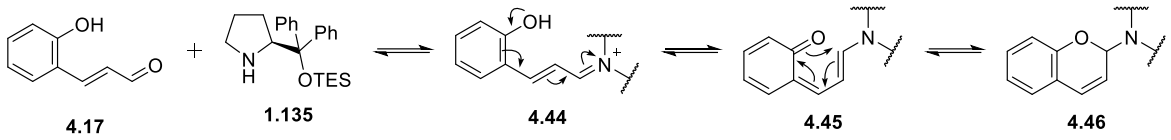
While the methyl ester had proved inefficient during initial screening, it posed no problem under the optimised conditions. 1,2-Dihydroquinoline *ent*-**4.6** (or **4.6**) was produced in both high yield and excellent ee, with a shorter reaction time than required for the isopropyl ester. The benzyl substituent of the *N*-protecting group was found to be unimportant, with methyl carbamate *ent*-**4.20** formed in similar rate, yield, and ee. Increased steric bulk at this position is fairly well-tolerated, albeit with slightly decreased rate and yield (*ent*-**4.21**). The carbamate itself appears key to a highly enantioselective transformation, as tosylated product *ent*-**4.22** was formed relatively rapidly but at notably lower ee. Variation at R^1 of keto ester **4.18** was generally well-tolerated, with high yields and ee's for the majority of products (*ent*-**4.23**-**4.27**). The one exception here is the 4,6-dichloro keto ester, **3.23**, which offered an excellent yield of *ent*-**4.28** but with decreased enantioselectivity. A range of synthetically useful functionality on α,β-unsaturated aldehyde **1.71** is also well-tolerated, with halides (*ent*-**4.29**), oxygenation (*ent*-**4.30**) and nitro groups (*ent*-**4.31**) showing no adverse effects on the yield or ee. Even the more sterically demanding *ortho*-nitro product, *ent*-**4.32**, is produced in good yield and ee, with only a slight increase in reaction time necessary. However, these substituents are all electron withdrawing.[139] When more electron donating substituents are present, the reaction tends to slow. With the catalyst appearing to be significantly deactivated after a period of several days, potentially due to desilylation, some of the slower reactions fail to reach complete conversion of **1.71**. Both the *para*-methoxy, *ent*-**4.33**, and 2-furyl products, *ent*-**4.36** and **4.36**, are prime examples of this. In each case, the reaction is still reasonably clean, with no other products observed in notable yield. Interestingly, the ee is slightly lower for the more electron rich α,β-unsaturated aldehyde substrates. This does not appear to be degradation of ee over extended reaction times, as samples of *ent*-**4.33** isolated after 49 h and 165 h had the same ee, within error. Furthermore, the presence of an *ortho*-methoxy (*ent*-**4.34**) or bromide

(*ent*-**4.35**) gives rise to another interesting result. Conversion of **1.71** proceeds to a similar level, but in contrast with *ent*-**4.32**, the substituent appears to disfavour dehydration. In both cases, two diastereomeric aldol species were isolated alongside the desired 1,2-dihydroquinolines, *ent*-**4.34** and *ent*-**4.35**, (Scheme 4.7). See section 4.4 for a discussion of the stereochemical assignment of these species.



Scheme 4.7: Isolation of two diastereomeric aldol products from the cyclisation of certain 2-substituted cinnamaldehydes. Reagents and conditions: reactions run on 0.15 mmol **4.39** or **4.15** (a) (*ent*-**4.34**) **3.5** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt, 172 h; (a) (*ent*-**4.35**) **3.5** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt, 93 h. [a] Average of two runs.

The unprotected phenol of **4.17** resulted in complete lack of conversion. Instead, a deep red solution was observed, likely indicating isomerisation to *ortho*-quinone methide **4.45**, as reported by Wang and co-workers (Scheme 4.8).[140,141] Iminium ion **4.44** and proposed aminal **4.46** appeared to be completely inert under the reaction conditions. Disappointingly, the reaction appears to be restricted to aldehyde substrates, with ketone **4.37** showing no conversion. This observation is likely due to the additional strain present in ketimines, along with the ability to form a lower energy enamine. Indeed, acyclic ketones are a considerably less common substrate with organocatalysts such as **1.135**, with some reactions even proposed to proceed by a distinct, non-covalent mechanism for ketone substrates.[142,143] Somewhat surprisingly, crotonaldehyde (**4.38**) showed no conversion in the reaction, although it is not clear whether this is due to volatility, deprotonation to the dienamine form,[71] or another reason.



Scheme 4.8: Side reaction of 2-hydroxycinnamaldehydes with amines.

In conclusion, the range of tolerated substitution in *ent*-**4.19** is reasonably broad. In the three positions investigated on the keto ester reactant, **4.18**, only the sulfonyl-protecting group and substitution at C4 of the starting isatin had an adverse effect. For the other coupling partner, **1.71**, electron donating groups and some *ortho*- substitution results in a slower and potentially incomplete reaction under the standard conditions. Enantioselectivity also drops slightly for these cases.

4.4 Stereochemical assignment of cyclisation products

4.4.1 Absolute configuration

The absolute configuration for the 1,2-dihydroquinoline products, *ent*-**4.19**, arising from the natural proline-derived (*S*)-catalyst, **1.135**, has been assigned as (*R*) where the R^4 group takes third priority according to the Cahn-Ingold-Prelog rules.[144,145] This is the opposite configuration to the analogous position in unciaphenol (**1.1**). Several observations have contributed to this judgement. Firstly, it follows from the simple model used to explain enantioselectivity in asymmetric Michael addition with catalysts such as **1.135** (Figure 4.1, see also section 1.2.2).[146] With the α,β-unsaturated iminium ion in the lower energy s-*trans* conformation, the steric bulk of the pyrrolidine's substituent sterically shields the upper face from nucleophile approach. The assignment also matches the stereochemistry of similar cascades reported in the literature,[96–99,103] with all of the products reported in Scheme 4.6 possessing optical rotations of the same sign and similar magnitude to the products reported

by Wang and co-workers.[96] Finally, there is further supporting evidence from X-ray crystallography (Figure 4.2). While the absolute structure parameter from the crystal of *ent*-**4.10** rendered determination of the absolute configuration ambiguous, a later crystal of *ent*-**4.29** offered greater certainty: the Flack parameter[147] for the latter crystal was 0.002 with a standard uncertainty of 0.003. Taken with the other evidence, this allowed confident assignment of the absolute configuration of *ent*-**4.29**, and hence all other products by analogy.

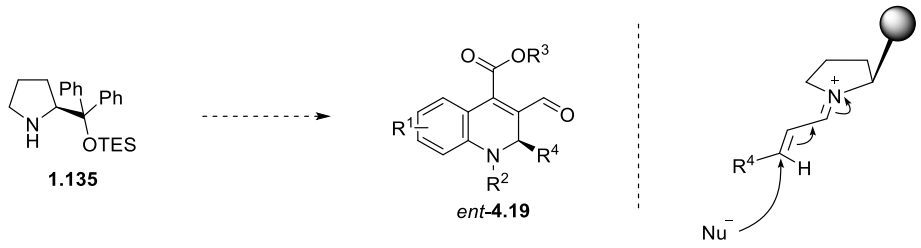


Figure 4.1: Left: (*S*)-catalyst leads to (*R*)-products; right: simple model for enantioselective Michael addition.

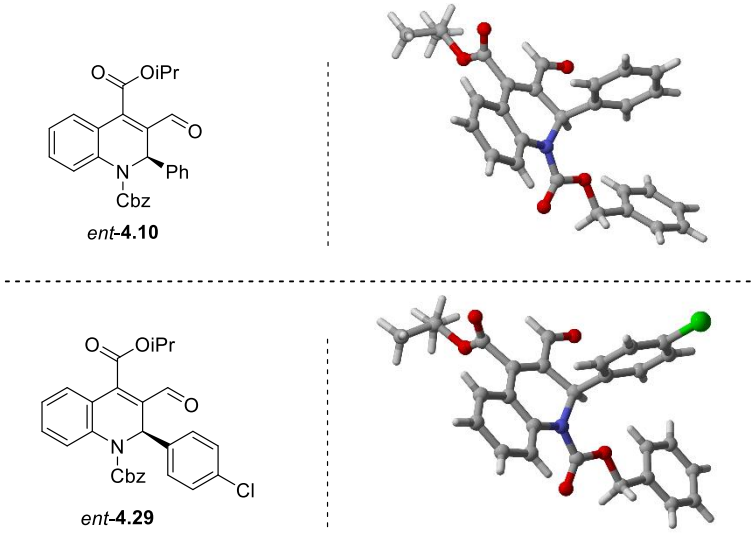
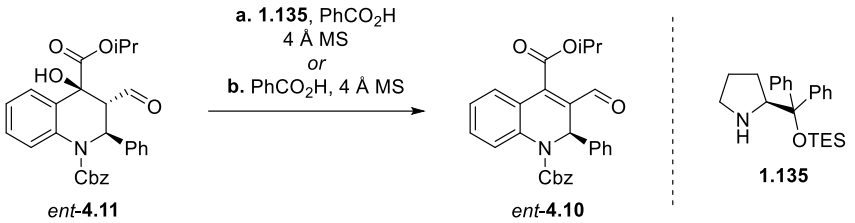


Figure 4.2: X-ray crystallographic structures for 1,2-dihydroquinoline products.

Subjection of aldol species *ent*-**4.11** to the optimised reaction conditions both with and without catalyst **1.135** resulted in dehydration to *ent*-**4.10** (Scheme 4.9), albeit slightly faster with **1.135** present. That the enantiomeric excess of both samples of **4.10** was equivalent, within error, confirms the absolute configuration at C9 of *ent*-**4.11**. It also suggests that

formation of *ent*-**4.11** may be effectively irreversible. See section 4.5 for a more detailed discussion of the mechanism.



Scheme 4.9: Separate dehydration of aldol intermediate *ent*-**4.11** both with and without catalyst **1.135**. Reagents and conditions: (a) **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground), CH_2Cl_2, rt, 24 h, 93% conversion by NMR, 95% ee; (b) $PhCO_2H$ (50 mol %), activated 4 Å MS (ground), CH_2Cl_2, rt, 24 h, 81% conversion by NMR, 97% ee.

4.4.2 Relative configuration of aldol product diastereoisomers

From the ^1H NMR spectrum of aldol product *ent*-**4.9**, the vicinal coupling constant between H8 and H9 was found to be 10.1 Hz. From the Karplus equation,[148] this is indicative of a dihedral angle closer to either 0° or 180°, of which the latter (a 1,2-*trans* diaxial arrangement) would likely be favoured to reduce torsional strain. This *trans* configuration of aldehyde and phenyl ring is also as predicted by the simple stereochemical model for enamine reactions of **1.135**, in a similar manner to Michael addition onto the iminium ion (see section 1.2.2). Further to this, ^1H-^1H NOESY analysis of *ent*-**4.9** suggests that H9 is on the same face as the ester carrying H23, resulting in the relative configuration shown (Figure 4.3).

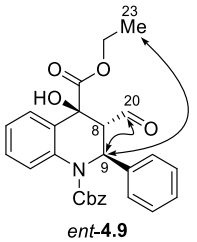


Figure 4.3: Key ^1H-^1H nOe correlations for stereochemical assignment of aldol intermediate *ent*-**4.9**.

Where two aldol products were isolated, the ^{1}H and ^{13}C NMR spectra of the major diastereoisomers correlated reasonably well with those of *ent*-**4.9**. Further ^{1}H-^{1}H NOESY analysis supported the assignment of *ent*-**4.40** as analogous to *ent*-**4.9** (Figure 4.4). Since the second aldol isomer had thus far only been observed for species bearing an *ortho*- substituent, it was considered that *ent*-**4.41** may be atropisomeric to *ent*-**4.40**. However, traces of analogous aldol products have since been observed with unsubstituted arenes. ^{1}H-^{1}H NOESY analysis of *ent*-**4.41** revealed the lack of an nOe correlation between H9 and H25, which had been relatively strong for *ent*-**4.40**. With the large H8–H9 coupling retained, *ent*-**4.41** was deduced to be the C7 epimer of *ent*-**4.40**. The relative configurations of most aldol products arising from other substrates were assigned by analogy with *ent*-**4.40** and *ent*-**4.41**. Room temperature NMR signals of both the 1,2-dihydroquinolines and aldol intermediates are generally broad with strong splitting of diastereotopic protons, which is likely due to restricted rotation of the *N*-carbamate moiety.

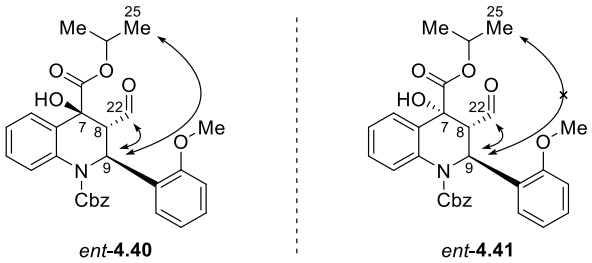
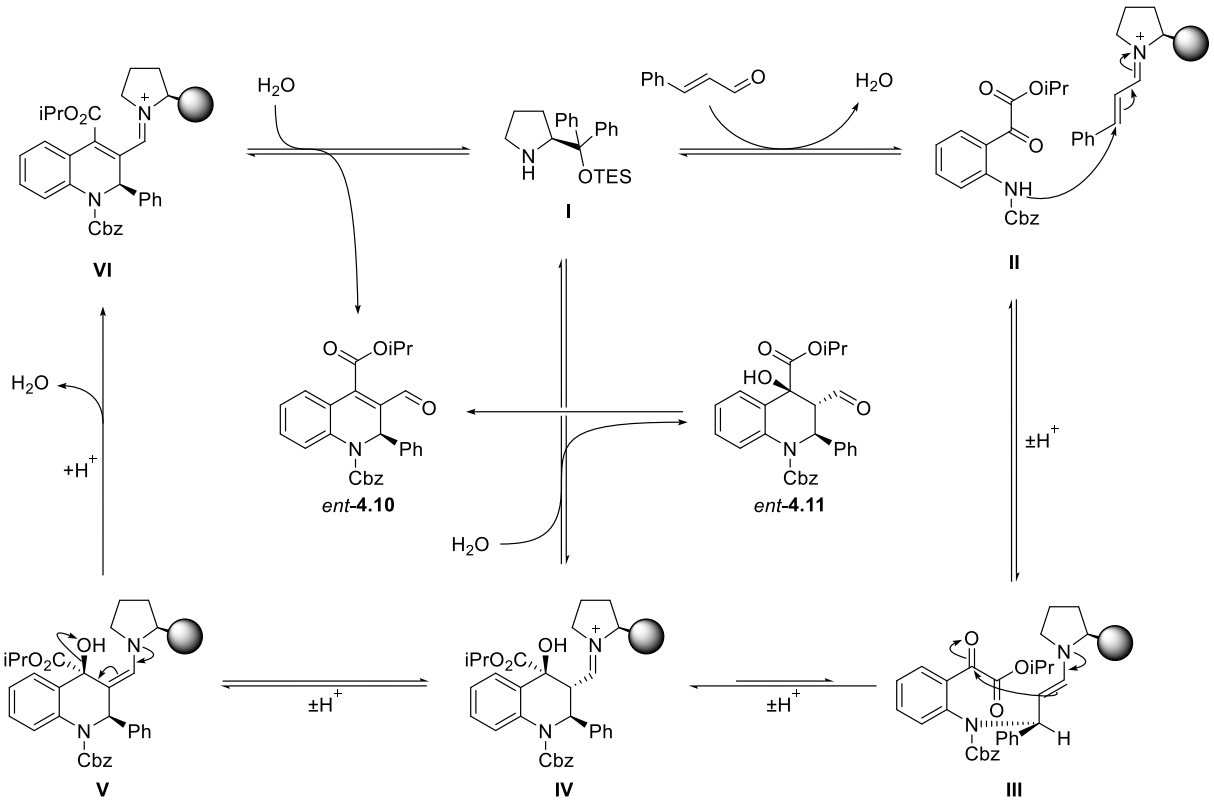


Figure 4.4: Key ^{1}H-^{1}H nOe correlations for stereochemical assignment of epimeric aldol products *ent*-**4.40** and *ent*-**4.41**.

4.5 Proposed mechanism of the organocatalysed cyclisation

The putative mechanism for the organocatalysed coupling detailed in Scheme 4.4 is shown below (Scheme 4.10). Condensation of the catalyst, **I**, with cinnamaldehyde generates an α,β-unsaturated iminium ion. Possessing both increased positive charge and a lower energy

LUMO, this species is more reactive towards nucleophilic addition at the β-carbon than the starting α,β-unsaturated aldehyde (**II**). Direct (1,2-) addition is likely to be fully reversible and a non-productive pathway. As mentioned earlier, the s-*trans* conformation of the iminium ion should be lower in energy and the bulky group of the catalyst will shield the upper face, as drawn in Figure 4.5.[146] At intermediate **III**, a 6-*exo*-*trig* cyclisation of the *in situ* generated enamine onto the ketone would form catalyst-bound aldol intermediate **IV**. Reaction should occur on the *Re* face of the enamine, for similar considerations as the Michael addition, while addition to the *Re* face of the ketone is known to lead to the major observed product. As the preferred orientation of the molecule is not known, the explanation for this latter selectivity is unclear. It may be due to reducing steric clash between the ester and pyrrolidine ring, or due to closer interaction between the developing charges on the nitrogen and oxygen atoms (Figure 4.5). The ratio of formation of the two alcohol epimers of **IV** (or *ent*-**4.11**) is also unknown, as their dehydrations to *ent*-**4.10** are likely to occur at different rates. Given the retention of enantiomeric purity in the amine-free dehydration of *ent*-**4.11** to *ent*-**4.10**, it would seem that the cyclisation (**III** to **IV**) is effectively irreversible. Hydrolysis of **IV** would release *ent*-**4.11** (and similarly for its epimer) to regenerate the free catalyst. Alternatively, deprotonation to **V** would facilitate loss of water *via* an $E1_{cB}$ mechanism, with subsequent hydrolysis of **VI** releasing *ent*-**4.10** and free catalyst. Direct dehydration of *ent*-**4.11** to *ent*-**4.10** would likely involve a similar $E1_{cB}$ pathway.



Scheme 4.10: Proposed mechanism for the organocatalysed cyclisation shown in Scheme 4.4.

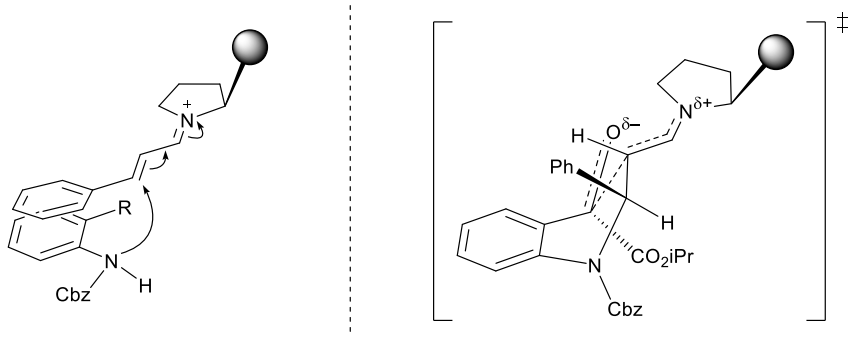


Figure 4.5: Proposed origin of the major stereoisomers of both *ent*-**4.10** (left) and *ent*-**4.11** (right).

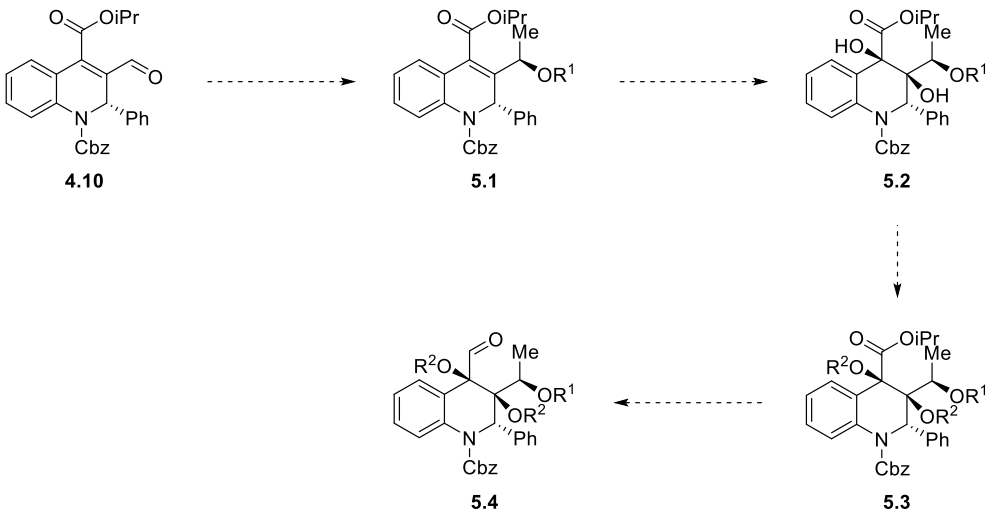
It is important to note that Scheme 4.10 represents the simplest mechanism that fits the current observations. Recently, there have been several detailed mechanistic studies on various diarylprolinol ether-catalysed reactions, relating to the origin of their enantioselectivity.[72,73,149,150] In particular, Blackmond and co-workers have demonstrated that the enantiocontrol *via* steric shielding during bond formation is often tempered or reinforced by downstream species. The existence of intermediates occurring after bond formation but

before the rate-determining step can result in a Curtin-Hammett situation, depending on their location on- or off-cycle, their relative stabilities, rates of interconversion, and their rates of conversion to final product. Structural changes in any of the species involved can also shift the predominant enantiodetermining step.

The reaction developed in this chapter will almost certainly involve a more complex mechanism than that shown above (Scheme 4.10). While observations such as the slower dehydration of aldol intermediates bearing *ortho*- substituents could feasibly be explained by steric arguments, there are other results that are less clear. That this reaction with keto ester substrates seems generally more enantioselective than the transformation it was inspired by,[96] along with the notably lower ee's for *ent*-**4.22** and *ent*-**4.28**, could well be due to unidentified downstream intermediates. A more detailed study would be required to shed light on the mechanism, although this may be hindered somewhat by the size and relative complexity of the substrates. Identification of the catalyst resting state(s) could also assist in improving the reaction rate, as described by Burés and Companyó.[101] However, the cyclisation appeared to work well enough to enable investigation further into the proposed synthetic route to unciaphenol (**1.1**).

5 Retrosynthetic route investigations using a model system

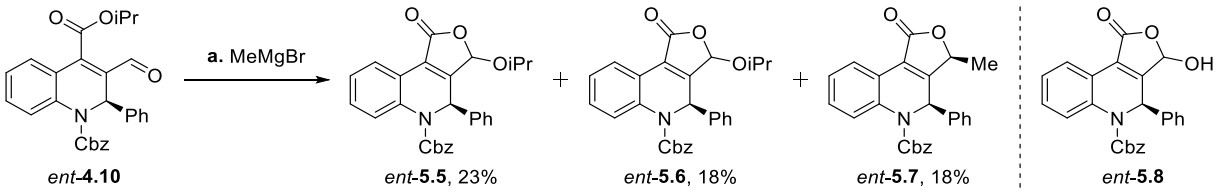
With the organocatalysed cyclisation developed, the remainder of the retrosynthesis from chapter 2 could now be investigated. Given that both portions of the desired substrate require several synthetic steps, a simpler model system was first considered (Scheme 5.1). 1,2-Dihydroquinoline **4.10** lacks the oxygenation *para* to the nitrogen, as well as the two *ortho*-substituents on the cinnamaldehyde portion. However, it was expected that these groups would have little effect on the reactions leading to the organometallic cyclisation. First, diastereoselective methylation would give a secondary alcohol that will subsequently be protected to give **5.1**. Dihydroxylation on the more sterically accessible face of the dihydroquinoline provides **5.2**, and thence **5.3** after protection of the *syn*-diol. Finally, reduction of the ester to an aldehyde, whether in one step or *via* the primary alcohol, provides **5.4** as the furthest this model system can go.



Scheme 5.1: Synthetic route towards unciaphenol using model system **4.10**.

5.1 Diastereoselective aldehyde methylation

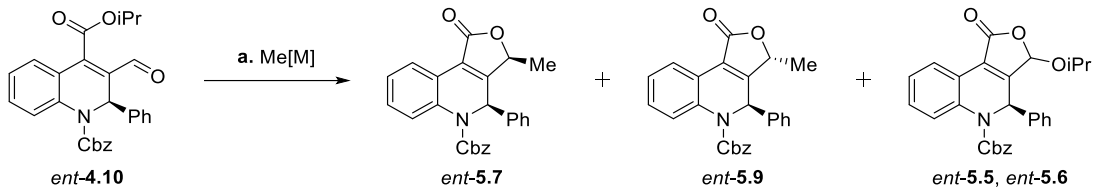
To first observe the natural stereoinduction of *ent*-**4.10**, the aldehyde was treated with methylmagnesium bromide at 0 °C (Scheme 5.2). These conditions resulted in three major products: two epimers of a lactone-lactol, *ent*-**5.5** and *ent*-**5.6**, and a lactone, *ent*-**5.7**. The latter of these arises from the desired addition of methylmagnesium bromide, followed by lactonisation onto the adjacent ester. The stereochemical identities of *ent*-**5.5** and *ent*-**5.6** were not determined but they did not appear to interconvert during purification or characterisation. The *cis* configuration of *ent*-**5.7** was confirmed at a later point (*vide infra*). Trace quantities of the *trans*-lactone were observed in the crude ^{1}H NMR spectrum. Lactone-lactols *ent*-**5.5** and *ent*-**5.6** likely form by addition of isopropoxide, generated in lactonisation to *ent*-**5.7**, to the aldehyde, followed by lactonisation to regenerate the alkoxide. As this isomerisation is catalytic in isopropoxide, it is able to effectively compete with the more reactive Grignard reagent. Ideally, the formation of *ent*-**5.5** and *ent*-**5.6** would be avoided, though they could likely be converted to the desired lactone *via* hydrolysis to *ent*-**5.8**.[151]



Scheme 5.2: Initial result from reaction of aldehyde *ent*-**4.10** with a Grignard reagent. Reagents and conditions: MeMgBr (1 M THF) (1.1 equiv), THF, 0 °C to rt, 120 min.

A report from Mal and Roy on a similar butenolide-forming Grignard reagent addition encouraged the use of a lower temperature in subsequent conditions screening (Table 5.1).[152] Running the same reaction at –78 °C did begin to suppress formation of *ent*-**5.5** and *ent*-**5.6** (Table 5.1, entry 1). With the increased yield of lactones, the high diastereoselectivity could

be more accurately determined. While methyllithium almost completely shut down participation of isopropoxide, it came with a reduced dr (Table 5.1, entry 2). The presence of recovered *ent*-**4.10** was likely due to insufficient organometallic reagent or reaction time. Allowing the reaction to warm to room temperature before quenching resulted in complete consumption of starting aldehyde, primarily due to both degradation and isomerisation to **5.5** and **5.6** (Table 5.1, entries 3-4). The use of Et_2O as bulk solvent was hindered by the poor solubility of *ent*-**4.10**. A solution of predominantly Et_2O, however, bore little difference to solely THF (Table 5.1, entries 5-6).



ent-**4.10** *ent*-**5.7** *ent*-**5.9** *ent*-**5.5**, *ent*-**5.6**

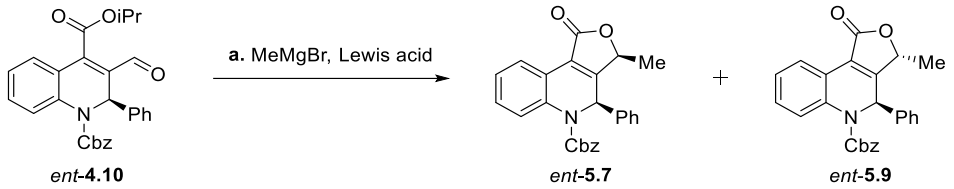
entry	reagent	solvent	temp	time/ min	rsm[a]	yield (*ent*-5.7+ *ent*-5.9)[b]	dr (*ent*-5.7: *ent*-5.9)[c]	yield (*ent*-5.5+ *ent*-5.6)[d]
1	MeMgBr	THF	–78 °C	70	16%	64%	95:5	18%
2	MeLi	THF	–78 °C	70	13%	67%	83:17	0%
3[e]	MeMgBr	THF	–78 °C to 0 °C	125	0%	47%	93:7	37%
4[e]	MeLi	THF	–78 °C to 0 °C	125	0%	51%	73:27	7%
5	MeMgBr	3:1 Et_2O:THF	–78 °C	90	10%	44%	93:7	38%
6	MeLi	3:1 Et_2O:THF	–78 °C	90	14%	75%	85:15	0%
7[f]	MeMgBr[g]	THF	–78 °C	75	13%	46%	93:7	31%

Table 5.1: Preliminary conditions screening for methylation of aldehyde *ent*-**4.10**. Reagents and conditions: all reactions run on 0.10 mmol *ent*-**4.10**; (a) MeMgBr (1 M THF) or MeLi (1.6 M Et_2O) (1.1 equiv), solvent. [a] rsm = Recovered starting material, isolated yield; [b] isolated yield; [c] based on integration of crude ^{1}H NMR spectrum; [d] isolated yield [e] reaction run on **4.10**, giving **5.5**, **5.6**, **5.7**, and **5.9** as products; [f] reaction run on 1.3 mmol *ent*-**4.10**; [g] MeMgBr (3.0 M Et_2O) (5.0 equiv).

Scaling up the reaction with a greater excess of Grignard reagent offered similar results, with a slightly poorer combined yield of lactones *ent*-**5.7** and *ent*-**5.9** (Table 5.1, entry 7). This suggests that, as the organometallic reagent was added dropwise to a solution of *ent*-**4.10**, full conversion of the substrate had taken place before the majority of Grignard reagent entered the solution. Pleasingly, the ee of both *ent*-**5.7** and *ent*-**5.9** were measured to be equal to that of *ent*-**4.10**, within error, suggesting that deprotonation of either starting aldehyde or product lactones is disfavoured.

Despite the lower diastereoselectivity of the methyllithium additions, the suppression of lactol formation was interesting. While the organolithium reagent is a more reactive nucleophile than the corresponding Grignard reagent, dropwise addition would seem to negate this effect, as demonstrated in Table 5.1, entry 7. It seemed more likely that the observed differences in yield and dr were due to the change in countercation. Coordination of the lithium cation to the initially generated alkoxide may slow lactonisation and hence release of isopropoxide. Alternatively, its coordination may simply reduce the isopropoxide's nucleophilicity. To a similar goal, a range of Lewis acidic additives were screened (Table 5.2). The solvent for these reactions was changed to the non-Lewis basic CH_2Cl_2, to reduce competition for the Lewis acids. This in turn necessitated a larger excess of Grignard reagent to compensate for its reaction with CH_2Cl_2.[153] Initial results using $MgBr_2$ were mixed: participation of isopropoxide was almost completely suppressed, resulting in a much higher yield of lactones *ent*-**5.7** and *ent*-**5.9**, though in a considerably lower dr (Table 5.2, entry 1). Removal of the Lewis basic Et_2O from the commercial Grignard reagent solution, followed by suspension in CH_2Cl_2,[154] offered similar results (Table 5.2, entry 2). While the addition of Grignard reagent to a solution of *ent*-**4.10** and $TiCl_4$ resulted in a complex mixture of species, the preformation of $MeTiCl_3$

offered a much cleaner reaction of low diastereoselectivity (Table 5.2, entries 3-4).[155–157] Interestingly, when the $MeTiCl_3$, prepared at –30 °C, was cooled to –78 °C for the addition of *ent*-**4.10**, the reaction showed some return to the diastereoselectivities observed in Table 5.1 (Table 5.2, entry 5). Use of anhydrous $CeCl_3$ offered similar results, but preparation of an organocerium, following literature procedure,[158] produced a complex mixture (Table 5.2, entries 6-7).



ent-**4.10** *ent*-**5.7** *ent*-**5.9**

entry	Lewis acid	method	temp	time/min	rsm[a]	yield (*ent*-5.7+*ent*-5.9)[b]	dr (*ent*-5.7:*ent*-5.9)[c]
1	$MgBr_2$	A	–78 °C	60	9%	89%	55:45
2[d]	$MgBr_2$	A[e]	–78 °C	40	<5%	>95%	47:53
3	$TiCl_4$[f]	A	–78 °C	65	n.d.[g]	n.d.[g]	60:40
4	$TiCl_4$	B	–30 °C	30	0%	93%	57:43
5	$TiCl_4$	B	–78 °C[h]	40	18%	73%	83:17
6	$CeCl_3$[i]	A	–78 °C	35	19%	79%	60:40
7	$CeCl_3$[i]	B	0 °C	30	n.d.[g]	n.d.[g]	55:45

Table 5.2: Screening of Lewis acids in the methylation of aldehyde *ent*-**4.10**. Method A: Lewis acid pre-stirred with *ent*-**4.10** in CH_2Cl_2 at room temperature before cooling and dropwise addition of MeMgBr; method B: MeMgBr added dropwise to Lewis acid in CH_2Cl_2 at the stated temperature before dropwise addition of *ent*-**4.10** in CH_2Cl_2. Reagents and conditions: all reactions run on 0.10 mmol *ent*-**4.10**; (a) MeMgBr (3 M Et_2O) (5.0 equiv), Lewis acid (5.0 equiv), CH_2Cl_2. [a] rsm = Recovered starting material, isolated yield; [b] isolated yield; [c] based on integration of crude ^1H NMR spectrum; [d] reaction run on **4.10**, giving **5.7** and **5.9** as products; [e] Et_2O removed from MeMgBr (10.0 equiv) *in vacuo*, followed by suspension in CH_2Cl_2 and dropwise addition of a mixture of *ent*-**4.10** and $MgBr_2$; [f] 1.1 equiv $TiCl_4$, 1.1 equiv MeMgBr; [g] n.d. = not determined; [h] MeMgBr added to $TiCl_4$ in CH_2Cl_2 at –30 °C; [i] anhydrous $CeCl_3$ prepared by dehydration of $CeCl_3{\cdot}7H_2O$.[158,159]

The lower diastereoselectivities obtained in Table 5.2 enabled more thorough consideration of the relative configurations of *ent*-**5.7** and *ent*-**5.9**. Comparison of the ^1H-^1H nOe spectra offered some evidence towards the assignment of *ent*-**5.7** as the *cis*- product and *ent*-**5.9** as

trans (Figure 5.1). Due to the predominance of sp^2-hybridised carbons, however, this stereochemical information was somewhat ambiguous.

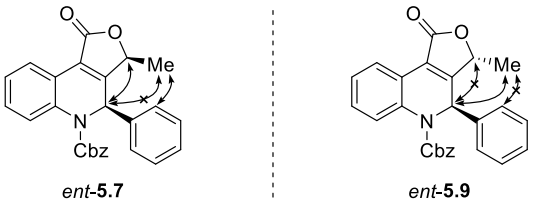
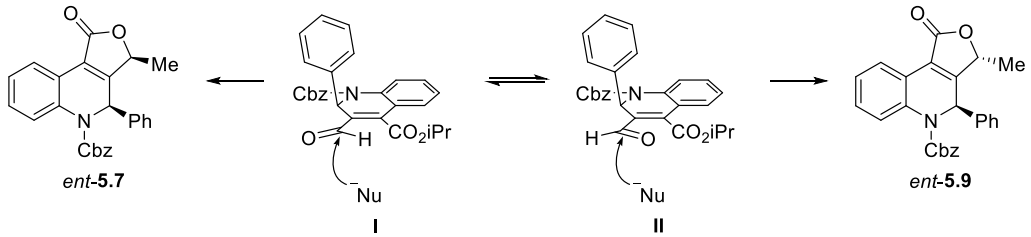


Figure 5.1: Relevant ^{1}H-^{1}H nOe correlations in support of the stereochemical assignments of *ent*-**5.7** and *ent*-**5.9**.

Seeking more information for stereochemical assignments, the decreased diastereoselectivities in Table 5.2 were considered. It seems unlikely that Lewis acid additives would affect the approach of the organometallic reagent towards the dihydroquinoline. From the X-ray crystal structure of *ent*-**4.10** (Figure 4.2), the C–Ph bond would be expected to lie almost perpendicular to the aldehyde C–O bond, sterically blocking the upper face. However, the aldehyde could occupy two conformations while maintaining conjugation with the alkene: oriented away from (**I**) or towards (**II**) the ester, exposing the *Si* or *Re* face respectively (Scheme 5.3). The Lewis acids in Table 5.2 could feasibly chelate the aldehyde and ester, favouring **II** and leading to increased *ent*-**5.9**.



Scheme 5.3: Different conformations of the aldehyde lead to diastereoisomeric products.

Additional support for the stereochemical assignments was found in density functional theory calculations performed by Thomas Sheridan on *ent*-**4.10** to investigate the aldehyde's conformation (Figure 5.2). Following geometry optimisation of *ent*-**4.10**, the aldehyde

O=C–C=C dihedral angle was systematically increased with energy minimisation after each step. Generally, the energy minima found during this process had the aldehyde held in conjugation with the alkene while the ester was twisted out of plane. In support of Scheme 5.3, relating to the diastereoselectivity without added Lewis acid, the lowest energy state was found to have the aldehyde oriented away from the ester (**I-a**).

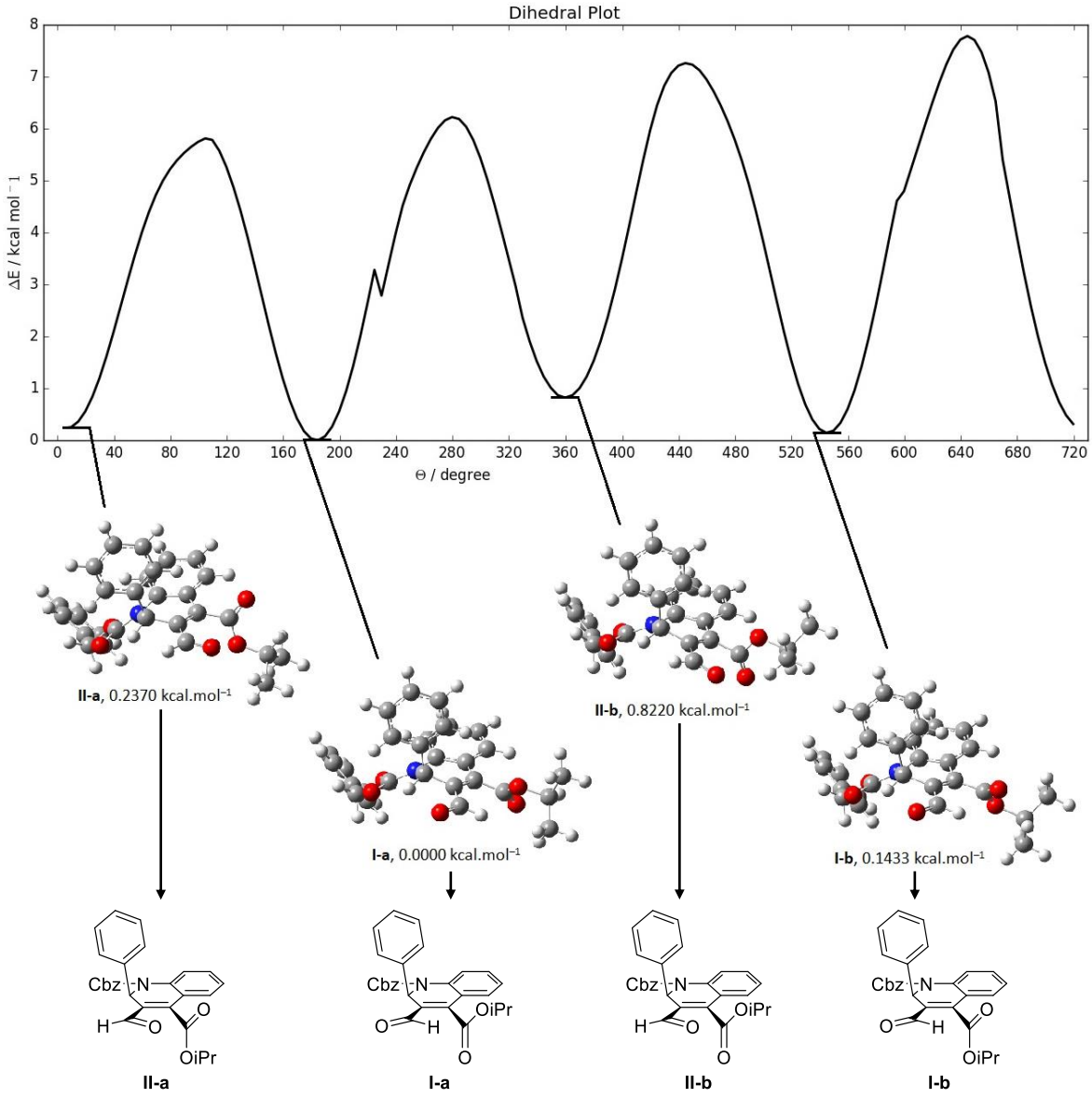
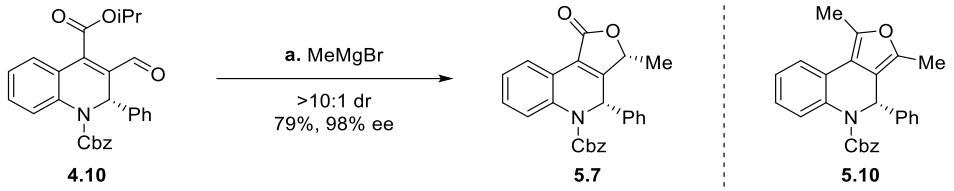


Figure 5.2: Plot of energy on increasing aldehyde O=C–C=C dihedral angle in gas-phase *ent*-**4.10**, with optimised structures for calculated energy minima. Density functional theory (DFT) calculations were performed by Thomas Sheridan, using Gaussian16.[160] All calculations were performed with the B3LYP/6-311G level of theory. A dihedral scan (OPT=MODREDUDANT) of the aldehyde through 144 steps, with a step of 5 degrees, was conducted on the minimised structure of *ent*-**4.10**.

Interestingly, the second lowest energy state also possessed this aldehyde orientation, but with the ester pointing to the other face of the 1,2-dihydroquinoline (**I-b**). Addition to the aldehyde from the less sterically hindered face in either of these conformations would give rise to the *cis*- product, *ent*-**5.7**. A similar pair of minima were found where the aldehyde points towards the ester (**II-a** and **II-b**). Reaction of these conformers should instead produce the *trans*- product, *ent*-**5.9**. While **II-a** was calculated to be only 0.2370 kcal.mol^{-1} above **I-a**, the barriers to interconversion were of the order of 6 kcal.mol^{-1}, similar to that of acrolein.[161] This fits the observation from Table 5.2, entry 5, as at lower temperature, a greater proportion of molecules would occupy the lowest energy state. Interconversion between the conformers would occur less readily so reaction would likely more often proceed *via* **I-a**.

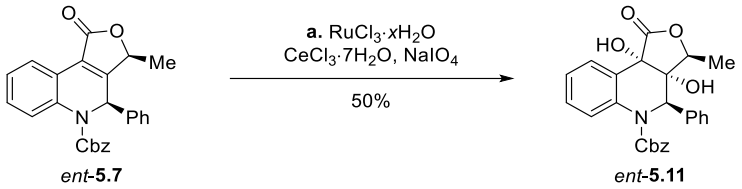
Instead of reducing the nucleophilicity of the isopropoxide generated in the methylation, an alternative approach was to simply flood the system with a large excess of Grignard reagent. Using a reverse addition procedure, **4.10** in THF was added to 10.0 equivalents of methylmagnesium bromide in THF (Scheme 5.4). Due to poor solubility of the Grignard reagent, and seeking a homogeneous solution, the reaction was first run at 0 °C. Although isopropoxide participation was completely suppressed, a complex mixture of products was formed. In this was identified 33% of a double-addition product, furan **5.10**. Pleasingly, using a suspension of methylmagnesium bromide in THF at lower temperature solved all the previous issues, offering a scalable route to **5.7** in high yield, diastereoselectivity, and with little to no erosion of enantiomeric excess. One potential issue with this new method is the presence of Grignard reagent as a suspension. Inefficient reaction stirring could result in poor mixing and higher local concentrations of isopropoxide, leading to formation of **5.5** and **5.6**.



Scheme 5.4: Optimised reverse addition procedure for highly selective aldehyde methylation. Reagents and conditions: reaction run on 3.3 mmol **4.10**; **4.10** in THF added dropwise to MeMgBr in THF; MeMgBr (1 M THF) (10.0 equiv), THF, –78 °C, 30 min, >10:1 dr, 79% of **5.7**, 98% ee.

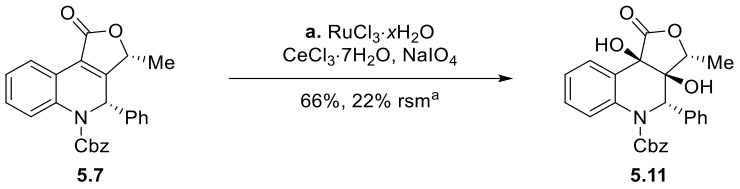
5.2 Facially selective dihydroxylation

The next transformation in the retrosynthesis was *syn*-dihydroxylation onto the less sterically crowded face of the butenolide alkene. There are several reagents reported in the literature for similar oxidations, including potassium permanganate,[162,163] osmium tetroxide,[164–166] and ruthenium tetroxide.[167] Although osmium-based systems are perhaps more widespread,[168] an alternative was first sought due to cost and safety considerations. To this end, a ruthenium-catalysed process was trialled (Scheme 5.5).[169] Pleasingly, complete consumption of *ent*-**5.7** was observed after only 5 minutes at 0 °C. Although the yield was moderate, the crude ^{1}H NMR spectrum was exceptionally clean, with a single diastereoisomer of diol the only species visible. While the relative configuration of diol *ent*-**5.11** has not been proved, it is presumed to have reacted on the less hindered face of the alkene. Ruthenium tetroxide dihydroxylations are known to proceed with *syn*-stereospecificity.[170] With only a single diastereoisomer observed, however, analysis by ^{1}H-^{1}H NOESY is ambiguous, due also to the complication of alcohol proton exchange.



Scheme 5.5: Initial attempt at ruthenium-catalysed dihydroxylation of butenolide *ent*-**5.7**. Reagents and conditions: reaction run on 0.10 mmol *ent*-**5.7**; (a) $RuCl_3 \cdot xH_2O$ (5 mol %), $CeCl_3 \cdot 7H_2O$ (10 mol %), $NaIO_4$ (1.5 equiv), 3:3:1 EtOAc:MeCN:H_2O, 0 °C, 10 min, 50%.

The low mass recovery from this reaction was believed to be due to the small scale, particularly with regards to solvent volumes, and its operational complexity. While there are numerous factors that could affect the performance, it is unclear how important they are. For example, the first stage of the reaction involves mixing the cerium(III) salt and the sodium periodate in water, proposed to form a cerium(IV) oxidant.[169] The literature protocol here is slightly ambiguous: the mixture should be 'gently heated until a bright yellow suspension was formed'. In subsequent reactions, it also seemed as though the sodium periodate failed to mix well with bulk solution once the organic solvents were added. Indeed, while the yield improved considerably when performed on larger scale, the rate of reaction in Scheme 5.5 has proven difficult to reproduce. However, this transformation has only been performed on three occasions. On scaling up to 0.46 mmol *ent*-**5.7**, the reaction was exceedingly sluggish and required warming to room temperature to complete. A further increase in scale and reduction of ruthenium loading also required warming to room temperature but seemed to stall by 6 hours (Scheme 5.6). This is of less concern, though, as ruthenium(III) chloride is a relatively inexpensive catalyst and its loading is still reasonably low. Despite the current issues, this unoptimised reaction seems scalable and already offers **5.11** in good yield and complete diastereoselectivity.

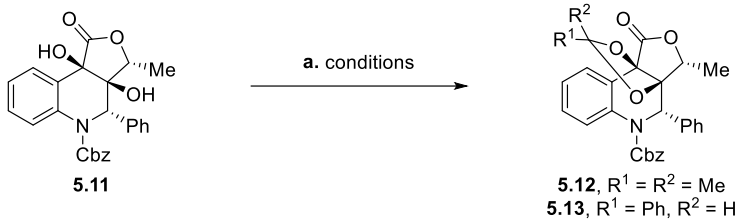


5.7 5.11

Scheme 5.6: Current best dihydroxylation conditions (non-optimised). Reagents and conditions: reaction run on 2.43 mmol **5.7**; (a) $RuCl_3 \cdot xH_2O$ (1 mol %), $CeCl_3 \cdot 7H_2O$ (10 mol %), $NaIO_4$ (1.5 equiv), 3:3:1 EtOAc:MeCN:H_2O, 0 °C to rt, 6 h, 66%, 22% rsm. [a] rsm = Recovered starting material.

5.3 Protection of the *syn*-diol

Given the plan to use organometallic reagents in the following steps of the synthesis, the diol would need protecting as a base- and nucleophile-stable moiety. The simplest solution would be using a single protecting group to tie up both alcohols in a cyclic motif. Acetals are most commonly used for such protection of 1,2-diols. Silylene units, while a consideration for 1,3-diols, are notably less stable in a five-membered ring and so unlikely to survive the subsequent reactions.[171] Hence, a variety of conditions were screened on **5.11** for acetal formation (Table 5.3).[172–174] Stirring with tosic acid in acetone showed no conversion at room temperature, but offered a complex mixture when heated (Table 5.3, entry 1). The addition of 2,2-dimethoxypropane, in an attempt to shift the equilibrium towards *ent*-**5.12**, resulted in a similar mixture (Table 5.3, entry 2). The only clean signals in the crude ^{1}H NMR spectrum were those from unreacted *ent*-**5.11**. The use of CSA and either a Dean-Stark trap or activated molecular sieves to rigorously exclude water and the methanol generated in the reaction imparted no noticeable difference (Table 5.3, entries 3-4). The more reactive 2-methoxypropene showed similar results immediately upon addition of CSA, even at 0 °C (Table 5.3, entry 5). Targeting **5.13** as a less hindered acetal simply resulted in no observable reaction (Table 5.3, entry 6).



5.11

5.12, $R^1 = R^2 = Me$
5.13, $R^1 = Ph$, $R^2 = H$

entry	target	conditions	temp	time/h	yield
1	*ent*-**5.12**[a]	TsOH·H_2O (2.0 equiv) acetone	rt to reflux	3 + 19	n.d.[b]
2	*ent*-**5.12**[a]	TsOH·H_2O (1.0 equiv) 2,2-dimethoxypropane (3.0 equiv) acetone	reflux	47	n.d.[b]
3	**5.12**	DL-CSA (1.0 equiv) 2,2-dimethoxypropane (100 equiv) PhMe	reflux[c]	69	n.d.[b]
4	**5.12**	DL-CSA (0.1 equiv) 2,2-dimethoxypropane (10 equiv) activated 4 Å MS (beads) CH_2Cl_2	rt to reflux	23 + 6	n.d.[b]
5	**5.12**	DL-CSA (0.1 equiv) 2-methoxypropene	0 °C	1.5	n.d.[b]
6	**5.13**	DL-CSA (0.1 equiv) benzaldehyde (10 equiv) PhMe	rt to 80 °C	23 + 6	0%

Table 5.3: Attempted conditions for acetal protection of **5.11**. Reagents and conditions: reactions run on 0.05 mmol **5.11**; see table for conditions. [a] *ent*-**5.11** Used as starting material; [b] n.d. = not determined; [c] Dean-Stark apparatus used, containing activated 4 Å MS (ground).

The degradation observed when trying to form acetonide **5.12** is likely due to oligomerisation of the acetone equivalent, since all of the reactions showed residual **5.11** (or *ent*-**5.11**) even after prolonged heating. Additionally, when **5.13** was targeted, no such degradation was present. While it is possible that the desired acetal products may undergo facile acid-catalysed hydrolysis, 2D-TLC provided no evidence for such instability, with no off-diagonal spots observed. Work-up was conducted under mildly basic conditions, to which **5.12** and **5.13** should be stable, and no signals that could be attributed to the desired products were ever observed by ^{1}H NMR spectroscopy. A lack of time has prevented further investigation into protection of diol **5.11**.

Future work would hence involve solving this issue. Possible avenues to explore would be methylene acetal **5.14**, or simply the use of separate protecting groups, such as in **5.15** (Figure 5.3).[175] The former has the advantage of reduced steric bulk and the possibility of installation under basic conditions, although typically requires stronger acid to deprotect.[176,177] The latter option introduces greater steric bulk, which could be an issue in the protection step. However, this may have little effect on subsequent transformations that would occur primarily on the opposite face of the molecule. Once a suitable protection strategy is in place, monoreduction of the lactone can be pursued.

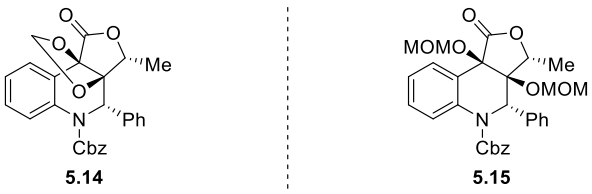


Figure 5.3: Possible alternative protection strategies for *syn*-diol **5.11**.

6 Towards the total synthesis of unciaphenol (1.1)

With both the organocatalysed cyclisation developed and the route investigations on a model system under way, the next step would be preparation of a cinnamaldehyde substrate possessing the functionality required for the total synthesis of unciaphenol (**1.1**). The primary target in this regard was 2,6-disubstituted cinnamaldehyde **2.6** (Figure 6.1). This possesses the *ortho*-oxygen present in the target molecule, along with a way to form an organometallic species (X = halide) for the late-stage cyclisation. However, from Scheme 4.6, it is known that the presence of either an *ortho*-methoxy or bromide results in a slower reaction. Hence, two alternative cinnamaldehydes, in which one of these groups has been exchanged, were also targeted for use in the case that **2.6** proved unsuitable. Species **6.1** retains the *ortho*-oxygen but replaces the halide with a *meta*-oxygen. Instead of an organometallic cyclisation, this would rely on a more electron rich arene to cyclise *via* an S_EAr mechanism, followed by subsequent deoxygenation (Scheme 6.1).[178] In contrast, **6.2** replaces the oxygen of **2.6** with a nitro group, which seems more tolerated in the *ortho*- position (Scheme 4.6). This would require conversion to a phenol following the cyclisation, most likely *via* reduction and diazotisation.

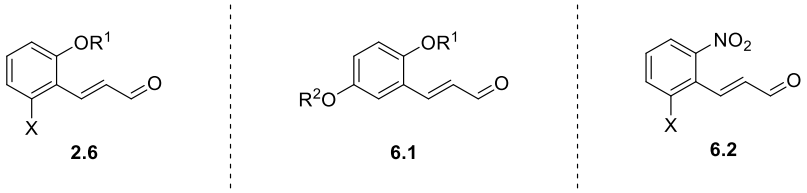
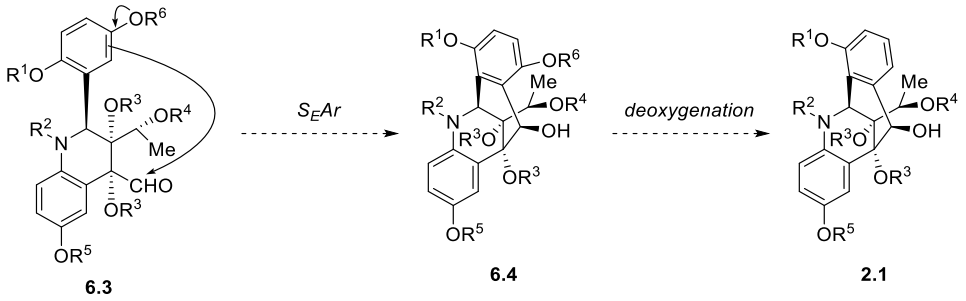


Figure 6.1: Cinnamaldehyde structures considered for the total synthesis of unciaphenol (**1.1**).

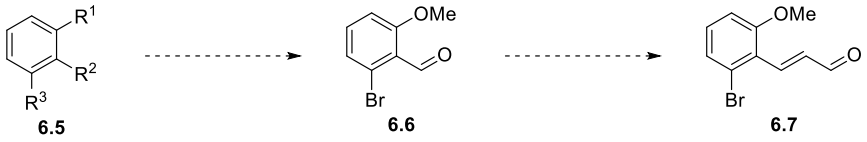


Scheme 6.1: Proposed cyclisation for alternative cinnamaldehyde **6.1**.

6.1 Synthesis of cinnamaldehyde substrates

6.1.1 Preparation of 2-RO-6-X-cinnamaldehydes

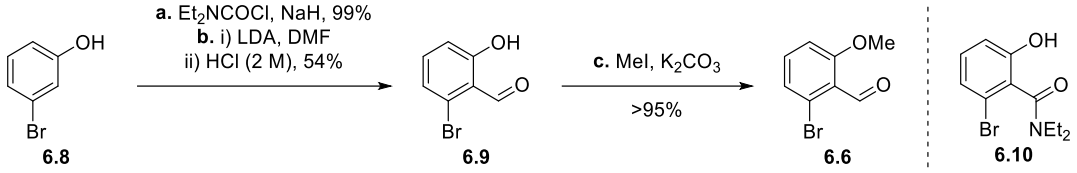
The synthesis of cinnamaldehyde **6.7** requires first the generation of a suitable 1,2,3-trisubstituted arene (Scheme 6.2). Considering first a benzaldehyde intermediate, **6.6**, opens up several reported pathways to **6.6** from simpler disubstituted arenes **6.5**, and thence homologation to **6.7**. A methyl protecting group was initially planned, due to its relatively small size and its tolerance to a wide range of reaction conditions.



Scheme 6.2: Synthesis of desired cinnamaldehyde **6.7** *via* a benzaldehyde intermediate.

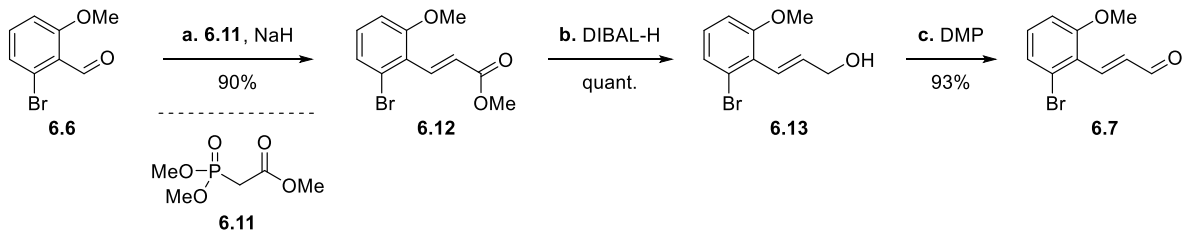
Of the reported routes to **6.6**,[179–183] an *ortho*-lithiation procedure from Evans and co-workers was selected, as it avoided the use of transition metals and was readily scalable.[179] Following carbamoylation of **6.8**,[184] the doubly-directed *ortho*-lithiation to **6.9** proceeded in moderate yield and with good regioselectivity (Scheme 6.3). Pleasingly, the carbamate directing group is hydrolysed under the weakly acidic quench, presumably due to participation of the neighbouring aldehyde. The major by-product observed in the lithiation step was the

Snieckus-Fries rearrangement product, **6.10**.[185] Methylation of **6.9** provided crude **6.6**, which was used without purification.[186]



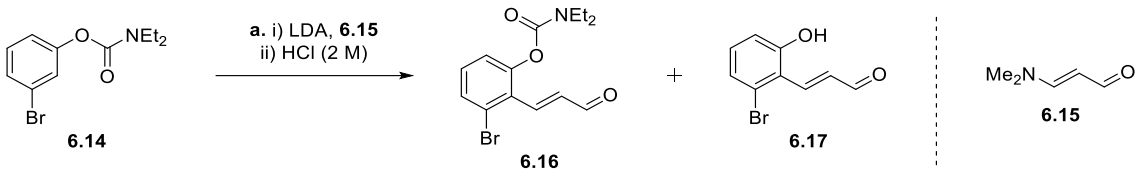
Scheme 6.3: Synthesis of 2,6-disubstituted benzaldehyde **6.6** *via* an *ortho*-lithiation reported by Evans and co-workers.[179] Reagents and conditions: (a) and (b) sequence run on 28.9 mmol **6.8**, (c) run on 1.4 mmol **6.9**; (a) Et_2NCOCl (2.0 equiv), NaH (3.5 equiv), THF, rt, 6 h, 99%; (b) i) iPr_2NH (1.2 equiv), *n*-BuLi (1.1 equiv), DMF (2.5 equiv), THF, –78 °C to 0 °C, 2.5 h, ii) HCl (2 M), rt, 64 h, 54%; (c) MeI (16 equiv), K_2CO_3 (3.6 equiv), acetone, rt, 16 h, >95%.

With benzaldehyde **6.6** in hand, the two-carbon homologation to **6.7** could now be considered. At first, a three-step sequence was used, due to its general applicability.[187] Horner-Wadsworth-Emmons reaction of **6.6** with **6.11** provided **6.12**, isolated as solely the (*E*)-isomer. Reduction of the ester with excess DIBAL-H offered cinnamyl alcohol **6.13** in quantitative yield, from which cinnamaldehyde **6.7** could be accessed *via* a Dess-Martin periodinane oxidation. This completed a six-step sequence to **6.7**, with 43% overall yield. While issues were encountered with the separation of by-products in the DMP oxidation of **6.13**, the yield and scalability of the route seems reasonable. However, preparing differently protected analogues of **6.7** would either significantly increase the number of reactions required, or decrease the efficiency by carrying a free phenol through the homologation.



Scheme 6.4: First generation homologation pathway to **6.7**. Reagents and conditions: sequence run on 2.3 mmol crude **6.6**; (a) **6.11** (3.0 equiv), NaH (2.5 equiv), THF, rt, 3 h, 90%; (b) DIBAL-H (3.0 equiv), CH_2Cl_2, –78 °C to rt, 45 min, quant.; (c) DMP (2.0 equiv), CH_2Cl_2, rt, 2 h, 93%.

An alternative strategy of using vinylogous DMF (**6.15**) in place of DMF during the *ortho*-lithiation of **6.14** was thus considered (Table 6.1). This would in theory generate a cinnamaldehyde directly, while also leaving protection of the phenol to the final step. Simply swapping the electrophile, however, provided much poorer mass recovery (Table 6.1, entry 1). While desired phenol **6.17** could be isolated, the major product was the carbamate protected cinnamaldehyde, **6.16**. No other identifiable species were present in the crude ^{1}H NMR spectrum.



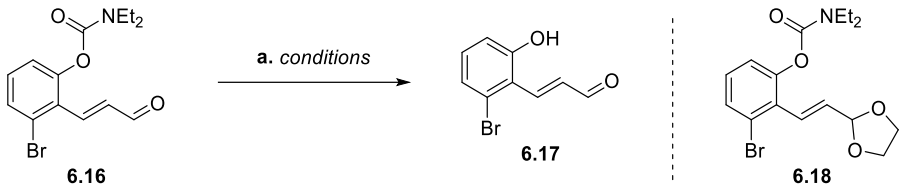
entry	change to conditions	yield(6.16)[a]	yield(6.17)[a]
1	-	19%	2%[b]
2	**6.15** added in THF	n.d.[c]	n.d.[c]
3	**6.15** added in THF, 2 × scale	25%	3%
4	**6.15** added in THF, 2 × scale, –78 °C quench[d]	30%	n.d.[c]
5	**6.15** added in THF, 2 × scale, 1.3 equiv **6.15**	31%	6%
6	**6.15** added in THF, 2 × scale, 90 min at rt pre-quench	52%	5%
7	**6.15** added in THF, 10 × scale, 90 min at rt pre-quench	22%[e]	4%[e]

Table 6.1: Conditions screening for *ortho*-lithiation with vinylogous DMF as electrophile. Reagents and conditions for entry 1: reaction run on 0.2 mmol **6.14**; (a) i) iPr_2NH (1.2 equiv), *n*-BuLi (1.1 equiv), **6.15** (2.5 equiv), THF, –78 °C to 0 °C, 110 min, ii) HCl (2 M), rt, 20 h. [a] Isolated yield; [b] based on integration of crude ^{1}H NMR spectrum; [c] n.d. = not determined; [d] sat. aq. NH_4Cl in place of HCl; [e] average of two runs.

Adding **6.15** in solution to aid mixing on addition improved the yield slightly, although highlighted decreased reproducibility compared to the original electrophile (Table 6.1, entries 2-3). To reduce any degradation that may be occurring, the reaction was quenched at lower temperature and, in another run, a smaller excess of electrophile was used (Table 6.1, entries 4-5). However, neither of these changes resulted in a significant difference in outcome.

Allowing the reaction to warm to, and stirring at, room temperature prior to the quench provided a notable increase in yield (Table 6.1, entry 6). Unfortunately, this result could not be replicated, leaving the typical yield for the reaction between 20-30% (Table 6.1, entry 7).

That **6.16** seems considerably more resistant to deprotection than the analogous benzaldehyde is support for neighbouring group participation in hydrolysis of the latter. In **6.16**, the aldehyde is further from the carbamate and more restricted in its conformation. Hence, a subsequent deprotection would be required. The use of basic conditions,[184] although effective, resulted in considerable degradation (Table 6.2, entries 1-3). These reactions produced complex mixtures of products, from which a moderate yield of **6.17** could be isolated. The temperature and reaction time could not be lowered to sufficiently avoid degradation without stopping the desired deprotection. Acidic conditions proved entirely ineffective (Table 6.2, entries 4-6).[188] The only conversion observed was to **6.18** when ethylene glycol was used in the solvent mixture, intended to allow access to a higher temperature.

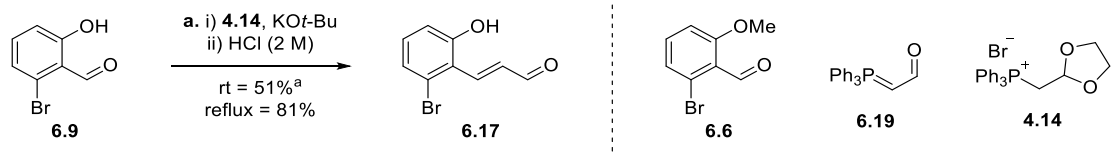


entry	conditions	temp	time	yield(6.17)[a]
1	NaOH (5 equiv), EtOH	rt to reflux	70 min + 70 min	45%
2	NaOH (2 equiv), EtOH	40 °C to 50 °C	3 h + 4 h	50%
3	NaOH (2 equiv), EtOH	reflux	50 min	44%
4	1:1 THF:HCl (2 M)	reflux	23 h	0%
5	1:1 $HOCH_2CH_2OH$:HCl (2 M)	100 °C	45 h	0%[b]
6	$TiCl_4$ (1.2 equiv), CH_2Cl_2	rt	19 h	0%

Table 6.2: Conditions attempted for carbamate deprotection of **6.16**. Reagents and conditions: reactions run on 0.1 mmol **6.16**; see table for conditions. [a] Isolated yields; [b] 20% yield of **6.18**.

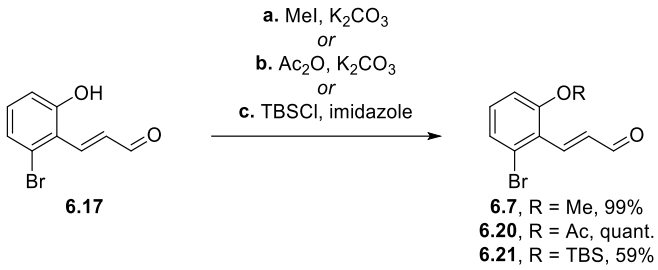
While there are other methods reported for carbamate deprotection[189,190] and more easily removed directing groups for ortho-lithiation,[191] the low yields and poor reproducibility in Table 6.1 resulted in the abandonment of this route.

A Wittig homologation was then investigated as a more direct strategy for the preparation of **6.7** (Scheme 6.5). The use of **6.19**[192,193] resulted in poor chemoselectivity for the benzaldehyde over homologated aldehydes and low overall yield. Switching instead to masked aldehyde reagent **4.14**[138] offered improved selectivity but challenging reaction monitoring and separation of remaining benzaldehyde **6.6**. Although less efficient, the use of a greater excess of base enabled clean reaction with the free phenol substrate, **6.9**. Heating was necessary to achieve high conversion, although the separation of **6.17** from residual **6.9** is greatly simplified by the intramolecular hydrogen bonding in **6.9** imparting a much lower effective polarity.

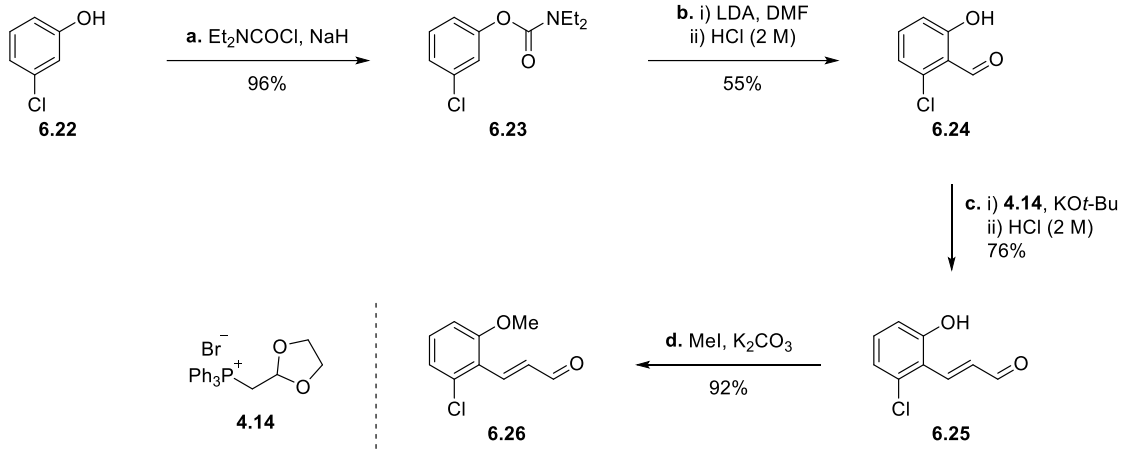


Scheme 6.5: Wittig homologation to access cinnamaldehydes. Reagents and conditions: reaction run on 4.1 mmol **6.9**; (a) i) **4.14** (2.0 equiv), KO*t*-Bu (3.5 equiv), THF, 17 h, ii) HCl (2 M), rt, 30 min, 81%. [a] Average of two runs.

The above homologation method has the added advantage that protection of the phenol functionality is the final step before subjection to the organocatalysed cyclisation, enabling the facile preparation of several analogues (Scheme 6.6). Methylation (**6.7**) and acylation (**6.20**) proceeded in excellent yield, while silylation offered a moderate yield of **6.21**. The methylated cinnamaldehyde, **6.7**, could now be produced over four steps in 43% yield (*cf*. six steps, 43% for the first-generation route). Chlorinated analogue **6.26** was prepared by the same method in similar yields (Scheme 6.7).



Scheme 6.6: Differential protection of phenol **6.17**. Reagents and conditions: (a) reaction run on 8.8 mmol **6.17**; (b) reaction run on 0.65 mmol **6.17**; (c) reaction run on 0.15 mmol **6.17**; (a) MeI (3.0 equiv), K_2CO_3 (3.0 equiv), acetone, rt, 23 h, 99%; (b) Ac_2O (2.5 equiv), K_2CO_3 (1.5 equiv), THF, rt, 110 min, quant.; (c) TBSCl (4.0 equiv), imidazole (9.0 equiv), DMF, 0 °C, 15 min, 59%.



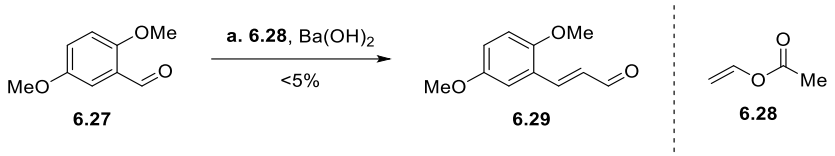
Scheme 6.7: Preparation of chlorinated cinnamaldehyde **6.26**. Reagents and conditions: (a) reaction run on 39 mmol **6.22**; (b) reaction run on 21 mmol **6.23**; (c) reaction run on 6.4 mmol **6.24**; (d) reaction run on 2.2 mmol **6.25**; (a) Et_2NCOCl (2.0 equiv), NaH (3.5 equiv), THF, rt, 6 h, 96%; (b) i) iPr_2NH (1.2 equiv), *n*-BuLi (1.1 equiv), DMF (2.5 equiv), THF, –78 °C to 0 °C, 2.5 h, ii) HCl (2 M), rt, 18 h, 55%; (c) i) **4.14** (2.0 equiv), KO*t*-Bu (3.0 equiv), THF, reflux, 17 h, ii) HCl (2 M), rt, 70 min, 76%. (d) MeI (3.0 equiv), K_2CO_3 (3.0 equiv), acetone, rt, 21 h, 92%.

6.1.2 Preparation of alternative cinnamaldehyde substrates

Despite the good results from the Wittig homologation in the previous section, alternative methods were still being considered. This was due in part to the large quantity of phosphorous-containing by-products generated, affecting the simplicity of purification. Additionally, benzaldehyde substrates lacking an *ortho*-hydroxy substituent typically have retention factors almost identical to their cinnamaldehyde products. This hinders reaction monitoring and can result in great difficulty obtaining clean products. A more general

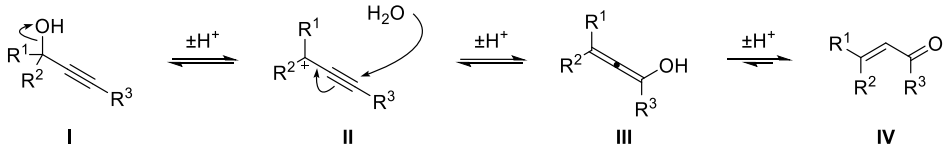
homologation was thus sought. For this, benzaldehyde **6.27** was selected as a model substrate for its similarity to **6.1** and its commercial availability.

The most efficient route would be direct reaction with acetaldehyde enolate. However, this is often poorly selective for single homologation and results in poorly separable mixtures of aldehyde products. More selective versions of the transformation are often accompanied by a significant increase in operational complexity.[194,195] One exception is the generation of the enolate *via* hydrolysis of vinyl acetate (**6.28**). Somewhat surprisingly, **6.27** showed little reactivity towards the acetaldehyde enolate generated from hydrolysis of vinyl acetate (**6.28**) and the reported yield of 70% could not be replicated (Scheme 6.8).[196]



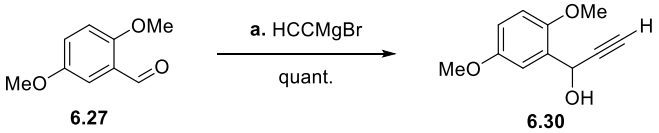
Scheme 6.8: Attempted homologation with an acetaldehyde enolate equivalent. Reagents and conditions: reaction run on 0.6 mmol **6.27**; (a) **6.28** (5 equiv), $Ba(OH)_2$ (1.2 equiv), THF, reflux, 23 h, <5%.

The final method trialled for homologation of **6.27** to **6.29** was the Meyer-Schuster rearrangement (Scheme 6.13).[197] In its simplest form, a propargylic alcohol (**I**) reversibly undergoes an acid-catalysed loss of water, leaving a stabilised carbocation (**II**). Should water add at the other end of this conjugated carbocation, it generates an enol (**III**). Tautomerisation to the keto form (**IV**) is generally the thermodynamic sink for the reaction and hence provides the major product. A wide range of catalysts have been reported for this transformation, including Brønsted acids,[198] Lewis acids,[199,200] oxovanadate complexes,[201] and methyl triflate.[202]



Scheme 6.9: Mechanism of the Meyer-Schuster rearrangement.

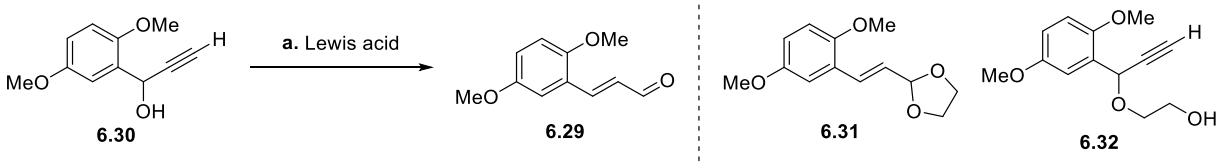
First, the propargylic alcohol substrate required for the Meyer-Schuster isomerisation, **6.30**, was prepared in a straightforward manner from the benzaldehyde, **6.27**.[203] Screening of literature Meyer-Schuster conditions for similar substrates was then conducted (Table 6.3).



Scheme 6.10: Preparation of propargylic alcohol **6.30**. Reagents and conditions: reaction run on 12 mmol **6.27**; (a) HCCMgBr (1.25 equiv), THF, rt, 30 min, quant.

Following reported conditions using tosic acid[198] and iron(III) chloride[199] initially looked promising (Table 6.3, entries 1-2). While indium(III) chloride showed no conversion with these temperatures and solvents (Table 6.3, entries 3-4), the former showed **6.29** as the only species present by ^{1}H NMR spectroscopy. However, repeating the reactions with closer monitoring revealed that there was considerable degradation occurring, resulting in low yields of **6.29** (Table 6.3, entries 5-7). While this is perhaps unsurprising for tosic acid, given the reported increase in degradation for an *ortho*-methoxy- substituent, there is no such decreased yield reported with iron(III) chloride. Trialling instead microwave-heated indium(III) chloride conditions[200] allowed isolation of an improved yield of **6.32**, though with considerable degradation even at shorter reaction times (Table 6.3, entries 8-9). This was particularly surprising given the high reported yields for both *ortho*- and *meta*-methoxy substituents (88% and 86% respectively). While reducing the concentration of the reaction slowed conversion, the mass recovery was notably higher (Table 6.3, entry 10). This likely suggests

that the degradation involves reaction of **6.30** (or **6.29**) with the carbocation of a separate molecule, potentially leading to oligomerisation. Pleasingly, doubling the catalyst loading had little effect on the degradation but increased the rate (Table 6.3, entry 11).



6.30 **6.29** **6.31** **6.32**

entry	cat. (mol %)	solvent (conc./M)	temp/ °C	time	(6.30+6.32): (6.29+6.31)[a]	E:Z(6.29)[a]	yield[b]	yield brsm[c]
1	$TsOH·H_2O$ (30)	$ClCH_2CH_2Cl$ (0.2)	60	16 h	<1:99	n.d.[d]	n.d.[d]	n.d.[d]
2	$FeCl_3$ (100)	THF (0.2)	60	16 h	<1:99	n.d.[d]	n.d.[d]	n.d.[d]
3	$InCl_3$ (10)	$ClCH_2CH_2Cl$ (0.2)	60	16 h	>99:1	n.d.[d]	n.d.[d]	n.d.[d]
4	$InCl_3$ (10)	THF (0.2)	60	16 h	>99:1	n.d.[d]	n.d.[d]	n.d.[d]
5[e]	$TsOH·H_2O$ (30)	$ClCH_2CH_2Cl$ (0.2)	60	90 min	<1:99	>99:1	9%	9%
6[e]	$FeCl_3$ (100)	THF (0.2)	60	90 min	n.d.[d]	97:3[f]	9%	n.d.[d]
7[e]	$FeCl_3$ (100)	THF (0.1)	60	25 min	n.d.[d]	90:10[f]	17%	n.d.[d]
8[g]	$InCl_3$ (2)	H_2O (1.0)	160 (µw)	30 min	<1:99	99:1	33%	33%
9[g]	$InCl_3$ (1)	H_2O (1.0)	160 (µw)	10 min	21:79	96:4	38%	48%
10	$InCl_3$ (1)	H_2O (0.1)	160 (µw)	30 min	44:56	91:9	36%	64%
11	$InCl_3$ (2)	H_2O (0.1)	160 (µw)	30 min	8:92[h]	97:3[h]	56%[h]	61%[h]
12[i]	$InCl_3$ (2)	H_2O (0.1)	160 (µw)	30 min	<1:99	98:2	52%	52%
13	$InCl_3$ (2)	H_2O (0.1)	150 (µw)	30 min	21:79	95:5	44%	56%

entry	cat. (mol %)	solvent (conc./M)	temp/ °C	time	(6.30+6.32): (6.29+6.31)[a]	E:Z(6.29)[a]	yield[b]	yield brsm[c]
14	$InCl_3$ (2)	H_2O (0.1)	120 (μw)	60 min	76:24	87:13	<15%	n.d.[d]
15	$InCl_3$ (2)	5:2 H_2O:THF (0.1)	150 (μw)	30 min	44:56	94:6	41%	73%
16	$InCl_3$ (2)	1:4 H_2O:THF (0.1)	150 (μw)	30 min	>99:1	n.d.[d]	n.d.[d]	n.d.[d]
17	$InCl_3$ (2)	5:2 H_2O:THF (1.0)	150 (μw)	30 min	14:86	96:4	32%	37%
18	$InCl_3$ (2)	5:2 H_2O:THF (0.1)	150 (μw)	60 min	26:74	96:4	55%	74%
19	$InCl_3$ (2)	$HOCH_2CH_2OH$ (0.1)	160 (μw)	30 min	32:68	98:2	19% (30%)	72%
20[j]	$InCl_3$ (2)	$HOCH_2CH_2OH$ (0.1)	160	6.5 h	12:88	97:3	35% (3%)	43%
21[j]	$TsOH{\cdot}H_2O$ (30)	$HOCH_2CH_2OH$ (0.1)	rt to 50	23 h	92:8	>99:1	6% (1%)	88%
22[j]	H_2SO_4 (1 drop)	$HOCH_2CH_2OH$ (0.1)	rt to 50	23 h	61:39	>99:1	16% (3%)	49%
23[j]	$TsOH{\cdot}H_2O$ (30)	$HOCH_2CH_2OH$ (0.1)	50	65 h	21:79	95:5	21% (2%)	29%
24	$InCl_3$ (1)[k]	$HOCH_2CH_2OH$ (0.1)	180	23 h	<1:99	99:1	38% (6%)	44%

Table 6.3: Meyer-Schuster conditions screening. Reagents and conditions: reactions run on 0.2 mmol **6.30**; see table for conditions. [a] Based on integration of crude ^{1}H NMR spectrum; [b] isolated yield, numbers in parentheses refer to **6.31**; [c] brsm = based on recovered starting material, yield of (**6.29** + **6.31**) based on recovered (**6.30** + **6.32**); [d] n.d. = not determined; [e] reaction run on 0.5 mmol **6.30**; [f] ratio of isolated product; [g] reaction run on 2.0 mmol **6.30**; [h] reaction run on 0.4 mmol **6.30**; [i] average of two runs; [j] reaction stirred with HCl (2 M) prior to work-up; [k] catalyst added in $HOCH_2CH_2OH$ after pre-stirring at 180 °C for 17 h.

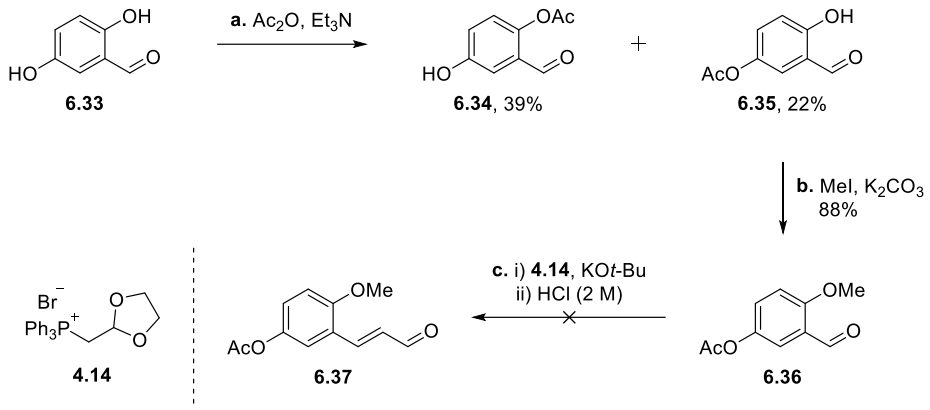
As these reactions are conducted with water as the solvent, the reaction is initially heterogeneous. An emulsion will form with rapid stirring, and **6.30** may even dissolve fully at the higher temperatures used.[204] When the vials were removed from the microwave synthesiser, the liquid was pale yellow with much brown insoluble material present. Filling the reaction vessel more, to reduce the headspace, offered no noticeable benefit (Table 6.3, entry 12). Similarly, reducing the temperature merely slowed the reaction rather than

reducing degradation (Table 6.3, entries 13-14). In an attempt to assist mixing, THF was added as a cosolvent, with a concomitant reduction in temperature for safety considerations. A cleaner but slower reaction was found with THF as the minor solvent component, although using THF as the major component resulted in no observed conversion (Table 6.3, entries 15-16). As before, a higher concentration lowered mass recovery (Table 6.3, entry 17). Interestingly, heating the reaction for longer offered increased yield of **6.29** but seemed to have no effect on the amount of degradation (Table 6.3, entry 18). As it was unknown whether the side reactions involve the alkyne, **6.30**, or the enal, **6.29**, ethylene glycol was used as solvent. It was hoped that this would prevent exposure of the aldehyde moiety, potentially disfavouring further reaction. However, this solvent switch produced similar conversion (Table 6.3, entry 19). Most of the cinnamaldehyde product was isolated as acetal **6.31**, although this was shown to cleanly hydrolyse to **6.29** in 1:2 THF:HCl (2 M). Generally, no **6.30** was observed in the crude ^{1}H NMR spectrum for any reaction using ethylene glycol as solvent. Instead, residual alkyne was present as the ether, **6.32**. With the solvent's higher boiling point, it was thought that this most recent result could be transferred outside the microwave synthesiser to allow easier monitoring and more flexibility on scale. The reaction proved to be considerably slower under conventional heating (Table 6.3, entry 20), with the lower mass recovery likely related to the vastly increased reaction time. Using Brønsted acids in ethylene glycol resulted in relatively rapid conversion of propargylic alcohol **6.30** to ether **6.32**, although no isomerisation was observed by TLC until heated at 50 °C (Table 6.3, entries 21-23). Even at this temperature, however, degradation outcompeted accumulation of **6.29**. Finally, **6.30** was stirred in ethylene glycol at 180 °C for 17 h. This effected full conversion of **6.30** to **6.32** without visible degradation or isomerisation. Addition of indium(III) chloride at this point, followed by further heating did not improve results, with significant degradation observed

(Table 6.3, entry 24). Due to the limitations imposed by microwave heating and the disappointing mass recovery of **6.29**, the Meyer-Schuster rearrangement was deemed unsuitable for the preparation of cinnamaldehydes towards the planned total synthesis of unciaphenol (**1.1**).

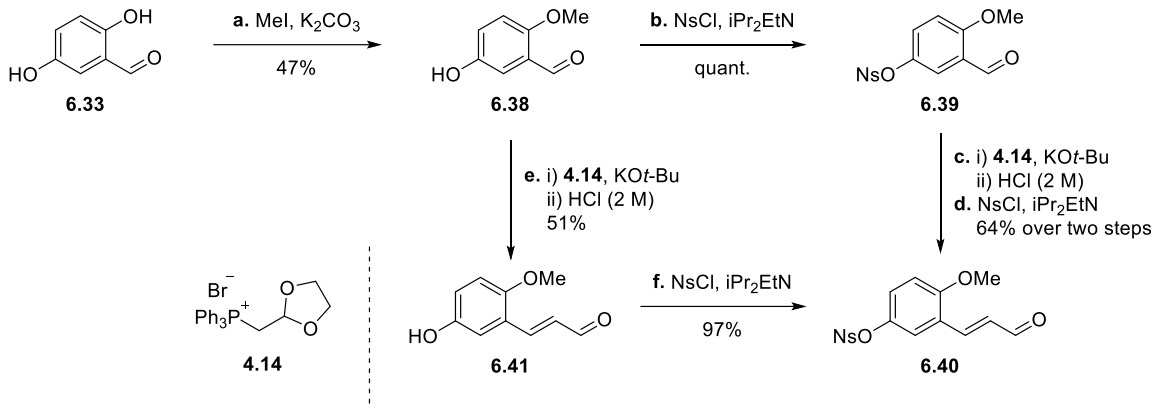
With other reported cinnamaldehyde preparations seeming less readily scalable or less general,[205–207] it was decided to return to the Wittig homologation shown in Scheme 6.5. While the intention with cinnamaldehyde **6.1** is to have a more electron rich arene, this would likely be a poor substrate for the organocatalysed cyclisation. Since the *ortho*-methoxy group is desired for its small size, the *meta*- substituent should be made more electron withdrawing. For this purpose, acetyl and sulfonyl protecting groups were targeted.[139]

Acetylation of 2,5-dihydroxybenzaldehyde (**6.33**) in DMF was poorly selective, producing both monoacetyl regioisomers, **6.34** and **6.35**, along with diacetyl and unreacted **6.33** (Scheme 6.11).[208,209] Fortunately, it was performed on large enough scale to retrieve a useful quantity of desired regioisomer **6.35**. Methylation proceeded smoothly to provide **6.36**. However, the conditions of the Wittig homologation resulted in loss of the acetyl group, with no **6.37** observed. Although the sequence of steps could be rearranged such that acylation would occur after homologation, it seems as though the acetyl group would be too labile to survive until the late-stage cyclisation planned for the total synthesis. Hence, a more stable protecting group was necessary.



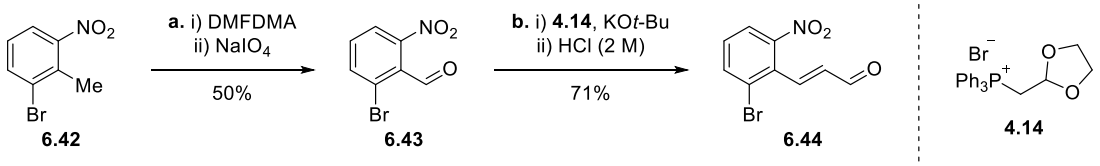
Scheme 6.11: Attempted synthesis of cinnamaldehyde **6.37**. Reagents and conditions: (a) reaction run on 7.2 mmol **6.33**; (b) reaction run on 1.4 mmol **6.35**; (c) reaction run on 1.0 mmol **6.36**; (a) Ac_2O (1.05 equiv), Et_3N (1.10 equiv), DMF, rt, 4 h, 39% (**6.34**), 22% (**6.35**); (b) MeI (3.0 equiv), K_2CO_3 (3.0 equiv), acetone, rt, 18 h, 88%; (c) **4.14** (1.5 equiv), KO*t*-Bu (1.5 equiv), THF, reflux, 23 h.

While sulfonyl groups are typically more electron withdrawing than acyl groups,[139] they often require harsher conditions to remove. For this reason, a nosyl group was selected, which should offer a mild and orthogonal deprotection strategy. Given the poor regioselectivity in acetylation of **6.33** (*vide supra*), methylation of the *ortho*-hydroxy was conducted first (Scheme 6.12).[210] Although column chromatography merely provided an inseparable mixture of species, the desired benzaldehyde, **6.38**, could be isolated in moderate yield *via* recrystallisation. Nosylation then provided **6.39** in quantitative yield. Wittig homologation, however, proved more challenging to control. Both **6.39** and **6.40** have almost identical retention factors on TLC and so consumption of benzaldehyde was difficult to follow. Additionally, the strongly basic conditions resulted in partial denosylation to **6.41**, which was also inseparable from **6.40** by column chromatography. Fortunately, restoring the protecting group could readily be accomplished on the mixture of products. The alternative order of steps was also investigated, conducting the Wittig homologation on **6.38**. This presented similar issues with reaction monitoring, though **6.41** was partially separable from unreacted **6.38**. Nosylation on this cleaner cinnamaldehyde sample provided **6.40**.



Scheme 6.12: Synthesis of nosylated cinnamaldehyde **6.40**. Reagents and conditions: (a) reaction run on 36 mmol **6.33**; (b) reaction run on 3.0 mmol **6.38**; (c) and (d) sequence run on 2.5 mmol **6.39**; (e) reaction run on 9.9 mmol **6.38**; (f) reaction run on 2.8 mmol **6.41**; (a) MeI (1.5 equiv), K_2CO_3 (1.0 equiv), DMF, rt, 20 h, 47%; (b) NsCl (1.5 equiv), iPr_2EtN (1.6 equiv), CH_2Cl_2, rt, 4 h, quant.; (c) **4.14** (2.5 equiv), KO*t*-Bu (2.6 equiv), THF, reflux, 24 h; (d) NsCl (1.0 equiv), iPr_2EtN (1.0 equiv), CH_2Cl_2, rt, 6 h, 64% over two steps; (e) **4.14** (2.0 equiv), KO*t*-Bu (3.0 equiv), THF, reflux, 30 h, 51%; (f) NsCl (1.5 equiv), iPr_2EtN (1.6 equiv), CH_2Cl_2, rt, 4 h, 97%.

The second alternative cinnamaldehyde proposed in Figure 6.1, **6.44**, was synthesised from **6.42** (Scheme 6.13). Treatment with DMFDMA generates an enamine off the methyl group of **6.42**, which is oxidatively cleaved on addition to sodium periodate.[211] Subjection of **6.43** to Wittig homologation (*vide supra*) produced **6.44** in good yield, albeit with challenging purification to separate residual **6.43**. Future syntheses of both **6.40** and **6.44** would probably be more efficient *via* a three step HWE-reduction-oxidation sequence. For the time being, though, sufficient material was prepared for initial investigations.

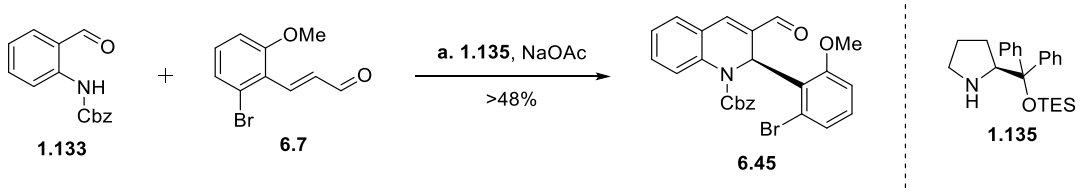


Scheme 6.13: Preparation of alternative cinnamaldehyde substrate **6.44**. Reagents and conditions: (a) reaction run on 4.6 mmol **6.42**; (b) reaction run on 6.0 mmol **6.43**; (a) i) DMFDMA (3.0 equiv), DMF, 135 °C, 19 h, ii) $NaIO_4$ (3.0 equiv), 1:1 DMF:H_2O, 0 °C to rt, 20 h, 50%; (b) i) **4.14** (2.5 equiv), KO*t*-Bu (2.6 equiv), THF, 27 h, ii) HCl (2 M), rt, 17 h, 71%.

6.2 Organocatalysed cyclisations of novel cinnamaldehydes towards unciaphenol (1.1)

6.2.1 Main cinnamaldehyde substrates

With the above cinnamaldehydes in hand, their performance in the optimised organocatalysed cyclisation (Scheme 4.4) was investigated. First, the principal cinnamaldehyde, **6.7**, was subjected to the optimised conditions of Wang and co-workers (Scheme 6.14).[96] Pleasingly, conversion to the 1,2-dihydroquinoline product, **6.45**, was reasonably good, although streaking of **6.45** during column chromatography prohibited determination of an accurate isolated yield. The absolute configuration of the product was also not confirmed but assigned as **6.45** by analogy with other substrates. A racemic sample was not prepared and so the enantiomeric excess was not measured. However, the small magnitude of specific rotation ($[\alpha]_D^{25}$ = –10.1) compared to all products reported by Wang and co-workers (–700 < $[\alpha]_D^{25}$ < –300)[96] may hint at low enantioselectivity for the reaction.



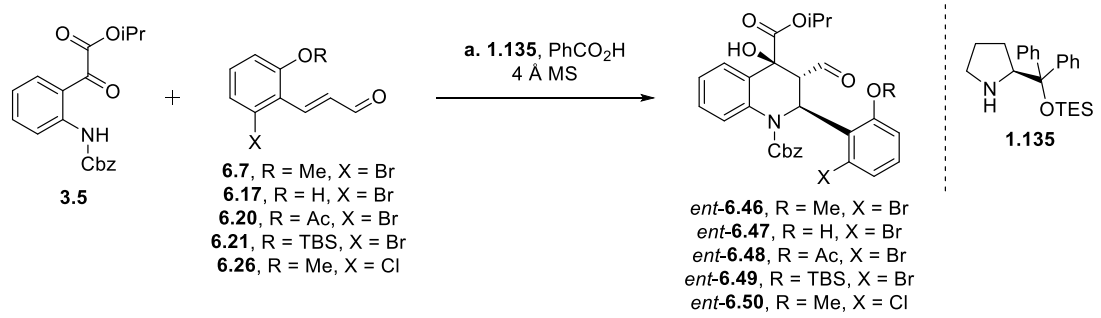
Scheme 6.14: Subjection of 2,6-disubstituted cinnamaldehyde **6.7** to Wang and co-workers' optimised conditions.[96] Reagents and conditions: reaction run on 0.15 mmol **6.7**; (a) **1.133** (3.0 equiv), **1.135** (20 mol %), NaOAc (50 mol %), activated 4 Å MS (ground) (75 mg), $ClCH_2CH_2Cl$, rt, 94 h, >48%.

Despite the positive signs in Scheme 6.14, the reaction with keto ester substrates has proven to sometimes be rather different to that with benzaldehydes. This was indeed found to be the case for the reaction of **6.7** with **3.5**, with low conversion of either reactant observed (Table 6.4, entry 1). Additionally, the only product isolated was the aldol intermediate,

ent-**6.46**. While its specific rotation ($[\alpha]_D^{25}$) had the opposite sign to all aldol products previously isolated from reaction with **1.135**, the corresponding 1,2-dihydroquinoline's (see section 6.3.1) specific rotation possessed the expected sign and larger magnitude. The absolute configuration at the benzylic centre of *ent*-**6.46** was hence assigned by analogy with previous cyclisation products. The relative configuration at the adjacent homobenzylic centre was assigned on the basis of a large $^3J_{HH}$ coupling constant (12 Hz), in a similar manner to previous aldol products (see section 4.4.2). Broadened NMR signals complicated assignment of relative configuration of the tertiary alcohol, with this stereochemical assignment occurring later (see section 6.3.1). Additionally, a clean chiral HPLC trace could not be obtained at this stage, so the enantiomeric excesses for the products in Table 6.4 are not known.

Unfortunately, the differently protected phenols showed no desired reactivity under the standard conditions (Table 6.4, entries 2-4). Free phenol **6.17** resulted in a bright red solution immediately upon mixing with **1.135**, suggesting formation of the *ortho*-quinone methide (see Scheme 4.8). While **6.20** could largely be reisolated unchanged from the reaction, it too produced a red colouration, albeit after a short delay. This could well indicate a similar pathway to remove the catalyst from the desired reaction pathway. The silylated cinnamaldehyde, **6.21**, did not give rise to any apparent change aside from partial desilylation. It was considered that the lack of reaction in this latter case could be due to the increased steric demands of the *ortho*- substituent. Attempts to enable turnover of the catalyst with **6.17** and **6.20** were ultimately fruitless (Table 6.4, entries 5-12), consisting of: increasing the concentration of available water by excluding molecular sieves; adjusting the pH of the reaction by use of a basic additive; heating the reaction, and using a less sterically demanding

keto ester, **3.1**. The observed outcomes of these experiments were all the same: formation of a red solution and no subsequent conversion by TLC or ^{1}H NMR spectroscopy.



entry	substrate	change to conditions	time	yield[a]
1	**6.7**	-	117 h	7%
2	**6.17**	-	143 h	0%
3	**6.20**	-	143 h	0%
4	**6.21**	-	144 h	0%[b]
5	**6.17**	4 Å MS omitted	143 h	0%
6	**6.20**	4 Å MS omitted	143 h	0%
7	**6.17**	50 mol % NaOAc in place of $PhCO_2H$	96 h	0%
8	**6.20**	50 mol % NaOAc in place of $PhCO_2H$	97 h	0%
9	**6.17**	PhMe in place of CH_2Cl_2, 50 °C	91 h	0%
10	**6.20**	PhMe in place of CH_2Cl_2, 50 °C	91 h	0%
11	**6.17**	Me ester (**3.1**) in place of **3.5**	90 h	0%
12	**6.20**	Me ester (**3.1**) in place of **3.5**	90 h	0%
13	**6.7**	4 Å MS omitted	117 h	11%
14	**6.7**	$PhCO_2H$ omitted	119 h	15%
15	**6.7**	100 mol % $PhCO_2H$	119 h	<5%
16	**6.7**	PhMe in place of CH_2Cl_2, 60 °C	117 h	trace
17	**6.7**	Me ester (**3.1**) in place of **3.5**	117 h	<5%
18	**6.26**	-	119 h	9%
19	**6.26**	4 Å MS omitted	119 h	15%

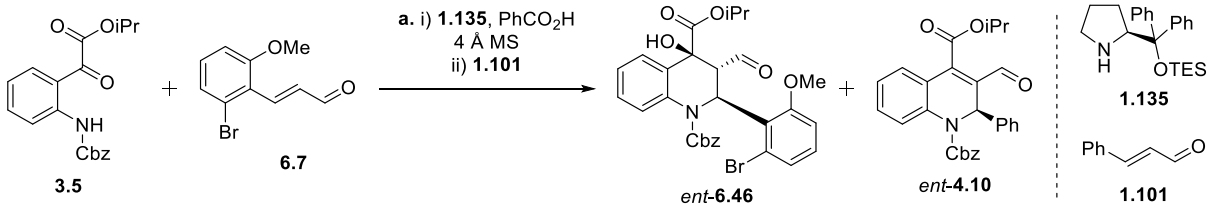
entry	substrate	change to conditions	time	yield[a]
20	**6.7**	100 mol % **1.135**, no MS	120 h	60%
21[c]	**6.7**	100 mol % **1.135**, no MS	160 h	52%[d]
22	**6.7**	100 mol % pyrrolidine in place of **1.135**[e]	18 h	15%[f]

Table 6.4: Conditions screening for the organocatalysed cyclisation of the main 2,6-disubstituted cinnamaldehyde substrates. Reagents and conditions: reactions run on 0.15 mmol cinnamaldehyde; (a) **3.5** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt. [a] Isolated yield; [b] some formation of **6.17** observed; [c] reaction run on 1.5 mmol **6.7**; [d] average of three runs; [e] *rac*-**6.46** produced; [f] complete consumption of **6.7** observed.

As **6.7** was the only 2,6-disubstituted cinnamaldehyde to react in the desired manner, an optimisation screen was conducted with the substrate. Excluding molecular sieves unexpectedly offered a small increase in yield, as did leaving out benzoic acid (Table 6.4, entries 13-14). In contrast, increasing the loading of benzoic acid caused a significant drop in yield (Table 6.4, entry 15). Heating the reaction did not noticeably increase conversion of **6.7** but resulted in a complex crude mixture with only trace quantities of *ent*-**6.46** (Table 6.4, entry 16). The less sterically demanding keto ester, **3.1**, also resulted in a complex crude mixture, with little to no improvement in conversion (Table 6.4, entry 17). Cinnamaldehyde **6.26**, possessing a smaller halide, performed similarly poorly in the cyclisation both with and without molecular sieves (Table 6.4, entries 18-19). Fortunately, the yield of *ent*-**6.46** could be increased to more useful levels by increasing the loading of catalyst **1.135** (Table 6.4, entry 20). These conditions could be performed on larger scale with little decrease in yield (Table 6.4, entry 21). Interestingly, the use of stoichiometric pyrrolidine in place of **1.135** resulted in complete consumption of **6.7**, with a low isolable yield of *rac*-**6.46** (Table 6.4, entry 22). The remaining mass balance, however, could not be identified.

To probe the reason for low yields with **6.7**, the cyclisation was run under the standard conditions for 22 h (Scheme 6.15). At this point, *trans*-cinnamaldehyde (**1.101**) was added and

the reaction continued for a further 53 h. Following work-up, the crude ^{1}H NMR spectrum showed almost complete conversion of **1.101** to *ent*-**4.10**, with little conversion of **6.7**. No new products were observed. Although the catalyst has low activity towards **6.7**, it does not seem to undergo irreversible deactivation. This likely indicates that the issue faced is one of a high on-cycle activation barrier, or formation of a stable catalyst-bound intermediate species. More detailed investigations would be needed to further elucidate the reaction mechanism.

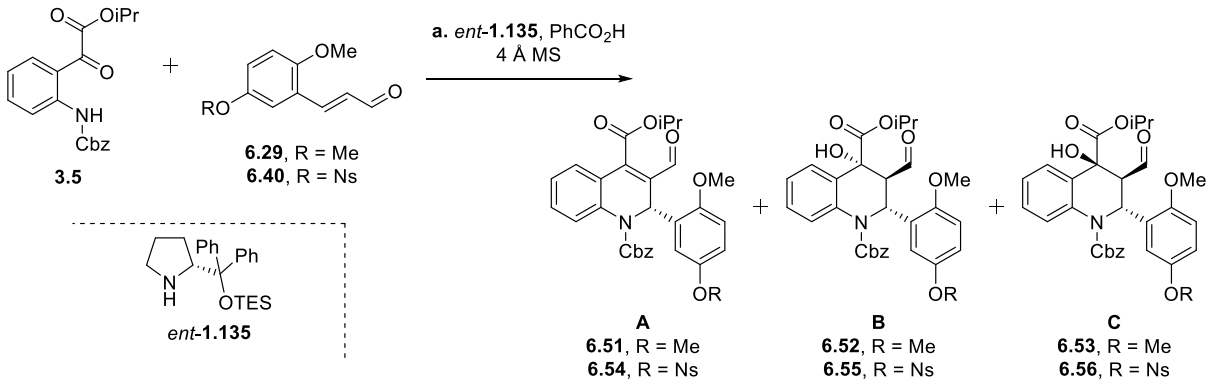


Scheme 6.15: Testing whether **6.7** results in irreversible loss of catalytic activity. Reagents and conditions: reaction run on 0.15 mmol **6.7**; (a) i) **3.5** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt, 22 h; ii) **1.101** (1.0 equiv), rt, 53 h, >85% *ent*-**4.10** NMR yield.

6.2.2 Alternative cinnamaldehyde substrates

Trying first 2,5-dimethoxycinnamaldehyde (**6.29**) offered mixed results (Table 6.5, entry 1). The conversion was considerably higher than for **6.7** under equivalent conditions, as was expected for a less sterically hindered cinnamaldehyde. However, the conversion was lower than for 2-methoxycinnamaldehyde (see Scheme 4.7), which runs counter to the trend that less electron rich α,β-unsaturated aldehydes are more reactive substrates. The exclusion of molecular sieves dramatically reduced conversion of **6.29** and dehydration to **6.51** (Table 6.5, entry 2). The use of stoichiometric catalyst produced greater conversion, with a more favourable ratio of **6.51**:(**6.52** + **6.53**) (Table 6.5, entries 3-4). Interestingly, resubjection of a mixture of all three products to the reaction conditions (excluding **3.5**) did not change the ratio of species over 45 h. Pleasingly, switching the *meta*-methoxy for a more electron withdrawing *meta*-nosyloxy group, **6.40**, did result in improved conversion under the standard

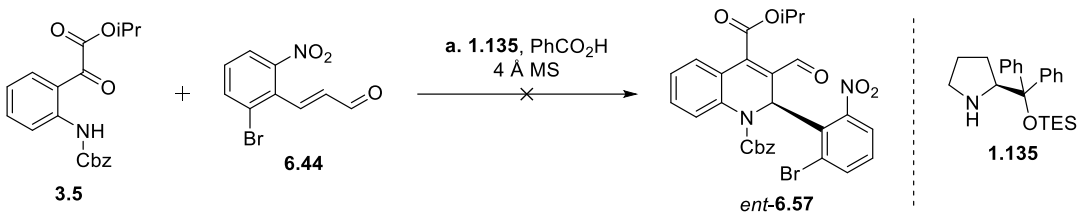
conditions (Table 6.5, entries 5-6). The ee of **6.54** from this reaction was also higher than that of **6.51**, although the formation conditions were not directly equivalent. That **6.40** can offer both better yield and ee under lower catalyst loadings than **6.7** is promising, should the latter be found unsuitable for the total synthesis.



entry	substrate	change to conditions	time	yield(A)[a]	% ee(A)	yield(B)[a]	yield(C)[a]
1	**6.29**	-	95 h	16%	n.d.[b]	24%	8%
2	**6.29**	4 Å MS omitted	95 h	2%	n.d.[b]	15%	3%
3	**6.29**	100 mol % *ent*-**1.135**	93 h	45%	91	17%	4%
4	**6.29**	100 mol % **1.135**	98 h	64%	93	17%	1%
5	**6.40**	-	166 h	40%	96	22%	7%
6	**6.40**	4 Å MS omitted	166 h	3%	n.d.	33%	10%

Table 6.5: Organocatalysed cyclisation with 2,5-dioxygenated cinnamaldehydes. Reagents and conditions: reactions run on 0.15 mmol cinnamaldehyde; (a) **3.5** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt. [a] Isolated yield; [b] n.d. = not determined.

When the standard organocatalysed cyclisation was performed with the second alternative cinnamaldehyde, **6.44**, no conversion was observed by TLC or ^{1}H NMR spectroscopy (Scheme 6.16). A similar lack of cyclised products was observed when conducted with 100 mol % pyrrolidine in place of **1.135**. It is not at all clear why **6.44** does not react, given 2-nitrocinnamaldehyde shows less trouble than 2-methoxycinnamaldehyde (see Scheme 4.6).



Scheme 6.16: Organocatalysed cyclisation with the second alternative cinnamaldehyde substrate. Reagents and conditions: reactions run on 0.15 mmol **6.44**; (a) **3.5** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt, 117 h.

Of the two alternative cinnamaldehydes investigated, only the 2,5-disubstituted substrates, **6.29** and **6.40**, showed potential for use in the planned total synthesis of unciaphenol (**1.1**). However, 2,6-disubstituted cinnamaldehyde **6.7** showed sufficient reactivity to continue with the originally proposed synthetic route. The elaboration of **6.46** towards unciaphenol (**1.1**) could now be investigated, following the transformations developed on the model system (see chapter 5).

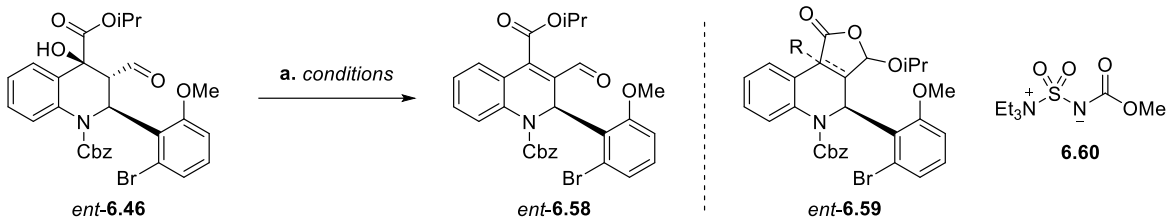
6.3 Retrosynthetic investigations using the desired cinnamaldehyde substrate

6.3.1 Dehydration to the 1,2-dihydroquinoline

In order to follow the transformations following 1,2-dihydroquinoline synthesis previously developed on the model system, **6.46** first required dehydration to **6.58** (Table 6.6). Activation of the alcohol by mesylation was tried first, followed by addition of DBU as a stronger base to effect the $E1_{cB}$ dehydration (Table 6.6, entry 1). This provided the desired product, *ent*-**6.58**, although in low yield. However, due to the broadness of ^1H NMR signals associated with **6.46**, **6.58**, and numerous related species, the fate of the missing mass balance could not be identified. It was noticed by TLC that the reaction mixture did not appear to change upon addition of DBU. Repeating the reaction with additional Et_3N instead offered an improved

yield of **6.58** (Table 6.6, entry 2). The use of a stronger base coupled with lower temperature to tune the reactivity resulted in a complex mixture of products, also containing considerable starting material (Table 6.6, entry 3). The use of sub-stoichiometric DMAP had little impact on the reaction outcome, with an earlier quench indicating considerable degradation already occurring (Table 6.6, entries 4-5). Thinking that the basic conditions may be contributing to side-reactions, acidic conditions were tried (Table 6.6, entries 6-8). A sub-stoichiometric amount of tosic acid showed no conversion at room temperature, with slow dehydration on heating to 80 °C. Degradation still occurred here, including isomerisation to a species matching lactone **6.59**. Stoichiometric tosic acid seemed to accelerate the accumulation of degradation products over **6.58**, with a complex crude mixture observed. Boron trifluoride showed slow consumption of *ent*-**6.46** but with no apparent conversion to *ent*-**6.58**. Returning to activation with base-catalysed elimination, acetic anhydride was used (Table 6.6, entry 9). With Et_3N as base, this showed slow conversion to **6.58** with similar levels of side-product formation as with mesylation. Conditions from Nicolaou and co-workers,[212] however, provided the cleanest conditions so far (Table 6.6, entries 10-11). The moderate yield of *ent*-**6.58** was accompanied by a low yield of acetylated aldol product *ent*-**6.61**, although an extended reaction time on scaling up had no apparent effect on the ratio of these species. Acetate **6.61** was shown to undergo slow elimination with DBU, supporting its assigned structure (Scheme 6.17). Even here, degradation was observed, suggesting that formation of the enolate may be rate-limiting, potentially due to increases in strain. Analogous conditions to dehydrate *via* trifluoroacetylation were entirely unsuccessful (Table 6.6, entry 12). Despite rapid and almost complete consumption of *ent*-**6.46** by TLC, the crude ^{1}H NMR spectrum showed only *ent*-**6.46**. Whatever change occurred, most likely trifluoroacetylation, was reversible and the resultant

species was otherwise inert to the reaction conditions. Interestingly, the ^{1}H NMR spectrum in this case showed negligible degradation.

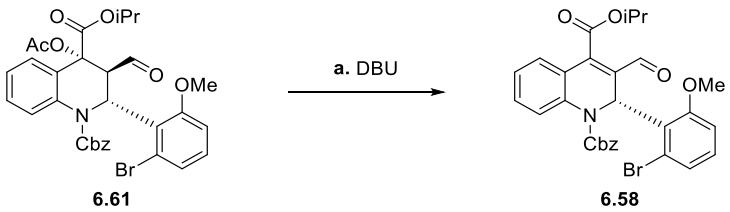


ent-**6.46** *ent*-**6.58** *ent*-**6.59**

entry	conditions	time	yield[a]	% ee
1	i) MsCl (2.0 equiv), Et_3N (2.2 equiv), CH_2Cl_2, rt ii) DBU (3.0 equiv), rt	2 h + 3 h	38%	87
2[b]	MsCl (2.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, rt	90 min	49%	88
3	MsCl (2.0 equiv), iPr_2EtN (5.0 equiv), CH_2Cl_2, –20 °C to 0 °C	3 h	13% (n.d.)[c]	86
4	MsCl (1.5 equiv), Et_3N (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt	90 min	44%	n.d.
5	MsCl (1.1 equiv), Et_3N (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt	35 min	26% (34%)	n.d.
6[b]	$TsOH·H_2O$ (0.1 equiv), PhMe, rt to 80 °C	22 h + 5 h	11% (55%)[c]	86
7[b]	$TsOH·H_2O$ (1.0 equiv), PhMe, 80 °C	7 h	n.d.[c]	n.d.
8	$BF_3·OEt_2$ (4.4 equiv), CH_2Cl_2, rt	7 h	0% (n.d.)	n.d.
9[b]	Ac_2O (2.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, rt	21 h	23% (33%)	85
10	$NaOAc·3H_2O$ (15.0 equiv), DMAP (3.0 equiv), 1:1 Ac_2O:pyridine, 50 °C	24 h	51%[d]	87
11[e]	$NaOAc·3H_2O$ (15.0 equiv), DMAP (3.0 equiv), 1:1 Ac_2O:pyridine, 50 °C	42 h	52%[d]	88
12	$CsOCOCF_3$ (15.0 equiv), DMAP (3.0 equiv), 1:1 TFAA:pyridine, 40 °C	16 h	0% (>90%[f])	n.d.
13	**6.60** (2.0 equiv), THF, rt	3 h	25% (62%)	84
14[g]	**6.60** (2.0 equiv), THF, reflux	90 min	57%	85
15	**6.60** (2.0 equiv), PhMe, 80 °C	2 h	64%	84

Table 6.6: Conditions screening for the dehydration of *ent*-**6.46**. Reagents and conditions: reactions run on 0.1 mmol *ent*-**6.46**; see table for conditions. [a] Isolated yield, numbers in parentheses refer to recovered *ent*-**6.46**; [b] enantiomeric **6.46** used to give **6.58**; [c] **6.59** observed; [d] isolated with 13% **6.61**; [e] reaction run on 0.34 mmol **6.46**; [f] NMR yield; [g] reaction run on 0.55 mmol **6.46**.

Given the hypothesis that enolisation was unfavourable, an alternative to the $E1_{cB}$ mechanism was sought. The Burgess reagent (**6.60**) is known to facilitate *syn*-stereospecific dehydrations without requiring assistance from other functional groups in the reactant.[213] Although the relative configuration of the alcohol centre in *ent*-**6.46** was at this stage unknown, treatment with **6.60** in THF resulted in formation of *ent*-**6.58** even at room temperature (Table 6.6, entry 13). This offers strong support for *syn*-configuration of the alcohol and adjacent C–H bond. Heating facilitated full conversion in both THF and toluene (Table 6.6, entries 14-15). Although the yields were improved over other dehydrations, the mass balance could not be accounted for owing to the lack of degradation shown in the crude ^{1}H NMR spectrum.

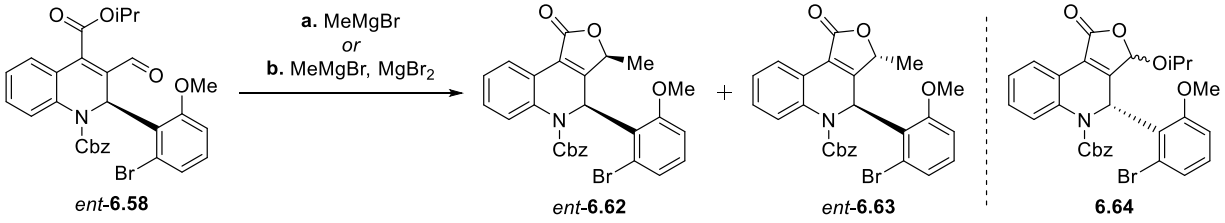


Scheme 6.17: Elimination from acetylated aldol product **6.61**. Reagents and conditions: reaction run on 0.05 mmol **6.61**; (a) DBU (1.1 equiv), CH_2Cl_2, rt, 7 h, >80% conversion.

Following dehydration, chiral HPLC could be used to measure the enantiomeric excess of **6.58**. Although lower than ideal, the ee's observed are reasonable, with possible opportunities for enantiomeric enrichment later in the total synthesis. Pleasingly, the ee's show little variation across a range of dehydrating conditions, suggesting that epimerisation of the benzylic centre is negligible. Differences can more realistically be attributed to different batches of **6.61** and measurement errors.

6.3.2 Aldehyde methylation

Subjecting *ent*-**6.58** to the methylation conditions developed on the model system (see Scheme 5.4) provided a high yield of lactone products (Table 6.7, entry 1). Unfortunately, the diastereoselectivity was considerably lower, with isolation giving an inseparable mixture of *ent*-**6.62** and *ent*-**6.63**. The relative configuration of each isomer has been tentatively assigned as shown, by comparison of the ^{1}H NMR spectra with those of **5.7** and **5.9** (Figure 6.2). Quenching the reaction earlier offered little change in dr, suggesting that epimerisation is unlikely to be playing a role (Table 6.7, entry 2). The use of magnesium bromide, previously shown to favour formation of *trans*-lactone **5.9**, also had little effect on product dr (Table 6.7, entry 3). Conducting the methylation at higher temperature reduced the diastereoselectivity, alongside increased isomerisation to both diastereoisomers of **6.64** (Table 6.7, entry 4).



ent-**6.58** *ent*-**6.62** *ent*-**6.63** **6.64**

entry	conditions	time	dr(*ent*-6.62:*ent*-6.63)[a]	yield(*ent*-6.62)[b]	yield(*ent*-6.63)[b]
1[c]	(a)	70 min	21:79	16%	69%
2	(a)	15 min	19:81	n.d.[d]	n.d.[d]
3	(b)	60 min	27:73	24%	61%
4[e]	(a)[f]	10 min	38:62	16%[g]	24%[g]

Table 6.7: Methylation of *ent*-**6.58**. Reagents and conditions: reactions run on 0.05 mmol *ent*-**6.58**; (a) *ent*-**6.58** in THF added dropwise to MeMgBr in THF; MeMgBr (1 M THF) (10.0 equiv), THF, –78 °C; (b) $MgBr_2$ pre-stirred with *ent*-**6.58** in CH_2Cl_2 at room temperature before cooling and dropwise addition of MeMgBr; MeMgBr (3 M Et_2O) (5.0 equiv), $MgBr_2$ (5.0 equiv), CH_2Cl_2, –78 °C. [a] Based on integration on crude ^{1}H NMR spectrum; [b] isolated yield; [c] reaction run on 0.1 mmol *ent*-**6.58**; [d] n.d. = not determined; [e] enantiomeric **6.58** used to give **6.62** and **6.63**; [f] 1.0 equiv MeMgBr added dropwise to *ent*-**6.58** in THF at 0 °C; [g] 47% **6.64** isolated in 71:29 dr.

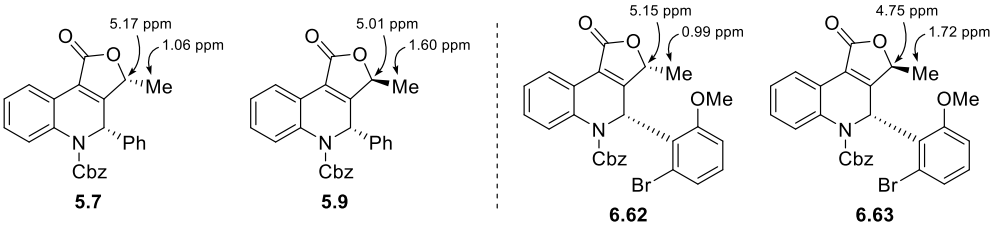


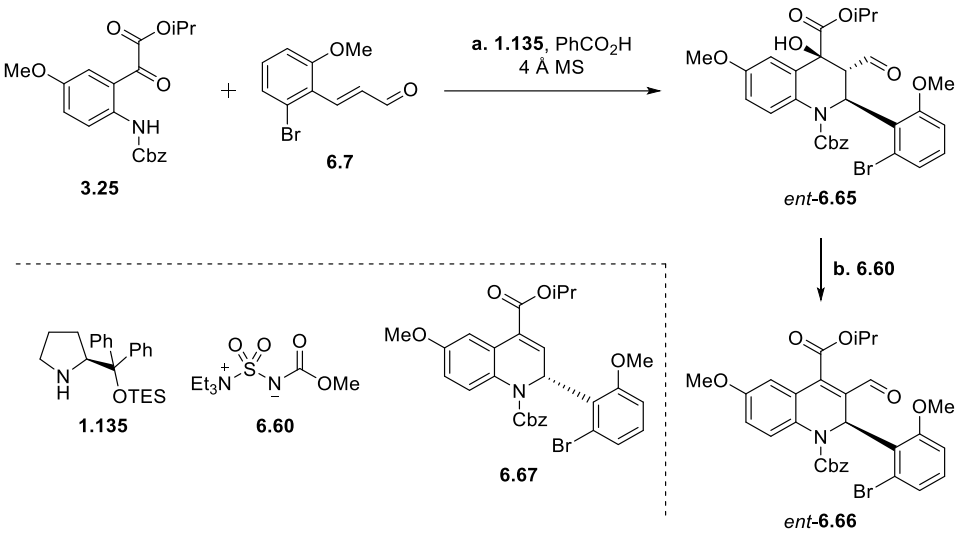
Figure 6.2: ^{1}H NMR shifts used to assign the relative configurations of **6.62** and **6.63**.

The above observations indicate that the s-*trans* conformation of the α,β-unsaturated aldehyde of **6.58** is relatively less favoured than in model system **4.10**. It seems plausible that this would be due to electrostatic repulsion between the aldehyde oxygen and either of the *ortho*- substituents present in **6.58**. The negligible effect of magnesium bromide could be through competition between the aldehyde chelating with the ester or the methoxy group, although this is less clear. While the inseparable diastereomers have hindered measurement of the enantiomeric excesses, it is expected that a decrease from the starting ee would be unlikely (see section 5.1).

6.3.3 Towards the total synthesis of unciaphenol with methoxy keto ester 3.25

Although **6.58** possesses the required substituents on the aryl ring, it lacks oxygenation *para*- to the nitrogen to provide the anthraquinone phenol of unciaphenol (**1.1**). For this, a keto ester derived from 5-methoxyisatin (**1.35**) would be required. Pleasingly, the organocatalysed coupling of **6.7** with **3.25** proceeds more efficiently than with **3.5** (Table 6.8, entry 1). Dehydration with the Burgess reagent (**6.60**) proceeds in similar yield to give *ent*-**6.66** with a higher ee. On larger scale dehydration of **6.65**, deformylated product **6.67** was observed. This would most likely form *via* addition to the aldehyde followed by fragmentation to eliminate the hydroxyl group. Unlike with **3.5**, molecular sieves benefit the coupling of **3.25** and **6.7** (Table 6.8, entry 2). Similar to **6.46**, the yield of aldol product *ent*-**6.65** can be increased by

adding more **1.135** to the reaction, with trace quantities of the desired 1,2-dihydroquinoline directly isolable from the scaled up reaction (Table 6.8, entry 3). Further increasing the catalyst loading, however, resulted in a decreased yield (Table 6.8, entry 4). Unexpectedly, higher catalyst loadings lead to a dramatic decrease in enantiomeric excess, measurable after dehydration to **6.66**. The portion of *ent*-**6.66** isolated directly from Table 6.8, entry 3 (a) even appeared to possess the opposite configuration (with 12% ee) to *ent*-**6.65** from the same reaction, although the sample was not entirely clean.

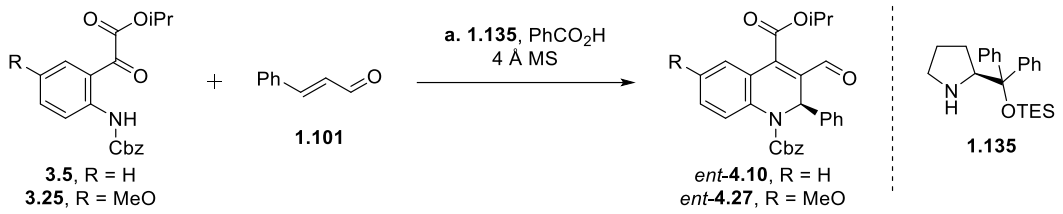


entry	6.7/mmol	1.135/mol %	yield(*ent*-6.65)[a]	yield(*ent*-6.66)[a]	% ee(*ent*-6.66)
1	0.15	20	46%	55%	92
2[b]	0.15	20	23%	n.d.[c]	n.d.[c]
3	1.50	40[d]	58%[e]	65%	77
4[f]	1.50	100	42%	63%[g]	51

Table 6.8: Preparation of fully functionalised 1,2-dihydroquinoline **6.66** for the total synthesis of unciaphenol (**1.1**). Reagents and conditions: (a) **3.25** (2.0 equiv), **1.135**, $PhCO_2H$ (50 mol %), activated 4 Å MS (50 mg), CH_2Cl_2, rt, 240 h; (b) **6.60** (2.0 equiv), PhMe, 80 °C, 90 min. [a] Isolated yield; [b] molecular sieves omitted; [c] n.d. = not determined; [d] 20 mol % present at start, with 20 mol % added after 76 h; [e] trace **6.66** isolated, 12% ee; [f] reaction run using enantiomeric catalyst *ent*-**1.135** to obtain **6.65** and **6.66**; [g] <5% **6.67** also isolated.

It is entirely unclear why this reaction should behave so differently to previous versions with similar substrates. Using stoichiometric catalyst with simpler substrates does seem to

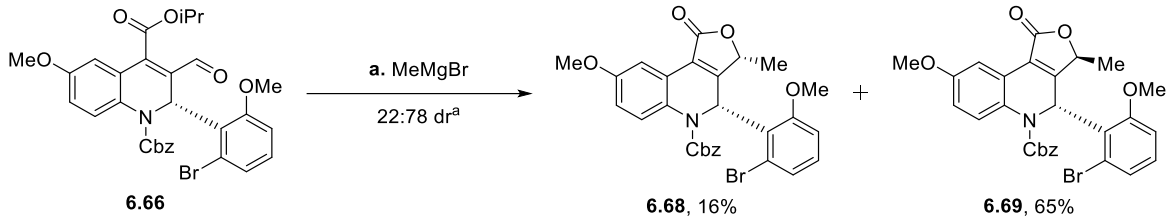
decrease the product's ee, although nowhere near as dramatically as for **6.65** (Table 6.9). This more than likely indicates the presence of unidentified intermediates within the reaction pathway, with the possibility of alternative product-forming pathways. The inverse relationship between catalyst loading and product ee could well suggest the involvement of intermediates containing more than one catalyst molecule. To properly understand and improve the reaction in Table 6.8, detailed mechanistic studies would be required. For the time being, however, **6.65** appears to be accessible in moderate yield and good ee.



entry	1.135/mol %	product	% ee
1	20	*ent*-**4.10**	98
2	100	*ent*-**4.10**	96
3	20	*ent*-**4.27**	98
4	100	*ent*-**4.27**	97

Table 6.9: Stoichiometric catalyst loading in the organocatalysed cyclisation. Reagents and conditions: reactions run on 0.15 mmol **1.101**; (a) **3.25** (2.0 equiv), **1.135**, $PhCO_2H$ (50 mol %), activated 4 Å MS (ground) (50 mg), CH_2Cl_2, rt.

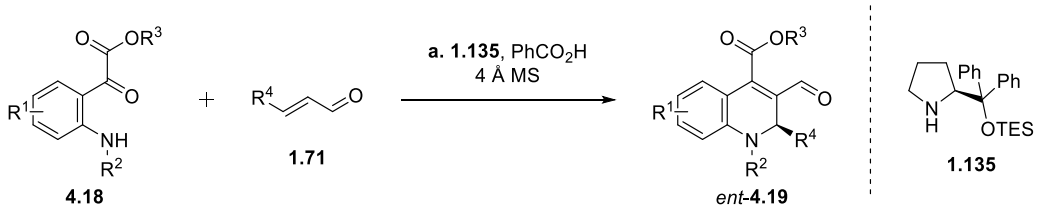
Finally, 1,2-dihydroquinoline **6.66** was shown to provide similar dr to **6.58** in methylation of the aldehyde moiety (Scheme 6.18). Desired diastereoisomer **6.68** was isolated as the minor component of an inseparable mixture with **6.69**. This situation is far from ideal, although separation and inversion of the undesired epimer could be feasible further into the synthetic route, should optimisation fail to improve the dr significantly. A lack of time has curtailed further progress with **6.66**.



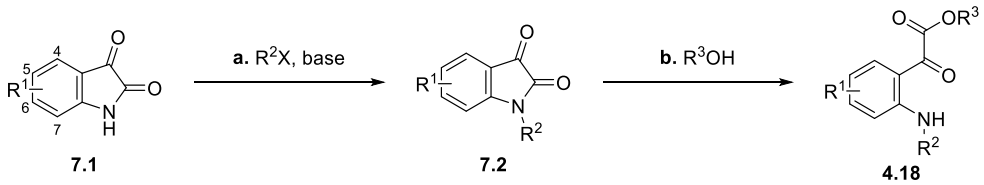
Scheme 6.18: Methylation of fully functionalised substrate **6.66**. Reagents and conditions: reaction run on 0.34 mmol **6.66**; MeMgBr (1 M THF) (10.0 equiv), THF, –78 °C, 50 min. [a] Based on integration of crude ^{1}H NMR spectrum.

7 Conclusions and future work

During initial investigations towards the total synthesis of unciaphenol (**1.1**), an organocatalysed cascade for the production of 1,2-dihydroquinolines was developed (Scheme 7.1). This operationally simple and scalable method, adapted from work by Wang and co-workers[96] to use α-keto ester substrates, **4.18**, permits access to the novel substructure **4.19** in generally high yields and ee's. A rapid and readily scalable preparation of isatin-derived α-keto esters, **4.18**, was also developed (Scheme 7.2). This allows facile variation at four positions around **4.19**, with a variety of functionality well-tolerated.



Scheme 7.1: Optimised organocatalytic synthesis of 1,2-dihydroquinolines **4.19**.Reagents and conditions: **4.18** (2.0 equiv), **1.135** (20 mol %), $PhCO_2H$ (50 mol %), activated 4 Å MS (ground), CH_2Cl_2, rt.



Scheme 7.2: Synthetic route for the preparation of isatin-derived α-keto esters.

The use of the above cyclisation in working towards the total synthesis of unciaphenol (**1.1**), however, has highlighted areas for improvement and future consideration. At present, the reaction does not run to completion for electron rich or highly sterically demanding substrates. Higher catalyst loadings have also brought to light the presence of unknown intermediate species that negatively affect both the yield and enantioselectivity. As such, mechanistic investigations would likely benefit understanding of the roots of the issues,

leading to directed improvements. Alternatively, a more thorough catalyst screen could be conducted, seeking one that either offers a faster reaction or is more long-lived under the optimal conditions. Another area for future consideration would be the expansion of the scope concerning **1.71**, as at present, only β-(hetero)aromatic α,β-unsaturated aldehydes have shown conversion.

The organocatalysed cascade above has been used as a key step towards the total synthesis of unciaphenol (**1.1**). However, the model system chosen to investigate subsequent transformations, **4.10**, has proven to be a poor mimic of the actual substrate, **6.66** (Figure 7.1). Its use has been beneficial in that it is considerably easier and less expensive to prepare, as well as aiding the identification of side products subsequently found with **6.66**. Unfortunately, the natural diastereoinduction during methylation of the aldehyde is rather different, believed to be due to different ground state conformations.

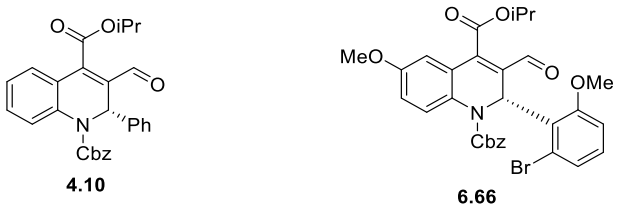
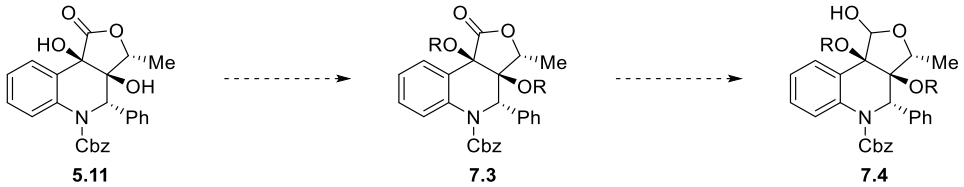


Figure 7.1: Left: model system used to probe the proposed retrosynthesis of unciaphenol (**1.1**); right: actual substrate required.

Future work will continue with the model system, as the investigation of future transformations primarily concerns chemoselectivity (Scheme 7.3). Protection of the *syn*-diol of **5.11** and monoreduction of the lactone of **7.3** would provide **7.4**, possessing the aldehyde equivalent needed for the key Barbier cyclisation. While protection of the secondary alcohol may be required, initial investigations will be conducted on the hemiacetal.



Scheme 7.3: Future work to be conducted on model system **5.11**.

Future work on the actual substrate would simply involve following the proposed retrosynthesis further. This may be dependent on decisions taken to improve its organocatalysed synthesis, although the current reaction is scalable and so sufficient material can be carried through if desired. Despite the troubles encountered, the originally proposed retrosynthesis is still considered viable for the total synthesis of the target natural product.

8 Experimental

8.1 General remarks

Solvents and reagents

All reactions were performed using flame-dried reaction vessels under an atmosphere of argon unless stated otherwise. Anhydrous diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), chloroform ($CHCl_3$), *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), tetrahydrofuran (THF), and toluene (PhMe) were obtained from solvent dispenser units having been passed through an activated alumina column under argon. Diisopropylamine was distilled from sodium hydroxide and stored over sodium hydroxide pellets. 3-(Dimethylamino)acrylaldehyde (**6.15**) was distilled prior to use and stored at low temperature. All other chemical reagents used were commercially available from Alfa Aesar, Fluorochem, and Sigma-Aldrich and used as supplied. Molecular sieves were sold as beads of diameter 1.6 – 2.5 mm and were either used as supplied or ground before use. Activation was performed by flame-drying under vacuum.

Microwave reactor

All reactions performed with microwave heating used a CEM Discover microwave reactor. Power was held at 250 W until the desired temperature was reached, from which point the power was automatically regulated to maintain this temperature for the duration of the experiment.

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, vanillin, or 2,4-dinitrophenylhydrazine. 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 Fisher Scientific, Sigma Aldrich, VWR, or Rathburn Chemicals.

Optical rotation

Specific optical rotations were measured on a Perkin Elmer 241 Polarimeter in a cell of path length 10 cm at the sodium D line (589.3 nm) in $CHCl_3$ at 25 °C and are reported in the units of deg.cm^2.g^{-1}. Solution concentrations are given in units of 10^{-2} g.mL^{-1}.

Melting points

Melting points were measured on a Griffin heated metal block apparatus and are reported uncorrected.

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. ^{13}C spectra were recorded with broadband decoupling. Chemical shifts (δ_H, δ_C, δ_F) are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR or

0.1 ppm for ^{13}C NMR and ^{19}F 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-d_6, δ 2.50 and 39.52 ppm respectively; acetone-d_6, δ 2.05 and 29.84 ppm respectively).[214] ^{19}F spectra were referenced relative to $CFCl_3$. Peak assignments were made on the basis of chemical shifts, integrations, coupling constants, and comparison to known compounds, using COSY, HSQC, HMBC, and NOESY 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 0.1 Hz. Where relevant, A and B refer to diastereotopic atoms. Missing assignments are due to low confidence in the identification of relevant signals, usually as a result of broadened or overlapping signals.

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.

HPLC

HPLC analysis was performed using an Agilent 1200 machine with a Chiralcel OD chiral column (4.6 mm × 250 mm) and a Chiralcel AD-H chiral column (4.6 mm × 250 mm). Compounds were detected using wavelengths of 250 nm and 254 nm, with integrations taken from the 254 nm trace. Where not specified, a 'racemic' sample was obtained by mixing approximately equal quantities of each enantiomer, prepared *via* identical reaction conditions.

Reporting of compounds

Compounds are reported in order of the number assigned in the main text. Additional compounds appear at the end of this section. 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.

8.2 General procedures

General procedure A

Conducted according to procedure of Wang.[96]

To the pyrrolidine catalyst (0.03 mmol, 0.2 equiv) in 1,2-dichloroethane (0.15 mL) was added sequentially (*E*)-cinnamaldehyde (0.15 mmol, 1.0 equiv), sodium acetate (6.2 mg, 0.08 mmol, 0.5 equiv), freshly activated 4 Å molecular sieves (ground) (75 mg), and the appropriate carbamate (0.45 mmol, 3.0 equiv), then the mixture stirred at room temperature for the stated time. The reaction was purified directly by column chromatography (SiO_2, eluent load) to give the title compound.

General Procedure B

Optimised organocatalytic cyclisation conditions.

To (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (11.0 mg, 0.03 mmol, 0.2 equiv) in CH_2Cl_2 (0.15 mL) were added sequentially α,β-unsaturated aldehyde (0.15 mmol, 1.0 equiv), benzoic acid (9.2 mg, 0.08 mmol, 0.5 equiv), freshly activated 4 Å molecular sieves (ground) (50 mg), and then keto ester (0.30 mmol, 2.0 equiv) in CH_2Cl_2 (0.15 mL), then the

mixture stirred at room temperature for the stated time. Additional CH_2Cl_2 (0.15 mL) was added after 24 h to compensate for solvent loss. The reaction was filtered with ethyl acetate, and then washed sequentially with sat. aq. sodium bicarbonate solution, hydrochloric acid (2 M), and brine. The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load) to give the title product.

General Procedure C

Cbz protection of isatin derivatives.

To the isatin (1.0 equiv) in tetrahydrofuran at 0 °C was added triethylamine (1.2 equiv) followed by dropwise benzyl chloroformate (95%) (1.2 equiv) and the mixture stirred at room temperature for the stated time. The reaction was concentrated *in vacuo*, then water added and the solid collected by filtration, washing with water, to give the title product.

General Procedure D

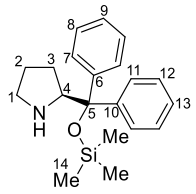
Solvolysis of Cbz-protected isatin derivatives with 2-propanol.

Cbz-protected isatin (1.0 equiv) was dissolved in 2-propanol and heated at reflux for the stated time. The solution was allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load) to give the title product.

8.3 Experimental procedures and characterisation

(*S*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (1.102)

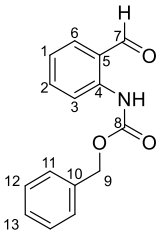
Prepared by procedure of Boeckman.[135]



To (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**4.4**) (1.0 g, 3.9 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at –78 °C was added triethylamine (0.8 mL, 5.5 mmol, 1.4 equiv) followed by dropwise trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.4 equiv) over 10 min and the mixture allowed to warm to room temperature over 2 h. The reaction was stirred for a further 2 h. To the solution was added sequentially sat. aq. sodium bicarbonate solution (6 mL) and water (6 mL) then the mixture was extracted with CH_2Cl_2 (× 3). The combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 30-40, 30:70 to 70:30) to give (*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (**1.102**) as a viscous yellow oil (940 mg, 2.9 mmol, 73%); R_f: 0.09 (EtOAc); $[\alpha]_D^{25} = -51.1$ (*c* = 1.00, $CHCl_3$) (lit.[215] $[\alpha]_D^{33} = -52.4$ (*c* = 1.04, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 – 7.44 (m, 2H, 2 × C7H), 7.37 – 7.34 (m, 2H, 2 × C11H), 7.30 – 7.18 (m, 6H, 2 × C8H, 2 × C12H, C9H, C13H), 4.03 (t, *J* = 7.3 Hz, 1H, C4H), 2.89 – 2.82 (m, 1H, C1H_AH$_B$), 2.82 – 2.76 (m, 1H, C1H$_A$$H_B$), 1.69 (s, 1H, NH), 1.63 – 1.49 (m, 3H, C2H_AH$_B$, C3H$_2$), 1.42 – 1.33 (m, 1H, C2H$_A$$H_B$), -0.09 (s, 9H, 3 × C14H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 147.0 (C10), 145.9 (C6), 128.5 (2 × C7H), 127.7 (2 × C8H or 2 × C11H or 2 × C12H), 127.7 (2 × C8H or 2 × C11H or 2 × C12H), 127.7 (2 × C8H or 2 × C11H or 2 × C12H), 127.0 (C9H), 126.8 (C13H), 83.3 (C5), 65.5 (C4H), 47.3 (C1H$_2$), 27.6 (C3H$_2$), 25.2 (C2H$_2$), 2.3 (3 × C14H$_3$); IR ν_{max} (cm^{-1}): 3086, 3059, 3025, 2954, 2874, 1599; data in accordance with literature.[135]

Benzyl (2-formylphenyl)carbamate (1.133)

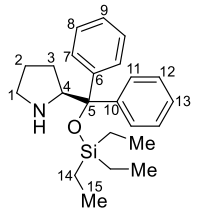
Prepared by procedure of Lin.[137]



To 2-amino benzyl alcohol (**4.5**) (2.0 g, 16.2 mmol, 1.0 equiv) in tetrahydrofuran (55 mL) under was added potassium carbonate (22.4 g, 162.4 mmol, 10.0 equiv) followed by dropwise benzyl chloroformate (95%) (2.6 mL, 17.9 mmol, 1.1 equiv), and the mixture was stirred at room temperature for 16 h. To this was added ethyl acetate (24 mL) and sat. aq. sodium bicarbonate solution (24 mL) and the layers separated. The aqueous portion was extracted with ethyl acetate then the combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (40 mL) and a spatula of Celite® added. To this was added portionwise pyridinium chlorochromate (4.2 g, 19.5 mmol, 1.2 equiv) and the mixture stirred at room temperature for 6.5 h. The reaction was filtered through Celite®, washing with CH_2Cl_2, and then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 20:80) to give benzyl (2-formylphenyl)carbamate (**1.133**) as a white crystalline solid (3.3 g, 13.0 mmol, 80%); R_f: 0.22 (Et_2O:petroleum ether 40-60, 20:80); m.p.: 61.0–63.0 °C (lit.[137] 66.0–66.5°C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.68 (s, 1H, NH), 9.90 (d, *J* = 0.7 Hz, 1H, C7H), 8.48 (d, *J* = 8.4 Hz, 1H, C3H), 7.64 (dd, *J* = 7.7, 1.7 Hz, 1H, C6H), 7.60 (dddd, *J* = 8.5, 7.4, 1.7, 0.5 Hz, 1H, C2H), 7.47 – 7.41 (m, 2H, 2 × C11H), 7.41 – 7.37 (m, 2H, 2 × C12H), 7.37 – 7.32 (m, 1H, C13H), 7.17 (td, *J* = 7.5, 1.0 Hz, 1H, C1H), 5.24 (s, 2H, $C9H_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 195.2 (C7H), 153.6 (C10), 141.3 (C4), 136.1 (C2H, C6H), 136.0 (C10), 128.7 (2 × C12H), 128.4 (C13H), 128.4 (2 × C11H), 122.2 (C1H), 121.5 (C5), 118.5 (C3H), 67.2 ($C9H_2$); IR ν_{max} (cm^{-1}): 3280, 2840, 2754, 1735, 1668, 1608, 1587, 1530; HRMS (ESI)

[M–H]$^-$: calculated for $C_{15}H_{12}NO_3^-$ 254.0823, found 254.0823, Δ 0.03 ppm; data in accordance with literature.[137]

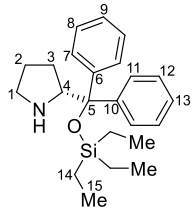
(*S*)-2-(Diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (1.135)



To (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**4.4**) (2.0 g, 7.9 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at –78 °C was added triethylamine (2.0 mL, 14.2 mmol, 1.8 equiv) followed by dropwise triethylsilyl triflate (3.2 mL, 14.2 mmol, 1.8 equiv) over 10 min and the mixture stirred at –78 °C for 1 h. The reaction was then allowed to warm to room temperature and stirred at room temperature for a further 4.5 h total. To the solution were added sequentially sat. aq. sodium bicarbonate solution (15 mL) and water (15 mL) then the mixture was extracted with CH_2Cl_2 (× 3). The combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, Et_2O:pentane, 10:90 to 100:0) gave (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) as a viscous yellow oil (2.5 g, 6.9 mmol, 87%); R_f: 0.21 (Et_2O); $[\alpha]_D^{25} = -31.5$ (*c* = 1.00, $CHCl_3$) (lit.[216] $[\alpha]_D^{25} = -29.6$ (*c* = 1.00, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 – 7.45 (m, 2H, 2 × C7H), 7.37 – 7.33 (m, 2H, 2 × C11H), 7.29 – 7.20 (m, 6H, 2 × C8H, C9H, 2 × C12H, C13H), 4.02 (t, *J* = 7.3 Hz, 1H, C4H), 2.82 (ddd, *J* = 10.0, 7.5, 6.2 Hz, 1H, C1H_AH$_B$), 2.69 (ddd, *J* = 10.0, 7.4, 5.6 Hz, 1H, C1H$_A$$H_B$), 1.80 (br s, 1H, NH), 1.62 – 1.48 (m, 3H, C1H$_2$, C2H_AH$_B$), 1.32 – 1.19 (m, 1H, C2H$_A$$H_B$), 0.85 (t, *J* = 7.9 Hz, 9H, 3 × C15H$_3$), 0.35 (q, *J* = 8.0 Hz, 6H, 3 × C14H$_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 146.7 (C10), 145.6 (C6), 129.0 (2 × C7H), 128.2 (2 × C11H), 127.7 (2 × C8H or 2 × C12H), 127.5

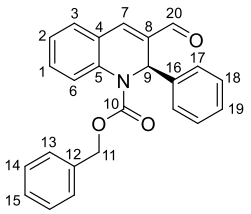
(2 × C8H or 2 × C12H), 127.1 (C13H), 127.1 (C9H), 83.0 (C5), 65.8 (C4H), 47.4 ($C1H_2$), 27.8 ($C3H_2$), 25.3 ($C2H_2$), 7.4 (3 × $C15H_3$), 6.6 (3 × $C14H_2$); IR ν_{max} (cm^{-1}): 3086, 3059, 3025, 2954, 2911, 2875; HRMS (Methane CI) $[M+H]^+$: calculated for $C_{23}H_{34}NOSi^+$ 368.2404, found 368.2398, Δ –1.63 ppm; data in accordance with literature.[215]

(*R*)-2-(Diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-1.135)



To (*R*)-diphenyl(pyrrolidin-2-yl)methanol (*ent*-**4.4**) (2.0 g, 7.9 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at –78 °C was added triethylamine (1.5 mL, 11.1 mmol, 1.4 equiv) followed by dropwise triethylsilyl triflate (2.5 mL, 11.1 mmol, 1.4 equiv) over 15 min. The mixture was stirred at –78 °C for 1 h, and then allowed to warm to room temperature and stirred for a further 4.5 h. To the solution was added sequentially sat. aq. sodium bicarbonate solution (15 mL) and water (15 mL) and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (× 2) and the combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:pentane, 10:80 to 100:0) to give (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**) as a viscous yellow oil (2.1 g, 5.8 mmol, 73%); $[\alpha]_D^{25} = +31.8$ (*c* = 1.00, $CHCl_3$); all other characterisation identical to **1.135**.

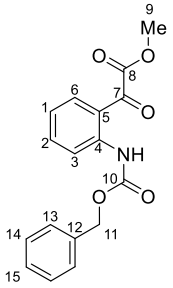
Benzyl (*R*)-3-formyl-2-phenylquinoline-1(2H)-carboxylate (1.136)



(*S*)-2-(Diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (11.0 mg, 0.03 mmol, 0.2 equiv), (*E*)-cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv), and benzyl (2-formylphenyl)carbamate (**1.133**) (114.9 mg, 0.45 mmol, 3.0 equiv) were subjected to **General Procedure A**, stirring at room temperature for 70 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85) gave benzyl (*R*)-3-formyl-2-phenylquinoline-1(2H)-carboxylate (**1.136**) as a viscous yellow oil (53.3 mg, 0.14 mmol, 96%); R_f: 0.27 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -510.7$ (*c* = 1.00, $CHCl_3$) (lit.[96] $[\alpha]_D^{23} = -619.1$ (*c* = 1.0, $CHCl_3$)); ee: 95% (Chiralcel OD; hexane:2-propanol, 80:20; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 25.85 min, t_R (major) = 34.15 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (s, 1H, C20H), 7.74 (br s, 1H, C6H), 7.44 (d, *J* = 0.5 Hz, 1H, C7H), 7.42 – 7.30 (m, 7H, C1H, C3H, 2 × C13H, 2 × C14H, C15H), 7.21 – 7.16 (m, 5H, 2 × C17H, 2 × C18H, C19H), 7.15 (td, *J* = 7.5, 1.1 Hz, 1H, C2H), 6.70 (s, 1H, C9H), 5.30 (s, 2H, $C11H_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.0 (C20H), 154.0 (C10), 141.8 (C7H), 138.7 (C16), 138.3 (C8), 137.4 (C5), 135.8 (C12), 131.9 (C1H), 129.1 (C3H), 128.7 (2 × C14H or 2 × C18H), 128.6 (2 × C14H or 2 × C18H), 128.5 (C15H or C19H), 128.3 (2 × C13H), 128.2 (C15H or C19H), 126.9 (2 × C17H), 125.4 (C4), 124.8 (C6H), 124.7 (C2H), 68.5 ($C11H_2$), 53.3 (C9H); IR ν_{max} (cm^{-1}): 3063, 3033, 2956, 2816, 2721, 1703, 1673, 1636, 1601, 1568; HRMS (ESI) [M+Na]$^+$: calculated for $C_{24}H_{19}NNaO_3^+$ 392.1257, found 392.1255, Δ –0.66 ppm; data in accordance with literature.[96]

A racemic sample of benzyl 3-formyl-2-phenylquinoline-1(2H)-carboxylate (*rac*-**1.136**) was prepared as above using pyrrolidine (3.0 µL, 0.03 mmol, 0.2 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

Methyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (3.1)

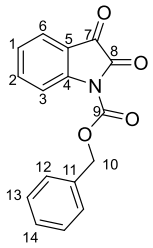


Benzyl 2,3-dioxoindoline-1-carboxylate (**3.2**) (3.9 g, 13.9 mmol, 1.0 equiv) was dissolved in methanol (50 mL) and heated at reflux for 90 min. The solution was allowed to cool to room temperature and was then cooled to 0 °C. The crystals were collected by filtration, washing with ice cold methanol, and dried *in vacuo* to give methyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.1**) as a pale yellow solid (2.9 g, 9.4 mmol, 68%). The filtrate was concentrated *in vacuo*, and then methanol (16 mL) added and the mixture heated at reflux for 90 min. Cooling to room temperature then to 0 °C provided a second batch of crystalline product identical to the first (0.6 g, 1.9 mmol, 13%) to give the combined yield (3.5 g, 11.3 mmol, 81%); R_f: 0.42 (Et_2O:petroleum ether 40-60, 20:80), with a spot at 0.06 (MeOH:CH_2Cl_2, 10:90) likely arising from recyclisation; m.p.: 86.5–88.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.15 (s, 1H, NH), 7.83 – 7.77 (m, 1H, C3H), 7.73 – 7.66 (m, 2H, C2H, C6H), 7.44 – 7.38 (m, 4H, 2 × C13H, 2 × C14H), 7.37 – 7.33 (m, 1H, C15H), 7.28 (ddd, *J* = 7.7, 7.3, 1.1 Hz, 1H, C1H), 5.15 (s, 2H, $C11H_2$), 3.83 (s, 3H, $C9H_3$); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 187.3 (C7), 163.1 (C8), 153.7 (C10), 139.5 (C4), 136.1 (C12), 135.3 (C2H), 131.8 (C6H),

128.5 (2 × C14H), 128.2 (C15H), 128.2 (2 × C13H), 123.7 (C1H), 123.1 (C5), 121.5 (C3H), 66.6 ($C11H_2$), 53.0 ($C9H_3$); IR ν_{max} (cm^{-1}): 3298 (br), 2955, 2924, 2853, 1736, 1650, 1607, 1583, 1526; HRMS (ESI) $[M–H]^-$: calculated for $C_{17}H_{14}NO_5^-$ 312.0878, found 312.0875, Δ –0.84 ppm.

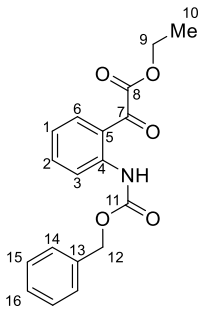
Benzyl 2,3-dioxoindoline-1-carboxylate (3.2)

Prepared by procedure of Suzuki.[121]



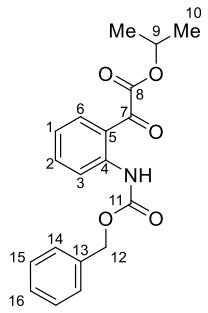
Isatin (**3.3**) (5.0 g, 34.0 mmol, 1.0 equiv), tetrahydrofuran (60 mL), triethylamine (5.7 mL, 40.8 mmol, 1.2 equiv), and benzyl chloroformate (95%) (6.0 mL, 40.8 mmol, 1.2 equiv) were subjected to **General Procedure C**, stirring for 90 min to give benzyl 2,3-dioxoindoline-1-carboxylate (**3.2**) as a bright yellow solid (9.1 g, 32.4 mmol, 95%); R_f: 0.06 (MeOH:CH_2Cl_2, 10:90); m.p.: 153.5–155.5 °C (lit.[121] 153–154 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.00 (dt, *J* = 8.2, 0.9 Hz, 1H, C3H), 7.77 (ddd, *J* = 8.3, 7.5, 1.5 Hz, 1H, C2H), 7.72 (ddd, *J* = 7.5, 1.5, 0.6 Hz, 1H, C6H), 7.55 – 7.50 (m, 2H, 2 × C12H), 7.46 – 7.39 (m, 2H, 2 × C13H), 7.41 – 7.34 (m, 1H, C14H), 7.34 (td, *J* = 7.5, 0.9 Hz, 1H, C1H), 5.46 (s, 2H, $C10H_2$); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 179.5 (C7), 155.9 (C8), 149.9 (C9), 147.1 (C4), 137.8 (C2H), 135.3 (C11), 128.5 (2 × C13H), 128.3 (C14H), 127.9 (2 × C12H), 125.1 (C1H), 124.4 (C6H), 119.7 (C5), 116.1 (C3H), 68.0 ($C10H_2$); IR ν_{max} (cm^{-1}): 1793, 1732, 1612, 1595; HRMS (Ammonia CI) $[M+NH_4]^+$: calculated for $C_{16}H_{15}N_2O_4^+$ 299.1026, found 299.1024, Δ –0.67; data in accordance with literature.[121]

Ethyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (3.4)



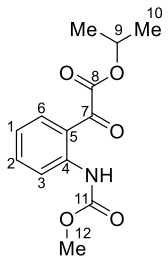
Benzyl 2,3-dioxoindoline-1-carboxylate (**3.2**) (563 mg, 2.0 mmol, 1.0 equiv) was dissolved in ethanol (8 mL) and heated at reflux for 2 h. The solution was allowed to cool to room temperature and concentrated *in vacuo*. The residue was dissolved in the minimum required ethyl acetate and hexane added. This was cooled to –78 °C and the lower layer isolated by pipette. This was concentrated *in vacuo* to give ethyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.4**) as an orange oily crystalline solid (306.6 mg, 0.94 mmol, 47%); R_f: 0.50 (EtOAc:petroleum ether 40-60, 15:85), with a spot at 0.06 (MeOH:CH_2Cl_2, 10:90) likely arising from recyclisation; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.67 (s, 1H, NH), 8.55 (dd, *J* = 8.6, 1.0 Hz, 1H, C3H), 7.67 (dd, *J* = 8.0, 1.6 Hz, 1H, C6H), 7.64 (dddd, *J* = 8.6, 7.3, 1.6, 0.5 Hz, 1H, C2H), 7.45 – 7.41 (m, 2H, 2 × C14H), 7.41 – 7.36 (m, 2H, 2 × C15H), 7.36 – 7.32 (m, 1H, C16H), 7.10 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H, C1H), 5.24 (s, 2H, $C12H_2$), 4.45 (q, *J* = 7.2 Hz, 2H, $C9H_2$), 1.42 (t, *J* = 7.2 Hz, 3H, $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.3 (C7), 163.8 (C8), 153.5 (C11), 143.1 (C4), 137.0 (C2H), 135.9 (C13), 133.7 (C6H), 128.7 (2 × C15H), 128.5 (C16H), 128.4 (2 × C14H), 121.9 (C1H), 119.4 (C3H), 117.0 (C5), 67.3 ($C12H_2$), 62.7 ($C9H_2$), 14.2 ($C10H_3$); IR ν_{max} (cm^{-1}): 3297, 3034, 2983, 1736, 1650, 1607, 1583, 1527; HRMS (ESI) $[M–H]^–$: calculated for $C_{18}H_{16}NO_5^–$ 326.1034, found 326.1036, Δ 0.55 ppm; data in accordance with literature.[217]

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (3.5)



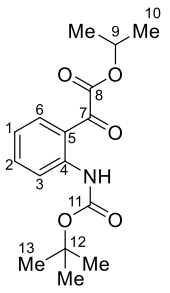
Benzyl 2,3-dioxoindoline-1-carboxylate (**3.2**) (5.0 g, 17.8 mmol, 1.0 equiv) and 2-propanol (160 mL) were subjected to **General Procedure D**, heating for 6 h. Purification by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 20:80) gave isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) as a viscous yellow oil that solidified on standing in the freezer (5.9 g, 17.3 mmol, 97%); R_f: 0.29 (EtOAc:petroleum ether 40-60, 8:92); m.p.: 38.5–40.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.69 (s, 1H, NH), 8.55 (dd, *J* = 8.6, 1.1 Hz, 1H, C3H), 7.66 (ddd, *J* = 8.0, 1.6, 0.4 Hz, 1H, C6H), 7.63 (dddd, *J* = 8.6, 7.3, 1.6, 0.6 Hz, 1H, C2H), 7.44 – 7.40 (m, 2H, 2 × C14H), 7.40 – 7.36 (m, 2H, 2 × C15H), 7.36 – 7.32 (m, 1H, C16H), 7.10 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H, C1H), 5.32 (hept, *J* = 6.3 Hz, 1H, C9H), 5.23 (s, 2H, $C12H_2$), 1.41 (d, *J* = 6.3 Hz, 6H, 2 × $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.5 (C7), 163.4 (C8), 153.5 (C11), 143.1 (C4), 137.0 (C2H), 136.0 (C13), 133.6 (C6H), 128.7 (2 × C15H), 128.5 (C16H), 128.4 (2 × C14H), 121.9 (C1H), 119.4 (C3H), 117.0 (C5), 71.1 (C9H), 67.3 ($C12H_2$), 21.8 (2 × $C10H_3$); IR ν_{max} (cm^{-1}): 3295 (br), 3035, 2984, 2937, 1734, 1649, 1608, 1583, 1528; HRMS (ESI) $[M–H]^–$: calculated for $C_{19}H_{18}NO_5^–$ 340.1191, found 340.1192, Δ 0.37 ppm.

Isopropyl 2-(2-((methoxycarbonyl)amino)phenyl)-2-oxoacetate (3.6)



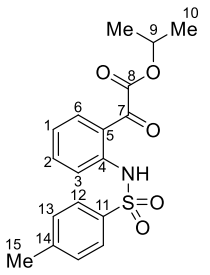
Methyl 2,3-dioxoindoline-1-carboxylate (**8.1**) (300 mg, 1.5 mmol, 1.0 equiv) was dissolved in 2-propanol (15 mL) and heated at reflux for 6.5 h. The solution was allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 20:80) to give isopropyl 2-(2-((methoxycarbonyl)amino)phenyl)-2-oxoacetate (**3.6**) as a pale yellow solid (335 mg, 1.3 mmol, 86%); R_f: 0.53 (Et_2O:petroleum ether 40-60, 30:70); m.p.: 56.5–58.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.62 (s, 1H, NH), 8.52 (dd, *J* = 8.6, 1.0 Hz, 1H, C3H), 7.68 – 7.59 (m, 2H, C2H, C6H), 7.09 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H, C1H), 5.32 (hept, *J* = 6.3 Hz, 1H, C9H), 3.80 (s, 3H, $C12H_3$), 1.41 (d, *J* = 6.3 Hz, 6H, 2 × $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.5 (C7), 163.5 (C8), 154.1 (C11), 143.2 (C4), 136.9 (C2H), 133.5 (C6H), 121.8 (C1H), 119.3 (C3H), 117.0 (C5), 71.1 (C9H), 52.7 ($C12H_3$), 21.8 (2 × $C10H_3$); IR ν_{max} (cm^{-1}): 3299 (br), 2985, 2956, 1735, 1650, 1608, 1583, 1528; HRMS (ESI) $[M+H]^+$: calculated for $C_{13}H_{16}NO_5^+$ 266.1023, found 266.1023, Δ –0.13 ppm.

Isopropyl 2-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-oxoacetate (3.7)



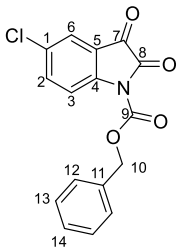
To isatin (**3.3**) (500 mg, 3.40 mmol, 1.0 equiv) in tetrahydrofuran (8 mL) at 0 °C was added 4-(dimethylamino)pyridine (42 mg, 0.34 mmol, 0.1 equiv) followed by dropwise di-*tert*-butyl dicarbonate (890 mg, 4.10 mmol, 1.2 equiv) in tetrahydrofuran (2 mL). The solution was stirred at room temperature for 4 h, and then the solvent was removed *in vacuo* to give a yellow solid that was used without further purification. To a portion of the product (200 mg, 0.77 mmol, 1.0 equiv) was added 2-propanol and the mixture heated at reflux for 7 h. The reaction was allowed to cool and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 10:90) to give isopropyl 2-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-oxoacetate (**3.7**) as a viscous yellow oil that solidified on standing in the freezer (206 mg, 0.67 mmol, 74% from isatin); R_f: 0.54 (Et_2O:petroleum ether 40-60, 10:90); m.p.: 57.5–58.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.43 (s, 1H, NH), 8.52 (dd, *J* = 8.6, 1.2 Hz, 1H, C3H), 7.64 (ddd, *J* = 8.0, 1.6, 0.5 Hz, 1H, C6H), 7.60 (dddd, *J* = 8.6, 7.2, 1.6, 0.6 Hz, 1H, C2H), 7.05 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H, C1H), 5.32 (hept, *J* = 6.3 Hz, 1H, C9H), 1.53 (s, 9H, 3 × C13H$_3$), 1.40 (d, *J* = 6.3 Hz, 6H, 2 × C10H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.5 (C7), 163.6 (C8), 152.8 (C11), 143.8 (C4), 136.9 (C2H), 133.5 (C6H), 121.3 (C1H), 119.3 (C3H), 116.8 (C5), 81.3 (C12), 71.0 (C9H), 28.4 (3 × C13H$_3$), 21.8 (2 × C10H$_3$); IR ν_{max} (cm^{-1}): 3305 (br), 2983, 2936, 1732, 1650, 1608, 1580, 1525; HRMS (ESI) [M+H]$^+$: calculated for $C_{16}H_{21}NNaO_5^+$ 330.1312, found 330.1311, Δ –0.37 ppm.

Isopropyl 2-(2-((4-methylphenyl)sulfonamido)phenyl)-2-oxoacetate (3.8)



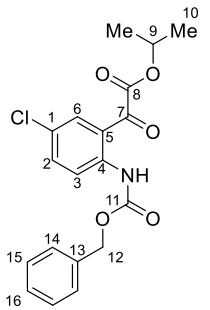
To 1-tosylindoline-2,3-dione (**8.2**) (260 mg, 0.90 mmol, 1.0 equiv) was added 2-propanol (6 mL) and tetrahydrofuran (6 mL), and then the solution was heated at reflux for 67 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 30:70) to give isopropyl 2-(2-((4-methylphenyl)sulfonamido)phenyl)-2-oxoacetate (**3.8**) as a pale yellow oil (265 mg, 0.73 mmol, 85%); R_f: 0.37 (Et_2O:petroleum ether 40-60, 30:70); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.78 (s, 1H, NH), 7.81 – 7.74 (m, 2H, 2 × C12H), 7.73 (ddd, *J* = 8.5, 1.1, 0.5 Hz, 1H, C3H), 7.61 (ddd, *J* = 8.0, 1.6, 0.5 Hz, 1H, C6H), 7.53 (dddd, *J* = 8.5, 7.4, 1.6, 0.6 Hz, 1H, C2H), 7.29 – 7.23 (m, 2H, 2 × C13H), 7.08 (ddd, *J* = 8.0, 7.3, 1.1 Hz, 1H, C1H), 5.29 (hept, *J* = 6.2 Hz, 1H, C9H), 2.38 (s, 3H, $C15H_3$), 1.39 (d, *J* = 6.3 Hz, 6H, 2 × $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.3 (C7), 162.9 (C8), 144.5 (C14), 141.9 (C4), 136.7 (C2H), 136.3 (C11H), 133.9 (C6H), 130.0 (2 × C13H), 127.5 (2 × C12H), 122.7 (C1H), 118.6 (C3H), 117.6 (C5), 71.4 (C9H), 21.8 (2 × $C10H_3$), 21.7 ($C15H_3$); IR ν_{max} (cm^{-1}): 3198 (br), 2985, 2937, 1732, 1649, 1605, 1576; HRMS (ESI) $[M+H]^+$: calculated for $C_{18}H_{20}NO_5S^+$ 362.1057, found 362.1060, Δ 0.88 ppm.

Benzyl 5-chloro-2,3-dioxoindoline-1-carboxylate (3.10)



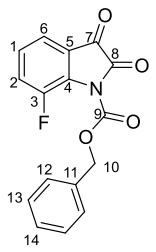
5-Chloroisatin (**3.9**) (420 mg, 2.3 mmol, 1.0 equiv), tetrahydrofuran (10 mL), triethylamine (0.38 mL, 2.8 mmol, 1.2 equiv), and benzyl chloroformate (95%) (0.41 mL, 2.8 mmol, 1.2 equiv) were subjected to **General Procedure C**, stirring for 90 min to give benzyl 5-chloro-2,3-dioxoindoline-1-carboxylate (**3.10**) as a yellow solid (673 mg, 2.13 mmol, 93%); R_f: 0.10 (MeOH:CH_2Cl_2, 10:90); m.p.: 168.0–170.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.01 (dd, J = 8.7, 0.6 Hz, 1H, C3H), 7.82 (dd, J = 8.7, 2.4 Hz, 1H, C2H), 7.79 (dd, J = 2.4, 0.5 Hz, 1H, C6H), 7.54 – 7.50 (m, 2H, 2 × C12H), 7.45 – 7.40 (m, 2H, 2 × C13H), 7.40 – 7.35 (m, 1H, C14H), 5.47 (s, 2H, $C10H_2$); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 178.4 (C7), 155.4 (C8), 149.8 (C9), 145.5 (C4), 136.7 (C2H), 135.2 (C11), 129.5 (C1), 128.5 (2 × C13H), 128.3 (C14H), 127.9 (2 × C12H), 123.8 (C6H), 121.2 (C5), 117.9 (C3H), 68.2 ($C10H_2$); IR ν_{max} (cm^{-1}): 3136, 3075, 3035, 1799, 1774, 1752, 1724, 1605, 1589; HRMS (ESI) $[M+Na]^+$: calculated for $C_{16}H_{10}{}^{35}ClNNaO_4^+$ 338.0191, found 338.0191, Δ 0.23 ppm.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-chlorophenyl)-2-oxoacetate (3.11)



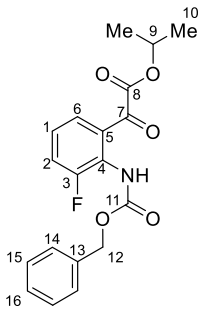
Benzyl 5-chloro-2,3-dioxoindoline-1-carboxylate (**3.10**) (600 mg, 1.9 mmol, 1.0 equiv) and 2-propanol (20 mL) were subjected to **General Procedure D**, heating for 7 h. Purification by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 10:90) gave isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-chlorophenyl)-2-oxoacetate (**3.11**) as a pale yellow solid (521 g, 1.4 mmol, 73%); R_f: 0.43 (Et_2O:petroleum ether 40-60, 10:90); m.p.: 87.0–88.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.58 (s, 1H, NH), 8.54 (d, *J* = 9.2 Hz, 1H, C3H), 7.66 (d, *J* = 2.5 Hz, 1H, C6H), 7.57 (dd, *J* = 9.2, 2.5 Hz, 1H, C2H), 7.44 – 7.32 (m, 5H, 2 × C14H, 2 × C15H, C16H), 5.33 (hept, *J* = 6.3 Hz, 1H, C9H), 5.22 (s, 2H, C12H_2), 1.42 (d, *J* = 6.2 Hz, 6H, 2 × C10H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 189.3 (C7), 162.7 (C8), 153.3 (C11), 141.6 (C4), 136.7 (C2H), 135.7 (C13), 132.7 (C6H), 128.8 (2 × C15H), 128.6 (C16H), 128.4 (2 × C14H), 127.0 (C1), 121.0 (C3H), 118.1 (C5), 71.6 (C9H), 67.5 (C12H_2), 21.8 (2 × C10H_3); IR ν_{max} (cm^{-1}): 3295 (br), 3066, 3035, 2986, 2938, 1735, 1661, 1579, 1516; HRMS (ESI) $[M+H]^+$: calculated for $C_{19}H_{19}{}^{35}ClNO_5^+$ 376.0946, found 376.0946, Δ –0.06 ppm.

Benzyl 7-fluoro-2,3-dioxoindoline-1-carboxylate (3.13)



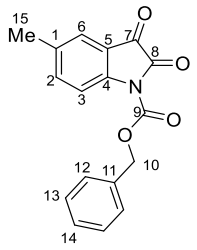
7-Fluoroisatin (**3.12**) (380 mg, 2.3 mmol, 1.0 equiv), tetrahydrofuran (10 mL), triethylamine (0.38 mL, 2.8 mmol, 1.2 equiv), and benzyl chloroformate (95%) (0.41 mL, 2.8 mmol, 1.2 equiv) were subjected to **General Procedure C**, stirring for 90 min to give benzyl 7-fluoro-2,3-dioxoindoline-1-carboxylate (**3.13**) as an orange solid (578 mg, 1.9 mmol, 84%); R_f: 0.07 (MeOH:CH_2Cl_2, 10:90); m.p.: 155.0–157.0 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.68 (ddd, *J* = 11.4, 8.3, 1.1 Hz, 1H, C2H), 7.59 (dd, *J* = 7.4, 1.1 Hz, 1H, C6H), 7.53 – 7.47 (m, 2H, 2 × C12H), 7.48 – 7.31 (m, 4H, C1H, 2 × C13H, C19H), 5.42 (s, 2H, C10H_2); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 178.8 (d, *J* = 3.1 Hz, C7), 156.1 (s, C8), 149.2 (d, *J* = 253.3 Hz, C3), 148.5 (s, C9), 135.0 (s, C11), 133.3 (d, *J* = 9.9 Hz, C4), 128.5 (s, 2 × C13H), 128.4 (s, C14H), 128.1 (s, 2 × C12H), 127.0 (d, *J* = 6.7 Hz, C1H), 125.5 (d, *J* = 21.1 Hz, C2H), 123.3 (d, *J* = 1.7 Hz, C5), 120.5 (d, *J* = 3.6 Hz, C6H), 68.8 (s, C10H_2); ^{19}F NMR (DMSO-d_6, 471 MHz): δ -116.2 (dd, *J* = 11.4, 4.2 Hz); IR ν_{max} (cm^{-1}): 3082, 3037, 2962, 1802, 1746, 1621; HRMS (ESI) $[M+Na]^+$: calculated for $C_{16}H_{10}FNNaO_4^+$ 322.0486, found 322.0487, Δ 0.31 ppm.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-3-fluorophenyl)-2-oxoacetate (3.14)



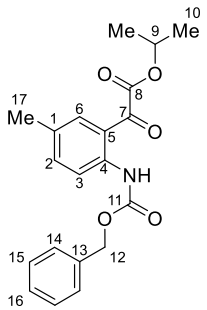
Benzyl 7-fluoro-2,3-dioxoindoline-1-carboxylate (**3.13**) (500 mg, 1.7 mmol, 1.0 equiv) and 2-propanol (18 mL) were subjected to **General Procedure D**, heating for 7 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90) gave isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-3-fluorophenyl)-2-oxoacetate (**3.14**) as a viscous orange oil (502 mg, 1.4 mmol, 84%); R_f: 0.47 (Et_2O:petroleum ether 40-60, 40:60); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (s, 1H, NH), 7.52 (dt, *J* = 7.9, 1.2 Hz, 1H, C6H), 7.42 – 7.30 (m, 6H, C2H, 2 × C14H, 2 ×C15H, C16H), 7.25 (td, *J* = 7.9, 4.8 Hz, 1H, C1H), 5.23 (hept, *J* = 6.3 Hz, 1H, C9H), 5.20 (s, 2H, C12H_2), 1.37 (d, *J* = 6.3 Hz, 6H, 2 × C10H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 186.4 (d, *J* = 2.9 Hz, C7), 162.1 (s, C8), 155.5 (d, *J* = 251.2 Hz, C3), 153.6 (s, C11), 135.6 (s, C13), 128.7 (s, 2 × C15H), 128.6 (s, C16H), 128.5 (s, 2 × C14H), 127.9 (d, *J* = 1.4 Hz, C5), 127.1 (d, *J* = 3.4 Hz, C6H), 126.7 (d, *J* = 12.8 Hz, C4), 125.7 (d, *J* = 8.1 Hz, C1H), 121.5 (d, *J* = 20.9 Hz, C2H), 71.3 (s, C9H), 68.2 (s, C12H_2), 21.7 (s, 2 × C10H_3); ^{19}F {^{1}H} NMR ($CDCl_3$, 471 MHz): δ -119.1; IR ν_{max} (cm^{-1}): 3331 (br), 3035, 2984, 2940, 1728, 1616, 1588, 1506; HRMS (ESI) $[M+H]^+$: calculated for $C_{19}H_{19}FNO_5^+$ 360.1248, found 360.12402, Δ –0.43 ppm.

Benzyl 5-methyl-2,3-dioxoindoline-1-carboxylate (3.16)



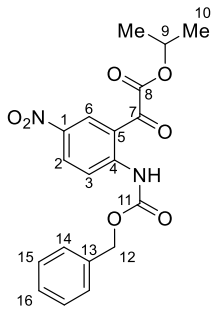
5-Methylindoline-2,3-dione (**3.15**) (371 mg, 2.3 mmol, 1.0 equiv), tetrahydrofuran (10 mL), triethylamine (0.38 mL, 2.8 mmol, 1.2 equiv), and benzyl chloroformate (95%) (0.41 mL, 2.8 mmol, 1.2 equiv) were subjected to **General Procedure C**, stirring for 90 min to give benzyl 5-methyl-2,3-dioxoindoline-1-carboxylate (**3.16**) as a brown solid (579 mg, 2.0 mmol, 85%); R_f: 0.10 (MeOH:CH_2Cl_2, 10:90); m.p.: 159.5–161.5 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.88 (dt, J = 8.3, 0.5 Hz, 1H, C3H), 7.58 (ddd, J = 8.4, 2.0, 0.8 Hz, 1H, C2H), 7.54 – 7.49 (m, 3H, C6H, 2 × C12H), 7.45 – 7.40 (m, 2H, 2 × C13H), 7.40 – 7.35 (m, 1H, C14H), 5.44 (s, 2H, $C10H_2$), 2.34 (t, J = 0.8 Hz, 3H, $C15H_3$); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 179.6 (C7), 156.0 (C8), 149.8 (C9), 145.1 (C4), 138.3 (C2H), 135.3 (C11), 134.7 (C1), 128.5 (2 × C13H), 128.3 (C14H), 127.9 (2 × C12H), 124.4 (C6H), 119.6 (C5), 116.0 (C3H), 68.0 ($C10H_2$), 20.1 ($C15H_3$); IR ν_{max} (cm^{-1}): 3063, 3032, 2952, 2925, 1784, 1723, 1655, 1620, 1527; HRMS (ESI) $[M+Na]^+$: calculated for $C_{17}H_{13}NNaO_4^+$ 318.0737, found 318.0739, Δ 0.64 ppm.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methylphenyl)-2-oxoacetate (3.17)



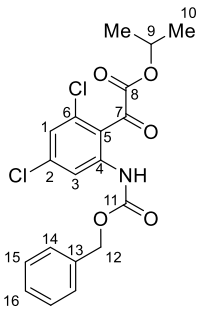
Benzyl 5-methyl-2,3-dioxoindoline-1-carboxylate (**3.16**) (500 mg, 1.7 mmol, 1.0 equiv) and 2-propanol (17 mL) were subjected to **General Procedure D**, heating for 23 h. Purification by column chromatography (SiO_2, eluent load, Et_2O:pentane, 15:85) gave isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methylphenyl)-2-oxoacetate (**3.17**) as a pale yellow solid (528 mg, 1.5 mmol, 88%); R_f: 0.48 (Et_2O:petroleum ether 40-60, 20:80); m.p.: 73.0–75.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.58 (s, 1H, NH), 8.43 (d, *J* = 8.5 Hz, 1H, C3H), 7.48 – 7.31 (m, 7H, C2H, C6H, 2 × C14H, 2 × C15H, C16H), 5.33 (hept, *J* = 6.3 Hz, 1H, C9H), 5.22 (s, 2H, $C12H_2$), 2.33 (t, *J* = 0.8 Hz, 3H, $C17H_3$), 1.41 (d, *J* = 6.3 Hz, 6H, 2 × $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.5 (C7), 163.5 (C8), 153.5 (C11), 140.8 (C4), 137.9 (C2H), 136.0 (C13), 133.4 (C6H), 131.4 (C1), 128.7 (2 × C15H), 128.4 (C16H), 128.3 (2 × C14H), 119.4 (C3H), 117.0 (C5), 71.0 (C9H), 67.2 ($C12H_2$), 21.8 (2 × $C10H_3$), 20.7 ($C17H_3$); IR ν_{max} (cm^{-1}): 3298 (br), 3034, 2983, 2939, 1733, 1651, 1586, 1524; HRMS (ESI) $[M+H]^+$: calculated for $C_{20}H_{22}NO_5^+$ 356.1493, found 356.1494, Δ 0.29 ppm.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-nitrophenyl)-2-oxoacetate (3.20)



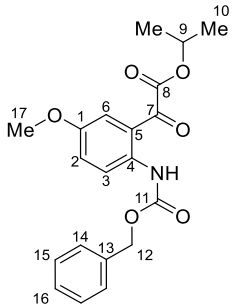
5-Nitroindoline-2,3-dione (**3.18**) (442 mg, 2.3 mmol, 1.0 equiv), tetrahydrofuran (10 mL), triethylamine (0.38 mL, 2.8 mmol, 1.2 equiv), and benzyl chloroformate (95%) (0.41 mL, 2.8 mmol, 1.2 equiv) were subjected to **General Procedure C**, stirring for 90 min to give a light brown solid (718 mg) that was used without further purification. The previous product (600 mg, 1.8 mmol, 1.0 equiv) and 2-propanol (18 mL) were subjected to **General Procedure D**, heating for 15 h. Purification by column chromatography (SiO_2, eluent load, Et_2O:pentane, 20:80) gave isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-nitrophenyl)-2-oxoacetate (**3.20**) as a pale yellow solid (517 mg, 1.3 mmol, 70% from 5-nitroindoline-2,3-dione (**3.18**)); R_f: 0.44 (Et_2O:petroleum ether 40-60, 20:80); m.p.: 130.5–132.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.96 (s, 1H, NH), 8.77 (d, *J* = 9.5 Hz, 1H, C3H), 8.68 (dd, *J* = 2.7, 0.5 Hz, 1H, C6H), 8.45 (ddd, *J* = 9.5, 2.6, 0.6 Hz, 1H, C2H), 7.46 – 7.32 (m, 5H, 2 × C14H, 2 × C15H, C16H), 5.39 (hept, *J* = 6.3 Hz, 1H, C9H), 5.27 (s, 2H, $C12H_2$), 1.45 (d, *J* = 6.3 Hz, 6H, 2 × $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 189.0 (C7), 162.1 (C8), 152.9 (C11), 148.0 (C4), 141.3 (C1), 135.2 (C13), 131.2 (C2H), 129.4 (C6H), 128.8 (2 × C15H), 128.6 (2 × C14H), 119.7 (C3H), 116.3 (C5), 72.2 (C9H), 68.2 ($C12H_2$), 21.8 (2 ×$C10H_3$); IR ν_{max} (cm^{-1}): 3273 (br), 2986, 2938, 1737, 1665, 1618, 1583, 1542, 1511; HRMS (ESI) $[M+Na]^+$: calculated for $C_{19}H_{18}N_2NaO_7^+$ 409.1006, found 409.1007, Δ 0.14 ppm.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-4,6-dichlorophenyl)-2-oxoacetate (3.23)



4,6-Dichloroindoline-2,3-dione (**3.21**) (497 mg, 2.3 mmol, 1.0 equiv), tetrahydrofuran (10 mL), triethylamine (0.38 mL, 2.8 mmol, 1.2 equiv), and benzyl chloroformate (95%) (0.41 mL, 2.8 mmol, 1.2 equiv) were subjected to **General Procedure C**, stirring for 90 min to give a brown solid (814 mg) that was used without further purification. The previous product (683 mg, 2.0 mmol, 1.0 equiv) and 2-propanol (20 mL) were subjected to **General Procedure D**, heating for 6 h. Purification by column chromatography (SiO_2, eluent load, Et_2O:pentane, 10:90) gave isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-4,6-dichlorophenyl)-2-oxoacetate (**3.23**) as an orange solid (426 mg, 1.0 mmol, 50% from 4,6-dichloroindoline-2,3-dione (**3.21**)); R_f: 0.41 (Et_2O:petroleum ether 40-60, 15:85); m.p.: 66.0–68.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.36 (s, 1H, NH), 8.42 (d, *J* = 1.9 Hz, 1H, C3H), 7.43 – 7.33 (m, 5H, 2 × C14H, 2 × C15H, C16H), 7.12 (d, *J* = 1.9 Hz, 1H, C1H), 5.21 (hept, *J* = 6.3 Hz, 1H, C9H), 5.20 (s, 2H, $C12H_2$), 1.36 (d, *J* = 6.3 Hz, 6H, 2 × $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.5 (C7), 162.2 (C8), 152.9 (C11), 142.6 (C4), 141.3 (C2), 135.9 (C6), 135.5 (C13), 128.8 (2 × C15H), 128.7 (C16H), 128.6 (2 × C14H), 124.3 (C1H), 119.0 (C3H), 118.5 (C5), 71.7 (C9H), 67.9 ($C12H_2$), 21.5 (2 × $C10H_3$); IR ν_{max} (cm^{-1}): 3340 (br), 3107, 3069, 3034, 2984, 2938, 1732, 1672, 1589, 1562, 1510; HRMS (ESI) $[M–H]^–$: calculated for $C_{19}H_{16}{}^{35}Cl_2NO_5^–$ 408.0411, found 408.0407, Δ –1.11 ppm.

Isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methoxyphenyl)-2-oxoacetate (3.25)

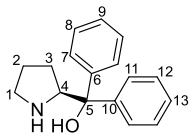


To a well-stirred suspension of sodium hydride (60% in mineral oil) (1.8 g, 45.2 mmol, 2.0 equiv) in tetrahydrofuran (90 mL) at 0 °C was added portionwise 5-methoxyindoline-2,3-dione (**1.35**) (4.0 g, 22.6 mmol, 1.0 equiv) over 5 min and the mixture stirred at room temperature for 35 min. To this was added dropwise benzyl chloroformate (95%) (4.0 mL, 27.1 mmol, 1.2 equiv) and the mixture stirred for 3.5 h. The reaction was cooled to 0 °C and hydrochloric acid (2 M) (50 mL) carefully added. The tetrahydrofuran was removed *in vacuo* then CH_2Cl_2 added and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (× 4) and the combined organic portions dried (Na_2SO_4) and concentrated *in vacuo* to give a dark brown solid that was used without further purification. To this was added 2-propanol (250 mL) and concentrated sulfuric acid (30 drops) then the mixture was heated at reflux for 61 h. Purification by column chromatography (SiO_2, eluent load, Et_2O:pentane, 20:80) gave isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methoxyphenyl)-2-oxoacetate (**3.25**) as a yellow solid (6.5 g, 17.6 mmol, 78% from 5-methoxyindoline-2,3-dione (**1.35**)); R_f: 0.33 (Et_2O:petroleum ether 40-60, 20:80); m.p.: 57.5–59.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.39 (s, 1H, NH), 8.46 (d, *J* = 9.3 Hz, 1H, C3H), 7.44 – 7.31 (m, 5H, 2 × C14H, 2 × C15H, C16H), 7.22 (ddd, *J* = 9.3, 3.0, 0.6 Hz, 1H, C2H), 7.15 (d, *J* = 3.0 Hz, 1H, C6H), 5.32 (hept, *J* = 6.2 Hz, 1H, C9H), 5.21 (s, 2H, C12H_2), 3.80 (s, 3H, C17H_3), 1.41 (d, *J* = 6.3 Hz, 6H, 2 × C10H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.0 (C7), 163.3 (C8), 154.0 (C1), 153.6 (C11), 136.7 (C4), 136.1 (C13), 128.7 (2 × C15H), 128.4 (C16H), 128.3 (2 × C14H), 123.7 (C2H), 121.1 (C3H), 117.8 (C5), 116.7 (C6H),

71.1 (C9H), 67.2 (C12H_2), 55.8 (C17H_3), 21.8 (2 × C10H_3); IR ν_{max} (cm^{-1}): 3307 (br), 3034, 2983, 2939, 2838, 1732, 1655, 1619, 1588, 1523; HRMS (ESI) $[M+Na]^+$: calculated for $C_{20}H_{21}NNaO_6^+$ 394.1261, found 394.1263, Δ 0.57 ppm.

(*S*)-Diphenyl(pyrrolidin-2-yl)methanol (4.4)

Prepared by procedures of Keller[134] and Boeckman[135].



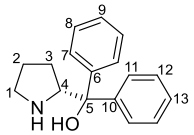
To sodium hydroxide (3.8 g, 95.5 mmol, 1.1 equiv) in water (95 mL) were added sequentially L-proline (**1.81**) (10.0 g, 86.9 mmol, 1.0 equiv), *tert*-butyl alcohol (65 mL). To this solution was added di-*tert*-butyl dicarbonate (19.0 g, 86.9 mmol, 1.0 equiv) over 20 min and the solution stirred at room temperature for 18 h. The reaction was extracted with pentane (× 2), and then the combined organic portions were extracted with sat. aq. sodium bicarbonate solution (× 3). The combined aqueous fractions were acidified to pH 1 with concentrated hydrochloric acid, and then this was extracted with diethyl ether (× 4). The combined ethereal portions were washed sequentially with water and brine, then were dried (Na_2SO_4) and concentrated *in vacuo* to yield a white powdery solid that was used without further purification. The product (14.3 g, 67.4 mmol, 1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (170 mL) and cooled to 0 °C. Potassium carbonate (10.2 g, 74.1 mmol, 1.1 equiv) was added and the mixture stirred at 0 °C for 15 min. To this was added iodomethane (9.2 mL, 148.0 mmol, 2.2 equiv) then the reaction was allowed to warm to room temperature and stirred for 24 h. Water (100 mL) was added and the reaction extracted with diethyl ether (× 4). The combined organic portions were washed sequentially with water (50 mL × 5) and brine, then were dried (Na_2SO_4) and

concentrated *in vacuo* to yield a yellow oil that was used without further purification. Phenylmagnesium bromide (2.7 M diethyl ether solution) (61 mL, 165.7 mmol, 2.5 equiv) and tetrahydrofuran (100 mL) were added to a flame-dried three-necked round-bottomed flask equipped with a Friedrich's condenser and a pressure-equalising dropping funnel. The previous product (15.2 g, 66.3 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (130 mL) and transferred to the dropping funnel. This solution was added dropwise to the Grignard reagent over 45 min then the reaction stirred for 4 h. The solution was cooled to 0 °C and sat. aq. ammonium chloride solution (100 mL) added *via* the dropping funnel over 5 min. Water (100 mL) was added and the layers separated. The aqueous portion was extracted with diethyl ether (100 mL × 3) and the combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale yellow solid that was used without further purification. The product (23.2 g, 65.6 mmol, 1.0 equiv) was dissolved in ethanol (350 mL). Sodium hydroxide (26.3 g, 656.0 mmol, 10.0 equiv) was added and the reaction heated at reflux for 105 min before being allowed to cool to room temperature. The reaction was concentrated *in vacuo* then water (130 mL) and diethyl ether (130 mL) added and the layers separated. The aqueous phase was extracted with diethyl ether (130 mL × 2) then the combined organic portions were washed sequentially with water (130 mL) and brine (130 mL). The organic fraction was then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in boiling hexane (130 mL), activated charcoal (1.6 g) added, and the mixture filtered onto boiling hexane (20 mL). The solution was allowed to cool to room temperature and was left until crystallisation occurred. The flask was cooled to 0 °C, the solvent decanted, and the crystals washed with ice cold hexane (20 mL × 3) and dried *in vacuo* to give (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**4.4**) as a white crystalline solid (8.9 g). The filtrate was concentrated *in vacuo*, dissolved in boiling hexane (50 mL), and cooled to yield a second batch of crystals (4.0 g) to give a combined yield

(12.9 g, 51.0 mmol, 59% from L-proline (**1.81**)); R_f: 0.06 (EtOAc); $[\alpha]_D^{25} = -68.7$ (*c* = 1.00, $CHCl_3$) (lit.[218] $[\alpha]_D^{25} = -68$ (*c* = 1.0, $CHCl_3$)); m.p.: 76.0–78.0 °C (lit.[218] 75.5–76.5 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 – 7.57 (m, 2H, 2 × C7H), 7.53 – 7.50 (m, 2H, 2 × C11H), 7.33 – 7.27 (m, 4H, 2 × C8H, 2 × C12H), 7.21 – 7.16 (m, 2H, C9H, C13H), 4.57 (br s, 1H, NH), 4.27 (t, *J* = 7.7 Hz, 1H, C4H), 3.04 (ddd, *J* = 9.3, 6.7, 4.9 Hz, 1H, C1H_AH$_B$), 2.95 (dt, *J* = 9.3, 7.5 Hz, 1H, C1H$_A$$H_B$), 1.81 – 1.54 (m, 5H, $C2H_2$, $C3H_2$, OH); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.3 (C6), 145.5 (C10), 128.3 (2 × C8H), 128.1 (2 × C12H), 126.6 (C9H), 126.4 (C13H), 126.0 (2 × C7H), 125.6 (2 × C11H), 77.2 (C5), 64.6 (C4H), 46.9 ($C1H_2$), 26.4 ($C3H_2$), 25.6 ($C2H_2$); IR ν_{max} (cm^{-1}): 3351 (br), 3085, 3058, 3026, 2969, 2946, 2871, 1598; data in accordance with literature.[135]

(*R*)-Diphenyl(pyrrolidin-2-yl)methanol (*ent*-4.4)

Prepared by procedures of Keller[134] and Boeckman.[135]

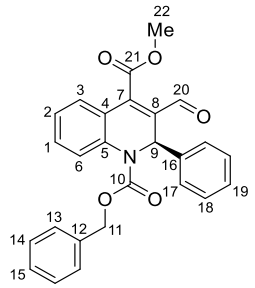


To sodium hydroxide (1.9 g, 47.8 mmol, 1.1 equiv) in water (47 mL) were added sequentially D-proline (*ent*-**1.81**) (5.0 g, 43.4 mmol, 1.0 equiv), *tert*-butyl alcohol (33 mL). To this solution was added di-*tert*-butyl dicarbonate (9.5 g, 43.4 mmol, 1.0 equiv) over 10 min and the solution stirred at room temperature for 17 h. The reaction was extracted with pentane (× 2), and then the combined organic portions were extracted with sat. aq. sodium bicarbonate solution (× 3). The combined aqueous fractions were acidified to pH 1 with concentrated hydrochloric acid, and then this was extracted with diethyl ether (× 4). The combined ethereal portions were washed sequentially with water and brine, then were dried (Na_2SO_4) and concentrated *in vacuo* to yield a white powdery solid that was used without further purification. The product

(8.1 g, 37.6 mmol, 1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (90 mL) and cooled to 0 °C. Potassium carbonate (5.7 g, 41.4 mmol, 1.1 equiv) was added and the mixture stirred at 0 °C for 20 min. To this was added iodomethane (5.2 mL, 82.8 mmol, 2.2 equiv) then the reaction was allowed to warm to room temperature and stirred for 18 h. Water (50 mL) was added and the reaction extracted with diethyl ether (× 5). The combined organic portions were washed sequentially with water (35 mL × 5) and brine, then were dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow oil that was used without further purification. Phenylmagnesium bromide (3.0 M diethyl ether solution) (30.1 mL, 91.6 mmol, 2.5 equiv) and tetrahydrofuran (60 mL) were added to a flame-dried three-necked round-bottomed flask equipped with a Friedrich's condenser and a pressure-equalising dropping funnel. The previous product (8.4 g, 36.6 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (75 mL) and transferred to the dropping funnel. This solution was added dropwise to the Grignard reagent over 40 min then the reaction stirred for 5 h. The solution was cooled to 0 °C and sat. aq. ammonium chloride solution (60 mL) added *via* the dropping funnel over 5 min. Water (60 mL) was added and the layers separated. The aqueous portion was extracted with diethyl ether (60 mL × 3) and the combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale yellow solid that was used without further purification. The product (13.1 g, 37.1 mmol, 1.0 equiv) was dissolved in ethanol (190 mL). Sodium hydroxide (14.8 g, 371.2 mmol, 10.0 equiv) was added and the reaction heated at reflux for 120 min before being allowed to cool to room temperature. The reaction was concentrated *in vacuo* then water (80 mL) and diethyl ether (80 mL) added and the layers separated. The aqueous phase was extracted with diethyl ether (80 mL × 2) then the combined organic portions were washed sequentially with water (80 mL) and brine (80 mL). The organic fraction was then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in boiling hexane (70 mL),

activated charcoal (0.8 g) added, and the mixture filtered onto boiling hexane (10 mL). The solution was allowed to cool to room temperature and was left until crystallisation occurred. The flask was cooled to 0 °C, the solvent decanted, and the crystals washed with ice cold hexane (10 mL × 3) and dried *in vacuo* to give (*R*)-diphenyl(pyrrolidin-2-yl)methanol (*ent*-**4.4**) as a white crystalline solid (5.2 g, 20.3 mmol, 47% from D-proline); $[\alpha]_{\mathrm{D}}^{25} = +71.0$ (*c* = 1.00, $CHCl_3$) (lit.[136] $[\alpha]_{\mathrm{D}}^{25} = +73.8$ (*c* = 3.37, $CHCl_3$)); m.p.: 76.0–78.0 °C (lit.[136] 76–77 °C); all other characterisation identical to **4.4**.

1-Benzyl 4-methyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.6)



(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and methyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.1**) (94.0 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 24 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 15:85) gave 1-benzyl 4-methyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.6**) as a viscous yellow oil (54.0 mg, 0.13 mmol, 84%); R_f: 0.36 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_{\mathrm{D}}^{25} = -487.7$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 13.30 min, t_R (major) = 17.38 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.85 (s, 1H, C20H), 7.67 (br s, 1H, C6H), 7.43 – 7.32 (m, 7H, C1H, C3H, 2 × C13H, 2 × C14H, C15H), 7.19 – 7.11 (m, 6H, C2H, 2 × C17H, 2 × C18H, C19H), 6.83 (s, 1H, C9H), 5.33

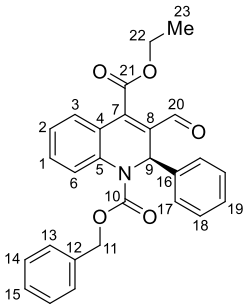
(d, *J* = 12.3 Hz, 1H, C11$H_A$$H_B$), 5.32 (d, *J* = 12.3 Hz, 1H, C11$H_A$$H_B$), 4.02 (s, 3H, C22$H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9 (C20H), 166.1 (C21), 153.7 (C10), 142.7 (C7), 137.5 (C16), 136.9 (C5), 135.6 (C12), 134.6 (C8), 132.2 (C1H), 128.8 (2 × C14H), 128.7 (2 × C18H), 128.6 (C15H), 128.4 (C19H), 128.3 (2 ×C13H), 127.0 (2 × C17H), 126.7 (C3H), 125.4 (C6H), 124.9 (C2H), 123.4 (C4), 68.7 (C11H_2), 53.2 (C22H_3), 52.1 (C9H); IR ν_{max} (cm^{-1}): 3064, 3034, 2952, 1778, 1708, 1674, 1619, 1600, 1567; HRMS (ESI) $[M+Na]^+$: calculated for $C_{26}H_{21}NNaO_5^+$ 450.1312, found 450.1310, Δ –0.54 ppm.

A sample of the enantiomer, 1-benzyl 4-methyl (*S*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (**4.6**) (56.3 mg, 0.13 mmol, 88%) was prepared as above using (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**), stirring for 28 h; $[\alpha]_D^{25} = +455.8$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 $mL.min^{-1}$; λ = 254 nm): t_R (major) = 13.31 min, t_R (minor) = 17.50 min; all other characterisation identical.

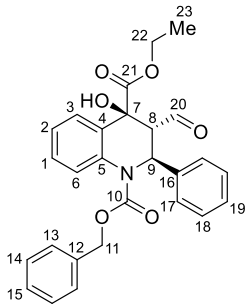
1-Benzyl 4-ethyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.8)

and

1-Benzyl 4-ethyl (2*S*,3*R*,4*S*)-3-formyl-4-hydroxy-2-phenyl-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-4.9)



ent-**4.8**



ent-**4.9**

(*S*)-2-(Diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (11.0 mg, 0.03 mmol, 0.2 equiv), (*E*)-cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv), and ethyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.4**) (139.0 mg, 0.42 mmol, 2.8 equiv) were subjected to **General Procedure A**, stirring at room temperature for 69 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 30:70) gave 1-benzyl 4-ethyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.8**), as a viscous yellow oil (12.3 mg, 0.04 mmol, 25%) and 1-benzyl 4-ethyl (2S,3R,4S)-3-formyl-4-hydroxy-2-phenyl-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-**4.9**) as a viscous yellow oil (4.7 mg, 0.01 mmol, 7%); *ent*-**4.8**: R_f: 0.55 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = -383.9$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.88 (s, 1H, C20H), 7.67 (br s, 1H, C6H), 7.45 – 7.24 (m, 7H, C1H, C3H, 2 × C13H, 2 × C14H, C15H), 7.26 – 7.10 (m, 6H, C2H, 2 × C17H, 2 × C18H, C19H), 6.82 (s, 1H, C9H), 5.33 (d, *J* = 11.8 Hz, 1H, C11H_AH$_B$), 5.32 (d, *J* = 11.8 Hz, 1H, C11H$_A$$H_B$), 4.51 (qd, *J* = 7.2, 1.6 Hz, 2H, C22H$_2$), 1.43 (t, *J* = 7.2 Hz, 3H, C23H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9 (C20H), 165.7 (C21), 153.7 (C10), 143.1 (C7), 137.5 (C16), 136.9 (C5), 135.7 (C12), 134.3 (C8), 132.1 (C1H), 128.8 (2 × C14H or

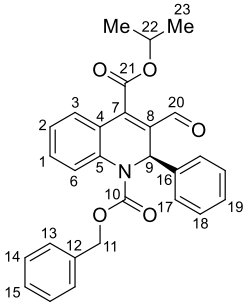
2 × C18H), 128.7 (2 × C14H or 2 × C18H), 128.6 (C15H or C19H), 128.4 (2 × C13H), 128.3 (C15H or C19H), 127.1 (2 × C17H), 126.7 (C3H), 125.4 (C6H), 124.9 (C2H), 123.5 (C4), 68.6 ($C11H_2$), 62.8 ($C22H_2$), 52.1 (C9H), 14.4 ($C23H_3$); IR ν_{max} (cm^{-1}): 3064, 3033, 2960, 2927, 2854, 1772,1709, 1675, 1621, 1600, 1568; HRMS (ESI) $[M+Na]^+$: calculated for $C_{27}H_{23}NNaO_5^+$ 464.1468, found 464.1468, Δ –0.18 ppm; *ent*-**4.9**: R_f: 0.52 (EtOAc:petroleum ether 40-60, 30:70); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.82 (d, *J* = 0.7 Hz, 1H, C20H), 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H, C3H), 7.57 (br d, *J* = 8.2 Hz, 1H, C6H), 7.39 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H, C1H), 7.33 – 7.22 (m, 7H, C2H, 2 × C14H, C15H, 2 × C18H, C19H), 7.23 – 7.11 (m, 4H, 2 × C13H, 2 × C17H), 5.76 (d, *J* = 10.1 Hz, 1H, C9H), 5.14 (s, 2H, $C11H_2$), 4.53 (br s, 1H, OH), 4.15 (dq, *J* = 10.8, 7.2 Hz, 1H, C22H_AH$_B$), 3.92 (dq, *J* = 10.7, 7.1 Hz, 1H, C22H$_A$$H_B$), 3.37 (dd, *J* = 10.1, 0.6 Hz, 1H, C8H), 1.08 (t, *J* = 7.1 Hz, 3H, $C23H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 199.9 (C20H), 172.5 (C21), 154.4 (C10), 142.6 (C16), 136.6 (C5), 136.0 (C12), 131.9 (C4), 129.0 (C1H, 2 × C14H or 2 × C18H), 128.6 (2 × C14H or 2 × C18H), 128.3 (C15H or C19H), 128.2 (2 × C13H), 127.9 (C15H or C19H), 127.0 (2 × C17H), 126.2 (C6H), 125.3 (C2H), 124.3 (C3H), 74.6 (C7), 68.0 ($C11H_2$), 65.2 (C8H), 63.6 ($C22H_2$), 55.9 (C9H), 13.8 ($C23H_3$); IR ν_{max} (cm^{-1}): 3437 (br), 3065, 3033, 2981, 2935, 2853, 1707, 1603, 1587, 1528; HRMS (ESI) $[M–H]^–$: calculated for $C_{27}H_{24}NO_6^–$ 458.1609, found 458.1606, Δ –0.71 ppm.

A racemic sample of 1-benzyl 4-ethyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.8**) was prepared as above using pyrrolidine (3.0 µL, 0.03 mmol, 0.2 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

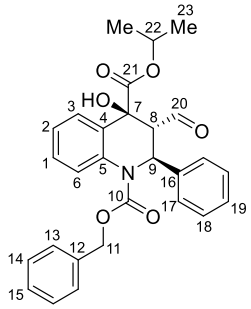
1-Benzyl 4-isopropyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.10)

and

1-Benzyl 4-isopropyl (2*S*,3*R*,4*S*)-3-formyl-4-hydroxy-2-phenyl-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-4.11)



ent-**4.10**



ent-**4.11**

(*S*)-2-(Diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (11.0 mg, 0.03 mmol, 0.2 equiv), (*E*)-cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv), and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (153.6 mg, 0.45 mmol, 3.0 equiv) were subjected to **General Procedure A**, stirring at room temperature for 137 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 20:80) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.10**), as a yellow solid (5.7 mg, 0.01 mmol, 8%) and 1-benzyl 4-isopropyl (2S,3R,4S)-3-formyl-4-hydroxy-2-phenyl-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-**4.11**) as a viscous yellow oil (7.0 mg, 0.01 mmol, 10%); *ent*-**4.10**: R_f: 0.29 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -456.2$ (*c* = 1.00, $CHCl_3$); m.p.: 130.5–132.5 °C; ee: 99% (Chiralcel OD; hexane:2-propanol, 90:10; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 14.80 min, t_R (minor) = 16.29 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.89 (s, 1H, C20H), 7.67 (br s, 1H, C6H), 7.43 – 7.32 (m, 7H, C1H, C3H, 2 × C13H, 2 × C14H, C15H), 7.22 – 7.12 (m, 6H, C2H, 2 × C17H, 2 × C18H, C19H), 6.82 (s, 1H, C9H), 5.42 (h, *J* = 6.3 Hz, 1H, C22H), 5.32 (d, *J* = 12.3 Hz, 1H, C11H_AH$_B$), 5.32 (d, *J* = 12.4 Hz, 1H, C11H$_A$$H_B$), 1.43 (d, *J* = 6.2 Hz, 3H, C23$_A$H$_3$), 1.41 (d, *J* = 6.3 Hz,

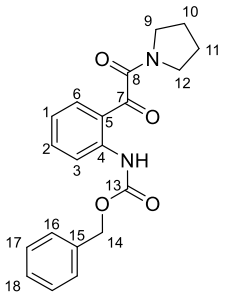
3H, C23$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9 (C20H), 165.2 (C21), 153.7 (C10), 143.5 (C7), 137.6 (C16), 137.0 (C5), 135.7 (C12), 133.9 (C8), 132.0 (C1H), 128.8 (2 × C14H), 128.7 (2 × C18H), 128.6 (C15H), 128.4 (2 × C13H), 128.3 (C19H), 127.1 (2 × C17H), 126.5 (C3H), 125.4 (C6H), 124.8 (C2H), 123.6 (C4), 71.2 (C22H), 68.6 (C11H$_2$), 52.1 (C9H), 22.1 (C23$_A$H$_3$), 22.0 (C23$_B$H$_3$); IR ν_{max} (cm^{-1}): 3034, 2983, 1710, 1674, 1619, 1600, 1567; HRMS (ESI) [M+Na]$^+$: calculated for $C_{28}H_{25}NNaO_5^+$ 478.1625, found 478.1622, Δ –0.61 ppm; ent-**4.11**: R_f: 0.14 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -41.0$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.82 (d, *J* = 0.6 Hz, 1H, C20H), 7.68 (dd, *J* = 7.8, 1.6 Hz, 1H, C3H), 7.57 (br d, *J* = 8.1 Hz, 1H, C6H), 7.38 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1H, C1H), 7.31 – 7.24 (m, 7H, C2H, 2 × C14H, C15H, 2 × C18H, C19H), 7.22 – 7.16 (m, 4H, 2 × C13H, 2 × C17H), 5.76 (d, *J* = 10.1 Hz, 1H, C9H), 5.13 (d, *J* = 12.4 Hz, 1H, C11*H$_A$*H$_B$), 5.13 (d, *J* = 12.3 Hz, 1H, C11H$_A$*H$_B$*), 5.00 (hept, *J* = 6.3 Hz, 1H, C22H), 4.55 (s, 1H, OH), 3.37 (dd, *J* = 10.1, 0.6 Hz, 1H, C8H), 1.20 (d, *J* = 6.2 Hz, 3H, C23$_A$H$_3$), 1.02 (d, *J* = 6.3 Hz, 3H, C23$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 199.7 (C20H), 172.2 (C21), 154.3 (C10), 142.8 (C16), 136.6 (C5), 135.8 (C12), 131.8 (C4), 128.9 (2 × C14H or 2 × C18H), 128.9 (C1H), 128.6 (2 × C14H or 2 × C18H), 128.3 (C15H), 128.1 (2 × C13H), 127.9 (C19H), 127.0 (2 × C17H), 126.0 (C6H), 125.2 (C2H), 124.3 (C3H), 74.4 (C7), 71.9 (C22H), 68.0 (C11H$_2$), 65.1 (C8H), 55.9 (C9H), 21.5 (C23$_A$H$_3$), 21.2 (C23$_B$H$_3$); IR ν_{max} (cm^{-1}): 3468 (br), 3033, 2984, 1708, 1603, 1586; HRMS (N_2 APCI) [M+H]$^+$: calculated for $C_{28}H_{28}NO_6^+$ 474.1911, found 474.1911, Δ –0.03 ppm.

Using optimised cyclisation conditions to prepare a sample of the enantiomer: To (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**) (221 mg, 0.6 mmol, 0.2 equiv) in CH_2Cl_2 (6.0 mL) were added sequentially (*E*)-cinnamaldehyde (**1.101**) (0.38 mL, 3.0 mmol, 1.0 equiv), benzoic acid (183 mg, 1.5 mmol, 0.5 equiv), freshly activated 4 Å molecular sieves

(beads) (1.0 g), and then isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (2.05 g, 6.0 mmol, 2.0 equiv), then the mixture stirred at room temperature for 71 h. The reaction was filtered with ethyl acetate, and then washed sequentially with sat. aq. sodium bicarbonate solution, hydrochloric acid (2 M), and brine. The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 15:85) gave 1-benzyl 4-isopropyl (*S*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (**4.10**) as a yellow solid (1.25 g, 2.7 mmol, 92%); $[\alpha]_{\mathrm{D}}^{25} = +487.9$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel OD; hexane:2-propanol, 90:10; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 13.17 min, t_R (major) = 14.82 min; all other characterisation identical.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.10**) was prepared as above using pyrrolidine (3.0 µL, 0.03 mmol, 0.2 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

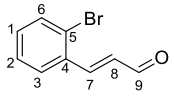
Benzyl (2-(2-oxo-2-(pyrrolidin-1-yl)acetyl)phenyl)carbamate (4.12)



Pyrrolidine (3.0 µL, 0.03 mmol, 0.2 equiv), (*E*)-cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv), and methyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.1**) (141 mg, 0.45 mmol, 3.0 equiv) were subjected to **General Procedure A**, stirring at room temperature for 65 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether

40-60, 40:60) gave benzyl (2-(2-oxo-2-(pyrrolidin-1-yl)acetyl)phenyl)carbamate (**4.12**) as a pale yellow solid (9.1 mg, 0.03 mmol, 86% with respect to pyrrolidine); R_f: 0.39 (EtOAc:petroleum ether 40-60, 60:40); m.p.: 134.5–136.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.85 (s, 1H, NH), 8.54 (dd, *J* = 8.6, 1.0 Hz, 1H, C3H), 7.70 (dd, *J* = 8.0, 1.6 Hz, 1H, C6H), 7.61 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H, C2H), 7.45 – 7.42 (m, 2H, 2 × C16H), 7.41 – 7.37 (m, 2H, 2 × C17H), 7.36 – 7.32 (m, 1H, C18H), 7.08 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H, C1H), 5.24 (s, 2H, $C14H_2$), 3.65 (t, *J* = 6.7 Hz, 2H, $C9H_2$), 3.37 (t, *J* = 6.5 Hz, 2H, $C12H_2$), 2.01 – 1.91 (m, 4H, $C10H_2$, $C11H_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 195.5 (C7), 164.4 (C8), 153.6 (C13), 143.1 (C4), 136.7 (C2H), 136.0 (C15), 133.8 (C6H), 128.7 (2 × C17H), 128.5 (C18H), 128.5 (2 × C16H), 122.1 (C1H), 119.3 (C3H), 117.5 (C5), 67.3 ($C14H_2$), 46.8 ($C12H_2$), 45.4 ($C9H_2$), 26.0 ($C11H_2$), 24.2 ($C10H_2$); IR ν_{max} (cm^{-1}): 3282 (br), 2955, 2881, 1737, 1639, 1607, 1584, 1529; HRMS (ESI) $[M+Na]^+$: calculated for $C_{20}H_{20}N_2NaO_4^+$ 375.1315, found 375.1314, Δ –0.48 ppm.

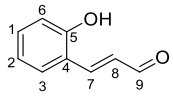
(*E*)-3-(2-Bromophenyl)acrylaldehyde (4.15)



To (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**4.14**) (17.3 g, 40.0 mmol, 2.0 equiv) in tetrahydrofuran (120 mL) at 0 °C was added in one portion potassium *tert*-butoxide (2.5 g, 22.0 mmol, 1.1 equiv) and the mixture stirred at room temperature for 15 min. To this was added 2-bromobenzaldehyde (**4.13**) (2.3 mL, 20.0 mmol, 1.0 equiv) in tetrahydrofuran (30 mL). The reaction was heated to reflux and stirred for 26 h before being allowed to cool to room temperature and hydrochloric acid (2 M) (130 mL) added. This was stirred at room temperature for a further 16 h and then extracted with ethyl acetate (× 3). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and

concentrated *in vacuo*. The residue was filtered through a short plug of silica, eluting with EtOAc/petroleum ether 40-60, 20:80. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 2:98 to 8:92) gave (*E*)-3-(2-bromophenyl)acrylaldehyde (**4.15**) as a white solid (1.0 g, 4.6 mmol, 23%); R_f: 0.28 (EtOAc:petroleum ether 40-60, 5:95); m.p.: 65.0–67.0 °C (lit.[219] 67–69°C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.77 (d, *J* = 7.7 Hz, 1H, C9H), 7.90 (d, *J* = 15.9 Hz, 1H, C7H), 7.67 – 7.64 (m, 2H, C3H, C6H), 7.37 (tdd, *J* = 7.9, 1.3, 0.6 Hz, 1H, C2H), 7.29 (ddd, *J* = 9.1, 7.4, 1.6 Hz, 1H, C1H), 6.67 (dd, *J* = 15.9, 7.7 Hz, 1H, C8H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 193.6 (C9H), 150.7 (C7H), 134.0 (C4), 133.8 (C6H), 132.3 (C1H), 130.9 (C8H), 128.2 (C3H), 128.1 (C2H), 125.9 (C5); IR ν_{max} (cm^{-1}): 2810, 2737, 2697, 1681, 1619, 1587, 1560; HRMS (ESI) $[M+H]^+$: calculated for $C_9H_8{}^{79}BrO^+$ 210.9753, found 210.9754, Δ 0.47 ppm; data in accordance with literature.[219]

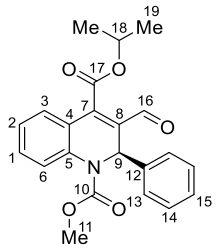
(*E*)-3-(2-Hydroxyphenyl)acrylaldehyde (4.17)



To (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**4.14**) (1.0 g, 2.4 mmol, 1.2 equiv) in tetrahydrofuran (10 mL) at 0 °C was added in one portion potassium *tert*-butoxide (0.5 g, 4.4 mmol, 2.2 equiv) and the mixture stirred at room temperature for 15 min. To this was added salicylaldehyde (**4.16**) (0.21 mL, 2.0 mmol, 1.0 equiv) in tetrahydrofuran (6 mL). The reaction was heated to reflux and stirred for 22 h before being allowed to cool to room temperature and hydrochloric acid (2 M) (30 mL) added. This was stirred at room temperature for a further 30 min and then extracted with ethyl acetate (× 3). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load,

EtOAc:petroleum ether 40-60, 20:80) gave (*E*)-3-(2-hydroxyphenyl)acrylaldehyde (**4.17**) as a yellow solid (0.1 g, 0.7 mmol, 34%); R_f: 0.43 (EtOAc:petroleum ether 40-60, 30:70); m.p.: 124.0–126.0 °C (lit.[220] 122–123 °C); ^{1}H NMR (acetone-d_6, 500 MHz): δ 9.70 (d, *J* = 7.8 Hz, 1H, C9H), 9.30 (s, 1H, OH), 7.90 (d, *J* = 16.1 Hz, 1H, C7H), 7.65 (ddt, *J* = 7.8, 1.7, 0.6 Hz, 1H, C3H), 7.31 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 2H, C1H), 7.00 (dd, *J* = 8.1, 1.1 Hz, 1H, C6H), 6.93 (dddd, *J* = 7.8, 7.2, 1.2, 0.5 Hz, 1H, C2H), 6.86 (dd, *J* = 16.1, 7.7 Hz, 1H, C8H); ^{13}C NMR (acetone-d_6, 126 MHz): δ 194.7 (C9H), 157.5 (C5), 149.0 (C7H), 133.3 (C1H), 130.1 (C3H), 129.6 (C8H), 122.2 (C4), 121.0 (C2H), 117.1 (C6H); IR ν_{max} (cm^{-1}): 3179 (br), 2948, 2862, 2824, 2751, 1655, 1614, 1601, 1500; HRMS (ESI) [M+H]$^+$: calculated for $C_9H_9O_2^+$ 149.0597, found 149.0597, Δ 0.01 ppm; data in accordance with literature.[220]

4-Isopropyl 1-methyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.20)

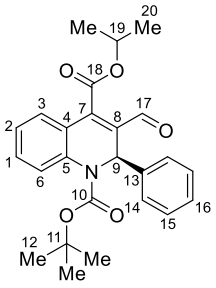


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-((methoxycarbonyl)amino)phenyl)-2-oxoacetate (**3.6**) (79.6 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 49 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 15:85) gave 4-isopropyl 1-methyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.20**) as a yellow solid (46.4 mg, 0.12 mmol, 82%); R_f: 0.24 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -518.7$ (*c* = 1.00, $CHCl_3$); m.p.: 111.0–113.0 °C; ee: 99% (Chiralcel OD; hexane: 2-propanol, 98:2; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 23.49 min,

t_R (minor) = 26.31 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.89 (s, 1H, C16H), 7.66 (br s, 1H, C6H), 7.39 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1H, C1H), 7.37 (ddd, *J* = 7.9, 1.5, 0.5 Hz, 1H, C3H), 7.22 – 7.12 (m, 6H, C2H, 2 × C13H, 2 × C14H, C15H), 6.77 (s, 1H, C9H), 5.42 (hept, *J* = 6.3 Hz, 1H, C18H), 3.88 (s, 3H, $C11H_3$), 1.43 (d, *J* = 6.3 Hz, 3H, $C19_AH_3$), 1.41 (d, *J* = 6.3 Hz, 3H, $C19_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.0 (C16H), 165.2 (C17), 154.4 (C10), 143.5 (C7), 137.6 (C12), 137.0 (C5), 134.0 (C8), 132.1 (C1H), 128.7 (2 × C14H), 128.3 (C15H), 127.0 (2 × C13H), 126.5 (C3H), 125.4 (C6H), 124.8 (C2H), 123.6 (C4), 71.2 (C18H), 53.8 ($C11H_3$), 52.0 (C9H), 22.1 ($C19_AH_3$), 22.0 ($C19_BH_3$); IR ν_{max} (cm^{-1}): 3065, 3034, 2983, 2957,2850, 1717, 1676, 1620, 1601, 1567; HRMS (ESI) $[M+Na]^+$: calculated for $C_{22}H_{21}NNaO_5^+$ 402.1312, found 402.1311, Δ –0.3 ppm.

A racemic sample of 4-isopropyl 1-methyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.20**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-(*tert*-Butyl) 4-isopropyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.21)

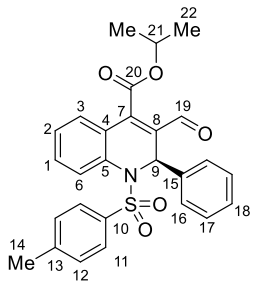


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-((*tert*-butoxycarbonyl)amino)phenyl)-2-oxoacetate (**3.7**) (92.2 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 121 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 15:85) gave 1-(*tert*-butyl) 4-isopropyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate

(*ent*-**4.21**) as a viscous yellow oil (43.9 mg, 0.10 mmol, 69%); R_f: 0.45 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -449.9$ (*c* = 1.00, $CHCl_3$); ee: 99% (Chiralcel OD; hexane:2-propanol, 99:1; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 14.73 min, t_R (minor) = 17.13 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.89 (s, 1H, C17H), 7.67 (br d, *J* = 8.2 Hz, 1H, C6H), 7.36 (dd, *J* = 7.8, 1.6 Hz, 1H, C3H), 7.36 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H, C1H), 7.22 – 7.14 (m, 5H, 2 × C14H, 2 × C15H, C16H), 7.11 (ddd, *J* = 8.5, 7.2, 1.1 Hz, 1H, C2H), 6.72 (s, 1H, C9H), 5.43 (hept, *J* = 6.3 Hz, 1H, C19H), 1.57 (s, 9H, 3 × C12H_3), 1.44 (d, *J* = 6.3 Hz, 3H, C20$_A$$H_3$), 1.42 (d, *J* = 6.3 Hz, 3H, C20$_B$$H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.0 (C17H), 165.5 (C18), 152.6 (C10), 143.5 (C7), 138.2 (C13), 137.6 (C5), 133.9 (C8), 131.8 (C1H), 128.6 (2 × C15H), 128.2 (C16H), 127.0 (2 × C14H), 126.4 (C3H), 125.5 (C6H), 124.3 (C2H), 123.5 (C4), 82.8 (C11), 71.1 (C19H), 51.7 (C9H), 28.5 (3 × C12H_3), 22.1 (C20$_A$$H_3$), 22.0 (C20$_B$$H_3$); IR ν_{max} (cm^{-1}): 3064, 3033, 2980, 2935, 2877, 1703, 1674, 1618, 1600, 1566; HRMS (ESI) [M+Na]$^+$: calculated for $C_{25}H_{27}NNaO_5^+$ 444.1781, found 444.1778, Δ –0.79 ppm.

A racemic sample of 1-(*tert*-butyl) 4-isopropyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.21**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

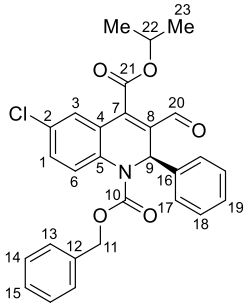
Isopropyl (*R*)-3-formyl-2-phenyl-1-tosyl-1,2-dihydroquinoline-4-carboxylate (*ent*-4.22)



(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-((4-methylphenyl)sulfonamido)phenyl)-2-oxoacetate (**3.8**) (108.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 24 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 15:85) gave an inseparable mixture of isopropyl (*R*)-3-formyl-2-phenyl-1-tosyl-1,2-dihydroquinoline-4-carboxylate (*ent*-**4.22**) and isopropyl 2-(2-((4-methylphenyl)sulfonamido)phenyl)-2-oxoacetate (**3.8**) as a yellow semi-solid (81:19 ratio by NMR) (NMR yield of desired product: 56.7 mg, 0.12 mmol, 79%); R_f: 0.29 (EtOAc:petroleum ether 40-60, 15:85); ee: 70% (Chiralcel OD; hexane:2-propanol, 95:5; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 16.89 min, t_R (minor) = 18.97 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.54 (s, 1H, C19H), 7.77 (dt, *J* = 8.0, 0.8 Hz, 1H, C6H), 7.44 (ddd, *J* = 8.2, 5.8, 3.2 Hz, 1H, C1H), 7.33 – 7.27 (m, 2H, 2 × C11H), 7.29 – 7.23 (m, 2H, C2H, C3H), 7.24 – 7.15 (m, 5H, 2 × C16H, 2 × C17H, C18H), 7.15 – 7.09 (m, 2H, 2 × C12H), 6.54 (s, 1H, C9H), 5.25 (hept, *J* = 6.4 Hz, 1H, C21H), 2.36 (s, 3H, $C14H_3$), 1.31 (d, *J* = 6.3 Hz, 6H, 2 × $C22H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.8 (C19H), 164.3 (C20), 144.0 (C13), 143.0 (C7), 136.2 (C15), 135.7 (C10), 135.2 (C5), 132.8 (C8), 132.4 (C1H), 129.8 (2 × C12H), 129.0 (C6H), 128.6 (2 × C17H), 128.4 (C18H), 127.2 (2 × C16H), 127.1 (C2H), 126.9 (2 × C11H), 126.6 (C3H), 125.1 (C4), 70.7 (C21H), 53.3 (C9H), 22.0 ($C22_AH_3$), 21.9 ($C22_BH_3$), 21.8 ($C14H_3$); IR ν_{max} (cm^{-1}): 3064, 3033, 2987, 2935, 1724, 1673, 1598, 1566; HRMS (ESI) $[M+Na]^+$: calculated for $C_{27}H_{25}NNaO_5S^+$ 498.1346, found 498.1346, Δ 0.04 ppm.

A racemic sample of 4-isopropyl 1-methyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.22**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-6-chloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.23)

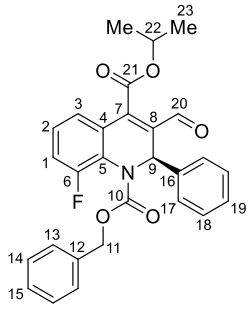


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-chlorophenyl)-2-oxoacetate (**3.11**) (112.7 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 47 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 10:90) gave 1-benzyl 4-isopropyl (*R*)-6-chloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.23**) as a viscous yellow oil (67.3 mg, 0.14 mmol, 92%); R_f: 0.43 (EtOAc:petroleum ether 40-60, 10:90); $[\alpha]_D^{25} = -402.0$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel OD; hexane:2-propanol, 98.4:1.6; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 30.29 min, t_R (minor) = 34.60 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.91 (s, 1H, C20H), 7.62 (br s, 1H, C6H), 7.43 – 7.28 (m, 7H, C3H, C1H, 2 × C13H, 2 × C14H, C15H), 7.24 – 7.16 (m, 3H, 2 × C18H, C19H), 7.14 – 7.09 (m, 2H, 2 × C17H), 6.81 (s, 1H, C9H), 5.43 (hept, *J* = 6.3 Hz, 1H, C22H), 5.31 (s, 2H, $C11H_2$), 1.44 (d, *J* = 6.3 Hz, 3H, $C23_AH_3$), 1.42 (d, *J* = 6.3 Hz, 3H, $C23_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.8 (C20H), 164.6 (C21), 153.5 (C10), 141.9 (C7), 137.1 (C16), 135.4 (C12), 135.4

(C5), 135.1 (C8), 131.7 (C1H), 130.2 (C2), 128.8 (2 × C14H or 2 × C18H), 128.8 (2 × C14H or 2 × C18H), 128.7 (C15H), 128.6 (C19H), 128.4 (2 × C13H), 127.0 (2 × C17H), 126.6 (C6H), 126.2 (C3H), 125.0 (C4), 71.6 (C22H), 68.9 ($C11H_2$), 52.2 (C9H), 22.1 ($C23_AH_3$), 22.0 ($C23_BH_3$); IR ν_{max} (cm^{-1}): 3065, 3034, 2982, 1780, 1713, 1678, 1620, 1558; HRMS (ESI) $[M+Na]^+$: calculated for $C_{28}H_{24}{}^{35}ClNNaO_5{}^+$ 512.1235, found 512.1236, Δ 0.15 ppm.

A racemic sample of 1-benzyl 4-isopropyl 6-chloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.23**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-8-fluoro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.24)

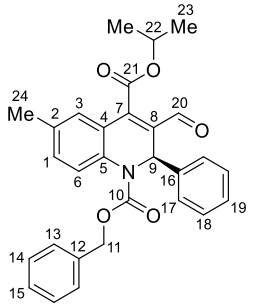


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-3-fluorophenyl)-2-oxoacetate (**3.14**) (107.8 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 25 h. Purification by column chromatography (SiO_2, eluent load, Et_2O:pentane, 10:90 to 20:80) gave 1-benzyl 4-isopropyl (*R*)-8-fluoro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.24**) as a viscous yellow oil (55.5 mg, 0.12 mmol, 78%); R_f: 0.28 (Et_2O:pentane, 20:80); $[\alpha]_D^{25} = -376.6$ (*c* = 1.00, $CHCl_3$); ee: 97% (Chiralcel AD-H; hexane:

2-propanol, 70:30; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 14.38 min, t_R (major) = 16.73 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.00 (s, 1H, C20H), 7.44 – 7.29 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.25 – 7.08 (m, 8H, C1H, C2H, C3H, 2 × C17H, 2 × C18H, C19H), 6.81 (s, 1H, C9H), 5.43 (hept, *J* = 6.3 Hz, 1H, C22H), 5.35 – 5.27 (m, 2H, $C11H_2$), 1.44 (d, *J* = 6.3 Hz, 3H, $C23_AH_3$), 1.42 (d, *J* = 6.3 Hz, 3H, $C23_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (signals for C4 and C16 could not be identified): δ 188.1 (s, C20H), 164.8 (s C21), 156.1 (d, *J* = 253.5 Hz, C6), 153.9 (s, C10), 142.5 (s, C7), 136.5 (s, C8), 135.5 (s, C12), 128.9 – 128.0 (m, 2 × C13H, 2 × C14H, C15H, 2 × C18H, C19H), 127.1 – 126.4 (m, C2H, 2 × C17H), 124.6 (d, *J* = 12.8 Hz, C5), 122.1 (d, *J* = 3.3 Hz, C3H), 119.4 (d, *J* = 14.7 Hz, C1H), 71.4 (s, C22H), 69.1 (s, $C11H_2$), 52.3 (s, C9H), 22.1 (s, $C23_AH_3$), 21.9 (s, $C23_BH_3$); ^{19}F {^{1}H} NMR ($CDCl_3$, 471 MHz): δ -116.0; IR ν_{max} (cm^{-1}): 3089, 3066, 3033, 2985, 2923, 2851, 1716, 1677, 1612, 1574; HRMS (ESI) $[M+Na]^+$: calculated for $C_{28}H_{24}FNNaO_5^+$ 496.1531, found 496.1530, Δ –0.18 ppm.

A racemic sample of 1-benzyl 4-isopropyl 8-fluoro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.24**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-3-formyl-6-methyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.25)

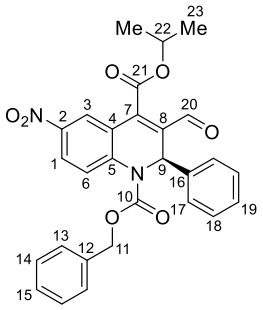


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methylphenyl)-2-oxoacetate (**3.17**) (106.6 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 48 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 15:85) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-6-methyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.25**) as a viscous yellow oil (66.2 mg, 0.14 mmol, 94%); R_f: 0.33 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -422.2$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel AD-H; hexane:2-propanol, 90:10; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 22.02 min, t_R (major) = 30.01 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.89 (s, 1H, C20H), 7.56 (br s, 1H, C6H), 7.44 – 7.31 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.24 – 7.12 (m, 7H, C1H, C3H, 2 × C17H, 2 × C18H, C19H), 6.81 (s, 1H, C9H), 5.44 (hept, *J* = 6.2 Hz, 1H, C22H), 5.32 (d, *J* = 11.9 Hz, 1H, C11H_AH$_B$), 5.30 (d, *J* = 11.9 Hz, 1H, C11H$_A$$H_B$), 2.31 (s, 3H, C24H$_3$), 1.44 (d, *J* = 6.3 Hz, 3H, C23$_A$H$_3$), 1.42 (d, *J* = 6.3 Hz, 3H, C23$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9 (C20H), 165.3 (C21), 153.8 (C10), 143.6 (C7), 137.6 (C16), 135.7 (C12), 134.5 (C2), 134.5 (C5), 133.8 (C8), 133.0 (C1H), 128.8 (2 × C14H or 2 × C18H), 128.6 (2 × C14H or 2 × C18H), 128.5 (C15H or C19H), 128.3 (2 × C13H), 128.2 (C15H or C19H), 127.1 (2 × C17H), 126.7 (C3H), 125.2 (C6H), 123.4 (C4), 71.1 (C22H), 68.5 (C11H$_2$), 52.0 (C9H), 22.1 (C23$_A$H$_3$), 21.9 (C23$_B$H$_3$), 21.0 (C24H$_3$);

IR ν_{max} (cm^{-1}): 3064, 3033, 2981, 2934, 2858, 1774, 1708, 1674, 1617, 1567; HRMS (ESI) $[M+Na]^+$: calculated for $C_{29}H_{27}NNaO_5^+$ 492.1781, found 492.1779, Δ –0.52 ppm.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-6-methyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.25**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-3-formyl-6-nitro-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.26)

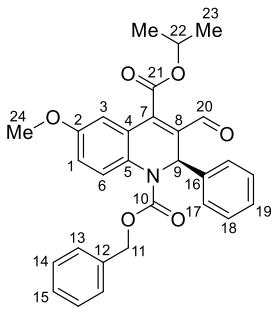


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-nitrophenyl)-2-oxoacetate (**3.20**) (115.9 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 47 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 15:85) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-6-nitro-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.26**) as a viscous yellow oil (57.6 mg, 0.12 mmol, 77%); R_f: 0.30 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -409.0$ (*c* = 1.00, $CHCl_3$); ee: 97% (Chiralcel AD-H; hexane:2-propanol, 70:30; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 13.93 min, t_R (major) = 18.13 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.97 (s, 1H, C20H), 8.37 (d, *J* = 2.6 Hz, 1H, C3H), 8.19 (dd, *J* = 9.2, 2.6 Hz, 1H, C1H), 7.88 (d, *J* = 9.2 Hz, 2H, C6H), 7.44 – 7.34 (m, 5H,

2 × C13H, 2 × C14H, C15H), 7.25 – 7.16 (m, 3H, 2 × C18H, C19H), 7.15 – 7.08 (m, 2H, 2 × C17H), 6.85 (s, 1H, C9H), 5.48 (hept, *J* = 6.3 Hz, 2H, C22H), 5.35 (d, *J* = 12.2 Hz, 1H, C11H_AH_B), 5.35 (d, *J* = 12.2 Hz, 1H, C11H_AH_B), 1.47 (d, *J* = 6.3 Hz, 3H, C23$_A$H$_3$), 1.46 (d, *J* = 6.3 Hz, 1H, C23$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.6 (C20H), 164.0 (C21), 153.2 (C10), 143.8 (C2), 142.4 (C5), 140.8 (C7), 136.8 (C16), 136.0 (C8), 134.9 (C12), 129.0 (2 × C14H or 2 × C18H), 129.0 (C15H), 128.9 (2 × C14H or 2 × C18H), 128.9 (C19H), 128.6 (2 × C13H), 127.0 (2 × C17H), 126.4 (C1H), 125.5 (C6H), 123.9 (C4), 122.4 (C3H), 72.0 (C22H), 69.4 (C11H_2), 52.7 (C9H), 22.1 (C23$_A$H$_3$), 22.0 (C23$_B$H$_3$); IR ν_{max} (cm^{-1}): 3066, 3034, 2983, 2936, 2875, 1720, 1680, 1608, 1576, 1522; HRMS (ESI) [M+Na]$^+$: calculated for $C_{28}H_{24}N_2NaO_7^+$ 523.1476, found 523.1478, Δ 0.49 ppm.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-6-nitro-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.26**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-3-formyl-6-methoxy-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.27)

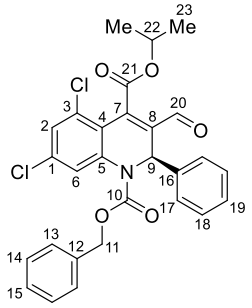


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-5-methoxyphenyl)-2-oxoacetate (**3.25**) (111.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature

for 25 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 20:80) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-6-methoxy-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.27**) as a viscous yellow oil (60.2 mg, 0.12 mmol, 83%); R_f: 0.23 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -453.8$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 12.87 min, t_R (major) = 15.00 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.91 (s, 1H, C20H), 7.60 (br s, 1H, C6H), 7.46 – 7.30 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.21 – 7.17 (m, 3H, 2 × C18H, C19H), 7.17 – 7.10 (m, 2H, 2 × C17H), 6.93 (br s, 1H, C1H), 6.91 (d, *J* = 2.7 Hz, 1H, C3H), 6.82 (s, 1H, C9H), 5.43 (hept, *J* = 6.3 Hz, 1H, C22H), 5.32 (br s, 2H, $C11H_2$), 3.78 (s, 3H, $C24H_3$), 1.44 (d, *J* = 6.3 Hz, 3H, $C23_AH_3$), 1.42 (d, *J* = 6.3 Hz, 3H, $C23_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9 (C20H), 165.1 (C21), 156.3 (C2), 153.8 (C10), 143.3 (C7), 137.4 (C16), 135.8 (C12), 134.5 (C8), 130.0 (C5), 128.7 (2 × C14H or 2 × C18H), 128.6 (2 × C14H or 2 × C18H), 128.5 (C15H), 128.3 (2 × C13H), 128.3 (C19H), 127.1 (2 × C17H), 126.6 (C6H), 124.4 (C4), 118.1 (C1H), 110.6 (C3H), 71.1 (C22H), 68.5 ($C11H_2$), 55.6 ($C24H_3$), 52.0 (C9H), 22.1 ($C23_BH_3$), 21.9 ($C23_AH_3$); IR ν_{max} (cm^{-1}): 3064, 3032, 2981, 2938, 2838, 1707, 1674, 1609, 1568; HRMS (ESI) [M+Na]$^+$: calculated for $C_{29}H_{27}NNaO_6^+$ 508.1731, found 508.1732, Δ 0.31 ppm.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-6-methoxy-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.27**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-5,7-dichloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-4.28)

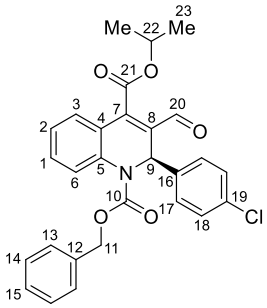


(*E*)-Cinnamaldehyde (**1.101**) (18.9 µL, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)-4,6-dichlorophenyl)-2-oxoacetate (**3.23**) (123.1 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 49 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 10:90) gave 1-benzyl 4-isopropyl (*R*)-5,7-dichloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.28**) as a viscous yellow oil (77.1 mg, 0.15 mmol, 98%); R_f: 0.26 (EtOAc:petroleum ether 40-60, 10:90); $[\alpha]_D^{25} = -199.8$ (*c* = 1.00, $CHCl_3$); ee: 78% (Chiralcel AD-H; hexane:2-propanol, 95:5; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 16.82 min, t_R (major) = 19.36 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.13 (s, 1H, C20H), 7.69 (br s, 1H, C6H), 7.44 – 7.34 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.22 – 7.19 (m, 3H, 2 × C18H, C19H), 7.17 (d, *J* = 2.0 Hz, 1H, C2H), 7.09 – 7.04 (m, 2H, 2 × C17H), 6.88 (s, 1H, C9H), 5.36 (d, *J* = 12.2 Hz, 1H, C11H_AH$_B$), 5.33 (d, *J* = 12.2 Hz, 1H, C11H$_A$$H_B$), 5.32 (hept, *J* = 6.3 Hz, 1H, C22H), 1.39 (d, *J* = 6.3 Hz, 3H, C23$_A$H$_3$), 1.38 (d, *J* = 6.3 Hz, 3H, C23$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.4 (C20H), 164.4 (C21), 153.1 (C10), 140.6 (C7), 139.8 (C5), 137.4 (C1), 137.3 (C8), 136.1 (C16), 135.2 (C12), 133.4 (C3), 128.9 (2 × C14H or 2 × C18H), 128.8 (C15H, 2 × C14H or 2 × C18H), 128.5 (C19H), 128.4 (2 × C13H), 126.8 (2 × C17H), 126.8 (C2H), 124.2 (C6H), 122.3 (C4), 71.6 (C22H), 69.1 (C11H$_2$), 51.4 (C9H), 21.8 (C23$_A$H$_3$), 21.8 (C23$_B$H$_3$); IR ν_{max} (cm^{-1}): 3089, 3066, 3033,

2981, 2936, 2880, 1718, 1674, 1603, 1585, 1543; HRMS (ESI) $[M+H]^+$: calculated for $C_{28}H_{24}{}^{35}Cl_2NO_5^+$ 524.1026, found 524.1027, Δ 0.11 ppm.

A racemic sample of 1-benzyl 4-isopropyl 5,7-dichloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.28**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-2-(4-chlorophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-4.29)

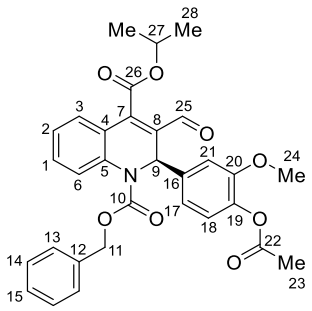


(*E*)-3-(4-Chlorophenyl)acrylaldehyde (25.0 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 48 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 12:88) gave 1-benzyl 4-isopropyl (*R*)-2-(4-chlorophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.29**) as a yellow solid (67.4 mg, 0.14 mmol, 92%); R_f: 0.31 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -447.6$ (*c* = 1.00, $CHCl_3$); m.p.: 134.0–136.0 °C; ee: 98% (Chiralcel OD; hexane:2-propanol, 90:10; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 13.31 min, t_R (minor) = 16.55 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.87 (s, 1H, C20H), 7.65 (br s, 1H, C6H), 7.43 – 7.33 (m, 7H, C1H, C3H, 2 × C13H,

2 × C14H, C15H), 7.15 (ddd, *J* = 7.8, 7.4, 1.2 Hz, 1H, C2H), 7.17 – 7.11 (m, 2H, 2 × C18H), 7.10 – 7.04 (m, 2H, 2 × C17H), 6.76 (s, 1H, C9H), 5.42 (hept, *J* = 6.4 Hz, 1H, C22H), 5.32 (s, 2H, $C11H_2$), 1.43 (d, *J* = 6.3 Hz, 3H, $C23_AH_3$), 1.41 (d, *J* = 6.3 Hz, 3H, $C23_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.8 (C20H), 165.1 (C21), 153.6 (C10), 143.7 (C7), 136.7 (C5), 136.1 (C16), 135.5 (C12), 134.2 (C19), 133.5 (C8), 132.2 (C1H), 128.9 (2 × C14H or 2 × C18H), 128.8 (2 × C14H or 2 × C18H), 128.7 (C15H), 128.5 (2 × C17H), 128.4 (2 × C13H), 126.6 (C3H), 125.3 (C6H), 125.0 (C2H), 123.4 (C4), 71.3 (C22H), 68.8 ($C11H_2$), 51.5 (C9H), 22.1 ($C23_AH_3$), 22.0 ($C23_BH_3$); IR ν_{max} (cm^{-1}): 3067, 3035, 2987, 2936, 1710, 1673, 1619, 1600, 1567; HRMS (ESI) $[M+Na]^+$: calculated for $C_{28}H_{25}{}^{35}ClNO_5^+$ 490.1416, found 490.1415, Δ –0.14 ppm.

A racemic sample of 1-benzyl 4-isopropyl 2-(4-chlorophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.29**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-2-(4-acetoxy-3-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-4.30)

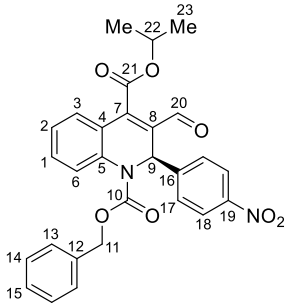


(*E*)-2-Methoxy-4-(3-oxoprop-1-en-1-yl)phenyl acetate (33.0 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature

for 49 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 25:75) gave 1-benzyl 4-isopropyl (*R*)-2-(4-acetoxy-3-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.30**) as a viscous yellow oil (73.2 mg, 0.13 mmol, 90%); R_f: 0.43 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = -364.8$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 13.90 min, t_R (minor) = 16.36 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.86 (s, 1H, C25H), 7.70 (br s, 1H, C6H), 7.45 – 7.32 (m, 7H, C3H, C1H, 2 × C13H, 2 × C14H, C15H), 7.16 (ddd, *J* = 7.9, 7.3, 1.1 Hz, 1H, C2H), 6.83 – 6.73 (m, 2H, C18H, C21H), 6.76 (br s, 1H, C9H), 6.64 (ddd, *J* = 8.2, 2.1, 0.6 Hz, 1H, C17H), 5.42 (hept, *J* = 6.3 Hz, 1H, C27H), 5.34 (d, *J* = 12.1 Hz, 1H, C11H_AH$_B$), 5.29 (d, *J* = 12.1 Hz, 1H, C11H$_A$$H_B$), 3.57 (s, 3H, C24$H_3$), 2.24 (s, 3H, C23$H_3$), 1.43 (d, *J* = 6.3 Hz, 3H, C28$_A$H$_3$), 1.41 (d, *J* = 6.3 Hz, 3H, C28$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.8 (C25H), 169.0 (C22), 165.2 (C26), 153.6 (C10), 151.0 (C20), 143.5 (C7), 139.7 (C19), 136.9 (C5), 136.5 (C16), 135.6 (C12), 133.5 (C8), 132.2 (C1H), 128.8 (2 × C14H), 128.6 (C15H), 128.5 (2 × C13H), 126.6 (C3H), 125.4 (C6H), 124.9 (C2H), 123.4 (C4), 122.8 (C18H), 119.2 (C17H), 111.6 (C21H), 71.2 (C27H), 68.7 (C11H_2), 55.7 (C24H_3), 51.9 (C9H), 22.1 (C28$_A$H$_3$), 22.0 (C28$_B$H$_3$), 20.8 (C23H_3); IR ν_{max} (cm^{-1}): 3068, 3035, 2982, 2939, 1766, 1713, 1674, 1602, 1567, 1510; HRMS (ESI) [M+Na]$^+$: calculated for $C_{31}H_{29}NNaO_8^+$ 566.1785, found 566.1783, Δ –0.45 ppm.

A racemic sample of 1-benzyl 4-isopropyl 2-(4-acetoxy-3-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.30**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-3-formyl-2-(4-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-4.31)

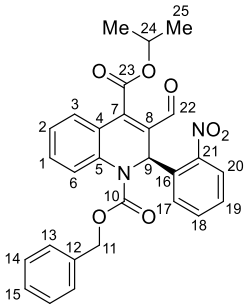


(*E*)-3-(4-Nitrophenyl)acrylaldehyde (26.6 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 23 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 15:85) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-2-(4-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-**4.31**) as a yellow solid (68.3 mg, 0.13 mmol, 91%); R_f: 0.29 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -431.3$ (*c* = 1.00, $CHCl_3$); m.p.: 113.0–115.0 °C; ee: 98% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 17.57 min, t_R (minor) = 22.11 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.90 (s, 1H, C20H), 8.05 – 8.00 (m, 2H, 2 × C18H), 7.67 (br s, 1H, C6H), 7.45 – 7.34 (m, 7H, C3H, C1H, 2 × C13H, 2 × C14H, C15H), 7.32 – 7.28 (m, 2H, 2 × C17H), 7.18 (ddd, *J* = 7.9, 6.8, 1.2 Hz, 1H, C2H), 6.87 (s, 1H, C9H), 5.43 (hept, *J* = 6.4 Hz, 1H, C22H), 5.33 (s, 2H, $C11H_2$), 1.44 (d, *J* = 6.4 Hz, 3H, $C23_AH_3$), 1.42 (d, *J* = 6.4 Hz, 3H, $C23_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.7 (C20H), 164.8 (C21), 153.5 (C10), 147.8 (C19), 144.8 (C16), 144.3 (C7), 136.6 (C5), 135.3 (C12), 132.8 (C8), 132.6 (C1H), 128.9 (2 × C14H), 128.8 (C15H), 128.5 (2 × C13H), 128.0 (2 × C17H), 126.9 (C3H), 125.3 (C2H), 125.3 (C6H), 124.0 (2 ×C18H), 123.2 (C4), 71.6 (C22H), 69.0 ($C11H_2$), 51.5 (C9H), 22.1 ($C23_AH_3$), 22.0 ($C23_BH_3$); IR ν_{max} (cm^{-1}): 3076, 3035, 2987, 2935,

2855, 1716, 1673, 1600, 1567, 1523; HRMS (ESI) $[M+H]^+$: calculated for $C_{28}H_{25}N_2O_7^+$ 501.1656, found 501.1657, Δ 0.17 ppm.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-2-(4-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (*rac*-**4.31**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-3-formyl-2-(2-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-4.32)

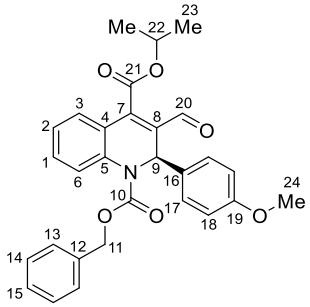


(*E*)-3-(2-Nitrophenyl)acrylaldehyde (26.6 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 72 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 25:75) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-2-(2-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-**4.32**) as a viscous yellow oil (52.8 mg, 0.11 mmol, 70%); R_f: 0.30 (EtOAc:petroleum ether 40-60, 20:80); $[\alpha]_D^{25} = -225.8$ (*c* = 1.00, $CHCl_3$); ee: 96% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 24.27 min, t_R (minor) = 29.10 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.86 (s, 1H, C22H), 7.69 (dd, *J* = 8.0, 1.4 Hz, 1H, C20H), 7.52 (dd, *J* = 8.3, 1.3 Hz, 1H, C6H), 7.44 – 7.28 (m, 9H, C3H, C1H, C9H, C19H,

2 × C13H, 2 × C14H, C15H), 7.28 (td, *J* = 7.7, 1.5 Hz, 1H, C18H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H, C2H), 7.01 (dd, *J* = 7.9, 1.4 Hz, 1H, C17H), 5.42 (hept, *J* = 6.3 Hz, 1H, C24H), 5.37 (d, *J* = 12.1 Hz, 1H, C11H_AH_B), 5.15 (d, *J* = 12.1 Hz, 1H, C11H_AH_B), 1.43 (d, *J* = 6.3 Hz, 3H, C25$_A$H$_3$), 1.41 (d, *J* = 6.3 Hz, 3H, C25$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.3 (C22H), 165.0 (C23), 153.6 (C10), 149.3 (C21), 143.6 (C7), 136.4 (C5), 135.5 (C12), 133.2 (C8), 132.4 (C18H), 132.3 (C1H), 130.5 (C16), 129.6 (C19H), 128.8 (2 × C13H), 128.7 (2 × C14H), 128.6 (C17H), 128.5 (C15H), 126.4 (C3H), 126.2 (C6H), 125.5 (C2H), 124.8 (C20H), 123.6 (C4), 71.4 (C24H), 68.9 (C11H_2), 48.0 (C9H), 22.0 (C25$_A$H$_3$), 21.9 (C25$_B$H$_3$); IR ν_{max} (cm^{-1}): 3067, 3035, 2987, 2937, 1718, 1676, 1600, 1567, 1532; HRMS (ESI) $[M+H]^+$: calculated for $C_{28}H_{25}N_2O_7^+$ 501.1656, found 501.1657, Δ 0.17 ppm.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-2-(2-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (*rac*-**4.32**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*R*)-3-formyl-2-(4-methoxyphenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-4.33)



(*E*)-3-(4-Methoxyphenyl)acrylaldehyde (24.3 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol,

2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 165 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 15:85) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-2-(4-methoxyphenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-**4.33**) as a yellow solid (54.2 mg, 0.11 mmol, 74%); R_f: 0.27 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -466.8$ (*c* = 1.00, $CHCl_3$); m.p.: 160.0–162.0°C; ee: 93% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 16.21 min, t_R (major) = 19.16 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.86 (s, 1H, C20H), 7.65 (br s, 1H, C6H), 7.43 – 7.32 (m, 7H, C3H, C1H, 2 × C13H, 2 × C14H, C15H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1H, C2H), 7.10 – 7.05 (m, 2H, 2 × C17H), 6.75 (s, 1H, C9H), 6.72 – 6.67 (m, 2H, 2 × C18H), 5.42 (hept, *J* = 6.3 Hz, 1H, C22H), 5.31 (s, 2H, $C11H_2$), 3.70 (s, 3H, $C24H_3$), 1.43 (d, *J* = 6.3 Hz, 3H, $C23_AH_3$), 1.41 (d, *J* = 6.3 Hz, 3H, $C23_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.8 (C20H), 165.3 (C21), 159.6 (C19), 153.7 (C10), 143.2 (C7), 136.9 (C5), 135.7 (C12), 134.0 (C8), 132.0 (C1H), 129.7 (C16), 128.8 (2 × C14H), 128.5 (C15H), 128.4 (2 × C17H), 128.4 (2 × C13H), 126.4 (C3H), 125.4 (C6H), 124.8 (C2H), 123.6 (C4), 114.1 (2 × C18H), 71.1 (C22H), 68.6 ($C11H_2$), 55.3 ($C24H_3$), 51.7 (C9H), 22.1 ($C23_AH_3$), 22.0 ($C23_BH_3$); IR ν_{max} (cm^{-1}): 3066, 3035, 2982, 2935, 2838, 1709, 1674, 1609, 1601, 1585, 1567, 1511; HRMS (ESI) $[M+Na]^+$: calculated for $C_{29}H_{27}NNaO_6^+$ 508.1731, found 508.1730, Δ –0.11 ppm.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-2-(4-methoxyphenyl)quinoline-1,4(2H)-dicarboxylate (*rac*-**4.33**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

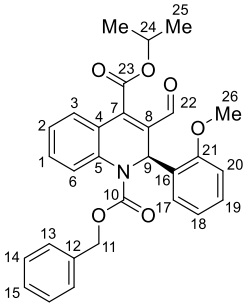
1-Benzyl 4-isopropyl (*R*)-3-formyl-2-(2-methoxyphenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-4.34)

and

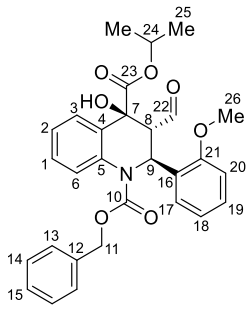
1-Benzyl 4-isopropyl (2*S*,3*R*,4*S*)-3-formyl-4-hydroxy-2-(2-methoxyphenyl)-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-4.40)

and

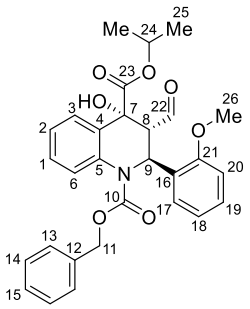
1-Benzyl 4-isopropyl (2*S*,3*R*,4*R*)-3-formyl-4-hydroxy-2-(2-methoxyphenyl)-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-4.41)



ent-**4.34**



ent-**4.40**



ent-**4.41**

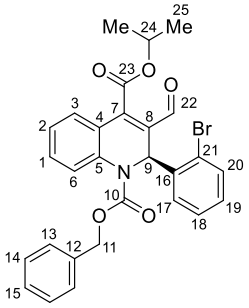
(*E*)-3-(2-Methoxyphenyl)acrylaldehyde (**4.39**) (24.3 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 172 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-2-(2-methoxyphenyl)quinoline-1,4(2H)-dicarboxylate (*ent*-**4.34**) as a viscous yellow oil (28.5 mg, 0.06 mmol, 39%), 1-benzyl 4-isopropyl (2*S*,3*R*,4*S*)-3-formyl-4-hydroxy-2-(2-methoxyphenyl)-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-**4.40**) as a viscous yellow oil (20.6 mg, 0.04 mmol, 27%), and 1-benzyl 4-isopropyl (2*S*,3*R*,4*R*)-3-formyl-4-hydroxy-2-(2-methoxyphenyl)-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-**4.41**) as a viscous yellow oil (6.8 mg, 0.01 mmol, 9%); *ent*-**4.34**: R_f: 0.32 (EtOAc:petroleum ether 40-60, 20:80); $[\alpha]_D^{25} = -349.5$ (*c* = 1.00,

$CHCl_3$); ee: 91% (Chiralcel AD-H; hexane:2-propanol, 80:20; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 20.45 min, t_R (major) = 26.95 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.83 (s, 1H, C22H), 7.65 (br d, *J* = 7.4 Hz, 1H, C6H), 7.45 – 7.41 (m, 2H, 2 × C13H), 7.41 – 7.32 (m, 5H, C3H, C1H, 2 × C14H, C15H), 7.18 – 7.12 (m, 2H, C2H, C19H), 7.11 (s, 1H, C9H), 6.90 (dd, *J* = 7.7, 1.7 Hz, 1H, C17H), 6.78 (dd, *J* = 8.2, 1.1 Hz, 1H, C20H), 6.68 (td, *J* = 7.5, 1.1 Hz, 1H, C18H), 5.41 (hept, *J* = 6.3 Hz, 1H, C24H), 5.30 (d, *J* = 12.4 Hz, 1H, C11H_AH$_B$), 5.28 (d, *J* = 12.4 Hz, 1H, C11H$_A$$H_B$), 3.57 (s, 3H, C26H$_3$), 1.43 (d, *J* = 6.3 Hz, 3H, C25$_A$H$_3$), 1.40 (d, *J* = 6.3 Hz, 3H, C25$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9 (C22H), 165.6 (C23), 157.6 (C21), 153.8 (C10), 142.5 (C7), 137.4 (C5), 136.0 (C12), 133.8 (C8), 131.5 (C1H), 129.7 (C19H), 128.7 (C17H, 2 × C14H), 128.3 (C15H), 128.3 (2 × C13H), 126.1 (C3H), 125.7 (C6H), 125.0 (C16), 124.7 (C2H), 124.3 (C4), 120.3 (C18H), 111.3 (C20H), 70.8 (C24H), 68.3 (C11H$_2$), 55.3 (C26H$_3$), 48.6 (C9H), 22.0 (C25$_A$H$_3$), 21.9 (C25$_B$H$_3$); IR ν_{max} (cm^{-1}): 3067, 3033, 2981, 2937, 2839, 2745, 1775, 1714, 1676, 1599, 1567; HRMS (ESI) [M+H]$^+$: calculated for $C_{29}H_{28}NO_6^+$ 486.1911, found 486.1910, Δ –0.34 ppm; *ent*-**4.40**: R_f: 0.19 (EtOAc:petroleum ether 40-60, 20:80); $[\alpha]_D^{25} = -16.1$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.77 (d, *J* = 1.3 Hz, 1H, C22H), 7.66 (dd, *J* = 7.8, 1.6 Hz, 1H, C3H), 7.58 (br d, *J* = 8.2 Hz, 1H, C6H), 7.36 (ddd, *J* = 9.0, 7.4, 1.7 Hz, 1H, C1H), 7.31 – 7.27 (m, 3H, 2 × C14H, C15H), 7.26 – 7.15 (m, 5H, C2H, C17H, C19H, 2 × C13H), 6.88 (td, *J* = 7.5, 1.1 Hz, 1H, C18H), 6.80 (dd, *J* = 8.4, 1.1 Hz, 1H, C20H), 5.93 (d, *J* = 10.2 Hz, 1H, C9H), 5.14 (d, *J* = 12.5 Hz, 1H, C11H_AH$_B$), 5.11 (d, *J* = 12.5 Hz, 1H, C11H$_A$$H_B$), 5.00 (hept, *J* = 6.2 Hz, 1H, C24H), 4.54 (s, 1H, OH), 3.51 (s, 3H, C26H$_3$), 3.32 (dd, *J* = 10.2, 1.2 Hz, 1H, C8H), 1.19 (d, *J* = 6.2 Hz, 3H, C25$_A$H$_3$), 1.04 (d, *J* = 6.2 Hz, 3H, C25$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 200.7 (C22H), 172.2 (C23), 156.3 (C21), 154.4 (C10), 137.4 (C5), 135.9 (C12), 131.3 (C4), 130.0 (C16), 129.2 (C17H or C19H), 128.7 (C17H or C19H), 128.5 (2 × C14H), 128.5 (C1H), 128.2 (C15H), 128.0 (2 × C13H), 125.7 (C6H), 124.8 (C2H), 124.1 (C3H), 121.0 (C18H), 110.9 (C20H), 74.6 (C7),

71.4 (C24H), 67.9 ($C11H_2$), 63.1 (C8H), 54.9 ($C26H_3$), 53.0 (C9H), 21.5 ($C25_AH_3$), 21.3 ($C25_BH_3$); IR ν_{max} (cm^{-1}): 3470 (br), 3066, 3034, 2982, 2936, 2848, 1707, 1602, 1588; HRMS (ESI) $[M+Na]^+$: calculated for $C_{29}H_{29}NNaO_7$ 526.1836, found 526.1834, Δ –0.52 ppm; *ent*-**4.41** (isolated as a 4:1 mixture with *ent*-**4.40**): R_f: 0.15 (EtOAc:petroleum ether 40-60, 20:80); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.60 (d, *J* = 1.5 Hz, 1H, C22H), 7.73 (d, *J* = 8.2 Hz, 1H, C6H), 7.40 (td, *J* = 7.8, 1.6 Hz, 1H, C1H), 7.31 – 7.23 (m, 5H, C17H, C19H, 2 × C14H, C15H), 7.14 – 7.10 (m, 3H, C2H, 2 × C13H), 6.94 (dd, *J* = 7.7, 1.6 Hz, 1H, C3H), 6.92 (td, *J* = 7.5, 1.2 Hz, 1H, C18H), 6.82 (dd, *J* = 8.3, 1.1 Hz, 1H, C20H), 6.05 (d, *J* = 10.8 Hz, 1H, C9H), 5.28 (hept, *J* = 6.3 Hz, 1H, C24H), 5.13 (s, 2H, $C11H_2$), 3.64 (d, *J* = 1.1 Hz, 1H, OH), 3.55 (s, 3H, $C26H_3$), 3.31 (dt, *J* = 10.8, 1.3 Hz, 1H, C8H), 1.33 (d, *J* = 6.3 Hz, 3H, $C25_AH_3$), 1.26 (d, *J* = 6.3 Hz, 3H, $C25_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 199.5 (C22H), 172.6 (C23), 156.2 (C21), 154.6 (C10), 138.4 (C5), 136.1 (C12), 131.7 (C4), 130.5 (C16), 129.3 (C1H), 129.0 (C19H), 128.5 (2 × C14H), 128.0 (C15H), 127.8 (C17H), 127.8 (2 × C13H), 126.6 (C6H), 124.4 (C2H), 124.2 (C3H), 121.2 (C18H), 111.0 (C20H), 74.8 (C7), 71.2 (C24H), 68.0 ($C11H_2$), 61.3 (C8H), 55.0 ($C26H_3$), 50.6 (C9H), 21.8 ($C25_AH_3$), 21.7 ($C25H_BH_3$).

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-2-(2-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (*rac*-**4.34**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*S*)-2-(2-bromophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-4.35)

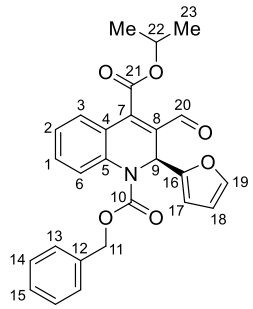


(*E*)-3-(2-Bromophenyl)acrylaldehyde (**4.15**) (31.7 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 93 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 15:85) gave 1-benzyl 4-isopropyl (*S*)-2-(2-bromophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.35**) as a viscous yellow oil (32.3 mg, 0.06 mmol, 40%); R_f: 0.35 (EtOAc:petroleum ether 40-60, 20:80); $[\alpha]_D^{25} = -342.5$ (*c* = 1.00, $CHCl_3$); ee: 96% (Chiralcel OD; hexane:2-propanol, 93:7; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 18.01 min, t_R (minor) = 22.43 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.86 (s, 1H, C22H), 7.58 – 7.51 (m, 2H, C6H, C20H), 7.44 (dd, *J* = 7.9, 1.5 Hz, 1H, C3H), 7.42 – 7.30 (m, 6H, C1H, 2 × 13H, 2 × C14H, C15H), 7.20 (td, *J* = 7.7, 1.2 Hz, 1H, C2H), 7.14 (s, 1H, C9H), 7.03 (td, *J* = 7.6, 1.8 Hz, 1H, C19H), 6.98 (td, *J* = 7.6, 1.4 Hz, 1H, C18H), 6.83 (dd, *J* = 7.8, 1.7 Hz, 1H, C17H), 5.43 (hept, *J* = 6.3 Hz, 1H, C24H), 5.36 (d, *J* = 12.3 Hz, 1H, C11H_AH$_B$), 5.24 (d, *J* = 12.3 Hz, 1H, C11H$_A$$H_B$), 1.44 (d, *J* = 6.3 Hz, 3H, C25$_A$H$_3$), 1.42 (d, *J* = 6.3 Hz, 3H, C25$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.4 (C22H), 165.1 (C23), 153.7 (C10), 143.3 (C7), 136.8 (C5), 135.8 (C12), 135.7 (C16), 134.9 (C8), 134.2 (C20H), 131.9 (C1H), 130.1 (C19H), 128.8 (C17H), 128.7 (2 × C14H), 128.5 (2 × C13H), 128.4 (C15H), 127.5 (C18H), 127.0 (C6H), 126.2 (C3H), 125.6 (C2H), 124.6 (C4), 123.7 (C21), 71.2 (C24H), 68.6 (C11H$_2$), 52.0 (C9H), 22.1 (C25$_A$H$_3$), 22.0 (C25$_B$H$_3$); IR ν_{max} (cm^{-1}): 3066, 3033,

2982, 2934, 2873, 2855, 1716, 1676, 1600, 1567; HRMS (ESI) $[M+Na]^+$: calculated for $C_{28}H_{24}{}^{79}BrNNaO_5^+$ 556.0730, found 556.0731, Δ 0.2 ppm.

A racemic sample of 1-benzyl 4-isopropyl 2-(2-bromophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*rac*-**4.35**) was prepared as above using pyrrolidine (12.3 µL, 0.15 mmol, 1.0 equiv) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**).

1-Benzyl 4-isopropyl (*S*)-3-formyl-2-(furan-2-yl)quinoline-1,4(2H)-dicarboxylate (*ent*-4.36)



(*E*)-3-(Furan-2-yl)acrylaldehyde (18.3 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, stirring at room temperature for 143 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 15:95) gave 1-benzyl 4-isopropyl (*S*)-3-formyl-2-(furan-2-yl)quinoline-1,4(2H)-dicarboxylate (*ent*-**4.36**) as a yellow solid (30.4 mg, 0.07 mmol, 45%); R_f: 0.35 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -316.5$ (*c* = 1.00, $CHCl_3$); m.p.: 132.0–134.0°C; ee: 92% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 10.75 min, t_R (major) = 13.88 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.85 (s, 1H, C20H), 7.72 (br s, 1H, C6H), 7.47 – 7.31 (m, 7H, C1H, C3H, 2 × C13H, 2 × C14H, C15H), 7.24 (dd, *J* = 1.9, 0.9 Hz, 1H, C19H), 7.16 (td, *J* = 7.6, 1.2 Hz, 1H, C2H), 6.91 (d, *J* = 1.0 Hz, 1H, C9H), 6.14 (ddd,

J = 3.3, 1.9, 0.4 Hz, 1H, C18H), 6.01 (dt, *J* = 3.3, 0.9 Hz, 1H, C17H), 5.41 (hept, *J* = 6.3 Hz, 1H, C22H), 5.33 (s, 2H, $C11H_2$), 1.43 (d, *J* = 6.3 Hz, 3H, $C23_AH_3$), 1.40 (d, *J* = 6.3 Hz, 3H, $C23_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.2 (C20H), 165.0 (C21), 153.3 (C10), 150.0 (C16), 143.7 (C7), 143.1 (C19H), 136.8 (C5), 135.7 (C12), 132.0 (C1H), 131.5 (C8), 128.8 (2 × C14H), 128.5 (C15H), 128.2 (2 × C13H), 126.6 (C3H), 125.0 (C6H), 124.8 (C2H), 123.3 (C4), 110.3 (C18H), 108.6 (C17H), 71.2 (C22H), 68.6 ($C11H_2$), 46.7 (C9H), 22.1 ($C23_AH_3$), 21.9 ($C23_BH_3$); IR ν_{max} (cm^{-1}): 3067, 3035, 2982, 2935, 2874, 1715, 1675, 1620, 1600, 1567; HRMS (ESI) $[M+Na]^+$: calculated for $C_{26}H_{23}NNaO_6^+$ 468.1418, found 468.1416, Δ –0.34 ppm.

A sample of the enantiomer, 1-benzyl 4-isopropyl (*R*)-3-formyl-2-(furan-2-yl)quinoline-1,4(2H)-dicarboxylate (**4.36**) (38.9 mg, 0.09 mmol, 58%) was prepared as above using (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**), stirring for 144 h; $[\alpha]_D^{25} = +357.5$ (*c* = 1.00, $CHCl_3$); ee: 94% (Chiralcel AD-H; hexane:2-propanol, 60:40; flow rate 0.8 $mL.min^{-1}$; λ = 254 nm): t_R (major) = 10.79 min, t_R (minor) = 14.06 min; all other characterisation identical.

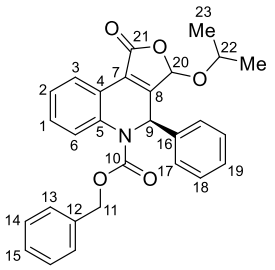
Benzyl (4*R*)-3-isopropoxy-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-5.5 and *ent*-5.6)

and

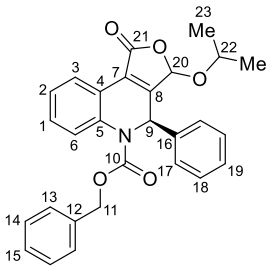
Benzyl (3*S*,4*R*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-5.7)

and

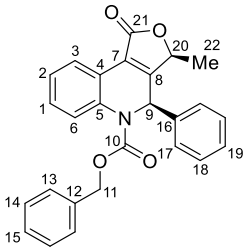
Benzyl (3*R*,4*R*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-5.9)



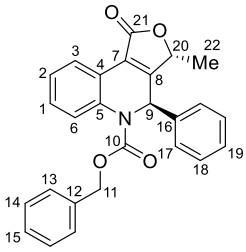
ent-**5.5**
(*ent*-**5.5** and *ent*-**5.6** are diastereomeric)



ent-**5.6**
(*ent*-**5.5** and *ent*-**5.6** are diastereomeric)



ent-**5.7**



ent-**5.9**

To 1-benzyl 4-isopropyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.10**) (46.0 mg, 0.10 mmol, 1.0 equiv) in tetrahydrofuran (1.0 mL) at 0 °C was added dropwise methylmagnesium bromide (1 M tetrahydrofuran solution) (0.11 mL, 0.11 mmol, 1.1 equiv) and the reaction stirred at 0 °C for 35 min. The mixture was allowed to warm to room temperature and stirred for a further 85 min. The reaction was quenched by addition of sat. aq. ammonium chloride solution (2 mL) and extracted with ethyl acetate (× 3). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*.

Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 20:80) gave benzyl (3*S*,4*R*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.7**) as a viscous yellow oil (9.4 mg, 0.02 mmol, 18%), benzyl (3*R*,4*R*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.9**) as a viscous yellow oil (trace quantity), benzyl (4*R*)-3-isopropoxy-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.5**) as a viscous yellow oil (13.2 mg, 0.02 mmol, 23%), and benzyl (4*R*)-3-isopropoxy-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.6**) as a viscous yellow oil (9.9 mg, 0.02 mmol, 18%); *ent*-**5.7**: R_f: 0.39 (EtOAc:petroleum ether 40-60, 25:75); $[\alpha]_D^{25} = -440.5$ (*c* = 1.00, $CHCl_3$); ee: 97% (Chiralcel OD; hexane:2-propanol, 85:15; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 26.12 min, t_R (minor) = 30.34 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.20 (dd, *J* = 7.5, 1.8 Hz, 1H, C3H), 7.48 (br s, 1H, C6H), 7.40 – 7.32 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.32 – 7.20 (m, 6H, C1H, C2H, 2 × C18H, C19H), 7.15 – 7.09 (m, 2H, 2 × C17H), 6.45 (br s, 1H, C9H), 5.29 (d, *J* = 12.2 Hz, 1H, C11H_AH$_B$), 5.25 (d, *J* = 12.2 Hz, 1H, C11H$_A$$H_B$), 5.17 (qd, *J* = 6.8, 0.9 Hz, 1H, C20H), 1.06 (d, *J* = 6.8 Hz, 3H, C22H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.2 (C21), 161.0 (C8), 154.2 (C10), 136.3 (C16), 135.6 (C12), 133.8 (C5), 129.5 (C19H), 129.4 (C1H), 129.2 (2 × C18H), 128.8 (2 × C14H), 128.6 (C15H), 128.4 (2 × C13H), 127.8 (2 × C17H), 125.4 (C6H), 125.2 (C2H), 124.0 (C3H), 122.3 (C7), 120.5 (C4), 77.9 (C20H), 68.7 (C11H_2), 56.0 (C9H), 19.3 (C22H_3); IR ν_{max} (cm^{-1}): 3064, 3034, 2986, 2930, 2853, 1758, 1702, 1603, 1586, 1573; HRMS (ESI) [M+H]$^+$: calculated for $C_{26}H_{22}NO_4^+$ 412.1543, found 412.1545, Δ 0.35 ppm; *ent*-**5.9**: R_f: 0.46 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = -463.5$ (*c* = 1.00, $CHCl_3$); ee: 95% (Chiralcel AD-H; hexane:2-propanol, 70:30; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 10.95 min, t_R (major) = 25.56 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.19 (dd, *J* = 7.7, 1.7 Hz, 1H, C3H), 7.56 (br d, *J* = 5.7 Hz, 1H, C6H), 7.41 – 7.31 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.31 – 7.23 (m, 4H, C1H,

2 × C18H, C19H), 7.21 (td, *J* = 7.6, 1.3 Hz, 1H, C2H), 7.16 – 7.11 (m, 2H, 2 × C17H), 6.47 (s, 1H, C9H), 5.34 (d, *J* = 12.3 Hz, 1H, C11$H_A$$H_B$), 5.24 (d, *J* = 12.3 Hz, 1H, C11$H_A$$H_B$), 5.01 (q, *J* = 6.9 Hz, 1H, C20H), 1.60 (d, *J* = 6.9 Hz, 3H, C22H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.2 (C21), 161.5 (C8), 154.5 (C10), 136.9 (C16), 135.6 (C12), 133.8 (C5), 129.4 (C1H), 129.4 (2 × C18H), 129.3 (C19H), 128.8 (2 × C14H), 128.6 (C15H), 128.2 (2 × C13H), 127.0 (2 × C17H), 125.2 (C2H), 125.2 (C6H), 124.0 (C3H), 121.4 (C7), 120.3 (C4), 76.6 (C20H), 68.7 (C11H_2), 55.6 (C9H), 18.5 (C22H_3); IR ν_{max} (cm^{-1}): 3064, 3032, 2980, 2931, 1758, 1700, 1603, 1586, 1573; HRMS (ESI) $[M+H]^+$: calculated for $C_{26}H_{22}NO_4^+$ 412.1543, found 412.1545, Δ 0.28 ppm; *ent*-**5.5**: R_f: 0.54 (EtOAc:petroleum ether 40-60, 25:75); $[\alpha]_D^{25} = -387.8$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.16 (dd, *J* = 7.7, 1.7 Hz, 1H, C3H), 7.64 (br d, *J* = 8.3 Hz, 1H, C6H), 7.39 – 7.24 (m, 9H, C1H, 2 × C18H, C19H, 2 × C13H, 2 × C14H, C15H), 7.19 (td, *J* = 7.6, 1.1 Hz, 1H, C2H), 7.16 – 7.11 (m, 2H, 2 × C17H), 6.47 (s, 1H, C9H), 5.78 (s, 1H, C20H), 5.32 (d, *J* = 12.3 Hz, 1H, C11$H_A$$H_B$), 5.23 (d, *J* = 12.3 Hz, 1H, C11$H_A$$H_B$), 4.09 (hept, *J* = 6.3 Hz, 1H, C22H), 1.33 (d, *J* = 6.2 Hz, 3H, C23$_A$$H_3$), 1.27 (d, *J* = 6.2 Hz, 3H, C13$_B$$H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.7 (C21), 154.7 (C8), 154.3 (C10), 137.6 (C16), 135.7 (C12), 134.9 (C5), 130.0 (C1H), 129.4 (2 × C18H), 129.2 (C19H), 128.7 (2 × C14H), 128.5 (C15H), 128.2 (2 × C13H), 126.8 (2 × C17H), 124.9 (C2H, C6H), 124.4 (C3H), 123.7 (C7), 119.6 (C4), 99.2 (C20H), 74.4 (C22H), 68.6 (C11H_2), 55.8 (C9H), 23.3 (C23$_A$$H_3$), 22.3 (C23$_B$$H_3$); IR ν_{max} (cm^{-1}): 3064, 3033, 2975, 2929, 1770, 1707, 1602, 1587, 1573; HRMS (ESI) $[M+H]^+$: calculated for $C_{28}H_{26}NO_5^+$ 456.1806, found 456.1807, Δ 0.39 ppm; *ent*-**5.6**: R_f: 0.46 (EtOAc:petroleum ether 40-60, 25:75); $[\alpha]_D^{25} = -414.7$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (dd, *J* = 7.7, 1.7 Hz, 1H, C3H), 7.53 (br s, 1H, C6H), 7.40 – 7.27 (m, 6H, C1H, 2 × C13H, 2 × C14H, C15H), 7.25 – 7.14 (m, 6H, C2H, 2 × C17H, 2 × C18H, C19H), 6.48 (s, 1H, C9H), 6.06 (d, *J* = 1.0 Hz, 1H, C20H), 5.31 (d, *J* = 12.3 Hz, 1H, C11$H_A$$H_B$), 5.26 (d, *J* = 12.2 Hz, 1H, C11$H_A$$H_B$), 4.00 (hept, *J* = 6.2 Hz, 1H, C22H), 1.13 (d, *J* = 6.2 Hz, 3H, C23$_A$$H_3$), 1.03 (d, *J* = 6.2 Hz,

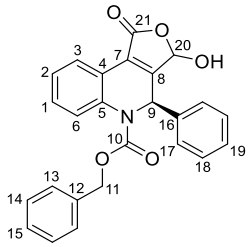
3H, C23$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.5 (C21), 154.4 (C10), 154.1 (C8), 136.9 (C16), 135.6 (C12), 134.6 (C5), 129.8 (C1H), 128.8 (2 × C14H or 2 × C18H), 128.7 (C15H or C19H), 128.6 (C15H or C19H), 128.6 (2 × C14H or 2 × C18H), 128.3 (2 × C13H), 127.6 (2 × C17H), 125.5 (C6H), 125.4 (C7), 125.2 (C2H), 124.7 (C3H), 120.2 (C4), 101.1 (C20H), 74.6 (C22H), 68.7 (C11H$_2$), 55.7 (C9H), 23.0 (C23$_A$H$_3$), 22.0 (C23$_B$H$_3$); IR ν_{max} (cm^{-1}): 3065, 3034, 2975, 2929, 1766, 1702, 1603, 1587, 1572; HRMS (ESI) $[M+H]^+$: calculated for $C_{28}H_{26}NO_5^+$ 456.1806, found 456.1807, Δ 0.25 ppm.

Samples of the enantiomers, benzyl (3*R*,4*S*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**5.7**) and benzyl (3*S*,4*S*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**5.9**) (484 mg, 0.83 mmol, 55%) were prepared as above using (*S*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (**4.10**) in place of (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.10**); **5.7**: $[\alpha]_D^{25} = +528.2$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel OD; hexane:2-propanol, 85:15; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 25.99 min, t_R (major) = 29.58 min; all other characterisation identical; **5.9**: $[\alpha]_D^{25} = +503.1$ (*c* = 1.00, $CHCl_3$); ee: 98% (Chiralcel AD-H; hexane:2-propanol, 70:30; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 10.90 min, t_R (minor) = 25.53 min; all other characterisation identical.

Using optimised conditions: Methylmagnesium bromide (1 M tetrahydrofuran solution) (33.0 mL, 33.0 mmol, 10.0 equiv) was diluted with tetrahydrofuran (15 mL) and cooled to –78 °C. To this well-stirred suspension was added dropwise 1-benzyl 4-isopropyl (*S*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (**4.10**) (1.5 g, 3.3 mmol, 1.0 equiv) in tetrahydrofuran (18 mL) over 35 min and the reaction stirred at –78 °C for a further 30 min. The reaction was quenched with DL-camphorsulfonic acid (1 M tetrahydrofuran solution)

(33.0 mL) and the mixture allowed to warm to room temperature. Water and ethyl acetate were added, and the layers separated. The aqueous portion was extracted with ethyl acetate (× 3). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 5:95 to 25:75) gave benzyl (3*R*,4*S*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**5.7**) as a viscous yellow oil (1.1 g, 2.6 mmol, 79%).

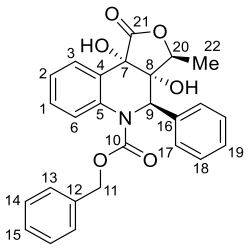
Benzyl (4*R*)-3-hydroxy-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-5.8)



To 1-benzyl 4-isopropyl (*R*)-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (*ent*-**4.10**) (456 mg, 1.0 mmol, 1.0 equiv) in tetrahydrofuran (5.0 mL) at 0 °C was added aq. sodium hydroxide (2 M) (5 mL) and the reaction stirred vigorously at room temperature for 30 min. The reaction was quenched at 0 °C with hydrochloric acid (2 M) (8 mL) and the mixture stirred at room temperature for 20 min. The reaction was extracted with ethyl acetate (× 3), and then the combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 100:0) gave benzyl (4*R*)-3-hydroxy-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.8**) as a viscous yellow oil (244 mg, 0.59 mmol, 59%); R_f: 0.41 (EtOAc); $[\alpha]_D^{25} = -518.0$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) (signal for OH

could not be identified): δ 8.07 (dd, *J* = 7.5, 1.7 Hz, 1H, C3H), 7.58 (br s, 1H, C6H), 7.36 – 7.09 (m, 11H, C1H, 2 × C13H, 2 × C14H, C15H, 2 × C17H, 2 × C18H, C19H), 7.18 (t, *J* = 7.6 Hz, 1H, C2H), 6.54 (s, 1H, C9H), 5.98 (br s, 1H, C20H), 5.25 – 5.07 (br m, 2H, $C11H_2$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.7 (C21), 155.4 (C8), 154.6 (C10), 136.9 (C16), 135.2 (C12), 134.6 (C5), 130.2 (C1H), 129.3 (2 × C18H), 129.2 (C19H), 128.7 (2 × C13H or 2 × C14H), 128.6 (C15H), 128.2 (2 × C13H or 2 × C14H), 127.0 (2 × C17H), 125.3 (C2H), 125.1 (C6H), 124.6 (C3H), 123.9 (C7), 119.7 (C4), 96.0 (C20H), 68.9 ($C11H_2$), 55.4 (C9H); IR ν_{max} (cm^{-1}): 3368 (br), 3064, 3033, 2956, 1769, 1700, 1602, 1586, 1573; HRMS (ESI) $[M–H]^–$: calculated for $C_{25}H_{18}NO_5^–$ 412.1191, found 412.1190, Δ –0.24 ppm.

Benzyl (3*S*,3a*S*,4*R*,9b*S*)-3a,9b-dihydroxy-3-methyl-1-oxo-4-phenyl-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-5.11)



To cerium(III) chloride heptahydrate (3.7 mg, 0.01 mmol, 0.1 equiv) and sodium periodate (32.1 mg, 0.15 mmol, 1.5 equiv) was added water (60 µL) and the suspension stirred with gentle warming until a yellow colour was apparent. The reaction was cooled to 0 °C and then ethyl acetate (70 µL) and acetonitrile (170 µL) were added. Ruthenium(III) chloride (1.3 mg, 0.005 mmol, 0.05 equiv) was added and the suspension stirred for 2 min. To this was added benzyl (3*S*,4*R*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.7**) (41.1 mg, 0.1 mmol, 1.0 equiv) in ethyl acetate (100 µL) and the reaction stirred at 0 °C for 10 min. To this was added sequentially sodium sulfate (50 mg) and ethyl acetate and

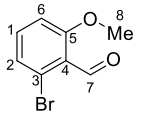
the mixture was filtered through Celite®, washing with ethyl acetate. The filtrate was washed with sat. aq. sodium sulphite solution, then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 40:60) gave benzyl (3*S*,3a*S*,4*R*,9b*S*)-3a,9b-dihydroxy-3-methyl-1-oxo-4-phenyl-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.11**) as a yellow oil (23.0 mg, 0.05 mmol, 52%); R_f: 0.30 (EtOAc:petroleum ether 40-60, 40:60); $[\alpha]_D^{25} = -118.7$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74 (dd, *J* = 8.3, 1.1 Hz, 1H, C6H), 7.59 (dd, *J* = 7.8, 1.5 Hz, 1H, C3H), 7.44 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H, C1H), 7.30 – 7.26 (m, 8H, 2 × C14H, C15H, 2 × C17H, 2 × C18H, C19H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H, C2H), 7.16 – 7.10 (m, 2H, 2 × C13H), 5.92 (s, 1H, C9H), 5.17 (s, 2H, $C11H_2$), 4.38 (q, *J* = 7.1 Hz, 1H, C20H), 4.19 (s, 1H, C17OH), 3.99 (s, 1H, C8OH), 0.37 (d, *J* = 7.1 Hz, 3H, $C22H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 173.9 (C21), 154.7 (C10), 137.0 (C5 or C16), 136.9 (C5 or C16), 135.7 (C12), 130.7 (C1H), 128.9 (2 × C14H or 2 × C18H), 128.6 (2 × C14H or 2 × C18H), 128.3 (C15H), 128.2 (C19H), 127.8 (C3H), 127.7 (2 × C13H), 127.0 (C4), 126.6 (2 × C17H), 126.5 (C6H), 126.0 (C2H), 82.7 (C20H), 79.6 (C8), 74.0 (C7), 68.4 ($C11H_2$), 63.6 (C9H), 14.4 ($C22H_3$); IR ν_{max} (cm^{-1}): 3393 (br), 3064, 3034, 3011, 2946, 2850, 1777, 1691, 1604, 1584; HRMS (ESI) $[M+Na]^+$: calculated for $C_{26}H_{23}NNaO_6^+$ 468.1418, found 468.1418, Δ –0.01 ppm.

A sample of the enantiomer, benzyl (3*R*,3a*R*,4*S*,9b*R*)-3a,9b-dihydroxy-3-methyl-1-oxo-4-phenyl-1,3a,4,9b-tetrahydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**5.11**) (712 mg, 1.6 mmol, 66%) was prepared as above using benzyl (3*R*,4*S*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**5.7**) in place of benzyl (3*S*,4*R*)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**5.7**), using 5× all

quantities except ruthenium(III) chloride; $[\alpha]_{\mathrm{D}}^{25} = +102.5$ (c = 1.00, $CHCl_3$); all other characterisation identical.

2-Bromo-6-methoxybenzaldehyde (6.6)

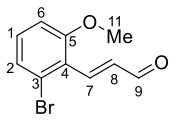
Prepared by procedure of Durst.[186]



To 2-bromo-6-hydroxybenzaldehyde (**6.9**) (280.0 mg, 1.4 mmol, 1.0 equiv) and potassium carbonate (697 mg, 5.0 mmol, 3.6 equiv) was added acetone (7.0 mL) and the mixture stirred at room temperature for 15 min. To this was added iodomethane (1.4 mL, 22.4 mmol, 16 equiv) and the reaction was stirred at room temperature for 15.5 h. Water (21 mL) was added and this solution was extracted with diethyl ether, then the organic fraction was dried ($MgSO_4$) and concentrated *in vacuo* to give 2-bromo-6-methoxybenzaldehyde (**6.6**) as an off-white solid which was used without further purification.

To obtain a pure sample, the above product was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 15:85) to give 2-bromo-6-methoxybenzaldehyde (**6.6**) as an off-white solid; R_f: 0.30 (Et_2O:petroleum ether 40-60, 30:70); m.p.: 56.5–58.0 °C (lit.[180] 55–57 °C); ^{1}H NMR (CDCl3, 500 MHz): δ 10.40 (s, 1H, C7H), 7.31 (dd, J = 8.4, 8.0 Hz, 1H, C1H), 7.23 (dd, J = 8.0, 1.0 Hz, 1H, C2H), 6.95 (dd, J = 8.4, 1.0 Hz, 1H, C6H), 3.91 (s, 3H, $C8H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.5 (C7H), 162.1 (C5), 134.9 (C1H), 126.6 (C2H), 125.0 (C3), 123.5 (C4), 111.2 (C6H), 56.3 ($C8H_3$); IR ν_{max} (cm^{-1}): 2980, 2884, 1694, 1583, 1566; HRMS (Methane CI) $[M+H]^+$: calculated for $C_8H_8{}^{79}BrO_2^+$ 214.9702, found 214.9702, Δ 0.09 ppm; data in accordance with literature.[180]

(*E*)-3-(2-Bromo-6-methoxyphenyl)acrylaldehyde (6.7)



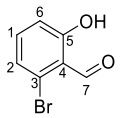
To (*E*)-3-(2-bromo-6-methoxyphenyl)prop-2-en-1-ol (**6.13**) (162 mg, 0.67 mmol, 1.0 equiv) in CH_2Cl_2 (6.5 mL) was added Dess-Martin periodinane (565 mg, 1.33 mmol, 2.0 equiv) and the solution stirred at room temperature for 2 h. The reaction was quenched with sat. aq. sodium thiosulfate solution (7.0 mL) and the mixture stirred until it became clear (3 h). The reaction was extracted with ethyl acetate (× 3) and the combined organic portions were washed with brine, then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 20:80) to give (*E*)-3-(2-bromo-6-methoxyphenyl)acrylaldehyde (**6.7**) as an off-white crystalline solid (149 mg, 0.62 mmol, 93%); R_f: 0.23 (Et_2O:petroleum ether 40-60, 30:70); m.p.: 69.5–71.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.71 (d, *J* = 7.9 Hz, 1H, C9H), 7.79 (dd, *J* = 16.1, 0.5 Hz, 1H, C7H), 7.29 (dd, *J* = 8.0, 1.1 Hz, 1H, C2H), 7.20 (t, *J* = 8.2 Hz, 1H, C1H), 7.13 (dd, *J* = 16.0, 7.9 Hz, 1H, C8H), 6.92 (d, *J* = 8.4 Hz, 1H, C6H), 3.91 (s, 3H, C10H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 195.8 (C9H), 160.1 (C5), 148.5 (C7H), 134.4 (C8H), 132.1 (C1H), 127.6 (C3), 125.9 (C2H), 122.7 (C4), 110.6 (C6H), 56.0 (C10H_3); IR ν_{max} (cm^{-1}): 3005, 2972, 2943, 2913, 2838, 2808, 2738, 2707, 1674, 1618, 1583, 1561; HRMS (EI) $[M+H]^+$: calculated for $C_{10}H_8{}^{79}BrO_2^+$ 238.9702, found 238.9707, Δ 2.09 ppm.

Alternative preparation: To (*E*)-3-(2-bromo-6-hydroxyphenyl)acrylaldehyde (**6.17**) (2.0 g, 8.8 mmol, 1.0 equiv) and potassium carbonate (3.7 g, 26.4 mmol, 3.0 equiv) was added acetone (45 mL) and the mixture stirred at room temperature for 15 min. To this was added iodomethane (1.6 mL, 26.4 mmol, 3.0 equiv) and the reaction was stirred at room temperature for 23 h. Water (140 mL) was added and the reaction extracted with ethyl acetate (× 2). The combined organic fractions were washed with brine, dried (Na_2SO_4), and

concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80) to give (*E*)-3-(2-bromo-6-methoxyphenyl)acrylaldehyde (**6.7**) as a pale yellow solid (2.1 g, 8.7 mmol, 99%).

2-Bromo-6-hydroxybenzaldehyde (6.9)

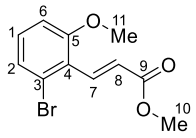
Prepared by procedure of Evans.[179]



Diisopropylamine (4.6 mL, 32.9 mmol, 1.2 equiv) was dissolved in tetrahydrofuran (75 mL) and cooled to 0 °C. To this was added dropwise *n*-butyllithium (1.46 M hexanes solution) (20.7 mL, 30.2 mmol, 1.1 equiv) over 30 min, keeping the internal temperature < 10 °C. The solution was stirred at 0 °C for 20 min, and then cooled to –78 °C. 3-Bromophenyl diethylcarbamate (**6.14**) (7.5 g, 27.4 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (75 mL) and cooled to –78 °C. This was added dropwise to the LDA solution over 70 min, keeping the internal temperature < –70 °C, and the mixture stirred for 35 min. *N*,*N*-Dimethylformamide (5.3 mL, 68.6 mmol, 2.5 equiv) was added dropwise over 25 min, keeping the internal temperature < –70 °C, and the solution stirred at –78 °C for 135 min before being allowed to warm to 0 °C over 15 min. The reaction was added *via* cannula to hydrochloric acid (2 M) (150 mL) at 0 °C over 30 min and the mixture stirred at room temperature for 63.5 h. The organic layer was separated and the aqueous extracted with petroleum ether 30-40 (× 4). The combined organics were washed with water (× 2), then brine, and were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 5:95) to give 2-bromo-6-hydroxybenzaldehyde (**6.9**) as a pale yellow solid (3.0 g, 14.9 mmol, 54%); R_f: 0.48

(Et_2O:petroleum ether 40-60, 5:95); m.p.: 50.5–52.0 °C (lit.[181] 50–52 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.98 (s, 1H, OH), 10.33 (s, 1H, C7H), 7.33 (dd, *J* = 8.5, 7.8 Hz, 1H, C1H), 7.16 (dd, *J* = 7.9, 1.0 Hz, 1H, C2H), 6.94 (dt, *J* = 8.5, 0.8 Hz, 1H, C6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 198.0 (C7H), 164.1 (C5), 137.7 (C1H), 127.6 (C3), 124.6 (C2H), 118.0 (C6H), 117.9 (C4); IR ν_{max} (cm^{-1}): 3082, 3032, 2902, 1649, 1612, 1569; HRMS (ESI) $[M–H]^–$: calculated for $C_7H_4{}^{79}BrO_2^–$ 198.9400, found 198.9398, Δ –1.07 ppm; data in accordance with literature.[181]

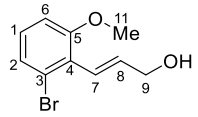
Methyl (*E*)-3-(2-bromo-6-methoxyphenyl)acrylate (6.12)



To a well-stirred suspension of sodium hydride (60% in mineral oil) (93 mg, 2.3 mmol, 2.5 equiv) in tetrahydrofuran (23 mL) at 0 °C was added dropwise trimethyl phosphonoacetate (**6.11**) (0.45 mL, 2.8 mmol, 3.0 equiv), then the mixture was allowed to warm to room temperature and stirred for 35 min. To this was added dropwise 2-bromo-6-methoxybenzaldehyde (**6.6**) (195 mg, 0.9 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL) and the reaction stirred for 3 h. Water (30 mL) was added and the mixture extracted with ethyl acetate (× 3). The combined organic portions were washed with brine then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 30:70) to give methyl (*E*)-3-(2-bromo-6-methoxyphenyl)acrylate (**6.12**) as a white solid (221 mg, 0.82 mmol, 90%); R_f: 0.42 (Et_2O:petroleum ether 40-60, 30:70); m.p.: 86.5–88.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (d, *J* = 16.2 Hz, 1H, C7H), 7.25 (dd, *J* = 8.0, 1.1 Hz, 1H, C2H), 7.14 (t, *J* = 8.2 Hz, 1H, C1H), 6.88 (d, *J* = 8.3 Hz, 1H, C6H), 6.83 (d, *J* = 16.1 Hz, 1H, C8H), 3.89 (s, 3H, $C11H_3$), 3.82 (s, 3H, $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz):

δ 168.1 (C9), 159.9 (C5), 140.0 (C7H), 131.0 (C1H), 127.2 (C3), 125.8 (C2H), 123.9 (C8H), 123.3 (C4), 110.4 (C6H), 56.0 ($C11H_3$), 51.9 ($C10H_3$); IR ν_{max} (cm^{-1}): 3003, 2948, 2839, 1713, 1626, 1584, 1561; HRMS (EI) $[M]^+$: calculated for $C_{11}H_{11}{}^{79}BrO_3{}^+$ 269.9886, found 269.9885, Δ –0.37 ppm.

(*E*)-3-(2-Bromo-6-methoxyphenyl)prop-2-en-1-ol (6.13)

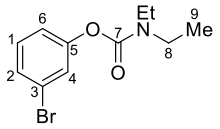


To methyl (*E*)-3-(2-bromo-6-methoxyphenyl)acrylate (**6.12**) (200 mg, 0.74 mmol, 1.0 equiv) in CH_2Cl_2 (7.5 mL) at –78 °C was added dropwise diisobutylaluminium hydride (1 M hexanes solution) (2.21 mL, 2.21 mmol, 3.0 equiv) over 10 min and the solution stirred for 30 min. The reaction was allowed to warm to 0 °C over 15 min and was quenched by sequential addition of water (89 µL), sodium hydroxide (15% aqueous solution) (89 µL), and water (220 µL). The mixture was allowed to warm to room temperature and stirred for 20 min, and then magnesium sulfate added until it was free-flowing, and the mixture stirred for a further 15 min. The reaction was filtered through Celite®, washing with CH_2Cl_2, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 50:50) to give (*E*)-3-(2-bromo-6-methoxyphenyl)prop-2-en-1-ol (**6.13**) as an off-white solid (179.0 mg, 0.74 mmol, quant.); R_f: 0.23 (Et_2O:petroleum ether 40-60, 50:50); m.p.: 36.0–38.0 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (dd, *J* = 8.0, 1.1 Hz, 1H, C2H), 7.04 (t, *J* = 8.2 Hz, 1H, C1H), 6.85 (dd, *J* = 8.2, 1.1 Hz, 1H, C6H), 6.74 (dt, *J* = 16.0, 1.4 Hz, 1H, C7H), 6.65 (dt, *J* = 16.1, 5.3 Hz, 1H, C8H), 4.37 (ddd, *J* = 6.0, 5.4, 1.4 Hz, 2H, $C9H_2$), 3.85 (s, 3H, $C10H_3$), 1.50 (t, *J* = 6.1 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.6 (C5), 135.7 (C8H), 128.6

(C1H), 125.9 (C7H), 125.6 (C4), 125.5 (C2H), 125.2 (C3), 110.2 (C6H), 64.6 ($C9H_2$), 55.9 ($C10H_3$); IR ν_{max} (cm^{-1}): 3333 (br), 3004, 2938, 2915, 2861, 2836, 1585, 1562; HRMS (EI) $[M]^+$: calculated for $C_{10}H_{11}{}^{79}BrO_2{}^+$ 241.9937, found 241.9935, Δ –0.81 ppm.

3-Bromophenyl diethylcarbamate (6.14)

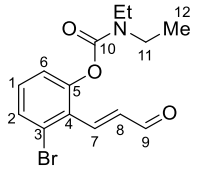
Prepared by procedure of Sanz.[184]



To a well-stirred suspension of sodium hydride (60% in mineral oil) (4.0 g, 101.1 mmol, 3.5 equiv) in tetrahydrofuran (40 mL) was added dropwise 3-bromophenol (**6.8**) (5.0 g, 28.9 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) and the mixture stirred at room temperature for 50 min. To this was added dropwise diethylcarbamoyl chloride (7.3 mL, 57.8 mmol, 2.0 equiv) in tetrahydrofuran (10 mL) and the mixture stirred for 6 h. The mixture was cooled to 0 °C, quenched with water (50 mL), and the organic layer separated. The aqueous phase was extracted with diethyl ether (× 2) and the combined organic fractions were stirred vigorously with aq. sodium hydroxide (2 M) for 15 h. The layers were separated, and the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 7:93) to give 3-bromophenyl diethylcarbamate (**6.14**) as a pale yellow oil (7.8 g, 28.6 mmol, 99%); R_f: 0.27 (EtOAc:petroleum ether 40-60, 9:91); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 – 7.30 (m, 2H, C2H, C4H), 7.21 (t, *J* = 8.3 Hz, 1H, C1H), 7.08 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H, C6H), 3.42 (q, *J* = 7.1 Hz, 2H, $C8_AH_2$), 3.38 (q, *J* = 7.1 Hz, 2H, $C8_BH_2$), 1.24 (t, *J* = 7.1 Hz, 3H, $C9_AH_3$), 1.20 (t, *J* = 7.1 Hz, 3H,

$C9_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.7 (C7), 152.2 (C5), 130.3 (C1H), 128.3 (C4H), 125.4 (C2H), 122.2 (C3), 120.7 (C6H), 42.5 ($C8_BH_2$), 42.1 ($C8_AH_2$), 14.3 ($C9_AH_3$), 13.4 ($C9_BH_3$); IR ν_{max} (cm^{-1}): 2975, 2934, 1716, 1582; HRMS (ESI) $[M+Na]^+$: calculated for $C_{11}H_{14}{}^{79}BrNNaO_2^+$ 294.0100, found 294.0101, Δ 0.3 ppm; data in accordance with literature.[184]

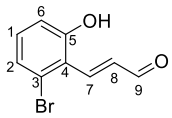
(*E*)-3-Bromo-2-(3-oxoprop-1-en-1-yl)phenyl diethylcarbamate (6.16)



Diisopropylamine (67 µL, 0.48 mmol, 1.2 equiv) was dissolved in tetrahydrofuran (0.7 mL) and cooled to 0 °C. To this was added dropwise *n*-butyllithium (1.50 M hexanes solution) (0.29 mL, 0.44 mmol, 1.1 equiv) over 10 min. The solution was stirred at 0 °C for 15 min, and then cooled to –78 °C. 3-Bromophenyl diethylcarbamate (**6.14**) (107 mg, 0.40 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (0.7 mL) and cooled to –78 °C. This was added dropwise to the LDA solution over 10 min and the mixture stirred for 25 min. 3-(Dimethylamino)acrylaldehyde (**6.15**) (52 µL, 0.52 mmol, 1.3 equiv) was dissolved in tetrahydrofuran (0.3 mL), cooled to –78 °C, and added dropwise over 10 min. The solution was stirred at –78 °C for 100 min before being allowed to warm to room temperature and stirred for 90 min total. To this was added hydrochloric acid (2 M) (2.0 mL) at 0 °C and the mixture was stirred at room temperature for 15 min. The organic layer was separated and the aqueous extracted with ethyl acetate (× 3). The combined organics were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90) to give (*E*)-3-bromo-2-(3-oxoprop-1-en-1-yl)phenyl diethylcarbamate (**6.16**) as a pale yellow oil (68.4 mg 0.21 mmol, 52%) along with

(*E*)-3-(2-bromo-6-hydroxyphenyl)acrylaldehyde (**6.17**) (*vide infra*) as an off-white solid (4.9 mg, 0.02 mmol, 5%); R_f: 0.25 (Et_2O:petroleum ether 40-60, 30:70); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.71 (d, *J* = 7.8 Hz, 1H, C9H), 7.60 (d, *J* = 16.3 Hz, 1H, C7H), 7.52 (dd, *J* = 8.1, 1.2 Hz, 1H, C2H), 7.25 (td, *J* = 8.1, 0.5 Hz, 1H, C1H), 7.14 (ddd, *J* = 8.2, 1.2, 0.5 Hz, 1H, C6H), 6.61 (dd, *J* = 16.3, 7.8 Hz, 1H, C8H), 3.44 (q, *J* = 7.1 Hz, 2H, $C11_AH_2$), 3.35 (q, *J* = 7.1 Hz, 2H, $C11_BH_2$), 1.24 (t, *J* = 7.1 Hz, 3H, $C12_AH_3$), 1.16 (t, *J* = 7.1 Hz, 3H, $C12_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 194.1 (C9H), 153.0 (C10), 150.5 (C5), 147.7 (C7H), 134.5 (C8H), 131.3 (C1H), 130.5 (C2H), 128.6 (C4), 125.2 (C3), 123.1 (C6H), 42.5 ($C11_BH_2$), 42.0 ($C11_AH_2$), 14.4 ($C12_AH_3$), 13.4 ($C12_BH_3$); IR ν_{max} (cm^{-1}): 2975, 2935, 2876, 2811, 2733, 1719, 1683, 1624, 1591, 1562; HRMS (ESI) $[M+Na]^+$: calculated for $C_{14}H_{16}{}^{79}BrNNaO_3{}^+$ 348.0206, found 348.0206, Δ 0.06 ppm.

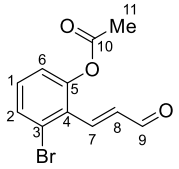
(*E*)-3-(2-Bromo-6-hydroxyphenyl)acrylaldehyde (6.17)



To (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**4.14**) (3.51 g, 8.1 mmol, 2.0 equiv) in tetrahydrofuran (25 mL) at 0 °C was added in one portion potassium *tert*-butoxide (1.60 g, 14.2 mmol, 3.5 equiv) and the mixture stirred at room temperature for 15 min. To this was added 2-bromo-6-hydroxybenzaldehyde (**6.9**) (0.82 g, 4.1 mmol, 1.0 equiv) in tetrahydrofuran (15 mL). The reaction was heated to reflux and stirred for 17 h before being allowed to cool to room temperature and hydrochloric acid (2 M) (50 mL) added. This was stirred at room temperature for a further 30 min and then extracted with ethyl acetate (× 3). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent

load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave (*E*)-3-(2-bromo-6-hydroxyphenyl)acrylaldehyde (**6.17**) as a pale yellow solid (0.75 g, 3.3 mmol, 81%); R_f: 0.15 (EtOAc:petroleum ether 40-60, 20:80); m.p.: 144.5–146.5 °C; ^{1}H NMR (acetone-d_6, 500 MHz): δ 9.88 (br s, 1H, OH), 9.74 (d, *J* = 7.8 Hz, 1H, C9H), 7.87 (dd, *J* = 16.0, 0.6 Hz, 1H, C7H), 7.26 (dd, *J* = 8.0, 1.2 Hz, 1H, C2H), 7.20 (t, *J* = 8.1 Hz, 1H, C1H), 7.20 (dd, *J* = 16.0, 7.8 Hz, 1H, C8H), 7.05 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H, C6H); ^{13}C NMR (acetone-d_6, 126 MHz): δ 195.5 (C9H), 159.2 (C5), 148.6 (C7H), 134.9 (C8H), 133.1 (C1H), 127.5 (C3), 125.7 (C2H), 121.7 (C4), 116.9 (C6H); IR ν_{max} (cm^{-1}): 3153 (br), 2834, 2830, 2752, 1642, 1608, 1585, 1573; HRMS (ESI) $[M–H]^–$: calculated for $C_9H_6{}^{79}BrO_2^–$ 224.9557, found 224.9556, Δ –0.3 ppm.

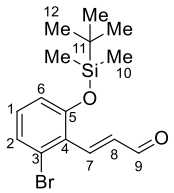
(*E*)-3-Bromo-2-(3-oxoprop-1-en-1-yl)phenyl acetate (6.20)



To (*E*)-3-(2-bromo-6-hydroxyphenyl)acrylaldehyde (**6.17**) (147 mg, 0.65 mmol, 1.0 equiv) in tetrahydrofuran (3.5 mL) at 0 °C was added potassium carbonate (134 mg, 0.97 mmol, 1.5 equiv) and the mixture stirred at 0 °C for 15 min. Acetic anhydride (0.15 mL, 1.62 mmol, 2.5 equiv) was added dropwise then the reaction allowed to warm to room temperature and stirred for 110 min. The reaction was quenched by the addition of water and ethyl acetate, and the layers were separated. The aqueous portion was extracted with ethyl acetate. The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80) gave (*E*)-3-bromo-2-(3-oxoprop-1-en-1-yl)phenyl acetate (**6.20**) as an off-white solid (174 mg, 0.65 mmol, quant.); R_f: 0.34 (20:80,

EtOAc:petroleum ether 40-60); m.p.: 80.5–82.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.71 (d, *J* = 7.7 Hz, 1H, C9H), 7.57 (d, *J* = 16.4 Hz, 1H, C7H), 7.56 (dd, *J* = 8.1, 1.1 Hz, 1H, C2H), 7.27 (t, *J* = 8.1 Hz, 1H, C1H), 7.11 (ddd, *J* = 8.2, 1.2, 0.5 Hz, 1H, C6H), 6.69 (dd, *J* = 16.3, 7.7 Hz, 1H, C8H), 2.29 (s, 3H, C11H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 194.0 (C9H), 168.6 (C10), 149.5 (C5), 147.2 (C7H), 134.6 (C8H), 131.5 (C1H), 131.2 (C2H), 128.0 (C4), 125.6 (C3), 122.9 (C6H), 21.2 (C11H_3); IR ν_{max} (cm^{-1}): 3081, 3030, 2828, 2816, 2737, 1767, 1681, 1621, 1591, 1561; HRMS (EI) $[M]^+$: calculated for $C_{11}H_9{}^{79}BrO_3^+$ 267.9730, found 267.9734, Δ –1.65 ppm.

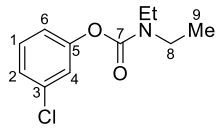
(*E*)-3-(2-Bromo-6-((*tert*-butyldimethylsilyl)oxy)phenyl)acrylaldehyde (6.21)



To (*E*)-3-(2-bromo-6-hydroxyphenyl)acrylaldehyde (**6.17**) (34.1 mg, 0.15 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (0.75 mL) at 0 °C was added imidazole (91.9 mg, 1.35 mmol, 9.0 equiv) followed by *tert*-butyldimethylsilyl chloride (90.4 mg, 0.60 mmol, 4.0 equiv), and the reaction stirred at 0 °C for 15 min. Water (2 mL) and ethyl acetate (2 mL) were added and the layers separated. The aqueous portion was extracted with ethyl acetate, and then the combined organic portions were washed with water (× 2). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, diethyl ether:pentane, 1:99 to 6:94) gave (*E*)-3-(2-bromo-6-((*tert*-butyldimethylsilyl)oxy)phenyl)acrylaldehyde (**6.21**) as a pale yellow oil (30.0 mg, 0.09 mmol, 59%); R_f: 0.54 (10:90, Et_2O:petroleum ether 40-60); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.70 (d, *J* = 7.9 Hz, 1H, C9H), 7.70 (d, *J* = 16.2 Hz, 1H, C7H), 7.27 (dd, *J* = 8.0, 1.1 Hz,

1H, C2H), 7.09 (t, *J* = 8.2 Hz, 1H, C1H), 7.01 (dd, *J* = 16.2, 7.9 Hz, 1H, C8H), 6.84 (ddd, *J* = 8.3, 1.2, 0.6 Hz, 1H, C6H), 0.98 (s, 9H, 3 × C12H_3), 0.25 (s, 6H, 2 × C10H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 194.8 (C9H), 155.9 (C5), 148.6 (C7H), 134.6 (C8H), 131.4 (C1H), 126.6 (C2H), 126.1 (C3), 125.8 (C4), 119.2 (C6H), 25.9 (3 × C12H_3), 18.5 (C11), -3.8 (2 × C10H_3); IR ν_{max} (cm^{-1}): 2955, 2930, 2896, 2885, 2859, 2821, 2804, 2729, 1681, 1621, 1583, 1556; HRMS (ESI) $[M+H]^+$: calculated for $C_{15}H_{22}{}^{79}BrO_2Si^+$ 341.0567, found 341.0569, Δ 0.47 ppm.

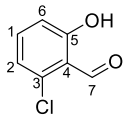
3-Chlorophenyl diethylcarbamate (6.23)



To a well-stirred suspension of sodium hydride (60% in mineral oil) (5.4 g, 136.1 mmol, 3.5 equiv) in tetrahydrofuran (50 mL) was added dropwise 3-chlorophenol (**6.22**) (5.0 g, 38.9 mmol, 1.0 equiv) in tetrahydrofuran (15 mL) and the mixture stirred at room temperature for 25 min. To this was added dropwise diethylcarbamoyl chloride (9.9 mL, 77.8 mmol, 2.0 equiv) in tetrahydrofuran (15 mL) and the mixture stirred for 6 h. The mixture was cooled to 0 °C, quenched with water (60 mL), and the organic layer separated. The aqueous phase was extracted with diethyl ether (× 2) and the combined organic fractions were stirred vigorously with aq. sodium hydroxide (2 M) for 16 h. The layers were separated, and the aqueous phase was extracted with diethyl ether. The combined organic fractions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 10:90 to 25:75) to give 3-chlorophenyl diethylcarbamate (**6.23**) as an amber oil (8.5 g, 37.2 mmol, 96%); R_f: 0.31 (EtOAc:petroleum ether 40-60, 10:90); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (t, *J* = 8.3 Hz, 1H,

C1H), 7.20 – 7.15 (m, 2H, C2H, C4H), 7.04 (ddd, *J* = 8.2, 2.2, 1.1 Hz, 1H, C6H), 3.42 (q, *J* = 7.1 Hz, 2H, $C8_AH_2$), 3.38 (q, *J* = 7.1 Hz, 2H, $C8_BH_2$), 1.25 (t, *J* = 7.1 Hz, 3H, $C9_AH_3$), 1.20 (t, *J* = 7.1 Hz, 3H, $C9_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.8 (C7), 152.2 (C5), 134.5 (C3), 130.0 (C1H), 125.4 (C2H), 122.5 (C4H), 120.3 (C6H), 42.5 ($C8_BH_2$), 42.1 ($C8_AH_2$), 14.4 ($C9_AH_3$), 13.5 ($C9_BH_3$); IR ν_{max} (cm^{-1}): 2976, 2936, 2877, 1717, 1591; HRMS (ESI) $[M+Na]^+$: calculated for $C_{11}H_{15}{}^{35}ClNO_2^+$ 228.0786, found 228.0786, Δ 0.2 ppm; data in accordance with literature.[184]

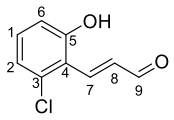
2-Chloro-6-hydroxybenzaldehyde (6.24)



Diisopropylamine (3.5 mL, 25.3 mmol, 1.2 equiv) was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C. To this was added dropwise *n*-butyllithium (1.54 M hexanes solution) (15.1 mL, 23.2 mmol, 1.1 equiv) over 30 min. The solution was stirred at 0 °C for 20 min, and then cooled to –78 °C. 3-Chlorophenyl diethylcarbamate (**6.23**) (4.8 g, 21.1 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (20 mL) and cooled to –78 °C. This was added dropwise to the LDA solution over 30 min, and the mixture stirred for 30 min. *N*,*N*-Dimethylformamide (4.1 mL, 52.7 mmol, 2.5 equiv) was added dropwise over 20 min, and the solution stirred at –78 °C for 120 min before being allowed to warm to 0 °C over 20 min. The reaction was added *via* cannula to hydrochloric acid (2 M) (50 mL) at 0 °C and the mixture stirred at room temperature for 18 h. The organic layer was separated and the aqueous extracted with petroleum ether 40-60 (× 3). The combined organics were washed with water (× 2), then brine, and were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, Et_2O:petroleum ether 40-60, 5:95) to give

2-chloro-6-hydroxybenzaldehyde (**6.24**) as an off-white solid (1.8 g, 11.5 mmol, 55%); R_f: 0.57 (Et_2O:petroleum ether 40-60, 5:95); m.p.: 51.0–52.0 °C (lit. 51–52 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.90 (s, 1H, OH), 10.40 (s, 1H, C7H), 7.40 (dd, *J* = 8.4, 7.9 Hz, 1H, C1H), 6.94 (dd, *J* = 7.9, 1.0 Hz, 1H, C2H), 6.89 (dt, *J* = 8.5, 0.8 Hz, 1H, C6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 195.5 (C7H), 164.0 (C5), 138.2 (C3), 137.5 (C1H), 121.1 (C2H), 117.2 (C6H), 117.1 (C4); IR ν_{max} (cm^{-1}): 3136, 3078, 3001, 2962, 2916, 1646, 1625, 1604, 1573, 1518, 1508; HRMS (ESI) $[M–H]^–$: calculated for $C_7H_4{}^{35}ClO_2^–$ 154.9905, found 154.9904, Δ –1.12 ppm; data in accordance with literature.[182]

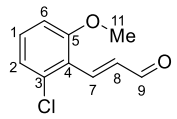
(*E*)-3-(2-Chloro-6-hydroxyphenyl)acrylaldehyde (6.25)



To (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**4.14**) (5.5 g, 12.8 mmol, 2.0 equiv) in tetrahydrofuran (30mL) at 0 °C was added in one portion potassium *tert*-butoxide (2.2 g, 19.2 mmol, 3.0 equiv) and the mixture stirred at room temperature for 15 min. To this was added 2-chloro-6-hydroxybenzaldehyde (**6.24**) (1.0 g, 6.4 mmol, 1.0 equiv) in tetrahydrofuran (30 mL). The reaction was heated to reflux and stirred for 17 h before being allowed to cool to room temperature and hydrochloric acid (2 M) (80 mL) added. This was stirred at room temperature for a further 70 min and then extracted with ethyl acetate (× 3). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 30:70) gave (*E*)-3-(2-chloro-6-hydroxyphenyl)acrylaldehyde (**6.25**) as a pale yellow solid (0.9 g, 4.8 mmol, 76%); R_f: 0.15

(EtOAc:petroleum ether 40-60, 20:80); m.p.: 142.0–143.5 °C; ^{1}H NMR (acetone-d_6, 500 MHz): δ 9.92 (s, 1H, OH), 9.73 (d, *J* = 7.8 Hz, 1H, C9H), 7.92 (dd, *J* = 16.0, 0.7 Hz, 1H, C7H), 7.27 (t, *J* = 8.1 Hz, 1H, C1H), 7.22 (dd, *J* = 16.0, 7.8 Hz, 1H, C8H), 7.06 (dd, *J* = 8.0, 1.1 Hz, 1H, C2H), 7.01 (ddd, *J* = 8.2, 1.1, 0.7 Hz, 1H, C6H); ^{13}C NMR (acetone-d_6, 126 MHz): δ 195.6 (C9H), 159.5 (C5), 145.8 (C7H), 136.7 (C3), 134.6 (C8H), 132.8 (C1H), 122.2 (C2H), 120.2 (C4), 116.2 (C6H); IR ν_{max} (cm^{-1}): 3123 (br), 2835, 2822, 2748, 1645, 1610, 1586, 1575; HRMS (ESI) $[M–H]^-$: calculated for $C_9H_6{}^{35}ClO_2^-$ 181.0062, found 181.0062, Δ 0.25 ppm.

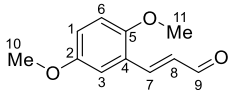
(*E*)-3-(2-Chloro-6-methoxyphenyl)acrylaldehyde (6.26)



To (*E*)-3-(2-chloro-6-hydroxyphenyl)acrylaldehyde (**6.25**) (400 mg, 2.2 mmol, 1.0 equiv) and potassium carbonate (910 mg, 6.6 mmol, 3.0 equiv) was added acetone (11 mL) and the mixture stirred at room temperature for 20 min. To this was added iodomethane (0.41 mL, 6.6 mmol, 3.0 equiv) and the reaction was stirred at room temperature for 21 h. Water (30 mL) was added and the reaction extracted with ethyl acetate (× 3). The combined organic fractions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80) to give (*E*)-3-(2-chloro-6-methoxyphenyl)acrylaldehyde (**6.26**) as a pale yellow solid (400 mg, 2.0 mmol, 92%); R_f: 0.35 (Et_2O:petroleum ether 40-60, 20:80); m.p.: 55.5–57.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.69 (d, *J* = 8.0 Hz, 1H, C9H), 7.83 (dd, *J* = 16.1, 0.6 Hz, 1H, C7H), 7.28 (t, *J* = 8.3 Hz, 1H, C1H), 7.16 (dd, *J* = 16.1, 7.9 Hz, 1H, C8H), 7.08 (dd, *J* = 8.1, 1.1 Hz, 1H, C2H), 6.87 (ddd, *J* = 8.4, 1.0, 0.6 Hz, 1H, C6H), 3.91 (s, 3H, $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 195.9

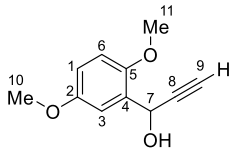
(C9H), 160.3 (C5), 145.7 (C7H), 136.8 (C3), 134.1 (C8H), 131.8 (C1H), 122.6 (C2H), 121.2 (C4), 109.9 (C6H), 56.0 ($C10H_3$); IR ν_{max} (cm^{-1}): 3092, 3009, 2972, 2944, 2840, 2811, 2741, 2708, 1672, 1616, 1585, 1566; HRMS (EI) $[M+H]^+$: calculated for $C_{10}H_{10}{}^{35}ClO_2^+$ 197.0364, found 197.0365, Δ 0.64 ppm.

(*E*)-3-(2,5-Dimethoxyphenyl)acrylaldehyde (6.29)



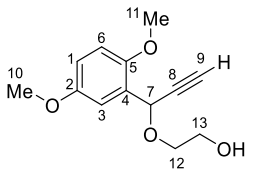
To 1-(2,5-dimethoxyphenyl)prop-2-yn-1-ol (**6.30**) (384.4 mg, 2.0 mmol, 1.0 equiv) in a microwave vial was added indium(III) chloride (8.8 mg, 0.04 mmol, 0.02 equiv) in water (2 mL), and then the vial was sealed and placed into a microwave. The reaction was heated at 250 W to 160 °C and was held at this temperature for 10 min before being allowed to cool. The mixture was extracted with ethyl acetate (× 3) and the organic fractions dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, methyl *tert*-butyl ether:isohexane, 20:80 to 35:65) gave (*E*)-3-(2,5-dimethoxyphenyl)acrylaldehyde (**6.29**) as a yellow solid (126.5 mg, 0.7 mmol, 33%); R_f: 0.39 (methyl *tert*-butyl ether:isohexane, 40:60); m.p.: 85.0–86.5 °C (lit.[196] 86–87 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.70 (d, *J* = 7.8 Hz, 1H, C9H), 7.83 (d, *J* = 16.1 Hz, 1H, C7H), 7.08 (d, *J* = 3.1 Hz, 1H, C3H), 6.98 (dd, *J* = 9.0, 3.1 Hz, 1H, C1H), 6.89 (d, *J* = 9.0 Hz, 1H, C6H), 6.75 (dd, *J* = 16.1, 7.8 Hz, 1H, C8H), 3.87 (s, 3H, $C11H_3$), 3.80 (s, 3H, $C10H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 194.6 (C11H), 153.7 (C2), 152.9 (C5), 148.0 (C7H), 129.3 (C8H), 123.6 (C4), 118.7 (C1H), 113.0 (C3H), 112.7 (C6H), 56.2 ($C11H_3$), 56.0 ($C10H_3$); IR ν_{max} (cm^{-1}): 3010, 2966, 2951, 2921, 2838, 2809, 2738, 2711, 1672, 1612; HRMS (ESI) $[M+H]^+$: calculated for $C_{11}H_{13}O_3$ 193.0859, found 193.0861, Δ 1.11 ppm.

1-(2,5-Dimethoxyphenyl)prop-2-yn-1-ol (6.30)



To 2,5-dimethoxybenzaldehyde (**6.27**) (2.0 g, 12.0 mmol, 1.0 equiv) in tetrahydrofuran (5.0 mL) at 0 °C was added dropwise ethynylmagnesium bromide (0.5 M tetrahydrofuran solution) (30.0 mL, 15.0 mmol, 1.25 equiv) over 10 min. The reaction was stirred at room temperature for 30 min before being cooled to 0 °C and hydrochloric acid (2 M) (20 mL) added. This mixture was extracted with methyl *tert*-butyl ether (× 3), and then the combined organic fractions were washed with 20% aq. sodium chloride solution and were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, methyl *tert*-butyl ether:isohexane, 40:60 to 50:50) gave 1-(2,5-dimethoxyphenyl)prop-2-yn-1-ol (**6.30**) as a yellow oil (2.3 g, 12.0 mmol, quant.); R_f: 0.25 (methyl tert-butyl ether:isohexane, 30:70); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.16 (d, *J* = 2.3 Hz, 1H, C3H), 6.81 – 6.86 (m, 2H, C1H, C6H), 5.66 (dd, *J* = 6.3, 2.3 Hz, 1H, C7H), 3.86 (s, 3H, C11H_3), 3.79 (s, 3H, C13H_3), 3.12 (d, *J* = 6.3 Hz, 1H, OH), 2.62 (d, *J* = 2.3 Hz, 1H, C9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.7 (C2), 150.9 (C5), 129.2 (C4), 114.2 (C1H), 113.9 (C3H), 112.0 (C6H), 83.0 (C8), 74.2 (C9H), 61.1 (C7H), 56.2 (C11H_3), 55.8 (C10H_3); IR ν_{max} (cm^{-1}): 3410 (br), 3283, 3001, 2943, 2911, 2836, 1613, 1591; HRMS (ESI) $[M+Na]^+$: calculated for $C_{11}H_{12}NaO_3$ 215.0679, found 215.0681, Δ 1.02 ppm.

2-((1-(2,5-Dimethoxyphenyl)prop-2-yn-1-yl)oxy)ethan-1-ol (6.32)

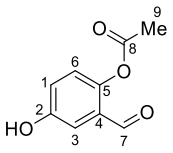


To 1-(2,5-dimethoxyphenyl)prop-2-yn-1-ol (**6.30**) (38.4 mg, 0.20 mmol, 1.0 equiv) in a microwave vial was added indium(III) chloride (0.9 mg, 0.004 mmol, 0.02 equiv) in ethylene glycol (2 mL), and then the vial was sealed and placed into a microwave. The reaction was heated at 250 W to 160 °C and was held at this temperature for 30 min before being allowed to cool. The mixture was extracted with ethyl acetate (× 5) and the combined organic fractions were washed with 20% aq. sodium chloride solution (× 2), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, methyl *tert*-butyl ether:isohexane, 20:80 to 60:40) gave (*E*)-3-(2,5-dimethoxyphenyl)acrylaldehyde (**6.29**) and (*E*)-2-(2,5-dimethoxystyryl)-1,3-dioxolane (**6.31**) as an inseparable yellow solid (21.5 mg, 0.10 mmol, 49%) and 2-((1-(2,5-dimethoxyphenyl)prop-2-yn-1-yl)oxy)ethan-1-ol (**6.32**) as a yellow oil (13.7 mg, 0.06 mmol, 29%); **6.32**: R_f: 0.25 (methyl *tert*-butyl ether:isohexane, 40:60); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (dd, *J* = 2.6, 1.0 Hz, 1H, C3H), 6.88 – 6.83 (m, 2H, C1H, C6H), 5.57 (d, *J* = 2.2 Hz, 1H, C7H), 3.85 (ddd, *J* = 9.9, 5.4, 3.0 Hz, 1H, C12H_AH$_B$), 3.83 (s, 3H, C11H_3), 3.79 (s, 3H, C10H_3), 3.78 – 3.74 (m, 2H, C13H_2), 3.68 (ddd, *J* = 10.0, 6.0, 3.3 Hz, 1H, C12H$_A$$H_B$), 2.62 (d, *J* = 2.2 Hz, 1H, C9H), 2.35 (t, *J* = 6.1 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.9 (C2), 151.1 (C5), 127.1 (C4), 114.9 (C1H), 114.6 (C3H), 112.2 (C6H), 81.4 (C8), 75.3 (C9H), 70.3 (C12H_2), 66.3 (C7H), 61.7 (C13H_2), 56.4 (C11H_3), 55.9 (C10H_3); IR ν_{max} (cm^{-1}): 3437 (br), 3282, 2934, 2870, 2836; HRMS (ESI) [M+Na]$^+$: calculated for $C_{13}H_{16}NaO_4$ 259.0941, found 259.0942, Δ 0.26 ppm.

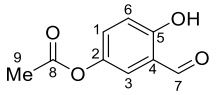
2-Formyl-4-hydroxyphenyl acetate (6.34)

and

3-Formyl-4-hydroxyphenyl acetate (6.35)



6.34

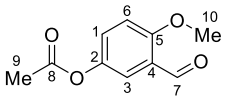


6.35

To 2,5-dihydroxybenzaldehyde (**6.33**) (1.00 g, 7.2 mmol, 1.00 equiv) in *N*,*N*-dimethylformamide (24 mL) at 0 °C was added triethylamine (1.11 mL, 8.0 mmol, 1.10 equiv). To this was added acetic anhydride (0.72 mL, 7.6 mmol, 1.05 equiv) dropwise over 60 min, then the solution allowed to warm to room temperature and stirred for 4 h. Water (50 mL) was added and the mixture extracted with ethyl acetate (25 mL × 5). The combined organic portions were washed with brine (25 mL × 3), then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:pentane, 15:85 to 30:70) gave 3-formyl-4-hydroxyphenyl acetate (**6.35**) as a yellow solid (290 mg, 1.6 mmol, 22%) and 2-formyl-4-hydroxyphenyl acetate (**6.34**) as a pale yellow solid (510 mg, 2.8 mmol, 39%); **6.35**: R_f: 0.50 (EtOAc:petroleum ether 40-60, 30:70); m.p.: 75.0–77.0 °C (lit.[221] 77.0–77.5 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.90 (d, *J* = 0.6 Hz, 1H, OH), 9.84 (d, *J* = 0.6 Hz, 1H, C7H), 7.32 (d, *J* = 2.9 Hz, 1H, C3H), 7.25 (dd, *J* = 9.0, 2.9 Hz, 1H, C1H), 6.99 (d, *J* = 9.0 Hz, 1H, C6H), 2.30 (s, 3H, $C9H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 195.9 (C7H), 169.6 (C8), 159.4 (C5), 143.1 (C2), 130.8 (C1H), 125.5 (C3H), 120.3 (C4), 118.8 (C6H), 21.1 ($C9H_3$); IR ν_{max} (cm^{-1}): 3186 (br), 3074, 2897, 1790, 1757, 1715, 1670, 1657, 1627, 1586, 1512; HRMS (ESI) $[M–H]^–$: calculated for $C_9H_7O_4^–$ 179.0350, found 179.0349, Δ –0.73 ppm; data in accordance with literature[222]; **6.34**: R_f: 0.22 (EtOAc:petroleum ether 40-60, 30:70); m.p.: 80.0–82.0 °C; ^{1}H NMR (acetone-d_6, 500 MHz): δ 10.06 (s, 1H, C7H), 8.84 (s, 1H, OH), 7.31 (d, *J* = 3.0 Hz, 1H,

C3H), 7.16 (dd, *J* = 8.8, 3.0 Hz, 1H, C1H), 7.11 (d, *J* = 8.8 Hz, 1H, C6H), 2.32 (s, 3H, $C9H_3$); ^{13}C NMR (acetone-d_6, 126 MHz): δ 189.4 (C7H), 170.2 (C12), 156.3 (C2), 145.8 (C5), 129.9 (C4), 125.6 (C6H), 123.0 (C1H), 115.8 (C3H), 20.7 ($C9H_3$); IR ν_{max} (cm^{-1}): 3391 (br), 2944, 2867, 1762, 1687, 1605, 1586; HRMS (ESI) $[M–H]^–$: calculated for $C_9H_7O_4^–$ 179.0350, found 179.0347, Δ –1.33 ppm.

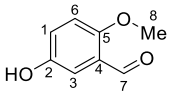
3-Formyl-4-methoxyphenyl acetate (6.36)



To 3-formyl-4-hydroxyphenyl acetate (**6.35**) (250 mg, 1.4 mmol, 1.0 equiv) and potassium carbonate (580 mg, 4.2 mmol, 3.0 equiv) was added acetone (7 mL) and the mixture stirred at room temperature for 20 min. To this was added iodomethane (0.26 mL, 4.2 mmol, 3.0 equiv) and the reaction was stirred at room temperature for 18 h. Water (20 mL) was added and the reaction extracted with ethyl acetate (× 3). The combined organic fractions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:pentane, 25:75) gave 3-formyl-4-methoxyphenyl acetate (**6.36**) as a pale yellow solid (240 mg, 1.2 mmol, 88%); R_f: 0.36 (EtOAc:petroleum ether 40-60, 30:70); m.p.: 78.0–80.0 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 10.42 (s, 1H, C7H), 7.52 (d, *J* = 3.0 Hz, 1H, C3H), 7.28 (dd, *J* = 9.0, 3.0 Hz, 1H, C1H), 6.99 (d, *J* = 9.0 Hz, 1H, C6H), 3.92 (s, 3H, $C10H_3$), 2.28 (s, 3H, $C9H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.9 (C7H), 169.7 (C8), 159.6 (C5), 144.2 (C2), 129.1 (C1H), 125.3 (C4), 121.1 (C3H), 112.7 (C6H), 56.2 ($C10H_3$), 21.1 ($C9H_3$); IR ν_{max} (cm^{-1}): 3068, 3014, 2974, 2946, 2871, 2848, 1759, 1683, 1609; HRMS (ESI) $[M+H]^+$: calculated for $C_{10}H_{11}O_4^+$ 195.0652, found 195.0655, Δ 1.64 ppm.

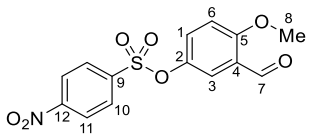
5-Hydroxy-2-methoxybenzaldehyde (6.38)

Prepared by procedure of Wu.[210]



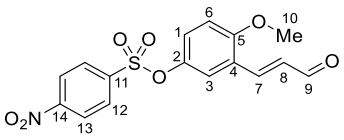
To 2,5-dihydroxybenzaldehyde (**6.33**) (5.0 g, 36.2 mmol, 1.0 equiv) and potassium carbonate (5.0 g, 36.2 mmol, 1.0 equiv) was added *N*,*N*-dimethylformamide (70 mL) and the mixture stirred at room temperature for 40 min. Iodomethane (3.4 mL, 54.4 mmol, 1.5 equiv) was added and the reaction stirred for 20 h. Water (100 mL) and hydrochloric acid (2 M) (50 mL) were added and the reaction extracted with ethyl acetate (100 mL × 6). The combined organic portions were washed with brine (50 mL × 5), dried (Na_2SO_4), and concentrate *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 25:75 to 35:65) followed by recrystallisation from hexane/acetone gave 5-hydroxy-2-methoxy-benzaldehyde (**6.38**) as a yellow crystalline solid (2.6 g, 16.9 mmol, 47%); R_f: 0.18 (EtOAc:petroleum ether 40-60, 20:80); m.p.: 112.5–114.0°C (lit.[223] 111–113 °C); ^{1}H NMR (acetone-d_6, 500 MHz): δ 10.38 (s, 1H, C7H), 8.27 (s, 1H, OH), 7.20 (d, J = 3.1 Hz, 1H, C3H), 7.12 (dd, J = 8.9, 3.1 Hz, 1H, C1H), 7.07 (d, J = 8.9 Hz, 1H, C6H), 3.90 (s, 3H, $C8H_3$); ^{13}C NMR (acetone-d_6, 126 MHz): δ 189.3 (C7H), 156.7 (C5), 152.0 (C2), 126.1 (C4), 124.0 (C1H), 114.7 (C6H), 113.3 (C3H), 56.7 ($C8H_3$); IR ν_{max} (cm^{-1}): 3230 (br), 3005, 2973, 2938, 2898, 2841, 1657, 1609, 1601, 1505; HRMS (ESI) $[M+H]^+$: calculated for $C_8H_9O_3^+$ 153.0546, found 153.0547, Δ 0.75 ppm; data in accordance with literature.[210]

3-Formyl-4-methoxyphenyl 4-nitrobenzenesulfonate (6.39)



To 5-hydroxy-2-methoxybenzaldehyde (**6.38**) (460 mg, 3.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added *N*,*N*-diisopropylethylamine (0.84 mL, 4.8 mmol, 1.6 equiv) and the reaction stirred at room temperature for 10 min. To this was added a suspension of 4-nitrobenzenesulfonyl chloride (1.0 g, 4.5 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) and the reaction was stirred for 4 h. Hydrochloric acid (2 M) (20 mL) was added and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (× 3), and then the combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 30:70) gave 3-formyl-4-methoxyphenyl 4-nitrobenzenesulfonate (**6.39**) as an off-white solid (1.0 g, 3.0 mmol, quant.); R_f: 0.30 (EtOAc:petroleum ether 40-60, 30:70); m.p.: 160.5–162.0 °C; ^{1}H NMR (acetone-d_6, 500 MHz): δ 10.32 (s, 1H, C7H), 8.53 – 8.49 (m, 2H, 2 × C11H), 8.21 – 8.17 (m, 2H, 2 × C10H), 7.38 (dd, *J* = 3.1, 0.5 Hz, 1H, C3H), 7.35 (dd, *J* = 9.0, 3.1 Hz, 1H, C1H), 7.24 (d, *J* = 9.0 Hz, 1H, C6H), 3.98 (s, 3H, C8H$_3$); ^{13}C NMR (acetone-d_6, 126 MHz): δ 188.2 (C7H), 161.6 (C5), 152.4 (C12), 143.5 (C2), 141.1 (C9), 131.1 (2 ×C10H), 130.4 (C1H), 126.2 (C4), 125.7 (2 × C11H), 121.6 (C3H), 115.0 (C6H), 56.9 (C8H$_3$); IR ν_{max} (cm^{-1}): 3108, 3070, 2981, 2949, 2875, 2851, 1684, 1607, 1532; HRMS (ESI) [M+H]$^+$: calculated for $C_{14}H_{12}NO_7S^+$ 338.0329, found 338.0332, Δ 0.81 ppm.

(*E*)-4-Methoxy-3-(3-oxoprop-1-en-1-yl)phenyl 4-nitrobenzenesulfonate (6.40)



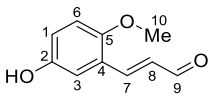
To (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**4.14**) (2.7 g, 6.3 mmol, 2.5 equiv) in tetrahydrofuran (25 mL) at 0 °C was added in one portion potassium *tert*-butoxide (730 mg, 6.5 mmol, 2.6 equiv) and the mixture stirred at room temperature for 20 min. To this was added 3-formyl-4-methoxyphenyl 4-nitrobenzenesulfonate (**6.39**) (840 mg, 2.5 mmol, 1.0 equiv) in one portion. The reaction was heated to reflux and stirred for 24 h before being allowed to cool to room temperature and hydrochloric acid (2 M) (50 mL) added. This was stirred at room temperature for a further 15 h and then extracted with ethyl acetate (× 3). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 40:60) to give partially purified product (640 mg).

A portion of this product (550 mg) was dissolved in CH_2Cl_2 (5 mL), *N*,*N*-diisopropylethylamine (0.26 mL, 1.5 mmol, 1.0 equiv) added, and the mixture stirred at room temperature for 10 min. To this was added a suspension of 4-nitrobenzenesulfonyl chloride (330 mg, 1.5 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) and the reaction was stirred for 6 h. Hydrochloric acid (2 M) (30 mL) was added and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (× 3), and then the combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 40:60) gave (*E*)-4-methoxy-3-(3-oxoprop-1-en-1-yl)phenyl 4-nitrobenzenesulfonate (**6.40**) as a pale yellow solid (498.0 mg, 1.4 mmol, 64% from 3-formyl-4-methoxyphenyl 4-

nitrobenzenesulfonate (**6.39**)); R_f: 0.31 (EtOAc:petroleum ether 40-60, 30:70); m.p.: 155.0–157.0 °C; ^{1}H NMR (acetone-d_6, 500 MHz): δ 9.67 (d, *J* = 7.6 Hz, 1H, C9H), 8.54 – 8.49 (m, 2H, 2 × C13H), 8.21 – 8.16 (m, 2H, 2 × C12H), 7.77 (d, *J* = 16.1 Hz, 1H, C7H), 7.45 (d, *J* = 2.9 Hz, 1H, C3H), 7.16 (dd, *J* = 9.1, 2.9 Hz, 1H, C1H), 7.12 (d, *J* = 9.1 Hz, 1H, C6H), 6.71 (dd, *J* = 16.1, 7.6 Hz, 1H, C8H), 3.96 (s, 3H, C10H_3); ^{13}C NMR (acetone-d_6, 126 MHz): δ 194.4 (C9H), 158.1 (C5), 152.3 (C14), 146.4 (C7H), 143.6 (C2), 141.3 (C11H), 131.3 (C8H), 131.1 (2 × C12H), 126.7 (C1H), 125.6 (2 × C13H), 125.0 (C4), 123.2 (C3H), 113.7 (C6H), 56.7 (C10H_3); IR ν_{max} (cm^{-1}): 3107, 3070, 3042, 2946, 2842, 2745, 1673, 1621, 1608, 1578, 1532; HRMS (ESI) $[M+H]^+$: calculated for $C_{16}H_{14}NO_7S^+$ 364.0486, found 364.0486, Δ 0.1 ppm.

Alternative preparation: To (*E*)-3-(5-hydroxy-2-methoxyphenyl)acrylaldehyde (**6.41**) (500 mg, 2.8 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) was added *N*,*N*-diisopropylethylamine (0.78 mL, 4.5 mmol, 1.6 equiv), and the mixture stirred at room temperature for 15 min. To this was added a suspension of 4-nitrobenzenesulfonyl chloride (930 mg, 4.2 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) and the reaction was stirred for 4 h. Hydrochloric acid (2 M) (20 mL) was added and the layers separated. The aqueous portion was extracted with CH_2Cl_2 (× 3), and then the combined organic portions were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 50:50) gave (*E*)-4-methoxy-3-(3-oxoprop-1-en-1-yl)phenyl 4-nitrobenzenesulfonate (**6.40**)as a pale yellow solid (990 mg, 2.7 mmol, 97%).

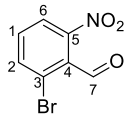
(*E*)-3-(5-Hydroxy-2-methoxyphenyl)acrylaldehyde (6.41)



To (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**4.14**) (8.5 g, 19.7 mmol, 2.0 equiv) in tetrahydrofuran (70mL) at 0 °C was added in one portion potassium *tert*-butoxide (3.3 g, 29.6 mmol, 3.0 equiv) and the mixture stirred at room temperature for 15 min. To this was added 5-hydroxy-2-methoxybenzaldehyde (**6.38**) (1.5 g, 9.9 mmol, 1.0 equiv) in tetrahydrofuran (30 mL). The reaction was heated to reflux and stirred for 30 h before being allowed to cool to room temperature and hydrochloric acid (2 M) (150 mL) added. This was stirred at room temperature for a further 7 h and then extracted with ethyl acetate (× 3). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was filtered through a short plug of silica, eluting with EtOAc/petroleum ether 40-60, 50:50. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 30:70 to 45:55) gave (*E*)-3-(5-hydroxy-2-methoxyphenyl)acrylaldehyde (**6.41**) as a yellow solid (450 mg, 2.5 mmol, 26%); R_f: 0.20 (EtOAc:petroleum ether 40-60, 30:70); m.p.: 128.5–130.5 °C; ^{1}H NMR (acetone-d_6, 500 MHz): δ 9.68 (d, *J* = 7.7 Hz, 1H, C9H), 8.16 (s, 1H, OH), 7.84 (d, *J* = 16.1 Hz, 1H, C7H), 7.14 (ddd, *J* = 2.5, 1.3, 0.7 Hz, 1H, C3H), 6.98 (dd, *J* = 8.9, 0.8 Hz, 1H, C6H), 6.96 (dd, *J* = 8.9, 2.5 Hz, 1H, C1H), 6.71 (dd, *J* = 16.1, 7.7 Hz, 1H, C8H), 3.87 (s, 3H, C10H$_3$); ^{13}C NMR (acetone-d_6, 126 MHz): δ 194.5 (C9H), 153.0 (C5), 152.1 (C2), 148.3 (C7H), 129.8 (C8H), 124.3 (C4), 120.4 (C1H), 115.3 (C3H), 113.8 (C6H), 56.5 (C10H$_3$); IR ν_{max} (cm^{-1}): 3225 (br), 3014, 2940, 2837, 1650, 1617, 1573; HRMS (ESI) [M–H]$^-$: calculated for $C_{10}H_9O_3^-$ 177.0557, found 177.0554, Δ –1.86 ppm.

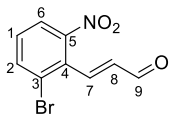
2-Bromo-6-nitrobenzaldehyde (6.43)

Prepared by procedure of Carter.[211]



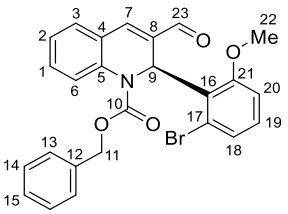
To 2-bromo-6-nitrotoluene (**6.42**) (1.0 g, 4.6 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (5 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (1.8 mL, 13.9 mmol, 3.0 equiv) and the solution stirred at 135 °C for 19 h. The reaction was cooled to 0 °C, and then poured onto a well-stirred suspension of sodium periodate (3.0 g, 13.9 mmol, 3.0 equiv) in *N*,*N*-dimethylformamide (5 mL) and water (10 mL) at 0 °C, rinsing the reaction flask with *N*,*N*-dimethylformamide (5 mL). This mixture was stirred at 0 °C for 3 h and then at room temperature for 17 h. The reaction was filtered through Celite®, washing with ethyl acetate (80 mL). The filtrate was washed sequentially with water (30 mL × 3) and brine (30 mL × 3). The combined organic portions were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:pentane, 15:85 to 20:80), followed by trituration with pentane until the solution came off colourless, gave 2-bromo-6-nitrobenzaldehyde (**6.43**) as an off-white solid (536 mg, 2.3 mmol, 50%); R_f: 0.33 (EtOAc:petroleum ether 40-60, 20:80); m.p.: 78.5–80.0 °C (lit.[224] 78–80 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.27 (s, 1H, C7H), 8.01 (dd, *J* = 8.2, 1.0 Hz, 1H, C6H), 7.93 (dd, *J* = 8.1, 1.0 Hz, 1H, C2H), 7.53 (t, *J* = 8.1 Hz, 1H, C1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.7 (C7H), 148.5 (C5), 138.7 (C2H), 133.0 (C4), 132.5 (C1H), 123.5 (C6H), 122.1 (C3); IR ν_{max} (cm^{-1}): 3097, 2870, 1709, 1683, 1604, 1557, 1527; HRMS (N_2 APCI) $[M+H]^+$: calculated for $C_7H_5{}^{79}BrNO_3^+$ 229.9447, found 229.9446, Δ –0.59 ppm; data in accordance with literature.[211]

(*E*)-3-(2-Bromo-6-nitrophenyl)acrylaldehyde (6.44)



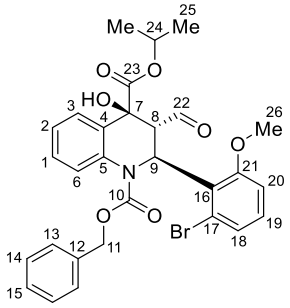
To (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (**4.14**) (6.5 g, 15.0 mmol, 2.5 equiv) in tetrahydrofuran (40 mL) at 0 °C was added in one portion potassium *tert*-butoxide (1.8 g, 15.6 mmol, 2.6 equiv) and the mixture stirred at room temperature for 15 min. To this was added 2-bromo-6-nitrobenzaldehyde (**6.43**) (1.4 g, 6.0 mmol, 1.0 equiv) in tetrahydrofuran (20 mL). The reaction was heated to reflux and stirred for 27 h before being allowed to cool to room temperature and hydrochloric acid (2 M) (150 mL) added. This was stirred at room temperature for a further 17 h and then extracted with ethyl acetate (× 3). The combined organic portions were washed with brine and were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 25:75) gave (*E*)-3-(2-bromo-6-nitrophenyl)acrylaldehyde (**6.44**) as a yellow solid (1.1 g, 4.2 mmol, 71%); R_f: 0.35 (EtOAc:petroleum ether 40-60, 20:80); m.p.: 60.0–62.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.78 (d, *J* = 7.5 Hz, 1H, C9H), 7.94 – 7.91 (m, 2H, C2H, C6H), 7.66 (dd, *J* = 16.4, 0.5 Hz, 1H, C7H), 7.42 (td, *J* = 8.1, 0.6 Hz, 1H, C1H), 6.33 (dd, *J* = 16.3, 7.5 Hz, 1H, C8H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 192.4 (C9H), 149.4 (C5), 146.5 (C7H), 137.7 (C2H), 135.5 (C8H), 130.7 (C4), 130.6 (C1H), 124.4 (C3), 123.7 (C6H); IR ν_{max} (cm^{-1}): 3121, 3080, 3052, 2830, 2739, 1693, 1630, 1593, 1556, 1523; HRMS (ESI) $[M+H]^+$: calculated for $C_9H_7{}^{79}BrNO_3^+$ 255.9604, found 255.9605, Δ 0.36 ppm.

Benzyl 2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1(2H)-carboxylate (6.45)



(*S*)-2-(Diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (11.0 mg, 0.03 mmol, 0.2 equiv), methyl (*E*)-3-(2-bromo-6-methoxyphenyl)acrylate (**6.7**) (36.2 mg, 0.15 mmol, 1.0 equiv), and benzyl (2-formylphenyl)carbamate (**1.133**) (114.9 mg, 0.45 mmol, 3.0 equiv) were subjected to **General Procedure A**, stirring at room temperature for 91 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 50:50) followed by further column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 30:70) gave benzyl 2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1(2H)-carboxylate (**6.45**) as a yellow solid (16.1 mg, 0.03 mmol, 22%); R_f: 0.26 (EtOAc:petroleum ether 40-60, 15:85); $[\alpha]_D^{25} = -10.1$ (*c* = 1.00, $CHCl_3$); m.p.: 175.0–177.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.47 (s, 1H, C23H), 7.70 (d, *J* = 8.3 Hz, 1H, C6H), 7.39 – 7.31 (m, 3H, C1H, 2 × C13H), 7.34 – 7.26 (m, 5H, C3H, C7H, 2 × C14H, C15H), 7.21 (dd, *J* = 8.1, 1.1 Hz, 1H, C18H), 7.08 (td, *J* = 7.5, 1.1 Hz, 1H, C2H), 7.07 (d, *J* = 1.3 Hz, 1H, C9H), 7.02 (t, *J* = 8.1 Hz, 1H, C19H), 6.65 (dd, *J* = 8.2, 1.1 Hz, 1H, C20H), 5.33 (d, *J* = 12.1 Hz, 1H, C11H_AH$_B$), 5.23 (d, *J* = 12.1 Hz, 1H, C11H$_A$$H_B$), 2.97 (s, 3H, C22H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 190.3 (C23H), 160.7 (C21), 154.9 (C10), 142.1 (C7H), 139.6 (C5), 136.2 (C12), 135.1 (C8), 131.5 (C1H), 129.7 (C19H), 128.9 (2 × C13H), 128.6 (C3H or C15H), 128.6 (2 × C14H), 128.3 (C3H or C15H), 127.7 (C16), 126.1 (C17), 126.0 (C18H), 125.0 (C4), 123.2 (C2H), 122.7 (C6H), 110.2 (C20H), 68.1 (C11H$_2$), 55.4 (C9H), 54.6 (C22H$_3$); IR ν_{max} (cm^{-1}): 3063, 3032, 2937, 2874, 2837, 2722, 1708, 1679, 1645, 1598, 1584, 1572; HRMS (ESI) [M+H]$^+$: calculated for $C_{25}H_{21}{}^{79}BrNO_4^+$ 478.0649, found 478.0648, Δ –0.19 ppm.

1-Benzyl 4-isopropyl (2*S*,3*R*,4*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-6.46)

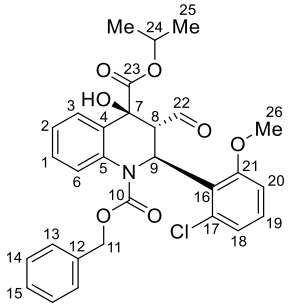


To (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (55.0 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (0.15 mL) were added sequentially (*E*)-3-(2-bromo-6-methoxyphenyl)acrylaldehyde (**6.7**) (36.2 mg, 0.15 mmol, 1.0 equiv), benzoic acid (9.2 mg, 0.08 mmol, 0.5 equiv), freshly activated 4 Å molecular sieves (ground) (50 mg), and then isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) in CH_2Cl_2 (0.15 mL), then the mixture stirred at room temperature for 120 h. Additional CH_2Cl_2 (0.15 mL) was added after 24 h to compensate for solvent loss. The reaction was filtered with ethyl acetate, and then washed sequentially with sat. aq. sodium bicarbonate solution, hydrochloric acid (2 M), and brine. The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 35:65) gave 1-benzyl 4-isopropyl (2*S*,3*R*,4*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-**6.46**) as a viscous yellow oil (52.7 mg, 0.09 mmol, 60%); R_f: 0.36 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = +25.5$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.70 (s, 1H, C22H), 7.65 (dd, *J* = 7.9, 1.6 Hz, 1H, C3H), 7.46 (s, 1H, C6H), 7.32 (td, *J* = 7.8, 1.7 Hz, 1H, C1H), 7.26 (d, *J* = 4.2 Hz, 3H, 2 × C14H, C15H), 7.21 – 7.14 (m, 4H, C2H, C18H, 2 × C13H), 7.13 (t, *J* = 8.1 Hz, 1H, C19H), 6.77 (d, *J* = 8.1 Hz, 1H, C20H), 6.12 (d, *J* = 11.2 Hz, 1H, C9H), 5.20 – 5.09 (m, 2H, $C11H_2$), 5.07 (hept, *J* = 6.3 Hz, 1H, C24H), 4.53 (s, 1H,

OH), 3.57 (d, *J* = 12.1 Hz, 1H, C8H), 3.28 (s, 3H, $C26H_3$), 1.25 (d, *J* = 6.3 Hz, 3H, $C25_AH_3$), 1.03 (d, *J* = 6.3 Hz, 3H, $C25_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (signals for C14H and C15H could not be identified): δ 199.7 (C22H), 172.3 (C23), 158.7 (C21), 154.7 (C10), 138.4 (C5), 136.0 (C12), 130.1 (C19H), 130.0 (C4), 128.5 (2 × C13H), 128.1 (C1H), 127.2 (C16), 126.0 (C17), 125.5 (C6H, C18H), 124.2 (C2H), 124.0 (C3H), 110.6 (C20H), 73.4 (C7), 71.2 (C24H), 67.9 ($C11H_2$), 60.7 (C8H), 55.8 (C9H), 54.9 ($C26H_3$), 21.7 ($C25_AH_3$), 21.3 ($C25_BH_3$); IR ν_{max} (cm^{-1}): 3478 (br), 3067, 3033, 2981, 2939, 2874, 2838, 2735, 1709, 1602, 1587, 1572; HRMS (ESI) $[M+Na]^+$: calculated for $C_{29}H_{28}{}^{79}BrNNaO_7^+$ 604.0941, found 604.0939, Δ –0.44 ppm.

A sample of the enantiomer, 1-benzyl 4-isopropyl (2*R*,3*S*,4*R*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (**6.46**) (484 mg, 0.83 mmol, 55%) was prepared as above using 10× all quantities and (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**), stirring for 121 h; $[\alpha]_D^{25} = -31.8$ (*c* = 1.00, $CHCl_3$); all other characterisation identical.

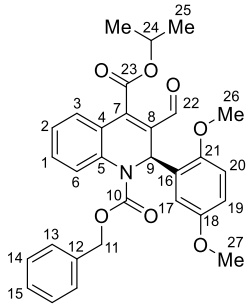
1-Benzyl 4-isopropyl (2*S*,3*R*,4*S*)-2-(2-chloro-6-methoxyphenyl)-3-formyl-4-hydroxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-6.50)



To (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (11.0 mg, 0.03 mmol, 0.2 equiv) in CH_2Cl_2 (0.15 mL) were added sequentially (*E*)-3-(2-chloro-6-methoxyphenyl)acrylaldehyde (**6.26**) (29.4 mg, 0.15 mmol, 1.0 equiv), benzoic acid (9.2 mg, 0.08 mmol, 0.5 equiv), and then isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) in CH_2Cl_2 (0.15 mL), then the mixture stirred at room temperature for 119 h. Additional CH_2Cl_2 (0.15 mL) was added after 24 h to compensate for solvent loss. The reaction was filtered with ethyl acetate, and then washed sequentially with sat. aq. sodium bicarbonate solution, hydrochloric acid (2 M), and brine. The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave 1-benzyl 4-isopropyl (2*S*,3*R*,4*S*)-2-(2-chloro-6-methoxyphenyl)-3-formyl-4-hydroxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-**6.50**) as a viscous yellow oil (12.3 mg, 0.02 mmol, 15%); R_f: 0.36 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = +34.8$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65 (s, 1H, C22H), 7.65 (dd, *J* = 7.9, 1.6 Hz, 1H, C3H), 7.48 (s, 1H, C6H), 7.32 (td, *J* = 7.9, 1.7 Hz, 1H, C1H), 7.29 – 7.22 (m, 3H, 2 × C14H, C15H), 7.22 – 7.13 (m, 4H, C2H, C19H, 2 × C13H), 6.97 (d, *J* = 8.1 Hz, 1H, C18H), 6.72 (d, *J* = 8.3 Hz, 1H, C20H), 6.18 (d, *J* = 9.8 Hz, 1H, C9H), 5.13 (s, 2H, $C11H_2$), 5.06 (hept, *J* = 6.3 Hz, 1H, C24H), 4.53 (s, 1H, OH), 3.57 (dd, *J* = 12.1, 1.2 Hz, 1H, C8H), 3.30 (s, 3H, $C26H_3$), 1.23 (d, *J* = 6.3 Hz, 3H, $C25_AH_3$), 1.02 (d,

J = 6.3 Hz, 3H, $C25_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (signals for C14H and C15H could not be identified): δ 199.8 (C22H), 172.3 (C23), 158.7 (C21), 154.7 (C10), 138.3 (C5), 135.9 (C12), 135.2 (C17), 130.0 (C4), 129.7 (C19H), 128.5 (2 × C13H), 128.1 (C1H), 125.8 (C16), 125.5 (C6H), 124.2 (C2H), 124.0 (C3H), 122.3 (C18H), 109.9 (C20H), 73.6 (C7), 71.3 (C24H), 68.0 ($C11H_2$), 60.5 (C8H), 55.0 ($C26H_3$), 52.6 (C9H), 21.6 ($C25_AH_3$), 21.3 ($C25_BH_3$); IR ν_{max} (cm^{-1}): 3476 (br), 3067, 3033, 2980, 2960, 2933, 2874, 2850, 2741, 1709, 1588, 1578; HRMS (ESI) $[M+H]^+$: calculated for $C_{29}H_{29}{}^{35}ClNO_7{}^+$ 538.1627, found 538.1628, Δ 0.25 ppm.

1-Benzyl 4-isopropyl (*R*)-2-(2,5-dimethoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-6.51)



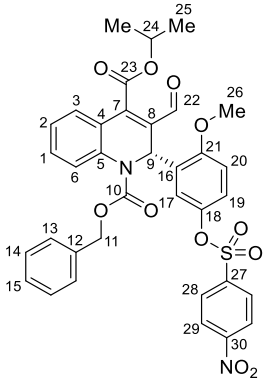
To (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (55.0 mg, 0.15 mmol, 1.0 equiv) in CH_2Cl_2 (0.15 mL) were added sequentially (*E*)-3-(2,5-dimethoxyphenyl)acrylaldehyde (**6.29**) (28.8 mg, 0.15 mmol, 1.0 equiv), benzoic acid (9.2 mg, 0.08 mmol, 0.5 equiv), freshly activated 4 Å molecular sieves (beads) (50 mg), and then isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) in CH_2Cl_2 (0.15 mL), then the mixture stirred at room temperature for 98 h. Additional CH_2Cl_2 (0.15 mL) was added after 24 h to compensate for solvent loss. The reaction was filtered with ethyl acetate, and then washed sequentially with sat. aq. sodium bicarbonate solution, hydrochloric acid (2 M), and brine. The organic portion was dried

(Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 10:90 to 25:75) gave 1-benzyl 4-isopropyl (*R*)-2-(2,5-dimethoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-**6.51**) as a viscous yellow oil (47.8 mg, 0.10 mmol, 64%); R_f: 0.36 (methyl *tert*-butyl ether:isohexane, 40:60); $[\alpha]_D^{25} = -338.5$ (*c* = 1.00, $CHCl_3$); ee: 93% (Chiralcel OD; hexane:2-propanol, 90:10; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 23.41 min, t_R (minor) = 27.55 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.82 (s, 1H, C22H), 7.67 (d, *J* = 7.9 Hz, 1H, C6H), 7.3 – 7.46 (m, 7H, C1H, C3H, 2 × C13H, 2 × C14H, C15H), 7.14 (td, *J* = 7.7, 1.1 Hz, 1H, C2H), 7.07 (s, 1H, C9H), 6.71 (d, *J* = 8.9 Hz, 1H, C17H), 6.67 (dd, *J* = 8.9, 3.0 Hz, 1H, C19H), 6.48 (d, *J* = 2.9 Hz, 1H, C20H), 5.40 (hept, *J* = 6.3 Hz, 1H, C24H), 5.30 (d, *J* = 12.4 Hz, 1H, C11H_AH$_B$), 5.27 (d, *J* = 12.4 Hz, 1H, C11H$_A$$H_B$), 3.55 (s, 3H, C26$H_3$), 3.52 (s, 3H, C27$H_3$), 1.42 (d, *J* = 6.3 Hz, 3H, C25$_A$H$_3$), 1.39 (d, *J* = 6.3 Hz, 3H, C25H$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9 (C22H), 165.5 (C23), 153.8 (C10), 153.2 (C18), 151.8 (C21), 142.2 (C7), 137.4 (C5), 136.0 (C12), 133.8 (C8), 131.6 (C1H), 128.7 (2 × C14H), 128.4 (C15H), 128.3 (2 × C13H), 126.2 (C16), 126.2 (C3H), 125.7 (C6H), 124.8 (C2H), 124.3 (C4), 114.7 (C20H), 114.2 (C19H), 112.6 (C17H), 70.8 (C24H), 68.4 (C11H_2), 56.1 (C26H_3), 55.5 (C27H_3), 48.6 (C9H), 22.0 (C25$_A$H$_3$), 21.9 (C25$_B$H$_3$); IR ν_{max} (cm^{-1}): 3066, 3034, 2982, 2937, 2835, 1714, 1677, 1613, 1600, 1567; HRMS (ESI) [M+H]$^+$: calculated for $C_{30}H_{30}NO_7^+$ 516.2017, found 516.2017, Δ 0.08 ppm;

A sample of the enantiomer, 1-benzyl 4-isopropyl (*S*)-2-(2,5-dimethoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (**6.51**) (35.0 mg, 0.07 mmol, 45%) was prepared as above using (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**), stirring for 93 h; $[\alpha]_D^{25} = +364.6$

(c = 1.00, $CHCl_3$); ee: 91% (Chiralcel OD; hexane:2-propanol, 90:10; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 23.76 min, t_R (major) = 27.32 min; all other characterisation identical.

1-Benzyl 4-isopropyl (*S*)-3-formyl-2-(2-methoxy-5-(((4-nitrophenyl)sulfonyl)oxy)phenyl)quinoline-1,4(2H)-dicarboxylate (6.54)

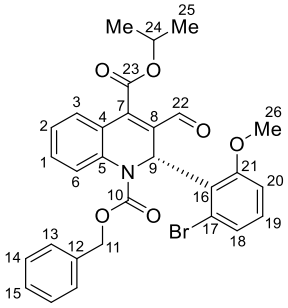


(*E*)-4-Methoxy-3-(3-oxoprop-1-en-1-yl)phenyl 4-nitrobenzenesulfonate (**6.40**) (54.5 mg, 0.15 mmol, 1.0 equiv) and isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.5**) (102.4 mg, 0.30 mmol, 2.0 equiv) were subjected to **General Procedure B**, using enantiomeric (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**), stirring at room temperature for 166 h. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 35:65) gave 1-benzyl 4-isopropyl (*R*)-3-formyl-2-(2-methoxy-5-(((4-nitrophenyl)sulfonyl)oxy)phenyl)quinoline-1,4(2H)-dicarboxylate (**6.54**) as a viscous yellow oil (41.4 mg, 0.06 mmol, 40%); R_f: 0.32 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = +259.0$ (c = 1.00, $CHCl_3$); ee: 96% (Chiralcel AD-H; hexane:2-propanol, 50:50; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 27.94 min, t_R (minor) = 38.33 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65 (s, 1H, C22H), 8.28 – 8.24 (m, 2H, 2 × C29H), 7.77 – 7.71 (m, 2H, 2 × C28H), 7.57 (br d, J = 8.3 Hz, 1H, C6H), 7.43 – 7.31 (m, 6H, C1H, 2 × C13H, 2 × C14H, C15H), 7.29 (dd, J = 8.0, 1.5 Hz, 1H, C3H), 7.14 (ddd, J = 7.8, 7.4, 1.2 Hz, 1H, C2H), 6.97 (dd, J = 9.0, 3.0 Hz, 1H,

C19H), 6.87 (s, 1H, C9H), 6.71 (d, *J* = 9.0 Hz, 1H, C20H), 6.28 (dd, *J* = 2.9, 0.5 Hz, 1H, C17H), 5.38 (hept, *J* = 6.3 Hz, 1H, C24H), 5.25 (s, 2H, $C11H_2$), 3.51 (s, 3H, $C26H_3$), 1.42 (d, *J* = 6.3 Hz, 3H, $C25_AH_3$), 1.40 (d, *J* = 6.3 Hz, 3H, $C25_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.3 (C22H), 165.0 (C23), 156.9 (C21), 153.5 (C10), 151.1 (C30), 143.7 (C7), 142.1 (C18), 140.4 (C27), 137.0 (C5), 135.8 (C12), 132.5 (C8), 131.8 (C1H), 129.8 (2 × C28H), 128.7 (2 × C14H), 128.5 (C15H), 128.4 (2 × C13H), 126.3 (C3H), 126.2 (C16), 125.7 (C6H), 124.9 (C2H), 124.5 (2 × C29H), 123.8 (C4), 123.7 (C19H), 122.0 (C17H), 112.0 (C20H), 71.3 (C24H), 68.5 ($C11H_2$), 55.7 ($C26H_3$), 48.1 (C9H), 22.0 ($C25_AH_3$), 21.9 ($C25_BH_3$); IR ν_{max} (cm^{-1}): 3108, 3069, 3034, 2982, 2941, 2874, 2843, 1771, 1715, 1675, 1607, 1567, 1535; HRMS (ESI) $[M+Na]^+$: calculated for $C_{35}H_{30}N_2NaO_{11}S^+$ 709.1463, found 709.1462, Δ –0.02 ppm.

A racemic sample of 1-benzyl 4-isopropyl 3-formyl-2-(2-methoxy-5-(((4-nitrophenyl)sulfonyl)oxy)phenyl)quinoline-1,4(2H)-dicarboxylate (*rac*-**6.54**) was prepared as above using pyrrolidine (12.3 μL, 0.15 mmol, 1.0 equiv) in place of (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**).

1-Benzyl 4-isopropyl (*R*)-2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (6.58)



To 1-benzyl 4-isopropyl (2*R*,3*S*,4*R*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (**6.46**) (200 mg, 0.34 mmol, 1.0 equiv), sodium acetate trihydrate (701 mg, 5.15 mmol, 15.0 equiv), and 4-dimethylaminopyridine (126 mg, 1.03 mmol, 3.0 equiv) was added pyridine (1.6 mL) and acetic anhydride (1.6 mL). The mixture was stirred at 50 °C for 42 h before being allowed to cool to room temperature. Sat. aq. sodium bicarbonate solution was added carefully, followed by ethyl acetate, and the layers separated. The aqueous portion was extracted with ethyl acetate (× 2). The combined organic portions were washed with hydrochloric acid (2 M) (× 3), back-extracting with ethyl acetate (× 3). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave 1-benzyl 4-isopropyl (*R*)-2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (**6.58**) as a viscous yellow oil (100 mg, 0.18 mmol, 52%); R_f: 0.38 (EtOAc:petroleum ether 40-60, 25:75); $[\alpha]_D^{25} = +346.9$ (*c* = 1.00, $CHCl_3$); ee: 88% (Chiralcel OD; hexane:2-propanol, 80:20; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (major) = 21.97 min, t_R (minor) = 32.87 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (s, 1H, C22H), 7.64 (dd, *J* = 8.4, 1.1 Hz, 1H, C6H), 7.40 – 7.30 (m, 6H, C1H, 2 × C13H, 2 × C14H, C15H), 7.28 (dd, *J* = 7.8, 1.6 Hz, 1H, C3H), 7.21 (dd, *J* = 8.1, 1.1 Hz, 1H, C18H), 7.17 (s, 1H, C9H), 7.10 (ddd, *J* = 8.5, 7.3, 1.1 Hz, 1H, C2H), 7.04 (t, *J* = 8.1 Hz, 1H, C19H), 6.66 (dd, *J* = 8.3, 1.1 Hz,

1H, C20H), 5.38 (hept, *J* = 6.3 Hz, 1H, C24H), 5.34 (d, *J* = 12.1 Hz, 1H, C11H_AH_B), 5.23 (d, *J* = 12.1 Hz, 1H, C11H_AH_B), 3.00 (s, 3H, C26H_3), 1.39 (d, *J* = 6.3 Hz, 3H, C25$_A$H$_3$), 1.38 (d, *J* = 6.3 Hz, 3H, C25$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.2 (C22H), 166.0 (C23), 161.1 (C21), 154.7 (C10), 142.5 (C7), 139.0 (C5), 136.0 (C12), 131.5 (C1H), 130.2 (C8), 130.1 (C19H), 128.9 (2 × C13H), 128.6 (2 × C14H), 128.4 (C15H), 127.2 (C16), 126.0 (C18H), 126.0 (C17), 125.6 (C3H), 123.5 (C6H), 123.4 (C2H), 123.1 (C4), 110.5 (C20H), 70.6 (C24H), 68.4 (C11H_2), 54.7 (C26H_3), 54.6 (C9H), 22.0 (C25H_3), 21.9 (C25H_3); IR ν_{max} (cm^{-1}): 3065, 3032, 2980, 2939, 2873, 2839, 2750, 1768, 1715, 1683, 1618, 1597, 1585, 1572; HRMS (ESI) $[M+H]^+$: calculated for $C_{29}H_{27}{}^{79}BrNO_6^+$ 564.1016, found 564.1021, Δ 0.85 ppm.

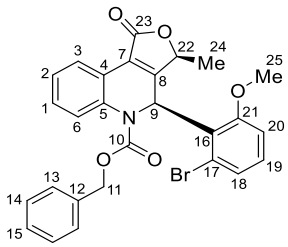
A sample of the enantiomer, 1-benzyl 4-isopropyl (*S*)-2-(2,5-dimethoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-**6.58**) was prepared as follows: To 1-benzyl 4-isopropyl (2*S*,3*R*,4*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-**6.46**) (63.9 mg, 0.1 mmol, 1.0 equiv), sodium acetate trihydrate (204.1 mg, 1.5 mmol, 15.0 equiv), and 4-dimethylaminopyridine (36.7 mg, 0.3 mmol, 3.0 equiv) was added pyridine (0.5 mL) and acetic anhydride (0.5 mL). The mixture was stirred at 50 °C for 24 h before being allowed to cool to room temperature. Sat. aq. sodium bicarbonate solution was added carefully, followed by ethyl acetate, and the layers separated. The aqueous portion was extracted with ethyl acetate. The combined organic portions were washed with hydrochloric acid (2 M) (× 3), back-extracting with ethyl acetate. The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave 1-benzyl 4-isopropyl (*S*)-2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-**6.58**) as a viscous yellow oil (29.0 mg, 0.05 mmol,

51%); $[\alpha]_D^{25} = -386.5$ (*c* = 1.00, $CHCl_3$); ee: 87% (Chiralcel OD; hexane:2-propanol, 80:20; flow rate 0.8 mL.min^{-1}; λ = 254 nm): t_R (minor) = 22.15 min, t_R (major) = 32.66 min; all other characterisation identical.

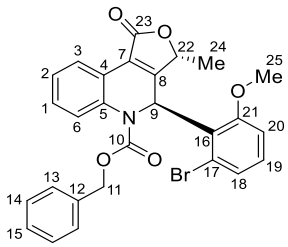
Benzyl (3*S*,4*S*)-4-(2-bromo-6-methoxyphenyl)-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-6.62)

and

Benzyl (3*R*,4*S*)-4-(2-bromo-6-methoxyphenyl)-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-6.63)



ent-**6.62**

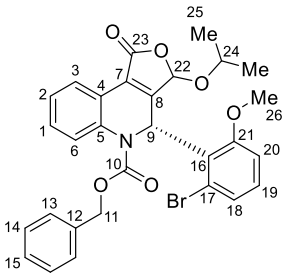


ent-**6.63**

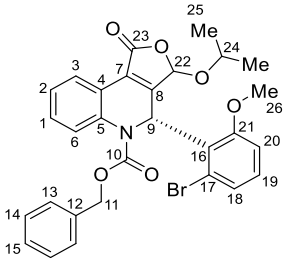
Methylmagnesium bromide (1 M tetrahydrofuran solution) (1.0 mL, 1.0 mmol, 10.0 equiv) was diluted with tetrahydrofuran (0.5 mL) and cooled to –78 °C. To this well-stirred suspension was added dropwise 1-benzyl 4-isopropyl (*S*)-2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (*ent*-**6.58**) (56.4 mg, 0.1 mmol, 1.0 equiv) in tetrahydrofuran (0.5 mL) over 10 min and the reaction stirred at –78 °C for a further 70 min. The reaction was quenched with DL-camphorsulfonic acid (1 M tetrahydrofuran solution) (1.0 mL) and the mixture allowed to warm to room temperature. Water and ethyl acetate were added, and the layers separated. The aqueous portion was extracted with ethyl acetate (× 3). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load,

EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave an inseparable mixture of benzyl (3*R*,4*S*)-4-(2-bromo-6-methoxyphenyl)-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**6.63**) and benzyl (3*S*,4*S*)-4-(2-bromo-6-methoxyphenyl)-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**6.62**) as a viscous yellow oil (NMR yield: *ent*-**6.63**: 35.7 mg, 0.07 mmol, 69%; *ent*-**6.62**: 8.1 mg, 0.02 mmol, 16%); R_f: 0.26 (EtOAc:petroleum ether 40-60, 30:70); ^{1}H NMR ($CDCl_3$, 500 MHz) (*ent*-**6.62**) (signals for C13H, C14H, C15H, and C18H could not be identified): δ 8.21 (dd, *J* = 7.7, 1.7 Hz, 1H, C3H), 7.62 (d, *J* = 8.5 Hz, 1H, C6H), 7.34 – 7.27 (m, C1H), 7.15 – 7.09 (m, C2H, C19H), 7.08 (d, *J* = 1.5 Hz, 1H, C9H), 6.72 (dd, *J* = 8.4, 1.1 Hz, 1H, C20H), 5.29 (d, *J* = 12.2 Hz, 1H, C11H_AH$_B$), 5.21 (d, *J* = 12.2 Hz, 1H, C11H$_A$$H_B$), 5.15 (qd, *J* = 6.7, 1.4 Hz, 1H, C22H), 2.98 (s, 3H, C25H$_3$), 0.99 (d, *J* = 6.7 Hz, 3H, C24H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (*ent*-**6.62**) (signals for C13, C14, C15, and C17 could not be identified): δ 169.5 (C23), 160.6 (C21), 157.0 (C8), 154.9 (C10), 137.1 (C5), 135.8 (C12), 130.8 (C19H), 128.9 (C1H), 128.7, 128.6, 125.1 (C18H), 124.9 (C16), 123.5 (C2H), 123.4 (C3H), 122.7 (C6H), 121.5 (C7), 120.0 (C4), 110.7 (C20H), 77.7 (C22H), 68.4 (C11H$_2$), 56.9 (C9H), 54.9 (C25H$_3$), 19.2 (C24H$_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) (*ent*-**6.63**): δ 8.25 (dd, *J* = 7.7, 1.7 Hz, 1H, C3H), 7.66 (d, *J* = 8.4 Hz, 1H, C6H), 7.32 – 7.28 (m, 6H, C1H, 2 × C13H, 2 × C14H, C15H), 7.18 (dd, *J* = 8.1, 1.1 Hz, 1H, C18H), 7.14 – 7.10 (m, 2H, C2H, C19H), 7.06 (s, 1H, C9H), 6.71 (dd, *J* = 8.3, 1.1 Hz, 1H, C20H), 5.30 (d, *J* = 12.2 Hz, 1H, C11H_AH$_B$), 5.24 (d, *J* = 12.2 Hz, 1H, C11H$_A$$H_B$), 4.75 (q, *J* = 6.8 Hz, 1H, C22H), 2.97 (s, 3H, C25H$_3$), 1.72 (d, *J* = 6.8 Hz, 3H, C24H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (*ent*-**6.63**): δ 169.7 (C23), 160.6 (C21), 157.9 (C8), 155.0 (C10), 137.0 (C5), 135.8 (C12), 130.8 (C19H), 129.0 (C1H), 128.6 (2 × C13H, 2 × C14H), 128.4 (C15H), 126.0 (C16), 125.4 (C18H), 123.8 (C17), 123.4 (C2H), 123.3 (C3H), 122.5 (C6H), 121.1 (C7), 120.0 (C4), 110.7 (C20H), 76.5 (C22H), 68.4 (C11H$_2$), 56.2 (C9H), 54.8 (C25H$_3$), 19.6 (C24H$_3$); HRMS (ESI) $[M+H]^+$: calculated for $C_{27}H_{23}{}^{79}BrNO_5^+$ 520.0754, found 520.0752, Δ –0.42 ppm.

Benzyl (4*R*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (6.64a and 6.64b)



6.64a
(**6.64a** and **6.64b** are diastereomeric)



6.64b
(**6.64a** and **6.64b** are diastereomeric)

To 1-benzyl 4-isopropyl (*R*)-2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (**6.58**) (28.2 mg, 0.05 mmol, 1.0 equiv) in tetrahydrofuran (0.5 mL) at 0 °C was added in one portion methylmagnesium bromide (1 M tetrahydrofuran solution) (60 µL, 0.06 mmol, 1.2 equiv) and the reaction stirred at 0 °C for 10 min. The reaction was quenched with DL-camphorsulfonic acid (1 M tetrahydrofuran solution) (60 µL) and the mixture allowed to warm to room temperature. Water and ethyl acetate were added, and the layers separated. The aqueous portion was extracted with ethyl acetate (× 3). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave an inseparable mixture of benzyl (4*R*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**6.64a**), benzyl (4*R*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**6.64b**), benzyl (3*S*,4*R*)-4-(2-bromo-6-methoxyphenyl)-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**6.63**, *vide supra*), and benzyl (3*R*,4*R*)-4-(2-bromo-6-methoxyphenyl)-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**6.62**, *vide supra*) as a viscous yellow oil (NMR yield: **6.64a**: 9.4 mg, 0.02 mmol, 33%; **6.64b**: 3.9 mg, 0.01 mmol, 14%; **6.63**: 6.2 mg, 0.01 mmol, 24%; **6.62**: 4.2 mg, 0.01 mmol, 16%); **6.64**: R_f: 0.38

(EtOAc:petroleum ether 40-60, 30:70); ^{1}H NMR ($CDCl_3$, 500 MHz) (**6.64a**): δ 8.17 (dd, *J* = 7.7, 1.6 Hz, 1H, C3H), 7.66 (br d, *J* = 8.4 Hz, 1H, C6H), 7.34 – 7.29 (m, 6H, C1H, 2 × C13H, 2 × C14H, C15H), 7.14 (dd, *J* = 8.1, 1.2 Hz, 1H, C18H), 7.12 (td, *J* = 7.6, 1.1 Hz, 1H, C2H), 7.08 (d, *J* = 1.3 Hz, 1H, C9H), 7.07 (t, *J* = 8.2 Hz, 1H, C19H), 6.69 (dd, *J* = 8.3, 1.1 Hz, 1H, C20H), 5.98 (d, *J* = 1.3 Hz, 1H, C22H), 5.29 (d, *J* = 12.2 Hz, 1H, C11H_AH$_B$), 5.20 (d, *J* = 12.2 Hz, 1H, C11H$_A$$H_B$), 3.94 (hept, *J* = 6.1 Hz, 1H, C24H), 2.99 (s, 3H, C26H$_3$), 1.07 (d, *J* = 6.1 Hz, 3H, C25$_A$H$_3$), 0.91 (d, *J* = 6.1 Hz, 3H, C25$_B$H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (**6.64a**): δ 168.1 (C23), 160.6 (C21), 154.9 (C10), 150.2 (C8), 137.8 (C7), 135.9 (C12), 130.1 (C19H), 129.5 (C1H), 128.8 (2 × C13H), 128.6 (2 × C14H), 128.4 (C15H), 126.5 (C16), 124.9 (C17), 124.7 (C18H), 124.1 (C3H), 124.0 (C5), 123.4 (C2H), 122.8 (C6H), 119.5 (C4), 110.5 (C20H), 101.0 (C22H), 74.8 (C24H), 68.4 (C11H$_2$), 57.0 (C9H), 54.9 (C26H$_3$), 23.0 (C25$_A$H$_3$), 21.7 (C25$_B$H$_3$); HRMS (ESI) $[M+H]^+$: calculated for $C_{29}H_{27}{}^{79}BrNO_6^+$ 564.1016, found 564.1014, Δ –0.44 ppm.

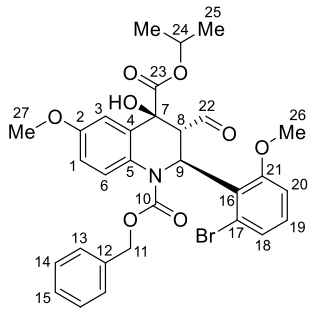
1-Benzyl 4-isopropyl (2*S*,3*R*,4*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-6-methoxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (*ent*-6.65)

and

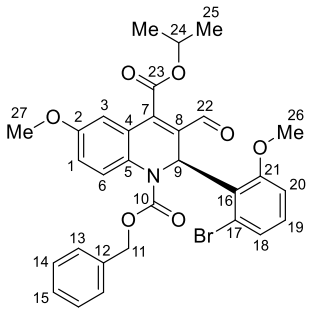
1-Benzyl 4-isopropyl (*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-6-methoxyquinoline-1,4(2H)-dicarboxylate (*ent*-6.66)

and

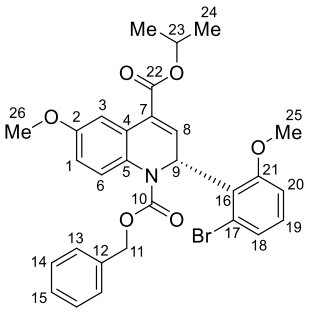
1-Benzyl 4-isopropyl (*R*)-2-(2-bromo-6-methoxyphenyl)-6-methoxyquinoline-1,4(2H)-dicarboxylate (6.67)



ent-**6.65**



ent-**6.66**



6.67

To (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**) (11.0 mg, 0.02 mmol, 0.2 equiv) in CH_2Cl_2 (0.15 mL) were added sequentially (*E*)-3-(2-bromo-6-methoxyphenyl)acrylaldehyde (**6.7**) (36.2 mg, 0.15 mmol, 1.0 equiv), benzoic acid (9.2 mg, 0.08 mmol, 0.5 equiv), freshly activated 4 Å molecular sieves (ground) (50 mg), and then isopropyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate (**3.25**) (111.3 mg, 0.30 mmol, 2.0 equiv), then the mixture stirred at room temperature for 239 h. The reaction was filtered with ethyl acetate, and then washed sequentially with sat. aq. sodium bicarbonate solution, hydrochloric acid (2 M), and brine. The organic portion was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 20:80 to 30:70) gave 1-benzyl 4-isopropyl (2*S*,3*R*,4*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-6-methoxy-3,4-dihydroquinoline-1,4(2H)-

dicarboxylate (*ent*-**6.65**) as a viscous yellow oil (42.4 mg, 0.07 mmol, 46%). To this product (40 mg, 0.07 mmol, 1.0 equiv) in toluene (0.7 mL) was added Burgess reagent (**6.60**) (31 mg, 0.13 mmol, 2.0 equiv) and the reaction heated to 80 °C and stirred for 90 min. The mixture was allowed to cool to room temperature and then water added. The reaction was extracted with ethyl acetate (× 3) and the combined organic portions washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave 1-benzyl 4-isopropyl (*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-6-methoxyquinoline-1,4(2H)-dicarboxylate (*ent*-**6.66**) as a viscous yellow oil (21.4 mg, 0.04 mmol, 55%); *ent*-**6.65**: R_f: 0.23 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = +21.8$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.68 (s, 1H, C22H), 7.37 (br s, 1H, C6H), 7.28 – 7.22 (m, 3H, 2 ×C14H, C15H), 7.18 (d, *J* = 3.0 Hz, 1H, C3H), 7.17 – 7.14 (m, 3H, C18H, 2 × C13H), 7.12 (t, *J* = 8.0 Hz, 1H, C19H), 6.88 (dd, *J* = 8.9, 3.0 Hz, 1H, C1H), 6.78 (d, *J* = 8.1 Hz, 1H, C20H), 6.10 (d, *J* = 11.5 Hz, 1H, C9H), 5.19 – 5.09 (m, 2H, $C11H_2$), 5.08 (hept, *J* = 6.4 Hz, 1H, C24H), 4.54 (s, 1H, OH), 3.83 (s, 3H, $C27H_3$), 3.55 (d, *J* = 12.1 Hz, 1H, C8H), 3.33 (s, 3H, $C26H_3$), 1.26 (d, *J* = 6.4 Hz, 3H, $C25_AH_3$), 1.04 (d, *J* = 6.4 Hz, 3H, $C25_BH_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 199.8 (C22H), 172.2 (C23), 158.8 (C21), 156.3 (C2), 154.8 (C10), 136.0 (C12), 131.5 (C5), 131.0 (C4), 130.1 (C19H), 128.4 (2 × C14H, C15H), 128.1 (2 × C13H), 127.1 (C16), 126.7 (C6H), 126.0 (C17H), 125.5 (C18H), 114.8 (C1H), 110.6 (C20H), 107.9 (C3H), 73.5 (C7), 71.3 (C24H), 67.8 ($C11H_2$), 60.7 (C8H), 55.8 (C9H), 55.7 ($C27H_3$), 55.1 ($C26H_3$), 21.7 ($C25_AH_3$), 21.3 ($C25_BH_3$); IR ν_{max} (cm^{-1}): 3480 (br), 2981, 2938, 2837, 1705, 1614, 1587, 1572, 1500; HRMS (ESI) $[M+H]^+$: calculated for $C_{30}H_{31}{}^{79}BrNO_8^+$ 612.1228, found 612.1227, Δ –0.12 ppm; *ent*-**6.66**: R_f: 0.36 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = -426.7$ (*c* = 1.00, $CHCl_3$); ee: 92% (Chiralcel OD; hexane:2-propanol, 70:30; flow rate 0.8 $mL.min^{-1}$; λ = 254 nm): t_R (minor) = 19.46 min, t_R (major) = 29.51 min; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.66 (s, 1H, C22H),

7.55 (d, *J* = 9.1 Hz, 1H, C6H), 7.39 – 7.35 (m, 2H, 2 × C13H), 7.34 – 7.28 (m, 3H, 2 × C14H, C15H), 7.20 (dd, *J* = 8.1, 1.1 Hz, 1H, C18H), 7.18 (s, 1H, C9H), 7.03 (t, *J* = 8.1 Hz, 1H, C19H), 6.93 (dd, *J* = 9.1, 2.9 Hz, 1H, C1H), 6.82 (d, *J* = 2.9 Hz, 1H, C3H), 6.66 (dd, *J* = 8.3, 1.1 Hz, 1H, C20H), 5.38 (hept, *J* = 6.3 Hz, 1H, C24H), 5.32 (d, *J* = 12.1 Hz, 1H, C11H_AH_B), 5.21 (d, *J* = 12.1 Hz, 1H, C11H_AH_B), 3.81 (s, 3H, C27H_3), 3.07 (s, 3H, C26H_3), 1.40 (d, *J* = 6.3 Hz, 3H, C25H_3), 1.39 (d, *J* = 6.3 Hz, 3H, C25H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 188.3 (C22H), 166.0 (C23), 161.1 (C21), 155.4 (C2), 154.8 (C10), 142.2 (C7), 136.0 (C12), 132.3 (C5), 131.1 (C8), 130.1 (C19H), 128.9 (2 × C13H), 128.6 (2 × C14H), 128.4 (C15H), 127.1 (C16), 126.1 (C18H), 126.0 (C17), 124.7 (C6H), 124.0 (C4), 117.1 (C1H), 110.6 (C20H), 110.2 (C3H), 70.5 (C24H), 68.3 (C11H_2), 55.8 (C27H_3), 55.0 (C26H_3), 54.5 (C9H), 22.0 (C25H_3), 21.9 (C25H_3); IR ν_{max} (cm^{-1}): 2980, 2939, 2837, 2749, 1713, 1681, 1612, 1572; HRMS (ESI) $[M+H]^+$: calculated for $C_{30}H_{29}{}^{79}BrNO_7{}^+$ 594.1122, found 594.1121, Δ –0.22 ppm.

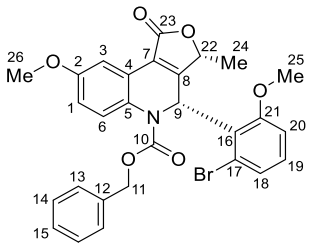
A sample of the enantiomer, 1-benzyl 4-isopropyl (2*R*,3*S*,4*R*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-4-hydroxy-6-methoxy-3,4-dihydroquinoline-1,4(2H)-dicarboxylate (**6.65**) (389 mg, 0.63 mmol, 42%) was prepared as above at 10× scale using 1.0 equiv of (*R*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (*ent*-**1.135**) in place of (*S*)-2-(diphenyl((triethylsilyl)oxy)methyl)pyrrolidine (**1.135**), stirring for 218 h. This product was subjected to the above conditions at 9× scale, stirring for 60 min, to provide enantiomeric 1-benzyl 4-isopropyl (*R*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-6-methoxyquinoline-1,4(2H)-dicarboxylate (**6.66**), along with 1-benzyl 4-isopropyl (*R*)-2-(2-bromo-6-methoxyphenyl)-6-methoxyquinoline-1,4(2H)-dicarboxylate (**6.67**) as a yellow oil (13 mg, 0.02 mmol, 4%); **6.65**: $[\alpha]_D^{25} = -3.2$ (*c* = 1.00, $CHCl_3$); **6.66**: $[\alpha]_D^{25} = +234.1$ (*c* = 1.00, $CHCl_3$); ee: 51% (Chiralcel OD; hexane:2-propanol, 70:30; flow rate 0.8 mL.min^{-1}; λ = 254 nm):

t_R (major) = 19.72 min, t_R (minor) = 30.33 min; all other characterisation identical; **6.67**: R_f: 0.42 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = +121.6$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, *J* = 3.0 Hz, 1H, C3H), 7.53 (s, 1H, C6H), 7.32 – 7.27 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.16 (dd, *J* = 8.1, 1.0 Hz, 1H, C18H), 7.06 (t, *J* = 8.1 Hz, 1H, C19H), 6.86 (d, *J* = 6.2 Hz, 1H, C9H), 6.82 (dd, *J* = 9.0, 3.0 Hz, 1H, C1H), 6.72 – 6.66 (m, 2H, C8H, C20H), 5.26 (d, *J* = 12.3 Hz, 1H, C11H_AH$_B$), 5.19 (hept, *J* = 6.3 Hz, 1H, C23H), 5.15 (d, *J* = 12.3 Hz, 1H, C11H$_A$$H_B$), 3.82 (s, 3H, C26$H_3$), 3.07 (s, 3H, C25$H_3$), 1.35 (d, *J* = 6.3 Hz, 3H, C24H_3), 1.31 (d, *J* = 6.3 Hz, 3H, C24H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 165.4 (C22), 160.7 (C21), 155.1 (C2), 155.0 (C10), 136.2 (C12), 133.4 (C8H), 131.2 (C5), 129.9 (C19H), 128.6 (2 × C13H), 128.5 (2 × C14H), 128.2 (C15H), 127.6 (C4 or C7), 127.0 (C16), 125.1 (C18H), 124.3 (C17), 124.2 (C4 or C7), 124.0 (C6H), 114.0 (C1H), 110.6 (C20H), 110.4 (C3H), 68.7 (C23H), 68.0 (C11H_2), 57.4 (C9H), 55.7 (C26H_3), 55.1 (C25H_3), 22.0 (C24H_3), 22.0 (C24H_3); IR ν_{max} (cm^{-1}): 2955, 2927, 2874, 2850, 1711, 1607, 1583, 1573; HRMS (ESI) $[M+H]^+$: calculated for $C_{29}H_{29}{}^{79}BrNO_6^+$ 566.1173, found 566.1172, Δ –0.18 ppm.

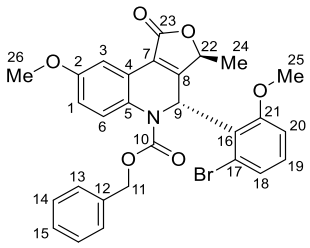
Benzyl (3*R*,4*R*)-4-(2-bromo-6-methoxyphenyl)-8-methoxy-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (6.68)

and

Benzyl (3*S*,4*R*)-4-(2-bromo-6-methoxyphenyl)-8-methoxy-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (6.69)



6.68

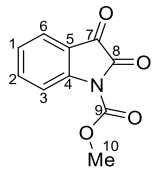


6.69

Methylmagnesium bromide (1 M tetrahydrofuran solution) (3.5 mL, 3.5 mmol, 12.0 equiv) was diluted with tetrahydrofuran (1.8 mL) and cooled to –78 °C. To this well-stirred suspension was added dropwise 1-benzyl 4-isopropyl (*R*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-6-methoxyquinoline-1,4(2H)-dicarboxylate (**6.66**) (51% ee) (180 mg, 0.30 mmol, 1.0 equiv) in tetrahydrofuran (1.8 mL) over 10 min and the reaction stirred at –78 °C for a further 50 min. The reaction was quenched with DL-camphorsulfonic acid (1 M tetrahydrofuran solution) (3.5 mL) and the mixture allowed to warm to room temperature. Water and ethyl acetate were added, and the layers separated. The aqueous portion was extracted with ethyl acetate (× 3). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave an inseparable mixture of benzyl (3*S*,4*R*)-4-(2-bromo-6-methoxyphenyl)-8-methoxy-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**6.69**), benzyl (3*R*,4*R*)-4-(2-bromo-6-methoxyphenyl)-8-methoxy-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (**6.68**) (NMR yield: **6.69**: 109 mg, 0.20 mmol, 65%; **6.68**: 26.4 mg, 0.05 mmol, 16%)

as a viscous yellow oil; R_f: 0.38 (EtOAc:petroleum ether 40-60, 30:70); ^{1}H NMR ($CDCl_3$, 500 MHz) (**6.69**): δ 7.84 (d, *J* = 3.0 Hz, 1H, C3H), 7.56 (br d, *J* = 9.1 Hz, 1H, C6H), 7.30 (d, *J* = 1.2 Hz, 5H, 2 × C13H, 2 × C14H, C15H), 7.18 (dd, *J* = 8.0, 1.0 Hz, 1H, C18H), 7.11 (t, *J* = 8.1 Hz, 1H, C19H), 7.05 (s, 1H, C9H), 6.85 (dd, *J* = 9.0, 3.2 Hz, 1H, C1H), 6.71 (d, *J* = 8.1 Hz, 1H, C20H), 5.28 (d, *J* = 12.2 Hz, 1H, C11H_AH$_B$), 5.22 (d, *J* = 12.2 Hz, 1H, C11H$_A$$H_B$), 4.75 (q, *J* = 6.7 Hz, 1H, C22H), 3.86 (s, 3H, C26H$_3$), 3.04 (s, 3H, C25H$_3$), 1.72 (d, *J* = 6.7 Hz, 3H, C24H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (**6.69**): δ 169.7 (C23), 160.6 (C21), 158.7 (C8), 155.5 (C2), 155.2 (C10), 135.9 (C12), 130.9 (C19H), 130.3 (C5), 128.6 (2 × C13H or 2 × C14H), 128.6 (2 × C13H or 2 × C14H), 128.4 (C15H), 126.0 (C16), 125.5 (C18H), 123.9 (C17), 123.8 (C6H), 121.0 (C7), 120.9 (C4), 115.3 (C1H), 110.7 (C20H), 107.4 (C3H), 76.5 (C22H), 68.3 (C11H$_2$), 56.1 (C9H), 55.8 (C26H$_3$), 55.1 (C25H$_3$), 19.7 (C24H$_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) (**6.68**): δ 7.80 (d, *J* = 3.0 Hz, 1H, C3H), 7.51 (br s, 1H, C6H), 7.35 – 7.26 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.18 (d, *J* = 7.9 Hz, 1H, C18H), 7.12 (t, *J* = 8.1 Hz, 1H, C19H), 7.07 (s, 1H, C9H), 6.87 (dd, *J* = 9.1, 2.9 Hz, 1H, C1H), 6.72 (d, *J* = 8.0 Hz, 1H, C20H), 5.27 (d, *J* = 12.2 Hz, 1H, C11H_AH$_B$), 5.19 (d, *J* = 12.2 Hz, 1H, C11H$_A$$H_B$), 5.15 (qd, *J* = 6.7, 1.5 Hz, 1H, C22H), 3.86 (s, 3H, C26H$_3$), 3.05 (s, 3H, C25H$_3$), 0.99 (d, *J* = 6.7 Hz, 3H, C24H$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) (**6.68**): δ 169.5 (C23), 160.7 (C21), 157.8 (C8), 155.6 (C2), 155.0 (C10), 135.9 (C12), 130.8 (C19H), 130.5 (C5), 128.6 (2 × C13H or 2 × C14H), 128.5 (2 × C13H or 2 × C14H), 128.4 (C15H), 126.0 (C16), 125.2 (C18H), 124.0 (C6H), 123.9 (C17), 121.5 (C7), 120.9 (C4), 115.3 (C1H), 110.7 (C20H), 107.5 (C3H), 77.8 (C22H), 68.3 (C11H$_2$), 56.8 (C9H), 55.8 (C26H$_3$), 55.1 (C25H$_3$), 19.2 (C24H$_3$); HRMS (ESI) $[M+H]^+$: calculated for $C_{28}H_{25}{}^{79}BrNO_6^+$ 550.0860, found 550.0858, Δ –0.29 ppm.

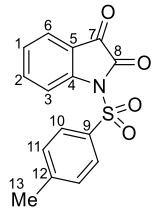
Methyl 2,3-dioxoindoline-1-carboxylate (8.1)



To isatin (**3.3**) (500 mg, 3.4 mmol, 1.0 equiv) in tetrahydrofuran (10 mL) at 0 °C was added triethylamine (0.57 mL, 4.1 mmol, 1.2 equiv) followed by dropwise methyl chloroformate (0.32 mL, 4.1 mmol, 1.2 equiv) and the mixture stirred at room temperature for 60 min. The reaction was concentrated *in vacuo*, then water added and the solid collected by filtration, washing with water, to give methyl 2,3-dioxoindoline-1-carboxylate (**8.1**) as a bright yellow solid (608 mg, 3.0 mmol, 87%); R_f: 0.03 (MeOH:CH_2Cl_2, 10:90); m.p.: 181.5–183.5 °C (lit.[132] 179–180 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.99 (dt, *J* = 8.3, 0.8 Hz, 1H, C3H), 7.78 (ddd, *J* = 8.3, 7.5, 1.5 Hz, 1H, C2H), 7.72 (ddd, *J* = 7.5, 1.5, 0.6 Hz, 1H, C6H), 7.34 (td, *J* = 7.5, 0.9 Hz, 1H, C1H), 3.94 (s, 3H, C10H_3); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 179.6 (C7), 155.8 (C8), 150.5 (C9), 147.2 (C4), 137.8 (C2H), 125.1 (C1H), 124.4 (C6H), 119.6 (C5), 116.2 (C3H), 53.9 (C10H_3); IR ν_{max} (cm^{-1}): 3140, 3035, 2966, 1784, 1744, 1728, 1614, 1596; HRMS (ESI) $[M+Na]^+$: calculated for $C_{10}H_7NNaO_4^+$ 228.0267, found 228.0264, Δ –1.32.

1-Tosylindoline-2,3-dione (8.2)

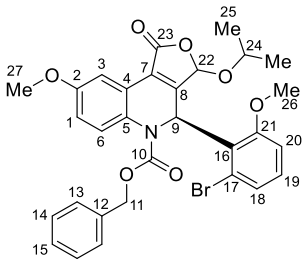
Prepared by modified procedure of Tomchin.[130]



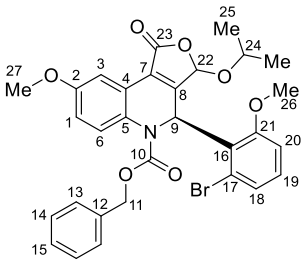
To a suspension of isatin (**3.3**) (500 mg, 3.4 mmol, 1.0 equiv) in toluene (3.3 mL) was added triethylamine (0.47 mL, 3.4 mmol, 1.0 equiv) followed by portionwise tosyl chloride (650 mg,

3.4 mmol, 1.0 equiv), then the mixture was heated at 90 °C for 3 h. The reaction was filtered while hot onto boiling toluene and the collected solid stirred in water (2.0 mL) for 45 min. The remaining solid was collected by filtration, washing thoroughly with water, and dried *in vacuo* to give 1-tosylindoline-2,3-dione (**8.2**) as a yellow solid (169 mg, 0.6 mmol, 17%); R_f: 0.03 (MeOH:CH_2Cl_2, 10:90); m.p.: 213–214 °C (lit.[225] 206 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (d, *J* = 8.4 Hz, 2H, 2 × C10H), 7.86 (ddd, *J* = 8.2, 1.4, 0.8 Hz, 1H, C3H), 7.77 (ddd, *J* = 9.0, 7.5, 1.5 Hz, 1H, C2H), 7.68 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H, C6H), 7.48 (d, *J* = 8.0 Hz, 2H, 2 × C11H), 7.32 (td, *J* = 7.5, 0.9 Hz, 1H, C1H), 2.40 (s, 3H, C13H_3); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 178.3 (C7), 155.8 (C8), 146.0 (C4), 145.9 (C12), 137.9 (C2H), 134.5 (C9), 130.1 (2 × C11H), 127.7 (2 × C10H), 125.3 (C1H), 125.0 (C6H), 119.7 (C5), 114.2 (C3H), 21.2 (C13H_3); IR ν_{max} (cm^{-1}): 3071, 2923, 2853, 1777, 1745, 1608, 1595; HRMS (ESI) $[M+H]^+$: calculated for $C_{15}H_{12}NO_4S^+$ 302.0482, found 302.0483, Δ 0.38 ppm.

Benzyl (4*S*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-8.3a and *ent*-8.3b)



ent-**8.3a**
(*ent*-**8.3a** and *ent*-**8.3b** are diastereomeric)



ent-**8.3b**
(*ent*-**8.3a** and *ent*-**8.3b** are diastereomeric)

Methylmagnesium bromide (1 M tetrahydrofuran solution) (5.0 mL, 5.0 mmol, 10.0 equiv) was diluted with tetrahydrofuran (2.5 mL) and cooled to –78 °C. To this poorly-stirred suspension was added dropwise 1-benzyl 4-isopropyl (*S*)-2-(2-bromo-6-methoxyphenyl)-3-formyl-6-methoxyquinoline-1,4(2H)-dicarboxylate (*ent*-**6.66**) (77% ee) (300 mg, 0.5 mmol,

1.0 equiv) in tetrahydrofuran (2.5 mL) over 10 min and the reaction stirred at –78 °C for a further 60 min. The reaction was quenched with DL-camphorsulfonic acid (1 M tetrahydrofuran solution) (5.0 mL) and the mixture allowed to warm to room temperature. Water and ethyl acetate were added, and the layers separated. The aqueous portion was extracted with ethyl acetate (× 3). The combined organic portions were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:petroleum ether 40-60, 15:85 to 25:75) gave benzyl (4*S*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**8.3a**) as an viscous pale yellow oil (74.6 mg, 0.13 mmol, 25%), a mixture of benzyl (4*S*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**8.3a**) and benzyl (4*S*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**8.3b**) (NMR yield: *ent*-**8.3a**: 33.2 mg, 0.06 mmol, 11%; *ent*-**8.3b**: 24.9 mg, 0.04 mmol, 8%) as a viscous yellow oil, and an inseparable mixture of benzyl (3*R*,4*S*)-4-(2-bromo-6-methoxyphenyl)-8-methoxy-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**6.69**, *vide supra*), benzyl (3*S*,4*S*)-4-(2-bromo-6-methoxyphenyl)-8-methoxy-3-methyl-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**6.68**, *vide supra*), and benzyl (4*S*)-4-(2-bromo-6-methoxyphenyl)-3-isopropoxy-8-methoxy-1-oxo-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (*ent*-**8.3b**) (NMR yield: *ent*-**6.69**: 94.6 mg, 0.17 mmol, 34%; *ent*-**6.68**: 42.0 mg, 0.08 mmol, 15%; *ent*-**8.3b**: 10.0 mg, 0.02 mmol, 3%) as a viscous yellow oil; *ent*-**8.3a**: R_f: 0.47 (EtOAc:petroleum ether 40-60, 30:70); $[\alpha]_D^{25} = -283.8$ (*c* = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.75 (d, *J* = 3.1 Hz, 1H, C3H), 7.57 (br s, 1H, C6H), 7.33 – 7.27 (m, 5H, 2 × C13H, 2 × C14H, C15H), 7.13 (dd, *J* = 8.1, 1.0 Hz, 1H, C18H), 7.08 (br s, 1H, C9H), 7.07 (t, *J* = 8.1 Hz, 1H, C19H), 6.88 (dd, *J* = 9.1, 3.1 Hz, 1H, C1H), 6.69 (dd, *J* = 8.2,

1.0 Hz, 1H, C20H), 5.98 (d, *J* = 1.3 Hz, 1H, C22H), 5.28 (d, *J* = 12.2 Hz, 1H, C11H_AH_B), 5.18 (d, *J* = 12.2 Hz, 1H, C11H_AH_B), 3.93 (hept, *J* = 6.2 Hz, 1H, C24H), 3.85 (s, 3H, C27H_3), 3.06 (s, 3H, C26H_3), 1.06 (d, *J* = 6.2 Hz, 3H, C25$_A$$H_3$), 0.90 (d, *J* = 6.2 Hz, 3H, C25$_B$$H_3$); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 168.1 (C23), 160.7 (C21), 155.5 (C2), 155.0 (C10), 151.0 (C8), 136.0 (C12), 131.1 (C5), 130.1 (C19H), 128.7 (2 × C13H), 128.6 (2 × C14H), 128.4 (C15H), 126.4 (C16), 124.9 (C17), 124.7 (C18H), 124.1 (C6H), 123.9 (C7), 120.3 (C4), 115.8 (C1H), 110.5 (C20H), 108.1 (C3H), 101.0 (C22H), 74.7 (C24H), 68.3 (C11H_2), 56.9 (C9H), 55.8 (C27H_3), 55.1 (C26H_3), 23.0 (C25$_A$$H_3$), 21.7 (C25$_B$$H_3$); IR ν_{max} (cm^{-1}): 2974, 2938, 2837, 1765, 1711, 1609, 1585, 1574; HRMS (ESI) $[M+Na]^+$: calculated for $C_{30}H_{28}{}^{79}BrNNaO_7^+$ 616.0941, found 616.0938, Δ –0.63 ppm.

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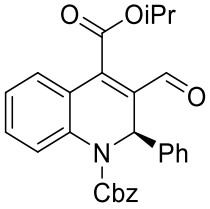
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10 Appendix

10.1 X-ray crystallographic data

10.1.1 *ent*-4.10



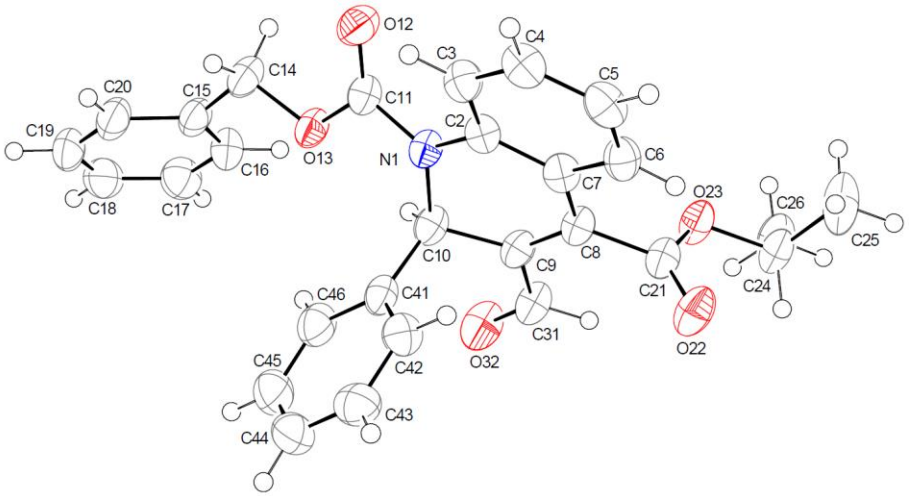


Table 1. Crystal data and structure refinement for 6796.

Identification code	6796
Empirical formula	C28 H25 N O5
Formula weight	455.51
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 11.9537(4) Å α= 90°. b = 6.1904(2) Å β= 102.519(4)°. c = 16.0313(6) Å γ = 90°.
Volume	1158.08(7) Å^3
Z	2
Density (calculated)	1.306 Mg/m^3
Absorption coefficient	0.730 mm^{-1}
F(000)	480
Crystal size	0.40 x 0.05 x 0.02 mm^3
Theta range for data collection	2.824 to 75.911°.
Index ranges	-13<=h<=15, -7<=k<=7, -20<=l<=19
Reflections collected	11221
Independent reflections	4774 [R(int) = 0.053]
Completeness to theta = 75.911°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.51
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4774 / 1 / 308
Goodness-of-fit on F^2	1.0020
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1302
R indices (all data)	R1 = 0.0578, wR2 = 0.1396
Absolute structure parameter	0.2(2)
Largest diff. peak and hole	0.34 and -0.27 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6796. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	8371(2)	4527(3)	2957(1)	36
C(2)	8627(2)	6347(4)	3505(1)	36
C(3)	9386(2)	7971(4)	3375(2)	40
C(4)	9613(2)	9715(4)	3926(2)	44
C(5)	9085(2)	9919(4)	4609(2)	45
C(6)	8318(2)	8346(4)	4738(2)	42
C(7)	8075(2)	6552(4)	4195(2)	38
C(8)	7263(2)	4899(4)	4314(1)	38
C(9)	6878(2)	3428(4)	3700(2)	37
C(10)	7244(2)	3437(4)	2858(2)	37
C(11)	9127(2)	3825(4)	2480(2)	38
O(12)	10111(2)	4390(3)	2569(1)	50
O(13)	8630(2)	2372(3)	1885(1)	41
C(14)	9366(2)	1660(5)	1331(2)	47
C(15)	8750(2)	38(4)	706(2)	43
C(16)	8215(3)	-1758(5)	968(2)	49
C(17)	7728(3)	-3332(6)	387(2)	57
C(18)	7759(3)	-3113(6)	-464(2)	59
C(19)	8262(3)	-1315(7)	-736(2)	60
C(20)	8754(3)	251(5)	-160(2)	52
C(21)	6783(2)	4929(4)	5109(2)	41
O(22)	6108(2)	6281(3)	5230(1)	54
O(23)	7205(2)	3336(3)	5640(1)	48
C(24)	6753(3)	3100(5)	6428(2)	49
C(25)	7480(4)	4444(6)	7117(2)	74
C(26)	6806(3)	719(5)	6623(2)	59
C(31)	5997(2)	1834(4)	3791(2)	45
O(32)	5601(2)	557(3)	3229(2)	59
C(41)	6318(2)	4379(4)	2153(2)	39
C(42)	5889(2)	6441(4)	2231(2)	45
C(43)	5001(3)	7264(5)	1608(2)	55
C(44)	4525(3)	6026(7)	910(2)	64
C(45)	4947(3)	3974(7)	821(2)	66
C(46)	5841(2)	3165(5)	1438(2)	53

Table 3. Bond lengths [Å] and angles [°] for 6796.

N(1)-C(2)	1.421(3)	C(19)-C(20)	1.379(5)
N(1)-C(10)	1.484(3)	C(19)-H(191)	0.943
N(1)-C(11)	1.375(3)	C(20)-H(201)	0.930
C(2)-C(3)	1.400(3)	C(21)-O(22)	1.207(3)
C(2)-C(7)	1.410(3)	C(21)-O(23)	1.329(3)
C(3)-C(4)	1.384(4)	O(23)-C(24)	1.484(3)
C(3)-H(31)	0.942	C(24)-C(25)	1.501(4)
C(4)-C(5)	1.384(4)	C(24)-C(26)	1.505(4)
C(4)-H(41)	0.935	C(24)-H(241)	0.996
C(5)-C(6)	1.383(4)	C(25)-H(252)	0.966
C(5)-H(51)	0.928	C(25)-H(251)	0.964
C(6)-C(7)	1.402(3)	C(25)-H(253)	0.953
C(6)-H(61)	0.931	C(26)-H(262)	0.969
C(7)-C(8)	1.451(3)	C(26)-H(261)	0.969
C(8)-C(9)	1.347(3)	C(26)-H(263)	0.977
C(8)-C(21)	1.506(3)	C(31)-O(32)	1.214(3)
C(9)-C(10)	1.507(3)	C(31)-H(311)	1.001
C(9)-C(31)	1.473(3)	C(41)-C(42)	1.392(4)
C(10)-C(41)	1.516(3)	C(41)-C(46)	1.387(4)
C(10)-H(101)	0.994	C(42)-C(43)	1.388(4)
C(11)-O(12)	1.206(3)	C(42)-H(421)	0.919
C(11)-O(13)	1.351(3)	C(43)-C(44)	1.373(5)
O(13)-C(14)	1.448(3)	C(43)-H(431)	0.929
C(14)-C(15)	1.495(4)	C(44)-C(45)	1.385(6)
C(14)-H(141)	0.982	C(44)-H(441)	0.931
C(14)-H(142)	0.974	C(45)-C(46)	1.382(5)
C(15)-C(16)	1.392(4)	C(45)-H(451)	0.933
C(15)-C(20)	1.396(4)	C(46)-H(461)	0.942
C(16)-C(17)	1.386(4)		
C(16)-H(161)	0.934	C(2)-N(1)-C(10)	119.69(18)
C(17)-C(18)	1.380(5)	C(2)-N(1)-C(11)	121.07(19)
C(17)-H(171)	0.953	C(10)-N(1)-C(11)	119.15(19)
C(18)-C(19)	1.379(5)	N(1)-C(2)-C(3)	122.5(2)
C(18)-H(181)	0.941	N(1)-C(2)-C(7)	118.8(2)
C(3)-C(2)-C(7)	118.7(2)	C(15)-C(14)-H(142)	109.0
C(2)-C(3)-C(4)	120.6(2)	H(141)-C(14)-H(142)	109.0
C(2)-C(3)-H(31)	119.2	C(14)-C(15)-C(16)	121.8(2)
C(4)-C(3)-H(31)	120.2	C(14)-C(15)-C(20)	119.7(3)
C(3)-C(4)-C(5)	121.0(2)	C(16)-C(15)-C(20)	118.4(3)
C(3)-C(4)-H(41)	119.2	C(15)-C(16)-C(17)	120.9(3)
C(5)-C(4)-H(41)	119.7	C(15)-C(16)-H(161)	118.9
C(4)-C(5)-C(6)	119.0(2)	C(17)-C(16)-H(161)	120.2
C(4)-C(5)-H(51)	120.4	C(16)-C(17)-C(18)	119.9(3)
C(6)-C(5)-H(51)	120.6	C(16)-C(17)-H(171)	120.7
C(5)-C(6)-C(7)	121.4(2)	C(18)-C(17)-H(171)	119.5
C(5)-C(6)-H(61)	119.8	C(17)-C(18)-C(19)	119.9(3)
C(7)-C(6)-H(61)	118.9	C(17)-C(18)-H(181)	120.1
C(2)-C(7)-C(6)	119.2(2)	C(19)-C(18)-H(181)	120.0
C(2)-C(7)-C(8)	118.7(2)	C(18)-C(19)-C(20)	120.5(3)
C(6)-C(7)-C(8)	122.1(2)	C(18)-C(19)-H(191)	120.5
C(7)-C(8)-C(9)	120.9(2)	C(20)-C(19)-H(191)	119.0
C(7)-C(8)-C(21)	119.4(2)	C(15)-C(20)-C(19)	120.4(3)
C(9)-C(8)-C(21)	119.6(2)	C(15)-C(20)-H(201)	120.7
C(8)-C(9)-C(10)	122.2(2)	C(19)-C(20)-H(201)	118.9
C(8)-C(9)-C(31)	121.3(2)	C(8)-C(21)-O(22)	122.3(2)
C(10)-C(9)-C(31)	116.4(2)	C(8)-C(21)-O(23)	111.8(2)
C(9)-C(10)-N(1)	109.80(18)	O(22)-C(21)-O(23)	125.8(2)
C(9)-C(10)-C(41)	111.23(19)	C(21)-O(23)-C(24)	117.5(2)
N(1)-C(10)-C(41)	113.87(19)	O(23)-C(24)-C(25)	108.2(2)
C(9)-C(10)-H(101)	108.4	O(23)-C(24)-C(26)	105.5(2)
N(1)-C(10)-H(101)	105.3	C(25)-C(24)-C(26)	113.5(3)
C(41)-C(10)-H(101)	107.9	O(23)-C(24)-H(241)	109.9
N(1)-C(11)-O(12)	125.7(2)	C(25)-C(24)-H(241)	110.5
N(1)-C(11)-O(13)	111.2(2)	C(26)-C(24)-H(241)	109.1
O(12)-C(11)-O(13)	123.1(2)	C(24)-C(25)-H(252)	110.6
C(11)-O(13)-C(14)	113.71(19)	C(24)-C(25)-H(251)	109.3
O(13)-C(14)-C(15)	109.8(2)	H(252)-C(25)-H(251)	106.0
O(13)-C(14)-H(141)	106.7	C(24)-C(25)-H(253)	112.0
C(15)-C(14)-H(141)	112.4	H(252)-C(25)-H(253)	110.6
O(13)-C(14)-H(142)	110.0	H(251)-C(25)-H(253)	108.1

C(24)-C(26)-H(262)	110.5	C(43)-C(42)-H(421)	118.6
C(24)-C(26)-H(261)	110.2	C(42)-C(43)-C(44)	119.9(3)
H(262)-C(26)-H(261)	109.9	C(42)-C(43)-H(431)	121.1
C(24)-C(26)-H(263)	108.6	C(44)-C(43)-H(431)	119.0
H(262)-C(26)-H(263)	109.3	C(43)-C(44)-C(45)	120.0(3)
H(261)-C(26)-H(263)	108.3	C(43)-C(44)-H(441)	120.9
C(9)-C(31)-O(32)	122.3(2)	C(45)-C(44)-H(441)	119.0
C(9)-C(31)-H(311)	116.2	C(44)-C(45)-C(46)	120.1(3)
O(32)-C(31)-H(311)	121.6	C(44)-C(45)-H(451)	119.0
C(10)-C(41)-C(42)	120.6(2)	C(46)-C(45)-H(451)	120.9
C(10)-C(41)-C(46)	120.7(2)	C(41)-C(46)-C(45)	120.7(3)
C(42)-C(41)-C(46)	118.6(3)	C(41)-C(46)-H(461)	119.4
C(41)-C(42)-C(43)	120.8(3)	C(45)-C(46)-H(461)	119.9
C(41)-C(42)-H(421)	120.6		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6796. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	41(1)	34(1)	35(1)	-3(1)	14(1)	-3(1)
C(2)	42(1)	31(1)	33(1)	0(1)	7(1)	0(1)
C(3)	47(1)	37(1)	38(1)	5(1)	10(1)	-4(1)
C(4)	50(1)	35(1)	44(1)	5(1)	4(1)	-6(1)
C(5)	54(1)	31(1)	45(1)	-6(1)	1(1)	-1(1)
C(6)	52(1)	36(1)	37(1)	-4(1)	10(1)	2(1)
C(7)	43(1)	32(1)	37(1)	0(1)	8(1)	3(1)
C(8)	44(1)	35(1)	37(1)	-2(1)	15(1)	1(1)
C(9)	43(1)	33(1)	40(1)	-2(1)	17(1)	1(1)
C(10)	46(1)	30(1)	40(1)	-6(1)	18(1)	-5(1)
C(11)	45(1)	36(1)	36(1)	0(1)	15(1)	-2(1)
O(12)	45(1)	54(1)	55(1)	-9(1)	20(1)	-7(1)
O(13)	45(1)	42(1)	40(1)	-8(1)	20(1)	-5(1)
C(14)	50(1)	51(1)	48(1)	-8(1)	26(1)	-3(1)
C(15)	46(1)	49(1)	39(1)	-2(1)	19(1)	7(1)
C(16)	58(2)	53(1)	37(1)	0(1)	15(1)	-2(1)
C(17)	60(2)	56(2)	56(2)	-5(1)	12(1)	-5(1)
C(18)	54(2)	72(2)	51(2)	-20(1)	8(1)	4(1)
C(19)	61(2)	87(2)	36(1)	-4(1)	17(1)	18(2)
C(20)	57(2)	61(2)	43(1)	4(1)	24(1)	13(1)
C(21)	48(1)	40(1)	39(1)	-5(1)	18(1)	-3(1)
O(22)	70(1)	44(1)	58(1)	0(1)	33(1)	11(1)
O(23)	60(1)	48(1)	42(1)	2(1)	25(1)	9(1)
C(24)	60(2)	52(2)	43(1)	-1(1)	27(1)	6(1)
C(25)	112(3)	71(2)	50(2)	-17(2)	38(2)	-22(2)
C(26)	82(2)	53(2)	51(2)	3(1)	31(2)	1(1)
C(31)	56(1)	39(1)	48(1)	-3(1)	25(1)	-3(1)
O(32)	70(1)	45(1)	69(1)	-15(1)	33(1)	-20(1)
C(41)	45(1)	41(1)	36(1)	-4(1)	18(1)	-8(1)
C(42)	50(1)	41(1)	45(1)	-3(1)	9(1)	-3(1)
C(43)	47(1)	58(2)	60(2)	10(1)	13(1)	-4(1)
C(44)	45(2)	96(3)	47(2)	6(2)	5(1)	-10(2)
C(45)	54(2)	96(3)	46(2)	-20(2)	8(1)	-18(2)
C(46)	52(2)	61(2)	49(1)	-16(1)	17(1)	-13(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 6796.

	x	y	z	U(eq)
H(31)	9752	7851	2913	47
H(41)	10124	10780	3828	53
H(51)	9246	11091	4977	53
H(61)	7946	8480	5189	50
H(101)	7378	1921	2702	44
H(141)	10059	1060	1704	57
H(142)	9582	2885	1019	57
H(161)	8189	-1890	1543	58
H(171)	7359	-4557	567	69
H(181)	7415	-4163	-863	70
H(191)	8263	-1127	-1320	72
H(201)	9096	1438	-358	62
H(241)	5940	3586	6318	58
H(252)	7186	4392	7633	110
H(251)	8241	3840	7265	110
H(253)	7541	5902	6940	111
H(262)	6495	423	7122	88
H(261)	7590	212	6718	88
H(263)	6355	-50	6131	88
H(311)	5729	1879	4340	53
H(421)	6194	7294	2694	53
H(431)	4718	8647	1653	66
H(441)	3906	6528	500	76
H(451)	4623	3160	340	80
H(461)	6124	1767	1376	63

Table 6. Hydrogen bonds for 6796 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(6)-H(61)...O(22)	0.93	2.60	3.185(4)	121
C(24)-H(241)...O(32)#1	1.00	2.45	3.348(4)	150
C(31)-H(311)...O(22)#2	1.00	2.47	3.259(4)	136
C(42)-H(421)...O(32)#3	0.92	2.36	3.068(4)	133

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z+1 #2 -x+1,y-1/2,-z+1 #3 x,y+1,z

10.1.2 ent-4.29

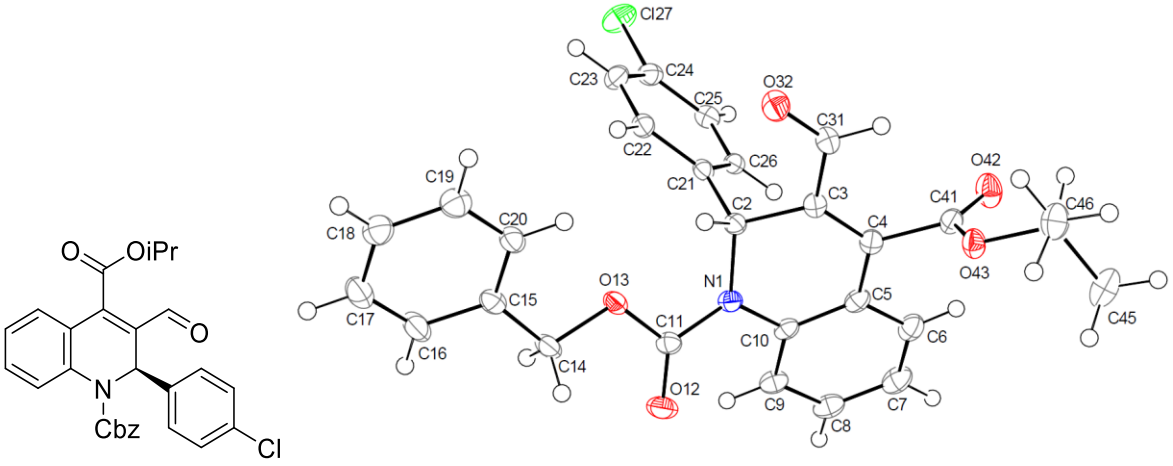


Table 1. Crystal data and structure refinement for 6900.

Identification code	6900
Empirical formula	C28 H24 Cl N O5
Formula weight	489.95
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	P 1
Unit cell dimensions	a = 6.3621(2) Å α= 98.137(2)°. b = 9.4058(3) Å β= 99.359(2)°. c = 10.6203(3) Å γ = 102.050(3)°.
Volume	603.02(3) Å^3
Z	1
Density (calculated)	1.349 Mg/m^3
Absorption coefficient	1.736 mm^{-1}
F(000)	256
Crystal size	0.25 x 0.21 x 0.17 mm^3
Theta range for data collection	4.889 to 75.749°.
Index ranges	-7<=h<=7, -11<=k<=11, -12<=l<=13
Reflections collected	10900
Independent reflections	4657 [R(int) = 0.018]
Completeness to theta = 73.477°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.74 and 0.64
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4656 / 3 / 318
Goodness-of-fit on F^2	0.9996
Final R indices [I>2sigma(I)]	R1 = 0.0270, wR2 = 0.0717
R indices (all data)	R1 = 0.0270, wR2 = 0.0717
Absolute structure parameter	0.002(3)
Extinction coefficient	22(3)
Largest diff. peak and hole	0.15 and -0.17 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6900. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	4089(2)	7221(1)	1202(1)	19
C(2)	3077(2)	8181(1)	421(1)	17
C(3)	3735(2)	9759(2)	1150(1)	18
C(4)	5573(2)	10263(2)	2062(1)	19
C(5)	7022(2)	9301(2)	2401(1)	21
C(6)	9137(2)	9852(2)	3145(2)	26
C(7)	10490(2)	8931(2)	3454(2)	30
C(8)	9730(2)	7418(2)	2996(2)	27
C(9)	7637(2)	6830(2)	2247(2)	23
C(10)	6250(2)	7764(2)	1952(1)	19
C(11)	2951(2)	5792(2)	1161(1)	20
O(12)	3520(2)	4961(1)	1840(1)	30
O(13)	1071(2)	5432(1)	265(1)	21
C(14)	-168(2)	3936(2)	196(2)	24
C(15)	-2384(2)	3677(2)	-655(2)	22
C(16)	-3510(3)	2203(2)	-1117(2)	31
C(17)	-5642(3)	1850(2)	-1814(2)	33
C(18)	-6671(2)	2961(2)	-2082(2)	28
C(19)	-5543(3)	4428(2)	-1661(2)	28
C(20)	-3415(2)	4783(2)	-944(2)	23
C(21)	3613(2)	8070(1)	-926(1)	17
C(22)	1963(2)	7558(1)	-2037(1)	19
C(23)	2452(2)	7482(2)	-3271(2)	23
C(24)	4623(2)	7918(2)	-3385(2)	22
C(25)	6296(2)	8417(2)	-2299(2)	21
C(26)	5785(2)	8497(1)	-1076(1)	18
Cl(27)	5297(1)	7825(1)	-4915(1)	35
C(31)	2296(2)	10728(2)	760(2)	21
O(32)	614(2)	10288(1)	-43(1)	27
C(41)	6222(2)	11856(2)	2759(1)	21
O(42)	7731(2)	12759(1)	2570(1)	31
O(43)	4946(2)	12091(1)	3596(1)	23
C(44)	5369(2)	13607(2)	4346(2)	25
C(45)	7160(3)	13786(2)	5521(2)	37
C(46)	3183(3)	13734(2)	4665(2)	31

Table 3. Bond lengths [Å] and angles [°] for 6900.

N(1)-C(2)	1.4828(16)	C(19)-C(20)	1.388(2)
N(1)-C(10)	1.4214(17)	C(19)-H(191)	0.947
N(1)-C(11)	1.3790(18)	C(20)-H(201)	0.945
C(2)-C(3)	1.5122(18)	C(21)-C(22)	1.3965(18)
C(2)-C(21)	1.5188(19)	C(21)-C(26)	1.3979(18)
C(2)-H(21)	0.991	C(22)-C(23)	1.391(2)
C(3)-C(4)	1.3422(19)	C(22)-H(221)	0.991
C(3)-C(31)	1.4737(18)	C(23)-C(24)	1.387(2)
C(4)-C(5)	1.4597(18)	C(23)-H(231)	0.941
C(4)-C(41)	1.5144(18)	C(24)-C(25)	1.3866(19)
C(5)-C(6)	1.3965(19)	C(24)-Cl(27)	1.7415(15)
C(5)-C(10)	1.4106(19)	C(25)-C(26)	1.385(2)
C(6)-C(7)	1.379(2)	C(25)-H(251)	0.942
C(6)-H(61)	0.912	C(26)-H(261)	0.944
C(7)-C(8)	1.392(2)	C(31)-O(32)	1.2095(18)
C(7)-H(71)	0.965	C(31)-H(311)	0.986
C(8)-C(9)	1.391(2)	C(41)-O(42)	1.2052(18)
C(8)-H(81)	0.935	C(41)-O(43)	1.3237(18)
C(9)-C(10)	1.4003(19)	O(43)-C(44)	1.4793(16)
C(9)-H(91)	0.958	C(44)-C(45)	1.510(2)
C(11)-O(12)	1.2058(17)	C(44)-C(46)	1.508(2)
C(11)-O(13)	1.3493(16)	C(44)-H(441)	0.992
O(13)-C(14)	1.4479(15)	C(45)-H(453)	0.959
C(14)-C(15)	1.4978(19)	C(45)-H(452)	0.973
C(14)-H(141)	0.952	C(45)-H(451)	0.966
C(14)-H(142)	0.965	C(46)-H(463)	0.962
C(15)-C(16)	1.398(2)	C(46)-H(462)	0.974
C(15)-C(20)	1.3844(19)	C(46)-H(461)	0.979
C(16)-C(17)	1.384(2)		
C(16)-H(161)	0.951	C(2)-N(1)-C(10)	119.83(10)
C(17)-C(18)	1.383(2)	C(2)-N(1)-C(11)	119.62(11)
C(17)-H(171)	0.948	C(10)-N(1)-C(11)	120.52(11)
C(18)-C(19)	1.388(2)	N(1)-C(2)-C(3)	109.88(11)
C(18)-H(181)	0.927	N(1)-C(2)-C(21)	112.46(10)
C(3)-C(2)-C(21)	111.71(10)	C(15)-C(14)-H(142)	110.7
N(1)-C(2)-H(21)	105.8	H(141)-C(14)-H(142)	108.6
C(3)-C(2)-H(21)	108.3	C(14)-C(15)-C(16)	116.53(12)
C(21)-C(2)-H(21)	108.4	C(14)-C(15)-C(20)	124.56(13)
C(2)-C(3)-C(4)	121.81(12)	C(16)-C(15)-C(20)	118.80(13)
C(2)-C(3)-C(31)	116.21(11)	C(15)-C(16)-C(17)	120.83(14)
C(4)-C(3)-C(31)	121.93(12)	C(15)-C(16)-H(161)	117.4
C(3)-C(4)-C(5)	121.19(12)	C(17)-C(16)-H(161)	121.7
C(3)-C(4)-C(41)	120.86(12)	C(16)-C(17)-C(18)	119.97(14)
C(5)-C(4)-C(41)	117.95(12)	C(16)-C(17)-H(171)	119.8
C(4)-C(5)-C(6)	122.22(13)	C(18)-C(17)-H(171)	120.2
C(4)-C(5)-C(10)	118.47(12)	C(17)-C(18)-C(19)	119.59(14)
C(6)-C(5)-C(10)	119.31(13)	C(17)-C(18)-H(181)	120.7
C(5)-C(6)-C(7)	121.59(14)	C(19)-C(18)-H(181)	119.7
C(5)-C(6)-H(61)	118.8	C(18)-C(19)-C(20)	120.43(13)
C(7)-C(6)-H(61)	119.6	C(18)-C(19)-H(191)	118.6
C(6)-C(7)-C(8)	118.86(14)	C(20)-C(19)-H(191)	120.9
C(6)-C(7)-H(71)	122.3	C(19)-C(20)-C(15)	120.34(13)
C(8)-C(7)-H(71)	118.9	C(19)-C(20)-H(201)	119.5
C(7)-C(8)-C(9)	121.12(14)	C(15)-C(20)-H(201)	120.1
C(7)-C(8)-H(81)	119.6	C(2)-C(21)-C(22)	121.16(11)
C(9)-C(8)-H(81)	119.2	C(2)-C(21)-C(26)	120.22(11)
C(8)-C(9)-C(10)	119.96(14)	C(22)-C(21)-C(26)	118.62(13)
C(8)-C(9)-H(91)	119.5	C(21)-C(22)-C(23)	121.13(12)
C(10)-C(9)-H(91)	120.6	C(21)-C(22)-H(221)	120.0
N(1)-C(10)-C(5)	118.54(11)	C(23)-C(22)-H(221)	118.9
N(1)-C(10)-C(9)	122.31(13)	C(22)-C(23)-C(24)	118.75(13)
C(5)-C(10)-C(9)	119.14(12)	C(22)-C(23)-H(231)	121.0
N(1)-C(11)-O(12)	125.29(13)	C(24)-C(23)-H(231)	120.3
N(1)-C(11)-O(13)	111.15(11)	C(23)-C(24)-C(25)	121.33(13)
O(12)-C(11)-O(13)	123.56(12)	C(23)-C(24)-Cl(27)	120.00(11)
C(11)-O(13)-C(14)	112.63(10)	C(25)-C(24)-Cl(27)	118.67(11)
O(13)-C(14)-C(15)	110.27(11)	C(24)-C(25)-C(26)	119.31(12)
O(13)-C(14)-H(141)	108.0	C(24)-C(25)-H(251)	120.6
C(15)-C(14)-H(141)	110.2	C(26)-C(25)-H(251)	120.1
O(13)-C(14)-H(142)	109.0	C(21)-C(26)-C(25)	120.85(12)

C(21)-C(26)-H(261)	119.5	C(46)-C(44)-H(441)	111.6
C(25)-C(26)-H(261)	119.6	C(44)-C(45)-H(453)	111.5
C(3)-C(31)-O(32)	122.85(12)	C(44)-C(45)-H(452)	110.2
C(3)-C(31)-H(311)	115.3	H(453)-C(45)-H(452)	106.6
O(32)-C(31)-H(311)	121.9	C(44)-C(45)-H(451)	110.4
C(4)-C(41)-O(42)	123.16(13)	H(453)-C(45)-H(451)	109.7
C(4)-C(41)-O(43)	110.89(11)	H(452)-C(45)-H(451)	108.2
O(42)-C(41)-O(43)	125.94(13)	C(44)-C(46)-H(463)	109.1
C(41)-O(43)-C(44)	117.22(11)	C(44)-C(46)-H(462)	109.9
O(43)-C(44)-C(45)	108.79(12)	H(463)-C(46)-H(462)	111.3
O(43)-C(44)-C(46)	104.43(11)	C(44)-C(46)-H(461)	107.2
C(45)-C(44)-C(46)	114.17(13)	H(463)-C(46)-H(461)	111.2
O(43)-C(44)-H(441)	105.7	H(462)-C(46)-H(461)	107.9
C(45)-C(44)-H(441)	111.5		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 6900. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

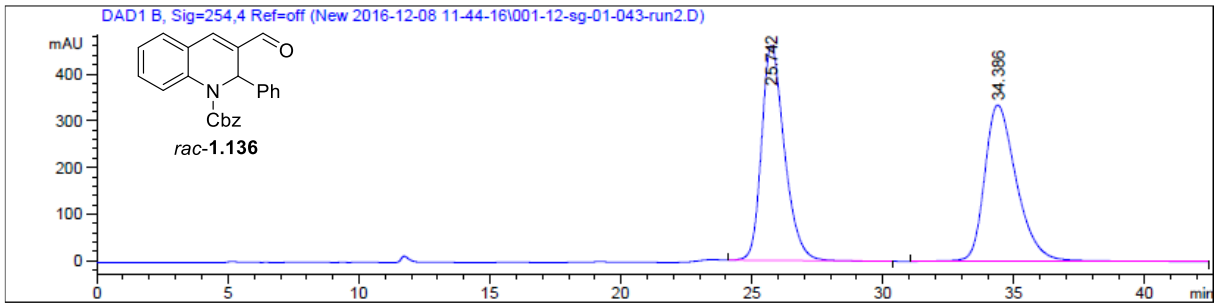
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	18(1)	20(1)	19(1)	6(1)	3(1)	4(1)
C(2)	15(1)	16(1)	19(1)	5(1)	2(1)	4(1)
C(3)	18(1)	19(1)	18(1)	3(1)	7(1)	4(1)
C(4)	19(1)	21(1)	18(1)	3(1)	7(1)	1(1)
C(5)	19(1)	28(1)	15(1)	5(1)	5(1)	5(1)
C(6)	23(1)	30(1)	21(1)	4(1)	3(1)	0(1)
C(7)	19(1)	43(1)	25(1)	8(1)	1(1)	5(1)
C(8)	22(1)	39(1)	24(1)	11(1)	5(1)	13(1)
C(9)	23(1)	31(1)	20(1)	8(1)	6(1)	10(1)
C(10)	18(1)	25(1)	14(1)	6(1)	4(1)	4(1)
C(11)	21(1)	21(1)	19(1)	7(1)	6(1)	5(1)
O(12)	30(1)	29(1)	32(1)	17(1)	1(1)	4(1)
O(13)	21(1)	16(1)	25(1)	7(1)	3(1)	1(1)
C(14)	24(1)	17(1)	32(1)	11(1)	4(1)	2(1)
C(15)	23(1)	20(1)	23(1)	7(1)	8(1)	4(1)
C(16)	29(1)	18(1)	44(1)	10(1)	1(1)	3(1)
C(17)	32(1)	22(1)	42(1)	9(1)	2(1)	-2(1)
C(18)	23(1)	33(1)	28(1)	8(1)	4(1)	4(1)
C(19)	32(1)	27(1)	27(1)	5(1)	6(1)	13(1)
C(20)	30(1)	17(1)	22(1)	3(1)	6(1)	6(1)
C(21)	17(1)	13(1)	20(1)	4(1)	2(1)	4(1)
C(22)	17(1)	18(1)	22(1)	3(1)	1(1)	4(1)
C(23)	23(1)	25(1)	19(1)	3(1)	-1(1)	6(1)
C(24)	29(1)	22(1)	19(1)	6(1)	7(1)	9(1)
C(25)	18(1)	21(1)	25(1)	7(1)	6(1)	6(1)
C(26)	17(1)	16(1)	20(1)	5(1)	1(1)	3(1)
Cl(27)	36(1)	53(1)	19(1)	9(1)	10(1)	13(1)
C(31)	20(1)	18(1)	25(1)	3(1)	5(1)	3(1)
O(32)	19(1)	25(1)	35(1)	4(1)	0(1)	6(1)
C(41)	20(1)	22(1)	17(1)	2(1)	3(1)	2(1)
O(42)	29(1)	27(1)	33(1)	1(1)	13(1)	-4(1)
O(43)	26(1)	20(1)	21(1)	-1(1)	9(1)	0(1)
C(44)	30(1)	21(1)	21(1)	-3(1)	6(1)	1(1)
C(45)	29(1)	48(1)	26(1)	-6(1)	2(1)	5(1)
C(46)	32(1)	30(1)	29(1)	-3(1)	7(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 6900.

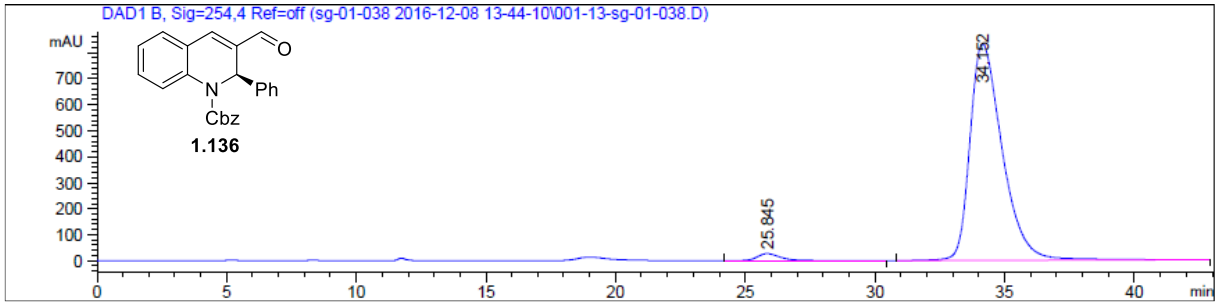
	x	y	z	U(eq)
H(21)	1471	7817	330	19
H(61)	9632	10848	3421	31
H(71)	11950	9300	3973	36
H(81)	10655	6786	3168	33
H(91)	7162	5785	1932	28
H(141)	631	3275	-149	29
H(142)	-304	3782	1062	29
H(161)	-2738	1462	-958	38
H(171)	-6389	845	-2112	40
H(181)	-8107	2737	-2536	33
H(191)	-6258	5177	-1868	33
H(201)	-2680	5786	-645	28
H(221)	416	7229	-1953	23
H(231)	1339	7130	-4018	29
H(251)	7766	8709	-2388	23
H(261)	6915	8855	-334	20
H(311)	2808	11772	1194	26
H(441)	5831	14277	3749	28
H(453)	7466	14751	6046	54
H(452)	8519	13678	5252	54
H(451)	6758	13042	6035	54
H(463)	3354	14679	5204	47
H(462)	2107	13606	3867	46
H(461)	2702	12923	5116	46

10.2 HPLC traces

Benzyl 3-formyl-2-phenylquinoline-1(2H)-carboxylate (1.136)

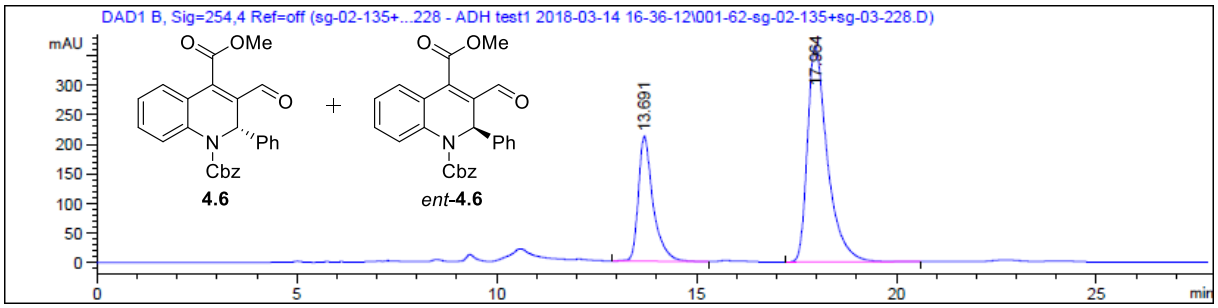


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.742	BB	0.9299	2.81220e4	460.87027	49.5485
2	34.386	BBA	1.2936	2.86345e4	335.53754	50.4515

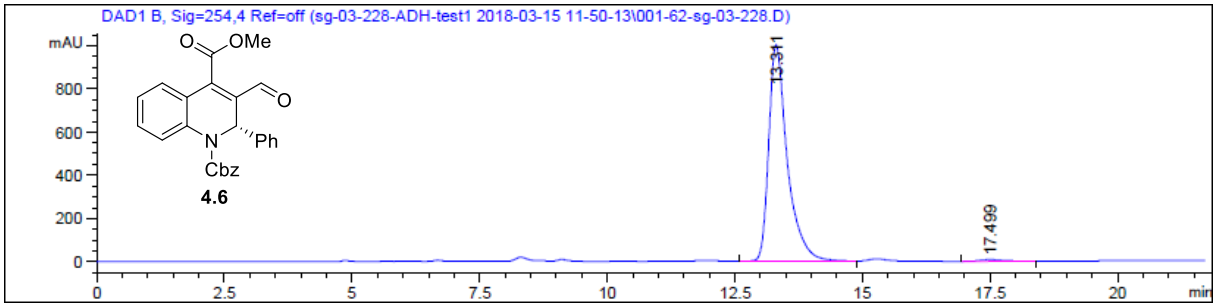


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.845	BB	0.9449	1711.03333	26.87121	2.3063
2	34.152	BBA	1.3308	7.24792e4	833.24353	97.6937

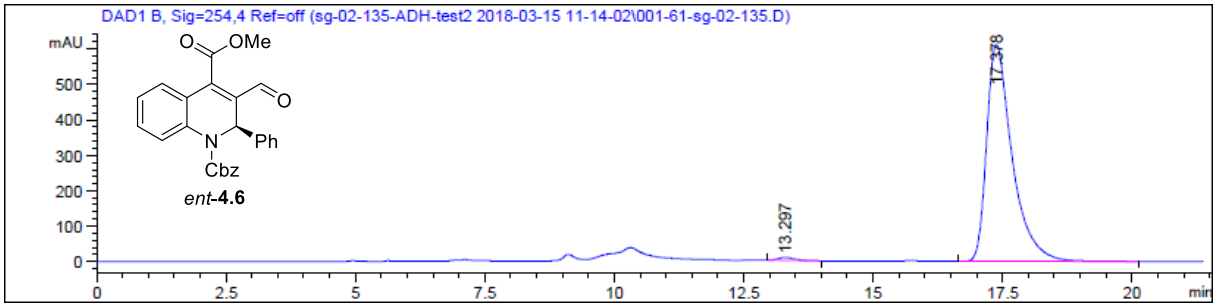
1-Benzyl 4-methyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.6)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.691	BB	0.3802	5428.18945	210.92751	29.9585
2	17.964	BB	0.5174	1.26908e4	365.21381	70.0415

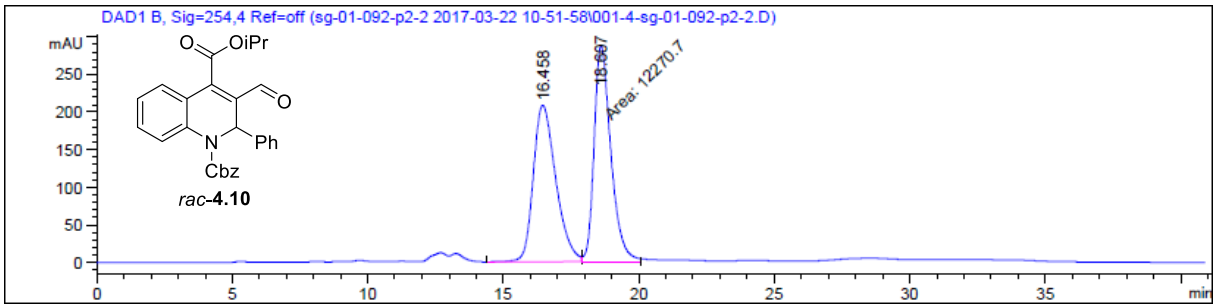


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.311	BB	0.3729	2.51474e4	1001.59125	99.1067
2	17.499	BB	0.4650	226.65834	7.28512	0.8933

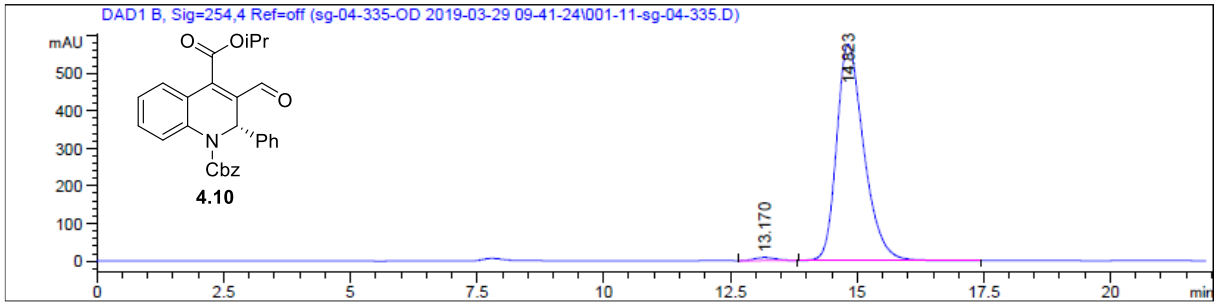


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.297	BB	0.3351	180.63298	8.19638	0.8547
2	17.378	BB	0.5120	2.09536e4	611.11902	99.1453

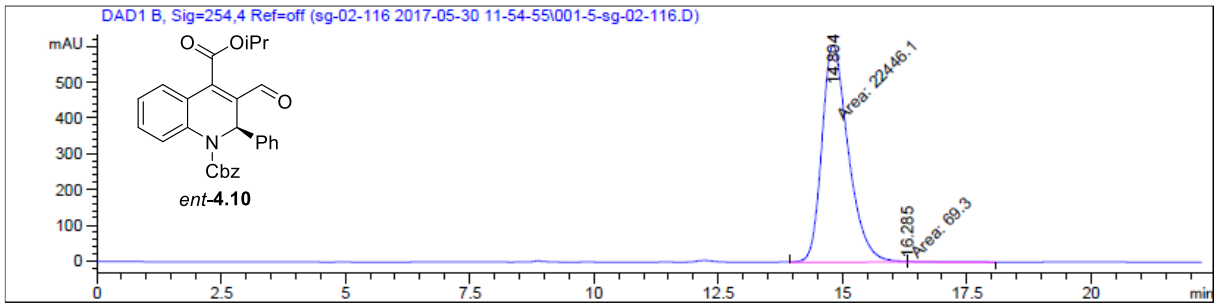
1-Benzyl 4-isopropyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.10)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.458	BV	0.8838	1.19935e4	207.65910	49.4286
2	18.607	MF	0.7141	1.22707e4	286.37646	50.5714

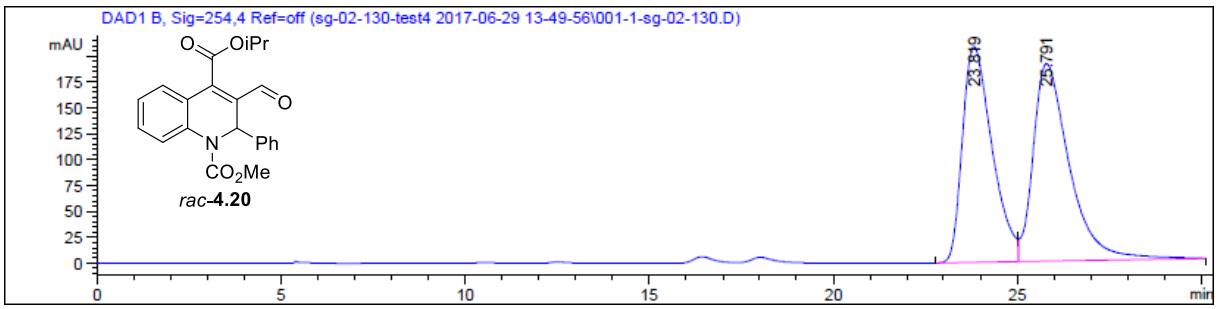


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.170	BB	0.4441	233.40739	8.19972	1.0762
2	14.823	BB	0.5690	2.14556e4	575.48285	98.9238

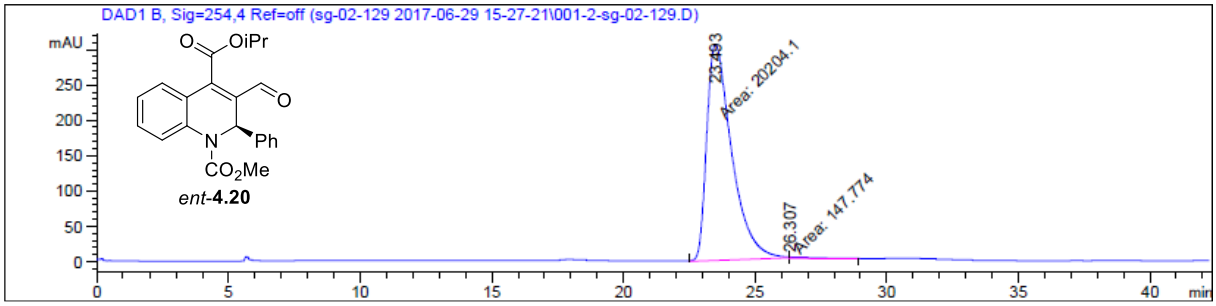


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.804	MM	0.6149	2.24461e4	608.42542	99.6922
2	16.285	MM	0.9932	69.30003	8.32548e-1	0.3078

4-Isopropyl 1-methyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.20)

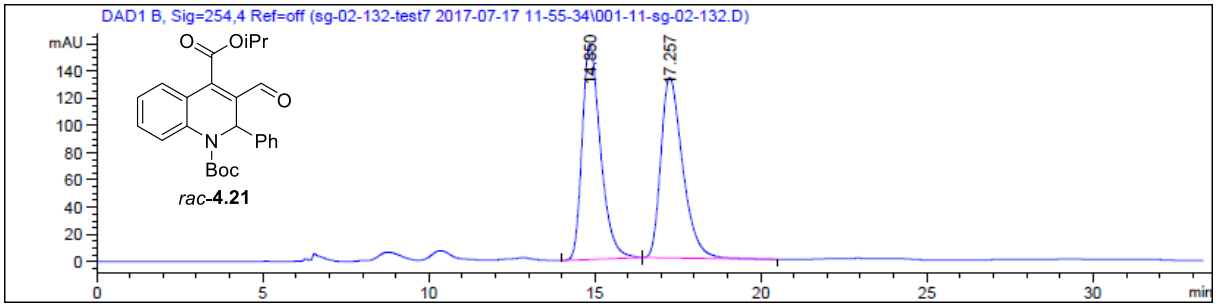


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.819	BV	0.8564	1.16731e4	208.10388	47.2057
2	25.791	VBA	1.0288	1.30551e4	190.67403	52.7943

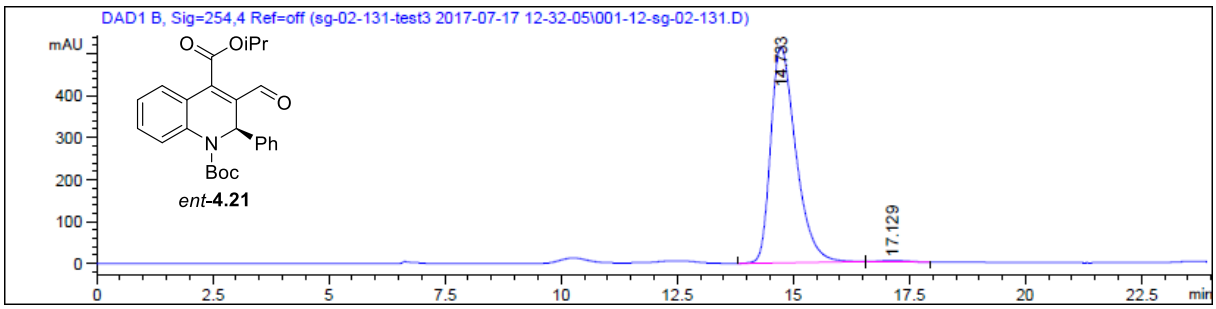


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.493	MM T	1.1854	2.02041e4	306.22610	99.2739
2	26.307	MM	0.9161	147.77391	1.89455	0.7261

1-(*tert*-Butyl) 4-isopropyl 3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.21)

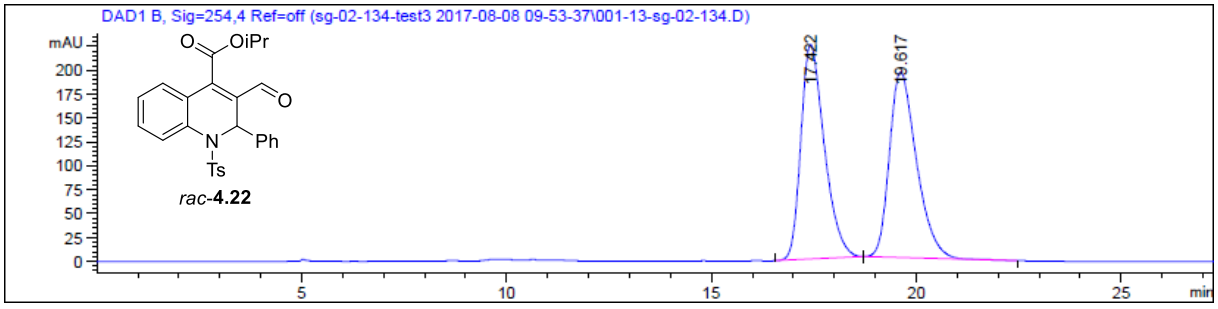


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.850	BB	0.5878	6081.12207	157.72731	50.0930
2	17.257	BB	0.6973	6058.54053	132.55003	49.9070

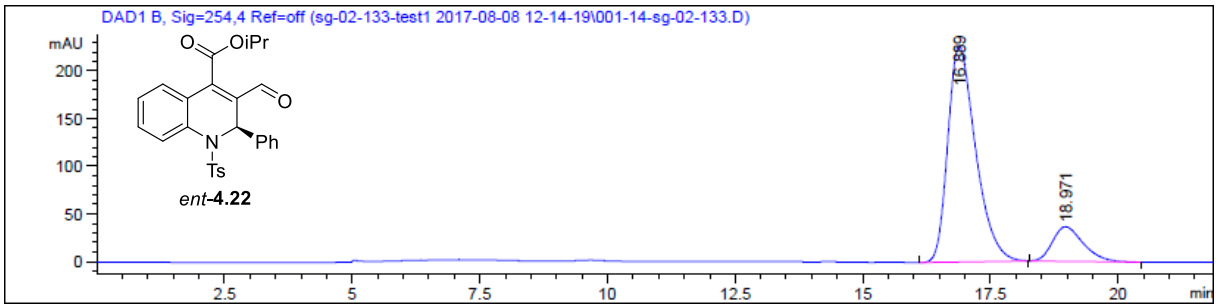


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.733	BB	0.5752	1.93839e4	514.84888	99.3393
2	17.129	BB	0.5564	128.92627	3.51117	0.6607

Isopropyl 3-formyl-2-phenyl-1-tosyl-1,2-dihydroquinoline-4-carboxylate (4.22)

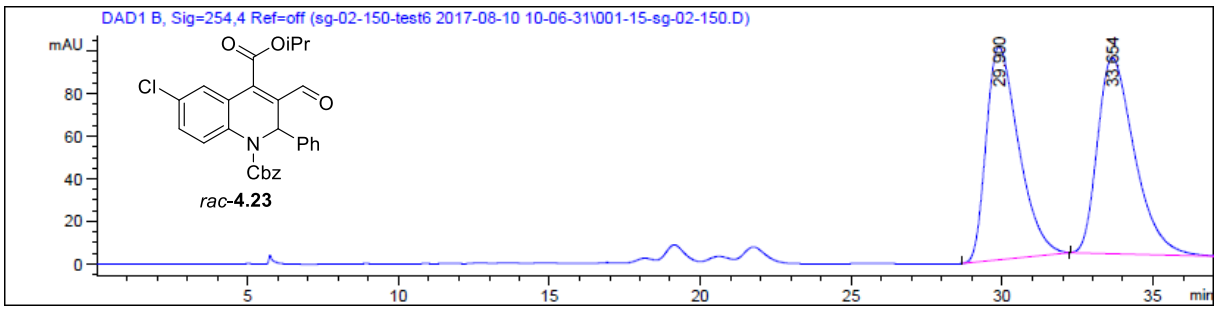


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.422	BB	0.6074	8947.27539	224.27510	49.9958
2	19.617	BB	0.7017	8948.77051	194.17883	50.0042

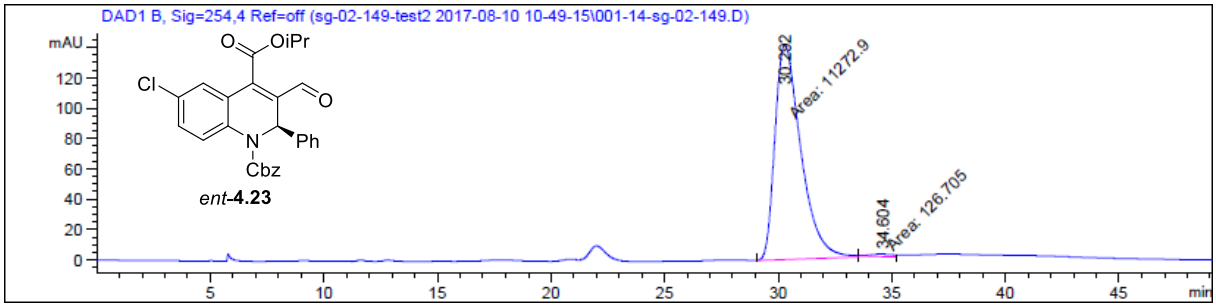


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.889	BB	0.5749	8570.31250	226.79810	84.8956
2	18.971	BBA	0.6404	1524.80847	36.27428	15.1044

1-Benzyl 4-isopropyl 6-chloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.23)

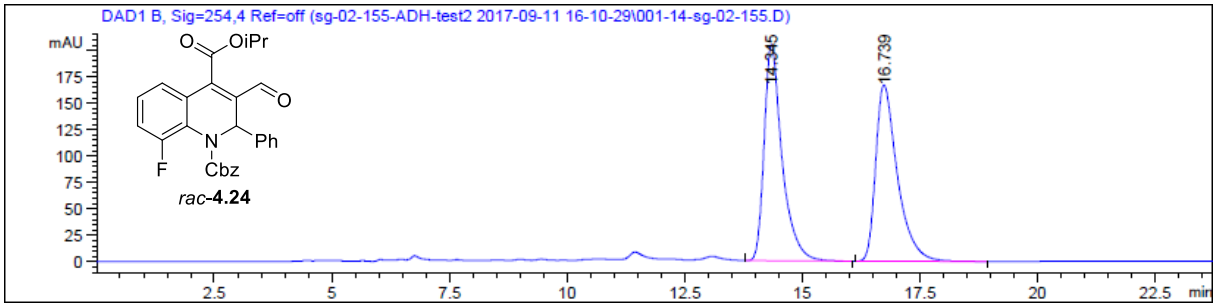


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.900	BB	1.1328	7485.05713	100.05692	48.8292
2	33.654	BBA	1.2871	7844.01660	91.96558	51.1708

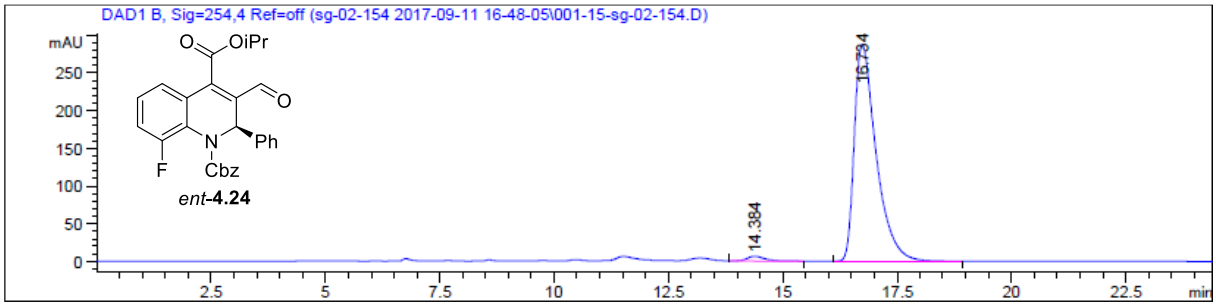


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.292	MM	1.3265	1.12729e4	141.63913	98.8885
2	34.604	MM	1.2075	126.70549	1.74885	1.1115

1-Benzyl 4-isopropyl 8-fluoro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.24)

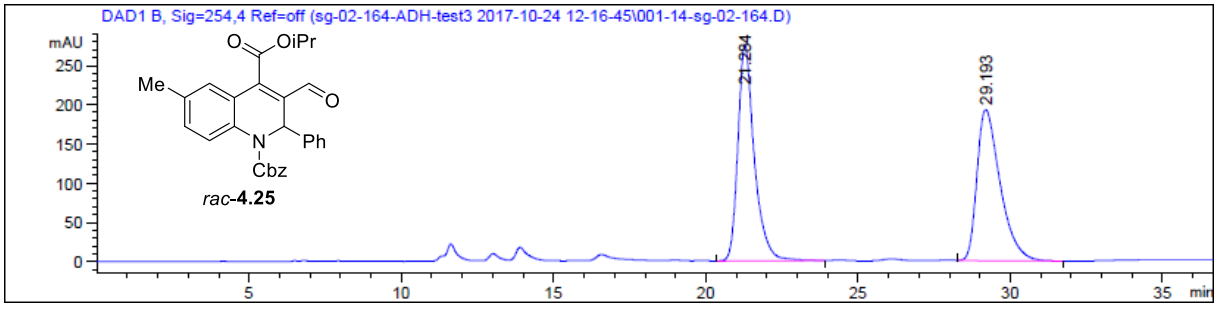


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.345	BB	0.3932	5424.83545	204.69643	50.2762
2	16.739	BB	0.4827	5365.22705	167.06026	49.7238

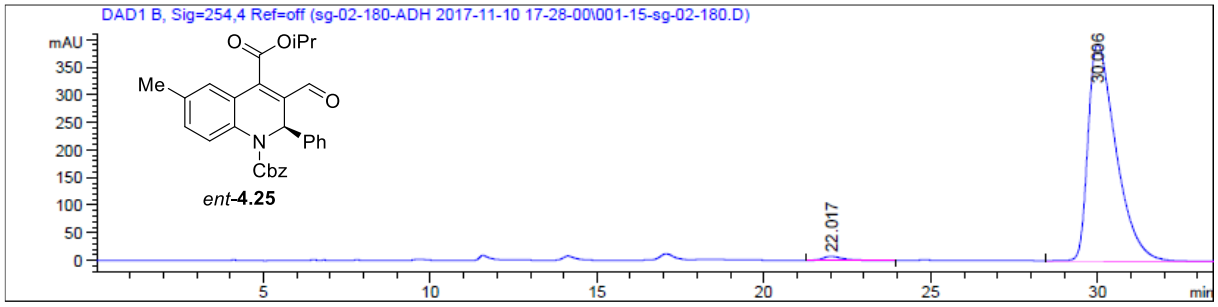


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.384	BB	0.3792	160.40793	6.29767	1.6489
2	16.734	BB	0.5000	9568.05273	287.68857	98.3511

1-Benzyl 4-isopropyl 3-formyl-6-methyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.25)

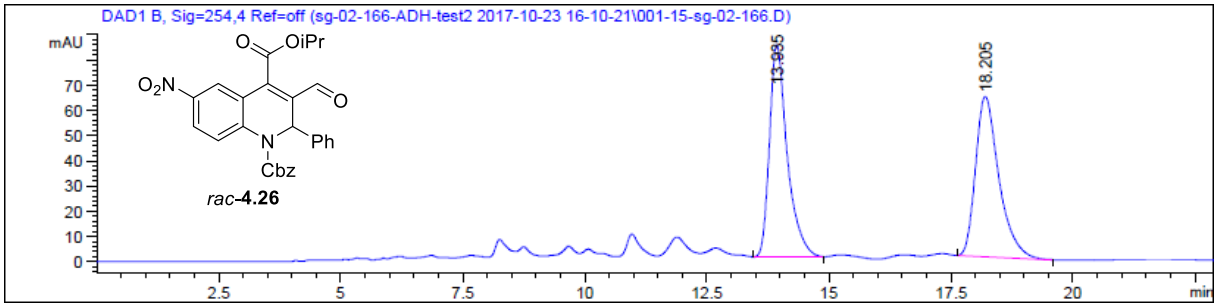


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.284	BB	0.5603	1.03434e4	275.30930	50.4397
2	29.193	BB	0.8005	1.01631e4	192.32527	49.5603

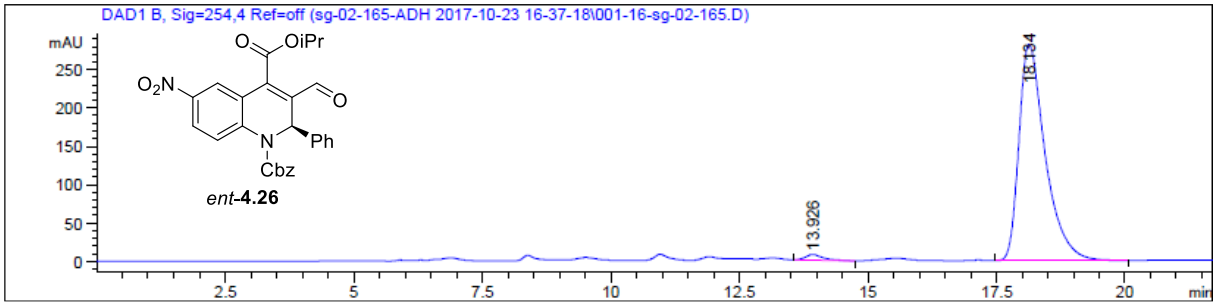


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.017	BB	0.5741	284.23578	7.23878	1.2314
2	30.006	BBA	0.8836	2.27979e4	392.53006	98.7686

1-Benzyl 4-isopropyl 3-formyl-6-nitro-2-phenylquinoline-1,4(2H)-dicarboxylate (4.26)



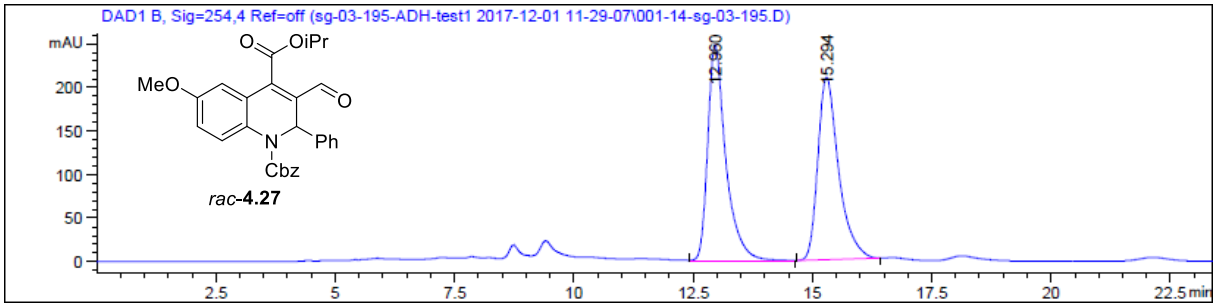
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.935	BB	0.3768	2125.27075	84.11686	50.0693
2	18.205	BB	0.5026	2119.38843	63.63688	49.9307



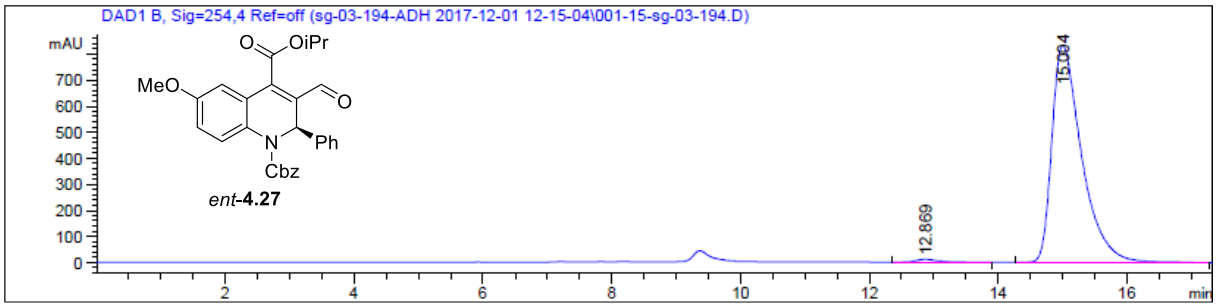
Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.926	BB	0.3548	170.00771	7.21775	1.6746
2	18.134	BB	0.5311	9982.29590	281.93933	98.3254

1-Benzyl 4-isopropyl 3-formyl-6-methoxy-2-phenylquinoline-1,4(2H)-dicarboxylate (4.27)

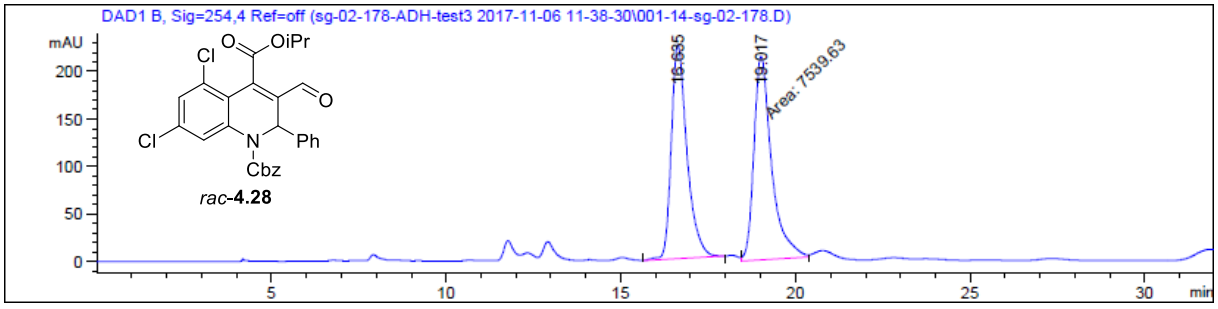


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.960	BB	0.3898	6486.04443	247.47212	50.6396
2	15.294	BB	0.4546	6322.21143	209.20850	49.3604

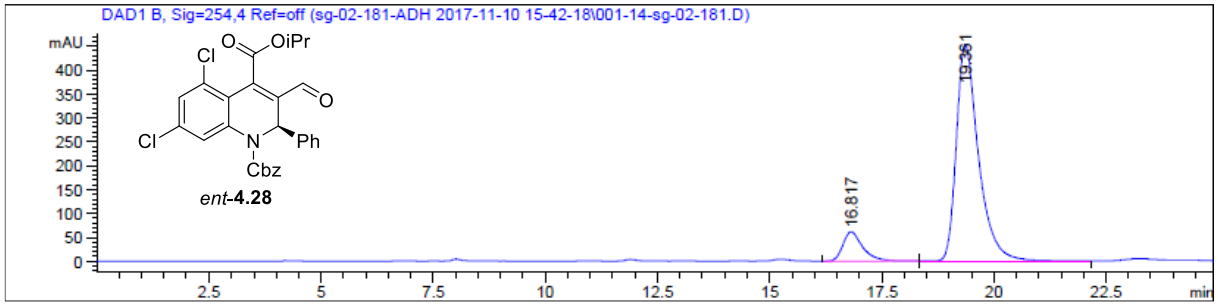


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.869	BB	0.3815	272.78918	10.62615	1.0138
2	15.004	BB	0.4830	2.66355e4	833.05023	98.9862

1-Benzyl 4-isopropyl 5,7-dichloro-3-formyl-2-phenylquinoline-1,4(2H)-dicarboxylate (4.28)

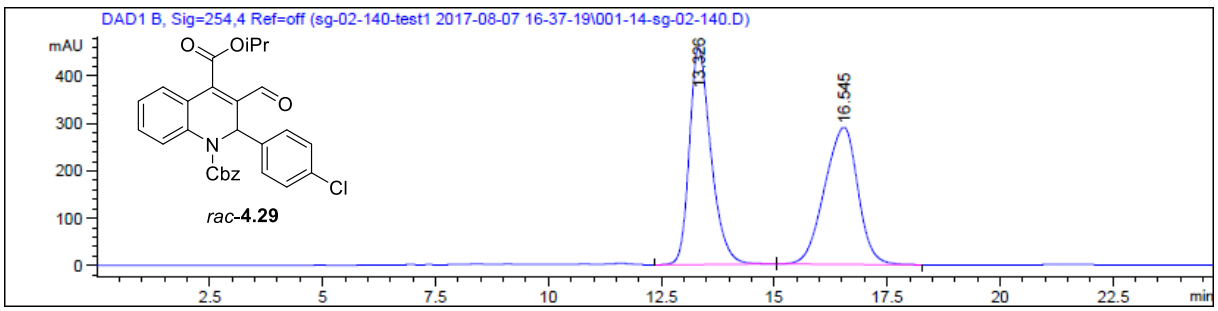


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.635	BB	0.4697	7012.37158	224.96436	48.1884
2	19.017	MM	0.5874	7539.63330	213.94432	51.8116

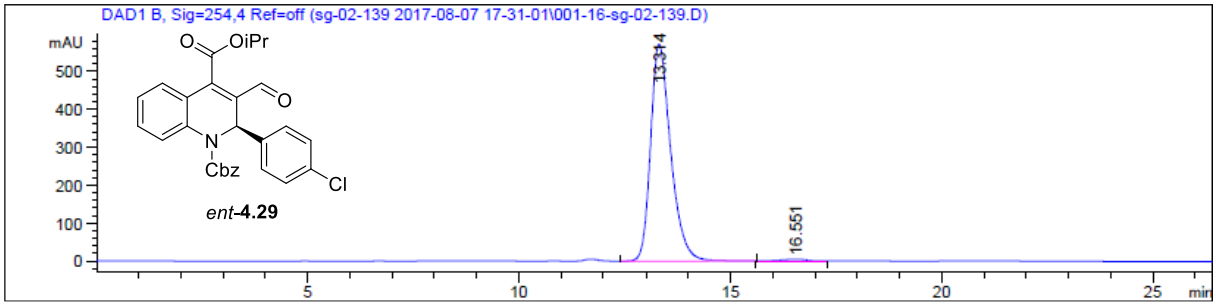


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.817	BB	0.4581	1869.16162	61.22960	10.7580
2	19.361	BB	0.5132	1.55055e4	453.14215	89.2420

1-Benzyl 4-isopropyl 2-(4-chlorophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (4.29)

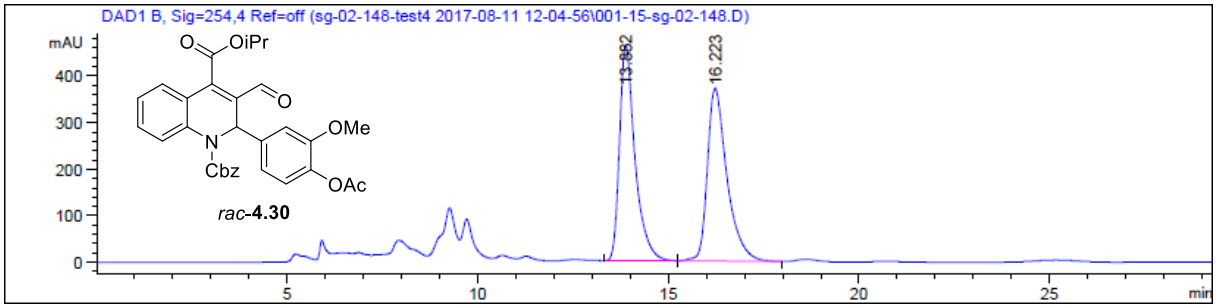


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.326	BB	0.5048	1.52594e4	457.86078	50.6220
2	16.545	BB	0.8173	1.48844e4	289.76080	49.3780

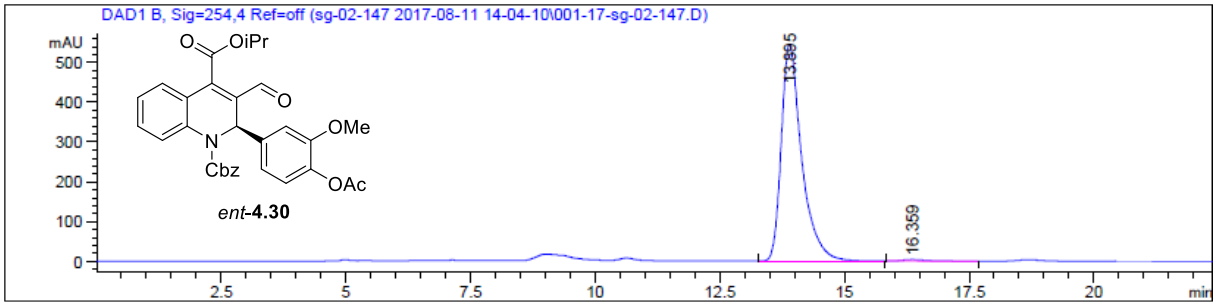


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.314	BB	0.5005	1.89269e4	571.32819	98.9954
2	16.551	BB	0.5718	192.07631	4.89457	1.0046

1-Benzyl 4-isopropyl 2-(4-acetoxy-3-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (4.30)

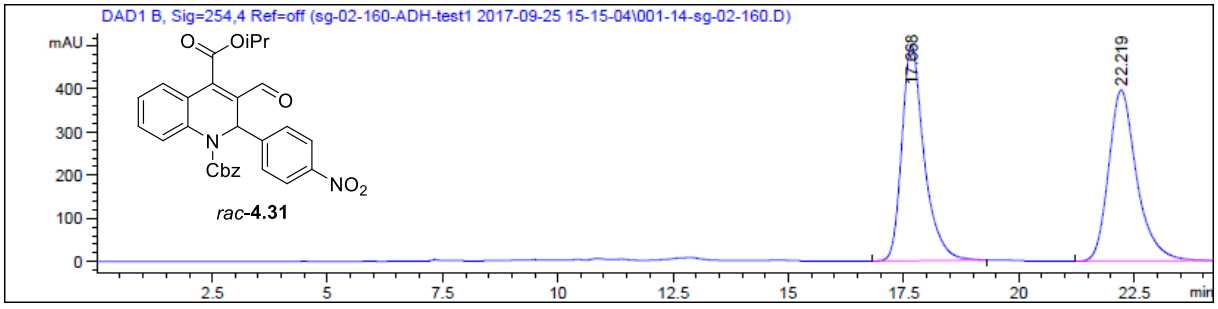


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.882	BB	0.4185	1.30549e4	463.67188	49.5730
2	16.223	BB	0.5359	1.32799e4	370.73804	50.4270

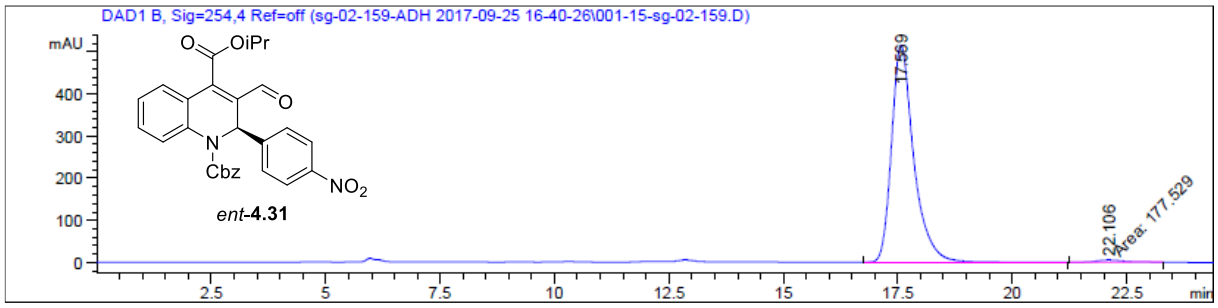


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.895	BB	0.4262	1.55184e4	545.07544	99.1229
2	16.359	BB	0.5022	137.31680	3.94374	0.8771

1-Benzyl 4-isopropyl 3-formyl-2-(4-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (4.31)

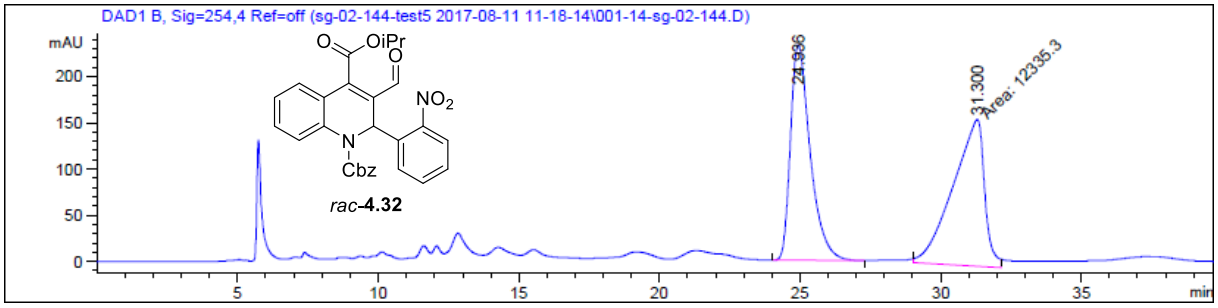


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.668	BB	0.5011	1.68012e4	501.14804	49.9788
2	22.219	BBA	0.6364	1.68155e4	396.80652	50.0212

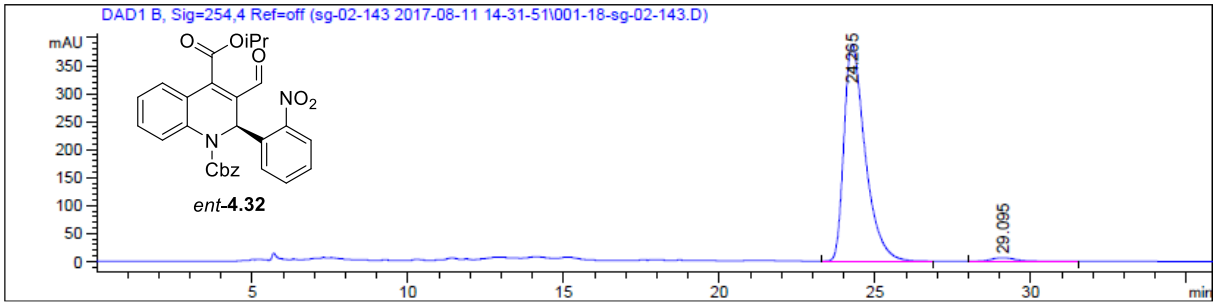


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.569	BB	0.5034	1.73678e4	515.03973	98.9882
2	22.106	MM	0.6108	177.52859	4.84420	1.0118

1-Benzyl 4-isopropyl 3-formyl-2-(2-nitrophenyl)quinoline-1,4(2H)-dicarboxylate (4.32)

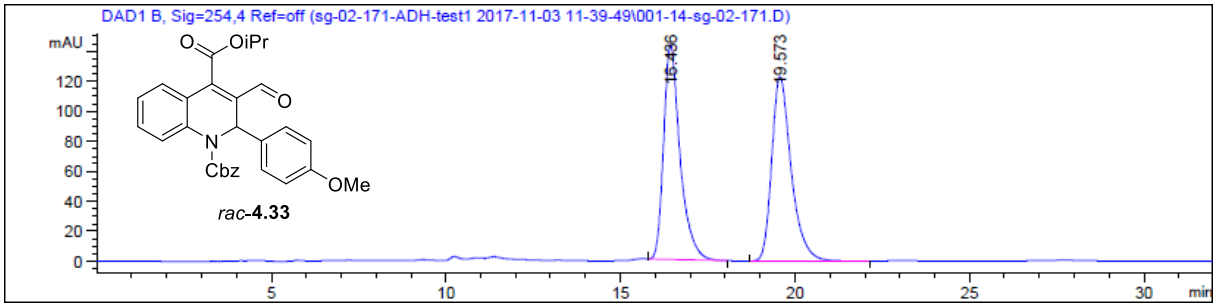


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.936	BB	0.7364	1.13494e4	232.93228	47.9187
2	31.300	MM	1.2973	1.23353e4	158.47493	52.0813

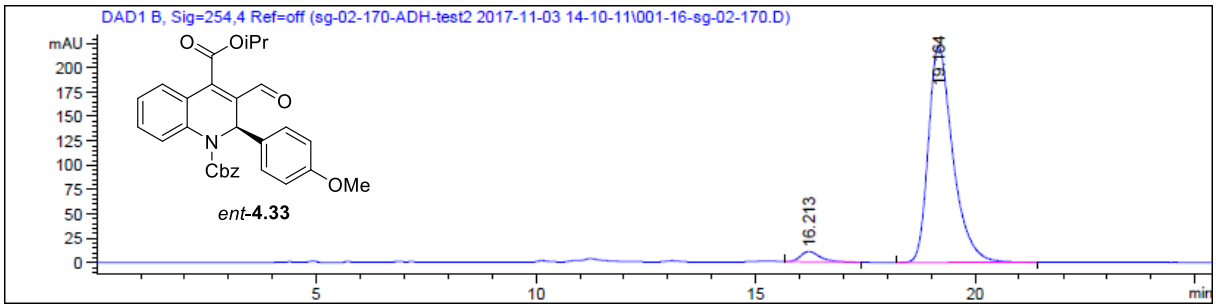


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.265	BB	0.7149	1.83327e4	388.22983	98.1065
2	29.095	BB	0.7688	353.83435	6.64951	1.8935

1-Benzyl 4-isopropyl 3-formyl-2-(4-methoxyphenyl)quinoline-1,4(2H)-dicarboxylate (4.33)

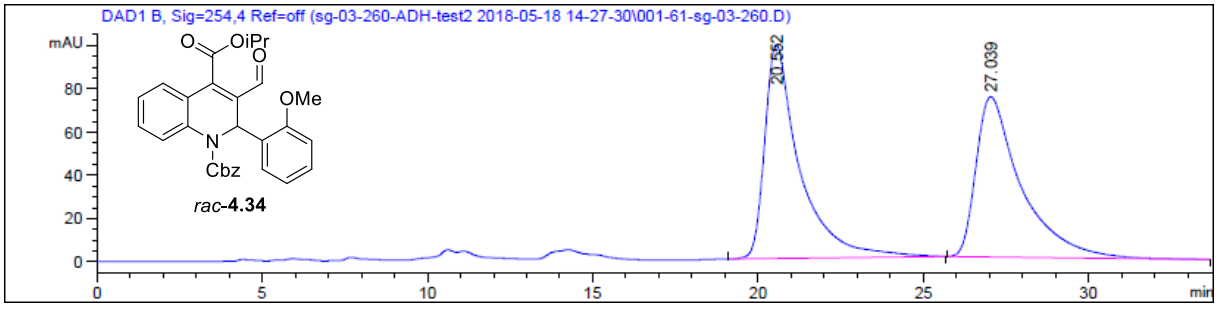


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.436	BB	0.4890	4671.82324	143.07367	49.5172
2	19.573	BB	0.5842	4762.92920	122.87673	50.4828

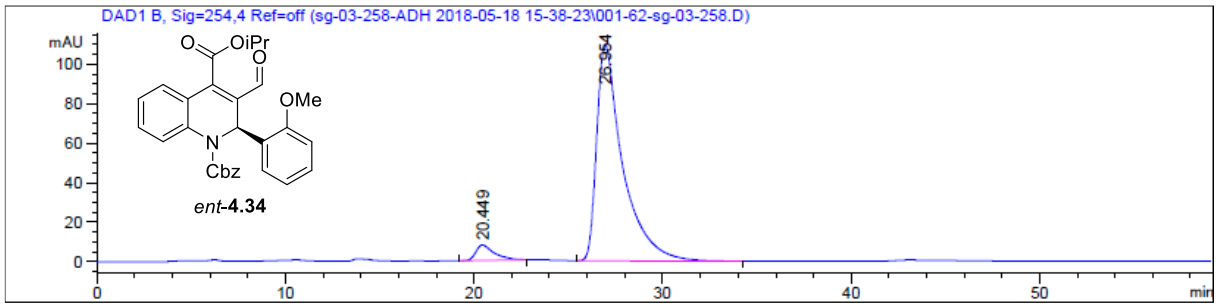


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.213	BB	0.4657	332.79495	10.73558	3.7281
2	19.164	BB	0.5848	8593.77148	222.42657	96.2719

1-Benzyl 4-isopropyl 3-formyl-2-(2-methoxyphenyl)quinoline-1,4(2H)-dicarboxylate (4.34)

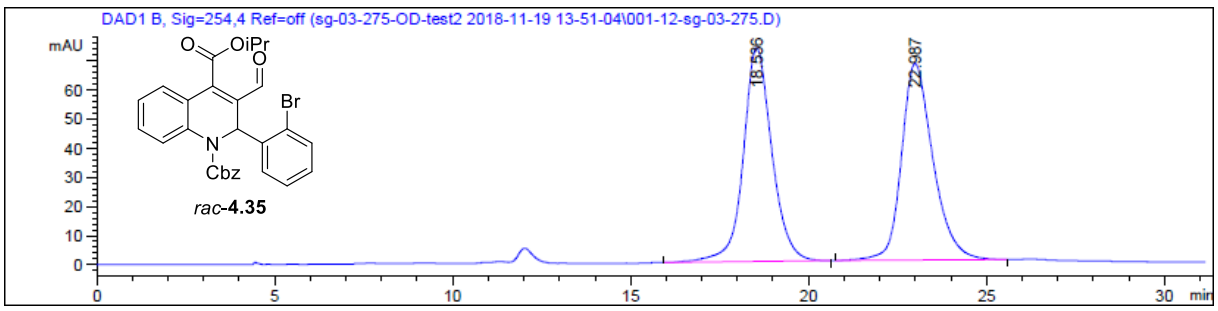


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.552	BB	1.0486	7297.14990	98.92015	50.9081
2	27.039	BBA	1.3640	7036.80713	74.09521	49.0919

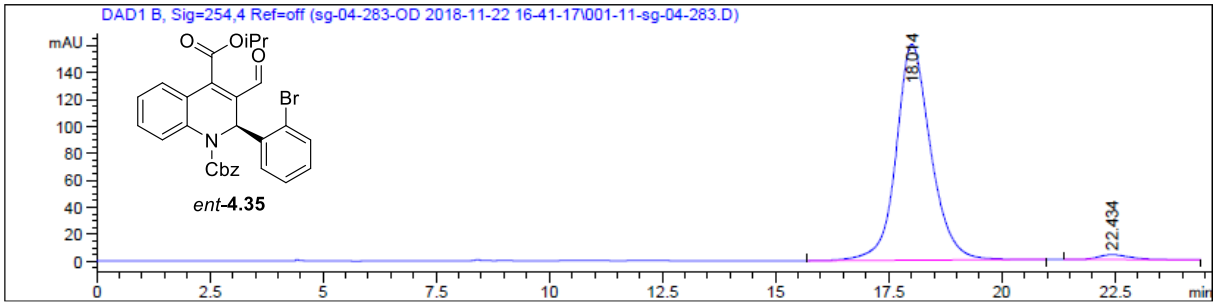


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.449	BB	0.9087	516.61249	7.74040	4.7021
2	26.954	BB	1.3682	1.04702e4	109.24422	95.2979

1-Benzyl 4-isopropyl 2-(2-bromophenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (4.35)

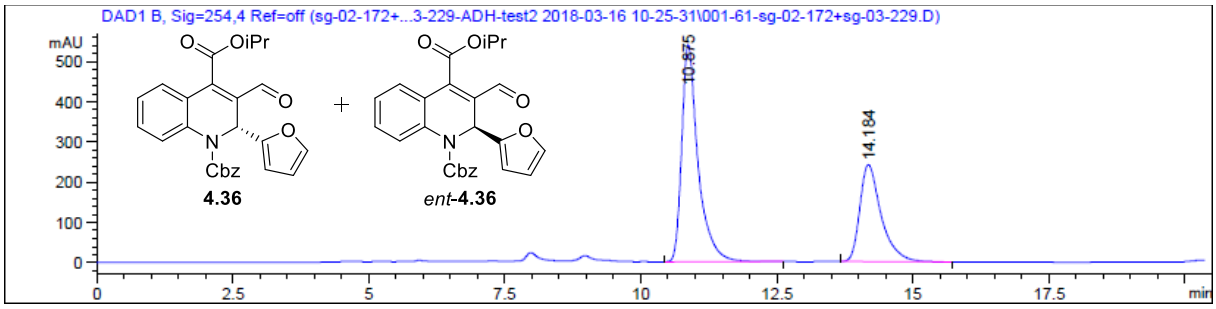


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.536	BB	0.8408	4115.17871	73.31831	49.7089
2	22.987	BB	0.9368	4163.38379	67.38495	50.2911

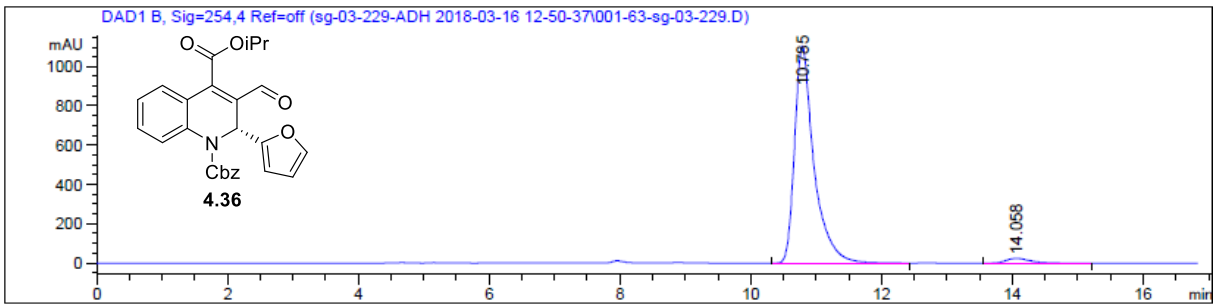


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.014	BB	0.7990	8541.43066	160.47438	97.8353
2	22.434	BBA	0.7321	188.98563	3.67408	2.1647

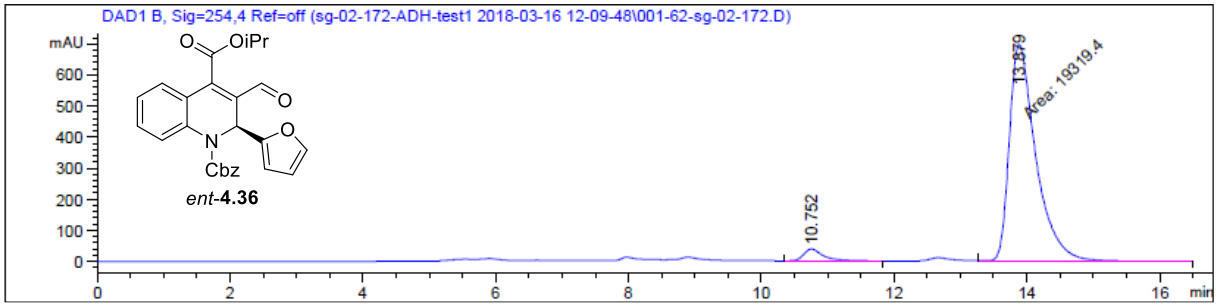
1-Benzyl 4-isopropyl 3-formyl-2-(furan-2-yl)quinoline-1,4(2H)-dicarboxylate (4.36)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.875	BB	0.3048	1.12350e4	539.82043	63.1447
2	14.184	BB	0.4078	6557.43701	240.76237	36.8553

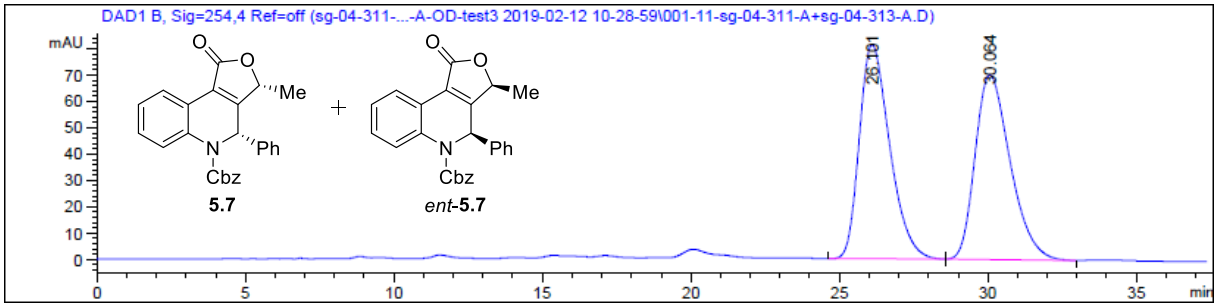


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.785	BB	0.3052	2.28719e4	1106.24609	97.1429
2	14.058	BB	0.3921	672.70001	25.63554	2.8571

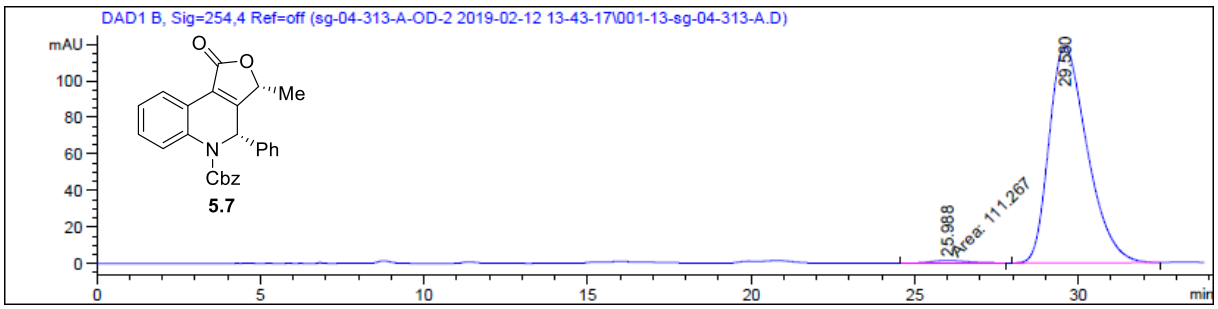


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.752	BB	0.3038	783.81158	38.13664	3.8989
2	13.879	FM	0.4631	1.93194e4	695.33588	96.1011

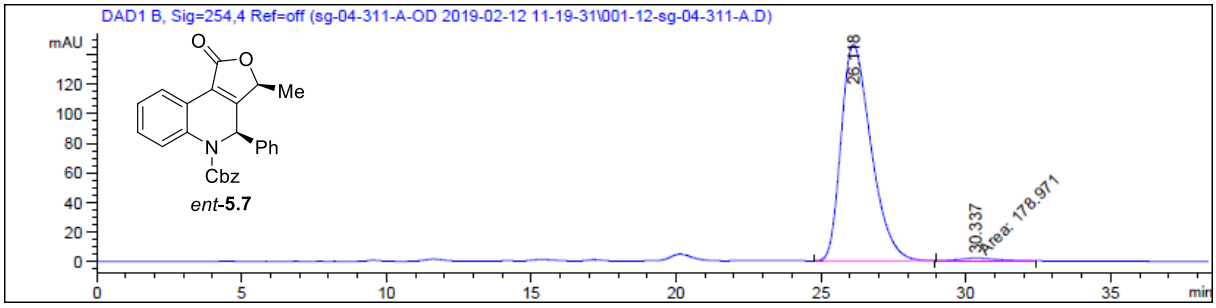
Benzyl (3*S,4*R**)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (5.7)**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.101	BB	1.0742	5784.69873	81.28764	50.1355
2	30.064	BB	1.2412	5753.43799	70.12389	49.8645

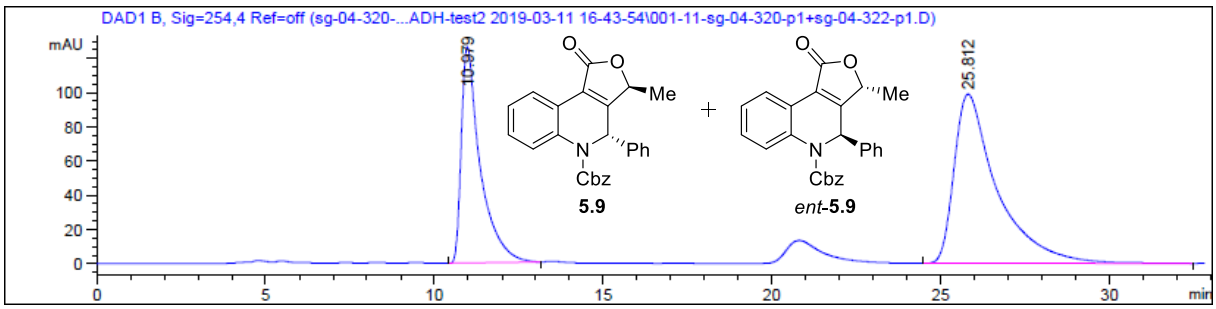


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.988	MM	1.2448	111.26743	1.48980	1.1504
2	29.580	BB	1.2260	9560.65625	118.15717	98.8496

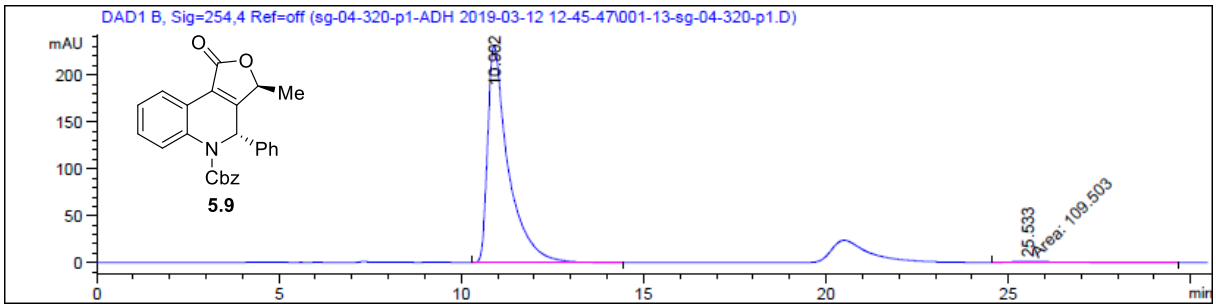


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.118	BB	1.1011	1.04957e4	145.93408	98.3234
2	30.337	MM	1.5582	178.97067	1.91431	1.6766

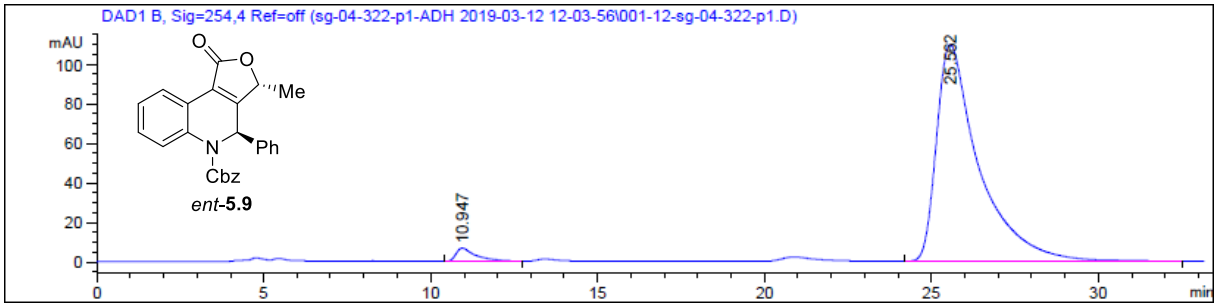
Benzyl (3*R,4*R**)-3-methyl-1-oxo-4-phenyl-1,4-dihydrofuro[3,4-c]quinoline-5(3H)-carboxylate (5.9)**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.979	BB	0.5590	4924.90283	126.29311	36.0470
2	25.812	BB	1.2682	8737.56250	98.76265	63.9530

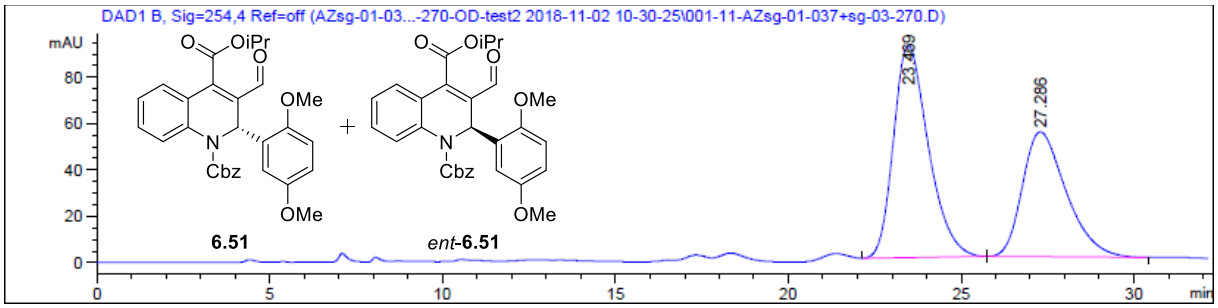


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.902	BB	0.5615	9052.47070	230.82156	98.8048
2	25.533	MM	1.4552	109.50291	1.25416	1.1952

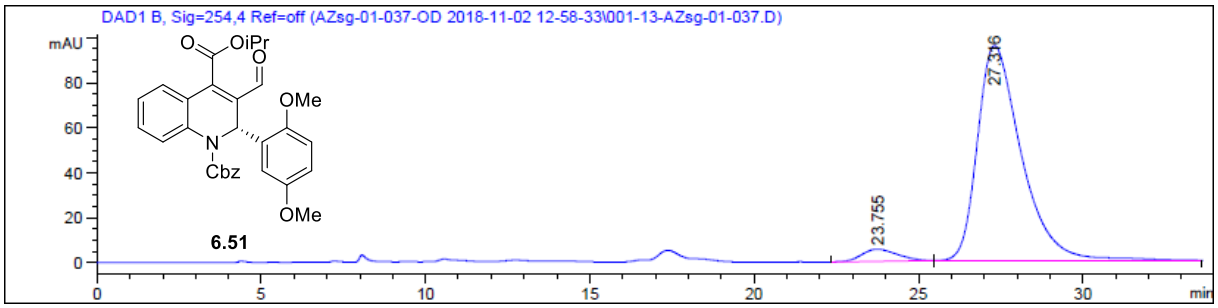


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.947	BB	0.5739	270.82544	6.66679	2.7163
2	25.562	BB	1.2699	9699.60254	109.66661	97.2837

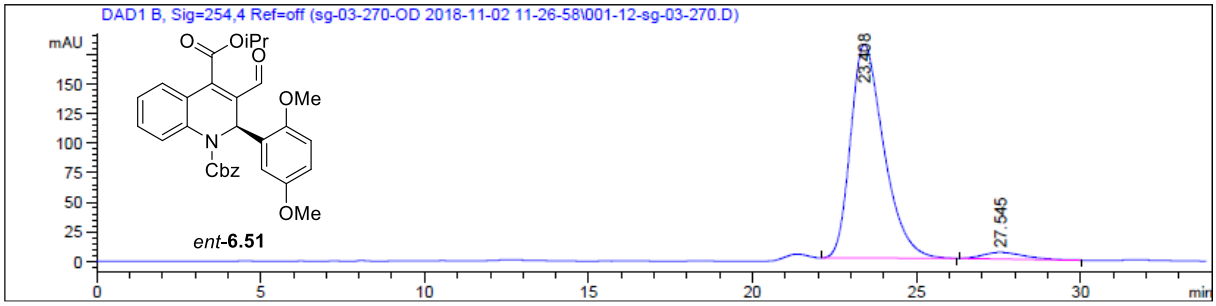
1-Benzyl 4-isopropyl 2-(2,5-dimethoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (6.51)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.469	BB	1.0669	6421.22266	91.70887	57.4673
2	27.286	BB	1.3211	4752.47266	53.87904	42.5327

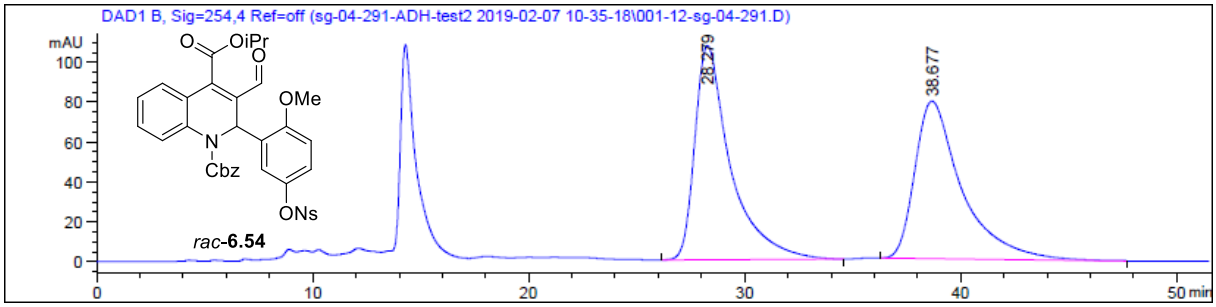


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.755	BB	0.9191	405.96448	5.39974	4.3705
2	27.316	BBA	1.3971	8882.81934	95.50904	95.6295

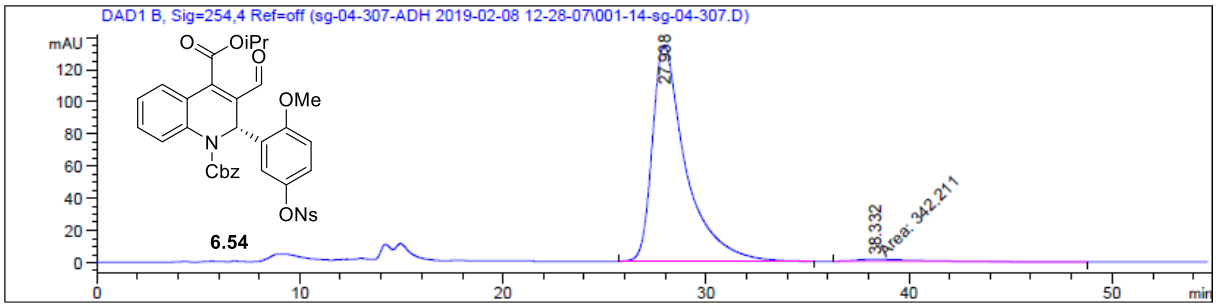


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.408	BB	1.0688	1.27240e4	180.42403	96.4317
2	27.545	BB	1.0270	470.82394	5.48759	3.5683

1-Benzyl 4-isopropyl 3-formyl-2-(2-methoxy-5-(((4-nitrophenyl)sulfonyl)oxy)phenyl)quinoline-1,4(2H)-dicarboxylate (6.54)

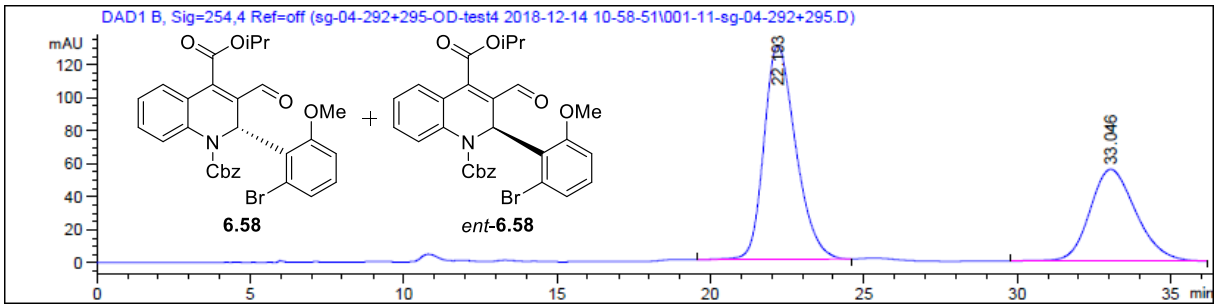


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.279	BB	1.6602	1.23275e4	107.31348	50.8663
2	38.677	BB	2.1573	1.19076e4	78.96268	49.1337

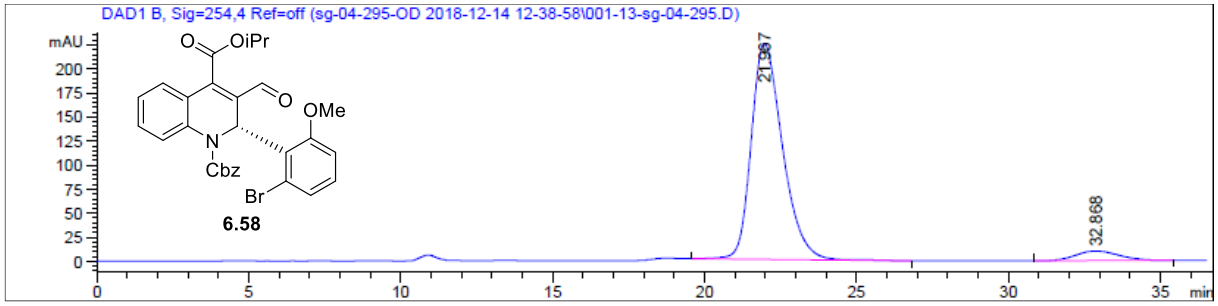


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.938	BB	1.6469	1.53026e4	134.34854	97.8126
2	38.332	MM	4.1992	342.21091	1.35825	2.1874

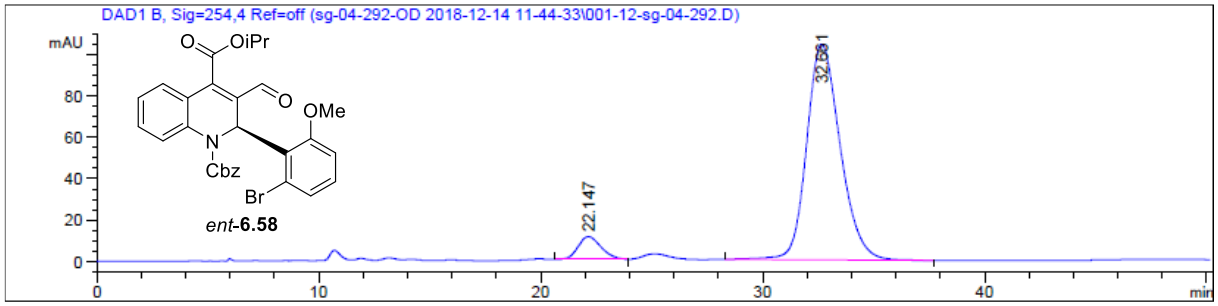
1-Benzyl 4-isopropyl 2-(2-bromo-6-methoxyphenyl)-3-formylquinoline-1,4(2H)-dicarboxylate (6.58)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.193	BB	1.0989	9318.42090	129.28931	61.6418
2	33.046	BBA	1.5332	5798.61768	55.57718	38.3582

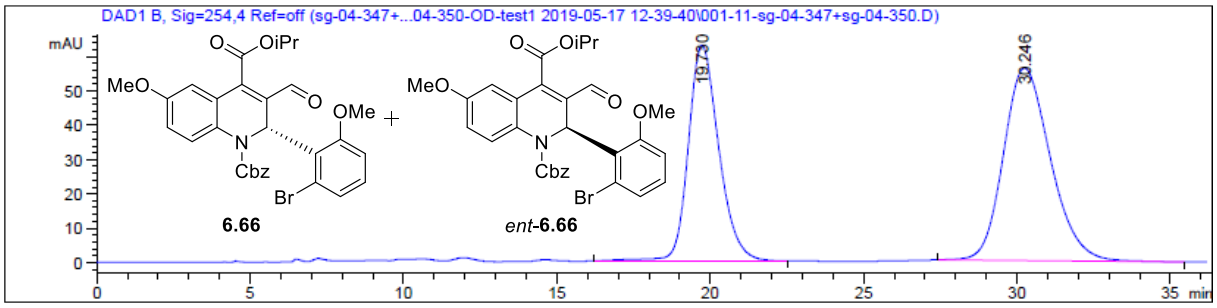


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.967	BB	1.0980	1.61323e4	224.60686	94.1145
2	32.868	BB	1.2095	1008.85077	10.08132	5.8855

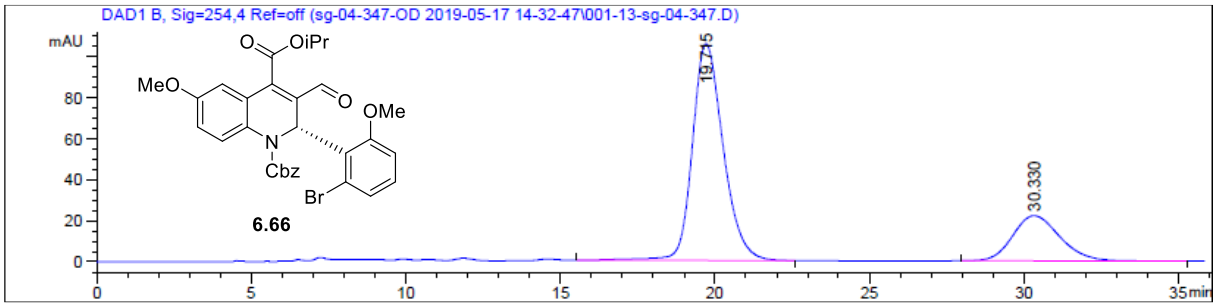


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.147	BB	0.9904	786.25269	10.96740	6.7154
2	32.661	BB	1.5860	1.09220e4	103.93211	93.2846

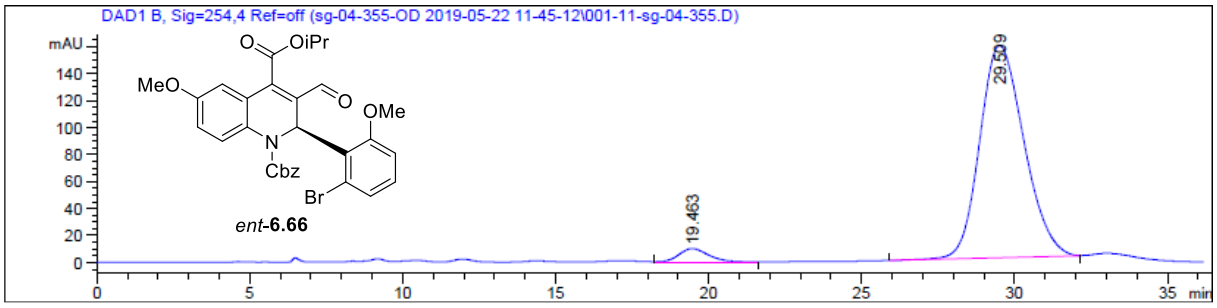
1-Benzyl 4-isopropyl 2-(2-bromo-6-methoxyphenyl)-3-formyl-6-methoxyquinoline-1,4(2H)-dicarboxylate (6.66)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.730	BB	1.0442	4351.33789	62.81588	42.1122
2	30.246	BBA	1.5622	5981.38184	56.08527	57.8878



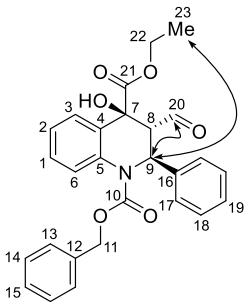
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.715	BB	1.0518	7321.08203	105.47192	75.6559
2	30.330	BB	1.4655	2355.73364	22.06692	24.3441



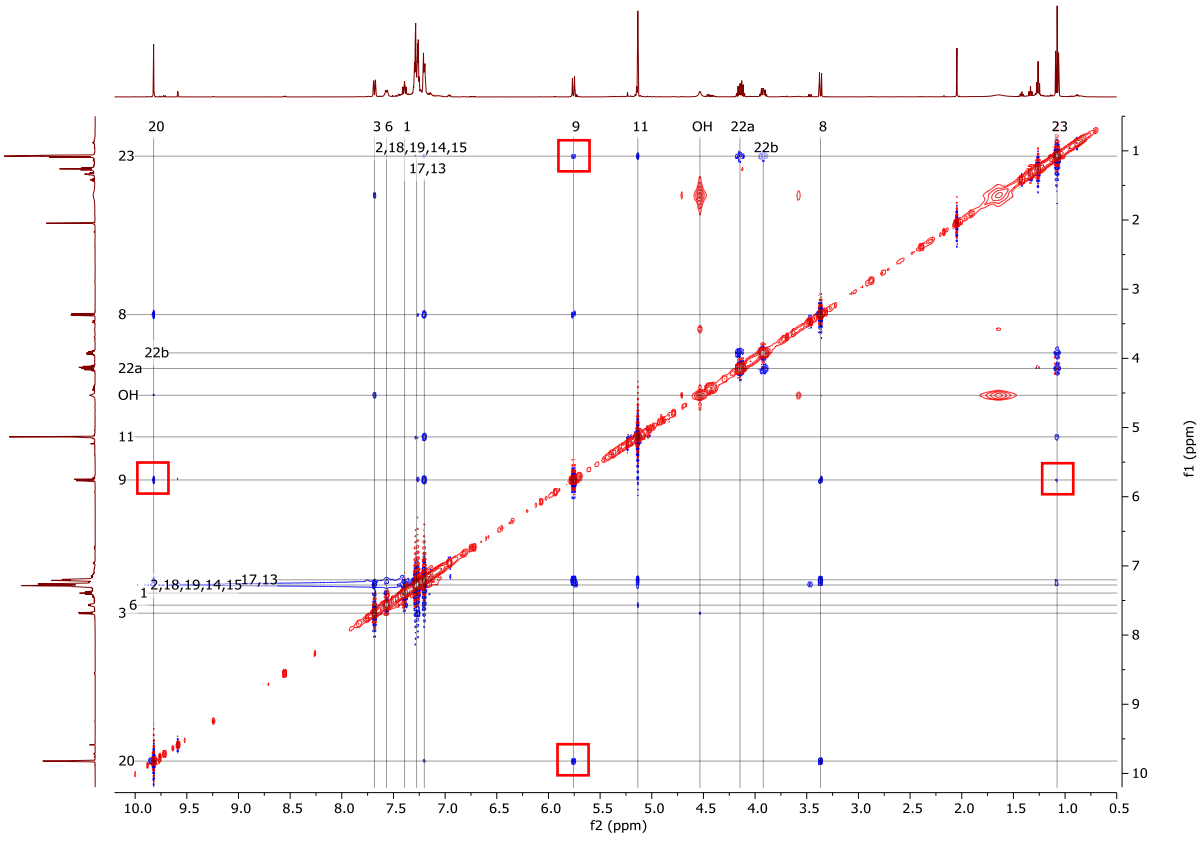
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.463	BB	0.9525	638.26666	9.68931	3.8889
2	29.509	BB	1.5287	1.57742e4	157.46391	96.1111

10.3 NOESY spectra

10.3.1 *ent*-4.9

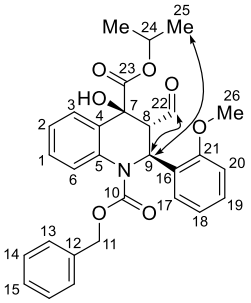


ent-**4.9**
key ^{1}H-^{1}H nOe correlations indicated

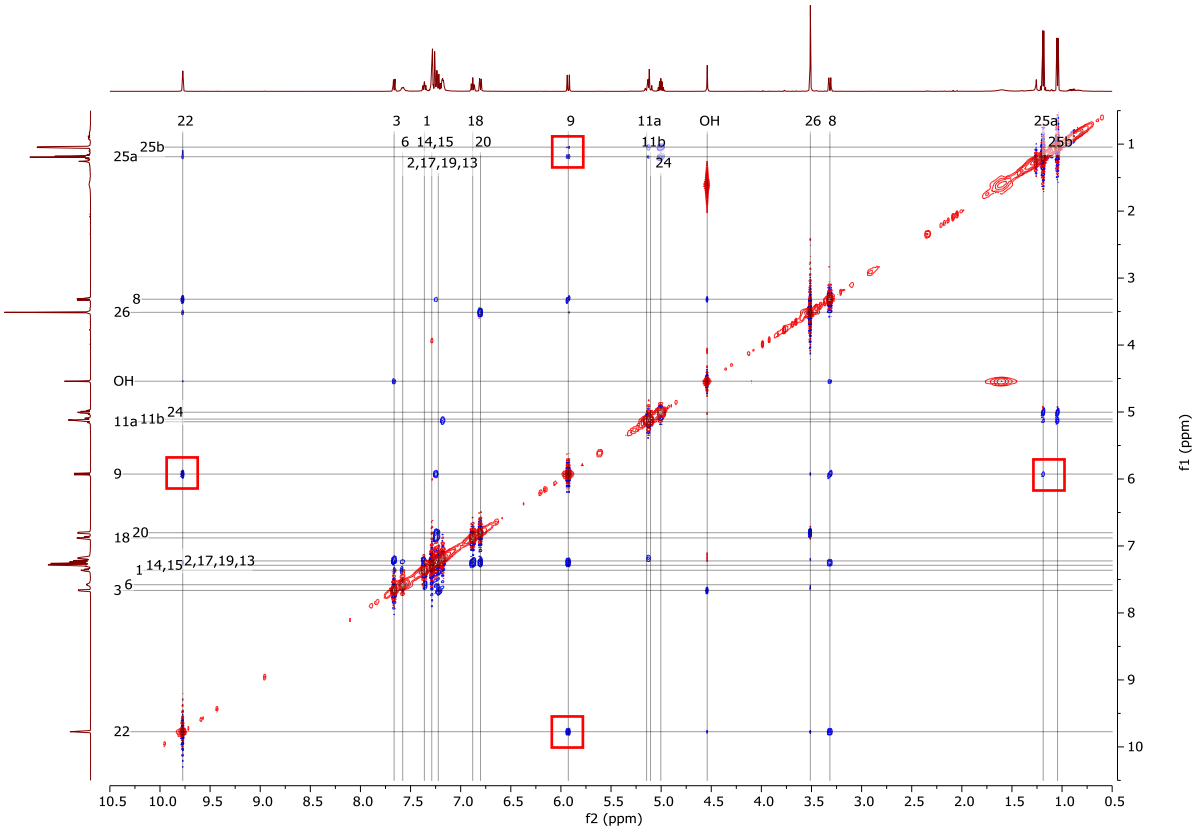


A large coupling constant between H8 and H9 (10.1 Hz) suggests a 1,2-*trans* diaxial configuration of these C–H bonds. From there, nOe correlations can be observed between H9 and both the aldehyde proton, H20, and the ethyl chain, H23. It was inferred from this that these three protons all lie on the same face of the heterocycle, providing the relative configuration shown above.

10.3.2 *ent*-4.40

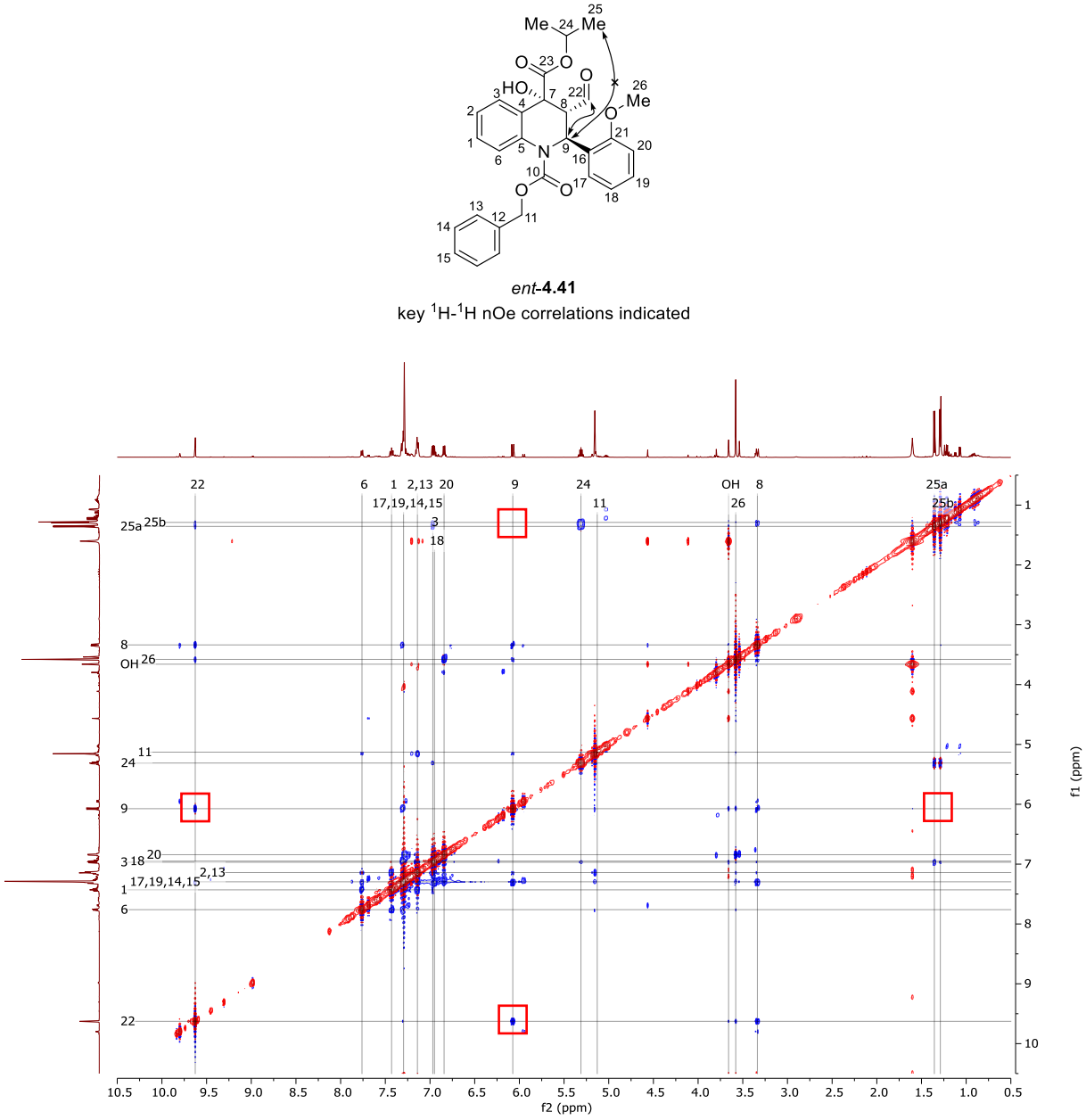


ent-**4.40**
key ^{1}H-^{1}H nOe correlations indicated



The relative configuration of *ent*-**4.40** was assigned in an analogous manner to *ent*-**4.9** (*vide supra*). A strong coupling between H8 and H9 (10.2 Hz) supports a 1,2-*trans* diaxial arrangement of the corresponding C–H bonds. From there, nOe correlations can be observed between H9 and both the aldehyde proton, H22, and the isopropyl moiety, H25a and H25b. As before, this was used to infer that all three groups are on the same face on the heterocycle, providing the relative configuration shown above.

10.3.3 ent-4.41

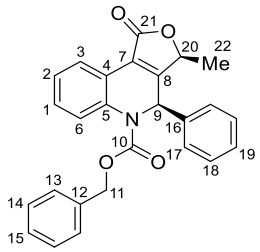


ent-**4.41**
key ^{1}H-^{1}H nOe correlations indicated

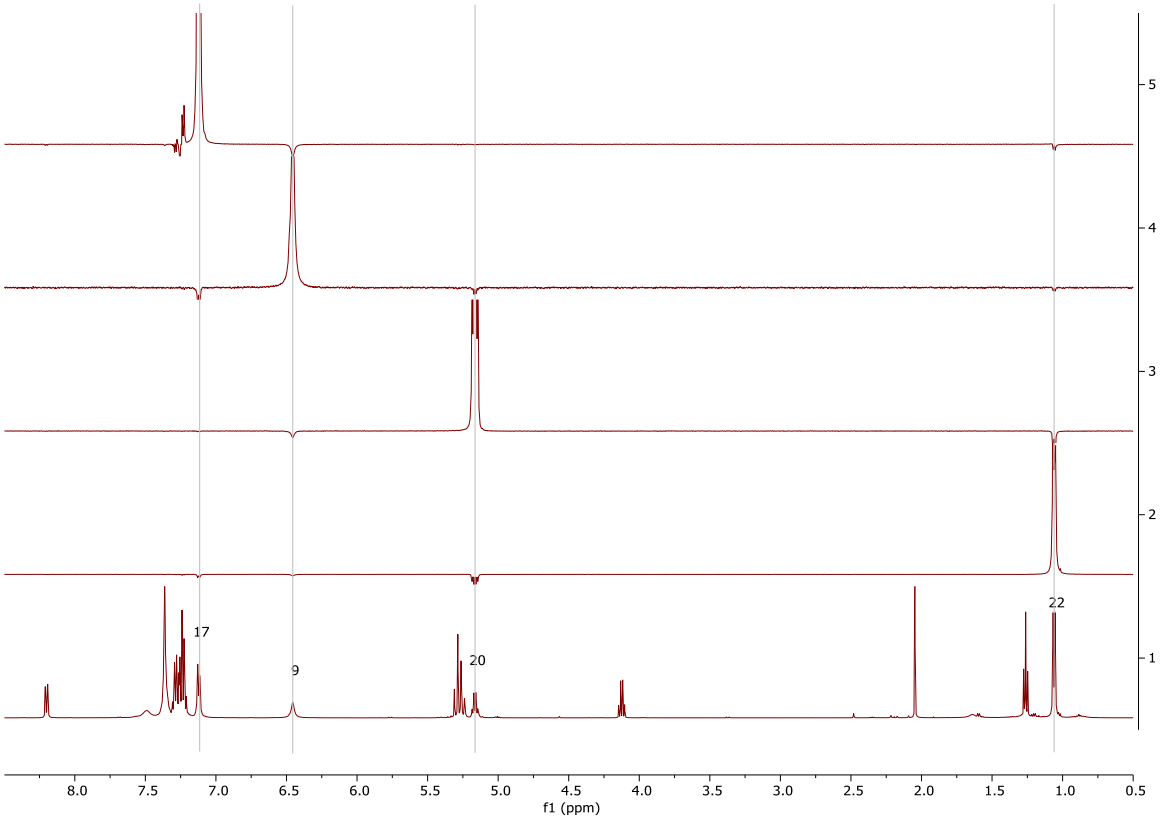
[Note: *ent*-**4.41** was isolated and analysed as a 4:1 mixture with *ent*-**4.40**.] The large coupling between H8 and H9 (10.8 Hz) suggests a 1,2-*trans* diaxial arrangement of the corresponding C–H bonds. This is supported by an nOe correlation between H9 and the aldehyde proton, H22. In contrast to *ent*-**4.40** (*vide supra*), however, there is no nOe correlation visible between H9 and the isopropyl moiety, H25a and H25b. This was used to infer that H9 and the isopropyl

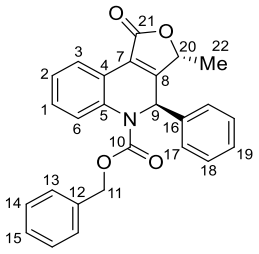
ester are not on the same face of the heterocycle, providing the relative configuration shown above.

10.3.4 *ent*-5.7 and *ent*-5.9

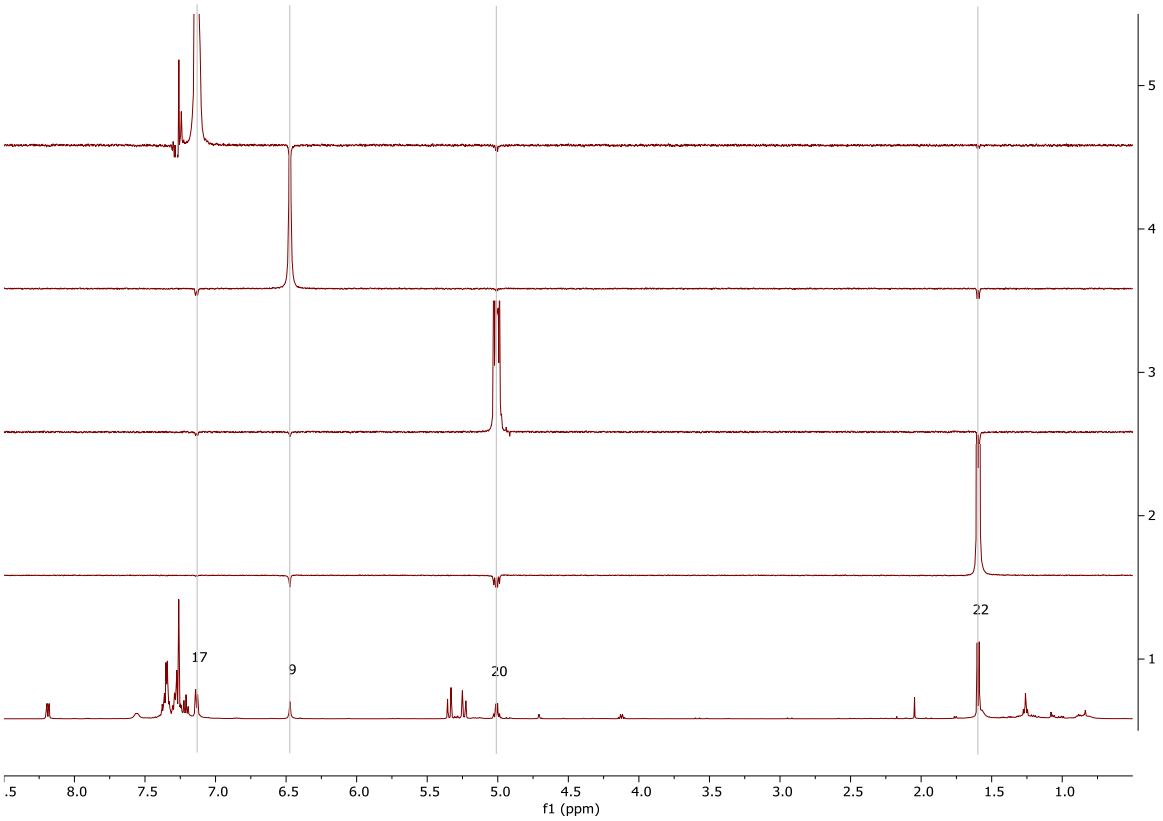


ent-**5.7**





ent-**5.9**



It had previously been determined that *ent*-**5.7** and *ent*-**5.9** shared the same connectivity, differing only in the relative configuration at C20. However, due to the abundance of sp^2-hybridised carbons in *ent*-**5.7** and *ent*-**5.9**, the individual ^1H-^1H nOe NMR spectra presented above are insufficient for unambiguous assignment of configuration. Comparison of the spectra indicate that *ent*-**5.7** has stronger correlations between H9 and H20, as well as between H17 and H22, than in *ent*-**5.9**. In contrast, *ent*-**5.9** bears a stronger correlation between H9 and H22. These nOe's were used to tentatively assign the associated protons to

the same face of the heterocycle. Further evidence from DFT calculations and experimental observations provided further support for the relative configurations shown above.