Studies Towards the Total Synthesis of Manzamine A

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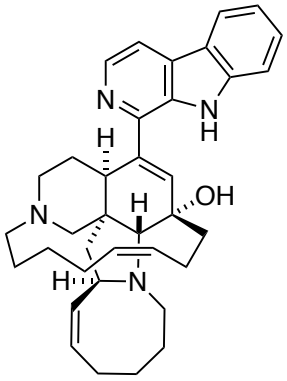
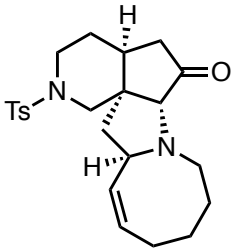
Abstract

Manzamine A was isolated from a marine sponge of the genus *Haliclona* by Higa and co-workers in 1986.[8] The structure of manzamine A consists of complicated 5-, 6-, 6-, 8-, and 13-membered rings, two tertiary amines and a tertiary alcohol functionality, in addition to a β-carboline. The synthetically challenging structure and the extremely potent biological activity of manzamine A makes it an attractive synthetic target.

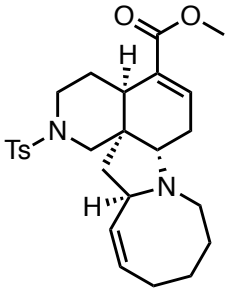
Previous work in the Clark group had established the ring expansion of the tetracyclic ketone, which served as the key intermediate in the total synthesis of nakadomarin A published by the group in 2016.



manzamine A (1)



tetracyclic ketone



functionalised ring-expanded intermediate

In this thesis, the initial focus was towards optimization of the synthesis of the tetracyclic ketone. The second part was exploring the ring expansion of the tetracyclic advanced intermediate via different strategies. Finally, work was carried out towards the elaboration of the ring expanded tetracyclic ketone to give the functionalised ring expanded intermediate.

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Dedication

To my mother, for all your love and support
To my father, who is in the sky
To my little sons, Hashim and Abdullaziz
To my sisters and brothers, for all your support

Acknowledgements

I would like to express my appreciation to my academic supervisor Professor *J.* Stephen Clark for his help invaluable advice, continuous support, and patience during my PhD study. His knowledge and experience has encouraged me in all the time of my academic research and daily life. I would also like to thank him for offering me this opportunity to work on such an exciting project in such an encouraging environment.

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I would like to thank the technical staff who have helped during my time at the University of Glasgow.

Lastly, I would like to thank all my family for their support during my PhD. A warm thanks to my little sons who were very patient with being away from me, and very supportive during my PhD.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, that the substance of this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Hibah Alharbi

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Prof. J. Stephen Clark

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Abbreviations

acac	acetylacetonate
AIBN	azobis-*iso*-butyronitrile
AIDS	acquired immune deficiency syndrome
Alloc	allyloxycarbonyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
BOP	(benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
brsm	based on recovered starting material
Bs	benzenesulfonyl
CAN	ceric ammonium nitrate
cat.	catalyst
Cbz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
CI	chemical ionisation
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DHQD	dihydroquinidine
DIBAL	di-*iso*-butylaluminium hydride
DIPEA	*N,N*-di-*iso*-propylethylamine
DMAP	*N,N*-dimethyl-4-aminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DMP	Dess-Martin Periodinane
DNA	deoxyribonucleic acid

DPPA	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
ee	*enantiomeric excess*
EI	electron ionisation
ESI	electrospray ionisation
hfacac	hexafluoroacetylacetone
H-G II	Hoveyda-Grubbs 2nd generation catalyst
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
G I	Grubbs 1st generation catalyst
G II	Grubbs 2nd generation catalyst
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
IBX	2-Iodoxybenzoic acid
IR	infrared
LDA	lithium di-*iso*-propylamide
L-Selectride	lithium tri-*sec*-butyl(hydrido)borate
m.p.	melting point
*m*CPBA	*meta*-chloroperoxybenzoic acid
MEM	2-methoxyethylmethyl
MOM	methoxymethyl
mRNA	messenger ribonucleic acid
MS	molecular sieves
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ns	4-nitrobenzenesulfonyl
PHAL	phthalazine

PHT	pyrrolidone hydrotribromide
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
pyr	pyridine
RCEYM	ring-closing enyne metathesis
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminium dihydride
SES	2-(trimethylsilyl)ethanesulfonyl
Sia	*sec*-isoamyl
SM	starting material
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMOF	trimethyl orthoformate
TMS	trimethylsilyl
TMTU	tetramethylthiourea
Ts	*para*-toluenesulfonyl
UV	ultraviolet

1. Introduction

1.1 Manzamine Alkaloids Family of Natural Products

Natural products are chemical compounds that are produced by living organisms such as animals and plants. They have been used for thousands of years as cures for diseases and within the pharmaceutical industry.[1] Many natural products have biological activities such as cytotoxicity, anti-bacterial, anti-fungal, anti-viral, immunosuppressive and antiparasitic activities.[2]

Scientific researchers are inspired by the discovery of new natural products for use as potential drug leads, as well as providing material to understand the mechanisms of biological activities.[1] The scarcity of most natural products is a significant reason for their role as crucial targets to be synthesized by researchers. Nowadays, more than 28% of the drugs on the market are natural products or their derivatives.[1]

The manzamine alkaloids are a family of novel marine alkaloids that have become interesting targets to both synthetic chemists and biochemists.[2] Since the late 1980s, various marine alkaloids have been extracted from sponges in the Pacific and Indian Oceans of the genera Amphimedon, Acanthostrongylophora, Haliclona, and Xestspongia. As with many families of natural products, the manzamine alkaloids possess a variety of potent biological activities. For example, they have antimicrobial[4], insecticidal, pesticidal[5], antimalarial, proteasome inhibitory, and antiinflammatory[6] properties. They also possess activity against HIV and AIDS opportunistic infections.[6,7] Most manzamine alkaloids possesses a novel polycyclic ring system that bears a β-carboline moiety. However, there are differences in their polycyclic skeletons (Figure 1.1).[3] The β-carboline moiety that is attached to pentacyclic ring system is absent in some of the manzamine alkaloids *i.e;* ircinal A (**4**) (Figure 1.1).[3] The synthetically challenging structures and the extremely potent biological activities of the manzamine alkaloids make them attractive synthetic targets.

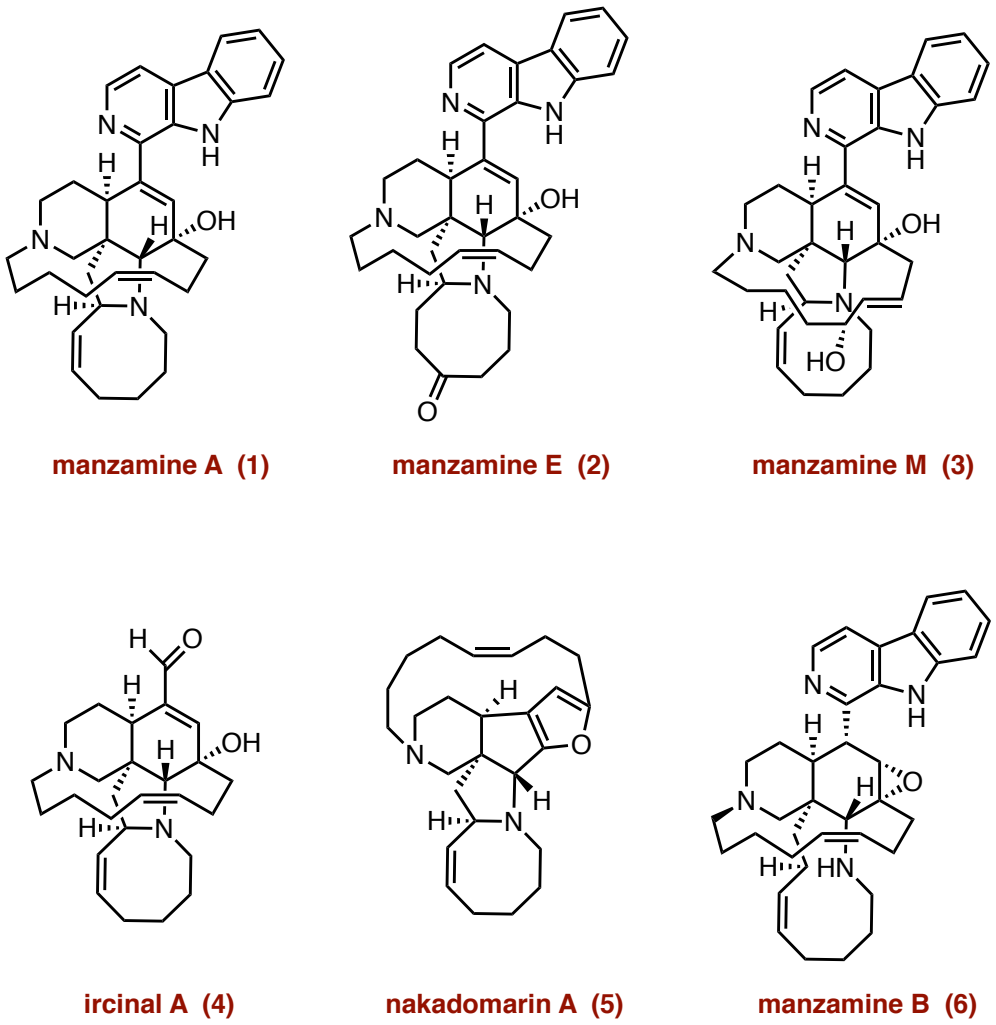


Figure 1.1 Manzamine A (1) and a selection of some of other members of the manzamine family of marine alkaloids

1.2 The Structure of Manzamine A and Biological Activities

In 1986, the first manzamine alkaloid, manzamine A (**1**), was isolated from an Okinawan sponge of the genus *Haliclona* by Higa, and his coworkers. The absolute configuration of manzamine A (**1**) was determined by X-ray diffraction crystallographic analysis. The unusual ring systems of the manzamine A (**1**) consists of a complex 5-, 6-, 6-, 8- and 13-membered polycyclic ring system, two tertiary amines, a tertiary alcohol and a β-carboline unit (Figure

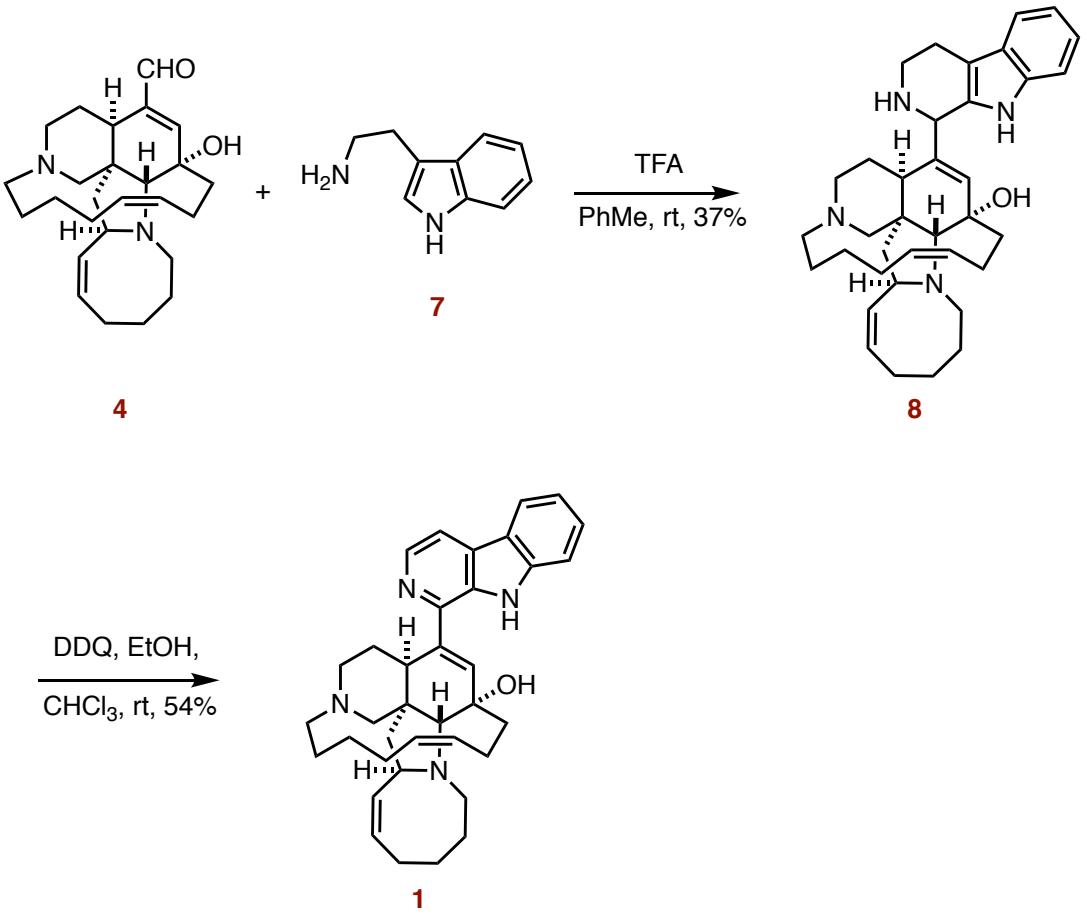
1.1).[8] Manzamine A (**1)** displays diverse and potent biological activities. For instance, it has the highest antimalarial activity against *Plasmodium falciparum*. Additionally, it exhibits activity against the HIV-1 virus, *Leishmania donovani, Mycobacterium tuberculosis* and *Staphylococcus aureus* (Table 1.1).[9,10]

Disease/ Microoranism	**Activity**
Plasmodium falciparum	IC_{50} 4.5 ng/ml
HIV-1	EC_{50} 4.2 μM
Leishmania donovani	IC_{50} 1.8 μg/ml
Mycobacterium tuberculosis	MIC 1.5 μg/ml
Staphylococcus aureus	IC_{50} 0.5 μg/ml
P-388 leukaemia cells	IC_{50} 0.07 μg/ml

Table 1.1 Selection the biological activities of manzamine A (**1**)

1.3 Semi-Synthesis of Manzamine A

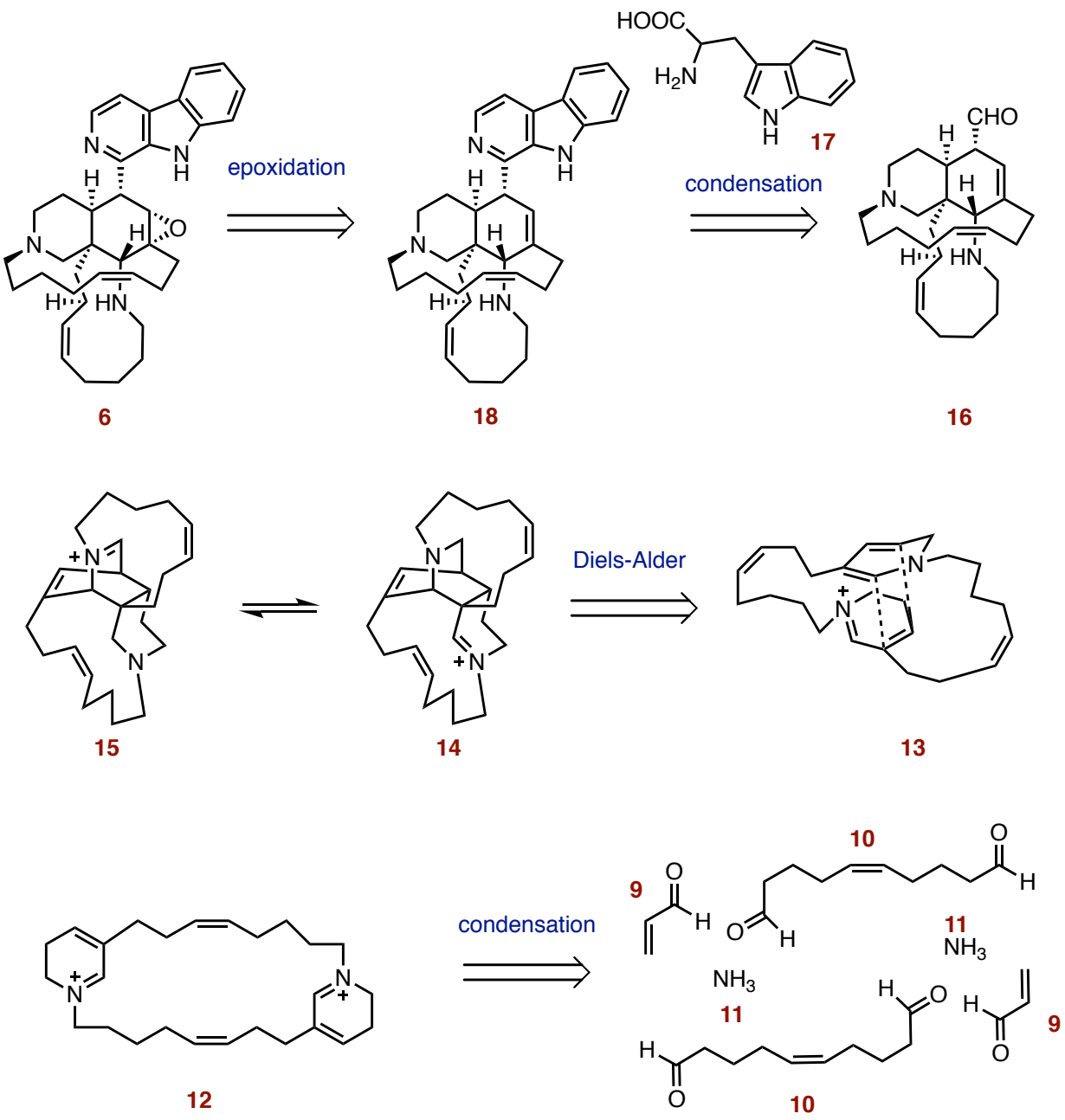
In 1992, ircinal A (**4**) was isolated from Okinawan marine organisms by Kobayashi and co-workers.[11] The first semi-synthesis of manzamine A (**1**) was also accomplished by Kobayashi and co-workers who synthesised manzmine A (**1**) from ircinal A (**4**) .[11] Their semi-synthesis was based on treatment of ircinal A (**4**) with tryptamine (**7**). Manzamine D (**8**) was achieved using an acid-mediated Pictet-Spengler cyclisation reaction. Oxidation of manzamine D (**8**) with DDQ resulted in manzamine A (**1**) (Scheme 1.1). [12]



Scheme 1.1. Semi-synthesis of manzamine A (**1**)

1.4 Biosynthetic Route

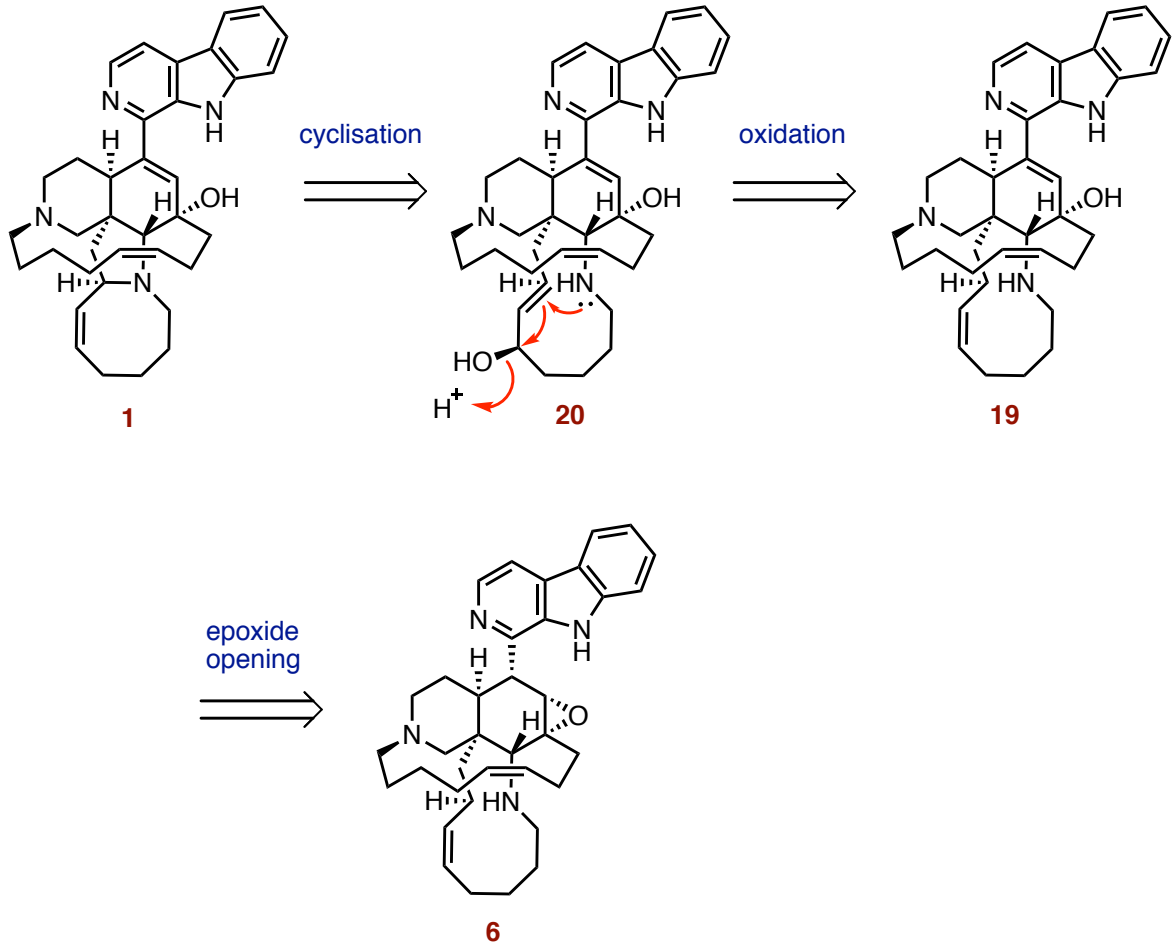
Baldwin and his co-workers[17] proposed a biosynthetic route for manzamine A (**1**) in 1992. The proposed pathway started with a reductive condensation between the three building blocks – two equivalents each of ammonia (**11**), the symmetrical dialdehyde **10**, and acrolein (**9**) – to provide the symmetrical macrocyclic **12**. Intramolecular *endo* Diels-Alder [4+2] cycloaddition of macrocycle **12**, which is the conjugate base of symmetrical macrocyclic **13** could result in intermediate **14**. Redox equilibrium between the two piperidines **14** and **15**, followed by hydrolysis of the iminium ion **15** would produce the aldehyde **16** intermediate. Installation of tryptophan unit in aldehyde **16** would provide **18**, which could be followed by epoxidation to result manzamine B (**6**) (Scheme 1.2).[17,18,19]



Scheme 1.2. Biosynthetic retrosynthesis of manzamine B (**6**)

Further branching from this pathway could give access to other members of the manzamine family. In the case of manzamine A (**1**), trans-eliminative opening of the epoxide in the B-ring of manzamine B (**6**) would result in the intermediate **19**. This could be followed by

allylic oxidation of a double bond to produce alcohol intermediate **20**. Subsequent closure of the C-ring would yield the manzamine A (**1**) (Scheme 1.3).[17,18,19]



Scheme 1.3. Biosynthetic retrosynthesis to manzamine A (1)

Following the discovery of manzamine A (**1**) and ircinal A (**4**), many other manzamine alkaloids were discovered and the theoretical pathway above was modified by researchers in order to accommodate potential biosynthetic routes to these new manzamine alkaloids. In the biosynthetic route of the manzamine alkaloids, keramaphidin B (**21**) has been proposed as common intermediate (Figure 1.2). [17,18]

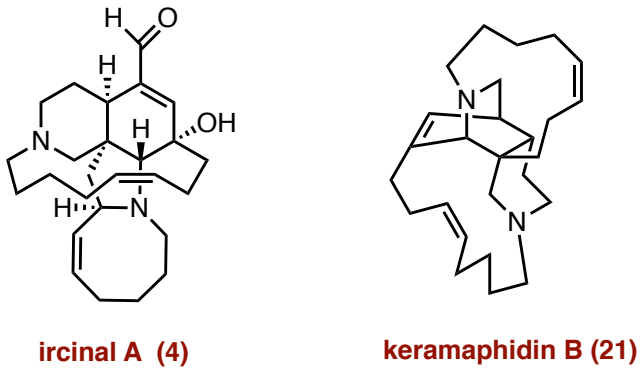
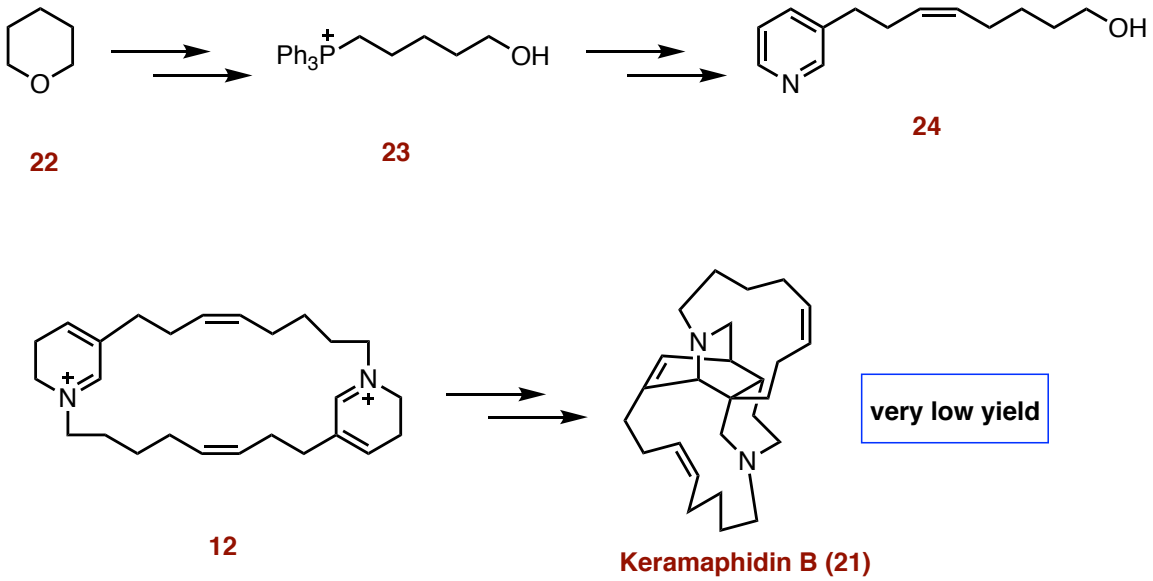


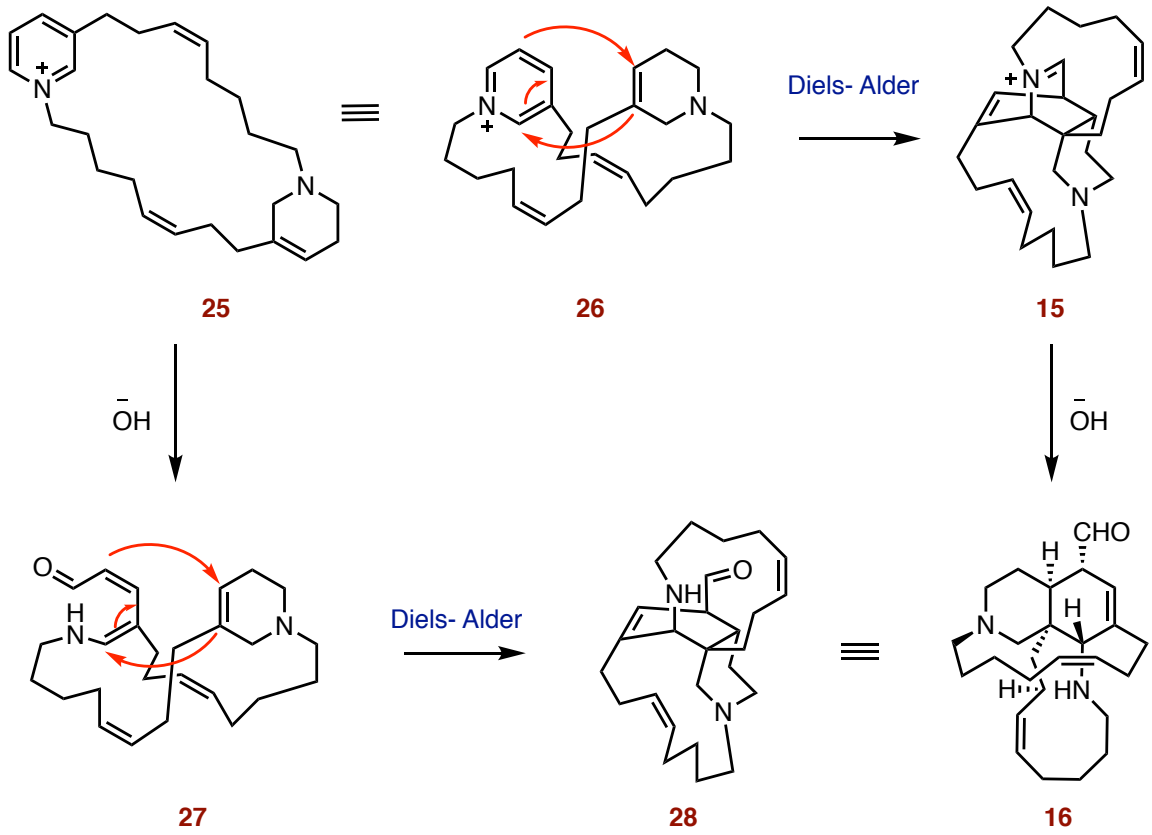
Figure 1.2. Ircinal A (4) and keramaphidin B (21)

In 1999, the theoretical biosynthetic pathway was shown to be chemically feasible by Baldwin and his co-workers. They completed a biosynthetically inspired total synthesis of keramaphidin B (**21**) from very simple building-blocks. Hydroxyphosphonium salt **23** was converted into the symmetrical macrocyclic **12** in 15 steps. Optimizations were applied to the biomimetic Diels-Alder reaction to form the polycyclic system. A small amount of keramaphidin B (**21**) was observed when optimized reaction conditions were employed. In this case, **12** was dissolved in a 1:1 mixture of 1 M aq. TRIS/ HCl (pH 7.3) and MeOH, and reduction of the polycyclic imine / iminium ion was accomplished with $NaBH_4$ after one hour. Although the synthesis proved that the hypothetical biosynthetic route was possible chemically, the very low yield of keramaphidin B (**21**) suggests that the Diels-Alder reaction is unfavorable (Scheme 1.4).[17,18,19]



Scheme 1.4. The Baldwin-Whitehead model for the synthesis of keramaphidin B (21)

Because of unfavorable disproportionation in their bis-dihydropyridine pathway, Baldwin and his coworkers modified their proposal. They proposed that the [4.2] cycloaddition reaction would directly provide pentacyclic iminium ion **15**, if a pyridinium salt were used as the diene and a tetrahydropyridine as the dienophile in **25** (Scheme 1.5). This new proposed pathway would avoid the problem of disproportionation as well as removing questions over the redox equilibrium between the cycloadduct **14** and the ircinal precursor **15** shown in Scheme 1.2. [17,18,19]



Scheme 1.5. Alternative biosynthetic hypotheses

Marazano and his co-workers[20] proposed that the biomimetic Diels-Alder reaction could include a substituted 5-amino-2,4-pentadienal as the diene. Their hypothesis would avoid the problems with disproportionation and ring strain during the Diels-Alder cycloaddition reaction. Amino-aldehyde **27** could be obtained by ring-opening of pyridinium salt **25**, followed by Diels-Alder cycloaddition to produce the ircinal intermediate **16** (Scheme 1.5).[20]

Waters and co-workers[74] reported the first sustainable method to produce manzamine A (1). Their method is a biomimetic fermentation using Micromonospora *sp*. M42. They proved that the M42 is a potential way to produce manzamine A (1) continuously. Their study started with exploration in fermentation and isolation of M42, which produced a pure manzamine A (1) and was proved by correlation of the ^{1}H NMR to that of the sponge derived manzamine A (1). Due to the moderate yield obtained, a series of optimisation conditions were applied using different media and growth conditions. However, no improvement of the yield was observed and most results gave a yield of less than 1mg/L. In addition, detection of manzamine A (1) production can be seen on day 4, and excreted and 9etabolized could be detected by day 10. Despite the fact that this study gives an essential starting point for the biomimetic fermentation pathway to produce manzamine A (1), the yield was humble and the methods will need to be developed.

1.5 Total Synthesis of Manzamine A

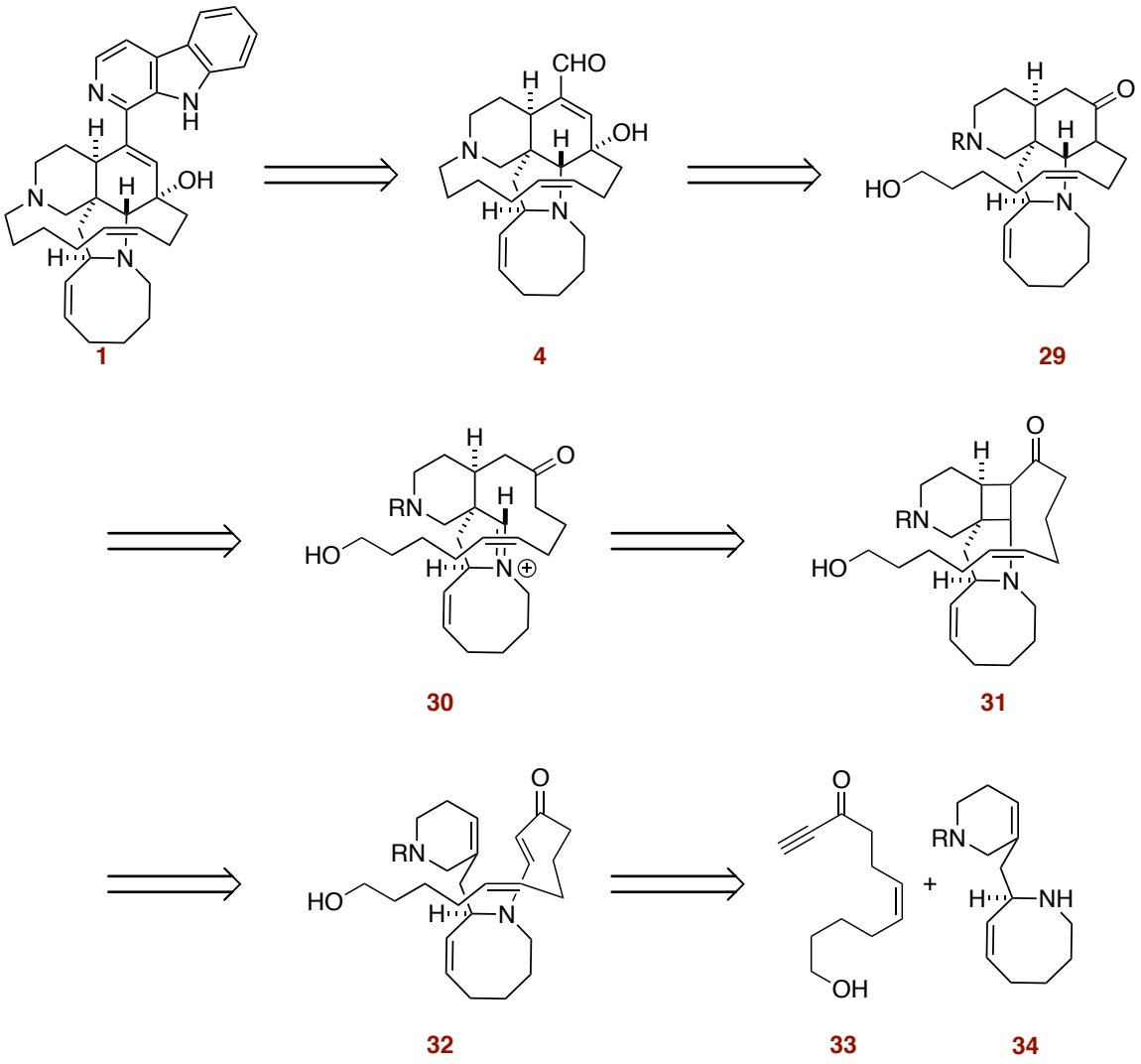
Since the initial isolation of manzamine A (**1**), several research groups have initiated programs focusing on the total synthesis of this compound. To date, there have been four total syntheses of manzamine A (**1**), which have been reported by the groups of Winkler,[13] Martin,[14] Fukuyama[15] and Dixon.[16]

1.5.1 Winkler's Total Synthesis of Manzamine A

In 1998, Winkler *et al.*[13] published the first total synthesis of manzamine A (**1**), in which a photochemical cascade reaction was used as a key step. This total synthesis was accomplished in 17 steps starting from the amine **34**. [13]

Winkler and co-worker's retrosynthesis started with removal of the *β*-carboline unit from manzamine A (**1**) to produce ircinal A (**4**), which has been converted to manzamine A (**1**) by Pictet-Spengler cyclization followed by DDQ oxidation. Winkler and co-workers predicted that the formation of ircinal A (**4**) could be achieved by macrocyclisation of **29** and B-ring functionalization. The tetracyclic ring structure of **29** can be produced through Mannich closure

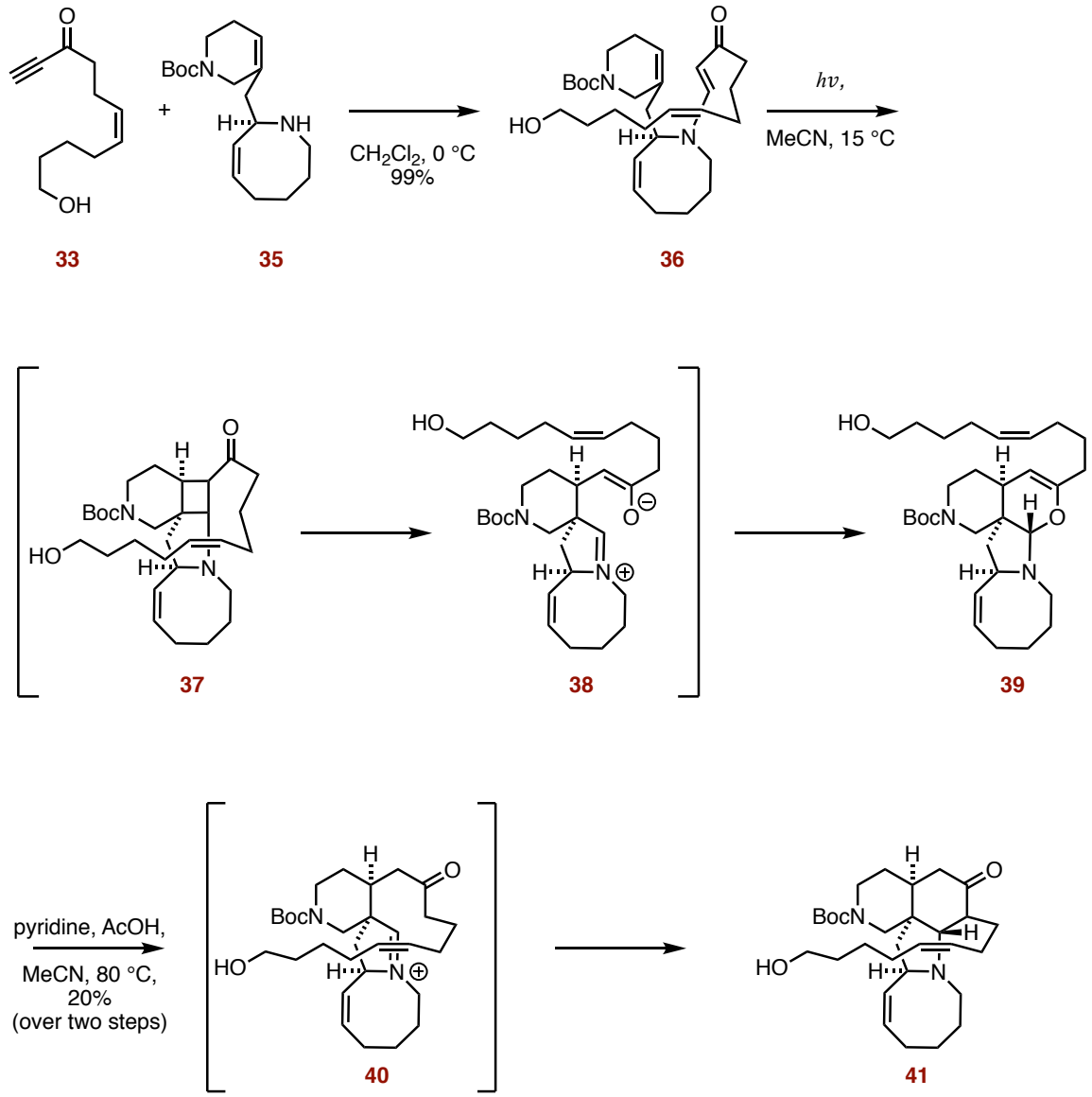
of ketoiminium **30**. The formation of ketoiminium **30** can be obtained by retro-Mannich fragmentation of **31**, which is obtained by intramolecular cycloaddition of enamine **32**. The enamine **32** could be accomplished by an intramolecular [2+2] photoaddition and disconnection of the amine **34** to the propargylic ketone **33**.[13]



Scheme 1.6. Winkler's retrosynthetic analysis of manzamine A (1)

Winkler and co-workers began their synthesis with aza-Michael addition of the cyclic dialkylamine **35** to the acetylenic ketone **33** to give the tertiary vinylogous amide **36** in excellent yield (Scheme 1.7). Photochemical cyclisation of amide **36** delivered the tetracyclic ketone **37** and subsequent retro-Mannich fragmentation produced **38**. Amine **39** was produced by

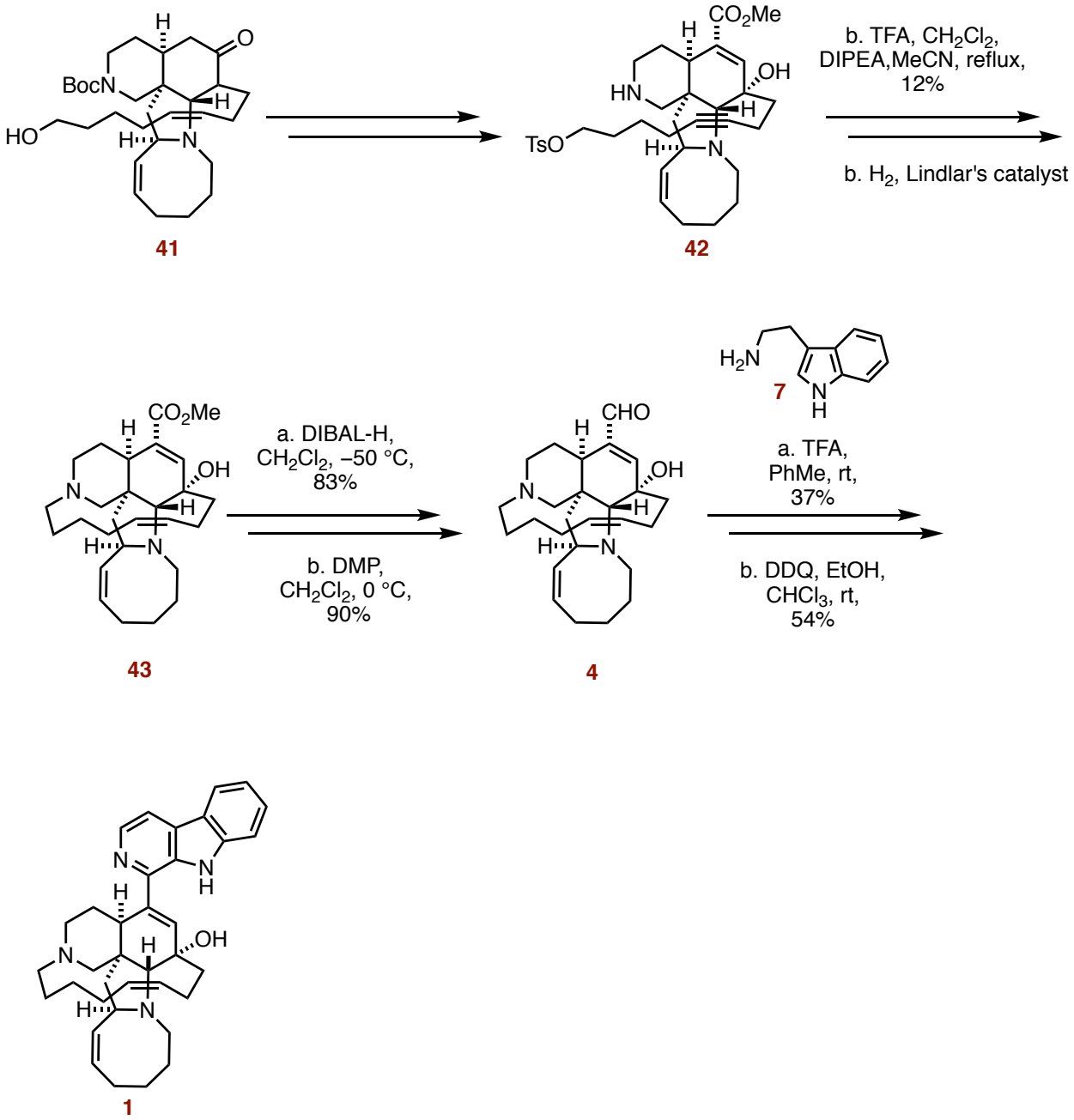
cyclisation of the enolate onto the iminium ion via intramolecular nucleophilic attack of the intermediate **38**. Amine **39** was converted into the iminium ion **40** by treatment with acetic acid in pyridine. The iminium ion **40** underwent a Mannich ring-closure reaction to generate tetracyclic amine **41** (Scheme 1.7).[13]



Scheme 1.7. Winkler's forward synthesis of manzamine A (1)

Functionalisation of tetracyclic ketone **41** was accomplished in 10 steps to generate the acetylenic substrate **42.** Installation of the 13-membered ring was accomplished from the acetylenic substrate **42** using Hunig's base, followed by Lindlar reduction of the alkyne to afford the alkene **43**. Reduction of the ester in **43** using DIBAL-H followed by oxidation of the ircinol

A using Dess-Martin reagent generated ircinal A (**4**). Pictet Spengler cyclisation and instillation of tryptamine **7** under acidic conditions produced manzamine D (**8**). This was followed by oxidation with DDQ to generate manzamine A (**1**) (Scheme 1.8).[13]

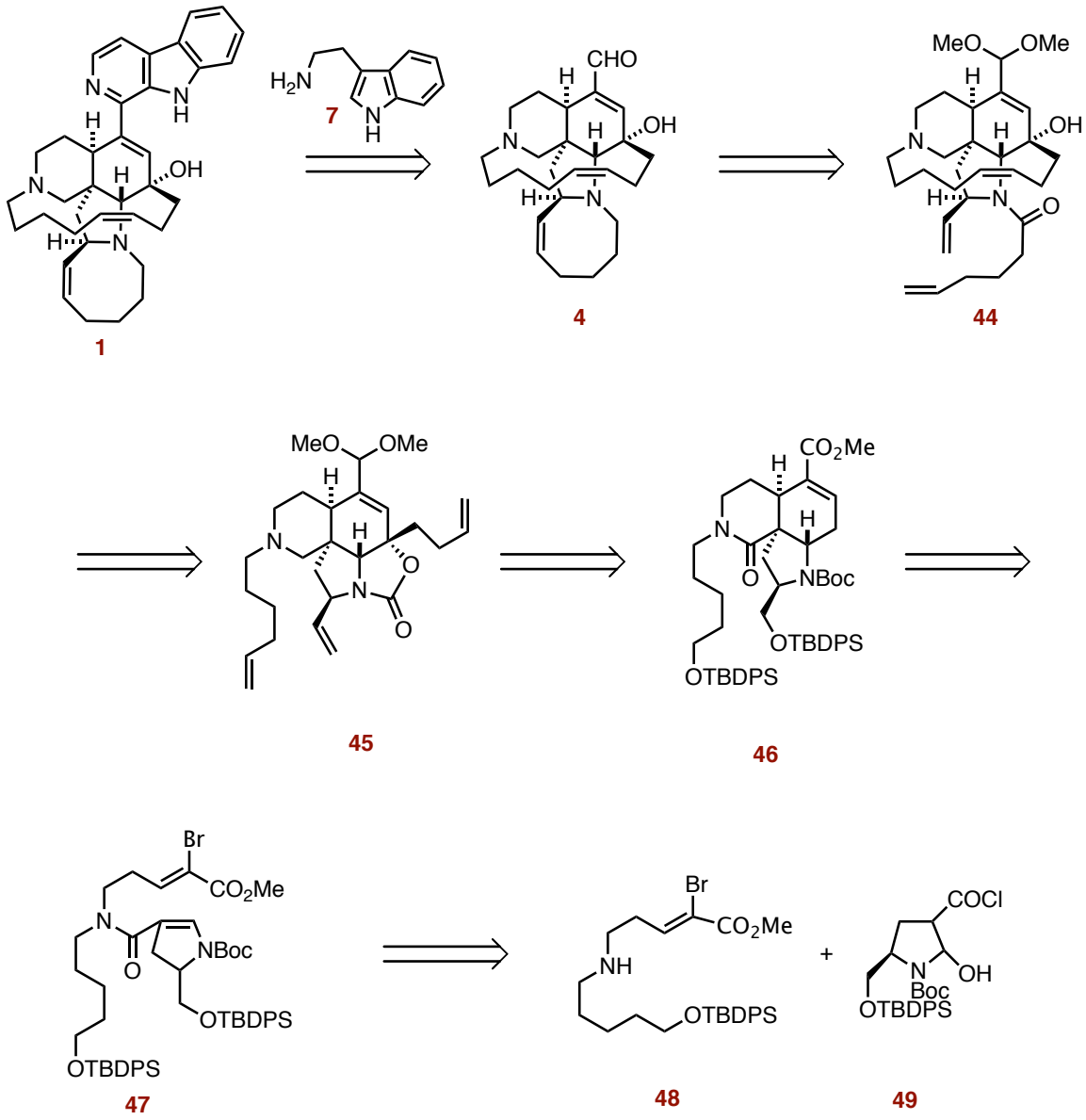


Scheme 1.8. Winkler's total synthesis of manzamine A (1)

1.5.2 Martin's Total Synthesis of Manzamine A

In 1999, Martin *et al*,[14] reported the second total synthesis of manzamine A (**1**). Their synthetic strategy was based on the use of a domino Stille/Diels–Alder reaction to construct the 6,6,5-tricyclic manzamine core and two sequential ring-closing metathesis reactions to form the 8- and 13-membered rings. They completed the enantioselective synthesis of manzamine A (**1**) in 24 steps total with a longest linear sequence of 21 steps.[14]

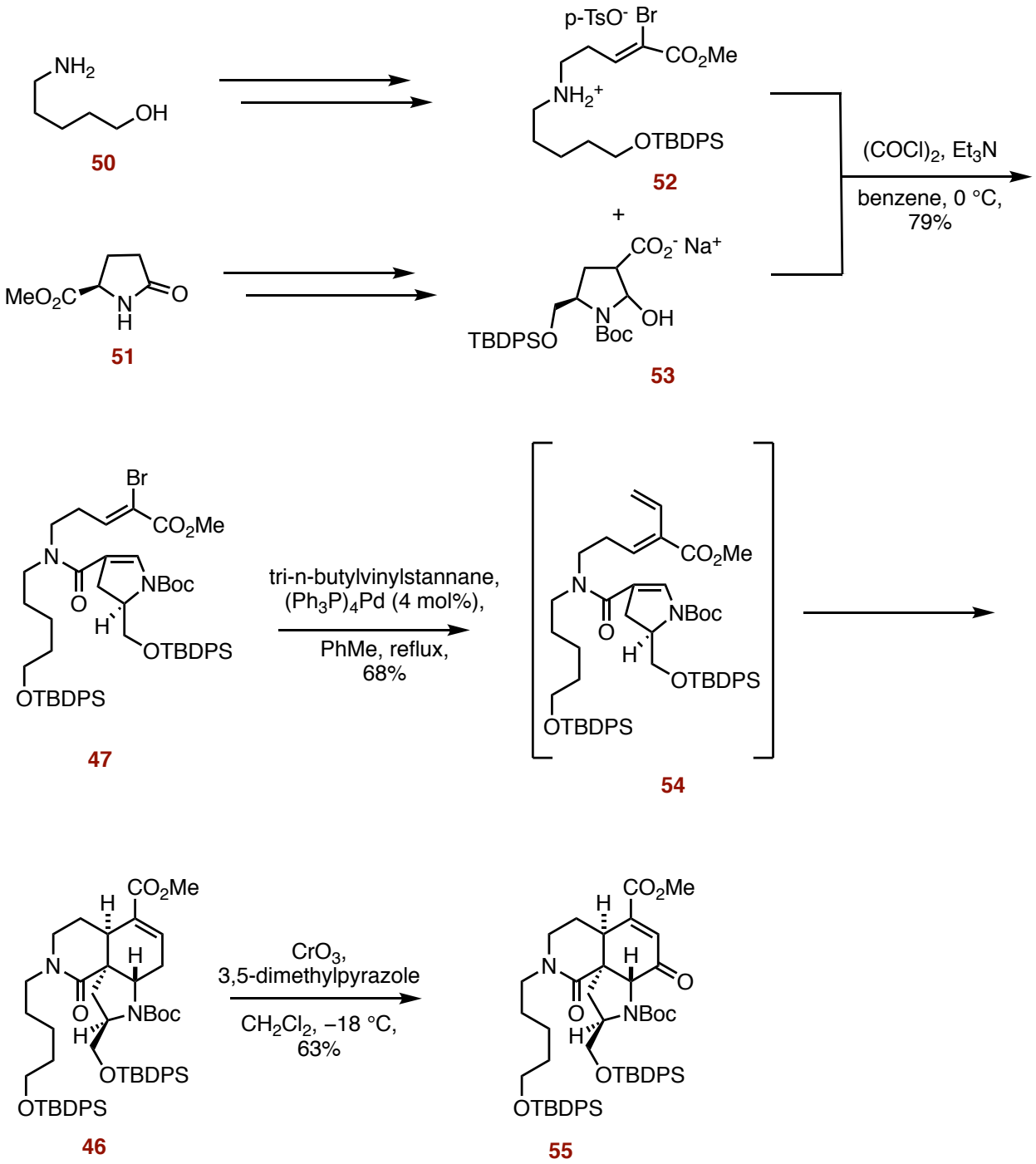
Ircinal A (**4**) was produced by de-installation of the β-carboline subunit from manzamine A **1** produced ircinal A (**4**), which can been converted to manzamine A (**1**) by treatment with tryptamine **7**, followed by Pictet-Spengler cyclization and DDQ oxidation.[11,12] Ircinal A (**4**) can be obtained through a ring-closing metathesis of compound **44** to form the D ring. The formation of **44** can be done by a second metathesis-based ring-closing disconnection of the E ring, and amide formation of compound **45**. Compound **45** can be formed by functionalisation and modification of protecting groups of ester **46**. The tricyclic core **46** can be obtained using Stille cross-coupling of vinyl-bromide **47** and tributyl(vinyl)stannane followed by Diels-Alder cycloaddition. Formation of the vinyl-bromide **47** can be achieved by amide formation of a chiral carboxylic acid derivative **49** and an unsaturated amino ester **48** (Scheme 1.9). [14]



Scheme 1.9. Martin's retrosynthetic analysis of manzamine A (1)

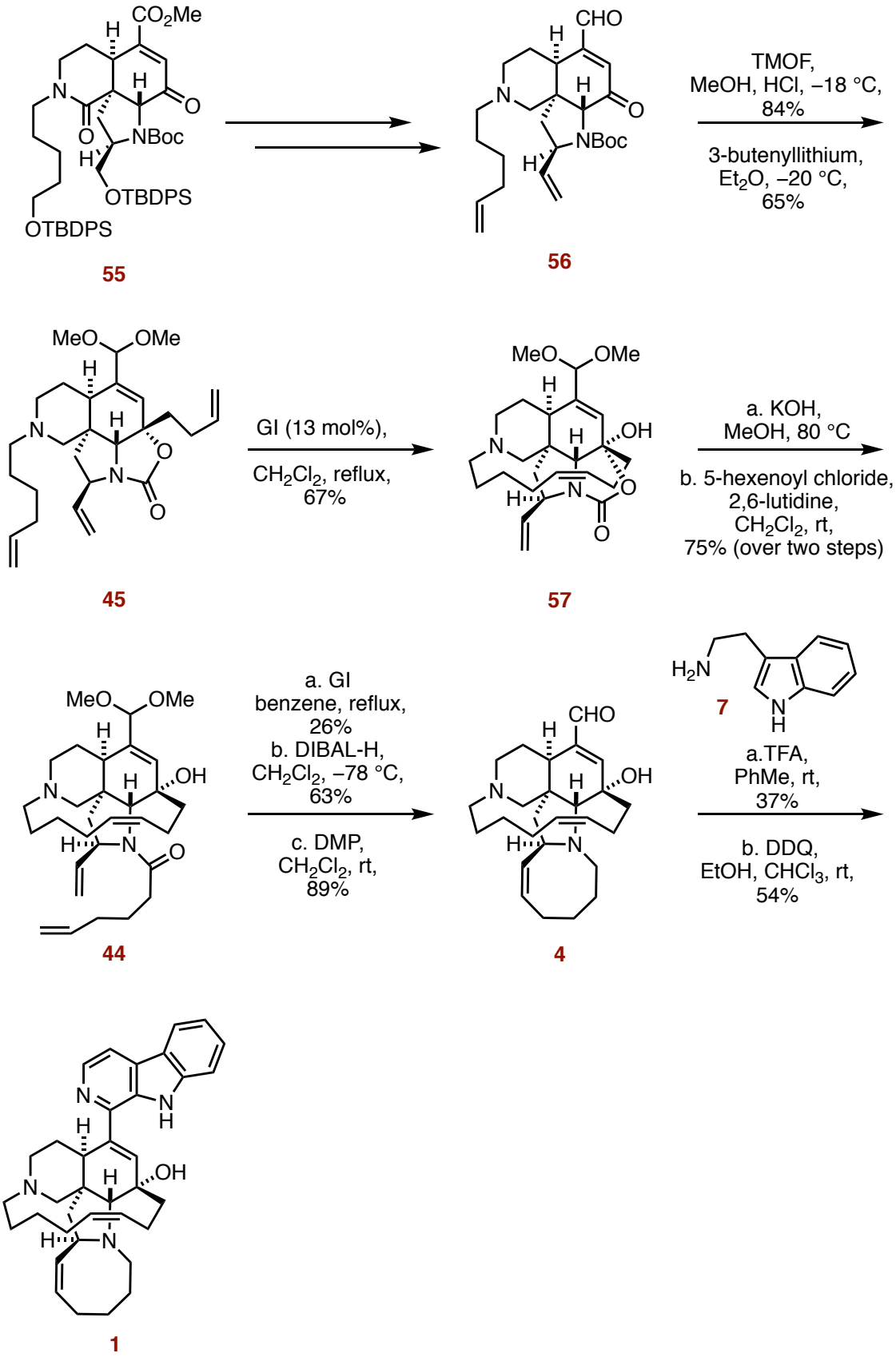
Compound **52** was synthesized in four steps from 5-amino-pentan-1-ol **50**, and **53** was synthesized in three steps from (*R*)-5-(methoxycarbonyl)-2-pyrrolidinone **51**. Treatment of the carboxylate salt **53** with oxalyl chloride, followed by addition of **52** in the presence of triethylamine generated the amide dienophile **47** in a 79% overall yield. Reaction of vinylic bromide **47** with vinyl stannane and palladium(0) gave the intermediate diene **54** which then underwent the domino Stille/Diels–Alder reactions to afford the tricyclic intermediate **46** in 68%

overall yield. The tricyclic intermediate **46** underwent oxidation using an excess of CrO_3 and 3,2-dimethylpyrazole in CH_2Cl_2 at room temperature for two days, to give the enone **55** in 64% yield (Scheme 1.10). [14]



Scheme 1.10. Martin's forward synthesis of manzamine A (1)

The TBDPS protected alcohol functionalities in enone **55** were converted into terminal alkenes and the methyl ester moiety was reduced to give the aldehyde **56**. Protection of aldehyde using dimethyl acetal followed by addition of 3-butenyllithium resulted in stereoselective 1,2-addition to the α,β-unsaturated ketone with simultaneous protection of the resulting tertiary alcohol as the cyclic carbamate **45**. The formation of the 13-membered ring was accomplished by a ring-closing metathesis reaction using the Grubbs' 1st generation catalyst, to generate a mixture of *Z/E* isomers and the macrocycle **57** was isolated in 67% yield. Hydrolytic cleavage of carbamate and *N*-acylation of amine generated the amide **44** in 75% overall yield. Formation of the 8-membered ring was achieved in low yield by ring-closing metathesis of alkene **44** with Grubbs' 1st generation catalyst using high temperature. This due to construction of the 8-membered D ring being disfavored. This was followed deprotection of the dimethyl acetal group, DIBAL-H reduction of the lactam and oxidation of the primary alcohol to generate ircinal A (**4)**. Manzamine A (**1)** was obtained from ircinal A (**4)** through the sequence reported by Kobayashi (Scheme 1.11). [14]

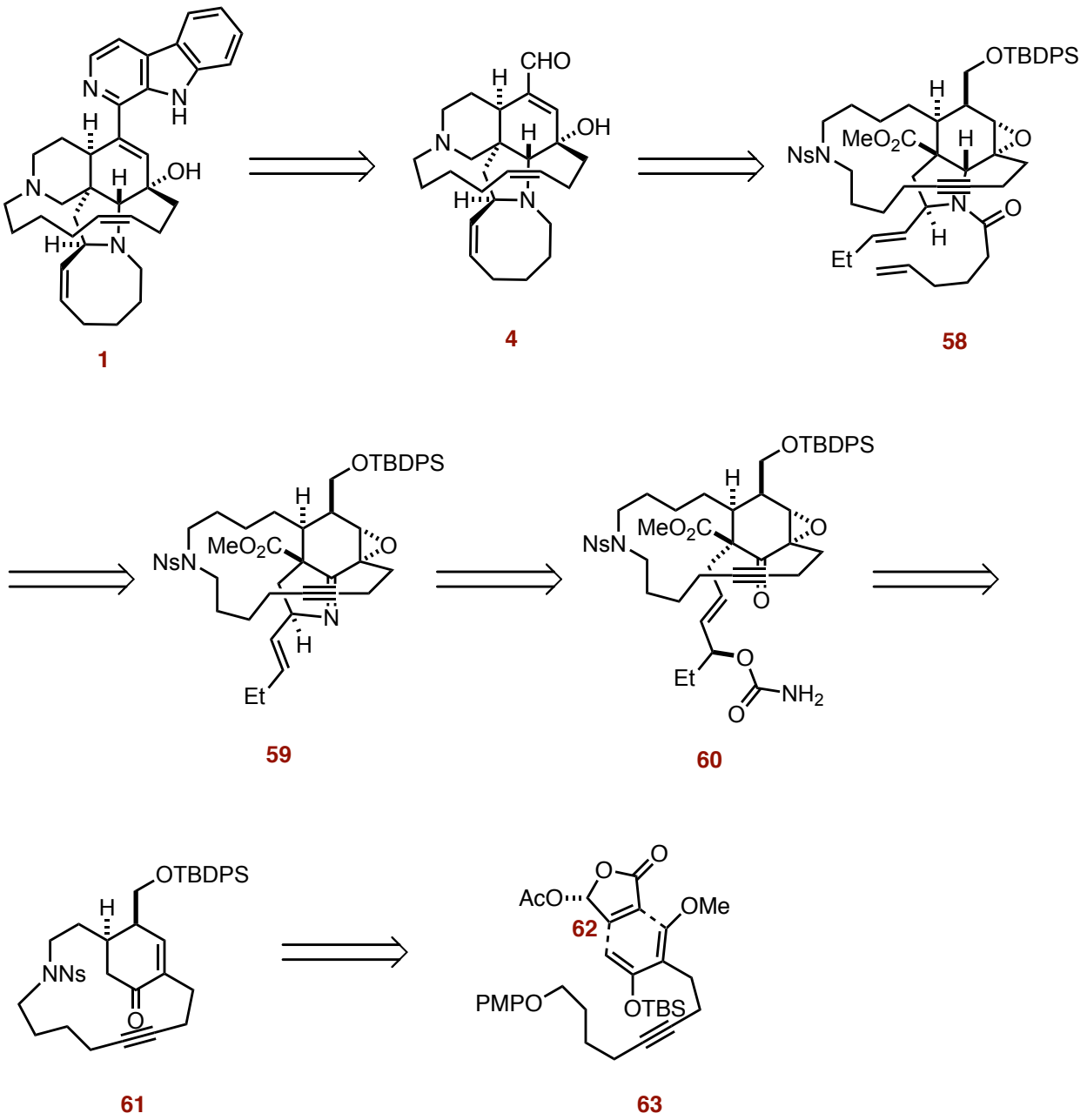


Scheme 1.11. Martin's forward synthesis of manzamine A (1)

1.5.3 Fukuyama's Total Synthesis of Manzamine A

The third total synthesis of manzamine A (**1)** was reported in 2010 by Fukuyama and co-workers.[15] Their synthesis included the construction of the macrocycle early in the synthesis to avoid the challenge of late-stage ring formation. This total synthesis was completed in 30 steps from commercially available starting materials.[15]

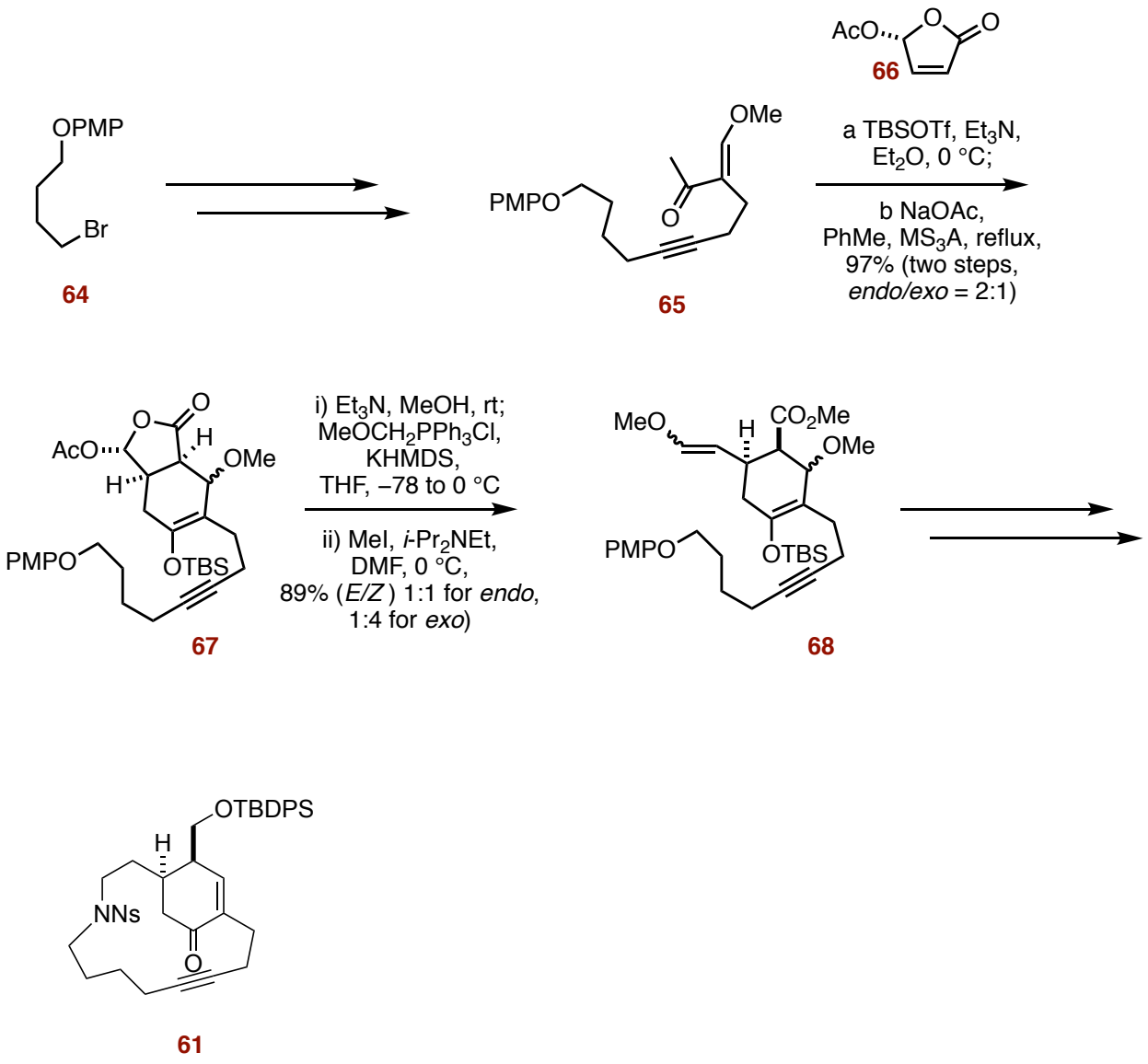
The key steps of their retrosynthesis involved a formation of the 8-membered ring using a ring-closing metathesis reaction of **58** and construction of a 15-membered macrocycle in aldehyde **58** to form the 13,6-ring system. Formation of the 5-membered ring *via* imine **59** was achieved using a [3,3]-sigmatropic rearrangement. Epoxy-ketone **60** was generated from bicyclic ketone **61**. The stereochemistry of all the stereogenic centers on the B ring and stereoselective introduction of a C1 unit to build the A-ring can be controlled by using bicyclic ketone **61**. The formation of the strained 15-membered ring **61** could be achieved by use of a nosyl group to protect nitrogen. A Diels-Alder reaction was applied in which the butenolide **62**, which is readily available, was reacted with the siloxydiene **63** to form the B-ring (Scheme 8). [15]



Scheme 1.12. Fukuyama's retrosynthetic analysis of manzamine A (1)

Bromide **64** was converted into the ester **65** in 6 steps: iodination, alkylation with methyl acetoacetate, reduction of both carbonyl groups, Dess-Martin oxidation of the 1,3-diol in the presence of *t*-BuOH, and esterification. The Diels-Alder reaction between siloxydiene **63** (which was readily prepared from **65**) and **66** with the addition of a solid base such as sodium acetate and molecular sieves to prevent hydrolysis of **63,** gave **67** in 97% yield. Methanolysis of acetoxylactone **67** afforded a mixture of aldehyde and hydroxylactone, which were converted

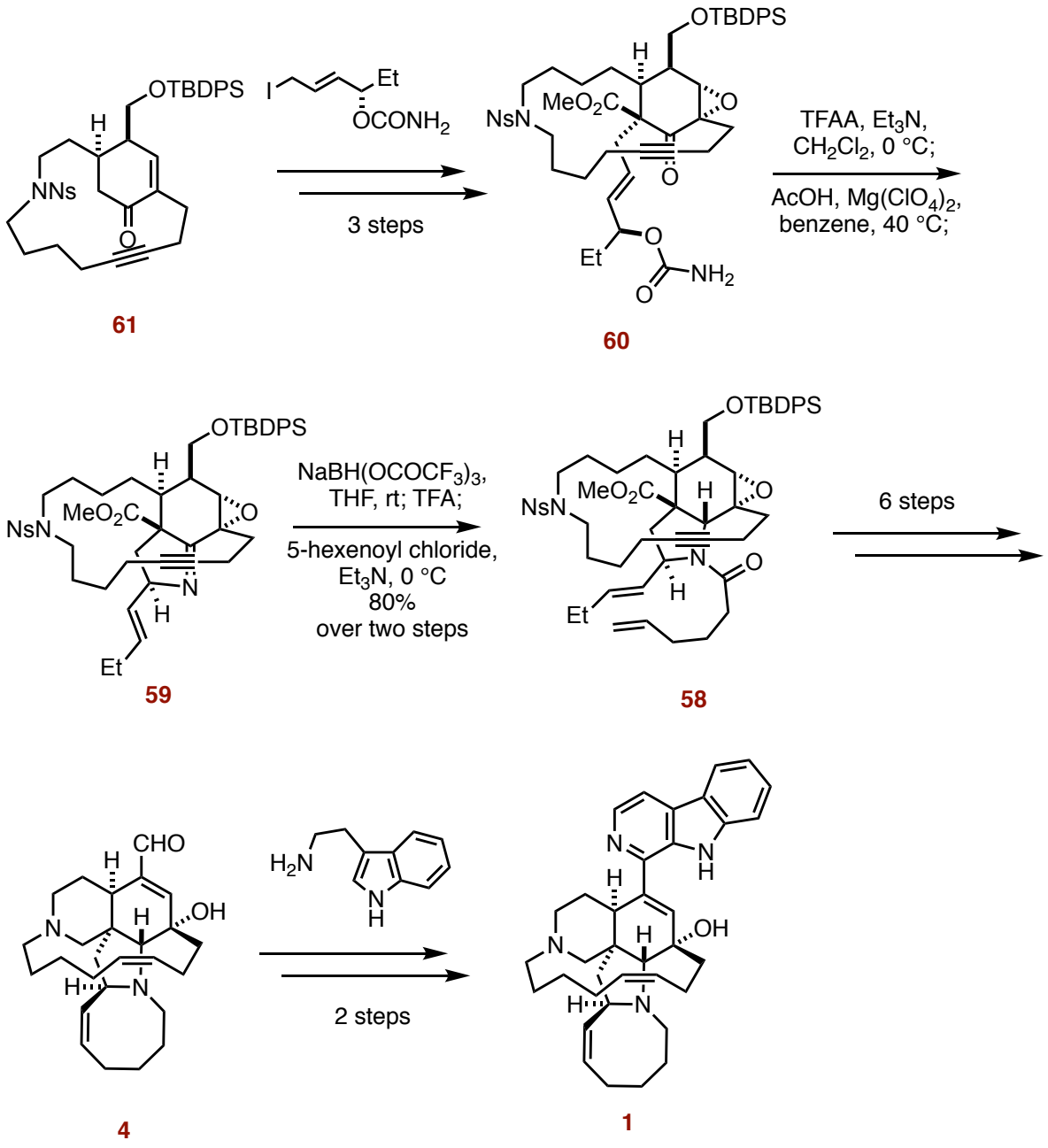
into the methyl ester **68** using a one-pot Wittig reaction and methylation procedure. The formation of the 15-membered ring through an intramolecular Mitsunobu reaction proceeded smoothly without the need for high dilution and gave the ketone **61** in good yield despite the target molecule having a relatively strained 15-membered ring that contains both a cyclohexenone and an alkyne (Scheme 1.13).[15]



Scheme 1.13. Fukuyama's forward synthesis of manzamine A (1)

Ketone **61** was converted to a *β*-ketoester using Mander's reagent, which was then subjected to allylation to generate epoxyketone **60** as a single diastereomer. This was followed

by dehydration with TFAA and Et_3N, and subsequent [3,3]-sigmatropic rearrangement at low temperature to offer the isocyanate with excellent stereochemistry. Treatment of the isocyanate with magnesium perchlorate and acetic acid under anhydrous conditions gave the desired imine **59.** Subsequently, reduction of imine **59** and acylation with 5-hexenoyl chloride obtained amine **58**. Amine **58** was then converted to ircinal A (**4)** in six steps. Manzamine A (**1)** was offered from ircinal A (**4)** through the sequence reported by Kobayashi[11,12] (Scheme 1.14).[15]

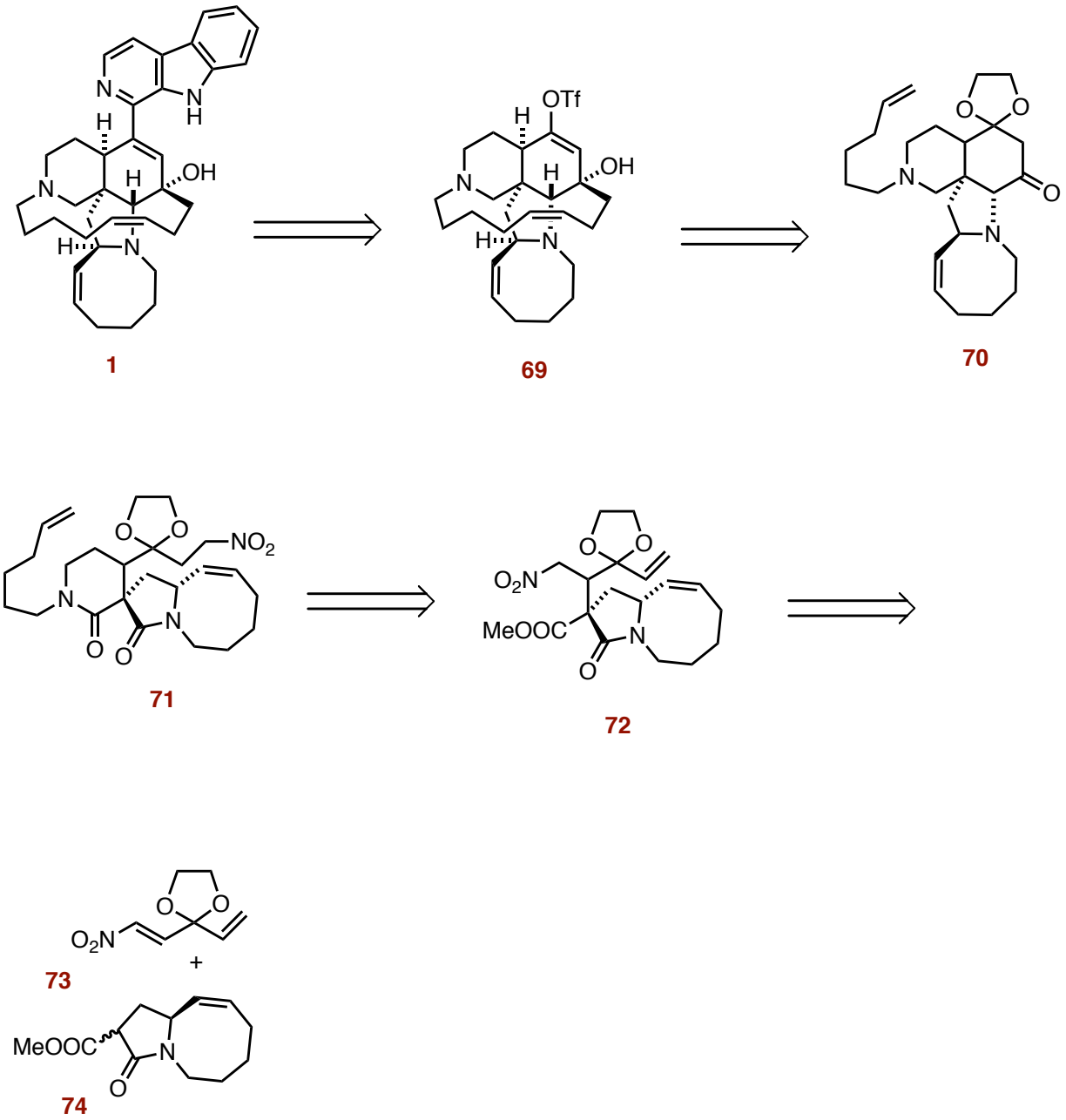


Scheme 1.14. Fukuyama's forward synthesis of manzamine A (1)

1.5.4 Dixon's Total Synthesis of Manzamine A

In 2012, Dixon's group published the fourth total synthesis of manzamine A (**1)**. This short and stereoselective synthesis of manzamine A (**1)** differs from other synthetic routes in that a cross-coupling strategy is employed to attach the β-carboline to key late-stage intermediate enol triflate.[16]

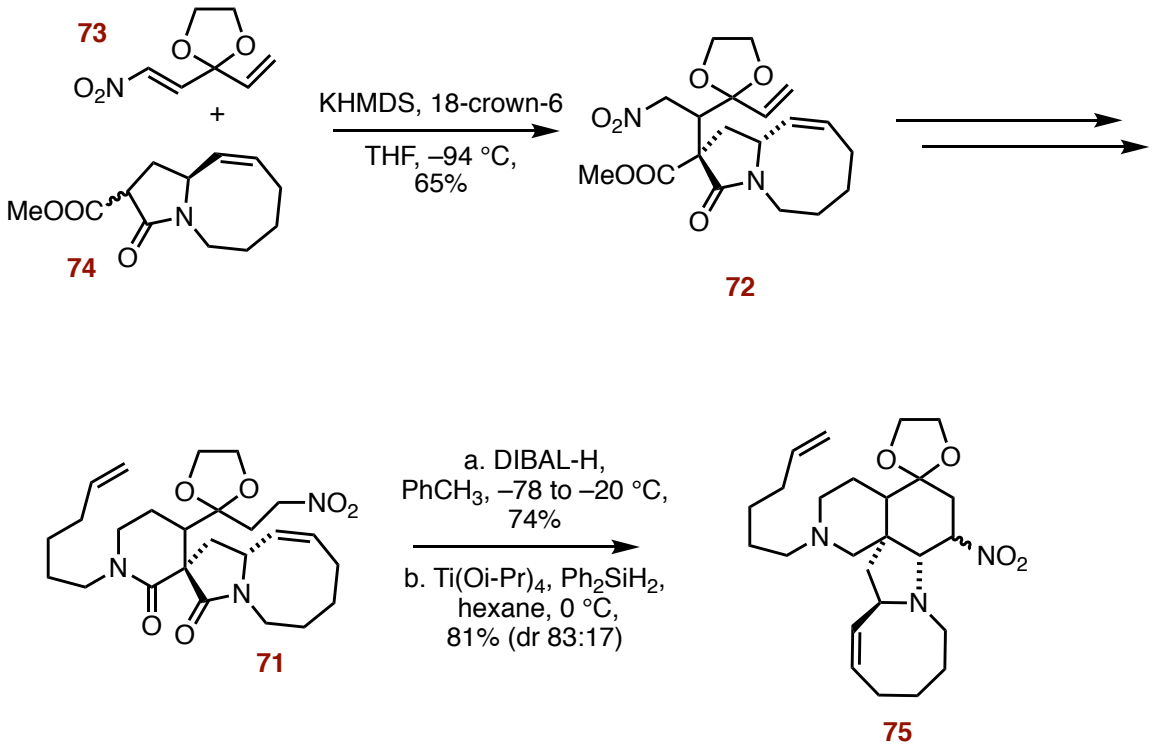
Installation the fully assembled β-carboline moiety by Stille cross coupling reaction in **69** produced manzamine A (**1)**. The key late-stage intermediate **69** could be accessed from the ketone **70** by stereoselective addition of a 3-butenyl anion equivalent to the carbonyl group, followed by enol triflate formation and a Z-selective ring-closing metathesis. Cyclohexanone **70** can be generated by reduction of the piperidinone carbonyl group, partial reduction of the pyrrolidinone carbonyl group and a subsequent oxidation via a Nef reaction in compound **71**. An intermediate nitroalkane **71** could be generated via a nitro-Mannich/lactamization cascade. Compound **72** could be prepared by conjugate addition of **74** onto a nitro olefin **73** (Scheme 1.15).[16]



Scheme 1.15. Dixon's retrosynthetic analysis of manzamine A (1)

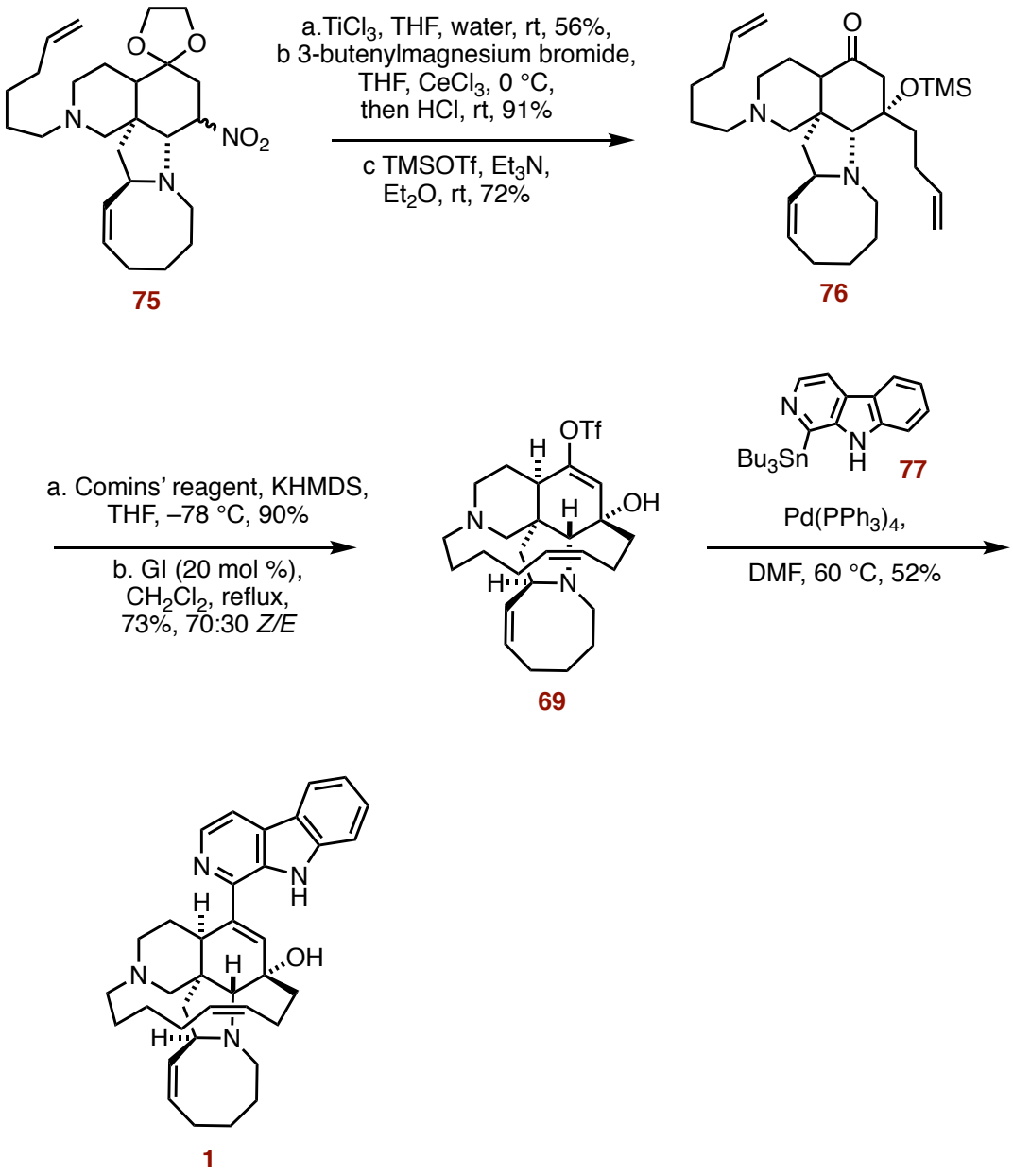
The diastereoisomer **72** was prepared from Michael addition of the anion of **74** to the nitro olefin coupling partner **73** using stoichiometric potassium hexamethyldisilazide as the base in conjunction with 1 equivalent of 18-crown-6. Nitroalkane **71** was generated from a nitro-Mannich / lactamisation cascade using formaldehyde and hex-5-en-1-amine. DIBAL-H was used

to reduce the piperidone carbonyl group to generate the corresponding piperidine ring. Product **75** was obtained by reduction of the pyrrolidone using Ti(O*i*-Pr)$_4$ and Ph_2SiH_2 , halted after the first hydride addition, followed by intramolecular nitro-Mannich addition (Scheme 1.16).[16]



Scheme 1.16. Dixon's forward synthesis of manzamine A (1)

A reductive Nef reaction using titanium trichloride in water was used to convert the nitro group into a ketone. Subsequent addition of an organocerium reagent prepared from 3-butenylmagnsium bromide and protection of the resulting tertiary alcohol using TMS gave diene **76.** The enol triflate was generated using base and the Comins reagent, and then subjected to Grubbs 1st generation catalyst followed by an acidic work-up, in order to form the 13-membered ring in a 70:30 *Z*/*E*-mixture of olefins **69**. Finally, Stille cross coupling reaction of the stannylated β-carboline **77** and the vinyl triflate **69** gave manzamine A (**1**) (Scheme 1.17).[16]



Scheme 1.17. Dixon's forward synthesis of manzamine A (1)

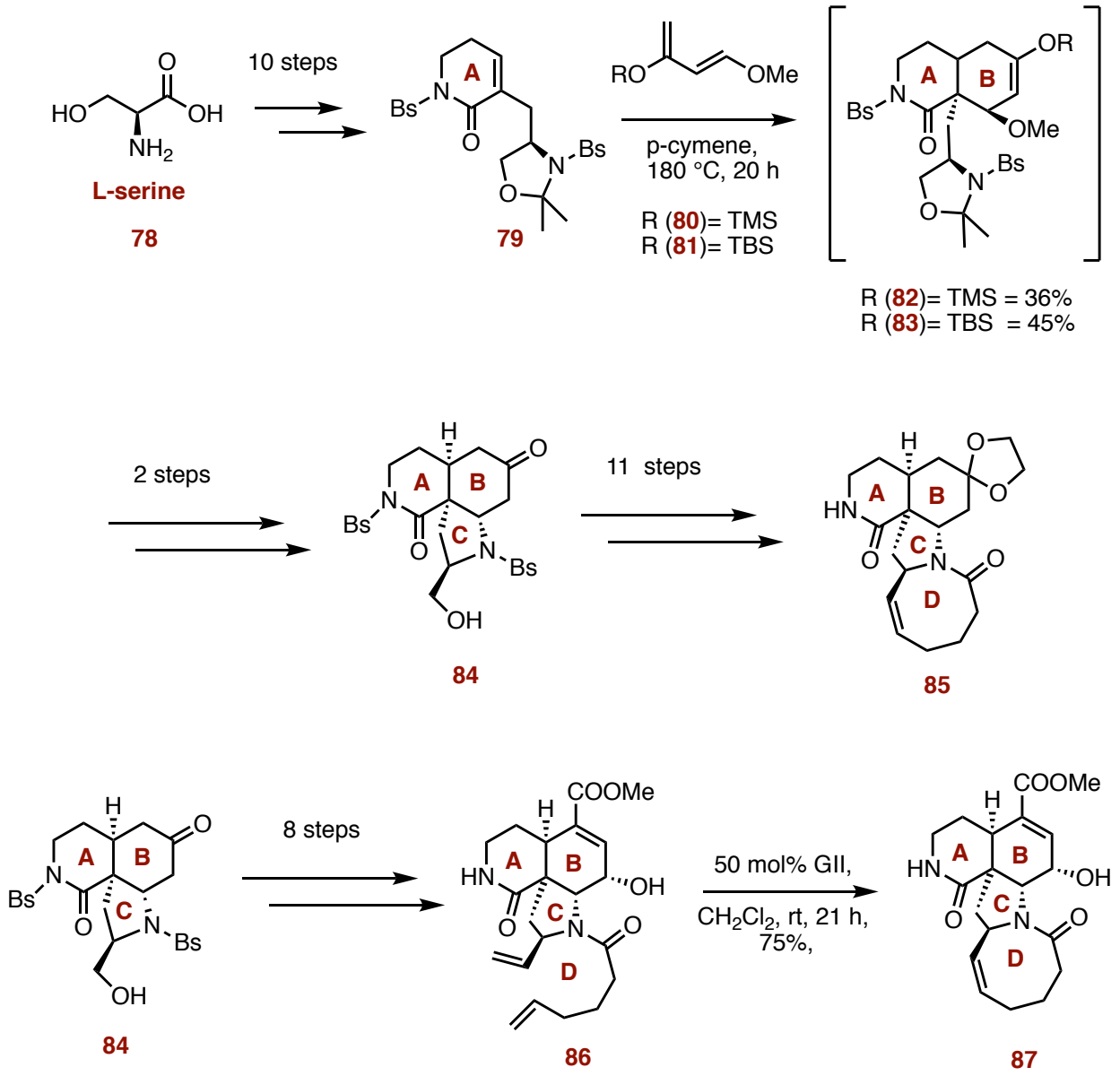
1.6 Synthetic Approaches of the Core of Manzamine A

There are many reported synthetic efforts towards the synthesis of the skeletal cores of manzamine A. The most common approach to the synthesis of the core of manzamine A (**1**) is based on a Diels-Alder reaction. It is a classic way to construct the fused ring systems and is inspired by the putative biosynthetic route.

1.6.1 Intermolecular Diels-Alder reaction

One of the reactions with good stereochemical control that has been used to construct the fused ring system is Diels-Alder reaction. Both inter- or intramolecular Diels-Alder reactions have been used to access the A and B rings. This includes the functionalisation and introduction of stereocentres on the fused rings.

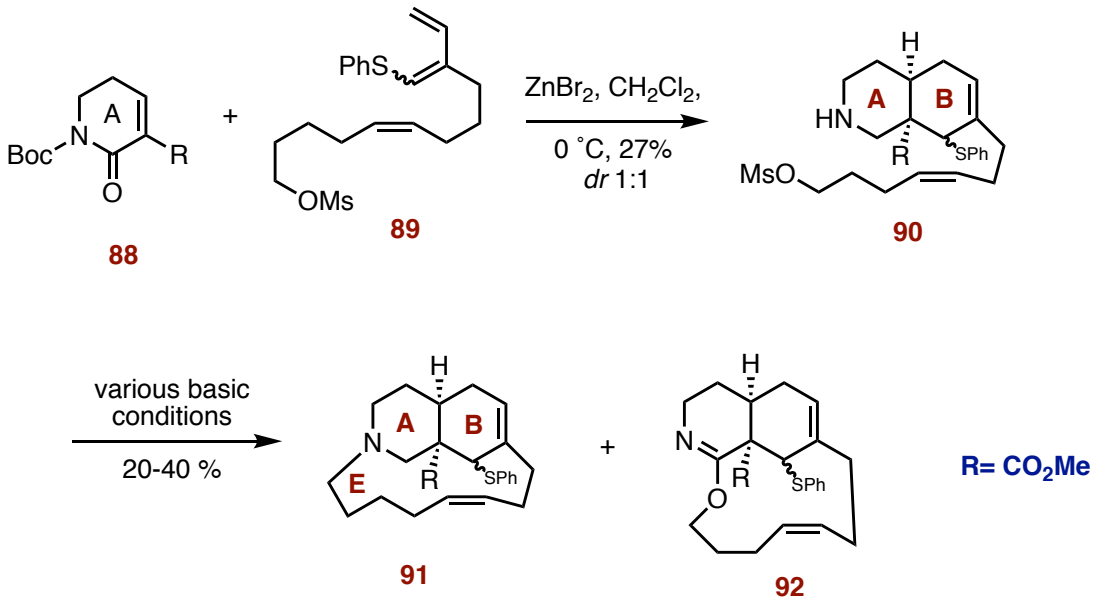
Marazano[20] and Nakagawa[21] reported construction of the ABC core of manzamine A (**1**) using an intermolecular Diels-Alder reaction. In the case of Nakagawa and his co-workers[21], dienophile **79** was synthesised from L-serine **78** in 10 steps (Scheme 1.18). Dienophile **79** and the highly reactive Danishefsky dienes **80** or **81** were subjected to an intermolecular Diels-Alder reaction to produce **84**.[21] The intermediates **82** and **83** were treated with acid to produce the tricyclic ABC system **84** in 36% (from **82**) or 45% (from **83**) yield through the elimination of MeOH and stereoselective 1,4-Michael addition. Tetracycle **85** was prepared in 11 steps from **84** including a Wittig reaction, which was used to introduce the *Z*-alkene in the 8-membered ring,[9] with most other steps being manipulations of functional groups. The construction of the other tetracyclic core **78** was also reported using similar chemistry. The α,β-unsaturated ester was installed using Mander's reagent.[22] A series of protecting group exchanges, functional group interconversion and redox chemistry produced tetracyclic intermediate **86**. Formation of the D ring of **87** was achieved in 75% yield (*Z*:*E* ratio not specified) by use of a ring-closing metathesis reaction mediated by the Grubbs second generation catalyst (50 mol %).



Scheme 1.18. Nakagawa's synthesis of ABCD core of manzamine A (1)

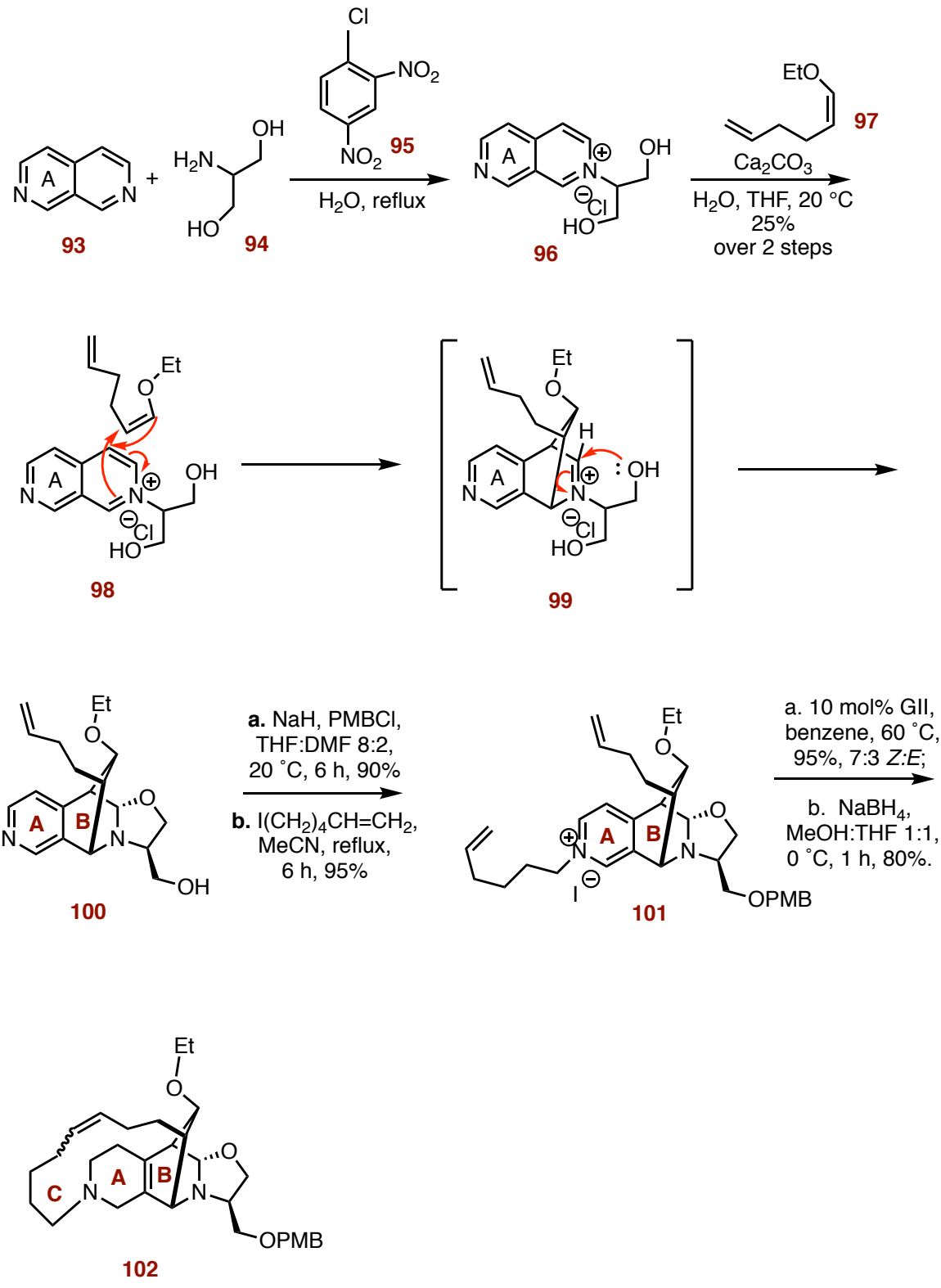
Both Simpkins and co-workers[23] and Langlois and co-workers[24,25] used an intermolecular Diels-Alder reaction to prepare the AB core of manzamine A (**1**) and then constructed the E ring by different routes. Simpkins and co-workers[23] were one of the earliest groups to report the use of a Diels-Alder reaction with diene **89** to enable later construction of ring E. The Boc-lactam **88** and diene **89** underwent Diels-Alder reaction to form the AB ring system **90** in 27% yield using optimised conditions ($ZnBr_2$ in CH_2Cl_2) with concomitant loss of the Boc group. The low yield was attributed to the instability of Boc-lactam **88** under the reaction conditions. In their next step,

the ring closure sequence, they faced some issues. After a variety of different basic conditions were investigated, they reported a small amount of material was obtained after purification by HPLC, which was related to intermediates **91** and **92.** However, the characterisation data was not reported (Scheme 1.19).[23]



Scheme 1.19. Simpkins' synthesis of AB core of manzamine A (1)

Langlois and co-workers[24,25] also used a Diels-Alder reaction to construct the AB ring system but employed a different strategy to those used by Nakagawa[21], Marazano[20] and Simpkins[23]. Their route relied on the formation of the ABD core by late stage ring-closing metathesis. A Zincke reaction[26] in water with 2-amino-1,3-propanediol **94** using 2,7-naphthyridine **93** and 1-chloro-2,4-dinitrobenzene **95** gave the naphthyridinium salt **96**. A Bradsher cycloaddition[24] reaction was performed on **96** with dienophile **97** to produce **100** in 25% yield over two steps. The stereochemistry of the product was confirmed by NOE experiments and single crystal X-Ray diffraction. Pyridinium ion **101** was formed by *N*-alkylation and then ring-closing metathesis was used to construct the D ring with the product formed as a 7:3 inseparable mixture of *Z* and *E* isomers. Subsequent reduction of the pyridinium ring gave tetracyclic core **102** (Scheme 1.20).

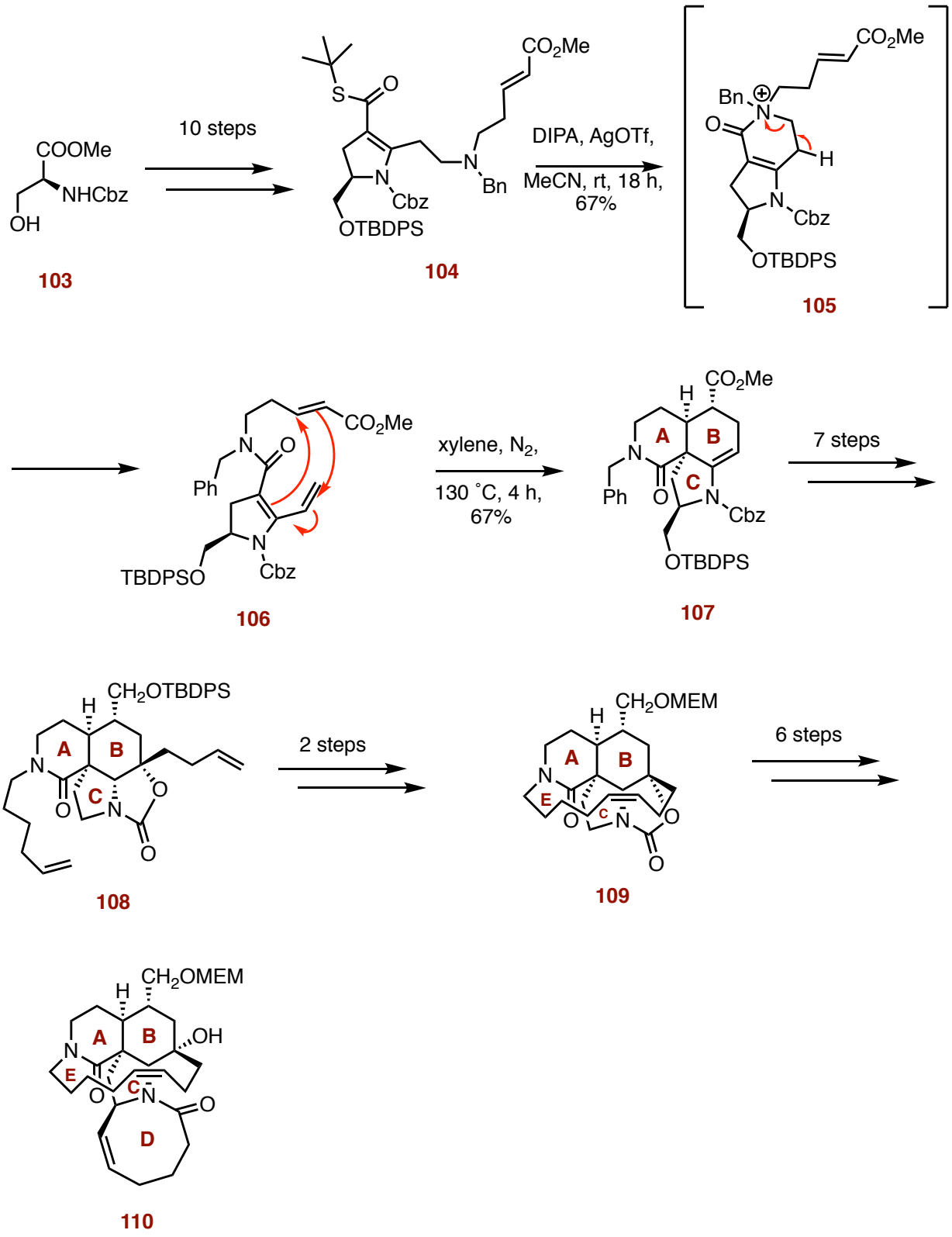


Scheme 1.20. Langlois' synthesis of the ABD tricycle.

1.6.2 Intramolecular Diels-Alder

Intramolecular Diels-Alder reactions have been used for the synthesis of the manzamine A (**1**) cores, and in Martin's[14] total synthesis of manzamine A (**1**) (discussed in Section 1.5.2). Reports from Marko *et al.*[28,29] and Leonard *et al.*[27] also outlined the use of an intramolecular Diels-Alder reaction and are not discussed. Pandit and co-workers have made considerable contributions to the field and their synthetic efforts are outlined in Scheme 1.21.

Pandit and co-workers[30] chose the intramolecular Diels-Alder pathway for the synthesis of the ABC core on the basis of the biomimetic route and used it to introduce the desired substitution pattern. Their synthesis commenced with conversion of the L-serine derivative **103** into the thiol-ester **104** in ten steps. Diels-Alder precursor **106** was obtained by elimination and subsequent fragmentation of **105**, and then subjected to the intramolecular cycloaddition, which proceeded with the electron-rich diene and electron-poor dienophile. Two diastereomeric products were formed **107** and the other diastereomer in a ratio of 3.5:1 with a 67% yield of the desired diasteromer. Ring-closing metathesis precursor **108** was prepared from the tricyclic intermediate **107** in seven steps. The E ring was constructed from **108** using ring-closing metathesis. The pentacyclic core was produced via a similar pathway to Martin's total synthesis (described in Chapter 1.5.2). In this case, the D-ring was formed in a further six steps to produce the complete ABCDE-ring system **110**. No yields were reported for these final steps (Scheme 1.21).[30]

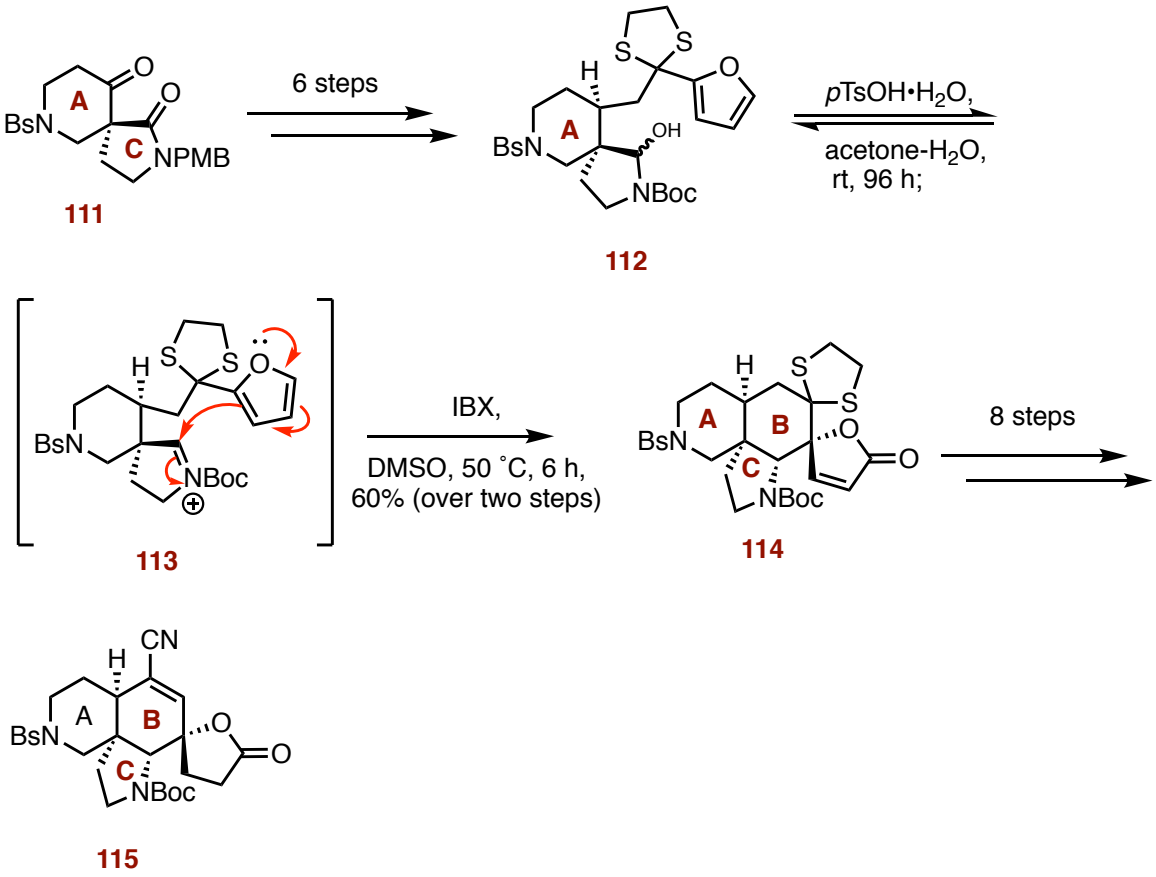


Scheme 1.21. Pandit's synthesis of the ABCDE core

1.6.3 Intramolecular Mannich ring-closure

The core of manzamine A (**1**) was has been prepared by use of the intramolecular Mannich reaction. Nishida and co-workers[21,31,33] and Overman and co-workers[32] have used the Mannich reaction[34] to assemble the B and A rings respectively.[56]

Nishida and co-workers[21,31,33] assembled the ABC core of manzamine A (**1**) using furan-iminium cation cyclisation. Aminol **112** was formed in 6 steps from spirocycle **111**. Iminium **113** was prepared from aminol **112** through elimination under acidic conditions. This was followed by diastereoselective nucleophilic attack of the furan onto the iminium ion **113** to form the ABC diastereoisomeric core **114** in 60% yield. The structure was confirmed by single crystal X-ray diffraction. The ABC tricycle intermediate **115** was then achieved in 8 steps (Scheme 1.22).[21,31,33]

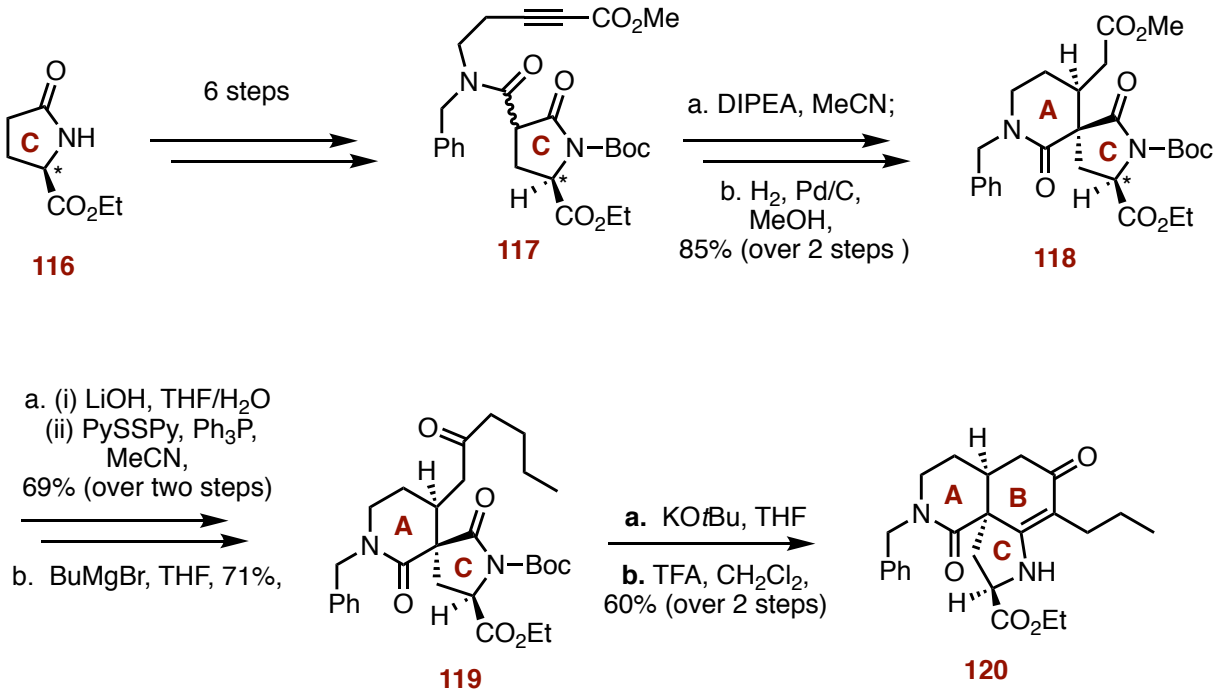


Scheme 1.22. Nishida's synthesis of the ABC core

1.6.4 Intramolecular Michael addition

An intramolecular Michael addition reaction has been also used to construct ABC core of manzamine A (**1**). Brands and co-workers[35] and Fürstner and co-workers[36] constructed the ABC and ACE tricyclic cores respectively via an intramolecular Michael addition pathway[35,36] Brands and co-workers[35] reported installation of the pyrrolo[*2*,*3*-*i*]isoquinoline ABC ring system via an intramolecular Michael addition.

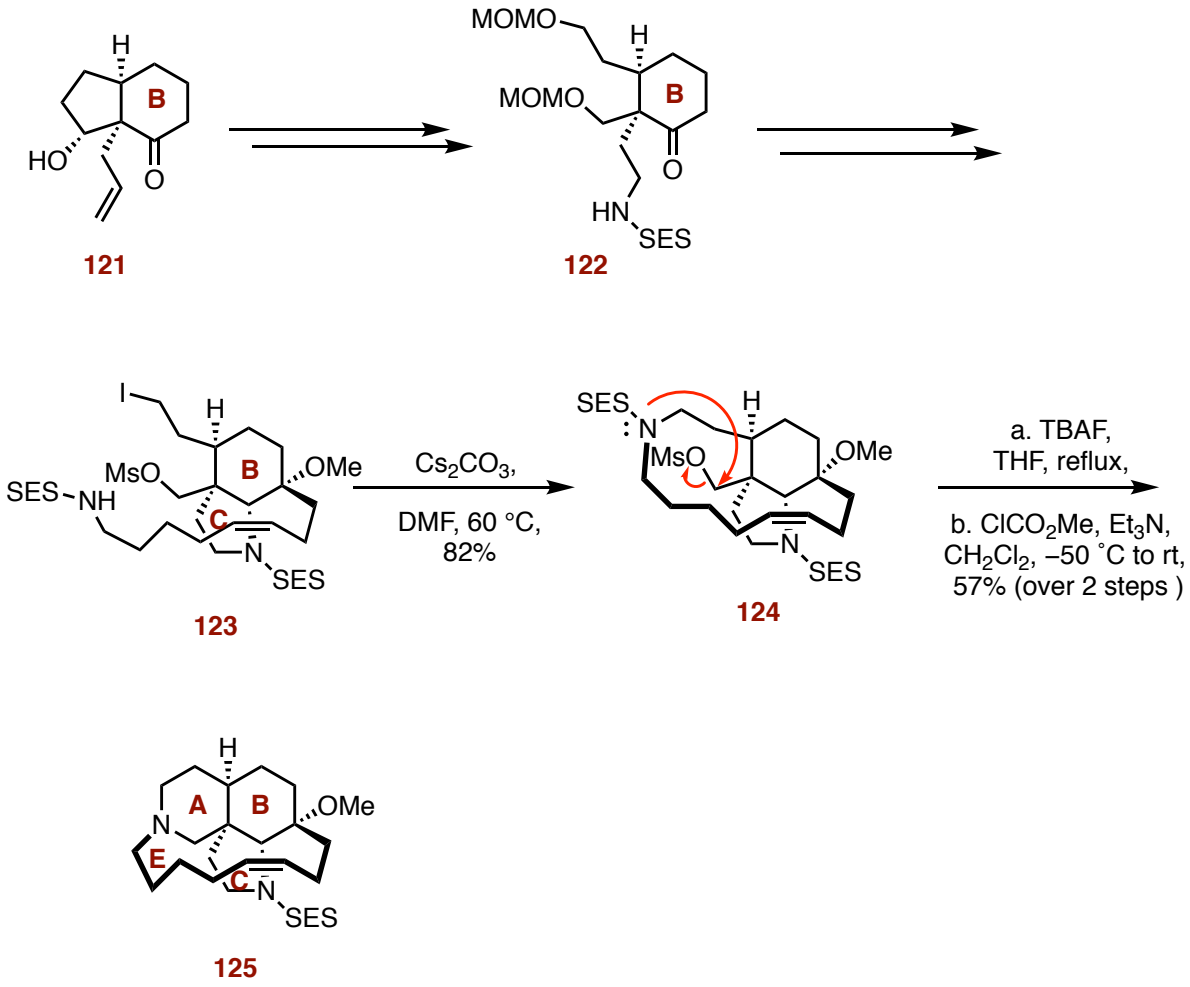
Commercially available pyroglutamic acid ester **116** was converted into the Michael addition precursor **117** in six steps. Michael addition of the β-dicarbonyl unit onto the propargylic ester followed by hydrogenation to afford the diastereomer **118** in 85% yield over the two steps. The stereochemistry at C* resulted from substrate stereocontrol upon generation of spirocycle in **118**. A single diastereomer at the spirocyclic centre was produced in **118** because the ester moiety blocked the top face of ring C. The ketone **119** was synthesised by hydrolysis of ester **118** followed by a Grignard addition. Subjection of the ketone **119** to basic conditions and subsequent treatment with trifluoroacetic acid (a Dieckmann-type cyclisation) delivered the amine **120** in 60% over two steps (Scheme 1.23).[35]



Scheme 1.23. Brands' synthesis of the ABC core

1.6.5 Intramolecular Substitution

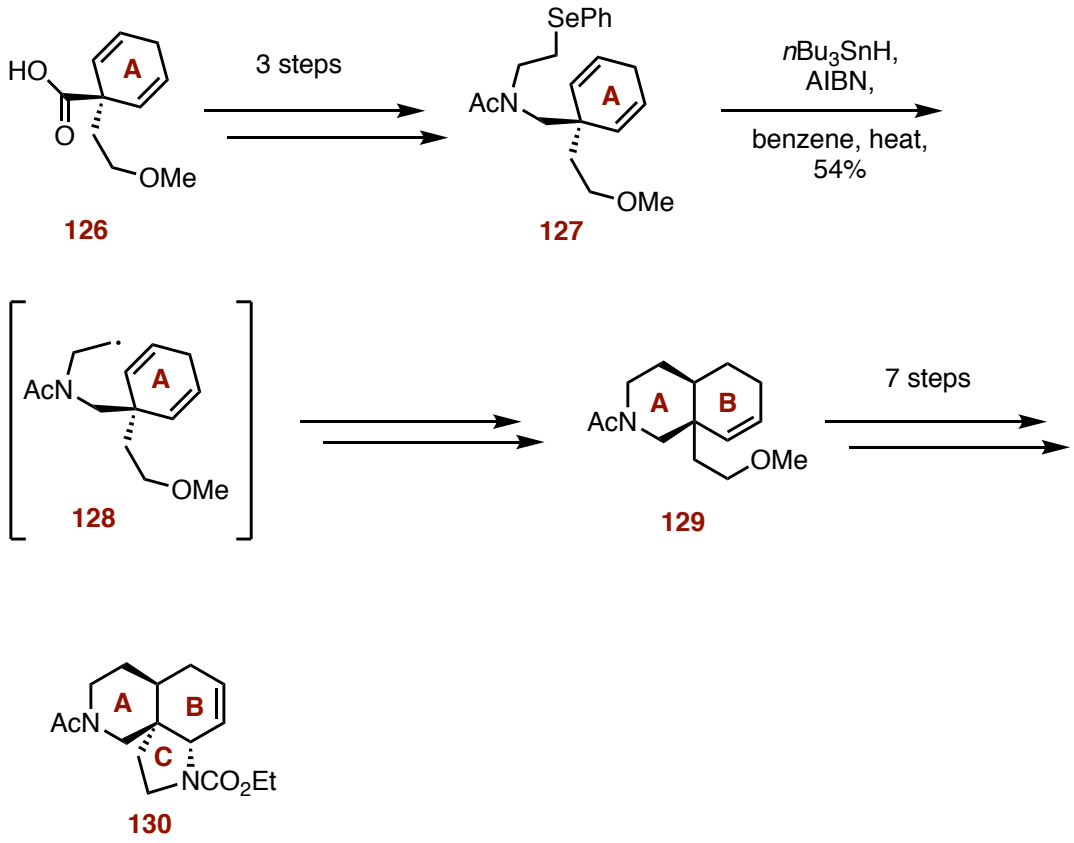
Yamamura and co-workers[37,38] developed a strategy to construct the ABCE ring system through multiple intramolecular S_N2 reactions (Scheme 2.24). The MOM-protected alcohol **122** was prepared from the bicyclic hydroxyketone **121** in eighteen steps. The MOM-protected diol **122** was converted to bicyclic iodide **123** in further thirteen steps. The iodide **123** was subjected to macrocyclisation by intramolecular *N*-alkylation using Cs_2CO_3 to produce the tricyclic intermediate **124** in 82% yield. Cleavage of the silyl protecting group followed by double cyclisation constructed A and E rings and produced the tetracyclic compound **125** in 57% yield over two steps (Scheme 1.24).[38]



Scheme 1.24. Yamamura's synthesis of the ABCE core

1.6.6 Alternative and less developed synthetic approaches

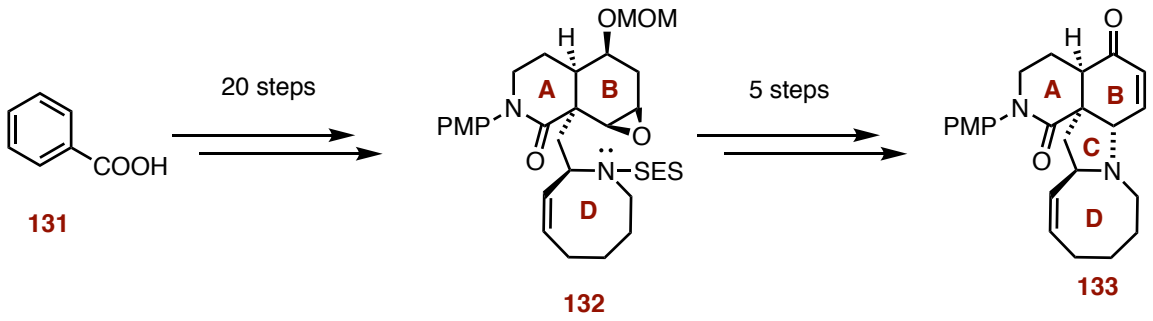
In 1989, the first group to report a synthetic pathway of the core of manzamine A (**1**) was Hart and co-workers.[39] Their pathway was based upon the use of a 6-*exo*-trig radical cyclisation reaction to install rings A and B in order to produce the hydroisoquinoline core **129.** The selenide **127** was prepared from the carboxylic acid **126** in 3 step. Formation of the radical **128** under standard conditions followed by cyclisation gave the bicyclic alkene **129**. This reaction was followed by elimination and an electrophile-initiated ring closing sequence to produce tricyclic carbamate **130** in 62% yield (Scheme 1.25).



Scheme 1.25. Hart's synthesis of the ABC core

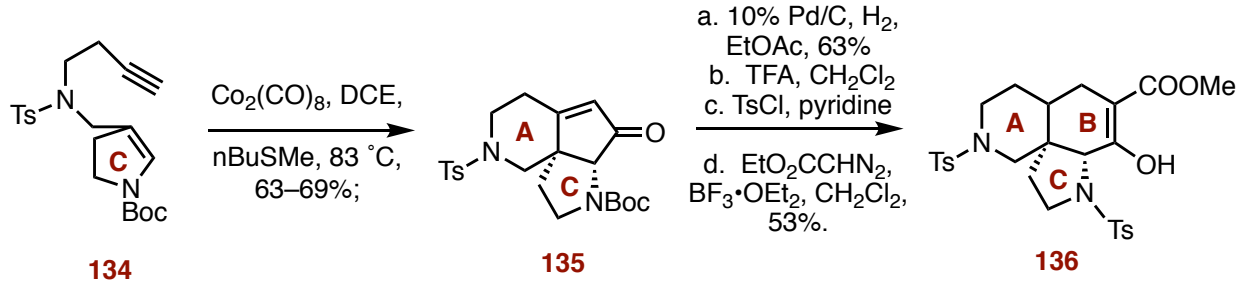
In 1992, another approach to the construction of the tetracyclic core of manzamine A (**1**) was reported by Hart and co-workers.[39] Benzoic acid **131** was converted to the ABD core in 20 steps. An intramolecular nucleophilic epoxide-opening reaction was applied using the nitrogen of

the azocine ring **132** to form ring C and thereby produce the ABCD core of manzamine A **133** (Scheme 1.26).



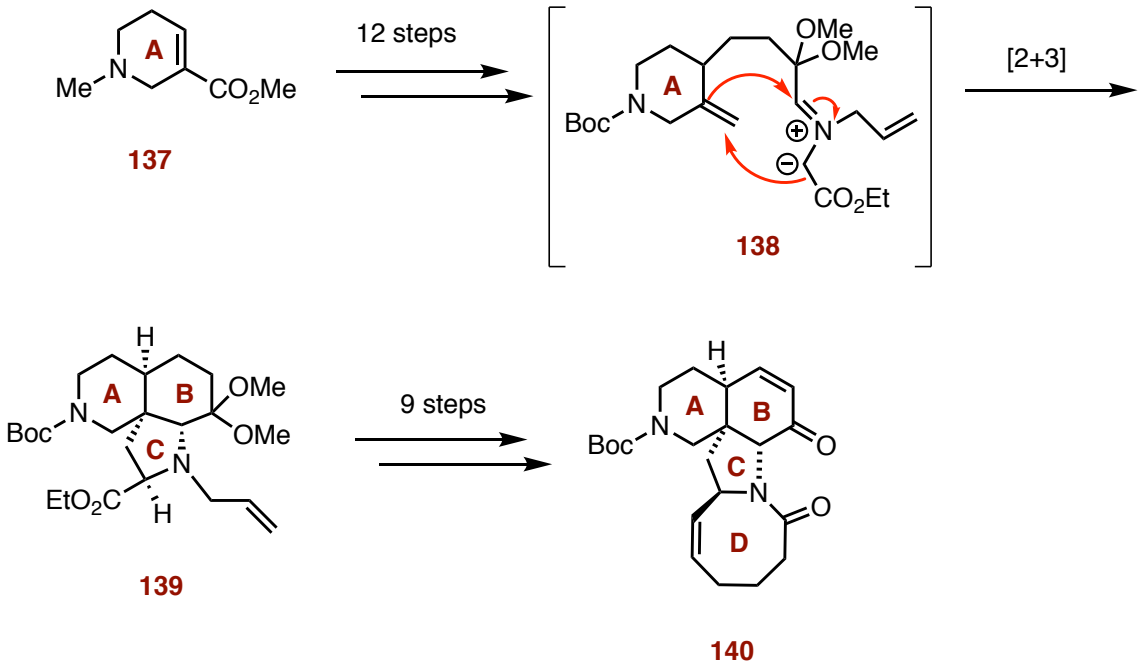
Scheme 1.26. Hart's synthesis of the ABCD core

Magnus and co-workers[40] constructed the ABC core of manzamine A (**1**) by use of a Pauson-Khand reaction[41] with an enamide or enamine and a subsequent ring expansion reaction. They were the first group to use an enamide as the alkene partner for a Pauson-Khand reaction. Enamide **134** was prepared from *N*-Boc pyrrolidinone in five steps in 44% yield. A modified Pauson-Khand reaction was applied using Sugihara conditions to produce the desired tricyclic enone **135** in 63-69% yield, which possesses two stereocentres. Hydrogenation of the enone followed by protecting group exchange and ring expansion by Lewis acid activation and treatment of ethyl diazoacetate resulted in enol **136** in 53% yield. The stereochemistry of **136** was confirmed by single crystal X-ray diffraction (Scheme 1.27).



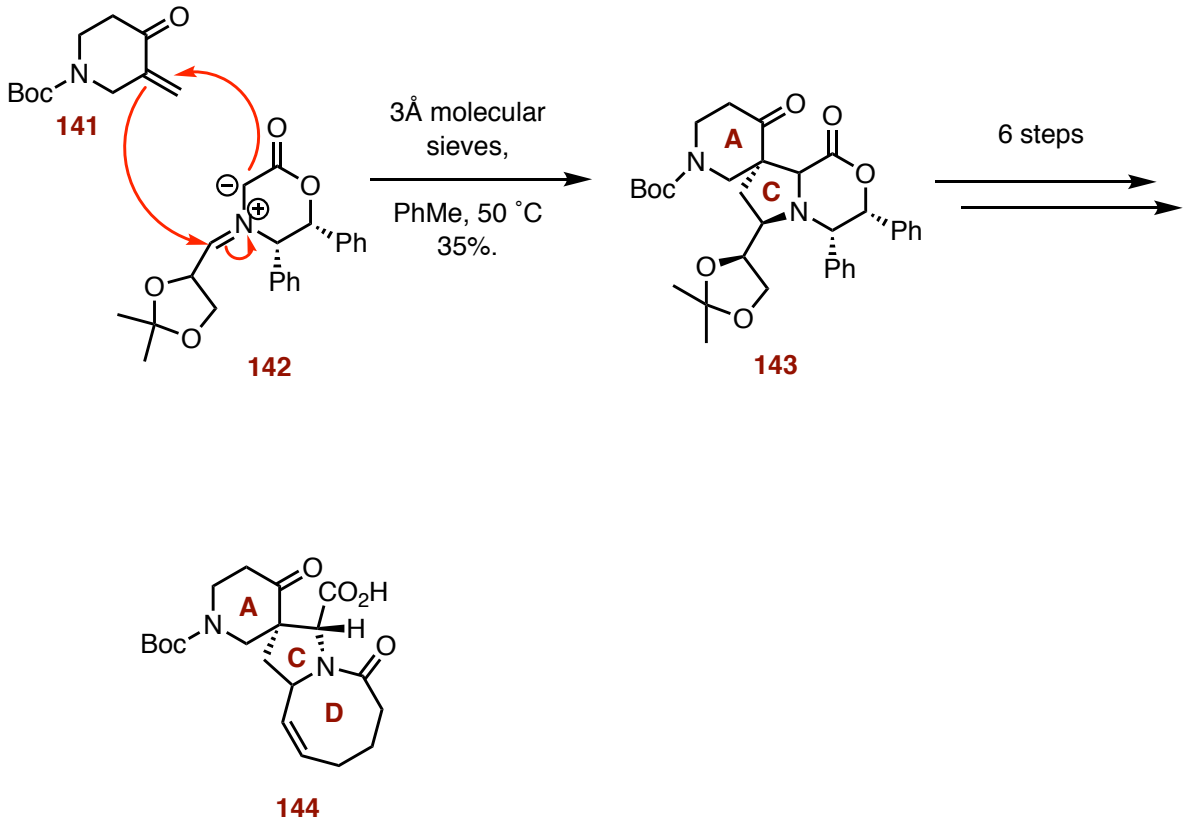
Scheme 1.27. Magnus' synthesis of the ABCD core

Coldham and co-workers[42,43] have reported a synthetic route to construct the tetracyclic ABCD core based on an intramolecular [2+3]-cycloaddition reaction. The azomethine ylide **138** was prepared from the commercially available arecoline **137** in 12 steps. The ylide **138** then underwent cycloaddition to the alkene to produce the tricyclic acetal **139,** which was then converted into the tetracyclic enone **140** in 9 further steps (Scheme 1.28).



Scheme 1.28. Coldham's synthesis of the ABCD core

Williams and co-workers[44] reported a strategy that relied on an intermolecular [3+2]-dipolar cycloaddition reaction to construct the ACD core **144** of manzamine A (**1**). An intermolecular cycloaddition reaction was performed using the enone **141** and the azomethine ylide **142** to afford the desired cycloadduct **143**. Cycloadduct **143** was converted into the lactam **144** corresponding to the ACD core in six steps (Scheme 1.29).



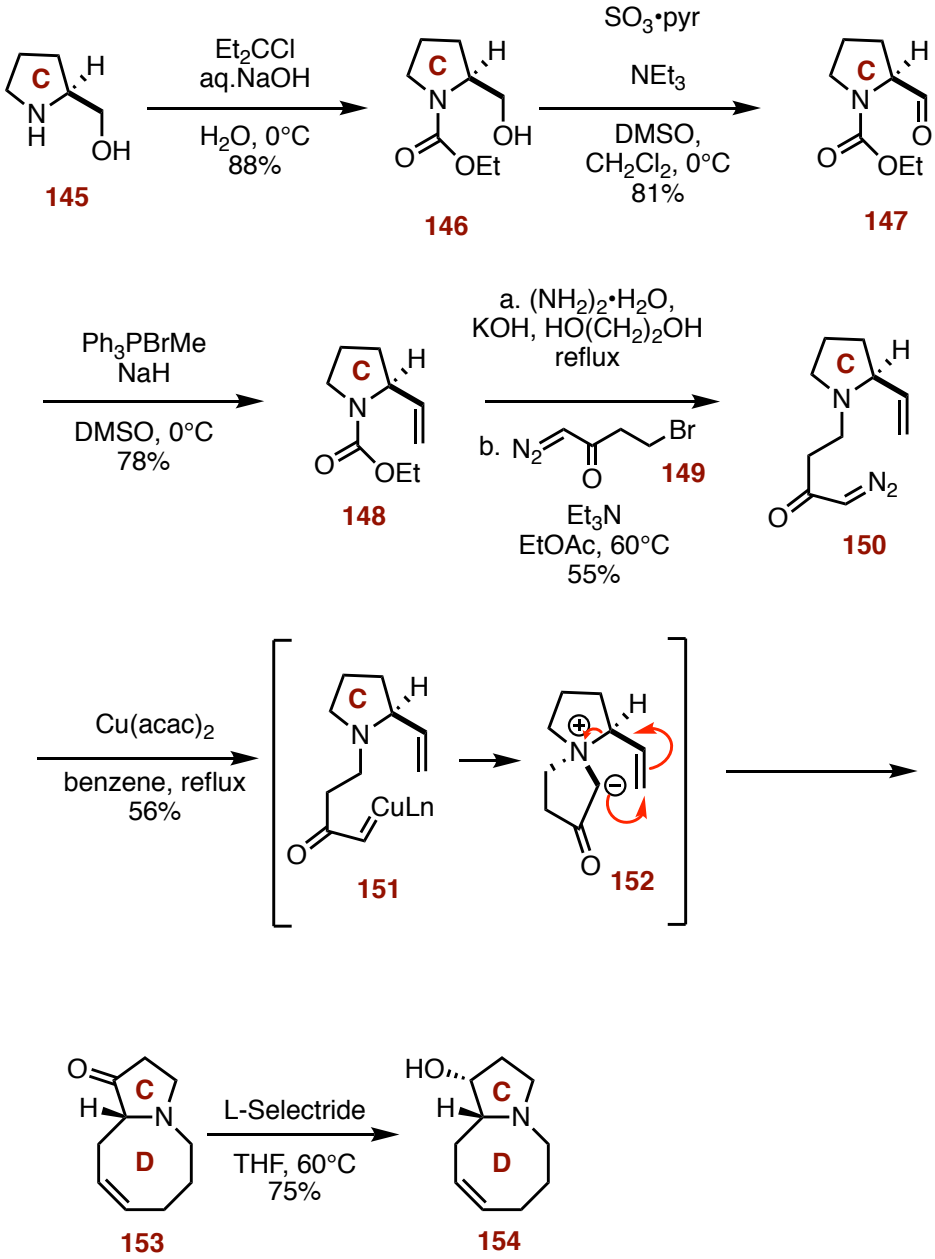
Scheme 1.29. Williams' synthesis of the ACD core

2 Clark Group Previous Work Towards Manzamine A Core

The Clark group have developed and reported many efficient synthetic approaches towards the cores of manzamine A (**1)** including the core manzamine rings and advanced intermediates. For example, routes towards bicyclic CD ring core and AB ring core as well as ABCD core of manzamine A **(1).**

2.1 Synthesis of the CD ring core

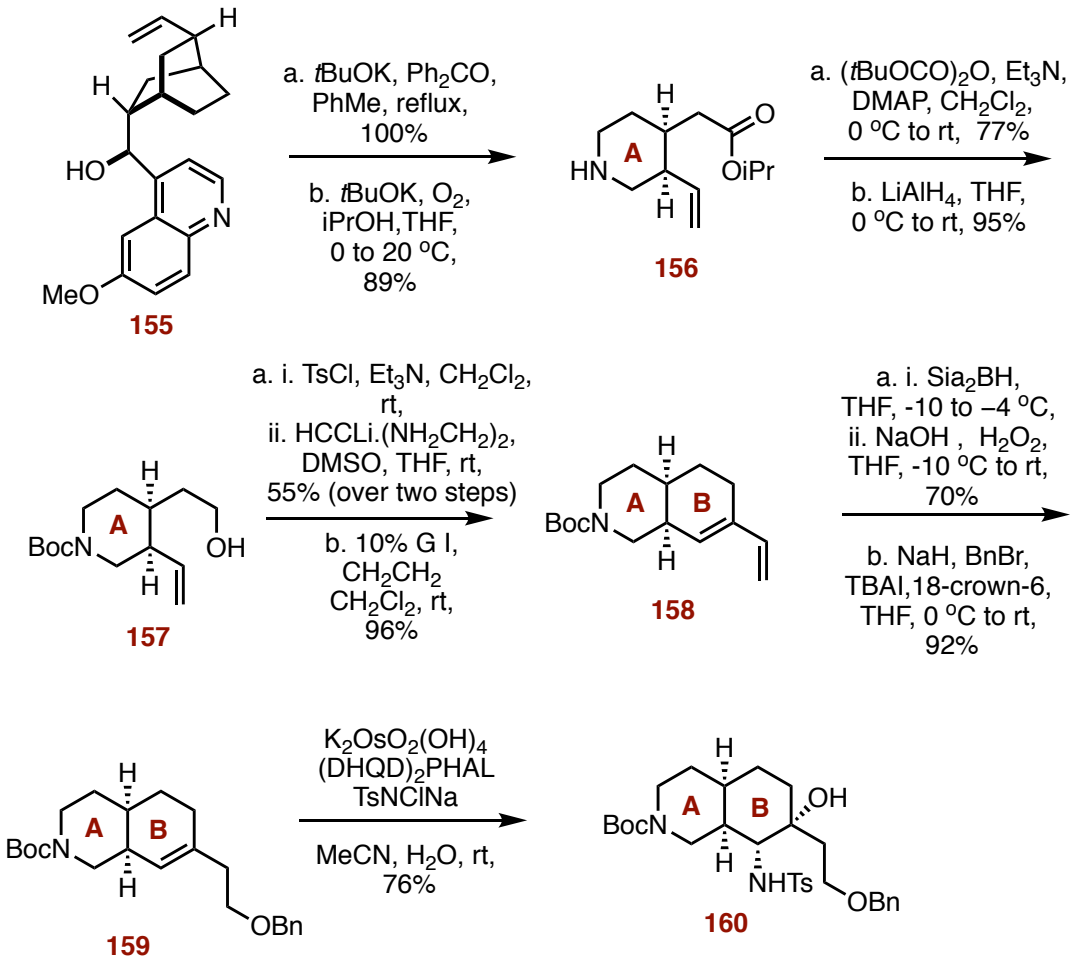
In 1992, Clark and co-workers[45] established an enantioselective route to construct the CD ring core of manzamine A (**1**), manzamine E, manzamine F and ircinal A (**5**). This route started with *N*-protection of the aminoalcohol **145,** resulting in carbamate **146** in 88% yield. This was followed by oxidation of the hydroxyl group to deliver the aldehyde **147** in 81% yield. The aldehyde **147** converted into the allylic amine **148** by methylenation. Deprotection was accomplished using hydrazine and subsequent *N*-alkylation with 4-bromo-1-diazobutan-2-one **149** produced the diazoketone **150** in 55% yield over two steps. Cyclisation mediated by $Cu(acac)_2$ as the catalyst delivered the fused CD bicyclic core **153** in 56%. [2,3]-Sigmatropic rearrangement of the spiro-fused bicyclic ammonium ylide **152** resulted in three-carbon ring-expansion of the pyrrolidine. The CD bicyclic core **153** underwent ketone reduction to produce alcohol **154** in 75% yield (Scheme 2.1).[45]



Scheme 2.1. Clark's synthesis of the CD core

2.2 Synthesis of the AB ring core

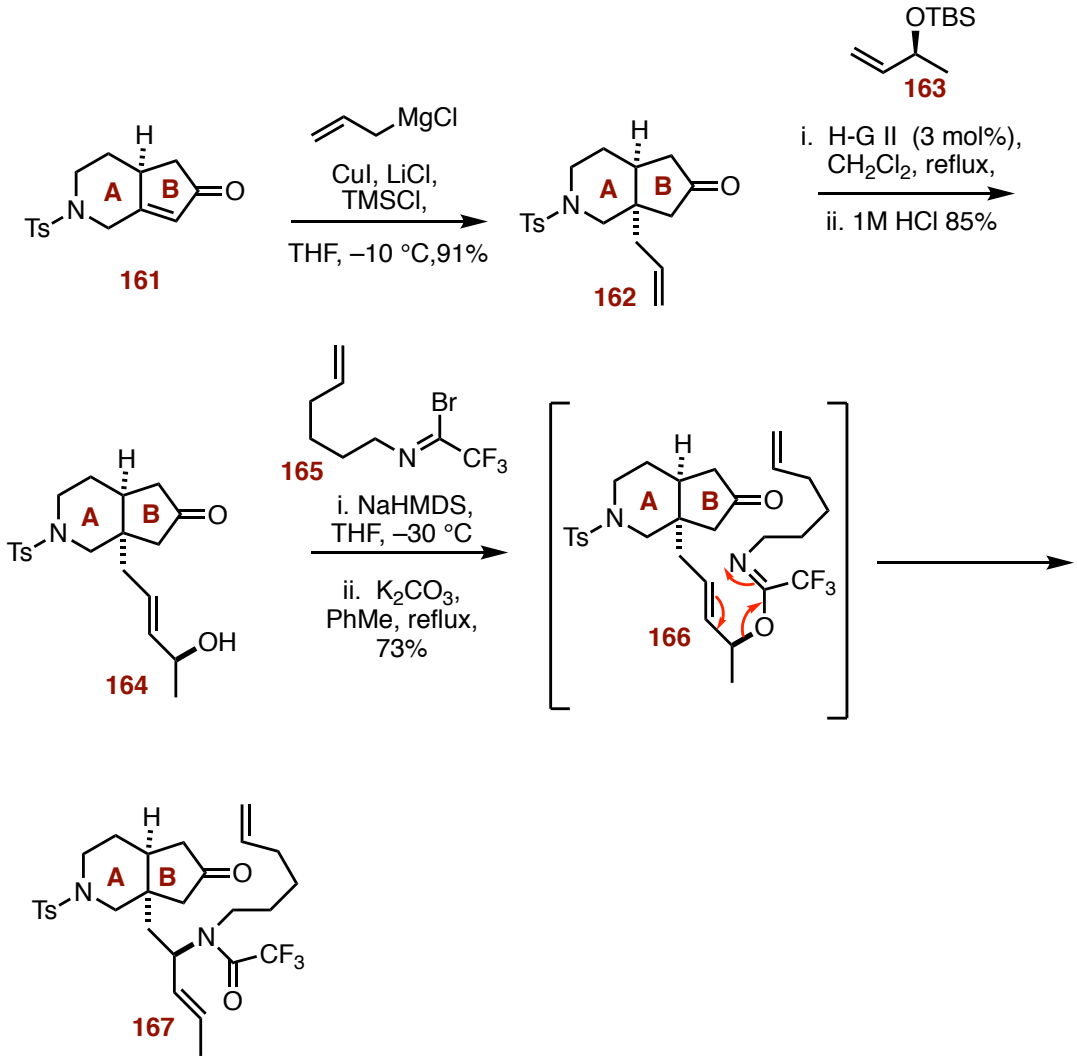
In 2001, Clark and co-workers[46] reported an enantioselective synthesis of the AB ring core **160**. This synthesis started with oxidation of quinine **155** to the quininone followed by ring cleavage to give the piperidinyl ester **156** in 89% yield. Amine **156** was protected and then reduction of the ester delivered alcohol **157** in 95% yield. AB ring core **158** was constructed by conversion of the hydroxyl group into a tosylate, displacement with lithium acetylide ethylene diamine complex and ring-closing enyne metathesis using the Grubbs first generation catalyst. Benzyl ether **159** was produced by a regioselective hydroboration of the diene followed by benzyl protection of the alcohol. Sharpless aminohydroxylation was applied to the benzyl ether **159** to produce the AB ring core **160** in 76% yield (Scheme 2.2).[46]



Scheme 2.2. Clark's synthesis and elaboration of the AB core

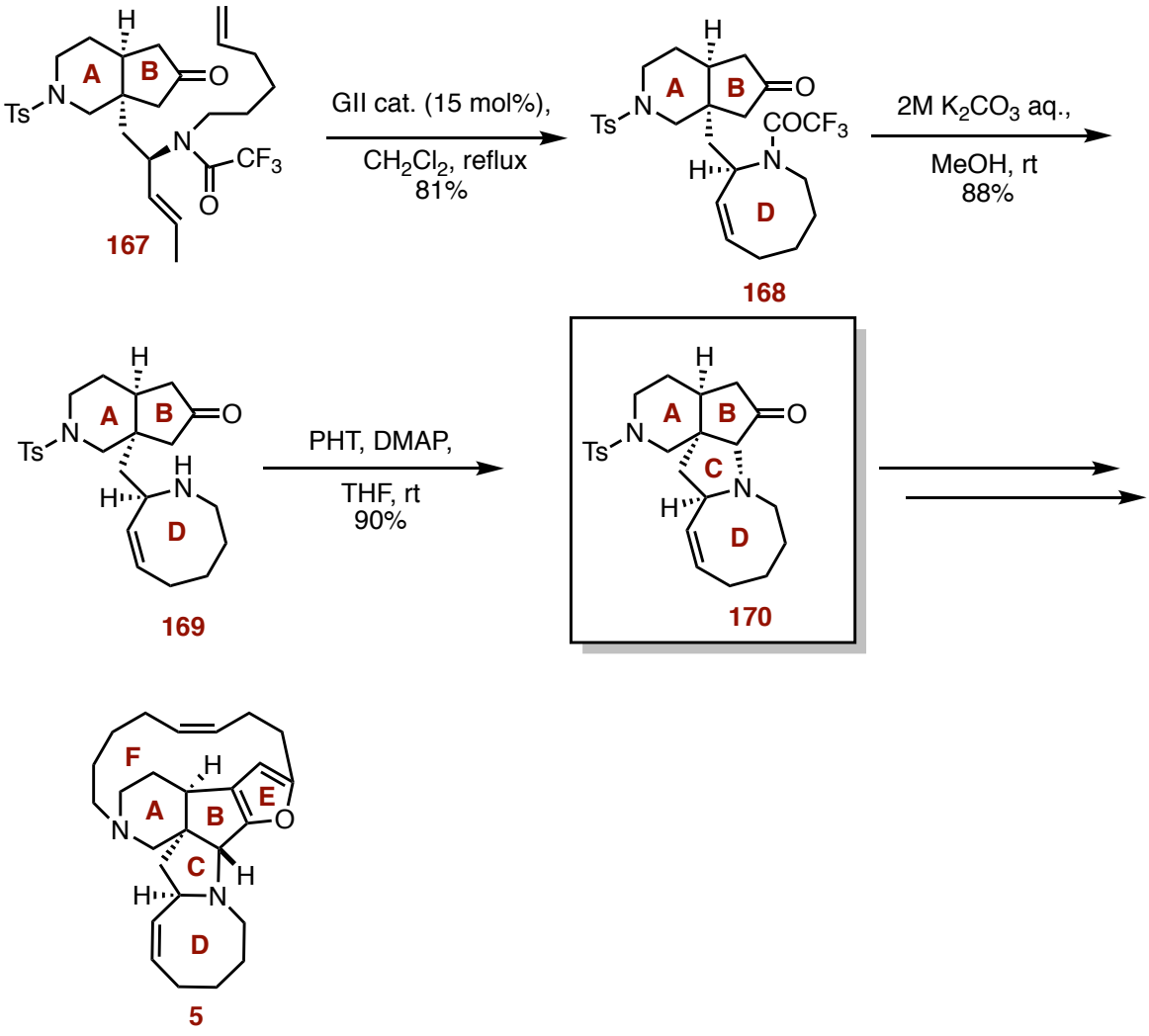
2.3 Nakadomarin A and ABCD tetracyclic ketone core of manzamine A

In 2016, Clark and co-workers[48] completed a short and efficient total synthesis of nakadomarin A (**5**) by late-stage furan formation from the tetracyclic ketone **170**. This ketone could also be used as an intermediate for the total synthesis of manzamine A. The tetracyclic ketone **170** was accessed from bicyclic enone **161**. The enone **161** was converted into the ketone **162** using conjugate addition, which then underwent cross metathesis to produce the allylic alcohol **164**. Treatment of alcohol **164** with bromide **165** gave the imidate **166**. Thermal [3,3]-sigmatropic rearrangement of imidate **166** provided the allylic amine **167** with a high level of stereocontrol (Scheme 2.3).[47,48]



Scheme 2.3. Clark's synthesis of ABCD core and nakadomarin A (5)

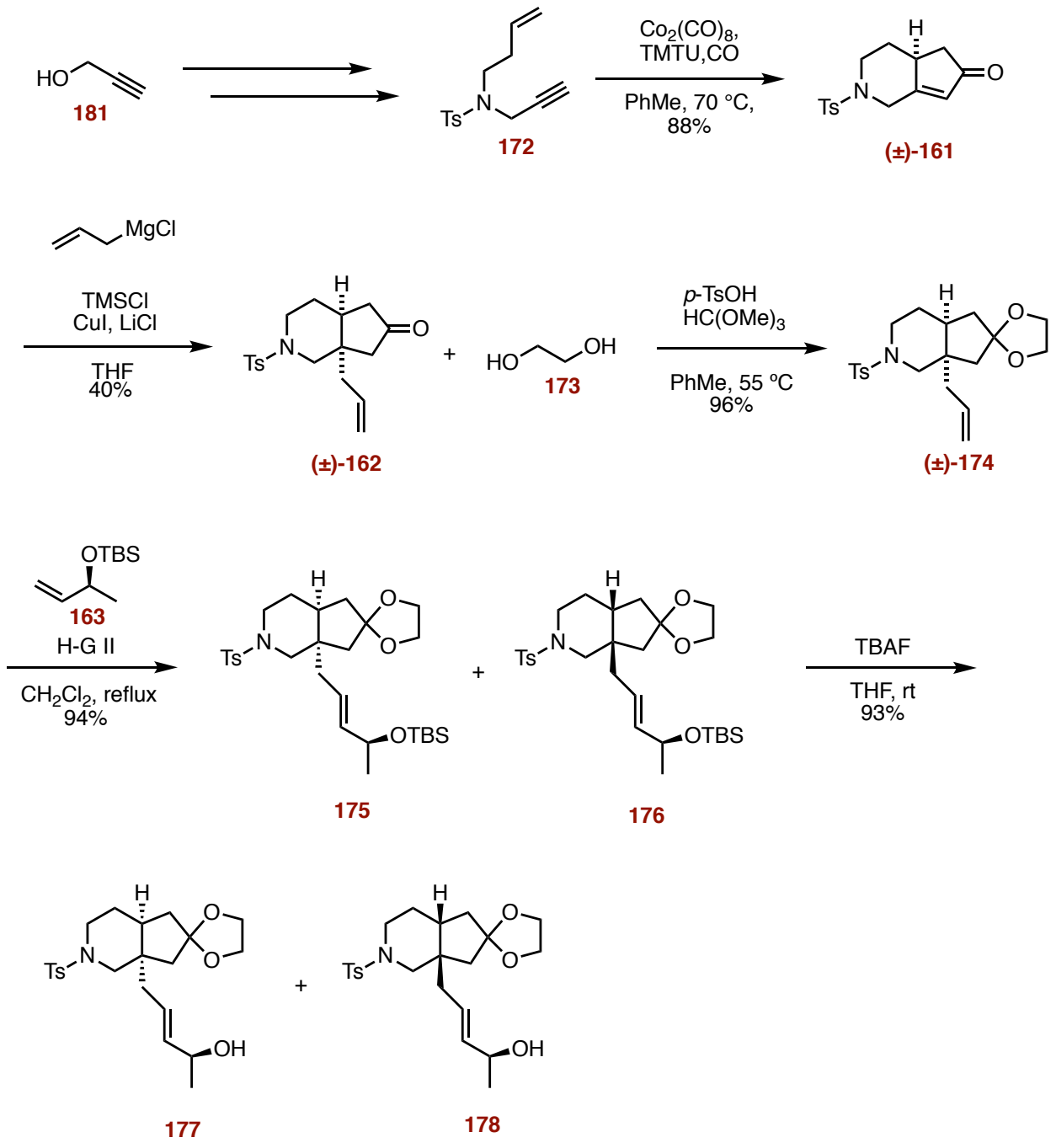
Formation of the 8-membered ring using a ring-closing metathesis reaction produced amide **168**, which was deacylated carefully to generate the tetracyclic amine **169**. Tetracyclic ketone **170** was obtained using a novel amination reaction to close the ring D. Nakadomarin A (**5**) was produced from tetracyclic ketone **170** in just five steps (Scheme 2.4).[47,48]



Scheme 2.4. Clark's synthesis of ABCD core and nakadomarin A (5)

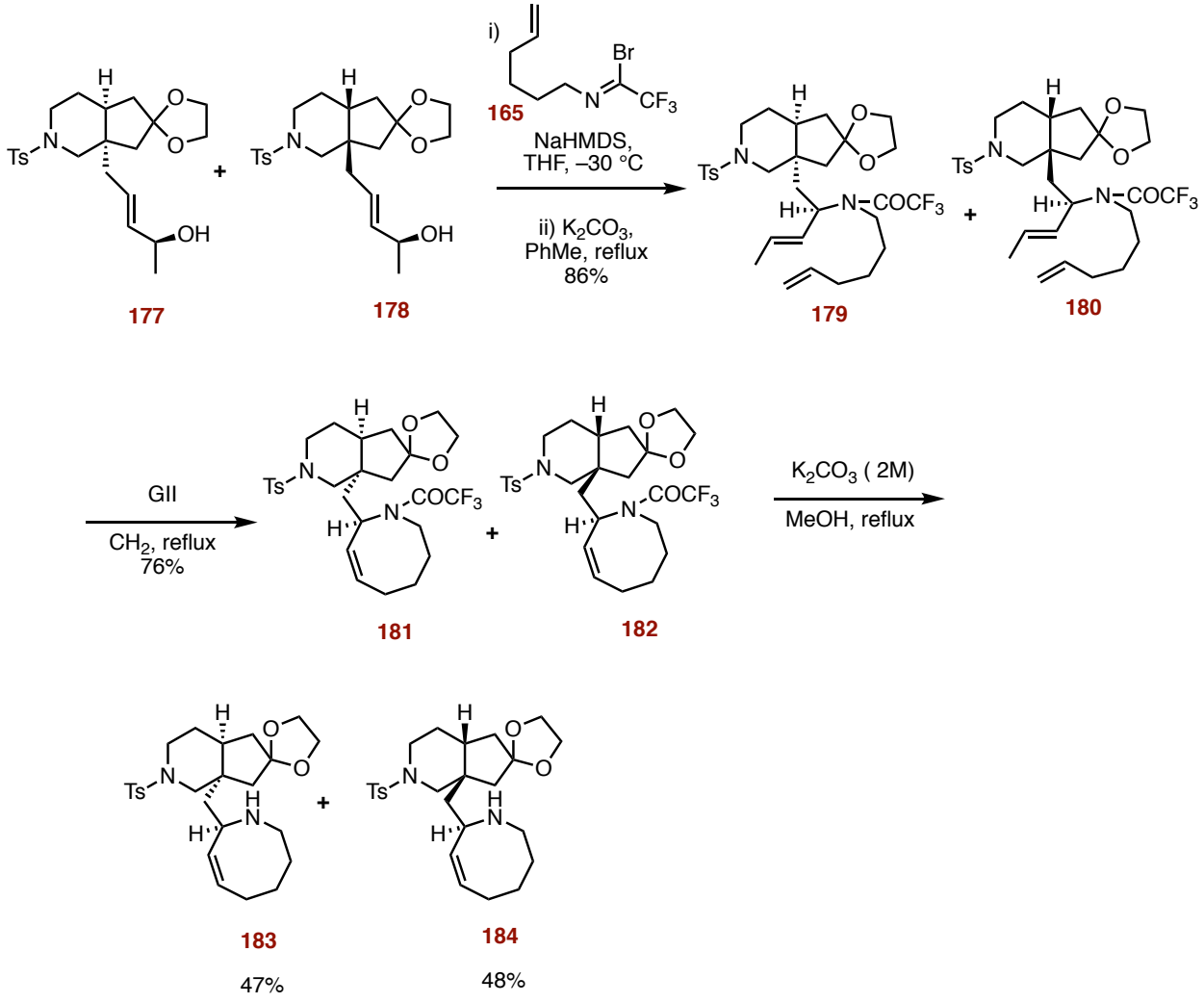
2.4 Previous work towards manzamine A

During previous work in the Clark group towards manzamine A (1)[49], the key tetracyclic ketone intermediate **170** has been prepared from propargylic alcohol **181** in five steps. A Pauson-Khand reaction followed by 1,4-addition produced the racemic alkene **(±)-162** and subsequent protection of the ketone functionality provided **(±)-174**. Cross metathesis of **(±)-174** with the chiral side chain **163** provided a mixture of two diastereomeric allylic TBS-protected alcohols **175** and **176.** Deprotection of TBS-protected alcohols **175** and **176** resulted in allylic alcohols **177** and **178** (Scheme 2.5).[49]

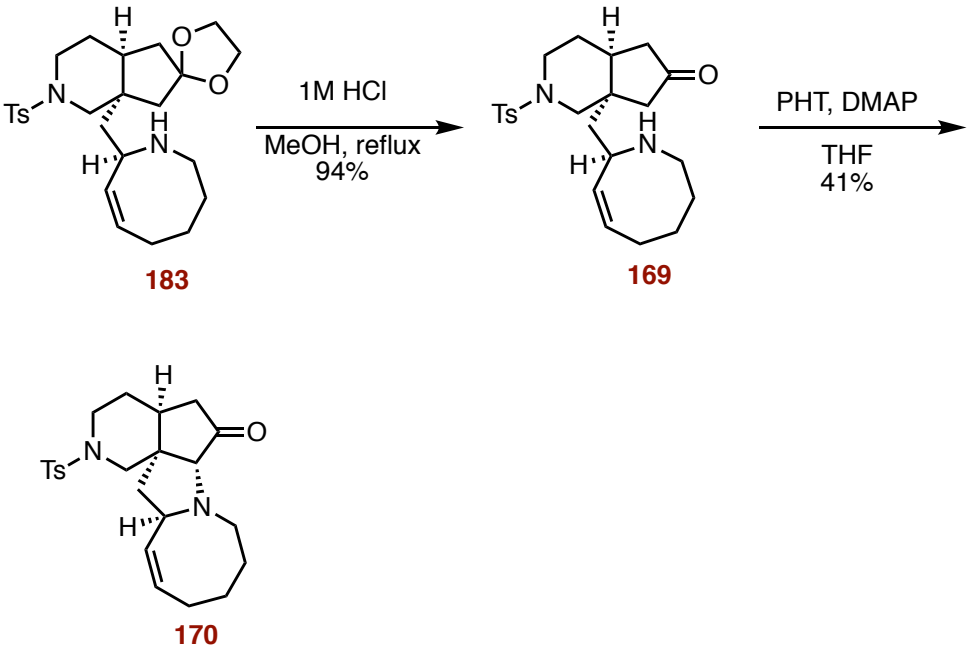


Scheme 2.5. Clark's synthesis of alcohol from the racemic materials

An *O*-alkylation/[3,3]-sigmatropic rearrangement sequence of the inseparable mixture of diastereomers **177** and **178** provided **179** and **180.** Ring-closing metathesis of the mixture of **179** and **180** constructed the 8-membered ring and delivered a mixture of the amides **181** and **182**. Hydrolysis of trifluoroacetamides **181** and **182** produced the diastereomeric amimes **183** and **184** (Scheme 2.6).[49] The diastereomers **183** and **184** were separated by column chromatography and **183** underwent acetal deprotection deliver the ketone **169**. A PHT-mediated cyclisation of amine **169** provided the tetracyclic ketone **170** (Scheme 2.7).[49]



Scheme 2.6. Clark's synthesis of ABD core from the racemic materials

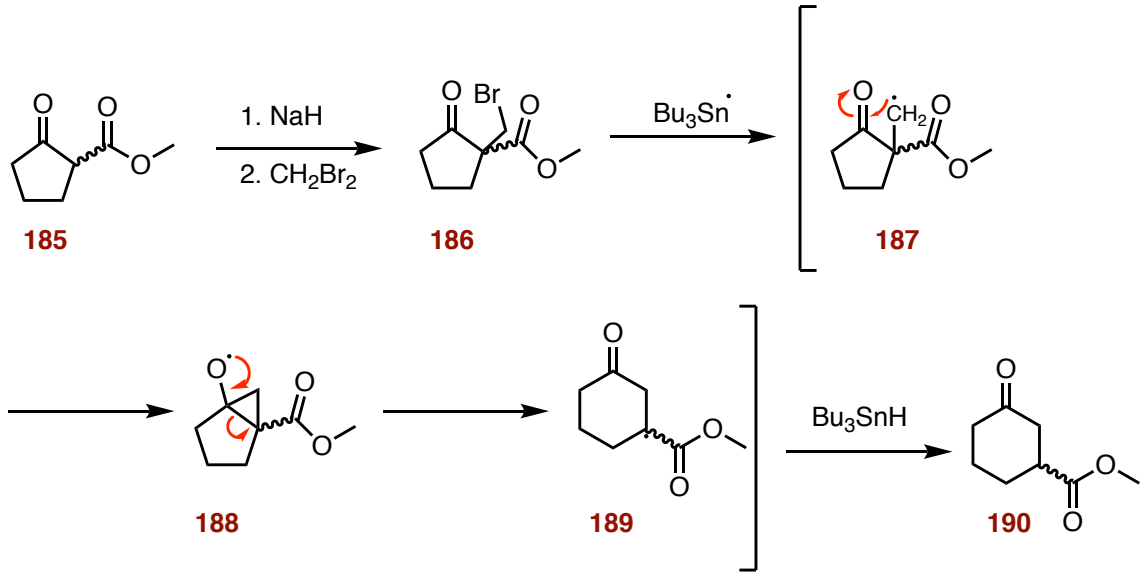


Scheme 2.7. Clark's synthesis of ABCD core from the racemic materials

2.5 Ring expansion and elaboration strategy of ABCD tetracyclic core of manzamine A

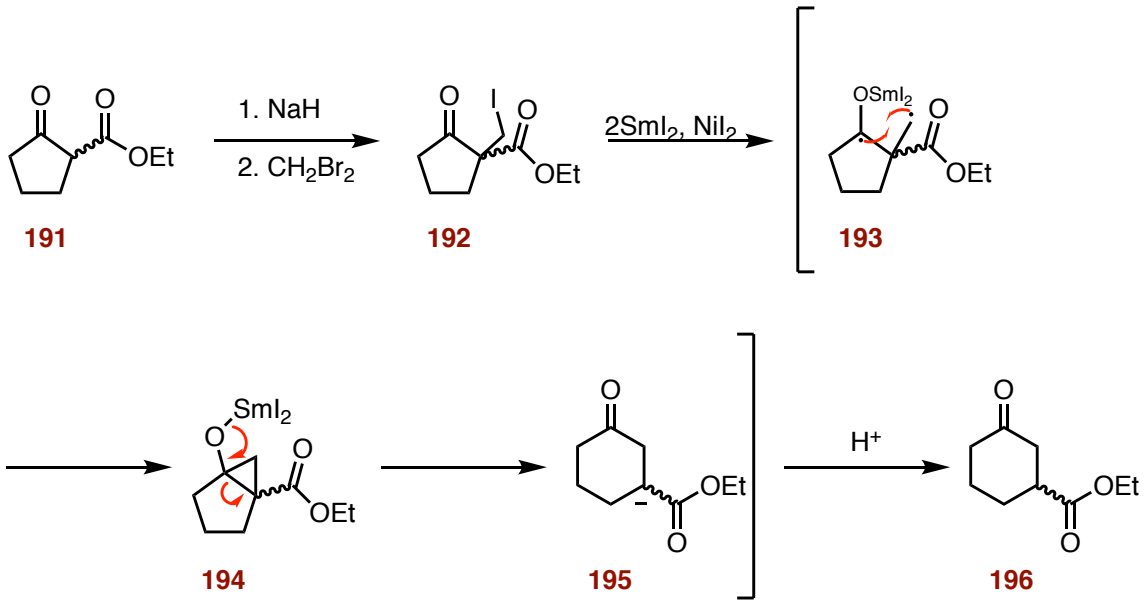
Several strategies that have been considered by the Clark group[49] for ring expansion of the tetracyclic ketone **170,** which served as a key intermediate in the total synthesis of nakadomarin A (5). The ring expansion could be achieved in many ways, some of which are discussed in this thesis.

The first approach to ring expansion to be considered was by use of the well-known Dowd–Beckwith[51,52] ring expansion reaction. This general method of one-carbon ring expansion of cyclic ketones was discovered in 1987[51,52]. It involves ring expansion of the cyclic *β*-keto ester via free radical ring expansion using α-alkylhalo fragments. For example, alkylation of the cyclic *β*-keto ester **185** delivered the bromo intermediate **186**. This was followed by ring expansion of the **186** via a free radical to give the ketone **190** (Scheme 2.8).



Scheme 2.8. Dowd–Beckwith ring expansion reaction

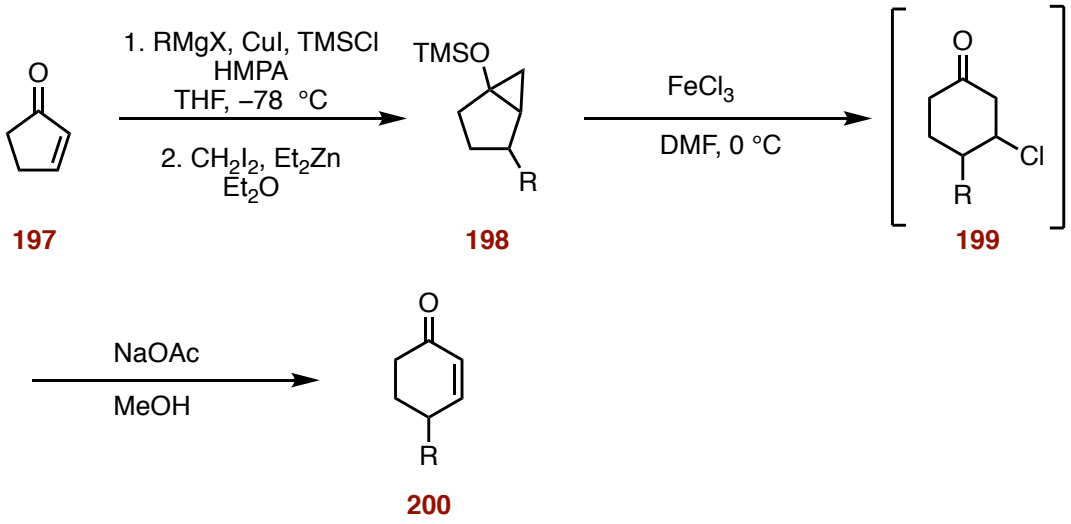
According to Chung and co-workers[53], ring expansion of the cyclic *β*-keto ester could be initiated by use of the strong one-electron donor samarium diiodide, which generates a ketyl radical. Alkylation of *β*-keto ester **191** with diiodomethane results in the α-iodomethyl intermediate **192**. This was followed by addition of SmI_2 in the presence of NiI_2 to give the ring expanded the γ-keto ester **196** (Scheme 2.9).



Scheme 2.9. Chung ring-expansion reaction

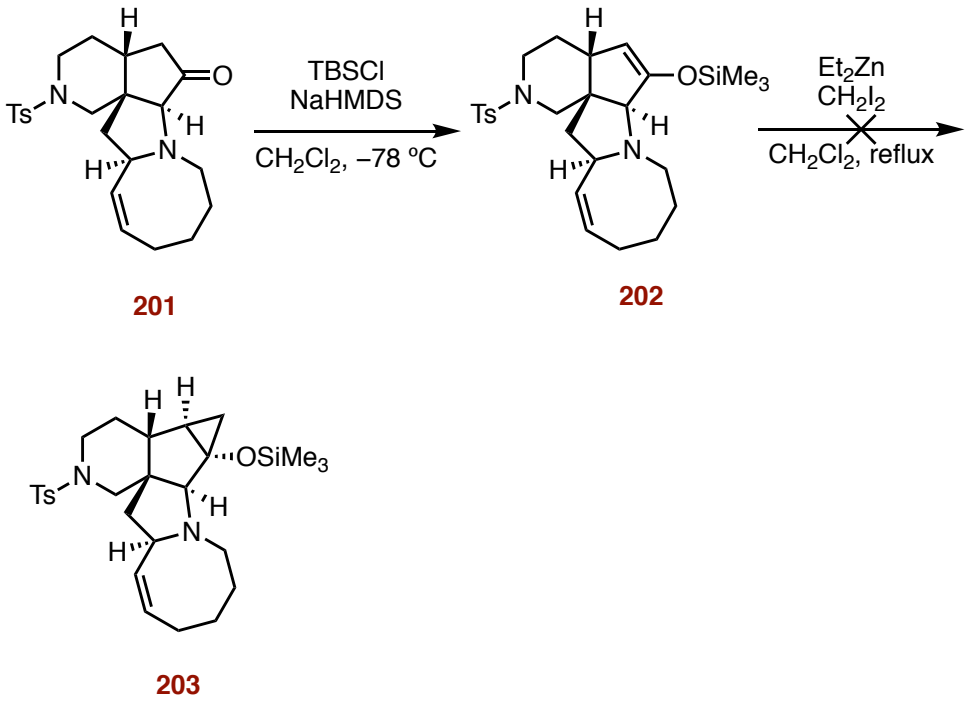
The cyclic the α-iodomethyl intermediate **192** can also be treated with activated zinc[45] or indium[54] to initiate the rearrangement reaction to give the ring-expanded γ-keto ester **196**.[54] This approach to ring expansion has the potential to be applied to tetracyclic intermediate **170**, and is discussed more in the synthetic strategy in chapter **4.1**.

An alternative ring-expansion method, developed by Booker-Milbun[58] and co-workers, involves regioselective conversion of cyclopentenone **197** into the enone **200**. Cyclopentenone underwent conjugate addition with Grignard reagent to produce cyclopropyl ethers **198**. Treatment of the corresponding **198** with ferric chloride provided the ring expanded β-chloro ketone **199**. Elimination with NaOAc and MeOH produced the cyclohexenone **200** (Scheme 2.10). This approach has been applied to the tetracyclic ketone **201** by the Clark group[49] but unfortunately, the reaction was not successful and silyloxycyclopropanes **203** were not formed (Scheme 2.11).



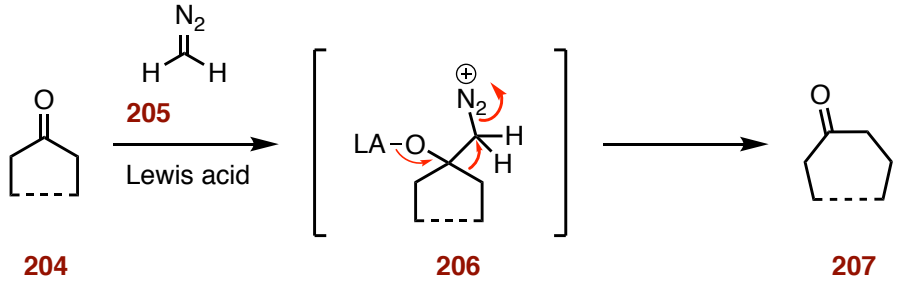
197 **198** **199** **200**

Scheme 2.10. Booker-Milburn ring expansion

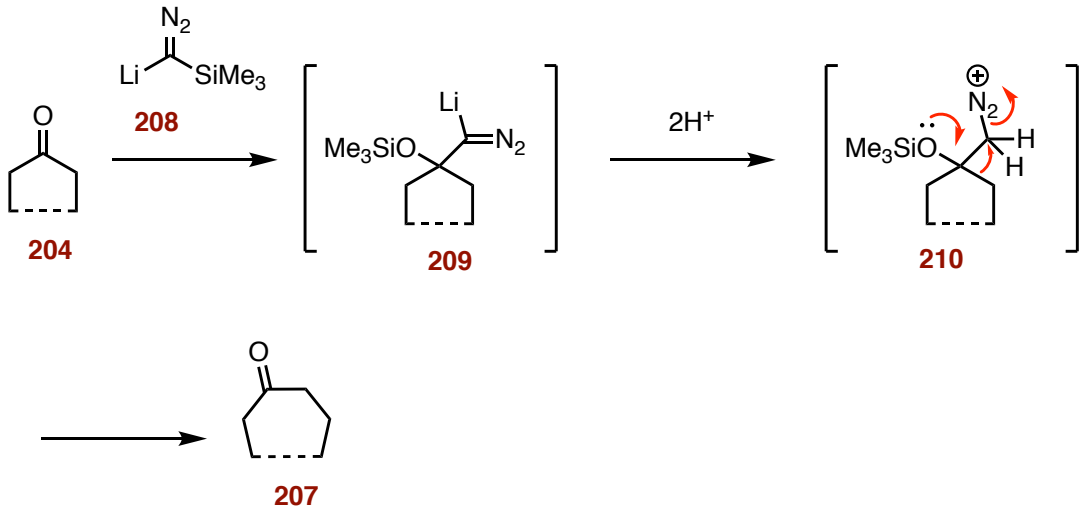


Scheme 2.11 Clark group ring expansion attempt

Another approach to ring expansion has been developed by Lee and co-workers.[55-57] Ketones of the general type **204** were subjected to direct ring expansion to give ketones **207** by treatment with diazomethane **205** in the presence of a Lewis acid (Scheme 2.12) or by reaction with lithiated trimethylsilyldiazomethane **208** (Scheme 2.13).[55]

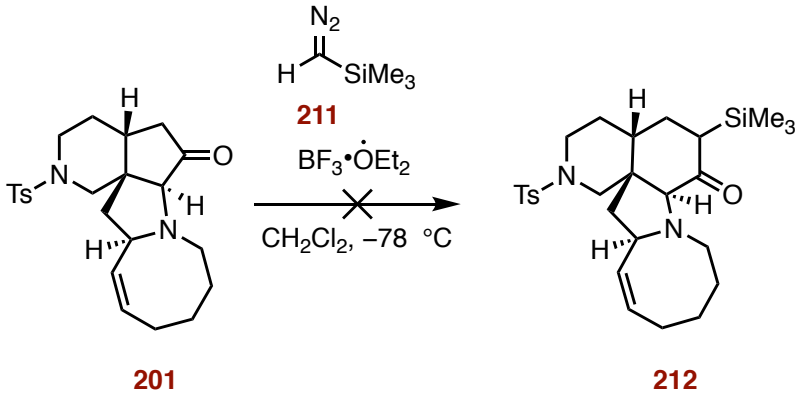


Scheme 2.12. Lee ring expansion sequence

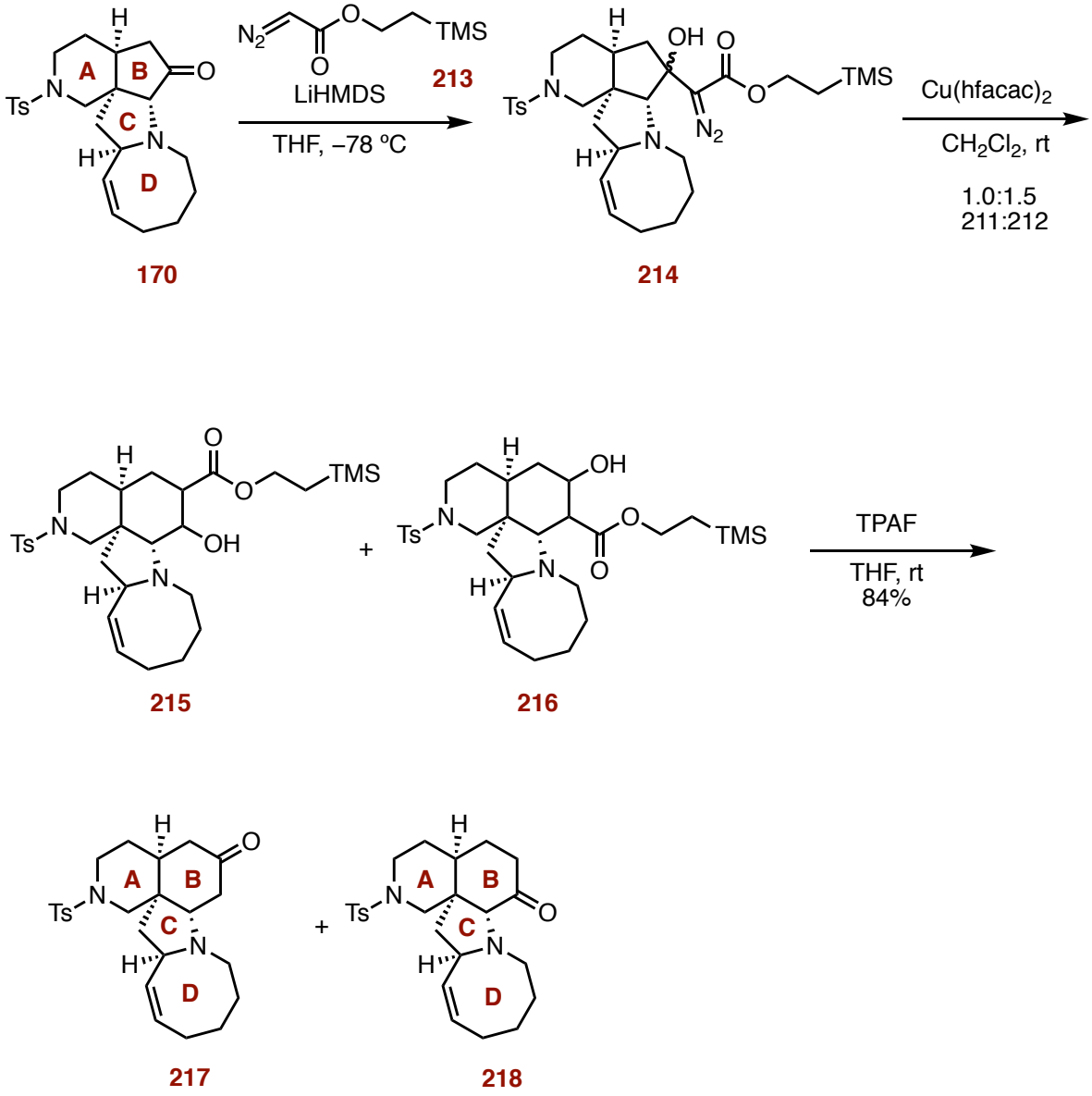


Scheme 2.13. Lee ring expansion sequence

These approaches were also tested within the Clark group but unfortunately these reactions were not successful (Scheme 2.14).[49] However, the Clark group developed a modified lithiated trimethylsilyldiazomethane addition to the ketone to construct the ring expansion and form ABCD skeleton. The tetracyclic ketone **170** was converted into the α-diazo-β-hydroxyester **214** which then underwent ring expansion using $Cu(hfacac)_2$ to produce the ring expanded β-ketoesters **215** and **216**. Decarboxylation of β-ketoesters **215** and **216** produced the regioisomeric ketones **217** and **218**, corresponding to the desired manzamine ABCD skeleton, in 84% yield (Scheme 2.15).[49]



Scheme 2.14. Clark group ring expansion attempt

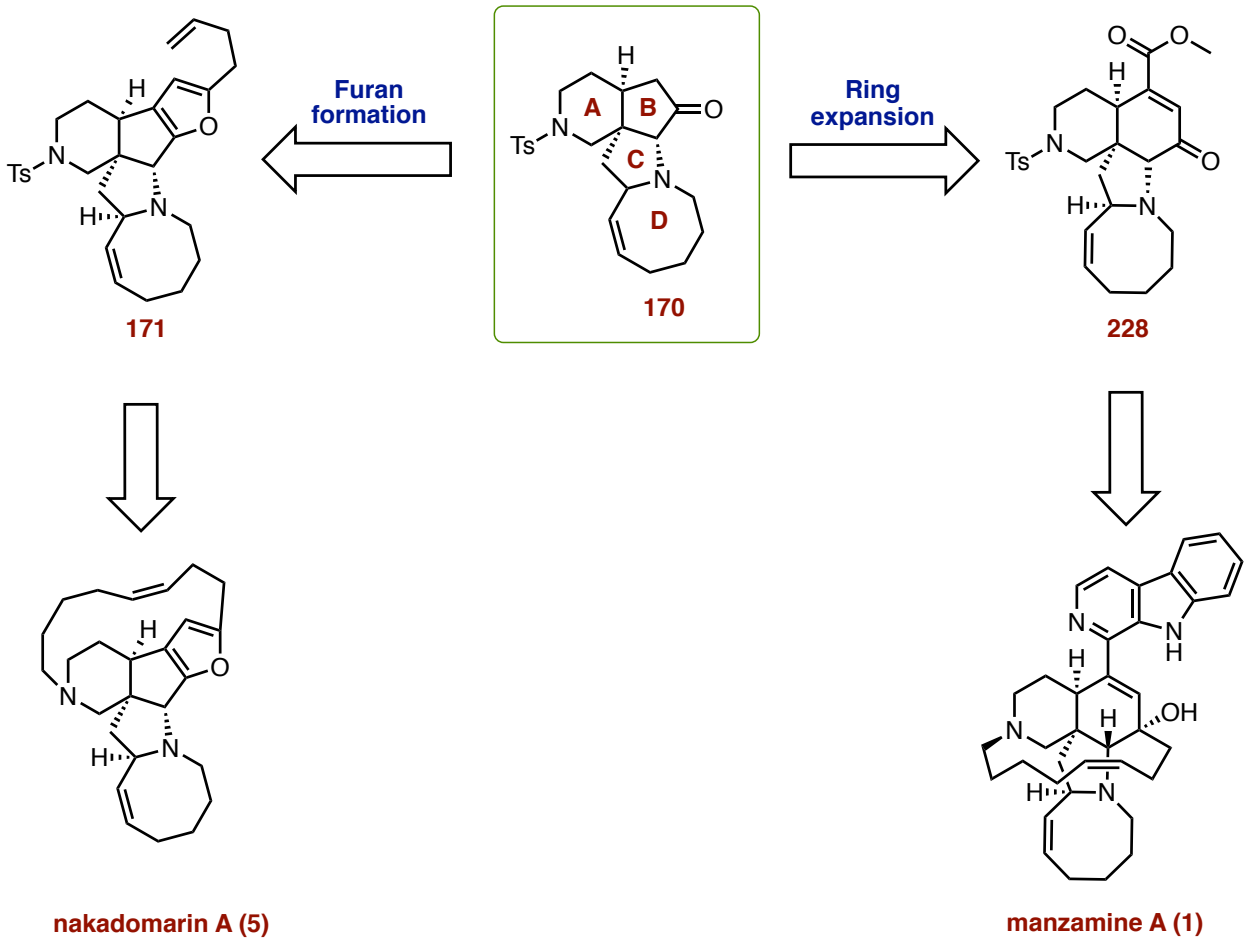


Scheme 2.15. Clark group ring expansion sequence

3. Results and Discussion

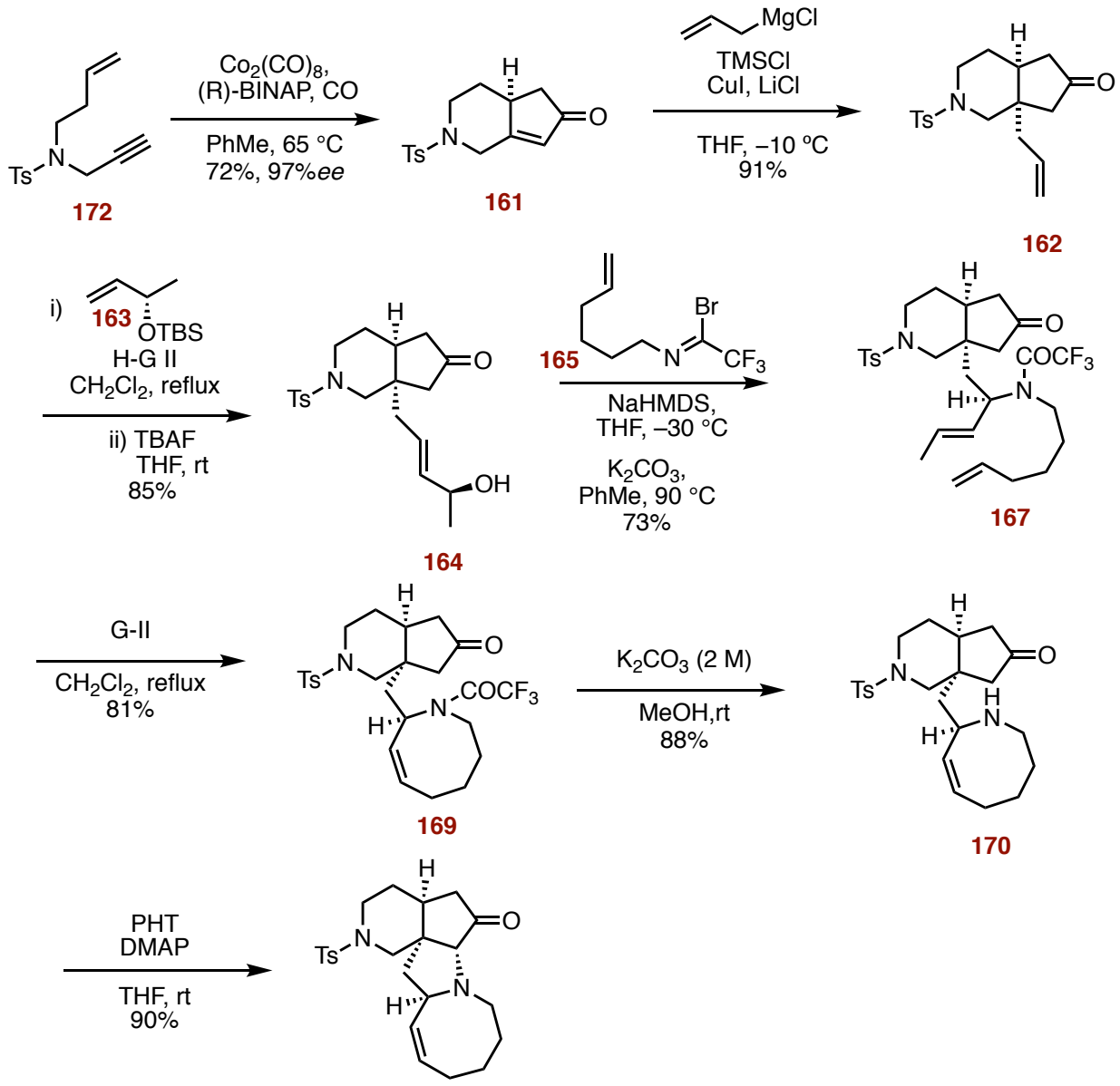
3.1 Synthetic strategy

As discussed previously (chapter 2), the advanced tetracyclic ketone **170**, which was the key intermediate in the total synthesis of nakadomarin A **(5)**,[46,47] could be used as a key intermediate in the total synthesis of manzamine A **(1)**. Ring expansion of the cyclopentanone unit in the key intermediate **171** results in cyclohexenone **228** which can be used for the construction of manzamine A **(1)**. On the other hand, furan formation from the same ketone **170** provides the pentacyclic intermediate **171,** which has been used to prepare nakadomarin A **(5)** (Scheme 3.1).[46,47] Thus, the ketone **170** serves as a common intermediate for manzamine A **(1)** and nakadomarin A **(5)**.



Scheme 3.1. Disconnective approach towards common intermediate **170** and the relationship between the manzamine and nakadomarin skeletons

Previous work performed by the Clark group had established a method for the construction of the tetracyclic ketone core present in the nakadomarin A (**5**). [46,47] The synthetic strategy in this project focused on the large-scale synthesis of the tetracyclic key intermediate **170** following the procedure used within the Clark group previously. Optimization of key steps was carried out in order to improve the route (Scheme 3.2).



Scheme 3.2. Synthesis of the advanced tetracyclic ketone

The synthetic strategy also focused on expansion of ring B of the tetracyclic ketone **170** (Figure 3.1). As discussed in chapters 1 and 2, many pathways for the one-carbon ring expansion of cyclic ketones have been used in the total synthesis natural products. Consequently, several routes were considered to carry out this transformation.

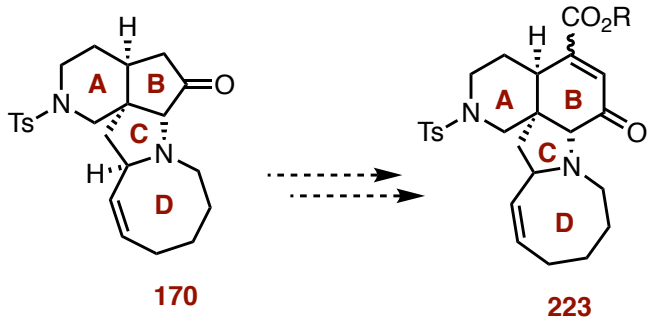
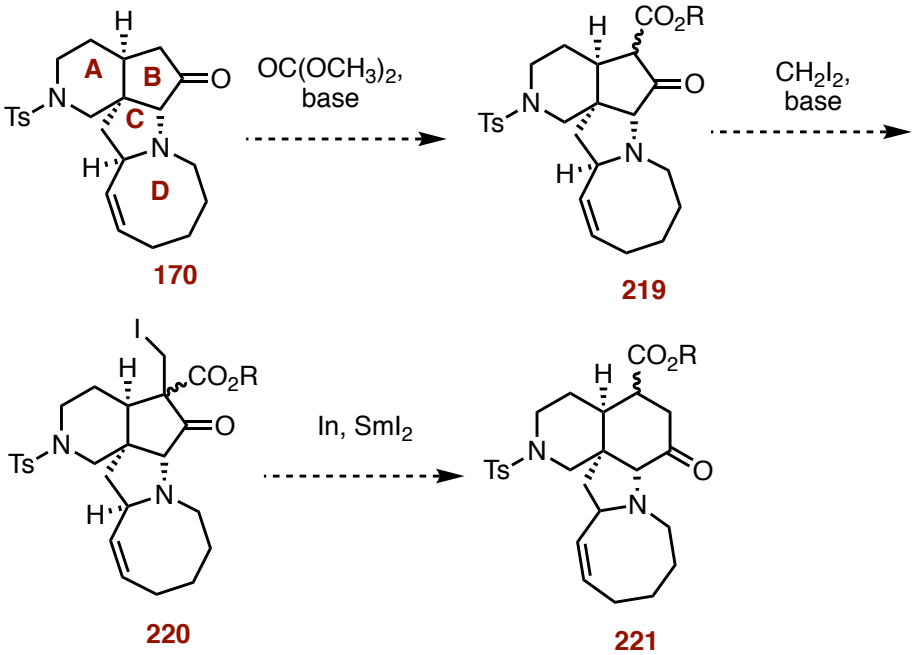


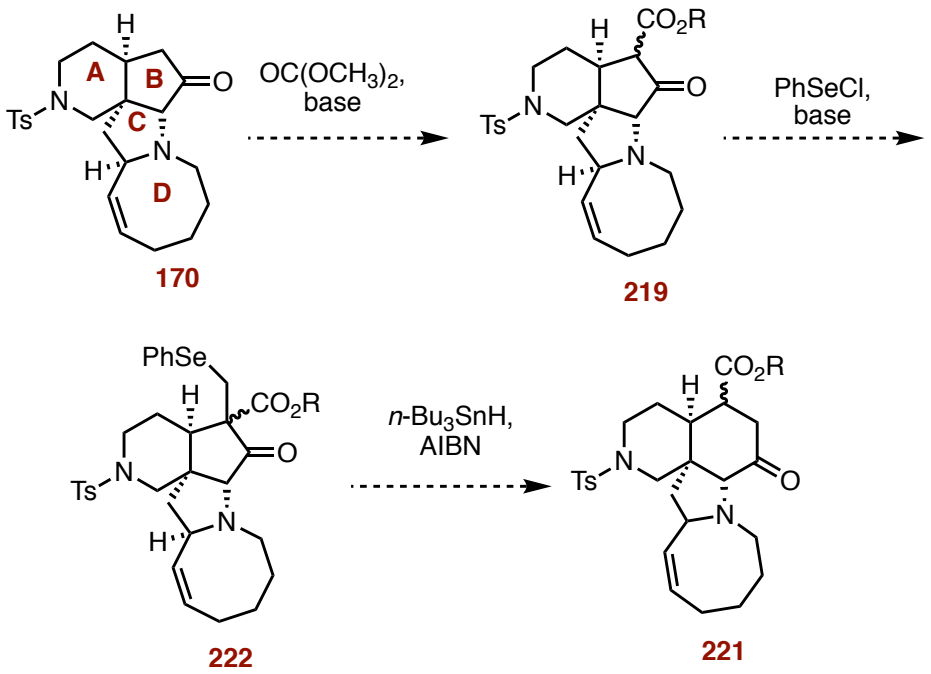
Figure 3.1. Expansion of the B ring

The first route involved regioselective conversion of the ketone **170** into the *β*-keto ester **219.** This could be achieved by C-acylation of the ketone **170** using dimethyl carbonate (Scheme 3.3, 3.4, 3.5).[59] Alkylation of the *β*-ketoester **219** with diiodomethane[50] gave the resulting iodide **220** which could be treated with activated zinc[53,54,63] or other metal reagents such as (In, SmI_2)[53,54] to initiate rearrangement to give the ring-expanded γ-keto ester **221** (Scheme 3.3).

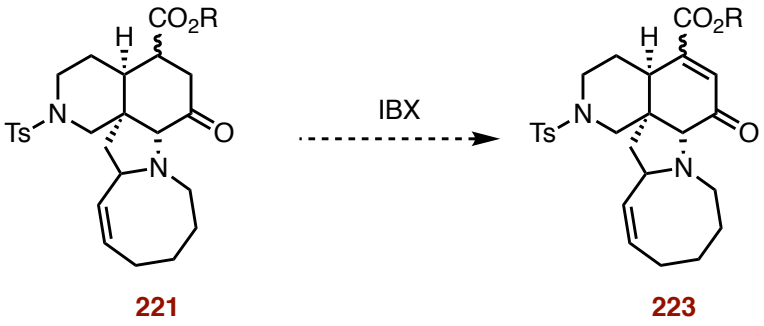


Scheme 3.3. Proposed route towards the B ring expansion

Alternatively the conversion could also be established under radical conditions using the Beckwith-Dowd reaction (Scheme 3.4).[51,52] Finally, dehydrogenation of the γ-keto ester **221** using the conditions described by Trost and co-workers[62] during their synthesis of oseltamivir could yield the conjugated enone **223** (Scheme 3.5).[51,52]

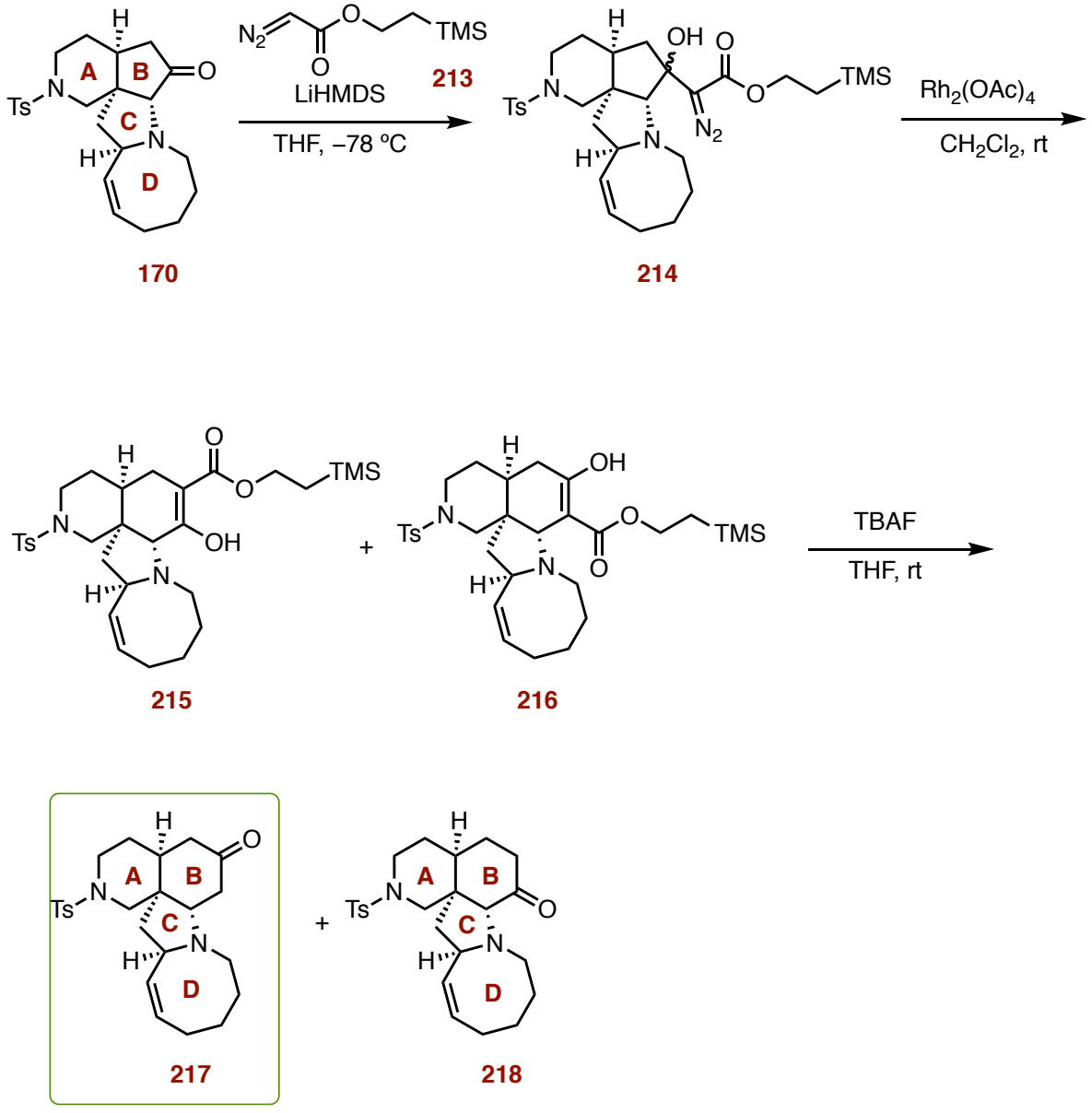


Scheme 3.4. Proposed route towards the B ring expansion



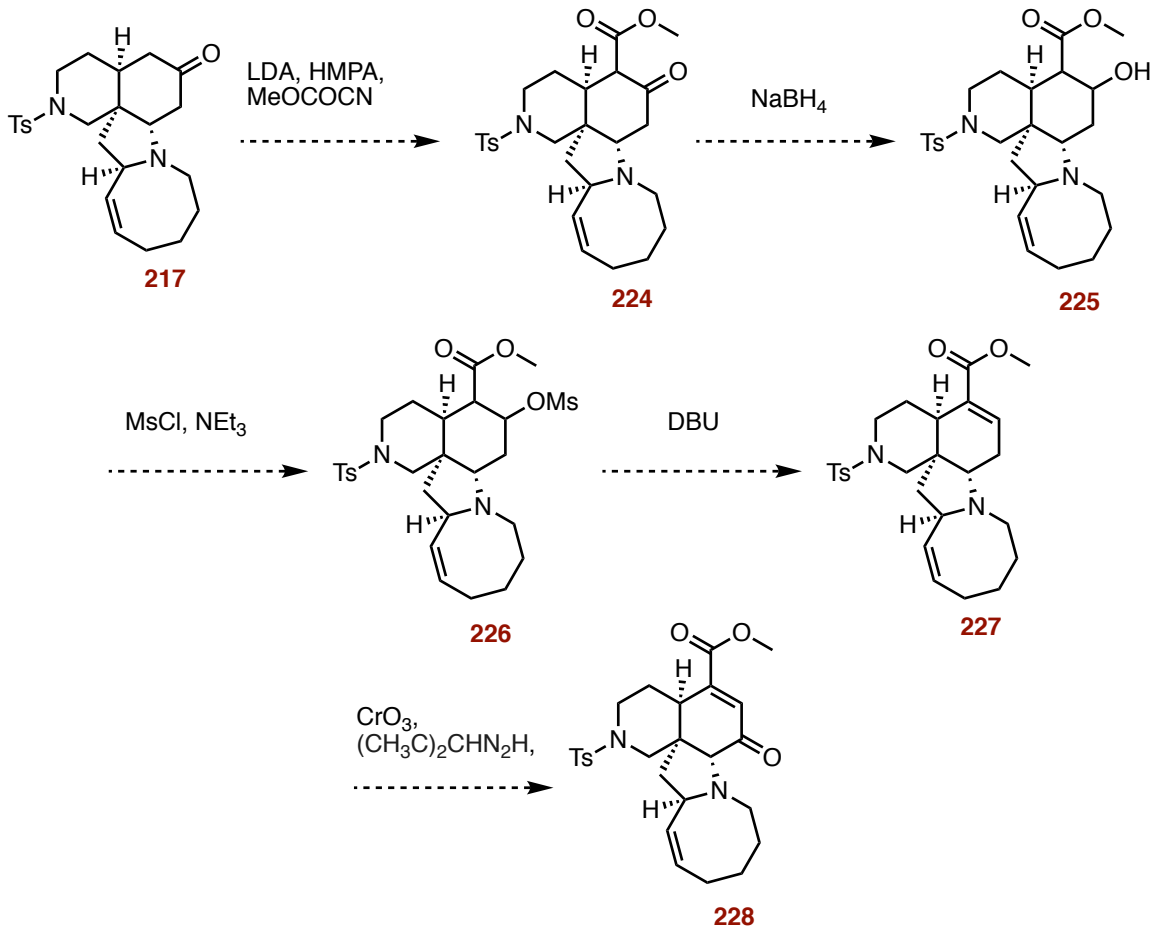
Scheme 3.5. Proposed route towards the B ring expansion

An alternative approach would involve nucleophilic addition a diazo ester to ketone **170** to get the diazoalcohol **214**. Activation of this intermediate with rhodium(II) acetate would then result in the formation of a mixture of the tetracycles **215** and **216**. Decarboxylation of these intermediates using TPAF would deliver the isomer ring-expanded tetracyclic ketones **217** and **218** (Scheme 3.6).[49,60,61,66]



Scheme 3.6. Clark group strategy diazoalcohol rearrangement

Inspired by the work of Winkler and co-workers[68] on the synthesis of manzamine analogues, the next step would begin with conversion of the ketone **217** into the *β*-ketoester **224** using Manders' reagent. Treatment of the resulting intermediate with sodium borohydride should give the *β*-hydroxyester **225**, which could be treated with methane sulfonyl chloride to result in the formation of the mesylate **226**. The mesylate **226** could be converted into unsaturated ester **227** by treatment with DBU under elevated temperatures. Oxidation of the unsaturated ester **227** could be achieved by use of conditions described by Martin and co-workers[14] (Scheme 3.7).[68,69]

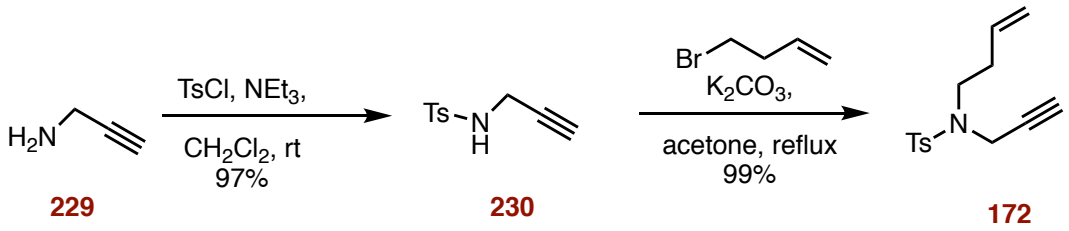


Scheme3.7. Winkler and co-workers strategy

3.2 Synthesis of the tetracyclic ketone ABCD and route optimisation

3.2.1 Preparation of the bicyclic enone AB

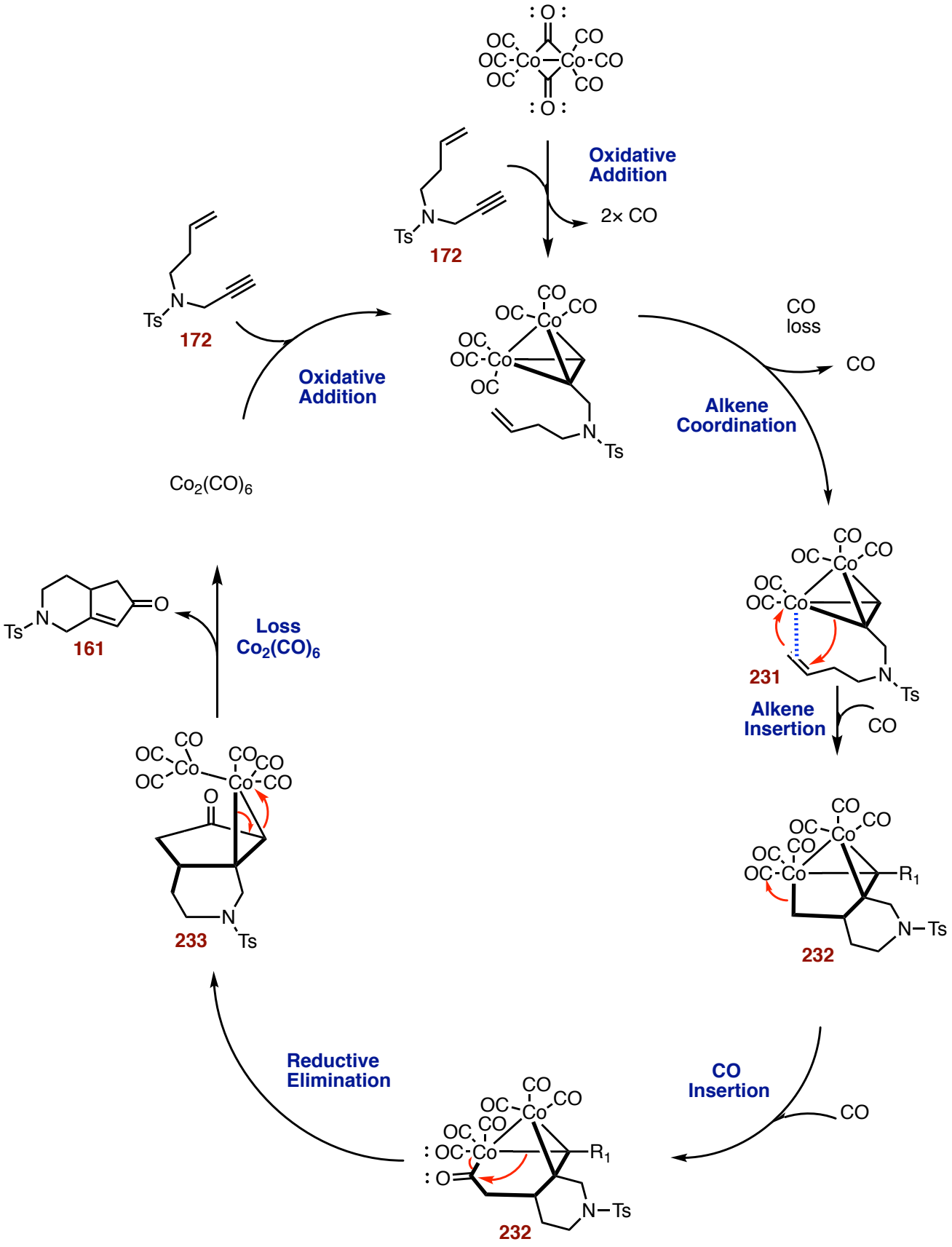
Synthesis of the bicyclic enone **161** has been well established in our group.[47,48] Enyne **172** was obtained by tosylation of commercially available propargylamine **229** to provide *N*-tosyl propargylamine **230**. This was followed by alkylation of tosyl amine **230** with 4-bromobut-1-ene to give the desired enyne **172** (Scheme 3.8). These early steps proceeded with excellent yields on large scale and column chromatography was necessary to purify the last product **172**.



229 230 172

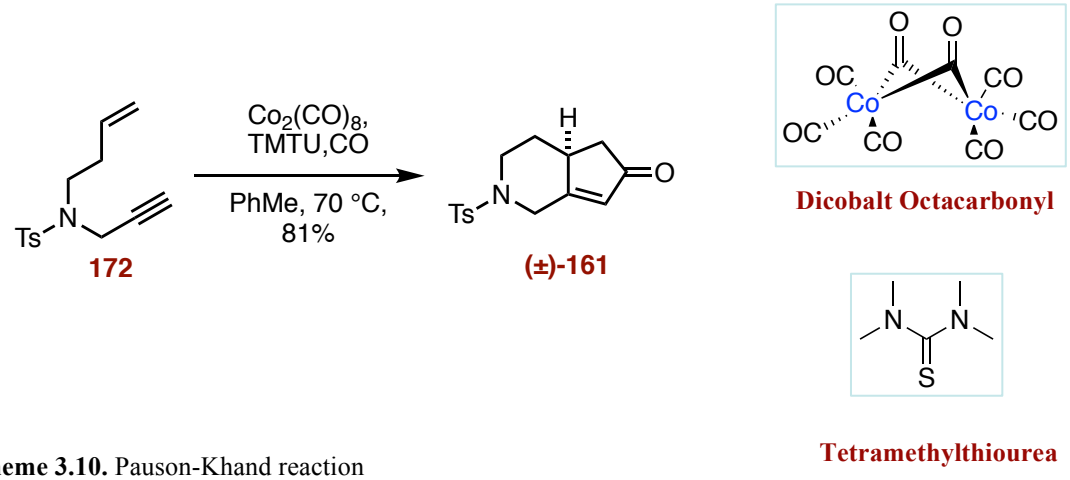
Scheme 3.8. Synthesis of the enyne 172

The catalytic Pauson-Khand reaction under a carbon monoxide atmosphere is a well-known [2+2+1] cycloaddition process. This reaction can be used to convert an alkene and alkyne to cyclopentenone. The mechanism of this reaction starts with oxidative addition of the alkyne **172** to the metal complex. This is followed by the loss of carbon monoxide, alkene coordination and then alkene insertion to give **232**. Carbon monoxide insertion followed by reductive elimination produces the cyclopentanone product **161** and regenerates the cobalt octacarbonyl catalyst (Scheme 3.9).[71,72]



Scheme 3.9. Proposed mechanism of the Pauson-Khand reaction

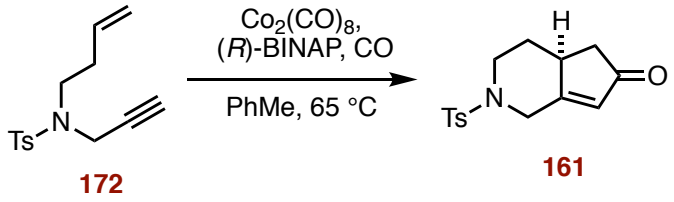
The catalytic Pauson-Khand reaction under a carbon monoxide atmosphere to generate the racemic enone **(±)-161** was found to be successful using the reported conditions.[49] The only modification required to improve the yield was to increase the loading of the cobalt octacarbonyl catalyst from 0.1 to 0.3 equivalents. Synthesis of the racemic mixture of enone **(±)-161** was successfully scaled up to 30.0 g (114 mmol) without the need to increase catalyst loading or carbon monoxide pressure. Purification of enone **(±)-161** required filtration of the crude product through a pad of silica gel before flash column chromatography due to the quantity of catalyst present on a large scale (Scheme 3.10).



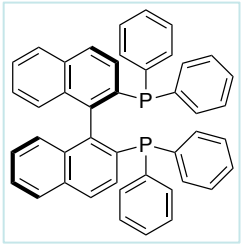
Scheme 3.10. Pauson-Khand reaction

An alternative method to access the bicyclic enone **161** is to use a chiral catalyst to furnish this product in an enantioselective manner.[47,48] Unfortunately, when the reported reaction conditions was applied, the enantioenriched bicyclic enone **161** was formed in 28% yield and with an enantiomeric excess of 65% (Table 3.1, entry 6). The reaction was performed by treatment of the alkyne **172** with 0.3 equivalent of cobalt octacarbonyl catalyst and 0.3 equivalent of (*R*)-BINAP under a carbon monoxide atmosphere (Table 3.1, entry 6). Hence, optimization of this step was necessary to get a higher yield and improve the enantiomeric excess. When decreasing the number of equivalents of the cobalt catalyst and (*R*)-BINAP, there were no improvements in the yield and the enantiomeric excess (Table 3.1, entries 1–5). Addition of the tetramethylthiourea delivered a small improvement of yield (Table 3.1 entry 4). Increasing the amount of the cobalt octacarbonyl catalyst to 0.5 equivalent and (*R*)-BINAP to 0.5

equivalent improved the yield to 72% and enantiomeric excess to 69% (Table 3.1, entry 8). Further optimizations were applied to improve the enantiomeric excess. The best results were achieved with 78% yield and 94% enantiomeric excess when using 0.5 equivalents of cobalt catalyst and 0.8 equivalents of (*R*)-BINAP (table 3.1, entry 11). When these optimised conditions were applied on a larger scale, the yield unfortunately dropped (Table 3.1, entries 12–14).



172 **161**



(*R*)-BINAP

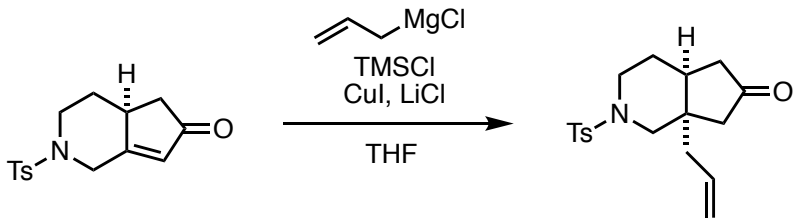
Entry	mmols	$Co_2(CO)_8$ equiv.	(*R*)-BINAP equiv.	Yield (%)	*ee* (%)	Additive
1	1.89	0.1	0.1	10	50	-
2	1.89	0.1	0.2	20	55	-
3	1.89	0.1	0.3	22	55	-
4	1.89	0.1	0.3	35	58	TMTU
5	1.89	0.2	0.3	30	60	-
6	1.89	0.3	0.3	28	65	-
7	1.89	0.4	0.3	35	60	-
8	1.89	0.5	0.5	72	69	-
9	1.89	0.5	0.6	74	73	-
10	1.89	0.5	0.7	78	79	-
11	1.89	0.5	0.8	78	94	-
12	11.4	0.5	0.8	63	92	-
13	18.9	0.5	0.8	49	89	-

14	37.9	0.5	0.8	43	88	-

Table 3.1. Equivalents of the reagents employed in the Pauson-Khand reaction, mmols and the resulting yield and *ee*

3.2.2 Preparation of the *β*-allyl ketone

The 1,4-addition of an allyl cuprate onto the racemic enone (±)-**161** gave the desired product in low yield. The quality of the copper(I) iodide was crucial to the success of this reaction and activation of copper(I) iodide was important to get a good yield. Addition of freshly distillated TMSCl was also important to accelerate the conjugate addition of the copper reagent to the enone (±)-**161** by activating the carbonyl group. In addition, the temperature of this reaction needed to be well controlled to get a good yield because of the instability of the organocopper reagent. When the reaction was performed at 0 °C, only a small amount of the product was formed and mostly starting material was recovered (Table 3.2). However, decreasing the temperature to −10 °C using the reported procedure gave 60% of the ketone (±)-**162** as the highest yield (Table 3.2, entry 3). When scaling this reaction to gram scales there was a large excess of *in situ* formed allyl cuprate and TMSCl. This led to the presence of large quantities of copper salts, making this procedure impractical for scale-up and decreasing the yield to 47%. Ketone (±)-**162** can be purified by recrystallization from EtOH. For the enantoriched material there is no need to change the reagents or conditions.[47-49]



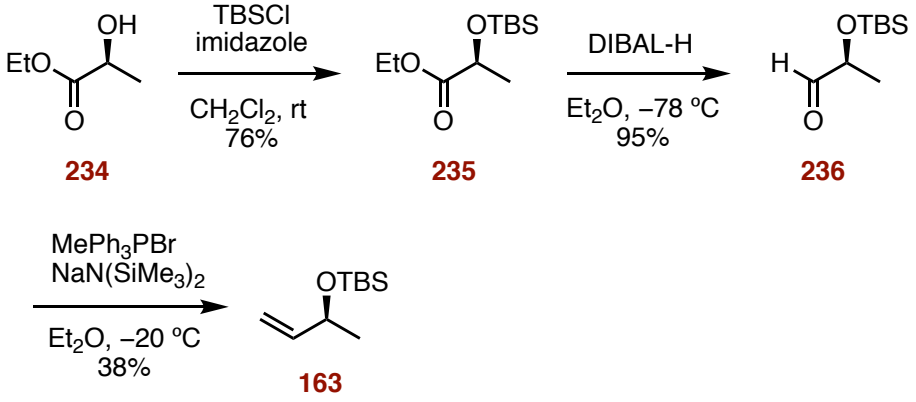
(±)-161 (±)-162

Entry	CH_2CHCH_2MgCl	CuI equiv.	LiCl equiv.	Me_3SiCl equiv.	T °C	S.M (%)	Product (%)
1	2.0	3.0	3.0	1.1	0	82	8
2	2.5	3.0	3.3	1.2	0	72	12
3	3.0	3.0	3.3	1.2	−10	-	60

Table 3.2. Equivalents of the reagents employed in the 1,4-addition, temperature and the resulting yields

3.2.3 Preparation of the chiral allylic silyl ether and cross metathesis

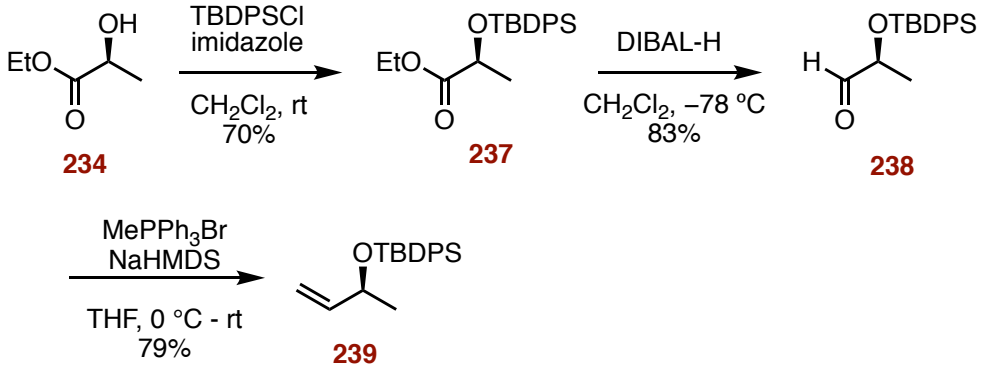
Ethyl (*S*)-(–)-lactate **234** could be converted into enantiomerically pure allylic ether **163** in three steps. [75,76] Protection of commercially available ethyl (*S*)-(–)-lactate **234** gave TBS ether **235** in 77% yield. Reduction of ester **235** gave the aldehyde **236** in 98% yield and subsequent Wittig reaction of aldehyde **236** provided allylic *tert*-butyldimethylsilyl ether **163** in only 38% yield as a consequence of the volatility of the product (Scheme 3.11).



234 235 236 163

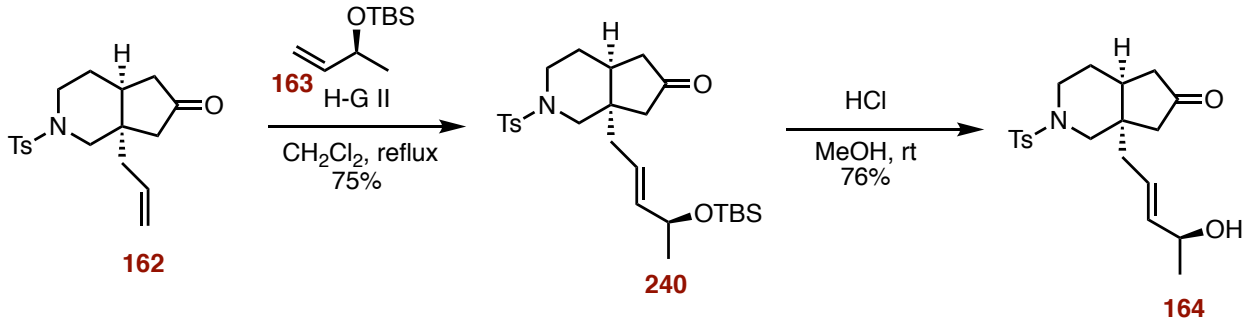
Scheme 3.11. Synthesis of the TBS ether side chain

Due to the volatility of allyl *tert*-butyldimethylsilyl ether **163**, preparation of allylic *tert*-butyldiphenylsilyl ether **239** was required to circumvent this problem. Protection of the (S)-(–)-lactate **234** provided the silyl ether **237** in 70% yield and subsequent ester reduction delivered the aldehyde **238**. Wittig olefination of aldehyde **238** using $MePh_3PBr$ and NaHMDS in THF gave the desired allylic *tert*-butyldiphenylsilyl ether **239** in 79% yield over two steps (Scheme 3.12).[83,84]



Scheme 3.12. Synthesis of the TBDPS ether side chain

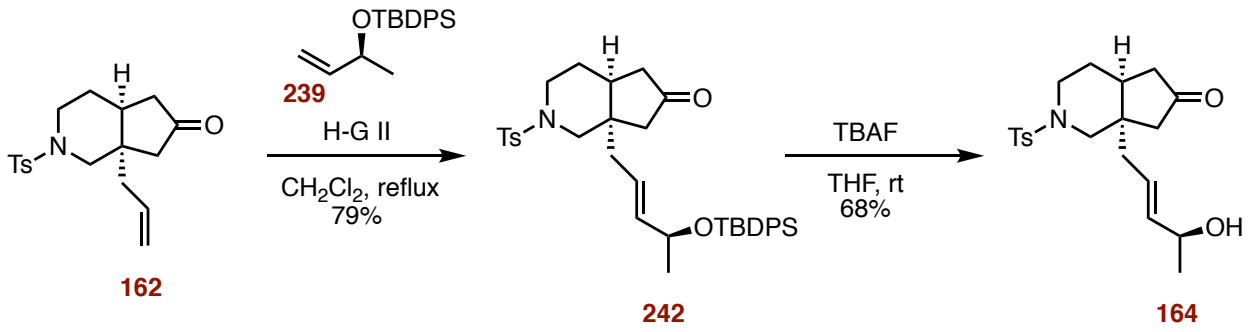
Cross metathesis of ketone **162** and allylic TBS ether **163** using H-G II catalyst CH_2Cl_2 at reflux delivered protected alcohol **240** in 74% yield. Deprotection of alcohol using 1M of HCl promoted the cleavage of the TBS ether and delivered alcohol **164** in 89% yield (Scheme 3.13).[47-49,80]



Scheme 3.13. Synthesis of the alcohol 164

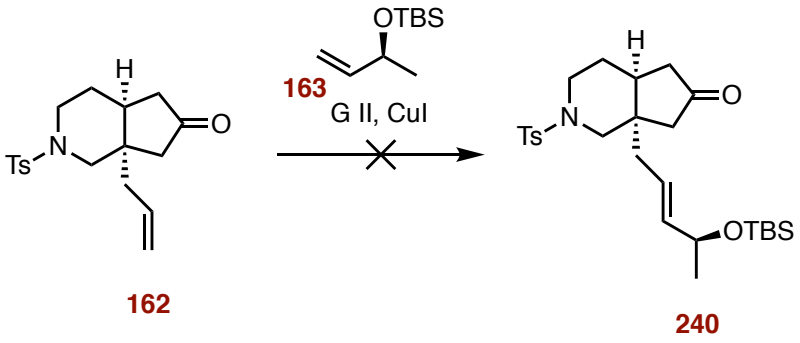
With the TBDPS ether **239** and ketone **162** in hand, the TBDPS ether and ketone **162** underwent cross metathesis with H-G II catalyst very smoothly to produce the protected alcohol

242 in 79% yield. Cleavage of the silyl ether **242** using TBAF provided the alcohol **164** in 68% yield (Scheme 3.14). At this stage, reactions were performed using the racemic and enantioenriched materials.[47-49]



Scheme 3.14. Synthesis of the alcohol 164

An alternative method to improve the yield in the cross metathesis reaction by the use of copper iodide as an additive was tested. According to Voigtritter and his co-workers[73], the use of copper iodide as a co-catalyst for the olefin cross-metathesis reaction gave improved results with Grubbs-2 catalyst. This is because the copper iodide has phosphine-scavenging properties and the iodide ion has a catalyst-stabilizing effect, which can be applied with the use of the Grubbs-2 catalyst. The reaction could also be run under mild conditions in diethyl ether or THF at reflux to avoid chlorinated solvents.[73] Unfortunately, applying the reported conditions to the cross-metathesis reaction between **162** and **163** resulted in no conversion and the starting material was recovered (Scheme 3.15). Changing the solvent to CH_2Cl_2, the standard cross-metathesis solvent also did not result in any conversion of starting materials into the product (Table 3.3).

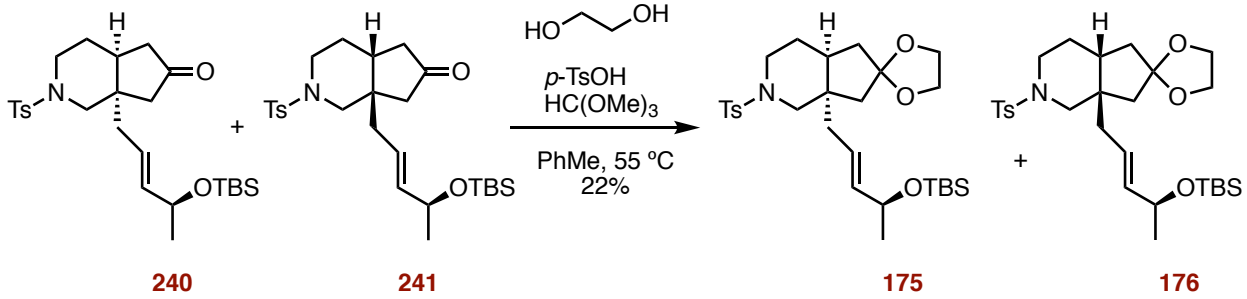


Scheme 3.15 Attempted cross metathesis using CuI

Entry	Solvent	Time	Temp. °C	Outcome
1	Et_2O	16	35	Recovered SM
2	THF	16	35	Recovered SM
3	THF	16	reflux	Recovered SM
4	CH_2Cl_2	16	35	Recovered SM
5	CH_2Cl_2	16	reflux	Recovered SM

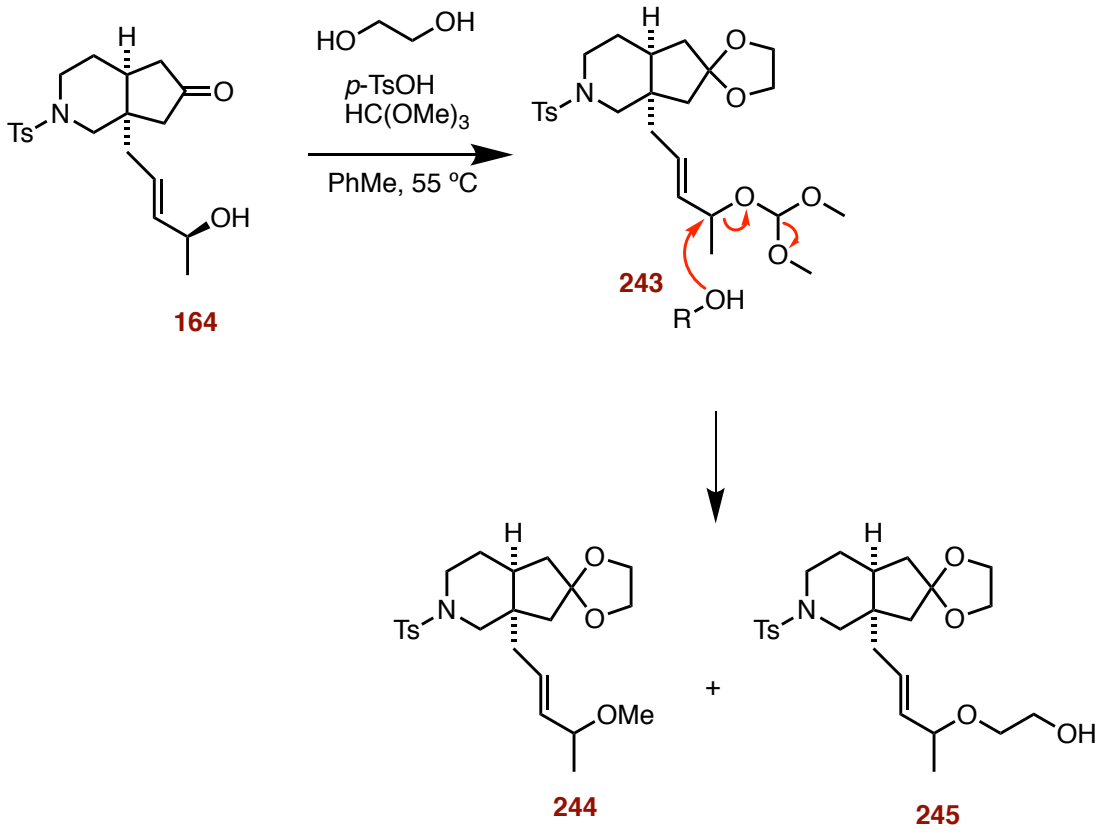
Table 3.3 Equivalents of the reagents employed in the cross-metathesis reaction between 162 and 163

Before moving on to the Overman rearrangement reaction, it was necessary to protect the diastereoisomers **240** and **241**. This was because it increases the yields in subsequent steps and allows for easier separation of the diastereoisomers. Ketal **175** and **176** were prepared from ketones **240** and **241** using ethylene glycol under acidic conditions in 22% yield (Scheme 3.16).[47-49]



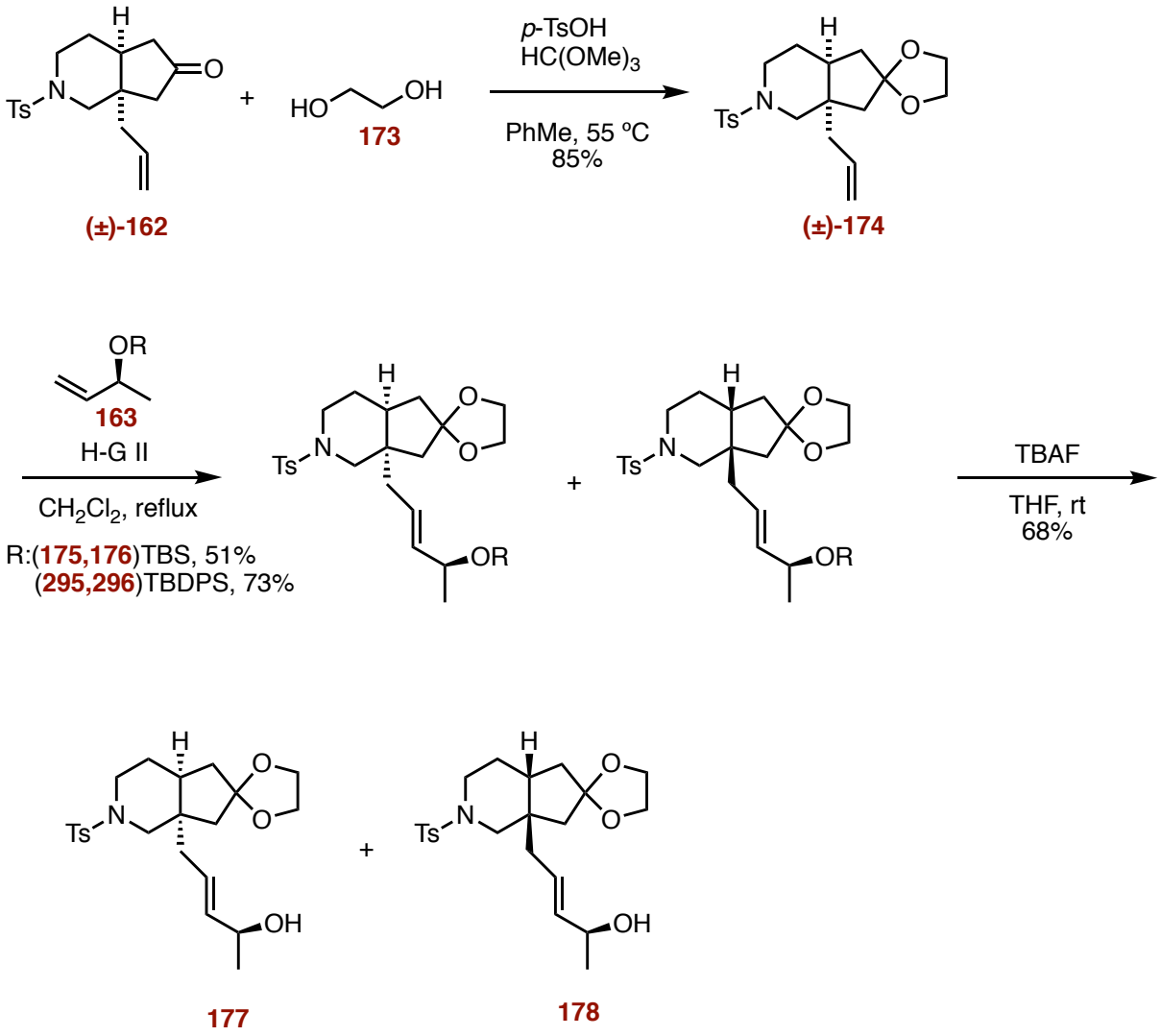
Scheme 3.16. Ketone protection of alcohol intermediate

The low yield was obtained because the acidic conditions caused deprotection of the alcohol **177**. The free alcohol intermediate **164** was then going on to form side products (Scheme 3.15). Trimethyl orthoformate attacked the free alcohol to produce ortho-ester **243**, which underwent nucleophilic substitution by both *in situ* generated MeOH and ethylene glycol (Scheme 3.17).



Scheme 3.17. Formation of side products during ketone protection and a putative mechanism for their formation

Because of the low yield of the ketal intermediate **175** and **176**, protection of a simpler intermediate, ketone **(±)-162** was required to circumvent this problem. Protection of the ketone **(±)-162** was achieved using ethylene glycol in 85% yield. Cross metathesis of ketal **(±)-174** with allyl TBS ether **163** using the Hoveyda Grubbs second-generation catalyst provided the protected alcohols **175** and **176** with a combined yield of 51%. Cross metathesis also was applied using allyl TBDPS ether **239** gave the protected alcohols **295** and **296** in 73% yield. Deprotection of the mixture of diastereomers **175** and **176** and **295** and **296** gave alcohols **177** and **178** in 68% yield (Scheme 3.18).

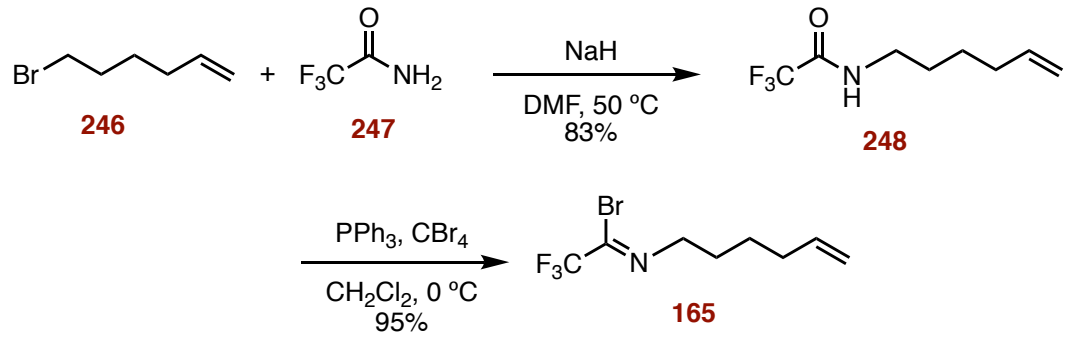


Scheme 3.18. Ketone protection of (±)-162, cross metathesis and alcohol formation

3.2.4 Preparation of the amide intermediate

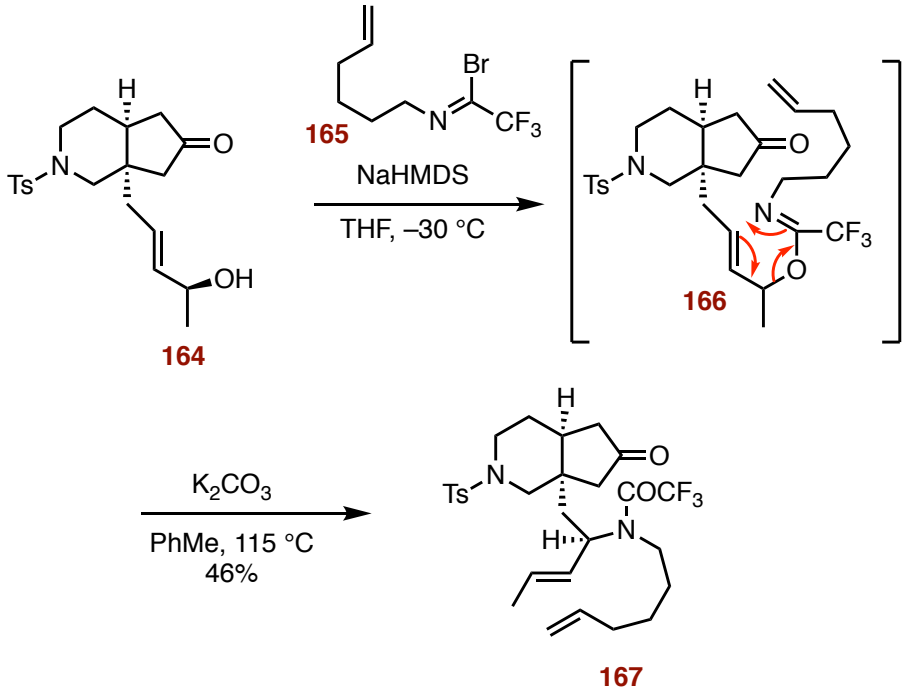
The side chain acetimidoyl bromide **165** can be obtained in two steps from 6-bromo-1-hexene **246**. [77,78] *N*-alkylation of trifluoroacetamide **247** with 6-bromo-1-hexene **246** produced the acetamide **247** followed by bromination using triphenylphosphine and carbon tetrabromide to give the desired acetimidoyl bromide **165** in 28% yield. [47-49] The low yield was due to the acetimidoyl bromide decomposing during silica gel column chromatography. The first attempt to overcome this issue was to use the crude acetimidoyl bromide in the next step without

purification. Unfortunately, this led to a poor yield in the next step. The second approach involved purification using basic silica gel column chromatography and eluting with 2% NEt_3 in pentane. Unfortunately, no product was obtained when this purification procedure was used. The last way was to filter the crude of the reaction mixture over a celite pad to remove most of the triphenylphosphine oxide and then distil the filtrate, which gave the pure product in 95% yield (Scheme 3.19).

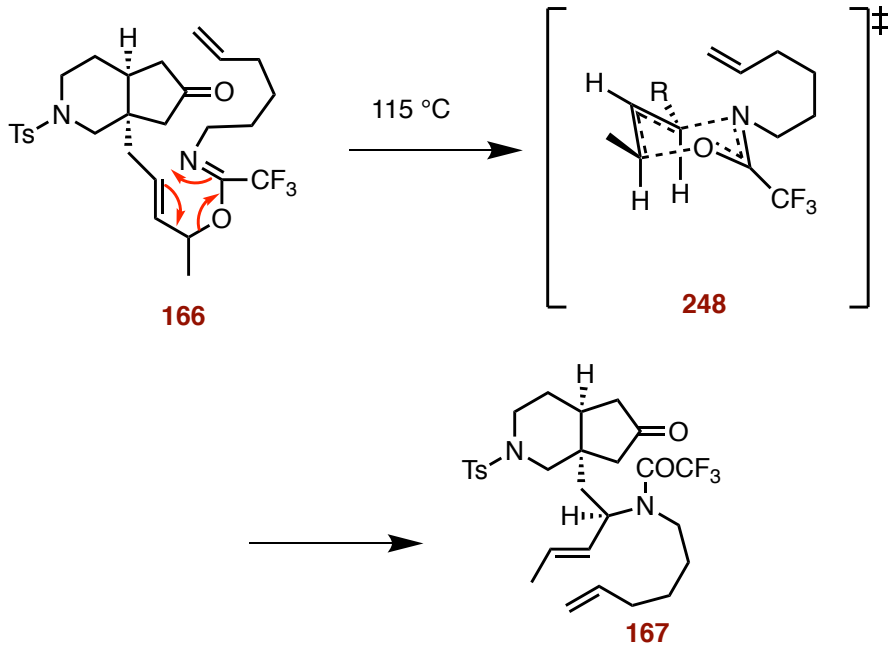


Scheme 3.19. Synthesis of acetimidoyl bromide 165 as a side chain

Overman Rearrangement[79] was used to achieve the conversion of enantioenriched allylic alcohol **164** into amides **167** through a two-step synthesis. This consisted of treatment of the allylic alcohol **164** with NaHMDS and acetimidoyl bromide **165** to form the intermediate **166** and subsequent rearrangement of the allylic trifluoroacetimidate **166** to produce an allylic trifluoroacetamide **167** with clean 1,3-transposition of the alkenyl moiety (Scheme 3.20). Thermal [3,3]-sigmatropic rearrangement to form the allylic amine **167** proceeds *via* a chair-like transition state (Scheme 3.21).[79,81]



Scheme 3.20. Overman rearrangement



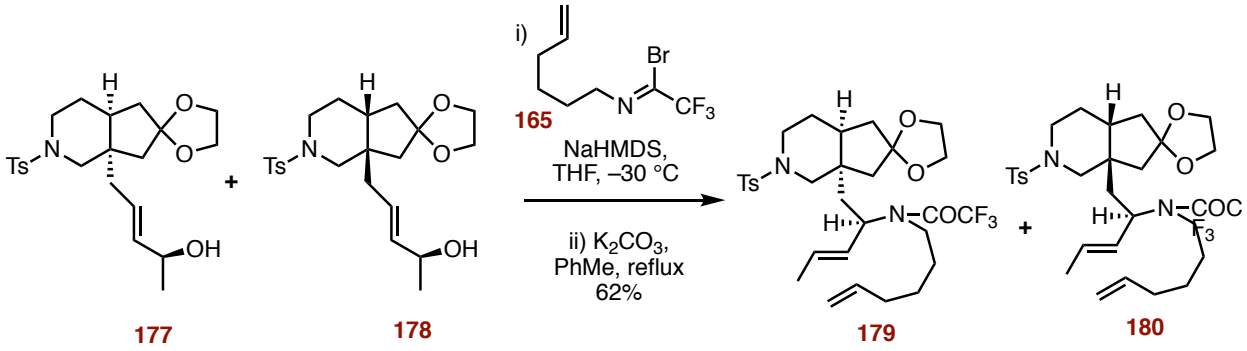
Scheme 3.21. Transition state and selectivity of the Overman rearrangement reaction

The first step proceeded well when the reported reaction conditions were used. When the next step was performed with 6 equivalents of K_2CO_3 as reported, [47-49] a low yield was obtained. It was found that a reduction in the amount of K_2CO_3 to 1.5 equivalents was necessary to circumvent this issue. In addition, the use of toluene rather than *p*-xylene as the reaction solvent resulted in better conversion (Table 3.4). For the protected ketone **177** and **178**, applying the

same optimized conditions resulted in a 62% yield over the two steps (Scheme 3.22).

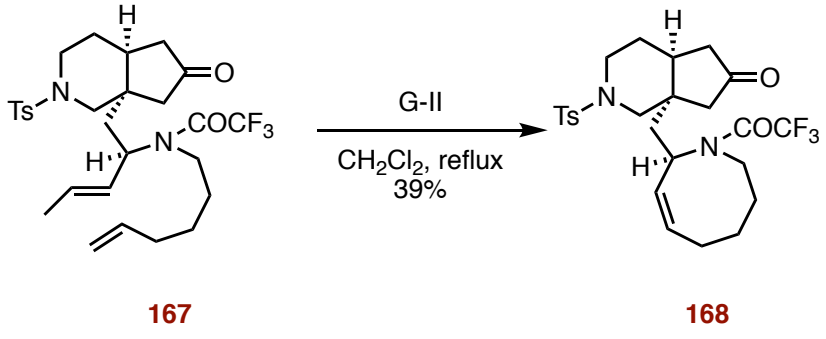
Entry	Equiv. Of acetimidoyl bromide 156	Equiv. of K_2CO_3	Time	Solvent	Yield (%)
1	1.1	1.1	48 h	*p*-xylene	23
2	1.5	6	96 h	*p*-xylene	18
3	2	2	48 h	PhMe	28
4	1.1	1.5	72 h	PhMe	46

Table 3.4. Equivalents of the reagents and the solvents employed in the Overman rearrangement



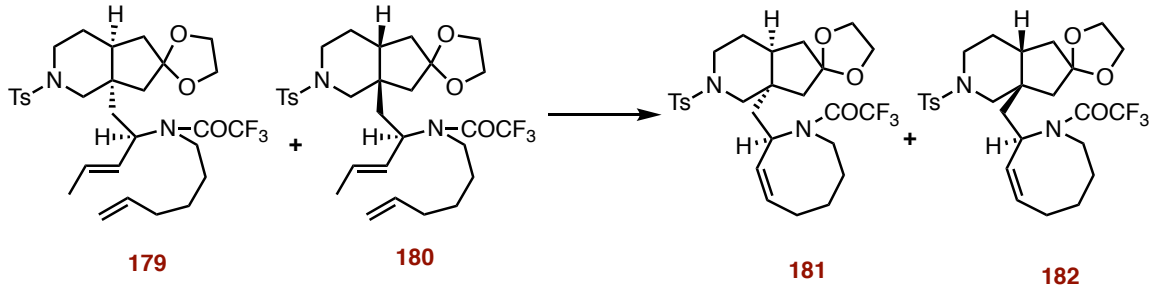
Scheme 3.22. Overman rearrangement of the racemic alcohol 177 and 178

The next step was the ring-closing metathesis of enantioenriched diene **167**. When the reported conditions – 10 mol % of the Grubbs second generation catalyst in CH_2Cl_2 at reflux – were employed, the amide **168** was obtained in 39% yield (Scheme 3.23). [47-49,82]



Scheme 3.23. Ring closing metathesis reaction

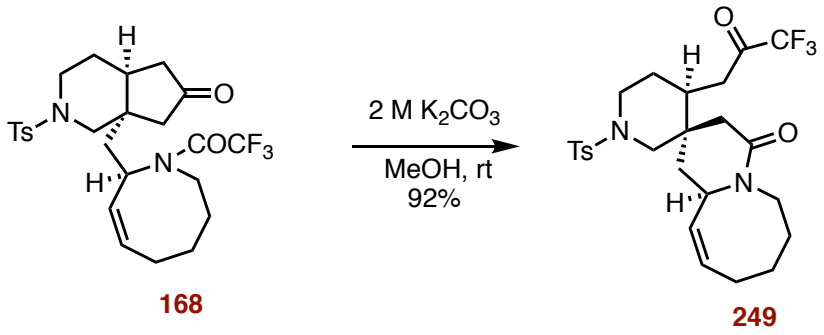
Application of the reported RCM conditions to the racemic protected ketone **179** and **180** resulted in formation of the racemic amide **181** and **182** in low yield. Therefore, optimizing this step by increasing the amount of the Grubbs second-generation catalyst and changing the solvent was beneficial and increased the reaction yields (Table 3.5). Application of the optimized conditions (Table 3.5, entry 6) to the enantioenriched material **167** increased the yield to 73%.



Entry	Cat.	Solvent	Time (h)	Temp. (°C)	Yield (%)	S.M recovered (%)
1	10% G-II	Dry CH_2Cl_2 (0.001 mmol)	16	50	22	25
2	10% G-II	Dry CH_2Cl_2 (0.002 mmol)	16	50	28	53
3	10% G-II	Wet CH_2Cl_2 (0.001 mmol)	16	50	14	80
4	10% G-II	Wet CH_2Cl_2 (0.002 mmol)	16	50	17	73
5	10% G-II	Dry PhMe (0.002 mmol)	16	70	36	63
6	20% G-II	Dry PhMe (0.002 mmol)	16	70	73	22
7	10% H-G-II	Dry PhMe (0.002 mmol)	16	45	16	60
8	20% H-G-II	Dry CH_2Cl_2 (0.002 mmol)	48	45	53	12
9	20% G-II (2 portion)	Dry CH_2Cl_2 (0.002 mmol)	48	45	41	54

Table 3.5. Various conditions and solvents employed for the RCM of the diene 179 and 180

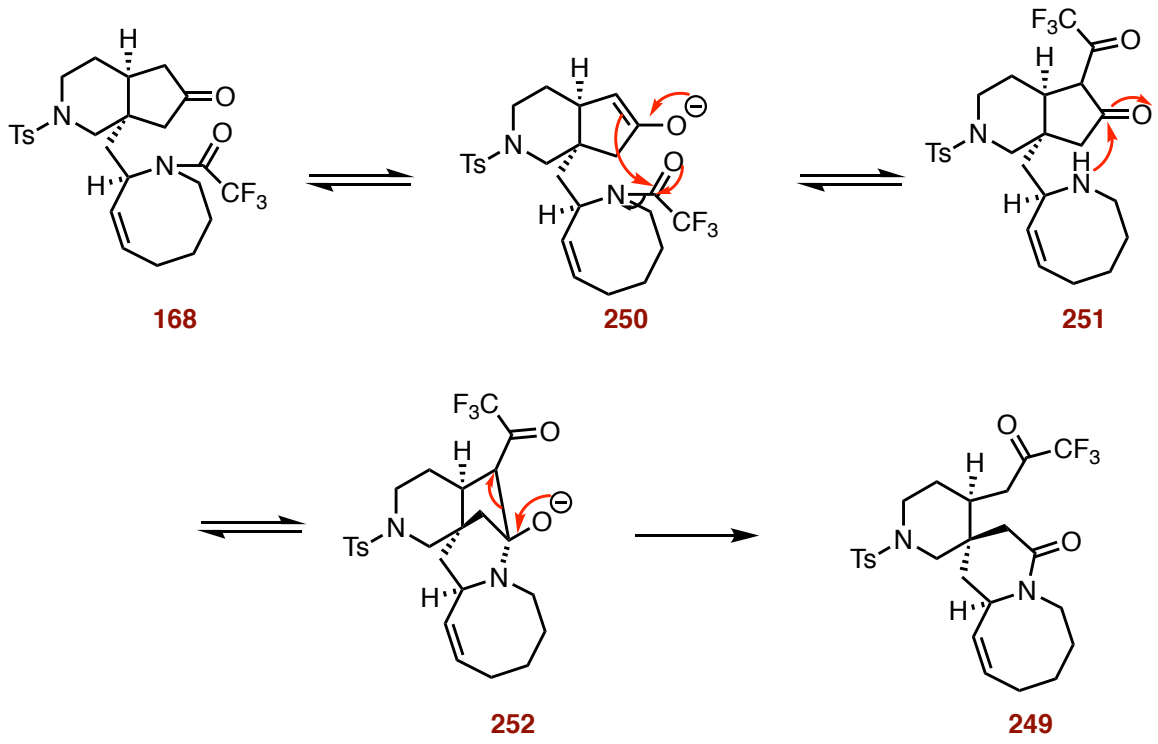
The next step was deacylation of the amide **168** to give the tricyclic amine **170**. Application of the reported reaction conditions – 2 M of K_2CO_3, MeOH at rt for 3 days – to the enantioenriched amide **168** did not provide the desired product and unexpected product **249** was formed (scheme 3.24).



168 **249**

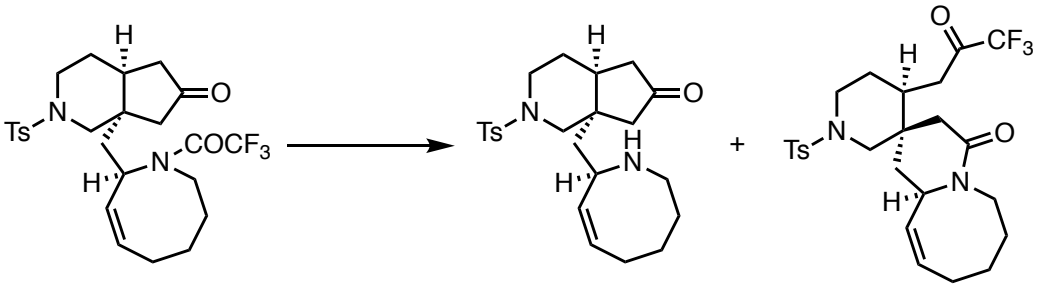
Scheme 3.24. Formation of the side product 249

A reported proposed mechanism could explain this transformation (scheme 3.25). [47-49] The basic conditions could generate the ketone enolate **250** which could then attack the trifluoroacetyl group and provide the free secondary amine **251**. Intramolecular nucleophilic attack of the free amine onto the ketone could form the intermediate **252**. The lactam **249** could then be formed from intermediate **252** through a retro-aldol fragmentation reaction. [47-49]



Scheme 3.25. Proposed mechanism for formation of the side product 249.

Several approaches were considered to circumvent this issue. The first method involved deprotection by the use of ammonia in methanol at room temperature, but there was no reaction under these conditions and the starting material was recovered (Table 3.6, entry1). Exposure of the substrate to 1M HCl in MeOH also resulted in no reaction at room temperature (Table 3.6, entry 2). Increasing the temperature to 60 °C resulted in no conversion and 60% of the starting material was recovered (Table 3.6 entry 4). A 10% solution of K_2CO_3 in MeOH was also tested, but the required product was not obtained and starting material was recovered. Finally, when a 1M solution of the K_2CO_3 in MeOH was tested at room temperature, the desired product **169** was obtained but the reaction rate was very low. Up to a week was required and the yield was still very low (Table 3.6, entry 6). Appling a gentle heat to the reaction resulted in an increase in the reaction rate and an improvement in the yield. The reaction was completed in 2 days with a 30 % yield, but some of undesired product **249** was formed (Table 3.6, entry 7).

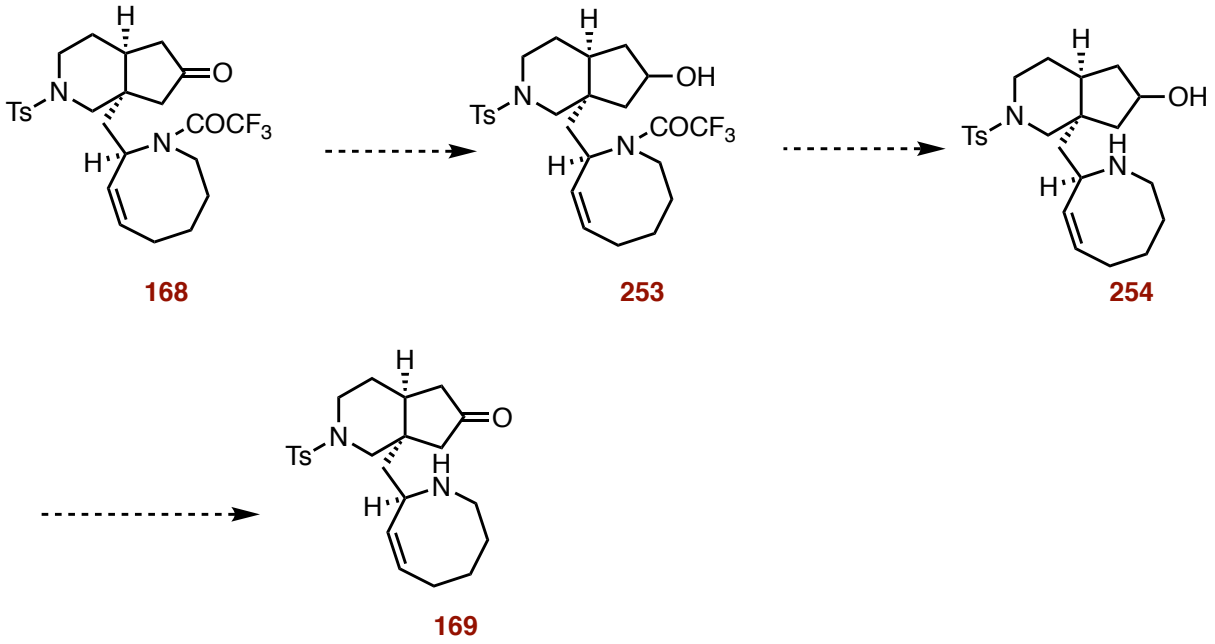


168 169 249

Entry	Conditions	Solvent	Time	Temp. °C	Outcome
1	NH_3 MeOH	MeOH	72 h	rt	S.M recovered
2	1M HCl	MeOH	72 h	rt	S.M recovered
3	1M HCl	MeOH	72 h	40	S.M recovered + Decomposition
4	1M HCl	MeOH	72 h	60	S.M recovered + Decomposition
5	10% K_2CO_3	MeOH	72 h	rt	S.M recovered
6	1M K_2CO_3	MeOH	72 h	rt	S.M recovered + Terrace of product **169**
7	1M K_2CO_3	MeOH	48 h	40	20% S.M recovered + 30% product + 40% Undesired product **249**

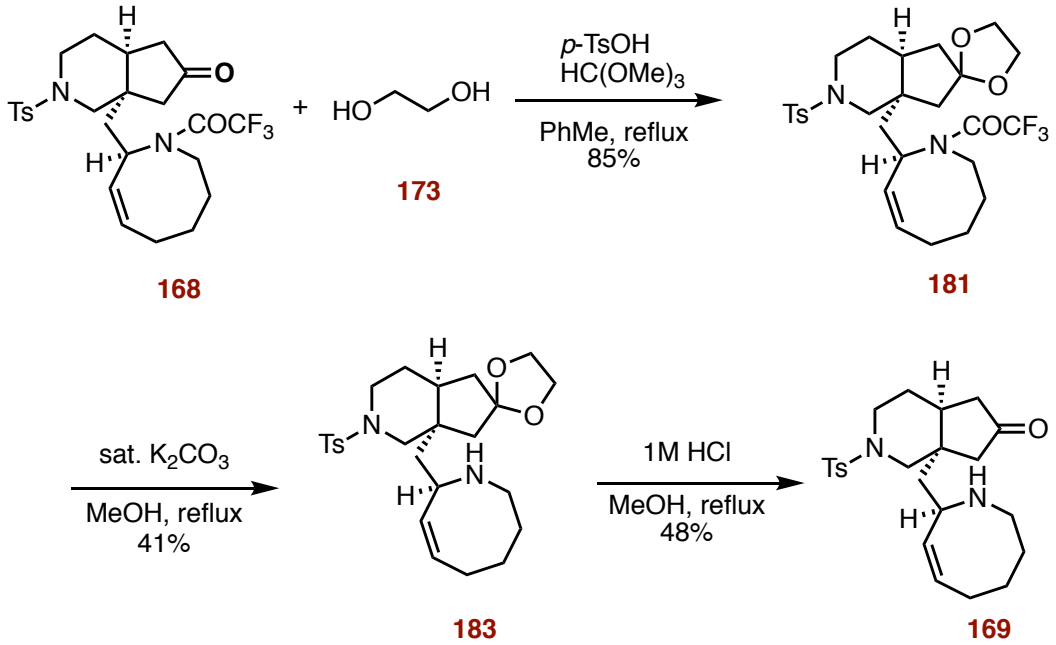
Table 3.6. Various conditions and solvents employed for the deacylation of the amide 168

An alternative method for the deacylation of the amide **168** involves reduction of the ketone **168** to alcohol **253** followed by deacylation of the alcohol **253** to get the free amine **254**. Oxidation of alcohol **254** could then provide the tricyclic amine **169**. When this method was applied to the intermediate **168**, the material decomposed (Scheme 3.27).



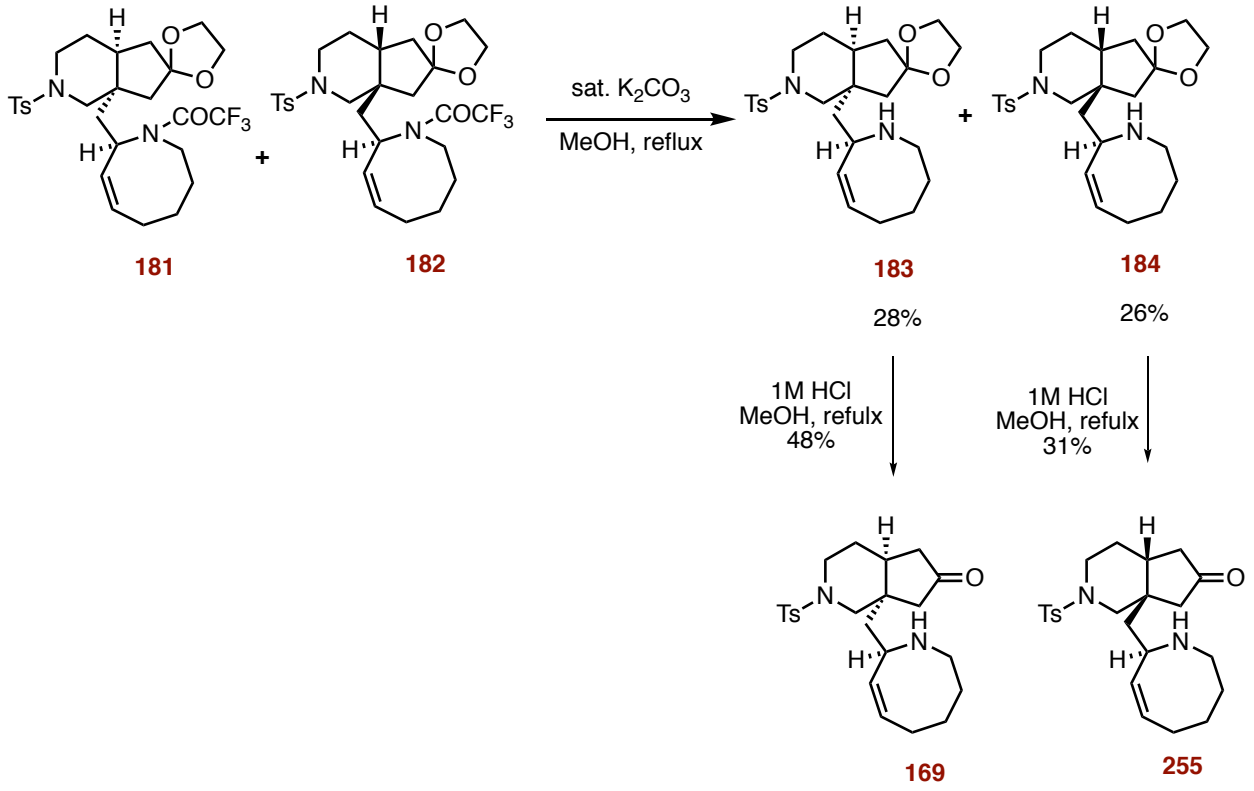
Scheme 3.27. Attempted deacylation of the amide 168

The last and the most successful way involved protection of the carbonyl group in the enantioenriched ketone **168** to prevent the unwanted side reactions. Protection of the ketone using ethylene glycol was accomplished to get the dioxolane **181.** This was followed by deacylation using saturated K_2CO_3 to give **183** in 41% yield. Deprotection of the ketal **183** using 1 M of HCl provided the tricyclic amine **169** in 48% yield (Scheme 3.28).



Scheme 3.28. Late stage ketone protection, deprotection and deacylation of the enantioenriched materials

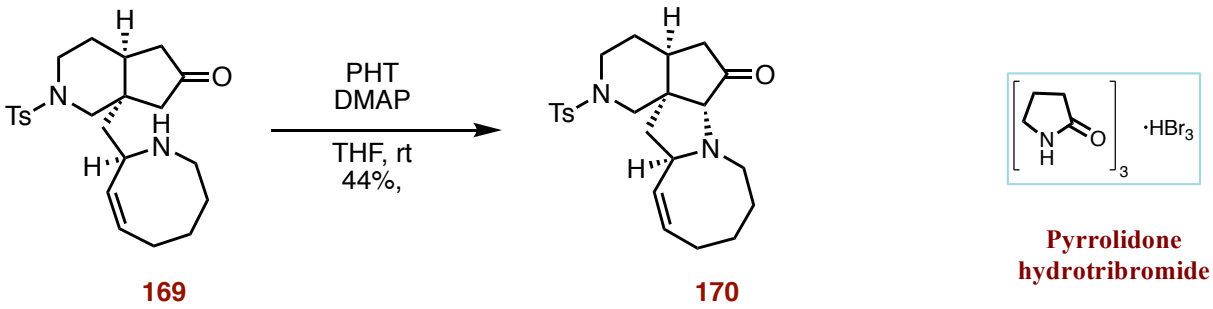
For the racemic material, the cleavage of trifluoroacetyl group was achieved under basic conditions using saturated K_2CO_3 under refluxing conditions and the resulting diastereoisomers **183** and **184** were separated by column chromatography. Despite the fact that the separation of the diasteromers wasn't possible at an earlier stage in the synthesis, the undesired diastereoisomer **184**, which was separable at this stage, could be used as a model system to test the reagents and reaction conditions of the key transformations later in the synthesis. Deprotection of the dioxolane **183** and **184** were performed under acidic conditions to give the tricyclic amine **169** and **255** (Scheme 3.29).



Scheme 3.29. Ketone deprotection and deacylation of the racemic materials

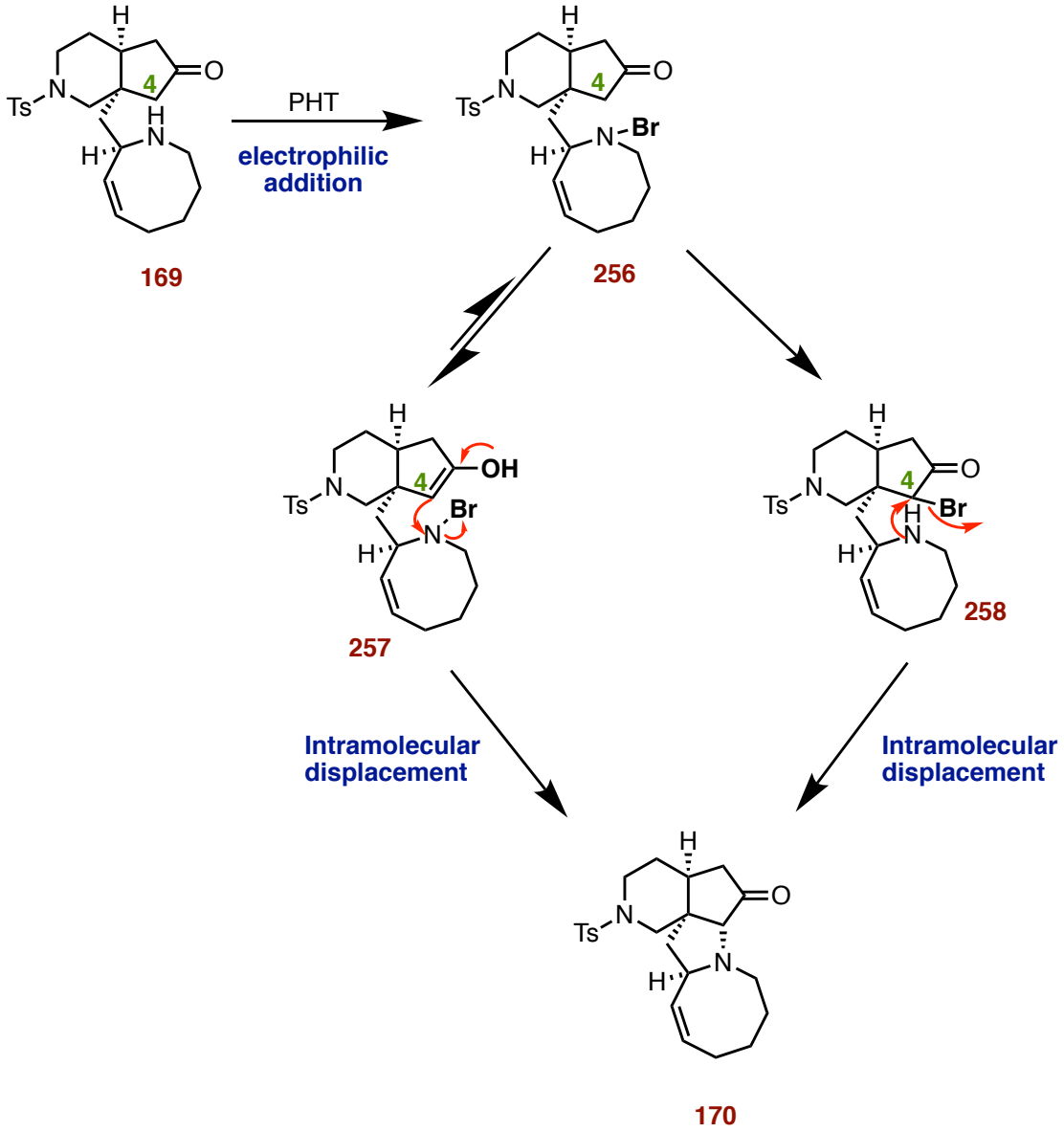
3.2.5 Ring Construction and the formation of tetracyclic ketone

Construction of the C-ring was accomplished using an amination reaction developed by Carreira and co-workers.[70] The highly selective electrophilic brominating agent, pyrrolidone hydrotribromide (PHT) was used in THF to produce the tetracyclic ketone **170** in 44% (Scheme 3.30).



Scheme 3.30. Synthesis of tetracyclic advanced intermediate 170

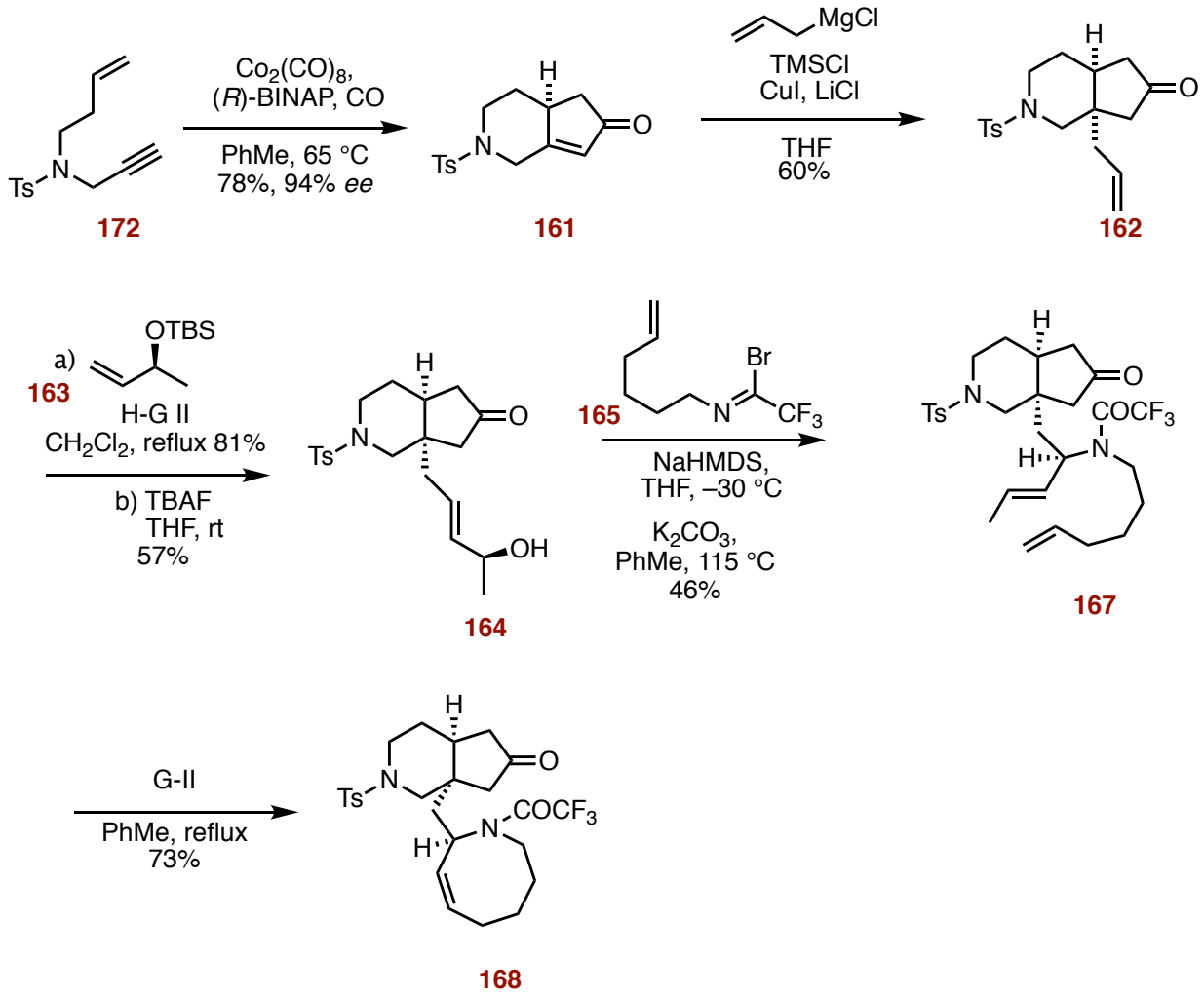
The proposed mechanism to this reaction starts with electrophilic bromination to form *N*-bromo intermediate **256**. The enolate can then attack the *N*-bromo intermediate **257** to construct the five-membered ring and produce ketone **170**. Another path could be through intramolecular transfer of the bromide onto the alpha carbon C4 in **258**. This is then followed by intramolecular elimination of bromide and constructing of the five-membered ring **170** (Scheme 3.31). [47-49]



Scheme 3.31. Proposed mechanism of the C-ring construction

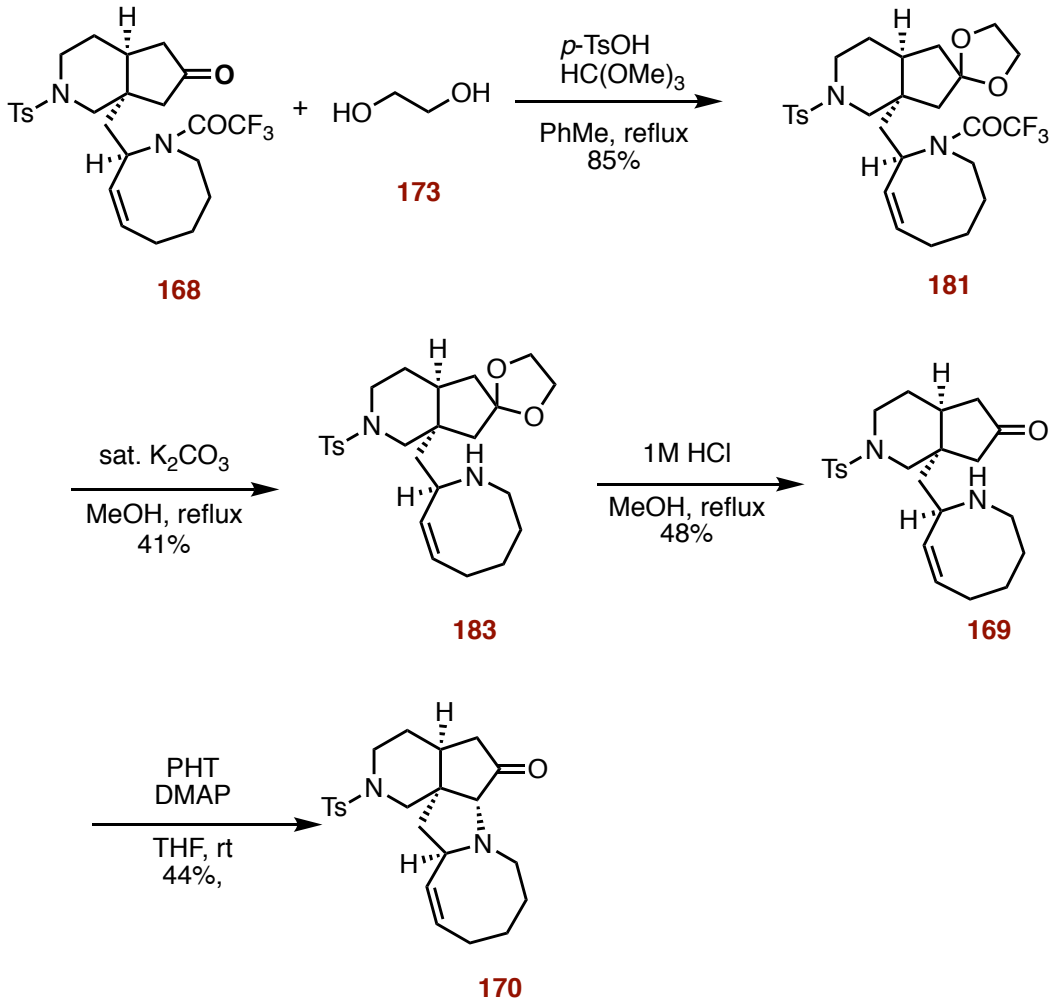
With these optimizations in hand, the best route towards the enantioenriched tetracyclic ketone is summarised in scheme 3.32. When the Pauson-Khand reaction of the enyne **172** was performed using *R*-BINAP under CO atmosphere, the enone **161** was obtained with good *ee*. Conjugate addition of an allyl copper reagent to the enone **161** delivered ketone **162** which was followed by cross metathesis and deprotection of TBS to provide allylic alcohol **164**. Allylic alcohol **164** was subjected to Overman rearrangement to produce the allylic amine **167**.

RCM reaction of allylic amine **167** resulted closure of the eight-membered E-ring and yielded amide **168** (Scheme 3.32).



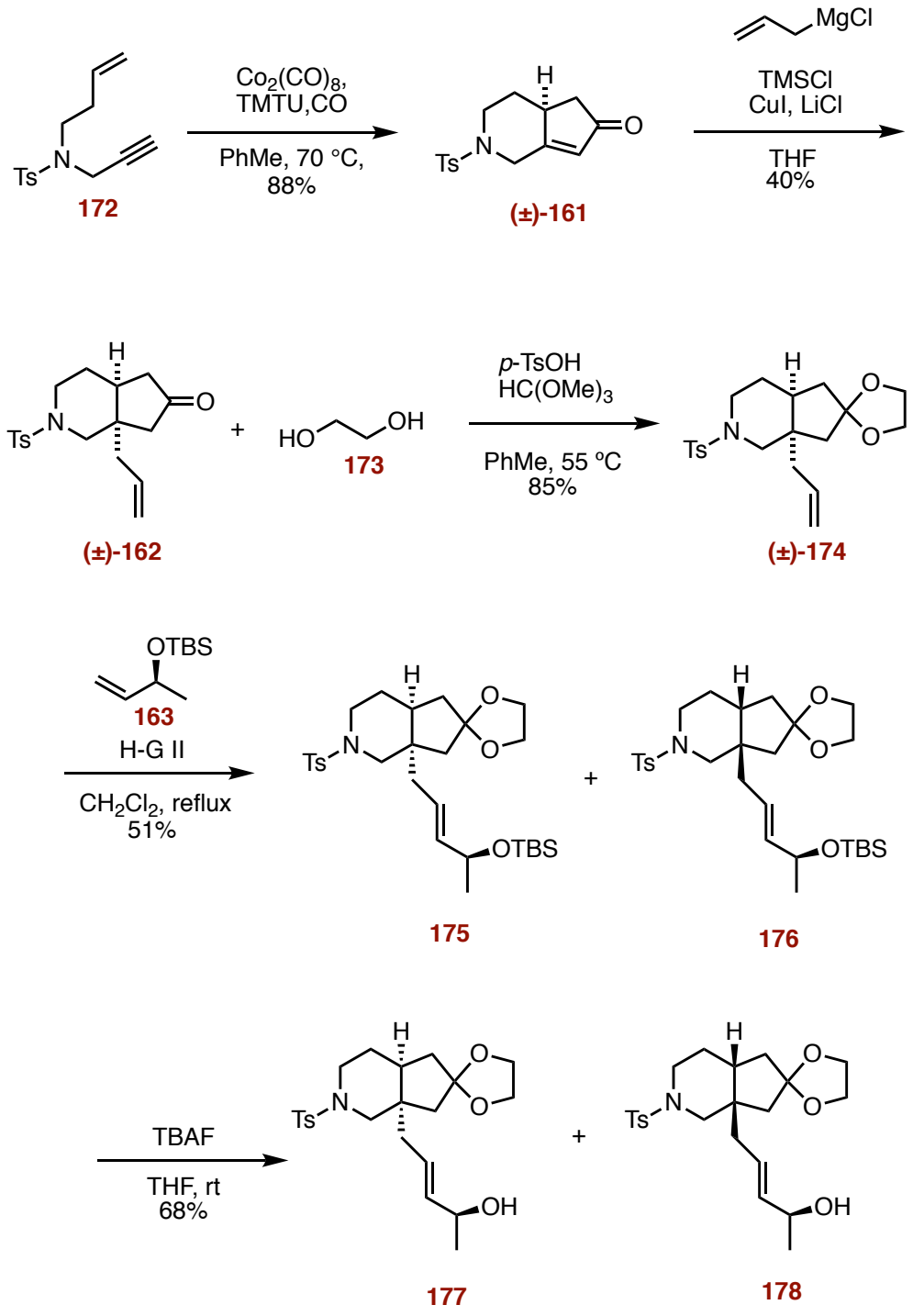
Scheme 3.32. Synthesis of tricyclic advanced intermediate enantioenriched materials

Protection of the ketone **168** afforded the ketal **181**, which was subjected to amide deacylation followed by deprotection of the ketone to give the tricyclic amine **169**. Closure of the five-membered ring was accomplished using a novel amination reaction and resulted in formation of the tetracyclic ketone intermediate **170** (Scheme 3.33).



Scheme 3.33. Synthesis of tetracyclic advanced intermediate 170 of the enantioenriched materials

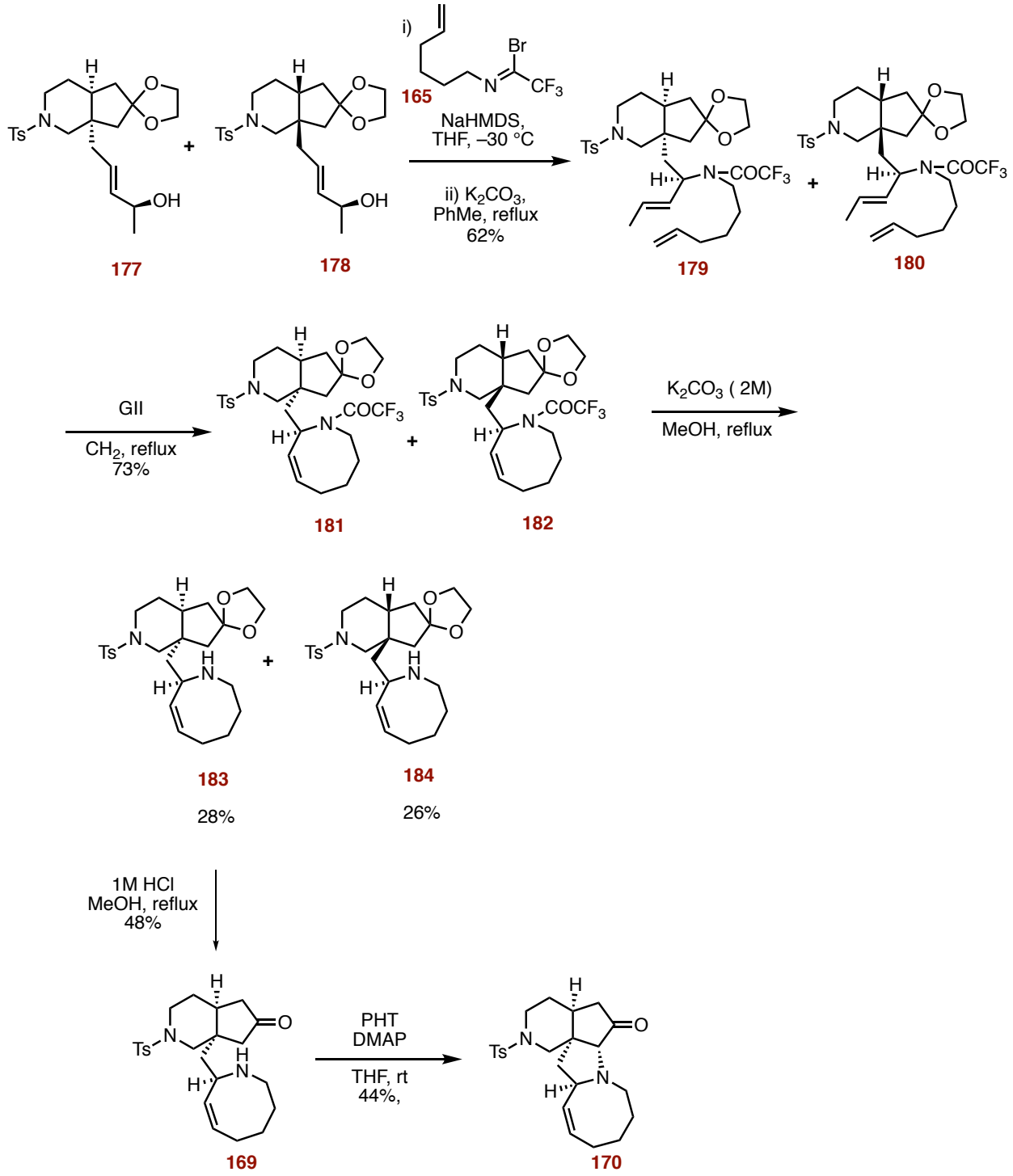
The racemic bicyclic enone **161** was used in the second route. The racemic enone **161** was synthesised through the Pauson-Khand reaction performed in the presence of TMTU under CO atmosphere (Scheme 3.34). Conjugate addition to the enone **161** delivered ketone **162** and protection of this ketone **162** resulted in ketal **174**. Subsequent cross-metathesis and removal of the TBS groups provided the allylic alcohol as a mixture of diastereomers **177** and **178**.



Scheme 3.34. Synthesis of alcohol 177 and 178 of the racemic materials

The racemic allylic alcohol **177** and **178** underwent Overman rearrangement to give the allylic amine **179** and **180** (Scheme 3.35). Amide **181** and **182** were synthesised by RCM of the allylic amine **179** and **180**. Deacylation of amide **181** and **182** followed by deprotection of

the ketone provided the tricyclic amine **169**. The five-membered ring construction was accomplished using a novel amination reaction and provided the tetracyclic advanced intermediate **170**.

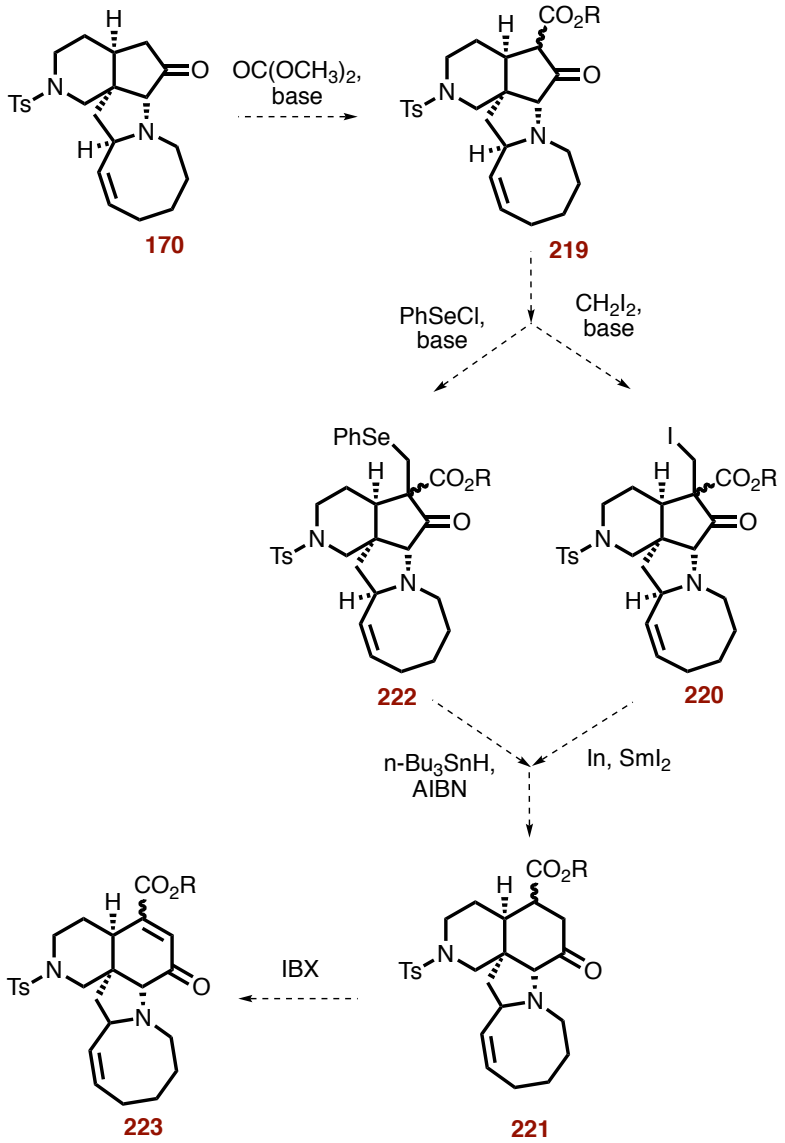


Scheme 3.35. Synthesis of tetracyclic advanced intermediate 170 of the racemic materials

3.3 The expansion of cyclopentanone to cyclohexanone, B ring

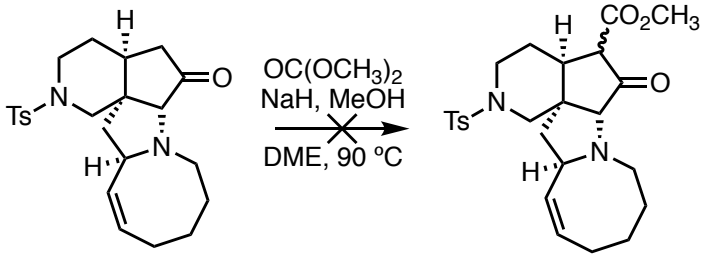
3.3.1 Rearrangement of a functionalised *β*-ketoester

As discussed in the project aims and retrosynthetic analysis (chapter 3.2.), the first route that was investigated involved regioselective introduction of a methyl ester group in the less hindered alpha position. This could be followed by alkylation of the *β*-ketoester **219** with diiodomethane and treatment with anionic conditions using activated zinc or other metal reagents to initiate rearrangement to give the ring-expanded γ-keto ester **221** (Scheme 3.36).[53,59,63]



Scheme 3.36. Proposed route towards the B ring expansion

Acylation of the advanced tetracyclic ketone **170** using dimethyl carbonate, sodium hydride and catalytic methanol in DME at 90 °C to produce the required *β*-ketoester **259** was explored first. However, the reaction was not successful and the starting material was recovered (Table 3.6, entry 1). Increasing the time of the reaction led to no conversion and resulted in decomposition of the starting material. Increasing the equivalents of dimethyl carbonate also resulted no conversion (Table 3.6).

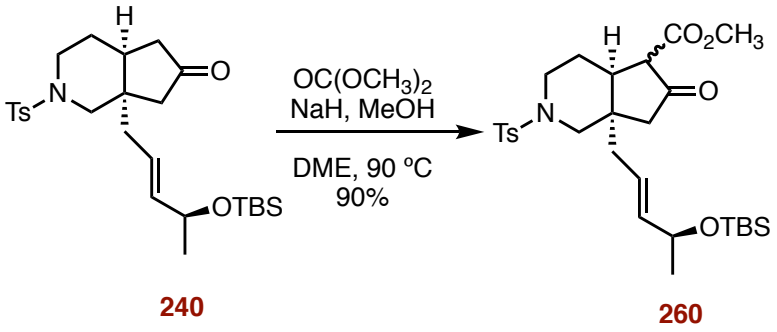


170 **259**

Entry	$OC(OCH_3)_2$ equiv.	NaH equiv.	Time (h)	S.M (%)	Product (%)
1	2.0	3.0	2.5	80	-
2	2.0	3.0	6	40	-
3	2.0	3.0	16	26	-
4	2.5	3.0	6	38	-
5	3.0	3.0	6	20	-
6	3.0	3.0	14	-	-

Table 3.6. Attempted synthesis of *β*-ketoester intermediate

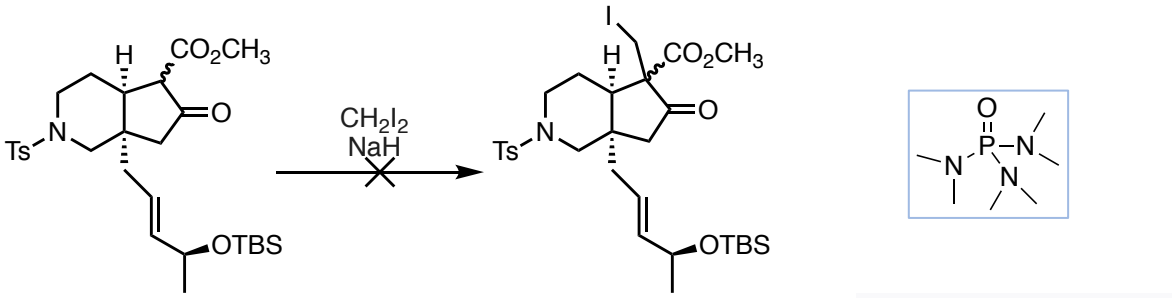
In the light of the negative initial results, it was found to be more efficient to test potential reaction conditions on a simpler model intermediate for further investigation of the ring expansion sequence. Treatment of the protected alcohol intermediate **240** with dimethyl carbonate and sodium hydride in DME at 90 °C produced the required *β*-ketoester regioisomer **260** in 88% yield (Scheme 3.37).[59]



240 260

Scheme 3.37. Synthesis of β-ketoester intermediate 260

With *β*-ketoester **260** in hand, the next was to investigate the alkylation of the *β*-keto ester **260** with diiodomethane to afford iodide **261** .[53,54,63] Unfortunately, when using the standard conditions, the formation of the desired product was not observed. Many different reaction conditions were explored in order to get the desired product, but the reagents and reactions conditions used did not give any positive results (Table 3.7).



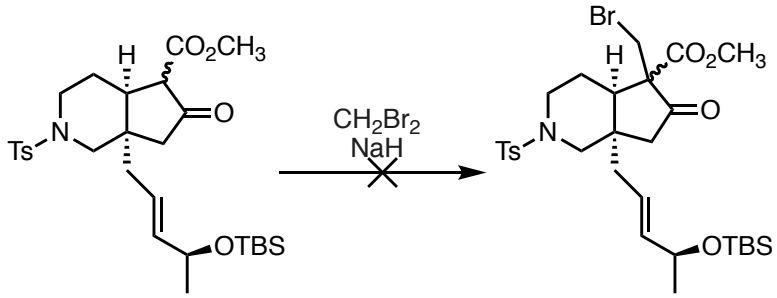
260 261 Hexamethylphosphoramide

Entry	CH_2I_2 equiv.	NaH equiv.	Additive	Solvent	Time (h)	T (°C)	Results
1	5.0	1.2	HMPA	THF	1	rt	76% S.M
2	3.0	1.6	-	DMSO	4	rt	50% S.M
3	5.0	1.6	-	DMSO	4	rt	84% S.M
4	10.0	1.6	-	DMSO	4	rt	74% S.M
5	10.0	1.6	-	DMSO	14	rt	48% S.M
6	10.0	1.6	-	DMSO	4	40	40% S.M

7	10.0	1.6	-	DMSO	4	80	decomposition
8	5.0	1.6	-	DMSO	3	40	38% S.M
9	5.0	1.6	-	DMSO	14	40	decomposition

Table 3.7. Attempted alkylation of the β-ketoester using diiodomethane

An alternative method was explored in which the electrophile was changed to a a less reactive electrophile. Dibromomethane was tested using the same reported conditions (Table 3.8)[53]. Again the desired product **262** was not formed and some of the starting material was recovered.



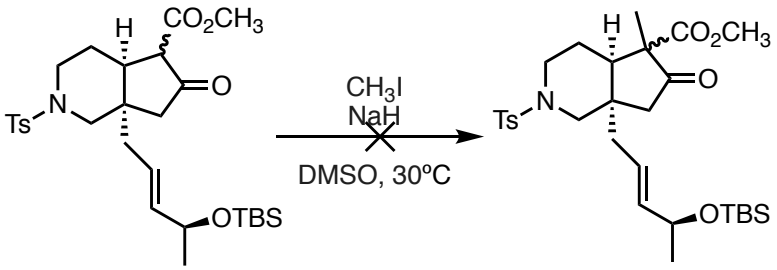
260 **262**

Entry	CH_2Br_2 equiv.	NaH equiv.	Additive	Solvent	Time (h)	T (°C)	Results
1	5.0	1.6	HMPA	DMF	1	rt	88% S.M
2	5.0	1.6	-	DMF	14	rt	61% S.M
3	5.0	1.6	-	DMF	14	80	35% S.M
4	5.0	1.6	-	DMSO	14	rt	93% S.M
5	5.0	1.6	-	DMSO	14	40	55% S.M

Table 3.8. Attempted alkylation of the β-ketoester using dibromomethane

Using the iodomethane as electrophile was also investigated. Unfortunately, the expected product was not obtained and only starting material was recovered. When the temperature was

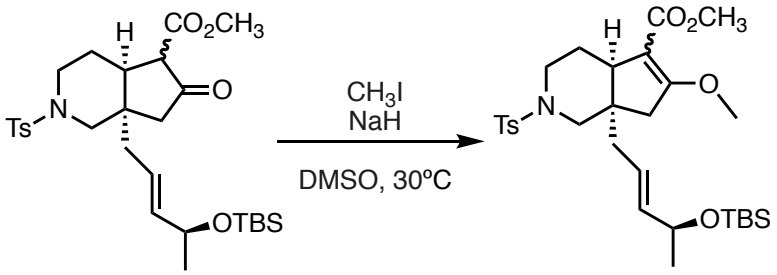
increased, 20% of the undesired *O*-alkylation product **264** was formed (Table 3.9). Increasing the reaction times did not provide the desired product (Scheme 3.38). [54]



260 **263**

Entry	CH_3I equiv.	NaH equiv.	Time (h)	T (°C)	Results
1	5.0	1.6	4	rt	60% S.M
2	5.0	1.6	14	rt	61% S.M
3	5.0	1.6	4	30	20% *O*-Alkylation
3	5.0	1.6	14	30	83% *O*-Alkylation

Table 3.9. Attempted alkylation of the β-ketoester using iodomethane

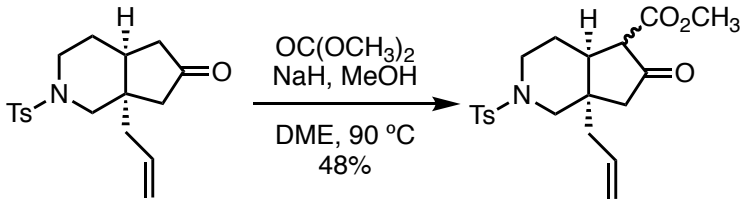


260 **264**

Scheme 3.38. Undesired *O*-Alkylation formation

Alkylation of the *β*-ketoester intermediate **260** did not give the desired product and so alkylation of a simpler intermediate was necessary to establish appropriate conditions. Using the

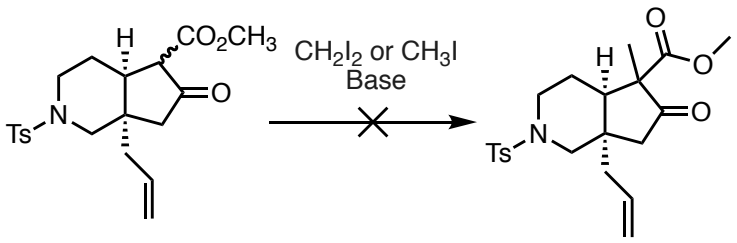
same procedure described before, acylation of the *β*-allyl ketone using dimethyl carbonate and sodium hydride in DME resulted in formation of the desired *β*-ketoester **265** in 48% yield (Scheme 3.39).[59]



163 **265**

Scheme 3.39. Synthesis of *β*-ketoester intermediate

The *β*–ketoester **265** was then subjected to alkylation with either iodomethane or diiodomethane as the electrophil. Unfortunately, the reaction was not successful and changing the base to *t*BuOLi or LiHMDS did not improve matters. When NaH was used as the base and the temperature was increased, some *O*-alkylation was observed. Changing the solvents or increasing the reaction time sadly did not provide the desired product (Table 3.10).



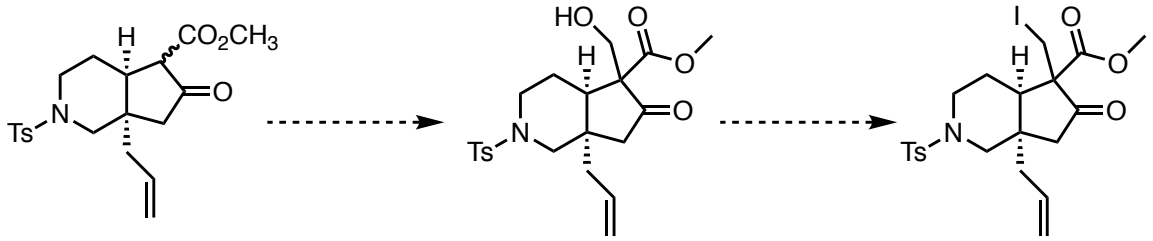
265 **266**

Entry	CH_3I equiv.	Base (equiv.)	Solvent	Time (h)	T (°C)	Results
1	5.0	NaH (1.6)	DMSO	4	rt	40% S.M
2	3.0	NaH (1.6)	DMSO	4	30	20% *O*-Alkylation
3	5.0	NaH (1.6)	DMF	4	rt	84% S.M
4	5.0	NaH (2.0)	DMF	14	rt	74% S.M

5	5.0	NaH (1.6)	DMF	2	30	32% *O*-Alkylation
6	5.0	NaH (1.6)	THF	4	30	24% *O*-Alkylation
7	5.0	*t*BuOLi (1.5)	DME	2	rt	90% S.M
8	5.0	*t*BuOLi (2.5)	DME	14	rt	38% S.M
9	5.0	*t*BuOLi (2.5)	DME	6	30	60% S.M
10	5.0	*t*BuOLi (4.0)	DME	6	30	54% S.M
11	5.0	LiHMDS (2.5)	THF	3	−78	78% S.M
12	5.0	LiHMDS (2.5)	THF	2	0	86% S.M
13	5.0	LiHMDS (2.5)	THF	14	rt	38% S.M

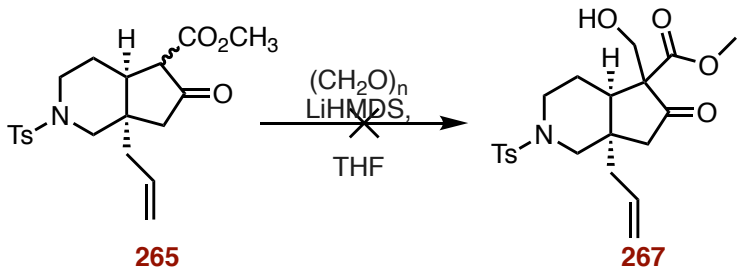
Table 3.10. Attempted alkylation of the *β*-ketoester 265 using iodomethane

Alkylation of the *β*-ketoesters using simple alkyl halides (*i.e.*, CH_2I_2, CH_3I, CH_2Br) did not provide any promising results, aldol addition was explored as an alternative functionalization reaction. The expectation was that the aldol product **267** could be prepared and then a substitution reaction could be used to produce iodomethyl *β*-ketoester **268** intermediate (Scheme 3.40). Aldol addition using paraformaldehyde was tested. Sadly, the reaction was not successful and the desired product was not formed (Scheme 3.41).



265 **267** **268**

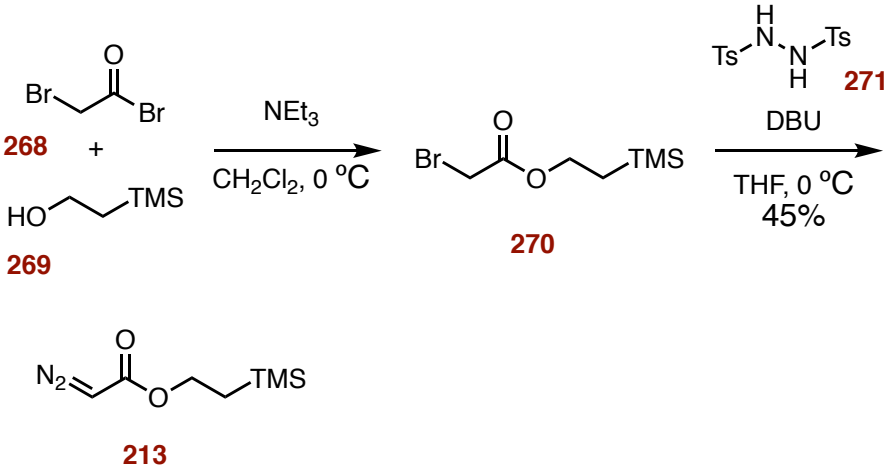
Scheme 3.40. proposed Aldol addition



Scheme 3.41. Attempted aldol addition

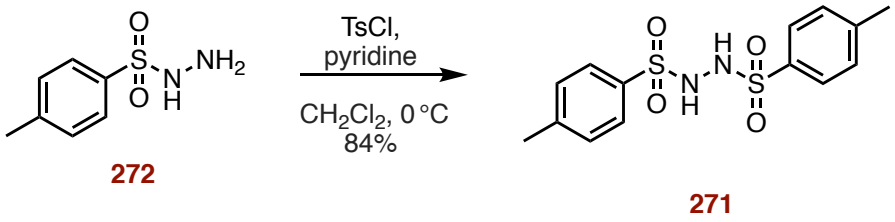
3.3.2 Ring expansion using the modified diazoester nucleophilic addition

The second route that was tested was the nucleophilic addition of the modified 2-(trimethylsilyl)ethyl diazoacetate **213** to the carbonyl group in the ketone **170** (described in chapter 3. Scheme 3.4). The first step was to synthesise the modified 2-(trimethylsilyl)ethyl diazoacetate **213** using Fukuyama's method.[65] Acylation of TMS-ethanol **269** using bromoacetyl bromide **268** and NEt_3 produced acetate **270**. The crude acetate **270** was carried forward to the next step without purification and treatment of the acetate **270** with a mixture of *N,N'*-ditosylhydrazine **271** and DBU delivered 2-(trimethylsilyl)ethyl diazoacetate **213** (Scheme 3.42).[65]



Scheme 3.42. Synthesis of diazoester 213 side chain

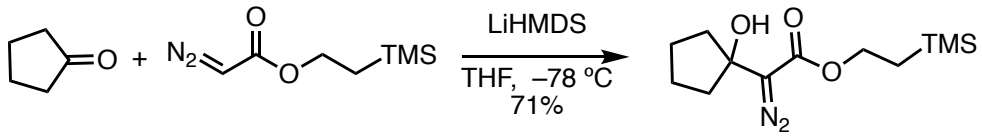
N,N'-ditosylhydrazine **271** was prepared in 84% yield by the reaction of commercially-available *p*-toluenesulfonyl chloride with *p*-toluenesulfonyl hydrazide using pyridine in CH_2Cl_2 at 0 °C. (Scheme 3.43).[65]



272 **271**

Scheme 3.43. Synthesis of *N,N'*-ditosylhydrazine 271

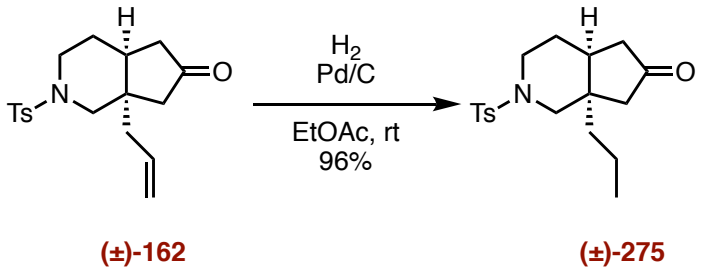
With 2-(trimethylsilyl)ethyl diazoacetate **213** in hand, the nucleophilic addition to the carbonyl group was explored. To start with, the nucleophilic addition reaction was tested using a model substrate. Cyclopentanone and TMS-diazoacetate **274** were treated with NaHMDS in THF at –78 °C to deliver the alcohol **274** in 71% yield (Scheme 3.44).



273 **213** **274**

Scheme 3.44. synthesis of alcohol 274

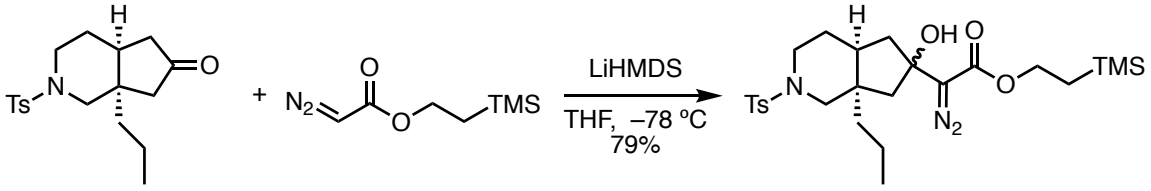
Synthesis of a simple bicyclic model compound was required in order to test the feasibility of the reaction sequence, described in chapter 3.1 scheme 3.4. The bicyclic ketone **(±)-275** was synthesised by hydrogenation of the *β*-allyl ketone **(±)-162**. (Scheme 3.45).[3] This hydrogenation reaction was carried out to prevent any reaction of the terminal alkene in the *β*-allyl ketone **(±)-162**.[49]



(±)-162 **(±)-275**

Scheme 3.45. Synthesis of test substrate (±)- 275.

Using the reported conditions, nucleophilic addition to the bicyclic ketone **(±)-275** using LDA delivered α-diazo-*β*-hydroxyester **(±)-276** in low yield and 60% of the starting materials were recovered (Table 3.11, entry 1) and so further optimization studies were carried out. First, changing the base to NaHMDS showed no improvement of the yield. Using LiHMDS showed some improvement of the yield to 55% (Table 3.11, entry 3), but still some starting material was recovered. Manipulation of the procedure was carried out to see if alterations could be made that would increase the yield of the required product. The first alteration was to increase the reaction time from 1 to 8 hours, but increases in the yield were not observed (Table 3.11, entry 4). Second, adding the 2-(trimethylsilyl)ethyl diazoacetate **213** in 3 equal portions in intervals of 30 minutes also did not result in a higher yield (Table 3.11, entry 5). Finally, generation of the nucleophile by pre-mixing 2-(trimethylsilyl)ethyl diazoacetate **213** with LiHMDS, followed by slow addition of the bicyclic ketone **(±)-275** to the mixture resulted in an increase in the yield to 79 % (Table 3.11, entry 6).

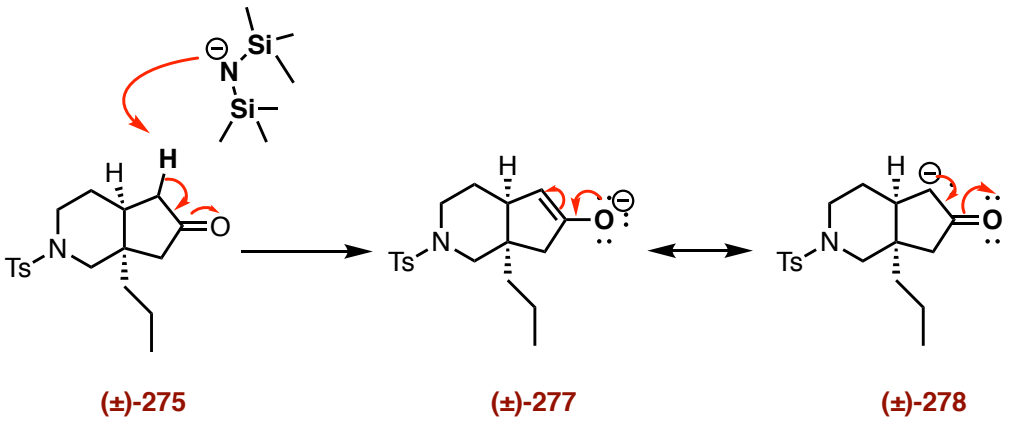


(±)-275 **213** **(±)-276**

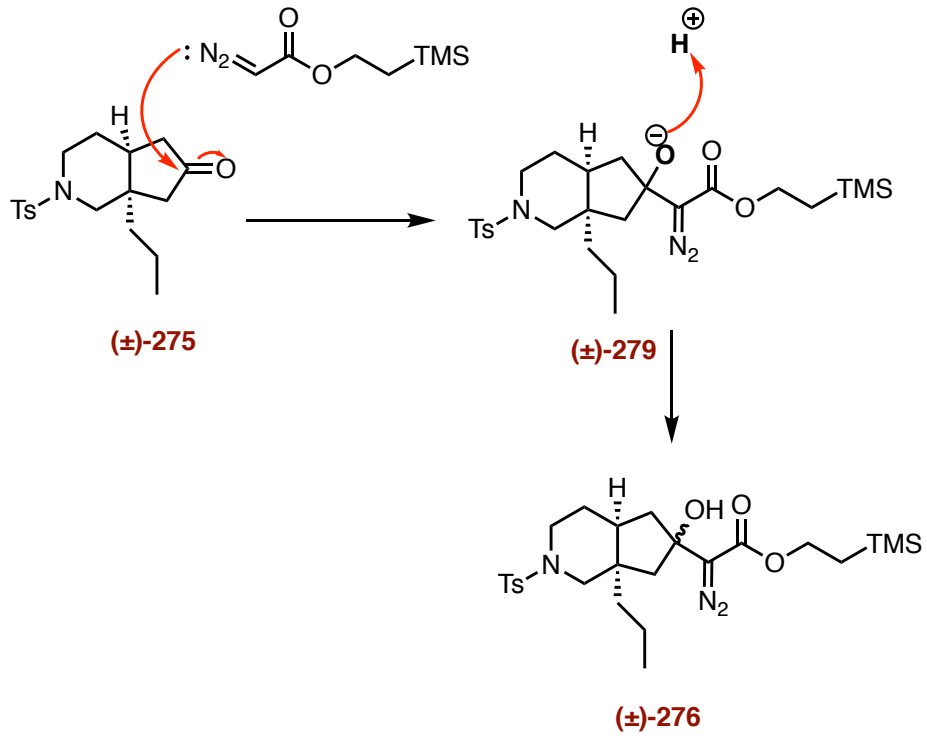
Entry	Base	Time (h)	Yield (%)	Note
1	LDA	1	30	_
2	NaHMDS	1	38	_
3	LiHMDS	1	55	_
4	LiHMDS	8	58	_
5	LiHMDS	6	63	Added **213** in 3equal portions every 30 minutes
6	LiHMDS	3	79	Added the base to **213** then added the **(±)-275**

Table 3.11. Diazoester addition optimisation.

The reason for the initial poor yields could be to abstraction of the alpha-hydrogen of the carbonyl group to form the enolate **(±)-277** when the ketone is exposed to LiHMDS. At the same time, 2-(trimethylsilyl)ethyl diazoacetate **213** would form the nucleophile. The nucleophile would react with the ketone **(±)-275** but not with the ketone enolate, meaning that a portion of the starting material would remained unreacted (Scheme 3.46). On the other hand, when adding LiHMDS to the 2-(trimethylsilyl)ethyl diazoacetate **213** and allowing it to react to ensure complete consumption of the base prior to addition of the ketone, the nucleophile would form and generation of the enolate would be avoided. Adding the ketone **(±)-275** to the mixture means that most of the starting material would be consumed to give the desired product, rather than getting trapped as the enolate. (Scheme 3.47).

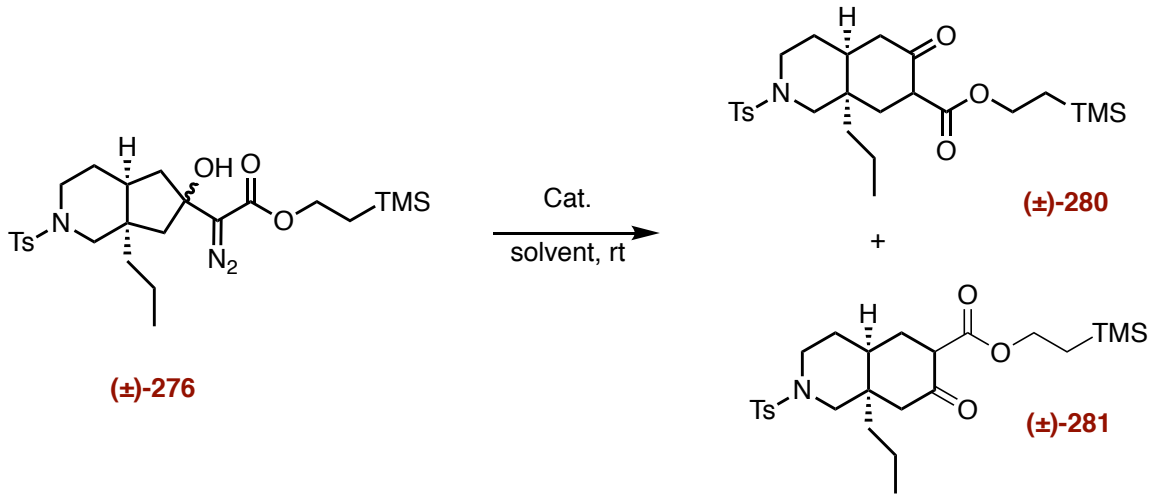


Scheme 3.46. Resonance stabilization to form the enolate ion



Scheme 3.47. Nucleophilic addition to the ketone (±)-275

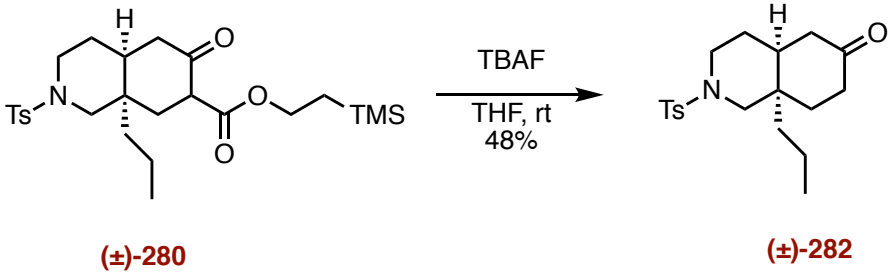
The next step was the catalytic ring expansion reaction using a metal catalyst at room temperature to produce the ring expanded intermediate **(±)-280** and **(±)-281**. Several catalysts were screened in order to identify the most suitable metal complex (Table 3.12).[66] The best conversion was obtained when $Rh_2(OAc)_4$ was use and in this case an inseparable mixture of silyl enol ethers **(±)-280** and **(±)-281** (Table 3.12, entry 4) was obtained in a ratio of 9:1 (**(±)-280**:**(±)-281**). This mixture was purified by rapid filtration to remove any catalyst, and the filtrate was carried forward to the next step without further purification. Decarboxylation of *β*-ketoester **(±)-280** using TBAF delivered the desired ring expanded ketone **(±)-282** in 48% (Scheme 3.48).[66]



Entry	Cat. (0.3 equiv.)	Solvent	Time (h)	Yield (%)	Ratio.
1	$PdCl_2$	CH_2Cl_2	2	85%	2:1
2	$RhCl(PPh_3)_3$	CH_2Cl_2	16	88%	3:1
3	$Rh_2(OAc)_4$	Pentane	1	69% *	9:1
4	$Rh_2(OAc)_4$	CH_2Cl_2	1	81%	9:1

* S.M doesn't fully dissolve in pentane

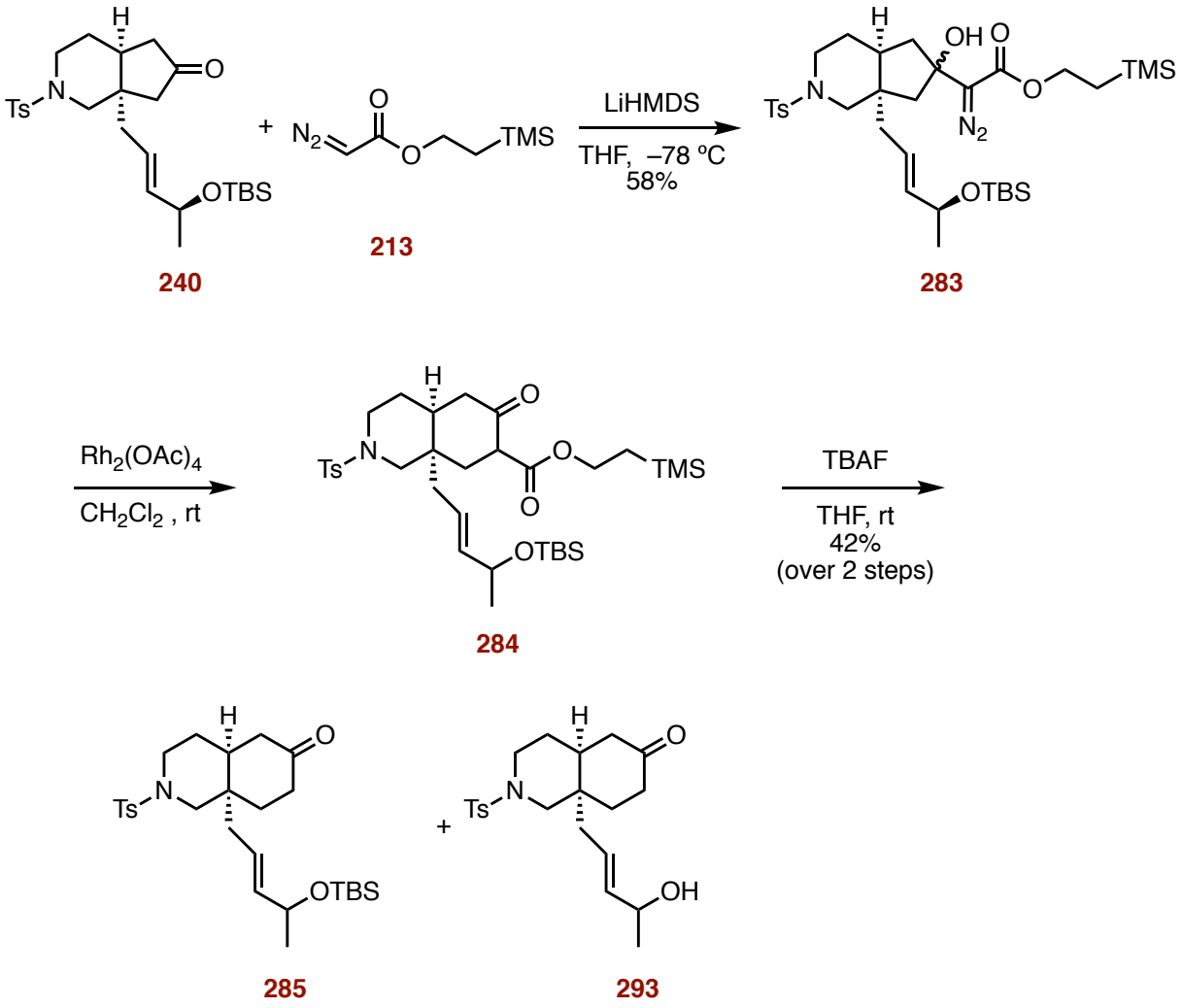
Table 3.12. Conditions for α-diazo-β-hydroxyester rearrangement



Scheme 3.48. Decarboxylation of the *β*-keto ester (±)-282

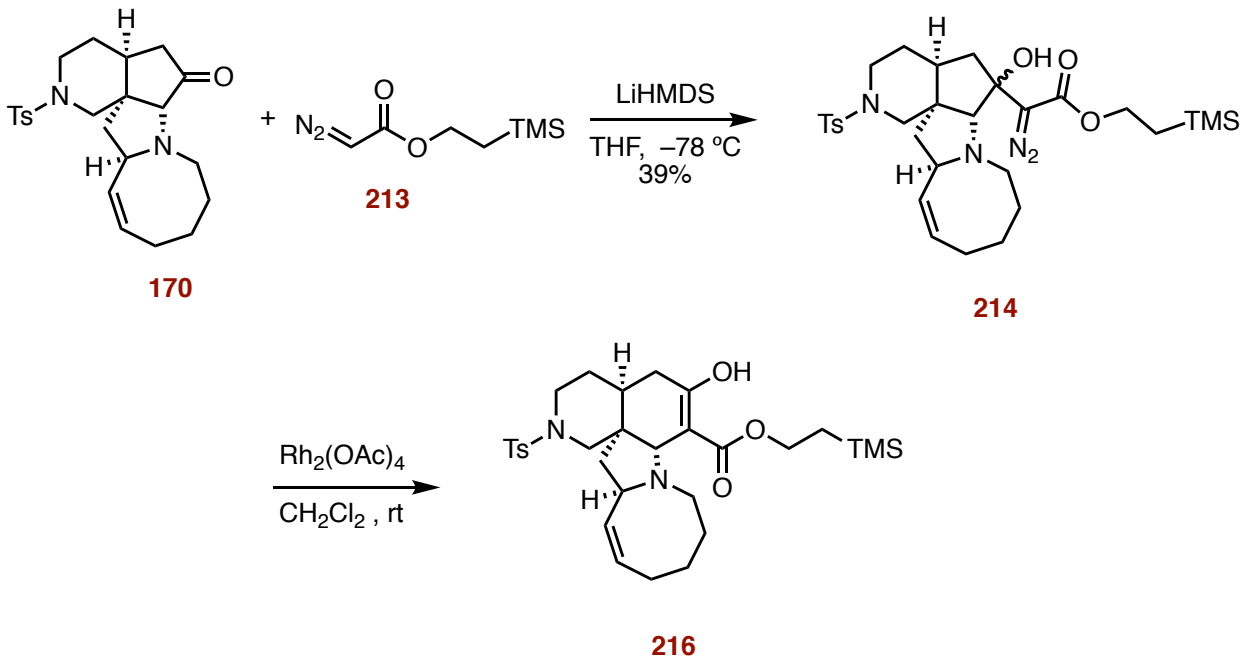
After the success of the reaction sequence on the model substrate, the same sequence was applied to the protected alcohol **240**. Nucleophilic addition to the ketone was performed using 2-(trimethylsilyl)ethyl diazoacetate **213** and LiHMDS to provide the corresponding α-diazo-β-hydroxyester **283** in 58% yield. This was followed by treatment with $Rh_2(OAc)_4$ to give the

desired ring-expanded carboxylate **284**. Decarboxylation of **284** by treatment with TBAF provided the desired ring-expanded ketone **285 and 293** in 42 % yield over the two steps (Scheme 3.49).[49]



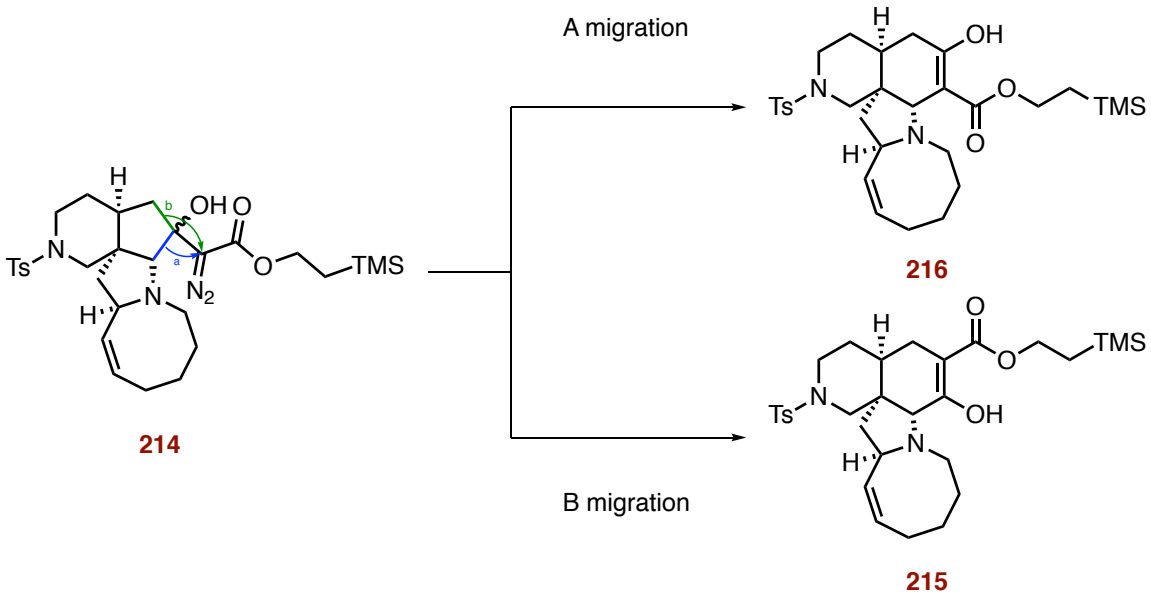
Scheme 3.49. Synthesis of ring-expanded intermediate 285

Following the same established protocol, 2-(trimethylsilyl)ethyl diazoacetate **213** was reacted with tetracyclic ketone **170** in the presence of LiHMDS to form α-diazo-β-hydroxyester **214**. Limited purification was performed and rapid filtration was undertaken before proceeding to the next step. Ring expansion of α-diazo-β-hydroxyester **216** was achieved using $Rh_2(OAc)_4$ (Scheme 3.50).[49]



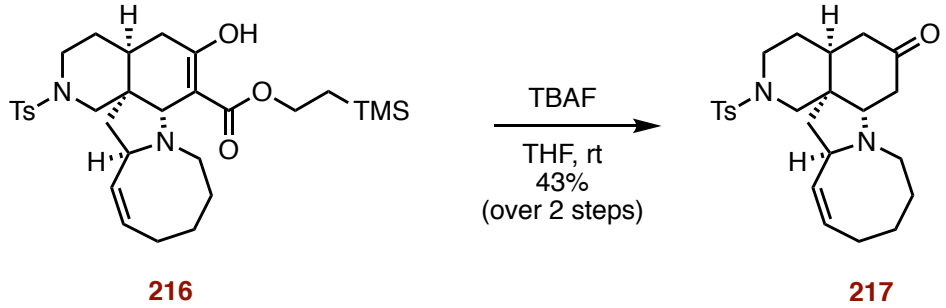
Scheme 3.50. α-diazo-β-hydroxyester rearrangement

The ^{1}H NMR spectra of ring-expanded carboxylate **215** and **216** indicated that the transformation mostly provided the desired regioisomers **216**, with the presence of a trace of the other regioisomers **215**. Both the steric hindrance effect and nature of the transition metal catalyst appears to play a major role in the regioselectivity of the reaction. The favoured pathway results in formation of ring-expanded intermediate **216** (A migration) (Scheme 3.51).[61,66]



Scheme 3.51. Proposed alkyl migration pathway of 214

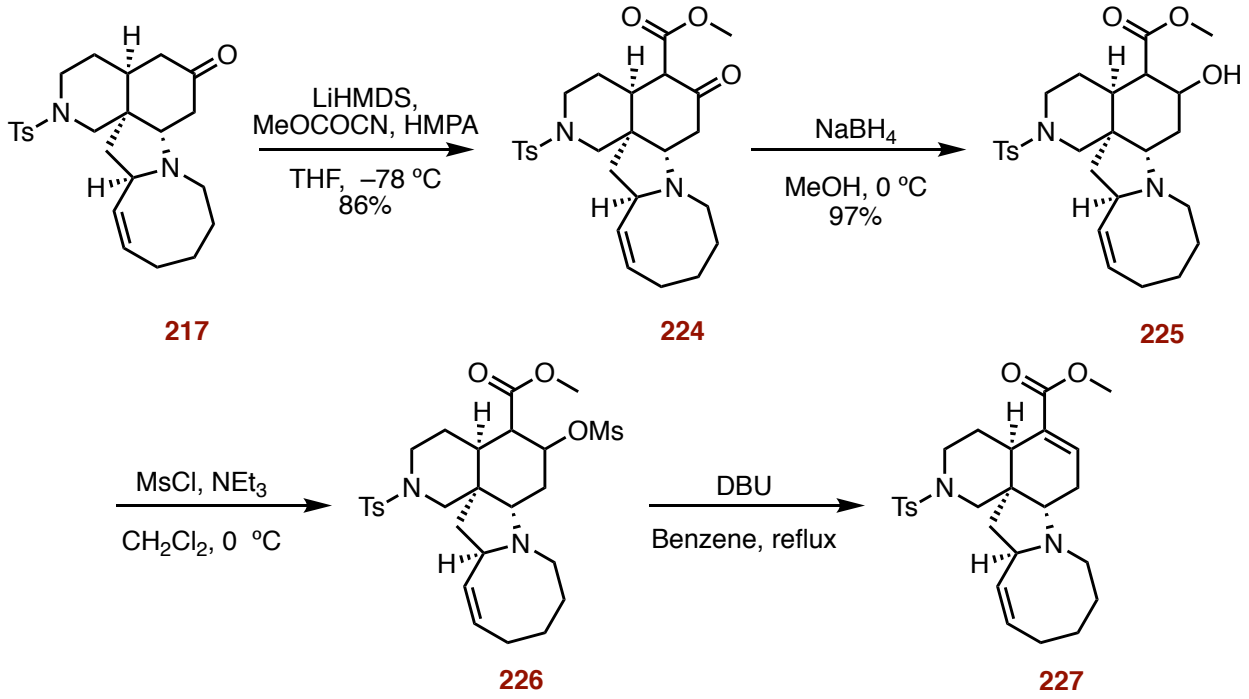
Intermediate **216** was subjected to the next step and treated with TBAF to deliver the desired ring-expanded intermediate **217** in 43% yield over 2 steps (Scheme 3.52).[49]



Scheme 3.52. Decarboxylation of 216

Inspired by Winkler and co-workers,[68] ketone **217** was converted to *β*-ketoester **224** using Manders' reagent and HMPA in 86% yield. *β*-ketoester **224** was then treated with sodium borohydride to generate the *β*-hydroxyester **225** in 88% yield. The *β*-hydroxyester **225** was subjected to *mesylation* using freshly distilled methane sulfonyl chloride and freshly distilled triethylamine to produce the mesylate **226**. The mesylate **226** was carried forward without purification and the *β*-elimination reaction to produce the unsaturated ester 227 was performed

by heating the mesylate with DBU in benzene at reflux. Unfortunately, the required product was not obtained from the reaction. Increasing the reaction time provided some product, which was confirmed by mass spectrometry. However, there was insufficient material to get the full NMR data (Scheme 3.53).



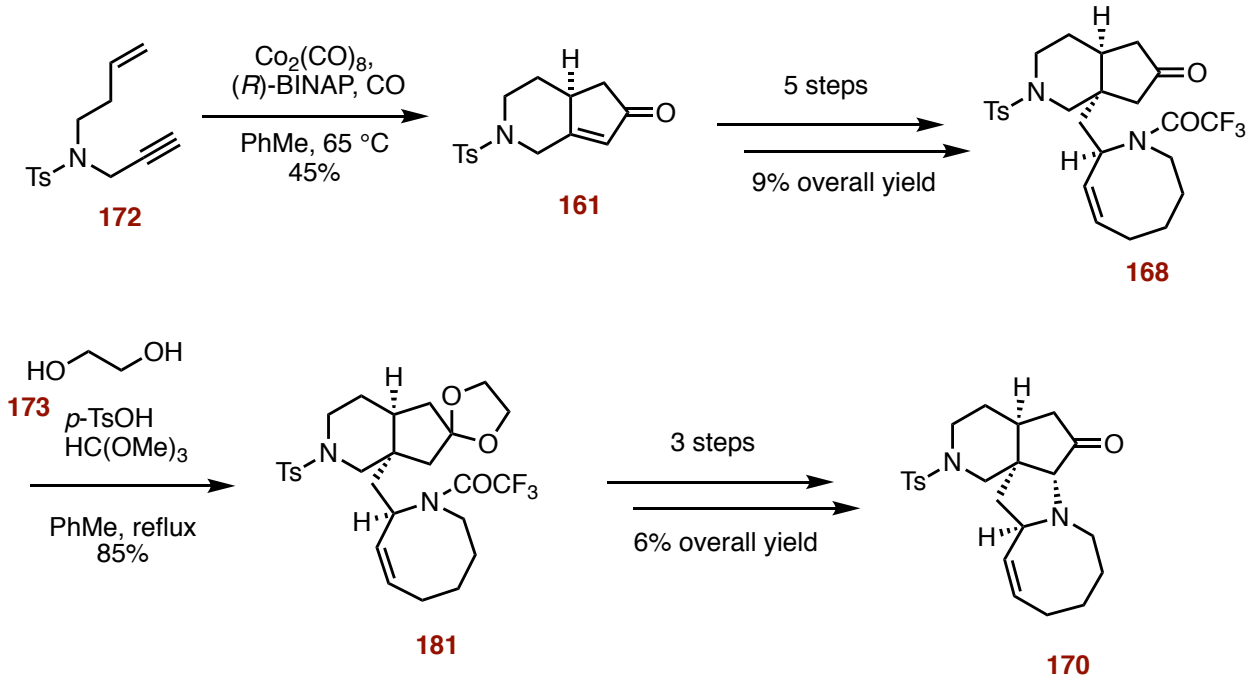
Scheme3.53. functionalisation of 217 intermediate

4. Conclusions

4.1 Summary of Work

A tetracyclic advanced intermediate towards the total synthesis of manzamine A has been prepared and the early steps of the routes optimized using enantioenriched and racemic pathways.

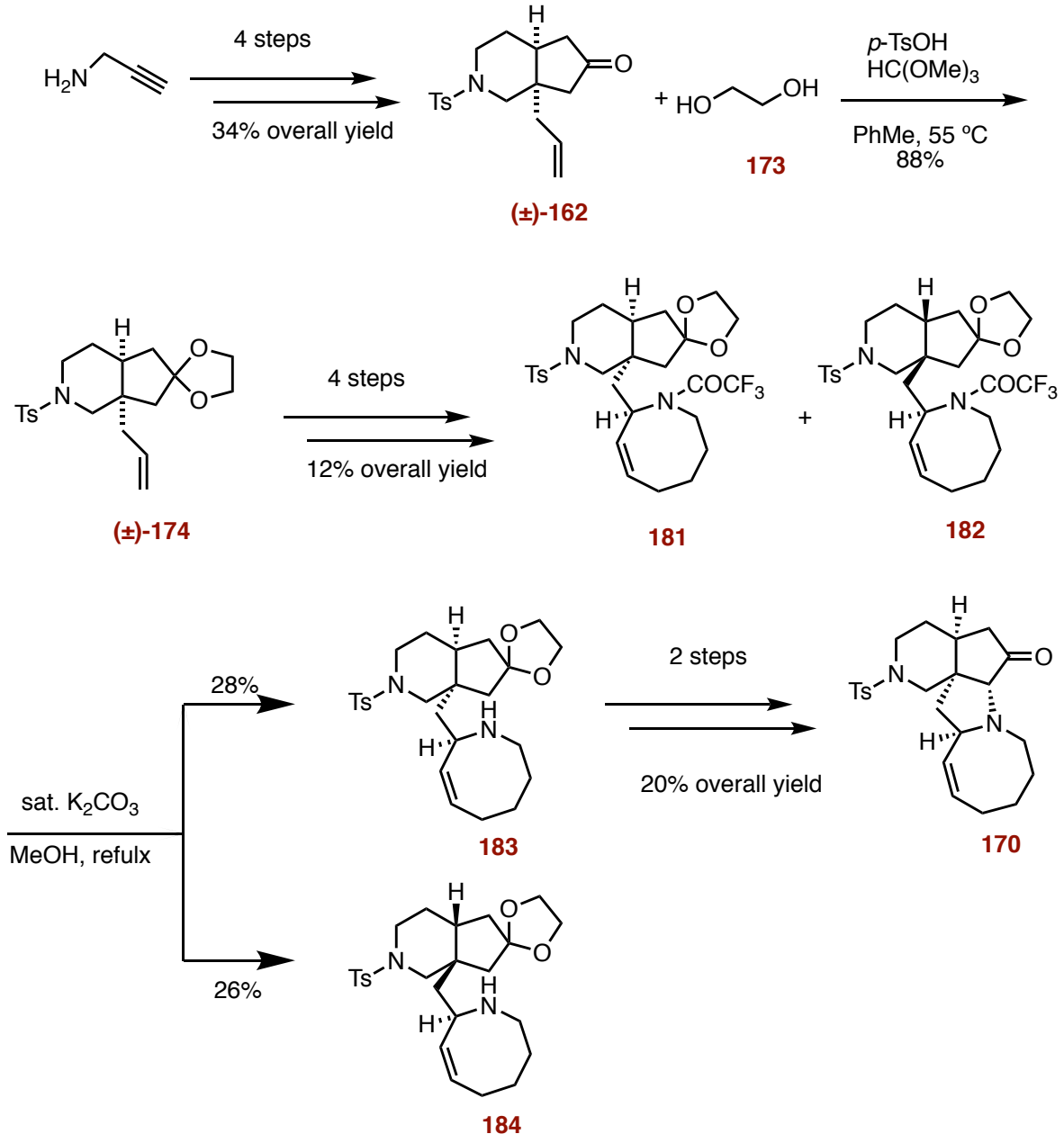
In the synthetic route towards the enantioenriched material, a Pauson-Khand reaction was performed using *R*-BINAP under CO atmosphere to provide the enone **161**. From here, the enantioenriched bicyclic ketone **161** could be transformed into amide **168** in 5 steps. Protecting the ketone **168** was necessary to avoid side reactions and deliver the desired amide **181**. Amide **181** was converted into the tetracyclic key intermediate **170** in 11 steps with overall 0.36% yield (Scheme 3.54).



Scheme 3.54. Synthesis of tetracyclic ketone 170

An alternative route in which the racemic bicyclic enone **(±)-161** was synthesized through a Pauson-Khand reaction in presence of TMTU under a CO atmosphere was also completed. Protection of the ketone **(±)-162** at an earlier stage produced the ketal **(±)-174**. Ketal

(±)-174 was converted to amide **181** and **182** in 4 steps. The diastereomeric amines **183** and **184** were separated at a later stage and transformed into the corresponding tetracyclic advanced intermediates **170** in 11 steps and 0.27% overall yield (Scheme 3.55).

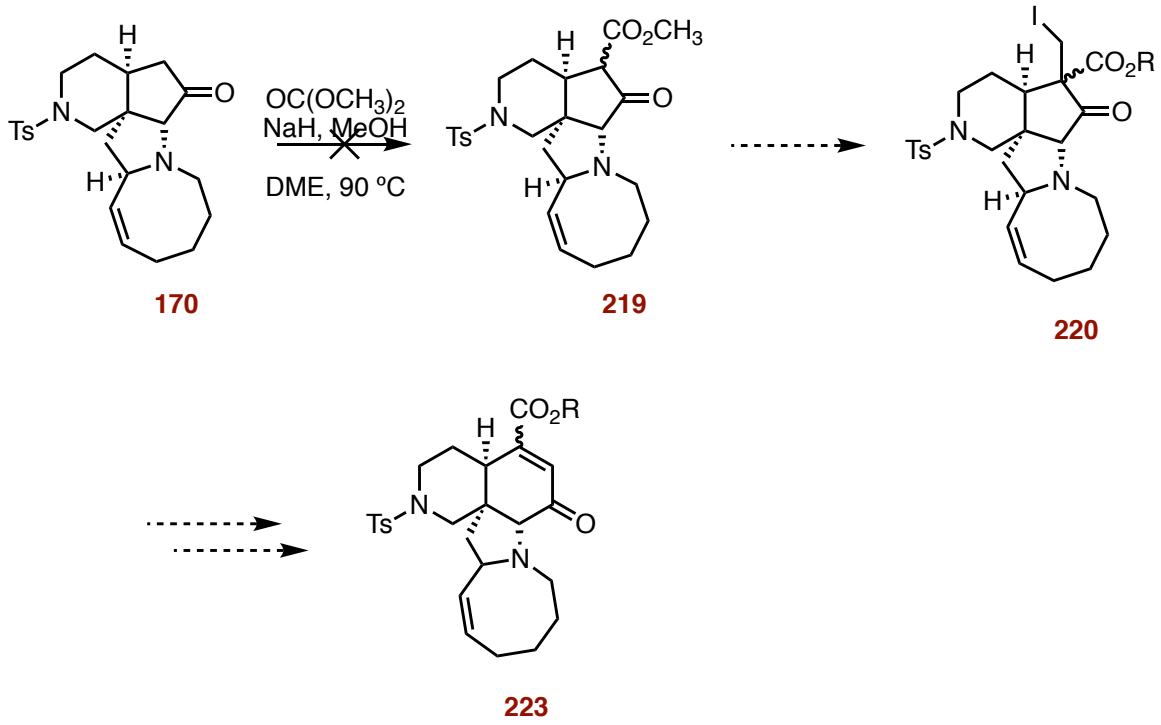


Scheme 3.55. Synthesis of the tetracyclic ketone 170

Optimisation and manipulation of the regents and conditions were carried out for most of the previous steps in order to get better yield, *i.e* Pasuon-Khand reaction, 1,4 addition, Overman

rearrangement, ring closing metathesis, and hydrolysis of trifluoroacetamide. Changing the protecting group from the allylic TBS ether side chain **163** to allylic TBDPS ether **239** to avoid the volatility was also achieved. A different purification technique was optimised to purify the acetimidoyl side chain **165** in order to avoid its decomposition was also carried out.

The other part of this project concerned the ring expansion of key tetracyclic ketone **170**. The first route that was tested involved regioselective conversion of the ketone **170** into the *β*-keto ester **219,** followed by alkylation of *β*-keto ester **219** with diiodomethane and subjection to anionic conditions to initiate the rearrangement and produce the ring expanded intermediate **223**. The reaction was not successful and the starting material was recovered (Scheme 3.56).

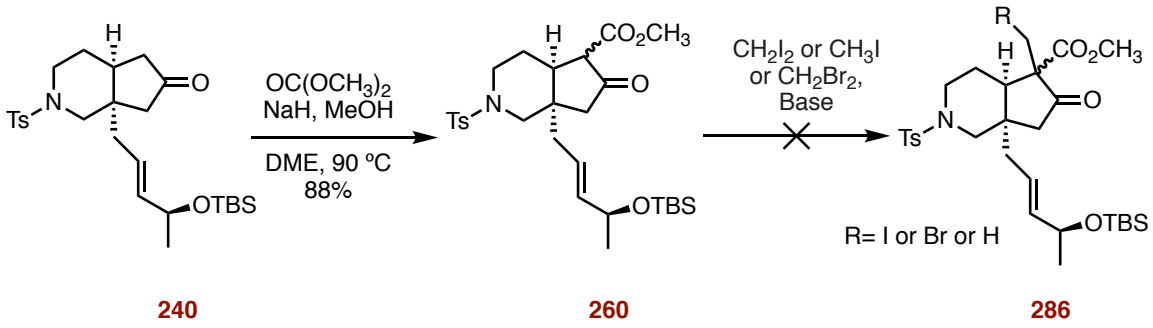


170 **219** **220**

223

Scheme 3.56. Attempted ring expansion of tetracyclic ketone170

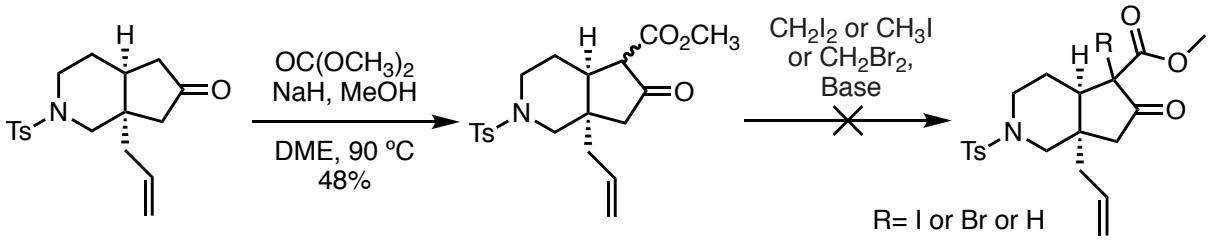
The reaction was also tested using a simpler substrate. Acylation of protected alcohol intermediate **240** afforded *β*-ketoester **260**. This was subjected to alkylation using diiodomethane, iodomethane and dibromomethane. However, the alkylation reaction did not proceed as expected (Scheme 3.57).



240 260 286

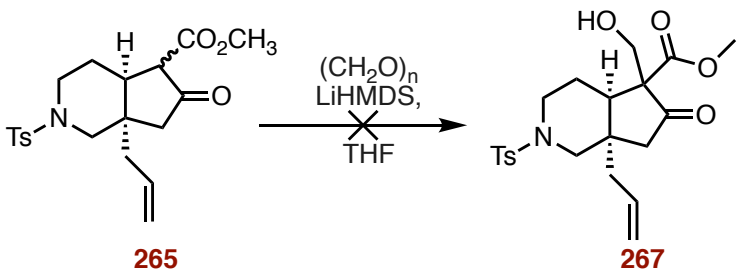
Scheme 3.57. Attempted ring expansion of tetracyclic ketone

An alternative study involving the ring expansion of a simpler intermediate was performed. The *β*–allyl ketone **162** was converted to *β*–ketoester **265** using dimethyl carbonate. Alkylation of *β*–ketoester **265** to give the alkylated intermediate **287** was then explored. Unfortunately the required product was not formed (Scheme 3.58). An aldol addition reaction between paraformaldehyde and the anion generated from *β*-ketoester **265** was also attempted but it was not successful and the required product was not obtained (Scheme 3.59).



162 265 287

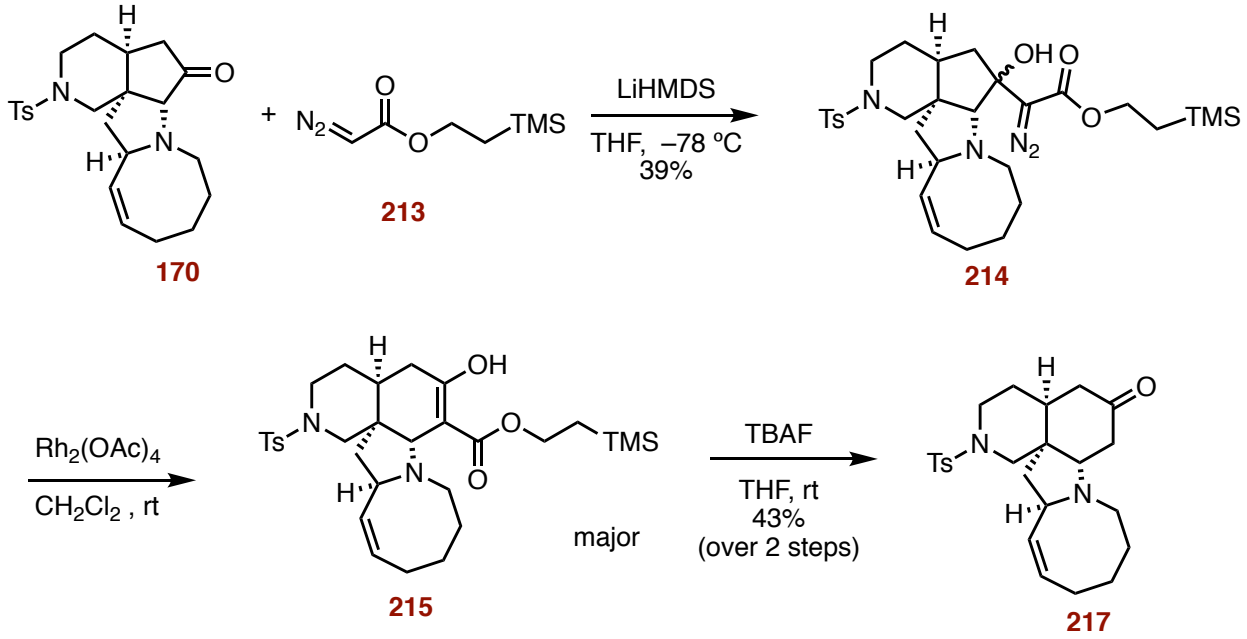
Scheme 3.58. Unsuccessful trials for the synthesis of the functionalised *β*-keto ester



265 267

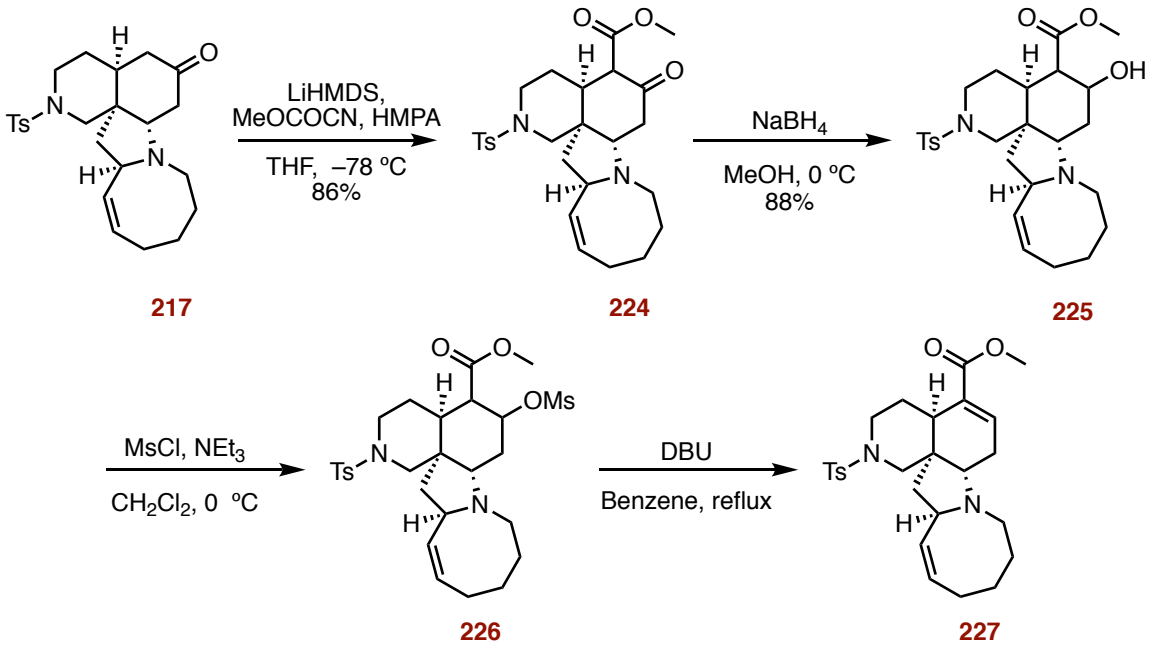
Scheme 3.59. Attempted alkylation of the *β*-ketoester

The second synthetic strategy to be explored involved ring expansion of a modified diazoester obtained by nucleophilic addition. Ketone **170** was treated with lithiated diazoester **213** to produce α-diazo-β-hydroxyester **214**. This was followed by the rearrangement reaction promoted by $Rh_2(OAc)_4$ to provide the regioselective ring expanded *β*-ketoesters **215**. *β*-ketoesters **215** were then subjected to desilylation-decarboxylation to provide the desired ring expanded ketone **217** (Scheme 3.60)**.**



Scheme 3.60. Synthesis of ring expanded ketone 217

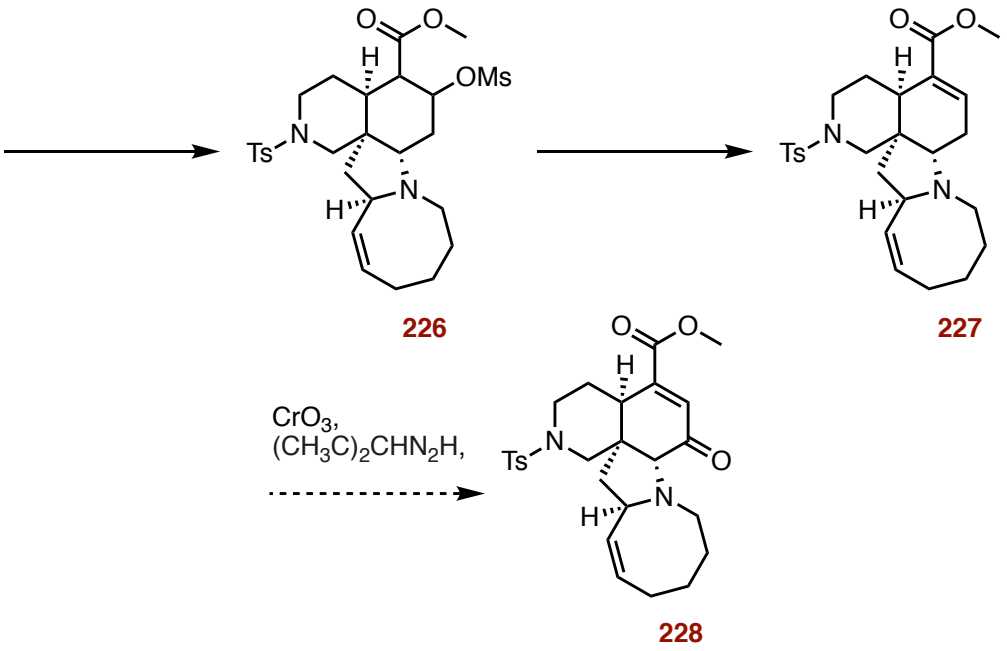
In late-stage studies, the *β*-ketoester **224** was prepared from ketone **217** using Mander's reagent. The *β*-ketoester **224** was then converted into the *β*-hydroxyester **225** using sodium borohydride and the alcohol was converted into the corresponding methanesulfonate **226**. Subsequent *β*-elimination prodcued the unsaturated ester **227**, a valuable intermediate for the future completion of manzamine A **1**. The identity of the final two products were confirmed by mass spectrometry, but there was insufficient material to get the full NMR data (Scheme 3.61).



Scheme 3.61. Synthesis of the functionalised tetracyclic ketone 227

4.2 Future Work

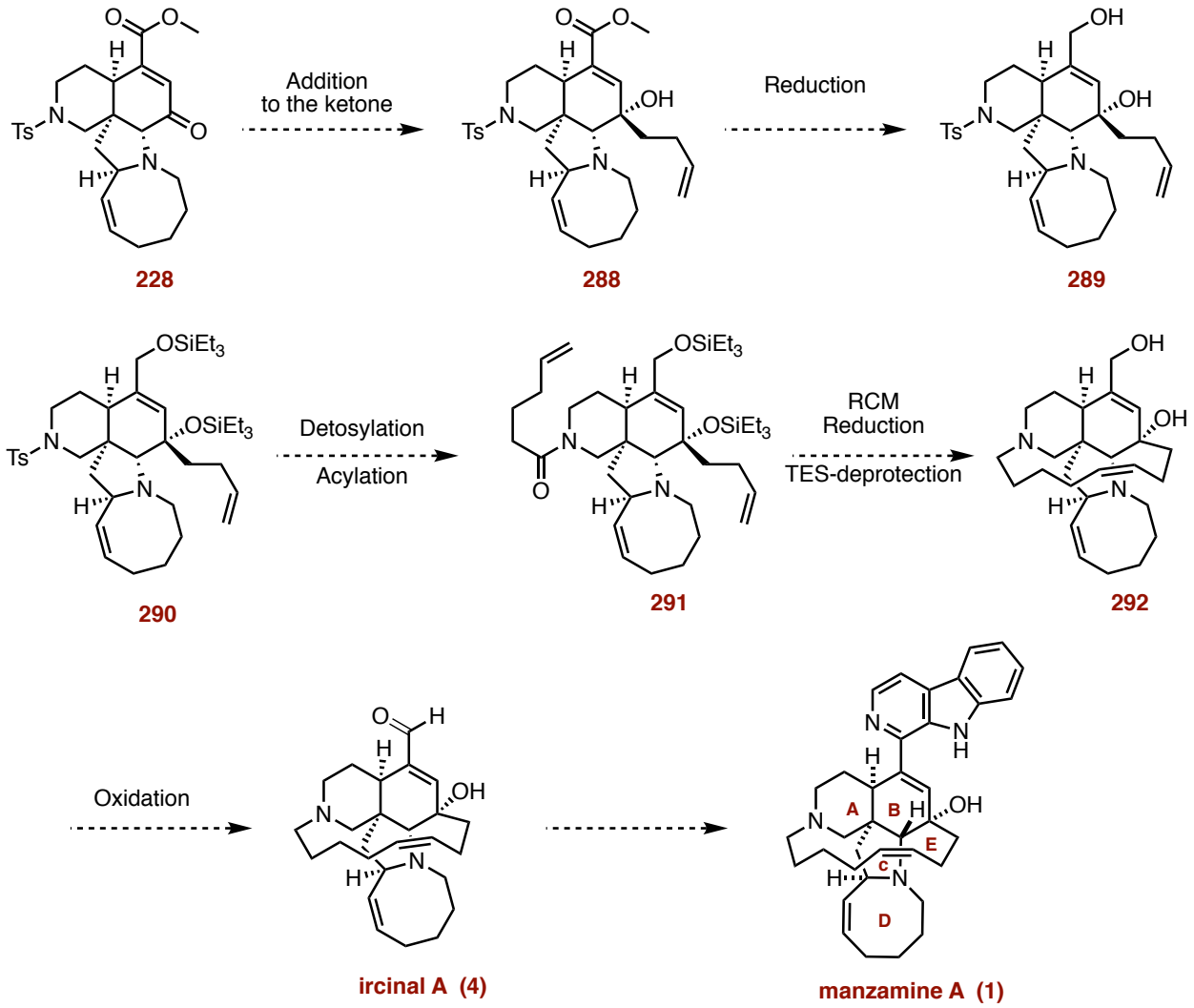
The future work should focus on two main areas. The first area will involve optimization of the conditions for the formation of the mesylate intermediate **226** as well as the reduction of ketone and *β*–elimination to produce the unsaturated ester **227**. With the unsaturated ester **227** in hand, it should be possible to perform as oxidation reaction to give the fully functionalised advanced intermediate **228** using the conditions described by Martin and co-workers (Scheme 3.62).



Scheme 3.62. Proposed synthesis of the fully functionalised advanced intermediate 228

The second area of future research should involve elaboration of the fully functionalised tetracyclic intermediate **228** to give manzamine A **1**. It should be possible to prepare manzamine A **(1)** from the tetracyclic intermediate **228** following the proposed strategy shown in scheme 3.63. Addition of 1-butenylmagnesium bromide to the tetracyclic ketones **228** will provide the ester **288**. Reduction of the ester **288** will result in diol **289** and subsequent double protection of the alcohols will produce the protected ether **290**. *N*-Deprotection of **290** followed by *N*-acylation with 5-hexenoyl chloride will result in amide **291**. The tungsten complex can be used

to close the D ring with high *Z* selectivity, as shown during their use to promote RCM reactions of similar dienes. This could be followed by reduction of the lactam and cleavage of both of TES ethers in **291** to produce the diol **292**. Ircinal A **(4)** can be provided by oxidation of diol **292** which can be converted into manzamine A **(1)** using published procedures (Scheme 3.63).



Scheme 3.63. Envisioned completion of the total synthesis of manzamine A (**1**) from the fully functionalised advanced intermediate 228

5. Experimental Section

5.1 General Experimental Information

Reagents and solvents were purchased from commercial suppliers and were used without further purification, unless otherwise stated.

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame-dried apparatus. THF, toluene, acetonitrile, dichloromethane and diethyl ether were purified using a Pure-SolvTM 500 Solvent Purification System. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminium backed plates F254. TLC plates were visualised under UV light and stained using potassium permanganate solution or acidic ethanolic anisaldehyde solution. Flash column chromatography was performed with silica gel (Geduran Si 60 35-70 μm, purchased from Merck and SilicaGel 60A 40-63 μm, purchased from Fluorochem) as the solid support. Petroleum ether used for column chromatography was the 40–60 °C fraction.

IR spectra were recorded as thin films employing a Shimadzu FTIR-8400S spectrometer equipped with a Pike Technologies MIRacle ATR accessory; selected frequencies (ν_{max}) are reported.

NMR spectra were recorded using dilute solutions in deuterated chloroform or benzene on a Bruker AvanceIII 400 MHz, or Bruker AvanceIII UltraShield 500 MHz spectrometer using the deuterated solvent as the internal deuterium lock. ^{1}H chemical shift data are given in units δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm and δ (C_6D_6) = 7.16 ppm. ^{1}H signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), broad (br), apparent (app) or a combination of these. ^{13}C chemical shift data were recorded with broadband proton decoupling and are given in units δ relative to the solvent where δ ($CDCl_3$) = 77.16 ppm and δ (C_6D_6) = 128.1 ppm. Assignments were determined using 2D NMR spectra (COSY, HSQC and HMBC).

High-resolution mass spectra (HRMS) were recorded using positive chemical ionisation (CI+) and ion impact (EI+) on a Joel MStation JMS-700 instrument or using positive ion electrospray (ESI+) technique on a Bruker micrOTOF-Q instrument by technical staff at the University of Glasgow.

Melting points were recorded using a Barnstead Electrothermal 9100 melting point apparatus. Where no solvent is indicated, the solids obtained from the described procedure were melted directly without recrystallisation. Optical rotations ($[\alpha]_D$) were determined using a Rudolph Research Analytical Autopol IV or V digital polarimeter.

5.2 Nomenclature

The carbon numbering drawn on the molecule corresponds to the conventional manzamine A **(1)** numbering used for NMR signal assignment (Figure 1.5).[1] The molecular structures in the experimental section were named using IUPAC rules.

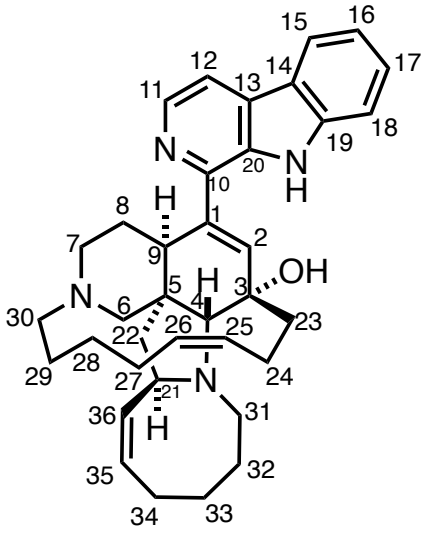
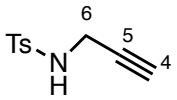


Figure 1.5 Carbon Numbering of Manzamine A (1)

5.3 Experimental Procedures

4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (230)



Chemical Formula: $C_{10}H_{11}NO_2S$
Exact Mass: 209.05

A stirred solution of propargylamine **229** (5.00 g, 90.7 mmol) in anhydrous CH_2Cl_2 (55.0 mL) was cooled to 0 °C and Et_3N (18.3 g, 25.4 mL, 182 mmol) was added dropwise. To this mixture was added *p*-toluenesulfonyl chloride (17.3 g, 90.7 mmol) portionwise. The resulting suspension was slowly warmed to rt and stirred for 12 h followed by dilution with Et_2O (130 mL) and addition of HCl (1 M aqueous solution, 35.0 mL). The phases were separated, and the organic extracts were washed with NH_4Cl (saturated aqueous solution, 35.0 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound (18.5 g, 97%) as a white crystalline solid.

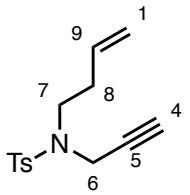
R_f = 0.27 (petroleum ether: EtOAc, 4:1); m.p. 69–71 °C; ν_{max} 3278, 1597, 1423, 1325, 1157, 1093 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.0 Hz, CH-Ts), 4.57 (1H, t, *J* = 6.0 Hz, NH), 3.84 (2H, dd, *J*= 6.0, 2.5 Hz, CH_2-C6), 2.44 (3H, s, CH_3-Ts), 2.11 (1H, t, *J* = 2.5 Hz, CH-C4);

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (C-Ts), 136.3 (C-Ts), 129.5 (CH-Ts), 129.5 (CH-Ts), 127.2 (CH-Ts), 127.2 (CH-Ts), 77.7 (C-C5), 72.9 (CH-C4), 32.7 (CH_2-C6), 21.4 (CH_3-Ts);

HRMS (ESI) calculated for $C_{10}H_{11}NNaO_2S$ ($[M+Na]^+$) calcd. 232.0403 found 232.0398. The observed analytical data are in accordance with previous reports.[47-49]

***N*-(but-3-en-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (172)**



Chemical Formula: $C_{14}H_{17}NO_2S$
Exact Mass: 263.10

To a stirred solution of sulfonamide **230** (13.0 g, 62.1 mmol) in acetone (250 mL) was added K_2CO_3 (34.3 g, 248 mmol) and 4-bromo-1-butene (16.7 g, 12.6 mL, 124 mmol) and the mixture was heated to reflux for 14 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was suspended in EtOAc (120 mL) and water (120 mL) was added. The phases were separated, the aqueous phase was extracted with EtOAc (3 × 60.0 mL), and the combined organic extracts were washed with water (60.0 mL) and brine (60.0 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give orange oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 6:1) afforded the title compound (14.1 g, 96%) as yellow oil.

R_f = 0.51 (petroleum ether: EtOAc, 6:1); ν_{max} 3277, 2978, 2924, 1641, 1599, 1495, 1454, 1346, 1331, 1157, 1090, 1053 cm^{-1};

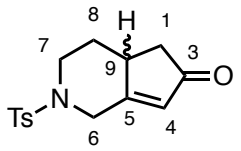
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.3 Hz, CH-Ts), 7.29 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.77 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C9), 5.11 (1H, ddt, *J* = 17.1, 1.6, 1.3 Hz, CH_2-C1), 5.07 (1H, ddt, *J* = 10.2, 1.6, 1.3 Hz, CH_2-C1), 4.14 (2H, d, *J* = 2.5 Hz, CH_2-C6), 3.26 (2H, t, *J* = 7.5 Hz, CH_2-C7), 2.41, (3H, s, CH_3-Ts), 2.35 (2H, tddd, *J* = 7.5, 6.9, 1.3, 1.3 Hz, CH_2-C8), 2.03 (1H, t, *J* = 2.5 Hz, CH-C4);

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C-Ts), 135.9 (C-Ts), 134.5 (CH-C9), 129.4 (CH-Ts), 129.4 (CH-Ts), 127.7 (CH-Ts), 127.7 (CH-Ts),117.2 (CH_2-C1), 76.5 (C-C5), 73.7 (CH-C4), 45.7 (CH_2-C7), 36.4 (CH_2-C6), 32.1 (CH_2-C8), 21.5 (CH_3-Ts);

HRMS (ESI) calculated for $C_{14}H_{17}NNaO_2S$ ($[M+Na]^+$) calcd. 286.0872 found 286.0872.

The observed analytical data are in accordance with previous reports.[47-49]

2-Tosyl-3,4,4a,5-tetrahydro-cyclopenta[c]pyridin-6-one ((±)-161)



Chemical Formula: $C_{15}H_{17}NO_3S$
Exact Mass: 291.09

A solution of $Co_2(CO)_8$ (1.01 g, 2.96 mmol) and TMTU (2.35 g, 17.8 mmol) in degassed toluene (490 mL) was sparged with CO while stirring vigorously and then fitted with a balloon of CO. The resulting dark orange solution was heated to 70 °C and a solution of alkyne **172** (7.00 g, 29.6 mmol) in degassed toluene (30.0 mL) was added and the reaction mixture was stirred for 16 h. The resulting black suspension was concentrated under reduced pressure, the residue was redissolved in EtOAc (30.0 mL), filtered over a pad of silica gel and washed with petroleum ether: EtOAc, 1:1. The resulting orange solution was concentrated under reduced pressure to give an orange solid. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 6:4) afforded the title compound (6.30 g, 81.1%) as a pale yellow crystalline solid.

R_f = 0.23 (petroleum ether: EtOAc, 1:1); m.p. 125–127 °C; ν_{max} 2924, 2854, 1712, 1635, 1350, 1165, 1095 cm^{-1};

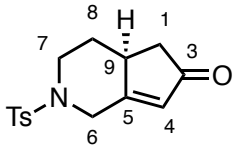
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.36 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.01 (1H, s, CH-C4), 4.75 (1H, d, *J* = 13.3, 1.7 Hz, CH_2-C6), 3.98 (1H, m, CH_2-C7), 3.22 (1H, d, *J* = 13.3 Hz, 1.3 Hz, CH_2-C6), 2.56–2.51 (3H, m, CH_2-C1, CH-C7, CH_2-C9), 2.45 (3H, s, CH_3-Ts), 2.14 (1H, m, CH_2-C8), 2.06–1.99 (1H, m, CH_2-C1), 1.53–142 (1H, dtd, *J* = 13.0, 12.5, 4.0 Hz, CH_2-C8);

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2 (C-C3), 172.2 (C-C5), 144.2 (C-Ts), 133.0 (C-Ts), 130.0 (CH-Ts), 130.0 (CH-Ts), 129.2 (CH-C4), 127.8 (CH-Ts), 127.8 (CH-Ts), 47.5 (CH_2-C6), 45.7 (CH_2-C7), 41.3 (CH_2-C1), 39.2 (CH-C9), 32.1 (CH_2-C8), 21.6 (CH_3-Ts);

HRMS (ESI) calculated for $C_{15}H_{17}NNaO_3S$ ($[M+Na]^+$) calcd. 314.0821 found 314.0815.

The observed analytical data are in accordance with previous reports.[49]

(*S*)-2-Tosyl-3,4,4a,5-tetrahydro-cyclopenta[c]pyridin-6-one (161)



Chemical Formula: $C_{15}H_{17}NO_3S$
Exact Mass: 291.0929

To a stirred solution of dicobalt octacarbonyl (0.60 g, 1.90 mmol) in toluene (30 mL) was added (*R*)-BINAP (1.90 g, 3.04 mmol) in one portion. The mixture was sparged with carbon monoxide for 10 min and stirred under a CO atmosphere for 1 h at 65 °C. A solution of the alkene **172** (1.00 g, 3.80 mmol) in toluene (5 mL) was added dropwise to the reaction. The mixture was stirred at 65 °C for 16 h and then concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether: EtOAc, 1:1) provided the title compound **161** (0.86 g, 78%, 94% *ee*) as a pale yellow solid. Enantiomeric excess was determined by HPLC analysis of intermediate **161**. Column chiral pak OD-H, temperature 25 °C, hexane: propan-2-ol 67:33, flow-rate 1.0 mL.min^{-1}, and retention time 18.0 min.

R_f = 0.23 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{20}$ –96.6 (c= 1.0, $CHCl_3$); m.p. 125–127 °C; ν_{max} 2922, 2853, 1705, 1634, 1348, 1331, 1159, 1092 cm^{-1};

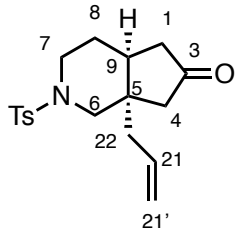
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.99 (1H, s, CH-C4), 4.71 (1H, dd, *J* = 13.3, 1.7 Hz, CH_2-C6), 3.94 (1H, m, CH_2-C7), 3.19 (1H, dd, *J* = 13.3, 1.3 Hz, CH_2-C6), 2.70–2.47 (3H, m, CH_2-C1, CH-C7, CH_2-C9), 2.43 (3H, s, CH_3-Ts), 2.11 (1H, m, CH_2-C8), 2.04–1.97 (1H, m, CH_2-C1), 1.45 (1H, ddt, *J* = 13.0, 12.5, 4.0 Hz, CH_2-C8);

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3 (C-C3), 172.3 (C-C5), 144.3 (C-Ts), 133.0 (C-Ts), 130.0 (CH-Ts), 130.0 (CH-Ts), 129.2 (CH-C4), 127.8 (CH-Ts), 127.8 (CH-Ts), 47.6 (CH_2-C6), 45.8 (CH_2-C7), 41.4 (CH_2-C1), 39.3 (CH-C9), 32.1 (CH_2-C8), 21.7 (CH_3-Ts);

HRMS (ESI) calculated for $C_{15}H_{17}NNaO_3S$ $[M+Na]^+$ calcd. 314.0821 found 314.0815.

The analytical and spectroscopic data are in agreement with those reported in the literature. [47,48]

(4a*S*,7a*R*)-7a-Allyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one (162)



Chemical Formula: $C_{18}H_{23}NO_3S$
Exact Mass: 333.14

To CuI (purified by washing with water, EtOH, Et_2O and pentane followed by drying for a day at 60 °C *in vacuo*, 9.80 g, 51.5 mmol) and LiCl (dried for 1 h at 100 °C *in vacuo*, 2.20 g, 51.5 mmol), was added THF (200 mL) and the mixture was stirred at rt until complete dissolution. The yellow solution was cooled to –10 °C and allylmagnesium chloride (2 M in THF, 26. 0 mL, 51.5 mmol) was added dropwise, upon which the solution turned dark brown. To this was quickly added a solution of enone **162** (5.00 g, 17.2 mmol) and freshly distilled trimethylchlorosilane (2.52 mL, 20.6 mmol) in THF (15.0 mL). The reaction mixture was stirred at −10 °C for 1 h and warmed to rt. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (150 mL), saturated aqueous Na_2CO_3 solution (150 mL) and EtOAc (250 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 250 mL). The combined organic phases were washed with water (450 mL) and brine (450 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give yellow oil. Purification by recrystallization from EtOH (22.0 mL) afforded the title compound (2.40 g, 47 %) as a white crystalline solid.

R_f = 0.53 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{14}$ +33 (c= 0.66, $CHCl_3$); m.p. 124−126 °C; ν_{max} 2922, 2848, 1743, 1338, 1163, 1091 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.35 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.75 (1H, ddt, *J* = 17.8, 10.3, 7.5 Hz, CH-C21), 5.19–5.12 (2H, m, CH_2-C21'), 3.17–3.08 (1H, m, CH_2-C7), 2.99 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.91–2.82 (1H, m, CH_2-C7), 2.59 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.45 (3H, s, CH_3-Ts), 2.47–2.40 (1H, m, CH_2-C22), 2.36 (1H, dd, *J* = 18.8, 8.1 Hz, CH_2-C1), 2.26 (1H, dddd, *J* = 14.0, 7.5, 1.2, 1.2 Hz CH_2-C22), 2.19 (2H, s,

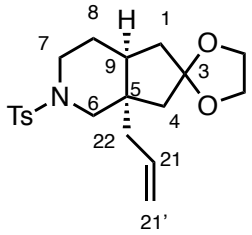
CH_2-C4), 2.13 (1H, ddd, *J* = 13.7, 8.1, 5.7 Hz, CH-C9), 2.07–1.98 (2H, m, CH_2-C1, CH_2-C8), 1.55 (1H, ddt, *J* = 13.7, 5.7, 3.6 Hz, CH_2-C8);

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2 (C-C3), 143.6 (C-Ts), 132.9 (C-Ts), 132.4 (CH-C21), 129.6 (CH-Ts), 129.6 (CH-Ts), 127.4 (CH-Ts), 127.4 (CH-Ts), 119.5 (CH_2-C21'), 49.5 (CH_2-C6), 46.3 (CH_2-C4), 42.5 (CH_2-C7), 41.4 (C-C5), 40.9 (CH_2-C1), 40.3 (CH_2-C22), 36.8 (CH-C9), 25.2 (CH_2-C8), 21.4 (CH_3-Ts);

HRMS (ESI) calculated for $C_{18}H_{23}NNaO_3S$ ($[M+Na]^+$) calcd. 356.1291 found 356.1285.

The observed analytical data are in accordance with previous reports.[47,48]

(4a*S*,7a*R*)-7a-Allyl-2-tosylhexahydro-cyclopenta[c]pyridin-6-one-(1,3)dioxlane ((±)-174)



Chemical Formula: $C_{20}H_{27}NO_4S$
Exact Mass: 377.17

To a solution of the ketone **(±)-162** (1.00 g, 3.00 mmol) in toluene (100 mL) was added ethylene glycol (1.64 mL, 15.0 mmol), trimethyl orthoformate (1.68 mL, 30.0 mmol) and *p*-toluenesulfonic acid monohydrate (85.6 mg, 450 μmol). The mixture was heated at 55 °C for 2 h with vigorous stirring. After cooling the mixture to rt, the mixture was quenched by addition of saturated aqueous $NaHCO_3$ (150 mL) solution. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated in *vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether: EtOAc, 4:1 to 2:1) afforded the title compound **(±)-174** (1.00 mg, 85%) as colorless oil.

R_f = 0.59 (petroleum ether: EtOAc, 1:1); ν_{max} 2926, 2854, 1469,1336, 1253, 1161,1091,1073, 1009 cm^{-1};

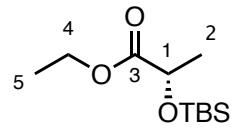
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* = 8.2 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.2 Hz, CH-Ts), 5.77 (1H, ddt, *J* = 17.6, 10.2, 7.3 Hz, CH-C21), 5.19−5.10 (2H, m, CH_2 C21'), 3.90−3.80 (4H, m, OCH_2CH_2O), 3.28 (1H, dt, *J* = 9.6, 4.0 Hz, CH_2-C7), 3.10 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.74−2.66 (1H, m, CH_2-C7), 2.62 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.49−2.41 (1H, m, CH_2-C22), 2.44 (3H, s, CH_3-Ts), 2.16 (1H, dd, *J* = 14.0, 7.3 Hz, CH_2-C22), 1.96−1.85 (4H, m, CH_2-C1, CH-C4, CH_2-C8, CH-C9), 1.82−1.71 (2H, m, CH_2-C1, CH_2-C4), 1.63−1.54 (1H, m, CH_2-C8);

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (C-Ts), 133.6 (C-Ts), 133.5 (CH-C21), 129.5 (CH-Ts), 129.5 (CH-Ts), 127.4 (CH-Ts), 127.4 (CH-Ts), 118.5 (CH_2-C21'), 115.7 (C-C3), 64.1 (OCH_2), 63.7 (OCH_2), 49.0 (CH_2-C7), 45.0 (CH_2-C4), 42.6 (C-C5), 42.1 (CH_2-C6), 40.3 (CH_2-C22), 38.7 (CH-C1), 24.1 (CH_2-C8), 21.4 (CH_3- Ts);

HRMS (ESI) calculated for $C_{20}H_{27}NNaO_4S$ ($[M+Na]^+$) calcd. 400.1553 found 400.1551.

The observed data are in accordance with previous reports.[49]

Ethyl (*S*)-2-(*tert*-butyldimethylsilyloxy)propanoate (235)



Chemical Formula: $C_{11}H_{24}O_3Si$
Exact Mass: 232.15

To a solution of (*S*)-(–)-ethyl lactate **234** (10.3 g, 10.0 mL, 87.2 mmol) in CH_2Cl_2 (70 mL) was cooled to 0 °C, imidazole (7.00 g, 105 mmol) and TBSCl were added (13.9 g, 91.5 mmol). The reaction mixture was stirred at rt for 4 h. The reaction was quenched by the addition of water (70 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 35 mL). The combined organic extracts were washed with water (70 mL) and brine (70 mL) dried over $MgSO_4$ and concentrated under reduced pressure to give a colourless oil. Purification by column chromatography on silica gel (petroleum ether: Et_2O, 20:1) to afford the title compound (15.5 g, 76 %) as a colourless oil

R_f = 0.65 (petroleum ether: EtOAc, 19:1); $[\alpha]_D^{22}$ −39 (c= 2.0, $CHCl_3$); ν_{max} 2953, 2929, 2856, 1751, 1735, 1471, 1251, 1144, 1060 cm^{-1};

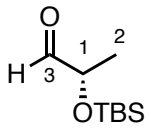
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (1H, q, *J* = 6.8 Hz, CH-C1), 4.16 (2H, m, CH_2-C4), 1.39 (3H, d, *J* = 6.8 Hz, CH_3-C2), 1.26 (3H, t, *J* = 7.5 Hz, CH_3-C5), 0.89 (9H, s, CH_3- TBS), 0.09 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C- 3), 68.3 (C-1), 60.5 (C-4), 25.5 (TBS), 21.1 (C-2), 18.1 (TBS), 14.2 (C-5), −5.0 (TBS), −5.4 (TBS);

HRMS (ESI) calculated for $C_{11}H_{24}NaO_3Si$ ($[M+Na]^+$) calcd. 255.1387 found 255.1379.

The observed data are in accordance with previous reports.[49]

(*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal (236)



Chemical Formula: $C_9H_{20}O_2Si$
Exact Mass: 188.12

A stirred solution of ester **235** (15.0 g, 64.5 mmol) in Et_2O (230 mL) was cooled to −78 °C and DIBAL-H (1 M in hexanes, 64.5 g, 69.8 mL, 64.5 mmol) was added dropwise over 40 min. The resulting colourless solution was stirred for 30 min, warmed to 0° C and the reaction was quenched by the addition of sodium potassium tartrate (saturated aqueous solution, 150 mL). The mixture was stirred at rt until a clear biphasic solution was obtained. The phases were separated, the aqueous phase was extracted with Et_2O (3 × 75 mL) and the combined organic extracts were washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give a colourless oil. Purification by column chromatography on silica gel (petroleum ether–Et_2O 19:1) afforded the title compound (11.6 g, 95.4%) as a colourless oil.

R_f = 0.29 (pentane); $[\alpha]_D^{20}$ −53 (c= 0.20, $CHCl_3$); ν_{max} 2953, 2927, 2856, 1737, 1728, 1249, 1089 cm^{-1};

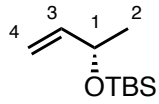
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (1H, d, *J* = 1.3 Hz, CH-C3), 4.07 (1H, qd, *J* = 6.9, 1.3 Hz, CH-C1), 1.25 (3H, d, *J* = 6.9 Hz, CH_3-C2), 0.89 (9H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (C- 3), 73.6 (C-1), 25.5 (TBS), 22.4 (C-2), 18.3 (TBS), −4.93 (TBS), −4.98 (TBS);

HRMS (ESI) calculated for $C_{20}H_{27}NNaO_4S$ ($[M+Na]^+$) calcd. 211.1124 found 211.1125.

The observed data are in accordance with previous reports.[49]

(*S*)-(But-3-en-2-yloxy)(*tert*-butyl)dimethylsilane (163)



Chemical Formula: $C_{10}H_{22}OSi$
Exact Mass: 186.14

A stirred solution of methyltriphenylphosphonium bromide (19.9 g, 55.7 mmol) in Et_2O (200 mL) was added NaHMDS (2 M in THF, 25.9 mL, 51.8 mmol) at rt. The resulting yellow solution was stirred at rt for 1h, and cooled to −20 °C. A solution of aldehyde **236** (7.0 g, 37 mmol) in Et_2O (20 mL) was added dropwise. The reaction mixture was stirred for 10 min, warmed to 0 °C and quenched by the addition of NH_4Cl (saturated aqueous solution, 150 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with water (80 mL) and brine (80 mL), dried over $MgSO_4$ and concentrated at 42 °C at atmospheric pressure. Purification by short column chromatography on silica gel (pentane) followed by distillation at 50 ºC afforded the title compound (2.60 g, 38%) as a colourless solution.

R_f = 0.74 (pentane); $[\alpha]_D^{20}$ 46.5 (c= 0.50, $CHCl_3$); ν_{max} 2954, 2927, 2856, 1153, 1087 cm^{-1};

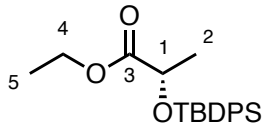
^{1}H NMR (400 MHz $CDCl_3$) δ 5.85 (1H, ddd, *J* = 17.1, 10.4, 5.1 Hz, 1H, CH-C3), 5.19 (1H, ddd, *J* = 17.1, 1.7, 1.7 Hz, CH-C4), 5.00 (1H, ddd, *J* = 10.4, 1.7, 1.7 Hz, CH-C4), 4.31 (1H, qddd, *J* = 6.3, 5.1, 1.7, 1.7, CH-C1), 1.23 (3H, d, *J* = 6.3 Hz, CH_3-C2), 0.91 (9H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (C3), 112.2 (C4), 69.3 (C1), 25.7 (TBS), 24.1 (C2), 18.1 (TBS), −4.79 (TBS), −4.94 (TBS);

HRMS (ESI) calculated for $C_{10}H_{22}NaOSi$ ($[M+Na]^+$) calcd. 209.1332 found 209.1325.

The observed data are in accordance with previous reports. [49]

Ethyl (*S*)-2-((*tert*-butyldimethylsilyloxy)propanoate (237)



Chemical Formula: $C_{21}H_{28}O_3Si$
Exact Mass: 356.1808

To a solution of (*S*)-(–)-ethyl lactate **234** (20.0 g, 169 mmol) in CH_2Cl_2 (400 mL) was added imidazole (23.0 g, 338 mmol) and TBDPSCl (70.0 g, 254 mmol), at 0 °C. The reaction mixture was stirred at rt for 6 h. Then, The reaction was quenched by the addition of NH_4Cl (100 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water (70 mL) and brine (70 mL) dried over $MgSO_4$ and concentrated under reduced pressure to afford a residual oil, which was purified by column chromatography on silica gel with petroleum ether to afford the title compound (42.0 g, 70%) as a colourless oil.

R_f = 0.60 (petroleum ether: EtOAc, 19:1); $[\alpha]_D^{22}$ –61.63 (c= 3.0, $CHCl_3$); ν_{max} 3070, 2954, 2929, 2889, 2856, 1737, 1716, 1471, 1427, 1373, 1265, 1205, 1136, 1112, 1022, 972, 821, 738, 704, 609 cm^{-1};

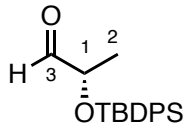
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (4 H, t, *J* = 8.4 Hz, Ar-H), 7.40 (6 H, m, Ar-H), 4.31 (1H, q, *J* = 6.8, CH-C1), 4.04 (2 H, q, *J* = 7.2 Hz, CH_2-C4), 1.40 (3 H d, *J* = 6.8 Hz, CH_3-C2), 1.16 (3 H, t, *J* = 7.2 Hz, CH_3-C5), 1.13 (9 H, s, 3CH_3-TBDPS);

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C3), 135.7 (2 TBDPS), 135.6 (2 TBDPS), 133.5 (TBDPS), 133.1 (TBDPS), 129.6 (TBDPS), 129.5 (2 TBDPS), 127.4 (2 TBDPS), 127.3 (TBDPS), 68.8 (C1), 60.4 (C4), 26.7 (3 TBDPS), 21.1 (C2), 19.1 (TBDPS), 13.9 (C5);

MS (ESI) calculated for $C_{21}H_{28}O_3Si$ ($[M+Na]^+$) calcd. 379.1700, found 379.1698.

The observed data are in accordance with previous reports.[83,84]

(*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal (238)



Chemical Formula: $C_{19}H_{24}O_2Si$
Exact Mass: 312.15

A stirred solution of ester **237** (3.00 g, 8.40 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C and DIBAL-H (1M in hexanes, 10.1 mL, 10.1 mmol) was added dropwise over 10 min. The resulting colourless solution was stirred for 30 min, warmed to 0° C and the reaction was quenched by the addition of sodium potassium tartrate (saturated aqueous solution, 30 mL). The mixture was stirred at rt until a clear biphasic solution was obtained. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated reduced pressure to give a colourless oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc 20:1) to afford the title compound (2.20 g, 83 %) as a colourless oil.

R_f = 0.32 (petroleum ether: EtOAc 19:1); $[\alpha]_D^{20}$ –14.2 (c= 3.0, $CHCl_3$); ν_{max} 3072, 3047, 2968, 2895, 2856, 1737, 1471, 1427, 1111, 962, 821, 732, 702, 613 cm^{-1};

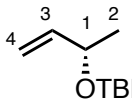
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (1H, d, *J* = 1.3 Hz, CH-C3), 7.71 (4 H, t, *J* = 7.7 Hz, Ar-H), 7.43 (6 H, m, Ar-H) 4.14 (1H, q, *J* = 6.9 Hz, CH-C1), 1.28 (3H, d, *J* = 6.9 Hz, CH_3-C2), 1.17 (9H, s, 3CH_3-TBDPS);

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3 (C3), 135.5 (2 TBDPS), 135.5 (2 TBDPS), 133.1 (TBDPS), 132.8 (TBDPS), 129.8 (2 TBDPS), 129.8 (2 TBDPS), 127.6 (TBDPS), 127.6 (TBDPS), 74.2 (C1), 26.7 (3 TBDPS), 19.0 (C2), 18.2 (TBDPS);

MS (ESI) calculated for $C_{19}H_{24}O_2Si$ ($[M+Na]^+$) calcd. 335.1438, found 335.1441.

The observed data are in accordance with previous reports.[83,84]

***tert*-Butyl {[(1*S*)-1-Methyl-2-propenyl]oxy}diphenylsilane (239)**



Chemical Formula: $C_{20}H_{26}OSi$
Exact Mass: 310.18

To a solution of (methyl)triphenylphosphonium bromide (6.86 g, 19.3 mmol) in dry THF (40 mL) was added KOtBu (1.79 g, 16.0 mmol) at –5 °C, and the mixture was stirred for 3 h at the same temperature. A solution aldehyde **238** (2.00 g, 6.41 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred for 3 h to room temperature. the reaction was quenched by the addition of saturated aq. NH_4Cl (10 mL) The phases were separated, the aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated reduced pressure to give a colourless oil. The obtained residue was purified by column chromatography (petroleum ether: EtOAc, 9.7:0.3) to furnish olefin **45** (1.50 g, 79%).

R_f = 0.85 (petroleum ether: EtOAc, 19:1); $[\alpha]_D^{20}$ –35.6 (c= 10, $CHCl_3$); ν_{max} 3430, 2985, 2885, 1720, 1680, 1520, 1265, 1035, 815, 715cm^{-1};

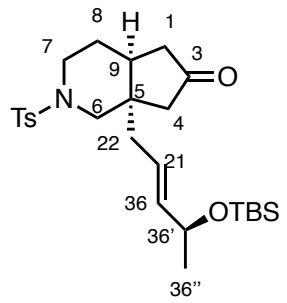
^{1}H NMR (400 MHz $CDCl_3$) δ 7.80 (4 H, t, *J* = 7.7 Hz, Ar-H), 7.47 (6 H, m, Ar-H), 6.01–5.92 (1 H, m, CH-C3), 5.23 (1H, d, *J* = 16.9, Hz, CH-C4), 5.07 (1H, d, *J* = 10.4, Hz CH-C4), 4.42 (1H, m, CH-C1), 1.25 (3H, d, *J* = 6.3 Hz, CH_3-C2), 1.19 (9H, s, $3CH_3$-TBDPS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3 (C3), 135.7 (2 TBDPS), 135.6 (2 TBDPS), 134.4 (TBDPS), 134.0 (TBDPS), 129.3(3 TBDPS), 129.2(3 TBDPS), 127.3 (TBDPS), 127.3 (TBDPS), 112.8 (C4), 70.5 (C1), 27.1 (3 TBDPS), 24.1 (C2), 19.4 (TBDPS);

MS (ESI) calculated for $C_{20}H_{26}NaOSi$ ($[M^+Na]^+$) calcd. 333.1645, found 333.1644.

The observed data are in accordance with previous reports.[83,84]

(4a*S*,7a*R*)-7a-((*S*,*E*)-4-((*tert*-Butyldimethylsilyl)oxy)pent-2-en-1-yl)-2-tosyloctahydro-6*H*-cyclopenta[*c*]pyridin-6-one (240)



Chemical Formula: $C_{26}H_{41}NO_4SSi$
Exact Mass: 491.25

To a solution of the alkene **162** (3.00, 9.00 mmol) and TBS ether **163** (8. 30 g, 45.0 mmol) was added to CH_2Cl_2 (40 mL) and degaesed for 10 mintutes. Hoveyda-Grubbs 2nd generation catalyst (282 mg, 45.0 μmol) was added to reaction mixture. The resulting green solution was heated to reflux for 14 h. The reaction mixture was cooled to rt, MeOH (10 mL) was added, and the mixture was concentrated under reduced pressure to give the crude as a dark brown oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 7:2) afforded the desired product (3.30 g, 75%) as a colourless oil.

R_f = 0.75 (petroleum ether: EtOAc, 2:1); $[\alpha]_D^{17}$ –132 (c= 0.56, $CHCl_3$); ν_{max} 2970, 2926, 2881, 1742, 1597, 1463, 1344, 1253, 1163, 1091 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.30 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.57−5.53 (1H, m, CH-C36), 5.51−5.43 (1H, m, CH-C21), 4.27-4.22 (1H, dq, *J* = 6.5, 6.5 Hz, CH-C36'), 2.94 (2H, m, CH_2-C7), 2.84 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.68 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.40 (3H, s, CH_3-Ts), 2.35-2.26 (2 H, m, CH_2-C1, CH_2-C22), 2.24−2.13 (3H, m, CH_2-C4, CH_2-C22,), 2.08−2.02 (1H, m, CH_2-C9), 2.99−1.92 (2H, m, CH_2-C1, CH_2-C8), 1.53−1.48 (1H, m, CH_2-C8), 1.16 (3H, d, *J* = 6.5 Hz, CH_3-C36"), 0.86 (9H, s, 3CH_3-TBS), 0.02 (3H, s, CH_3-TBS), 0.01 (s, 3H, CH_3-TBS);

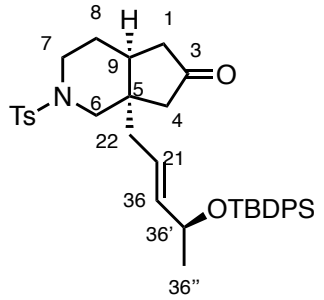
^{13}C NMR (101 MHz, $CDCl_3$) δ 216.3(C-C3), 143.4(C-Ts), 139.7(CH-C36), 132.8(C-Ts), 129.5(CH-Ts), 129.5(CH-Ts), 127.3(CH-Ts), 127.3(CH-Ts), 121.6(CH-21), 68.4(CH-C36'), 49.6(CH_2-C6), 45.8(CH_2-C4), 42.8(CH_2-C7), 41.5(C-C5), 41.2 (CH_2-C1), 38.6(CH_2-C22),

36.5(CH-C9), 25.6(CH_3-36"), 24.3(CH_2-C8), 21.2(CH_3-Ts), 18.0(3CH_3-TBS), −4.8(CH_3-TBS), −4.9(CH_3-TBS);

HRMS (ESI) for $C_{26}H_{41}NNaO_4SSi$ ($[M+Na]^+$) calcd 514.2418, found 514.2407.

The observed data are in accordance with previous reports.[49]

(4a*S*,7a*R*)-7a-((*S*,*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)pent-2-en-1-yl)-2-tosyloctahydro-6*H*-cyclopenta[*c*]pyridin-6-one (242)



Chemical Formula: $C_{36}H_{45}NO_4SSi$
Exact Mass: 615.28

Alkene **162** (900 mg, 2.38 mmol) and TBDPS ether **239** (2.47 g, 7.15 mmol) were dissolved in CH_2Cl_2 (50 mL). The colourless solution was heated to reflux, and Hoveyda-Grubbs 2nd generation catalyst (7.14 mg, 5.00 μmol) was added in two equal portions with 2 h intervals. The resulting green solution was heated to reflux for 14 h. The reaction mixture was cooled to rt, MeOH (3 mL) was added, and the mixture was concentrated under reduced pressure to give the crude as a dark brown oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 7:2) afforded the desired product (0.60 g, 41%) as a colourless oil.

R_f = 0.51 (petroleum ether: EtOAc, 2:1); $[\alpha]_D^{18}$ –68 (c= 0.56, $CHCl_3$); ν_{max} 2963, 2924, 2845, 1739, 1597, 1472, 1427,1344, 1257, 1163, 1091, cm^{-1};

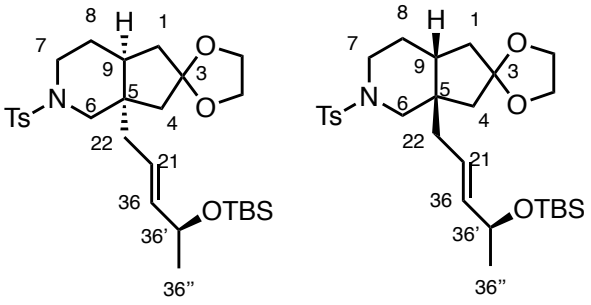
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (4 H, t, *J* = 7.7 Hz, Ar-H-TBDPS), 7.60 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.42–7.29 (8 H, m, CH-Ts, Ar-H-TBDPS), 5.60 (1H, m, CH-C36), 5.33 (1H, m, CH-C21), 4.31 (1H, dq, *J* = 6.5, 6.5 Hz, CH-C36'), 3.12–2.79 (3H, m, CH_2-C7, CH_2-C6), 2.64 – 2.43 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.42 (3H, s, CH_3-Ts), 2.31–2.19 (2H, m, CH_2-C1, CH_2-C22), 2.19–2.01 (3H, m, CH_2-C4, CH_2-C22), 2.00−1.89 (3H, m, CH-C9, CH_2-C8, CH_2-C1), 1.55−1.45 (1H, m, CH_2-C8), 1.16 (3H, d, *J* = 6.5 Hz, CH_3-C36"), 1.05 (9H, s, 3CH_3-TBDPS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.3(C-C3), 143.5(C-Ts), 139.3 (CH-C36), 135.6 (2 TBDPS), 135.6 (2 TBDPS), 134.2 (TBDPS), 134.1 (TBDPS), 133.0(C-Ts), 129.6(CH-Ts), 129.6(CH-Ts), 129.4(2 TBDPS), 129.4(2 TBDPS), 127.5 (CH-Ts), 127.5 (CH-Ts), 127.3 (TBDPS), 127.3 (TBDPS), 122.3(CH-21), 69.7(CH-C36'), 49.7(CH_2-C6), 46.3(CH_2-C4),

42.7(CH_2-C7), 41.5(C-C5), 41.2 (CH_2-C1), 38.4(CH_2-C22), 36.3(CH-C9), 26.8 (3 TBDPS), 25.5(CH_3-36"), 24.3(CH_2-C8), 21.3(CH_3-Ts), 19.8 (3CH_3-TBDPS).

HRMS (ESI) for $C_{26}H_{41}NNaO_4SSi$ ($[M+Na]^+$) calcd 638.2731, found 638.2724.

(4a*S*,7a*R*)-7a-[(2*E*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]pent-2-en-1-yl]-2-(4-_methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolane (175) and (4a*R*,7a*S*)-7a-[(2*E*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]pent-2-en-1-yl]-2-(4-_methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolane (176)



Chemical Formula: $C_{28}H_{45}NO_5SSi$
Exact Mass: 535.28

To a solution of the acetal **(±)-174** (500 mg, 1.32 mmol) and TBS ether **163** (700 mg, 3.90 mmol) in CH_2Cl_2 (20 mL) was heated to reflux. Hoveyda-Grubbs 2nd generation catalyst (3.00 mg, 3.90 μmol) was added to the mixture. The resulting green solution was heated to reflux for 16 h. The reaction mixture was cooled to rt, MeOH (5 mL) was added, and the mixture was concentrated under reduced pressure to give the crude as a dark brown oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 3:1) afforded the protected alcohol **175** and **176** (0.36 g, 51%) as a brown oil.

R_f = 0.53 (petroleum ether: EtOAc, 2:1); ν_{max} 2928, 2855, 1464, 1344, 1256, 1163, 1092, 1073, 1009 cm^{-1};

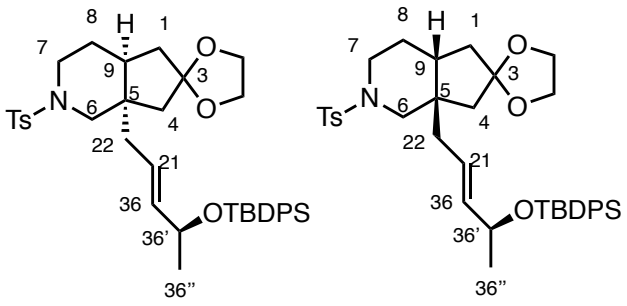
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (4H, d, *J* = 8.0 Hz, CH-Ts), 7.30 (4H, d, *J* = 8.0 Hz, CH-Ts), 5.61−5.53 (2H, m, CH-C36), 5.53−5.45 (2H, m, CH-C21), 4.27-4.21 (2H, dq, *J* = 6.5, 6.2 Hz, CH-C36'), 3.77 (8H, m, OCH_2CH_2O), 3.16–3.02 (2H, m, CH_2-C7), 2.93–2.86 (2H, m, CH_2-C7), 2.94 (2H, d, *J* = 12.0 Hz, CH_2-C6), 2.70-2.60 (2H, d, *J* = 12.0 Hz, CH_2-C6), 2.42 (6H, s, CH_3-Ts), 2.40-2.32 (2H, dd, *J* = 13.9, 8.2 Hz, CH_2-C22), 2.15-2.08 (2H, dd, *J* = 13.9, 8.2 Hz, CH_2-C22), 2.00−1.82 (8H, m, CH_2-C1, CH_2-C4, CH_2-C8, CH-C9), 1.80−1.70 (4H, m, CH_2-C1, CH_2-C4), 1.65−1.55(2H, m, CH_2-C8),1.17 (6H, d, *J* = 6.4 Hz, CH_3-C36"), 0.90 (18H, s, 3CH_3-TBS), 0.04 (6H, s, CH_3-TBS), 0.02 (6H, s, CH_3-TBS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7(2 C-C3), 143.7(2 C-Ts), 140.0(2 CH-C36), 133.0(2 C-Ts), 129.8(CH-Ts), 129.8(CH-Ts), 127.6 (CH-Ts), 127.6 (CH-Ts), 122.9(CH-21), 68.7(2 CH-C36'), 64.6 (2 CH_2-O), 63.9 (2 CH_2-O), 49.6(2 CH_2-C6), 45.5 (2 CH_2-C1), 43.2 (2 CH_2-C5), 42.5(2 CH_2-C7), 40.8 (2 C-C4), 39.1 (2 CH_2-C9), 38.8 (2 CH_2-C22),26.0, 25.5 (2 CH_3-36"), 24.6 (2 CH_2-C8), 21.6 (2 CH_3-Ts), 18.3(2C-TBS), −4.6(CH_3-TBS), −4.8(CH_3-TBS).

HRMS (ESI) for $C_{36}H_{45}NNaO_4SSi$ [($[M+Na]^+$) calcd 558.2680, found 558.2667.

The observed data are in accordance with previous reports. [49]

(4a*S*,7a*R*)-7a-((*S*,*E*)-4-((tert-Butyldiphenylsilyl)oxy)pent-2-en-1-yl)-2tosyloctahydro-6*H*-cyclopenta[*c*]pyridin-6-one-(1,3)dioxlane (295) and (4a*R*,7a*S*)-7a-((*S*,*E*)-4-((tert-Butyldiphenylsilyl)oxy)pent-2-en-1-yl)-2-tosyloctahydro-6*H*cyclopenta[*c*]pyridin-6-one-(1,3)dioxlane (296)



Chemical Formula: $C_{38}H_{49}NO_5SSi$
Exact Mass: 659.31

To a solution of the acetal **(±)-174** (500 mg, 1.32 mmol) and TBDPS ether **239** (1.65 g, 5.30 mmol) in CH_2Cl_2 (35 mL) was degassed with argon for 5 minutes and heated to reflux. Hoveyda-Grubbs 2nd generation catalyst (24.00 mg, 3.96 μmol) was added to the mixture. The resulting green solution was heated to reflux for 16 h. The reaction mixture was cooled to rt, MeOH (5 mL) was added, and the mixture was concentrated under reduced pressure to give the crude as a dark brown oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 3:1) afforded the tittle products (0.64 g, 73%) as a brown oil.

R_f = 0.56 (petroleum ether: EtOAc, 3:1); ν_{max} 2970, 2925, 2852, 1741, 1596, 1469, 1424,1338, 1217, 1163, 1092, cm^{-1};

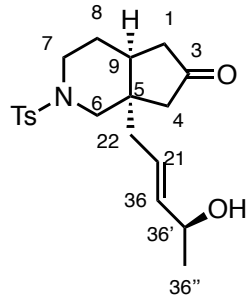
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (8 H, t, *J* = 7.7 Hz, Ar-H-TBDPS), 7.61 (4H, d, *J* = 8.0 Hz, CH-Ts), 7.37 (12 H, m, Ar-H-TBDPS), 7.30 (4H, d, *J* = 8.0 Hz, CH-Ts), 5.61 (2H, m, CH-C36), 5.38 (2H, m, CH-C21), 4.30 (2H, dq, *J* = 6.5, 6.5 Hz, CH-C36'), 3.80 (8H, m, OCH_2CH_2O), 3.22–3.06 (2H, m, CH_2-C7), 2.99–2.90 (2H, m, CH_2-C7), 2.86–2.72 (2H, d, *J* = 12.0 Hz, CH_2-C6), 2.70-2.57 (2H, d, *J* = 12.0 Hz, CH_2-C6), 2.42 (6H, s, CH_3-Ts), 2.29-2.28 (2H, dd, *J* = 13.9, 8.2 Hz, CH_2-C22), 3.09-2.00 (2H, dd, *J* = 13.9, 8.2 Hz, CH_2-C22), 1.93−1.54 (14H,

m, CH_2-C1, CH_2-C4, CH_2-C8, CH-C9), 1.13 (6H, d, J = 6.4 Hz, CH_3-C36"), 1.06 (18H, s, $3CH_3$-TBDPS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1(C-Ts), 143.0(C-Ts), 138.4(2 CH-C36), 135.7(4 TBDPS), 135.6(4 TBDPS), 134.4(2 TBDPS), 134.1(2 TBDPS), 133.4(C-Ts), 129.4(CH-Ts), 129.4(CH-Ts), 129.3(4 TBDPS), 129.2(4 TBDPS), 127.3(CH-Ts), 127.3(CH-Ts), 127.3(4 TBDPS), 123.5(CH-21), 123.3(CH-21), 69.9(CH-C36'), 69.7(CH-C36'), 64.0(2 CH_2-O), 63.6(2 CH_2-O) 49.2(CH_2-C6), 48.9(CH_2-C6), 45.0(CH_2-C4), 44.5(CH_2-C4), 42.9(CH_2-C7), 42.7(CH_2-C7), 42.5(C-C5), 42.1(C-C5), 39.8(CH_2-C1), 39.4(CH_2-C1), 38.7(CH_2-C22), 38.5(CH_2-C22), 38.4(2 CH-C9), 38.4(CH-C9), 26.8(6 TBDPS), 24.5(CH_3-36"), 24.4(CH_3-36"), 24.3(CH_2-C8), 24.1(CH_2-C8), 21.3(CH_3-Ts), 21.3(CH_3-Ts), 19.0(2 CH_3-TBDPS);

HRMS (ESI) for $C_{38}H_{49}NNaO_5SSi$ ($[M+Na]^+$) calcd 682.2993, found 682.2969.

(4a*S*,7a*R*)-7a-((*S*,*E*)-4-Hydroxypent-2-en-1-yl)-2-tosyloctahydro-6*H*-cyclopenta[*c*]pyridin-6-one (164)



Chemical Formula: $C_{20}H_{27}NO_4S$
Exact Mass: 377.17

A solution of silylether **240** (2.50 g, 2.11 mmol) in MeOH (125 mL) was treated with HCl (1 M aqueous solution, 35.6 mL), and stirred at rt for 1 h. The reaction mixture was diluted with EtOAc (20 mL) and quenched by the addition of $NaHCO_3$ (1M aqueous solution, 150 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude as yellowish oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 1:2) afforded the desired products (1.46 g, 76%) as a colourless foam.

R_f = 0.26 (petroleum ether: EtOAc, 1:2); $[\alpha]_D^{18}$ 46 (c= 0.10, $CHCl_3$); ν_{max} 3479, 2970, 2926, 2852, 1737, 1334, 1163, 1091 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58(2H, d, *J* = 8.0 Hz, CH-Ts), 7.30(2H, d, *J* = 8.0 Hz, CH-Ts), 5.68(1H, m, CH-C36), 5.53(1H, m, CH-C21), 4.26(1H, dq, *J* = 6.5, 6.5 Hz, CH-C36'), 3.13(1H, m, CH_2-C7), 3.05(1H, d, *J* = 12.1 Hz, CH_2-C6), 2.74(1H, dt, *J* = 10.3, 5.3 Hz, CH_2-C7), 2.46(1H, dd, *J* = 13.9, 8.2 Hz, CH_2-C22), 2.42(3H, s, CH_3-Ts), 2.32–2.17(3H, m, CH_2-C6, CH_2-C1, CH_2-C22), 2.16(2H, s, CH_2-C4), 2.22–2.02(3H, m, CH_2-C1, CH-C9, CH_2-C8), 1.58(1H, m, CH_2- C8), 1.24(3H, d, *J* = 6.5 Hz, CH_3-C36");

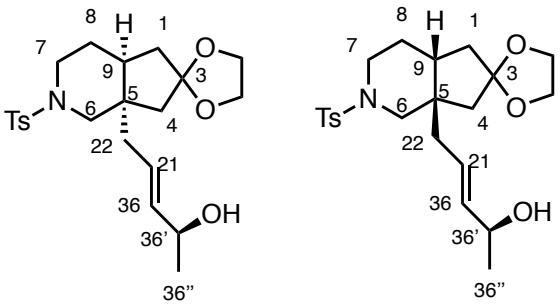
^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2(C-C3), 143.6(C-Ts), 139.4(CH-C36), 133.6(C-Ts), 132.5(CH-Ts), 129.6(CH-Ts), 129.6(CH-Ts), 127.3(CH-Ts), 123.6(CH-C21), 67.9(CH-C36'), 49.1(CH_2-C6), 46.7(CH_2-C4), 42.2(C-C5), 41.4(CH_2-C7), 40.6(CH_2-C1), 38.7(CH_2-C22),

36.8(CH-C9), 24.8(CH_2-C8), 23.1(CH_3-C36"), 21.3(CH_3-Ts);

HRMS (ESI) for $C_{20}H_{27}NNaO_4S$ ($[M+Na]^+$) calcd. 400.1553, found 400.1531.

The observed data are in accordance with previous reports.[47-49]

(2*S*,3*E*)-5-[(4a*S*,7a*R*)-2-(4-Methylbenzenesulfonyl)-octahydrospi-ro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolan]-7a-yl]pent-3-en-2-ol (177) and (2*S*,3*E*)-5-[(4a*R*,7a*S*)-2-(4-methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolan]-7a-yl]pent-3-en-2-ol (178)



Chemical Formula: $C_{22}H_{31}NO_5S$
Exact Mass: 421.1923

A solution of silylethers **175** and **176** (0.25 g, 0.47 mmol) in THF (8 mL) was treated with TBAF (1 M in THF, 0.70 mL, 0.70 mmol), and stirred at rt for 12 h. The reaction mixture was diluted with Et_2O (10 mL) and quenched by the addition of NH_4Cl (saturated aqueous solution, 5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude as yellowish oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 1:2) afforded the title compounds **177** and **178** (130 mg, 68%) as white foam.

R_f = 0.44 (petroleum ether: EtOAc, 1:2); ν_{max} 3476, 2967, 2885, 1597, 1337, 1163, 1092, 1073, 1009 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61(4H, d, *J* = 8.0 Hz, CH-Ts), 7.31(4H, d, *J* = 8.0 Hz, CH-Ts), 5.65(2H, m, CH-C36), 5.57(2H, m, CH-C21), 4.28(2H, m, CH-C36'), 3.88−3.78(8H, m, OCH_2CH_2O), 3.28(2H, m, CH_2-C7), 3.14(2H, d, *J* = 12.0 Hz, CH_2-C6), 2.66–2.44(6H, m, CH_2-C7, CH_2-C6, CH_2-C22), 2.43(6H, s, CH_3-Ts), 2.06(2H, dd, *J* = 13.9, 6.6 Hz, CH_2-C22), 1.95-1.81(8H, m, CH_2-C1, CH_2-C4, CH_2-C8, CH-C9), 1.67−1.54 (6H, m,CH_2-C1, CH_2-C4, CH_2-C8),1.27(6H, d, *J* = 6.4 Hz, CH_3-C36");

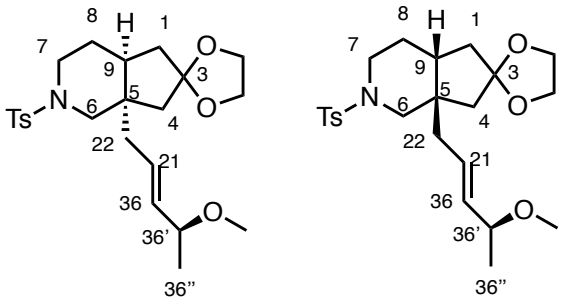
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2(2 C-Ts), 138.6(2 CH-C36), 133.3(2 C-Ts), 129.5(4 CH-Ts), 127.3(4 CH-Ts), 125.2(2 CH-C21), 115.6(2 C-C3), 68.4(2 CH-C36'), 63.7(2 CH_2-O), 48.7(2 CH_2- C6), 45.6(2 CH_2-C1), 42.6(2 C-C5), 42.06(2 CH_2-C7), 39.4(2 CH_2-C4), 38.9(2 CH-C9), 38.9(2 CH_2-C22), 23.8(2 CH_2-C8), 23.1(2 CH_3-36"), 21.3(2 CH_3-Ts);

HRMS (ESI) for $C_{22}H_{31}NNaO_5S$ ($[M+Na]^+$) calcd. 444.1815, found 444.1805.

The observed data are in accordance with previous reports.[49]

(4a*S*,7a*R*)-7a-[(2*E*)-4-Methoxypent-2-en-1-yl]-2-(4-methylbenzenesulfonyl) octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolane] (244)

and(4a*R*,7a*S*)-7a-[(2*E*)-4-methoxypent-2-en-1-yl]-2-(4-methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolane] (244')



Chemical Formula: $C_{23}H_{33}NO_5S$
Exact Mass: 435.2079

To a solution of TBDPS alcohols **244** and **244'** (0.20 g, 0.33 mmol) in PhMe (20 mL) was added ethylene glycol (0.10 mL, 1.6 mmol), trimethyl orthoformate (0.35 gm, 3.3 mmol) and *p*-toluenesulfonic acid monohydrate (9.4 mg, 49 μmol). The resulting solution was heated to 55 °C for 12 h and then cooled to rt and diluted with EtOAc (20 mL). The reaction was quenched by addition of $NaHCO_3$ (saturated aqueous solution, 20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ (saturated aqueous solution, 10mL), water (10 mL) and brine (10 mL), dried over MgSO4 and concentrated under reduced pressure to give a brown oil. Purification by column chromatography on silica gel (petroleum ether–EtOAc, 1:1) afforded an inseparable mixture (1:1) of the methyl ethers **244** and **244'** (58 mg, 41%) as a colourless foam.

R_f = 0.40 (petroleum ether–EtOAc, 1:1); ν_{max} 2972, 2850, 1336, 1163, 1092, 1009 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63(2H, d, *J* = 8.0 Hz, 2 × CH-Ts), 7.33(2H, d, *J*= 8.0 Hz, 2 × CH-Ts), 5.60 (1H, dt, *J*= 15.4, 7.4 Hz, 2 × CH-C21), 5.45(1H, dd, *J*= 15.4, 7.6 Hz, 2 × CH-C36), 3.86–3.78(8H, m, 2 × OCH_2CH_2O), 3.72(1H, dq, *J* =7.6, 6.6 Hz, 2 × CH-C36'), 3.29 (3H, s, CH_3-OMe), 3.24 (3H, s, CH_3-OMe), 3.20–3.13(2H, m, 2 × CH_2-C7), 3.04(1H, m, 2 × CH_2-C6), 2.80–2.68(2H, m, 2 × CH_2-C7), 2.68(1H, d, *J* = 13.1 Hz, CH_2-C6), 2.65(1H, d, *J* = 13.1 Hz, CH_2-C6), 2.43(3H, s, 2 × CH_3-Ts), 2.47–2.38(2H, m, CH_2-C22, CH_2-C22), 2.24(1H,

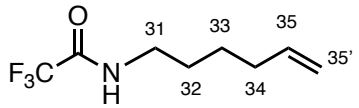
dd, J = 13.9, 7.4 Hz, 2 × CH_2-C22), 1.96–1.88(8H, m, 2 × CH_2-C1, 2 × CH_2-C4, 2 × CH_2-C8, 2 × CH-C9), 1.81–1.69(4H, m, 2 × CH_2-C1, 2 × CH_2-C4), 1.65–1.50(2H, m, 2 × CH_2-C8), 1.26(3H, d, J = 6.6 Hz, CH_3-C36''), 1.25(3H, d, J = 6.6 Hz, CH_3-C36'');

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6(2 × C-Ts), 136.3(CH-C36), 136.2(CH-C36), 133.9(C-Ts), 133.8(C-Ts), 129.7(8 × CH-Ts), 127.7(2 × CH-C21), 127.7(CH-Ts), 127.5(CH-Ts), 116.0(2 × C-C3), 78.1(2 × CH-C36'), 64.5(2 × CH_2O), 63.9(2 × CH_2O), 56.1(CH_3-OMe), 56.0(CH_3-OMe), 49.6(CH_2-C6), 49.5(CH_2-C6), 43.0(2 × C-C5), 42.7(CH_2-C7), 42.6(CH_2-C7), 39.8(2 × CH_2-C1), 39.3 (2 × CH-C9), 39.1 (CH_2-C22), 38.9 (CH_2-C22), 24.7 (CH_2-C8), 24.6 (CH_2-C8), 21.6 (2 × CH_3-C36''), 21.3 (2 × CH_3-Ts);

HRMS (ESI) for $C_{23}H_{33}NNaO_5S$ ($[M+Na]^+$) calcd. 458.1972, found 458.1965.

The observed analytical data are in accordance with previous reports.[49]

2,2,2-Trifluoro-*N*-(hex-5-en-1-yl)acetamide (248)



Chemical Formula: $C_8H_{12}F_3NO$
Exact Mass: 195.09

A stirred solution of trifluoroacetamide **247** (3.80 g, 33.7 mmol) in DMF (250 mL) was treated at 0 °C with NaH (60% dispersion in mineral oil, 1.46 g, 36.8 mmol) and stirred for 15 min at rt. 6-bromo-1-hexene **246** (5.00 g, 30.7 mmol) was added dropwise and the mixture was heated to 50 °C for 12 h. The reaction mixture was cooled to rt, diluted with EtOAc (330 mL) and quenched by the addition of NH_4Cl (saturated aqueous solution, 330 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 160 mL). The combined organic extracts were washed with water (3 × 160 mL) and brine (160 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude as a yellow oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 9:1) afforded the desired product (3.80 g, 64%) as a colourless oil.

R_f = 0.38 (petroleum ether: EtOAc, 9:1); ν_{max} 3302, 2937, 2863, 1700,1559, 1153 cm^{-1};

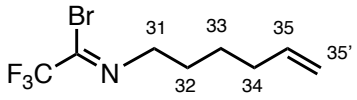
^{1}H NMR (400 MHz, $CHCl_3$) δ 6.58 (1H, br, s, NH), 5.75 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, CH-C35), 4.98 (2H, m, CH_2-C35'), 3.35 (2H, dt, *J* = 7.0, 6.6, Hz, CH_2-C31), 2.08 (2H, tdd, *J* = 7.1, 6.7, 1.5, CH_2-C34), 1.59 (2H, tt, *J* = 8.4, 6.6 Hz, CH_2-C32), 1.43 (2H, tt, *J* = 8.4, 7.1 Hz, CH_2-C33);

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3 (q, $^2J_{C\text{-}F}$ = 36.6 Hz, NCO), 137.7 (CH-C35), 115.7 (q, $^1J_{C\text{-}F}$ = 287.7 Hz, CF_3), 114.9 (CH_2-C35'), 39.6 (CH_2-C31), 32.9 (CH_2-C34), 28.1 (CH_2-C32), 25.7 (CH_2-C33);

HRMS (ESI) for $C_8H_{12}F_3NNaO$ ($[M+Na]^+$) calcd. 218.0871, found 218.0872.

The observed data are in accordance with previous reports. [48,49]

(*Z*)-2,2,2-Trifluoro-*N*-(hex-5-en-1-yl)acetimidoyl bromide (165)



Chemical Formula: $C_8H_{11}BrF_3N$
Exact Mass: 257.00

A solution of PPh_3 (18.1 g, 69.1 mmol) in CH_2Cl_2 (150 mL) was cooled to 0° C and CBr_4 (21.8 g, 65.6 mmol) was added in one portion. The resulting yellow solution was stirred at 0 °C for 5 min and a solution of acetamide **248** (3.28 g, 17.2 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred at 0°C for 2 h and warmed to rt. The mixture was filtered through celite. The filtrate was concentrated as a pale yellow solution. Purification by distillation at 60 °C in full high vacuum afforded the desired product (4.25 g, 95%) as a colourless oil.

R_f = 0.43 (pentane); ν_{max} 2939, 2855, 1702, 1641, 1457, 1295, 1203, 1154 cm $^{-1}$;

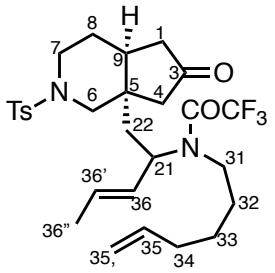
^{1}HNMR (400 MHz, $CDCl_3$) δ 5.81 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, CH-C35), 5.01 (2H, m, CH_2-C35'), 3.60 (2H, tq, *J* = 6.9, 1.5 Hz, CH_2-C31), 2.13 (2H, tddd, *J* = 7.0, 6.7, 1.6, 1.2 Hz, CH_2-C34), 1.77 (2H, tt, *J* = 8.2, 6.9 Hz, CH_2-C32), 1.52 (2H, tt, *J* = 8.2, 7.0 Hz, CH_2-C33);

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (CH-C35), 124.9 (q, $^2J_{C\text{-}F}$ = 43.3 Hz, C-C=N), 116.0 (q, $^1J_{C\text{-}F}$ = 277 Hz, C-CF_3) 114.9 (CH_2-C35'), 57.1 (CH_2-C31), 33.2 (CH_2-C34), 28.0 (CH_2-C32), 26.3 (CH_2-C33).

HRMS (ESI) for $C_8H_{11}{}^{79}BrF_3N$ ($[M+H]^+$) calcd. 258.0027, found 258.0101.

The observed data are in accordance with previous reports. [48,49]

2,2,2-Trifluoro-*N*-(hex-5-en-1-yl)-*N*-((*R*,*E*)-1-((4a*S*,7a*R*)-6-oxo-2-tosyloctahydro-7a*H*-cyclopenta[*c*]pyridin-7a-yl)pent-3-en-2-yl)acetamide (167)



Chemical Formula: $C_{28}H_{37}F_3N_2O_4S$
Exact Mass: 554.24

A solution of alcohol **164** (500 mg, 1.33 mmol) in THF (10 mL) was cooled to –30 °C and NaHMDS (2 M in THF, 1.45 mL, 1.45 mmol) was added dropwise. The resulting suspension was stirred for 1 h, and imidoyl bromide **165** (372 mg, 1.45 mmol) was added. The reaction mixture was stirred at −30 °C for 1 h, warmed to rt, and then added to the reaction mixture K_2CO_3 (274 mg, 1.99 mmol) in degassed toluene (10 mL) and the reaction mixture was heated in a sealed tube at 115 °C for 48 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give the crude as a yellow oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 2:1) afforded the title compound (340 mg, 46%) as a colourless foam.

R_f = 0.54 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{18}$ +657 (c= 0.56, $CHCl_3$); ν_{max} 2926, 2850, 1739, 1680, 1448, 1336, 1184, 1163, 1091, 979 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.01 (1H, ddq, *J* = 15.7, 8.7, 1.5 Hz, CH-C36), 5.81 (2H, m, CH-C35, CH-C36'), 4.98 (2H, m, CH-C35'), 4.07 (1H, dd, *J* = 8.7, 8.7 Hz, CH-C21), 3.56 (1H, d, *J* = 11.2 Hz, CH_2-C6), 3.42−3.23 (3H, m, CH_2-C7, CH_2-C31), 2.54−2.45 (1H, m, CH_2-C22), 2.44 (3H, s, CH_3-Ts), 2.42 (1H, m, CH_2-C6), 2.27−2.01 (8H, m, CH_2-C1, CH_2-C4, CH_2-C8, CH-C9, CH_2-C22, CH_2-C34), 1.97−1.85 (2H, m, CH_2-C1, CH_2-C7), 1.82−1.74 (2H, m, CH_2-C32), 1.73−1.64 (3H, dd, *J* = 6.4, 1.5 Hz, CH_3-C36"), 1.66−1.52 (3H, m, CH_2-C8, CH_2-C33);

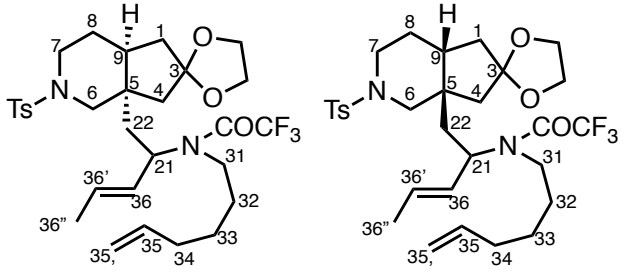
^{13}C NMR (101 MHz, $CDCl_3$) δ 216.2 (C-C3), 156.3 (q, $^2J_{C\text{-}F}$ = 35.0 Hz, NCO), 143.9 (C-Ts), 138.2 (CH-C35), 132.2 (C-Ts), 131.0 (CH-C36'), 129.8 (CH-Ts), 129.8 (CH-Ts), 128.7

(CH-C36), 127.9 (CH-Ts), 127.9 (CH-Ts), 115.9 (q, $^{1}J_{C\text{-}F}$ = 270.1 Hz, C-CF_3), 114.5 (CH_2-C35'), 61.3 (CH-C21), 50.0 (CH_2-C4), 49.2 (CH_2-C31), 47.4 (CH_2-C7), 41.5 (CH_2-C6), 40.2 (C-C5), 38.3 (CH_2-C1), 38.0 (CH-C9), 36.6 (CH_2-C22), 32.9 (CH_2-C34), 28.4 (CH_2-C32), 25.6 (CH_2-C33), 23.1 (CH_2-C8), 21.3 (CH_3-Ts), 17.7 (CH_3-C36'');

HRMS (ESI) for $C_{28}H_{37}N_2NaO_4S$ ($[M+Na]^+$) calcd. 577.2318, found 577.2294.

The observed data are in accordance with previous reports.[47-49]

***N*-[(2*R*,3*E*)-1-[(4a*S*,7a*R*)-2-(4-Methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolan]-7a-yl]pent-3-en-2-yl]-2,2,2-trifluoro-*N*- _(hex-5-en-1-yl)acetamide (179) And *N*-[(2*R*,3*E*)-1-[(4a*R*,7a*S*)-2-(4-methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolan]-7a-yl]pent-3-en-2-yl]-2,2,2-trifluoro-*N*-(hex-5-en-1-yl)acetamide (180)**



Chemical Formula: $C_{30}H_{41}F_3N_2O_5S$
Exact Mass: 598.27

A solution of alcohol **177** and **178** (1.0 gm, 2.4 mmol) in THF (25 mL) was cooled to –30 °C and NaHMDS (2 M in THF, 1.3 mL, 2.6 mmol) was added dropwise. The resulting suspension was stirred for 1 h, and imidoyl bromide **165** (0.6 g, 2.6 mmol) was added. The reaction mixture was stirred at −30 °C for 1 h, warmed to rt, and then added to the reaction mixture K_2CO_3 (0.49 g, 3.6 mmol) in degassed toluene (100 mL) and the reaction mixture was heated in a sealed tube at 115 °C for 48 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give the crude as a yellow oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 2:1) afforded the title compound (0.88 gm, 62%) as a colourless oil.

R_f = 0.40 (petroleum ether–EtOAc, 1:1); ν_{max} 2931, 2889, 2856, 1681, 1598, 1446, 1336, 1267, 1199, 1161, 1091cm^{-1};

^{1}H NMR (400 MHz, CDCl3) δ 7.60−7.54 (4H, m, CH-Ts), 7.32−7.26 (4H, m, CH-Ts), 6.01 (1H, m, CH-C36), 5.82−5.70 (5H, m, CH-C35, CH-C36, CH-C36'), 5.02−4.89 (4H, m, CH_2-C35'), 4.44 (1H, dd, *J* = 13.5, 7.4, 6.8 Hz, CH-C21), 4.07 (1H, m, CH-C21), 3.85–3.72 (8H, m, OCH_2CH_2O), 3.45 (1H, m, CH_2-C7), 3.41−3.17 (7H, m, CH_2-C4, CH_2-C6, CH_2-C7, CH_2-C31), 2.64−2.47 (2H, m, CH_2-C7, CH_2-C22), 2.49−2.35 ((1H, m, CH_2-C6), 2.40 (6H, s, CH_3-

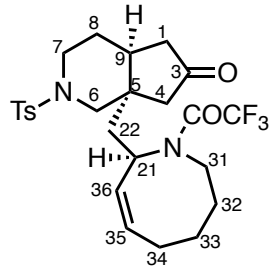
Ts), 2.36−2.24 (4H, m, CH_2-C4, CH_2-C7, 2 CH_2-C22), 2.10−2.02 (5H, m, CH_2-C22, CH_2-C34), 1.99−1.80 (7H, m, CH_2-C1, CH_2-C4, CH-C9, CH_2-C8, CH_2-C31),1.77−1.58 (15H, m, CH_2-C1, CH_2-C4, CH_2-C31, CH_2-C32, CH_3-C36''), 1.56−1.46 (2H, m, CH_2-C8), 1.43−1.33 (4H, m, CH_2-C33);

^{13}C NMR (101 MHz, $CDCl_3$) 156.0 (q, $^2J_{C\text{-}F}$ = 35.3 Hz, NCO), 156.0 (q, $^2J_{C\text{-}F}$ = 35.3 Hz, NCO), 143.4 (C-Ts), 143.2 (C-Ts), 138.2 (CH-C35), 138.2 (CH-C35), 133.2 (C-Ts), 133.2 (C-Ts), 130.9 (CH-C36'), 130.6 (CH-C36'), 129.6 (CH-Ts), 129.5 (CH-Ts), 129.5 (CH-Ts), 129.5 (CH-Ts), 129.2 (CH-C36), 129.1 (CH-C36), 127.4 (CH-Ts), 127.2 (CH-Ts), 127.2 (CH-Ts), 127.2 (CH-Ts), 116.7 (q, $^1J_{C-F}$ = 288.5 Hz, CF_3), 116.7 (q, $^1J_{C-F}$ = 288.5 Hz, CF_3), 115.5, (C-C3), 115.5, (C-C3), 114.9 (CH-C35'), 114.6 (CH-C35'), 64.2 (CH_2O), 64.1 (CH_2O), 64.0 (CH_2O), 63.6 (CH_2O), 61.3 (CH-C21), 57.3 (CH-C21), 48.9 (CH_2-C6), 48.6 (CH_2-C6), 47.8 (CH_2- C4), 47.5(CH_2- C4), 44.8 (CH_2-C31), 44.4 (CH_2-C31), 42.1 (C-C5), 41.7 (CH_2-C7), 41.6 (CH_2-C7), 41.2 (C-C5), 40.5 (CH-C9), 39.9 (CH-C9), 38.9 (CH_2-C1), 38.5 (CH_2-C22), 37.9 (CH_2-C1), 37.0 (CH_2-C22), 32.9 (CH_2-C34), 32.8 (CH_2-C34), 28.5 (CH_2-C32), 27.3 (CH_2-C32), 26.2 (CH_2-C33), 25.8 (CH_2-C33), 23.8 (CH_2-C8), 22.9 (CH_2-C8), 21.3 (CH_3-Ts), 21.3 (CH_3-Ts), 17.7 (CH_3-C36''), 17.6 (CH_3-C36'');

HRMS (ESI) for $C_{30}H_{41}F_3N_2NaO_5S$ ($[M+Na]^+$) calcd 621.2580, found 621.2559.

The observed analytical data are in accordance with previous reports.[49]

(4a*S*,7a*R*)-2-Tosyl-7a-(((*R*,*Z*)-1-(2,2,2-trifluoroacetyl)-1,2,5,6,7,8-hexahydroazocin-2-yl)methyl)octahydro-1*H*-cyclopenta[*c*]pyridin-6-one (168)



Chemical Formula: $C_{25}H_{31}F_3N_2O_4S$
Exact Mass: 512.20

Diene **167** (0.50 g, 0.90 mmol) was dissolved PhMe (10 mL) and added to a solution of Grubb 2nd generation catalyst (15 mg, 18 μmol) in PhMe (500 mL). The resulting brown solution was heated to reflux for 14 h. The reaction mixture was cooled to rt, MeOH (15 mL) was added and the mixture was concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 2:1) afforded the title compound **168** (0.34 mg, 73%) as a colourless foam.

R_f = 0.50 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{17}$ −69.6 (c= 0.56, $CHCl_3$); ν_{max} 2918, 2848, 2256, 1739, 1685, 1448, 1336, 1161, 1091 cm^{-1};

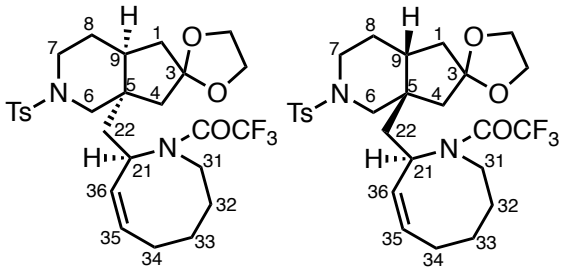
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 8.3 Hz, CH-Ts), 7.35 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.77−5.64 (2H, m, CH-C35, CHC36), 4.58 (1H, m, CH-C21), 3.85 (1H, m, CH_2- C31), 3.60−3.45 (2H, m, CH_2-C7, CH_2-C31), 3.23 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.56−2.48 (2H, m, CH_2-C7, CH_2-C34), 2.43 (3H, s, CH_3-Ts) 2.34−2.26 (2H, m, CH_2-C4), 2.24−2.09 (7H, m, CH_2-C1, CH_2-C6, CH_2-C8, CH-C9, CH_2-C22, CH_2-C34), 2.02−1.94 (3H, m, CH_2-C1, CH_2-C32, CH_2-C33), 1.77−1.70 (2H, m, CH_2-C32, CH_2-C33), 1.64−1.59 (1H, m, CH_2-C8);

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.4 (C-C3), 156.3 (q, $^2J_{C\text{-}F}$ = 35.3 Hz, NCO), 143.8 (C-Ts), 132.2 (C-Ts), 131.1 (CH-C35), 130.4 (CH-C36), 129.7 (CH-Ts), 129.7 (CH-Ts), 127.2 (CH-Ts), 127.2 (CH-Ts), 116.2 (q, $^1J_{C–F}$ = 288.5 Hz, CF_3), 54.5 (CH-C21), 48.6 (CH_2-C4), 48.1 (CH_2-C6), 47.9 (CH_2- C31), 41.5 (CH_2-C7), 40.7 (C-C5), 38.7 (CH_2-C1), 37.6 (CH-C9), 37.2 (CH_2-C22), 28.1 (CH_2-C34), 26.3 (CH_2-C33), 24.5 (CH_2-C32), 23.4 (CH_2-C8), 21.2 (CH_3-Ts);

HRMS (ESI) for $C_{25}H_{31}F_3N_2NaO_4S$ ($[M+Na]^+$) calcd 535.1849, found 535.1842.

The observed data are in accordance with previous reports.[11,12]

1-[(2*R*,3*Z*)-2-{[(4a*S*,7a*R*)-2-(4-Methylbenzenesulfonyl)-octahydrospi-ro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolan]-7a-yl]methyl}-1,2,5,6,7,8-hexahy-droazocin-1-yl]-2,2,2-trifluoroethan-1-one (181) and 1-[(2*R*,3*Z*)-2-{[(4a*R*,7a*S*)-2-(4-_methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolan]-7a-yl]methyl}-1,2,5,6,7,8-hexahydroazocin-1-yl]-2,2,2-trifluoroethan-1-one (182).



Chemical Formula: $C_{27}H_{35}F_3N_2O_5S$
Exact Mass: 556.22

Diene **179** and **180** (0.50 g, 0.83 mmol) was dissolved PhMe (10 mL) and added to a solution of Grubb 2nd generation catalyst (14 mg, 16 μmol) in PhMe (500 mL). The resulting brown solution was heated to reflux for 14 h. The reaction mixture was cooled to rt, MeOH (15 mL) was added and the mixture was concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether–EtOAc, 2:1) afforded the title compounds **181** and **182** (0.34 mg, 73%) as a colourless foam.

R_f = 0.40 (petroleum ether–EtOAc, 1:1); ν_{max} 2954, 2860, 1652, 1592, 1455, 1340, 1229, 1196, 1163, 1140, 1092, 1011 cm^{-1};

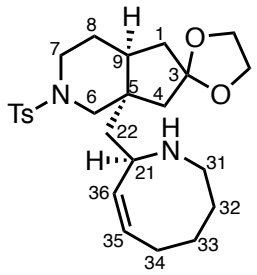
^{1}H NMR (400 MHz, CDCl3) δ 7.64−7.57 (4H, m, CH-Ts), 7.34−7.29 (4H, m, CH-Ts), 5.72 (2H, m, CH-C36, CHC36), 5.60 (2H, m, CH-C35, CHC35), 4.97 (1H, m, CH-C21), 4.69 (1H, m, CH-C21), 3.89–3.70 (9H, m, OCH_2CH_2O, CH_2- C31) 3.60 (1H, m, CH_2- C31), 3.46−3.35 (2H, m, CH_2-C7), 3.32 (1H, d, *J* = 12.1 Hz, CH_2-C6), 3.14 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.63−2.34 (12H, m, CH_2-C6, CH_2-C7, CH_2-C31, CH_3-Ts), 2.29−2.06 (6H, m, CH_2-C1, CH_2-C22, CH_2-C34), 2.01−1.86 (8H, m, CH_2-C4, CH_2-C8, CH_2-C9, CH_2-C22), 1.85−1.75 (6H, m, CH_2-C1, CH_2-C32), 1.73−1.66 (4H, m, CH_2-C4, CH_2-C34), 1.66−1.57 (4H, m, CH_2-C33), 1.56−1.48 (2H, m, CH_2-C8);

^{13}C NMR (101 MHz, $CDCl_3$) 156.3 (q, $^{2}J_{C\text{-}F}$ = 35.3 Hz, NCO), 156.3 (q, $^{2}J_{C\text{-}F}$ = 35.3 Hz, NCO), 143.3 (C-Ts), 138.3 (C-Ts), 135.5 (C-Ts), 134.6 (C-Ts), 134.3 (CH-C36), 133.6 (CH-C36), 129.6 (CH-Ts), 129.6 (CH-Ts), 129.5 (CH-Ts), 129.5 (CH-Ts), 127.5 (CH-C35), 127.5(CH-C35), 127.4 (CH-Ts), 127.4 (CH-Ts), 127.3 (CH-Ts), 127.1 (CH-Ts), 117.4 (q, $^{1}J_{C-F}$ = 288.5 Hz, CF_3), 117.4 (q, $^{1}J_{C-F}$ = 288.5 Hz, CF_3), 115.9 (C-C3), 115.9 (C-C3), 64.2 (CH_2O), 64.2 (CH_2O), 63.8 (CH_2O), 63.8 (CH_2O), 54.6 (CH-C21), 54.0 (CH-C21), 49.0 (CH_2-C6), 49.0 (CH_2-C6), 47.4 (CH_2- C31), 46.7 (CH_2- C31), 46.5 (CH_2-C4), 45.3 (CH_2-C4), 42.3 (C-C5), 42.1 (C-C5), 39.9 (CH_2-C7), 39.9 (CH_2-C7), 38.9 (CH-C9), 38.6 (CH-C9), 37.7 (CH_2-C1), 37.7 (CH_2-C1), 27.0 (CH_2-C33), 27.0 (CH_2-C33), 24.7 (CH_2-C34), 24.7 (CH_2-C34), 24.6 (CH_2-C32), 24.5 (CH_2-C32), 24.3 (CH_2-C22), 24.3 (CH_2-C22), 23.4 (CH_2-C8), 23.4 (CH_2-C8), 21.5 (CH_3-Ts);

HRMS (ESI) for $C_{27}H_{35}F_3N_2NaO_5S$ ($[M+Na]^+$) calcd 579.2111, found 579.2106.

The observed analytical data are in accordance with previous reports.[49]

(4a*S*,7a*R*)-7[a]-{[(2*R*,3*Z*)-1,2,5,6,7,8-Hexahydroazocin-2-yl]methyl}-2-(4-_methylbenzenesulfonyl)-octahydrospiro[cyclopenta[*c*]pyridine-6,2'-[1,3]dioxolane] (183).



Chemical Formula: $C_{25}H_{36}N_2O_4S$
Exact Mass: 460.2396

To a solution of dioxolane **181** (185 mg, 332 μmol) in MeOH (35 mL) was added K_2CO_3 (saturated aqueous solution, 7 mL). The resulting solution was heated to reflux for 16 h. The reaction mixture was cooled to rt, diluted with EtOAc (50 mL) and the reaction was quenched by addition of NH_4Cl (saturated aqueous solution, 50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with NH_4Cl (saturated aqueous solution, 15 mL) water (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a colourless oil. Purification by column chromatography on silica gel (EtOAc–MeOH, 20:1 + 3% NEt_3) afforded the title compound **183** (41.7 mg, 41%) as a colourless foam.

R_f = 0.26 (EtOAc–MeOH, 9:1 + 3% Et_3N); $[\alpha]_D^{18}$= +52 (c = 1.0, $CHCl_3$); ν_{max} 3461,2924, 2852, 1711, 1455, 1398, 1162, 751 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.3 Hz, 2CH-Ts), 7.32 (2H, d, *J* = 8.3 Hz, 2CH-Ts), 5.89 (1H, ddd, *J* = 10.4, 8.1, 8.1 Hz, CH-C35), 5.17 (1H, dd, *J* = 10.4, 9.1 Hz, CH-C36), 3.90–3.76 (5H, m, OCH_2CH_2O, CH-C21), 3.49 (1H, dddd, *J* = 11.7, 5.1, 3.0, 2.0 Hz, CH_2-C31), 3.37 (1H, d, *J* = 12.4 Hz, CH_2-C6), 3.31 (1H, s, br, NH), 3.05 (1H, dd, *J* = 13.7, 9.1 Hz, CH_2-C7), 2.76 (1H, dd, *J* = 13.7, 8.0 Hz, 1H, CH_2-C7), 2.49–2.42 (2H, m, CH_2-C31, CH_2-C34), 2.44 (3H, s, CH_3-Ts), 2.40 (1H, d, *J* = 12.4 Hz, CH_2-C6), 2.22–2.16 (1H, m, CH_2-C34), 2.15 (1H, dd, *J* = 13.8, 3.7 Hz, CH-C22), 2.09–1.99 (1H, m, CH_2-C32), 1.96–1.81 (3H, m, CH_2-C4,

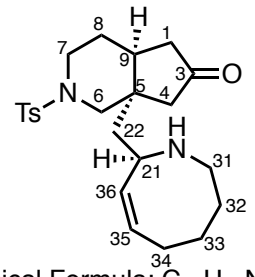
CH_2-C8, CH-C9), 1.81–1.70 (4H, m, CH_2-C1, CH_2-C1, CH_2-C4, CH_2-C33), 1.63–1.54 (1H, m, CH_2-C8), 1.55–1.48 (2H, m, CH_2-C22, CH_2-C32), 1.28–1.19 (1H, m, CH_2-C33);

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5 (C-Ts), 133.8 (C-Ts), 132.8 (CH-C35), 131.5 (CH-C36), 129.7 (CH-Ts), 129.7 (CH-Ts), 127.8 (CH-Ts), 127.8 (CH-Ts), 116.2 (C-C3), 64.6 (CH_2-CH_2O), 64.3 (CH_2- CH_2O), 49.1 (CH_2-C6), 48.3 (CH-C21), 47.8 (CH_2-C4), 45.6 (CH_2-C7), 42.5 (CH_2-C22), 42.3 (C-C5), 41.9 (CH_2-C31), 40.3 (CH-C9), 38.7 (CH_2-C1), 28.7 (CH_2-C33), 28.4 (CH_2-C8), 26.8 (CH_2-C34), 23.5 (CH_2-C32), 21.6 (CH_3-Ts);

HRMS (ESI) for $C_{25}H_{37}N_2O_4S$ ($[M+H]^+$) calcd 461.2471, found 461.2451.

The observed analytical data are in accordance with previous reports.[49]

(4a*S*,7a*R*)-7a-{[(2*R*,3*Z*)-1,2,5,6,7,8-Hexahydroazocin-2-yl]methyl}-2-(4-_methylbenzenesulfonyl)-octahydro-1H-cyclopenta[*c*]pyridine-6-one (169)



Chemical Formula: $C_{23}H_{32}N_2O_3S$
Exact Mass: 416.21

To a solution of amine **183** (90.0 mg, 195 μmol) in MeOH (15 mL) was added HCl (1M aqueous solution, 1.5 mL). The resulting solution was heated to reflux for 6 h. The reaction mixture was cooled to rt, diluted with EtOAc (10 mL) and the reaction was quenched by addition of $NaHCO_3$ (saturated aqueous solution, 10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a colourless oil. Purification by column chromatography on silica gel (EtOAc–MeOH, 9:1 + 3% NEt_3) afforded the title compound (39 mg, 48%) as a colourless foam

R_f = 0.10 (EtOAc–MeOH, 9:1 + 3% NEt_3); $[\alpha]_D^{17}$ +89 (c= 0.56, $CHCl_3$); ν_{max} 3473, 2920, 2846, 1739, 1469, 1446, 1336, 1161, 1092 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ 7.67 (2H, d, *J* = 8.3 Hz, CH-Ts), 6.86 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.74 (1H, ddd, *J* = 10.4, 8.3, 7.9 Hz, CH-C35), 5.23 (1H, ddd, *J* = 10.4, 9.1, 1.5 Hz, CH-C36), 4.98 (1H, brs, NH), 3.97 (1H, m, CH-C21), 3.47 (1H, m, CH_2-C6), 3.24–3.12 (2H, m, CH_2-C7, CH_2-C31), 2.87 (1H, m, CH_2-C31), 2.46−2.36 (2H, m, CH_2-C22, CH_2-C34), 2.23–2.18 (2H, m, CH_2-C6, CH_2-C7), 2.10–1.94 (2H, m, CH_2-C4, CH_2-C1), 1. 90 (3H, s, CH_3-Ts), 1.87–1.63 (6H, m, CH_2-C8, CH-C9, CH_2-C22, CH_2-C32, CH_2-C34), 1.58–1.52 (1H, m, CH_2-C33), 1.47 (1H, m, CH_2-C1), 1.14–0.94 (2H, m, CH_2-C8, CH_2-C33);

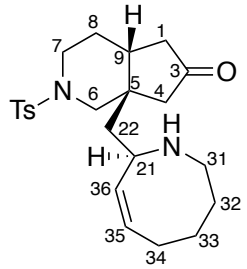
^{13}C NMR (126 MHz, C_6D_6) δ 216.8 (C-C3), 143.4 (C-Ts), 134.1 (C-Ts), 134.1 (CH-C36), 129.9 (CH-Ts), 129.9 (CH-Ts), 128.2 (CH-C35), 127.7 (CH-Ts), 127.7 (CH-Ts), 49.4 (CH_2-C4), 49.4 (CH_2-C21), 49.3 (CH-C6), 45.2 (CH_2-C31), 42.3 (CH_2-C7), 41.1 (CH_2-C5), 40.7 (C-C22), 39.4 (CH-C1), 38.1 (CH-C9), 28.6 (CH_2-C33), 27.1 (CH_2-C34), 26.6 (CH_2-C32), 24.4

(CH_2-C8), 21.2 (CH_3-Ts);

HRMS (ESI) for $C_{23}H_{33}N_2O_3S$ ([M+H]+) calcd 417.2206, found 417.2190.

The observed data are in accordance with previous reports.[47-49]

(4a*R*,7a*S*)-7a-{[(2*R*,3*Z*)-1,2,5,6,7,8-Hexahydroazocin-2-yl]methyl}-2-(4-_methylbenzenesulfonyl)-octahydro-1H-cyclopenta[*c*]pyridine-6-one (255)



Chemical Formula: $C_{23}H_{32}N_2O_3S$
Exact Mass: 416.2134

To a solution of amine **184** (100 mg, 217 μmol) in MeOH (15 mL) was added HCl (1 M aqueous solution, 2 mL). The resulting solution was heated to reflux for 6 h. The reaction mixture was cooled to rt, diluted with EtOAc (15 mL) and the reaction was quenched by addition of $NaHCO_3$ (saturated aqueous solution, 15 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a colourless oil. Purification by column chromatography on silica gel (EtOAc–MeOH, 9:1 + 3% NEt_3) afforded the title compound (28 mg, 31%) as a colourless foam.

R_f = 0.17 (EtOAc–MeOH, 9:1 + 3% NEt_3); $[\alpha]_D^{23}$ −44 (c= 0.56, $CHCl_3$); ν_{max} 3473, 2918, 2846, 1740, 1469, 1446, 1334, 1161, 1091 cm^{-1};

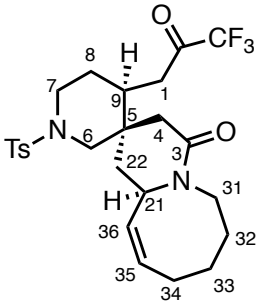
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.3 Hz, CH-Ts), 7.35 (2H, d, *J* = 8.3 Hz, CH-Ts), 5.89 (1H, ddd, *J* = 10.4, 8.1, 8.1 Hz, CH-C35), 5.21 (1H, dd, *J* = 10.4, 8.9 Hz, CH-C36), 3.73 (1H, ddd, *J* = 8.9, 6.6, 6.6 Hz, CH-C21), 3.36(1H, d, *J* = 12.3 Hz, CH_2-C6), 3.34–3.29 (1H, m, CH_2-C7), 2.97 (1H, dd, *J* = 12.1, 9.3 Hz, CH_2-C31), 2.78 (1H, dd, *J* = 12.1, 7.9 Hz, CH_2-C31), 2.61 (1H, dd, *J* = 10.0, 5.5 Hz, CH_2-C7), 2.43 (3H, s, CH_3-Ts), 2.35–2.26 (5H, m, CH_2-C1, CH_2-C4, CH_2-C4, CH_2-C6, CH_2-C34), 2.21–2.08 (4H, m, CH-C8, CH_2-C9, CH_2-C22, CH_2-C34), 1.97 (1H, dd, *J* = 19.5, 9.0 Hz, CH_2-C1), 1.89 (1H, m, CH_2-C33) 1.77 (1H, m, CH_2-C33) 1.65–1.58 (2H, m, CH_2-C8, CH_2-C22), 1.54 (1H, dddd, *J* = 15.0, 11.1, 7.9, 3.0 Hz, CH_2-C32), 1.33–1.26 (1H, m, CH_2-C32);

^{13}C NMR (126 MHz, $CDCl_3$) 217.0 (C-C3), 143.8 (C-Ts) 132.7 (C-Ts), 132.0 (CH-C35), 131.3 (CH-C36), 129.8 (CH-Ts), 129.8 (CH-Ts), 127.8 (CH-Ts), 127.8 (CH-Ts), 49.5 (CH_2-C6), 49.1 (CH_2-C1), 48.3 (CH-C21), 45.3 (CH_2-C31), 42.2 (CH_2-C7), 42.1 (CH_2-C22), 41.1 (C-C5), 39.8 (CH_2-C4), 38.4(CH-C9), 28.2 (CH_2-C33), 28.2 (CH_2-32), 26.6 (CH_2-34), 24.5 (CH_2-C8), 21.7 (CH_3-Ts);

HRMS (ESI) for $C_{23}H_{33}N_2O_3S$ ($[M+H]^+$) calcd 417.2206, found 417.2190.

The observed analytical data are in accordance with previous reports.[49]

(2'R,4S,11a'R,Z)-1-Tosyl-4-(3,3,3-trifluoro-2-oxopropyl)-1',6',7',8',9',11a'-hexahydrospiro[piperidine-3,2'-pyrido[1,2-a]azocin]-4'-one (249)



Chemical Formula: $C_{25}H_{31}F_3N_2O_4S$
Exact Mass: 512.20

To a solution of the trifluoroamide **168** (60 mg, 0.11 mmol) in MeOH (15 mL) was added saturated aqueous K_2CO_3 (2 mL) and the mixture was stired with vigorous stirring at rt for 72 h. The mixture was filtered through a short pad of celite and washed with DCM (50 mL). The organic phases were concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether: EtOAc, 2:1) afforded the title compound **249** (72 mg, 92%) as a colourless solid.

R_f = 0.53 (petroleum ether: EtOAc, 1:1); $[\alpha]_D^{20}$+99 (c = 0.5, $CHCl_3$); m.p. 166−170°C; ν_{max} 2926, 2854, 1763, 1631, 1454, 1338, 1207, 1149, 1091, 979, 750 cm^{-1};

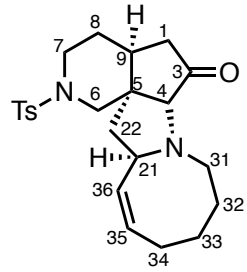
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.30 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.86 (1H, dt, *J* = 10.7, 8.4 Hz, CH-C35), 5.24 (1H, dd, *J* = 10.7, 7.7 Hz, CH C36), 4.34−4.25 (1H, m, CH-C21), 4.07 (1H, dd, *J* = 13.7, 10.1 Hz, CH_2-C31), 3.17 (1H, dd, *J* = 13.7, 7.0 Hz, CH_2-C31), 3.24−3.15 (1H, m, CH_2-C7), 3.01 (1H, d, *J* = 12.0 Hz, CH_2-C6), 2.71−2.64 (1H, m, CH_2-C7), 2.62 (1H, dd, *J* = 18.5, 2.8 Hz, CH_2-C1), 2.49 (1H, d, *J* = 12.0 Hz, CH_2-C6), 2.48−2.42 (1H, m, CH_2-C1), 2.39 (3H, s, CH_3-Ts), 2.36−2.17 (4H, m, CH_2-C4, CH_2-C22, CH_2-C34), 2.14 (1H, d, *J* = 16.9 Hz, CH_2-C33), 2.08−1.92 (4H, m, CH-C9, CH_2-C8, CH_2-C32), 1.68−1.59 (1H, m, CH_2-C4), 1.46−1.33 (4H, m, CH_2-C8, CH_2- C22, CH_2-C33);

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.2 (q, J^2_{C-F} = 36.8 Hz, $COCF_3$), 167.5 (C-C3), 144.0 (C-Ts), 134.7 (CH C35), 132.8 (C-Ts), 139.9 (CH-Ts), 139.9 (CH-Ts), 128.7 (CH-C36), 127.5

(CH-Ts), 127.5 (CH-Ts), 116.7 (q, J^1_{C-F} = 287.9 Hz, CF_3), 49.8 (CH-C21), 49.8 (CH_2- C6), 43.0 (CH_2-C7), 42.5 (CH_2-C31), 38.9 (CH_2-C4), 37.2 (CH_2-C22), 36.2 (CH-C9), 34.8 (C-C5), 34.6 (CH_2-C1), 27.7 (CH_2-C8), 26.5 (CH_2-C34), 26.3 (CH_2-C33), 25.7 (CH_2-C32), 21.2 (CH_3-Ts);

HRMS (ESI) for $C_{25}H_{31}F_3N_2NaO_4S$ ($[M+Na]^+$) calcd 535.1849, found 535.1846.

(1*R*,3*R*,4*Z*,11*R*,14*S*)-17-(4-Methylbenzenesulfonyl)-10,17-diazatetracy-clooctadec-4-en-12-one (170)



Chemical Formula: $C_{23}H_{30}N_2O_3S$
Exact Mass: 414.1977

To a solution of amine **169** (62.3 mg, 150 μmol) in THF (10 mL) was added a solution of pyrrolidone hydrotribromide (81.6 mg, 165 μmol) in THF (3 mL) and the resulting orange solution was stirred at rt for 24 h. A solution of DMAP (36.5 mg, 299 μmol) in THF (1 mL) was added and the reaction mixture was stirred for 48 h at rt. The reaction was quenched by addition of $Na_2S_2O_3$ (saturated aqueous solution, 5 mL) and stirred for 30 min, EtOAc (30 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with $Na_2S_2O_3$ (saturated aqueous solution, 10 mL), Na_2CO_3 (saturated aqueous solution, 10 mL) and brine (10 mL), dried over Na_2CO_3 and concentrated under reduced pressure to give an orange oil. Purification by column chromatography on silica gel (petroleum ether–EtOAc, 2:1) afforded the title compound (19.9 mg, 32%) as a yellow foam:

R_f = 0.23 (petroleum ether–EtOAc, 3:2); $[\alpha]_D^{18}$ −44 (c= 0.56, $CHCl_3$); ν_{max} 2922, 2852, 1743, 1462, 1339,1305, 1164, 1141, 1091 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ 7.82 (2H, d, *J* = 8.3 Hz, CH-Ts), 6.82 (2H, d, J = 8.3 Hz, CH-Ts), 5.58(1H, dddd, *J* = 10.9, 8.8, 7.7, 1.3 Hz, CH-C35), 5.28 (1H, dd, *J* = 10.9, 6.5 Hz, CH-C36), 3.50 (1H, ddd, *J* = 8.1, 6.6, 6.5 Hz, CH-C21), 3.53 (1H, d, *J* = 12.4 Hz, CH_2-C6), 3.44 (1H, ddd, *J* = 12.6, 4.9, 4.1 Hz, CH_2-C31), 3.26 (1H, ddd, *J* = 11.3, 5.4, 4.0 Hz, CH_2-C7), 2.99(1H, s, CH-C4), 2.94 (1H, ddd, *J* = 12.6, 6.7, 6.2 Hz, CH_2-C31), 2.56–2.48 (1H, m, CH_2-34), 2.44 (1H, d, *J* = 12.4 Hz, CH_2-C6), 2.32 (1H, ddd, *J* = 11.3, 10.0, 3.2 Hz, CH_2-C7), 2.06 (1H, dddd, *J* = 13.4, 9.2, 8.8, 4.5 Hz, CH_2 C34), 1.96 (3H, s, CH_3-Ts), 1.93 (1H, ddd, *J* = 17.8, 7.3, 1.1 Hz, CH_2-C1),

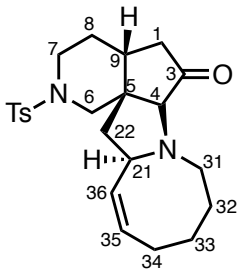
1.70 (1H, dd, J = 13.6, 8.1 Hz, CH_2-C22), 1.68–1.56 (3H, m, CH_2-C1, CH_2-C32), 1.42–1.36 (3H, m, CH-C9, CH_2-C22, CH_2-C33), 1.33–1.25 (1H, m, CH_2-C33), 1.31–1.21 (1H, m, CH_2-C8), 0.85 (1H, dddd, J = 13.7, 10.0, 9.1, 4.0 Hz, CH_2-C8);

^{13}C NMR (126 MHz, C_6D_6) δ 215.3 (C-C3), 143.4 (C-Ts), 134.9 (C-Ts), 132.6 (CH-C36), 130.6 (CH-C35), 129.8 (CH-Ts), 129.8 (CH-Ts), 128.6 (CH-Ts), 128.6 (CH-Ts), 72.5 (CH-C4), 59.8 (CH-C21), 52.4 (CH_2-C6), 49.3 (CH_2-C31), 48.9 (C-C5), 44.9 (CH_2-C22), 44.8 (CH_2-C1), 44.3 (CH_2-C7), 36.9 (CH-C9), 28.3 (CH_2-C8), 27.6 (CH_2-C33), 26.5 (CH_2-C32), 26.0 (CH_2-C34), 21.3 (CH_3-Ts);

HRMS (ESI) for $C_{23}H_{31}N_2O_3S$ ($[M+H]^+$) calcd 415.2050, found 415.2044.

The observed data are in accordance with previous reports.[47-49]

(1*S*,3*R*,4*Z*,11*S*,14*R*)-17-(4-Methylbenzenesulfonyl)-10,17-diazatetracy-clooctadec-4-en-12-one (294)



Chemical Formula: $C_{23}H_{30}N_2O_3S$
Exact Mass: 414.1977

To a solution of amine **255** (137 mg, 329 μmol) in THF (10 mL) was added a solution of pyrrolidone hydrotribromide (196 mg, 395 μmol) in THF (3 mL) and the resulting orange solution was stirred at rt for 24 h. A solution of DMAP (80.4 mg, 658 μmol) in THF (1 mL) was added and the reaction mixture was stirred at rt for 48 h. The reaction was quenched by addition of $Na_2S_2O_3$ (saturated aqueous solution, 5 mL) and stirred for 30 min, EtOAc (30 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with $Na_2S_2O_3$ (saturated aqueous solution, 10 mL), Na_2CO_3 (saturated aqueous solution, 10 mL) and brine (10 mL), dried over Na_2CO_3 and concentrated under reduced pressure to give an orange oil. Purification by column chromatography on silica gel (petroleum ether–EtOAc, 2:1) afforded the title compound (62.0 mg, 45%) as a yellow foam:

R_f = 0.34 (petroleum ether–EtOAc, 3:2); $[\alpha]_D^{18}$ +23 (c= 0.10, $CHCl_3$); ν_{max} 2922, 2853, 1742, 1597, 1449, 1344, 1163, 1092 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.0 Hz, 2CH-Ts), 7.32 (2H, d, *J* = 8.0 Hz, 2CH-Ts), 5.55−5.42 (2H, m, CH-C35, CH-C36), 3.60 (1H, ddd, *J* = 8.3, 8.2, 2.6 Hz, CH-C21), 3.17 (1H, ddd, *J* = 11.7, 5.2, 5.2 Hz, CH_2-C7), 3.06 (1H, d, *J* = 11.8 Hz, CH_2-C6), 3.02 (1H, ddd, *J* = 12.4, 12.3, 5.3 Hz, CH_2-C31), 2.86 (1H, dddd, *J* = 14.2, 7.1, 7.0, 7.0 Hz, CH_2-C34), 2.73 (1H, ddd, *J* = 11.7, 9.5, 3.6 Hz, CH_2-C7), 2.66 (1H, d, *J* = 11.8 Hz, 1H, CH_2-C6), 2.62–2.53 (2H, m, CH_2-C1, CH_2-C31), 2.43 (3H, s, CH_3-Ts), 2.43 (1H, s, CH-C4), 2.37–2.28 (1H, m, CH-C9),

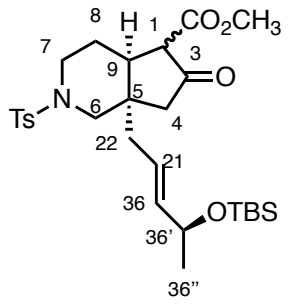
2.09 (1H, dd, *J*= 13.2, 8.2 Hz, CH_2-C22), 2.05–1.93 (3H, m, CH_2-C1, CH_2-C8, CH_2-C34), 1.80 (1H, dd, *J*= 13.2, 8.3 Hz, CH_2-C22), 1.71 (1H, ddd, *J*= 15.6, 6.4, 5.3 Hz, CH_2-C32), 1.56–1.43 (m, 4H, CH_2-C8, CH_2-C32, CH_2-C33);

^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9 (C3), 143.8 (C-Ts), 133.0 (CH-C11), 132.8 (C-Ts), 129.9 (CH-Ts), 129.9 (CH-Ts), 127.7 (CH-Ts), 127.7 (CH-Ts), 127.4 (CH-C36), 75.6 (CH-C4), 64.7 (CH-C21), 54.1 (CH_2-C31), 50.6 (CH_2-C6), 49.0 (C-C22), 43.4 (CH_2-C5), 43.0 (CH_2-C7), 41.1 (CH_2-C1), 35.9 (CH-C9), 26.8 (CH_2-C33), 25.9 (CH_2-C8), 24.6 (CH_2-C34), 23.9 (CH_2-C32), 21.7 (CH_3-Ts);

HRMS (ESI) for $C_{23}H_{31}N_2O_3S$ ($[M+H]^+$) calcd 415.2050, found 415.2044.

The observed analytical data are in accordance with previous reports.[49]

methyl (4a*S*,7a*R*)-7a-((S,E)-4-((*tert*-butyldimethylsilyl)oxy)pent-2-en-1-yl)-6-oxo-2-tosyloctahydro-1H-cyclopenta[c]pyridine-5-carboxylate (260)



Chemical Formula: $C_{28}H_{43}NO_6SSi$
Exact Mass: 549.26

To a stirred solution of NaH (150 mg, 6.10 mmol) and dimethyl carbonate (916 mg, 10.1 mmol) in DME (5 mL) was added a solution of compound **240** (1 g, 2.04 mmol) in DME (5 mL) followed by methanol (2 drops) at room temperature under argon. The mixture was heated to 90 °C and stirred for 2 h. The mixture was then diluted with Et_2O (15 mL) and quenched by the addition of NH_4Cl (saturated aqueous solution, 10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel chromatography (petroleum ether–EtOAc, 7:3) to afford the title compound (1.01 g, 90%) as colorless oil. (Characterization for a major isomer)

R_f = 0.46 (petroleum ether–EtOAc, 7:3); ν_{max} 2970, 2926, 2854, 1739, 1597, 1463, 1344, 1253, 1163, 1091, 1053 cm^{-1};

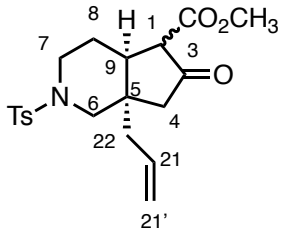
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.66 (1H, m, CH-C36), 5.60−5.47 (1H, m, CH-C21), 4.30 (1H, dq, *J* = 6.5, 6.5 Hz, CH-C36'), 3.70 (3H, s, CO_2CH_3), 3.49 (1H, m, CH_2-C7), 3.07 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.74−2.59 (2H, m, CH_2-C6, CH_2-C22), 2.44 (3H, s, CH_3-Ts), 2.36 (1H, d, *J* = 12.1 Hz, CH_2-C1), 2.29-2.14 (3 H, m, CH_2-C22, CH_2-C7, CH-C9), 2.00 (2H, d, *J* = 12.0 Hz, CH-Ts), 2.08−2.02

(1H, d, *J* = 12.1 Hz, CH_2-C4), 1.82 (1H, m, CH_2-C8), 1.65 (1H, m, CH_2-C4), 1.30−1.14 (4H, m, CH_2-C8, CH_3-C36"), 0.86 (9H, s, 3CH_3-TBS), 0.02 (3H, s, CH_3-TBS), 0.01 (s, 3H, CH_3-TBS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2(C-C3), 168.32 (CO_2CH_3), 143.9(C-Ts), 140.5(CH-C36), 132.8(C-Ts), 129.9(CH-Ts), 129.9(CH-Ts), 127.5 (CH-Ts), 127.5 (CH-Ts), 121.5(CH-21), 68.7(CH-C36'), 55.83 (CO_2CH_3), 49.3(CH_2-C7), 47.9(CH_2-C6), 41.1(C-C22), 40.2(CH_2-C4), 37.5 (CH_2-C1), 38.6(CH_2-C5), 37.4(CH-C9), 25.8(CH_3-36"), 24.6(CH_2-C8), 21.2(CH_3-Ts), 18.2(3CH_3-TBS), −4.6(CH_3-TBS), −4.8(CH_3-TBS);

HRMS (ESI) for $C_{28}H_{43}NNaO_6SSi$ ($[M+Na]^+$) calcd 572.2473, found 572.2472.

methyl(4aS,7aR)-7a-allyl-6-oxo-2-tosyloctahydro-1H-cyclopenta[c]pyridine-5-carboxylate (265)



Chemical Formula: $C_{20}H_{25}NO_5S$
Exact Mass: 391.1453

To a stirred solution of NaH (20 mg, 0.90 mmol) and dimethyl carbonate (135 mg, 1.50 mmol) in DME (1 mL) was added a solution of compound **162** (100 mg, 0.30 mmol) in DME (2 mL) followed by methanol (1 drop) at room temperature under argon. The mixture was heated to 90 °C and stirred for 2 h. The mixture was then diluted with Et_2O (5 mL) and quenched by the addition of NH_4Cl (saturated aqueous solution, 3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 2 mL). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel chromatography (petroleum ether–EtOAc, 7:3) to afford the title compound (57 mg, 48%) as colorless foam.

R_f = 0.39 (petroleum ether–EtOAc, 7:3); ν_{max} 2951, 2854, 1737, 1365, 1217, 1165, 1091, 1054 cm^{-1};

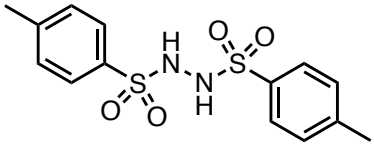
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.77 (1H, ddt, *J* = 17.8, 10.3, 7.5 Hz, CH-C21), 5.25–5.09 (2H, m, CH_2-C21'), 3.70 (3H, s, CO_2CH_3), 3.53 (1H, m, CH_2-C7), 3.06 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.75–2.58 (2H, m, CH_2-C7, CH_2-C6), 2.44 (3H, s, CH_3-Ts), 2.35–2.14 (3H, m, CH_2-C22, CH_2-C1), 2.09 (2H, s, CH_2-C4), 1.82 (1H, ddd, *J* = 13.7, 8.1, 5.7 Hz, CH-C9), 1.67–1.55 (1H, m, CH_2-C8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6 (C-C3), 168.55 (CO_2CH_3), 144.4 (C-Ts), 132.7 (C-Ts), 130.3 (CH-C21), 129.6 (CH-Ts), 129.6 (CH-Ts), 127.9 (CH-Ts), 127.9 (CH-Ts), 112.0

(CH_2-C21'), 55.31 (CO_2CH_3), 49.7 (CH_2-C6), 48.4 (CH_2-C4), 41.5 (CH_2-C7), 41.4 (C-C5), 40.9 (CH_2-C1), 40.4 (CH_2-C22), 39.4 (CH-C9), 22.9 (CH_2-C8), 21.9 (CH_3-Ts);

HRMS (ESI) for $C_{28}H_{43}NNaO_6SSi$ ($[M+Na]^+$) calcd 414.1346, found 414.1336.

***N*,*N*′-ditosylhydrazine (271)**



Chemical Formula: $C_{14}H_{16}N_2O_4S_2$
Exact Mass: 340.06

To a stirred solution of *p*-toluenesulfonyl hydrazide **272** (1.0 g, 5.3 mmol) and *p*-toluenesulfonyl chloride (1.5 g, 8.0 mmol) in anhydrous CH_2Cl_2 (6 mL) at room tempertatre was added pyridine (0.63 mL, 8.0 mmol) dropwise and the resulting solution was stirred for 2 h. Et_2O (200 mL) and H_2O (100 mL) were added and stirred at 0 °C for 15 min. The white crystal was collected and washed with Et_2O. Purification by recrystallization after dissolving the white crystal in MeOH (25.0 mL) afforded *N*,*N*′-ditosylhydrazine **271** (1.55 g, 84%). as a white crystalline solid.

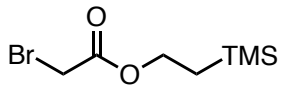
R_f = 0.60 (petroleum ether: EtOAc, 1:1); m.p. 212 °C; ν_{max} 3202, 3202, 1596, 1328, 1162, 1118, 1087, 812 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d^6) δ 9.60 (2H, s, NH), 7.63 (4H, d, J = 8.2Hz, CH-Ts), 7.40 (4H, d, J = 8.2 Hz, CH-Ts), 2.39 (6H, s, CH_3-Ts);

^{13}C NMR (DMSO-d^6, 100 MHz) δ 143.8(CH-Ts), 135.9(CH-Ts), 129.9(CH-Ts), 128.2(CH-Ts), 21.5(CH_3-Ts);

HRMS (ESI) for $C_{14}H_{16}N_2NaO_4S_2$ $[M+Na]^+$ calcd 363.0444, Found 363.0442.

2-(Trimethylsilyl)ethyl bromoacetate (270)



Chemical Formula: $C_7H_{15}BrO_2Si$
Exact Mass: 238.00

The corresponding trimethylsilyl ethanol **269** (1.0 gm, 8.4 mmol) was dissolved in CH_2Cl_2 (25 mL) and Et_3N(1.7 gm, 17 mmol) was added. Bromoacetyl bromide **268** (1.5 gm, 12 mmol) was added slowly at 0 °C. After stirring for 30 min at this temperature, the reaction was quenched with H_2O. The solution was extracted with CH_2Cl_2 two times. The organic phase was washed with $NaHCO_3$ (saturated aqueous solution, 5 mL), water (20 mL) and brine (20 mL) and dried over $MgSO_4$. The solvent was evaporated, and the residue was used in the next reaction without purification.

R_f = 0.49 (petroleum ether: EtOAc, 9:1); ν_{max} 2954, 2899, 2674, 1732, 1422, 1277, 1163, 1109 cm^{-1};

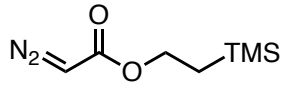
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28-4.21 (2H, m, CH_2O), 3.79 (2H, s, CH_2-CBr), 1.06-0.96 (2H, m, CH_2Si), 0.03(9H, *s*, $SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (CO_2), 64.8 (CH_2O), 26.2 (CH_2-CBr), 17.3 (CH_2Si), –1.4 ($SiMe_3$);

HRMS (ESI) for $C_7H_{15}Na^{79}BrO_2Si$ $[M+Na]^+$ calcd 260.9917, Found 260.9915.

The observed analytical data are in accordance with previous reports.[47-49]

2-(Trimethylsilyl)ethyl diazoacetate (213)



Chemical Formula: $C_7H_{14}N_2O_2Si$
Exact Mass: 186.08

The bromoacetate **270** (1.0 gm, 4.1 mmol) and *N*,*N*′-ditosylhydrazine **271** (2.8 gm, 8.3 mmol) were dissolved in THF (5.0 mL), and the solution was cooled to 0 °C. DBU (3.1 mL, 20 mmol) was added dropwise and stirred into the solution at 0 °C for 30 min. After quenching the reaction by the addition of saturated $NaHCO_3$ solution, this was extracted with Et_2O two times. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the crude diazoacetate. The obtained crude product was purified by by column chromatography on silica gel using petroleum ether and EtOAc (9:1) as the eluent to afford the desired product **213** (62.0 mg, 45%) as bright green oil.

R_f = 0.56 (petroleum ether: EtOAc, 9:1); ν_{max} 2950, 2897, 2111, 1742, 1682, 1391, 1250, 1177, 1061 cm^{-1};

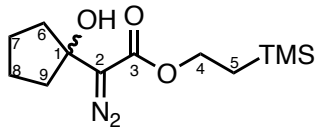
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (1H, s, $CH{=}N_2$), 4.28-4.22 (2H, m, CH_2O), 1.04-0.96 (2H, m, CH_2Si), 0.03(9H, s, $SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (CO_2), 63.3 (CH_2O), 46.2 ($CH{=}N_2$), 17.7 (CH_2Si), –1.4 ($SiMe_3$);

HRMS (ESI) for $C_7H_{14}N_2NaO_2S_i$ $[M+Na]^+$ calcd 209.0717, Found 209.0715.

The observed analytical data are in accordance with previous reports. [47-49]

2-(trimethylsilyl)ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate (274)



Chemical Formula: $C_{12}H_{22}N_2O_3Si$
Exact Mass: 270.1400

To a stirred solution of TMS-ethyl diazoacetate **213** (0.66 mg, 3.5 mmol) in anhydrous THF (5 mL) was cooled to −78 °C. The LiHMDS was added (3.5 ml of a 1.0 M solution in THF, 3.5 mmol) and was stirred for 20 minutes. cyclopentanone **273** (0.1 mg, 1.1 mmol) in (0.5 mL) of THF was added dropwise to reaction mixture. The resulting solution and was stirred for 3 hour at −78 °C before the reaction mixture was quenched by addition of NH_4Cl (saturated solution, 3 mL) and diluted with EtOAc (5 mL). The aqueous phase was separated and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether–diethyl ether, 10:1) to afford diastereoisomer **274** (230 mg, 72%) as a colourless oil.

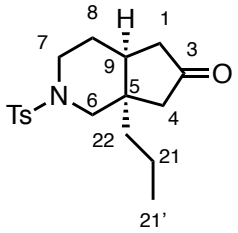
R_f = 0.48 (petroleum ether: ether, 19:1); ν_{max} 3552, 2951, 2551, 2158, 1711, 1650, 1398, 1248, 1172, 1059 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (2H, dt, *J* = 9.9, 7.71 Hz, CH_2-C4), 3.31 (1H, brs, OH), 2.08 (2H, m, CH_2-C6, CH_2-C9), 2.01 (2H, m, CH_2-C6, CH_2-C9), 1.80–1.69 (4H, m, CH_2-C7, CH_2-C8), 1.03 (2H, dd, *J* = 8.2, 8.0 Hz, CH_2-C5), 0.01 (9H, s, $SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5 (C-C3), 78.6 (C-C1), 77.20 (C-C2), 63.2 (CH_2-C4), 39.2 (CH_2-C6, CH_2-C9), 22.93 (CH_2-C7, CH_2-C8), 17.5 (CH_2-C5), 1.53 (CH_2- $SiMe_3$);

HRMS (ESI) for $C_{12}H_{22}N_2NaO_3S_i$ ($[M+Na]^+$) calcd 293.1292, Found 293.1292.

(4a*S*,7a*R*)-2-(4-Methylbenzenesulfonyl)-7[a]-propyl-octahydro-1H-cyclo-penta[*c*]pyridin-6-one ((±)-275)



Chemical Formula: $C_{18}H_{25}NO_3S$
Exact Mass: 335.1555

To a stirred solution of alkyne **(±)-163** (1.0 g, 3.0 mmol) in EtOAc (50 mL) at room temperature was added Pd/C (95 mg, 0.90 mmol) and the mixture was saturated with H_2. The reaction mixture was left to stir for 12 h under H_2-atmosphere. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give the crude as a yellow oil. Purification by column chromatography on silica gel (petroleum ether: EtOAc, 2:1) afforded the title compound **275** (920 mg, 92%) as a colourless solid.

R_f = 0.28 (petroleum ether-ethyl acetate, 3:2); m.p. = 98–102 °C; ν_{max} 2926, 2850, 1739, 1465, 1336, 1159, 1092.

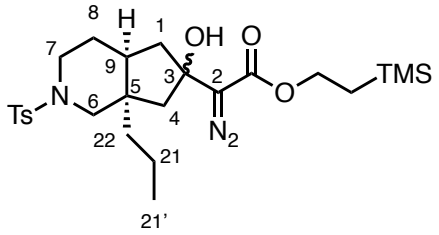
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.32 (2H, d, *J* = 8.0 Hz, CH-Ts), 3.10 (1H, m, CH_2-C7), 2.97 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.81 (1H, m, CH_2-C7), 2.53 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.41 (3H, s, CH_3-Ts), 2.29 (1H, dd, *J* = 18.8, 8.1 Hz, CH_2-C1), 2.23 (1H, d, *J* = 18.5 Hz, CH_2-C4), 2.12 (1H, d, *J* = 18.5 Hz, CH_2-C4), 2.07–1.93 (3H, m, CH_2-C1, CH_2-C21, CH_2-C9), 1.73–1.65 (1H, m, CH_2-C22), 1.56–1.49 (1H, m, CH_2-C8), 1.39–1.27 (2H, m, CH_2-C21, CH_2-C22), 1.20–1.11 (1H, m, CH_2-C8), 0.92 (3H, t, *J* = 6.8 Hz, CH_3-C21');

^{13}C NMR (101 MHz, $CDCl_3$) δ 217.4 (C-C3), 143.8 (C-Ts), 133.1 (C-Ts), 129.9 (CH-Ts), 129.9 (CH-Ts), 127.7 (CH-Ts), 127.7 (CH-Ts), 49.4 (CH_2-C6), 47.0 (CH_2-C4), 42.8 (CH_2-C7), 41.8 (C-C5), 41.1 (CH_2-C1), 39.0 (CH_2-C22), 37.9 (CH-C9), 25.5 (CH_2-C8), 21.7 (CH_3-Ts), 17.5 (CH-C21), 14.8 (CH_2-C21');

HRMS (ESI) calculated for $C_{18}H_{25}NNaO_3S$ ($[M+Na]^+$) calcd. 358.1447 found 358.1438.

The observed analytical data are in accordance with previous reports.[49]

(±)-2-(Trimethylsilyl)ethyl 2-[(4a*S,7a*R**)-6-hydroxy-2-(4-methylbenzenesulfonyl)-7a-propyl-octahydro-1H-cyclopenta[c]pyridine-6-yl]-2-diazoacetate ((±)-276)**



Chemical Formula: $C_{25}H_{39}N_3O_5SSi$
Exact Mass: 521.24

To a stirred solution of TMS-ethyl diazoacetate **213** (0.26 g, 1.4 mmol) in anhydrous THF (8 mL) was cooled to −78 °C. The LiHMDS was added (1.4 ml of a 1 M solution in THF, 1.4 mmol) and was stirred for 20 minutes. Ketone **(±)-275** (0.16 g, 0.47 mmol) in (1 mL) of THF was added dropwise to reaction mixture. The resulting solution and was stirred for 3 hour at −78 °C before the reaction mixture was quenched by addition of NH_4Cl (saturated solution, 4 mL) and diluted with EtOAc (4 mL). The aqueous phase was separated and extracted with EtOAc (3 × 4 mL). The combined organic extracts were washed with brine (4 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 2:1) to afford diastereoisomer **(±)-276** (196 mg, 79%) as a colourless oil.

R_f = 0.28 (petroleum ether–EtOAc, 4:1); ν_{max} 3330, 2952, 2151, 1684, 1457, 1339, 1250. 1163, 1091 cm^{-1}

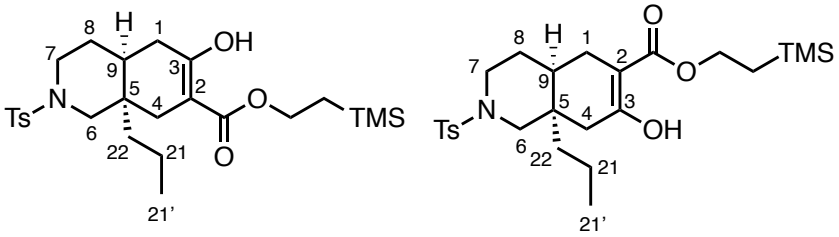
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.0 Hz, CH-Ts), 4.25 (2H, dt, *J* = 9.9, 7.71 Hz, CH_2O), 3.62 (1H, s, OH), 3.43 (1H, m, CH_2-C7), 3.31 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.71 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.58 (1H, ddd, *J* = 11.5, 11.5, 3.5 Hz, CH_2-C7), 2.42 (3H, s, CH_3-Ts), 2.01–1.87 (4H, m, CH_2-C1, CH_2-C4, CH_2-C8), 1.82–1.73 (2H, m, CH_2-C1, CH-C9), 1.62–1.54 (1H, m, CH_2-C21), 1.43–1.33 (1H, m, CH_2-C8), 1.24–1.06 (3H, m, CH_2-C21, CH_2-C22), 0.99 (2H, dd, *J* = 8.2, 8.0 Hz, CH_2Si), 0.89 (3H, t, *J* = 6.8 Hz, CH_3-C21'), 0.02 (9H, s, $SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C=O), 143.6 (C-Ts), 134.1 (C-Ts), 129.9 (CH-Ts), 129.9 (CH-Ts), 127.7 (CH-Ts), 127.7 (CH-Ts), 77.1 (C-C3), 76.5 (C-C2), 63.8 (CH_2O), 50.3 (CH_2-C6), 48.7 (CH_2-C4), 44.2 (CH_2-C7), 43.0 (C-C5), 42.2 (CH_2-C1), 41.4 (CH_2-C22), 39.4 (CH-C9), 24.0 (CH_2-C8), 21.7 (CH_3-Ts), 17.8 (CH_2Si), 17.5 (CH-C21), 15.0 (CH_2-C21') −1.2 ($SiMe_3$);

HRMS (ESI) calculated for $C_{18}H_{25}NNaO_3S$ ($[M+Na]^+$) calcd. 544.2272 found 544.2257.

The observed analytical data are in accordance with previous reports.[49]

(±)-2-(Trimethylsilyl)ethyl (4a*R,8a*R**)-7-hydroxy-2-(4-methylbenzenesulfonyl)-8a-propyl-1,2,3,4,4a,5,8,8a-octahydroisoquinoline-6-carboxylate ((±)-281) and (±)-2-(trimethylsilyl)ethyl (4a*S**,8a*R**)-6-hydroxy-2-(4-methylbenzenesulfonyl)-8a-propyl-1,2,3,4,4a,5,8,8a-octahydroisoquinoline-7-carboxylate ((±)-280)**



Chemical Formula: $C_{25}H_{39}NO_5SSi$
Exact Mass: 493.2318

To a solution of diazoester **(±)-276 (**60.0 mg, 115 μmol) in CH_2Cl_2 (6 mL) was added $Rh_2(OAc)_4$ (15.2 mg, 34.5 μmol) and the resulting green solution was stirred at rt for 1 h. The mixture was filtered through celite and concentrated under reduced pressure to give a dark green oil. The residue was used in the next reaction without purification.

R_f = 0.58 (petroleum ether–EtOAc, 4:1); ν_{max} 3341, 2923, 2861, 1646, 1621, 1339, 1250. 1163, 1092 cm^{-1}

***β*-ketoester (280):**

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.2 (1H, s, OH), 7.64 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.0 Hz, CH-Ts), 4.26 (2H, m, CH_2O), 3.74 (1H, m, CH_2-C7), 3.43 (1H, d, *J* = 11.2 Hz, CH_2-C6), 2.67 (1H, d, *J* = 16.8 Hz, CH_2-C4), 2.61–2.53 (1H, m, CH_2-C1), 2.44 (3H, s, CH_3-Ts), 2.19 (1H, ddd, *J* = 11.9, 11.5, 3.5 Hz, CH_2-C7), 2.09 (1H, m, CH_2-C6), 2.04 (1H, d, *J* = 16.8 Hz, CH_2-C4), 1.93 (1H, d, *J* = 18.5 Hz, CH_2-C1), 1.66 (1H, m, CH_2-C8), 1.53–1.43 (2H, m, CH_2-C8, CH-C9), 1.34–1.30 (1H, m, CH_2-C22), 1.25–1.18 (3H, m, CH_2-C21, CH_2-C22), 1.13–1.08 (2H, m, CH_2Si), 0.89 (3H, m, CH_3-C21'), 0.08 (9H, s, $SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5 (C=O), 169.7 (C-C3), 145.1 (C-Ts), 135.0 (C-Ts), 130.0 (CH-Ts), 129.7 (CH-Ts), 128.4 (CH-Ts), 128.0 (CH-Ts), 93.6 (C-C2), 62.5 (CH_2O), 63.2 (CH_2O), 52.2 (CH_2-C4), 48.4 (CH_2-C6), 46.0 (CH_2-C5), 42.9 (C-C1), 41.9 (CH_2-C7), 41.7 (CH-C9), 39.4 (CH_2-C22), 24.0 (CH_2-C8), 22.0 (CH_3-Ts), 18.0 (CH-C21), 17.7 (CH_2Si), 15.2 (CH_2-C21'), −1.3 ($SiMe_3$);

***β*-ketoester (281)**

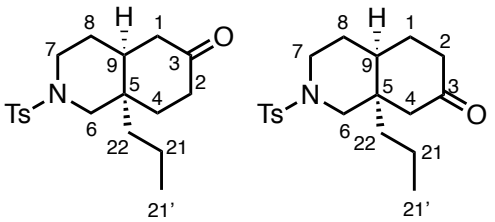
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.1 (1H, s, OH), 7.64 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.0 Hz, CH-Ts), 4.26 (2H, m, CH_2O), 3.74 (1H, m, CH_2-C7), 3.38 (1H, d, *J* = 11.2 Hz, CH_2-C6), 2.84 (1H, d, *J* = 16.8 Hz, CH_2-C4), 2.44 (3H, s, CH_3-Ts), 2.42–2.37 (1H, m, CH_2-C1), 2.21 (1H, m, CH_2-C7), 2.09 (1H, m, CH_2-C6), 2.04 –1.93 (2H, m, CH_2-C1, CH_2-C4), 1.66 (1H, m, CH_2-C8), 1.43–1.39 (2H, m, CH_2-C8, CH-C9), 1.29 (1H, m, CH_2-C22), 1.23–1.19 (3H, m, CH_2-C21, CH_2-C22), 1.06–0.99 (2H, m, CH_2Si), 0.89 (3H, m, CH_3-C21'), 0.04 (9H, s, $SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7 (C=O), 169.9 (C-C3), 143.7 (C-Ts), 133.7 (C-Ts), 130.1 (CH-Ts), 128.4 (CH-Ts), 127.6 (CH-Ts), 127.5 (CH-Ts), 94.1 (C-C2), 63.2 (CH_2O), 50.4 (CH_2-C4), 47.7 (CH_2-C6), 44.2 (CH_2-C5), 43.0 (C-C1), 42.2 (CH_2-C7), 41.4 (CH-C9), 39.5 (CH_2-C22), 23.8 (CH_2-C8), 22.0 (CH_3-Ts), 17.9 (CH-C21), 17.4 (CH_2Si), 15.2 (CH_2-C21'), −1.3 ($SiMe_3$);

HRMS (ESI) calculated for $C_{25}H_{39}NNaO_5SSi$ ($[M+Na]^+$) calcd. 516.2210 found 516.2203.

The observed analytical data are in accordance with previous reports.[49]

(±)-(4a*S,8a*R**)-2-(4-Methylbenzenesulfonyl)-8a-propyl-decahydroisoquinolin-6-one ((±)-282) and(±)-(4a*R**,8a*R**)-2-(4-Methylbenzenesulfonyl)-8a-propyl decahydroisoquinolin-7-one ((±)-282')**



Chemical Formula: $C_{19}H_{27}NO_3S$
Exact Mass: 349.1712

To a solution of β-ketoester **(±)-280** and **(±)-281** (60.0 mg, 104 μmol) in THF (3 mL) was added TBAF (209 μL of a 1.0 M solution in THF, 209 μmol) and the mixture was stirred at rt for 1h. The reaction was quenched by addition of NH_4Cl (saturated aqueous solution, 5 mL) and diluted with EtOAc (5 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether–EtOAc, 3:2) afforded title compound **(±)-282** and **(±)-282'**(6.3 mg, 68%) as a colourless foam.

R_f = 0.30 (petroleum ether-ethyl acetate, 3:2); ν_{max} 2921, 2850, 1728, 1462, 1339, 1164, 1095.

Compound (282):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.0 Hz, CH-Ts), 3.10 (1H, m, CH_2-C7), 2.77 (1H, d, *J* = 11.6 Hz, CH_2-C6), 2.50 (1H, m, CH_2-C1) 2.43 (3H, s, CH_3-Ts), 2.41–2.34 (4H, m, CH_2-C2, CH_2-C4, CH_2-C7), 2.13 (2H, m, CH_2-C1, CH_2-C6), 1.78–1.65 (3H, m, CH_2-C4, CH_2-C9, CH_2-C22), 1.62–1.57 (2H, m, CH_2-C8), 1.44–1.36 (1H, m, CH_2-C22), 1.35–1.27 (2H, m, CH_2-C21), 0.96 (3H, t, *J* = 6.8 Hz, CH_3-C21');

^{13}C NMR (101 MHz, $CDCl_3$) δ 211 (C-C3), 144.8 (C-Ts), 133.6 (C-Ts), 130.1 (CH-Ts), 130.1 (CH-Ts), 127.9 (CH-Ts), 127.9 (CH-Ts), 53.5 (CH_2-C6), 46.1 (CH_2-C4), 41.5 (CH_2-C7),

40.8 (C-C5), 40.1 (CH_2-C1), 38.5 (CH_2-C22), 37.1 (CH_2- C2), 36.5 (CH-C9), 26.9 (CH_2-C8), 21.9 (CH_3-Ts), 16.4 (CH-C21), 15.2 (CH_2-C21');

Compound (282')

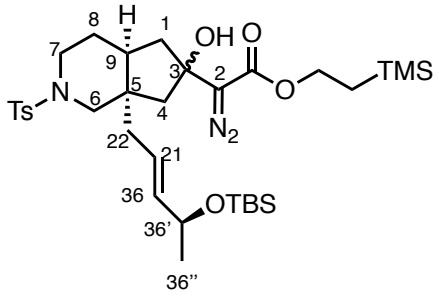
R_f = 0.35 (petroleum ether-ethyl acetate, 3:2); ν_{max} 2921, 2850, 1728, 1462, 1339, 1164, 1095.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.33 (2H, d, *J* = 8.0 Hz, CH-Ts), 3.63 (1H, m, CH_2-C7), 2.62 (1H, dd, *J* = 15.5, 5.6 Hz, CH_2-C6) 2.43 (3H, s, CH_3-Ts), 2.41–2.34 (3H, m, CH_2-C1, CH_2-C2, CH_2-C4), 2.13 (2H, m, CH_2-C2, CH_2-C7), 2.00 (2H, m, CH_2-C1, CH_2-C6) 1.78–1.65 (3H, m, CH_2-C4, CH_2-C9, CH_2-C22), 1.55–1.48 (2H, m, CH_2-C8), 1.44–1.36 (1H, m, CH_2-C22), 1.35–1.27 (2H, m, CH_2-C21), 0.86 (3H, t, *J* = 6.8 Hz, CH_3-C21');

^{13}C NMR (101 MHz, $CDCl_3$) δ 209 (C-C3), 144.8 (C-Ts), 133.6 (C-Ts), 130.1 (CH-Ts), 130.1 (CH-Ts), 127.9 (CH-Ts), 127.9 (CH-Ts), 53.5 (CH_2-C6), 45.9 (CH_2-C4), 41.5 (CH_2-C7), 40.8 (C-C5), 40.1 (CH_2-C1), 38.5 (CH_2-C22), 37.1 (CH_2- C2), 36.5 (CH-C9), 26.9 (CH_2-C8), 21.9 (CH_3-Ts), 16.4 (CH-C21), 15.0 (CH_2-C21');

HRMS (ESI) calculated for $C_{19}H_{27}NNaO_3S$ ($[M+Na]^+$) calcd. 372.1604 found 372.1606.

methyl (4aS,7aR)-7a-((S,E)-4-((tert-butyldimethylsilyl)oxy)pent-2-en-1-yl)-6-oxo-2-tosyloctahydro-1H-cyclopenta[c]pyridine-5-carboxylate (283)



Chemical Formula: $C_{33}H_{55}N_3O_6SSi_2$
Exact Mass: 677.3350

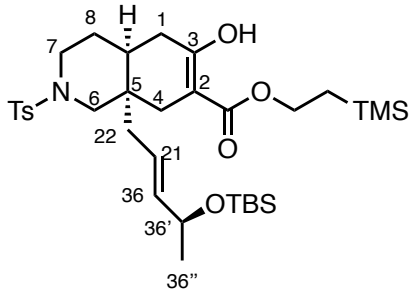
To a stirred solution of silylethers **240** (50 mg, 0.10 mmol) in anhydrous THF (1 mL) was cooled to −78 °C. The TMS-ethyl diazoacetate **213** (57 mg, 0.30 mmol) and the LiHMDS were added (0.25 mL of a 1.0 M solution in THF, 0.25 mmol) in 3 portions in every 30 minutes. The resulting solution was stirred for 3 h at −78 °C before the reaction mixture was quenched by addition of NH_4Cl (saturated solution, 3 mL) and diluted with EtOAc (5 mL). The aqueous phase was separated and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, 10:1) to afford **283** (40 mg, 58%) as a colourless oil.

R_f = 0.6 (petroleum ether: EtOAc, 7:3); ν_{max} 3468, 2955, 2126, 1744, 1686, 1364, 1240. 1170, 1092 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.31 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.60−5.47 (2H, m, CH-C36, CH-C21), 4.25 (3H, m, CH_2O, CH-C36'), 3.58 (1H, s, OH), 3.35 (1H, m, CH_2-C7), 3.20 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.79 (1H, d, *J* = 12.2 Hz, CH_2-C6), 2.66 (1H, ddd, *J* = 11.5, 11.5, 3.5 Hz, CH_2-C7), 2.42 (3H, s, CH_3-Ts), 2.35 (1 H, m, CH_2-C22), 2.08−1.97 (3H, m, CH_2-C4, CH_2-C22,), 1.95−1.79 (4H, m, CH_2-C1, CH_2-C8, CH_2-C9), 1.66−1.62 (1H, m, CH_2-C8), 1.20 (3H, d, *J* = 6.5 Hz, CH_3-C36"), 0.99 (2H, dd, *J* = 8.2, 8.0 Hz, CH_2Si), 0.89 (9H, s, $3CH_3$-TBS), (15H, m, CH_3-TBS, $SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C=O), 143.3(C-Ts), 139.4(CH-C36), 133.7(C-Ts), 129.6 (CH-Ts), 129.6 (CH-Ts), 127.4 (CH-Ts), 127.4 (CH-Ts), 122.7 (CH-21), 77.2 (C-C3), 77.0 (C-C2), 68.4(CH-C36'), 63.5 (CH_2O), 49.3(CH_2-C6), 45.8(CH_2-C4), 43.0(CH_2-C7), 42.1(C-C5), 49.9 (CH_2-C1), 38.7(CH_2-C22), 36.5(CH-C9), 25.8(CH_3-36"), 24.6(CH_2-C8), 21.5 (CH_3-Ts), 18.2(3CH_3-TBS), 17.6 (CH_2Si), −1.52 ($SiMe_3$), −4.62 (CH_3-TBS), −4.79 (CH_3-TBS); HRMS (ESI) for $C_{33}H_{55}N_3O_6SSi_2$ ($[M+H]^+$) calcd 678.3423, found 678.3416.

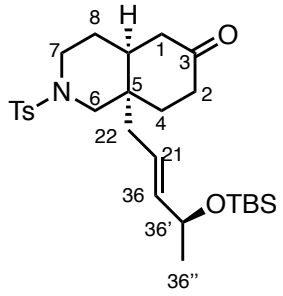
2-(trimethylsilyl)ethyl (4aS,8aR)-8a-((E)-4-((tert-butyldimethylsilyl)oxy)pent-2-en-1-yl)-6-oxo-2-tosyldecahydroisoquinoline-7-carboxylate (284)



Chemical Formula: $C_{33}H_{55}NO_6SSi_2$
Exact Mass: 649.3289

To a solution of α-diazo-β-hydroxyester **283 (**200 mg, 295 μmol) in CH_2Cl_2 (20 mL) was added $Rh_2(OAc)_4$ (39.1 mg, 88.5 μmol) and the resulting green solution was stirred at rt for 1 h. The mixture was filtered through celite and concentrated under reduced pressure to give a dark green oil. The residue was used in the next reaction without purification.

(4aS,8aS)-8a-((E)-4-((tert-butyldimethylsilyl)oxy)pent-2-en-1-yl)-2-tosyloctahydroisoquinolin-6(2H)-one (285)



Chemical Formula: $C_{27}H_{43}NO_4SSi$
Exact Mass: 505.2682

To a solution of carboxylate **284** (30 mg, 46 μmol) in THF (4 mL) was added TBAF (92 μL, 92 μmol) and the mixture was stirred at rt for 2h. The reaction was quenched by addition of NH_4Cl (saturated aqueous solution, 5 mL) and diluted with EtOAc (5 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether–EtOAc, 3:2) afforded title compound **285** (7.3 mg, 42%) as a colourless foam.

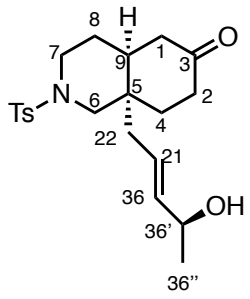
R_f = 0.56 (petroleum ether: EtOAc, 2:1); ν_{max} 2977, 2927, 2854, 1742, 1597, 1463, 1340, 1255, 1163, 1092 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.32 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.61−5.56 (1H, m, CH-C36), 5.53−5.49 (1H, m, CH-C21), 4.28 (1H, dq, *J* = 6.5, 6.5 Hz, CH-C36'), 3.10 (1H, m, CH_2-C6), 3.06−2.92 (2H, m, CH_2-C6, CH_2-C7), 2.88 (1H, m, CH_2-C7), 2.70−2.50 (1H, m, CH_2-C1), 2.43 (3H, s, CH_3-Ts), 2.41−2.27 (3H, m, CH_2-C1, CH_2-C2, CH_2-C4), 2.24−2.10 (2H, m, CH_2-C22), 2.13−2.07 (1H, m, CH_2-C2), 2.03−1.95 (2H, m, CH_2-C8, CH-C9), 1.61−1.51 (2H, m, CH_2-C4, CH_2-C8), 1.19 (3H, m, CH_3-C36"), 0.89 (9H, s, 3CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.03 (s, 3H, CH_3-TBS).

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.7(C-C3), 143.7(C-Ts), 139.9(CH-C36), 139.5(CH-C21), 132.9(C-Ts), 129.8(CH-Ts), 129.8(CH-Ts), 127.5(CH-Ts), 127.5 (CH-Ts), 68.7 (CH-C36'), 49.5(CH_2-C6), 47.1 (CH_2-C7), 41.8 (CH_2-C1), 41.4 (C-C5), 41.5 (CH_2-C9), 38.7(CH_2-C2), 36.7 (CH-C22), 29.7 (CH_2-C4), 25.8 (CH_3-36"), 24.6 (CH_2-C8), 21.5 (CH_3-Ts), 18.3(3CH_3-TBS), −4.7 (CH_3-TBS), −4.9 (CH_3-TBS);

HRMS (ESI) for $C_{27}H_{43}NO_4SSi$ ($[M+H]^+$) calcd 506.2731, found 506.2755.

(4aS,8aS)-8a-((E)-4-Hydroxypent-2-en-1-yl)-2-tosyloctahydroisoquinolin-6(2H)-one (293)



Chemical Formula: $C_{21}H_{29}NO_4S$
Exact Mass: 391.1817

To a solution of carboxylate **284** (30 mg, 46 μmol) in THF (4 mL) was added TBAF (92 μL, 92 μmol) and the mixture was stirred at rt for 6h. The reaction was quenched by addition of NH_4Cl (saturated aqueous solution, 5 mL) and diluted with EtOAc (5 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether–EtOAc, 3:2) afforded title compound **293** (7.3 mg, 42%) as a colourless foam.

R_f = 0.30 (petroleum ether: EtOAc, 1:2); ν_{max} 3455, 2979, 2922, 2851, 1735, 1334, 1159, 1089 cm^{-1};

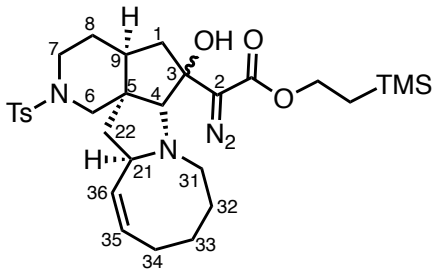
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.27 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.65−5.60 (1H, m, CH-C36), 5.54−5.45 (1H, m, CH-C21), 4.25-4.19 (1H, dq, *J* = 6.5, 6.5 Hz, CH-C36'), 3.14 (1H, m, CH_2-C7), 3.03 (1H, d, *J* = 12.1 Hz, CH_2-C6), 2.70 (1H, m, CH_2-C7), 2.43 (1H, m, CH_2-C1), 2.38 (3H, s, CH_3-Ts), 2.33 (1H, m, CH_2-C6), 2.35(1H, m, CH_2-C2), 2.24−2.10 (3H, m, CH_2-C1, CH_2-C22), 2.07−1.91 (3H, m, CH_2-C2, CH_2-C8, CH-C9), 2.38 (1H, bs, OH), 1.56−1.54 (3H, m, CH_2-C4, CH_2-C8), 1.18 (3H, m, CH_3-C36").

^{13}C NMR (101 MHz, $CDCl_3$) δ 216.1(C-C3), 143.7(C-Ts), 139.5(CH-C36), 139.5(CH-C21), 132.7(C-Ts), 129.7(CH-Ts), 129.5(CH-Ts), 127.4(CH-Ts), 127.4 (CH-Ts), 68.16(CH-

C36'), 49.6(CH_2-C6), 45.8 (CH_2-C7), 41.5 (CH_2-C1), 40.7 (C-C5), 40.6 (CH_2-C9), 38.6(CH_2-C2), 36.9 (CH-C22), 29.5 (CH_2-C4), 25.0 (CH_3-36"), 23.4 (CH_2-C8), 21.4 (CH_3-Ts).

HRMS (ESI) for $C_{21}H_{29}NO_4S$ ($[M+H]^+$) calcd 392.1890, found 392.1889.

2-(Trimethylsilyl)ethyl 2-diazo-2-[(1*S*,3*R*,4*Z*,11*S*,14*R*)-12-hydroxy-17-(4-methylbenzenesulfonyl)-10,17-diazatetracyclo[9.7.0.01,14.03,10]octadec-4-en-12- yl]acetate (214)



Chemical Formula: $C_{30}H_{44}N_4O_5SSi$
Exact Mass: 600.2802

To a stirred solution of TMS-ethyl diazoacetate **213** (18 mg, 0.18 mmol) in anhydrous THF (0.5 mL) was cooled to −78 °C. The LiHMDS was added (0.18 ml of a 1 M solution in THF, 0.18 mmol) and was staired for 15 minutes. The solution of ketone **170** (20 mg, 0.38 mmol) in anhydrous THF (0.1 mL) was added dropwise and the resulting solution was stirred for 3 hour at −78 °C before the reaction mixture was quenched by addition of NH_4Cl (saturated solution, 3 mL) and diluted with EtOAc (5 mL). The aqueous phase was separated and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane-ethyl acetate, 9:1) to afford diastereoisomer **214** (14 mg, 53%) as a colourless oil.

R_f = 0.25 (pentane–EtOAc, 1:1); ν_{max} 2927, 2013, 1675, 1330, 1200, 1163, 1091 cm^{-1};

Major diastereoisomer:

^{1}H NMR (500 MHz, C_6D_6) δ 7.73 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.82 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.09 (1H, s, OH), 5.69 (1H, dtd, *J* = 10.6, 7.6, 1.3 Hz, CH-C35), 5.43 (1H, td, *J* = 10.6, 1.5 Hz, CH-C36), 4.25–4.07 (3H, m, CH-C21, CH_2O), 3.96 (1H, d, *J* = 12.1 Hz, CH_2-C6), 3.60–3.52 (1H, m, CH_2-C7), 3.15 (1H, d, *J* = 12.1 Hz, CH_2-C6), 3.11 (1H, s, CH-C4), 2.53 (1H, dd, *J* = 12.4, 9.5 Hz, CH_2-C31), 2.44 (1H, dd, *J* = 13.8, 12.4 Hz, CH_2-C1), 2.30–2.20 (3H, m, CH_2-C7, CH_2-C22, CH_2-C31), 2.20–2.14 (1H, m, CH-C9), 1.89 (3H, s, CH_3-Ts), 1.88–1.82 (1H, m, CH_2-C34), 1.80–1.69 (3H, m, CH_2-C1, CH_2-C8, CH_2-C34), 1.68–1.62 (1H, m, CH_2-C22), 1.50

(1H, m, CH_2-C32), 1.40–1.30 (1H, m, CH_2-C33), 1.15–1.09 (2H, m, CH_2-C8, CH_2-C32), 0.95–0.86 (1H, m, CH_2-C33), 0.79 (2H, t, *J* = 8.4 Hz, CH_2Si), −0.13 (9H, s, $SiMe_3$),

^{13}C NMR (126 MHz, C_6D_6) δ 165.8 (CO_2), 142.8 (C-Ts), 135.8 (C-Ts), 134.4 (CH-C35), 129.8 (2 × CH-Ts), 128.6 (2 × CH-Ts), 128.4 (CH-C36), 78.0 (CH-C4), 70.2 (C-C3), 63.3 (C-C2), 62.5 (CH_2O), 60.8 (CH-C21), 52.5 (C-C5), 52.0 (CH_2-C6), 50.0 (CH_2-C31), 43.0 (CH_2-C1), 42.6 (CH_2-C7), 42.0 (CH-C9), 41.0 (CH_2-C22), 28.5 (CH_2-C32), 27.4 (CH_2-C33), 27.3 (CH_2-C34), 24.0 (CH_2-C8), 21.2 (CH_3-Ts), 17.7 (CH_2Si), −1.6 ($SiMe_3$).

Minor diastereoisomer:

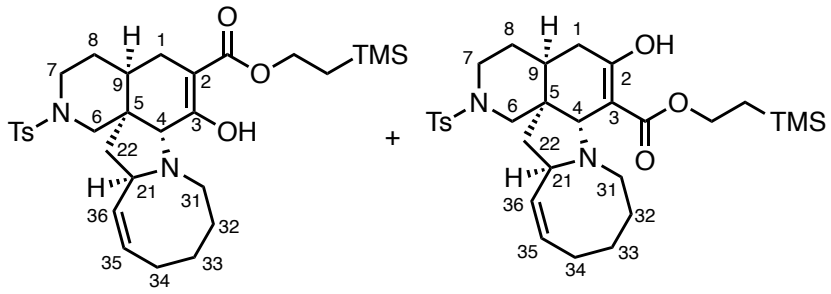
^{1}H NMR (500 MHz, C_6D_6) δ 7.71 (2H, d, *J* = 8.0 Hz, 2 × CH-Ts), 6.82 (2H, d, *J* = 8.0 Hz, 2 × CH-Ts), 6.09 (1H, s, OH), 5.81 (1H, dtd, *J* = 10.2, 6.8, 1.4 Hz, CH-C35), 5.48 (1H, ddd, *J* = 10.2, 9.7, 1.7 Hz, CH-C36), 4.22–4.07 (3H, m, CH-C21, CH_2O), 3.75 (1H, d, *J* = 12.0 Hz, CH_2-C6), 3.34 (1H, dt, *J* = 11.9, 6.0 Hz, CH_2-C7), 2.98 (1H, s, CH-C4), 2.93 (1H, d, *J* = 12.0 Hz, CH_2-C6), 2.68 (1H, dd, *J* = 13.0, 7.9 Hz, CH_2-C31), 2.61 (1H, ddd, *J* = 11.9, 7.4, 4.5 Hz, CH_2-C7), 2.44 (1H, m, CH_2-C1), 2.29–2.13 (3H, m, CH-C9, CH_2-C22, CH_2-C31), 2.00 (1H, dd, *J* = 12.9, 6.8 Hz, CH_2-C34), 1.91 (3H, s, CH_3-Ts), 1.88–1.82 (2H, m, CH_2-C33, CH_2-C34), 1.80–1.68 (2H, m, CH_2-C1, CH_2-C22), 1.51–1.56 (1H, m, CH_2-C33), 1.55–1.47 (2H, m, CH_2-C8, CH_2-C32), 1.39–1.32 (1H, m, CH_2-C8), 1.30–1.23 (1H, m, CH_2-C32), 0.84–0.81 (2H, m, CH_2Si), −0.13 (9H, s, $SiMe_3$);

^{13}C NMR (126 MHz, C_6D_6) δ 165.8 (CO_2), 142.8 (C-Ts), 135.9 (C-Ts), 134.0 (CH-C35), 129.8 (2 × CH-Ts), 128.5 (CH-C36), 128.4 (2 × CH-Ts), 83.1 (CH-C4), 81.0 (C-C3), 63.5 (CH_2O), 63.3 (C-C2), 58.9 (CH-C21), 54.1 (C-C5), 52.1 (CH_2-C6), 49.8 (CH_2-C31), 43.4 (CH_2-C7), 43.0 (CH_2-C22), 42.7 (CH_2-C1), 42.0 (CH-C9), 29.5 (CH_2-C33), 29.0 (CH_2-C32), 27.4 (CH_2-C34), 25.4 (CH_2-C8), 21.2 (CH_3-Ts), 17.7 (CH_2Si), −1.6 ($SiMe_3$).

HRMS (ESI) for $C_{30}H_{45}N_4O_5SSi$ ($[M+H]^+$) calcd. 601.2874, found 601.2861.

The observed analytical data are in accordance with previous reports.[49]

2-(trimethylsilyl)ethyl (1*R*,3*R*,4*Z*,11*R*,15*S*)-13-hydroxy-18-(4-methylbenzenesulfonyl)-10,18 diazatetracyclo[9.8.0.01,15.03,10]nonadeca-4,12-diene-12- carboxylate (216) methylbenzene-sulfonyl)-10,18-diazatetracyclo[9.8.0.01,15.03,10]nonadeca-4,12-diene-13-carboxylate (215)



Chemical Formula: $C_{30}H_{44}N_2O_5SSi$
Exact Mass: 572.27

To a solution of diazoester **(±)-214 (**16 mg, 26 μmol) in CH_2Cl_2 (6 mL) was added $Rh_2(OAc)_4$ (3.53 mg, 8 μmol) and the resulting green solution was stirred at rt for 16 h. The mixture was filtered through celite and concentrated under reduced pressure to give a dark green oil. Purification by column chromatography on silica gel (pentane–EtOAc, 2:1) afforded *β*-Ketoesters **216** and **215** (8 mg, 52%) as colourless oil. (Characterization of major tautomers)

Major regioisomer:

R_f = 0.21 (petroleum ether–EtOAc, 4:1); ν_{max} 2926. 2855, 1712, 1649, 1456, 1350, 1303. 1208, 1165, 1069, 1038 cm^{-1};

^{1}H NMR (500 MHz, C_6D_6) δ 13.4 (1H, s, OH), 7.80 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.92 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.69 (1H, ddd, *J* = 10.9, 8.3, 7.8 Hz, CH-C35), 5.46 (1H, dd, *J* = 10.9, 6.9 Hz, CH-C36), 4.45–4.33 (2H, m, CH_2O), 3.94–3.86 (2H, m, CH-C4, CH_2-C6), 3.84–3.76 (1H, m, CH-C21), 3.56–3.48 (2H, m, CH_2-C7, CH_2-C31), 3.23 (1H, dd, *J* = 11.4, 7.9 Hz, CH_2-C7), 2.68–2.58 (1H, m, CH_2-C34), 2.32–2.08 (4H, m, CH_2-C6, CH_2-C22, CH_2-C31, CH_2-C34), 1.99 (3H, s, CH_3-Ts), 1.92–1.85 (1H, m, CH_2-C1), 1.82–1.76 (1H, m, CH_2-C8), 1.65–1.56 (1H, m, CH_2-C32), 1.53–1.33 (5H, m, CH_2-C1, CH_2-C8, CH_2-C32, CH_2-C33), 1.33–1.24 (2H,

m, CH-C9, CH_2-C22), 0.98 (2H, t, *J* = 8.3 Hz, CH_2Si), 0.00 (9H, s, $SiMe_3$);

^{13}C NMR (126 MHz, C_6D_6) δ 175.1 (C-C3), 159.1 (CO_2), 144.9 (C-Ts), 134.2 (C-Ts), 131.7 (CH-C36), 131.4 (CH-C35), 129.2 (CH-Ts), 129.2 (CH-Ts), 128.8 (CH-Ts), 128.8 (CH-Ts), 97.2 (C-C2), 65.4 (CH-C4), 63.0 (CH_2O), 55.7 (CH-C21), 54.3 (CH_2-C6), 49.7 (CH_2-C31), 48.2 (C-C5), 44.6 (CH_2-C1), 43.9 (CH_2-C7), 41.3 (CH_2-C22), 36.5 (CH-C9), 30.4 (CH_2-C33), 28.5 (CH_2-C32), 27.9 (CH_2-C8), 24.9 (CH_2-C34), 22.1 (CH_2-Ts), 16.5 (CH_2Si), −0.6 (SiMe3);

Minor regioisomer:

R_f = 0.30 (petroleum ether–EtOAc, 1:1); ν_{max} 2923, 2836, 1733, 1653, 1540, 1421, 1344, 1265, 1164, 1074 cm^{-1};

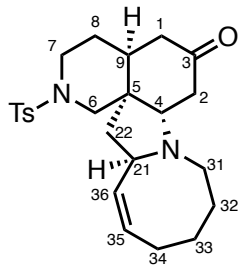
^{1}H NMR (500 MHz, C_6D_6) δ 13.4 (1H, s, OH), 7.62 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.74 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.90 (1H, ddd, *J* = 9.1, 8.5, 7.8 Hz, CH-C35), 5.36 (1H, dd, *J* = 9.5, 9.1 Hz, CH-C36), 4.33–4.19 (2H, m, CH_2O), 4.08 (1H, s, CH-C4), 3.98–3.87 (1H, m, CH-C21), 3.18–3.01 (2H, m, CH_2-C6, CH_2-C7), 2.99 (1H, dd, *J* = 12.2, 8.7 Hz, CH_2-C31), 2.86 (1H, d, *J* = 11.3 Hz, CH_2-C6), 2.73–2.63 (1H, m, CH_2-C31), 2.64–2.52 (1H, m, CH_2-C7), 2.20–2.06 (4H, m, CH_2-C1, CH_2-C22, CH_2-C34), 1.90 (3H, s, CH_3-Ts), 1.85–1.77 (2H, m, CH_2-C1, CH-C9), 1.77–1.65 (2H, m, CH_2-C22, CH_2-C32), 1.66–1.45(2H, m, CH_2-C8, CH_2-C32), 1.37–1.23 (2H, m, CH_2-C33), 1.00–0.94 (1H, m, CH_2-C8), 0.95–0.86 (2H, m, CH_2Si) −0.05 (9H, s, $SiMe_3$);

^{13}C NMR (126 MHz, C_6D_6) δ 175.1 (C-C3), 159.1 (CO_2), 144.9 (C-Ts), 134.2 (C-Ts), 131.7 (CH-C36), 131.4 (CH-C35), 129.2 (CH-Ts), 129.2 (CH-Ts), 128.8 (CH-Ts), 128.8 (CH-Ts), 97.2 (C-C2), 65.4 (CH-C4), 63.0 (CH_2O), 55.7 (CH-C21), 54.3 (CH_2-C6), 49.7 (CH_2-C31), 47.2 (C-C5), 44.3 (CH_2-C1), 43.6 (CH_2-C7), 43.9 (CH_2-C22), 36.5 (CH-C9), 30.4 (CH_2-C33), 28.5 (CH_2-C32), 27.9 (CH_2-C8), 24.9 (CH_2-C34), 22.1 (CH_2-Ts), 16.5 (CH_2Si), −0.6 (SiMe3);

HRMS (ESI) for $C_{30}H_{44}N_2O_5SSi$ ([M+H]+) calcd. 573.2818, found 573.2809.

The observed analytical data are in accordance with previous reports.[49]

(1*R*,3*R*,4*Z*,11*S*,15*S*)-18-(4-Methylbenzenesulfonyl)-10,18-diazatetracyclo[9.8.0.0^{1,15}.0^{3,10}]nonadec-4-en-13-one (217)



Chemical Formula: $C_{24}H_{32}N_2O_3S$
Exact Mass: 428.21

To a solution of *β*-ketoester **216 (**16.0 mg, 27.9 μmol) in THF (3 mL) was added TBAF (55.9 μL of a 1 M solution in THF, 55.9 μmol), and the reaction mixture was stirred at rt for 16 h. The reaction was quenched by addition of NH_4Cl (saturated aqueous solution, 2 mL) and the mixture was diluted with EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on silica gel (petroleum ether– EtOAc 2:1) afforded the title compound **217** (8.0 mg, 72%) as a colourless foam:

R_f = 0.26 (petroleum ether–EtOAc, 1:1);); $[\alpha]_D^{16}$+22 (c = 0.56, $CHCl_3$); ν_{max} 2923, 2851, 1733, 1436, 1344, 1164, 1092 cm^{-1};

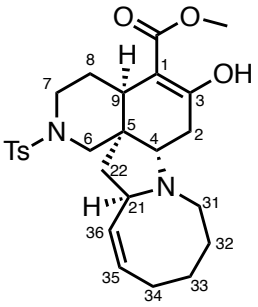
^{1}H NMR (500 MHz, C_6D_6) δ 7.68 (2H, d, *J* = 8.0 Hz, CH-Ts), 6.82 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.65 (1H, dddd, *J* = 10.3, 8.9, 7.6, 1.6 Hz, CH-C35), 5.39 (1H, dd, *J* = 10.3, 5.5 Hz, CH-C36), 3.63 (1H, d, *J* = 11.5 Hz, CH_2-C6), 3.34 (1H, m, CH-C21), 3.16 (1H, m, CH_2-C7), 3.08 (1H, dd, *J* = 7.7, 5.8 Hz, CH-C4), 2.99 (1H, m, CH_2-C34), 2.40–2.34 (2H, m, CH_2-C7, CH2-C31), 2.27–2.23 (2H, m, CH_2-C6, CH_2-C31), 2.17–2.11 (2H, m, CH_2-C2, CH_2-C34), 1.95 (1H, dd, *J* = 14.8, 5.0 Hz, CH_2-C1), 1.90 (3H, s, CH_3-Ts), 1.88–1.84 (2H, m, CH_2-C2, CH_2-C22), 1.68–1.61 (1H, dd, *J* = 14.8, 5.0, Hz. CH_2-C1), 1.58–1.49 (4H, m, CH_2-C32, CH_2-C33), 1.24–1.15 (3H, m, CH_2-C8, CH-C9, CH_2-C22), 1.07–1.01 (1H, m, CH_2-C8);

^{13}C NMR (126 MHz, C_6D_6) δ 207.9 (C-C3), 143.1 (C-Ts), 135.2 (C-Ts), 133.8 (CH-C36), 129.8 (CH-Ts), 129.8 (CH-Ts), 128.7 (CH-C35), 127.7 (CH-Ts), 127.7 (CH-Ts), 65.0 (CH-C4), 57.4 (CH-C21), 53.6 (CH_2-C6), 48.8 (CH_2-C31), 45.1 (CH_2-C7), 44.1 (C-C5), 41.8 (CH_2-C1), 40.8 (CH_2-C22), 39.3 (CH_2-C2), 37.1 (CH-C9), 30.4 (CH_2-C8), 27.3 (CH_2-C34), 26.1 (CH_2-C33), 25.9 (CH_2-C32), 21.9 (CH_3-Ts);

HRMS (ESI) for $C_{24}H_{33}N_2O_3S$ ($[M+H]^+$) calcd. 429.2206, found 429.2207.

The observed analytical data are in accordance with previous reports.[49]

methyl (4aR,7aS,14aR,15aR,Z)-6-hydroxy-2-tosyl-2,3,4,4a,7,7a,9,10,11,12,14a,15-dodecahydro-1H-azocino[1',2':1,5]pyrrolo[2,3-i]isoquinoline-5-carboxylate (224)



Chemical Formula: $C_{26}H_{34}N_2O_5S$
Exact Mass: 486.22

To a solution of tetracyclic ketone **217 (**10.0 mg, 23.3 μmol) in THF (0.5 mL) at a –78 °C was added LiHMDS (26.1 μL of a 1 M solution in THF, 26.1 μmol) dropwise. The reaction was stirred for 30 minutes at –78 °C. HMPA (5.00 μL, 279 μmol) and Manders' reagent (2.30 μL, 327 μmol) were then added in sequence. The reaction was stirred at –78 °C for an additional 45 minutes. The reaction mixture was quenched by addition of cold H_2O (1 mL) and extracted with Et_2O (3x1.5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography on silica gel (Et_2O–CH_2Cl_2 3:7) afforded the title compound **224** (9.0 mg, 81%) as a colourless foam: (Characterization for a major tautomer)

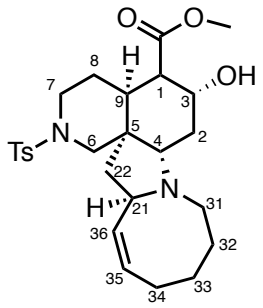
R_f = 0.46 (petroleum ether–EtOAc, 1:1); $[\alpha]_D^{16}$+8 (c = 0.1, $CHCl_3$); ν_{max} 2928, 2856, 1742, 1684, 1653, 1635, 1427, 1349, 1257, 1164, 1091 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) 12 (1H, br s, OH), δ 7.63 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.43 (1H, m, CH-C36), 5.40 (1H, dd, *J* = 10.3, 5.5 Hz, CH-C35), 4.17 (1H, dd, *J* = 14.8, 5.0 Hz, CH-C21), 3.80 (1H, d, *J* = 11.5 Hz, CH_2-C6), 3.74 (3H, s, CO_2CH_3), 3.64 (1H, m, CH_2-C7), 3.40 (1H, m, CH_2-C6), 3.18–2.99 (2H, m, CH_2-C2, CH_2-C31), 2.81–2.60 (4H, m, CH_2-C2, CH-C4, CH_2-C7, CH_2-C31), 2.48–2.45 (1H, m, CH-C9), 2.44 (3H, s, CH_3-Ts), 2.33–2.28 (2H, m, CH_2-C34), 2.09–2.01 (2H, m, CH_2-C22, CH_2-C32), 1.98 (1H, d, *J* = 11.6 Hz, CH_2-C22), 1.84–1.79 (1H, m, CH_2-C8), 1.58–1.479 (3H, m, CH_2-C32, CH_2-C33), 1.09–1.06 (1H, m, CH_2-C8);

^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7 (C-C3), 171.9 (CO_2Me), 143.2 (C-Ts), 134.2(C-Ts), (CH-Ts), 133.5 (CH-C36), 129.8 (CH-Ts), 129.5 (CH-Ts), 127.6 (CH-Ts), 127.4 (CH-Ts), 126.7 (CH-35), 99.1 (C-C1), 60.4 (CH-C4), 57.6 (CH-C21), 54.9 (CH_2-C6), 51.4 (CO_2Me), 49.1 (CH_2-C31), 46.4 (CH_2-C7), 43.6 (CH-C9), 42.0 (C-C5), 36.3 (CH_2-C22), 30.9 (CH_2-C2), 29.6 (CH_2-C8), 26.4 (CH_2-C32), 25.1 (CH_2-C33), 24.5 (CH_2-C34), 21.4 (CH_3-Ts);

HRMS (ESI) for $C_{26}H_{34}N_2O_5S$ ($[M+H]^+$) calcd. 487.2261, found 487.2264.

methyl (4aS,7aS,14aR,15aR,Z)-6-hydroxy-2-tosyl-2,3,4,4a,5,6,7,7a,9,10,11,12,14a,15-tetradecahydro-1H-azocino[1',2':1,5]pyrrolo[2,3-i]isoquinoline-5-carboxylate (225)



Chemical Formula: $C_{26}H_{36}N_2O_5S$
Exact Mass: 488.23

To a stirred solution of *β*-ketoester **224 (**8.0 mg, 16 μmol) in MeOH (0.5 mL) at 0 °C was added Sodium borohydride (1.2 mg, 33 μmol). The reaction was stirred at 0 °C for 1hr and then quenched with sat. NH_4Cl (1 mL) The reaction was extracted with Et_2O (3x1.5 mL). The organics were dried (Na_2SO_4) and evacuated. Purification by column chromatography on silica gel (petroleum ether– EtOAc 2:1 to 1:1) afforded the *β*-hydroxyester **225** (7.5 mg, 97%) as a mixture of diastereomers. (Stereochemistry is not assigned)

R_f = 0.34 (petroleum ether–EtOAc, 1:1); $[\alpha]_D^{18}$–26 (c = 0.1, $CHCl_3$); ν_{max} 3542, 2889, 2850, 1727, 1686, 1653, 1635, 1459, 1163, 1095 cm^{-1};

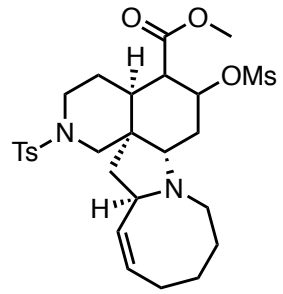
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.0 Hz, CH-Ts), 7.34 (2H, d, *J* = 8.0 Hz, CH-Ts), 5.46 (2H, m, CH-C35, CH-C36), 4.35 (1H, m, CH-C3), 4.22 (1H, m, CH-C21), 3.74 (1H, m, CH_2-C7), 3.70 (3H, s, CO_2Me), 3.45 (1H, m, CH_2-C6), 3.42–3.26 (3H, m, CH_2-C6, CH_2-C7, CH_2-C31), 2.74 (1H, m, CH-C4), 2.71–2.63 (2H, m, CH-C1, CH_2-C31), 2.60–2.51 (1H, m, CH-C9), 2.42 (3H, s, CH_3-Ts), 2.29–2.15 (2H, m, CH_2-C2, CH_2-C34), 2.05 (1H,m, CH_2-C34), 2.05–1.99 (2H, m, CH_2-C2, CH_2-C33), 1.92 (1H, m, CH_2-C32), 1.82 (1H, m, CH_2-C8), 1.70–1.63 (2H, m, CH_2-C32, CH_2-C33), 1.07 (1H, m, CH_2-C8);

^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6 (CO_2Me), 143.1 (C-Ts), 135.5 (CH-C36), 133.7 (C-Ts), 129.4 (CH-Ts), 129.4 (CH-Ts), 127.7 (CH-Ts), 127.7 (CH-Ts), 125.3 (CH-C35), 66.5 (CH-C3), 58.0 (CH-C21), 57.2 (CH-C4), 54.4 (CO_2Me), 51.9 (CH-C1), 49.5 (CH_2-C31), 46.8

(CH_2-C6), 44.6 (C-C7), 44.6 (C-C9), 39.8 (CH_2-C5), 37.8 (CH_2-C22), 37.4 (CH_2-C2), 29.7 (CH_2-C8), 26.8 (CH_2-C34), 24.6 (CH_2-C32), 24.2 (CH_2-C33), 21.5 (CH_3-Ts);

HRMS (ESI) for $C_{26}H_{34}N_2O_5S$ ($[M+H]^+$) calcd. 489.2418, found 489.2419.

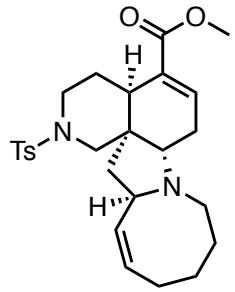
methyl (4aS,7aS,14aR,15aR,Z)-6-((methylsulfonyl)oxy)-2-tosyl-2,3,4,4a,5,6,7,7a,9,10,11,12,14a,15-tetradecahydro-1H-azocino[1',2':1,5]pyrrolo[2,3-i]isoquinoline-5-carboxylate (226)



Chemical Formula: $C_{27}H_{38}N_2O_7S_2$
Exact Mass: 566.21

To a stirred solution of β-hydroxyester **225 (**8.0 mg, 16 μmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added freshly distilled triethylamine (2.5 μL, 18 μmol). Freshly distilled methane sulfonyl chloride (1.8 μL, 24 μmol) was then added dropwise. The reaction was stirred at 0 °C for 45 minutes. Saturated $NaHCO_3$ (0.1 mL) was then added to quench the reaction. The reaction mixture was then extracted with with Et_2O (3x1 mL). The organics were dried (Na_2SO_4) and evacuated. The residue was used in the next reaction without purification.

methyl (4aR,7aS,14aR,15aR,Z)-2-tosyl-2,3,4,4a,7,7a,9,10,11,12,14a,15-dodecahydro-1H-azocino[1',2':1,5]pyrrolo[2,3-i]isoquinoline-5-carboxylate (227)



Chemical Formula: $C_{26}H_{34}N_2O_4S$
Exact Mass: 470.22

To a solution of mesylate **226** (8.0 mg, 14 μmol) in benzene (0.5 mL) was added DBU (4 μL, 2.8 μmol). The reaction was then heated to reflux overnight. After cooling to room temperature saturated $NaHCO_3$ (0.5 mL) was added. The reaction was extracted with Et_2O (2x2 mL), dried (Na_2SO_4), and evacuated to afford the title compound **227** as crude material. (There is no enough material to get the NMR data).

HRMS (ESI) for $C_{26}H_{34}N_2O_4S$ ($[M+H]^+$) calcd. 471.2263, found 471.2310.

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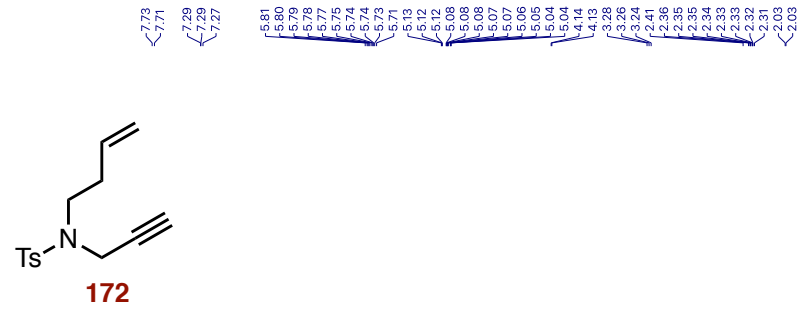
7. Appendix

7.1NMR Spectra of Selected Compounds



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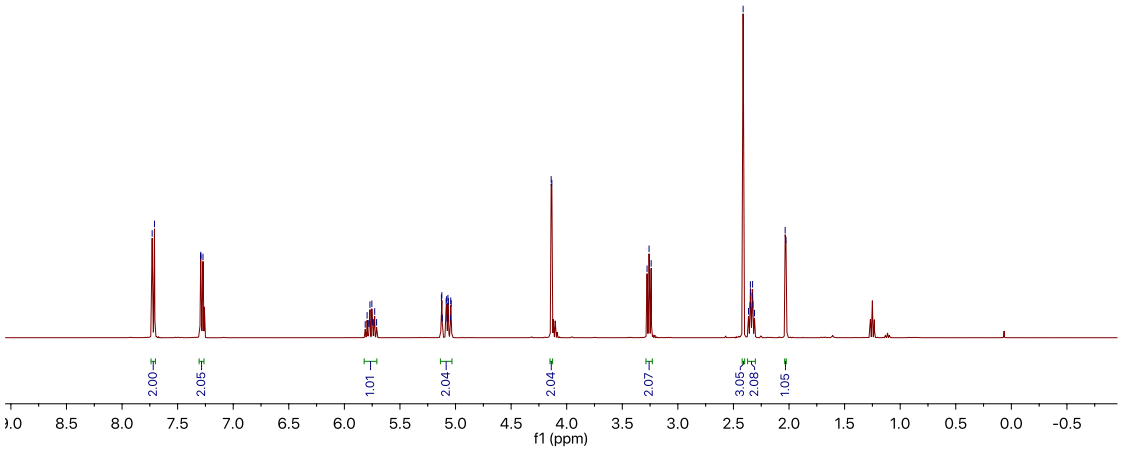

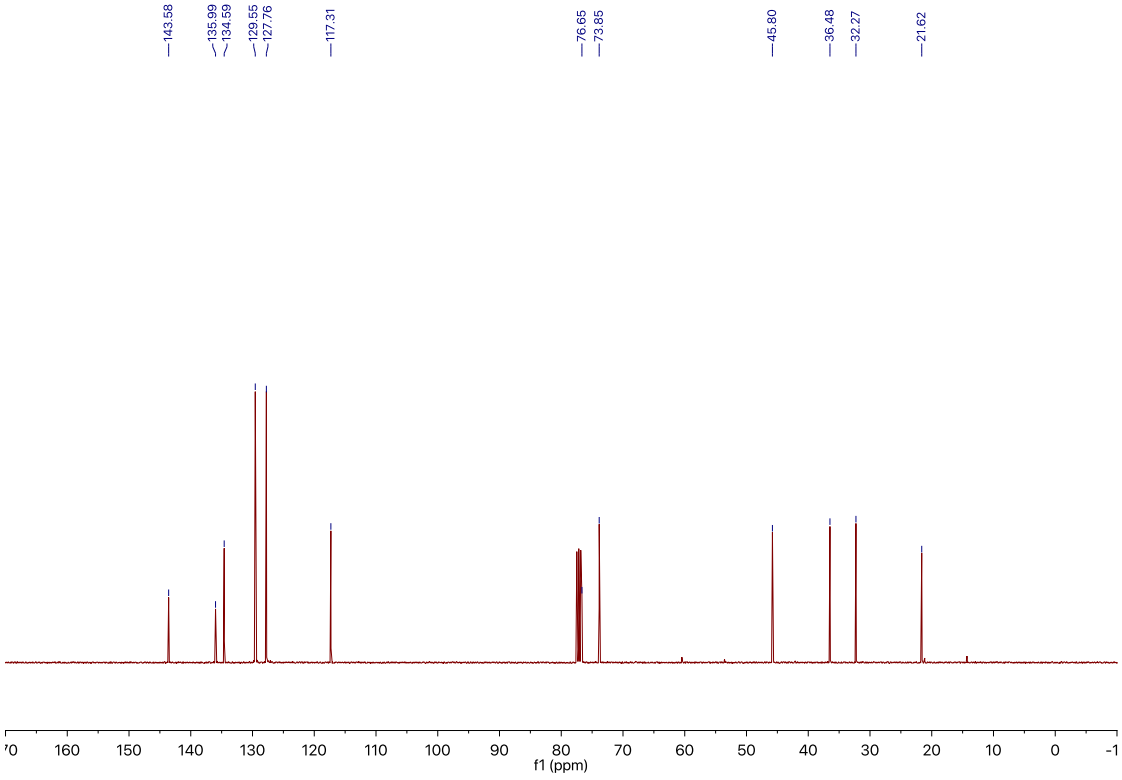

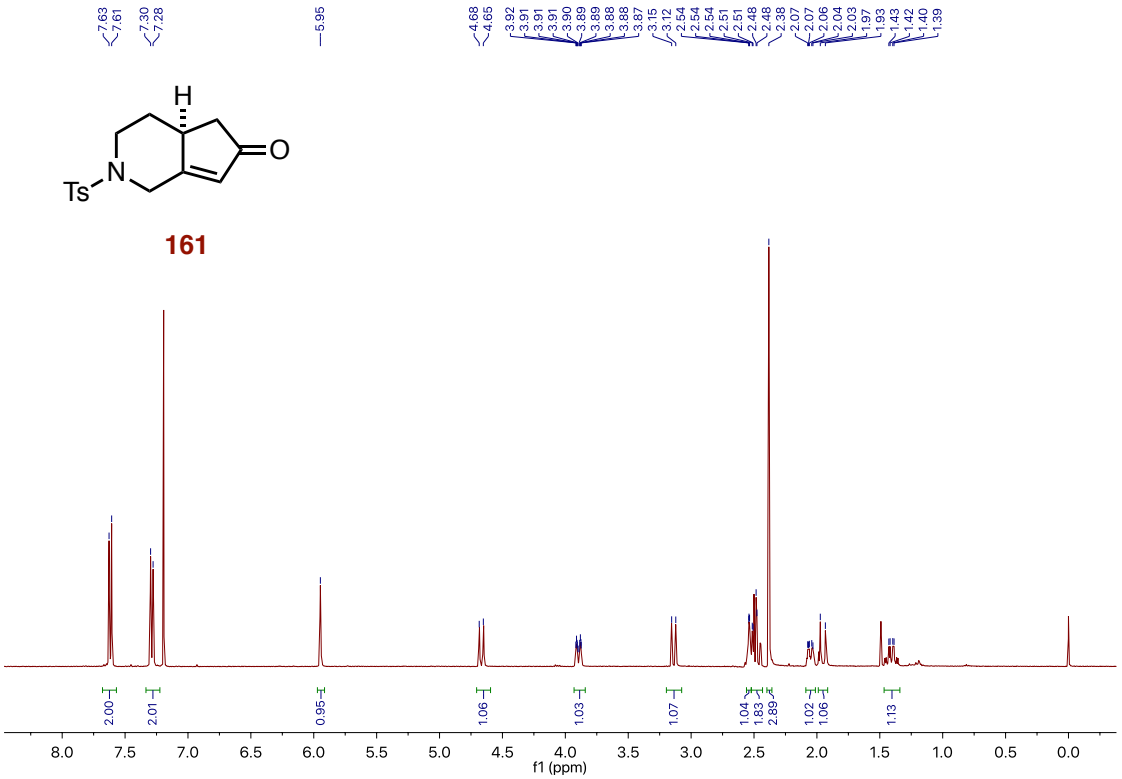
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2.04
2.03
1.97
1.93
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1.39
H
N
Ts
O
2.00
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0.95
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1.03
1.07
1.04
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2.89
1.02
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1.13
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7.5
7.0
6.5
6.0
5.5
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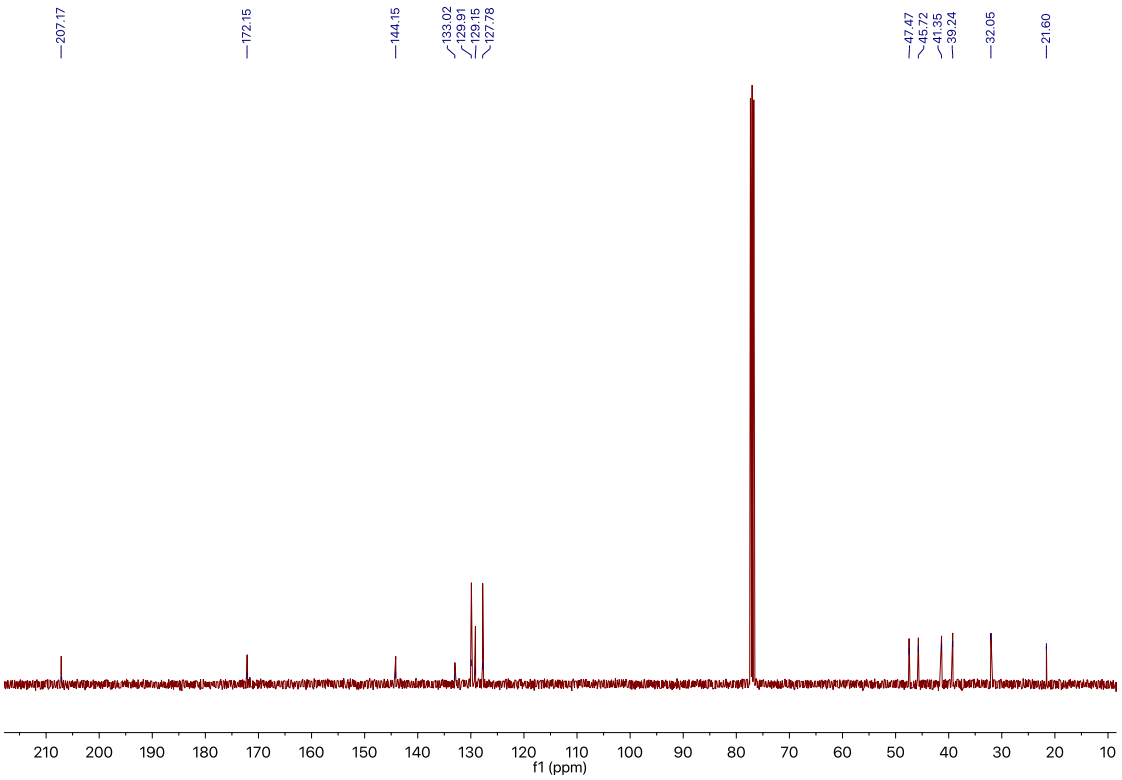
0.0
f1 (ppm)

161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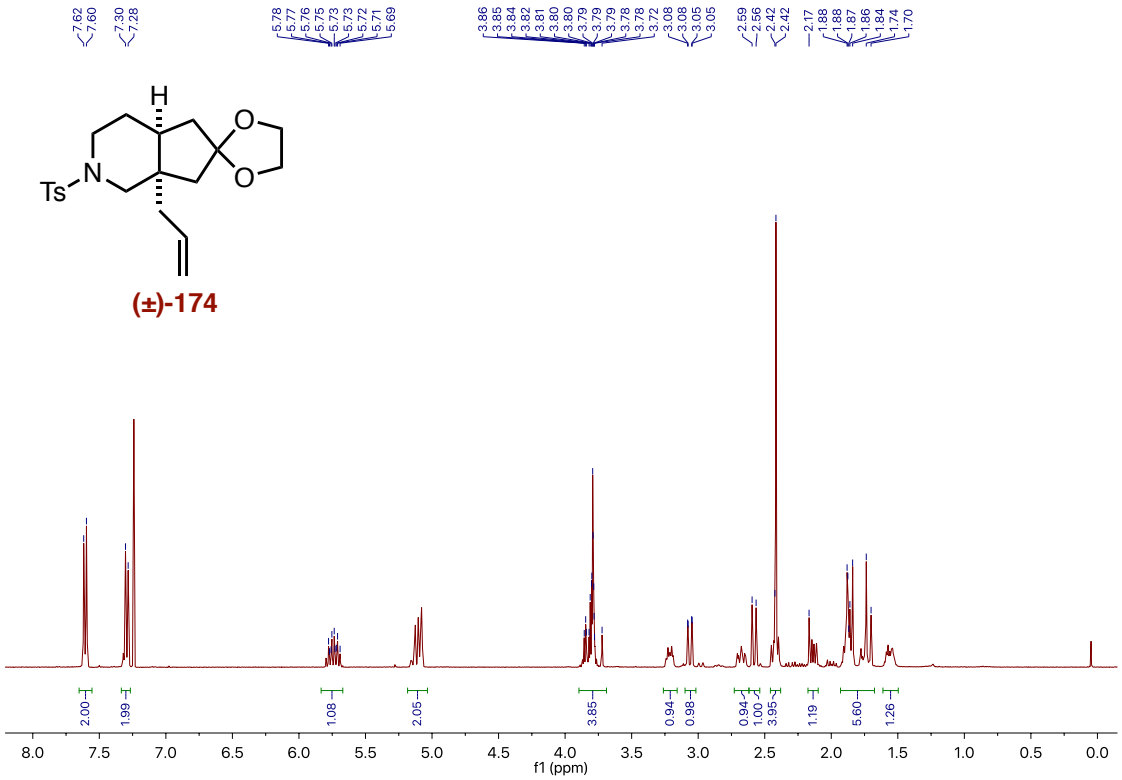
f1 (ppm)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1.74
1.70
H
O
O
N
Ts
2.00
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1.08
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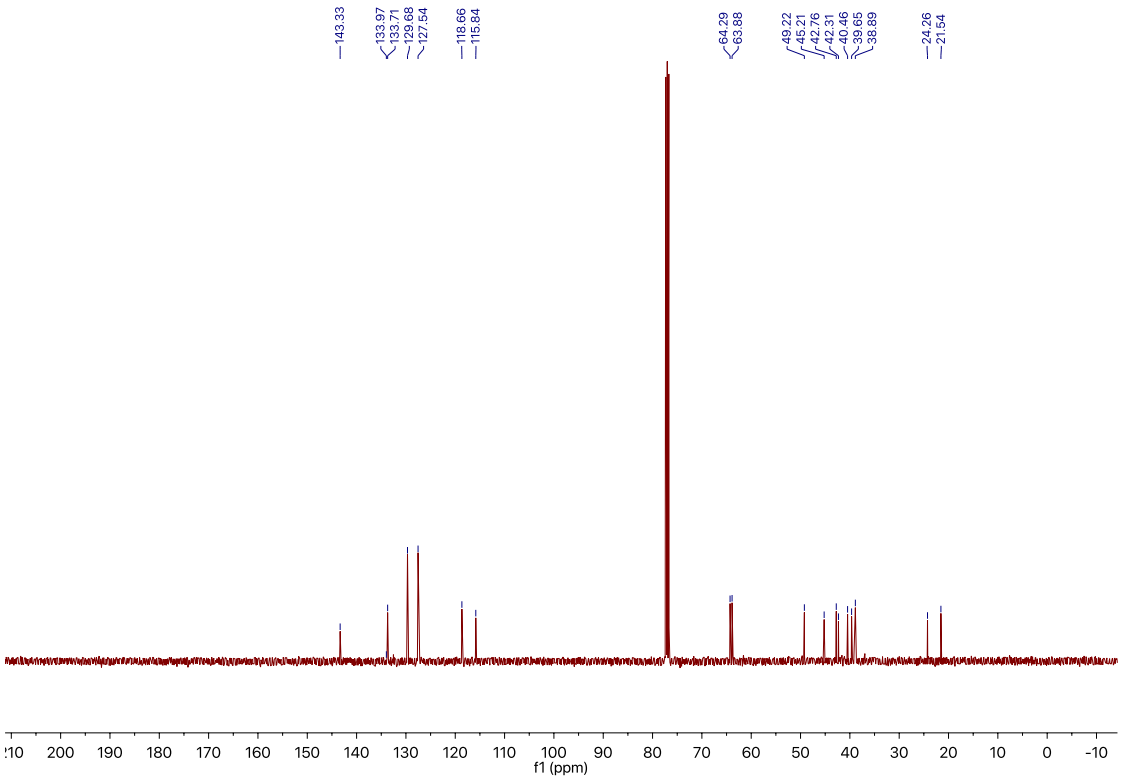
f1 (ppm)

(±)-174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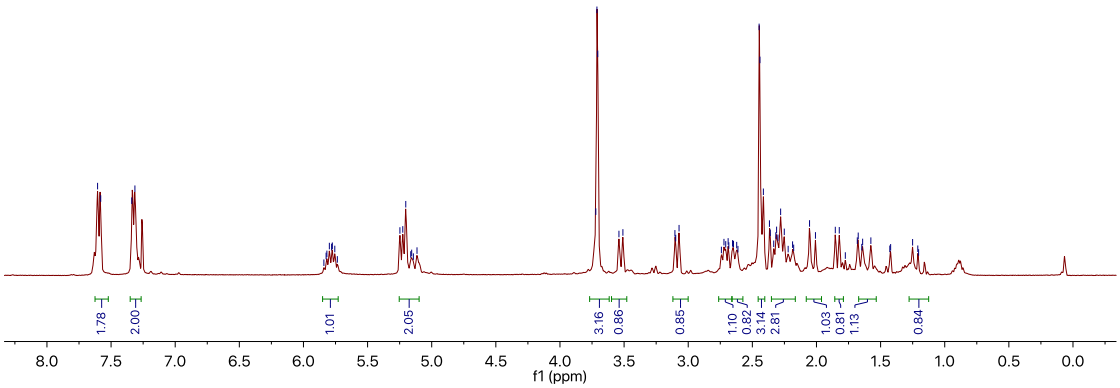
f1 (ppm)

265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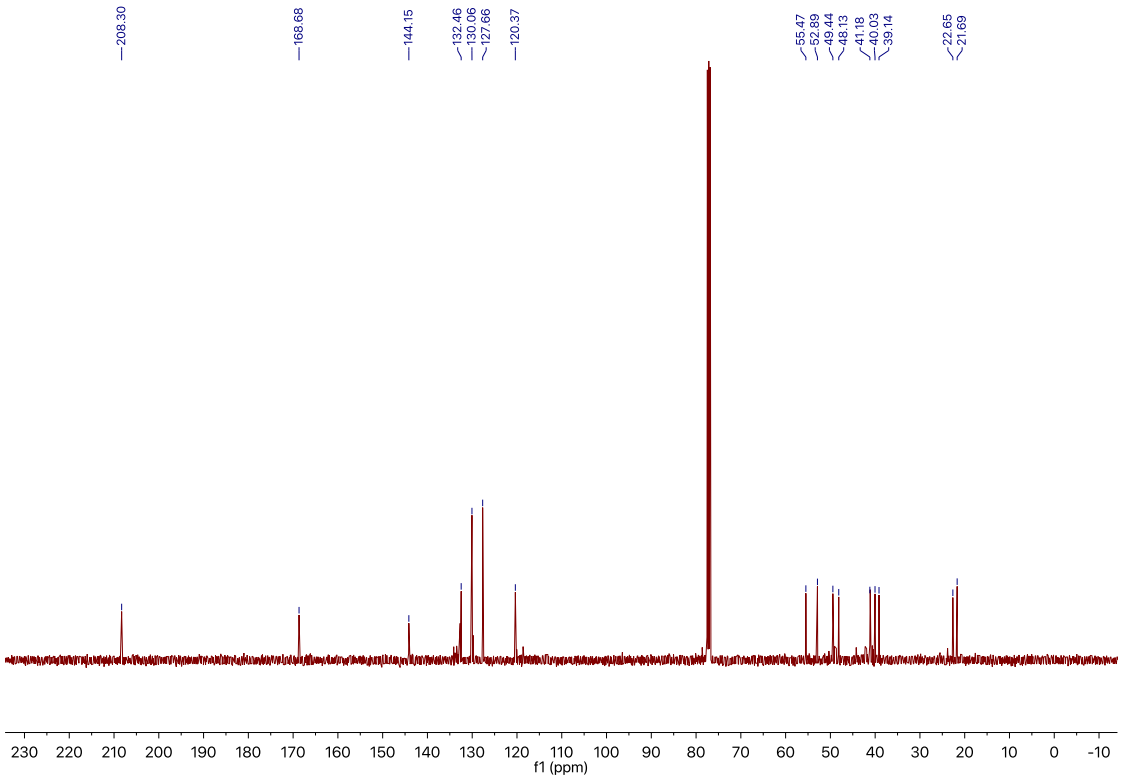
f1 (ppm)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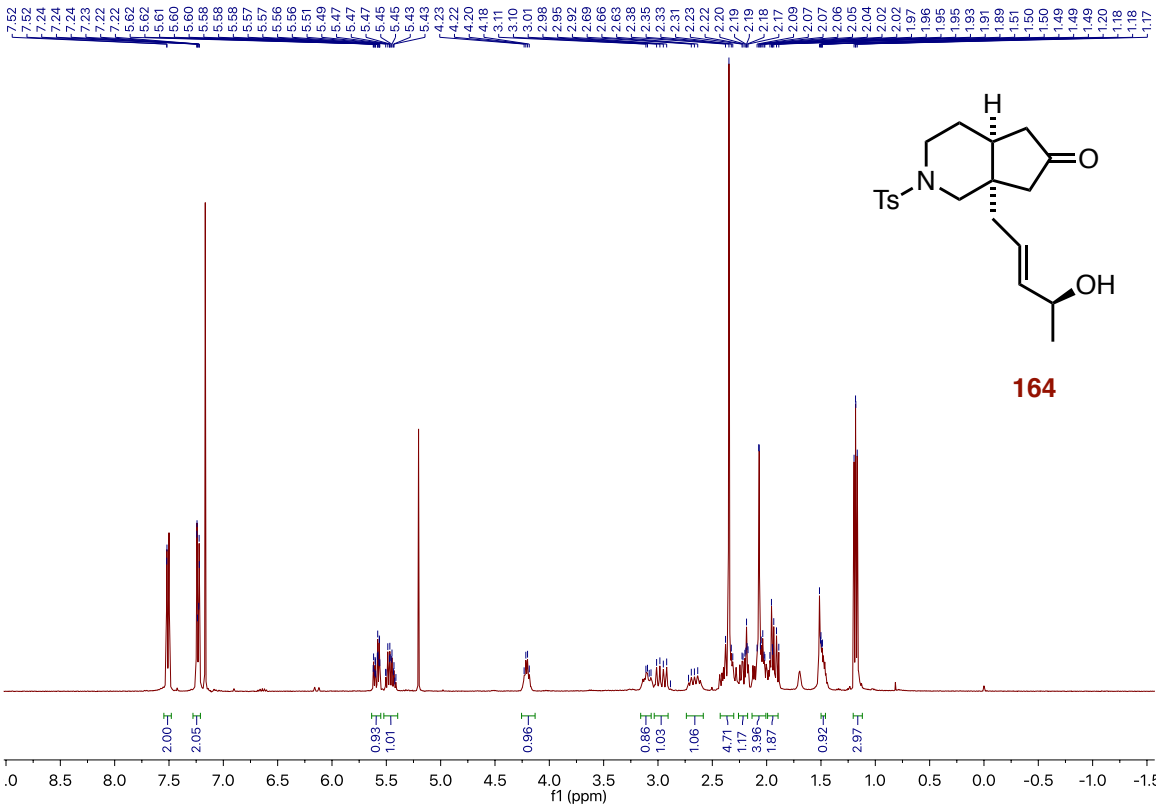
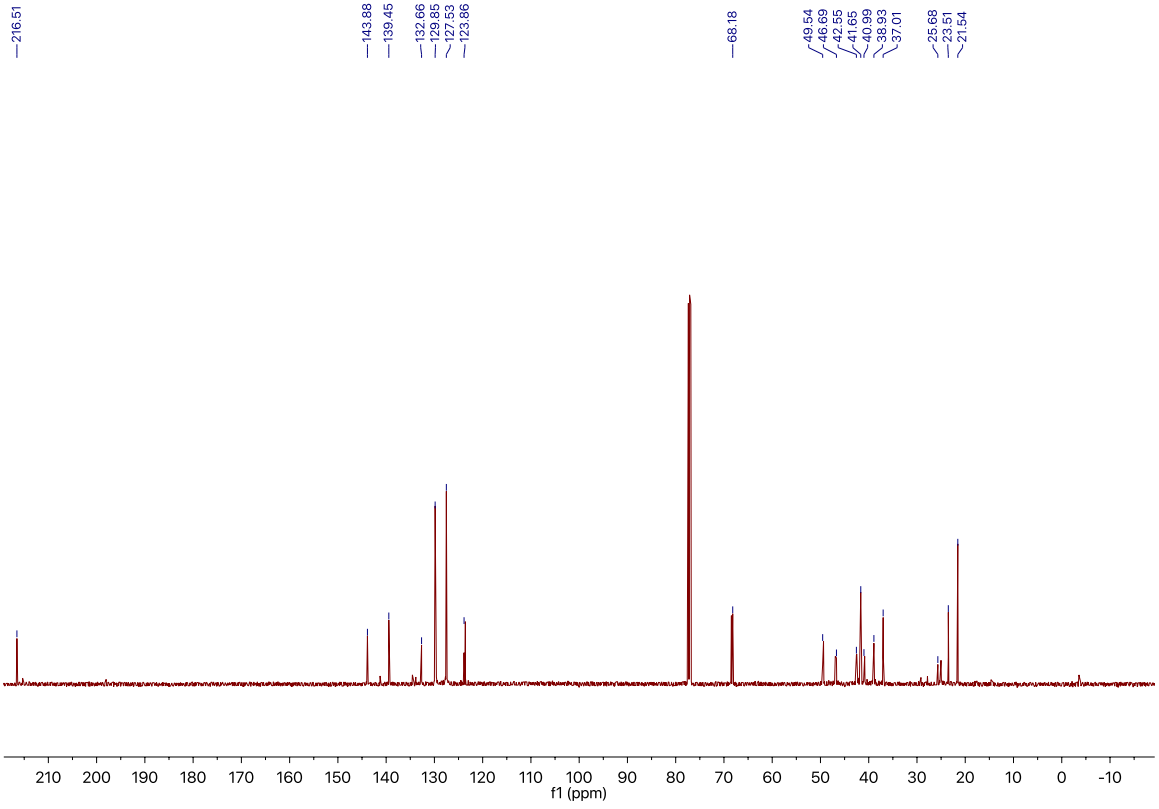
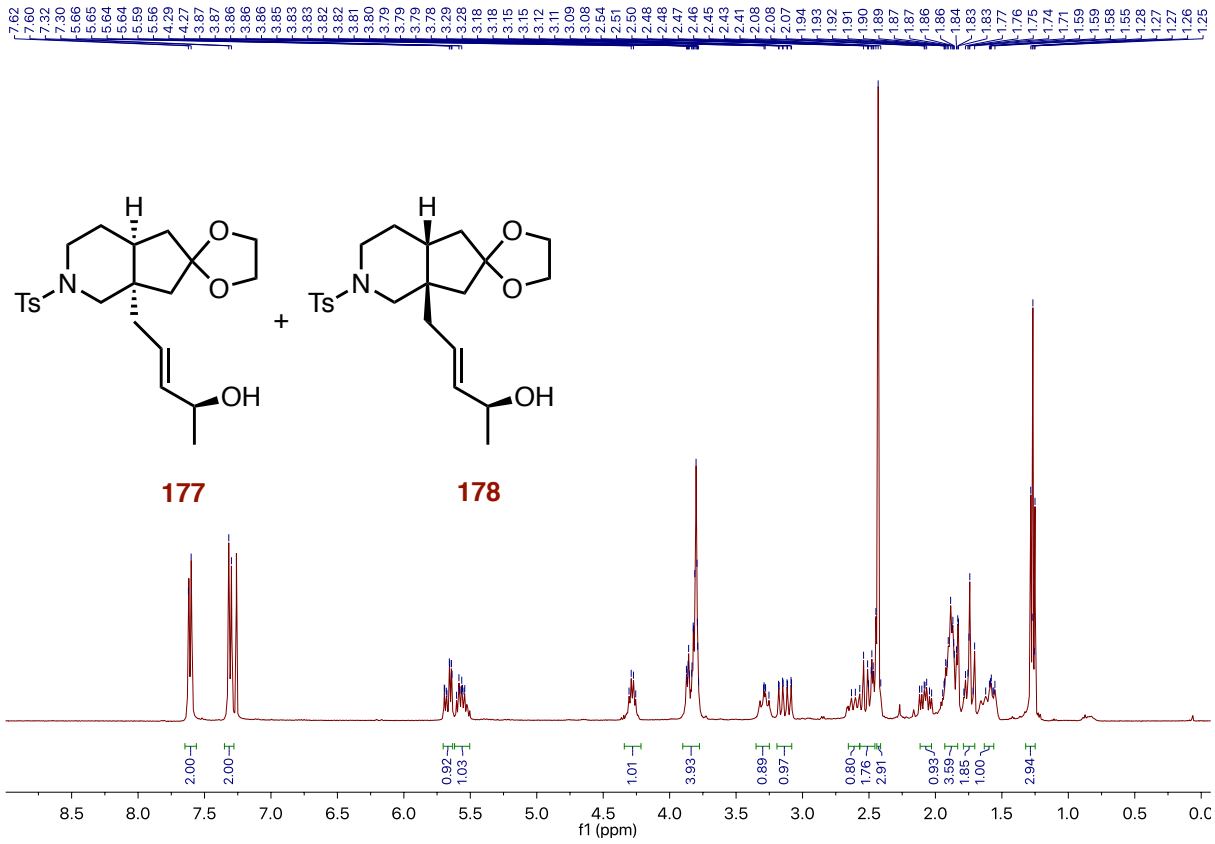
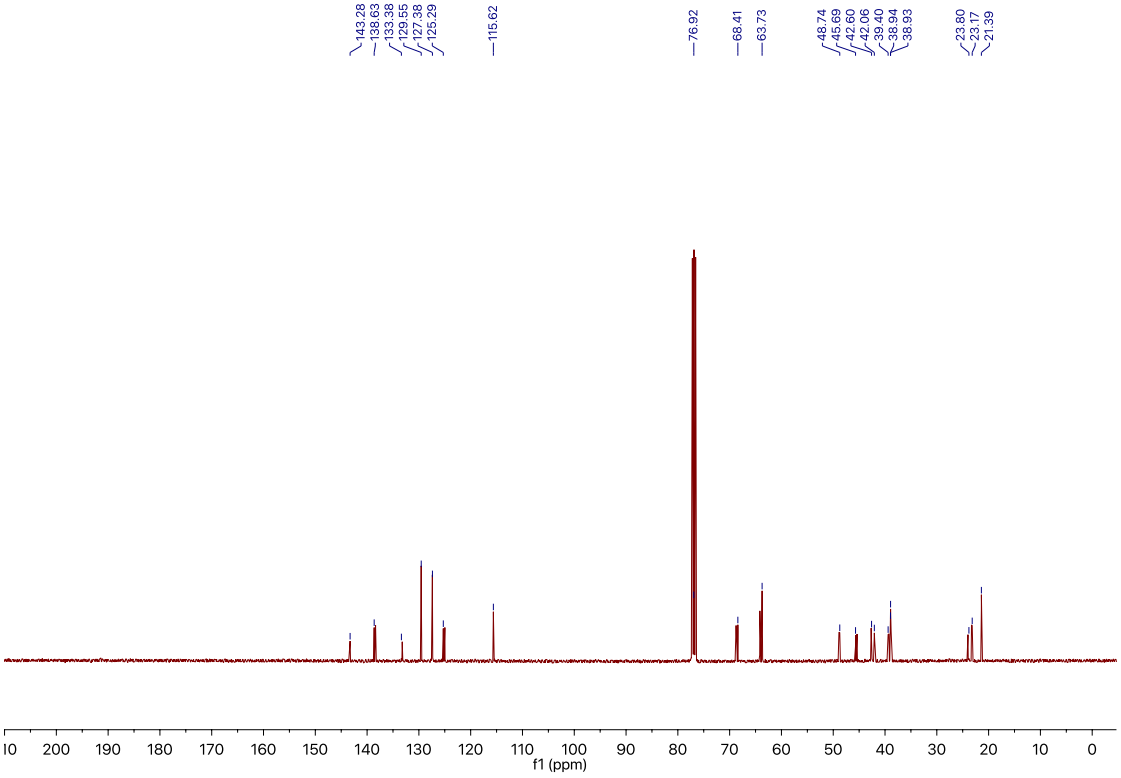
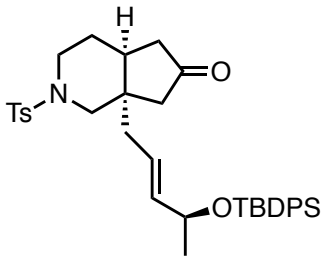
f1 (ppm)


H
O
N
Ts
OH
164
f1 (ppm)

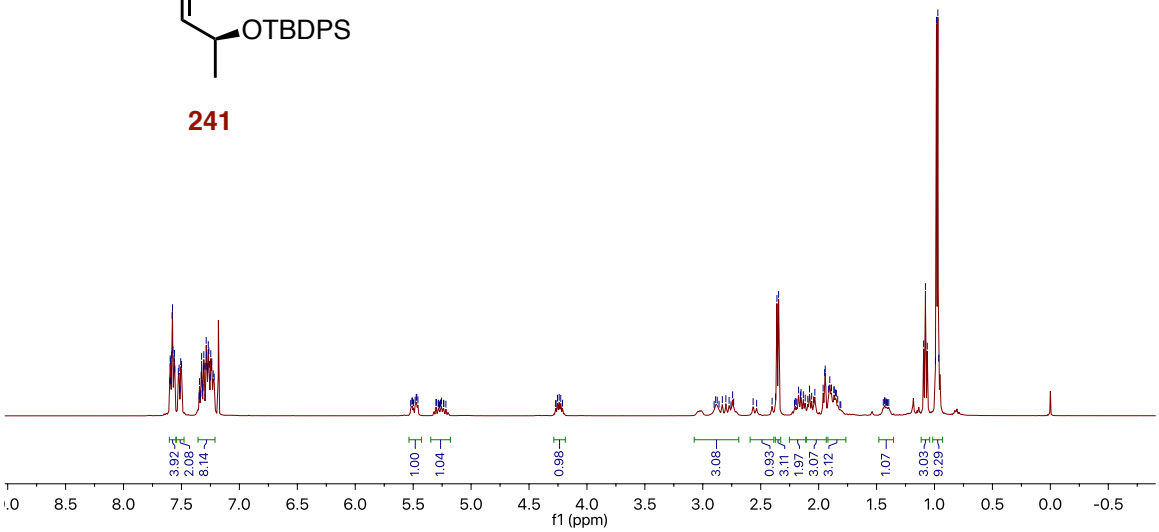

f1 (ppm)

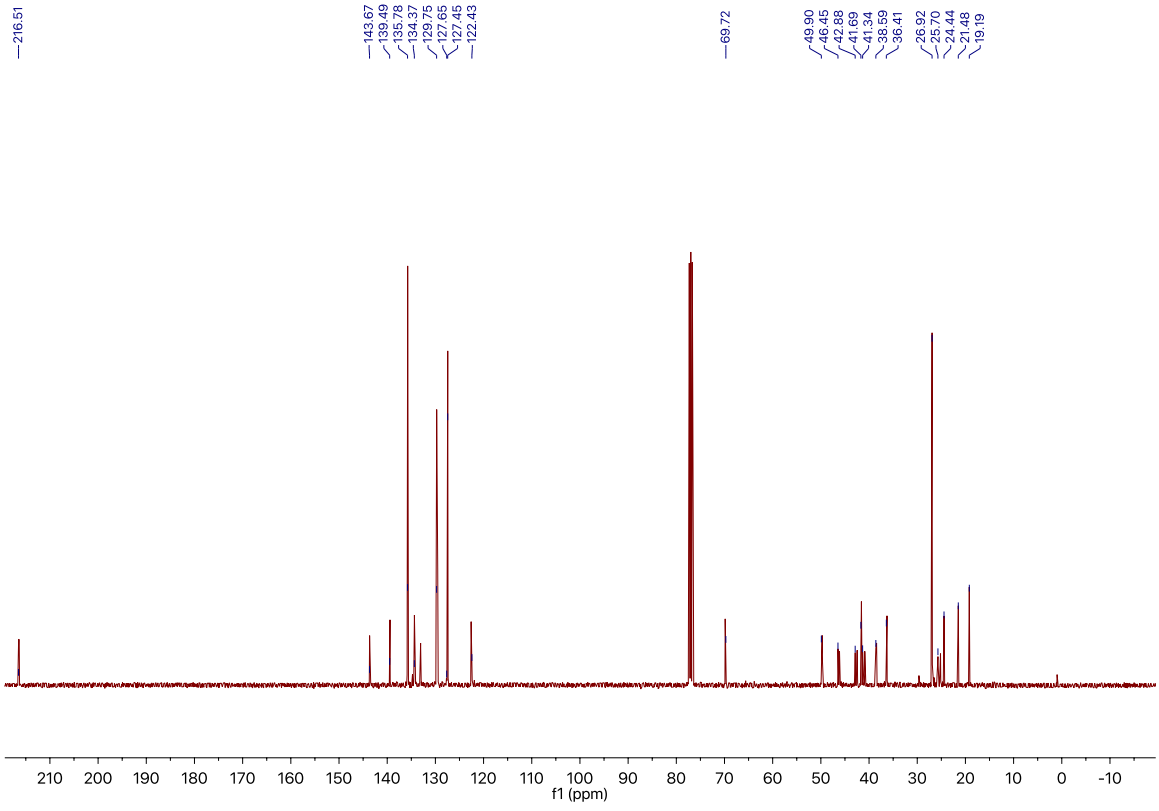

7.62 7.60 7.32 7.30 5.66 5.65 5.64 5.64 5.59 5.56 4.29 4.27 3.87 3.87 3.86 3.86 3.86 3.85 3.83 3.83 3.82 3.82 3.81 3.80 3.79 3.79 3.79 3.78 3.29 3.28 3.18 3.15 3.15 3.12 3.11 3.09 3.08 2.54 2.51 2.50 2.48 2.48 2.47 2.46 2.45 2.43 2.41 2.08 2.08 2.07 1.94 1.93 1.92 1.91 1.90 1.89 1.87 1.87 1.86 1.86 1.84 1.83 1.83 1.77 1.76 1.75 1.74 1.71 1.59 1.59 1.58 1.55 1.28 1.27 1.27 1.26 1.25
H
O
O
N
Ts
OH
+
H
O
O
N
Ts
OH
177
178
2.00 2.00 0.92 1.03 1.01 3.93 0.89 0.97 0.80 1.76 2.91 0.93 3.59 1.85 1.00 2.94
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

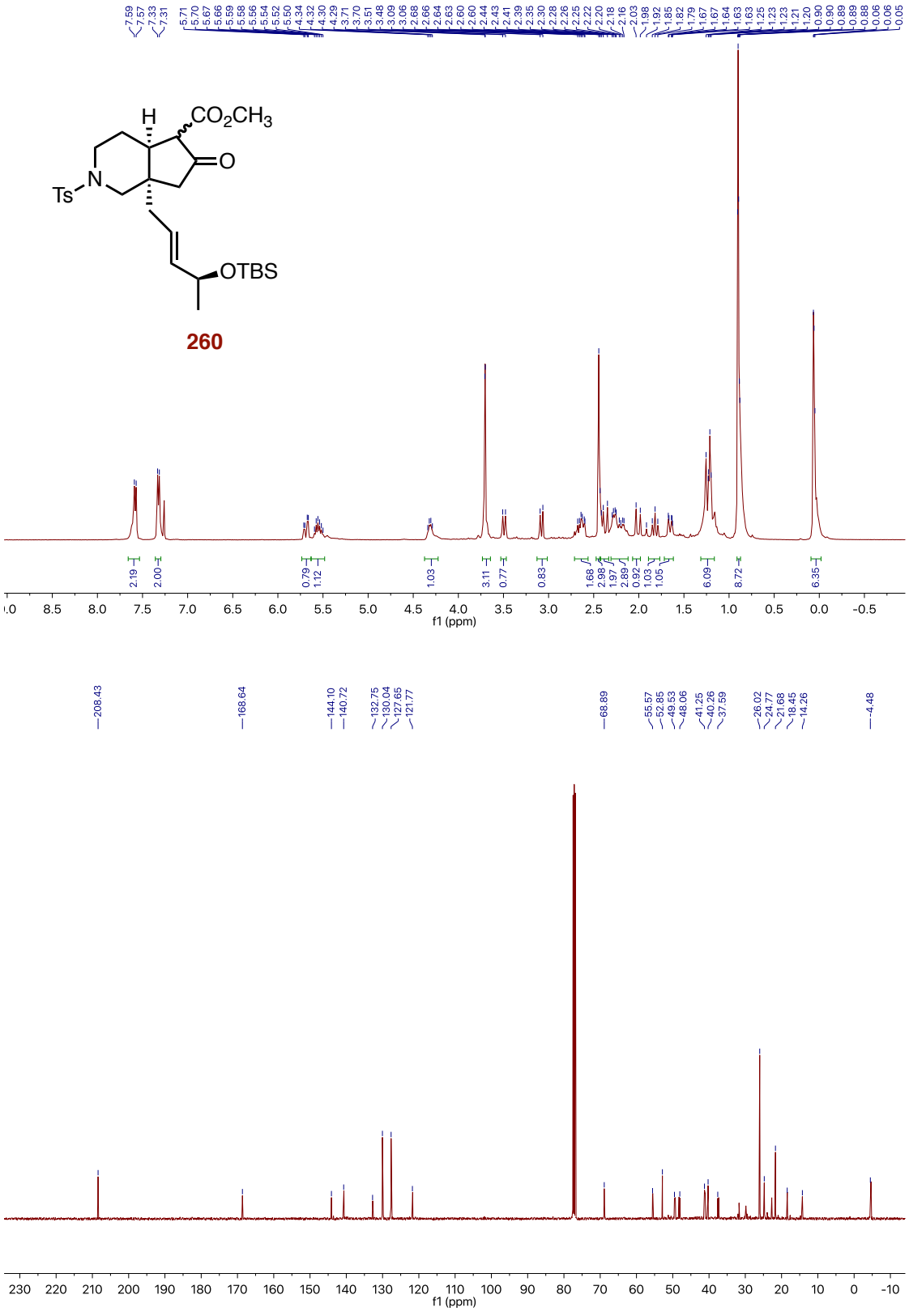

143.28 138.63 133.38 129.55 127.38 125.29 115.62 76.92 68.41 63.73 48.74 45.69 42.60 42.06 39.40 38.94 38.93 23.80 23.17 21.39
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

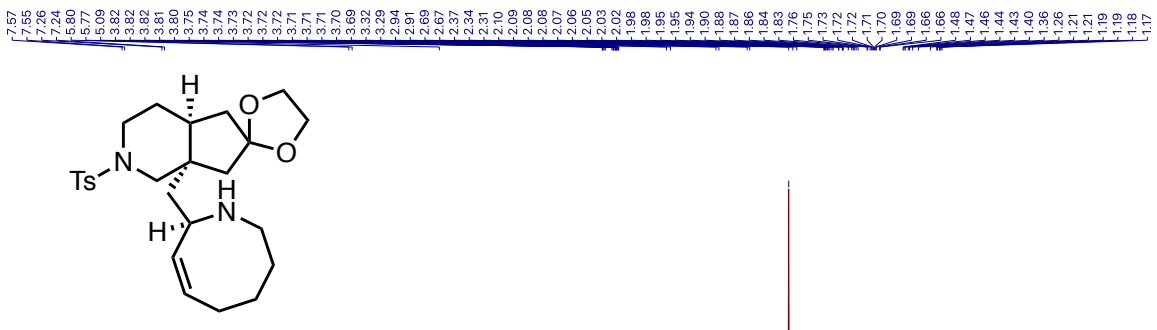

H
O
N
Ts
OTBDPS

241


3.92
2.08
8.14
1.00
1.04
0.98
3.08
0.93
3.11
1.97
3.07
3.12
1.07
3.03
9.29
f1 (ppm)

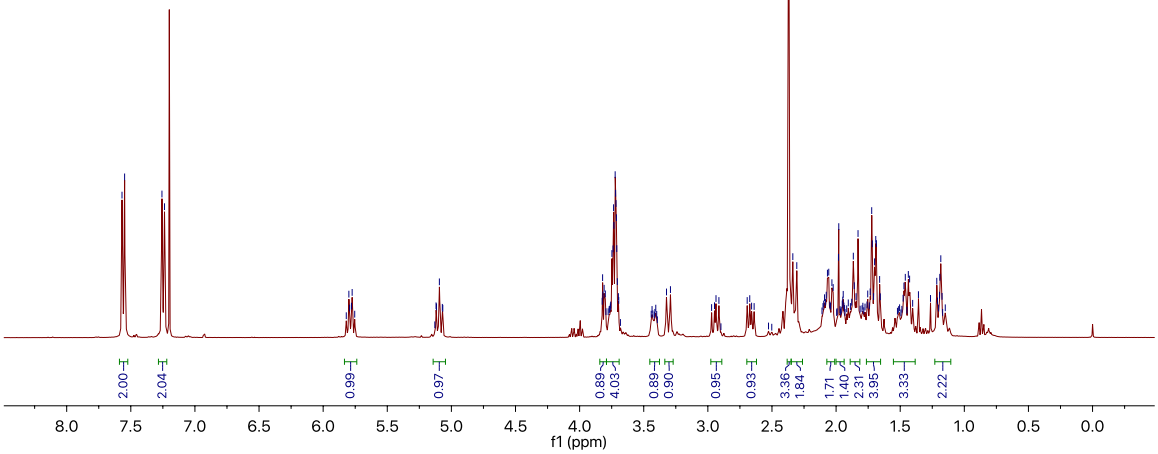

216.51
143.67
139.49
135.78
134.37
129.75
127.65
127.45
122.43
69.72
49.90
46.45
42.88
41.69
41.34
38.59
36.41
26.92
25.70
24.44
21.48
19.19
f1 (ppm)

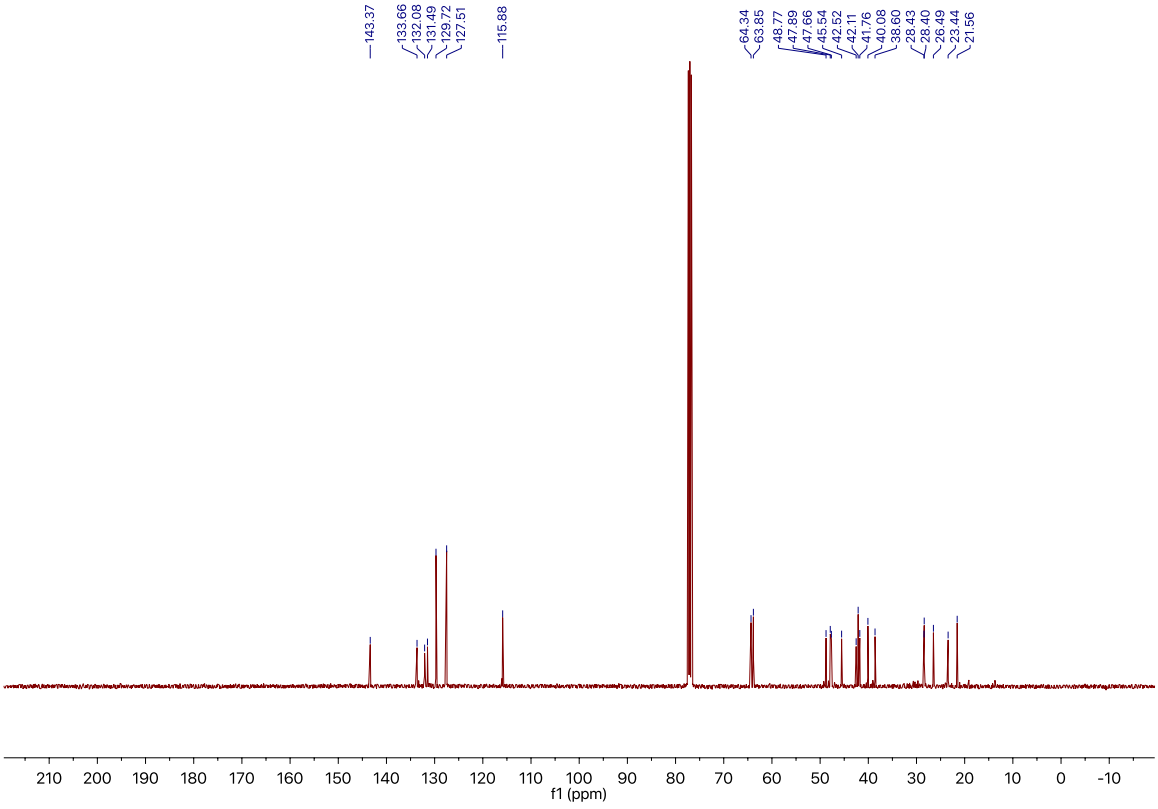

H
CO2CH3
O
N
Ts
OTBS
260
f1 (ppm)
f1 (ppm)

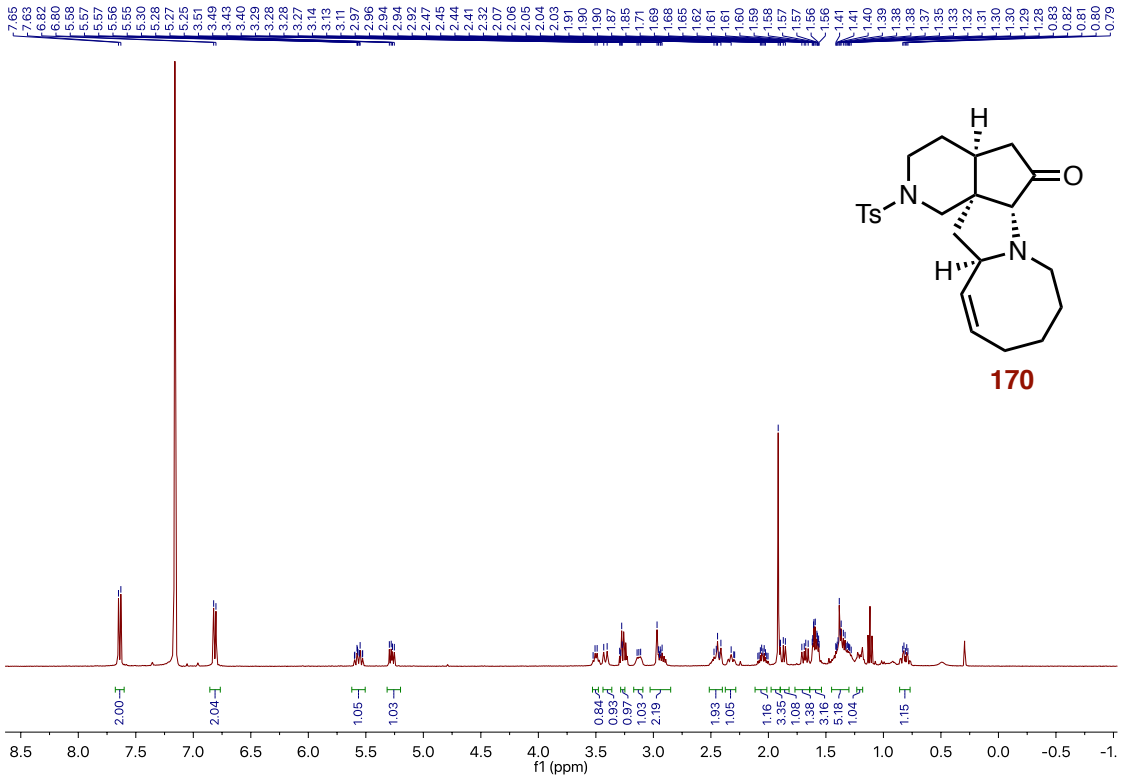

7.57
7.55
7.26
7.24
5.80
5.77
5.09
3.82
3.82
3.82
3.81
3.80
3.75
3.74
3.74
3.73
3.72
3.72
3.72
3.71
3.71
3.71
3.70
3.69
3.32
3.29
2.94
2.91
2.69
2.67
2.37
2.34
2.31
2.10
2.09
2.08
2.08
2.07
2.06
2.05
2.03
2.02
1.98
1.98
1.95
1.95
1.94
1.90
1.88
1.87
1.86
1.84
1.83
1.76
1.75
1.73
1.72
1.72
1.71
1.70
1.69
1.69
1.66
1.66
1.48
1.47
1.46
1.44
1.43
1.40
1.36
1.26
1.21
1.21
1.19
1.19
1.18
1.17

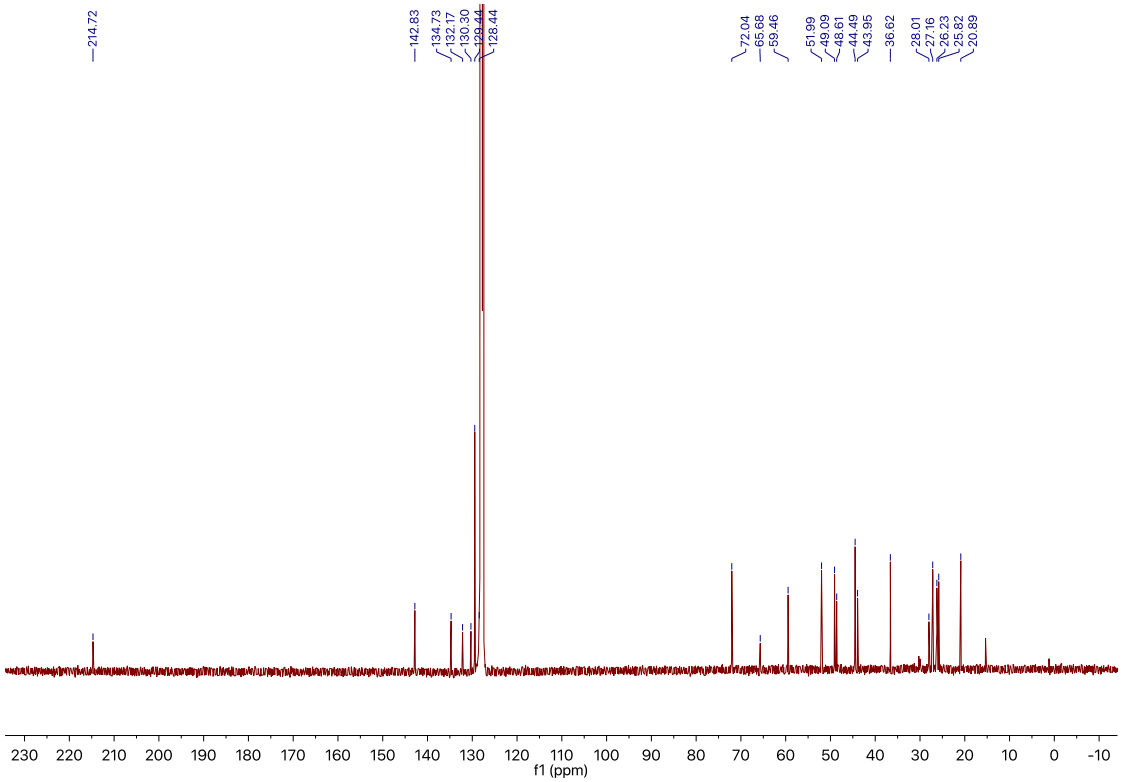
H
O
O
Ts
N
H
N
H

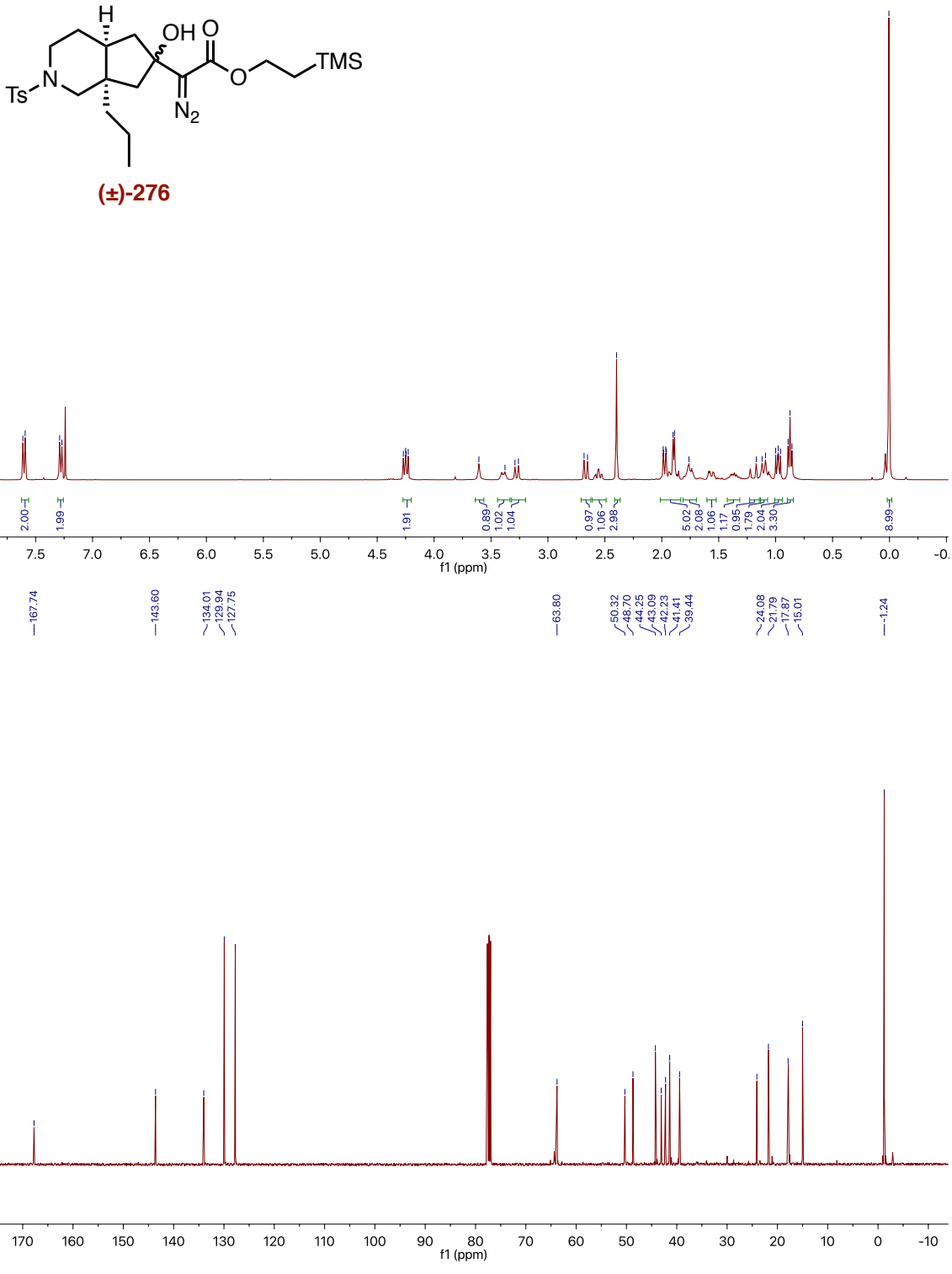
183

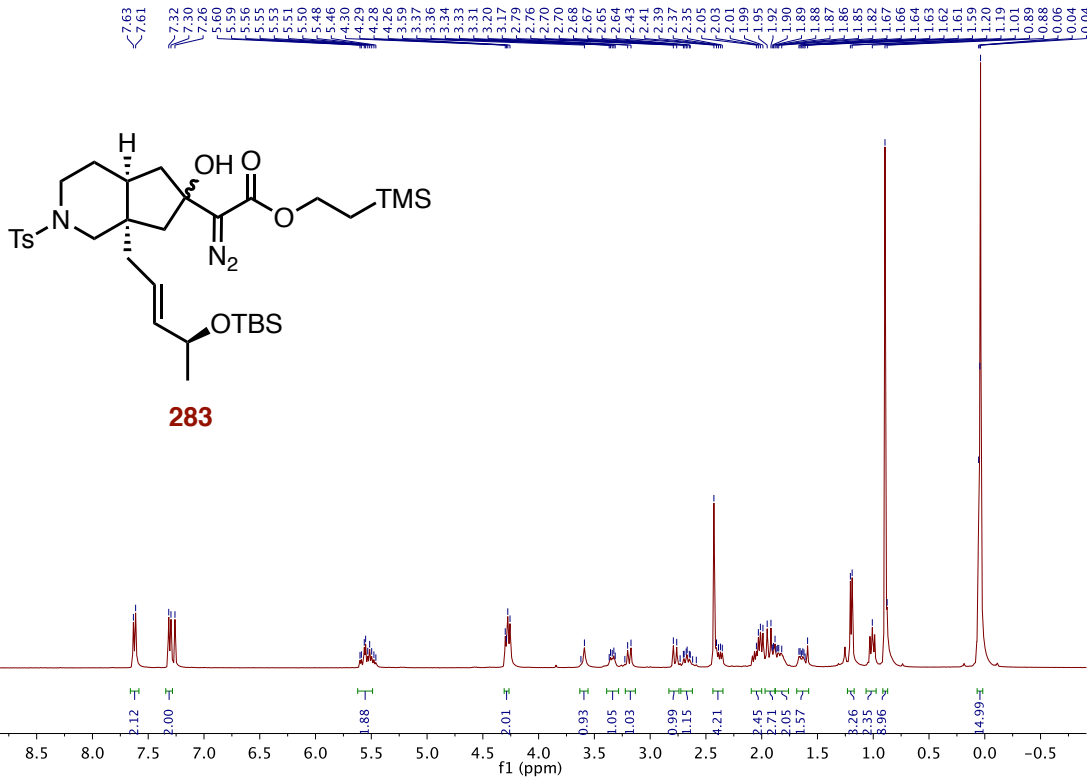

2.00
2.04
0.99
0.97
0.89
4.03
0.89
0.90
0.95
0.93
3.36
1.84
1.71
1.40
2.31
3.95
3.33
2.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


143.37
133.66
132.08
131.49
129.72
127.51
115.88
64.34
63.85
48.77
47.89
47.66
45.54
42.52
42.11
41.76
40.08
38.60
28.43
28.40
26.49
23.44
21.56
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

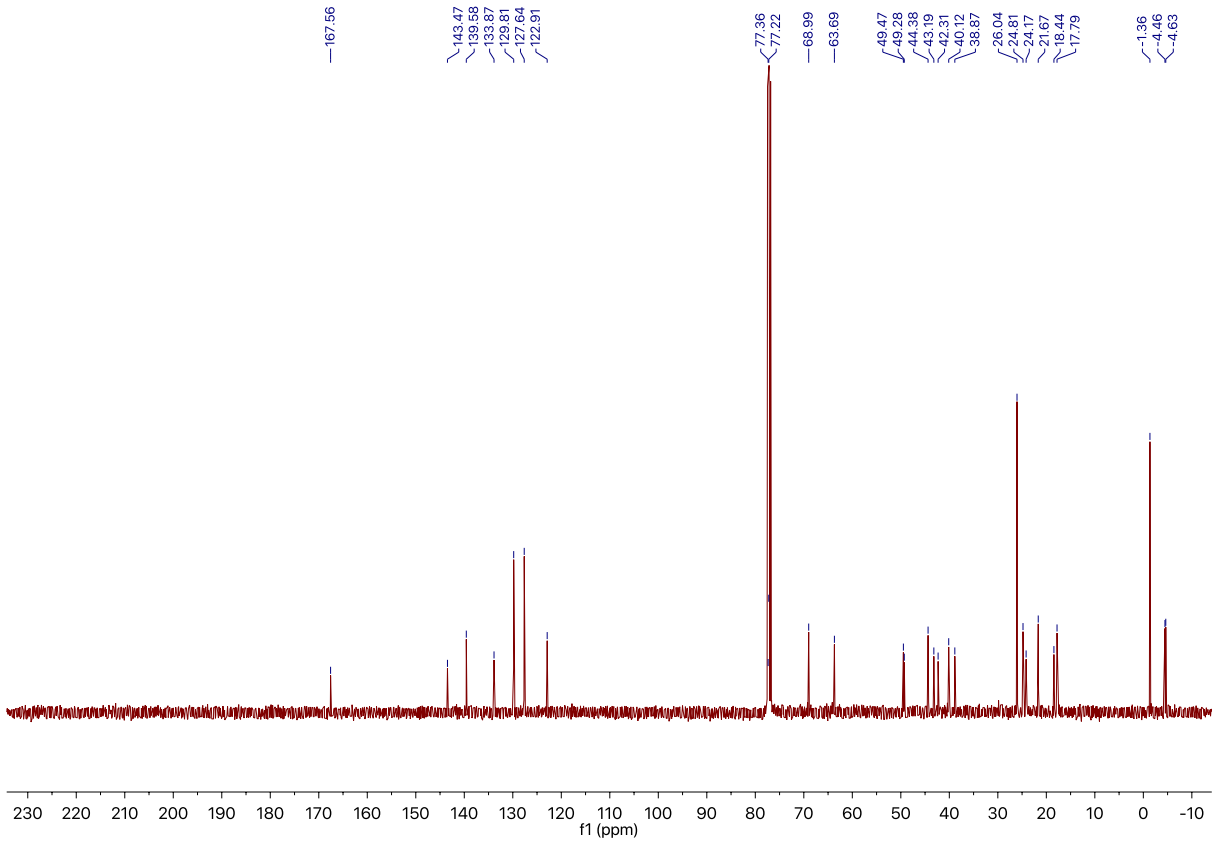

H
O
N
Ts
N
H
170
f1 (ppm)

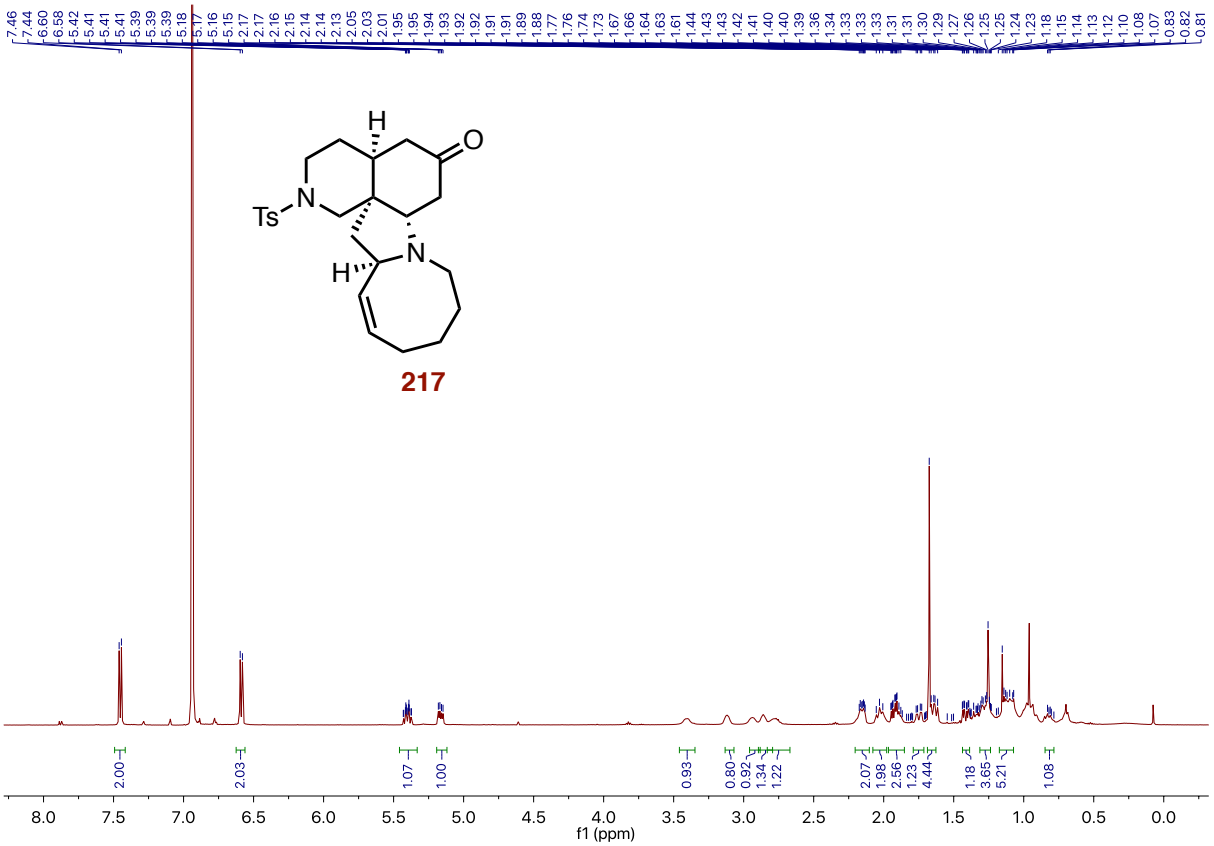

214.72
142.83
134.73
132.17
130.30
129.44
128.44
72.04
65.68
59.46
51.99
49.09
48.61
44.49
43.95
36.62
28.01
27.16
26.23
25.82
20.89
f1 (ppm)


7.61
7.59
7.29
7.27
4.27
4.25
4.25
4.23
3.61
3.38
3.29
3.26
2.68
2.65
2.40
1.99
1.98
1.97
1.96
1.90
1.89
1.76
1.17
1.12
1.09
1.00
0.98
0.98
0.97
0.96
0.89
0.87
0.86
0.01
H
OH
O
TMS
N
Ts
O
N2
(±)-276
2.00
1.99
1.91
0.89
1.02
1.04
0.97
1.06
2.98
5.02
2.08
1.06
1.17
0.95
1.79
2.04
3.30
8.99
f1 (ppm)
167.74
143.60
134.01
129.94
127.75
63.80
50.32
48.70
44.25
43.09
42.23
41.41
39.44
24.08
21.79
17.87
15.01
1.24
f1 (ppm)

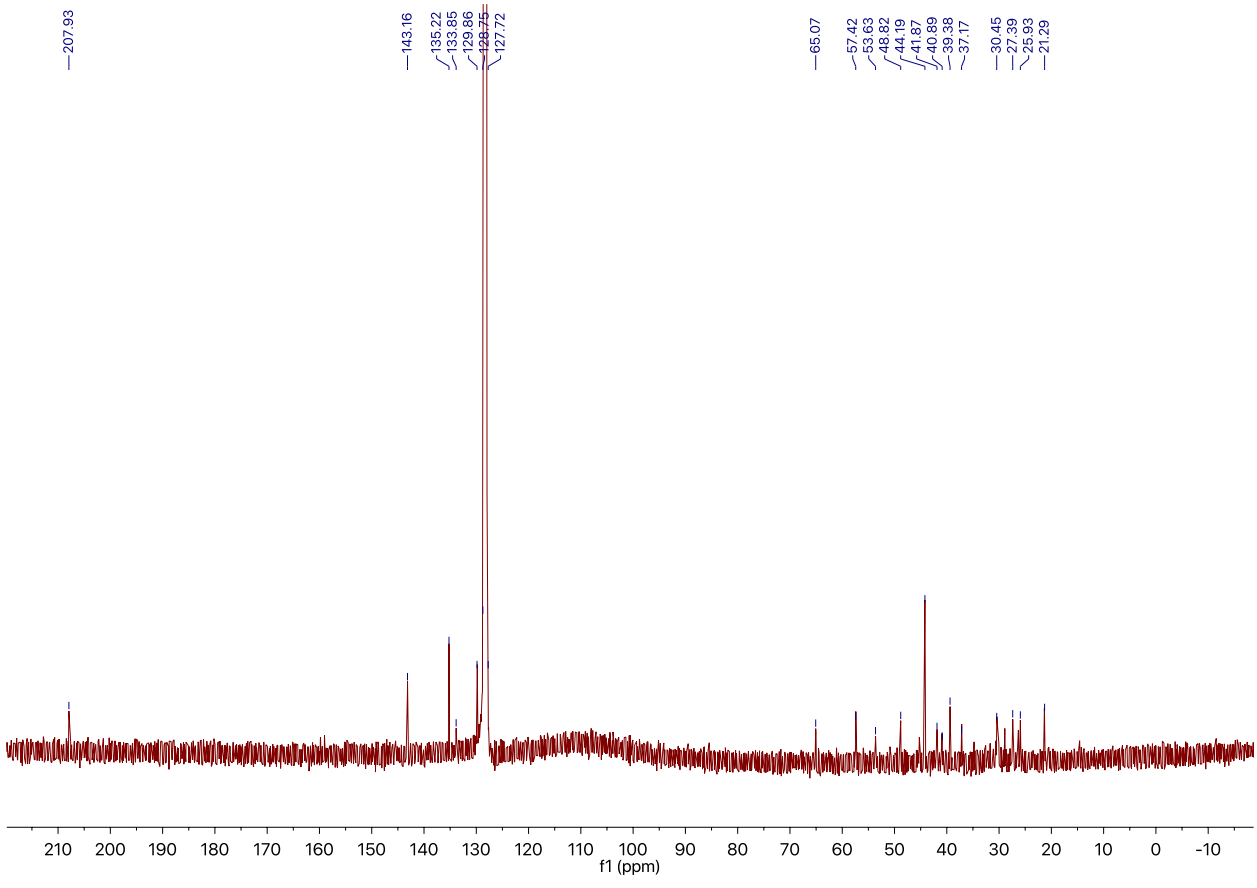


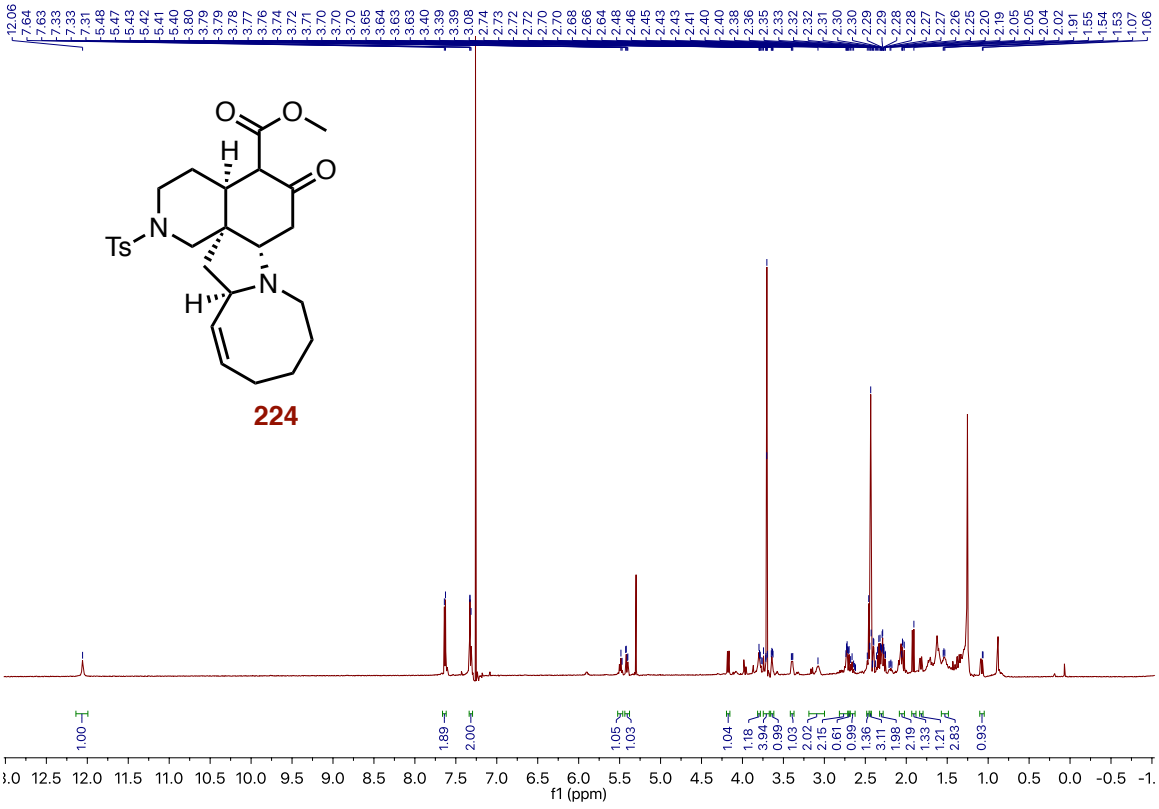
283



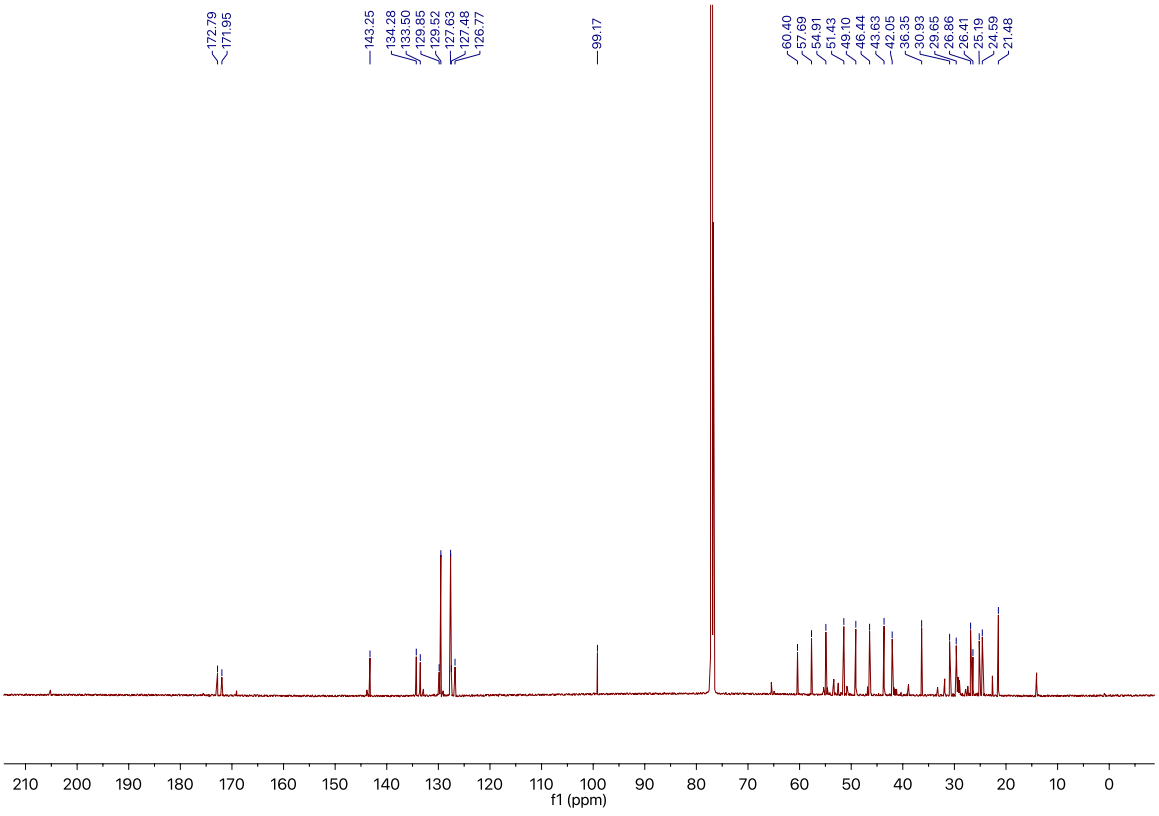


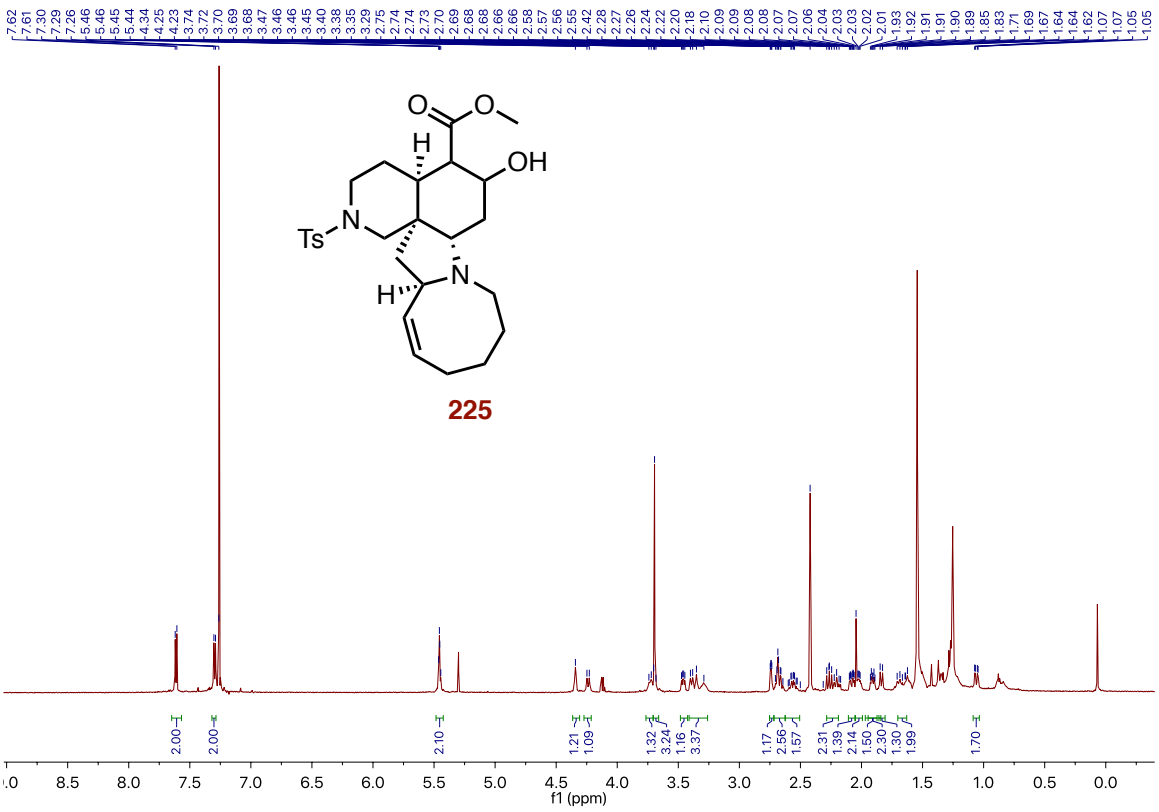
217




12.06
7.64
7.63
7.33
7.33
7.31
5.48
5.47
5.43
5.42
5.41
5.40
3.80
3.79
3.79
3.78
3.77
3.76
3.74
3.72
3.71
3.70
3.70
3.70
3.65
3.64
3.63
3.63
3.40
3.39
3.39
3.08
2.74
2.73
2.72
2.72
2.70
2.70
2.68
2.66
2.64
2.48
2.46
2.45
2.43
2.43
2.41
2.40
2.40
2.38
2.36
2.35
2.33
2.32
2.32
2.31
2.30
2.30
2.29
2.29
2.28
2.28
2.27
2.27
2.26
2.25
2.20
2.19
2.05
2.05
2.04
2.02
1.91
1.55
1.54
1.53
1.07
1.06
O
O
O
H
N
Ts
N
H
1.00
1.89
2.00
1.05
1.03
1.04
1.18
3.94
0.99
1.03
2.02
2.15
0.61
0.99
1.36
3.11
1.98
2.19
1.33
1.21
2.83
0.93
f1 (ppm)

224


172.79
171.95
143.25
134.28
133.50
129.85
129.52
127.63
127.48
126.77
99.17
60.40
57.69
54.91
51.43
49.10
46.44
43.63
42.05
36.35
30.93
29.65
26.86
26.41
25.19
24.59
21.48
f1 (ppm)



225