Total Syntheses of (–)-Gephyrotoxin and (±)-Morphine

Shuyu Chu

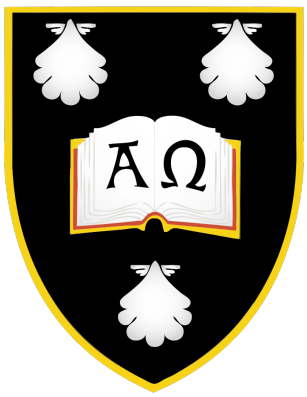
A dissertation presented in partial fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

of the

University of Oxford





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January 2017

In memory of my father, Zhenlin Chu

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory, Mansfield Road, Oxford between October 2013 and December 2016. The dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Shuyu Chu

Acknowledgements

I would like to start by thanking my supervisor, Prof Martin D. Smith, for taking me into his friendly, positive and motivated group, and allowing me to work on total synthesis that I have dreamed of.

Sincere thanks to all the group members, present and past, for providing such a wonderful Oxford experience both in and out of the lab. Special thanks go to Antti Lahdenperä and Phil Gerken for organising the awesome Finland and US trip.

I would like to thank John Jolliffe and Dr Russell Driver for running the crystal structures. I also would like to thank the analytical staff at the CRL for their help during my DPhil. Special thanks go to Dr Barbara Odell for her help with my VT NMRs, and Terri Adams for her amazing glasswork of the UV reactor.

I must thank my proof-readers for helping me finish this thesis and "housekeeper" Sizhu Lu for her delicious and nutritious cooking during my writing up.

Thank you to my parents for your love, support and guidance over the years. My thanks also go to my family members and friends for their help and support.

Abbreviations

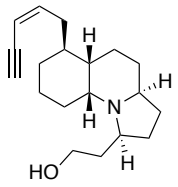
Ac	acetyl
ATR	attenuated total reflectance
Å	angstrom
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
cat.	catalyst *or* catalytic
CSA	camphorsulfonic acid
δ	chemical shift
d	days
dba	dibenzylideneacetone
DIBAL-H	di*iso*butylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
d.r.	diastereomeric ratio
ºC	degree Celsius
EDCI	1-ethyl-3-(3-dimethylaminopropy)carbodiimide hydrochloride
eq.	equivalents
e.r.	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
FI	field ionisation

g	gram
h	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE reaction	Horner – Wadsworth – Emmons reaction
Hz	Hertz
i	*iso*-
IPA	*iso*-propyl alcohol
J	coupling constant
K	Kelvin
KHMDS	potassium hexamethyldisilazane
L	litre
LCMS	liquid chromatography – mass spectrometry
LiHMDS	lithium hexamethyldisilazane
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
L-Selectride®	lithium tri-*sec*-butylborohydride
m	milli
M	mega *or* mol dm^{-3}
Me	methyl
min	minutes
mol	mole
MP	melting point
MS	mass spectrometry
μ	micro
n	normal
*n*BuLi	*n*-butyllithium solution
NMR	nuclear magnetic resonance
PG	protecting group
Ph	phenyl
PIDA	(diacetoxyiodo)benzene

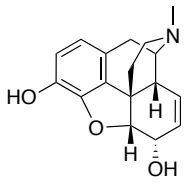
ppm	parts per million
*p*TSA	*para*-toluenesulfonic acid
RT	room temperature
Super-Hydride®	lithium triethylborohydride
$[\alpha]_D^{20}$	specific optical rotation at 20 ºC and 589 nm
t	*tertiary*
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
tert	*tertiary*
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
υ	wavenumber

Abstract

The aim of this DPhil research project is to apply cascade reactions to the total syntheses of gephyrotoxin and morphine.

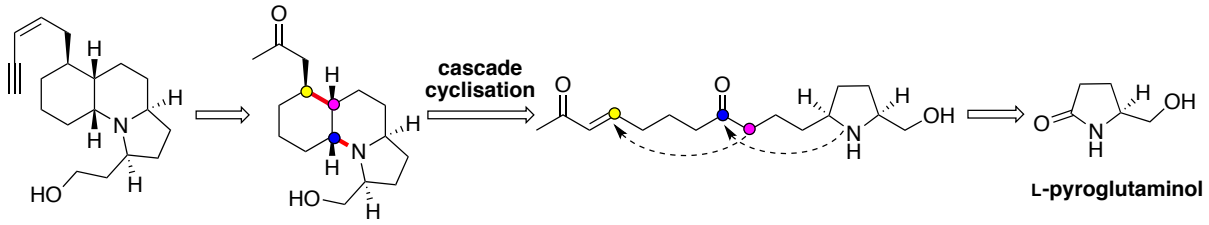


gephyrotoxin



morphine

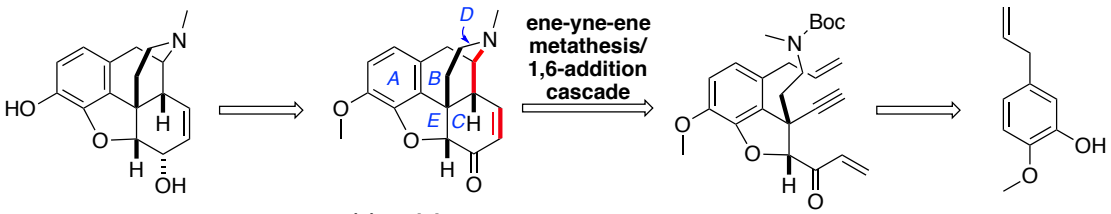
This thesis describes a novel approach towards gephyrotoxin in which the key disconnection is a nucleophilic cascade reaction that constructs the core structure bearing three rings and five stereocentres. This cascade approach enables the total synthesis of gephyrotoxin in nine steps with 14% overall yield.



(–)-gephyrotoxin

L-pyroglutaminol

In addition, a new approach towards morphine, involving an ene-yne-ene cascade ring closing metathesis and 1,6-addition to efficiently construct the B/C/D ring systems in a single operation, shortening the synthesis to nine steps with 6.6% overall yield is discussed.



(±)-morphine

(±)-codeinone

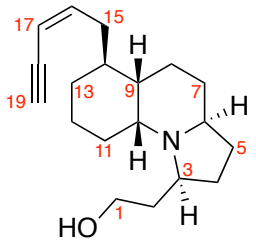
chavibetol

The cascade shortcuts enable rapid approaches to these natural products, which results in the most concise total syntheses of gephyrotoxin and morphine described to date.

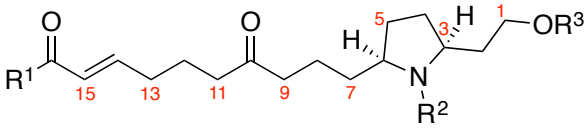
Nomenclature and Numbering

Compounds have been named according to IUPAC recommendations in the experimental section.

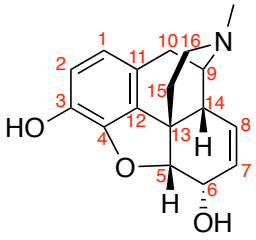
The atomic numbering system for compounds in this report does not correspond to the IUPAC names but was chosen to maximise the clarity.



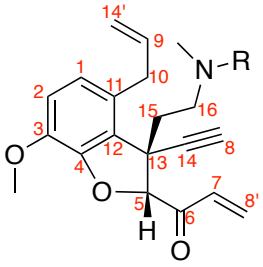
gephyrotoxin



cascade precursors



morphine



cascade precursors

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1. Introduction

1.1 Total Synthesis and Cascade Reactions

Total synthesis is a fascinating facet of organic chemistry. It offers possibilities to access highly scarce natural products. It explores the applicability and the value of new methodologies. It is a showcase of human intelligence with respect to design and strategy. It obscures the boundary between science and art.

A brief history of total synthesis began with Friedrich Wöhler's synthesis of urea from ammonium cyanate in 1821.[1] The synthesis discredited vitalism, the theory that organic matter possessed a vital force inherent to living things, demonstrated that organic matter could be produced synthetically. In 1902, Richard Willstätter published the first total synthesis of tropinone *via* a 21-step sequence with 0.75% yield, an elegant example of early multistep synthesis.[2] In 1965, the Nobel Prize in Chemistry was awarded to Professor Woodward for his outstanding achievements in the art of organic synthesis. His selected masterpieces

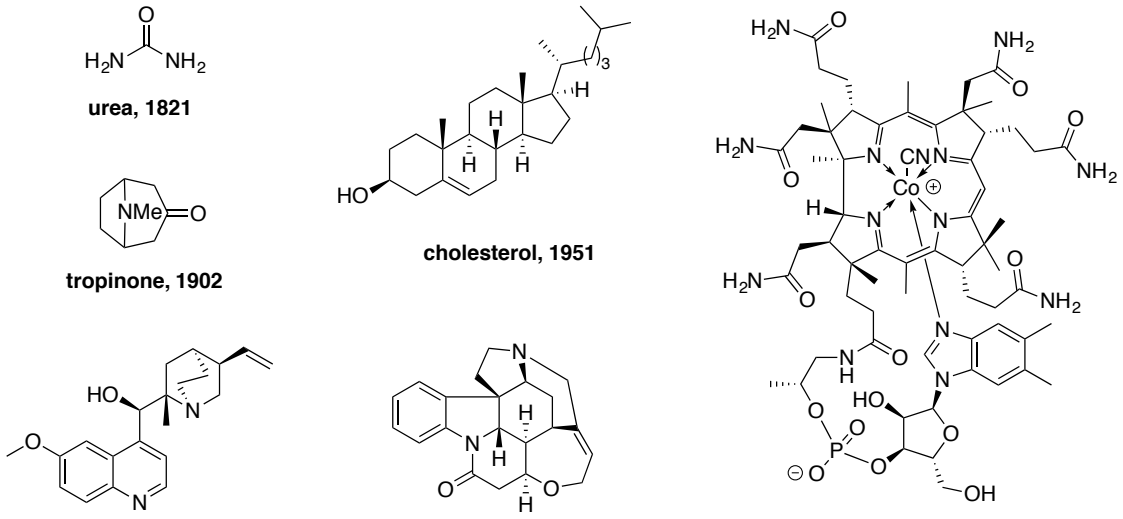
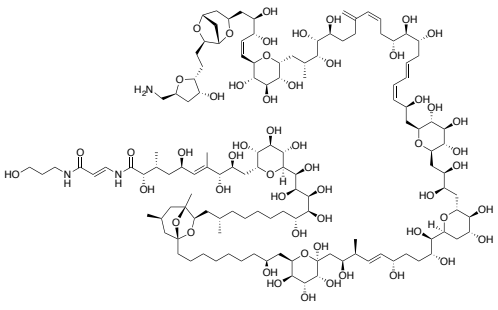


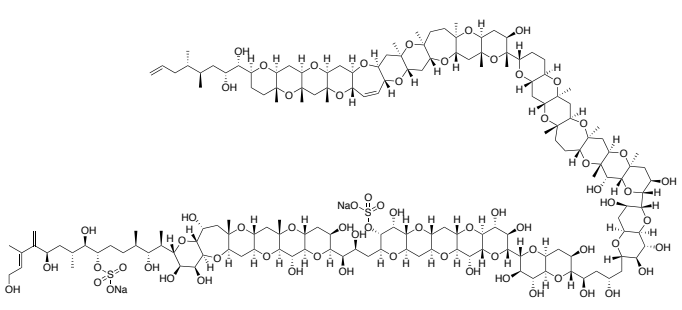
Figure 1.1

include: quinine (1945),[3] cholesterol (1951),[4] strychnine (1954),[5] and vitamin B12 (1972).[6] Today, even with more advanced synthetic methods, these molecules still represent challenging synthetic targets. It is therefore remarkable that the total syntheses of these complex molecules could be accomplished with the limited analytical techniques available in the mid-twentieth century. In the 1960's, the game-changing synthetic concept of retrosynthetic analysis was developed by Nobel laureate Professor Corey and heralded a new era of total synthesis.[7] With the help of this concept, a tremendous amount of effort has been poured into the field of natural product synthesis, resulting in the solution of numerous challenges set by nature.

Notably, in 1994, Professor Kishi and co-workers completed the total synthesis of palytoxin ($C_{129}H_{223}N_3O_{54}$),[8] the Mount Everest of chemical synthesis. This achievement greatly shocked and stimulated the field of total synthesis, as it implied that the size limit of synthetically-accessible natural products was expanding. Currently, studies towards total synthesis of maitotoxin, the largest non-biopolymer ever known, are ongoing in the Nicolaou group.[9] In this case, total synthesis is no longer driven by the craving for a valuable or scarce natural product, rather aims to explore the boundaries of organic synthesis.



palytoxin, 1994

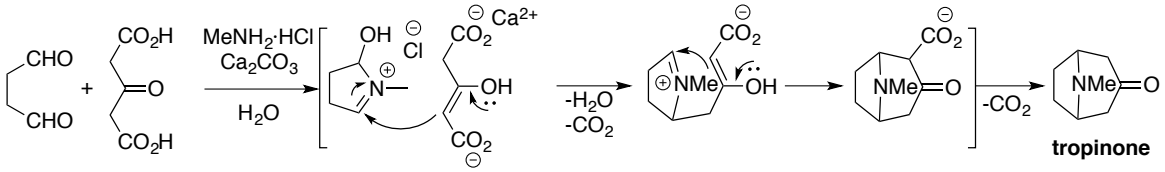


maitotoxin

Figure 1.2

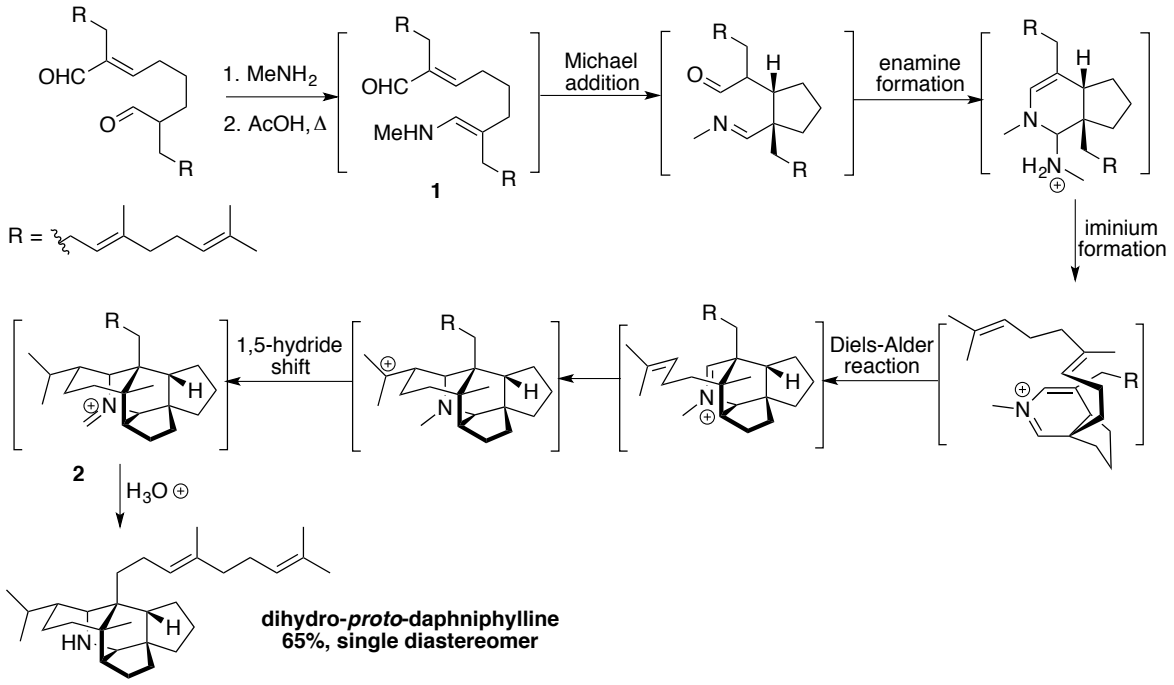
Apart from these supermolecules, hundreds of routes to moderately complex novel and known natural products are being discovered annually, with researchers benefitting from emerging elegant methodologies. However, in order to achieve high conciseness and efficiency in a total synthesis, synthetic strategy also plays an important role.

A cascade reaction is a synthetic strategy that can potentially provide elegant and expeditious solutions to construct complex structures. The obvious benefits of this shortcut include: saving chemicals, labour, time and generating less waste. In addition, synthetic routes involving cascade reactions add an artistic element to organic synthesis. According to most definitions, Robinson's one-pot total synthesis of tropinone published in 1917 is considered to be the first example of cascade reaction (Scheme 1.1).[10] In comparison, the first total synthesis of tropinone published by Richard Willstätter took 21 steps.



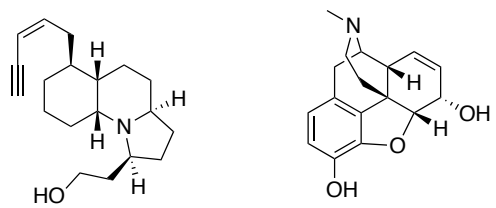
Scheme 1.1

Heathcock's remarkable cascade approach to dihydro-*proto*-daphniphylline is a masterpiece in the history of total synthesis (Scheme 1.2).[11] The cascade is initiated by an intermolecular condensation to give enamine **1**. This is followed by a series of intramolecular reactions. Sequential Michael addition, condensation, *aza*-Diels-Alder, Prins reaction, and [1,5]-hydride shift give iminium **2**, which is hydrolyzed during the aqueous work-up to give the final product dihydro-*proto*-daphniphylline as a single diastereomer.



Scheme 1.2

The value of cascade reactions has been well demonstrated by numerous stunning examples over a wide range of chemical syntheses. A well-planned cascade disconnection can greatly simplify the route to a complex natural product and rapidly access high levels of structural complexity. Based on the mechanism of the steps involved, a cascade can be classified as nucleo/electrophilic, catalytic, radical or pericyclic. The aim of this project is to apply cascade reactions to the syntheses of gephyrotoxin and morphine and thereby achieve more concise and efficient routes to these natural products.



gephyrotoxin **morphine**

Figure 1.3

1.2 Gephyrotoxin

Gephyrotoxin is an alkaloid and was first isolated from the skin extracts of the Columbian poison dart frog *Dendrobates histrionicus* by Daly *et al.* in 1974.[12] Unlike many other dendrobatid alkaloids, gephyrotoxin is relatively non-toxic.[13] A study was conducted, showing that a reduction in spontaneous activity in mice was observed after an 80 μg intravenous dose of gephyrotoxin. In comparison, administration of a 1 μg dose of batrachotoxin caused death in less than one minute.[14]



Dendrobates histrionicus

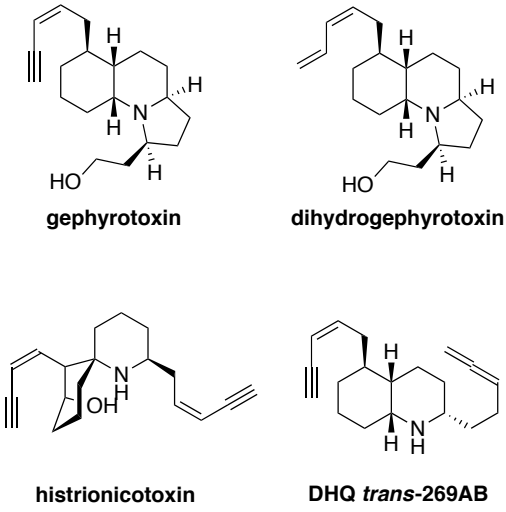


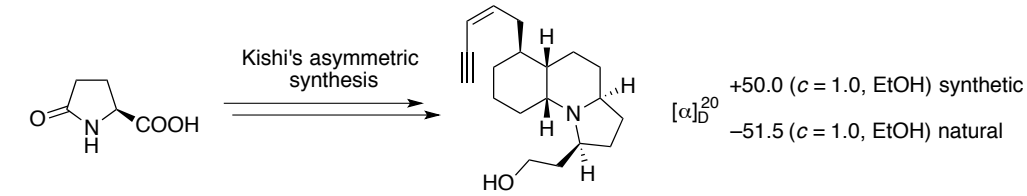
Figure 1.4

The natural abundance of gephyrotoxin is extremely low. Only 15 mg of gephyrotoxin were isolated from the skin extracts of 3200 frogs, along with 1 mg of dihydrogephyrotoxin and various amounts of histrionicotoxins.[14]

Interestingly, studies suggest gephyrotoxin is a secondary metabolite originating from rainforest arthropods.[15, 16] The presence of gephyrotoxin and many other amphibian alkaloids in anuran skin exudate is not a consequence of its native biosynthesis as a defense toxin, but a

result of dietary accumulation. Even so, the precise biosynthetic mechanism for the endogenous synthesis of gephyrotoxin is still unknown, and its function within the native ant is virtually uninvestigated.

Structurally, gephyrotoxin possesses an interesting tricyclic perhydropyrroloquinoline core with five stereocentres, three of which are contiguous. This unique structure "bridges" several classes of frog skin alkaloid: decahydroquinolines, indolizidines, and the enyne side-chain-containing histrionicotoxins. Therefore, its name derives from the Greek *gephyra* meaning bridge. The extremely low natural abundance and unique structural profile of gephyrotoxin has led to significant synthetic interest in this alkaloid.

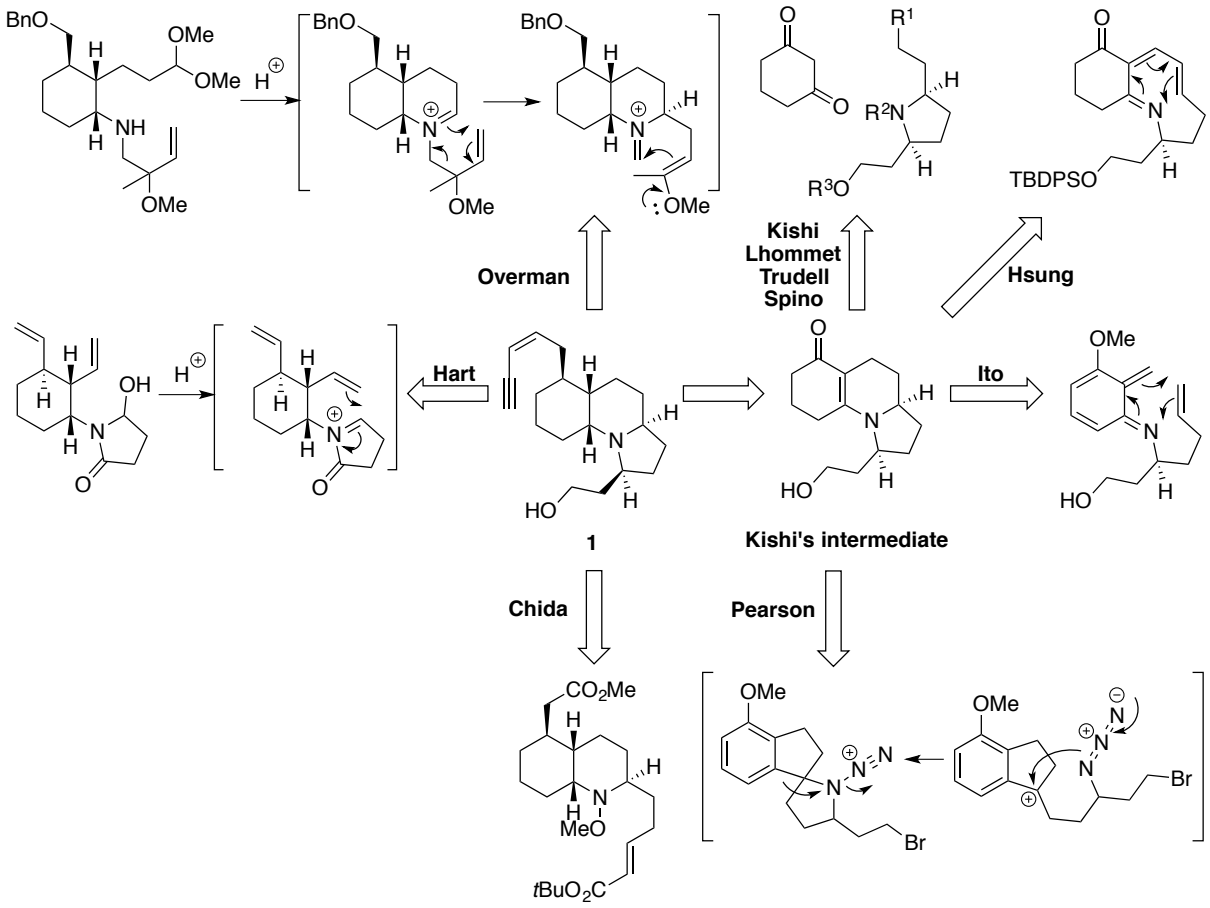


L-pyroglutamic acid **(+)-gephyrotoxin**

Scheme 1.3

The first asymmetric total synthesis of gephyrotoxin was achieved by the Kishi Group in 1981.[17] The absolute configuration of the target was based on the X-ray crystal structure of the hydrobromide salt of naturally occurring gephyrotoxin.[14] However, the synthetic material was found to exhibit the opposite sign of optical rotation to the naturally occurring enantiomer. Re-examination of the original X-ray diffraction data found no mis-assignment. In the absence of a more modern X-ray diffraction study to confirm the absolute configuration of naturally occurring gephyrotoxin or a more recent asymmetric synthetic effort, the absolute

configuration of gephyrotoxin is still debated.[18]

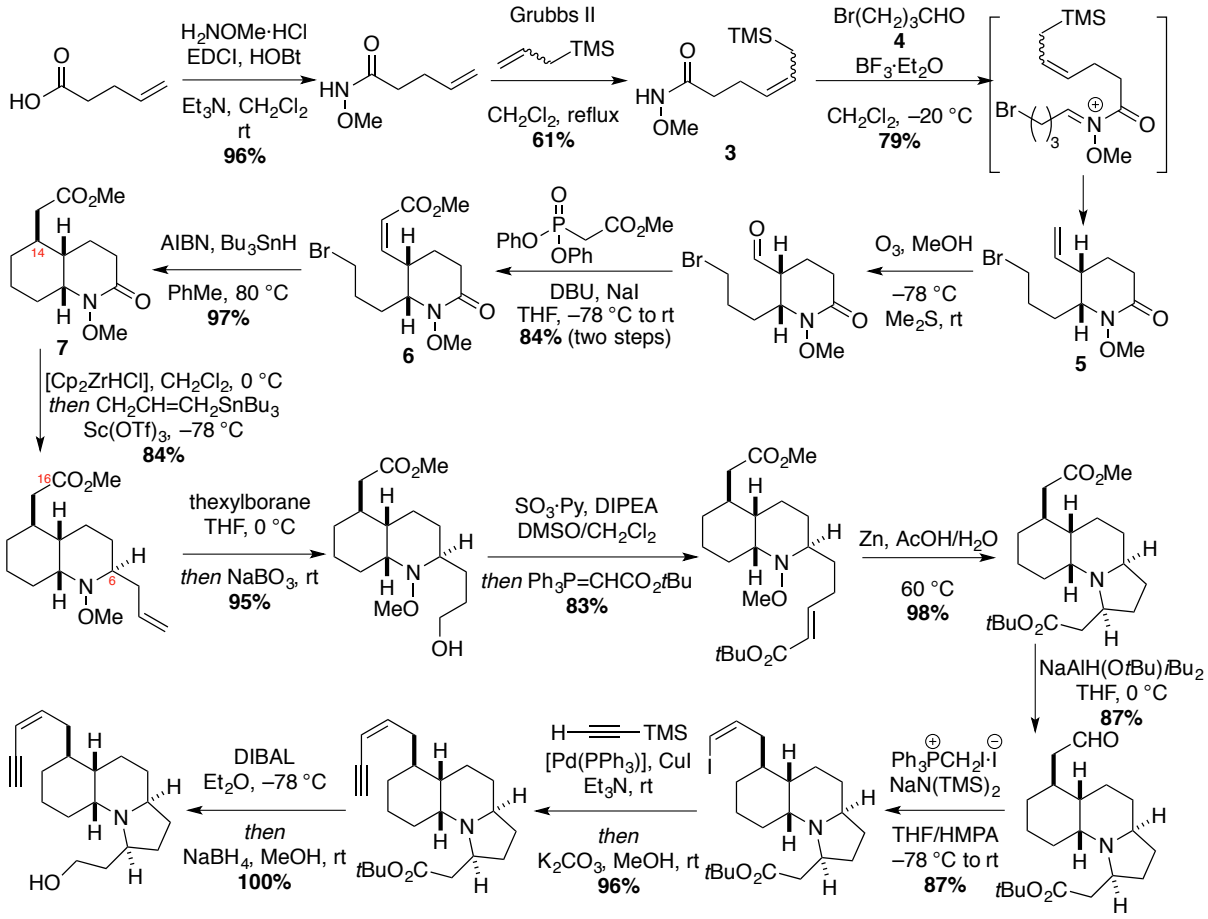


Scheme 1.4

Prior to this project, there have been five total syntheses of gephyrotoxin from the laboratories of Kishi,[17, 19] Hart,[20] Overman,[21] Sato and Chida,[22] alongside six formal syntheses that intersect with an intermediate from Kishi's approach.[23-28] As the construction of the tricyclic core is the key battlefield towards the total synthesis of gephyrotoxin, numerous methods have been applied to construct the core (Scheme 1.4).

Sato and Chida reported a concise total synthesis of (±)-gephyrotoxin in 2013, *via* an amide-selective reductive nucleophilic addition approach (Scheme 1.5).[22] The stepwise

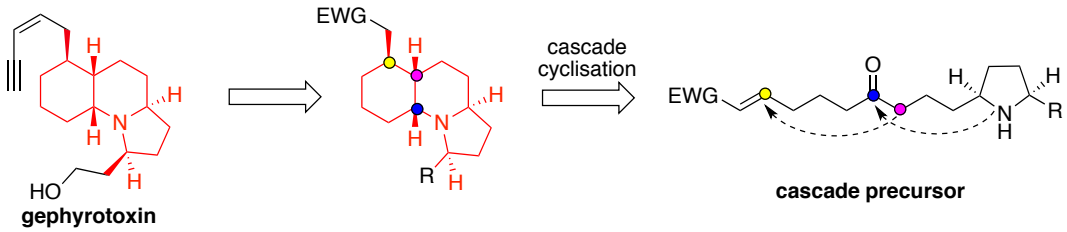
construction of tricyclic system started with the direct coupling of *N*-methoxyamide **3** with aldehyde **4** to give piperidone **5** with complete stereocontrol. Then the *cis*-6,6-fused system with desired *C*14 configuration was formed by a stereoselective radical cyclisation of **6**. Sequential selective reductive nucleophilic addition of **7** installed the *C*6 sidechain which was then functionalised and cyclised to furnish the tricyclic core. This chemoselective reductive addition minimized the use of protecting-group manipulations and redox reactions raised by *C*16 methyl ester, resulted in a concise total synthesis of (±)-gephyrotoxin.



Scheme 1.5

We anticipate that gephyrotoxin's complex tricyclic core is potentially an ideal template for a cascade disconnection (Scheme 1.6). Therefore, a nucleophilic cascade reaction that

constructs the core structure bearing three rings and five stereocentres from a disubstituted pyrrolidine precursor is planned as the key step in our cascade approach.



Scheme 1.6

1.3 Morphine

Morphine, a well-known analgesic widely used today, was first isolated from opium poppy latex in 1804 by German pharmacist Serturner.[29] It was originally named *morphium* after the Greek god of dreams, Morpheus, as it has a tendency to induce sleep. Morphine is the most abundant alkaloid in opium, which contains a mixture of chemicals including 10-16% morphine, alongside other phenanthrenes such as codeine (1-3%) and thebaine (0.2%), and isoquinolines that have no significant central nerve system effects such as noscapine (3-8%) and papaverine (0.5-1%).[30]



Latex from opium poppy

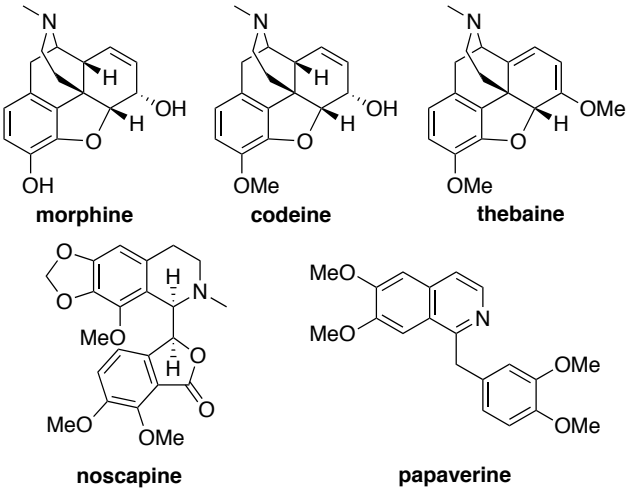


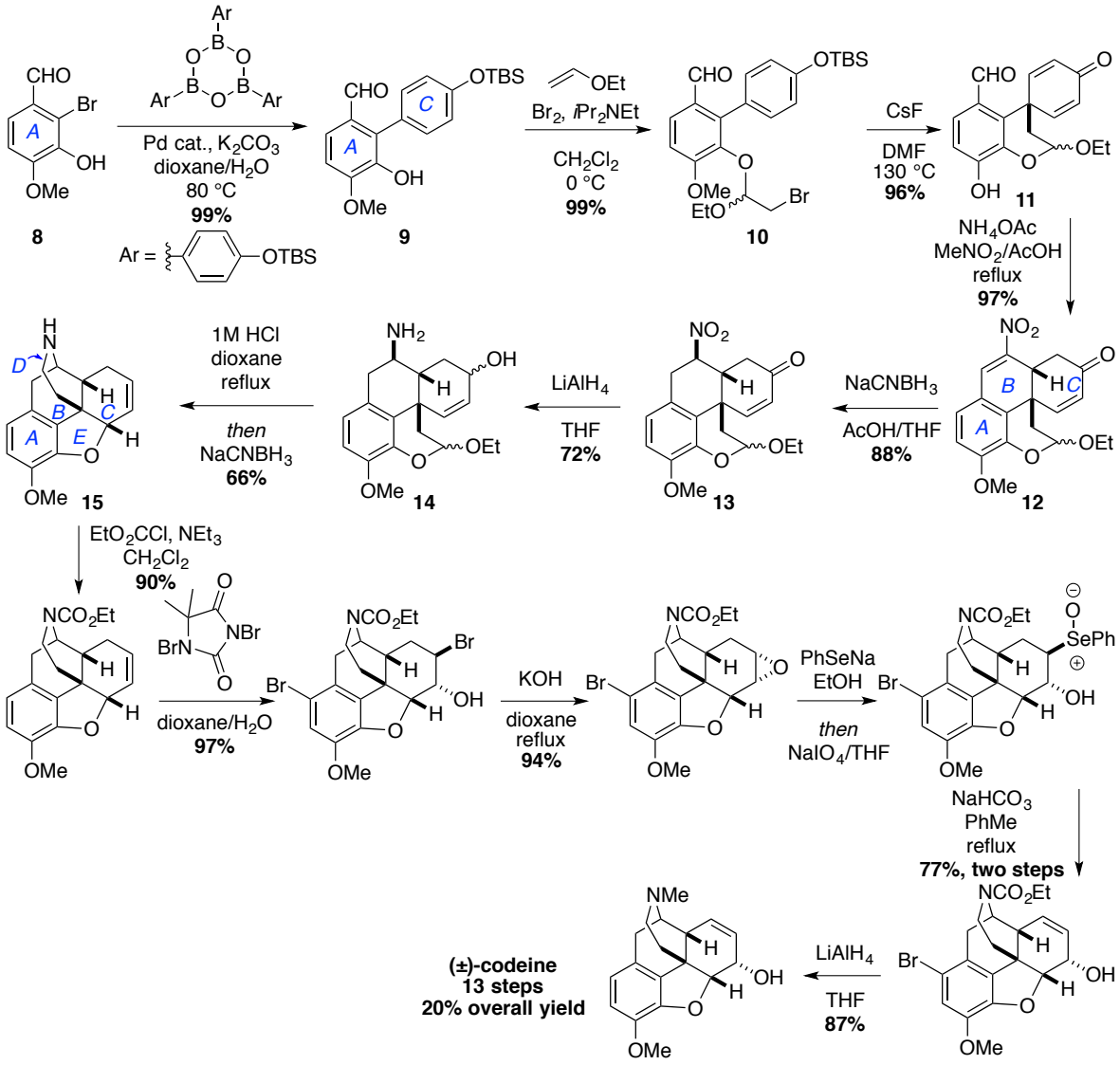
Figure 1.5

As the main constituent of opium, morphine's pain relieving properties have been exploited for thousands of years.[31] The first documented evidence of opium cultivation comes from the Sumerians in Mesopotamia ca. 3400 BC. The cultivation and usage of opium spread across Europe and Asia since the trade between East and West. In 1525, Swiss-German physician Paracelsus invented laudanum, a tincture of opium, as an analgesic and cough suppressant. In 1804, morphine was isolated and named by German scientist Serturner. A more potent analgesic, marketed as heroin by Bayer, was synthesised by diacetylation of morphine in 1874. Today, in spite of extensive substance abuse, morphine is still widely used in the healthcare industry due to its relatively low cost and outstanding pain relieving properties. It has therefore been placed on the World Health Organization's list of essential medicines.

The elucidation of the structure of morphine was an area of focus shortly after its isolation. In 1831, Liebig established the first empirical formula for morphine, which was later corrected to $C_{17}H_{19}NO_3$ by Laurent in 1847.[31] Robinson proposed morphine's correct structure in 1925,[32] which was confirmed by Gates through the first total synthesis of morphine in 1952.[33] Three years later, Hodgkin published the structure of morphine based on single crystal X-ray crystallography using morphine hydroiodide dihydrate.[34]

Even though opiate alkaloids can be readily obtained from natural resources on an industrial scale, organic chemists never lost interest in the synthetic challenge posed by morphine due to its structural complexity. Over the years, more than 30 total/formal syntheses of morphine and its analogues have been published.[33, 35, 36] Indeed, all medicinal (and illicit) morphine is

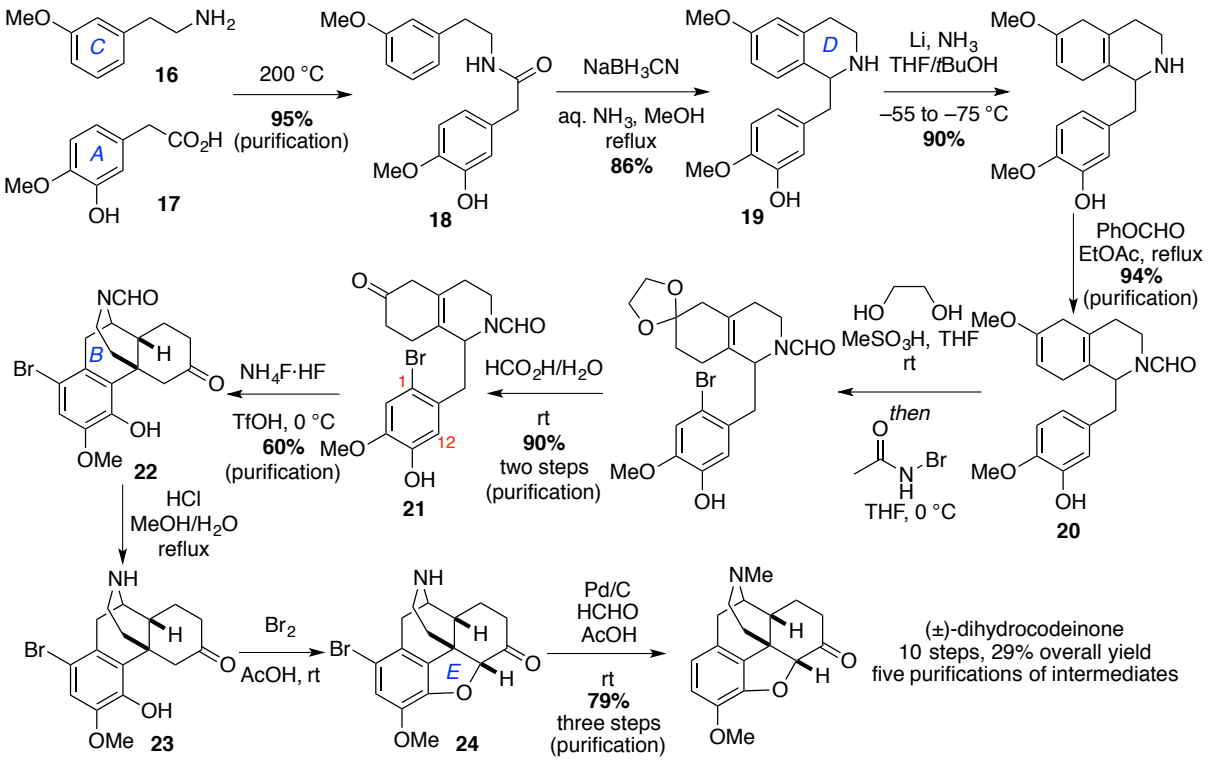
derived from natural sources and currently, there is no synthetic route that competes on scale and cost with isolation of natural morphine.



Scheme 1.7

To-date, one of the most efficient syntheses of codeine, a key precursor to morphine, is that published by Magnus.[35n] The route begins with a Suzuki coupling of commercially available compound bromovanilin **8** with a boron reagent corresponding to the masked C ring to give biaryl **9**. Alkylation of biaryl **9** gives bromoacetal **10**, which is poised for the key intramolecular phenolate alkylation. Treating **10** with cesium fluoride at elevated temperature

gives **11** *via* formation of a quaternary carbon centre, which is one of the most challenging moieties of codeine. Thereafter, a Henry reaction followed by sequential reductions gives amine **14**. Further treatment with acid and intramolecular reductive amination affords the pentacyclic intermediate **15**. At this point, the core has been constructed in only seven steps and excellent overall yield. However, from this point, the endgame takes another six steps to introduce the allylic alcohol on the C ring and therefore reduces the overall step efficiency.



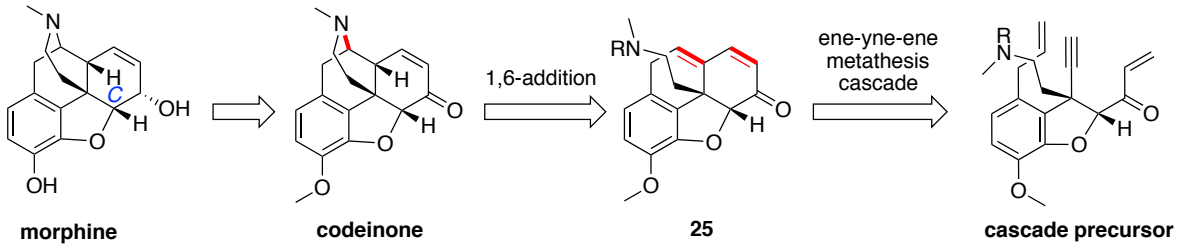
Scheme 1.8

Another high yielding route to dihydrocodeinone described by Rice applies Grewe-type cyclisation and oxide bridge closure to construct ring B and E, respectively.[36d] The route begins with condensation of commercially available amine **16** and acid **17**. Reductive cyclisation of amide **18** forms ring D to give amine **19**, which is used as crude for the following Birch reduction and formamidation. In order to direct the Grewe-type cyclisation

on the desired *C*12 centre during the construction of ring B, *C*1 is protected by bromination to give bromide **21**. Formation of ring B is accomplished by treating a solution of **21** in triflic acid with $NH_4F{\cdot}HF$, which affords the tetracycle **22** in 60% yield. Bromination of *N*-deprotected intermediate **23** forms the oxide bridge to afford pentacyclic core **24**. Hydrogenation of **24** in the presence of formaldehyde removes *C*1 bromine atom and methylate the amine to give dihydrocodeinone in 10 steps with 29% overall yield.

This highly practical route requires only five purifications of intermediates, which would show promise for a large-scale manufacturing. However, conversion of dihydrocodeinone to morphine involves introducing the allylic alcohol moiety on the C ring *via* a five-step sequence which reduces the overall step efficiency as that discussed earlier in Magnus's route.

We identify two criteria for an efficient route to morphine: a quick access to the pentacyclic core and a concise endgame to make the C ring. The transformation of codeinone to morphine has been well precedented in the literature. A previous study by Fuchs demonstrates that the D ring of codeinone can be made by an intramolecular 1,6-addition of an *α*,*β*,*γ*,*δ*-unsaturated ketone **25**.[35d] We envisage that this intermediate can be disconnected *via* a cascade ene-yne-ene ring closing metathesis cascade.

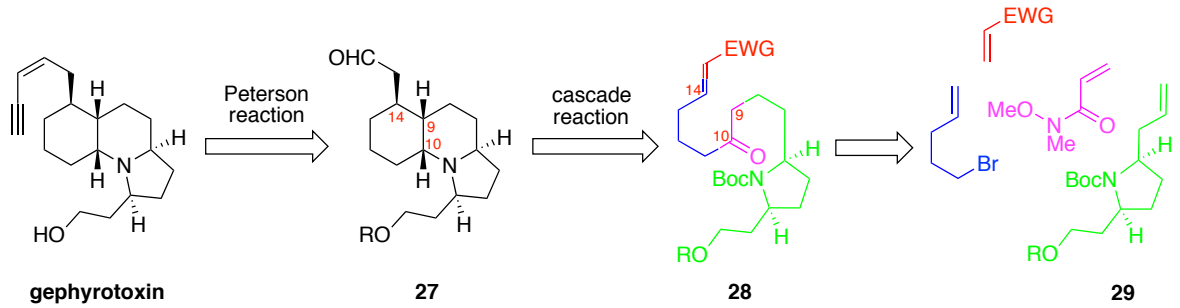


Scheme 1.9

2. Gephyrotoxin

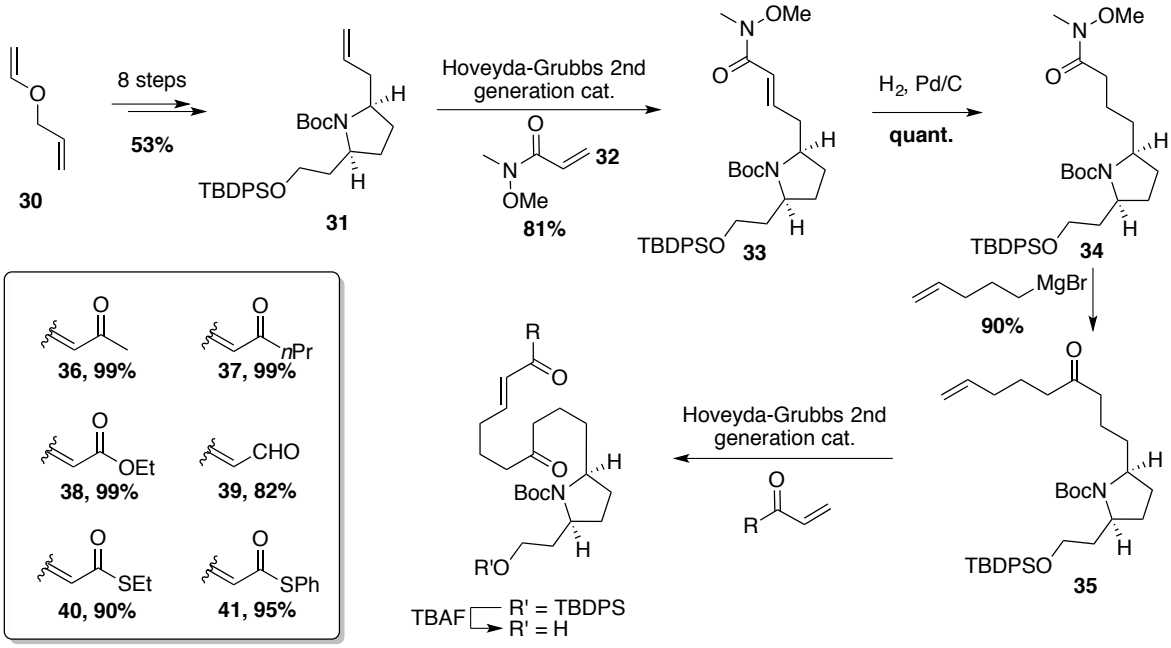
2.1 Previous Study Towards Gephyrotoxin

The previous disconnection towards gephyrotoxin in the Smith Group started with Peterson olefination to install the *cis*-ene-yne system from aldehyde **27** (Scheme 2.1).[37] The tricyclic core was disconnected *via* a cascade cyclisation through the formation of *N*-*C*10 and *C*9-*C*14 bonds. Further fragmentation of cascade precursor **28** gave four main building blocks: *cis*-disubstituted pyrrolidine **29**, vinyl Weinreb amide, 5-bromo-1-pentene, and a Michael acceptor that could be transformed to an aldehyde after the cascade reaction.



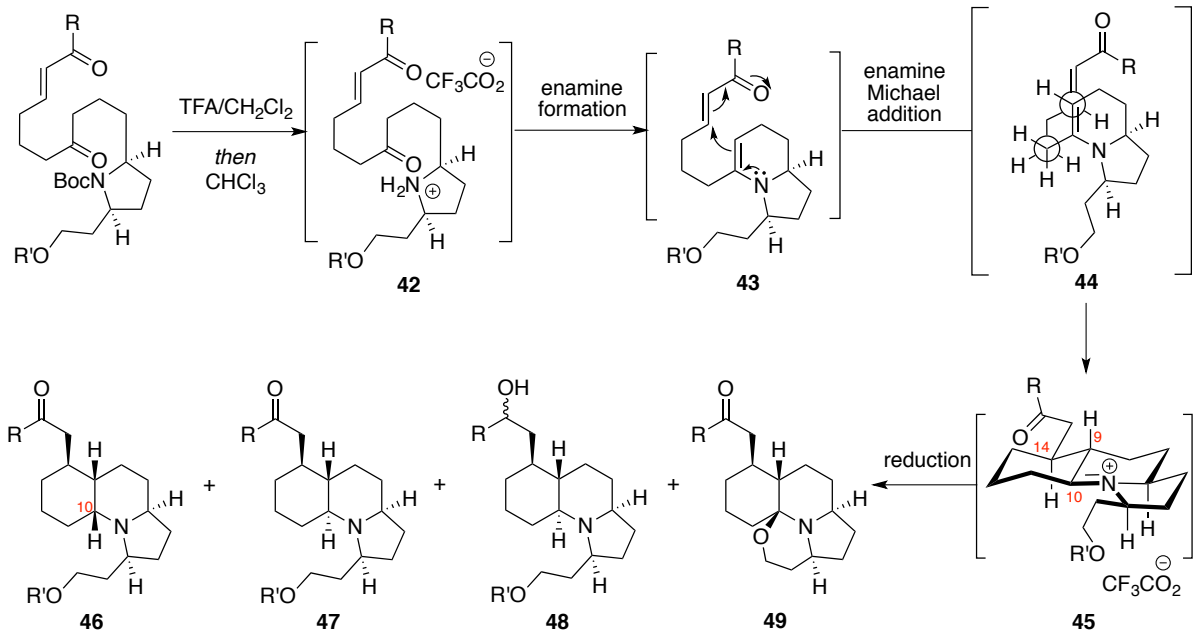
Scheme 2.1

Based on this disconnection, the synthesis began with the preparation of pyrrolidine **31** (Scheme 2.2). An eight-step sequence from commercially available allyl vinyl ether **30** provided pyrrolidine **31** on gram scale. Cross metathesis of pyrrolidine **31** and Weinreb amide **32** proceeded efficiently in the presence of Hoveyda-Grubbs second-generation catalyst to give unsaturated amide **33** in good yield. Hydrogenation of amide **33** was followed by a Grignard reaction to yield pentenyl ketone **35**, which served as a divergent intermediate for the introduction of a set of *C*16 electrophiles *via* cross metathesis to give cascade precursors **36** – **41**.



Scheme 2.2

Deprotection of the nucleophilic pyrrolidine amine of the cascade precursors triggered the cascade reaction and led to the formation of a tricyclic iminium cation **45**, exclusively with the required *C*9 and *C*14 configuration (Scheme 2.3).



Scheme 2.3

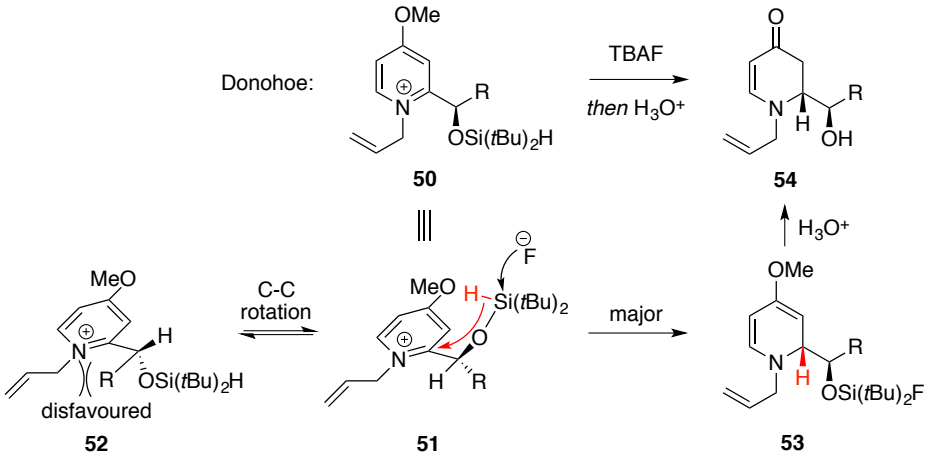
This transformation likely proceeded *via* intramolecular condensation of the pyrrolidine amine onto the *C*10 ketone to afford a bicyclic enamine **43** that underwent a diastereoselective intramolecular Michael addition onto the *C*14 enone. The stereochemistry could be rationalised by a chair-like transition state in which the Michael acceptor adopted a pseudoequatorial orientation to minimise diaxial interactions; facial discrimination of the bicyclic enamine was a consequence of the *C*3 substituent and its effect on the conformation of the pyrrolidine ring. The tricyclic iminium species **45** was subjected to reduction conditions *in situ*. A screening of reducing agents and conditions unfortunately gave the major product as the non-natural 9,10-*trans* diastereomer **47**/**48** (Table 2.1).

Entry	R	R'	Reducing agent	Yield	46:47:48:49
1	Me	TBDPS	$NaBH_3CN$	83%	0:1:0:0
2	Me	TBDPS	$NaBH(OAc)_3$	79%	0:10:1:0
3	*n*Pr	H	Red-Al	84%	0:1:0:0
4	*n*Pr	H	DIBAL-H	91%	0:0:0:1
5	*n*Pr	H	$NaBH_3CN$	75%	0:1:0:0
6	*n*Pr	H	Me_4N^+ $[BH(OAc)_3]^-$	80%	0:2:1:0
7	*n*Pr	H	$NaBH(OAc)_3$	80%	1:10:1:0

Table 2.1

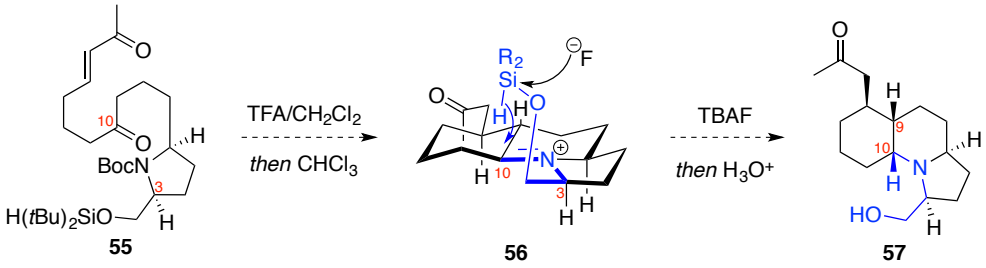
2.2 An Intramolecular Hydride Transfer Approach

Given the problematic reduction step, we decided to modify the cascade precursor using an intramolecular hydride transfer method. Such examples were demonstrated by Donohoe *et al.* in the synthesis of enantiopure dihydropyridones (Scheme 2.4).[38] Pyridinium cation **50** was treated with fluoride, which triggered the hydride transfer in the less strained conformation to give dihydropyridone **54** with complete control of diastereoselectivity.



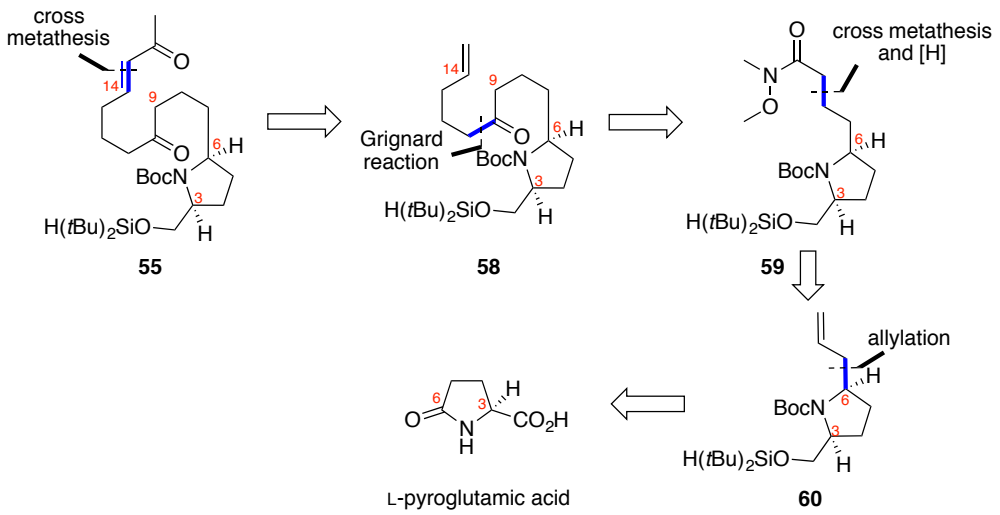
Scheme 2.4

Applied to our system, we proposed the 9,10-*cis* core **57** could be constructed *via* an analogous intramolecular hydride transfer (Scheme 2.5). The silyl ether played both protecting group and hydride resource roles, while truncation of the *C*3 side chain by one carbon, provided a more rigid 7-membered ring transition-state to direct the hydride addition.



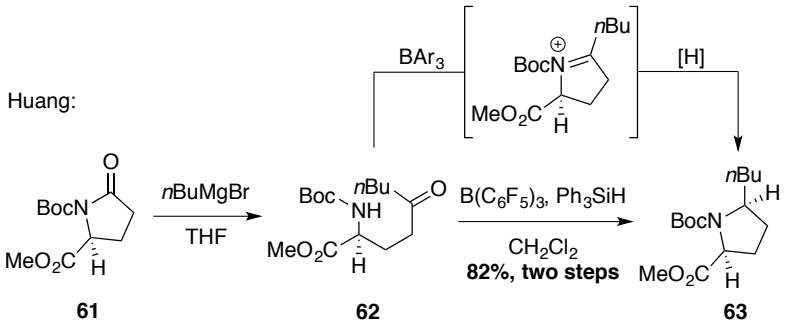
Scheme 2.5

Our modified strategy required redesign of the asymmetric synthesis of precursor **55**. Retrosynthetic analysis tracked the route back to the commercially available L-pyroglutamic acid (Scheme 2.6). The key transformation was the installation of the *cis*-allyl group. It was also important to consider the compatibility of the silyl ether under the conditions used in construction of the *C*6 side chain.



Scheme 2.6

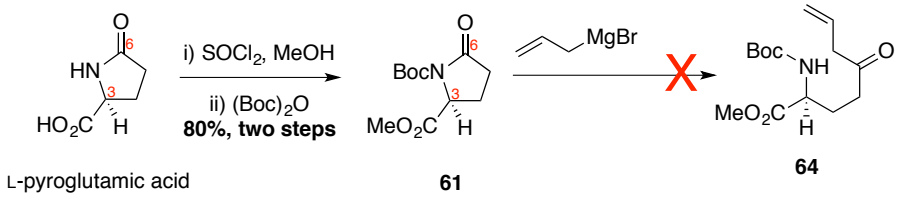
Huang *et al.* demonstrated a two-step synthesis of *cis*-disubstituted pyrrolidine **63** by reacting *N*,*C*-diprotected L-pyroglutamic acid with butylmagnesium bromide (Scheme 2.7). The resulting ketone **62** was subjected to reduction in the presence of tris(pentafluorophenyl)-borane to yield pyrrolidine **63** as a single diastereomer; presumably *via* hydride delivery to the less hindered face of the *in situ* generated *N*-acyliminium cation.[39]



Scheme 2.7

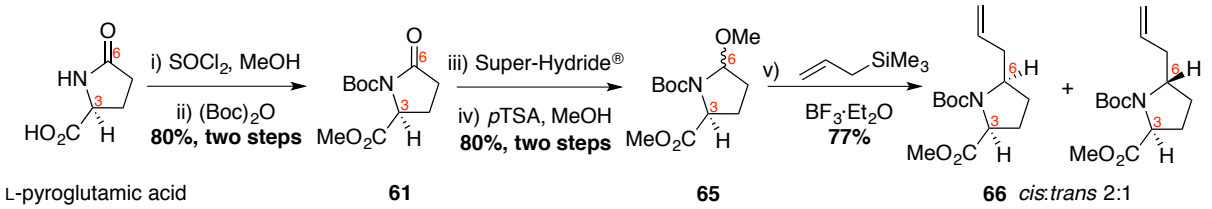
In our hands, synthesis of pyrrolidine **60** began with esterification and *N*-protection of L-pyroglutamic acid (Scheme 2.8). Employing Huang's Grignard addition procedure using allylmagnesium bromide resulted in a complex mixture, with no detectable quantities of

ketone **64**.



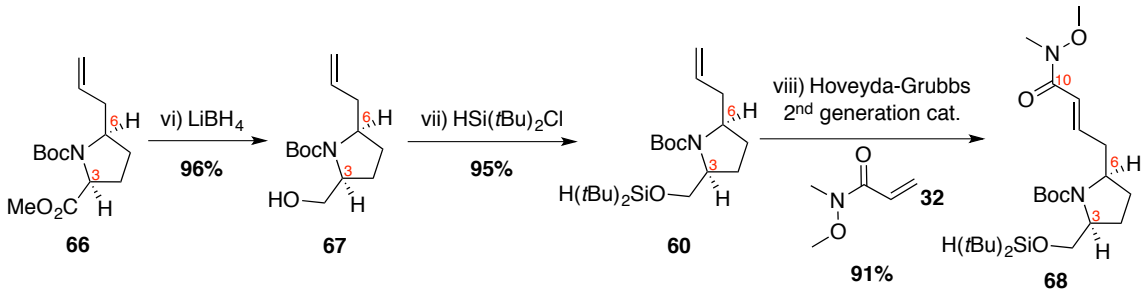
Scheme 2.8

As an alternative route, pyrrolidine **66** was prepared by a three-step sequence *via* allylation of hemiaminal ether **65** in the presence of boron trifluoride etherate. This afforded a mixture of *C*6-diastereomers of **66**,[40] which were inseparable by silica gel chromatography.



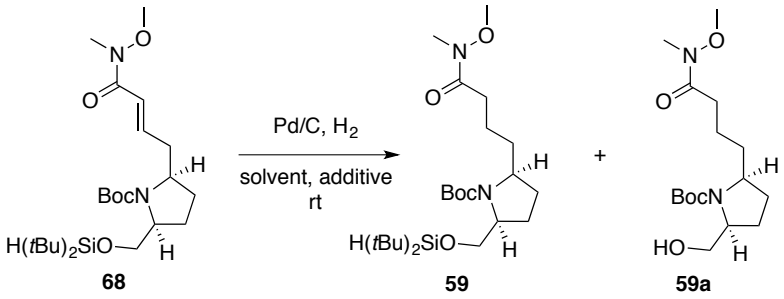
Scheme 2.9 Synthesis of pyrrolidine 66: i) $SOCl_2$, (0.10 eq.), MeOH, 0 °C to rt. ii) $(Boc)_2O$ (1.05 eq.), Et_3N (1.05 eq.), DMAP (0.10 eq.), CH_2Cl_2, 0 °C to rt. iii) Super-Hydride® (1.60 eq.), THF, – 78 °C to 0 °C; *then* H_2O_2 (1.60 eq.), 0 °C to rt. iv) *p*TSA (0.10 eq.), MeOH, rt. v) Allyltrimethyl-silane (4.70 eq.), $BF_3{\cdot}Et_2O$ (1.20 eq.), Et_2O, –40 °C to rt.

Pleasingly, reduction of the *C*2 ester of **66** gave alcohol **67** (Scheme 2.10). The diastereomers of alcohol **67** could be easily separated by silica gel chromatography, thus, the *cis*-pyrrolidine fragment was constructed. Silylation of alcohol **67** afforded silyl ether **60** in high yield. Subsequent cross metathesis pleasingly showed no noticeable cleavage of the silyl ether; amide **68** was formed in excellent yield.



Scheme 2.10 Synthesis of Weinreb amide 68: vi) $LiBH_4$ (4.20 eq.), THF, 0 °C to rt. vii) $HSi(tBu)_2Cl$ (1.20 eq.), imidazole (2.05 eq.), THF, reflux. viii) Amide **32** (6.00 eq.), Hoveyda-Grubbs second-generation catalyst (0.05 eq.), CH_2Cl_2, rt.

Our initial attempts to hydrogenate unsaturated amide **68** resulted in cleavage of the silyl ether (Scheme 2.11). We presumed the cleavage was attributed to methanolysis caused by acid contamination of palladium on charcoal. However, addition of triethylamine or sodium carbonate to the reaction mixture did not prevent the desilylation. Sajiki *et al.* demonstrated that aprotic solvents decreased the rate of silyl ether cleavage under similar conditions.[41] We therefore screened aprotic solvents in the reaction. Satisfyingly, using acetonitrile as the solvent afforded amide **59** in excellent yield with no detectable desilylation.

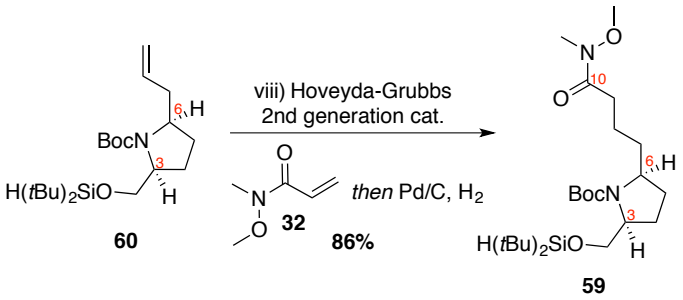


Solvent/Additive	Isolated yield (%)	
	59	59a
MeOH	0	95
MeOH/Et_3N	0	86
MeOH/Na_2CO_3	0	92
THF	81	6
PhMe	91	0
EtOAc	85	0
MeCN	97	0

Scheme 2.11

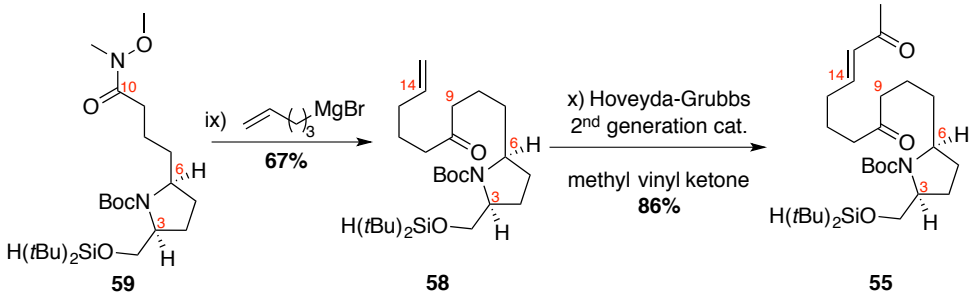
During purification, we found unsaturated amide **68** decomposed upon prolonged contact with silica. Unfortunately, this led to a drop in the obtained yield during large-scale preparation of

unsaturated amide **68**. We therefore devised a pseudo one-pot synthesis that combined the metathesis and hydrogenation steps (Scheme 2.12). Following formation of unsaturated amide **68** under the cross metathesis reaction conditions, excess remaining vinyl amide **32** and the solvent were removed; the crude mixture was directly subjected to hydrogenation conditions to give amide **59** with a comparable yield.



Scheme 2.12 One-pot preparation of Weinreb amide 59: viii) Acrylamide (6.00 eq.), Hoveyda-Grubbs 2nd generation catalyst (0.05 eq.), CH_2Cl_2, rt; *then* Pd/C cat., H_2, MeCN, rt.

Final steps to access the cascade precursor first involved treatment of Weinreb amide **59** with Grignard reagent. Cross metathesis of the addition product **58** produced cascade precursor **55** in high yield.

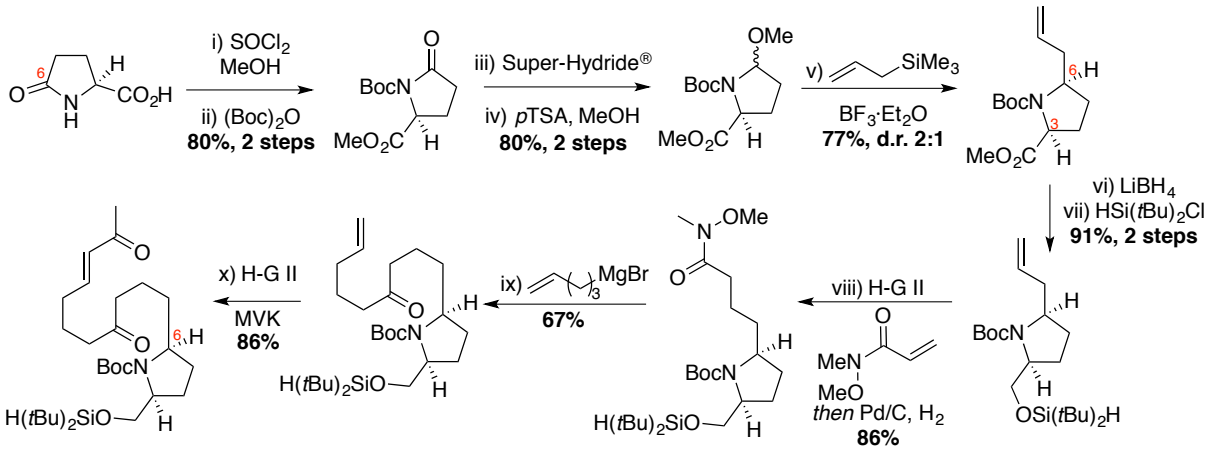


Scheme 2.13 Synthesis of cascade precursor 59: ix) Grignard reagent (4.00 eq.), Et_2O, reflux. x) Methyl vinyl ketone (10.0 eq.), Hoveyda-Grubbs 2nd generation catalyst (0.04 eq.), CH_2Cl_2, rt.

Silyl ether	Conditions	Cleavage priority
ROSi(*t*Bu)$_2$H	1 eq. TFA, CH_2Cl_2, 0 °C	silyl ether
ROSi(*t*Bu)$_2$H	1 eq. HCl, EtOAc, 0 °C	silyl ether
ROSi(*t*Bu)$_2$H	1 eq. AcOH, CH_2Cl_2, 0 °C	NR
ROSi(*t*Bu)$_2$H	1 eq. AcOH, CH_2Cl_2, reflux	silyl ether
ROSi(*t*Bu)$_2$H	1 eq. I_2, CH_2Cl_2, rt	simultaneous
$ROSiPh_2H$	1 eq. AcOH, CH_2Cl_2, 0 °C	NR
$ROSiPh_2H$	1 eq. AcOH, CH_2Cl_2, reflux	silyl ether
$ROSiPh_2H$	1 eq. I_2, CH_2Cl_2, rt	simultaneous
ROSi(*i*Pr)$_2$H	unstable on silica	

Table 2.2

Unfortunately, the silyl moiety of precursor **55** was highly unstable under the acidic conditions required for removal of the *tert*-butoxycarbonyl group – the crucial step to initiate the cascade reaction. We prepared various silyl ethers and employed alternative conditions, but in all cases, the silyl ethers were more susceptible to acidic cleavage than the *tert*-butoxycarbonyl group (Table 2.2).



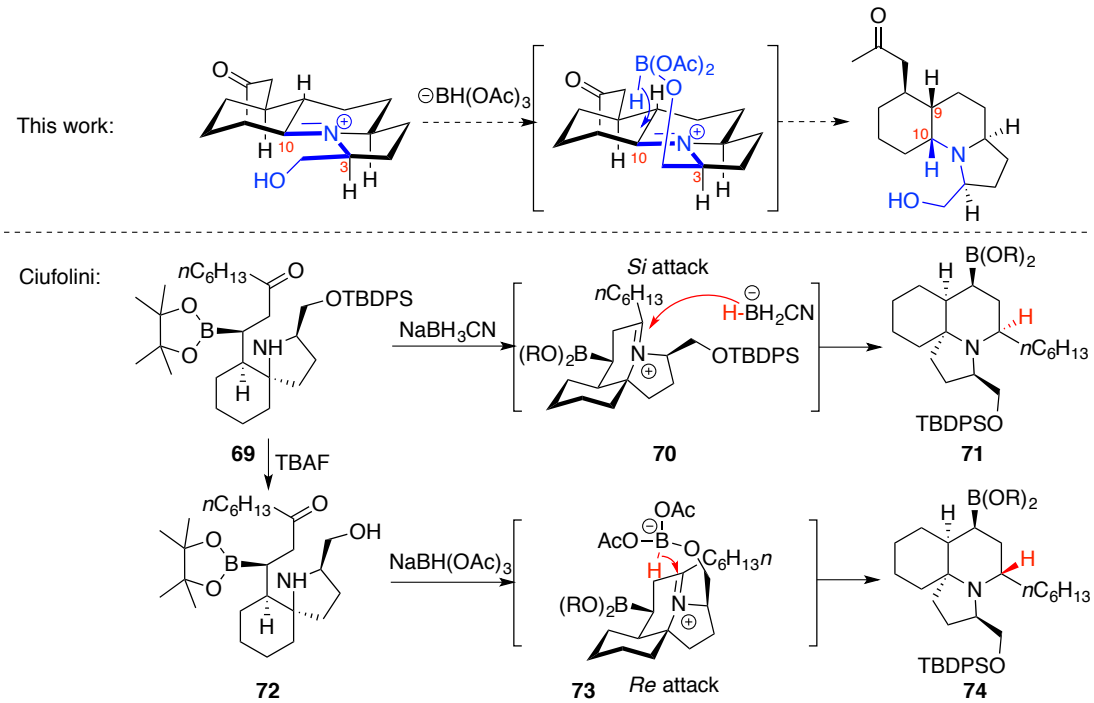
Scheme 2.14

Another drawback of this disconnection was its low efficiency attributed to the fragment-based construction of the *C*6 substituent: eight out of ten of the steps to the cascade precursor involved functionalisation of the side chain (Scheme 2.14). A more integrated way of introducing this side chain could potentially provide a concise route to the cascade

precursor. Therefore, a new disconnection needed to be planned to facilitate the diastereoselective reduction and increase the step efficiency.

2.3 A New Reduction Strategy and Disconnection

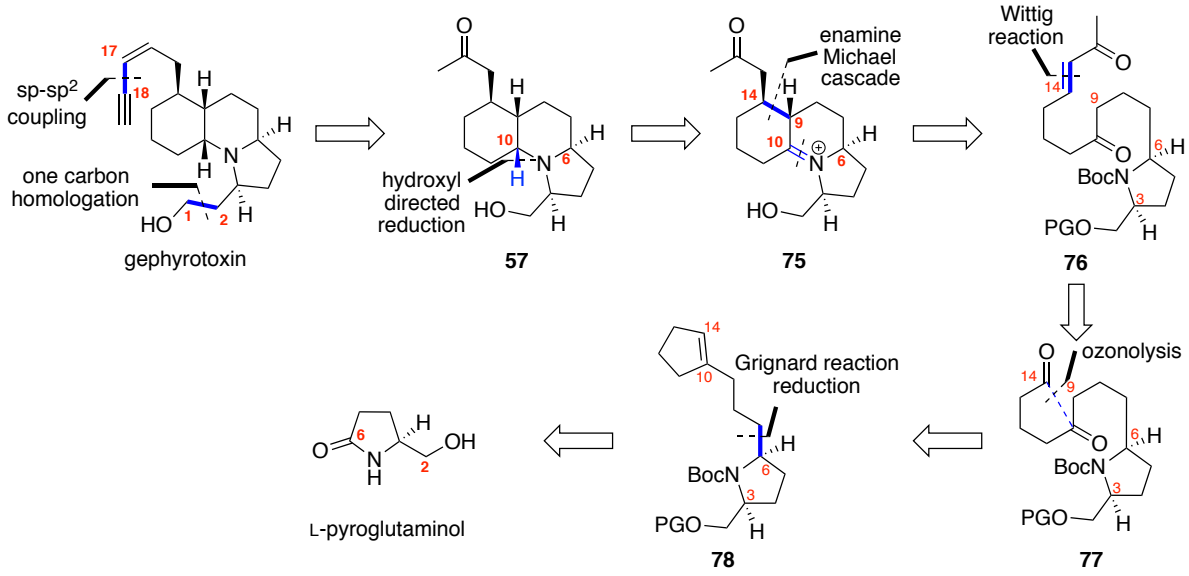
We anticipated that the *C*3 substituent bearing a hydroxyl group could coordinate and direct the reducing agent (Scheme 2.15), which resembled intramolecular hydride transfer by using silyl ethers. Such directed reductions have been demonstrated in Ciufolini's total synthesis of (–)-cylindricine C and (–)-2-epicylindricine C (Scheme 2.15).[42] The intermediate iminium **73**, formed from condensation of keto-pyrrolidine **72**, was reduced using sodium triacetoxyborohydride to give tricyclic amine **74**. This presumably proceeded *via* a 7-membered boron-chelate formed by coordination of the reducing agent to the hydroxyl group. Alternatively, the epimer of amine **74** was obtained by reduction of the *O*-protected keto-pyrrolidine **69** through a non-coordination mechanism.



Scheme 2.15

2.3.1 Retrosynthetic Analysis

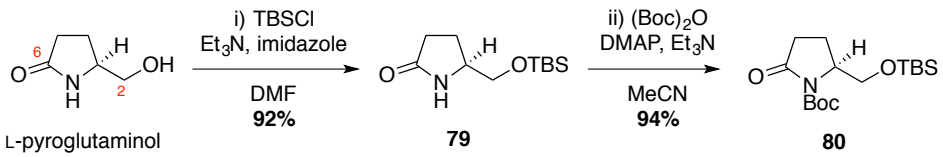
Our revised strategy started with commercially available L-pyroglutaminol (Scheme 2.16). Key features of this approach (in the forward direction) were: a diastereoselective installation of the *C*6 side chain, a cascade cyclisation followed by a hydroxyl directed reduction, a one-carbon homologation of the *C*3 side chain, and construction of the ene-yne motif.



Scheme 2.16

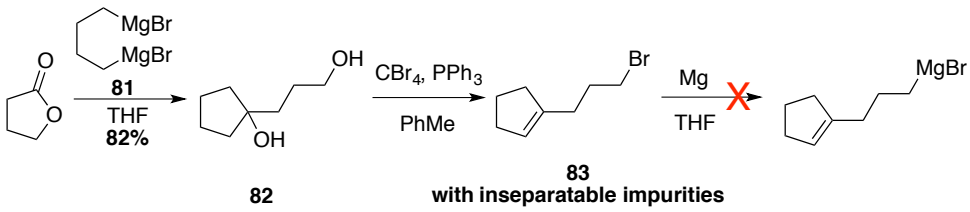
2.3.2 Synthesis of the Cascade Precursor

Synthesis of the precursor began with *N*,*O*-diprotection of L-pyroglutaminol under conventional conditions. Pyrrolidinone **80** was obtained in excellent yield. The integrity of the *C*3 stereocentre in **80** was confirmed by chiral stationary phase HPLC (>99:1 e.r., detailed in experimental section).



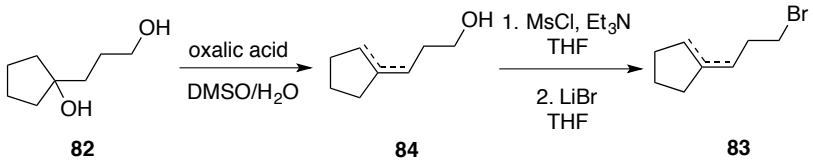
Scheme 2.17

Installation of the sidechain at *C*6 required bromide **83**. Only one preparation was described, which required two steps from γ-butyrolactone (Scheme 2.18).[43] In our hands, treatment of γ-butyrolactone with Grignard reagent **81** gave diol **82**, which was then subjected under Appel bromination conditions to afford bromide **83**. Unfortunately, the desired bromide **83** was contaminated by the inseparable *exo*-alkene isomer. After several failed attempts to prepare the Grignard reagent from bromide **83**, a wide sweep width ^{13}C-NMR analysis of the sample showed contamination of inseparable carbon tetrabromide (–29.7 ppm). Formation of bromide **83** *via* Appel reaction was not a viable option. Therefore alternative preparation methods were investigated.



Scheme 2.18

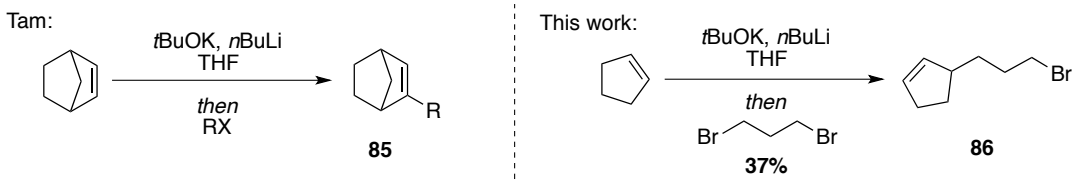
Dehydration of diol **82** gave alcohol **84** in poor yield as a mixture of inseparable alkene isomers. Mesylation of the isomers gave quantitative yield, however, the mesylates still could not be purified to give the pure *endo*-isomer.



Scheme 2.19

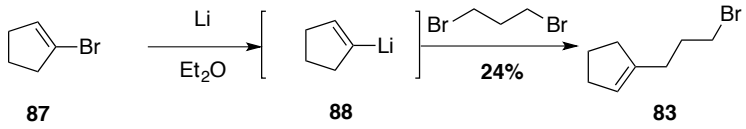
Tam *et al.* have demonstrated the synthesis of norbornene derivatives **85** by using Schlosser's

base (Scheme 2.20).[44] In our hands, deprotonation of cyclopentene and quenching with 1,3-dibromopropane gave only 3-substituted cyclopentene **86**. We rationalised the result by feasible deprotonation of the more acidic proton adjacent to the alkene to give a delocalised anion, subsequent attack of the anion on the bromide delivered the undesired isomer **86**.



Scheme 2.20

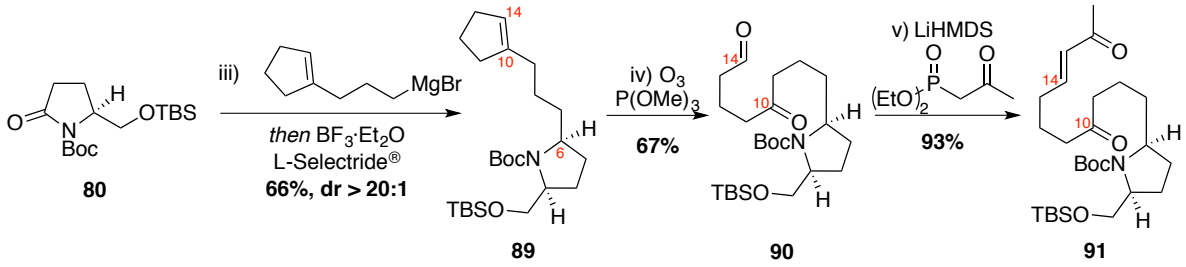
The limited success of existing methods led us to explore a lithium exchange strategy (Scheme 2.21). Treatment of bromide **87** with metallic lithium generated alkenyl lithium **88**, which was reacted *in situ* with 1,3-dibromopropane to give bromide **42** in its pure form after distillation and silica gel chromatography, which was suitable for the subsequent Grignard reaction.



Scheme 2.21

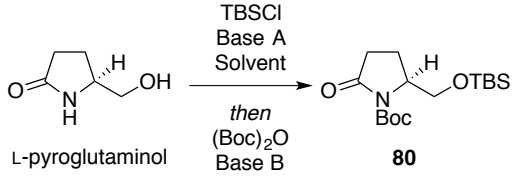
The freshly prepared Grignard reagent from bromide **83** was reacted with pyrrolidinone **80** to give an inconsequential mixture of *C*6 diastereoisomers. Subsequent *in situ* reduction using L-Selectride® in the presence of $BF_3 \cdot Et_2O$ gave pyrrolidine **89** in moderate yield (Scheme 2.22).[45] The 3,6-*cis*-pyrrolidine **89** was generated exclusively, presumably *via* hydride delivery to the less hindered face of the *in situ* generated *N*-acyliminium cation. The

*C*10/*C*14 dicarbonyl unit was unmasked with ozone, and the resultant terminal aldehyde **49** was subjected to HWE reaction conditions. The key cascade precursor for the generation of the gephyrotoxin core – ketone **89** – was obtained in excellent yield.



Scheme 2.22 Synthesis of cascade precursor 91: iii) Grignard (2.00 eq.), THF, –78 °C; $BF_3{\cdot}Et_2O$ (6.00 eq.), L-Selectride (2.00 eq.), –78 °C to rt. iv) O_3, CH_2Cl_2, –78 °C; *then* $P(OMe)_3$ (1.05 eq.), – 78 °C to rt. v) LiHMDS (1.10 eq.), $(EtO)_2POCH_2COCH_3$ (1.10 eq.), THF, rt.

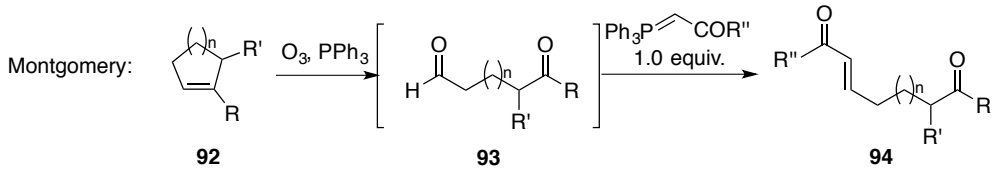
At this stage of our synthesis of gephyrotoxin, we introduced minor improvement to the synthetic procedure. Namely, in the preparation of pyrrolidinone **80**, we conducted a screen of various solvents and bases, and developed a one-pot *N*,*O*-diprotection process that delivered the product in 84% overall yield. Compared with the two-step sequence, we obtained comparable yield to a process that previously required two separate steps and eliminated the need for DMF as the solvent.



Solvent	Base A	Base B	Yield
CH_2Cl_2	KHMDS	Et_3N, DMAP	33%
PhMe	KHMDS	Et_3N, DMAP	48%
THF	KHMDS	Et_3N, DMAP	29%
THF	LiHMDS	Et_3N, DMAP	35%
MeCN	KHMDS	Et_3N, DMAP	82%
MeCN	LiHMDS	Et_3N, DMAP	69%
MeCN	Et_3N, imidazole	Et_3N, DMAP	silylation only
MeCN	KHMDS	DMAP	84%

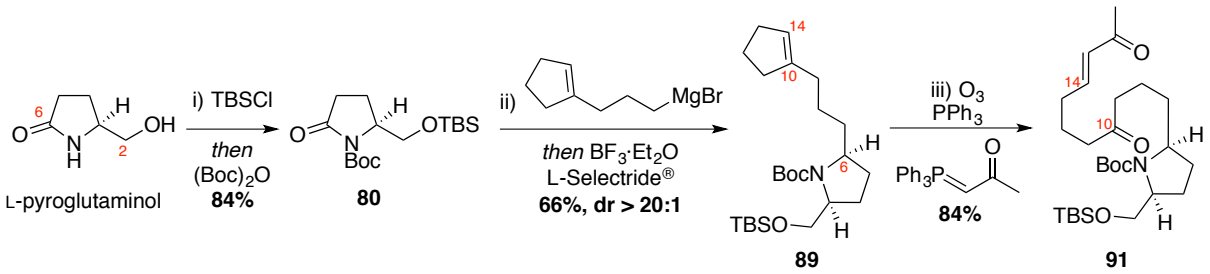
Scheme 2.23

In addition, a previous study by Montgomery *et al.* demonstrated a one-pot preparation procedure to enones **94** from cyclopentenes **92** by treating the *in situ* generated dicarbonyl intermediates **93** with various Wittig reagents (Scheme 2.24).[46] This was applied to the synthesis of cascade precursor **91** to minimize the decomposition of diketone **90** upon prolonged contact with silica during large-scale purification procedures.



Scheme 2.24

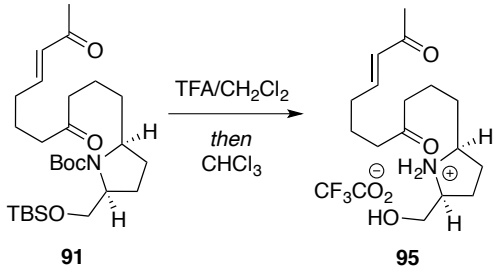
Combining these new one-pot procedures enabled a highly practical three-step sequence to the cascade precursor on gram-scale (Scheme 2.25). In comparison, our previous approach required ten steps with a much lower yield. The current approach allowed us to access large quantities of precursor **91** in a short period of time, which was of great convenience in the investigation of the next step: the key cascade cyclisation.



Scheme 2.25 Synthesis of cascade precursor 91: i) TBSCl (1.15 eq.), KHMDS (1.20 eq.), MeCN, rt; *then* Boc_2O (3.00 eq.), DMAP (0.05 eq.), rt. ii) Grignard (2.00 eq.), THF, –78 °C; $BF_3{\cdot}Et_2O$ (6.00 eq.), L-Selectride® (2.00 eq.), –78 °C to rt. iii) O_3, CH_2Cl_2, –78 °C; *then* PPh_3 (1.05 eq.), –78 °C to rt; *then* $Ph_3PCH_2COCH_3$ (1.10 eq.), rt.

2.3.3 The Cascade Reaction

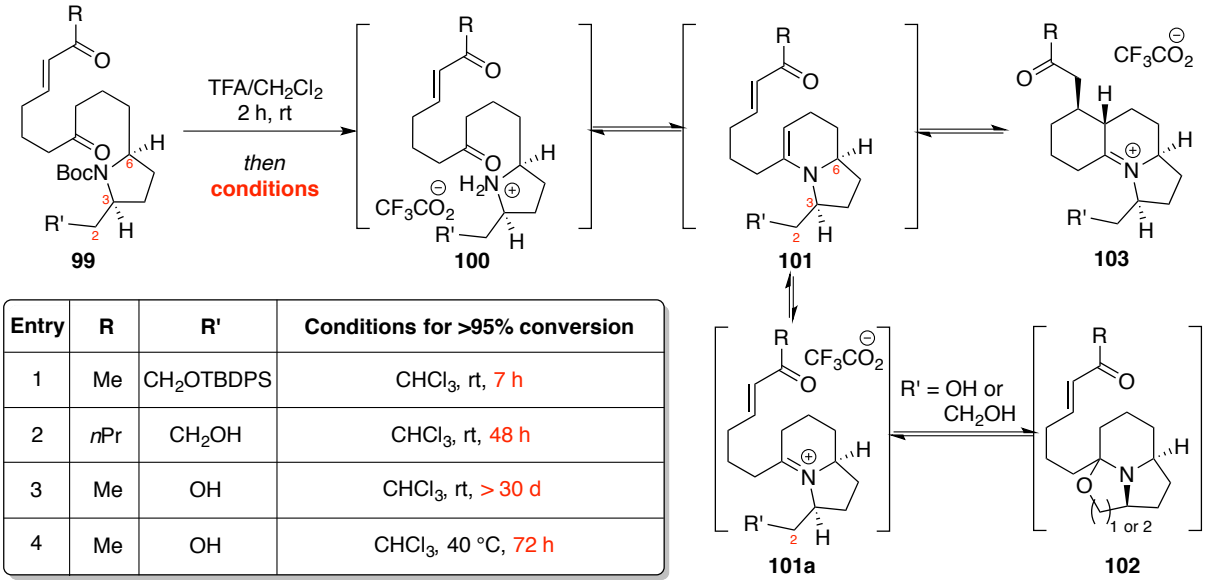
The key cascade reaction was initiated by removal of the *tert*-butoxycarbonyl group of precursor **91** (Scheme 2.26), which was achieved by treating **91** with TFA in dichloromethane at room temperature. This also led to hydrolysis of the primary silyl ether, which was crucial as the free hydroxyl group would later act as a directing group in the reduction step.



91 **95**

Scheme 2.26

A previous study (Entry 1 & 2, Scheme 2.27) has shown that cyclisation of substrates with free *C*1 hydroxyl group is notably slower, which is presumably a consequence of a competing equilibrium between iminium **101a** and hemiaminal **102**.[37]



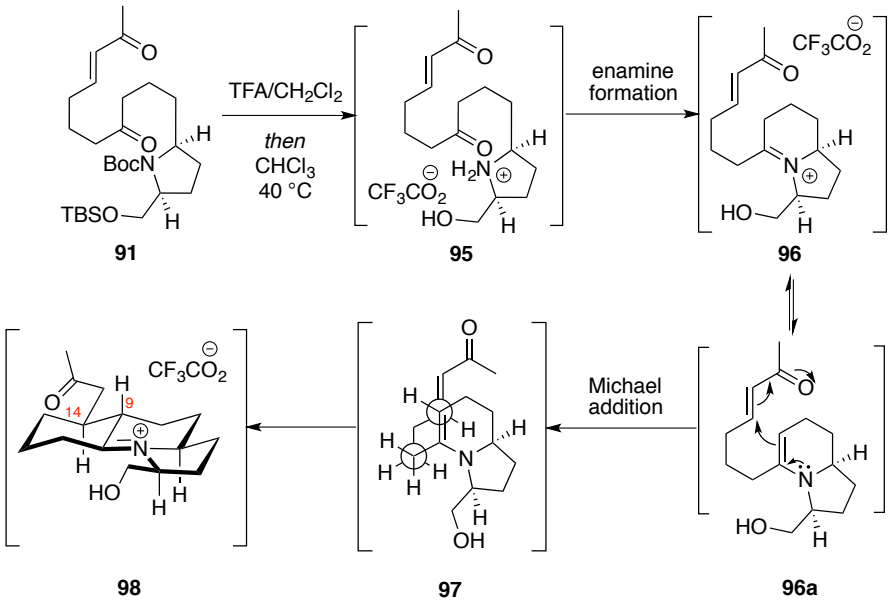
99 **100** **101** **103**

Entry	R	R'	Conditions for >95% conversion
1	Me	$CH_2OTBDPS$	$CHCl_3$, rt, 7 h
2	*n*Pr	CH_2OH	$CHCl_3$, rt, 48 h
3	Me	OH	$CHCl_3$, rt, > 30 d
4	Me	OH	$CHCl_3$, 40 °C, 72 h

101a **102**

Scheme 2.27

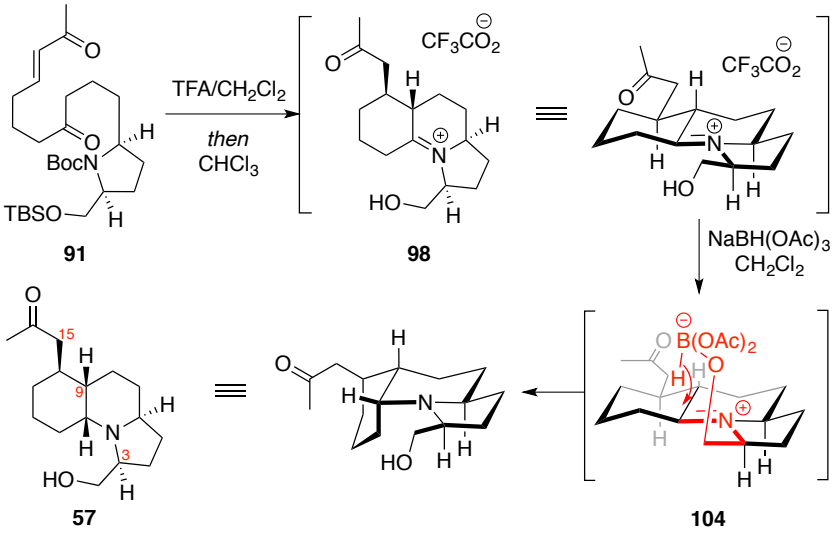
Subjecting precursor **91** under the previous cascade conditions did not give full conversion even after one month (Entry 3, Scheme 2.27). Pleasingly, at elevated temperature, the cyclisation was complete within 72 h with no observed deterioration in stereointegrity at *C*9 and *C*14.



Scheme 2.28

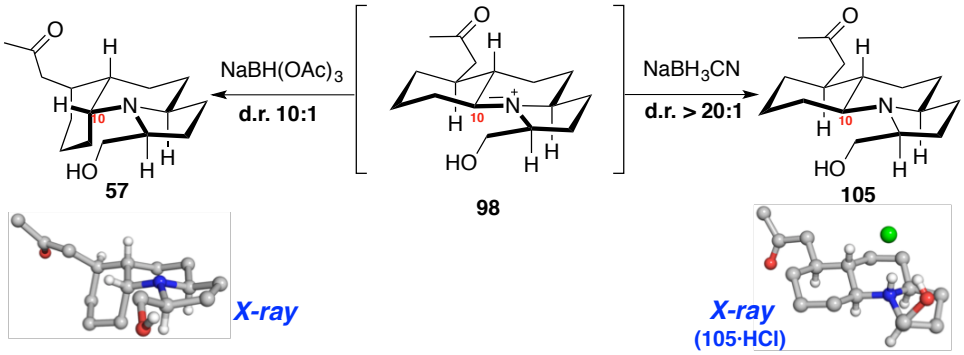
The mechanism for the cascade is analogous to that as described in Scheme 2.3: the condensation product iminium ion **96** was in an equilibrium with enamine **96a**, which was the active species for the diastereoselective intramolecular Michael addition (Scheme 2.28). The stereochemistry of this transformation could be rationalised through a chair-like transition state in which the Michael acceptor adopted a pseudoequatorial orientation to minimise diaxial interactions, with facial discrimination of the bicyclic enamine a consequence of the *C*3 substituent and its effect on the conformation of the pyrrolidine ring.

The tricyclic iminium **98** was sufficiently stable to be isolable as its trifluoroacetate salt, though in practice it was reduced *in situ*. Most pleasingly, this afforded the tricyclic gephyrotoxin core **57**, featuring the requisite 9,10-*cis*-stereochemistry, with good diastereoselectivity (10:1, *cis*:*trans*, separable by chromatography) and in 79% overall yield from precursor **91**. The diastereoselective reduction was presumably achieved by an intramolecular delivery of hydride *via* the borohydride tethered to the hydroxymethyl group at *C*3 (Scheme 2.29). The stereochemical outcome of this cascade was examined by single crystal X-ray diffraction, which confirmed that all five stereocentres for the natural product were installed correctly.



Scheme 2.29 The cascade reaction: iv) TFA/CH_2Cl_2 (1:3, v/v), 0 °C to rt; *then* $CHCl_3$, 40 °C, 72 h; then $NaBH(OAc)_3$ (1.5 eq.), CH_2Cl_2, rt.

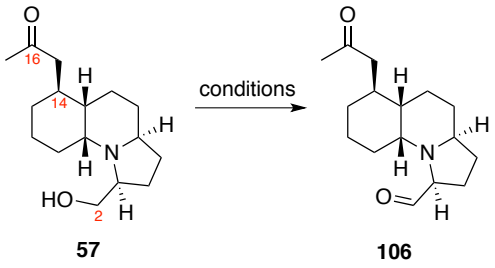
Reduction of **98** under the same conditions with a non-coordinating reducing agent, such as sodium cyanoborohydride, afforded exclusive 9,10-*trans*-isomer **105** (Scheme 2.30), which indicated the *C*3 substituent played a key stereodirecting role for reduction of the iminium cation.



Scheme 2.30

2.3.4 The Endgame

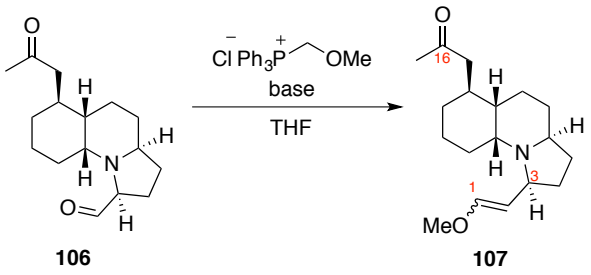
At this stage, conversion of the tricyclic core **57** to the natural product required a one-carbon homologation at *C*2, utilising an oxidation of *C*2 to facilitate a nucleophilic addition reaction to introduce *C*1. It also required introduction of the ene-yne moiety through functional group transformations from the *C*16 ketone, and C-C bond formation to extend the length of the *C*14 side chain.



Conditions	Yield
Dess-Martin oxidation	74%
IBX	69%
Ley oxidation	62%
Swern oxidation	quant.

Scheme 2.31

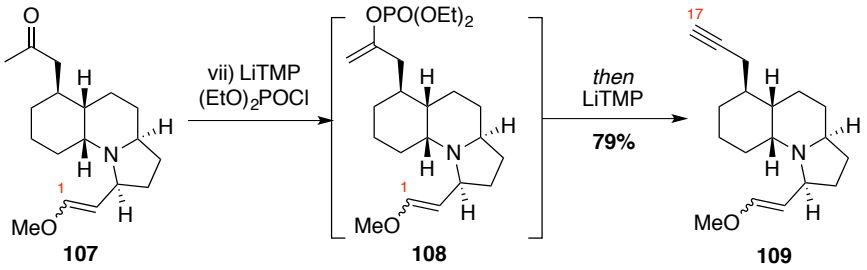
Proceeding with the C2 oxidation, alcohol **57** was subjected under various conditions. The highest yield was obtained under Swern oxidation conditions (Scheme 2.31).[47] In practice, to avoid decomposition of aldehyde **106**, the crude oxidation product was treated with an ylide, generated by reacting (methoxymethyl)triphenylphosphonium chloride with KHMDS in THF, to give vinyl ether **107** as an 1:1 mixture of geometrical isomers (Scheme 2.32).



Base	Yield
*n*BuLi	23%
*t*BuOK	62%
LDA	78%
KHMDS	87%

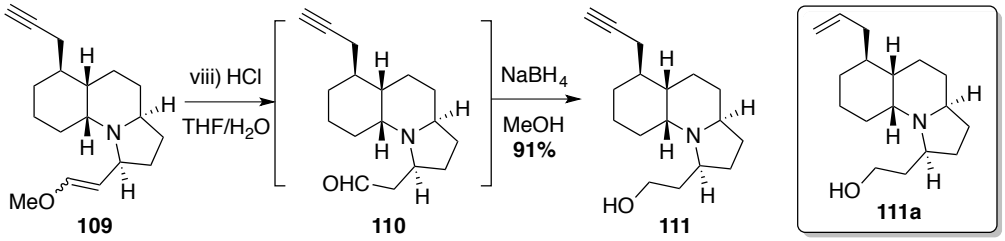
Scheme 2.32

Hydrolysis and reduction of ether **107** would lead to completion of *C*3 side chain. However, it would be wise to consider the functional group manipulations on the *C*16 ketone before the hydrolysis and reduction; the methyl vinyl ether moiety could act as a protected *C*1 aldehyde group. Indeed, construction of the ene-yne motif required an alkynylation of the *C*16 ketone to give the desired terminal alkyne (Scheme 2.33). This involved using a strong base, lithium tetramethylpiperidine, which would cause undesired side reactions in the presence of an aldehyde. The ketone functional group in **107** was transformed into an intermediate enol phosphate through kinetic deprotonation with lithium tetramethylpiperidine in THF and trapping with diethylphosphoryl chloride; subsequent addition of excess lithium tetramethylpiperindine led to elimination to afford terminal alkyne **109**, consistent with the method described by Negishi.[48]



Scheme 2.33 vii) LiTMP (1.05 eq.), $(EtO)_2POCl$ (1.1 eq.), THF, –78 °C to rt; *then* LiTMP (2.25 eq.), THF, –78 °C to rt.

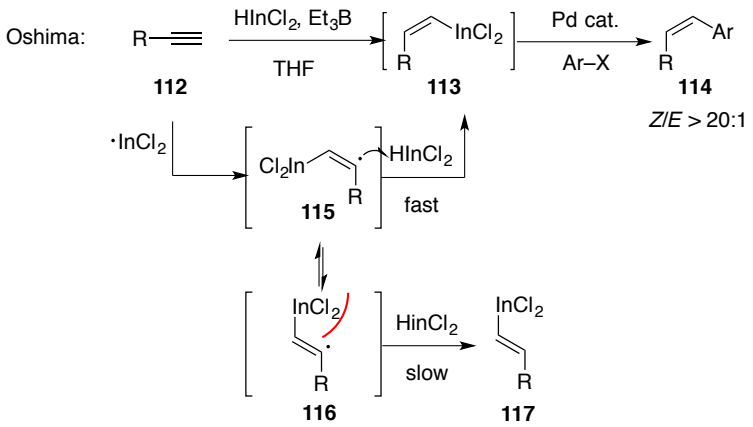
Next, acidic hydrolysis of methyl vinyl ether **109** afforded a *C*1 aldehyde which, after removal of aqueous THF and subsequent dissolution in methanol, was reduced with sodium borohydride to afford *C*1 alcohol **111**.



Scheme 2.34 viii) HCl (20 eq.), THF/H_2O, 25 °C; *then* $NaBH_4$ (2.0 eq.), MeOH, 0 °C to rt

Interestingly, in our initial attempts at the reduction, the procedure gave exclusively alkyne-hydrogenated product alkene **111a** (Scheme 2.34). We then noticed that an aqueous workup after the hydrolysis could suppress the hydrogenation of the alkyne, which indicated some process was excluded by the workup. Evaporation of the hydrochloric acid stock solution left a yellowish residue. It is also known that nickel boride is an efficient reducing agent for the partial reduction of alkynes to alkenes, and is usually generated *in situ* by reacting $NiCl_2$ with $NaBH_4$.[49] These pieces of evidence suggested the presence of nickel in the hydrolysis mixture. Records from a laboratory note book indicated that a syringe equipped with a stainless steel needle was used for transferring the concentrated hydrochloric acid in the preparation of the stock solution. No reduction of the alkyne was observed by using a new batch of hydrochloric acid, without using a metal syringe needle.

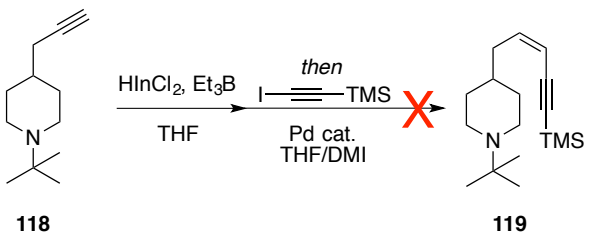
The final carbon-carbon bond was formed through a one-pot radical hydroindation/cross-coupling strategy described by Oshima *et al.* (Scheme 2.35).[50]



Scheme 2.35

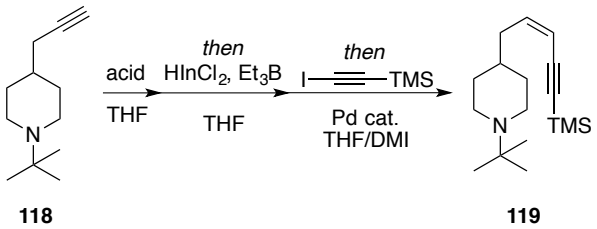
This process generates a *cis*-vinyl dichloroindium intermediate by treating alkyne **112** with *in situ* formed $HInCl_2$ in the presence of triethylborane. The stereoselectivity is controlled by the kinetically preferred hydrogen abstraction of radical **115** over **116**. This organoindium compound was then subjected to cross-coupling conditions with an aryl halide to yield *cis*-disubstituted olefin **114** with superb stereoselectivity.

We prepared a model substrate, alkyne **118**, to test the hydroindation/cross-coupling reaction, so we could avoid wasting the late-stage compound **111** (Scheme 2.36). The first attempt only gave starting material back, which suggested the radical hydroindation had not occurred. We recognized that the tertiary amine was a functional group that could interfere with the reaction, as $HInCl_2$ is expected to be a Lewis acid.



Scheme 2.36

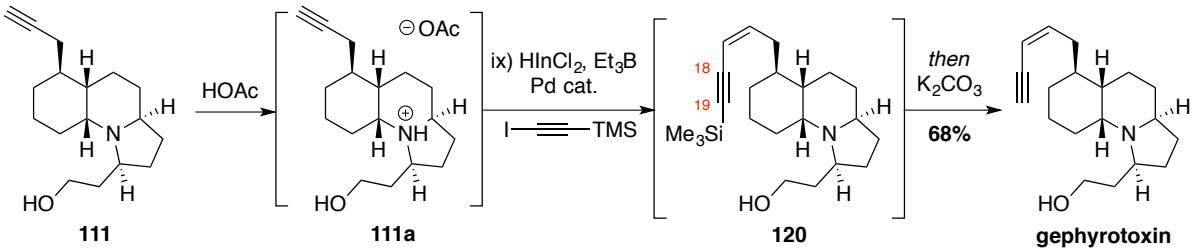
Therefore, by protecting the tertiary amine with acid prior to the hydroindation, we expected to avoid this problem. A series of Brønsted and Lewis acids were tested, and we found that acetic acid gave the highest yield of cross-coupled product **119**.



Acid	Yield
HCl	NR
HOAc	81%
TFA	77%
$BF_3{\cdot}Et_2O$	69%
$InCl_3$	< 5%
$HInCl_2$	< 5%

Scheme 2.37

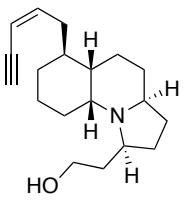
Hydroindation of freshly prepared acetate **111a** (Scheme 2.38) using *in situ* generated dichloroindium hydride in the presence of the radical initiator triethylborane afforded a vinylindium species. This then underwent cross-coupling with trimethylsilyl-protected iodoacetylene in the presence of pre-mixed $Pd_2(dba)_3{\cdot}CHCl_3$ and tri(2-furyl)phosphine affording **120**. A work-up with potassium carbonate and methanol cleaved the terminal silyl group to afford gephyrotoxin which exhibited identical ^1H and ^{13}C NMR spectroscopic data to that previously published.[51]

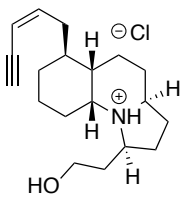


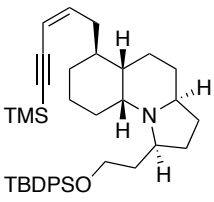
Scheme 2.38 ix) HOAc (1.0 eq.), THF, rt; *then* $HInCl_2$ (1.5 eq.), Et_3B (1.0 eq.), –78 °C; *then* TMS-iodoacetylene (1.5 eq.), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.005 eq.), tri(2-furyl)phosphine (0.045 eq.), DMF/THF, reflux; *then* K_2CO_3 (50 eq.), MeOH, rt.

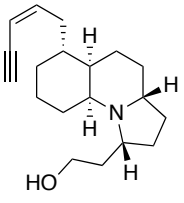
2.4 The Mystery of Optical Rotation

The specific rotation of our synthetic gephyrotoxin was measured to be –52.4 (*c* 1.0, EtOH) (Table 2.3). This was consistent with the value reported for material isolated from natural sources,[14] where the absolute configuration was assigned through X-ray analysis of a single crystal of gephyrotoxin hydrobromide. However, this value was opposite in sign to that reported by Kishi for synthetic material of the same proposed absolute configuration ($[\alpha]_D^{20}$ = +50.0 (*c* 1.0, EtOH)).[17] Exchange of information with Professor Yoshito Kishi revealed the specific rotation of their unpublished intermediate **121**, which was also opposite in sign to that prepared by us (see experimental chapter for full details). A recent asymmetric synthesis of (+)-gephyrotoxin **122** strongly supports natural gephyrotoxin being levorotatory.[52]







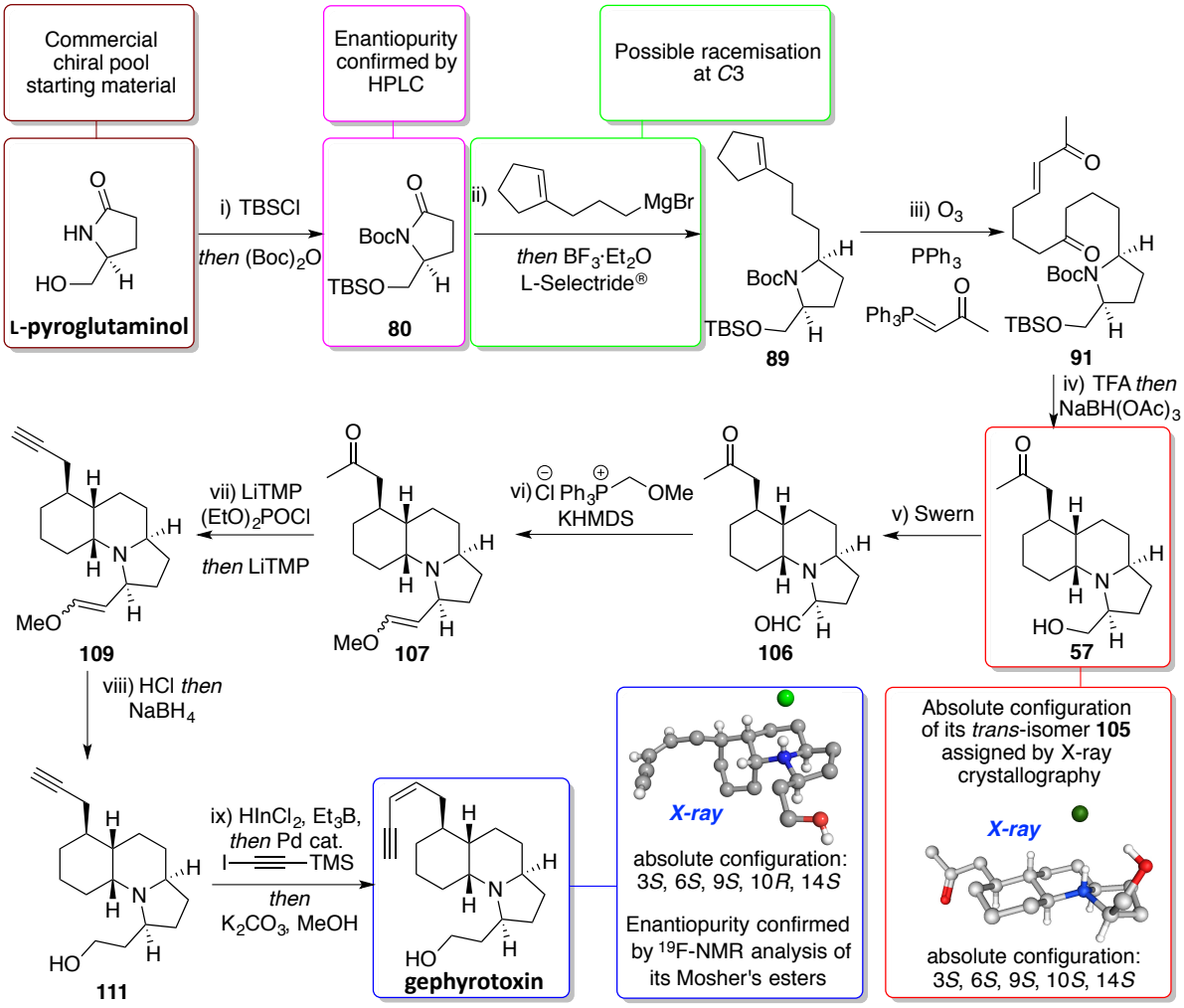


	gephyrotoxin $[\alpha]_D^{20}$ (*c* 1.0, EtOH)	gephyrotoxin·HCl $[\alpha]_D^{20}$ (*c* 1.1, MeOH)	**121** $[\alpha]_D^{20}$ (*c* 1.0, EtOH)	**122** $[\alpha]_D^{19}$ (*c* 0.13, EtOH)
natural	–51.5	NA	NA	NA
synthetic (Kishi)	+50.0	NA	+20.0 (*c* 1.4)	NA
synthetic (this work)	–52.4	–89.1	–32.0	NA
synthetic (Hamada)	NA	NA	NA	+49.8

Table 2.3

A step-by-step revision of our synthetic route was important to prove the absolute configuration of our synthetic material (Scheme 2.39). The starting material used in our synthesis, L-pyroglutaminol, a chiral pool reagent, was used directly as supplied by major chemical suppliers. Two batches of L-pyroglutaminol from different suppliers were used in

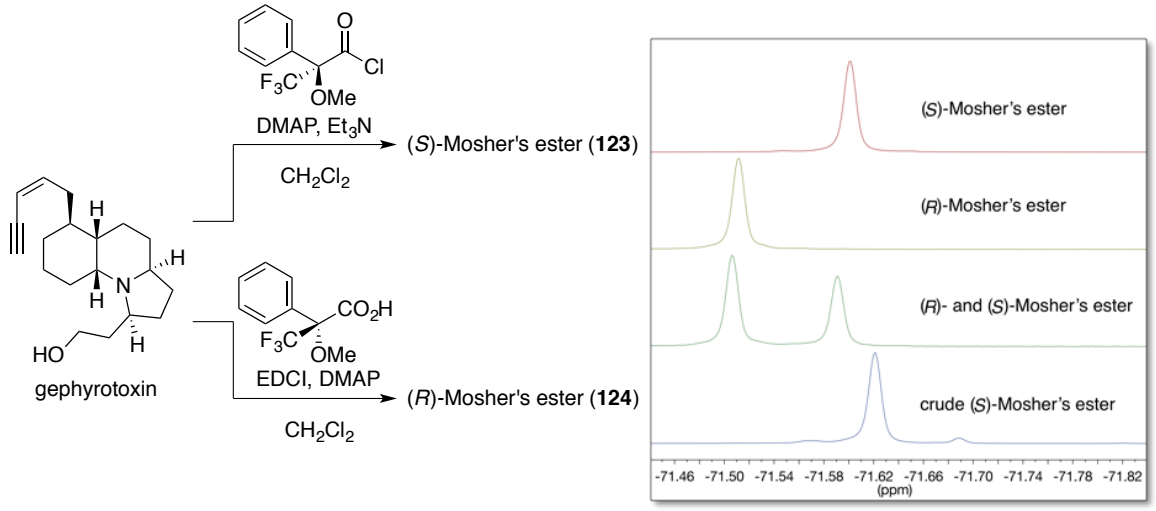
this research, thereby the possibility of starting with the undesired enantiomer was extremely low. In addition, after the diprotection, the optical purity of intermediate **80** was examined by chiral stationary phase HPLC (> 99:1 er). Single crystal X-ray analysis of the hydrochloride salt of by-product **105** from the cascade reaction, and our synthesised gephyrotoxin, also confirmed the absolute configurations are as depicted in Scheme 2.39.



Scheme 2.39

Following preparation and isolation of diastereomerically pure (*S*)- and (*R*)-Mosher's esters of (–)-gephyrotoxin (**123** and **124**, respectively) (Scheme 2.40), ^{19}F NMR spectroscopic analysis of the crude (*S*)-Mosher's ester indicated that it was obtained as a single diastereomer.

Therefore, as no detectable racemization occurred during the Grignard reaction, we assume synthetic (−)-gephyrotoxin was obtained as a single enantiomer for the assignment of absolute configuration by X-ray crystallographic analysis.



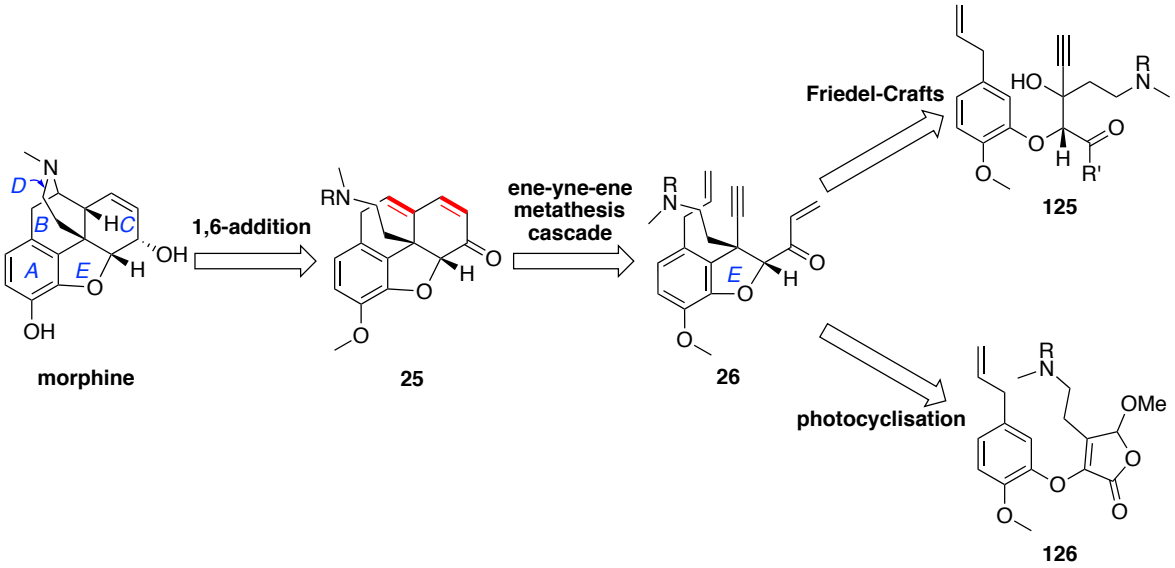
Scheme 2.40

These data strongly suggest natural gephyrotoxin being levorotatory. Unfortunately, a sample of natural gephyrotoxin is not available for direct comparison with the synthetic material and hence the absolute configuration of the natural product cannot be confirmed unequivocally.

3. Morphine

3.1 Retrosynthetic Analysis

Fuchs *et al.* have demonstrated that the piperidine ring in morphine can be made by an intramolecular 1,6-addition of amine analogue **25** (Scheme 3.1).[35d] The highly conjugated *α*,*β*,*γ*,*δ*-unsaturated system in **25** represents an ideal scaffold for a cascade ene-yne-ene ring closing metathesis. This requires a heavily functionalised precursor, benzofuran **26**, which can be further disconnected *via* two possible methods to construct the E ring with the quaternary carbon centre.



Scheme 3.1

We envisaged a Friedel-Crafts reaction of tertiary alcohol **125** could lead to formation of the benzofuran ring. Enantioenriched alcohol **125** could be formed from a phenol and a trisubstituted epoxide which could be made by asymmetric epoxidations.

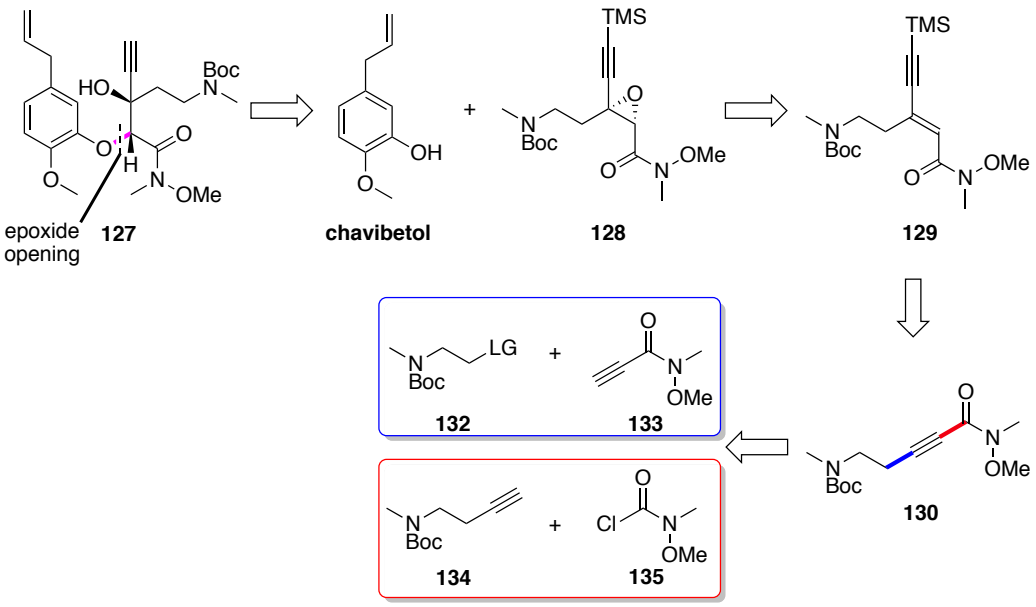
Alternatively, Schultz *et al.* have demonstrated phenyl vinyl ethers can cyclise efficiently

under high-pressure mercury vapour lamp irradiation to give benzofurans.[53] Therefore, as an alternative route, benzofuran **26** can also be disconnected to butenolide **126**.

3.2 Synthesis of the Cascade Precursor *via* Friedel-Crafts Reaction

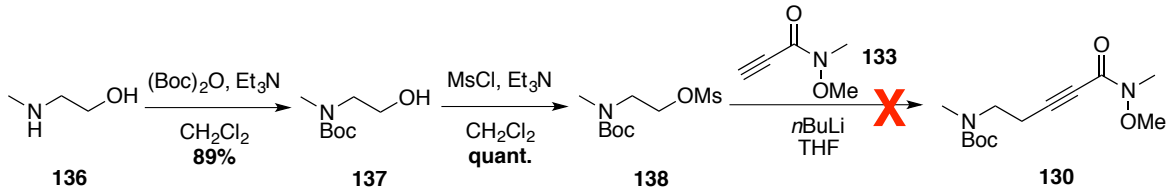
3.2.1 The Epoxide Approach

Our first approach to the cascade precursor was *via* a Friedel-Crafts strategy. Preparation of tertiary alcohol **127** can be achieved by opening epoxide **128** with chavibetol[54] (Scheme 3.2). Shi epoxidations of *α*,*β*-unsaturated esters are known to give high enantioselectivity by using a modified catalyst.[55] The asymmetry of this synthesis can be introduced by Shi epoxidation of unsaturated Weinreb amide **129**. Synthesis of unsaturated amide **129**, bearing a protected alkyne *trans* to the amide, requires a palladium-catalyzed hydroalkynylation. Such stereoselective hydroalkynylations have been described by Trost *et al.* in the synthesis of *β*-alkynyl esters.[56] Further disconnection of amide **130** gives two pairs of subunits, which are easily obtained from commercially available chemicals.



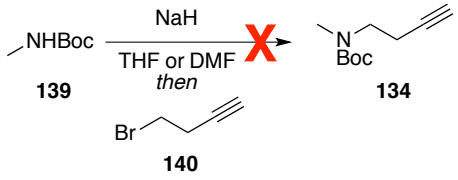
Scheme 3.2

Synthesis of the cascade precursor began with *N*-protection of amine **136** followed by mesylation of the hydroxyl group (Scheme 3.3). However, treating mesylate **138** with deprotonated alkyne **133** did not afford amide **130**, possibly due to the polymerisation of deprotonated amide **133**.



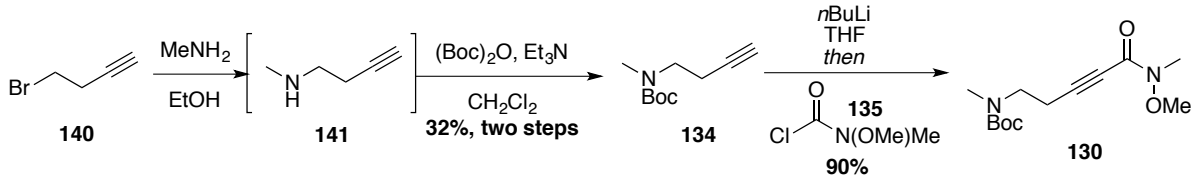
Scheme 3.3

A one-pot process by treating bromide **140** with deprotonated carbamate **139** also failed to give the product, as the carbamate anion could be conceivably quenched by the acidic alkyne proton (Scheme 3.4).



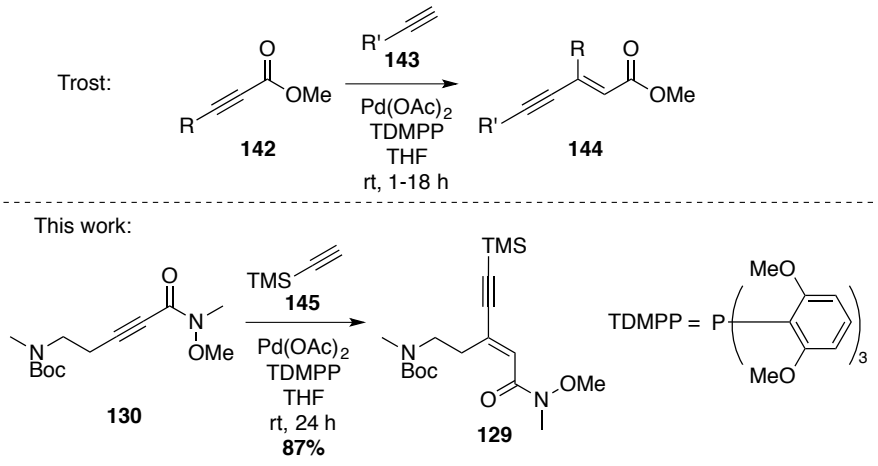
Scheme 3.4

Pleasingly, treating bromide **140** with ethanolic methylamine followed by *N*-protection afforded alkyne **134** in acceptable yield. Deprotonation of alkyne **134** using *n*BuLi and subsequent quenching with carbamoyl chloride **135** gave amide **130** in very good yield.



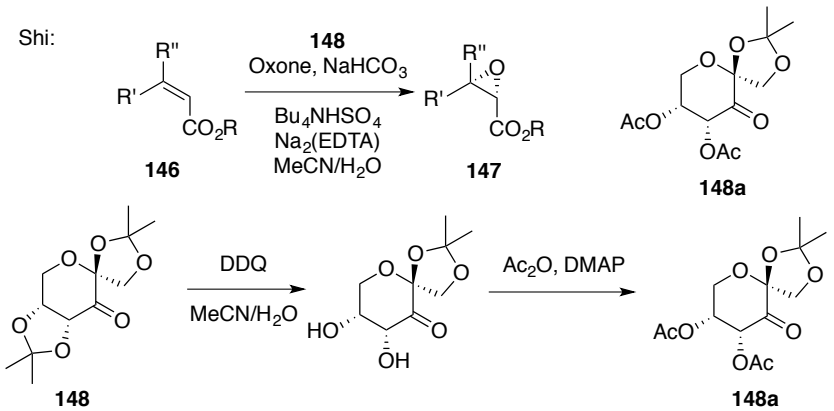
Scheme 3.5

Trost *et al.* demonstrated a stereoselective hydroalkynylation of ynoates **142** (Scheme 3.6),[56] which was successfully applied to our synthesis of trisubstituted olefin **129** in good yield with a noticeably longer reaction time possibly due to the lower reactivity of ynoamide system.



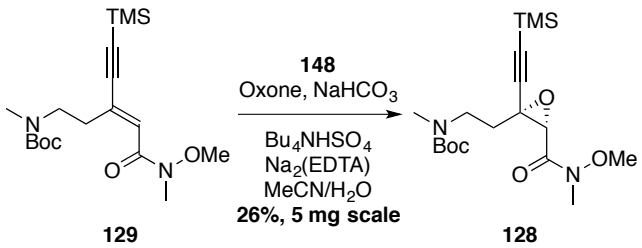
Scheme 3.6

We then investigated the Shi epoxidation of amide **129** to introduce the asymmetry. It has been reported that asymmetric epoxidations of electron deficient trisubstituted olefins by using the modified Shi catalyst **148a** gave excellent yield and enantioselectivity (93-98 e.e.) (Scheme 3.7). Catalyst **148a** can be prepared in two steps from the commercially available Shi catalyst **148**.[55]



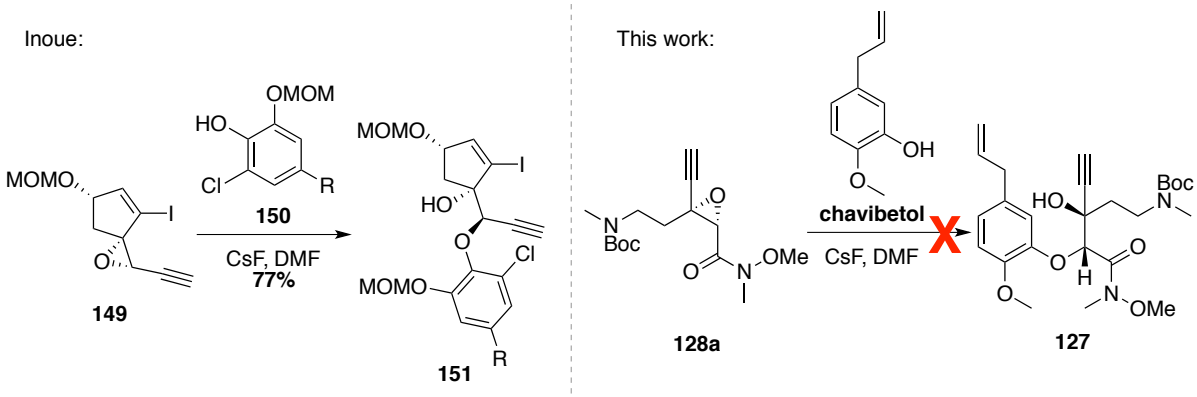
Scheme 3.7

However, in our case, the biphasic reaction system resulted in poor yield, possibly influenced by inefficient stirring during small-scale preparations. Due to the high polarity of epoxide **128**, we were unable to determine its enantiopurity by using HPLC, but decided to proceed with the synthesis.



Scheme 3.8

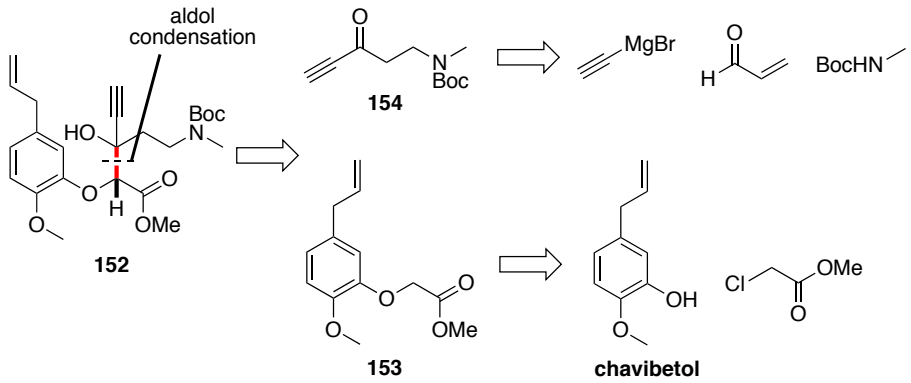
Considering the highly hindered nature of epoxide **128** to ring opening, we decided to apply a procedure described by Inoue *et al.* in their total synthesis of C-1027 (Scheme 3.9);[57] epoxide **149** was reacted with phenol **150** in the presence of cesium fluoride in DMF at elevated temperatures to give tertiary alcohol **151** in high yield. Unfortunately, epoxide **128a** proved difficult to open; despite applying Inoue's conditions; we recovered only starting material. Employing alternative bases led to decomposition of the amide. The troublesome and inefficient route dictated we revisit our disconnection strategy.



Scheme 3.9

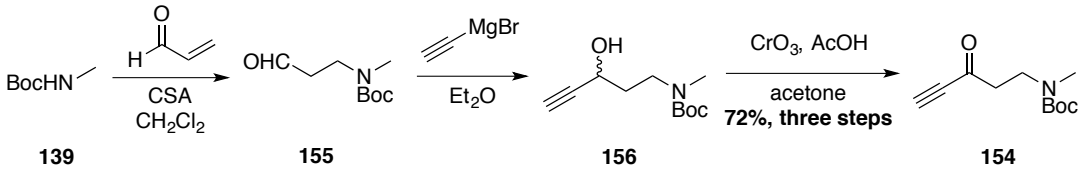
3.2.2 The Aldol Approach

We rationalised the precursor could potentially be accessed *via* an aldol reaction. Disconnecting alcohol **152** *via* a condensation reaction gives phenoxyacetate **153** and ynone **154**. It is possible to control the enantioselectivity of the condensation by using chiral auxiliary derived **153**. However, at this stage, only a racemic synthesis was investigated for simplicity and quick access to the advanced intermediates. Further fragmentation gives five commercial available starting materials.



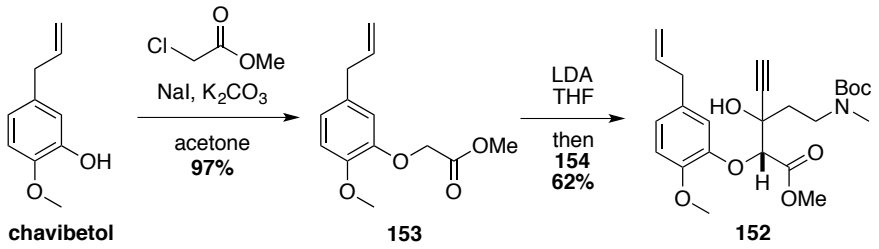
Scheme 3.10

We applied a known procedure to obtain ynone **154** (Scheme 3.11).[58] Acrolein was reacted with carbamate **139** in the presence of CSA to give aldehyde **155**, which was unstable and used as crude in the subsequent Grignard reaction to give propargylic alcohol **156**. Oxidation of the secondary alcohol was achieved by treating the substrate with Jones reagent. The desired product **154** was obtained in good yield over three steps.



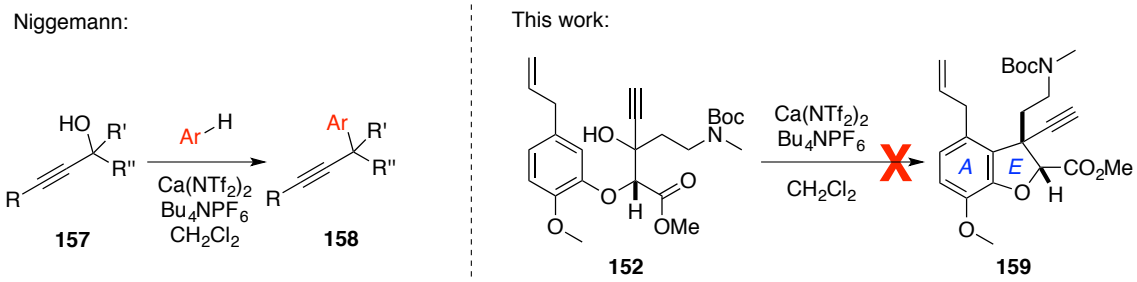
Scheme 3.11

Combining amide **154** with the chavibetol derived ester **153** was achieved *via* an aldol condensation. Acetate **153** was obtained in excellent yield by reacting methyl chloroacetate with chavibetol under Finkelstein condition. The acetate was then deprotonated and condensed with ynone **154** to give tertiary alcohol **152** as a mixture of diastereomers in moderate yield.



Scheme 3.12

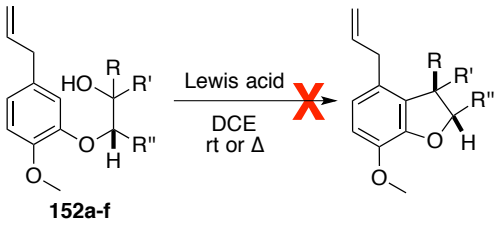
We next investigated the Friedel-Crafts reaction of tertiary alcohol **152** to construct the E ring of morphine. Niggemann *et al.* demonstrated a calcium-catalysed alkylation of arenes using propargylic alcohols at room temperature in the absence of strong acids or bases (Scheme 3.13).[59] The mild conditions were crucial for the *tert*-butoxycarbonyl group of alcohol **152** to remain intact.



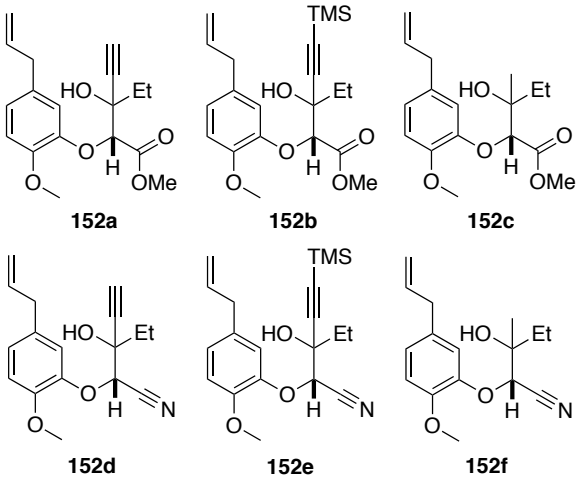
Scheme 3.13

However, upon treating alcohol **152** to Niggemann's Friedel-Crafts condition, no cyclised product **159** was formed (Scheme 3.13). To further investigate the cyclisation, simplified

derivatives of alcohol **152** were prepared and treated with a selection of Brønsted and Lewis acids (Scheme 3.14). However, none of the substrates cyclised under these conditions, even for the least functionalised derivatives **152c**/**f**.

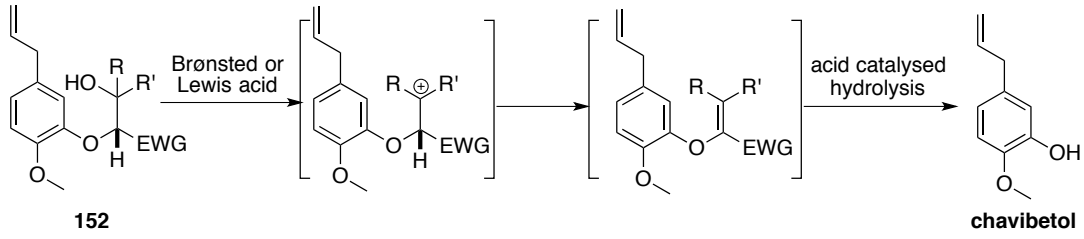


Brønsted/Lewis acid	Brønsted/Lewis acid
$Ca(NTf_2)_2/Bu_4NPF_6$	$SnCl_4$
TFA	$TiCl_4$
HCl	$BF_3{\cdot}Et_2O$
CSA	$Ce(OTf)_3$
*p*TSA	$Cu(OTf)_2$
TfOH	$In(OTf)_3$
$ZnCl_2$	$Bi(OTf)_3$
$AlCl_3$	$Sc(OTf)_3$
$AuAl_3$	$Yb(OTf)_3$
$InCl_3$	$Zn(OTf)_2$
$FeCl_3$	$In(OTf)_3$



Scheme 3.14

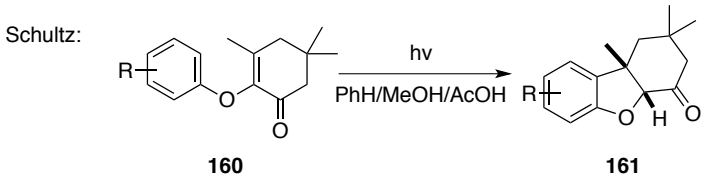
Throughout our screening, we found chavibetol was one identifiable compound found in the reaction mixtures, which suggested a possible acid-catalysed decomposition of the tertiary alcohol *via* the formation of phenyl vinyl ether (Scheme 3.15). We were again required to redesign our approach to construct the A/E ring (benzofuran) moiety of morphine.



Scheme 3.15

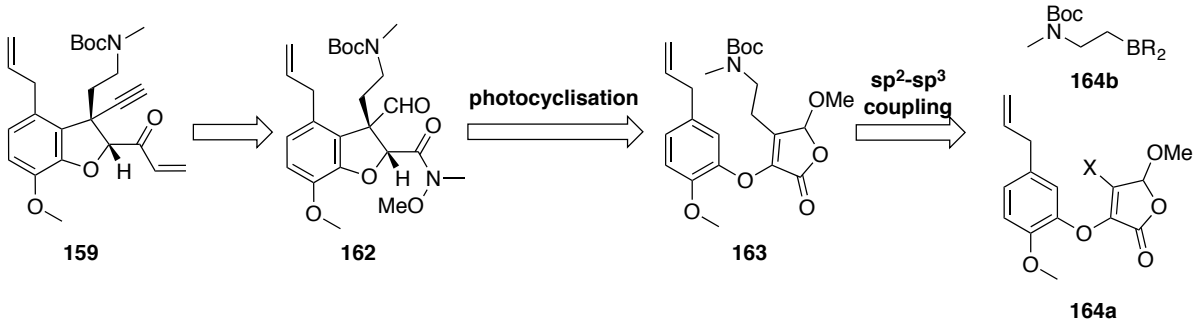
3.3 Synthesis of the Cascade Precursor *via* Photocyclisation

Upon investigation of the property of phenyl vinyl ethers, we were pleased to realise that this moiety could be cyclised under high-pressure mercury vapour lamp irradiation to give benzofuran. Such photocyclisations were demonstrated by Schultz in the synthesis of tricyclic benzofurans *via* a process which is best described as a 6π-photoelectrocyclisation followed by a concerted 1,4-hydrogen shift, to give benzofurans **161** (Scheme 3.16).[53]



Scheme 3.16

We expected photocyclisation of butenolide **163** would give the benzofuran with the required diastereoselectivity (Scheme 3.17). The associated ring-strain of a 5,5-*trans* fused system would result in only the *cis*-fused 5,5-system being formed. The cyclised product could be transformed into aldehyde **162** by an amidation and oxidation sequence. The formation of cascade precursor **159** could be achieved by Grignard reaction of vinylmagnium bromide with the resulting Weinreb amide and Ohira-Bestmann alkynylation[60] of the aldehyde.

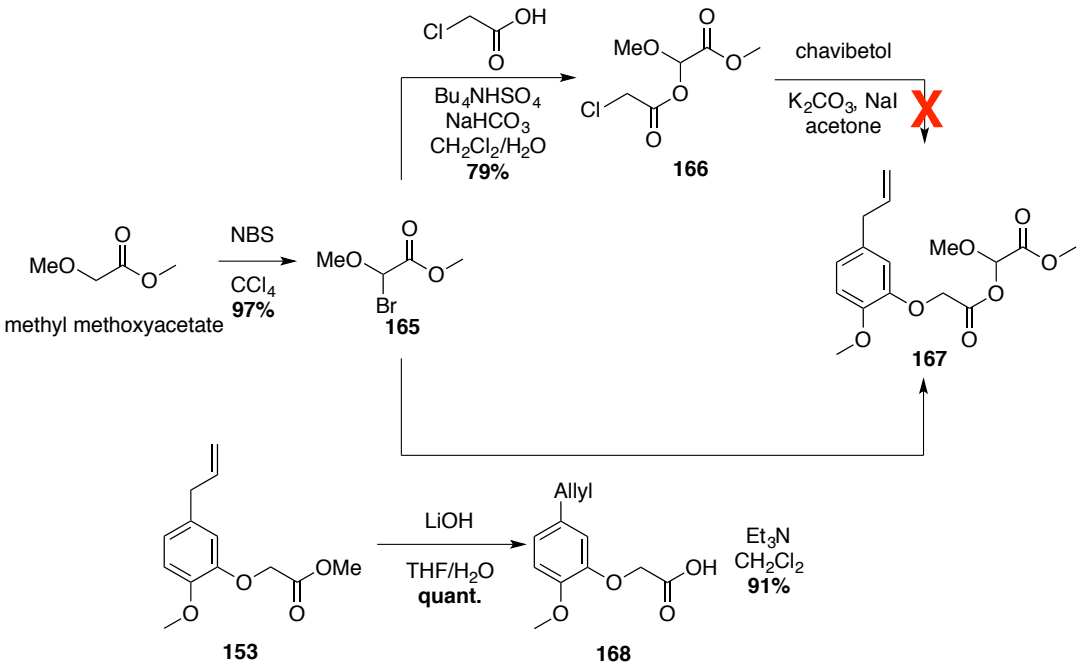


Scheme 3.17

We anticipated butenolide **163** could be constructed *via* an sp^2-sp^3 coupling of *β*-halobutenolide **164a** with boron reagent **164b** (Scheme 3.17). Therefore, the early stage of this route mainly focused on the synthesis of *β*-halobutenolides.

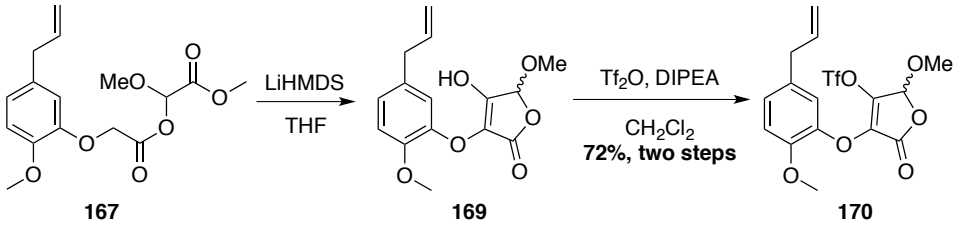
3.3.1 Synthesis of the *β*-Halobutenolide

Radical bromination of methyl methoxyacetate gave bromide **165** in excellent yield (Scheme 3.18).[61] At this point, there were two possible pathways to intermediate **167**. We initially treated bromide **165** with chloroacetic acid under phase transfer condition to give chloride **166**. However, the chloride did not undergo substitution with chavibetol to give **167**. Pleasingly, by altering the order of the reactions, reacting bromide **165** with the hydrolysis product of acetate **153** in the presence of triethylamine gave intermediate **167** in excellent yield.



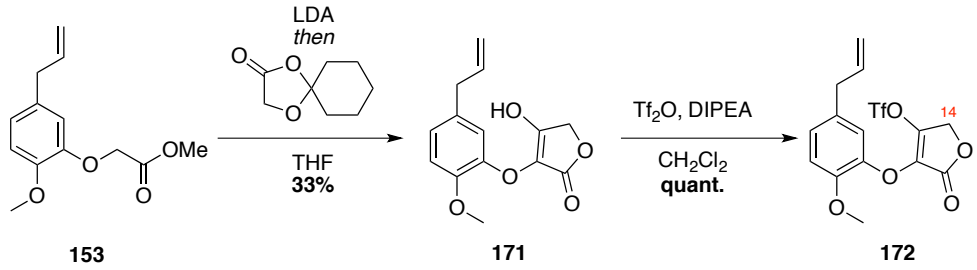
Scheme 3.18

Intermediate **167** was cyclised upon reacting with 2.1 equivalents of LiHMDS to afford tetronic acid **169** (Scheme 3.19).[62] We were unable to purify the crude acid, therefore it was used as crude under the triflation conditions to give triflate **170**. Triflate **170** was suitably stable to be purified by silica gel chromatography, giving 72% isolated yield over two steps.



Scheme 3.19

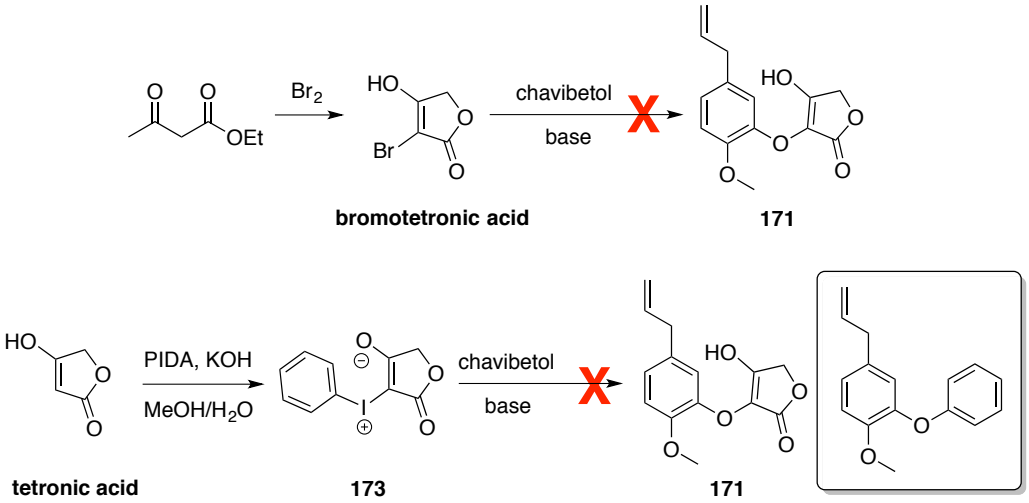
In order to provide different substrates for the optimisation of cross-coupling reactions, the syntheses of derivatives of triflate **170** were investigated. Trifate **172**, with *C*14 at alcohol oxidation level, was synthesized from a two-step sequence from acetate **153** (Scheme 3.20).[63] However, this synthesis was highly inefficient, as the formation of tetronic acid **171** required an extra equivalent amount of deprotonated starting material to quench acid **171** which was formed *in situ*.



Scheme 3.20

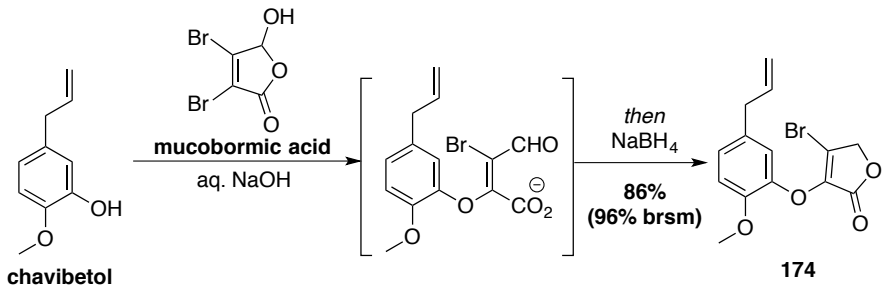
More economic routes were investigated, where in bromotetronic acid was synthesised by reacting ethyl acetoacetate with bromine (Scheme 3.21).[64] However, treating the acid with

chavibetol in the presence of base did not afford acid **171**, presumably due to the low reactivity of the negatively charged bromide towards substitution by phenoxide anion. Iodonium salts are known for their high reactivity in substitution reactions due to the hyper leaving group iodobenzene.[65] Inner salt **173** was prepared by reacting tetronic acid with PIDA in the presence of base. However, treating inner salt **173** with chavibetol gave exclusively the unwanted biaryl ether.



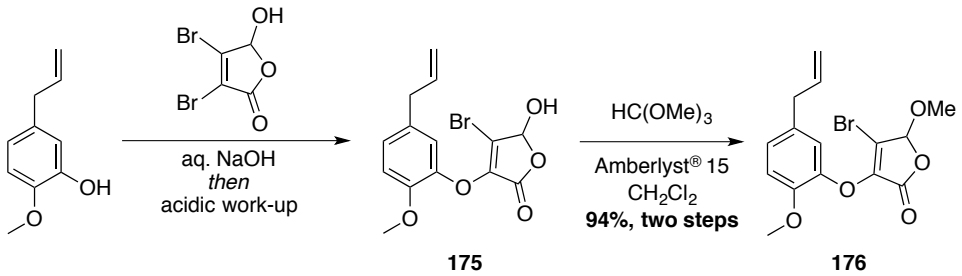
Scheme 3.21

The limited success of preparation of triflate **172** led us to explore the synthesis of bromide **174**. The bromide derivate was prepared *via* a modified procedure reported by Smyth *et al.* (Scheme 3.22).[66] Treatment of chavibetol with an excess of mucobromic acid in the presence of aqueous sodium hydroxide led to effective 1,4-addition-elimination with exclusive displacement of the bromide beta to the masked aldehyde. *In situ* reduction of the resultant aldehyde and sequential work-up with aqueous citric acid afforded bromide **174** in 86% overall yield on gram scale (plus 10% recovered chavibetol).



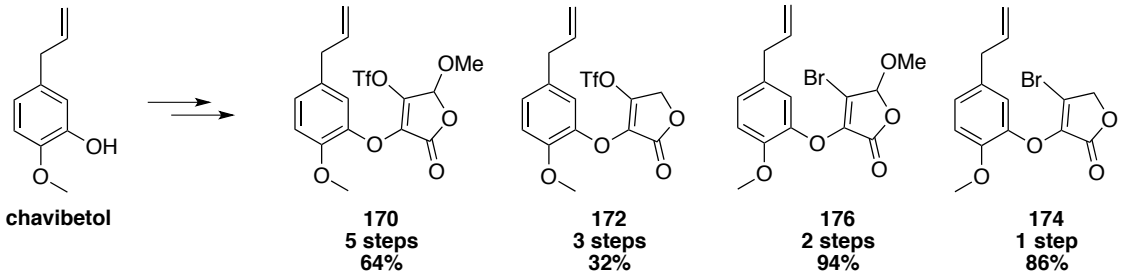
Scheme 3.22

Similar procedure was applied to the synthesis of bromide **176**. Instead of reducing the aldehyde intermediate, hemiacetal **175** was isolated as crude product and methylated with orthoester in the presence of Amberlyst® 15 to give bromide **176** in excellent yield.



Scheme 3.23

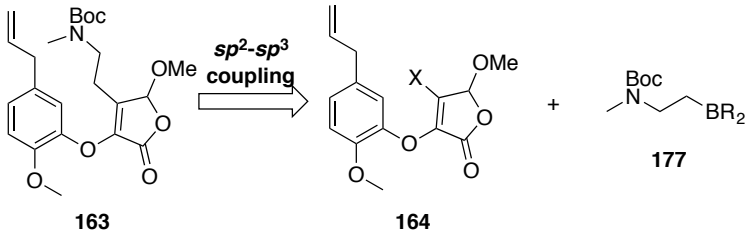
Thus, four substrates for the cross-coupling reactions were prepared on gram scale from chavibetol with variable yields (Scheme 3.24). Generally, bromides were more practically accessible, because of the short preparative sequences, higher yields, and the readily available starting materials.



Scheme 3.24

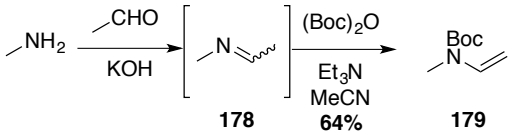
3.3.2 The sp^2-sp^3 Coupling

Suzuki coupling is one of the most important methods for the construction of carbon-carbon bonds. The synthesis of butenolide **163** requires an sp^2-sp^3 coupling between halide **164** and boron reagent **177**. However, sp^2-sp^3 coupling reactions can be particularly challenging, requiring special catalytic system or boron reagent to achieve high yield.



Scheme 3.25

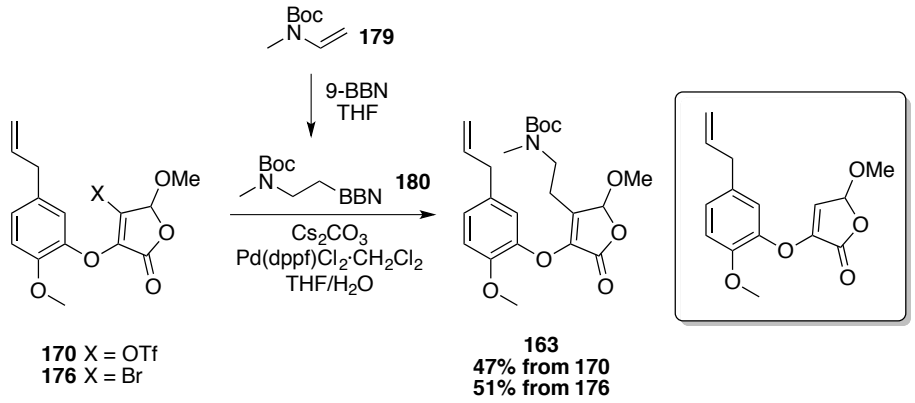
We realised **177** could be formed by hydroboration of protected enamine **179** with 9-BBN. The preparation of enamine **178** was achieved on gram scale *via* a two-pot sequence described by Bach *et al.* (Scheme 3.26)[67].



Scheme 3.26

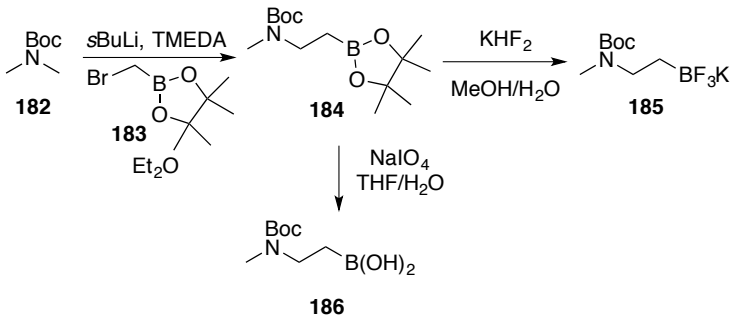
Treating enamine **179** with 9-BBN in THF gave borane **180** which was used directly as a solution in THF for the cross-coupling reaction (Scheme 3.27). This sp^2-sp^3 coupling was catalysed by Pd(dppf)Cl_2 in the presence of cesium carbonate in a THF/H_2O mixture, as described by Suzuki *et al.*.[68] The dppf ligand is known for its large bite angle, which is believed to provide a more favourable ratio of rate constants for reductive elimination versus

β-hydride elimination.[69] After complete conversion of triflate **170** as indicated by TLC, the reaction afforded butenolide **163** in 47% yield with the formation of about 30% of the dehalogenated product. Subjecting bromide **176** under the same conditions resulted in slight higher yield with similar level of dehalogenation.



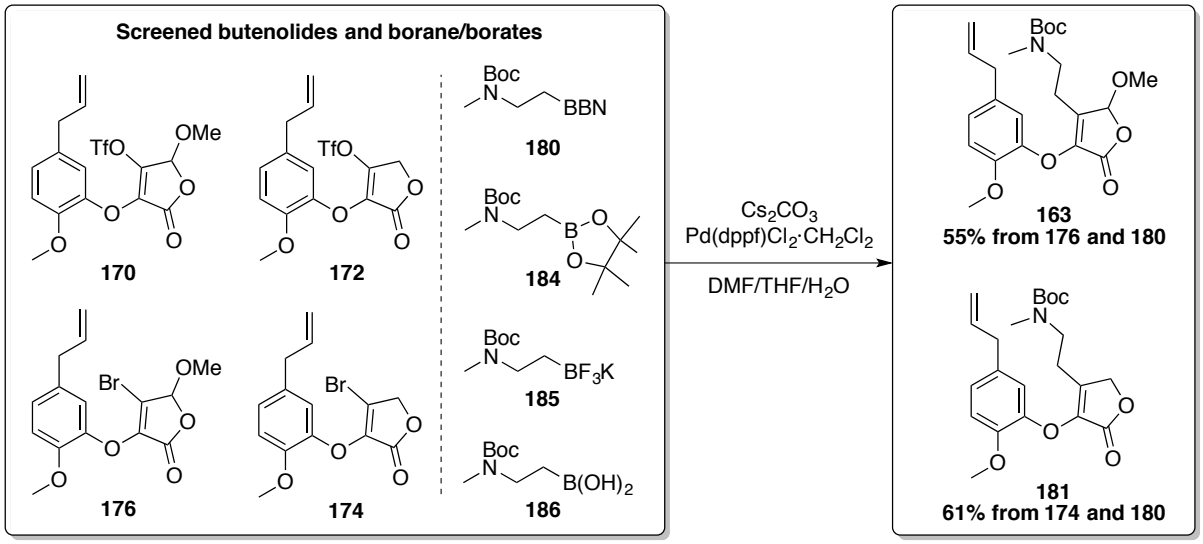
Scheme 3.27

In order to conduct a comprehensive screening of the coupling conditions, derivatives of the boron reagent, including pinacol ester **184**, trifluoroborate **185**,[70] and boronic acid **186**, were prepared (Scheme 3.28). All of these reagents were stable enough to be purified by recrystallisation or silica gel chromatography and proved to be indefinitely stable at room temperature.



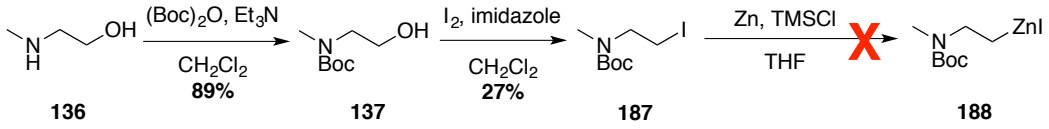
Scheme 3.28

The challenging sp^2-sp^3 cross-coupling required extensive experimentation to discover the optimum conditions. We found catalytic $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ in the presence of cesium carbonate in an aqueous DMF/THF mixture at 40 °C (Scheme 3.29, see Appendices for details) was optimal. The conditions afforded the required butenolide **163** and **181** in 55% and 61% yield, respectively.



Scheme 3.29

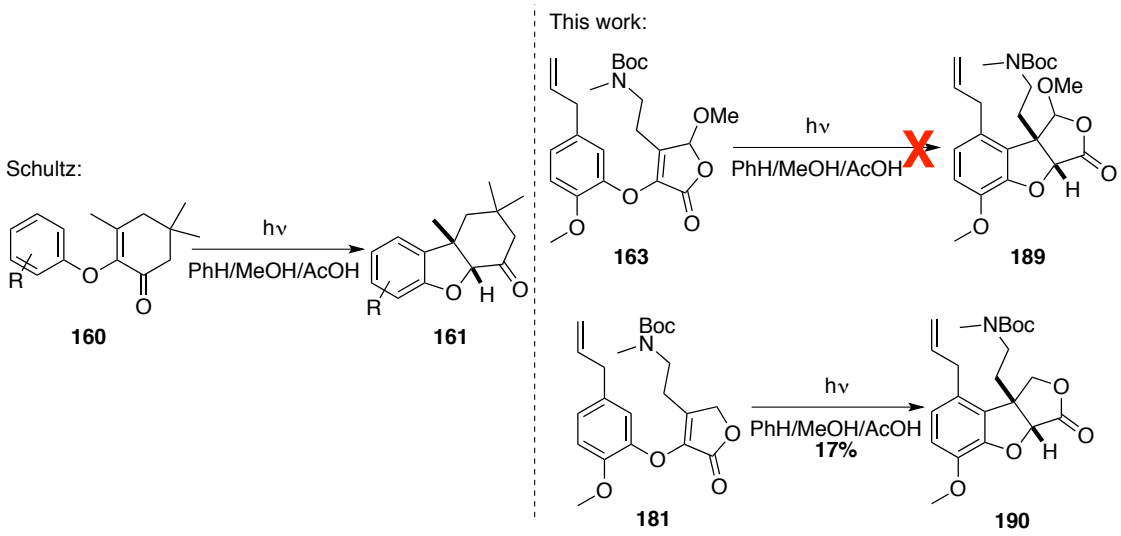
In addition, we also investigated a potential Negishi coupling approach to the butenolides. Iodide **187** was prepared from 2-(methylamino)ethanol by a sequential *N*-protection and Appel reaction (Scheme 3.30). Unfortunately, the organozinc species formed from iodide **187** readily decomposed at room temperature, thus we were unable to test the Negishi coupling on our substrates.



Scheme 3.30

3.3.3 The Photocyclisation

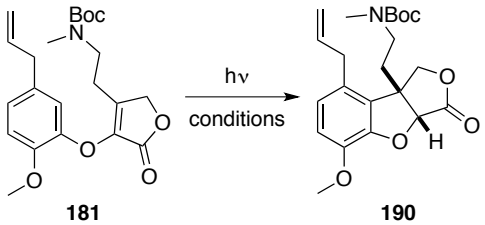
With the butenolides **163** and **181** in hand, we investigated the photocyclisation, key to accessing the benzofuran moiety of morphine (Scheme 3.31). Initial attempts of applying our substrates under the photocyclisation conditions described by Schultz led to a complex reaction mixture for butenolide **163**.[53] Fortunately, we observed cyclisation of butenolide **181**, giving exclusively the *cis*-fused 5,5-system, but in poor yield.



Scheme 3.31

To optimise the photocyclisation, we first screened the effect of additives. Initial investigations suggested addition of photosensitisers to the reaction mixture had a negative effect on the reaction yields (Entry 1 & 2, Scheme 3.32). It is known that Lewis acids can cause bathochromic shift of enones and change the cyclisation wavelength of the substrate, such method has been demonstrated by Bach *et al.* on the enantioselective Lewis acid-catalysed intramolecular enone [2+2] photocycloaddition reactions.[71] Unfortunately, our substrate suffered from cleavage of the *tert*-butoxycarbonyl group upon addition of Brønsted/Lewis acids (Entry 3-7). Interestingly, irradiating butenolide **181** in a

benzene/methanol mixture without any additive offered higher yield (Entry 8).

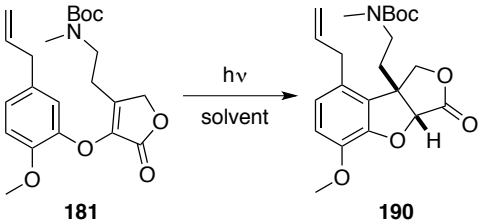


181 190

Entry	Conditions	Yield
1	PhCOMe, PhH/MeOH	< 5%
2	Ph_2CO, PhH/MeOH	< 5%
3	$EtAlCl_2$, PhH/MeOH	< 5%
4	$ZnCl_2$, PhH/MeOH	< 5%
5	$Cu(OTf)_2$, PhH/MeOH	< 5%
6	$Bi(OTf)_3$, PhH/MeOH	< 5%
7	TFA, PhH/MeOH	< 5%
8	PhH/MeOH	21%

Scheme 3.32

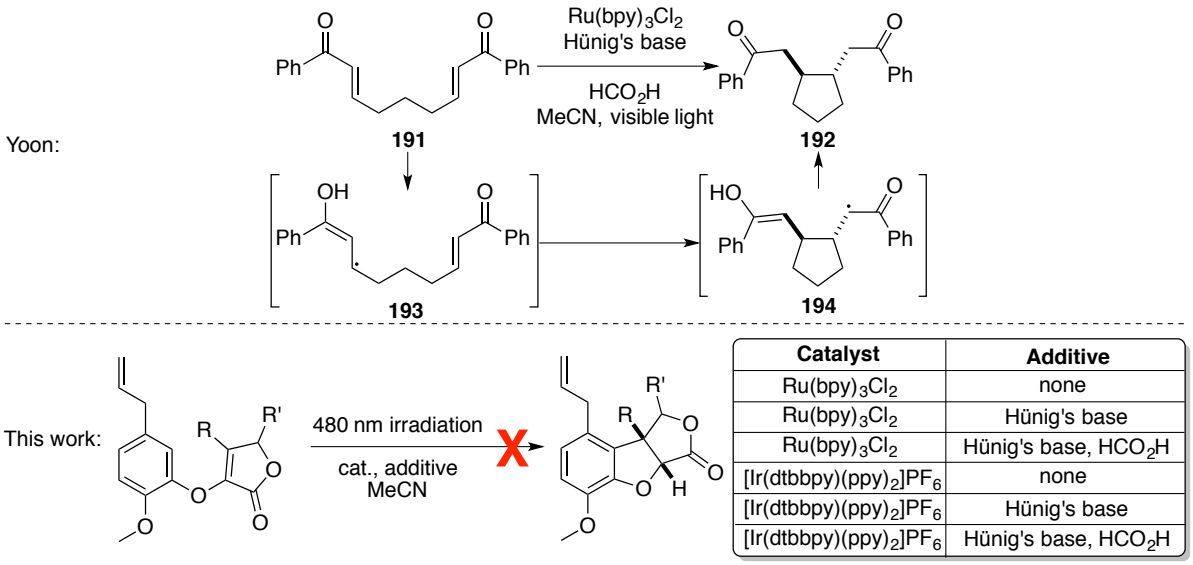
Solvent screening (Scheme 3.33) revealed that: Aprotic environments led to severe decomposition (Entry 1-4). Among mixed solvent systems (1:1, v/v), hexafluoroisopropanol in benzene gave the highest yield, possibly due to its mild acidity (Entry 5-9). Using only hexafluoroisopropanol as the solvent resulted in lower yield (Entry 9 & 10). After an extensive investigation we were able to demonstrate that a mixed dichloroethane/hexafluoroisopropanol solvent system was optimal (Entry 11-15), conditions led to the formation of benzofuran **190** in an isolated yield of 37% after 120 h of irradiation.



181 190

Entry	Solvent	Yield
1	PhH	< 5%
2	DCE	< 5%
3	MeCN	< 5%
4	$PhCF_3$	< 5%
5	PhH/EtOH	9%
6	PhH/IPA	12%
7	PhH/*t*BuOH	25%
8	PhH/CF_3CH_2OH	32%
9	PhH/HFIP	33%
10	HFIP	22%
11	HFIP/MeCN	17%
12	HFIP/dioxane	25%
13	HFIP/DMF	30%
14	HFIP/DMSO	32%
15	HFIP/DCE	37%

Scheme 3.33

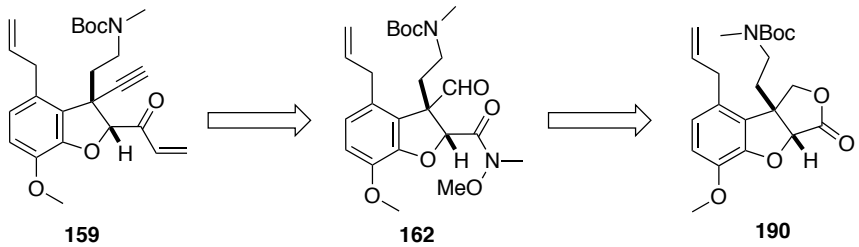


Catalyst	Additive
$Ru(bpy)_3Cl_2$	none
$Ru(bpy)_3Cl_2$	Hünig's base
$Ru(bpy)_3Cl_2$	Hünig's base, HCO_2H
$[Ir(dtbbpy)(ppy)_2]PF_6$	none
$[Ir(dtbbpy)(ppy)_2]PF_6$	Hünig's base
$[Ir(dtbbpy)(ppy)_2]PF_6$	Hünig's base, HCO_2H

Scheme 3.34

Yoon *et al.* have demonstrated cyclisations of enones by a radical pathway under photoredox conditions (Scheme 3.34).[72] One major advantage of this photoredox catalysis is its easy reaction setup and mild reaction conditions, in comparison to the UV irradiation, which is considerably more dangerous and requires a powerful 500 W mercury arc lamp. Unfortunately, after screening several catalytic photoredox systems, no reactivity was observed for any of our substrates.

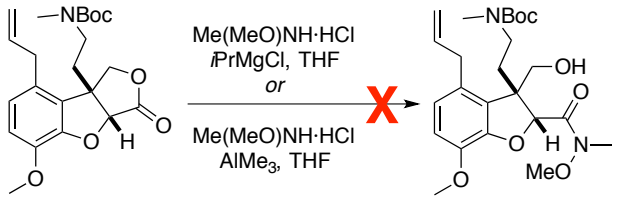
3.3.4 Synthesis of the Cascade Precursor



Scheme 3.35

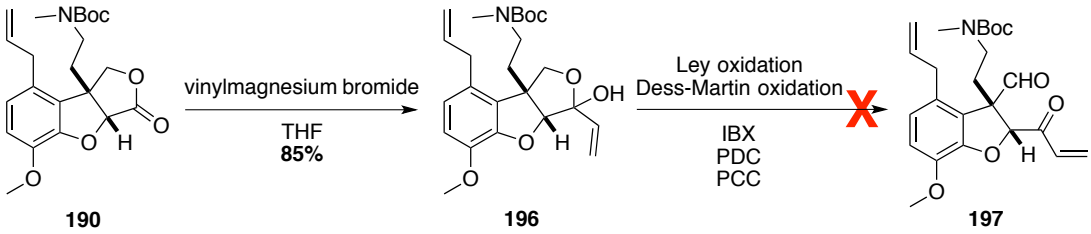
The preparation of cascade precursor **159** required a series of functional group

transformations of the lactone moiety of benzofuran **190** (Scheme 3.35). We envisaged that amidation of lactone **190** with Weinreb amine followed by oxidation would give aldehyde **162**, which could be converted to precursor **159** bearing ene-yne-ene system, by a sequential Ohira-Bestmann alkynylation[60] and Grignard reaction.



Scheme 3.36

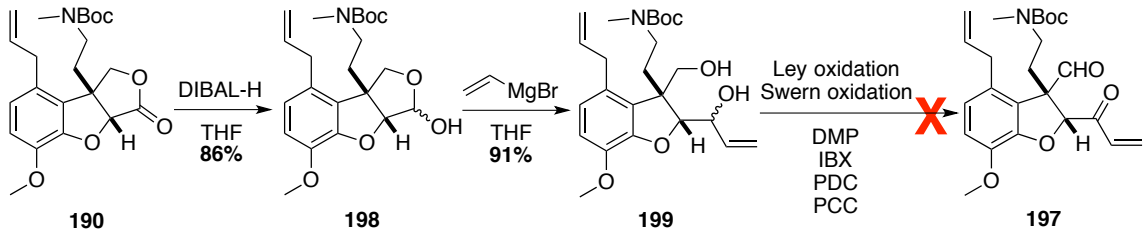
Subjecting lactone **190** to standard Weinreb amidation conditions appeared to afford the desired amide by TLC analysis (Scheme 3.36). However, the amide spontaneously underwent lactonisation upon aqueous work-up. *In situ* oxidation of the alcohol intermediate was attempted but failed to yield the desired aldehyde **162**.



Scheme 3.37

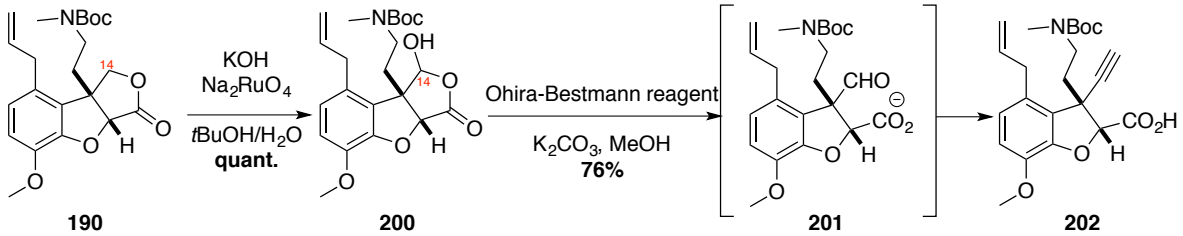
It was then decided to change the order of the transformations. Starting with the Grignard addition to lactone **190**, hemiacetal **196** was formed in good yield (Scheme 3.37). ^{1}H-NMR analysis showed this intermediate existed exclusively in hemiacetal form as indicated by the absence of aldehyde proton signal in $CDCl_3$, which could be caused by the Thorpe-Ingold

effect.[73] This offered a potential explanation to the Grignard reaction of lactone **190** stopped at mono-addition stage. Unfortunately, for the same reason, oxidation of hemiacetal **196** could not be achieved to give aldehyde **197** after an extensive screening of oxidation conditions. We realised it was important to avoid carrying out reactions on these heavily substituted intermediates that could exist in an inert closed-ring form due to a potential Thorpe-Ingold effect.



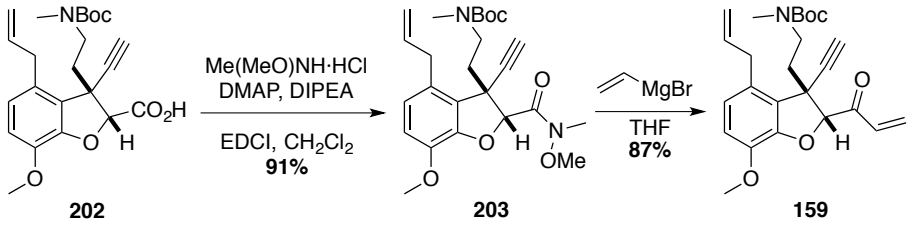
Scheme 3.38

Reduction of lactone **190** with DIBAL-H afforded hemiacetal **198**, which was followed by treatment with vinylmagnesium bromide to give diol **199** (Scheme 3.38). Simultaneous oxidation of the two hydroxyl groups of diol **199** is important, as hemiacetal formation will occur upon mono-oxidation. We expected a Swern oxidation[47] could facilitate the simultaneous dioxidation *via* an alkoxysulfonium intermediate. However, after a screening of different oxidation conditions, oxidation of diol **199** resulted in complex crude mixtures without the formation of aldehyde as indicated by ^{1}H-NMR analysis.



Scheme 3.39

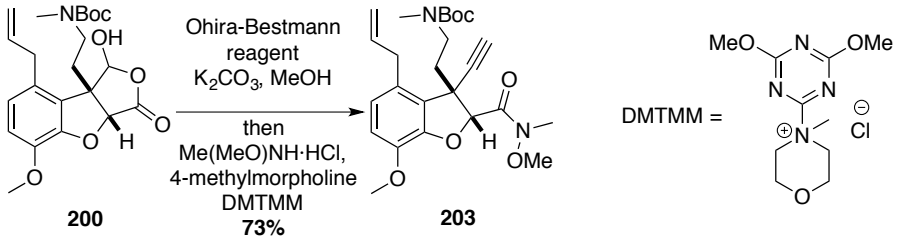
We then proposed that hemiacetal **200** with *C*14 as a masked aldehyde could undergo an Ohira-Bestmann reaction,[60] as the result of a preferred open ring form between hemiacetal **200** and carboxylate **201** in the presence of base (Scheme 3.39). Oxidation of *C*14 was achieved by using sodium ruthenate in aqueous base as described by Coates *et al.*.[74] As expected, alkynylation of aldehyde **201** successfully afforded alkyne **202** in 76% yield.



202 **203** **159**

Scheme 3.40

Crude carboxylic acid **202** was subjected to EDCI coupling conditions to afford Weinreb amide **203**, and following a Grignard addition, cascade precursor **159** was afforded in good yield (Scheme 3.40).



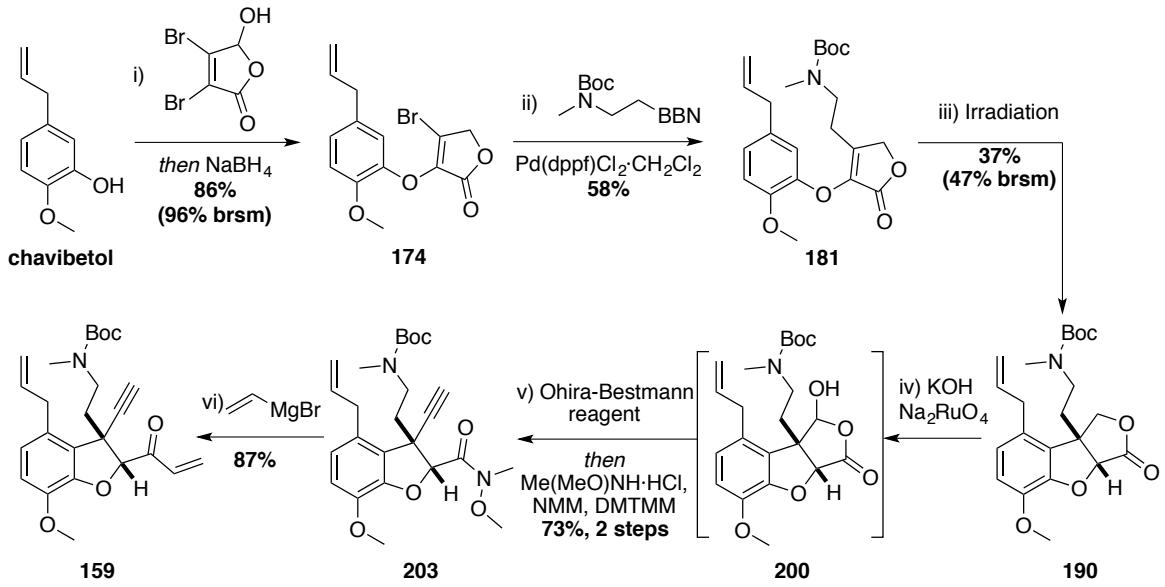
200 **203**

Scheme 3.41

As methanol could be used as the solvent in the preparation of Weinreb amides by using DMTMM as the coupling reagent,[75] combining the Ohira-Bestmann reaction and the amidation to save an aqueous work-up appeared feasible (Scheme 3.41). After completion of the alkynylation (monitored by LCMS), 4-methylmorpholine, Weinreb amine hydrochloride

salt, and DMTMM were successively added as described by Kunishima *et al.*.[75] Pleasingly, this led to the formation of Weinreb amide **203** in a competitive yield when compared with the two-step procedure.

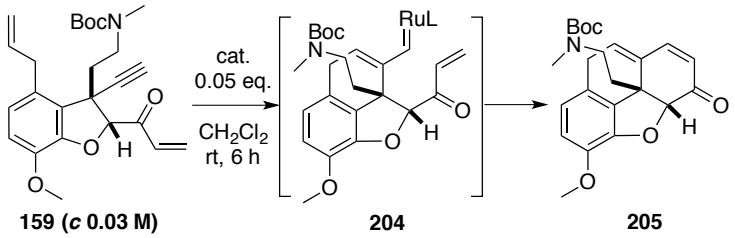
The heavily functionalised benzofuran **159** is the key intermediate for our cascade approach to the morphine skeleton. The current route offers a quick access to this intermediate through a six-step sequence from chavibetol in 12% yield on a hundred milligram scale (Scheme 3.42).



Scheme 3.42 Synthesis of the cascade precursor i) Mucobromic acid (5.0 eq.), aq. NaOH (9.5 eq.), 20 °C; then $NaBH_4$ (4.5 eq.), 0 °C. ii) *B*-alkyl-9-BBN reagent (1.2 eq.), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.1 eq.), Cs_2CO_3 (2.0 eq.), DMF/THF/H_2O, 40 °C. iii) High-pressure mercury vapor lamp irradiation with Pyrex filter, DCE/HFIP, 20 °C. iv) aq. KOH (20 eq.), *t*BuOH/H_2O, 20 °C ; then aq. Na_2RuO_4 (1.1 eq.), 50 °C. v) Dimethyl(diazomethyl)phosphonate (2.0 eq.), K_2CO_3 (5.0 eq.), MeOH, 20 °C; then Me(MeO)NH·HCl (6.0 eq.), NMM (6.0 eq.), DMTMM (4.0 eq.), 20 °C. vi) Vinylmagnesium bromide (4.0 eq.), THF, 0 °C.

3.4 The Cascade Reaction and Endgame

Treatment of cascade precursor **159** with 5 mol % of the most commonly used ruthenium catalysts in dichloromethane afforded tetracycle **205** (Scheme 3.43). The highest yield was observed when using the Hoveyda-Grubbs second-generation catalyst at ambient temperature.[76] It is likely that this transformation proceeds *via* reaction of the ruthenium alkylidene precatalyst with the allyl component of **159**, followed by an intramolecular reaction with the alkyne to give alkylidene intermediate **204**. Ring closing metathesis with the *α,β*-unsaturated ketone affords the tetracycle **205** as the sole product in this transformation.

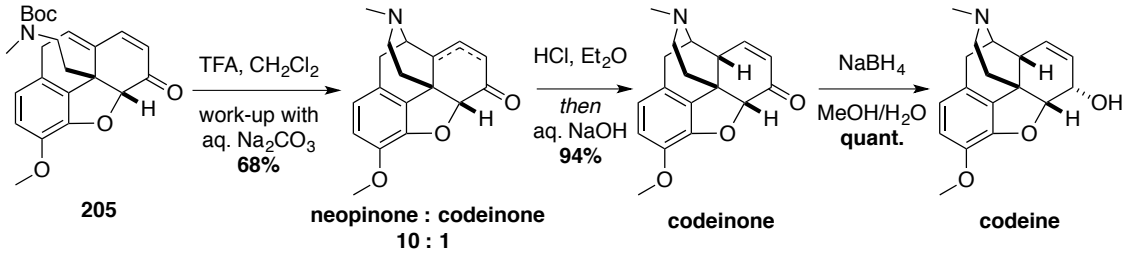


Catalyst	Yield
Grubbs I	89%
Grubbs II	87%
Hoveyda-Grubbs I	92%
Hoveyda-Grubbs II	94%
Hoveyda-Grubbs II (40 °C, 2 h)	90%

Scheme 3.43

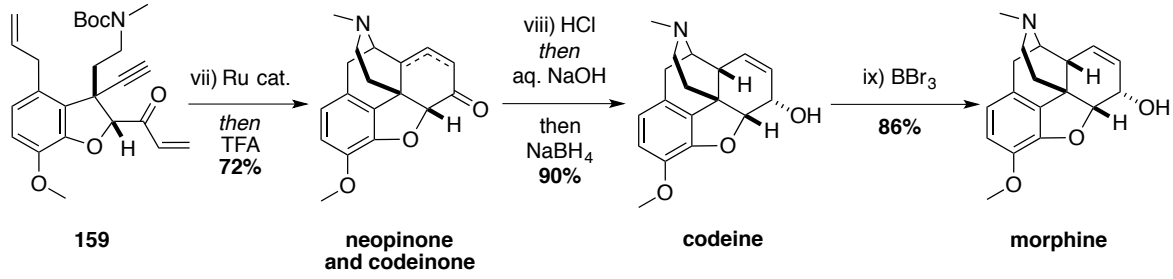
The pentacyclic skeleton was formed by a subsequent 1,6-addition through removal of the *tert*-butoxycarbonyl group with trifluoroacetic acid to afford an ammonium salt followed by free-basing with sodium carbonate to trigger the carbon–nitrogen bond formation. (Scheme 3.44). This afforded a 10:1 mixture of neopinone and codeinone that could be transformed into codeinone by treatment with anhydrous HCl in a mixture of dichloromethane and ether, using the method employed by Rapoport.[77] This reaction likely proceeds *via* the transient formation of a *β*-halo ketone followed by elimination on treatment with aqueous sodium hydroxide to afford the thermodynamically favoured product. Following the procedure described by Gates,[78] codeinone was reduced by the addition of sodium

borohydride to its methanolic solution and sequentially quenched by aqueous sodium hydroxide to give codeine in quantitative yield.



Scheme 3.44

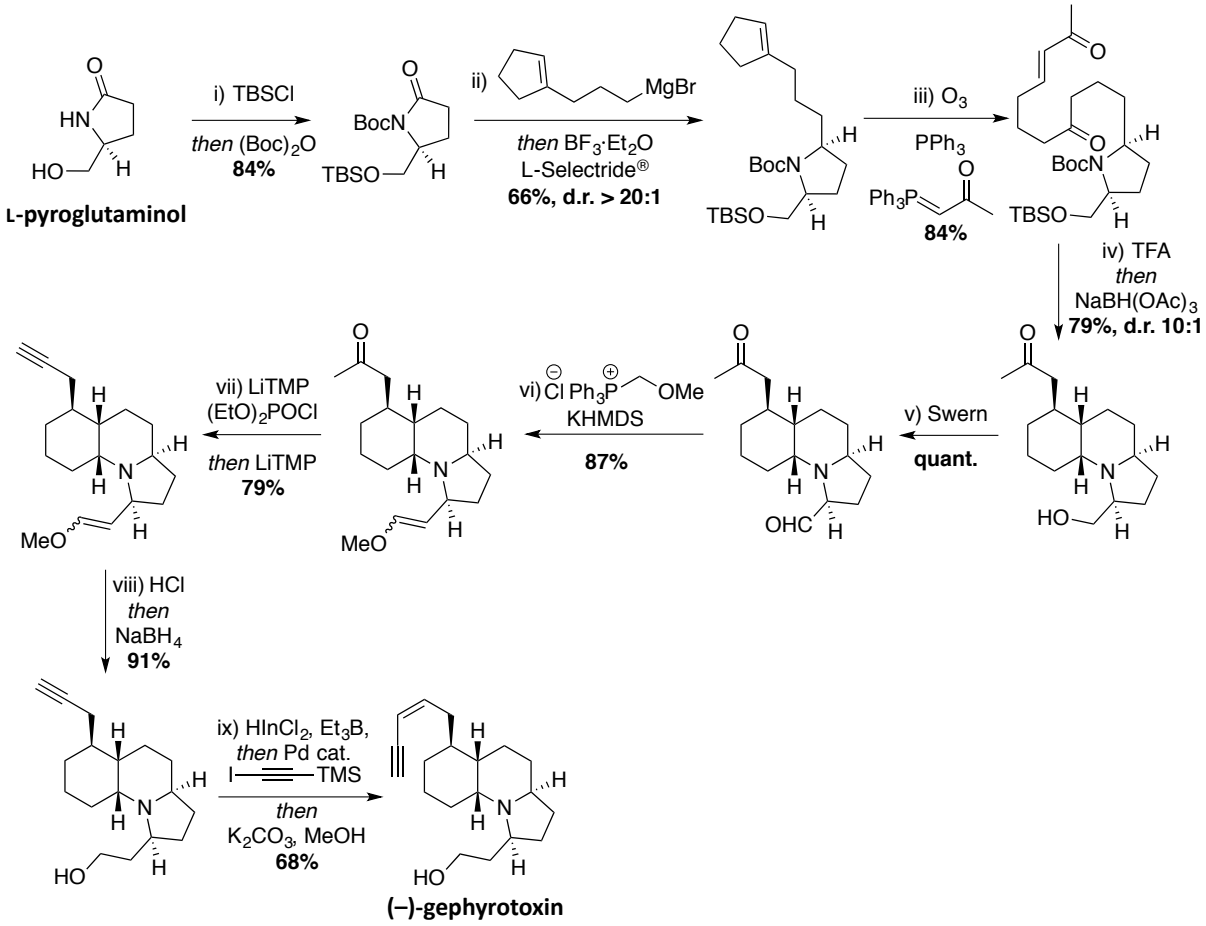
We revisited the four-step sequence from the cascade precursor to codeine and managed to combine these steps into a two-pot procedure (Scheme 3.45). Thereafter, demethylation of the *C*3 methyl ether with boron tribromide afforded our target molecule, morphine, in 86% yield.[79] The ^{1}H and ^{13}C NMR spectra of our synthetic material were identical to those reported for both natural and other synthetic materials.



Scheme 3.45 vii) Hoveyda–Grubbs second-generation catalyst (0.05 eq.), CH_2Cl_2, 20 °C; then TFA (40 eq.), 20 °C; then aq. Na_2CO_3(60 eq.), 20 °C. viii) HCl (4.0 eq.), Et_2O/CH_2Cl_2, 20 °C; then aq. NaOH (8.0 eq.), 20 °C ; then $NaBH_4$ (10 eq.), 20 °C. ix) BBr_3 (6.0 equiv), $CH_2Cl_2/CHCl_3$, 20 °C.

3. Summary

We have demonstrated a concise and efficient total synthesis of gephyrotoxin *via* a cascade approach. The absolute configuration of our synthetic material was confirmed by single crystal X-ray diffraction and is consistent with the structure originally proposed for the naturally isolated material. Key features of the synthesis are a diastereoselective nucleophilic cascade reaction and a hydroxyl-directed reduction to generate the tricyclic core with three new stereocentres in a single step.

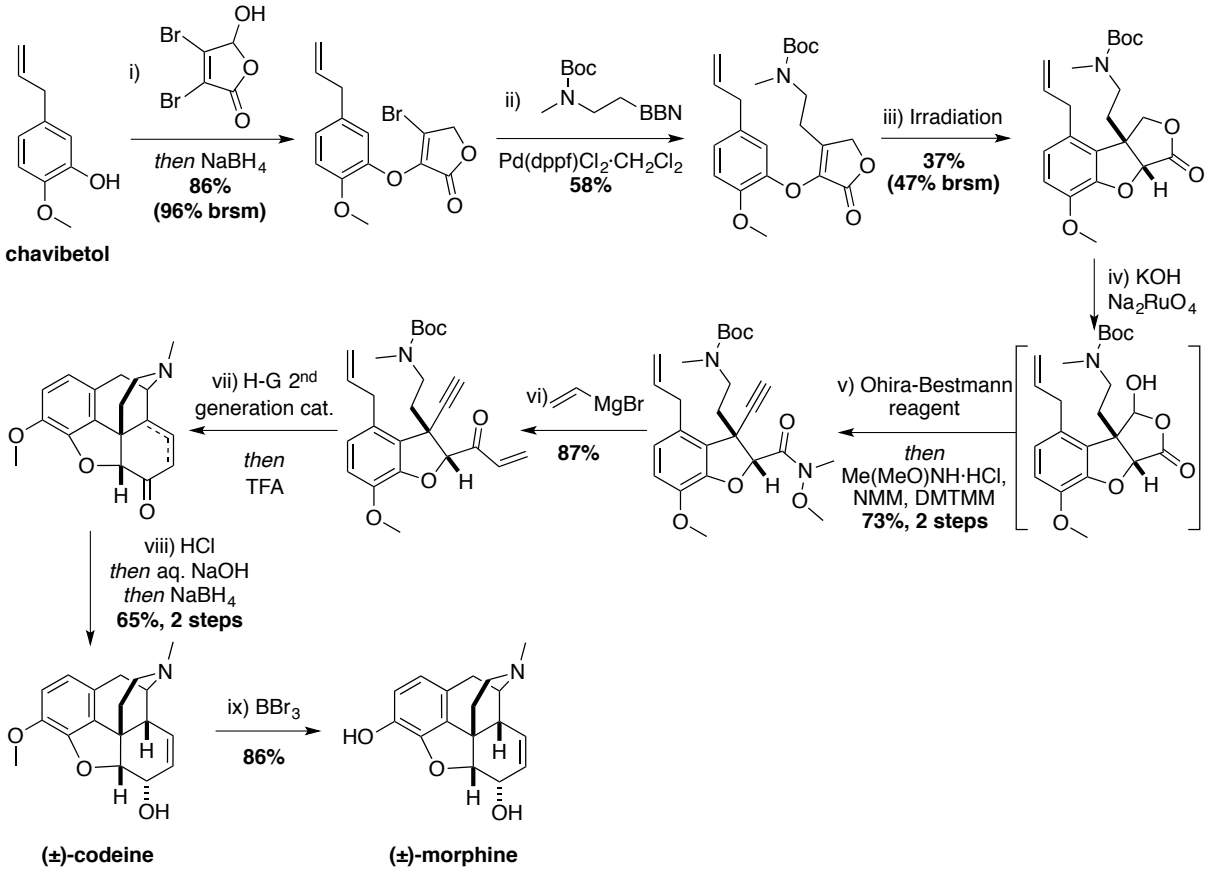


Scheme 3.1 Total synthesis of (–)-gephyrotoxin

Though the one-carbon homologation of the primary alcohol in this synthesis is limited by the currently available methodologies and is both redox and step inefficient, this approach still

compares well with other syntheses of gephyrotoxin: our synthesis offers rapid and stereoselective access to this class of natural products and may provide a more practical approach to decahydroquinoline-containing alkaloids.

In our total synthesis of morphine, on the other hand, a transition metal catalyzed ene-yne-ene ring closing metathesis cascade is applied, enabling a short and efficient approach to this structurally challenging alkaloid. This efficiency is achieved *via* the installation of key functional groups at an appropriate oxidation level, which minimizes late stage transformations and protecting group manipulations.



Scheme 3.2 Total synthesis of (±)-morphine

Currently, work within the Smith Group focuses on optimizing the photocyclisation step

applied in this synthesis with the aim of improving conversion and potentially achieving enantioselectivity. If accomplished, we hope that this will result in an even more efficient and scalable synthetic route.

The cascade shortcuts discussed in this thesis enable the most concise total syntheses of gephyrotoxin and morphine described to date. This clearly illustrates the unparalleled ability of cascade reactions to accomplish the rapid construction of molecular complexity.

5. References

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6. Experimental

6.1 General Information

Reactions requiring moisture-sensitive reagents were carried out in oven-dried glassware, under an atmosphere of argon (balloon pressure). Dichloromethane, diethyl ether, toluene, tetrahydrofuran and methanol were purified by filtration through activated alumina columns employing the method of Grubbs *et al*.[i] Water was purified by an Elix® UV-10 system. Reagents were used directly as supplied by major chemical suppliers, or following purification procedures described by Perrin and Armarego.[ii] Petroleum ether refers to the fraction of petroleum ether which boils in the range 40 – 60 ºC. Brine refers to a saturated aqueous solution of sodium chloride.

Silica gel chromatography was carried out using Merck Geduran® Silicagel (40 – 63 mm particle size). Analytical thin layer chromatography was carried out using pre-coated, aluminum backed plates (Merck Kieselgel 60 F254). Visualisation was achieved with ultraviolet irradiation (254 nm) and staining with basic permanganate.

NMR spectroscopy was carried out using Bruker Avance spectrometers in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference (^{1}H NMR: $CDCl_3$ 7.26 ppm, CD_3OD 3.31 ppm, C_6D_6 7.16 ppm, d_8-toluene 7.09, 7.01, 6.97, 2.08 ppm; ^{13}C NMR: $CDCl_3$ 77.16 ppm, CD_3OD 49.00 ppm, C_6D_6 128.06 ppm, d_8-toluene 137.48, 128.87, 127.96, 125.13, 20.43 ppm). Chemical shifts are quoted in ppm, based on appearance rather than interpretation. Signal patterns are indicated as: br, broad; s, singlet; d,

doublet; t, triplet; q, quartet; m, multiplet.

Infrared spectra (IR) samples were prepared as a neat film and were recorded using a Bruker Tensor 27 FTIR spectrometer using an ATR module.

Low resolution mass spectroscopy was carried out using ESI and was performed on a Micromass LCT Premier spectrometer. HRMS was carried out using Bruker MicroTOF and Micromass GCT spectrometers under ESI or FI conditions, respectively.

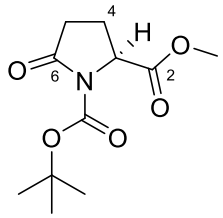
Analytical chiral HPLC was carried out using a Dionex UltiMate 3000 HPLC system comprising a Dionex LPG-3400A pump, WPS-3000SL autosampler and TCC-3000SD column compartment, and a Daicel Chiralpak column (0.46 cm × 25 cm), equipped with an appropriate guard column (0.4 cm × 1 cm).

Melting points were determined using a Reichert melting point apparatus and are uncorrected.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter and values are quoted [º mL g^{-1} dm^{-1}]. Concentrations are quoted in g/100 mL.

6.2 Synthetic Procedures

tert-Butyl (*S*)-2-(2-methoxy-2-oxoethyl)-5-oxopyrrolidine-1-carboxylate (61)



Thionyl chloride (0.570 mL, 7.85 mmol) was added to a solution of L-pyroglutamic acid (10.0 g, 77.5 mmol) in methanol (40 mL) at 0 ºC. After the addition, the mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was quenched by the addition of saturated aqueous sodium carbonate (20 mL) and then methanol was removed under reduced pressure. The mixture was extracted with dichloromethane (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated to give crude methyl L-pyroglutamate (10.5 g, 73.6 mmol) as a light yellow oil which was redissolved in dichloromethane (200 mL) and cooled to 0 ºC before 4-(dimethylamino)- pyridine (0.895 g, 7.32 mmol), triethylamine (11.0 mL, 78.9 mmol) and di-*tert*-butyl dicarbonate (16.9 g, 77.4 mmol) were added sequentially. The mixture was warmed to room temperature and stirred overnight. Hydrochloric acid (1.0 M, 120 mL) was added and the organic layer was separated, washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give pyrrolidinone **61** (15.0 g, 84%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (dd, *J* = 9.4, 3.0 Hz, 1H, *H*3), 3.78 (s, 3H, OCH_3), 2.63

(dt, J = 17.5, 9.8 Hz, 1H, $H5_a$), 2.48 (ddd, J = 17.5, 9.4, 3.6 Hz, 1H, $H5_b$), 2.32 (dq, J = 13.4, 9.6 Hz, 1H, $H4_a$), 2.03 (ddt, J = 13.4, 9.6, 3.3 Hz, 1H, $H4_b$), 1.49 (s, 9H, *t*Bu)

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (*C*6), 172.0 (urethane), 149.5 (*C*2), 83.8 (*t*Bu), 59.0 (*C*3), 52.7 (O*C*H$_3$), 31.3 (*C*5), 28.1 (*t*Bu), 21.7 (*C*4)

IR (film, cm^{-1}) ν_{max} 1790 (C=O), 1747 (C=O) 1715 (C=O)

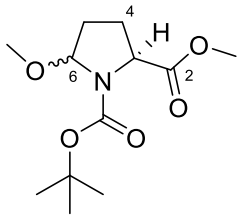
MS (ESI) 266.1 $[M+Na]^+$

MP: 68 – 69 ºC

$[\alpha]_D^{20}$ −29.8 (*c* 1.0, $CHCl_3$)

These data are consistent with that previously published for this compound.[iii]

***tert*-Butyl (5*S*)-2-methoxy-5-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (65)**



Super-Hydride® (1.0 M solution in tetrahydrofuran, 20.0 mL, 20.0 mmol) was added to a solution of pyrrolidinone **61** (3.00 g, 12.3 mmol) in tetrahydrofuran (90 mL) at −78 ºC. After stirring for 2 h at −78 ºC, saturated aqueous sodium bicarbonate (15 mL) was added and the mixture was allowed to warm to 0 ºC over 15 min before the addition of aqueous hydrogen peroxide (30 wt. %, 2.25 mL, 22.0 mmol). The mixture was warmed to room temperature and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (4 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, concentrated and redissolved in methanol (75 mL). *p*-Toluenesulfonic acid monohydrate (250 mg, 1.32 mmol) was added and the solution was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate (20 mL) was added to the solution before the removal of methanol under reduced pressure. The resulting suspension was extracted with diethyl ether (3 × 20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:3) to give hemiaminal **65** (2.71 g, 80%) as a colourless oil (~1:1 mixture of *cis*/*trans* diastereomers).

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 5.32 (br, 0.5H, *H*6), 5.20 (br, 0.5H, *H*6), 4.23 (br, 1H, *H*3), 3.45 – 3.35 (m, 6H, OCH_3 and CO_2CH_3), 2.25 (br, 0.5H, $H4_a$), 2.06 (ddt, *J* = 12.4,

9.5, 6.2 Hz, 0.5H, *H*4$_a$), 1.92 (dtd, *J* = 12.3, 8.0, 1.3 Hz, 0.5H, *H*4$_b$), 1.84 (br, 0.5H, *H*4$_b$), 1.71 (dd, *J* = 12.5, 7.0 Hz, 0.5H, *H*5), 1.66 – 1.61 (m, 1.5H, H5), 1.49 (s, 9H, *t*Bu)

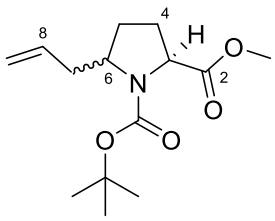
^{13}C NMR (125 MHz, d$_8$-toluene, 363 K) δ 172.5 (urethane), 154.1 (*C*2), 89.7 (*C*6), 88.9 (*C*6), 79.9 (*t*Bu), 59.8 (*C*3), 59.6 (O*C*H$_3$), 55.0 (O*C*H$_3$), 51.1 (CO$_2$*C*H$_3$), 32.7 (*C*5), 30.9 (*C*5), 28.3 (*t*Bu) 28.3 (*C*4), 27.8 (*C*4)

IR (film, cm^{-1}) ν_{max} 1749 (C=O), 1706 (C=O)

MS (ESI) 282.1 [M+Na]$^+$

These data are consistent with that previously published for this compound.[iv]

***tert*-Butyl (5*S*)-2-allyl-5-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (66)**



Boron trifluoride diethyl etherate (1.80 mL, 14.6 mmol) was added to a solution of hemiaminal **65** (3.30 g, 12.1 mmol) and allyltrimethylsilane (9.00 mL, 56.6 mmol) in diethyl ether (65 mL) at −40 ºC. After stirring for 15 min at the same temperature, the solution was allowed to warm to room temperature and stirred for 1 h before the addition of saturated aqueous sodium bicarbonate (30 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:10) to give pyrrolidine **66** (2.65 g, 77%) as a colourless oil (2:1 mixture of *cis*/*trans* diastereomers).

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 5.81 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 0.67H, major *H*8), 5.72 – 5.62 (m, 0.33H, minor *H*8), 5.05 − 4.93 (m, 2H, *H*9), 4.23 (br, 1H, *H*3), 4.08 (br, 0.33H, minor *H*6), 3.85 (br, 0.67H, major *H*6), 3.46 (s, 2H, major OCH_3), 3.44 (s, 1H, minor OCH_3), 2.78 (br, 0.67H, major *H*7$_a$), 2.52 (br, 0.33H, minor *H*7$_a$), 2.31 − 2.24 (m, 0.67H, major *H*7$_b$), 2.09 (br, 0.33H, minor *H*7$_b$), 1.91 (br, 0.67H, major *H*4$_a$), 1.83 − 1.72 (m, 1.33H, minor *H*4$_a$ and *H*4$_b$), 1.68 − 1.51 (m, 2H, *H*5), 1.42 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 173.2 (urethane), 153.7 (*C*2), 136.0 (major *C*8),

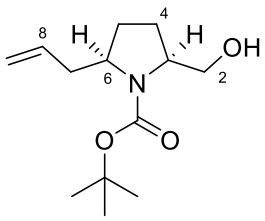
135.6 (minor *C*8), 116.7 (minor *C*9), 116.4 (major *C*9), 79.3 (broad, *t*Bu), 60.4 (broad, *C*6), 58.5 (major *C*3), 58.0 (minor *C*3), 51.1 (OCH_3), 39.2 (broad, *C*7), 29.4 (broad, *C*4), 28.6 (broad, *C*5), 28.4 (*t*Bu)

IR (film, cm^{-1}) ν_{max} 1751 (C=O), 1698 (C=O)

MS (ESI) 292.1 $[M+Na]^+$

These data are consistent with that previously published for this compound.[iv]

***tert*-Butyl (2*R*,5*S*)-2-allyl-5-(hydroxymethyl)pyrrolidine-1-carboxylate (67)**



Lithium borohydride (2.0 M solution in tetrahydrofuran, 16.2 mL, 32.4 mmol) was added to a solution of pyrrolidine **66** (2:1 mixture of *cis*/*trans* diastereomers, 2.20 g, 7.76 mmol) in tetrahydrofuran (65 mL) at 0 ºC, followed by the addition of methanol (9 mL) and then the mixture was stirred at the same temperature for 30 min. The mixture was then allowed to warm to room temperature and stirred for 3 h before being quenched with water (50 mL). Tetrahydrofuran was removed under reduced pressure and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (diethyl ether/dichloromethane 1:6) to give alcohol **67** (1.20 g, 96% based on *cis*-**66**) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 − 5.68 (m, 1H, *H*8), 5.08 − 5.01 (m, 2H, *H*9), 4.07 (br, 1H, O*H*), 3.96 − 3.87 (m, 2H, *H*3 and *H*6), 3.67 (dd, *J* = 11.2, 2.5 Hz, 1H, $H2_a$), 3.53 (dd, *J* = 11.2, 7.7 Hz, 1H, $H2_b$), 2.36 (br, 1H, $H7_a$), 2.17 − 2.08 (m, 1H, $H7_b$), 2.02 − 1.93 (m, 1H, $H4_a$), 1.90 − 1.79 (m, 1H, $H5_a$) 1.72 − 1.64 (m, 1H, $H5_b$), 1.57 (br, 1H, $H4_b$), 1.47 (s, 9H, *t*Bu)

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (urethane), 135.1 (*C*8), 117.3 (*C*9), 80.5 (*t*Bu), 68.3 (*C*2), 61.5 (*C*6), 58.8 (*C*3), 39.8 (*C*7), 28.5 (*t*Bu), 28.5 (*C*5), 26.9 (*C*4)

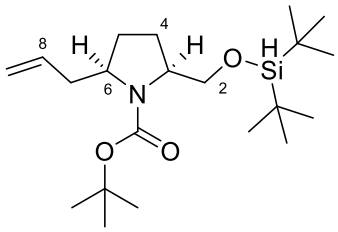
IR (film, cm^{-1}) ν_{max} 3410 (broad, O–H), 2974, 1691, 1666

MS (ESI) 264.2 $[M+Na]^+$

$[\alpha]_D^{20}$ +5.9 (*c* 1.0, $CHCl_3$)

These data are consistent with that previously published for this compound.[v]

tert-Butyl (2*R*,5*S*)-2-allyl-5-(((di-_tert_-butylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (60)



A solution of di-*tert*-butylchlorosilane (1.04 mL, 5.10 mmol) in tetrahydrofuran (8 mL) was added dropwise to a solution of alcohol **67** (1.00 g, 4.15 mmol) and imidazole (0.580 g, 8.52 mmol) in tetrahydrofuran (36 mL) at room temperature. The cloudy mixture was heated at reflux for 2 h and then the solvent was removed under reduced pressure. The residue was partitioned between diethyl ether (20 mL) and water (20 mL), and then the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 15 mL) and the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:20) to give silyl ether **60** (1.52 g, 95%) as a colourless oil.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 5.74 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H, *H*8), 5.05 − 4.96 (m, 2H, *H*9), 4.18 (s, 1H, Si*H*), 4.04 (dd, *J* = 9.5, 3.7 Hz, 1H, $H2_a$), 3.96 − 3.91 (m, 1H, *H*3), 3.86 − 3.80 (m, 1H, *H*6), 3.73 (dd, *J* = 9.5, 7.5 Hz, 1H, $H2_b$), 2.67 − 2.60 (m, 1H, $H7_a$), 2.20 − 2.13 (m, 1H, $H7_b$), 1.97 − 1.89 (m, 1H, $H4_a$), 1.74 − 1.52 (m, 3H, $H4_b$ and *H*5), 1.46 (s, 9H, *t*Bu (Boc)), 1.06 (s, 9H, *t*Bu (silyl ether)), 1.05 (s, 9H, *t*Bu (silyl ether))

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 154.6 (urethane), 135.9 (*C*8), 116.4 (*C*9), 78.9 (*t*Bu

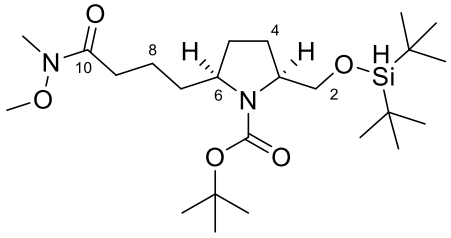
(Boc)), 68.8 (*C*2), 60.4 (*C*3), 58.8 (*C*6), 40.2 (*C*7), 29.0 (*C*4), 28.6 (*t*Bu (Boc)), 27.5 (*t*Bu (silyl ether)), 27.1 (*C*5), 20.2 (*t*Bu (silyl ether))

IR (film, cm^{-1}) ν_{max} 2929, 2086 (Si–H), 1695 (C=O)

HRMS (ESI) calcd for $C_{21}H_{42}NO_3Si$ $[M+H]^+$ 384.2929, found 384.2920

$[\alpha]_D^{20}$ −22.0 (*c* 1.2, EtOH)

***tert*-Butyl (2*S*,5*S*)-2-(((di-*tert*-butylsilyl)oxy)methyl)-5-(4-(methoxy(methyl)amino)-4-oxobutyl) pyrrolidine-1-carboxylate (59)**



N-Methoxy-*N*-methylacrylamide (0.903 g, 7.82 mmol) was added to a solution of silyl ether **60** (0.500 g, 1.30 mmol) and Hoveyda-Grubbs 2nd generation catalyst (40.0 mg, 63.8 μmol) in dichloromethane (6 mL). After stirring at room temperature overnight, the solvent and the remaining acrylamide were removed under reduced pressure. The crude residue was dissolved in acetonitrile (15 mL) and palladium on carbon (60.0 mg, 10 wt. % loading) was added. The mixture was stirred under an atmosphere of hydrogen for 4 h then filtered through a short plug of Celite®. The filter cake was washed with dichloromethane (3 × 10 mL) and the filtrates were concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3) to give amide **59** (0.528 g, 86%) as a colourless oil.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 4.18 (s, 1H, Si*H*), 4.06 (dd, *J* = 9.4, 3.7 Hz, 1H, *H*2$_a$), 3.97 – 3.90 (m, 1H, *H*3), 3.84 – 3.77 (m, 1H, *H*6), 3.77 – 3.69 (m, 1H, *H*2$_b$), 3.23 (s, 3H, OC*H*$_3$), 2.91 (s, 3H, NC*H*$_3$), 2.35 (t, *J* = 7.4 Hz, 2H, *H*9), 1.97 – 1.88 (m, 2H, *H*4$_a$ and *H*7$_a$), 1.77 – 1.63 (m, 4H, *H*4$_b$, *H*5$_a$ and *H*8), 1.55 – 1.48 (m, 1H, *H*5$_b$), 1.47 (s, 9H, *t*Bu (Boc)), 1.41 – 1.33 (m, 1H, *H*7$_b$), 1.06 (s, 9H, *t*Bu (silyl ether)), 1.05 (s, 9H, *t*Bu (silyl ether))

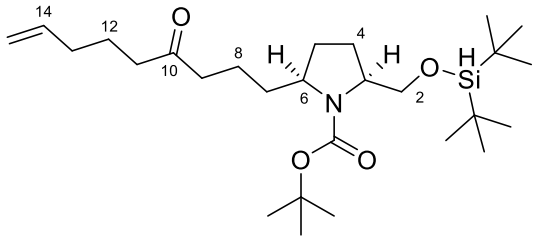
^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 174.2 (*C*10), 154.8 (urethane), 78.8 (*t*Bu (Boc)), 68.8 (*C*2), 60.6 (O*C*H$_3$), 60.3 (*C*3), 59.0 (*C*6), 36.1 (*C*7), 32.3 (N*C*H$_3$), 32.1 (*C*9), 29.7 (*C*4), 28.7 (*t*Bu (Boc)), 27.5 (*t*Bu (silyl ether)), 27.4 (*C*5), 21.7 (*C*8), 20.2 (*t*Bu (silyl ether))

IR (film, cm^{-1}) ν_{max} 2931, 2085 (Si–H), 1692 (C=O)

HRMS (ESI) calcd for $C_{24}H_{49}N_2O_5Si$ $[M+H]^+$ 473.3405, found 473.3393

$[\alpha]_D^{20}$ −18.3 (*c* 1.1, EtOH)

***tert*-Butyl (2*S*,5*S*)-2-(((di-*tert*-butylsilyl)oxy)methyl)-5-(4-oxonon-8-en-1-yl)pyrrolidine-1-carboxylate (58)**



5-Bromo-1-pentene (0.100 mL, 0.844 mmol) was added dropwise to a vigorously stirred suspension of magnesium turnings (41.1 mg, 1.69 mmol) in diethyl ether (2 mL). The mixture was heated at a gentle reflux for 1 h and then allowed to cool to room temperature before being transferred *via* cannula to a solution of amide **59** (100 mg, 0.219 mmol) in diethyl ether (2 mL) at 0 ºC. The mixture was heated at a gentle reflux for 1 h, cooled to 0 ºC and quenched with saturated aqueous ammonium chloride (2 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 3 mL). The combined organic layers were washed with brine (1 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:5) to give ketone **58** (67.4 mg, 67%) as a colourless oil.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 5.69 (ddt, *J* = 17.0, 10.3, 7.2 Hz, 1H, *H*14), 4.99 – 4.91 (m, 2H, *H*15), 4.19 (s, 1H, Si*H*), 4.06 (dd, *J* = 9.5, 3.6 Hz, 1H, $H2_a$), 3.97 – 3.90 (m, 1H, *H*3), 3.81 – 3.70 (m, 2H, $H2_b$ and *H*6), 2.16 (td, *J* = 7.3, 1.9 Hz, 2H, *H*11), 2.13 – 2.09 (m, 2H, *H*9), 1.97 – 1.90 (m, 3H, $H4_a$ and *H*13), 1.87 – 1.79 (m, 1H, $H7_a$), 1.78 – 1.63 (m, 2H, $H4_b$ and $H5_a$), 1.63 – 1.50 (m, 4H, *H*8 and *H*12), 1.50 – 1.44 (m, 10H, $H5_b$ and *t*Bu (Boc)), 1.32 – 1.24 (m, 1H, $H7_b$), 1.07 (s, 9H, *t*Bu (silyl ether)), 1.06 (s, 9H, *t*Bu

(silyl ether))

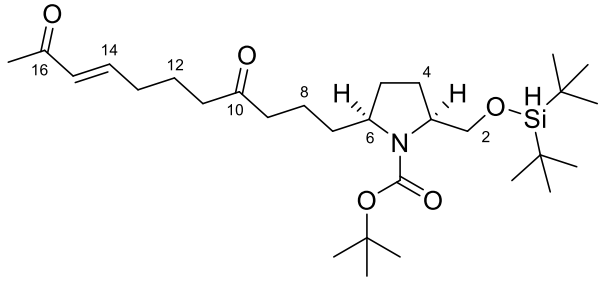
^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 207.7 (*C*10), 154.9 (urethane), 138.4 (*C*14), 114.9 (*C*15), 78.9 (*t*Bu (Boc)), 69.1 (*C*2), 60.3 (*C*3), 58.9 (*C*6), 42.6 (*C*11), 41.9 (*C*9), 36.0 (*C*7), 33.4 (*C*13), 29.7 (*C*4), 28.7 (*t*Bu (Boc)), 27.5 (*t*Bu (silyl ether)), 27.4 (*C*5), 23.4 (*C*12), 21.0 (*C*8), 20.2 (*t*Bu (silyl ether))

IR (film, cm^{-1}) ν_{max} 2930, 2086 (Si–H), 1692 (broad, C=O, Boc and ketone)

HRMS (ESI) calcd for $C_{27}H_{52}NO_4Si$ $[M+H]^+$ 482.3660, found 482.3648

$[\alpha]_D^{20}$ −19.3 (*c* 1.5, EtOH)

***tert*-Butyl (2*S*,5*S*)-2-(((di-*tert*-butylsilyl)oxy)methyl)-5-((*E*)-4,10-dioxoundec-8-en-1-yl) pyrrolidine-1-carboxylate (55)**



3-Buten-2-one (132 μL, 1.62 mmol) was added to a solution of ketone **58** (78.2 mg, 0.162 mmol) and Hoveyda-Grubbs 2nd generation catalyst (4.0 mg, 6.4 μmol) in dichloromethane (1 mL). After stirring overnight at room temperature, the mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3) to give diketone **55** (70.8 mg, 83%) as a colourless oil.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.44 (dt, *J* = 16.0, 6.9 Hz, 1H, *H*14), 5.91 (dt, *J* = 16.0, 1.5 Hz, 1H, *H*15), 4.19 (s, 1H, Si*H*), 4.06 (dd, *J* = 9.5, 3.7 Hz, 1H, $H2_a$), 3.96 – 3.90 (m, 1H, *H*3), 3.81 – 3.70 (m, 2H, $H2_b$ and *H*6), 2.20 – 2.08 (m, 2H, *H*11), 2.04 (t, *J* = 7.1 Hz, 2H, *H*9), 1.98 – 1.80 (m, 7H, $H4_a$, $H7_a$, *H*13 and *H*17), 1.80 – 1.64 (m, 2H, $H4_b$ and $H5_a$), 1.62 – 1.42 (m, 14H, $H5_b$, *H*8, *H*12 and *t*Bu (Boc)), 1.33 – 1.24 (m, 1H, $H7_b$), 1.07 (s, 9H, *t*Bu (silyl ether)), 1.06 (s, 9H, *t*Bu (silyl ether))

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 207.4 (*C*10), 195.3 (*C*16), 154.9 (urethane), 145.2 (*C*14), 132.0 (*C*15), 78.9 (*t*Bu (Boc)), 69.1 (*C*2), 60.3 (*C*3), 58.8 (*C*6), 42.6 (*C*9), 41.6 (*C*11), 35.9 (*C*7), 31.8 (*C*13), 29.7 (*C*4), 28.7 (*t*Bu (Boc)), 27.5 (*t*Bu (silyl ether)), 27.5 (*C*5), 26.5

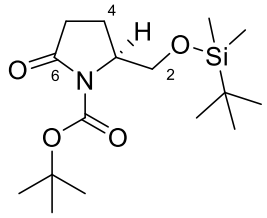
(*C*17), 22.5 (*C*12), 21.0 (*C*8), 20.2 (*t*Bu (silyl ether))

IR (film, cm^{-1}) ν_{max} 2930, 2085 (Si–H), 1690 (broad, C=O, Boc and ketones)

HRMS (ESI) calcd for $C_{29}H_{54}NO_5Si$ $[M+H]^+$ 524.3766, found 524.3754

$[\alpha]_D^{20}$ −16.0 (*c* 0.9, EtOH)

***tert*-Butyl (*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxopyrrolidine-1-carboxylate (80)**



Potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 10.4 mL, 5.20 mmol) was added dropwise to a solution of L-pyroglutaminol (0.503 g, 4.35 mmol) in acetonitrile (50 mL) at 0 ºC. After stirring for 15 min, a solution of *tert*-butyldimethylsilyl chloride (0.755 g, 5.01 mmol) in acetonitrile (5 mL) was added dropwise at 0 ºC and the mixture was stirred overnight at room temperature. 4-(Dimethylamino)pyridine (50.0 mg, 0.409 mmol) and a solution of di-*tert*-butyl dicarbonate (2.85 g, 13.1 mmol) in acetonitrile (5 mL) were added. After stirring overnight, the solvent was removed under reduced pressure, the residue was diluted with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:4) to give pyrrolidinone **80** (1.21 g, 84%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 – 4.12 (m, 1H, *H*2$_a$), 3.89 (dd, *J* = 10.4, 4.0 Hz, 1H, *H*2$_b$), 3.66 (dd, *J* = 10.4, 2.2 Hz, 1H, *H*3), 2.68 (td, *J* = 17.6, 10.4 Hz, 1H, *H*5$_a$), 2.35 (ddd, *J* = 17.6, 9.8, 2.1 Hz, 1H, *H*5$_b$), 2.13 – 1.96 (m, 2H, *H*4), 1.51 (s, 9H, *t*Bu (Boc)), 0.85 (s, 9H, *t*Bu (silyl ether)), 0.02 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (*C*6), 150.2 (urethane), 82.8 (*t*Bu (Boc)), 64.4 (*C*2), 59.0 (*C*3), 32.5 (*C*5), 28.2 (*t*Bu (Boc)), 25.9 (*t*Bu (silyl ether)), 21.2 (*C*4), 18.3 (*t*Bu (silyl ether), −5.4 (Si*C*H_3), −5.5 (Si*C*H_3)

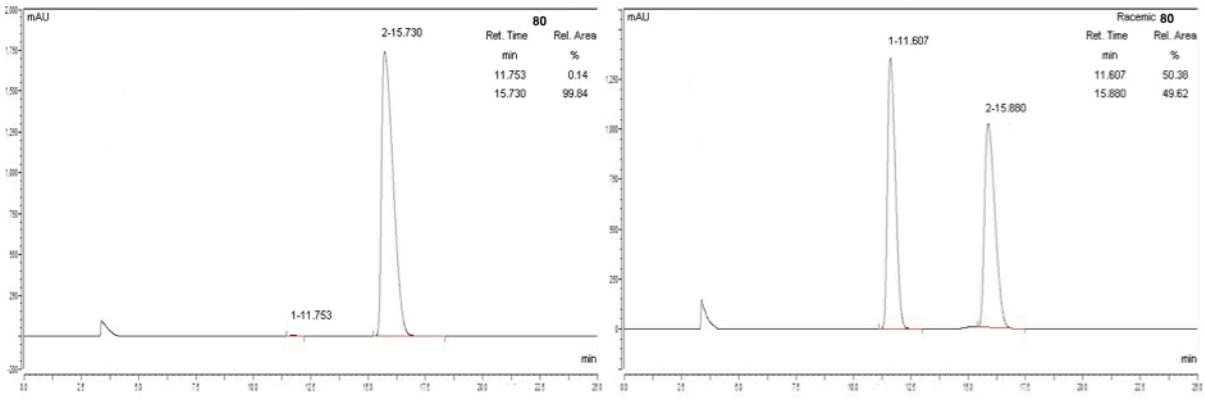
IR (film, cm^{-1}) ν_{max} 1789 (C=O), 1709 (C=O)

MS (ESI) 352.2 $[M+Na]^+$

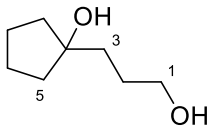
$[\alpha]_D^{20}$ −64.5 (*c* 1.0, $CHCl_3$)

These data are consistent with that previously published for this compound.[vi]

HPLC traces of **80** and racemic **80**: (Column: Chiralpak IC, isopropanol/hexane 10:90, 1 mL min^{-1}, loaded in isopropanol)



1-(3-Hydroxypropyl)cyclopentan-1-ol (82)



A solution of 1,4-dibromobutane (16.0 g, 74.1 mmol) in tetrahydrofuran (10 mL) was added dropwise to a vigorously stirred suspension of magnesium turnings (5.40 g, 0.222 mol) in tetrahydrofuran (30 mL) at a rate to maintain the mixture at a gentle reflux. After the addition, the mixture was heated at reflux for 1 h before a solution of γ-butyrolactone (7.20 g, 83.6 mmol) in tetrahydrofuran (15 mL) was added dropwise to maintain the mixture at a gentle reflux. After the addition, the mixture was allowed to cool to room temperature over 1 h. The mixture was quenched with saturated aqueous ammonium chloride (60 mL) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (4 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. The residue was distilled under vacuum (110 – 115 ºC, 0.1 mmHg) to give diol **82** (8.06 g, 75%) as a colourless oil that solidified upon standing at room temperature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (t, *J* = 5.7 Hz, 2H, *H*1), 2.40 (br, 2H, 2 × O*H*), 1.83 – 1.53 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 82.4 (*C*4), 63.5 (*C*1), 40.0 (*C*6), 38.7 (*C*3), 28.3 (*C*2), 23.9 (*C*5)

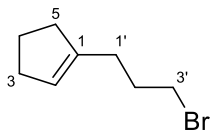
IR (film, cm^{-1}) ν_{max} 3329 (broad, O–H), 2950, 1057 (C–O)

MS (ESI) 167.1 $[M+Na]^+$

MP: 29 – 32 ºC

These data are consistent with that previously published for this compound.[vii]

1-(3-Bromopropyl)cyclopent-1-ene (83)



Several drops of 1-bromocyclopentene were added to a vigorously stirred suspension of finely cut lithium (0.560 g, 81.1 mmol) in diethyl ether (3 mL). After the reaction was initiated (as indicated by the bubbles formed on the surface of the lithium turnings), the suspension was diluted with diethyl ether (24 mL) and 1-bromocyclopentene (5.88 g in total, 40.0 mmol) was slowly added to maintain the mixture at a gentle reflux. The yellow suspension was stirred for 1 h at room temperature, before being transferred *via* cannula to a solution of 1,3-dibromopropane (8.10 mL, 80.0 mmol) in diethyl ether (8 mL) at −78 ºC. The mixture was gradually warmed to room temperature overnight before being quenched with saturated aqueous ammonium chloride (20 mL) at 0 ºC and extracted with petroleum ether (b.p. 30 – 40 ºC, 3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, concentrated and distilled under reduced pressure. The fraction (40 – 70 ºC, 0.1 mmHg) was collected and purified by silica gel chromatography (petroleum ether b.p. 30 – 40 ºC) to give bromide **83** (1.79 g, 24%) as a colourless oil.

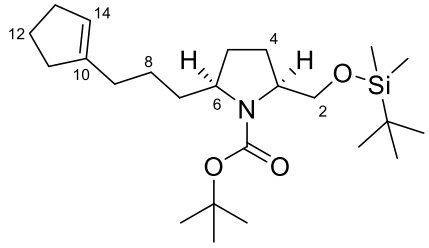
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H, *H*2), 3.40 (t, *J* = 6.8 Hz, 2H, *H*3'), 2.34 – 2.27 (m, 2H, *H*3), 2.26 – 2.19 (m, 4H, *H*1' and *H*5), 2.05 – 1.97 (m, 2H, *H*2'), 1.90 – 1.82 (m, 2H, *H*4)

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (*C*1), 124.7 (*C*2), 35.1 (*C*5), 33.8 (*C*1'), 32.6 (*C*3'), 31.0 (*C*3), 29.7 (*C*2'), 23.6 (*C*4)

IR (film, cm^{-1}) ν_{max} 2945, 1650 (C=C)

HRMS (FI) calcd for $C_8H_{13}Br$ $[M]^+$ 188.0201, found 188.0192

***tert*-Butyl (2*S*,5*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(3-(cyclopent-1-en-1-yl) propyl) pyrrolidine-1-carboxylate (89)**



Bromide **83** (1.84 g, 9.74 mmol) was added to a stirred suspension of magnesium turnings (0.462 g, 19.0 mmol) in tetrahydrofuran (20 mL) and heated to reflux for 1 h. The resulting solution was transferred *via* cannula to a solution of pyrrolidinone **80** (1.61 g, 4.90 mmol) in tetrahydrofuran (25 mL) at −78 ºC and stirred for 1 h. To this solution, boron trifluoride diethyl etherate (3.60 mL, 29.2 mmol) and L-Selectride® (1.0 M solution in tetrahydrofuran, 9.70 mL, 9.70 mmol) were successively added dropwise before being stirred for 1.5 h at −78 ºC. After warming to room temperature, the suspension was diluted with diethyl ether (75 mL) and quenched with saturated aqueous sodium bicarbonate (150 mL). The aqueous layer was extracted with diethyl ether (4 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:50 to 1:25) to give pyrrolidine **89** (1.35 g, 66%) as a colourless oil.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 5.37 – 5.35 (m, 1H, *H*14), 3.91 – 3.86 (m, 1H, *H*3), 3.84 (dd, *J* = 9.6, 3.5 Hz, 1H, $H2_a$), 3.82 – 3.77 (m, 1H, *H*6), 3.65 (dd, *J* = 9.6, 7.1 Hz, 1H, $H2_b$), 2.33 – 2.27 (m, 2H, *H*13), 2.25 – 2.19 (m, 2H, *H*11), 2.14 – 2.09 (m, 2H, *H*9), 1.96 – 1.87 (m, 2H, $H4_a$ and $H7_a$), 1.86 – 1.80 (m, 2H, *H*12), 1.73 – 1.63 (m, 2H, $H4_b$ and

*H*5$_a$), 1.53 – 1.41 (m, 12H, *H*5$_b$, *H*8 and *t*Bu (Boc)), 1.38 – 1.30 (m, 1H, *H*7$_b$), 0.95 (s, 9H, *t*Bu (silyl ether)), 0.09 (s, 3H, SiC*H*$_3$), 0.08 (s, 3H, SiC*H*$_3$)

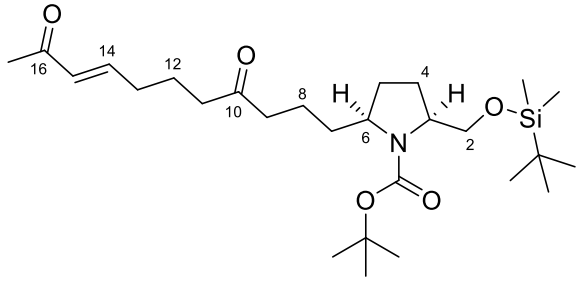
^{13}C NMR (125 MHz, d$_8$-toluene, 363 K) δ 154.8 (urethane), 144.9 (*C*10), 123.6 (*C*14), 78.6 (*t*Bu (Boc)), 65.1 (*C*2), 60.4 (*C*3), 59.2 (*C*6), 36.2 (*C*7), 35.5 (*C*11), 32.8 (*C*13), 31.6 (*C*9), 29.9 (*C*5), 28.7 (*t*Bu (Boc)), 27.0 (*C*4), 26.1 (*t*Bu (silyl ether)), 25.2 (*C*8), 23.9 (*C*12), 18.5 (*t*Bu (silyl ether)), −5.2 (Si*C*H$_3$)

IR (film, cm^{-1}) ν_{max} 2929, 1693 (C=O)

HRMS (ESI) calcd for $C_{24}H_{46}NO_3Si$ $[M+H]^+$ 424.3242, found 424.3229

$[\alpha]_D^{20}$ −22.0 (*c* 0.6, EtOH)

***tert*-Butyl (2*S*,5*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((*E*)-4,10-dioxoundec-8-en-1-yl) pyrrolidine-1-carboxylate (91)**



Ozone was bubbled through a solution of pyrrolidine **89** (1.27 g, 3.00 mmol) in dichloromethane (10 mL) at −78 ºC until a persistent blue colour formed, then a flow of argon was introduced into the solution until the solution was decolourised. Triphenylphosphine (0.827 g, 3.15 mmol) and 1-(triphenylphosphoranylidene)-2-propanone (1.05 g, 3.30 mmol) were added at −78 ºC. Then the mixture was allowed to warm to room temperature and stirred overnight. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3) to give diketone **91** (1.25 g, 84%) as a colourless oil.

^{1}H NMR (500 MHz, d$_8$-toluene, 363 K) δ 6.45 (dt, *J* = 16.0, 6.9 Hz, 1H, *H*14), 5.91 (d, *J* = 16.0 Hz, 1H, *H*15), 3.90 – 3.85 (m, 1H, *H*3), 3.83 (dd, *J* = 9.6, 3.5 Hz, 1H, *H*2$_a$), 3.80 – 3.75 (m, 1H, *H*6), 3.68 – 3.63 (m, 1H, *H*2$_b$), 2.22 – 2.13 (m, 2H, *H*11), 2.04 (t, *J* = 7.1 Hz, 2H, *H*9), 1.95 – 1.87 (m, 6H, *H*4$_a$, *H*13 and *H*17), 1.85 – 1.77 (m, 1H, *H*7$_a$), 1.73 – 1.63 (m, 2H, *H*4$_b$ and *H*5$_a$), 1.62 – 1.50 (m, 4H, *H*8 and *H*12), 1.50 – 1.44 (m, 10H, *H*5$_b$ and *t*Bu (Boc)), 1.36 – 1.26 (m, 1H, *H*7$_b$), 0.95 (s, 9H, *t*Bu (silyl ether)), 0.10 (s, 3H, SiC*H*$_3$), 0.09 (s, 3H, SiC*H*$_3$)

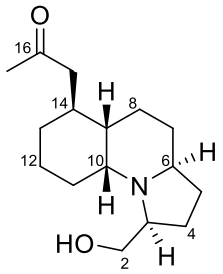
^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 207.4 (*C*10), 195.3 (*C*16), 154.9 (urethane), 145.2 (*C*14), 132.0 (*C*15), 78.8 (*t*Bu (Boc)), 65.1 (*C*2), 60.4 (*C*3), 58.8 (*C*6), 42.7 (*C*9), 41.6 (*C*11), 35.8 (*C*7), 31.8 (*C*13), 29.8 (*C*4), 28.7 (*t*Bu (Boc)), 27.4 (*C*5), 26.5 (*C*17), 26.2 (*t*Bu (silyl ether)), 22.5 (*C*12), 21.0 (*C*8), 18.5 (*t*Bu (silyl ether)), −5.2 (Si*C*H$_3$)

IR (film, cm^{-1}) ν_{max} 2955, 1689 (broad, C=O, Boc and ketones)

HRMS (ESI) calcd for $C_{27}H_{50}NO_5Si$ $[M+H]^+$ 496.3453, found 496.3442

$[\alpha]_D^{20}$ −17.0 (*c* 1.1, EtOH)

1-((1*S*,3a*S*,5a*S*,6*S*,9a*R*)-1-(Hydroxymethyl)dodecahydropyrrolo[1,2-*a*]quinolin-6-yl) propan-2-one (57)



Trifluoroacetic acid (1.5 mL) was added to a solution of diketone **91** (200 mg, 0.404 mmol) in dichloromethane (4.5 mL) at 0 ºC. The mixture was allowed to warm to room temperature and stirred for 2 h before the solvent was removed. The residue was redissolved in chloroform (7.0 mL) and stirred for 72 h at 40 ºC. After removal of the solvent, the flask was charged with dichloromethane (10 mL) followed by the addition of sodium triacetoxyborohydride (128 mg, 0.604 mmol) and stirred for 1 h at room temperature. The reaction was quenched by saturated aqueous sodium carbonate (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (methanol/dichloromethane 1:100 with 0.1% v/v triethylamine) to give alcohol **57** (76.2 mg, 72%) as a colourless solid.

^{1}H NMR (400 MHz, C_6D_6) δ 3.63 (dd, *J* = 10.6, 3.1 Hz, 1H, *H*2$_a$), 3.35 (dd, *J* = 10.6, 1.6 Hz, 1H, *H*2$_b$), 2.92 – 2.85 (m, 1H, *H*10), 2.78 – 2.72 (m, 1H, *H*6), 2.44 – 2.36 (m, 1H, *H*3), 2.22 – 2.03 (m, 3H, *H*14 and *H*15), 1.83 – 1.70 (m, 1H, *H*7$_a$), 1.67 (s, 3H, C*H*$_3$), 1.64 – 1.48 (m, 3H, *H*4$_a$, *H*5$_a$ and H7$_b$), 1.48 – 1.33 (m, 4H, *H*8$_a$, *H*9, *H*12$_a$ and *H*13$_a$), 1.32 – 1.13 (m, 5H, *H*5$_b$, *H*8$_b$, *H*11 and *H*13$_b$), 1.13 – 0.97 (m, 2H, *H*4$_b$ and *H*12$_b$)

^{13}C NMR (100 MHz, C_6D_6) δ 205.8 (*C*16), 60.9 (*C*2), 57.8 (*C*6), 56.1 (*C*3), 50.9 (*C*10), 46.8 (*C*15), 41.8 (*C*9), 34.9 (*C*14), 32.6 (*C*4), 31.3 (*C*5), 30.0 (*C*17), 26.7 (*C*7), 26.3 (*C*8), 25.3 (*C*13), 20.6 (*C*12), 17.3 (*C*11)

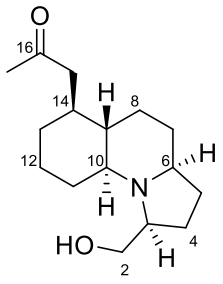
IR (film, cm^{-1}) ν_{max} 3415 (broad, O–H), 2925, 1713 (C=O).

HRMS (ESI) calcd for $C_{16}H_{28}NO_2$ $[M+H]^+$ 266.2115, found 266.2110

MP: 75 – 77 ºC

$[\alpha]_D^{20}$ −15.7 (*c* 1.3, EtOH)

1-((1*S*,3a*S*,5a*S*,6*S*,9a*S*)-1-(Hydroxymethyl)dodecahydropyrrolo[1,2-*a*]quinolin-6-yl) propan-2-one (105)



Trifluoroacetic acid (1.5 mL) was added to a solution of pyrrolidine **91** (200 mg, 0.404 mmol) in dichloromethane (4.5 mL) at 0 ºC. The mixture was allowed to warm to room temperature and stirred for 2 h before the solvent was removed. The residue was redissolved in chloroform (7.0 mL) and stirred for 72 h at 40 ºC. After removal of the solvent, the flask was charged with dichloromethane (10 mL) followed by the addition of sodium cyanoborohydride (12.5 mg, 0.200 mmol) and stirred for 1 h at room temperature. The reaction was quenched by saturated aqueous sodium carbonate (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (methanol/dichloromethane 1:100 with 0.1% v/v triethylamine) to give alcohol **105** (64.8 mg, 61%) as a colourless solid.

^{1}H NMR (400 MHz, C_6D_6) δ 3.47 (dd, *J* = 10.1, 3.8 Hz, 1H, *H*2$_a$), 3.34 (d, *J* = 10.1 Hz, 1H, *H*2$_b$), 2.61 (dt, *J* = 8.2, 3.8 Hz, 1H, *H*3), 2.13 (dd, *J* = 16.1, 3.9 Hz, 1H, *H*15$_a$), 2.06 (tdd, *J* = 10.9, 4.6, 2.1 Hz, 1H, *H*6), 1.79 (ddd, *J* = 11.3, 8.6, 3.6 Hz, 1H, *H*10), 1.76 – 1.64 (m, 7H, *H*4, *H*11$_a$, *H*15$_b$ and *H*17), 1.64 – 1.54 (m, 3H, *H*7$_a$, *H*8$_a$ and *H*14), 1.54 – 1.37 (m, 4H, *H*5, *H*12$_a$ and *H*13$_a$), 1.20 – 1.12 (m, 1H, *H*12$_b$), 1.12 – 1.00 (m, 2H, *H*7$_b$ and *H*11$_b$), 0.79 – 0.64

(m, 3H, *H*8$_b$, *H*9 and *H*13$_b$)

^{13}C NMR (100 MHz, C_6D_6) δ 206.2 (*C*16), 67.8 (*C*2), 66.8 (*C*10), 66.7 (*C*6), 61.0 (*C*3), 48.22 (*C*15), 47.3 (*C*9), 37.2 (*C*14), 32.9 (*C*8), 32.4 (*C*11), 32.2 (*C*5), 31.4 (*C*7), 30.4 (*C*4), 30.1 (*C*17), 29.7 (*C*13), 24.8 (*C*12)

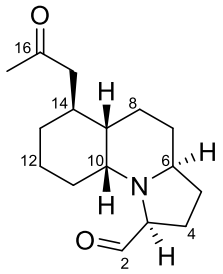
IR (film, cm^{-1}) ν_{max} 3415 (broad, O–H), 2925, 1713 (C=O)

HRMS (ESI) calcd for $C_{16}H_{28}NO_2$ $[M+H]^+$ 266.2114, found 266.2109

MP: 106 – 107 ºC

$[\alpha]_D^{20}$ −18.1 (*c* 1.3, EtOH)

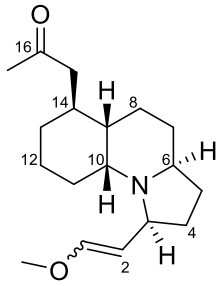
(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-(2-Oxopropyl)dodecahydropyrrolo[1,2-*a*]quinoline-1-carbaldehyde (106)



Dimethyl sulfoxide (5.0 M solution in dichloromethane, 92.0 μL, 0.460 mmol) was added to a stock solution of oxalyl chloride (0.4 M solution in dichloromethane, 0.53 mL, 0.21 mmol) at −78 ºC. After stirring for 10 min, a solution of alcohol **57** (50.0 mg, 0.189 mmol) in dichloromethane (0.2 mL) was added and the mixture was stirred for 30 min. Triethylamine (0.130 mL, 0.933 mmol) was added to the solution and the mixture was stirred for 1 h at −78 ºC and then gradually warmed to room temperature over 1 h. The mixture was quenched by saturated aqueous sodium carbonate (5 mL) and extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give crude aldehyde **106** (49.8 mg, quantitative) as a yellow oil, which was directly used in the next step without further purification.

HRMS (ESI) calcd for $C_{16}H_{26}NO_2$ $[M+H]^+$ 264.1958, found 264.1954

1-((1*S*,3a*S*,5a*S*,6*S*,9a*R*)-1-(2-Methoxyvinyl)dodecahydropyrrolo[1,2-*a*]quinolin-6-yl) propan-2-one (107)



Potassium bis(trimethylsilyl)amide (0.5 M solution in toluene, 0.570 mL, 0.290 mmol) was added to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (100 mg, 0.291 mmol) in tetrahydrofuran (0.12 mL) at −78 ºC. The red mixture was allowed to warm to room temperature over 30 min before being transferred *via* cannula to a solution of aldehyde **106** (50.0 mg, 0.190 mmol) in tetrahydrofuran (0.64 mL) at −78 ºC until a persistent red colour was observed. The solution was allowed to warm to room temperature and stirred for 5 h. The resulting colourless suspension was quenched with saturated aqueous sodium carbonate (5 mL) and extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed by brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3 with 0.1% v/v triethylamine) to give ketone **107** (48.3 mg, 87%) as a yellow oil (11:9 mixture of *E*:*Z* isomers).

^{1}H NMR (400 MHz, C_6D_6) δ 6.48 (d, *J* = 13.3 Hz, 0.55H, major *H*1), 5.77 (dd, *J* = 6.4, 0.8 Hz, 0.45H, minor *H*1), 4.66 (dd, *J* = 13.3, 9.1 Hz, 0.55H, major *H*2), 4.48 (dd, *J* = 9.2, 6.4 Hz, 0.45H, minor *H*2), 3.98 (q, *J* = 8.3 Hz, 0.45H, minor *H*3), 3.26 (dt, *J* = 12.0, 4.0 Hz, 0.45H, minor *H*10), 3.21 – 3.15 (m, 2.2H, major *H*10 and major OCH_3), 3.09 (s, 1.35H, minor OCH_3),

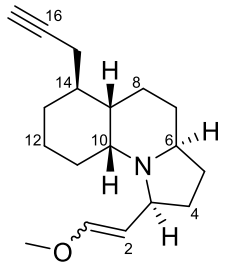
3.03 (dt, J = 9.1, 7.8 Hz, 0.55H, major *H*3), 2.52 – 2.38 (m, 1H, *H*6), 2.32 – 2.11 (m, 3H, *H*14 and *H*15), 1.97 – 1.87 (m, 0.45H, minor $H4_a$), 1.84 – 1.73 (m, 1H, major $H4_a$ and minor $H11_a$), 1.73 – 1.59 (m, 3H, $H5_a$, $H7_a$ and *H*9), 1.62 (s, 1.35H, minor *H*17), 1.60 (s, 1.65H, major *H*17), 1.57 – 1.49 (m, 2H, $H4_b$ and $H8_a$), 1.49 – 1.35 (m, 3H, major $H11_a$, minor $H11_b$, $H12_a$ and $H13_a$), 1.35 – 1.13 (m, 5.55H, $H5_b$, $H7_b$, $H8_b$, major $H11_b$, $H12_b$ and $H13_b$)

^{13}C NMR (100 MHz, C_6D_6) δ 206.0 (205.9) (*C*16), 148.7 (148.3) (*C*1), 105.8 (110.3) (*C*2), 57.8 (53.2) (*C*3), 55.6 (59.3) (O*C*H$_3$), 55.5 (55.5) (*C*6), 50.8 (51.5) (*C*10), 47.1 (47.2) (*C*15), 41.5 (41.5) (*C*9), 35.2 (35.3) (*C*14), 33.3 (33.2) (*C*7), 32.0 (30.8) (*C*4), 30.1 (30.4) (*C*5), 29.9 (29.8) (*C*17), 26.8 (26.8) (*C*8), 25.6 (25.6) (*C*13), 20.6 (20.8) (*C*12), 16.8 (17.1) (*C*11)

IR (film, cm^{-1}) ν_{max} 2929, 1715 (C=O), 1654 (broad, C=C of isomers)

HRMS (ESI) calcd for $C_{18}H_{30}NO_2$ $[M+H]^+$ 292.2271, found 292.2266

(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-1-(2-Methoxyvinyl)-6-(prop-2-yn-1-yl)dodecahydropyrrolo[1,2-*a*] quinolone (109)



n-Butyllithium (2.5 M solution in hexanes, 0.220 mL, 0.550 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (93.0 μL, 0.551 mmol) in tetrahydrofuran (0.5 mL) at −78 ºC and stirred for 30 min at the same temperature. To this mixture was added a solution of ketone **107** (145 mg, 0.498 mmol) in tetrahydrofuran (0.4 mL) at −78 ºC. After stirring the mixture for 1 h at the same temperature, diethyl chlorophosphate (83.0 μL, 0.571 mmol) was added. The mixture was allowed to warm to room temperature over 3 h and then transferred to a solution of lithium 2,2,6,6-tetramethylpiperidide in tetrahydrofuran (1.15 mmol, prepared by addition of *n*-butyllithium (2.5 M solution in hexanes, 0.460 mL, 1.15 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.200 mL, 1.15 mmol) in tetrahydrofuran (1.0 mL) at −78 ºC, followed by stirring for 30 min at the same temperature). The mixture was stirred for 20 min at −78 ºC and then was allowed to warm to room temperature over 3 h. The reaction was quenched with saturated aqueous sodium carbonate (15 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:8 to 1:1 with 0.1% v/v triethylamine) to give alkyne **109** (106 mg, 79%) as a colourless oil (11:9 mixture of *E*:*Z* isomers).

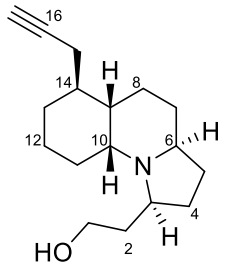
^{1}H NMR (400 MHz, C_6D_6) δ 6.46 (d, *J* = 12.9 Hz, 0.55H, major *H*1), 5.71 (d, *J* = 6.1 Hz, 0.45H, minor *H*1), 4.60 (dd, *J* = 12.9, 9.0 Hz, 0.55H, major *H*2), 4.41 (dd, *J* = 9.2, 6.1 Hz, 0.45H, minor *H*2), 3.93 (q, *J* = 8.5 Hz, 0.45H, minor *H*3), 3.21 (dt, *J* = 12.0, 4.0 Hz, 0.45H, minor *H*10), 3.18 – 3.12 (m, 2.2H, major *H*10 and major O*C*H$_3$), 3.07 (s, 1.35H, minor O*C*H$_3$), 3.00 (q, *J* = 8.2 Hz, 0.55H, major *H*3), 2.50 – 2.35 (m, 1H, *H*6), 2.32 – 2.11 (m, 2H, *H*13), 1.98 – 1.86 (m, 1.45H, minor *H*4$_a$ and *H*9), 1.82 – 1.59 (m, 5H, major *H*4$_a$, *H*5$_a$, *H*7$_a$, minor *H*11$_a$, *H*14 and *H*17), 1.61 – 1.44 (m, 3.45H, *H*4$_b$, *H*8$_a$, *H*15$_a$ and minor *H*12$_a$), 1.47 – 1.22 (m, 5.55H, *H*5$_b$, *H*7$_b$, major *H*11$_a$, major *H*11$_b$, minor *H*11$_b$, major *H*12$_a$, minor *H*12$_b$ and *H*15$_b$), 1.22 – 1.12 (m, 1.55H, *H*8$_b$ and major *H*12$_b$)

^{13}C NMR (100 MHz, C_6D_6) δ 148.6 (148.3) (*C*1), 105.5 (110.2) (*C*2), 84.1 (84.1) (*C*16), 69.6 (69.6) (*C*17), 57.8 (53.2) (*C*3), 55.4 (59.2) (O*C*H$_3$), 55.4 (55.4) (*C*6), 50.2 (51.0) (*C*10), 40.4 (40.4) (*C*9), 39.9 (39.9) (*C*14), 33.2 (33.2) (*C*7), 31.9 (30.7) (*C*4), 30.0 (30.4) (*C*5), 27.0 (27.0) (*C*8), 24.9 (25.0) (*C*15), 22.6 (22.6) (*C*13), 20.1 (20.3) (*C*12), 16.8 (17.1) (*C*11)

IR (film, cm^{-1}) ν_{max} 3307 (C–H, alkyne), 2930, 1654 (broad, C=C of isomers)

HRMS (ESI) calcd for $C_{18}H_{28}NO$ $[M+H]^+$ 274.2165, found 274.2158

2-((1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-(Prop-2-yn-1-yl)dodecahydropyrrolo[1,2-*a*]quinolin-1-yl) ethan-1-ol (111)



Hydrochloric acid (4.0 M, 1.83 mL, 7.32 mmol) was added to a solution of alkyne **109** (100 mg, 0.366 mmol) in tetrahydrofuran (1.8 mL) at 0 ºC. After stirring overnight at room temperature, the solvent was removed and the residue was dissolved in water (0.1 mL), evaporated and dried under vacuum. The resulting colourless foam was dissolved in methanol (3.0 mL) and cooled to 0 ºC. Sodium borohydride (28.0 mg, 0.740 mmol) was added in four portions over 30 min and the mixture was stirred at 0 ºC for 1 h. The reaction mixture was quenched with saturated aqueous sodium carbonate (10 mL) and extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (methanol/dichloromethane 1:100 with 0.1% v/v triethylamine) to give alcohol **111** (88.1 mg, 91%) as a colourless solid.

^{1}H NMR (500 MHz, C_6D_6) δ 4.61 (br, 1H, O*H*), 3.98 (td, *J* = 11.0, 2.8 Hz, 1H, *H*1$_a$), 3.68 (dt, *J* = 11.0, 4.0 Hz, 1H, *H*1$_b$), 3.16 – 3.11 (m, 1H, *H*10), 2.95 – 2.90 (m, 1H, *H*3), 2.28 – 2.12 (m, 3H, *H*6 and *H*15), 1.94 – 1.86 (m, 1H, *H*2$_a$), 1.83 (t, *J* = 2.7 Hz, 1H, *H*17), 1.70 – 1.63 (m, 2H, *H*9 and *H*14), 1.60 – 1.41 (m, 5H, *H*4, *H*5$_a$, *H*7$_a$ and *H*13$_a$), 1.41 – 1.21 (m, 5H, *H*5$_b$, *H*8$_a$, *H*11$_a$, *H*12$_a$ and *H*13$_b$), 1.17 – 1.03 (m, 5H, *H*2$_b$, *H*7$_b$, *H*8$_b$, *H*11$_b$ and *H*12$_b$)

^{13}C NMR (125 MHz, C_6D_6) δ 83.7 (*C*16), 69.8 (*C*17), 59.6 (*C*1), 56.1 (*C*6), 55.8 (*C*3), 50.3 (*C*10), 40.6 (*C*9), 39.5 (*C*14), 32.6 (*C*7), 31.2 (broad, *C*2 and *C*5), 26.5 (*C*4), 26.3 (*C*8), 24.5 (*C*13), 22.4 (*C*15), 20.1 (*C*12), 16.6 (*C*11)

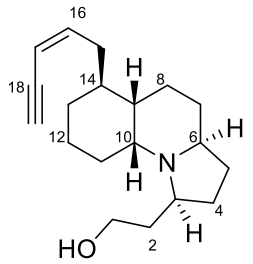
IR (film, cm^{-1}) ν_{max} 3215 (C–H, alkyne), 3200 (broad, O–H), 2924

HRMS (ESI) calcd for $C_{17}H_{28}NO$ $[M+H]^+$ 262.2165, found 262.2160

MP: 145 – 148 ºC (dec.)

$[\alpha]_D^{20}$ +3.7 (*c* 2.5, EtOH)

(−)-Gephyrotoxin



Anhydrous indium(III) chloride (37.5 mg, 0.170 mmol) was dried under vacuum at 150 ºC for 5 min and cooled to room temperature under argon. The solid was dissolved in tetrahydrofuran (0.5 mL) and cooled to −78 ºC to form a white suspension. Diisobutylaluminum hydride (1.0 M in hexanes, 0.160 mL, 0.160 mmol) was added to the suspension and stirred for 45 min at −78 ºC. A pre-mixed solution of alcohol **111** (28.5 mg, 0.110 mmol) and acetic acid (6.3 μL, 0.11 mmol) in tetrahydrofuran (0.7 mL), was added, followed by triethylborane (1.0 M solution in hexanes, 0.110 mL, 0.110 mmol), then the mixture was stirred at −78 ºC for 4 h. The mixture was allowed to warm to room temperature, dimethylformamide (0.5 mL), 1-iodo-2-(trimethylsilyl)acetylene (24.0 μL, 0.165 mmol) and a palladium-tri(2-furyl)phosphine complex (84.0 μL of a solution prepared from tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (7.0 mg, 6.8 μmol), tri(2-furyl)phosphine (14.0 mg, 60.0 μmol) in tetrahydrofuran (1.0 mL)), was added successively. The mixture was shielded from light and stirred for 3 h at 70 ºC. After being cooled to room temperature, the mixture was transferred to a suspension of potassium carbonate (0.780 g, 5.64 mmol) in methanol (6.8 mL) and stirred for 30 min. Saturated aqueous sodium carbonate (20 mL) was added to the mixture and the suspension was extracted with diethyl ether (4 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over sodium sulfate, filtered and concentrated. The residue was

purified by silica gel chromatography (methanol/dichloromethane 1:1000 to 1:200 with 0.1% v/v triethylamine) to give (−)-gephyrotoxin (21.6 mg, 68%) as a colourless solid.

^{1}H NMR (400 MHz, C_6D_6) δ 5.74 – 5.66 (m, 1H, *H*16), 5.42 (d, *J* = 10.9 Hz, 1H, *H*17), 4.35 (br, 1H, O*H*), 3.98 (td, *J* = 10.8, 2.8 Hz, 1H, $H1_a$), 3.69 (dt, *J* = 10.8, 4.2 Hz, 1H, $H1_b$), 3.41 – 3.34 (m, 1H, *H*10), 3.03 – 2.95 (m, 1H, *H*3), 2.84 (s, 1H, *H*19), 2.65 (dt, *J* = 14.1, 8.6 Hz, 1H, $H15_a$), 2.41 – 2.24 (m, 2H, *H*6 and $H15_b$), 1.94 (ddt, *J* = 14.6, 10.4, 4.6 Hz, 1H, $H2_a$), 1.69 – 1.60 (m, 2H, $H7_a$ and *H*9), 1.60 – 1.48 (m, 4H, $H2_b$, $H4_a$, $H5_a$ and $H8_a$), 1.48 – 1.36 (m, 4H, *H*12, $H13_a$ and *H*14), 1.36 – 1.20 (m, 4H, $H4_b$, *H*11 and $H13_b$), 1.20 – 1.06 (m, 3H, $H5_b$, $H7_b$ and $H8_b$)

^{13}C NMR (100 MHz, C_6D_6) δ 145.0 (*C*16), 109.6 (*C*17), 82.0 (*C*19), 81.0 (*C*18), 59.7 (*C*1), 56.2 (*C*6), 55.9 (*C*3), 50.6 (*C*10), 41.1 (*C*9), 39.8 (*C*14), 33.8 (*C*15), 32.7 (*C*7), 31.5 (*C*5), 31.2 (*C*2), 26.8 (*C*4), 26.4 (*C*8), 25.0 (*C*13), 20.6 (*C*12), 16.7 (*C*11)

IR (film, cm^{-1}) ν_{max} 3400 (broad, O−H), 3310 (C−H, alkyne), 2925, 1447 (C=C)

HRMS (ESI) calcd for $C_{19}H_{30}NO_3$ $[M+H]^+$ 288.2322, found 288.2316

MP: 87 – 89 ºC

$[\alpha]_D^{20}$ −52.4 (*c* 1.0, EtOH)

Hydrochloride salt of (−)-gephyrotoxin:

^{1}H NMR (500 MHz, CD_3OD) δ 6.06 – 6.00 (m, 1H, *H*16), 5.62 – 5.58 (m, 1H, *H*17), 3.82 – 3.74 (m, 2H, $H1_a$ and *H*10), 3.62 (ddd, *J* = 11.0, 8.4, 4.9 Hz, 1H, $H1_b$), 3.58 (d, *J* = 2.2 Hz, 1H, *H*19), 3.57 – 3.49 (m, 1H, *H*3), 3.41 – 3.30 (m, 1H, *H*6), 2.67 (dt, *J* = 14.2, 8.5 Hz, 1H, $H15_a$), 2.45 (dt, *J* = 14.2, 7.1, 1.0 Hz, 1H, $H15_b$), 2.32 – 2.23 (m, 1H, $H4_a$), 2.20 – 2.08 (m, 3H, $H2_a$, $H5_a$ and $H7_a$), 2.04 – 1.87 (m, 3H, $H8_a$, *H*9 and *H*14), 1.85 – 1.65 (m, 7H, $H2_b$, $H4_b$, *H*11, *H*12 and $H13_a$), 1.65 – 1.58 (m, 1H, $H5_b$), 1.58 – 1.51 (m, 2H, $H7_b$ and $H8_b$) 1.51 – 1.41 (m, 1H, $H13_b$)

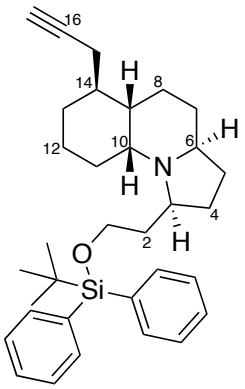
^{13}C NMR (125 MHz, CD_3OD) δ 144.7 (*C*16), 111.1 (*C*17), 83.6 (*C*19), 81.4 (*C*18), 60.6 (*C*6), 59.6 (*C*3), 59.3 (*C*1), 55.1 (*C*10), 39.8 (*C*14), 39.4 (*C*9), 33.8 (*C*15), 33.2 (*C*2), 30.2 (*C*7), 28.0 (*C*5), 27.3 (*C*4), 25.7 (*C*8), 25.3 (*C*13), 20.7 (*C*12), 18.8 (*C*11)

IR (film, cm^{-1}) ν_{max} 3200 (broad, N–H and O–H), 2938

MP: 244 – 248 ºC (dec.)

$[\alpha]_D^{20}$ −89.1 (*c* 1.1, MeOH)

(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-1-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-(prop-2-yn-1-yl) dodecahydropyrrolo[1,2-*a*]quinolone



tert-Butyl(chloro)diphenylsilane (57.0 μL, 0.219 mmol) was added to a solution of alcohol **111** (28.7 mg, 0.110 mmol) and imidazole (15.0 mg, 0.220 mmol) in dimethylformamide (0.8 mL) and stirred at room temperature overnight. The mixture was diluted with diethyl ether (20 mL), then washed with water (5 mL), saturated aqueous sodium carbonate (5 mL), brine (5 mL), dried over sodium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:20 to 1:10 with 0.1% v/v triethylamine) to give alkyne **121a** (39.7 mg, 72%) as a colourless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.83 – 7.79 (m, 4H, Ar*H*), 7.27 – 7.23 (m, 6H, Ar*H*), 3.83 – 3.73 (m, 2H, *H*1), 3.01 (dt, *J* = 12.2, 3.9 Hz, 1H, *H*10), 2.77 (dtd, *J* = 8.9, 8.0 3.1 Hz, 1H, *H*3), 2.35 (tdd, *J* = 9.9, 6.7, 2.8 Hz, 1H, *H*6), 2.2 (ddd, *J* = 16.8, 9.0, 2.6 Hz, 1H, $H15_a$), 2.13 (ddd, *J* = 16.8, 9.0, 2.6 Hz, 1H, $H15_b$), 2.04 (dtd, *J* = 13.2, 7.3, 3.0 Hz, 1H, $H2_a$), 1.85 – 1.79 (m, 1H, *H*9), 1.81 (t, *J* = 2.6 Hz, 1H, *H*17), 1.77 – 1.71 (m, 1H, *H*14), 1.68 – 1.64 (m, 1H, $H7_a$), 1.64 – 1.59 (m, 1H, $H4_a$), 1.59 – 1.52 (m, 2H, $H5_a$ and $H13_a$), 1.52 – 1.45 (m, 2H, $H2_a$ and

*H*8$_a$), 1.45 – 1.35 (m, 3H, *H*11$_a$, *H*12$_a$ and *H*13$_b$), 1.35 – 1.29 (m, 1H, *H*4$_b$), 1.29 – 1.24 (m, 1H, *H*11$_b$), 1.24 – 1.13 (m, 13H, *H*5$_b$, *H*7$_b$, *H*8$_b$, *H*12$_b$ and *t*Bu (silyl ether))

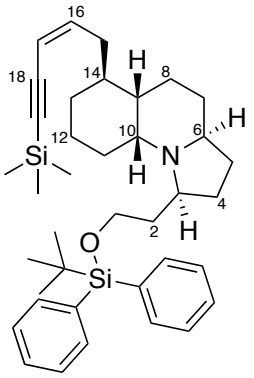
^{13}C NMR (125 MHz, C_6D_6) δ 136.1 (Ar), 134.4 (Ar), 130.0 (Ar), 128.4 (Ar), 84.0 (*C*16), 69.7 (*C*17), 62.3 (*C*1), 56.0 (*C*6), 54.9 (*C*3), 50.5 (*C*10), 40.4 (*C*9), 39.7 (*C*14), 36.7 (*C*2), 32.9 (*C*7), 30.1 (*C*5), 29.4 (*C*4), 27.2 (*t*Bu (silyl ether)), 27.0 (*C*8), 24.8 (*C*13), 22.6 (*C*15), 20.2 (*C*12), 19.5 (*t*Bu (silyl ether)), 16.7 (*C*11)

IR (film, cm^{-1}) ν_{max} 3309 (C–H, alkyne), 2929, 2165, 1110, 701

HRMS (ESI) calcd for $C_{33}H_{46}NOSi$ $[M+H]^+$ 500.3343, found 500.3335

$[\alpha]_D^{20}$ −11.3 (*c* 1.4, EtOH)

(1*S*,3a*S*,5a*S*,6*S*,9a*R*)-1-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-6-((*Z*)-5-(trimethylsilyl) pent-2-en-4-yn-1-yl)dodecahydropyrrolo[1,2-*a*]quinoline (121)



Anhydrous indium(III) chloride (26.4 mg, 0.120 mmol) was dried under vacuum at 150 ºC for 5 min and cooled to room temperature under argon. tetrahydrofuran (0.32 mL) was added and the mixture was cooled to −78 ºC to form a white suspension. Diisobutylaluminum hydride (1.0 M in hexanes, 0.110 mL, 0.110 mmol) was added to the suspension and stirred for 45 min at −78 ºC. A pre-mixed solution of alkyne **121a** (37.8 mg, 75.7 μmol) in tetrahydrofuran (0.35 mL) and acetic acid (4.4 μL, 76 μmol), was added, followed by triethylborane solution (1.0 M in hexanes, 76.0 μL, 76.0 μmol) and the mixture was stirred at −78 ºC for 4 h. After the mixture was allowed to warm to room temperature, 1,3-dimethyl-2-imidazolidinone (0.35 mL), 1-iodo-2-(trimethylsilyl)acetylene (17.0 μL, 0.110 mmol) and a palladium-tri-(2-furyl)phosphine complex (58.0 μL of a solution prepared from tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (7.0 mg, 6.8 μmol) and tri(2-furyl)phosphine (13.9 mg, 60.0 μmol) in tetrahydrofuran (1.0 mL)), was added successively. The mixture was shielded from light and stirred for 3 h at 70 ºC. The reaction mixture was quenched by saturated aqueous sodium carbonate and extracted with petroleum ether (4 × 3 mL). The combined organic layers were washed with brine (2 mL), dried over

sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:20 to 1:10 with 0.1% v/v triethylamine) to give silyl ether **121** (32.7 mg, 72%) as a colourless oil.

^{1}H NMR (500 MHz, C_6D_6) δ 7.83 – 7.79 (m, 4H, Ar*H*), 7.29 – 7.22 (m, 6H, Ar*H*), 5.71 – 5.64 (m, 1H, *H*16), 5.51 (d, *J* = 10.9 Hz, 1H, *H*17), 3.86 – 3.75 (m, 2H, *H*1), 3.35 – 3.29 (m, 1H, *H*10), 2.90 – 2.83 (m, 1H, *H*3), 2.80 (dt, *J* = 13.9, 9.0 Hz, 1H, *H*6), 2.47 – 2.40 (m, 1H, $H15_a$), 2.36 – 2.29 (m, 1H, $H15_b$), 2.20 (dtd, *J* = 13.2, 7.3, 2.6, 1H, $H2_a$), 1.79 – 1.52 (m, 10H, $H2_b$, $H4_a$, $H5_a$, $H7_a$, $H8_a$, *H*9, $H11_a$, $H12_a$, $H13_a$ and *H*14), 1.45 – 1.31 (m, 4H, $H4_b$, $H5_b$, $H11_b$ and $H13_b$), 1.29 – 1.18 (m, 12H, $H7_b$, $H8_b$, $H12_b$ and *t*Bu (silyl ether)), 0.24 (s, 9H, Si(CH_3)$_3$)

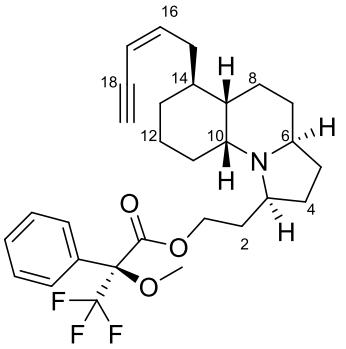
^{13}C NMR (125 MHz, C_6D_6) δ 145.1 (*C*16), 136.1 (136.1) (Ar), 134.5 (134.4) (Ar), 130.0 (Ar), 128.4 (Ar), 110.5 (*C*17), 103.3 (*C*18), 98.7 (*C*19), 62.3 (*C*1), 56.0 (*C*6), 55.2 (*C*3), 50.8 (*C*10), 41.6 (*C*9), 40.0 (*C*14), 36.5 (*C*2), 34.2 (*C*15), 33.1 (*C*7), 30.2 (*C*5), 29.3 (*C*4), 27.2 (*t*Bu (silyl ether), 27.1 (*C*8), 25.0 (*C*13), 20.8 (*C*12), 19.5 (*t*Bu (silyl ether)), 16.8 (*C*11), 0.25 (Si(*C*H_3)$_3$)

IR (film, cm^{-1}) ν_{max} 2930, 2153, 842

HRMS (ESI) calcd for $C_{38}H_{56}NOSi_2$ $[M+H]^+$ 598.3895, found 598.3878

$[\alpha]_D^{20}$ −32.0 (*c* 1.0, EtOH)

2-((1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-((*Z*)-Pent-2-en-4-yn-1-yl)dodecahydropyrrolo[1,2-*a*]quinolin-1-yl)ethyl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (123)



(*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (27 uL, 0.15 mmol) was added to a stirred solution of gephyrotoxin (14.7 mg, 51.2 μmol), 4-(dimethylamino)pyridine (1.0 mg, 8.1 μmol) and triethylamine (22 μL, 0.158 mmol) in dichloromethane (1.0 mL) at room temperature. After 2 h, the reaction mixture was diluted with diethyl ether (10 mL) and quenched with saturated aqueous sodium carbonate (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:20 to 1:5 with 0.1% v/v triethylamine) to give ester **123** as a yellow oil (22.6 mg, 89%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.72 – 7.69 (m, 2H, Ar*H*), 7.12 – 7.01 (m, 3H, Ar*H*), 5.63 (dt, *J* = 10.8, 7.6 Hz, 1H, *H*16), 5.40 (ddt, *J* = 10.8, 2.0, 1.2 Hz, 1H, *H*17), 4.30 – 4.20 (m, 2H, *H*1), 3.43 – 3.42 (m, 3H, OC*H*$_3$), 3.15 (dt, *J* = 12.0, 4.3 Hz, 1H, *H*10), 2.89 (d, *J* = 2.0 Hz, 1H, *H*19), 2.69 – 2.62 (m, 1H, *H*3), 2.58 (dt, *J* = 14.0, 8.2 Hz, 1H, *H*15$_a$), 2.39 – 2.28 (m, 2H, *H*6 and *H*15$_b$), 1.90 (dtd, *J* = 13.8, 7.6, 3.0 Hz, 1H, *H*2$_a$), 1.73 – 1.63 (m, 2H, *H*7$_a$ and *H*9), 1.60 – 1.47 (m, 4H, *H*2$_b$, *H*4$_a$, *H*5$_a$ and *H*8$_a$), 1.47 – 1.33 (m, 4H, *H*12, *H*13$_a$ and *H*14),

1.33 – 1.19 (m, 4H, *H*4$_b$, *H*11 and *H*13$_b$), 1.19 – 1.09 (m, 3H, *H*5$_b$, *H*7$_b$ and *H*8$_b$)

^{13}C NMR (125 MHz, C_6D_6) δ 166.7 (ester), 145.2 (*C*16), 133.2 (Ar), 129.7 (Ar), 128.7 (Ar), 128.4 (Ar), 124.3 (q, *J* = 288 Hz, *C*F$_3$), 109.6 (*C*17), 85.1 (q, *J* = 27 Hz, *C*CF$_3$), 82.0 (*C*19), 81.0 (*C*18), 64.3 (*C*1), 55.9 (*C*6), 55.4 (O*C*H$_3$), 54.3 (*C*3), 50.6 (*C*10), 40.2 (*C*9), 39.7 (*C*14), 34.0 (*C*15), 32.8 (*C*7), 32.1 (*C*2), 30.2 (*C*5), 28.6 (*C*4), 26.8 (*C*8), 25.8 (*C*13), 20.7 (*C*12), 16.6 (*C*11)

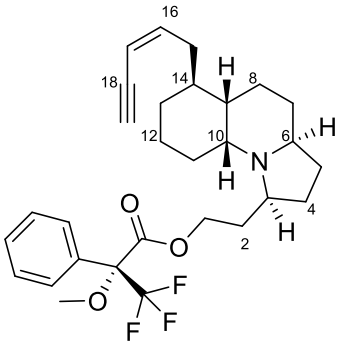
^{19}F NMR (376 MHz, C_6D_6) δ −71.6

IR (film, cm^{-1}) ν_{max} 3290 (C–H, alkyne), 2929, 1747 (C=O), 1451 (C=C)

HRMS (ESI) calcd for $C_{29}H_{37}NO_3F_3$ $[M+H]^+$ 504.2720, found 504.2704

$[\alpha]_D^{20}$ −77.5 (*c* 1.4, EtOH)

2-((1*S*,3a*S*,5a*S*,6*S*,9a*R*)-6-((*Z*)-Pent-2-en-4-yn-1-yl)dodecahydropyrrolo[1,2-*a*]quinolin-1-yl)ethyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (124)



A solution of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (7.5 mg, 39 μmol) in dichloromethane (1.0 mL) was added to a solution of gephyrotoxin (3.2 mg, 11 μmol), 4-(dimethylamino)pyridine (0.8 mg, 6.0 μmol) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (7.9 mg, 34 μmol) in dichloromethane (2.0 mL) at room temperature. The mixture was stirred for 24 h and quenched with saturated aqueous sodium carbonate (5 mL). The mixture was extracted with diethyl ether (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:20 to 1:5 with 0.1% v/v triethylamine) to give ester **124** as a yellow oil (3.8 mg, 68%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.72 – 7.69 (m, 2H, Ar*H*), 7.12 – 7.02 (m, 3H, Ar*H*), 5.63 (dt, *J* = 10.8, 7.6 Hz, 1H, *H*16), 5.40 (ddt, *J* = 10.8, 2.1, 1.2 Hz, 1H, *H*17), 4.30 (ddd, *J* = 11.0, 7.7, 5.5 Hz, 1H, $H1_a$), 4.20 (dt, *J* = 11.0, 7.4 Hz, 1H, $H1_b$), 3.43 – 3.42 (m, 3H, OCH_3), 3.16 (dt, *J* = 12.1, 4.3 Hz, 1H, *H*10), 2.91 (d, *J* = 2.1 Hz, 1H, *H*19), 2.69 (tdd, *J* = 8.0, 6.7, 3.0 Hz, 1H, *H*3), 2.59 (dt, *J* = 13.9, 8.3 Hz, 1H, $H15_a$), 2.39 – 2.28 (m, 2H, *H*6 and $H15_b$), 1.91 (dtd,

J = 13.8, 7.7, 3.0 Hz, 1H, $H2_a$), 1.73 – 1.65 (m, 2H, $H7_a$ and $H9$), 1.58 – 1.47 (m, 4H, $H2_b$, $H4_a$, $H5_a$ and $H8_a$), 1.47 – 1.35 (m, 4H, $H12$, $H13_a$ and $H14$), 1.35 – 1.19 (m, 4H, $H4_b$, $H11$ and $H13_b$), 1.19 – 1.11 (m, 3H, $H5_b$, $H7_b$ and $H8_b$)

^{13}C NMR (125 MHz, C_6D_6) δ 166.7 (ester), 145.2 (*C*16), 133.2 (Ar), 129.7 (Ar), 128.7 (Ar), 128.4 (Ar), 124.3 (q, J = 288 Hz, CF_3), 109.6 (*C*17), 85.2 (q, J = 27 Hz, CCF_3), 82.0 (*C*19), 81.0 (*C*18), 64.4 (*C*1), 55.9 (*C*6), 55.3 (OCH_3), 54.4 (*C*3), 50.6 (*C*10), 40.2 (*C*9), 39.7 (*C*14), 34.0 (*C*15), 32.9 (*C*7), 32.1 (*C*2), 30.3 (*C*5), 28.7 (*C*4), 26.8 (*C*8), 25.8 (*C*13), 20.7 (*C*12), 16.7 (*C*11)

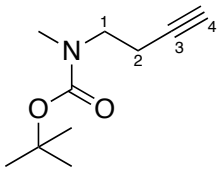
^{19}F NMR (376 MHz, C_6D_6) δ −71.5

IR (film, cm^{-1}) ν_{max} 3291 (C–H, alkyne), 2930, 1747 (C=O), 1451 (C=C)

HRMS (ESI) calcd for $C_{29}H_{37}NO_3F_3$ $[M+H]^+$ 504.2720, found 504.2707

$[\alpha]_D^{20}$ −22.1 (*c* 0.3, EtOH)

***tert*-Butyl but-3-yn-1-yl(methyl)carbamate (134)**



A solution of methylamine (12.5 g, 0.396 mol), 4-bromo-1-butyne (3.80 mL, 40.0 mmol) and sodium iodide (0.300 g, 2.00 mmol) in ethanol (80 mL) was stirred at 60 °C overnight in a sealed tube. The solution was then cooled to 0 °C and concentrated hydrochloric acid was added dropwise until pH < 2. After approximately 80 mL of the solvent was removed under reduced pressure, the residue was cooled to 0 °C and aqueous sodium hydroxide (50 wt. %) was slowly added until pH > 12. The aqueous solution was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure (40 °C, 400 mmHg) to give a yellow oil, which was directly used in the next step without further purification.

The crude amine was dissolved in tetrahydrofuran (25 mL) and cooled to 0 °C. Di-*tert*-butyl dicarbonate (13.0 g, 60.0 mmol) and triethylamine (8.40 mL, 60.0 mmol) were added to the mixture successively. The mixture was warmed to room temperature and stirred overnight before the solvent was removed under reduced pressure. The residue was redissolved in diethyl ether (50 mL) and washed with hydrochloric acid (1.0 M, 20 mL), saturated aqueous sodium bicarbonate (20 mL), brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:10) to give alkyne **134** (2.35 g, 32%) as a colourless oil.

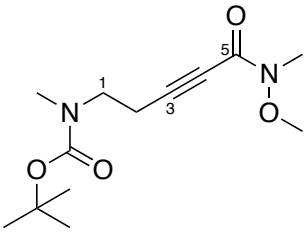
^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 3.19 (t, *J* = 7.0 Hz, 2H, *H*1), 2.69 (s, 3H, NC*H*$_3$), 2.19 (td, *J* = 7.0, 2.6 Hz, 2H, *H*2), 1.71 (t, *J* = 2.6 Hz, 1H, *H*4), 1.41 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 155.1 (urethane), 82.1 (*C*3), 79.0 (*t*Bu), 69.6 (*C*4), 48.3 (*C*1), 34.6 (N*C*H$_3$), 28.5 (*t*Bu), 18.2 (*C*2)

IR (film, cm^{-1}) ν_{max} 3302 (C–H, alkyne), 2972, 2932, 1689 (C=O), 1141

HRMS (ESI) calcd for $C_{10}H_{17}NO_2Na$ $[M+Na]^+$ 206.1152, found 206.1153

***tert*-Butyl (5-(methoxy(methyl)amino)-5-oxopent-3-yn-1-yl)(methyl)carbamate (130)**



Alkyne **134** (1.40 g, 7.65 mmol) was dissolved in tetrahydrofuran (40 mL) and cooled to −78 °C. *n*-Butyllithium (2.5 M solution in hexanes, 3.50 mL, 8.75 mmol) was added dropwise and the solution was stirred at −78 °C for 30 min before *N*-methoxy-*N*-methylcarbamoyl chloride (0.920 mL, 9.15 mmol) was added. The mixture was stirred at −78 °C for 3 h and then slowly warmed to room temperature. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:1) to give amide **130** (1.85 g, 90%) as a colourless oil.

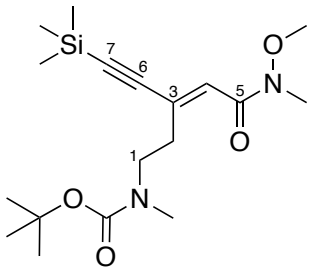
^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 3.42 (s, 3H, OCH_3), 3.15 (t, J = 6.8 Hz, 2H, *H*1), 2.90 (s, 3H, NCH_3, Weinreb amide), 2.69 (s, 3H, NCH_3), 2.26 (t, J = 6.8 Hz, 2H, *H*2), 1.41 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 155.1 (urethane), 154.1 (*C*5), 89.5 (*C*3), 79.2 (*t*Bu), 75.7 (*C*4), 61.3 (OCH_3), 47.6 (*C*1), 34.7 (NCH_3), 32.9 (NCH_3, Weinreb amide), 28.4 (*t*Bu), 18.6 (*C*2)

IR (film, cm^{-1}) ν_{max} 2975, 2236 (C≡C), 1691 (C=O), 1640 (C=O), 1142

HRMS (ESI) calcd for $C_{13}H_{22}N_2O_4Na$ $[M+Na]^+$ 293.1472, found 293.1466

***tert*-Butyl (*E*)-(5-(methoxy(methyl)amino)-5-oxo-3-((trimethylsilyl)ethynyl)pent-3-en-1-yl)(methyl)carbamate (129)**



A solution of palladium(II) acetate (63.0 mg, 0.281 mmol) and tris(2,6-dimethoxyphenyl)-phosphine (83.0 mg, 0.188 mmol) in tetrahydrofuran (10 mL) were stirred at room temperature for 15 min before being transferred *via* a cannula to a solution of amide **130** (700 mg, 2.70 mmol) in tetrahydrofuran (7 mL) and stirred for 5 min. Ethynyltrimethylsilane (0.420 mL, 3.00 mmol) was added and the black mixture was stirred at room temperature for 24 h before the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3) to give amide **129** (0.867 g, 87%) as a colourless oil.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.70 (s, 1H, *H*4), 3.58 (t, *J* = 6.9 Hz, 2H, *H*1), 3.15 (s, 3H, OCH_3), 3.08 (t, *J* = 6.9 Hz, 2H, *H*2), 2.89 (s, 3H, NCH_3), 2.88 (s, 3H, NCH_3, Weinreb amide), 1.50 (s, 9H, *t*Bu), 0.20 (s, 9H, Si(CH_3)$_3$)

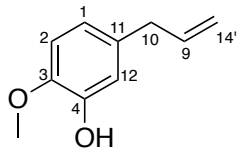
^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 166.5 (*C*5), 155.3 (urethane), 136.8 (*C*3), 125.5 (*C*4), 107.4 (*C*6), 92.7 (*C*7), 78.6 (*t*Bu), 61.0 (O*C*H$_3$), 48.5 (*C*1), 34.4 (N*C*H$_3$), 32.0 (N*C*H$_3$, Weinreb amide), 31.8 (*C*2), 28.6 (*t*Bu), -0.2 (Si(*C*H$_3$)$_3$)

IR (film, cm^{-1}) ν_{max} 2971, 1687 (C=O), 1637 (C=O), 1158

HRMS (ESI) calcd for $C_{18}H_{32}N_2O_4SiNa$ $[M+Na]^+$ 391.2024, found 391.2028

MP: 45 – 47 ºC

Chavibetol



4-Allylanisole (8.00 g, 54.0 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (8.00 mL, 53.4 mmol) were dissolved in tetrahydrofuran (180 mL) and cooled to −78 °C. *sec*-Buyllithium (1.4 M solution in cyclohexane, 50.1 mL, 70.2 mmol) was added dropwise over 15 min and the resulting mixture was stirred for 2 h at −78 °C. Then the cooling bath was removed. After 15 min the reaction mixture was put into an ice bath and stirred for additional 10 min before trimethyl borate (9.00 mL, 81.0 mmol) was added in one portion and the mixture was stirred for a further 1 h at 0 °C. Aqueous sodium hydroxide (1.0 M, 54.0 mL, 54.0 mmol) and aqueous hydrogen peroxide (30 wt. %, 26 mL) were added and the mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by addition of saturated aqueous sodium sulfite (100 mL) and poured into saturated aqueous ammonium chloride (100 mL). The mixture was extracted with diethyl ether (3 × 100 mL) and the combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:20 to 1:10) to give chavibetol (6.37 g, 72%) as a colourless liquid.

From extraction: Ground leaves of *Piper betle* (dried, 200 g, from Jawa Island, Indonesia) was suspended in aqueous sodium hydroxide (0.5 M, 1.5 L) and the container was flushed with nitrogen gas. The mixture was left standing at room temperature for 2 days with gentle

agitation every 12 h. Then the mixture was filtered and the filter cake was thoroughly washed with aqueous sodium hydroxide (0.5 M, 500 mL). Silica gel (100 g) was added to the filtrate and, with vigorous stirring, concentrated hydrochloric acid was added until pH < 3. The aqueous suspension was filtered and the filter cake was washed with ethanol (500 mL). The filtrate was saturated with sodium chloride and extracted with diethyl ether (3 × 300 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether 1:4) to give chavibetol (4.14 g, 2.1% dry weight of the leaves) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.2 Hz, 1H, *H*2), 6.79 (d, *J* = 2.1 Hz, 1H, *H*12), 6.67 (dd, *J* = 8.2, 2.1 Hz, 1H, *H*1), 5.95 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H, *H*9), 5.59 (s, 1H, O*H*), 5.09 – 5.03 (m, 2H, *H*14'), 3.87 (s, 3H, OCH_3), 3.30 (d, *J* = 6.8 Hz, 2H, *H*10)

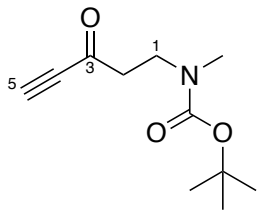
^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7 (*C*4), 145.1 (*C*3), 137.8 (*C*9), 133.6 (*C*11), 120.0 (*C*1), 115.7 (*C*14'), 115.0 (*C*12), 110.8 (*C*2), 56.2 (O*C*H_3), 39.7 (*C*10)

IR (film, cm^{-1}) ν_{max} 3400 (broad, O–H), 3077, 2938, 2840, 1509, 1270

MS (ESI) 187.1 $[M+Na]^+$

These data are consistent with that previously published for this compound.[viii]

tert-Butyl methyl(3-oxopent-4-yn-1-yl)carbamate (154)



(+)-Camphor-10-sulfonic acid (2.32 g, 10.0 mmol) was added to a solution of *tert*-butyl-*N*-methylcarbamate (6.62 g, 50.0 mmol) and acrolein (36.9 mL, 90% (wet), 0.500 mol) in dichloromethane (210 mL) at 0 °C and stirred for 15 min. Then the solution was warmed to room temperature and stirred for 1 h. Saturated aqueous sodium bicarbonate (350 mL) was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL) and the organic layers was combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a colourless oil (8.70 g, 46.5 mmol). The crude product was directly used in the next step by dissolving in diethyl ether (350 mL) and cooled to 0 °C before ethynylmagnesium bromide (0.5 M solution in tetrahydrofuran, 111 mL, 55.5 mmol) was added. The reaction mixture was stirred for 15 min and then quenched with saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layer was washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil (9.39 g, 44.0 mmol), which was directly used in the next step without further purification.

The above oil was dissolved in acetone (500 mL) and cooled to 0 °C. Then chromium(VI) oxide (8.80 g, 88.0 mmol) and acetic acid (25.0 mL, 0.440 mol) was added successively and

the reaction mixture was stirred for 3 h at 0 °C. The reaction mixture was diluted with diethyl ether (300 mL), washed with saturated aqueous sodium carbonate (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:5) to give ketone **154** (7.65 g, 72%) as a colourless oil.

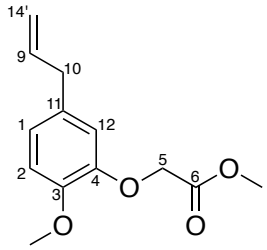
^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 3.32 (t, *J* = 6.7 Hz, 2H, *H*1), 2.62 (s, 3H, NC*H*$_3$), 2.52 (t, *J* = 6.7 Hz, 2H, *H*2), 2.50 (s, 1H, *H*5), 1.40 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 184.1 (*C*3), 155.1 (urethane), 82.0 (*C*4), 79.2 (*t*Bu), 77.9 (*C*5), 44.5 (*C*1), 44.4 (*C*2), 34.6 (N*C*H$_3$), 28.4 (*t*Bu)

IR (film, cm^{-1}) ν_{max} 3295 (C–H, alkyne), 2977, 2090 (C≡C), 1678 (broad, C=O, Boc and ketone), 1151

HRMS (ESI) calcd for $C_{11}H_{17}NO_3Na$ $[M+Na]^+$ 234.1101, found 234.1102

Methyl 2-(5-allyl-2-methoxyphenoxy)acetate (153)



A mixture of chavibetol (23.7 g, 0.144 mol), methyl chloroacetate (14.0 mL, 0.160 mol), sodium iodide (23.8 g, 0.160 mol) and potassium carbonate (44.2 g, 0.320 mol) in acetone (160 mL) was kept under gentle reflux overnight. Then the mixture was cooled to room temperature and filtered. The filter cake was washed with dichloromethane (250 mL) and the combined filtrates were concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3) to give ester **153** (33.1 g, 97%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.2 Hz, 1H, *H*2), 6.79 (dd, *J* = 8.2, 1.9 Hz, 1H, *H*1), 6.67 (d, *J* = 1.9 Hz, 1H, *H*12), 5.92 (ddt, *J* = 17.5, 9.6, 6.7 Hz, 1H, *H*9), 5.07 – 5.03 (m, 2H, *H*14'), 4.68 (s, 2H, *H*5), 3.86 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3, ester), 3.30 (d, *J* = 6.7 Hz, 2H, *H*10)

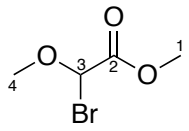
^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7 (*C*6), 148.2 (*C*3), 147.2 (*C*4), 137.6 (*C*9), 132.7 (*C*11), 122.5 (*C*1), 115.9 (*C*14'), 115.1 (*C*12), 112.2 (*C*2), 66.7 (*C*5), 56.2 (OCH_3), 52.3 (OCH_3, ester), 39.7 (*C*10)

IR (film, cm^{-1}) ν_{max} 3073, 2959, 1734 (C=O), 1140

HRMS (ESI) calcd for $C_{13}H_{17}O_4$ $[M+H]^+$ 237.1121, found 237.1124

MP: 40 – 41 ºC

Methyl 2-bromo-2-methoxyacetate (165)



A mixture of methyl methoxyacetate (13.0 mL, 0.130 mol), *N*-bromosuccinimide (23.0 g, 0.130 mol) and benzoyl peroxide (93.0 mg, 70% (wet), 0.269 mmol) in carbon tetrachloride (70 mL) was vigorously stirred and *carefully* warmed up to reflux. After the initial exothermic reaction ceased, the mixture was kept under gentle reflux overnight. Then the mixture was cooled to room temperature and filtered. The filtrated was concentrated under reduced pressure. The residue was purified by distillation (78 – 83 ºC, 14 mmHg) to give bromide **165** (33.1 g, 97%) as a colourless oil.

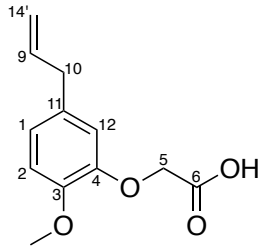
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 1H, *H*3), 3.85 (s, 3H, *H*1), 3.57 (s, 3H, *H*4)

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (*C*2), 83.3 (*C*3), 58.8 (*C*1), 53.4 (*C*4)

IR (film, cm^{-1}) ν_{max} 2957, 1750 (C=O), 1098

HRMS (CI) calcd for $C_4H_{11}BrNO_3$ $[M+NH_4]^+$ 199.9917, found 199.9915

2-(5-Allyl-2-methoxyphenoxy)acetic acid (168)



Lithium hydroxide monohydrate (0.630 g, 15.0 mmol) was dissolved in water (30 mL) and added to a solution of bromide **165** (2.36 g 10.0 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 4 h. Then the reaction mixture was diluted with ethyl acetate (150 mL), acidified with hydrochloric acid (1.0 M, 20 mL), washed with water (2 × 50 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give acid **168** (2.22 g, quantitative) as a colourless solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 – 6.87 (m, 2H, *H*1 and *H*2), 6.79 (d, *J* = 1.4 Hz, 1H, *H*12), 5.96 – 5.88 (m, 1H, *H*9), 5.09 – 5.08 (m, 1H, *H*14'$_a$), 5.07 – 5.05 (m, 1H, *H*14'$_b$), 4.66 (s, 2H, *H*5), 3.89 (s, 3H, OC*H*$_3$), 3.32 (d, *J* = 6.7 Hz, 2H, *H*10)

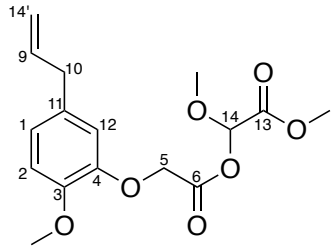
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1 (*C*6), 148.3 (*C*3), 147.1 (*C*4), 137.3 (*C*9), 133.6 (*C*11), 124.0 (*C*1), 117.8 (*C*12), 116.2 (*C*14'), 112.3 (*C*2), 68.8 (*C*5), 56.2 (O*C*H$_3$), 39.5 (*C*10)

IR (film, cm^{-1}) ν_{max} 3150 (broad, O–H), 2935, 1737 (C=O), 1220, 1156, 1138

HRMS (ESI) calcd for $C_{12}H_{14}O_4Na$ $[M+Na]^+$ 245.0784, found 245.0785

MP: 88 – 90 ºC

Methyl 2-(2-(5-allyl-2-methoxyphenoxy)acetoxy)-2-methoxyacetate (167)



A solution of acid **168** (2.22 g, 10.0 mmol), **165** (2.19 g, 12.0 mmol) and triethylamine (4.20 mL, 30.0 mmol) in dichloromethane (20 mL) was kept under gentle reflux for 4 h. The mixture was cooled to room temperature, diluted with dichloromethane (50 mL) and washed with water (30 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:4) to give ester **167** (2.96 g, 91%) as a colourless oil.

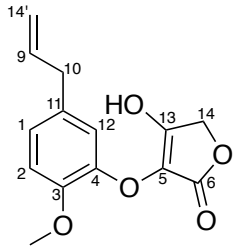
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.2 Hz, 1H, *H*2), 6.80 (dd, *J* = 8.2, 1.8 Hz, 1H, *H*1), 6.72 (d, *J* = 1.8 Hz, 1H, *H*12), 6.04 (s, *H*14), 5.92 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, *H*9), 5.07 – 5.04 (m, 1H, *H*14'$_a$), 5.04 – 5.03 (m, 1H, *H*14'$_b$), 4.80 (d, *J* = 1.4 Hz, 2H, *H*5), 3.86 (s, 3H, ArOCH_3), 3.81 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3, ester), 3.30 (d, *J* = 6.6 Hz, 2H, *H*10)

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5 (*C*6), 165.7 (*C*13), 148.2 (*C*3), 147.0 (*C*4), 137.5 (*C*9), 132.8 (*C*11), 122.7 (*C*1), 115.9 (*C*14'), 115.5 (*C*12), 112.4 (*C*2), 93.8 (*C*14), 66.3 (*C*5), 57.6 (O*C*H_3, ester), 56.2 (ArO*C*H_3), 53.1 (O*C*H_3), 39.7 (*C*10)

IR (film, cm^{-1}) ν_{max} 3003, 2954, 1759 (broad, C=O), 1123

HRMS (ESI) calcd for $C_{16}H_{29}O_7Na$ $[M+Na]^+$ 347.1101, found 347.1096

3-(5-Allyl-2-methoxyphenoxy)-4-hydroxyfuran-2(5*H*)-one (171)



n-Butyllithium (2.5 M solution in hexanes, 11.6 mL, 29.0 mmol) was added to a solution of diisopropylamine (3.10 g, 30.6 mmol) in tetrahydrofuran (100 mL) at −78 °C and stirred for 15 min at the same temperature. Then a solution of ester **153** (6.88 g, 29.0 mmol) in tetrahydrofuran (50 mL) was added to the above solution dropwise and stirred for 1.5 h at −78 °C. A solution of 1,4-dioxaspiro[4.5]decan-2-one (2.05 g, 13.1 mmol) in tetrahydrofuran (25 mL) was added and the reaction mixture was allowed to slowly warm to room temperature overnight. Then the solvent was removed under reduced pressure at room temperature. The residue was diluted with water (100 mL), acidified with hydrochloric acid (1.0 M, 60 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were extracted with aqueous sodium hydroxide (0.5 M, 3 × 50 mL) and then the combined aqueous layers were acidified with hydrochloric acid (1.0 M, 80 mL), extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was triturated with a mixture of petroleum ether (40 mL) and diethyl ether (20 mL). This suspension was filtered and the filter cake was dried under reduced pressure to give acid **171** (2.54 g, 33% based on **153**) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.0 Hz, 1H, *H*12), 6.97 (dd, *J* = 8.4, 2.0 Hz, 1H, *H*1), 6.94 (d, *J* = 8.4 Hz, 1H, *H*2), 5.95 – 5.86 (m, 1H, *H*9), 5.09 – 5.05 (m, 2H, *H*14'), 4.61 (s, 2H, *H*14), 3.97 (s, 3H, OC*H*$_3$), 3.31 (d, *J* = 6.8 Hz, 2H, *H*10)

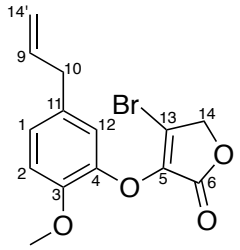
^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2 (*C*6), 161.8 (*C*13), 148.0 (*C*3), 146.4 (*C*4), 136.9 (*C*9), 135.6 (*C*11), 125.9 (*C*1), 122.6 (*C*5), 121.5 (*C*12), 116.4 (*C*14'), 114.0 (*C*2), 64.5 (*C*14), 57.6 (O*C*H$_3$), 39.4 (*C*10)

IR (film, cm^{-1}) ν_{max} 3100 (broad, O–H), 2965, 1661 (C=O), 1144

HRMS (ESI) calcd for $C_{14}H_{13}O_5$ $[M-H]^-$ 261.0769, found 261.0770

MP: 125 – 128 ºC (dec.)

3-(5-Allyl-2-methoxyphenoxy)-4-bromofuran-2(5*H*)-one (174)



Mucobromic acid (10.5 g, 40.7 mmol) was suspended in water (12.5 mL) under sonication and vigorous agitation before aqueous sodium hydroxide (1.0 M, 42.5 mL, 42.5 mmol) was added dropwise. The resulting slightly hazy solution was added to a solution of chavibetol (1.33 g, 8.10 mmol) in aqueous sodium hydroxide (0.75 M, 12.5 mL, 9.38 mmol) in one portion to give a yellow emulsion. Aqueous sodium hydroxide (1.0 M) was added every 5 minutes for 1 h to keep the reaction mixture as a slightly hazy solution (approx. 17 mL required). Then the solution was cooled to 0 ºC before sodium borohdyride (1.38 g, 36.5 mmol) was added in one portion and the solution was stirred for 1 h at 0 ºC. The reaction mixture was quenched by the addition of aqueous citric acid (3.0 M, 38.0 mL) at 0 ºC. After the addition, chloroform (75 mL) was added and the biphasic mixture was stirred overnight at room temperature. Then the organic layer was separated and the aqueous layer was further extracted with chloroform (2 × 60 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:5) to give bromide **174** (2.25 g, 86%) as a colourless solid, and recovered chavibetol (0.130 g, 10%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 8.3, 2.1 Hz, 1H, *H*1), 6.90 (d, *J* = 2.1 Hz, 1H, *H*12), 6.87 (d, *J* = 8.3 Hz, 1H, *H*2), 5.92 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, *H*9), 5.08 – 5.02 (m,

2H, *H*14'), 4.81 (s, 2H, *H*14), 3.82 (s, 3H, OC*H*$_3$), 3.31 (d, *J* = 6.6 Hz, 2H, *H*10)

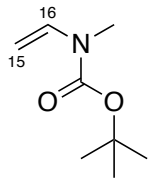
^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1 (*C*6), 149.1 (*C*3), 142.9 (*C*4), 141.3 (*C*5), 137.3 (*C*9), 132.8 (*C*11), 126.0 (*C*1), 120.5 (*C*12), 116.2 (*C*14'), 115.6 (*C*13), 112.7 (*C*2), 70.1 (*C*14), 56.4 (O*C*H$_3$), 39.3 (*C*10)

IR (film, cm^{-1}) ν_{max} 3027, 2933, 1775 (C=O), 1670, 1509, 1261, 1165, 1085, 1024

HRMS (ESI) calcd for $C_{14}H_{13}O_4BrNa$ $[M+Na]^+$ 346.9889, found 346.9890

MP: 34 – 35 ºC

***tert*-Butyl methyl(vinyl)carbamate (179)**



Acetaldehyde (33.8 mL, 0.602 mol) was added to methylamine (18.6 g, 0.599 mol) dropwise under vigorous stirring at −30 ºC. Then the viscous mixture was warmed to −10 ºC and stirred for 0.5 h before potassium hydroxide (15.0 g) was added in one portion. The mixture was gradually warmed to room temperature over 1 h and the aqueous layer was separated. Potassium hydroxide (10.0 g) was added to the organic layer and the mixture was stirred at room temperature for 1 h. Then the organic layer (containing mainly *N*-ethylidenemethylamine trimer) was transferred to a distillation apparatus fitted with a Vigreux column and dry-ice trap. The temperature of heating bath was set to 90 ºC and the fraction with boiling range 28 – 34 ºC was collected to give *N*-ethylidenemethylamine (24.7 g, 0.433 mol) as a colourless liquid. This compound was used immediately without storage by adding to a mixture of di-*tert*-butyl dicarbonate (79.1 g, 0.363 mol) and triethylamine (60.4 mL, 0.433 mol) in acetonitrile (180 mL) at 0 ºC. After the addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Then the reaction mixture was kept at reflux overnight. Solvent was then removed under reduced pressure (40 ºC, 100 mmHg) until approx. 70 mL of residue left. The residue was purified by silica gel chromatography (diethyl ether/petroleum ether b.p. 30 – 40 ºC 1:40) to give enamine **179** (36.5 g, 64% based on di-*tert*-butyl dicarbonate) as a colourless liquid.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 7.26 (dd, *J* = 15.8, 9.3 Hz, 1H, *H*16), 4.07 (d,

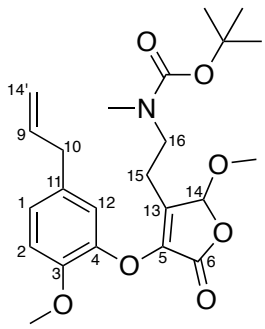
J = 9.3 Hz, 1H, $H15_a$), 4.06 (d, J = 15.8 Hz, 1H, $H15_b$), 2.79 (s, 3H, NCH_3), 1.38 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 152.9 (urethane), 135.0 (*C*16), 90.0 (*C*15), 80.5 (*t*Bu), 29.7 (N*C*H$_3$), 28.2 (*t*Bu)

IR (film, cm^{-1}) ν_{max} 2980, 2933, 1708 (C=O), 1626 (C=C), 1319, 1147

HRMS (FI) calcd for $C_8H_{15}NO_2$ $[M]^+$ 157.1103, found 157.1107

***tert*-Butyl (2-(4-(5-allyl-2-methoxyphenoxy)-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl) ethyl)(methyl)carbamate (163)**



n-Butyllithium (2.5 M solution in hexanes, 3.40 mL, 8.50 mmol) was added to a solution of hexamethyldisilazane (1.85 mL, 8.92 mmol) in tetrahydrofuran (40 mL) at −78 °C and stirred for 15 min at the same temperature. A solution of ester **167** (1.30 g, 4.00 mmol) in tetrahydrofuran (10 mL) was added to the above solution dropwise and stirred for 4 h at −78 °C. The reaction mixture was diluted with diethyl ether (50 mL) and hydrochloric acid (1.0 M, 20 mL) was added. The organic layer was separated and washed with brine (2 × 20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil (1.15 g, 4.00 mmol), which was directly used in the next step without further purification.

Triflic anhydride (0.850 mL, 5.11 mmol) was added to a solution of the above crude product (1.15 g, 4.00 mmol) and *N*,*N*-diisopropylethylamine (1.05 mL, 6.03 mmol) in dichloromethane (50 mL) at – 78 ºC and stirred for 5 h. Then the reaction mixture was warmed to room temperature, diluted with diethyl ether (150 mL), washed with water (50 mL), brine (50 mL), dried over sodium sulfate, filtered through a short pad of silica and

concentrated under reduced pressure to give crude a brown oil(1.21 g, 2.84 mmol), which was directly used in the next step without further purification.

9-Borabicyclo[3.3.1]nonane (0.5 M in tetrahydrofuran, 11.4 mL, 5.68 mmol) was added to a solution of enamine **179** (0.893 g, 5.68 mmol) in tetrahydrofuran (15 mL, degassed) at 0 ºC. After the addition, the solution was warmed to room temperature and stirred for 3 h before water (2.5 mL, degassed) was added. The content in the flask was transferred to a mixture of above crude product (1.21 g, 2.84 mmol), tetrakis- (triphenylphosphine)palladium(0) (0.328 g, 0.284 mmol), and cesium carbonate (0.922 g, 5.68 mmol) in tetrahydrofuran (30 mL, degassed) and the flask was further washed with tetrahydrofuran (2.0 mL, degassed). The brown biphasic mixture was warmed to 40 ºC and stirred overnight. Then the reaction mixture was diluted with water (30 mL), brine (30 mL), and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3) to give butenolide **163** (0.589 g, 34%) as a yellow oil.

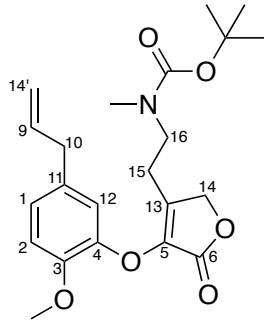
^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.94 (d, *J* = 1.7 Hz, 1H, *H*12), 6.74 (dd, *J* = 8.3, 1.7 Hz, 1H, *H*1), 6.61 (d, *J* = 8.3 Hz, 1H, *H*2), 5.88 – 5.80 (m, 1H, *H*9), 5.54 (s, 1H, *H*14), 5.00 – 4.95 (m, 2H, *H*14'), 3.48 (s, 3H, ArOCH_3), 3.44 – 3.36 (m, 1H, *H*16$_a$), 3.26 (s, 3H, OCH_3), 3.14 (d, *J* = 6.5 Hz, 2H, *H*10), 3.13 – 3.06 (m, 1H, *H*16$_b$), 2.62 (s, 3H, NCH_3), 2.51 – 2.43 (m, 1H, *H*15$_a$), 2.31 – 2.25 (m, 1H, *H*15$_b$), 1.41 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 163.6 (*C*6), 154.9 (urethane), 149.2 (*C*3), 145.0 (*C*4), 142.9 (*C*5), 134.6 (*C*9), 137.6 (*C*13), 133.1 (*C*11), 124.7 (*C*1), 120.0 (*C*12), 115.2 (*C*14'), 113.7 (*C*2), 100.7 (*C*14), 78.9 (*t*Bu), 55.8 (ArO*C*H$_3$), 55.0 (O*C*H$_3$), 46.0 (*C*16), 38.9 (*C*10), 33.4 (N*C*H$_3$), 28.0 (*t*Bu), 22.8 (*C*15)

IR (film, cm^{-1}) ν_{max} 2930, 1784 (C=O), 1693 (C=O), 1161, 1127, 1124, 1088

HRMS (ESI) calcd for $C_{23}H_{31}NO_7Na$ $[M+Na]^+$ 456.1993, found 456.1994

***tert*-Butyl (2-(4-(5-allyl-2-methoxyphenoxy)-5-oxo-2,5-dihydrofuran-3-yl)ethyl)(methyl) carbamate (181)**



From bromide 174: 9-Borabicyclo[3.3.1]nonane (0.5 M solution in tetrahydrofuran, 39.0 mL, 19.5 mmol) was added to enamine **179** (3.84 g, 24.4 mmol) at 0 ºC. After the addition, the solution was warmed to room temperature and stirred for 3 h before water (6.5 mL, degassed) was added. The content in the flask was transferred to a mixture of bromide **174** (5.30 g, 16.3 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane adduct (1.33 g, 1.63 mmol), and cesium carbonate (10.6 g, 32.6 mmol) in dimethylformamide (110 mL, degassed) and the flask was further washed with dimethylformamide (20 mL, degassed). The brown biphasic mixture was warmed to 40 ºC and stirred for 45 min. Then the reaction mixture was diluted with water (250 mL) and brine (250 mL), then extracted with diethyl ether (3 × 300 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:2) to give butenolide **181** (3.81 g, 58%) as an off-white solid.

From acid 171: Triflic anhydride (4.60 mL, 27.3 mmol) was added to a solution of acid **171** (5.60 g, 21.4 mmol) and *N*,*N*-diisopropylethylamine (5.50 mL, 31.6 mmol) in

dichloromethane (230 mL) at –78 ºC and stirred for 5 h. Then the reaction mixture was warmed to room temperature and washed with water (100 mL), brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a brown oil (8.43 g, 21.4 mmol), which was immediately used in the next reaction without further purification.

9-Borabicyclo[3.3.1]nonane (0.5 M solution in tetrahydrofuran, 85.6 mL, 42.8 mmol) was added to a solution of enamine **179** (6.73 g, 42.8 mmol) in tetrahydrofuran (120 mL, degassed) at 0 ºC. After the addition, the solution was warmed to room temperature and stirred for 3 h before water (20 mL, degassed) was added. The content in the flask was transferred to a mixture of the above crude product (8.43 g, 21.4 mmol), [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)-dichloromethane adduct (1.75 g, 2.14 mmol), and cesium carbonate (13.9 g, 42.8 mmol) in tetrahydrofuran (240 mL, degassed) and the flask was further washed with tetrahydrofuran (20 mL, degassed). The brown biphasic mixture was warmed to 40 ºC and stirred for 1 h. Then the reaction mixture was diluted with water (200 mL), brine (200 mL), and extracted with diethyl ether (3 × 400 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:2) to give butenolide **181** (3.97 g, 46%) as an off-white solid.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.94 (d, *J* = 2.1 Hz, 1H, *H*12), 6.73 (dd, *J* = 8.3, 2.1 Hz, 1H, *H*1), 6.62 (d, *J* = 8.3 Hz, 1H, *H*2), 5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, *H*9),

5.01 – 4.95 (m, 2H, *H*14'), 4.25 (s, 2H, *H*14), 3.50 (s, 3H, OCH_3), 3.16 (d, *J* = 6.6 Hz, 2H, *H*10), 3.10 (t, *J* = 7.0 Hz, 2H, *H*16), 2.57 (s, 3H, NCH_3), 2.24 (t, *J* = 7.0 Hz, 2H, *H*15), 1.39 (s, 9H, *t*Bu)

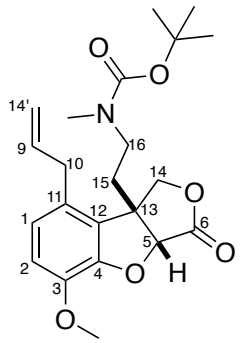
^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 166.5 (*C*6), 155.3 (urethane), 149.6 (*C*3), 145.9 (*C*4), 140.4 (*C*5), 138.7 (*C*13), 137.6 (*C*9), 133.5 (*C*11), 124.7 (*C*1), 119.9 (*C*12), 115.6 (*C*14'), 114.3 (*C*2), 79.4 (*t*Bu), 68.1 (*C*14), 56.4 (O*C*H$_3$), 46.5 (*C*16), 39.5 (*C*10), 33.8 (N*C*H$_3$), 28.4 (*t*Bu), 24.0 (*C*15)

IR (film, cm^{-1}) ν_{max} 2976, 1766 (C=O), 1691 (C=O), 1516, 1399, 1248, 1127

HRMS (ESI) calcd for $C_{22}H_{29}NO_6Na$ $[M+Na]^+$ 426.1886, found 426.1887

MP: 78 – 80 ºC

***tert*-Butyl (2-(8-allyl-5-methoxy-3-oxo-3,3a-dihydrofuro[3,4-*b*]benzofuran-8b(1*H*)-yl) ethyl)(methyl)carbamate (190)**



Butenolide **181** (2.80 g, 6.94 mmol) was dissolved in a mixture of dichloroethane and hexafluoroisopropanol (1:1 v/v, 350 mL, degassed) and irradiated with a 500 W high-pressure mercury-vapour lamp in a Pyrex® immersion well reactor at room temperature for 120 h. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:2) to give benzofuran **190** (1.04 g, 37%) as a colourless amorphous solid, and recovered butenolide **181** (0.603 g, 22%).

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.60 (d, *J* = 8.3 Hz, 1H, *H*2), 6.57 (d, *J* = 8.3 Hz, 1H, *H*1), 5.81 (ddt, *J* = 16.6, 10.0, 6.2 Hz, 1H, *H*9), 4.99 (d, *J* = 10.0 Hz, 1H, *H*14'$_a$), 4.93 (d, *J* = 16.6 Hz, 1H, *H*14'$_b$), 4.65 (s, 1H, *H*5), 4.30 (d, *J* = 9.2 Hz, 1H, *H*14$_a$), 3.77 (d, *J* = 9.2 Hz, 1H, *H*14$_b$), 3.56 (s, 3H, OC*H*$_3$), 3.13 – 3.03 (m, 2H, *H*10), 2.90 (ddd, *J* = 13.9, 10.6, 4.9 Hz, 1H, *H*16$_a$), 2.63 (ddd, *J* = 13.9, 10.4, 5.5 Hz, 1H, *H*16$_b$), 2.49 (s, 3H, NC*H*$_3$), 1.92 (ddd, *J* = 13.6, 10.6, 5.5 Hz, 1H, *H*15$_a$), 1.59 (ddd, *J* = 13.6, 10.4, 4.9 Hz, 1H, *H*15$_b$), 1.40 (s, 9H, *t*Bu)

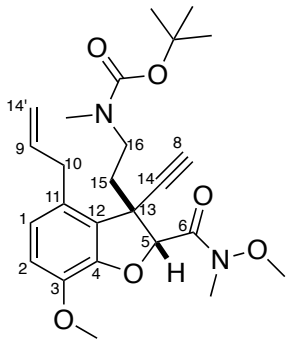
^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 172.1 (*C*6), 155.2 (urethane), 148.6 (*C*4), 144.5

(*C*3), 137.0 (*C*9), 128.6 (*C*11), 127.4 (*C*12), 124.3 (*C*1), 116.4 (*C*14'), 116.2 (*C*2), 83.9 (*C*5), 79.3 (*t*Bu), 74.6 (*C*14), 56.8 (O*C*H_3), 52.9 (*C*13), 45.5 (*C*16), 35.4 (*C*10), 34.4 (N*C*H_3), 33.9 (*C*15), 28.5 (*t*Bu)

IR (film, cm^{-1}) ν_{max} 2956, 1795 (C=O), 1693 (C=O), 1508, 1280, 1169, 1156, 1031

HRMS (ESI) calcd for $C_{22}H_{29}NO_6Na$ $[M+Na]^+$ 426.1886, found 426.1887

***tert*-Butyl (2-(4-allyl-3-ethynyl-7-methoxy-2-(methoxy(methyl)carbamoyl)-2,3-dihydrobenzofuran-3-yl)ethyl)(methyl)carbamate (203)**



Aqueous potassium hydroxide (1.0 M, 9.30 mL, 9.30 mmol) was added to a solution of benzofuran **190** (190 mg, 0.471 mmol) in *tert*-butanol (9.3 mL) and the biphasic mixture was stirred at room temperature overnight. Then sodium ruthenate[ix] (0.0085 M solution in 1.0 M aqueous sodium hydroxide, 61.0 mL, 0.519 mmol) was added in one portion and the reaction mixture was warmed to 50 ºC for 30 min. The black suspension was filtered and the filter cake was successively washed with water (10 mL) and isopropanol (20 mL). The filtrate was diluted with brine (50 mL), acidified with hydrochloric acid (3.0 M, 30 mL), and extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude product was dissolved in methanol (18.6 mL) followed by addition of Ohira-Bestmann reagent (181 mg, 0.942 mmol) and potassium carbonate (325 mg, 2.35 mmol) at room temperature. The mixture was stirred for 6 h, then *N*,*O*-dimethylhydroxylamine hydrochloride (276 mg, 2.83 mmol), 4-methylmorpholine (0.310 mL, 2.83 mmol), and 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (628 mg, with ≤ 17 wt. % water, 1.88 mmol) were successively added and stirred for 6 h at room temperature. The solvent was then removed under reduced pressure and the residue was suspended in a mixture of hydrochloric

acid (1.0 M, 15 mL) and brine (30 mL), and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:1) to give amide **203** (158 mg, 73% from benzofuran **190**) as a colourless amorphous solid.

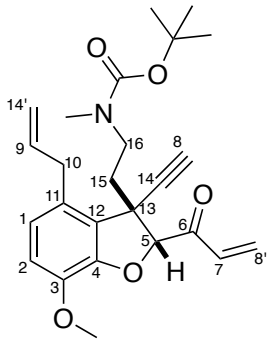
^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.68 (d, *J* = 8.3 Hz, 1H, *H*2), 6.63 (d, *J* = 8.3 Hz, 1H, *H*1), 6.00 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, *H*9), 5.58 (s, 1H, *H*5), 5.08 (ddt, *J* = 16.9, 1.7, 1.7 Hz, 1H, *H*14'$_a$), 5.03 (ddt, *J* = 10.1, 1.7, 1.4 Hz, 1H, *H*14'$_b$), 3.68 (s, 3H, OC*H*$_3$), 3.66 – 3.63 (m, 2H, *H*10), 3.46 (ddd, *J* = 13.8, 11.3, 4.8 Hz, 1H, *H*16$_a$), 3.37 (s, 3H, OC*H*$_3$, Weinreb amide), 3.16 (ddd, *J* = 13.8, 11.3, 4.8 Hz, 1H, *H*16$_b$), 2.95 (s, 3H, NC*H*$_3$, Weinreb amide), 2.62 (s, 3H, NC*H*$_3$), 2.32 (ddd, *J* = 13.8, 11.3, 4.8 Hz, 1H, *H*15$_a$), 2.17 (ddd, *J* = 13.8, 11.3, 4.8 Hz, 1H, *H*15$_b$), 2.04 (s, 1H, *H*8), 1.42 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 169.9 (*C*6), 155.3 (urethane), 149.7 (*C*4), 143.9 (*C*3), 137.9 (*C*9), 129.4 (*C*11), 127.9 (*C*12), 123.1 (*C*1), 116.3 (*C*2), 115.6 (*C*14'), 86.8 (*C*5), 83.6 (*C*14), 79.0 (*t*Bu), 73.7 (*C*8), 60.7 (O*C*H$_3$), 57.2 (ArO*C*H$_3$), 48.6 (*C*13), 45.6 (*C*16), 39.0 (*C*15), 34.8 (*C*10), 34.4 (N*C*H$_3$), 32.7 (N*C*H$_3$, Weinreb amide), 28.5 (*t*Bu)

IR (film, cm^{-1}) ν_{max} 3259, 2972, 1688 (broad, C=O, Boc and Weinreb amide), 1507, 1437, 1392, 1283, 1155

HRMS (ESI) calcd for $C_{25}H_{34}N_2O_6Na$ $[M+Na]^+$ 481.2309, found 481.2306

***tert*-Butyl (2-(2-acryloyl-4-allyl-3-ethynyl-7-methoxy-2,3-dihydrobenzofuran-3-yl) ethyl)(methyl) carbamate (159)**



Vinylmagnesium bromide (1.0 M solution in tetrahydrofuran, 1.40 mL, 1.40 mmol) was added dropwise to a solution of amide **203** (160 mg, 0.349 mmol) in tetrahydrofuran (9.5 mL) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC before quenched by the addition of hydrochloric acid (1.0 M, 30 mL, pre-cooled to 0 ºC). The mixture was further diluted with brine (20 mL) and extracted with diethyl ether (4 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:3.5) to give vinyl ketone **159** (129 mg, 87%) as a colourless amorphous solid.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.68 (d, *J* = 8.4 Hz, 1H, *H*1), 6.66 (d, *J* = 8.4 Hz, 1H, *H*2), 6.63 (dd, *J* = 17.3, 10.6 Hz, 1H, *H*7), 6.27 (dd, *J* = 17.3, 1.9 Hz, 1H, *H*8'$_a$), 5.98 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H, *H*9), 5.27 (dd, *J* = 10.6, 1.9 Hz, 1H, *H*8'$_b$), 5.08 (ddt, *J* = 16.9, 1.7, 1.6 Hz, 1H, *H*14'$_a$), 5.08 (s, 1H, *H*5), 5.03 (ddt, *J* = 10.1, 1.7, 1.6 Hz, 1H, *H*14'$_b$), 3.62 – 3.58 (m, 2H, *H*10), 3.59 (s, 3H, OC*H*$_3$), 3.38 (ddd, *J* = 13.9, 11.0, 5.0 Hz, 1H, *H*16$_a$), 3.24 (ddd, *J* = 13.9, 11.0, 4.7 Hz, 1H, *H*16$_b$), 2.64 (s, 3H, NC*H*$_3$), 2.34 (ddd, *J* = 13.5, 11.0, 5.0 Hz, 1H,

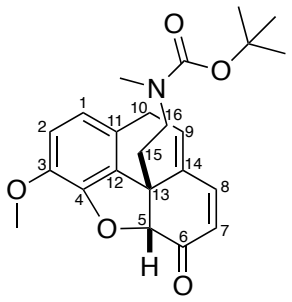
*H*15$_a$), 2.16 – 2.09 (m, 1H, *H*15$_b$), 2.07 (s, 1H, *H*8), 1.43 (s, 9H, *t*Bu)

^{13}C NMR (125 MHz, d$_8$-toluene, 363 K) δ 194.5 (*C*6), 155.2 (urethane), 148.4 (*C*4), 144.1 (*C*3), 137.4 (*C*9), 132.4 (*C*7), 129.8 (*C*11), 128.8 (*C*12), 128.1 (*C*8'), 123.8 (*C*1), 116.0 (*C*14'), 115.5 (*C*2), 92.7 (*C*5), 82.4 (*C*14), 79.1 (*t*Bu), 76.6 (*C*8), 56.6 (O*C*H$_3$), 48.3 (*C*13), 45.5 (*C*16), 39.2 (*C*15), 34.8 (*C*10), 34.4 (N*C*H$_3$), 28.5 (*t*Bu)

IR (film, cm^{-1}) ν_{max} 3275 (alkyne C–H), 3078, 2953, 1737 (C=O), 1699 (C=O), 1507, 1366, 1282, 1155

HRMS (ESI) calcd for $C_{25}H_{31}NO_5Na$ $[M+Na]^+$ 448.2094, found 448.2089

tert-Butyl (2-(5-methoxy-3-oxo-3,8-dihydrophenanthro[4,5-_bcd_]furan-3a[1](3a_H_)-yl)ethyl) (methyl) carbamate (205)



A solution of vinyl ketone **159** (4.0 mg, 9.5 μmol) and Hoveyda-Grubbs 2nd generation catalyst (0.3 mg, 0.5 μmol) in dichloromethane (0.3 mL) was stirred for 6 h at room temperature. Then the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/petroleum ether 1:1) to give carbamate **205** (3.5 mg, 94%) as a colourless amorphous solid.

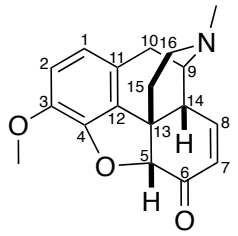
^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ 6.59 (d, J = 8.0 Hz, 1H, H2), 6.61 – 6.57 (m, 1H, H8), 6.46 (d, J = 8.0 Hz, 1H, H1), 5.73 (d, J = 6.8 Hz, 1H, H9), 5.63 (d, J = 10.1 Hz, 1H, H7), 4.94 (s, 1H, H5), 3.74 (s, 3H, OCH_3), 3.27 (d, J = 19.7 Hz, 1H, $H10_a$), 3.21 – 3.13 (m, 1H, $H16_a$), 3.01 – 2.93 (m, 1H, $H16_b$), 2.92 (dd, J = 19.7, 6.8 Hz, 1H, $H10_b$), 2.53 (s, 3H, NCH_3), 1.89 – 1.82 (m, 1H, $H15_a$), 1.81 – 1.74 (m, 1H, $H15_b$), 1.39 (s, 9H, tBu)

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ 192.0 (C6), 155.1 (urethane), 146.4 (C4), 143.8 (C3), 142.4 (C8), 140.7 (C13), 133.4 (C14), 131.7 (C9), 126.9 (C11), 125.6 (C7), 120.0 (C1), 116.8 (C2), 87.2 (C5), 79.1 (tBu), 57.6 (OCH_3), 48.5 (C13), 45.6 (C16), 37.7 (C15), 34.2 (NCH_3), 28.5 (tBu)

IR (film, cm^{-1}) ν_{max} 2972, 1681 (broad, C=O, Boc and ketone), 1153

HRMS (ESI) calcd for $C_{23}H_{27}NO_5Na$ $[M+Na]^+$ 420.1781, found 420.1778

(±)-Codeinone



Trifluoroacetic acid (77.2 μL, 1.00 mmol) was added to a solution of carbamate **205** (10.0 mg, 25.2 μmol) in dichloromethane (0.4 mL) and stirred at room temperature for 30 min. The reaction mixture was cooled to 0 ºC, diluted with dichloromethane (0.8 mL) and saturated aqueous sodium carbonate (1.6 mL) was added dropwise. After the addition, the biphasic mixture was warmed to room temperature and vigorously stirred for 30 min. Then the reaction mixture was diluted with water (2.5 mL) and the organic layer was separated. The aqueous layer was further extracted with dichloromethane (4 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (methanol/dichloromethane 1:50 to 1:10) to give a mixture of neopinone and codeinone (5.1 mg, 17.1 μmol) as a yellow amorphous solid.

The above solid was dissolved in dichloromethane (0.3 mL) followed by the addition of hydrogen chloride (2.0 M solution in diethyl ether, 34.2 μL, 68.4 μmol) and stirred at room temperature for 30 min. Then the reaction mixture was cooled to 0 ºC before aqueous sodium hydroxide (0.4 M, 0.340 mL, 0.136 mmol) was added. The biphasic mixture was warmed to room temperature and vigorously stirred for 30 min. Then the reaction mixture was diluted with water (2.5 mL) and the organic layer was separated. The aqueous layer was further

extracted with dichloromethane (4 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (methanol/dichloromethane 1:50 to 1:10) to give codeinone (4.8 mg, 64%) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.2 Hz, 1H, *H*2), 6.64 (dd, *J* = 10.2, 1.9 Hz, 1H, *H*8), 6.61 (d, *J* = 8.2 Hz, 1H, *H*1), 6.09 (dd, *J* = 10.2, 1.9 Hz, 1H, *H*7), 4.70 (s, 1H, *H*5), 3.85 (s, 3H, OCH_3), 3.42 (dd, *J* = 5.6, 3.3 Hz, 1H, *H*9), 3.22 – 3.19 (m, 1H, *H*14), 3.11 (d, *J* = 18.5 Hz, 1H, $H10_a$), 2.61 (ddd, *J* = 12.2, 4.9, 1.2 Hz, 1H, $H16_a$), 2.46 (s, 3H, NCH_3), 2.31 (dd, *J* = 18.5, 5.6 Hz, 1H, $H10_b$), 2.30 (td, *J* = 12.2, 3.7 Hz, 1H, $H16_b$), 2.07 (td, *J* = 12.2, 4.9 Hz, 1H, $H15_a$), 1.86 (ddd, *J* = 12.2, 3.7, 1.2 Hz, 1H, $H15_b$)

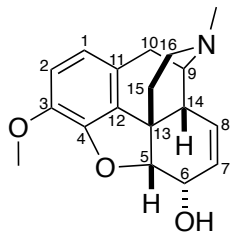
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7 (*C*6), 149.1 (*C*8), 145.1 (*C*4), 142.7 (*C*3), 132.7 (*C*7), 129.2 (*C*12), 126.2 (*C*11), 120.1 (*C*1), 115.0 (*C*2), 88.3 (*C*5), 59.2 (*C*9), 57.0 (O*C*H_3), 47.0 (*C*16), 43.3 (N*C*H_3), 43.1 (*C*13), 41.7 (*C*14), 34.2 (*C*15), 20.6 (*C*10)

IR (film, cm^{-1}) ν_{max} 2992, 1669 (C=O), 1500, 1056

HRMS (ESI) calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$ 298.1438, found 298.1439

MP: 175 – 180 ºC (dec.)

(±)-Codeine



From codeinone: Sodium borohydride (12.8 mg, 0.339 mmol) was added to a solution of codeinone (5.0 mg, 16.8 μmol) in methanol (1.2 mL) and stirred at room temperature for 30 min. Then about half of the solvent was removed under a flow of nitrogen gas. Aqueous sodium hydroxide (2.0 M, 0.6 mL) was added and the mixture was warmed to 70 ºC for 5 min. The resulting mixture was diluted with water (2 mL) and extracted with chloroform (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethanol/dichloromethane 1:10) to give codeine (5.0 mg, quantitative) as a white solid.

From carbamate 205: A solution of carbamate **205** (40.5 mg, 95.7 μmol) and Hoveyda-Grubbs 2nd generation catalyst (3.0 mg, 4.8 μmol) in dichloromethane (3.2 mL) was stirred for 6 h at room temperature. Then trifluoroacetic acid (0.290 mL, 3.79 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 ºC and saturated aqueous sodium carbonate (1.6 mL) was added dropwise. After the addition, the biphasic mixture was warmed to room temperature and vigorously stirred for 30 min. Then the reaction mixture was diluted with water (2.5 mL) and

the organic layer was separated. The aqueous layer was further extracted with dichloromethane (4 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (methanol/dichloromethane 1:50 to 1:10) to give a mixture of neopinone and codeinone (20.4 mg, 0.069 mmol) as a yellow amorphous solid.

The above solid was dissolved in dichloromethane (0.3 mL) followed by addition of hydrogen chloride (2.0 M solution in diethyl ether, 0.140 mL, 0.280 mmol) and stirred at room temperature for 30 min. Then the reaction mixture was cooled to 0 ºC before aqueous sodium hydroxide (0.4 M, 1.4 mL, 0.56 mmol) was added. The biphasic mixture was warmed to room temperature and vigorously stirred for 30 min. Then sodium borohydride (26.0 mg, 0.687 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with ethanol in dichloromethane (10% v/v, 1.5 mL) and the organic layer was separated. The aqueous layer was further extracted with ethanol in dichloromethane (10% v/v, 3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethanol/dichloromethane 1:10) to give codeine (18.5 mg, 65%) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.2 Hz, 1H, *H*2), 6.57 (d, *J* = 8.2 Hz, 1H, *H*1), 5.71 (dddd, *J* = 9.9, 3.2, 1.9, 1.3 Hz, 1H, *H*7), 5.30 (ddd, *J* = 9.9, 3.2, 2.6 Hz, 1H, *H*8), 4.89 (dd, *J* = 6.5, 1.3 Hz, 1H, *H*5), 4.18 (ddd, *J* = 6.5, 3.2, 2.6 Hz, 1H, *H*6), 3.84 (s, 3H, OCH_3), 3.35

(dd, J = 6.2, 3.2 Hz, 1H, $H9$), 3.05 (d, J = 18.6 Hz, 1H, $H10_a$), 2.67 (ddd, J = 3.2, 3.2, 1.9 Hz, 1H, $H14$), 2.59 (dd, J = 12.5, 5.3 Hz, 1H, $H16_a$), 2.44 (s, 3H, NCH_3), 2.40 (td, J = 12.5, 3.6 Hz, 1H, $H16_b$), 2.29 (dd, J = 18.6, 6.2 Hz, 1H, $H10_b$), 2.06 (td, J = 12.5, 5.3 Hz, 1H, $H15_a$), 1.88 (ddd, J = 12.5, 3.6, 1.7 Hz, 1H, $H15_b$)

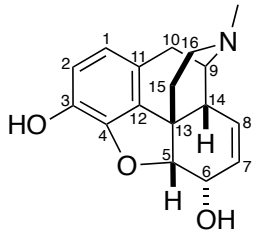
^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4 ($C4$), 142.4 ($C3$), 133.6 ($C7$), 131.2 ($C12$), 128.4 ($C8$), 127.4 ($C11$), 119.7 ($C1$), 113.0 ($C2$), 91.5 ($C5$), 66.5 ($C6$), 59.0 ($C9$), 56.5 (OCH_3), 46.6 ($C16$), 43.3 (NCH_3), 43.1 ($C13$), 41.0 ($C14$), 36.0 ($C15$), 20.5 ($C10$)

IR (film, cm^{-1}) ν_{max} 3531 (O–H), 3022, 2929, 1501, 1453, 1385, 1250, 1115, 1027

HRMS (ESI) calcd for $C_{18}H_{22}NO_3$ $[M+H]^+$ 300.1593, found 300.1594

MP: 152 – 153 ºC

(±)-Morphine



Boron tribromide (1.0 M solution in dichloromethane, 0.21 mL, 0.21 mmol) was added to a solution of codeine (10.5 mg, 0.035 mmol) in chloroform (0.72 mL) at room temperature. After stirring for 20 min, the reaction was quenched by the addition of aqueous ammonium hydroxide (10 wt. %, 1.8 mL) at 0 ºC. The mixture was extracted with ethanol in dichloromethane (10% v/v, 4 × 3 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was triturated with diethyl ether (2 × 1 mL) under sonication to give morphine (8.6 mg, 86%) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (d, *J* = 8.1 Hz, 1H, *H*2), 6.50 (d, *J* = 8.1 Hz, 1H, *H*1), 5.67 (dddd, *J* = 9.9, 3.1, 1.6, 1.1 Hz, 1H, *H*7), 5.28 (ddd, *J* = 9.9, 3.3, 1.9 Hz, 1H, *H*8), 4.89 (dd, *J* = 6.5, 1.1 Hz, 1H, *H*5), 4.20 (ddd, *J* = 6.5, 3.1, 1.9 Hz, 1H, *H*6), 3.41 (dd, *J* = 6.4, 3.2 Hz, 1H, *H*9), 3.03 (d, *J* = 18.7 Hz, 1H, $H10_a$), 2.73 (br, 1H, *H*14), 2.66 (dd, *J* = 12.5, 4.7 Hz, 1H, $H16_a$), 2.47 (s, 3H, NCH_3), 2.45 (td, *J* = 12.5, 3.4 Hz, 1H, $H16_b$), 2.33 (dd, *J* = 18.7, 6.4 Hz, 1H, $H10_b$), 2.12 (td, *J* = 12.5, 4.7 Hz, 1H, $H15_a$), 1.88 (ddd, *J* = 12.5, 3.4, 1.7 Hz, 1H, $H15_b$)

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2 (*C*4), 138.0 (*C*3), 133.2 (*C*7), 130.9 (*C*12), 128.5 (*C*8), 126.6 (*C*11), 120.2 (*C*1), 116.8 (*C*2), 91.9 (*C*5), 66.6 (*C*6), 59.1 (*C*9), 46.6 (*C*16), 43.3 (*C*13),

43.1 (N*C*H$_3$), 40.7 (*C*14), 35.6 (*C*15), 20.7 (*C*10)

IR (film, cm^{-1}) ν_{max} 3297 (broad, O–H), 2926, 1612, 1457, 1246, 1118, 1032

HRMS (ESI) calcd for $C_{17}H_{20}NO_3$ $[M+H]^+$ 286.1438, found 286.1440

MP: 215 – 221 ºC (dec.)

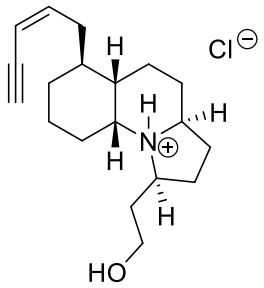
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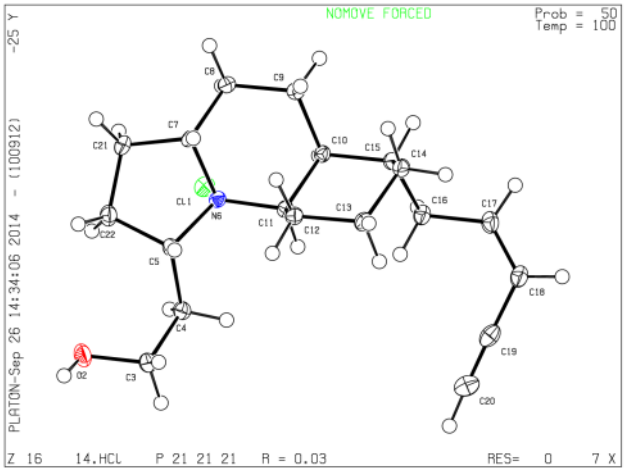
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7. Appendices

7.1 X-ray Crystallography Data

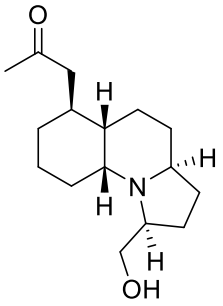
X-Ray Crystallographic data and structure refinement for gephyrotoxin·HCl, 013JDJ14

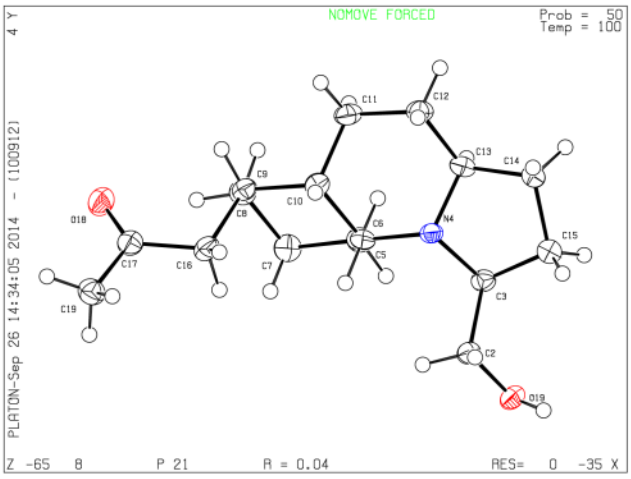




Identification code	013JDJ14	
Empirical formula	$C_{19}H_{30}ClNO$	
Formula weight	323.91	
Temperature	100 K	
Wavelength	0.68890 Å (Synchrotron)	
Crystal system	Orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 9.6940 Å	α = 90 °
	b = 10.2101 Å	β = 90 °
	c = 17.1589 Å	γ = 90 °
Volume	1698.33 $Å^3$	
Z,Z’	Z: 4 Z': 0	
Density (calculated)	1.267 g cm^{-3}	
Absorption coefficient	0.228 mm^{-1}	
F(000)	704	
Crystal size	0.1 x 0.05 x 0.02 mm^3	
Theta range for data collection	2.250 to 27.224 °	
Reflections collected	23637	
Independent reflections	3950 (Without Friedel’s Law)	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.980	
Final R indices [I>2σ(I)]	R^1 = 0.0288, wR^2 = 0.0762	
R indices (all data)	R^1 = 0.0302, wR^2 = 0.0796	

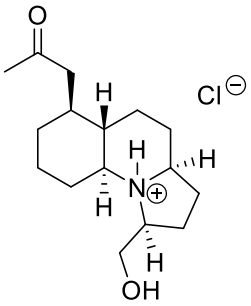
X-Ray Crystallographic data and structure refinement for compound 57, 078RWD14

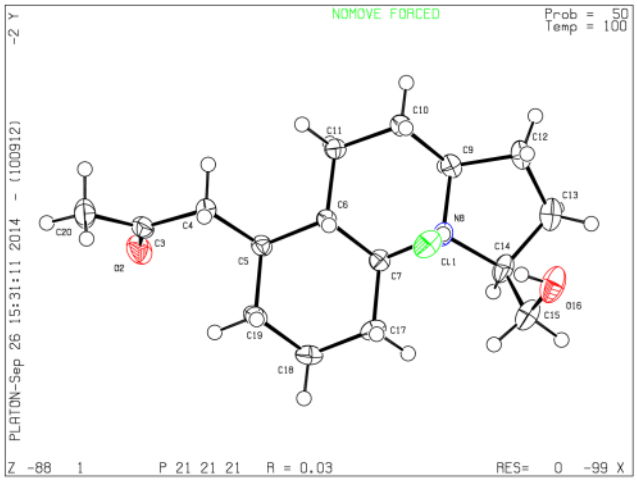




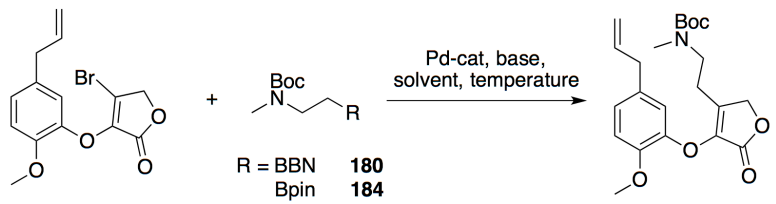
Identification code	078RWD14	
Empirical formula	$C_{16}H_{27}lNO_2$	
Formula weight	265.39	
Temperature	100 K	
Wavelength	0.68890 Å (Synchrotron)	
Crystal system	monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 7.6750 Å	α = 90 °
	b = 8.0593 Å	β = 101.553 °
	c = 12.9538 Å	γ = 90 °
Volume	785.03 $Å^3$	
Z,Z’	Z: 2 Z': 0	
Density (calculated)	1.123 g cm^{-3}	
Absorption coefficient	0.073 mm^{-1}	
F(000)	292	
Crystal size	0.05 x 0.02 x 0.01 mm^3	
Theta range for data collection	1.555 to 26.163 °	
Reflections collected	9248	
Independent reflections	3023 (Without Friedel’s Law)	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.997	
Final R indices [I>2σ(I)]	R^1 = 0.0398, wR^2 = 0.0892	
R indices (all data)	R^1 = 0.0518, wR^2 = 0.1121	

X-Ray Crystallographic data and structure refinement for compound 57·HCl, 014JDJ14





Identification code	014JDJ14	
Empirical formula	$C_{16}H_{28}ClNO_2$	
Formula weight	301.84	
Temperature	100 K	
Wavelength	0.68890 Å (Synchrotron)	
Crystal system	Orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 8.4067 Å	α = 90 °
	b = 13.7393 Å	β = 90 °
	c = 13.9623 Å	γ = 90 °
Volume	1612.68 $Å^3$	
Z,Z’	Z: 4 Z': 0	
Density (calculated)	1.243 g cm^{-3}	
Absorption coefficient	0.239 mm^{-1}	
F(000)	656	
Crystal size	0.1 x 0.02 x 0.02 mm^3	
Theta range for data collection	2.016 to 27.254 °	
Reflections collected	22090	
Independent reflections	3664 (Without Friedel’s Law)	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2σ(I)]	R^1 = 0.0301, wR^2 = 0.0737	
R indices (all data)	R^1 = 0.0317, wR^2 = 0.0756	



Entry[a]	*B*-Alkylreagent	Pd-cat.	Base	Solvent	H_2O	T (°C)	Yield[b]
1	**180** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	K_2CO_3 (2.0 eq.)	DMF/THF 2:1	28 eq.	rt	41%
2	**180** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	KF (4.0 eq.)	DMF/THF 2:1	5 eq.	70	-
3	**180** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%), $AsPh_3$ (20 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	28 eq.	rt	48%
4	**180** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	28 eq.	rt	59%
5	**180** 1.5 eq.	$Pd(OAc)_2$ (10 mol%), RuPhos (20 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	28 eq.	rt	52%
6	**180** 1.5 eq.	XPhos Pd G3 (5 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	25%
7	**180** 1.5 eq.	$Pd(OAc)_2$ (10 mol%), XPhos (20 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	25%
8	**180** 1.1 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	13 eq.	rt	37%
9	**180** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	62%
10	**180** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	NaOH (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	44%
11	**185** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	28%
12	**185** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	NaOH (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	23%
13	**184** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	31%
14	**184** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	NaOH (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	29%
15	**186** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	-
16	**186** 1.5 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	NaOH (2.0 eq.)	DMF/THF 2:1	22 eq.	rt	
17	**180** 1.2 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 3.3:1	22 eq.	rt	61%
18	**180** 1.2 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 3.3:1	22 eq.	40	63%
19[c]	**180** 1.2 eq.	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (10 mol%)	Cs_2CO_3 (2.0 eq.)	DMF/THF 3.3:1	22 eq.	40	58%

All reactions were carried out under inert atmosphere following the procedure described in the experimental section. The reactions were monitored via TLC and stirred until the starting material was consumed. [a] Reactions were carried out on 20-200 mg scale, unless otherwise stated. [b] Isolated yield. [c] The reaction was carried out on 5.30 g scale.