CATALYTIC DIVERGENT SYNTHESIS OF QUINAZOLINONE ALKALOIDS

A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (DPhil)

Tao Wei
Corpus Christi College
University of Oxford
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Supervisor: Professor Darren J. Dixon

Abstract

The general goal of this thesis was to implement a new, catalytic, enantioselective isocyanoacetate ketone aldol reaction into a challenging total synthesis plan, in order to achieve a catalyst controlled stereoselective total synthesis of a specific subset of quinazolinone alkaloids - tryptoquivalines and chaetominines.

Chapter 1 firstly introduces the panorama of quinazolinone alkaloids and pioneering synthetic achievements on tryptoquivalines and chaetominines. Subsequently, previous crucial development of isocyanoacetate ester aldol/Mannich reactions were concisely reviewed.

Chapter 2 demonstrates our first-generation catalytic divergent synthetic approach towards both tryptoquivaline F and chaetominine.

Chapter 3 mainly illustrates the second-generation total synthetic approach towards tryptoquivaline F.

Chapter 4 shows our total synthesis work on a naturally occurring pentacyclic quinazolinone natural product and core of tryptoquivalines, followed with homologations towards tryptoquivaline F.

Declarations and copyright

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

I was admitted as a probationary research student in April 2016 and as a candidate for the degree of Doctor of Philosophy in October 2017; the higher study for which this is a record was carried out in the University of Oxford between 2015 and 2018.

Tao Wei

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In the end, I would like to thank my families for their tremendous support and endless love over the years.

Abbreviations

°C	Degrees Celsius
Å	Ångström
Ac	Acetyl
Ad	Adamantyl
Aq	Aqueous
App	Apparent
Ar	Aryl
atm	atmosphere
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bp	Boiling point
bpy	2,2'-Bipyridine
br	Broad
n-Bu	*n*-Butyl
CDI	1,1'-Carbonyldiimidazole
Conc	Concentration
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	Dimethylacetamide
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DG	Directing group
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dq	Doublet of quartets
dr	Diastereoisomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess

EI	Electron impact
ent	enantiomer
equiv	equivalents
ES	ElectroSpray Ionisation
Et	Ethyl
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	Electron donating group
EWG	Electron withdrawing group
FCC	Flash column chromatography
g	Gram
h	Hour(s)
HMBC	Heteronuclear multiple-bond correlation experiment
HPLC	High performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear single-quantum coherence experiment
Hz	Hertz
IBX	2-iodoxybenzoic acid
IMDA	Intramolecular Diels-Alder
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
IPA	*Iso*-propylalcohol
J	Coupling constant
LDA	Lithium diisopropylamide
M	Molar concentration
m	Multiplet
MBS	*p*-methoxybenzenesulfonyl
Me	Methyl
mg	Milligram
MHz	Mega hertz
min	Minute(s)
mL	Millilitre
µL	Microlitre
mmol	Millimole
mM	millimolar
mol	mole
mp	Melting point
Ms	Methanesulfonyl
m/z	Mass to charge ratio
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	4-Methylmorpholine *N*-oxide
Nu	nucleophile
o	ortho
OH	Hydroxy
OTf	Trifluoromethanesulfonate

p	para
PE	Petroleum ether bp 30-40 °C
PG	Protecting group
Ph	Phenyl
PMB	*Para*-methoxybenzyl
ppm	Parts per million
Pr	propyl
pyr	pyridine
q	Quartet
R	Generic substituent
RE	Reductive elimination
rac	Racemic
quint	Quintet
rt	Room temperature
s	Singlet
t	Triplet
TBA	tetra-*n*-butylammonium
TBAF	Tetrabutylammonium fluoride
t-Bu	*tert*-butyl
TES	Triethylsilane
Temp	temperature
t/*tert*	*tertiary*
Tf	triflate
TFA	trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilane
TLC	Thin layer chromatography
TMDS	1,1,3,3-Tetramethyldisiloxane
TMS	Trimethylsilyl
TMSI	Trimethylsilyl iodide
Ts	*Para*-toluenesulfonyl
TS	Transition state
UV	ultraviolet
XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

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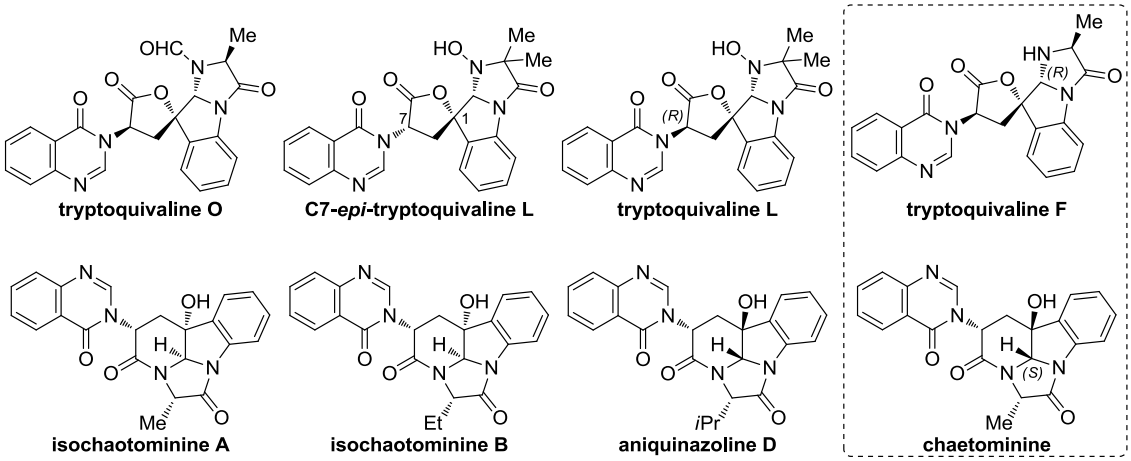
Chapter 1. General Introduction

1.1 The quinazolinone alkaloids

1.1.1 Tryptoquivalines and chaetominines

Quinazolinone alkaloids are an important class of fused heterocyclic natural products, with a wide range of biological activities. To date, over 200 known and isolated compounds[1,2,11,3–10]. Furthermore, both natural and unnatural quinazolinone have drawn attention in academia and industry due to their therapeutic potential with viable application as anticancer, antidiabetic, antibacterial, sedative, hypnotic and anti-inflammatory agents[12–20].

Among the family of quinazolinones, two structure types - tryptoquivalines[18,21–25] and chaetominines[26,27–29] - have attracted particular attention, **Scheme 1-1**, partially because of their close structural relationships.



Scheme 1-1 *A selection of quinazolinone alkaloids*

The tertiary alcohol (either free or as part of a γ-lactone) and the *N,N*-aminal moieties are present in both of the above two scaffolds. Interestingly, tryptoquivaline F and chaetominine are constitutional isomers; however, to date these two compounds have not

been isolated from the same fungus. Chaetominine was isolated from *Chaetomium* sp. IFB-E015[26], an endophytic fungus found on healthy *Adenophora axilliflora* leaves, more than two decades later than tryptoquivaline F which was isolated from *aspergillus fumigatus* in 1978[21].

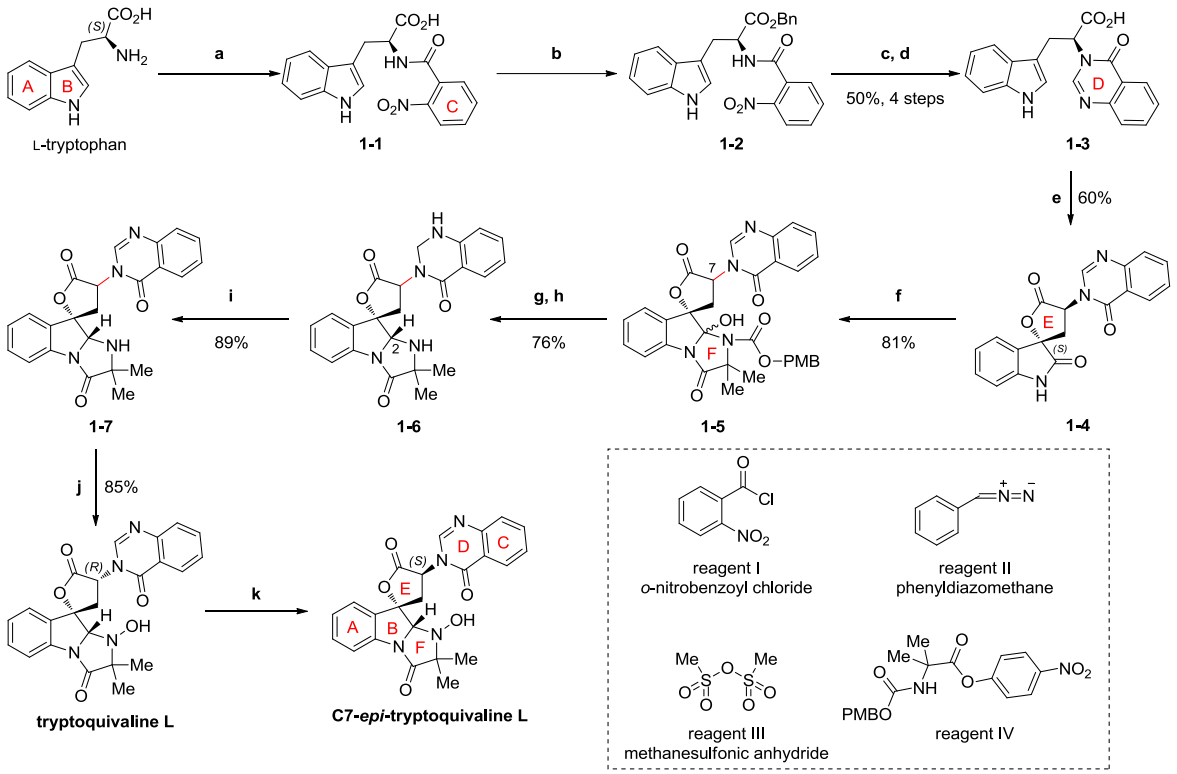
In this document, selected previous total syntheses are briefly described in the following sections; they are either the first reported total synthesis route or the classic example for alternative synthetic strategies. Work leading to formal synthetic routes and other derivative approaches are not documented[23–25,27–33].

1.1.2 Total synthesis of tryptoquivalines by Büchi *et al*.

The first total synthesis of tryptoquivaline family was reported[22] by Büchi and co-workers in 1979, and the route featured an efficient and elegant ring introduction sequence, **Scheme 1-2**.

Starting from the natural amino acid L-tryptophan, the researchers introduced the quinazolinone side chain via amide bond formation with *o*-nitrobenzoyl chloride to afford amide **1-1**. Esterification with phenyldiazomethane to yield benzyl ester **1-2**, nitro group reduction with iron and condensation with formic acid then dehydration with TsOH gave acid **1-3** in 50% overall yield. Oxidation of **1-3** with methanesulfonic anhydride-dimethyl sulfoxide gave 60% spirolactone **1-4** as the major epimeric product with stereochemical control originating from L-tryptophan. The spirolactone **1-4** was silylated with *N,O*-bis(trimethylsilyl)acetamide (BSA) and the crude product condensed with *o*-nitrobenzyl chloride in the presence of tetramethylammonium chloride (TMAC), then subsequently treated with triethylamine to give alcohol **1-5** in 81% overall yield. The PMB group was

removed with trifluoroacetic acid in the presence of anisole to give the alcohol intermediate, which was subsequently reduced with sodium cyanoborohydride to give dihydroquinazolinones **1-6** in 76% yield (4:1 mixture at the C2 position). Next, DDQ reoxidation gave quinazolinone **1-7** in 89% yield, followed with mCPBA to give tryptoquivaline L in 85% yield. Epimerization at C7 was facilitated by potassium hydroxide deprotonation in dry THF-DMF, and reprotonation of the resulting enolate with 1% HCl in THF at -70 °C, affording C7-*epi*-tryptoquivaline L.



a. reagent I; **b**. reagent II; **c**. Fe, HCl; **d**. HCO_2H, benzene, then TsOH, xylene; **e**. reagent III, dimethyl sulfoxide; **f**. reagent IV, BSA, TMAC, then TEA; **g**. anisole, TFA; **h**. $NaBH_3CN$, H_2O, THF, HCl; **i**. DDQ; **j**. mCPBA; **k**. KOH, THF / DMF, then 1% HCl, -70 °C

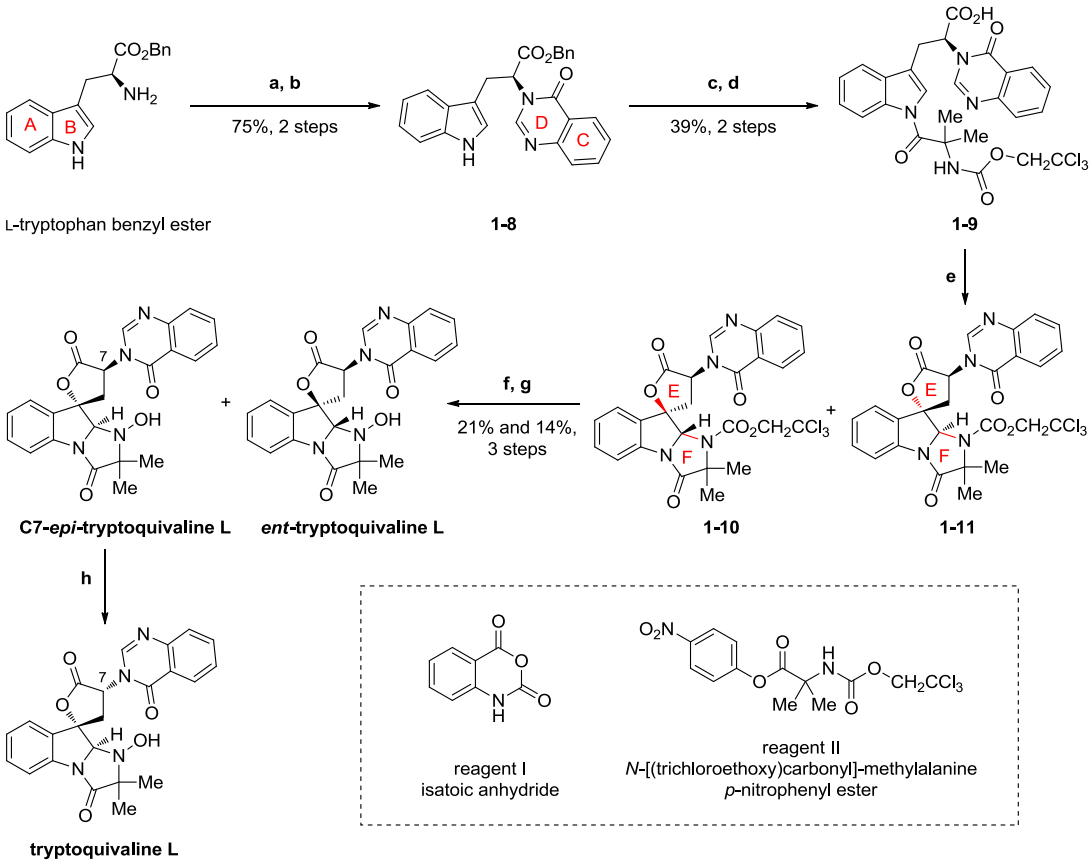
Scheme 1-2 *The Büchi synthesis of tryptoquivaline L and its C7 epimer*

C7-*epi*-tryptoquivaline L was originally named as tryptoquivaline L, and tryptoquivaline L was originally named tryptoquivaline G. The most recent isolation paper[8] by Kijjoa *et al.* revised tryptoquivaline L's structure after careful spectroscopic crystallographic analyses as presented in **Scheme 1-2**, and therefore the previously named

tryptoquivaline L is referred to here as C7-*epi*-tryptoquivaline L. Therefore, Büchi *et al.* actually synthesized tryptoquivaline L in the first instance, and then subsequently its C7 epimer from an inversion of configuration at C7 since Büchi started from *S*-configured L-tryptophan, it is most likely that an epimerization took place at C7 position unexpectedly through step **f** to **j** in this route.

1.1.3 Total synthesis of tryptoquivalines by Nakagawa *et al*.

In 1983, Nakagawa and co-workers[24] reported a biomimetic total synthetic sequence to various family members, utilizing an oxidative double cyclization of *N*-acyltryptophan precursor **1-9** to efficiently construct the tryptoquivaline core system by the simultaneous formation of the E and F rings, **Scheme 1-3**.



a. reagent **I**, benzene; **b.** $(EtO)_3CH$, TsOH; **c.** reagent **II**, KF, 18-C-6, DIPEA; **d.** H_2, Pd/C; **e.** NBS, TFA; **f.** Zn, AcOH; **g.** mCPBA; **h.** *t*BuLi, AcOH, -70 °C

Scheme 1-3 *The Nakagawa synthesis of (ent-) tryptoquivaline L and its C7 epimer*

The double cyclization precursor **1-9** was synthesized from L-tryptophan benzyl ester smoothly in 4 steps by firstly installing the quinazolinone unit to the tryptophan benzyl ester, and then introducing the methyl alanine unit to the indole amine **1-8** by amide bond formation.

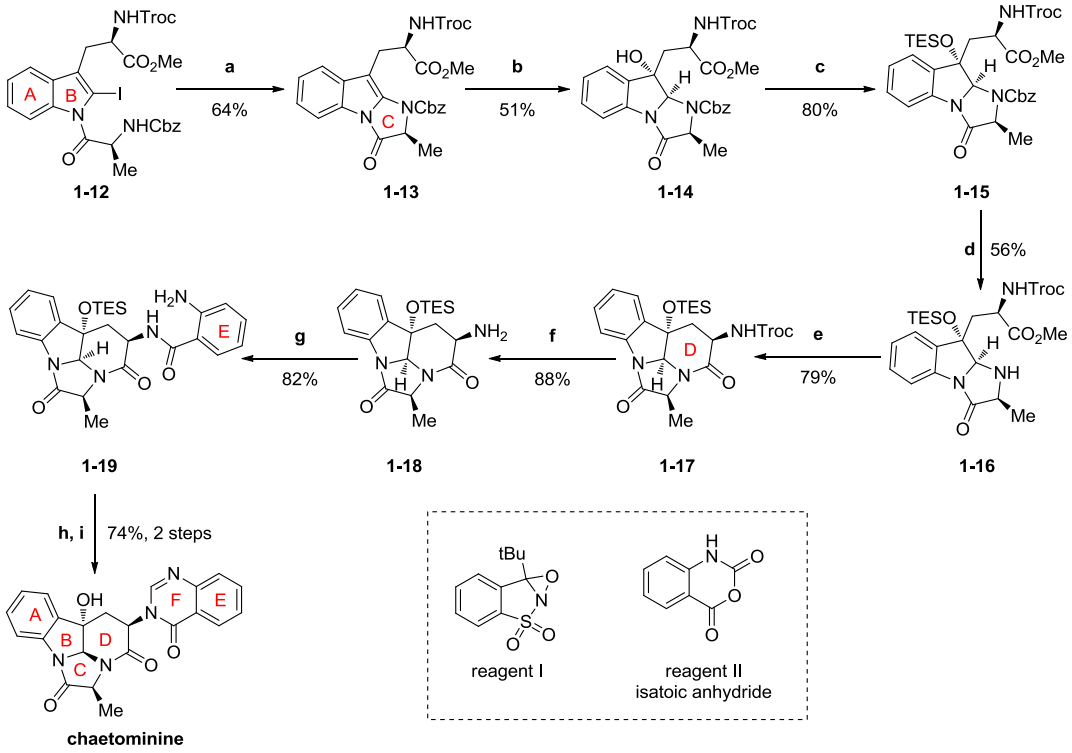
The key double cyclization was initiated by *N*-bromosuccinimide (NBS) in TFA; which resulted in the formation of the tryptoquivaline core, **1-10** and **1-11**, without control of the configuration of the newly generated spirocyclic centre. The mixture was deprotected under reductive conditions (zinc with acetic acid) and mCPBA oxidation gave C7-*epi*-tryptoquivaline L and *ent*-tryptoquivaline L. Finally, natural tryptoquivaline L was obtained by epimerizing C7-*epi*-tryptoquivaline L with *tert*-butyllithium followed by treatment with acetic acid at -70^{o}C.

1.1.4 Total synthesis of chaetominine by Snider *et al*.

The chaetominine family was first isolated in 2006 by Tan and co-workers[26], and the first total synthesis of chaetominine was reported by Snider and Wu in 2007[34]. Their work includes the construction of the δ-lactam (D-ring) by heating amino ester **1-16** with a catalytic amount of DMAP in toluene at reflux, **Scheme 1-4**.

Snider and Wu started from iodocarbamate **1-12**, on which Buchwald-Hartwig palladium catalysed cyclisation provided tricycle **1-13** in 64% yield. Stereoselective oxidation from the β-face of tricycle **1-13** with the oxaziridine, and subsequent reduction with $NaBH_4$ in acetic acid afforded hydroxyl imidazolidinone **1-14** in 51% yield. Reaction of **1-14** with TESOTf and 2,6-lutidine gave silyl ether **1-15** in 80% yield. Following this,

palladium on charcoal *N*-Cbz deprotection gave **1-16** in 56% yield. Subsequent lactamization of the resulted amino ester **1-16** was accomplished using DMAP to give tetracyclic **1-17** in 79% yield. Deprotection of the *N*-Troc group was achieved with zinc in methanol and acetic acid affording amine **1-18** in 88% yield. Reaction between amine **1-18** and isatoic anhydride in benzene afforded aniline **1-19** in 82% yield. Next, the quinazolinone formation was achieved with triethyl orthoformate and TsOH in 83% yield. Finally, TES group removal with HF/MeCN afforded chaetominine in 89% yield.

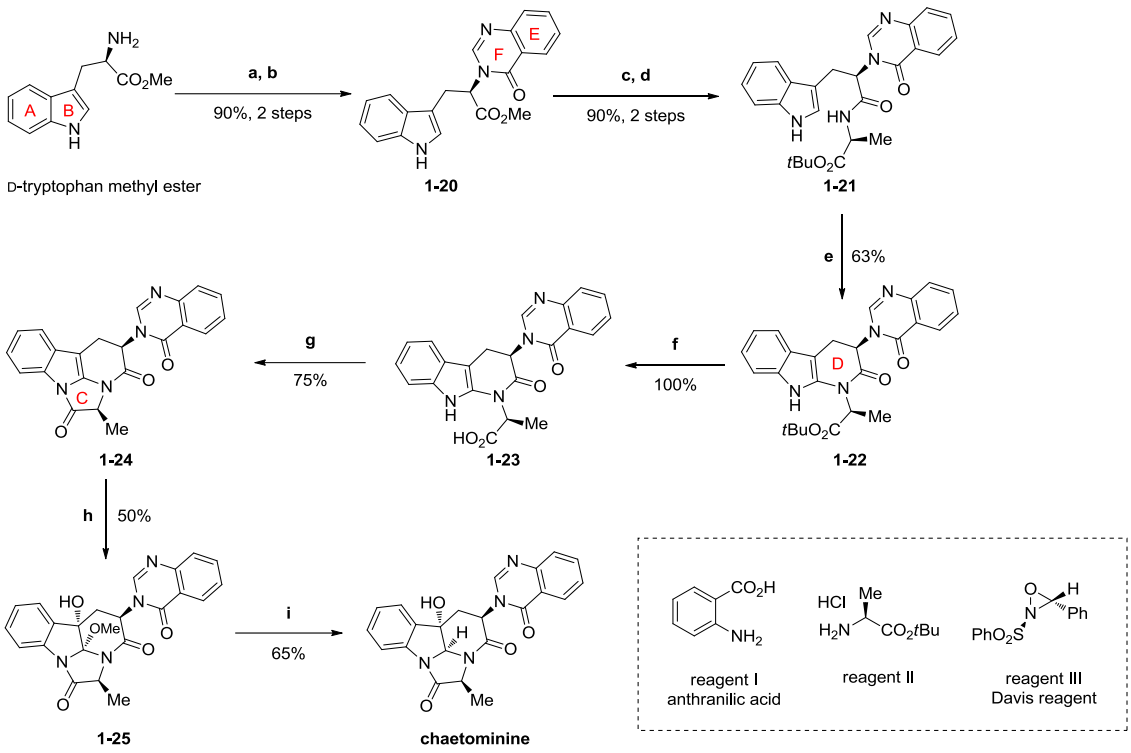


a. $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, K_2CO_3, toluene; **b.** reagent **I**, $NaBH_4$, AcOH; **c.** TESOTf, 2,6-lutidine; **d.** H_2, Pd/C; **e.** DMAP, toluene, 115 °C; **f.** Zn, MeOH / AcOH; **g.** reagent **II**, benzene, reflux; **h.** $HC(OEt)_3$, TsOH, benzene, reflux; **i.** HF / MeCN

Scheme 1-4 *The Snider and Wu synthesis of chaetominine*

1.1.5 Total synthesis of chaetominine by Papeo *et al*.

Papeo and co-workers reported[35] an alternative total synthetic route of chaetominine by attempted one-step closure of the C and D rings (actually realised stepwise in their route). Their biomimetic synthetic sequence is shown in **Scheme 1-5**.



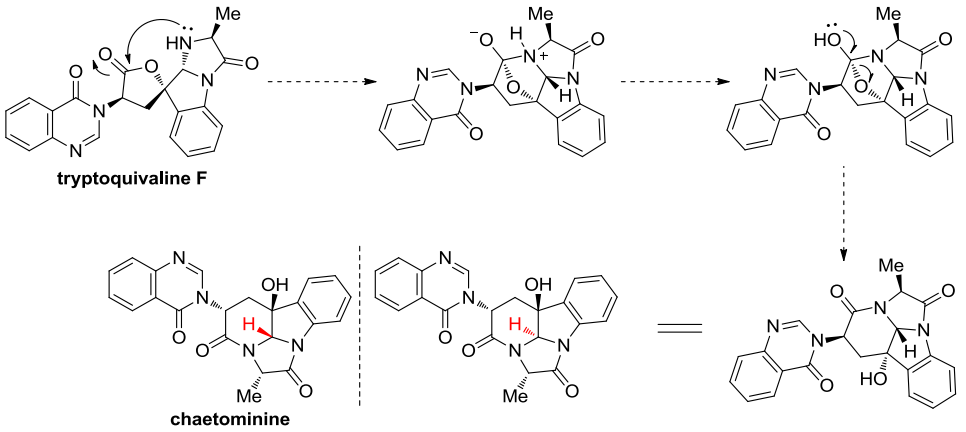
a. reagent I, TBTU, DIPEA; **b**. $(EtO)_3CH$, TsOH, AcOEt; **c**. 0.2 N LiOH, THF; **d**. reagent II, EDCI, DhBtOH, DIPEA, DMF; **e**. NCS, TEA, CH_2Cl_2; **f**. TFA, CH_2Cl_2; **g**. $(COCl)_2$, DIPEA, DMF cat., CH_2Cl_2; **h**. reagent III, CH_2Cl_2 / MeOH 2:1; **i**. Et_3SiH, CH_2Cl_2, TFA

Scheme 1-5 *The Papeo synthesis of chaetominine*

Reaction of D-tryptophan methyl ester with anthranilic acid using TBTU as coupling reagent, followed by treatment with triethyl orthoformate and catalytic TsOH delivered quinazolinone **1-20** in 90% yield. Subsequent hydrolysis of the methyl ester with LiOH gave the corresponding acid, which was then coupled with L-alanine *tert*-butyl ester to afford dipeptide **1-21** in 90% yield. Using a slight excess of NCS in the presence of triethylamine afforded **1-22** in 63% yield. TFA-mediated *tert*-butyl ester deprotection gave acid **1-23** in quantitative yield. Cyclisation of the carboxylic acid onto the nitrogen atom of the indole unit produced **1-24** in 75% yield upon treatment with oxalyl chloride. Treatment of **1-24** with Davis (±)-oxaziridine smoothly afforded *cis*-diastereoisomer **1-25** in 50% yield. Finally, chaetominine was achieved upon treatment of **1-25** with Et_3SiH in CH_2Cl_2 / TFA in 65% yield.

1.1.6 Structural link between tryptoquivaline F and chaetominine

Analysis of the structures of the various family members reveals that conversion of tryptoquivaline F and chaetominine could be envisaged to occur via an intramolecular attack of one of the aminal nitrogen atoms onto the gamma lactone carbonyl with subsequent collapse of the tetrahedral intermediate. This proposed transformation would give an epimer of natural chaetominine, **Scheme 1-6**.



Scheme 1-6 *Hypothetical interconversion between tryptoquivaline core and chaetominine core*

Based on the above idea, an assumption for this thesis work was originally made that if the aminal stereocentre could be epimerised, and the two nitrogen atoms could be distinguished, both chaetominine and tryptoquivaline should be accessible from a common intermediate. Our approach to explore this theory would be enabled by an appropriate catalytic enantioselective aldol methodology which is briefly introduced in the following sections.

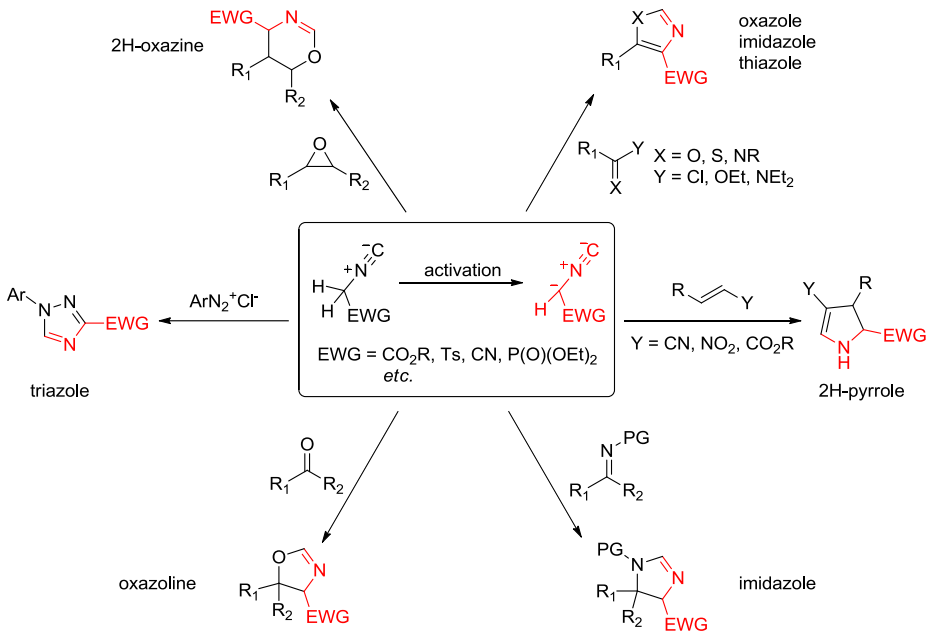
1.2 Aldol and Mannich reaction of isocyanoacetate esters

1.2.1 Isocyanides and isocyanoacetate esters

Isocyanides are valuable building blocks with broad applicability in organic synthesis and pharmaceutical chemistry to build up nitrogen containing heterocyclic compounds[36–

[39]. When an ester functionality is attached alpha to the nitrogen atom of the isocyanide, the specific type of compound is termed an isocyanoacetate ester, which is a glycine equivalent in organic synthesis. Other electron withdrawing groups (tosyl, nitrile, phosphonate) can also be attached to the alpha carbon[40].

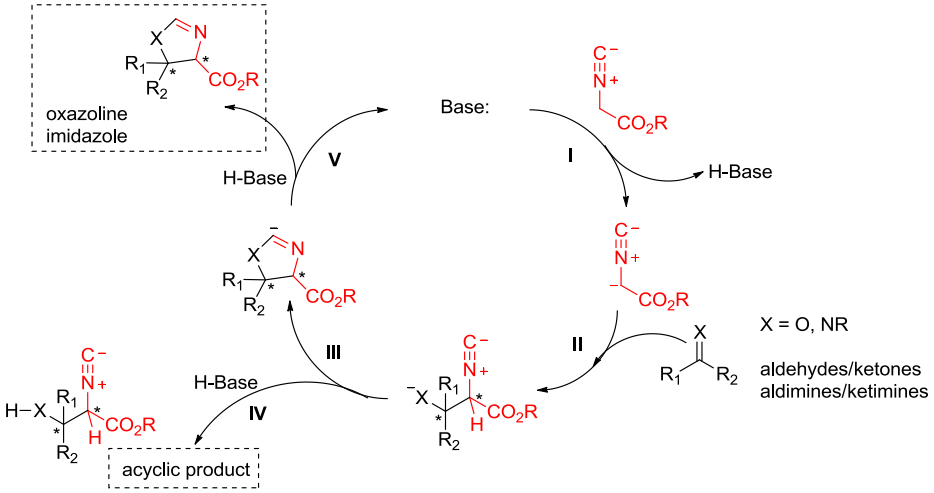
Scheme 1-7 shows a variety of transformations using[41–49] isocyanides as nucleophiles: when reacted with epoxides, they gave 2H-oxazines; with esters, amides and thioates, they afforded oxazoles, imidazoles and thiazoles respectively; with α,β-unsaturated carbon-carbon double bonds they yielded 2H-pyrroles; with aldimines and ketimines they produced imidazoles; with aldehydes and ketones they afforded oxazolines; and with diazonium salts they gave triazoles.



Scheme 1-7 *Isocyanides in nitrogen containing heterocycles synthesis*

In particular, aldol or Mannich reactions between isocyanoacetate esters and C=O or C=N double bonds respectively have been shown to take place stepwise[37,48]: in the first instance, a base catalyst deprotonates an isocyanoacetate and the resulting stabilized enolate subsequently attacks the C=O or C=N bond to form a new C-C bond with two newly generated contiguous stereocentres simultaneously and an oxygen or nitrogen centred

anion, which can then attack the terminal isocyanoacetate carbon intramolecularly (if not reprotonated at this stage to yield an acyclic compound, pathway **IV**) to afford a [2+3] cycloaddition heterocyclic product after reprotonation[36,38,39]. This process is illustrated in **Scheme 1-8**.



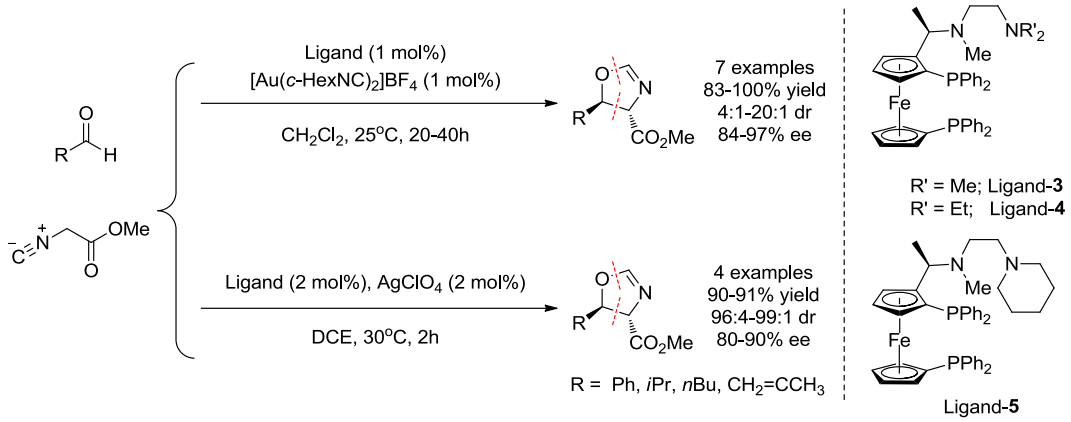
Scheme 1-8 *Stepwise construction of oxazolines and imidazoles with isocyanoacetate esters*

Previous work within the Dixon group[50–54,55,56,57] has resulted in the development of a number of highly enantioselective and efficient, catalytic aldol and Mannich reactions of isocyanoacetate esters, which are directly relevant to the total synthetic study in this thesis. In order to align the reader to the current state of the art, a series of selected isocyanoacetate ester aldol or Mannich reactions (either the first reported or the most noteworthy work) are demonstrated in the following sections.

1.2.2 Previous achievements in isocyanoacetate aldol chemistry

Schöllkopf and Gerhart pioneered the study of isocyanoacetate esters reactivity towards aldehydes and ketones in the late 1960s[58,59]. Despite their early pioneering studies,

this field is still progressing up to date[36–39,60], especially for incorporation of new electrophiles, enantio- and diastereo- selectivity and transformation efficiency.

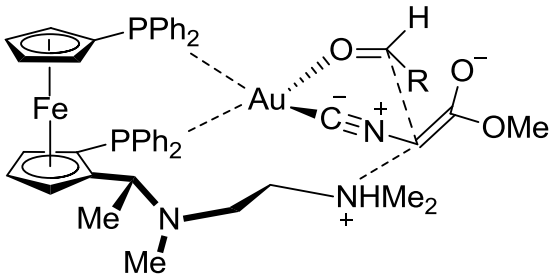


Scheme 1-9 *Ito, Hayashi and Sawamura's Ag(I) catalysed enantioselective aldol reactions*

In 1986, Ito, Hayashi and Sawamura reported the first gold catalysed enantioselective aldol reaction of isocyanoacetate esters with aldehydes[61]. The ligated gold(I) acts as a Lewis acid to activate the isocyanoacetate and the ferrocenyl bisphosphine tertiary amine as the chiral ligand for imparting stereocontrol upon addition of the isocyanoacetate to the aldehyde. This groundbreaking reaction gave oxazoline products in excellent yields and with good levels of diastereo- and enantioselectivity. In 1991, the same research group reported that a silver(I) salt[62] in combination with a similar ferrocenyl bisphosphine tertiary amine ligand was also capable of catalysing the enantioselective aldol reaction with good outcomes, **Scheme 1-9**. Besides Ag(I) and Au(I), it has been reported by Pregosin[63], Ahn[64], Richards[65], Zhang[66], Swager[67], van Koten[68], Motoyama[69], Gebbink[65] and Venanzi[70] groups that Pt(II) and Pd(II) with chiral pincer ligands have been shown to promote enantioselective isocyanoacetate ester aldol reaction with typically less than 65% ee.

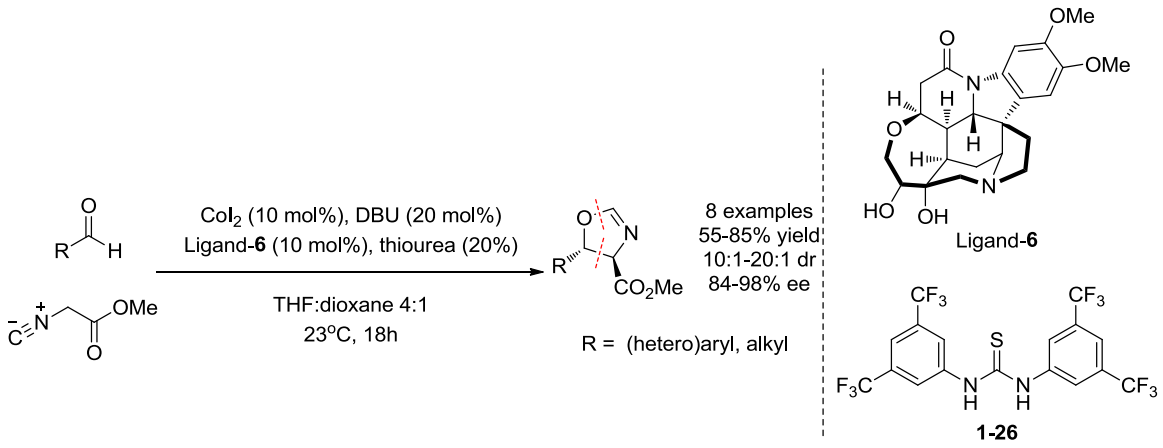
Ito, Hayashi and Swamura proposed a stereochemical model[62,71–73] for the Au-catalytically active species, supported by modified ligand and NMR studies of gold(I)

complexes with ferrocenyl Ligand-**3**. In this model[74], the distal amine acted as a Brønsted base which was responsible for depronating the α position of the activated isocyanoacetate ester, and the resulting ammonium ion assisted the enolate to react with the electrophile. Both the electrophile and the nucleophile are postulated to coordinate to the Au centre facilitating stereoselective bond formation, **Scheme 1-10**.



Scheme 1-10 *Proposed transition structure of the Au(I) catalysed aldol reaction by Ito, Hayashi and Sawamura et al.*

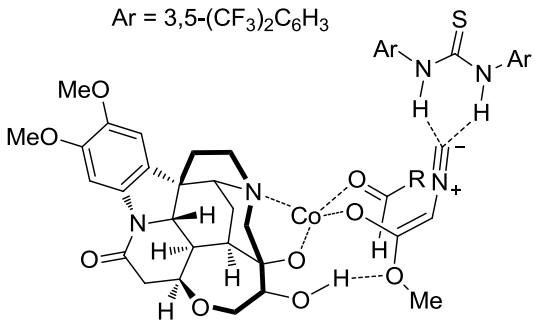
In 2011, the Oh group reported[75] the first co-catalytic system[76,77] composed of a chiral Co(II) complex with a brucine-derived Ligand-**6**, Schreiner's thiourea **1-26** and DBU for the aldol reaction of isocyanoacetate esters with aldehydes, **Scheme 1-11**. This report presented good chemical yields (55-85%) and high levels of enantioselectivity (84-98% ee).



Scheme 1-11 *Oh's Co(II)/thiourea co-catalysed enantioselective aldol reaction*

In this co-catalytic system, the authors proposed that the isocyanoacetate was deprotonated by DBU with concomitant activation by the thiourea **1-26** through H-bonding;

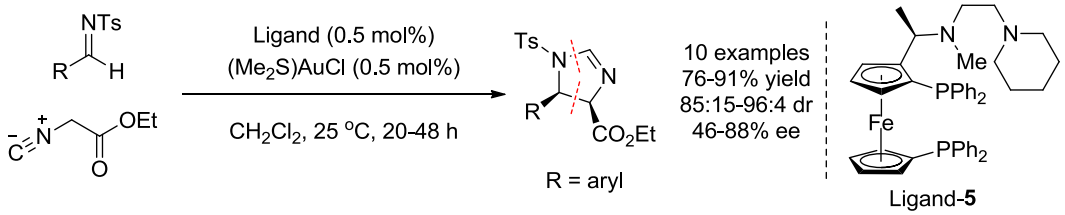
the resulting (*Z*)-configured cobalt enolate was primed to attack the aldehyde electrophile in a chair transition state, **Scheme 1-12**.



Scheme 1-12 *Proposed transition state of Co(II)/thiourea co-catalytic system by Oh et al.*

1.2.3 Previous achievements in isocyanoacetate Mannich chemistry

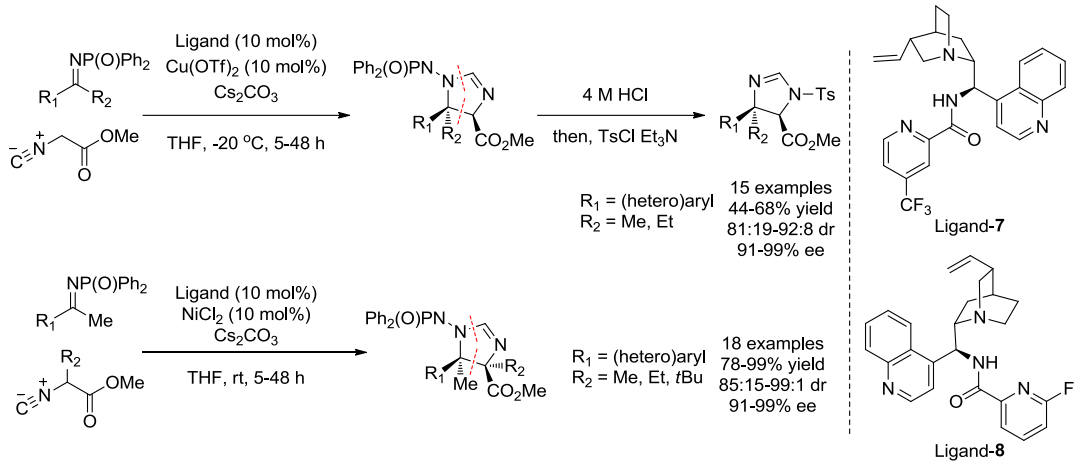
In 1999, Lin *et al.* reported[78] the first catalytic enantioselective Mannich reaction of isocyanoacetate esters with *N*-tosyl aldimines. The Au(I) and Hayashi's type ferrocenyl ligand composed catalytic system afforded the *cis*-imidazoline product in good yield (76-91%) and with moderate levels of enantioselectivity (46-88% ee), **Scheme 1-13**. The authors did not propose a mechanism to rationalize the observed enantio- or diastereoselectivity.



Scheme 1-13 *Lin's Au catalysed enantioselective Mannich reactions*

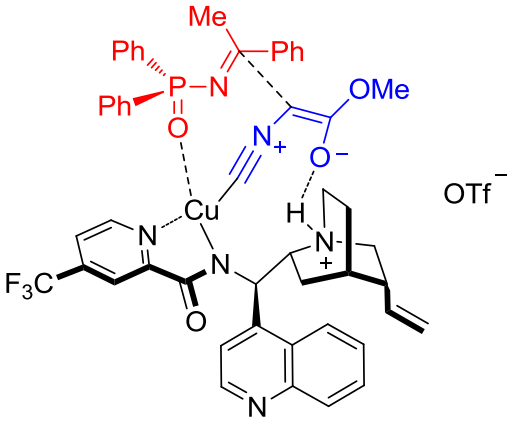
Following the Dixon group[53] report of a new amino phosphine ligand for silver(I) catalysed isocyanoacetate aldol reaction, in 2014, the Nakamura[79] and Dixon[55] group independently made breakthroughs in the field of isocyanoacetate ketimine Mannich reactions. Nakamura *et al.* reported an enantioselective Mannich reaction of

isocyanoacetate pronucleophiles with *N*-DPP ketimines, where in the presence of cinchona-derived picolinamides, $Cu(OTf)_2$ and Cs_2CO_3, *N*-tosyl *cis*-imidazolines were obtained in good yield with excellent level of diastereo- and enantioselectivity. In 2016, the Nakamura group[80] also found that reactions between *N*-DPP ketimines and α-substituted isocyanoacetate could be catalysed by $NiCl_2$ and picolinamide in the presence of Cs_2CO_3, where contiguously substituted imidazolines could be obtained with good yield and high levels of stereoselectivity, **Scheme 1-14**.



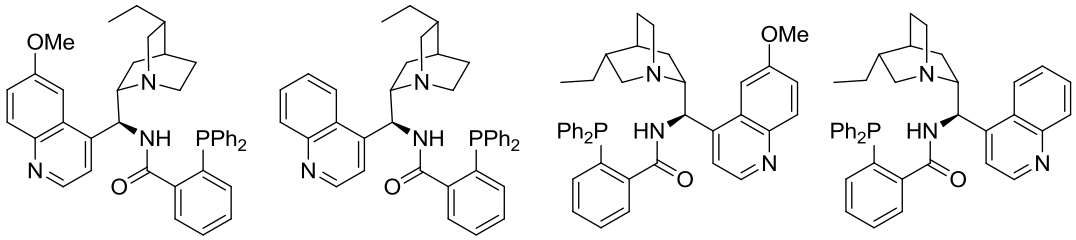
Scheme 1-14 *Nakamura's Cu(II) and Ni(II) catalysed enantioselective Mannich reactions*

In the stereochemical model[80] that Nakamura and co-workers proposed to explain the observed *cis*-imidazoline products, the terminal carbon of the deprotonated isocyanoacetate ester coordinated to the Cu centre and the enolate oxygen anion was simultaneously activated by the tertiary amine on the cinchona-derived ligand via H-bonding; *N*-DPP ketimine also coordinated to the Cu centre by the phosphinoyl oxygen and approached the electrophile from the less hindered side to afford the observed *cis*-imidazoline products, **Scheme 1-15**.



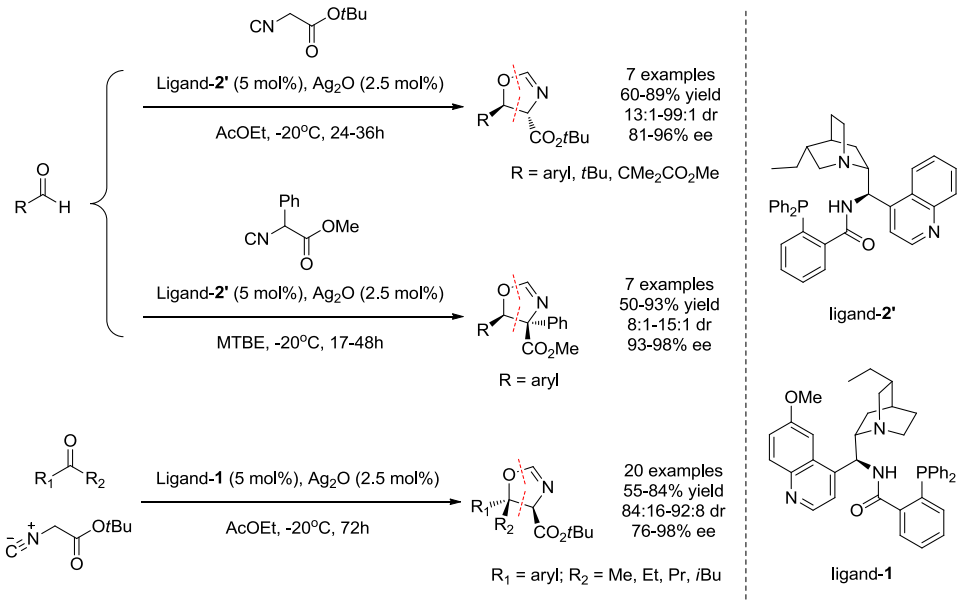
Scheme 1-15 *Proposed transition state model by Nakamura et al.*

1.2.4 Ag(I)/Amino phosphine dual catalytic system



Scheme 1-16 *Amino phosphine ligands developed by the Dixon group*

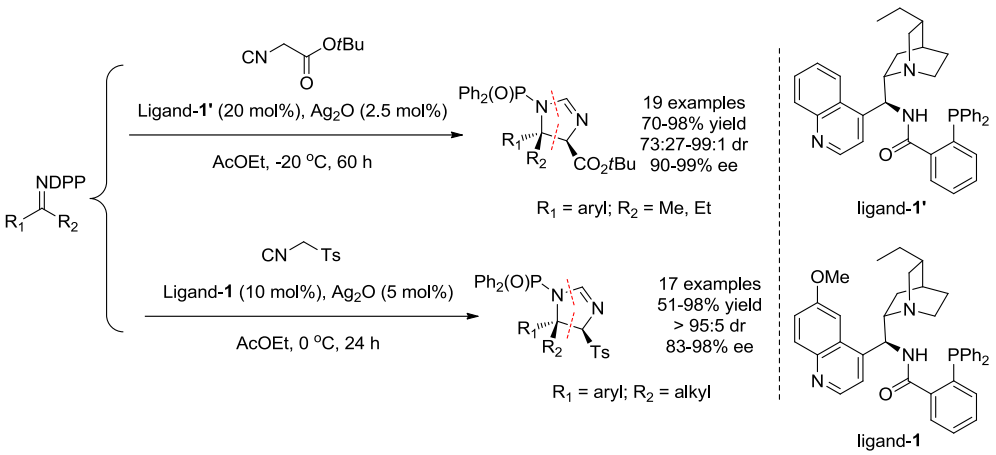
Prior and contemporaneously to the above reports, the Dixon group has made some significant contributions to the field of catalytic enantio- and diastereoselective aldol and Mannich chemistry[50–57]. In 2011, Dixon and co-workers developed a novel catalytic system for isocyanoacetate aldol and Mannich reactions, composed of a silver(I) salt and a cinchona-derived amino phosphine ligand[53] (**Scheme 1-16**).



Scheme 1-17 *Dixon group catalytic enantioselective isocyanoacetate aldol reactions*

In the initial report[53], the aminophosphine/silver system was first demonstrated to be capable of catalysing the enantio- and diastereoselective aldol reaction between *tert*-butyl isocyanoacetate and a variety of aromatic and aliphatic aldehydes and ketones to give highly substituted oxazolines, where with unsubstituted isocyanoacetate esters the highest enantioselectivities were found with aromatic or bulky aldehyde substrates. In 2014, the system was pleasingly proved to be extremely effective in catalysing the isocyanoacetate ketone aldol reactions with good yields and excellent stereocontrol affording highly substituted oxazolines[56], **Scheme 1-17**.

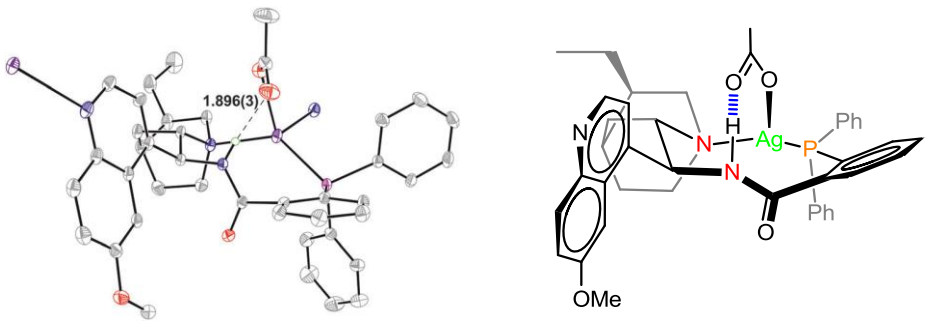
In 2014, the Dixon group also reported that a similar catalytic system could be applied to an expanded range of electrophiles - diphenylphosphinoyl protected ketimines especially - delivering 2-imidazolines in good yield and excellent level of stereocontrol[55]. Furthermore and most recently, TosMic isocyanide was found to be a competent pronucleophile, allowing the producing of Tosyl substituted imidazolines in excellent enantio- diastereoselectivity and yields[52], **Scheme 1-18**.



Scheme 1-18 *Dixon group catalytic enantioselective isocyanoacetate and TosMic Mannich reactions*

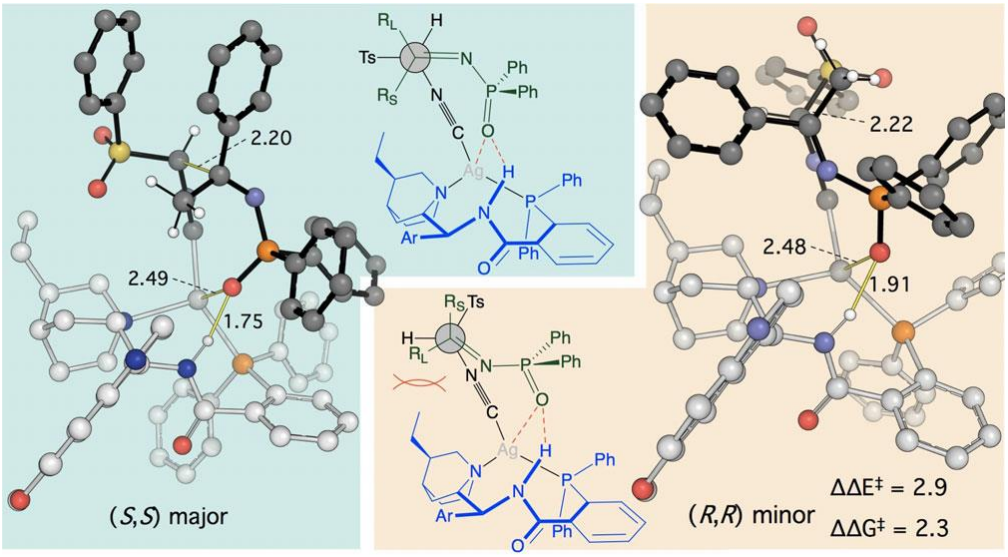
It is important to note that both ketones and ketimines are challenging electrophiles for the transformation, since they are much less reactive than aldehydes and aldimines. The Dixon group's disclosures were a breakthrough in the field of isocyanoacetate aldol and Mannich chemistry, which demonstrated for the first time that these type of catalytic enantioselective reactions could be realised on ketone and ketimine substrates.

In addition, the Dixon group performed comprehensive studies on the reaction mechanism, in order to illustrate the enantioselectivity and transition states of the amino phosphine dual catalytic system. Their work included catalyst structure/performance studies, single-crystal X-ray diffraction, NMR studies[57], and recently conducted quantum chemical calculation analysis[52] (DFT and QM/MM).



Scheme 1-19 *Single crystal X-ray structure for [(AgOAc)Ligand-**1**] complex*

Specifically, the first observation came from both the NMR and decisive single crystal X-ray evidence of the complex formation between AgOAc and Ligand-**1**, **Scheme 1-19**, where Ligand-**1** acts as bidentate *P,N*-ligand coordinating to silver centre via the phosphine P atom and the tertiary amine N atoms. A noticeable H-bond between the amide N*H* and acetate oxygen is also present with O-H distance of 1.896Å.



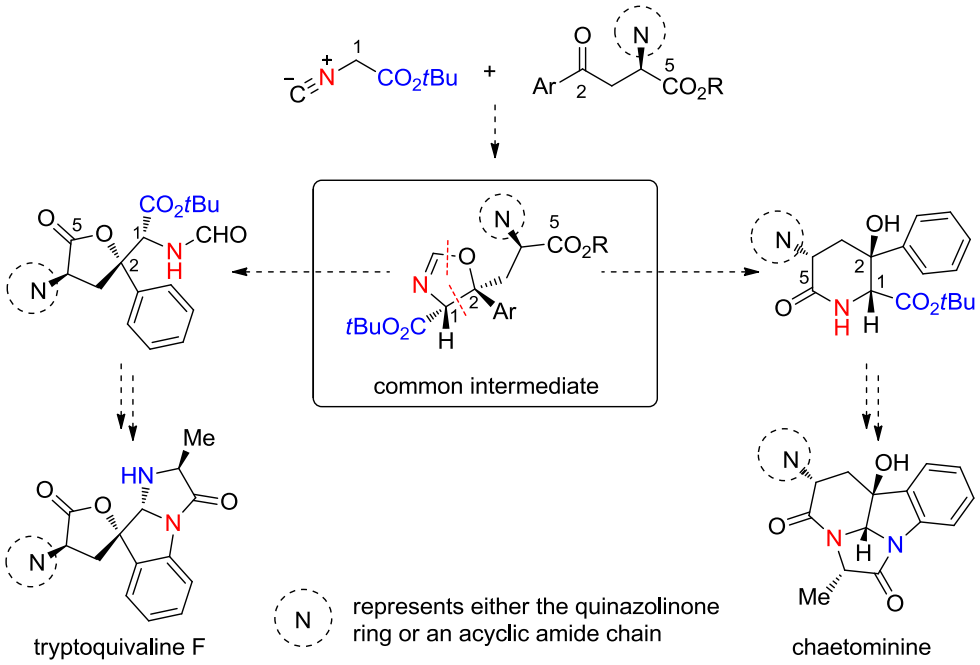
Scheme 1-20 *Proposed C-C bond forming transition states (copyright permitted by Wiley group)*

In addition to the insight upon the ground state of the reaction built up by the previous NMR and X-ray studies, recent DFT calculation analysis conducted in collaboration with Prof. Robert Paton and co-workers[52], further understanding on this catalytic system has been obtained. It is known that at room temperature *N*-DPP ketimine exists in the mixture of *E*- and *Z*-configuration, and thus both configurations have been computationally examined. The calculation showed that *E*-configuration is sterically favoured in the most stable TSs, where besides the X-ray differentiation proved *N,P*-coordination of silver, the phosphinoyl oxygen is postulated to coordinate to the amide N*H* proton and the silver centre simultaneously. In the major TS, the electrophile (*N*-DPP ketimine) and nucleophile are in a perfect staggered configuration when C-C bond is about to be formed; whereas in the minor TS, the two reactive components poise in an eclipsed configuration and sterically

interact with Ligand-**1**'s quinuclidine region, which results in a less stable TS ($\Delta\Delta G^{\ddagger}$ = 2.3 kJ/mol) leading to the minor enantiomer.

1.3 Thesis aims

The overarching aim of this thesis was to implement a new, catalytic, enantioselective oxazoline ring forming ketone aldol reaction into a challenging total synthesis plan, in order to achieve a catalyst controlled stereoselective total synthesis.



Scheme 1-21 *Original proposed general synthetic strategy*

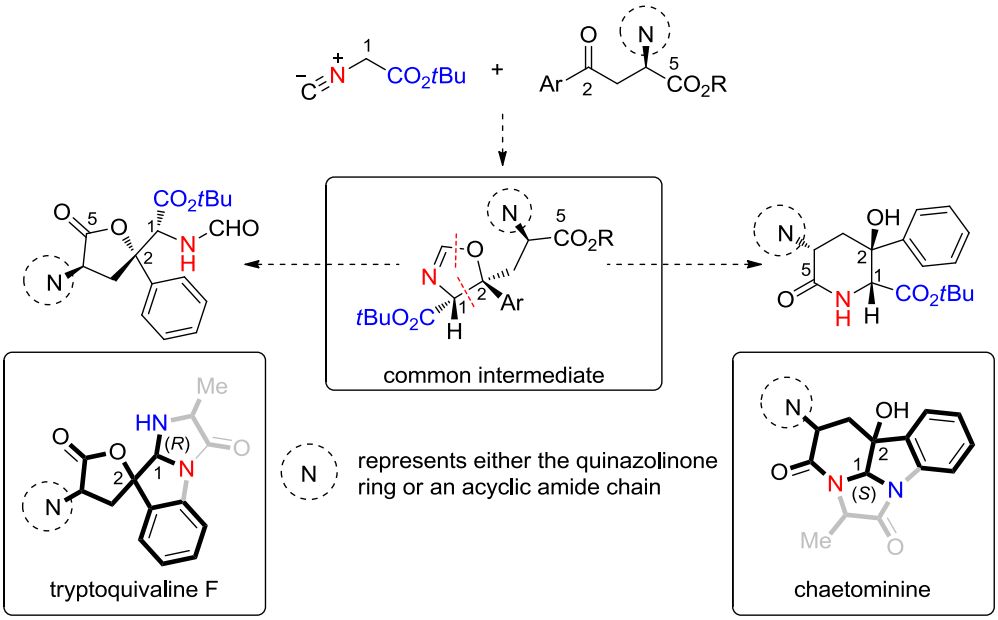
Our original design is shown in **Scheme 1-21**, where we hoped to apply our catalytic enantioselective isocyanoacetate aldol reaction to an advanced ketone substrate to prepare a common oxazoline intermediate and then continue the synthetic studies towards this alkaloid family. Once the enantioselective isocyanoacetate aldol reactions had been established using an appropriate aryl ketone, and under the most optimistic circumstances, we envisaged to test C-H activation conditions on the indoline core formation. Despite these initial plans we were aware that the synthetic strategy would evolve as the study

progressed. Additionally, it was hoped to establish a general synthetic approach that would diverge towards both tryptoquivalines and chaetominines.

Chapter 2. The first-generation synthetic approach

2.1 Retrosynthetic analysis

Our overall synthesis plan was based on a contemporary enantioselective ketone aldol methodology, allowing stereocontrolled access to an oxazoline product bearing a masked tertiary alcohol (at C2) adjacent to a masked amino acid (at C1), **Scheme 2-1**.



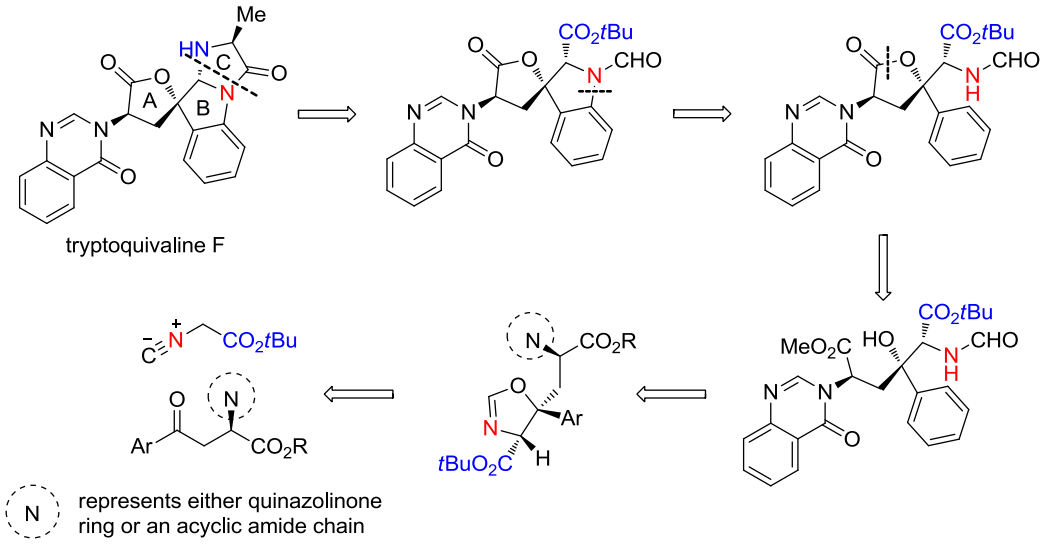
Scheme 2-1 *Proposed general synthetic sequence overview*

In both tryptoquivalines and chaetominines, the tertiary alcohol moiety at the C2 position is prominent and obvious, and the *N,N*-aminal part at the C1 position could be envisaged to originate from the masked amino acid structure of an oxazoline.

Since tryptoquivaline F and chaetominine possess opposite configuration at the *N,N*-aminal carbon, it appeared possible to build up both *R*- and *S*-configured stereocentres respectively by selectively forming the indoline C-N bond with different nitrogen atoms. When the nitrogen atom (red) on C1 position was incorporated into the indole, it would lead to the *R*-configured *N,N*-aminal centre in tryptoquivaline F; whereas when the ester

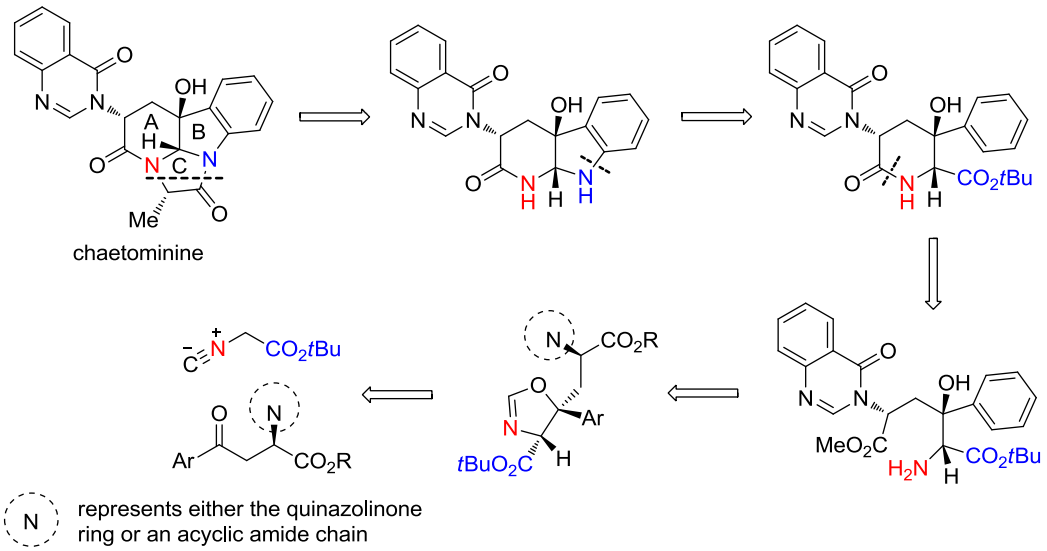
functionality was envisaged as a masked nitrogen (blue) and linked to the phenyl ring, the *S*-configured centre existed in chaetominine would be constructed.

Accordingly, a retrosynthetic strategy for tryptoquivaline F was constructed based on the above considerations, **Scheme 2-2**.



Scheme 2-2 *Retrosynthetic analysis of tryptoquivaline F*

For tryptoquivaline F, the C ring containing two nitrogen atoms could be generated by deriving the B ring by acylation, condensation or substitution with an appropriate three-carbon unit. An important functional group transformation in the synthesis would be the interconversion of an ester group into an amine functionality after B ring formation but prior C ring construction. At this point, the key bond formation - CN bond formation via CH activation – would then be performed. The A ring could be constructed by a lactone formation between an ester and the tertiary alcohol. At this point, all three important components of the oxazoline ring could be identified. The foundation of the route was that the oxazoline ring could be prepared using a catalytic enantioselective aldol reaction between an appropriate isocyanoacetate ester and a suitably substituted ketone.

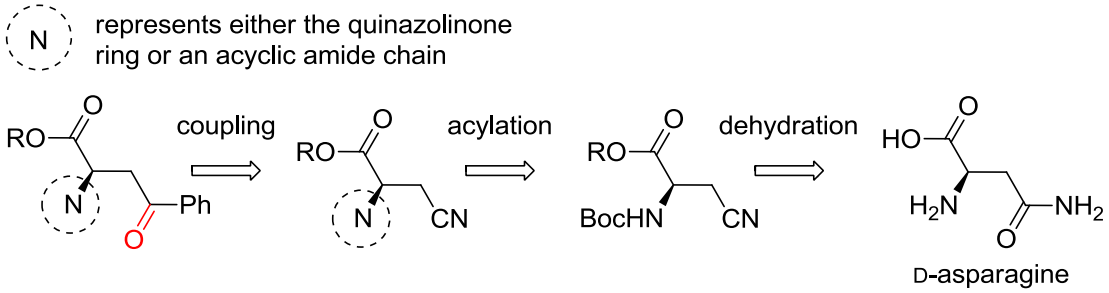


Scheme 2-3 *Retrosynthetic analysis of chaetominine*

Retrosynthetic analysis of chaetominine (**Scheme 2-3**) revealed that the B and C rings could be built up in a similar fashion to tryptoquivaline F. The masked nitrogen atom could be installed via functional group conversion from an ester group. The A ring could be built up by an intramolecular amide bond formation. Again, the three key components of the oxazoline ring revealed that it could again be used as a common intermediate and prepared via isocyanoacetate ketone aldol methodology as already described.

Both retrosynthetic analyses trace back to the same starting materials, an isocyanoacetate ester and a suitably substituted ketone. Upon aldol reaction these would give the same intermediate - the appropriately decorated oxazoline ring. Subsequently, different hydrolysis conditions should allow for divergence between the two synthetic routes.

To synthesise the desired ketone substrate for the catalytic enantioselective ketone aldol reaction, a sequence starting from D-asparagine was considered. This retrosynthesis takes advantage of a readily available amino acid building block, which would allow the potential introduction of both a heteroaromatic side ring and a phenyl group, **Scheme 2-4**.

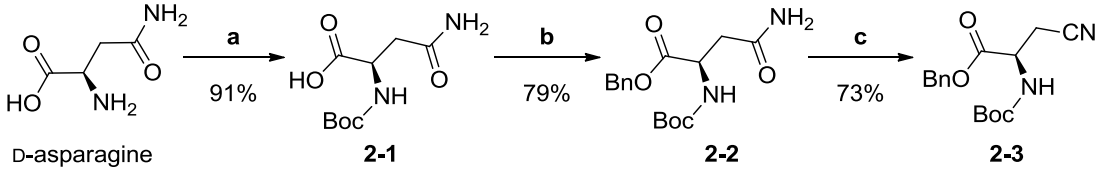


Scheme 2-4 *Retrosynthetic analysis of the key ketone substrate*

2.2 Results and discussion

2.2.1 Ketone substrate 2-7 synthesis

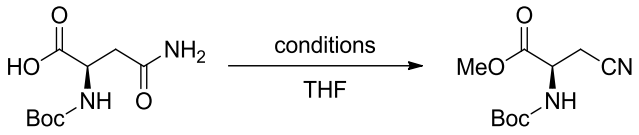
Our synthetic route to ketone **2-7** used the commercially available D-asparagine monohydrate as the starting material. Firstly, a Boc protecting group[81–85] was installed onto the primary amine functionality to afford *N*-Boc protected amino acid **2-1** in 91% yield. Subsequent esterification with benzyl bromide and triethylamine converted the carboxylic acid into the benzyl ester **2-2** in 79% yield[86–90]. The *N*-Boc protected benzyl ester **2-2** was then dehydrated[90,91] with TsCl and pyridine to give nitrile **2-3** in 73% yield, which was primed for coupling with a phenyl organometallic species to afford the phenyl ketone later in the sequence, **Scheme 2-5**.



a. Boc_2O, Na_2CO_3, H_2O, 1,4-dioxane; **b**. BnBr, Et_3N, THF; **c**. TsCl, pyridine, CH_2Cl_2

Scheme 2-5 *Preparation of N-Boc amino benzyl ester nitrile **2-3***

Attempts to carry out both of the above transformations (esterification and dehydration) in one pot could be achieved, albeit inefficiently under various conditions involving methanol and carbonyldiimidazole (CDI), **Table 2-1**.



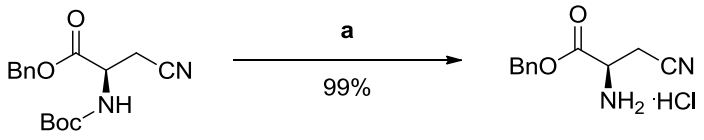
2-1 **2-4**

Table 2-1 *One pot conditions to prepare N-Boc amino methyl ester nitrile **2-4***

entry	reagent	additive	conversion[a], %	yield[b], %
1	CDI / MeOH	NA	45	36
2	CDI / MeOH	imidazole	44	35
3	CDI / MeOH	pyridine	45	36
4	CDI / MeOH	triethylamine	40	30

CDI 3.0 equiv.; THF as solvent; MeOH excessive at quenching; **a.** measured by starting material recovery; **b.** isolated yield after column chromatography

Accordingly, the previous more efficient stepwise approach was used to bring forward gram quantities of nitrile **2-3**, which was then subjected to *N*-Boc deprotection with 4 N HCl dioxane solution[92–94]. The resulting primary amine hydrogen chloride salt **2-5** was obtained in 99% yield, **Scheme 2-6**.

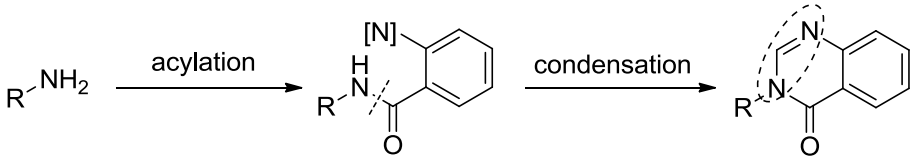


2-3 **2-5**

a. 4N HCl dioxane solution

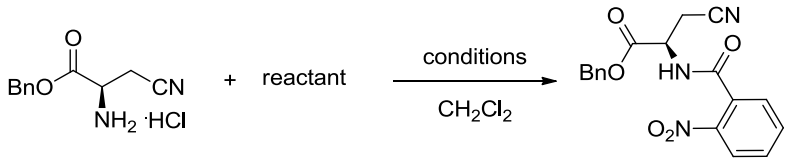
Scheme 2-6 *Removal of N-Boc protecting group*

Formation of the quinazolinone side ring commonly involves a two-step[95–100] acylation and condensation protocol, as demonstrated in **Scheme 2-7**.



Scheme 2-7 *General approach to construct a quinazolinone ring*

In this synthesis it was found that the acylation reaction of the primary amine salt **2-5** was inefficient under some very common coupling conditions, such as EDCI[101,102], DCC[103–106] or HATU[107–109]. Also, when the hydrochloride salt was firstly freebased and used as the pure primary amine form, attempted coupling reactions did not show significant improvement in terms of isolated yield under similar coupling conditions either. However, the primary amine salt did react well in fact with acyl chloride in the presence of pyridine, **Table 2-2**.



2-5 **2-6**

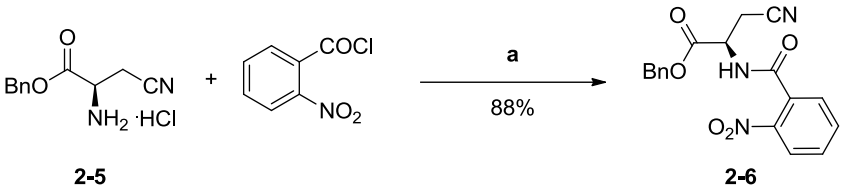
Table 2-2 *Amine coupling conditions to prepare **2-6***

entry	reagent	reactant	base	yield, %
1	DCC	2-nitrobenzoic acid	TEA or DIPEA	0
2	EDCI	2-nitrobenzoic acid	TEA or DIPEA	0
3	HATU	2-nitrobenzoic acid	TEA or DIPEA	0
4	NA	2-nitrobenzoyl chloride	TEA or DIPEA	0
5	NA	2-nitrobenzoyl chloride	pyridine	85

Pyridine exerted such a dramatic beneficial effect on the reaction, while other reagents, such as triethylamine and *N,N*-diisopropylethylamine did not. This observation is most likely caused by pyridine being able to perform as a nucleophilic catalyst[110,111].

Although **entry 5** conditions in **table 2-2** provided us with satisfactory yield (85%), we hoped to improve the reaction to be more convenient for large scales. The bi-phasic Schotten-Baumann conditions[112–114] were found to be superior and gave reproducible yields (88-90%) for the preparation of amide **2-6** with an easy procedure, especially when

employed on multi-gram scales of salt **2-5**. The produced crude amide **2-6** was usually pure enough without further chromatographic purification, **Scheme 2-8**.



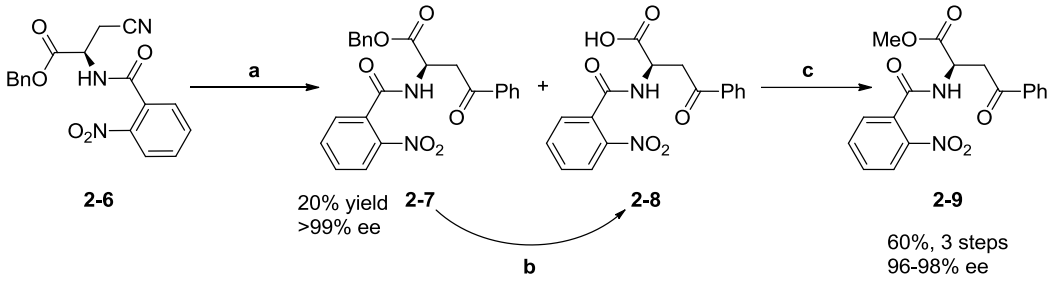
2-5 **2-6**

a. $NaHCO_3$, CH_2Cl_2, H_2O

Scheme 2-8 *Bi-phasic coupling conditions to prepare amide **2-6***

In this synthetic sequence, since an amide bond and a nitro group were considered stable enough to tolerate a variety of potential conditions for further transformations, the acyclic side chain of amide **2-6** was chosen to carry on further steps and the quinazolinone ring would be formed in a later stage.

To introduce the phenyl ring into nitrile **2-6**, we first performed a palladium(II) trifluoroacetate catalysed coupling reaction with 2,2'-bipyridine as ligand under recently reported conditions[115]. However, under these conditions the isolated yield of phenyl ketone **2-7** was only 20% and no starting material was recovered. It was found that in fact the coupling reaction happened as expected but the benzyl ester was unexpectedly hydrolysed to the carboxylic acid **2-8** under the reaction conditions. In order to obtain a satisfactory yield, subsequently a continuous two-step hydrolysis (aq. LiOH)[116–124] and acid catalysed methanolic esterification[125–129] sequence was carried out following the coupling reaction in order to convert both the benzyl ester **2-7** and the acid **2-8** into methyl ester ketone **2-9**, **Scheme 2-9**.

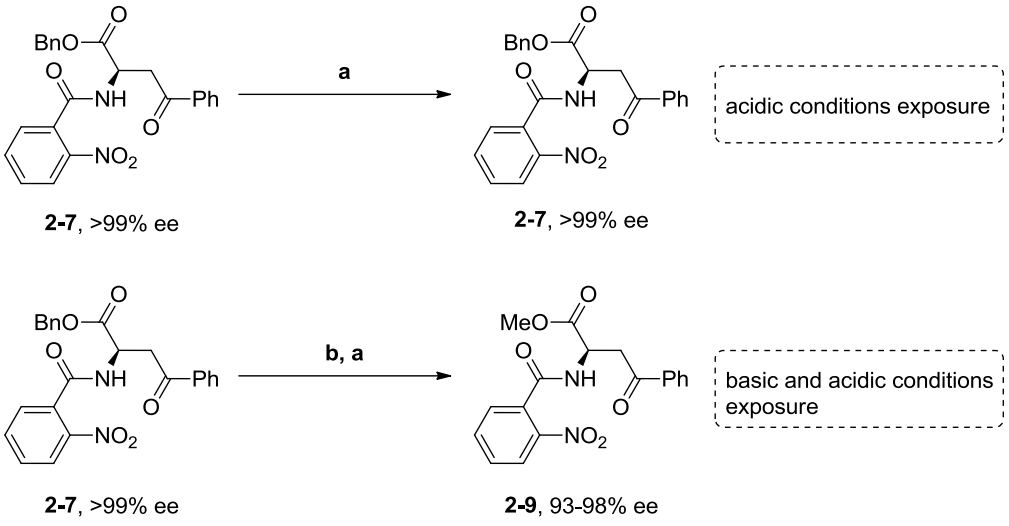


a. $PhBF_3K$, $Pd(TFA)_2$, 2,2'-bipyridyl, THF, H_2O, TFA, 80°C, 36h; **b.** 1M LiOH, THF, H_2O; **c.** MeOH, $SOCl_2$

Scheme 2-9 *Preparation of phenyl ketone **2-9***

The three-step sequence improved the overall isolated yield to 60%, which was satisfactory for further synthetic studies. However, when the optical purity of methyl ketone **2-9** was measured by chiral HPLC analysis, we found its level of optical purity was commonly 96-98% ee. Since the synthetic route started from the optical pure D-asparagine (>99.9% ee), a small but significant amount of racemization was occurring somewhere in the sequence.

To identify the point of racemization, racemic nitrile (±)-**2-6** and racemic benzyl ester ketone (±)-**2-7** were synthesized respectively. HPLC analysis indicated that nitrile **2-6**, which was the starting material for the coupling reaction, was >99% ee. Furthermore, the directly isolated coupling product **2-7** was also found to be >99% ee by analysis. Based on these observation, we assumed that the racemization happened either in the hydrolysis process of benzyl ester ketone **2-7** or in the acid catalysed esterification of carboxylic acid **2-8**.



Scheme 2-10 *Detection of racemization*

Firstly, when the benzyl ester ketone **2-7** was submitted to the same esterification conditions, hydrogen chloride in methanol solution, it maintained an ee as high as >99%. However, when elongating the reaction time for the hydrolysis of ester **2-7** with aqueous 1.0 M lithium hydroxide, after esterification the ee of methyl ester ketone **2-9** dropped to as low as 93% ee. This result demonstrated that even very mildly basic hydrolysis conditions were sufficient to compromise the stereochemical integrity of **2-7** afforded a slightly racemized product **2-9**.

Next, a series of optimization efforts were made on the coupling conditions in order to avoid the hydrolysis of benzyl ester functionality and the consequent erosion of optical purity, **Table 2-3**.

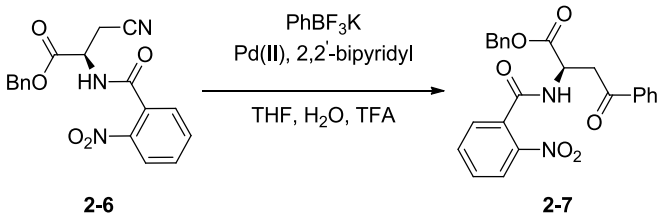


Table 2-3 *Optimization of the nitrile phenyl coupling conditions*

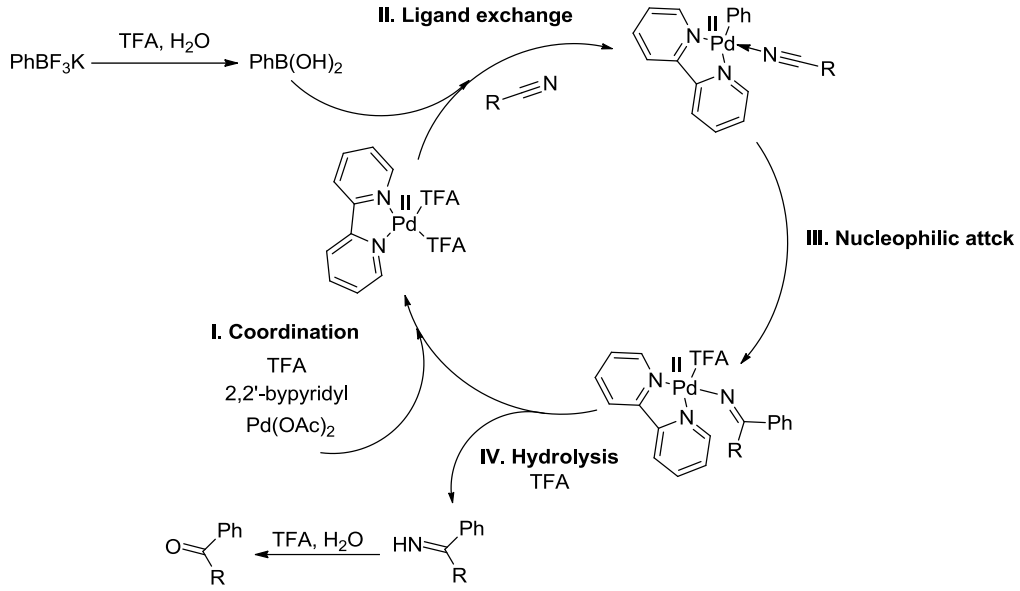
entry	Pd source	Pd Eq.	temp. °C	time, h	concentr., mmol/mL	yield, %
1	$Pd(TFA)_2$	0.05	80	36	0.17	20
2	$Pd(TFA)_2$	0.05	70	36	0.17	25
3	$Pd(TFA)_2$	0.05	80	15	0.11	55
4	$Pd(TFA)_2$	0.05	70	15	0.11	40
5	$Pd(OAc)_2$	0.05	80	15	0.11	60
6	$Pd(OAc)_2$	0.05	70	15	0.11	80
7	$Pd(OAc)_2$	0.075	70	15	0.11	83

Pd:2,2'-bipyridyl = 1:2 (mmol/mmol); TFA:nitrile = 10:1 (mmol/mmol); THF:H_2O = 5:1 (v/v);
concentration measured on nitrile **2-6** in overall volume of (THF + H_2O);
isolated yield of benzyl ester ketone **2-7**

As shown in **Table 2-3**, the isolated yield of **2-7** was systematically affected by reaction temperature, reaction time and concentration. Lower concentration, lower temperature and shorter reaction time suppressed the benzyl ester hydrolysis process, but a balance point for the above three main factors was also required. Pleasingly, we found the combination of conditions in **entry 7** gave an improved isolated yield of **2-7** from merely 20% to 83% with a convenient reaction time and a concentration for the subsequent scale up purposes. We also found that palladium(II) trifluoroacetate could be smoothly replaced with palladium(II) acetate with even better outcomes (**entry 5**). The optical purity of **2-7** was maintained at >99% ee as expected.

Although in the literature[115] there was no postulated mechanism reported, a possible catalytic cycle has been proposed here based on various observations, **Scheme 2-11**. In the mechanism, $Pd(OAc)_2$ would first coordinate with the ligand 2,2'-bipyridyl to form a Pd(II) species; the reactive phenyl boronic acid species and nitrile would then coordinate to the Pd(II) centre in a ligand exchange process rather than oxidative addition. The activated nitrile as an electrophile would then be attacked by the phenyl group from the

same Pd(II) centre to afford an imine product, which could be hydrolysed from the Pd species and finally into the ketone functionality.

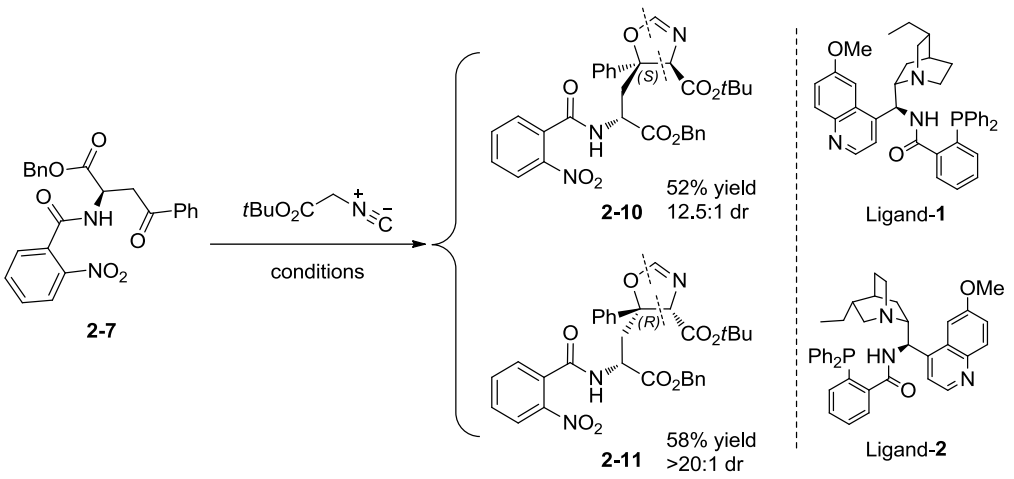


Scheme 2-11 *Proposed Pd(II) complex catalytic cycle*

Having established a scalable route to desired ketone **2-7** from D-asparagine without loss of enantiopurity, we then moved on to study the key catalytic stereoselective isocyanoacetate ketone aldol reactions.

2.2.2 Catalytic stereoselective ketone aldol reaction

Previous work in the Dixon group has clearly demonstrated the link between the absolute configuration of the newly generated quaternary sterocentres and the ligand used in the catalytic system[50–57]: the quinine derived Ligand-**1** would produce the (*S*)-configured quaternary centre, while the quinidine derived Ligand-**2** would generate the (*R*)-configured quaternary centre on the resulting oxazoline rings. The *tert*-butyl ester group on the adjacent tertiary stereocentre is commonly *trans*- to the phenyl or aromatic ring, which in most cases is considered a larger group than the substituted methyl group.



0.1 mmol of **2-7**; isocyanoacetate ester 0.15 mmol; Ag_2O 2.5% mmol; Ligand 5% mmol; -20 °C, 8.5 days, EtOAc

Scheme 2-12 *Original outcomes from catalytic enantioselective ketone aldol reaction*

In the very first attempt shown in **Scheme 2-12**, at 0.1 mmol scale, the catalytic aldol reaction was examined with 2.5% silver oxide as the Ag(I) source and 5% of cinchona-derived amino phosphine ligand at –20°C for 8.5 days. Pleasingly, when using Ligand-**1** we found that (*S*)-configured **2-10** was isolated in 52% yield (in addition to 25% recovered starting material) and with a dr of 12.5:1 at the quaternary stereocentre based on NMR analysis, while (*R*)-configured **2-11** was isolated in 58% yield (25% starting material recovered as well) and the dr was more than 20:1 on the quaternary stereocentre when Ligand-**2** was employed in this reaction. While this observation suggested that the ketone **2-7** and Ligand-**1** is a mismatched combination caused by the existing amide side chain, oxazoline **2-10** with the *S*-configured quaternary stereocentre was the desired product for further synthetic study.

From this lead result, the reaction conditions were further optimized, **Table 2-4**.

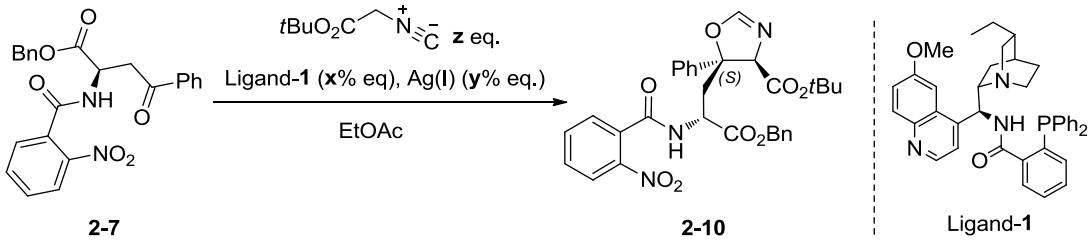


Table 2-4 *Optimization for the catalytic isocyanoacetate ester aldol reaction*

entry	silver	x%, y%, z eq.[a]	temp. °C	time, days	yield,[b] %	d.r.[c]
1	Ag_2O	5, 2.5, 1.2	-20	8.5	52	12.5:1
2	Ag_2O	10, 5, 1.2	-20	8.5	50	12.5:1
3	Ag_2O	10, 5, 1.2	-10	8.5	55	12.5:1
4	Ag_2O	10, 5, 1.2	0	8.5	60	12.5:1
5	Ag_2O	10, 5, 1.5	0	8.5	65	12.5:1
6	AgOAc	10, 5, 1.5	0	8.5	65	12.5:1
7	AgOAc	10, 5, 1.5	0	5	73	12.5:1
8	AgOAc	10, 5, 1.2	0	5	69	12.5:1

a. All reactions were carried out at 0.1 mmol of ketone **2-7** in 0.75 mL of EtOAc; **b.** isolated yield after column chromatography; **c.**determined by ^{1}H NMR analysis of the crude reaction mixture

The first discovery based on **Table 2-4** was that silver(I) acetate as the silver source gave improved reaction kinetics than the normally applied silver(I) oxide, probably because AgOAc was fully soluble and the resulting homogeneous system could be more catalytically efficient for the transformation. Additionally, it was found that temperature affected more the reaction speed/conversion than the stereoselectivity; the dr was constantly 12.5:1 at −20 °C, −10 °C and 0 °C. Moreover, due to the sensitivity of the oxazoline to hydrolysis, the isolated yield of **2-10** was affected by work up in purification.

Next, in order to carry out the catalytic aldol reaction on larger scale, ideally gram scale, the effect of scale on the reaction was then investigated, **Table 2-5**.

Table 2-5 *Scale up optimization for the catalytic isocyanoacetate aldol reaction[a]*

entry	scale, mmol	c, mmol/mL	temp. °C	yield, %	d.r.
1	0.1	0.13	0	73	12.5:1
2	0.2	0.13	0	72	12.5:1
3	0.5	0.13	0	51	12.5:1
4	1.0	0.13	0	30	12.5:1
5	1.0	0.08	0	55	12.5:1
6	1.0	0.05	0	71	12.5:1
7	1.0	0.025	0	52[b]	12.5:1
8	2.0	0.05	0	68	12.5:1

a. The ratio of $Pd(OAc)_2$:Ligand**-1**, the ratio of ketone **2-7**:isocyanoacetate ester and solvent were as same as in **Table 2-4; b.** reaction was stopped at Day 5 before full conversion

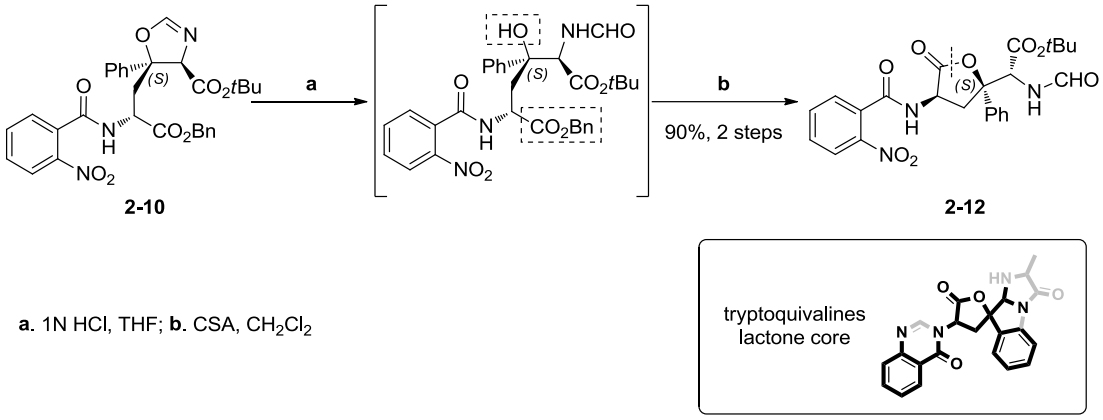
As ketone **2-7** scale increased from 0.1 mmol to 1.0 mmol from **entry 1** to **entry 4**, the yield at 0.13 mmol/mL dropped drastically, probably due to the formation of catalyst aggregates[130–138]. Lowering the concentration helped reduce this effect with higher isolated yields of oxazoline **2-10** (**entry 4** to **entry 6**). On 1.0 mmol scale, when the concentration was adjusted to 0.05 mmol/mL (**entry 6**), the isolated yield was similar to the one observed on small scale (**entry 1**). When the reaction concentration was decreased to 0.025 mmol/mL on 1.0 mmol scale, the rate of reaction dropped too low to be practical. On 2.0 mmol scale, at a concentration of 0.05 mmol/mL, the yield was maintained and the stereoselectivity was pleasingly unaffected.

In this section, details of the successful key silver(I), cinchona-derived amino phosphine catalysed stereoselective ketone aldol reaction on benzyl ester ketone **2-7** was described. With successful gram scale preparation of the desired **2-7**, we next moved to study divergent ring formation transformations.

2.2.3 Oxazoline hydrolysis and divergent ring formation

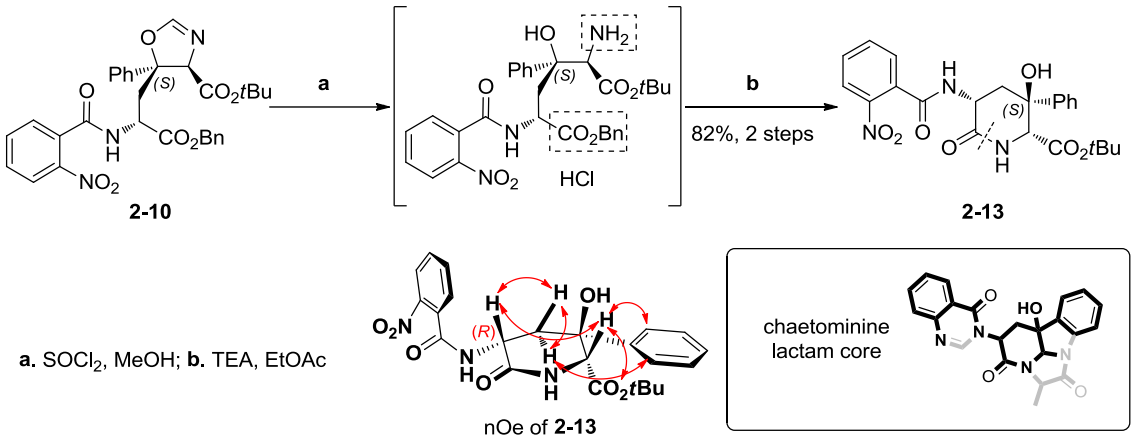
From our retrosynthetic analysis, the oxazoline **2-10** resulting from the key catalytic stereoselective ketone aldol reaction then needed to be hydrolysed into two different forms. Different hydrolysis conditions led to either formation of a γ-lactone or a δ-lactam.

Treatment of **2-10** with 1 N HCl aqueous solution converted the oxazoline into formamide intermediate immediately, and subsequent camphor sulfonic acid catalysed the formation of the γ-lactone ring affording **2-12** in 90% yield over two steps, **Scheme 2-13**.



Scheme 2-13 *Preparation of γ-Lactone **2-12***

In a parallel approach, oxazoline **2-10** was fully hydrolysed with methanolic HCl solution to the corresponding amino alcohol intermediate, which following basification cyclised to the δ-lactam **2-13** in 82% yield, **Scheme 2-14**. nOe studies were performed on **2-13** to establish the relative configuration of the newly formed stereocentres. Taking the stereocentre bearing the amide chain derived from D-asparagine as a reference point, the absolute configuration of all three stereocentres were then determined and found to be consisted with the original design plan[92].

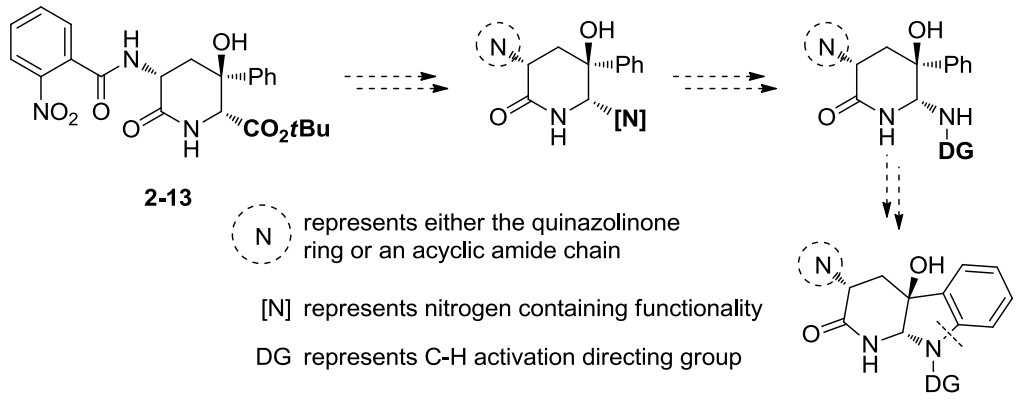


Scheme 2-14 *Preparation of δ-Lactam* ***2-13***

With the successful preparation of γ-lactone **2-12** and δ-lactam **2-13** in this section, we then moved further to synthetic studies towards tryptoquivalines and chaetominines.

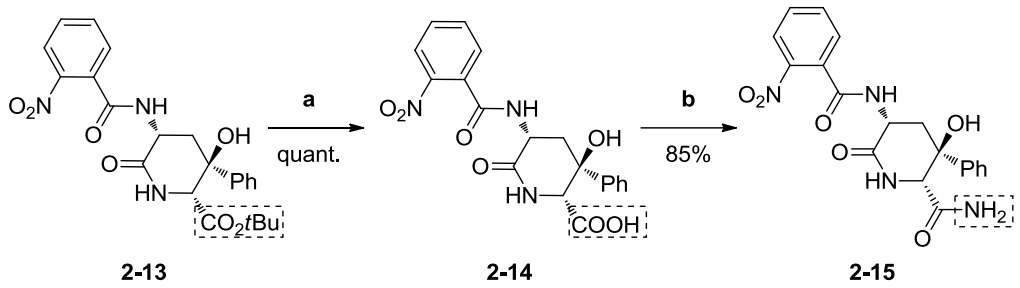
2.2.4 Lactam approach towards chaetominine

The route towards chaetominines from δ-lactam **2-13** was firstly selected to be focused. In this scenario, the *tert*-butyl ester needed to be converted into a nitrogen containing group in the first instance, and then a directing group was required to be introduced on the new nitrogen atom in order to facilitate subsequent C-H activation to build the C-N bond of the indoline, **Scheme 2-15**.



Scheme 2-15 *Section plan towards chaetominine indoline core*

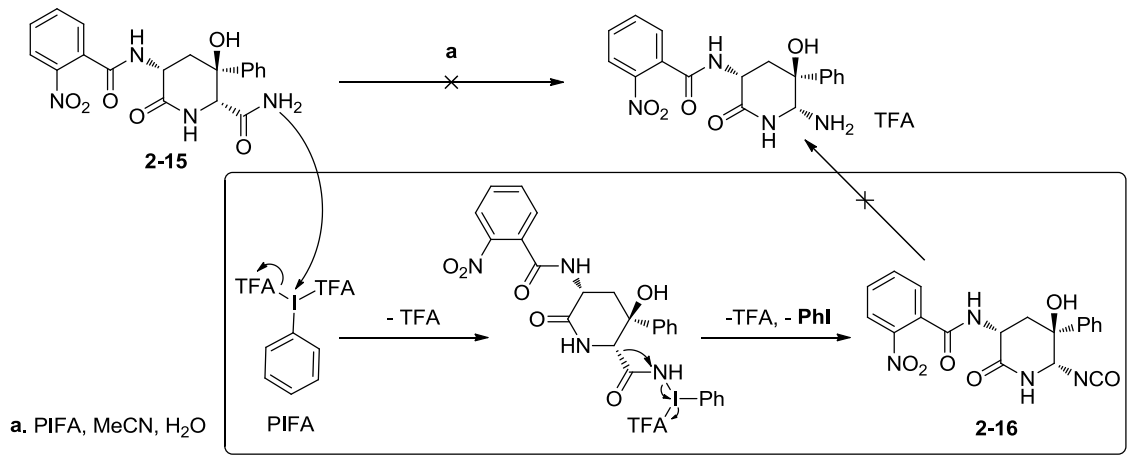
Accordingly, a Hofmann degradation approach, where a primary amide is converted via rearrangement into the isocyanate, was to be examined. *tert*-Butyl ester **2-13** was treated with TFA[139–143], which smoothly converted the ester group into carboxylic acid **2-14** in quantitative yield. Acid **2-14** was then activated with ethyl chloroformate[144–146] and subsequently reacted with aqueous ammonia solution (25%) to give the primary amide **2-15** in 85% yield, which was the Hofmann degradation precursor, **Scheme 2-16**.



a. TFA, CH_2Cl_2; **b**. $ClCO_2Et$, NMM, then NH_4OH

Scheme 2-16 *Preparation of Hofmann degradation precursor **2-15***

Next, in order to introduce the second nitrogen atom for the *N,N*-aminal moiety, Hofmann degradation conditions[147,148] were performed on amide **2-15**, but unfortunately no desired primary amine product could be isolated from the reaction mixture even when the very mild and substrate friendly hypervalent iodine reagent PIFA was employed[149–151], **Scheme 2-17**.

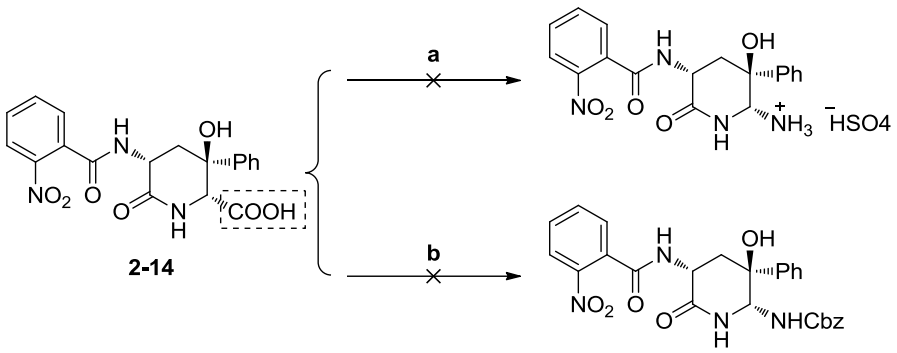


a. PIFA, MeCN, H_2O

Scheme 2-17 *Unsuccessful Hofmann degradation attempt*

However, the reduced side product iodobenzene could always be identified in the crude reaction mixture indicating that a 1,2-shift rearrangement may have occurred with a reasonable possibility of affording isocyanate **2-16**. We assumed that decomposition of the isocyanate took place under the reaction conditions, but to what remained unclear, as no meaningful amount of product could be isolated.

Considering that the single primary amine *N,N*-aminal structures have been reported as stable under acidic conditions[152,153], we initially assumed that the product could be formed as a salt. As a result, the following one pot acidic Curtius conditions[154–157] in **Scheme 2-18** were explored. Unfortunately, the approach did not produce the desired product, likely due to limited solubility of **2-14** in chloroform. Diphenylphosphoryl azide offered another one pot method to generate the amine form the acid group[156], however its deployment was unsuccessful, mainly due to very poor solubility of acid **2-14** in the presence of a variety of bases (triethylamine, DIPEA, pyridine).



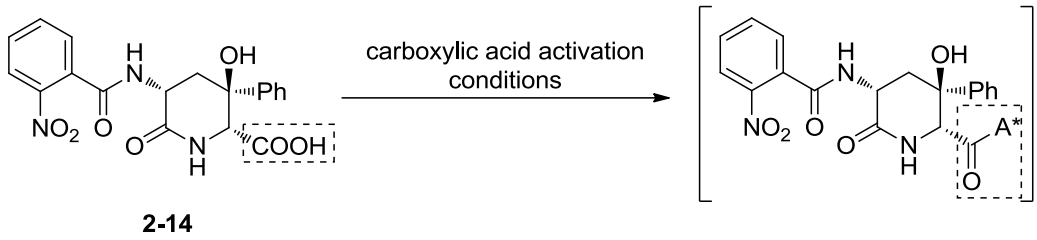
a. NaN_3, H_2SO_4, $CHCl_3$; **b**. DPPA, toluene, base (TEA / DIPEA / Py), BnOH

Scheme 2-18 *Unsuccessful one pot Curtius conditions*

Following these unsuccessful attempts, efforts then focused on a stepwise transformation sequence, aiming to obtain isocyanate functionality first and then to convert it to an amine in a subsequent second step. The stepwise transformation ideally

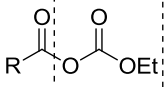
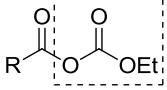
would start with the activation of carboxylic acid **2-14**, followed by a subsequent reaction with a nucleophilic azide species to form an acyl azide functionality.

Among various conditions to activate the acid, generating the mixed anhydride[149,158] proved to be the most convenient and reliable approach. Other conditions, as shown in **Table 2-6**, were also explored, but did not perform as well as the mixed anhydride method for acid activation on **2-14**.



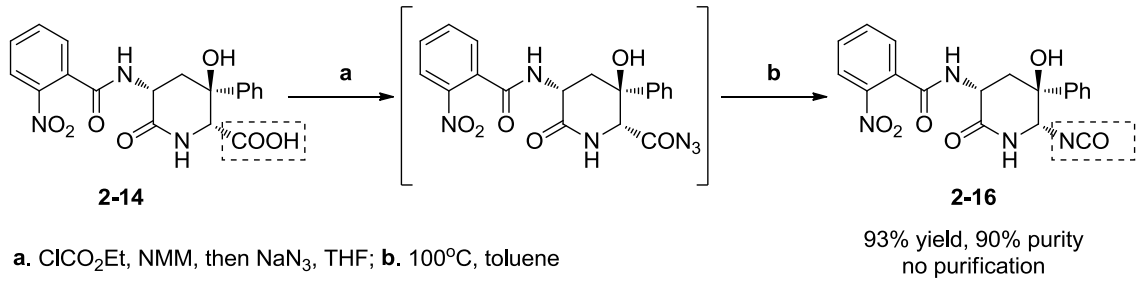
2-14

Table 2-6 *Summary of acid group activation conditions carried out on **2-14***

condtions	solvent	activated form	observation and outcome
$SOCl_2$	neat		Poor solubility of SM; slowly decomposing
$(COCl)_2$, cat. DMF	CH_2Cl_2		Poor solubility of SM; low conversion
T_3P, $TMSN_3$, pyridine	THF		SM precipitated as salt
$ClCO_2Et$, then *N*-methylmorpholine	THF		Successful
N-methylmorpholine, then $ClCO_2Et$	THF		SM precipitated as salt

Accordingly, acid **2-14** was activated with ethyl chloroformate forming the mixed anhydride intermediate, which in one-pot reacted rapidly with sodium azide to give the acyl azide; this could be monitored by TLC and confirmed with an IR assay. The acyl azide intermediate was subsequently subjected to heating conditions at 100 ^{o}C for 30 minutes to release nitrogen gas and trigger the 1,2-rearrangement. This process successfully provided the desired isocyanate product **2-16** in 93% crude yield of 90% purity with the configuration

of the *N*,*N*-aminal stereocentre retention according to the nature of Curtius rearrangement chemistry[149,158]; **2-16** was characterized without further purification, **Scheme 2-19**.



Scheme 2-19 *Stepwise Curtius rearrangement to prepare isocyanate **2-19***

With isocyanate **2-16** in hand, the first approach was to insert alcohols into the isocyanate moiety in order to generate carbamate type compounds. Various conditions were examined in **Table 2-7**, but none gave a promising outcome for the desired compound, and the reaction usually ended up producing a complex mixture, and LCMS analysis only showed a small peak for the carbamate compound. When using *tert*-butyl alcohol as the solvent and reagent, an unidentifiable compound was found.

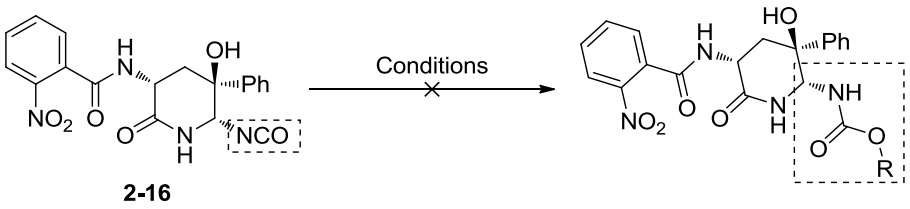
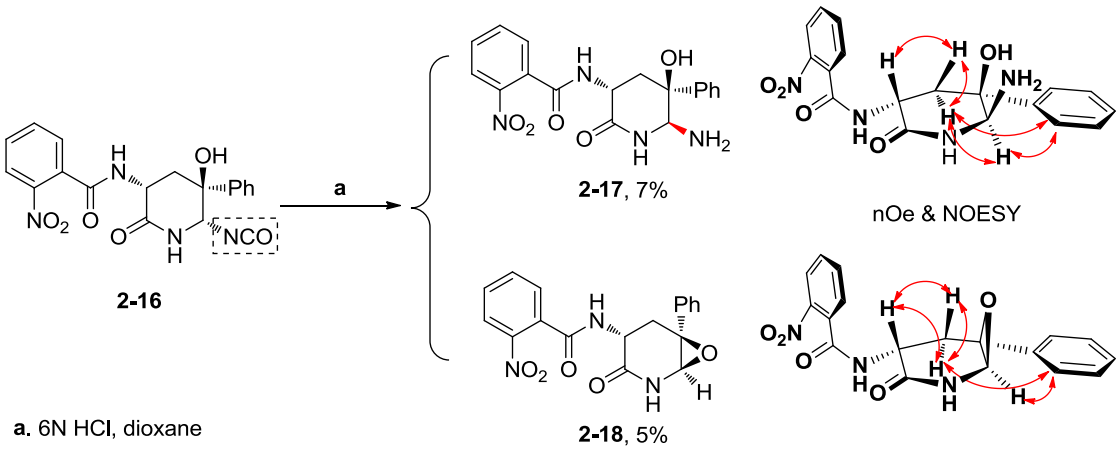


Table 2-7 *Preparation of carbamate compounds*

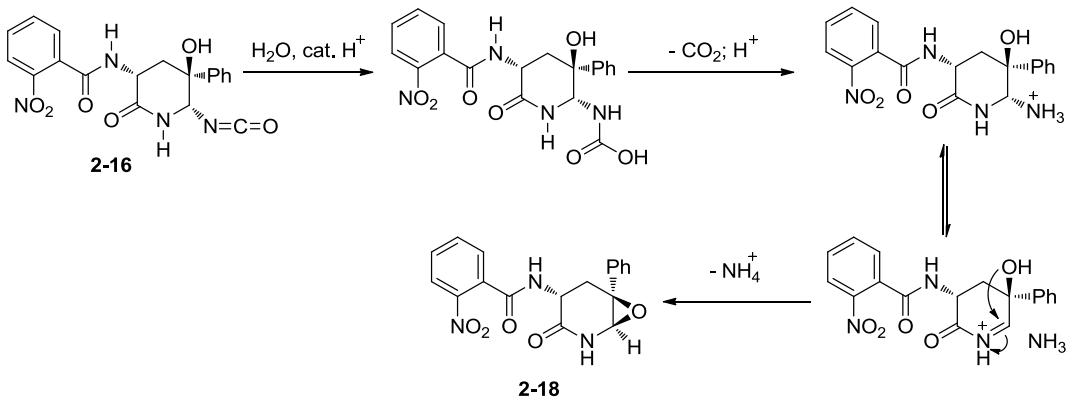
entry	solvent	reagent	temp. °C	outcome
1	toluene	MeOH, 2 eq	100	complex mixture
2	toluene	BnOH, 2 eq	100	complex mixture
3	Dioxane	MeOH, 2 eq	100	complex mixture
4	Dioxane	BnOH, 2 eq	100	complex mixture
5	*t*BuOH	N/A	100	unidentified

Since no identifiable carbamate compound was obtained, full hydrolysis conditions were explored on isocyanate **2-14** as a subsequent alternative to introduce the desired *N,N*-aminal moiety, **Scheme 2-20**.



Scheme 2-20 *full hydrolysis to prepare N,N-aminal moiety*

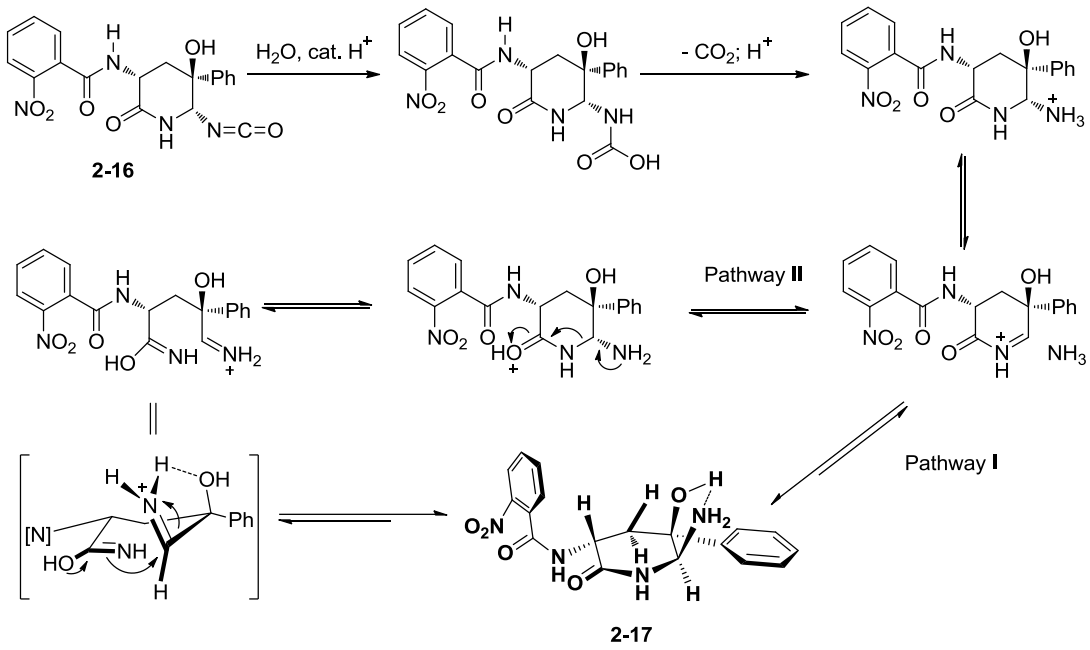
As shown in **Scheme 2-20**, under strongly acidic aqueous conditions in dioxane, only trace amounts of two side products – reverse configured **2-17** and epoxide **2-18** - were isolated and characterized from a very complex reaction outcome, and no desired primary amine *N,N*-aminal compound was detected. The proposed mechanism **Scheme 2-21** and **Scheme 2-22** were postulated to illustrate what could have happened in the above reaction.



Scheme 2-21 *Proposed mechanism for generating **2-18***

Seemingly, the adjacent tertiary alcohol on the lactam core become involved in the reaction to unexpectedly giving rise to epoxide **2-18**, showing previously unrevealed

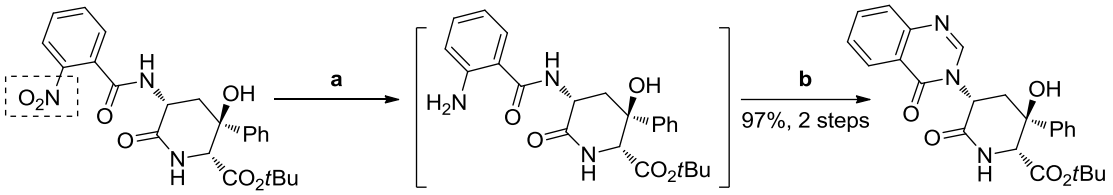
reactivity on **2-16**. Additionally, epimerisation of the *N,N*-aminal moiety was observed, indicating the undesired epimer **2-17** was accessible through reversible loss and addition of an NH_3 group or a reversible lactam ring opening and closing process. These isolated side products indicated a variety of possible pathways for how the lactam core could behave under acidic conditions, justifying the complex reaction outcome for the full hydrolysis attempt.



Scheme 2-22 *Proposed mechanism for generating* ***2-17***

Although this result was not what we expected, it gave us structural insight into the behaviour of the lactam core helping us to redesign the synthetic sequence. Firstly, acidic conditions was not a good choice for converting the isocyanate functionality into other forms. Secondly, since the lactam amide nitrogen atom made a contribution in the generation of both side products, to protect the lactam amide could be an alternative in order to delocalise the electron pair on the lactam nitrogen atom and minimize the possibility of producing side products. In that way, we hoped an alcohol would have more time to capture the isocyanate intermediate to afford the desired carbamate compounds.

Due to the presence of two amides and one alcohol, the side chain amide was firstly protected by closing the heterocyclic quinazolinone ring, as shown in **Scheme 2-23**. The nitro group was reduced under a hydrogen atmosphere with palladium on charcoal and the produced aniline was subsequently treated *in situ* with trimethyl orthoformate and catalytic pTSA to afford quinazolinone **2-19** with 97% yield over 2 steps.

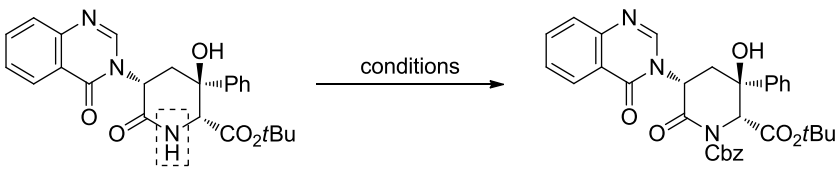


2-13 **2-19**

a. Pd/C, H_2, MeOH; **b.** pTSA, $CH(OMe)_3$, MeOH

Scheme 2-23 *Preparation of quinazolinone **2-19***

Next, we aimed to protect the amide with a Cbz group without affecting the configuration of the lactam's α position and the *tert*-butyl ester's α position. The Cbz protecting group was selected because various methods are known for its later removal, and it is stable towards acidic conditions (acid stability was required for converting the *tert*-butyl ester group to acid). A range of kinetic base and electrophile combinations were then tested as shown in **Table 2-8**.



2-19 **2-20**

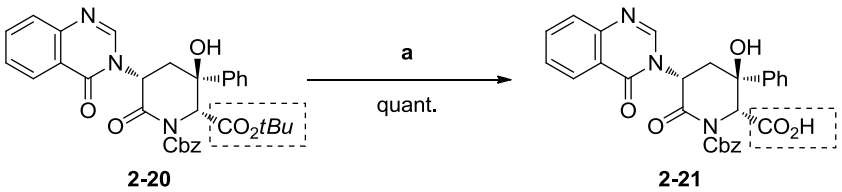
Table 2-8 *Preparation of imide **2-20***

entry	base	electrophile	S.M.[a], %	product[b], %
1	LHMDS	CbzCl	20	35
2	NaHMDS	CbzCl	30	30
3	KHMDS	CbzCl	30	30
4	LHMDS	$(Cbz)_2O$	13	48
5	LDA	$(Cbz)_2O$	15	40

base 2.2 eq.; electrophile 1.1 eq., -78 ^{o}C quench; **a**. recovered S.M.; **b**. isolated yield of product after flash column chromatography

LHMDS showed the best performance in that it gave the highest isolated yield of imide **2-20**, and no protection of the tertiary alcohol was observed when 2.2 equivalent of base and 1.1 equivalent of electrophile were used in all entries. Cbz anhydride provided a better yield and reproducibility on larger scale reactions than CbzCl.

Subsequently, the *tert*-butyl ester on **2-20** was successfully hydrolysed to acid **2-21** with quantitative yield by treating imide **2-20** with TFA, **Scheme 2-24**.



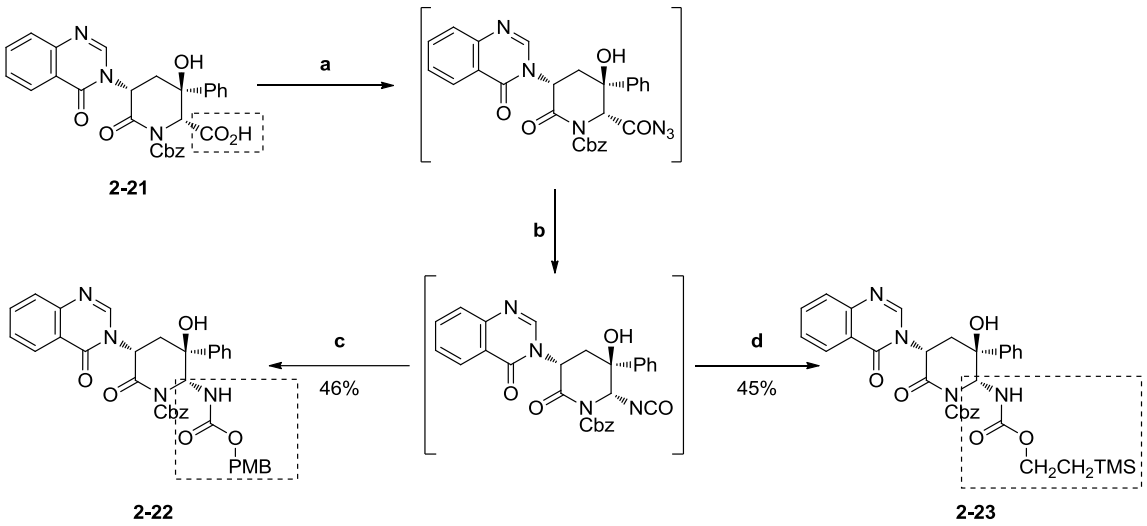
2-20 **2-21**

a. TFA, CH_2Cl_2, rt

Scheme 2-24 *Preparation of acid **2-24***

Next, acid **2-21** was treated with ethyl chloroformate and *N*-methylmorpholine (NMM) to activate the carboxylic acid functionality, which was subsequently treated with sodium azide to give an acyl azide intermediate that smoothly converted to the putative isocyanate intermediate upon heating. When the isocyanate intermediate with subsequently treated with PMBOH and TMS-ethanol, PMB carbamate **2-22** and substituted ethanol carbamate **2-23** were provided in 46% and 45% yield respectively, **Scheme 2-25**.

This result indicated that amide protection was effective for adjusting the reactivity and stability of the isocyanate intermediate. For the first time in this investigation, the synthesis and isolation of the desired *N,N*-aminal structures with both PMB carbamate **2-22** and 2-(trimethylsilyl)ethanol carbamate **2-23** had been achieved.

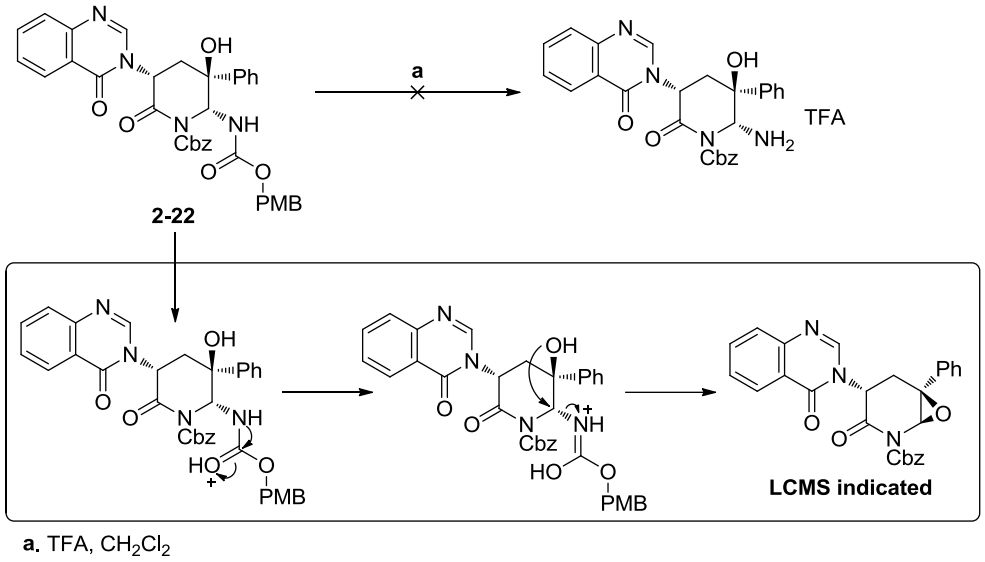


a. $ClCO_2Et$, NMM, then NaN_3, THF; **b**. 100°C, toluene; **c**. PMBOH, toluene, 100°C; **d**. $TMSCH_2CH_2OH$, toluene, 100°C

Scheme 2-25 *Preparation of N,N-aminal carbamate **2-22** and **2-23***

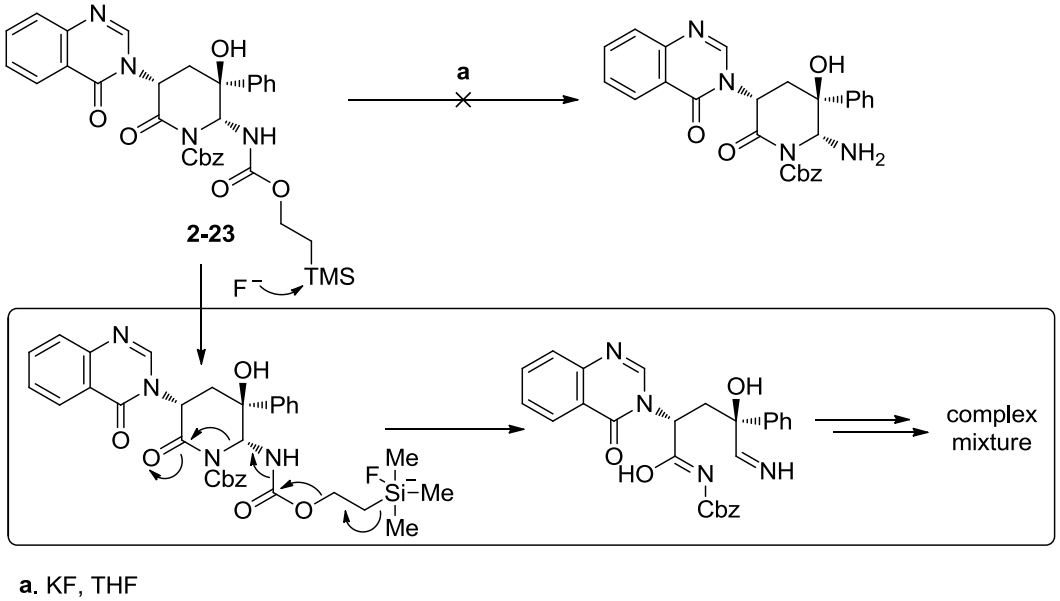
For the next stage of the synthetic plan, installation of a suitable directing group was required to enable the C-H activation/indoline formation. From **2-22** and **2-23**, the unprotected primary amine had to be obtained in the first instance.

Initial attempts were to remove the PMB group carbamate from **2-22** under acidic conditions, but no desired primary amine salt could be detected after careful analysis. Along with the full consuming of the starting material carbamate **2-22**, LCMS monitoring indicated a cation intermediate might be formed during the process followed by epoxide formation, as shown in **Scheme 2-26**.



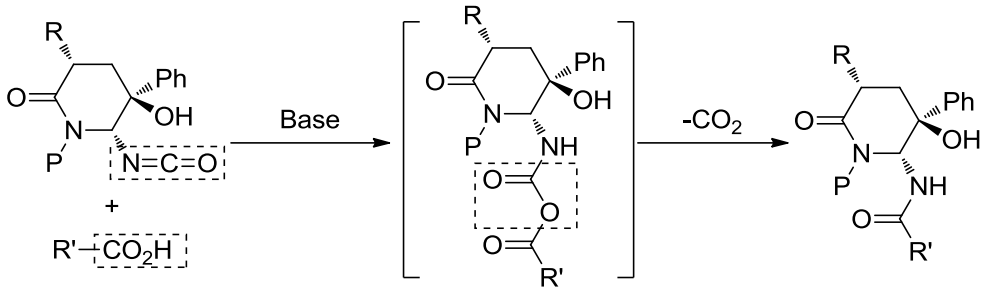
Scheme 2-26 *Attempted removal of PMB from **2-22** under acidic conditions*

In a parallel fashion, TMS-ethanol carbamate **2-23** was treated with potassium fluoride in an attempt to obtain a primary amine substrate. However, TLC monitoring and later spectroscopic analysis demonstrated that the skeleton of **2-23** had collapsed almost immediately when it was reacted with KF, very likely via a fragmentation reaction, **Scheme 2-27**.



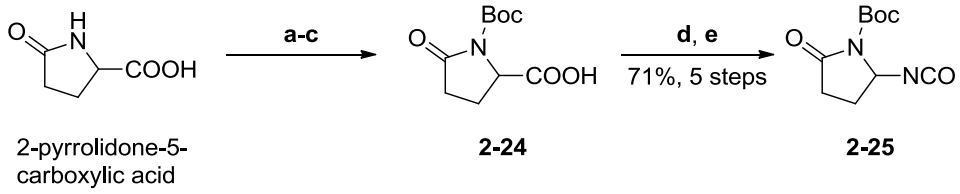
Scheme 2-27 *Attempted deprotection of TMS-ethanol carbamate of **2-23***

Our above attempts showed it was challenging to obtain the desired primary amine. Accordingly, a sequence to produce the desired amide without the involvement of a primary amine was proposed in **Scheme 2-28**, where the two parts of the amide arose from an isocyanate and a carboxylic acid respectively[159,160]. The resulting anhydride intermediate would release one molecule of carbon dioxide upon heating and rearrange to afford an amide structure.



Scheme 2-28 *Proposed transformation to avoid primary amine isolation*

In order to investigate this idea, a suitable model substrate **2-25** was designed, which was then synthesized in 5 steps in 71% overall yield from 2-pyrrolidone-5-carboxylic acid, **Scheme 2-29**.



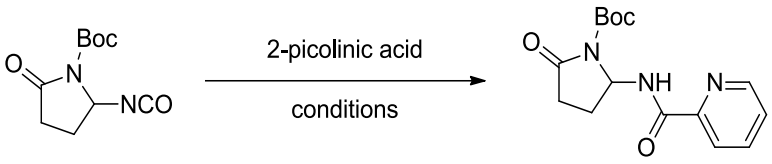
2-pyrrolidone-5-carboxylic acid **2-24** **2-25**

a. BnBr, DIPEA, CH_2Cl_2; **b**. Boc_2O, DMAP, MeCN; **c**. Pd/C, H_2, EtOAc; **d**. $ClCO_2Et$, NMM, then NaN_3; **e**. 100°C, toluene

Scheme 2-29 *Preparation of model substrate **2-26***

In the subsequent model study, 2-picolinic acid was employed because this reagent could produce a picolinicamide product which was an ideal directing group for a downstream indoline forming C-H activation reaction[161–164]. Under various reaction conditions, **2-26** was formed with low to moderate yields. **Table 2-9** presents the findings

and among which **entry 7** was the most promising. Treating **2-25** with 2-picolinic acid and DIPEA in DMF at 100 °C for 12 hours resulted in the formation of **2-26** in 60% yield. With this promising result we looked forwards the real system.



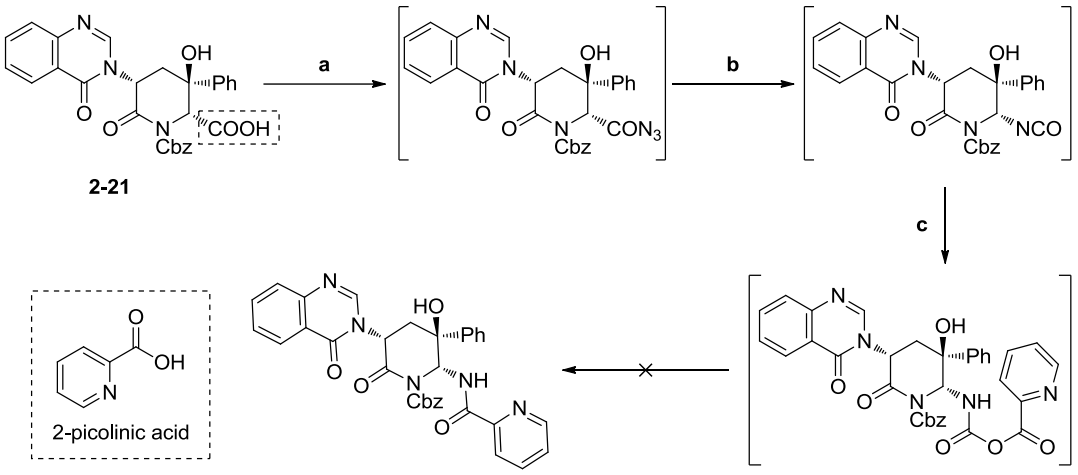
2-25 **2-26**

Table 2-9 *Aminal amide formation on model isocyanate substrate **2-25***

entry	solvent	base	temp. °C	time, h	yield[a], %
1	MeCN	TEA	80	12	40
2	MeCN	Pyridine	80	12	30
3	MeCN	DIPEA	80	12	50
4	DMF	TEA	80	12	20
5	DMF	Pyridine	80	12	--
6	DMF	DIPEA	100	3	20
7	DMF	DIPEA	100	12	60

base 2.0 eq.; 2-picolinic acid 1.5 eq.; **a**. isolated yield of product after column chromatography

However unfortunately, when applying the optimized conditions (**entry 7** in **Table 2-9**) on the real *in situ* generated isocyanate substrate in a one-pot sequence from imide protected acid **2-21** as shown in **Scheme 2-30**, no desired picolinic amide could be isolated.

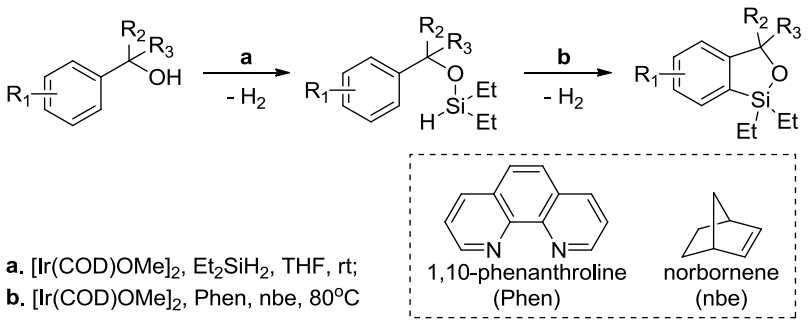


a. $ClCO_2Et$, NMM, then NaN_3, THF; **b.**100°C, toluene; **c.** 2-picolinic acid, DIPEA, DMF, 100°C

Scheme 2-30 *Attempted aminal amide formation on the real isocyanate substrate*

Since none of the previous approaches gave the desired C-H activation precursor, the synthetic potential of the lactam core was revisited, and the tertiary alcohol adjacent to the phenyl ring appeared to be a potential C-H activation directing group to facilitate our designed bond formation.

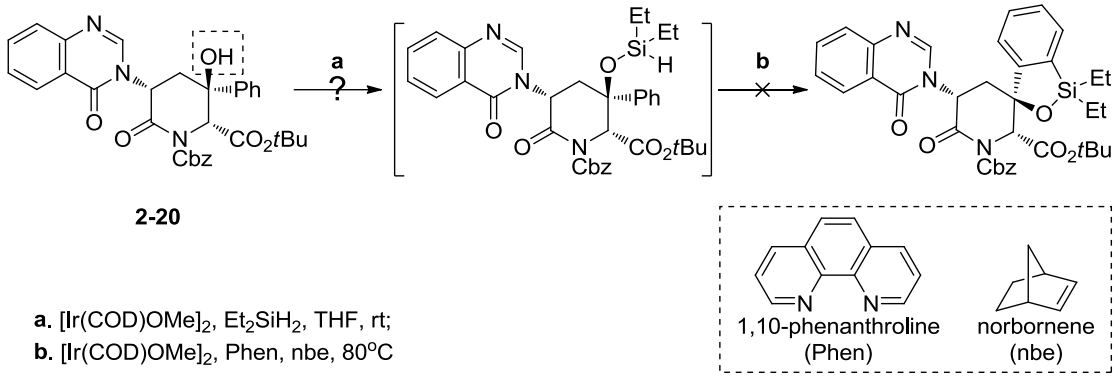
Recently, Hartwig[165–168] published a series of paper on C-H silylation of benzyl alcohols via an iridium catalysed Si-C bond formation, **Scheme 2-31**.



a. $[Ir(COD)OMe]_2$, Et_2SiH_2, THF, rt;
b. $[Ir(COD)OMe]_2$, Phen, nbe, 80°C

Scheme 2-31 *Hartwig's Ir catalysed Si-C bond formation chemistry*

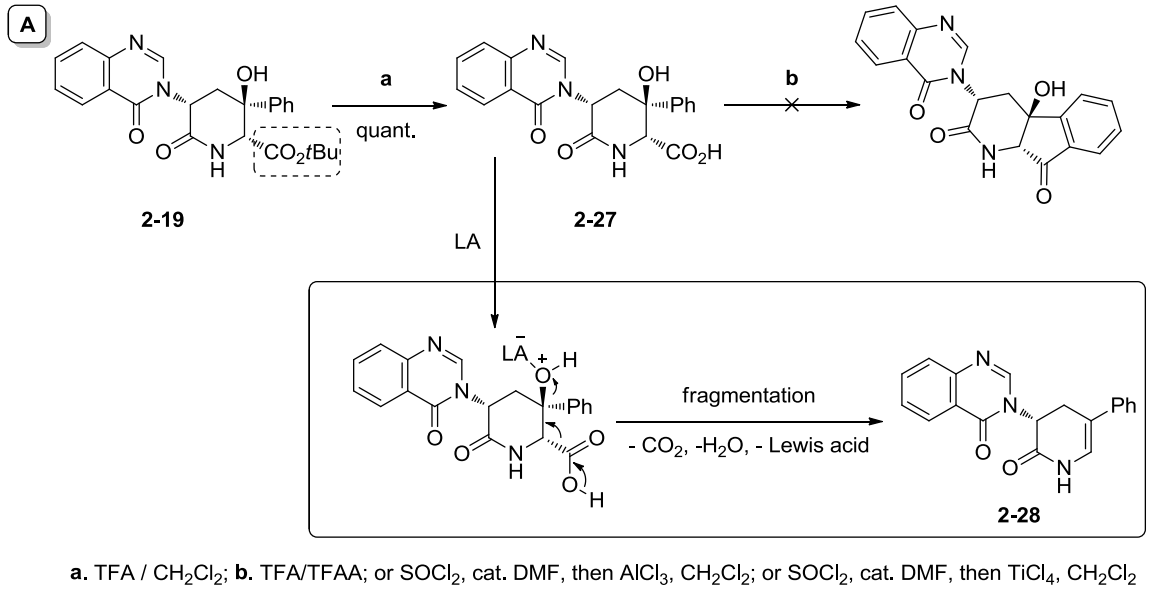
Indeed, the literature conditions were applied to imide **2-20** but the desired Si-C bond formation was not observed and it was also unclear if the silyl group was installed on the tertiary alcohol, **Scheme 2-32**. Again, the structural complexity and functional group rich nature of this compound was believed to be a reason of the lack of reactivity.



Scheme 2-32 *Ir catalysed Si-C bond formation on* ***2-20***

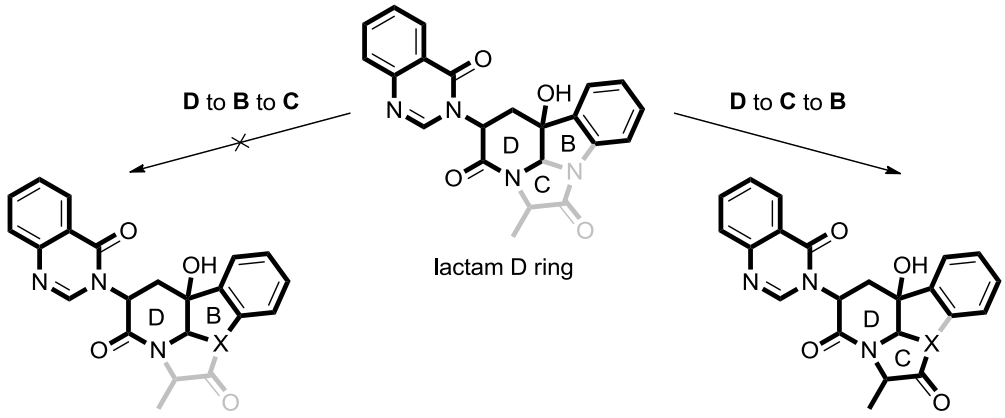
Another method devised to activate the phenyl ring was simple Friedel Crafts[169–173] type reactions. However, using the activated carboxylic acid as a potential acylium ion electrophile, it was not found to afford the desired phenyl ketone product, **Scheme 2-33**. Friedel Crafts conditions - TFA/TFAA, $SOCl_2/AlCl_3$, $SOCl_2/TiCl_4$ - have been explored, but the only isolated compound was **2-28**, which was believed to be generated through a fragmentation under strong acidic conditions.

An alternative to reverse the observed elimination trend was to boost the carboxylic acid group a "stronger" Lewis base, such as an amide, to compete against the tertiary alcohol towards binding to Lewis acid under Vilsmeier conditions[174–178]. Accordingly, the *N,N*-dimethyl amide **2-29** was synthesized in 96% yield from acid **2-27** by HATU coupling conditions. But amide **2-29** turned out to be too stable under $POCl_3$ conditions, **Scheme 2-33**.



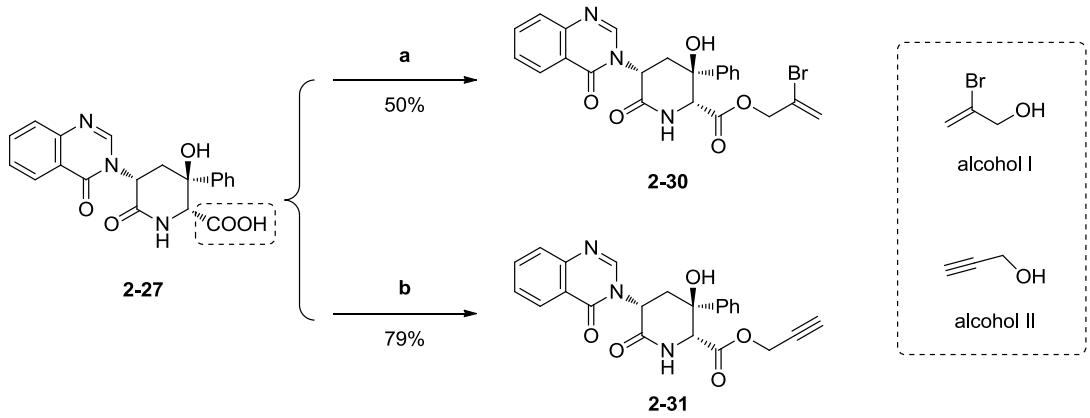
Scheme 2-33 *Friedel Crafts and Vilsmeier conditions for phenyl ring activation and the observed fragmentation product*

Previous studies in this section have demonstrated the aminal moiety is difficult to generate and handle under a variety of reaction conditions, so it was hypothesized that the ring formation sequence could be adjusted to avert this issue, **Scheme 2-34**.



Scheme 2-34 *Ring formation sequence adjustment from D-B-C to D-C-B*

Instead of constructing the indoline ring first (B ring), the bottom C ring could in principle be constructed before the B ring. This could bypass the reactive aminal issue, because the closed form of the aminal would likely be more stable. Following this idea, compound **2-30** and **2-31** were prepared by HATU reagent coupling of acid **2-27** with suitable alcohols with 50% and 79% yields respectively, **Scheme 2-35**.



a. alcohol I, HATU, DMAP, DIPEA, DMF; **b**. alcohol II, HATU, DMAP, DIPEA, DMF

Scheme 2-35 *Preparation of C-ring precursor **2-30** and **2-31***

Next, we hoped that compound **2-30** could participate in a 6-exo-dig ring formation reaction under Buchwald-Hartwig type cross coupling conditions[179–188], however, under many typical copper and palladium catalysed C-N bond formation conditions, either a fast decomposition of **2-30** under copper conditions or no conversion under palladium chemistry were observed, **Table 2-10**. Plausible factors contributing to this observed outcome were: the 2-bromoallyl ester structure, which might interrupt the metal insertion process; or the ester group oxygen atom might participate in the reaction; or the allyl acetate structure may be labile to Tsuji Trost type conditions[189–192].

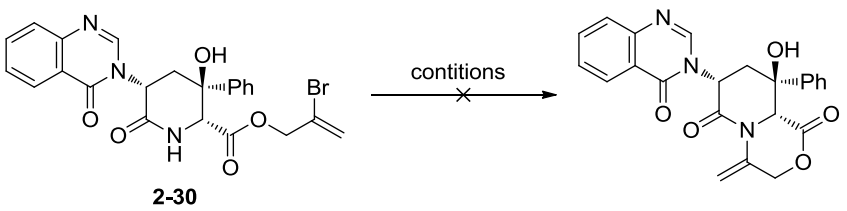
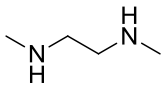
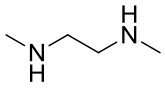
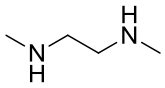
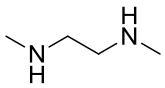
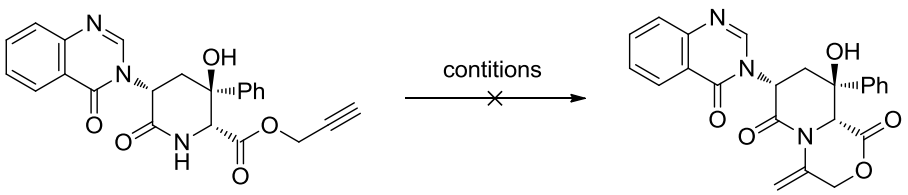


Table 2-10 *Attempted C ring formation by Buchwald-Hartwig type chemistry*

entry	metal[a]	ligand	base	solvent	temp. °C	outcome
1	CuI		K_2CO_3	THF	80	decomp.
2	CuI		K_2CO_3	Toluene	110	decomp.
3	CuI		Cs_2CO_3	THF	80	decomp.
4	CuI		CsOAc	DMSO	rt	decomp.
5	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF	80	NR
6	$Pd(dppf)_2$	X-Phos	Cs_2CO_3	THF	80	NR
7	$Pd(dba)_2$	X-Phos	Cs_2CO_3	THF	80	NR
8	$Pd(dba)_2$	X-Phos	Cs_2CO_3	toluene	110	decomp.
9	$Pd(dba)_2$	X-Phos	K_2CO_3	THF	80	NR

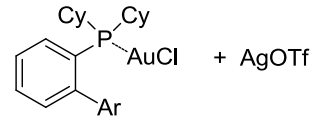
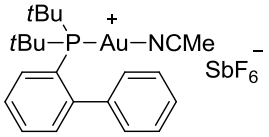
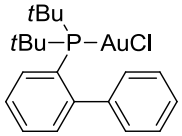
a. CuI 1.2 eq.; Pd 10% mmol

In an alternative approach, propargyl ester was introduced to carry out a 6-exo-trig ring formation with transition metals, particularly silver and gold, **Table 2-11**. However, the desired C-N bond formation was never observed. In **entry 3, 4** and **5**, the starting material was directly recovered after flash column chromatography, whilst in **entry 1** and **2**, acid base wash were required to recover the starting material. It is plausible that substrate **2-31** has too many coordination spots, thus hindering the Au/Ag catalyst system[193–198] from working properly.



2-31

Table 2-11 *Attempted C ring formation by Au/Ag catalysed cycloisomerization*

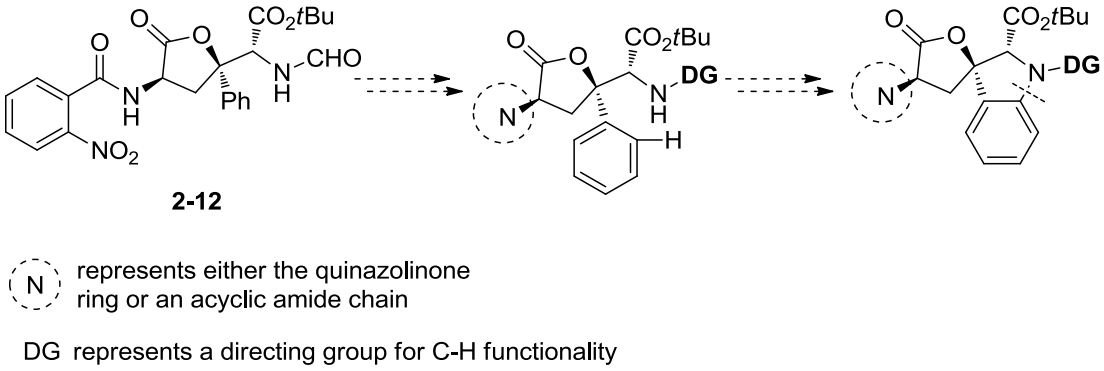
entry	catalyst	solvent	outcome
1	 + AgOTf Ar = 2,6-(*i*PrO)$_2$-C$_6$H$_3$	toluene or CH_2Cl_2	NR
2		toluene or CH_2Cl_2	NR
3	Ph_3PAuCl + AgOTf	CH_2Cl_2	NR
4	 + AgOTf	CH_2Cl_2	NR
5	$AgBF_4$	CH_2Cl_2	NR

Previous outcomes in this section indicated that the sequence starting with lactam core was very challenging, especially as the aminal moiety was too reactive under various kinds of conditions to be converted into desired products. In addition, the functional group rich nature of the substrates (alcohol, amides, ester and heteroatoms) made the approach even harder by imposing extra constraints on a variety of reactions.

Based on our previously accumulated knowledge and encountered challenges in the lactam core approach, we decided to give an equal chance for the parallel lactone approach towards tryptoquivaline studies in the following section.

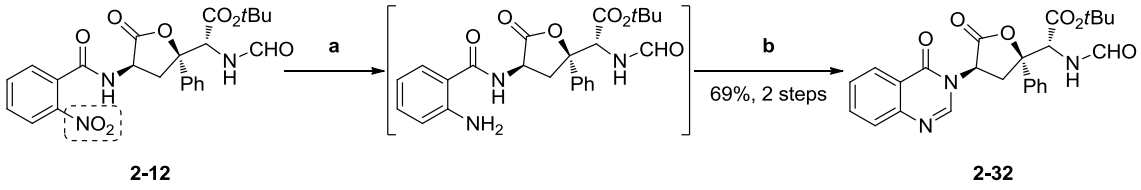
2.2.5 Lactone approach towards tryptoquivalines

The lactone core provided another starting point to continue the synthetic study, which ultimately could lead to tryptoquivalines spirolactone structures. **Scheme 2-36** highlighted the intended transformations.



Scheme 2-36 *Plan towards tryptoquivalines spirolactone indoline core*

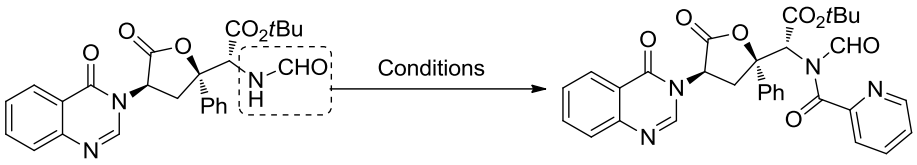
Starting from lactone **2-12**, the quinazolinone ring was formed in the first instance to minimize potential side reactions in later steps. As shown in **Scheme 2-37**, the nitro group was reduced under a hydrogen atmosphere with palladium on charcoal, and then treated with trimethyl orthoformate catalysed by pTSA to close the quinazolinone ring providing **2-32** with 69% yield over 2 steps.



Scheme 2-37 *Quinazolinone ring formation from **2-12***

The next step was to convert the formamide into a picolinamide, which would be a desirable directing group for C-H activation[161–164]. First of all, several coupling conditions were employed to install a carbonyl group in the presence of a formamide, **Table 2-12**. Outcomes from **Table 2-12** indicated the reactivity of the formamide nitrogen atom on **2-32** was quite low under mild conditions, and the product stability was poor as well. In

addition, when extended the reaction time with T3P reagent, decomposition of the starting material was observed.



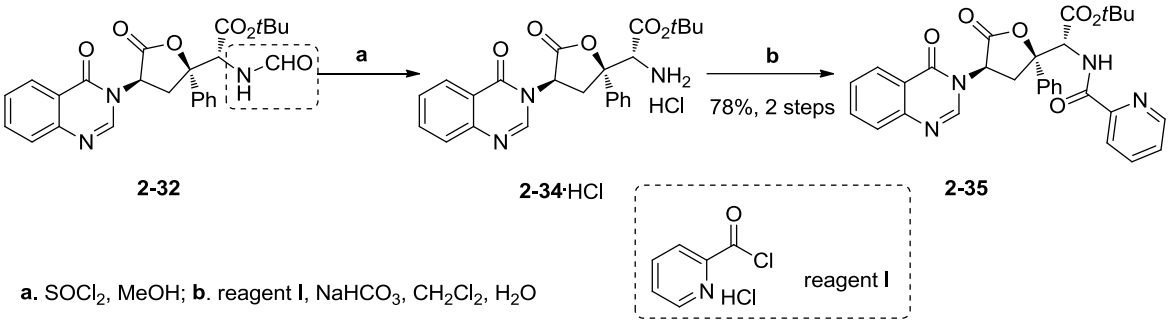
2-32 **2-33**

Table 2-12 *Preparation of imide **2-33***

entry	reagent	reactant	additive	result
1	DIPEA	2-pyridinecarbonyl chloride	DMAP	NR
2	HATU / DIPEA	2-picolinic acid	DMAP	NR
3	DCC	2-picolinic acid	NA	trace
4	DCC	2-picolinic acid	DMAP	7%[a]
5	T3P	2-picolinic acid	NA	decomp.[b]
6	TBTU / DIPEA	2-picolinic acid	DMAP	NR
7	PyBroP / DIPEA	2-picolinic acid	NA	trace

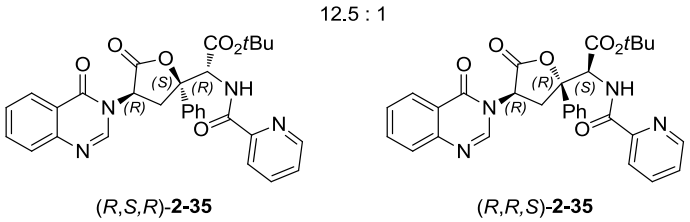
a. decomposing at rt, 1H NMR obtained; **b**. suspected dehydration followed by other side reactions

Alternatively, the formamide could be removed under methanolic hydrogen chloride conditions, and the resulting primary amine formed the HCl salt *in situ* (characterised in freebase form **2-34**). Subsequent biphasic Schotten-Baumann acylation conditions, where primary amine hydrochloride salt and 2-pyridinecarbonyl chloride hydrochloride reacted in the presence of sodium hydrocarbonate in a mixture of water and CH_2Cl_2, was used to afford picolinamide **2-35** smoothly with 78% yield over 2 steps, **Scheme 2-38**.



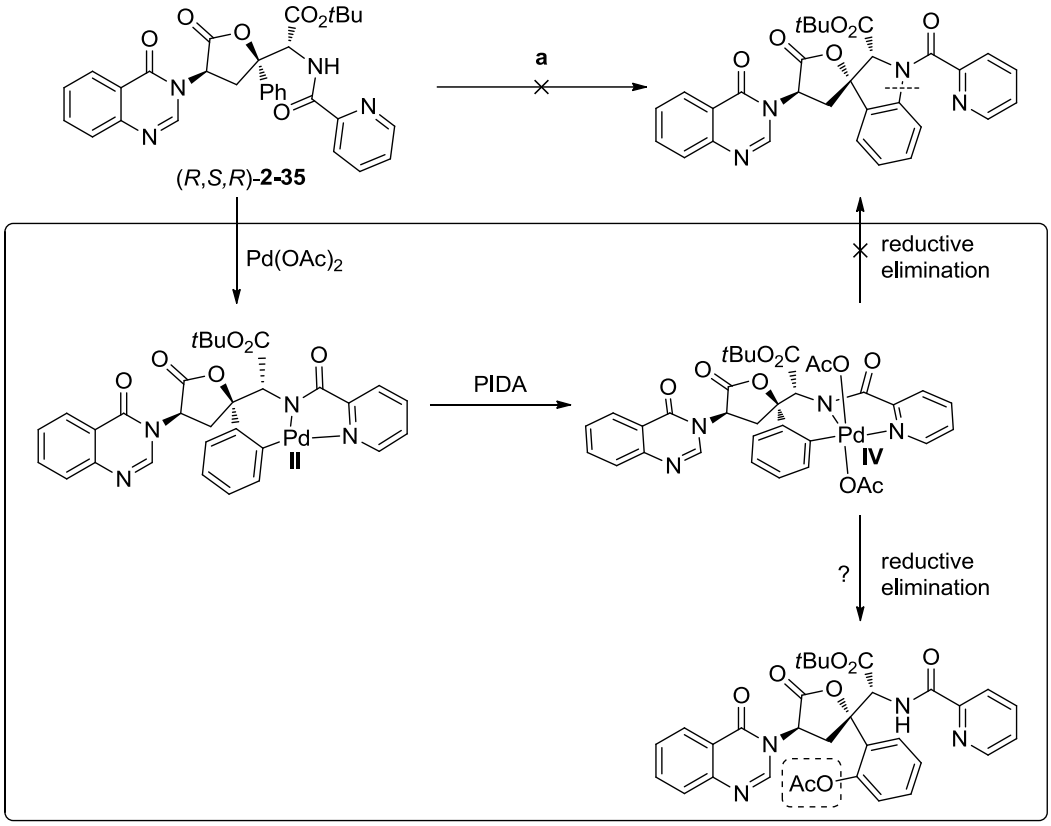
Scheme 2-38 *Preparation picolinamide **2-35***

As described in this chapter **Section 2.2.2**, the catalytic stereoselective aldol reaction afforded oxazoline **2-10** as a 12.5:1 pair of diastereomers (*R*,*S*,*R* : *R*,*R*,*S*). As such, all subsequently synthesized compounds were isolated as 12.5:1 mixture of diastereomers. Interestingly, after picolinamide installation, the pair of diastereomers became separable by silica gel chromatography, **Scheme 2-39**. Accordingly, the following reactions involving (*R*,*R,S*)-**2-35** were carried out on the single diastereomers.



Scheme 2-39 *Diastereomer separation*

Finally, C-H activation on (*R*,*S,R*)-**2-35** was explored using the reported conditions (palladium acetate with PIDA in toluene)[163], **Scheme 2-40**. LCMS monitoring indicated a seemingly small amount of new compound generated in the reaction (MS suggested a phenyl-OAc compound, plausibly generated in the reductive elimination step in an undesired way) along with the majority of starting material intact. However, no successful isolation method was found to purify the mixture in order to perform further analysis, even the preparative-HPLC cannot separate the mixture properly. This result suggested us to move forward to alternatives to continue the synthetic study on these natural products.



a. $Pd(OAc)_2$, $PhI(OAc)_2$, toluene, 80°C

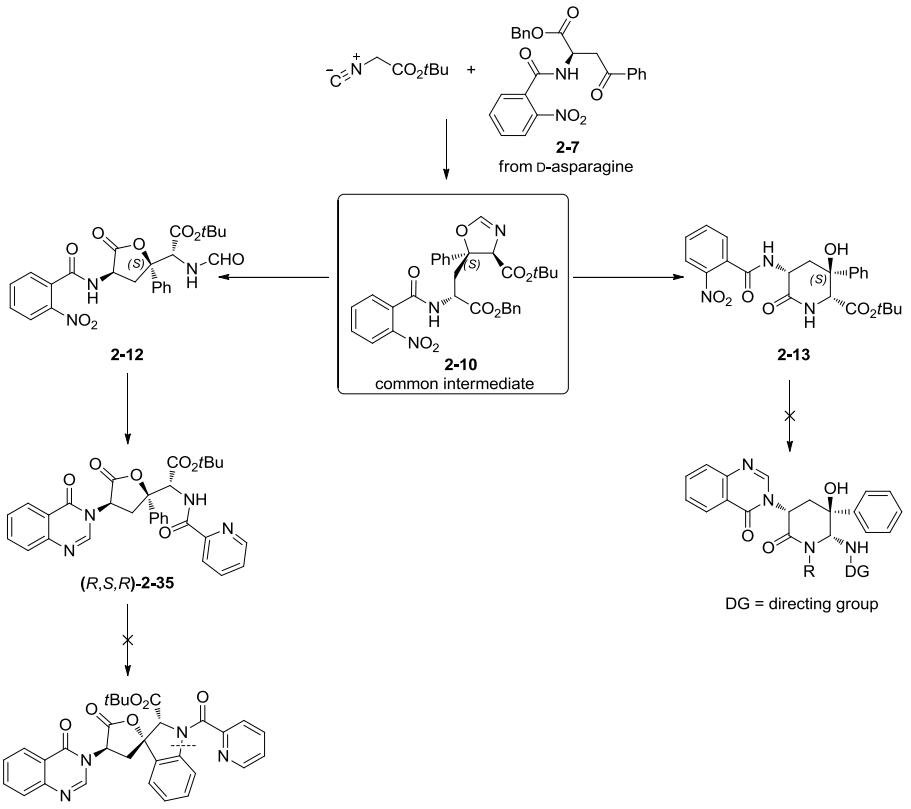
Scheme 2-40 *Attempted but unsuccessful palladium catalysed C-H activation*

2.3 Conclusion

In this chapter, chiral phenyl ketone **2-7** was successfully synthesized, starting from D-asparagine, as the substrate for a catalytic stereoselctive isocyanoacetate aldol reaction. This chemistry had been developed previously in the group and applied on a wide range of simple substrates. Pleasingly, while the substituted chiral phenyl ketone **2-7** was a much more complicated substrate than those previously reported, the catalytic stereoselective aldol reaction performed at a satisfying level to produce the desired highly substituted chiral oxazoline **2-10**. In the following divergent approach, oxazoline **2-10** was subsequently hydrolysed to either the amino alcohol form or the hydroxyl formamide form.

Thereafter, for the purpose of generating a divergent approach the lactam **2-13** and lactone **2-12** were constructed separately. In a couple of additional steps, from the lactone core **2-12**, a structurally advanced and complex C-H activation reaction substrate (*R*,*S*,*R*)-**2-35** was obtained in order for us to investigate C-N bond formation reactions. The C-H activation reaction we employed is still under development, and we believe in near future it could enable C-N bond formation on very complex substrates.

Moreover, taking advantage of the complex substrates that have been synthesized during this work, starting from lactam **2-13** a variety of ring forming reactions have been explored on specific lactam cores in order to get closer to the natural chaetominine's fused ring system. This work led to some in-depth understanding of subtle structural effects on such ring forming reactions.



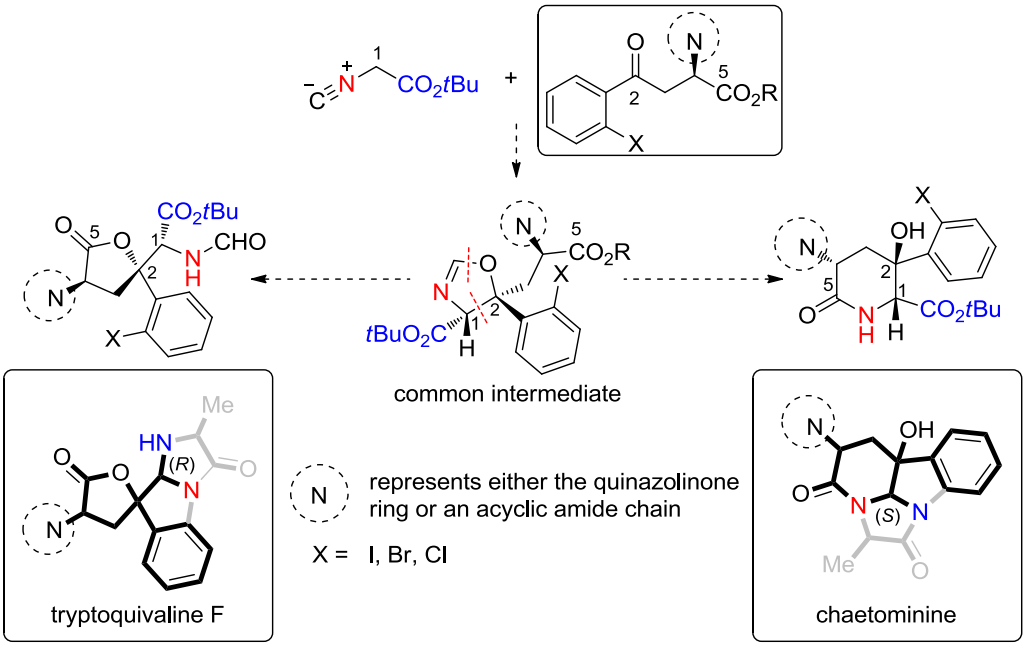
Scheme 2-41 *Chapter summary*

Afterwards, previously proposed C-H activation indoline construction was replaced by a Buchwald-Hartwig type C-N bond chemistry in next chapter. Detailed synthetic study was largely focused on the direction towards tryptoquivaline cores.

Chapter 3. The second-generation synthetic approach

3.1 Retrosynthetic analysis

An alternative synthetic route based on a Buchwald-Hartwig type C-N coupling approach was then considered in order to build the indoline C-N bond. Accordingly, a halogen atom required installation onto the phenyl ring much earlier in the overall synthetic sequence, **Scheme 3-1**.



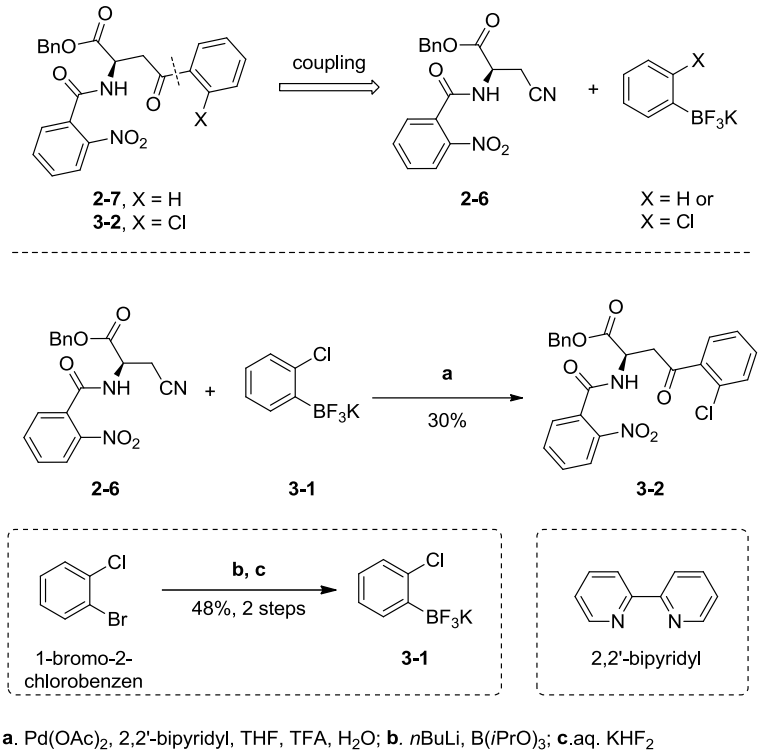
Scheme 3-1 *Overview of the revised general synthetic sequence*

3.2 Results and discussion

3.2.1 Halogen substituted aryl ketone substrate synthesis

The most straightforward way to introduce a halogen atom on the aromatic ring of **2-7** would be via the phenyltrifluoroborate in the Pd catalysed addition reactions to the

nitrile group of **2-6**. Therefore, the chloride substituted potassium phenyltrifluoroborate was prepared and the coupling conditions were investigated, **Scheme 3-2**.

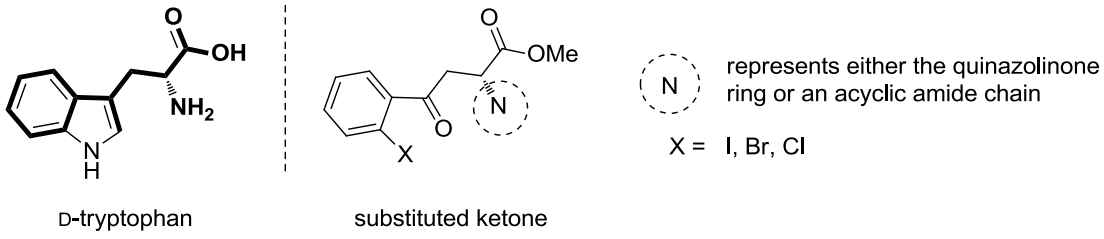


a. $Pd(OAc)_2$, 2,2'-bipyridyl, THF, TFA, H_2O; **b**. *n*BuLi, $B(iPrO)_3$; **c**.aq. KHF_2

Scheme 3-2 *Preparation of chloride substituted ketone **3-2***

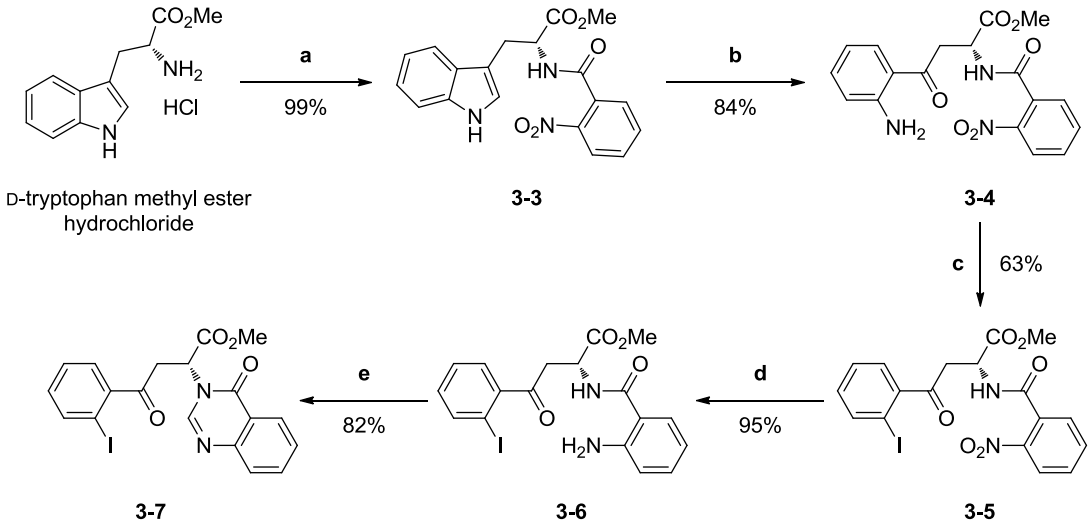
High quality potassium 2-chloro-phenyltrifluoroborate **3-1** was synthesized and recrystallized on multi gram scale with 48% yield over 2 steps. However, the previously optimized palladium catalysed coupling conditions afforded ketone **3-2** in only 30% yield. The *ortho* substitution on the phenyl ring adversely affected the coupling yield.

Accordingly, an alternative *de novo* route, inspired by the structural analogy between the desired ketone skeleton and D-tryptophan was designed with the hope of overcoming the low yield described above, **Scheme 3-3**.



Scheme 3-3 *Similarity between D-tryptophan and desired ketone substrates*

Based on the observation presented in **Scheme 3-3**, commercially available D-tryptophan methyl ester hydrochloride was used as the starting material in this route, **Scheme 3-4**.



D-tryptophan methyl ester hydrochloride

a. 2-nitrobenzoyl chloride, $NaHCO_3$, CH_2Cl_2, H_2O; **b.** $NaIO_4$, MeOH / H_2O, then $SOCl_2$, MeOH; **c.** HBF_4, *t*$BuNO_2$, EtOH, then KI, Acetone; **d.** Fe, NH_4Cl, EtOH, H_2O; **e.**pTSA, $CH(OMe)_3$, CH_3OH

Scheme 3-4 *Preparation of iodide substituted ketone **3-7***

This sequence started with Schotten-Baumann acylation conditions to afford amide **3-3** with 99% yield. Next, the indole ring was subsequently subjected to an oxidative cleavage with sodium periodate to afford a mixture of free aniline **3-4** and its formamide derivative, which upon methanolysis with methanolic HCl, yielded aniline **3-4** with 84% overall yield. While ozonolysis was also examined to cleave the indole ring into ketone form, it appeared to be a less selective transformation which generated more side products and overall a lower yield, and therefore was not chosen for the later scale up. Diazotisation with *tert*-butyl nitrite and subsequent treatment with KI afforded iodoarene **3-5** with 63% yield. The nitro group **3-5** was reduced to give **3-6** using iron powder in the presence of ammonium chloride, a method that was sufficiently mild to leave the previously installed iodide intact. No further purification was required for the reduction product **3-6**, and

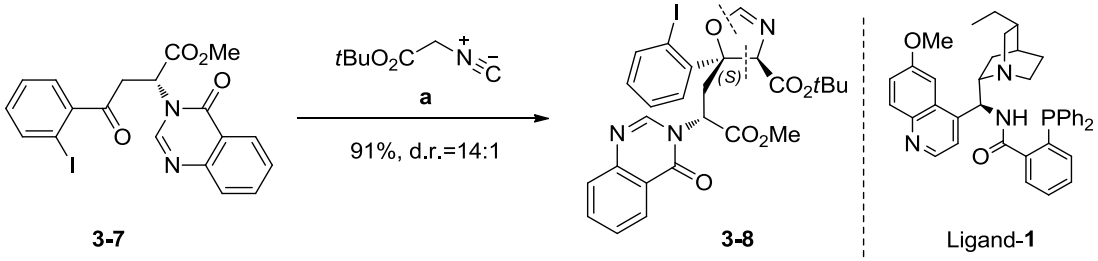
subsequently treated it with trimethyl orthoformate and *p*-toluenesulfonic acid lead to the efficient formation of the quinazolinone ring of the desired ketone **3-7** in 82% yield.

In summary, this smooth sequence successfully prepared the iodide substituted aryl ketone **3-7**, which was desired as a substrate for the catalytic stereoselective isocyanoacetate aldol reaction.

3.2.2 Catalytic stereoselective isocyanoacetate aldol reaction with aryl ketone 3-7

Our previous studies discussed in **Chapter 2** established the producible catalyst-controlled stereochemical outcome of the silver catalysed stereoselective isocyanoacetate aldol reaction.

Accordingly, the isocyanoacetate ester aldol reaction was carried out on iodide ketone **3-7**, using the silver(I)-cinchona-derived amino phosphine catalytic system to construct the oxazoline ring, **Scheme 3-5**. The reaction proceeded smoothly under the optimized conditions as shown in **Table 2-5 - entry 6**, but with a shorter reaction time. In 48 hours, the reaction gave almost full conversion of the starting material with much higher yield (91%) of the expected oxazoline **3-8**, and an improved dr ratio of 14:1.



3-7 **3-8** Ligand-**1**

a. Ligand-**1**, AgOAc, EtOAc, 0 ^{o}C, 48h;

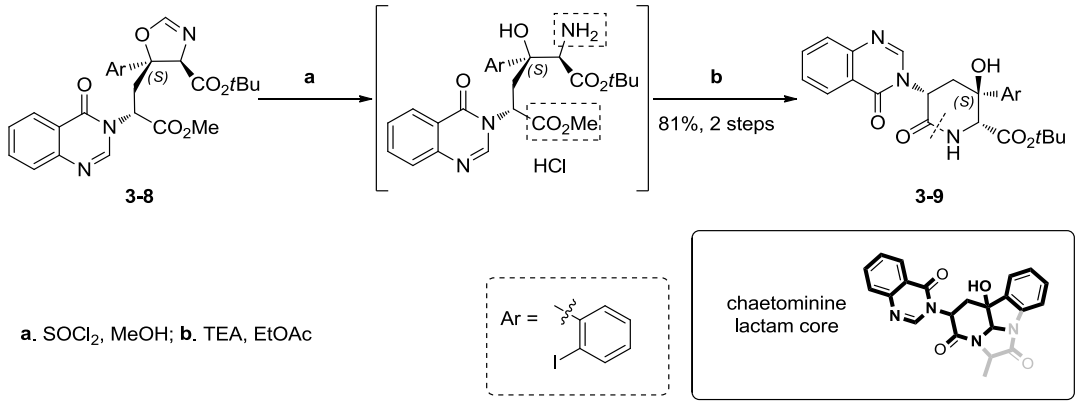
Scheme 3-5 *Catalytic enantioselective ketons aldol reaction on **3-7***

Ketone **3-7** with the quinazolinone ring intact, possessed fewer hydrogen bond donors and acceptors in comparison with ketone **2-7** from **Chapter 2**. Since the silver(I), cinchona-derived aminophosphine catalytic system is supposed to benefit from the hydrogen bonding effect from cinchona derivative (as demonstrated in **Chapter 1 Scheme 1-19/20**), fewer hydrogen bond donors and acceptors on ketone **3-7** were plausibly the major contributor towards the improved yield and stereoselectivity. Indirectly, this observation provided evidence to support the DFT computations which indicated the H-bond effect[52], on a real substrate.

3.2.3 Oxazoline hydrolysis and divergent ring formation

Hydrolysis of the iodide substituted oxazoline **3-8** could be carried out under different conditions to allow access to either γ-lactone or δ-lactam core.

In the first instance, oxazoline **3-8** was treated with methanolic HCl solution, which fully hydrolysed the oxazoline ring to generate a putative amino ethanol intermediate, which under basic conditions efficiently closed to afford δ-lactam **3-9** in 81% yield in a 2 step procedure.



Scheme 3-6 *δ-Lactam **3-9** construction*

Secondly, oxazoline **3-8** was treated with 1 N HCl solution in THF which provided amino ethanol **3-10** in 99% yield, and subsequent lactone ring formation was studied under various conditions in order to afford γ-lactone **3-11**, as shown in **Table 3-1**. Surprisingly, lactone formation proved to be challenging despite the structural similarities between **3-11** and **2-12**. Mildly acidic catalytic conditions, **entry 1-5**, failed to give any conversion; **entry 6/9** appeared too harsh as decomposition of **3-10** was observed; basic conditions in **entry 10** afforded **3-11**'s C7 epimer **3-12** (see experimental); pleasingly, however, gentle heating of **3-10** in toluene containing acetic acid for 3 days afforded **3-11** in 70% yield. It is most likely the *o*-iodide substituent caused steric crowding on the tertiary alcohol, which hampered the desired lactonization.

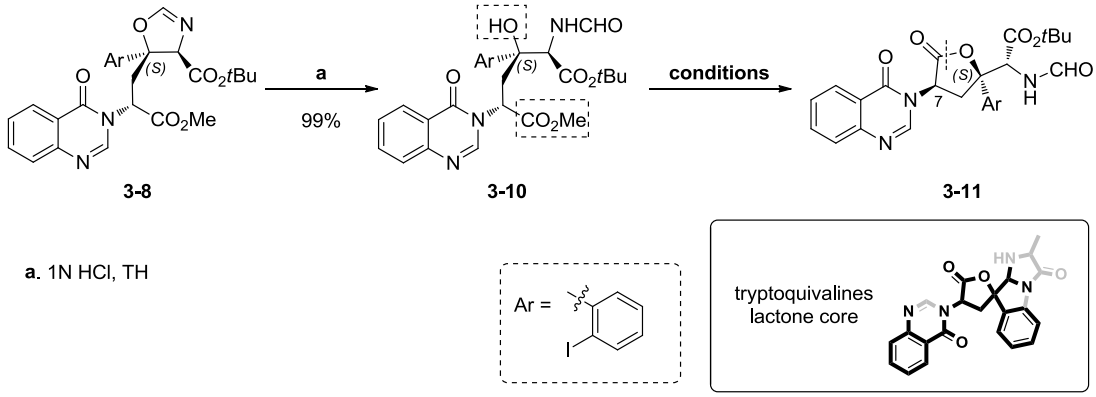


Table 3-1 *γ-Lactone **3-11** construction*

entry	catalyst	solvent	temp. °C	time	outcome
1	CSA	CH_2Cl_2	rt	overnight	NR
2	CSA	CH_2Cl_2	45	overnight	NR
3	pTSA	CH_2Cl_2	rt	overnight	NR
4	pTSA	CH_2Cl_2	45	overnight	NR
5	H_2SO_4	CH_2Cl_2	45	overnight	NR
6	H_2SO_4	toluene	90	overnight	SM decomp.
7	AcOH	toluene	90	overnight	40%
8	AcOH	toluene	75	overnight	40%
9	AcOH	toluene	75	3 days	70%
10	K_2CO_3	toluene	70	4 h	55%, epimer[a]
11	NA	silica	100, high vac	3 h	SM decomp.

a. alpha position of the formed lactone was epimerized under the indicated conditions, affording **3-12** as major product (see experimental section)

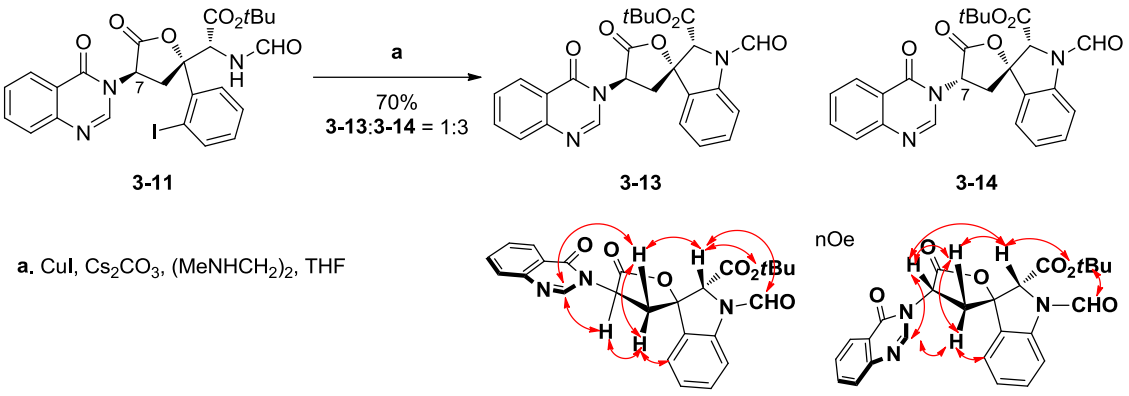
In summary, in this section both the desired iodide substituted δ-lactam **3-9** and γ-lactone **3-11** cores were successfully synthesized allowing further synthetic investigation.

3.2.4 Ullmann type C-N bond formation

Based on our previous knowledge and experiences (see **Chapter 2**), the lactone core became the priority to be explored in this chapter. The main purpose of this section was to build the C-N bond in order to generate the spirolactone structure of tryptoquivalines.

In our first attempt to build the C-N bond from compound **3-11**, under the conditions of CuI, Cs_2CO_3 and the amine ligand (*N*,*N*'-dimethylethylenediamine) in 1 hour reaction time, both the desired spirolactone **3-13** and its C7 epimer **3-14** were afforded with a 1:3 ratio respectively and in 70% overall yield, before preparative-HPLC separation. The relative stereochemical configures of compounds **3-13** and **3-14** were determined by

nOe analysis. Based on the outcomes from the above reaction, the undesired compound **3-14** appeared more thermodynamically stable than **3-13**, **Scheme 3-7**.



Scheme 3-7 *Preparation of spirolactone core*

Subsequent optimization efforts were undertaken to minimize the epimerization of spirolactone **3-13**. It should be noted that the epimerization may have happened on lactone **3-11** before forming the indoline C-N bond. Accordingly, a series of C-N coupling conditions were examined, **Table 3-2**.

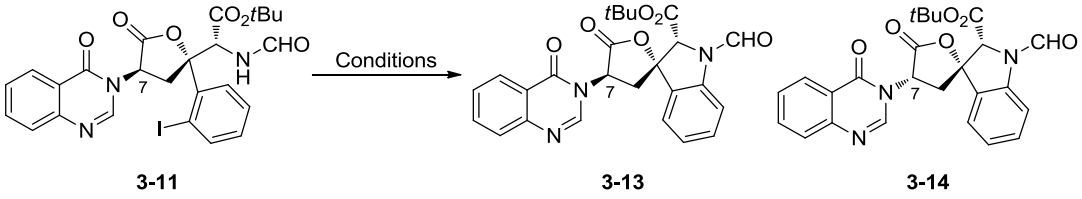


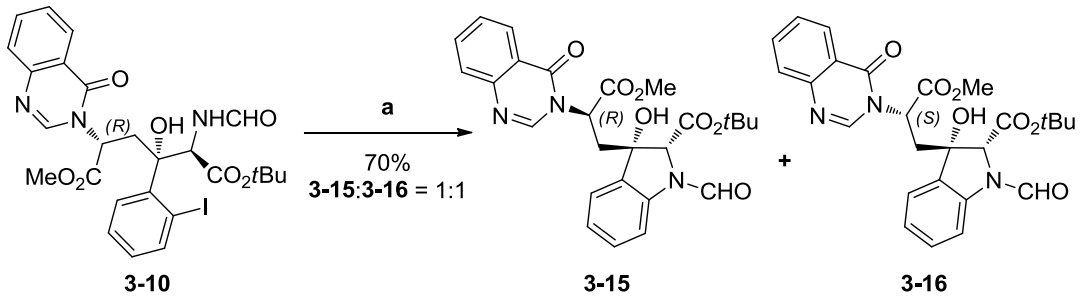
Table 3-2 *Optimisation of C-N coupling conditions screening*

Entry	Metal	Base	Solvent	Yield	Ratio 3-13:3-14
1	CuI	CsOAc	DMSO	90%	1:5
2	CuI	CsOAc	THF	~5%	1:5
3	CuI	KOAc	DMSO	90%	1:5
4	CuI	NaOAc	DMSO	85%	1:1
5	CuI	LiOAc	DMSO	85%	1:1

6	CuI	$Mg(OAc)_2 \cdot 4H_2O$	DMSO	70%	20:1
7	CuI	MgO	DMSO	0%	--
8	CuI	NaOAc / AcOH	DMSO	10%	pure **3-13**
9	CuOAc	NaOAc / AcOH	DMSO	trace	--

dr ratio was determined by HPLC analysis

All conditions requiring strong base, heating and long reaction times were deselected, and hence no palladium catalyst was investigated. Initially, the attempt using CsOAc/CuI system in DMSO afforded the coupled pair of diastereomers within 15 min at room temperature (**Table 3-2**, **entry 1**). It was found that dimethyl sulfoxide afforded the best yields, and the acetate counterion was also crucial. When the base cation was varied from cesium to lithium, the dr ratio showed significant improvement from 1:5 in **entry 1** to 1:1 in **entry 5** whilst the yields were comparable. It was possible that the acetate anion was not only acting as a base, but also as a ligand for Cu, as unionizable bases, such as magnesium oxide in **entry 7**, did not promote the reaction. When the reaction was placed in a buffer of sodium acetate and acetic acid, the transformation proceeded in low yield but gave no epimerization (**entry 8**). The optimal conditions considering both yield and dr were found to be magnesium acetate tetrahydrate in DMSO to provide **3-13** with 70% yield and more than 20:1 dr ratio.

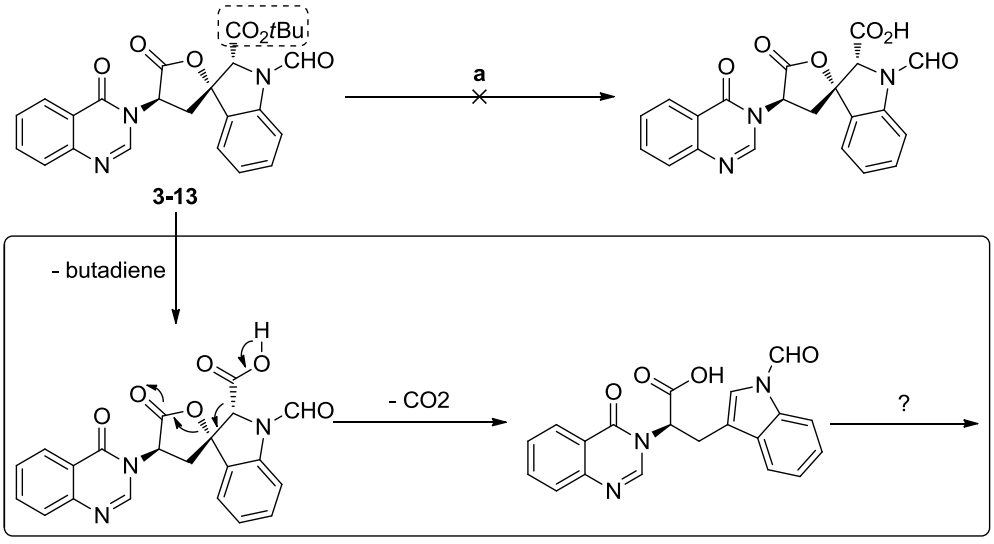


a. CuI, CsOAc, DMSO

Scheme 3-8 *C-N bond coupling on acyclic **3-10***

In order to better understand the epimerisation of spirolactones **3-13/14**, the cesium acetate conditions (**Table 3-2**, **entry 1**) were investigated on acyclic ester **3-10** to compare with the outcome from **3-11**, **Scheme 3-8**. The reaction proceeded to provide yield of 70%, and HPLC showed a 1:1 mixture of diastereomers **3-15** and **3-16**, which indicated that under these conditions epimerisation was taking place before and after constructing the spirolactone system. After preparative-HPLC separation, both isomers were isolated and characterized.

The next aim was the introduction of the last nitrogen atom of tryptoquivalines before using hopefully an elegant approach to form the last ring. Initially, we believed that either Hofmann degradation or Curtius rearrangement could be appealing. For both these approaches, conversion of the ester group into the corresponding carboxylic acid was required. However, this seemingly simple transformation did not occur as expected. When spirolactone **3-13** was treated with trifluoroacetic acid, it decomposed rapidly and completely. Although no major side product was isolated, we postulated that a decarboxylation and rearomatization sequence may have occurred, **Scheme 3-9**.



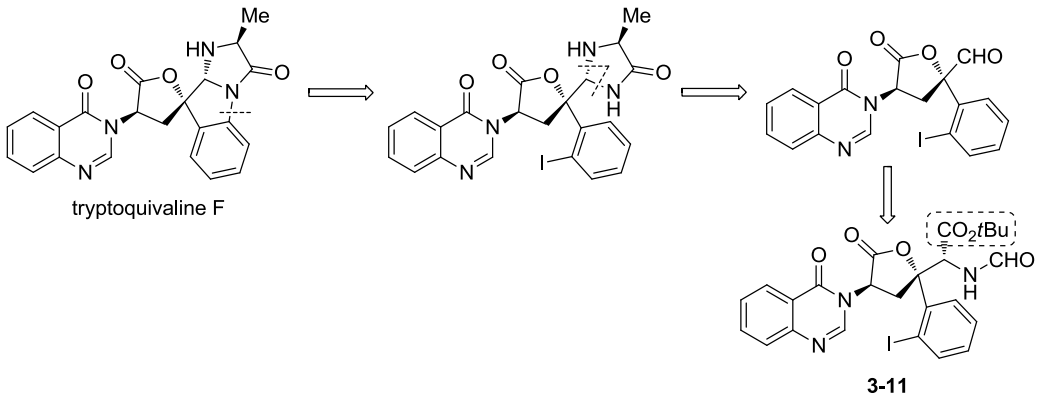
a. TFA, CH_2Cl_2, rt

Scheme 3-9 *Preparation of Hofmann degradation precursor with a carboxylic acid functionality*

In this section, the spirolactone **3-13** was successfully synthesized, however, the following step – the preparation of the precursor of Hofmann degradation - gave an undesired outcome. Generally, the synthetic route starting from lactone core was more attractive when compared with that from lactam core. However, the construction of the *N,N*-aminal moiety was not straightforward and required further efforts.

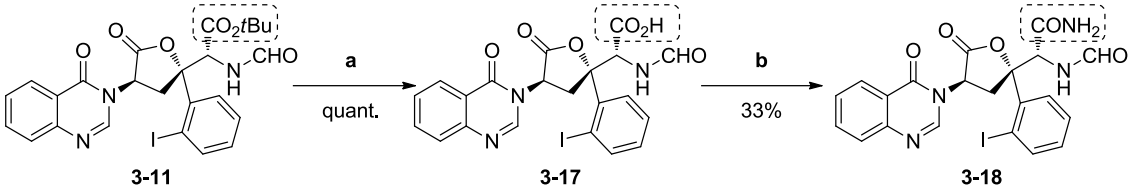
3.2.5 Introducing nitrogen atom from alanine

Previously we demonstrated that the *N,N*-aminal moiety was a challenge in the synthetic sequences starting from both lactam and lactone cores. But to construct the aminal moiety by forming an imidazolidinone ring before building the indoline ring in tryptoquivalines could be an alternative for this synthesis, **Scheme 3-10**.



Scheme 3-10 *Retrosynthetic analysis for* ***section 3.3.5***

Starting from lactone **3-11**, aldehyde precursor **3-18** was prepared in a two-step sequence. The *tert*-butyl ester was firstly removed with trifluoroacetic acid affording acid **3-17**, and the resulting acid functionality was coupled with ammonium hydroxide to provide amide **3-18** with 33% yield as the Hofmann degradation precursor, **Scheme 3-11**.

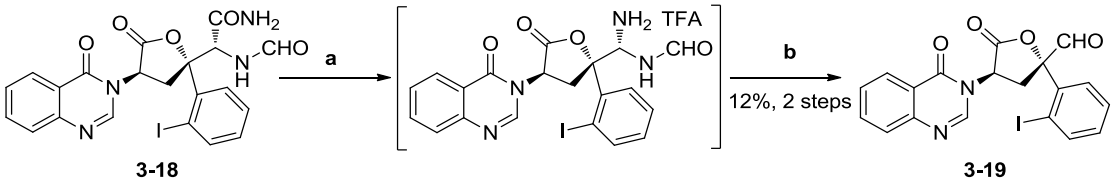


a. TFA, CH_2Cl_2; **b.** $ClCO_2Et$, NMM, then NH_4OH, THF

Scheme 3-11 *Preparation of aldehyde precursor **3-18** for Hofmann degradation*

The isolated yield in the conversion of **3-17** to **3-18** was low. This was possibly caused by the ammonium hydroxide reactant, which was too strong and able to destroy the spirolactone core (for comparison, the same conditions were investigated on lactam-acid **2-14** and provided amide **2-15** with 85% yield, **Scheme 2-16**).

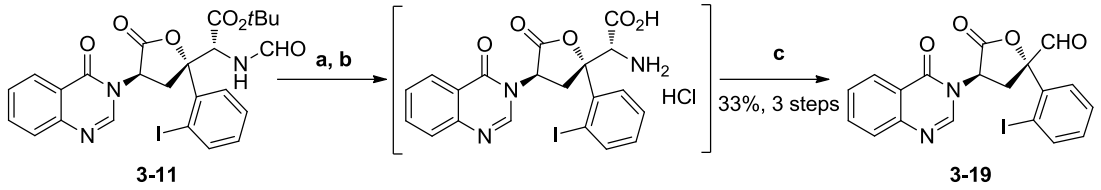
Amide **3-18** was subsequently treated with [bis(trifluoroacetoxy)iodo]benzene (PIFA) under mild Hofmann degradation conditions, and the crude *N,N*-aminal intermediate was immediately hydrolysed with concentrated hydrochloric acid to afford aldehyde **3-19** in 12% yield, **Scheme 3-12**.



a. PIFA, MeCN, H_2O; **b.** con.HCl

Scheme 3-12 *Preparation of aldehyde **3-19***

In order to improve the yield, an alternative approach was employed to avoid the *N,N*-aminal intermediate, where lactone **3-11** was directly converted into an amino acid intermediate under two continuous acidic conditions in the first instance, and subsequently subjected to an oxidative cleavage with PIFA to afford aldehyde in 33% yield in a one pot sequence, **Scheme 3-13**.

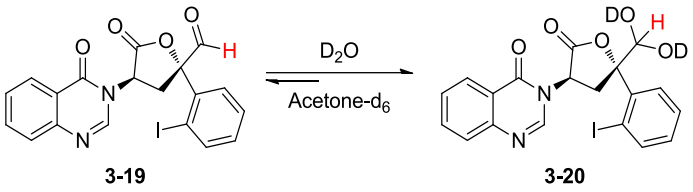


3-11 3-19

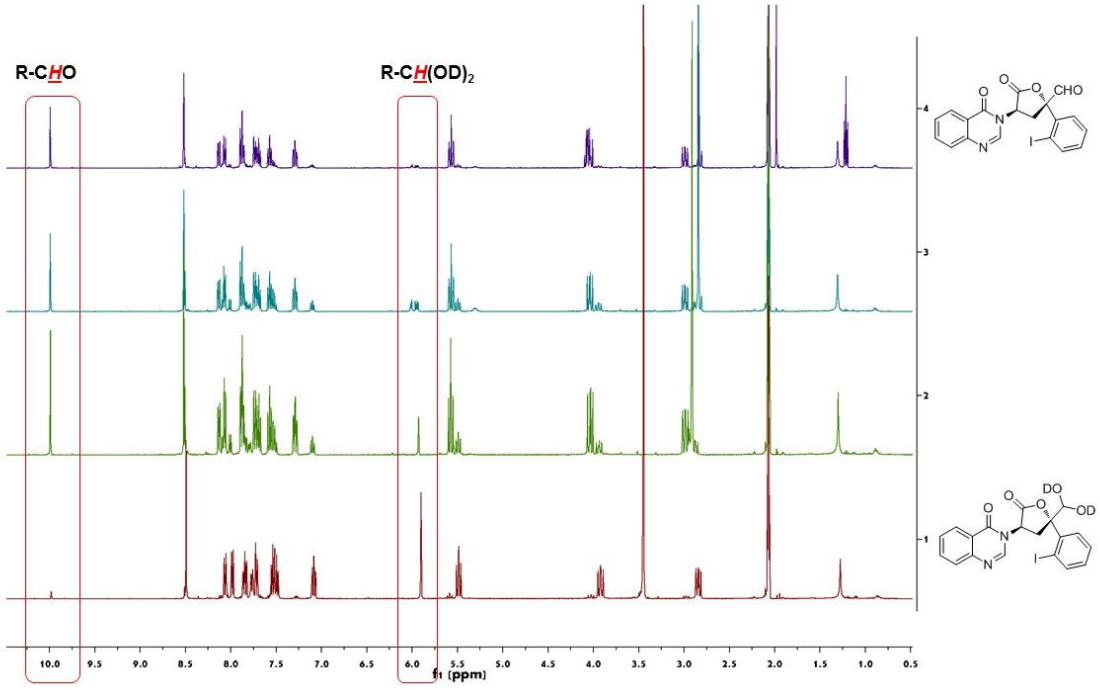
a. $SOCl_2$, MeOH; **b.** TFA; **c.** PIFA, MeCN, pH 7.0 buffer

Scheme 3-13 *Preparation of aldehyde **3-19** via oxidative cleavage conditions*

When characterizing aldehyde **3-19** in an NMR tube with Acetone-d_6, it showed interconversion with its hydrate form **3-20**. Aldehyde **3-19** eventually shifted towards the hydrate form **3-20** almost completely when a drop of deuterium oxide was added into the NMR tube, **Scheme 3-14**.



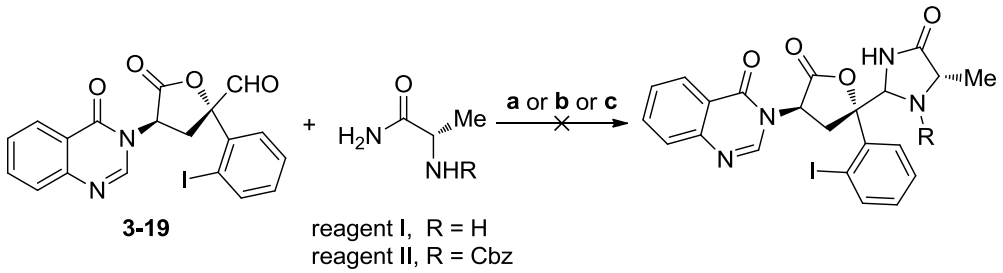
3-19 3-20



Scheme 3-14 *Aldehyde-hydrate interconversion*

These results indicated that the aldehyde could be quite reactive for the proposed condensation with alanine derivatives to give the imidazolidinone ring. However, no

desired product was found in condensation tests under either acidic or neutral conditions, **Scheme 3-15**.



a. reagent **I**, AcOH, toluene, 100 ^{o}C; **b**. reagent **II**, CSA, toluene, 100 ^{o}C; **c**. reagent **II**, toluene, reflux

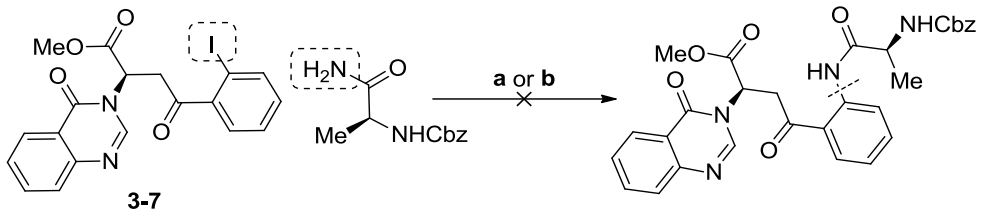
Scheme 3-15 *Unsuccessful attempts to prepare the imidazolidinone ring*

Furthermore, due to the poor yields over the whole sequence towards the preparation of aldehyde compound **3-19**, it became unaffordable to screen the condensation conditions thoroughly. Other methods to introduce the alanine counterpart will be further discussed in the following section.

3.2.6 Introduction of the Alanine

The problem of introducing the alanine unit late in the synthesis was described in the previous section. As a result, it was decided to introduce it much earlier and investigated as appropriate C-N coupling reactions to complete the synthesis of the necessary ring system.

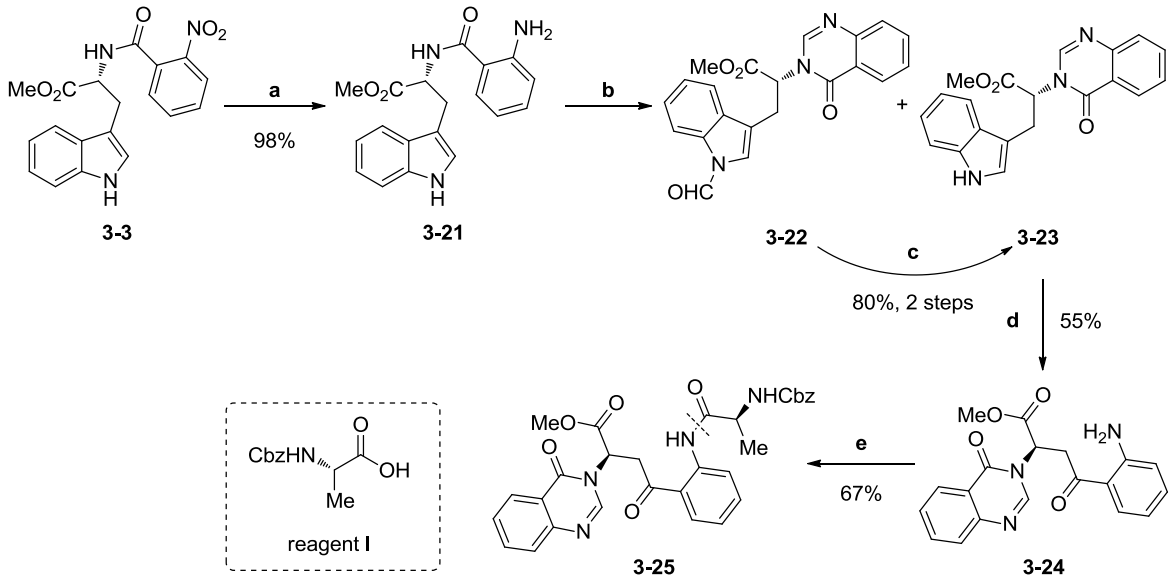
Firstly, an intermolecular Ullmann cross coupling between phenyl iodide ketone **3-7** and alanine derived amide was examined using copper catalysis under various conditions[199–202]. However, even under highly basic conditions and at high temperature, no desired coupling product was found, **Scheme 3-16**.



a. K_3PO_4, CuI, 1,4-dioxane, 100 °C; **b.** K_3PO_4, CuI, DMSO, 110-130 °C,

Scheme 3-16 *Attempted introduction of the alanine unit by cross coupling*

In a second attempt, the nitrogen atom from tryptophan was used for coupling to an alanine unit. This strategy required an adjustment of that synthesis sequence from the very beginning, as shown in **Scheme 3-17**.



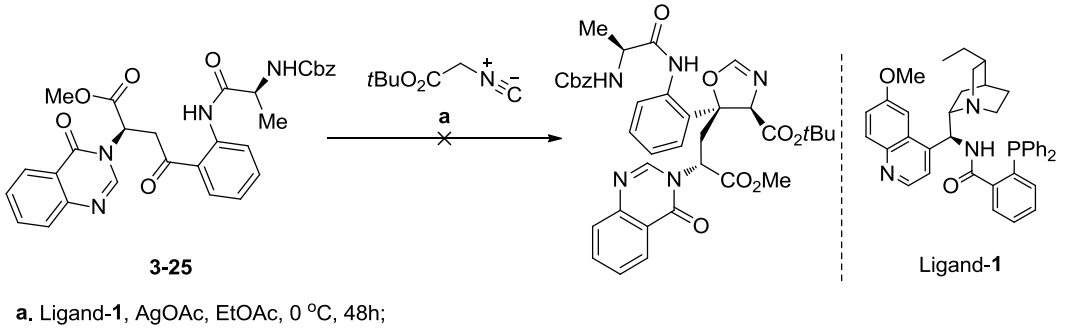
a. H_2, 10% Pd/C, MeOH; **b.** pTSA, MeOH, $CH(OMe)_3$; **c.** $SOCl_2$, MeOH; **d.** $NaIO_4$, MeOH, H_2O, then $SOCl_2$, MeOH; **e.** reagent **I**, DCC, CH_2Cl_2

Scheme 3-17 *Introduction of the alanine unit by amide bond formation*

Beginning from the tryptophan amide **3-3**, hydrogenation with gaseous hydrogen atmosphere catalysed by palladium on charcoal, followed by quinazolinone ring formation with trimethyl orthoformate occurred smoothly to provide formamide indole **3-22** and indole **3-23**, which were both isolated for characterization. In practice, the above mixture was treated directly with *in situ* generated hydrogen chloride methanolic solution to convert **3-22** into **3-23** with 80% yield over 2 steps. Subsequently, the Indole ring was

cleaved with sodium periodate to afford aniline **3-24** in 55% yield (aniline formamide was also present after reaction but was converted into aniline **3-24** with hydrogen chloride in methanol in one pot). DCC was found to be the most effective condensation reagent to provide the alanine coupled product **3-25** in 67% yield.

At this stage, the alanine chain moiety was introduced into the ketone **3-25** in a short sequence. Alanine containing ketone **3-25** was then investigated as a substrate in catalytic stereoselective aldol reaction under the previously used optimal conditions (**Table 2-5, entry 6**), **Scheme 3-18**.

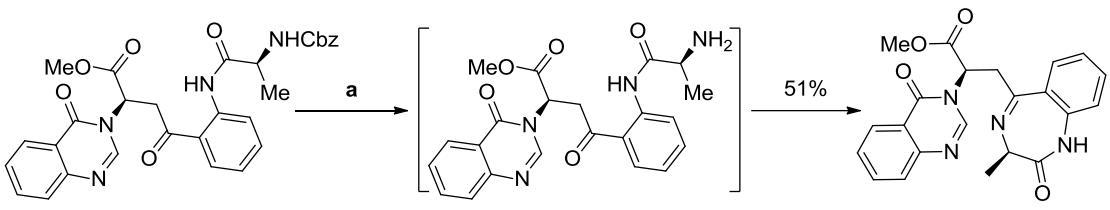


a. Ligand-**1**, AgOAc, EtOAc, 0 ^{o}C, 48h;

Scheme 3-18 *Catalytic stereoselective ketone aldol reaction on* ***3-25***

However, this time, it was observed that about 40% ketone starting material was consumed and no desired oxazoline product could be isolated from the reaction mixture. An explanation for the messy outcome could be that ketone **3-25** was too functionalized and the catalytic system was somehow poisoned by **3-25** possessing two more amide groups than **3-7** closely located to the ketone functionality.

To circumvent this, we firstly considered to convert the *N*-Cbz protected amine into an azido group in order to remove one amide functionality. However, when *N*-Cbz was deprotected under a hydrogen atmosphere with Pearlman's catalyst, the desired primary amine was not found. Instead, cyclized imine **3-26** was isolated in 51% yield, **Scheme 3-19**.

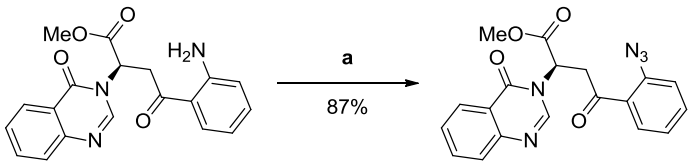


3-25 not isolatable **3-26**

a. $Pd(OH)_2$, H_2, MeOH

Scheme 3-19 *Cbz deprotection of* ***3-25***

As an alternative potential solution, the alanine moiety on **3-25** was substituted by an azido group as a masked nitrogen atom which could later be transformed into an amine group and allow the introduction of the alanine component - an azide forming reaction involving *tert*-butyl nitrite and TMS azide was investigated on aniline **3-24** and pleasingly afforded aryl azide ketone **3-27** in 87% yield, **Scheme 3-20**.

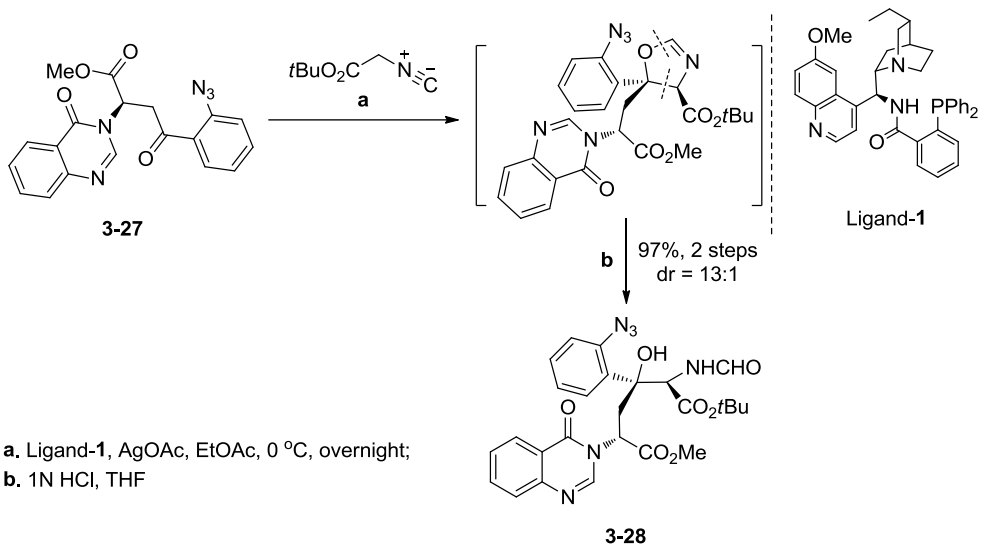


3-24 **3-27**

a. *t*BuONO, $TMSN_3$, MeCN

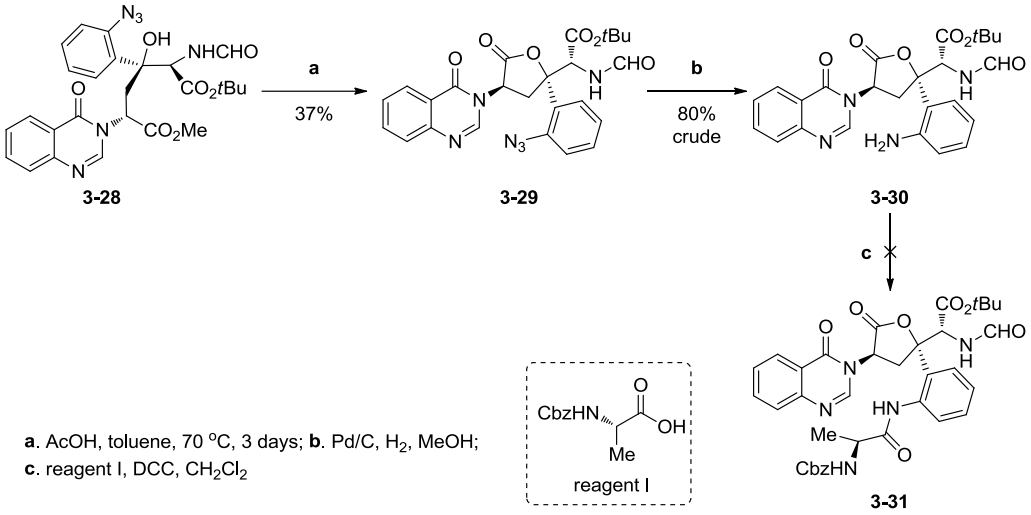
Scheme 3-20 *Preparation of azido ketone* ***3-27***

Next, the catalytic stereoselective isocyanoacetate aldol reaction was investigated on ketone **3-27**. Pleasingly, the reaction took place smoothly under the previously described conditions (**Table 2-5**, **entry 6**), and the resulting oxazoline intermediate was immediately hydrolysed with 1 N hydrogen chloride to provide hydroxyl formamide **3-28** in 97% yield and 13:1 dr for two steps, **Scheme 3-21**.



Scheme 3-21 *Catalytic enantioselective isocyanoacetate aldol and subsequent hydrolysis*

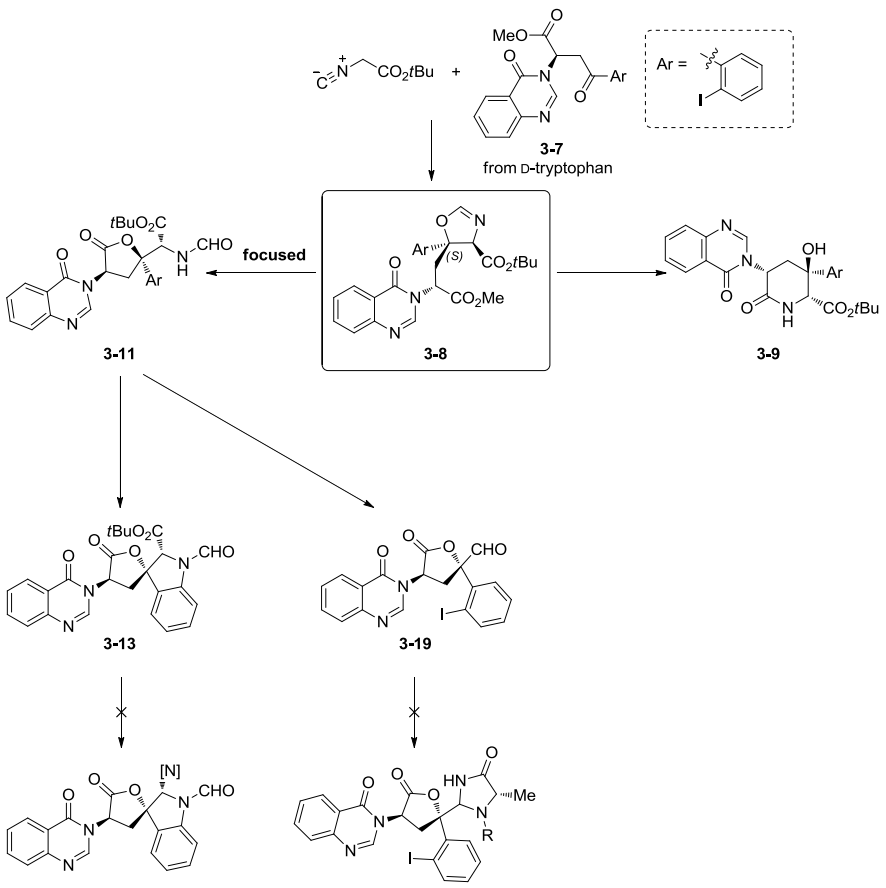
Hydroxyl formamide **3-28** was converted to azido lactone **3-29** in 37% isolated yield (with 35% recovery of starting material **3-28**) under acetic acid catalysed conditions in hot toluene (70 °C), **Scheme 3-22**. Interestingly, the azide group did not tolerate relatively high temperatures (70°C) for long reaction times. With lactone **3-29** in hands, the azide group was reduced under a hydrogen atmosphere with palladium on charcoal to afford aniline **3-30**. Upon attempted purification by flash column chromatography on silica gel, complete decomposition of aniline **3-30** was observed, therefore, alanine **3-30** was characterized as a crude product and amide coupling with alanine was performed on crude **3-30** after hydrogenation. However unfortunately, the subsequent mild coupling conditions (DCC) only gave undesired complex outcomes. Aniline **3-30** was also found to be sensitive towards base conditions, such TEA and DIPEA, and this fact further limited optional coupling reagents that could be used on **3-30**.



Scheme 3-22 *Unsuccessful preparation of alanine lactone **3-31***

3.3 Conclusion

In this chapter, iodide substituted chiral phenyl ketone **3-7** was synthesized concisely, and the catalytic stereoselective aldol reaction was carried out on it pleasingly affording oxazoline **3-8** with good yield and dr. Hydrolysis conditions transformed **3-8** into hydroxyl formamide which was further transformed into lactam **3-9** and lactone **3-11** respectively. Due to limited time, we focused on the synthetic route starting from lactone **3-11**. Buchwald-Hartwig coupling reaction constructed the [5,5]spirolactone **3-13** prevalent in the tryptoquivalines, but subsequent deprotection of the *tert*-butyl ester decomposed the advanced structure. Several alternative protocols were explored on intermediate **3-11**, but failed to move the synthesis forward, **Scheme 3-23**.

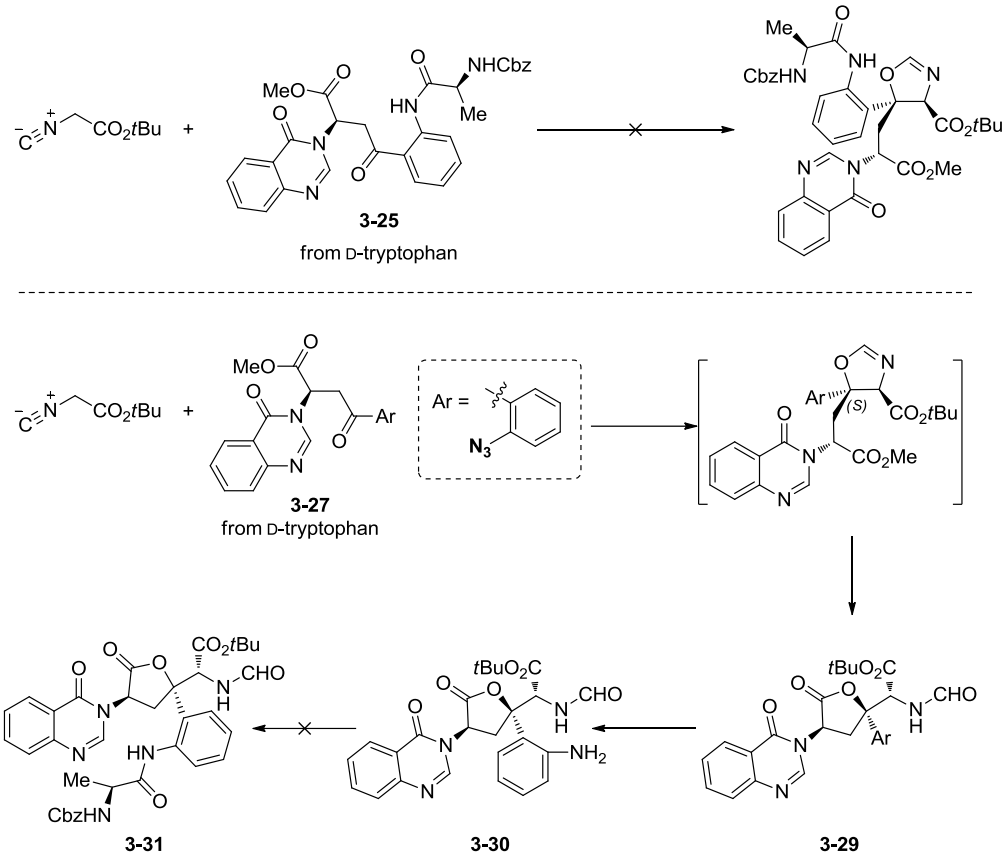


Scheme 3-23 *Chapter summary I*

Attempts to introduce the alanine unit at an early stage were also explored with unsatisfying outcomes, as summarised in **Scheme 3-24**. We found that the catalytic stereoselective isocyanoacetate aldol reaction was quite powerful on most of the ketone substrates, but not on the amide-rich ketone **3-25**. Azido lactone **3-29** provided a potential good chance to mildly introduce the alanine unit into the system, but its reduced product - aniline **3-30** - was unexpectedly sensitive towards both silica gel for further purification and bases required in most of the powerful peptide coupling reactions.

According to our accumulated knowledge from previous chapters and limited time left for the PhD program, we decided to simplify the primary total synthesis aim to a naturally occurring pentacyclic quinazolinone natural product and core of tryptoquivalines. Additionally, under the most optimistic circumstances this pentacyclic quinazolinone

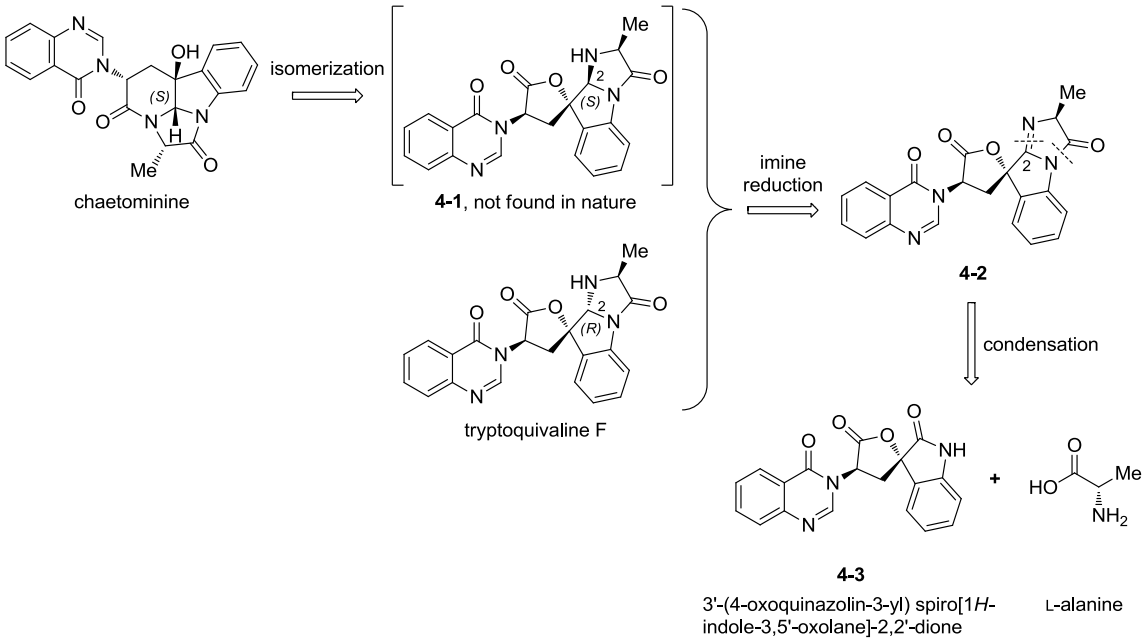
alkaloid would provide us with further synthetic access to tryptoquivalines and chaetominines with one more ring homologation. This work is described in the next chapter.



Scheme 3-24 *Chapter summary II*

Chapter 4. Synthesis of a naturally occurring spiro-oxindole alkaloid and pentacyclic core of tryptoquivalines

4.1 Retrosynthetic analysis

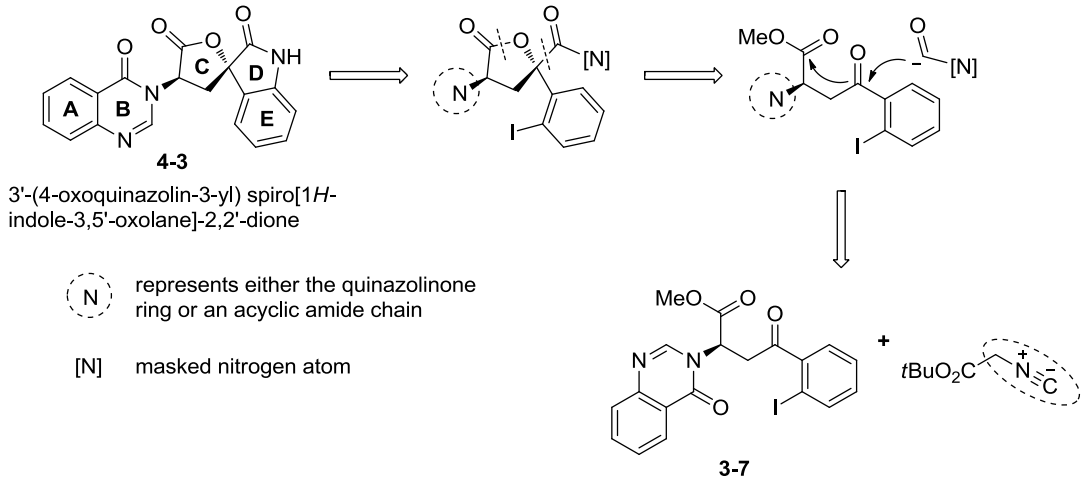


Scheme 4-1 *Retrosynthetic analysis of tryptoquivaline F and chaetominine based on the pentacyclic quinazolinone alkaloid building block*

In 2012, spirolactone **4-3**, featuring structural similarity with both tryptoquivalines and chaetominines, was isolated as a naturally occurred pentacyclic quinazolinone alkaloid[8]. Growing from this discovery, we proposed a synthetic pathway could involve the condensation of natural product **4-3** with L-alanine leading to imidazolinone **4-2**, which would subsequently be subjected to imine reduction conditions. One stereoisomer of the reduction product would be tryptoquivaline F, whilst the other would be its C2 epimer **4-2** which so far has not been found in nature and hopefully could undergo an isomerization to afford chaetominine, **Scheme 4-3**.

Consequently, we chose spirolactone **4-3** as the target for our synthetic studies in the first instance. Key to this approach was the stereoselective addition reaction of a

masked one-carbon nucleophilic unit into a suitably functionalised quinazolinone containing aryl ketone system where the resulting tertiary alcohol was primed to form the C-ring in a lactonisation process. In turn, the spiro oxindole D-ring could be accessed through Ullmann intramolecular C-N coupling conditions. We pleasingly recognized that the broad-scope silver catalysed enantio- and diastereoselective isocyanoacetate aldol methodology previously described and employed in this thesis, could be again applied to deliver the necessary one carbon unit through oxidative manipulation en route to the desired target **4-3**, **Scheme 4-2**.



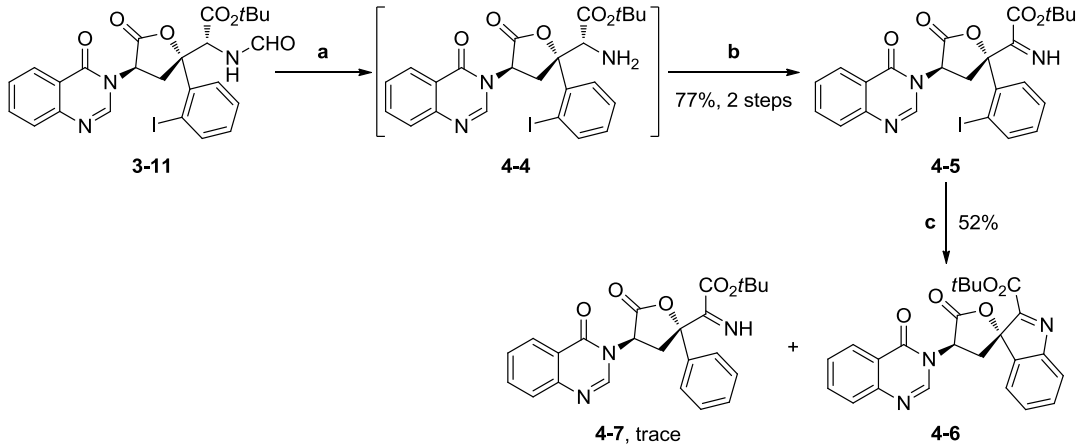
Scheme 4-2 *Retrosynthetic analysis of pentacyclic quinazolinone alkaloid* ***4-3***

4.2 Results and discussion

4.2.1 End game for the pentacyclic spirolactone natural product

Since the catalytic stereoselective isocyanoacetate aldol reaction between aryl ketone **3-7** and *tert*-butyl isocyanoacetate ester was successfully carried out as shown in **Scheme 3-5**, and the subsequent preparation of spirolactone **3-11** was also demonstrated in **Table 3-1**, we directly describe the work in this chapter starting from lactone **3-11**. Firstly, the cleavage of the formamide using hydrogen chloride/methanol gave the primary amine

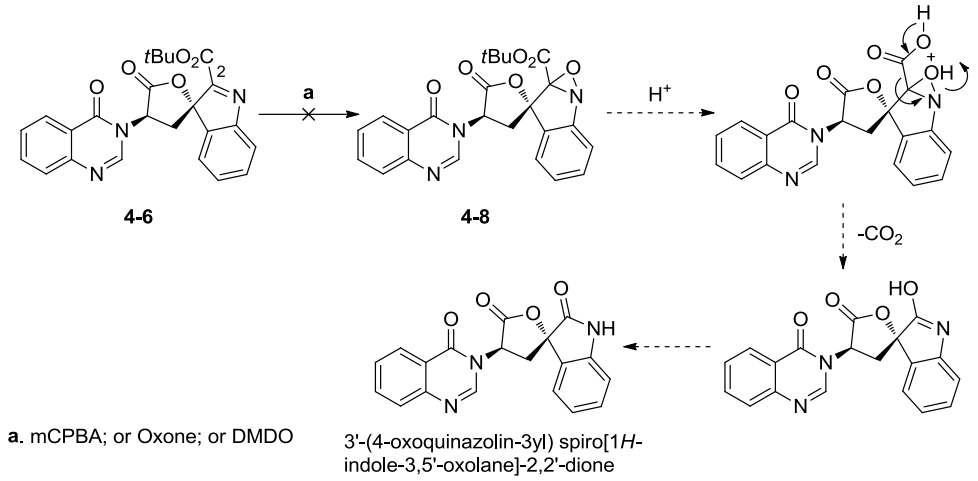
hydrochloride salt, which was neutralized with saturated sodium hydrogen carbonate. Without further purification, the free primary amine was oxidized with IBX to deliver imine ester **4-5** in 77% yield over two steps[203]. Applying the previously optimized mild copper mediated C-N coupling conditions (**Table 3-2**, **entry 6**: copper iodide, magnesium acetate tetrahydrate in DMSO) the spirolactone indolenine **4-6** was obtained in 52% yield, along with a trace amount of **4-7**, **Scheme 4-3**.



a. $SOCl_2$, MeOH, then sat. $NaHCO_3$; **b**. IBX, CH_2Cl_2, DMSO; **c**. CuI, $Mg(OAc)_2.4H_2O$, DMSO

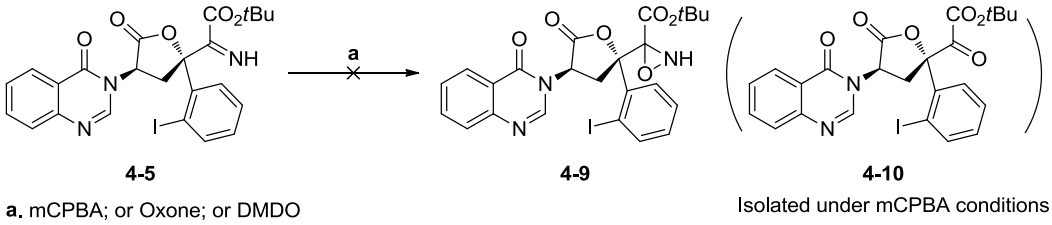
Scheme 4-3 *Preparation of spirolactone indolenine **4-6***

The pentacyclic natural product **4-3** could then be obtained from **4-6** by removal of the ester functionality with concomitant oxidation of C2. A possible strategy would involve formation of oxaziridine **4-8**, followed by decarboxylative rearrangement[204–207] to produce the desired natural product, **Scheme 4-4**.



Scheme 4-4 *Proposed last stage modification and unsuccessful preparation of oxaziridine* ***4-8***

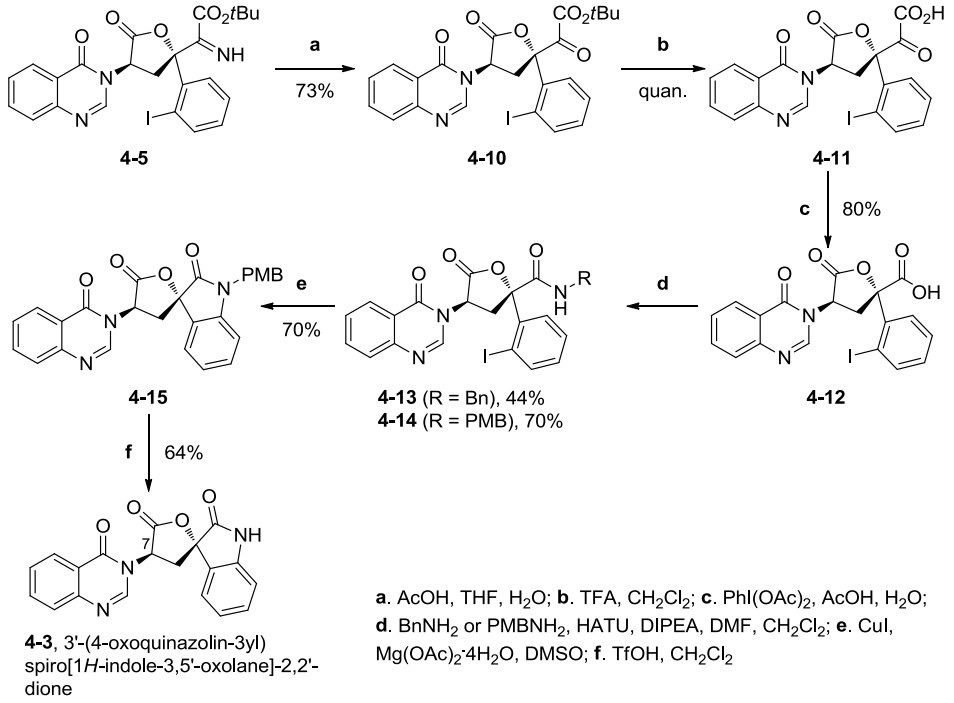
However, meta-chloroperoxybenzoic acid (mCPBA), Oxone and *in situ* generated DMDO all failed to provide the oxaziridine **4-8**. We considered that a stronger imine electrophile may facilitate the desired transformation. Thus similar conditions were applied to α-iminoester **4-5** prior to cyclisation, **Scheme 4-5**. The desired oxaziridine **4-9** was again not detected, and with mCPBA a very small amount of α-ketoester **4-10** was isolated along with a majority of starting material **4-5**.



Scheme 4-5 *Unsuccessful attempted preparation of* ***4-9***

Since ketoester **4-10** could be utilized to finish the sequence as well, the hydrolysis of **4-5** was performed with aqueous acetic acid affording **4-10** with 73% yield. The resulting ketone **4-10** was subsequently converted to the α-ketoacid **4-11** in quantitative yield by treatment with TFA. The generated α-ketoacid moiety was then oxidatively cleaved to afford carboxylic acid **4-12** in 80% yield under PIDA conditions[208]. Pyridinium dichromate[209] was also trialled but was found to be far less efficient. Next, HATU-mediated amide

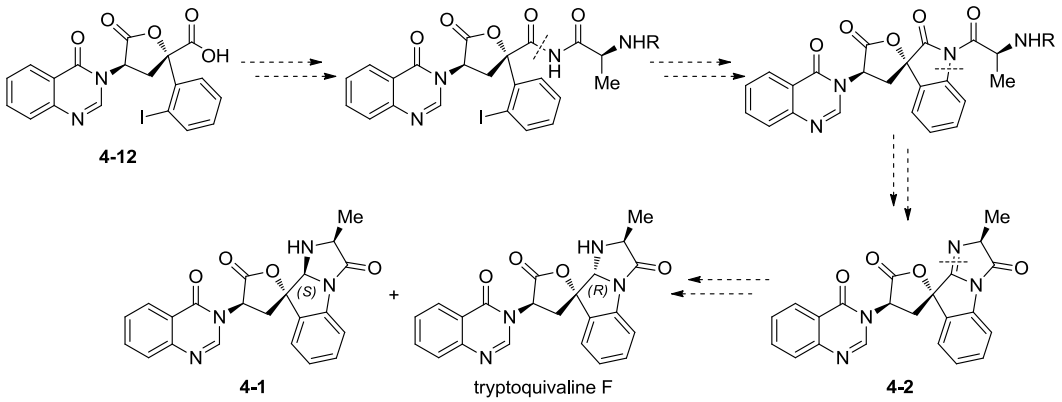
coupling delivered **4-13** and **4-14** in 44% and 70% yield respectively. We chose to continue the synthesis with PMB-amide as its deprotection can be effected under a number of fairly mild conditions. The final ring was formed by a copper(I) mediated Ullmann type C-N bond coupling reaction, providing spirolactone oxindole **4-15** in 70% yield. Due to the ease of epimerization at the C7 position, strong bases were avoided. As shown in **Table 3-2**, magnesium acetate tetrahydrate was found to be optimal. Pentacyclic spirolactone natural product **4-3** was finally obtained by deprotection of the PMB group with triflic acid in 64% yield. The spectroscopic data, specific rotation and melting point of the synthetic material were in good agreement with that of the isolated natural product (lit.[8] $\mathbf{[\alpha]_D^{20}}$ +250 *c* 0.3 MeOH, **m.p.** 267−269 °C; synthetic $\mathbf{[\alpha]_D^{25}}$ +278.6 *c* 0.03 MeOH, **m.p.** 271−276 °C), hence confirming the total synthesis of **4-3** in a linear route of 15 steps from D-tryptophan methyl ester hydrochloride with overall 6.4% yield, **Scheme 4-6**.



Scheme 4-6 *End game for pentacyclic natural product **4-3***

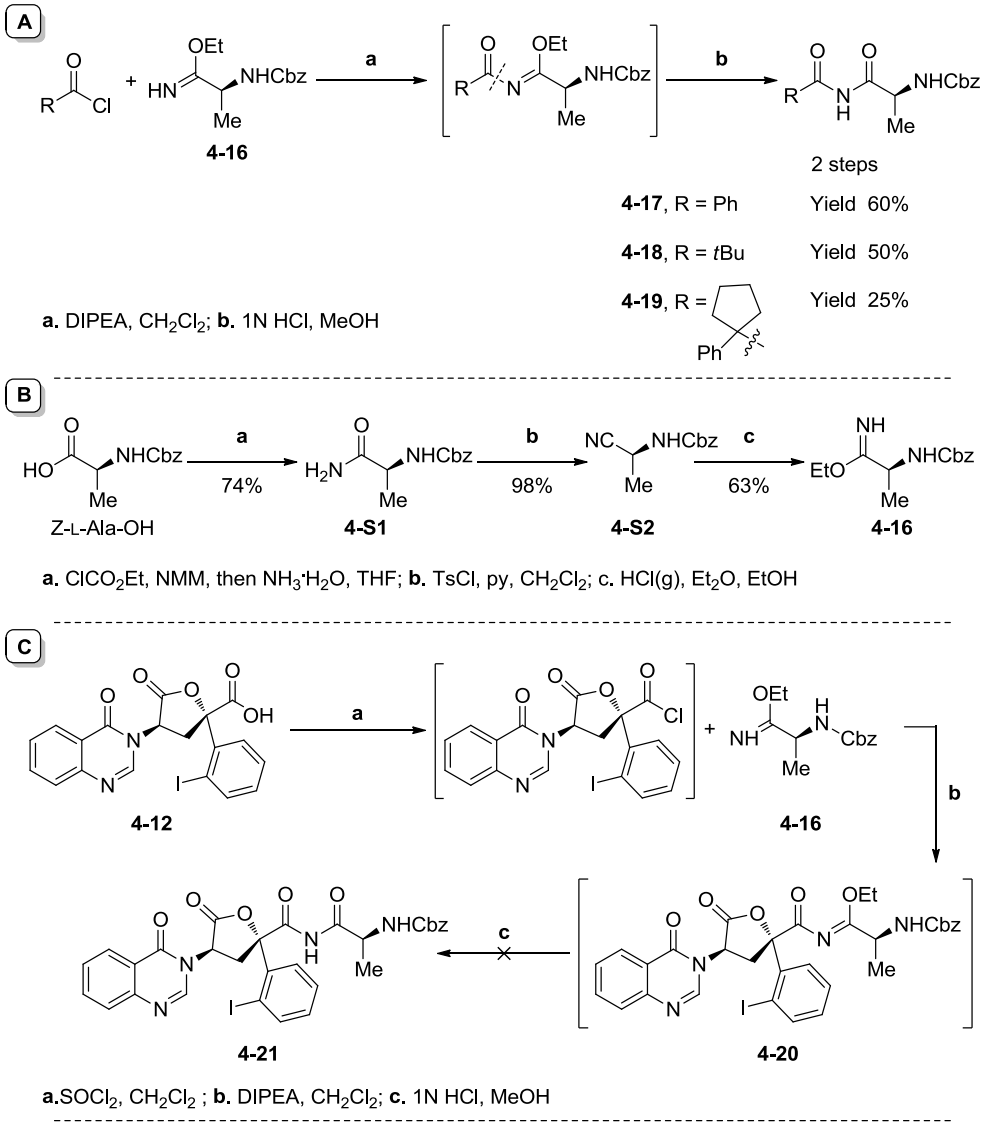
4.2.2 Undertaken and future homologations towards tryptoquivaline F

Firstly, in this section a sequence starting from oxidative cleavage product **4-12** was explored towards a totoal synthesis of tryptoquivaline F. We conceived the conversion of acid **4-12** to an imide intermediate and subsequent cyclisation could deliver an alanine acylated imide. Manipulation of the protected primary amine would then allow formation of the imidazolinone ring; further imine reduction would afford tryptoquivaline F and its epimer **4-1**, **Scheme 4-7**.



Scheme 4-7 *Synthesis plan based on imide formation*

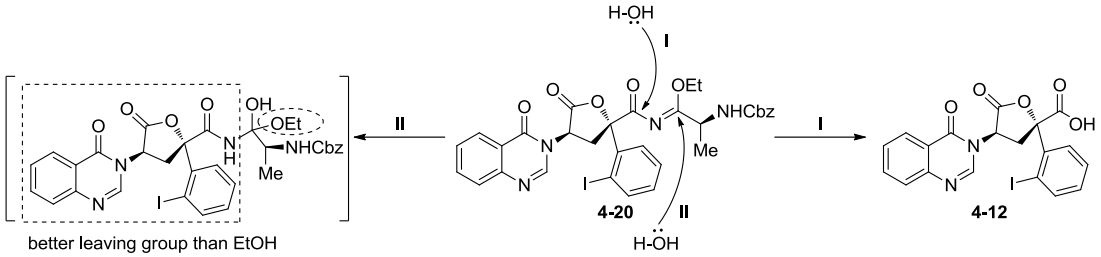
In the first instance, the proposed imide formation was tested on model substrates, **Scheme 4-8**. The one pot procedure between acyl chloride and freshly prepared imidate **4-16** gave the desired imide products but with yields that decreased with increasing size of R. The ketimine intermediate could be monitored by TLC. This procedure was attempted on pentacyclic **4-12**. However, although ketimine intermediate **4-20** could be detected by LCMS and observed on TLC, the desired imide **4-21** was not isolated after hydrolysis conditions.



A. model study; **B.** preparation of imidate **4-16**; **C.** attempted application to real substrate **4-12**

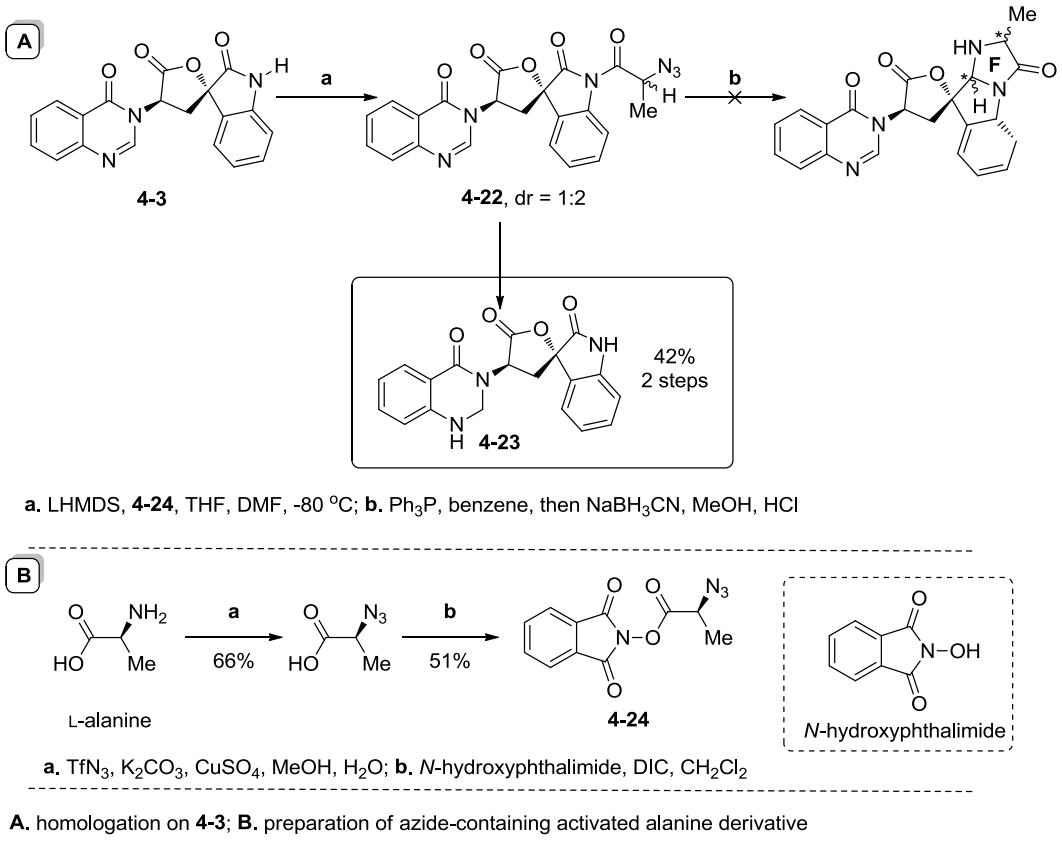
Scheme 4-8 *Attempted preparation of imide **4-21***

According to our observations, a plausible explanation for the unsuccessful hydrolysis could be the possibility of hydrolysis at different positions of **4-20**. As shown below, hydrolysis at the amide bond would regenerate the starting material **4-12**, while addition of water to the imidate would lead to a tetrahedral intermediate in which the amide could act as the leaving group rather than ethanol, **Scheme 4-9**.



Scheme 4-9 *Hydrolysis reaction outcome analysis*

Consequently, an alternative homologation approach could be developed from the condensation between natural product **4-3** and a suitable alanine derivative **4-24**, as proposed in **Scheme 4-1**. In this case, an azide-containing alanine chain introduction was attempted on pentacyclic spirolactone **4-3**, as shown in **Scheme 4-10**.



Scheme 4-10 *Attempted condensation homologation on **4-3***

Although DMF is not an ideal solvent for kinetic deprotonation conditions, the poor solubility of **4-3** required its use as a co-solvent. The outcome indicated that the α position of the azido-propionyl side chain epimerized during the reaction affording **4-22** with 1:2 dr.

Inspired by Magomedov *et al*.[210], Staudinger reaction on this type of system should trigger an intramolecular cycloaddition leading to an iminophosphorane intermediate, which could undergo an aza-Wittig reaction to provide tryptoquivalines' core structure; whilst the resulting C-N double bond could then be reduced to yield F-ring. Unfortunately, attempted Staudinger reaction followed by *in situ* reduction did not give the desired cyclised structure but compound **4-23**, in which the alanine chain was cleaved off and the quinazolinone ring was reduced. In all likelihood, the Staudinger reaction did not afford the desired cyclic imine structure and the reduction proceeded to cleave off the carbonyl group.

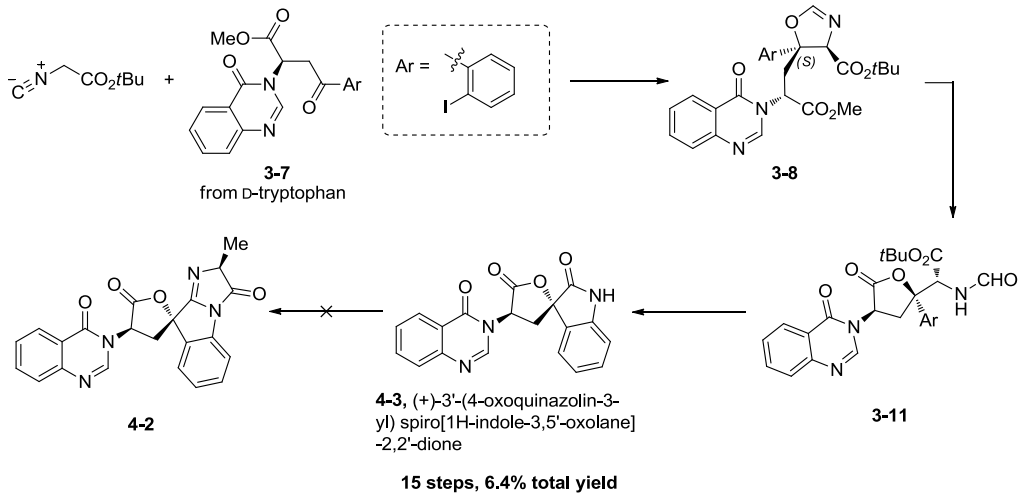
Due to time constraints, our research efforts halted at this point. Future work will continue to look at the acylation reaction (such as the amide silylation conditions[22] with BSA reagent employed by Büchi *et al.*) on pentacyclic natural product **4-3** in order to synthesize cyclic imine **4-2** and subsequent downstream activity towards tryptoquivalines and chaetominines.

4.3 Conclusion

The pentacyclic natural molecule 3'-(4-oxoquinazolin-3-yl)spiro[1*H*-indole-3,5'-oxolane]-2,2'-dione ,**4-3**, was achieved from D-tryptophan methyl ester hydrochloride in a linear route of 15 steps with an overall yield of 6.4%. The key step featured a gram scale catalyst controlled stereoselective aldol reaction to construct the highly substituted oxazoline ring bearing two contiguous stereocentres in 91% yield with a dr 14:1, poised for downstream manipulation.

The work in this chapter modified the chain length of **3-11** and a readjustment of oxidation state of the side chain afforded amide **4-14**. Subsequently, the [5,5]spirolactone

system was obtained with concomitant formation of the indolone ring in a Ullmann coupling reaction. Then the desired natural product **4-3** was obtained after deprotection, **Scheme 4-14**.



Scheme 4-14 *Chapter summary*

4-3 is a member of the quinazolinone alkaloids and also possesses the embedded core of tryptoquivalines. Using it as an advanced synthetic intermediate, reactions to derive one more ring from it were investigated in order to access the tryptoquivaline skeleton. In these studies, solubility constraints limited the scope of possible transformations. Furthermore, some reactions of complex, highly functionalised late-stage intermediates proved ineffective. In summary, our efforts towards elaboration of **4-3** into structurally related tryptoquivalines and chaetominines were largely hampered by unfavourable physical property constraints of the advanced intermediates, especially solubility, and time constraints ultimately drew our research efforts to a close.

I. Experimental

I.a General experimental

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

Compound names are those generated by ChemDraw Professional 16.0 software following IUPAC nomenclature.

All reagents purchased from commercial sources were used as received. Organic solvents were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were used directly as received from commercial suppliers. Petroleum ether (PE) refers to the 40 – 60 °C fraction of distilled light petroleum. Anhydrous solvents were dried by passing through a Glass Contour Solvent Purification System Model-AOCSOLCOL. Brine refers to a saturated aqueous solution of NaCl. Reagents used were obtained from commercial suppliers and used without purification. Na_2SO_4 refers to anhydrous sodium sulphate.

Thin layer chromatography (TLC) analyses were performed using Merck silica gel 60 F_{254} (230 – 400 mesh) fluorescent treated silica plates and visualised under UV light and/or stained with aqueous potassium permanganate solutions as appropriate. Flash column

chromatography (FCC) was carried out on Merck Kieselgel (230 – 400 mesh) and Macheney-nagel silica 60M (0.04 – 0.063 mm).

All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 500 MHz and Bruker 400 MHz spectrometers against a residual solvent peak as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz).

^{1}H NMR spectra are reported as follows: δ/ppm (multiplicity, coupling constant(s) *J*/Hz, number of protons, assignment). Multiplicity is abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, dq = doublet of quartets, quin = quintet, sept = septet m = multiplet; "app" is used to denote the apparent splitting of a signal. ^{13}C NMR spectra are reported in δ/ppm. Two-dimensional NMR spectroscopy experiments (COSY, HSQC, HMBC) were used to assist in the assignment of signals in ^{1}H and ^{13}C NMR spectra.

IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film or from a compressed sample of the solid, and only selected maximum absorbances (ν_{max}) of the most intense peaks are reported (cm^{-1}).

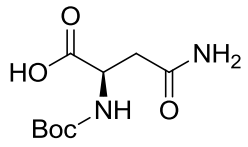
High resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer (equipped with an ESI source unless otherwise stated).

Melting points were recorded using a Leica Galen III hot-stage microscope apparatus or Büchi Melting Point B-540 apparatus and are reported uncorrected in degrees Celsius (°C).

Specific rotations were recorded using an Optical Activity AA-1000 polarimeter; $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is given in g/100 ml; measured at 589 nm.

I.b Synthesis and characterization

Compound 2-1[211]

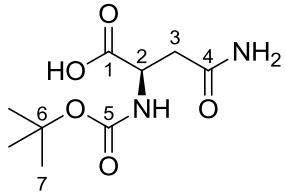


D-asparagine (10.0 g, 66.7 mmol, 1.0 eq) and sodium carbonate (7.1 g, 66.7 mmol, 1.0 eq) were dissolved in water (150 mL) and 1,4-dioxane (150 mL) at rt. Di-*tert*-butyl-dicarbonate (17.5 g, 80.0 mmol, 1.2 eq) was added and the mixture was stirred overnight. The solvent was evaporated under reduced pressure untill 1,4-dioxane was removed and the pH was adjusted to about 2.0 with concentrated HCl. The solid was filtered, washed with water and dried to give a colourless solid 14.1 g (91%);

m.p. 179 – 180 °C (lit.[212] 175-180 °C);

$[\alpha]_D^{25}$ +8.6 (*c* 1.00, MeOH); lit.[213] for the enantiomer -1.6 (*c* 1.00, MeOH);

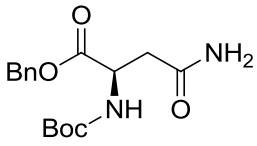
IR (film) ν_{max}/cm^{-1}: 3345, 1665, 1506, 1394, 1368, 1336, 1251, 1161, 1056, 1026, 968, 862, 782, 756;



^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 12.51 (bs, 1H, $CO_2\underline{H}$), 7.31 (s, 1H, N$\underline{H}$Boc), 6.75 – 7.00 (m, 2H, CON$\underline{H}_2$), 4.23 (q, *J* = 7.5 Hz, 1H, $C_{[2]}H$), 2.43 (td, *J* = 15.4, 14.8, 6.4 Hz, 2H, $C_{[3]}H$), 1.37 (s, 9H, $C_{[7]}H$);

^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 173.4 ($C_{[1]}$), 171.4 ($C_{[4]}$), 155.2 ($C_{[5]}$), 78.1 ($C_{[6]}$), 50.2 ($C_{[2]}$), 36.7 ($C_{[3]}$), 28.2 ($C_{[7]}$).

Compound 2-2[211]

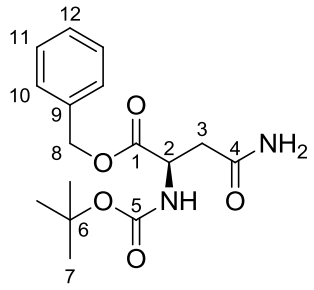


Compound **2-1** *N-tert*-butoxycarbonyl-D-asparagine (14.1 g, 60.7 mmol, 1.0 eq) was dissolved in THF (40 mL), and Et_3N (10 mL) was then added. After stirred at rt for 10 min, solvents were removed under vacuum. The residual was dissolved in THF (40 mL) and benzyl bromide (12.0 g, 70.0 mmol, 1.15 eq) was added subsequently. After the reaction was refluxed for 2 h, the precipitatee was filtered out and solvents evaporated. The resulting residual was dissolved in ethyl acetate (100 mL), washed with saturated $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was recrystallized in toluene (200 mL) to give 15.4 g (79%) of colourless solid;

m.p. 113 – 116 ^{o}C; lit.[211] not characterized

$[\alpha]_D^{25}$ –13.2 (*c* 1.00, $CHCl_3$); lit.[211] not characterized

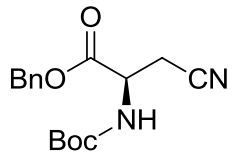
IR (film) ν_{max}/cm^{-1}: 3355, 1676, 1616, 1499, 1392, 1367, 1342, 1165, 1056, 1027, 749, 698, 623;



^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32 – 7.35 (m, 5H, $C_{[10][11][12]}H$), 5.72 (d, *J* = 8.6 Hz, 1H, N*H*Boc), 5.58 (bs, 1H, CONH_2'), 5.42 (bs, 1H, CONH_2''), 5.18 – 5.19 (m, 2H, $C_{[8]}H$), 4.56 (dt, *J* = 9.3, 4.8 Hz, 1H, $C_{[2]}H$), 2.94 (dd, *J* = 16.1, 4.9 Hz, 1H, $C_{[3]}H$'), 2.75 (dd, *J* = 16.1, 4.4 Hz, 1H, $C_{[3]}H$''), 1.43 (s, 9H, $C_{[7]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 172.0 ($C_{[1]}$), 171.2 ($C_{[4]}$), 155.7 ($C_{[5]}$), 135.4 ($C_{[9]}$), 128.5 ($C_{[10]}$), 128.3 ($C_{[11]}$), 128.2 ($C_{[12]}$), 80.1 ($C_{[6]}$), 67.4 ($C_{[8]}$), 50.3 ($C_{[2]}$), 37.4 ($C_{[3]}$), 28.3 ($C_{[7]}$).

Compound 2-3[211]

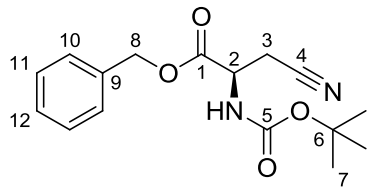


Compound **2-2** *N-tert*-butoxycarbonyl-D-asparagine benzyl ester (16.0 g, 49.7 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (80 mL) and pyridine (20 mL). TsCl (20.0 g, 104.9 mmol, 2.1 eq) was subsequently added and the reaction was stirred for 48 h at rt. Saturated $NaHCO_3$ (200 mL) was then added into the flask and after stirring for an additional 1 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The organic phase was separated and washed with 1 M H_3PO_4 (300 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was recrystallized from EtOH / H_2O (150 mL / 100 mL) to give 11.0 g (73%) of colourless solid;

m.p. 97 – 98 °C; lit.[211] not characterized;

[α]$_D^{25}$ –25.4 (*c* 1.00, $CHCl_3$); lit.[211] for the enantiomer +26.1 (*c* 1.00, $CHCl_3$);

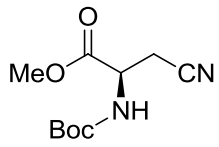
IR (film) ν_{max}/cm^{-1}: 3357, 2252, 1727, 1680, 1523, 1341, 1297, 1195, 1163, 1016, 966, 754, 700;



^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.33 – 7.43 (m, 5H, $C_{[ar]}H$), 5.45 (d, *J* = 7.2 Hz, 1H, N*H*Boc), 5.25 (s, 2H, $C_{[8]}H$), 4.53 (q, *J* = 5.8 Hz, 1H, $C_{[2]}H$), 2.97 (qd, *J* = 16.9, 5.2 Hz, 1H, $C_{[3]}H$), 1.45 (s, 9H, $C_{[7]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 168.8 ($C_{[1]}$), 154.8 ($C_{[5]}$), 134.4 ($C_{[9]}$), 128.9 ($C_{[10]}$), 128.8 ($C_{[11]}$), 128.6 ($C_{[12]}$), 116.1 ($C_{[4]}$), 81.0 ($C_{[6]}$), 68.4 ($C_{[8]}$), 50.4 ($C_{[2]}$), 28.2 ($C_{[3]}$), 21.8 ($C_{[7]}$).

Compound 2-4



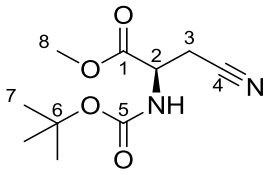
Compound **2-2** *N-tert*-butoxycarbonyl-D-asparagine (232 mg, 1.0 mmol, 1.0 eq) was dissolved in dry THF (2.0 mL), followed by the portionwise addition of 1,1'-carbonyldiimidazole (486 mg, 3.0 mmol, 3.0 eq). After stirring 30 min at rt, dry MeOH (0.1 mL) was added. The reaction was kept stirring overnight before diluted with ethyl acetate

(5 mL), washed with brine, dried and removed solvent. Residue was purified by FCC Et_2O/CH_2Cl_2 (1/20) gave 83 mg (36%) of colourless solid;

m.p. 92 – 93 °C; lit.[214] 80 – 82 °C

$[\alpha]_D^{25}$ –11.8 (*c* 1.00, $CHCl_3$); lit.[214] for the enantiomer +36.0 (*c* 1.70, $CHCl_3$);

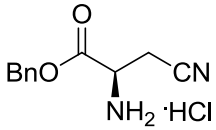
IR (film) ν_{max}/cm^{-1}: 1748, 1715, 1518, 1439, 1394, 1368, 1252, 1226, 1162, 1063, 1026, 782;



^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.45 (s, 1H, N*H*Boc), 4.53 (q, *J* = 5.0 Hz, 1H, $C_{[2]}H$), 3.84 (s, 3H, $C_{[8]}H$), 2.97 (qd, *J* = 16.9, 5.0 Hz, 2H, $C_{[3]}H$), 1.46 (s, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 169.4 ($C_{[1]}$), 154.8 ($C_{[5]}$), 116.1 ($C_{[4]}$), 81.0 ($C_{[6]}$), 53.4 ($C_{[8]}$), 50.3 ($C_{[2]}$), 28.2 ($C_{[7]}$), 21.9 ($C_{[3]}$).

Compound 2-5[211]

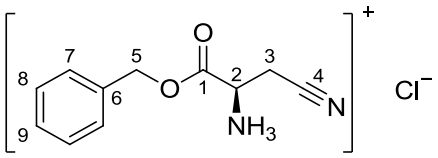


Compound **2-3** *N*-(*tert*-butoxycarbonyl)-3-cyanoalanine benzyl ester (16.2 g, 53.2 mmol) was dissolved in 4 M HCl dioxane solution (165 mL). The reaction was then stirred for 25 min at the rt before all solvents were evaporated under vacuum. The residue was triturated by Et_2O (50 mL) and dried under high vacuum overnight to give a colourless solid. 12.7 g (99%);

m.p. 157 – 160 °C; lit.[211] 158 – 160 °C;

[α]$_D^{25}$ +14.0 (*c* 1.00, MeOH); lit.[211] for the enantiomer –22.2 (*c* 1.00, H_2O);

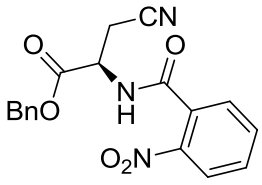
IR (neat) ν_{max}/cm^{-1}: 2830, 1743, 1486, 1413, 1223, 1152, 1069, 935, 753, 701;



^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.92 (s, 3H, N*H*$_3$), 7.34 – 7.50 (m, 5H, $C_{[ar]}H$), 5.29 (s, 2H, $C_{[5]}H$), 4.60 (dd, *J* = 6.7, 5.3 Hz, 1H, $C_{[2]}H$), 3.14 – 3.31 (m, 2H, $C_{[3]}H$);

^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 166.6 ($C_{[1]}$), 134.3 ($C_{[6]}$), 128.0 ($C_{[7]}$), 127.9 ($C_{[9]}$), 127.7 ($C_{[8]}$), 115.8 ($C_{[4]}$), 67.3 ($C_{[5]}$), 47.7 ($C_{[2]}$), 18.1 ($C_{[3]}$).

Compound 2-6

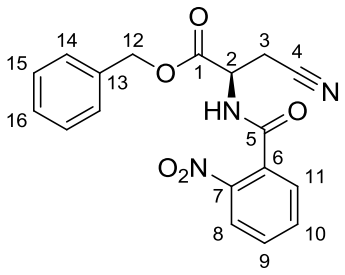


Compound **2-5**, 3-cyanoalanine benzyl ester hydrochloride (3.22 g, 13.4 mmol, 1.0 eq) was dissolved in H_2O (50 mL) and CH_2Cl_2 (100 mL). To the heterogeneous mixture, $NaHCO_3$ (3.37 g, 40.1 mmol, 3.0 eq) and 2-nitrobenzoyl chloride (2.98 g, 2.1 mL, 16.1 mmol, 1.2 eq) were added. After the reaction mixture was stirred at rt for 30 min, the organic phase was separated, and the aqueous phase was extracted by 20 mL of CH_2Cl_2 twice. Combined organic phase was washed with NaOH (aq, 0.5 M, 20 mL) and brine, dried over $MgSO_4$,

filtered and concentrated to give 4.70 g crude product. Recrystallization from PE/EtOAc afforded 4.18 g (88%) of colourless solid;

m.p. 162 – 164 °C; **$[\alpha]_D^{25}$** –31.4 (*c* 1.00, $CHCl_3$)

IR (film) ν_{max}/cm^{-1}: 2922, 2852, 1742, 1669, 1532, 1349, 1214, 770, 630;

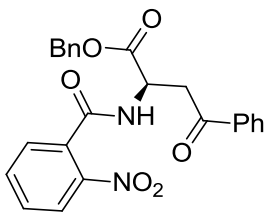


^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.61 (d, *J* = 7.8 Hz, 1H, CON*H*), 8.07 (dd, *J* = 8.1, 1.2 Hz, 1H, $C_{[8]}H$), 7.70 – 7.85 (m, 2H, $C_{[9][11]}H$), 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H, $C_{[10]}H$), 7.32 – 7.44 (m, 5H, $C_{[14][15][16]}H$), 5.21 (s, 1H, $C_{[12]}H'$), 5.20 (s, 1H, $C_{[12]}H''$), 4.86 (td, *J* = 8.1, 5.4 Hz, 1H, $C_{[2]}H$), 3.13 (dd, *J* = 17.0, 5.5 Hz, 1H, $C_{[3]}H'$), 3.05 (dd, *J* = 17.0, 8.4 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 168.2 ($C_{[1]}$), 165.2 ($C_{[5]}$), 146.4 ($C_{[7]}$), 135.0 ($C_{[ar]}$), 133.2 ($C_{[ar]}$), 130.8 ($C_{[ar]}$), 130.7 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.7 ($C_{[ar]}$), 127.4 ($C_{[ar]}$), 123.8 ($C_{[ar]}$), 117.2 ($C_{[4]}$), 66.4 ($C_{[12]}$), 48.4 ($C_{[2]}$), 18.9 ($C_{[3]}$);

HRMS (ESI) $[C_{18}H_{15}N_3O_5+Na]^+$ requires *m/z* 376.0915, found *m/z* 376.0914.

Compound 2-7

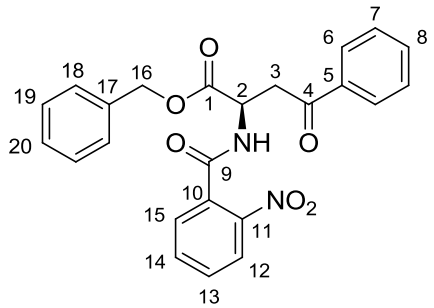


Compound **2-6** *N*-(2-nitrobenzoy)-3-cyanoalanine benzyl ester (3.25g, 9.2 mmol, 1.0 eq), potassium phenyltrifluoroborate (3.38g, 18.4 mmol, 2.0 eq), palladium(II) acetate (155 mg, 0.69 mmol, 0.075 eq) and 2,2'-bipyridyl (215 mg, 1.38 mmol, 0.15 eq) were dissolved in the mixture of THF (69 mL) and H_2O (13.8 mL). TFA (10.5 g, 7.0 mL, 92.0 mmol, 10.0 eq) was then added. After the reaction was stirred at 70 ^oC under Ar for 15 hours, the mixture was diluted with ethyl acetate (100 mL), washed with 1 N HCl, 0.5 M NaOH and brine, dried over $MgSO_4$, filtered and concentrated under vacuum to give the dark yellow solid residue, which was purified by FCC Et_2O/CH_2Cl_2 (from 1/50 to 1/20) gave the crude product 3.61 g. Recrystallized from EtOH/H_2O (70 mL / 35 mL) afforded a yellow crystal 3.35 g, which was again purified with FCC Et_2O/CH_2Cl_2 (1/20) provided a colourless solid 3.30 g (83%);

The ee was determined by HPLC analysis (chiralpak AD-H, hexane/*iso*-propanol 80:20, λ 210 nm, 1.0 mL/min): t (minor) = 47.62 min, t (major) = 52.99 min (>99 %);

m.p. 121 – 122 ^oC; **$[\alpha]_D^{25}$** +53.6 (*c* 1.00, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1742, 1674, 1529, 1451, 1348, 1215, 1111, 1039, 995, 909, 734, 696;

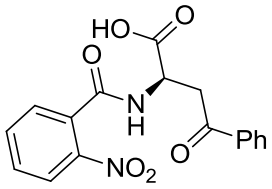


^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.04 (dd, *J* = 8.1, 1.2 Hz, 1H, $C_{[12]}H$), 7.95 – 8.02 (m, 2H, $C_{[ar]}H$), 7.58 – 7.72 (m, 3H, $C_{[ar]}H$), 7.50 – 7.58 (m, 3H, $C_{[ar]}H$), 7.37 (s, 5H, $C_{[ar]}H$), 7.12 (d, *J* = 8.3 Hz, 1H, N*H*CO), 5.22 (m, 3H, $C_{[2]}H$ & $C_{[16]}H$), 3.95 – 3.76 (m, 2H);

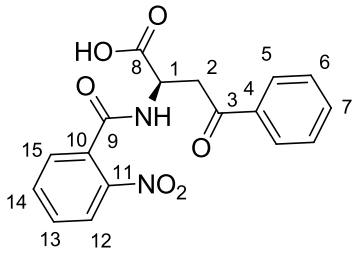
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.2 ($C_{[4]}$), 170.6 ($C_{[1]}$), 166.1 ($C_{[9]}$), 146.4 ($C_{[11]}$), 135.9 ($C_{[ar]}$), 135.1 ($C_{[ar]}$), 133.8 ($C_{[ar]}$), 133.7 ($C_{[ar]}$), 132.3 ($C_{[ar]}$), 130.6 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 128.2 ($C_{[ar]}$), 124.6 ($C_{[ar]}$), 67.6 ($C_{[16]}$), 48.9 ($C_{[2]}$), 39.9 ($C_{[3]}$);

HRMS (ESI) $[C_{24}H_{20}N_2O_6+Na]^+$ requires *m/z* 455.1214, found *m/z* 455.1213.

Compound 2-8



Compound **2-6**, *N*-(2-Nitrobenzoy)-3-cyanoalanine benzyl ester (353 mg, 1.0 mmol, 1.0 eq), potassium phenyltrifluoroborate (368 mg, 2.0 mmol, 2.0 eq), palladium(II) trifluoroacetate (16.5 mg, 0.05 mmol, 0.05 eq) and 2,2'-bipyridyl (15.5 mg, 0.1 mmol, 0.1 eq) were dissolved in THF 5.0 mL and H_2O 1.0 mL; and TFA (970 mg, 10.0 mmol, 10.0 eq) was added. The reaction was stirred at 80 ^oC under Ar for 15 hours. Then the mixture was diluted with ethyl acetate 100 mL, washed with 1 M HCl, and brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in the mixture of 5 mL of THF and 3 mL of 1 M aq. LiOH, stirred for 1 hour at rt and adjusted the pH to 1.0 with 3 M HCl, extract with ethyl acetate, combined organic fractions was washed with brine, dried over $MgSO_4$, concentrated. This crude acid **2-8** could be used for further reactions without additional purification;

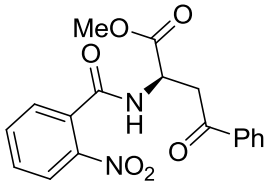


^{1}H NMR (CD_3OD, 400 MHz) δ (ppm): 8.08 (d, *J* = 8.2 Hz, 1H, $C_{[ar]}H$), 8.02 (d, *J* = 7.2 Hz, 2H, $C_{[ar]}H$), 7.76 (td, *J* = 7.5, 1.2 Hz, 1H, $C_{[ar]}H$), 7.69 – 7.58 (m, 3H, $C_{[ar]}H$), 7.51 (t, *J* = 7.6 Hz, 2H, $C_{[ar]}H$), 5.11 (t, *J* = 5.4 Hz, 1H, $C_{[1]}H$), 3.82 – 3.63 (m, 2H, $C_{[2]}H$);

^{13}C NMR (CD_3OD, 100 MHz) δ (ppm): 198.8 ($C_{[3]}$), 174.1 ($C_{[8]}$), 169.2 ($C_{[9]}$), 148.0 ($C_{[ar]}$), 138.0 ($C_{[ar]}$), 135.1 ($C_{[ar]}$), 134.7 ($C_{[ar]}$), 133.7 ($C_{[ar]}$), 132.0 ($C_{[ar]}$), 130.3 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 129.4 ($C_{[ar]}$), 125.6 ($C_{[ar]}$), 50.4 ($C_{[1]}$), 41.0 ($C_{[2]}$);

HRMS (ESI) $[C_{17}H_{14}N_2O_6+Na]^+$ requires *m/z* 365.0744, found *m/z* 365.0744.

Compound 2-9

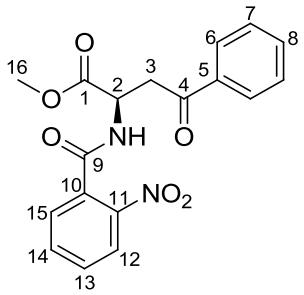


Acid **2-8** was dissolved in methanol (5 mL); thionyl chloride (1 mL) was added into the solution at 0 ^{o}C and stirred for 3 hours. The reaction was quenched by sat. $NaHCO_3$, extract with ethyl acetate, washed with brine and dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC Et_2O/CH_2Cl_2 (1/20) to give a colourless thick foam 214 mg (60%);

The ee was determined by HPLC analysis (chiralpak AD-H, hexane/*iso*-propanol 80:20, λ 240 nm, 1.0 mL/min): t (minor) = 29.94 min, t (major) = 33.70 min (98% ee);

$[\alpha]_D^{25}$ +36.1 (*c* 1.00, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1743, 1674, 1597, 1529, 1449, 1349, 1310, 1220, 1115, 1044, 1001, 912, 856, 790, 760, 737, 691;

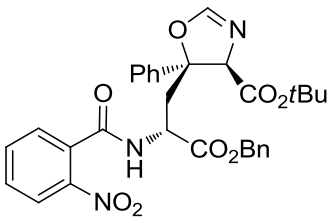


^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.08 (dt, *J* = 8.2, 1.3 Hz, 1H, $C_{[12]}H$), 8.04 – 7.96 (m, 2H, $C_{[ar]}H$), 7.75 – 7.69 (m, 1H, $C_{[ar]}H$), 7.66 – 7.59 (m, 3H, $C_{[ar]}H$), 7.53 (t, *J* = 7.6 Hz, 2H, $C_{[ar]}H$), 7.09 (d, *J* = 8.2 Hz, 1H, CON*H*), 5.22 (dt, *J* = 8.0, 3.9 Hz, 1H, $C_{[2]}H$), 3.93 – 3.88 (m, 2H, $C_{[3]}H$), 3.84 (s, 3H, $C_{[16]}H$, with rotamer peak);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 198.3 ($C_{[4]}$), 171.4 ($C_{[1]}$), 166.2 ($C_{[9]}$), 146.6 ($C_{[11]}$), 136.1 ($C_{[ar]}$), 134.1 ($C_{[ar]}$), 134.0 ($C_{[ar]}$), 132.5 ($C_{[ar]}$), 130.9 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 124.8 ($C_{[ar]}$), 53.1 ($C_{[16]}$), 49.0 ($C_{[2]}$), 40.2 ($C_{[3]}$);

HRMS (ESI) $[C_{18}H_{16}N_2O_6+Na]^+$ requires *m/z* 379.0901, found *m/z* 379.0899.

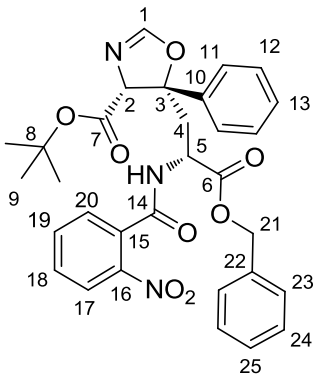
Compound 2-10



Ketone **2-7** (432 mg, 1.0 mmol, 1.0 eq), Ligand-**1** (30 mg, 0.05 mmol, 0.05 eq), AgOAc (8 mg, 0.05 mmol, 0.05 eq) and activated 4Å molecular sieve (300 mg) were placed in ethyl acetate (18 mL). After stirring at 0 ^{o}C for 30 min, *tert*-butyl isocyanoacetate (216 mg, 1.5 mmol, 1.5 eq) in ethyl acetate (2 mL) was added to the reaction mixture. The reaction was stirred at 0 ^{o}C for 5 days. The reaction mixture was then filtered through the Celite, followed by the removal of solvents and purified by FCC Et_2O/CH_2Cl_2 (from 1/10 to 1/8) to give the colourless foam 410 mg (71%, d.r. = 12.5:1);

m.p. 64 – 66 ^{o}C; **$[\alpha]_D^{25}$** –40.4 (*c* 1.27, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1742, 1670, 1636, 1533, 1450, 1350, 1312, 1154, 1024, 960, 913, 846, 790, 735, 700;



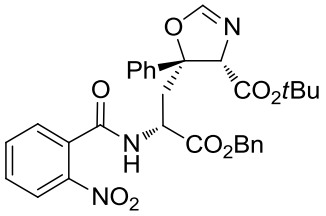
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.94 – 8.05 (m, 1H, $C_{[17]}H$), 7.50 – 7.60 (m, 2H, $C_{[ar]}H$), 7.41 – 7.48 (m, 2H, $C_{[ar]}H$), 7.32 – 7.40 (m, 7H, $C_{[ar]}H$), 7.27 – 7.32 (m, 1H, $C_{[ar]}H$), 7.07 – 7.12 (m, 1H, $C_{[ar]}H$), 6.87 (d, *J* = 1.5 Hz, 1H, CON*H*), 6.09 (s, 1H, $C_{[1]}H$, with rotamer peak), 5.01 –

4.99 (m, 2H, $C_{[21]}H$), 4.75 (q, *J* = 6.5 Hz, 1H, $C_{[5]}H$), 4.59 (s, 1H, $C_{[2]}H$), 2.77 (dd, *J* = 14.5, 6.2 Hz, 1H, $C_{[4]}H'$), 2.58 (dd, *J* = 14.4, 6.6 Hz, 1H, $C_{[4]}H''$), 1.54 (s, 9H, $C_{[9]}H$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 170.7 ($C_{[6]}$), 167.7 ($C_{[7]}$), 165.3 ($C_{[14]}$), 154.7 ($C_{[1]}$), 146.5 ($C_{[16]}$), 142.1 ($C_{[10]}$), 134.9 ($C_{[ar]}$), 133.3 ($C_{[ar]}$), 131.8 ($C_{[ar]}$), 130.7 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 124.6 ($C_{[ar]}$), 124.5 ($C_{[ar]}$), 87.9 ($C_{[3]}$), 83.3 ($C_{[8]}$), 80.4 ($C_{[2]}$), 67.5 ($C_{[21]}$), 50.2 ($C_{[5]}$), 38.0 ($C_{[4]}$), 28.0 ($C_{[9]}$);

HRMS (ESI) $[C_{31}H_{31}N_3O_8+Na]^+$ requires *m/z* 596.2003, found *m/z* 596.2000.

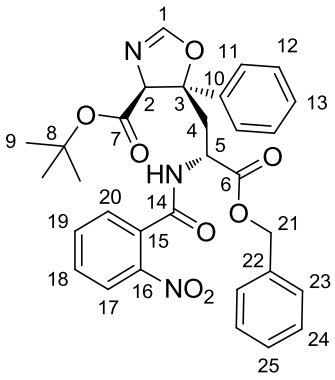
Compound 2-11



Ketone **2-7** (432 mg, 1.0 mmol, 1.0 eq), Ligand-**2** (30 mg, 0.05 mmol, 0.05 eq), AgOAc (8 mg, 0.05 mmol, 0.05 eq) and activated 4Å molecular sieve 300 mg were placed in ethyl (18 mL) acetate. After stirring at 0 ^oC for 30 min, *tert*-butyl isocyanoacetate (216 mg, 1.5 mmol, 1.5 eq) in ethyl acetate (2 mL) was added into the reaction mixture. The reaction was stirred at 0 ^oC for 5 days. The reaction mixture was then filtered through the Celite, followed by the removal of solvents and purified via FCC Et_2O/CH_2Cl_2 (from 1/10 to 1/8) to give the colourless foam 430 mg (75%, d.r. > 20:1);

m.p. 55 – 58 ^oC; **$[\alpha]_D^{25}$** +10.7 (*c* 1.50, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1739, 1672, 1635, 1531, 1456, 1369, 1349, 1214, 1153, 1019, 963, 912, 843, 791, 733, 700, 647;

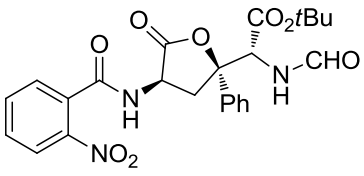


^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.92 – 8.01 (m, 1H, $C_{[17]}H$), 7.50 –7.60 (m, 2H, $C_{[ar]}H$), 7.45 (d, *J* = 7.4 Hz, 2H, $C_{[ar]}H$), 7.32 – 7.41 (m, 7H, $C_{[ar]}H$), 7.23 – 7.28 (m, 1H, $C_{[ar]}H$), 7.04 – 7.10 (m, 1H, $C_{[ar]}H$), 6.68 (d, *J* = 1.9 Hz, 1H, CON*H*), 6.21 (s, 1H, $C_{[1]}H$, with rotamer peak), 5.22 (d, *J* = 12.1 Hz, 1H, $C_{[21]}H'$), 5.09 (d, *J* = 12.1 Hz, 1H, $C_{[21]}H''$), 4.63 (s, 1H, $C_{[2]}H$, with rotamer peak), 4.60 (dt, *J* = 7.6, 3.9 Hz, 1H, $C_{[5]}H$), 2.81 (dd, *J* = 14.8, 3.8 Hz, 1H, $C_{[4]}H'$), 2.50 (dd, *J* = 14.8, 7.9 Hz, 1H, $C_{[4]}H''$), 1.51 (s, 9H, $C_{[9]}H$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 170.7 ($C_{[6]}$), 167.7 ($C_{[7]}$), 165.4 ($C_{[14]}$), 154.6 ($C_{[1]}$), 146.7 ($C_{[16]}$), 142.1 ($C_{[10]}$), 135.1 ($C_{[ar]}$), 133.2 ($C_{[ar]}$), 131.8 ($C_{[ar]}$), 130.6 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.2 ($C_{[ar]}$), 124.4 ($C_{[ar]}$), 88.5 ($C_{[3]}$), 83.3 ($C_{[8]}$), 80.3 ($C_{[2]}$), 67.5 ($C_{[21]}$), 50.3 ($C_{[5]}$), 37.4 ($C_{[4]}$), 28.0 ($C_{[9]}$);

HRMS (ESI) $[C_{31}H_{31}N_3O_8+H]^+$ requires *m/z* 574.2184, found *m/z* 574.2182.

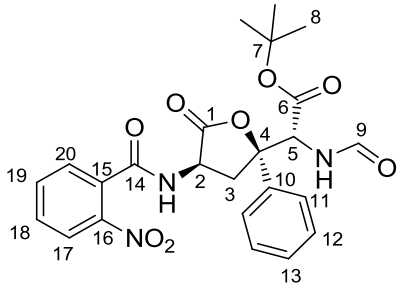
Compound 2-12



Oxazoline **2-10** (227 mg, 0.4 mmol) was dissolved in THF (5 mL), and 1 N HCl (0.5 mL) was then added. The reaction mixture was stirred at rt for 5 min and extracted with ethyl acetate, washed with brine and dried over $MgSO_4$, filtered and concentrated. The crude residue was dissolved in CH_2Cl_2 (14 mL) and followed by the addition of 10-camphorsulfonic acid (70 mg). The reaction mixture was stirred at rt overnight. The reaction was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, concentrated under vacuum. The residue was purified by FCC ethyl acetate/Et_2O (from 1/20 to 1/5) to give colourless solid 172 mg (90%);

m.p. 115 – 118 ^oC; **$[\alpha]_D^{25}$** –1.6 (*c* 1.41, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1794, 1734, 1666, 1531, 1450, 1369, 1348, 1310, 1253, 1221, 1153, 971, 855, 780, 736, 700;



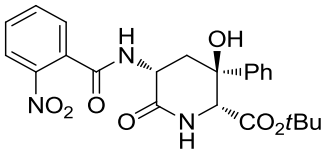
^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.14 (dd, *J* = 8.2, 1.1 Hz, 1H, $C_{[17]}H$), 7.98 (s, 1H, $C_{[9]}H$), 7.80 (td, *J* = 7.6, 1.2 Hz, 1H, $C_{[ar]}H$), 7.70 (td, *J* = 7.9, 1.5 Hz, 1H, $C_{[ar]}H$), 7.64 (dd, *J* = 7.5, 1.4 Hz, 1H, $C_{[ar]}H$), 7.57 – 7.53 (m, 2H, $C_{[ar]}H$), 7.51 – 7.37 (m, 3H, $C_{[ar]}H$), 5.10 (s, 1H, $C_{[5]}H$), 4.44 (dd, *J* = 11.2, 9.3 Hz, 1H, $C_{[2]}H$), 3.23 – 3.09 (m, 2H, $C_{[3]}H$), 1.40 (s, 9H, $C_{[8]}H$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 174.1 ($C_{[1]}$), 169.7 ($C_{[14]}$), 168.0 ($C_{[6]}$), 163.4 ($C_{[9]}$), 148.0 ($C_{[ar]}$), 139.9 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 133.2 ($C_{[ar]}$), 132.3 ($C_{[ar]}$), 130.4 ($C_{[ar]}$), 130.2 ($C_{[ar]}$),

130.0 ($C_{[ar]}$), 127.1 ($C_{[ar]}$), 125.7 ($C_{[ar]}$), 87.3 ($C_{[4]}$), 84.6 ($C_{[7]}$), 59.8 ($C_{[5]}$), 50.8 ($C_{[2]}$), 37.1 ($C_{[3]}$), 28.2 ($C_{[8]}$);

HRMS (ESI) $[C_{24}H_{25}N_3O_8+Na]^+$ requires *m/z* 506.1534, found *m/z* 506.1534.

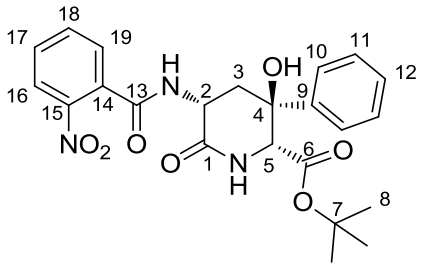
Compound 2-13



Oxazoline **2-10** (660 mg, 1.15 mmol) was dissolved in methanol (40 mL), and thionyl chloride (3.0 mL) was added at –78 °C. The reaction mixture could be warmed to rt and stirred for 90 min. Upon the completion, the reaction was quenched by saturated $NaHCO_3$, exacted with ethyl acetate (20 mL) thrice, organic phase was combined and washed with brine (15 mL), dried over $MgSO_4$, filter and concentrated. The crude was redissolved in ethyl acetate (10 mL) and triethylamine (1 mL) was added. The mixture was stirred at 70 °C for 90 min. After cooling down, the mixture was filtered and the solid was washed with ether to give colourless solid 430 mg (82%, single diastereomer);

m.p. 206 – 208 °C; **$[\alpha]_D^{25}$** –101.3 (*c* 0.63, MeOH);

IR (neat) ν_{max}/cm^{-1}: 3392, 1736, 78, 1658, 1640, 1541, 1482, 1410, 1356, 1325, 1273, 1223, 1157, 1094, 1068, 1046, 957, 943, 912, 899, 855, 790, 759, 733, 696, 643;

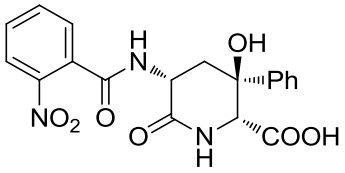


^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.14 (dd, *J* = 8.0, 0.9 Hz, 1H, $C_{[16]}H$), 7.78 – 7.83 (m, 2H, $C_{[ar]}H$), 7.70 (ddd, *J* = 8.2, 5.5, 3.5 Hz, 1H, $C_{[ar]}H$), 7.51 – 7.56 (m, 2H, $C_{[ar]}H$), 7.38 – 7.44 (m, 2H, $C_{[ar]}H$), 7.33 – 7.38 (m, 1H, $C_{[ar]}H$), 5.21 (dd, *J* = 12.0, 6.1 Hz, 1H, $C_{[2]}H$), 4.17 (d, *J* = 1.6 Hz, 1H, $C_{[5]}H$), 2.99 (dd, *J* = 12.9, 12.1 Hz, 1H, $C_{[3]}H'$), 2.57 (ddd, *J* = 12.8, 6.2, 1.7 Hz, 1H, $C_{[3]}H''$), 1.03 (s, 9H, $C_{[8]}H$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 172.9 ($C_{[6]}$), 171.1 ($C_{[1]}$), 169.7 ($C_{[13]}$), 148.1 ($C_{[15]}$), 144.2 ($C_{[9]}$), 135.2 ($C_{[ar]}$), 134.1 ($C_{[ar]}$), 132.0 ($C_{[ar]}$), 130.6 ($C_{[ar]}$), 130.0 ($C_{[ar]}$), 127.7 ($C_{[ar]}$), 125.6 ($C_{[ar]}$), 83.2 ($C_{[7]}$), 72.9 ($C_{[4]}$), 67.4 ($C_{[5]}$), 48.6 ($C_{[2]}$), 35.6 ($C_{[3]}$), 27.8 ($C_{[8]}$);

HRMS (ESI) $[C_{23}H_{25}N_3O_7+Na]^+$ requires *m/z* 478.1585, found *m/z* 478.1581.

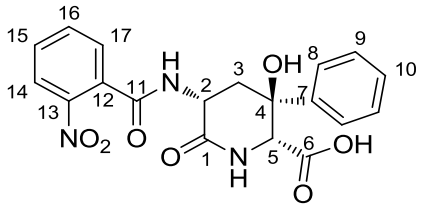
Compound 2-14



tert-Butyl ester **2-13** (400 mg, 0.88 mmol) was dissolved in CH_2Cl_2 (6mL) and trifluoroacetic acid (6 mL). The mixture was stirred 3 h at rt, then concentrated and dried under high vacuum overnight to give light yellow solid 350 mg (quant.), which was pure enough for further steps;

m.p. 164 – 168 °C; **$[\alpha]_D^{25}$** –54.2 (*c* 0.71, MeOH);

IR (neat) ν_{max}/cm^{-1}: 3340, 1708, 1678, 1645, 1530, 1472, 1348, 1267, 1161, 1069, 781, 747, 697;

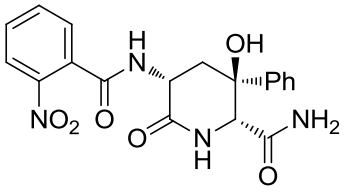


^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 12.32 (s, 1H, COO*H*), 9.05 (d, *J* = 8.7 Hz, 1H, ArCON*H*), 8.04 (dd, *J* = 8.1, 1.1 Hz, 1H, $C_{[14]}H$), 7.99 (d, *J* = 3.1 Hz, 1H, CON*H*), 7.82 (td, *J* = 7.6, 1.2 Hz, 1H, $C_{[ar]}H$), 7.72 – 7.61 (m, 2H, $C_{[ar]}H$), 7.51 – 7.40 (m, 2H, $C_{[ar]}H$), 7.35 (dd, *J* = 8.4, 6.8 Hz, 2H, $C_{[ar]}H$), 7.31 – 7.25 (m, 1H, $C_{[ar]}H$), 6.11 (s, 1H, O*H*), 4.97 (ddd, *J* = 12.2, 8.7, 6.0 Hz, 1H, $C_{[2]}H$), 3.95 (dd, *J* = 3.2, 1.4 Hz, 1H, $C_{[5]}H$), 2.93 (t, *J* = 12.4 Hz, 1H, $C_{[3]}H'$), 2.20 (ddd, *J* = 12.5, 6.0, 1.7 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 171.8 ($C_{[6]}$), 169.3 ($C_{[1]}$), 165.5 ($C_{[11]}$), 147.0 ($C_{[13]}$), 143.6 ($C_{[7]}$), 133.5 ($C_{[ar]}$), 132.5 ($C_{[ar]}$), 130.6 ($C_{[ar]}$), 129.4 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 125.7 ($C_{[ar]}$), 123.9 ($C_{[ar]}$), 71.1 ($C_{[4]}$), 65.6 ($C_{[5]}$), 46.4 ($C_{[2]}$), 34.3 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{16}N_3O_7]^-$ requires *m/z* 398.0994, found *m/z* 398.1000.

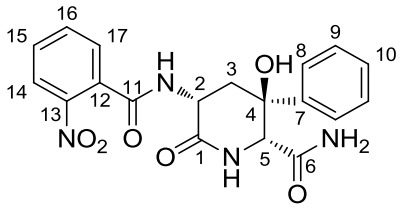
Compound 2-15



Acid **2-14** (200 mg, 0.5 mmol, 1.0 eq) was dissolved in THF (6.0 mL). The solution was cooled to –20 °C, then ethyl chloroformate (65 mg, 0.6 mmol, 1.2 eq) and 4-methylmorpholine (60 mg, 0.6 mmol, 1.2 eq) were added dropwise. The reaction could be stirred at –20 °C to –15 °C for 30 min and aq. NH_4OH (35%, 1.0 mL) was then added in one portion. The temperature could be warmed to rt overnight and the reaction was extracted with ethyl acetate, washed with brine and dried over $MgSO_4$; filtered and concentrated; the residue was purified with FCC methanol / CH_2Cl_2 (from 1/20 to 1/10) to give colourless solid 171 mg (85%);

m.p. 167 – 170 °C; **$[\alpha]_D^{25}$** –106.3 (*c* 0.63, MeOH);

IR (neat) ν_{max}/cm^{-1}: 3271, 1692, 1643, 1529, 1448, 1414, 1349, 1288, 1263, 1069, 1042, 856, 790, 759, 700, 665, 621;

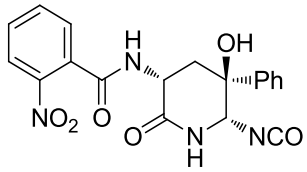


^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.13 (dt, *J* = 8.1, 0.9 Hz, 1H, $C_{[14]}H$), 7.86 – 7.78 (m, 2H, $C_{[ar]}H$), 7.70 (ddd, *J* = 8.3, 5.0, 3.9 Hz, 1H, $C_{[ar]}H$), 7.59 – 7.52 (m, 2H, $C_{[ar]}H$), 7.40 – 7.34 (m, 2H, $C_{[ar]}H$), 7.33 – 7.28 (m, 1H, $C_{[ar]}H$), 4.97 (dd, *J* = 11.7, 6.6 Hz, 1H, $C_{[2]}H$), 4.11 (d, *J* = 1.5 Hz, 1H, $C_{[5]}H$), 3.19 (dd, *J* = 13.2, 11.8 Hz, 1H, $C_{[3]}H'$), 2.46 (ddd, *J* = 13.2, 6.6, 1.7 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 174.0 ($C_{[6]}$), 172.7 ($C_{[1]}$), 169.6 ($C_{[11]}$), 148.2 ($C_{[13]}$), 144.4 ($C_{[7]}$), 135.2 ($C_{[ar]}$), 133.8 ($C_{[ar]}$), 132.1 ($C_{[ar]}$), 130.5 ($C_{[ar]}$), 129.4 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 125.6 ($C_{[ar]}$), 73.3 ($C_{[4]}$), 67.6 ($C_{[5]}$), 49.0 ($C_{[2]}$), 36.3 ($C_{[3]}$);

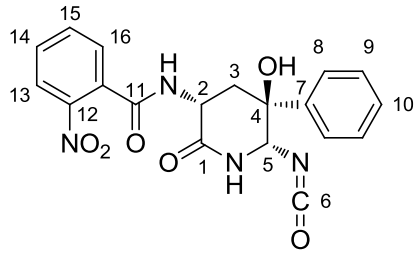
HRMS (ESI) $[C_{19}H_{18}N_4O_6+Na]^+$ requires *m/z* 421.1119, found *m/z* 421.1112.

Compound 2-16



Acid **2-14** (40 mg, 0.1 mmol, 1.0 eq) was dissolved in 3 mL of THF. The solution was cooled to –20 °C, then ethyl chloroformate (13 mg, 0.12 mmol, 1.2 eq) and 4-methylmorpholine (12 mg, 0.12 mmol, 1.2 eq) were added dropwise. The reaction could be stirred at –20 °C to –15 °C for 30 min and aqueous NaN_3 (3 M, 0.1 mL, 3.0 eq) was then added in one portion. After the reaction was further stirred at –15 °C for 30 min, the reaction mixture could be warmed to rt, diluted with brine, extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The resulting residue was dissolved in 3 mL of toluene, and then heated at 100 °C for 30 min. Removal of solvents gave colourless solid 37 mg (93%, 90% purity), which could be used for further steps without purification;

IR (neat) ν_{max}/cm^{-1}: 2253, 1678, 1652, 1530, 1481, 1358, 1319, 1261, 1171, 1161, 921, 887, 794, 770, 729, 696;



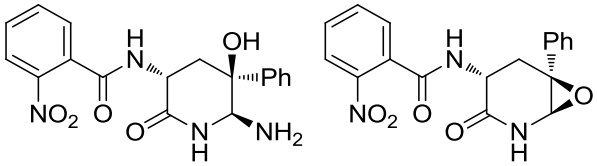
^{1}H NMR (MeCN-d_3, 500 MHz) δ (ppm): 8.01 (dd, *J* = 8.2, 1.2 Hz, 1H, $C_{[14]}H$); 7.77 (tt, *J* = 7.6, 1.0 Hz, 1H, $C_{[ar]}H$), 7.72 – 7.61 (m, 2H, $C_{[ar]}H$), 7.57 (dt, *J* = 8.3, 1.2 Hz, 2H, $C_{[ar]}H$), 7.50 – 7.42 (m, 2H, $C_{[ar]}H$), 7.36 – 7.42 (m, 2H, $C_{[ar]}H$+ArCONH), 6.96 (s, 1H, CONH), 5.17 – 5.13 (m, 1H,

$C_{[5]}H$), 4.79 (ddd, *J* = 12.0, 8.1, 6.3 Hz, 1H, $C_{[2]}H$), 4.14 (s, 1H, O*H*, with rotamer peak), 2.96 (dd, *J* = 13.2, 12.0 Hz, 1H, $C_{[3]}H'$), 2.52 (ddd, *J* = 13.2, 6.4, 2.1 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (MeCN-d_3, 125 MHz) δ (ppm): 169.8 ($C_{[1]}$), 167.0 ($C_{[11]}$), 148.3 ($C_{[12]}$), 143.9 ($C_{[7]}$), 134.7 ($C_{[ar]}$), 133.2 ($C_{[ar]}$), 132.0 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 129.5 ($C_{[ar]}$), 129.5 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 126.2 ($C_{[6]}$), 125.4 ($C_{[ar]}$), 74.2 ($C_{[4]}$), 71.4 ($C_{[5]}$), 48.7 ($C_{[2]}$), 33.3 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{16}N_4O_6+Na]^+$ requires *m/z* 419.0962, found *m/z* 419.0954.

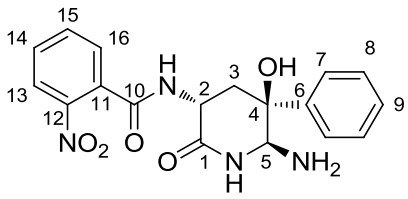
Compound 2-17 & 2-18



2-17 **2-18**

Isocyanate **2-16** (20 mg, 90% purity) from the previous step was dissolved 1,4-dioxane (1.0 mL), then 6 N HCl (1.0 mL) was added in. After the mixture was stirred for 5 min at rt, all volatiles were then removed under high vacuum. The residue was subjected to FCC MeOH(NH_3)/CH_2Cl_2 (from 1/100 to 1/25) gave **2-17** 3 mg (7%) and epoxide **2-18** 1 mg (5%) respectively;

Compound **2-17**



m.p. 188 – 195 °C; **$[\alpha]_D^{25}$** –2.3 (*c* 0.03, MeOH);

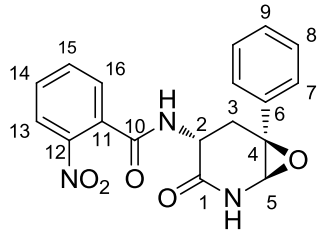
IR (film) ν_{max}/cm^{-1}: 3286, 1654, 1531, 1481, 1445, 1349, 1310, 1284, 1108, 854, 790, 761, 701, 669;

^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.20 – 8.01 (m, 1H, $C_{[13]}H$), 7.86 – 7.76 (m, 2H, $C_{[ar]}H$), 7.68 (ddd, *J* = 8.2, 6.2, 2.8 Hz, 1H, $C_{[ar]}H$), 7.62 – 7.53 (m, 2H, $C_{[ar]}H$), 7.41 (dd, *J* = 8.5, 7.1 Hz, 2H, $C_{[ar]}H$), 7.35 – 7.21 (m, 1H, $C_{[ar]}H$), 4.84 (dd, *J* = 12.0, 6.0 Hz, 1H, $C_{[2]}H$), 4.65 (s, 1H, $C_{[5]}H$), 2.70 (dd, *J* = 13.6, 12.0 Hz, 1H, $C_{[3]}H'$), 2.34 (dd, *J* = 13.5, 6.0 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 172.1 ($C_{[1]}$), 169.4 ($C_{[10]}$), 148.1 ($C_{[12]}$), 145.4 ($C_{[6]}$), 135.1 ($C_{[ar]}$), 133.9 ($C_{[ar]}$), 132.1 ($C_{[ar]}$), 130.5 ($C_{[ar]}$), 129.6 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 126.5 ($C_{[ar]}$), 125.6 ($C_{[ar]}$), 74.5 ($C_{[4]}$), 70.8 ($C_{[5]}$), 49.0 ($C_{[2]}$), 40.3 ($C_{[3]}$);

HRMS (ESI) $[C_{18}H_{18}N_4O_5+H]^+$ requires *m/z* 371.1350, found *m/z* 371.1350.

Compound **2-18**



m.p. 125 – 138 °C; **$[\alpha]_D^{25}$** –71.0 (*c* 0.01, MeOH);

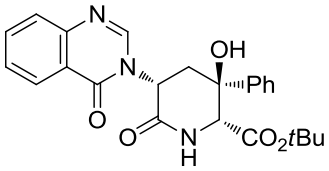
IR (film) ν_{max}/cm^{-1}: 1763, 1532, 1486, 1445, 1350, 1103, 1016, 765, 701;

^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.19 – 8.02 (m, 1H, $C_{[13]}H$), 7.87 – 7.77 (m, 2H, $C_{[ar]}H$), 7.71 (ddd, *J* = 8.2, 6.4, 2.5 Hz, 1H, $C_{[ar]}H$), 7.61 – 7.51 (m, 2H, $C_{[ar]}$), 7.43 (dd, *J* = 8.4, 7.0 Hz, 2H, $C_{[ar]}H$), 7.38 – 7.27 (m, 1H, $C_{[ar]}H$), 4.76 (dd, *J* = 11.5, 6.8 Hz, 1H, $C_{[2]}H$), 4.34 (d, *J* = 1.7 Hz, 1H, $C_{[5]}H$), 3.04 (dd, *J* = 13.4, 11.5 Hz, 1H, $C_{[3]}H'$), 2.47 (ddd, *J* = 13.3, 6.8, 1.8 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 172.1 ($C_{[1]}$), 169.5 ($C_{[10]}$), 148.2 ($C_{[12]}$), 145.4 ($C_{[6]}$), 135.2 ($C_{[ar]}$), 133.8 ($C_{[ar]}$), 132.1 ($C_{[ar]}$), 130.5 ($C_{[ar]}$), 129.7 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 127.3 ($C_{[ar]}$), 125.6 ($C_{[ar]}$), 74.8 ($C_{[6]}$), 70.4 ($C_{[5]}$), 49.6 ($C_{[2]}$), 33.0 ($C_{[3]}$);

HRMS (ESI) $[C_{18}H_{15}N_3O_5+H]^+$ requires *m/z* 354.1085, found *m/z* 354.1086.

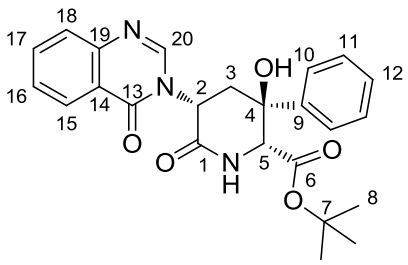
Compound 2-19



Compound **2-13** (420 mg, 0.94 mmol) was suspended in methanol (40 mL), and 40 mg of 10% palladium on charcoal was added. The flask was charged with hydrogen balloon, and stirred at rt for 45 min. After filtering through Celite, all volatiles were removed, and the residue was dissolved in MeOH (20 mL) and trimethyl orthoformate (20 mL). The mixture was added 100 mg of pTSA and was subsequently heated at 65 ^oC for 2 hours. After cooling down, volatiles were removed, and the residue was purified by FCC MeOH/CH_2Cl_2 (1/50 to 1/25) to give colourless solid 400 mg (97%);

m.p. 135 – 140 ^oC; **$[\alpha]_D^{25}$** –160.0 (*c* 0.59, MeOH);

IR (neat) ν_{max}/cm^{-1}: 2928, 1724, 1676, 1610, 1473, 1371, 1324, 1267, 1154, 777, 697;

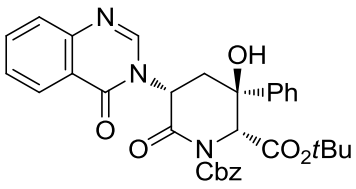


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.38 (s, 1H, $C_{[20]}H$), 8.24 (dt, *J* = 7.9, 1.5 Hz, 1H, $C_{[15]}H$), 7.85 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.72 (dd, *J* = 8.2, 1.1 Hz, 1H, $C_{[ar]}H$), 7.67 (s, 1H, CON*H*), 7.67 – 7.63 (m, 2H, $C_{[ar]}H$), 7.57 (ddt, *J* = 8.1, 7.1, 1.1 Hz, 1H, $C_{[ar]}H$), 7.44 – 7.32 (m, 2H, $C_{[ar]}H$), 6.11 (bs., 1H, $C_{[2]}H$), 5.45 (s, 1H, O*H*), 4.38 (dd, *J* = 3.9, 1.9 Hz, 1H, $C_{[5]}H$), 3.29 (bs., 1H, $C_{[3]}H'$), 2.66 (ddd, *J* = 13.0, 6.9, 2.0 Hz, 1H, $C_{[3]}H''$), 1.08 (s, 9H, $C_{[8]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 171.8 ($C_{[6]}$), 169.6 ($C_{[1]}$), 161.6 ($C_{[13]}$), 149.6 ($C_{[19]}$), 147.8 ($C_{[20]}$), 144.1 ($C_{[9]}$), 135.6 ($C_{[ar]}$), 129.6 ($C_{[ar]}$), 129.6 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 123.3 ($C_{[ar]}$), 83.1 ($C_{[7]}$), 73.3 ($C_{[4]}$), 67.6 ($C_{[5]}$), 52.2 ($C_{[2]}$), 36.7 ($C_{[3]}$), 28.1 ($C_{[8]}$);

HRMS (ESI) $[C_{24}H_{25}N_3O_5+H]^+$ requires *m/z* 436.1867, found *m/z* 436.1867.

Compound 2-20

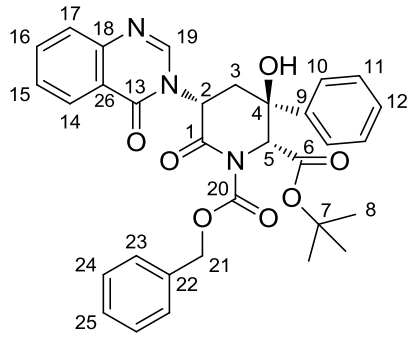


Lactam **2-13** (420 mg, 1.0 mmol, 1.0 eq) was dissolved in dry THF (10 mL). At –78 °C, lithium hexamethyldisilazide (1.0 M in THF, 2.2 mL, 2.2 eq) was added dropwise during 3 min, then the reaction was stirred at the same temperature for 20 min. A solution of dibenzyl dicarbonate (315 mg, 1.1 mmol, 1.1 eq) in dry THF (1.0 mL) was then added into the reaction at –78 °C. After the reaction was stirred for another 20 min, the reaction mixture was quenched with sat. NH_4Cl (4.0 mL), extracted with ethyl acetate and washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified with FCC

CH_2Cl_2/Et_2O (from 50/1 to 20/1) then CH_2Cl_2/MeOH (20/1) gave colourless solid 275 mg (48%) and 70 mg of the starting material;

m.p. 96 – 100 °C; **$[\alpha]_D^{25}$** –10.6 (*c* 1.05, $CHCl_3$);

IR (neat) ν_{max}/cm^{-1}: 1794, 1722, 1677, 1610, 1523, 1475, 1454, 1370, 1325, 1248, 1221, 1188, 1054, 1028, 974, 912, 776, 733, 698;

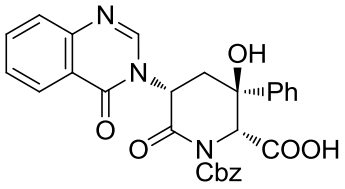


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.94 (s, 1H, $C_{[19]}H$), 7.78 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.71 (dd, *J* = 8.2, 1.1 Hz, 1H, $C_{[ar]}H$), 7.51 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H, $C_{[ar]}H$), 7.46 – 7.36 (m, 5H, $C_{[ar]}H$), 7.34 – 7.24 (m, 5H, $C_{[ar]}H$), 5.79 (s, , 1H, O*H*, with rotamer peak), 5.07 – 4.94 (m, 3H, $C_{[21][2]}H$), 4.87 (s, 1H, $C_{[5]}H$, with rotamer peak), 3.53 (t, *J* = 12.3 Hz, 1H, $C_{[3]}H'$), 3.09 (t, *J* = 11.0 Hz, 1H, $C_{[3]}H''$), 1.39 (s, 9H, $C_{[8]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.3 ($C_{[1]}$), 167.4 ($C_{[6]}$), 160.5 ($C_{[13]}$), 156.1 ($C_{[20]}$), 147.8 ($C_{[18]}$), 144.9 ($C_{[19]}$), 138.0 ($C_{[ar]}$), 136.3 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 129.5 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 125.9 ($C_{[ar]}$), 121.8 ($C_{[ar]}$), 86.4 ($C_{[4]}$), 84.1 ($C_{[7]}$), 67.4 ($C_{[21]}$), 61.9 ($C_{[5]}$), 55.3 ($C_{[2]}$), 36.1 ($C_{[3]}$), 28.1 ($C_{[8]}$);

HRMS (ESI) $[C_{32}H_{31}N_3O_7+H]^+$ requires *m/z* 570.2235, found *m/z* 570.2230.

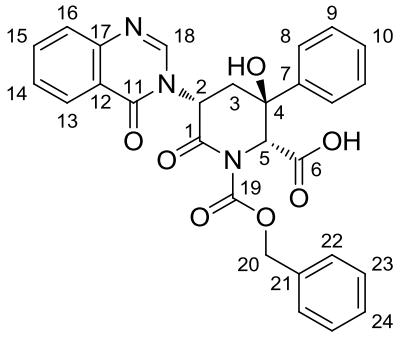
Compound 2-21



Compound **2-20** (250 mg, 0.44 mmol) was dissolved in the mixture of CH_2Cl_2 (3.0 mL) and trifluoroacetic acid (3.0 mL). The reaction was stirred for 5 h at rt. The volatiles were removed, and the residue was dried under high vacuum overnight to give colourless solid 220 mg (quant.) which was pure enough for further steps;

m.p. 190 – 194 °C; **$[\alpha]_D^{25}$** +18.0 (*c* 0.64, MeOH);

IR (neat) ν_{max}/cm^{-1}: 1790, 1718, 1681, 1616, 1504, 1452, 1304, 1243, 1203, 1177, 1093, 1053, 1027, 942, 767, 744, 695;



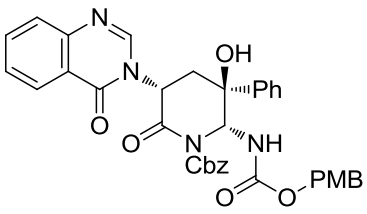
^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.33 – 8.13 (m, 2H, $C_{[ar]}H$), 7.87 (t, *J* = 7.7 Hz, 1H, $C_{[ar]}H$), 7.72 (d, *J* = 8.1 Hz, 1H, $C_{[ar]}H$), 7.53 – 7.63 (m, 3H), 7.37 – 7.48 (m, 3H), 7.34 – 7.18 (m, 5H), 5.18 (t, *J* = 10.2 Hz, 1H, $C_{[2]}H$), 5.08 (d, *J* = 12.8 Hz, 1H, $C_{[20]}H'$), 4.94 – 4.98 (m, 2H, $C_{[20]}H''$ &$C_{[5]}H$), 3.67 (t, *J* = 12.2 Hz, 1H, $C_{[3]}H'$), 3.22 (dd, *J* = 13.0, 9.0 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 172.6 ($C_{[1]}$), 171.4 ($C_{[6]}$), 161.7 ($C_{[11]}$), 158.6 ($C_{[19]}$), 148.7 ($C_{[ar]}$), 148.6 ($C_{[ar]}$), 140.4 ($C_{[ar]}$), 138.2 ($C_{[ar]}$), 136.4 ($C_{[ar]}$), 130.1 ($C_{[ar]}$), 129.9 ($C_{[ar]}$),

129.6 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.2 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 88.1 ($C_{[4]}$), 67.9 ($C_{[20]}$), 62.6 ($C_{[5]}$), 57.8 ($C_{[2]}$), 35.8 ($C_{[3]}$);

HRMS (ESI) $[C_{28}H_{23}N_3O_7+H]^+$ requires *m/z* 514.1609, found *m/z* 514.1608.

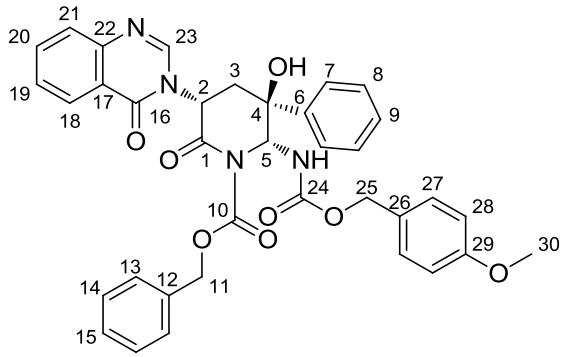
Compound 2-22



Acid **2-21** (25 mg, 0.05 mmol, 1.0 eq) was dissolved in THF (2.0 mL). After the solution was cooled to –20 °C, ethyl chloroformate (6.5 mg, 0.06 mmol, 1.2 eq) and 4-methylmorpholine (6.1 mg, 0.06 mmol, 1.2 eq) were then added. The reaction was stirred at –20 °C to –15 °C for 30 min and aqueous NaN_3 (3 M, 0.05 mL, 3.0 eq) was then added in one portion. The reaction was further stirred at –15 °C for 30 min. Subsequently, the reaction mixture was diluted with brine, and extracted with ethyl acetate, dried over $MgSO_4$, removed all solvents. To the crude residue, 3 mL of toluene was added and heated at 100 °C for 30 min. 4-methoxybenzyl alcohol (14 mg, 0.1 mmol, 2.0 eq) was then added and stirred at 100 °C for 3 hs. After cooling down, removed all volatiles and the residue was purified by FCC CH_2Cl_2/MeOH (from 1/100 to 1/25) to give colourless solid 15 mg (46%);

m.p. 112 – 115 °C; **$[\alpha]_D^{25}$** +39.2 (*c* 0.59, $CHCl_3$);

IR (neat) ν_{max}/cm^{-1}: 3305, 1790, 1717, 1680, 1611, 1513, 1473, 1326, 1245, 1181, 1093, 1026, 775, 733, 698;

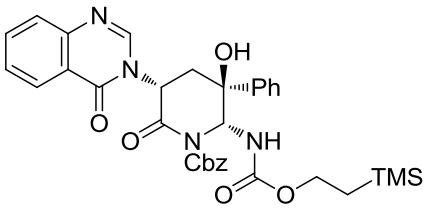


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.15 (d, *J* = 8.0 Hz, 1H, $C_{[23]}H$), 7.85 (s, 1H, $C_{[ar]}H$), 7.77 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.69 (dd, *J* = 8.3, 1.1 Hz, 1H, $C_{[ar]}H$), 7.49 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.43 (bs., 2H), 7.39 – 7.30 (m, 3H, $C_{[ar]}H$), 7.27 (m, 5H, $C_{[ar]}H$), 7.04 (br., 2H, $C_{[ar]}H$), 6.78 – 6.68 (m, 2H, $C_{[ar]}H$), 6.47 (bs., 1H, PMBOCON*H*), 6.13 (bs., 1H, $C_{[5]}H$), 5.51 (s, 1H, O*H*, with rotamer peak), 5.13 (d, *J* = 12.2 Hz, 1H, $C_{[11]}H'$), 4.98 (d, *J* = 12.3 Hz, 1H, $C_{[11]}H''$), 4.90 (d, *J* = 12.2 Hz, 1H, $C_{[25]}H'$), 4.80 (d, *J* = 12.3 Hz, 1H, $C_{[25]}H''$), 4.67 (t, *J* = 10.1 Hz, 1H, $C_{[2]}H$), 3.71 (s, 3H, $C_{[3]}H$), 3.26 (t, *J* = 11.9 Hz, 1H, $C_{[3]}H'$), 2.95 – 2.81 (m, 1H, $C_{[3]}H''$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.2 ($C_{[1]}$), 160.4 ($C_{[16]}$), 159.6 ($C_{[29]}$), 156.2 ($C_{[10]}$), 155.1 ($C_{[24]}$), 147.9 ($C_{[ar]}$), 145.2 ($C_{[ar]}$), 138.8 ($C_{[ar]}$), 136.2 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 129.3 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.2 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 125.1 ($C_{[ar]}$), 121.9 ($C_{[ar]}$), 114.0 ($C_{[ar]}$), 88.7 ($C_{[4]}$), 67.2 ($C_{[11]}$), 67.0 ($C_{[25]}$), 64.7 ($C_{[5]}$), 56.9 ($C_{[2]}$), 55.4 ($C_{[30]}$), 36.7 ($C_{[3]}$);

HRMS (ESI) $[C_{36}H_{32}N_4O_8+H]^+$ requires *m/z* 649.2293, found *m/z* 649.2290.

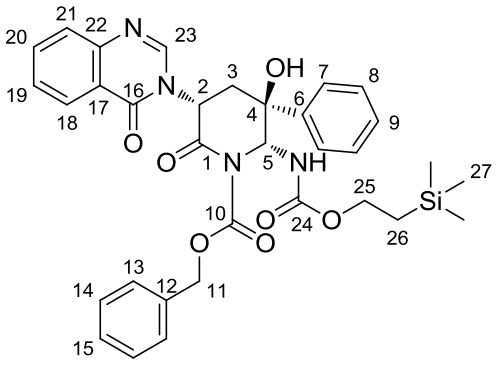
Compound 2-23



Acid **2-21** (25 mg, 0.05 mmol, 1.0 eq) was dissolved in THF (2.0 mL). The resulting solution was then cooled to –20 °C, and ethyl chloroformate (6.5 mg, 0.06 mmol, 1.2 eq) and 4-methylmorpholine (6.1 mg, 0.06 mmol, 1.2 eq) were added subsequently. The reaction was stirred at –20 °C to –15 °C for 30 min, and aq. NaN_3 (3 M, 0.05 mL, 3.0 eq) was then added in one portion. After further stirring at –15 °C for 30 min, the reaction mixture was diluted with brine, extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The residue was redissolved in toluene (3.0 mL). The resulting solution was heated at 100 °C for 30 min, and 2-(trimethylsilyl)ethanol (12 mg, 0.1 mmol, 2.0 eq) was added. Kept stirring at the same temperature for another 3 hours before cooling down, all volatiles were removed, and the residue was purified by FCC ethyl acetate/petro ether (from 1/4 to 1/1) to give colourless solid 12 mg (45%);

m.p. 92 – 94 °C; **$[\alpha]_D^{25}$** +36.2 (*c* 1.00, $CHCl_3$);

IR (neat) ν_{max}/cm^{-1}: 3309, 1792, 1717, 1682, 1611, 1508, 1476, 1326, 1248, 1188, 1093, 1024, 860, 839, 774, 698;

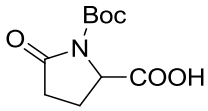


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.25 (d, *J* = 8.0 Hz, 1H, $C_{[23]}H$), 7.88 (s, 1H, $C_{[ar]}H$), 7.77 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.69 (dd, *J* = 8.3, 1.1 Hz, 1H, $C_{[ar]}H$), 7.51 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.40 – 7.45 (m, 2H, $C_{[ar]}H$), 7.29 – 7.40 (m, 2H, $C_{[ar]}H$), 7.27 – 7.20 (m, 4H, $C_{[ar]}H$), 7.06 (s, 2H, $C_{[ar]}H$), 6.22 (bs., 1H, OCON*H*), 6.08 (bs., 1H, $C_{[5]}H$), 5.45 (s, 1H, O*H*, with rotamer peak), 4.91 (d, *J* = 12.2 Hz, 1H, $C_{[11]}H'$), 4.82 (d, *J* = 12.5 Hz, 1H, $C_{[11]}H''$), 4.70 (t, *J* = 10.2 Hz, 1H, $C_{[2]}H$), 4.24 – 4.11 (m, 2H, $C_{[25]}H$), 3.32 (t, *J* = 12.1 Hz, 1H, $C_{[3]}H'$), 2.91 (t, *J* = 11.2 Hz, 1H, $C_{[3]}H''$), 1.05 – 0.94 (m, 2H, $C_{[26]}H$), 0.01 (s, 9H, $C_{[27]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.2 ($C_{[1]}$), 160.4 ($C_{[16]}$), 156.5 ($C_{[10]}$), 155.0 ($C_{[24]}$), 147.9 ($C_{[22]}$), 145.3 ($C_{[23]}$), 138.7 ($C_{[ar]}$), 136.3 ($C_{[ar]}$), 135.3 ($C_{[ar]}$), 129.3 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.2 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 125.1 ($C_{[ar]}$), 121.9 ($C_{[ar]}$), 88.7 ($C_{[4]}$), 67.0 ($C_{[11]}$), 64.6 ($C_{[5]}$), 64.1 ($C_{[25]}$), 56.7 ($C_{[2]}$), 36.6 ($C_{[3]}$), 17.9 ($C_{[26]}$), –1.24 ($C_{[27]}$);

HRMS (ESI) $[C_{33}H_{36}N_4O_7Si+Na]^+$ requires *m/z* 651.2246, found *m/z* 651.2245.

Compound 2-24



At 0 °C, benzyl bromide (7.4 mL, 62 mmol, 1.0 eq) was added into the solution of pyroglutamic acid (8.0 g, 62 mmol, 1.0 eq) of DIPEA (13.0 mL, 74 mmol, 1.2 eq) and CH_2Cl_2 (160 mL). The reaction was refluxing overnight and cooled to rt before it could be washed with sat. NH_4Cl and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was then redissolved in CH_3CN (160 mL). DMAP (755 mg, 6.2 mmol, 0.1 eq) and di-*tert*-butyl dicarbonate (16.3 g, 74 mmol, 1.2 eq) were then added. The reaction stirred at rt for

3 hours and the reaction mixture was washed with sat. NH_4Cl and brine, dried over $MgSO_4$, filtered and concentrated again. The residue was purified by FCC ethyl acetate/petrol ether (2/5) to give a colourless solid 15.5 g; this compound was redissolved in ethyl acetate 80 mL, added 10% Pd/C (850 mg); then the mixture was stirred under hydrogen atmosphere for 3 hours. The mixture was filtered and concentrated to give 10.5 g colourless solid (74%, 3 steps);

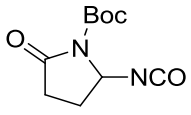
m.p. 80 – 82 ^oC;

IR (neat) ν_{max}/cm^{-1}: 3254, 1772, 1745, 1687, 1362, 1311, 1286, 1259, 1234, 1192, 1150, 1052, 1029, 839, 817, 792, 777, 747, 639, 619;

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.91 (s, 1H, COO*H*), 4.63 (dd, *J* = 9.5, 3.0 Hz, 1H, CONBocC*H*), 2.64 (dt, *J* = 17.5, 9.8 Hz, 1H, COC*H*H), 2.51 (ddd, *J* = 17.5, 9.3, 3.6 Hz, 1H, COCH*H*), 2.43 – 2.24 (m, 1H, CH_2C*H*H), 2.11 (ddt, *J* = 13.1, 9.6, 3.4 Hz, 1H, CH_2CH*H*), 1.48 (s, 9H, *t*Bu);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 176.7 (C=OOH), 173.5 (CH_2C=O), 149.6 (*t*BuOC=O), 84.3 (Me_3C–O), 58.8 (CH_2CH_2CH), 31.4 (C=OCH_2), 28.1 (Me_3C–O), 21.6 (C=OCH_2CH_2).

Compound 2-25



Acid **2-24** (920 mg, 4.0 mmol, 1.0 eq) was dissolved in THF (15 mL). The solution was cooled to –20 ^oC, and ethyl chloroformate (485 mg, 4.8 mmol, 1.2 eq) and 4-methylmorpholine (520 mg, 4.8 mmol, 1.2 eq) were then added dropwise. Kept the reaction at –20 ^oC to –15

°C for 30 min, and aq. NaN_3 (3 M, 3.5 mL, 3.0 eq) was added in one portion. After stirring at –15 °C for additional 30 min, the mixture was diluted with brine, extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in toluene (3.0 mL); heated the mixture at 100 °C 30 min; concentration again gave light yellow solid 868 mg (96%);

m.p. 65 – 66 °C;

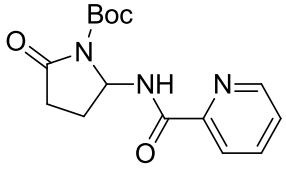
IR (neat) ν_{max}/cm^{-1}: 2266, 1789, 1711, 1444, 1403, 1366, 1325, 1288, 1256, 1178, 1147, 1056, 1016, 960, 878, 850, 830, 805, 777, 747, 666, 632;

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 5.80 (dd, *J* = 6.4, 0.8 Hz, 1H, CONBocC*H*), 2.72 (ddd, *J* = 17.6, 11.7, 8.8 Hz, 1H, COC*H*H), 2.43 (ddd, *J* = 17.6, 8.9, 1.5 Hz, 1H, COCH*H*), 2.17 (dddd, *J* = 13.3, 11.7, 8.9, 6.5 Hz, 1H, $COCH_2CHH$), 1.97 (dddd, *J* = 13.4, 8.8, 1.5, 0.9 Hz, 1H, $COCH_2CHH$), 1.54 (s, 9H, *t*Bu);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 172.8 (CH_2C=O), 148.9 (*t*BuOC=O), 128.3 (CHN=C=O), 84.9 (Me_3C–O), 68.3 (CH_2CH), 30.4 (C=OCH_2), 28.1 (Me_3C–O), 26.8 (CH_2CH_2);

HRMS (CI) $[C_{10}H_{14}N_2O_4+H]^+$ requires *m/z* 227.1026, found *m/z* 227.1028.

Compound 2-26



Isocyanate **2-25** (23 mg, 0.1 mmol, 1.0 eq) and 2-picolinic acid (18 mg, 0.15 mmol, 1.5 eq) were dissolved in dry DMF (1.0 mL), then DIPEA (26 mg, 2.0 mmol, 2.0 eq) was added into the resulting solution. The reaction was stirred at 100 ^{o}C overnight before it was diluted with ethyl acetate, washed with sat. NH_4Cl, dried over $MgSO_4$, filtered and concentrated. The residue was purified with FCC ethyl acetate/CH_2Cl_2 (1/10 to 1/5) to give the colourless solid 18 mg (60%);

m.p. 179 – 182 ^{o}C;

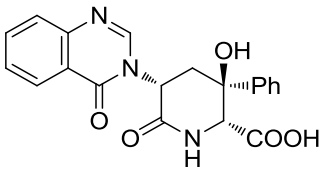
IR (neat) ν_{max}/cm^{-1}: 3301, 1776, 1658, 1514, 1466, 1352, 1318, 1282, 1255, 1211, 1178, 1147, 1044, 1020, 998, 849, 823, 781, 754, 672, 620;

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.54 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H, $C_{[ar]}H$), 8.50 (d, *J* = 8.4 Hz, 1H, CON*H*), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H, $C_{[ar]}H$), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H, $C_{[ar]}H$), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, $C_{[ar]}H$), 6.12 (td, *J* = 7.9, 1.9 Hz, 1H, CH_2CHNH), 2.89 (dt, *J* = 17.1, 9.6 Hz, 1H, COC*H*H), 2.59 – 2.37 (m, 2H, COCH*H*C*H*H), 2.17 – 2.07 (m, 1H, CH_2CHH), 1.41 (s, 9H, *t*Bu);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 174.0 (C=OCH_2), 163.6 (C=ONH), 149.3 (*t*BuOC=O), 149.2 (HNCO$C_{[Ar]}$), 148.4 ($C_{[ar]}$), 137.8 ($C_{[ar]}$), 126.9 ($C_{[ar]}$), 122.5 ($C_{[ar]}$), 83.9 (Me_3C–O), 64.5 (CH_2CH), 31.1 (C=OCH_2), 28.1 (Me_3C–O), 25.6 (CH_2CH_2);

HRMS (ESI) $[C_{15}H_{19}N_3O_4+Na]^+$ requires *m/z* 328.1268, found *m/z* 328.1268.

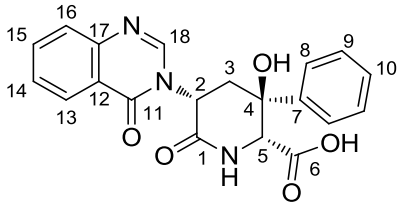
Compound 2-27



The *tert*-butyl ester **2-19** (250 mg, 0.57 mmol) was dissolved in trifluoroacetic acid (6.0 mL). The mixture was stirred 8 h at rt before removing all volatiles and drying the residue under high vacuum overnight to give light yellow solid 220 mg (quant.). The product was pure enough for further reactions;

m.p. 188 – 190 °C; **$[\alpha]_D^{25}$** –144.3 (*c* 0.68, MeOH);

IR (neat) ν_{max}/cm^{-1}: 1661, 1612, 1476, 1377, 1324, 1268, 1243, 1189, 1164, 1070, 910, 772, 721, 696;

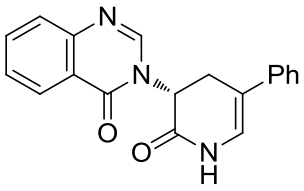


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.54 – 8.41 (m, 1H, $C_{[18]}H$), 8.26 (dt, *J* = 8.4, 1.2 Hz, 1H, $C_{[ar]}H$), 7.85 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H, $C_{[ar]}H$), 7.70 – 7.63 (m, 3H, $C_{[ar]}H$), 7.58 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.41 – 7.35 (m, 2H, $C_{[ar]}H$), 7.34 – 7.29 (m, 1H, $C_{[ar]}H$), 6.12 (bs., 1H, $C_{[2]}H$), 4.44 – 4.40 (m, 1H, $C_{[5]}H$), 3.40 – 3.33 (m, 1H, $C_{[3]}H'$), 2.63 (ddd, *J* = 13.1, 7.1, 1.8 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 173.3 ($C_{[6]}$), 169.1 ($C_{[1]}$), 161.2 ($C_{[11]}$), 148.6 ($C_{[ar]}$), 147.9 ($C_{[ar]}$), 143.6 ($C_{[ar]}$), 135.3 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 126.8 ($C_{[ar]}$), 122.7 ($C_{[ar]}$), 72.9 ($C_{[4]}$), 66.5 ($C_{[5]}$), 51.9 ($C_{[2]}$), 36.5 ($C_{[3]}$);

HRMS (ESI) $[C_{20}H_{17}N_3O_5+H]^+$ requires *m/z* 380.1241, found *m/z* 380.1241.

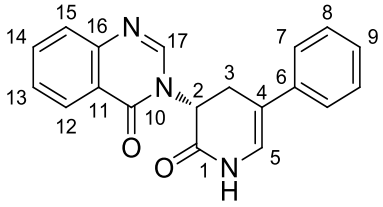
Compound 2-28



Acid **2-27** (20 mg, 0.05 mmol) was dissolved in trifluoroacetic anhydride (0.75 mL) and mL of trifluoroacetic acid (0.15 mL). The resulting mixture was stirred for 24 h at rt. After removing all volatiles, the residue was purified with FCC CH_2Cl_2/MeOH (1/50 to 1/25) to give colourless solid 13 mg (82%);

m.p. T_{dec} >260 ^oC; **$[\alpha]_D^{25}$** +55.2 (*c* 0.16, 10% TFA in $CHCl_3$);

IR (neat) ν_{max}/cm^{-1}: 1677, 1646, 1608, 1478, 1369, 1327, 1297, 1257, 1134, 1109, 775, 753, 689;

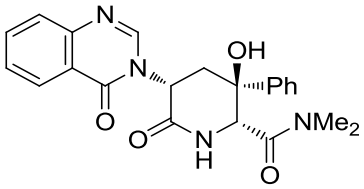


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.94 (s, 1H, CON*H*), 8.36 (s, 1H, $C_{[17]}H$), 8.24 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.85 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.76 – 7.67 (m, 1H, $C_{[ar]}H$), 7.57 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, $C_{[ar]}H$), 7.52 – 7.42 (m, 2H, $C_{[ar]}H$), 7.39 – 7.31 (m, 2H, $C_{[ar]}H$), 7.27 – 7.13 (m, 1H, $C_{[ar]}H$), 6.90 – 6.72 (m, 1H, $C_{[5]}H$), 5.72 (dd, *J* = 14.8, 7.8 Hz, 1H, $C_{[2]}H$), 3.59 (td, *J* = 15.2, 2.9 Hz, 1H, $C_{[3]}H'$), 3.16 (dd, *J* = 15.7, 7.8 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 166.6 (d, $C_{[1]}$), 161.1 ($C_{[10]}$), 149.2 ($C_{[ar]}$), 148.0 ($C_{[ar]}$), 139.0 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 129.5 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.4 ($C_{[ar]}$), 127.4 ($C_{[ar]}$), 125.2 ($C_{[ar]}$), 123.1 ($C_{[ar]}$), 123.0 (d, $C_{[5]}$), 116.4 (d, $C_{[4]}$), 55.2 ($C_{[2]}$), 30.2 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{15}N_3O_2+H]^+$ requires *m/z* 318.1237, found *m/z* 318.1239.

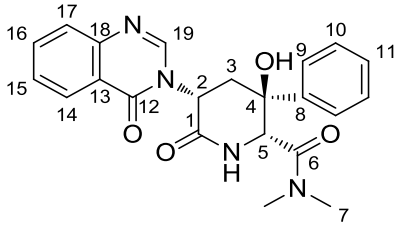
Compound 2-29



Acid **2-27** (38 mg, 0.1 mmol, 1.0 eq), HATU (45 mg, 0.12 mmol, 1.2 eq), $HNMe_2$·HCl (12 mg, 0.15 mmol, 1.5 eq) and 4-dimethylaminopyridine (1.2 mg, 0.01 mmol, 0.1 eq) were dissolved in DMF (1.0 mL) and DIPEA (0.2 mL). The mixture was stirred overnight, and all volatiles were removed under vacuum. The residue was purified by FCC ethyl acetate/triethylamine (from 100/1 to 10/1) to give the colourless solid 39 mg (96%);

m.p. T_{dec} >260 °C; **$[\alpha]_D^{25}$** +156.3 (*c* 0.40, MeOH);

IR (neat) ν_{max}/cm^{-1}: 2923, 2853, 1644, 1611, 1565, 1470, 1375, 1325, 1295, 1265, 1243, 1158, 1068, 773, 698;

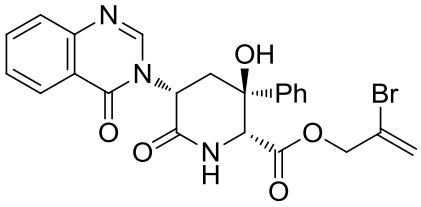


^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 8.66 (s, 1H, $C_{[19]}H$), 8.20 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.06 (d, *J* = 3.7 Hz, 1H, CON*H*), 7.88 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H, $C_{[ar]}H$), 7.74 (dd, *J* = 8.1, 1.1 Hz, 1H, $C_{[ar]}H$), 7.60 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H, $C_{[ar]}H$), 7.55 – 7.43 (m, 2H, $C_{[ar]}H$), 7.42 – 7.26 (m, 3H, $C_{[ar]}H$), 6.36 (s, 1H, O*H*), 5.87 (t, *J* = 9.1 Hz, 1H, $C_{[2]}H$), 4.54 (dd, *J* = 3.8, 1.6 Hz, 1H, $C_{[5]}H$), 3.22 (t, *J* = 12.2 Hz, 1H, $C_{[3]}H'$), 2.62 (s, 3H, $C_{[7]}H'$), 2.18 (ddd, *J* = 12.8, 7.4, 1.6 Hz, 1H, $C_{[3]}H''$), 2.12 (s, 3H, $C_{[7]}H''$);

^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 169.9 ($C_{[6]}$), 168.9 ($C_{[1]}$), 160.0 ($C_{[12]}$), 147.5 ($C_{[18]}$), 146.7 ($C_{[19]}$), 142.5 ($C_{[8]}$), 134.6 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.4 ($C_{[ar]}$), 127.3 ($C_{[ar]}$), 126.4 ($C_{[ar]}$), 125.7 ($C_{[ar]}$), 121.2 ($C_{[ar]}$), 72.1 ($C_{[4]}$), 59.7 ($C_{[5]}$), 50.2 ($C_{[2]}$), 36.1 ($C_{[3]}$), 35.4 ($C_{[7]}$), one aromatic carbon did not appear;

HRMS (ESI) $[C_{22}H_{22}N_4O_4+H]^+$ requires *m/z* 407.1714, found *m/z* 407.1707.

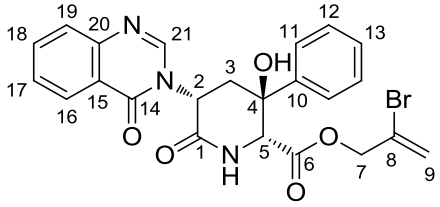
Compound 2-30



Acid **2-27** (38 mg, 0.1 mmol, 1.0 eq), HATU (45 mg, 0.12 mmol, 1.2 eq), 2-bromoallyl alcohol (16.4 mg, 0.12 mmol, 1.2 eq), DIPEA (39 mg, 0.3 mmol, 3.0 eq) and DMAP (1.2 mg, 0.01 mmol, 0.1 eq) were dissolved in DMF (1.0 mL). The mixture was stirred overnight and all volatiles were removed under vacuum. The residue was purified by FCC ethyl acetate/hexane (from 1/1 to 4/1) to give the colourless solid 25 mg (50%) after triturated with Et_2O;

m.p. 184 – 188 °C; **$[\alpha]_D^{25}$** –114.6 (*c* 0.59, MeOH);

IR (neat) ν_{max}/cm^{-1}: 1737, 1667, 1610, 1476, 1449, 1376, 1324, 1267, 1245, 1184, 1162, 1090, 1070, 990, 963, 912, 773, 697, 650;

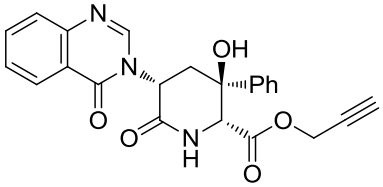


^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.38 (s, 1H, $C_{[21]}H$), 8.30 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.88 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H, $C_{[ar]}H$), 7.75 (dd, *J* = 8.2, 1.1 Hz, 1H, $C_{[ar]}H$), 7.61 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.57 – 7.51 (m, 2H, $C_{[ar]}H$), 7.43 – 7.36 (m, 2H, $C_{[ar]}H$), 7.36 – 7.29 (m, 1H, $C_{[ar]}H$), 6.21 (bs., 1H, $C_{[2]}H$), 5.55 (d, *J* = 2.2 Hz, 1H, $C_{[9]}H'$), 5.49 (d, *J* = 2.2 Hz, 1H, $C_{[9]}H''$), 4.59 (d, *J* = 13.7 Hz, 1H, $C_{[7]}H'$), 4.38 (d, *J* = 1.7 Hz, 1H, $C_{[5]}H$), 4.22 (d, *J* = 13.8 Hz, 1H, $C_{[7]}H''$), 3.30 (bs., 1H, $C_{[3]}H'$), 2.54 (s, 1H, $C_{[3]}H''$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 171.8 ($C_{[6]}$), 170.9 ($C_{[1]}$), 162.4 ($C_{[14]}$), 148.9 ($C_{[20]}$), 147.6 ($C_{[21]}$), 143.5 ($C_{[10]}$), 136.1 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 129.8 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 125.9 ($C_{[ar]}$), 123.0 ($C_{[8]}$), 121.0 ($C_{[9]}$), 73.2 ($C_{[4]}$), 70.0 ($C_{[7]}$), 67.1 ($C_{[5]}$), 52.2 ($C_{[2]}$), 36.4 ($C_{[3]}$);

HRMS (ESI) $[C_{23}H_{20}BrN_3O_5+H]^+$ requires *m/z* 498.0659, found *m/z* 498.0658.

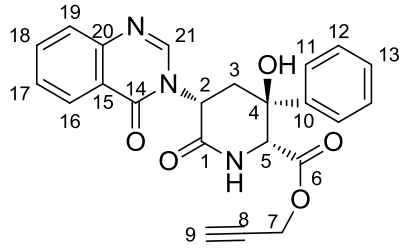
Compound 2-31



Acid **2-27** (38 mg, 0.1 mmol, 1.0 eq), HATU (45 mg, 0.12 mmol, 1.2 eq), propargyl alcohol (6.7 mg, 0.12 mmol, 1.2 eq), DIPEA (39 mg, 0.3 mmol, 3.0 eq) and DMAP (1.2 mg, 0.01 mmol, 0.1 eq) were dissolved in DMF (1.0 mL). The mixture was stirred overnight and all volatiles were removed under vacuum. The residue was purified by FCC ethyl acetate/hexane (from 2/1 to 4/1) to give the colourless solid 33 mg (79%);

m.p. 157 – 164 °C; **$[\alpha]_D^{25}$** –97.5 (*c* 0.80, MeOH);

IR (neat) ν_{max}/cm^{-1}: 3294, 1739, 1668, 1612, 1477, 1376, 1325, 1267, 1244, 1178, 1162, 1091, 932, 915, 848, 774, 756, 698, 658;



^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.34 (s, 1H, $C_{[21]}H$), 8.26 (dd, *J* = 8.1, 1.4 Hz, 1H, $C_{[ar]}H$), 7.85 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.72 (dt, *J* = 8.0, 0.9 Hz, 1H, $C_{[ar]}H$), 7.64 – 7.60 (m, 2H, C[ar]H), 7.58 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.43 – 7.37 (m, 2H, $C_{[ar]}H$), 7.36 – 7.32 (m, 1H, $C_{[ar]}H$), 6.14 (bs., 1H, $C_{[2]}H$), 4.57 (dd, *J* = 15.7, 2.5 Hz, 1H, $C_{[7]}H'$), 4.43 (dd, *J* = 4.0, 1.8 Hz, 1H, $C_{[5]}H$), 4.22 (dd, *J* = 15.8, 2.5 Hz, 1H, $C_{[7]}H''$), 3.40 – 3.35 (m, 1H, $C_{[3]}H'$), 2.99 (t, *J* = 2.5 Hz, 1H, $C_{[9]}H$), 2.60 (ddd, *J* = 13.5, 6.7, 1.1 Hz, 1H, $C_{[3]}H''$);

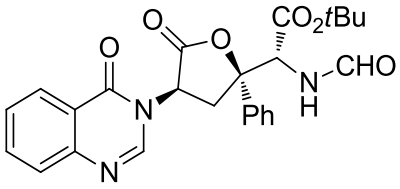
^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 172.1 ($C_{[6]}$), 169.3 ($C_{[1]}$), 161.7 ($C_{[14]}$), 149.6 ($C_{[20]}$), 147.7 ($C_{[21]}$), 143.8 ($C_{[10]}$), 135.7 ($C_{[ar]}$), 129.8 ($C_{[ar]}$), 129.8 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.1 ($C_{[ar]}$), 123.4 ($C_{[ar]}$), 78.2 ($C_{[8]}$), 77.7 ($C_{[9]}$), 73.6 ($C_{[4]}'$), 73.5 ($C_{[4]}''$), 67.4 ($C_{[5]}'$), 67.3 ($C_{[5]}''$), 67.3 ($C_{[5]}'''$), 67.2 ($C_{[5]}''''$), 54.0 ($C_{[7]}$), 36.8 ($C_{[3]}$), $C_{[2]}$ does not show out;

^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 8.39 (s, 1H, $C_{[21]}H$), 8.30 (dd, *J* = 7.9, 1.5 Hz, 1H, $C_{[ar]}H$), 7.88 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H, $C_{[ar]}H$), 7.75 (dd, *J* = 8.3, 1.1 Hz, 1H, $C_{[ar]}H$), 7.61 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H, $C_{[ar]}H$), 7.56 – 7.50 (m, 2H, $C_{[ar]}H$), 7.41 – 7.36 (m, 2H, $C_{[ar]}H$), 7.35 – 7.31 (m, 1H, $C_{[ar]}H$), 6.21 (bs., 1H, $C_{[2]}H$), 4.53 (dd, *J* = 15.6, 2.5 Hz, 1H, $C_{[7]}H'$), 4.33 (d, *J* = 1.7 Hz, 1H, $C_{[5]}H$), 4.21 (dd, *J* = 15.6, 2.4 Hz, 1H, $C_{[7]}H''$), 3.16 – 3.29 (br., 1H, $C_{[3]}H'$), 2.86 (s, 1H, $C_{[9]}H$), 2.53 (bs., 1H, $C_{[3]}H''$);

^{13}C NMR (MeOD-d_4, 125 MHz) δ (ppm): 172.0 ($C_{[6]}$), 170.9 ($C_{[1]}$), 162.4 ($C_{[14]}$), 162.4 ($C_{[20]}$), 147.6 ($C_{[21]}$), 143.3 ($C_{[10]}$), 136.1 ($C_{[ar]}$), 129.8 ($C_{[ar]}$), 129.8 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 126.9 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 77.6 ($C_{[8]}$), 77.2 ($C_{[9]}$), 73.2 ($C_{[4]}$), 67.0 ($C_{[5]}$), 54.1 ($C_{[7]}$), 52.2 ($C_{[2]}$), 36.4 ($C_{[3]}$);

HRMS (ESI) $[C_{23}H_{19}N_3O_5+H]^+$ requires *m/z* 418.1398, found *m/z* 418.1396.

Compound 2-32

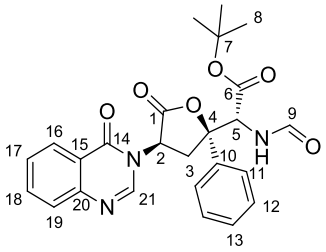


Compound **2-12** (350 mg, 0.72 mmol) was suspended in methanol (35 mL), and then 35 mg of 10% Pd/C was added. The flask was charged with a hydrogen balloon, and stirred at rt for 30 min. The reaction was filtrated through Celite, and solid was washed with tetrahydrofuran. All combined solventss were removed and the residue (about 320 mg) was redissolved in MeOH (15 mL) and trimethyl orthoformate (15 mL). After adding pTSA (80 mg) into the solution, the mixture was heated at 65 ^oC for 1 h. After cooling down, all volatiles were removed, and the residue was redissolved in CH_2Cl_2 and washed with sat.

$NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by FCC MeOH/CH_2Cl_2 (1/100 to 1/50) to give colourless solid 230 mg (69%);

m.p. 128 – 135 °C; **$[\alpha]_D^{25}$** +32.0 (*c* 1.27, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2360, 2339, 1793, 1734, 1679, 1611, 1526, 1475, 1370, 1325, 1299, 1253, 1222, 1188, 1154, 1015, 969, 920, 898, 776, 733, 699;

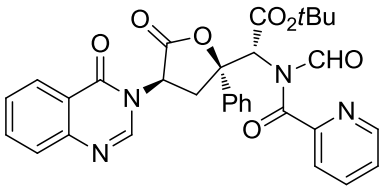


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.29 (dd, *J* = 8.1, 1.4 Hz, 1H, $C_{[16]}H$), 8.21 (t, *J* = 1.1 Hz, 1H, $C_{[9]}H$), 7.95 (s, 1H, $C_{[21]}H$), 7.81 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.73 (dd, *J* = 8.3, 1.1 Hz, 1H, $C_{[ar]}H$), 7.55 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.49 – 7.38 (m, 5H, $C_{[ar]}H$), 7.09 (d, *J* = 7.1 Hz, 1H, N*H*CHO), 5.03 (dd, *J* = 7.2, 0.9 Hz, 1H, $C_{[5]}H$), 4.83 (dd, *J* = 11.2, 9.3 Hz, 1H, $C_{[2]}H$), 3.57 (dd, *J* = 13.5, 11.2 Hz, 1H, $C_{[3]}H'$), 3.14 (dd, *J* = 13.5, 9.4 Hz, 1H, $C_{[3]}H''$), 1.35 (s, 9H, $C_{[8]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 169.9 ($C_{[1]}$), 167.1 ($C_{[6]}$), 161.0 ($C_{[9]}$), 160.8 ($C_{[14]}$), 148.0 ($C_{[20]}$), 145.0 ($C_{[21]}$), 137.9 ($C_{[ar]}$), 135.4 ($C_{[ar]}$), 129.7 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.1 ($C_{[ar]}$), 126.0 ($C_{[ar]}$), 121.8 ($C_{[ar]}$), 85.9 ($C_{[4]}$), 84.0 ($C_{[7]}$), 59.5 ($C_{[5]}$), 56.6 ($C_{[2]}$), 34.1 ($C_{[3]}$), 28.0 ($C_{[8]}$);

HRMS (ESI) $[C_{25}H_{25}N_3O_6+H]^+$ requires *m/z* 464.1816, found *m/z* 464.1817.

Compound 2-33



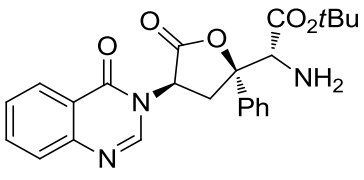
To a 2 mL CH_2Cl_2 solution of the formamide **2-32** (23 mg, 0.05 mmol, 1.0 eq), 2-picolinic acid (12.3 mg, 0.1 mmol, 2.0 eq) and DMAP (0.6 mg, 0.005 mmol, 0.1 eq), *N*,*N*'-dicyclohexylcarbodiimide (20.6 mg, 0.1 mmol, 2.0 eq) were added. The reaction was stirred at rt for 60 h, before the mixture was filtered through a pad of Celite, concentrated and purified with FCC ethyl acetate / CH_2Cl_2 (from 1/50 to 1/20) to give a white solid 2 mg (7%), which was decomposing at rt;

IR (film) ν_{max}/cm^{-1}: 1792, 1741, 1674, 1611, 1473, 1371, 1337, 1294, 1256, 1207, 1155, 1017, 892, 775, 749, 695, 618;

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 9.24 (s, 1H, NC*H*O), 8.67 (d, *J* = 4.7 Hz, 1H, $C_{[ar]}H$), 8.33 (s, 1H, NC*H*N), 8.23 (dd, *J* = 8.0, 1.4 Hz, 1H, $C_{[ar]}H$), 8.02 (d, *J* = 7.8 Hz, 1H, $C_{[ar]}H$), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H, $C_{[ar]}H$), 7.70 – 7.81 (m, 2H, $C_{[ar]}H$), 7.63 (d, *J* = 7.2 Hz, 2H, $C_{[ar]}H$), 7.47 – 7.53 (m, 2H, $C_{[ar]}H$), 7.34 – 7.44 (m, 3H, $C_{[ar]}H$), 5.88 (s, 1H, C*H*CO_2*t*Bu), 5.44 (t, *J* = 10.2 Hz, 1H, C*H*CH_2), 3.51 – 3.71 (m, CHC*H*$_2$), 1.36 (s, 9H, *t*Bu);

HRMS (ESI) $[C_{31}H_{28}N_4O_7+H]^+$ requires *m/z* 569.2031, found *m/z* 569.2031.

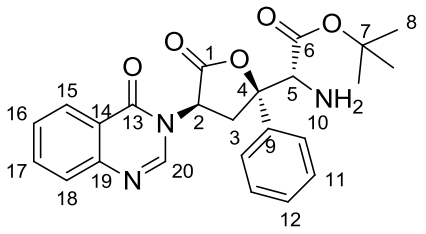
Compound 2-34



Formamide **2-32** (23 mg, 0.05 mmol, 1.0 eq) was dissolved in methanol (1.5 mL), and then thionyl chloride (178 mg, 1.5 mmol) was added dropwise at 0 °C dropwise. The reaction was stirred at rt for another 15 min before concentrated under vacuum and triturated with diethyl ether. The solid residue was dried at 50 °C under high vacuum overnight. The light green salt could be used for further reactions with no more purification. The freebase primary amine **2-34** was extracted from sat. $NaHCO_3$ with CH_2Cl_2 and characterized;

m.p. 70 – 78 °C; **$[\alpha]_D^{25}$** +1.7 (*c* 0.55, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2978, 2928, 1787, 1727, 1677, 1610, 1567, 1475, 1450, 1393, 1369, 1325, 1295, 1252, 1209, 1188, 1155, 1108, 1015, 972, 911, 843, 775, 732, 699, 647, 619;

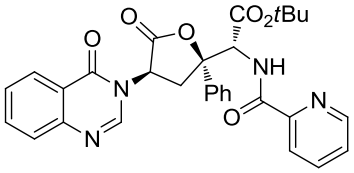


^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.27 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.02 (s, 1H, $C_{[20]}H$), 7.78 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.71 (dd, *J* = 8.2, 1.1 Hz, 1H, $C_{[ar]}H$), 7.52 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.47 – 7.50 (m, 2H, $C_{[ar]}H$), 7.38 – 7.44 (m, 3H, $C_{[ar]}H$), 4.97 (dd, *J* = 11.4, 9.1 Hz, 1H, $C_{[2]}H$), 3.94 (s, 1H, $C_{[5]}H$), 3.39 (dd, *J* = 13.1, 11.4 Hz, 1H, $C_{[3]}H'$), 3.09 (dd, *J* = 13.1, 9.2 Hz, 1H, $C_{[3]}H''$), 1.85 (bs., 2H, $N\underline{H}_2$), 1.28 (s, 9H, $C_{[8]}H$);

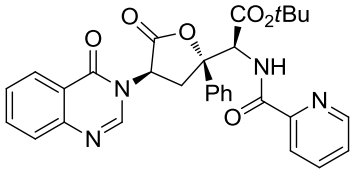
^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 170.7 ($C_{[1]}$), 170.2 ($C_{[6]}$), 160.7 ($C_{[13]}$), 147.9 ($C_{[ar]}$), 145.3 ($C_{[20]}$), 138.7 ($C_{[ar]}$), 135.1 ($C_{[ar]}$), 129.3 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.1 ($C_{[ar]}$), 126.1 ($C_{[ar]}$), 121.9 ($C_{[ar]}$), 87.9 ($C_{[4]}$), 82.8 ($C_{[7]}$), 63.4 ($C_{[5]}$), 56.4 ($C_{[2]}$), 33.4 ($C_{[3]}$), 28.0 ($C_{[8]}$);

HRMS (ESI) $[C_{24}H_{25}N_3O_5+H]^+$ requires *m/z* 436.1867, found *m/z* 436.1867.

Compound (*R,S,R*)-2-35 & (*R,R,S*)-2-35



(*R,S,R*)-**2-35**



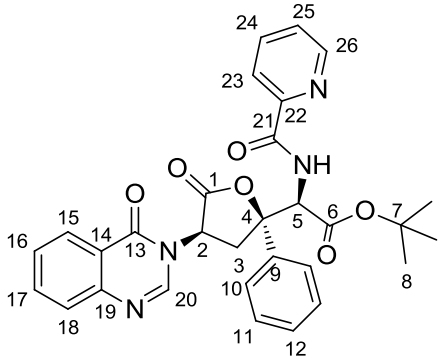
(*R,R,S*)-**2-35**

The light green solid (**2-34**·HCl) and 2-pyridinecarbonyl chloride hydrochloride (17.8 mg, 0.1 mmol, 2.0 eq) were suspended in CH_2Cl_2 (1.5 mL). To the stirring suspension at rt, 1.5 mL of aq. $NaHCO_3$ (84 mg, 1.0 mmol, 20 eq) was added. The bi-phasic reaction mixture was stirred at rt for another 15 min before diluted with CH_2Cl_2 and separated. Orgnanic phase was washed with brine and dried over $MgSO_4$, filtered and concentrated. The residue was purified with FCC CH_2Cl_2 / ethyl acetate (20/1 to 8/1) to give the minor diastereomer (*R,R,S*)-**2-35** as a colorless solid 2 mg (6%) and the major diastereomer (*R,S,R*)-**2-35** as a colorless solid 23 mg (78%);

Compound (*R,S,R*)-**2-35**:

m.p. 115 – 122 °C; **$[\alpha]_D^{25}$** –23.7 (*c* 0.34, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3377, 2979, 2361, 1795, 1732, 1682, 1610, 1557, 1512, 1474, 1394, 1370, 1325, 1253, 1155, 1022, 970, 899, 842, 777, 740, 698;



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.60 (d, *J* = 9.7 Hz, 1H, N*H*), 8.45 (d, *J* = 5.2 Hz, 1H, $C_{[ar]}H$), 8.25 (dd, *J* = 7.9, 1.5 Hz, 1H, $C_{[ar]}H$), 8.03 (d, *J* = 2.0 Hz, 1H, $C_{[ar]}H$), 7.99 (s, 1H, $C_{[20]}H$), 7.77 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.71 (dd, *J* = 8.3, 1.1 Hz, 1H, $C_{[ar]}H$), 7.55 – 7.31 (m, 8H), 5.36 (d, *J* = 9.6 Hz, 1H, $C_{[5]}H$), 5.14 (dd, *J* = 11.8, 8.8 Hz, 1H, $C_{[2]}H$), 3.63 (t, *J* = 12.2 Hz, 1H, $C_{[3]}H'$), 3.12 (dd, *J* = 12.6, 8.9 Hz, 1H, $C_{[3]}H''$), 1.44 (s, 9H, $C_{[8]}H$);

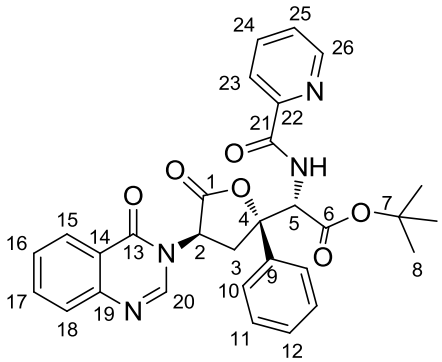
^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.6 ($C_{[1]}$), 167.0 ($C_{[6]}$), 163.2 ($C_{[21]}$), 160.5 ($C_{[13]}$), 150.4 ($C_{[ar]}$), 149.5 ($C_{[ar]}$), 147.8 ($C_{[ar]}$), 146.0 ($C_{[ar]}$), 144.8 ($C_{[20]}$), 138.1 ($C_{[ar]}$), 135.1 ($C_{[ar]}$), 129.4 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 126.9 ($C_{[ar]}$), 125.6 ($C_{[ar]}$), 123.2 ($C_{[ar]}$), 121.8 ($C_{[ar]}$), 86.7 ($C_{[4]}$), 84.4 ($C_{[7]}$), 59.6 ($C_{[5]}$), 54.6 ($C_{[2]}$), 37.4 ($C_{[3]}$), 28.1 ($C_{[8]}$);

HRMS (ESI) $[C_{30}H_{28}N_4O_6+H]^+$ requires *m/z* 541.2082, found *m/z* 541.2080.

Compound (*R*,*R*,*S*)-**2-35**:

m.p. 108 – 115 °C; **$[\alpha]_D^{25}$** –12.6 (*c* 1.33, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2956, 1793, 1731, 1680, 1610, 1568, 1512, 1471, 1369, 1348, 1325, 1295, 1252, 1186, 1154, 1105, 1021, 967, 913, 842, 776, 733, 698, 621;



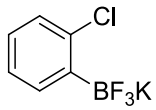
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.70 (d, *J* = 9.7 Hz, 1H, N*H*), 8.55 (dt, *J* = 4.6, 1.3 Hz, 1H, $C_{[ar]}H$), 8.25 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.03 (dt, *J* = 7.8, 1.1 Hz, 1H, $C_{[ar]}H$), 8.00 (s, 1H, $C_{[20]}H$), 7.73 – 7.83 (m, 2H, $C_{[ar]}H$), 7.70 (dd, *J* = 8.2, 1.2 Hz, 1H, $C_{[ar]}H$), 7.44 – 7.55 (m, 3H,

$C_{[ar]}H$), 7.29 – 7.44 (m, 4H, $C_{[ar]}H$), 5.40 (d, *J* = 9.7 Hz, 1H, $C_{[5]}H$), 5.16 (dd, *J* = 11.9, 8.8 Hz, 1H, $C_{[2]}H$), 3.61 (t, *J* = 12.3 Hz, 1H, $C_{[3]}H'$), 3.13 (dd, *J* = 12.6, 8.8 Hz, 1H, $C_{[3]}H''$), 1.43 (s, 9H, $C_{[8]}$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 170.7 ($C_{[1]}$), 167.2 ($C_{[6]}$), 164.3 ($C_{[21]}$), 160.5 ($C_{[13]}$), 148.9 ($C_{[ar]}$), 148.6 ($C_{[ar]}$), 147.8 ($C_{[ar]}$), 144.7 ($C_{[ar]}$), 138.1 ($C_{[ar]}$), 137.5 ($C_{[ar]}$), 135.0 ($C_{[ar]}$), 129.4 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 126.8 ($C_{[ar]}$), 125.7 ($C_{[ar]}$), 122.6 ($C_{[ar]}$), 121.8 ($C_{[ar]}$), 86.8 ($C_{[4]}$), 84.2 ($C_{[7]}$), 59.6 ($C_{[5]}$), 54.4 ($C_{[2]}$), 37.6 ($C_{[3]}$), 28.1 ($C_{[8]}$);

HRMS (ESI) $[C_{30}H_{28}N_4O_6+H]^+$ requires *m/z* 541.2082, found *m/z* 541.2081.

Compound 3-1



1-Bromo-2-chlorobenzene (9.57 g, 50 mmol, 1.0 eq) and triisopropyl borate (14 mL, 60 mmol, 1.2 eq) were dissolved in toluene (80 mL) and THF (20 mL). The mixture was cooled to – 80 °C whilst 2.5 M *n*-butyllithium solution in hexane (24 mL, 60 mmol, 1.2 eq) was added dropwise within 1 hour. The reaction was kept at – 80 °C for 30 min before allowing to warm to – 20 °C, where aq. KHF_2 (23.4 g, 300 mmol, 6.0 eq) in 100 mL of H_2O was added and then warm to rt for stirring overnight. All volatiles were removed under high vacuum, and the residue was dissolved in acetone, filtered off solids, and concentrated again. The residue was recrystallized in acetone nitrile twice to give colourless layer structured crystal 5.2 g (48%);

m.p. 208 – 224 °C;

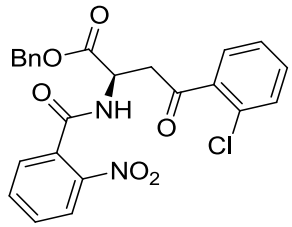
^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 7.62 – 7.47 (m, 1H, $C_{[ar]}H$), 7.16 – 7.10 (m, 1H, $C_{[ar]}H$), 7.07 – 6.97 (m, 2H, $C_{[ar]}H$);

^{19}F NMR (Acetone-d_6, 376 MHz) δ (ppm): –141.8, –141.9, –142.0, –142.2;

^{13}C NMR (Acetone-d_6, 100 MHz) δ (ppm): 139.2 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 135.1 ($C_{[ar]}$), 135.1 ($C_{[ar]}$), 135.1 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 125.7 ($C_{[ar]}$); peaks split from 135.1 to 135.2 ppm;

HRMS (ESI) dissociates in solution to $[K^+(C_6H_4ClBF_3)^-]$; $[C_6H_4ClBF_3]^-$ requires *m/z* 179.0052, found *m/z* 179.0051.

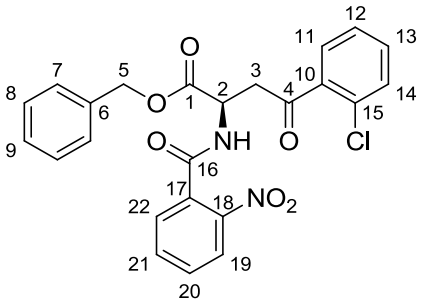
Compound 3-2



Ketone **2-7** (35 mg, 0.1 mmol, 1.0 eq), potassium trifluoroborate **3-1** (44 mg, 0.2 mmol, 2.0 eq), palladium(II) acetate (22 mg, 0.1 mmol, 1.0 eq) and 2,2'-bipyridyl (23 mg, 0.15 mmol, 1.5 eq) were placed in the mixture of THF (1.0 mL) and H_2O (0.2 mL), and TFA (76 µL, 1.0 mmol, 10.0 eq) was added into the resulting solution. The reaction was stirred at 70 °C under Ar for 15 hours before it was diluted with ethyl acetate, washed with 1 M HCl, 0.5 M NaOH and brine, dried over $MgSO_4$, filtered and concentrated to give the dark yellow solid residue. The crude product was purified with FCC Et_2O/CH_2Cl_2 (from 1/50 to 1/20) to give the colourless solid 14 mg (30%);

m.p. 78 – 80 °C; **$[\alpha]_D^{25}$** +24.9 (*c* 0.43, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1744, 1674, 1650, 1590, 1531, 1472, 1434, 1349, 1262, 1214, 1108, 1070, 1035, 989, 956, 905, 853, 791, 761, 752, 742;

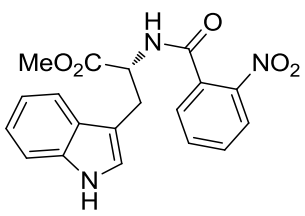


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.06 (dd, *J* = 8.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.65 (td, *J* = 7.5, 1.2 Hz, 1H, $C_{[ar]}H$), 7.60 – 7.55 (m, 1H, $C_{[ar]}H$), 7.52 (ddd, *J* = 7.4, 3.2, 1.5 Hz, 2H, $C_{[ar]}H$), 7.42 – 7.37 (m, 2H, $C_{[ar]}H$), 7.36 – 7.27 (m, 6H, $C_{[ar]}H$), 6.99 (d, *J* = 8.1 Hz, 1H, CON*H*), 5.22 (s, 2H, $C_{[5]}H$), 5.14 (dt, *J* = 8.0, 3.9 Hz, 1H, $C_{[2]}H$), 3.86 – 3.80 (m, 2H, $C_{[3]}H$);

^{13}C NMR ($CDCl_3$, 120 MHz) δ (ppm): 200.8 ($C_{[4]}$), 170.6 ($C_{[1]}$), 166.3 ($C_{[16]}$), 146.6 ($C_{[ar]}$), 137.5 ($C_{[ar]}$), 135.3 ($C_{[ar]}$), 134.1 ($C_{[ar]}$), 132.7 ($C_{[ar]}$), 132.5 ($C_{[ar]}$), 131.6 ($C_{[ar]}$), 131.1 ($C_{[ar]}$), 130.9 ($C_{[ar]}$), 129.8 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 127.3 ($C_{[ar]}$), 124.9 ($C_{[ar]}$), 68.1 ($C_{[5]}$), 49.3 ($C_{[2]}$), 44.1 ($C_{[3]}$);

HRMS (ESI) $[C_{24}H_{19}N_2O_6Cl+H]^+$ requires *m/z* 467.1004, found *m/z* 467.1006.

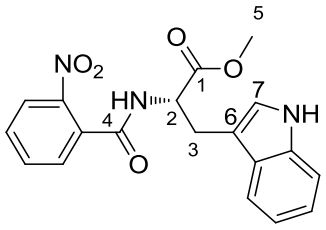
Compound 3-3



D-Tryptophan methyl ester hydrochloride (10 g, 39 mmol, 1.0 eq) and sodium hydrogen carbonate (13 g, 156 mmol, 4.0 eq) were dissolved in water (130 mL) and CH_2Cl_2 (130 mL). Then 2-nitrobenzoyl chloride (7.2 g, 39 mmol, 1.0 eq) was added into the reaction mixture dropwise. After stirring for 15 min, the bi-phasic reaction mixture was separated, and the aqueous phase was extract with CH_2Cl_2. The combined organic phase was washed with 1 N HCl, brine and dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC CH_2Cl_2/Et_2O (from 100/1 to 8/1) to give light yellow foam 14.28 g (99%);

m.p. 50 – 55 ^oC; **$[\alpha]_D^{25}$** –58.4 (*c* 0.48, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3405, 3346, 1738, 1652, 1528, 1458, 1439, 1349, 1311, 1253, 1217, 1101, 1011, 910, 850, 789, 735, 699, 648;

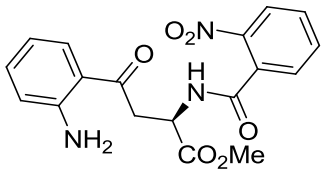


^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.19 (s, 1H, Indole), 7.98 (dd, *J* = 7.9, 1.4 Hz, 1H, $C_{[ar]}H$), 7.68 – 7.44 (m, 3H, $C_{[ar]}H$), 7.36 – 7.27 (m, 2H, $C_{[ar]}H$), 7.15 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, C[ar]H), 7.09 – 7.03 (m, 2H, $C_{[ar]}H$), 6.43 (d, *J* = 8.0 Hz, 1H, CON*H*), 5.15 (dt, *J* = 8.0, 5.2 Hz, 1H, $C_{[2]}H$), 3.70 (s, 3H, $C_{[5]}H$), 3.45 (d, *J* = 5.3 Hz, 2H, $C_{[3]}H$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 172.2 ($C_{[1]}$), 166.0 ($C_{[4]}$), 146.8 ($C_{[ar]}$), 136.3 ($C_{[ar]}$), 133.8 ($C_{[ar]}$), 132.5 ($C_{[ar]}$), 130.8 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 124.7 ($C_{[ar]}$), 123.4 ($C_{[ar]}$), 122.4 ($C_{[ar]}$), 119.9 ($C_{[ar]}$), 118.7 ($C_{[ar]}$), 111.5 ($C_{[ar]}$), 109.8 ($C_{[ar]}$), 53.5 ($C_{[2]}$), 52.8 ($C_{[5]}$), 27.6 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{17}N_3O_5+H]^+$ requires *m/z* 368.1241, found *m/z* 368.1238.

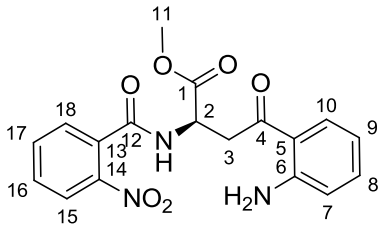
Compound 3-4



Indole **3-3** (3.67 g, 10.0 mmol, 1.0 eq) was dissolved in methanol (250 mL) and water (100 mL). Then sodium periodate (8.6 g, 40.0 mmol, 4.0 eq) was added into the solution in one portion at rt. The reaction was stirred at rt for 3 days before 300 mL water was added. The mixture was extracted with chloroform, washed with sat. $NaHCO_3$, brine, and dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in methanol (150 mL) and water (100 mL) again, sodium periodate (6.45 g, 30 mmol) was added in one portion. The reaction was stirred at rt for another 3 days, before 300 mL water was added. Then the mixture was extracted with chloroform, washed with sat. $NaHCO_3$, brine, and dried over $MgSO_4$, filtered and concentrated. The residue was dissolved methanol (240 mL), and $SOCl_2$ (3 mL) was then added dropwise into the resulting solution at 0 ^oC. Then the reaction was stirred for 1 h at rt, before it was basified with sat. $NaHCO_3$ and extracted with CH_2Cl_2. Combined organic phase was washed with brine and dried over $MgSO_4$, filtered and concentrated. The residue was purified with FCC (methanol / CH_2Cl_2 from 1/200 to 1/50) to give the yellow thick oil 3.12 g (84 %);

$[\alpha]_D^{25}$ – 62.6 (*c 1.01*, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3470, 3350, 1742, 1648, 1616, 1584, 1529, 1485, 1451, 1349, 1313, 1216, 1162, 1114, 1042, 980, 905, 856, 790, 735, 700;

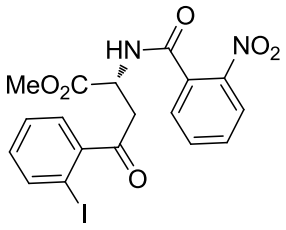


^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.99 (dd, *J* = 8.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.70 (dd, *J* = 8.2, 1.5 Hz, 1H, $C_{[ar]}H$), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H, $C_{[ar]}H$), 7.59 – 7.47 (m, 2H, $C_{[ar]}H$), 7.25 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.04 (d, *J* = 8.5 Hz, 1H, CON*H*), 6.65 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 6.60 (dd, *J* = 8.4, 1.1 Hz, 1H, $C_{[ar]}H$), 6.19 (s, 2H, NH_2), 5.13 (dt, *J* = 8.1, 3.9 Hz, 1H, $C_{[2]}H$), 3.87 – 3.68 (m, 5H, $C_{[11]}H$+$C_{[3]}H$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 199.6 ($C_{[4]}$), 171.8 ($C_{[1]}$), 166.2 ($C_{[12]}$), 150.7 ($C_{[ar]}$), 146.7 ($C_{[ar]}$), 135.3 ($C_{[ar]}$), 133.9 ($C_{[ar]}$), 132.6 ($C_{[ar]}$), 131.3 ($C_{[ar]}$), 130.8 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 124.7 ($C_{[ar]}$), 117.6 ($C_{[ar]}$), 117.2 ($C_{[ar]}$), 116.3 ($C_{[ar]}$), 53.0 ($C_{[11]}$), 48.9 ($C_{[2]}$), 40.7 ($C_{[3]}$);

HRMS (ESI) $[C_{18}H_{17}N_3O_6+H]^+$ requires *m/z* 372.1190, found *m/z* 372.1184.

Compound 3-5

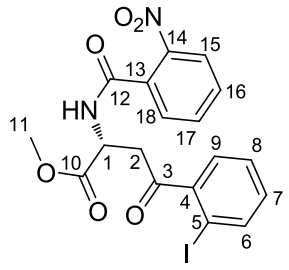


Aniline **3-4** (1.6 g, 4.3 mmol, 1.0 eq) was dissolved in EtOH (15 mL) and 48% HBF_4 (1.13 mL, 8.6 mmol, 2.0 eq). The mixture was stirred for 30 min before at 0 °C 2-methyl-2-nitropropane (1.0 mL, 9.5 mmol, 2.2 eq) was added dropwise. Then at the same temperature, acetone (50 mL) was added to dissolve the participation, and the solution

was kept stirring for another 1 hour. At 0 °C, the above solution was added into a potassium iodide (9.7 g, 58.6 mmol, 14 eq) acetone solution (50 mL), and the reaction was kept stirring at the same temperature for another 1 hours. The reaction was exacted with ethyl acetate, and combined organic phase was washed with sat. $Na_2S_2O_3$, brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC ethyl acetate / petro ether (from 1/2 to 1/1) to give light yellow foam 1.30 g (63%);

m.p. 46 – 47 °C; **$[\alpha]_D^{25}$** –9.9 (*c* 0.95, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1745, 1690, 1653, 1615, 1578, 1530, 1437, 1349, 1312, 1220, 1219, 1041, 990, 963, 911, 854, 760, 733, 698;

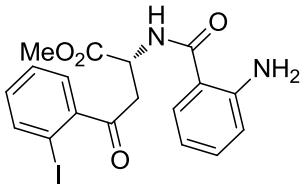


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.07 (dd, *J* = 8.6, 1.2 Hz, 1H, $C_{[ar]}H$), 7.93 (dd, *J* = 7.9, 1.1 Hz, 1H, $C_{[ar]}H$), 7.74 – 7.65 (m, 1H, $C_{[ar]}H$), 7.63 – 7.53 (m, 3H, $C_{[ar]}H$), 7.44 (td, *J* = 7.6, 1.1 Hz, 1H, $C_{[ar]}H$), 7.20 – 7.10 (m, 1H, $C_{[ar]}H$), 7.01 (d, *J* = 8.1 Hz, 1H, CON*H*), 5.09 (dt, *J* = 7.9, 3.9 Hz, 1H, $C_{[1]}H$), 3.82 (s, 3H, $C_{[11]}H$), 3.77 (d, *J* = 2.9 Hz, 1H, $C_{[2]}H'$), 3.76 (d, *J* = 3.1 Hz, 1H, $C_{[2]}H''$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 202.2 ($C_{[3]}$), 171.0 ($C_{[10]}$), 166.3 ($C_{[12]}$), 146.6 ($C_{[ar]}$), 142.2 ($C_{[ar]}$), 141.3 ($C_{[ar]}$), 134.1 ($C_{[ar]}$), 132.7 ($C_{[ar]}$), 132.5 ($C_{[ar]}$), 131.0 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 124.9 ($C_{[ar]}$), 91.3 ($C_{[5]}$), 53.3 ($C_{[11]}$), 49.2 ($C_{[1]}$), 43.0 ($C_{[2]}$);

HRMS (ESI) $[C_{18}H_{15}N_2O_6I+Na]^+$ requires *m/z* 504.9867, found *m/z* 504.9866.

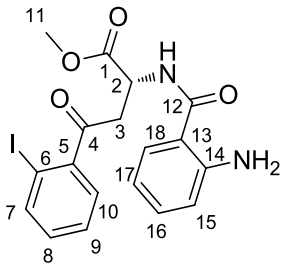
Compound 3-6



Fe powder (2.3 g, 41 mmol, 10.0 eq) and NH_4Cl (4.4 g, 82 mmol, 20.0 eq) was suspended in ethanol (40 mL) and water (40 mL). The mixture was heated in 70 ^oC for 15 min, and at this temperature iodide **3-5** (2.0 g, 4.1 mmol, 1.0 eq) in 40 mL of ethanol was then added. The reaction was kept stirring for 1 hour at 70 ^oC. The mixture was then filtered with Celite, washed with methanol, and the solid residue was refluxing in ethyl acetate / methanol for 60 min and filtered with Celite again. Combined solution was extracted with ethyl acetate and washed with brine, dried over $MgSO_4$, filtered and concentrated to give light yellow foam 1.85 g, which was used directly without further purification;

m.p. 35 – 40 ^oC; **$[\alpha]_D^{25}$** – 61.0 (*c 0.50*, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3461, 3358, 1741, 1694, 1642, 1615, 1583, 1555, 1511, 1435, 1395, 1353, 1261, 1215, 1162, 1093, 1021, 909, 859, 801, 752, 664, 643;



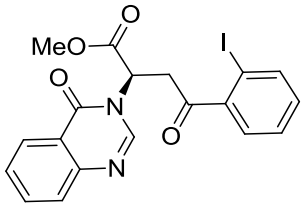
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.92 (dd, *J* = 7.9, 1.0 Hz, 1H, $C_{[ar]}H$), 7.47 – 7.36 (m, 3H, $C_{[ar]}H$), 7.21 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 2H, $C_{[ar]}H$), 7.13 (ddd, *J* = 7.9, 7.2, 1.8 Hz, 1H, $C_{[ar]}H$),

6.72 – 6.59 (m, 2H, $C_{[ar]}H$ & CON*H*), 5.48 (s, 2H, N*H*$_2$), 5.09 (dt, *J* = 8.1, 4.1 Hz, 1H, $C_{[2]}H$), 3.80 (s, 3H, $C_{[11]}H$), 3.75 – 3.55 (m, 2H, $C_{[3]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 202.4 ($C_{[4]}$), 171.8 ($C_{[1]}$), 169.0 ($C_{[12]}$), 149.1 ($C_{[ar]}$), 142.7 ($C_{[ar]}$), 141.3 ($C_{[ar]}$), 133.0 ($C_{[ar]}$), 132.5 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 117.5 ($C_{[ar]}$), 117.0 ($C_{[ar]}$), 115.3 ($C_{[ar]}$), 91.3 ($C_{[6]}$), 53.2 ($C_{[11]}$), 48.7 ($C_{[2]}$), 43.8 ($C_{[3]}$);

HRMS (ESI) $[C_{18}H_{17}N_2O_4I+H]^+$ requires *m/z* 453.0306, found *m/z* 453.0307.

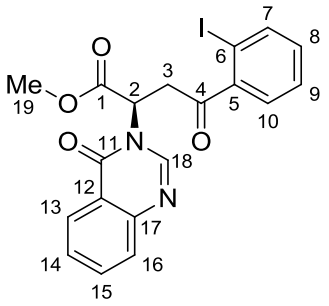
Compound 3-7



Aniline **3-6** (1.85 g) and p-Toluenesulfonic acid monohydrate (450 mg) were dissolved in methanol (30 mL) and trimethyl orthoformate (30 mL). The mixture was stirred at 70 °C for 2.5 hours before all volatiles were removed. The residue was dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC ethyl acetate / petro ether (from 1/2 to 1/1) to give colorless solid 1.56 g (82%, 2 steps).

m.p. 137 – 140 °C; **$[\alpha]_D^{25}$** +115.8 (*c 0.67*, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1747, 1674, 1608, 1581, 1564, 1473, 1434, 1382, 1354, 1287, 1232, 1213, 1196, 1163, 1108, 1084, 1015, 998, 978, 913, 776, 760, 731, 701, 675, 644;

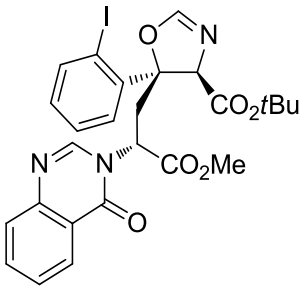


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.29 (s, 1H, $C_{[18]}H$), 8.24 (dd, *J* = 8.0, 1.4 Hz, 1H, $C_{[ar]}H$), 7.88 (dd, *J* = 8.0, 1.1 Hz, 1H, $C_{[ar]}H$), 7.80 – 7.69 (m, 2H, $C_{[ar]}H$), 7.54 – 7.44 (m, 2H, $C_{[ar]}H$), 7.38 (td, *J* = 7.6, 1.1 Hz, 1H, $C_{[ar]}H$), 7.11 (td, *J* = 7.7, 1.7 Hz, 1H, $C_{[ar]}H$), 5.35 (dd, *J* = 8.0, 4.3 Hz, 1H, $C_{[2]}H$), 4.06 (dd, *J* = 19.1, 4.3 Hz, 1H, $C_{[3]}H'$), 3.86 (dd, *J* = 19.1, 8.0 Hz, 1H, $C_{[3]}H''$), 3.76 (s, 3H, $C_{[19]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 200.7 ($C_{[4]}$), 168.8 ($C_{[1]}$), 161.2 ($C_{[11]}$), 148.2 ($C_{[ar]}$), 147.2 ($C_{[18]}$), 142.5 ($C_{[ar]}$), 141.2 ($C_{[ar]}$), 134.9 ($C_{[ar]}$), 132.6 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.7 ($C_{[ar]}$), 126.8 ($C_{[ar]}$), 122.2 ($C_{[ar]}$), 91.3 ($C_{[6]}$), 57.4 ($C_{[2]}$), 53.5 ($C_{[19]}$), 41.8 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{15}N_2O_4I+H]^+$ requires *m/z* 463.0149, found *m/z* 463.0149.

Compound 3-8

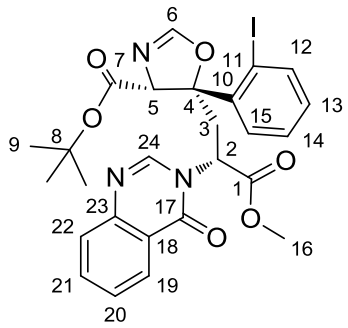


Ketone **3-7** (600 mg, 1.30 mmol, 1.0 eq), Ligand-**1** (40 mg, 0.065 mmol, 5% eq), silver acetate (10.5 mg, 0.065 mmol, 5% eq) were dissolved in ethyl acetate (38 mL). The mixture

was stirred at rt for 20 min, and then cooled to 0 °C. At this temperature, *tert*-butyl isocyanoacetate (275 mg, 1.95 mmol, 1.5 eq) in ethyl acetate (2.0 mL) was injected into the reaction. Left the reaction stirring at the same temperature for 48 h before it was filtered with Celite, concentrated and purified with FCC petro ether / ethyl acetate (from 60/40 to 30/70, then 100% ethyl acetate) gave colorless foam 710 mg (91%, dr = 14:1);

m.p. 42 – 45 °C; **$[\alpha]_D^{25}$** +0.6 (*c 0.83*, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1735, 1678, 1636, 1609, 1565, 1473, 1435, 1389, 1370, 1326, 1265, 1213, 1153, 1106, 1073, 1037, 1005, 949, 904, 848, 755, 700, 669, 643;

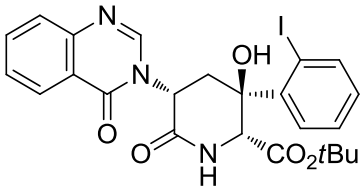


^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.01 (d, *J* = 7.7 Hz, 1H, $C_{[ar]}H$), 7.65 (t, *J* = 7.6 Hz, 1H, $C_{[ar]}H$), 7.45 – 7.54 (m, 3H, $C_{[ar]}H$), 7.37 (t, *J* = 7.6 Hz, 1H, $C_{[ar]}H$), 7.30 (d, *J* = 7.7 Hz, 1H, $C_{[ar]}H$), 7.22 (s, 1H, $C_{[24]}H$), 6.91 (t, *J* = 7.7 Hz, 1H, $C_{[ar]}H$), 6.37 (s, 1H, $C_{[6]}H$, with rotamer peak), 5.10 (d, *J* = 10.1 Hz, 1H, $C_{[2]}H$), 4.80 (s, 1H, $C_{[5]}H$), 3.98 (t, *J* = 13.0 Hz, 1H, $C_{[3]}H'$), 3.69 (s, 3H, $C_{[16]}H$), 3.16 (d, *J* = 15.9 Hz, 1H, $C_{[3]}H''$), 1.57 (s, 9H, $C_{[9]}H$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 170.8 ($C_{[1]}$), 169.3 ($C_{[7]}$), 167.4 ($C_{[17]}$), 160.3 ($C_{[ar]}$), 155.3 ($C_{[24]}$), 147.4 ($C_{[ar]}$), 145.6 ($C_{[ar]}$), 142.9 ($C_{[ar]}$), 140.6 ($C_{[ar]}$), 134.0 ($C_{[ar]}$), 129.5 ($C_{[6]}$), 128.2 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 126.7 ($C_{[ar]}$), 121.6 ($C_{[ar]}$), 92.7 ($C_{[11]}$), 89.7 ($C_{[4]}$), 83.5 ($C_{[8]}$), 77.4 ($C_{[5]}$), 56.8 ($C_{[2]}$), 53.4 ($C_{[16]}$), 32.8 ($C_{[3]}$), 28.3 ($C_{[9]}$), one aromatic carbon did not appear;

HRMS (ESI) $[C_{26}H_{26}N_3O_6I+H]^+$ requires *m/z* 604.0939, found *m/z* 604.0935.

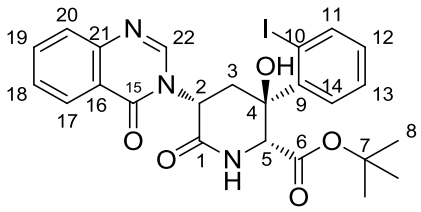
Compound 3-9



Oxazoline **3-8** (28 mg) was dissolved in methanol (1.5 mL), and at 0 °C thionyl chloride (0.1 mL) was then added into the solution dropwise. The reaction was stirred at rt for 1 h before it was diluted with ethyl acetate and washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was dissolved in ethyl acetate (2 mL) and triethylamine (0.2 mL). The resulting mixture was heated at 65 °C overnight before concentrated under vacuum. The residue was purified with FCC MeOH / CH_2Cl_2 (from 1:100 to 3:100) to give colourless solid 22 mg (81%);

m.p. 159 – 164 °C; **$[\alpha]_D^{25}$** – 158.6 (*c* 0.91, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1727, 1681, 1611, 1566, 1475, 1426, 1370, 1324, 1259, 1230, 1155, 1108, 1083, 1052, 1015, 911, 876, 842, 775, 730, 699, 649;



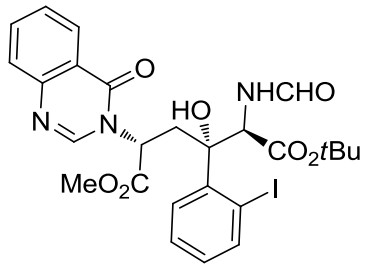
^{1}H NMR (CD_3CN, 500 MHz) δ (ppm): 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.20 (s, 1H, $C_{[22]}H$), 8.10 (dd, *J* = 7.9, 1.4 Hz, 1H, $C_{[ar]}H$), 7.84 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.72 (d, *J* = 8.1 Hz, 1H, $C_{[ar]}H$), 7.57 (t, *J* = 7.6 Hz, 1H, $C_{[ar]}H$), 7.33 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H, $C_{[ar]}H$), 7.27

(dd, *J* = 8.0, 1.8 Hz, 1H, $C_{[ar]}H$), 7.05 (td, *J* = 7.5, 1.7 Hz, 1H, $C_{[ar]}H$), 6.73 (bs., 1H, CON*H*), 6.04 (bs., 1H, O*H*), 5.29 (bs., 1H, $C_{[2]}H$ or $C_{[5]}H$), 4.20 (bs., 1H, $C_{[5]}H$ or $C_{[2]}H$), 3.11 (bs., 1H, $C_{[3]}H'$), 2.57 (s, 1H, $C_{[3]}H''$), 1.06 (s, 9H, $C_{[8]}H$);

^{13}C NMR (CD_3CN, 125 MHz) δ (ppm): 171.3 ($C_{[6]}$), 169.5 ($C_{[1]}$), 161.8 ($C_{[15]}$), 149.3 ($C_{[21]}$), 147.3 ($C_{[22]}$), 144.7 ($C_{[ar]}$), 143.0 ($C_{[ar]}$), 135.9 ($C_{[ar]}$), 131.5 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 129.5 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 123.1 ($C_{[ar]}$), 96.0 ($C_{[10]}$), 83.6 ($C_{[7]}$), 74.4 ($C_{[4]}$), 62.6 ($C_{[2]}$ or $C_{[5]}$), 52.0 ($C_{[5]}$ or $C_{[2]}$), 38.3 ($C_{[3]}$), 28.0 ($C_{[8]}$);

HRMS (ESI) $[C_{24}H_{24}N_3O_5I+H]^+$ requires *m/z* 562.0833, found *m/z* 562.0830.

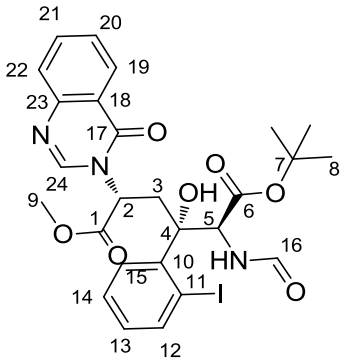
Compound 3-10



Oxazoline **3-8** (710 mg, 1.17 mmol) was dissolved in THF (30 mL), and 3 mL of 1 N HCl was then added into the solution. The reaction was stirred at rt for 5 min before it was extract with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified with FCC CH_2Cl_2 / methanol (from 200/1 to 200/6) to give colourless solid 728 mg (99%);

m.p. 88 – 92 °C; **$[\alpha]_D^{25}$** +62.7 (*c* 0.51, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3417, 2979, 2922, 1743, 1678, 1610, 1505, 1474, 1457, 1437, 1374, 1346, 1325, 1266, 1234, 1154, 1037, 1104, 912, 841, 774, 732, 700, 646;

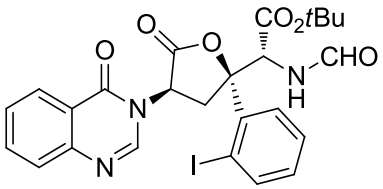


^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 8.02 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.84 – 7.70 (m, 3H, NHC*H*O, $C_{[ar]}H$), 7.56 (s, 1H, $C_{[24]}H$), 7.52 (d, *J* = 8.1 Hz, 2H, $C_{[ar]}H$), 7.46 (t, *J* = 7.6 Hz, 1H, $C_{[ar]}H$), 7.38 (d, *J* = 8.4 Hz, 1H, N*H*CHO), 7.08 (t, *J* = 7.7 Hz, 1H, $C_{[ar]}H$), 6.53 (t, *J* = 7.6 Hz, 1H, $C_{[ar]}H$), 5.68 (s, 1H, $C_{[5]}H$), 5.08 (d, *J* = 5.8 Hz, 1H, $C_{[2]}H$), 4.14 – 3.89 (m, 1H, $C_{[3]}H$), 3.65 (s, 3H, $C_{[9]}H$), 3.30 (dd, *J* = 15.7, 3.0 Hz, 1H, $C_{[3]}H'$), 1.59 (s, 9H, $C_{[8]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 171.2 ($C_{[1]}$), 169.4 ($C_{[6]}$), 161.9 ($C_{[16]}$), 161.0 ($C_{[17]}$), 148.9 ($C_{[ar]}$), 147.8 ($C_{[24]}$), 143.2 ($C_{[ar]}$), 143.0 ($C_{[ar]}$), 134.9 ($C_{[ar]}$), 130.4 ($C_{[ar]}$), 129.7 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 122.8 ($C_{[ar]}$), 94.5 ($C_{[11]}$), 83.3 ($C_{[7]}$), 77.8 ($C_{[4]}$), 59.0 ($C_{[5]}$), 57.9 ($C_{[2]}$), 53.2 ($C_{[9]}$), 35.5 ($C_{[3]}$), 28.3 ($C_{[8]}$);

HRMS (ESI) $[C_{26}H_{28}N_3O_7I+H]^+$ requires *m/z* 622.1045, found *m/z* 622.1042.

Compound 3-11

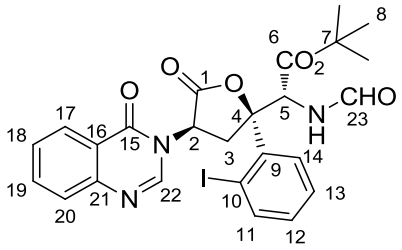


Compound **3-10** (730 mg, 1.18 mmol) was dissolved in toluene (50 mL) and acetic acid (2.3 mL). The resulting solution was stirred at 75 °C for 3 days before it was concentrated under

vacuum, redissolved in ethyl acetate, washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated again. The residue was purified with FCC CH_2Cl_2 / methanol (from 200:1 to 200:4) to give a colourless solid 510 mg (70%) and recovered 100 mg of starting material;

m.p. 100 – 112 °C; **$[\alpha]_D^{25}$** –34.0 (*c* 1.33, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2925, 1796, 1723, 1682, 1610, 1517, 1475, 1460, 1424, 1386, 1370, 1324, 1298, 1252, 1200, 1187, 1153, 1108, 1029, 1005, 967, 929, 892, 774, 753, 699;

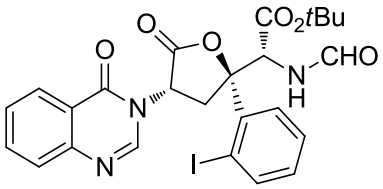


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.24 (s, 1H, $C_{[22]}H$), 8.20 (dd, *J* = 8.1, 1.4 Hz, 1H, $C_{[ar]}H$), 8.09 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}H$), 7.96 (d, *J* = 1.0 Hz, 1H, $C_{[23]}H$), 7.87 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.70 (d, *J* = 8.1 Hz, 1H, $C_{[ar]}H$), 7.68 (s, 1H, N*H*CHO), 7.61 – 7.55 (m, 2H, $C_{[ar]}H$), 7.53 – 7.49 (m, 1H, C[ar]H), 7.15 (td, *J* = 7.5, 1.7 Hz, 1H, $C_{[ar]}H$), 6.03 (d, *J* = 9.5 Hz, 1H, $C_{[5]}H$), 5.16 (dd, *J* = 11.3, 9.0 Hz, 1H, $C_{[2]}H$), 3.81 – 3.71 (m, 2H, $C_{[3]}H$), 1.56 (s, 9H, $C_{[8]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 170.7 ($C_{[1]}$), 167.6 ($C_{[6]}$), 161.1 ($C_{[23]}$), 160.6 ($C_{[15]}$), 149.0 ($C_{[ar]}$), 147.7 ($C_{[22]}$), 144.1 ($C_{[ar]}$), 140.9 ($C_{[ar]}$), 135.6 ($C_{[ar]}$), 131.4 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 122.9 ($C_{[ar]}$), 94.9 ($C_{[10]}$), 87.8 ($C_{[4]}$), 83.9 ($C_{[7]}$), 57.3 ($C_{[2]}$), 56.6 ($C_{[5]}$), 34.5 ($C_{[3]}$), 28.4 ($C_{[8]}$);

HRMS (ESI) $[C_{25}H_{24}N_3O_6I+H]^+$ requires *m/z* 590.0783, found *m/z* 590.0783.

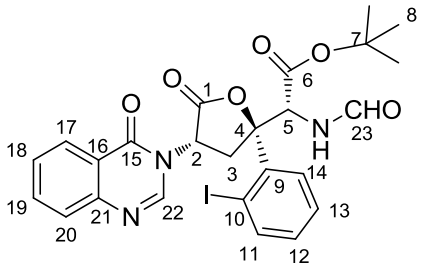
Compound 3-12



Compound **3-10** (7.5 mg) and potassium carbonate (1.5 mg) were dissolved in toluene (0.5 mL), which was heated at 70 °C for 4 hours. After filtered through a pad of Celite, concentrated under vacuum, the residue was purified with Prep-HPLC (*i*PrOH:hexane = 20:80, flow 20 mL/min) to give the colourless solid 4 mg (56%);

m.p. 138 – 145 °C; **$[\alpha]_D^{25}$** –81.7 (*c* 0.10, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1792, 1724, 1682, 1610, 1506, 1473, 1390, 1371, 1322, 1296, 1252, 1210, 1190, 1153, 982, 967, 921, 884, 838, 777, 742, 699;



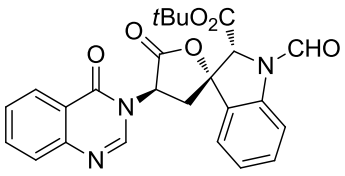
^{1}H NMR (CD_3CN, 500 MHz) δ (ppm): 8.14 (s, 1H, $C_{[22]}H$), 7.96 (d, *J* = 8.0 Hz, 2H, $C_{[ar]}H$), 7.82 – 7.74 (m, 3H, $C_{[ar]}H$ & C*H*O), 7.71 – 7.66 (m, 1H, $C_{[ar]}$), 7.53 – 7.45 (m, 2H, $C_{[ar]}H$), 7.08 (tt, *J* = 7.6, 1.7 Hz, 2H, $C_{[ar]}H$ & N*H*CHO), 5.81 (d, *J* = 10.0 Hz, 1H, $C_{[5]}H$), 5.01 (t, *J* = 7.8 Hz, $C_{[2]}H$), 4.01 (m, 1H, $C_{[3]}H'$), 2.90 (dd, *J* = 12.5, 7.6 Hz, 1H, $C_{[3]}H''$), 1.54 (s, 9H, $C_{[8]}H$);

^{13}C NMR (CD_3CN, 125 MHz) δ (ppm): 171.7 ($C_{[1]}$), 169.3 ($C_{[6]}$), 161.1 ($C_{[15]}$), 161.0 ($C_{[23]}$), 149.1 ($C_{[ar]}$), 148.1 ($C_{[22]}$), 144.0 ($C_{[ar]}$), 142.9 ($C_{[ar]}$), 135.8 ($C_{[ar]}$), 131.0 ($C_{[ar]}$), 129.8 ($C_{[ar]}$),

128.7 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 122.8 ($C_{[ar]}$), 93.1 ($C_{[10]}$), 88.4 ($C_{[4]}$), 84.7 ($C_{[7]}$), 59.0 ($C_{[2]}$), 56.7 ($C_{[5]}$), 38.5 ($C_{[3]}$), 28.2 ($C_{[8]}$);

HRMS (ESI) $[C_{25}H_{24}N_3O_6I+H]^+$ requires *m/z* 590.0783, found *m/z* 590.0780.

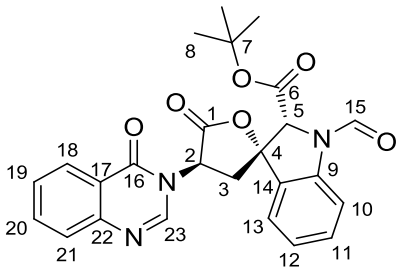
Compound 3-13



Lactone **3-11** (35 mg, 0.06 mmol, 1.0 eq), copper(I) iodide (13.7 mg, 0.072 mmol, 1.2 eq) and magnesium acetate tetrahydrate (19.3 mg, 0.09 mmol, 1.5 eq) were placed in a dry flask and charged with Ar. Then dry DMSO (3.5 mL) was injected. The reaction was stirred at the rt for 3 hours before quenched with sat. NH_4Cl and exacted with CH_2Cl_2, washed with water and dried over $MgSO_4$. Then the mixture was filtered and concentrated under vacuum. The residue was triturated with ethyl acetate and the mother liquid was concentrated again and triturated with methanol, combine the solid to give a colourless solid 20 mg (71%);

m.p. 190 – 195 ^oC; **$[\alpha]_D^{25}$** +129.0 (*c* 0.10, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1794, 1744, 1682, 1611, 1494, 1472, 1364, 1252, 1228, 1183, 1156, 1026, 930, 900, 815, 771, 751, 700, 681;



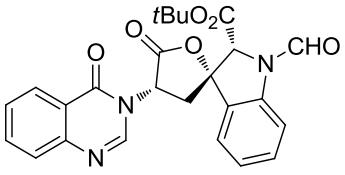
*NMR with rotamers, the major set of peak is assigned as following (confirmed from Noesy)

^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 9.16 (d, *J* = 1.1 Hz, 1H, C*H*O), 8.44 (s, 1H, $C_{[23]}H$), 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.89 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H, $C_{[ar]}H$), 7.75 (tt, *J* = 8.6, 0.9 Hz, 2H, $C_{[ar]}H$), 7.66 – 7.59 (m, 2H, $C_{[ar]}H$), 7.49 (ddd, *J* = 8.3, 7.4, 1.2 Hz, 1H, $C_{[ar]}H$), 7.23 (td, *J* = 7.6, 1.0 Hz, 1H, $C_{[ar]}H$), 6.03 (dd, *J* = 11.1, 9.5 Hz, 1H, $C_{[2]}H$), 5.02 (d, *J* = 1.0 Hz, 1H, $C_{[5]}H$), 3.61 (dd, *J* = 13.3, 11.1 Hz, 1H, $C_{[3]}H$), 3.32 (dd, *J* = 13.2, 9.5 Hz, 1H, $C_{[3]}H'$), 1.64 (s, 9H, $C_{[8]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 170.6 ($C_{[1]}$), 164.7 ($C_{[6]}$), 160.6 ($C_{[16]}$), 158.3 ($C_{[15]}$), 149.1 ($C_{[ar]}$), 148.1 ($C_{[23]}$), 142.4 ($C_{[ar]}$), 135.6 ($C_{[ar]}$), 132.3 ($C_{[ar]}$), 131.8 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 125.6 ($C_{[ar]}$), 125.5 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 111.0 ($C_{[ar]}$), 87.2 ($C_{[4]}$), 83.5 ($C_{[7]}$), 69.6 ($C_{[5]}$), 58.2 ($C_{[2]}$), 39.9 ($C_{[3]}$), 28.2 ($C_{[8]}$);

HRMS (ESI) $[C_{25}H_{23}N_3O_6+H]^+$ requires *m/z* 462.1660, found *m/z* 462.1660.

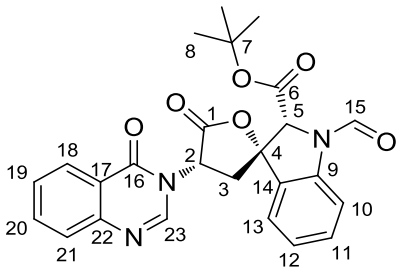
Compound 3-14



Lactone **3-11** (30 mg, 0.05 mmol, 1.0 eq), copper(I) iodide (9.5 mg, 0.05 mmol, 1.0 eq) and cesium carbonate (32 mg, 0.1 mmol, 2.0 eq) were placed into a Schlenk tube and charged with Ar, and dry THF (2 mL) and *N*,*N*'-dimethylethylenediamine (11 µL, 0.1 mmol, 2.0 eq) were added into the tube. The reaction was stirred at rt for 1 h before quenched with sat. NH_4Cl and exacted with ethyl acetate, washed with brine, dried with $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC CH_2Cl_2 / methanol (100:1) to give colourless solid 20 mg (87%), where **3-13** / **3-14** = 1 / 3 according to NMR. The mixture was further purified with prep-HPLC (*i*PrOH:hexane = 40:60, flow 20 mL/min) to give the colourless solid 5 mg (25min, **3-14**) and 1 mg (40min, **3-13**);

m.p. 170 – 174 °C; **$[\alpha]_D^{25}$** –130.8 (*c* 0.50, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1794, 1751, 1719, 1678, 1608, 1493, 1473, 1329, 1288, 1263, 1244, 1226, 1198, 1181, 1150, 1025, 962, 908, 822, 774, 756, 700, 672;



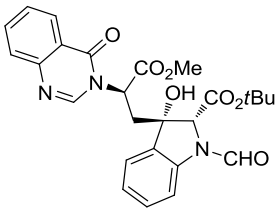
*NMR with rotamers, the major set of peaks is assigned as following (confirmed from Noesy)

^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 9.16 (d, *J* = 1.0 Hz, 1H, $C_{[23]}H$), 8.50 (s, 1H, NC*H*O), 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.92 – 7.86 (m, 2H, $C_{[ar]}H$), 7.75 (dd, *J* = 8.3, 1.3 Hz, 1H, $C_{[ar]}H$), 7.63 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H, $C_{[ar]}H$), 7.60 (d, *J* = 8.1 Hz, 1H, $C_{[ar]}H$), 7.50 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H, $C_{[ar]}H$), 7.31 (td, *J* = 7.5, 0.9 Hz, 1H, $C_{[ar]}H$), 5.69 (dd, *J* = 10.9, 9.2 Hz, 1H, $C_{[2]}H$), 5.21 (d, *J* = 1.1 Hz, 1H, $C_{[5]}H$), 3.50 – 3.36 (m, 2H, $C_{[3]}H$), 1.49 (s, 9H, $C_{[8]}H$);

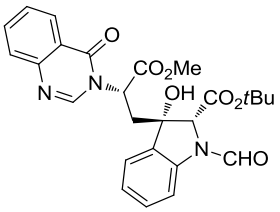
^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 171.5 ($C_{[1]}$), 165.2 ($C_{[6]}$), 161.1 ($C_{[16]}$), 158.4($C_{[15]}$), 149.2 ($C_{[ar]}$), 148.0 ($C_{[23]}$), 142.7 ($C_{[ar]}$), 135.7 ($C_{[ar]}$), 132.6 ($C_{[ar]}$), 130.9 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 126.9 ($C_{[ar]}$), 125.7 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 110.7 ($C_{[ar]}$), 87.2 ($C_{[4]}$), 84.0 ($C_{[7]}$), 69.8 ($C_{[5]}$), 58.6 ($C_{[2]}$), 40.8 ($C_{[3]}$), 28.1 ($C_{[8]}$);

HRMS (ESI) $[C_{25}H_{23}N_3O_6+H]^+$ requires *m/z* 462.1660, found *m/z* 462.1644.

Compound 3-15 & 3-16



3-15/16



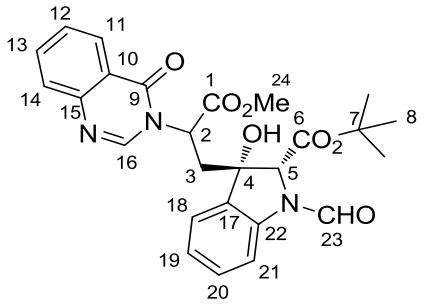
3-16/15

Compound **3-10** (30 mg, 0.05 mmol, 1.0 eq), copper(I) iodide (14 mg, 0.075 mmol, 1.5 eq) and cesium acetate (30 mg, 0.15 mmol, 3.0 eq) were dissolved in 1 mL of dry DMSO. The reaction was stirred under Ar for 10 hours. The reaction was diluted with ethyl acetate and washed with brine, dried over $MgSO_4$ and concentrated under vacuum, then the residue was passed through a silicon column, concentrated again. The NMR indicated a 1:1 ratio of two compounds. This crude mixture was further separated on prep-HPLC (*i*PrOH:hexane = 20:80, flow 20 mL/min) to give **3-15**/**16** 1.2 mg and **3-16**/**15** 1.0 mg for each (5%);

Compound **3-15/16**

m.p. 105 – 110 ^oC; **$[\alpha]_D^{25}$** + 58.0 (*c* 0.10, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2920, 1746, 1677, 1609, 1493, 1473, 1367, 1261, 1216, 1157, 1072, 911, 776, 732, 701;



^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.97 (d, *J* = 1.0 Hz, 1H, C*H*O), 8.28 (dd, *J* = 8.1, 1.0 Hz, 1H, $C_{[ar]}H$), 8.11 (s, 1H, $C_{[16]}H$), 7.81 – 7.69 (m, 2H, $C_{[ar]}H$), 7.52 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H, $C_{[ar]}H$)， 7.35 – 7.22 (m, 3H, $C_{[ar]}H$), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H, $C_{[ar]}H$), 5.22 (dd, *J* = 6.6, 3.1 Hz, 1H, $C_{[2]}H$), 4.90 (s, 1H, $C_{[5]}H$), 3.75 (s, 3H, $C_{[24]}H$), 3.07 (dt, *J* = 15.4, 2.4 Hz, 1H, $C_{[3]}H'$), 2.73 (dd, *J* = 15.6, 6.6 Hz, 1H, $C_{[3]}H''$), 2.65 (s, 1H, O*H*, with rotamer peak), 1.54 (s, 9H, $C_{[8]}H$);

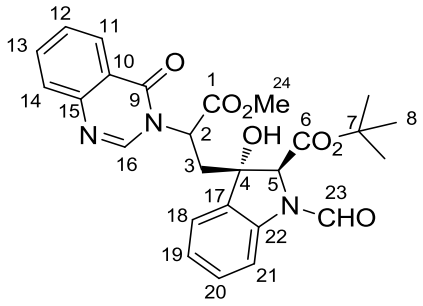
^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 169.5 ($C_{[1]}$), 166.8 ($C_{[6]}$), 161.0 ($C_{[9]}$), 157.0 ($C_{[23]}$), 148.3 ($C_{[ar]}$), 147.1 ($C_{[16]}$), 140.3 ($C_{[ar]}$), 134.8 ($C_{[ar]}$), 133.5 ($C_{[ar]}$), 131.3 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 125.2 ($C_{[ar]}$), 125.1 ($C_{[ar]}$), 122.3 ($C_{[ar]}$), 109.7 ($C_{[ar]}$), 84.1 ($C_{[7]}$), 79.9 ($C_{[4]}$), 68.7 ($C_{[5]}$), 57.6 ($C_{[2]}$), 53.6 ($C_{[24]}$), 42.0 ($C_{[3]}$), 28.3 ($C_{[8]}$);

HRMS (ESI) $[C_{26}H_{27}N_3O_7+H]^+$ requires *m/z* 494.1922, found *m/z* 494.1921.

Compound **3-16/15**

m.p. 76 – 88 ^{o}C; **$[\alpha]_D^{25}$** – 22.8 (*c* 0.08, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2922, 1745, 1677, 1609, 1492, 1473, 1368, 1297, 1258, 1225, 1158, 1078, 1037, 913, 811, 733, 702;

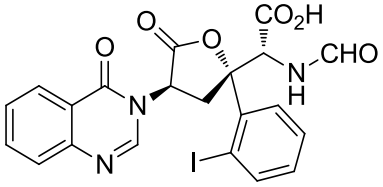


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.93 (d, *J* = 1.0 Hz, 1H, C*H*O), 8.14 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.03 (s, 1H, $C_{[16]}H$), 7.74 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.66 (d, *J* = 8.1 Hz, 1H, $C_{[ar]}H$), 7.46 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.32 (d, *J* = 7.9 Hz, 1H, $C_{[ar]}H$), 7.10 – 7.07 (m, 2H, $C_{[ar]}H$), 6.90 (ddd, *J* = 7.9, 5.7, 2.6 Hz, 1H, $C_{[ar]}H$), 5.53 (t, *J* = 6.1 Hz, 1H, $C_{[2]}H$), 4.78 (s, 1H, $C_{[5]}H$), 3.77 (s, 3H, $C_{[24]}H$), 3.39 (s, 1H, O*H*), 3.32 (dd, *J* = 15.2, 5.3 Hz, 1H, $C_{[3]}H'$), 2.50 (dd, *J* = 15.2, 6.9 Hz, 1H, $C_{[3]}H''$), 1.48 (s, 9H, $C_{[8]}$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.7 ($C_{[1]}$), 166.3 ($C_{[6]}$), 160.7 ($C_{[9]}$), 157.2 ($C_{[23]}$), 147.8 ($C_{[ar]}$), 145.2 ($C_{[16]}$), 140.4 ($C_{[ar]}$), 134.9 ($C_{[ar]}$), 133.0 ($C_{[ar]}$), 130.8 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 127.7 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 125.0 ($C_{[ar]}$), 124.8 ($C_{[ar]}$), 121.8 ($C_{[ar]}$), 109.6 ($C_{[ar]}$), 83.8 ($C_{[7]}$), 79.0 ($C_{[4]}$), 68.3 ($C_{[5]}$), 55.0 ($C_{[2]}$), 53.8 ($C_{[24]}$), 42.5 ($C_{[3]}$), 28.2 ($C_{[8]}$);

HRMS (ESI) $[C_{26}H_{27}N_3O_7+H]^+$ requires *m/z* 494.1922, found *m/z* 494.1920.

Compound 3-17

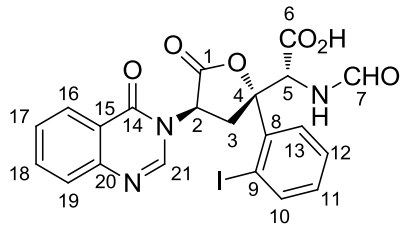


Compound **3-11** (410 mg) was dissolved in CH_2Cl_2 (20 mL) and trifluoroacetic acid (40 mL). The reaction was stirred at rt for 90 min and all volatiles were then removed under vacuum.

The residue was dried under high vacuum at 50 °C to give light brown solid (quant.), which can be used without further purification;

m.p. T_{dec} >180 °C; **$[\alpha]_D^{25}$** +0.8 (*c* 1.00, MeOH);

IR (film) ν_{max}/cm^{-1}: 3350, 1796, 1680, 1613, 1563, 1523, 1477, 1424, 1390, 1323, 1302, 1255, 1194, 1109, 1030, 1003, 955, 895, 773, 723, 696, 657, 623;

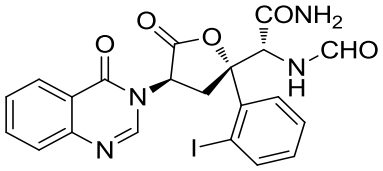


^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 12.40 (s, 1H, COO*H*), 8.47 (s, 1H, $C_{[21]}H$), 8.18 (dd, *J* = 7.9, 1.6 Hz, 1H, $C_{[ar]}H$), 8.08 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}H$), 7.99 (d, *J* = 0.9 Hz, 1H, $C_{[7]}H$), 7.95 (bs., 1H, N*H*CHO), 7.90 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H, $C_{[ar]}H$), 7.76 (d, *J* = 8.1 Hz, 1H, $C_{[ar]}H$), 7.63 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H, $C_{[ar]}H$), 7.58 (dd, *J* = 8.0, 1.7 Hz, 1H, $C_{[ar]}H$), 7.50 (td, *J* = 7.6, 1.3 Hz, 1H, $C_{[ar]}H$), 7.14 (ddd, *J* = 7.8, 1.3, 1.8 Hz, 1H, $C_{[ar]}H$), 6.21 (d, *J* = 9.8 Hz, 1H, $C_{[5]}H$), 5.29 (dd, *J* = 11.2, 9.2 Hz, 1H, $C_{[2]}H$), 3.90 (dd, *J* = 13.2, 11.2 Hz, 1H, $C_{[3]}H'$), 3.78 (dd, *J* = 13.1, 9.3 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 170.9 ($C_{[1]}$), 169.3 ($C_{[6]}$), 161.1 ($C_{[7]}$), 160.7 ($C_{[14]}$), 149.1 ($C_{[ar]}$), 147.7 ($C_{[21]}$), 144.0 ($C_{[ar]}$), 141.2 ($C_{[ar]}$), 135.6 ($C_{[ar]}$), 131.3 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 122.9 ($C_{[ar]}$), 94.8 ($C_{[9]}$), 87.9 ($C_{[4]}$), 57.1 ($C_{[2]}$), 55.6 ($C_{[5]}$), 34.7 ($C_{[3]}$);

HRMS (ESI) $[C_{21}H_{16}N_3O_6I+H]^+$ requires *m/z* 534.0157, found *m/z* 534.0156.

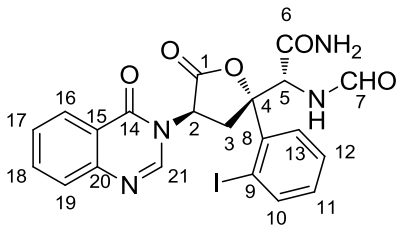
Compound 3-18



Acid **3-17** (266 mg, 0.5 mmol, 1.0 eq) was dissolved in THF (6.0 mL). Resulting solution was cooled to –20 °C, and ethyl chloroformate (65 mg, 0.6 mmol, 1.2 eq) and 4-methylmorpholine (60 mg, 0.6 mmol, 1.2 eq) were then added dropwise. Kept the reaction at –20 °C to –15 °C for another 30 min and 35% NH_4OH (1.0 mL) was added in one portion. Then temperature could be warmed to rt overnight before the mixture was exacted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by FCC methanol / CH_2Cl_2 (from 1/50 to 1/20) to give colourless solid 88 mg (33%);

m.p. 198 – 205 °C; **$[\alpha]_D^{25}$** –88.8 (*c* 0.25, MeOH);

IR (film) ν_{max}/cm^{-1}: 3324, 3196, 1784, 1665, 1608, 1564, 1510, 1475, 1415, 1385, 1325, 1295, 1250, 1213, 1188, 1122, 1108, 1083, 1032, 1002, 980, 923, 883, 774, 757, 734, 700, 670;



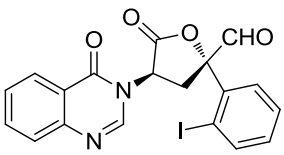
^{1}H NMR (CD_3OD, 500 MHz) δ (ppm): 8.37 (s, 1H, $C_{[21]}H$), 8.04 (dd, *J* = 8.1, 1.4 Hz, 1H, $C_{[ar]}H$), 7.95 (dd, *J* = 7.9, 1.2 Hz, 1H, $C_{[ar]}H$), 7.90 – 7.81 (m, 2H, $C_{[ar]}H$), 7.80 (s, 1H, C*H*O), 7.71 (d, *J* = 8.2 Hz, 1H, $C_{[ar]}H$), 7.47 – 7.54 (m, 2H, $C_{[ar]}H$), 7.06 (td, *J* = 7.6, 1.7 Hz, 1H, $C_{[ar]}H$), 5.90 (s, 1H,

$C_{[5]}H$), 5.37 (dd, *J* = 10.9, 7.9 Hz, 1H, $C_{[2]}H$), 4.16 (dd, *J* = 13.8, 10.9 Hz, 1H, $C_{[3]}H'$), 2.85 (dd, *J* = 13.8, 7.9 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (CD_3OD, 125 MHz) δ (ppm): 173.1 ($C_{[1]}$ or $C_{[6]}$), 173.1 ($C_{[6]}$ or $C_{[1]}$), 163.2 ($C_{[7]}$), 161.7 ($C_{[14]}$), 149.2 ($C_{[ar]}$), 149.0 ($C_{[21]}$), 144.7 ($C_{[ar]}$), 143.3 ($C_{[ar]}$), 136.3 ($C_{[ar]}$), 130.9 ($C_{[ar]}$), 130.1 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 127.5 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 93.1 ($C_{[9]}$), 89.2 ($C_{[4]}$), 60.2 ($C_{[2]}$), 56.2 ($C_{[5]}$), 39.6 ($C_{[3]}$);

HRMS (ESI) $[C_{21}H_{18}N_4O_5I+H]^+$ requires *m/z* 533.0316, found *m/z* 533.0316.

Compound 3-19

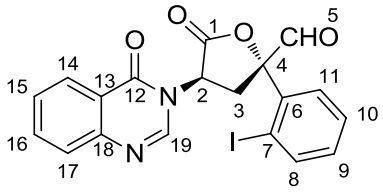


Procedure I:

Amide **3-18** (30 mg, 0.056 mmol, 1.0 eq) and PIFA (27 mg, 0.062 mmol, 1.1 eq) were dissolved in acetonitrile (0.7 mL) and water (0.7 mL). Resulting solution was stirred at rt overnight before con. HCl (0.7 mL) and methanol (0.5 mL) were added. The reaction was then stirred for another 2 h before extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in acetone (5 mL) and 1 N HCl (1.5 mL) was added. The resulting solution was stirred for another 3 h before extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The residue was purified with FCC ethyl acetate / CH_2Cl_2 (from 1/3 to 2/1) to give colourless oil 3 mg (12%);

Procedure II:

Compound **3-12** (36 mg, 0.061 mmol, 1.0 eq) was dissolved in methanol (2 mL), and thionyl chloride (0.15 mL) was then added dropwise at 0 °C. The reaction was stirred for 1 h before all volatiles were removed under vacuum. The residue was dried overnight under high vacuum at 40 °C before it was redissolved in TFA (2 mL) and stirred for 1.5 h. Volatiles were removed under vacuum and the residue was dried overnight under high vacuum at 40 °C again. Then the residue was dissolved in acetonitrile (3 mL) and pH 7.0 phosphate buffer (0.1 M, 3 mL) and PIFA (43 mg, 0.1 mmol, 1.6 eq) was then added into the reaction mixture for overnight stirring before it was extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC ethyl acetate / CH_2Cl_2 (from 1/3 to 2/1) to give colourless oil 7 mg (25%);

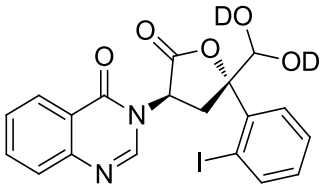


Since the equilibrium between aldehyde and hydrate form **3-20** was always observed, only ^{1}H-NMR of **3-19** was reported;

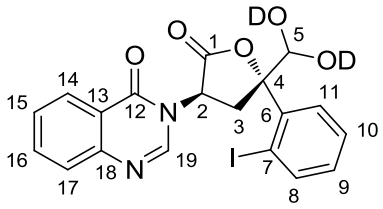
^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 9.97 (d, *J* = 0.8 Hz, 1H, C*H*O), 8.50 (s, 1H, $C_{[19]}H$), 8.11 (ddd, *J* = 7.9, 1.6, 0.6 Hz, 1H, $C_{[ar]}H$), 8.05 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}H$), 7.88 (t, *J* = 1.6 Hz, 1H, $C_{[ar]}H$), 7.85 – 7.87 (m, 1H), 7.72 (dt, *J* = 8.2, 0.8 Hz, 1H, $C_{[ar]}H$), 7.67 (td, *J* = 7.7, 1.3 Hz, 1H, $C_{[ar]}H$), 7.55 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.27 (td, *J* = 7.6, 1.7 Hz, 1H, $C_{[ar]}H$), 5.55 (t, *J* = 9.8 Hz, 1H, $C_{[2]}H$), 4.02 (dd, *J* = 13.2, 10.0 Hz, 1H, $C_{[3]}H'$), 2.97 (ddd, *J* = 13.3, 9.7, 0.9 Hz, 1H, $C_{[3]}H''$);

HRMS (ESI) $[C_{19}H_{13}N_2O_4I+H]^+$ requires *m/z* 461.0004, found *m/z* 460.9992.

Compound 3-20



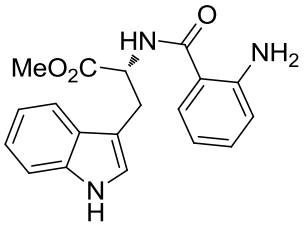
Adding 1 drop of D_2O into compound **3-19**'s acetone-d_6 solution in an NMR tube, after 2 days standing only hemiacetal form existed in the tube;



^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.47 (s, 1H, $C_{[19]}H$), 8.05 (dd, *J* = 8.0, 1.6 Hz, 1H, $C_{[ar]}H$), 7.96 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}H$), 7.83 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.75 (dd, *J* = 8.0, 1.7 Hz, 1H, $C_{[ar]}H$), 7.70 (dd, *J* = 8.2, 1.1 Hz, 1H, $C_{[ar]}H$), 7.52 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.51 – 7.44 (m, 1H, $C_{[ar]}H$), 7.06 (td, *J* = 7.6, 1.7 Hz, 1H, $C_{[ar]}H$), 5.88 (s, 1H, $C_{[5]}H$), 5.47 (dd, *J* = 10.1, 9.2 Hz, 1H, $C_{[2]}H$), 3.90 (dd, *J* = 12.8, 10.1 Hz, 1H, $C_{[3]}H'$), 2.82 (dd, *J* = 12.8, 9.2 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 172.4 ($C_{[1]}$), 160.6 ($C_{[12]}$), 148.9 ($C_{[ar]}$), 148.6 ($C_{[19]}$), 144.4 ($C_{[ar]}$), 142.6 ($C_{[ar]}$), 135.5 ($C_{[ar]}$), 130.4 ($C_{[ar]}$), 130.3 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 122.8 ($C_{[ar]}$), 91.8 ($C_{[7]}$), 91.8 ($C_{[5]}$), 89.6 ($C_{[4]}$), 59.5 ($C_{[2]}$), 36.8 ($C_{[3]}$).

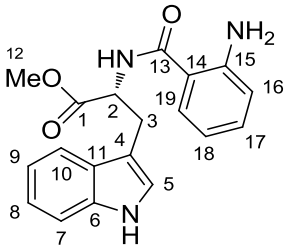
Compound 3-21



Nitro **3-3** (566 mg, 1.54 mmol) was dissolved in methanol (15 mL), and 30 mg of 10% Pd/C was then added. The reaction was stirred under hydrogen atmosphere for 40 min before it was filtered through Celite and concentrated. The residue was purified with FCC (Et_2O / CH_2Cl_2 = 1 / 1) to give colourless solid 510 mg (98%);

m.p. 48 – 53 ^oC; **$[\alpha]_D^{25}$** – 69.3 (*c* 0.29, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3416, 3365, 3056, 1736, 1638, 1617, 1585, 1553, 1514, 1456, 1438, 1341, 1261, 1216, 1099, 1010, 887, 853, 746;

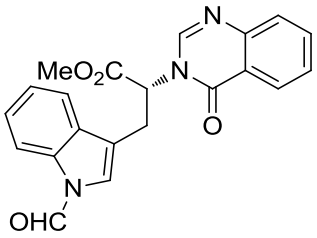


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.07 (bs., 1H, N*H*), 7.55 (dd, *J* = 8.0, 1.0 Hz, 1H, $C_{[ar]}H$), 7.34 (dt, *J* = 8.2, 0.9 Hz, 1H, $C_{[ar]}H$), 7.20 – 7.14 (m, 3H, $C_{[ar]}H$), 7.08 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, $C_{[ar]}H$), 7.01 (d, *J* = 2.4 Hz, 1H, $C_{[ar]}H$), 6.66 – 6.61 (m, 1H, $C_{[ar]}H$), 6.58 – 6.52 (m, 2H, $C_{[ar]}H$ & N*H*), 5.06 (dt, *J* = 7.4, 5.3 Hz, 1H, $C_{[2]}H$), 3.70 (s, 3H, $C_{[12]}H$), 3.44 – 3.38 (m, 2H, $C_{[3]}H$), ArNH_2 does not appear;

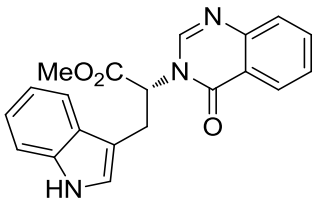
^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 172.7 ($C_{[1]}$), 169.0 ($C_{[13]}$), 149.1 ($C_{[ar]}$), 136.3 ($C_{[ar]}$), 132.8 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 127.7 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 122.6 ($C_{[ar]}$), 120.0 ($C_{[ar]}$), 118.9 ($C_{[ar]}$), 117.5 ($C_{[ar]}$), 116.8 ($C_{[ar]}$), 115.5 ($C_{[ar]}$), 111.5 ($C_{[ar]}$), 110.4 ($C_{[ar]}$), 53.3 ($C_{[2]}$), 52.7 ($C_{[12]}$), 27.9 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{19}N_3O_3+Na]^+$ requires *m/z* 360.1319, found *m/z* 360.1315.

Compound 3-22 & 3-23



3-22



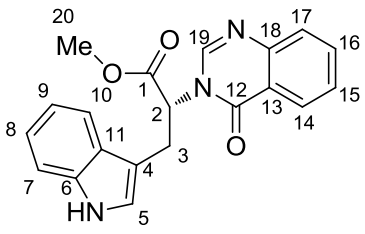
3-23

Aniline **3-21** (1.5 g) and pTSA (300 mg) was dissolved in methanol (25 mL) and trimethyl orthoformate (25 mL). The mixture was stirred at 75 ^oC for 1.5 h before all volatiles were removed. The residue was dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC diethyl ether / CH_2Cl_2 (1 / 10) to give colorless solid **3-22** 700 mg (45%) and **3-23** 600 mg (36%) respectively. **3-22** could be dissolved in 15 mL of methanol and treated with 1 mL of $SOCl_2$ at 0 ^oC; after 30 min all **3-22** was converted into **3-23**;

Compound **3-23**

m.p. 56 – 60 ^oC; **$[\alpha]_D^{25}$** + 199.0 (*c* 0.50, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3393, 1744, 1672, 1609, 1565, 1474, 1459, 1437, 1384, 1327, 1268, 1224, 1182, 1163, 1103, 1073, 1011, 926, 774, 746, 700;



*NMR with rotamers, the major set of peaks was assigned as following

^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 10.80 (s, 1H, N*H*), 8.12 (dt, *J* = 8.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.99 (d, *J* = 1.7 Hz, 1H, $C_{[19]}H$), 7.80 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H, $C_{[ar]}H$), 7.64 – 7.51 (m, 2H, $C_{[ar]}H$), 7.46 (d, *J* = 7.9 Hz, 1H, $C_{[ar]}H$), 7.26 (dd, *J* = 8.2, 1.2 Hz, 1H, $C_{[ar]}H$), 7.06 – 6.95 (m, 2H, $C_{[ar]}H$), 6.90 – 6.77 (m, 1H, $C_{[ar]}H$), 5.53 (ddd, *J* = 10.7, 5.2, 1.5 Hz, 1H, $C_{[2]}H$), 3.73 (s, 3H, $C_{[20]}H$), 3.70 – 3.56 (m, 2H, $C_{[3]}H$);

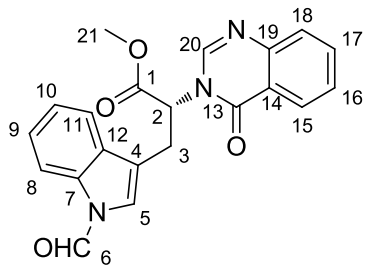
^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 169.5 ($C_{[1]}$), 159.9($C_{[12]}$), 147.3 ($C_{[ar]}H$), 147.0 ($C_{[19]}$), 136.0 ($C_{[ar]}H$), 134.7 ($C_{[ar]}H$), 127.3 ($C_{[ar]}H$), 127.1 ($C_{[ar]}H$), 126.7 ($C_{[ar]}H$), 126.1 ($C_{[ar]}H$), 123.9 ($C_{[ar]}H$), 121.2 ($C_{[ar]}H$), 121.1 ($C_{[ar]}H$), 118.5 ($C_{[ar]}H$), 117.9 ($C_{[ar]}H$), 111.5 ($C_{[ar]}H$), 108.6 ($C_{[ar]}H$), 59.5 ($C_{[2]}$), 52.6 ($C_{[20]}$), 24.5 ($C_{[3]}$);

HRMS (ESI) $[C_{20}H_{17}N_3O_3+H]^+$ requires *m/z* 348.1343, found *m/z* 348.1345.

Compound **3-22**

m.p. 45 – 50 ^{o}C; **$[\alpha]_D^{25}$** + 174.8 (*c* 1.98, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 1745, 1707, 1676, 1608, 1566, 1459, 1382, 1328, 1267, 1228, 1200, 1157, 1104, 1014, 927, 910, 793, 751, 799;



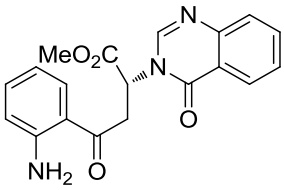
*NMR with rotamers, the ^{1}H was assigned at 363 K, and ^{13}C was assigned at rt

^{1}H NMR (DMSO-d_6, 363 K, 500 MHz) δ (ppm): 9.30 (s, 1H, C*H*O), 8.26 – 8.05 (m, 3H, $C_{[ar]}H$), 7.86 – 7.76 (m, 1H, $C_{[ar]}H$), 7.65 – 7.57(m, 3H, $C_{[ar]}H$), 7.57 – 7.49 (m, 1H, $C_{[ar]}H$), 7.35 – 7.28 (m, 1H, $C_{[ar]}H$), 7.25 – 7.17 (m, 1H, $C_{[ar]}H$), 5.63 (dd, *J* = 9.0, 6.3 Hz, 1H, $C_{[2]}H$), 3.75 (s, 3H, $C_{[21]}H$, with rotamer peak), 3.72 – 3.66 (m, 2H, $C_{[3]}H$);

^{13}C NMR (DMSO-d_6, 363 K, 125 MHz) δ (ppm): 168.6 ($C_{[1]}$), 161.0 ($C_{[6]}$), 159.6 ($C_{[13]}$), 147.0 ($C_{[ar]}$), 146.1 ($C_{[ar]}$), 134.1 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 126.8 ($C_{[ar]}$), 126.7 ($C_{[ar]}$), 125.7 ($C_{[ar]}$), 124.3 ($C_{[ar]}$), 123.3 ($C_{[ar]}$), 120.8 ($C_{[ar]}$), 118.7 ($C_{[ar]}$), 117.5 ($C_{[ar]}$), 58.0 ($C_{[2]}$), 52.1 ($C_{[21]}$), 24.2 ($C_{[3]}$), three aromatic carbons do not appear;

HRMS (ESI) $[C_{21}H_{17}N_3O_4+H]^+$ requires *m/z* 376.1292, found *m/z* 376.1281.

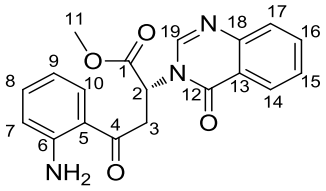
Compound 3-24



Indole **3-23** (410 mg) was dissolved in methanol (20 mL) and water (20 mL), and 1.0 g of sodium periodate was then added in one portion. The reaction was stirred at rt for 3 days until all starting material disappeared on TLC. To the reaction, water (50 mL) was then added before it was extracted with chloroform, washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. The residute was redissolved in methanol (4.2 mL), and thionyl chloride (0.3 mL) was added dropwise subsequently at 0 ^{o}C. The reaction was stirred at 0 ^{o}C for 2 h before all volatiles were removed under vacuum. The residue was extracted with ethyl acetate from sat. $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered and purified with FCC diethyl ether / CH_2Cl_2 (1 / 10) to give light yellow solid 230 mg (55%);

m.p. 163 – 165 °C; **$[\alpha]_D^{25}$** + 363.9 (*c* 0.56, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3465, 3350, 2361, 1746, 1673, 1611, 1586, 1551, 1474, 1452, 1415, 1383, 1325, 1298, 1266, 1217, 1163, 1030, 1013, 974, 927, 774, 752, 701;

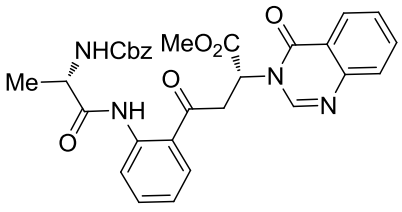


^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 8.54 (s, 1H, $C_{[19]}H$), 8.13 (dd, *J* = 7.9, 1.6 Hz, 1H, $C_{[ar]}H$), 7.86 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.71 (ddd, *J* = 12.5, 8.2, 1.3 Hz, 2H, $C_{[ar]}H$), 7.57 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, $C_{[ar]}H$), 7.24 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, $C_{[ar]}H$), 7.18 (s, 2H, $N\underline{H}_2$), 6.74 (dd, *J* = 8.4, 1.2 Hz, 1H, $C_{[ar]}H$), 6.53 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, $C_{[ar]}H$), 5.77 (dd, *J* = 7.4, 5.5 Hz, 1H, $C_{[2]}H$), 4.04 (dd, *J* = 18.1, 5.5 Hz, 1H, $C_{[3]}H'$), 3.85 (dd, *J* = 18.2, 7.5 Hz, 1H, $C_{[3]}H''$), 3.66 (s, 3H, $C_{[11]}H$);

^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 197.5 ($C_{[4]}$), 169.4 ($C_{[1]}$), 160.0 ($C_{[12]}$), 151.2 ($C_{[ar]}$), 148.1 ($C_{[19]}$), 147.5 ($C_{[ar]}$), 134.8 ($C_{[ar]}$), 134.5 ($C_{[ar]}$), 131.0 ($C_{[ar]}$), 127.3 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 126.1 ($C_{[ar]}$), 121.3 ($C_{[ar]}$), 117.0 ($C_{[ar]}$), 115.8 ($C_{[ar]}$), 114.5 ($C_{[ar]}$), 55.7 ($C_{[2]}$), 52.7 ($C_{[11]}$), 38.1 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{17}N_3O_4+H]^+$ requires *m/z* 352.1292, found *m/z* 352.1290.

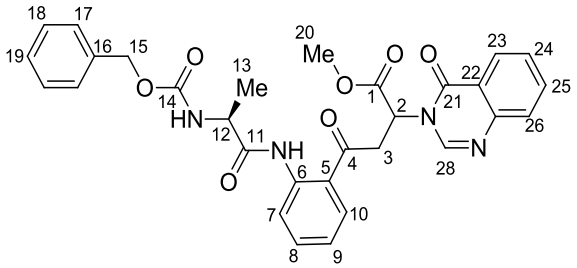
Compound 3-25



Aniline **3-24** (1.45 g, 3.9 mmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (50 mL), and the resulting solution was added into a suspension of dicyclohexylcarbodiimide (1.05 g, 5.1 mmol, 1.3 eq) and Z-Ala-OH (1.14 g, 5.1 mmol, 1.3 eq) in dry CH_2Cl_2 (50 mL) at rt. The reaction was stirred for 48 h before it was filtered through Celite, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified with FCC diethyl ether / petro ether (1/1 to pure ether) to give light yellow foam 1.45 g (67%) and 450 mg of starting material **3-24**;

m.p. 82 – 85 ^oC; $\mathbf{[\alpha]_D^{25}}$ + 191.0 (*c* 0.67, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3296, 1745, 1677, 1609, 1583, 1520, 1450, 1302, 1280, 1219, 1028, 910, 756, 700;

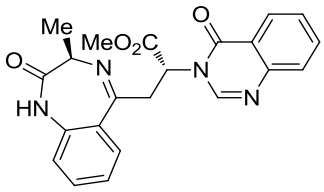


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 11.87 (s, 1H, CON*H*), 8.69 (d, *J* = 8.4 Hz, 1H, $C_{[ar]}H$), 8.41 (s, 1H, $C_{[28]}H$), 8.17 (ddd, *J* = 12.6, 8.0, 1.5 Hz, 2H, $C_{[ar]}H$), 7.82 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.69 (d, *J* = 8.1 Hz, 1H, $C_{[ar]}H$), 7.61 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H, $C_{[ar]}H$), 7.54 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.47 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H, $C_{[ar]}H$), 7.31 (t, *J* = 7.3 Hz, 1H, $C_{[ar]}H$), 7.22 (ddd, *J* = 8.3, 7.4, 1.2 Hz, 1H, $C_{[ar]}H$), 6.93 (d, *J* = 7.0 Hz, 1H, CbzN*H*), 5.64 (dd, *J* = 7.1, 4.9 Hz, 1H, $C_{[2]}H$), 5.22 (d, *J* = 12.6 Hz, 1H, $C_{[15]}H'$), 5.18 (d, *J* = 12.6 Hz, 1H, $C_{[15]}H''$), 4.45 – 4.22 (m, 2H, $C_{[12]}H$+$C_{[3]}H'$), 4.07 (dd, *J* = 18.6, 7.2 Hz, 1H, $C_{[3]}H''$), 3.71 (s, 3H, $C_{[20]}H$), 1.46 (d, *J* = 7.3 Hz, 3H, $C_{[13]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 201.7 ($C_{[4]}$), 173.0 ($C_{[11]}$), 170.0 ($C_{[1]}$), 161.4 ($C_{[21]}$), 157.1 ($C_{[14]}$), 149.1 ($C_{[ar]}$), 148.7 ($C_{[28]}$), 141.4 ($C_{[ar]}$), 138.3 ($C_{[ar]}$), 135.8 ($C_{[ar]}$), 135.4 ($C_{[ar]}$), 132.1 ($C_{[ar]}$), 129.3 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 123.7 ($C_{[ar]}$), 123.2 ($C_{[ar]}$), 123.1 ($C_{[ar]}$), 121.3 ($C_{[ar]}$), 67.2 ($C_{[15]}$), 57.3 ($C_{[2]}$), 53.3* ($C_{[12]}$+$C_{[20]}$), 40.6 ($C_{[3]}$), 18.2 ($C_{[13]}$), *two peaks overlapping;

HRMS (ESI) $[C_{30}H_{28}N_4O_7+H]^+$ requires *m/z* 557.2031, found *m/z* 557.2025.

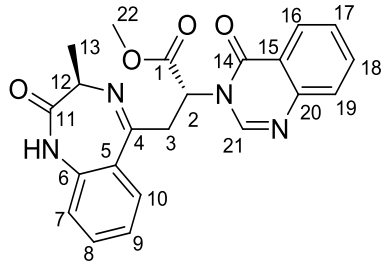
Compound 3-26



3-25 (500 mg) was dissolved in methanol (20 mL), and 35 mg of 20% $Pd(OH)_2$ on charcoal was then added into the resulting solution. The reaction was stirred under hydrogen atmosphere (balloon) for 12 h before the mixture was filtered and concentrated under vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (1 / 100 to 1 / 30) to give the imine, as colourless solid, 190 mg (51%);

m.p. 158 – 160 ^oC; **$[\alpha]_D^{25}$** –226.7 (*c* 0.33, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3226, 3067, 2981, 2936, 1748, 1680, 1609, 1571, 1475, 1438, 1376, 1302, 1283, 1243, 1177, 1108, 1015, 916, 772, 732, 702, 645;

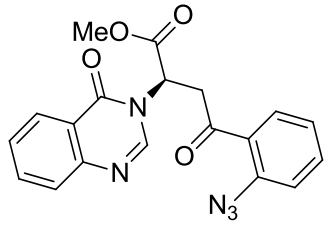


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.29 (d, *J* = 1.5 Hz, 1H, $C_{[ar]}H$), 8.27 (s, 1H, $C_{[21]}H$), 8.05 (s, 1H, N*H*), 7.76 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, $C_{[ar]}H$), 7.71 (dd, *J* = 8.2, 1.3 Hz, 1H, $C_{[ar]}H$), 7.52 – 7.39 (m, 3H, $C_{[ar]}H$), 7.17 (td, *J* = 7.6, 1.1 Hz, 1H, $C_{[ar]}H$), 7.00 (dd, *J* = 8.1, 1.1 Hz, 1H, $C_{[ar]}H$), 5.39 (dd, *J* = 10.0, 2.9 Hz, 1H,, $C_{[2]}H$), 4.04 (ddd, *J* = 18.8, 10.0, 1.4 Hz, 1H, $C_{[3]}H'$), 3.72 (s, 3H, $C_{[22]}H$), 3.58 (ddd, *J* = 18.8, 3.0, 2.0 Hz, 1H, $C_{[3]}H''$), 3.52 (qt, *J* = 6.6, 1.6 Hz, 1H, $C_{[12]}H$), 1.61 (d, *J* = 6.6 Hz, 3H, $C_{[13]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 172.2 ($C_{[11]}$), 169.4 ($C_{[1]}$), 166.4 ($C_{[4]}$), 161.3 ($C_{[14]}$), 148.7 ($C_{[21]}$), 148.2 ($C_{[ar]}$), 136.8 ($C_{[ar]}$), 134.8 ($C_{[ar]}$), 132.0 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 128.2 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 127.4 ($C_{[ar]}$), 126.9 ($C_{[ar]}$), 124.6 ($C_{[ar]}$), 122.3 ($C_{[ar]}$), 121.3 ($C_{[ar]}$), 59.1 ($C_{[2]}$), 58.0 ($C_{[12]}$), 53.2 ($C_{[22]}$), 36.7 ($C_{[3]}$), 16.9 ($C_{[13]}$);

HRMS (ESI) $[C_{22}H_{19}N_4O_4+H]^+$ requires *m/z* 405.1557, found *m/z* 405.1555.

Compound 3-27

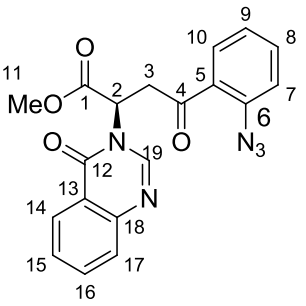


At 0 °C, to the solution of **3-24** (810 mg, 2.3 mmol, 1.0 eq) in dry acetonitrile (30 mL), *tert*-butyl nitrite (360 mg, 3.5 mmol, 1.5 eq) and azidotrimethylsilane (400 mg, 3.5 mmol, 1.5

eq) were added subsequently. The reaction was firstly stirred at 0 °C for 1 h, and then at rt for another 2 h. After adding 1 M HCl into the reaction, the mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with FCC ethyl acetate / petro ether (1 / 10 to 4 / 10) to give colourless foam 750 mg (87%);

m.p. 40 – 42 °C; **$[\alpha]_D^{25}$** +42.2 (*c* 1.01, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2924, 2125, 1747, 1675, 1607, 1570, 1476, 1143, 1381, 1278, 1189, 1165, 1104, 1009, 979, 912, 774, 731, 700, 647;

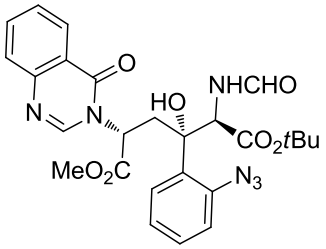


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.26 (s, 1H, $C_{[19]}H$), 8.24 (dd, *J* = 8.0, 1.4 Hz, 1H, $C_{[ar]}H$), 7.81 – 7.65 (m, 3H, $C_{[ar]}H$), 7.51 – 7.46 (m, 2H, $C_{[ar]}H$), 7.21 – 7.09 (m, 2H, $C_{[ar]}H$), 5.39 (dd, *J* = 8.1, 4.3 Hz, 1H, $C_{[2]}H$), 4.14 (dd, *J* = 19.1, 4.3 Hz, 1H, $C_{[3]}H'$), 3.98 (dd, *J* = 19.1, 8.1 Hz, 1H, $C_{[3]}H''$), 3.75 (s, 3H, $C_{[11]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 197.7 ($C_{[4]}$), 169.1 ($C_{[1]}$), 161.0 ($C_{[12]}$), 148.1 ($C_{[ar]}$), 147.2 ($C_{[19]}$), 139.4 ($C_{[ar]}$), 134.8 ($C_{[ar]}$), 134.0 ($C_{[ar]}$), 130.8 ($C_{[ar]}$), 129.5 ($C_{[ar]}$), 127.8 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 126.8 ($C_{[ar]}$), 125.0 ($C_{[ar]}$), 122.2 ($C_{[ar]}$), 119.3 ($C_{[ar]}$), 57.3 ($C_{[2]}$), 53.4 ($C_{[11]}$), 43.3 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{15}O_4N_5+H]^+$ requires *m/z* 378.1197, found *m/z* 378.1196.

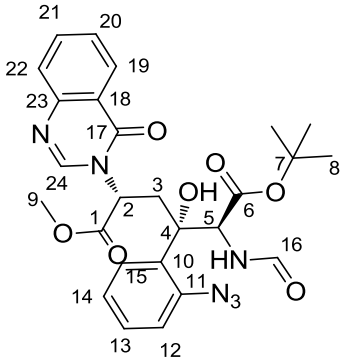
Compound 3-28



Ligand-**1** (61.4 mg, 0.1 mmol, 5% eq) and silver acetate (16.7 mg, 0.1 mmol, 5% eq) were dissolved in ethyl acetate (4 mL), and stirred for 20 min at rt. The resulting solution was then added into a solution of azido ketone **3-27** (766 mg, 2.0 mmol, 1.0 eq) in ethyl acetate (50 mL) at 0 °C. The mixture was then stirred for 20 min at 0 °C before *tert*-butyl isocyanoacetate (423 mg, 3.0 mmol, 1.5 eq) in ethyl acetate (5 mL) was injected. This reaction was kept stirring at 0 °C overnight before it was concentrated under vacuum and re-dissolved in THF (30 mL). After adding 1 N HCl (3 mL), the reaction was stirred for additional 10 min at rt, and diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and concentrated again. The residue was finally purified with FCC MeOH / CH_2Cl_2 (1/200 to 1/50) to give colourless solid 1.04 g (97%, d.r. 13:1);

m.p. 120 – 125 °C; **$[\alpha]_D^{25}$** +14.4 (*c* 0.35, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3349, 2980, 2128, 1741, 1679, 1610, 1578, 1477, 1440, 1371, 1325, 1272, 1225, 1153, 1118, 1037, 942, 910, 842, 755, 700, 666;

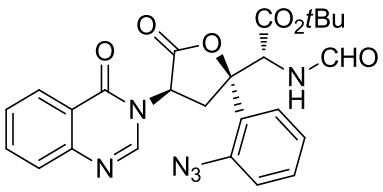


^{1}H NMR (MeOD, 500 MHz) δ (ppm): 8.01 (dd, *J* = 8.0, 1.4 Hz, 1H, $C_{[ar]}H$), 7.78 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.70 (bs., 1H, $C_{[24]}H$), 7.64 (s, 1H, $C_{[16]}H$), 7.56 (dd, *J* = 7.8, 1.7 Hz, 1H, $C_{[ar]}H$), 7.53 – 7.45 (m, 2H, $C_{[ar]}H$), 6.83 (td, *J* = 7.6, 1.3 Hz, 1H, $C_{[ar]}H$), 6.77 (td, *J* = 7.6, 1.7 Hz, 1H, $C_{[ar]}H$), 6.44 (dd, *J* = 7.9, 1.2 Hz, 1H, $C_{[ar]}H$), 5.35 (s, 1H, $C_{[5]}H$), 5.18 (bs., 1H, $C_{[2]}H$), 3.77 (dd, *J* = 15.7, 10.8 Hz, 1H, $C_{[3]}H'$), 3.72 (s, 3H, $C_{[9]}H$), 3.12 (dd, *J* = 15.7, 2.3 Hz, 1H, $C_{[3]}H''$), 1.62 (s, 9H, $C_{[8]}H$);

^{13}C NMR (MeOD, 125 MHz) δ (ppm): 171.5 ($C_{[1]}$), 170.5 ($C_{[6]}$), 163.1 ($C_{[16]}$), 162.0 ($C_{[17]}$), 148.9 ($C_{[24]}$), 148.4 ($C_{[ar]}$), 137.0 ($C_{[ar]}$), 136.0 ($C_{[ar]}$), 132.5 ($C_{[ar]}$), 130.2 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 127.7 ($C_{[ar]}$), 127.5 ($C_{[ar]}$), 125.8 ($C_{[ar]}$), 122.4 ($C_{[ar]}$), 119.5 ($C_{[ar]}$), 84.4 ($C_{[7]}$), 76.7 ($C_{[4]}$), 59.0 ($C_{[5]}$), 58.4* ($C_{[2]}$), 53.6 ($C_{[9]}$), 35.8 ($C_{[3]}$), 28.5 ($C_{[8]}$), *bulk peak;

HRMS (ESI) $[C_{26}H_{28}O_7N_6+H]^+$ requires *m/z* 537.2092, found *m/z* 537.2090.

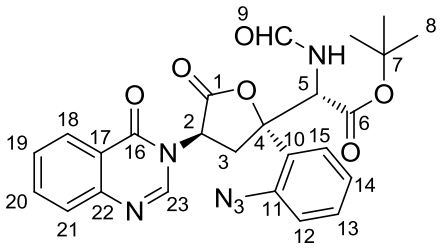
Compound 3-29



3-28 (425 mg, 1.18 mmol) was dissolved in toluene (45 mL) and acetic acid (2.25 mL), and the resulting solution was stirred at 70 °C for 3 days before it was concentrated under vacuum, redissolved in ethyl acetate, washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated again. The residue was purified with FCC CH_2Cl_2 / ether (from 4:1 to 3:2) then CH_2Cl_2 / methanol (from 100:1 to 25:1) to give product as colourless solid 165 mg (37%) and 150 mg (35%) of starting material **3-28**;

m.p. decompose at 170 °C; **$[\alpha]_D^{25}$** –48.7 (*c* 0.15, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2924, 2854, 2361, 2338, 2130, 1797, 1733, 1686, 1611, 1580, 1479, 1373, 1293, 1253, 1186, 1154, 1107, 1054, 1031, 968, 930, 892, 840, 756, 697;

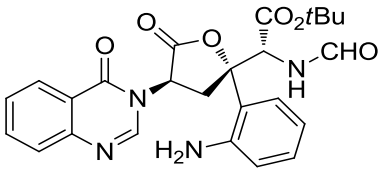


^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 8.22 (s, 1H, $C_{[9]}H$), 8.22 – 8.17 (m, 2H, $C_{[ar]}H$), 7.93 – 7.89 (m, 1H, $C_{[23]}H$), 7.87 (ddd, *J* = 8.2, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.71 (s, 1H, $C_{[ar]}H$), 7.69 (s, 1H, N*H*), 7.59 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, $C_{[ar]}H$), 7.53 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H, $C_{[ar]}H$), 7.45 (dd, *J* = 7.9, 1.5 Hz, 1H, $C_{[ar]}H$), 7.39 (dd, *J* = 8.0, 1.2 Hz, 1H, $C_{[ar]}H$), 7.31 – 7.23 (m, 1H, $C_{[ar]}H$), 5.79 (dd, *J* = 10.0, 0.7 Hz, 1H, $C_{[5]}H$), 5.16 (dd, *J* = 11.8, 8.6 Hz, 1H, $C_{[2]}H$), 3.75 (dd, *J* = 12.8, 11.8 Hz, 1H, $C_{[3]}H'$), 3.48 (dd, *J* = 12.7, 8.6 Hz, 1H, $C_{[3]}H''$), 1.56 (s, 9H, $C_{[8]}H$);

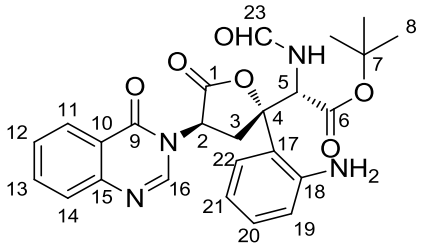
^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 171.1 ($C_{[1]}$), 167.8 ($C_{[6]}$), 160.9* ($C_{[9]}$), 160.6 ($C_{[16]}$), 149.0 ($C_{[ar]}$), 147.6 ($C_{[23]}$), 137.6 ($C_{[ar]}$), 135.6 ($C_{[ar]}$), 131.3 ($C_{[ar]}$), 130.9 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 125.8 ($C_{[ar]}$), 122.8 ($C_{[ar]}$), 120.9 ($C_{[ar]}$), 86.5 ($C_{[4]}$), 84.0 ($C_{[7]}$), 57.0 ($C_{[2]}$), 56.5* ($C_{[5]}$), 34.7 ($C_{[3]}$), 28.3 ($C_{[8]}$), *with rotamer peak;

HRMS (ESI) $[C_{25}H_{24}O_6N_6+H]^+$ requires *m/z* 505.1830, found *m/z* 505.1829.

Compound 3-30



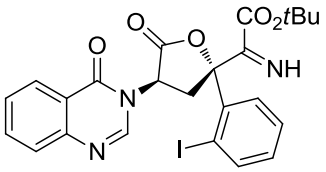
Azide **3-29** (10 mg) was dissolved in methanol (1.5 mL) and 1 mg of 10% palladium on charcoal was then added in one portion. The reaction was stirred under hydrogen atmosphere for 3 before it was filtered through a short Celite pad and concentrated under vacuum. The white solid residue was sensitive with silicon and decomposing in NMR tube, so it was used for further steps without purification;



^{1}H NMR (MeOD-d_4, 400 MHz) δ (ppm): 8.45 (s, 1H, C*H*O), 8.18 (dd, *J* = 8.1, 1.5 Hz, 1H, $C_{[ar]}H$), 8.02 (d, *J* = 0.8 Hz, 1H, $C_{[16]}H$), 7.86 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.72 (d, *J* = 8.2 Hz, 1H, $C_{[ar]}H$), 7.56 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.47 (dd, *J* = 8.0, 1.4 Hz, 1H, $C_{[ar]}H$), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H, $C_{[ar]}H$), 7.23 (td, *J* = 7.7, 1.4 Hz, 1H, $C_{[ar]}H$), 7.17 (dd, *J* = 7.8, 1.3 Hz, 1H, $C_{[ar]}H$), 5.83 (dd, *J* = 11.8, 7.9 Hz, 1H, $C_{[2]}H$), 5.22 (s, 1H, $C_{[5]}H$), 2.96 (dd, *J* = 13.5, 7.7 Hz, 1H, $C_{[3]}H'$), 2.81 (dd, *J* = 13.4, 12.0 Hz, 1H, $C_{[3]}H''$), 1.50 (s, 9H, $C_{[8]}H$);

HRMS (ESI) $[C_{25}H_{26}O_6N_4+H]^+$ requires *m/z* 479.1925, found *m/z* 479.1922.

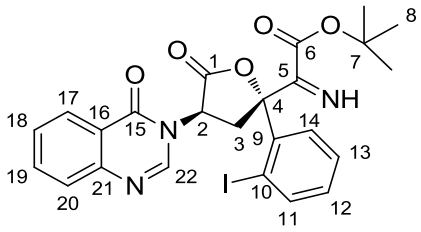
Compound 4-5



Compound **3-11** (75 mg, 0.13 mmol, 1.0 eq) was dissolved in methanol (7.0 mL), and thionyl chloride (0.5 mL) was then added dropwise at 0 °C. The resulting solution was stirred for 2 h at rt before all volatiles were removed under vacuum and the residue was dried overnight under high vacuum. The dried residue was subsequently suspended in sat. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL), after stirring for 15 min at rt the organic phase was collected, and the aqueous phase was exacted with CH_2Cl_2. Combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and DMSO (1 mL), and 2-iodoxybenzoic acid (42 mg, 0.15 mmol, 1.2 eq) was then added. The reaction was stirred at 0°C overnight before diluted with CH_2Cl_2 and washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (from 1/200 to 2.5/200) to give colourless solid 55 mg (77%);

m.p. 95 – 105 °C; **$[\alpha]_D^{25}$** – 76.2 (*c* 0.83, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2980, 2931, 1797, 1725, 1679, 1610, 1565, 1474, 1425, 1370, 1325, 1251, 1203, 1187, 1154, 1103, 1029, 1006, 963, 909, 840, 760, 699;



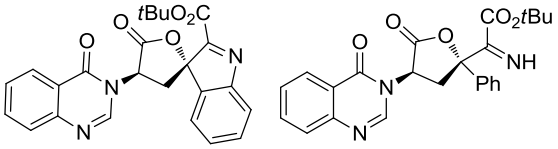
^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 12.36 (s, 1H, N*H*), 8.32 (s, 1H, $C_{[22]}$), 8.22 (ddd, *J* = 8.0, 1.6, 0.6 Hz, 1H, $C_{[ar]}$H), 8.06 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}$H), 7.87 (ddd, *J* = 8.2, 7.2, 1.6 Hz,

1H, $C_{[ar]}H$), 7.75 – 7.68 (m, 2H, $C_{[ar]}H$), 7.65 – 7.54 (m, 2H, $C_{[ar]}H$), 7.20 (td, *J* = 7.6, 1.7 Hz, 1H, $C_{[ar]}H$), 5.35 (dd, *J* = 11.3, 9.3 Hz, 1H, $C_{[2]}H$), 4.53 (dd, *J* = 12.8, 11.3 Hz, 1H, $C_{[3]}H'$), 3.17 (dd, *J* = 12.8, 9.3 Hz, 1H, $C_{[3]}H''$), 1.25 (s, 9H, $C_{[8]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 171.6 ($C_{[1]}$), 168.0 ($C_{[6]}$), 160.6 ($C_{[15]}$), 159.9 ($C_{[5]}$), 149.1 ($C_{[ar]}$), 148.0* ($C_{[22]}$), 143.6 ($C_{[ar]}H$), 143.2* ($C_{[ar]}H$), 135.5* ($C_{[ar]}H$), 131.0 ($C_{[ar]}H$), 129.5 ($C_{[ar]}H$), 128.6 ($C_{[ar]}H$), 128.3 ($C_{[ar]}H$), 128.3 ($C_{[ar]}H$), 127.3* ($C_{[ar]}H$), 123.0 ($C_{[ar]}H$), 93.2 ($C_{[10]}$), 86.9 ($C_{[4]}$), 84.5 ($C_{[7]}$), 57.1 ($C_{[2]}$), 35.1 ($C_{[3]}$), 27.7 ($C_{[8]}$), * peak splits;

HRMS (ESI) $[C_{24}H_{22}N_3O_5I+H]^+$ requires *m/z* 560.0677, found *m/z* 560.0654.

Compound 4-6 & 4-7



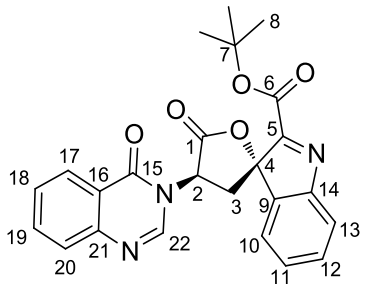
4-6 **4-7**

Imine **4-5** (11 mg, 0.02 mmol, 1.0 eq), copper(I) iodide (4.6 mg, 0.024 mmol, 1.2 eq) and magnesium acetate tetrahydrate (6.4 mg, 0.03 mmol, 1.5 eq) were placed in a dry flask and charged with Ar, and dry DMSO (1.2 mL) was injected into the flash. The solution was stirred at rt for 3 h before the reaction was quenched with sat. NH_4Cl, exacted with CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified with FCC diethyl ether / CH_2Cl_2 (1 / 10) to give the cyclized **4-6** as colourless solid 4.5 mg (52%) and trace of elimination product **4-7**;

Compound **4-6**:

m.p. T_{dec} >210 ^oC; **$[\alpha]_D^{25}$** + 175.5 (*c* 0.38, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2979, 2922, 2852, 1795, 1730, 1677, 1610, 1567, 1472, 1370, 1326, 1254, 1196, 1135, 1059, 1033, 971, 910, 841, 773, 698;



^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.61 (s, 1H, $C_{[22]}H$), 8.34 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.27 – 8.11 (m, 1H, $C_{[ar]}H$), 7.91 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.76 (dt, *J* = 8.1, 1.0 Hz, 1H, $C_{[ar]}H$), 7.75 – 7.68 (m, 1H, $C_{[ar]}H$), 7.65 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, $C_{[ar]}H$), 7.60 – 7.54 (m, 2H, $C_{[ar]}H$), 5.78 (dd, *J* = 10.7, 8.5 Hz, 1H, $C_{[2]}H$), 3.33 (dd, *J* = 14.0, 10.7 Hz, 1H, $C_{[3]}H'$), 3.17 (dd, *J* = 14.0, 8.6 Hz, 1H, $C_{[3]}H''$), 1.65 (s, 9H, $C_{[8]}H$);

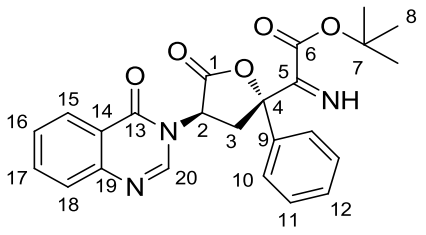
^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 173.1 ($C_{[1]}$), 170.7 ($C_{[6]}$), 161.6 ($C_{[5]}$), 161.4 ($C_{[15]}$), 152.8 ($C_{[ar]}$), 149.4 ($C_{[ar]}$), 148.5 ($C_{[22]}$), 139.9 ($C_{[ar]}$), 135.8 ($C_{[ar]}$), 132.3 ($C_{[ar]}$), 131.0 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 125.8 ($C_{[ar]}$), 124.3 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 89.8 ($C_{[4]}$), 84.8 ($C_{[7]}$), 59.3 ($C_{[2]}$), 32.6 ($C_{[3]}$), 28.3 ($C_{[8]}$);

HRMS (ESI) $[C_{24}H_{21}N_3O_5+H]^+$ requires *m/z* 432.1554, found *m/z* 432.1555.

Compound **4-7**:

m.p. 158 – 161 °C; **$[\alpha]_D^{25}$** + 8.3 (*c* 0.35, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2917, 2849, 1794, 1726, 1680, 1610, 1474, 1450, 1394, 1370, 1325, 1298, 1251, 1206, 1188, 1155, 1109, 1088, 1049, 1028, 962, 841, 774, 720, 699;



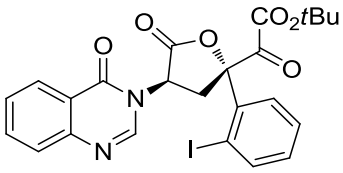
*NMR with rotamers, the major set of peak was assigned as following

^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 11.79 (s, 1H, N*H*), 8.35 (s, 1H, $C_{[20]}H$), 8.20 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 7.86 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H, $C_{[ar]}H$), 7.71 (dt, *J* = 8.2, 0.8 Hz, 1H, $C_{[ar]}H$), 7.64 – 7.56 (m, 1H, $C_{[ar]}H$), 7.52 – 7.46 (m, 4H, $C_{[ar]}H$), 7.46 – 7.39 (m, 1H, $C_{[ar]}H$), 5.34 (dd, *J* = 11.3, 9.0 Hz, 1H, $C_{[2]}H$), 3.99 (dd, *J* = 12.9, 11.3 Hz, 1H, $C_{[3]}H'$), 3.10 (dd, *J* = 12.9, 9.0 Hz, 1H, $C_{[3]}H''$), 1.34 (s, 9H, $C_{[8]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 171.5 ($C_{[1]}$), 170.2 ($C_{[6]}$), 160.8 ($C_{[13]}$), 160.0 ($C_{[5]}$), 149.1 ($C_{[ar]}$), 148.1 ($C_{[20]}$), 141.3 ($C_{[ar]}$), 135.6 ($C_{[ar]}$), 129.7 ($C_{[ar]}$), 129.2 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 125.7 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 86.7 ($C_{[4]}$), 84.6 ($C_{[7]}$), 57.2 ($C_{[2]}$), 38.3 ($C_{[3]}$), 27.9 ($C_{[8]}$);

HRMS (ESI) $[C_{24}H_{23}N_3O_5+H]^+$ requires *m/z* 434.1711, found *m/z* 434.1703.

Compound 4-10

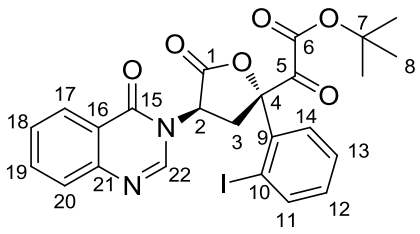


Imine **4-6** (70 mg, 0.13 mmol) was dissolved in THF (4 mL) and H_2O (3 mL), and acetic acid (0.15 mL) was then added. The reaction was stirred at 50 ^{o}C for 5 h before it was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated under

vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (1/70 to 1/50) to give colourless solid 55 mg (73%);

m.p. 105 – 108 °C; **$[\alpha]_D^{25}$** –77.4 (*c* 0.65, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3063, 2981, 2926, 2853, 2362, 2335, 1802, 1742, 1680, 1609, 1565, 1469, 1428, 1372, 1296, 1252, 1196, 1162, 1108, 964, 904, 837, 757, 697, 662;

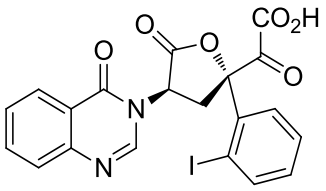


^{1}H NMR (CD_3CN-d_3, 500 MHz) δ (ppm): 8.22 (dd, *J* = 8.0, 1.6 Hz, 1H, $C_{[ar]}H$), 8.04 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}H$), 8.01 (s, 1H, $C_{[22]}H$), 7.85 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H, $C_{[ar]}H$), 7.72 (dt, *J* = 8.3, 0.8 Hz, 1H, $C_{[ar]}H$), 7.67 (dd, *J* = 8.0, 1.6 Hz, 1H, $C_{[ar]}H$), 7.62 – 7.53 (m, 2H, $C_{[ar]}H$), 7.21 (td, *J* = 7.7, 1.7 Hz, 1H, $C_{[ar]}H$), 5.04 (dd, *J* = 10.4, 9.6 Hz, 1H, $C_{[2]}H$), 3.83 (dd, *J* = 13.3, 10.5 Hz, 1H, $C_{[3]}H'$), 3.13 (dd, *J* = 13.3, 9.6 Hz, 1H, $C_{[3]}H''$), 1.30 (s, 9H, $C_{[8]}H$);

^{13}C NMR (CD_3CN-d_3, 125 MHz) δ (ppm): 187.5 ($C_{[5]}$), 171.2 ($C_{[1]}$), 161.0 ($C_{[15]}$), 160.4 ($C_{[6]}$), 149.0 ($C_{[ar]}$), 147.6 ($C_{[22]}$), 142.9 ($C_{[ar]}$), 140.9 ($C_{[ar]}$), 136.0 ($C_{[ar]}$), 132.0 ($C_{[ar]}$), 129.9 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 122.9 ($C_{[ar]}$), 94.0 ($C_{[10]}$), 88.0 ($C_{[4]}$), 86.3 ($C_{[7]}$), 57.5 ($C_{[2]}$), 34.1 ($C_{[3]}$), 27.8 ($C_{[8]}$);

HRMS (ESI) $[C_{24}H_{21}N_2O_6I+H]^+$ requires *m/z* 561.0517, found *m/z* 561.0516.

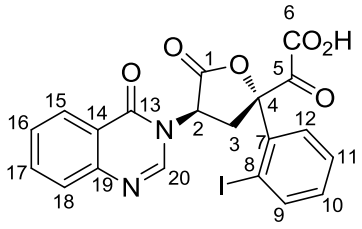
Compound 4-11



Ketoacid **4-10** (55 mg) was dissolved in CH_2Cl_2 (1.5 mL) and trifluoroacetic acid (3.0 mL), and the reaction was stirred at rt for 2 h before all volatiles were removed. The residue was dried under high vacuum overnight to give light yellow solid 50 mg (quant.) which was used for further reactions without extra purification;

m.p. 178 – 184 °C; **$[\alpha]_D^{25}$** –66.2 (*c* 1.21, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3065, 2973, 2923, 2853, 2362, 2335, 1799, 1727, 1680, 1612, 1470, 1429, 1389, 1322, 1251, 1198, 1114, 1073, 1030, 961, 760, 698;

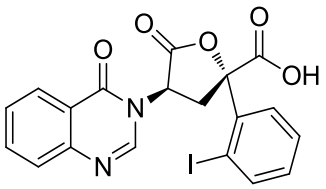


^{1}H NMR ($CDCl_3$, with one drop D_2O, 400 MHz) δ (ppm): 8.76 (s, 1H, $C_{[20]}H$), 8.45 – 8.23 (m, 1H, $C_{[ar]}H$), 8.04 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}H$), 7.91 – 7.78 (m, 2H, $C_{[ar]}H$), 7.70 – 7.56 (m, 2H, $C_{[ar]}H$), 7.51 (td, *J* = 7.6, 1.3 Hz, 1H, $C_{[ar]}H$), 7.18 (td, *J* = 7.6, 1.7 Hz, 1H), 5.88 (t, *J* = 10.6 Hz, 1H, $C_{[2]}H$), 3.64 (d, *J* = 10.6 Hz, 2H, $C_{[3]}H$);

^{13}C NMR ($CDCl_3$, with one drop of D_2O, 125 MHz) δ (ppm): 186.7 ($C_{[5]}$), 170.6 ($C_{[1]}$), 162.4 ($C_{[6]}$), 160.3 ($C_{[13]}$), 146.1 ($C_{[20]}$), 145.0 ($C_{[ar]}$), 142.3 ($C_{[ar]}$), 139.0 ($C_{[ar]}$), 136.1 ($C_{[ar]}$), 131.4 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 127.7 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 125.9 ($C_{[ar]}$), 120.7 ($C_{[ar]}$), 96.0 ($C_{[8]}$), 87.7 ($C_{[4]}$), 52.3 ($C_{[3]}$), 37.5 ($C_{[3]}$);

HRMS (ESI) $[C_{20}H_{13}N_2O_6I+H]^+$ requires *m/z* 504.9891, found *m/z* 504.9889.

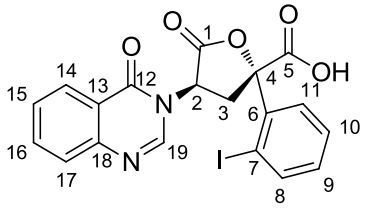
Compound 4-12



α-Ketone acid **4-11** (50 mg, 0.1 mmol, 1.0 eq) and PIDA (50 mg, 0.15 mmol, 1.5 eq) were dissolved in acetic acid (3.6 mL) and water (0.4 mL), and the reaction was stirred for 20 hours at rt before all volatiles was removed under vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (1 / 100 to 1 / 9 with acetic acid) to give colourless solid 39 mg (80%);

m.p. 183 – 187 °C; **$[\alpha]_D^{25}$** +45.6 (*c* 0.54, Acetone);

R (film) ν_{max}/cm^{-1}: 2979, 2362, 2335, 1799, 1728, 1681, 1614, 1567, 1476, 1429, 1393, 1318, 1275, 1239, 1201, 1083, 1003, 978, 927, 769, 733, 693;

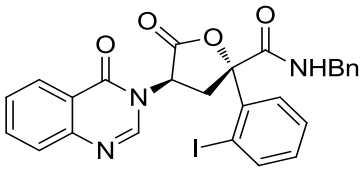


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.31 (s, 1H, $C_{[19]}H$), 8.23 (dd, *J* = 8.1, 1.5 Hz, 1H, $C_{[ar]}H$), 8.07 (dd, *J* = 7.8, 1.2 Hz, 1H, $C_{[ar]}H$), 7.87 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H, $C_{[ar]}H$), 7.72 (dd, *J* = 8.3, 1.2 Hz, 1H, $C_{[ar]}H$), 7.65 – 7.53 (m, 3H, $C_{[ar]}H$), 7.22 (td, *J* = 7.5, 1.9 Hz, 1H, $C_{[ar]}H$), 5.30 (dd, *J* = 10.9, 9.3 Hz, 1H, $C_{[2]}H$), 4.06 (dd, *J* = 12.9, 10.9 Hz, 1H, $C_{[3]}H'$), 3.28 (dd, *J* = 12.9, 9.4 Hz, 1H, $C_{[3]}H''$), COO*H* does not appear;

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 171.3 ($C_{[1]}$), 168.4 ($C_{[5]}$), 160.7 ($C_{[12]}$), 149.1 ($C_{[ar]}$), 148.0 ($C_{[19]}$), 142.7 ($C_{[ar]}$), 142.3 ($C_{[ar]}$), 135.6 ($C_{[ar]}$), 131.3 ($C_{[ar]}$), 129.4 ($C_{[ar]}$), 128.6 ($C_{[ar]}$), 128.4 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 123.0 ($C_{[ar]}$), 95.1 ($C_{[7]}$), 87.6 ($C_{[4]}$), 57.3 ($C_{[2]}$), 35.4 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{13}O_5N_2I+H]^+$ requires *m/z* 476.9942, found *m/z* 476.9942.

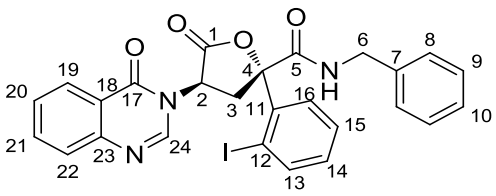
Compound 4-13



Acid **4-12** (9.8 mg, 0.02 mmol, 1.0 eq), benzylamine (3 mg, 0.03 mmol, 1.5 eq) and HATU (11.4 mg, 0.03 mmol, 1.5 eq) were dissolved in CH_2Cl_2 (1.8 mL) and DMF (0.2 mL), and *N,N*-diisopropylethylamine (6.45 mg, 0.05 mmol, 2.5 eq) was then added into the resulting solution. The reaction was stirred for 45 min at rt before quenched with 1 N HCl, exacted with CH_2Cl_2, washed with brine dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (1 / 100 to 1 / 50) to give colourless solid 5 mg (44%);

m.p. 242 – 246 °C; **$[\alpha]_D^{25}$** +12.0 (*c* 0.03, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3066, 1797, 1677, 1610, 1520, 1429, 1300, 1201, 1106, 1018, 908, 776, 751, 697;

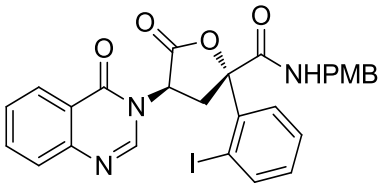


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.08 (s, 1H, $C_{[24]}H$), 8.01 (dd, *J* = 7.8, 1.3 Hz, 1H, $C_{[ar]}H$), 7.79 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, $C_{[ar]}H$), 7.74 (d, *J* = 7.4 Hz, 1H, $C_{[ar]}H$), 7.59 (dd, *J* = 8.0, 1.6 Hz, 1H, $C_{[ar]}H$), 7.53 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H, $C_{[ar]}H$), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H, $C_{[ar]}H$), 7.35 – 7.30 (m, 4H, $C_{[ar]}H$), 7.27 (dd, *J* = 6.0, 2.8 Hz, 1H, $C_{[ar]}H$), 7.10 (td, *J* = 7.6, 1.7 Hz, 1H, $C_{[ar]}H$), 6.49 (t, *J* = 5.1 Hz, 1H, CON*H*), 5.22 (dd, *J* = 10.6, 9.2 Hz, 1H, $C_{[2]}H$), 4.59 (dd, *J* = 14.6, 5.6 Hz, 1H, $C_{[6]}H'$), 4.53 (dd, *J* = 14.6, 5.5 Hz, 1H, $C_{[6]}H''$), 3.76 (dd, *J* = 14.0, 9.3 Hz, 1H, $C_{[3]}H'$), 3.25 (dd, *J* = 14.0, 10.6 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.9 ($C_{[1]}$), 167.6 ($C_{[5]}$), 160.7 ($C_{[17]}$), 148.0 ($C_{[ar]}$), 144.9 ($C_{[24]}$), 142.9 ($C_{[ar]}$), 139.6 ($C_{[ar]}$), 137.3 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 131.2 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.9 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 121.7 ($C_{[ar]}$), 94.8 ($C_{[12]}$)， 87.9 ($C_{[4]}$), 55.6 ($C_{[2]}$), 44.9 ($C_{[6]}$), 36.4 ($C_{[3]}$);

HRMS (ESI) $[C_{26}H_{20}O_4N_3I+H]^+$ requires *m/z* 566.0571, found *m/z* 566.0571.

Compound 4-14

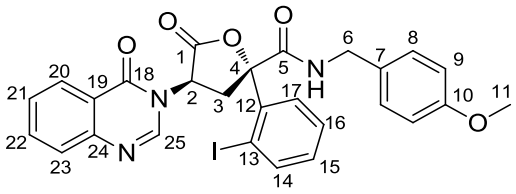


Acid **4-12** (9.5 mg, 0.02 mmol, 1.0 eq), 4-methoxybenzylamine (4.11 mg, 0.03 mmol, 1.5 eq), HATU (11.4 mg, 0.03 mmol, 1.5 eq) were dissolved in CH_2Cl_2 (1.8 mL) and DMF (0.2 mL), and *N*,*N*-diisopropylethylamine (6.45 mg, 0.05 mmol, 2.5 eq) was then added into the resulting solution. The reaction was stirred for 40 min at rt before quenched with 1 N HCl, exacted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered and concentrated

under vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (1 / 100 to 1 / 50) to give colourless solid 8.5 mg (70%);

m.p. 90 – 95 ^{o}C; **$[\alpha]_D^{25}$** –39.1 (*c* 0.54, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3027, 2878, 2802, 1746, 1679, 1610, 1520, 1495, 1471, 1451, 1348, 1262, 1203, 1074, 1049, 1035, 996, 880, 794, 756, 726, 699;

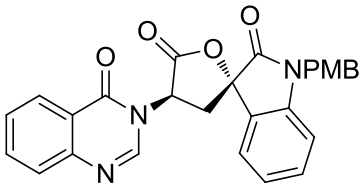


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.26 (dd, *J* = 8.0, 1.5 Hz, 1H, $C_{[ar]}H$), 8.08 (s, 1H, $C_{[25]}H$), 8.01 (dd, *J* = 7.9, 1.3 Hz, 1H, $C_{[ar]}H$), 7.79 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.74 (dd, *J* = 8.2, 1.2 Hz, 1H, $C_{[ar]}H$), 7.58 (dd, *J* = 7.9, 1.6 Hz, 1H, $C_{[ar]}H$), 7.52 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, $C_{[ar]}H$), 7.43 (td, *J* = 7.7, 1.3 Hz, 1H, $C_{[ar]}H$), 7.24 – 7.26 (d, *J* = 8.4 Hz, 2H, $C_{[ar]}H$), 7.10 (td, *J* = 7.6, 1.6 Hz, 1H, $C_{[ar]}H$), 6.84 (d, *J* = 8.6 Hz, 2H, $C_{[ar]}H$), 6.39 (t, *J* = 5.6 Hz, 1H, CON*H*), 5.23 (dd, *J* = 10.6, 9.3 Hz, 1H, $C_{[2]}H$), 4.54 – 4.44 (m, 2H, $C_{[6]}H$), 3.77 (s, 3H, $C_{[11]}H$), 3.77 – 3.72 (m, 1H, $C_{[3]}H'$), 3.23 (dd, *J* = 14.0, 10.7 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 170.9 ($C_{[1]}$), 167.4 ($C_{[5]}$), 160.6 ($C_{[18]}$), 159.4 ($C_{[10]}$), 148.0 ($C_{[ar]}$), 144.9 ($C_{[25]}$), 142.8 ($C_{[ar]}$), 139.7 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 131.2 ($C_{[ar]}$), 129.7 ($C_{[ar]}$), 129.4 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 128.0 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 121.7 ($C_{[ar]}$), 114.3 ($C_{[ar]}$), 94.8 ($C_{[13]}$), 87.9 ($C_{[4]}$), 55.5 ($C_{[2]}$ & $C_{[11]}$), 44.4 ($C_{[6]}$), 36.4 ($C_{[3]}$);

HRMS (ESI) $[C_{27}H_{22}O_5N_3I+H]^+$ requires *m/z* 596.0677, found *m/z* 596.0676.

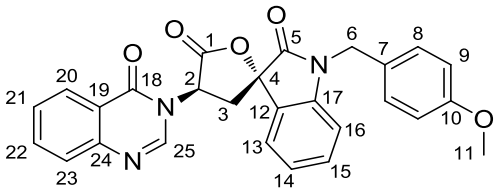
Compound 4-15



Amide **4-14** (7.5 mg, 0.013 mmol, 1.0 eq), copper(I) iodide (2.9 mg, 0.015 mmol, 1.2 eq) and magnesium acetate tetrahydrate (4.1 mg, 0.019 mmol, 1.5 eq) were placed in a dry flask and charged with Ar, and dry DMSO (0.76 mL) was then injected. The solution was stirred at rt for 3 h before quenched with sat. NH_4Cl, exacted with CH_2Cl_2, washed with water, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (1 / 150) to give the protected oxindole product as colourless solid 4.2 mg (70%);

m.p. 204 – 210 ^oC; **$[\alpha]_D^{25}$** –33.9 (*c* 0.23, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 2926, 1779, 1731, 1673, 1611, 1514, 1469, 1373, 1322, 1300, 1256, 1191, 1109, 1047, 977, 908, 839, 812, 774, 748, 690;

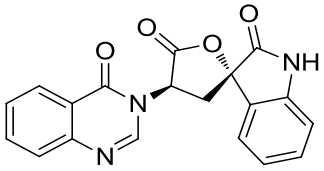


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.38 (d, *J* = 1.6 Hz, 1H, $C_{[ar]}H$), 8.37 (d, *J* = 1.4 Hz, 1H, $C_{[ar]}H$), 7.89 – 7.78 (m, 2H, $C_{[ar]}H$), 7.58 (ddd, *J* = 8.2, 6.9, 1.5 Hz, 1H, $C_{[ar]}H$), 7.47 (dd, *J* = 7.5, 1.2 Hz, 1H, $C_{[ar]}H$), 7.37 (td, *J* = 7.8, 1.2 Hz, 1H, $C_{[ar]}H$), 7.27 (d, *J* = 8.7 Hz, 2H, $C_{[ar]}H$), 7.18 (td, *J* = 7.6, 0.9 Hz, 1H, $C_{[ar]}H$), 6.92 – 6.84 (m, 3H, $C_{[ar]}H$), 6.18 (t, *J* = 10.1 Hz, 1H, $C_{[2]}H$), 4.94 (d, *J* = 15.4 Hz, 1H, $C_{[6]}H'$), 4.84 (d, *J* = 15.4 Hz, 1H, $C_{[6]}H''$), 3.80 (s, 3H, $C_{[11]}H$), 3.08 (dd, *J* = 13.6, 10.4 Hz, 1H, $C_{[3]}H'$), 3.00 (dd, *J* = 13.6, 9.8 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 172.7 ($C_{[5]}$), 171.2 ($C_{[1]}$), 160.9 ($C_{[18]}$), 159.6 ($C_{[10]}$), 147.9 ($C_{[ar]}$), 144.2 ($C_{[25]}$), 143.2 ($C_{[ar]}$), 135.2 ($C_{[ar]}$), 131.9 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 128.2 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 127.3 ($C_{[ar]}$), 126.8 ($C_{[ar]}$), 126.4 ($C_{[ar]}$), 124.3 ($C_{[ar]}$), 124.1 ($C_{[ar]}$), 121.6 ($C_{[ar]}$), 114.6 ($C_{[ar]}$), 110.7 ($C_{[ar]}$), 80.7 ($C_{[4]}$), 55.5 ($C_{[11]}$), 52.9 ($C_{[2]}$), 44.1 ($C_{[6]}$), 36.5 ($C_{[3]}$);

HRMS (ESI) $[C_{27}H_{21}O_5N_3+H]^+$ requires *m/z* 468.1554, found *m/z* 468.1555.

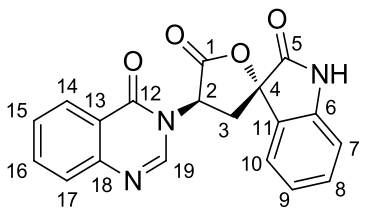
Compound 4-3



4-15 (2.5 mg) was dissolved in CH_2Cl_2 (1.5 mL), and trifluoromethanesulfonic acid (15 μL) was added into the resulting solution at rt. The reaction was stirred at rt for another 5 min until the starting material disappeared when monitored wtih TLC. After quenched with aq. $NaHCO_3$, the mixture was extracted with chloroform and ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with FCC methanol / CH_2Cl_2 (1 / 100 to 1 / 30) to give colourless solid 1.3 mg (64%);

m.p. 271 – 276 °C; **$[\alpha]_D^{25}$** +278.6 (*c* 0.03, MeOH);

IR (film) ν_{max}/cm^{-1}: 2920, 2851, 1787, 1743, 1673, 1612, 1563, 1473, 1439, 1387, 1327, 1280, 1251, 1207, 1186, 1112, 1058, 776, 752, 700;



^{1}H NMR (DMSO, 500 MHz) δ (ppm): 10.90 (s, 1H, CON*H*), 8.64 (s, 1H, $C_{[19]}H$), 8.24 (dd, *J* = 7.9, 1.5 Hz, 1H, $C_{[14]}H$), 7.93 (ddd, *J* = 8.4, 7.1, 1.6 Hz, 1H, $C_{[16]}H$), 7.76 (d, *J* = 8.2 Hz, 1H, $C_{[17]}H$), 7.68 – 7.62 (m, 2H, $C_{[10]}H$ & $C_{[15]}H$), 7.42 (td, *J* = 7.7, 1.3 Hz, 1H, $C_{[8]}H$), 7.18 (td, *J* = 7.6, 1.0 Hz, 1H, $C_{[9]}H$), 6.96 (d, *J* = 7.8 Hz, 1H, $C_{[7]}H$), 5.86 (t, *J* = 10.0 Hz, 1H, $C_{[2]}H$), 3.04 – 2.99 (m, 2H, $C_{[3]}H$);

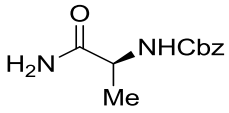
^{13}C NMR (DMSO, 125 MHz) δ (ppm): 175.4 ($C_{[5]}$), 171.9 ($C_{[1]}$), 159.9 ($C_{[12]}$), 147.8 ($C_{[19]}$), 147.7 ($C_{[18]}$), 142.8 ($C_{[6]}$), 135.1 ($C_{[16]}$), 131.7 ($C_{[8]}$), 127.7 ($C_{[15]}$), 127.5 ($C_{[17]}$), 126.4 ($C_{[11]}$), 126.1 ($C_{[14]}$), 125.3 ($C_{[10]}$), 123.1 ($C_{[9]}$), 121.4 ($C_{[13]}$), 110.7 ($C_{[7]}$), 80.9 ($C_{[4]}$), 56.5 ($C_{[2]}$), 33.4 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{13}O_4N_3+H]^+$ requires *m/z* 348.0979, found *m/z* 348.0979.

No.	Isolated	Synthetic	Difference
5	175.4	175.4	0
1	171.9	171.9	0
12	159.8	159.9	-0.1
19	147.8	147.8	0
18	147.7	147.7	0
6	142.9	142.8	0.1
16	135.1	135.1	0
8	131.6	131.7	-0.1
15	127.7	127.7	0
17	127.4	127.5	-0.1
11	126.4	126.4	0
14	126.1	126.1	0
10	125.2	125.3	-0.1
9	123.0	123.1	-0.1
13	121.4	121.4	0

7	110.8	110.7	0.1
4	80.9	80.9	0
2	56.5	56.5	0
3	33.4	33.4	0

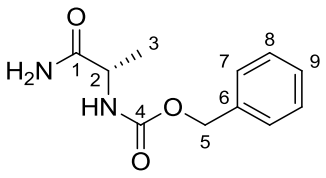
Compound 4-S1



N-carbobenzyloxy-L-alanine (1.12 g, 5 mmol, 1.0 eq) was dissolved in THF (20 mL). The resulting solution was cooled to –20 °C, and ethyl chloroformate (0.65 g, 0.58 mL, 6 mmol, 1.2 eq) and 4-methylmorpholine (0.6 g, 0.65 mL, 6 mmol, 1.2 eq) were then added dropwise. Kept the reaction between –20 °C to –15 °C for 30 min and 35% amonia hydroxide (1.0 mL, 18 mmol, 3.6 eq) was subsequently added into the mixture in one portion. Kept stirring at –15 °C for another 30 min and the reaction could be warmed to rt overnight. The reaction mixture was diluted with brine, extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The residue was triturated with ether to give white fluffy crystal 820 mg (74%);

m.p. 130 – 134 °C; **$[\alpha]_D^{25}$** –20.2 (*c* 0.5, $CHCl_3$);

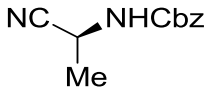
IR (film) ν_{max}/cm^{-1}: 3311, 3210, 1672, 1530, 1455, 1408, 1373, 1329, 1253, 1116, 1067, 1027, 778, 740, 698;



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.38 – 7.28 (m, 5H, $C_{[ar]}H$), 6.04 (s, 1H, CON*H*), 5.48 (s, 1H, CON*H*H), 5.32 (s, 1H, CONH*H*), 5.09 (d, *J* = 3.7 Hz, 2H, $C_{[5]}H$), 4.31 – 4.19 (m, 1H, $C_{[2]}H$), 1.38 (d, *J* = 7.1 Hz, 3H, $C_{[3]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 174.6 ($C_{[1]}$), 156.2 ($C_{[4]}$), 136.3 ($C_{[6]}$), 128.8 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 128.3 ($C_{[ar]}$), 67.4 ($C_{[5]}$), 50.3 ($C_{[2]}$), 18.6 ($C_{[3]}$).

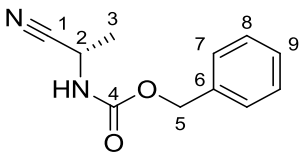
Compound 4-S2



4-S1 (550 mg, 2.5 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (10 mL) and pyridine (1.0 mL), and TsCl (970 mg, 5.1 mmol, 2.1 eq) was then added in one portion. The reaction was stirred for 48 h at the rt. Next, sat. $NaHCO_3$ (20 mL) was added into the flask gradually, and stirred for an additional 1 h, diluted with CH_2Cl_2. The organic phase was washed with 1 M H_3PO_4 and brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue purified with FCC ether / CH_2Cl_2 (4 / 100 to 7 / 100) to give colourless solid 500 mg (98%);

m.p. 80 – 82 °C; **$[\alpha]_D^{25}$** –66.1 (*c* 0.5, $CHCl_3$);

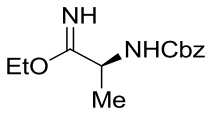
IR (film) ν_{max}/cm^{-1}: 3334, 3035, 2949, 1727, 1691, 1524, 1454, 1384, 1337, 1328, 1292, 1255, 1078, 1033, 937, 914, 779, 757, 740, 736, 698;



^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.50 – 7.28 (m, 5H, $C_{[ar]}H$), 5.27 – 5.02 (m, 3H, $C_{[5]}H$+N*H*), 4.66 (t, *J* = 7.8 Hz, 1H, $C_{[2]}H$), 1.53 (d, *J* = 7.3 Hz, 3H, $C_{[3]}H$);

^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 155.1 ($C_{[4]}$), 135.7 ($C_{[6]}$), 128.9 ($C_{[ar]}$), 128.7 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 119.3 ($C_{[1]}$), 67.9 ($C_{[5]}$), 38.3 ($C_{[2]}$), 19.8 ($C_{[3]}$).

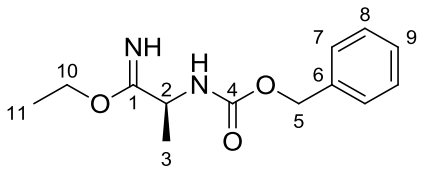
Compound 4-16



A solution of 1.7 g (7.66 mmol) **4-S2** in a mixture of ether (10 mL) and ethanol (0.7 mL) was saturated with dry hydrogen chloride gas on an ice/NaCl bath, and the reaction was then stirred at rt for 2 h. The reaction was quenched into sat. K_2CO_3 with ice, extracted with ether, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was crystalized from ether and hexane to give colourless solid 1.2 g (63%);

m.p. 70 – 71 ^{o}C; **$[\alpha]_D^{25}$** –12.4 (*c* 0.5, $CHCl_3$);

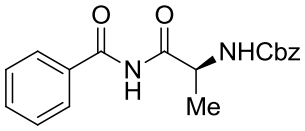
IR (film) ν_{max}/cm^{-1}: 3219, 3033, 2981, 2931, 1715, 1645, 1542, 1457, 1419, 1378, 1351, 1315, 1278, 1249, 1118, 1070, 1024, 943, 861, 746, 695;



^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 7.55 (s, 1H, N*H*), 7.47 – 7.19 (m, 5H, $C_{[ar]}H$, $C_{[5]}H$), 6.74 (s, 1H, N*H*), 4.25 – 4.04 (m, 3H, $C_{[10]}H$+$C_{[2]}H$), 1.33 (d, *J* = 7.2 Hz, 3H, $C_{[3]}H$), 1.24 (t, *J* = 7.1 Hz, 2H, $C_{[11]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 173.3 ($C_{[1]}$), 156.6 ($C_{[4]}$), 138.2 ($C_{[6]}$), 129.3 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 66.9 ($C_{[5]}$), 62.0 ($C_{[10]}$), 50.7 ($C_{[2]}$), 18.8 ($C_{[3]}$), 14.6 ($C_{[11]}$), one aromatic carbon did not appear.

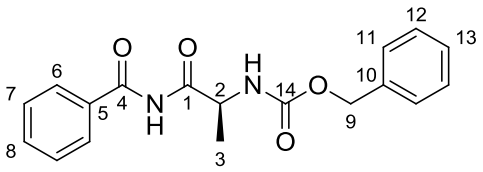
Compound 4-17



To a solution of the **4-16** (12.5 mg, 0.05 mmol, 1.0 eq) in dry CH_2Cl_2 (1.5 mL), *N,N*-diisopropylethylamine (15 mg, 0.15 mmol, 3.0 eq) and benzoyl chloride (10 mg, 0.075 mmol, 1.5 eq) were added subsequently. The reaction was left for 3 h at rt before all volatiles were removed. The residue was dissolved in methanol (1.5 mL) and 1 N HCl (1.5 mL). The resulting mixture was stirred for 1 h before it was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with FCC ethyl acetate / CH_2Cl_2 (1 / 100 to 1 / 10) to give colourless oil 10 mg (61%);

m.p. 117 – 118 °C; **$[\alpha]_D^{25}$** –22.4 (*c* 0.8, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3312, 1691, 1506, 1248, 1069, 702;

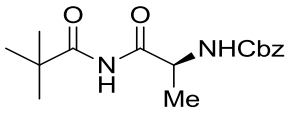


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 7.98 (d, *J* = 7.7 Hz, 2H, $C_{[ar]}H$), 7.71 – 7.60 (m, 1H, $C_{[ar]}H$), 7.53 (t, *J* = 7.8 Hz, 2H, $C_{[ar]}H$), 7.42 – 7.20 (m, 5H, $C_{[ar]}H$), 5.10 (s, 2H, $C_{[9]}H$), 4.99 (t, *J* = 7.0 Hz, 1H, $C_{[2]}H$), 1.45 (d, *J* = 7.1 Hz, 3H, $C_{[3]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 174.9* ($C_{[1]}$), 166.6* ($C_{[4]}$), 157.1* ($C_{[14]}$), 138.2 ($C_{[ar]}$), 134.4 ($C_{[ar]}$), 134.4 ($C_{[ar]}$), 133.8 ($C_{[ar]}$), 129.6 ($C_{[ar]}$), 129.3 ($C_{[ar]}$), 129.1 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 66.9 ($C_{[9]}$), 52.4** ($C_{[2]}$), 17.7* ($C_{[3]}$), * peaks split into doublet, ** peak split into dd style;

HRMS (ESI) $[C_{18}H_{18}O_4N_2+H]^+$ requires *m/z* 327.1339, found *m/z* 327.1340.

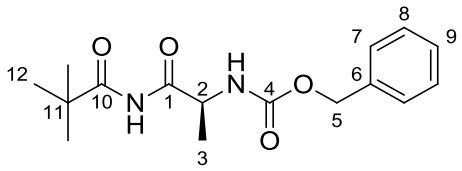
Compound 4-18



To a solution of the **4-16** (12.5 mg, 0.05 mmol, 1.0 eq) in dry CH_2Cl_2 (1.5 mL), *N,N*-diisopropylethylamine (15 mg, 0.15 mmol, 3.0 eq) and trimethylacetyl chloride (9 mg, 0.075 mmol, 1.5 eq) were added subsequently. The reaction was left overnight at rt before all volatiles were removed and the residue was dissolved again in methanol (1.5 mL) and 1 N HCl (1.5 mL). The resulting mixture was stirred for another 1 h before it was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with FCC ethyl acetate / CH_2Cl_2 (1 / 100 to 1 / 10) to give colourless solid 8 mg (52%);

m.p. 138 – 139 ^oC; **$[\alpha]_D^{25}$** –45.5 (*c* 0.1, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3315, 2964, 2922, 2852, 1762, 1694, 1496, 1458, 1346, 1233, 1211, 1130, 1069, 1043, 740, 698;

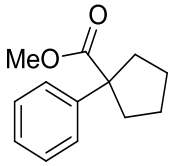


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 7.39 – 7.33 (m, 4H, $C_{[ar]}H$), 7.33 – 7.28 (m, 1H, $C_{[ar]}H$), 5.08 (d, *J* = 2.8 Hz, 2H, $C_{[5]}H$), 4.94 – 4.85 (m, 1H, $C_{[2]}H$), 1.33 (d, *J* = 7.1 Hz, 3H, $C_{[3]}H$), 1.24 (s, 9H, $C_{[12]}H$);

^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 177.5* ($C_{[10]}$), 174.9* ($C_{[1]}$), 157.1 ($C_{[4]}$), 138.2 ($C_{[ar]}$), 129.3 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 66.9 ($C_{[5]}$), 52.5* ($C_{[2]}$), 40.9* ($C_{[11]}$), 27.0* ($C_{[12]}$), 17.6 ($C_{[3]}$), * peaks split into doublet, one aromatic carbon did not appear;

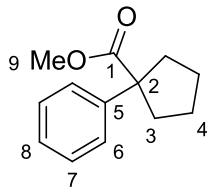
HRMS (ESI) $[C_{16}H_{22}O_4N_2+H]^+$ requires *m/z* 307.1652, found *m/z* 307.1653.

Compound 4-S3



Methyl phenylacetate 750 mg (5 mmol, 1.0 eq) was dissolved in dry DMF (25 mL), and sodium hydride (60%, 500 mg, 12.5 mmol, 2.5 eq) and 18-crown-6 (cat. 20 mg) were then added into the resulting solution. The reaction was stirred for 25 min before 1,4-dibromobutane (1.2 g, 5.5 mmol, 1.1 eq) was added dropwise. The reaction was left for another 18 h before quenched with sat. NH_4Cl, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified with FCC diethyl ether / petrol ether (from 1/ 100 to 1 / 20) to give the light-yellow oil 450 mg (44%);

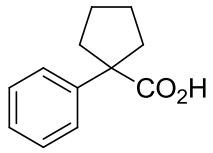
IR (film) ν_{max}/cm^{-1}: 2952, 2875, 1728, 1434, 1426, 1194, 1159, 734, 699;



^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.38 – 7.32 (m, 2H, $C_{[ar]}H$), 7.29 (ddd, *J* = 7.8, 6.7, 1.3 Hz, 1H, $C_{[ar]}H$), 7.24 – 7.18 (m, 1H, $C_{[ar]}H$), 3.59 (s, 3H, $C_{[9]}H$), 2.72 – 2.54 (m, 2H, $C_{[3]}H'$), 2.02 – 1.84 (m, 2H, $C_{[3]}H''$), 1.74 – 1.65 (m, 4H, $C_{[4]}H$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 176.7 ($C_{[1]}$), 143.5 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 127.0 ($C_{[ar]}$), 126.9 ($C_{[ar]}$), 59.3 ($C_{[2]}$), 52.6 ($C_{[9]}$), 36.4 ($C_{[3]}$), 23.8 ($C_{[4]}$).

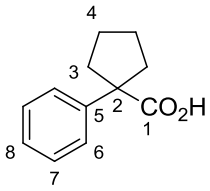
Compound 4-S4



4-S3 420 mg was dissolved in THF (9 mL), and 1 N KOH solution (3 mL) was then added. The mixture was stirred at 60 ^oC until all starting material disappeared when monitored with TLC. The reaction was diluted with water, washed with ethyl acetate, and the pH was adjusted to 1 with 1 N HCl before it was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was triturated with diethyl ether to give colourless solid 325 mg (83%);

m.p. 150 – 154 ^oC;

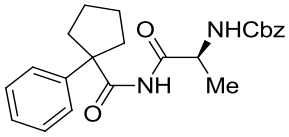
IR (film) ν_{max}/cm^{-1}: 2965, 2875, 1680, 1597, 1495, 1450, 1402, 1304, 1267, 1216, 1179, 937, 912, 727, 698, 630;



^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.47 – 7.40 (m, 2H, $C_{[ar]}H$), 7.37 – 7.32 (m, 2H, $C_{[ar]}H$), 7.30 – 7.22 (m, 1H, $C_{[ar]}H$), 2.75 – 2.62 (m, 2H, $C_{[3]}H'$), 2.01 – 1.89 (m, 1H, $C_{[3]}H''$), 1.82 – 1.72 (m, 4H, $C_{[4]}H$);

^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 182.2 ($C_{[1]}$), 143.0 ($C_{[ar]}$), 128.5 ($C_{[ar]}$), 127.3 ($C_{[ar]}$), 127.2 ($C_{[ar]}$), 59.0 ($C_{[2]}$), 36.2 ($C_{[3]}$), 23.8 ($C_{[4]}$).

Compound 4-19

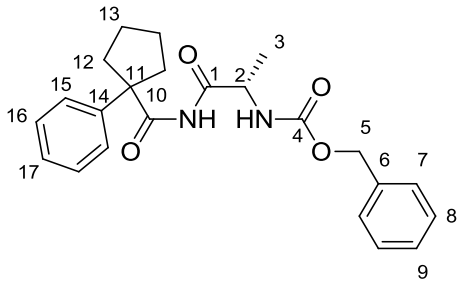


To the solution of **4-S4** (19 mg, 0.1 mmol, 0.3 eq) in 1.5 mL of dry CH_2Cl_2, 4 drops of oxychloride and 1 drop of DMF were added. Then the reaction was stirred overnight before all volatiles were removed under vacuum and kept under high vacuum for 2 h. The crude acyl chloride was dissolved in another 1.5 mL of dry CH_2Cl_2. To the resulting solution, 3 drops of DIPEA, 7.5 mg of **4-16** (0.03 mmol, 1.0 eq) and catalytic amount of DMAP were added as well. The reaction was stirred overnight at rt before all volatiles were removed and the residue was dissolved in methanol (1.5 mL) and 1 N HCl (1.5 mL). The resulting mixture was stirred for 3 before it was extracted with ethyl acetate, washed with brine,

dried over Na_2SO_4, filtered and concentrated. The residue was purified with FCC ethyl acetate / CH_2Cl_2 (1 / 100 to 1 / 10) to give colourless oil 3 mg (25%);

$[\alpha]_D^{25}$ –29.5 (*c* 0.2, $CHCl_3$);

IR (film) ν_{max}/cm^{-1}: 3323, 2956, 2924, 2362, 2334, 1762, 1695, 1495, 1456, 1385, 1345, 1250, 1215, 1068, 1037, 740, 699;

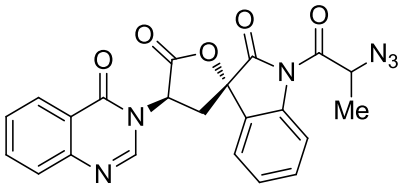


^{1}H NMR (Acetone-d_6, 500 MHz) δ (ppm): 8.98 (s, 1H, CON*H*), 7.43 – 7.24 (m, 10H, $C_{[ar]}H$), 6.58 (d, *J* = 7.7 Hz, 1H, N*H*Cbz), 5.04 (s, 2H, $C_{[5]}H$), 4.72 – 4.81 (m, 1H, $C_{[2]}H$), 2.58 (ddd, *J* = 12.2, 8.8, 5.5 Hz, 2H, $C_{[12]}H'$), 2.03 – 1.95 (m, 2H, $C_{[12]}H''$), 1.73 (dd, *J* = 9.6, 5.7 Hz, 4H, $C_{[13]}H$), 1.25 (d, *J* = 7.1 Hz, 3H, $C_{[3]}H$);

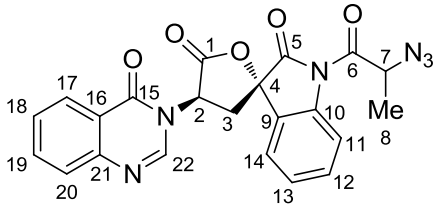
^{13}C NMR (Acetone-d_6, 125 MHz) δ (ppm): 174.7 ($C_{[10]}$ or $C_{[1]}$), 174.4 ($C_{[1]}$ or $C_{[10]}$), 157.0 ($C_{[4]}$), 143.5 ($C_{[ar]}$), 138.1 ($C_{[ar]}$), 129.7 ($C_{[ar]}$), 129.3 ($C_{[ar]}$), 128.8 ($C_{[ar]}$), 128.1 ($C_{[ar]}$), 127.6 ($C_{[ar]}$), 66.9 ($C_{[5]}$), 61.9 ($C_{[11]}$), 52.1 ($C_{[2]}$), 36.3 ($C_{[12]}$), 24.5 ($C_{[13]}$), 17.4 ($C_{[3]}$);

HRMS (ESI) $[C_{23}H_{26}O_4N_2+Na]^+$ requires *m/z* 417.1785, found *m/z* 417.1790.

Compound 4-22

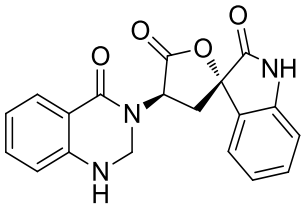


4-3 (26 mg, 0.075 mmol, 1.0 eq) and the *N*-hydroxyphthalimide ester **4-24** (39 mg, 0.15 mmol, 2.0 eq) were dissolved in dry THF / DMF (2.0 mL / 0.2 mL), and the resulting solution was cooled to –80 ^{o}C. LHMDS solution (1.0 M in THF, 0.075 mL, 1.0 eq) was then added dropwise followed by stirring for another 20 min at the same temperature before quenching with 1 N HCl. The mixture was diluted and extracted with ethyl acetate, washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was found prone to decompose on FCC, but one clean portion of fractions was isolated and characterized (the crude NMR before FCC shows a 1:2 diastereomers ratio);



^{1}H NMR (Acetone-d_6, 400 MHz) δ (ppm): 8.57 (d, *J* = 5.0 Hz, 1H, $C_{[22]}H$), 8.36 – 8.20 (m, 2H, $C_{[ar]}H$), 7.99 (dddd, *J* = 7.6, 2.3, 1.5, 0.6 Hz, 1H, $C_{[ar]}H$), 7.91 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H, $C_{[ar]}H$), 7.81 – 7.74 (m, 1H, $C_{[ar]}H$), 7.68 – 7.57 (m, 2H, $C_{[ar]}H$), 7.50 (tdd, *J* = 7.6, 1.7, 1.0 Hz, 1H, $C_{[ar]}H$), 5.78 (m, 1H, $C_{[2]}H$), 5.23 (q, *J* = 6.9 Hz, 0.4H, $C_{[7]}H'$), 5.12 (q, *J* = 6.9 Hz, 0.6H, $C_{[7]}H''$), 3.40 (m, 1H, $C_{[3]}H'$), 3.28 (m, 1H, C[3]H''), 1.66 (d, *J* = 6.9 Hz, 1.8H, $C_{[8]}H'$), 1.62 (d, *J* = 6.9 Hz, 1.2H, $C_{[8]}H''$).

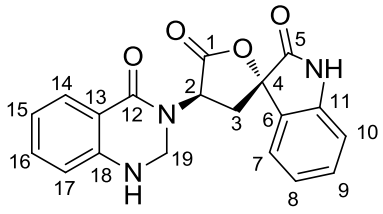
Compound 4-23



Crude **4-22** (cal. 0.075 mmol) was dissolved in 8 mL of dry benzene, and triphenylphosphine (39 mg, 0.15 mmol) was then added. The reaction was stirred at rt for 4 hours. After removal of all volatiles, the residue was dissolved in methanol (10 mL) before 5 drops of 1 N HCl was subsequently added. Next, one portion of sodium cyanoborohydride (9.45 mg, 0.15 mmol) was added into the resulting mixture. The reaction was stirred at rt for 2 h before it was diluted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with FCC, to give the colourless compound 11 mg (42%);

m.p. 273 – 276 ^{o}C; **$[\alpha]_D^{25}$** +17.3 (*c* 0.08, Acetone);

IR (film) ν_{max}/cm^{-1}: 3373, 3297, 1750, 1678, 1615, 1494, 1472, 1425, 1358, 1329, 1282, 1213, 1078, 1047, 1006, 969, 798, 748, 678, 651, 620;



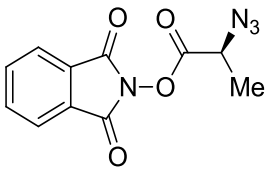
^{1}H NMR (DMSO, 500 MHz) δ (ppm): 10.80 (s, 1H, CON*H*), 7.69 (dd, *J* = 7.7, 1.5 Hz, 1H, $C_{[ar]}H$), 7.65 (dd, *J* = 7.5, 1.2 Hz, 1H, $C_{[ar]}H$), 7.37 (td, *J* = 7.7, 1.3 Hz, 1H, $C_{[ar]}H$), 7.32 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H, $C_{[ar]}H$), 7.13 (td, *J* = 7.5, 1.0 Hz, 1H, $C_{[ar]}H$), 6.95 (d, *J* = 2.3 Hz, 1H, N*H*), 6.92 (d, *J* = 7.8 Hz, 1H, $C_{[ar]}H$), 6.79 – 6.70 (m, 2H, $C_{[ar]}H$), 5.10 (t, *J* = 10.0 Hz, 1H, $C_{[2]}H$), 4.84 (dt,

J = 9.1, 2.0 Hz, 1H, $C_{[19]}H'$), 4.76 (dt, *J* = 9.1, 2.0 Hz, 1H, $C_{[19]}H''$), 2.87 (dd, *J* = 13.0, 9.6 Hz, 1H, $C_{[3]}H'$), 2.76 (dd, *J* = 13.0, 10.6 Hz, 1H, $C_{[3]}H''$);

^{13}C NMR (DMSO, 125 MHz) δ (ppm): 175.6 ($C_{[5]}$), 173.0 ($C_{[1]}$), 163.6 ($C_{[12]}$), 149.2 ($C_{[ar]}$), 142.5 ($C_{[ar]}$), 133.7 ($C_{[ar]}$), 131.3 ($C_{[ar]}$), 127.9 ($C_{[ar]}$), 126.7 ($C_{[ar]}$), 125.3 ($C_{[ar]}$), 122.8 ($C_{[ar]}$), 117.7 ($C_{[ar]}$), 114.9 ($C_{[ar]}$), 114.8 ($C_{[ar]}$), 114.8 ($C_{[ar]}$), 110.5 ($C_{[ar]}$), 80.5 ($C_{[4]}$), 59.4 ($C_{[19]}$), 55.0 ($C_{[2]}$), 33.5 ($C_{[3]}$);

HRMS (ESI) $[C_{19}H_{15}O_4N_3+H]^+$ requires *m/z* 350.1135, found *m/z* 350.1137.

Compound 4-24

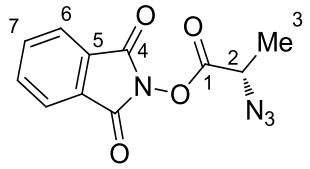


Sodium azide (5 g, 77.0 mmol) was dissolved in distilled H_2O (13 mL) and CH_2Cl_2 (22 mL). The resulting mixture was cooled on an ice bath, and triflyl anhydride (2.5 mL, 15.0 mmol) was then added dropwise. The reaction was kept stirring for 2 h before it was placed in a separator funnel and the organic phase was collected. The aqueous phase was extracted with CH_2Cl_2. The organic fractions containing the triflyl azide were combined and washed once with sat. Na_2CO_3 and used without further purification. L-Alanine (715 mg, 8.0 mmol), K_2CO_3 (1.63 g, 11.8 mmol) and $CuSO_4$ pentahydrate (28 mg, 0.112 mmol) were dissolved in H_2O (25 mL) and methanol (50 mL), and previously prepared triflyl azide in CH_2Cl_2 was added into the resulting mixture. The reaction was stirred at ambient temperature overnight before organic solvents were removed under vacuum and the aqueous slurry was diluted with H_2O (150 mL), acidified to pH 6 with conc. HCl, diluted with phosphate buffer

(0.25 M, pH 6.2, 150 mL) and extracted with EtOAc to remove sulfonamide by-product. The aqueous phase was then acidified to pH 2 with conc. HCl. The product was obtained from another round of EtOAc extraction. Combined, dried over $MgSO_4$ and evaporated to dryness giving 600 mg of (2*S*)-2-azido-propanoic acid as a pale oil (66%) with no further purification;

To a solution of the carboxylic acid (600 mg, 5.22 mmol) and *N*-hydroxyphthalimide (851 mg, 5.22 mmol) in CH_2Cl_2 (30 mL), DIC (724 mg, 5.74 mmol) was then added dropwise. The reaction was stirred at rt for 4 h before it was filtered through a short Celite pad. The resulting solution was concentrated under vacuum and purified with FCC EtOAc / hexane (from 1:10 to 1:4) to give colorless solid 700 mg (51%), which could be recrystallized when necessary;

IR (film) ν_{max}/cm^{-1}: 2105, 1818, 1790, 1744, 1187, 1050, 1018, 876, 696;

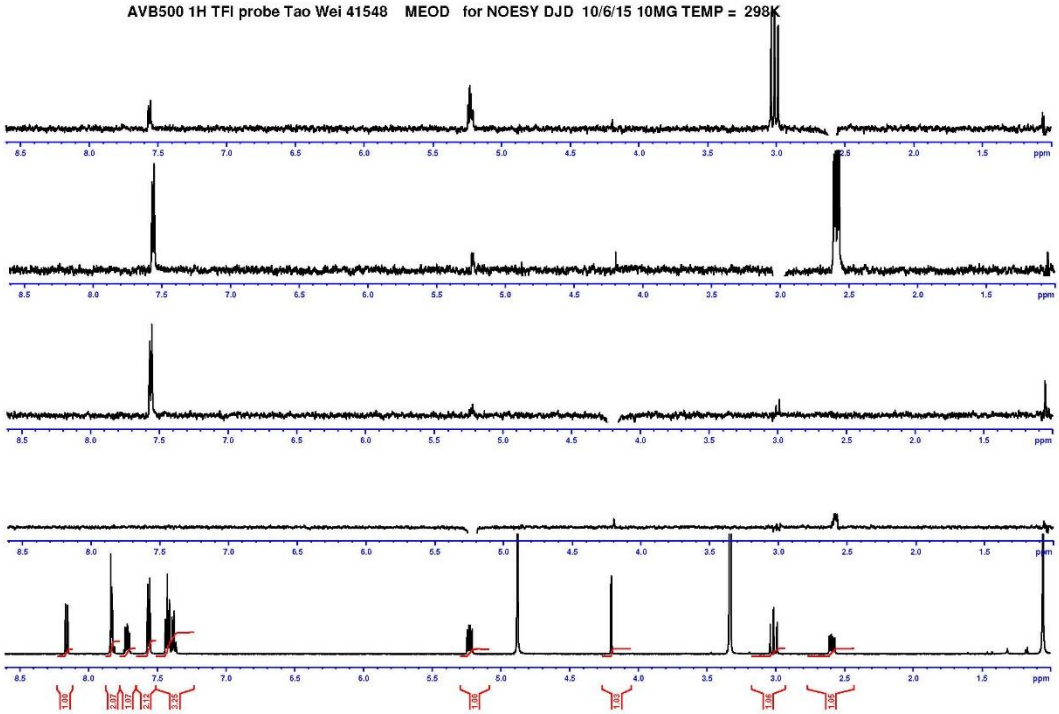


^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H, $C_{[ar]}H$), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H, $C_{[ar]}H$), 4.33 (q, *J* = 7.2 Hz, 1H, $C_{[2]}H$), 1.70 (d, *J* = 7.1 Hz, 3H, $C_{[3]}H$);

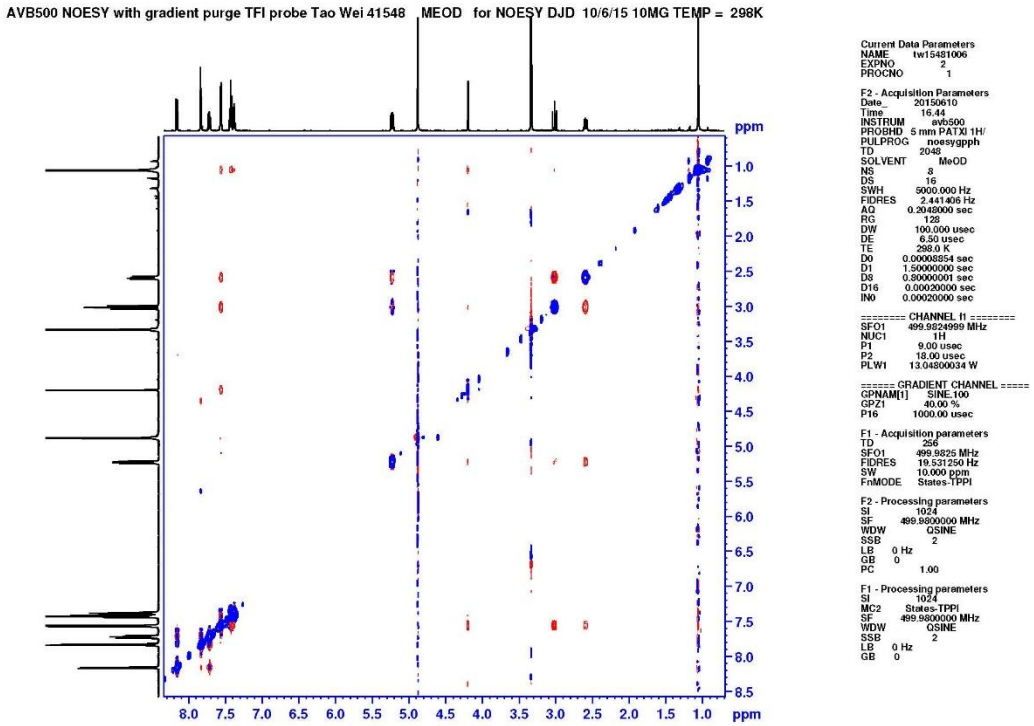
^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 167.9 ($C_{[1]}$), 161.6 ($C_{[4]}$), 135.2 ($C_{[ar]}$), 129.0 ($C_{[ar]}$), 124.4 ($C_{[ar]}$), 55.6 ($C_{[2]}$), 17.3 ($C_{[3]}$).

I.c Important spectrum

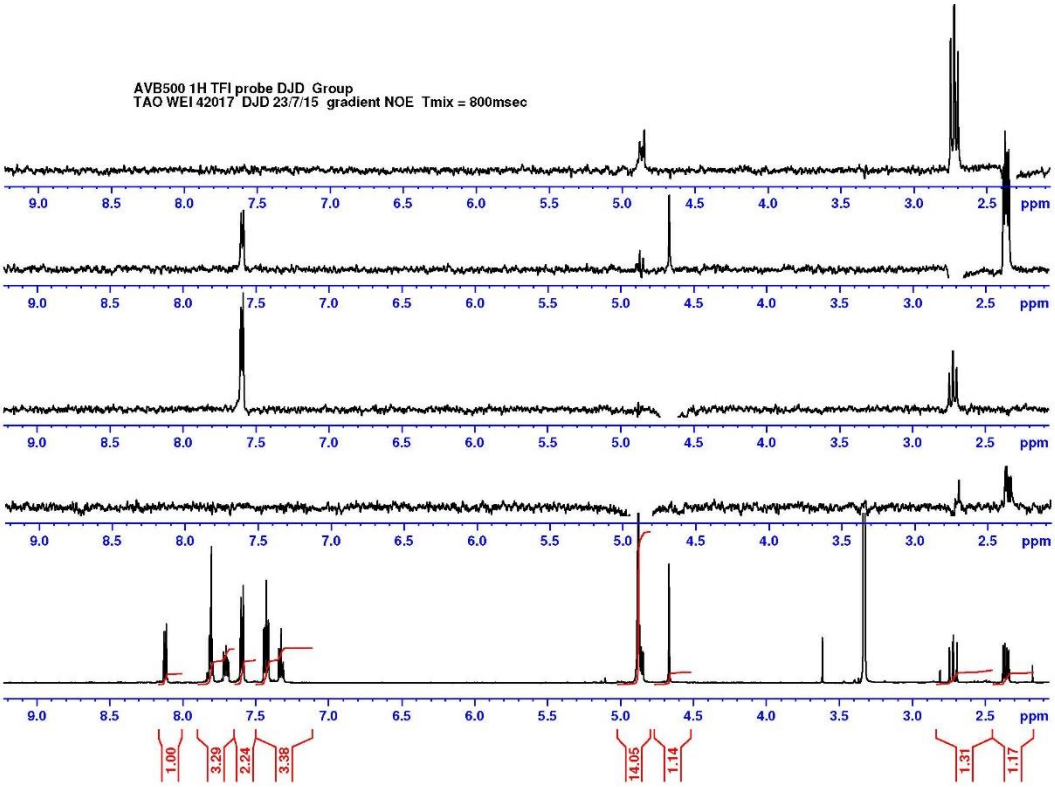
nOe of **2-13**



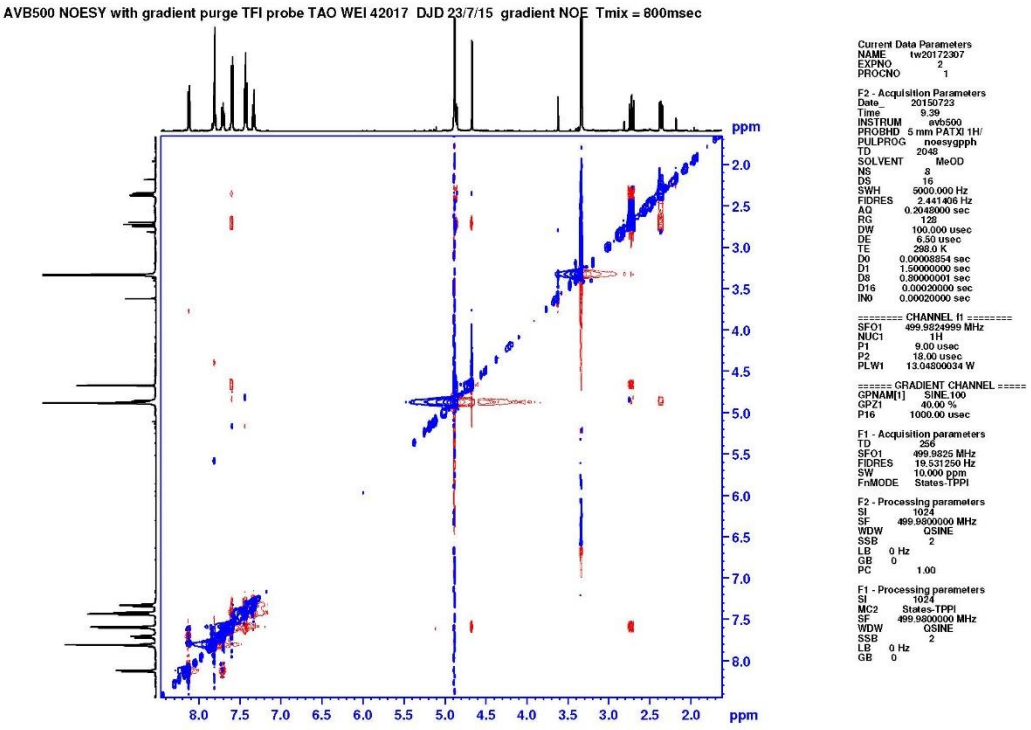
NOESY of **2-13**



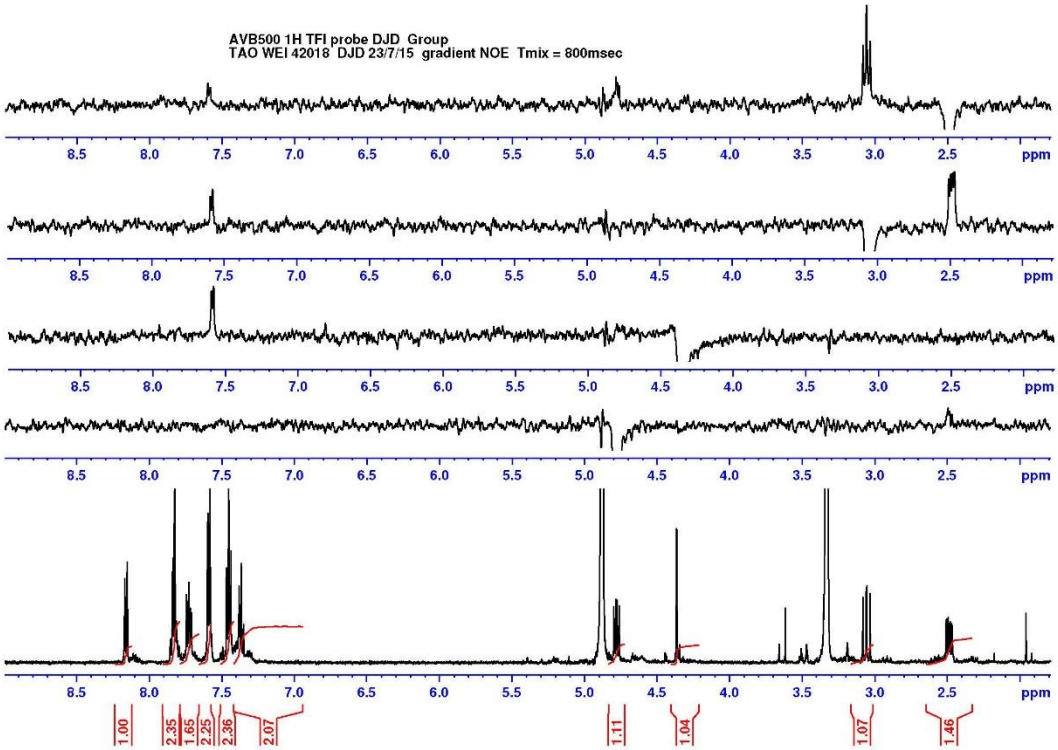
nOe of **2-17**



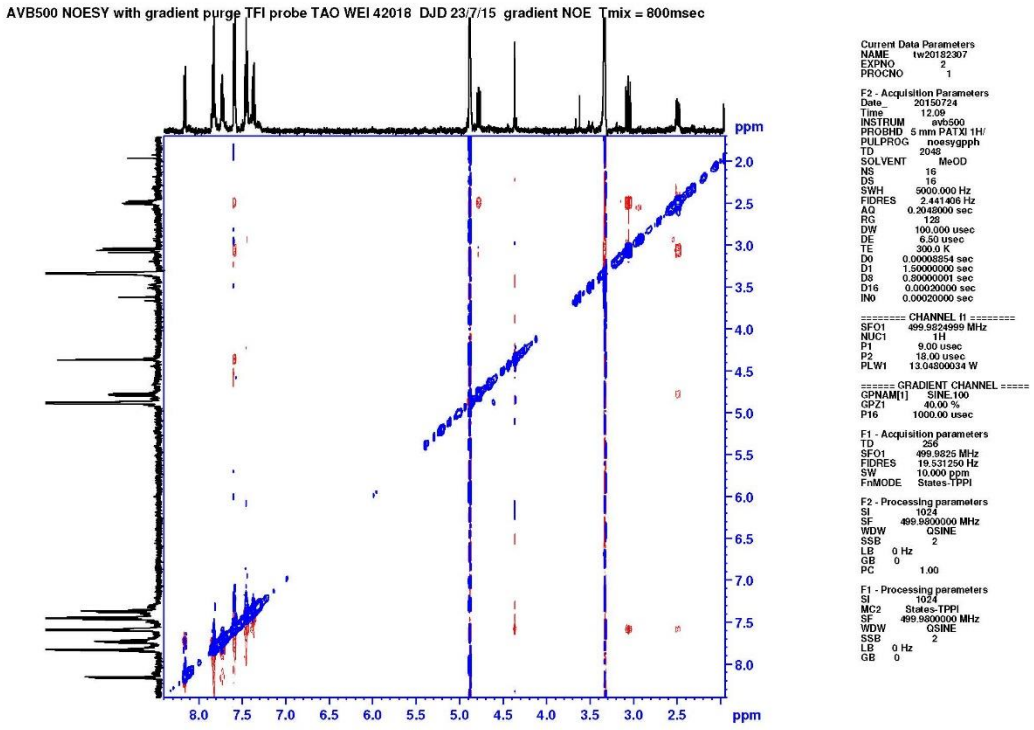
NOESY of **2-17**



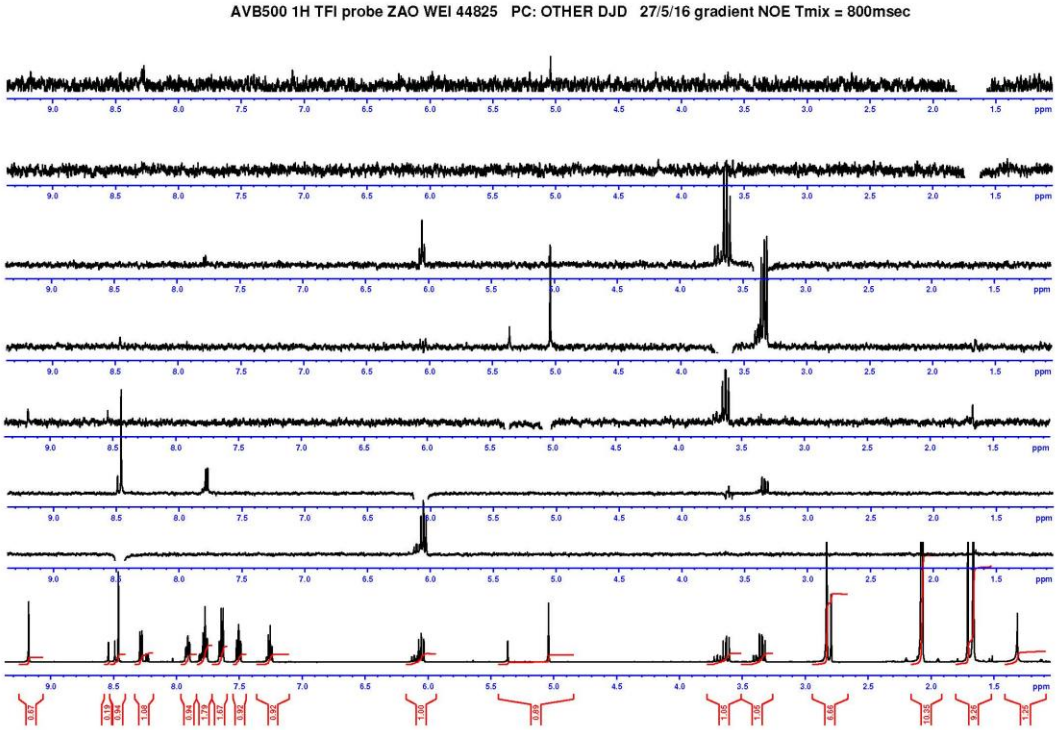
nOe of **2-18**



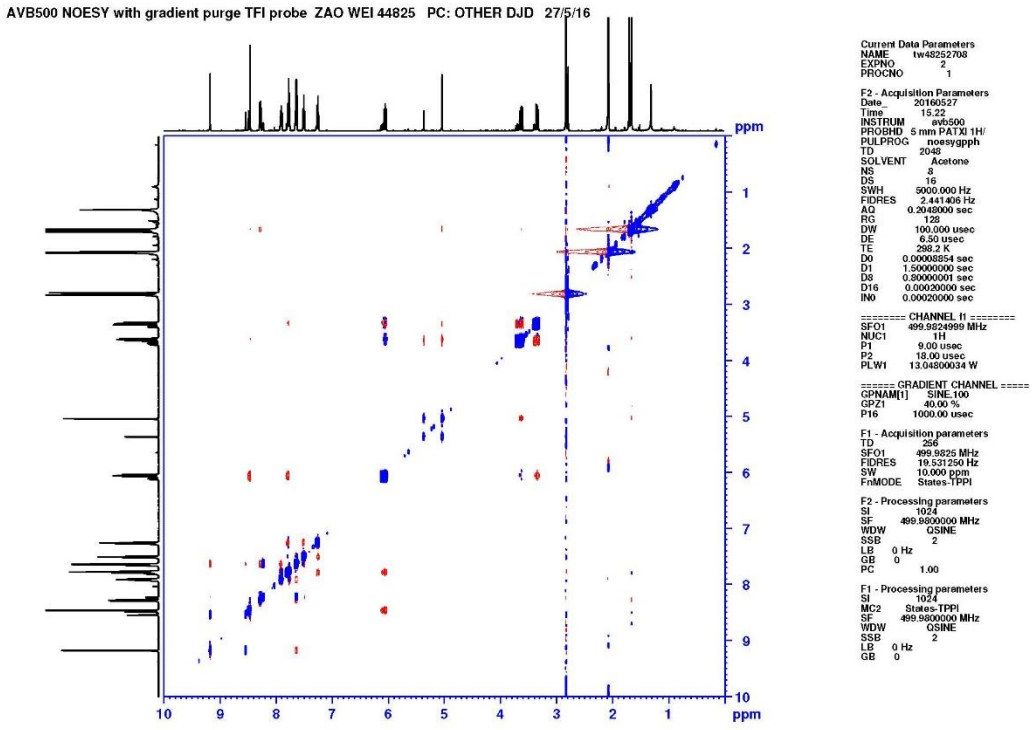
NOESY of **2-18**



nOe of **3-13**

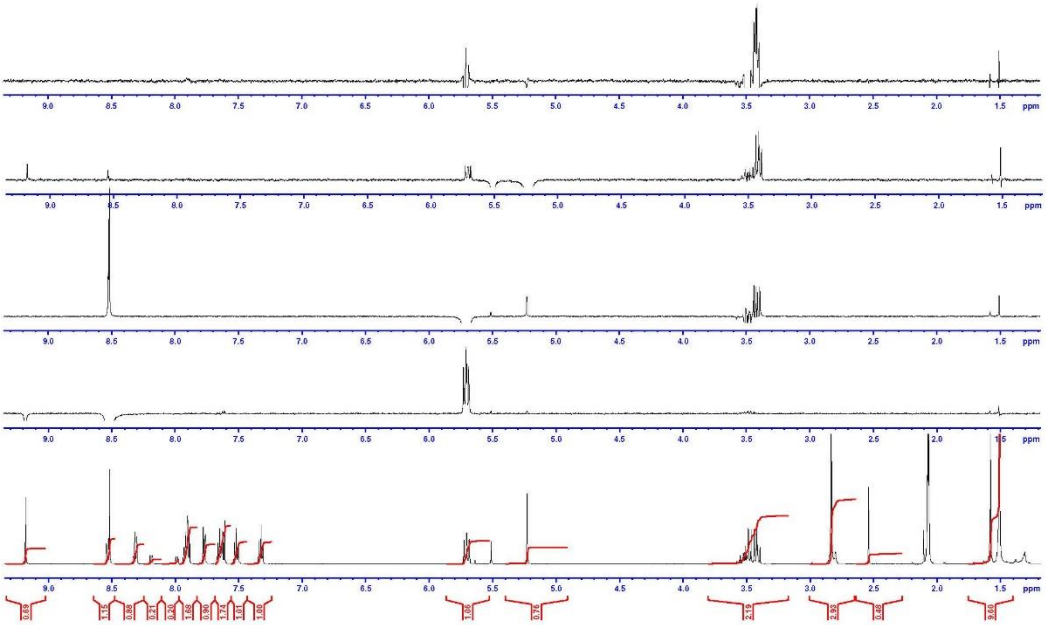


NOESY of **3-13**



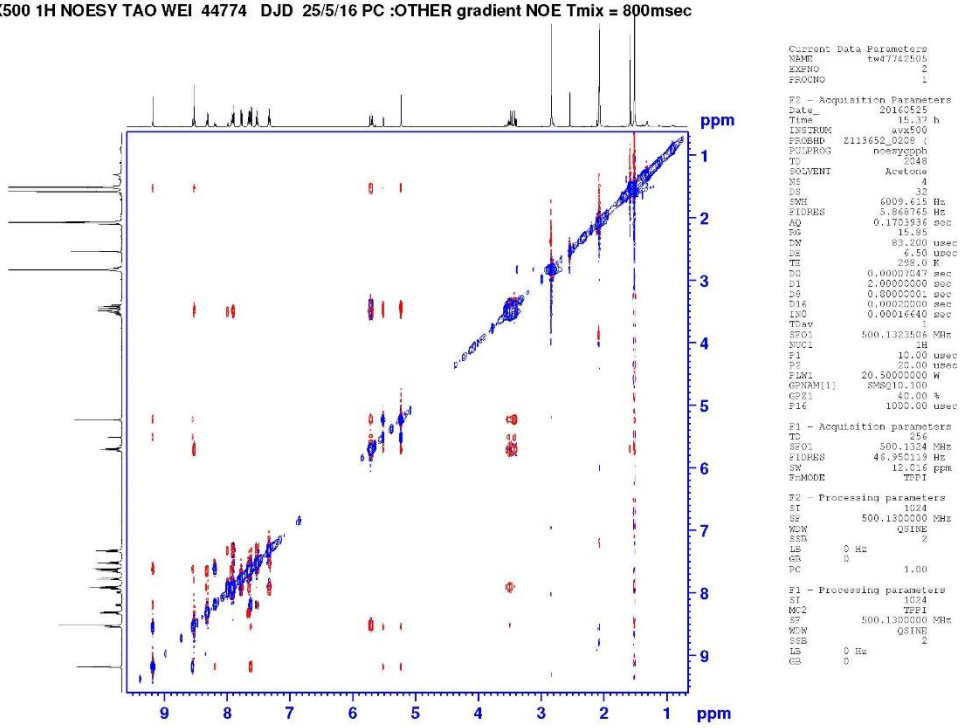
nOe of **3-14**

AVX500 1H TAO WEI 44774 DJD 25/5/16 PC :OTHER gradient NOE Tmix = 800msec

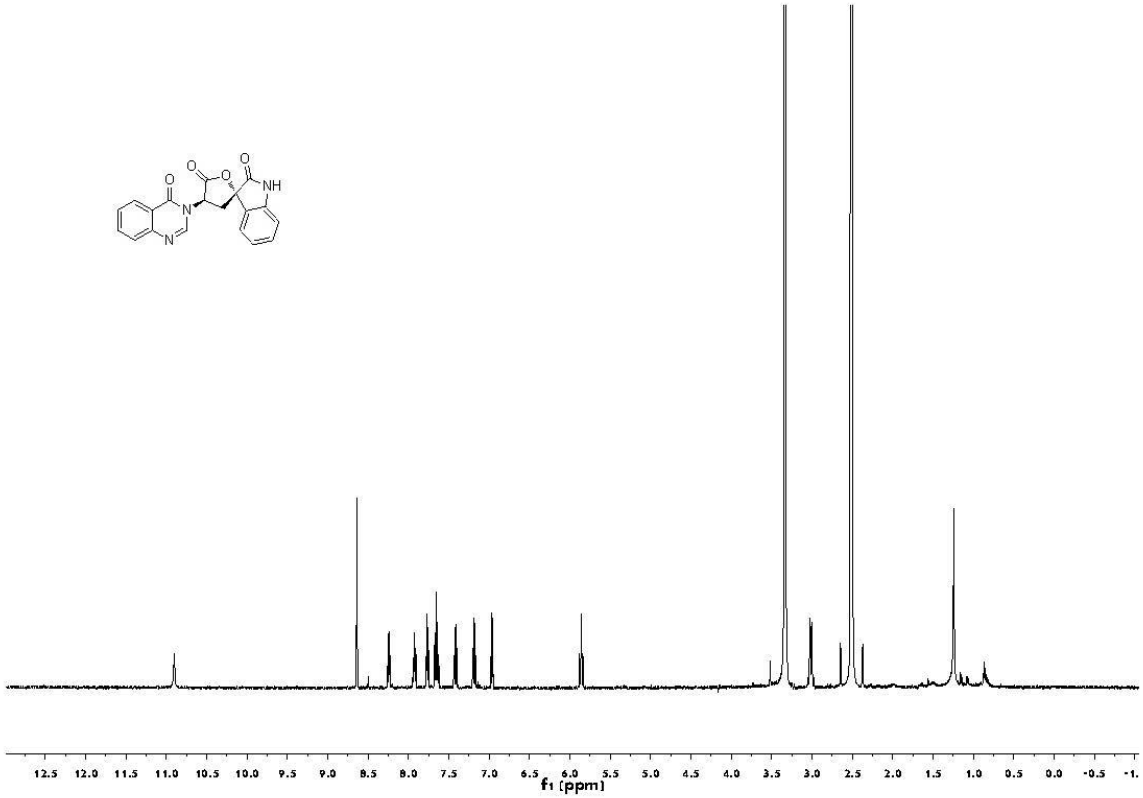


NOESY of **3-14**

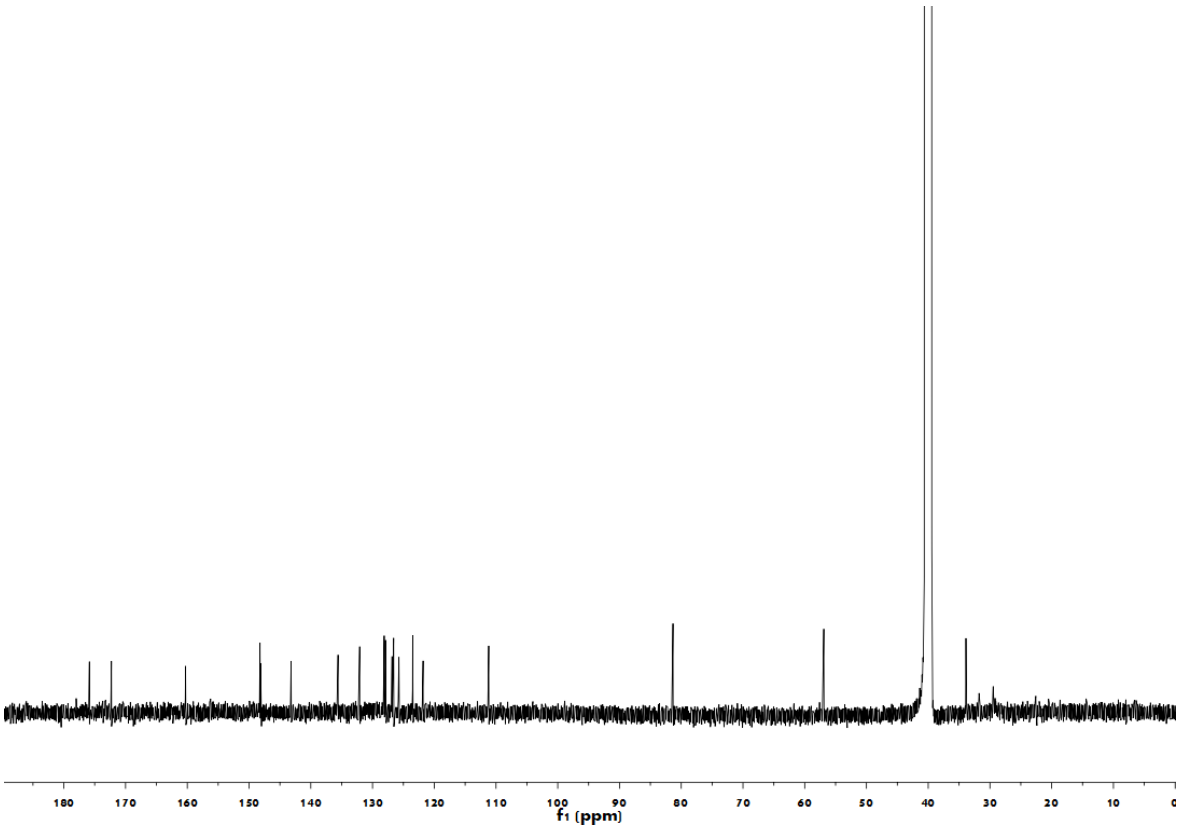
AVX500 1H NOESY TAO WEI 44774 DJD 25/5/16 PC :OTHER gradient NOE Tmix = 800msec



^{1}H NMR of **4-3**



^{13}C NRM of **4-3**



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III. Appendix

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Catalytic stereoselective total synthesis of a spiro-oxindole alkaloid and the pentacyclic core of tryptoquivalines†

Tao Wei and Darren J. Dixon *

An expedient route to the pentacyclic core of the tryptoquivaline alkaloids and the total synthesis of natural product (+)-3′-(4-oxoquinazolin-3-yl)spiro[1*H*-indole-3,5′-oxolane]-2,2′-dione (1) have been achieved. The route is enabled by a key, highly stereoselective, aldol reaction catalysed by a Ag(I) and cinchona-derived amino-phosphine ligand system, forming a highly substituted oxazoline ring, and setting the C1 spirocyclic stereocentre for downstream manipulation.

Among the large family of quinazolinone alkaloids,[1–3] tryptoquivalines[4–6] represent a unique subset characterised by their [5,5]oxo-spirocyclic core, *N*,*N*-aminal moiety and quinazolinone ring systems (Fig. 1). Previous approaches to construct the spirocyclic core have focussed on oxidative cyclisation approaches. For example, Büchi[7] (Scheme 1) and Ban[8] explored oxidative lactonization for establishing the spirocyclic C1 position, with stereocontrol arising from the existing C7 position. Subsequent introduction of the methyl alanine moiety to form the final *N*,*N*-aminal ring structure then afforded tryptoquivaline L and its C7-epimer.‡ The thermodynamically stable *epi*-**1** of natural product **1** was chosen by the Büchi group to complete the synthesis of both tryptoquivaline L and C7-*epi*-tryptoquivaline L. In an alternative approach, Nakagawa and co-workers[9,10] reported an oxidative double cyclization where the generation of the new C1 stereocentre was followed by conversion to tryptoquivaline L, its C7 epimer and *ent*-tryptoquivaline L within a concise synthetic sequence (Scheme 2).

Against these precedents our aim was to develop a new total synthesis of **1** based on a catalytic stereoselective approach to generate the C1 stereocentre which would be independent of any substrate bias, thus potentially enabling access to other family members. Our general strategy to natural product **1**, (+)-3′-(4-oxoquinazolin-3-yl)spiro[1*H*-indole-3,5′-oxolane]-2,2′-dione, is presented in Scheme 3. Pivotal to our approach was the

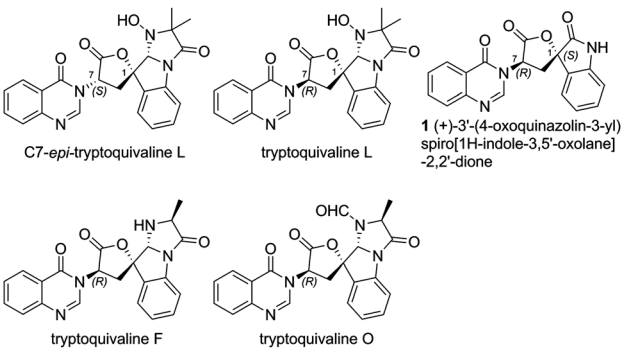
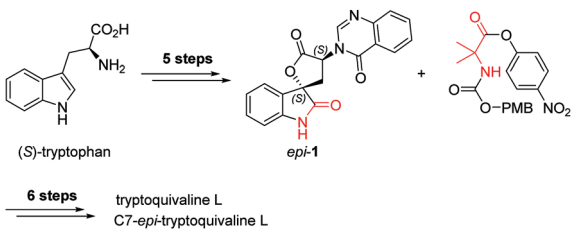


Fig. 1 Selected quinazolinone alkaloids.



Scheme 1 Previous synthetic route by Büchi *et al.*

stereoselective addition reaction of a masked one-carbon nucleophilic unit into a suitably functionalised quinazolinone-containing aryl ketone derivative where the resulting tertiary alcohol was poised to form the C-ring in a lactonisation process. In turn, the spiro oxindole D-ring could be accessed through a suitable intramolecular C–N coupling reaction. We recognized that the broad-scope silver catalysed enantio- and diastereoselective isocyanoacetate aldol methodology recently developed in our group,[11,12] Scheme 4, could be applied to deliver the necessary one carbon unit through oxidative manipulation en route to the target.

Our route to the key functionalised aryl ketone substrate **5** (poised for the stereoselective isocyanoacetate ketone aldol reaction) is shown in Scheme 5. Starting from commercially

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: darren.dixon@chem.ox.ac.uk

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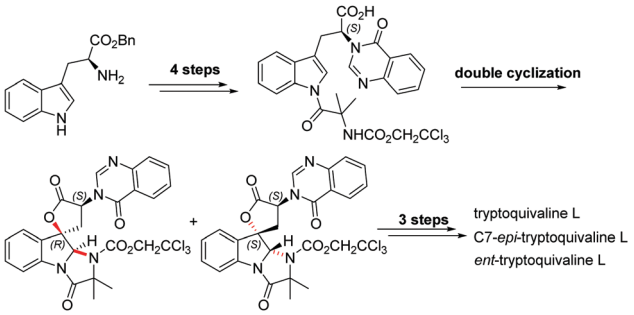
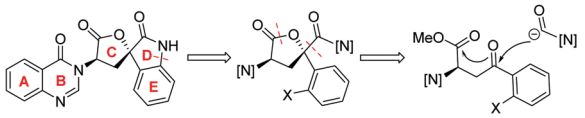
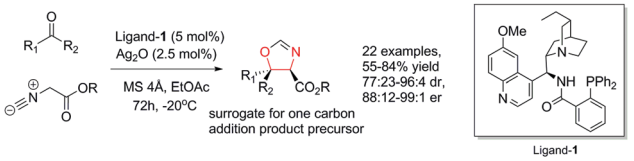


Scheme 2 Previous synthetic route by Nakagawa *et al.*



Scheme 3 This work synthetic plan.

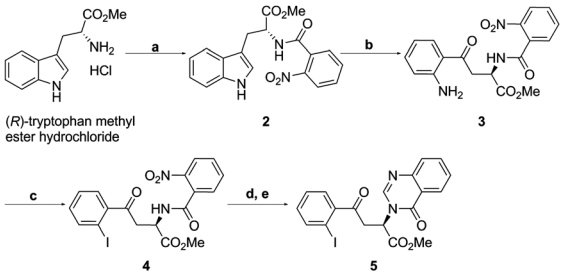


Scheme 4 Underpinning enantioselective isocyanoacetate ketone aldol methodology.

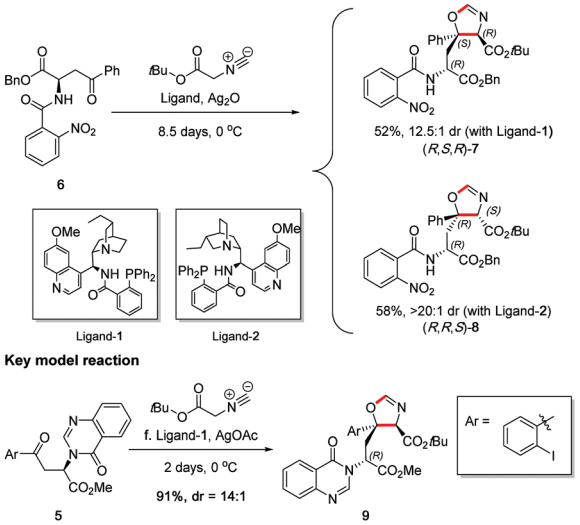
available D-tryptophan methyl ester hydrochloride, amine acylation with 2-nitrobenzoyl chloride gave the amide **2** in excellent yield. The indole ring was then subjected to an oxidative cleavage[13,14] with sodium periodate to afford a mixture of free aniline **3** and its formamide derivative, which upon methanolysis with methanolic HCl, gave aniline **3** in 84% yield. Diazotisation with *tert*-butyl nitrite and subsequent treatment with KI afforded iodoarene **4** in 63% yield. The nitro group of **4** was reduced using iron powder in the presence of ammonium chloride, a method that was sufficiently mild to leave the previously installed iodide intact. Subsequent treatment with trimethyl orthoformate and *p*-toluenesulfonic acid lead to the efficient formation of the quinazolinone ring[15] of desired ketone **5**.

Before carrying out the key stereoselective isocyanoacetate aldol reaction on **5**, the viability of the planned methodology was first investigated on a readily prepared model substrate **6**,§ as shown in Scheme 6. In the study, both quinine and quinidine-derived aminophosphine ligands,[16] ligand-**1** and ligand-**2** respectively, were tested to ascertain reactivity and stereocontrol. It was found that ligand-**1** resulted in a mismatched outcome as shown by a 12.5 : 1 dr, whereas ligand-**2** afforded a matched result with a 20 : 1 dr.¶ This study uncovered that the natural diastereoselectivity of the substrate was weak and could be readily overridden with ligand control, thus giving us confidence to perform the reaction on real substrate **5** with accurate prediction of stereochemical outcome.

The key stereoselective reaction was then performed between the chiral aryl ketone **5** and *tert*-butyl isocyanoacetate, catalysed



Scheme 5 (a) 2-Nitrobenzoyl chloride, $NaHCO_3$, CH_2Cl_2/H_2O, 99%; (b) $NaIO_4$, $MeOH/H_2O$; then $SOCl_2$, MeOH, 84%; (c) HBF_4, *t*BuONO, EtOH, then KI, acetone, 63%; (d) Fe, NH_4Cl, $EtOH/H_2O$, 95%; (e) pTSA, $CH(OMe)_3$, CH_3OH, 82%.

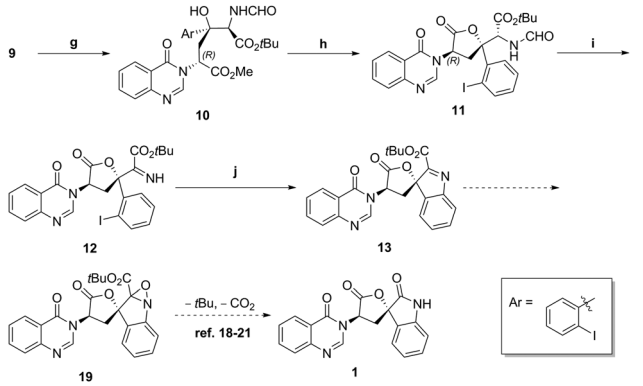


Scheme 6 Key catalyst-controlled isocyanoacetate stereoselective Aldol reaction.

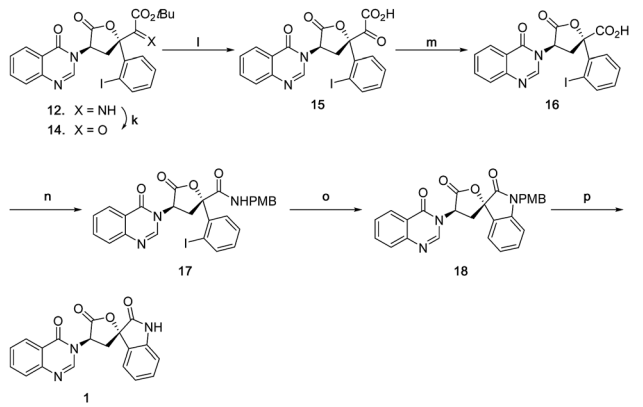
by silver(I) acetate and quinine-derived aminophosphine ligand-**1** (Scheme 6) which pleasingly afforded oxazoline **9** bearing two contiguous stereocentres in high yield (91%) and high diastereoselectivity (dr = 14 : 1) on gram scale. The application of this robust and general methodology on the highly functionalized ketone substrate demonstrates its excellent performance, adaptability and functional group tolerance.

The manipulation of isocyanoacetate aldol product **9** into spirocyclic products is shown in Scheme 7. The oxazoline was readily hydrolysed to amino formamide **10** with 1 N hydrogen chloride solution[11] in quantitative yield. Then, an acetic acid mediated lactonisation gave lactone **11** in 70% yield. Formamide deprotection with HCl in methanol took place smoothly, and then the amino ester intermediate was oxidized with IBX[17] to give imine **12** in 77% yield. Copper mediated Buchwald type C–N bond formation, to ester indolenine **13** was achieved in 52% yield as shown in Scheme 5. With **13** in hand and inspired by Bode[18] and others,[19–21] we conceived the decarboxylative rearrangement of oxaziridine intermediate **19** to directly give natural product **1**. However, various conditions failed to realise this transformation.

Accordingly, an alternative sequence to **1** was followed as shown in Scheme 8. Imine **12** was first hydrolysed to α-ketoester



Scheme 7 (g) 1 N HCl, THF, quant; (h) AcOH, toluene, 70%; (i) $SOCl_2$, MeOH, then IBX, CH_2Cl_2/DMSO, 77%; (j) CuI, $Mg(OAc)_2{\cdot}4H_2O$, DMSO, 52%.



Scheme 8 (k) AcOH, THF/H_2O, 73%; (l) TFA/CH_2Cl_2, quant; (m) $PhI(OAc)_2$, AcOH/H_2O, 80%; (n) $PMBNH_2$, DIPEA, HATU, CH_2Cl_2/DMF, 70%; (o) CuI, $Mg(OAc)_2{\cdot}4H_2O$. DMSO, 70%; (p) TfOH, CH_2Cl_2, 64%.

14 with acetic acid in good yield, then subsequently treated with TFA to afford α-keto acid **15** in quantitative yield. The generated α-keto acid moiety was oxidatively cleaved with PIDA[22] to give carboxylic acid **16** in good yield (pyridinium dichromate[23] was far less efficient). Acid **16** was then converted to amide **17** in 70% yield, using a HATU mediated coupling with 4-methoxybenzylamine. The final D-ring was formed by a copper(I) mediated Buchwald type C–N bond coupling condition, giving spiro oxindole **18** in 70% yield. Due to the ease of epimerization at the C7 position, only weak bases were tolerated, magnesium acetate tetrahydrate being found to be optimal. Natural product **1** was finally obtained by deprotection of the PMB group with triflic acid[24,25] in good yield. The spectroscopic data and specific rotation of the synthetic material were in good agreement with that of the isolated material[4] confirming the total synthesis of **1** in 15 steps from D-tryptophan methyl ester.

In summary, the catalytic stereoselective total synthesis of natural product **1**, 3′-(4-oxoquinazolin-3-yl)spiro[1*H*-indole-3,5′-oxolane]-2,2′-dione, was achieved from D-tryptophan methyl ester hydrochloride in a linear route of 15 steps with an overall yield of 6.4%. The key step featured a gram scale catalyst controlled stereoselective aldol reaction to construct the highly substituted oxazoline ring bearing two contiguous stereocentres in 91% yield with a dr 14 : 1, poised for downstream manipulation. Our approach to **1** lays the foundation for further synthetic approaches to quinazolinone alkaloids and the details will be reported in due course.

TW wishes to thank the China Scholarship Council for PhD funding.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Originally reported tryptoquivaline G was structurally revised to tryptoquivaline L (ref. 4) and accordingly in this paper the originally reported tryptoquivaline L was referred to as C7-*epi*-tryptoquivaline L for clarity.
§ For the preparation of **6**, see the ESI.†
¶ Stereochemical configuration was predicted by analogy to previous work and confirmed by NOE on a lactam derivative of (*R*,*S*,*R*)-**7**; see **S3** in the ESI.†

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