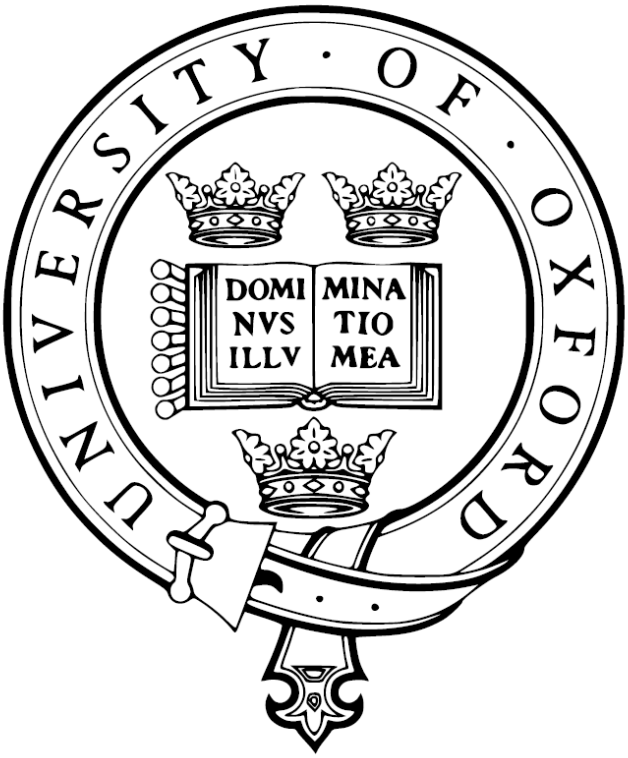
Total Synthesis of Complex Natural Products



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

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Trinity Term 2023

Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from February 2019 until April 2023, under the supervision of Professor Darren J. Dixon. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

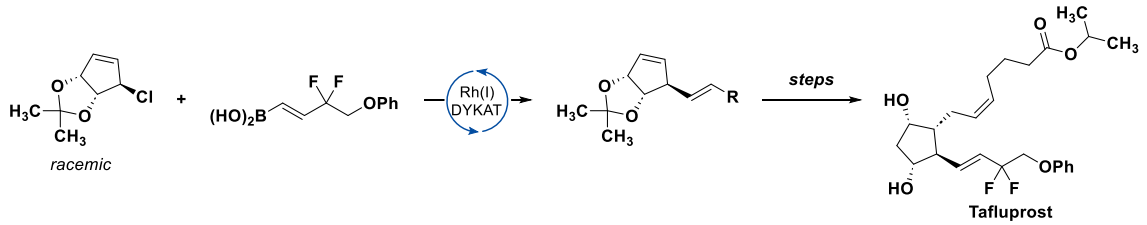


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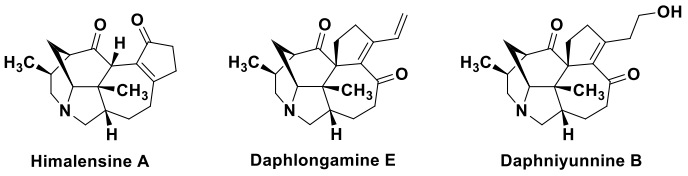
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Abstract

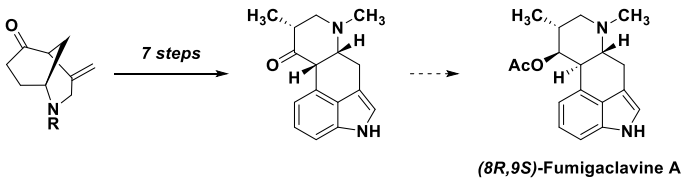
Chapter 1 describes the development of a new enantioselective synthesis of prostaglandins employing a recently developed rhodium-catalysed enantio- and diastereoselective Suzuki-Miyaura reaction of a racemic bicyclic allyl chloride and an alkenyl boronic acid. This new synthetic strategy was successfully applied for the preparation of Tafluprost, a synthetic analogue of $PGF_{2\alpha}$ used for the treatment of intraocular pressure in open-angle glaucoma and ocular hypertension.



Chapter 2 details the development of the enantioselective synthesis of *Daphniphyllum* alkaloids based on the previous accomplishments of our research group. The combination of palladium/enamine co-catalysed enantioselective synthesis of the morphan core and Michael addition – ketone allylation – ring-closing metathesis sequence enabled a highly convergent total synthesis of Himalensine A. This approach also allowed the formal synthesis of several other members of this family. In addition, the synthesis of Daphlongamine E and Daphniyunnine D was investigated.



Chapter 3 introduces Clavine (Ergot) alkaloids and their previous syntheses before a new synthetic strategy towards this family of natural products is investigated. A convergent synthesis of an advanced tetracyclic intermediate was achieved by utilising the key intermediate from our synthesis of Daphniphyllum alkaloids, unlocking the potential for the collective synthesis of the Clavine alkaloids.



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First and foremost, I would like to thank Darren not only for his mentorship, advice and support throughout these past four years but also for the freedom to explore new research ideas. His contagious enthusiasm and passion for chemistry have been both motivating and inspiring, and I am deeply appreciative of the opportunity to work in such a creative and enthusiastic collective.

I am profoundly thankful for the privilege of becoming a member of the SBM program and having a chance to meet so many talented and motivated people. For all the moments we spent together, from our synthetic discussions and excursions to pub trips and endless jianzi sessions. At this place, I would like to thank all program managers, directors and industrial partners for this life-changing opportunity and my industrial supervisors, Iacovos and Adrian, for the fruitful discussions.

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Last but not least, I would like to express my deepest gratitude to my parents and partner, Majka, for their unwavering love and support throughout this journey.

Abbreviations

Ac	Acetyl
AIBN	2,2'-azobisisobutyronitrile
Ar	Aryl
AZADO	2-Azaadamantane *N*-oxyl
BAIB	Bis(acetoxy)iodobenzene
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BHT	2,6-Di-*tert*-butyl-4-methylphenol
BIMP	Bifunctional iminophosphorane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine)
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOX	Bis(oxazoline)
BQ	Benzoquinone
BRSM	Based on recovered starting material
BSA	Bis(trimethylsilyl)acetamide
Bu	Butyl
Bz	Benzoyl
CBS	Corey-Bakshi-Shibata
CDI	1,1'-Carbonyldiimidazole
CDT	Centre for Doctoral Training
CNS	Central nervous system
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
d.r.	Diastereomeric ratio
DABCO	1,4-Diazabicyclo[2.2.2]octane

DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylalumnium hydride
DIPA	Diisopropylamine
DIPCl	Diisopinocamphenyl chloroborane
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DM-BINAP	2,2'-Bis[bis(3,5-dimethylphenyl)phosphino]-1,1'-binaphthyl
DMF	*N,N*-Dimethylformamide
DMP	Dess–Martin periodinane
DMPU	*N,N*'-Dimethylpropyleneurea
DM-SEGPHOS	5,5'−Bis[di(3,5-xylyl)phosphino]-4,4'-bi-1,3-benzodioxole
DMSO	Dimethylsulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DTBMP	2,6-di-*tert*-Butyl-4-methylpyridine
DYKAT	Dynamic kinetic asymmetric transformation
ED50	Effective dose
EDC.HCl	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
EDG	Electron donating group
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron withdrawing group
FGI	Functional group interconversion
H8-BINAP	2,2'-Bis(diphenylphospino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl
HMPA	Hexamethylphosphoramide
HMTA	Hexamethylenetetramine
HOBt	Hydroxybenzotriazole

HRMS	High-resolution mass spectrometry
IC_{50}	Half maximal inhibitory concentration
IMDAF	Intramolecular Diels-Alder reaction
IR	Infrared
JCR	Johnson-Claisen rearrangement
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LSD	Lysergic acid diethylamide
LTMP	Lithium tetramethylpiperidide
MBS	4-Methoxybenzenesulfonyl
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MOM	Methoxymethyl
MS	Mass spectrometry
Ms	Methanesulfonate
NaHMDS	Sodium hexamethyldisilazide
NCS	*N*-Chlorosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
ORTEP	Oak ridge thermal ellipsoid plot
p-ABSA	para-Aminobenzenesulfonyl azide
PCC	Pyridinium chlorochromate
PG(s)	Protecting group(s)
Ph	Phenyl
PIDA	Phenyliodine(III) diacetate
P-Phos	4,4'-Bis(diphenylphosphino)-2,2',6,6'-tetramethoxy-3,3'-bipyridine

Pr	Propyl
PS	Polystyrene
PTSA	*p*-Toluenesulfonic acid
RBF	Round-bottom flask
RCM	Ring-closing metathesis
SBM	Synthesis for Biology and Medicine
SEGPHOS	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
TBAF	Tetra-*n*-butylammonium fluoride
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TCDI	Thiocarbonyldiimidazole
TEBAC	Benzyltriethylammonium chloride
TEMPO	2,2,6,6-Tetramethylpiperidinyl-1-oxyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl
Tol-BINAP	2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl
TPAP	Tetrapropylammonium perruthenate
Ts	Toluenesulfonyl
TTR	Tsuji-Trost reaction
UHP	Urea hydrogen peroxide
W	Watt
Xyl	Xylyl

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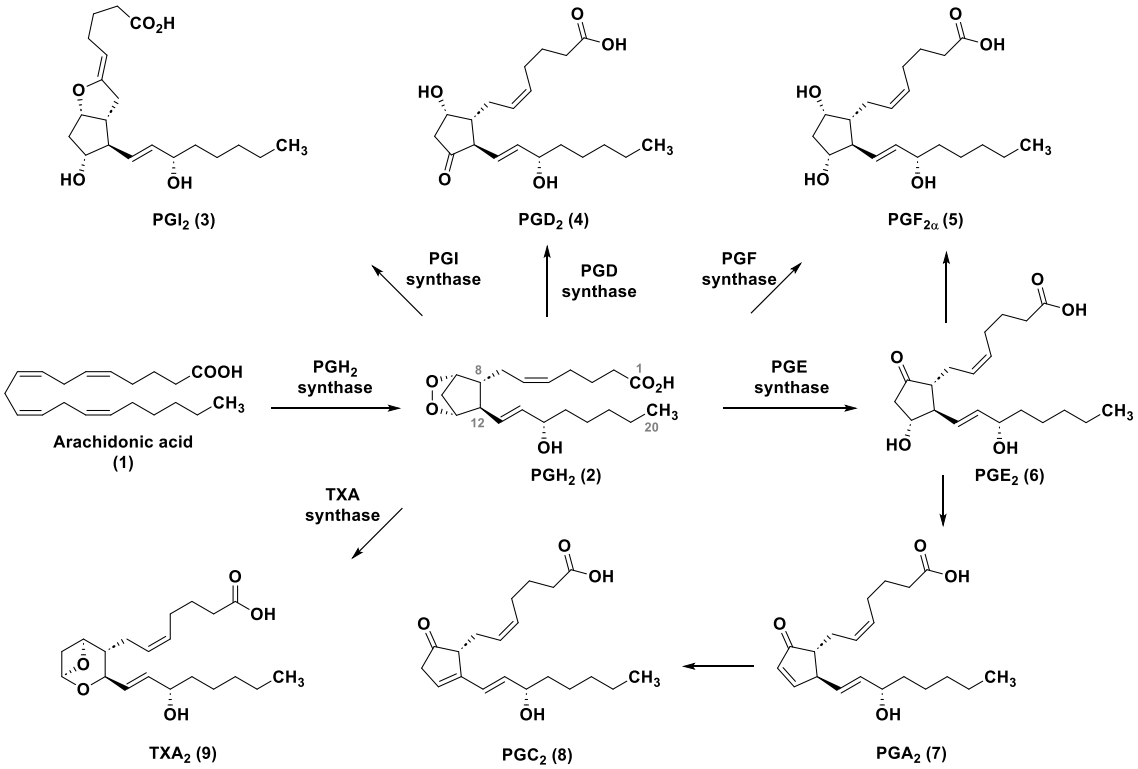
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Chapter 1: Synthesis of Tafluprost

The synthesis of Tafluprost presented in this chapter was conducted in the research group of Stephen P. Fletcher under the co-supervision of F. Wieland Goetzke during the 1st SBM CDT rotation between February and May 2019.

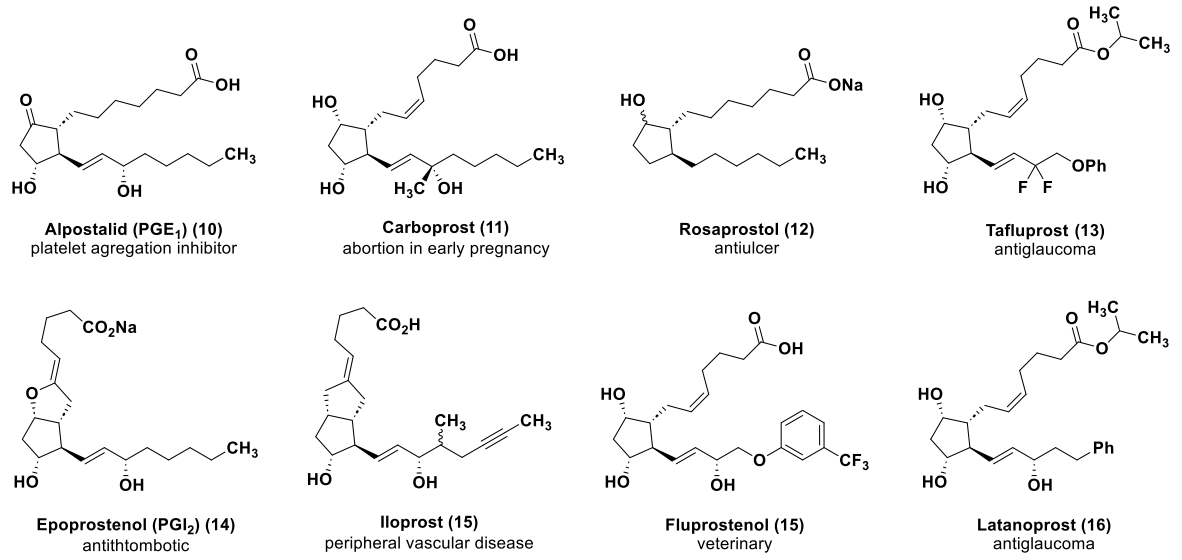
1.1 Introduction

Prostaglandins (PGs) are a class of hormone-like biologically active lipid compounds that elicit an unusually diverse array of biological responses. Specifically, PGs play a role in the origin of pain and fever and regulate inflammation, coagulation, growth, blood pressure, reproductive functions and sleep.[1] Unlike hormones, which are biosynthesised and stored in specific glands, PGs are produced locally in response to a specific stimulus and then get rapidly inactivated by metabolic enzymes or chemical degradation. Biochemically, PGs are synthesised from arachidonic acid, a polyunsaturated fatty acid (**1**). In the first stage of PG biosynthesis, arachidonic acid reacts with molecular oxygen in the presence of PGH_2 synthase, a cyclooxygenase enzyme, to form a key and versatile intermediate known as prostaglandin H_2 (**2**) (**Scheme 1.1**, centre). In the next stage, PGH_2 is transformed into different prostaglandins, as well as prostacyclin (PGI_2) and thromboxane (TXA_2).[2] Consequently, all prostaglandins share a 20-carbon atom structure arranged in a 5-membered core bearing two aliphatic side-chains and differ in the oxidation level of this core and the level of unsaturation of side-chains.



Scheme 1.1. *Biosynthesis of selected prostaglandins.*

The significant biological importance and potential therapeutic applications of PGs led to enormous interest from the synthetic community, leading to the development of numerous total syntheses.[2-3] However, the development of PGs-based pharmaceutics has been hindered by three key challenges: 1) inherent chemical instability, 2) rapid metabolic degradation, and 3) the occurrence of numerous side effects.[4] As a result, the majority of currently commercially available PG-based drugs (>20)[5] are synthetic derivatives, with structural modifications introduced to overcome these issues (**Scheme 1.2**). Latanoprost (**16**) – Pfizer's drug for the treatment of glaucoma and high ocular pressure, and Tafluprost (**13**) – Merck's antiglaucoma drug, are representative examples of these synthetic prostaglandin-based drugs.



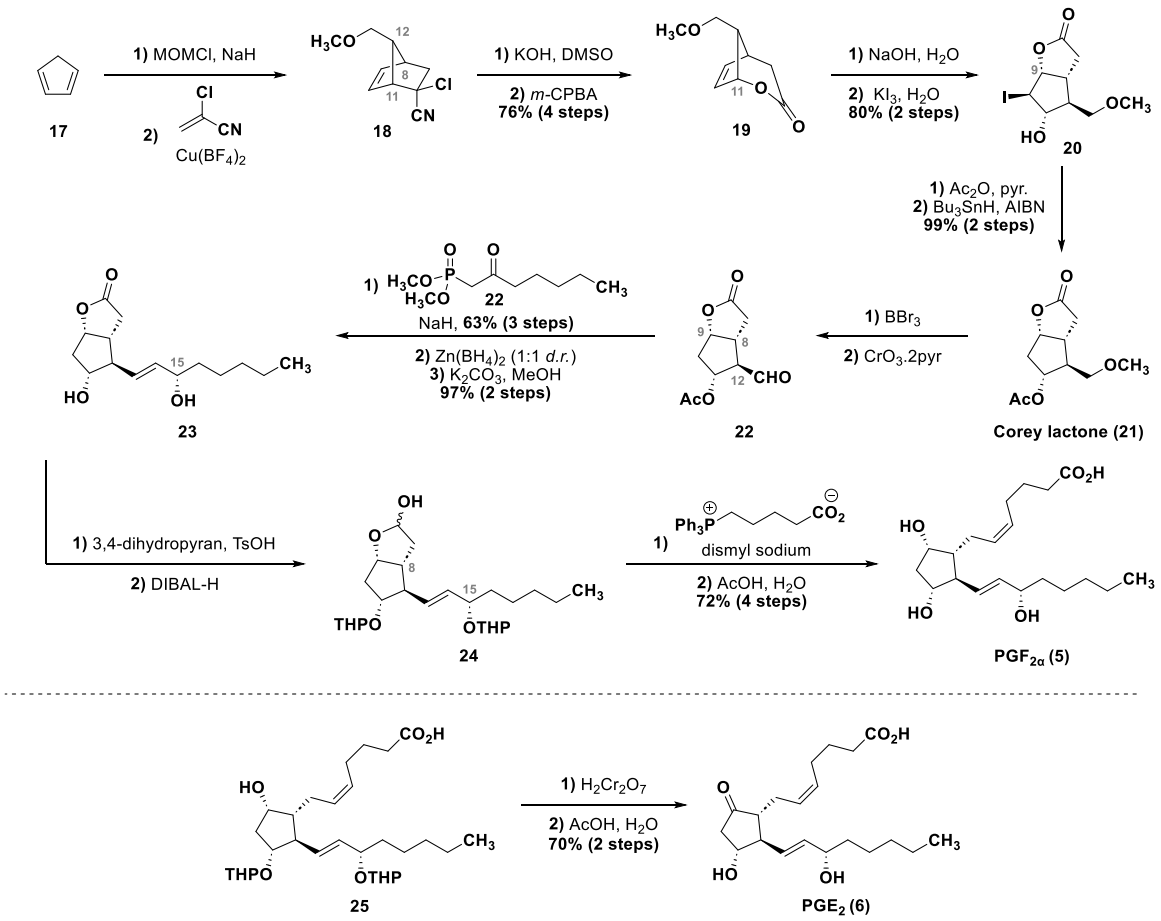
Scheme 1.2. *Selected prostaglandin-based drugs and their therapeutic indication.*

Although prostaglandins were first isolated in the 1930s independently by Swedish physiologist Ulf von Euler (1970 Nobel prize laureate for Physiology and Medicine) and Irish-English physiologist Maurice Walter, it took almost three decades until their structure was determined. In the early 1960s, Bergström *et al.* successfully determined the structures of prostaglandins E_1, $F_{1\alpha}$, $F_{1\beta}$[6] and F_{2a}[7] using a combination of spectroscopic methods (IR, MS and NMR) and chemical derivatisation. This breakthrough unlocked the possibility of their laboratory preparation by the synthetic community. During the following decades, dozens of PGs syntheses have been developed, and PGs have become a popular target of synthetic chemists, stimulating their creativity and the development of new synthetic methods. The following section highlights several selected and most notable achievements in this field.

1.2 Selected syntheses of prostaglandins

1.2.1 Corey's prostaglandin synthesis

By the end of the 1960s, Corey's group had accomplished several syntheses of prostaglandins,[8] marking a significant milestone in this field. Arguably, the most notable achievements, the synthesis of $PGF_{2\alpha}$ (**5**) and PGE_2 (**6**), widely considered to be a classic by the total synthesis community, were reported in 1969 (**Scheme 1.3**).[9]

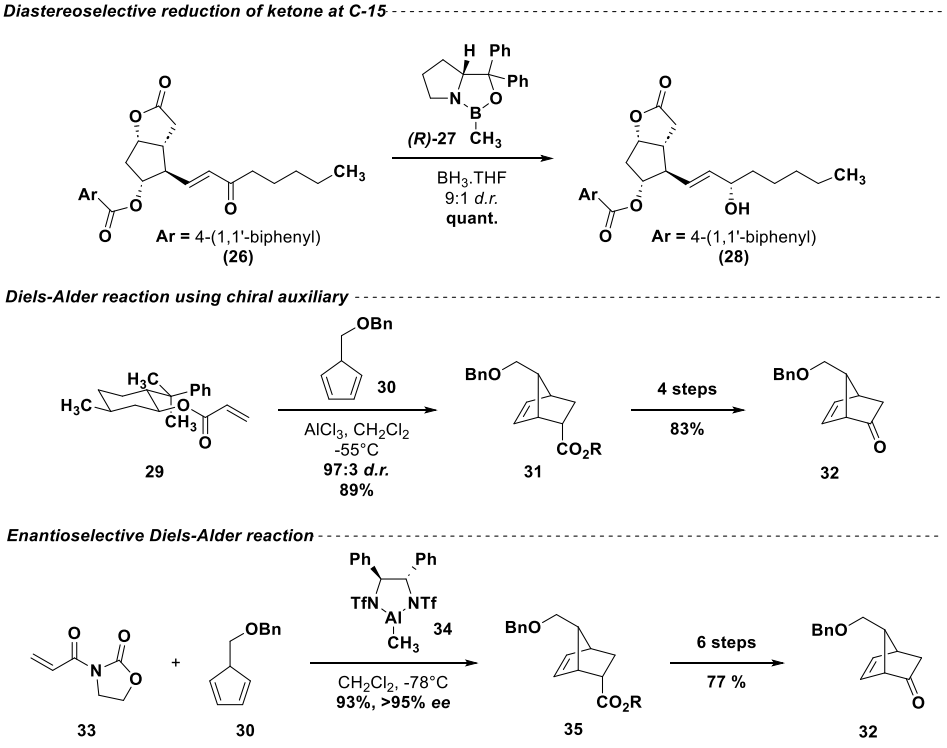


Scheme 1.3. *Corey's synthesis of prostaglandins.*

In this seminal synthesis, Corey *et al.* started from cyclopentadiene (**17**), representing the 5-membered core of the eventual natural products. Employing a meticulously designed sequence of highly stereoselective transformations, they adeptly introduced two hydroxyl groups and two aliphatic side chains (**Scheme 1.3**). In the first step, cyclopentadiene was alkylated using chloromethyl methyl ether to introduce a synthetic handle for the subsequent installation of the C-12 side chain. The facially selective copper-catalysed Diels-Alder reaction with a masked ketene equivalent, 2-chloroacrylonitrile, was used to functionalize the C-8 position. Subsequent Baeyer-Villiger oxidation of the ketone, revealed by basic hydrolysis of chloronitrile moiety in **18**, introduced the future C-11 hydroxyl group. For the stereoselective installation of the C-9

hydroxyl group, lactone **19** was first hydrolysed to the corresponding acid, which, upon treatment with KI_3, afforded the product of iodolactonisation **20**. Protection of secondary alcohol in **20** and radical deiodination provided compound **21.** This versatile intermediate, known as Corey lactone, is a pivotal building block in the synthesis of numerous prostaglandins and their derivatives (see discussion below). Deprotection of primary alcohol in **21** and its oxidation provided aldehyde **22**, which was used to install the C-12 side-chain by a Horner-Wadsworth-Emmons reaction. A subsequent series of redox and protecting group manipulations provided hemiacetal **24** as a 1:1 mixture of diastereomers at C-15. Finally, a Wittig reaction was used to introduce the C-8 side-chain, and global deprotection accomplished the synthesis of $PGF_{2\alpha}$. Notably, oxidation of product **25** by chromic acid and alcohol deprotection provided prostaglandin E_2.

Despite its elegance, this synthesis did encounter two main drawbacks: the nonselective reduction of C-15 ketone, yielding corresponding alcohol as a 1:1 mixture of diastereomers, and the fact that the final products are obtained in racemic form. In the 1980s, Corey and his team developed an efficient catalytic system for asymmetric ketone reduction using proline-derive oxazaborolidine catalyst and BH_3 as a reductant, also known as a Corey-Bakshi-Shibata reduction (CBS reduction).[10] This advancement enabled the selective reduction of the C-15 ketone in **26** with 9:1 *d.r.* (**Scheme 1.4**, top).[11]



Scheme 1.4. *Improvements in Corey's synthesis of prostaglandins.*

In order to obtain prostaglandins in their enantiomerically pure form, Corey *et al.* performed the resolution of carboxylic acid, obtained by hydrolysis of lactone **19**, using *(+)*-ephedrine.[12] However, this approach wastes at least 50% of the initially obtained material and requires the use of a controlled substance. As a solution to these issues, in 1975, Corey's group reported a diastereoselective Diels-Alder reaction between

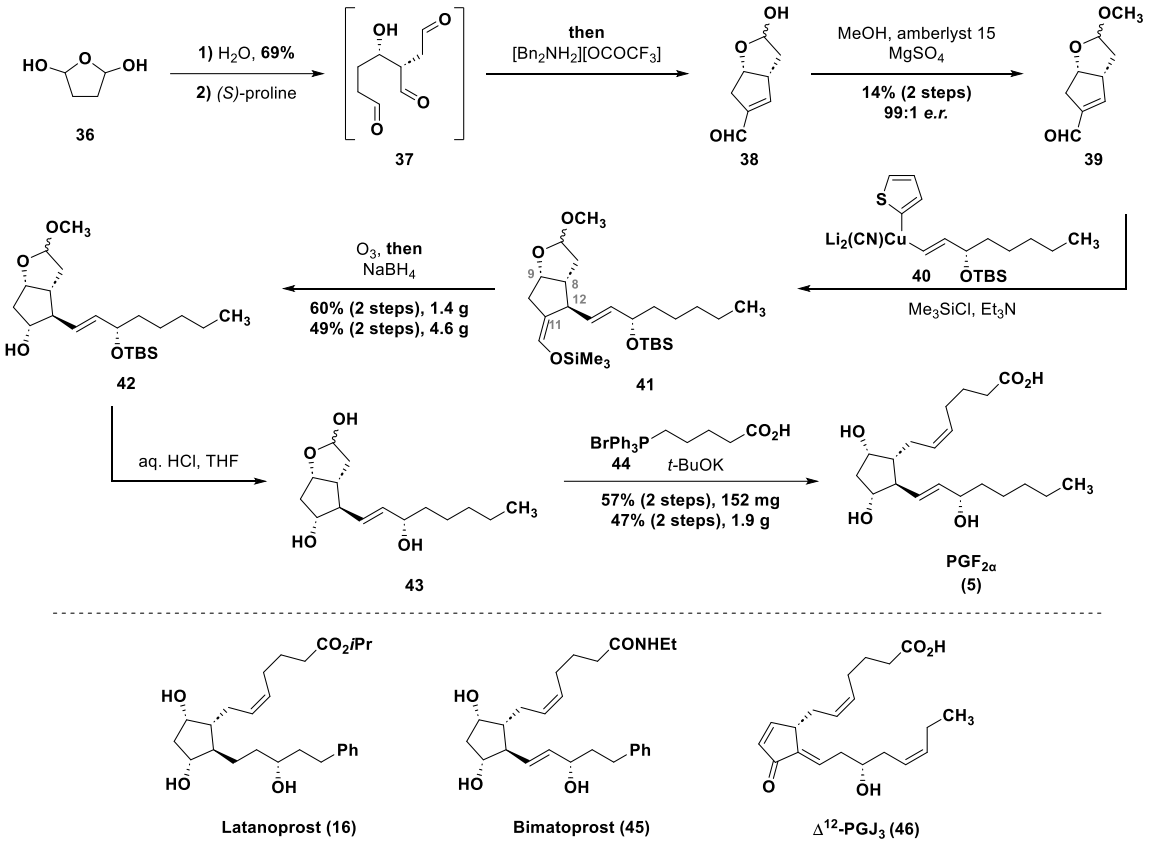
enantiomerically pure 8-phenylmenthol-derived acrylate **29** and 5-(benzoxymethyl)-1,3-cyclopentadiene (**30**) providing product **31** in 97:3 *d.r.* and 89% yield (**Scheme 1.4**, middle).[13] Compound **31** can be converted to ketone **32** in 4 steps and 83% yield.

Finally, in 1991, Corey *et al.* reported a catalytic asymmetric version of the key Diels-Alder reaction using diene **30** and 3-acrylyl-1,3-oxazolidin-2-one (**33**) in the presence of catalyst **34** (**Scheme 1.4**, bottom).[14] These conditions provided the desired product **35** in >95% *ee* and 93% yield, which can be converted into ketone **32** in 6 synthetic steps and 77% yield. Moreover, the C_2-symmetric bissulfonamide used for the preparation of the catalyst **34** can be easily recovered from the reaction mixture.

Corey's ingenious approach, characterised by the convergent disconnection of both sidechains leaving the fully functionalized 5-membered core in the form of intermediate **21** (Corey lactone), not only facilitated the syntheses of numerous natural PGs but also provided a universal source of multiple PG derivatives needed for further structure-activity relationship studies and development of PG-based drugs. Indeed, Corey's lactone played a pivotal role in the syntheses of $PGA_{1\alpha}$ and PGE_1 (Corey, 1972),[15] PGA_2[16] and PGC_2[17] (Corey, 1973), PGI_2 (Johnson, Whittaker, 1977),[18] PGD_2 (Shibasaki, 1986),[19] PGJ_2 (Zanoni, 2003),[20]carboprost,[21] fluprostenol,[22] sulprostone,[23] latanoprost[24] and tafluprost[25] amongst many others.

1.2.2 Aggarwal's prostaglandin synthesis

In 2012, Aggarwal *et al.* published an elegant 7-step synthesis of $PGF_{2\alpha}$ (**Scheme 1.5**).[26] Inspired by previous syntheses of $PGF_{2\alpha}$[27], they realized that hemiacetal **43** was an ideal late-stage intermediate. They envision that the C-12 side-chain could be introduced by conjugate addition of cuprate **40** to enal **39**, potentially accessible in enantiomerically enriched form through proline-catalysed dimerization of succinaldehyde. However, the selective dimerization of succinaldehyde to **38** posed considerable challenges due to the tendency of the initially formed aldol product **37** to oligomerize. Nevertheless, by identifying the appropriate catalyst for the second part of the cascade and the precise timing of its addition, Aggarwal's group managed to obtain the desired product in 14% (after subsequent acetalisation) and excellent *d.r.* (99:1) on a decagram scale. Later re-optimisation of the reaction conditions and replacement of the second catalyst with thiomorpholinium trifluoroacetate significantly increased the overall yield (29%).[28] Next, the C-12 side-chain was introduced by the diastereoselective conjugate addition of cuprate **40** and the resulting enolate was trapped as a silyl enol ether **41**. Selective ozonolysis of the more electron-rich double bond in **41**, followed by reductive work up with $NaBH_4$, provided intermediate **42**. Subsequent acetal hydrolysis and subsequent Wittig reaction accomplished the synthesis of $PGF_{2\alpha}$.



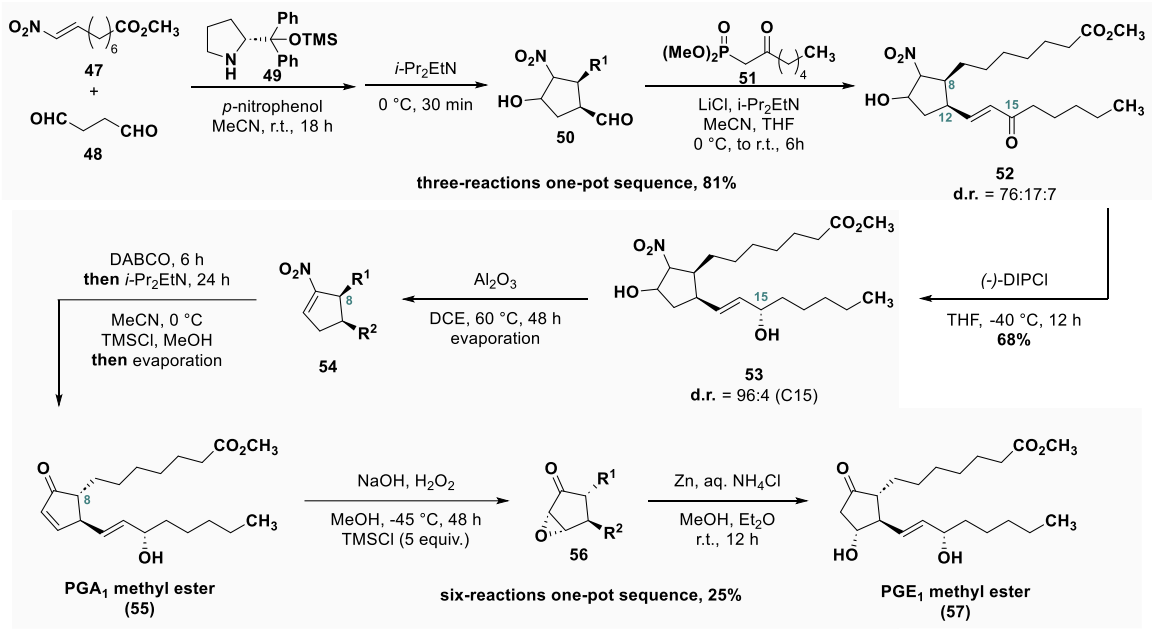
Scheme 1.5. *Aggarwal's synthesis of prostaglandins.*

Employing different coupling partners in the conjugate addition and Wittig reaction, Aggarwal and his team successfully utilized their synthetic strategy for the synthesis of latanoprost (**16**) and bimatoprost (**46**).[29] The synthetic versatility of enal **38** was further demonstrated through its application in the total synthesis of Δ^{12}-PGJ_3.[28]

1.2.3 Hayashi's prostaglandin synthesis

With experience in enantioselective domino reactions and pot-economic syntheses,[30] in 2013, Hayashi *et al.* reported the highly efficient three-pot synthesis of prostaglandin A_1 and E_1 methyl esters utilizing a similar organocatalytic domino reaction as Aggarwal (**Scheme 1.6**).[31] In this approach, succinaldehyde (**48**) and nitroalkene **47** were first treated with diphenylprolinolsilyl ether catalyst **49,** leading to the formation of the desired Michael product (not shown). The addition of DIPEA facilitated an otherwise slow Henry reaction, providing aldehyde **50**, which was treated with Horner-Wadsworth-Emmons reagent **51** and converted into alkene **52** in the same pot. This three-step, one-pot sequence provided the prostaglandin skeleton with 81% yield and 76:17:7 *d.r.* (only the relative configuration at C-8 and C-12 was determined). Next, the diastereoselective reduction of the C-15 keto group was achieved using (-)-diisopinocamphenyl chloroborane (DIPCl) in 68% yield and 96:4 *d.r.* Treatment of intermediate **53** with acidic alumina led to elimination of the C-10 alcohol group (*ee* of the first aldol reaction was determined at this point, 94%), and

the newly formed C=C double bond was migrated out of conjugation using DABCO. The addition of DIPEA to the same pot resulted in a relatively uncommon base-promoted Nef reaction accompanied by epimerisation of the C-8 position, providing PGA_1 methyl ester (**55**) in 45% (4 steps from **53**). Alternatively, intermediate **53** can be converted into PGE_1 by epoxidation of **55** under basic conditions and subsequent reduction of the unstable epoxyketone **56** with zinc in 25% yield over 6 steps from **53**.



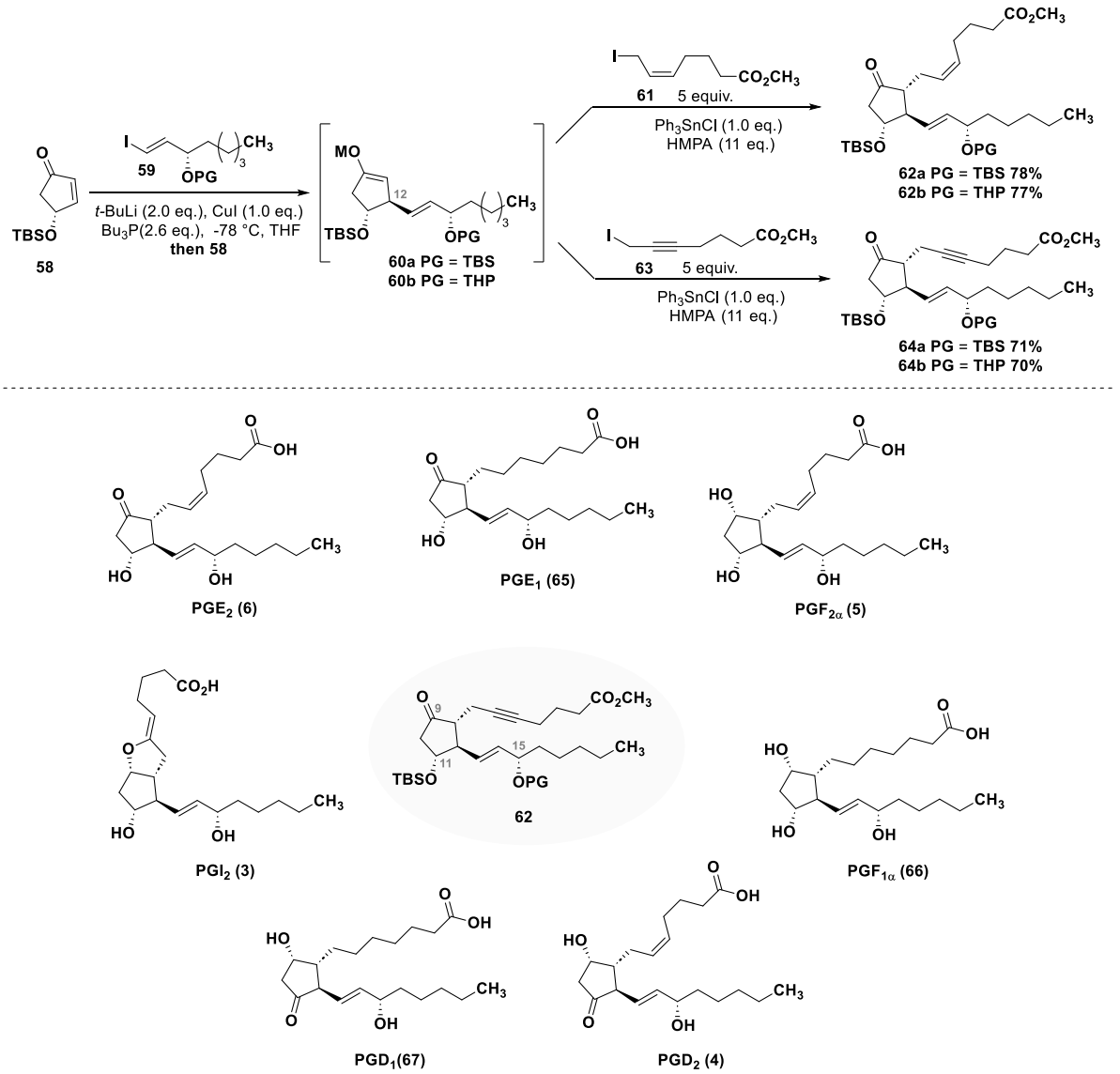
Scheme 1.6. *Hayashi's synthesis of prostaglandins.*

Hayashi's synthesis provides PGA_1 and PGE_1 methyl esters in 25% and 14% overall yield in three one-pot reactions. This efficient strategy necessitated only three chromatography purification, effectively minimising solvent consumption and waste generation. The protecting-group-free nature of this synthesis and the use of alkali metals (Na and Li) and non-toxic zinc reagents make this synthesis attractive also from an environmental point of view.

1.2.4 Noyori's prostaglandin synthesis

The last selected example of PGs' synthesis represents probably the most straightforward and convergent approach to these natural products. The C-8 and C-12 side-chains in the E-series of prostaglandins are ideally placed and oriented to be introduced by conjugate addition of the ω-chain to cyclopentanone **58** using vinylcuprate followed by enolate alkylation (**Scheme 1.7**). Even though model studies done by Patterson and Fried in 1974[32] using cyclopentenone confirmed the feasibility of this approach and 11-deoxy-PGE_2 and 11-deoxy-8,12-*epi*-PGE_2 methyl esters were obtained in 17 and 13% yield, respectively, it took

another decade and significant development in the field of enolate chemistry before Noyori *et al.* revealed a direct[i] three-component coupling approach.[34]



Scheme 1.7. *Noyori's synthesis of prostaglandins.*

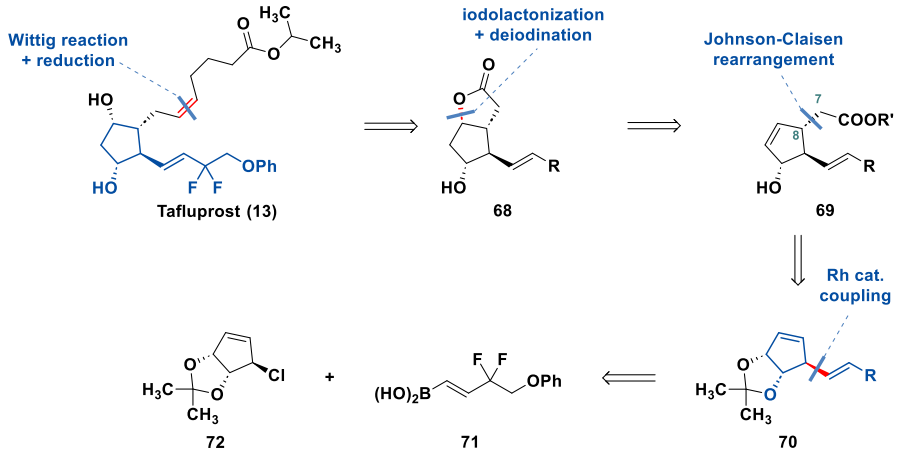
In this approach, enantiomerically enriched enone **58**[35] was first treated with *in situ* generated vinyl cuprate **59**, leading to the diastereoselective introduction of the ω-chain *anti* to bulky OTBS group. The obtained enolate was transmetalated with Ph_3SnCl, and subsequent treatment of this tin enolate with vinyl or propargyl iodides **61** or **63** led to facially selective alkylation (anti to C-12 chain) with impressive yields ranging from 70% to 78%. The tin enolate was crucial for enolate alkylation as it is less basic but maintains nucleophilicity towards alkyl iodides. Intermediate **62** (and **64** after hydrogenation in the presence of Lindlar's catalyst) were converted to PGE_2 (**6**) after simple alcohol deprotection and ester hydrolysis.

[i] In 1982, Noyori *et al.* published a synthesis based on trapping the enolate with the corresponding aldehyde, followed by dehydration and enone reduction.[33]

Furthermore, the reduction of the C-9 keto group with L-selectride led to F_2-series of PG (**5**). The synthesis of D_2-series required orthogonal protection of C-11 and C-15 hydroxyls and 6 steps sequence: *(1)* reduction of ketone, *(2)* THP protection of C-9 hydroxyl, *(3)* TBS deprotection, *(4)* ester hydrolysis, *(5)* oxidation of C-11 hydroxyl and *(6)* THP deprotection. Replacement of Lindlar's catalyst with $Pd/BaSO_4$ led to prostaglandins E_1 (**65**), $F_{1\alpha}$ (**66**) and D_1 (**67**). Finally, PGI_2 (**3**) was prepared from alkyne **62** by reduction of the ketone functionality followed by an intramolecular alkoxypalladation/depalladation reaction and subsequent deprotection. Finally, it should be noted that the use of toxic (organotin) and carcinogenic (HMPA) reagents and additives impose practical limitations to this otherwise appealing synthesis, given the environmental and safety concerns associated with such substances.

1.3 Retrosynthetic analysis of Tafluprost

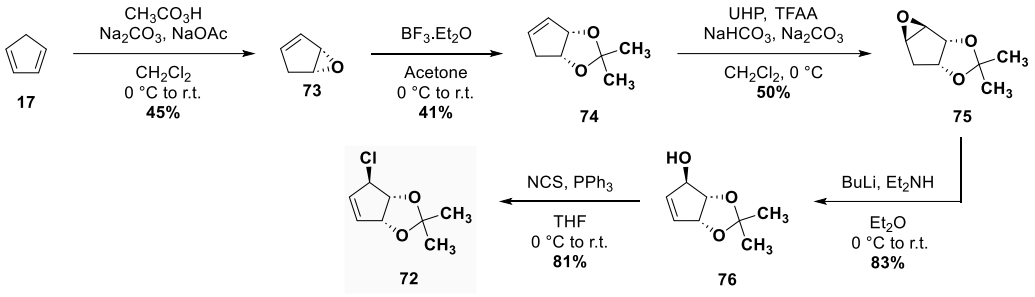
The significant structural similarity between the products of the Suzuki-Miyaura cross-coupling reaction developed by Wieland Goetzke in the Fletcher group[36] and prostaglandins (**Scheme 1.8**, shown in blue) inspired us to explore the applicability of this reaction in the synthesis of this class of natural products, and we chose Tafluprost as our target molecule. The c*is*-alkene in compound **13** can be disconnected by a Wittig reaction to the corresponding aldehyde, accessible by the reduction of lactone **68**, a known intermediate in Tafluprost synthesis.[25] Lactone **68** can be further disconnected to ester **69** by employing well-established disconnections frequently used in prostaglandin chemistry, specifically iodolactonisation and deiodination reactions (see **Chapter 1.1** and **Scheme 1.3** for details). We speculated that the C-8 acetyl group could be introduced by a Johnson-Claisen rearrangement after deprotection of the diol moiety in compound **70**. Finally, intermediate **70** could be prepared by the newly developed enantioselective desymmetrisation reaction from allylchloride **72** and boronic acid **71**.



Scheme 1.8. *Retrosynthetic analysis of Tafluprost.*

1.4 Synthesis of allyl chloride 72

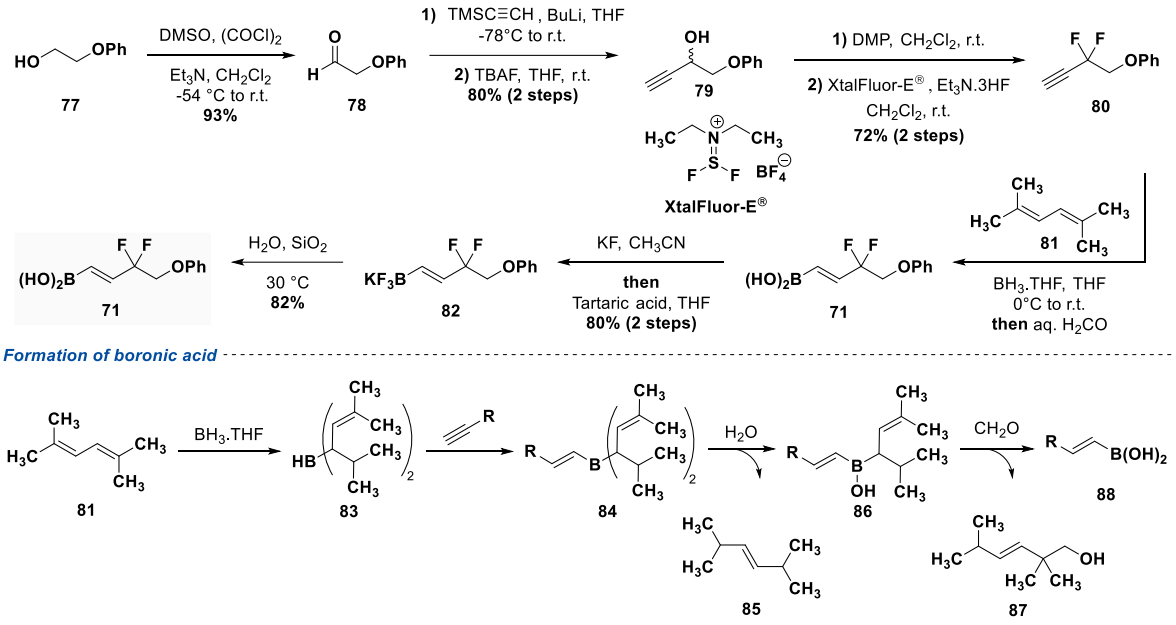
Our synthetic studies towards Tafluprost commenced with the synthesis of allyl chloride building block **72,** previously described by Wieland Goetzke (**Scheme 1.9**).[36] Treatment of cyclopentadiene (**17**) with peracetic acid provided volatile monoepoxide **73,**[37] which was converted to the corresponding acetonide **74** by treatment of its solution in acetone with $BF_3 \cdot Et_2O$.[38] A second epoxidation using *in situ* generated trifluoroperacetic acid gave rise to *trans*-epoxide **75,** which was isomerized to allylic alcohol **76** after exposure to two equivalents of lithium diethylamide.[38] The preparation of allyl chloride was accomplished by chlorination of allylic alcohol **76** in an Appel reaction, using *N*-chlorosuccinimide in the presence of triphenylphosphine.



Scheme 1.9. *Synthesis of allyl chloride* ***72.***

1.5 Preparation of boronic acid 71

Boronic acid **71** was prepared in 8 linear steps from 2-phenoxyethanol (**77**) using the modification of a synthetic sequence previously reported in the literature (**Scheme 1.10**).[39] Swern oxidation of alcohol **77** provided aldehyde **78**,[40] which was subsequently converted to propargylic alcohol **79**, in a two-step procedure based on the addition of *in situ* generated trimethylsilylacetylide followed by cleavage of the TMS protecting group by TBAF.[41] Notably, the preparation of alcohol **79** required only a single purification step by silica gel chromatography. In the next step, alcohol **79** was oxidized to the corresponding ketone. To avoid working with gram quantities of toxic chromium trioxide, less toxic Dess-Martin periodinane was utilised, replacing the previous Jones oxidation strategy. This modification also resulted in a significant increase in the yield (62% → 87%). The geminal difluoro group was installed using XtalFluor-E® in the presence of $Et_3N{\cdot}3HF$.[42] The realisation of the volatility of alkyne **80** and taking adequate precautions in the experimental procedure increased the yield of this step from 63% to 83%.



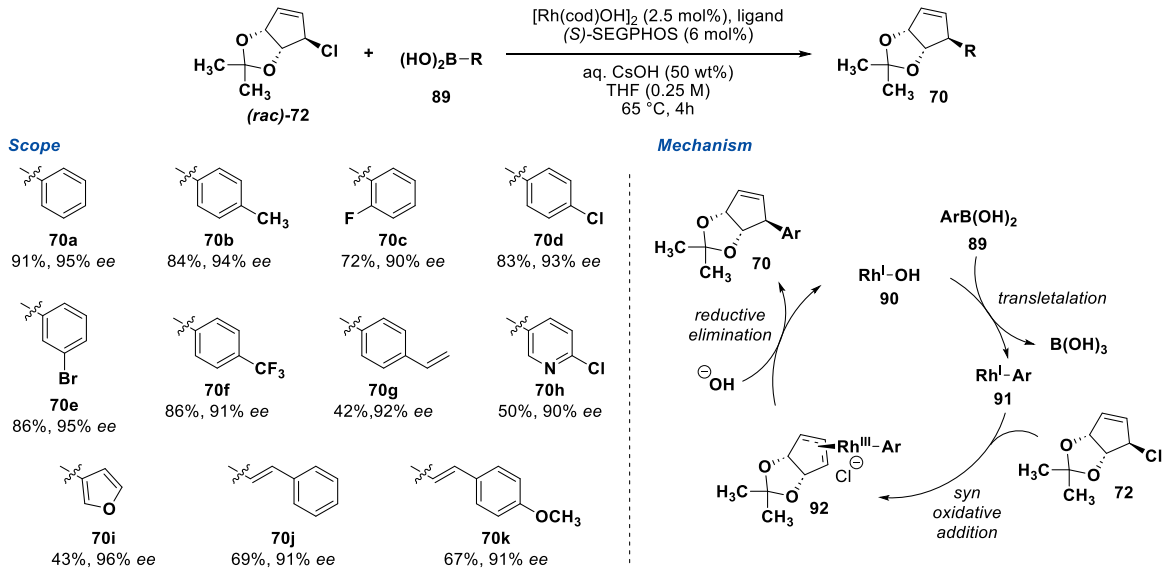
Scheme 1.10. *Synthesis of boronic acid* ***71****.*

Finally, alkyne **80** was converted to the corresponding vinyl boronic acid **71** in a three-step sequence (**Scheme 1.10,** middle).[39] In the first step, alkyne **80** reacted with *in situ* generated dialkyl borane **83** (**Scheme 1.10**, bottom),[43] which, upon work-up, provided the desired boronic acid **71**. Although this step led to the formation of boronic acid **71** in high yield, the formation of non-volatile alcohol **87** during the work-up (see mechanism in **Scheme 1.10**, bottom) made its purification challenging. To facilitate its purification, boronic acid **71** was converted to trifluoroborate **82** under Lloyd-Jones' conditions,[44] allowing for its separation from alcohol **87** by filtration. Trifluoroborate **82** was subsequently hydrolysed back to boronic acid **71** using silica gel and water.[39] In summary, boronic

acid **71** was prepared on a gram-scale in 8 linear steps, in 37% overall yield requiring only 3 chromatography purification steps.

1.6 Asymmetric Suzuki-Miyaura coupling

In 2019, Stephen Fletcher and Wieland Goetzke reported the rhodium-catalysed enantio- and diastereoselective Suzuki-Miyaura cross-coupling reaction of racemic allyl chlorides with aryl- and vinylboronic acids (**Scheme 1.11**).[36] They demonstrated that various racemic "symmetrically" substituted cyclopentenyl chlorides (e.g. **72**) could be coupled with a broad range of (hetero)aryl boronic acids, including vinylboronic acids, in good yields (up to 94%) and high enantiomeric excess (up to 99% ee). Based on their experimental observation, they proposed the following mechanism (**Scheme 1.11**, right): the Rh^{I}-hydroxide complex **90** undergoes transmetalation with aryl/vinyl boronic acid, followed by oxidative addition into C-Cl bond of **72**, where both enantiomers of the substrate form the same pseudo-*meso* Rh-π-allyl complex **92**. Subsequent *syn* reductive elimination leads to the formation of a single enantiomer of product **70** with overall retention of the relative configuration. This process represents an example of so-called dynamic kinetic asymmetric transformation (DYKAT), allowing the conversion of racemic starting material into a single enantiomer of product.

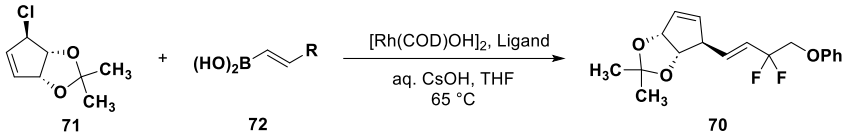


Scheme 1.11. *Enantioselective Suzuki-Miyaura coupling.*

With access to gram-scale quantities of boronic acid **71** and allyl chloride **72**, the stage was set to explore the potential applicability of this transformation for prostaglandin synthesis. Preliminary experiments using original conditions and racemic BINAP showed that a vinyl boronic acid equipped with a geminal difluoro group (**71**) is a competent coupling partner in this transformation, and the desired coupling product **70** can be obtained in excellent yield and diastereoselectivity (**Table 1.1**, **entry 1**). However, the reaction with *(S)*-BINAP provided the desired product at a relatively modest 77% ee, necessitating further ligand optimisation. The use of sterically bulkier BINAP-based ligands, *(R)*-Tol-BINAP and *(R)*-DM-BINAP (**entry 3** and **4**), did not lead to a

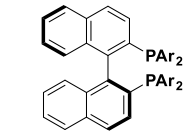
significant increase in *ee* (-80%[ii] and -78%[ii], respectively). Similarly, the use of *(S)*-H_8-BINAP (70%, **entry 5**), a partially hydrogenated BINAP analogue with increased biphenyl dihedral angle, did not improve the *ee*. On the other hand, *(S)*-SEGPHOS and *(S)*-DM-SEGPHOS (**entries 6** and **7**) provided the desired product with significantly increased ee (90 and 91%, respectively); albeit, at the cost of reduced d.r. (7.2:1). P-Phos and BIPHEP-based ligands performed similarly to *(S)*-BINAP in terms of *ee* (**entries 8-11**), while ferrocene-based *(R)*-SL-J001-1 led to the formation of **70** with only 10% *ee* (**entry 12**). Considering these results, we decided to carry out our synthetic studies using the *(S)*-DM-SEGPHOS ligand.

Table 1.1. *Ligand screening.*

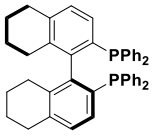


	Ligand	*ee*	*dr*[a]	yield[b]
1	*(±)*-BINAP	0	>20:1	85 (94)[c]%
2	*(S)*-BINAP	77%	>20:1	87%
3	*(R)*-Tol-BINAP	-80%[ii]	>20:1	79%
4	*(R)*-DM-BINAP	-78%[ii]	>20:1	83%
5	*(S)*-H8-BANAP	70%	>20:1	n.d.
6	*(S)*-SEGPHOS	90%	7.2:1	79%
7	***(S)*-DM-SEGPHOS**	**91%**	**7.2:1**	**80%**
8	*(S)*-P-Phos	70%	n.d.	n.d.
9	*(S)*-Xyl-P-Phos	77%	11.5:1	83%
10	*(R)*-MeO-BIPHEP	-66%[ii]	n.d.	n.d.
11	*(S)*-Cl-MeO-BIPHEP	65%	n.d.	n.d.
12	*(R)*-SL-J001-1	10%	n.d.	n.d.

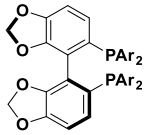
Standard conditions: 0.20 mmol scale, 2.5 mol % $[Rh(COD)OH]_2$, 6 mol % ligand, 1.5 equiv. boronic acid, 1.0 equiv. 50% aq. CsOH, concentration 0.25M, reaction time 4 h; a – determined by NMR; b – isolated yield, c – 2.58 mmol scale.



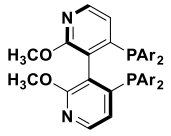
Ar = Ph *(S)*-BINAP
Ar = Tol *(S)*-Tol-BINAP
Ar = Xyl *(S)*-DM-BINAP



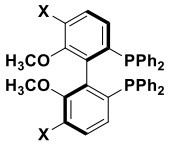
(S)-H_8-BINAP



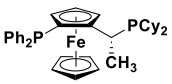
Ar = Ph *(S)*-SEGPHOS
Ar = Xyl *(S)*-DM-SEGPHOS



Ar = Ph *(S)*-P-Phos
Ar = Xyl *(S)*-Xyl-P-Phos



X = H *(R)*-MeO-BIPHEP
X = Cl *(R)*-Cl-MeO-BIPHEP

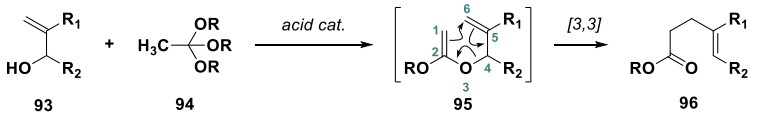


(R)-SL-J001-1

[ii] A negative value of the *ee* indicates the formation of the opposite enantiomer.

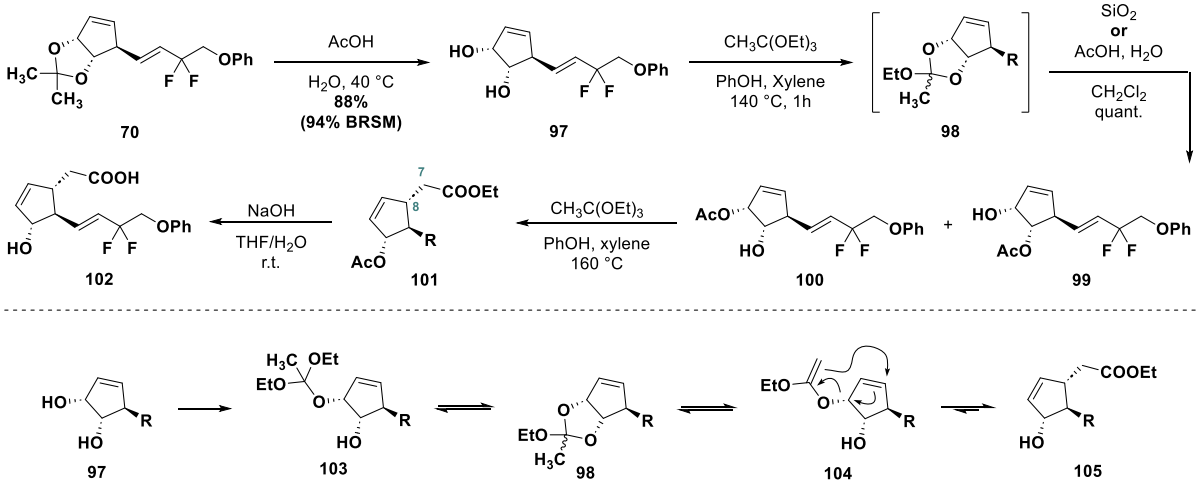
1.7 Johnson-Claisen rearrangement as a strategy for the α-chain introduction

The Johnson-Claisen rearrangement (JCR) is a variation of the Claisen [3,3]-sigmatropic rearrangement.[45] In a typical JCR reaction (**Scheme 1.12**), allylic alcohol (**93**) is heated (100 – 180 °C) with an excess of trialkyl orthoacetate (**94**) in the presence of the acid catalyst, leading to the formation of ketene acetal (**95**). This intermediate then undergoes a rearrangement through a 6-membered transition state providing γ,δ-unsaturated ester (**96**). Overall, this reaction leads to the regioselective substitution of an allylic alcohol with an acetate functional group. In our case, the JCR was envisioned as a strategy for the introduction of C-8 acetate moiety in **69** (**Scheme 1.8**), needed for the subsequent installation of the C-8 side-chain of Tafluprost.



Scheme 1.12. *Johnson-Claisen rearrangement.*

In our first attempted JCR reaction, diol **97**, liberated by acidic cleavage of acetonide **70**, was treated with triethyl orthoacetate in the presence of phenol as an acid catalyst (**Scheme 1.13**, top). We speculated that under these reaction conditions, the initially formed orthoesters **103** and **98** might exist in equilibrium with each other and ketene acetal **104** (**Scheme 1.13**, bottom). The subsequent consumption of intermediate **104** in the Johnson-Claisen rearrangement could, in theory, push the equilibrium towards product **105**. However, only the formation of orthoester **98** was observed under these conditions. Attempted purification of compound **98** by column chromatography on silica gel led to its cleavage to isomeric acetates **99** and **100** (1:1.3), which were inseparable due to the relatively fast migration of the acetyl group. Nevertheless, because of its high yield, this transformation was used for the monoacetylation of diol **97**.

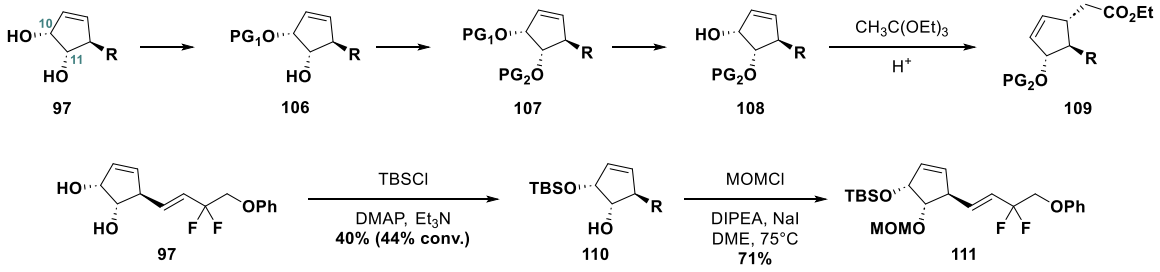


Scheme 1.13. *Johnson-Claisen approach to acid **30**.*

Although isomer **99**, needed for Johnson-Claisen rearrangement, was only a minor component of the product mixture (**99** + **100**), we decided to explore the feasibility of this transformation for the introduction of the C-8 acetate group. Re-exposure of the mixture of isomers **99** and **100** to the same reaction conditions led to full consumption of the starting material, and desired ester **101** was isolated in 49% yield, accompanied by 38% recovered starting material. The re-isolation of the starting material was unexpected, as the formation of the corresponding bis-acetate, a side-product from the "non-reactive" isomer **100**, was anticipated. 2D TLC analysis of the reaction mixture revealed that one of the products present in the reaction mixture at the end of the reaction (R_f of ethyl orthoacetate) was decomposing to the starting material upon prolonged exposure to silica gel. The low stability of this unknown intermediate did not allow its separation and characterisation, leaving room for speculation about its structure.

Motivated by the initial results, we tried to optimise the JCR (for more details, see Experimental section). However, the optimisation of this reaction was complicated by the acetate scrambling and the observation that undesired isomer **100** was slowly crystallizing from the product mixture, resulting in the shift of equilibrium towards this "unreactive" isomer (21:1). Using this 21:1 mixture of isomers **100** and **99**, the isolated yields dropped to 24%, and the yields of recovered starting material increased to 58%. This disparity between the ratio of acetates (**100:99**) and the isolated yields of product **101** and recovered starting material could be rationalised by the observation that heating of the reaction mixture in the absence of ortho ester led to quick equilibration of **100** and **99**, with the final 2:1 (**100:99**) ratio.

Nevertheless, several repetitions of the Johnson-Claisen rearrangement with recovered starting material provided us with a sufficient quantity of compound **101** for further synthetic studies. In the next step, ester **101** was treated with 1 M aq. NaOH, resulting in the quantitative cleavage of both esters and the obtained hydroxy acid **102**, later proved to be a key intermediate in the synthesis of Tafluprost (see **Chapter 1.9**).

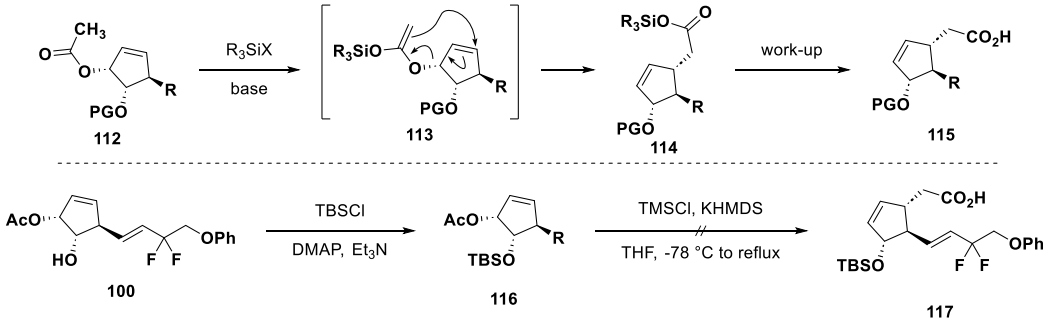


Scheme 1.14. *Strategy based on the use of orthogonal protecting groups.*

As the acetate migration rendered the JCR with monoacetylated diol impractical, we examined alternative approaches. The most obvious solution could be the protection of the C-11 OH group in **97** with a group unable to migrate. However, given the higher reactivity of the C-10 hydroxyl, this

strategy would require multi-step protecting group manipulation (see **Scheme 1.14**), and therefore this strategy was abandoned.

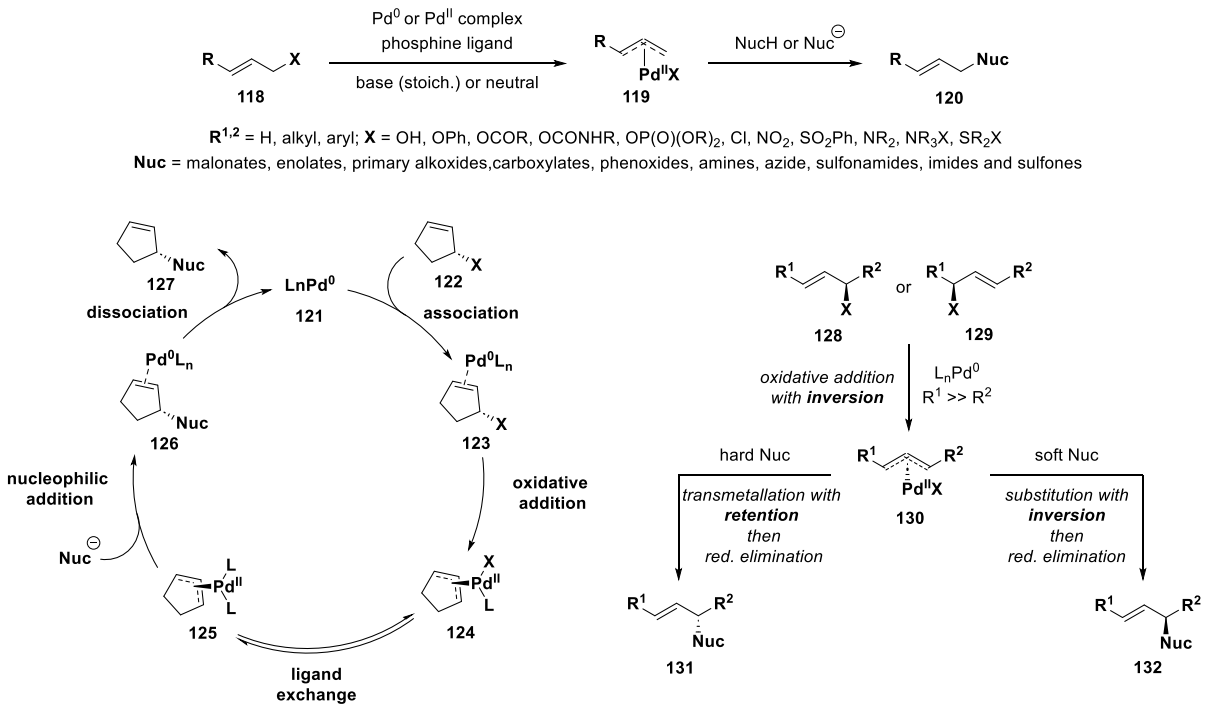
In our next approach, we decided to utilize the crystallisation-driven shift of the acetate ratio towards **100** (21:1). We hypothesized that after the protection of the C-11 OH group, the C-10 acetate could be employed in Ireland-Claisen rearrangement (**Scheme 1.15**, top).[46] Motivated by multiple successful applications of this rearrangement for the acetylation of cyclohex-2-en-1-ols,[47] we briefly examined its application on our system (**116**). However, the formation of the desired product **117** was not observed.



Scheme 1.15. *Strategy based on the Ireland-Claisen rearrangement.*

1.8 Tsuji-Trost allylic substitution as a strategy for the α-chain introduction

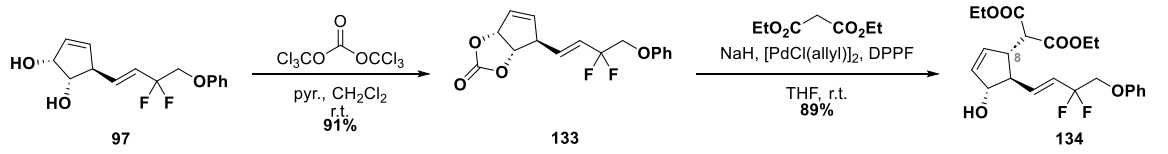
The Tsuji-Trost reaction (TTR) is a palladium-catalysed allylic substitution reaction discovered by J. Tsuji in 1965[48] and further developed by B. M. Trost during the 1970s (**Scheme 1.16**, top).[49] In this reaction, a substrate with a leaving group in an allylic position (e.g. halide, acetate or carbonate, amongst many others) reacts with a palladium catalyst and forms a π-allylpalladium complex (**119**). Subsequent reaction of this palladium complex with a nucleophile leads to the formation of a product of substitution (for a more detailed mechanism, see **Scheme 1.16**, left). In the case of unsymmetrical π-allylpalladium complex, the addition of nucleophile is regioselective, preferring the less substituted allyl terminus, regardless of the initial position of the leaving group. Depending on the nature of the nucleophile (soft or hard), the reaction can occur either with overall retention (soft) or inversion (hard) of the configuration of the substrate. After the formation of π-allylpalladium complex **130**, through the oxidative addition with inversion of the configuration (**Scheme 1.16**, right), soft nucleophiles attack the carbon of the allyl group, and this substitution leads to second inversion and thus overall retention of the configuration (**129/128 → 132**). On the other hand, hard nucleophiles attack the metal centre, not changing the configuration of the π-allylpalladium complex, resulting in overall inversion of the configuration (**129/128 → 131**).[50]



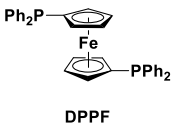
Scheme 1.16. *Tsuji-Trost reaction.*[50]

We envisioned that the Tsuji-Trost allylic substitution with a malonate anion as a nucleophile followed by malonate decarboxylation could provide an alternative strategy for acetate introduction

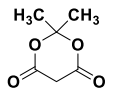
(**Scheme 1.17**). Malonate, as a soft nucleophile, should be introduced with the overall retention of the configuration at the sterically less hindered C-8 position. Cyclic carbamate was anticipated to be the best way to activate the allylic alcohol as it does not require selective reaction of only one of the present OH-groups and is cleaved during the reaction, leaving the second OH group unprotected and thus unactivated towards the second allylic substitution.



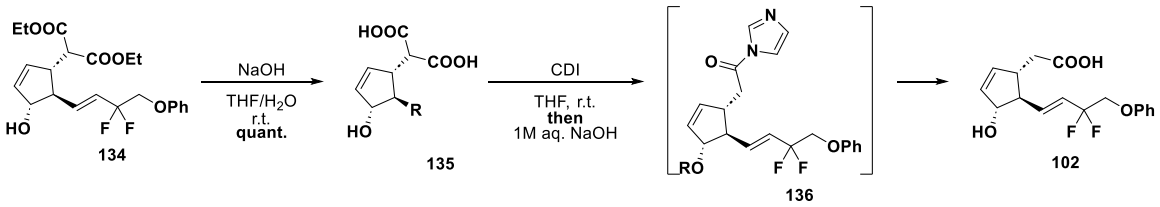
	catalyst	scale	cat. loading	nucleophile	yield
1	$Pd(PPh_3)_4$	10 mg	30 mol%	$CH_2(CO_2Et)_2$, NaH	**38%**
2	$[PdCl(allyl)]_2$, DPPF	10 mg	12 mol%	$CH_2(CO_2Et)_2$, NaH	**75%**
3	$[PdCl(allyl)]_2$, DPPF	20 mg	12 mol%	Meldrum's acid, Cs_2CO_3	**n.a.**
4	$[PdCl(allyl)]_2$, DPPF	80 mg	12 mol%	$CH_2(CO_2Et)_2$, NaH	**89%**
5	$Pd(dppf)Cl_2$	20 mg	5 mol%	$CH_2(CO_2Et)_2$, NaH	**85%**
6	$Pd(dppf)Cl_2$	20 mg	1 mol%	$CH_2(CO_2Et)_2$, NaH	**74%**
7	$Pd(dppf)Cl_2$	280 mg	3 mol%	$CH_2(CO_2Et)_2$, NaH	**89%**



DPPF



Meldrum's acid



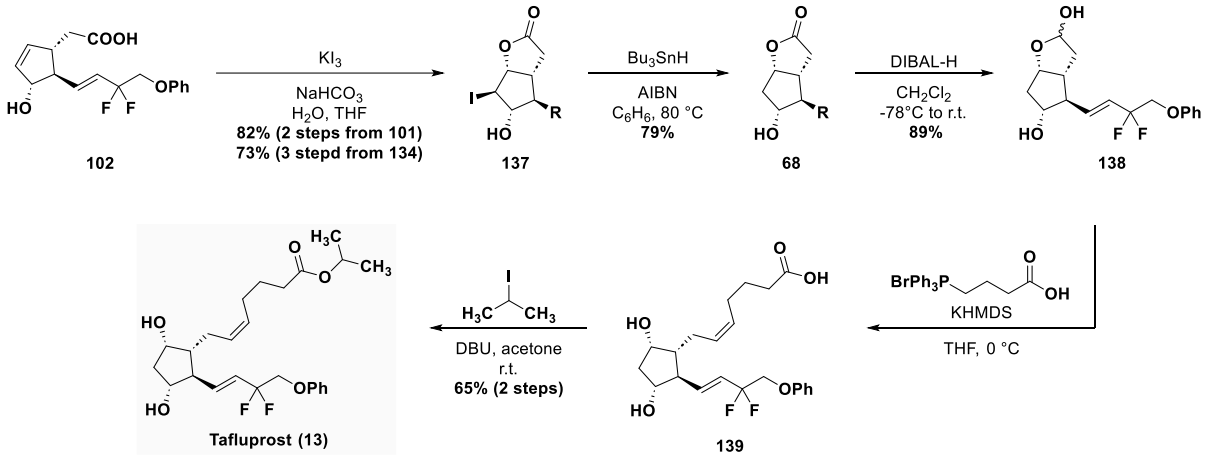
Scheme 1.17. *Synthesis of hydroxy acid* ***102*** *using Tsuji-Trost reaction.*

To this end, diol **97** was reacted with triphosgene to provide carbamate **133** in high yield (**Scheme 1.17**, top). Its treatment with sodium enolate of diethyl malonate in the presence of $Pd(PPh_3)_4$ resulted in the slow formation of the desired product in 38% yield (**entry 1**).[51] The change to *in situ* generated catalyst from allylpalladium(II) chloride and DPPF ligand led to a very fast and high-yielding reaction (89%, **entry 2**).[52] Replacement of malonate with Meldrum's acid also led to fast consumption of the starting material; however, the desired product was not isolated (**entry 3**). Further screening revealed that commercially available $Pd(dppf)Cl_2$ could be used instead of *in situ* generated catalyst (**entry 5-7**), thereby simplifying the reaction set-up. Moreover, the high activity of this catalyst allowed us to reduce its loading to only 3 mol% while maintaining the same yield (**entry 7**).

In order to convert malonate **134** to hydroxy acid **102**, malonic ester **134** was first quantitatively hydrolysed to the corresponding malonic acid **135** and then decarboxylated under mild conditions using CDI.[53] Because of the high purity of the hydrolysis and decarboxylation reactions, the products **135** and **102** were used in the next steps without further purification, and the overall yield of this sequence was determined only after the iodonactonization step (68% over 3 steps, **Scheme 1.18**).

1.9 Completion of the synthesis

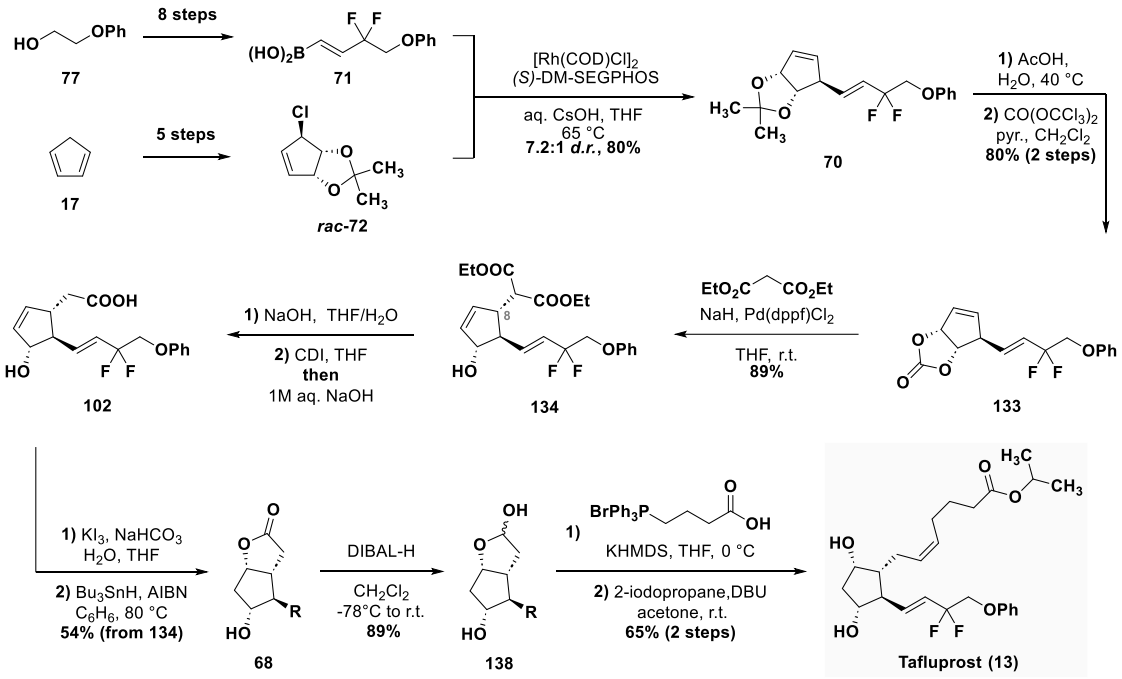
From intermediate **102** on, all steps were relatively well precedented in prostaglandin literature and followed the strategy used by Corey in his seminal prostaglandin synthesis (**Scheme 1.3**).[9] Treatment of carboxylic acid **102** with KI_3[54] afforded iodolactone **137** in 82% (2 steps from **101**) and 68% yield (3 steps from **134**), respectively (**Scheme 1.18**). The subsequent radical deiodination using Bu_3SnH[54] followed by lactone reduction[29] gave rise to hemiacetal **138**, an intermediate known from previous Tafluprost syntheses.[25] The synthesis of Tafluprost was accomplished by *Z*-selective Wittig reaction of hemiacetal **138** with an excess of non-stabilised ylide, followed by esterification using isopropyl iodide (60% yield over 2 steps).[25, 55]



Scheme 1.18. *End game.*

1.10 Conclusion

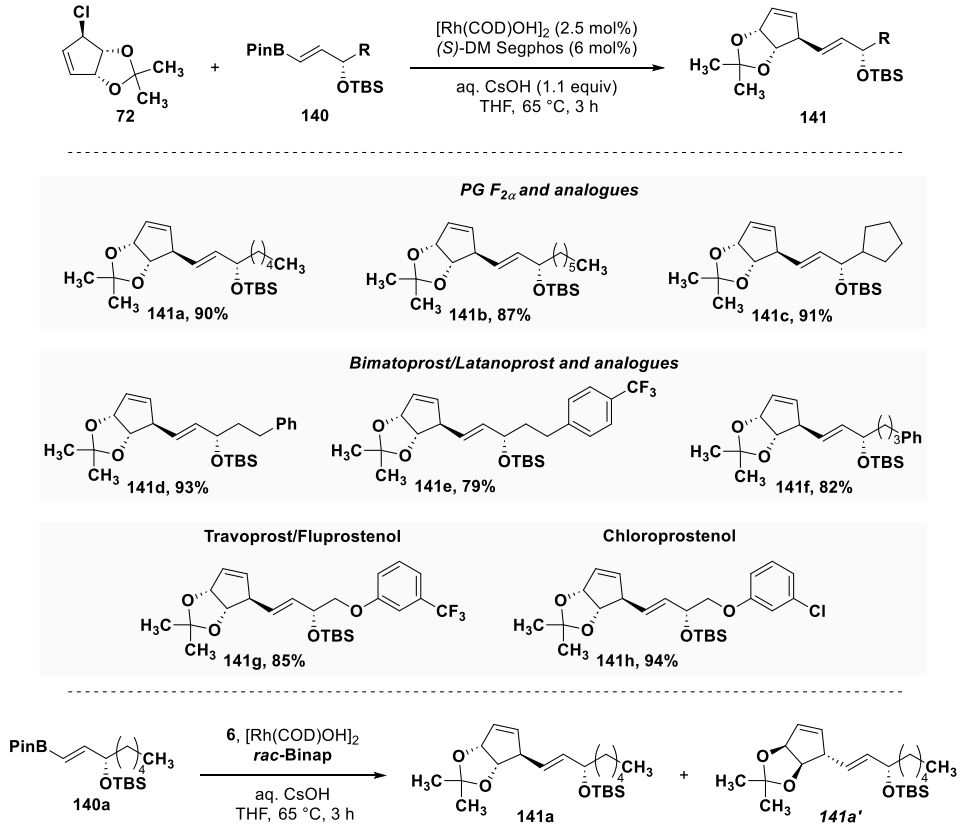
By the synthesis of Tafluprost, we have demonstrated the applicability of the newly developed enantio- and diastereoselective rhodium-catalyzed Suzuki-Miyaura cross-coupling reaction for the synthesis of prostaglandins. Combining this new synthetic methodology with key steps from Corey's prostaglandin synthesis and highly selective Tsuji-Trost allylic substitution allowed the synthesis of Tafluprost in 19 linear steps (longest linear sequence) in 6.7% overall yield with minimal protecting group manipulations. The results of this work were published in Organic Letters.[56]



Scheme 1.19. *Overview of the synthesis of Tafluprost.*

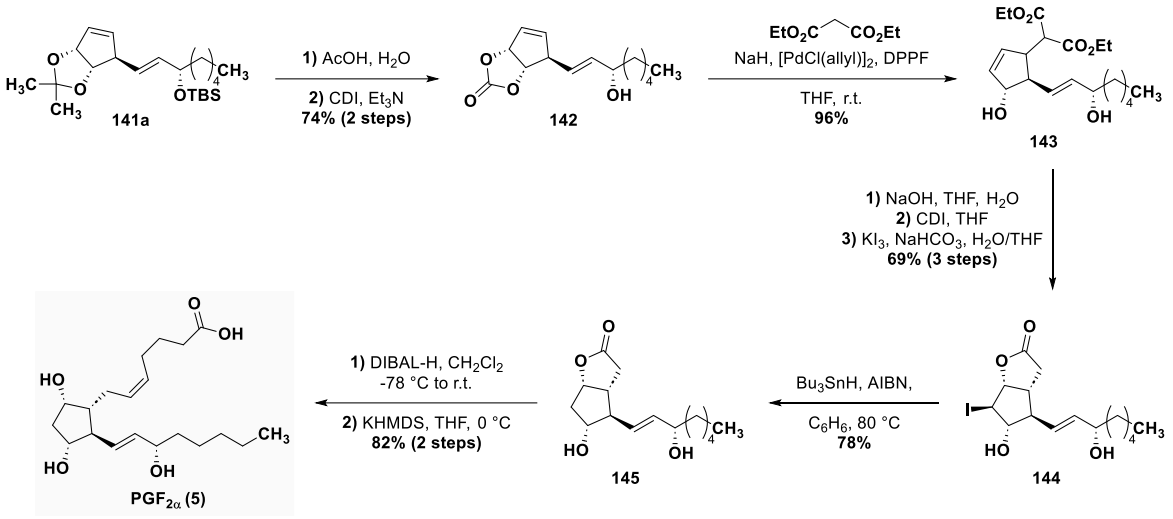
1.11 Recent work

The newly developed synthesis of Tafluprost proved to be a robust and versatile strategy for the synthesis of prostaglandins. In the follow-up research, Laura Cunningham, Sourabh Mishra and Leon Matthews (Stephen Fletcher's research group)[57] synthesised a series of chiral boronic esters representing the side-chains found in multiple prostaglandins and their derivatives. These boronic esters were then successfully coupled with allyl chloride **72** with excellent diastereoselectivity and high yields (**Scheme 1.20**). It is worth noting that enantiomerically enriched DM-SEGPHOS was still required in the Suzuki-Miyaura cross-coupling for control of the diastereoselectivity. In the presence of the racemic ligand, a 1:1 mixture of diastereomer **141a** and **141a'** was obtained (**Scheme 1.20**, bottom).



Scheme 1.20. *Scope of the desymmetrisation reaction.*

Employing the previously described synthetic sequence, coupling product **141a** was successfully converted into $PGF_{2\alpha}$ in 9 steps (16 steps longest linear sequence) and 19% overall yield (**Scheme 1.21**). The robustness of this newly developed approach was underscored by the fact that only the formation of cyclic carbonate **142** required optimisation of the reaction conditions. Under the original conditions, the C-15 OH group reacted with the triphosgene.



Scheme 1.21. *Synthesis of $PGF_{2\alpha}$.*

1.12 References for Chapter 1

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Chapter 2: Synthesis of *Daphniphyllum* alkaloids

2.1 Daphniphyllum alkaloids

Daphniphyllum alkaloids are a structurally diverse family of natural products isolated from the plant genus *Daphniphyllum*. This genus consists of 34 species of evergreen trees and shrubs that thrive across tropical and subtropical Asia, including countries such as China, Japan and New Guinea.[1]

The modern history of *Daphniphyllum* alkaloid began in 1909 with the isolation of the first member of this family, Daphnimacrine, by Yagi from *D. macropodum Miquel*. However, the complexity of its structure remained a mystery due to the limited analytical techniques available in that era.[2] It wasn't until over fifty years later that the pioneering work of Hirata *et al.* in 1966 finally unveiled the structure of the first *Daphniphyllum* alkaloids. Exploration of the same botanical source led to the isolation of several new alkaloids,[3,4] among which the structures of Daphniphylline (**150**)[5] and Yuzurimine (**151**),[6] were definitively elucidated by X-ray diffraction studies (**Figure 2.1**).

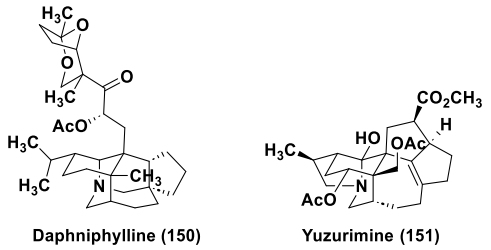


Figure 2.1. *Structures of Daphniphylline and Yuzurimine.*

From 1960s onwards, the family of *Daphniphyllum* alkaloids has expanded remarkably, and to this day, the isolation of more than 320 members has been reported.[7] While these polycyclic triterpenoids all originate from a common precursor (as discussed in the following section), their structural diversity is striking (**Figure 2.2**). They can be divided into 35 distinct structural types based on their backbone skeleton (**Figure 2.3**).[8] Generally, *Daphniphyllum* alkaloids consist of intricately fused five- to seven-membered rings, often totalling 5 or 6, and possess multiple continuous stereogenic centres, of which at least one is quaternary carbon.

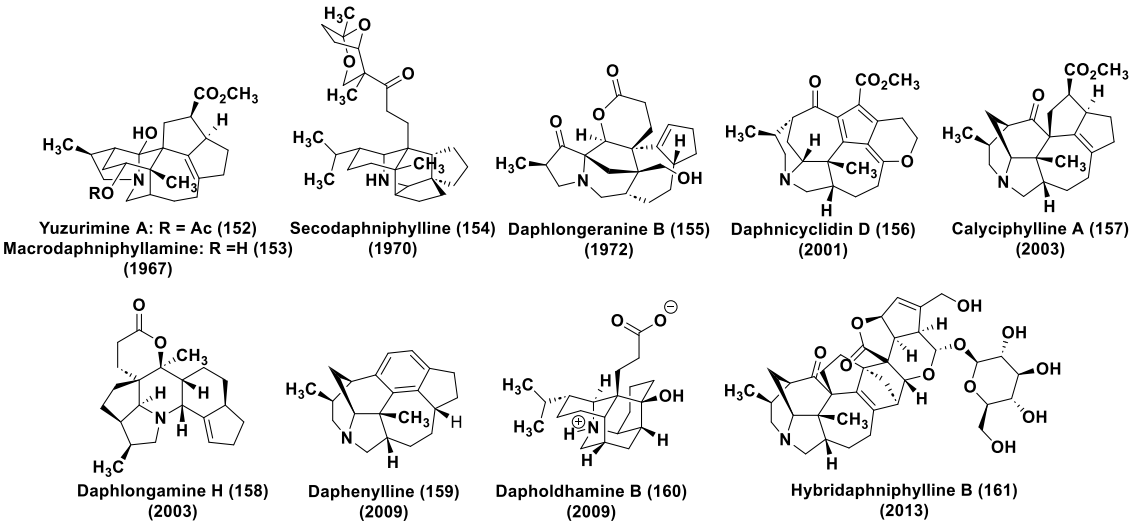


Figure 2.2. *Structures of selected Daphniphyllum alkaloids and years of their isolations.*

The extracts from the leaves and bark of the *Daphniphyllum* plant were used in traditional Chinese medicine for addressing various health conditions, such as asthma,[8] inflammation, dysentery and acute gastroenteritis.[7] This traditional use served as a catalyst for the exploration of the biological activity of *Daphniphyllum* alkaloids. Results of these studies were comprehensively summarised by Gao *et al.*[7] *Daphniphyllum* alkaloids exhibit cytotoxicity against various cancer cell lines and display vasorelaxant, insecticidal or pesticidal properties. Moreover, some of these alkaloids have shown the ability to inhibit platelet aggregation and exhibit activity against influenza virus.[8,7] While these findings underscore the promising pharmacological attributes of *Daphniphyllum* alkaloids, it is worth noting that their full spectrum of pharmacological activities remains relatively understudied.[9,10]

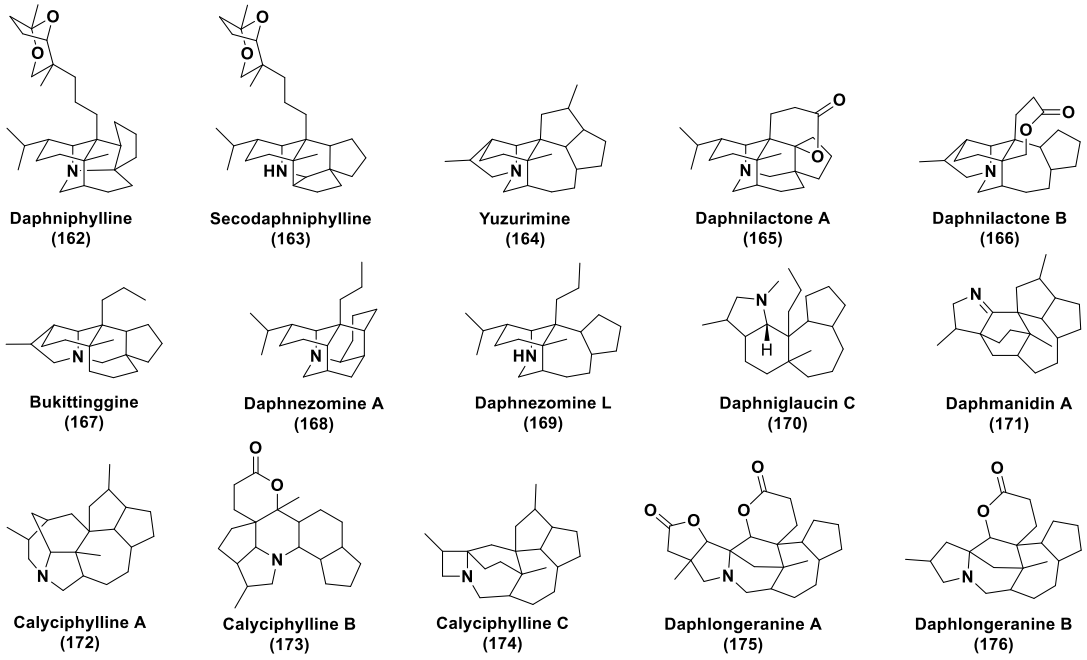
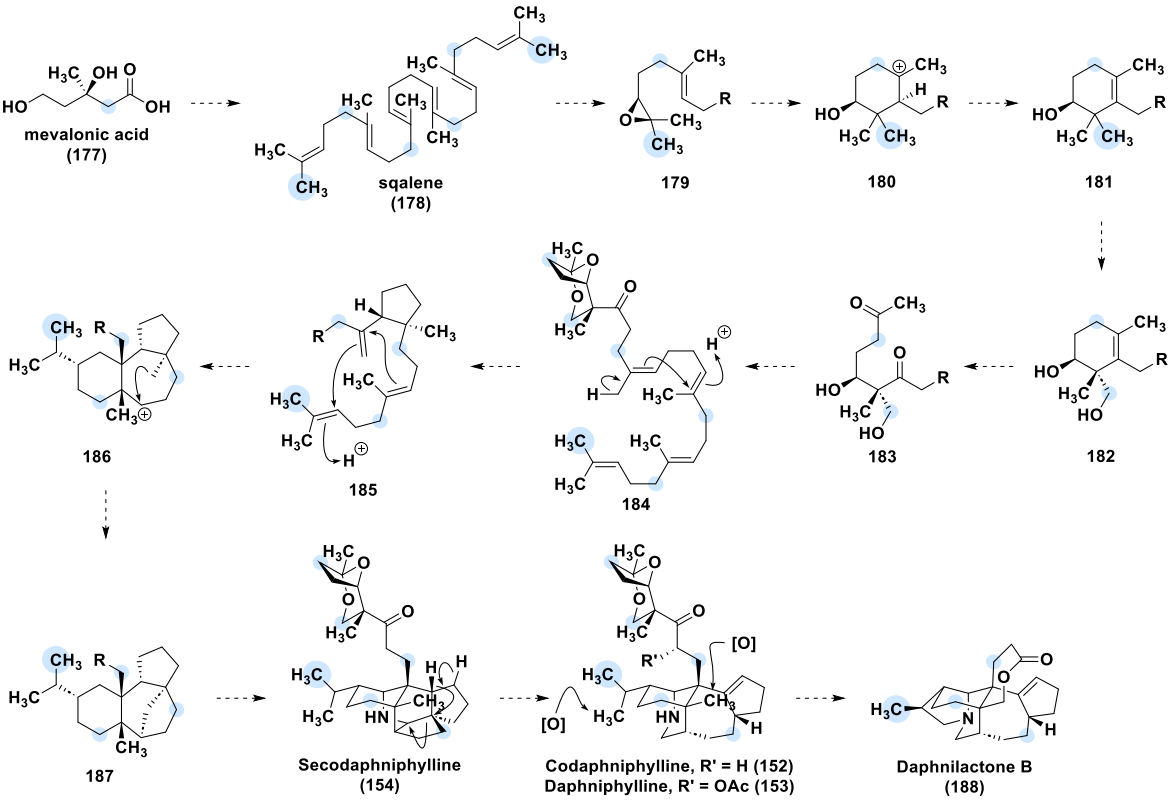


Figure 2.3. *Selected Daphniphyllum alkaloid skeletal structures.*

2.1.1 Biosynthesis of *Daphniphyllum* alkaloids

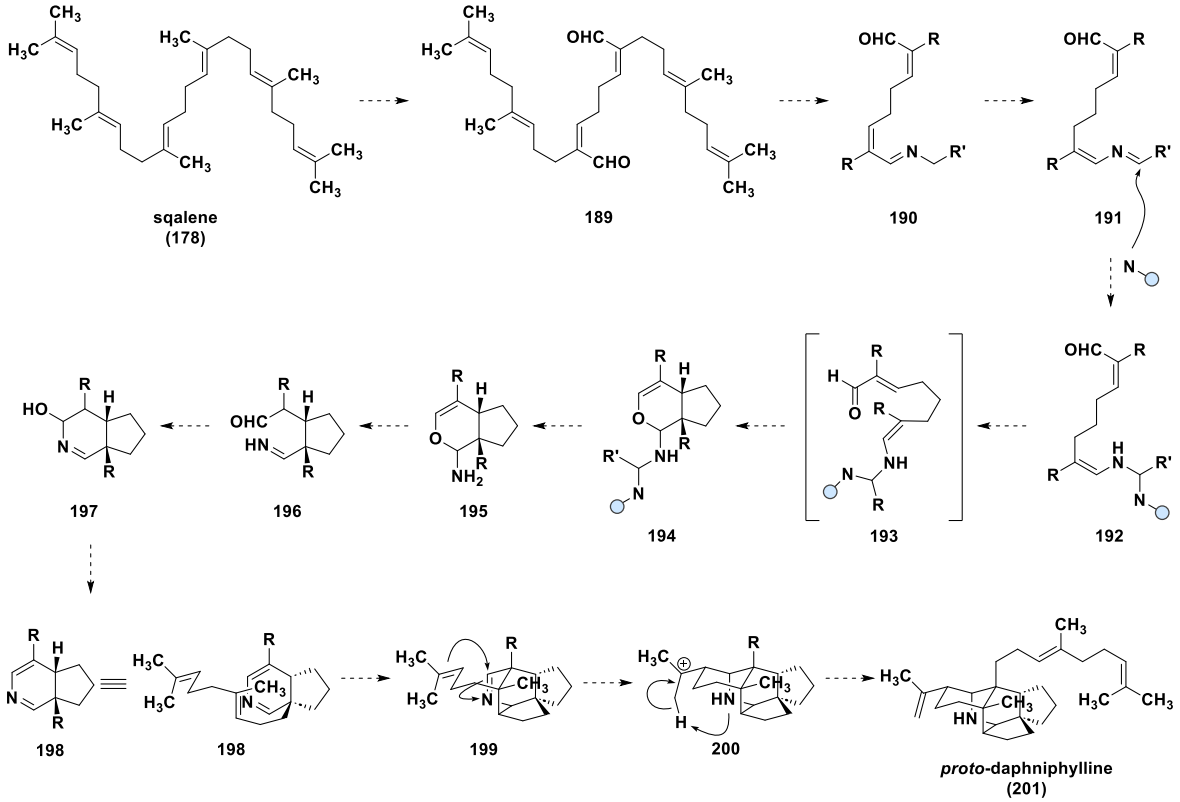
To illuminate the biosynthetic pathway of *Daphnyphyllum* alkaloids, Suzuki, Yamamura *et al.* performed a series of feeding experiments on growing leaves of *Daphniphyllum macropodum Miq* and fruits of *Daphniphyllum teijsmanni* using ^{14}C- and ^{3}H-labelled DL-mevalonic acid.[11,12] Based on the incorporation of these isotopes into the isolated alkaloids, authors proposed that Daphniphylline (**153**) and Daphnilactone B (**188**) are formed from six molecules of mevalonic acid (**177**) through squalene-type intermediate (**Scheme 2.1**). Its epoxidation, followed by cationic cyclisation through **180** leads to intermediate **181**. Hydroxylation of the methyl group (**181** → **182**) and oxidative cleavage of the alkene then generates diketone **183**. A subsequent cyclisation of **183** leads to the formation of bridged ketal **184**. The proposed biosynthesis of the amine part is initiated with an ene-type cyclisation of **184**, followed by cationic cyclisation resulting in the formation of six- and seven-membered rings (**185** → **186**). Intermediate **186** is converted to Secodaphniphylline (**154**) in an undefined pathway. 1,2-Hydride shift and ring opening in **154** provides Codaphniphylline (**152**), the oxidation of which leads to Daphnilactone B (**188**).



Scheme 2.1. *Biosynthesis of Daphniphyllum alkaloids proposed by Yamamura. Isotope incorporation showed in colour.*

Analysing the connectivity in multiple types of *Daphniphyllum* alkaloids, Heathcock *et al.* proposed an alternative biosynthetic pathway (**Scheme 2.2**).[13,14] They envisioned that in the first step, squalene (**178**) is oxidised to dialdehyde **189**. Next, one of the aldehydes moieties condenses with a primary amine, such as pyridoxamine or an amino acid, to form imine **190**. Prototropic rearrangement of 1-azadiene to 2-

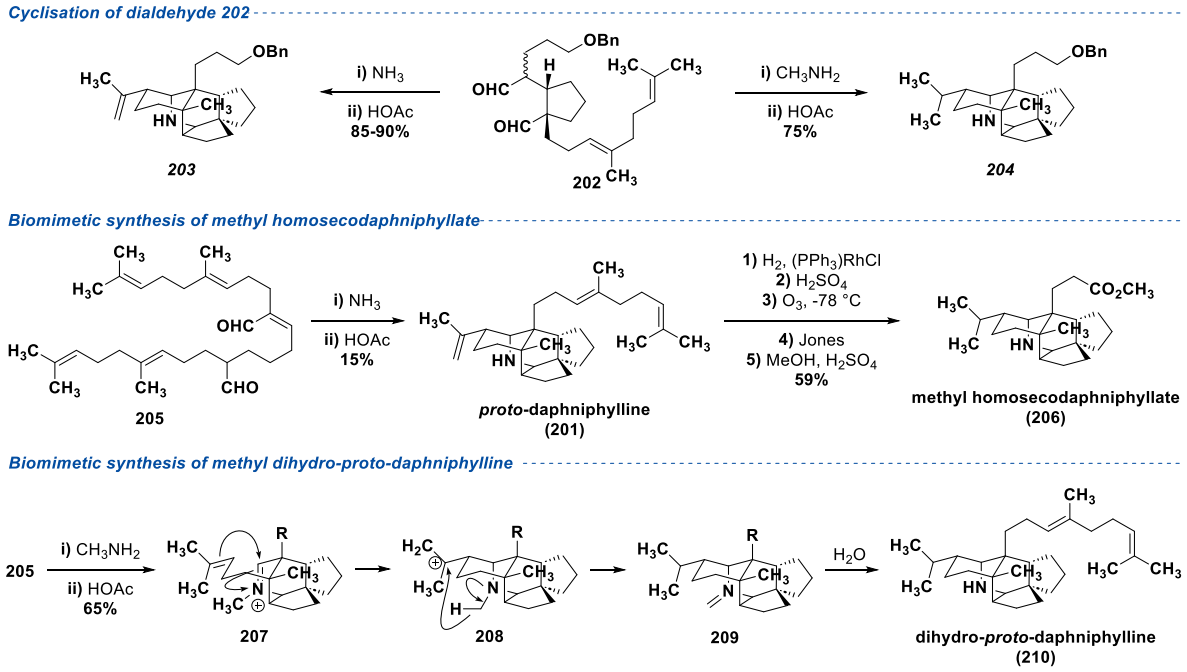
azadiene provides enimine **191**, which is then activated by the addition of nucleophilic species. The resulting enamine **192** then cyclises through either stepwise Michael addition or concerned Diels-Alder reaction, leading to the formation of bicyclic intermediate **194**. A sequence of proton-mediated addition and elimination steps then transforms this intermediate into dihydropyridine **198**, which undergoes a second Diels-Alder reaction. Finally, the ene-like cyclisation accomplished the proposed biosynthesis of the secodaphniphylline skeleton. Because the compound **201** is probably the first intermediate in the biosynthesis of *Daphniphyllum* alkaloids, Heathcock *et al.* named it *proto*-daphniphylline.



Scheme 2.2. *Biosynthesis of Daphniphyllum alkaloids proposed by Heathcock.*

To prove this hypothesis, Heathcock *et al.* commenced their synthetic studies with a second part of the proposed polycyclisation reaction – a cyclisation cascade of dialdehyde **202** (**Scheme 2.3**, top).[13] A sequential treatment of compound **202** with ammonia and acetic acid proved to be fruitful, leading to the formation of four new rings, and compound **203** was isolated in remarkable yield (65%).

Encouraged by these promising outcomes, they examined the polycyclisation cascade with an earlier intermediate, dihydrosqualene dialdehyde **205** (**Scheme 2.3**, middle).[13] Treatment of this compound with ammonia and acetic acid led to the formation of six new σ-bonds and five rings in one pot, and *proto*-daphniphylline **201** was isolated in 15% yield. The structure *proto*-daphniphylline **201** was confirmed by its conversion to methyl homosecodaphniphyllate **206**, and a comparison of its NMR spectra with an authentic sample.



Scheme 2.3. *Biomimetic synthesis of methyl homosecodaphniphyllate and dihydro-proto-daphniphylline.*

Considering the highly efficient conversion of **202** to **203** (85-90% yield), the relatively low yield of cyclisation of dihydrosqualene dialdehyde **205** to *proto*-daphniphylline **201** must be the result of the inefficiency of the first C-C bond formation. Heathcock *et al.* assumed this might originate from the high reactivity of the primary enamine.[14] On the other hand, they expected that cyclisation with less reactive secondary or tertiary enamine could increase the yield. However, this would also lead to the introduction of an alkyl chain to the nitrogen atom, which is not present in these natural products.

During the repetition of the cyclisation of dialdehyde **202,** one of Heathcock's co-workers, through a fortunate accident, used a gas cylinder of methylamine instead of ammonia. Interestingly, this led to the formation of compound **204**, a hydrogenated analogue of **203,** and the methyl group derived from methylamine was not incorporated into the product (**Scheme 2.3**, top right).[14] When these conditions were applied to dialdehyde **205** (**Scheme 2.3**, bottom) dihydro-*proto*-daphniphylline (**210**) was formed in excellent yield (65%). The formation of this unexpected product can be rationalised by the mechanism depicted in the same scheme: the second Diels-Alder reaction led to the formation of compound **207,** which subsequently cyclises as expected to intermediate **208**. However, now, instead of 1,5-proton transfer, a 1,5-hydride shift occurs, leading to the formation of imine **209**, which is hydrolysed during the aqueous work up to dihydro-*proto*-daphniphylline **210**. This observation, together with the absence of the isopropenyl group in *Daphniphyllum* alkaloids suggest that the source of the biosynthetic nitrogen may originate from an alkyl amine, such as pyridoxamine or an amino acid.

2.1.2 Calyciphylline A-type alkaloids

Calyciphylline A-type alkaloids represent one of the largest sub-families of *Daphniphyllum* alkaloids, which contains more than 40 members. It was named after the first member of this group, which was isolated by Kobayashi *et al.* in 2003 from *Daphnyphyllum calycinum* (**Figure 2.4**).[15] They all share a common tetracyclic [6-6-5-7] core, with additional rings fused to the seven-membered ring.

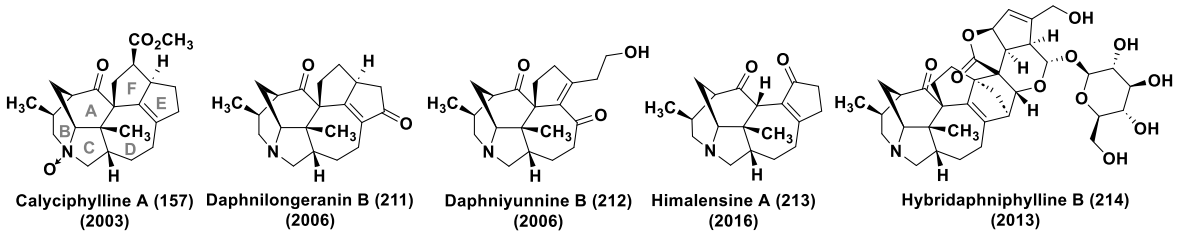
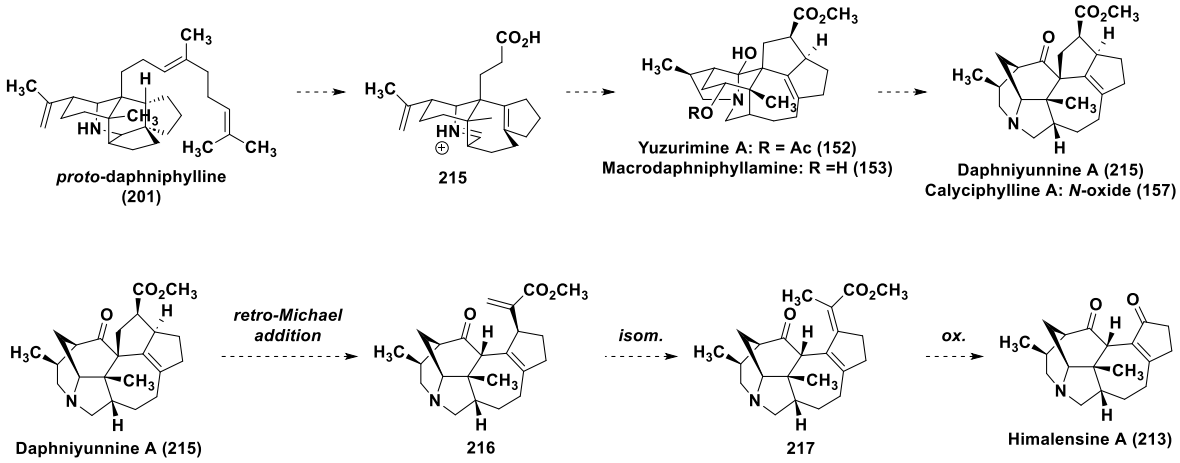


Figure 2.4. *Representative examples of Calyciphylline A-type alkaloids.*

A plausible biosynthetic pathway to Calyciphylline A (**157**) was proposed by Kobayashi *et al.* (**Scheme 2.4**, top).[15] Calyciphylline A (**157**) might be generated from *proto*-daphniphylline (**201**) through yuzurimine-type alkaloids, such as Yuzurimine A (**152**) or Marcodaphniphylline (**153**). Hydrolysis of the hemiaminal group, followed by a formal substitution of the acetoxy/hydroxy group would lead to the formation of Daphniyunnine A. Further oxidation of the nitrogen atom to the corresponding *N*-oxide would provide Calyciphylline A (**157**). The other members of the Calyciphylline A sub-family might be generated either by oxidation of Calyciphylline A (Daphniyunnine A) or rearrangement of the corresponding yuzurimine alkaloids.



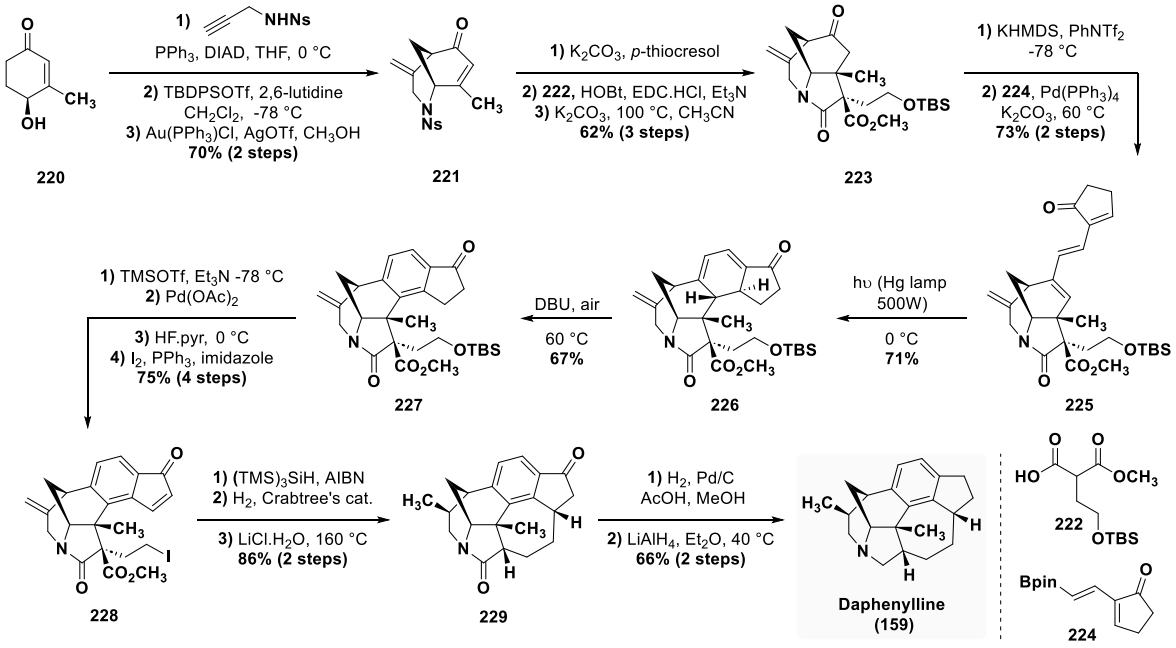
Scheme 2.4. *Proposed biosynthesis of Calyciphylline A and Himalensine A.*

Himalensine A (**Figure 2.4**) was isolated by Yue *et al.* from *Daphnyphillum himalense Mull. Arg.*, a species growing only in the southern lower regions of the Himalaya mountains, during a project that aimed to explore bioactive molecules originating from plants used in traditional Nepalese medicine.[16,17] It boasts a unique pentacyclic skeleton, standing as the sole example of the Calyciphylline A alkaloids not bearing the F-ring. As proposed by Shi (**Scheme 2.4**, bottom), Himalensine A might originate from Daphniyunnine A. Cleavage of the F-ring through retro-Michael addition would lead to the formation of intermediate **216**, which upon isomerisation of the double bond and its oxidative cleavage would lead to formation of Himalensine A.

2.2 Selected total syntheses and synthetic studies towards *Daphniphyllum* alkaloids

2.2.1 Ang Li's syntheses of *Daphniphyllum* alkaloids

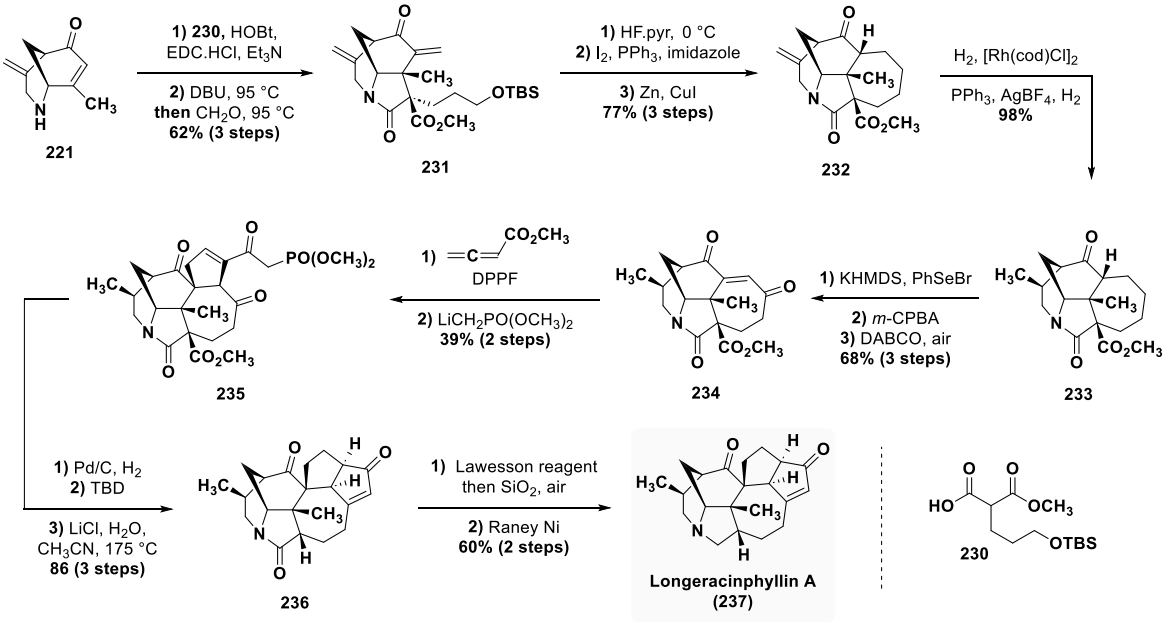
The first successful total synthesis of Calyciphylline A-type alkaloid, Daphenylline, was reported by Ang Li and coworkers in 2013 (**Scheme 2.5**).[18] Starting from enone **220**, available in 6 steps from *m*-methylanisole, Li first constructed the B-ring by gold-catalysed cyclisation of an alkyne, synthetised from **220** by Mitsunobu substitution of the secondary alcohol with nosyl-protected propargylamine, and subsequent conversion of the ketone group into corresponding silyl enol ether. Drawing inspiration from the work of the Dixon group (see **Section 2.3.2**), the C-ring was introduced by intramolecular Michael addition of malonamate, obtained by cleavage of the nosyl group and subsequent coupling of the obtained amine with acid **222**.



Scheme 2.5. *Ang Li's synthesis of Daphnylline.*

The E- and F-rings were introduced in a very convergent fashion by Suzuki cross-coupling of an enol triflate, prepared from intermediate **223**, with pinacol boronate **224**, followed by photoisomerization – 6π-electrocyclisation of the obtained triene **225**. Aerobic oxidation accomplished the synthesis of the benzene ring. Next, the ketone moiety in **227** was converted to an enone by Seagusa-Ito oxidation and the pendant TBS-protected alcohol was transformed into the iodide by Appel reaction (**227** → **228**). This set the stage for the construction of the final ring by intramolecular radical cyclisation. Directed hydrogenation of the *exo*-methylene group and Krapcho decarboxylation provided intermediate **229**, which, upon reduction of the ketone and amide group, provided Daphenylline (**159**).

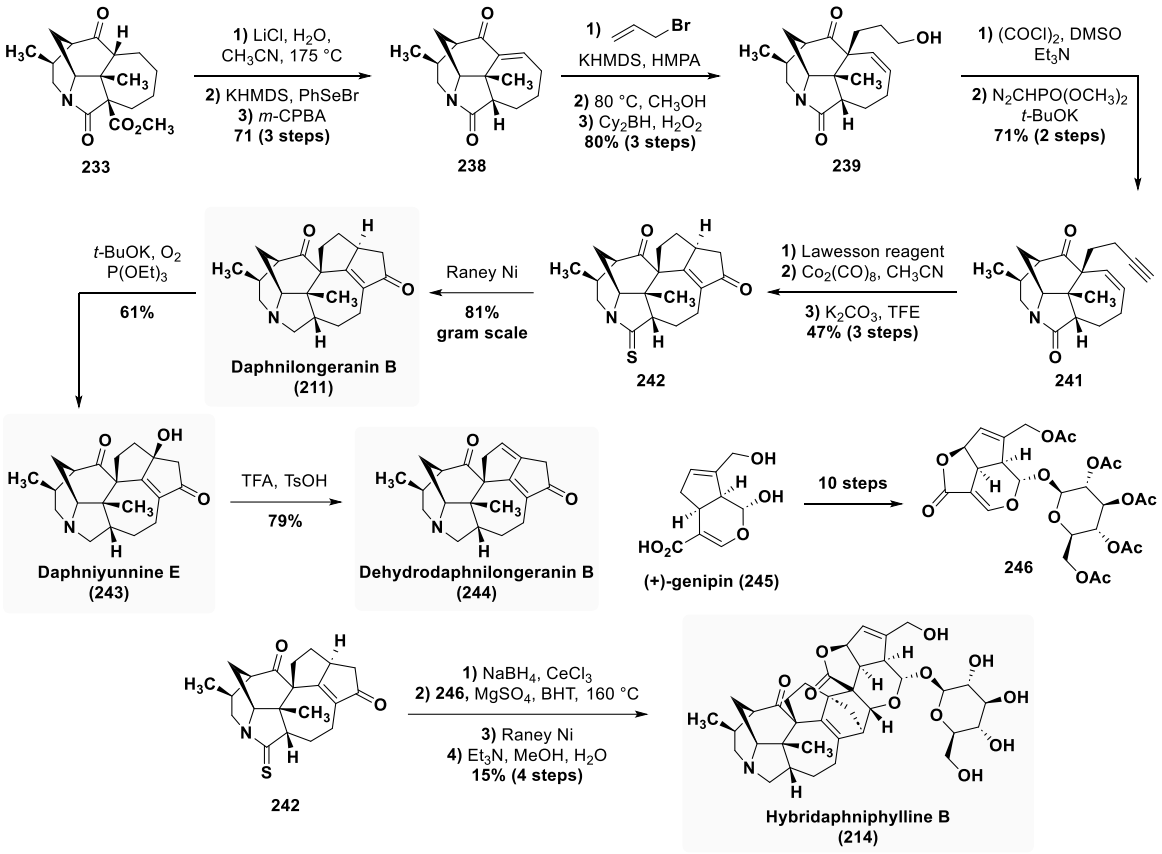
In 2017, Ang Li reported the total synthesis of another Calyciphylline A-type alkaloid, Longeracinphyllin A (**Scheme 2.6**).[19] Similarly, as in their synthesis of Daphenylline, the C-ring was constructed by intramolecular Michael addition. To this end, amine **221** was coupled with acid **230** and the resulting amide was treated with DBU. Subsequent addition of formaldehyde into the cyclisation step introduced the enone moiety, required for the D-ring formation. Subsequent TBS deprotection and Appel iodination of the obtained alcohol provided alkyl iodide, which, after treatment with zinc and copper iodide, underwent another intramolecular conjugate addition, furnishing the tetracyclic intermediate **232**.



Scheme 2.6. *Ang Li's synthesis of Longeracinphyllin A.*

A series of redox manipulations, namely, directed hydrogenation of the exo-methylene group, α-selenation – selenoxide elimination and aerobic oxidation of the extended enolate provided intermediate **234**. The introduction of the E-ring was accomplished *via* phosphine-catalysed [3+2] cycloaddition of methyl buta-2,3-dienoate to enone **234**. Subsequent treatment of the obtained intermediate with $LiCH_2PO(OMe)_2$ converted the ester group into *β*-ketophosphonate, later used for the introduction of the F-ring. Hydrogenation of **235**, followed by intramolecular Horner-Wadsworth-Emmons (HWE) reaction and Krapcho decarboxylation, provided pentacycle **236**. Selective reduction of amide in **236** to the amine by its conversion to thioamide using Lawesson's reagent and subsequent desulphurisation accomplished the total synthesis of *Longeracinphyllin A*.

In 2018, Ang Li and coworkers published a collective total synthesis of four additional Calyciphylline A-type alkaloids (**Scheme 2.7**),[20] including the most complex member of this family, Hybridaphniphylline B, a Diels-Alder adduct of deacetylasperuloside and a diene derived from Daphnilongeranin B, possessing 11 rings and 19 stereocenters. Inspired by Dixon's synthetic studies towards Daphnilongeranin B and Daphniyunnine D (see **Section 2.3.1.3** for more details), Li's team based their synthetic strategy on the introduction of the E- and F- rings *via* intramolecular Pauson-Khand cyclisation.



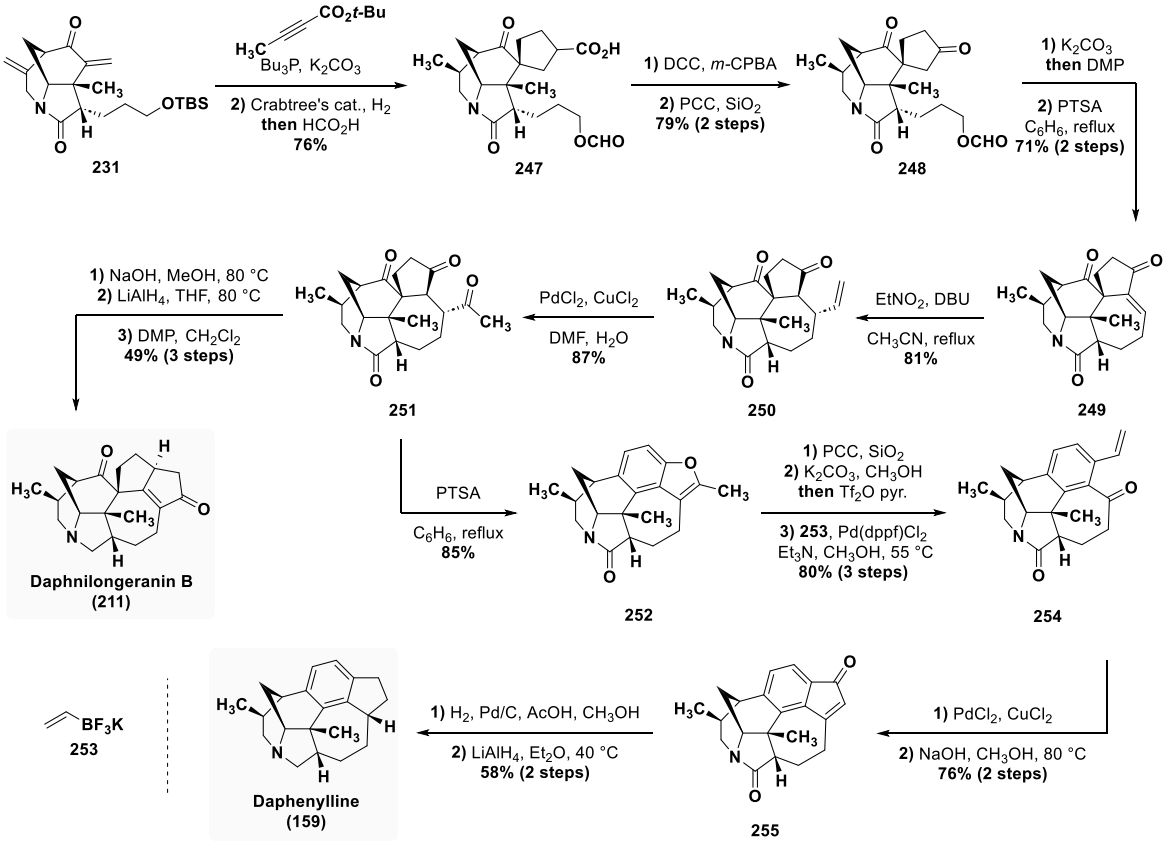
Scheme 2.7. *Ang Li's 2018 synthesis of Calyciphylline A-type alkaloids.*

Li and coworkers initiated their synthesis from tetracycle **233,** a common intermediate in the previous synthesis of *Longeracinphyllin A*. Krapcho decarboxylated followed by α-selenation – selenoxide elimination provided intermediate **238**. To introduce the C-8 alkyne side chain required for the ensuing Pauson-Khand cyclisation, compound **238** was allylated by an *O*-allylation – Claisen rearrangement sequence. Subsequent hydroboration – oxidation followed by Swern oxidation and Seyfert-Gilbert homologation of the obtained aldehyde afforded alkyne **241**. Treatment of compound **241** with Lawesson's reagent converted the amide group into the thioamide. Heating of this intermediate with $Co_2(CO)_8$ provided the hexacyclic product as a mixture of two diastereomers in 73% yield. A base-catalysed double bond migration led to the formation of more substituted enone **242** as a single diastereomer. Desulphurisation of **242** employing Raney nickel culminated in the gram-scale synthesis of Daphnilongeranin B **(211**). Its aerobic oxidation in the presence of *t*-BuOK and $P(OEt)_3$ afforded Daphniyunnine E (**243**) as a single diastereomer. Treatment of Daphniyunnine E with acid provided Dehydrodaphnilongeranin B (**244**).

Finally, Luche reduction of the enone moiety in intermediate **242** provided the corresponding secondary alcohol. Its *in situ* dehydration with magnesium sulphate produced cyclopentadiene (not shown), which underwent a Diels-Alder reaction with dienophile **246,** giving rise to 4 isomers in 79% yield. HPLC separation of this mixture provided the main and desired isomer in 24% yield. Desulphurisation and hydrolysis of 5 acetyl groups concluded the total synthesis of Hybridaphniphylline B (**214**).

2.2.2 Hongbin Zhai's synthesis of Daphnilongeranin B and Daphenylline

Drawing inspiration from Ang Li's synthetic studies towards the ABCD-tetracyclic core of Calyciphylline A-type alkaloids,[21] in 2018, Hongbin Zhai and coworkers reported the total synthesis of Daphnilongeranin B and Daphenylline (**Scheme 2.8**)[22] using a very similar approach to that shown in **Scheme 2.5.** Starting from Li's intermediate **231**, the E-ring was installed by phosphine-catalysed [3+2] cycloaddition of *tert*-butyl but-2-ynoate to enone moiety in **231**. Subsequent directed hydrogenation of the *exo*-methylene group followed by hydrolysis of the TBS- and *tert*-butyl ester moieties afforded compound **247**. Treatment of this intermediate with DCC and *m*-CPBA provided a secondary alcohol which was oxidised by PCC to ketone **248**. Hydrolysis of the formyl group in **248** followed by oxidation of the primary alcohol gave rise to an aldehyde, which upon treatment with PTSA underwent intramolecular aldol condensation forming the D-ring (**248** → **249**). Zhai planned to introduce the F-ring by another intramolecular aldol condensation. This required the installation of an acetyl group at position C-10, for example, by Michael addition of nitroethane followed by Nef reaction. Surprisingly, treatment of intermediate **249** with nitroethane in the presence of DBU led to the formation of vinylated product **250** in 81% yield. Wacker oxidation of the vinyl group afforded intermediate **251**, which, upon heating with sodium hydroxide, underwent the planned aldol condensation. Reduction of the amide group to amine by $LiAlH_4$ followed by reoxidation of the other affected groups provided Daphnilongeranin B (**211**).

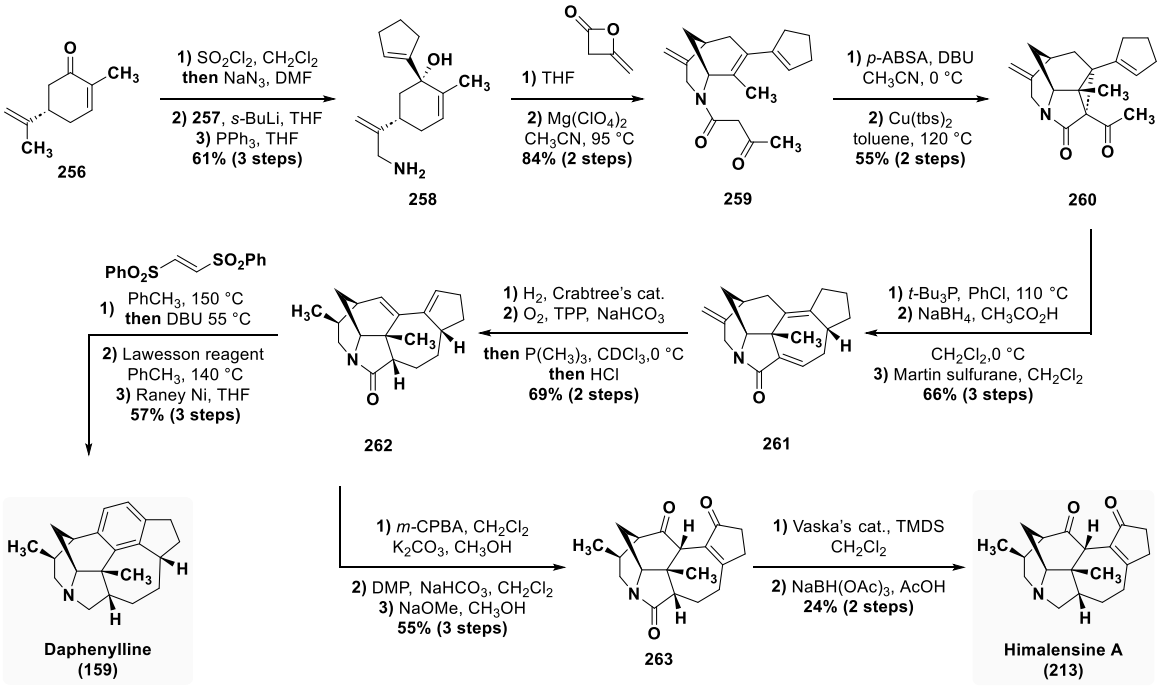


Scheme 2.8. *Hongbin Zhai's synthesis of Daphnilongeranin B and Daphenylline.*

The benzene ring of Daphenylline was introduced by rearrangement of intermediate **251** under acidic conditions. The possible mechanism for this transformation involves the formation of a furan ring accompanied by Wagner–Meerwein-type 1,2-migration, followed by aromatisation. Oxidative cleavage of the furane ring in **252** provided the acetylated phenol, which was, upon methanolysis and conversion to the corresponding triflate vinylated by Suzuki cross-coupling with trifluoroboronate **253** (**252** → **254**). Wacker oxidation of the newly installed vinyl group afforded the ketone, which was used for the introduction of the final F-ring *via* another intramolecular aldol condensation (**254** → **255**). The reduction of compound **255** under Li's condition concluded the synthesis of Daphenylline.

2.2.3 Fayang Qiu's synthesis of Himalensine A and Daphenylline

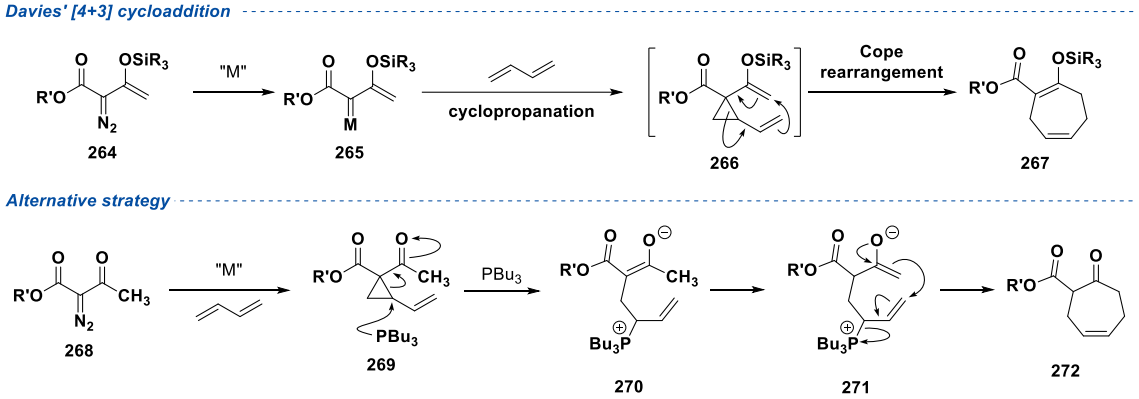
In 2021, Fayang Qiu reported a very efficient synthesis of Himalensine A and Daphenylline in only 17 and 15 synthetic steps, respectively (**Scheme 2.9**).[23] Choosing (S)-carvone (**256**) as a starting point, the future C-ring amino group was introduced by the allylic chlorination of the isopropenyl group, followed by substitution with sodium azide. The E-ring was introduced in the early stage *via* 1,2-addition of cyclopentenyl lithium (**257**) and Staudinger reduction of the azide group afforded intermediate **258**. Its acylation with diketene followed by $Mg(ClO_4)_2$-catalysed substitution of allylic alcohol introduced the B-ring (**258** → **259**).



Scheme 2.9. *Fayang Qiu's synthesis of Himalensine A and Daphenylline.*

The D-ring was envisioned to be installed through Davies' [4+3] cycloaddition (see **Scheme 2.10** for details).[24] However, this transformation provided the desired product in a modest yield of only 21%. Consequently, an alternative, stepwise sequence, was adopted. To this end, the β-ketoamide **259** was subjected to Regitz diazo-transfer using *p*-ABSA, followed by Cu^{II}-catalysed cyclopropanation (**259** →

260). Treatment of compound **260** with *t*-Bu_3P then led to its rearrangement to cycloheptenone in 82% yield.[25] Its reduction with $NaBH_4$ and alcohol elimination with Martin's sulfurane afforded triene **261**. The two more sterically accessible alkenes in triene **261** were hydrogenated using Crabtree's catalyst, followed by the conversion of the remaining alkene to a diene by an allylic hydroxylation – alcohol elimination sequence (**261** → **262**).



Scheme 2.10. *Mechanism of Davies' [4+3] cycloaddition and alternative strategy to cyclohexanone.*

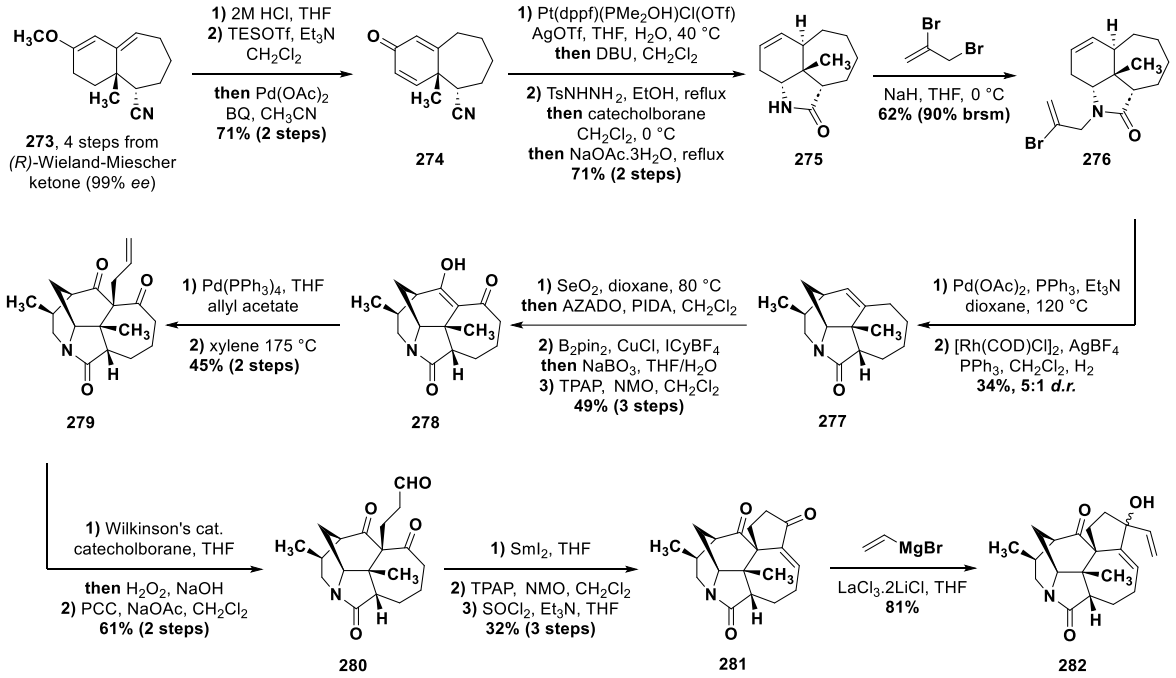
The benzene ring of Daphenylline was introduced by the Diels-Alder reaction of diene **262** with *trans*-1,2-bis(phenylsulfonyl)ethylene, followed by double sulfonyl group elimination. The previously described thioamide desulphurisation sequence finalised the synthesis of Daphenylline.

Alternatively, a series of redox manipulations converted intermediate **262** in 5 steps to Himalensine A. Treatment of diene **262** with *m*-CPBA led to regioselective epoxide formation, which underwent S_N2' epoxide opening with *in situ* generated *m*-chlorobenzoic acid. Methanolysis of the benzoyl moiety afforded the diol, which was oxidised to corresponding diketone. Base mediated alkene migration then provided intermediate **263**. Final chemoselective reduction of the amide group with Vaska's catalyst provided Himalensine A.

2.2.4 Jing Xu's synthesis of 10-Deoxydaphnipaxianine A and Daphlongamine E

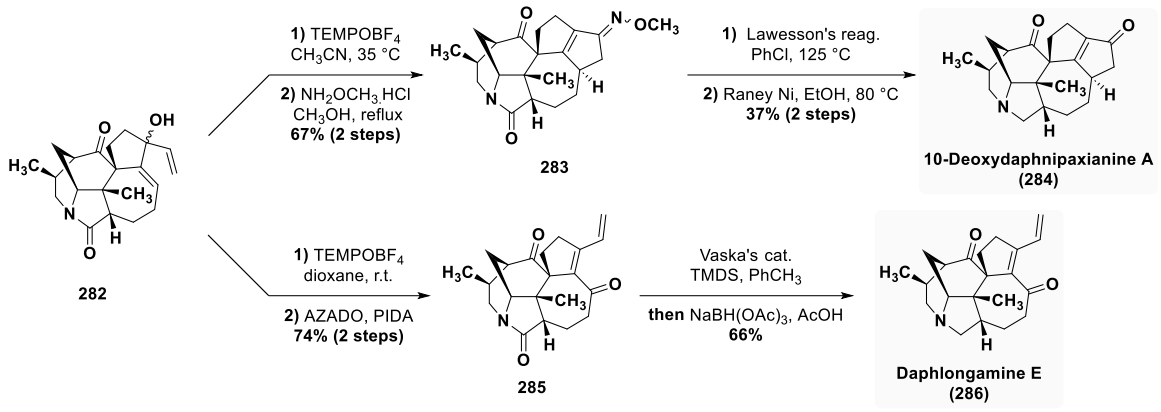
The final selected example of *Daphniphyllum* alkaloid synthesis is Jing Xu's 2022 synthesis of 10-Deoxydaphnipaxianine A and Daphlongamine E (**Scheme 2.11**).[26] Xu and coworkers commenced their synthesis from enol ether **273**, available in 4 steps from Wieland-Miescher ketone. For the introduction of the C-ring by intramolecular Michael addition, compound **273** was first hydrolysed and then converted to enone **274** by Seagusa-Ito oxidation. Subsequent catalytic hydration of the nitrile group in **274** followed by the addition of DBU to the reaction mixture afforded the cyclised product, which was converted to alkene **275** by Hutchins-Kabalka reductive rearrangement.[27,28] Next, Xu used an intramolecular Heck reaction to introduce the B-ring. To this end, amide **275** was allylated with 2,3-dibromoprop-1-ene, providing intermediate **276**. Treatment of **276** with $Pd(OAc)_2$ in the presence of PPh_3 and Et_3N afforded the cyclised product, which was then subjected to directed hydrogenation (**276**

→ **277**). Next, alkene **277** was converted to diketone **278** by a sequence of oxidation steps: Riley oxidation afforded the allylic alcohol, which was subsequently oxidised to the enone by AZADO/PIDA. Its hydroboration – oxidation provided *β*-hydroxy ketone, and Ley-Griffith oxidation gave rise to diketone **278**. *O*-allylation – Claisen rearrangement provided C-8 alkylated intermediate **279**. Its hydroboration – oxidation afforded aldehyde **280**, which was used for introduction of the E-ring *via* pinacol coupling. Oxidation of the secondary hydroxyl to ketone followed by elimination of the tertiary OH-group gave rise to intermediate **281**. Finally, 1,2-addition of vinylmagnesium bromide to **281** provided commom **282**.



Scheme 2.11. *Jing Xu's synthesis of 10-Deoxydaphnipaxianine A and Daphlongamine E (part I).*

In the next step towards Daphlongamine E, Xu and coworkers attempted oxidative transposition of tertiary allylic alcohol using $TEMPOBF_4$ in acetonitrile (**Scheme 2.12**, top). To their surprise, this led to the formation of a product of oxidative Nazarov cyclisation in 80%, requiring only the final amide reduction to accomplish the total synthesis of 10-Deoxydaphnipaxianine A. To achieve this tranformation, the F-ring ketone group had to be first masked as an *O*-methyloxime (**282** → **283**). Subsequent formation of thioamide, its desulphurisation and oxime hydrolysis afforded *10-Deoxydaphnipaxianine A*.



Scheme 2.12. *Jing Xu's synthesis of 10-Deoxydaphnipaxianine A and Daphlongamine E (part II).*

Surprisingly, the change of the reaction solvent from acetonitrile to dioxane yielded secondary alcohol, which was not oxidised under the reaction conditions (presumably due to the steric hindrance; **Scheme 2.12**, bottom). The use of the less sterically hindered nitroxyl radical catalyst, 2-azaadamantane *N*-oxyl (AZADO), provided ketone **285** in 98% yield. The final selective Vaska's reduction of the amide group accomplished the first total synthesis of Daphlongamine E.

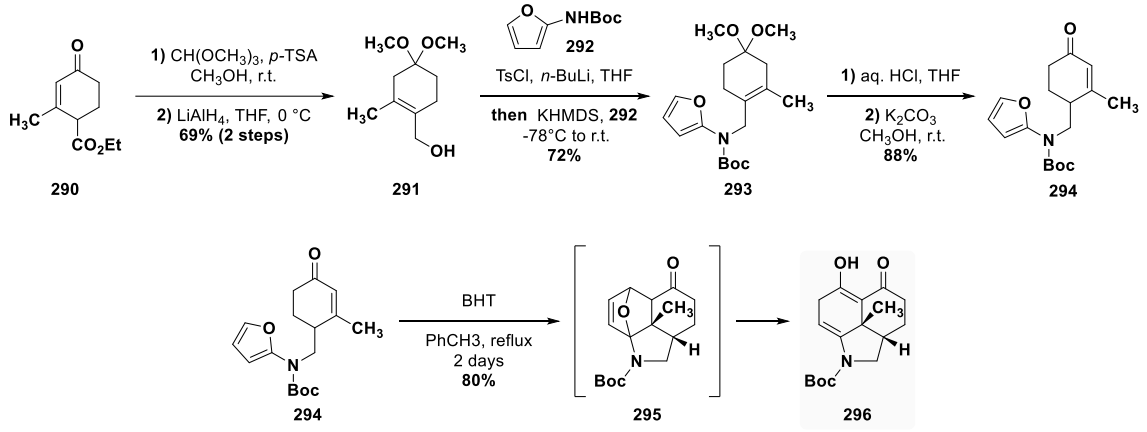
2.3 Synthetic studies towards *Daphniphyllum* alkaloids in the Dixon group

The calyciphylline A-type alkaloids were in the focus of the Dixon group for over a decade. During this period, several synthetic strategies targeting the polycyclic core of these natural products were developed,[29] many of which were later successfully adopted by the synthetic community for their total syntheses. [18-22, 30] Moreover, these synthetic studies led to the development of multiple new reactions, including novel cyclisations,[31] enantioselective desymmetrisations[32] or selective amide group reduction.[33]

2.3.1 Synthetic strategy based on IMDAF

2.3.1.1 Synthesis of ACD-core

The origin of these synthetic studies can be traced back to the late 2000s and the work of John Ward, who investigated several strategies towards the ACD-core of Daphniyunnine B.[34] The most successful strategy, based on the intramolecular Diels-Alder reaction of furan (abbreviated as IMDAF) is shown in **Scheme 2.13**. Ward realised that the IMDAF between amino group-bearing furan and appropriately substituted 7-membered enone could be used for highly convergent assembly of the A and C-rings.

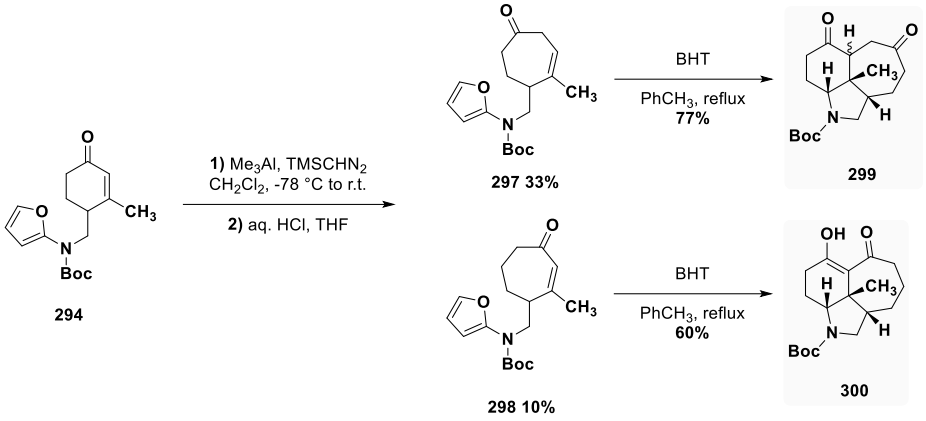


Scheme 2.13. *Ward's synthesis of ACD core based on IMDAF (model system).*

In the model study, the commercially available Hagemann's ester (**290**) was used as the starting material. The protection of ketone in **290** as a dimethyl acetal allowed the reduction of the ester group to a primary alcohol. This alcohol was then activated as a tosylate ester and then substituted with Boc-protected 2-aminofuran (**292**) in the same pot. Hydrolysis of the acetal group in **293** and base-mediated migration of the double bond into conjugation with the ketone furnished the model substrate **294** in only 5 steps and 44% overall yield. Pleasingly, heating of **294** in the presence of antioxidant (BHT) resulted in the formation of the product **296** as a single diastereomer in 80% yield through a Diels-Alder reaction followed by the fragmentation of the initially formed dihydrofuran intermediate **295**.

Encouraged by these results, Ward investigated the preparation of the 7-membered dienophile employing one-carbon homologation of ketone **294** (**Scheme 2.14**). However, this transformation

proved to quite challenging and after screening of multiple reaction conditions, the desired homologated ketone **297** could be obtained in only 33% yield, alongside the undesired regioisomer **298** in 10% yield. Nevertheless, subjecting the homologated ketone **297** to the previously optimised conditions provided the desired tricyclic product **299** in 77% yield as a 2:1 mixture of diastereomers. Moreover, the undesired homologation regioisomer **298** was successfully converted into tricycle **300** under the same reaction condition in 60% yield.



Scheme 2.14. *Ward's synthesis of ACD core based on IMDAF (real system).*

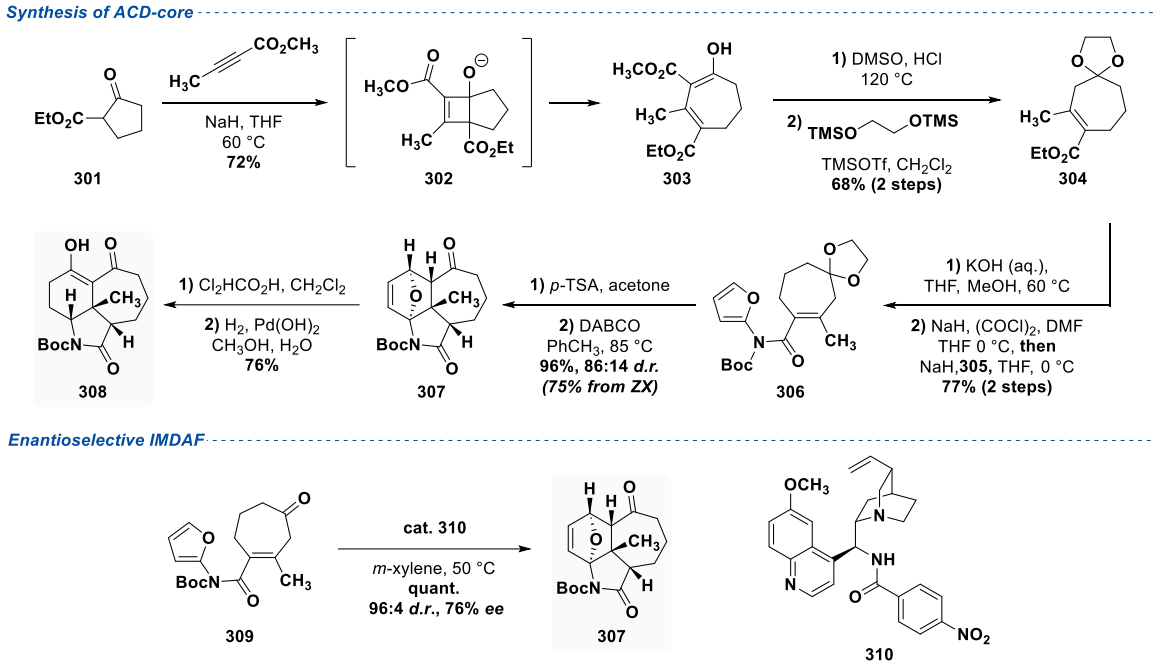
Although the low-yielding ketone homologation hindered the preparation of tricyclic intermediated **299** and **300** on a synthetically useful scale, Ward's synthetic studies validated the feasibility of the IMDAF approach and represented a crucial milestone on the path towards the synthesis of *Daphniphyllum* alkaloids.

2.3.1.2 Improved synthesis of the ACD core

Expanding upon Ward's seminal work, Iacovos N. Michaelides and Benjamin Darses envisioned that the tricycle **300** originating from the IMDAF of the undesired homologation regioisomer could serve as a promising intermediate for the synthesis of Daphniyunnine D (**Scheme 2.14**). Building on this concept, they developed a scalable synthesis of a similar cyclisation precursor **309** (**Scheme 2.15**).[35] In this modified approach, the researchers opted to replace the problematic one-carbon homologation of 6-membered enone with a more efficient two-carbon homologation of 5-membered β-ketoester. Treatment of sodium enolate of ethyl 2-oxocyclopentane-1-carboxylate (**301**) with methyl but-2-ynoate provided compound **303** in 72% yield *via* a sequence consisting of Michael addition followed by intramolecular aldol condensation and Grobb fragmentation. Selective decarboxylation of the β-ketoester through Krapcho decarboxylation, followed by protection of the resulting ketone afforded ester **304**.

Deviating from Ward's strategy, Michaelides and Darses decided not to reduce the ester functional group in **304**; instead, they used it for the introduction of the diene moiety through amide coupling. To this end, the ester group in **304** was hydrolysed with potassium hydroxide to the corresponding acid, which

was then converted into acyl chloride and coupled with *N*-Boc-protected 2-aminofuran (**305**). Deprotection of the acetal in **306** afforded corresponding ketone in 78% yield, which, upon heating in the presence of a base (DABCO) underwent double bond migration, triggering the IMDAF reaction and providing tetracyclic intermediate **307** in 96% yield and 86:14 *d.r.* Finally, hydrolysis of the dihydrofuran moiety and enamine hydrogenation completed the synthesis of the racemic ACD core of *Daphniphyllum* alkaloids (**308**).



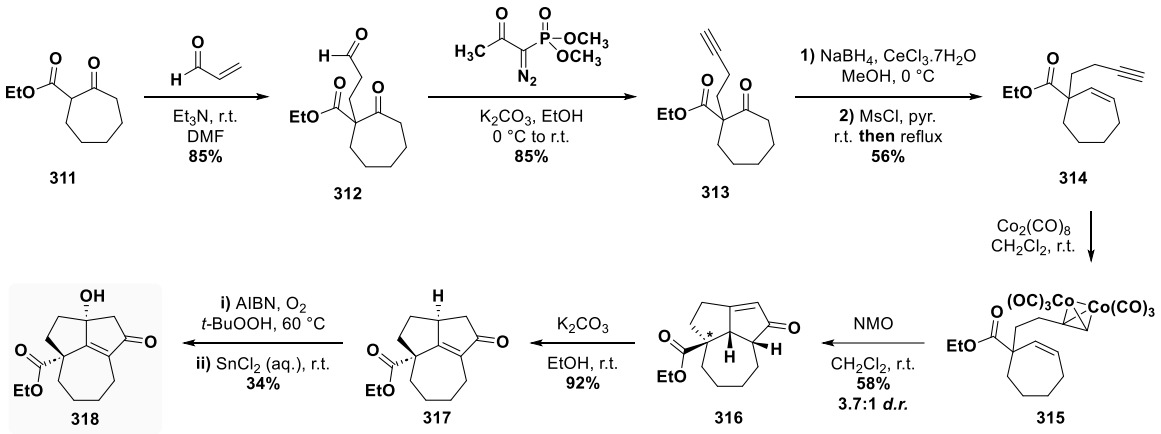
Scheme 2.15. *Synthesis of ACD core by Michaelides and Darses.*

During their synthetic studies, Michaelides and Darses explored the possibility of enantioselective synthesis of compound **307** (**Scheme 2.15**, bottom).[35] Through extensive screening of a library of *cinchona*-derived bifunctional organocatalysts, they identified catalyst **310**, which provided the IMDAF adduct **307** in 76% *ee,* quantitative yield and 96:4 *d.r.* Michaelides and Darses postulated that asymmetric induction occurs during the initial proton transfer from the α to the γ-position. The benzoyl amide moiety of catalyst **310** forms a hydrogen bond with the amide group of the substrate **309** before the deprotonation of the α-position by the quinuclidine core. Subsequent enantiocontrolled proton transfer from protonated quinuclidine to the γ-position of compound **309** yields an enantiomerically enriched dienophile that then undergoes the IMDAF reaction.

2.3.1.3 Synthesis of the EF-rings of Daphniyunnine D

Having successfully synthesised the ACD core, Michaelides and Darses shifted their attention to the synthesis of the EF-rings Daphniyunnine D (**Scheme 2.16**).[29b,35] They envisioned that these rings could be rapidly introduced through intramolecular Pauson-Khand reaction. To prove this hypothesis, they synthesised model system **314**. Starting from β-ketoester **311**, they introduced the alkyne side chain through Michael addition of **311** with acrolein, followed by conversion of the aldehyde to corresponding

alkyne by its treatment with Ohira-Bestmann reagent. The alkene part of the molecule was installed by Luche reduction of the ketone group in **313** followed by mesylation and elimination of the obtained secondary alcohol (**313** → **314**). Treatment of the alkyne **314** with $Co_2(CO)_8$ led to the quantitative formation of the Co-alkyne complex **315**, which upon refluxing in acetonitrile provided the desired tricyclic product **316** in 43% yield and 4:1 *d.r.* (the main diastereomer shown). Using NMO as a promoter allowed the reaction to be run under milder conditions, increasing the yield to 58% (NMO oxidises CO ligand to CO_2 (g) and thus assists the coordination of the alkene to cobalt centre is the rate-limiting step). Treatment of enone **316** with K_2CO_3 in ethanol facilitated the double bond migration as well as epimerisation of the ester group in 92% yield and accomplished the synthesis of EF-rings present in Daphnilongeranin B. Finally, oxidation of the enone **317** at γ-position using Watt's protocol[36] provided the DEF-rings of Daphniyunnine D in 34% yield (**317** → **318**).

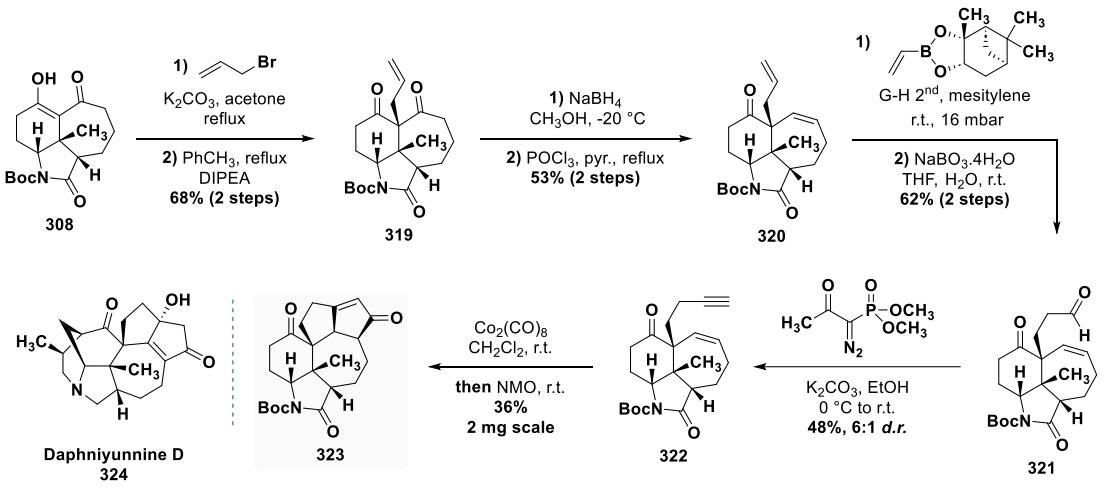


Scheme 2.16. *Synthesis of the EF-rings of Daphniyunnine D on a model system.*

2.3.1.4 Synthesis of EF-rings of Daphniyunnine D on a real system

Next, Michaelides and Darses shifted their focus to the introduction of the EF-rings to real system **308** (**Scheme 2.17**).[35] Initial attempts to treat ketone **308** with acrolein proved unproductive, likely due to the H-bonded hydroxyenone moiety acting as a protecting group for the targeted central carbon atom. This issue was overcome by a two-step procedure based on the *O*-allylation of the enol in **308** followed by the Claisen rearrangement of obtained allyl enol ether (**308** → **319**). The reduction of the ketone group in **319** to alcohol and its elimination installed the endocyclic alkene in 53% yield. Next, the allyl group in **320** was converted to aldehyde **321**. However, hydroboration of the allyl group was not productive and alternative methods for oxidation of the terminal position of this alkene had to be sought. Pleasingly, cross-metathesis with vinyl pinanediol boronate and oxidation of the obtained vinyl boronate with sodium perborate afforded aldehyde **321** in 62% over 2 steps. The conversion of aldehyde **321** to alkyne **322** proved problematic, and the desired alkyne was obtained only in 29% yield. Furthermore, a small amount of the epimerised alkyne (19%, 1:0.55 *d.r.*) and the product of intramolecular aldol condensation of aldehyde and ketone (13%) were isolated. With a very limited amount of the material

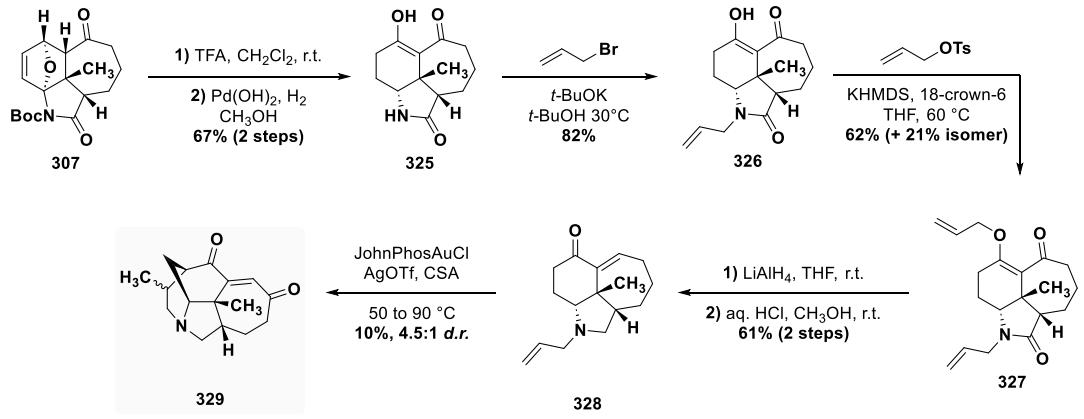
available (2 mg), the Pauson-Khand reaction was attempted. Sequential treatment of alkyne **322** with $Co_2(CO)_8$ and NMO under the previously optimised conditions provided pentacycle **323** in 36% yield. Unfortunately, the material throughput hindered further synthetic studies towards Daphniyunnine D and Daphnilongeranin B.



Scheme 2.17. *Synthesis of EF-rings of Daphniyunnine D on a real system.*

2.3.1.5 Synthetic studies towards the B-ring

Finally, the construction of the B-ring *via* hydroalkylation of unactivated alkenes and ketones was investigated (**Scheme 2.18**). The substrate for this cyclisation, **328,** was prepared in 6 steps from IMDAF adduct **307**. First, the dihydrofuran and Boc groups were hydrolysed, and the resulting enamine was hydrogenated in the presence of a palladium catalyst (**307** → **325**). A regioselective allylation with allyl bromide in the presence of potassium *tert*-butoxide provided compound **326** in 55% yield over 3 steps. In order to achieve a selective reduction of the 7-membered ketone, the ketone on the 6-membered ring was protected as an allyl enol ether (**326** → **327**). Subsequent global reduction with $LiAlH_4$ followed by acidic hydrolysis of enol ether and elimination of the secondary alcohol provided the substrate for the cyclisation (**328**).



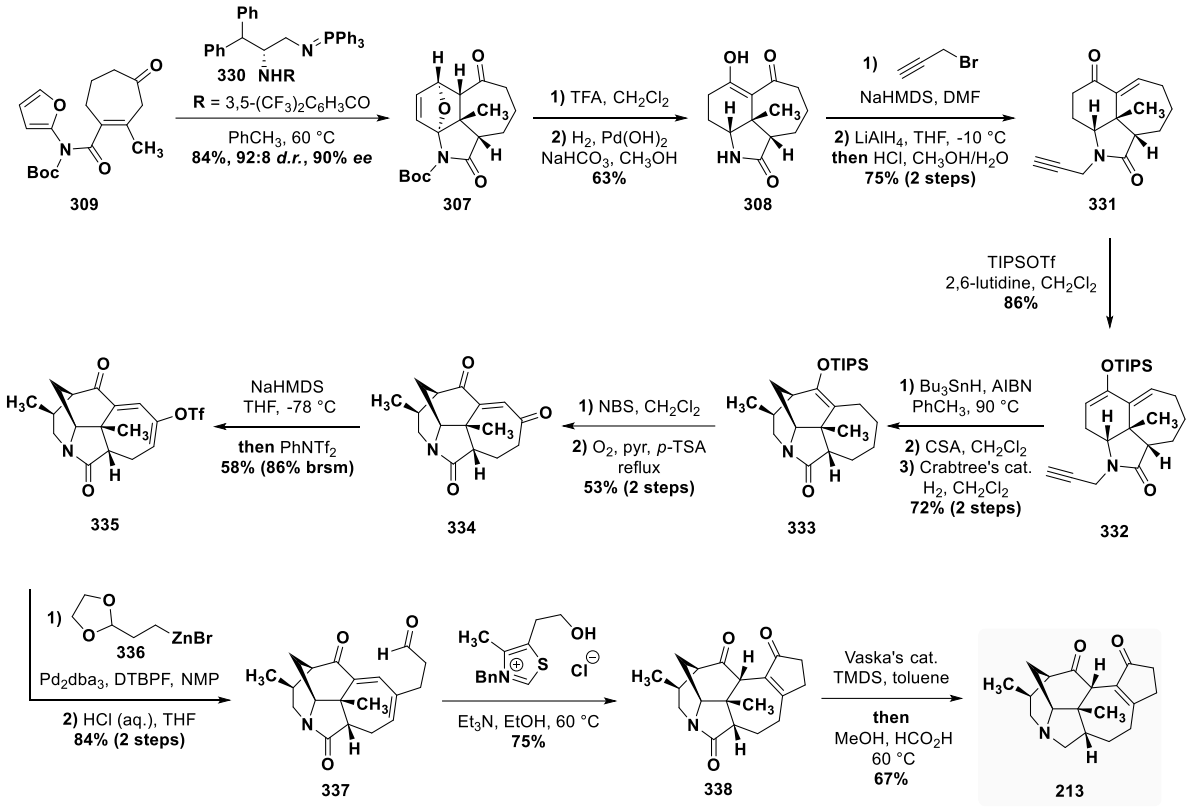
Scheme 2.18. *Synthesis of the B-ring.*

Despite extensive screening, synthetically useful conditions for the cyclisation of alkene **328** and structurally similar substrates were not identified. The best conditions, using JohnPhos-based gold(I) catalyst, provided the cyclised product **329** in only 10% yield as an inseparable 4.5:1 mixture of diastereomers. Moreover, the cyclisation was accompanied by unexpected ketone formation, presumably through aerobic oxidation of extended enolate.

Although Michaelides and Darses didn't manage to synthesise the targeted *Daphniphyllum* alkaloids, their work provided the foundation for the synthesis of these natural products, within but also outside the Dixon group.[33a,20]

2.3.1.6 The first total synthesis of Himalensine A

The synthetic studies towards *Daphnyphyllum* alkaloids based on the IMDAF reaction culminated in 2017 with Shi's total synthesis of Himalensine A (**Scheme 2.19**).[33a,37] Shi and Jakubec further optimised the enantioselective synthesis of the IMDAF adduct (from the previous 78% to 90% *ee*) utilising the in-house-developed bifunctional iminophosphorane (BIMP) catalyst **330**. Given the challenges encountered in introducing the B-ring *via* alkene hydroalkylation and the unknown diastereoselectivity of this process, Shi embarked on exploring the applicability of the Conia-ene cyclization reaction for this transformation. To this end, compound **307** was converted in 4 steps to cyclisation substrate **331**. However, attempted transition metal catalysed (Au^{I}, Cu^{I}, Ag^{I}, Pd^{II}) cyclisations of **331** proved unfruitful. On the other hand, the conversion of ketone **331** to silyl enol ether **332** significantly improved its reactivity. However, the 7-endo-dig cyclisation was formed preferentially. To resolve this issue, a radical hydrostannylation cyclization followed by protodestannylation under acidic conditions was successfully employed. Directed hydrogenation of the *exo*-methylene group accomplished the installation of the B-ring (**332** → **333**).



Scheme 2.19. *Shi's synthesis of Himalensine A.*

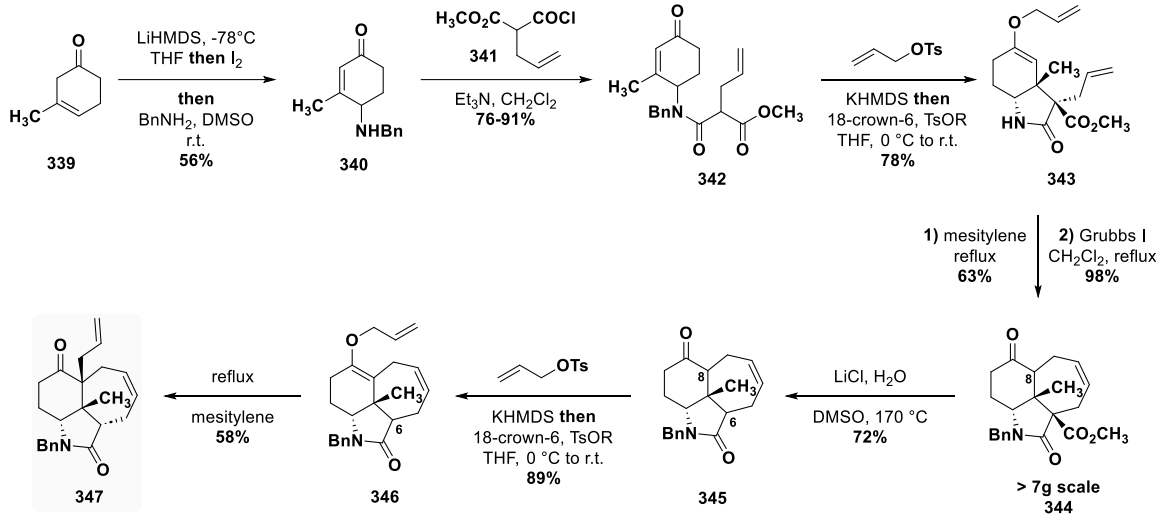
The double bond lost during the reductive cyclisation was *re*-installed by the bromination of the silyl enol ether **333** and subsequent elimination of the bromine atom. Shi noticed that during the bromine elimination, a small amount of diketone **334** was also formed, presumably, similarly as in Michaelides' and Darses' case, by aerobic oxidation of the extended enolate. Optimising this reaction, Shi was able to increase the yield of this unexpected product to 65%. Moreover, the formation of diketone **334** was used for the introduction of the E-ring. The diketone **334** was first converted to enol triflate **335** and then employed in Negishi coupling with organozinc reagent **336**. After the acetal hydrolysis, aldehyde **336** was employed in intramolecular Stetter reaction accompanied by the migration of the double bond to conjugation with ketone (**336** → **337**). Finally, the selective reduction of the amide group in the presence of the ketone and enone was achieved using Vaska's catalyst, culminating in the first total synthesis of Himalensine A.

Shi's work solved the previous issue of the introduction of the B-ring (see **Section 2.3.1.5**) and opened the possibility of the total synthesis of Daphniyunnine D *via* Michaelides' and Darses' intramolecular Pauson-Khand reaction. However, only 3 months after the publication of the total synthesis of Himalensine A, Ang Li and coworkers submitted a successful synthesis of Daphniyunnine E (an epimer of Daphniyunnine D) based on the Michaelides' and Darses' synthesis of E,F-rings.[20] Moreover, their synthesis passed through the same intermediate as reported by Shi (compound **238, Scheme 2.7**), and therefore, the synthesis of these natural products was not further investigated.

2.3.2 Synthetic strategy based on Michael addition – allylation – RCM sequence

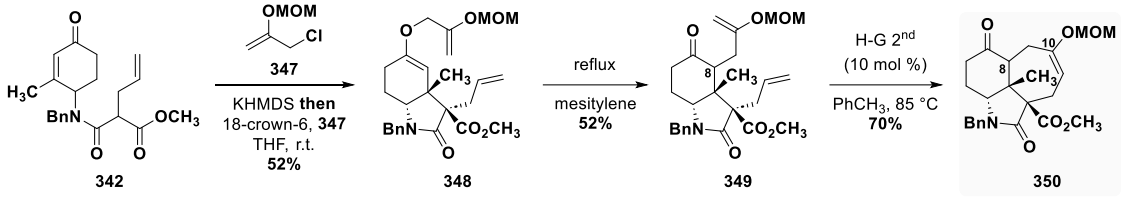
2.3.2.1 Synthesis of the ACD-core

Parallel to Iacovos Michaelides' and Benjamin Darses' synthetic studies towards *Daphniphyllum* alkaloids based on IMDAF reaction (**section 2.3.1**), Filippo Sladojevich (2011) developed an alternative synthetic strategy for the construction of the tricyclic ACD-core based on highly convergent Michael addition – allylation – RCM sequence (**Scheme 2.20**).[29a]



Scheme 2.20. *Synthesis of ACD-core using Michael addition – allylation – RCM strategy.*

Starting from ketone **339** representing the A-ring, the γ-amino group was introduced *via* iodination of the extended enolate, followed by its substitution with benzylamine. The coupling of amine **340** with acyl chloride **341** provided compound **342,** which, upon treatment with KHMDS, underwent C-ring-forming intramolecular Michael addition. Conveniently, the Michael addition could be combined with the *O*-allylation of the resulting enolate, avoiding the potential regioselectivity issue of the stepwise allylation of the Michael product. Heating of allyl enol ether **343** in mesitylene provided Claisen product in 63% as a 6:1 mixture of diastereomers, and the installation of the D-ring was accomplished by ring-closing metathesis using Grubbs 1st generation catalyst (**343** → **344**; *d.r.* was not affected by RCM and the cyclised product was isolated with the same 6:1 *d.r.*). Subsequent Krapcho decarboxylation provided compound **345** as an inseparable mixture of C-6 and C-8 diastereomers in 73% yield. The alkylation of the C-8 position in **345** proved challenging due to the lack of reactivity. This issue was overcome by repeating the second *O*-allylation – Claisen rearrangement sequence. Treatment of ketone **345** with KHMDS, 18-crown-6, and allyl tosylate led to completely regioselective *O*-allylation, providing compound **346** as a 3.2:1 mixture of diastereomers at C-6. Subsequent Claisen rearrangement afforded a mixture of 3 diastereomers, of which compound **347** was isolated in 58% (configuration confirmed by single-crystal X-ray analysis).



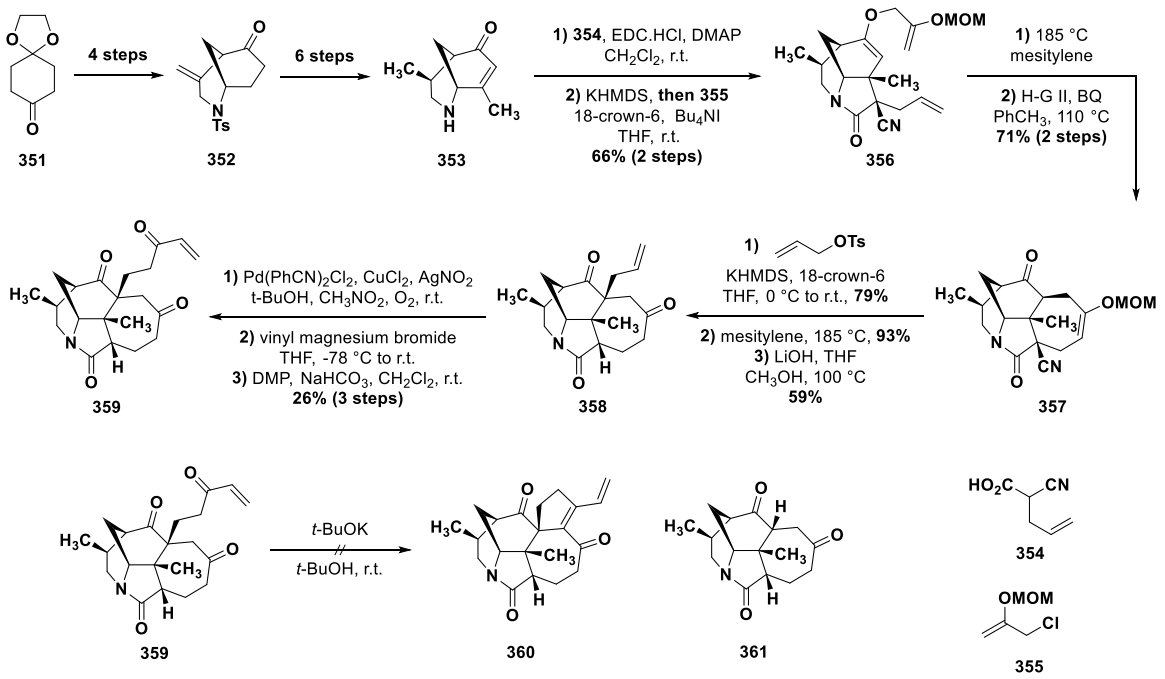
Scheme 2.21. *Synthesis of C-10 oxygenated of ACD-core.*

By simple altering the *O*-allylating reagent in the Michael addition, Sladojevich efficiently introduced the ketone group onto the C-10 position of the 7-membered ring (**Scheme 2.21**). Michael addition of compound **342** in the presence of allyl chloride **347** yielded the *O*-allylated product **348** in 52% yield. Subsequent Claisen rearrangement led to the formation of compound **349** in 52% yield (undefined mixture of diastereomers at C-8). Finally, the RCM of **349** provided the desired tricycle **350** as a separable mixture of diastereomers, and the main diastereomer was isolated in 70% yield. The configuration of C-8 was not assigned.

Despite its elegance and high convergency, the presented synthetic routes suffered from low diastereoselectivity in the key Claisen rearrangement and Krapcho decarboxylation steps. Because of the more stereocontrolled synthesis of the ACD-core *via* a parallelly developed IMDAF sequence, Sladojevich's approach was temporally abandoned. However, several key transformations, such as the construction of the C-ring *via* intramolecular Michael addition and functionalisation of the C-8 position *via* *O*-allylation – Claisen rearrangement, were applied by the synthetic community in the syntheses of multiple *Daphniphyllum* alkaloids. [18-22, 30]

2.3.2.2 Synthetic studies towards Daphlongamine E

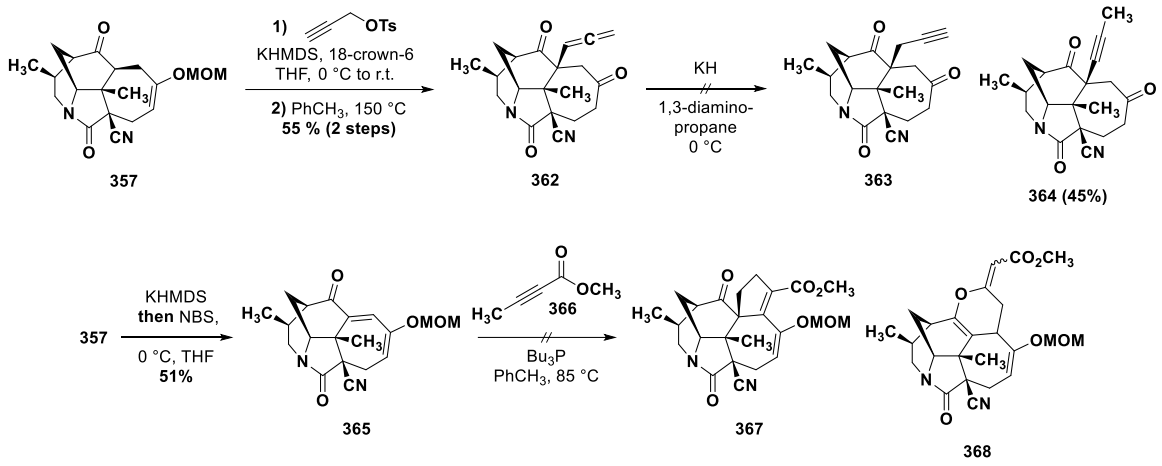
Several years later, Sam R. Ellis (a DPhil student in the Dixon group between 2014 and 2019) revisited the Michael addition – allylation – RCM sequence.[38] In his new synthetic strategy (**Scheme 2.22**), Ellis decided first to form the AB-ring system – intermediate **353**, so-called morphan core, and then construct the rest of the tetracyclic core using chemistry described in **Schemes 2.22** and **2.23**. This novel approach aimed to enhance the diastereoselectivity of previously challenging steps through the formation of a more rigid morphan core. The key intermediate **353** was tracked back to simpler nonfunctionalised bicyclic intermediate **352**, accessible by intramolecular Conia-ene cyclisation reaction of symmetrical cyclohexanone (see **Section 2.3.2.3**).



Scheme 2.22. *Synthetic studies towards Daphlongamine E by Sam Ellis.*

The synthesis of the substituted morphan core **353** is discussed in detail in **Section 2.5.2** and therefore, only a brief overview will be provided here. The non-substituted morphan core was synthesised in 4 steps from monoprotected diketone **351** *via* a synthetic sequence consisting of reductive amination, followed by acetal deprotection, amine tosylation and intramolecular Conia-ene reaction. A subsequent series of redox and protecting group manipulations converted compound **352** to fully substituted morphan core **353**. Amine **353** was then converted in 4 steps into tetracyclic intermediate **357,** adopting Sladojevich's strategy with some minor modifications. Similarly to Sladojevich's work, deprotonation at C-8 provided enolate unreactive towards carbon electrophiles and therefore, an indirect method, based on O-allylation – Claisen rearrangement sequence, had to be used for its alkylation. Heating of the allylated intermediate with lithium hydroxide led to its decyanation accompanied by hydrolysis of MOM enol ether (**357** → **358**). Notably, the rigid bowl-shaped geometry of this polycyclic system likely contributed to the high diastereoselectivity observed throughout these transformations.

The E-ring of Daphlongamine E was planned to be introduced by intramolecular aldol condensation. To this end, the allyl chain in **358** was converted to enone **359** by a sequence consisting of nitrite-Wacker oxidation, the addition of vinyl magnesium bromide and the oxidation of secondary alcohol with DMP. With enone **359** in hand, the planned aldol condensation was attempted. However, the treatment of compound **259** did not provide the desired pentacyclic compound **360** and only rapid formation of product **361**, *via* E1cB elimination, was observed.

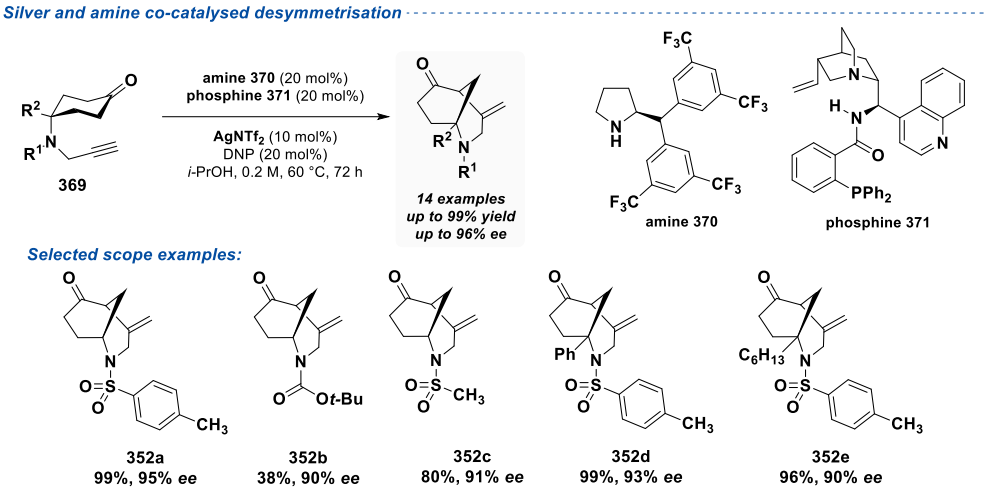


Scheme 2.23. *Synthetic studies towards Daphlongamine E – alternative strategies.*

After the failure of the original strategy for the introduction of the E-ring, various alternative approaches were explored (a few selected examples are shown in **Scheme 2.23**). 5-Endo-dig cyclisation of compound **363** represents one of the attractive strategies. Due to the previously mentioned reactivity challenges posed by the enolate derived from ketone **357**, an indirect method for C-8 propargylation had to be used (**Scheme 22**, top). *O*-propargylation of ketone **357** followed by Claisen rearrangement provided allene **362**. Unfortunately, the attempted isomerisation of this allene to terminal alkyne using a Zipper reaction failed, and only less hindered internal alkyne was formed. Inspired by Li's[19] and Zhai's[22] syntheses of Calyciphylline A-type alkaloids, [3+2] cycloaddition of alkynoate and **366** to enone **365** was explored (**Scheme 2.23**, bottom). Unfortunately, only the formation of undesired [4+2] side products was observed. The substantial steric hindrance inherent in the contiguous all-carbon quaternary stereocentre motif in the advanced intermediates, such as **357**, resulted in challenging functionalisation of the C-8 position and contributed to failure of most of the examined end game strategies.

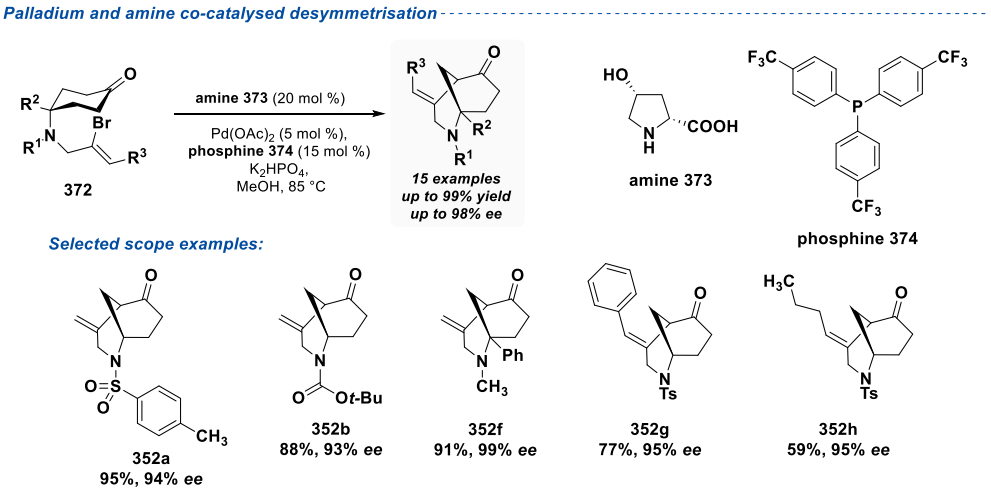
2.3.2.3 Enantioselective synthesis of the morphan core

To support Ellis' synthetic studies toward *Daphniphyllum* alkaloids, Ruben Manzano successfully developed an enantioselective silver and amine co-catalysed desymmetrisation reaction,[32a] providing access to the non-functionalised morphan core of Calyciphylline A type alkaloids in enantiomerically enriched form (**Scheme 2.24**). In this transformation, the chiral enamine, formed from ketone **369** and chiral amine **370,** reacts with a tethered alkyne group activated by a chiral silver catalyst, generated *in situ* from silver triflimide and phosphine **371** in a Conia-ene type reaction, leading to the formation of cyclised products in excellent yields and high *ee*.



Scheme 2.24. *Enantioselective synthesis of the morphan core.*

Although this reaction provided the key intermediate in gram-scale quantities, the used organocatalysts are not commercially available and require relatively lengthy synthesis (3 steps for amine **370** and 2 steps for phosphine **373**) in multigram quantities. This, together with the use of light-sensitive and hygroscopic silver salt, motivated our group to explore alternative, more practical approaches to intermediate **352**.



Scheme 2.25. *Enantioselective synthesis of the morphan core.*

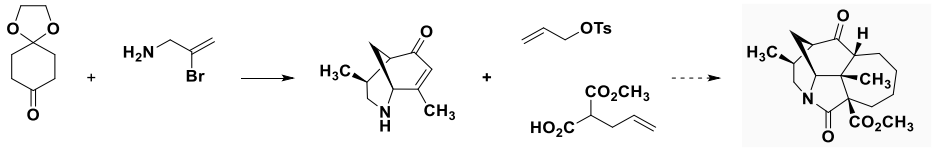
Drawing inspiration from the work of Jia[39] and Bonjoch,[40] Sam Ellis, together with Jack Cooke and Nikita Chekshin, devised a palladium and amine co-catalysed desymmetrisation of vinyl-bromide-tethered cyclohexanones, employing a much simpler catalytic system consisting of commercially available 4-hydroxyproline (**373**), phosphine **374** and bench-stable palladium source – palladium acetate (**Scheme 2.25**).[32c] Moreover, this new catalytic system allowed the synthesis of trisubstituted alkenes, such as **352g** and **352h**. The density functional theory (DFT) calculation revealed that the reaction proceeds through a Heck-type mechanism. In the first step, palladium(0) catalyst undergoes oxidative addition into the C-Br bond of vinyl bromide, followed by enantion-determining migratory insertion into the *in situ* generated enamine. The catalytic cycle is then completed by a β-hydride elimination and enamine hydrolysis.

2.4 Aim of the project

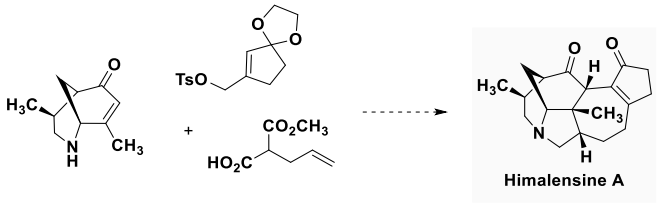
In our synthetic studies towards *Daphniphyllum* alkaloids, we decided to utilise a highly convergent Michael addition – allylation – ring closing metathesis sequence (see **Chapter 2.3.2.1**), developed in our group by Filippo Sladojevich and Iacovos Michaelides[29a] during their synthetic studies towards *Daphniphyllum* alkaloids (synthesis of the ACD-tricyclic core) and further elaborated by Sam Ellis.[38] Although Sam Ellis managed to employ this strategy to synthesise the enantiomerically enriched ABCD-tetracyclic core, present in multiple members of this family of natural products, incorporation of the final ring proved challenging and yielded no fruitful results.

Drawing inspiration from these accomplishments, we devised a new synthetic plan, targeting three progressively harder goals:

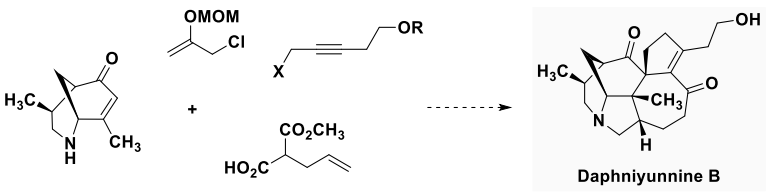
1) In the initial phase of our synthetic studies, **Chapter 2.5**, our efforts centred around completing the formal synthesis of Calyciphylline A alkaloids. To achieve this, we focused on preparing a common intermediate, which had been utilised in previously published syntheses of these natural products.



2) In the second stage, **Chapter 2.6**, our attention shifted to the total synthesis of Himalensine A. Modifying the strategy developed in the first stage, we hypothesised that this particular natural product could be formed in a very convergent manner by utilising more elaborated building blocks, allowing the direct introduction of the E-ring core.

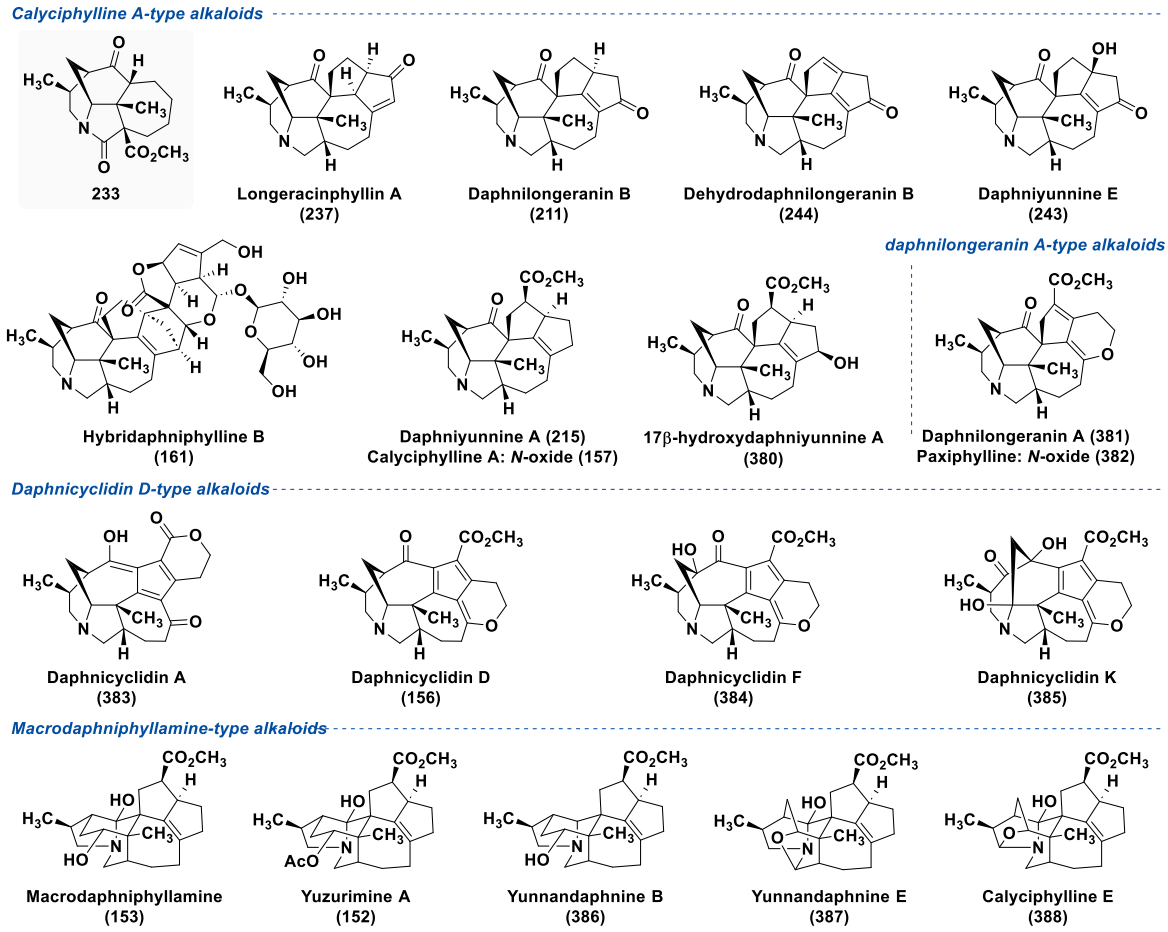


3) In the final stage, **Chapter 2.7**, the syntheses of more complex members of the Calyciphylline A sub-family were explored.



2.5 Formal synthesis of *Daphniphyllum* alkaloids

The structural complexity and biological significance of Daphniphyllum alkaloids have sparked widespread interest within the synthetic community, leading to numerous total syntheses. The presence of a highly conserved ABCD-tetracyclic core in the Calyciphylline A sub-family makes this group of natural products an attractive target for collective synthesis from a common tetracyclic intermediate. Our research group embarked on efforts to achieve this goal in the early 2010s.[29] However, it was Li *et al.* who managed to materialise this idea. In 2017, they reported the synthesis of Longeracinphyllin A (see **Section 2.2.1**),[19] followed shortly (2018) by the collective syntheses of Daphnilongeranin B, Dehydrodaphnilongeranin B, Daphniyunnine E, and Hybridaphniphylline B.[20] Nonetheless, the most significant breakthrough in this field occurred in 2022 when the same group reported a collective synthesis of five additional Calyciphylline A-type alkaloids, along with nine other alkaloids containing a modified tetracyclic core (**Scheme 2.26**).[30a] Interestingly, all these natural products, even those outside the Calyciphylline A sub-family, were prepared from the same tetracyclic intermediate **233**.

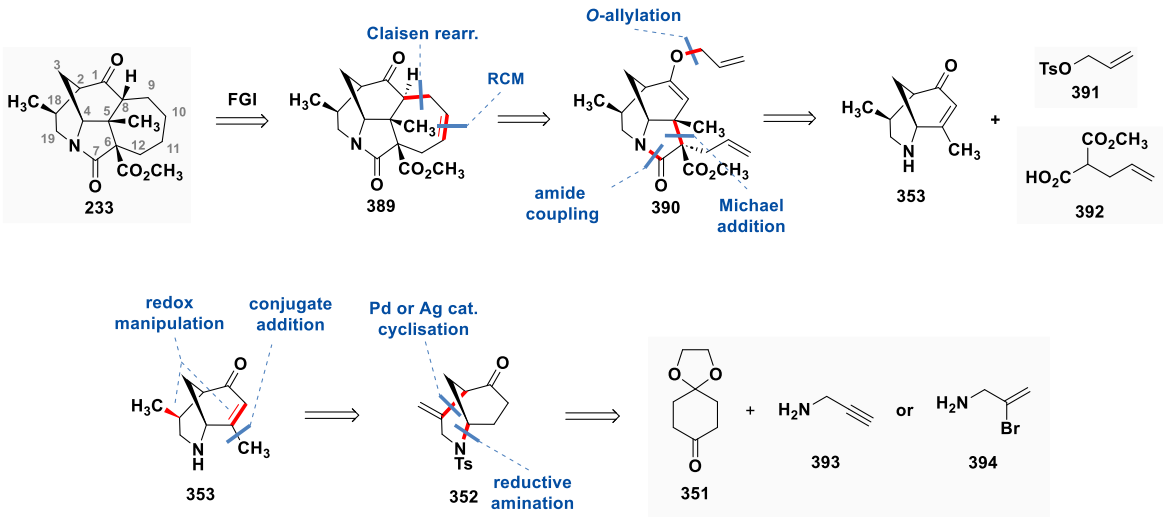


Scheme 2.26. *Overview of Daphnyphillum alkaloids synthesised from common intermediate* ***233****.*

Given the remarkable similarity between Li's common intermediate **233**, and the intermediates accessible by our synthetic approach, such as compound **357** (see **Chapter 2.3.2.2**), we decided to undertake the formal synthesis of these natural products and bring this more than a decade-long endeavour to its end.

2.5.1 Retrosynthetic analysis

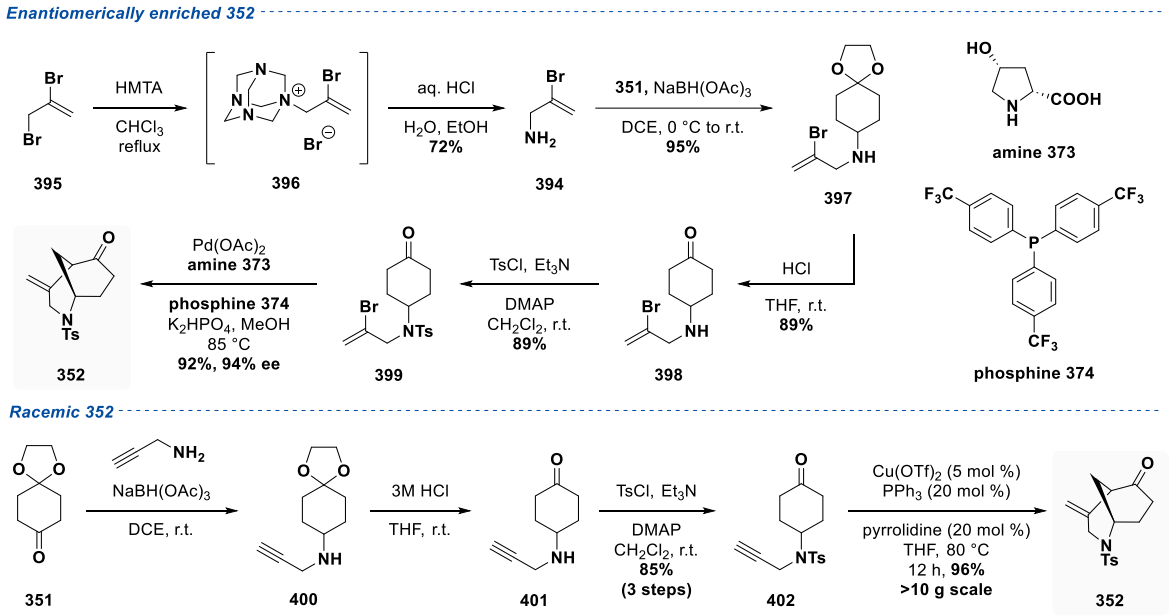
In order to render compound **233** into a substrate potentially accessible by our synthetic strategy, based on a Michael addition – allylation – ring closing metathesis sequence, several key transformations are required in the retrosynthetic direction (**Scheme 2.27**). First, an alkene must be introduced into the 7-membered D-ring and C-8 epimerised (**233** ⇒ **389**). Subsequently, the D-ring can be disconnected *via* ring-closing metathesis (RCM) to a compound containing two allyl groups, where the C-8 allyl group can be introduced by a Claisen rearrangement of enol ether **390.** The enol ether **390** can be obtained by trapping the enolate formed after the intramolecular Michael reaction between enone and malonamate moiety. The Michael donor can be disconnected through a simple amide coupling to acid **392,** leaving amine **353**. The latter has been previously prepared in our group by Sam Ellis from bicyclic compound **352** utilizing a series of redox manipulations and conjugate addition of the C-5 methyl group. Finally, compound **352** can be obtained from monoprotected cyclohexane-1,4-dione using enantioselective desymmetrisation *via* silver-catalysed Conia-ene reaction[32a] or palladium-catalysed vinyl bromide cyclisation reactions,[32c] both of which have been previously developed in our group.



Scheme 2.27. *Retrosynthetic analysis of compound* ***233.***

2.5.2 Synthesis of the morphan core

Owing to its numerous advantages (see **Section 2.3.2.3**) the palladium-catalyzed desymmetrisation reaction was selected as the preferred method for the preparation of the enantiomerically enriched fragment **352** in this study. The substrate for cyclization, **399**, was efficiently prepared through a concise five-step sequence starting from 2,3-dibromoprop-1-ene (**395**) (**Scheme 2.28**).[38] The process began with the conversion of allyl bromide **395** into the corresponding allylic amine **394** using a two-step protocol. First, allyl bromide **395** reacted with urotropine (HMTA) to form ammonium salt **396**, which was then hydrolysed to amine **394** by hydrochloric acid in the second step.[41] Subsequently, this amine was employed in the reductive amination with monoprotected diketone **351**, followed by acetal deprotection and amine tosylation (**397** → **399**).[38] Remarkably, the preparation of the cyclization precursor **399** necessitated only a single chromatographic purification step.



Scheme 2.28. *Synthesis of the morphan core.*

Employing the newly developed palladium-based catalytic system, vinyl bromide **399** underwent smooth cyclisation affording the desired bicyclic compound **352** in 95% yield and 94% *ee*. Pleasingly, upscaling this pivotal reaction from 40 mg to 4.0 g proved straightforward, and the desired cyclised product **352** was obtained in 92% yield and 94% *ee* (>12 g prepared in one campaign).

For the synthesis of the racemic building block **352**, utilised in the earlier stages of this project the approach based on the metal-catalysed Conia-ene cyclisation reaction[32a] proved more viable (**Scheme 2.28**, bottom). The primary reason behind this choice was that while the racemic Conia-ene reaction can be catalysed by simple pyrrolidine, the cyclisation of the vinyl bromides requires the presence of the palladium-coordinating carboxylic moiety in the amine catalyst. As a result, the racemic products are available only by using the pseudo racemic 4-hydroxyproline, prepared by combining equivalent amounts of significantly more expensive *(+)* and *(-)* 4-hydroxyproline in a 1:1 ratio. Moreover, the cyclisation

precursor **402** can be prepared from commercially available propargylamine in a 2 steps shorter sequence, and the cyclisation can be catalysed by Cu^{2+} salts, rendering it more economically feasible and environmentally friendly.

The cyclisation precurson **402** was prepared in 85% yield on decagram scale using an identical synthetic approach as in the case of compound **399**, only the 2-bromoprop-2-en-1-amine (**394**) was replaced with propargylamine. Subsequent copper(I) and pyrrolidine co-catalysed Conia-ene cyclisation provided the bicycle **352** in 96% yield.

2.5.3 Functionalisation of the morphan core

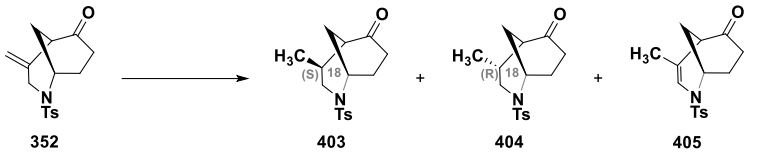
The synthetic sequence in ***Scheme 2.30*** *was developed by Sam Ellis, and the only deviation from his procedure was that the directed hydrogenation was performed at higher pressure.*

With access to sufficient quantities of enantiomerically enriched bicyclic morphan core, the work focused on the elaboration of intermediate **352** to the fully functionalised AB-core of Calyciphylline A alkaloids. This required the reduction of the exocyclic double bond, installation of the C-5 methyl group and subsequent oxidation to afford the enone moiety necessary for the construction of the 5-membered C-ring through Michael addition.

To achieve the *18S* configuration in **403**, hydrogenation of the exo-methylene group needed to occur from the more hindered concave face. During the screening of conditions for diastereoselective hydrogenation conducted by Sam Ellis,[38] it was observed that hydrogenation in the presence of Pd on charcoal, which typically results in hydrogenation from a more sterically accessible face, indeed favoured the formation of the undesired *18R* diastereomer 3:1 *d.r.,* **Table 2.1, entry 1**). Additionally, a significant amount of the product of double bond migration, **405,** was formed.

On the other hand, directed hydrogenation with Crabtree's catalyst, previously used in the synthesis of calyciphylline A-type alkaloids by Dixon,[33a] Li,[19] Qui,[42] and Zhai,[22] provided desired product **403** with excellent diastereoselectivity (>20:1 *d.r.,* **entry 2**). However, the isomerised product **405** was still formed in significant amounts (50%). Intensive optimisation of the reaction conditions using Crabtree's catalyst revealed a positive effect of the hydrogen pressure on the ratio of hydrogenated product **403** to isomer **405** (**entries 3-7**). While the products **403** and **405** were obtained at atmospheric pressure in a 1:1 ratio, an increase of hydrogen pressure to 9 bar (**entry 4**) significantly suppressed the isomer formation (2.7:1, favouring hydrogenation). Notably, the *d.r.* of the hydrogenation was not affected by hydrogen pressure, in contrast to the observation of Shi and Dixon,[33a] who reported a negative effect of hydrogen pressure on the *d.r.* of the hydrogenation reaction. In their case, good selectivity was achieved only after reducing the partial pressure of hydrogen by diluting it with argon. The authors postulated that at higher hydrogen pressure, the hydrogen could outcompete the binding of the catalyst to the lactam directing group, resulting in non-directed hydrogenation from a more sterically accessible face.

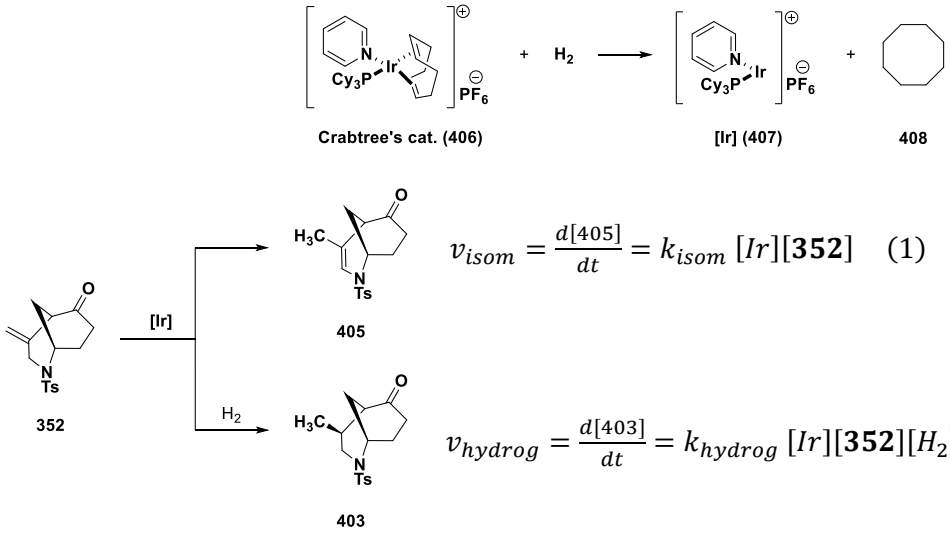
Table 2.1. Catalyst screening.



Entry	Catalyst	Cat. Loading (mol%)	Pressure (bar)	Hydrog. (%)	d.r. (403:404)	405 (%)
1[a,b]	Pd/C	10	1	15	1:3	40
2[b]	[Ir(cod)(PCy$_3$)py]PF$_6$	5.0	1	50	>20:1	50
3[b]	[Ir(cod)(PPy$_3$)py]PF$_6$	5.0	5	60	>20:1	40
4	[Ir(cod)(PPy$_3$)py]PF$_6$	2.0	9	73	>20:1	27
5	[Ir(cod)(PPy)py]PF$_6$	2.0	40	88	>20:1	12
6	[Ir(cod)(PCy$_3$)py]PF$_6$	2.0	58	92	>20:1	8
7[c]	**[Ir(cod)(PCy$_3$)py]PF$_6$**	**1.5**	**58**	**96**[d]	**>20:1**	**4**

Reagents and conditions: Catalyst, H_2 (1 bar), CH_2Cl_2, r.t., 5–16 h. [a]EtOAc used as a solvent. [b] Experiments performed by Sam Ellis. Yields were determined by analysis of ^{1}H NMR spectra of crude reaction mixtures. [c] More thoroughly purified batch of **352**. [d] Isolated yield.

The effect of hydrogen pressure on the ratio of hydrogenation to isomerisation can be elucidated by the rate equations of these two competing processes (**Scheme 2.29**). After the initial activation of the catalyst **406** with hydrogen and the release of cyclooctane (**408**), the active iridium species **407** can bind to the substrate and catalyse either the double bond migration in a process not involving hydrogen (**Scheme 2.29, eq. 1**) or coordinate and deliver a molecule of hydrogen, leading to selective hydrogenation in a process which rate depends on the hydrogen pressure (**Scheme 2.29, eq. 2**).



Scheme 2.29. *Rate equations for isomerisation and hydrogenation.*

A comparison of these two rate equations reveals that the ratio of **403** to **405** (eq. 3) depends solely on the rate constants and the concentration of dissolved hydrogen, which, according to Henry's law, is proportional to the hydrogen pressure.

$$\frac{[\mathbf{403}]}{[\mathbf{405}]} = \frac{k_{hydrog}\,[Ir][\mathbf{352}][H_2]}{k_{isom}\,[Ir][\mathbf{352}]} = \frac{k_{hydrog}}{k_{isom}}\,[H_2] \quad (3)$$

Plotting the ratio of **405:403** against the reaction pressure (data from **Table 2.1**) demonstrates that the product distribution is indeed linearly proportional to hydrogen pressure ($R^2 = 0.99$).

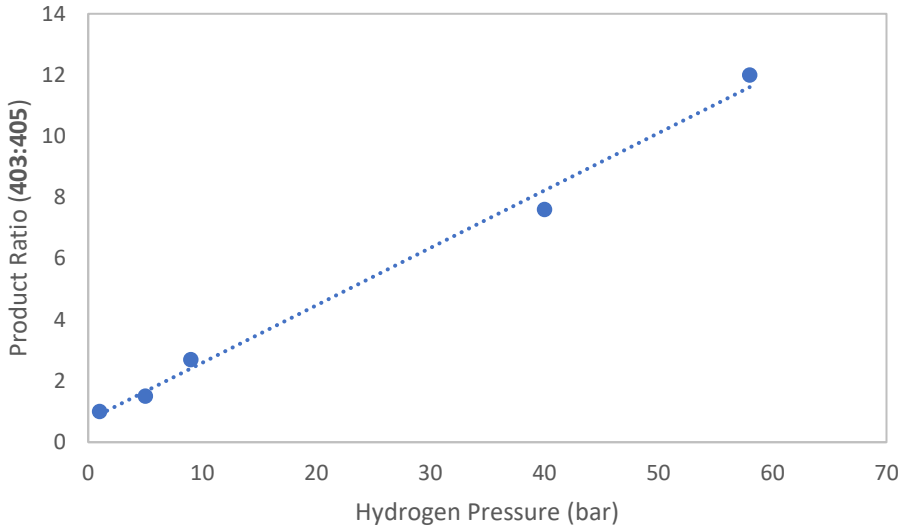


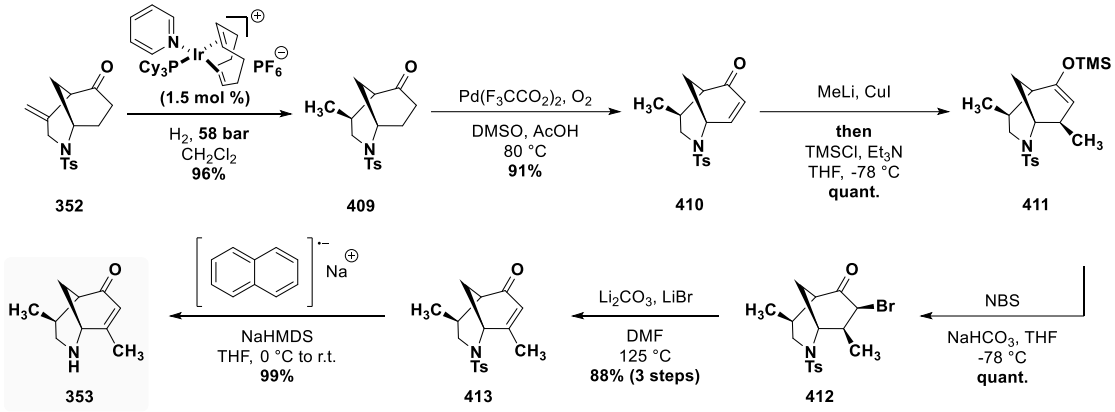
Figure 2.5. *Dependence of product ration (**403:405**) on the reaction pressure.*

During these synthetic studies, in an attempt to fully avoid the formation of the undesired product **405**, the reaction was conducted under the highest possible pressure of hydrogen.[i] Remarkably, an increase of the hydrogen pressure to 58 bar nearly completely suppressed the double bond migration (**405**:**403** = 22:1), while the *d.r.* remained unchanged. Additionally, the increased pressure allowed the reduction of the catalyst loading to only 1.5 mol%.

To introduce the C-5 methyl group *via* a conjugate addition reaction, ketone **409** was first converted to enone **410** under Stahl's conditions.[43] This enone was then treated with the Gilman reagent $Me_2CuLi.LiI$ (generated in situ from MeLi and CuI) in the presence of TMSCl. Bromination of the obtained silyl enol ether **411** with NBS, followed by HBr elimination (**411** → **413**), restored the unsaturation essential for the later stages of the synthesis. Notably, this three-step methylation sequence required only a single chromatographic purification and was scalable to over 10 g. Both methyl addition and bromination

[i] Due to safety regulations in the CRL, it was not possible to conduct hydrogenation at pressures exceeding 9 bar. The high-pressure hydrogenation was carried out in the Inorganic Chemistry Laboratories in the research group of Prof. Edman Tsang, with the assistance of Dr. Janwei Zheng.

products, **411** and **412**, respectively, were obtained as single diastereomers and their relative stereochemical configuration was confirmed by single-crystal X-ray diffraction analysis.[38]

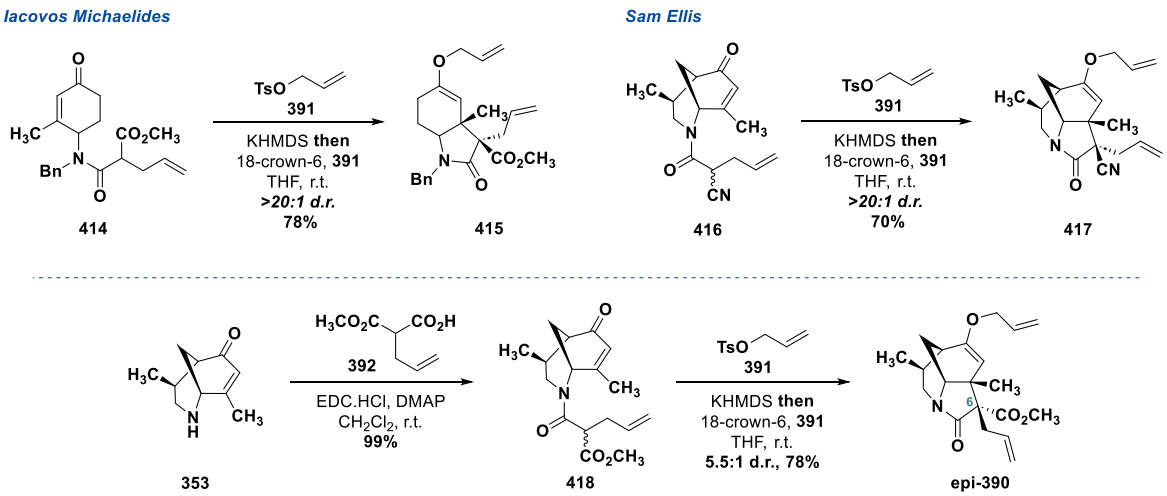


Scheme 2.30. *Synthesis of functionalised morphan core.*

The synthesis of the AB-ring system was accomplished by the cleavage of the tosyl group with sodium naphthalenide. To avoid undesired reduction of the enone moiety under these conditions, enone **413** was first treated with NaHMDS, forming the extended enolate that was inert to dissolving metal reduction. The desired deprotection of the amine then proceeded with high selectivity and yield.

2.5.4 Synthesis of the C-ring

The structure of Li's common intermediate **233** required a modification of the Michael donor fragment – a replacement of the cyano group with a methyl ester group. This subtle structural change was not expected to affect the planned Michael addition, as both Michael donors had been previously used successfully for the C-ring formation through a highly diastereoselective one-pot Michael addition – *O*-allylation sequence (**Scheme 2.31**, top).[29a, 38]

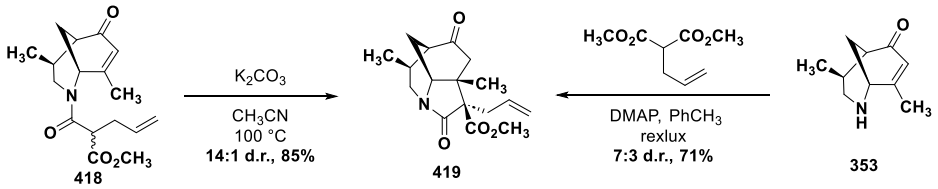


Scheme 2.31. *C-ring formation via intramolecular Michael addition.*

The substrate for the Michael reaction was prepared by amide coupling of acid **392**, which could be obtained in one step by basic hydrolysis of commercially available dimethyl 2-allylmalonate, and amine

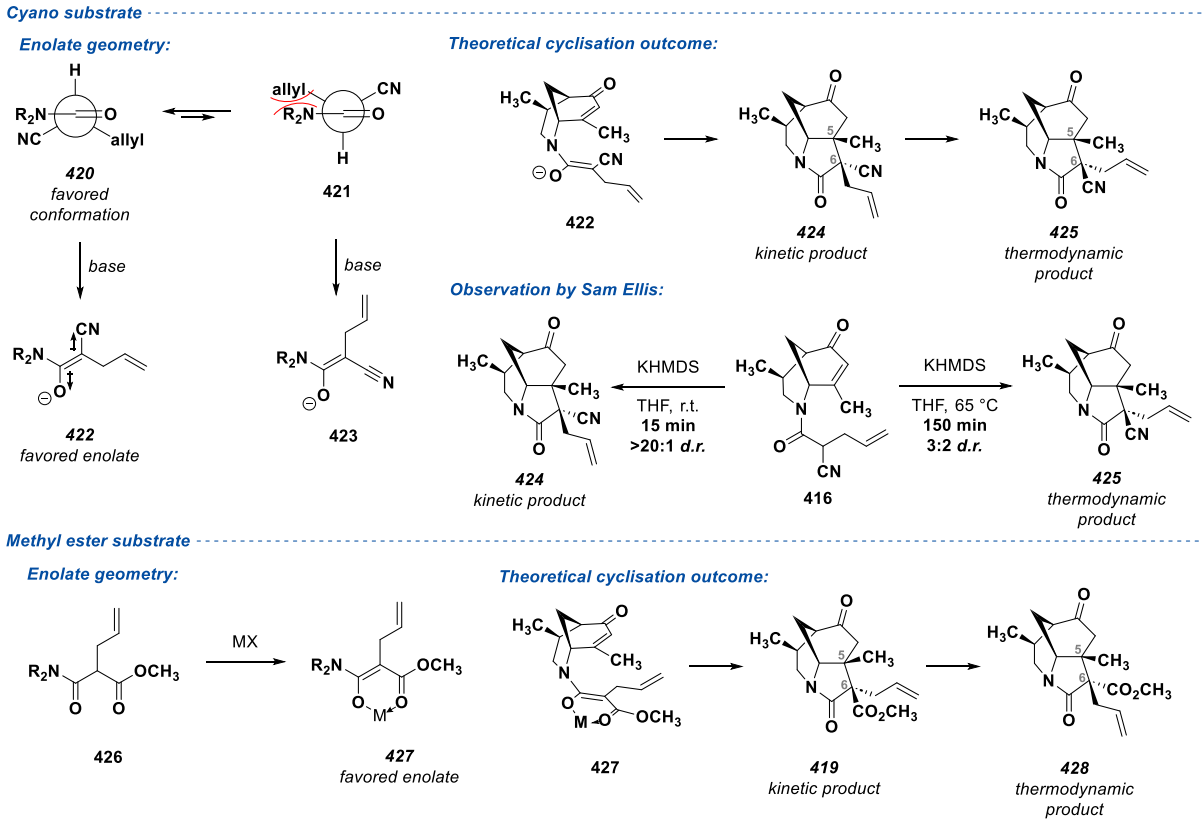
353 (**Scheme 2.31**, bottom).[38] Treatment of the resulting malonamate **418** with KHMDS in the presence of 18-crown-6, followed by the addition of the tosylate **391,** led to the fast formation of the *O*-allylated product. However, the *O*-allylated product **epi-390** was formed with 5.5:1 *d.r.* favouring the undesired isomer in 78% yield (combined). The literature search revealed that Li *et al.*[18] encountered a similar selectivity issue during their synthesis. The configuration of the C-6 is crucial for the subsequent D-ring formation, as only the *6S* diastereomer, with an allyl group trans to the C-5 methyl group, can successfully undergo RCM.

To achieve the desired selectivity in the Michael addition, we had to abandon the one-pot Michael addition – *O*-allylation sequence and perform these steps separately (**Scheme 2.32**). By employing Li`s conditions (reflux in acetonitrile in the presence of K_2CO_3),[18] the tricyclic compound **419** was rapidly formed in a 14:1 diastereomeric ratio, and the desired diastereomer was isolated in 85% yield. Interestingly, re-exposure of the undesired diastereomer to the same reaction conditions did not lead to epimerisation of the C-6 stereogenic centre, suggesting that this Michael addition is not reversible under the utilised conditions. Alternatively, compound **419** could also be efficiently obtained in one step from amine **353** *via* 4-dimethylaminopyridine (DMAP) catalysed transamidation – Michael addition with dimethyl 2-allylmalonate, albeit with lower diastereoselectivity (7:3 *d.r.*, 71% yield of the desired isomer).



Scheme 2.32. *Synthesis of the C-ring.*

To explain the observed inversion of selectivity in Michael reaction, we need to consider the geometry of the reacting enolates as well as the strain in the formed products (**Scheme 2.33**). The cyanoacetamide substrate **416** prefers conformation **420**, avoiding steric interaction between allyl group and substituents on nitrogen atom of the amide group (conformer **421**). Its deprotonation should lead to the *trans* enolate **422**. Moreover, the opposing dipole moments in **422** further stabilise this enolate. Intramolecular Michael addition of this enolate (**422**) should, therefore, lead to formation of undesired kinetic product **424**. Presence of the steric interactions between the adjacent C-5 methyl and C-6 allyl groups make this product higher in energy, compared to its C-6 epimer **425** (allyl>>CN), and therefore, under the thermodynamic conditions, the product **425** should be formed eventually.



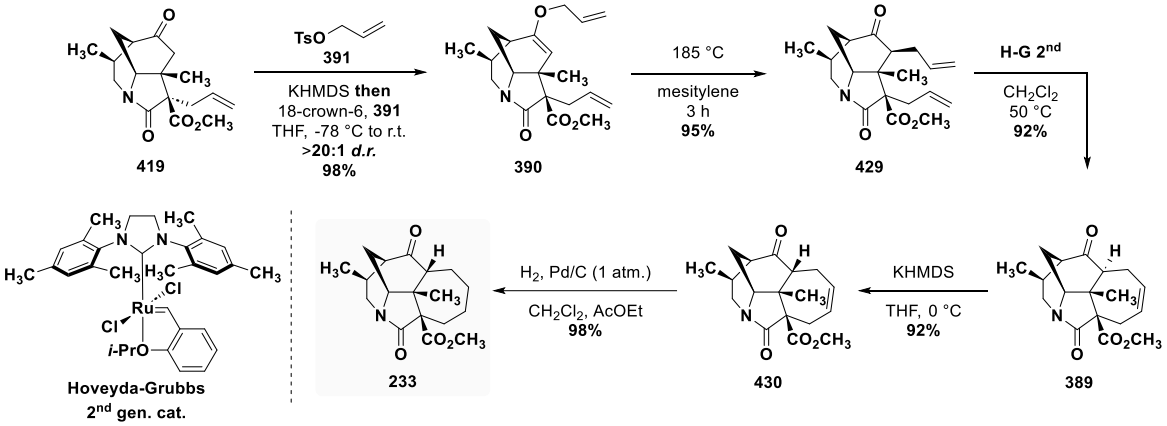
Scheme 2.33. *Stereochemical model for Michael addition.*

Interestingly, a set of experiments conducted by Sam Ellis revealed that treatment of substrate **416** with KHMDS at room temperature indeed leads to quick formation (<15 min) of the undesired isomer **424** (>20:1 *d.r.*), and relatively slow epimerisation to the desired epimer **425** was observed after heating the reaction mixture to 65 °C for 2.5 h (3:2 *d.r.*).

On the other hand, deprotonation of the malonamate **426** leads to formation of chelation-stabilised *cis* enolate **427** and its cyclisation should provide the desired kinetic product **419**. However, replacement of the cyano group with much larger methyl ester group (A-values 0.17 vs 1.27), considerably increases the steric interactions between the C-5 and C-6 substituents in diastereomer **419**, making its C-6 epimer, compound **428**, the thermodynamic product. This is in agreement with our observations – irreversible cyclisation with K_2CO_3 provided kinetic product **419**, while its treatment with strong base at higher temperature led to epimerisation at C-6.

2.5.5 Introduction of the D-ring and completion of the synthesis

The C-8 allyl group, crucial for the formation of the D-ring through RCM, was introduced *via* a two-step *O*-allylation – Claisen rearrangement sequence (**Scheme 2.34**). To prevent undesired epimerisation of C-6 through reversible Michael addition, the *O*-allylation had to be conducted at low temperature. Deprotonation of ketone **419** with potassium hexamethyldisilazide (KHMDS) at -78 °C, followed by treatment of the resulting enolate with allyl tosylate **391** in the presence of 18-crown-6, provided enol ether **390** in excellent yield as a single diastereomer. Heating of the obtained intermediate **390** to 185 °C in mesitylene, provided diene **429**, which, upon exposure to Hoveyda-Grubbs 2nd generation catalyst (H-G 2nd) under a gentle flow of argon, underwent smooth RCM to yield tetracyclic compound **389** in 92%.

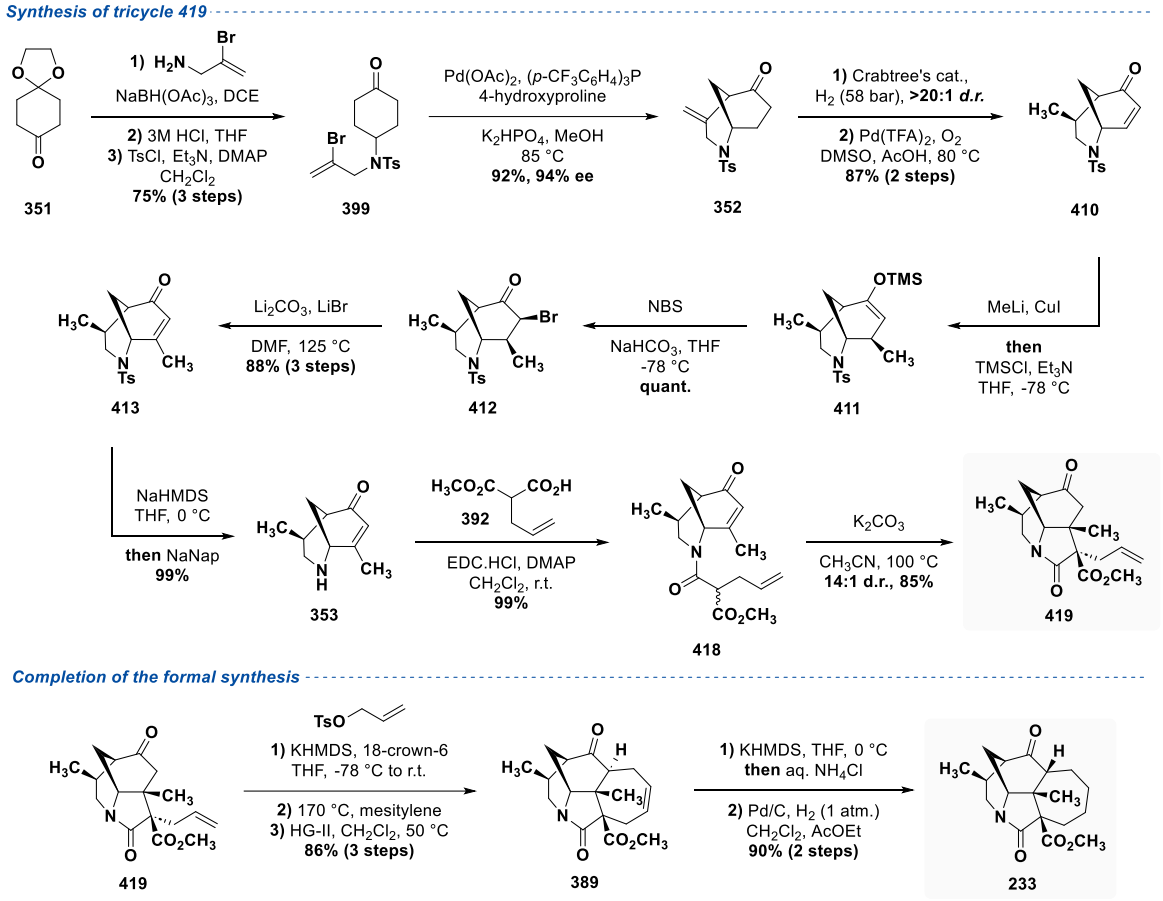


Scheme 2.34. *Completion of the formal synthesis.*

Ketone **389** was epimerised through deprotonation with KHMDS and subsequent re-protonation of the formed enolate with aqueous NH_4Cl from the more sterically accessible convex face. Quantitative epimerisation of ketone **389** could also be achieved by its heating with potassium carbonate in methanol, indicating that compound **430** is also the thermodynamic product. Notably, the presence of an alkene bond in **389** was essential for the epimerisation to occur, as the hydrogenated analogue of **389** did not undergo epimerisation. Finally, the hydrogenation of alkene in **430** concluded the synthesis of compound **233**, a versatile intermediate in *Daphniphyllum* alkaloid synthesis.

2.5.6 Summary of the formal synthesis

In Chapter 2.5, a formal synthesis of 19 *Daphniphyllum* alkaloids by synthesis of Li's common intermediate **233** was achieved (**Scheme 2.45**). Starting from ketone **351**, a key bicyclic intermediate **352** was synthesised on a gram-scale by upscaling a novel enantioselective ketone desymmetrisation reaction recently developed in the Dixon group. This intermediate was subsequently converted into complex amine **353** through a highly efficient sequence developed in our group by Sam Ellis. The coupling of amine **353** with acid **392**, followed by base-mediated intramolecular Michael addition, afforded tricyclic intermediate **419**, which served as an advanced common intermediate in our synthetic studies towards *Daphniphyllum* alkaloids.



Scheme 2.45. *Summary of the formal synthesis.*

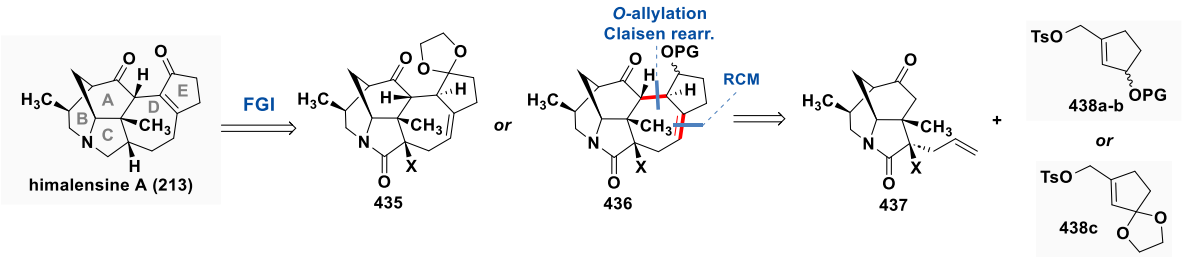
O-allylation of intermediate **419** with allyl tosylate, followed by Claisen rearrangement and ring-closing metathesis, provided tetracycle **389**, which upon epimerisation and hydrogenation of the alkene afforded Li's common intermediate and thus concluded the formal synthesis.

Synthetic studies dedicated to the utilisation of tricyclic intermediate **419** for the synthesis of other *Daphniphyllum* alkaloids are the subject of the next chapters.

2.6 Synthesis of Himalensine A

2.6.1 Retrosynthetic analysis of Himalensine A

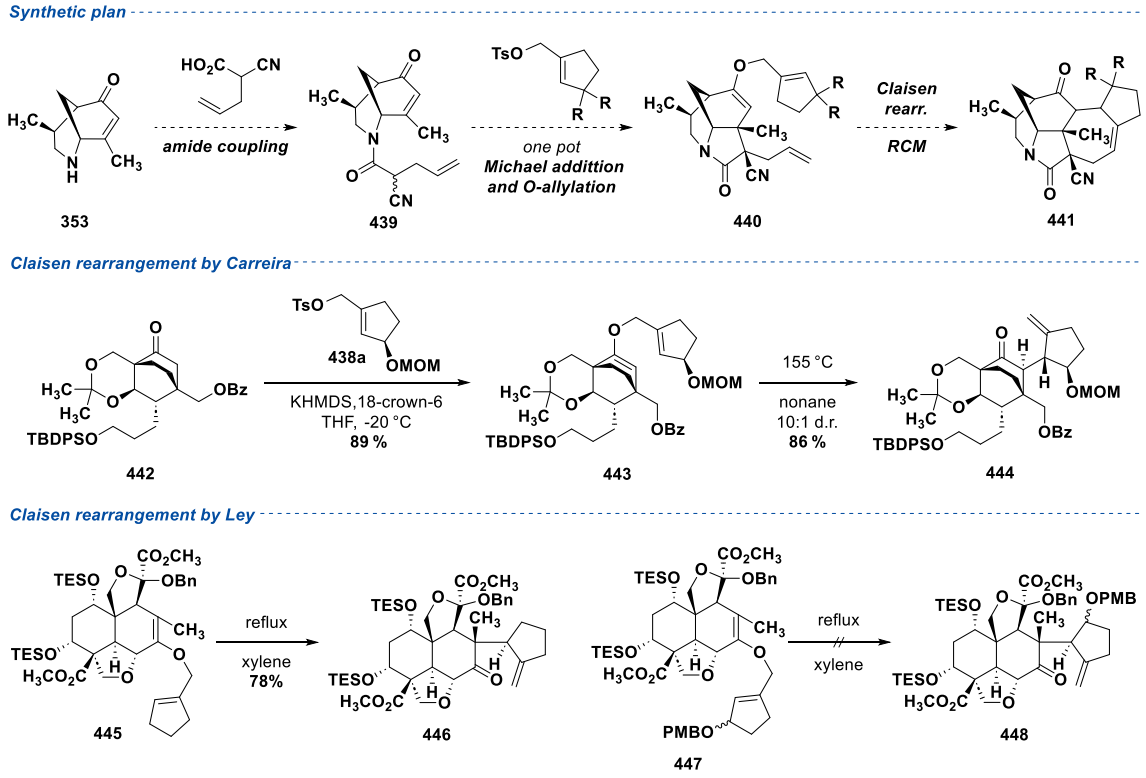
Having successfully completed the formal synthesis of *Daphniphyllum* alkaloids, our focus turned to the synthesis of Himalensine A. We envisioned that after the retrosynthetic introduction of several synthetic handles, namely: i) the conversion of the amine into an amide, ii) the introduction of a cyano or ester group, iii) the migration of the C=C bond of the enone moiety and iv) the protection of the ketone (**213** ⇒ **435**) or its conversion into protected alcohol (**435** ⇒ **436**); the central 7-membered D-ring could be disconnected in a highly convergent fashion employing the previously discussed allylation – ring-closing metathesis (RCM) sequence to complex allyl tosylates **438a-c**, representing the E-ring, and tricyclic intermediate **437** (**Scheme 2.46**). While both allyl tosylates **438a** and **438b** are known from the literature and have been previously successfully employed in Claisen rearrangement,[44] the preparation and reactivity of intermediate **439c** were unknown. The synthesis of tricyclic intermediate **437** was described in the previous chapter.



Scheme 2.46. *Retrosynthetic analysis of Himalensine A.*

2.6.2 Synthesis of the E-ring building block

Inspired by the successful application of allyl tosylate **438a** (PG = MOM) in Claisen rearrangement by Carreira *et al.* [44a](**Scheme 2.47**, middle), we hypothesised that these complex allyl tosylates could be used for the direct introduction of the E-ring of Himalensine A, utilising a highly convergent amide coupling – Michael addition – allylation – RCM sequence developed by Filippo Sladojevich and Iacovos Michaelides in our group during the preliminary studies towards Calyciphylline A alkaloids.[29a]

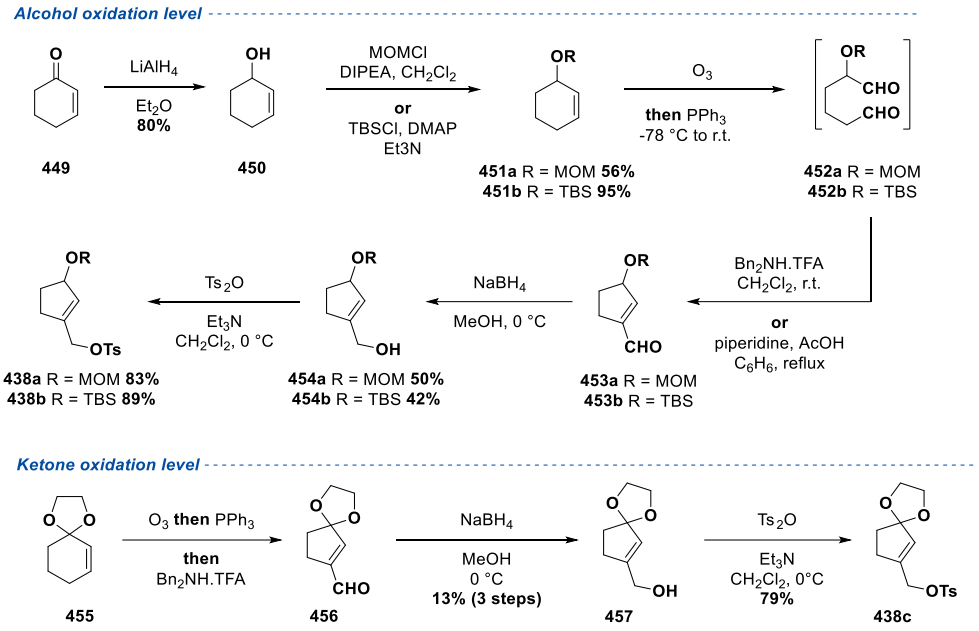


Scheme 2.47. *Overview of synthetic strategy.*

During their synthetic studies towards Azadirachtin, Ley *et al.*[45] attempted to use a similar Claisen rearrangement (**Scheme 2.47**, bottom). However, their attempts were unsuccessful and revealed the sensitivity of this reaction to steric effects. While non-substituted cyclopentene **445** provided the product of rearrangement **446** in 78% yield, the substrate bearing PMB-protected alcohol (**447**) failed to provide any product. Considering these results, we decided to synthesise a series of allyl tosylates with protecting groups of different sizes and robustness, as well as different oxidation levels of the 5-membered ring (**Scheme 2.48**).

Racemic allylic alcohols **438a** and **438b** were prepared following procedures published by Carreira (MOM)[44a] and Nicolaou (TBS).[44b] In the first step, cyclohex-2-en-1-one (**449**) was reduced by $LiAlH_4$ to corresponding alcohol (**450**), which was then protected as a methoxymethyl ether (MOM) or *tert*-butyldimethylsilyl ether (TBS), respectively. The lower yield of the MOM protection can be attributed to the relatively low boiling point of compound **451a** (67 °C). Ozonolysis of alkenes **451a-b,** followed by reductive workup with PPh_3, provided the corresponding dialdehydes **452a-b,** which were used without

further purification in an intramolecular aldol condensation reaction catalysed by secondary ammonium salts. Finally, the reduction of the crude aldehydes **453a-b** with $NaBH_4$ yielded alcohols **454a-b** in 50% and 42% (over 3 steps from **451a-b**), respectively.



Scheme 2.48. *Synthesis of allyl tosylates* ***438a-c****.*

Although the tosylation of **454a** had been previously described by Carreira *et al.,*[44a] attempts to reproduce this procedure were not fruitful, yielding only a complex mixture of products. This can be attributed to the relatively low stability of resulting allyl tosylate **438a** and the harsh conditions used in this reaction (sodium hydride as a base). The replacement of sodium hydride with DIPEA as a milder, non-nucleophilic base resulted in a clean but very slow formation of the desired product. The use triethylamine as a sterically less hindered base led to much faster consumption of the starting material (<2 h); however, the isolated product was found to be the corresponding allyl chloride. Unlike in the case of NaH, when the chloride leaving group precipitates from the reaction mixture in the form of NaCl, in this case, the triethylammonium counterion acts as a phase-transfer catalyst, leading to the substitution of initially formed allyl tosylate with chloride. The use of a symmetrical tosylating reagent (Ts_2O) resolved this issue, and the desired allyl tosylates **438a** and **438b** were obtained in 83% and 89% yields, respectively.

The same synthetic strategy was used for the synthesis of the oxidated E-ring fragment **438c**. It was expected that the acetal-protected ketone should be compatible with all planned transformations and that 5-membered cyclic acetal might have a greater chance of undergoing steric-sensitive Claisen rearrangement than a corresponding acyclic acetal.

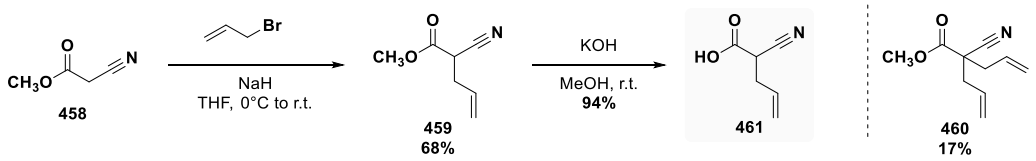
Allyl tosylate **438c** was prepared from acetal-protected cyclohex-2-en-1-one (**455**). Ozonolysis of the alkene in **455**, followed by intramolecular aldol condensation under Carreiras's conditions,[44a] provided

aldehyde **456**, which was reduced with $NaBH_4$ to yield corresponding allylic alcohol **457**. Despite its low yield (13% over 3 steps), this sequence provided enough material for subsequent synthetic studies and was not further optimised. Finally, the tosylation with Ts_2O successfully completed the synthesis of building block **438c**.

In the end, it should be noted that even though tosylates **438a-c** can survive aqueous workup and be purified by column chromatography, they tend to rapidly polymerise if kept neat at room temperature. Therefore, they needed to be freshly prepared before their use. Storage for several days in the form of a frozen solution in benzene at -20 °C was possible.

2.6.3 Formation of the C- and D-rings

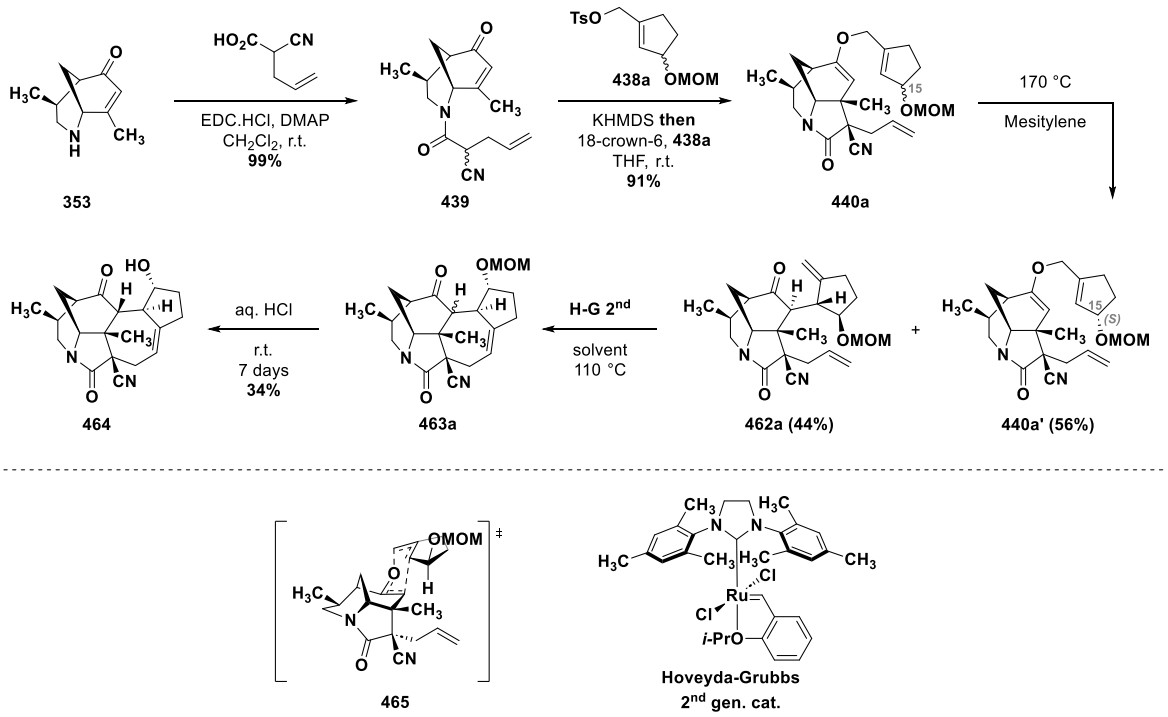
In the preliminary synthetic studies towards *Daphniphyllum* alkaloids, Sam Ellis[38] utilised 2-cyanopent-4-enoic acid **461** for the highly diastereoselective introduction of the C-ring through Michael addition. Additionally, the use of this building block allowed the coupling of this step with the subsequent *O*-allylation reaction. Therefore, in our synthetic studies towards Himalensine A, we decided to adopt the same building block.



Scheme 2.49. *Preparation of 2-cyanopent-4-enoic acid.*

The acid **461** was prepared in two steps (**Scheme 2.49**). In the first step, the excess methyl 2-cyanoacetate (**458**) was treated with one equivalent of sodium hydride and allyl bromide.[46] The use of excess **458** was crucial for limiting the formation of the bis-allylated side product **460** and increased the yield from 19% to 68%. Moreover, the unreacted excess of **458** could be isolated in 95% yield. In the subsequent step, the methyl ester group in **459** was hydrolysed with aqueous potassium hydroxide to provide acid **461**.

After the successful preparation of all building blocks, the stage was set for the convergent assembly of the pentacyclic core of Himalensine A (**Scheme 2.50**). First, amine **353** was coupled with acid **461** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride complex (EDC.HCl) as an amide coupling reagent, providing amide **439** as a mixture of rotamers and diastereomers in quantitative yield. Subsequently, amide **439** was treated with KHMDS, followed by the addition of 18-crown-6 and allyl tosylate **438a**. Gratifyingly, the desired product **440a** was isolated in 91% yield as an inseparable 1:1 mixture of diastereomers at C-15. The diastereoselectivity of the Michael addition was verified by comparing the NMR spectra of compound **440a** with compound **356** (see **Chapter 2.3.2.2**, **Scheme 2.22**), for which relative stereochemical configuration was previously determined by nOe studies.[38]



Scheme 2.50. *Formation of C- and D-rings of Himalensine A.*

In order to perform the Claisen rearrangement, a thermal [3,3]-sigmatropic rearrangement, allyl vinyl ether **440a** was heated to 170 °C in a dry and degassed mesitylene. Initial attempts revealed that compound **440a** is highly sensitive to acid residues, and under standard reaction conditions, hydrolysis of the enol ether moiety occurs even in base-washed glassware, resulting in the formation of the corresponding ketone as one of the decomposition products. To overcome this issue, the passivation of the glassware by its silylation with bis(trimethylsilyl)acetamide (BSA)[44a] was explored. Pleasingly, when **440a** was heated in the treated glassware to 170 °C, a slow reaction ensued, stalling after approximately 24 hours at around 50% conversion. Analysis of the newly formed product confirmed the formation of Claisen product **462a** as a single diastereomer in 44% yield. Interestingly, the isolated unreacted starting material (56%) was diastereomerically enriched in the *15S* isomer.

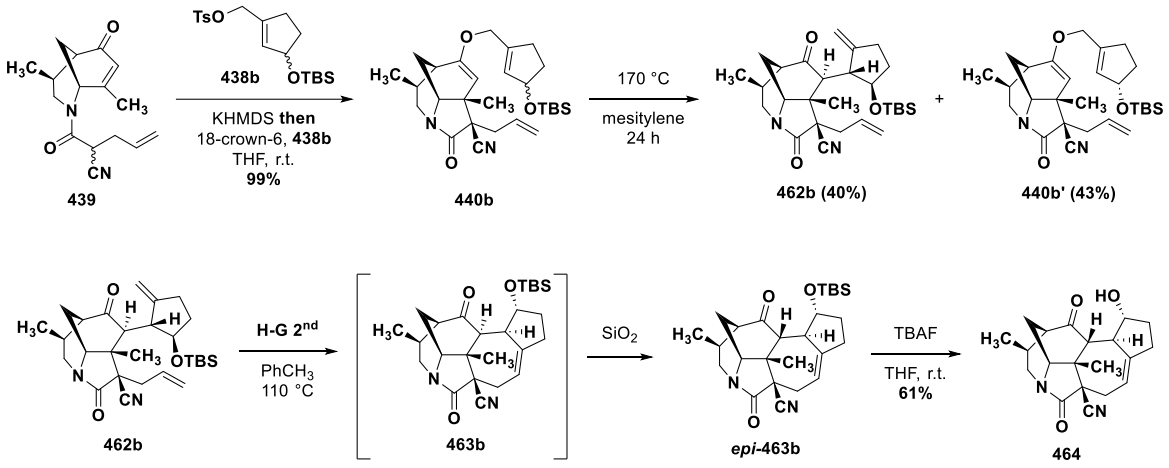
This observation can be attributed to the fact that the Claisen rearrangement proceeds through a highly ordered cyclic transition state (**Scheme 2.50, bottom**). In the case of the compound **440a,** only the 15*R* isomer, with an OMOM group pointing away from the C-5 methyl group, can adopt the reactive chair-like transition state (**465**) and is thus being consumed in the reaction, while the 15*S* isomer (**440a'**) remains unreacted. The relative configuration of **462a** was later confirmed by single crystal X-ray crystallographic analysis (**Figure 2.6, page 76**) and proved to be in agreement with the proposed model.

The final step required for the preparation of the carbon skeleton of Himalensine A was the C-ring-forming alkene metathesis. Although this reaction was previously successfully used for the C-ring formation in simpler substrates during the preliminary studies (see **Schemes 2.20** and **2.22**), we anticipated that in the case of compound **462a,** this reaction might be particularly challenging. This

transformation required not only the formation of a 7-membered ring bearing a tri-substituted double bond in a relatively strained ring system but also because of the potentially restricted rotation around the C-8 and C-9 bond, which could hinder the adoption of the reactive conformation with both alkene-ends in close proximity.

Using the previously optimised conditions – the reflux of the substrate in toluene in the presence of Hoveyda-Grubbs 2nd generation catalyst (H-G2nd) and benzoquinone (to prevent double bond migration), led to fast consumption of the starting material and the formation of two inseparable products (presumably diastereomers at C-8, for epimerisation of the product of RCM also refer to **Scheme 2.69, Chapter 2.7.4**). To facilitate their purification, deprotection of the MOM group was attempted. Treatment of mixture of products **463a** with 1M aq. HCl in THF at room temperature resulted in slow deprotection (7 days), and the desired pentacyclic alcohol **464** was isolated in 34% yield (over 2 steps).

Motivated by these results and experiencing complicated cleavage of the MOM group, we decided to repeat the described synthetic sequence with an E-ring building block bearing a TBS-protected alcohol **438b** (**Scheme 2.51**). TBS ethers are known for their stability towards a wide range of reaction conditions yet can be cleaved under very mild conditions, making them one of the most popular protecting groups for alcohols.[47]

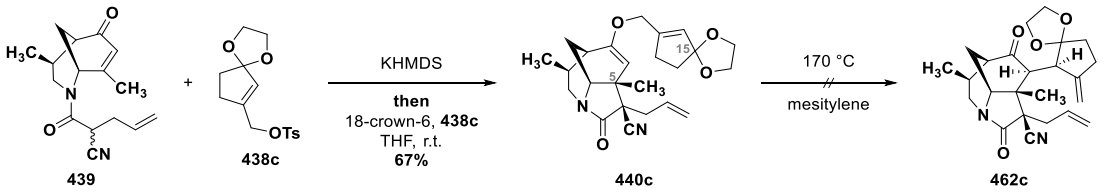


Scheme 2.51. *Formation of C- and D-rings of Himalensine A.*

The replacement of the MOM with the TBS protecting group had minimal impact on the reactivity. Coupling of amide **439** with allyl tosylate **438b** provided the corresponding enol ether **440b** in 99% yield as a 1:1 mixture of diastereomers. Similarly, as in the case of the MOM-protected substrate **440a**, Claisen rearrangement performed with TBS-protected substrate **440b** stopped at 50% conversion, providing the rearranged product **462b** in 40% yield and the unreactive diastereomer **440b'** in 43% yield. Ring-closing metathesis with **462b** led to the formation of pentacycle ***epi*-463b** in 80% yield. The initially formed product of RCM, **463b**, was observed to be undergoing rapid epimerisation to the thermodynamically more stable isomer ***epi*-463b** upon standing in chloroform or when exposed to silica. Finally, cleavage

of the TBS group in ***epi*-463b** under standard conditions (TBAF/THF) resulted in the fast formation of alcohol **464** in a significantly improved yield (61% vs the previous 30%).

Finally, the application of allyl tosylate **438c** in the *O*-allylation – Claisen rearrangement – RCM sequence was examined. The introduction of the protected ketone had the potential to make the synthesis more redox efficient and consequently one step shorter. Moreover, the nonchiral nature of this building block would not result in the formation of a mixture of diastereomers in the *O*-allylation reaction, further simplifying our synthesis.



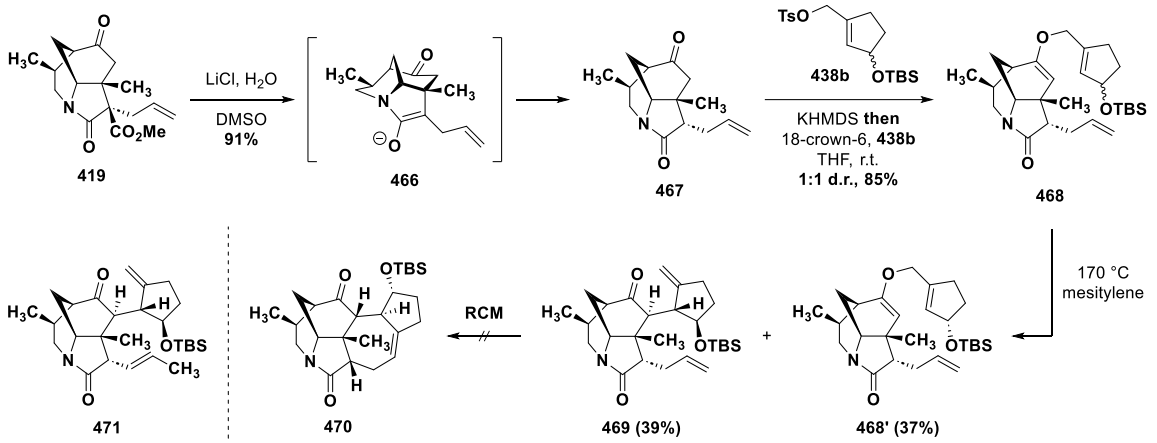
Scheme 2.52. *CD-rings formation using allyl tosylate* ***438c.***

Pleasingly, coupling of allyl tosylate **438c** with amide **439** under standard conditions provided the coupling product **440c** in 90% yield; however, heating of **440c** to 170 °C for a prolonged time (48 h) led to its slow decomposition, and the formation of the desired product **462c** was not observed. Considering our previous results, the reluctance of compound **440c** to undergo Claisen rearrangement can be attributed to its inability to adopt the reactive conformation, caused by the steric clash between the C-5 methyl group and the C-15 acetal group.

2.6.4 Optimisation of the C-ring synthesis

Building upon the previous results of Sam Ellis, all synthetic studies presented thus far were based on the use of Michael donor bearing a cyano group. While this building block allowed us to perform the Michael addition – *O*-allylation sequence in one pot with excellent yield and diastereoselectivity, preliminary studies[38] indicated that removal of the cyano group might be complicated. On the other hand, Sladojevich and Michaelides (Dixon group) showed during their studies that the one-pot Michael addition – *O*-allylation sequence can be effectively performed with a Michael donor bearing an ester group (see **Scheme 2.31**).[29a] Moreover, this group can be easily removed in high yield using a Krapcho decarboxylation (se **Scheme 2.20** in **Chapter 2.3.2.1**).

To address the diastereoselectivity issue, the Michael addition – *O*-allylation sequence was performed in two separate steps employing Li's conditions[18], as discussed in **Chapter 2.5.5**. We expected that the removal of the methyl ester moiety in **419**, necessary for the activation of the Michael donor, would prevent the C-6 epimerisation through retro-Michael addition. Moreover, the planned Krapcho decarboxylation often requires relatively harsh conditions (heating to >150 °C in wet solvent) and therefore, performing this transformation earlier in the synthesis while still working with less functionalised and, thus, more robust substrates would be advantageous.



Scheme 2.53. *Strategy based on decarboxylated tricycle* ***419.***

Heating of the tricyclic compound **419** (for preparation, see **Scheme 2.53**) in the presence of lithium chloride in wet DMSO to 170 °C[29a] provided compound **467** as a single diastereomer in 91% yield. The stereochemical outcome of this reaction can be attributed to the bowl-shaped nature of the tricyclic intermediate **466**, which led to facially selective protonation from a more sterically accessible convex face.

Coupling of ketone **467** with racemic allyl tosylate **438b** under standard conditions led to the formation of the desired enol ether **468** as a 1:1 mixture of diastereomers at C-15. Importantly, as expected, the configuration of the C-6 stereocentre was not affected by this reaction. Heating of mixture of diastereomers **468** to 170 °C provided alkene **469** in 35% and unreactive diastereomer **468'** in 36% yield, respectively. The highly crystalline nature of the compound **469** allowed the preparation of the sample for single crystal X-ray crystallography (**Figure 2.6**), which unambiguously confirmed the configuration of the C-6 stereogenic centre, as well as the configuration of two newly formed stereogenic centres formed during the Claisen rearrangement.

With diene **469** in hand, the D-ring forming alkene metathesis was attempted using the optimised conditions previously successfully used with a similar substrates **462a-b (Scheme 2.50** and **2.51**). Surprisingly, the formation of the pentacyclic product was not observed, and only the product of double bond migration **471** was isolated as the main side product formed in this reaction.

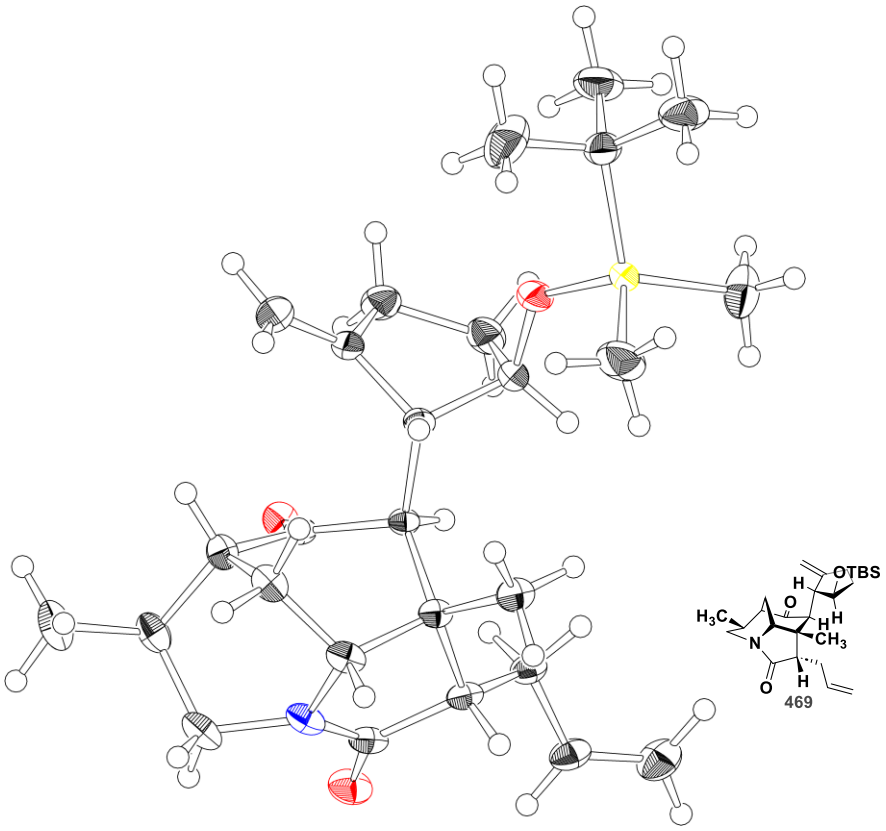


Figure 2.6. *ORTEP diagram of compound* ***469*** *with thermal ellipsoids drawn at 50% probability.*[ii]

Considering the successful cyclisation of the substrates **462a-b** bearing cyano group at C-6 (and the results discussed in the following sections), the dramatic difference in the reactivity might be attributed to the Thorpe-Ingold effect caused by the C-6 substituent. The increased steric hindrance introduced by this group could change the bond angle of the allyl group and its conformation, pushing it closer to the alkene of the E-ring, thus accelerating this challenging reaction. This raised the question of how the presence of the methyl ester group at C-6 would affect the discussed RCM reaction. The synthesis of methyl ester analogue of **462b** and its application in RCM reaction is discussed in the later chapters of this work.

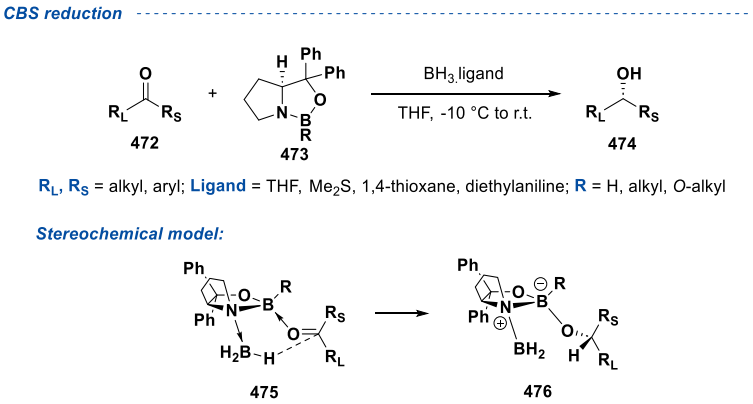
[ii] Figure 2.6 was generated using the Molby software.[48] In the representation, carbon atoms are depicted in black, oxygen in red, nitrogen in blue, silicon in yellow and hydrogen in white with a fixed diameter for clarity.

2.6.5 Enantioselective synthesis of the E-ring fragment

Although the E-ring building blocks **438a-b** are chiral, the stereogenic centre present in these fragments will be lost in the later stages of the synthesis. Therefore, all the described experiments so far were performed with racemic building blocks **438a-b** and **353**. As discussed in the previous chapter, the combination of these racemic building blocks led to the formation of an inseparable statistical mixture of two diastereomers, where only one of them was undergoing subsequent Claisen rearrangement. To avoid wasting 50% of the material in the form of unreactive diastereomer, after successfully identifying the best building block for E-ring introduction (TBS-protected allyl tosylate **438b**), we decided to prepare this building block in enantiomerically enriched form (**Scheme 2.56**). The enantioselective synthesis of building block containing the morphan core **353** was already described in **Chapter 2.5.3.**

The enantioselective preparation of **438b** required only minor modification of the previously discussed synthesis of this fragment and was already reported by Nicolaou *et al.*[44b] Because the first and simplest chiral intermediate in the synthesis of **438b** was cyclohex-2-en-1-ol (**450**), the problem of enantioselective preparation of fragment **438b** was reduced to the enantioselective reduction of the cyclohexenone (**Scheme 2.56**).

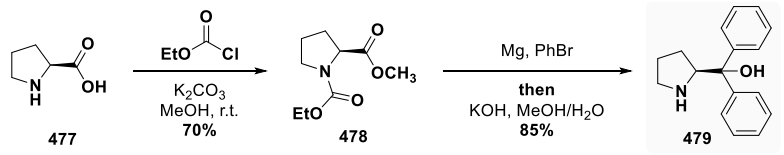
The major method for asymmetric reduction of carbonyl compounds is Corey-Bakshi-Shibata (CBS) reduction (**Scheme 2.54**).[49] In this reaction, the carbonyl compound is being enantioselectively reduced with borane in the presence of oxazaborolidine catalyst **473.** The main reasons for the popularity of this transformation are its typically high yields and enantioselectivity, short reaction times and predictable absolute stereochemistry of the product. Moreover, the catalyst **473** is easy to prepare (see **Scheme 2.56**), stable to moisture and air and its precursor (compound **479**, **Scheme 2.55**) can be recovered from the reaction mixture.[50]



Scheme 2.54. *Corey-Bakshi-Shibata reduction.*

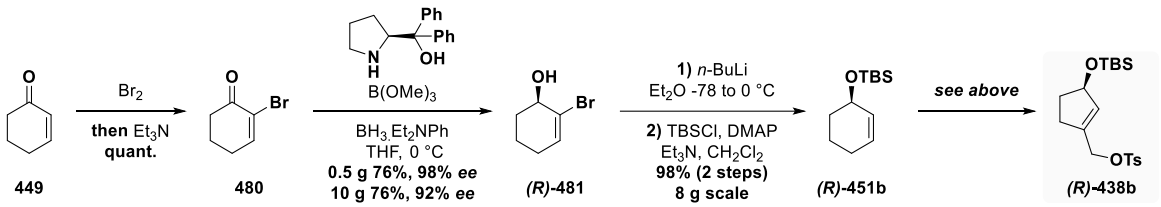
The oxazaborolidine plays two important roles in this reaction. Firstly, coordination of borane to the nitrogen atom of the CBS catalyst **473** activates borane as a hydride donor and increases the rate of otherwise slow background reduction of ketones with borane. This coordination also diminishes the π-interaction between the nitrogen and the endocyclic boron atom, increasing Lewis acidity on boron,

which in turn activates the carbonyl group of the substrate by coordination. Secondly, the shielded upper face of the CBS catalyst forces the ketone to approach from the bottom face (**Scheme 2.54**, bottom), which then binds through the sterically more accessible lone pair (avoiding interaction between its α-substituent and substituent on endocyclic boron) cis to the borane group (**475**). This leads to the hydride transfer from the front side of coordinated carbonyl and observed enantioselectivity.[51]



Scheme 2.55. *Synthesis of CBS pre-catalyst* ***479****.*

To be a suitable substrate for the CBS reduction, the carbonyl substituents R_L and R_S must sufficiently differ in their size. However, this condition is not fulfilled in the case of unsubstituted **449**. A popular approach to overcome this limitation is the installation of a temporary auxiliary to the α-position of the carbonyl, which can be removed after successful CBS reduction. Therefore, enone **449** was first α-brominated by its treatment with Br_2 in the presence of triethylamine (**Scheme 2.56**). Reduction of α-bromoketone **480** in the presence of *in situ* generated MeO.CBS catalyst using conditions reported by Blechert *et al.*[52] led to formation of alcohol **481** with 98% *ee* and 76% yield on 0.5g scale. Repeating the reaction on 10 g scale provided alcohol **481** in the same yield, however, with slightly decreased *ee* (92% *ee*).

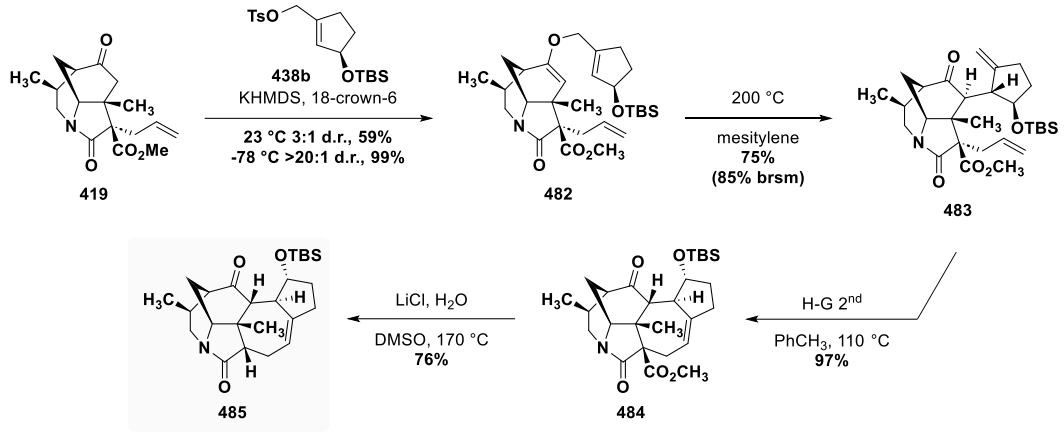


Scheme 2.56. *Enantioselective synthesis of tosylate* ***438b.***

To remove the α-bromine atom, halogen-metal exchange using *n*-BuLi was carried out, followed by protic quench of the obtained vinyl lithium species, resulting in the formation of cyclohex-2-en-1-ol. The crude alcohol was protected with TBSCl to yield compound compound **451b** in 98% yield (over 2 steps), which was converted to *(R)*-tosylate **438b** using the above-described synthetic sequence.

2.6.6 Synthesis of the pentacyclic core

With access to enantiomerically enriched building blocks **419** and **438b** in gram quantities, we proceeded to their coupling (**Scheme 2.57**). Interestingly, the presence of the methyl ester group at C-6 in **419** rendered the C-ring forming Michael addition reversible and partial epimerisation of the C-6 was observed at room temperature (3:1 *d.r.*). To mitigate the retro-Michael reaction, **419** was deprotonated at -78 °C, treated with allyl tosylate **438b** in the presence of 18-crown-6 and allowed to warm up slowly to room temperature. Pleasingly, this modification provided compound **482** as a single isomer in quantitative yield. Heating of the enol ether **482** to 200 °C in BSA-passivated glassware for 2 days afforded diene **483** in 75% yield (85% based on recovered starting material).



Scheme 2.57. *Coupling of enantiomerically enriched building blocks and D-ring synthesis.*

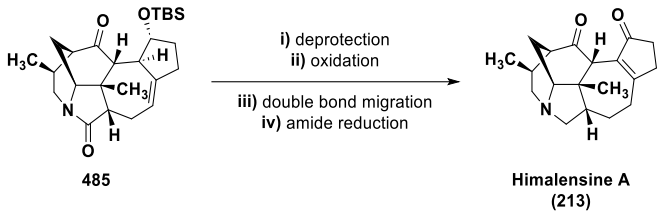
With diene **483** in hand, we could test the influence of the C-6 methyl ester group on the RCM. Gratifyingly, treatment of diene **483** with Hoveyda-Grubbs 2nd generation catalyst in boiling toluene led to relatively fast closure of a 7-membered ring, which was accompanied by C-8 epimerisation, leading to the thermodynamically more stable bowl-shaped epimer in excellent yield (97%). This result highlights the importance of C-6 substituent on the RCM reaction. Furthermore, this synthetic sequence proved to be scalable, and almost 1 g of intermediate **484** was prepared in a single campaign.

The similarity of the reaction conditions used for Claisen rearrangement (mesitylene, high temp.) and RCM (toluene, high temp., catalyst) triggered speculation if these reactions could be performed sequentially in one pot. Indeed, dilution of the reaction mixture after successful Claisen rearrangement with toluene and addition of the H-G2nd catalyst and benzoquinone provided the pentacyclic compound **485** in almost identical yield (75% over 2 steps).

Finally, after the successful RCM reaction, the C-6 methyl ester group in intermediate **484** became redundant and was removed using Krapcho decarboxylation in 76% yield, which concluded the synthesis of the carbon skeleton of Himalensine A.

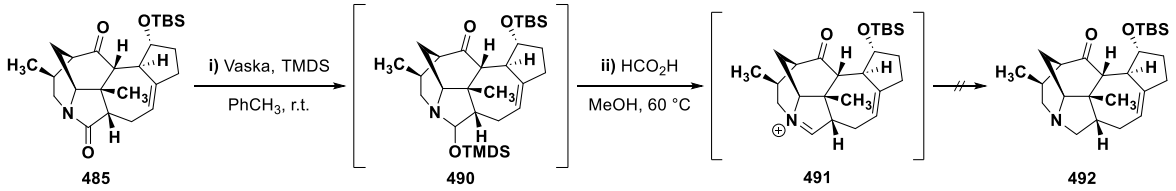
2.6.7 End game

At this point, the completion of the synthesis of Himalensine A required only a few redox and functional group manipulations, namely alcohol deprotection, its oxidation, double bond migration and reduction of amide into amine (**Scheme 2.58**). Although the double bond migration and the final reduction of the amide group in oxy-Himalensine to Himalensine A, were previously reported by our group in the first synthesis of Himalensine A by Yao Shi (2017)[33a], the relatively fast reduction of the enone moiety with Vaska's catalyst and TMDS makes this reduction especially challenging. Although the final amide reduction step was subsequently adopted (with some modifications) by several other research groups in their syntheses of Himalensine A,[23, 53] the relatively low yields (14 – 67%) highlight the difficulty of this transformation. However, this issue could be avoided in our case by changing the relative order of the required transformations and performing the amide reduction before the introduction of the enone moiety. On the other hand, work with amines is often challenging due to their high polarity, which complicates their purification, and tendency to undergo oxidation, for example, to *N*-oxides. The determination of the optimal step order and optimisation of these reactions is the subject of this chapter.



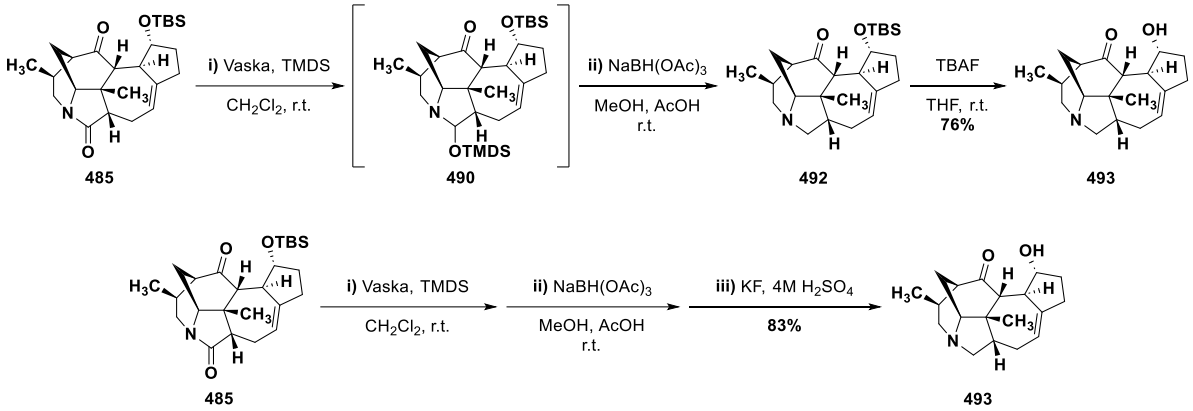
Scheme 2.58. *List of transformations required for the synthesis of Himalensine A.*

Although both of two possible end-game strategies were examined in parallel, the strategy based on the reduction of the amide before introduction of the enone will be discussed first. Our initial attempt to reduce the amide group in **485** employed the protocol previously used by Yao Shi (**Scheme 2.59**).[33a] Under these conditions, the amide group of **485** is first reduced with TMDS in the presence of Vaska's catalyst to corresponding hemiaminal, which is then silylated under the reaction conditions (**485** → **490**). Subsequently, intermediate **490** is treated in the same pot with formic acid, resulting in the collapse of the **490** into iminium ion **491**, which is then reduced by an excess of formic acid to amine. Unfortunately, the successful reduction of the amide group in **485** was accompanied by deprotection of the TBS group and partial formylation of obtained alcohol, rendering the original conditions inapplicable in our case.



Scheme 2.59. *Reduction of compound **485** under Shi's conditions.*

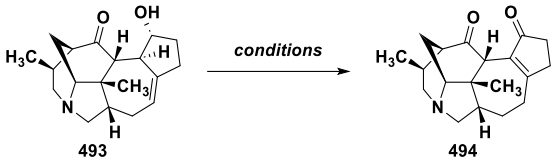
To overcome the issue of undesired TBS deprotection, we decided to avoid using formic acid as a reducing agent for the reduction of the iminium ion. In his 2020 synthesis of Lyconadins A-E, Yang *et al.*[54] demonstrated that a combination of Vaska's reduction and $NaBH(OAc)_3$ could be used for the convenient reduction of amide to amine. Employing these conditions (**Scheme 2.60**), amine **492** was obtained in 85% yield. Subsequent deprotection of the TBS group with TBAF provided alcohol **493** in 76% yield. Further optimisation of this synthetic sequence revealed that the yield of the TBS deprotection could be significantly increased by using KF in the presence of 4M H_2SO_4. Moreover, all these steps – reduction of amine to hemiaminal, its reduction to amine and TBS deprotection, can be performed in one pot with 83% yield (**Scheme 2.60, bottom**), substantially simplifying the synthesis by eliminating the need to isolate and purify intermediate **492**.



Scheme 2.60. *Synthesis of alcohol* ***493****.*

The presence of the amino group in compound **493** made the final oxidation of the homoallylic alcohol more challenging, as it required identifying the conditions compatible with this functional group. Swern oxidation of alcohol **493** led to the formation of the desired product, albeit in a rather low yield (**Table 2.2, entry 1**). To avoid relatively complicated setup of the Swern oxidation (especially on a milligram scale), an alternative method based on activated dimethyl sulfoxide was examined. The Parikh-Doering oxidation (**entry 2-3**), based on the sulphur trioxide pyridine complex as a DMSO activator, represents an operationally simple variant that can be run at non-cryogenic conditions. However, this modification didn't lead to the formation of any product, and only the unreacted starting material was isolated, even when a large excess of the reagents was used (**Table 2.2**, **entry 2-3**).

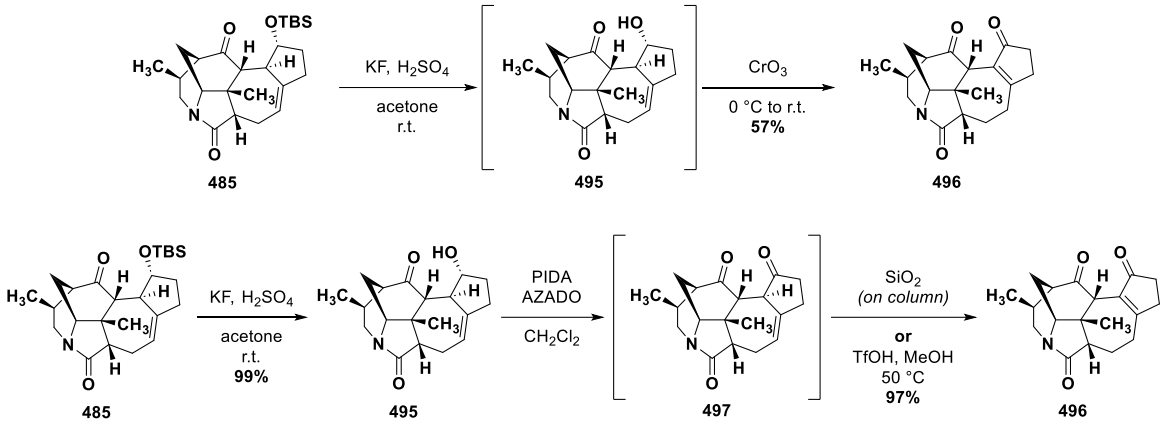
Table 2.2. Screening of conditions for oxidation of alcohol **493.**



Entry	Reaction	Conditions	Yield
1	Swern oxidation	DMSO (3.0 eq.), $(COCl)_2$ (1.5 eq.), Et_3N (6.0 eq.) CH_2Cl_2, -78 °C to r.t.	<50%
2-3	Parikh-Doering ox.	SO_3.pyr (3.0 eq.), DMSO (10.0 eq.), Et_3N (4.0 eq.) *and* SO_3.pyr (15.0 eq.), DMSO (40.0 eq.), Et_3N (20.0 eq.) 0 °C to r.t.	no reaction
4	Ley oxidation	TPAP (5 mol %), MNO (5.0 eq.), 4Å MS, CH_2Cl_2, r.t.	decomp.
5	Jones oxidation	CrO_3 (1.1 eq.), 4M H_2SO_4 (7.0 eq.)	traces
6	Dess-Martin ox.	DMP (2.4 eq.), CH_2Cl_2, r.t.	traces
7	PIDA/AZADO	AZADO (0.2 eq.), PIDA (4.0 eq.), CH_2Cl_2, r.t.	no reaction

Treatment of **493** with NMO in the presence of the catalytic amount of TPAP (Ley oxidation, **entry 4**) led to slow decomposition of the starting material. Titration of **493** with Jones reagent, successfully used in the alternative end-game strategy (see discussion below), provided compound **494** in only low yield and purity (**entry 5**). Trace amounts of compound **494** were also obtained by oxidation of alcohol **493** with Dess-Martin reagent, a selective and mild oxidation method based on hypervalent iodine (**entry 6**). Finally, the oxidation with AZADO,[55] a sterically less hindered analogue of TEMPO, and phenyliodine(III) diacetate as a terminal oxidant was not fruitful, despite excelling in the oxidation of the amide analogue of **493** (see **Scheme 2.61**). The problematic oxidation of compound **493** could be attributed to the presence of the amino group, which can undergo undesired oxidation processes. Moreover, unlike their amide group-bearing analogues, which were bench-stable solids, both amines **492** and **493** underwent slow decomposition when stored at room temperature.

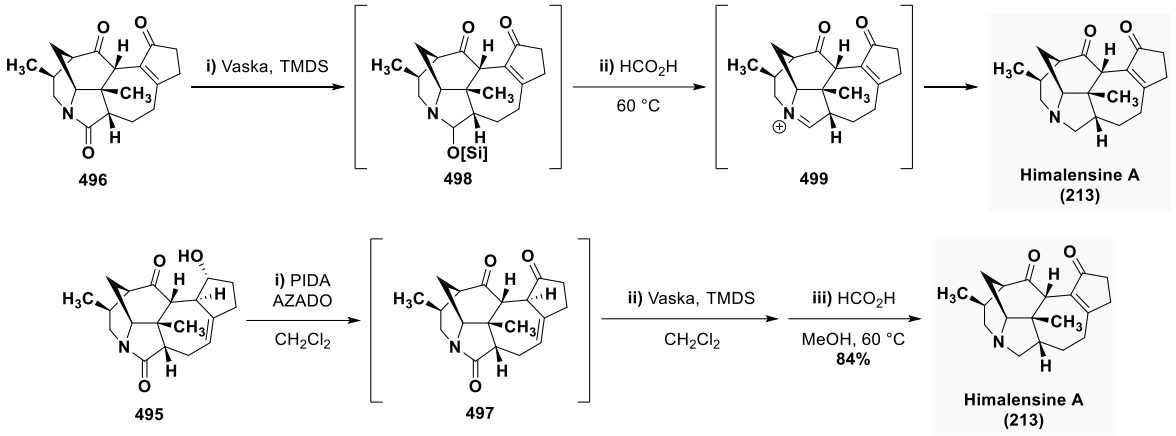
Facing the issues introduced by the presence of the amino group, we decided to perform the reduction of the amide group as the last step of our synthesis (**Scheme 2.61**). Treatment of compound **495** with TBAF led to relatively slow cleavage of the TBS group, in a rather disappointing yield (66%). On the other hand, using KF in the presence of acid resulted in fast deprotection and alcohol **495** was obtained in almost quantitative yield. We speculated that this deprotection step could be coupled with a subsequent oxidation step using an appropriate oxidant. Moreover, strong acid in protic solvent should facilitate the migration of the double bond into conjugation with the carbonyl of the cyclopentanone E-ring. Indeed, the treatment of the crude reaction mixture containing alcohol **495** with CrO_3 (Jones oxidation) provided enone **496** in 40% yield, a common intermediate in previous syntheses of Himalensine A. Further optimisation of the oxidation step – titration of the alcohol **495** with the solution of CrO_3 at a lower temperature and careful monitoring of the reaction progress increased the overall yield to 57%.



Scheme 2.61. *Formal synthesis of Himalensine A.*

To further increase the yield of the oxidation step, we decided to abandon the one-pot deprotection–oxidation sequence. Treatment of alcohol **495** with PCC at room temperature didn't lead to the formation of the desired product, and heating of the reaction mixture to 50 °C resulted in slow decomposition. Oxidation with Dess-Martin periodinane was synthetically impractical due to the long reaction time (>2 days) and low purity of the obtained material caused by residues originating from this reagent. Finally, treatment of the alcohol **495** with a catalytic amount of AZADO and PIDA[55] as a terminal oxidant led to fast and quantitative oxidation to non-conjugated ketone **497**, which isomerised to enone **496** during its purification by column chromatography. Alternatively, the double bond migration in ketone **497** can be achieved by heating the crude reaction mixture in the presence of strong acid (TfOH) and protic solvent (MeOH). Interestingly, the replacement of AZADO with sterically more hindered (but considerably cheaper) TEMPO significantly slowed the reaction, and only a trace amount of the product was formed after several hours, indicating the important role of sterics in this oxidation.

With access to sufficient quantities of oxy-Himalensine A (**496**), the final reduction of the amide group was attempted (**Scheme 2.62**, top). Employing the original procedure developed by Yao Shi[33a] – dropwise addition of TMDS to the solution of amide **496** and Vaska's catalyst in toluene led to fast consumption of the starting material and formation of the silylated hemiaminal **498** (confirmed by low-resolution MS); however, substantial formation of the over-reduced produced product was also observed (MS). Treatment of crude hemiaminal **498** with formic acid led to the formation of iminium ion **499** which was reduced by the excess of formic acid to Himalensine A (**213**). Although the NMR analysis of the crude reaction mixture confirmed the formation of Himalensine A, its purification was complicated by the presence of side products that were difficult to separate. Consequently, Himalensine A (**213**) was not obtained in satisfying yield and purity.

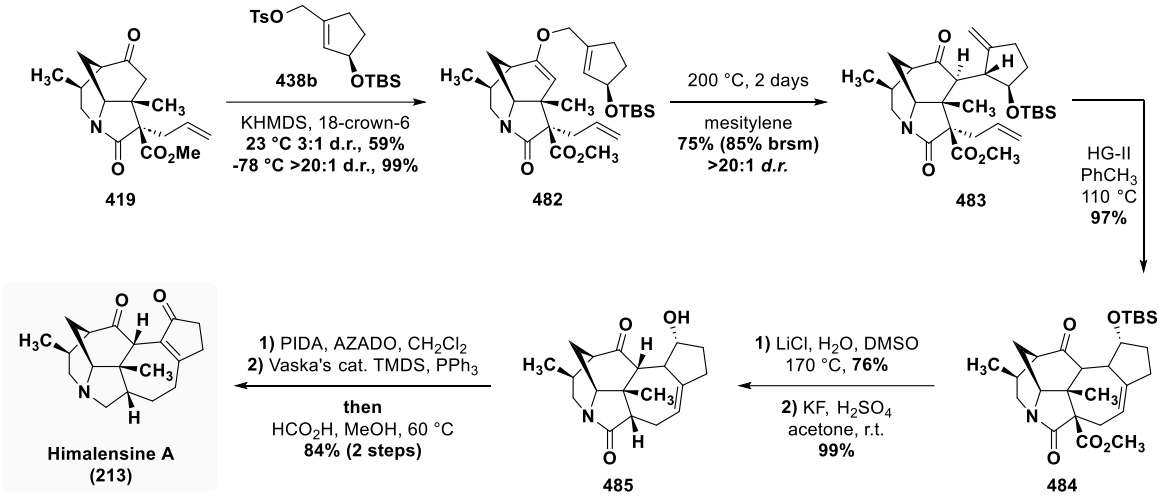


Scheme 2.62. *Final reduction of amide.*

The selectivity of the Vaska reduction is given by the ability of the functional group to coordinate the catalyst.[33b] Therefore, functional groups with higher Lewis basicity, such as amides, can be selectively reduced in the presence of less Lewis basic functional groups like esters and ketones. We hypothesised that the conformational and electronic properties of non-conjugated ketone **497** might significantly alter its reactivity in Vaska's reduction compared to enone **496**, potentially increasing the selectivity of this reaction. To test this hypothesis, the crude non-conjugated keto **497**, accessible in quantitative yield by AZADO/PIDA oxidation of alcohol **495**, was subjected to the previously described reduction protocol (**Scheme 2.62**, bottom). Pleasingly, the MS analysis of Vaska's reduction step showed only traces of over-reduced side product, which was reflected in the formation of significantly cleaner product **213** (NMR of the crude reaction mixture). Purification by simple column chromatography afforded Himalensine A in yield 84% over 3 steps.

2.6.8 Summary of the Himalensine A synthesis

Chapter 2.6 described the development of a novel enantioselective synthesis of Himalensine A (**Scheme 2.63**). *O*-allylation of tricyclic intermediate **419** (preparation discussed in **Chapter 2.5**) with complex allyl tosylate **438b**, followed by Claisen rearrangement and ring-closing metathesis allowed for rapid introduction of D- and E-rings of Himalensine A in only 3 steps (2 after telescoping). After the synthesis of the carbon core, the synthesis of Himalensine A was finalised in only 4 more steps, namely: Krapcho decarboxylation, alcohol deprotection and its oxidation and reduction of the amide group to amine accompanied by migration of the alkene group into conjugation. In summary, Himalensine A was prepared in 20 steps and 10% overall yield (18 steps and 9% yield after telescoping). The total synthesis of Himalensine A and formal synthesis of *Daphniphyllum* alkaloids were published in the Journal of American Chemical Society.[32c]

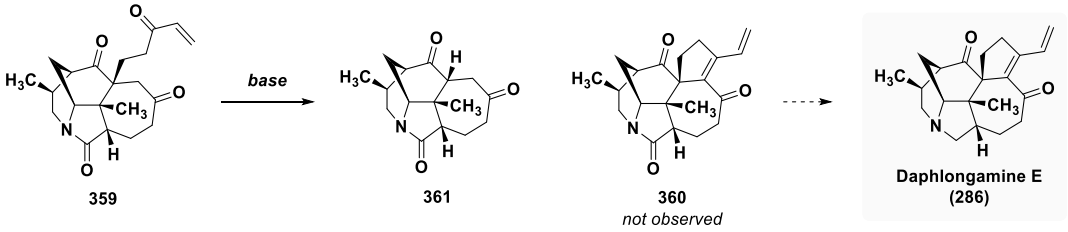


Scheme 2.63. *Overview of total synthesis of Himalensine A.*

2.7 Synthetic studies towards Daphniyunnine B and Daphlongamine E

After successfully completing the synthesis of Himalensine A, as described in the previous chapter, we set out to explore the potential application of our synthetic strategy and advanced intermediates for the preparation of other *Daphniphyllum* alkaloids. Building upon the work of Sam Ellis, Daphniyunnine B and Daphlongamine E were chosen as our next synthetic targets.

Previous work showed that the most obvious disconnection of enone moiety in Daphlongamine E (**286**) by aldol condensation is not feasible, as the corresponding compound **359** was undergoing retro-Michael addition during the attempted cyclisation (**Scheme 2.64**).[38] The Conia-ene reaction was proposed as an alternative strategy for the introduction of the enone moiety. However, the challenging preparation of the substrates for this transformation previously hindered its exploration.

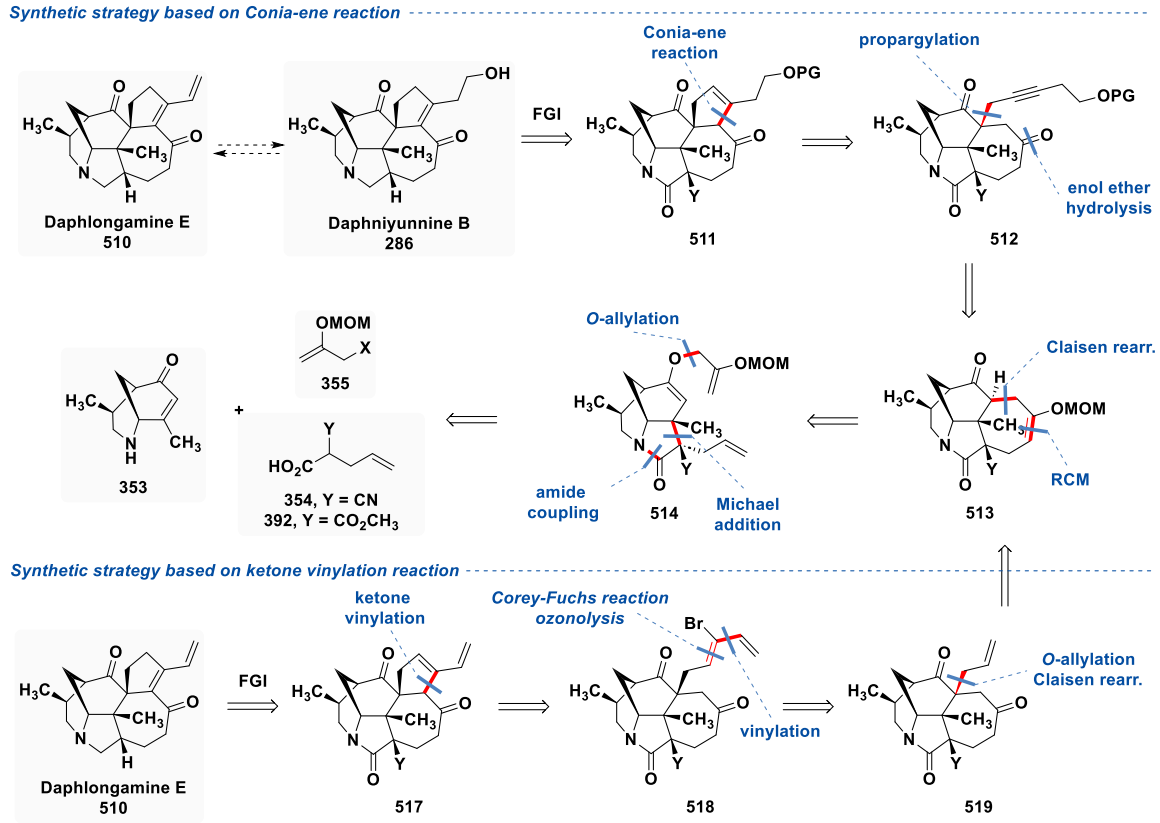


Scheme 2.64. *The synthetic approach based on aldol condensation.*

This chapter presents a new synthetic approach for the preparation of substrates suitable for the Conia-ene reaction and explores the application of this reaction for the introduction of the E-ring of Daphniyunnine B and Daphlongamine E.

2.7.1 Retrosynthetic analysis

Daphniyunnine B (**510**) and Daphlongamine E (**286**) can be potentially converted into each other by dehydration or alkene hydration, respectively, at the appropriate stage of the synthesis. Employing several functional group interconversions (FGI) such as i) conversion of amine to amide, ii) installation of an activating group **Y** for Michael reaction, iii) double bond migration and iv) protection of a primary alcohol, Daphniyunnine B can be retrosynthetically transformed into ketone **511** (**Scheme 2.65**, top). Subsequently, the E-ring can be disconnected through Conia-ene reaction to alkyne **512**, which can be further simplified to compound **513** through ketone propargylation. The synthesis of compound **513**, where **Y** = CN, has previously been described by Sam Ellis[38] and can be can be disconnected in a highly convergent manner to building blocks **353, 355** and **354** employing the preciously discussed synthetic strategy.



Scheme 2.65. *Retrosynthetic analysis of Daphniyunnine B and Daphlongamine E.*

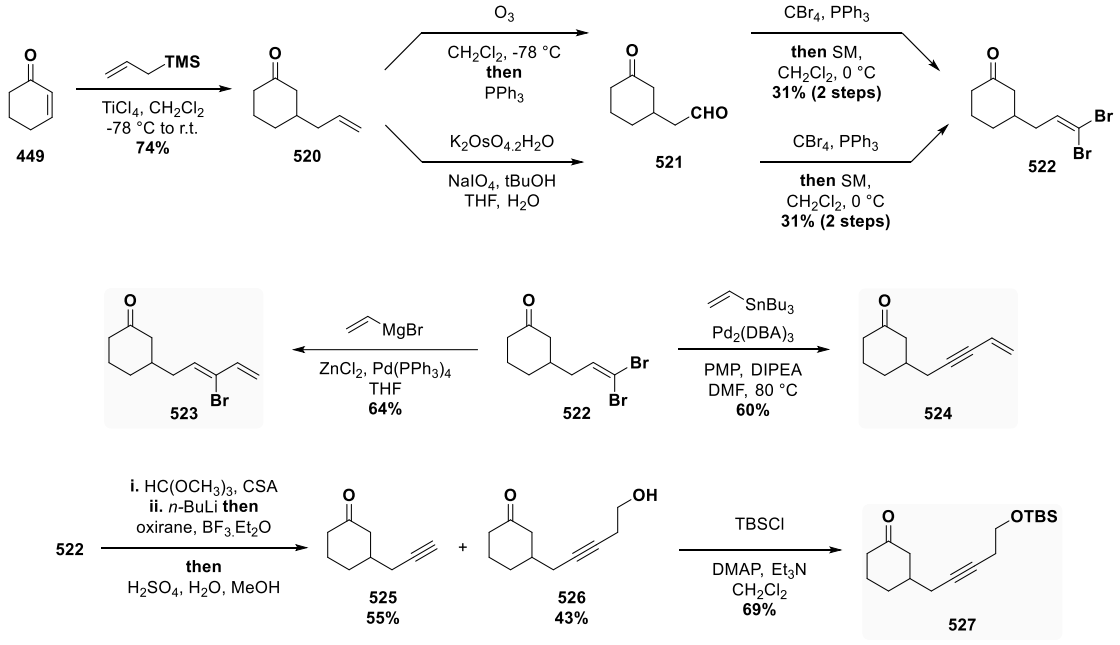
Alternatively, application of the same FGI i) – iii) to Daphlongamine E (**Scheme 2.65**, bottom), allows the disconnection of the E-ring in **517** to vinyl bromide **518**, attainable through selective vinylation of corresponding geminal dibromide. The dibromide can be synthesised by the Corey-Fuchs reaction from the aldehyde obtained by ozonolysis of the allyl group in compound **519**. The synthesis of compound **519** (Y = CN), was previously described by Sam Ellis and can be obtained from compound **513** by ketone *O*-allylation followed by Claisen rearrangement.[38]

2.7.2 Synthesis and reactivity of the model system

Before embarking on the synthesis of the complex cyclisation precursors **512** and **518**, we decided to assess the viability of both strategies – Conia-ene and ketone vinylation reactions – using a simpler model system. While the ideal model system would consist of a 7-membered ketone with a corresponding sidechain at β-position, the relatively high price of the starting material for the synthesis of such compounds led us to opt for 6-membered analogues in our model studies (**Scheme 2.66**).

Starting from cyclohex-2-en-1-one (**449**), the β-chain was introduced by Sakurai allylation using allyltrimethylsilane in 74% yield.[56,57] Subsequent ozonolysis of the alkene in **520** provided aldehyde **52**, which was then subjected to the Corey-Fuchs reaction[58] to yield geminal dibromoalkene **522**. Due to the relatively low yield of this synthetic sequence (31% over 2 steps), an alternative strategy based on Johnson–Lemieux oxidation was examined. Using a catalytic amount of potassium osmate in the presence of sodium periodate, alkene **520** was cleanly cleaved to aldehyde **521**; however, the subsequent Corey-Fuchs reaction provided the dibromide **522** in an unchanged yield (31% over 2 steps).

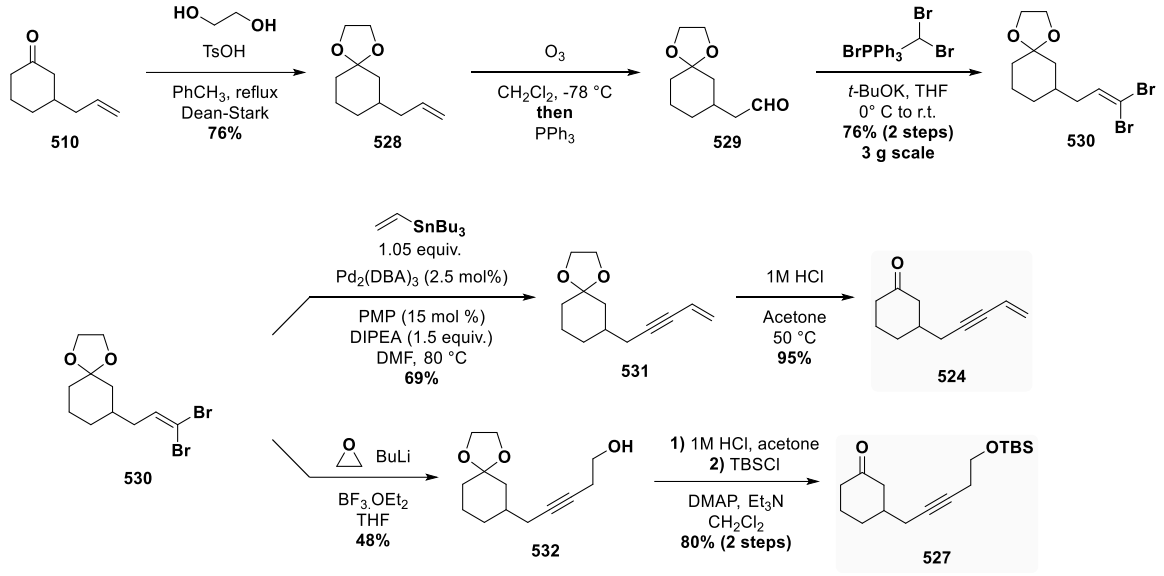
Geminal dibromides are a very versatile functional group for the preparation of substituted alkynes and alkenes, either through cross-coupling reactions[59] or their conversion to terminal acetylides followed by trapping with an electrophile.[60] In our case, dibromoalkene **522** served as a common intermediate for the synthesis of three model systems (**Scheme 2.66**, bottom).



Scheme 2.66. *Synthesis of model systems* ***523, 524*** *and* ***527****.*

Substitution of the more reactive *trans*-bromine atom in **522** through Negishi coupling with *in situ* generated vinyl zinc reagent provided model substrate for ketone vinylation **523** in 64% yield.[61] The Stille coupling of **522** with vinyl tributyltin under Wang's conditions[62] led to the introduction of the vinyl group and elimination of the second bromine atom, providing enyne **524** in 60% yield. Lastly, dibromide

522 was converted to alcohol **526** by a three-step one-pot procedure. First, the ketone in **522** was protected as a dimethyl acetal by its treatment with trimethyl orthoformate. Next, the 1,1-dibromoalkene was converted to the corresponding lithium acetylide by its reaction with *n*-BuLi and the resulting acetylide was trapped with oxirane.[63] Finally, acidic hydrolysis provided alcohol **526** (43%) along with alkyne **525** (55%). TBS protection of the primary alcohol in **526** accomplished the synthesis of the last model substrate (**527**).



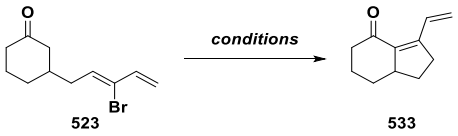
Scheme 2.67. *Alternative synthesis of compounds* ***524*** *and* ***527****.*

Although the synthetic pathways described in **Scheme 2.66** granted access to model systems **523, 524** and **527**, the relatively low yield of the Corey-Fuchs reaction (31% over 2 steps) limited the material throughput. In order to obtain compound **524** and **527** in larger quantities required for the optimisation of the cyclisation reaction, an alternative method for generating the phosphonium ylide was employed (**Scheme 2.67, top**). To prevent undesired reactivity of the ketone moiety, such as ketone α-bromination, compound **210** was first protected as a cyclic acetal (**528**). Subsequent ozonolysis of the alkene in **528**, followed by the Wittig reaction with Wolkoff's reagent,[64] provided the desired 1,1-dibromoalkene **530** in more than double the yield compared to the Corey-Fuchs strategy (76% over 2 steps vs 31%) on a gram scale. Stille coupling of **530** with vinyl tributyltin followed by acetal hydrolysis provide enyne **524** in 66% yield (over 2 steps).[62] Treatment of **530** with *n*-BuLi and trapping the generated acetylide with oxirane led to the formation of alcohol **532** in 48% yield and terminal alkyne in 44% yield. The hydrolysis of the acetal in **532** and protection of the primary alcohol with a TBS group provided compound **527** in 80% yield (over 2 steps). This modified synthetic sequence almost doubled the yields of compound **524** and **527**, and provided the key intermediate, dibromide **530**, in gram quantities.

2.7.3 Cyclisation on the model system

As a first method for the formation of the 5-membered ring, the cyclisation of vinylbromide **523** (**Table 2.3**) was investigated. Screening of multiple conditions for coupling of enolates with vinyl bromides previously published in the literature[65] didn't lead to the formation of the desired cyclised product and only the product of bromine elimination (enyne **524**) was formed predominantly. Compound **523** showed a high tendency to undergo elimination or decomposition under conditions commonly used for similar cyclisations, which led us to abandon this strategy.

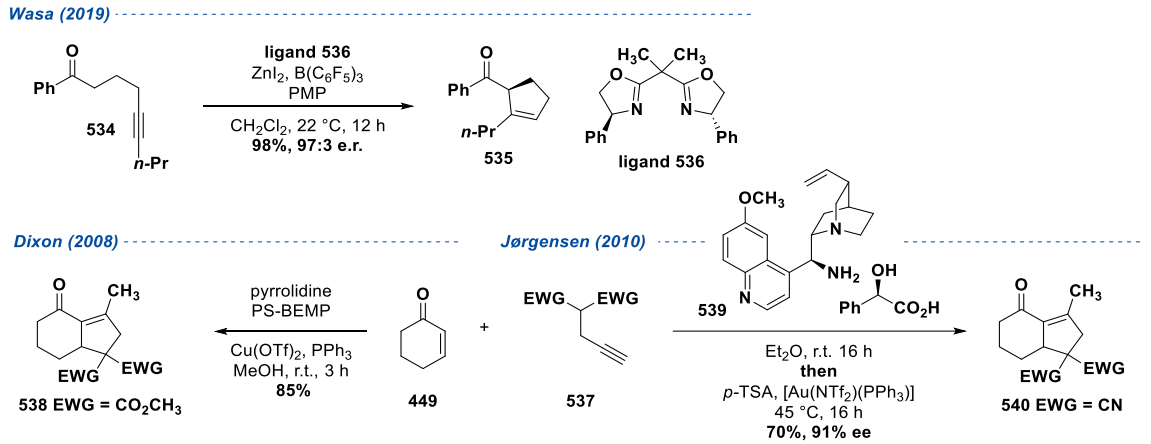
Table 2.3. *Screening of conditions for cyclisation of vinyl bromide* ***523.***



523 533

Entry	Conditions	Observation	Yield
1	$Pd(PPh_3)_4$ (5 mol%), PPh_3 (20 mol%), K_3PO_4 (2.0 eq.), NMP, 75 °C[65a]	elimination	n.a.
2	$Pd(PPh_3)_4$ (20 mol%), *t*-BuOK (1.5 eq.), THF, reflux[65b]	decomposition	n.a.
3	$Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%), K_2CO_3 (7.0 eq.), DMF, 100 °C	no reaction	n.a.
4	$[Pd_2(dba)_3]$ (2 mol%), Q-Phos (4 mol%), *t*-BuOLi (4.0 eq.), THF, r.t.[65c]	no reaction	n.a.
5	$[Pdt\text{-}Bu_3PBr]_2$ (6 mol%), LiHMDS (2.5 eq.), $PhCH_3$, 80 °C[65d]	decomposition	n.a.
6	CuI (20 mol %), tetramethylphenanthroline (40 mol %), Cs_2CO_3 (3.0 eq.), THF, reflux[65e]	no reaction	n.a.

Next, we examined the strategy based on Conia-ene-type cyclisation with enyne **524**. In 2019, Wasa *et al.* published a highly enantioselective cyclisation using a combination of $B(C_6F_5)$, *N*-alkylamine and BOX-ZnI_2 complex (**Scheme 2.68**, top).[66] Employing the racemic version of this reaction with two different bases (**Table 2.3, entry 1-2**) didn't lead to the formation of the desired product.

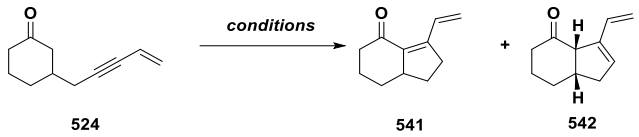


Scheme 2.68. *Conia-ene-type cyclisation reactions.*

In 2008 Dixon *et al.* reported a synthesis of structurally similar cyclopentenes through an enamine-transition metal-catalysed cascade based on one-pot Michael addition – Conia-ene-type cyclisation (**Scheme 2.68**, bottom left).[67] Inspired by this work, several sets of reported conditions were examined.

Under the original conditions, enyne **524** underwent relatively fast cyclisation, providing a 11:1 mixture of isomers **541** and **542** in 60% yield (**entry 3**). After this initial hit, several other transition metals were examined. The replacement of the *in situ* generated copper(I) with gold(I) catalyst led to the fast formation of dimethyl acetal (**entry 4**). To avoid this undesired reaction, the cyclisation reaction was performed in chloroform, which was identified as an optimal solvent for the Conia-ene step during the reaction development.[68] Unfortunately, this modification of reaction conditions led to a very slow reaction and only traces of cyclised product were observed after 48 h (**entry 5**). Slow formation of the cyclisation product was also observed with $AgNTf_2$ (**entry 6**). Interestingly, employing the conditions used for the synthesis of racemic morphan core[32a] (**Scheme 2.28**) provided the cyclised product in a significantly improved yield (**entry 7**, 83%, 3.5:1 mixture of isomers). Replacement of copper with palladium was not productive (**entry 8**).

Table 2.4. *Screening of conditions for cyclisation of alkyne* ***524.***



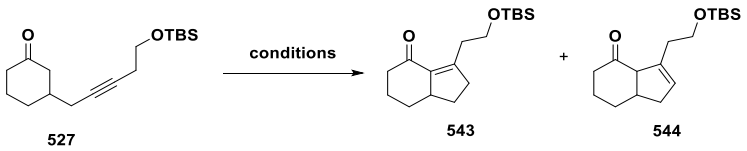
Entry	Conditions	Observation	Yield
1	ZnI_2 (10 mol%), $(F_5C_6)_3B$ (10 mol%), **Et_3N** (20 mol%), CH_2Cl_2, 40 °C[66]	no reaction	n.a.
2	ZnI_2 (10 mol%), $(F_5C_6)_3B$ (10 nmol%), **PMP** (20 mol%), CH_2Cl_2, 40 °C[66]	no reaction	n.a.
3	$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%)[67] PS-BEMP (10 mol%), MeOH, 65 °C	**541:542** 11:1	60%[a]
4	**$Au(PPh_3)Cl$** (5 mol%), **AgOTf** (5 mol%), pyrrolidine (20 mol%) PS-BEMP (10 mol%), MeOH, 65 °C	formation of acetal	n.a.
5	$Au(PPh_3)Cl$ (5 mol%), AgOTf (5 mol%), pyrrolidine (20 mol%) PS-BEMP (10 mol%), **$CHCl_3$**, 60 °C	traces of product	n.d.
6	**$AgNTf_2$ (5 mol%)**, PPh_3 (20 mol%), pyrrolidine (20 mol%) PS-BEMP (10 mol%), MeOH, 65 °C	traces of prod. (84% SM)[b]	8%(B)[b]
7	**$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%) THF, 80 °C**[32a]	**541:542 3.5:1**	**83%[a]**
8	**$Pd(PPh_3)_4$** (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%) PS-BEMP (10 mol%), THF, 80 °C	no reaction	n.a.
9	$[AuPPh_3NTf_2]$ (5 mol %), CH_2Cl_2, 40 °C[69]	partial conv. (35% SM)[b]	11%(B)[b]
10	$[AuPPh_3NTf_2]$ (5 mol %), **pyrrolidine** (40 mol %), CH_2Cl_2, 40 °C[69]	partial covn. (55% SM)[b]	13%(B)[b]
11	$[AuPPh_3NTf_2]$ (5 mol %), **THF**, 80 °C	no reaction (22% SM)[b]	n.a.
12	$[AuPPh_3NTf_2]$ (5 mol %), **pyrrolidine** (40 mol %), **THF**, 80 °C	partial conv. (26% SM)[b]	30%(B)[b]

Reactions were performed on 20 mg scale in degassed solvent in a sealed tube. [a] isolated yield, [b] NMR yield, mesitylene used as an internal standard, PMP = 1,2,2,6,6-pentamethylpiperidine, PS-BEMP = polystyrene supported BEMP, BEMP = 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

In 2010, Jørgensen *et al.*[69] published an enantioselective modification of Dixon's cascade (**Scheme 2.68**, bottom right). Drawing inspiration from their screening of conditions for the cyclisation step, several sets of conditions using $Au(PPh_3)(NTf)_2$ were examined (**entries 9 – 12**). In dichloromethane, the

cyclised product was formed in a very low yield, both with and without pyrrolidine as an organocatalyst (**entry 9 – 10**). The reaction in THF without pyrrolidine was not productive (**entry 11**), while its presence led to only a minimal increase of the yield (**entry 12**). The low mass recovery indicates that the starting material and/or products of cyclisation are likely undergoing decomposition under the reaction conditions (e.g., **entries 9-12**).

Table 2.5. *The cyclisation of alkyne* ***527.***



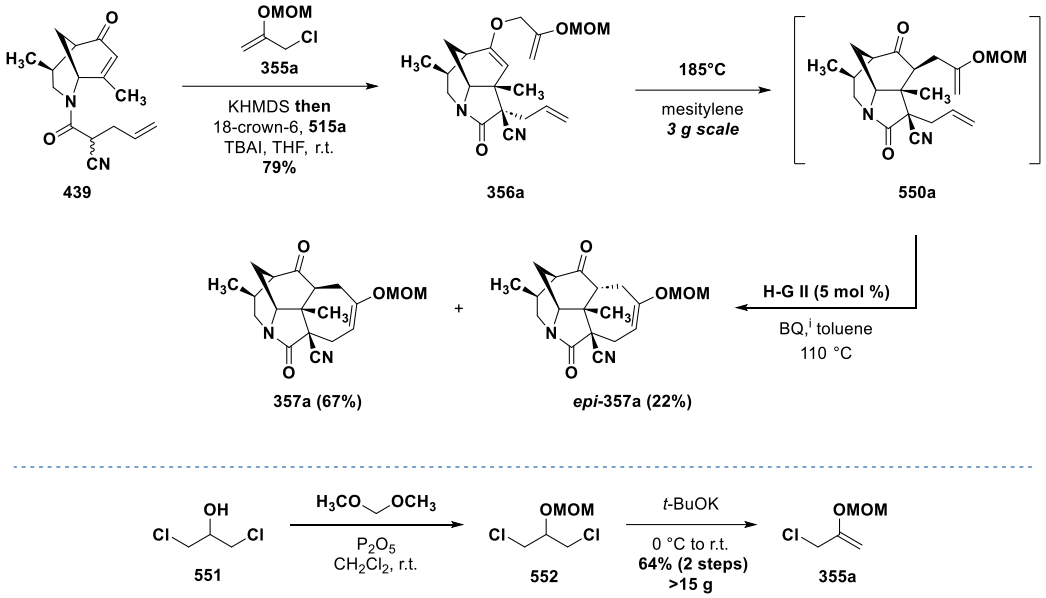
Entry	Conditions	Observation	Yield
1	$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%)[67] PS-BEMP (10 mol%), MeOH, 65 °C	20:1	87%[a]
2	$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%) THF, 80 °C[32a]	6.3:1	66%[a]

Reactions were performed on 24 mg scale in degassed solvent in a sealed tube. [a] isolated yield, [b] based on NMR of isolated product. PMP = 1,2,2,6,6-pentamethylpiperidine, PS-BEMP = polystyrene supported BEMP, BEMP = 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

Finally, the cyclisation of model system **527** representing Daphniyunnine B (**286**) was examined. Applying the two best conditions from **Table 2.4** (**entries 3** and **7**), alkyne **527** underwent smooth cyclisation and provided compounds **543** and **544** as an inseparable mixture of products in 87% and 66% yield (**Table 2.5**, **entry 1**). Not surprisingly, the presence of BEMP facilitated the migration of the alkene double bond into the conjugation with ketone, and enone **543** was the dominant product (**543**:**544** = 20:1). In the absence of the strong base (**entry 2**) isolated alkene **544** was the dominant product (**543**:**544** = 6.3:1).

2.7.4 Synthesis of the C- and D-rings

Having successfully identified the most promising approach to the E-ring of Daphniyunnine B and Daphlongamine E on model systems **524** and **527**, we proceeded to the synthesis of advanced tetracyclic intermediate **357a** and the attachment of the alkyne sidechain(s) required for the intended E-ring-forming cyclisation reaction.



***Scheme 2.69**. Synthesis of tetracycle **357a**.[iii]*

We initiated our synthetic studies by preparation of a cyano group-bearing tetracycle **357a**. Although the removal of the cyano group in **357a** was reported to be challenging, its short and high-yielding synthesis made it a good starting point. Starting from amide **439**, the compound **357a** was prepared on multigram scale using a slightly modified synthetic sequence developed by Sam Ellis (**Scheme 2.69**, top).[38] Treatment of amide **439** with KHMDS led to the fast formation of the C-ring *via* intramolecular Michael addition and subsequent trapping of the enolate with allyl chloride **355a** provided enol ether **356a** as a single diastereomer. Due to the presence of two enol ether moieties in **356a,** this compound might be susceptible to acid hydrolysis. For example, enol ether **550a** was found to be highly acid sensitive.[38] Furthermore, its decomposition has been observed when exposed to air for several hours or in solution. As a preventive measure, Claisen rearrangement of compound **356a** was performed in glassware passivated by bis(trimethylsilyl)acetamide. Heating allyl enol ether **356a** to 185 °C in mesitylene led to the clean and fast formation of diene **550a**. The similar nature of the reaction solvents (mesitylene vs toluene) allowed the subsequent RCM reaction to be performed in the same pot, avoiding the isolation of this relatively unstable intermediate. After the completion of Claisen rearrangement, the reaction mixture was simply diluted with toluene, and the RCM was performed under the previously optimised

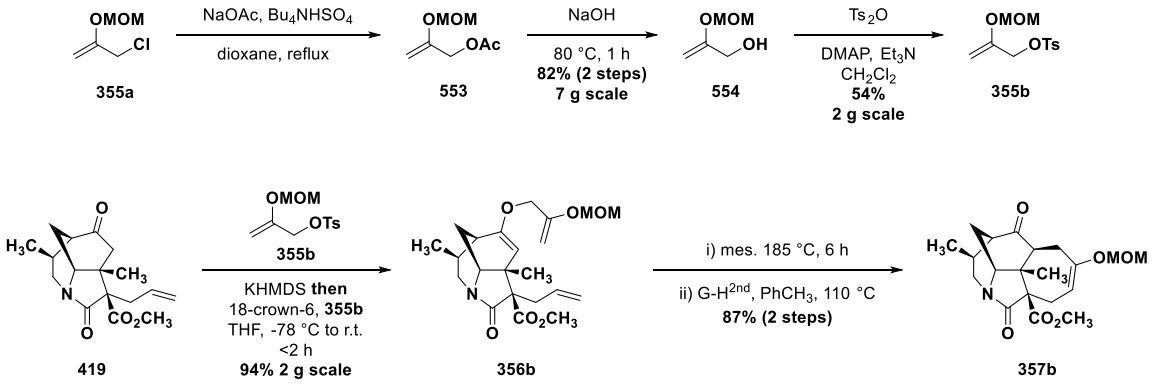
[iii] BQ was used to prevent previously reported double bond migration caused by the formation of ruthenium hydride complexes at high temperatures.

conditions. Although the compound **357a** was initially formed as the only product of the reaction, partial epimerisation at C-8 was observed during the purification on silica, and compounds **357a** and ***epi*-357a** were isolated in 67% and 22% yield, respectively, together with 5% of uncyclised intermediate **550a.**

Allyl chloride **355a** used for the *O*-allylation of the enolate formed during the Michael reaction was prepared in two steps from 1,3-dichloropropan-2-ol (**Scheme 2.69, bottom**). First, the alcohol in **551** was protected as methoxymethyl ether by its treatment with dimethoxymethane in the presence of phosphorus pentoxide to remove methanol, formed in the course of the reaction.[70] Subsequent elimination of the chloride in **552** with potassium *tert*-butoxide provided enol ether **355a**.[71]

We anticipated that, similarly to synthesis of Himalensine A, we would need to swich from cyano- to methyl ester group-bearing substrates in the later stages of our synthetic studies. The methyl ester group-bearing tetracyclic compound **357b** was prepared following the same strategy. The relatively low reactivity of allyl chloride **355a** required the *O*-allylation reaction to be conducted at room temperature and for a longer reaction time (16 h). However, these conditions were not applicable to compound **419**, as it would result in the epimerisation of C-6 through reversible Michael addition. To avoid the epimerisation of C-6, the *O*-allylation reaction needs to be performed at low temperatures.

To accelerate the *O*-allylation reaction, allyl chloride **355a** was replaced with corresponding more reactive allyl tosylate **355b** (**Scheme 2.70, top**). Following Okahara's procedure,[72] the chloro group in **355a** was substituted with acetate under phase transfer conditions, and subsequent basic hydrolysis provided alcohol **554** in excellent yield (82%, over 2 steps). Tosylation of **554** employing conditions developed during the synthesis of Himalensine A led to the formation of tosylate **355b**, however, in rather low yield.

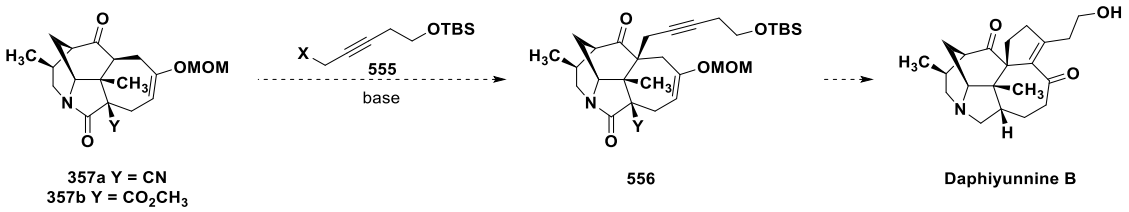


Scheme 2.70. *Synthesis of tetracycle* ***554.***

Coupling of tricycle **419** with allyl tosylate **355b** under the modified conditions provided enol ether **356b** in excellent yield. The subsequent one-pot Claisen rearrangement – RCM afforded tetracycle **357b** as a single isomer in 87% yield on a gram scale.

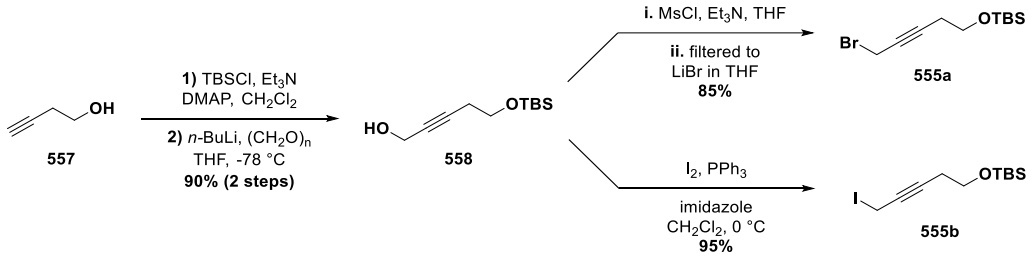
2.7.5 Introduction of the alkyne chain by ketone propargylation

The convenient position of the ketone group in compounds **357a-b** could be potentially used for a convergent introduction of the C-8 alkyne side chain through ketone propargylation (**Scheme 2.71**). Although ketones **357a-b** contains two α-hydrogens, deprotonation at position C-2 would lead to the formation of strained bridgehead double bond. On the other hand, enolisation of C-8 occurs spontaneously during the purification on silica, leading to partial epimerisation of compound **357a**, indicating that selective enolisation of ketones **357a-b** should not be problematic.



Scheme 2.71. *Introduction of the alkyne chain by ketone propargylation.*

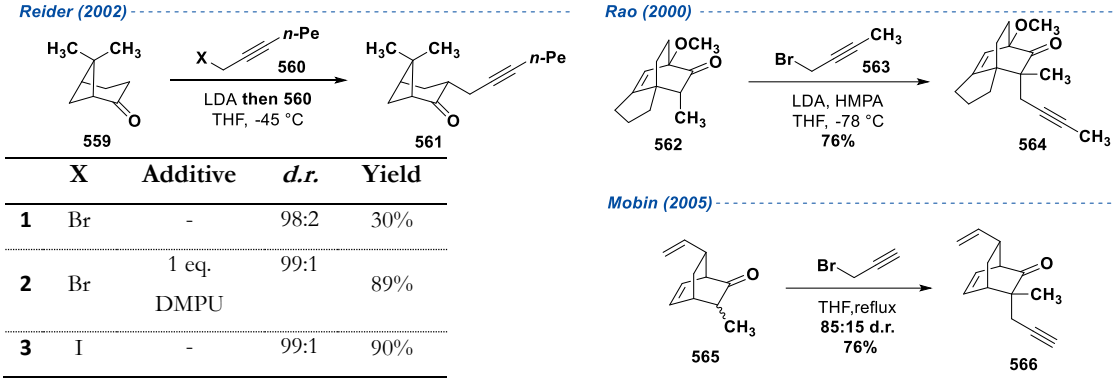
To test this approach, two propargylation reagents, bromide **555a** and iodide **555b,** were synthesised. Starting from but-3-yn-1-ol (**557**), the alcohol group was first protected as a silyl ether, and the terminal alkyne was converted to lithium acetylide by its treatment with *n*-BuLi. The reaction of this acetylide with paraformaldehyde provided propargylic alcohol **558** in excellent yield (90%, over 2 steps).[73] Activation of the primary alcohol in **558** by its mesylation, followed by substitution with LiBr, provided bromide **555a** in 85% yield.[74] Iodination of alcohol **558** using an Appel reaction afforded iodide **555b** in 95% yield.[75]



Scheme 2.72. *Synthesis of propargylation reagents* ***555a-b.***

Although the C-8 position in compounds **357a-b** is relatively hindered, a comprehensive literature search has identified a set of promising conditions for the propargylation of sterically hindered ketones (**Scheme 2.73**). In 2002, Reider *et al.* reported highly efficient propargylation of bicyclic ketone **559** (**Scheme 2.73, left**) using propargyl bromide and iodide **560** and LDA as a base.[76] Moreover, they demonstrated that the lower reactivity of propargyl bromide can be compensated by the addition of suitable additives, such a DMPU. During their synthetic studies towards modhephene, Rao *et al.* employed ketone propargylation as a key step for the formation of the quaternary carbon centre in intermediate **564** (**Scheme 2.73, top right**).[77] Once again, the use of an appropriate additive, in this case HMPA, proved necessary. The advantage of using LDA in combination with an additive for the ketone

propargylation becomes evident when considering the example of the propargylation of structurally similar ketone **565** (**Scheme 2.73, bottom left**), where the use of sodium hydride required increased temperature (reflux in THF) and longer reaction time (10 h).[78] As polar aprotic compounds, HMPA and DMPU coordinate the lithium cation and help to break up aggregates, their addition often leads to dramatic enhancements of the reaction rates, regio- or stereoselectivity. It is worth noting that due to HMPA's suspected carcinogenic properties, DMPU is often used as a safer alternative.

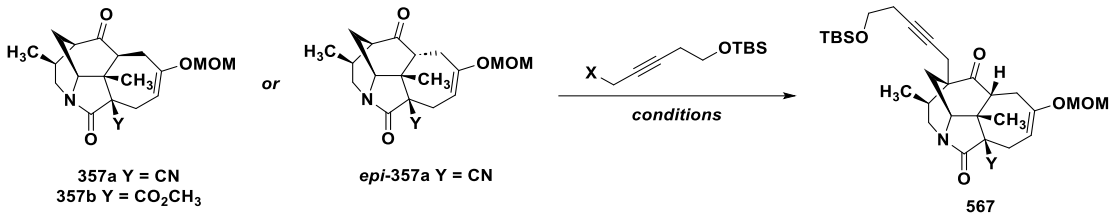


	X	Additive	*d.r.*	Yield
1	Br	-	98:2	30%
2	Br	1 eq. DMPU	99:1	89%
3	I	-	99:1	90%

Scheme 2.73. *Selected examples of propargylation of cyclic ketones.*

Inspired by these literature examples, we investigated the potential union of tetracyclic core **357** and alkyne side-chain **555a-b** through ketone propargylation. Our investigation began with the cyano group-bearing tetracycle ***epi*-357a**, as it was the only available substrate at this point. Treatment of ***epi*-357a** with a slight excess of LDA (1.1 eq.) at -78 °C followed by the addition of propargyl bromide **555b** did not lead to the formation of any product. The formation of new products was observed after warming the reaction to room temperature (**Table 2.6, entry 1**), and the product of propargylation was isolated in 42% yield. An almost identical result was obtained in a parallel reaction with DMPU as an additive (**entry 2**). The replacement of propargyl bromide **555a** with more reactive propargyl iodide **555b** led to a negligible increase in yield (**entry 3**). In all cases, the formation of propargylated product was accompanied by the decomposition of the starting material. A much cleaner outcome was observed when the reaction mixture was warmed up only to -30 °C after the initial deprotonation with LDA, and the product of propargylation was isolated in 67% yield (**entry 4**).

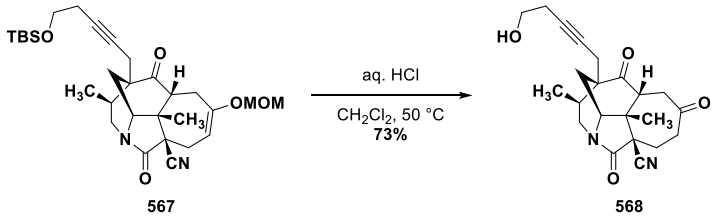
Table 2.6. *Screening of conditions for the introduction of the alkyne side chain.*



Entry	SM	X	Conditions	Observation	Yield
1	*epi*-357a	Br	LDA (1.1 eq.), RX (1.3 eq.), -78 °C to r.t., overnight	full conv. multiple prod.	42%[a]
2	*epi*-357a	Br	LDA (1.1 eq.), RX (1.3 eq.), DMPU (1.5 eq.) -78 °C to r.t., overnight	full conv. multiple prod.	45%[a]
3	*epi*-357a	I	LDA (1.1 eq.), RX (1.3 eq.), -78 °C to r.t., overnight	full conv. multiple prod.	48%[a]
4	*epi*-357a	**I**	**LDA (1.7 eq.), RX (1.8 eq.), -78 to -30 °C overnight**	**full conv. single prod.**	**67%[a]**
5	357a	I	LDA (1.2 eq.), RX (1.8 eq.), -78 to -30 °C overnight	decomp.	n.a.
6	357b	I	LDA (1.7 eq.), RX (1.8 eq.), -78 to -30 °C overnight	mixture of prod.	<39%[a,b]
7	357b	I	LDA (1.2 eq.), RX (1.3 eq.), DMPU (1.5 eq.) -78 to -30 °C overnight	decomp.	n.a.
8	357b	I	LDA (3.0 eq.), RX (3.2 eq.), -78 °C, 5 h	decomp.	n.a.

Reactions performed on 20 mg scale. [a] isolated yield, [b] mixture of inseparable propargylated products, formation of desired product not confirmed.

Although the incorporation of the propargyl chain was clearly visible in the NMR spectrum of the obtained product and the *O*-propargylation could be easily ruled out, the regioselectivity of this reaction couldn't be determined by the NMR due to the overlap of the key diagnostic signals.



Scheme 2.74. *Hydrolysis of enol ether* ***567****.*

To elaborate the propargylated product into a suitable substrate for the intended Conia-ene reaction, the enol ether moiety in **567** had to be hydrolysed to the ketone. Treatment of the enol ether **567** with aqueous HCl at 50 °C led to its fast (<20 min) hydrolysis accompanied by cleavage of the TBS group (**Scheme 2.74**). The highly crystalline character of the hydrolysed product **568** allowed for the preparation of a sample for single-crystal X-ray diffraction analysis. To our great surprise, the propargylation occurred with undesired regioselectivity, indicating that the unexpected bridgehead enolate must have been formed after the deprotonation of compound ***epi*-357a** (**Scheme 2.75**).

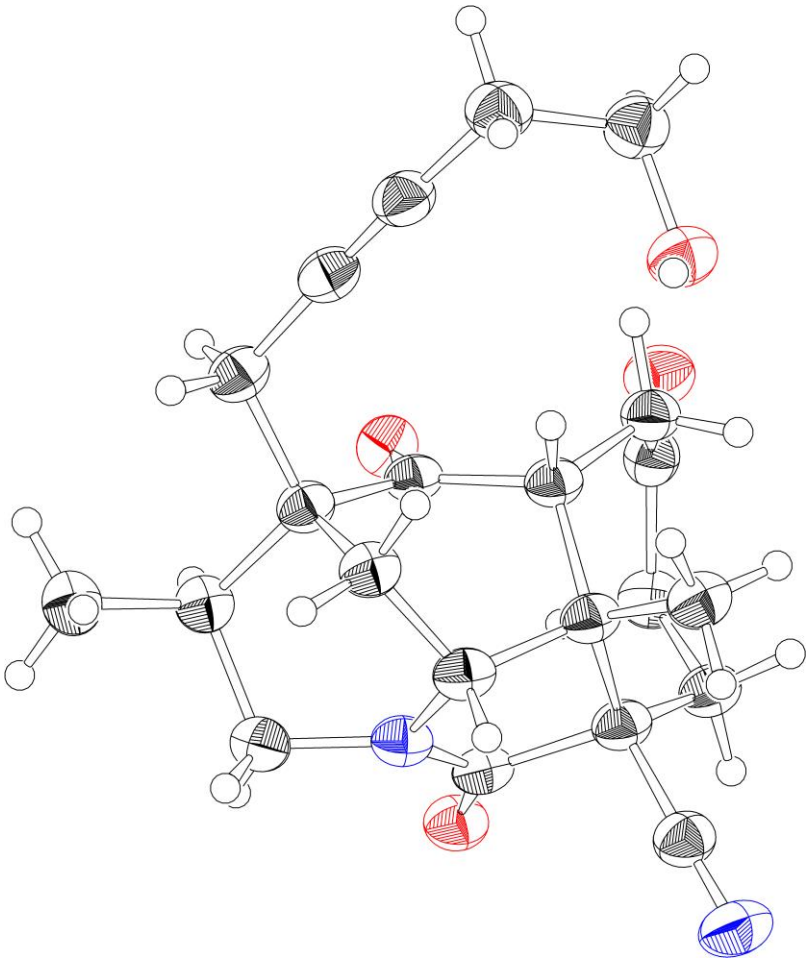


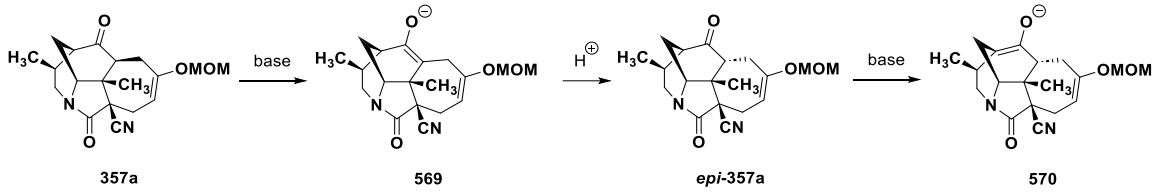
Figure 2.7. *ORTEP diagram of compound* ***568*** *with thermal ellipsoids drawn at 50% probability.*[iv]

Although the formation of the bridgehead enolate was unexpected, it does not violate Bredt's rule (the number of non-bridgehead atoms S in the bicyclic system should be S≥7). In fact, the formation of bridgehead enolates by deprotonation of carbonyl group-bearing bicyclo[3.3.1]nonane scaffolds has been previously reported.[79,80]

Previous work by Sam Ellis showed that the desired enolate can be obtained by deprotonation of compound **357a** (see also **Scheme 2.22** in **Chapter 2.3.2.2**). This was demonstrated by the quantitative epimerisation of compound **357a** to compound ***epi*-357a** by its deprotonation by KHMDS fallowed by aqueous work up, as well as the epimerisation step in the formal synthesis of *Daphniphyllum* alkaloids (**Scheme 2.34** in **Chapter 2.5.5**). Logically, the propargylation reaction was attempted with compound **357a**. Its deprotonation with LDA resulted in the formation of the desired enolate (compound ***epi*-357a** observed by TLC). However, the formation of propargylated product was not observed, and only decomposition of compound **357a** occurred after a prolonged time (**Table 2.6, entry 5**).

[iv] Figure 2.7 was generated using the Molby software.[48] In the representation, carbon atoms are depicted in black, oxygen in red, nitrogen in blue and hydrogen in white with a fixed diameter for clarity.

Finally, the propargylation of a substrate bearing the C-6 methyl ester group (compound **357b**) was examined. Under the previously optimised conditions, compound **357b** provided a mixture of inseparable products (<39%), and the formation of the desired isomer couldn't be confirmed (**entry 6**). Repeating the reaction with DMPU as an additive didn't lead to the formation of any product, and only the decomposition of starting material was observed (**entry 7**). Increasing the equivalents of the base and propargyl iodide **555b** while keeping the reaction at -78 °C was also not productive.



Scheme 2.75. *Enolisation of tetracyclic intermediates.*

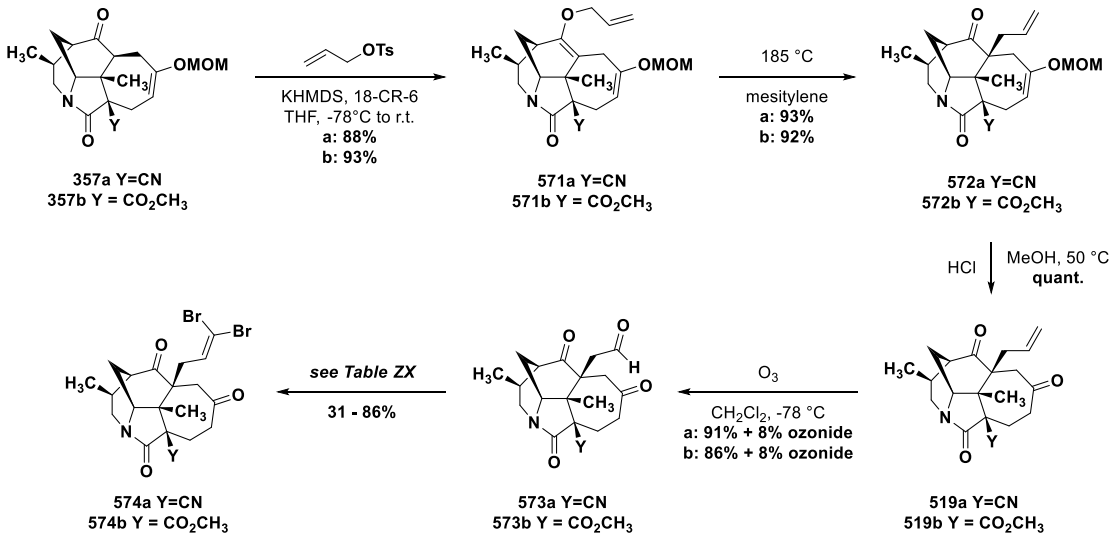
In summary, deprotonation of tetracycle **357a** led to the formation of the desired enolate **569** (**Scheme 2.75**). However, this enolate was not reactive in the propargylation reaction, likely due to the steric hindrance introduced by the pseudo-axial C-5 methyl group. Protonation of enolate **569** provided thermodynamically more stable bowl-shaped compound ***epi*-357a**, while its stirring for a prolonged time leads to its decomposition. After the epimerisation, deprotonation at C-2 position becomes more feasible, leading to the reactive bridgehead enolate **570,** undergoing propargylation at C-2.

Alternative methods for the selective introduction of the C-8 alkyne side chain are discussed in the following Chapter.

2.7.6 Introduction of the alkyne chain by Claisen rearrangement

During the preliminary studies towards *Daphniphyllum* alkaloids, Fillipo Sladojevich and Iacovos Michaelides demonstrated that the C-8 position can be conveniently allylated using *O*-allylation – Claisen rearrangement sequence (**Scheme 2.20**).[29a] Later, Sam Ellis applied this strategy to introduce the allyl group to the C-8 position of tetracycle **357a** (**Scheme 2.22**). We envisioned that the C-8 allyl group could be elaborated to the substituted alkyne, as demonstrated during the synthesis of model systems **523, 524 and 527** (**Scheme 2.66-67**).

As discussed above, the C-8 allyl group can be introduced by *O*-allylation – Claisen rearrangement sequence (**Scheme 2.77**). Treatment of tetracycle **357a** with KHMDS followed by the addition of 18-crown-6 and allyl tosylate provided enol ether **571a** in excellent yield (88%). Heating of this compound to 185 °C provided C-8 allylated product in 93% yield. In preparation for the oxidative cleavage of alkene to aldehyde by ozonolysis, the enol ether moiety in **572a** had to be hydrolysed, as this electron-rich alkene would be cleaved under these conditions. Heating of enol ether **572a** in methanol in the presence of acid led to fast and quantitative formation of ketone **519a**. Ozonolysis of the allyl group in **519a** led to the fast formation of the corresponding ozonide (not shown). Although ozonides can be conveniently reduced to aldehydes with triphenylphosphine, the relatively high polarity of the aldehyde **573a** made its separation from triphenylphosphine oxide challenging. Therefore, the less popular reduction method employing malodorous dimethylsulfide had to be used. Stirring of the initially formed ozonide with an excess of Me_2S led to its slow reduction providing aldehyde **573a** in 91% yield.

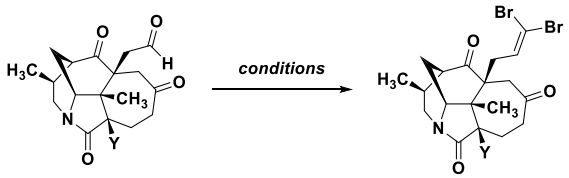


Scheme 2.77. *Synthesis of dibromoalkenes* ***574a-b****.*

The same synthetic sequence was used for the preparation of aldehyde **573b**. The presence of the methyl ester group at C-6 had minimal impact on the reactivity, and aldehyde **573b** was obtained in 71% overall yield, only 5% lower than aldehyde **573a**.

The conversion of aldehydes **573a-b** to dibromoalkenes **573a-b** proved to be challenging. Under standard Corey-Fuchs reaction conditions, bromination of the C-10 ketone group occurred, resulting in formation in the formation of compound **574a** as an inseparable mixture of products in 70% combined yield (**Table 2.7, entry 1**). During the synthesis of the model substrates, the use of the Wittig reaction proved to be higher yielding that the Corey-Fuchs reaction. The reaction of aldehyde **573a** with an excess of phosphonium ylide, generated by treatment of Wolkoff's reagent with KHMDS, led to the formation of the desired product; however, the addition of another portion of this reagent was needed to achieve full conversion (**entry 2**). Pleasingly, the dibromoalkene **574a** was obtained as a single product with 74% yield. To achieve the full conversion directly, without the need to generate additional phosphonium ylide *ex situ*, the amount of phosphonium ylide was increased (3.5 eq., **entry 3**). Additionally, the more commonly used base for this type of transformation, *t*-BuOK, was used instead of KHMDS. This modification led to fast (<5 min) and clean formation of the desired product and compound **574a** was isolated in slightly improved yield (86%). Encouraged by this result, the reaction was upscaled from 10 to 150 mg (**entry 4**). However, running the reaction for an extended time (1 h) proved to be problematic, as only inseparable products of bromination were obtained. This result was very surprising, especially

Table 2.7. *Conversion of aldehydes* ***573a-b*** *to dibromoalkene* ***574a-b****.*



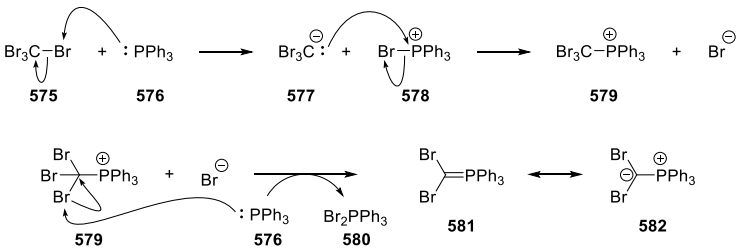
Entry	SM	Conditions	Observation	Yield[a]
1	573a	CBr_4 (4.0 eq.), PPh_3 (8.0 eq.), CH_2Cl_2, 0 °C to r.t., 24 h	4:1 mixture of products	70%[b]
2	573a	Br_2CPPh_3Br.MeCN (3.0 + 0.8 eq.), KHMDS (2.4 + 0.6 eq.) THF, r.t., 60 + 50 min	single prod.	74%[c]
3	573a	Br_2CPPh_3Br.MeCN (4.0 eq.), *t*-BuOK (3.5 eq.) THF, r.t., 5 min	single prod.	86%[c]
4	573a	Br_2CPPh_3Br.MeCN (3.0 eq.), *t*-BuOK (2.8 eq.), THF, r.t., 1 h	no desired prod.[d]	<70%[e]
5	573a	Br_2CPPh_3Br.MeCN (2.5 + 1.3 eq.), *t*-BuOK (2.0 + 1.0 eq.) THF, r.t., 40 + 5 min	single prod.	84%[b]
6	573a	Br_2CPPh_3Br.MeCN (3.2 eq.), *t*-BuOK (3.0 eq.) THF, r.t., 5 min	1:1 mixture of products	41% (+40%)[f]
7	573a	CBr_4 (5.0 eq.), PPh_3 (5.0 eq.), Zn (5.0 eq.) CH_2Cl_2, 0 °C to r.t., 2 h	single prod.	67%[b]
8	573b	CBr_4 (5.0 eq.), PPh_3 (5.0 eq.), Zn (10.0 eq.) CH_2Cl_2, 0 °C to r.t., 30 min[g]	single prod.	61%[h]
9	573b	CBr_4 (2.0 eq.), PPh_3 (2.0 eq.), Zn (4.0 eq.) CH_2Cl_2, 0 °C to r.t., 30 min[h]	single prod.	31%[i]

Reactions were performed in degassed solvent under inert atmosphere. [a] isolated yield, [b] reaction performed on 40 mg scale, [c] 10 mg scale, [d] mixture of α-brominated ketone and unidentified side product, [e] 150 mg scale, [f] 240 mg scale, [g] CBr_4 added by syringe pump, [h] 70 mg scale, [i] 500 mg scale.

considering the results from **entries 2** and **5**, where no side products of bromination were observed despite the relatively large excess of the ylide and longer reaction times.

To prevent the undesired bromination, the reaction was repeated with decreased loading of phosphonium ylide (2.0 eq., **entry 5**). After 5 minutes, aldehyde **573a** was the main constituent of the reaction mixture, and no change was observed after additional 35 minutes. The addition of 1.0 equivalent of phosphonium ylide at this point resulted in full conversion of the remaining starting material in under 5 minutes. Surprisingly, only the product **574a** was isolated in 84% yield, despite the final amount of phosphonium ylide being the same as in the failed experiment (**entry 4**). Finally, the conditions from **entry 5** were repeated on a bigger scale (240 mg, **entry 6**). Treatment of aldehyde **573a** with 3.0 equivalents of phosphonium ylide (the final loading of the ylide in **entry 5**) led to quick consumption of the starting material; however, the desired product was isolated in only 40% yield along with the product of bromination (41% yield).

Due to the low reproducibility of the Wittig reaction on a larger scale, alternative methods for the conversion of aldehyde **573a** to dibromo alkene **574a** were sought. In a typical Corey-Fuchs reaction, two equivalent of triphenylphosphine reacts with one equivalent of tetrabromomethane (**Scheme 2.78**). The first equivalent of triphenylphosphine attacks the bromine atom of tetrabromomethane, leading to intermediate **579**. The second equivalent of triphenylphosphine acts as a reducing agent and bromine scavenger, converting intermediate **579** to phosphonium ylide **581.** The formed dibromotriphenylphosporane **580** side product is known to be a strong electrophile as well as brominating agent, in our case, responsible for α-bromination of ketone group in compound **573a**.[60] To avoid the formation of this highly reactive side product, the second equivalent of triphenylphosphine can be replaced with zinc,[58] and inert zinc bromide is formed instead of **580**. Under these modified conditions, aldehyde **573a** was successfully converted to dibromoalkene **574a** in 67% yield without the formation of undesired side products (**entry 7**). These conditions were successfully applied for the preparation of methyl ester analogue **574b** (61%, **entry 8**). Unfortunately, the yield of the reaction dropped significantly during the upscaling (31%, **entry 9**), despite the fact that the formation of other products was not observed.

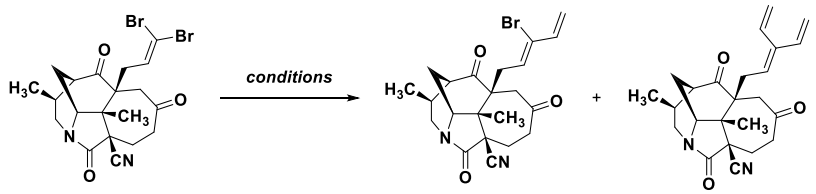


Scheme 2.78. *Mechanism of formation of ylide* ***582.***

Although the conversion of aldehydes **573a-b** to dibromoalkenes **574a-b** was not optimised, experiments from **Table 2.7** provided enough material for subsequent synthetic studies.

First, the conversion of dibromoalkene **574a** to vinyl bromide **518** was investigated (**Table 2.8**). Negishi coupling of compound **574a** with *in situ* generated vinyl zinc reagent under the conditions used for the preparation of the model system **523** was not selective enough and 1:2:1 mixture of mono- and disubstituted products together with starting material was obtained (**entry 1**).[61] Moreover, the substitution of bromine atom in **574a** with the vinyl group did not change the R_f of the products, making all three compounds inseparable. In an attempt to slow down the rate of the second substitution the loading of vinyl zinc reagent was decreased (2.0 eq., **entry 2**). However, only traces of product **518** were observed after 3 h. Relatively good selectivity (3.5:1, **entry 3**) was obtained with less reactive vinyl tributyltin reagent,[81] even though it was used in relatively big excess (1.7 eq.). Undoubtedly, by tuning these reaction conditions, such as changing the amount of organotin reagent and reaction time, even better selectivity could have been obtained. However, due to the inability to identify cyclisation conditions for the model substrate and more promising results with the enyne approach, the vinyl bromide strategy was abandoned.

Table 2.8. *Preparation of vinylbromide* ***518.***

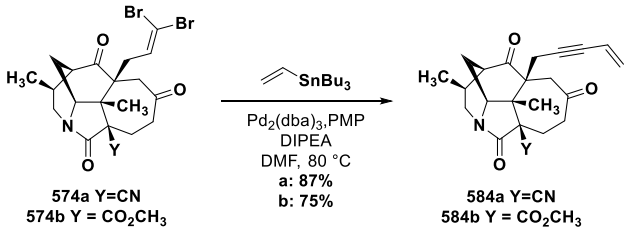


574a 518 583

Entry	Conditions	Observation	Yield[a]
1	vinyl magnesium bromide (3.0 eq.), $ZnCl_2$ (3.0 eq.) $Pd(PPh_3)_4$ (5 mol%), THF, 0 ° to r.t., 3 h[61]	1:2:1 mixture of **574a:518:583**[b]	69%[c]
2	vinyl magnesium bromide (2.0 eq.), $ZnCl_2$ (2.0 eq.) $Pd(PPh_3)_4$ (5 mol%), THF, 0 ° to r.t., 3 h	low conv. (<10%)[b]	n.d.
3	vinyl tributyltin (1.7 eq.), $Pd_2(dba)_3$ (5 mol%), $AsPh_3$ (40 mol%) THF, 50 °C, 17 h[81]	3.5:1 mixture of **518:583**[b]	n.d.

Reactions were performed in degassed solvent under inert atmosphere. [a] isolated yield, [b] determined by NMR of the crude reaction mixture, [c] combined yield.

The conversion of dibromoalkenes **574a-b** to enynes **584a-b** was more straightforward. Applying the same condition[62] as in the case of the model substrate **524** led to the formation of compounds **584a** and **584b** in 87% and 75% yield (**Scheme 2.79**).

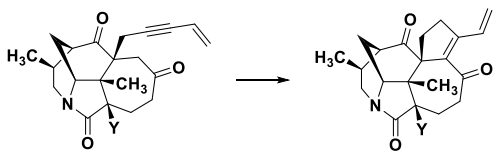


Scheme 2.79. *Preparation of enynes* ***584a-b.***

2.7.7 Conia-ene cyclisation

With access to cyclisation precursors **584a-b** the final C-C bond forming transformation was investigated (**Table 2.9**). Unfortunately, under the optimal conditions for cyclisation of the model system, no new product was formed, and the low yield of recovered starting material (18%) suggested that compound **584a** was decomposing during the reaction. The second-best conditions (**entry 2**) also led to decomposition of most of the starting material, while no formation of the desired product was observed. Cyclisation under Wasa's conditions was not successful either (**entry 3**). Replacement of the cyano group with ester group did not affect the reactivity and both Cu(I)-catalysed cyclisation failed to yield any product (**entries 4** and **5**). Finally, a set of NMR experiments with a common gold(I) catalysts and different bases was conducted (**entries 6 - 8**). However, formation of any product was not observed under any of the listed conditions.

Table 2.9. *Screening conditions for Conia-ene cyclisation.*

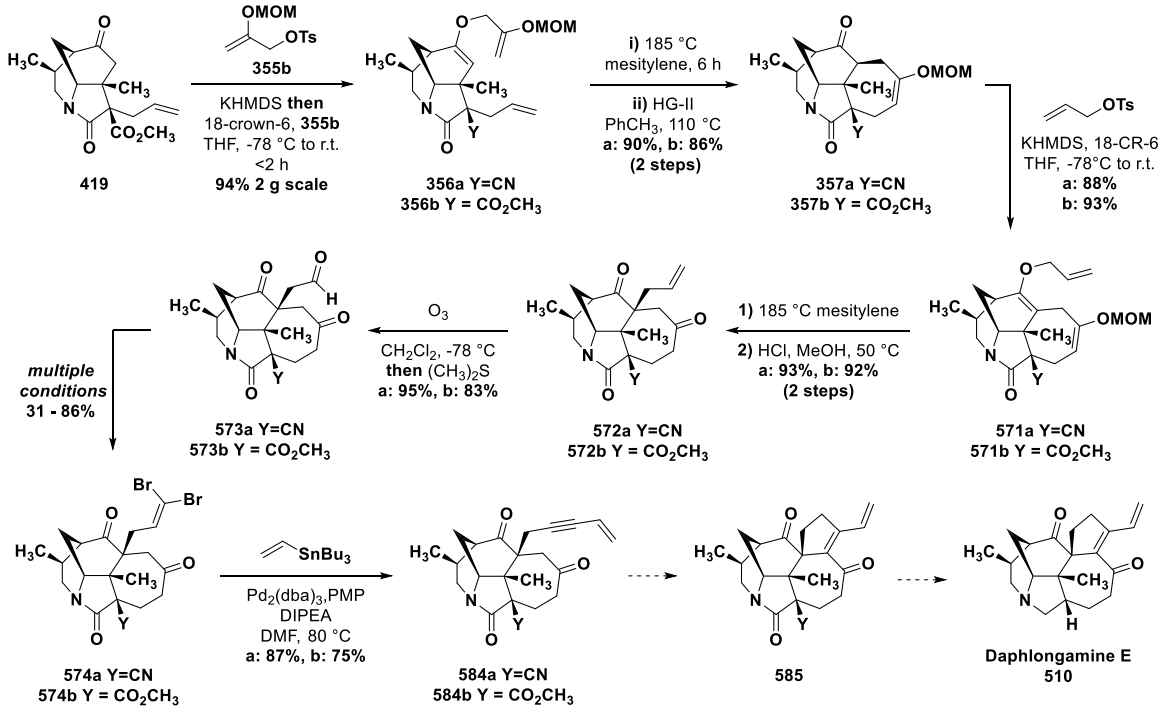


Entry	Substrate	Conditions	Observation
1	584a	$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%) THF, 80 °C, 16 h[32a]	no reaction 18% rec. SM
2	584a	$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%)[67] PS-BEMP (10 mol%), MeOH, 65 °C, 24 h	no reaction 33% rec. SM
3	584a	ZnI_2 (10 mol%), $(F_5C_6)_3B$ (10 mol%), Et_3N (20 mol%), CH_2Cl_2, 40 °C[66]	no reaction 90% rec. SM
4	584b	$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%) THF, 80 °C, 16 h[32a]	no reaction
5	584b	$Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%), pyrrolidine (20 mol%)[67] PS-BEMP (10 mol%), MeOH, 65 °C, 16 h	no reaction
6	584b	$Au(PPh_3)Cl$ (20 mol%), $AgSbF_6$ (20 mol%), pyrrolidine (30 mol%) $CDCl_3$, 45 °C, 24 h	no reaction
7	584b	$[Au(PPh_3)_3O]BF_4$ (10 mol%), pyrrolidine (30 mol%) DIPA (20 mol%), $CDCl_3$, 45 °C, 24 h	no reaction
8	584b	$[Au(PPh_3)_3O]BF_4$ (10 mol%), pyrrolidine (30 mol%) Cy_2NH (20 mol%), $CDCl_3$, 45 °C, 24 h	no reaction

Further screening of the reaction conditions was hindered by the limited amount of substrates, mainly due to the problematic Corey-Fuchs reaction.

2.7.8 Summary of the synthetic studies towards Daphniyunnine B and Daphlongamine E

In Chapter 2.7, a synthesis of Daphniyunnine B and Daphlongamine E *via* 5-endo-dig cyclisation (catalytic Conia-ene reaction) was investigated. After the feasibility of this approach was confirmed using the model system, tricyclic intermediate **419** was converted into enynes **548a-b** (**Scheme 2.80**). Similarly to previous chapters, the D-ring was constructed by highly convergent *O*-allylation – Claisen rearrangement – ring-closing metathesis sequence. The steric hindrance did not allow direct propargylation of ketone **357** at the C-8 position. Therefore, an indirect and longer synthetic sequence *via* second ketone *O*-allylation and Claisen rearrangement had to be used. Subsequent transformation of the C-8 allyl group to enyne was achieved in 3 steps, employing Corey-Fuchs reaction as a key step. With access to enynes **584a-b,** the final 5-endo-dig cyclisation was attempted. Unfortunately, the conditions successfully used for the cyclisation of the model substrate were not fruitful, and deeper exploration of this transformation was hindered due to the limited access to the cyclisation substrates caused by the challenging synthesis of key intermediates **574a-b**.



Scheme 2.80. *Summary of Chapter 2.7.*

2.8 References for Chapter 2

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Chapter 3: Synthetic studies towards clavine alkaloids

The research presented in this chapter represents a collaborative effort that took place during Daniel Cox's Part II and 1st SBM CDT rotation. His results have been incorporated herein for completeness.

3.1 Brief history of ergot alkaloids

Ergot alkaloids are a group of more than 90 natural products isolated from the ergot fungi families *Clavicipitaceae* and *Trichocomaceae.*[1] These fungi infect cereal grains, causing ergot, the dark brown horn-shaped pegs (**Picture 3.1**). From a biological viewpoint, these compact structures are sclerotia, the form in which the fungus passes the winter.[2] Ergot fungi are the oldest known producers of mycotoxins, and the consumption of ergot-contaminated rye and wheat led to severe mass poisoning during the Middle Ages in Central Europe.[3] Long-term ergot poisoning leads to a condition called "ergotism" with symptoms that can be divided into two categories: convulsive (hallucinations, convulsions, psychosis and fever) and gangrenous (gangrene of the feet, legs, hands and arms).[1-2, 4]

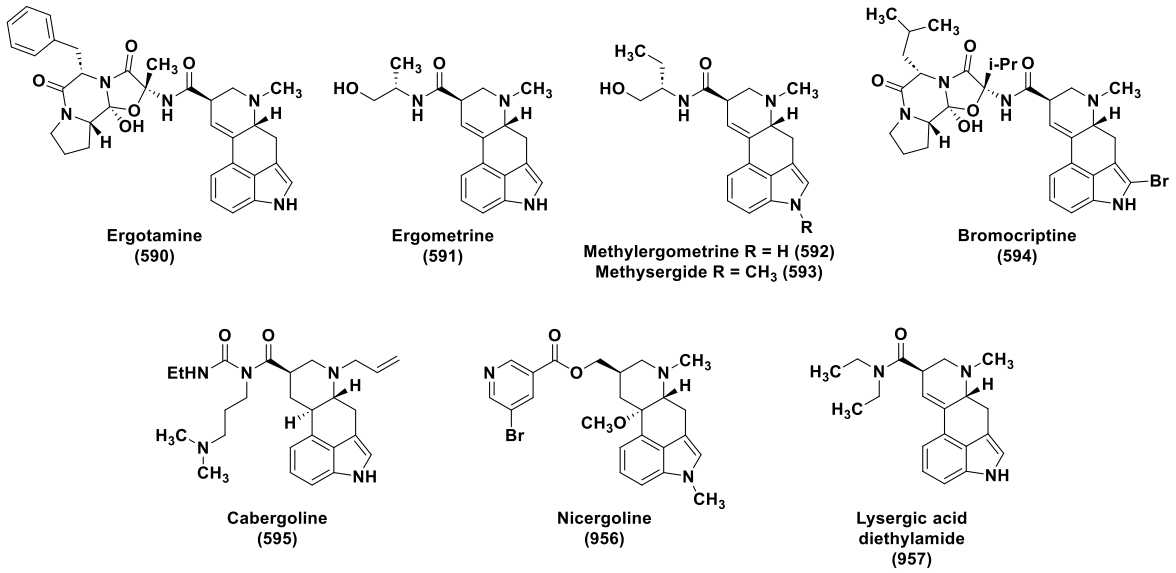


Picture 3.1. *Claviceps purpurea fungal sclerotium growing on barley.*[5]

Despite these adverse effects, ergot alkaloids have found application in the field of medicine. For instance, the use of powdered ergot by midwives to accelerate labour and prevent uterine haemorrhage was documented by Adam Lonicer in his "Kreuterbuch" (herbal) from 1582.[2-3] At the turn of the 18th and 19th centuries, a powdered preparation of ergot, known as "*pulvis ad partum"* or "the powder of birth" came into widespread use. The alkaloids involved in this preparation induced powerful uterine

contractions. However, due to the variable composition and low stability of the early ergot-based remedies, which often lost their activity within 2-3 months, they did not find lasting clinical application.[3]

The true pharmacological potential of ergot alkaloids was unlocked only in the first half of the 20th century. In 1918, Stoll at Sandoz in Basel isolated pure Ergotamine (**590**) from ergot (**Scheme 3.1**)[6] and fully determined its structure in 1951.[7] Due to its vasoconstriction properties, Ergotamine was marketed in 1921 for the treatment of acute migraines and cluster headaches. Additionally, Ergotamine induces uterine contractions and has been used for the treatment of post-partum haemorrhage, a childbirth complication responsible for 25% of maternal deaths.[4b]



Scheme 3.1. *Selected ergot alkaloids and ergot-based drugs.*

Another significant breakthrough in the pharmacological research of ergot alkaloids came in 1935, when Dudley, a member of Dale's research team, isolated "the substance responsible for traditional clinical effect of ergot" and named it Ergometrine (**591**).[8] Remarkably, this discovery come more than 30 years after Dale embarked on his mission to solve the "ergot problem".[9, i] The relatively simple structure of Ergometrine was determined the same year by Jacobs and Craig.[11, ii]

Ergometrine and its synthetic derivative, Methylergometrine (**592**), exhibit pronounced uterotonic effects and are therefore utilised in the treatment of post-partum haemorrhage. The introduction of Ergometrine into clinical practice significantly contributed to the decrease in maternal mortality rates in more developed counties.[12]

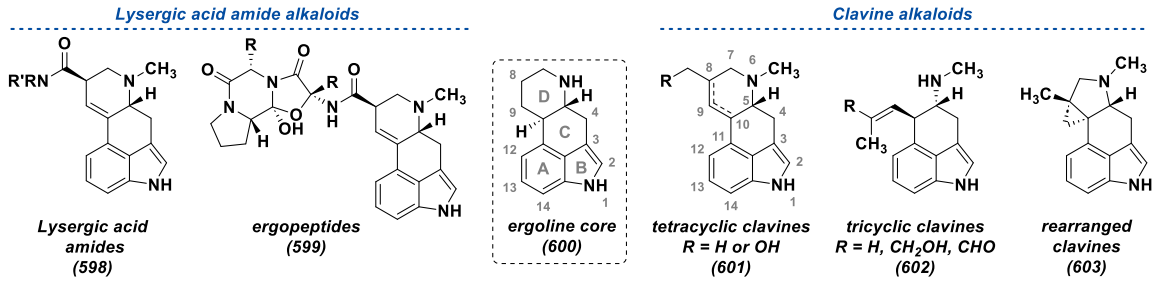
Further research in this field led to the development of multiple ergot-based therapeutics, including Bromocriptine (**594**) (treatment of pituitary tumours, Parkinson's disease, type 2 diabetes), Cabergoline

[i] During his work on *Ergot* alkaloid, Dale discovered and analysed the action of the neurotransmitter acetylcholine. In 1936, he and O. Loewi received the Nobel Prize in Physiology or Medicine "for their discoveries relating to chemical transmission of nerve impulses".[10]
[ii] The exact structure of Lysergic acid was not known at this point.

(**595**) (early-stage Parkinson's disease, hyperprolactinemia, suppress lactation), Methysergide (**593**) (chronic cluster headaches) or Nicergoline (**956**) (treatment of dementia, vascular disease and balance disorder).[4b] Last but not least, Hofmann's attempt to prepare an ergot-based analogue of the potent analeptic agent nikethamide (nicotinic acid diethylamide) led to the discovery of extremely potent hallucinogen – lysergic acid diethylamide (**957**) (LSD).[13]

3.2 Structure of ergot alkaloids

The main structural element shared amongst most ergot alkaloids is the tetracyclic ergoline core (**600**). Based on the substitution pattern of this core, ergot alkaloids can be divided into two main groups (**Scheme 3.2**). The first group comprises derivatives of lysergic acid – lysergic acid amides and ergopeptides (**Scheme 3.2, right**). The second group, known as clavine alkaloids (**Scheme 3.2, right**), covers all other tetracyclic, rearranged and uncyclized alkaloids.[2]

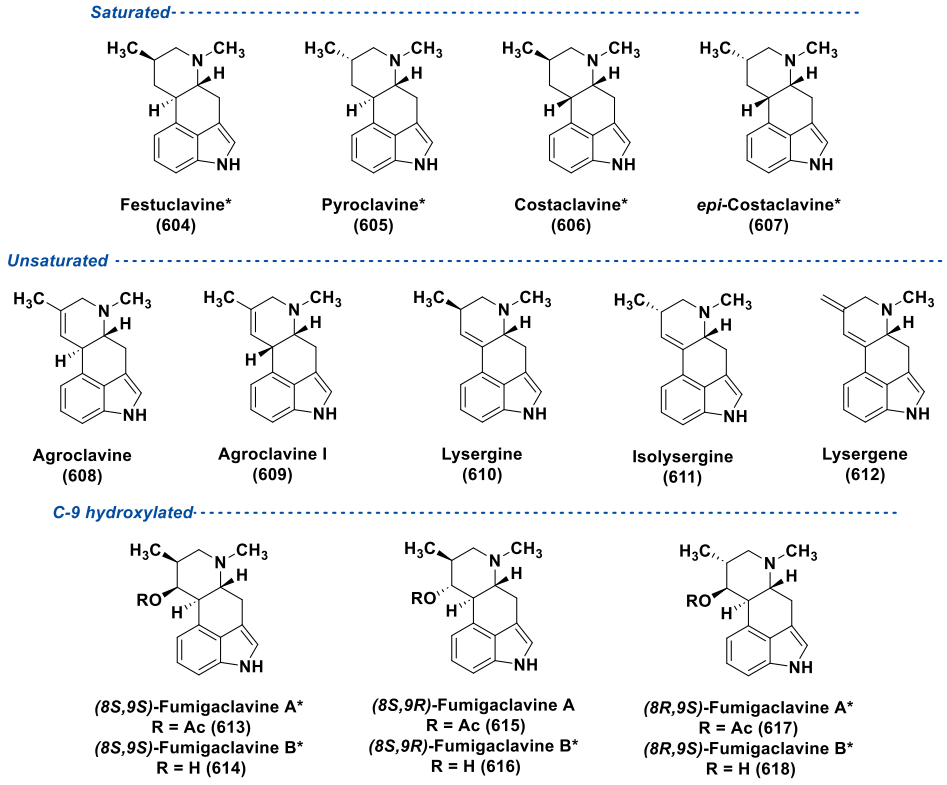


Scheme 3.2. *Overview of ergot alkaloids.*

The tetracyclic clavine alkaloids bear a methyl or a hydroxymethyl methyl group at position C-8, a 6-*N*-methyl group, and might contain either a fully saturated D-ring or a double bond between C-8 and C-9 or C-9 and C-10. Additionally, the D-ring can be hydroxylated at the C-8 or C-9 position, and the indole ring prenylated at the C-2 position (bearing 3,3-dimethylprop-1-ene-1-yl group). Typically, the C/D-ring fusion is trans; however, several natural products containing *cis*-junction were reported. In derivatives of the Lysergic acid, the C-8-(hydroxy)methyl group is replaced with an amide group, and the D-ring contains a double bond between C-8 and C-9. All ergot alkaloids have an *R* configuration of the C-5 stereogenic centre.

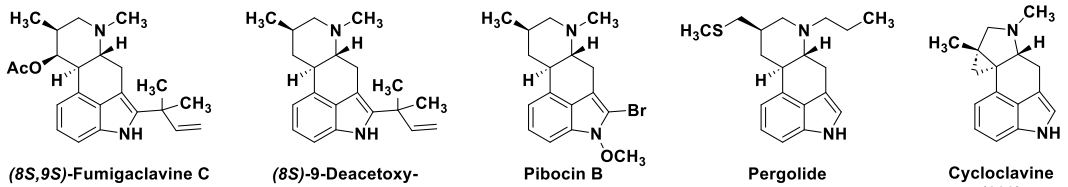
Several examples of tetracyclic clavine alkaloids, most relevant to this work, are shown in **Scheme 3.3.** A comprehensive list of all clavine alkaloids isolated to date can be found in a recent review by Liu and Jia.[1] These examples include Festuclavine (**604**), Pyroclavine (**605**), Costaclavine (**606**) and *epi*-Costalavine (**607**), representing all possible diastereomers of (5R)-6,8-dimethylergoline. Additionally, their prenylated analogues (bearing 3,3-dimethylprop-1-ene-1-yl group at C-2) were also reported (**Scheme 3.3, top**). Similarly, Agroclavine (**608**), Agroclavine I (**609**), Lesergine (**610**) and Isolysergine (**611**) represent isomers of clavine alkaloids bearing one C=C bond in the D-ring (**Scheme 3.3, middle**). Lastly, clavine alkaloids with hydroxy and acetoxy groups at C-9 were named Fumigaclavines (**Scheme 3.3, bottom**). Previously, both (*8R,9S*) and (*8S,9S*) diastereomers were assigned the same name,

Fumigaclavine A (R = Ac) and Fumigaclavine B (R = H), while the (*8S,9R*) diastereomers were named Isofumigaclavines A (R = Ac) and B (R = H) or Roquefortines A and B. The (*8R,9R*) diastereomers of Fumigaclavines A and B have not been reported yet, even though their biosynthesis is theoretically possible. To prevent potential confusion, the nomenclature proposed by Li[14] is adopted in this text – the names Fumigaclavine A and B will be applied to all four possible diastereomers and the configuration of the C-8 and C-9 stereogenic centres will be described by prefixes *R* and *S*. Similarly, as in the case of saturated clavine alkaloids (**604** - **607**) prenylated analogues of some Fumigaclavines have been reported (marked with * in the **Scheme 3.3**) and named Fumigaclavines C (R = Ac) and D (R = H).[1]



Scheme 3.3. *Selected tetracyclic clavine alkaloids.*

It is worth noting that the therapeutic potential of clavine alkaloids has been less explored than that of lysergic acid derivatives. This can be attributed, in part, to the absence of the C-8 amide group, a readily modifiable pharmacophore responsible for the binding of lysergic acid derivatives to specific CNS receptors. Consequently, the preparation of clavine analogues for structure-activity relationship (SAR) studies is more challenging. Nevertheless, several clavine alkaloids have exhibited promising anti-cancer activities.



Scheme 3.4. *Selected bioactive clavine alkaloids and their derivatives.*

For instance, Fumigaclavine C (**619**) (**Scheme 3.4**) has demonstrated cytotoxic effects in both mouse leukaemia P388 and human MCF-7 breast cancer cell lines. Its derivative, 9-deacetoxyfumigaclavine C (**620**), has exhibited selective cytotoxicity against the human leukaemia cell line K562, with an IC_{50} of 3.1 μM. Pibosin B (**621**) has shown cytotoxic activity in mouse Ehrlich carcinoma cells, with an ED_{50} of 25 μg mL^{-1}, while Agroclavine (**608**) has displayed cytotoxic effects against a mouse lymphoma cell line L5178y. Pergolide (**622**), a semi-synthetic clavine alkaloid developed by Eli Lilly, is currently available on the market for the treatment of early-onset Parkinson's disease. Furthermore, Cycloclavine (**623**) and its derivatives have recently emerged as potential candidates for use as insecticides.

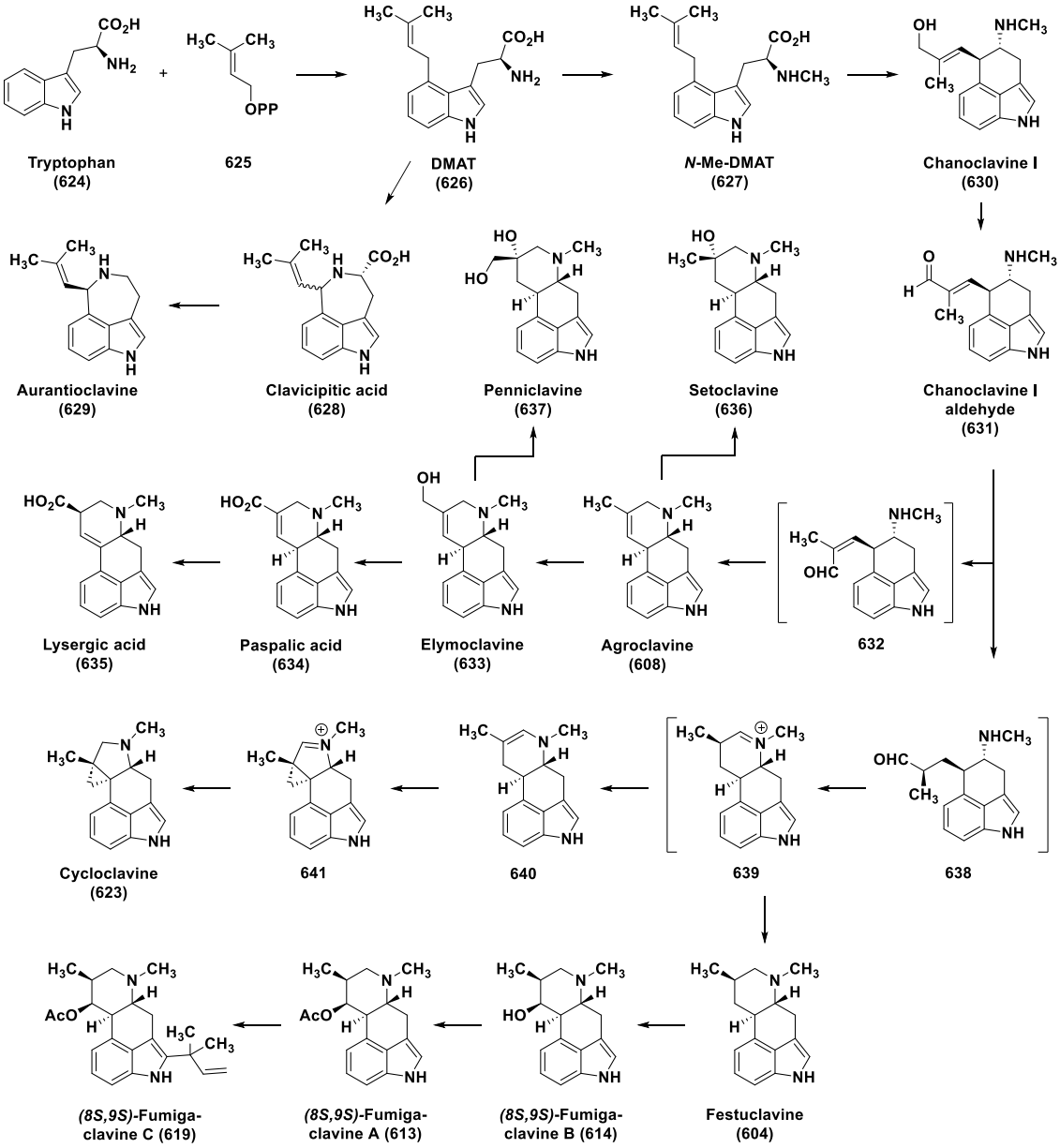
3.3 Biosynthesis of ergot alkaloids

As suggested by the presence of the indole ring, ergot alkaloids are biosynthesised from the amino acid tryptophan (**Scheme 3.5**). In the first step, tryptophan is prenylated with dimethylallyl pyrophosphate (**625**) to provide 4-dimethylallyltryptophan (**626**) (4-DMAT), which is then *N*-methylated by *S*-adenosylmethionine to afford *N*-methyl-DMAT (**627**). Alternatively, 4-DMAT can undergo cyclisation to form Clavicipitic acid (**628**) *via* benzylic oxidation followed by intramolecular addition of amino group. Decarboxylation of *trans*-Clavicipitic acid provides Aurantioclavine (**629**).[4b]

In the next step, *N*-methyl-DMAT (**627**) is converted into Chanoclavine-I (**630**) through a series of oxidation, decarboxylation, and cyclisation reactions. Oxidation of Chanoclavine-I (**630**) provides Chanoclavine-I aldehyde (**631**). Enzymatic isomerisation of the enal moiety in **631** affords intermediate **632,** which upon spontaneous cyclisation followed by reduction of the iminium ion provides Agroclavine (**608**). Subsequent hydroxylation of the C-8 methyl group yields Elymoclavine (**633**), which, through further oxidation and double bond migration, provides Paspalic and Lysergic acids (**634** and **635**), respectively. Alternatively, C-8 oxidation of Agroclavine (**608**) and Elymoclavine (**633**) could provide Setoclavine (**636**) and Penniclavine (**637**), respectively.[4b]

The reduction of the enal moiety in Chanoclavine-I aldehyde (**631**) generates aldehyde **638**, which spontaneously cyclises to iminium ion **639**. This intermediate can be subsequently reduced to Festuclavine (**604**) or undergo deprotonation to form enamine **640**. Subsequent transformation of intermediate **640** to iminium ion **641** (*via* unknown mechanism) followed by its reduction affords

Cycloclavine (**623**). Finally, C-9 hydroxylation of Festuclavine (**604**) followed by acetylation and prenylation gives rise to Fumigaclavines A-C (**614, 613** and **619**).[4b]



Scheme 3.5. *Biosynthesis of selected prostaglandins.*

3.4 Selected syntheses of ergot alkaloids

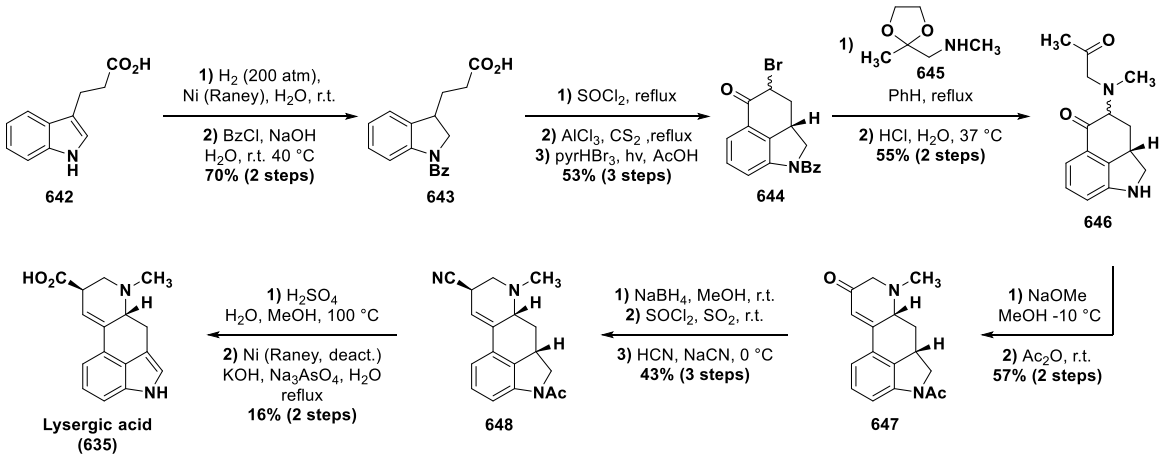
While all the fully saturated and unsaturated clavine alkaloids shown in **Scheme 3.3** have previously been prepared by total synthesis or semisynthesis from Lysergic acid, the records of successful preparation of Fumigaclavines, the primary focus of this study, are much scarcer. In fact, to this day, no semi- synthesis and only two total syntheses of racemic (*8S,9R*)-Fumigaclavine B (**616**)[15] and (*8R,9S*)-Fumigaclavine B (**618**) have been reported.[16] The interesting biological activity of (*8S,9S*)-Fumigaclavine C (**619**), makes this class of natural products as attractive target for total synthesis.

In the case of Lysergic acid (**635**), the situation is dramatically different. To this day, more than 20 syntheses have been reported.[17] However, considering the relative complexity of Lysergic acid and the fact that it is produced on an industrial scale in multi-ton quantities (10 – 15 t/year[iii]) through either fermentation or large field cultivation,[4b, 18] these syntheses serve more as synthetic exercise rather than a viable source of this alkaloid.[iv]

This sub-chapter presents several selected syntheses of Lysergic acid (**635**) and (*8S,9R*)-Fumigaclavine B (**616**).

3.4.1 Woodward's synthesis of *(±)*-Lysergic acid

The first total synthesis of Lysergic acid was reported by R. B. Woodward[v] *et al.* in 1954 (**Scheme 3.6**).[20] Woodward based his strategy on simplifying Lysergic acid to enone **647**, which could be efficiently disconnected through an aldol condensation, ketone α-substitution and intramolecular Friedel-Crafts acylation to simple building blocks **642** and **645**.



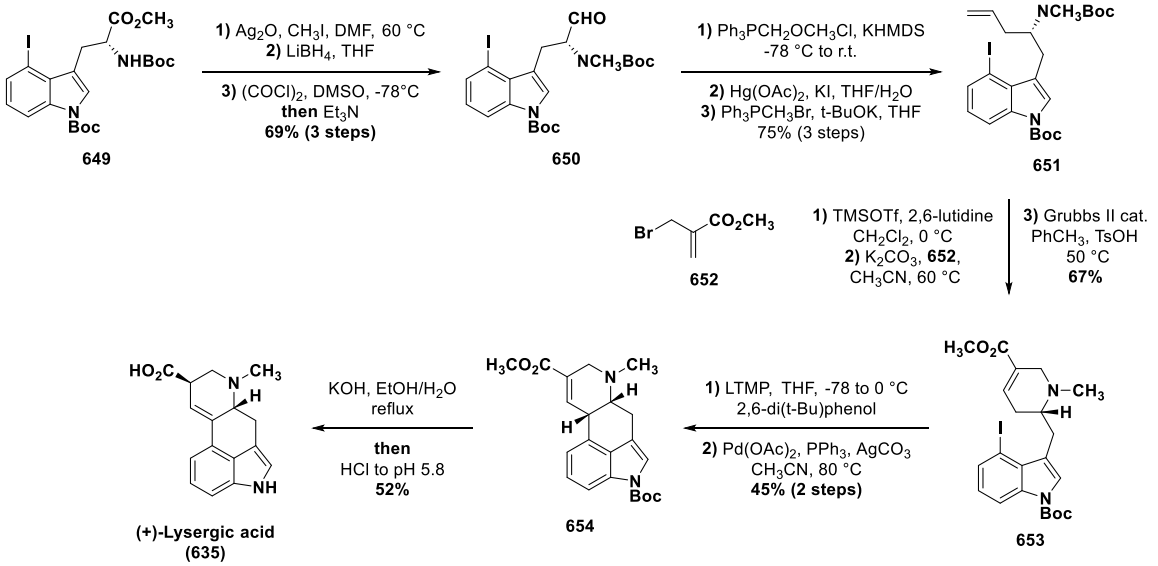
Scheme 3.6. *Woodward's total synthesis of (±)-Lysergic acid.*

[iii] Estimated number appearing in the literature from 2006.
[iv] The only potential exception might be Wipf's 2022 synthesis of *(±)-Lysergic acid (Chapter 3.4.3).*
[v] Robert B. Woodward received the 1965 Nobel Prize in Chemistry "for his outstanding achievements in the art of organic synthesis".[19]

To achieve the required selectivity in the intramolecular Friedel-Crafts acylation, the pyrrole ring in starting material **642** was saturated and its nitrogen atom protected (**642** → **643**). Treatment of **643** with thionyl chloride yielded the corresponding acyl chloride, which, upon refluxing with $AlCl_3$, furnished the tricyclic ketone in 77% yield. To introduce the future piperidine nitrogen atom, this ketone was subjected to α-bromination under photochemical conditions with pyridine hydrobromide perbromide. The bromide atom in **644** was subsequently substituted with amine **645**. Hydrolysis of the acetal and benzoyl groups afforded compound **646**, which, upon treatment with sodium methoxide, underwent an intramolecular aldol condensation, accomplishing the synthesis of the tetracyclic core. The C-8 carboxyl group of Lysergic acid was introduced in 4 steps. After the protection of the pyrrolidine nitrogen, the ketone moiety in **647** was reduced to the corresponding allylic alcohol, which was then chlorinated with thionyl chloride and subsequently substituted by sodium cyanide (**647** → **648**). The introduction of the carboxyl group was accomplished by hydrolysis of the nitrile group in intermediate **648**, which also cleaved the acetyl group. Dehydrogenation of the resulting intermediate with deactivated Raney nickel yielded *(±)*-Lysergic acid (**635**).

3.4.2 Jia's syntheses of *(+)-Lysergic acid*

In their 2011 synthesis of *(+)*-Lysergic acid, Jia *et al.* decided to utilise the conveniently placed double bond in the D-ring as a synthetic handle for the introduction of both C-ring and D-rings (**Scheme 3.7**) .[21] First, the C-ring in intermediate **654** was conveniently disconnected by an intramolecular Heck coupling reaction and double bond migration to intermediate **653**. Compound **653** could be accessed by ring-closing metathesis following amine allylation of amine **651**, which was available in several steps from protected *(R)*-4-iodotryptophan **649.**[vi]

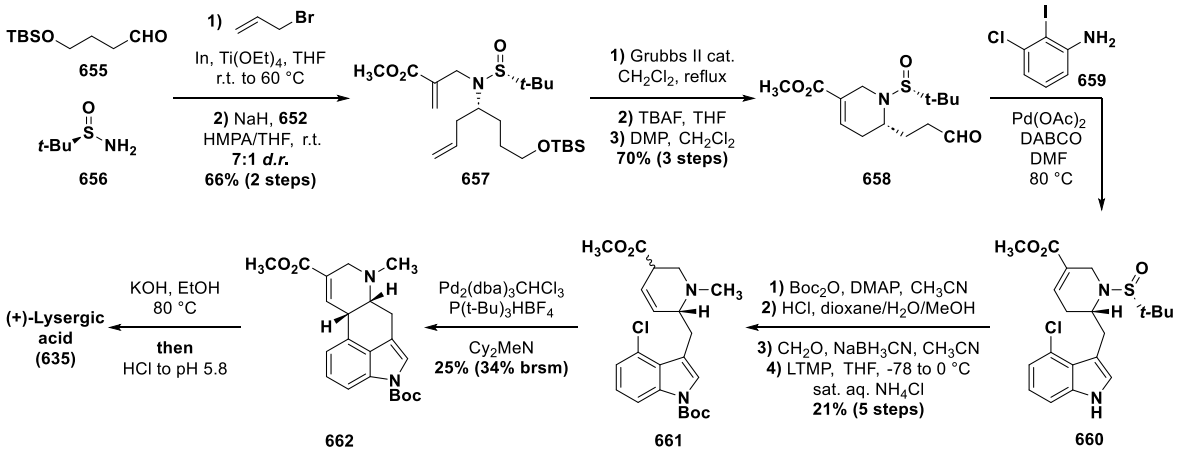


Scheme 3.7. *Jia's 2011 synthesis of (+)-Lysergic acid.*

[vi] Although not specified in the original paper, the starting material **649** can be obtained in 8 steps.

4-Iodotryptophan **649** was first methylated and then transformed to aldehyde **650**. A one-carbon aldehyde homologation *via* a Wittig reaction – hydrolysis sequence, followed by another Wittig reaction converted aldehyde **650** into allyl-group-bearing intermediate **651**. Selective Boc-group cleavage and allylation of the obtained amine with compound **652** yielded the corresponding diene, which upon treatment with Grubbs II catalyst furnished tricyclic intermediate **653**. To convert compound **653** to a suitable substrate for an intramolecular Heck reaction, the double bond in **653** was migrated out of conjugation with the ester group. This was accomplished by its deprotonation with LTMP followed by regioselective reprotonation with 2,6-di(t-butyl)phenol (84% yield). Subsequent Heck reaction resulted in formation of tetracyclic intermediate **654**. Finally, hydrolysis of the methyl ester and Boc groups under basic conditions completed the synthesis of *(+)*-Lysergic acid (**635**).

In 2013, Jia *et al.* presented a second-generation synthesis of *(+)*-Lysergic acid (**Scheme 3.8**).[22] They envisioned that intermediate **653** could be obtained in a more convergent fashion by altering the step order of their previous strategy. They decided first to form the D-ring and then introduce the indole ring. The closure of the C-ring using the previously described intramolecular Heck reaction would then provide Lysergic acid in a significantly lowered step count.



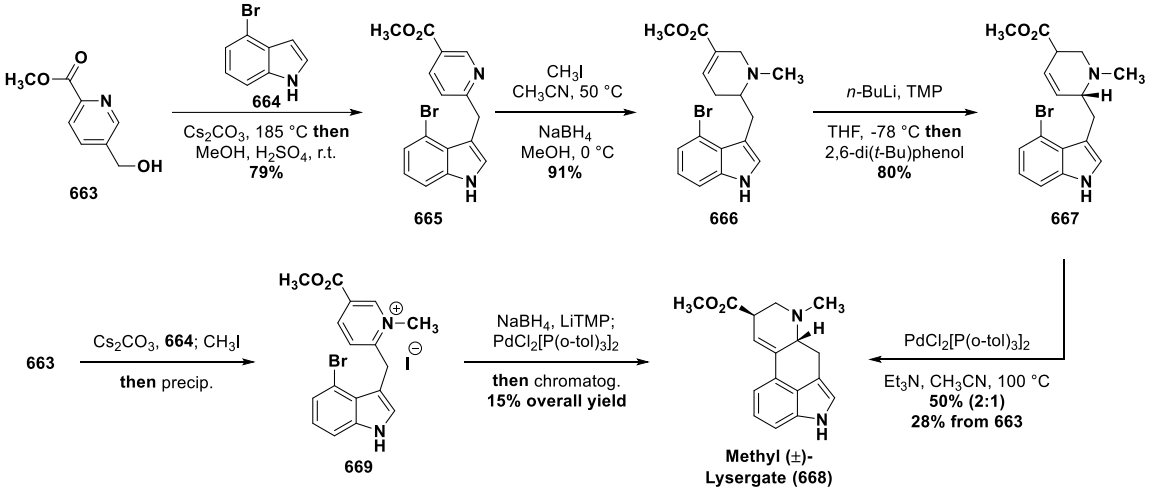
Scheme 3.8. *Jia's 2013 synthesis of (+)-Lysergic acid.*

The synthesis of the D-ring started with a one-pot condensation of aldehyde **655** with Ellman's sulfinamide **656**, followed by the addition of *in situ* generated allyl indium reagent. Allylation of the resulting amine with allyl bromide **652** afforded compound **657** in 66% yield over 2 steps. Treatment of intermediate **657** with Grubbs II catalyst led to the formation of the D-ring in 90% yield. Subsequent deprotection of the primary alcohol and its oxidation with DMP provided aldehyde **658**. The indole ring was then constructed *via* palladium-catalysed coupling reaction between aldehyde **658** and 3-chloro-2-iodoaniline (**659**). The resulting intermediate **660** was converted to Heck cyclisation substrate in 4 steps: first, the indole ring was protected with the Boc group (39% from **658**), followed by cleavage of the Ellman's auxiliary and methylation of the released amine. The preparation of compound **661** was finalised by a double bond migration. With intermediate **661** in hand, the stage was set for the final intramolecular Heck reaction. However, this reaction proved challenging due to the low reactivity of the chloro group,

and the cyclised product could be obtained in only 25% yield (34% brsm). The introduction of the better-leaving group was not possible due to its incompatibility with the indole-forming reaction (**658** → **660**). Hydrolysis under the previously described conditions yielded *(+)*-Lysergic acid (**635**). The synthesis of the indole ring through the coupling of aldehyde and aniline **659** would become a key step in our synthetic studies.

3.4.3 Wipf's synthesis of methyl (±)-Lysergate acid

Probably the most impressive achievement is the 4-step synthesis of methyl *(±)*-Lysergate acid reported by Wipf *et al.* (**Scheme 3.9**).[23] In a manner similar to Jia's approach, Wipf and co-workers constructed the C-ring *via* intramolecular Heck reaction. However, to avoid lengthy construction of the D-ring, they initiated their synthesis from pyridine **663**, already containing all the necessary functional groups.



Scheme 3.9. *Wipf's total synthesis of (±)-Lysergic acid.*

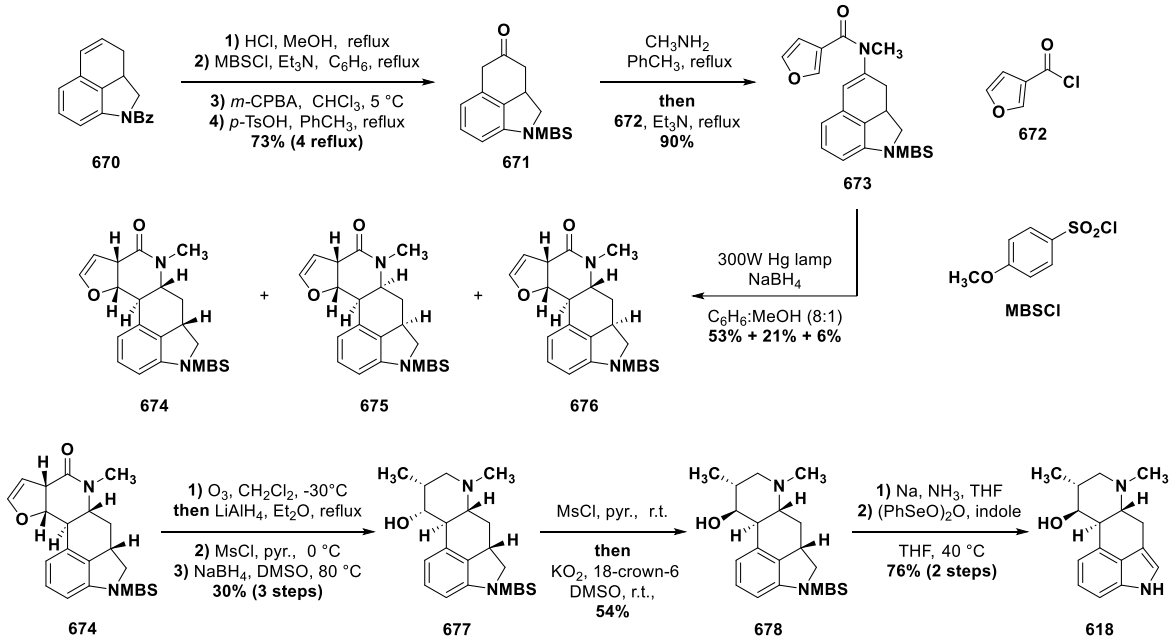
Heating of pyridine **663** and indole **664** in the presence of caesium carbonate provided intermediate **665** through a formal alcohol substitution. Wipf's mechanistic studies revealed that this reaction is catalysed by oxygen and proposed a mechanism in which the pyridine **663** is first oxidised to the corresponding aldehyde, which then condenses with indole **664**. Subsequent hydride transfer from another molecule of alcohol **663** to the condensation product yields compound **665**, with another molecule of aldehyde entering the catalytic cycle. Methylation of the pyridine ring in **665**, followed by the reduction of the resulting pyridinium salt **669** in the same pot provided alkene **666** in 91%. Double bond migration in **666**, followed by Heck reaction, afforded methyl Lysergate **668** in 50% as a 2:1 mixture of diastereomers (28% from **663**). The authors speculated that the absence of the protecting group on the indole ring might influence the orientation of the double bond in the final cyclisation product.

Remarkably, the authors were able to telescope most of the steps and perform the whole synthesis in two pots with 15% overall yield and only a single chromatographic purification.

3.4.4 Naito's collective synthesis of ergot alkaloids

The last selected example is Naito's collective synthesis of ergot alkaloids, including *(8S,9R)-* and *(8R,9S)-*Fumigaclavine B (**Schemes 3.10 and 3.11**).[15b, 16] Naito and co-workers planned to prepare the D-ring by reductive photochemical cyclisation of enamide **673** derived from known tricycle **670**. The resulting pentacycle **674** and its isomer **675** would then serve as advanced common intermediates for the synthesis of various ergot alkaloids.

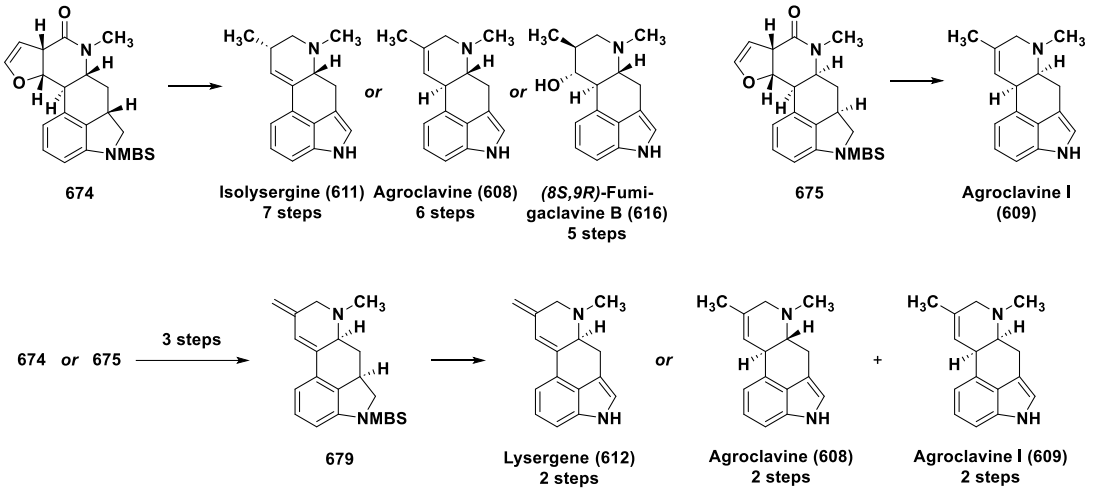
First, tricycle **670** was converted to ketone **671** in 4 steps by protecting group swap followed by epoxidation of the alkene and its acid-induced isomerisation to ketone. Next, the ketone was condensed with methyl amine and acylated with acyl chloride **672**, generating enamide **673**. Irradiation of enamide **673** in the presence of excess sodium borohydride afforded the cyclised product as a separable mixture of 3 diastereomers **674**, **675** and **676** in 53%, 21% and 6% yield, respectively.



Scheme 3.10. *Naito's synthesis of (±)-(8R,9S)-Fumigaclavine B.*

Ozonolysis of the dihydrofuran ring in **674**, followed by a reductive workup with lithium aluminium hydride, resulted in the formation of the corresponding diol and the reduction of the amide to an amine. Selective mesylation of the primary alcohol and subsequent reduction with sodium borohydride afforded intermediate **677**. However, due to the mismatched configuration of the C-9 stereogenic centre with the final natural product, the configuration of the secondary alcohol in **677** had to be inverted. This was achieved by activation of the alcohol in compound **677** by its mesylation and its subsequent displacement with potassium superoxide.[24] Cleavage of the *p*-methoxyphenylsulfonyl group by sodium in liquid ammonia and subsequent oxidation of indoline by phenylseleninic anhydride in the presence of indole accomplished the synthesis of *(±)-(8R,9S)-*Fumigaclavine B (**618**).

Using alternative end game strategies, pentacyclic intermediate **674** was converted (*via* alcohol **677**) to Isolysergene (**611**) and Agroclavine (**608**). By employing different oxidative cleavage of dihydrofurane ring in **674**, *(±)-(8S,9R)*-Fumigaclavine B (**616**) was obtained in 5 steps. Additionally, compound **675**, a minor isomer from the photochemical cyclisation of enamide **673,** was transformed into Agroclavine I (**609**) in 6 steps.

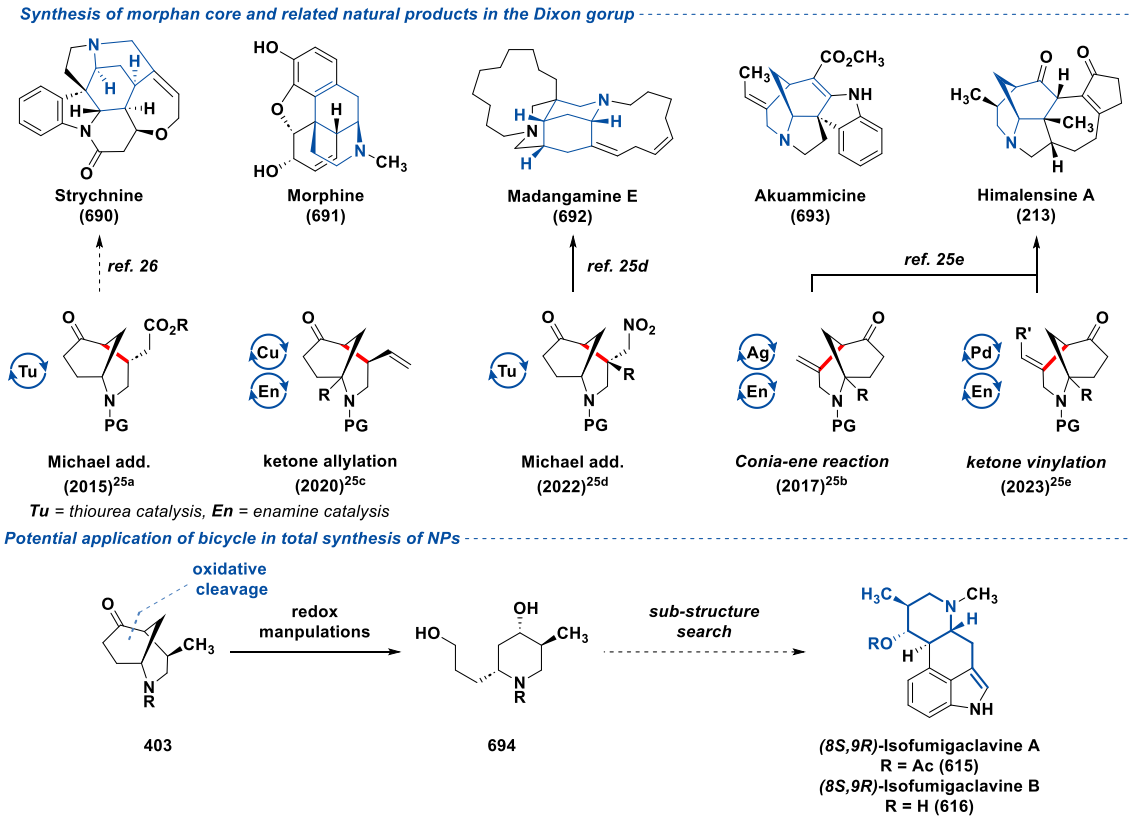


Scheme 3.11*. Naito's synthesis of clavine alkaloids.*

Finally, cyclisation isomers **674** and **675** could be transformed to the same diene **679** by double mesylation – elimination of diols obtained by their ozonolysis. Diene **679** could then be converted into Lysergene (**612**) or a mixture of Agroclavine (**608**) and Agroclavine I (**609**).

3.5 Retrosynthetic analysis of clavine alkaloids

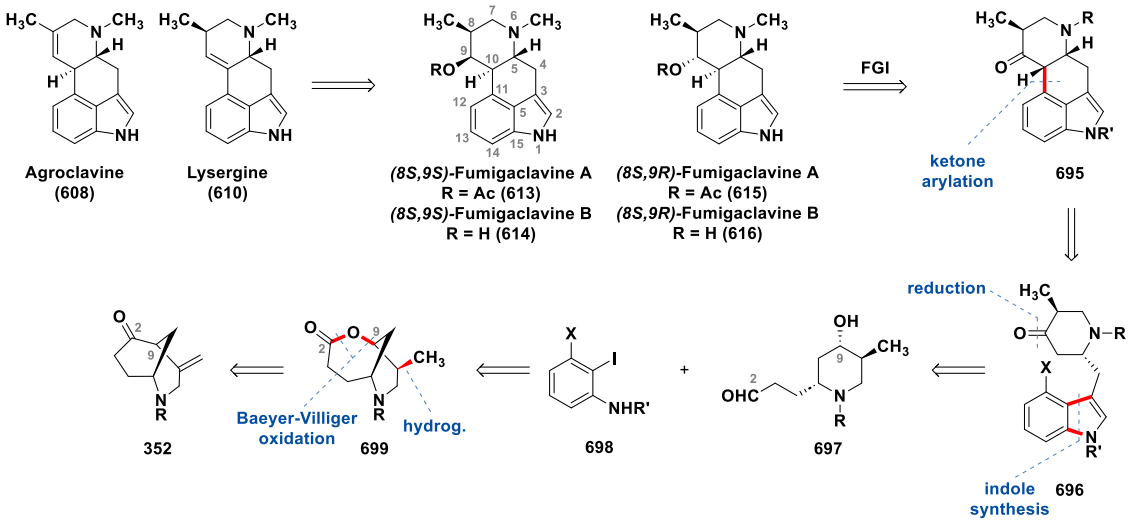
The 2-azabicyclo[3.3.1]nonane, known as morphan core, is a recurring structural motif within a diverse range of natural products, including *Strychnos*, *Morphine*, *Madangamine* and *Daphnyphyllum* alkaloids (**Scheme 3.12**). Many of these compounds exhibit significant biological activity and find application in the pharmaceutical industry. With their research centred on the development of enantioselective methodologies and total synthesis of natural products, among many others, the Dixon research group has developed multiple enantioselective methods that grant access to substituted morphan core,[25] facilitating laboratory syntheses of these interesting natural products.[25d, e, 26]



Scheme 3.12. *Synthesis of morphan core and related natural products.*

Having recently achieved the successful synthesis of the *Daphniphyllum* alkaloid Himalensine A, we embarked on an exploration of utilising some of our key synthetic intermediates to synthesise another class of natural products. Through the virtual application of chemical transformation to the morphan core containing intermediate **403**, we envisioned its potential conversion to diol **694** (**Scheme 3.12, bottom**). A subsequent structural search revealed perfect structural overlap with clavine alkaloids, a subfamily of more famous ergot alkaloids. Remarkably, this intermediate not only contains all carbon atoms, with the exception of the benzene ring, but also incorporates three stereogenic centres with relative configurations matching those of (*8S,9R*)-Fumigaclavine A and B. Additionally, the presence of the C-2 hydroxyl group allows the installation of the aldehyde group – a versatile functionality widely used for the introduction of the indole ring.

The presence of the highly conserved tetracyclic core in multiple clavine alkaloids renders them an ideal target for a collective synthesis. Many of these alkaloids could be tracked back to common intermediate **695** (**Scheme 3.13**). Epimerisation of ketone **A**, followed by its reduction and acetylation, would afford *(8S,9S)*-Fumigaclavines A-B and *(8S,9R)*-Fumigaclavine A-B. Subsequent dehydration/elimination would lead to Argoclavine and Lyserge, which, upon hydrogenation, would give rise to fully saturated analogues **604-607** (**Scheme 3.3**). Given the high synthetic versatility of the ketone group, various alternative strategies for the conversion of intermediate **695** into diverse clavine alkaloids, can be envisioned.

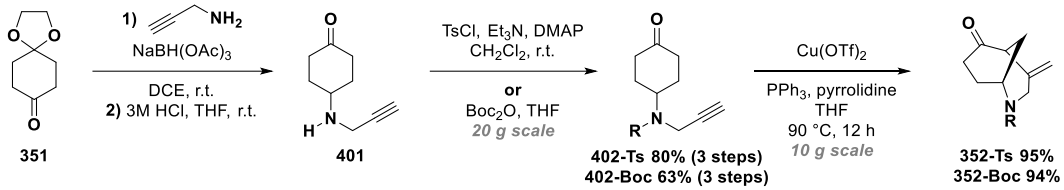


Scheme 3.13. *Retrosynthetic analysis of selected clavine alkaloids.*

The central C-ring in **695** could be efficiently disconnected in a highly convergent fashion by ketone arylation and indole-forming reaction to aldehyde **697** and iodoaniline **698**,[27] bearing an appropriate leaving group **X**, or its precursor. Aldehyde **697** was envisioned to be accessible from bicycle **352** through a sequence of redox steps, including Baeyer-Villiger oxidation, lactone reduction and hydrogenation of the *exo*-methylene group. Bicyclic starting material **352** can be obtained in enantiomerically enriched form using one of the desymmetrisation reactions previously developed in the Dixon group.[25b, e]

3.6 Synthesis of aldehyde building blocks

Although the bicyclic intermediates **352a-b (Scheme 4.13)** can be prepared in enantiomerically enriched form using methodologies previously developed in the Dixon group (see **Chapter 2**), for practical reasons, we decided to initiate our synthetic studies towards clavine alkaloids using racemic substrates. After successfully synthesising these natural products in their racemic form, the enantioselective version of the Conia-ene or ketone vinylation reaction would be used for their syntheses in enantiomerically pure form.



Scheme 3.14. *Synthesis of bicyclic substrates* ***352-Ts/Boc****.*

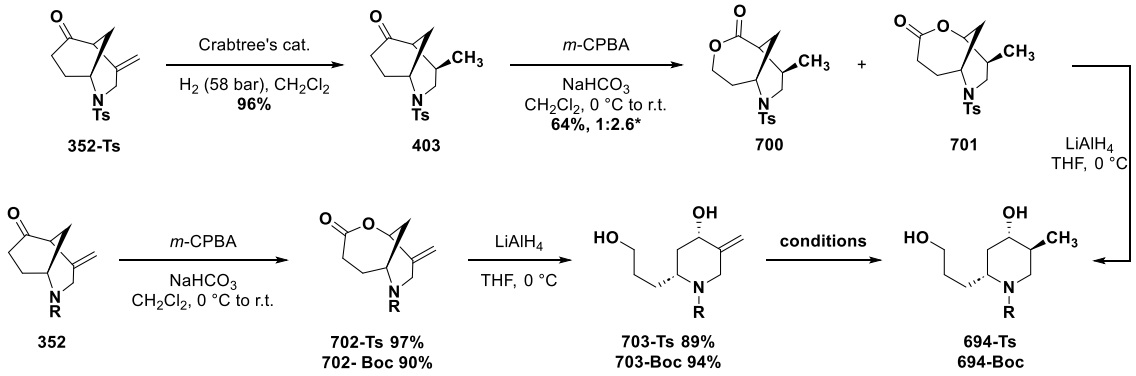
Bicyclic substrates **352-Ts/Boc** were prepared by copper – enamine co-catalysed Conia-ene cyclisation of alkynes **402-Ts/Boc** obtained from monoprotected diketone **351** in three steps. First, ketone **351** was coupled with propargyl amine by reductive amination followed by acetal hydrolysis. For our synthetic studies, we opted for two different protecting groups – tosyl and Boc. While both groups can be used in the enantioselective version of the cyclisation reaction with high yield and *ee*, the tosyl group is more robust, making it compatible with all planned transformations. However, its robustness may pose a challenge during its deprotection in the later stages of the synthesis. Conversly, the Boc group can be easily cleaved under acidic conditions. Moreover, it can be reduced to the *N*-methyl group present in the final products. However, the main disadvantage of this protecting group (*vide infra*) is its rotameric behaviour, which significantly complicates the analysis of the NMR spectra.

Treatment of amine **401** with tosyl chloride provided cyclisation substrate **402-Ts** in 80% yield over 3 steps, while Boc protection of amine **401** afforded intermediate **402-Boc** in a slightly lower yield of 63%. Both **402-Ts** and **402-Boc** were prepared on a decagram scale, requiring only a single purification by column chromatography. Cyclisation of compounds **402-Ts** and **402-Boc** afforded the bicycles **352-Ts/Boc** in excellent yields (95% and 94%, respectively).

With access to multigram quantities of bicyclic intermediated **352-Ts** and **352-Boc**, the installation of the C-9 hydroxy group of Fumigaclavines A-C through oxidative cleavage of the C-C bond between C-9 and C-2 using regioselective Baeyer-Villiger oxidation was examined (**Scheme 3.15**). The relative configuration of the C-8 methyl group in *(8S,9S)-* and *(8S,9R)-*Fumigaclavines A-C matches the configuration of the methyl group present in the B-core of *Daphniphyllum* alkaloids. Therefore, the *exo*-methylene group in **352-Ts** was selectively hydrogenated, utilising conditions identified during our previous synthetic studies. Treatment of the hydrogenated product **403** with *m*-CPBA in the presence of

base led to the formation of the Baeyer-Villiger product, albeit with low regioselectivity (2.6:1 favouring isomer **700**, 64% combined yield).[vii]

Given the similar migration rate of the primary and secondary alkyl groups in the B-V oxidation of compound **403**, we hypothesise that the double bond in **352** might increase the migration rate of the secondary alkyl substituent due to allylic stabilisation. Indeed, repeating the B-V oxidation with substrate **352-Ts** yielded the desired regioisomer as a single product, however, in highly variable yields, especially during the upscaling of the reaction. While the oxidation of **352-Ts** and **352-Boc** on a small scale (50 mg) provided the desired lactones in >90% yield, the reaction performed on a larger scale (≈1 g) often suffered from poor conversion, requiring the addition of another portion of oxidising agent and resulted in low isolated yields (30 – 50%). We suspected that this inconsistency might arise from inefficient heat transfer on a larger scale in combination with varying quantities of 3-chlorobenzoic acid in commercial (<77%) *m*-CPBA. The slow addition of *m*-CPBA to the reaction mixture as a solution using a syringe pump partially solved this issue. However, perfect reproducibility was achieved using pure *m*-CPBA[28] in combination with finely ground $NaHCO_3$. Under these improved conditions, lactone **702-Ts** and **702-Boc** were obtained in multigram quantities in 97% and 90% yield.



Scheme 3.15. *Synthesis of saturated diols* ***694-Ts/Boc.***[viii]

Following the successful Baeyer-Villiger oxidation, the directed hydrogenation of **702-Ts** was attempted. Surprisingly, high-pressure hydrogenation (10 bar) of compound **702-Ts** using Crabtree's catalyst did not yield any product. In an alternative strategy, we decided to reduce lactones **702-Ts** and **702-Boc** to the corresponding diols and then utilise the secondary hydroxyl group for directed hydrogenation of the alkene group. To this end, lactones **702-Ts/Boc** were treated with $LiAlH_4$ and provided the desired diols **703-Ts/Boc** in 89% and 94% yields, respectively.

A series of conditions for selective hydrogenation was screened (**Table 3.1**). High-pressure hydrogenation of *N*-tosyl protected substrate (**entries 1** and **2**) led to the formation of the desired product with excellent *d.r.* (>20:1). However, low conversion and substantial double bond migration

[vii] The outcome of the reaction repeated with purified *m*-CPBA under the optimal conditions; see text below.
[viii] Reactions marked with '*' were performed by Daniel Cox.

rendered this method impractical. On the other hand, hydrogenation in the presence of palladium on charcoal (**entry 3-5**) achieved full conversion at atmospheric pressure with good *d.r.* (4.6-7.0:1) and isolated yield (70 – 80%). Moreover, these conditions were successfully scaled up, with diol **694-Ts** obtained in 82% yield on a 4-gram scale (**entry 6**). During the later screening of conditions for selective hydrogenation of compound **702-Boc** (see discussion below), we revisited the hydrogenation of substrates **703-Ts/Boc**. Hydrogenation of alkene **703-Ts** in the presence of freshly prepared Wilkinson's catalyst (**entry 7**) provided the diol **694-Ts** with excellent *d.r.* and yield (>20:1, 96%).

Table 3.1. *Hydrogenation of diols* ***703-Ts/Boc***.



703-Ts
703-Boc **694-Ts**
694-Boc

Entry	Substrate	Conditions	Pressure	Conv.[g]	Isom.[g]	d.r.[g]	Yield
1[a]	703-Ts	Crabtree's cat. (5 mol %), CH_2Cl_2	5 atm	66%	19%	>20:1	n.d.
2[a]	703-Ts	Crabtree's cat. (5 mol %), CH_2Cl_2	10 atm	66%	20%	>20:1	n.d.
3[a]	703-Ts	Pd/C (10 mol %), EtOAc	1 atm	100%	0%	4.6:1	80%
4[b]	703-Ts	Pd/C (5 mol %), EtOAc	1 atm	100%	0%	4.6:1	70%
5[c]	703-Ts	Pd/C (5 mol %), EtOAc	1 atm	100%	0%	7.0:1	76%
6[d]	703-Ts	Pd/C (5 mol %), EtOAc	1 atm	100%	0%	8.0:1	82%*
7[e]	703-Ts	**[$Rh(PPh_3)_3Cl$] (5 mol %) degassed benzene**	**1** atm	**100%**	**0%**	**>20:1**	**96%**
8[f]	703-Boc	**Pd/C (5 mol %), EtOAc**	**1** atm	**100%**	**0%**	**5.5:1**	**60%**
9[e]	703-Boc	[$Rh(PPh_3)_3Cl$] (5 mol %) degassed benzene	1 atm	100%	0%	3:1	n.d.

Reagents and conditions: [a] reaction performed on a 10 mg scale; [b] 250 mg scale; [c] 930 mg scale; [d]4g scale; [e]30 mg scale; [f]960 mg scale; [g]Conversion, *d.r.* and amount of isomerised product were determined by NMR. *Experiments performed by Daniel Cox.

The relative configuration of the newly formed C-8 stereogenic centre in diol **694-Ts** was confirmed by the conversion of lactone **701**, prepared from substrate **403** with known stereochemistry, to diol **694-Ts** (see **Scheme 3.15**), and verified by single crystal X-ray diffraction analysis (**Figure 3.1**).

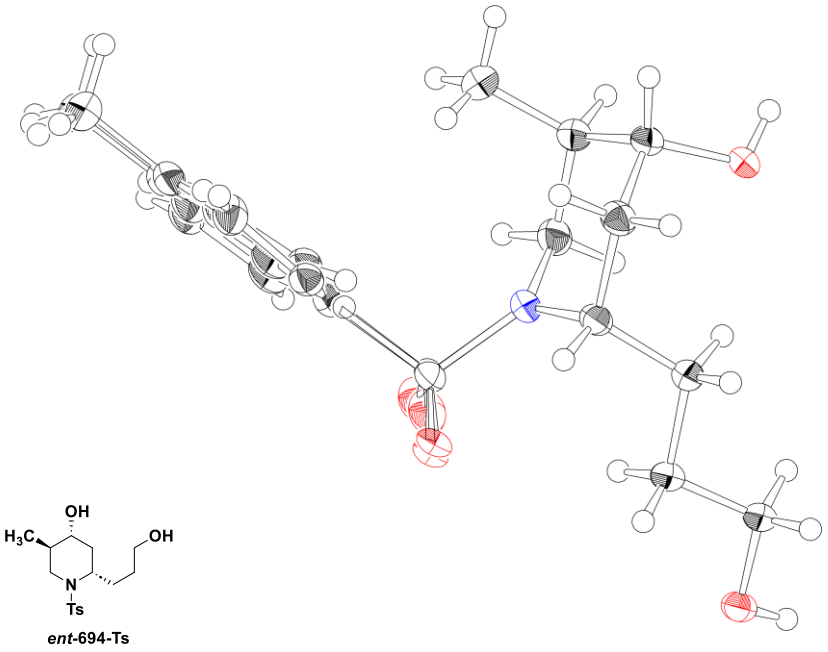


Figure 3.1. *ORTEP diagram of compound* ***ent-694-Ts*** *with thermal ellipsoids drawn at 50% probability.*[ix]

The optimal hydrogenation conditions were also applied to *N*-Boc-protected substrate **703-Boc**. Hydrogenation catalysed by palladium on charcoal (**entry 8**) produced the desired product **694-Boc** with slightly decreased *d.r.* and yield (5.5:1 d.r., 60% yield). Finally, hydrogenation in the presence of Wilkison's catalyst (**entry 9**) provided the reduced product with a disappointing 3:1 *d.r.*

Due to the low diastereoselectivity in the hydrogenation of *N*-Boc-protected alkene **703-Boc**, we revisited the hydrogenation of the Baeyer-Villiger products **702-Ts/Boc** (**Table 3.2**). Using Shenvi's conditions, which should lead to chemoselective reduction with thermodynamic control[30] (**entry 1**), a 1:1 mixture of diastereomers was obtained in a relatively low yield (36%). Hydrogenation in the presence of 10 mol % of Wilkinson's catalyst (commercial source, **entry 2**) led to excellent selectivity (>20:1) but low conversion. To increase the rate of this hydrogenation reaction, the hydrogen pressure was increased to 9 atmospheres (**entry 3**). However, under these conditions, no product was formed. This unexpected outcome can be attributed to the experimental setup, which did not allow the reaction to be performed under oxygen-free conditions. Repeating the reaction at atmospheric pressure with extended reaction time led to better conversion, but the required high catalyst loading was not economically feasible. Hydrogenations with ruthenium complex (**entry 5-6**) and Crabtree's catalyst were not productive, while hydrogenation in the presence of palladium and rhodium on charcoal (**entry 6-8**) generated a complex mixture of products (amount of the desired isomer showed in bold; for NMR spectra of crude reaction mixtures, refer to the Experimental section).

[ix] Figure 3.1 was generated using the Molby software.[29] In the representation, carbon atoms are depicted in black, oxygen in red, nitrogen in blue, and hydrogen in white with a fixed diameter for clarity.

Table 3.2. *Screening of conditions for selective hydrogenation of alkene* ***702-Ts/Boc****.*



702-Ts/Boc **704-Ts/Boc**

Entry	R	Conditions	Press.	"d.r."[a]	Outcome[b]
1[c]	Boc	$Mn(dpm)_3$, $PhSiH_3$, TBHP, IPA, 13 h	n.a.	**1**:1	36% yield
2[d]	Boc	$Rh(PPh_3)_3Cl$ (10 mol %), benzene, **1 h**	1 atm	>**20**:1	57% conv.
3[d]	Boc	$Rh(PPh_3)_3Cl$ (10 mol %), benzene, **2 h**	9 atm	n.a.	traces of prod.
4[d]	Boc	$Rh(PPh_3)_3Cl$ (10 mol %), benzene, **18 h**	1 atm	>**20**:1	≈90% conv.
5[d]	Boc	$Ru(PPh_3)_3Cl_2$ (10 mol %), benzene, 18 h	1 atm	n.a.	no reaction
6[d]	Boc	$[Ir(cod)(PPh_3)py]PF_6$ (5 mol %), CH_2Cl_2, 1 h	9 atm	n.a.	no reaction
7[d]	Boc	Pd/C (10 mol %), EtOAc, 1 h	9 atm	1.0 : **1.9** : 4.8 : 2.4	full conv.
8[d]	Boc	Rh/C (10 mol %), EtOAc, 1 h	9 atm	1.0 : **7.8** : 1.3 : 2.0	full conv.
9[d]	Boc	Rh/C (10 mol %), EtOH, 1 h	9 atm	**1.0** : 3.3 : 3.3 : 5.0	full conv.
10[d,g]	Boc	$Rh(PPh_3)_3Cl$ (10 mol %), benzene, **16 h**	1 atm	>20:1	full conv.
11[d,g]	Boc	$Rh(PPh_3)_3Cl$ (5 mol %), benzene, **16 h**	1 atm	>20:1	full conv.
12[d,g]	Boc	**$Rh(PPh_3)_3Cl$ (2 mol %), benzene, 16 h**	**1 atm**	**>20:1**	**full conv.**
13[d,g]	Boc	$Rh(PPh_3)_3Cl$ (1 mol %), benzene, **16 h**	1 atm	>20:1	low conv.
14[e,g]	Boc	**$Rh(PPh_3)_3Cl$ (2 mol %), benzene, 16 h**	**1 atm**	**>20:1**	**97% yield**
15[f,g,h]	Ts	**$Rh(PPh_3)_3Cl$ (2 mol %), benzene, 16 h**	**1 atm**	**>20:1**	**96% yield**

Reagents and conditions: [a] the d.r. or the selectivity of the reaction, respectively, were determined by ^1H NMR. A number representing the fraction of the desired isomer is shown in bold. [b]"Yield" refers to isolated yield. [c]Reaction performed on 50 mg scale; [d]25 mg scale; [e]1.0 g scale; [f]2.0 g scale. [g]Freshly prepared Wilkinson's catalyst was used. [h]Reaction performed by Daniel Cox.

Notably, Wilkinson's catalyst is known to undergo slow oxidation when exposed to air, leading to a loss of catalytic activity.[31] To ensure reproducible results, the use of a freshly prepared catalyst is recommended. Therefore, our best result (**entry 4**) was repeated with freshly prepared Wilkinson's catalyst. Gratifyingly, this led to the complete conversion of alkene **702-Boc** to compound **704-Boc** (**entry 10**). Moreover, the superior activity of freshly prepared catalyst allowed us to reduce its loading to a more economically acceptable level of 2 mol % (**entry 12**). Further decrease of catalyst loading to 1 mol % led to only partial hydrogenation of the substrate. Equipped with these optimised conditions, hydrogenation of alkene **702-Boc** was scaled up to 1 g. Impressively, compound **704-Boc** was obtained with excellent *d.r.* (>20:1) in 97% yield. Additionally, Daniel Cox showed that *N*-tosyl-protected substrate **702-Ts** could also be selectively hydrogenated under these conditions, providing compound **704-Ts** in excellent yield and gram quantities (**entry 15**).

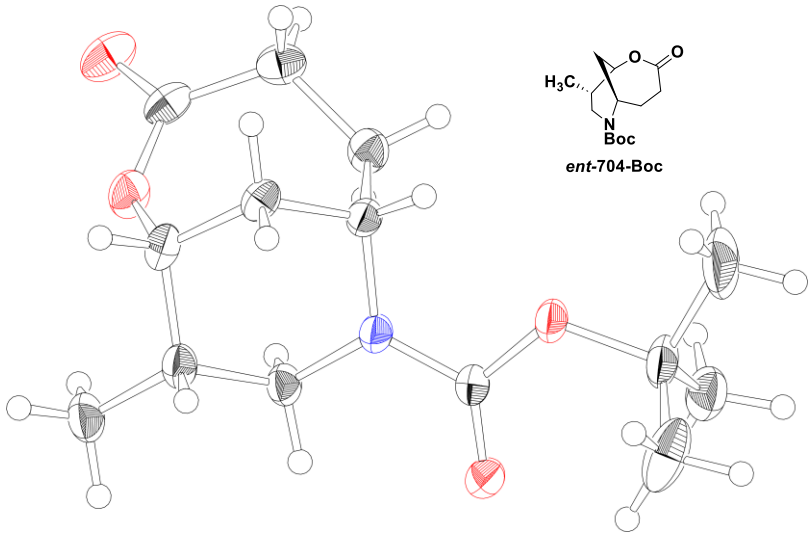
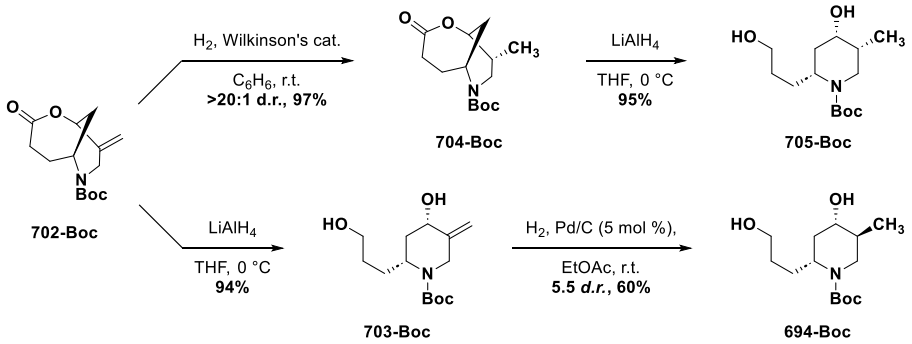


Figure 3.2. *ORTEP diagram of compound* ***ent-704-Boc*** *with thermal ellipsoids drawn at 50% probability.*[x]

The stereochemical outcome of the hydrogenation of alkene **702-Boc** was determined by single-crystal X-ray diffraction analysis (**Figure 3.2**). This analysis revealed that the use of Wilkinson's catalyst led to the formation of *8R* diastereomer *via* hydrogen delivery from the more sterically accessible convex face. While intermediate **704-Boc** possesses a mismatched configuration at the C-8 stereogenic centre compared to the natural products presented in the retrosynthetic analysis, it aligns with the configuration of Pyroclavine, *epi*-Costaclavine and Isolysergene, indicating potential utility in the preparation of these natural products. Furthermore, the stereochemical configuration of intermediate **704-Boc** was used to confirm the relative configuration of diol **694-Boc**. A comparison of the NMR data of diol **694-Boc** and the diol **705-Boc** obtained by reduction of intermediate **704-Boc** with $LiAlH_4$ identified them as diastereomers, confirming our original assignment (*8S* for **694-Boc**). The configuration of the *N*-tosylated product **704-Ts** was determined by comparison of its NMR spectra with those of Baeyer-Villiger product **701** (**Scheme 3.15**), validating a matching relative configuration with *N*-Boc-protected product **704-Boc**.

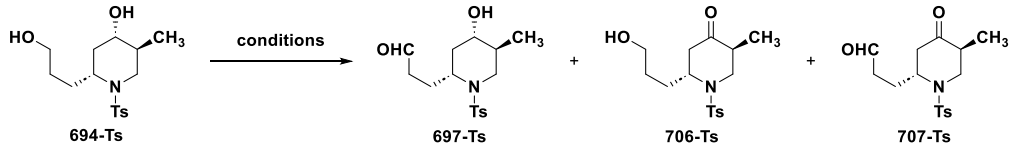


Scheme 3.16. *Determination of stereochemical outcome of the hydrogenation reactions.*

[x] Figure 3.2 was generated using the Molby software.[29] In the representation, carbon atoms are depicted in black, oxygen in red, nitrogen in blue, and hydrogen in white with a fixed diameter for clarity.

With access to sufficient quantities of diols **694-Ts/Boc**, the selective oxidation of their primary hydroxyl group to the aldehyde, required for the formation of the indole ring, was investigated (**Table 3.3**). To this end, diol **694-Ts** was treated with Dess-Martin periodinane (**entry 1**).[32] Surprisingly, relatively fast and selective oxidation of the secondary alcohol in the presence of primary alcohol was observed, accompanied by slower overoxidation of hydroxyketone **706-Ts** to ketoaldehyde **707-Ts**. Oxidation with TEMPO/PIDA[33] (**entry 2**) led to slow oxidation of the primary alcohol, but full conversion could not be achieved before the formation of the overoxidised product **707-Ts** in substantial quantities. Similar reactivity was observed with Parikh-Doering oxidation, an operationally simpler variant of Swern oxidation (**entry 3**). Encouraged by the promising result of the TEMPO-catalysed oxidation, alternative conditions based on nitroxyl radical catalysts were sought. Gratifyingly, substituing PIDA with sodium hypochlorite as a terminal oxidant enabled fast and selective oxidation of the primary alcohol in **694-Ts** (**entry 4**).[34]

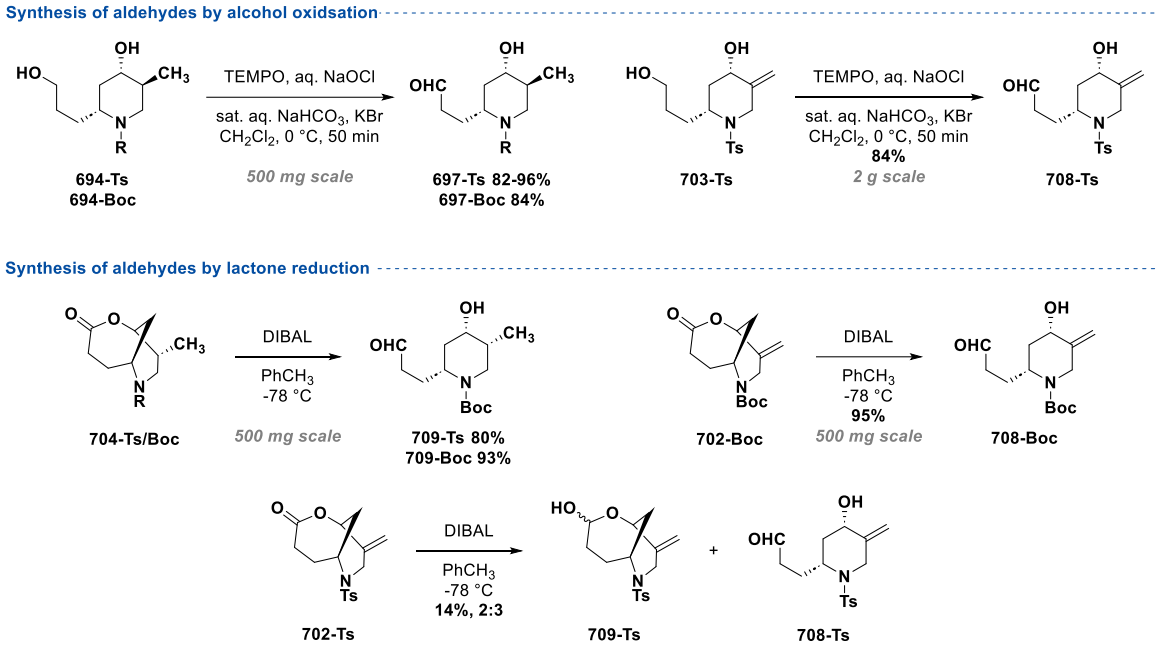
Table 3.3. *Screening of conditions for selective diol oxidation.*



Entry	Conditions	Yield[a]
1[b]	DMP, CH_2Cl_2, 0 °C, 4 h	55% (**706**) + 28% (**707**)
2[b]	TEMPO, PIDA, CH_2Cl_2, r.t., 4 h	37%
3[b]	DMSO, DIPEA, SO_3.py, CH_2Cl_2, 0 °C, 20 h	n.d.
4	TEMPO, NaOCl, $NaHCO_3$, KBr, CH_2Cl_2, 0 °C, 50 min	85%

[a]Isolated yield. [b]Reactions performed by Daniel Cox.

However, due to the variable concentration of the commercially available aqueous solution of sodium hypochlorite and to avoid potential overoxidation, careful titration of the starting material **694-Ts** with this oxidant was necessary. This protocol provided aldehydes **697-Ts** and **697-Boc** in very good yields (**Scheme 3.17**, top left). Furthermore, chemoselective oxidation of the primary alcohol in the presence of an allylic alcohol in compound **703-Ts** could be achieved, affording the unsaturated aldehyde **708-Ts** on a multigram scale (**Scheme 3.17**, top right).



Scheme 3.17. *Synthesis of aldehyde building blocks.*

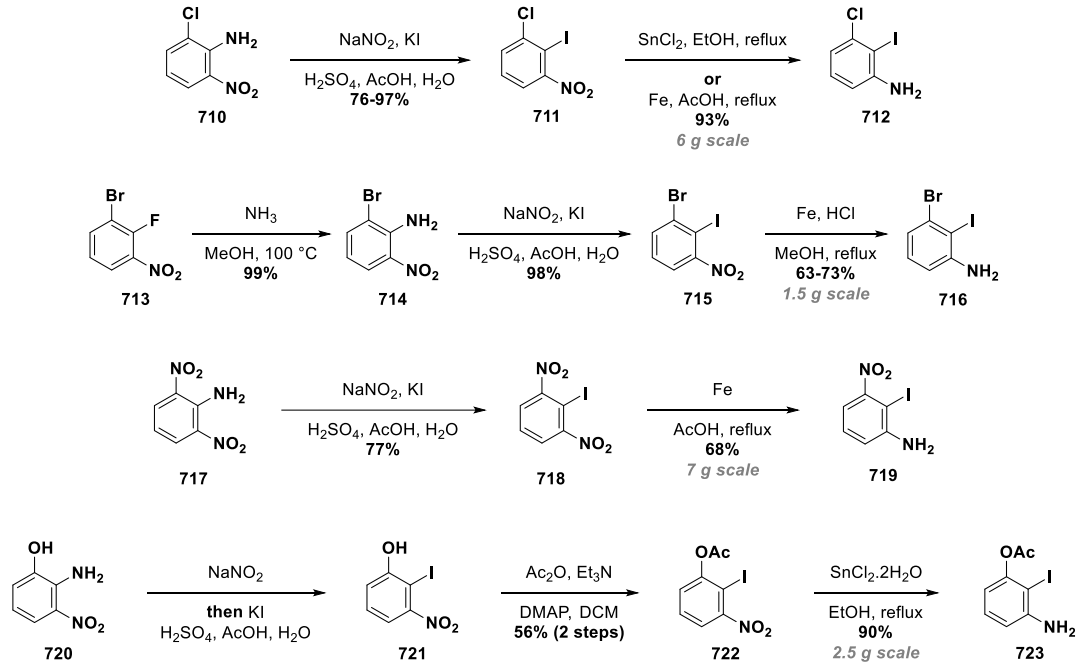
Since the *8S*-selective hydrogenation of the alkene group in Baeyer-Villiger products **702-Ts/Boc** did not require its reduction to the corresponding diol, an alternative, more redox-efficient, strategy could be used for the preparation of aldehydes **709-Ts/Boc** (C-8 epimer of **697-Ts/Boc, Scheme 3.17, bottom**). Reduction of lactones **702-Ts/Boc** with DIBAL-H[35] directly yielded the desired aldehydes **709-Ts/Boc** in good to excellent yield. This method could also be effectively applied for the synthesis of unsaturated *N*-boc-protected substrate **708-Boc**. On the other hand, treatment of *N*-tosyl-protected unsaturated lactone **702-Ts** with DIBAL-H afforded the product of reduction as a 2:3 inseparable mixture of acetal and aldehyde in a poor 14% yield, despite a clear reaction profile. The stark difference in the isolated yield of the DIBAL-H reduction of the saturated and unsaturated *N*-tosyl-protected intermediates **704-Ts** and **702-Ts** suggests that the presence of the *N*-tosyl-protected allyl amine moiety might be responsible for this poor yield, likely *via* the allylic substitution of the tosylamide in **702-Ts** (or in the products of the reduction of the lactone group **708-Ts** and **709-Ts**) with a hydride ion. The afforded *N*-tosylated primary amine would be significantly more polar than products **708-Ts** and **709-Ts** and, thereby evading detection by TLC analysis.

3.7 Synthesis of substituted anilines

For the synthesis of the indole ring, we opted for Zhu's indole synthesis, a palladium-catalysed coupling reaction of aldehydes with 2-iodoanilines.[27] The subsequent introduction of the central C-ring *via* ketone arylation reaction would require an appropriate leaving group (or its precursor) in the *meta*-position of the 2-iodoaniline used for indole synthesis. We faced several considerations regarding the choice of this leaving group:

1. *meta*-Bromo group would be the ideal leaving group for the planned C-ring synthesis. However, its relatively high reactivity might not be compatible with the indole formation reaction.
2. *meta*-Chloro group should be compatible with indole formation, but it could make the subsequent ketone arylation more challenging.
3. *meta*-Nitro group could be converted to any leaving group, albeit at the cost of a longer synthetic sequence. Moreover, the recent progress in cross-coupling chemistry allows the use of nitro-substituted substrates in direct denitrative ketone arylation.[36]
4. *meta*-Acetoxy group could be converted in two steps to highly reactive triflate.

With these considerations in mind, a small library of 2-iodoanilines was prepared (**Scheme 3.18**). 3-chloro-2-iodoaniline (**712**) was prepared from 2-chloro-6-nitroaniline (**710**) in 2 steps. First, a diazotisation–iodination introduced the iodine atom, followed by reduction of the nitro group using either tin(II) chloride or iron in acetic acid.



Scheme 3.18. *Synthesis of para-substituted 2-iodoanilines.*

3-bromo-2-iodoaniline (**716**) was synthesised in 3 steps from 1-bromo-2-fluoro-3-nitrobenzene (**713**). The synthesis involved nucleophilic aromatic substitution of the fluoro group in **713**, followed by the

diazotisation–iodination sequence to introduce the 2-iodo group. The final reduction of the nitro group with iron in acetic acid afforded iodoaniline **716**.

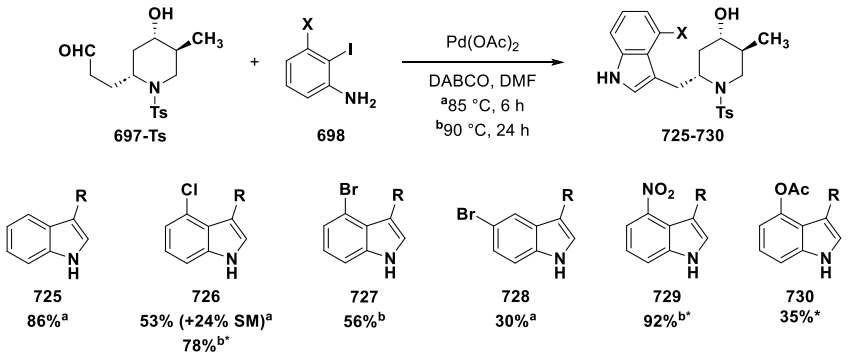
2-iodo-3-nitroaniline (**719**) was prepared using a similar strategy. Diazotisation – iodination of 2,6-dinitroaniline (**717**) afforded 2-iodo-1,3-dinitrobenzene (**718**), which after selective monoreduction of the nitro group yielded 2-iodo-3-nitroaniline (**719**).

Finally, 3-amino-2-iodophenyl acetate (**723**) was prepared in 3 steps from 2-amino-3-nitrophenol (**720**). First, the amino group was converted to the iodo group under the previously established conditions. The resulting iodophenol **721** was subsequently acetylated, and the synthesis of iodoaniline **723** was accomplished by reduction of the nitro group with tin(II) chloride.

3.8 Synthesis of the indole ring

With access to several aldehyde and iodoaniline building blocks, the key indole formation reaction was then examined. Due to the complicated NMR spectra of *N*-Boc-protected substrates caused by the rotameric behaviour of this protecting group, for simplicity we initiated our synthetic studies with the *N*-tosyl-protected substrates **697-Ts** and **708-Ts** (**Schemes 3.19** and **3.20**).

To determine whether the non-protected hydroxyaldehyde **697-Ts** could serve as a viable substrate for the indole-forming reaction, in our first attempt, a simple non-substituted 2-iodoaniline was used (**Scheme 3.19**). Gratifyingly, employing Zhu's conditions[27] resulted in the desired indole **725** with an impressive yield of 86% in a very clean reaction, demonstrating that aldehyde **697-Ts** does not require protection of its alcohol group. Encouraged by these findings, aldehyde **697-Ts** was next coupled with 3-chloro-substituted aniline **712**. However, the presence of the *meta*-substituent on the aniline ring slightly decreased its reactivity, initially yielding the desired product **726** in only 53% yield, together with 24% of recovered starting material. Fortunately, with an extended reaction time and higher reaction temperature, complete conversion was achieved, and indole **726** was isolated in 78% yield.

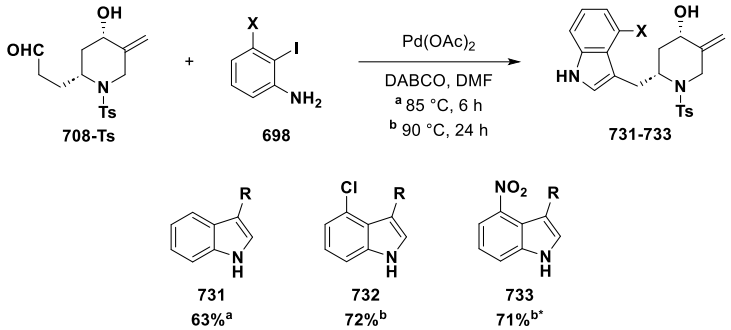


Scheme 3.19. *Synthesis of indoles with N-tosyl-protected substrate* ***697-Ts****.*[xi]

In contrast, when aldehyde **697-Ts** was subjected to the reaction with *meta*-bromo-substituted aniline **716**, a formation of multiple products was observed and the desired indole **727** was obtained in low purity and yield (<56%). To identify whether this poor reactivity was a result of the steric hindrance introduced by the *meta*-bromo group or incompatibility of this group with reaction conditions, the reaction was repeated with *para*-bromo aniline. The poor yield of this reaction, together with isolation of substantial amounts of debrominated indole product confirmed the incompatibility of the bromo group with these reaction conditions. Next, the coupling of the *meta*-nitro aniline **719** with aldehyde **697-Ts** was investigated. Pleasingly, desired indole **729** was obtained in an impressive 92% yield, opening up the possibility to introduce any desired leaving group *via* transformation of the nitro group. Finally, the coupling of aldehyde **697-Ts** with *meta*-acetoxy aniline **723** afforded the corresponding aniline **730** in a low yield (35%).

[xi] Reactions marked with '*' were performed by Daniel Cox.

Parallel to indole synthesis with saturated aldehyde **697-Ts**, the coupling of 2-iodoanilines with its unsaturated analogue, compound **708-Ts**, was explored (**Scheme 3.20**). The main advantage of this strategy was the presence of only one enolisable position in the subsequent ketone arylation reaction, circumventing potential epimerisation of the C-8 position. Additionally, late-stage hydrogenation could grant access to the *8R* and 8*S* series of clavine alkaloids.



Scheme 3.20. *Synthesis of indoles with N-tosyl-protected substrate* ***708-Ts****.*[xii]

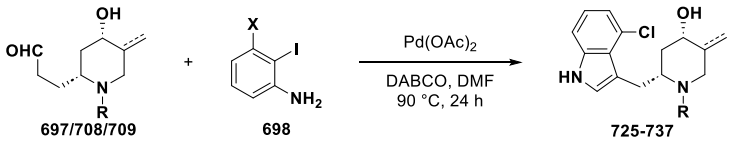
Similarly, as in the case of aldehyde **697-Ts**, the suitability of aldehyde **708-Ts** for the indole-forming reaction was first verified by its coupling with simple 2-iodoamine. Under Zhu's conditions,[27] the corresponding indole **731** was obtained in a useful 63% yield. The coupling of aldehyde **708-Ts** with *meta*-chloro aniline **712** occurred with a similar yield as its saturated analogue (78% vs 72%). A similar result was also observed with *meta*-nitro-substituted aniline **719** and the corresponding indole **733** was isolated in 71% yield.

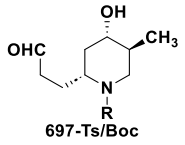
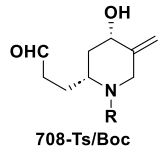
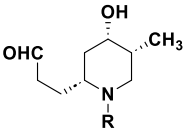
Upscaling of the indole core-forming reaction proved to be challenging. Despite a very clean reaction employing *meta*-chloro- and nitroindoles,[xiii] the isolated yields of corresponding indoles varied significantly depending on the scale and substrates used. This variability could be attributed to several factors, including the inherent instability of aldehyde substrates. For instance, the cyclisation of aldehyde **697-Ts** with *meta*-chloro-substituted aniline **712** in the absence of palladium revealed that approximately 40% of the aldehyde undergoes decomposition. Furthermore, despite being stored in a freezer, aldehyde **697-Ts** underwent slow polymerisation. However, only the decomposition of aldehyde alone could not solely account for the low yields, as the yield of parallel reactions might vary by up to 50%. Part of this yield fluctuation may be attributed to the precipitation of palladium(0) during the reaction, which could slow down or potentially halt the cyclisation, with the unreacted aldehyde undergoing decomposition. To ensure high reproducibility, the reactions were conducted with freshly prepared aldehydes under strictly oxygen-free conditions in a thoroughly degassed solvent. Introducing these measures, indoles derived from aldehyde **697-Ts** could be obtained in up to 67% yield on a half-gram scale (**Table 3.4**).

[xii] Reactions marked with '*' were performed by Daniel Cox.
[xiii] Full conversion of aldehyde, no side product observed by TLC

Similarly, unsaturated aldehydes **708-Ts/Boc** were successfully coupled with *meta*-chloro- and *meta*-nitroanilines **712/719** in comparable yields.

Table 3.4. *Synthesis of substituted indoles.*



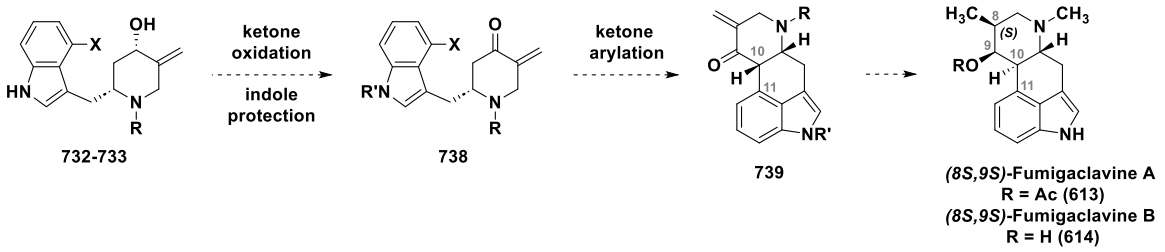
Aldehyde	R	X	Scale	Yield[a]	Product
 697-Ts/Boc	Ts	Cl	500 mg	66%	726-Ts
		NO_2	100 mg	62-70%[b]	729-Ts
	Boc	Cl	400 mg	67%	726-Boc
 708-Ts/Boc	Ts	Cl	100 mg	63%[b]	732-Ts
		NO_2	250 mg	60%[b]	733-Ts
	Boc	Cl	500 mg	56-67%	732-Boc
		NO_2	300 mg	71%	733-Boc
		OAc	300 mg	26%	734-Boc
		Br	100 mg	27%	735-Boc
 709-Ts/Boc	Ts	H	100 mg	90%[b]	736-Ts
		Cl	300 mg	76%[b]	737-Ts
			1.0 g	81%[b]	
	Boc	Cl	500 mg	75%	737-Boc
			2.0 g	79%	
			2.5 g	90%[b]	

[a]*Isolated yield.* [b]*Reactions performed by Daniel Cox.*

Nonetheless, the best results were achieved employing aldehydes **709-Ts/Boc** used in the later stages of our studies. Aldehyde **709-Ts** could be coupled with *meta*-chloroaniline **712** in an impressive 81% on a 1.0-gram scale and its Boc-protected analogue **709-Boc** in an excellent 90% yield on a 2.5-gram scale. This enhanced yield of the indole core-forming reaction with aldehydes **709-Ts/Boc** could be attributed to their higher stability compared to aldehydes **697-Ts/Boc** and **708-Ts/Boc**.

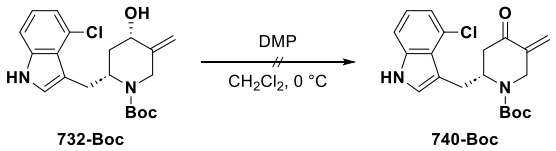
3.9 Enone arylation strategy

The next crucial step required for the success of our synthetic approach towards clavine alkaloids was the formation of the C-ring *via* enone arylation (**Scheme 3.21**). To convert substituted indoles **732-733**, obtained in the previous step, into suitable substrates for this transformation, the relatively acidic nitrogen of the indole ring had to be protected, and the C-9-hydroxyl group oxidised to the corresponding enone. Drawing inspiration from Cuny's[37] intramolecular ketone arylation with chloro-substituted *N*-benzyl-protected indoles, we logically opted for this protecting group.



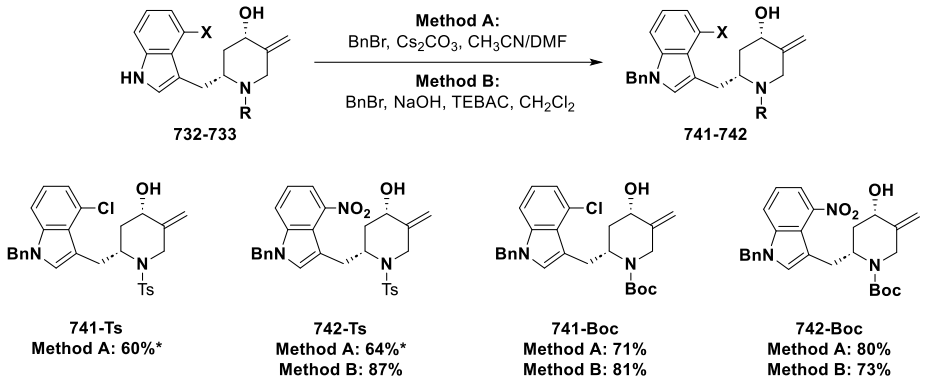
Scheme 3.21. *Overview of the enone arylation strategy.*

To avoid potential competing *O*-benzylation, the oxidation of the allylic alcohol in **732-Boc** was first attempted (**Scheme 3.22**). However, although the treatment of the intermediate **732-Boc** with Dess-Martin periodinane let to its rapid consumption, TLC analysis indicated potential polymerisation (indicated by a long spot across the entire TLC plate), suggesting the incompatibility of the enone moiety with an unprotected indole NH group under the reaction conditions.



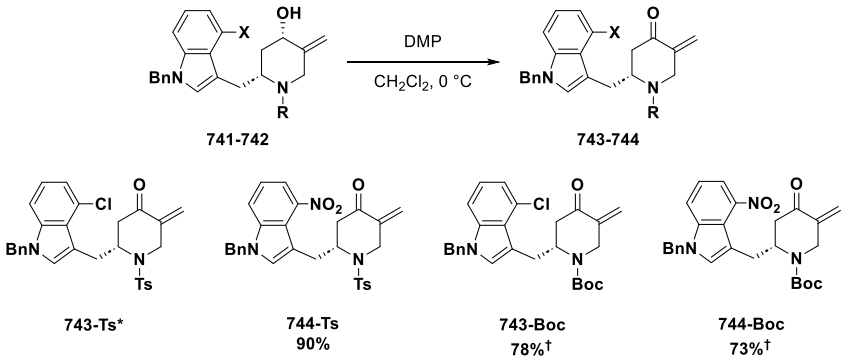
Scheme 3.22. *Oxidation of non-protected indole substrate* ***732-Boc****.*

To overcome this issue, the benzylation of the indole NH group was performed before the oxidation of the allylic alcohol (**Scheme 3.23**). Inspired by literature precedent,[38] a combination of benzyl bromide and caesium carbonate in the mixture of acetonitrile and DMF (**Method A**) was initially chosen for selective benzylation of indoles **732-Ts** and **732-Boc**. However, under these conditions, the benzyl-protected indoles **741-Ts** and **742-Ts** were obtained in relatively low yields of 60% and 64%, respectively. Dissatisfied with these results, an alternative procedure for indole benzylation using sodium hydroxide as a base in the presence of a phase-transfer catalyst (**Method B**)[39] was tried. Pleasingly, the benzylation under these conditions was significantly faster and afforded the benzylated product **742-Ts** in good yield (87%). Finally, benzylation of indoles **732-Boc** and **733-Boc** afforded the corresponding benzylated indoles **741-Boc** and **742-Boc** in similar yields.



Scheme 3.23*. N-benzylation of indoles* ***732-733****.*[xiii]

With protected indoles **741-742** in hand, the oxidation of allylic alcohol to corresponding enones was attempted (**Scheme 3.24**). The initial oxidation of nitroindole **742-Ts** with DMP afforded enone **744-Ts**, a potential substrate for intramolecular denitrative ketone arylation,[36a] in 90% yield. Surprisingly, the oxidation of chloroindole **741-Ts** under the same reaction conditions led to its decomposition.



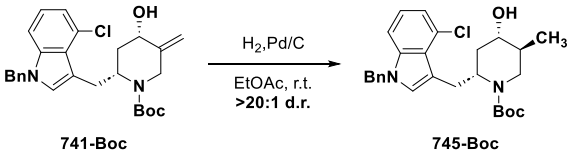
Scheme 3.24. *Oxidation of substrates* ***741-742****.*[xiv]

Subsequently, the oxidation of *N*-Boc-protected compounds **741-Boc** and **742-Boc** was examined. Treatment of these substrates with DMP yielded a single product in both cases (judged by TLC analysis), with good mass recovery (78% and 73%, respectively). However, subsequent NMR analysis revealed complex spectra, not corresponding to the desired enones. Based on these findings, the oxidation of nitroindole **742-Ts** was re-examined. The NMR analysis revealed that the initially formed enone **744-Ts** undergoes slow decomposition at room temperature. Given these observations and supported by a relevant literature precedent,[40] we postulated that after the successful oxidation of the allylic alcohol, the newly formed enone moiety undergoes dimerisation *via* a hetero-Diels-Alder reaction.

While unsaturated intermediates **741-742** have not proven to be synthetically useful for the C-ring formation, the introduction of the C-8 stereogenic centre by catalytic hydrogenation offers a more

[xiv] In the reactions marked with '†', the yield refers to the isolated yield of supposed dimerization product(s) purified by FCC.

stereo-divergent approach, potentially enabling the synthesis of both *8S*- and *9R*-series of clavine alkaloids from this same late-stage intermediate.



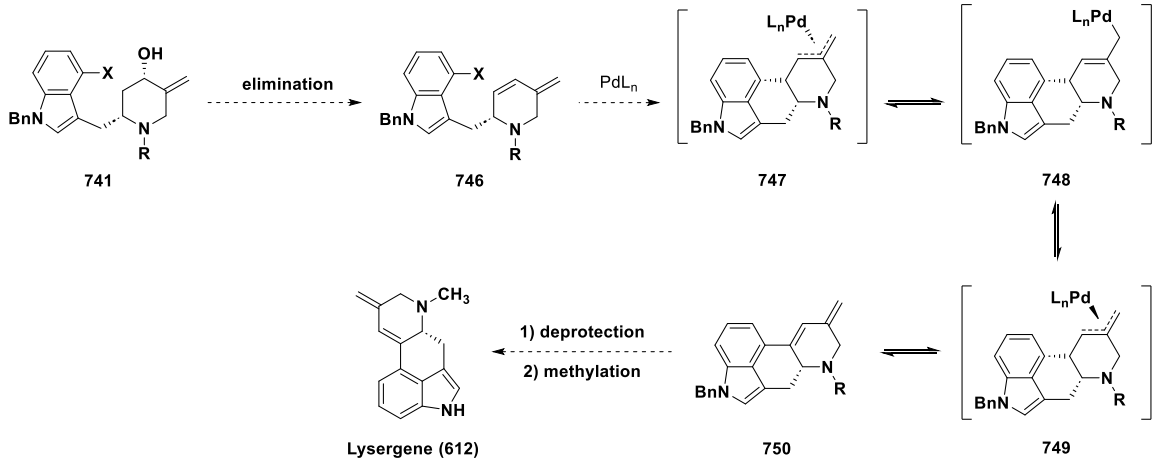
741-Boc **745-Boc**

Scheme 3.25. *Introduction of 8S stereogenic centre by late-stage hydrogenation.*

Hydrogenation of intermediate **741-Boc** in the presence of palladium on charcoal led to the highly diastereoselective introduction of the *8S* stereogenic centre (*d.r.* >20:1), offering an alternative approach to this intermediate. In contrast, the previously described strategy, based on the catalytic hydrogenation of unsaturated diol **703-Boc** in the earlier stages of the synthesis (**Scheme 3.16**), resulted in a relatively low 5.5:1 *d.r.* (**Table 3.1, entry 8**). The improved *d.r.* of this transformation could be attributed to the more rigid structure of compound **741-Boc** compared to **703-Boc**. Reaction conditions for the selective formation of *8R* epimer of **745-Boc** are yet to be determined.

3.10 Synthetic studies towards Lysergene

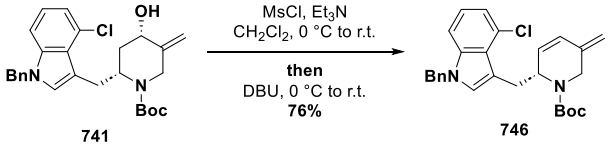
Facing the setbacks in our synthetic strategy towards clavine alkaloids based on the intramolecular enone arylation, we sought an alternative utilisation for the intermediates described in the previous chapter. One such application is depicted in **Scheme 3.26**.



Scheme 3.26. *Synthetic strategy towards Lysergene.*

The elimination of the C-9-hydroxy group in compounds **741-Ts/Boc** would provide diene **746,** which could be used for the formation of the central C-ring *via* palladium-catalysed Heck-type intramolecular cyclisation. Although such a process involving diene and aryl chloride is not presented in the scientific literature, a similar cyclisation of a simple alkene was previously successfully used for the synthesis of Lysergic acid, albeit in a relatively low yield.[22] We postulated that the oxidative addition of a palladium catalyst into the C-Cl bond, followed by *syn*-addition to diene moiety, would provide (π-allyl)palladium complex **474**. Subsequent isomerisation π-σ-π mechanism (**747→749**) would enable *syn*-β-hydride elimination, resulting in the formation of cyclised diene **750** and closing the catalytic cycle.

Given that the chloro-substituted substrate for the Heck-cyclisation, diene **746-Boc**, could be prepared in a single step from allylic alcohol **741-Boc** (**Scheme 3.27**), we briefly explored this challenging strategy. Treatment of alcohol **741-Boc** with mesyl chloride in the presence of triethylamine led to its rapid and clean conversion to corresponding mesylate. Subsequent addition of DBU facilitated a relatively slow elimination, providing the desired diene **746-Boc** in 76% yield.

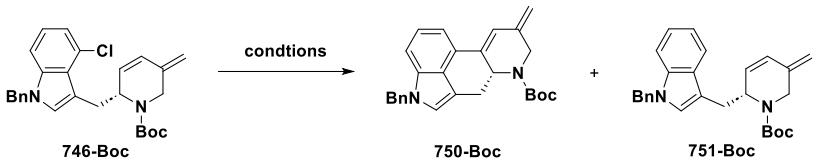


Scheme 3.27. *Synthesis of diene* ***746-Boc****.*

With diene **746-Boc** in hand, several literature-reported conditions for Heck coupling of aryl chlorides with nonactivated alkenes and modifications thereof were examined (**Table 3.5**).[41] However, none of

these conditions yielded the desired product. In most cases (e.g. **entries 1, 6** and **7**), only the dechlorination of the starting material was observed, indicating the successful oxidative insertion of Pd into the C-Cl bond.

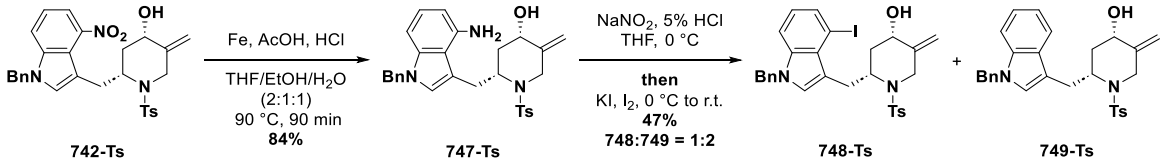
Table 3.5. *Screening of conditions for intramolecular Heck reaction.*



Entry	Conditions	Observation
1	$Pd(OAc)_2$, Davephos, Bu_4NOAc, dioxane, 100 °C, 15 h[41a]	55% **746**[a] + 40% **751**[a]
2	$Pd(OAc)_2$, Davephos, Ag_2CO_3, dioxane, 100 °C, 16 h	no reaction
3	XPhos-G1-Pd, Bu_4NOAc, dioxane, 80 °C, 16 h	**746**:**751** = 5:1[b]
4	$Pd(OAc)_2$, PPh_2-$(CH_2)_3$-PPh_2,K_2CO_3, DMF, 120 °C, 15 h	traces of **751**
5	$Pd(OAc)_2$, Cy_3P, K_2CO_3, dioxane, 120 °C, 12 h[41b]	traces of **751**
6	$PdCl_2(Cy_3P)$, Cs_2CO_3, dioxane, 120 °C 12 h[41c]	**746**:**751** = 2:1[b]
7	XPhos-Pd-G3, Cs_2CO_3, dioxane, 120 °C 12 h	**746**:**751** = 1:1[b]

[a] Isolated yield. [b] Determined by ^1H NMR.

The intramolecular Heck-type cyclisation of bromo- and iodo-substituted indoles with 1,2,3,6-tetrahydropyridines stands as a well-established strategy for the synthesis of the ergoline core (see **Section 3.4** for selected examples).[42] In parallel, Daniel Cox explored the conversion of nitro-substituted indole **742-Ts** into corresponding bromo- or iodo-substituted indoles.[22, 43] During extensive screening of multiple reaction conditions for the reduction of the nitro group, he successfully identified a suitable method for transformation of nitroindole **742-Ts** into the corresponding aromatic amine **747-Ts** (**Scheme 3.28**).[44]

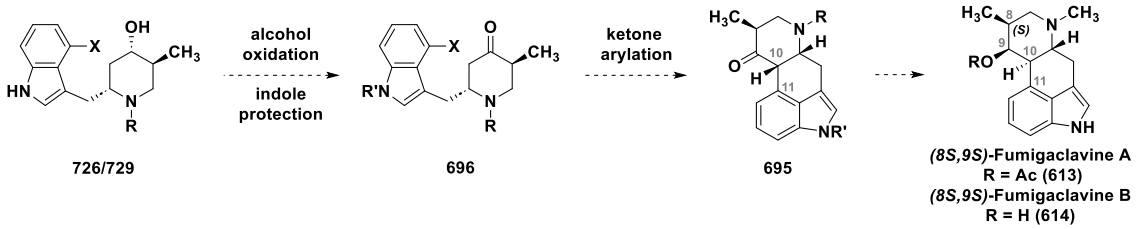


Scheme 3.28. *Synthesis of iodo-substituted aniline **748-Ts**.*

Subsequent efforts to convert the amino group in **747-Ts** into iodide *via* a diazotisation–iodination sequence proved to be challenging. Under the best conditions, iodide **748-Ts** was obtained in 47% yield as an inseparable mixture with the deaminated product **749-Ts** (equivalent to 17% yield of pure iodide **748-Ts**). Alternative methods for the halogenation of amine **747-Ts**, such as Sandmeyer bromination, were not fruitful either. Given these challenges and more promising results in the parallelly investigated strategies, this approach was abandoned at this point.

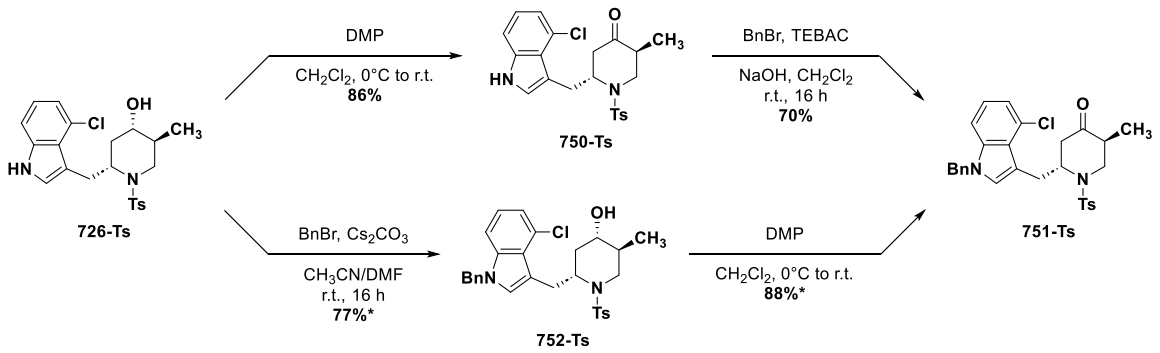
3.11 Ketone arylation strategy

Following the setbacks in our enone arylation strategy caused by the undesired reactivity of the enone moiety, we shifted our focus to an alternative approach for the construction of the C-ring *via* the arylation of hydrogenated substrates (**Scheme 3.29**). While this strategy offers a solution to the challenges related to the synthesis of cyclisation substrates, it introduces a new concern - the presence of an acidic proton at C-8 that might lead to partial epimerisation of this stereogenic centre during the arylation step. Subsequent epimerisation of the C-10-stereogenic centre, followed by ketone reduction and protecting group manipulation, would accomplish the synthesis of *(8S,9S)*-Fumigaclavines A and B.



Scheme 3.29. *Overview of the ketone arylation strategy.*

In the early stage of our synthetic studies, we focused on the *N*-tosyl-protected substrates since their *N*-Boc-protected analogues often exhibited rotameric behaviour, thus complicating the NMR analysis. To put this plan into motion, intermediate **726-Ts** was converted to cyclisation substrate **751-Ts** (**Scheme 3.30**). Oxidation of the secondary alcohol in **726-Ts** with DMP provided ketone **750-Ts** in 86% yield. Subsequent indole protection under phase-transfer conditions afforded intermediate **751-Ts** in 70% yield. Notably, compound **751-Ts** could be prepared in a slightly increased yield by changing the step order and benzylation conditions.



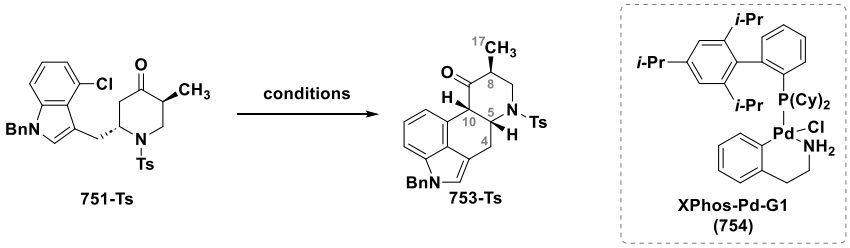
Scheme 3.30. *Synthesis of cyclisation substrate* ***751-Ts***.[xv]

With intermediate **751-Ts** in hand, we investigated the final C-C bond-forming reaction required for the synthesis of the ergoline core. Our initial attempt, inspired by Xu's work,[45] was not fruitful, resulting only in dechlorination and dimerisation of the starting material (**Table 3.6, entry 1**). In 2012, Cuny and co-workers reported intramolecular ketone arylation of structurally similar bromo- and chloro-indoles,[37]

[xv] Reactions marked with '*' were performed by Daniel Cox.

revealing that the use of Buchwald's pre-catalysts[46] was crucial for obtaining the desired products in high yield. This class of air- and moisture-stable pre-catalyst is activated under standard reaction conditions at or below room temperature, providing a highly active monoligated Pd(0) complex.[46] The efficiency of these catalysts can be demonstrated by one of the optimisation entries in Cuny's report. While the attempted cyclisation of aryl bromide in the presence of $Pd(OAc)_2$ and XPhos was not productive, the same reaction with XPhos pre-catalyst provided the desired product in 91% yield. Moreover, change of aryl bromide to aryl chloride led to formation of same product in 96% yield.

Table 3.6. *Screening of conditions for intramolecular ketone arylation.*



Entry	Conditions	*d.r.*[b]	Yield
1	$Pd_2(dba)_3$, XPhos, K_3PO_4, dioxane, 90 °C, 22 h	-	-
2[a]	XPhos-Pd-G1, NaO*t*-Bu (1.1 equiv.), dioxane, 0 °C then 60 °C 2 h	4:1	67%[c]
3[a]	XPhos-Pd-G1, KHMDS (1.05 equiv.), dioxane, 0 °C then 60 °C 2 h	5:1	60%

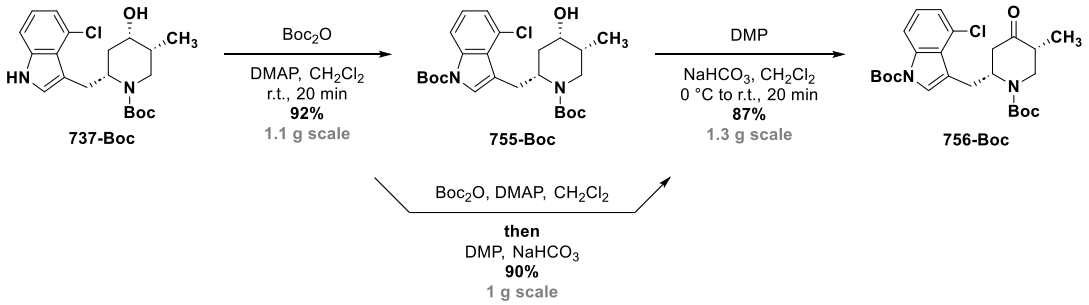
[a] *Experiments performed by Daniel Cox.* [b] *Based on 1H NMR of the crude reaction mixture.* [c] *Isolated as a mixture of diastereomers.*

Inspired by this work, we tested the cyclisation of compound **751-Ts** under Cuny's conditions. Pleasingly, deprotonation of substrate **751-Ts** with NaO*t*-Bu, followed by its heating in the presence of XPhos-Pd-G1 pre-catalyst, resulted in fast cyclisation and the desired product **753-Ts** was obtained as a 4:1 mixture of diastereomers (presumably at C-8) in 67% yield (53% major epimer). Changing the base to KHMDS and reducing its loading improved both the diastereomeric ratio (5:1) and the yield (60% single epimer).

We expected the *cis*-decalin to be formed in this cyclisation due to the aryl chloride being tethered to the bottom face of the piperidinone ring. Our assumption was confirmed by nOe experiments, showing a correlation between C-10 and C-5 protons. Correlation between protons at C-17 and C-10, as well as between C-8 and C-4, indicated that the configuration of the C-8-stereogenic centre was not changed.

Motivated by these results and facing the scalability issue during the synthesis of *N*-tosyl-protected indole **751-Ts** (see **Section 3.8**), we turned our attention to *N*-Boc protected indole **737-Boc** (**Scheme 3.31**), available in gram quantities. For the protection of indole nitrogen, we decided to use the Boc group, allowing global deprotection in the later stages of the synthesis. To this end, indole **737-Boc** was treated with Boc_2O in the presence of a catalytic amount of DMAP, resulting in a rapid and high-yielding introduction of the Boc group. Subsequent oxidation using DMP in the presence of $NaHCO_3$ to ensure

neutral condition and prevent potential cleavage of the Boc group, provided the desired ketone **756-Boc** in 88% yield. Moreover, the preparation of intermediate **756-Boc** could be streamlined by conducting both steps sequentially in the same reaction pot with a slightly increased yield (89% vs. 81% for the 2-step procedure).

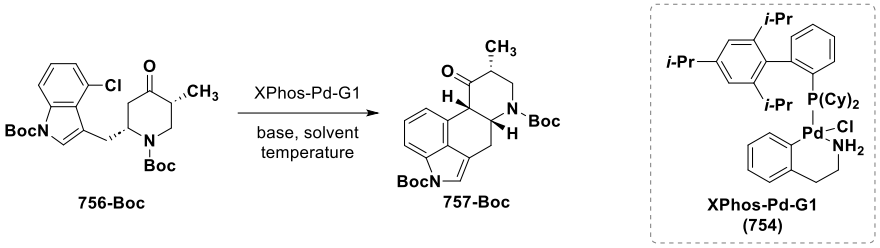


Scheme 3.31. *Synthesis of Boc-protected ketone* ***756-Boc****.*

With access to gram quantities of cyclisation substrate **756-Boc**, the palladium-catalysed cyclisation was investigated (**Table 3.7**). Heating of compound **756-Boc** with 1.5 equivalents of NaO*t*-Bu in the presence of XPhos-Pd-G1 pre-catalyst led to full conversion and the formation of a single product in satisfying 75% isolated yield (**entry 1**). Repeating this experiment under the same condition provided compound **757-Boc** in an even higher yield of 89% (**entry 2**). Encouraged by these results, the rest of the material available at that point was subjected to cyclisation (**entry 3**). To our surprise, the identical reaction conditions did not lead to full conversion and a significant drop in yield was observed (56%). To identify the source of the decreased yield, the reaction was repeated (**entry 4**) and, after the workup, analysed by quantitative ^{1}H NMR. This analysis revealed that the presumed residual starting material is was in fact a new product (presumably C-8 epimer) responsible for missing 14% of product mass. To avoid this undesired reaction, the effect of the base loading on the outcome of the cyclisation reaction was examined (**entries 5-7**). Using only 1.1 equivalents of the base resulted in a clean reaction and an 80% NMR yield (**entry 5**), while increased base loadings (**entries 6** and **7**) decreased the yield of the desired product **757-Boc** and led to the formation of multiple side products. At this point, we ran out of the previously used NaO*t*-Bu, and therefore, a new source of this reagent was used. To validate its quality, the cyclisation reaction was repeated using the optimal reaction conditions, **entry 5**. Disappointingly, variation in the base source led to low conversion (**entry 8**) and diminished product ratio (3.1:1). To increase its quality, NaOt-Bu was resublimed.[xvi] Unfortunately, this had only minimal impact on the outcome of the reaction (**entry 9**).

[xvi] Treatment of the solid residue obtained after sublimation with aq. HCl led to the violent formation of gas, indicating that NaOt-Bu was contaminated with carbonates.

Table 3.7. *Screening of conditions for intramolecular ketone arylation.*



Entry	Conditions	Scale	Conv.[a]	Product ration[a]	Yield
1	NaO*t*-Bu (1.5 equiv.), dioxane, 60 °C, 2 h	20 mg	full	**>20**:1	75%
2	as **entry 1**	20 mg	full	n.d.	89%
3	as **entry 1**	50 mg	partial[b]	n.d.	56%
4	as **entry 1**	40 mg	full	**4.5**:1	59 (62%)
5	as **entry 1** but **1.1 eq.** of NaO*t*-Bu	40 mg	full	**15**:1	(80%)
6	as **entry 1** but **1.5 eq.** of NaO*t*-Bu	40 mg	full	**4.0:**1	(56%)
7	as **entry 1** but **2.0 eq.** of NaO*t*-Bu	40 mg	full	**2.1:**1	(34%)
8	as **entry 1** but **1.1 eq.** of NaO*t*-Bu[c]	40 mg	62%	**3.1:**1	(45%)
9	as **entry 1** but **1.2 eq.** of resublimed NaO*t*-Bu[c]	40 mg	70%	**6.2**:1	(51%)
10	as **entry 1,** but **NaHMDS** (1.1 eq.)	40 mg	70%	**3.0**:1	(52%)
11	as **entry 1** but 2M NaO*t*-Bu (1.2 eq.)	40 mg	full	**7.5**:1	(80%)
12	as **entry 11**	40 mg	full	**6.6**:1	(85%)
13	as **entry 11** but in THF	40 mg	full	**6.5**:1	(69%)
14	as **entry 11**	600 mg	51%	**3.7**:1	32%

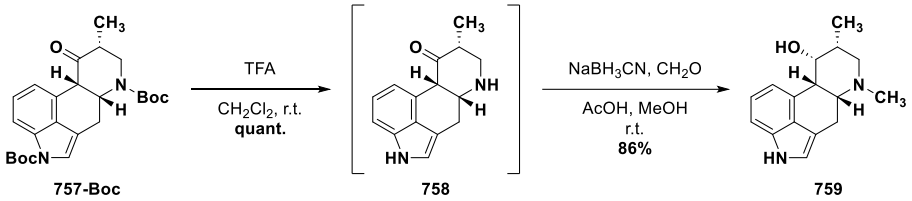
*Yield refers to the isolated yield of compound **757-Boc**. The Number in parentheses represents the NMR yield determined by analysis of the crude reaction mixture with TMB as an internal standard. [a] Based on ^{1}H NMR of the crude reaction mixture. [b] Determined by TLC analysis. [c] Different source of solid NaOt-Bu was used in entries 8-9.*

Due to the reproducibility issues related to the use of solid NaOt-Bu and other considerations such as simplified reaction setup, increased accuracy of the amount of the added base and ability to handle the reagents under oxygen-free conditions, we decided to use bases in the form of stock solutions. While the use of NaHMDS did not improve the reaction outcome (**entry 10**), a 2 M solution of NaO*t*-Bu from a commercial source led to the formation of the desired product with an 80% yield (**entry 11**). To confirm the reproducibility of our setup, **entry 11** was repeated, with the cyclised product formed in 85% yield. An experiment conducted in THF showed that this solvent has only minimal impact on the reaction (**entry 13**). Finally, the upscaling of the reaction from 40 to 600 mg was attempted. Unfortunately, this reaction stalled at 51% conversion, providing product **757-Boc** with poor selectivity (3.7:1) and yield (32%). Presumably, the less effective heat transfer during the deprotonation phase on a bigger scale, has led to the formation of a decomposition product capable of poisoning the catalyst, resulting in the observed low conversion. Isolation of substrate with deprotected indole ring in 20% yield, as well as further work by Daniel Cox (see **Section 3.13**) supports this hypothesis.

One potential solution to this issue could be a replacement of the relatively labile indole N^{in}-Boc group with a more robust protecting group, such as the benzyl or tosyl group.[47] Unfortunately, a deeper investigation of the cyclisation of intermediate **757-Boc** and related compound was not possible due to time constraints.

3.12 End game

With a limited amount of tetracyclic intermediate **757-Boc** obtained during the optimisation of the cyclisation reaction, its elaboration towards the clavine alkaloids was explored. Based on the targeted natural product, this might require epimerisation of the C-10 stereogenic centre, cleavage of both Boc protecting groups, *N*-methylation of the piperidine ring and conversion of the ketone group into either an alcohol, alkene or alkane.



757-Boc 758 759

Scheme 3.32. *Protecting groups manipulation.*

Due to the rotameric behaviour of the piperidine Boc group, complicating the analysis of the NMR spectra, we decided to first change the *N*-Boc to the *N*-methyl group and subsequently focus on the other required transformations (**Scheme 3.32**). To this end, both Boc-protecting groups in tetracycle **757-Boc** were cleaved by its treatment with TFA, providing intermediate **758** as its TFA salt in quantitative yield. Subsequent solvent swap and reductive methylation with formalin and $NaBH_3CN$, conditions commonly used in the syntheses of clavine alkaloids,[42, 48] furnished product **759** in 86% yield. Unfortunately, the use of $NaBH_3CN$ as a reducing agent also reduced the ketone group. The configuration of this newly formed stereogenic centre, as well as all others, was confirmed by single crystal X-ray analysis of compound **759** and was in agreement with our assumption that the reduction took place from the less hindered convex face of the cis-decalin core (**Figure 3.3**). Unfortunately, the relative configuration of compound **759** did not match any known clavine alkaloids.

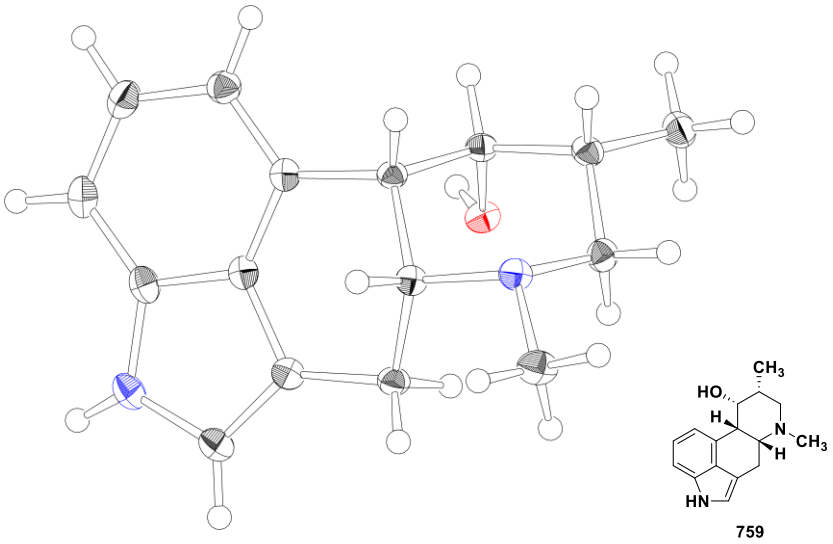
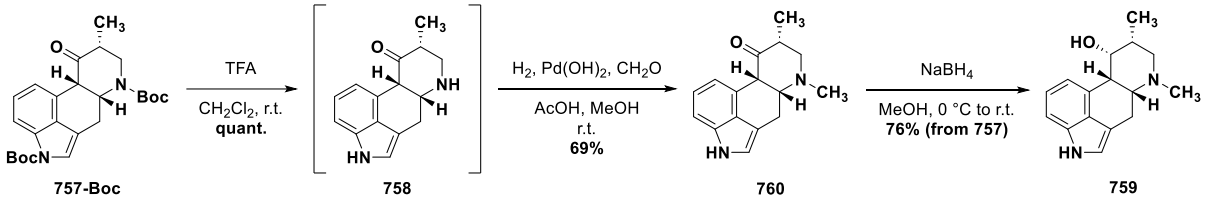


Figure 3.3. *ORTEP diagram of compound* ***759*** *with thermal ellipsoids drawn at 50% probability.*[xvii]

In our retrosynthetic analysis, we postulated that tetracyclic ketone **695** could serve as a versatile intermediate, providing access to various clavine alkaloids. Therefore, to gain access to this synthetically interesting intermediate, various methods for the reduction of the iminium ion were explored. Having good experience with formic acid as a reducing agent in the last step of our synthesis of Himalensine A, Eschweiler-Clarke methylation was tested. However, heating of intermediate **758** with formalin in the presence of formic acid did not provide the desired product. Drawing inspiration from Natsutani's work,[49] the reduction of iminium ion using catalytic hydrogenation with palladium hydroxide on charcoal was tested (**Scheme 3.33**). Pleasingly, these conditions provided ketone **760** in a 69% yield.[xviii] Treatment of crude ketone **760** with $NaBH_4$ provided alcohol **759**, albeit in a slightly lower yield compared to the sequence described in **Scheme 3.32** (76% from compound **757-Boc**).

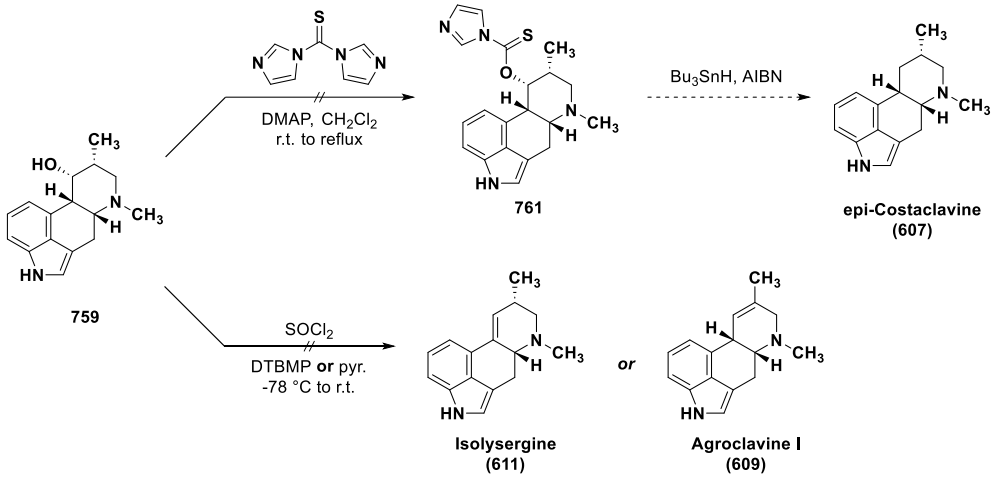


Scheme 3.33. *Alternative synthesis of alcohol* ***759*** *via ketone* ***760.***

To convert alcohol **759** into one of the clavine alkaloids, several transformations were briefly explored (**Scheme 3.34**). For instance, Barton-McCombie deoxygenation[50] of intermediate **759** would lead to epi-Costaclavine. To this end, activation of the C-9 hydroxyl group with 1,1'-thiocarbonyldiimidazole (TCDI) was attempted. Unfortunately, due to the hindered nature of the alcohol

[xvii] Figure 3.3 was generated using the Molby software. In the representation, carbon atoms are depicted in black, oxygen in red, nitrogen in blue, and hydrogen in white with a fixed diameter for clarity.
[xviii] The relatively low yield of ketone **760** compared to alcohol **579** might be caused by losses during its isolation/purification.

group, treatment of intermediate **759** with an excess of TCDI at elevated temperature did not lead to the formation of product **761**.

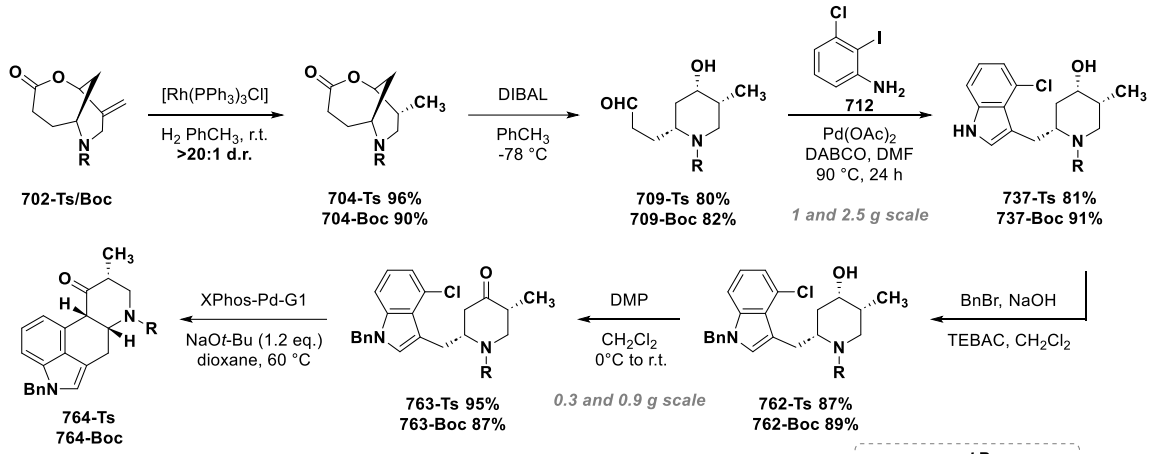


Scheme 3.34. *Attempted conversion of intermediate* ***759*** *to natural products.*

Alternatively, elimination of the C-9 hydroxy group would lead to the formation of Isolysergine (**611**) and/or Agroclavine I (**609**). Inspired by a key step in Ben Shennan's (Dixon research group) synthesis of Madangamine E,[25d] alcohol **759** was treated with thionyl chloride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). However, under these conditions, no reaction occured. Replacing DTBMP with a less hindered base (pyridine) was not productive either, while stirring of the reaction mixture for a prolonged time led to the formation of a complex mixture of products. Similarly, an attempt to re-oxidise C-9-hydroxyl back to ketone with DMP left this functional group intact.

3.13 Recent development

During his 1st SBM CDT rotation, Daniel Cox re-joined the Dixon research group and applied the previously discussed synthetic sequence to *the N-tosyl*-protected product of Baeyer-Villiger oxidation **704-Ts** (**Scheme 3.35**). He successfully synthesised both *N*-Boc- and *N*-tosyl-protected indoles **737** on a multigram scale. Building on the finding that the Boc group might be responsible for the problematic upscaling of the C-ring-forming ketone arylation reaction and, therefore, not being a suitable protecting group for the indole ring, he opted for the more robust benzyl group to protect the indole ring in compounds **737-Ts/Boc**.



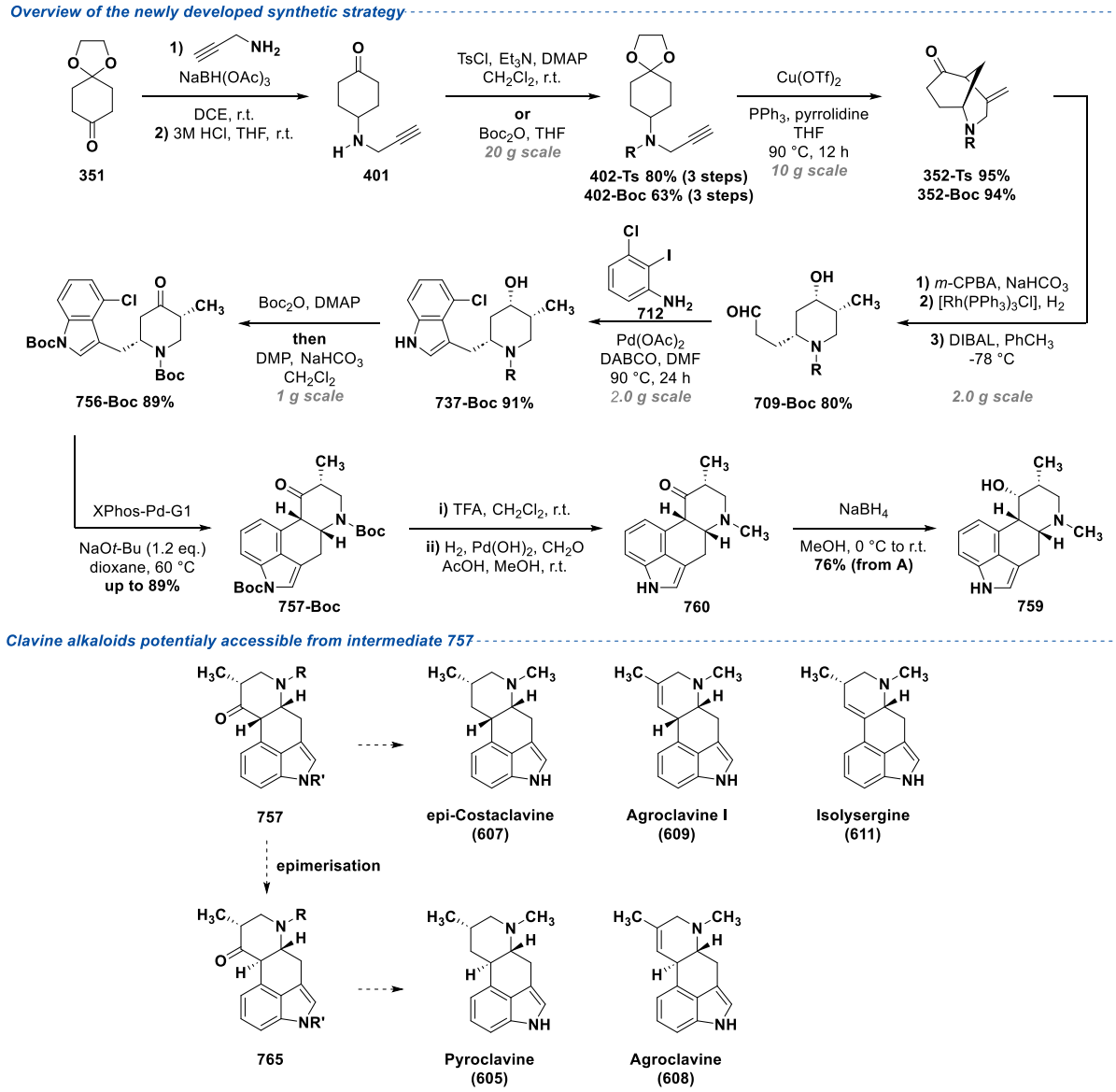
entry	substrate	scale	conversion	*d.r.*	yield of 794
1	**763-Ts**	40 mg	100%	**1**:0	63%*
2	**763-Boc**	40 mg	100%	**8.5**:1	85%*
3	**763-Ts**	100 mg	100%	**1**:0	51%
4	**763-Boc**	100 mg	100%	**4.6**:1	79%
5	**763-Boc**	150 mg	100%	*n.d.*	85%

Scheme 3.35. *Recent development by Daniel Cox.*

Subsequent oxidation of the alcohol in **762-Ts/Boc** with DMP provided the substrate for the final cyclisation. Pleasingly, both ketones **763-Ts** and **763-Boc** underwent smooth cyclisation, forming the corresponding tetracyclic compound **764-Ts** and **764-Boc** with good *d.r.* in 63% and 85% (NMR yield of **764**, **entry 1-2**). Careful upscaling to 100 and later to 150 mg scale afforded the *N*-Boc-protected tetracycle in up to 85% isolated yield (**entry 4-5**). The lower yield of *N*-tosyl-protected tetracycle indicated the potential base-sensitivity of this substrate. The elaboration of intermediates **764-Ts/Boc** into clavine alkaloids will be the subject of future research.

3.14 Conclusion and future work

In this chapter, a new convergent synthetic strategy for clavine alkaloids utilising an intermediate from our previous synthesis of *Daphniphyllum* alkaloids, compound **352-Ts/Boc**, was explored (**Scheme 3.36**). Compounds **352-Ts/Boc** were converted by an elegant sequence of highly selective transformations into advanced tetracyclic intermediate **757-Boc**, which could serve as a common intermediate for the collective synthesis of these natural products. The key feature of the synthesis is the convergent assembly of the ergoline core enabled by a palladium-catalysed coupling of aldehyde **709-Ts/Boc** and 2-iodoaniline **712**, followed by intramolecular ketone arylation. Moreover, strategically timed catalytic hydrogenation enabled the selective introduction of the C-8 stereogenic centre, providing access to both the *8R* and *8S* series of clavine alkaloids. The conversion of compound **757** and related intermediates into the clavine alkaloids will be the subject of further studies.



Scheme 3.36. *Summary of* ***Chapter 3.***

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Chapter 4: Experimental Details

4.1 General experimental details

General techniques: Procedures using oxygen and/or moisture-sensitive materials were performed with anhydrous solvents (*vide infra*) under an atmosphere of anhydrous argon in oven-dried flasks, using standard Schlenk techniques. Room temperature refers to 22 ± 2 °C. Reaction temperatures refer to external temperatures, for example, of a heating block or oil bath, not of internal reaction temperatures. Heating was performed using oil bath.

Solvent and reagents: Commercially available reagents and ligands were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics, Fluorochem and Strem Chemicals and, unless otherwise stated, were used without further purification. $[Rh(cod)OH]_2$ was synthesized according to a literature procedure.[1] Dry solvents were collected fresh from an mBraun SPS–800 solvent purification system after having passed through anhydrous alumina columns. Deuterated solvents were purchased from Sigma Aldrich.

Thin layer chromatography (TLC): Analytical thin-layer chromatography was performed using Merck aluminium-backed DC60 F254 plates (particle size 0.2 mm) and visualised using a combination of UV light (254 nm) and aqueous basic potassium permanganate stain.

Column chromatography: Purification by column chromatography was carried out using Merck silica gel 60 F254 (particle size 43–60 μm).

Nuclear magnetic resonance (NMR) spectroscopy measurements were carried out at room temperature, unless stated otherwise. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, COSY, HSQC, HMBC and NOESY experiments were carried out using Bruker AVG-400 (400/101 MHz), AVH-400 (400/101 MHz), AVX-500 (500/125 MHz) or AVC-500 (500/125 MHz) spectrometers. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak ($CHCl_3$: δ_H 7.26, δ_C 77.16 ppm) with corresponding coupling constants (*J*) in Hertz (Hz) and multiplicities (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet and combinations of these and app.: apparent multiplicities). The assignment follows HSQC, COSY or/and HMBC spectra, chemical shift and coupling constant analysis.

Infrared spectroscopy (IR, neat or thin film) was carried out on a Bruker Tensor 27 FT–IR spectrometer within an internal calibration range of 4000 – 600 cm^{-1}. Selected diagnostic absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

High resolution mass spectrometry (HRMS) was performed using Waters Bioaccord LC-MS system operating in positive ionisation mode or by Chemistry Research Laboratory staff using a Bruker Daltronics MicroTOF spectrometer (ESI). Mass to charge ratios (*m/z*) are reported in Daltons.

Melting points (m.p.) were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

Optical rotations were recorded using a Perkin Elmer 241 optical activity polarimeter at 25 °C. Specific rotations $[\alpha]_D^{25}$ are reported in 10^{-1} deg.cm^2.g^{-1}, with concentrations (c) in g/100 mL, and D refers to the D-line of sodium (589 nm).

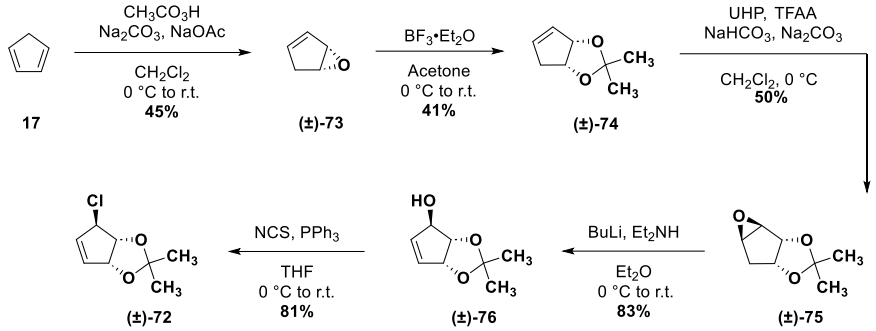
Enantiomeric excesses were determined by **HPLC** analysis on an Agilent 1200 Series instrument using a chiral stationary phase column specified in the individual experiment or by GC analysis on an Agilent 7820A instrument employing a chiral stationary phase column specified in the individual experiment or by **Chiral SFC** (supercritical fluid chromatography) analysis on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150×3 mm, particle size 3 μm) were used as specified in the text.

X-Ray Crystallography: Single crystal X-ray diffraction data were collected and solved by Dr Yao Shi (Dixon group), Timothy Davidson (Dixon group) or Dr Kirsten E Christenen (University of Oxford Chemical Crystallography department).

Nomenclature and Numbering: Compounds are named following IUPAC nomenclature as generated by ChemDraw. Carbon atoms are numbered in a systematic way where possible to ease comparison between related compounds in a synthetic sequence, not necessarily in accordance with IUPAC conventions.

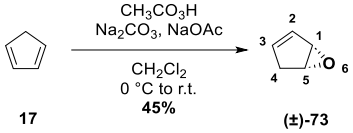
4.2 Experimental details for Chapter 1

4.2.1 Procedures for the synthesis of allyl chloride (±)-72



Scheme 4.1. *Overview of the synthesis of allyl chloride (±)-72.*

rac-6-oxabicyclo[3.1.0]hex-2-ene (*(±)*-73)



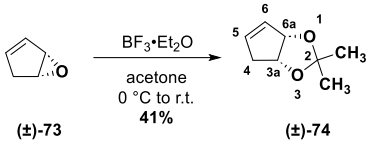
Epoxide **(±)-73** was prepared according to a procedure by M. E. Jung *et al.*[2]

Cyclopentadiene (15 mL, 210 mmol, 1.1 equiv.) was added to a suspension of Na_2CO_3 (49.7 g, 470 mmol, 2.47 equiv.) and NaOAc (950 mg, 11.5 mmol, 0.06 equiv.) in CH_2Cl_2 (235 mL). Peracetic acid (40 wt% in acetic acid, 32 mL, 190 mmol, 1.0 equiv.) was added dropwise at 0 °C. The reaction mixture was then allowed to reach r.t. and was stirred for a further 3 h. The mixture was filtered under reduced pressure, washed with CH_2Cl_2, and concentrated under reduced pressure (15 °C, 250 mbar). Vacuum distillation (25 mbar, 60 °C) afforded the desired product **(±)-73** as a colourless oil in a mixture with CH_2Cl_2 (estimated yield: 6.50 g, 45%). The spectroscopic data are in agreement with the literature.[2-3]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.14 (dtd, *J* = 5.6, 2.2, 1.1 Hz, 1H, C(2)-H), 5.98 (dp, *J* = 6.3, 2.1 Hz, 1H, C(3)-H), 3.91 (td, *J* = 3.3, 2.2 Hz, 1H, C(5)-H), 3.81 (dtd, *J* = 2.9, 1.9, 1.1 Hz, 1H, C(1)-H), 2.63 (dq, *J* = 19.1, 2.1 Hz, 1H, C(4)-H_2), 2.38 (ddt, *J* = 19.1, 3.5, 2.1 Hz, 1H, C(4)-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.0 (C-3), 131.4 (C-2), 59.3 (C-1), 57.0 (C-5), 35.7 (C-4).

***rac*-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[*d*][1,3]dioxole (*(±)*-74)**



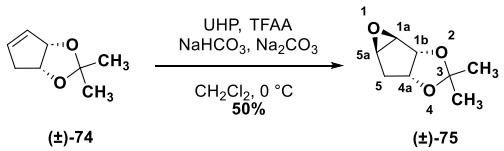
Acetal **(±)-74** was prepared according to a procedure by B. M. Trost *et al.*[4]

$BF_3{\cdot}Et_2O$ (0.98 mL, 7.9 mmol, 0.10 equiv.) was added dropwise to a solution of epoxide ***(±)*-73** (6.50 g, 79.2 mmol, 1.00 equiv.) in dry acetone (49 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and was stirred for 6 h. The reaction mixture was then concentrated under reduced pressure (35 °C, 300 mbar), dissolved in Et_2O (150 mL), and washed with an aq. sat. sol. of $NaHCO_3$ (2 x 25 mL) and an aq. sat. sol. of NH_4Cl (2 x 25 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O/pentane = 2.5% to 10%) afforded acetonide **(±)-74** as a colourless oil (4.62 g, 41%). The spectroscopic data are in agreement with the literature.[3-4]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.86 – 5.80 (m, 1H, C(5)-H), 5.77 (dq, *J* = 5.8, 1.9 Hz, 1H, C(6)-H), 5.10 (d, *J* = 6.0 Hz, 1H, C(6a)-H), 4.76 (td, *J* = 5.8, 1.5 Hz, 1H, C(3a)-H), 2.64 – 2.45 (m, 2H, C(4)-H_2), 1.41 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 132.6 (C-5), 130.8 (C-6), 109.8 (C-2), 85.6 (C-6a), 77.9 (C-3a), 38.9 (C-4)), 27.5 (CH_3), 25.7 (CH_3).

***rac*-(*trans*)-3,3-dimethyltetrahydro-5H-oxireno[2',3':3,4]cyclopenta[*1,2-d*][1,3]dioxole (*(±)*-75)**



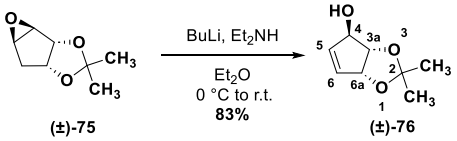
Epoxide **(±)-75** was prepared according to a procedure by B. M. Trost *et al.*[4]

Alkene **(±)-74** (4.55 g, 32.5 mmol, 1 equiv.) and urea hydrogen peroxide (UHP) (15.3 g, 162 mmol, 5.00 equiv.) were added to a suspension of $NaHCO_3$ (2.73 g, 32.5 mmol, 1.00 equiv.) and Na_2CO_3 (10.32 g, 97.7 mmol, 3.00 equiv.) in CH_2Cl_2 (330 mL) at 0 °C. A solution of trifluoroacetic anhydride (TFAA) (11 mL, 81 mmol, 2.5 equiv.) in CH_2Cl_2 (150 mL) was then added dropwise, and the resulting mixture was stirred for 3 h at 0 °C. The reaction mixture was then washed with an aq. sat. sol. of $NaHCO_3$ (3 x 50 mL), an aq. sat. sol. of $Na_2S_2O_3$ (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O/pentane = 10% to 25%) afforded epoxide **(±)-75** as a colourless oil (2.55 g, 50%). The spectroscopic data are in agreement with the literature.[3-4]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.55 (d, *J* = 5.5 Hz, 1H, C(1b)-H), 4.52 (tdd, *J* = 5.6, 1.9, 0.9 Hz, 1H, C(4a)-H), 3.60 – 3.54 (m, 2H, C(1a)-H and C(5a)-H), 2.27 (dd, *J* = 15.4, 6.0 Hz, 1H, C(5)-H_2), 1.94 (dt, *J* = 15.4, 2.0 Hz, 1H, C(5)-H_2), 1.45 (s, 3H, CH_3), 1.29 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 112.0 (C-3), 81.5 (C-4a), 80.2 (C-1b), 59.2 (C-1a or C-5a), 59.0 (C-1a or C-5a), 35.8 (C-5), 27.4 (CH_3), 24.9 (CH_3).

***rac*-(t*rans*)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[*d*][1,3]dioxol-4-ol (*(±)*-76)**



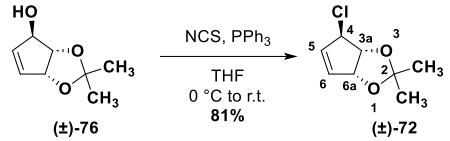
Allylic alcohol **(±)-76** was prepared according to a procedure by B. M. Trost *et al.*[4]

n-Butyl lithium (2.5 M in hexane, 13 mL, 32 mmol, 2.0 equiv.) was added dropwise to a solution of diethylamine (3.5 mL, 34 mmol, 2.1 equiv.) in Et_2O (18 mL) at 0 °C. After stirring for 30 min, a solution of epoxide **(±)-75** (2.50 g, 16.0 mmol, 1.00 equiv.) in Et_2O (18 mL) was added dropwise, and the reaction mixture was allowed to reach r.t. After 2 h, the reaction mixture was diluted with Et_2O (30 mL) and washed with an aq. sat. sol. of NH_4Cl (3 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate/pentane = 10% to 50%) afforded alcohol **(±)-76** as a colourless oil (2.08 g, 83%). The spectroscopic data are in agreement with the literature.[3-4]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.02 (dt, *J* = 5.8, 1.5 Hz, 1H, C(6)-H), 5.90 (ddt, *J* = 5.8, 2.1, 0.9 Hz, 1H, C(5)-H), 5.28 (dtd, *J* = 5.7, 1.7, 0.9 Hz, 1H, C(6a)-H), 4.78 (d, *J* = 5.0 Hz, 1H, C(4)-H), 4.51 (d, *J* = 5.6 Hz, 1H, C(3a)-H), 2.20 (m, 1H, OH), 1.39 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 135.7 (C-6), 134.8 (C-5), 111.9 (C-2), 86.1 (C-3a), 84.4 (C-6a), 81.1 (C-4), 27.4 (CH_3), 25.8 (CH_3).

***rac*-(*trans*)-4-chloro-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[*d*][1,3]dioxole (*(±)*-72)**



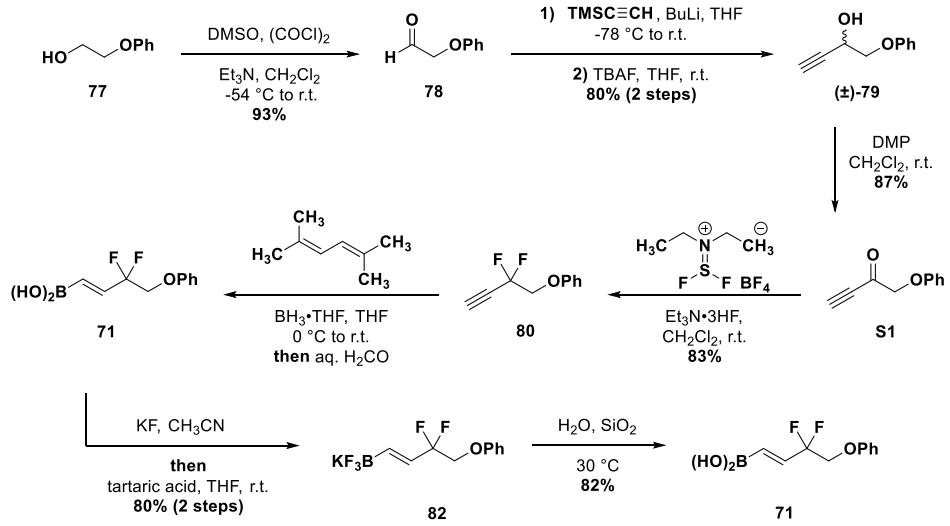
Allylic alcohol **(±)-72** was prepared according to a procedure by F. W. Goetzke *et al.*[3]

Triphenylphosphine (5.04 g, 19.2 mmol, 1.50 equiv.) and *N*-chlorosuccinimide (NCS) (2.74 g, 20.5 mmol, 1.60 equiv.) were added to a solution of alcohol **(±)-76** (2.00 g, 12.8 mmol, 1.00 equiv.) in THF (20 mL) at 0 °C. After 1 h, the reaction mixture was allowed to reach r.t. and was stirred for an additional 1 h. The reaction mixture was then filtered through a pad of Celite and concentrated under reduced pressure. Purification by gradient column chromatography (CH_2Cl_2/pentane = 0% to 50%) afforded allyl chloride **(±)-72** as a colourless oil (1.81 g, 81%). The spectroscopic data are in agreement with the literature.[3]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.01 (ddt, *J* = 5.7, 1.7, 0.7 Hz, 1H, C(6)-H), 5.91 (ddt, *J* = 5.6, 2.3, 0.9 Hz, 1H, C(5)-H), 5.32 (dq, *J* = 5.6, 1.4 Hz, 1H, C(6a)-H), 4.81 (ddt, *J* = 2.4, 1.5, 0.7 Hz, 1H, C(4)-H), 4.79 (dd, *J* = 5.5, 0.8 Hz, 1H, C(3a)-H), 1.38 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

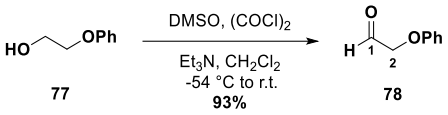
^{13}C NMR (101 MHz, $CDCl_3$) δ: 135.7 (C-6), 133.6 (C-5), 112.3 (C-2), 86.1 (C-3a), 84.4 (C-6a), 65.1 (C-4), 27.6 (CH_3), 26.3 (CH_3).

4.2.2 Procedures for the synthesis of boronic acid 71



Scheme 4.2. *Overview of the synthesis of boronic acid* ***71****.*

2-phenoxyacetaldehyde (78)



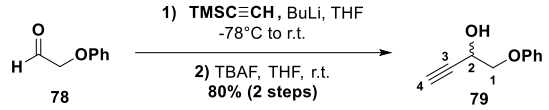
Aldehyde **78** was prepared according to a procedure by D. R. Dragoli *et al.*[5]

A solution of DMSO (11 mL, 160 mmol, 2.2 equiv.) in CH_2Cl_2 (36 mL) was added dropwise over 30 min to a solution of oxalyl chloride (6.7 mL, 80 mmol, 1.1 equiv.) in CH_2Cl_2 (290 mL) at -54 °C. After 10 min, a solution of 2-phenoxyethanol (10.0 g, 72.4 mmol, 1.00 equiv.) in CH_2Cl_2 (70 mL) was added dropwise over 30 min, and the reaction mixture was stirred with a mechanical stirrer for an additional 60 min. Triethylamine (40 mL, 290 mmol, 4.0 equiv.) was then added dropwise over 20 min. After 60 min, water (320 mL) was added, and the reaction mixture was allowed to reach r.t. The organic phase was separated, and the aq. phase extracted with CH_2Cl_2 (4 x 50 mL). The combined organic phases were washed with 1 M aq. HCl (5 x 50 mL), brine (2 x 60 mL), an aq. sat. sol. of $NaHCO_3$ (3 x 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **78** was obtained as a pale-yellow oil (9.17 g, 93%) and used in the next step without further purification. The spectroscopic data are in agreement with the literature.[6]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (t, *J* = 1.1 Hz, 1H, C(1)-H), 7.36 – 7.26 (m, 2H, C_{meta}-H), 7.06 – 7.00 (m, 1H, C_{para}-H), 6.94 – 6.87 (m, 2H, C_{ortho}-H), 4.57 (d, *J* = 1.1 Hz, 2H, C(2)-H_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.6 (C-1), 157.8 (C_q), 129.9 (C_{meta}), 122.1 (C_{para}), 114.7 (C_{ortho}), 72.8 (C-2).

rac-1-phenoxybut-3-yn-2-ol (_(±)_-79)



Alcohol **(±)-79** was prepared according to a procedure by E. J. Corey *et al.*[7]

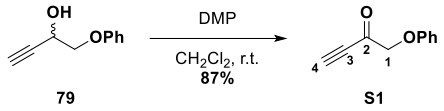
n-Butyl lithium (2.5 M in hexane, 22 mL, 55 mmol, 1.5 equiv.) was added to a solution of ethynyltrimethylsilane (10 mL, 73 mmol, 2.0 equiv.) in THF (220 mL) at -78 °C. After stirring for 30 min, a solution of aldehyde **78** (5.00 g, 36.7 mmol, 1.00 equiv.) in THF (30 mL) was added dropwise over 15 min. After 30 min, the reaction mixture was allowed to reach r.t. and stirred at this temperature for 30 min. The reaction mixture was then quenched with an aq. sat. sol. of NH_4Cl (150 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure.

The residue was dissolved in THF (150 mL), and a solution of tetrabutylammonium fluoride (TBAF) (1 M in THF, 38 mL, 37 mmol, 1.0 equiv.) was added dropwise at 0 °C. The resulting orange solution was stirred for 20 min at r.t. and then poured onto an aq. sat. sol. of $NaHCO_3$. The aq. phase was extracted with Et_2O (3 x 100 mL), and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate/hexane = 5% to 35%) afforded alcohol **(±)-79** as a colourless solid (4.75 g, 80%, over 2 steps). The spectroscopic data are in agreement with the literature.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.26 (m, 2H, C_{meta}-H), 7.00 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.97 – 6.90 (m, 2H, C_{ortho}-H), 4.77 (dddd, *J* = 7.4, 5.7, 3.6, 2.2 Hz, 1H, C(1)-H), 4.16 (dd, *J* = 9.6, 3.7 Hz, 1H, C(1)-H_2), 4.09 (dd, *J* = 9.6, 7.0 Hz, 1H, C(1)-H_2), 2.71 (d, *J* = 5.4 Hz, 1H, OH), 2.54 (d, *J* = 2.3 Hz, 1H, C(4)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.2 (C_q), 129.7 (C_{meta}), 121.7 (C_{para}), 114.9 (C_{ortho}), 81.2 (C-4), 74.5 (C-5), 71.4 (C-2), 61.4 (C-1).

1-phenoxybut-3-yn-2-one (S1)



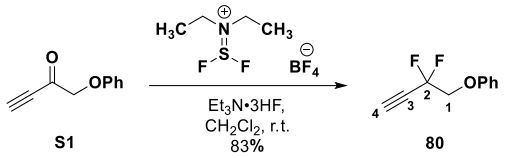
Dess-Martin periodinane (DMP) (21.9 g, 51.6 mmol, 1.20 equiv.) was added to a solution of alcohol **(±)-79** (6.97 g, 43.0 mmol, 1.00 equiv.) in CH_2Cl_2 (200 mL) and the resulting solution was stirred for 50 min at r.t. The reaction mixture was then poured onto an aq. sat. sol. of $NaHCO_3$ (200 mL) and the aq. phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with brine (100

mL), dried over Na_2SO_4, and concentrated under reduced pressure. The colourless residue was passed through a short plug of silica (6 cm) and eluted with a 15% mixture of ethyl acetate in hexane. The purified product **S1** was obtained as a colourless crystalline solid (5.99 g, 87%, >98% purity) contaminated with orange residue (product of decomposition on silica). The spectroscopic data are in agreement with the literature.[8]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.27 (m, 2H, C_{meta}-H), 7.05 – 6.99 (m, 1H, C_{para}-H), 6.93 – 6.87 (m, 2H, C_{ortho}-H), 4.75 (s, 2H, C(1)-H_2), 3.39 (s, 1H, C(4)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 182.7 (C-2), 157.6 (C_q), 129.7 (C_{meta}), 122.1 (C_{para}), 114.8 (C_{ortho}), 82.4 (C-4), 79.1 (C-3), 73.5 (C-1).

((2,2-difluorobut-3-yn-1-yl)oxy)benzene (80)



Compound **80** was prepared according to a procedure by J.-F. Syu *et al.*[9]

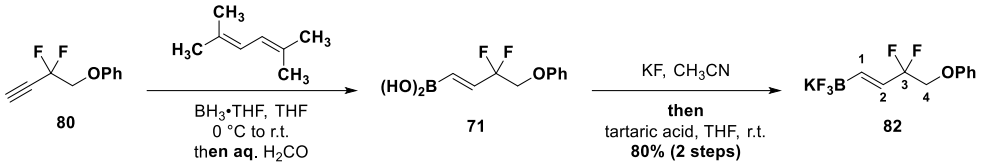
Triethylamine trihydrofluoride (12 mL, 74 mmol, 2.0 equiv.) was added to a suspension of XtalFluor-E (12.7 g, 55.3 mmol, 1.50 equiv.) in CH_2Cl_2 (13 mL) at r.t. After complete dissolution of solid reagent, a solution of ketone **S1** (5.90 g, 36.8 mmol, 1.00 equiv.) in CH_2Cl_2 (30 mL) was added, and the resulting mixture was stirred for 18 h. The reaction mixture was then poured onto an aq. sat. sol. of $NaHCO_3$ (150 mL) and was extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure (30 °C, 50 mbar). Purification by gradient column chromatography (ethyl acetate/pentane = 2% to 6%) afforded alkyne **80** as a pale-yellow oil (5.57 g, 83%). The spectroscopic data are in agreement with the literature.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 – 7.28 (m, 2H, C_{meta}-H), 7.07 – 7.01 (m, 1H, C_{para}-H), 6.99 – 6.94 (m, 2H, C_{ortho}-H), 4.30 (t, J = 11.3 Hz, 2H, C(1)-H_2), 2.86 (t, J = 5.1 Hz, 1H, C(4)-H).

^{13}C NMR (126 MHz, $CDCl_3$, ^{19}F decoupled) δ: 158.0 (C_q), 129.8 (C_{meta}), 122.3 (C_{para}), 115.2 (C_{ortho}), 111.0 (C-2), 77.2 (C-4), 74.8 (C-3), 70.3 (C-1). (Peak reported at 77.1 ppm overlaps with solvent peak).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -93.34.

Potassium (*E*)-(3,3-Difluoro-4-phenoxybut-1-en-1-yl)- trifluoroborate (82)



Compound **82** was prepared according to a procedure by J.-F. Syu *et al.*[9]

A solution of borane tetrahydrofuran complex (1 M in THF, 61 mL, 61 mmol, 2.5 equiv.) was added to a solution of 2,5-dimethylhexa-2,4-diene (20 mL, 130 mmol, 5.5 equiv.) in THF (11 mL) at 0 °C. After stirring for 3 h, a solution of alkyne **80** (4.44 g, 24.4 mmol, 1.00 equiv.) in THF (24 mL) was added dropwise, and the reaction mixture was stirred overnight at r.t. The reaction mixture was then carefully quenched by the addition of water (9.3 mL) (evolution of gas observed) at 0 °C. After stirring for 90 min at r.t., 37% aq. sol. of formaldehyde (22 mL) was added (slightly exothermic reaction, exothermicity compensated by water bath), and the resulting mixture was stirred overnight at r.t.

The reaction mixture was then poured onto brine (40 mL), and the aq. phase was extracted with ethyl acetate (4 x 60 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to provide crude boronic acid **71** together with (*E*)-2,2,5-trimethylhex-3-en-1-ol as a pale-yellow oil (25.4 g).

A solution of potassium fluoride (5.14 g, 88.5 mmol, 3.63 equiv.) in water (7.6 mL) was added to a solution of the above-prepared boronic acid **71** in CH_3CN (100 mL). The resulting mixture was vigorously stirred until dissolution was achieved (1 h). A solution of L-(+)-tartaric acid (6.84 g, 45.6 mmol, 1.87 equiv.) in THF (35 mL) was then added dropwise over 20 min (formation of a white precipitate). After stirring for 30 min, the solids were filtered off and washed with CH_3CN (50 mL). The collected solution was concentrated under reduced pressure, and the obtained residue was suspended in Et_2O (20 mL). After stirring for 1 h, the solid product was filtered off and washed with hexane to provide trifluoroborate **82** as a pale-yellow solid (4.83 g, 68%).

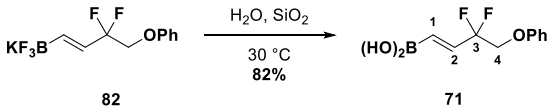
Note: The trifluoroborate **82** is partially soluble in (*E*)-2,2,5-trimethylhex-3-en-1-ol formed as a by-product in the hydroboration step. Therefore, an additional portion of trifluoroborate can be isolated from the solution obtained during the last filtration by removal of volatiles on rotavap and evaporation of the side product on kugelrohr, followed by precipitation of compound **82** with hexane (0.85 g, 12%; combined yield: 80%). The spectroscopic data are in agreement with the literature.[9]

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ: 7.37 – 7.20 (m, 2H, C_{meta}-H), 7.07 – 6.88 (m, 3H, C_{ortho}-H and C_{para}-H), 6.08 (dq, J = 18.3, 3.1 Hz, 1H, C(1)-H), 5.74 (dt, J = 18.2, 11.4 Hz, 1H, C(2)-H), 4.24 (t, J = 13.2 Hz, 2H, C(4)-H_2).

^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ: 157.9 (C_q), 129.6 (C_{meta}), 126.1 (tq, *J* = 24.6, 3.9 Hz, C-2), 121.2 (C_{para}), 119.7 (t, *J* = 238.6 Hz, C-3), 114.7 (C_{ortho}), 68.6 (t, *J* = 31.3 Hz, C-4). (The C−B signal was not observed due to quadrupolar relaxation.)

^{19}F NMR (471 MHz, $(CD_3)_2SO$, ^{1}H decoupled) δ: -101.32, -139.42.

(*E*)-(3,3-difluoro-4-phenoxybut-1-en-1-yl)boronic acid (71)



82 71

Compound **71** was prepared according to a procedure by J.-F. Syu *et al.*[9]

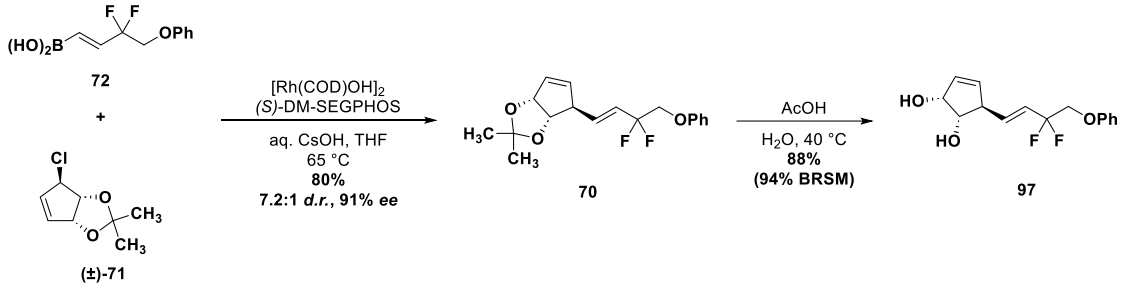
A suspension of trifluoroboronate **82** (4.75 g, 16.4 mmol, 1.00 equiv.) and silica gel (984 mg, 16.4 mmol, 1.00 equiv.) in water (16 mL) were stirred at 30 °C overnight. The solids were collected by vacuum filtration (pore size S4) and washed with water (5 mL). The solid was extracted several times with CH_3CN. The collected solution was concentrated under reduced pressure, and the obtained pale-yellow product was triturated with pentane (3 x 5 mL) to afford boronic acid **71** as a white solid (3.05 g, 82%). The spectroscopic data are in agreement with the literature.[9]

^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ: 8.12 (s, 2H, OH), 7.37 – 7.26 (m, 2H, C_{meta}-H), 7.05 – 6.94 (m, 3H, C_{ortho}-H and C_{para}-H), 6.56 (dt, *J* = 18.3, 11.1 Hz, 1H, C(1)-H), 6.07 (dt, *J* = 18.3, 2.4 Hz, 1H, C(2)-H), 4.37 (t, *J* = 12.9 Hz, 2H, C(4)-H_2).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, ^{19}F decoupled) δ: 157.6 (C_q), 138.2 (C-2), 129.6 (C_{meta}), 121.5 (C_{para}), 118.8 (C-3), 114.8 (C_{ortho}), 68.2 (C-4). (The C−B signal was not observed due to quadrupolar relaxation.)

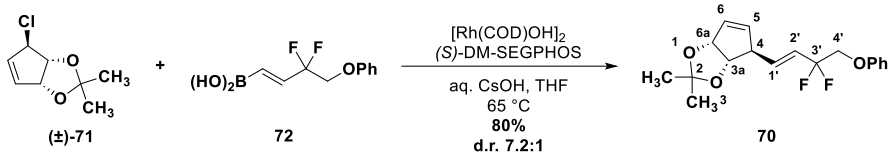
^{19}F NMR (471 MHz, $(CD_3)_2SO$, ^{1}H decoupled) δ: -103.99.

4.2.3 Synthesis of diol 97



Scheme 4.3. *Overview of the synthesis of diol* ***97****.*

(*3aS,4S,6aR*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[*d*][1,3]dioxole (70)



Compound **70** was prepared by adopting a procedure by F. W. Goetzke *et al.*[3]

An aq. sol. of CsOH (50 wt%, 330 µL, 1.9 mmol, 1.0 equiv.) was added to a solution of *(S)*-DM-SEGPHOS (82.4 mg, 114 µmol, 6.0 mol %) and $[Rh(cod)OH]_2$ (21.7 mg, 47.5 µmol, 2.5 mol%) in THF (3.3 mL) and the resulting mixture was stirred at 65 °C for 30 min. Then, a solution of boronic acid **72** (650 mg, 2.85 mmol, 1.50 equiv.) and allyl chloride **(±)-71** (300 µL, 1.9 mmol, 1.0 equiv.) in THF (3.3 mL) was added, the flask was rinsed with THF (0.9 mL). The resulting solution was stirred at 65 °C for 4 h. The unpurified reaction mixture showed a *d.r.* of 7.2:1. The reaction mixture was then diluted with Et_2O, loaded on silica, and the crude product was purified by column chromatography (ethyl acetate/hexane = 0% to 8%). Product **70** was obtained as a colourless oil (490 mg, 80%, 91% *ee*).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 – 7.27 (m, 2H, C_{meta}-H), 7.01 (tt, *J* = 7.4, 1.1 Hz, 1H, C_{para}-H), 6.94 – 6.87 (m, 2H, C_{ortho}-H), 6.21 (ddt, *J* = 15.9, 7.6, 2.5 Hz, 1H, C(1')-H), 5.92 (dt, *J* = 5.8, 1.8 Hz, 1H, C(6)-H), 5.80 – 5.69 (m, 2H, C(2')-H and C(5)-H), 5.16 (dq, *J* = 5.7, 1.4 Hz, 1H, C(6a)-H), 4.46 (d, *J* = 5.7 Hz, 1H, C(3a)-H), 4.18 (t, *J* = 11.5 Hz, 2H, C(4')-H_2), 3.54 (d, *J* = 6.6 Hz, 1H, C(4)-H), 1.43 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.1 (Cq), 137.3 (t, *J* = 8.9 Hz, C-1'), 133.8 (C-5), 132.9 (C-6), 129.8 (C_{meta}), 123.8 (t, J = 25.1 Hz, C-2'), 122.0 (C_{para}), 118.3 (t, *J* = 240.3 Hz, C-3'), 114.9 (C_{ortho}), 110.6 (C-2), 85.0 (C-6a), 83.1 (C-3a), 69.6 (t, *J* = 35.1 Hz, C-4'), 53.8 (C-4), 27.5 (CH_3), 25.8 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.69 (d, *J* = 257.7 Hz), -103.46 (d, *J* = 257.9 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 2987 (w), 1599 (w), 1496 (m), 1287 (m), 1210 (m), 1160 (m), 1050 (s), 754 (m).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{18}H_{20}O_3F_2Na)^+$ requires 345.1278, found 345.1273.

SFC Chiralpak® IF; 1500 psi, 30 °C; flow: 1.5 mL/min; from 1% to 30% MeOH in 5 min; 95.0:5.0 er (major enantiomer t_R = 1.66 min; minor enantiomer t_R = 1.76 min).

$[\alpha]^{25}_D$= -131.8 (c = 0.5, $CHCl_3$).

Table 4.1. *Ligand screening for* Asymmetric Suzuki-Miyaura coupling.

	Ligand	*ee*	*d.r.*[a]	yield[b]
1	*(±)*-BINAP	0	>20:1	85 (94)[c]%
2	*(S)*-BINAP	77%	>20:1	87%
3	*(R)*-Tol-BINAP	-80%[d]	>20:1	79%
4	*(R)*-DM-BINAP	-78%[d]	>20:1	83%
5	*(S)*-H8-BANAP	70%	>20:1	n.d.
6	*(S)*-SEGPHOS	90%	7.2:1	79%
7	***(S)*-DM-SEGPHOS**	**91%**	**7.2:1**	**80%**
8	*(S)*-P-Phos	70%	n.d.	n.d.
9	*(S)*-Xyl-P-Phos	77%	11.5:1	83%
10	*(R)*-MeO-BIPHEP	-66%[d]	n.d.	n.d.
11	*(S)*-Cl-MeO-BIPHEP	65%	n.d.	n.d.
12	*(R)*-SL-J001-1	10%	n.d.	n.d.

Standard conditions: 0.20 mmol scale, 2.5 mol % $[Rh(COD)OH]_2$, 6 mol % ligand, 1.5 equiv. boronic acid, 1.0 equiv. 50% aq. CsOH, concentration 0.25M, reaction time 4 h; [a] determined by NMR; [b] isolated yield, [c] 2.58 mmol scale. [d] A negative value of the ee indicates the formation of the opposite enantiomer.

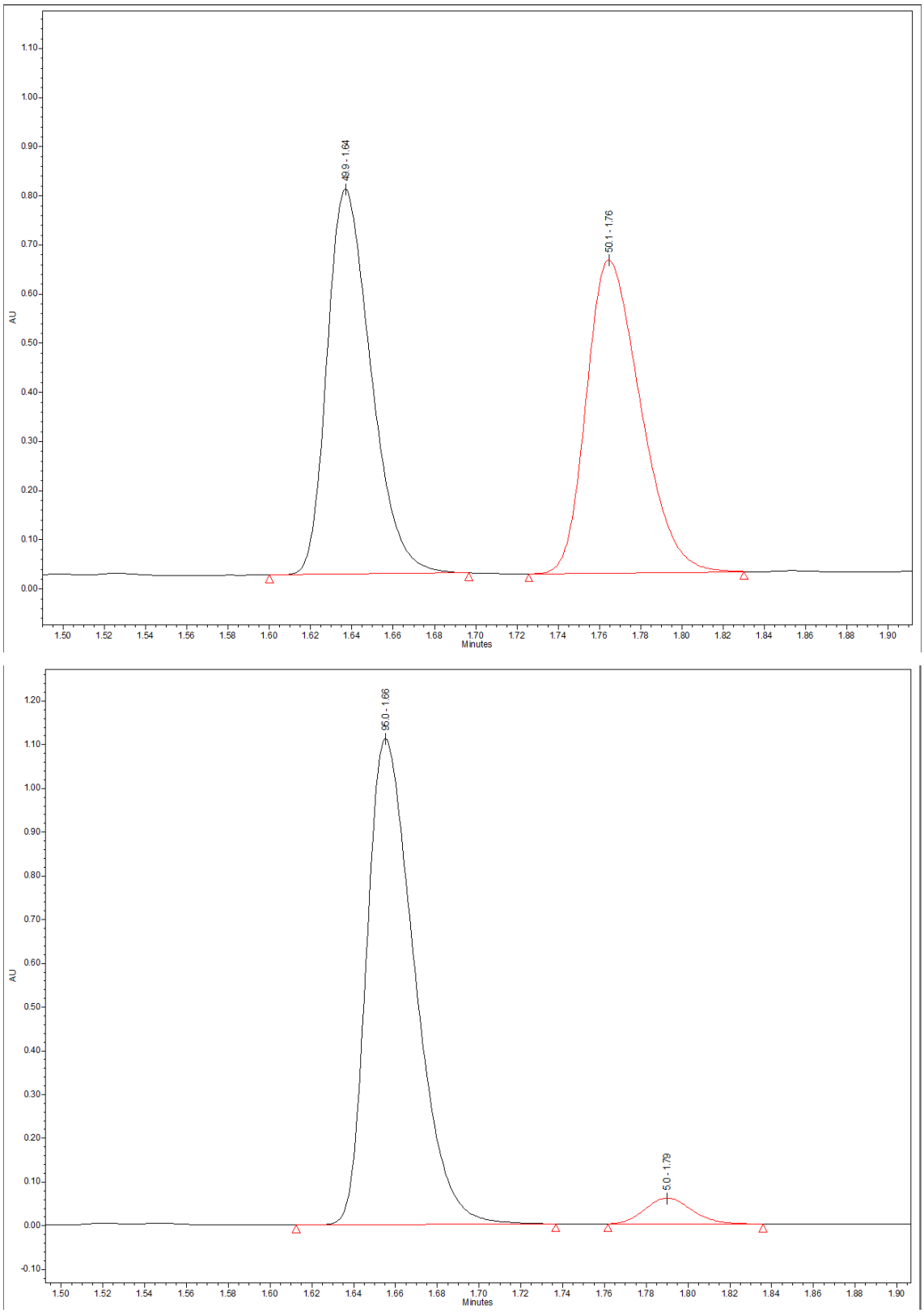
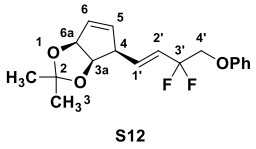


Figure 4.1. *SFC traces of the racemic* ***(±)-70*** *(top) and enantioenriched (–)-****70*** *(bottom).*

(*3aS,4R,6aR*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[*d*][1,3]dioxole (S2)



S12

Compound **S2** was isolated as a by-product of the above-described coupling reaction between allylchloride **(±)-71** and boronic acid **72** as a colourless oil (61 mg, 10%). The *ee* of the minor diastereomer was not determined.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, C_{meta}-H), 7.04 – 6.97 (m, 1H, C_{para}-H), 6.97 – 6.88 (m, 2H, C_{ortho}-H), 6.32 (ddt, *J* = 16.0, 8.2, 2.5 Hz, 1H, C(1')-H), 5.90 (dt, *J* = 5.8, 2.2 Hz, 1H, C(6)-H), 5.82 (dtd, *J* = 15.9, 11.1, 1.1 Hz, 1H, C(2')-H), 5.71 – 5.66 (m, 1H, C(5)-H), 5.13 (d, *J* = 5.6 Hz, 1H, C(6a)-H), 4.77 (t, *J* = 5.8 Hz, 1H, C(3a)-H), 4.21 (t, *J* = 11.6 Hz, 2H, C(4')-H_2), 3.44 – 3.37 (m, 1H, C(4)-H), 1.36 (s, 3H, CH_3), 1.34 (s, 3H, CH_3).

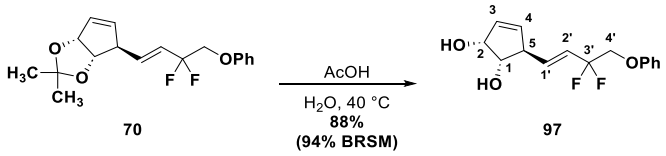
^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.2 (C_q), 135.2 (t, *J* = 9.1 Hz, C-1'), 134.3 (C-5), 132.3 (C-6), 129.7 (C_{meta}), 124.0 (t, *J* = 25.3 Hz, C-2'), 121.9 (C_{para}), 118.4 (t, *J* = 240.2 Hz, C-3'), 115.0 (C_{meta}), 111.1 (C-2), 85.6 (C-6a), 79.5 (C-3a), 69.8 (t, *J* = 34.6 Hz, C-4'), 50.2 (C-4), 27.4 (CH_3), 26.2 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.93, -102.95.

FT-IR ($CHCl_3$ film) cm^{-1}: 2987 (w), 1599 (w), 1497 (m), 1249 (m), 1161 (m), 1059 (vs), 755 (m).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}O_3F_2Na)^+$ requires 345.1278, found 345.1273.

(*1S,2R,5S*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)cyclopent-3-ene-1,2-diol (97)



Diol **97** was prepared adopting the procedure by F. W. Goetzke *et al.*[3]

A solution of acetonide **70** (764 mg) in AcOH (5.2 mL) and water (2.3 mL) was stirred for 19 h at 40 °C. The reaction mixture was then concentrated under reduced pressure. Purification by gradient chromatography (ethyl acetate/hexane = 50% to 60%) afforded diol **97** as a white solid (588 mg, 88%, 94% brsm).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, C_{meta}-H), 7.01 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.95 – 6.89 (m, 2H, C_{ortho}-H), 6.25 (ddt, *J* = 15.8, 7.6, 2.5 Hz, 1H, C(1')-H), 5.96 (dt, *J* = 6.1, 2.2 Hz, 1H, C(3)-H), 5.89 (dd, *J* = 6.1, 2.0 Hz, 1H, C(4)-H), 5.81 (dtd, *J* = 15.9, 11.2, 1.3 Hz, 1H, C(2')-H), 4.64 – 4.58 (m, 1H, C(2)-H), 4.19 (t, *J* = 11.6 Hz, 2H, C(4')-H_2), 3.97 (q, *J* = 5.6 Hz, 1H, C(1)-H), 3.38 (m, 1H, C(5)-H), 2.70 (d, *J* = 7.1 Hz, 1H, OH), 2.15 (d, *J* = 6.2 Hz, 1H, OH).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.1 (C_q), 137.1 (t, *J* = 8.9 Hz, C-1'), 136.1 (C-4), 132.7 (C-3), 129.8 (C_{meta}), 123.7 (t, *J* = 25.1 Hz, C-2'), 122.0 (C_{para}), 118.3 (t, *J* = 240.3 Hz, C-3'), 115.0 (C_{ortho}), 76.9 (C-1), 75.0 (C-2), 69.6 (t, *J* = 34.8 Hz, C-4'), 53.7 (C-5).

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.66 (d, *J* = 257.2 Hz), -103.38 (d, *J* = 256.5 Hz).

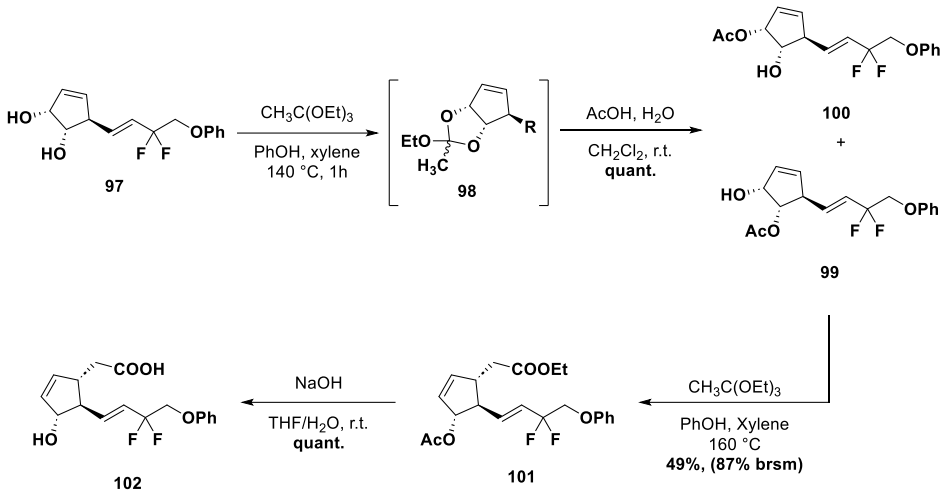
FT-IR ($CHCl_3$ film) cm^{-1}: 3360 (br, m), 1599 (m), 1496 (s), 1248 (s), 1163 (m), 1065 (s), 754 (s).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{15}H_{16}O_3F_2Na)^+$ requires 305.0965, found 305.0961.

MP: 45 – 48 °C.

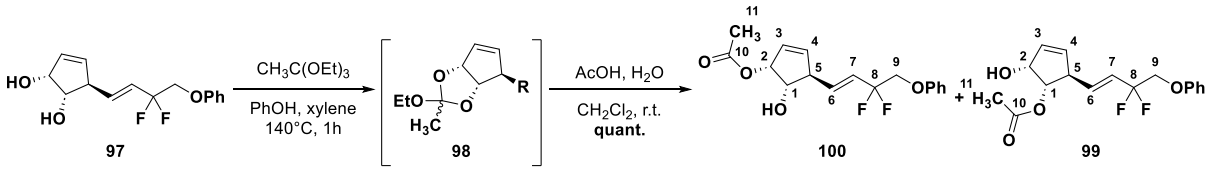
$[\alpha]^{25}_D$= -152.9 (c = 0.5, $CHCl_3$).

4.2.4 Synthesis of hydroxyacid 102 using a strategy based on Johnson-Claisen rearrangement



Scheme 4.4. *Synthesis of hydroxy acid* ***102*** *by Johnson-Claisen rearrangement.*

***rac*-(*1R,4S,5S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxycyclopent-2-en-1-yl acetate (100) and *rac*-(*1S,2S,5R*)-2-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxycyclopent-3-en-1-yl acetate (99)**



A solution of diol **97** (500 mg, 1.77 mmol, 1 equiv.), triethyl orthoacetate (2.27 mL, 12.4 mmol, 7.0 equiv.) and phenol (33.3 mg, 354 µmol, 0.20 equiv.) in xylene (13.4 mL) was stirred for 90 min at 140 °C. The reaction mixture was then diluted with ethyl acetate (60 mL) and washed with 1 M aqueous solution of NaOH (3 x 10 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure (45 °C).

The residue was dissolved in CH_2Cl_2 (20 mL), water (1.0 mL) and AcOH (0.1 mL) was added, and the solution was stirred for 15 min at room temperature. Then silica was added, solvent removed under reduced pressure, and the product purified by column chromatography (ethyl acetate/hexane = 10% to 50%). The monoacetylated product was obtained as a hardly separable mixture of isomers (equilibration on silica) as white wax (575.8 mg, >99%).

NOTE: Upon standing at room temperature, slow crystallisation of the product mixture was observed. Analysis of the solid material revealed that the equilibrium had shifted almost completely towards product **100** (**100:99** = 21:1).

Compound 100:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, H_{meta}), 7.01 (tt, *J* = 7.3, 1.1 Hz, 1H, H_{para}), 6.95 – 6.88 (m, 2H, H_{ortho}), 6.26 (ddt, *J* = 15.8, 7.5, 2.5 Hz, 1H, H-6), 5.98 (dd, *J* = 6.2, 1.8 Hz, 1H, H-3), 5.96 – 5.86 (m, 1H, H-4), 5.91 – 5.76 (m, 1H, H-7), 5.47 (ddd, *J* = 5.7, 2.5, 1.1 Hz, 1H, H-2), 4.20 (t, *J* = 11.5 Hz, 2H, H-9), 4.13 (dt, *J* = 7.0, 5.7 Hz, 1H, H-1), 3.47 – 3.39 (m, 1H, H-5), 2.19 (d, *J* = 7.0 Hz, 1H, OH), 2.12 (s, 3H, H-11).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.14 (C-10), 158.07 (C_q), 138.18 (C-3), 136.58 (t, *J* = 8.9 Hz, C-6), 129.76 (C_{meta}), 129.19 (C-4), 124.18 (t, *J* = 25.1 Hz, C-7), 122.00 (C_{para}), 118.24 (t, *J* = 240.4 Hz, C-8), 114.96 (C_{ortho}), 77.36 (C-2), 76.81 (C-1), 69.60 (t, *J* = 34.9 Hz, C-9), 53.14 (C-5), 21.15 (C-11).

Compound 99:

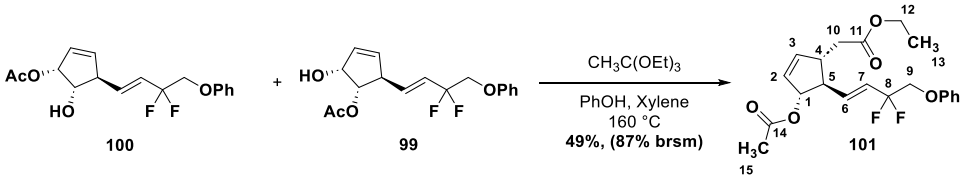
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, H_{meta}), 7.01 (tt, *J* = 7.3, 1.1 Hz, 1H, H_{para}), 6.95 – 6.88 (m, 2H, H_{ortho}), 6.26 – 6.18 (m, 1H, H-6), 5.98 (dd, *J* = 6.2, 1.8 Hz, 1H, H-3), 5.96 – 5.86 (m, 1H, H-4), 5.91 – 5.76 (m, 1H, H-7), 4.87 (m, 2H, H-1, H-2), 4.18 (t, *J* = 11.5 Hz, 2H, H-9), 3.61 – 3.55 (m, 1H, H-5), 2.12 (s, 3H, H-11), 1.79 (br s, 1H, OH).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.98 (C-10), 158.04 (C_q), 136.21 (t, *J* = 9.0 Hz, C-6),134.32 (C-4), 133.42 (C-3), 129.76 (C_{meta}), 124.13 (t, *J* = 25.2 Hz, C-7), 122.00 (C_{para}), 118.22 (t, *J* = 240.5 Hz, C-8), 114.93 (C_{ortho}), 78.08 (C-1), 74.28 (C-2), 69.57 (t, *J* = 35.1 Hz, C-9), 50.99 (C-5), 21.02 (C-11).

FT-IR (neat) cm^{-1}: 3444.1 (w, br), 1731.7 (m), 1599.0 (w), 1495.9 (m), 1243.7 (s), 1055.8 (m), 754.4 (m).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{17}H_{18}O_4F_2Na)^+$ requires 347.1065, found 347.1067.

***rac*-ethyl 2-((*1S,4R,5R*)-4-acetoxy-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)cyclopent-2-en-1-yl)acetate (101)**



Compound **101** was prepared adopting the procedure by Y. Kobayashi *et al.*[10]

A solution of isomeric alcohols **100** and **99** (103.4 mg, 319 μmol, 1 equiv.) and phenol (6.0 mg, 63.8 μmol, 0.20 equiv.) in triethyl orthoacetate (1.50 mL, 25.6 equiv.) and xylene (0.7 mL) was stirred for 16 h at 160 °C. The reaction mixture was then diluted with ethyl acetate (40 mL) and washed with 1 M aqueous solution of NaOH (3x5 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate/hexane =

2% to 20%) afforded desired product of rearrangement **101** as a colourless oil (61.6 mg, 49.0%, 87.1% BRSM).

NOTE: These results were unreproducible because of the acetate scrambling and equilibrium shift towards product **100** (21:1) after solidification. Compound **101** was obtained later in only 25% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.22 (m, 2H, H_{meta}), 6.99 (tt, *J* = 7.3, 1.0 Hz, 1H, H_{para}), 7.00 – 6.88 (m, 2H, H_{ortho}), 6.25 (ddt, *J* = 15.8, 8.8, 2.5 Hz, 1H, H-6), 5.99 (ddd, *J* = 5.7, 2.0, 1.3 Hz, 1H, H-3), 5.90 – 5.77 (m, 1H, H-7), 5.82 (dt, *J* = 5.8, 2.1 Hz, 1H, H-2), 5.52 (dq, *J* = 5.0, 1.5 Hz, 1H, H-1), 4.19 (t, *J* = 11.6 Hz, 2H, H-9), 4.13 (q, *J* = 7.2 Hz, 2H, H-12), 2.95 – 2.84 (m, 1H, H-4), 2.60 – 2.50 (m, 1H, H-5), 2.46 (dd, *J* = 15.4, 6.8 Hz, 1H, H-10a), 2.40 (dd, *J* = 15.4, 7.9 Hz, 1H, H-10b), 2.02 (s, 3H, H-15), 1.25 (t, *J* = 7.1 Hz, 3H, H-13).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.8 (C-11), 170.7 (C-14), 158.1 (C-C_q), 137.8 (C-3), 136.9 (t, *J* = 9.1 Hz, C-6), 129.9 (C-2), 129.7 (C_{meta}), 124.3 (t, *J* = 25.3 Hz, C-7), 121.9 (C_{para}), 118.2 (t, *J* = 241.7 Hz, C-8), 115.0 (C_{ortho}), 83.3 (C-1), 69.6 (t, *J* = 34.8 Hz, C-9), 60.7 (C-12), 53.3 (C-5), 46.2 (C-4), 39.1 (C-10), 21.2 (C-15), 14.3 (C-13).

FTIR (neat) cm^{-1}: 2929.9 (w), 1731.8 (s), 1599.2 (w), 1496.3 (m), 1236.1 (s), 1163.6 (m), 1057.7 (m), 1023.9 (m), 755.1 (m).

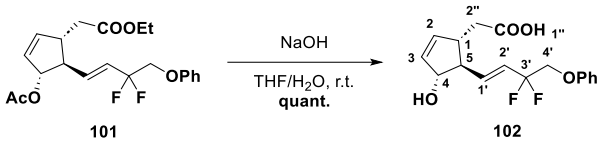
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{21}H_{24}O_5F_2Na)^+$ requires 417.1484, found 417.1477.

Table 4.2. *Additional experiments with Johnson-Claisen rearrangement.*

	99:100	Scale	$CH_3C(OEt)_3$	Xylene	Cat.	Temp.	Time	Yield	Rec. SM
1[a]	1:1.6	30 mg	600 µl	700 µl	PhOH 20 mol %	140 then 160 °C	24 h	53%	n.d.
2	n.d.	103 mg	1500 µl	700 µl	PhOH 20 mol %	160 °C	14 h	49%	38%
3	<1:21	25 mg	1000 µl	0 µl	EtCOOH 88 mol %	160 °C	3 h	25%	51%
4	<1:21	25 mg	1000 µl	0 µl	TsOH 31 mol %	160 °C	3 h	21%	62%
5	<1:21	25 mg	1000 µl	0 µl	PhOH 40 mol %	160 °C	16 h	25%	56%
6[b]	<1:21	50 mg	200 +750 µl[c]	350 µl	PhOH 28 mol %	160 °C	18 h	28%	57%
7[b]	1:2.8	25 mg	750 µl	350 µl	PhOH 28 mol %	160 °C	2 h	16%	62%
8[b]	1:2.8	25 mg	750 µl	350 µl	EtCOOH 70 mol%	160 °C	2 h	27%	62%
9[b]	1:1.3	16 mg[d]	465 µl	217 µl	EtCOOH 70 mol %	160 °C	3 h	22%	39 %
10[b]	1:2	24 mg	750 µl	350 µl	PhOH 20 mol %	160 °C	22 h	24%	51%

a) overnight at 140°C with 7.00 equiv. of orthoester, then added 0.5 ml and heated to 160°C. b) reaction mixture heated first without orthoester = ration of product according to NMR = 1:2, c) slow addition of 200 µl of orthoester over 4h, then added 750 µl of orthoester and heated overnight, d) set up with previously recovered SM.

***rac*-2-((*1S,4R,5R*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-4-hydroxycyclopent-2-en-1-yl)acetic acid (102)**



To a solution of ester **101** (56.7 mg, 1.43 mmol, 1 equiv.) in THF (770 µl) was added 1 M aq. solution of NaOH (1.15 mL, 1.15 mmol, 8.00 equiv.) and the resulting mixture was stirred for 24 h at room temperature. The reaction mixture was then acidified with 1 M aq. solution of HCl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **102** was obtained as a yellow oil (46.6 mg, >99%) and used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.24 (m, 2H, C_{meta}-H), 7.04 – 6.97 (m, 1H, C_{para}-H), 6.97 – 6.88 (m, 2H, C_{ortho}-H), 6.23 (ddt, *J* = 15.7, 9.1, 2.4 Hz, 1H, C(1')-H), 5.93 – 5.77 (m, 3H, C(2')-H, C(2)-H and C(3)-H), 4.61 (dq, *J* = 5.5, 1.7 Hz, 1H, C(4)-H), 4.19 (t, *J* = 11.6 Hz, 2H, C(4')-H_2), 2.81 (dtd, *J* = 8.2, 6.3, 1.9 Hz, 1H, C(1)-H), 2.47 (dd, *J* = 15.8, 6.1 Hz, 1H, C(2")-H), 2.40 (dd, *J* = 15.8, 8.0 Hz, 1H, C(2")-H), 2.38 – 2.30 (m, 1H, C(5)-H).

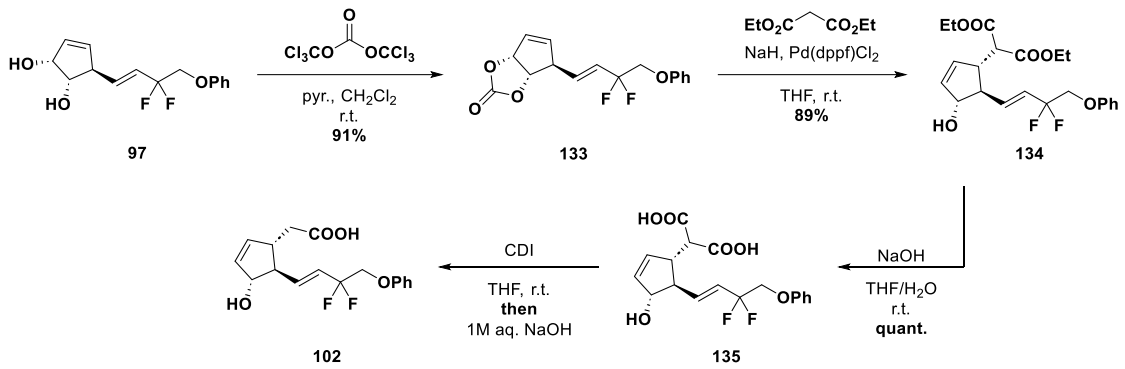
^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.6 (C-1"), 158.1 (C_q), 137.6 (t, *J* = 9.0 Hz, C-1'), 135.2 (C-2), 133.6 (C-3), 129.8 (C_{meta}), 124.5 (t, *J* = 25.0 Hz, C-2'), 122.0 (C_{para}), 118.2 (t, *J* = 240.6 Hz, C-3'), 115.0 (C_{ortho}), 82.0 (C-4), 69.5 (t, *J* = 34.6 Hz, C-4'), 57.7 (C-5), 45.9 (C-1), 38.4 (C-2").

^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.50 (d, *J* = 256.8 Hz), -103.31 (d, *J* = 256.5 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 2927 (br. w.), 1710 (s), 1599(m), 1496 (m), 1248 (s), 1161 (s), 1054 (s), 754 (s).

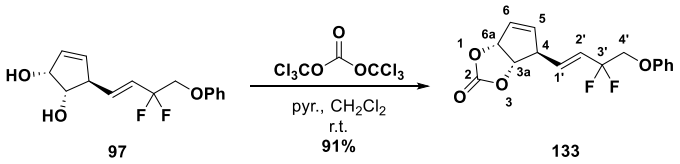
HRMS (ES+): exact mass calculated for $[M+Na]^+$ ($C_{17}H_{18}O_4F_2Na)^+$ requires 347.1065, found 347.1065.

4.2.5 Synthesis of hydroxyacid 102 based on Tsuji-Trost reaction



Scheme 4.5. *Synthesis of hydroxyacid* ***102*** *based on Tsuji-Trost reaction.*

(*3aS,4S,6aR*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-3a,6a-dihydro-4H-cyclopenta[*d*][1,3]-dioxol-2-one (133)



A solution of triphosgene (399 mg, 1.34 mmol, 1.10 equiv.) in CH_2Cl_2 (4.0 mL) was added to a solution of diol **97** (353 mg, 1.21 mmol, 1.00 equiv.) and pyridine (590 µL, 7.3 mmol, 6.0 equiv.) in CH_2Cl_2 (7.5 mL) at r.t. After stirring for 20 min, the reaction mixture was directly loaded onto silica and purification by gradient chromatography (ethyl acetate/hexane = 10% to 25%) afforded the product **133** as a colourless oil (352 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 – 7.26 (m, 2H, C_{meta}-H), 7.02 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.96 – 6.86 (m, 2H, C_{ortho}-H), 6.20 (ddt, *J* = 15.9, 7.3, 2.4 Hz, 1H, C(1')-H), 6.14 – 6.07 (m, 1H, C(5)-H), 6.03 (dt, *J* = 5.8, 1.8 Hz, 1H, C(6)-H), 5.78 (dtd, *J* = 15.9, 11.0, 1.4 Hz, 1H, C(2')-H), 5.59 (dtd, *J* = 6.6, 1.6, 0.9 Hz, 1H, C(6a)-H), 4.87 (dt, *J* = 6.5, 0.9 Hz, 1H, C(3a)-H), 4.19 (t, *J* = 11.3 Hz, 2H, C(4')-H), 3.84 – 3.76 (m, 1H, C(4)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.8 (C_q), 154.1 (C-2), 137.8 (C-5), 134.4 (t, *J* = 8.9 Hz, C-1'), 129.8 (C_{meta}), 129.5 (C-6), 125.8 (t, *J* = 25.4 Hz, C-2'), 122.2 (C_{para}), 118.0 (t, *J* = 240.8 Hz, C-3'), 114.9 (C_{ortho}), 84.6 (C-6a), 82.1 (t, *J* = 2.1 Hz, C-3a), 69.4 (t, *J* = 35.3 Hz, C-4'), 53.2 (C-4).

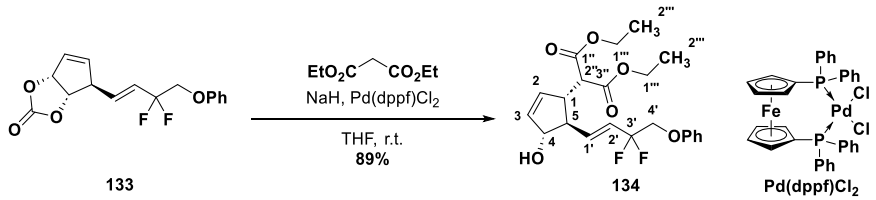
^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled) δ: -103.19 (d, *J* = 259.7 Hz), -103.97 (d, *J* = 259.2 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 1791 (s), 1598 (w), 1495 (m), 1248 (m), 1157 (s), 1047 (s), 7570 (s).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{16}H_{14}O_4F_2Na)^+$ requires 331.0752, found 331.0574.

$[\alpha]^{25}_D$ = -170.7 (c = 0.5, $CHCl_3$).

Diethyl 2-((*1S,4R,5R*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-4-hydroxycyclopent-2-en-1-yl)malonate (134)



Compound **134** was prepared adopting the procedure by H. L. Sebahar *et al.*[11]

A solution of malonate enolate, prepared by addition of diethyl malonate (480 µL, 3.2 mmol, 3.5 equiv.) to the mixture of NaH (60% in mineral oil, washed with pentane; 109 mg, 2.72 mmol, 3.00 equiv.) in THF (3.0 mL), was added to a solution of carbonate **133** (280 mg, 0.908 mmol, 1.00 equiv.) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium ($Pd(dppf)Cl_2$) (19.9 mg, 27.3 µmol, 0.03 equiv.) in THF (10 mL) at r.t. After stirring for 1 h, the reaction mixture was poured onto an aq. sat. sol. of NH_4Cl (30 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate/hexane = 10% to 40%) afforded **134** as a colourless oil (342 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.25 (m, 2H, C_{meta}-H), 7.04 – 6.96 (m, 1H, C_{para}-H), 6.96 – 6.88 (m, 2H, C_{ortho}-H), 6.17 (ddt, *J* = 15.7, 9.3, 2.5 Hz, 1H, C(1')-H), 5.92 – 5.84 (m, 2H, C(2)-H and C(3)-H), 5.88 – 5.74 (m, 1H, C(2')-H), 4.53 (dt, *J* = 5.4, 2.8 Hz, 1H, C(4)-H), 4.29 – 4.07 (m, 6H, C(4')-H_2 and C(1'')-H_2), 3.47 (d, *J* = 6.7 Hz, 1H, C(2'')-H), 3.13 – 3.04 (m, 1H, C(1)-H), 2.66 (dddd, *J* = 7.9, 5.3, 4.1, 1.1 Hz, 1H, C(5)-H), 2.44 (d, *J* = 8.4 Hz, 1H, OH), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.4 (C-1''), 168.2 (C-3''), 158.1 (C_q), 138.2 (t, *J* = 9.0 Hz, C-1'), 134.5 (C-2), 133.5 (C-3), 129.7 (C_{meta}), 123.7 (t, *J* = 25.1 Hz, C-2'), 122.0 (C_{para}), 118.2 (t, *J* = 239.0 Hz, C-3'), 115.0 (C_{ortho}), 82.4 (C-4), 69.6 (t, *J* = 34.8 Hz, C-4'), 61.8 (C-1'''), 61.7 (C-1''), 55.0 (C-2''), 54.3 (C-5), 49.6 (C-1), 14.2 (C-2'''), 14.1 (C-2''').

^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.03 (d, *J* = 257.0 Hz), -103.78 (d, *J* = 257.1 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3509 (br, w), 1729 (s), 1599 (w), 1496 (w), 1249 (s), 1177 (s), 1159 (s), 1033 (m), 756 (m).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{22}H_{26}O_6F_2Na)^+$ requires 447.1590, found 447.1588.

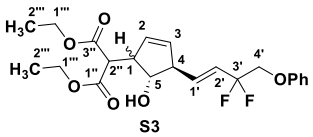
$[\alpha]^{25}_D$= +20.3 (c = 0.5, $CHCl_3$).

Table 4.3. *Conditions screening for Tsuji-Trost reaction.*

	catalyst	scale	cat. loading	nucleophile	yield
1	$Pd(PPh_3)_4$	10 mg	30 mol%	$CH_2(CO_2Et)_2$, NaH	**38%**
2	$[PdCl(allyl)]_2$, DPPF	10 mg	12 mol%	$CH_2(CO_2Et)_2$, NaH	**75%**
3	$[PdCl(allyl)]_2$, DPPF	20 mg	12 mol%	Meldrum's acid, Cs_2CO_3	**n.a.**
4	$[PdCl(allyl)]_2$, DPPF	80 mg	12 mol%	$CH_2(CO_2Et)_2$, NaH	**89%**
5	$Pd(dppf)Cl_2$	20 mg	5 mol%	$CH_2(CO_2Et)_2$, NaH	**85%**
6	$Pd(dppf)Cl_2$	20 mg	1 mol%	$CH_2(CO_2Et)_2$, NaH	**74%**
7	$Pd(dppf)Cl_2$	280 mg	3 mol%	$CH_2(CO_2Et)_2$, NaH	**89%**

Diethyl 2-((*4S,5S*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxycyclopent-2-en-1-yl)malonate (S3)

Compound **S3** was isolated as a by-product of an allylic substitution reaction between carbonate **133** and malonate anion as a colourless oil (33.4 mg, 9%).



S3

^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ: 7.36 – 7.28 (m, 2H, C_{meta}-H), 7.04 – 6.96 (m, 3H, C_{ortho}-H and C_{para}-H), 6.30 (ddt, *J* = 16.0, 7.3, 2.5 Hz, 1H, C(1‘)-H), 5.88 (dtd, *J* = 16.0, 11.2, 1.4 Hz, 1H, C(2‘)-H), 5.75 (dt, *J* = 6.1, 2.2 Hz, 1H, C(3)-H), 5.67 (dt, *J* = 6.1, 2.1 Hz, 1H, C(2)-H), 4.33 (t, *J* = 12.3 Hz, 2H, C(4‘)-H_2), 4.17 (m, 4H, C(1‘‘)-H_2), 4.04 (q, *J* = 6.0 Hz, 1H, C(5)-H), 3.47 (d, *J* = 7.9 Hz, 1H, C(2‘‘)-H), 3.37 – 3.29 (m, 1H, C(4)-H), 3.20 (ddq, *J* = 8.2, 6.3, 2.2 Hz, 1H, C(1)-H), 1.23 (t, *J* = 7.0 Hz, 3H, CH_3), 1.22 (t, *J* = 7.0 Hz, 3H, CH_3).

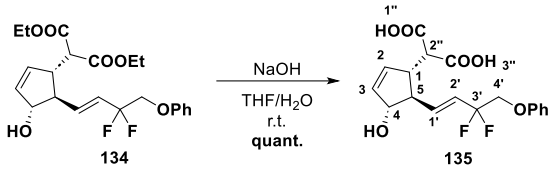
^{13}C NMR (126 MHz, $(CD_3)_2CO$) δ: 168.5 (C-3‘‘), 168.1 (C-1‘‘), 158.3 (C_q), 138.7 (t, *J* = 9.0 Hz, C-1‘), 131.4 (C-3), 131.1 (C-2), 129.6 (C_{meta}), 123.0 (t, *J* = 25.2 Hz, C-2‘), 121.5 (C_{para}), 118.8 (t, *J* = 239.1 Hz, C-3‘), 114.8 (C_{ortho}), 80.8 (t, *J* = 1.9 Hz, C-5), 69.1 (t, *J* = 33.3 Hz, C-4‘), 61.1 (C-1‘‘), 61.0 (C-1‘‘), 55.6 (C-4), 54.4 (C-2‘‘), 53.2 (C-1), 13.6 (C-2‘‘), 13.5 (C-2‘‘).

^{19}F NMR (377 MHz, $(CD_3)_2CO$) δ: -102.76 (d, *J* = 255.9 Hz), -103.47 (d, *J* = 256.8 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3511 (br, w), 1725 (s), 1599 (w), 1496 (w), 1247 (s), 1160 (s), 1041 (m), 755 (m).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{22}H_{26}O_6F_2Na)^+$ requires 447.1590, found 447.1585.

2-((*1S,4R,5R*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-4-hydroxycyclopent-2-en-1-yl)malonic acid (135)



An aq. sol. of NaOH (1 M, 14 mL, 14 mmol, 16 equiv.) was added to a solution of ester **134** (378 mg, 890 µmol, 1.00 equiv.) in THF (10 mL) at r.t. After stirring for 24 h, the reaction mixture was acidified with 1 M aq. solution of HCl (60 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic phases were washed with brine (60 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **135** was obtained as a pale-yellow oil (343 mg, >95%) and was used in the next step without further purification.

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 11.30 (br s, 2H, COOH), 7.35 – 7.26 (m, 2H, C_{meta}-H), 7.05 – 6.94 (m, 3H, C_{ortho}-H and C_{para}-H), 6.34 (ddt, *J* = 15.8, 8.9, 2.6 Hz, 1H, C(1')-H), 5.96 – 5.80 (m, 3H, C(2')-H, C(2)-H and C(3)-H), 4.61 (dq, *J* = 5.2, 1.7 Hz, 1H, C(4)-H), 4.33 (t, *J* = 12.7 Hz, 2H, C(4')-H_2), 3.42 (d, *J* = 7.8 Hz, 1H, C(2")-H), 3.15 – 3.05 (m, 1H, C(1)-H), 2.62 (dddd, *J* = 7.8, 6.7, 5.2, 1.2 Hz, 1H, C(5)-H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ: 169.9 (C-1"), 169.6 (C-3"), 159.3 (C_q), 139.6 (t, *J* = 9.2 Hz, C-1'), 135.8 (C-2), 133.5 (C-3), 130.4 (C_{meta}), 124.4 (t, *J* = 25.1 Hz, C-2'), 122.4 (C_{para}), 119.6 (t, *J* = 238.2 Hz, C-3'), 115.8 (C_{ortho}), 82.0 (C-4), 67.0 (t, *J* = 32.2 Hz, C-4'), 56.0 (C-5), 55.9 (C-2"), 49.6 (C-1).

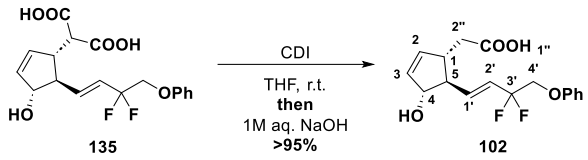
^{19}F NMR (377 MHz, $(CD_3)_2CO$, ^{1}H decoupled) δ: -103.33 (d, *J* = 252.4 Hz), -104.22 (d, *J* = 252.4 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 2918 (br. w), 1714(s), 1599 (m), 1495 (m), 1248 (s), 1164 (m), 1054 (m), 756 (s).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{18}H_{18}O_6F_2Na)^+$ requires 391.0964, found 391.0963.

$[\alpha]^{25}_D$= +14.8 (c = 0.5, $CHCl_3$).

2-((*1S,4R,5R*)-5-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-4-hydroxycyclopent-2-en-1-yl)acetic acid (102)



Compound **102** was prepared adopting the procedure by D. Lafrance *et al.*[12]

1,1'-Carbonyldiimidazole (CDI) (402 mg, 2.23 mmol, 2.50 equiv.) was added to a solution of acid **135** (333 mg, 864 μmol, 1.00 equiv.) in THF (18 mL) at r.t. After stirring the mixture for 3 h, an aq. sol. of 1 M NaOH (7.8 mL, 7.8 mmol, 8.7 equiv.) was added, and the reaction mixture was stirred for 20 h. The reaction mixture was then acidified with aq. 1 M HCl (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **102** was obtained as a pale-yellow oil (305 mg, >95%) and used in the next step without further purification.

NOTE: The reaction can be monitored by TLC using 80% THF/hexane +1% AcOH.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.24 (m, 2H, C_{meta}-H), 7.04 – 6.97 (m, 1H, C_{para}-H), 6.97 – 6.88 (m, 2H, C_{ortho}-H), 6.23 (ddt, *J* = 15.7, 9.1, 2.4 Hz, 1H, C(1')-H), 5.93 – 5.77 (m, 3H, C(2')-H, C(2)-H and C(3)-H), 4.61 (dq, *J* = 5.5, 1.7 Hz, 1H, C(4)-H), 4.19 (t, *J* = 11.6 Hz, 2H, C(4')-H_2), 2.81 (dtd, *J* = 8.2, 6.3, 1.9 Hz, 1H, C(1)-H), 2.47 (dd, *J* = 15.8, 6.1 Hz, 1H, C(2'')-H), 2.40 (dd, *J* = 15.8, 8.0 Hz, 1H, C(2'')-H), 2.38 – 2.30 (m, 1H, C(5)-H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.6 (C-1''), 158.1 (C_q), 137.6 (t, *J* = 9.0 Hz, C-1'), 135.2 (C-2), 133.6 (C-3), 129.8 (C_{meta}), 124.5 (t, *J* = 25.0 Hz, C-2'), 122.0 (C_{para}), 118.2 (t, *J* = 240.6 Hz, C-3'), 115.0 (C_{ortho}), 82.0 (C-4), 69.5 (t, *J* = 34.6 Hz, C-4'), 57.7 (C-5), 45.9 (C-1), 38.4 (C-2'').

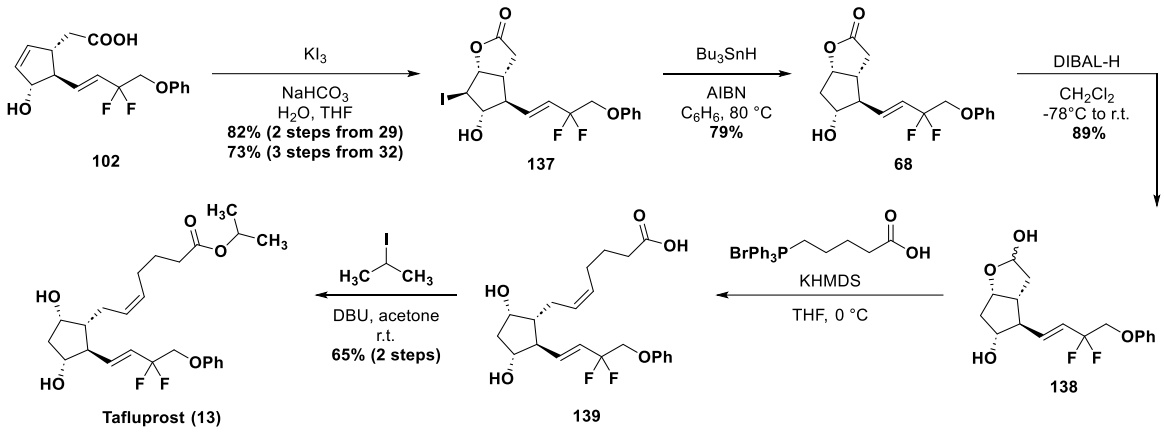
^{19}F NMR (377 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.50 (d, *J* = 256.8 Hz), -103.31 (d, *J* = 256.5 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 2927 (br. w.), 1710 (s), 1599(m), 1496 (m), 1248 (s), 1161 (s), 1054 (s), 754 (s).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{17}H_{18}O_4F_2Na)^+$ requires 347.1065, found 347.1065.

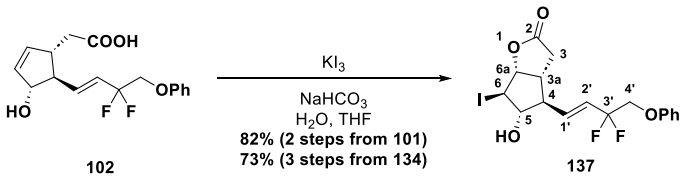
$[\alpha]^{25}_D$= -2.5 (c = 0.5, $CHCl_3$).

4.2.6 Completion of the synthesis of Tafluprost



Scheme 4.6. *Completion of Tafluprost synthesis.*

(*3aR,4R,5S,6R,6aR*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxy-6-iodohexahydro-2H-cyclopenta[b]furan-2-one (137)



Compound **137** was prepared adopting the procedure by K. Yagi *et al.*[13]

A solution of $NaHCO_3$ (676 mg, 8.04 mmol, 10.0 equiv.) in H_2O (5.7 mL) and a solution of KI (801 mg, 4.83 mmol, 6.00 equiv.) and I_2 (408 mg, 1.61 mmol, 2.00 equiv.) in H_2O (5.7 mL) was added to a solution of acid **102** (289 mg, 804 µmol, 1.00 equiv.) in THF (3.2 mL) at r.t. After stirring the mixture for 24 h in the dark, the reaction mixture was poured onto an aq. sat. sol. of $Na_2S_2O_3$ (30 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate/hexane = 10% to 40%) afforded **137** as a colourless oil (266 mg, 73% over 3 steps from **134**).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 7.37 – 7.27 (m, 2H, C_{meta}-H), 7.04 – 6.95 (m, 3H, C_{ortho}-H and C_{para}-H), 6.30 (ddt, *J* = 15.8, 7.8, 2.5 Hz, 1H, C(1')-H), 6.03 (dtd, *J* = 15.8, 11.2, 1.1 Hz, 1H, C(2')-H), 5.15 – 5.05 (m, 1H, C(6a)-H), 5.05 – 4.99 (m, 1H, OH), 4.34 (t, *J* = 12.4 Hz, 2H, C(4')-H_2), 4.18 – 4.08 (m, 1H, C(5)-H), 4.12 – 4.04 (m, 1H, C(6)-H), 3.01 (tdd, *J* = 10.2, 8.4, 3.1 Hz, 1H, C(3a)-H), 2.82 (dd, *J* = 18.2, 10.1 Hz, 1H, C(3)-H), 2.54 – 2.46 (m, 1H, C(4)-H), 2.42 (dd, *J* = 18.2, 3.1 Hz, 1H, C(3)-H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ: 175.8 (C-2), 159.2 (C_q), 137.0 (t, *J* = 9.2 Hz, C-1'), 130.4 (C_{meta}), 126.0 (t, *J* = 25.1 Hz, C-2'), 122.5 (C_{para}), 119.4 (t, *J* = 239.5 Hz, C-3'), 115.7 (C_{ortho}), 89.9 (C-6a), 83.6 (C-5), 70.0 (t, *J* = 33.0 Hz, C-4'), 53.9 (C-4), 41.3 (C-3a), 33.7 (C-6), 33.6 (C-3).

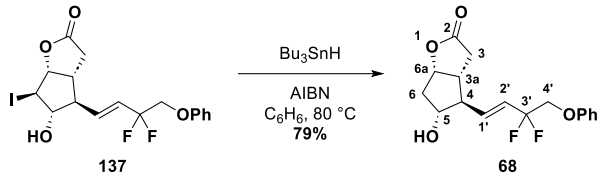
^{19}F NMR (376 MHz, $(CD_3)_2CO$, ^{1}H decoupled) δ: -103.62 (d, *J* = 254.3 Hz), -104.34 (d, *J* = 253.3 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3422.4 (br. w), 1760(s), 1598 (m), 1494 (m), 1247 (s), 1161 (s), 1052 (s), 973 (s), 756 (s).

HRMS (ES-): exact mass calculated for $[M-H]^-$ ($C_{17}H_{16}O_4F_2I)^-$ requires 449.0097, found 449.0066.

$[\alpha]^{25}_D$= +15.6 (c = 0.5, $CHCl_3$).

(*3aR,4R,5R,6aS*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-5-hydroxyhexahydro-2H-cyclopenta[*b*]furan-2-one (68)



Compound **68** was prepared adopting the procedure by K. Yagi *et al.*[13]

Tributyltinhydride (100 μL, 390 μmol, 3.0 equiv.) and azobisisobutyronitrile (AIBN) (2.1 mg, 13 μmol, 0.10 equiv.) were added to the solution of iodolactone **137** (58.2 mg, 129 μmol, 1.00 equiv.) in benzene (2.6 mL). The resulting mixture was stirred at 80 °C. After 1 h, the reaction mixture was cooled down to room temperature, solid KF (85 mg) was added, and the resulting mixture was stirred for an additional 1 h. The reaction mixture was then loaded on silica, and the crude product was purified by gradient column chromatography (ethyl acetate/hexane = 0% to 70%, stationary phase K_2CO_3/silica = 1:9). The product **68** was obtained as a colourless oil (33.1 mg, 79%).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ: 7.37 – 7.24 (m, 2H, C_{meta}-H), 7.06 – 6.93 (m, 3H, C_{ortho}-H and C_{para}-H), 6.23 (ddt, *J* = 15.9, 7.9, 2.5 Hz, 1H, C(1')-H), 5.97 (dtd, *J* = 15.9, 11.1, 1.1 Hz, 1H, C(2')-H), 4.94 (td, *J* = 7.0, 3.1 Hz, 1H, C(6a)-H), 4.33 (t, *J* = 12.4 Hz, 2H, C(4')-H_2), 4.25 (d, *J* = 5.0 Hz, 1H, OH), 4.09 (qd, *J* = 7.1, 5.1 Hz, 1H, C(5)-H), 2.82 – 2.71 (m, 2H, C(3a)-H and C(3)-H), 2.54 – 2.42 (m, 2H, C(4)-H and C(6)-H), 2.42 – 2.30 (m, 1H, C(3)-H), 1.84 (ddd, *J* = 14.5, 7.2, 3.2 Hz, 1H, C(6)-H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ: 176.8 (C-2), 159.2 (C_q), 138.3 (t, *J* = 9.1 Hz, C-1'), 130.4 (C_{meta}), 125.1 (t, *J* = 25.0 Hz, C-2'), 122.4 (C_{para}), 119.5 (t, *J* = 239.5 Hz, C-3'), 115.7 (C_{ortho}), 83.0 (C-6a), 76.9 (C-5), 69.9 (t, *J* = 33.1 Hz, C-4'), 56.5 (C-4), 42.8 (C-3a), 41.2 (C-6), 34.6 (C-3).

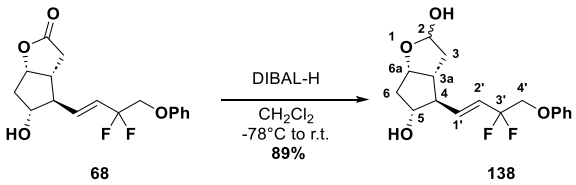
^{19}F NMR (377 MHz, $(CD_3)_2CO$, decoupled) δ: -103.41 (d, *J* = 253.7 Hz), -104.17 (d, *J* = 253.0 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3431 (br. w), 2932 (w), 1760 (s), 1598 (m), 1494 (m), 1247 (s), 1161 (s), 1079 (s), 1025 (s), 973 (s), 973 (m), 756 (s), 692 (s).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{17}H_{18}O_4F_2Na)^+$ requires 347.1065, found 347.1065.

$[\alpha]^{25}_D$= -1.9 (c = 0.5, $CHCl_3$).

(*3aR,4R,5R,6aS*)-4-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)hexahydro-2H-cyclopenta[*b*]furan-2,5-diol (138)



Compound **138** was prepared adopting the procedure by S. Prevost *et al.*[14]

A solution of diisobutylaluminium hydride (DIBAL-H) (1 M in CH_2Cl_2, 580 µL, 580 µmol, 2.2 equiv.) was added to a solution of **68** (85.0 mg, 262 µmol, 1.00 equiv.) in CH_2Cl_2 (5.4 mL) at -78 °C. After stirring for 1 h, the reaction mixture was allowed to warm to r.t., quenched with an aq. sat. sol. of potassium sodium tartrate (10 mL) and was stirred for an additional 1 h. The reaction mixture was then extracted with CH_2Cl_2 (4 x 15 mL), and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate/hexane = 70%) afforded **138** as collarless oil (76.4 mg, 89%) as an inseparable mixture of two diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 – 7.27 (m, 4H, C_{meta}-H and C‘$_{meta}$-H), 7.01 (ddt, *J* = 8.4, 7.2, 1.2 Hz, 2H, C_{para}-H and C‘$_{para}$-H), 6.95 – 6.88 (m, 4H, C_{ortho}-H and C_{ortho}-H), 6.15 – 6.04 (m, C(1‘)-H and C‘(1‘)-H), 5.88 – 5.74 (m, 2H, C(2‘)-H and C‘(2‘)-H), 5.67 (d, *J* = 5.0 Hz, 1H, C(2)-H), 5.58 (d, *J* = 5.5 Hz, 1H, C‘(2)-H), 4.69 (dt, *J* = 6.7, 3.3 Hz, 1H, C(6a)-H), 4.64 (td, *J* = 7.1, 3.4 Hz, 1H, C‘(6a)-H), 4.19 (t, *J* = 11.4 Hz, 4H, C(4‘)-H_2 and C‘(4‘)-H_2), 4.01 – 3.93 (m, 2H, C(5)-H and C‘(5)-H), 2.89 (q, *J* = 6.9 Hz, 1H, C‘(4)-H), 2.80 (s, 1H, C(2)-OH), 2.56 (dtd, *J* = 8.9, 7.2, 4.5 Hz, 1H, C(3a)-H), 2.49 (dtd, *J* = 8.5, 7.1, 1.3 Hz, 1H, C‘(3a)-H), 2.40 – 2.31 (m, 3H, C(4)-H, C(6)-H and C‘(6)-H), 2.24 (ddd, *J* = 13.8, 9.7, 5.6 Hz, 1H, C‘(3)-H), 2.14 (ddd, *J* = 13.6, 9.0, 1.6 Hz, 1H, C(3)-H), 2.09 (ddd, *J* = 14.2, 6.1, 3.5 Hz, 1H, C‘(6)-H), 2.06 – 1.97 (m, 2H, C(3)-H and C‘(3)-H), 1.85 (ddd, *J* = 14.2, 6.8, 3.1 Hz, 1H, C(6)-H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.9 (C‘$_q$), 157.9 (C_q), 138.4 (t, *J* = 8.8 Hz, C‘-1‘), 137.7 (t, *J* = 8.8 Hz, C-1‘), 129.79 (C_{meta}), 129.77(C‘$_{meta}$), 124.0 (t, *J* = 24.9 Hz, C-2‘), 123.5 (t, *J* = 24.8 Hz, C‘-2‘), 122.01 (C_{para}), 121.98 (C‘$_{para}$), 118.26 (t, *J* = 240.4 Hz, C‘-3‘), 118.20 (t, *J* = 240.5 Hz, C-3‘), 114.8 (C_{ortho} and C‘$_{ortho}$), 101.1 (C‘-2), 100.0 (C-2), 84.5 (C‘-6a), 81.3 (C-6a), 78.4 (C-5 and C‘-5), 69.4 (t, *J* = 35.3 Hz, C-4‘ and C-4‘), 57.2 (C-4), 57.0 (C‘-4), 46.6 (C‘-3a), 45.6 (C-3a), 42.8 (C‘-6), 39.8 (C-6 or C-3), 39.7 (C-6 or C-3), 39.3 (C‘-3).

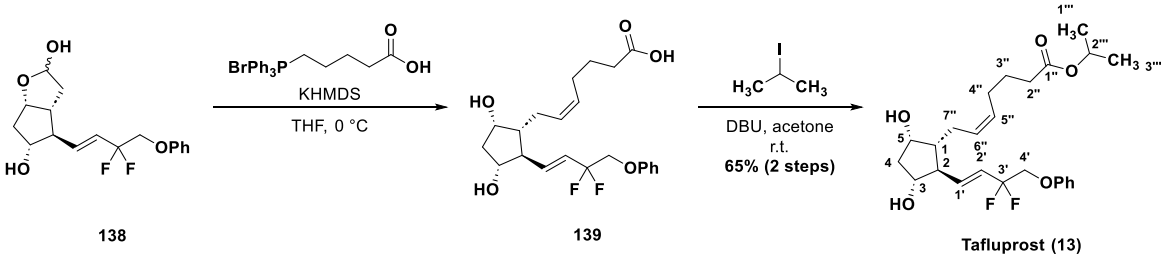
^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.44 (d, *J* = 256.8 Hz), -102.82 (d, *J* = 257.8 Hz), -102.87 (d, *J* = 256.5 Hz), -103.28 (d, *J* = 256.5 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3372 (br. w), 1496 (m), 1294 (m), 1060 (m).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{17}H_{20}O_4F_2Na)^+$ requires 349.1222, found 349.1223.

$[\alpha]^{25}_D$ = -10.4 (c = 0.5, $CHCl_3$).

Isopropyl (*Z*)-7-((*1R,2R,3R,5S*)-2-((*E*)-3,3-difluoro-4-phenoxybut-1-en-1-yl)-3,5-dihydroxycyclopen-tyl)hept-5-enoate (Tafluprost (13))



Compound **13** was prepared adopting the procedure by Y. Zhao *et al.*[15]

A solution of potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M in toluene, 490 µL, 250 µmol, 8.0 equiv.) was added to a suspension of (4-Carboxybutyl)triphenylphosphonium bromide (54.2 mg, 123 µmol, 4.00 equiv.) in THF (350 µL) at 0 °C (intensively orange solution). After stirring for 15 min, a solution of hemiacetal **138** (10 mg, 30.6 µmol, 1.00 equiv.) in THF (300 µL) was added, and the resulting solution was stirred for 2 h at 0 °C. H_2O (0.5 mL) was added, and the reaction mixture was acidified with 1 M aq. HCl and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product **139** was passed through a plug of silica (ethyl acetate/acetic acid = 99%) and used directly in the next step without further purification.

Crude **139** was dissolved in acetone (400 µL) and DBU (28 µL, 180 µmol, 6.0 equiv.). 2-iodopropane (18 µL, 180 µmol, 6.0 equiv.) was added to the mixture, and the resulting solution was stirred for 22 h at r.t. The reaction mixture was then directly loaded on silica and purified by gradient column chromatography (ethyl acetate/hexane = 30% to 70%). Tafluprost (**13**) was obtained as a colourless oil (9.0 mg, 65%, 90% brsm).

The spectroscopic data are in agreement with the literature.[16]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.26 (m, 2H, C_{meta}-H), 7.00 (tt, *J* = 7.3, 1.1 Hz, 1H, C_{para}-H), 6.95 – 6.88 (m, 2H, C_{ortho}-H), 6.10 (ddt, *J* = 15.8, 9.1, 2.5 Hz, 1H, C(1')-H), 5.80 (dt, *J* = 15.7, 11.3 Hz,

1H, C(2‘)-H), 5.44 – 5.32 (m, 2H, C(6“)-H and C(5“)-H), 4.99 (h, *J* = 6.3 Hz, 1H, C(2‘“)-H), 4.25 – 4.16 (m, 3H, C(4‘)-H_2 and C(5)-H), 4.06 – 3.99 (m, 1H, C(3)-H), 2.47 (td, *J* = 9.7, 4.0 Hz, 1H, C(2)-H), 2.42 (d, *J* = 7.2 Hz, 1H, C(3)-OH), 2.38 – 2.29 (m, 1H, C(7“)-H), 2.26 (td, *J* = 7.2, 2.4 Hz, 2H, C(2“)-H_2), 2.19 – 1.96 (m, 4H, C(4)-H, C(7“)-H and C(4“)-H_2), 1.85 (d, *J* = 14.6 Hz, 1H, C(4)-H), 1.73 – 1.63 (m, 2H, C(3“)-H_2), 1.61 (m, 1H, C(1)-H), 1.22 (d, *J* = 6.3 Hz, 6H, C(1‘“)-H_3 and C(3‘“)-H_3). (One exchanging proton of OH is not visible.)

^{13}C NMR (126 MHz, $CDCl_3$) δ: 173.6 (C-1”), 158.1 (C_q), 138.8 (t, *J* = 8.8 Hz, C-1‘), 130.3 (C-6“), 129.8 (C_{meta}), 128.8 (C-5“), 123.7 (t, *J* = 24.9 Hz, C-2‘), 122.0 (C_{para}), 118.3 (t, *J* = 240.3 Hz, C-3‘), 114.9 (C_{ortho}), 78.2 (C-3), 73.5 (C-5), 69.6 (t, *J* = 35.0 Hz, C-4‘), 67.8 (C-2‘“), 56.0 (C-2), 50.7 (C-1), 43.1 (C-4), 34.1 (C-2“), 26.8 (C-4“), 25.9 (C-7“), 25.0 (C-3“), 21.99 (C-1‘“), 21.97 (C-3‘“).

^{19}F NMR (470 MHz, $CDCl_3$, ^{1}H decoupled) δ: -102.46 (d, *J* = 255.7 Hz), -103.21 (d, *J* = 255.6 Hz).

FT-IR ($CHCl_3$ film) cm^{-1}: 3395 (br, w), 2933 (w), 1725 (s), 1599 (m), 1497(s), 1249 (s), 1108 (s), 755 (s).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{25}H_{34}O_5F_2Na)^+$ requires 475.2267, found 475.2264.

$[\alpha]^{25}_D$ = +22.4 (c = 0.5, $CHCl_3$), lit **$[\alpha]^{25}_D$ =** +21.6 (c = 1.0, $CHCl_3$).[16c]

Table 4.4. *Comparison of ^{1}H and ^{13}C NMR data of the synthesized Tafluprost with literature.*

Reported ^{1}H NMR (600 MHz, $CDCl_3$)[16b]	Reported ^{1}H NMR (unknown frequency, $CDCl_3$)[16a]	Measured ^{1}H NMR (500 MHz, $CDCl_3$)	Reported ^{13}C NMR (150 MHz, $CDCl_3$)[16b]	Measured ^{13}C NMR (126 MHz, $CDCl_3$)
1.22 (d, 6H)	1.22 (d, *J* = 6.2 Hz, 3H) and 1.22 (d, *J* = 6.2 Hz, 3H)	1.22 (d, *J* = 6.3 Hz, 6H)	21.8 (2s)	21.99 and 21.97
1.61 (m, 1H)	1.58 – 1.63 (m, 1H)	1.61 (m, 1H)	24.8	25.0
1.67 (m, 2H)	1.63 – 1.69 (m, 2H)	1.63 – 1.73 (m, 2H)	25.7	25.9
1.85 (m, 1H)	1.84 (d, *J* = 14,7 Hz, 1H)	1.85 (d, *J* = 14.6 Hz, 1H)	26.6	26.8
2.06 (m, 1H)	2.02 – 2.08 (m, 1H)	1.96 – 2.19 (m, 4H)	34.0	34.1
2.09 – 2.16 (m, 3H)	2.10 – 2.16 (m, 3H)		42.9	43.1
	2.25 (t, *J* = 7.3 Hz, 1H)	2.26 (td, *J* = 7.2, 2.4 Hz, 2H)	50.5	50.7
	2.26 (t, *J* = 7.1 Hz, 1H)		55.7	56.0
	2.30 – 2.35 (m, 1H)	2.29 – 2.38 (m, 1H)	67.7	67.8
[a]	2.46 – 2.49 (m, 2H)	2.42 (d, *J* = 7.2 Hz, 1H)	69.5 (*J* = 34.9 Hz)	69.6 (t, *J* = 35.0 Hz)
2.47 (m, 1H)		2.47 (td, *J* = 9.7, 4.0 Hz, 1H)	73.3	73.5
[b]	2.61–2.63 (m, 1H)	[b]	77.9	78.2
4.02 (m, 1H)	4.02 – 4.03 (m, 1H)	3.99 – 4.06 (m, 1H)	114.8	114.9
4.17 – 4.22 (m, 2H)[c]	4.18 – 4.21 (m, 3H)	4.16 – 4.25 (m, 3H)	118.2 (*J* = 240.0 Hz)	118.3 (t, *J* = 240.3 Hz)
5.00 (sept, *J* = 6.30 Hz, 1H)	5.00 (heptet, *J* = 6.2 Hz, 1H)	4.99 (h, *J* = 6.3 Hz, 1H)	121.8	122.0
5.33 – 5.42 (m, 2H)	5.35 – 5.42 (m, 2H),	5.32 – 5.44 (m, 2H)	123.6 (*J* = 25.0 Hz)	123.7 (t, *J* = 24.9 Hz)
5.80 (m, 1H)	5.80 (dt, *J* = 15.8, 11.2 Hz, 1H)	5.80 (dt, *J* = 15.7, 11.3 Hz, 1H)	128.6	128.8
6.10 (m, 1H)	6.10 (dd, *J* = 15.8, 8.8 Hz, 1H)	6.10 (ddt, *J* = 15.8, 9.1, 2.5 Hz, 1H)	129.6	129.8
6.92 (m, 2H)	6.91 (d, *J* = 8.8 Hz, 2H)	6.88 – 6.95 (m, 2H)	130.1	130.3
7.00 (m, 1H)	7.00 (t, *J* = 7.3 Hz, 1H)	7.00 (tt, *J* = 7.3, 1.1 Hz, 1H)	138.6 (*J* = 8.8 Hz)	138.8 (t, *J* = 8.8 Hz)
7.30 (m, 2H)	7.30 (dd, *J* = 8.8, 7.3 Hz, 2H)	7.26 – 7.34 (m, 2H)	157.9	158.1
			173.5	173.6

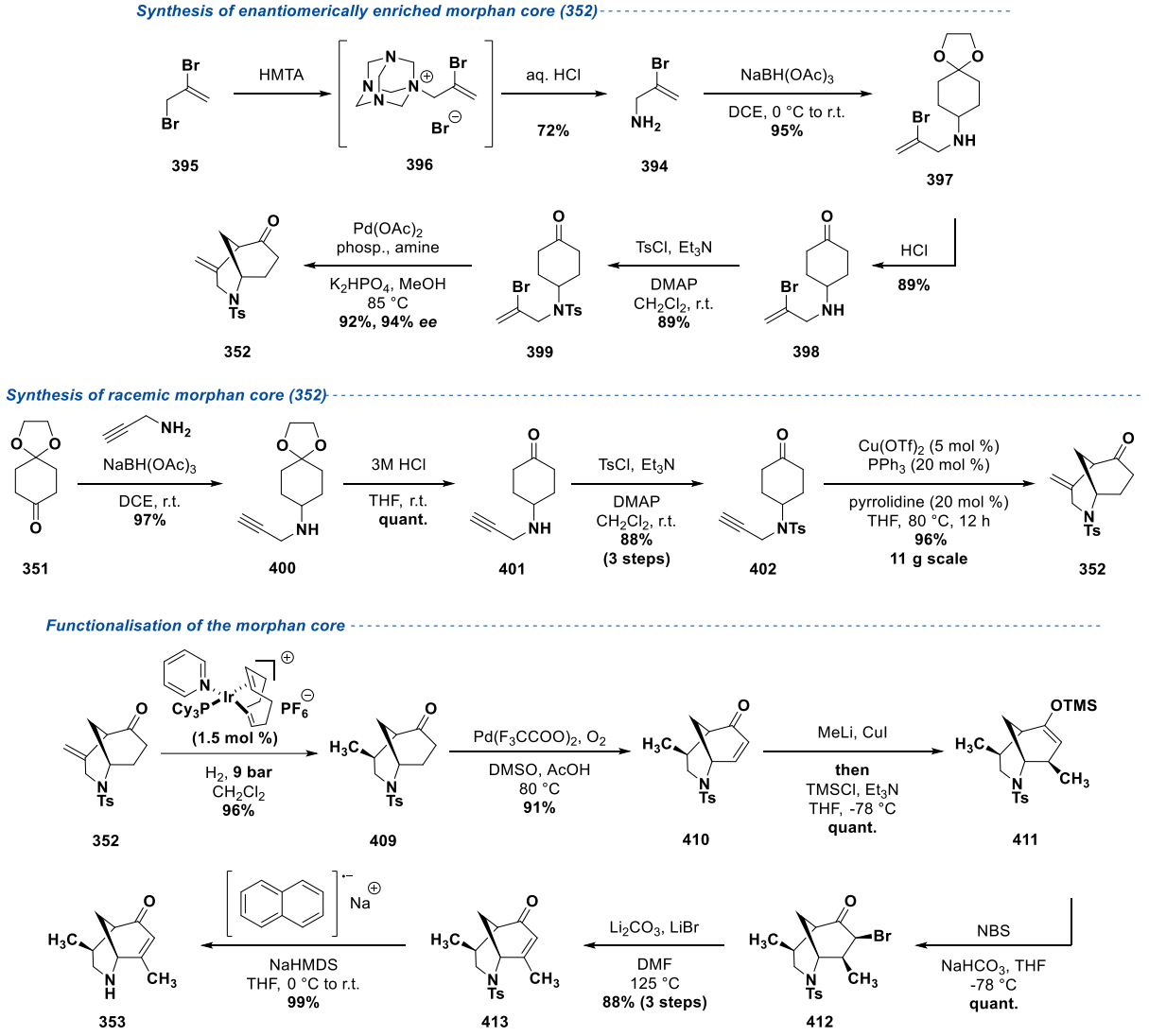
[a] Exchanging OH visible. [b] Exchanging OH not visible. [c] One proton not reported.

Table 4.5. *Comparison of ^{19}F NMR data of the synthesized Tafluprost with literature.*

Reported ^{19}F NMR (470 MHz, $CDCl_3$)[16b]	Reported ^{19}F NMR (unknown frequency, $CDCl_3$)[16a]	Measured ^{19}F NMR (470 MHz, $CDCl_3$)
−102.6 ($^{2}J_{F\text{-}F}$ = 255.8 Hz)	−102.8 ($^{2}J_{F\text{-}F}$ = 255.6 Hz)	-102.5 (d, *J* = 255.7 Hz)
−103.1 ($^{2}J_{F\text{-}F}$ = 255.8 Hz)	−103.6 ($^{2}J_{F\text{-}F}$ = 255.6 Hz)	-103.2 (d, *J* = 255.6 Hz)

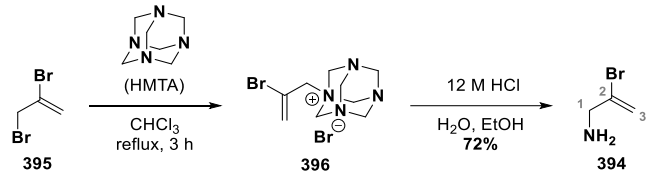
4.3 Experimental details for Chapter 2

4.3.1 Synthesis and functionalisation of the morphan core



Scheme 4.7. *Overview of the synthesis and functionalisation of the morphan core.*

2-bromoprop-2-en-1-amine (394)



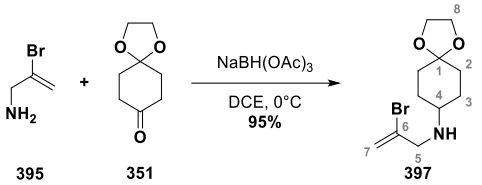
Compound **394** was prepared according to a literature procedure published by Bottiny *et al.*[17]

2,3-dibromoprop-1-ene (20.0 g, 90 wt %, 90.1 mmol, 0.91 equiv.) was added dropwise over 1 h using a syringe pump to a refluxed solution of urotropine (HMTA)(13.9 g, 99.0 mmol, 1 equiv.) in chloroform (170 mL). During the addition of bromide, the formation of a white precipitate was observed. The resulting suspension was refluxed for an additional 3 h and then allowed to cool down to room temperature. After standing for two days at room temperature and one day at 0 °C, the white crystalline ammonium salt was filtered off and dried on air (33.9 g). The obtained 2-bromoallylhexaminium bromide was dissolved in a mixture of water (57 mL), ethanol (200 mL) and 12 M HCl (68 mL) and the reaction mixture was left to stand at room temperature for 5 days. Then, the precipitated ammonium chloride was filtered off, washed with a small amount of ethanol and filtrated and concentrated under reduced pressure. The residue was dissolved in water (50 mL), and 3 M NaOH (100 mL) was added. The resulting mixture was extracted with Et_2O (4 x 75 mL), and the combined organic phases dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The vacuum distillation (120 mbar, 70 °C) of crude product afforded 2-bromoprop-2-en-1-amine (**394**) as a colorless oil in a mixture with Et_2O (10.4 g, 93 wt %, 72% yield). Data are in agreement with literature values.[18]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (q, J = 1.4 Hz, 1H, H-3a), 5.46 (dt, J = 1.8, 0.8 Hz, 1H, H-3b), 3.45 (d, J = 1.1 Hz, 2H, H-1), 1.46 (br s, 2H, NH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.9 (C-2), 115.4 (C-3), 51.2 (C-1).

***N*-(2-bromoallyl)-1,4-dioxaspiro[4.5]decan-8-amine (397)**



Compound **397** was prepared according to procedure developed in our group by Sam Ellis.[19]

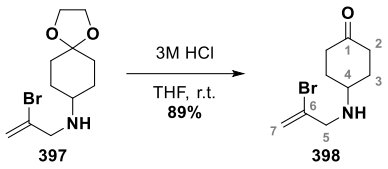
To a stirred solution of 2-bromoprop-2-en-1-amine (10.3 g, 93 wt%, 70.4 mmol, 1 equiv.) in DCE (195 mL) was added 1,4-dioxaspiro[4.5]decan-8-one (11.0 g, 70.4 mmol, 1.00 equiv.) and the resulting solution was cooled to 0 °C. Then, $NaBH(OAc)_3$ (20.9 g, 98.6 mmol, 1.40 equiv.) was added slowly, the ice bath

was removed, and the resulting solution was stirred at room temperature for 2 days. The reaction was quenched with 1 M aq. KOH (200 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product **397** was obtained as a yellow oil (18.5 g, 95%) and used in the next step without further purification. Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.78 (q, *J* = 1.3 Hz, 1H, H-7a), 5.53 (dd, *J* = 1.7, 0.9 Hz, 1H, H-7b), 3.92 (s, 4H, H-8), 3.46 (t, *J* = 1.0 Hz, 2H, H-5), 2.56 (tt, *J* = 9.4, 3.4 Hz, 1H, H-4), 1.91 – 1.71 (m, 4H, H-3, H-2), 1.70 – 1.37 (m, 4H, H-3, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 134.2 (C-6), 117.3 (C-7), 108.8 (C-1), 64.41 (C-8), 64.37 (C-8), 55.0 (C-5), 52.9 (C-4), 32.8 (2xC-3 or 2xC-2), 30.1 (2xC-3 or 2xC-2).

4-((2-bromoallyl)amino)cyclohexan-1-one (398)



397 398

Compound **398** was prepared according to procedure developed in our group by Sam Ellis.[19]

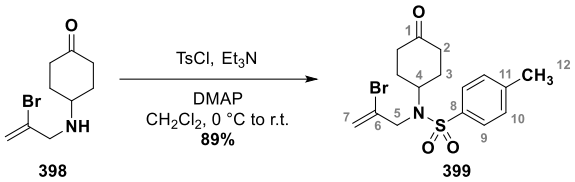
To a solution of acetal **397** (18.5 g, 67.0 mmol, 1 equiv.) in THF (185 mL) was added 3 M aq. HCl (185 mL) and the resulting solution was stirred for 2 days. Then, the reaction mixture was basified by adding 3 M aq. KOH (300 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic phases were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 2:1) afforded ketone **398** as a yellowish oil (13.9 g, 89%). Data are in agreement with the previously reported values.[19]

Note: The crude product can be used in the next step without further purification. However, when used in a tosylation reaction leading to product **399**, it is necessary to remove all ethylene glycol formed during the acetal hydrolysis. The ethylene glycol ditosylate side product is not separable by FCC and acts as a catalyst poison in the cyclization step.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.81 (dd, *J* = 2.0, 1.1 Hz, 1H, H-7a), 5.59 (d, *J* = 1.8 Hz, 1H, H-7b), 3.53 – 3.49 (m, 2H, H-5), 3.04 – 2.93 (m, 1H, H-4), 2.51 (dtd, *J* = 15.0, 5.8, 1.3 Hz, 2H, H-2a), 2.37 – 2.23 (m, 2H, H-2b), 2.10 – 1.97 (m, 2H, H-3a), 1.72 (dddd, *J* = 13.3, 9.6, 8.0, 5.2 Hz, 2H, H-3b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.2 (C-1), 133.8 (C-6), 117.9 (C-7), 54.8 (C-5), 50.8 (C-4), 38.2 (2xC-2), 31.7 (2xC-3).

_N_-(2-bromoallyl)-4-methyl-_N_-(4-oxocyclohexyl)benzenesulfonamide (399)



Compound **399** was prepared according to procedure developed in our group by Sam Ellis.[19]

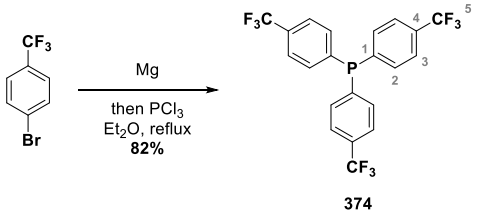
To a solution of amine **398** (13.8 g, 59.5 mmol, 1 equiv.) in CH_2Cl_2 (158 mL) at 0 °C was dropwise added Et_3N (14.5 mL, 104.0 mmol, 1.75 equiv.), DMAP (1.45 g, 11.9 mmol, 0.20 equiv.) and a solution of *p*-toluenesulfonyl chloride (19.8 g, 104.0 mmol, 1.75 equiv.) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at r.t. for 4 days and then acidified with 1 M aq. HCl (200 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 1:4 to 1:1) to ketone **399** as a white solid (20.5 g, 89%). Data are in agreement with the previously reported values.[19]

Note: If needed, the purity of the obtained material can be increased by recrystallization from boiling cyclohexane/ethyl acetate.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 – 7.71 (m, 2H, H-9), 7.32 (d, *J* = 8.2 Hz, 2H, H-10), 6.00 (q, *J* = 1.8 Hz, 1H, H-7a), 5.64 (dt, *J* = 2.5, 1.3 Hz, 1H, H-7b), 4.20 (tt, *J* = 11.8, 4.0 Hz, 1H, H-4), 4.01 (t, *J* = 1.5 Hz, 2H, H-5), 2.44 (s, 3H, H-12), 2.41 – 2.33 (m, 4H, H-2), 1.97 – 1.75 (m, 4H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.4 (C-1), 144.0 (C-11), 137.7 (C-8), 130.1 (2xC-10), 130.0 (C-6), 127.2 (2xC-9), 118.9 (C-7), 56.3 (C-4), 51.5 (C-5), 40.1 (2xC-2), 30.0 (2xC-3), 21.7 (C-12).

tris(4-(trifluoromethyl)phenyl)phosphane (374)



Prepared according to a literature procedure.[20] To a suspension of Mg (2.16 g, 88.9 mmol, 3.00 equiv.) in Et_2O (16 mL) was dropwise added solution of bromide 1-bromo-4-(trifluoromethyl)benzene (20 g, 88.9 mmol, 3.00 equiv.) in Et_2O (32 mL) over 1 h and the resulting mixture was stirred for additional 1 h. Then, a solution of PCl_3 (2.6 mL) in Et_2O (60 ml) was added dropwise over 45 min, and the reaction mixture was stirred for 2 h. The reaction was quenched with water (100 mL) and extracted with Et_2O (3

x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (pentane) afforded phosphine **374** as a white solid (11.35 g, 82%). The spectroscopic data are in agreement with the literature values.[20]

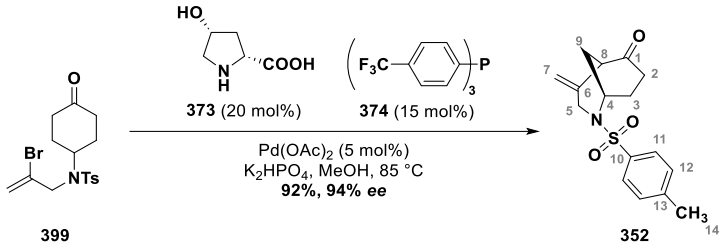
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 – 7.60 (m, 6H, H-2), 7.46 – 7.37 (m, 6H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 140.4 (d, J = 14.2 Hz, C-1), 134.1 (d, J = 20.1 Hz, C-2), 131.7 (q, J = 32.7 Hz, C-4), 125.8 (dq, J = 7.5, 3.7 Hz, C-3), 124.0 (q, J = 272.6 Hz, C-6).

^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.96.

^{31}P NMR (162 MHz, $CDCl_3$): δ -6.05.

(*1S,5R*)-4-methylene-2-tosyl-2-azabicyclo[3.3.1]nonan-6-one (352)



Compound **352** was prepared adopting the procedure developed in our group by Sam Ellis.[19]

Oven-dried thick-wall Schlenk tube under the argon atmosphere was charged with ketone **399** (4.02 g, 10.4 mmol, 1 equiv.), palladium acetate (116.8 mg, 0.520 mmol, 5.00 mol %), (*2R,4R*)-4-hydroxypyrrolidine-2-carboxylic acid (**373**) (273 mg, 2.08 mmol, 0.20 equiv.), tris(4-trifluoromethylphenyl)phosphine (**374**) (728 mg, 1.56 mmol, 0.15 equiv.) and K_2HPO_4 (2.72 g, 15.61 mmol, 1.50 equiv.). The reaction vessel was then degassed by 5 cycles of vacuum (oil pump) – argon. Methanol (200 mL), degassed by bubbling with nitrogen (1 h) and argon (1 h) prior to use, was added, and another 5 cycles of vacuum – argon were repeated. Then, the reaction vessel was sealed and submerged into a pre-heated oil bath (85 °C) and stirred at this temperature for 24 h. The reaction mixture was then allowed to cool down to room temperature, diluted with CH_2Cl_2 (200 mL), filtered through Celite® in a column by the pressure of nitrogen and washed out with additional CH_2Cl_2 (100 mL). Collected filtrate was concentrated under reduced pressure, combined with material from several other runs (total 16.9 g of starting material was used) and purified by gradient column chromatography (ethyl acetate/pentane = 0:1 to 6:4). The desired product of cyclization **352** was obtained as a white solid (12.36 g, 92%, 94% *ee*). Data are in agreement with literature values.[21]

Note: The product of the cyclization contained a trace amount of phosphine oxide that has a very similar R_f to the product. In order to obtain phosphine residues-free material, the product obtained after column chromatography was triturated from Et_2O (25 + 5 + 5 mL). The combined ether fraction concentrated

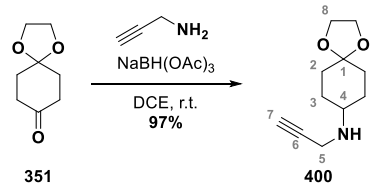
and trituration repeated. This method provided 11.5 g of phosphine-free material (93% yield of trituration, 86% overall yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 8.0 Hz, 2H, H-11), 7.36 (d, *J* = 8.0 Hz, 2H, H-12), 5.13 (t, *J* = 1.5 Hz, 1H, H-9a), 5.04 (t, *J* = 1.5 Hz, 1H, H-9b), 4.19 (d, *J* = 14.0 Hz, 1H, H-5a), 4.12 (p, *J* = 3.0 Hz, 1H, H-4), 3.77 (dq, *J* = 14.0, 1.5 Hz, 1H, H-5b), 3.25 (s, 1H, H-8), 2.83 (ddd, *J* = 15.5, 13.0, 7.5 Hz, 1H, H-2a), 2.46 (s, 3H, H-14), 2.43–2.34 (m, 1H, H-3a), 2.34–2.25 (m, 1H, H-2b), 1.99 (dq, *J* = 14.0, 3.0 Hz, 1H, H-9a), 1.94–1.82 (m, 2H, H-9b, H-3b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.3 (C-1), 143.9 (C-6), 138.2 (C-10), 134.8 (C-13), 130.0 (C-12), 127.4 (C-11), 115.2 (C-7), 50.2 (C-8), 48.0 (C-4), 47.2 (C-5), 34.8 (C-2), 32.5 (C-3), 30.5 (C-9), 21.7 (C-14).

HPLC (Chiralpak AD-H, hexane/isopropanol 90:10, 1.0 mL min^{-1}, λ =210 nm) t_R = 23.0 min (major), 27.2 min (minor).

N-(prop-2-yn-1-yl)-1,4-dioxaspiro[4.5]decan-8-amine (400)

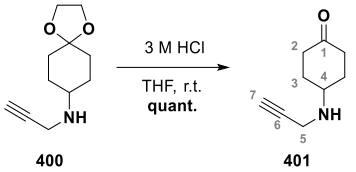


Compound **400** was prepared according to a literature procedure.[19] To a solution of ketone **351** (20.0 g, 128 mmol, 1 equiv.) in DCE (400 mL) was added propargyl amine (8.26 mL, 132 mmol, 1.03 equiv.) and after stirring for 5 min at room temperature, the reaction mixture was cooled to 0 °C. $NaBH(OAc)_3$ (38.0 g, 179 mmol, 1.40 equiv.) was then added in a small portion over 30 min and the resulting suspension was stirred at room temperature for 22 h. The reaction mixture was then quenched with 1 M KOH (400 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The amine **400** was obtained as a yellowish solid (24.2 g, 97%) and was used in the next step without further purification. Experimental data are in agreement with literature values.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.91 (s, 4H, H-8), 3.43 (d, J = 2.5 Hz, 2H, H-5), 2.75 (tt, J = 9.6, 3.7 Hz, 1H, H-4), 2.18 (t, J = 2.4 Hz, 1H, H-7), 1.89 – 1.70 (m, 4H, H-2a, H-3a), 1.55 (td, J = 12.5, 3.8 Hz, 2H, H-2b), 1.42 (tdd, J = 12.1, 9.5, 3.2 Hz, 2H, H-3b), 1.24 (br s, 1H, NH).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 108.7 (C-1), 82.6 (C-6), 71.2 (C-7), 64.38 (C-8), 64.36 (C-8), 53.4 (C-4), 35.6 (C-5), 32.8 (C-2), 29.9 (C-3).

4-(prop-2-yn-1-ylamino)cyclohexan-1-one (401)

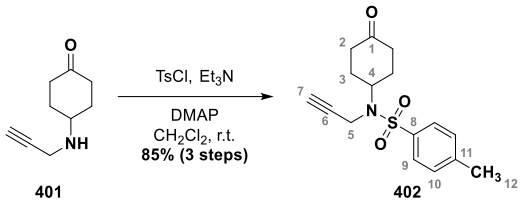


Compound **401** was prepared according to a literature procedure.[19] To a solution of acetal **400** (24.2 g, 124 mmol, 1 equiv.) in THF (320 mL) was added 3 M HCl (320 mL), and the resulting solution was stirred for 2 days at room temperature. The reaction mixture was then quenched with 3 M KOH (350 mL), phases separated, and the aqueous phase extracted with *i*-PrOH/$CHCl_3$ (1:5) (3 x 500 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Ketone **401** was obtained as a brown oil (18.7 g, quant.) and was used in the next step without further purification. Experimental data are in agreement with literature values.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49 (d, J = 2.4 Hz, 2H, H-5), 3.21 (tt, J = 8.2, 3.5 Hz, 1H, H-4), 2.56 – 2.41 (m, 2H, H-2a), 2.39 – 2.26 (m, 2H, H-2b), 2.24 (t, J = 2.4 Hz, 1H, H-7), 2.12 – 1.99 (m, 2H, H-3a), 1.77 – 1.63 (m, 2H, H-3b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.3 (C-1), 82.0 (6), 71.7 (C-7), 51.6 (C-4), 38.3 (C-2), 35.7 (C-5), 31.6 (C-3).

4-methyl-*N*-(4-oxocyclohexyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (402)

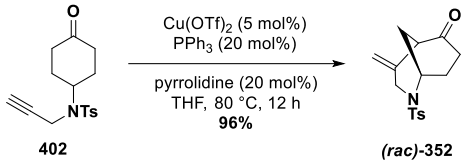


Compound **402** was prepared according to a literature procedure.[19] To a solution of amine **401** (18.7 g, 124 mmol, 1 equiv.) in CH_2Cl_2 (400 mL) was added Et_3N (20.3 mL, 146 mmol, 1.18 equiv.) followed by TsCl (27.8 g, 146 mmol, 1.18 equiv.) and DMAP (1.48 g, 12.1 mmol, 0.10 equiv.). After stirring for 24 h, the reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with 1 M HCl (100 mL), water (400 mL) and brine (300 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 30:70) afforded product **402** as a white solid (33.3 g, 88%, 85% over 3 steps). Experimental data are in agreement with literature values.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 – 7.75 (m, 2H, H-9), 7.33 – 7.23 (m, 2H, H-10), 4.19 (tt, J = 11.4, 4.6 Hz, 1H, H-4), 4.10 (d, J = 2.5 Hz, 2H, H-5), 2.42 (s, 3H, H-12), 2.45 – 2.34 (m, 4H, H-2), 2.17 (t, J = 2.5 Hz, 1H, H-7), 2.11 – 1.92 (m, 4H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.6 (C-1), 143.8 (C-8), 137.6 (C-11), 129.8 (C-10), 127.4 (C-9), 79.8 (C-6), 73.1 (C-7), 55.7 (C-C), 40.0 (C-2), 32.6 (C-5), 30.1 (C-3), 21.7 (C-12).

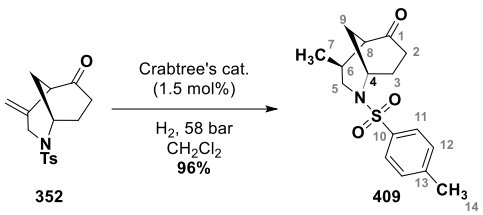
rac-(*1S,5R*)-4-methylene-2-tosyl-2-azabicyclo[3.3.1]nonan-6-one (*rac*-352)



402 ***(rac)*-352**

Compound ***(rac)*-352** was prepared according to a literature procedure.[19] An oven-dried round-bottom flask was changed with alkyne **402** (11.7 g, 38.3 mmol, 1 equiv.), $Cu(OTf)_2$ (693 mg, 1.92 mmol, 5.00 mol %) and PPh_3 (2.01 g, 7.66 mmol, 0.20 equiv.) and degassed using three vacuum – N_2 cycles. Degassed THF (250 mL) was then added, followed by pyrrolidine (630 μL, 7.66 mmol, 0.20 equiv.). The reaction vessel was sealed and heated to 90 °C for 18 h. The reaction mixture was then concentrated under reduced pressure and purified by column chromatography (ethyl acetate:pentane = 20:80). The product of cyclization ***(rac)*-352** was obtained as a white solid (11.2g, 96%). Experimental data are in agreement with literature values.[21]

(*1S,4S,5R*)-4-methyl-2-tosyl-2-azabicyclo[3.3.1]nonan-6-one (409)



352 **409**

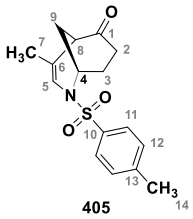
Compound **409** was prepared according to procedure developed in our group by Sam Ellis.[19]

A high-pressure steel reactor was charged with alkene **352** (3.00 g, 9.82 mmol, 1 equiv.), Crabtree's catalyst (119 mg, 0.147 mmol, 1.5 mol%) and CH_2Cl_2 (150 mL). While the reaction mixture was stirred vigorously, the reactor was pressurized with hydrogen (58 bar) and stirred at room temperature for 30 min. Then, the pressure was carefully released, and the reaction mixture was concentrated under reduced pressure. Purification of material obtained from several runs (total 11.0 g of starting material was used) by gradient column chromatography (ethyl acetate:pentane = 1:9 to 4:6) afforded desired product of reduction **409** as a white solid (10.58 g, 96%). Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 – 7.64 (m, 2H, H-11), 7.35 – 7.27 (m, 2H, H-12), 4.20 – 4.12 (m, 1H, H-4), 3.26 (dd, J = 12.5, 5.0 Hz, 1H, H-5a), 2.99 (dd, J = 12.5, 5.8 Hz, 1H, H-5b), 2.59 (dt, J = 16.7, 8.2 Hz, 1H, H-2a), 2.43 (s, 3H, H-14), 2.34 (dddd, J = 17.0, 7.9, 5.2, 1.0 Hz, 1H, H-2b), 2.23 (q, J = 3.0 Hz, 1H, H-8), 2.19 – 2.05 (m, 2H, H-6, H-9a), 2.00 – 1.83 (m, 2H, H-3), 1.74 (dt, J = 13.9, 3.0 Hz, 1H, H-9b), 1.07 (d, J = 6.9 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 213.4 (C-1), 143.6 (C-10), 136.0 (C-13), 129.9 (C-12), 127.3 (C-11), 48.3 (C-8), 47.3 (C-4), 45.5 (C-5), 35.7 (C-2), 32.0 (C-6), 28.2 (C-3), 26.1 (C-9), 21.6 (C-14), 18.6 (C-7).

rac-(*1S,5R*)-4-methyl-2-tosyl-2-azabicyclo[3.3.1]non-3-en-6-one (405)



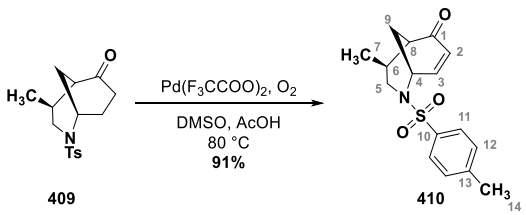
405

Enamide **405** was isolated as a side-product in the hydrogenation of **352**, when the reaction was performed at lower pressure of hydrogen and/or the starting material was contaminated with traces of phosphine. Data are in agreement with the previously reported values.[19]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (d, J = 8.0 Hz, 2H, H-11), 7.31 (d, J = 8.0 Hz, 2H, H-12), 6.82 (d, J = 1.5 Hz, 1H, H-5), 4.11–4.15 (m, 1H, H-4), 2.70–2.75 (m, 1H, H-8), 2.57 (ddd, J = 15.5, 13.5, 7.5 Hz, 1H, H-2a), 2.41 (s, 3H, H-14), 2.37 (dddd, J = 14.0, 7.5, 3.5, 1.5 Hz, 1H, H-3a), 2.15 (dd, J = 15.7, 6.0 Hz, 1H, H-2b), 1.85—1.92 (m, 1H, H-3b), 1.83 (dt, J = 13.0, 2.5, 2.5 Hz, 1H, H-9a), 1.65 (d, 3H, J = 1.5 Hz, H-7), 1.27–1.34 (m, 1H, H-9b).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.4 (C-1), 144.1 (C-10), 136.09 (C-13), 130.1 (C-12), 126.9 (C-11), 122.9 (C-5), 113.8 (C-6), 49.9 (C-8), 47.8 (C-4), 34.6 (C-3), 33.8 (C-2), 27.9 (C-9), 21.7 (C-14), 19.5 (C-7).

(*1R,4S,5R*)-4-methyl-2-tosyl-2-azabicyclo[3.3.1]non-7-en-6-one (410)



409 410

Compound **410** was prepared according to procedure developed in our group by Sam Ellis[19] using protocol published by Stahl *et al.*[22]

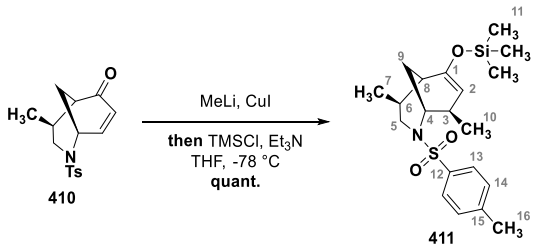
To a stirred solution of ketone **409** (16.7 g, 54.7 mmol, 1 equiv.) and $Pd(TFA)_2$ (727 mg, 2.19 mmol, 4.0 mol %) in acetic acid (164 mL) was added DMSO (311 μL, 2.75 mmol, 8.0 mol %), reflux condenser was attached, and the system was flushed with oxygen. The reaction mixture was heated to 80 °C for 2-3 days under the atmosphere of oxygen introduced from a double-coated balloon attached to the top of

the condenser. After completion (monitored by NMR), the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The brown residue was purified by gradient column chromatography (ethyl acetate:pentane = 1:9 to 3:7). Enone **410** was isolated as a white solid (15.1 g, 91%). Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 – 7.64 (m, 2H, H-11), 7.35 – 7.26 (m, 2H, H-12), 6.31 (ddd, J = 9.9, 6.1, 1.7 Hz, 1H, H-3), 6.07 (dd, J = 9.9, 1.1 Hz, 1H, H-2), 4.64 (dt, J = 6.4, 3.2 Hz, 1H, H-4), 3.42 (ddd, J = 12.7, 1.5, 0.8 Hz, 1H, H-5a), 3.02 (dd, J = 12.8, 4.0 Hz, 1H, H-5b), 2.43 (s, 3H, H-14), 2.37 (d, J = 3.0 Hz, 1H, H-8), 2.28 (dtd, J = 13.4, 3.0, 1.7 Hz, 1H, H-9a), 2.07 – 1.96 (m, 2H, H-6, H-9b), 1.18 (d, J = 7.0 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.3 (C-1), 143.9 (C-10), 140.8 (C-3), 136.7 (C-13), 133.0 (C-2), 130.0 (C-12), 127.3 (C-11), 47.1 (C4), 46.7 (C-8), 43.9 (C-5), 31.4 (C-6), 27.7 (C-9), 21.7 (C-14), 17.5 (C-7).

(*1R,4S,5R,8R*)-4,8-dimethyl-2-tosyl-6-((trimethylsilyl)oxy)-2-azabicyclo[3.3.1]non-6-ene (411)



Compound **411** was prepared according to procedure developed in our group by Sam Ellis.[19]

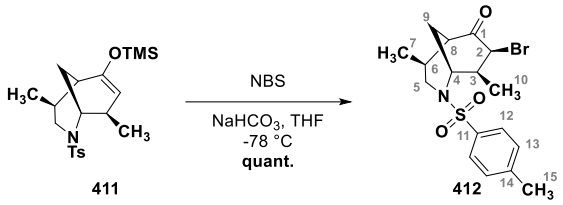
To a suspension of CuI (6.18 g, 32.5 mmol, 1.10 equiv.) in dry THF (150 mL) was dropwise added MeLi (1.6 M in Et_2O, 38.7 mL, 62.0 mmol, 2.10 equiv.) at 0 °C. During the addition of MeLi the suspension gradually turned from white to dark yellow and then brown and, after the complete addition of MeLi became a colorless solution. The resulting solution was stirred for 15 min at 0 °C before cooling to -78 °C. Then, a solution of ketone **410** (9.02 g, 29.5 mmol, 1 equiv.) in dry THF (70 mL) was added dropwise, followed by the addition of Et_3N (16.5 mL, 118.1 mmol, 4.00 equiv.) and TMSCl (11.2 mL, 88.6 mmol, 3.00 equiv.). (**Note:** *The solution becomes yellow on the addition of enone **16**, and darkens on the addition of TMSCl*). After 30 minutes, the reaction mixture was diluted with Et_2O (500 mL) and transferred to a separation funnel. The reaction mixture, while still cold, was washed with sat. aq. solution of NH_4Cl (5 x 100 mL) until the aq. phase was no longer blue. The combined aq. phases were back-extracted with Et_2O (200 mL), and combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Silyl enol ether **411** was obtained as a colorless oil (11.6 g, quant.) and was used in the next step without further purification. Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 – 7.62 (m, 2H, H-13), 7.31 – 7.24 (m, 2H, H-14), 4.65 (d, J = 3.9 Hz, 1H, H-2), 3.81 (t, J = 3.5 Hz, 1H, H-4), 3.32 (dd, J = 12.2, 1.4 Hz, 1H, H-5a), 3.20 (dd, J = 12.2, 3.7

Hz, 1H, H-5b), 2.42 (s, 3H, H-16), 1.97 – 1.89 (m, 1H, H-9a), 1.89 – 1.77 (m, 3H, H-3, H-8, H-6), 1.53 (dt, J = 13.3, 3.0 Hz, 1H, H-9b), 1.09 (d, J = 6.8 Hz, 3H, H-7), 0.88 (d, *J* = 7.2 Hz, 3H, H-10), 0.15 (s, 9H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 152.5 (C-1), 143.0 (C-12), 138.2 (C-15), 129.7 (C-14), 127.0 (C-13), 108.8 (C-2), 53.2 (C-4), 44.3 (C-5), 39.0 (C-8), 33.3 (C-3), 29.5 (C-6), 22.3 (C-9), 21.7 (C-10), 21.2 (C-16), 17.1 (C-7), 0.05 (C-11).

(*1R,4S,5R,7S,8S*)-7-bromo-4,8-dimethyl-2-tosyl-2-azabicyclo[3.3.1]nonan-6-one (412)



Compound **412** was prepared according to procedure developed in our group by Sam Ellis.[19]

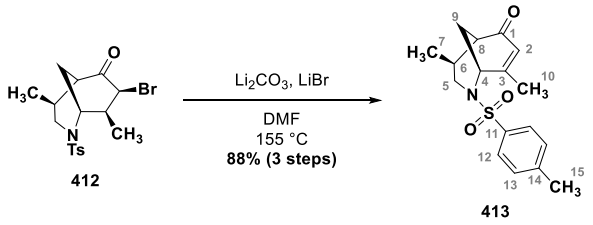
To a solution of silyl enol ether **411** (11.6 g, 29.5 mmol, 1 equiv.) in dry THF (270 mL) at -78 °C was added $NaHCO_3$ (2.98 g, 35.4 mmol, 1.20 equiv.) followed by NBS (6.31 g, 35.4 mmol, 1.20 equiv.). After stirring for 30 min at this temperature, the reaction mixture was diluted with Et_2O (250 mL) and washed with sat. aq. solution of $NaHCO_3$ (300 mL). The aqueous layer was back-extracted with Et_2O (3 x 200 mL), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The bromide **412** was obtained as a yellowish solid contaminated with traces of succinimide (13.8 g obtained, theoretical yield 11.8 g, supp. quant.). The obtained product was used in the next step without further purification. Data are in agreement with the previously reported values.[19]

NOTE: Decomposition occurs quickly on silica.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 – 7.64 (m, 2H, H-12), 7.39 – 7.27 (m, 2H, H-13), 5.29 (d, *J* = 6.2 Hz, 1H, H-2), 3.82 – 3.74 (m, 1H, H-4), 3.49 (dd, *J* = 12.1, 6.0 Hz, 1H, H-5a), 2.94 – 2.81 (m, 1H, H-3), 2.63 (dd, *J* = 12.1, 9.3 Hz, 1H, H-5b), 2.49 – 2.40 (m, 1H, H-8), 2.44 (s, 3H, H-15), 2.22 (dtd, *J* = 9.0, 6.4, 2.2 Hz, 1H, H-6), 2.09 (dt, *J* = 14.7, 3.0 Hz, 1H, H-9a), 1.82 (dddd, *J* = 14.6, 3.8, 2.8, 2.0 Hz, 1H, H-9b), 1.06 (d, *J* = 7.1 Hz, 3H, H-10), 1.01 (d, *J* = 6.8 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.2 (C-1), 144.1 (C-11), 134.6 (C-14), 130.1 (C-13), 127.6 (C-12), 56.1 (C-2), 55.2 (C-4), 48.4 (C-8), 45.9 (C-5), 43.4 (C-3), 31.8 (C-6), 22.4 (C-9), 21.7 (C-15), 19.4 (C-7), 16.3 (C-10).

(*1R,4S,5R*)-4,8-dimethyl-2-tosyl-2-azabicyclo[3.3.1]non-7-en-6-one (413)



Compound **413** was prepared according to procedure developed in our group by Sam Ellis.[19]

A solution of crude bromide **412** (11.8 g, 29.5 mmol, 1 equiv.), Li_2CO_3 (5.45 g, 73.8 mmol, 2.50 equiv.) and LiBr (3.84 g, 44.3 mmol, 1.50 equiv.) in DMF (122 mL) was heated to 155 °C for 3 h. Then, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (500 mL) and washed with 1 M aq. HCl (2 x 200 mL) and brine (6 x 150 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 15:85 to 25:75) afforded enone **413** as a white solid (8.30 g, 88% over 3 steps). Data are in agreement with the previously reported values.[19]

Note: The *ee* of product **413** can be increased at this stage by recrystallization from a boiling mixture of hexane and ethyl acetate (23 mL of hexane per g of **413** and 4.8 mL of ethyl acetate per g of **413**). The recrystallization was repeated with material obtained from mother liquor (74% yield of recrystallyzation, >99% *ee*).

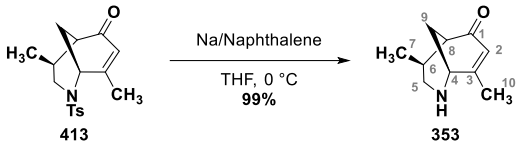
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 – 7.69 (m, 2H, H-12), 7.35 – 7.27 (m, 2H, H-13), 6.02 (p, J = 1.4 Hz, 1H, H-2), 4.52 (t, J = 3.2 Hz, 1H, H-4), 3.32 (d, J = 13.8 Hz, 1H, H-5a), 3.22 (dd, J = 13.9, 4.0 Hz, 1H, H-5b), 2.43 (s, 3H, H-15), 2.31 – 2.25 (m, 1H, H-8), 2.14 (dt, J = 13.2, 3.0 Hz, 1H, H-9a), 1.97 (dt, J = 13.3, 3.4 Hz, 1H, H-9b), 1.94 – 1.87 (m, 1H, H-6), 1.89 (d, J = 1.5 Hz, 3H, H-10), 0.90 (d, J = 7.0 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.4 (C-1), 154.8 (C-3), 143.7 (C-11), 137.8 (C-14), 129.8 (C-13), 129.5 (C-2), 127.3 (C-12), 51.6 (C-4), 45.7 (C-8), 43.9 (C-5), 31.4 (C-6), 27.2 (C-9), 22.1 (C-10), 21.7 (C-15), 17.6 (C-7).

$[\alpha]_D^{25}$= +385.86 (c = 1.00, $CHCl_3$).

SFC: Chiralpak® IA; 1500 psi, 30 °C; flow: 1.5 mL.min^{-1}; from 1% to 30% MeOH in 5 min; >99.8% *ee* (major enantiomer t_R = 3.96 min; minor enantiomer t_R = 3.81 min).

(*1R,4S,5R*)-4,8-dimethyl-2-azabicyclo[3.3.1]non-7-en-6-one (353)



Compound **353** was prepared according to procedure developed in our group by Sam Ellis.[19]

Preparation of sodium naphthalene: To 1 M solution of naphthalene in THF was added sodium (1.5 equiv. related to naphthalene) washed with pentane and cut to small pieces. The resulting mixture was placed into a sonicator for 60 min, which resulted in the slow dissolution of sodium and the formation of a dark blue-colored solution.

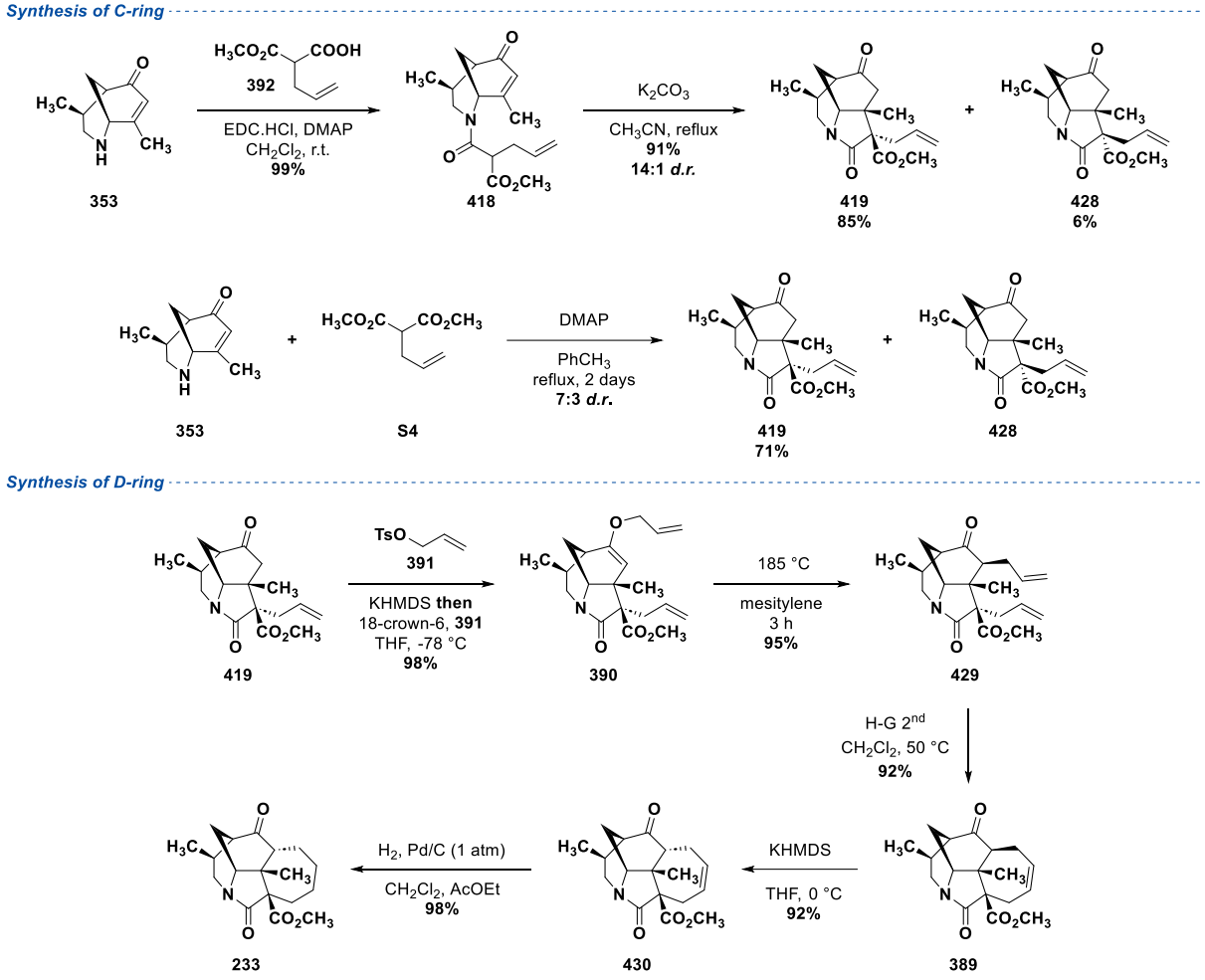
To a solution of enone **413** (5.00 g, 15.7 mmol, 1 equiv.) in dry THF (157 mL) was added NaHMDS (1 M in THF, 32.9 mL, 32.9 mmol, 2.10 equiv.) at 0 °C and after stirring for 30 min at this temperature, freshly prepared solution of sodium naphthalene (1M in THF, 62.6 mL, 62.6 mmol, 4.00 equiv.) was added dropwise, with the blue-black color dissipating during the addition until approximately 3 equiv. had been added, after which the solution remained black. After stirring for 30 min, the reaction was quenched with distilled water (150 mL) and diluted with Et_2O (150 mL). The layers were separated, and aq. phase washed with CH_2Cl_2/IPA (9:1) (6 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:methanol = 100:0 to 70:30) afforded amine **353** as a yellow oil (2.58 g, 99%). Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.07 (s, 1H, H-2), 3.42 (t, *J* = 3.4 Hz, 1H, H-4), 3.01 (dd, *J* = 12.7, 4.4 Hz, 1H, H-5a), 2.55 (d, *J* = 12.7 Hz, 1H, H-5b), 2.31 – 2.22 (m, 2H, H-8, H-9a), 1.97 (s, 3H, H-10), 1.93 (dt, *J* = 14.0, 3.7 Hz, 1H, H-9b), 1.89 – 1.79 (m, 2H, H-6, NH), 1.26 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.9 (C-1), 156.1 (C-3), 128.3 (C-2), 52.4 (C-1), 46.6 (C-8), 43.4 (C-5), 30.9 (C-6), 28.2 (C-9), 22.2 (C-10), 17.5 (C-7).

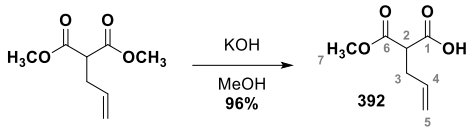
$[\alpha]_D^{25}$ = +250.3 (c = 1.00, $CHCl_3$).

4.3.2 Formal synthesis of Daphniphyllum alkaloids



Scheme 4.8. *Overview of formal synthesis of Daphniphyllum alkaloids.*

2-(methoxycarbonyl)pent-4-enoic acid (392)

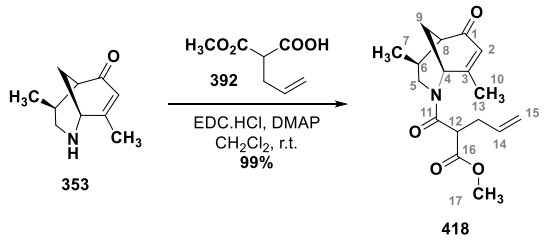


Prepared according to a literature procedure.[23] To a solution of dimethyl allylmalonate (10.0 g, 58.1 mmol, 1 equiv.) in MeOH (116 mL) was added KOH (3.26 g, 58.1 mmol, 1.00 equiv.), and after stirring for 26 h, the reaction mixture was diluted with water (120 mL) and extracted with Et_2O (3 x 100 mL). The aqueous phase was then acidified with 6 M HCl (40 mL) and extracted with CH_2Cl_2 (5 x 80 mL). The combined CH_2Cl_2 phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (50 mbar, 45 °C). The product of hydrolysis **392** was obtained as a yellowish oil (8.81 g, 96%). The spectroscopic data are in agreement with the literature values.[24]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.74 (s, 1H, OH), 5.77 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H, H-4), 5.13 (dq, *J* = 17.1, 1.5 Hz, 1H, H-5a), 5.08 (dq, *J* = 10.2, 1.3 Hz, 1H, H-5b), 3.75 (s, 3H, H-7), 3.49 (t, *J* = 7.5 Hz, 1H, H-2), 2.66 (dddd, *J* = 8.9, 7.4, 2.5, 1.3 Hz, 2H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.6 (C-1), 169.2 (C-6), 133.6 (C-4), 118.1 (C-5), 52.8 (C-7), 51.4 (C-2), 32.9 (C-3).

methyl 2-((*1R,4S,5R*)-4,8-dimethyl-6-oxo-2-azabicyclo[3.3.1]non-7-ene-2-carbonyl)pent-4-enoate (418)



Compound **418** was prepared according to procedure developed in our group by Sam Ellis.[19]

To a solution of amine **418** (2.58 g, 15.6 mmol, 1 equiv.) in CH_2Cl_2 (78.0 mL) at room temperature was added 2-(methoxycarbonyl)pent-4-enoic acid (**392**) (3.46 g, 21.9 mmol, 1.40 equiv.), followed by DMAP (477 mg, 3.90 mmol, 0.25 equiv.) and EDC.HCl (4.49 g, 23.4 mmol, 1.50 equiv.). After stirring for 3 h, the reaction mixture was diluted with water (80 mL) and extracted with CH_2Cl_2 (4 x 80 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 40:60) afforded amide **S35** as a colorless oil (4.73 g, 99%). Product **418** is a complex mixture of isomers – presumably diastereomers at C-12 and rotamers. Data are in agreement with the previously reported values.[19]

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2922, 1710, 1645, 1199.

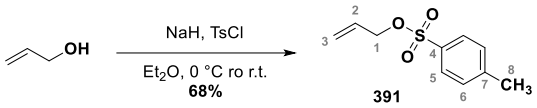
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.08 – 6.05 (m, 1H, H-2), 5.86 – 5.65 (m, 1H, H-14), 5.38 (s, 1H, H-4), 5.23 – 4.94 (m, 2H, H-15), 3.73 (s, 3H, H-17), 3.67 (s, 3H, H-17), 3.66 – 3.59 (m, 1H, H-12), 3.54 (d, *J* = 13.7 Hz, 1H, H-5), 3.43 – 3.30 (m, 1H, H-5), 2.81 – 2.61 (m, 2H, H-13), 2.42 – 2.35 (m, 1H, H-8), 2.24 – 2.09 (m, 1H, H-9), 2.06 – 2.00 (m, 1H-H9), 2.01 – 1.90 (m, 1H, H-6), 1.94 (d, *J* = 1.5 Hz, 3H, H-10), 1.90 (d, *J* = 1.5 Hz, 3H, H-10), 1.17 (d, *J* = 7.4 Hz, 3H, H-7), 1.15 (d, *J* = 7.4 Hz, 3H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 201.62 (C-1), 201.55 (C-1), 169.9 (C-16), 169.8 (C-16), 168.5 (C-11), 156.3 (C-3), 156.0 (C-3), 134.8 (C-14), 134.5 (C-14), 129.5 (C-2), 129.4 (C-2), 117.7 (C-15), 117.6 (C-15), 52.60 (C-17), 52.57 (C-17), 49.2 (C-12), 49.0 (C-12), 47.8 (C-4), 47.7 (C-4), 46.14 (C-8), 46.10 (C-8), 45.0 (C-5), 44.8 (C-5), 33.7 (C-13), 33.3 (C-13), 31.6 (C-6), 31.3 (C-6), 26.41 (C-9), 26.39 (C-9), 22.11 (C-10), 22.08 (C-10), 17.6 (C-7), 17.4 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{17}H_{24}O_4N)^+$ requires 306.1700, found 306.1699.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= +62.2° (c = 1.00, in $CHCl_3$, >99% ee).

allyl 4-methylbenzenesulfonate (391)

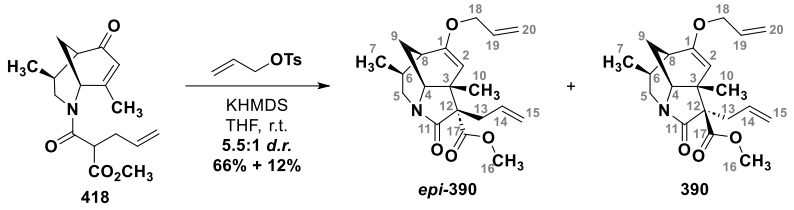


Compound **391** was prepared according to the literature.[25] To a suspension of NaH (60% in mineral oil, 1.26 g, 31.5 mmol, 1.5 equiv.) washed with pentane in Et_2O (32 mL) was added allyl alcohol (1.57 mL, 23.1 mmol, 1.10 equiv.). After gas evolution ceased, the reaction mixture was cooled to 0 °C, and a solution of TsCl (4.00 g, 21.0 mmol, 1 equiv.) in Et_2O (50 mL) was added dropwise. After stirring for 2 h at room temperature, the reaction mixture was quenched with sat. aq. solution of NH_4Cl (50 mL) and extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was washed with pentane (2 x 10 mL), and the volatiles were removed *in a vacuo*. Product **391** was obtained as a colorless oil (3.037 g, 68%). The spectroscopic data are in agreement with the literature values.[25]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 – 7.76 (m, 2H, H-5), 7.38 – 7.30 (m, 2H, H-6), 5.82 (ddt, *J* = 17.1, 10.3, 5.9 Hz, 1H, H-2), 5.32 (dq, *J* = 17.1, 1.4 Hz, 1H,H-3a), 5.25 (dq, *J* = 10.3, 1.1 Hz, 1H, H-3b), 4.53 (dt, *J* = 5.9, 1.3 Hz, 2H, H-1), 2.45 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.9 (C-4), 133.4 (C-7), 130.4 (C-2), 130.0 (C-6), 128.1 (C-5), 120.4 (C-3), 70.9 (C-1), 21.8 (C-8).

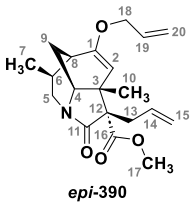
methyl *rac*-(3S,3aR,6R,7aS,8S)-3-allyl-5-(allyloxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carboxylate (*epi*-390) and methyl *rac*-(3R,3aR,6R,7aS,8S)-3-allyl-5-(allyloxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carboxylate (390)



Compounds ***epi*-390** and **390** were prepared adopting the procedure described by S. Ellis.[19]

To a solution of enone **418** (68.8 mg, 0.225 mmol, 1 equiv.) in degassed THF (0.4 mL) was added 0.5 M solution of KHMDS in toluene (674 μL, 0.337 mmol, 1.50 equiv.) at 0 °C. The ice bath was removed, and the reaction mixture stirred at room temperature for 15 min. To the resulting red solution of enolate was added solution of allyl tosylate (71.5 mg,0.337 mmol, 1.50 equiv.) and 18-crown-6 (29.7 mg, 0.112 mmol, 0.50 equiv.) in degasses THF (0.4 mL) and the resulting solution was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O (10 ml) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 3:7 to 4:6) afforded compound ***epi*-390** as a colourless oil (51.4 mg, 66%) and compound **390** as a colourless oil (9.6 mg, 12%).

Compound *epi*-390:



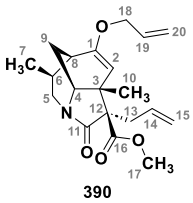
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.95 – 5.86 (m, 1H, h-19), 5.83 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H, H-14), 5.29 – 5.21 (m, 1H, H-20a), 5.21 – 5.15 (m, 1H, H-20b), 5.11 (dt, *J* = 17.0, 1.7 Hz, 1H, H-15a), 5.06 (ddd, *J* = 10.1, 2.1, 1.1 Hz, 1H, H-15b), 4.15 – 4.01 (m, 3H, H-5a, H-18), 3.87 (d, *J* = 1.3 Hz, 1H, H-2), 3.73 (s, 3H, H-17), 3.71 – 3.67 (m, 1H, H-4), 2.79 (ddt, *J* = 13.7, 7.6, 1.3 Hz, 1H, H-13a), 2.44 (ddd, *J* = 13.7, 6.8, 1.3 Hz, 1H, H-13b), 2.34 (dd, *J* = 13.7, 10.5 Hz, 1H, H-5b), 2.10 (dt, *J* = 10.3, 7.2 Hz, 1H, H-6), 1.95 (ddd, *J* = 13.7, 5.2, 2.3 Hz, 1H, H-9a), 1.91 (ddd, *J* = 3.8, 2.2, 1.0 Hz, 1H, H-8), 1.62 (dd, *J* = 13.7, 3.9 Hz, 1H, H-9b), 1.20 (s, 3H, H-10), 0.94 (d, *J* = 6.9 Hz, 3H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 173.0 (C-16), 170.9 (C-11), 159.5 (C-1), 133.3 (C-14), 133.2 (C-19), 118.6 (C-15), 117.4 (C-20), 96.8 (C-2), 67.9 (C-18), 62.0 (C-12), 55.9 (C-4), 51.7 (C-17), 48.8 (C-3), 41.4 (C-5), 37.3 (C-8), 35.0 (C-13), 31.9 (C-6), 20.1 (C-9), 19.4 (C-7), 17.4 (C-10).

IR (thin film) a$\tilde{\nu}_{max}$/cm^{-1}: 2949, 1754, 1695, 1650, 1409, 1194, 1159.

HRMS (ESI): m/z calcd for $C_{20}H_{27}O_4N+H^+$ 346.20128 found 346.20115.

Compound 390:



390

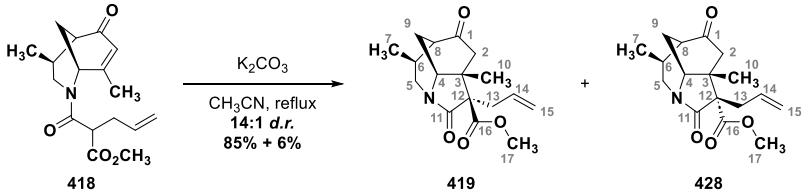
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (dddd, *J* = 17.2, 10.2, 9.2, 4.7 Hz, 1H, H-14), 5.91 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H, H-19), 5.28 (dq, *J* = 17.2, 1.6 Hz, 1H, H-20a), 5.21 (dq, *J* = 10.4, 1.4 Hz, 1H, H-20b), 5.13 (dtd, *J* = 17.2, 2.1, 0.9 Hz, 1H, H-15a), 5.12 – 5.05 (m, 1H, H-15b), 4.28 (d, *J* = 1.4 Hz, 1H, H-2), 4.21 (ddt, *J* = 12.6, 5.6, 1.5 Hz, 1H, H-18a), 4.14 (ddt, *J* = 12.6, 5.3, 1.5 Hz, 1H, H-18b), 4.06 (dd, *J* = 13.7, 8.0 Hz, 1H, H-5a), 3.85 – 3.80 (m, 1H, H-4), 3.70 (s, 3H, H-17), 2.73 (ddt, *J* = 14.6, 4.7, 1.9 Hz, 1H, H-13a), 2.46 – 2.36 (m, 2H, H-13b, H-5b), 2.11 – 1.98 (m, 1H, H-6), 1.95 (ddd, *J* = 13.8, 5.3, 2.4 Hz, 1H, H-9a), 1.93 – 1.88 (m, 1H, H-8), 1.62 (ddt, *J* = 13.8, 4.0, 1.1 Hz, 1H, H-9b), 1.14 (s, 3H, H-10), 0.96 (d, *J* = 6.9 Hz, 3H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 174.0 (C-16), 170.9 (C-11), 159.6 (C-1), 135.4 (C-14), 133.3 (C-19), 117.6 (C-15), 117.5 (C-20), 95.1 (C-2), 67.9 (C-18), 61.9 (C-12), 56.9 (C-4), 52.2 (C-17), 50.0 (C-3), 41.6 (C-5), 37.4 (C-8), 35.7 (C-13), 31.8 (C-6), 20.1 (C-9), 19.6 (C-10), 19.5 (C-7).

IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 2950, 1729, 1694, 1644, 1412, 1196, 1169.

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{20}H_{27}O_4N+Na^+)^+$ requires 368.1832, found 368.1834.

methyl (*3R,3aR,6R,7aS,8S*)-3-allyl-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-3-carboxylate (419) and methyl (*3S,3aR,6R,7aR,8S*)-3-allyl-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-3-carboxylate (428)



418 **419** **428**

Compound **419** was prepared adopting the procedure published by Li[26]

To a solution of enone **418** (4.63 g, 15.2 mmol, 1 equiv.) in CH_3CN (62.0 mL) was added K_2CO_3 (10.5 g, 75.8 mmol, 5.00 equiv.) and the resulting mixture was purged with argon for 10 minutes and then heated to 100 °C. After stirring for 15 h, the reaction mixture was cooled down to room temperature, concentrated under reduced pressure and loaded onto silica. Purification by gradient column chromatography (ethyl acetate:pentane = 30:70 to 50:50) afforded compound **419** as a white solid (3.93 g, 85%) and compound **S36** as a white amorphous solid (285 mg, 6.2%).

MP: 116 – 118 °C (>99% *ee*), 130 – 132 °C (*rac*).

IR (neat) $\tilde{\nu}_{max}$/cm^{-1}: 2972, 2934, 2878, 1712, 1686, 1430, 1226, 1152, 914.

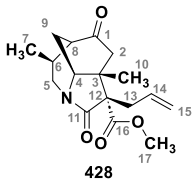
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.13 (dddd, J = 17.2, 10.2, 9.2, 4.5 Hz, 1H, H-14), 5.20 (dtd, J = 17.3, 2.1, 1.0 Hz, 1H, H-15a), 5.11 (dtd, J = 10.2, 2.0, 0.8 Hz, 1H, H-15b), 4.01 (dd, J = 13.5, 8.8 Hz, 1H, H-5a), 4.00 – 3.96 (m, 1H, H-4), 3.69 (s, 3H, H-7), 2.96 – 2.85 (m, 1H, H-6), 2.84 (ddt, J = 15.2, 4.3, 2.1 Hz, 1H, H-H-13a), 2.75 (d, J = 14.7 Hz, 1H, H-2a), 2.33 (dd, J = 15.2, 9.3 Hz, 1H, H-13b), 2.27 (dd, J = 13.5, 9.6 Hz, 1H, H-5b), 2.18 (d, J = 14.7 Hz, 1H, H2-b), 2.13 – 2.06 (m, 2H, H-9), 1.96 – 1.90 (m, 1H, H-8), 1.18 (s, 3H, H-10), 1.00 (d, J = 7.0 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.5 (C-1), 171.3 (C-16), 170.6 (C-11), 134.3 (C-14), 118.6 (C-15), 60.7 (C-12), 59.5 (C-4), 52.3 (C-17), 50.5 (C-3), 46.2 (C-8), 46.0 (C-2), 41.2 (C-5), 36.2 (C-6), 34.9 (C-13), 21.5 (C-10), 19.8 (C-9), 17.8 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{17}H_{24}NO_4)^+$ requires 306.1700, found 306.1964.

$[\alpha]^{25}_D$= -97.3 (c = 1.00, $CHCl_3$).

Minor diastereomer 428:



428

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2952, 2925, 2872, 1754, 1689, 1426, 1292, 1156.

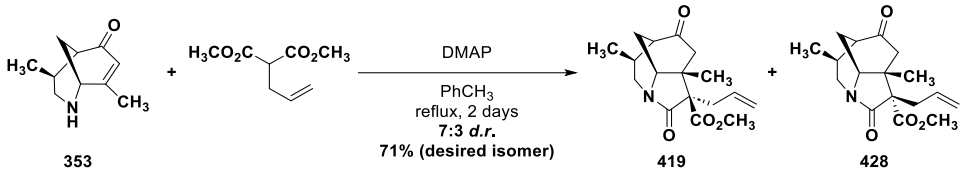
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H, H-14), 5.16 – 5.03 (m, 1H, H-15a, H-15b), 4.07 (dd, J = 13.6, 8.8 Hz, 1H, H-5a), 3.81 – 3.76 (m, 1H, H-4), 3.78 (s, 3H, H-17), 2.98 – 2.84 (m, 1H, H-6), 2.77 (ddt, J = 13.8, 7.2, 1.4 Hz, 1H, H-13a), 2.38 (ddt, J = 13.9, 7.2, 1.1 Hz, 1H, H-13b), 2.28 – 2.18 (m, 2H, H-2a, H-5b), 2.15 – 2.00 (m, 3H, H-2b, H-9a, H-9b), 1.98 – 1.92 (m, 1H, H-8), 1.30 (s, 3H, H-10), 1.00 (d, J = 7.0 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.9 (C-1), 170.5 (C-11 or C-16), 170.3 (C-16 or C-11), 132.6 (C-14), 119.1 (C-15), 61.5 (C-12), 58.3 (C-4), 52.0 (C-17), 49.17 (C-3 or C-2), 49.15 (C-2 or C-3), 45.8 (C-8), 40.9 (C-5), 37.1 (C-6), 36.3 (C-13), 19.40 (C-10 or C-9), 19.37 (C-9 or C-10), 18.1 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{17}H_{24}NO_4)^+$ requires 306.1700, found 306.1996.

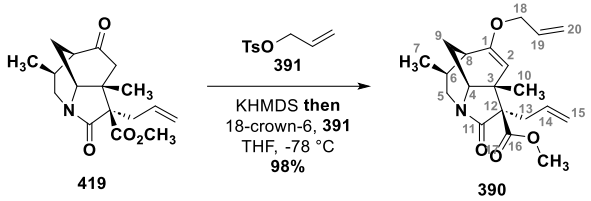
$[\alpha]^{25}_D$= -44.6 (c = 1.00, $CHCl_3$).

One-step procedure for the synthesis of compound 419 from amine 353



A solution of amine **353** (20.0 mg, 121 μmol, 1 equiv.), dimethyl allylmalonate (83.4 mg, 484 μmol, 3.00 equiv.) and DMAP (7.4 mg, 60.5 μmol, 0.50 equiv.) in dry toluene (3.6 mL) was refluxed for 2 days with Dean-Stark trap. The reaction mixture was then quenched with sat. aq. solution of NH_4Cl (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude reaction mixture was analyzed by NMR. Purification by gradient column chromatography (ethyl acetate:pentane = 30:70 to 60:40) provided isomer **419** as a white solid (26.1 mg, 71%).

methyl (*3R,3aR,6R,7aR,8S*)-3-allyl-5-(allyloxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carboxylate (390)



Compound **390** was prepared adopting the procedure developed in our group by Sam Ellis.[19]

To a solution of ketone **419** (200.0 mg, 0.655 mmol, 1 equiv.) in dry, degassed THF (4.0 ml) at -78 °C was dropwise added solution of KHMDS (0.5 M in toluene, 1.96 mL, 0.982 mmol, 1.50 equiv.) and the resulting solution was stirred at this temperature for 20 minutes. A solution of 18-crown-6 (173.0 mg, 655 mmol, 1.00 equiv.) in degassed THF (1.0 mL) and allyl *p*-toluenetosylate (208.5 mg, 0.982 mmol, 1.50 equiv.) were added dropwise at -78 °C. After stirring for 1.5 h at -78 °C the cooling bath was removed, and the reaction mixture was allowed to slowly warm up to room temperature (formation of white precipitate in the whole volume of the reaction mixture was observed). The reaction was then quenched with brine (20 mL), extracted with ethyl acetate (4 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 20:80 to 30:70) afforded allyl enol ether **390** as a colorless oil (221.1 mg, 98%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2951, 2920, 2872, 1729, 1694, 1644, 1419, 1217, 1196, 1169, 916.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.24 (dddd, J = 17.2, 10.2, 9.2, 4.7 Hz, 1H, H-14), 5.91 (ddt, J = 17.3, 10.6, 5.4 Hz, 1H, H-19), 5.28 (dq, J = 17.3, 1.6 Hz, 1H, H-20a), 5.21 (dq, J = 10.4, 1.4 Hz, 1H, H-20b),

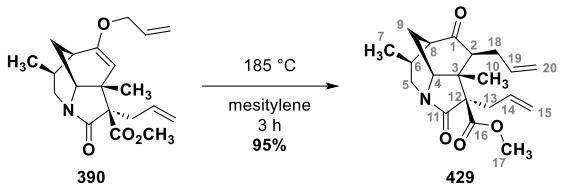
5.16 – 5.04 (m, 2H, H-15), 4.28 (d, J = 1.3 Hz, 1H, H-2), 4.22 (ddt, J = 12.6, 5.5, 1.5 Hz, 1H, H-18a), 4.13 (ddt, J = 12.6, 5.4, 1.6 Hz, 1H, H-18b), 4.06 (dd, J = 13.6, 8.0 Hz, 1H, H-5a), 3.85 – 3.79 (m, 1H, H-4), 3.70 (s, 3H, H-17), 2.73 (ddt, J = 14.6, 4.8, 2.0 Hz, 1H, H-13a), 2.47 – 2.35 (m, 2H, H-13b, H-5b), 2.12 – 1.95 (m, 1H, H-6), 1.95 (ddd, J = 13.7, 5.2, 2.3 Hz, 1H, H-9a), 1.93 – 1.87 (m, 1H, H-8), 1.62 (ddt, J = 13.8, 3.9, 1.0 Hz, 1H, H-9b), 1.14 (s, 3H, H-10), 0.96 (d, J = 6.9 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.0 (C-16), 170.9 (C-11), 159.6 (C-1), 135.4 (C-14), 133.3 (C-19), 117.6 (C-15), 117.5 (C-20), 95.1 (C-2), 67.9 (C-18), 61.9 (C-12), 56.9 (C-4), 52.1 (C-17), 50.0 (C-3), 41.6 (C-5), 37.4 (C-8), 35.7 (C-13), 31.8 (C-6), 20.1 (C-9), 19.6 (C-10), 19.5 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{20}H_{28}O_4N)^+$ requires 346.2013, found 346.2012.

$[\alpha]_D^{25}$= -151.0 (c = 1.00, $CHCl_3$).

methyl (*3R,3aR,4S,6R,7aR,8S*)-3,4-diallyl-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-3-carboxylate (429)



390 429

Compound **429** was prepared adopting the procedure published by Carreira *et al.*[27]

Glass passivation: A pressure tube with attached argon balloon was passivated by heating a solution of N,O-bis(trimethylsilyl) acetamide (0.1 mL) in hexane (10 mL) to 50 °C. The pressure tube was swirled for 5 minutes so that all surface of the reaction vessel was in contact with the reagent. The solution was then discarded and tube washed with hexane (2 x 15 mL) and MTBE (2 x 15 mL) and dried under a high vacuum.

The solution of enol **390** (190 mg, 0.550 mmol, 1 equiv.) was transferred to passivated pressure tube in benzene (3.0 mL), and the solvent was removed in a vacuum. The solvent-free enol was dissolved in mesitylene (18.3 mL, 0.030 M) (previously distilled and stored over molecular sieves). A PTFE syringe filter was used to ensure that no solid particles were transferred with the solvent into the reaction mixture. The resulting solution was purged with argon for 30 min, and the tube was sealed and heated to 185 °C for 3 h. After cooling to room temperature, the reaction mixture was directly poured onto a silica column and flushed with pentane until mesitylene was no longer eluted. Elution with ethyl acetate:pentane (60:40) afforded product **429** as a white solid (180 mg, 95%).

MP: 109-112 °C (>99% ee), 112-113 °C (rac).

IR (neat) $\tilde{\nu}_{max}/cm^{-1}$: 2973, 2951, 2930, 1735, 1705, 1639, 1427, 1210, 915, 1425, 1208, 912.

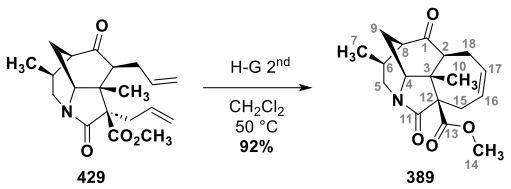
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (ddt, J = 17.2, 14.7, 4.5 Hz, 1H, H-14), 5.61 (ddt, J = 16.7, 10.3, 6.9 Hz, 1H, H-19), 5.22 – 5.09 (m, 2H, H-15a, H-15b), 5.03 – 4.93 (m, 2H, H-20a, H20b), 4.08 (dd, J = 13.6, 8.4 Hz, 1H, H-5a), 3.81 (d, J = 4.5 Hz, 1H, H-4), 3.70 (s, 3H, H-17), 2.84 – 2.70 (m, 3H, H-13a, H-2, H-6), 2.49 – 2.24 (m, 4H, H-13b, H-5b, H-18a, H18b), 2.21 – 2.05 (m, 2H, H-9a, H-9b), 2.05 – 1.99 (m, 1H, H-8), 1.12 (s, 3H, H-10), 1.01 (d, J = 6.9 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.4 (C-1), 172.3 (C-11), 170.7 (C-16), 135.8 (C-19), 134.3 (C-14), 118.8 (C-15), 116.9 (C-20), 64.1 (C-12), 59.7 (C-4), 53.1 (C-3), 52.3 (C-17), 51.2 (C-2), 46.2 (C-8), 41.1 (C-5), 35.4 (C-6), 35.0 (C-13), 33.0 (C-18), 20.2 (C-9), 18.2 (C-7), 16.7 (C-10).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{20}H_{28}NO_4)^+$ requires 346.2013, found 346.2010.

$[\alpha]_D^{25}$ = 10.2 (c = 1.00, $CHCl_3$).

methyl (*2R,3S,6aR,11S,11aR,11bR*)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[a]indolizine-6a(6H)-carboxylate (389)



To a solution of diene **429** (87.0 mg, 0.252 mmol, 1 equiv.) in degassed CH_2Cl_2 (50.5 mL) was added Grubbs-Hoveyda 2nd generation catalyst (10.7 mg, 12.6 μmol, 5.0 mol %), reflux condenser was attached, and the reaction mixture was heated to reflux for 19 h while gently bubbled with argon. The reaction was then quenched by the addition of a solution of potassium isocyanoacetate (25 mg) in methanol (3.0 mL). After stirring for 30 min at room temperature, the reaction mixture was concentrated under reduced pressure and loaded onto silica. Purification by gradient column chromatography (ethyl acetate:pentane = 40:60 to 60:40) afforded compound **389** as a white solid (73.6 mg, 92%).

MP: 196-199 °C (>99% ee), 186-188 °C (rac).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3024, 2969, 2951, 2922, 1725, 1695, 1414, 1292, 1209.

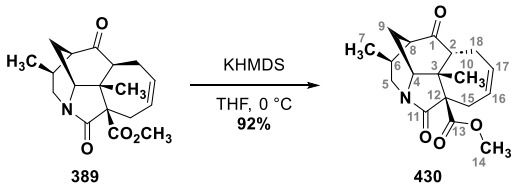
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 – 5.63 (m, 1H, H-16), 5.56 (ddt, J = 10.8, 5.3, 2.5 Hz, 1H, H-17), 4.10 (dd, J = 13.7, 6.8 Hz, 1H, H-5a), 3.87 (m, 1H, H-4), 3.73 (s, 3H, H-14), 3.17 (dd, J = 11.8, 4.8 Hz, 1H, H-2), 2.80 – 2.71 (m, 1H, H-15a), 2.74 (dd, J = 13.7, 11.3 Hz, 1H, H-5b), 2.66 (ddt, J = 19.3, 5.1, 2.8 Hz, 1H, H-18a), 2.58 (dd, J = 16.0, 8.6 Hz, 1H, H-15b), 2.37 – 2.22 (m, 3H, H-18b, H-8, H-9a), 2.15 – 2.01 (m, 1H, H-6), 1.85 – 1.75 (m, 1H, H-9b), 1.14 (s, 3H, H-10), 1.01 (d, J = 6.9 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.1 (C-1), 175.9 (C-11), 170.9 (C-13), 129.0 (C-17), 124.2 (C-16), 65.4 (C-12), 57.3 (C-4), 55.1 (C-3), 52.5 (C-14), 50.0 (C-8), 44.1 (C-2), 42.3 (C-5), 32.7 (C-6), 29.2 (C-15), 27.5 (C-18), 22.3 (C-9), 20.0 (C-7), 16.0 (C-10).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{18}H_{24}NO_4)^+$ requires 318.1700, found 318.1703.

$[\alpha]_D^{25}$**=** 175.3 (c = 1.00, $CHCl_3$).

methyl (*2R,3S,6aR,11R,11aR,11bR*)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[a]indolizine-6a(6H)-carboxylate (430)



389 430

To a solution of ketone **389** (60.0 mg, 0.189 mmol, 1 equiv.) in dry, degassed THF (4.0 mL) at 0 °C was dropwise added solution of KHMDS (0.5 M in toluene, 560 µL, 0.284 mmol, 1.50 equiv.) and the reaction mixture was stirred at this temperature for 50 min. The reaction was then quenched with sat. aq. sol. of NH_4Cl (15 mL), extracted with CH_2Cl_2 (4 x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 40:60 to 80:20) afforded compound **430** as a white solid (55.2 mg, 92%).

MP: 195-198 °C (>99% ee), 176-179 °C (rac).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2953, 2872, 1705, 1431, 1229.

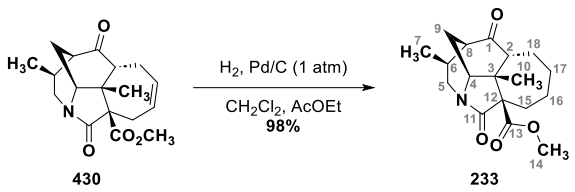
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.11 (dddd, J = 9.3, 7.2, 5.6, 1.9 Hz, 1H, H-17), 5.73 (dddd, J = 9.9, 8.1, 5.3, 1.8 Hz, 1H, H-16), 4.07 (dd, J = 13.6, 9.1 Hz, 1H, H-5a), 3.90 – 3.85 (m, 1H, H-4), 3.70 (s, 3H, H-14), 2.88 – 2.79 (m, 1H, H-6), 2.76 (ddd, J = 15.2, 5.3, 1.9 Hz, 1H, H-15a), 2.52 – 2.46 (m, 2H, H-18a, H-2), 2.46 (dd, J = 8.1, 7.1 Hz, 1H, H-15b), 2.32 (dd, J = 13.7, 9.5 Hz, 1H, H-5b), 2.33 – 2.25 (m, 1H, H-18b), 2.12 – 2.00 (m, 2H, H-9a, H-9b), 1.94 (ddd, J = 3.7, 2.1, 0.9 Hz, 1H, H-8), 1.32 (s, 3H, H-10), 1.03 (d, J = 7.0 Hz, 3H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 212.1 (C-1), 171.5 (C-13), 170.5 (C-11), 132.4 (C-17), 126.5 (C-16), 60.9 (C-12), 60.0 (C-4), 53.7 (C-2), 53.4 (C-3), 52.6 (C-14), 46.3 (C-8), 40.6 (C-5), 36.7 (C-6), 26.7 (C-15), 22.0 (C-10), 21.9 (C-18), 18.4 (C-9), 18.2 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{18}H_{24}NO_4)^+$ requires 318.1705, found 318.1701.

$[\alpha]_D^{25}$= -89.9 (c = 1.00, $CHCl_3$).

methyl (*2R,3S,6aR,11R,11aR,11bR*)-3,11a-dimethyl-6,12-dioxodecahydro-2H-2,11-methanocyclohepta[a]indolizine-6a(6H)-carboxylate (233)



To a solution of alkene **430** (29.0 mg, 91.4 μmol, 1 equiv.) in a mixture of ethyl acetate (6.0 mL) and CH_2Cl_2 (3.0 mL) was added palladium on charcoal (10 wt %, 4.9 mg, 4.57μmol, 5.0 mol %). After the introduction of hydrogen from the double-coated balloon and repeating 4 cycles of vacuum/hydrogen, the reaction mixture was stirred for 2 h. Then, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 40:60 to 80:20) afforded compound **233** as a white solid (28.6 mg, 98%). The spectroscopic data are in agreement with the literature values.[28]

MP: 189-193 °C (>99% ee), 174-177 (rac).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2951, 2928, 2878, 1730, 1703, 1693, 1454, 1435, 1248, 1213,1196, 752.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.11 (dd, J = 13.6, 8.7 Hz, 1H, H-5a), 3.96 (d, J = 5.2 Hz, 1H, H-4), 3.68 (s, 3H, H-14), 2.84 – 2.73 (m, 1H, H-6), 2.53 (dd, J = 6.0, 2.2 Hz, 1H, H-2), 2.37 (dd, J = 13.6, 9.8 Hz, 1H, H-5b), 2.30 – 2.20 (m, 1H, H-17a), 2.16 (dd, J = 15.2, 9.0 Hz, 1H, H-15a), 2.13 – 2.03 (m, 2H, H-9a, H-9b), 1.99 – 1.86 (m, 3H, H-15b, H-18a, H-8), 1.79 – 1.72 (m, 1H, H-18b), 1.72 – 1.63 (m, 1H, H-16a), 1.51 – 1.39 (m, 1H, H-17b), 1.23 (s, 3H, H-10), 1.18 – 1.06 (m, 1H, H-16b), 1.03 (d, J = 7.0 Hz, 3H, H-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 214.5 (C-1), 171.8 (C-13), 171.4 (C-11), 64.8 (C-12), 60.2 (C-4), 54.6 (C-2), 52.9 (C-3), 52.4 (C-14), 46.8 (C-8), 41.1 (C-5), 36.9 (C-6), 27.3 (C-15), 23.7 (C-17), 22.3 (C-10), 21.1 (C-16), 20.4 (C-18), 19.1 (C-9), 18.4 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{18}H_{26}NO_4)^+$ requires 320.1856, found 320.1857.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -118.0 (c = 1.00, $CHCl_3$, >99% *ee*), literature value $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -77.4 (c = 1.0, $CHCl_3$, 99.8% *ee*).[28]

HPLC (Chiralpak AD-H, hexane/isopropanol 85:15, 1.0 mL min^{-1}, λ =210 nm).

Table 4.6. *Comparison of [1]H and [13]C NMR spectra of compound* ***9*** *prepared by Li's[28] and our group.*

	[1]H NMR data				[13]C NMR data		
Atom	**Synthesised**	**Reported**	**Diff.**	**Atom**	**Synthesised**	**Reported**	**Diff.**
5a	4.11 (dd, J = 13.6, 8.7 Hz, 1H)	4.10 (dd, J = 13.5, 8.8 Hz, 1H)	0.01	**1**	214.5	214.4	0.1
4	3.96 (d, J = 5.2 Hz, 1H)	3.96 (d, J = 4.9 Hz, 1H)	0.00	**13**	171.8	171.6	0.2
14	3.68 (s, 3H)	3.67 (s, 3H)	0.01	**11**	171.4	171.3	0.1
6	2.84 – 2.73 (m, 1H)	2.85 – 2.70 (m, 1H)	0.01*	**12**	64.8	64.7	0.1
2	2.53 (dd, J = 6.0, 2.2 Hz, 1H)	2.52 (dd, J = 5.8, 1.9 Hz, 1H)	0.01	**4**	60.2	60.1	0.1
5b	2.37 (dd, J = 13.6, 9.8 Hz, 1H)	2.36 (dd, J = 13.5, 9.8 Hz, 1H)	0.01	**2**	54.6	54.3	0.3
17a	2.30 – 2.20 (m, 1H)	2.29 – 2.20 (m, 1H)	0.01*	**3**	52.9	52.8	0.1
15a	2.16 (dd, J = 15.2, 9.0 Hz, 1H)	2.15 (dd, J = 15.2, 9.0 Hz, 1H)	0.01	**14**	52.4	52.3	0.1
9a,9b	2.13 – 2.03 (m, 2H)	2.10 – 2.02 (m, 2H)	0.04*	**8**	46.8	46.7	0.1
18a, 15b, 8	1.99 – 1.86 (m, 3H)	1.97 – 1.84 (m, 3H)	0.02*	**5**	41.1	40.9	0.2
18b	1.79 – 1.72 (m, 1H)	1.79 – 1.62 (m, 2H)	0.01*	**6**	36.9	36.7	0.2
16a	1.72 – 1.63 (m, 1H)			**15**	27.3	27.2	0.1
17b	1.51 – 1.39 (m, 1H)	1.52 – 1.35 (m, 1H)	0.02*	**17**	23.7	23.6	0.1
10	1.23 (s, 3H)	1.22 (s, 3H)	0.01	**10**	22.3	22.1	0.2
16b	1.18 – 1.06 (m, 1H)	1.16 – 1.05 (m, 1H)	0.02*	**16**	21.1	21.0	0.1
7	1.03 (d, J = 7.0 Hz, 3H)	1.02 (d, J = 6.9 Hz, 3H)	0.01	**18**	20.4	20.2	0.2
				9	19.1	18.9	0.2
				7	18.4	18.3	0.1

*The differences in [1]H NMR shifts for multiples were calculated by using their centres, obtained by equation: centre = (left boundary + right boundary)/2.

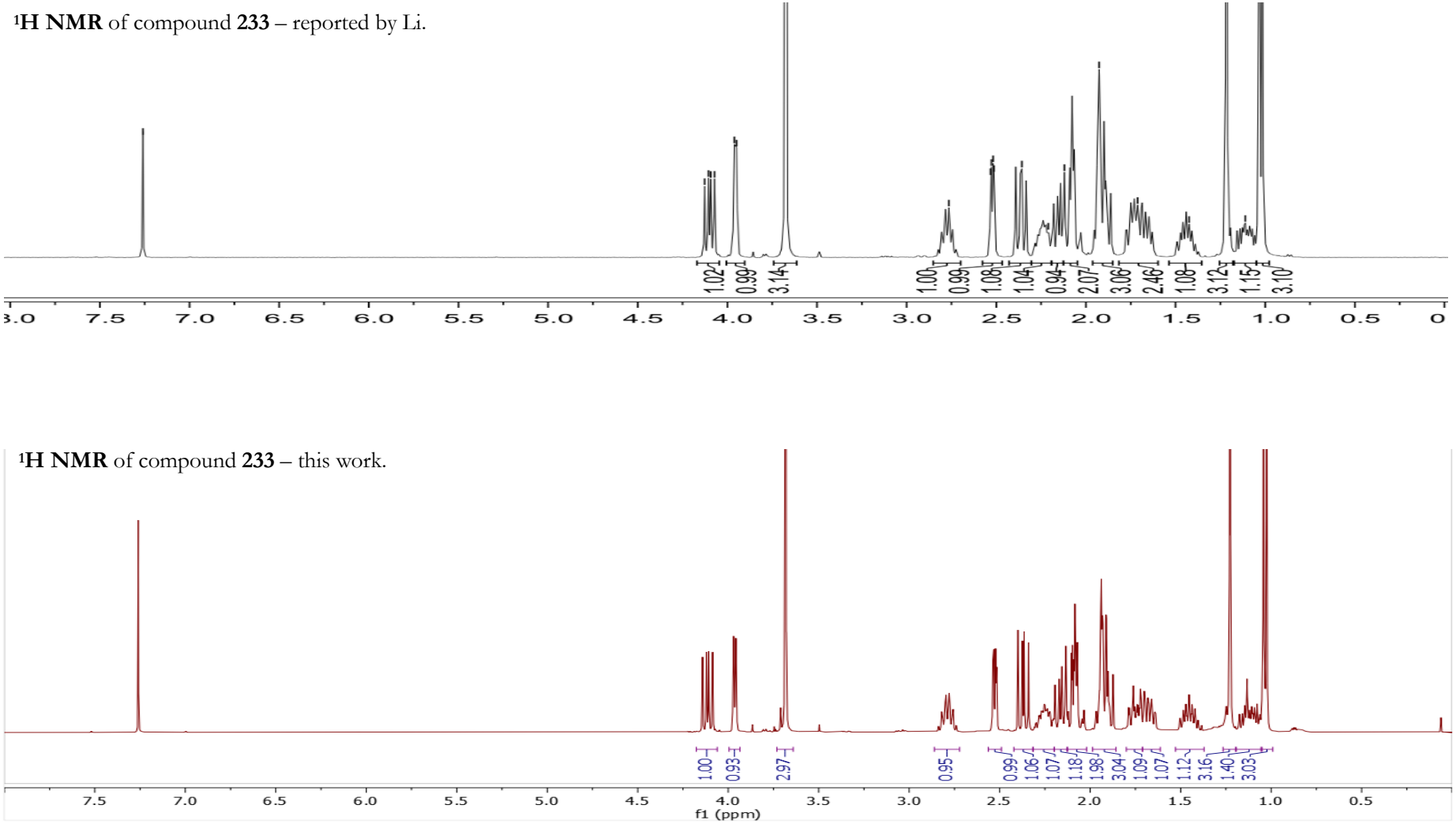
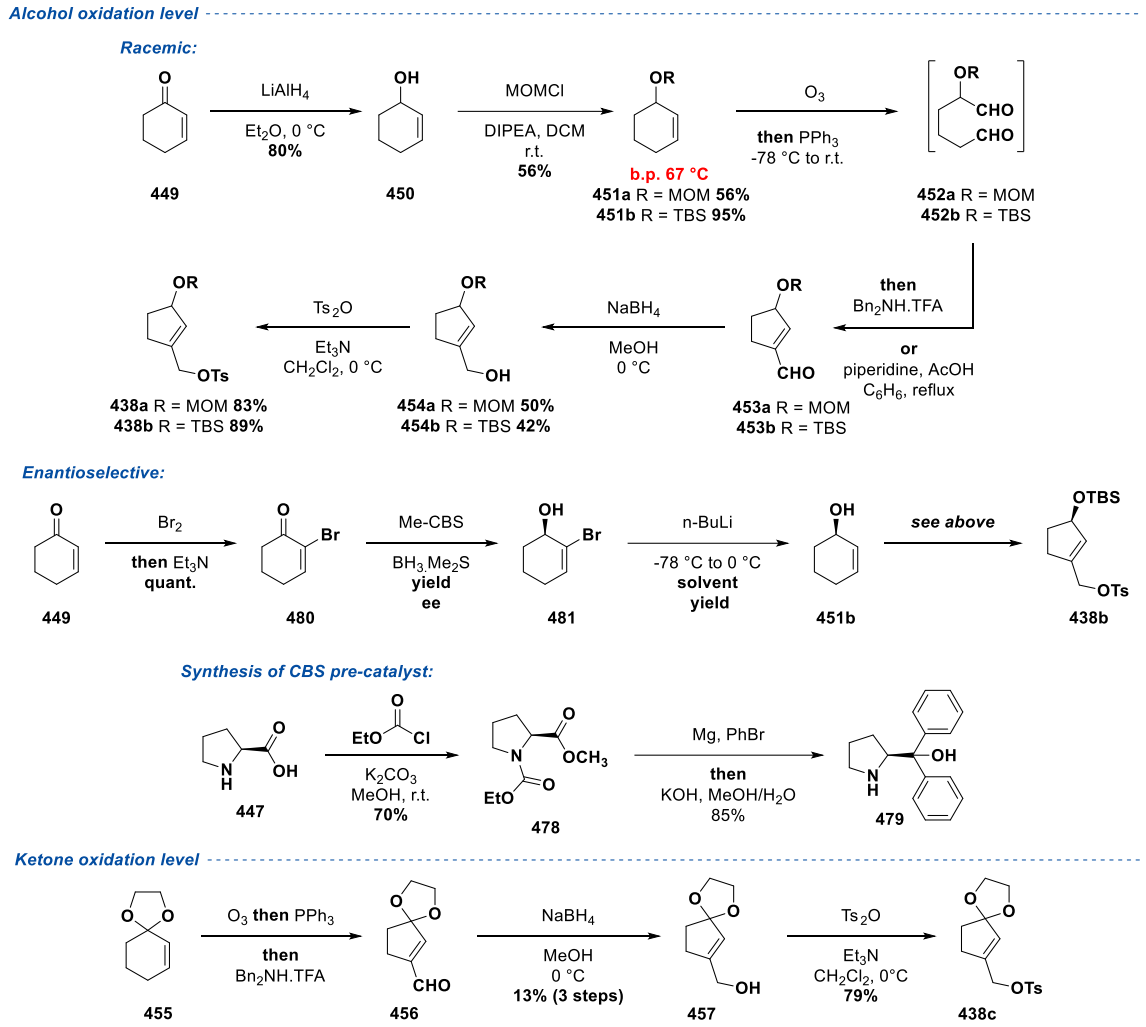


Figure 4.2. *Comparison of [1]H NMR spectra of compound* ***233*** *prepared by Li's[28] (top) and our group (bottom).*

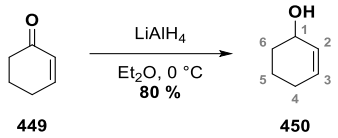
4.3.3 Total synthesis of Himalensine A

4.3.3.1 Synthesis of E-ring fragments



Scheme 4.9. *Overview of E-ring fragments synthesis.*

***rac*-cyclohex-2-en-1-ol (450)**

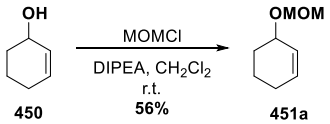


To a suspension of $LiAlH_4$ (987 mg, 26.0 mmol, 0.50 equiv.) in dry Et_2O (25 mL) was dropwise added solution of cyclohexenone (**449**) (5.00 g, 52.0 mmol, 1 equiv.) in dry Et_2O (13 mL) at 0 °C. After 30 min, the ice bath was removed, and the reaction mixture was stirred at room temperature for 5 h. The reaction was then carefully quenched with distilled water (20 mL), diluted with Et_2O (120 mL) and washed with water (3 x 30 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure (300 mbar, 40 °C). The crude product **450** was obtained as yellowish oil and used in the next step without further purification (4.82 g, 80%). The spectroscopic data are in agreement with the literature values.[29]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88 – 5.79 (m, 1H, H-3), 5.79 – 5.70 (m, 1H, H-2), 4.19 (s, 1H, H-1), 2.11 – 1.95 (m, 2H, H-4), 1.94 – 1.81 (m, 1H, H-6a), 1.80 – 1.67 (m, 1H, H-5a), 1.66 – 1.53 (m, 2H, H-6b, H-5b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 130.7 (C-3), 130.0 (C-2), 65.7 (C-1), 32.2 (C-6), 25.2 (C-4), 19.1 (C-5).

***rac*-3-(methoxymethoxy)cyclohex-1-ene (451a)**



Compound **451a** was prepared according to a literature procedure published by E. M. Carreira *et al.*[27]

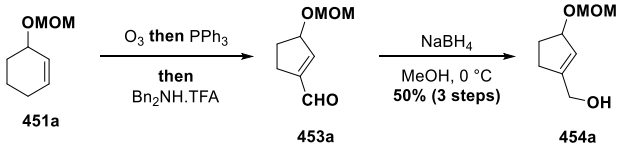
A solution of alcohol **450** (3.88 g, 39.5 mmol, 1 equiv.) was cooled to 0 °C, DIPEA (10.3 mL, 59.3 mmol, 1.50 equiv.) and MOMCl (4.50 mL, 59.3 mmol, 1.50 equiv.) were added slowly. The resulting solution was allowed to warm to room temperature and then was stirred overnight at this temperature. The reaction mixture was then quenched with half-saturated aq. solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic phases were dried over anhydrous Na_2SO_4 / Na_2CO_3, filtered through a short plug of silica and the plug was rinsed with Et_2O (300 mL). The colourless filtrate was concentrated under reduced pressure (40 °C, 150 mbar) to provide compound **451a** as a colourless oil (3.14 g, 56%). The spectroscopic data are in agreement with the literature values.[27]

NOTE: The low yield of this transformation may be attributed to low boiling point (67 °C) of the product and its co-evaporation with solvent during workup.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.86 (dtd, *J* = 10.2, 3.7, 1.3 Hz, 1H), 5.75 (m, 1H), 4.70 (m, 2H), 4.13 – 4.06 (m, 1H), 3.38 (s, 3H), 2.11 – 1.88 (m, 2H), 1.88 – 1.50 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 131.1, 128.0, 95.2, 70.8, 55.3, 29.3, 25.2, 19.3.

***rac*-(3-(methoxymethoxy)cyclopent-1-en-1-yl)methanol (454a)**



Compound **454a** was prepared according to a literature procedure published by E. M. Carreira *et al.*[27]

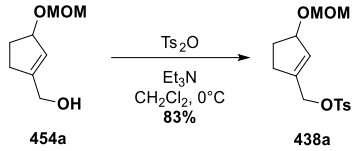
A solution of alkene **451a** (2.71 g, 19.1 mmol, 1 equiv.) in CH_2Cl_2 (35 mL) was cooled to -78 °C and then bubbled for 5 min with O_2. Ozone was then introduced through a sintered glass filter until a deep blue colour persisted, and its excess was removed by purging the solution with O_2 for 5 minutes. To the resulting solution PPh_3 (5.00 g, 19.1 mmol, 1.00 equiv.) in DCM (8 mL) was added dropwise and the cooling-bath temperature was slowly raised to 0 °C over 2h. A solution of dibenzylammonium trifluoroacetate, prepared in situ by adding TFA (292 μL, 3.81 mmol, 0.20 equiv.) to dibenzylamine (733 μL, 3.81 mmol, 0.20 equiv.) in CH_2Cl_2 (5.0 mL) at 0°C, was added at 0 °C and the light-yellow solution was warmed to room temperature over 1h. The reaction mixture was stirred overnight and then concentrated under reduced pressure to approx. 10 ml. The residue was diluted with Et_2O (80 mL) and H_2O (50 mL), the phases separated and aq. phase washed with Et_2O/pentane (1:1, 3 x 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (40 °C, 600 mbar). The crude aldehyde **453a** was used in next step without further purification.

The solution of crude aldehyde in MeOH (19 mL) was cooled to 0 °C and $NaBH_4$ (542 mg, 14.3 mmol, 0.75 equiv.) was then added portion-wise over 10 min. The resulting solution was stirred for 1h at 0 °C and the reaction was then quenched with brine (60 mL) and diluted with CH_2Cl_2. The phases were separated and the aq. phase extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient flash column chromatography (Et_2O /pentane = 1:1 to 2:1) afforded alcohol **454a** as a colorless oil (1.51 g, 50%). The spectroscopic data are in agreement with the literature values.[27]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.74 (m, 1H), 4.76 – 4.70 (m, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.26 – 4.15 (m, 2H), 3.36 (s, 3H), 2.53 – 2.41 (m, 1H), 2.31 – 2.17 (m, 2H), 1.92 – 1.84 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.8, 125.2, 95.7, 82.9, 62.1, 55.4, 31.2, 30.9.

***rac*-(3-(methoxymethoxy)cyclopent-1-en-1-yl)methyl 4-methylbenzenesulfonate (438a)**



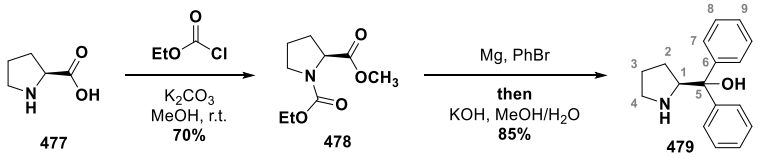
To a solution of alcohol **454a** (300 mg, 1.90 mmol, 1 equiv.) in CH_2Cl_2 (6.0 mL) was added Et_3N (396 μL, 2.84 mmol, 1.5 equiv.) at 0 °C followed by solution of Ts_2O (650 mg, 1.99 mmol, 1.05 equiv.) in CH_2Cl_2 (6.0 mL) and the resulting solution was stirred for 25 min. The reaction was quenched with sat. aq. solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (Et_2O /pentane = 1:2) afforded product **438a** as a colorless oil (489 mg, 83%). The spectroscopic data are in agreement with the literature.[27]

NOTE: The rapid decomposition of the purified material after column chromatography was observed several times, mostly after the evaporation of solvent and exposure of the residue to air. Allyl tosylate **438a** should be used immediately after its preparation. Short-term storage (for a few days) as a frozen solution in benzene is possible, but even this solution is undergoing slow decomposition/polymerization, indicated by the colour change of the solution and the formation of black particles.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 – 7.73 (m, 2H), 7.38 – 7.31 (m, 2H), 5.79 (m, 1H), 4.70 – 4.59 (m, 5H), 3.33 (s, 3H), 2.45 (s, 3H), 2.41 – 2.33 (m, 1H), 2.27 – 2.13 (m, 2H), 1.88 – 1.75 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 145.0, 141.7, 133.3, 130.6, 123.0, 128.1, 95.84, 82.6, 68.5, 55.4, 31.1, 30.9, 21.7.

(*S*)-diphenyl(pyrrolidin-2-yl)methanol (479)



Compound **479** was prepared according to a literature procedure published by Nishioka *et al.*[30]

To a stirred suspension of L-proline (6.00 g, 52.1 mmol, 1 equiv.) and K_2CO_3 (9.36 g, 67.8 mmol, 1.30 equiv.) in dry MeOH (90 mL) at 0 °C was dropwise added ethyl chloroformate (11.0 mL, 115 mmol, 2.20 equiv.) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure, and the residues dissolved in water (50 mL) and extracted with $CHCl_3$ (4 x 35 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure. The product **478** was obtained as light-yellow oil (7.36 g, 70%) and was used in the next step without further purification.

An oven-dried two-necked flask equipped with a reflux condenser was charged with Mg turnings (6.62 g, 272 mmol, 8.00 equiv.), a catalytic amount of I_2 and THF (103 mL). A solution of bromobenzene (17.9 mL, 170 mmol, 5.00 equiv.) in THF (51 mL) was added dropwise, resulting in an exothermic reaction that was compensated with a room-temperature water bath. After stirring for 1 h at room temperature, a solution of ester **478** (6.85 g, 34.0 mmol, 1 equiv.) in THF (34 mL) was added at 0 °C, and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was then cautiously quenched with sat. aq. solution of NH_4Cl (60 mL) and extracted with Et_2O (4 x 90 mL). The combined organic layers were washed with brine (90 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

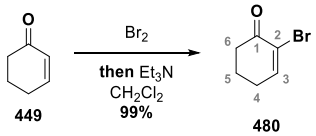
To a stirred solution of crude product obtained in the previous step in MeOH (11.0 mL) and toluene (38.4 mL) was added KOH (19.1 g, 340 mmol, 10.0 equiv.), and the resulting mixture was heated to 60 °C. After 1 h, water (65.8 mL) was added, and the resulting mixture was stirred under reflux for another 1 h. After cooling to room temperature, the phases were separated, and the aqueous phase was washed with toluene (3 x 50 mL). The combined organic phases were washed with brine (90 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 25:75 to 100:0) afforded alcohol **479** as a colorless solid (7.36 g, 85%). The spectroscopic data are in agreement with the literature values.[30]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 – 7.55 (m, 2H, H-7), 7.55 – 7.48 (m, 2H, H-7), 7.35 – 7.24 (m, 4H, H-8), 7.22 – 7.13 (m, 2H, H-9), 4.27 (t, J = 7.6 Hz, 1H, H-1), 3.05 (ddd, J = 9.3, 6.6, 5.1 Hz, 1H, H-4a), 2.95 (dt, J = 9.3, 7.4 Hz, 1H, H-4b), 1.82 – 1.67 (m, 2H, H-3), 1.67 – 1.51 (m, 2H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.3 (C-9), 145.6 (C-9), 128.4 (C-8), 128.1 (C-8), 126.6 (C-9), 126.5 (C-9), 126.0 (C-7), 125.7 (C-7), 77.2 (C-5), 64.6 (C-1), 46.9 (C-4), 26.4 (C-2), 25.6 (C-3).

$[\alpha]_D^{25}$= -53.0 (c = 1.0, MeOH), literature value $[\alpha]_D^{25}$= -56.1 (c = 2.5, MeOH).[30]

2-bromocyclohex-2-en-1-one (480)



Compound **480** was prepared according to a literature procedure published by Nicolaou *et al.*[31]

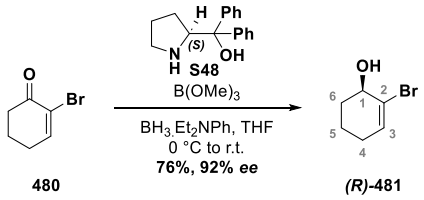
To a solution of cyclohexenone (3.00 g, 31.2 mmol, 1 equiv.) in CH_2Cl_2 (80 mL) was dropwise added solution of bromine (1.63 mL, 31.8 mmol, 1.02 equiv.) in CH_2Cl_2 (80 mL) at 0 °C. The immediate

consumption of bromine was observed. After stirring for 1.5 h, Et_3N (7.26 mL, 52.1 mmol, 1.67 equiv.) was added dropwise at 0 °C, and the resulting mixture was stirred for another 1.5 h at room temperature. The reaction mixture was then washed with 1 M HCl (50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product **480** was obtained as a brownish solid (5.43 g, 99%). The spectroscopic data are in agreement with the literature values.[32]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (t, *J* = 4.5 Hz, 1H, H-3), 2.66 – 2.58 (m, 2H, H-6), 2.44 (td, *J* = 6.0, 4.4 Hz, 2H, H-4), 2.12 – 1.97 (m, 2H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 191.4 (C-1), 151.3 (C-3), 124.0 (C-2), 38.5 (C-6), 28.5 (C-4), 22.8 (C-5).

***(R)*-2-bromocyclohex-2-en-1-ol (481)**



Compound ***(R)*-481** was prepared according to a literature procedure published by Holub *et al.*[33]

To a solution of *(S)-a,a*-diphenylprolinol (1.45 g, 5.71 mmol, 0.10 equiv.) in dry THF (170 mL) was added $B(OMe)_3$ (764 μL, 6.86 mmol, 0.12 equiv.) and the resulting solution was stirred at room temperature for 1 h. Then, BH_3.*N,N*-diethylaniline (10.2 mL, 57.1 mmol, 1.00 equiv.) was added, and the resulting solution was cooled to – 10°C before a solution of enone **480** (10.0 g, 57.1 mmol, 1 equiv.) in dry THF (20 mL) was added dropwise over 45 min using a syringe pump. The reaction was stirred for 2 days at 0 °C and the progress of the reaction was monitored by ^{1}H NMR. After the complete conversion of the enone, the reaction was quenched with 1 M HCl (100 mL), phases were separated, and the organic phase was extracted with Et_2O (3 x 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O:pentane = 15:85 to 20:80) afforded allylic alcohol **481** as a colorless oil (7.71 g, 76%, 92.3% *ee*). The spectroscopic data are in agreement with the literature values.[33]

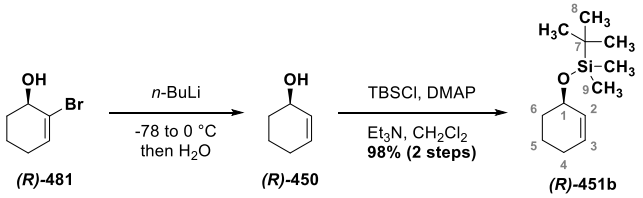
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.20 (t, *J* = 4.1 Hz, 1H, H-3), 4.21 (dtd, *J* = 6.4, 4.8, 1.6 Hz, 1H, H-1), 2.18 (d, *J* = 4.2 Hz, 1H, OH), 2.17 – 1.99 (m, 2H, H-4), 1.99 – 1.84 (m, 2H, H-6), 1.74 (m, 1H, H-5a), 1.68 – 1.58 (m, 1H, H-5b).

^{13}C NMR b.7 (C-3), 126.0 (C-2), 70.0 (C-1), 32.1 (C-6), 27.9 (C-4), 17.8 (C-5).

HPLC: (Chiralpak AD-H, hexane/isopropanol 95:5, 1.0 mL min^{-1}, λ=220 nm) t_R = 10.4 min (major), 9.4 min (minor).

$[\alpha]_D^{25}$ = 81.3 (c = 1.0, $CHCl_3$, >92.3% ee), literature value for enantiomer $[\alpha]_D^{25}$ = -85.2 (c = 1.89, $CHCl_3$, 99% ee).[33]

(R)-tert-butyl(cyclohex-2-en-1-yloxy)dimethylsilane (*(R)*-451b)



Compound ***(R)*-451b** was prepared according to a literature procedure published by Nicolaou *et al.*[31]

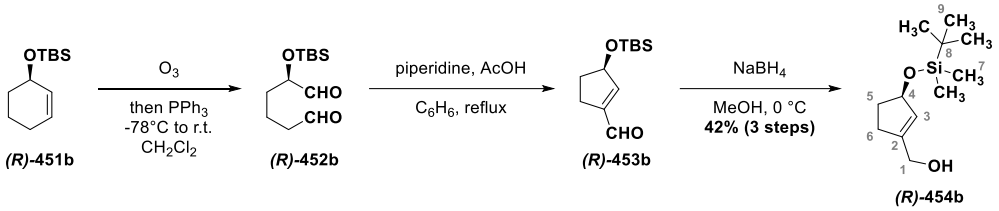
To a stirred solution of bromide **481** (7.70 g, 43.5 mmol, 1 equiv.) in dry Et_2O (220 mL) at -78 °C was dropwise added *n*-BuLi (2.5 M in hexanes, 60.9 mL, 3.50 equiv.). The resulting mixture was stirred at this temperature for 1 h and then 3 h at 0°C. The reaction was then quenched with distilled water (100 mL), phases were separated, and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **450** was obtained as a colorless oil and used in the next step without further purification.

To a stirred solution of *(R)*-cyclohex-2-en-1-ol (**450**) (43.5 mmol, 1 equiv.) in dry CH_2Cl_2 (80 mL) at room temperature was added Et_3N (9.10 mL, 65.3 mmol, 1.50 equiv.), TBSCl (8.52 g, 56.6 mmol, 1.30 equiv.) and DMAP (532 mg, 4.35 mmol, 0.10 equiv.). After stirring for 17 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 1 M HCl (100 mL), sat. aq. solution of $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (Et_2O:pentane = 0:100 to 5:95) afforded protected alcohol **451b** as a colorless oil (9.04 g, 98%). The spectroscopic data are in agreement with the literature values.[34]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.79 – 5.70 (m, 1H, H-3), 5.67 – 5.58 (m, 1H, H-2), 4.23 (m, 1H, H-1), 2.11 – 1.97 (m, 1H, H-4a), 1.97 – 1.87 (m, 1H, H-4b), 1.87 – 1.70 (m, 2H, H-6a, H-5a), 1.63 – 1.46 (m, 2H, H-6b, H-5b), 0.90 (s, 9H), 0.08 (s, 3H, H-9), 0.07 (s, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 131.4 (C-2), 129.2 (C-3), 66.9 (C-1), 32.7 (C-6), 26.1 (C-8), 25.1 (C-4), 19.9 (C-5), 18.4 (C-7), -4.37 (C-9), -4.43 (C-9).

***(R)*-(3-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)methanol (*(R)*-454b)**



Compound ***(R)*-451b** was prepared according to a literature procedure published by Nicolaou *et al.*[31]

A stirred solution of alkene **451b** (9.04 g, 42.6 mmol, 1 equiv.) in CH_2Cl_2 (100 mL) at -78 °C was bubbled with ozone until a persistent blue colour was observed. After removing the excess of ozone by bubbling the reaction mixture with oxygen for 10 min, the reaction mixture was quenched with a solution of PPh_3 (11.2 g, 42.6 mmol, 1.00 equiv.) in CH_2Cl_2, allowed to warm to room temperature overnight and then concentrated under reduced pressure (30 °C). The obtained residue was dissolved in Et_2O (100 mL), and the formed white precipitate was filtered off. If the formation of more precipitate was observed during the concentration of the filtered solution, the filtration was repeated. The crude dialdehyde **452b** was obtained as a yellowish oil and used in the next step without further purification.

To a solution of dialdehyde **452b** in benzene (50 mL) at room temperature were added acetic acid (97.4 µL, 1.70 mmol, 4.00 mol %) and piperidine (160 µL, 1.62 mmol, 3.80 mol %) and the resulting mixture was placed into pre-heated oil bath (90 °C) and stirred for 1 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with 1 M HCl (2 x 40 mL), sat. aq. solution of $NaHCO_3$ (40 mL) and brine (40 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The enal **453b** was obtained as a yellowish oil and used in the next step without further purification.

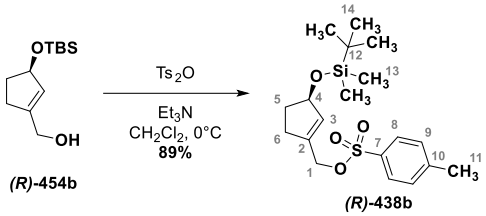
To a stirred solution of enal **453b** in MeOH (125 mL) at 0 °C was added $NaBH_4$ (1.61 g, 42.6 mmol, 1.00 equiv.) over a period of 20 min. After stirring for 30 min, the reaction mixture was quenched with water (60 mL) and extracted with CH_2Cl_2 (4 x 80 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 1:9 to 2:8) afforded alcohol **454b** as a yellowish oil (4.10 g, 42% over 3 steps). The spectroscopic data are in agreement with the literature values.[31]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.61 (h, *J* = 1.8 Hz, 1H, H-3), 4.91 (m, 1H, H-4), 4.21 (d, *J* = 14.5 Hz, 1H, H-1), 4.15 (d, *J* = 14.6 Hz, 1H, H-1), 2.50 – 2.38 (m, 1H, H-6), 2.29 (dddd, *J* = 16.2, 8.7, 7.2, 3.3 Hz, 1H, H-5), 2.24 – 2.13 (m, 1H, H-6), 1.80 – 1.64 (m, 2H, H-5), 0.89 (s, 9H, H-9), 0.07 (s, 6H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.4 (C-2), 127.9 (C-3), 78.0 (C-4), 62.2 (C-1), 34.3 (C-5), 30.9 (C-6), 26.1 (C-9), 18.5 (C-8), -4.45 (C-7), -4.48 (C-7).

$[\alpha]_D^{25}$= +57.7° (c = 1.00, $CHCl_3$, 92% *ee*), literature value for enantiomer $[\alpha]_D^{25}$= −50° (c = 1.00, $CHCl_3$, >95% *ee*).[31]

(*R*)-(3-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)methyl 4-methylbenzenesulfonate (*(R)*-438b)



To a solution of alcohol **454b** (400 mg, 1.75 mmol, 1 equiv.) in dry CH_2Cl_2 (6.0 mL) at 0 °C was added Et_3N (366 µL, 2.63 mmol, 1.50 equiv.) followed by a solution of Ts_2O (572 mg, 1.75 mmol, 1.00 equiv.) in CH_2Cl_2 (4.0 mL). After stirring for 30 min, the reaction mixture was quenched with MeOH (0.5 mL) and stirred for an additional 20 min. The reaction mixture was poured onto sat. aq. solution of $NaHCO_3$ (15 mL), extracted with CH_2Cl_2 (3 x 15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure at 30 °C. The crude tosylated allylic alcohol was purified by very fast gradient column chromatography (Et_2O:pentane = 0:100 to 10:90). The fractions containing the product were concentrated under reduced pressure at 30 °C and then transferred into a vial using Et_2O. Et_2O was blown down by a stream of nitrogen which afforded tosyl alcohol **438b** as a colourless oil (596 mg, 89%). Because of its relatively low stability, the pure product, while still under the atmosphere of nitrogen, was diluted with benzene (1.78 g) and stored in the freezer.

NOTE: The rapid decomposition of the purified material after column chromatography was observed several times, mostly after the evaporation of solvent and exposure of the residue to air. Allyl tosylate **6** should be used immediately after its preparation. Short-term storage (for a few days) as a frozen solution in benzene is possible, but even this solution is undergoing slow decomposition/polymerization, indicated by the colour change of the solution and the formation of black particles.

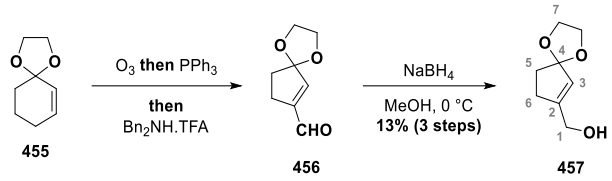
^{1}H NMR (400 MHz, C_6D_6) δ: 7.76 – 7.69 (m, 2H, H-8), 6.74 – 6.66 (m, 2H, H-9), 5.51 (m, 1H, H-3), 4.60 (m, 1H, H-4), 4.45 – 4.29 (m, 2H, H-1), 2.11 – 1.99 (m, 1H, H-6), 1.96 – 1.77 (m, 2H, H-6, H-5), 1.84 (s, 3H, H-11), 1.62 – 1.53 (m, 1H, H-5), 0.93 (s, 9H, H-14), 0.01 (s, 6H, H-13).

^{13}C NMR (101 MHz, C_6D_6) δ: 144.8 (C-7), 140.3 (C-10), 135.1 (C-2), 133.7 (C-3), 130.4 (C-9), 128.8 (C-8), 78.4 (C-4), 69.0 (C-1), 34.9 (C-5), 31.4 (C-6), 26.7 (C-14), 21.7 (C-11), 18.9 (C-12), -3.91 (C-13), -3.96 (C-13).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 – 7.75 (m, 2H, H-8), 7.37 – 7.30 (m, 2H, H-9), 5.65 (hept, *J* = 1.4 Hz, 1H, H-3), 4.82 (dddt, *J* = 6.9, 5.5, 3.2, 1.4 Hz, 1H, H-4), 4.65 – 4.52 (m, 2H, H-1), 2.45 (s, 3H, H-

11), 2.39 – 2.27 (m, 1H, H-6), 2.27 – 2.08 (m, 2H, H-5, H-6), 1.72 – 1.58 (m, 1H, H-5), 0.87 (s, 9H, H-14), 0.05 (s, 6H, H-13).

(1,4-dioxaspiro[4.4]non-6-en-7-yl)methanol (457)



Compound **457** was prepared adopting the literature procedure published by E. M. Carreira *et al.*[27]

A solution of alkene **455** (1.00 g, 7.13 mmol, 1 equiv.) in CH_2Cl_2 (50 mL) was cooled to -78 °C and then bubbled for 5 min with O_2. Ozone was then introduced through a sintered glass filter until a deep blue colour persisted, and its excess was removed by purging the solution with O_2 for 5 minutes. To the resulting solution PPh_3 (1.87 g, 7.13 mmol, 1.00 equiv.) in DCM (9.0 mL) was added dropwise and the cooling-bath temperature was slowly raised to 0 °C over 2h.

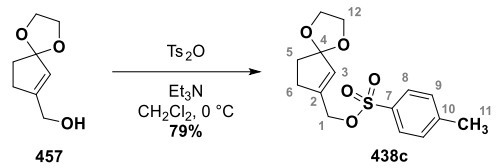
Next, a solution of dibenzylammonium trifluoroacetate, prepared *in situ* by adding TFA (109 μL, 1.43 mmol, 0.20 equiv.) to dibenzylamine (273 μl, 1.43 mmol, 0.20 equiv.) in CH_2Cl_2 (5 mL) at 0°C, was added at 0 °C. The resulting solution was warmed to room temperature over 1h. After being stirred overnight, the reaction mixture was concentrated under reduced pressure to approx. 10 mL. The residue was diluted with Et_2O (25 mL) and H_2O (15 mL), the phases separated, and aq. phase washed with Et_2O/pentane (1:1, 3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (40 °C, 800 mbar). The crude aldehyde **456** was used in next step without further purification.

The solution of crude aldehyde in MeOH (15 ml) was cooled to 0 °C and $NaBH_4$ (202 mg, 5.35 mmol, 0.75 equiv.) was added portion-wise over 10 min. The resulting solution was stirred for 1h at 0 °C and the reaction was then quenched with brine (30 mL) and diluted with CH_2Cl_2 (40 mL). The phases were separated, and the aq. phase extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O:pentane = 1:1 to 2:1) afforded alcohol **457** as a colourless oil contaminated with triphenylphosphine oxide (350 mg, 42 wt%, 13% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (1H, p, J = 1.8 Hz, H-3), 4.11 (2H, dt, J = 2.0, 1.1 Hz, H-1), 3.93 – 3.83 (4H, m, 7), 3.17 (1H, s, OH), 2.29 (2H, dddt, J = 7.7, 5.8, 2.1, 1.0 Hz, H-6), 2.17 – 2.05 (2H, m, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 151.69 (C-2), 123.57 (C-3), 120.06 (C-4), 64.57 (2xC-7), 61.65 (C-1), 34.98 (C-5), 29.15 (C-6).

(1,4-dioxaspiro[4.4]non-6-en-7-yl)methyl 4-methylbenzenesulfonate (438c)



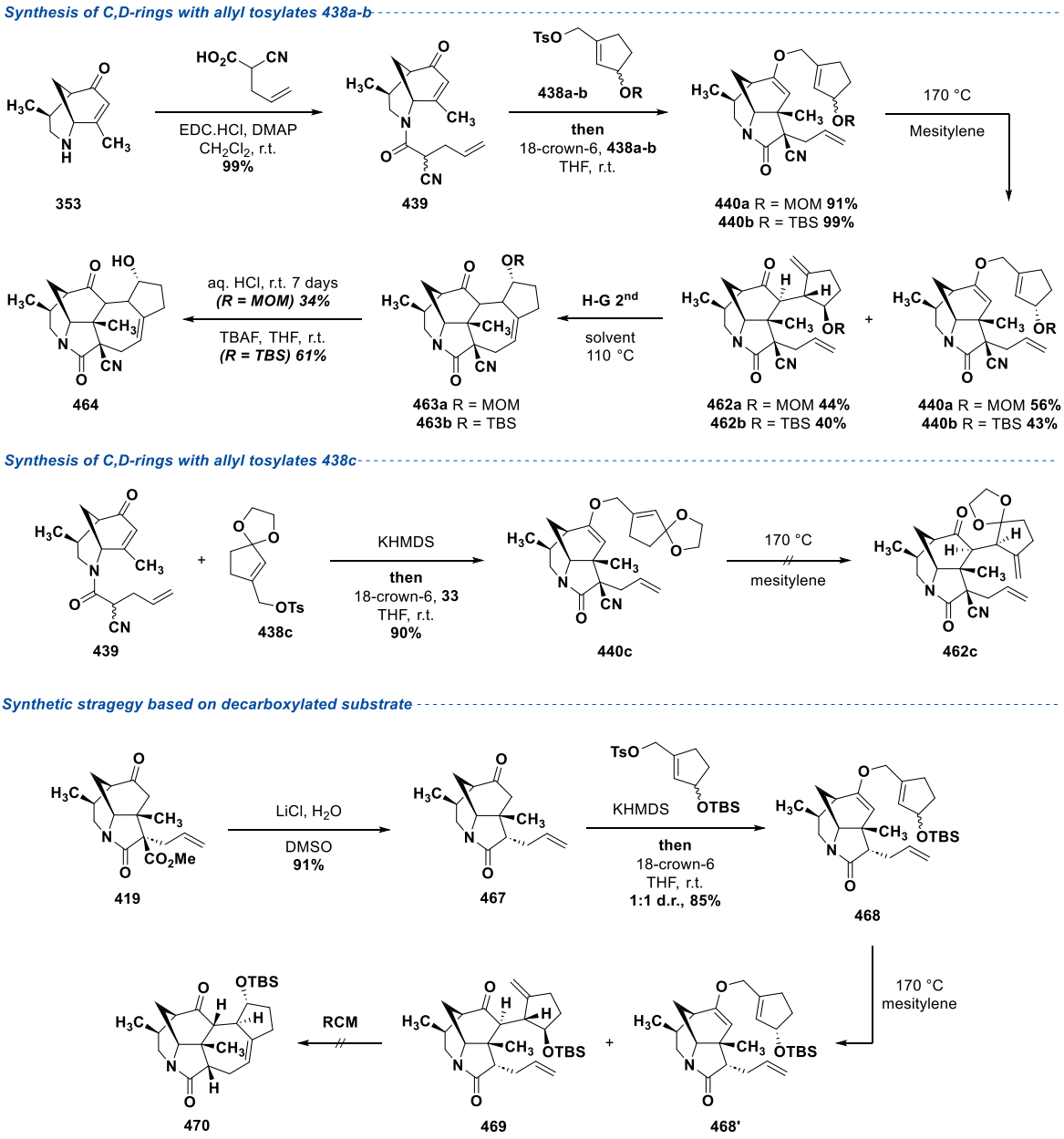
To a solution of alcohol **457** (150 mg, 960 μmol, 1 equiv.) in CH_2Cl_2 (9.0 mL) was added Et_3N (200 μL, 1.44 mmol, 1.5 equiv.) at 0 °C followed by solution of Ts_2O (329 mg, 1.01 mmol, 1.05 equiv.) in CH_2Cl_2 (4.0 mL) and the resulting solution was stirred for 30 min. The reaction was quenched with sat. aq. solution of $NaHCO_3$ (15 ml) and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (Et_2O:pentane = 1:1) afforded product **33** as a colourless solid (235 mg, 79%).

NOTE: The rapid decomposition of the purified material after column chromatography was observed with several similar substrates. Therefore, compound **438c** was immediately diluted with benzene and stored at -20 °C. However, even this solution is undergoing slow decomposition/polymerization, indicated by the colour change.

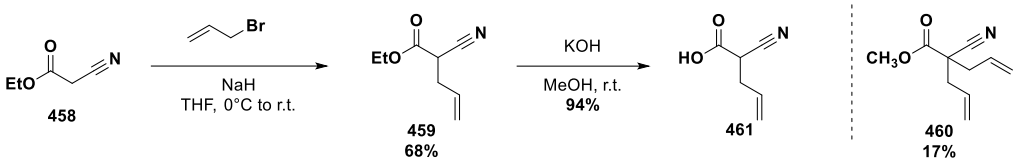
^{1}H NMR (400 MHz, C_6D_6) δ: 7.82 – 7.66 (2H, m, H-8), 6.74 – 6.61 (2H, m, H-9), 5.61 (1H, p, J = 1.7 Hz, H-3), 4.30 (3H, q, J = 1.2 Hz, H-1), 3.56 – 3.36 (4H, m, 12), 2.10 – 1.99 (2H, m, H-5), 1.86 (7H, ddt, J = 5.9, 1.9, 1.0 Hz, H-6), 1.83 (5H, s, H-11).

^{13}C NMR (101 MHz, C_6D_6) δ: 144.31 (C-7), 142.54 (C-10), 134.31 (C-2), 129.85 (C-9), 129.05 (C-3), 128.23 (C-8), 119.73 (C-4), 68.07 (C-1), 64.68 (C-12), 35.17 (C-5), 29.15 (C-6), 21.14 (C-11).

4.3.3.2 Synthetic studies towards the D-ring

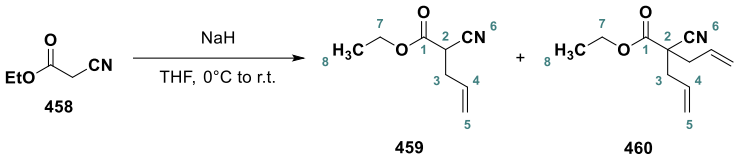


Scheme 4.10. *Overview of unsuccessful strategies towards Himalensine A.*



Scheme 4.11*. Synthesis of acid* ***461.***

ethyl 2-cyanopent-4-enoate (459)



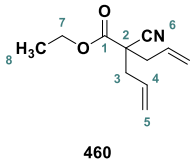
Compound **459** was prepared according to a literature procedure published by Suginome *et al.*[35]

To a suspension of NaH washed with pentane (60 wt%, 4.71 g, 118 mmol, 1 equiv.) in dry THF (240 mL) was dropwise added ester **458** (37.6 mL, 355 mmol, 3.00 equiv.) at 0 °C at the resulting mixture was stirred at this temperature for 1 h. Allyl bromide (10.2 mL, 118 mmol, 1.00 equiv.) was then added over 1 h using a syringe pump and the reaction mixture was allowed to warm up to room temperature. After stirring for 20 h, the reaction was quenched with distilled water (90 mL) and extracted with Et_2O (4 x 20 mL). The combined organic phases were washed with distilled water (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (dry loading, ethyl acetate:pentane = 10:90 to 15:85, then pure ethyl acetate) afforded product **460** as a colourless oil (3.83 g, 17%), product **459** as a colourless oil (12.3 g, 68%) and starting material **458** as a colourless oil (26.2 g, 1.97 eq.). The spectroscopic data are in agreement with the literature values.[36]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.82 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, H-4), 5.32 – 5.19 (m, 2H, H-5), 4.26 (q, *J* = 7.1 Hz, 2H, H-7), 3.55 (dd, *J* = 7.4, 6.1 Hz, 1H, H-2), 2.76 – 2.58 (m, 2H, H-3), 1.32 (t, *J* = 7.1 Hz, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.6 (C-1), 131.5 (C-4), 120.1 (C-5), 116.2 (C-6), 63.0 (C-7), 37.6 (C-2), 34.0 (C-3), 14.1 (C-8).

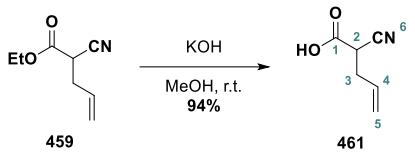
ethyl 2-allyl-2-cyanopent-4-enoate


460

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (ddt, *J* = 17.1, 9.8, 7.3 Hz, 2H, H-3), 5.27 – 5.09 (m, 4H, H-5), 4.18 (q, *J* = 7.1 Hz, 2H, H-7), 2.58 (ddt, *J* = 13.9, 7.4, 1.1 Hz, 2H, H-3), 2.48 (ddt, *J* = 13.9, 7.3, 1.2 Hz, 2H, H-3), 1.24 (t, *J* = 7.1 Hz, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.0 (C-1), 130.5 (C-4), 121.0 (C-5), 118.5 (C-6), 62.7 (C-7), 49.2 (C-2), 40.7 (C-3), 14.1 (C-8).

2-cyanopent-4-enoic acid (461)



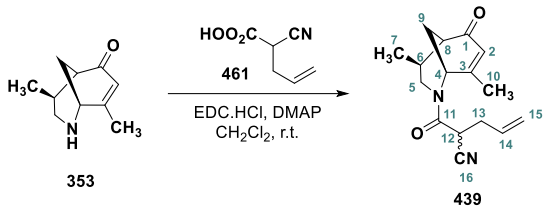
Compound **461** was prepared by adopting the procedure used for preparation of compound **392**.

To a solution of KOH (5.41 g, 96.4 mmol, 1.20 equiv.) in MeOH (80 mL) was added ester **459** (12.3 g, 80.3 mmol, 1 equiv.) at 0 °C, and the resulting solution was stirred for 21 h at room temperature. The reaction mixture was diluted with distilled water (80 mL) and washed with Et_2O (2 x 80 mL). The aqueous phase was then acidified with 12 M HCl to pH 1 and extracted with CH_2Cl_2 (3 x 80 mL). The combined CH_2Cl_2 phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (50 mbar, 45 °C, then 5 mbar at r.t.). The product of hydrolysis **7** was obtained as a yellowish oil (9.43 g, 94%). The spectroscopic data are in agreement with literature values.[37]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1H, H-1), 5.84 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H, H-4), 5.35 – 5.22 (m, 2H, H-5), 3.65 (dd, J = 7.4, 6.0 Hz, 1H, H-2), 2.81 – 2.64 (m, 2H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.4 (C-1), 131.1 (C-4), 120.6 (C-5), 115.5 (C-6), 37.7 (C-2), 33.8 (3).

rac-2-((1R,4S,5R)-4,8-dimethyl-6-oxo-2-azabicyclo[3.3.1]non-7-ene-2-carbonyl)pent-4-enenitrile (439)



Compound **439** was prepared according to procedure developed in our group by Sam Ellis.[19]

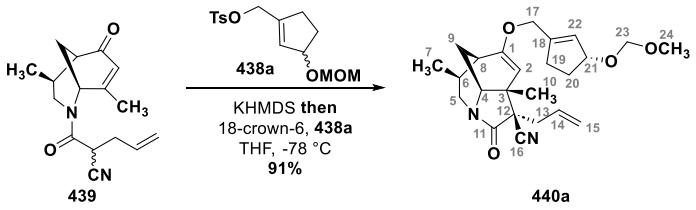
To a solution of amine **353** (2.26 g, 13.7 mmol, 1 equiv.) in CH_2Cl_2 (68 mL) at room temperature was added 2-(methoxycarbonyl)pent-4-enoic acid (**461**) (2.40 g, 19.2 mmol, 1.40 equiv.), followed by DMAP (418 mg, 3.42 mmol, 0.25 equiv.) and EDC.HCl (3.93 g, 20.5 mmol, 1.50 equiv.). After stirring for 3 h, the reaction mixture was diluted with water (80 mL) and extracted with CH_2Cl_2 (4 x 80 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 10:90 to 50:50) afforded amide **439** as a colourless oil (3.70 g, 99%). Product **439** is a complex mixture of isomers –

presumably diastereomers at C-12 and rotamers. Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.11 – 6.01 (1H, m, H-2), 5.78 (1H, dddt, *J* = 23.9, 17.1, 10.2, 6.9 Hz, H-14), 5.29 – 5.11 (3H, m, H-5a, H-15), 3.72 – 3.59 (1H, m, H-12), 3.43 – 3.31 (1H, m, H-5b), 2.78 – 2.54 (2H, m, H-13), 2.36 (1H, q, *J* = 3.1 Hz, H-8), 2.22 – 1.94 (3H, m, H-9, H-6), 1.90 (1.5H, d, *J* = 1.5 Hz, H-10), 1.86 (1.5H, d, *J* = 1.5 Hz, H-10), 1.23 (1.5H, d, *J* = 7.1 Hz, H-7), 1.16 (1.5H, d, *J* = 7.1 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 200.9 (C-1), 200.7 (C-1)*, 164.6 (C-11), 164.3 (C-11)*, 155.3 (C-3), 155.1 (C-3)*, 132.4 (C-14), 132.2 (C-14)*, 129.7 (C-2), 119.6 (C-15), 119.5 (C-15)*, 116.8 (C-16), 116.3 (C-16)*, 48.6 (C-4), 48.4 (C-4)*, 45.79 (C-8), 45.77 (C-8)*, 45.4 (C-5), 45.1 (C-5)*, 35.1 (C-12), 35.0 (C-12)*, 34.0 (C-13), 33.5 (C-13)*, 31.6 (C-6), 31.1 (C-6)*, 26.3 (C-9), 26.3 (C-9)*, 22.1 (C-10), 22.0 (C-10)*, 17.6 (C-7), 17.5 (C-7).

rac-(3S,3aR,6R,7aR,8S)-3-allyl-5-((3-(methoxymethoxy)cyclopent-1-en-1-yl)methoxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carbonitrile (440a)



Compound **440a** was prepared adopting the procedure developed in our group by Sam Ellis.[19]

To a solution of enone **439** (100.0 mg, 0.367 mmol, 1 equiv.) in degassed THF (1.0 ml) was added 0.5 M solution of KHMDS in toluene (1.10 ml, 0.551 mmol, 1.50 equiv.) at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 15 min. To the resulting opaque orange solution of enolate was added solution 18-crown-6 (97.1 mg, 0.367 mmol, 1.00 equiv.) in degasses THF (0.5 ml) (solution become transparent), followed by a solution of tosylate **438a** (172.1 mg, 0.551 mmol, 1.50 equiv.) in degassed THF (0.4 ml). The resulting solution was stirred for 4h and then quenched with H_2O (15 ml) and extracted with CH_2Cl_2 (4 x 15 ml). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 30:70 to 65:35) afforded compound **440a** as a white solid (137.7 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.16 – 6.00 (1H, m, H-14), 5.78 – 5.71 (1H, m, H-22), 5.31 – 5.20 (2H, m, H-15), 4.76 – 4.68 (1H, m, H-21), 4.72 – 4.61 (2H, m, H-23), 4.40 – 4.15 (2H, m, H-17), 4.06 (1H, t, *J* = 1.4 Hz, H-2), 4.00 (1H, ddd, *J* = 13.8, 8.1, 2.3 Hz, H-5a), 3.87 (1H, dt, *J* = 5.5, 1.5 Hz, H-4), 3.36 (3H, d, *J* = 2.1 Hz, H-24), 2.80 – 2.68 (1H, m, H-13a), 2.52 – 2.14 (5H, m, H-13b, H-5b, H-19, H-20a),

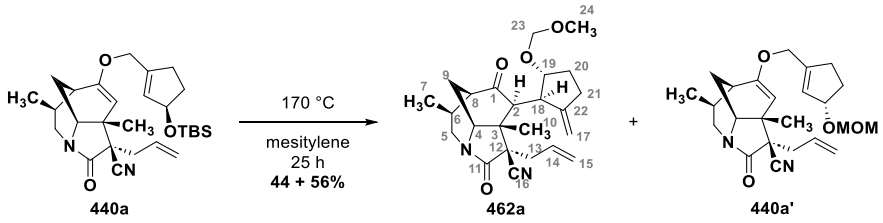
2.10 – 1.97 (2H, m, H-6, H-9a), 1.96 (1H, ddq, *J* = 3.5, 2.3, 1.2 Hz, H-8), 1.93 – 1.78 (1H, m, H-20b), 1.67 (1H, ddt, *J* = 13.9, 3.9, 1.0 Hz, H-9b), 1.33 (3H, d, *J* = 1.1 Hz, H-10), 0.97 (3H, dd, *J* = 6.9, 1.2 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.60 (C-11), 169.58 (C-11)*, 161.14 (C-1), 161.01 (C-1)*, 145.11 (C-18), 144.76 (C-18)*, 132.72 (C-14), 132.69 (C-14)*, 127.97 (C-22), 127.85 (C-22)*, 119.50 (C-15), 117.55 (C-16), 95.93 (C-23), 92.04 (C-2), 91.94 (C-2)*, 82.92 (C-21), 82.88 (C-21)*, 66.04 (C-17), 57.31 (C-4), 55.52 (C-24), 55.49 (C-24)*, 51.77 (C-12), 51.76 (C-12)*, 50.70 (C-3), 50.68 (C-3)*, 41.81 (C-5), 37.60 (C-8), 34.72 (C-13), 34.66 (C-13)*, 31.91 (C-6), 31.89 (C-6)*, 31.17 (C-19), 31.15 (C-19)*, 31.12 (C-20), 19.96 (C-10), 19.77 (C-9), 19.49 (C-7).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2926.0 (w), 1708.9 (vs), 1646.5 (m), 1413.8 (m), 1145.8 (s), 1032.4 (vs).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{24}H_{32}N_2O_4Na)^+$ requires 435.2254, found 435.2258.

***rac*-(3S,3aR,4S,6R,7aR,8S)-3-allyl-4-((1R,2R)-2-(methoxymethoxy)-5-methylenecyclopentyl)-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-3-carbonitrile (462a)**



Compound **462a** was prepared adopting the literature procedure published by E. M. Carreira *et al.*[27]

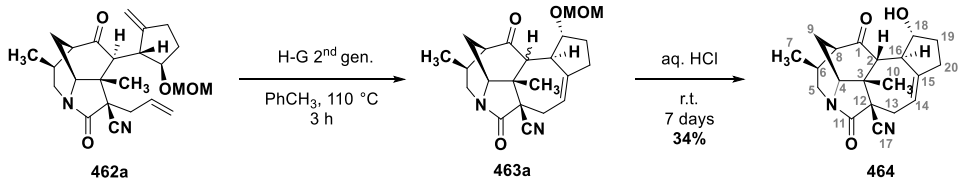
A solution of diastereomers **440a** (20.0 mg, 0.044 mmol, 1 equiv.) in mesitylene (2.5 ml, 0.018 M) was purged with Ar for 20 minutes and then heated is a sealed BSA-passivated vial to 170 °C for 25 h. The reaction mixture was then cooled down and directly loaded onto a silica gel column for purification by column chromatography. After eluting with pentane to remove mesitylene, the product was eluted with ethyl acetate:pentane (30:70 to 45:55) to afford ketone **462a** as a white solid (8.7 mg, 44%) and an unreacted starting material enriched in diastereomer **440a'** (11.0 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.00 (1H, dtd, *J* = 17.0, 9.8, 4.7 Hz, H-14), 5.38 – 5.26 (2H, m, H-15), 4.99 (1H, d, *J* = 2.2 Hz, H-17a), 4.93 (1H, d, *J* = 2.3 Hz, H-17b), 4.66 (1H, d, *J* = 7.1 Hz, H-223a), 4.58 (1H, d, *J* = 7.0 Hz, H-23b), 4.06 – 3.96 (2H, m, H-5a, H-19), 3.93 (1H, d, *J* = 5.9 Hz, H-4), 3.35 (3H, s, H-24), 2.99 – 2.87 (3H, m, H-13a, H-6, H-2), 2.47 (1H, dd, *J* = 15.5, 9.6 Hz, H-13b), 2.40 – 2.23 (5H, m, H-5b, H-9a, H-21, H-18), 2.17 – 2.00 (3H, m, H-20a, H-8, H-9b), 1.88 – 1.75 (1H, m, H-20b), 1.66 (3H, s, H-10), 1.02 (3H, d, *J* = 7.0 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.1 (C-1), 166.7 (C-11), 151.9 (C-22), 131.4 (C-14), 120.2 (C-15), 117.5 (C-16), 111.1 (C-17), 95.0 (C-23), 82.7 (C-19), 60.7 (C-4), 55.7 (C-24), 53.5 (C-12), 52.6 (C-18), 52.1 (C-2), 51.8 (C-3), 45.5 (C-8), 41.4 (C-5), 36.8 (C-6), 34.1 (C-13), 28.6 (C-21), 28.6 (C-20), 18.3 (C-9), 18.2 (C-10), 17.8 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{24}H_{32}N_2O_4Na)^+$ requires 435.2254, found 435.2249.

***rac*-(2R,3S,6aS,11R,11aR,12R,12aR,12bR)-11-hydroxy-3,12a-dimethyl-6,13-dioxo-1,2,3,4,7,9,10,11,11a,12,12a,12b-dodecahydro-2,12-methanoazuleno[5,6-a]indolizine-6a(6H)-carbonitrile (464)**



To a solution of diene **462a** (27 mg, 65.5 μmol, 1 equiv.) in dry degassed toluene (10 mL) was added benzoquinone (0.7 mg, 6.54 μmol, 0.10 equiv.) and Grubbs-Hoveyda 2nd generation catalyst (4.1 mg, 6.54 μmol, 10 mol%) and the reaction mixture was heated to reflux under argon atmosphere. After stirring for 3 h, the reaction mixture was cooled down and concentrated under reduced pressure.

The obtained residue was dissolved in THF (3.0 mL), 1M aq. HCl (3.0 mL) was added and the resulting solution was stirred for 7 days at room temperature. The reaction mixture was diluted with distilled water (10 mL) and extracted with distilled water (10 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 50:50 to 90:10) afforded product **464** as a white solid (7.5 mg, 34 %).

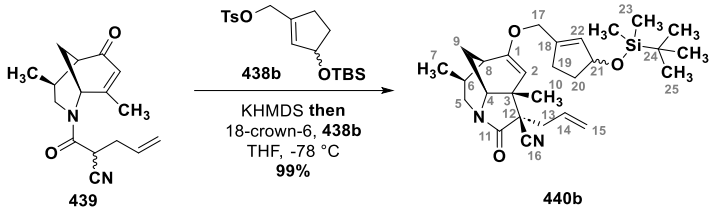
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.70 (1H, qd, *J* = 6.4, 4.2 Hz, H-14), 4.06 – 3.96 (1H, m, H-5a), 3.84 (1H, d, *J* = 5.5 Hz, H-4), 3.71 – 3.64 (1H, m, H-18), 3.41 – 3.35 (1H, m, H-16), 2.97 (1H, q, *J* = 8.6 Hz, H-6), 2.71 (1H, dd, *J* = 15.0, 7.2 Hz, H-13a), 2.61 – 2.47 (2H, m, H-20a, H-2), 2.44 – 2.21 (4H, m, H-13b, H-5b, H-9a, H-20b), 2.20 – 2.11 (1H, m, H-9b), 2.09 (1H, d, *J* = 4.4 Hz, H-8), 2.01 (1H, dd, *J* = 10.9, 6.0 Hz, H-19a), 1.69 – 1.56 (1H, m, H-19b), 1.51 (3H, s, H-10), 1.06 (3H, d, *J* = 6.9 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.8 (C-1), 167.7 (C-11), 148.4 (C-15), 118.5 (C-17), 114.6 (C-14), 83.2 (C-18), 61.3 (C-4), 54.9 (C-2), 52.8 (C-12), 47.4 (C-3), 46.7 (C-8), 45.5 (C-16), 41.5 (C-5), 35.9 (C-6), 34.0 (C-19), 31.7 (C-13), 29.9 (C-20), 24.4 (C-10), 18.6 (C-9), 17.8 (C-7).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3447, 2959, 2926, 1713, 1451, 1426, 1286, 1067, 915, 731.

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{20}H_{24}N_2O_4Na)^+$ requires 363.1679, found 363.1681.

***rac*-(3S,3aR,6R,7aS,8S)-3-allyl-5-((3-((tert-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)methoxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carbonitrile (440b)**



Compound **440b** was prepared adopting the procedure developed in our group by Sam Ellis.[19]

To a solution of enone **439** (50.0 mg, 184 μmol, 1 equiv.) in degassed THF (1.0 mL) was added 0.5 M solution of KHMDS in toluene (550 μL, 275 μmol, 1.50 equiv.) at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 15 min. To the resulting opaque orange solution of enolate was added solution 18-crown-6 (48.5 mg, 184 μmol, 1.00 equiv.) in degasses THF (0.5 mL), followed by a solution of tosylate **33** (105 mg, 275 μmol, 1.50 equiv.) in degassed THF (0.4 mL). The resulting solution was stirred for 2.5 h and then quenched with brine (15 mL) and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 5:95 to 10:90) afforded compound **440b** as a white wax (87.7 mg, 99%).

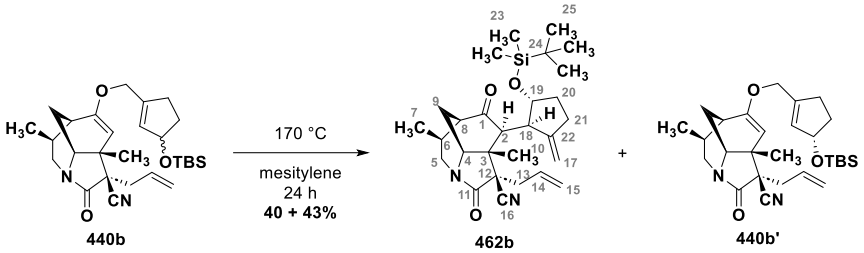
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.15 – 6.00 (1H, m, H-14), 5.61 (1H, dp, *J* = 5.2, 1.7 Hz, H-22), 5.32 – 5.20 (2H, m, H-15), 4.95 – 4.86 (1H, m, H-21), 4.36 – 4.13 (2H, m, H-17), 4.07 (1H, t, *J* = 1.4 Hz, H-2), 4.01 (1H, ddd, *J* = 13.8, 8.0, 3.0 Hz, H-5a), 3.87 (1H, dt, *J* = 5.3, 1.2 Hz, H-4), 2.74 (1H, dddt, *J* = 14.7, 11.0, 5.4, 1.8 Hz, H-13a), 2.49 – 2.37 (2H, m, H-5b, H-19a), 2.37 – 2.24 (2H, m, H-13b, H-20a), 2.23 – 2.09 (1H, m, H-19b), 2.07 – 1.92 (2H, m, H-9, H-6, H-9a), 1.80 – 1.70 (1H, m, H-20b), 1.70 – 1.61 (1H, m, H-9b), 1.34 (3H, d, *J* = 1.4 Hz, H-10), 0.98 (3H, dd, *J* = 7.0, 2.8 Hz, H-7), 0.89 (9H, s, H-25), 0.07 (6H, d, *J* = 2.0 Hz, H-30, H-23).

^{13}C NMR (101 MHz, $CDCl_3$) δ: δ 169.60 (C-11), 161.17 (C-1), 161.03 (C-1)*, 142.95 (C-18), 142.42 (C-18)*, 132.69 (C-14), 130.98 (C-22), 130.67 (C-22)*, 119.55 (C-15), 119.51 (C-15)*, 117.62 (C-16), 117.57 (C-16)*, 92.05 (C-2), 91.94 (C-2)*, 78.04 (C-21), 77.98 (C-21)*, 66.22 (C-17), 66.20 (C-17)*, 57.34 (C-4), 51.78 (C-12), 51.74 (C-12)*, 50.72 (C-3), 50.70 (C-3)*, 41.85 (C-5), 37.62 (C-8), 34.79 (C-13), 34.71 (C-13)*, 34.26 (C-20), 34.21 (C-20)*, 31.94 (C-6), 31.90 (C-6)*, 31.23 (C-19), 26.22 (C-25), 20.03 (C-10), 19.98 (C-10)*, 19.81 (C-9), 19.79 (C-9), 19.51 (C-7), 18.54 (C-25), -4.34 (C-23), -4.37 (C-23)*.

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2928, 2855, 1713, 1647, 1458, 1413, 1197, 1063, 835, 776.

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{28}H_{42}N_2O_3SiNa)^+$ requires 505.2857, found 505.2855.

***rac*-(3S,3aR,4S,6R,7aR,8S)-3-allyl-4-((1R,2R)-2-((tert-butyldimethylsilyl)oxy)-5-methylenecyclopentyl)-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-3-carbonitrile (462b)**



Compound **462b** was prepared adopting the literature procedure published by E. M. Carreira *et al.*[27]

A solution of diastereomers **440b** (64.4 mg, 133 μmol, 1 equiv.) in mesitylene (5.5 mL) was purged with Ar for 20 minutes and then heated in a sealed BSA-passivated vial to 170 °C for 24 h. The reaction mixture was then cooled down and directly loaded onto a silica gel column for purification by column chromatography. After eluting with pentane to remove mesitylene, the product was eluted with ethyl acetate:pentane (20:80) to afford ketone **462b** as a white foam (25.5 mg, 40%) and the unreacted starting material enriched in diastereomer **440b'** (27.7 mg, 43%).

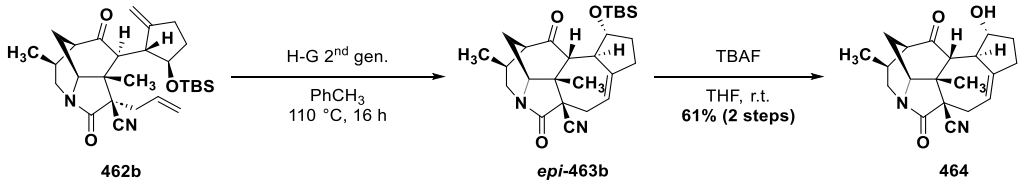
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.01 (1H, dtd, *J* = 17.0, 10.0, 4.4 Hz, H-14), 5.39 – 5.31 (1H, m, H-15a), 5.28 (1H, dt, *J* = 10.2, 1.8 Hz, H-15b), 4.96 – 4.90 (1H, m, H-17a), 4.76 (1H, q, *J* = 2.1 Hz, H-17b), 4.10 (1H, dt, *J* = 5.0, 3.1 Hz, H-19), 4.01 (1H, dd, *J* = 13.7, 8.7 Hz, H-5a), 3.97 – 3.92 (1H, m, H-4), 2.93 (1H, ddt, *J* = 15.7, 4.4, 2.2 Hz, H-13a), 2.83 – 2.69 (1H, m, H-6), 2.66 – 2.55 (2H, m, H-13b, H-18), 2.41 – 2.23 (5H, m, H-5b, H-9a, H-21, H-2), 2.18 – 2.08 (2H, m, H-8, H-9b), 2.03 (1H, dddd, *J* = 15.0, 10.1, 6.8, 4.9 Hz, H-20a), 1.69 – 1.52 (1H, m, H-20b), 1.58 (3H, s, H-10), 1.02 (3H, d, *J* = 7.0 Hz, H-7), 0.85 (9H, s, H-25), 0.02 (6H, d, *J* = 2.5 Hz, H-23).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.2 (C-1), 167.0 (C-11), 151.1 (C-22), 131.9 (C-14), 119.9 (C-15), 117.5 (C-16), 110.2 (C-17), 78.4 (C-19), 60.2 (C-4), 54.3 (C-18), 54.2 (C-12), 52.0 (C-3), 51.2 (C-2), 46.1 (C-8), 41.5 (C-5), 36.4 (C-6), 33.6 (C-13), 32.1 (C-20), 28.6 (C-21), 25.9 (C-25), 18.3 (C-7, C-10), 18.2 (C-9), 18.0 (C-24), -4.3 (C-23).

IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 2928, 2856, 1718, 1460, 1422, 1286, 1255, 1084, 996, 893, 838, 776.

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{28}H_{42}N_2O_3SiNa)^+$ requires 505.2857, found 505.2857.

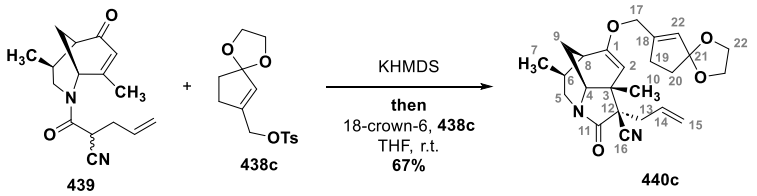
***rac*-(2R,3S,6aS,11R,11aR,12R,12aR,12bR)-11-hydroxy-3,12a-dimethyl-6,13-dioxo-1,2,3,4,7,9,10,11,11a,12,12a,12b-dodecahydro-2,12-methanoazuleno[5,6-a]indolizine-6a(6H)-carbonitrile (464)**



To a solution of diene **462b** (9.0 mg, 18.6 μmol, 1 equiv.) in dry degassed toluene (2.0 mL) was added benzoquinone (0.2 mg, 1.86 μmol, 10 mol%) and Grubbs-Hoveyda 2nd generation catalyst (1.2 mg, 1.86 μmol, 10 mol%) and the reaction mixture was heated to reflux under argon atmosphere. After stirring for 16 h, the reaction mixture was cooled down and concentrated under reduced pressure.

The obtained residue was dissolved in THF (1.5 mL) and 1M solution of TBAF in THF (28 μL, 28 μmol, 1.50 equiv.) was added. After stirring for 1 h at room temperature, the reaction mixture was poured onto sat. aq. solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient chromatography (ethyl acetate:CH_2Cl_2 = 40:60) afforded product **464** as a green foam (3.9 g, 61 %).

***rac-(3S,3aR,6R,7aR,8S)*-5-((1,4-dioxaspiro[4.4]non-6-en-7-yl)methoxy)-3-allyl-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carbonitrile (440c)**



Compound **440c** was prepared adopting the procedure developed in our group by Sam Ellis.[19]

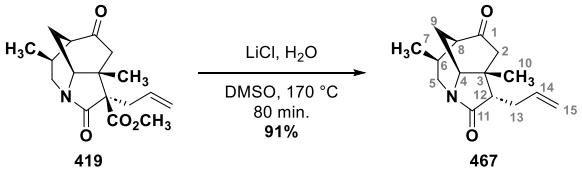
To a solution of enone **439** (50.0 mg, 184 μmol, 1 equiv.) in degassed THF (1.0 mL) was added 0.5 M solution of KHMDS in toluene (550 μL, 275 μmol, 1.50 equiv.) at 0 °C. The ice bath was removed, and the reaction mixture was stirred at room temperature for 15 min. To the resulting opaque orange solution of enolate was added solution 18-crown-6 (48.5 mg, 184 μmol, 1.00 equiv.) in degasses THF (0.5 mL), followed by a solution of tosylate **438c** (85.5 mg, μmol, 1.50 equiv.) in degassed THF (0.4 mL). The resulting solution was stirred for 4 h and then quenched with brine (15 mL) and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O:pentane = 30:70 to 50:50) afforded compound **45** as a white wax (50.0 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.08 (1H, dddd, *J* = 17.0, 10.1, 9.2, 5.2 Hz, H-14), 5.61 (1H, p, *J* = 1.7 Hz, H-22), 5.30 – 5.19 (2H, m, H-15), 4.32 (1H, dd, *J* = 13.7, 1.6 Hz, H-17a), 4.21 (1H, dd, *J* = 13.7, 1.5 Hz, H-17b), 4.05 (1H, d, *J* = 1.3 Hz, H-2), 4.01 (1H, dd, *J* = 13.8, 8.0 Hz, H-5a), 3.97 – 3.91 (4H, m, H-22), 3.89 – 3.84 (1H, m, H-4), 2.75 (1H, ddt, *J* = 14.9, 5.3, 1.9 Hz, H-13a), 2.42 (1H, dd, *J* = 13.8, 10.6 Hz, H-5b), 2.41 – 2.30 (3H, m, H-13b, H-19), 2.22 – 2.10 (2H, m, H-20), 2.13 – 1.98 (2H, m, H-6, H-9a), 1.98 – 1.93 (1H, m, H-8), 1.67 (1H, dd, *J* = 13.9, 3.9 Hz, H-9b), 1.33 (3H, s, H-10), 0.97 (3H, d, *J* = 6.9 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.5 (C-11), 160.9 (C-1), 146.2 (C-18), 132.7 (C-14), 126.4 (C-22), 119.8 (C-21), 119.3 (C-15), 117.5 (C-16), 92.0 (C-2), 65.8 (C-17), 64.89 (C-22), 64.84 (C-22), 57.2 (C-4), 51.7 (C-4), 50.6 (C-3), 41.7 (C-5), 37.5 (C-8), 34.9 (C-20), 34.6 (C-13), 31.8 (C-6), 29.5 (C-19), 19.9 (C-10), 19.7 (C-9), 19.4 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{24}H_{30}N_2O_4)^+$ requires 433.2098, found 433.2094.

***rac-(3S,3aR,6R,7aR,8S)*-3-allyl-3a,8-dimethyltetrahydro-6,1-ethanoindole-2,5(*3H,4H*)-dione (467)**



Compound **467** was prepared adopting the procedure published by Dixon.[23]

A stirred solution of compound **419** (120 mg, 0.393 mmol, 1 equiv.), LiCl (166 mg, 3.93 mmol, 10 equiv.) in a mixture of DMSO (5.4 mL) and water (21.2 μL, 1.18 mmol, 3.00 equiv.) was heated to 170 °C for 80 minutes. After cooling down, the reaction mixture was loaded onto silica and purified by column chromatography (ethyl acetate:pentane = 40:60). The compound **419** was obtained as a white solid (88.0 mg, 91%) after lyophilization overnight.

MP: 92-94 °C (rac).

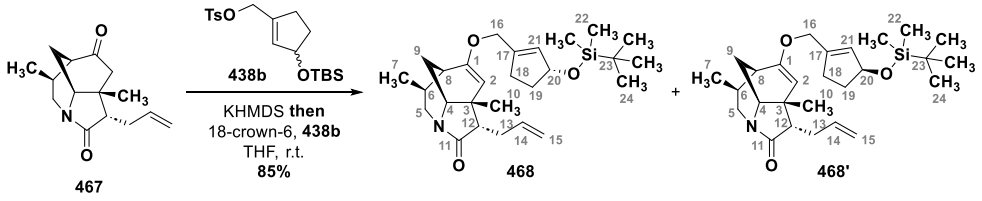
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.89 (dddd, J = 17.1, 10.1, 8.9, 5.2 Hz, 1H, H-14), 5.14 (dtd, J = 17.1, 1.9, 1.1 Hz, 1H, H-15a), 5.03 (dtd, J = 10.1, 1.8, 0.7 Hz, 1H, H-15b), 4.02 (dd, J = 13.6, 8.8 Hz, 1H, H-5a), 3.69 – 3.62 (m, 1H, H-4), 2.97 – 2.80 (m, 1H, H-6), 2.68 – 2.56 (m, 1H, H-13a), 2.47 (d, J = 14.7 Hz, 1H, H-2a), 2.31 (ddd, J = 8.6, 6.2, 1.0 Hz, 1H, H-12), 2.20 (ddd, J = 13.6, 9.6, 1.0 Hz, 1H, H-5b), 2.19 – 2.08 (m, 2H, H-13b, H-2b), 2.10 – 2.07 (m, 2H, H-9), 1.96 – 1.89 (m, 1H, H-8), 1.27 (s, 3H, H-10), 1.00 (d, J = 7.0 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 213.1 (C-8), 174.4 (C-11), 136.9 (C-14), 116.4 (C-15), 60.4 (C-4), 50.7 (C-12), 47.5 (C-3), 46.2 (C-8), 44.6 (C-2), 40.8 (C-5), 36.7 (C-6), 30.1 (C-13), 24.6 (C-10), 19.8 (C-9), 18.0 (C-7).

IR (neat) $\tilde{\nu}_{max}$/cm^{-1}: 2959, 2924, 2872, 2698, 1673, 1421, 1288, 929.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{15}H_{22}NO_2)^+$ requires 248.1645, found 248.1646.

***rac*-(*3S,3aR,6R,7aR,8S*)-3-allyl-5-(((*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)methoxy)-3a,8-dimethyl-3a,6,7,7a-tetrahydro-6,1-ethanoindol-2(*3H*)-one (468) and *rac*-(*3S,3aR,6R,7aR,8S*)-3-allyl-5-(((*S*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)methoxy)-3a,8-dimethyl-3a,6,7,7a-tetrahydro-6,1-ethanoindol-2(*3H*)-one (468')**



To a solution of ketone **467** (60 mg, 243 μmol, 1 equiv.) in degassed THF (3.0 mL) was added KHMDS (0.5 M solution in toluene, 730 μL, 364 μmol, 1.50 equiv.) at 0 °C and the resulting solution was stirred for 20 min at room temperature. Then, a solution of 18-crown-6 (64.1 mg, 242.6 μmol, 1.00 equiv.) in degassed THF (1.5 mL) followed by tosylate **438b** (14.7 wt % solution in benzene, 948 mg, 364 μmol, 1.50 equiv.) in THF (1.2 mL) were added. The solution was stirred for 1 h, and the formation of white precipitate and darkening of the reaction mixture was observed. The reaction mixture was then poured onto brine (20 mL) and extracted with ethyl acetate (4 x 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 20:80) afforded compounds **468** and **468'** as an inseparable mixture of diastereomer, colourless oil (94.2 mg, 85%).

Note: Carbon peaks of compound **S45b** are labelled by "*". The assignment was possible because this isomer is not undergoing Claisen rearrangement (see next page), which allowed its isolation. The proton spectra of both compounds are not distinguishable.

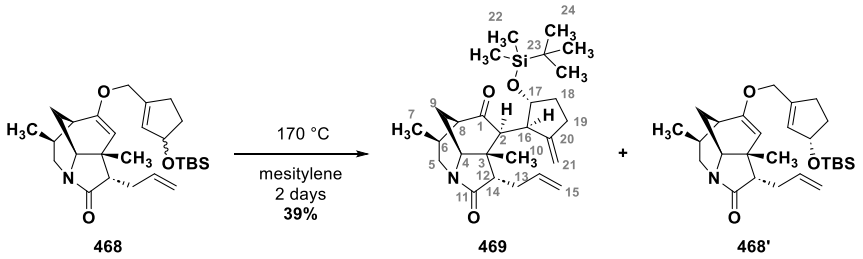
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.01 (dddd, *J* = 17.1, 10.1, 8.7, 5.3 Hz, 1H, H-14), 5.61 (m, 1H, H-21), 5.11 (dtd, *J* = 17.1, 2.0, 1.1 Hz, 1H, H-15a), 5.01 (dtd, *J* = 10.0, 1.8, 0.8 Hz, 1H, H-15b), 4.91 (m, 1H, H-20), 4.28 (d, *J* = 12.7 Hz, 1H, H-16a), 4.16 – 4.08 (m, 2H, H-16b, H-2), 4.01 (dd, *J* = 13.6, 8.0 Hz, 1H, H-5a), 3.51 (d, *J* = 3.7 Hz, 1H, H-4), 2.56 – 2.47 (m, 1H, H-13a), 2.46 – 2.37 (m, 1H, H-18a), 2.37 – 2.24 (m, 3H, H-12, H-5b, H-19a), 2.23 – 1.99 (m, 3H, H-13b, H-6, H-18b), 1.98 – 1.86 (m, 2H, H-8, H-9a), 1.74 (ddt, *J* = 13.3, 7.5, 4.3 Hz, 1H, H-19b), 1.66 – 1.57 (m, 1H, H-9b), 1.17 (s, 3H, H-10), 0.94 (d, *J* = 6.9 Hz, 3H, H-7), 0.89 (s, 9H, H-24), 0.07 (s, 6H, H-22).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.08 (C-11)*, 177.05 (C-11), 159.65 (C-1)*, 159.41 (C-1), 143.31 (C-17), 142.94 (C-17)*, 138.00 (2xC-14), 130.38 (C-21), 130.08 (C-21)*, 115.60 (C-15)*, 115.54 (C-15), 93.94 (C-2), 93.80 (C-2)*, 78.02 (C-20)*, 78.00 (C-20), 65.89 (C-16)*, 65.85 (C-16), 58.56 (2xC-4), 52.24 (2xC-12), 47.20 (2xC-3), 41.19 (2xC-5), 37.74 (2xC-8), 34.17 (C-19)*, 34.15 (C-19), 32.78 (C-6)*, 32.73 (C-6), 31.25 (C-18)*, 31.16 (C-18), 30.12 (C-13)*, 30.08 (C-13), 26.12 (6xC-24), 22.42 (C-10)*, 22.39 (C-10), 19.90 (2xC-9), 19.53 (2xC-7), 18.43 (3xC-23), -4.43 (2xC-22), -4.45 (2xC-22).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2952, 2928, 2856, 1697, 1650, 1411, 1159, 1063, 835.

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{27}H_{43}NO_3SiNa)^+$ requires 480.2904, found 480.2899.

***rac*-(*3S,3aR,4S,6R,7aR,8S*)-3-allyl-4-((*1R,2R*)-2-((*tert*-butyldimethylsilyl)oxy)-5-methylenecyclopentyl)-3a,8-dimethyltetrahydro-6,1-ethanoindole-2,5(*3H,4H*)-dione (469)**



Compound **469** was prepared adopting the procedure published by Carreira.[27]

A solution of compound **468** (1:1 mixture of diastereomers, 90.0 mg, 197 μmol, 1 equiv.) in dry degassed mesitylene (5.5 mL) was heated for 2 days in BSA-passivated pressure tube at 170 °C. Purification by gradient column chromatography (ethyl acetate:pentane = 0:100 to 30:70) afforded compound **469** as a crystalline solid (34.7 mg, 39%) and unreactive starting material enriched in diastereomer **468'** as oil (35.5 mg, 37%).

MP: 158 – 162 °C (*rac*).

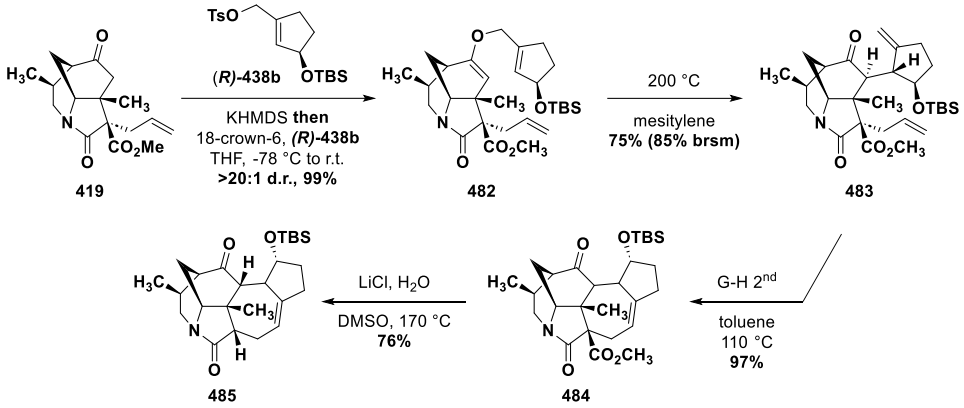
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.86 (dtd, *J* = 17.1, 9.8, 4.5 Hz, 1H, H-14), 5.15 (dtd, *J* = 17.1, 2.1, 0.9 Hz, 1H, H-15a), 5.05 (dt, *J* = 10.1, 1.9 Hz, 1H, H-15b), 4.89 (s, 1H, H-21a), 4.86 – 4.80 (m, 1H, H-21b), 4.04 – 3.99 (m, 1H, H-17), 3.98 (dd, *J* = 13.6, 8.9 Hz, 1H, H-5a), 3.60 (d, *J* = 5.7 Hz, 1H, H-), 2.86 (td, *J* = 9.2, 6.9 Hz, 1H, H-6), 2.69 (dddd, *J* = 15.2, 7.6, 4.4, 2.1 Hz, 1H, H-13a), 2.61 (d, *J* = 8.5 Hz, 1H, H-16), 2.40 (dd, *J* = 9.5, 5.5 Hz, 1H, H-12), 2.35 – 2.23 (m, 4H, H-9a, H-21a, H-21b, H-2), 2.22 – 2.13 (m, 2H, H-13b, H-5b), 2.14 – 2.05 (m, 1H, H-18a), 2.07 – 1.99 (m, 1H, H-9b), 1.98 (d, *J* = 4.6 Hz, 1H, H-8), 1.64 – 1.55 (m, 1H, H-18b), 1.40 (s, 3H, H-10), 0.97 (d, *J* = 7.0 Hz, 3H, H-7), 0.84 (s, 9H, H-24), 0.02 (s, 6H, H-22).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 213.2 (C-1), 173.8 (C-11), 152.7 (C-20), 137.1 (C-14), 116.3 (C-15), 109.7 (C-21), 78.9 (C-17), 61.7 (C-4), 54.3 (C-16), 53.4 (C-12), 53.1 (C-2), 48.8 (C-3), 45.8 (C-8), 40.7 (C-5), 37.0 (C-6), 32.0 (C-18), 29.9 (C-13), 28.6 (C-19), 25.8 (C-24), 21.9 (C-10), 18.6 (C-9), 18.0 (C-7, C-29), -4.3 (C-22), -4.4 (C-22).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2955, 2928, 2892, 1693, 1680, 1427, 1252, 1092, 999, 891, 837, 771.

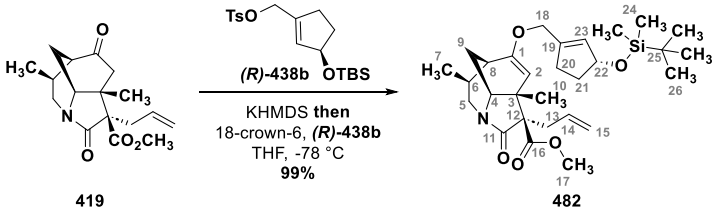
HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{27}H_{44}NO_3Si)^+$ requires 458.3085, found 458.3083.

4.3.3.3 The successful synthesis of the D-ring



Scheme 4.12. *Successful strategy for the introduction of the D-ring.*

methyl (*3R,3aR,6R,7aR,8S*)-3-allyl-5-(((*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)methoxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carboxylate (482)



To a solution of ketone **419** (205.0 mg, 0.671 mmol, 1 equiv.) in degassed THF (4.0 mL) at -78 °C was added KHMDS (0.5 M solution in toluene, 2.0 mL, 1.01 mmol, 1.50 equiv.) and the resulting solution was stirred at this temperature for 20 min. Then, a solution of 18-crown-6 (177.4 mg, 0.671 mmol, 1.00 equiv.) in degassed THF (2.0 mL) followed by tosylate ***(R)*-438b** (11.8 wt % solution in benzene, 2.61 g, 0.806 mmol, 1.20 equiv.) in THF (0.8 mL) were added. The solution was stirred for 1 h at this temperature and then warmed up slowly to 0 °C, which resulted in the formation of a white precipitate. The reaction mixture was then poured onto brine (20 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 5:95 to 30:70) afforded compound **482** as a colorless oil (344 mg, 99%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2951, 2929, 2856, 1731, 1697, 1649, 1417, 1216, 1195, 1167, 1061, 834, 775.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.24 (dddd, J = 17.2, 10.2, 9.2, 4.8 Hz, 1H, H-14), 5.65 – 5.58 (m, 1H, H-23), 5.18 – 5.05 (m, 2H, H-15), 4.95 – 4.87 (m, 1H, H-22), 4.30 – 4.25 (m, 1H, H-2), 4.33 – 4.18 (m, 2H, H-18), 4.06 (dd, J = 13.7, 8.0 Hz, 1H, H-5a), 3.85 – 3.79 (m, 1H, H-4), 3.71 (s, 3H, H-17), 2.69 (ddt, J = 14.6, 4.8, 2.0 Hz, 1H, H-13a), 2.49 – 2.34 (m, 3H, H-13b, H-5b, H-20a), 2.37 – 2.24 (m, 1H, H-21a), 2.24 – 2.12 (m, 1H, H-20b), 2.10 – 1.97 (m, 1H, H-6), 1.95 (ddd, J = 13.7, 5.3, 2.3 Hz, 1H, H-9a), 1.93

– 1.86 (m, 1H, H-8), 1.79 – 1.66 (m, 1H, H-21b), 1.62 (ddt, J = 13.7, 3.8, 1.0 Hz, 1H, H-9b), 1.14 (s, 3H, H-10), 0.95 (d, J = 6.9 Hz, 3H, H-7), 0.89 (s, 9H, H-26), 0.07 (s, 6H, H-24).

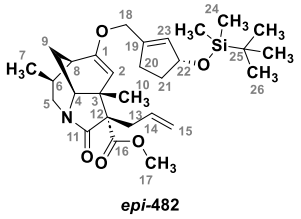
^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.9 (C-11), 170.9 (C-16), 159.6 (C-1), 143.1 (19), 135.3 (C-14), 130.6 (C-23), 117.6 (C-15), 95.0 (C-2), 78.0 (C-22), 65.9 (C-18), 62.0 (C-3), 56.9 (C-4), 52.1 (C-17), 50.0 (C-3), 41.6 (C-5), 37.5 (C-8), 35.7 (C-13), 34.2 (C-21), 31.9 (C-6), 31.2 (C-20), 26.1 (C-26), 20.1 (C-9), 19.6 (C-10), 19.5 (C-7), 18.5 (C-25), -4.42 (C-24), -4.44 (C-24).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{29}H_{45}NO_5SiNa)^+$ requires 538.2961, found 538.2957.

$[\alpha]_D^{25}$= -59.1 (c= 1.00, $CHCl_3$).

methyl (*3S,3aR,6R,7aR,8S*)-3-allyl-5-(((*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)methoxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carboxylate (*epi*-482)

C-12 diastereomer ***epi*-482** was formed as a side product when the reaction was performed at room temperature.



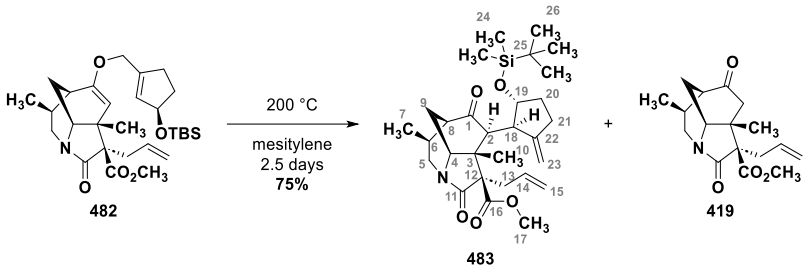
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.83 (dddd, *J* = 16.8, 10.0, 7.6, 6.7 Hz, 1H, H-14), 5.62 – 5.54 (m, 1H, H-23), 5.15 – 5.03 (m, 2H, H-15), 4.95 – 4.87 (m, 1H, H-22), 4.17 (d, *J* = 12.4 Hz, 1H, H-18), 4.14 – 4.00 (m, 1H, H-5a), 4.07 (d, *J* = 13.3 Hz, 1H, H-18), 3.86 (d, *J* = 1.3 Hz, 1H, H-2), 3.73 (s, 3H, H-18), 3.69 (d, *J* = 4.1 Hz, 1H, H-4), 2.78 (ddt, *J* = 13.7, 7.6, 1.2 Hz, 1H, H-13a), 2.49 – 2.36 (m, 2H, H-13b, H-20a), 2.34 (dd, *J* = 13.6, 10.5 Hz, 1H, H-5b), 2.31 – 2.23 (m, 1H, H-21a), 2.23 – 2.13 (m, 1H, H-20b), 2.14 – 2.03 (m, 1H, H-6), 1.95 (ddd, *J* = 13.7, 5.2, 2.3 Hz, 1H, H-9a), 1.93 – 1.87 (m, 1H, H-8), 1.76 – 1.65 (m, 1H, H-21b), 1.62 (dd, *J* = 13.8, 3.7 Hz, 1H, H-9b), 1.20 (s, 3H, H-10), 0.93 (d, *J* = 6.9 Hz, 3H, H-7), 0.89 (s, 9H, H-26), 0.06 (s, 6H, H-24).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.0 (C-11), 170.7 (C-16), 159.7 (C-1), 142.9 (C-19), 133.2 (C-14), 130.3 (C-23), 118.5 (C-15), 96.7 (C-2), 78.0 (C-22), 65.9 (C-18), 62.0 (C-12), 55.9 (C-4), 51.6 (C-17), 48.7 (C-3), 41.5 (C-5), 37.4 (C-8), 35.0 (C-13), 34.2 (C-21), 32.0 (C-6), 31.2 (C-20), 26.1 (-26), 20.2 (C-9), 19.5 (C-7), 18.4 (C-25), 17.4 (C-10), -4.42 (C-24), -4.44 (C-24).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{29}H_{45}NO_3SiNa)^+$ requires 538.2959, found 538.2975.

$[\alpha]_D^{25}$= -50.0 (c = 1.00, benzene).

methyl (*3R,3aR,4S,6R,7aR,8S*)-3-allyl-4-((*1R,2R*)-2-((*tert*-butyldimethylsilyl)oxy)-5-methylenecyclopentyl)-3a,8-dimethyl-2,5-dioxooctahydro-6,1-ethanoindole-3-carboxylate (483)



Compound **483** was prepared adopting the procedure published by Carreira.[27]

The solution of enol **482** (1.27 g, 2.46 mmol, 1 equiv.) was transferred to BSA-passivated pressure tube in benzene (5.0 mL), and the solvent was removed in a vacuum. The solvent-free enol was dissolved in mesitylene (78.0 mL, 0.032 M) (previously distilled and stored over molecular sieves). A PTFE syringe filter was used to ensure that no solid particles were transferred with the solvent into the reaction mixture. The resulting solution was degassed using freeze-pump-thaw (5 cycles), and the tube was backfilled with argon, sealed and heated to 200 °C for 60 h. After cooling to room temperature, the reaction mixture was directly poured onto a silica column and flushed with pentane until mesitylene was no longer eluted. Elution with ethyl acetate:pentane (10:90 to 25:75) afforded product **483** as a white amorphous solid (948 mg, 75%), unreacted starting material **482** (130 mg, 10%) and traces product of enol hydrolysis **419** (78 mg, 10%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2954, 2929, 2856, 1737, 1704, 1430, 1289, 1255, 1208, 1088, 838.

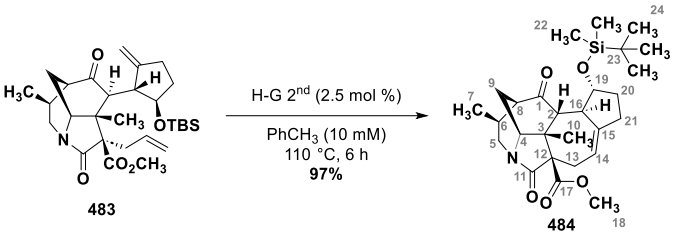
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.24 (dtd, *J* = 17.3, 9.9, 3.7 Hz, 1H, H-14), 5.25 (dt, *J* = 17.4, 1.9 Hz, 1H, H-15a), 5.16 (dt, *J* = 10.2, 2.1 Hz, 1H, H-15b), 4.92 (s, 1H, H-23a), 4.87 (s, 1H, H-23b), 4.04 (d, *J* = 4.1 Hz, 1H, H-19), 4.02 (dd, J = 13.6, 9.0 Hz, 1H, H-5a), 3.92 (d, *J* = 6.1 Hz, 1H, H-4), 3.73 (s, 3H, H-17), 3.00 – 2.87 (m, 2H, H-13a, H-6), 2.65 (d, *J* = 8.8 Hz, 1H, H-18), 2.51 (d, *J* = 8.9 Hz, 1H, H-2), 2.41 – 2.30 (m, 2H, H-13b, H-9a), 2.29 – 2.20 (m, 3H, H-5b, H-21a, H-21b), 2.09 – 1.98 (m, 3H, H-8, H-9b, H-20), 1.60 – 1.50 (m, 1H, H-20b), 1.31 (s, 3H, H-10), 0.99 (d, *J* = 7.0 Hz, 3H, H-7), 0.83 (s, 9H, H-36), 0.01 (s, 3H, H-24), 0.01 (s, 3H, H-24).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 212.8 (C-1), 171.3 (C-16), 171.2 (C-11), 152.6 (C-22), 134.4 (C-14), 118.7 (C-15), 110.5 (C-23), 78.4 (C-19), 62.8 (C-12), 60.8 (C-4), 54.8 (C-18), 54.1 (C-2), 52.5 (C-17), 51.6 (C-3), 45.6 (C-8), 41.2 (C-5), 36.8 (C-6), 34.8 (C-13), 32.0 (C-20), 28.8 (C-21), 25.8 (C-26), 18.6 (C-9), 18.2 (C-10), 18.0 (C-25), 17.8 (C-7), -4.2 (C-24), -4.3 (C-24).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{29}H_{45}NO_5Si^{23}Na)^+$ requires 538.2975, found 538.2957.

$[\alpha]_D^{25}$ = -46.9 (c = 1.00, $CHCl_3$).

methyl (*2R,3S,6aR,11R,11aR,12R,12aR,12bR*)-11-((*tert*-butyldimethylsilyl)oxy)-3,12a-dimethyl-6,13-dioxo-1,2,3,4,7,9,10,11,11a,12,12a,12b-dodecahydro-2,12-methanoazuleno[5,6-a]indolizine-6a(*6H*)-carboxylate (483)



To a solution of diene **483** (10 mM, 950 mg, 1.84 mmol, 1 equiv.) in dry toluene (185 mL) degassed by a stream of argon (30 min) was added Grubbs-Hoveyda 2nd generation catalyst (28.9 mg, 46.0 μmol, 2.5 mol%) and the reaction mixture was heated to reflux with attached condenser while gently bubbled with argon. After stirring for 6 h, the reaction mixture was cooled down, the catalyst was quenched by the addition of potassium isocyanoacetate (110 mg, 0.92 mmol, 0.50 equiv.) in methanol (10 mL) and the reaction mixture was stirred for another 30 min. Volatiles were removed under reduced pressure, and the crude product was purified by column chromatography (dry loading, ethyl acetate:pentane = 35:65). The product of cyclization **484** was obtained as a white solid (871 mg, 97%).

MP: 182 – 188 °C (>99% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.75 – 5.65 (m, 1H, H-14), 4.05 (dd, *J* = 13.5, 8.8 Hz, 1H, H-5a), 3.91 (d, *J* = 5.3 Hz, 1H, H-4), 3.68 (s, 3H, H-18), 3.60 (td, *J* = 8.3, 5.0 Hz, 1H, H-19), 3.55 (dd, *J* = 7.7, 3.6 Hz, 1H, H-16), 3.06 – 2.95 (m, 1H, H-6), 2.57 (dd, *J* = 14.6, 7.2 Hz, 1H, H-13a), 2.51 (d, *J* = 3.8 Hz, 1H, H-2), 2.44 (dd, *J* = 16.3, 7.4 Hz, 1H, H-21a), 2.31 (dd, *J* = 13.5, 9.7 Hz, 1H, H-5b), 2.26 – 2.12 (m, 2H, H-9a, H-21b), 2.14 – 2.07 (m, 1H, H9b), 2.11 – 2.02 (m, 1H, H-13b), 1.90 – 1.85 (m, 1H, H-8), 1.89 – 1.77 (m, 1H, H-20a), 1.61 – 1.49 (m, 1H, H-20b), 1.18 (s, 3H, H-10), 1.03 (d, *J* = 7.0 Hz, 3H, H-7), 0.81 (s, 9H, H-24), 0.01 (s, 6H, H-22).

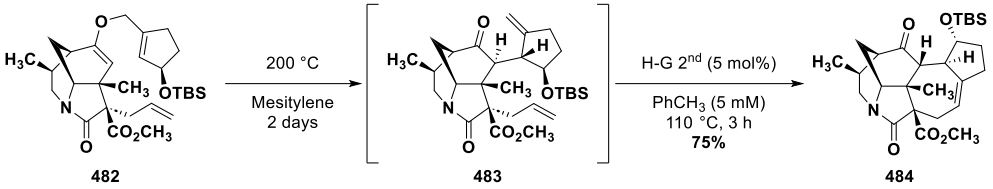
^{13}C NMR (126 MHz, $CDCl_3$) δ: 211.2 (C-10), 172.1 (C-11), 171.5 (C-17), 142.3 (C-15), 117.5 (C-14), 83.7 (C-19), 61.8 (C-4), 59.1 (C-12), 55.1 (C-2), 53.4 (C-3), 52.3 (C-18), 47.1 (C-8), 44.4 (C-16), 41.3 (C-5), 35.4 (C-6), 33.9 (C-20), 29.3 (C-13), 29.1 (C-21), 25.8 (C-24), 23.1 (C-10), 19.4 (C-9), 17.9 (C-23), 17.8 (C-7), -4.2 (C-22), -4.7 (C-22).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2954, 2929, 2857, 1739, 1713, 1693, 1429, 1288, 1133, 837, 775, 732.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{27}H_{42}NO_5Si)^+$ requires 488.2827, found 488.2825.

$[\alpha]^{25}_D$= -60.4 (c = 1.00, $CHCl_3$).

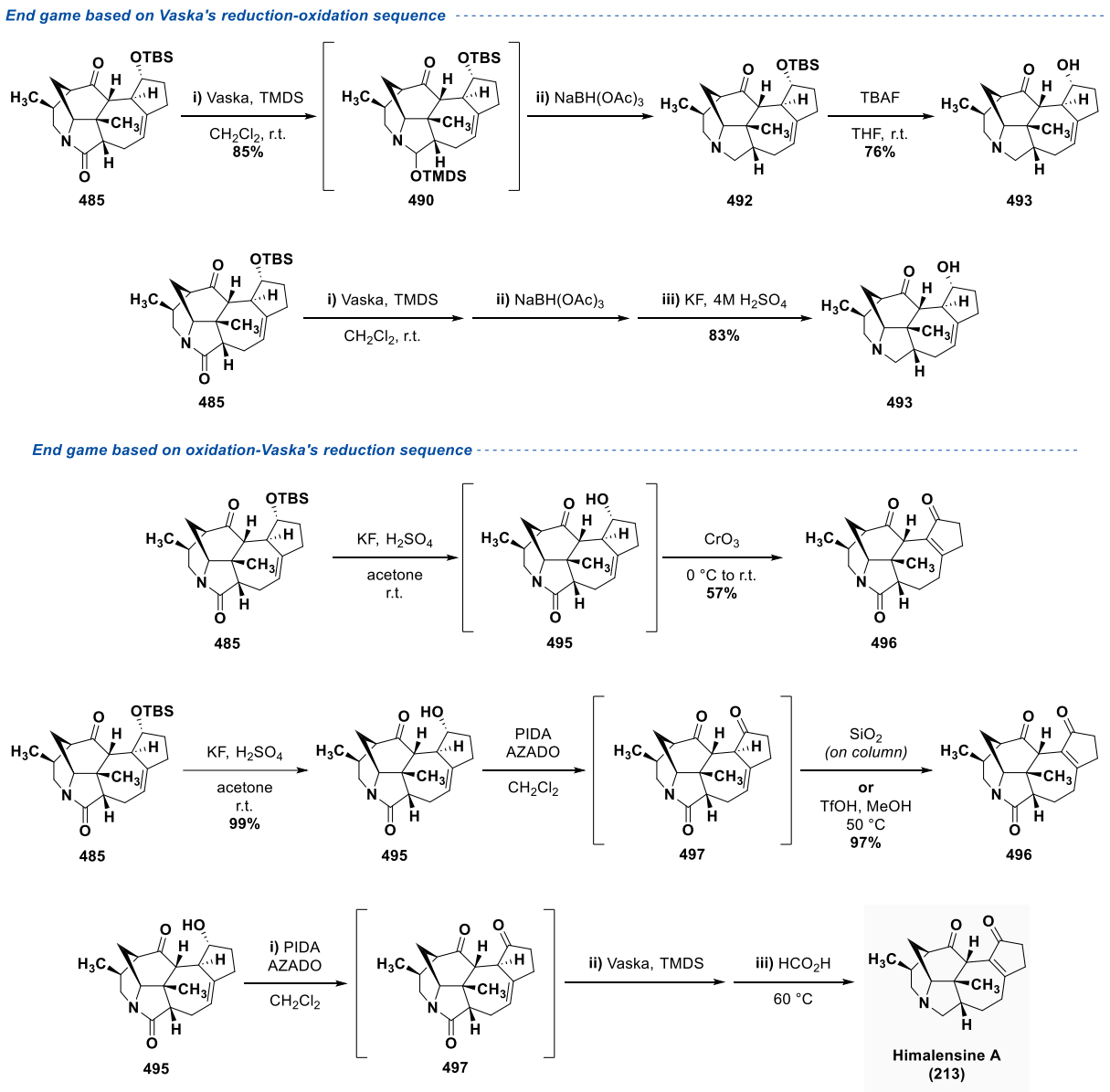
One-pot procedure for synthesis of compound 484 from compound 482



Claisen rearrangement and ring-closing metathesis can be telescoped using the reaction conditions described above.

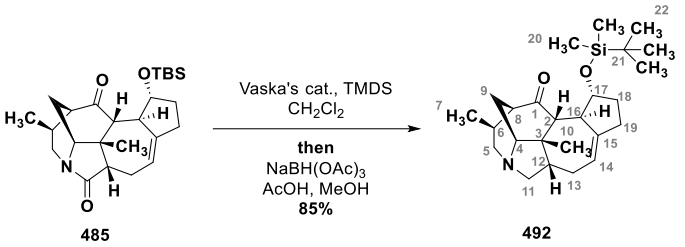
A solution of enol ether **482** (100 mg, 0.194 mmol, 32 mM, 1 equiv.) in mesitylene (6.1 mL) was heated for 2 days at 200 °C. The reaction mixture was then diluted with dry, degassed toluene (32.7 mL) to 5 mM concentration and, after the addition of Grubbs-Hoveyda 2nd generation catalyst (6.1 mg, 9.69 μmol, 5 mol%), heated to 125 °C for 3 h while gently bubbled with argon. The catalyst was then quenched with potassium isocyanoacetate (23.0 mg, 0.194 mmol, 1.00 equiv.) in methanol (5 mL), and the reaction mixture worked up as described above. Product **484** was obtained in unchanged yield as white solid (70.5 mg, 75%).

4.3.3.4 End game



Scheme 4.13. *Overview of the end game.*

***(2R,3S,6aS,11R,11aR,12R,12aS,12bS)*-11-((*tert*-butyldimethylsilyl)oxy)-3,12a-dimethyl-1,2,3,4,6,6a,7,9,10,11,11a,12,12a,12b-tetradecahydro-2,12-methanoazuleno[5,6-a]indolizin-13-one (492)**



Compound **492** was prepared adopting literature the procedure published by Yang *et al.*[38]

To a solution of amide **485** (50 mg, 116 μmol, 1 equiv.) in CH_2Cl_2 (5.0 mL) was added Vaska's catalyst (9.0 mg, 11.6 μmol, 0.10 mol) followed by TMDS (51.5 μL, 290 μmol, 2.50 equiv.) and the resulting solution was stirred for 45 min. MeOH (2.5 mL) was then added carefully added and when no more gas was formed, the reaction mixture was acidified by acetic acid (10 μL, 175 μmol, 1.50 equiv.) followed by addition of $NaBH(OAc)_3$ (49.3 mg, 233 μmol, 2.00 equiv.). After stirring for 30 min another 2 equivalents of $NaBH(OAc)_3$ was added and resulting solution stirred for 3 h. The reaction mixture was then poured onto sat. aq. solution of Na_2CO_3 (15 mL) and extracted with CH_2Cl_2 (5 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate + 2% Et_3N) afforded amine **492** as a yellowish oil (41.2 mg, 85%).

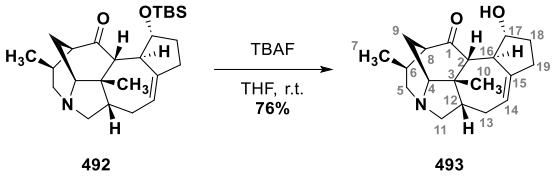
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.57 – 5.48 (m, 1H, H-14), 3.66 – 3.58 (m, 1H, H-17), 3.55 – 3.48 (m, 1H, H-16), 3.31 (d, *J* = 4.6 Hz, 1H, H-4), 2.99 (dd, *J* = 9.4, 6.5 Hz, 1H, H-11a), 2.85 – 2.74 (m, 1H, H-6), 2.75 – 2.66 (m, 1H, H-5a), 2.57 – 2.42 (m, 2H, H-5b, H-19a), 2.33 (t, *J* = 9.9 Hz, 1H, H-11b), 2.28 – 2.17 (m, 1H, H-19b), 2.17 – 2.09 (m, 2H, H-13a, H-2), 2.06 – 1.94 (m, 3H, H-13b, H-9a, H-12), 1.94 – 1.86 (m, 2H, H-8, H-9b), 1.77 (dddd, *J* = 12.0, 7.4, 6.1, 4.6 Hz, 1H, H-18a), 1.66 – 1.53 (m, 1H, H-18b), 1.16 (s, 3H, H-10), 0.97 (d, *J* = 6.6 Hz, 3H, H-7), 0.85 (s, 9H, H-22), 0.06 (s, 3H, H-20), 0.03 (s, 3H, H-20).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 216.2 (C-1), 145.9 (C-15), 117.6 (C-14), 82.7 (C-17), 67.6 (C-4), 59.6 (C-11), 55.4 (C-2), 51.0 (C-3), 49.7 (C-5), 46.6 (C-8), 45.0 (C-16), 44.0 (C-12), 33.9 (C-18), 31.5 (C-6), 30.2 (C-10), 29.6 (C-19), 28.5 (C-13), 25.9 (22), 19.5 (C-9), 19.2 (C-7), 18.1 (C-21), -4.4 (C-20), -4.5 (C-20).

IR (thin film)/cm^{-1} ν_{max}: 2949 (m), 2928 (m), 2855 (m), 1704 (m), 1254 (m), 1091 (s), 835 (s), 774 (s).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{25}H_{41}NO_2Si+H)^+$ requires 416,2979, found 416,2975.

***(2R,3S,6aS,11R,11aR,12R,12aS,12bS)*-11-hydroxy-3,12a-dimethyl-1,2,3,4,6,6a,7,9,10,11,11a,12,12a,12b-tetradecahydro-2,12-methanoazuleno[5,6-a]indolizin-13-one (493)**



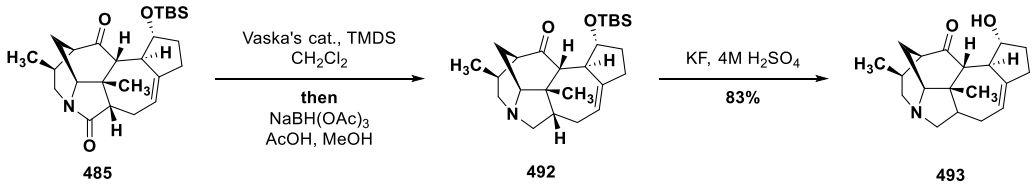
To a solution of protected alcohol **492** (40.0 mg, 96.2 μmol, 1 equiv.) in THF (1.0 mL) was added solution of TBAF (1.0 M, in THF, 115 μL, 115 μmol. 1.20 equiv.) and the resulting solution was stirred for 6 h. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography. The product of deprotection **493** was obtained as yellowish foam (22.1 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.58 (dddt, *J* = 8.6, 7.4, 4.2, 2.0 Hz, 1H, H-14), 3.70 (dt, *J* = 7.5, 5.5 Hz, 1H, H-17), 3.30 (d, *J* = 4.9 Hz, 1H, H-4), 3.25 (ddt, *J* = 8.0, 5.3, 2.6 Hz, 1H, H-16), 3.03 (dd, *J* = 9.5, 6.6 Hz, 1H, H-11a), 2.76 (dd, *J* = 13.7, 7.2 Hz, 1H, H-5a), 2.66 (dq, *J* = 17.3, 6.7 Hz, 1H, H-6), 2.51 (dd, *J* = 13.8, 10.1 Hz, 1H, H-5b), 2.52 – 2.40 (m, 1H, H-19a), 2.38 – 2.16 (m, 3H, H-11b, H-13a, H-19b), 2.12 (d, *J* = 7.7 Hz, 1H, H-2), 2.08 – 1.95 (m, 4H, H-12, H-8, H-18a, H-9a), 1.94 – 1.81 (m, 2H, H-9b, H-13b), 1.61 (ddt, *J* = 12.2, 10.1, 7.3 Hz, 1H, H-18b), 1.17 (s, 3H, H-10), 1.00 (d, *J* = 6.7 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 219.3 (C-1), 146.4 (C-15), 118.0 (C-14), 83.2 (C-17), 66.7 (C-4), 59.0 (C-11), 56.7 (C-2), 50.2 (C-3), 49.2 (C-5), 46.3 (C-8), 46.0 (C-16), 43.4 (C-12), 34.1 (C-18), 32.2 (C-6), 30.4 (C-19), 30.1 (C-10), 27.9 (C-13), 19.4 (C-7), 18.5 (C-9).

HRMS (ES+): exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}NO_2$+H)$^+$ requires 302.2115, found 302.2215.

***(2R,3S,6aS,11R,11aR,12R,12aS,12bS)*-11-hydroxy-3,12a-dimethyl-1,2,3,4,6,6a,7,9,10,11,11a,12,12a,12b-tetradecahydro-2,12-methanoazuleno[5,6-a]indolizin-13-one (493)**



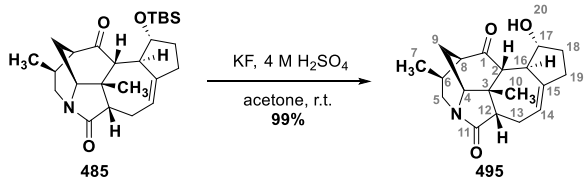
The first step is based on the procedure published by Yang *et al.*[38]

To a solution of amide **485** (50 mg, 116 μmol, 1 equiv.) in CH_2Cl_2 (5.0 mL) was added Vaska's catalyst (9.0 mg, 11.6 μmol, 0.10 mol) followed by TMDS (51.5 μL, 290 μmol, 2.50 equiv.) and the resulting solution was stirred for 45 min.

After the disappearance of all starting material (TLC 60% ethyl acetate in hexane) MeOH (2.5 mL) was then added carefully added and when no more gas was formed, the reaction mixture was acidified by acetic acid (10 μL, 175 μmol, 1.50 equiv.) followed by addition of $NaBH(OAc)_3$ (49.3 mg, 233 μmol, 2.00 equiv.). After stirring for 30 min another 2 equivalents of $NaBH(OAc)_3$ was added and resulting solution stirred for 1.5 h.

After reduction of iminium intermediate was confirmed by MS, KF (33.8 mg, 582 μmol. 5.00 equiv.) and 4M aq. solution of H_2SO_4 (291 μL, 1.16 mmol. 7.00 equiv.) and the resulting mixture was stirred for 5.5 h. The reaction mixture was then poured onto sat. aq. solution of Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography ($MeOH/CHCl_3$ + 2% Et_3N 0:100 to 1:99) afforded aminoalcohol **493** as a yellowish foam (29.1 mg, 83%).

(*2R,3S,6aS,11R,11aR,12R,12aR,12bS*)-11-hydroxy-3,12a-dimethyl-1,3,4,6a,7,9,10,11,11a,12,12a,12b-dodecahydro-2,12-methanoazuleno[5,6-a]indolizine-6,13(*2H*)-dione (495)



To a solution of protected alcohol **485** (50.0 mg, 116 μmol, 1 equiv.) in acetone (1.5 mL) was added KF (33.8 mg, 582 μmol. 5.00 equiv.) and 4 M aq. solution of H_2SO_4 (204 μL, 815 μmol. 7.00 equiv.) and the resulting mixture was stirred for 7.5 h. The reaction mixture was then quenched with sat. aq. solution of Na_2CO_3 (10 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (CH_3CN:CH_2Cl_2 = 60:40) afforded alcohol **495**as a white solid (36.5 mg, 99%).

MP: 220 – 224 °C (decomp., >99% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.63 – 5.56 (m, 1H, H-14), 4.01 (dd, *J* = 13.6, 8.9 Hz, 1H, H-5a), 3.67 (q, *J* = 6.3 Hz, 1H, H-17), 3.52 (d, *J* = 5.6 Hz, 1H, H-4), 3.26 (ddt, *J* = 7.9, 5.3, 2.6 Hz, 1H, H-16), 2.96 – 2.85 (m, 1H, H-6), 2.53 – 2.43 (m, 2H, H-20, H-19a), 2.39 (dt, *J* = 13.7, 7.8 Hz, 1H, H-13a), 2.34 – 2.27 (m, 1H, H-12), 2.27 – 2.14 (m, 4H, H-13b, H-5b, H-19b, H-2), 2.15 (dd, *J* = 14.6, 4.5 Hz, 1H, H-9a), 2.05 (ddd, *J* = 14.7, 5.7, 1.4 Hz, 1H, h-9b), 2.02 – 1.99 (m, 1H, H-8), 1.96 (tt, *J* = 10.1, 3.7 Hz, 1H),

2.00 – 1.91 (m, 1H, H-18a), 1.62 (ddt, *J* = 12.3, 9.5, 7.2 Hz, 1H, H-18b), 1.28 (s, 3H, H-10), 1.04 (d, *J* = 6.9 Hz, 3H, H-7).

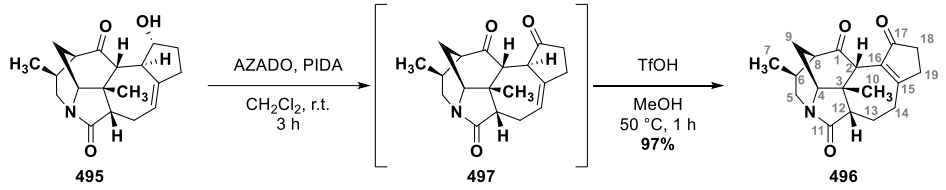
^{13}C NMR (101 MHz, $CDCl_3$) δ: 214.5 (C-1), 175.2 (C-11), 146.0 (C-15), 117.5 (C-14), 83.1 (C-17), 62.1 (C-4), 55.7 (C-2), 50.7 (C-3), 46.6 (C-8), 46.5 (C-12), 46.4 (C-16), 40.6 (C-5), 36.9 (C-6), 34.1 (C-18), 30.2 (C-19), 27.1 (C-10), 25.1 (C-13), 18.2 (C-9), 18.0 (C-7).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3398, 2953, 2926, 2870, 1703, 1668, 3432, 1290, 909.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{19}H_{26}NO_3)^+$ requires 316.1907, found 316.1906.

$[\alpha]_D^{25}$= -126.3 (c = 1.00, $CHCl_3$)

(*2R,3S,6aS,12S,12aR,12bR*)-3,12a-dimethyl-1,2,3,4,6a,7,8,9,10,12,12a,12b-dodecahydro-2,12-methanoazuleno[5,6-a]indolizine-6,11,13-trione (496)



To a solution of alcohol **495** (20.0 mg, 63.4 μmol, 1 equiv.) in CH_2Cl_2 (1.2 mL) was added AZADO (1.0 mg, 6.34 μmol, 10 mol%) fallowed by PIDA (73.6 mg, 253 μmol, 4.00 equiv.) and the resulting solution was stirred for 3 h. *i*-PrOH (200 μL) was then added to quench the excess of PIDA. After stirring for 30 min, the reaction mixture was diluted with MeOH (0.5 mL), acidified with TfOH (50 μL) and stirred for another 1 h at 50 °C. The reaction mixture was then poured onto sat. aq. solution of $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (CH_3CN:CH_2Cl_2 = 50:50) afforded oxy-himalensine A (**496**) as a white solid (19.5 mg, 97%). The spectroscopic data are in agreement with the literature values.[39]

NOTE: Double bond tends to partially migrate on silica gel, however, for full migration, heating with acid in the protic solvent is required.

MP: >240 °C (>99% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.08 (dd, J = 13.6, 9.0 Hz, 1H, H-5a), 3.73 – 3.68 (m, 2H, H-4, H-2), 3.03 (td, J = 8.6, 6.3 Hz, 1H, H-6), 2.81 – 2.72 (m, 1H, H-14a), 2.72 – 2.59 (m, 2H, H-21a, H-21b), 2.55 (t, J = 4.4 Hz, 1H, H-12), 2.51 – 2.39 (m, 2H, H-22a, H-22b), 2.42 – 2.35 (m, 1H, H-9a), 2.29 – 2.20 (m, 2H, H-14a, H-5b), 2.20 – 2.11 (m, 2H, H-13a, H-9b), 2.04 (d, J = 4.6 Hz, 1H, H-8), 1.65 (dddd, J = 14.7, 12.9, 4.1, 1.9 Hz, 1H, H-13b), 1.25 (s, 3H, H-10), 1.03 (d, J = 7.0 Hz, 3H, H-7).

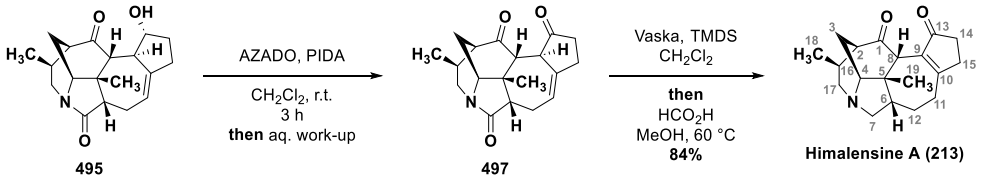
^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.7 (C-1), 208.5 (C-17), 182.0 (C-15), 173.4 (C-11), 134.2 (C-16), 61.9 (C-4), 51.7 (C-12), 50.3 (C-2), 49.1 (C-3), 46.3 (C-8), 40.6 (C-5), 36.2 (C-6), 34.6 (C-18), 31.9 (C-19), 28.2 (C-14), 23.7 (C-10), 20.9 (C-13), 19.6 (C-9), 17.7 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{19}H_{24}NO_3)^+$ requires 314.1751, found 314.1750.

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2956, 2925, 2871, 1689, 1654, 1433, 1289, 1258, 918, 734.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -70.1 (c = 0.10, $CHCl_3$), literature values: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -69.8 (c = 0.1, $CHCl_3$),[39] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -67.4 (c = 0.2, MeOH),[40] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -65 (c = 0.12, $CHCl_3$).[41]

(*2R,3S,6aS,12S,12aS,12bR*)-3,12a-dimethyl-1,3,4,6,6a,7,8,9,10,12,12a,12b-dodecahydro-2,12-methanoazuleno[5,6-a]indolizine-11,13(2*H*)-dione (Himalensine A) (213)



Reduction of intermediate **495** was accomplished by adopting the procedure previously reported by our group.[39]

To a solution of alcohol **495** (6.0 mg, 19.0 μmol, 1 equiv.) in CH_2Cl_2 (0.3 mL) was added AZADO (0.2 mg, 1.52 μmol, 8 mol%) fallowed by PIDA (22.1 mg, 4.00 equiv.) and the resulting solution was stirred for 3 h. The reaction mixture was then poured onto sat. aq. solution of $Na_2S_2O_3$ (7 mL) and extracted with CH_2Cl_2 (4 x 7 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

The obtained residue was dissolved in toluene (0.5 mL), and Vaska's catalyst (1.5 mg. 1.90 μmol, 0.10 equiv.) was added. TMDS (33.6 μL, 190 μmol, 10.0 equiv.) was added dropwise and the reaction was monitored by TLC after the addition of every drop (evolution of gas was observed). After full consumption of intermediate **25**, formic acid (2 mL) and MeOH (0.5 mL) were added, and the resulting mixture was heated to 60 °C for 22 h. The reaction mixture was then diluted with distilled water (10 mL) and basified by the careful addition of solid K_2CO_3. The resulting mixture was extracted with CH_2Cl_2 (4 x 10 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (MeOH:$CHCl_3$:Et_3N 0:98:2 to 0.2:97.8:2) afforded Himalensine A (**213**) as a yellowish foam (4.8 mg, 84%).

NOTE: It was reported,[39] that NMR shifts of Himalensine A depend on the purification method, solvent and time after purification. Residual acid from silica/chloroform is causing partial protonation

of himalensine A and shift of the peaks in ^{1}H NMR downfield. ^{1}H NMR spectrum of our synthetic sample is identical to ^{1}H NMR spectrum of a free-base form of himalensine A reported by Shi.[39]

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.63 (s, 1H, H8), 3.45 (d, *J* = 4.7 Hz, 1H, H-4), 2.86 (dd, *J* = 9.0, 6.7 Hz, 1H, H-7), 2.83 – 2.71 (m, 3H, H-7a, H-16a, H-17a), 2.71 – 2.67 (m, 1H, H-15a), 2.66 – 2.57 (m, 2H, H-15b, H-11a), 2.52 (dd, *J* = 13.4, 9.2 Hz, 1H, H-17b), 2.50 – 2.45 (m, 1H, H-14a), 2.42 (ddd, *J* = 18.9, 6.5, 2.9 Hz, 1H, H-14b), 2.30 – 2.24 (m, 1H, H-6), 2.24 – 2.18 (m, 1H, H-11b), 2.11 (dd, *J* = 14.5, 4.1 Hz, 1H, H-3a), 2.06 (ddd, *J* = 14.6, 4.7, 1.8 Hz, 1H, H-3b), 2.03 – 1.99 (m, 1H, H-2), 1.83 – 1.75 (m, 2H, H-12a, H-12b), 1.11 (s, 3H, H-19), 0.97 (d, *J* = 6.6 Hz, 3H, H-18).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 214.5 (C-1), 208.7 (C-13), 179.9 (C-10), 135.9 (C-9), 65.0 (C-4), 54.9 (C-7), 51.6 (C-8), 49.6 (C-17), 48.9 (C-6), 48.3 (C-5), 46.1 (C-2), 34.6 (C-14), 32.0 (C-15), 31.9 (C-16), 28.1 (11), 26.2 (C-19), 22.9 (C-12), 20.4 (3), 19.1 (C-1).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{19}H_{26}NO_2)^+$ requires 300.1958, found 300.1956.

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2953, 2918, 2867, 2849, 1699, 1657, 1440, 1280, 1255.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -91.9 (c = 0.10, MeOH), literature values: $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -44.0 (c = 0.10, MeOH),[42] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -74.0 (c = 0.12, MeOH),[39] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -71.2 (c = 0.1, MeOH),[40] $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$= -55 (c = 0.03, $CHCl_3$).[41]

Table 4.7. *NMR data comparison of isolated and synthetic Himalensine A.*

		^{1}H NMR data					^{13}C NMR data				
Atom		**Synthesized**	**Isolated[42]**	**Diff.**	**Synthesized (Shi)[39]**	**Diff.**	**Synt.**	**Isol.[42]**	**Diff.**	**Synt. (Shi)[39]**	**Diff**
1		-	-	-	-	-	214.5	214.4	0.1	214.5	0.0
2		2.01, m, 1H	2.04, brs	-0.03	2.02, app dp (4.2, 1.2 Hz)	-0.01	46.1	46.1	0.0	46.1	0.0
3	α	2.11, dd (14.5, 4.1 Hz)	2.14, dd (14.8, 3.5)	-0.03	2.11, dd (14.7, 4.4 Hz)	0.00	20.4	20.3	0.1	20.4	0.0
	β	2.06, ddd (14.6, 4.7, 1.8 Hz)	2.08, br dd (14.8, 4.9)	-0.02	2.06, ddd (14.7, 5.0, 1.8 Hz)	0.00					
4		3.45, d (4.7 Hz)	3.52, br s	-0.07	3.46, d (5.2 Hz)	-0.01	65.0	65.1	-0.1	65.0	0.0
5		-	-	-	-	-	48.3	48.3	0.0	48.3	0.0
6		2.27, m	2.30, m	-0.03	2.29 – 2.20, m	0.02*	48.9	48.8	0.1	48.9	0.0
7	α	2.81, m	2.80, m	0.01	2.84 – 2.73, m, 3H	0.02*	54.9	54.9	0.0	54.9	0.0
	β	2.86 (dd, *J* = 9.0, 6.7 Hz, 1H)	2.92, m	-0.06	2.87, dd (9.0, 6.7 Hz)	-0.01					
8		3.63, s	3.65, s	-0.02	3.63, s	0.00	51.6	51.7	-0.1	51.7	-0.1
9		-	-	-	-	-	135.9	135.8	0.1	135.9	0.0
10		-	-	-	-	-	179.9	179.9	0.0	179.9	0.0
11	α	2.62, m	3.65, s	-0.03	2.68 – 2.55, m	0.00*	28.1	28.1	0.0	28.1	0.0
	β	2.21, m	2.23, m	-0.02	2.29 – 2.20, m	-0.04*					
12		1.80, m, 2H	1.80, m, 2H	0.00	1.81 – 1.78, m, 2H	0.00*	22.9	22.9	0.0	23.0	-0.1
13		-	-	-	-	-	208.7	208.7	0.0	208.7	0.0
14	α	2.48, m	2.49, ddd (18.9, 6.5, 2.5)	-0.01	2.48, m	0.00	34.6	34.6	0.0	34.6	0.0
	β	2.42, ddd (18.9, 6.5, 2.9 Hz)	2.43, ddd (18.9, 6.5, 2.5)	-0.01	2.42, ddd (18.8, 6.7, 2.6 Hz)	0.00					
15	α	2.69, m	2.71, m	-0.02	2.84 – 2.73, m, 3H	-0.01*	32.0	32.0	0.0	32.0	0.0
	β	2.65, m	2.64, m	0.01	2.68-2.55, m	0.03*					
16		2.76, m	2.74, m	0.02	2.84 – 2.73, m, 3H	-0.03*	31.9	31.8	0.1	31.9	0.0
17	α	2.71, m	2.82, dd (14.1, 7.1)	-0.09	2.70, dddd (18.8, 6.9, 2.6, 1.2 Hz)	0.01	49.6	49.6	0.0	49.6	0.0
	β	2.52, dd (13.4, 9.2 Hz)	2.56, dd (14.1, 10.3)	-0.04	2.52, dd (14.1, 9.1 Hz)	0.00					
18		0.97, d (6.6 Hz)	0.99, d (6.8)	-0.02	0.97, d (6.8 Hz)	0.00	19.1	19.2	-0.1	19.1	0.0
19		1.11, s	1.12, s	-0.01	1.11, s	0.00	26.2	26.3	-0.1	26.3	-0.1

NOTE: It was reported,[39] that NMR shifts of himalensine A depend on the purification method, solvent and time after purification. Residual acid from silica/chloroform is causing partial protonation of himalensine A and shift of the peaks in ^{1}H NMR downfield. ^{1}H NMR spectrum of our synthetic sample is identical to ^{1}H NMR spectrum of a free-base form of himalensine A reported by Shi.[39] The centres of multiplets in ^{1}H NMR spectrum were determined using HSQC. *The differences in ^{1}H NMR shifts for multiples were calculated by using their centres, obtained by equation: centre = (left boundary + right boundary)/2.

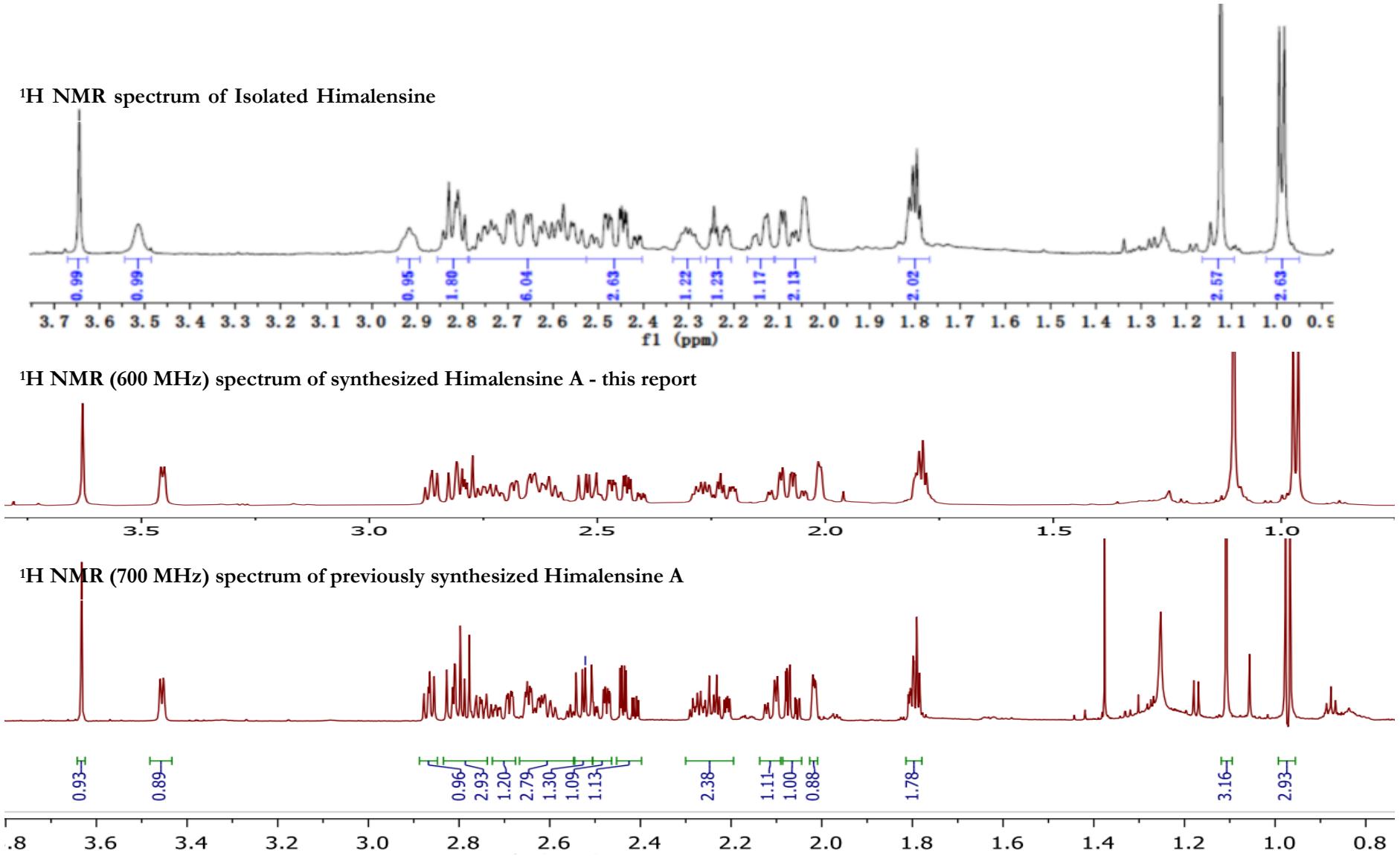
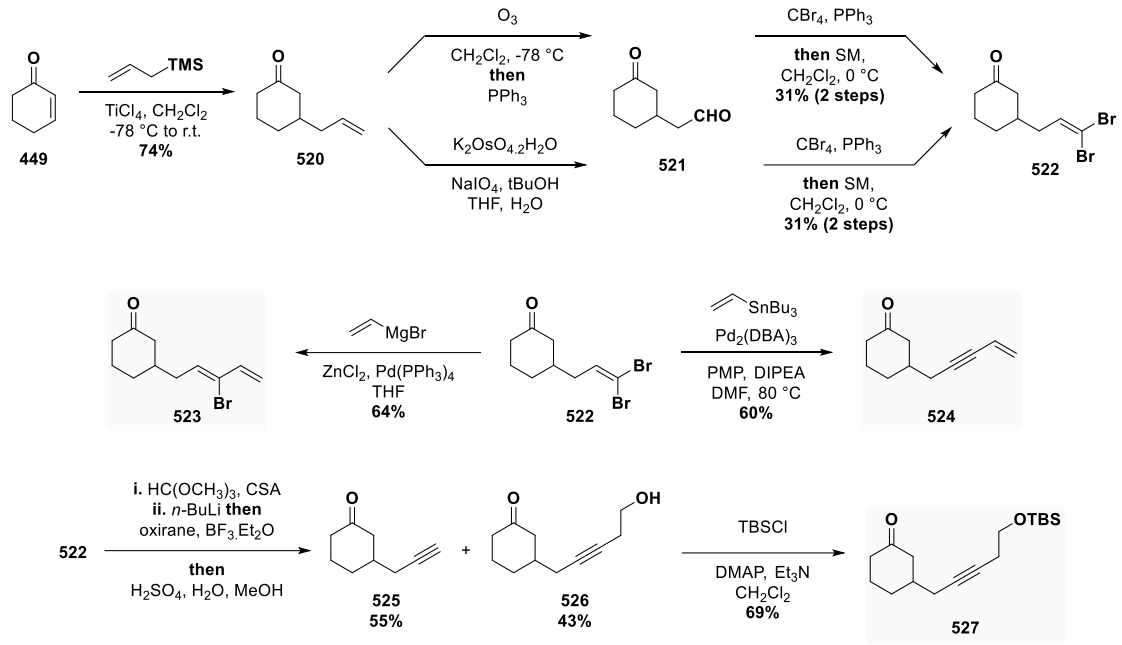


Figure 4.3. *Comparison of ¹H NMR spectra of isolated[42] (top), synthesized – this work (middle) and previously synthesized[39] (bottom) himalensine A.*

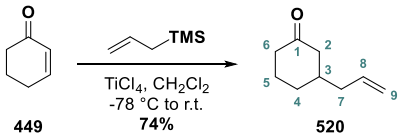
4.3.4 Synthetic studies towards Daphniyunnine B and Daphlongamine E

4.3.4.1 Synthesis and reactivity of the model system



Scheme 4.14. *Synthesis of the model system.*

3-allylcyclohexan-1-one (520)



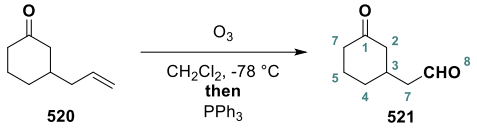
Compound **520** was prepared according to a literature procedure published by Clive *et. al.*[43]

To a stirred solution of cyclohexenone (2.00 g, 20.8 mmol, 1 equiv.) in dry CH_2Cl_2 (50 mL) at -78 °C was dropwise added $TiCl_4$ (2.62 mL, 23.9 mmol, 1.15 equiv.) over 20 min using syringe pump. After stirring at this temperature for 10 min, a solution of allyltrimethylsilane (3.64 mL, 22.9 mmol, 1.10 equiv.) in dry CH_2Cl_2 (17 mL) was added dropwise over 15 min using syringe pump and the resulting solution was stirred for 90 min at -78 °C. The reaction mixture was then warmed up to room temperature and quenched with water (33 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 5:95) afforded compound **520** as a colourless oil (2.13 g, 74%). The spectroscopic data are in agreement with the literature values.[44]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.81 – 5.66 (m, 1H, H-8), 5.06 – 4.94 (m, 2H, H-9), 2.45 – 2.31 (m, 2H, CH_2-A, CH_2-B), 2.30 – 2.18 (m, 1H, CH_2-B), 2.15 – 1.96 (m, 4H, 2xCH_2-C, CH_2-A, CH_2-D), 1.94 – 1.78 (m, 2H, CH_2-E, H-3), 1.72 – 1.55 (m, 1H, CH_2-D), 1.41 – 1.14 (m, 1H, CH_2-E).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.8 (C-1), 135.8 (C-7), 116.9 (C-8), 47.9 (CH_2-A), 41.5 (CH_2-B), 40.9 (CH_2-C), 38.9 (C-3), 31.0 (CH_2-E), 25.3 (CH_2-D).

2-(3-oxocyclohexyl)acetaldehyde (521)

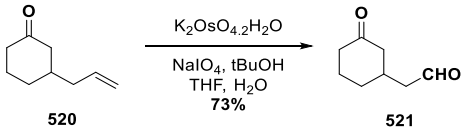


A stirred solution of alkene **520** (500 mg, 3.62 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) at -78 °C was bubbled with ozone until a persistent blue colour was observed. After removing the excess of ozone by bubbling the reaction mixture with oxygen for 10 min, the reaction mixture was quenched with a solution of PPh_3 (949 mg, 3.62 mmol, 1.00 equiv.), and allowed to warm to room temperature overnight. After removal of the volatiles under reduced pressure (30 °C), the obtained residue was dissolved in Et_2O and the formed white precipitate was filtered off. If the formation of more precipitate was observed during the concentration of the filtered solution, the filtration was repeated. The crude aldehyde aldehyde **521** was obtained as a yellowish oil and used in the next step without further purification. The spectroscopic data are in agreement with the literature values.[45]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.74 (t, *J* = 1.6 Hz, 1H, H-8), 2.54 – 2.33 (m, 5H, 2xCH_2-A, CH_2-B, CH_2-C, H-3), 2.32 – 2.18 (m, 1H, CH_2-C), 2.15 – 1.98 (m, 2H, CH_2-B, CH_2-D), 1.94 (dddt, *J* = 13.3, 4.7, 3.1, 1.5 Hz, 1H, CH_2-E), 1.71 (dtdd, *J* = 13.6, 12.1, 4.8, 3.6 Hz, 1H, CH_2-D), 1.50 – 1.34 (m, 1H, CH_2-E).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.5 (C-1), 200.9 (C-2), 50.2 (CH_2-A), 47.7 (CH_2-B), 41.3 (CH_2-C), 33.4 (C-3), 29.9 (CH_2-E), 25.1 (CH_2-D).

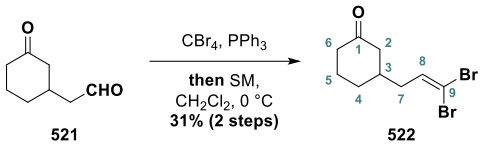
Alternative procedure for preparation of compound 521.



To a stirred solution of alkene **520** (437 mg, 3.16 mmol, 1 equiv.) in THF (14.2 mL) and *t*-BuOH (1.9 mL) was added $K_2OsO_4.2H_2O$ (11.7 mg, 31.6 μmol, 1.00 mol%), followed by $NaIO_4$ (2.03 g, 9.49 mmol, 3.00 equiv.) as a suspension in water (4.75 mL). After stirring for 1 h at room temperature, the reaction

mixture was poured onto water (30 mL) and extracted with Et_2O (3 x 50 mL). The combined organic phases were washed with water (50 mL) and then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Aldehyde **521** was obtained as a dark oil (320 mg, 73%) in sufficient purity and was used in next step without further purification.

3-(3,3-dibromoallyl)cyclohexan-1-one (522)



To a stirred solution of CBr_4 (1.77 g, 5.35 mmol, 2.5 equiv.) in CH_2Cl_2 (14 mL) at 0 °C was added solution of PPh_3 (2.81 g, 10.7 mmol, 5.00 equiv.) in CH_2Cl_2 (14 mL) and the resulting mixture was stirred for 40 min at this temperature. Next, a solution of aldehyde **521** (300 mg, 2.14 mmol, 1 equiv.) in CH_2Cl_2 (12 mL) was added and the resulting mixture was allowed to warm to room temperature. After stirring overnight, the reaction mixture was concentrated under reduced pressure, the obtained suspended in Et_2O, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O:pentane = 20:80 to 30:70) afforded compound **522** as a yellowish oil (199 mg, 31%).

NOTE: Using aldehyde **521** prepared by ozonolysis of alkene **520** (500 mg), provided compound **522** in the same yield (31%, over 2 steps).

Alternative procedure: PPh_3 (713 mg, 2.72 mmol, 3.00 equiv.), CBr_4 (301 mg, 2.72 mmol, 3.00 equiv.) and zinc (178 mg, 2.72 mg, 3.00 equiv.) were suspended in dry CH_2Cl_2 (20 mL) and the resulting suspension was stirred in dark for 24 h. Solution of aldehyde **521** (prepared from 127 mg of alkene **520** using osmium-based procedure) in CH_2Cl_2 (7 mL) was added and the reaction mixture was stirred for another 24 h. The volatiles were removed under reduced pressure and the obtained residue processed as described above to provide product **522** (130 mg, 44% over 2 steps).

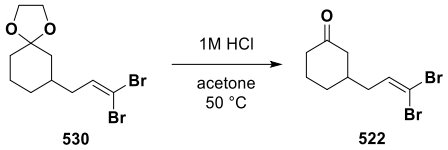
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.39 (t, *J* = 7.5 Hz, 1H, H-8), 2.49 – 2.33 (m, 2H, CH_2-A, CH_2-B), 2.34 – 2.24 (m, 1H, CH_2-B), 2.24 – 2.02 (m, 4H, 2xCH_2-C, CH_2-A, CH_2-D), 2.02 – 1.86 (m, 2H, H-3, CH_2-E), 1.74 – 1.57 (m, 1H, CH_2-D), 1.48 – 1.33 (m, 1H, CH_2-E).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.8 (C-1), 135.9 (C-8), 90.7 (C-9), 47.7 (CH_2-A), 41.4 (CH_2-B), 39.7 (CH_2-C), 38.3 (C-3), 30.1 (CH_2-E), 25.2 (CH_2-D).

IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 2937, 2867, 1712, 1147, 1426, 1347, 1313, 1282, 1225, 1108, 1060, 831, 778.

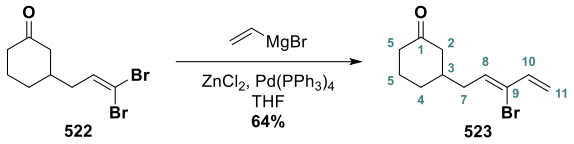
HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_9H_{13}Br_2O)^+$ requires 294.9328, found 294.9328.

Alternative preparation of compound 522 by hydrolysis of acetal 530



A solution of acetal **530** (500 mg, 1.47 mmol, 1 equiv.) in acetone (7.4 mL) and 1 M aq. HCl (1.5 mL) was stirred for 2 h at 50 °C. The reaction mixture was then neutralized with sat. aq. solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (Et_2O:pentane = 15:85) afforded compound **522** as a colourless oil (410 mg, 94%).

(Z)-3-(3-bromopenta-2,4-dien-1-yl)cyclohexan-1-one (523)



Compound **523** was prepared adopting procedure published by Ogasawara *et al.*[46]

A flask charged with $ZnCl_2$ (548 mg, 4.02 mmol, 3.00 equiv.) was evacuated and backfilled with argon (3x). The content of the flask was then suspended in degassed dry THF (8.0 mL) and cooled to 0 °C. Next, a solution of vinylmagnesium bromide (1.0 M, 4.0 mL, 4.0 mmol, 3.00 equiv.) was added dropwise and after stirring of the resulting mixture for 40 min a solution of compound **522** (397 mg, 1.34 mmol, 1 equiv.) and $Pd(PPh_3)_4$ (38.7 mg, 33.5 μmol, 2.5 mol%) in THF (2.0 + 2.0 mL) was added. NMR analysis of the reaction mixture after 5 h revealed full consumption of the starting material and the reaction was quenched with sat. aq. solution of NH_4Cl (15 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (dry loading, Et_2O:pentane = 10:90 to 15:85) afforded compound **523** as a colourless oil (210 mg, 64%).

NOTE: Starting material **522** and product **523** has the same R_f and therefore the reaction has to be monitored by NMR.

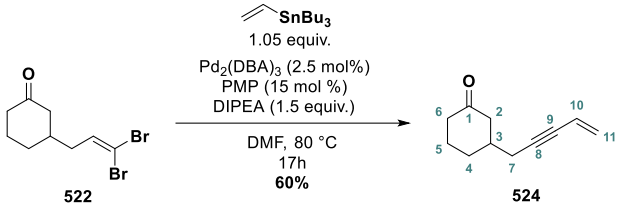
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.43 – 6.24 (m, 1H, H-10), 5.96 (dd, *J* = 7.6, 6.8 Hz, 1H, H-8), 5.56 (d, *J* = 16.3 Hz, 1H, H-11), 5.21 (d, *J* = 10.4 Hz, 1H, H-11), 2.52 – 2.32 (m, 4H. CH_2-A, CH_2-B. 2xCH_2-C), 2.27 (dddd, *J* = 14.1, 12.5, 6.1, 1.2 Hz, 1H, CH_2-B), 2.15 – 2.02 (m, 2H, CH_2-A, CH_2-D), 2.01 – 1.87 (m, 2H, H-3, CH_2-E), 1.65 (dtdd, *J* = 13.4, 12.2, 4.8, 3.4 Hz, 1H, CH_2-D), 1.50 – 1.34 (m, 1H, CH_2-E).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.3 (C-1), 135.8 (C-10), 131. 8 (C-8), 127.8 (C-9), 118.3 (C-11), 48.0 (CH_2-A), 41. 5 (CH_2-B), 39.0 (C-3), 38.3 (CH_2-C), 31.2 (CH_2-E), 25.3 (CH_2-D).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2936, 2868, 1712, 1632, 1225, 974, 911.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{11}H_{16}BrO)^+$ requires 243.0379, found 243.0376.

3-(pent-4-en-2-yn-1-yl)cyclohexan-1-one (524)



Compound **524** was prepared adopting procedure published by Wang *et al.*[47]

A flask charged with compound **522** (500 mg, 1.69 mmol, 1 equiv.), Pd_2dba_3 (38.7 mg, 42.2 μmol, 2.5 mol%) and tris(4-methoxyphenyl)phosphine (89.3 mg, 0.254 mmol, 15 mol%) was evacuated and backfilled with argon (3x). Degassed dry DMF (8.5 mL) was then added followed by DIPEA (452 μL, 2.53 mmol, 1.50 equiv.) and tributyl(vinyl)stannane (456 μL, 1.69 mmol, 1.00 equiv.). The reaction mixture was evacuated and backfilled with argon (3x) and then heated to 80 °C for 19 h. Solid KF was then added and after stirring for additional 30 min, the reaction mixture was diluted with ethyl acetate and washed with sat. aq. solution of NH_3 (2 x 10 mL), the organic phase dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (silica:K_2CO_3, 10:1, Et_2O:pentane = 15:85 to 25:75) afforded compound **524** as a colourless oil (164 mg, 60%).

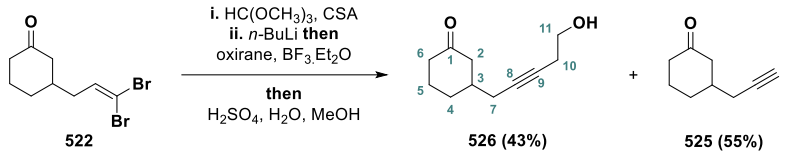
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (ddt, *J* = 17.6, 11.0, 2.1 Hz, 1H, H-10), 5.60 – 5.51 (m, 1H, H-11), 5.40 (dd, *J* = 11.0, 2.2 Hz, 1H, H-11), 2.48 (ddt, *J* = 13.9, 4.1, 2.1 Hz, 1H, CH_2-A), 2.42 – 2.32 (m, 3H, CH_2-B, 2xCH_2-C), 2.32 – 2.13 (m, 2H, CH_2-A, CH_2-B), 2.06 (dddd, *J* = 13.0, 10.2, 7.0, 3.7 Hz, 1H, CH_2-D), 2.03 – 1.89 (m, 2H, H-3, CH_2-E), 1.66 (dtdd, *J* = 13.3, 12.4, 4.7, 3.2 Hz, 1H, CH_2-D), 1.58 – 1.40 (m, 1H, CH_2-E).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.2 (C-1), 126.2 (C-11), 117.4 (C-10), 87.8 (C-8), 81.6 (C-9), 47.3 (CH_2-A), 41.2 (CH_2-B), 38.3 (C-3), 30.6 (CH_2-D), 26.5 (CH_2-C), 25.0 (CH-E).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2942, 1715, 1449, 1226, 978, 922.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{11}H_{15}O)^+$ requires 163.1117, found 163.1112.

3-(5-hydroxypent-2-yn-1-yl)cyclohexan-1-one (526)



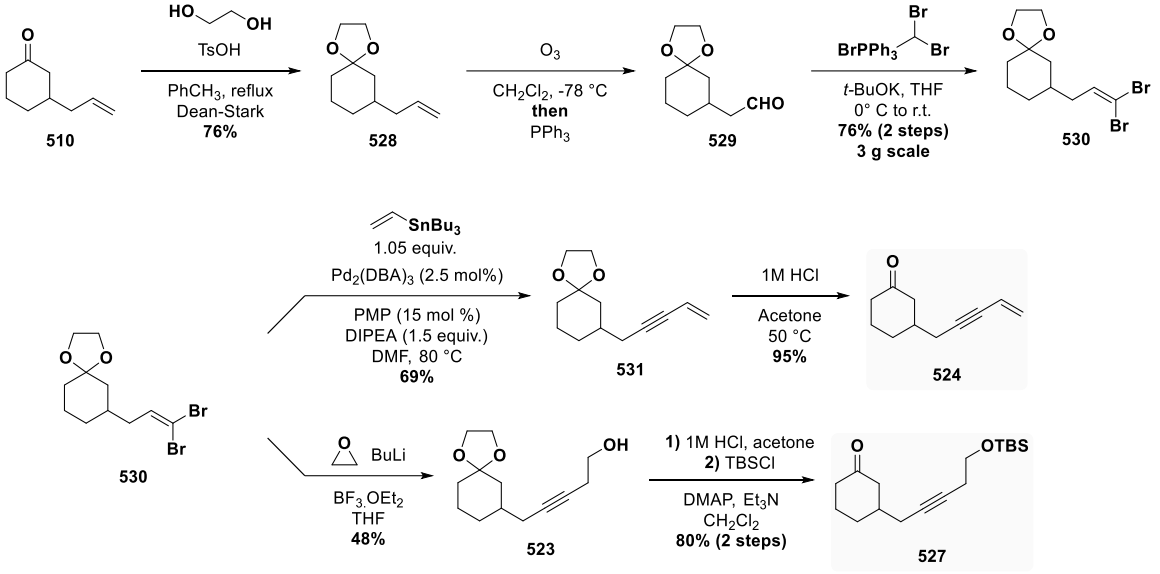
To a solution of ketone **522** (64.5 mg, 218 µmol, 1 equiv.) in MeOH (1.0 mL) was added trimethyl orthoformate (72 µL, 654 µmol, 3.00 equiv.) and CSA (2.5 mg, 10.9 µmol, 5 mol %). After stirring for 30 min at room temperature, the reaction mixture was concentrated under reduced pressure and then azeotroped from toluene.

The obtained residue was dissolved in THF (1.0 mL) and, after cooling to -78 °C, treated with a 2.5 M solution of *n*-BuLi (218 µL, 545 µmol, 3.00 equiv.). The resulting mixture was stirred at -78 °C for 60 min before $BF_3.OEt_2$ (84 µL, 676 µmol, 3.10 equiv.) was added. After stirring for another 30 min at -78 °C, a 2.5 M solution of oxirane in THF (174 µL, 436 µmol, 2.00 equiv.) was added, and the reaction mixture was allowed to warm to room temperature over 40 min.

The reaction mixture was diluted with MeOH (1.0 mL) and water (1.0 mL), 4 M aq. solution of H_2SO_4 (0.2 mL) was added, and the reaction was stirred at room temperature for 20 min. The reaction mixture was then neutralised with sat. aq. solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O:pentane = 30:70 to 50:50) afforded alcohol **526** as a colourless oil (16.9 mg, 43%) and alkyne **525** as a colourless oil (16.4 mg, 55%).

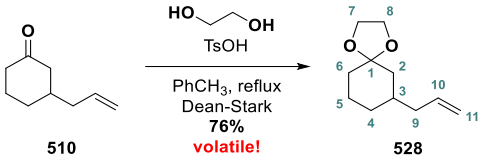
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.68 (t, *J* = 6.3 Hz, 2H, H-11z), 2.51 – 2.40 (m, 3H, CH_2-A, CH_2-F), 2.40 – 2.32 (m, 1H, CH_2-B), 2.30 – 2.20 (m, 3H, CH_2-B, CH_2-D), 2.16 (ddd, *J* = 14.0, 11.8, 1.2 Hz, 1H, CH_2-A), 2.11 – 2.03 (m, 1H, CH_2-E), 2.02 – 1.89 (m, 2H, H-3, CH_2-C), 1.87 (br s, 1H, OH), 1.66 (dtdd, *J* = 13.4, 12.3, 4.8, 3.4 Hz, 1H, CH_2-E), 1.48 (dtd, *J* = 13.4, 11.6, 3.5 Hz, 1H, CH_2-C).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.5 (C-1), 79.4 (C-8), 79.0 (C-9), 61.5 (C-11), 47.3 (CH_2-A), 41.3 (CH_2-B), 38.3 (C-3), 30.6 (CH_2-C), 25.9 (CH_2-D), 25.0 (CH_2-E), 23.3 (CH_2-E).



Scheme 4.15. *Synthesis of the model system (part II).*

7-allyl-1,4-dioxaspiro[4.5]decane (528)



A solution of ketone **510** (3.00 g, 21.7 mmol, 1 equiv.), ethylene glycol (12.1 mL, 217 mmol, 10.0 equiv.) and TsOH.H_2O (187 mg, 1.09 mmol, 5mol%) were refluxed for 12 h in toluene (72 mL) with a Dean-Stark trap. The reaction mixture was then neutralized with sat. aq. solution of $NaHCO_3$ (10 mL), diluted with brine (50 mL) and extracted with Et_2O (2 x 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O:pentane = 3:97 to 6:94) afforded compound **528** as a colourless oil (2.99 g, 76%).

NOTE: Compound **528** is slightly volatile, and its traces were found in receiving flask of rotavap during evaporation of the solvents after work up or column chromatography.

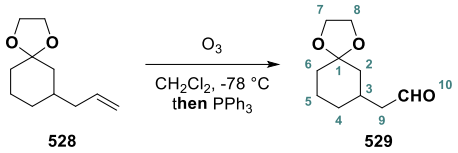
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (ddt, *J* = 16.3, 10.6, 7.1 Hz, 1H, H-10), 5.05 – 4.93 (m, 2H, H-11), 3.99 – 3.86 (m, 4H, H-7, H-8), 1.98 (dddt, *J* = 7.3, 4.9, 3.7, 1.2 Hz, 2H, 2xCH_2-A), 1.81 – 1.57 (m, 5H, H-3, CH_2-B, CH_2-C, CH_2-D, CH_2-E,), 1.57 – 1.34 (m, 2H, CH_2-C, CH_2-D), 1.24 – 1.11 (m, 1H, CH_2-B), 0.94 – 0.78 (m, 1H, CH_2-D).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.1 (C-10), 116.0 (C-11), 109.5 (C-1), 64.4 (C-7), 64.3 (C-8), 41.5 (CH_2-A), 41.4 (CH_2-B), 35.5 (C-3), 35.0 (CH_2-C), 31.7 (CH_2-D), 23.3 (CH_2-D).

IR (neat) $\tilde{\nu}_{max}$/cm^{-1}: 2976, 2936, 2881, 2847, 1447, 1353 1236, 1166, 1071, 967, 924, 913.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{11}H_{19}O_2)^+$ requires 183.1380, found 183.1382.

2-(1,4-dioxaspiro[4.5]decan-7-yl)acetaldehyde (529)

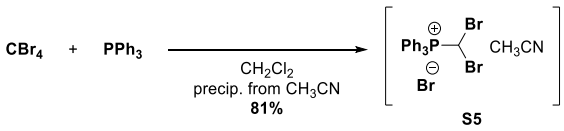


Compound **528** (2.00 g, 11.0 mmol, 1 equiv.) was ozonolysed using the procedure applied for the the ozonolysis of compound **520**, providing aldehyde **529** as a colourless oil (2.89 g, 2.02 g teor., assume quant.). Aldehyde **529** was used in next step without further purification. The spectroscopic data are in agreement with the literature values.[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.72 (t, *J* = 2.2 Hz, 1H, H-10), 3.95 – 3.85 (m, 4H, H-7, H-8), 2.37 – 2.28 (m, 2H, H-9), 2.32 – 2.12 (m, 1H, H-3), 1.80 – 1.64 (m, 4H, CH_2-B, CH_2-C, CH_2-D, CH_2-E), 1.64 – 1.47 (m, 1H, CH_2-E), 1.47 – 1.34 (m, 1H, CH_2-C), 1.24 (dd, *J* = 12.8, 11.9 Hz, 1H, CH_2-B), 1.03 – 0.88 (m, 1H, CH_2-D).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.1 (C-10), 108.8 (C-1), 64.4 (C-7), 64.3 (C-8), 50.6 (C-9), 41.4 (CH_2-A), 34.7 (CH_2-B), 31.7 (CH_2-C), 30.5 (C-3), 23.0 (CH_2-D).

Dibromomethyltriphenylphosphonium Bromide·CH_3CN (S5)



Compound **S5** was prepared according to a literature procedure published by Mattay *et. al.*[49]

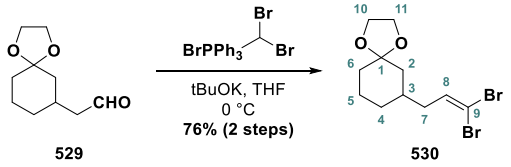
A solution of triphenylphosphine (17.0 g, 64.8 mmol, 2.15 equiv.) and tetrabromomethane (10.0 g, 30.15 mmol, 1 equiv.) in CH_2Cl_2 (160 mL) was stirred at room temperature for 30 min and the reaction was then quenched with water (50 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. To the obtained residue was added acetonitrile (100 mL) and the mixture was sonicating for 30 min. The precipitated white solid was filtered on sintered funnel, washed with acetonitrile (50 mL) and dried under high vacuum overnight. Compound **S5** was obtained as a white solid (13.5 g, 81%). The spectroscopic data are in agreement with the literature values.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (d, *J* = 2.4 Hz, 1H), 8.28 – 7.99 (m, 6H), 7.96 – 7.78 (m, 3H), 7.78 – 7.62 (m, 6H), 2.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 135.5 (d, *J* = 3.1 Hz), 134.7 (d, *J* = 9.9 Hz), 130.1 (d, *J* = 13.0 Hz), 115.9 (d, *J* = 88.8 Hz), 29.5 (d, *J* = 47.6 Hz), 1.8.

^{31}P NMR (162 MHz, $CDCl_3$) δ: 32.5.

7-(3,3-dibromoallyl)-1,4-dioxaspiro[4.5]decane (530)



To a suspension of Wolkoff's reagent (S5) (9.15 g, 16.5 mmol, 1.50 equiv.) was added 1.0 M solution *t*-BuOK (15.4 mL, 15.4 mmol, 1.40 equiv.) in THF at 0 °C and the resulting mixture was allowed to warm up to room temperature. After stirring for 30 min, a solution of aldehyde **529** (assume 11.0 mmol 1 equiv.) in THF (17 + 3 mL) was added dropwise at 0 °C. After 10 min, the reaction mixture was quenched with sat. aq. solution of NH_4Cl (50 mL) and extracted with Et_2O (3 x 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (dry loading, Et_2O:pentane = 15:85) afforded compound **530** as a yellowish oil (2.82 g, 76% over 2 steps).

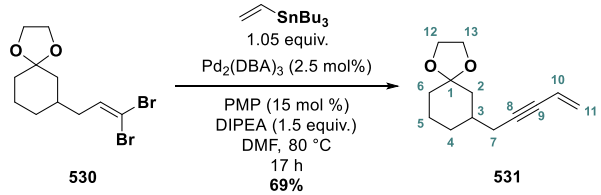
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.38 (t, *J* = 7.4 Hz, 1H, H-8), 3.99 – 3.85 (m, 4H, H-10, H-11), 2.13 – 1.95 (m, 2H, H-7), 1.81 – 1.65 (m, 5H, H-3 , CH_2-A, CH_2-B, CH_2-C, CH_2-D), 1.59 – 1.34 (m, 2H, CH_2-B, CH_2-D), 1.29 – 1.18 (m, 1H, CH_2-A), 1.01 – 0.85 (m, 1H, CH_2-C).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.2 (C-8), 109.2 (C-9), 89.5 (C-1), 64.5 (C-10), 64.4 (C-11), 41.4 (CH_2-S), 40.1 (C-7), 35.1 (C-3), 34.8 (CH_2-B), 31.6 (CH_2-C), 23.1 (CH_2-D).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2937, 2880, 1155, 1103, 1068, 1046, 929, 8485, 780.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{11}H_{17}O_2Br_2)^+$ requires 338.9590, found 338.9588.

7-(pent-4-en-2-yn-1-yl)-1,4-dioxaspiro[4.5]decane (531)



Compound **531** was prepared according to the procedure used for preparation of compound **524**, using compound **530** (1.50 g, 4.41 mmol, 1 equiv.), Pd_2dba_3 (101 mg, 110 μmol, 2.5 mol%), tris(4-

methoxyphenyl)phosphine (233 mg, 0.662 mmol, 15 mol%), DIPEA (1.18 mL, 6.62 mmol, 1.50 equiv.), tributyl(vinyl)stannane (1.36 mL, 4.63 mmol, 1.05 equiv.) and DMF (11 mL). Purification by grdient column chromatography (dry loading, Et_2O:pentane = 10:90 to 15:85) afforded compound **531** as as a colourless oil (629 mg, 69%).

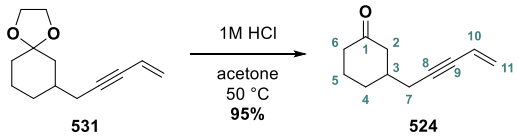
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77 (ddt, *J* = 17.5, 11.0, 2.2 Hz, 1H, H-10), 5.53 (dd, *J* = 17.5, 2.3 Hz, 1H, H-11), 5.37 (dd, *J* = 11.0, 2.3 Hz, 1H, H-11), 4.01 – 3.86 (m, 4H, H-12, H-13), 2.26 (dd, *J* = 6.1, 2.2 Hz, 2H, CH_2-D), 1.90 – 1.67 (m, 5H, H-3, CH_2-A, CH_2-B, CH_2-C, CH_2-E), 1.61 – 1.21 (m, 3H, CH_2-A, CH_2-B, CH_2-E), 1.09 – 0.94 (m, 1H, CH_2-C).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 125.7 (C-11), 117.8 (C-10), 109.4 (C-1), 89.2 (C-8), 80.8 (C-9), 64.5 (C-12), 64.3 (C-13), 40.9 (CH_2-A), 35.2 (C-3), 34.8 (CH_2-B), 31.2 (CH_2-C), 26.6 (CH_2-D), 23.0 (CH_2-E).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2942, 2886, 1371, 1355, 1154, 1063, 1045, 975, 930.

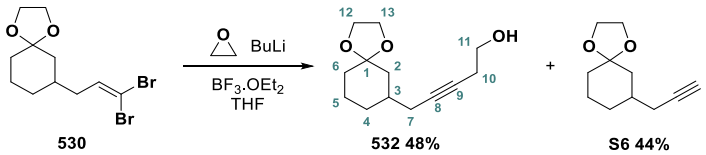
HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{13}H_{19}O_2)^+$ requires 207.1380, found 207.1378.

3-(pent-4-en-2-yn-1-yl)cyclohexan-1-one (524)



A solution of acetal **531** (200 mg, 0.970 mmol, 1 equiv.) in acetone (4.9 mL) and 1 M aq. HCl (1 mL) was stirred for 90 min at 50 °C. The reaction mixture was then neutralized with sat. aq. solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (dry loading, Et_2O:pentane = 10:90 to 20:80) afforded compound **524** as a colourless oil (150 mg, 95%).

5-(1,4-dioxaspiro[4.5]decan-7-yl)pent-3-yn-1-ol (532)



To a stirred solution of compound **530** (300 mg, 0.882 mmol, 1 equiv.) in THF (5.0 mL) at -78 °C was added 2.5 M solution of *n*-BuLi (882 µL, 882 mmol, 2.50 equiv.). After stirring for 60 min at this temperature, $BF_3.OEt_2$ (435 µL, 3.53 mmol, 4.00 equiv.) was added the resulting solution was stirred for another 30 min. 2.5 M solution of ethyleneoxide (1.41 mL, 3.53 mmol, 4.00 equiv.) was then added and

the reaction mixture was allowed to warm up to room temperature. After stirring for 30 min, the reaction was quenched with sat. aq. solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (dry loading, Et_2O:pentane = 20:80 to 40:60) afforded alcohol **532** as a colourless oil (94.9 mg, 48%) and alkyne **S6** as a colourless oil (70.1 mg, 44%).

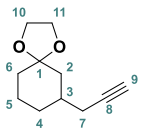
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.98 – 3.86 (m, 4H, H-12, H-13), 3.66 (t, *J* = 6.3 Hz, 2H, H-11), 2.41 (tt, *J* = 6.3, 2.4 Hz, 2H, H-10), 2.11 (dt, *J* = 6.1, 2.4 Hz, 2H, H-7), 1.95 (br s, 1H, OH), 1.85 – 1.59 (m, 5H, H-3, CH_2-A, CH_2-B, CH_2-C, CH_2-D), 1.59 – 1.33 (m, 2H, CH_2-B, CH_2-D), 1.33 – 1.20 (m, 1H, CH_2-A), 1.05 – 0.89 (m, 1H, CH_2-C).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 109.4 (C-1), 80.7 (C-8), 77.9 (C-9), 64.4 (C-12), 64.3 (C-13), 61.5 (C-11), 40.9 (CH_2-A), 35.3 (C-3), 34.7 (CH_2-B), 31.2 (CH_2-C), 26.1 (C-7), 23.3 (C-10), 23.0 (CH_2-D).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3430 (br), 2939, 2876, 1449, 1354, 1153, 1092, 1045, 929.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{13}H_{21}O_3)^+$ requires 225.1485, found 225.1475.

7-(prop-2-yn-1-yl)-1,4-dioxaspiro[4.5]decane (S6)



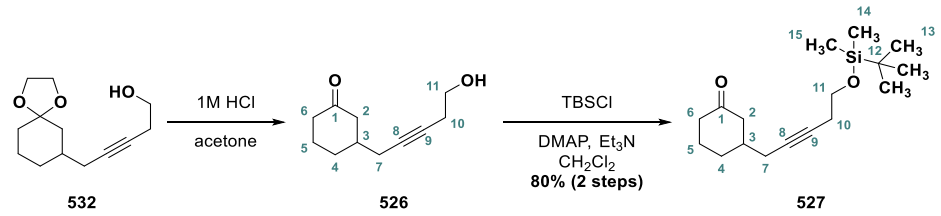
S6 44%

Compound **S6** was isolated as a side product in the epoxide-opening reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.00 – 3.85 (m, 4H, H-10, H-11), 2.13 (dd, *J* = 6.2, 2.7 Hz, 2H, CH_2-D), 1.96 (t, *J* = 2.7 Hz, 1H, H-9), 1.89 – 1.66 (m, 5H, H-3, CH_2-A, CH_2-B, CH_2-C, CH_2-E), 1.61 – 1.36 (m, 2H, CH_2-B, CH_2-E), 1.31 (t, *J* = 13.1 Hz, 1H, CH_2-A), 1.09 – 0.94 (m, 1H, CH_2-C).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 109.3 (C-1), 82.8 (C-8), 69.6 (C-9), 64.4 (C-10), 64.3 (C-11), 40.8 (CH_2-A), 34.9 (C-3), 34.8 (CH_2-B), 31.0 (CH_2-C), 25.7 (CH_2-D), 23.0 (CH_2-E).

3-(5-((tert-butyldimethylsilyl)oxy)pent-2-yn-1-yl)cyclohexan-1-one (527)



532 **526** **527**

Compound **526** was prepared according to the procedure used for preparation of compound **524**, using acetal **532** (94 mg, 419 μmol, 1 equiv.), acetone (2.1 mL) and 1 M aq. HCl (420 μL). The product was obtained as a colourless oil and used in next step without further purification.

To a stirred solution of alcohol **526** (obtained in previous step) in CH_2Cl_2 (4.2 mL) was added Et_3N (88 µL, 628 µmol, 1.50 equiv.), TBSCl (82.1 mg, 545 µmol, 1.30 equiv.) and DMAP (5.1 mg, 41.9 µmol, 0.10 equvi.) and the resulting solution was stirred for 16 h at room temperature. The reaction mixture was then poured onto sat. aq. solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (dry loading, Et_2O:pentane = 5:95 to 10:90) afforded alcohol **527** as a colourless oil (99 mg, 80% over 2 steps).

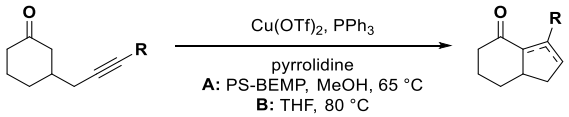
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (t, *J* = 7.1 Hz, 2H, H-11), 2.45 (ddt, *J* = 13.9, 4.1, 2.1 Hz, 1H, CH_2-A), 2.37 (tt, *J* = 7.1, 2.4 Hz, 3H, CH_2-B, CH_2-F), 2.30 – 2.12 (m, 4H, CH_2-A, CH_2-B, CH_2-D), 2.06 (ddq, *J* = 13.1, 6.9, 3.5 Hz, 1H, CH_2-E), 2.00 – 1.86 (m, 2H, H-3, CH_2-C), 1.65 (dtdd, *J* = 13.3, 12.4, 4.7, 3.3 Hz, 1H, CH_2-E), 1.48 (dtd, *J* = 13.9, 11.8, 3.4 Hz, 1H, CH_2-E), 0.89 (s, 9H, H-13), 0.06 (s, 6H, H-14).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.6 (C-1), 79.6 (C-8), 78.3 (C-9), 62.4 (C-11), 47.4 (CH_2-A), 41.3 (CH_2-B), 38.4 (C-3), 30.6 (CH_2-C), 26.0 (3xC-13), 25.8 (CH_2-D), 25.1 (CH_2-E), 23.3 (CH_2-F), 18.5 (C-12), -5.1 (2xC-14).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2956, 2931, 2858, 1715, 1256, 1106, 837, 777.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C17H31O2Si)^+$ requires 295.2088, found 295.2092.

General procedure for copper catalysed Conia-ene cyclisation

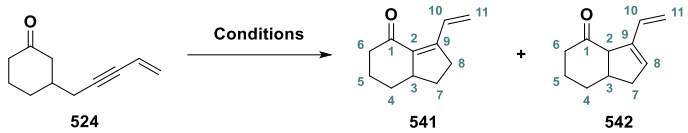


In the following procedure, degassing refers to three cycles of high vacuum followed by backfilling with argon.

Conditions A: An oven-dried 15 mL tube equipped with septum was charged with $Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%) and PS-BEMP (10 mol%) and the tube was degassed. Next, the solution of starting material in methanol (final concentration 0.125 M) and pyrrolidine (20 mol%) were added and the reaction mixture was again degassed. The septum was then replaced with cup and the sealed tube was heated to 65 °C for 12 h. The reaction mixture was then diluted with Et_2O and passed through short plug of celite and silica, concentrated under reduced pressure and analysed by NMR. Purification by column chromatography yielded the cyclised product.

Conditions B: Set up as **Conditions A**, without PS-BEMP and using THF (final concentration 0.2 M) instead of MeOH, at 80 °C.

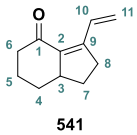
3-vinyl-1,2,5,6,7,7a-hexahydro-4H-inden-4-one (542) and 3-vinyl-1,3a,5,6,7,7a-hexahydro-4H-inden-4-one (542)



Cyclisation of compound **524** under **Conditions A:** alkyne **524** (50.0 mg, 308 μmol, 1 equiv.), $Cu(OTf)_2$ (5.6 mg, 15.4 μmol, 5 mol%), PPh_3 (16.2 mg, 61.6 μmol, 20 mol%), PS-BEMP (14.1 mg, 30.8 μmol, 10 mol%), pyrrolidine (5.1 μL, 61.6 μmol, 20 mol%) and MeOH (2.5 mL). Purification by column chromatography (dry loading, Et_2O:pentane = 5:95) afforded inseparable mixture of compounds **541** and **542** (11:1) as a colourless oil (29.8 mg, 60%).

Reaction without PS-bemp:

Cyclisation of compound **524** under **Conditions B:** alkyne **524** (50.0 mg, 308 μmol, 1 equiv.), $Cu(OTf)_2$ (5.6 mg, 15.4 μmol, 5 mol%), PPh_3 (16.2 mg, 61.6 μmol, 20 mol%), pyrrolidine (5.1 μL, 61.6 μmol, 20 mol%) and THF (1.5 mL). Purification by column chromatography (dry loading, Et_2O:pentane = 5:95) afforded inseparable mixture of compounds **541** and **542** (3.5:1) as a colourless oil (41.5 mg, 83%).

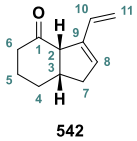

541

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, *J* = 17.6, 10.7 Hz, 1H, H-10), 5.46 (dt, *J* = 17.7, 1.5 Hz, 1H, H-11), 5.41 (dt, *J* = 10.7, 1.5 Hz, 1H, H-11), 2.96 (br s, 1H, H-3), 2.63 (ddt, *J* = 16.6, 9.5, 1.8 Hz, 1H, CH_2-C), 2.56 – 2.46 (m, 2H, CH_2-A, CH_2-C), 2.33 – 2.18 (m, 2H, CH_2-A, CH_2-D), 2.12 – 2.04 (m, 1H, CH_2-B), 2.04 – 1.95 (m, 1H, CH_2-E), 1.86 – 1.70 (m, 1H, CH_2-E), 1.53 – 1.45 (m, 1H, CH_2-D), 1.37 – 1.27 (m, 1H, CH_2-B).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 200.6 (C-1), 149.1 (C-9), 138.0 (C-2), 132.3 (C-10), 121.3 (C-12), 48.0 (C-3), 41.9 (CH_2-A), 32.2 (CH_2-B), 31.6 (CH_2-C), 31.4 (CH_2-D), 24.3 (CH_2-E).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2936, 2862, 1674, 1573, 1321, 1260, 1232, 924, 818.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{11}H_{15}O)^+$ requires 163.1117, found 163.1115.


542

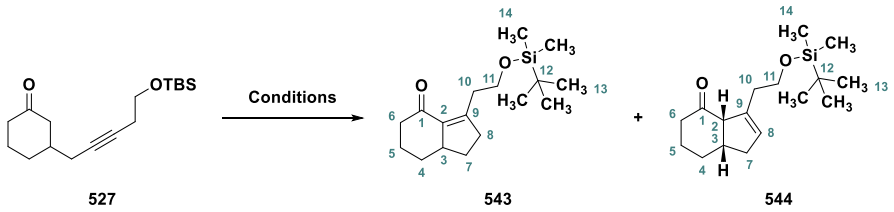
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.49 (ddt, *J* = 17.8, 10.9 Hz, 1H, H-10), 5.89 (q, *J* = 2.5 Hz, 1H, H-8), 5.11 (dt, *J* = 17.6, 1.0 Hz, 1H, H-11), 5.04 (dd, *J* = 11.0, 1.3 Hz, 1H, H-11), 3.48 (d, *J* = 7.7 Hz, 1H, H-2), 2.93 – 2.82 (m, 1H, H-3), 2.54 – 2.43 (m, 1H, H-7), 2.33 (t, *J* = 6.5 Hz, 2H, H-6), 2.22 – 2.12 (m, 1H, H-7), 2.04 – 1.74 (m, 3H. H-5, H-4), 1.67 – 1.53 (m, 1H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 213.8 (C-1), 141.5 (C-9), 132.9 (C-8), 132.7 (C-10), 115.2 (C-11), 58.1 (C-2), 43.0 (C-3), 40.5 (C-6), 37.9 (C-7), 28.2 (C-4), 23.6 (C-5).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2927, 2852, 1708 1572, 1439, 1320, 1259, 992, 912.

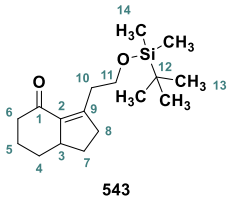
HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{11}H_{15}O)^+$ requires 163.1113, found 163.115.

3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1,2,5,6,7,7a-hexahydro-4H-inden-4-one (543) and (3aS,7aS)-3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1,3a,5,6,7,7a-hexahydro-4H-inden-4-one (544)



Cyclisation of compound **527** under **Conditions A:** alkyne **527** (24.0 mg, 81.5 μmol, 1 equiv.), $Cu(OTf)_2$ (1.5 mg, 4.1 μmol, 5 mol%), PPh_3 (4.3 mg, 16.3 μmol, 20 mol%), PS-BEMP (3.7 mg, 8.15 μmol, 10 mol%), pyrrolidine (1.3 μL, 16.3 μmol, 20 mol%) and MeOH (0.7 mL). Purification by column chromatography (dry loading, Et_2O:pentane = 8:92) afforded inseparable mixture of compounds **543** and **544** (20:1) as a colourless oil (20.9 mg, 87%).

Cyclisation of compound **527** under **Conditions B:** alkyne **527** (24.0 mg, 81.5 μmol, 1 equiv.), $Cu(OTf)_2$ (1.5 mg, 4.1 μmol, 5 mol%), PPh_3 (4.3 mg, 16.3 μmol, 20 mol%), pyrrolidine (1.3 μL, 16.3 μmol, 20 mol%) and THF (0.7 mL). Purification by column chromatography (dry loading, Et_2O:pentane = 8:92) afforded inseparable mixture of compounds **543** and **544** (6.3:1) as a colourless oil (15.8 mg, 66%).



^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 – 3.53 (m, 2H, H-11), 2.84 – 2.72 (m, 1H, H-3), 2.71 – 2.56 (m, 2H, H-10), 2.45 – 2.26 (m, 3H, CH_2-A, CH_2-B), 2.18 – 1.99 (m, 2H, CH_2-A, CH_2-D), 1.99 – 1.81 (m, 2H, CH_2-C, CH_2-E), 1.72 – 1.56 (m, 1H, CH_2-E), 1.48 – 1.27 (m, 1H, CH_2-D), 1.27 – 1.07 (m, 1H, CH_2-C), 0.77 (s, 9H, H-13), -0.06 (s, 6H, H-14).

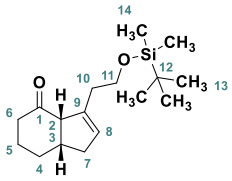
^{13}C NMR (101 MHz, $CDCl_3$) δ: 200.3 (C-1), 154.9 (C-9), 136.9 (C-2), 62.2 (C-11), 47.3 (C-3), 41.6 (CH_2-A), 37.3 (CH_2-B), 33.8 (C-10), 32.4 (CH_2-C), 31.7 (CH_2-D), 26.1 (C-13), 24.4 (CH_2-E), 18.4 (C-12), -5.18 (C-14), -5.23 (C-14).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2953, 2929, 2858, 1679, 1617, 1472.4, 1258, 1095, 836, 776

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{17}H_{31}O_2Si)^+$ requires 295.2088, found 295.2086.

Compound **544** was obtained in a mixture with compound **543** when reaction was performed in THF in the absence of PS-BEMP. Compounds **543** and **543** are inseparable on silica. Characteristic ^{1}H NMR peaks are listed below; rest of the peaks were overlapping with peaks of compound **543**. The peaks in

^{13}C NMR spectrum were obtained by comparison of ^{13}C NMR spectrum of clean compound **543** with ^{13}C NMR mixture of compounds **543** and **544**.

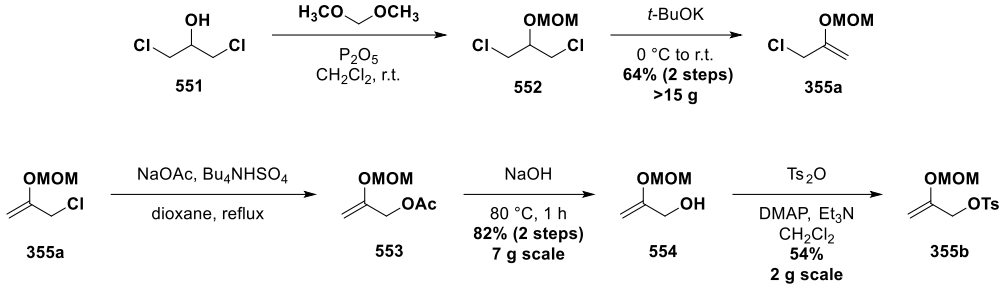


544

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.56 (qt, *J* = 2.5, 1.4 Hz, 1H, H-8), 3.23 (d, *J* = 7.9 Hz, 1H, H-2).

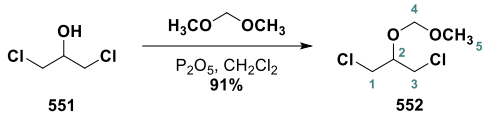
^{13}C NMR (101 MHz, $CDCl_3$) δ: 200.3 (C-1), 139.3 (C-9), 127.4 (C-8), 61.6 (C-11), 60.9 (C-2), 40.9, 40.6, 38.5, 33.4, 28.8, 26.1 (C-13), 23.1, 18.4 (C-12), -5.14 (C-14), -5.16 (C-14).

4.3.4.2 Synthesis of tetracycles 357a and 357b



Scheme 4.16. *Synthesis of allylation reagents* ***355a*** *and 355b.*

1,3-dichloro-2-(methoxymethoxy)propane (552)

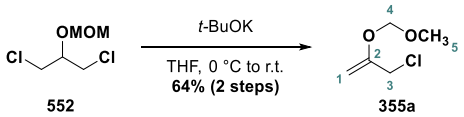


Compound **552** was prepared according to a literature procedure published by Schaeffer *et al.*[50]

To a stirred solution of alcohol **551** (37 mL, 391 mmol, 1 equiv.) in CH_2Cl_2 (80 mL) was added dimethoxymethane (80 mL, 904 mmol, 2.30 equiv.), followed by portionwise addition of P_2O_5 (33.0 g, 232 mmol, 0.60 equiv.). The resulting biphasic mixture was stirred for 24 h at room temperature. The supernatant solution was decanted and washed with water (100 mL), sat. aq. solution of $NaHCO_3$ (100 mL) and water (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford compound **552** as an orange liquid (61.8 g, 91%). Obtained material was sufficiently pure and was used without further purification in the next step. The spectroscopic data are in agreement with the literature values.[50]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.74 (s, 2H, H-4), 3.98 (p, *J* = 5.2 Hz, 1H, H-2), 3.72 (d, *J* = 4.9 Hz, 4H, H-3, H-1), 3.42 (s, 3H, H-5).

3-chloro-2-(methoxymethoxy)prop-1-ene (355a)



Compound **355a** was prepared according to a literature procedure published by Petillo *et al.*[51]

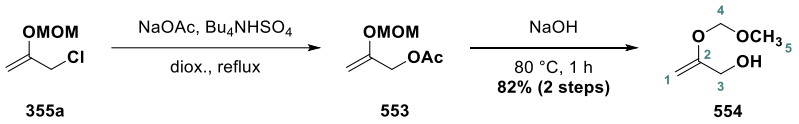
To a stirred solution of compound **552** (30.0 g, mmol, 1 equiv.) in dry THF (300 mL) at 0 °C was added *t*-BuOK (20.4 g, mmol, 1.05 equiv.) as a solution in dry THF (180 mL) and the reaction mixture was allowed to warm to room temperature. After stirring for 20 h, the reaction mixture was diluted with Et2O (800 mL) and washed with water (2 x 150 mL). The organic phase was dried over anhydrous

Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by fraction vacuum distillation (45 mbar) using an 8 inch Vigreux column, collecting fraction boiling at 64-74 °C (head of the column). The product was obtained as a colourless liquid (15.7 g, 66%). The spectroscopic data are in agreement with the literature values.[51]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.00 (s, 2H, H-4), 4.40 (s, 2H, H-1), 3.98 (s, 2H, H-3), 3.44 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.0 (C-2), 94.1 (C-4), 89.5 (C-1), 56.3 (C-5), 45.1 (C-3).

2-(methoxymethoxy)prop-2-en-1-ol (554)



355a 553 554

Compound **554** was prepared according to a literature procedure published by Okahara *et al.*[52]

To a stirred solution of chloride **355a** (7.00 g, 51.3 mmol, 1 equiv.) in dioxane (30 mL) was added sodium acetate (4.63 g, 56.4 mmol, 1.10 equiv.) and tetrabutylammonium hydrogensulfide (870 mg, 2.56 mmol, 5 mol%) and the resulting solution was stirred for 15 h at room temperature. The reaction mixture was then filtered through Celite and filtering medium was washed with Et_2O. Removal of solvents under reduced pressure (50 mbar) afforded acetate **553** as a colourless oil (11.3 g) with sufficient purity and was used in next step without further purification.

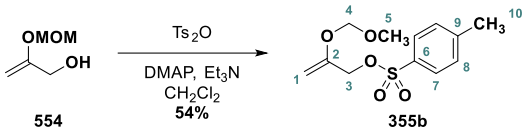
To a compound **553** obtained in previous step was added 10% aq. solution of NaOH (24 mL) and the resulting mixture was heated to 80 °C for 90 min. The reaction mixture was the diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (100 mbar). Purification by column chromatography (Et_2O:pentane 50:50 to 100:0) afforded compound **554** as a colourless oil (4.94 g, 82 % over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.99 (s, 2H, H-4), 4.29 (s, 2H, H-1), 4.05 (d, J = 6.3 Hz, 2H, H-3), 3.43 (s, 3H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.3 (C-2), 93.9 (C-4), 85.8 (C-1), 63.7 (3), 56.4 (C-5).

IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 3412, 2957, 2908, 1648, 1452, 1154, 1077, 1024, 828.

2-(methoxymethoxy)allyl 4-methylbenzenesulfonate (355b)

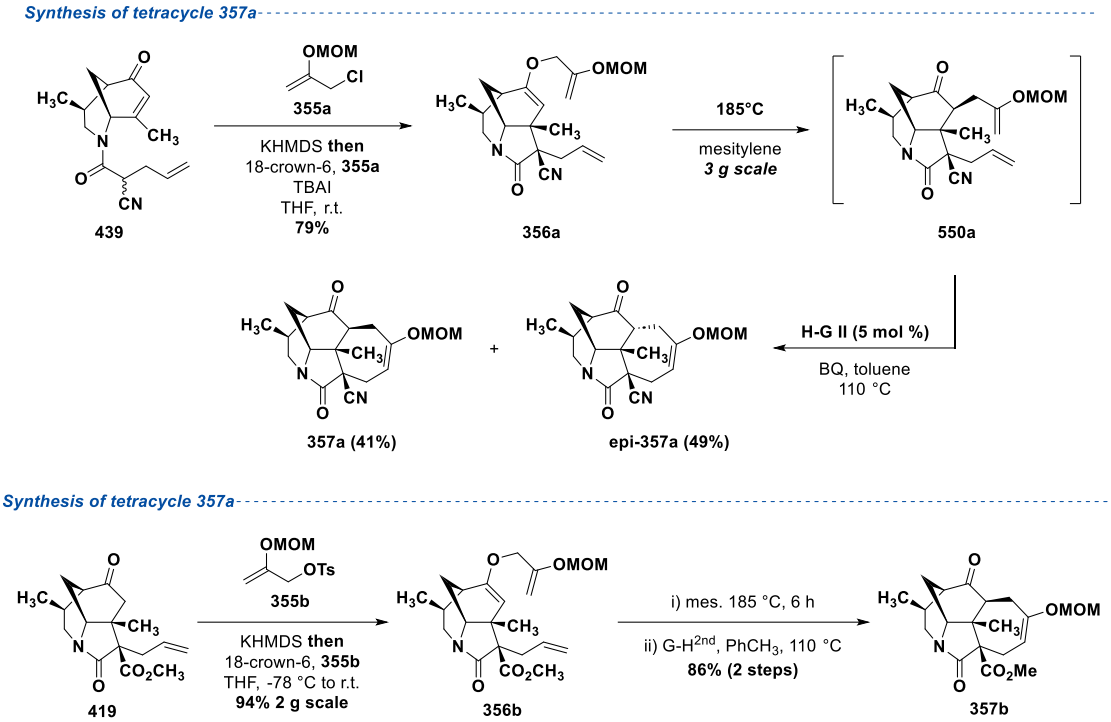


To a solution of alcohol **554** (2.00 g, 16.9 mmol, 1 equiv.) in dry CH_2Cl_2 (56 mL) at 0 °C was added Et_3N (3.6 mL, 25.4 mmol, 1.50 equiv.) followed by DMAP (207 mg, 1.69 mmol, 0.10 equiv.) and solution of Ts_2O (5.80 g, 17.8 mmol, 1.00 equiv.) in dry CH_2Cl_2 (37 mL). TLC analysis of the reaction mixture after 60 min revealed only partial conversion and full consumption of Ts_2O. Therefore, another portion of Et_3N (3.6 mL, 25.4 mmol, 1.50 equiv.) and Ts_2O (2.76 g, 8.47 mmol, 0.50 eqiuv.) was added and the reaction mixture was stirred for additional 1 h. TLC analysis shoved a better conversion and more Ts_2O was added (600 mg, 1.84 mmol, 0.10 equiv.) and reaction mixture stirred for another 1 h. The reaction mixture was then poured onto sat. aq. solution of $NaHCO_3$ (100 mL), extracted with CH_2Cl_2 (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure at 25 °C. The crude tosylated allylic alcohol was purified by fast column chromatography (Et_2O:pentane = 20:80). The fractions containing the product were concentrated under reduced pressure at 25 °C and then transferred into a vial using Et_2O. Et_2O was removed by a stream of nitrogen which afforded tosylate **355b** as a colourless oil (2.47 g, 54%). Because of its potential low stability, the pure product, while still under the atmosphere of nitrogen, was diluted with benzene (8.74 g) and stored in the freezer.

NOTE: A rapid decomposition of allyl tosylates was previously observed. Therefore, they should be used immediately after its preparation. In the case of compound **355b**, a short-term storage (for a few days) as a frozen solution in benzene is possible.

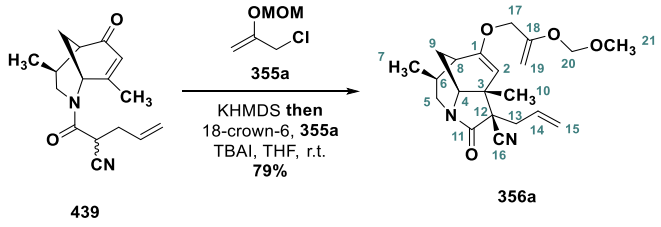
^{1}H NMR (400 MHz, C_6D_6) δ: 7.78 – 7.69 (m, 2H, H-7), 6.69 – 6.62 (m, 2H, H-8), 4.48 (s, 2H, H-4), 4.35 (d, J = 0.5 Hz, 2H, H-3), 4.30 (d, J = 2.3 Hz, 1H, H-1 4.12 (d, J = 2.3 Hz, 1H, H-1), 2.98 (s, 3H, H-5), 1.81 (s, 3H, H-10).

^{13}C NMR (101 MHz, C_6D_6) δ: 153. 9 (C-2), 144.2 ($C_{quat.}$), 134.5 ($C_{quat.}$), 129.7 (C-8), 94.0 (C-4), 90.6 (C-1), 70.0 (C-3), 55.7 (C-5), 21.1 (C-10), C-7 peak is hidden under the solvent peak.



Scheme 4.17. *Synthesis of tetracycles* ***357a-b.***

(*3S,3aR,6R,7aR,8S*)-3-allyl-5-((2-(methoxymethoxy)allyl)oxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carbonitrile (356a)



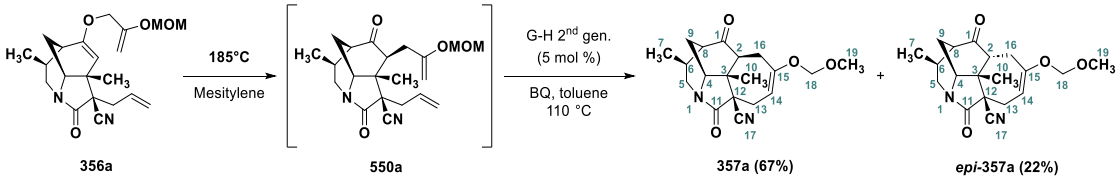
Compound **356a** was prepared adopting the procedure described by S. Ellis.[19]

To a solution of ketone **439** (3.73 g, 13.7 mmol, 1 equiv.) in degassed dry THF (35 mL) was added KHMDS (0.5 M solution in toluene, 41 mL, 20.5 mmol, 1.50 equiv.) at 0 °C and the resulting solution was stirred for 30 min at room temperature. Then, TBAI (809 mg, 2.19 mmol , 0.16 equiv.) followed by a solution of 18-crown-6 (1.81 mg, 6.85 mmol, 0.50 equiv.) and allyl chloride **355a** (2.81 g, 20.5 mmol , 1.50 equiv.) in degassed THF (19.0 mL) were added dropwise. After stirring for 14 h, the reaction mixture was quenched with water (50 mL), the phases separated, and the aqueous phase extracted with ethyl acetate (4 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 10:90 to 15:85) afforded compound **356a** as a colourless oil (4.05 g, 79%). Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.08 (dddd, 1H, *J* = 17.0, 10.1, 9.2, 5.4 Hz, H-14), 5.32 – 5.21 (m, 2H, H-15), 4.99 (d, 1H, *J* = 6.3 Hz, H-19a), 4.97 (d, 1H, *J* = 6.3 Hz, H-19b), 4.41 (d, 1H, *J* = 2.4 Hz, H-20a), 4.32 – 4.27 (m, 1H, H-20b), 4.18 (d, 1H, *J* = 12.5 Hz, H-17a), 4.12 (d, 1H, *J* = 1.3 Hz, H-2), 4.08 (d, 1H, *J* = 12.5 Hz, H-17b), 4.01 (dd, 1H, *J* = 13.7, 8.0 Hz, H-5a), 3.91 – 3.84 (m, 1H, H-4), 3.42 (s, 3H, H-21), 2.77 (ddt, 1H, *J* = 14.8, 5.4, 1.8 Hz, H-13a), 2.43 (dd, 1H, *J* = 13.7, 10.5 Hz, H-5b), 2.37 (dd, 1H, *J* = 14.7, 9.2 Hz, H-13b), 2.14 – 1.96 (m, 3H, H-6, H-8, H-9a), 1.73 – 1.63 (m, 1H, H-9b), 1.34 (s, 3H, H-10), 0.98 (d, 3H, *J* = 6.9 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.4 (C-11), 160.8 (C-1), 155.4 (C-18), 132.6 (C-14), 119.5 (C-15), 117.5 (C-16), 94.0 (C-19), 92.4 (C-2), 87.8 (C-20), 67.4 (C-17), 57.2 (C-4), 56.4 (C-21), 51.6 (C-12), 50.6 (C-3), 41.8 (C-5), 37.5 (C-8), 34.7 (C-13), 31.7 (C-6), 19.9 (C-10), 19.7 (C-9), 19.4 (C-7).

rac-(*2R,3S,6aS,11S,11aR,11bR*)-9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (357a)



Compound **357a** and **epi-357a** was prepared by modified procedure described by S. Ellis.

A solution of enol **356a** (4.05 g, 10.9 mmol, 1 equiv.) was transferred to passivated pressure tube in benzene (10.0 mL), and the solvent was removed in a vacuum. The solvent-free enol was dissolved in mesitylene (217 mL, 0.05 M) (previously distilled and stored over molecular sieves). A PTFE syringe filter was used to ensure that no solid particles were transferred with the solvent into the reaction mixture. The resulting solution was bubbled with nitrogen for 30 min, and the reaction vessel was then sealed and heated to 185 °C for 9 h.

After cooling to room temperature, the reaction mixture was transferred to RBF and diluted with dry degassed toluene (500 mL). The reaction mixture was then degassed by a stream of nitrogen (30 min), Grubbs-Hoveyda 2nd generation catalyst (341 mg, 0.544 mmol, 5.00 mol%) and benzoquinone (118 mg, 1.097 mmol, 0.10 equiv.) were added and the resulting solution was heated to reflux with attached condenser while gently bubbled with nitrogen. After stirring for 5 h, the reaction mixture was cooled down, the catalyst was quenched by the addition of potassium isocyanoacetate (270 mg, 2.17 mmol, 0.20 equiv.) in methanol (10 mL) and the reaction mixture was stirred for another 30 min. Toluene was then removed under reduced pressure, and the solution of the crude product in mesitylene was purified by gradient column chromatography, first eluting with pentane to remove mesitylene, then with diethyl ether:pentane (50:50 to 80:20) and finally ethyl acetate:pentane (60:40) to afford intermediate **550a** as a

colourless oil (200 mg, 5.0%), compound **357a** as a white solid (2.49 g, 67%) and compound ***epi*-357a** as a white solid (818 mg, 22%). Data are in agreement with the previously reported values.[19]

Compound 357a:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.97 – 4.93 (m, 1H, H-14), 4.93 (d, 1H, *J* = 6.4 Hz, H-18a), 4.89 (d, 1H, *J* = 6.4 Hz, H-18b), 4.08 (dd, 1H, *J* = 13.8, 6.8 Hz, H-5a), 3.82 (d, 1H, *J* = 3.6 Hz, H-4), 3.40 (s, 3H, H-19), 2.97 – 2.89 (m, 1H, H-13a), 2.89 (dd, 1H, *J* = 12.0, 5.4 Hz, H-2), 2.80 – 2.69 (m, 2H, H-5b, H-16a), 2.64 (dd, 1H, *J* = 16.6, 9.4 Hz, H-13b), 2.44 – 2.27 (m, 3H, H-8, H-9a, H-16b), 2.15 – 2.01 (m, 1H, H-6), 1.96 – 1.84 (m, 1H, H-b'), 1.39 (s, 3H, H-10), 1.04 (d, 3H, *J* = 6.9 Hz, H-7).

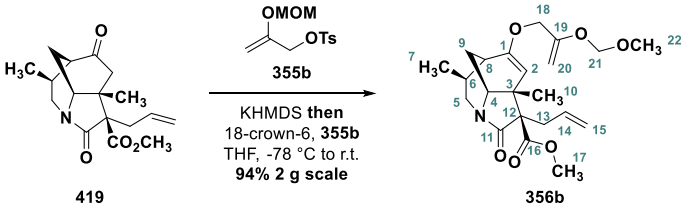
^{13}C NMR (101 MHz, $CDCl_3$) δ: 208.9 (C-10), 171.3 (C-2), 156.1 (C-7), 117.0 (C-22), 93.8 (C-21), 92.7 (C-6), 58.0 (C-15), 56.3 (C-25), 55.2 (C-4), 52.8 (C-3), 49.5 (C-11), 42.4 (C-13), 41.1 (C-9), 32.3 (C-12), 29.5 (C-8), 27.7 (C-5), 21.8 (C-16), 19.9 (C-14), 15.4 (C-17).

***rac-(2R,3S,6aS,11R,11aR,11bR)*-9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (*epi*-357a)**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.95 (d, 1H, *J* = 6.0 Hz, H-18a), 4.86 (d, 1H, *J* = 6.0 Hz, H-18b), 4.82 (dd, 1H, *J* = 8.1, 6.0 Hz, H-14), 4.00 (dd, 1H, *J* = 13.7, 9.0 Hz, H-5a), 3.92 (t, 1H, *J* = 3.0 Hz, H-4), 3.45 (s, 3H, H-19), 2.97 – 2.83 (m, 1H, H-6), 2.67 – 2.52 (m, 4H, H-2, H-16a, H-13), 2.49 – 2.33 (m, 1H, H-16b), 2.29 (dd, 1H, *J* = 13.8, 9.5 Hz, H-5b), 2.14 (dd, 2H, *J* = 3.9, 2.6 Hz, H-9), 1.97 (dt, 1H, *J* = 3.8, 1.8 Hz, H-8), 1.60 (s, 3H, H-10), 1.02 (d, 3H, *J* = 6.9 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.1 (C-1), 166.0 (C-11), 157.4 (C-15), 118.5 (C-17), 94.2 (C-18), 93.4 (C-14), 60.6 (C-4), 56.5 (C-19), 52.9 (C-12), 50.0 (C-2), 49.4 (C-3), 46.3 (C-8), 40.9 (C-5), 36.2 (C-6), 26.9 (C-16), 26.6 (C-13), 21.3 (C-10), 18.3 (C-9), 17.8 (C-7).

***rac*-methyl *(3R,3aR,6R,7aS,8S)*-3-allyl-5-((2-(methoxymethoxy)allyl)oxy)-3a,8-dimethyl-2-oxo-2,3,3a,6,7,7a-hexahydro-6,1-ethanoindole-3-carboxylate (356b)**



To a solution of ketone **419** (2.00 g, 6.55 mmol, 1 equiv.) in degassed dry THF (16.4 mL) was added KHMDS (0.5 M solution in toluene, 19.7 L, 9.82 mmol, 1.50 equiv.) at -78 °C and the resulting solution

was stirred for 30 min. Then, a solution of 18-crown-6 (866 mg, 3.27 mmol, 0.50 equiv.) in degassed THF (5.0 mL) followed by tosylate **355b** (22.0 wt % solution in benzene, 2.47 g, 9.07 mmol, 1.38 equiv.) were added. The reaction mixture was slowly allowed to warm to 0 °C over 3 h, during which the formation of white precipitate was formed. The reaction mixture was then poured onto brine (50 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 20:80 to 30:70) afforded compound **356b** as a colourless oil (2.50 g, 94%).

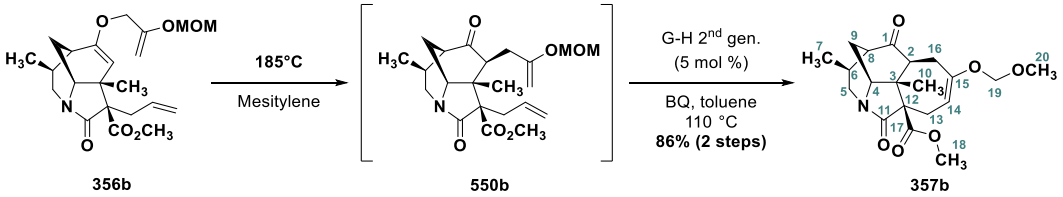
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2952, 1731, 1696, 1650, 1420, 1380, 1277, 1154, 1042, 999, 922, 838.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.23 (dddd, *J* = 17.2, 10.2, 9.2, 4.7 Hz, 1H, H-6), 5.14 (dtd, *J* = 17.2, 2.1, 0.9 Hz, 1H, H-15a), 5.08 (dtd, *J* = 10.2, 1.9, 0.7 Hz, 1H, H-15b), 5.02 – 4.93 (m, 2H, H-20), 4.38 (d, *J* = 2.3 Hz, 1H, H-21a), 4.36 – 4.27 (m, 2H, H-21b, H-2), 4.15 (d, *J* = 12.3 Hz, 1H, H-18a), 4.10 – 4.00 (m, 2H, H-18b, H-5a), 3.85 – 3.79 (m, 1H, H-4), 3.70 (s, 3H, H-17), 3.42 (s, 3H, H-22), 2.73 (ddt, *J* = 14.6, 4.7, 2.0 Hz, 1H, H-13a), 2.47 – 2.34 (m, 2H, H-13b, H-5b), 2.06 (dt, *J* = 10.4, 7.3 Hz, 1H, H-6), 2.00 – 1.90 (m, 2H, H-8, H-9a), 1.67 – 1.57 (m, 1H, H-9b), 1.13 (s, 3H, H-10), 0.95 (d, *J* = 6.9 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.9 (C-16), 170.8 (C-11), 159.5 (C-1), 155.7 (C-19), 135.3 (C-14), 117.7 (C-15), 95.4 (C-2), 93.9 (C-20), 87.5 (C-21), 67.2 (C-18), 61.8 (C-12), 56.8 (C-4), 56.3 (C-22), 52.2 (C-17), 50.0 (C-3), 41.6 (C-5), 37.3 (C-8), 35.7 (C-13), 31.7 (C-6), 20.1 (C-9), 19.6 (C-7), 19.5 (C-10).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{22}H_{31}NO_6Na)^+$ requires 428.2044, found 428.2061.

***rac*-methyl *(2R,3S,6aR,11S,11aR,11bS)*-9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carboxylate (357b)**



A solution of enol **356b** (2.50 g, 6.17 mmol, 1 equiv.) was transferred to passivated pressure tube in benzene (5.0 mL), and the solvent was removed in a vacuum. The solvent-free enol was dissolved in mesitylene (123 mL, 0.05 M) (previously distilled and stored over molecular sieves). A PTFE syringe filter was used to ensure that no solid particles were transferred with the solvent into the reaction mixture. The resulting solution was bubbled with nitrogen for 30 min, and the reaction vessel was then sealed and heated to 185 °C for 6 h.

After cooling to room temperature, the reaction mixture was transferred to RBF and diluted with dry degassed toluene (480 mL, 0.01 M). The reaction mixture was then degassed by a stream of nitrogen (30 min), Grubbs-Hoveyda 2nd generation catalyst (193.2 mg, 0.308 mmol, 5.00 mol%) and benzoquinone (66.7 mg, 0.617 mmol, 0.10 equiv.) were added and the resulting solution was heated to reflux with attached condenser while gently bubbled with nitrogen. After stirring for 5 h, the reaction mixture was cooled down, the catalyst was quenched by the addition of potassium isocyanoacetate (152 mg, 1.23 mmol, 0.20 equiv.) in methanol (6 mL) and the reaction mixture was stirred for another 30 min. toluene was removed under reduced pressure, and the solution of the crude product in mesitylene was purified by gradient column chromatography, first eluting with pentane to remove mesitylene and then with ethyl acetate:pentane (50:50 to 80:20) to afford compound **357b** as a white solid (2.01 g, 87%).

MP: 183 – 185 °C

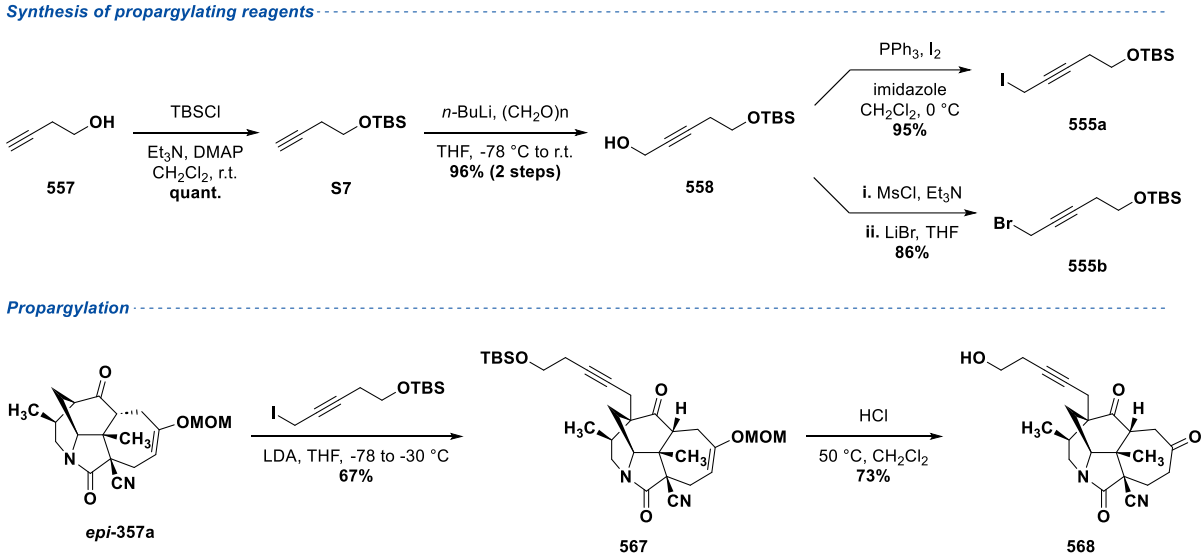
IR (neat) $\tilde{\nu}_{max}/cm^{-1}$: 2956.0, 2932.4, 1729.6, 1691.0, 1446.7, 1242.7, 1216.2, 1057.9, 987.5, 870.4

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.00 (ddd, 1H, *J* = 9.4, 5.5, 2.2 Hz, H-14), 4.90 (s, 2H, H-19), 4.15 – 4.05 (m, 1H, H-5a), 3.89 (t, 1H, *J* = 3.1 Hz, H-4), 3.73 (s, 3H, H-18), 3.40 (s, 3H, H-21), 3.06 (dd, 1H, *J* = 12.5, 4.9 Hz, H-2), 2.81 – 2.68 (m, 2H, H-5b, H-16a), 2.66 (dddd, 1H, *J* = 16.1, 5.6, 2.6, 1.4 Hz, H-13a), 2.57 (dd, 1H, *J* = 16.1, 9.4 Hz, H-13b), 2.40 – 2.26 (m, 3H, H-8, H-9a, H-16b), 2.15 – 2.01 (m, 1H, H-6), 1.87 – 1.77 (m, 1H, H-9b), 1.14 (s, 3H, H-10), 1.01 (d, 3H, *J* = 6.9 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.3 (C-1), 175.7 (C-11), 170.6 (C-17), 153.3 (C-15), 96.4 (C-14), 93.7 (C-19), 65.3 (C-12), 57.3 (C-4), 56.2 (C-21), 55.2 (C-3), 52.4 (C-18), 49.9 (C-8), 42.4 (C-2), 42.3 (C-5), 32.6 (C-6), 29.6 (C-16), 26.4 (C-13), 22.3 (C-9), 19.9 (C-7), 15.5 (C-10).

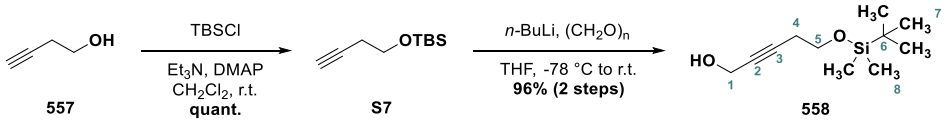
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{20}H_{27}NO_6Na)^+$ requires 400.1731, found 400.1738.

4.3.4.3 Introduction of the alkyne chain by ketone propargylation



Scheme 4.18. *Propargylation of tetracycle* ***357a.***

5-((tert-butyldimethylsilyl)oxy)pent-2-yn-1-ol (558)



To a stirred solution of alcohol **557** (3.00 g, 42.8 mmol, 1 equiv.) in dry CH_2Cl_2 (43 mL) was added Et_3N (9.0 mL, 64.2 mmol, 1.50 equiv.) followed by TBSCl (8.06 g, 53.5 mmol, 1.25 equiv.) and DMAP (523 mg, 4.28 mmol, 0.10 equiv.) and the resulting solution was stirred overnight at room temperature. The reaction mixture was then washed with 1M HCl (2 x 50 mL) and sat. aq. solution of $NaHCO_3$ (2 x 50 mL). and extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Obtained material was sufficiently pure and was used without further purification in the next step.

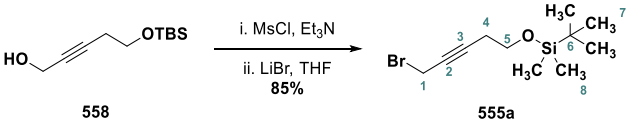
Prepared according to a literature procedure.[53] To a stirred solution of alkyne **S7** (7.89 g, 42.8 mmol, 1 equiv.) in dry THF (100 mL) at -78 °C was dropwise added *n*-BuLi (2.14 M, 24.0 mL, 51.4 mmol, 1.20 equiv.). After stirring for 30 min at -78 °C, paraformaldehyde (4.63 g, 154.1 mmol, 3.60 equiv.) was added and the reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was poured onto sat. aq. solution of $NaHCO_3$ (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 5:95 to 10:90) afforded compound **558** as a colourless oil (8.84 g, 96% over 2 steps).

The spectroscopic data are in agreement with the literature values. [54]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.27 – 4.19 (m, 2H, H-1), 3.72 (t, *J* = 7.2 Hz, 2H, H-5), 2.43 (tt, *J* = 7.1, 2.1 Hz, 2H, H-4), 0.90 (s, 9H, H-7), 0.07 (s, 6H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 83.6 (C-2), 79.6 (C-3), 62.0 (C-5), 51.5 (C-1), 26.0 (C-7), 23.3 (C-4), 18.5 (C-7), -5.1 (C-8).

((5-bromopent-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane (555a)



558 **555a**

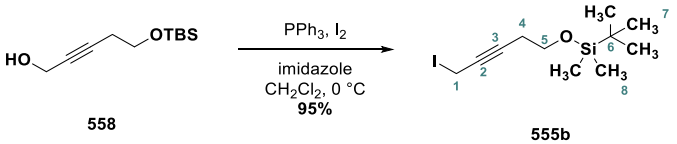
Prepared according to a literature procedure.[55] To a stirred solution of alcohol **558** (1.00 g, 4.66 mmol, 1 equiv.) in dry THF (14 mL) at 0 °C was added Et_3N (1.17 mL, 8.40 mmol, 1.80 equiv.) followed by dropwise addition of MsCl (541 μL, 7.00 mmol, 1.50 equiv.) over 5 min and the reaction mixture was allowed to slowly warm to room temperature. After stirring for 1 h, the reaction mixture was filtered through cotton to solution of LiBr (2.03 g, 23.3 mmol, 5.00 equiv.) in dry THF (14 mL) and the cotton and the first reaction flask were washed with THF (10 mL). The reaction mixture was stirred at room temperature for 1 h, and then filtered through Celite, and the reaction flask rinsed with Et_2O. Filtrate was washed with brine (30 mL) and the aqueous layer extracted with Et_2O (2 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (Et_2O:pentane = 5:95) afforded bromide **555a** as a colourless oil (1.10 g, 85%).

The spectroscopic data are in agreement with the literature values.[55]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.91 (t, *J* = 2.3 Hz, 2H, H-1), 3.71 (t, *J* = 7.0 Hz, 2H, H-5), 2.45 (tt, *J* = 7.0, 2.3 Hz, 2H, H-4), 0.89 (s, 9H, H-7), 0.07 (s, 6H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 85.2 (C-2), 76.5 (C-3), 61.7 (C-5), 26.0 (C-7), 23.5 (C-4), 18.5 (C-6), 15.5 (C-1), -5.1 (C-8).

tert-butyl((5-iodopent-3-yn-1-yl)oxy)dimethylsilane (555b)



Prepared according to a literature procedure.[56] To a stirred solution of alcohol **558** (500 mg, 2.33 mmol, 1 equiv.) in dry CH_2Cl_2 (4.7 mL) at 0 °C was added PPh_3 (734 mg, 2.80 mmol, 1.20 equiv.), imidazole (191 mg, 2.80 mmol, 1.20 equiv.) and iodine (710 mg, 2.80 mmol, 1.20 equiv.). After stirring for 30 min at 0 °C, the reaction was quenched with sat. aq. NaHCO3 (15 mL) and 1M aq. solution of $Na_2S_2O_3$ (15 mL) and extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (pentane) afforded bromide **555b** as a colourless oil (720 mg, 95%).

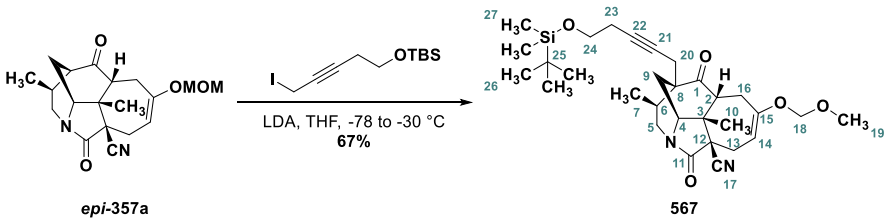
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2955, 2930, 2857, 1256, 1144, 1108, 837, 778.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 – 3.66 (m, 4H, H-1, H-5), 2.41 (tt, *J* = 7.1, 2.4 Hz, 2H, H-4), 0.89 (s, 9H, H-7), 0.07 (s, 6H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 83.6 (C-2), 78.3 (C-3), 61.6 (C-6), 26.0 (C-7), 23.6 (C-4), 18.5 (C-6), -5.1 (C-8), -17.2 (C-1).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ ($C_{11}H_{21}OISiNa)^+$ requires 347.0304, found 347.0327.

***rac*-(2R,3S,6aS,11R,11aR,11bS)-2-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-yn-1-yl)-9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (567)**



To a stirred solution of compound ***epi*-357a** (20 mg, 58.1 μmol, 1 equiv.) in dry THF (0.3 mL) at -78 °C was added 0.45 M stock solution of LDA (200 μL, 90.0 μmol, 1.55 equiv.). After stirring for 30 min at -78 °C, a solution of iodide **555b** (35 mg, 108 μmol, 1.86 equiv.) in THF (200 μL) was added and the resulting mixture was stirred for 1 h at -78 °C and then 15 h at -30 °C. The reaction was quenched with sat. aq. solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane) afforded compound **567** as a colourless oil (21.0 mg, 67%).

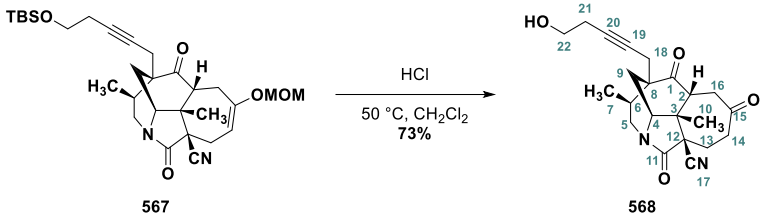
IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 2955, 2932, 2858, 1725, 1425, 1154, 1104, 915, 837, 779, 733.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.98 (d, *J* = 5.9 Hz, 1H, H-18), 4.90 (d, *J* = 6.0 Hz, 1H, H-18), 4.87 (dd, *J* = 8.9, 5.5 Hz, 1H, H-14), 4.04 (dd, *J* = 13.8, 9.1 Hz, 1H, H-5a), 3.91 (d, *J* = 6.0 Hz, 1H, H-4), 3.64 (t, *J* = 7.3 Hz, 2H, H-24), 3.46 (s, 3H, H-19), 2.90 – 2.75 (m, 2H, H-6, H-2), 2.63 (qd, *J* = 15.7, 7.0 Hz, 2H, H-13), 2.54 – 2.39 (m, 2H, H-16), 2.39 – 2.28 (m, 3H, H-9a, H-23), 2.25 (dd, *J* = 9.0, 4.8 Hz, 1H, H-5b), 2.24 (m, 1H, H-20a), 2.08 (dt, *J* = 16.0, 2.5 Hz, 1H, H-20b), 1.95 (dd, *J* = 14.8, 6.1 Hz, 1H, H-9b), 1.62 (s, 3H, H-10), 0.89 (s, 9H, H-26), 0.83 (d, *J* = 6.9 Hz, 3H, H-7), 0.06 (s, 6H, H-27).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.3 (C-1), 165.6 (C-11), 157.6 (C-15), 118.3 (C-17), 94.2 (C-18), 93.9 (C-14), 81.2 (C-21), 76.3 (C-22), 62.2 (C-24), 60.4 (C-4), 56.4 (C-19), 53.4 (C-12), 51.0 (C-2), 50.3 (C-8), 48.7 (C-3), 41.8 (C-5), 38.3 (C-6), 26.8 (C-16), 26.2 (C-13), 26.0 (C-26), 24.5 (C-20), 23.1 (C-23), 22.1 (C-9), 20.6 (C-10), 18.4 (C-25), 13.6 (C-7), -5.15 (C-27), -5.17 (C-27).

HRMS (ES+): exact mass calculated for $[M+H-MOM]^+$ $(C_{28}H_{41}O_4N_2{}^{28}Si)^+$ requires 497.2836, found 497.2856.

rac-(2R,3S,6aS,11R,11aR,11bS)-2-(5-hydroxypent-2-yn-1-yl)-3,11a-dimethyl-6,9,12-trioxodecahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (568)



567 568

To a stirred solution of compound **567** (40 mg, 74.0 μmol, 1 equiv.) in CH_2Cl_2 (1.0 mL) and MeOH (0.25 mL) was added conc. HCl (0.1 mL) and the resulting solution was stirred at 50 °C for 20 min. The reaction mixture was neutralized with sat. aq. solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane 50:50 to 100:0) afforded compound **568** as a white crystalline solid (20.7 mg, 73%).

Crystal for single crystal X-ray diffraction analysis was obtained by slow evaporation of solution of compound **568** from mixture of CH_2Cl_2 and acetone.

MP: 224 – 226 °C.

IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 2503 (br), 2927, 1716, 1435, 1287, 992, 713.

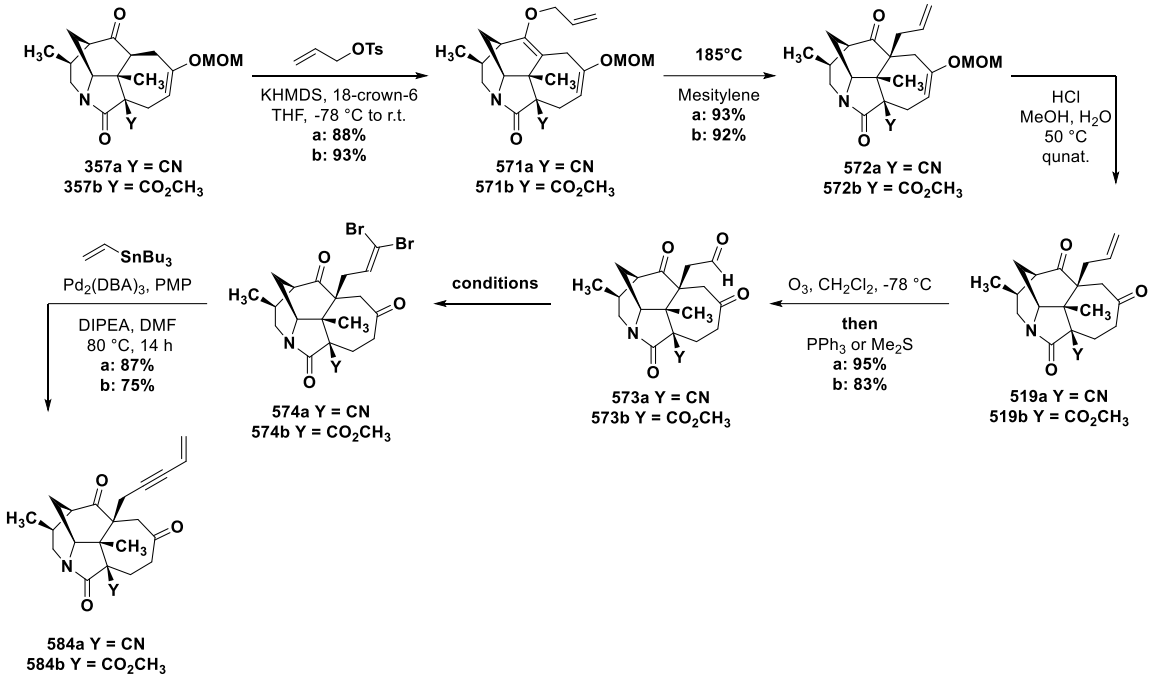
^{1}H NMR (400 MHz, CD_2Cl_2) δ: 4.05 (dd, *J* = 13.8, 8.9 Hz, 1H, H-5a), 4.02 (d, *J* = 5.8 Hz, 1H, H-4), 3.67 – 3.59 (m, 2H, H-22), 3.31 (t, *J* = 4.6 Hz, 1H, H-2), 2.91 – 2.76 (m, 1H, H-6), 2.64 – 2.50 (m, 3H,

H-16, H-14a), 2.47 – 2.27 (m, 6H, H-14b, H-5b, H-13a, H-21, H-9a), 2.26 – 2.12 (m, 3H, H-13b, H-18), 2.06 (dd, J = 15.0, 5.9 Hz, 1H, H-9b), 1.66 (s, 3H, H-10), 0.86 (d, J = 6.9 Hz, 3H, H-7).

^{13}C NMR (101 MHz, CD_2Cl_2) δ: 214.6 (C1), 209.6 (C-15), 165.6 (C-11), 118.1 (C-17), 82.2 (C-19), 76.1 (C-20), 61.5 (C-22), 60.7 (C-4), 52.6 (C-8), 52.3 (C-2), 49.1 (C-3), 42.2 (C-5), 38.4 (C-6), 38.3 (C-14), 37.2 (C-16), 25.3 (C-13), 24.4 (C-18), 23.4 (C-21), 23.2 (C-9), 21.1 (C-10), 13.5 (C-7), C-12 peak overlaps with residual solvent peak.

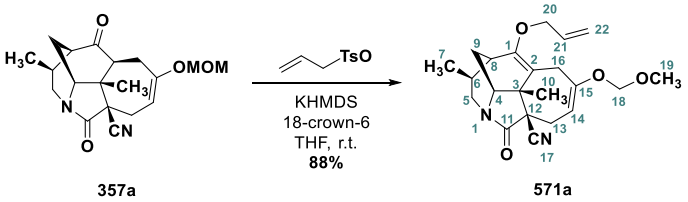
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{22}H_{26}O_4N_2Na)^+$ requires 405.1785, found 405.1803.

4.3.4.4 Introduction of the alkyne chain by Claisen rearrangement



Scheme 4.19. *Synthesis of enynes* ***584a-b****.*

***rac-(2R,3S,6aS,11aR,11bS)*-12-(allyloxy)-9-(methoxymethoxy)-3,11a-dimethyl-6-oxo-1,2,3,4,7,10,11a,11b-octahydro-2,11-(metheno)cyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (571a)**



Compound **571a** was prepared adopting the procedure described by S. Ellis.[19]

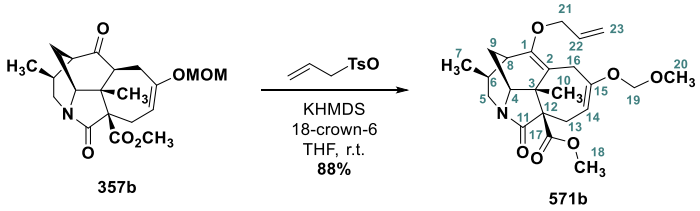
To a solution of ketone **357a** (1.10 g, 3.19 mmol, 1 equiv.) in degassed THF (57 mL) at -78 °C was added KHMDS (0.5 M solution in toluene, 9.6 mL, 4.80 mmol, 1.50 equiv.) and the resulting solution was stirred at this temperature for 20 min. Then, a solution of 18-crown-6 (844 mg, 3.19 mmol, 1.00 equiv.) and allyl tosylate (**391**) (1.02 mg, 4.79 mmol, 1.50 equiv.) in dry degassed THF (6.0 mL) was added and the flask was rinsed with THF (3.0 mL). After stirring for 10 min at -78 °C, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 60 min, the reaction was quenched with water (25 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification

by gradient column chromatography (ethyl acetate:pentane = 25:75 to 40:60) afforded compound **571a** as a colourless oil (1.08 g, 88%). Data are in agreement with the previously reported values.[19]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.90 (ddt, J = 17.2, 10.5, 5.0 Hz, 1H, H-21), 5.35 (dq, J = 17.3, 1.7 Hz, 1H, H-22a), 5.20 (dq, J = 10.5, 1.5 Hz, 1H, H-22b), 4.91 (d, J = 6.0 Hz, 1H, H-18a), 4.85 (d, J = 6.0 Hz, 1H, H-18b), 4.80 (dd, J = 8.1, 6.5 Hz, 1H, H-14), 4.28–4.16 (m, 2H, H-20), 4.00 (dd, J = 13.7, 8.0 Hz, 1H, H-5a), 3.77 (dt, J = 5.0, 1.1 Hz, 1H, H-4), 3.49 (d, J = 17.5 Hz, 1H, H-16a), 3.40 (s, 3H, H-19), 2.69–2.63 (m, 2H, H-13a, 16b), 2.56 (dd, J = 15.7, 8.0 Hz, 1H, H-13b), 2.45 (dd, J = 13.7, 10.5 Hz, 1H, H-5b), 2.19 (d, J = 3.3 Hz, 1H, H-8), 2.07–1.97 (m, 2H, H-6, 9a), 1.65 (s, 1H), 1.61 (ddt, J = 14.0, 4.0, 1.0 Hz, 1H, H-9b), 1.46 (s, 3H, H-10), 0.98 (d, J = 6.9 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.0 (C-11), 157.5 (C-15), 153.8 (C-1), 133.8 (C-21), 118.4 (C-17), 117.0 (C-22), 110.3 (C-2), 93.8 (C-18), 92.3 (C-14), 68.6 (C-20), 58.2 (C-4), 56.4 (C-19), 52.2 (C-3), 50.5 (C-12), 41.2 (C-5), 33.7 (C-8), 31.3 (C-6), 29.7 (C-16), 28.0 (C-13), 19.8 (C-9), 18.7 (C-10, C-7).

***rac*-methyl *(3S,6aR,11aR,11bS)*-12-(allyloxy)-9-(methoxymethoxy)-3,11a-dimethyl-6-oxo-1,2,3,4,7,10,11a,11b-octahydro-2,11-(metheno)cyclohepta[*a*]indolizine-6a(*6H*)-carboxylate (571b)**



357b 571b

To a solution of ketone **357b** (1.80 g, 4.77 mmol, 1 equiv.) in degassed THF (85 mL) at -78 °C was added KHMDS (0.5 M solution in toluene, 14.3 mL, 14.3 mmol, 1.50 equiv.) and the resulting solution was stirred at this temperature for 20 min. Then, a solution of 18-crown-6 (1.26 g, 4.77 mmol, 1.00 equiv.) and allyl tosylate (**391**) (1.52 g, 7.15 mmol, 1.50 equiv.) in dry degassed THF (6.0 mL) was added and the flask was rinsed with THF (4.0 mL). After stirring for 10 min at -78 °C, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After stirring for 60 min, the reaction was quenched with water (60 mL) and extracted with ethyl acetate (6 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 50:50) afforded compound **571b** as a colourless oil (1.85 g, 93%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2952, 29258, 1736, 1690, 1636, 1444, 1424, 1216, 1149, 1065.9, 1066, 993, 925.

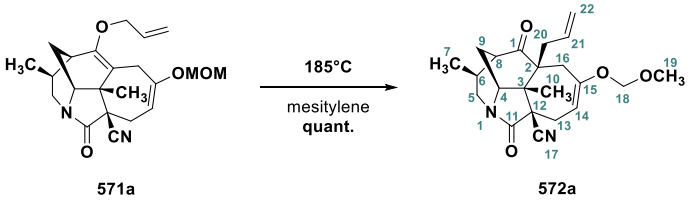
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.90 (ddt, 1H, *J* = 17.2, 10.3, 5.1 Hz, H-22), 5.30 (dq, 1H, *J* = 17.2, 1.7 Hz, H-23a), 5.18 (dq, 1H, *J* = 10.5, 1.5 Hz, H-23b), 4.97 (ddd, 1H, *J* = 8.8, 5.0, 2.0 Hz, H-14), 4.90 (d,

2H, *J* = 1.4 Hz, H-19), 4.21 (dq, 2H, *J* = 4.8, 1.6 Hz, H-21), 4.03 (dd, 1H, *J* = 13.5, 7.8 Hz, H-5a), 3.95 – 3.80 (m, 2H, H-4, H-16a), 3.70 (s, 3H, H-18), 3.40 (s, 3H, H-24), 2.65 – 2.53 (m, 2H, H-13a, H-16b), 2.46 (dd, 1H, *J* = 13.5, 10.5 Hz, H-5b), 2.22 (ddd, 1H, *J* = 15.0, 7.0, 1.3 Hz, H-13b), 2.14 – 2.01 (m, 2H, H-6, H-8), 1.98 (ddd, 1H, *J* = 13.7, 5.1, 2.5 Hz, H-9a), 1.54 (ddt, 1H, *J* = 13.7, 3.9, 1.0 Hz, H-9b), 1.19 (s, 3H, H-10), 0.96 (d, 3H, *J* = 6.9 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.2 (C-17), 171.3 (C-11), 153.2 (C-1), 152.9 (C-15), 134.1 (C-22), 116.9 (C-23), 113.1 (C-2), 95.5 (C-14), 93.7 (C-19), 68.8 (C-21), 62.3 (C-12), 58.2 (C-4), 56.3 (C-20), 52.1 (C-18), 51.8 (C-3), 41.5 (C-5), 34.5 (C-8), 32.0 (C-6), 30.7 (C-16), 27.6 (C-13), 20.8 (C-9), 18.9 (C-10), 18.8 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{23}H_{31}NO_6Na)^+$ requires 440.2044, found 440.2053.

***rac-(2R,3S,6aS,11R,11aR,11bS)*-11-allyl-9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(6*H*)-carbonitrile (572a)**

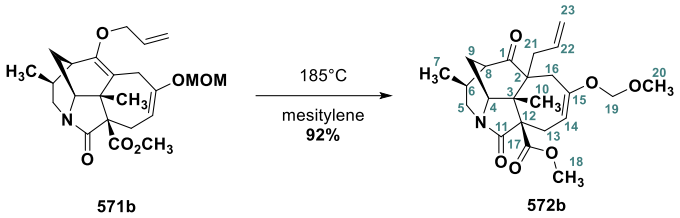


Compound **572a** was prepared adopting the procedure described by S. Ellis.[19]

A solution of enol **571a** (1.00 g, 2.60 mmol, 1 equiv.) was transferred to passivated pressure tube in benzene (5.0 mL), and the solvent was removed in a vacuum. The solvent-free enol was dissolved in mesitylene (120 mL) (previously distilled and stored over molecular sieves). A PTFE syringe filter was used to ensure that no solid particles were transferred with the solvent into the reaction mixture. The resulting solution was bubbled with nitrogen for 30 min, and the reaction vessel was then sealed and heated to 185 °C. After stirring for 2 h, the reaction mixture was cooled down and poured directly onto a silica column. After flushing with pentane to remove mesitylene, the product was eluted with ethyl acetate:pentane (50:50) to afford compound **572a** as a white solid (1.00 g, quant.).

Due to broad peaks in ^{1}H NMR shifts, characterisation of **572a** was not possible.

***rac*-methyl *(3S,6aR,11aR,11bS)*-11-allyl-9-(methoxymethoxy)-3,11a-dimethyl-6,12-dioxo-1,3,4,7,10,11,11a,11b-octahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carboxylate (572b)**



571b 572b

A solution of enol **571b** (1.82 g, 2.60 mmol, 1 equiv.) was transferred to passivated pressure tube in benzene (10.0 mL), and the solvent was removed in a vacuum. The solvent-free enol was dissolved in mesitylene (120 mL) (previously distilled and stored over molecular sieves). A PTFE syringe filter was used to ensure that no solid particles were transferred with the solvent into the reaction mixture. The resulting solution was bubbled with nitrogen for 30 min, and the reaction vessel was then sealed and heated to 185 °C. After stirring for 8 h, the reaction mixture was cooled down and poured directly onto a silica column. After flushing with pentane to remove mesitylene, the product was eluted with ethyl acetate:pentane (60:40) to afford compound **572b** as an amorphous foam (1.67 g, 92%).

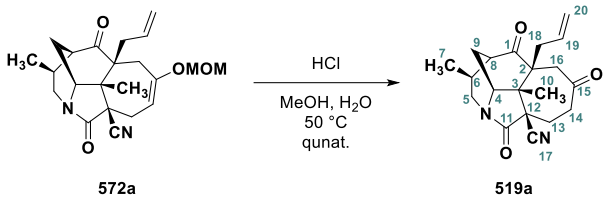
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2956, 2918, 1701, 1434, 1028, 1152, 922, 732.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.48 (ddt, 1H, *J* = 17.1, 10.0, 7.2 Hz, H-22), 5.18 – 5.05 (m, 2H, 23), 4.98 (d, 1H, *J* = 6.1 Hz, H-19a), 5.00 – 4.94 (m, 1H, H-14), 4.92 (d, 1H, *J* = 6.1 Hz, H-19b), 4.07 (dd, 1H, *J* = 13.6, 9.2 Hz, H-5a), 3.78 (d, 1H, *J* = 6.0 Hz, H-4), 3.70 (s, 3H, H-18), 3.43 (s, 3H, H-20), 3.11 – 2.87 (m, 2H, H-6, H-16a), 2.76 – 2.42 (m, 5H, H-9a, H-13, H-21), 2.36 – 2.21 (m, 1H, H-5b), 2.14 (d, 1H, *J* = 15.6 Hz, H-16b), 2.02 (dd, 1H, *J* = 15.1, 6.2 Hz, H-9b), 1.92 (d, 1H, *J* = 4.6 Hz, H-8), 1.20 (s, 3H, H-10), 1.04 (d, 3H, *J* = 6.9 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.9 (C-1), 172.8 (C-17), 171.8 (C-11), 153.8 (C-15), 133.2 (C-22), 120.1 (C-23), 95.3 (C-14), 93.5 (C-19), 62.2 (C-12), 61.3 (C-4), 56.5 (C-20), 55.7 (C-3), 52.7 (C-18), 52.1 (C-2), 45.8 (C-8), 40.6 (C-5), 40.2 (C-21), 37.1 (C-6), 33.8 (C-16), 28.9 (C-13), 19.0 (C-10), 18.7 (C-9), 17.6 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{23}H_{31}NO_6Na)^+$ requires 440.2044, found 440.2052.

***rac-(2R,3S,6aS,11R,11aR,11bS)*-11-allyl-3,11a-dimethyl-6,9,12-trioxodecahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (519a)**



572a 519a

To a solution of enol ether **572a** (300 mg, 0.780 mmol, 1 equiv.) in MeOH (15 mL) was added conc. HCl (1.0 mL) and the reaction mixture was heated to 50 °C. After stirring for 5 min at this temperature, water was added (10 mL) and the resulting opaque mixture was stirred for another 20 min. The reaction mixture was then cooled to room temperature, neutralised with sat. aq. sol. of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Ketone **519a** was obtained as a white solid (266 mg, quant.) and was used without further purification.

MP: 210 – 213 °C.

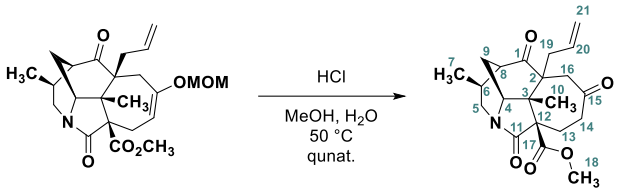
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2976, 2925, 1710, 1693, 1424, 1285, 1248, 1087, 993, 936.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.37 (ddt, 1H, *J* = 16.8, 9.9, 7.0 Hz, H-19), 5.24 – 5.12 (m, 2H, H-20), 4.05 (dd, 1H, *J* = 13.8, 9.1 Hz, H-5a), 3.95 (d, 1H, *J* = 5.8 Hz, H-4), 3.22 – 3.07 (m, 2H, H-6, H-16a), 2.80 (ddd, 1H, *J* = 15.9, 10.2, 7.1 Hz, H-13a), 2.70 – 2.53 (m, 4H, H-9a, H-14, H-18a), 2.53 – 2.41 (m, 2H, H-13b, H-18b), 2.32 (dd, 1H, *J* = 13.8, 9.2 Hz, H-5b), 2.26 (d, 1H, *J* = 12.9 Hz, H-16b), 2.15 (ddd, 1H, *J* = 15.6, 5.9, 1.0 Hz, H-9b), 2.00 (dd, 1H, *J* = 5.3, 1.1 Hz, H-8), 1.52 (s, 3H, H-10), 1.05 (d, 3H, *J* = 7.0 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.0 (C-15), 209.8 (C-1), 166.7 (C-11), 131.4 (C-19), 121.6 (C-20), 119.2 (C-17), 61.6 (C-4), 56.1 (C-3), 55.1 (C-2), 53.5 (C-12), 45.0 (C-8), 42.5 (C-16), 41.2 (C-5), 38.5 (C-18), 37.5 (C-14), 37.5 (C-6), 28.6 (C-13), 18.9 (C-9), 18.3 (C-10), 17.4 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ ($C_{20}H_{24}N_2O_3Na)^+$ requires 363.1679, found 363.1689.

***rac*-methyl *(3S,6aR,11aR,11bS)*-11-allyl-3,11a-dimethyl-6,9,12-trioxodecahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carboxylate (519b)**



572b 519b

To a solution of enol ether **572b** (1.633 g, 3.91 mmol, 1 equiv.) in MeOH (40 mL) was added conc. HCl (4.0 mL) and the reaction mixture was heated to 50 °C. After stirring for 5 min at this temperature, water was added (20 mL) and the resulting opaque mixture was stirred for another 20 min. The reaction mixture was then cooled to room temperature, neutralised with sat. aq. sol. of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Ketone **519b** was obtained as a white solid (1.46 g, quant.) and was used without further purification.

MP: 209-211 °C.

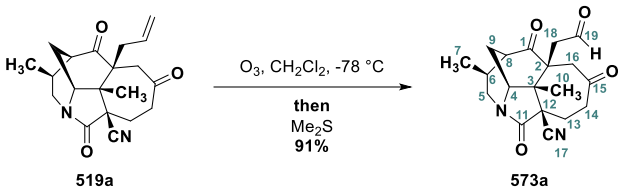
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 1704, 1434, 1289, 909, 730.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.41 (ddt, 1H, *J* = 17.0, 9.9, 7.0 Hz, H-20), 5.24 – 5.09 (m, 2H, H-21), 4.09 (dd, 1H, *J* = 13.7, 9.0 Hz, H-5a), 3.90 (d, 1H, *J* = 5.7 Hz, H-4), 3.71 (s, 3H, H-18), 3.24 (d, 1H, *J* = 13.2 Hz, H-16a), 3.07 (h, 1H, *J* = 7.4 Hz, H-6), 2.85 – 2.71 (m, 2H, H-14a, H-19a), 2.64 – 2.46 (m, 2H, H-9a, H-14b), 2.44 – 2.24 (m, 5H, H-5b, H-13, H-16b, H-19b), 2.08 (dd, 1H, *J* = 15.5, 5.8 Hz, H-9b), 1.96 – 1.92 (m, 1H, H-8), 1.15 (s, 3H, H-10), 1.02 (d, 3H, *J* = 7.0 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.7 (C-1), 211.4 (C-15), 171.8 (C-17), 170.9 (C-11), 132.1 (C-20), 121.1 (C-21), 64.5 (C-12), 61.1 (C-4), 56.6 (C-3), 55.6 (C-2), 52.9 (C-18), 45.4 (C-8), 43.4 (C-16), 40.8 (C-5), 40.1 (C-19), 39.1 (C-14), 37.7 (C-6), 26.8 (C-13), 19.4 (C-9), 18.2 (C-10), 17.5 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{21}H_{27}NO_5Na)^+$ requires 396.1781, found 396.1784.

***rac-(2R,3S,6aS,11R,11aR,11bS)*-3,11a-dimethyl-6,9,12-trioxo-11-(2-oxoethyl)decahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (573a)**



A solution of alkene **519a** (270 mg, mmol, 1 equiv.) in CH_2Cl_2 (40 mL) was cooled to -78°C and then bubble with ozone until persistent blue colour. The excess of ozone was then removed by bubbled the reaction mixture with oxygen for 5 min and Me_2S (1.0 mL) was then added. The reaction mixture was allowed to slowly warm up to room temperature and was stirred for 20 h. The volatiles were removed under the reduced pressure and the obtained residue was purified by gradient column chromatography (ethyl acetate:pentane = 60:40 to 100:0) to afford aldehyde **573a** as a white solid (247 mg, 91%) and corresponding ozonide, which after repeating the reductive workup provided another portion of aldehyde **573a** (23.0 mg, 8.0%).

MP: amorphous solid 130 – 150 °C.

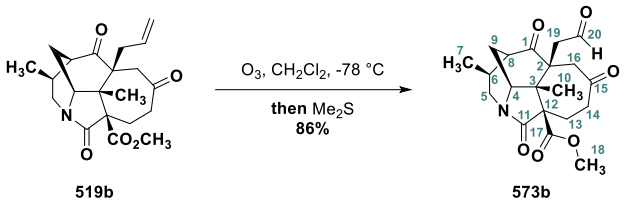
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2929, 1714, 1453, 1427, 1283, 1088, 1074, 1019, 994, 924, 861, 736.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (t, 1H, *J* = 1.7 Hz, H-19), 4.04 (dd, 1H, *J* = 13.8, 9.1 Hz, H-5a), 3.92 (d, 1H, *J* = 5.7 Hz, H-4), 3.51 (dd, 1H, *J* = 13.2, 2.1 Hz, H-16a), 3.24 (dt, 1H, *J* = 9.4, 7.5 Hz, H-6), 3.14 (dd, 1H, *J* = 16.4, 1.4 Hz, H-18a), 2.90 (dt, 1H, *J* = 16.7, 2.5 Hz, H-18b), 2.80 (ddd, 1H, *J* = 15.7, 10.8, 6.4 Hz, H-13a), 2.74 – 2.58 (m, 2H, H-14), 2.48 (ddd, 2H, *J* = 15.4, 5.2, 2.8 Hz, H-9a, H-13b), 2.32 (dd, 1H, *J* = 13.9, 9.1 Hz, H-5b), 2.22 – 2.13 (m, 2H, H-8, H-9b), 2.10 (d, 1H, *J* = 13.1 Hz, H-16b), 1.50 (s, 3H, H-10), 1.05 (d, 3H, *J* = 7.0 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.5 (C-15), 208.7 (C-1), 198.8 (C-19), 166.4 (C-11), 118.9 (C-17), 61.5 (C-4), 56.2 (C-3), 53.3(C-12), 52.6 (C-2), 47.6 (C-18), 44.7 (C-8), 44.6 (C-16), 41.2 (C-5), 37.6 (C-14), 37.0 (C-6), 28.4 (C-13), 19.2 (C-9), 18.9 (C-10), 17.1 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{19}H_{22}N_2O_4Na)^+$ requires 365.1472, found 365.1475.

***rac*-methyl *(3S,6aR,11R,11aR,11bS)*-3,11a-dimethyl-6,9,12-trioxo-11-(2-oxoethyl)decahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carboxylate (573b)**



A solution of alkene **519b** (1.00 g, 2.68 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) was cooled to -78°C and then bubble with ozone until persistent blue colour. The excess of ozone was then removed by bubbled the reaction mixture with oxygen for 5 min and Me_2S (5.0 mL) was then added. The reaction mixture was allowed to slowly warm up to room temperature and was stirred for 20 h. The volatiles were removed under the reduced pressure and the obtained residue was purified by gradient column chromatography (ethyl acetate:pentane = 50:50 to 100:0) to afford aldehyde **573b** as a white amorphous solid (862 mg, 86%) and corresponding ozonide (92.7 mg, 8.2%).

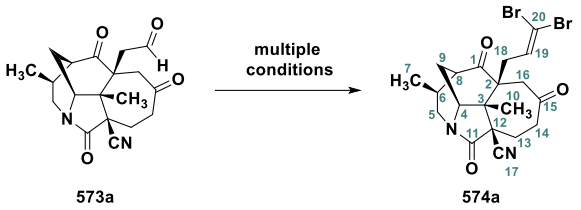
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2956, 2928, 1704, 1444, 1288, 1288, 1246, 1227, 1170, 916, 733.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.60 (dd, 1H, *J* = 2.1, 1.4 Hz, H-20), 4.18 – 4.05 (m, 1H, H-5a), 3.87 (d, 1H, *J* = 5.7 Hz, H-4), 3.72 (s, 3H, H-18), 3.74 – 3.64 (m, 1H, H-16a), 3.21 (dt, 1H, *J* = 15.9, 8.2 Hz, H-6), 3.11 (d, 1H, *J* = 16.4 Hz, H-19a), 2.98 (d, 1H, *J* = 16.7 Hz, H-19b), 2.94 – 2.79 (m, 1H, H-14a), 2.61 (dt, 1H, *J* = 19.8, 4.3 Hz, H-14b), 2.52 – 2.37 (m, 3H, H-9a, H-13), 2.32 (dd, 1H, *J* = 13.8, 9.1 Hz, H-5b), 2.16 – 2.05 (m, 3H, H-8, H-9b, H-16-b), 1.13 (s, 3H, H-10), 1.04 (d, 3H, *J* = 7.0 Hz, H-7)

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.4 (C-1), 210.1 (C-15), 199.5 (C-20), 171.7 (C-11), 170.9 (C-17), 64.0 (C-12), 61.3 (C-4), 55.9 (C-3), 53.9 (C-2), 53.1 (C-18), 49.1 (C-19), 45.5 (C-16), 45.0 (C-8), 40.8 (C-5), 39.4 (C-14), 37.3 (C-6), 26.9 (C-13), 19.8 (C-9), 19.0 (C-10), 17.4 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ ($C_{20}H_{25}NO_6Na)^+$ requires 398.1574, found 398.1566.

***rac-(2R,3S,6aS,11R,11aR,11bS)*-11-(3,3-dibromoallyl)-3,11a-dimethyl-6,9,12-trioxodecahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (574a)**



Conditions A: To a suspension of Wolkoff reagent (65 mg, 117 μmol, 4.00 equiv.) in THF (0.8 mL) was added 1.0 M solution *t*-BuOK (102 μL, 102 μmol, 3.50 equiv.) in THF at 0 °C and the resulting mixture was allowed to warm up to room temperature. After stirring for 15 min, a solution of aldehyde **573a** (10 mg, 29.2 μmol, 1 equiv.) in THF (0.8 mL) was added dropwise at room temperature. After 10 min, the reaction mixture was quenched with sat. aq. solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (Et_2O:pentane = 30:70 to 40:60) afforded compound **574a** as an off-white solid (12.5 mg, 86%).

Conditions B: To a vigorously stirred mixture of aldehyde **573a** (10.0 mg, 29.2 μmol, 1 equiv.), PPh_3 (15.3 mg, 58.4 μmol, 2.00 equiv.) and Zn dust (3.8 mg, 58.4 μmol, 2.00 equiv.) in dry CH_2Cl_2 (0.30 mL) at 0 °C was added CBr_4 (19.4 mg, 58.4 μmol, 2.00 equiv.) and the resulting mixture was stirred at room temperature for 30 min. The TLC analysis revealed only partial conversion, and therefore, another portion of reagents (2.00 equiv.) was added, and the reaction mixture was stirred for another 45 min. Subsequent TLC analysis revealed better, but still not full conversion. The full conversion was achieved after the addition of another 1.00 equiv. of reagent and stirring the reaction for an additional 40 min. The reaction mixture was then directly loaded onto a silica column, and the product was eluted with ethyl acetate:toluene (5:95 to 10:90). Compound **574a** was obtained as a white solid (9.8 mg, 67%).

MP: 244 – 246 °C (decomp.).

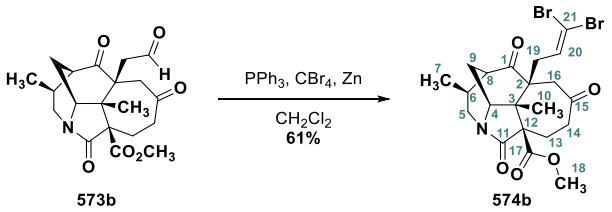
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2958, 2924, 1718, 1483, 1427, 1283, 1017, 926, 737.

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.07 (dd, 1H, *J* = 8.3, 5.2 Hz, H-19), 4.07 (dd, 1H, *J* = 13.9, 9.1 Hz, H-5a), 3.98 (d, 1H, *J* = 5.8 Hz, H-4), 3.25 (dd, 1H, *J* = 13.0, 2.0 Hz, H-16a), 3.22 – 3.11 (m, 1H, H-6), 2.89 – 2.76 (m, 2H, H-13a, H-18a), 2.69 – 2.58 (m, 3H, H-9a, H-14), 2.56 – 2.46 (m, 2H, H-13b, H-18b), 2.34 (dd, 1H, *J* = 13.9, 9.2 Hz, H-5b), 2.18 (ddd, 1H, *J* = 15.7, 5.9, 0.9 Hz, H-9b), 2.12 (d, 1H, *J* = 13.0 Hz, H-16b), 2.04 (d, 1H, *J* = 4.7 Hz, H-8), 1.56 (s, 3H, H-10), 1.09 (d, 3H, *J* = 6.9 Hz, H-7).

^{13}C NMR ($CDCl_3$, 126 MHz) δ: 210.3 (C-15), 210.1 (C-1), 166.5 (C-11), 131.7, 119.0 (C-17), 93.3 (C-20), 61.5 (C-4), 56.3 (C-3), 53.8 (C-12), 53.5 (C-2), 44.7 (C-8), 43.6, 41.2 (C-5), 37.8 (C-6), 37.6 (C-18), 37.5 (C-14), 28.5 (C-13), 19.1 (C-9), 18.3 (C-10), 17.4 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{20}H_{22}N_2O_3Na)^+$ requires 518.9889, found 518.9911.

***rac*-methyl *(3S,6aR,11R,11aR,11bS)*-11-(3,3-dibromoallyl)-3,11a-dimethyl-6,9,12-trioxodecahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carboxylate (574b)**



To a vigorously stirred mixture of aldehyde **573b** (70.0 mg, 186 µmol, 1 equiv.), PPh3 (245 mg, 932 µmol, 5.00 equiv.) and Zn dust (122 mg, 1.86 mmol, 10.0 equiv.) in dry CH_2Cl_2 (2.0 mL) was added solution of CBr_4 (309 mg, 932 µmol, 5.00 equiv.) in CH_2Cl_2 (1.0 mL) over 30 min using syringe pump. The reaction mixture was then directly loaded onto a silica column and the product was eluted with acetonitrile:CH_2Cl_2 (5:95 to 10:90) to afford compound **574b** as a white amorphous foam (60.5 mg, 61%).

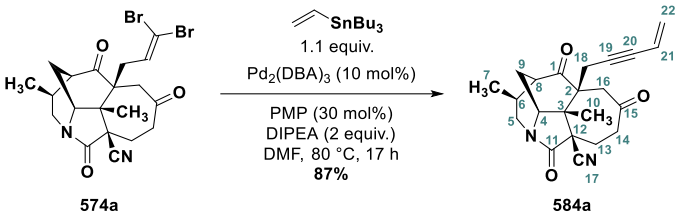
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2956, 1704, 1435, 1288, 1246, 1166, 1026, 914, 731.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.06 (dd, 1H, *J* = 8.0, 5.3 Hz, H-20), 4.10 (dd, 1H, *J* = 13.7, 9.0 Hz, H-5a), 3.91 (d, 1H, *J* = 5.7 Hz, H-4), 3.73 (s, 3H, H-18), 3.29 (d, 1H, *J* = 13.5 Hz, H-16a), 3.10 (h, 1H, *J* = 7.5 Hz, H-6), 2.91 (ddd, 1H, *J* = 16.0, 7.9, 0.9 Hz, H-19a), 2.81 (ddd, 1H *J* = 19.6, 9.1, 5.5 Hz, H-14a), 2.65 – 2.49 (m, 2H, H-9a, H-14b), 2.49 – 2.29 (m, 4H, H-5b, H-13, H-19b), 2.16 (d, 1H, *J* = 13.3 Hz, H-16b), 2.11 (dd, 1H, *J* = 15.7, 5.9 Hz, H-9b), 1.95 (d, 1H, *J* = 4.9 Hz, H-8), 1.18 (s, 3H, H-10), 1.06 (d, 3H, *J* = 7.0 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.9 (C-1), 211.6 (C-15), 171.6 (C-11), 170.7 (C-17), 132.3 (C-20), 92.9 (C-21), 64.4 (C-12), 61.0 (C-4), 55.8 (C-3), 55.4 (C-2), 53.0 (C-18), 45.0 (C-8), 44.4 (C-16), 40.8 (C-5), 39.1 (C-19), 39.0 (C-14), 38.0 (C-6), 26.8 (C-13), 19.5 (C-9), 18.2 (C-10), 17.5 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{21}H_{25}Br_2NO_5)^+$ requires 551.9992, found 551.9994.

***rac-(2R,3S,6aS,11R,11aR,11bS)*-3,11a-dimethyl-6,9,12-trioxo-11-(pent-4-en-2-yn-1-yl)decahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carbonitrile (584a)**



Compound **584a** was prepared adopting the procedure published by Wang.[47]

A flask charged with compound **574a** (70 mg, 141 µmol, 1 equiv.), Pd_2dba_3 (6.4 mg, 7.0 µmol, 5.0 mol%) and tris(4-methoxyphenyl)phosphine (9.9 mg, 28 µmol, 20 mol%) was evacuated and backfilled with argon (3x). Degassed dry DMF (5 mL) was then added followed by DIPEA (37 µL, 27 µmol, 1.50 equiv.) and tributyl(vinyl)stannane (46 µL, 155 µmol, 1.10 equiv.). The reaction mixture was evacuated and backfilled with argon (3x) and then heated to 80 °C for 17 h. Solid KF was then added and after stirring for additional 30 min, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with sat. aq. solution of NH_3 (2 x 10 mL), the organic phase dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (silica:K_2CO_3, 10:1, ethyl acetate:pentane = 40:60 to 50:50) afforded compound **584a** as a white foam (44.6 mg, 87%).

MP: 185 – 187 °C.

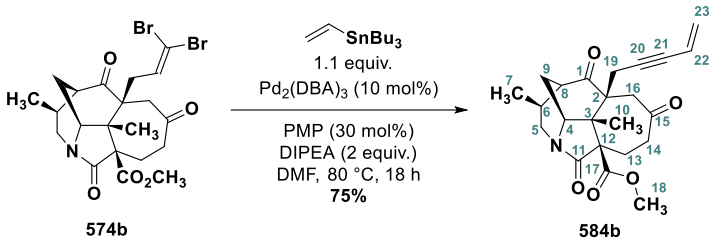
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2959, 2927, 1713, 1484, 1454, 1426, 1283, 926, 736.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.63 (ddt, 1H, *J* = 17.6, 10.7, 1.9 Hz, H-21), 5.52 (dd, 1H, *J* = 17.5, 2.4 Hz, H-22a), 5.41 (dd, 1H, *J* = 10.8, 2.4 Hz, H-22b), 4.05 (dd, 1H, *J* = 13.9, 9.1 Hz, H-5a), 3.92 (d, 1H, *J* = 6.2 Hz, H-4), 3.34 (dd, 1H, *J* = 13.1, 2.0 Hz, H-16a), 3.20 (h, 1H, *J* = 7.7 Hz, H-6), 3.01 (d, 1H, *J* = 17.0 Hz, H-18a), 2.82 – 2.70 (m, 2H, H-13a, H-18b), 2.70 – 2.58 (m, 2H, H-14), 2.53 (ddd, 1H, *J* = 15.9, 5.2, 1.5 Hz, H-9a), 2.51 – 2.40 (m, 1H, H-13b), 2.38 (d, 1H, *J* = 13.1 Hz, H-16b), 2.32 (dd, 1H, *J* = 13.8, 9.1 Hz, H-5b), 2.24 – 2.12 (m, 2H, H-8, H-9b), 1.47 (s, 3H, H-10), 1.06 (d, 3H, *J* = 7.0 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 210.8 (C-1), 208.2 (C-15), 166.5 (C-11), 127.9 (C-22), 118.8 (C-17), 116.5 (C-21), 83.6 (C-19), 83.6 (C-20), 61.5 (C-4), 55.5 (C-3), 54.8 (C-12), 53.4 (C-2), 44.1 (C-8), 43.7 (C-16), 41.2 (C-5), 37.5 (C-6), 37.3 (C-14), 28.4 (C-13), 26.4 (C-18), 19.5 (C-9), 18.0 (C-10), 17.3 (C-7).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ ($C_{22}H_{24}N_2O_3Na)^+$ requires 387.1679, found 387.1692.

***rac*-methyl *(3S,6aR,11R,11aR,11bS)*-3,11a-dimethyl-6,9,12-trioxo-11-(pent-4-en-2-yn-1-yl)decahydro-2H-2,11-methanocyclohepta[*a*]indolizine-6a(*6H*)-carboxylate (584b)**



Compound **584b** was prepared adopting the procedure published by Wang.[47]

A flask charged with compound **574b** (59 mg, 111 μmol, 1 equiv.), Pd_2dba_3 (5.1 mg, 5.6 μmol, 5.0 mol%) and tris(4-methoxyphenyl)phosphine (7.8 mg, 22 μmol, 20 mol%) was evacuated and backfilled with argon (3x). Degassed dry DMF (3.7 mL) was then added followed by DIPEA (29 μL, 167 μmol, 1.50 equiv.) and tributyl(vinyl)stannane (36 μL, 122 μmol, 1.10 equiv.). The reaction mixture was evacuated and backfilled with argon (3x) and then heated to 80 °C for 18 h. Solid KF was then added and after stirring for additional 30 min, the reaction mixture was diluted with diethyl ether (100 mL) and washed with brine (3 x 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (silica:K_2CO_3, 10:1, ethyl acetate:pentane = 50:50 to 60:40) afforded compound **584b** as a white foam (32.9 mg, 75%).

MP: 190 – 192 °C (rac).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2957, 2926, 1706, 1446, 1288, 1243, 1162, 972, 733.

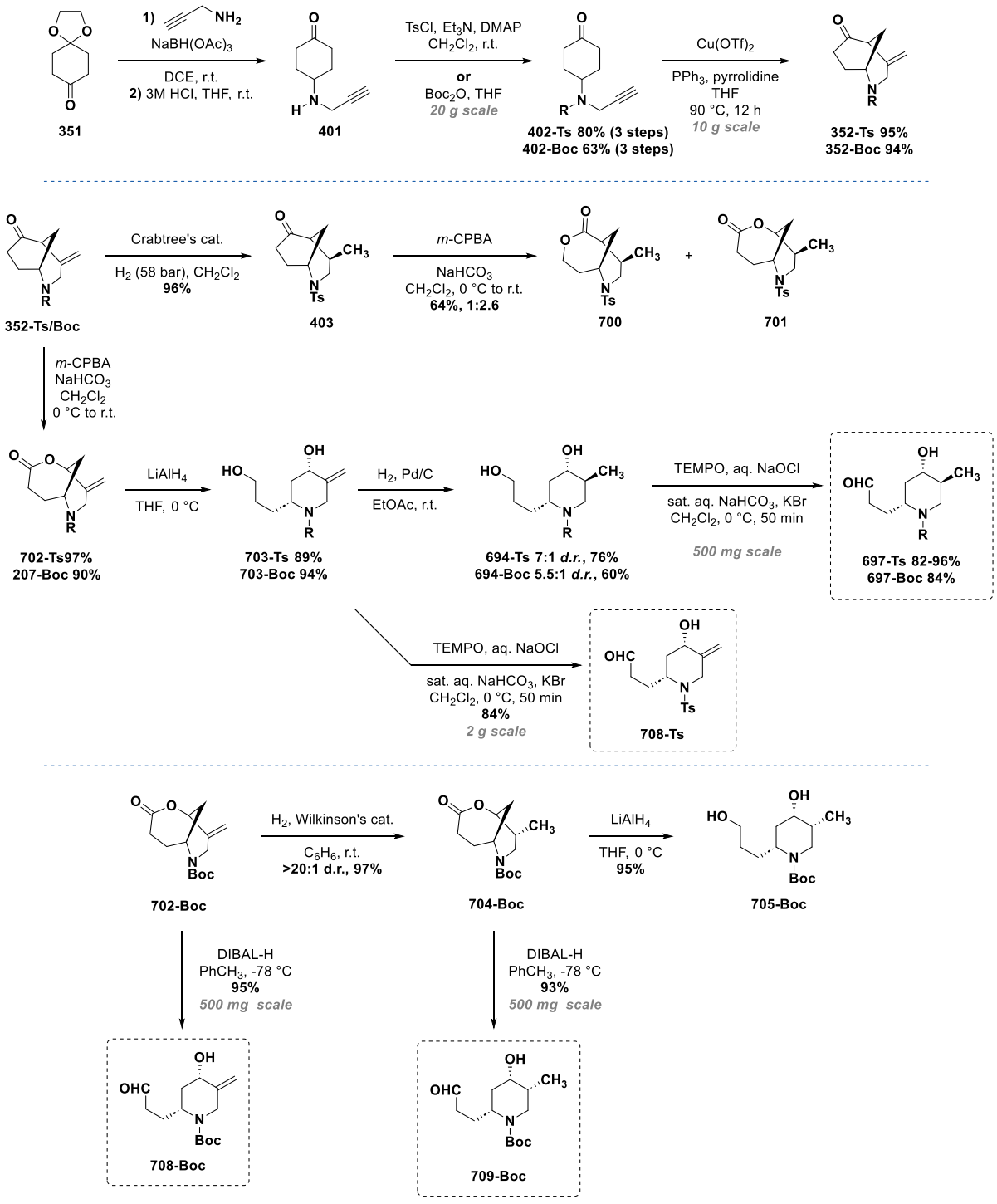
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.64 (ddt, 1H, *J* = 17.5, 10.8, 1.9 Hz, H-22), 5.51 (dd, 1H, *J* = 17.6, 2.4 Hz, H-23a), 5.40 (dd, 1H, *J* = 10.9, 2.4 Hz, H-23b), 4.10 (dd, 1H, *J* = 13.6, 9.0 Hz, H-5a), 3.90 (d, 1H, *J* = 5.6 Hz, H-4), 3.71 (s, 3H, H-18), 3.46 (d, 1H, *J* = 13.4 Hz, H-16a), 3.17 (dt, 1H, *J* = 15.4, 7.9 Hz, H-6), 3.08 (d, 1H, *J* = 17.1 Hz, H-19a), 2.80 (ddd, 1H, *J* = 19.5, 9.9, 4.6 Hz, H-14a), 2.71 (d, 1H, *J* = 16.8 Hz, H-19b), 2.61 – 2.47 (m, 2H, H-9a, H-14b), 2.46 – 2.35 (m, 3H, H-13, H-16b), 2.33 (dd, 1H, *J* = 13.7, 9.2 Hz, H-5b), 2.21 – 2.16 (m, 1H, H-8), 2.12 (dd, 1H, *J* = 15.7, 5.7 Hz, H-9b), 1.11 (s, 3H, H-10), 1.05 (d, 3H, *J* = 7.0 Hz, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 212.5 (C-1), 209.6 (C-15), 171.6 (C-11), 170.8 (C-17), 127.7 (C-23), 116.6 (C-22), 84.3 (C-20), 83.4 (C-21), 64.3 (C-12), 61.2 (C-4), 56.3 (C-2), 55.2 (C-3), 52.9 (C-18), 44.5 (C-8), 40.8 (C-5), 39.1 (C-14), 37.6 (C-6), 27.6 (C-19), 26.7 (C-13), 20.0 (C-9), 18.0 (C-10), 17.4 (C-7).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{23}H_{27}NO_5Na)^+$ requires 420.1781, found 420.1796.

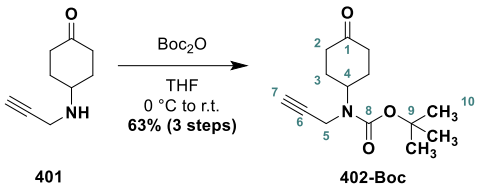
4.4 Experimental details for Chapter 3

4.4.1 Synthesis of aldehyde building blocks



Scheme 4.20. *Synthesis of aldehyde building blocks.*

***tert*-butyl (4-oxocyclohexyl)(prop-2-yn-1-yl)carbamate (402-Boc)**



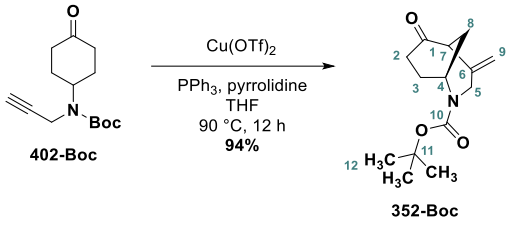
Compound **402-Boc** was prepared according to the procedure published in the literature.[21]

To a solution of amine **401** (19.4 g, 128.3 mmol, 1 equiv.) in THF (135 mL) at 0 °C was added Boc_2O (29.4 g, 134.7 mmol, 1.05 equiv.) and the resulting solution was stirred for 19 h at room temperature. The reaction mixture was then poured onto water (200 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (dry loading, ethyl acetate:pentane = 15:85 to 20:80) afforded protected amine **402-Boc** as a white solid (20.3 g, 63%, over 3 steps). The spectroscopic data are in agreement with the literature values.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.37 (br s, 1H, H-4), 3.93 (br s, 2H, H-5), 2.48 – 2.38 (m, 4H, H-2), 2.15 (t, J = 2.4 Hz, 1H, H-7), 2.18 – 2.07 (m, 4H, H-3), 2.07 – 1.93 (m, 2H, H-3), 1.49 (s, 9H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 209.6 (C-1), 154.8 (C-8), 81.2 (C-9), 80.9 (C-6), 70.8 (C-7), 53.6 (C-4), 40.2 (C-2), 32.6 (C-5), 29.8 (C-3), 28.5 (C10).

***rac-tert*-butyl (*1R,5S*)-4-methylene-6-oxo-2-azabicyclo[3.3.1]nonane-2-carboxylate (352-Boc)**



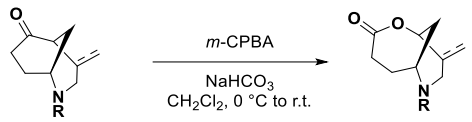
Compound **352-Boc** was prepared according to the procedure published in the literature.[21]

An oven-dried Schlenk flask was changed with alkyne **402-Boc** (10.0 g, 39.8 mmol, 1 equiv.), $Cu(OTf)_2$ (1.08 g, 2.98 mmol, 7.50 mol %) and PPh_3 (3.13 g, 11.9 mmol, 0.30 equiv.) and degassed using three vacuum – N_2 cycles. Degassed THF (160 mL) was then added, followed by pyrrolidine (996 µL, 11.9 mmol, 0.30 equiv.). The reaction vessel was sealed and heated to 90 °C for 18 h. The reaction mixture was then concentrated under reduced pressure and purified by gradient column chromatography (ethyl acetate:pentane = 10:90 to 15:85). The product of cyclisation **352-Boc** was obtained as a white solid (9.43, 94%). The spectroscopic data are in agreement with literature values.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.08 – 4.94 (m, 2H, H-9), 4.40 – 4.12 (m, 2H, H-4, H-5a), 4.10 – 3.95 (m, 1H, H-5b), 3.31 (s, 1H, H-7), 2.72 – 2.54 (m, 1H, H-2a), 2.41 – 2.17 (m, 3H, H-2b, H-8), 1.99 (ddt, J = 16.2, 13.3, 2.8 Hz, 1H, H-3a), 1.83 – 1.70 (m, 1H, H-3b), 1.47 (s, 9H, H-12).

^{13}C NMR (101 MHz, $CDCl_3$) δ: (rotameric, second rotamer marked with *); 209.1 (C-1*), 208.9 (C-1), 155.1 (C-10), 154.9 (C-10*), 139.7 (C-6*), 139.6 (C-6), 114.1 (C-9), 113.8 (C-9*), 80.2 (C-11, C-11*), 51.3 (C-7*), 50.8 (C-7), 46.3 (C-4), 46.3 (C-5*), 45.5 (C-4*), 45.3 (C-5), 35.3 (C-2*), 34.9 (C-2), 31.4 (C-3), 31.1 (C-8), 30.6 (C-3*), 28.5 (C-12).

General conditions for Baeyer-Villiger rearrangement (General procedure 3.1)



352/403 **700/701/702**

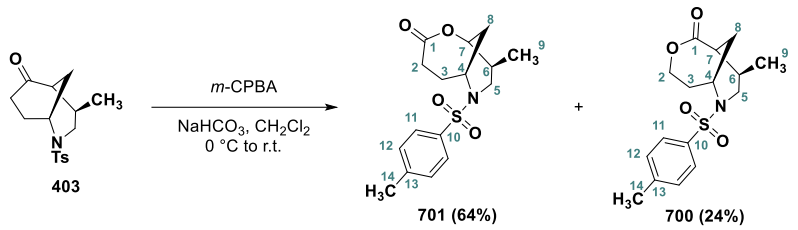
To a solution of substrate in CH_2Cl_2 (0.40 M) at 0 °C was added finely grounded $NaHCO_3$ (1.50 equiv.) fallowed by dropwise a solution of purified *m*-CPBA (1.25 equiv.) in CH_2Cl_2 (0.5 M) over 30 min using syringe pump. After completion of the addition, the reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The reaction was then quenched with 1:1 mixture of sat. aq. $NaHCO_3$ and 2 M $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography.

Purification of *m*-CPBA[57]

Preparation of pH 7.5 phosphate buffer solution: The pH 7.5 buffer was prepared by mixing of 0.1 M solution of NaOH (prepared by dissolving of 1.64 g of NaOH in 410 mL of distilled water) and 0.2 M solution of KH_2PO_4 (prepared by dissolving of 6.8 g of KH_2PO_4 in 250 mL of distilled water).

Purification of *m*-CPBA: Commercial *m*-CPBA (Sigma Aldrich) (30.0 g, 70-75%) was dissolved in Et_2O (200 mL) and was washed with a solution of phosphate buffer (3x150 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure (0 °C) to afford *m*-CPBA as a white solid which was stored in the freezer.

***rac*-(*1S,6R,9S*)-9-methyl-7-tosyl-2-oxa-7-azabicyclo[4.3.1]decan-3-one (701) and *rac(1S,6S,9R)-9-methyl-7-tosyl-3-oxa-7-azabicyclo[4.3.1]decan-2-one* (700)**[i]



Compounds **700** and **701** was prepared using ***General procedure 3.1*** from compound **403** (100.0 mg, 0.325 mmol, 1 equiv.) in reaction with *m*-CPBA (70.1 mg, 0.406 mmol, 1.25 equiv.) and $NaHCO_3$ (41.5 mg, 0.488 mmol, 1.50 equiv.) in CH_2Cl_2 (1.6 mL). Purification by PTCL (pure Et_2O) afforded compound **701** (67.3 mg, 64%) as a colourless oil and compound **700** (25.0 mg. 24%) as a colourless oil.

Compound 701:

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 1721, 1342, 1161, 916.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 – 7.64 (m, 2H, H-11), 7.38 – 7.30 (m, 2H, H-12), 4.08 (td, J = 4.7, 2.1 Hz, 1H, H-7), 4.03 (dt, J = 5.2, 2.9 Hz, 1H, H-4), 3.67 – 3.53 (m, 1H, H-5a), 3.08 (ddd, J = 15.9, 13.0, 3.1 Hz, 1H, H-2a), 2.73 (dddd, J = 15.7, 6.7, 2.5, 0.8 Hz, 1H, H-2b), 2.44 (s, 3H, H-14), 2.41 – 2.33 (m, 2H, H-5b, H-7), 2.33 – 2.22 (m, 1H, H-3a), 1.97 – 1.80 (m, 2H, H-8), 1.80 – 1.67 (m, 1H, H-3b), 1.10 (d, J = 6.4 Hz, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.3 (C-1), 144.1 (C-13), 134.1 (C-10), 130.1 (C-12), 127.5 (C-11), 77.4 (C-7), 49.7 (C-4), 45.9 (C-5), 36.5 (C-6), 32.3 (C-2), 31.7 (C-8), 30.3 (C-3), 21.7 (C-14), 19.0 (C-9).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{16}H_{21}NO_4S+Na)^+$ requires 324.1264, found 324.1267.

Compound 700:

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 1721, 1340, 1162, 1047.

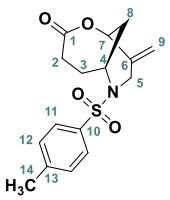
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71 – 7.67 (m, 2H, H-11), 7.37 – 7.28 (m, 2H, H-12), 4.84 – 4.77 (m, 1H, H-2a), 4.23 (ddd, J = 13.6, 4.7, 2.8 Hz, 1H, H-2b), 3.99 (tt, J = 5.3, 2.8 Hz, 1H, H-4), 3.62 – 3.59 (m, 1H, H-5a), 2.62 (td, J = 5.8, 2.9 Hz, 1H, H-7), 2.49 – 2.44 (m, 1H, H-6), 2.45 (s, 3H, H-14), 2.45 – 2.40 (m, 2H, H-8a, H-3), 1.97 (ddt, J = 14.7, 11.6, 2.7 Hz, 1H, H-3b), 1.78 – 1.69 (m, 2H, H-8), 1.11 (d, J = 6.1 Hz, 3H, H-9).

[i] Reaction was performed by Daniel Cox.

^{13}C NMR (151 MHz, $CDCl_3$) δ: 174.9 (C-1), 144.1 (C-13), 134.0 (C-10), 130.1 (C-12), 127.5 (C-11), 64.5 (C-2), 49.8 (C-4), 46.1 (C-5), 45.2 (C-7), 37.3 (C-3), 31.1 (C-7), 25.6 (C-8), 21.7 (C-14), 20.4 (C-9).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{16}H_{21}NO_4SNa)^+$ requires 324.1264, found 324.1267.

rac-(*1S,6R*)-9-methylene-7-tosyl-2-oxa-7-azabicyclo[4.3.1]decan-3-one (702-Ts)



702-Ts

Compound **702-Ts** was prepared using ***General procedure 3.1*** from compound **352-Ts** (2.00 g, 6.55 mmol. 1 equiv.) in reaction with *m*-CPBA (1.41 g, 8.19 mmol, 1.25 equiv.) and $NaHCO_3$ (835 mg, 9.82 mmol, 1.50 equiv.) in CH_2Cl_2 (33 mL). Purification by column chromatography (ethyl acetate:pentane = 40:60) afforded compound **702-Ts** (2.05 g, 97%) as a white solid.

m.p.: 58 – 60 °C.

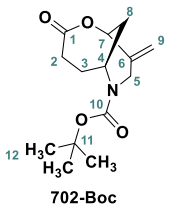
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2254, 1727, 1345, 1164, 676.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 – 7.64 (m, 2H, H-11), 7.37 – 7.31 (m, 2H, H-12), 5.52 – 5.45 (m, 2H, H-9), 4.89 (m, 1H, H-7), 4.24 (d, J = 12.9 Hz, 1H, H-5a), 4.14 (app. tt, J = 4.7, 2.4 Hz, 1H, H-4), 3.34 (m, 1H, H-5b), 3.04 (ddd, J = 15.3, 14.0, 2.7 Hz, 1H, H-2a), 2.59 (ddd, J = 15.3, 6.1, 2.0, Hz, 1H, H-2b), 2.43 (s, 3H, H-14), 2.28 – 2.16 (m, 1H, H-3a), 1.99 – 1.83 (m, 2H, H-8), 1.74 (m, 1H, H-3b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.6 (C-1), 144.2 (C-6), 140.4 (C-10), 133.9 (C-13), 130.1 (C-12), 127.4 (C-11), 118.7 (C-9), 70.1 (C-7), 50.6 (C-4), 47.8 (C-5), 32.9 (C-8), 31.7 (C-2), 31.0 (C-3), 21.7 (C-14).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{16}H_{20}NO_4SNa)^+$ requires 344.0927, found 344.0919.

rac-tert-butyl (*1S,6R*)-9-methylene-3-oxo-2-oxa-7-azabicyclo[4.3.1]decane-7-carboxylate (702-Boc)



702-Boc

Compound **702-Boc** was prepared using ***General procedure 3.1*** from compound **352-Boc** (5.90 g, 23.5 mmol. 1 equiv.) in reaction with *m*-CPBA (5.06 g, 29.3 mmol, 1.25 equiv.) and $NaHCO_3$ (2.96 g, 35.2 mmol, 1.50 equiv.) in CH_2Cl_2 (117 mL). Purification by column chromatography (ethyl acetate:pentane = 50:50) afforded compound **702-Boc** (5.68 g, 90%) as a white solid.

m.p.: 122 – 124 °C.

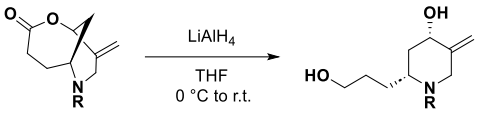
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2974, 2935, 1727, 1688, 1394, 1165, 1140, 868.

^{1}H NMR (500 MHz, DMSO, 363 K) δ: 5.45 – 5.40 (m, 1H, H-9a), 5.29 – 5.25 (m, 1H, H-9b), 5.07 – 5.00 (m, 1H, H-7), 4.31 (d, 1H, *J* = 15.0 Hz, H-5a), 4.20 (q, 1H, *J* = 3.9 Hz, H-4), 3.74 (d, 1H, *J* = 15.0 Hz, H-5b), 2.69 (ddd, 1H, *J* = 15.1, 13.9, 2.7 Hz, H-2a), 2.51 – 2.44 (m, 1H, H-8a), 2.41 (dddd, 1H, *J* = 15.1, 6.2, 2.1, 0.9 Hz, H-2b), 2.08 – 2.01 (m ,2H, H-3a), 2.05 – 1.99 (m, 1H, H-8b), 1.64 (tt, 1H, *J* = 14.2, 2.3 Hz, H-3b), 1.44 (s, 9H, H-12).

^{13}C NMR (126 MHz, DMSO, 363 K) δ: 173.2 (C-1), 153.6 (C-10), 142.2 (C-6), 115.5 (C-9), 78.8 (C-11), 70.3 (C-7), 48.0 (C-4), 45.2 (C-5), 32.2 (C-8), 31.2 (C-2), 27.7 (C-12), 27.1 (C-3).

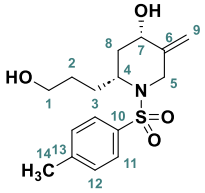
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{14}H_{21}NO_4Na)^+$ requires 290.1363, found 290.1367.

Synthesis of diols 703-Ts and 703-Boc



702-Ts/Boc **703-Ts 89%** **703-Boc 94%**

***rac*-(*2R,4S*)-2-(3-hydroxypropyl)-5-methylene-1-tosylpiperidin-4-ol (703-Ts)**



703-Ts (89%)

To a solution of lactone **702-Ts** (2.84 g, 8.84 mmol, 1 equiv.) in dry THF (35 mL) at 0 °C was dropwise added 1.0 M solution $LiAlH_4$ (9.7 mL, 9.7 mmol, 1.10 equiv.) in THF and the resulting solution was stirred for 30 min at this temperature. The reaction was then quenched with sat. aq. solution of Rochelle's salt (100 mL), and the resulting mixture was stirred for 15 min and then extracted with ethyl acetate (3x100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography (ethyl acetate:pentane = 50:50 to 100:0) afforded compound **703-Ts** (2.55 g, 89%) as a white solid.

m.p.: 80 – 82 °C.

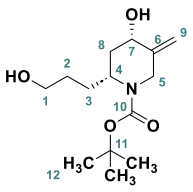
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3352, 3240, 2922, 1331, 1151, 905, 679.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 – 7.63 (m, 2H, H-11), 7.26 – 7.20 (m, 2H, H-12), 4.95 – 4.88 (m, 2H, H-9), 4.22 (d, J = 15.6 Hz, 1H, H-5a), 4.10 – 4.01 (m, 2H, H-5b, H-7), 3.93 (tdd, J = 9.3, 4.7, 1.9 Hz, 1H, H-4), 3.76 – 3.58 (m, 2H, H-1), 2.40 (s, 3H, H-14), 2.09 (dtd, J = 13.6, 8.9, 5.9 Hz, 1H, H-3a), 1.84 – 1.73 (m, 1H, H-3b), 1.71 – 1.66 (m, 1H, H-8a), 1.68 – 1.61 (m, 2H, H-2), 1.61 – 1.50 (m, 1H, H-8b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.3 (C-7), 142.9 (C-13), 137.9 (C-10), 129.6 (C-12), 127.5 (C-11), 113.0 (C-9), 69.7 (C-7), 62.9 (C-1), 52.2 (C-4), 43.0 (C-5), 34.8 (C-8), 30.1 (C-3), 29.7 (C-2), 21.7 (C-14).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{16}H_{23}NO_4SNa)^+$ requires 348.1240, found 348.1239.

***rac-tert*-butyl (*2R,4S*)-4-hydroxy-2-(3-hydroxypropyl)-5-methylenepiperidine-1-carboxylate (703-Boc)**



703-Boc (94%)

Compound **703-Boc** was prepared according to the procedure used for the preparation of compound **702-Ts.** Lactone **702-Boc** (1.00 g, 3.74 mmol., 1 equiv.) reacted with 1.0 M $LiAlH_4$ in THF (4.1 mL, 4.1 mmol, 1.1 equiv.) in THF (15 mL). Purification by gradient column chromatography (ethyl acetate:pentane 30:70 to 100:0) afforded compound **703-Boc** (960 mg, 94%) as a colourless oil.

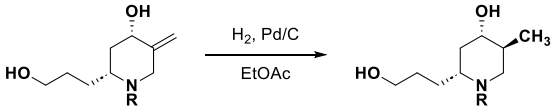
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3382, 2976, 1667, 1416, 1166.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.98 (d, *J* = 18.5 Hz, 2H, H-9), 4.31 (dd, *J* = 9.9, 5.2 Hz, 2H, H-5a, H-7), 4.21 – 4.05 (m, 1H, H-4), 3.76 (d, *J* = 15.0 Hz, 1H, H-5b), 3.62 (qt, *J* = 10.6, 6.3 Hz, 2H, H-1), 2.71 (br s, 2H, 2xOH), 2.04 – 1.86 (m, 2H, H-8a, H-3a), 1.81 – 1.66 (m, 2H, H-8b, H-3b), 1.53 (tt, *J* = 8.5, 6.6 Hz, 2H, H-2), 1.42 (s, 9H, H-12).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.1 (C-10), 145.1 (C-6), 111.1 (C-9), 79.9 (C-11), 69.8 (C-7), 62.6 (C-1), 50.0 (C-4), 42.1 (C-5), 36.1 (C-8), 29.7 (C-2), 29.6 (C-3), 28.6 (C-12).

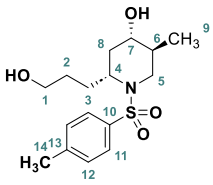
HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{14}H_{26}NO_4)^+$ requires 272.1856, found 272.1857.

Hydrogenation of diols 703-Ts and 703-Boc



703-Ts
703-Boc
694-Ts
694-Boc

***rac*-(*2R,4S,5S*)-2-(3-hydroxypropyl)-5-methyl-1-tosylpiperidin-4-ol (694-Ts)**



694-Ts (7:1 *d.r.*, 76%)

To a solution of alkene **703-Ts** (1.22 g, 3.75 mmol, 1 equiv.) in ethyl acetate (187 mL) was added 10% Pd/C (200 mg, 0.187 mmol, 5.00 mol%). The reaction flask was evacuated and backfilled with hydrogen (double-skin balloon) and then stirred for 2 h under an atmosphere of hydrogen. After full consumption of starting material (determined by ^{1}H NMR analysis, 7:1 *d.r.*), the reaction mixture was filtered through celite and concentrated under reduced pressure. The obtained residue was by gradient column chromatography (ethyl acetate:pentane = 50:50 to 100:0) to afford compound **694-Ts** (930 mg, 76%) as a white solid.

m.p.: 98 – 100 °C.

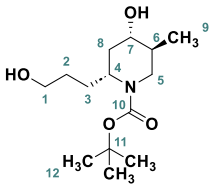
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3318, 2968, 1324, 1153, 684.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 – 7.67 (m, 2H, H-11), 7.29 – 7.23 (m, 2H, H-12), 4.01 – 3.89 (m, 1H, H-4), 3.75 (q, J = 3.0 Hz, 1H, H-7), 3.68 – 3.51 (m, 2H, H-1), 3.48 (dd, J = 14.2, 4.5 Hz, 1H, H-5a), 3.04 (dd, J = 14.3, 12.1 Hz, 1H, H-5b), 2.40 (s, 3H, H-14), 1.97 – 1.83 (m, 1H, H-3a), 1.83 – 1.68 (m, 2H, H-3b, H-8a), 1.64 – 1.50 (m, 3H, H8b, H-2), 1.49 – 1.37 (m, 1H, H-6), 0.83 (d, J = 6.9 Hz, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.1 (C-13), 138.8 (C-10), 129.8 (C-12), 127.0 (C-11), 68.4 (C-7), 62.8 (C-1), 51.7 (C-4), 41.4 (C-5), 34.3 (C-8), 33.7 (C-6), 29.9 (C-2), 29.7 (C-3), 21.6 (C-14), 14.8 (C-9).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{16}H_{26}NO_4S)^+$ requires 328.1577, found 328.1585.

***rac-tert*-butyl (*2R,4S,5S*)-4-hydroxy-2-(3-hydroxypropyl)-5-methylpiperidine-1-carboxylate (694-Boc)**



694-Boc (5.5:1 *d.r.*, 60%)

Compound **694-Boc** was prepared according to the procedure used for the preparation of compound **694-Ts.** Alkene **703-Boc** (1.60 g, 5.90 mmol., 1 equiv.) was hydrogenated in the presence of 10% Pd/C (314 mg, 0.294 mmol, 5.00 mol%) in ethyl acetate (200 mL). Purification by gradient column chromatography (ethyl acetate:pentane 80:20 to 100:0) afforded compound **694-Boc** (958 mg, 60%) as a colourless oil. The *d.r.* of the reaction was determined by ^{1}H NMR analysis of the crude product and was determined to be 5.5:1.

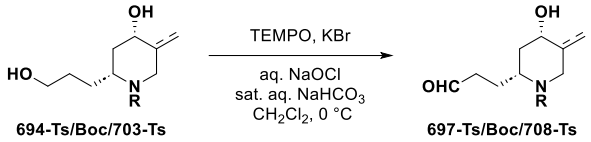
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3387, 2918, 1661, 1424, 1170.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.13 (dtd, *J* = 9.3, 6.5, 2.6 Hz, 1H, H-4), 3.72 (q, *J* = 3.7 Hz, 1H, H-7), 3.70 – 3.61 (m, 2H, H-1), 3.59 (dd, *J* = 11.4, 2.3 Hz, 1H, H-5a), 3.36 (dd, *J* = 13.6, 3.5 Hz, 1H, H-5b), 2.13 (br s, 2H, OH), 2.05 – 1.97 (m, 1H, H-3a), 1.97 – 1.92 (m, 1H, H-8a), 1.74 (dq, *J* = 8.1, 4.1 Hz, 1H, H-6), 1.69 (dt, *J* = 14.0, 7.0 Hz, 1H, H-3b), 1.59 – 1.55 (m, 1H, H-8b), 1.55 – 1.51 (m, 2H, H-2), 1.44 (s, 9H, H-12), 0.97 (d, *J* = 7.1 Hz, 3H, H-9).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 156.0 (C-10), 79.5 (C-11), 70.9 (C-7), 62.9 (C-1), 49.8 (C-4), 39.7 (C-5), 36.2 (C-6), 31.3 (C-8), 29.8 (C-3), 29.7 (C-2), 28.6 (C-12), 15.7 (C-9).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{14}H_{27}NO_4Na)^+$ requires 296.1832, found 296.1842.

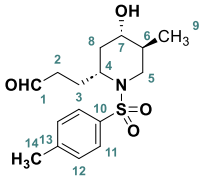
General procedure for TEMPO-catalysed oxidation of primary alcohol (General procedure 3.2)



Procedure based on the protocol published by Rosazza *et al.*[58]

To a solution of substrate in CH_2Cl_2 (0.1 M) at 0 °C was added KBr (0.35 equiv.), TEMPO (1.00 mol%) and saturated aq. sol. of $NaHCO_3$ (0.2 M). Then a solution of NaOCl (14 wt.%, 1.50 equiv.) was added resulting in the reaction mixture turning orange. After decolourisation of the reaction mixture, the progress of the reaction was determined by TLC, and another portion of NaOCl (14 wt.%, 0.50 equiv.) was added. The whole process was repeated until the TLC didn't show full conversion. The reaction mixture was then quenched with 1:1 mixture of saturated aq. sol. of $Na_2S_2O_3$ and $NaHCO_3$ (equal to volume of CH_2Cl_2 used for the reaction) and the resulting mixture was extracted with CH_2Cl_2 (3x volume of the aqueous phase). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography to afford the titled compound.

***rac*-3-((*2R,4S,5S*)-4-hydroxy-5-methyl-1-tosylpiperidin-2-yl)propanal (697-Ts)**



Compound **697-Ts** was prepared using ***General procedure 3.2*** from alcohol **694-Ts** (1.00 g, 3.05 mmol, 1 equiv.) in reaction with KBr (127 mg, 1.07 mmol, 0.35 equiv.), TEMPO (5.0 mg, 30.5 μmol, 1.00 mol%) and 14 wt.% solution of NaOCl (6.80 mL, 15.6 mmol, 5.10 equiv.) in CH_2Cl_2 (30 mL) and saturated aq. sol. of $NaHCO_3$ (15.3 mL, 0.2 M). Purification by gradient column chromatography (ethyl acetate:pexane 30:70 to 50:50) afforded compound **697-Ts** as a colourless oil (800 mg, 80%).

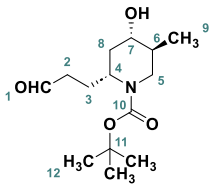
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3511, 2935, 1722, 1157, 704.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (t, J = 1.3 Hz, 1H, H-1), 7.75 – 7.64 (m, 2H, H-12), 7.33 – 7.27 (m, 2H, H-11), 3.82 (qd, J = 7.3, 2.9 Hz, 1H, H-4), 3.64 (q, J = 3.8 Hz, 1H, H-7), 3.59 (dd, J = 13.5, 3.4 Hz, 1H, H-5a), 3.21 (dd, J = 13.5, 3.5 Hz, 1H, H-5b), 2.60 – 2.36 (m, 2H, H-2), 2.43 (s, 3H, H-14), 2.17 (dq, J = 14.6, 7.3 Hz, 1H, H-3a), 2.05 (dtd, J = 14.0, 7.6, 6.2 Hz, 1H, H-3b), 1.86 (ddd, J = 14.6, 5.9, 3.5 Hz, 1H, H-8a), 1.82 – 1.70 (m, 1H, H-6), 1.63 – 1.55 (m, 1H, H-8b), 0.79 (d, J = 7.1 Hz, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.4 (C-1), 143.3 (C-13), 137.9 (C-10), 129.7 (C-11), 127.2 (C-12), 69.9 (C-7), 52.4 (C-4), 42.7 (C-5), 41.1 (C-2), 35.7 (C-6), 31.0 (C-8), 24.9 (C-3), 21.5 (C-14), 15.8 (C-9).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{16}H_{23}NO_4SNa)^+$ requires 324.1240, found 324.1241.

***rac-tert*-butyl (*2R,4S,5S*)-4-hydroxy-5-methyl-2-(3-oxopropyl)piperidine-1-carboxylate (697-Boc)**



697-Boc (84%)

Compound **697-Boc** was prepared using ***General procedure 3.2*** from alcohol **694-Boc** (500 mg, 1.84 mmol, 1 equiv.) in reaction with KBr (8.8 mg, 73.7 μmol, 4.0 mol%), TEMPO (5.8 mg, 36.9 μmol, 2.0 mol%) and 14 wt.% solution of NaOCl (4.50 mL, mmol, 5.60 equiv.) in CH_2Cl_2 (25 mL) and saturated aq. sol. of $NaHCO_3$ (25 mL). Purification by gradient column chromatography (ethyl acetate:pexane 40:60 to 60:40) afforded compound **697-Boc** as a colourless oil (416 mg, 84%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3479 (br), 2966, 2935, 1724, 1685, 1665, 1424, 1175, 1078.

^{1}H NMR (400 MHz, DMSO) δ: 9.68 – 9.60 (m, 1H, H-1), 4.08 – 3.85 (m, 1H, H-4), 3.62 – 3.40 (m, 2H, H-5a, H-7), 3.32 (s, 1H, OH), 3.27 – 3.12 (m, 1H, H-5b), 2.42 – 2.10 (m, 3H, H-3a, H-2), 1.81 – 1.66 (m, 2H, H-8a, H-3b), 1.69 – 1.57 (m, 1H, H-6), 1.48 – 1.39 (m, 1H, H-8b), 1.37 (s, 9H, H-12), 0.85 (d, 3H, J = 7.0 Hz, H-9).

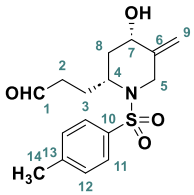
^{13}C NMR (101 MHz, DMSO) δ: 203.0 (C-1), 154.7 (C-10), 78.3 (C-11), 68.4 (C-7), 49.2 (C-4), 40.6 (C-2), 35.2 (C-6), 30.8 (C-8), 28.0 (C-12), 25.2 (C-3), 15.2 (C-9). The signal of carbon C-5 overlaps with solvent residual solvent peak.

^{1}H NMR (500 MHz, DMSO, 373 K) δ: 9.71 – 9.66 (m, 1H, H-1), 4.04 – 3.89 (m, 1H, H-4), 3.61 – 3.39 (m, 2H, H-5a, H-7), 3.34 – 3.21 (m, 1H, H-5b), 2.42 – 2.29 (m, 2H, H-2), 2.27 – 2.12 (m, 1H, H-3a), 1.90 – 1.78 (m, 2H, H-3b, H-8a), 1.66 (ddp, 1H, *J* = 12.7, 9.1, 4.2 Hz, H-6), 1.46 (dt, 1H, *J* = 13.8, 4.2 Hz, H-8b), 1.42 (s, 9H, H-12), 0.90 (d, 3H, *J* = 7.1 Hz, H-9).

^{13}C NMR (126 MHz, DMSO, 373 K) δ: 201.9 (C-1), 154.3, 77.8 (C-11), 68.6 (C-7), 49.4 (C-4), 40.1 (C-2), 39.7 (C-5), 35.2 (C-6), 31.1 (C-8), 27.6 (C-12), 25.2 (C-3), 15.0 (C-9).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{14}H_{25}NO_4+Na)^+$ requires 294.1676, found 294.1675.

***rac*-3-((*2R,4S*)-4-hydroxy-5-methylene-1-tosylpiperidin-2-yl)propanal (708-Ts)[ii]**



708-Ts (84%)

Compound **708-Ts** was prepared using ***General procedure 3.2*** from alcohol **703-Ts** (2.53 g, 7.77 mmol, 1 equiv.) in reaction with KBr (323 mg, 2.72 mmol, 0.35 equiv.), TEMPO (12.1 mg, 77.7 μmol, 1.0 mol%) and 14 wt.% solution of NaOCl (17.4 mL, 40.9 mmol, 5.50 equiv.) in CH_2Cl_2 (77 mL) and saturated aq. sol. of

[ii] Reaction was performed by Daniel Cox.

$NaHCO_3$ (39 mL). Purification by gradient column chromatography (ethyl acetate:pexane 30:70 to 50:50) afforded compound **708-Ts** as a colourless oil (2.10 g, 84%).

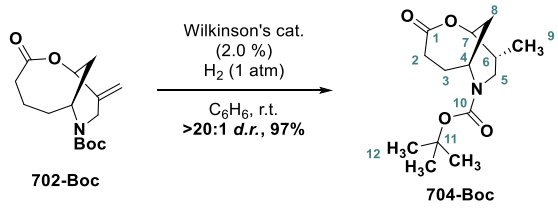
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3503, 2950, 1718, 1333, 1155, 1007, 679.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.80 (t, J = 1.0 Hz, 1H, H-1), 7.67 – 7.63 (m, 2H, H-11), 7.25 – 7.20 (m, 2H, H-12), 4.91 (dt, J = 15.6, 1.1 Hz, 2H, H-9), 4.24 (d, J = 15.7 Hz, 1H, H-5a), 4.07 – 3.98 (m, 2H, H-5b, H-7), 3.93 – 3.81 (m, 1H, H-4), 2.77 – 2.52 (m, 2H, H-2), 2.42 – 2.40 (m, 1H, H-3a), 2.39 (s, 3H, H-14), 1.91 (dddd, J = 14.7, 7.8, 6.9, 4.5 Hz, 1H, H-3b), 1.64 (ddd, J = 14.4, 3.9, 2.3 Hz, 1H, H-8a), 1.47 (ddd, J = 14.4, 6.7, 3.7 Hz, 1H, H-8b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.2 (C-1), 143.4 (C-6), 142.6 (C-13), 137.7 (C-10), 129.7 (C-12), 127.5 (C-11), 113.3 (C-9), 69.6 (C-7), 51.6 (C-4), 42.7 (C-5), 41.2 (C-2), 35.0 (C-8), 25.8 (C-3), 21.7 (C-14).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{16}H_{21}NO_4S)^+$ requires 346.1084, found 346.1078.

***rac-tert*-butyl (*1S,6R,9R*)-9-methyl-3-oxo-2-oxa-7-azabicyclo[4.3.1]decane-7-carboxylate (704-Boc)**



A solution of alkene **702-Boc** (1.00 g, 3.74 mmol, 1 equiv.) in dry benzene was bubbled with argon for 10 min, and then a freshly prepared Wilkinson's catalyst (69.2 mg, 74.8 μmol, 2.00 mol%) was added. After bubbling for another 5 min., the reaction vessel was evacuated and backfilled with hydrogen (3 cycles), and the reaction mixture was vigorously stirred for 16 h. The reaction mixture was then concentrated under reduced pressure and the obtained residue was purified by column chromatography (dry loading, ethyl acetate:pentane = 30:70). Compound **704-Boc** was obtained as a white solid (975 mg, 97%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 1707, 1680, 1474, 1419, 1367, 1183, 1170, 1152, 1020.

m.p.: 114 – 115 °C.

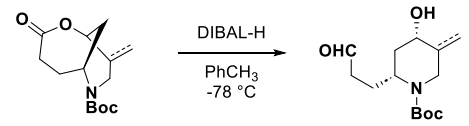
Note: Compound **704-Boc** was rotameric even at 363 K.

^{1}H NMR (DMSO, 500 MHz, 363 K) δ: 4.42 (q, 1H, *J* = 6.1 Hz, H-4), 4.37 (q, 1H, *J* = 3.2 Hz, H-7), 3.77 (dd, 1H, *J* = 14.0, 5.7 Hz, H-5a), 2.81 – 2.70 (m, 2H, H-2a, H-5b), 2.64 (ddd, 1H, *J* = 16.3, 8.2, 4.0 Hz, H-2b), 2.38 (dd, 1H, *J* = 3.5, 2.1 Hz, H-8a), 2.00 – 1.89 (m, 2H, H-3a, H-8b), 1.88 – 1.77 (m, 1H, H-6), 1.70 (tt, 1H, *J* = 14.6, 4.2 Hz, H-3b), 1.43 (s, 9H, H-12), 0.96 (d, 3H, *J* = 6.9 Hz, H-9).

^{13}C NMR (DMSO, 126 MHz, 363 K) δ: 172.7 (C-1), 153.6 (C-10), 78.6 (C-11), 75.4 (C-7), 44.7 (C-4), 41.5 (C-5), 33.9 (C-2), 33.9 (C-6), 31.2 (C-8), 27.7 (C-12), 26.1 (C-3), 14.4 (C-9).

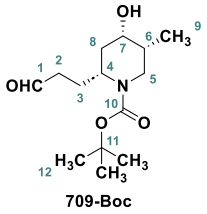
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{14}H_{23}NO_4Na)^+$ requires 292.1519, found 292.1520.

Reduction of lactones 702-Boc and 704-Boc using DIBAL-H



702-Boc/704-Boc **708-Boc/709-Boc**

***rac-tert*-butyl (*2R,4S,5R*)-4-hydroxy-5-methyl-2-(3-oxopropyl)piperidine-1-carboxylate**



709-Boc

To a solution of lactone **704-Boc** (500 mg, 1.86 mmol, 1 equiv.) in dry toluene (18.6 mL) was added 1 M solution of DIBAL-H (3.71 mL, 3.71 mmol, 2 equiv.) at -78 °C. After stirring for 1 h, the reaction mixture was quenched with sat. aq. solution of Rochelle salt (20 mL) at -78 °C. After warming to room temperature, the reaction mixture was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate:pentane = 60:40) to afford aldehyde **709-Boc** as a colourless oil (470 mg, 93%).

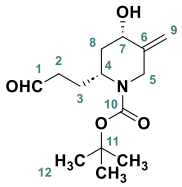
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3462, 2975, 2934, 2881, 1723, 1666, 1421, 1366, 1166, 734.

^{1}H NMR (500 MHz, DMSO, 373 K) δ: 9.68 (t, 1H, *J* = 1.8 Hz, H-1), 4.09 – 4.01 (m, 1H, H-4), 3.73 (q, 1H, *J* = 3.1 Hz, H-7), 3.57 (dd, 1H, *J* = 13.2, 4.5 Hz, H-5a), 2.75 (dd, 1H, *J* = 13.2, 11.9 Hz, H-5b), 2.43 – 2.26 (m, 2H, H-2), 2.20 (dddd, 1H, *J* = 14.2, 9.6, 8.0, 6.2 Hz, H-3a), 1.87 (dddd, 1H, *J* = 14.0, 7.9, 7.1, 5.9 Hz, H-3b), 1.74 (ddd, 1H, *J* = 14.1, 3.3, 1.8 Hz, H-8a), 1.63 (ddd, 1H, *J* = 14.2, 6.5, 3.0 Hz, H-8b), 1.58 – 1.48 (m, 1H, H-6), 1.41 (s, 9H, H-12), 0.86 (d, 3H, *J* = 6.9 Hz, H-9).

^{13}C NMR (126 MHz, DMSO, 373 K) δ: 201.9 (C-1), 153.6 (C-10), 77.9 (C-11), 66.1 (C-7), 48.5 (C-4), 40.4 (C-5), 34.8 (C-8), 34.4 (C-6), 27.6 (C-12), 24.8 (C-3), 14.3 (C-9).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{14}H_{25}NO_4Na)^+$ requires 294.1676, found 294.1668.

***rac-tert*-butyl (*2S,4R*)-4-hydroxy-5-methylene-2-(3-oxopropyl)piperidine-1-carboxylate (708-Boc)**



708-Boc

Compound **708-Boc** was prepared using procedure described for compound **709-Boc** from aldehyde **702-Boc** (500 mg, 1.87 mmol, 1 equiv.) in reaction with DIBAL-H (3.74 mL, 3.74 mmol, 2.00 equiv.) in dry toluene (18.7 mL). Purification by column chromatography (ethyl acetate:pentane = 75:25) afforded compound **708-Boc** as a colourless oil (475 mg, 94%).

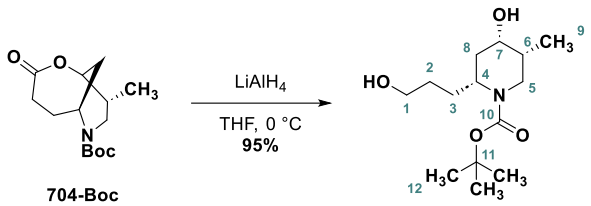
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3458, 2950, 1686, 1671, 1410, 1013.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.78 (t, *J* = 1.5 Hz, 1H, H-1), 5.01 (d, *J* = 10.2 Hz, 2H, H-9), 4.39 – 4.32 (m, 2H, H-5a, H-7), 4.25 – 4.18 (m, 1H, H-4), 3.77 (d, *J* = 14.8 Hz, 1H, H-5b), 2.56 – 2.38 (m, 2H, H-2), 2.38 – 2.25 (m, 1H, H-3a), 2.06 – 1.88 (m, 2H, H-8a, H-3b), 1.78 (dt, *J* = 14.3, 3.9 Hz, 1H, H-8b), 1.44 (s, 9H, H-12).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.0 (C-1), 154.9 (C-10), 144.7 (C-6), 111.5 (C-9), 80.0 (C-11), 69.9 (C-7), 49.4 (C-4), 41.3 (C-5, C-2), 36.2 (C-8), 28.4 (C-12), 25.5 (C-3).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{14}H_{23}NO_4Na)^+$ requires 292.1519, found 292.1525.

***rac-tert*-butyl (*2S,4R,5S*)-4-hydroxy-2-(3-hydroxypropyl)-5-methylpiperidine-1-carboxylate**



704-Boc **705-Boc**

To a solution of lactone **704-Boc** (50.0 mg, 186 μmol, 1 equiv.) in dry THF (0.75 mL) was added 1 M solution of $LiAlH_4$ (204 μL, 204 μmol, 1.1 equiv.) at 0 °C and the reaction mixture was stirred at this temperature for 40 min. The reaction mixture was then quenched with sat. aq. solution of Rochelle salt (10 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate) to afford alcohol **705-Boc** as a colourless oil (48.0 mg, 95%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3423 (br), 2931, 1665, 1424, 1367, 1103, 911, 733.

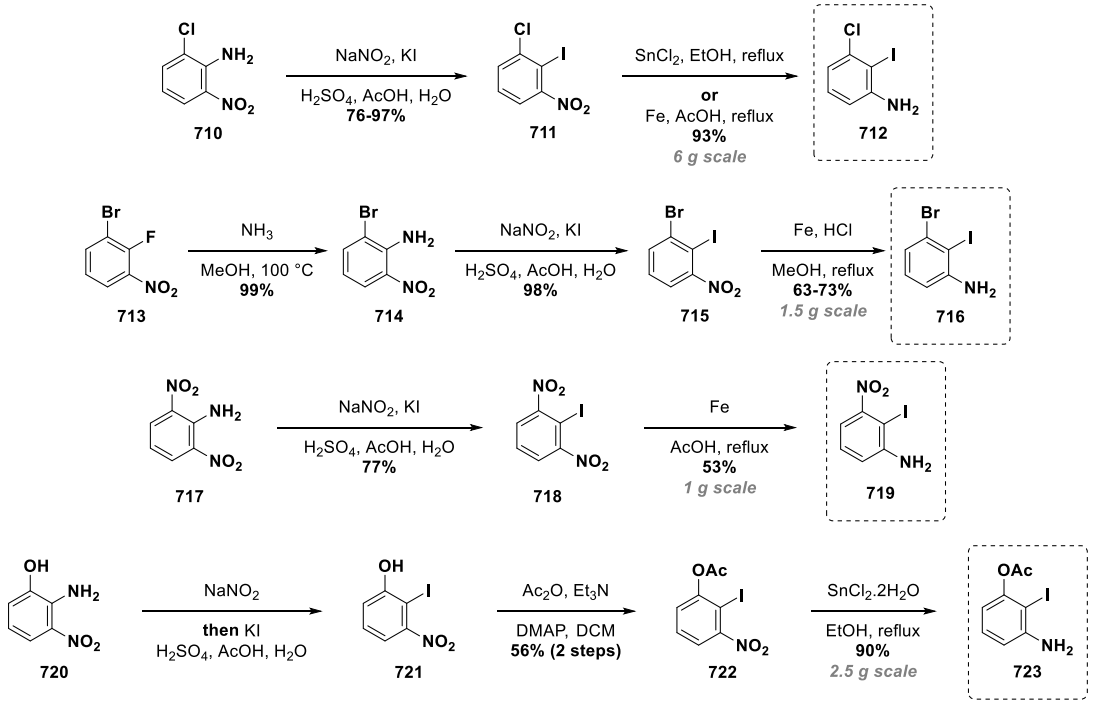
^{1}H NMR (500 MHz, DMSO, 373 K) δ: 4.18 (d, 1H, *J* = 3.7 Hz, 7-OH), 4.02 (q, 1H, *J* = 7.8 Hz, H-4), 3.91 (t, 1H, *J* = 5.1 Hz, 1-OH), 3.72 (p, 1H, *J* = 3.3 Hz, H-7), 3.56 (dd, 1H, *J* = 13.1, 4.4 Hz, H-5a), 3.41 (td, 2H, *J* = 6.6, 4.8 Hz, H-1), 2.74 (dd, 1H, *J* = 13.1, 11.8 Hz, H-5b), 1.85 (dtd, 1H, *J* = 13.6, 9.2, 5.7

Hz, H-3a), 1.74 (ddd, 1H, *J* = 14.1, 3.4, 1.8 Hz, H-8a), 1.69 – 1.58 (m, 2H, H-3b, H-8b), 1.58 – 1.46 (m, 1H, H-6), 1.41 (s, 9H, H-16), 1.47 – 1.31 (m, 2H, H-2), 0.86 (d, 3H, *J* = 6.9 Hz, H-9).

^{13}C NMR (126 MHz, DMSO, 373 K) δ: 153.7 (C-10), 77.6 (C-11), 66.3 (C-7), 60.5 (C-1), 48.9 (C-4), 39.2 (C-5), 34.8 (C-8), 34.6 (C-6), 29.7 (C-3), 28.7 (C-2), 27.7 (C-12), 14.3 (C-9).

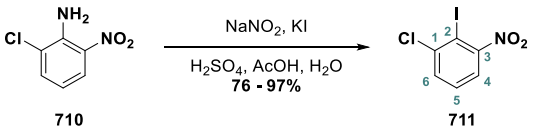
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{14}H_{27}NO_4Na)^+$ requires 296.1832, found 296.1836.

4.4.2 Synthesis of substituted anilines



Scheme 4.21. *Synthesis of substituted anilines.*

1-chloro-2-iodo-3-nitrobenzene (711)



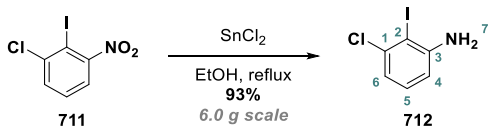
To a solution of **710** (1.00 g, 5.79 mmol, 1 equiv.) in acetic acid (4.1 mL) and conc. H_2SO_4 (4.1 mL) was added water (4.4 mL) while stirring. To the obtained suspension was added solution of $NaNO_2$ (640 mg, 9.28 mmol, 1.60 equiv.) in water (2.3 mL) and the resulting mixture was stirred for 30 min at this temperature. Next, a solution of KI (1.67 g, 10.1 mmol, 1.74 equiv.) in water (2.3 mL) was added at 0 °C and the resulting mixture was heated to 70 °C for 15 min. The reaction mixture was then diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were neutralised with sat. aq. solution of $NaHCO_3$ and then washed with sat. aq. solution of $Na_2S_2O_3$ to remove iodine residues. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **711** was obtained as a yellow solid (1.59 g, 97%) and was used in next step without further purification. The spectroscopic data are in agreement with the literature values.[59]

Reaction repeated on 5.0 g scale provided product **711** in 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (dd, *J* = 8.0, 1.5 Hz, 1H, H-4), 7.52 (dd, *J* = 8.0, 1.5 Hz, 1H, H-6), 7.42 (t, *J* = 8.0 Hz, 1H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.5 (C-3), 142.0 (C-1), 132.2 (C-6), 129.9 (C-5), 122.5 (C-4), 92.2 (C-2).

3-chloro-2-iodoaniline (712)



Compound **712** was prepared according to a literature procedure published by Jia et al.[60]

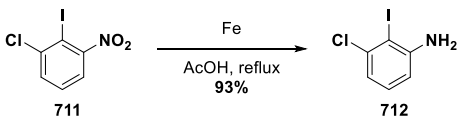
To solution of compound **711** (6.00 g, 21.2 mmol, 1 equiv.) in dry ethanol (42 mL) was added $SnCl_2x2H_2O$ (23.9 g, 109 mmol, 5.00 equiv.) and the resulting mixture was stirred for 10 min at 70 °C. The cold reaction mixture was poured onto sat. aq. solution of K_2CO_3 (150 mL) and was extracted with ethyl acetate (3 x 150 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (dry loading, Et_2O:pentane = 20:80) afforded compound **712** as a yellow solid (5.00 g, 93%).

The spectroscopic data are in agreement with the literature values.[60]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (t, *J* = 7.9 Hz, 1H, H-5), 6.84 (dd, *J* = 7.8, 1.4 Hz, 1H, H-6), 6.60 (dd, *J* = 8.1, 1.4 Hz, 1H, H-4), 4.32 (s, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.2 (C-3), 139.3 (C-1), 129.7 (C-5), 118.9 (C-6), 112.2 (C-4), 88.4 (C-2).

3-chloro-2-iodoaniline (712)

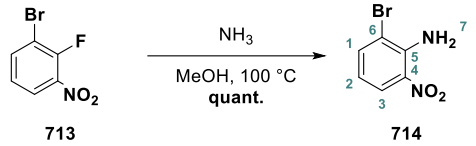


Aniline **712** can be prepared in identical yield avoiding the use of tin by using procedure described for compound **719.**

To a solution of **711** (1.00 g, 3.53 mmol. 1 equiv.) in acetic acid (10 mL) at 120 °C was added iron powder (570 mg, 10.2 mmol, 2.90 equiv.). The reaction mixture was heated for 15 min, then cooled to room temperature and concentrated under reduced pressure. The obtained

residue was dissolved in CH_2Cl_2 (50 mL) and neutralised by sat. aq. solution of NaHCO3. The phases were separated and aquous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (dry loading, Et_2O:pentane = 40:60) afforded compound **712** as a yellow solid (836 mg, 93%).

2-bromo-6-nitroaniline (714)



713 714

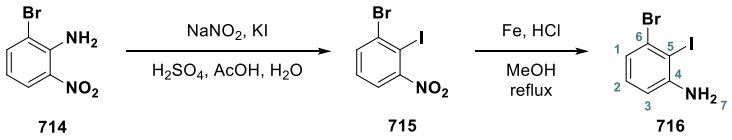
Compound **711** was prepared according to a literature procedure published by Long et al.[61]

To a pressure vial containing 3-bromo-2-fluoronitrobenzene (2.00 g, 9.10 mmol, 1 equiv.) was added 7 M solution of NH_3 in MeOH (6.7 mL), the vial was sealed and heated to 100 °C for 24 h. The reaction mixture was then concentrated under reduced pressure and the obtained residue passed through a short plug of silica gel (dry loading, Et_2O:pentane = 20:80). Amine **711** was obtained as a yellow solid in quantitative yield (1.97 g, quant.). The spectroscopic data are in agreement with the literature values.[62]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (dd, 1H, *J* = 8.7, 1.5 Hz, H-3), 7.69 (dd, 1H, *J* = 7.7, 1.5 Hz, H-1), 6.61 (dd, 1H, *J* = 8.6, 7.7 Hz, H-2), 6.57 (s, 2H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.3 (C-5), 138.9 (C-1), 133.1 (C-4), 126.1 (C-3), 116.6 (C-2), 112.2 (C-6).

3-bromo-2-iodoaniline (716)



714 715 716

Preparation of compound **716** was based on procedures published by Wen[63] and Podlech.[64]

To a solution of 2-bromo-6-nitroaniline (**714**) (1.00 g, 4.61 mmol, 1 equiv.) in acetic acid (3.3 mL) was added water (3.5 mL) and the resulting mixture was cooled to 0 °C before conc. H_2SO_4 (3.3 mL) was added. Next, a solution of $NaNO_2$ (381 mg, 5.53 mmol, 1.20 equiv.) in water (1.4 mL) was added dropwise over 1 h and the resulting solution was stirred for 30 min at 0 °C. Next, a solution of KI (994 mg, 6.00 mmol, 1.30 equiv.) in water (2.0 mL) was added dropwise

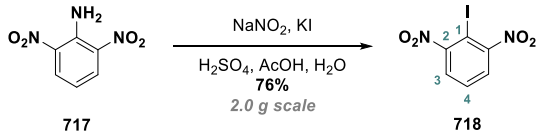
and the reaction mixture was then heated to 50 °C for 15 min. The reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 35 mL). The combined organic phases were neutralised with sat. aq. solution of $NaHCO_3$ and then washed with sat. aq. solution of $Na_2S_2O_3$ to remove iodine residues. The organic phase was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product **715** (1.48 g, 98%) was used in next step without further purification.

Compound **715** (1.48 g, 4.51 mmol, 1 equiv.) was dissolved in MeOH (38 mL) and iron dust (1.89 g, 33.9 mmol, 7.5 equiv.) and conc. hydrochloric acid (2.0 mL). The resulting mixture was refluxed for 90 min and then cooled to room temperature and filtered through celite. The volatiles were removed under the reduced pressure, the obtained poured onto sat. aq. solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases was then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (dry loading, Et_2O:pentane = 10:90) afforded compound **716** as a yellow solid (841 mg, 63%). The spectroscopic data are in agreement with the literature values.[65]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.06 – 6.94 (m, 2H, H-1, H-2), 6.64 (dd, J = 7.5, 1.9 Hz, 1H, H-3), 4.34 (s, 2H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.4 (C-4), 130.8 (C-6), 130.1 (C-2), 122.3 (C-1), 112.6 (C-3), 91.3 (C-5).

2-iodo-1,3-dinitrobenzene (718)



717 718

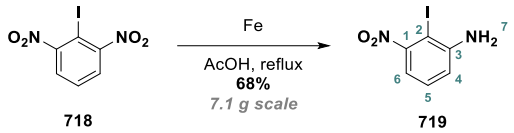
Compound **718** was prepared according to a literature procedure published by Podlech et al.[64]

To a solution of 2,6-dinitroaniline (2.00 g, 10.9 mmol, 1 equiv.) in acetic acid (50 mL) was added solution od $NaNO_2$ (832 mg, 12.1 mmol, 1.10 equiv.) in conc. H_2SO_4 (9 mL) with such a rate that the temperature of reaction mixture did not rise over 40 °C. The stirring was continued for 30 minutes. The reaction mixture was then cooled to 0 °C and solution of KI (2.07 g, 12.6 mmol, 1.15 equiv.) in water (30 mL) was added dropwise. The resulting solution was stirred at 70 °C for 15 min after which water (200 mL) was added and the resulting precipitate filtered off. Compound **718** was obtained as a yellow solid (2.45 g, 76%) and used in next step without further purification. The spectroscopic data are in agreement with the literature values.[64]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 8.1 Hz, 2H, H-3), 7.66 (dd, *J* = 8.4, 7.6 Hz, 1H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 130.5 (C-4), 127.0 (C-3), 80.3 (C-1), peak for C-2 was not observed.

2-iodo-3-nitroaniline (719)



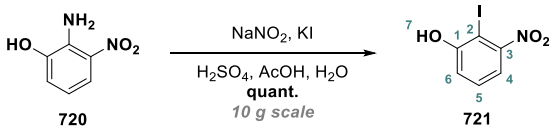
Compound **719** was prepared according to a literature procedure published by Podlech et al.[64]

To a solution of 2-iodo-1,3-dinitrobenzene (**718**) (7.11 g, 24.2 mmol, 1 equiv.) in acetic acid (70 mL) at 120 °C was added iron powder (3.92 g, 70.1 mmol, 2.90 equiv.). The reaction mixture was heated for 10 min, then cooled to room temperature and concentrated under reduced pressure. The obtained residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (150 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate:pentane = 20:80). Compound **719** was obtained as a yellow solid (4.35 g, 68%). The spectroscopic data are in agreement with the literature values.[64]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (t, *J* = 8.0 Hz, 1H, H-5), 7.05 (dd, *J* = 7.8, 1.4 Hz, 1H, H-6), 6.88 (dd, *J* = 8.1, 1.4 Hz, 1H, H-4), 4.56 (brs, 2H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.3 (C-1), 149.3 (C-3), 129.6 (C-5), 117.1 (C-4), 114.4 (C-6), 75.2 (C-2).

2-iodo-3-nitrophenol (721)



Compound **721** was prepared according to a literature procedure published by Yan et al.[66]

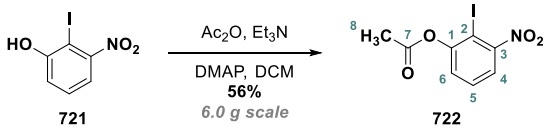
To a solution of compound **720** (10.0 g, 64.9 mmol, 1 equiv.) in DMSO (169 mL) was added 30% H_2SO_4 (337 mL) and the resulting mixture was stirred till complete dissolution of the starting material. After cooling to 0 °C a solution of $NaNO_2$ (6.71 g, 97.3 mmol, 1.50 equiv.) in H_2O (34 mL) was added dropwise over 15 min using dropping funnel. After stirring for additional 60 min, a solution of KI (16.2

g, 97.3 mmol, 1.50 equiv.) and I_2(12.4, 48.7 mmol, 0.75 equiv.) in H_2O (84 mL) was added at 0 °C using dropping funnel. After stirring for 60 min at room temperature another batch of KI (5.4 g, 34.4 mmol, 0.50 equiv.) and I_2(6.26, 24.7 mmol, 0.38 equiv.) in H_2O (84 mL) was added and the reaction mixture was stirred 60 min at room temperature and then 2 h at 80 °C. After cooling down, the reaction mixture was diluted with ethyl acetate (500 mL) and phases separated. The aqueous phase was extracted with ethyl acetate (200 mL) and combined organic phases washed with brine (250 mL), 10% aq. sol. of $NaHSO_3$ (250 mL) and water (200 mL). The organic phase was then died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Product **721** was obtained as a yellow solid (17.27 g, quant.) and was used in next step without further purification. The spectroscopic data are in agreement with the literature values.[60]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H, H-4), 7.37 (t, *J* = 8.0 Hz, 1H, H-5), 7.24 (dd, *J* = 8.1, 1.6 Hz, 1H, H-6), 5.94 (bs, 1H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 156.9 (C-3), 130.4 (C-5), 119.0 (C-4), 118.0 (C-6), 79.8 (C-2), peak for C-1 was not observed.

2-iodo-3-nitrophenyl acetate (722)



To a solution of **721** (6.00 g, 22.6 mmol, 1 equiv.) in CH_2Cl_2 (43 mL) was added Et_3N (4.73 mL, 34.0 mmol, 1.50 equiv.) and DMAP (276 mg, 277 mg, 0.10 equiv.) and the resulting solution was cooled to 0 °C. Ac2O was added dropwise, and the reaction mixture was then stirred for 50 min at room temperature. Next, reaction mixture was concentrated under reduced pressure and the obtained residue purified by gradient column chromatography (dry loading, ethyl acetate:pentane = 10:90 to 20:80). Compound **722** was obtained as a yellow solid (3.87 g, 56%).

m.p.: 90 – 92 °C.

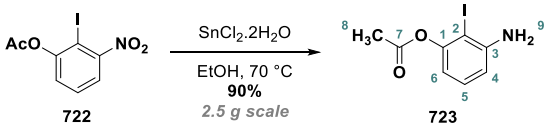
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 1749, 1531, 1367, 1200.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 8.1, 1.4 Hz, 1H, H-4), 7.50 (t, *J* = 8.1 Hz, 1H, H-5), 7.31 (dd, *J* = 8.1, 1.5 Hz, 1H, H-6), 2.42 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.3 (C-7), 155.1 (C-1), 153.1 (C-3), 129.9 (C-5), 126.7 (C-6), 122.7 (C-5), 85.7 (C-2), 21.3 (C-8).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_8H_7INO_4)^+$ requires 307.9414, found 307.9400.

3-amino-2-iodophenyl acetate (723)



Compound **723** was prepared using procedure described for compound **712.**[60]

To solution of compound **722** (2.5 g, 8.14 mmol, 1 equiv.) in dry ethanol (33 mL) was added $SnCl_2.2H_2O$ (9.18 g, 40.7 mmol, 5.00 equiv.) and the resulting mixture was stirred for 10 min at 70 °C. The cold reaction mixture was poured onto sat. aq. solution of $NaHCO_3$ (60 mL) and was extracted with ethyl acetate (3 x 60 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 15:75) afforded compound **723** as a yellow solid (2.03 g, 90%).

m.p.: 79 – 81 °C.

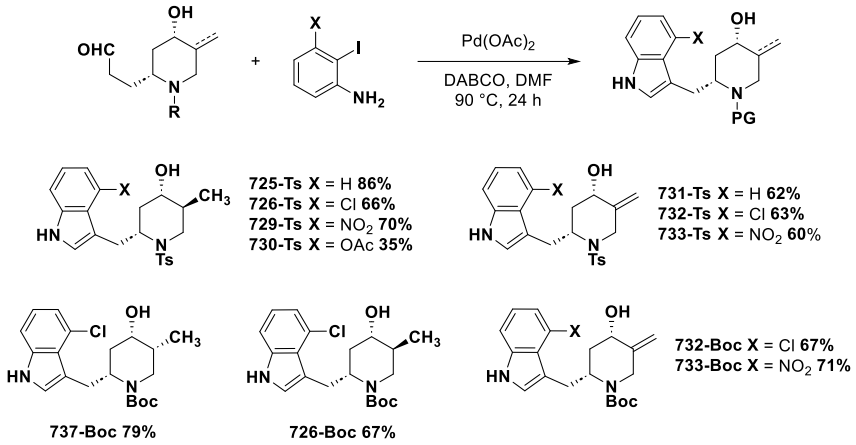
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3420, 3388, 1739, 1211.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (t, *J* = 8.0 Hz, 1H, H-5), 6.60 (dd, *J* = 8.1, 1.3 Hz, 1H, H-6), 6.48 (dd, *J* = 7.9, 1.3 Hz, 1H, H-4), 4.01 (brs, 2H, H-9), 2.36 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.8 (C-7), 152.1 (C-1), 148.9 (C-3), 129.7 (C-5), 112.2 (C-4), 112.1 (C-6), 81.0 (C-2), 21.5 (C-8).

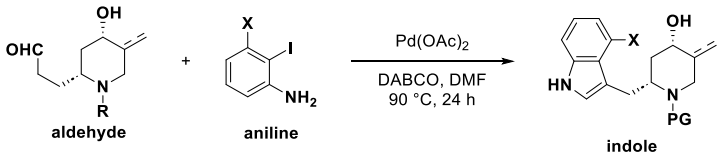
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_8H_8INO_2Na)^+$ requires 299.9492, found 299.9488.

4.4.3 Indole synthesis



Scheme 4.22. *Indole synthesis.*

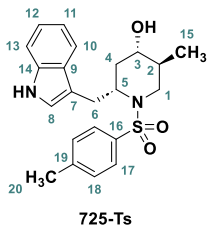
General procedure for indole synthesis (General procedure 3.3)



Synthetic procedure for indole synthesis is based on the procedure published by Cuny *et al.* [67]

A round bottom flask charged with aldehyde (1 equiv.), aniline (2.00 equiv.), DABCO (3.00 equiv.) and $Pd(OAc)_2$ (10.0 mol %) was evacuated and back-filled with argon three times. Then degassed DMF (reaction concentration = 0.1 M; degassed by freeze-pump-thaw technique) was added and the reaction vessel was again evacuated and back-filled with N_2 three times. The starting materials were dissolved and the solution bubbled with argon for 10 min. The reaction mixture was then placed to a pre-headed oil bath and stirred at 90 °C for 24 h (when *me*ta-substituted iodoaniline was used) or at 85 °C for 6 h (when substrate with hydrogen atoms in *meta*-potions were used). Reaction mixture was then poured onto brine (2x the volume of DMF) and extracted with ethyl acetate (3x(2x the volume of DMF)). The combine organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Residual DMF was azeotropically evaporated with toluene. The obtained residue was purified by column chromatography.

***rac*-(*2R,4S,5S*)-2-((1H-indol-3-yl)methyl)-5-methyl-1-tosylpiperidin-4-ol (725-Ts)**



Compound **725-Ts** was prepared using ***General procedure 3.3*** from aldehyde **697-Ts** (7.5 mg, 23.1 μmol, 1 equiv.) in reaction with 2-iodoaniline (10.2 mg, 49.1 μmol, 2.0 equiv.), DABCO (7.8 mg, 69.1 μmol, 3.0 equiv.) and $Pd(OAc)_2$ (0.5 mg, 2.30, μmol 0.10 equiv.) in DMF (0.3 mL). Purification by PTCL (ethyl acetate:hexane 70:30) afforded compound **725-Ts** as an off-white solid (7.9 mg, 86%).

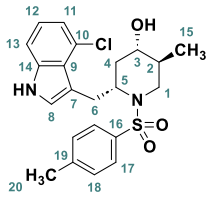
IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 3410, 2958, 2361, 2342, 1329, 1317, 1150, 911, 738.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (s, 1H, NH), 7.81 – 7.73 (m, 2H, H-17), 7.57 (dq, 1H, *J* = 7.8, 0.9 Hz, H-10), 7.33 (dt, 1H, *J* = 8.2, 1.0 Hz, H-13), 7.30 – 7.23 (m, 2H, H-18), 7.18 (ddd, 1H, *J* = 8.2, 7.0, 1.2 Hz, H-12), 7.11 (ddd, 1H, *J* = 8.0, 7.0, 1.1 Hz, H-11), 6.99 (dd, 1H, *J* = 2.4, 0.9 Hz, H-8), 4.18 (dt 1H, *J* = 13.9, 4.4 Hz, H-5), 3.76 (dd, 1H, *J* = 13.0, 3.4 Hz, H-1a), 3.62 (q, 1H, *J* = 3.8 Hz, H-3), 3.44 (dd, 1H, *J* = 13.7, 11.6 Hz, H-6a), 3.36 (dd, 1H, *J* = 13.1, 3.6 Hz, H-1b), 2.90 (dd, 1H, *J* = 13.6, 4.4 Hz, H-6b), 2.40 (s, 3H, H-20), 1.83 (tp, 1H, *J* = 7.1, 3.5 Hz, H-2), 1.70 (ddd, 1H, *J* = 14.5, 5.8, 3.6 Hz, H-4a), 1.61 (dt, 1H, *J* = 14.6, 3.3 Hz, H-4b), 0.97 (d, 3H, *J* = 7.0 Hz, H-15).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.1 (C-19), 138.5 (C-14), 136.4 (C-16), 129.7 (C-18), 127.6 (C-9), 127.3 (C-17), 123.1 (C-8), 122.2 (C-12), 119.6 (C-11), 119.3 (C-10), 113.2 (C-7), 111.2 (C-13), 70.7 (C-3), 53.2 (C-5), 43.0 (C-1), 36.16 (C-2), 29.5 (C-4), 28.2 (C-6), 21.6 (C-20), 15.8 (C-15).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{22}H_{26}N_2O_3SNa)^+$ requires 421.1556, found 421.1567.

***rac*-(*2R,4S,5S*)-2-((4-chloro-1H-indol-3-yl)methyl)-5-methyl-1-tosylpiperidin-4-ol (726-Ts)**



726-Ts

Compound **726-Ts** was prepared using ***General procedure 3.3*** from aldehyde **697-Ts** (450 mg, 1.39 mmol, 1 equiv.) in reaction with aniline **712** (701 mg, 2.79 mmol, 2.0 equiv.), DABCO (465 mg, 4.17 mmol, 3.0 equiv.) and $Pd(OAc)_2$ (31.2 mg, 139 μmol, 0.10 equiv.) in DMF (13.8 mL). Purification by gradient column chromatography (ethyl acetate:hexane 40:60 to 50:50) afforded compound **726-Ts** as a off-white foam (398 mg, 66%).

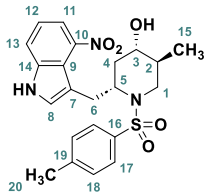
IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 3366, 2933, 1312, 1149, 691.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (s, 1H, H-NH), 7.64 – 7.56 (m, 2H, H-16), 7.16 (dd, 1H, *J* = 6.9, 2.1 Hz, H-13), 7.12 – 7.07 (m, 2H, H-18), 7.03 – 6.99 (m, 1H, H-12), 6.99 (s, 1H, H-8), 7.00 – 6.97 (m, 1H, H-11), 4.26 – 4.16 (m, 1H, H-5), 3.86 (dd, 1H, *J* = 13.5, 3.5 Hz, 1a), 3.60 (q, 1H, *J* = 4.7 Hz, H-3), 3.40 – 3.25 (m, 3H, H-1b, H-6), 2.33 (s, 3H, H-20), 1.92 (ddd, 1H *J* = 14.2, 5.4, 3.7 Hz, 4a), 1.79 (qt, 1H, *J* = 7.4, 3.7 Hz, H-2), 1.64 (dt, 1H, *J* = 14.1, 4.7 Hz, 4b), 1.03 (d, 3H, *J* = 7.0 Hz, H-15).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.6 (C-19), 138.8 (C-14), 137.9 (C-16), 129.3 (C-18), 127.0 (C-17), 126.2 (C-10), 125.4 (C-8), 124.3 (C-9), 122.4 (C-12), 120.4 (C-11), 113.1 (C-7), 110.0 (C-13), 71.5 (C-3), 55.2 (C-5), 44.6 (C-1), 36.8 (C-2), 31.6 (C-4), 28.9 (C-6), 21.6 (C-20), 15.7 (C-15).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{22}H_{25}ClN_2O_3SNa)^+$ requires 455.1167, found 455.1166.

***rac*-(*2R,4S,5S*)-5-methyl-2-((4-nitro-1H-indol-3-yl)methyl)-1-tosylpiperidin-4-ol (729-Ts)[iii]**



729-Ts

Compound **729-Ts** was prepared using ***General procedure 3.3*** from aldehyde **697-Ts** (93.1 mg, 285 μmol, 1 equiv.) in reaction with aniline **719** (151 mg, 572 μmol, 2.0 equiv.), DABCO (96.2 mg, 857 μmol, 3.0 equiv.) and $Pd(OAc)_2$ (6.4 mg, 29 μmol, 0.10 equiv.) in DMF (2.9 mL). Purification by gradient column chromatography (ethyl acetate:hexane 40:60 to 60:40) afforded compound **697-Ts** as yellow foam (88.5 mg, 70%).

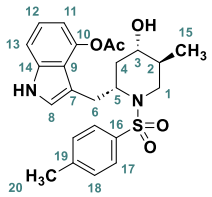
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3396, 2925, 1499, 1318, 728, 689.

^{1}H NMR (400 MHz, acetone) δ: 10.62 (s, 1H, NH), 7.72 (dd, 1H, *J* = 6.8, 1.0 Hz, H-13), 7.71 – 7.68 (m, 1H, H-11), 7.37 – 7.35 (m, 1H, H-8), 7.34 (d, 3H, *J* = 8.4 Hz, H-18, H-17), 7.20 (t, 1H, *J* = 7.9 Hz, H-12), 7.01 – 6.93 (m, 2H, H-18), 4.01 – 3.93 (m, 1H, H-5), 3.83 (dd, 1H, *J* = 13.7, 3.5 Hz, 1a), 3.67 (p, 1H, *J* = 3.7 Hz, H-3), 3.52 – 3.41 (m, 2H, H-1b, H-6a), 3.19 (ddd, 1H, *J* = 15.0, 5.9, 0.8 Hz, H-6b), 2.25 (s, 3H, H-20), 2.00 – 1.90 (m, 1H, H-4a), 1.86 – 1.74 (m, 1H, H-2), 1.68 (dddd, 1H, *J* = 14.1, 4.2, 3.1, 0.9 Hz, H-4b), 0.99 (d, 3H, *J* = 7.2 Hz, H-15).

^{13}C NMR (101 MHz , acetone) δ: 142.9 (C-10), 141.8 (C-19), 139.6 (C-14), 138.9 (C-16), 129.7 (C-8), 128.7 (C-18), 126.4 (C-17), 119.6 (C-12), 118.8 (C-9), 117.6 (C-11), 116.6 (C-13), 111.9 (C-7), 69.8 (C-3), 54.5 (C-5), 42.4 (C-1), 35.9 (C-2), 31.5 (C-4), 30.2 (C-6), 20.6 (C-5), 15.4 (C-15).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{22}H_{26}N_3O_5S)^+$ requires 444.1588, found 444.1592.

***rac*-3-(((*2S,4R,5R*)-4-hydroxy-5-methyl-1-tosylpiperidin-2-yl)methyl)-1H-indol-4-yl acetate (730-Ts)[xxi]**



730

Compound **730-Ts** was prepared using ***General procedure 3.3*** from aldehyde **697-Ts** (97.8 mg, 301 μmol, 1 equiv.) in reaction with aniline **723** (166.5 mg, 601 μmol, 2.0 equiv.), DABCO (101 mg, 902 μmol, 3.0 equiv.) and $Pd(OAc)_2$ (6.8 mg, 30.1 μmol, 0.10 equiv.) in DMF (3.0 mL). Purification by gradient column chromatography (ethyl acetate:hexane 40:60 to 60:40) afforded compound **730-Ts** as pale-yellow foam (47.7 mg, 35%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3383, 2928, 1753, 1210, 1150, 1040.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H, H-10,NH), 7.60 – 7.54 (m, 2H, H-17), 7.16 – 7.08 (m, 3H, H-13, H-18), 7.07 (t, 1H, *J* = 7.8 Hz, H-12), 6.76 (d, 1H, *J* = 2.2 Hz, H-8), 6.73 (dd, 1H, *J* = 7.5, 1.0 Hz, H-11), 4.07 (dq, 1H, *J* = 10.1, 5.3 Hz, H-5), 3.74 (dd, 1H, *J* = 13.5, 3.5 Hz, 1a), 3.44 (q, 1H, *J* = 4.5 Hz, H-3), 3.28 – 3.21 (m, 1H, H-6a), 3.22 – 3.15 (m, 1H, H-1b), 3.10 (dd, 1H, *J* = 14.6, 5.8 Hz, H-6b), 2.33

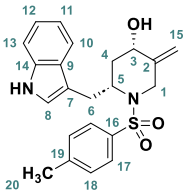
[iii] Reaction was performed by Daniel Cox.

(s, 3H, H-20), 2.32 (s, 3H, CH_3-Ac), 1.86 (ddd, 1H, *J* = 14.2, 5.4, 3.6 Hz, H-4a), 1.77 (tp, 1H, *J* = 7.2, 3.5 Hz, H-2), 1.56 (dt, 1H, *J* = 14.2, 4.7 Hz, H-4b), 0.92 (dm 3H, *J* = 7.0 Hz, H-15).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.6 (CO_2R), 144.1 (C-10), 142.8 (C-19), 138.6 (C-14, C-16), 129.5 (C-16), 126.9 (C-17), 123.8 (C-8), 122.0 (C-12), 119.8 (C-9), 112.6 (C-11), 111.5 (C-7), 109.4 (C-13), 71.0 (C-3), 55.0 (C-5), 44.4 (C-1), 36.1 (C-2), 31.7 (C-4), 29.0 (C-6), 21.6 (C-20), 21.3 (CH_3-Ac), 15.5 (C-15).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{24}H_{28}N_2O_5SNa)^+$ requires 479.1611, found 479.1618.

rac-(*2R,4S*)-2-((1*H*-indol-3-yl)methyl)-5-methylene-1-tosylpiperidin-4-ol (731-Ts)



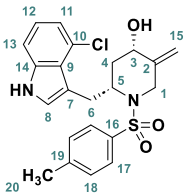
731-Ts

Compound **731-Ts** was prepared using ***General procedure 3.3*** from aldehyde **708-Ts** (10.2 mg, 31.5 μmol, 1 equiv.) in reaction with 2-iodoaniline (13.8 mg, 63.1 μmol, 2.0 equiv.), DABCO (10.6 mg, 94.6 μmol, 3.0 equiv.) and $Pd(OAc)_2$ (0.71 mg, 3.2 μmol, 0.10 equiv.) in DMF (0.3 mL). Purification by PTLC (ethyl acetate:hexane 70:30) afforded compound **731-Ts** as off-white foam (7.7 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (s, 1H, NH), 7.69 – 7.62 (m, 3H, H-10, H-17), 7.35 (dt, 1H, *J* = 8.1, 0.9 Hz, H-13), 7.22 – 7.16 (m, 3H, H-12, H-18), 7.12 (ddd, 1H, *J* = 8.1, 7.0, 1.1 Hz, H-11), 7.07 (d, 1H, *J* = 2.3 Hz, H-8), 5.02 – 4.95 (m, 2H, H-15), 4.32 (d, 1H, *J* = 15.4 Hz, H-1a), 4.26 – 4.18 (m, 1H, H-5), 4.15 (d, 1H, *J* = 15.7 Hz, H-1b), 4.03 (t, 1H, *J* = 4.5 Hz, H-3), 3.47 (dd, 1H, *J* = 13.8, 10.2 Hz, H-6a), 3.18 (dd, 1H, *J* = 13.8, 5.0 Hz, H-6b), 2.37 (s, 3H, H-20), 1.77 (ddd, 1H, *J* = 14.2, 5.0, 3.6 Hz, H-4a), 1.53 (ddd, 1H, *J* = 14.3, 6.5, 4.0 Hz, H-4b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.8 (C-2), 143.2 (C-19), 137.7 (C-14), 136.4 (C-16), 129.6 (C-18), 127.7 (C-9), 127.4 (C-17), 123.3 (C-8), 122.1 (C-12), 119.7 (C-11), 119.3 (C-10), 112.8 (C-7), 112.4 (C-15), 111.2 (C-13), 69.9 (C-3), 52.6 (C-5), 43.6 (C-1), 33.2 (C-4), 29.9 (C-6), 21.6 (C-20).

rac-(*2R,4S*)-2-((4-chloro-1*H*-indol-3-yl)methyl)-5-methylene-1-tosylpiperidin-4-ol (732-Ts)[iv]



732-Ts

Compound **732-Ts** was prepared using ***General procedure 3.3*** from aldehyde **708-Ts** (203 mg, 628 μmol, 1 equiv.) in reaction with aniline **712** (318 mg, 1.26 mmol, 2.00 equiv.), DABCO (211 mg, 1.88 mmol, 3.00 equiv.) and $Pd(OAc)_2$ (14.1 mg, 62.8 μmol, 0.10 equiv.) in DMF (6.3 mL). Purification by gradient column chromatography (MeCN:CH_2Cl_2 0:100 to 15:85) afforded compound **732-Ts** as off-white foam (59.2 mg, 22%).

[iv] Reaction was performed by Daniel Cox.

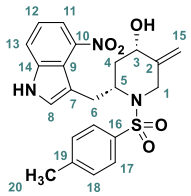
IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 3371, 2921, 1139, 1249, 1155.

^{1}H NMR (400 MHz , acetone) δ: 10.25 (s, 1H, NH), 7.57 – 7.48 (m, 2H, H-17), 7.32 (dd, 1H, *J* = 8.0, 1.1 Hz, H-11), 7.26 (d, 1H, *J* = 2.5 Hz, H-8), 7.18 – 7.11 (m, 2H, H-18), 7.02 (t, 1H, *J* = 7.8 Hz, H-12), 6.96 (dd, 1H, *J* = 7.6, 1.1 Hz, H-13), 4.93 (d, 2H, *J* = 11.8 Hz, H-15), 4.41 – 4.31 (m, 1H, H-5), 4.33 – 4.21 (m, 2H, H-1), 4.13 – 4.03 (m, 2H, H-3, OH), 3.58 (dd, 1H, *J* = 14.3, 7.7 Hz, H-6a), 3.42 (dd, 1H, *J* = 14.4, 7.6 Hz, H-6b), 2.31 (s, 3H, H-20), 1.89 – 1.77 (m, 1H, H-4a), 1.72 – 1.61 (m, 1H, H-4b).

^{13}C NMR (101 MHz, acetone) δ: 145.8 (C-2), 143.5 (C-19), 139.3 (C-14), 139.3 (C-16), 130.0 (C-18), 128.1 (C-17), 127.4 (C-8), 126.3 (C-10), 125.2 (C-9), 122.5 (C-12), 120.4 (C-13), 112.9 (C-7), 111.4 (C-11), 111.4 (C-15), 70.0 (C-3), 54.8 (C-5), 44.1 (C-1), 35.3 (C-4), 31.1 (C-6), 21.5 (C-20).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{22}H_{23}ClN_2O_3SNa)^+$ requires 453.1010, found 453.1009.

***rac*-(*2R,4S*)-5-methylene-2-((4-nitro-1H-indol-3-yl)methyl)-1-tosylpiperidin-4-ol (733-Ts)**[v]



733-Ts

Compound **733-Ts** was prepared using ***General procedure 3.3*** from aldehyde **708-Ts** (250 mg, 773 μmol, 1 equiv.) in reaction with aniline **719** (408 mg, 1.55 mmol, 2.00 equiv.), DABCO (260 mg, 2.32 mmol, 3.00 equiv.) and $Pd(OAc)_2$ (17.4 mg, 77.3 μmol, 0.10 equiv.) in DMF (3.9 mL). Purification by column chromatography (ethyl acetate:hexane 65:25) afforded compound **733-Ts** as off-white foam (205 mg, 60%).

IR (thin film) $\tilde{\nu}_{max}$/cm^{-1}: 3376, 2923, 1514, 1323, 1153.

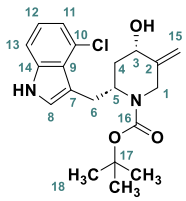
^{1}H NMR (600 MHz, acetone) δ: 10.73 (s, 1H, NH), 7.76 (dd, 2H, *J* = 7.9, 1.0 Hz, H-11, H-13), 7.49 (d, 1H, *J* = 2.5 Hz, H-8), 7.35 – 7.32 (m, 2H, H-17), 7.22 (t, 1H, *J* = 7.9 Hz, H-12), 7.02 (d, 2H, *J* = 7.9 Hz, H-18), 4.91 (d, 2H, *J* = 10.3 Hz, H-15), 4.27 – 4.18 (m, 2H, H-1), 4.16 (q, 1H, *J* = 3.8 Hz, H-3), 4.10 (d, 1H, *J* = 3.1 Hz, OH), 4.06 – 3.99 (m, 1H, H-5), 3.60 (dd, 1H, *J* = 15.0, 10.1 Hz, H-6a), 3.24 (dd, 1H, *J* = 15.0, 4.3 Hz, H-6b), 2.26 (s, 3H, H-20), 1.87 – 1.78 (m, 2H, H-4).

^{13}C NMR (151 MHz, acetone) δ: 145.5 (C-2), 143.8 (C-10), 143.2 (C-19), 140.7 (C-14), 138.9 (C-16), 130.8 (C-8), 129.8 (C-18), 127.8 (C-17), 120.8 (C-12), 119.9 (C-9), 118.6 (C-13), 117.7 (C-11), 112.8 (C-7), 111.5 (C-15), 70.0 (C-3), 54.8 (C-5), 43.4 (C-1), 36.8 (C-4), 32.2 (C-6), 21.5 (C-20).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{22}H_{24}N_3O_5S)^+$ requires 442.1431, found 442.1440.

[v] Reaction was performed by Daniel Cox.

***rac-tert*-butyl (*2R,4S*)-2-((4-chloro-1*H*-indol-3-yl)methyl)-4-hydroxy-5-methylenepiperidine-1-carboxylate (732-Boc)**



732-Boc

Compound **732-Boc** was prepared using ***General conditions 3.3*** from aldehyde **708-Boc** (473 mg, 1.76 mmol, 1 equiv.) in reaction with aniline **712** (890 mg, 3.51 mmol, 2.0 equiv.), DABCO (591 mg, 5.27 mmol, 3.0 equiv.) and $Pd(OAc)_2$ (39.4 mg, 176 µmol, 0.10 equiv.) in DMF (17.6 mL). Purification by gradient column chromatography (dry loading, ethyl acetate:hexane 50:50 to 60:40) afforded compound **732-Boc** as off-white foam (442 mg, 67%).

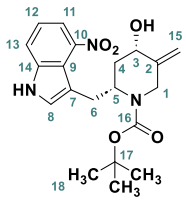
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3304 (br), 1666, 1420, 1365, 1339, 1255, 1165, 1088, 1058, 909, 733.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (s, 1H, NH), 7.23 (dd, 1H, *J* = 6.3, 2.7 Hz, H-13), 7.08 – 6.99 (m, 2H, H-11, H-12), 6.97 (d, 1H, *J* = 2.4 Hz, H-8), 5.04 (d, 2H, *J* = 5.7 Hz, H-15), 4.73 (ddt, 1H, *J* = 10.6, 7.1, 3.6 Hz, H-5), 4.52 (d, 1H, *J* = 14.7 Hz, H-1a), 4.42 (d, 1H, *J* = 4.4 Hz, H-3), 3.94 (d, 1H, *J* = 14.8 Hz, H-1b), 3.50 (dd, 1H, *J* = 14.7, 10.5 Hz, H-6a), 3.38 (dd, 1H, *J* = 14.6, 4.2 Hz, H-6b), 2.09 (ddd, 1H, *J* = 14.2, 6.8, 4.1 Hz, H-4a), 1.96 (ddd, 1H, *J* = 14.2, 4.4, 2.9 Hz, H-4b), 1.75 (s, 1H. OH), 0.92 (s, 9H, H-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.2 (C-16), 145.0 (C-2), 138.1 (C-14), 126.6 (C-10), 124.7 (C-9), 124.4 (C-8), 122.4 (C-12), 120.4 (C-11), 114.0 (C-7), 111.8 (C-15), 110.1 (C-13), 79.2 (C-17), 70.4 (C-3), 51.5 (C-5), 41.3 (C-1), 36.5 (C-4), 29.7 (C-6), 27.8 (C-18).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{20}H_{25}ClNO_2O_3Na)^+$ requires 399.1446, found 399.1464.

***rac-tert*-butyl (*2R,4S*)-4-hydroxy-5-methylene-2-((4-nitro-1*H*-indol-3-yl)methyl)piperidine-1-carboxylate (733-Boc)**



733-Boc

Compound **733-Boc** was prepared using ***General conditions 3.3*** from aldehyde **708-Boc** (330 mg, 1.23 mmol, 1 equiv.) in reaction with aniline **719** (485 mg, 1.84mmol, 1.5 equiv.), DABCO (412 mg, 3.68 mmol, 3.0 equiv.) and $Pd(OAc)_2$ (27.5 mg, 123 µmol, 0.10 equiv.) in DMF (12.3 mL). Purification by column chromatography (dry loading, ethyl acetate:hexane 70:30) afforded compound **733-Boc** as yellow solid (337 mg, 71%).

IR (neat) $\tilde{\nu}_{max}/cm^{-1}$: 3524, 3259 (br), 2890, 1670, 1659, 1511, 1422, 1319 1160, 1061, 911, 742.

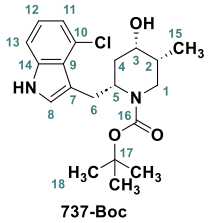
^{1}H NMR (600 MHz, DMSO, 373 K): δ 11.42 (s, 1H, NH), 7.75 (ddd, 2H, *J* = 7.8, 3.2, 1.0 Hz, H-11, H-13), 7.39 (d, 1H, *J* = 2.2 Hz, H-8), 7.21 (t, 1H, *J* = 7.9 Hz, H-12), 4.98 (s, 1H, H-15a), 4.88 (s, 1H, H-15b), 4.68 (s, 1H, OH), 4.27 (d, 1H, *J* = 14.9 Hz, H-1a), 4.23 (ddt, 1Ht, *J* = 11.0, 7.9, 3.9 Hz, H-5), 4.16

(s, 1H, H-3), 3.87 (d, 1H, *J* = 14.8 Hz, H-1b), 3.34 (dd, 1H, *J* = 14.8, 9.9 Hz, H-6a), 3.10 (dd, 1H, *J* = 15.0, 4.4 Hz, H-6b), 1.90 (ddd, 1H, *J* = 13.5, 7.0, 4.5 Hz, H-4a), 1.69 (ddd, 1H, *J* = 13.5, 6.0, 4.0 Hz, H-4b), 0.96 (s, 9H, H-18).

^{13}C NMR (151 MHz, DMSO, 373 K) δ: 153.4 (C-16), 146.0 (C-2), 142.2 (C-10), 139.0 (C-14), 128.9 (C-8), 119.0 (C-12), 118.3 (C-9), 117.1 (C-13), 115.8 (C-11), 111.3 (C-7), 108.1 (C-15), 77.4 (C-17), 67.4 (C-3), 51.1 (C-5), 41.7 (C-1), 36.6 (C-4), 30.2 (C-6), 27.0 (C-18).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{20}H_{26}N_3O_5)^+$ requires 388.1867, found 288.1867.

***rac-tert*-butyl (*2R,4S,5R*)-2-((4-chloro-1*H*-indol-3-yl)methyl)-4-hydroxy-5-methylpiperidine-1-carboxylate (737-Boc)**



737-Boc

Compound **737-Boc** was prepared using ***General conditions 3.3*** from aldehyde **709-Boc** (2.00 g, 7.37 mmol, 1 equiv.) in reaction with aniline **712** (3.74 g, 14.7 mmol, 2.0 equiv.), DABCO (2.48 g, 22.1 mmol, 3.0 equiv.) and $Pd(OAc)_2$ (166 mg, 737 μmol, 0.10 equiv.) in DMF (74 mL). Purification by column chromatography (dry loading, ethyl acetate:hexane 40:60) afforded compound **737-Boc** as off-white solid (2.20 g, 79%) and recovered aniline (2.08 g, 56%).

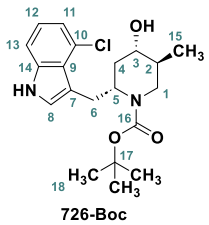
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3416 (br), 3285 (br), 2974, 2930, 2875, 1655, 1427, 1365, 1338, 1167, 1028, 909, 735.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (s, 1H, NH), 7.22 (dd, 1H, *J* = 6.4, 2.6 Hz, H-13), 7.07 – 6.96 (m, 2H, H-11, H-12), 6.92 (s, 1H, H-8), 4.76 – 4.66 (m, 1H, H-5), 4.00 (d, 1H, *J* = 3.2 Hz, H-3), 3.93 (d, 1H, *J* = 12.3 Hz, H-1a), 3.48 (dd, 1H, *J* = 14.6, 11.4 Hz, H-6a), 3.32 (dd, 1H, *J* = 14.9, 3.2 Hz, H-6b), 3.02 (t, 1H, *J* = 12.6 Hz, H-1b), 2.07 – 1.90 (m, 2H, H-4), 1.73 (dddd, 1H, *J* = 11.7, 7.1, 4.6, 2.6 Hz, H-2), 1.66 (s, 1H, OH), 1.00 (d, 3H, *J* = 7.0 Hz, H-15), 0.79 (s, 9H, H-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.5 (C-16), 138.2 (C-14), 126.5 (C-10), 124.7 (C-9), 124.3 (C-8), 122.2 (C-12), 120.2 (C-11), 114.3 (C-7), 110.1 (C-13), 78.8 (C-17), 69.2 (C-3), 51.1 (C-5), 38.7 (C-1), 36.4 (C-4), 35.4 (C-2), 29.7 (C-6), 27.6 (C-18), 15.0 (C-15).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{20}H_{27}ClN_2O_3Na)^+$ requires 401.1602, found 401.1602.

***rac-tert*-butyl (*2R,4S,5S*)-2-((4-chloro-1*H*-indol-3-yl)methyl)-4-hydroxy-5-methylpiperidine-1-carboxylate (726-Boc)**



726-Boc

Compound **726-Boc** was prepared using ***General conditions 3.3*** from aldehyde **697-Boc** (400 mg, 1.47 mmol, 1 equiv.) in reaction with aniline **712** (747 mg, 2.95 mmol, 2.0 equiv.), DABCO (496 mg, 4.42 mmol, 3.0 equiv.) and $Pd(OAc)_2$ (33.1 mg, 147 μmol, 0.10 equiv.) in DMF (14.7 mL). Purification by column chromatography (dry loading, ethyl acetate:hexane 50:50 to 75:25) afforded compound **726-Boc** as off-white solid (376 mg, 67%).

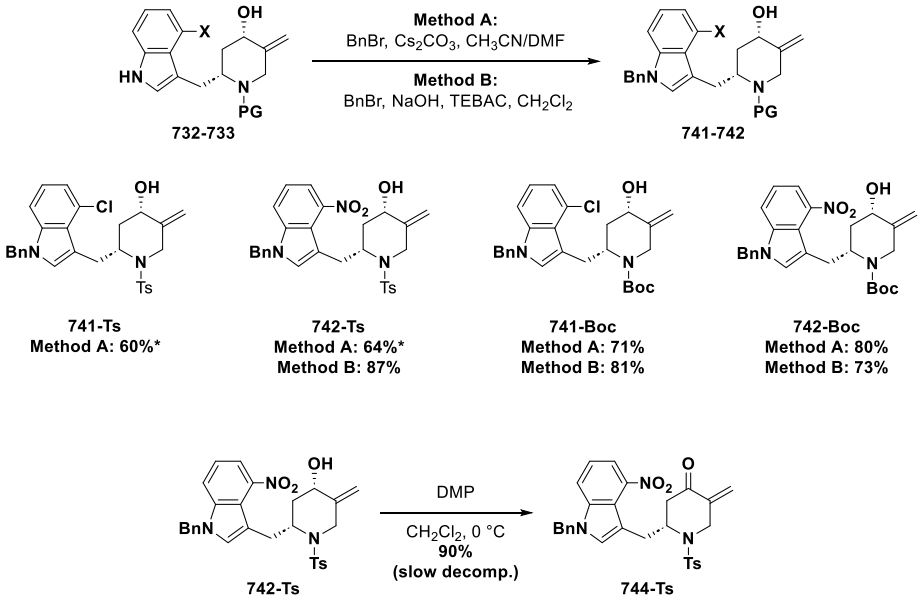
IR (neat) $\tilde{\nu}_{max}/cm^{-1}$: 3270 (br), 2929, 1658, 1429, 1341, 1163, 1139, 1061, 745.

^{1}H NMR (600 MHz, DMSO, 373 K) δ: 10.80 (s, 1H, NH), 7.29 (dd, 1H, *J* = 8.0, 1.0 Hz, H-13), 7.08 (s, 1H, H-8), 6.99 (t, 1H, *J* = 7.7 Hz, H-12), 6.95 (dd, 1H, *J* = 7.6, 1.0 Hz, H-11), 4.45 – 4.38 (m, 2H, H-5, OH), 3.56 – 3.51 (m, 2H, H-1a, H-3), 3.53 – 3.43 (m, 2H, H-1b, H-6a), 3.24 (dd, 1H, *J* = 14.7, 5.4 Hz, H-6b), 1.85 (ddd, 1H, *J* = 14.0, 6.5, 3.6 Hz, H-4a), 1.72 (qq, 1H, *J* = 7.1, 3.5 Hz, H-2), 1.60 (dt, 1H, *J* = 13.9, 4.0 Hz, H-4b), 1.06 (s, 9H, H-18), 0.90 (d, 3H, *J* = 7.1 Hz, H-15).

^{13}C NMR (151 MHz, DMSO, 373 K) δ: 154.2 (C-16), 137.7 (C-14), 124.8 (C-8), 124.6 (C-10), 123.7 (C-9), 120.6 (C-12), 118.5 (C-11), 112.1 (C-7), 109.9 (C-13), 76.9 (C-17), 68.9 (C-3), 51.3 (C-5), 39.3 (C-1), 35.3 (C-2), 31.1 (C-4), 29.0 (C-6), 27.2 (C-18), 15.0 (C-15).

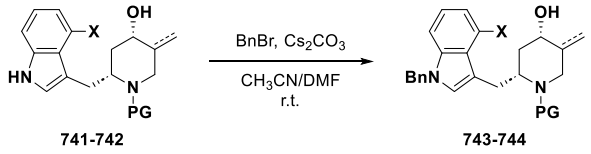
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{20}H_{27}ClN_2O_3Na)^+$ requires 401.1602, found 401.1613.

4.4.4 Enone cyclisation approach



Scheme 4.23. *Enone cyclisation approach.*

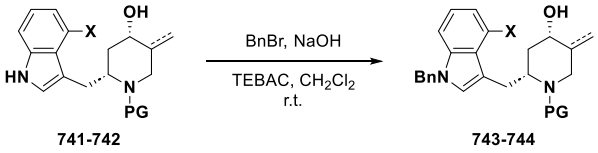
General procedures for indole benzylation (General procedure 3.4 = Method A)



Synthetic procedure for indole protection (Method A) is based on the procedure published by Zhang *et al.*[68]

To a solution of indole (1 eq.) in DMF (1.0 M) and CH_3CN (0.5 M) was added benzyl bromide (1.5 equiv.) and Cs_2CO_3 (1.5 equiv.) and the resulting solution was stirred for 16 h at room temperature. Reaction mixture was then filtered through cotton and concentrated under reduced pressure. The residues of DMF were removed by azeotropic evaporation with toluene. The obtained residue was purified by column chromatography.

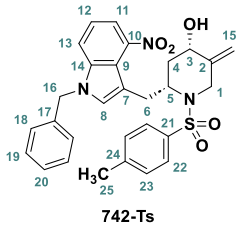
General procedures for indole benzylation (General procedure 3.5 = Method B)



Synthetic procedure for indole protection (Method A) is based on the procedure published by Crooks *et al.*[69]

To a solution of indole (1 equiv.) in CH_2Cl_2 (0.1 M) at 0 °C was added benzyl bromide (2.5 equiv.), finely ground NaOH (3.0 equiv.) and TEBAC (0.10 equiv.). The ice bath was removed, and the reaction mixture stirred at room temperature until full conversion of the starting material. The crude reaction mixture was directly poured onto a silica column and eluted with appropriate solvent mixture.

***rac*-(*2R,4S*)-2-((1-benzyl-4-nitro-1*H*-indol-3-yl)methyl)-5-methylene-1-tosylpiperidin-4-ol (742-Ts)**[vi]



742-Ts

Compound **742-Ts** was prepared using ***General procedure 3.4 (Method A)*** from indole **733-Ts** (68.2 mg, 154 μmol, 1 equiv.) in reaction with benzyl bromide (38 μL, 309 μmol, 2.00 equiv.), Cs_2CO_3 (101 mg, 309 μmol, 2.00 equiv.) in CH_3CN (2.0 mL) and DMF (1.0 mL). Purification by column chromatography (ethyl acetate:hexane 30:70) afforded compound **742-Ts** as a yellow foam (52.7 mg, 64%).

Compound **742-Ts** was prepared using ***General procedure 3.5 (Method B)*** from indole **733-Ts** (550 mg, 1.25 mmol, 1 equiv.) in reaction with benzyl bromide (222 μL, 1.87 mmol, 1.50 equiv.), NaOH (74.7 mg, 1.87 mol, 1.50 equiv.) and TEBAC (28.4 mg, 125 μmol, 0.10 equiv.) in CH_2Cl_2 (12.5 mL). Purification by column chromatography (ethyl acetate:hexane 30:70) afforded compound **742-Ts** as a yellow foam (574 mg, 87%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3485, 2924, 1517, 1350, 1147, 1084, 889.

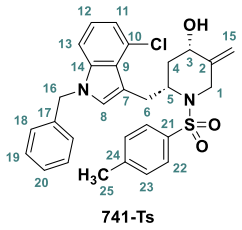
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (dd, 1H, *J* = 7.9, 0.9 Hz, H-11), 7.47 (dd, 1H, *J* = 8.2, 0.9 Hz, H-13), 7.46 – 7.42 (m, 2H, H-22), 7.31 (tdd, 3H, *J* = 8.6, 6.7, 3.6 Hz, H-19, H-20), 7.26 (s, 1H, H-8), 7.14 (t, 1H, *J* = 8.1 Hz, H-12), 7.12 – 7.08 (m 2H, H-18), 7.04 – 6.97 (m, 2H, H-23), 5.34 (dd, 2H, *J* = 2.2 Hz, H-16), 4.94 (d, 2H, *J* = 5.5 Hz, H-15), 4.27 (d, 1H, *J* = 15.6 Hz, H-1a), 4.17 – 4.04 (m, 3H, H-1b, H-3, H-5), 3.49 (dd, 1H, *J* = 15.0, 10.0 Hz, H-6a), 3.30 (dd, 1H, *J* = 15.0, 4.4 Hz, H-6b), 2.29 (s, 3H, H-25), 1.84 (ddd, 1H, *J* = 14.3, 4.2, 2.8 Hz, H-4a), 1.75 (ddd, 1H, *J* = 14.3, 6.5, 3.8 Hz, H-4b).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.3 (C-10), 143.2 (C-2), 142.8 (C-24), 139.3 (C-14), 137.6 (C-17), 136.5 (C-21), 133.2 (C-8), 129.2 (C-23), 129.1 (C-19), 128.1 (C-20), 127.3 (C-22), 126.8 (C-18), 120.2 (C-12), 120.2 (C-9), 117.8 (C-11), 115. 9 (C-13), 112.8 (C-15), 112.0 (C-7), 70.0 (C-3), 53.7 (C-5), 50.5 (C-16), 42.8 (C-1), 35.3 (C-4), 31.4 (C-6), 21.6 (C-25).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{29}H_{30}N_3O_5S)^+$ requires 532.1901, found 532.1910.

[vi] Reaction was performed by Daniel Cox.

***rac*-(*2R,4S*)-2-((1-benzyl-4-chloro-1*H*-indol-3-yl)methyl)-5-methylene-1-tosylpiperidin-4-ol (741-Ts)**[vii]



Compound **741-Ts** was prepared using ***General procedure 3.4 (Method A)*** from indole **732-Ts** (49.6 mg, 115 μmol, 1 equiv.) in reaction with benzyl bromide (20.5 μL, 173 μmol, 1.50 equiv.), Cs_2CO_3 (56.3 mg, 173 μmol, 1.50 equiv.) in CH_3CN (0.66 mL) and DMF (0.33 mL). Purification by column chromatography (ethyl acetate:hexane 30:70) afforded compound **741-Ts** as an off-white foam (35.7 mg, 60%).

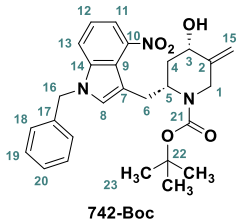
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3511, 2924, 1154, 677.0

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 – 7.40 (m, 2H, H-22), 7.23 – 7.13 (m, 3H, H-19, H-20), 7.01 – 6.97 (m, 3H, H-13, H-18), 6.96 (s, 1H, H-8), 6.93 (d, 2H, *J* = 7.9 Hz, H-23), 6.92 – 6.89 (m, 2H, H-11, H-12), 5.13 (d, 2H, *J* = 2.1 Hz, H-16), 4.91 (d, 2H, *J* = 10.9 Hz, H-15), 4.30 – 4.19 (m, 2H, H-1a, H-5), 4.10 – 4.01 (m, 2H, H-1b, H-3), 3.47 (dd, 1H, *J* = 14.4, 7.8 Hz, H-6a), 3.31 (dd, 1H, *J* = 14.5, 7.4 Hz, H-6b), 2.22 (s, 3H, H-25), 1.74 (ddd, 1H, *J* = 14.2, 4.6, 3.4 Hz, H-4a), 1.67 (ddd, 1H, *J* = 14.2, 6.4, 4.0 Hz, H-4b), 1.52 (s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 143.8 (C-2), 142.8 (C-24), 138.1 (C-14), 137.5 (C-17), 137.2 (C-21), 129.7 (C-8), 129.2 (C-23), 128.9 (C-19), 127.8 (C-20), 127.4 (C-22), 126.8 (C-18), 126.4 (C-10), 125.0 (C-9), 122.1 (C-12), 120.3 (C-11), 112.4 (C-15), 112.0 (C-7), 108.6 (C-13), 70.1 (C-3), 53.6 (C-5), 50.2 (C-16), 43.2 (C-1), 34.1 (C-4), 30.0 (C-6), 21.6 (C-25).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{29}H_{30}N_2O_3S)^+$ requires 521.1660, found 521.1670.

***rac-tert*-butyl (*2R,4S*)-2-((1-benzyl-4-nitro-1*H*-indol-3-yl)methyl)-4-hydroxy-5-methylenepiperidine-1-carboxylate (742-Boc)**



Compound **742-Boc** was prepared using ***General procedure 3.4 (Method A)*** from indole **733-Boc** (250 mg, 649 μmol, 1 equiv.) in reaction with benzyl bromide (116 μL, 973 μmol, 1.50 equiv.), Cs_2CO_3 (317 mg, 973 μmol, 1.50 equiv.) in CH_3CN (1.3 mL) and DMF (0.65 mL). Purification by gradient column chromatography (ethyl acetate:hexane 30:70 to 50:50) afforded compound **742-Boc** as a yellow foam (246 mg, 80%).

Compound **742-Boc** was prepared using ***General procedure 3.5 (Method B)*** from indole **733-Boc** (50 mg, 129 μmol, 1 equiv.) in reaction with benzyl bromide (23 μL, 194 μmol, 1.50 equiv.), NaOH (7.7 mg, 194 μmol, 1.50 equiv.) and TEBAC (2.9 mg, 12.9 μmol, 0.10 equiv.) in CH_2Cl_2 (1.3 mL). Purification by

[vii] Reaction was performed by Daniel Cox.

gradient column chromatography (ethyl acetate:hexane 20:80 to 30:70) afforded compound **-742-Boc** as a yellow foam (45.0 mg, 73%).

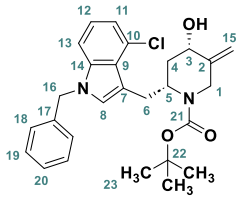
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3407 (br), 1676, 1517, 1363, 1318, 1163, 1058, 773, 703.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, 1H, *J* = 7.8 Hz, H-11), 7.50 (dd, 1H, *J* = 8.2, 0.7 Hz, H-13), 7.35 – 7.22 (m, 3H, H-19, H-20), 7.21 – 7.12 (m, 2H, H-8, H-12), 7.09 – 7.02 (m, 2H, H-18), 5.33 (d, 1H, *J* = 16.3 Hz, H-16a), 5.29 (d, 1H, *J* = 16.2 Hz, H-16b), 5.02 (d, 2H, *J* = 5.7 Hz, H-15), 4.49 – 4.40 (m, 2H, H-1a, H-5), 4.39 (t, 1H, *J* = 4.4 Hz, H-3), 3.87 (d, 1H, *J* = 14.7 Hz, H-1b), 3.49 (dd, 1H, *J* = 14.8, 10.7 Hz, H-6a), 3.30 (dd, 1H, *J* = 14.8, 4.0 Hz, H-6b), 2.03 (ddd, 1H, *J* = 14.2, 6.9, 4.1 Hz, H-4a), 1.94 (dt, 1H, *J* = 14.5, 3.5 Hz, H-4b), 1.70 (s, 1H, OH), 0.92 (s, 9H, H-23).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.9 (C-21), 145.0 (C-2), 143.4 (C-10), 139.4 (C-14), 136.4 (C-17), 132.7 (C-8), 129.1 (C-19), 128.1 (C-20), 126.7 (C-18), 120.3 (C-9, C-12), 117.8 (C-11), 115.8 (C-13), 112.9 (C-7), 111.6 (C-15), 79.1 (C-22), 70.3 (C-3), 51.3 (C-5), 50.4 (C-16), 41.3 (C-1), 36.6 (C-4), 30.8 (C-6), 27.9 (C-23 C).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{27}H_{31}N_3O_5Na)^+$ requires 500.2156, found 500.2160.

***rac-tert*-butyl (*2R,4S*)-2-((1-benzyl-4-chloro-1*H*-indol-3-yl)methyl)-4-hydroxy-5-methylenepiperidine-1-carboxylate (741-Boc)**



741-Boc

Compound **741-Boc** was prepared using ***General procedure 3.4 (Method A)*** from indole **732-Boc** (50.0 mg, 133 μmol, 1 equiv.) in reaction with benzyl bromide (19.7 μL, 166 μmol, 1.25 equiv.), Cs_2CO_3 (64.8 mg, 199 μmol, 1.50 equiv.) in CH_3CN (0.27 mL) and DMF (0.13 mL). Purification by column chromatography (ethyl acetate:hexane 30:70) afforded compound **741-Boc** as a white foam (44 mg, 71%).

Compound **741-Boc** was prepared using ***General procedure 3.5 (Method B)*** from indole **732-Boc** (100 mg, 265 μmol, 1 equiv.) in reaction with benzyl bromide (47 μL, 398 μmol, 1.50 equiv.), NaOH (15.9 mg, 398 μmol, 1.50 equiv.) and TEBAC (6.0 mg, 26.5 μmol, 0.10 equiv.) in CH_2Cl_2 (2.7 mL). Purification by gradient column chromatography (ethyl acetate:hexane 20:80 to 30:70) afforded compound **741-Boc** as a white foam (100.0 mg, 81%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3410 (br), 1667, 1656, 1418, 1363, 1163, 1059, 912, 868, 735.

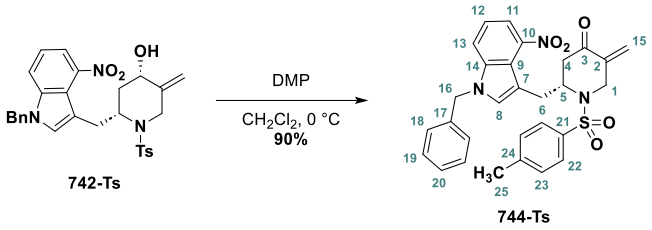
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 – 7.21 (m, 3H, H-19, H-20), 7.12 (dd, 1H, *J* = 7.6, 1.5 Hz, H-13), 7.09 – 6.98 (m, 4H, H-11, H-12, H-18), 6.96 (s, 1H, H-8), 5.30 – 5.15 (m, 2H, H-16), 5.04 (d, 2H, *J* = 4.2 Hz, H-15), 4.74 (dtd, 1H, *J* = 12.4, 6.3, 3.8 Hz, H-5), 4.50 (d, 1H, *J* = 14.8 Hz, H-1a), 4.41 (t, 1H, *J* = 4.5 Hz, H-3), 3.94 – 3.85 (m, 1H, H-1b), 3.50 (dd, 1H, *J* = 14.7, 10.0 Hz, H-6a), 3.39 (dd, 1H, *J* = 14.6,

4.9 Hz, H-6b), 2.07 (ddd, 1H, *J* = 14.1, 6.9, 4.2 Hz, H-4a), 1.95 (ddd, 1H, *J* = 14.1, 4.6, 3.1 Hz, H-4b), 1.67 (s, 1H, OH), 0.99 (s, 9H, H-23).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.0 (C-21), 145.3 (C-2), 138.3 (C-14), 137.2 (C-17), 128.9 (C-19), 128.8 (C-8), 127.8 (C-20), 126.8 (C-18), 126.7 (C-10), 125.3 (C-9), 122.2 (C-12), 120.2 (C-11), 113.3 (C-7), 111.4 (C-15), 108.6 (C-13), 79.1 (C-22), 70.4 (C-3), 51.5 (C-5), 50.2 (C-16), 41.4 (C-1), 36.3 (C-4), 29.6 (C-6), 27.9 (C-23).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{27}H_{31}ClN_2O_3Na)^+$ requires 489.1915, found 489.1920.

***(rac)*-2-((1-benzyl-4-nitro-1H-indol-3-yl)methyl)-5-methylene-1-tosylpiperidin-4-one (744-Ts)**



To a solution of allylic alcohol **742-Ts** (14.0 mg, 26.3 μmol, 1 equiv.) in CH_2Cl_2 (1.0 mL) was added DMP (22.3 mg, 52.7 μmol, 2.00 equiv.) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then directly loaded on a column and eluted with ethyl acetate:pentane (30:70), affording compound **744-Ts** as a yellow foam (12.6 mg, 90%).

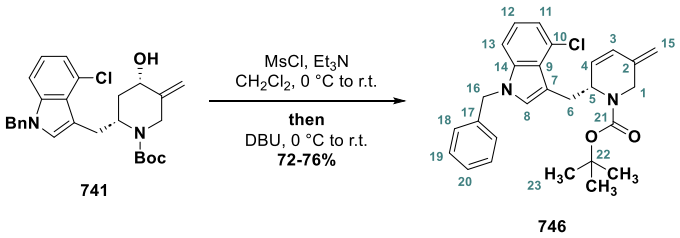
Note: Low stability of compound **744-Ts** did not allow its full characterisation.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (dd, 1H, *J* = 7.9, 0.9 Hz, H-11), 7.64 – 7.49 (m, 3H, H-13, H-22), 7.38 – 7.25 (m, 4H, H-8, H-19, H-20), 7.19 (t, 1H, *J* = 8.0 Hz, H-12), 7.18 – 7.03 (m, 4H, H-18, H-23), 6.03 (dt, 1H, *J* = 2.1, 1.2 Hz, H-15a), 5.36 (s, 2H, H-16), 5.34 – 5.28 (m, 1H, H-15b), 4.58 (dq, 1H, *J* = 16.5, 1.3 Hz, H-1a), 4.52 – 4.37 (m, 1H, H-5), 4.19 (dt, 1H, *J* = 16.5, 2.0 Hz, H-1b), 3.24 (ddd, 1H, *J* = 15.0, 5.7, 0.8 Hz, H-6a), 3.08 (dd, 1H, *J* = 14.9, 9.1 Hz, H-6b), 2.46 (d, 2H, *J* = 4.9 Hz, H-4), 2.34 (s, 3H, H-25).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.9 (C-3), 143.7 (C-10), 143.1 (C-24), 139.3 (C-14), 138.5 (C-17), 136.4 (C-21), 136.3 (C-2), 133.0 (C-8), 129.8 (C-23), 129.2 (C-19), 128.3 (C-20), 127.3 (C-22), 126.8 (C-18), 122.5 (C-15), 120.7 (C-12), 120.1 (C-9), 118.2 (C-11), 116.2 (C-13), 110.0 (C-7), 54.4 (C-5), 50.6 (C-16), 45.3 (C-1), 43.0 (C-4), 32.0 (C-6), 21.7 (C-25).

4.4.5 Synthetic studies towards Lysergene

***rac-tert*-butyl 6-((1-benzyl-4-chloro-1H-indol-3-yl)methyl)-3-methylene-3,6-dihydropyridine-1(2H)-carboxylate (746)**



To a solution of allylic alcohol **741** (200 mg, 439 µmol, 1 equiv.) was added Et_3N (122 µl, 878 µmol, 2 equiv.) and MsCl (47.6 µl, 615 µmol, 1.40 equiv.) at 0 °C and the resulting solution was stirred for 1 h at room temperature. After the full consumption of starting material, DBU (197 µl, 197 µmol, 3.00 equiv.) was added at 0 °C and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was loaded on silica gel and purified by column chromatography (diethyl ether:pentane = 20:80). Diene **746** was obtained as a white foam (144 mg, 73%).

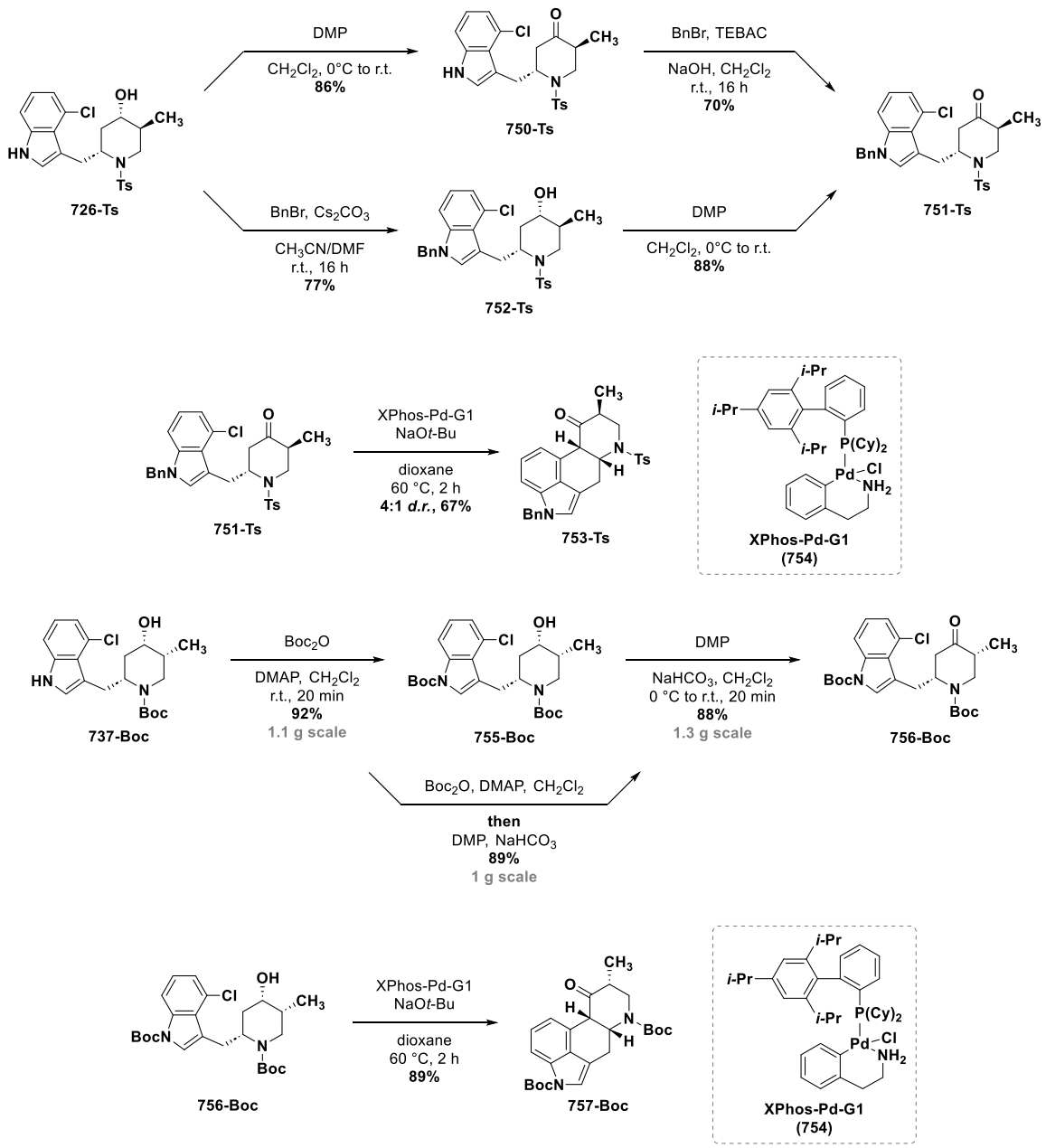
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2977, 1684, 1436, 1417, 1354, 1329, 1169, 891, 871, 734.

^{1}H NMR (500 MHz, DMSO, 373 K) δ: 7.35 (dd, 1H, *J* = 7.7, 1.5 Hz, H-13), 7.34 – 7.13 (m, 6H, H-8, H-18, H-19, H-20), 7.11 – 6.95 (m, 2H, H-11, H-12), 6.25 (d, 1H, *J* = 9.9 Hz, H-3), 5.96 (dd, 1H, *J* = 10.0, 4.9 Hz, H-4), 5.34 (d, 2H, *J* = 2.2 Hz, H-16), 4.96 – 4.88 (m, 3H, H-5, H-15), 4.55 (d, 1H, *J* = 15.6 Hz, H-1a), 3.71 (dt, 1H, *J* = 15.6, 2.2 Hz, H-1b), 3.36 (dd, 1H, *J* = 14.5, 4.9 Hz, H-6a), 3.08 – 2.96 (m, 1H, H-6b), 1.05 (s, 9H, H-23).

^{13}C NMR (126 MHz, DMSO, 373 K) δ: 153.1 (C-21), 137.9 (C-2), 137.5 (C-17), 137.1 (C-14), 130.8 (C-4), 129.2 (C-8), 127.9 (C-19), 126.8 (C-20), 126.5 (C-18), 126.2 (C-3), 124.8 (C-10), 124.0 (C-9), 121.2 (C-12), 119.1 (C-11), 110.4 (C-7), 110.3 (C-15), 108.7 (C-13), 77.9 (C-22), 52.8 (C-5), 48.9 (C-16), 41.2 (C-1), 28.2 (C-6), 27.1 (C-23).

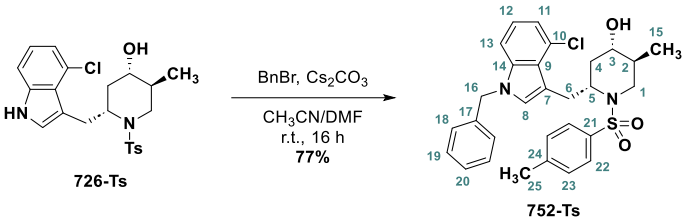
HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{27}H_{30}N_2O_2Cl)^+$ requires 449.1990, found 449.1990.

4.4.6 Ketone arylation strategy



Scheme 4.24. *Overview of ketone arylation strategy.*

***rac*-(*2R,4S,5S*)-2-((1-benzyl-4-chloro-1H-indol-3-yl)methyl)-5-methyl-1-tosylpiperidin-4-ol (752-Ts)**[viii]



Compound **752-Ts** was prepared using ***General procedure 3.4*** from indole **726-Ts** (78.0 mg, 181 μmol, 1 equiv.) in reaction with benzyl bromide (43 μL, 362 μmol, 2.00 equiv.), Cs_2CO_3 (117 mg, 362 μmol, 2.00 equiv.) in CH_3CN (1.2 mL) and DMF (0.6 mL). Purification by gradient column chromatography (ethyl acetate:pentane 30:70 to 40:60) afforded compound **752-Ts** as a white foam (72.1 mg, 77%).

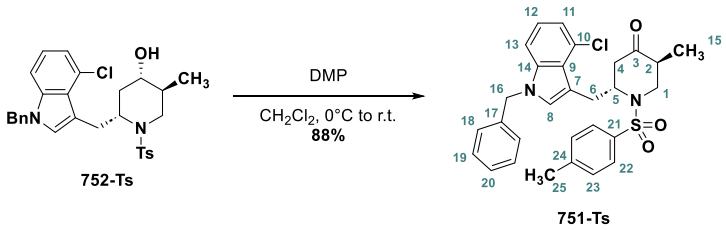
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 3524, 2931, 1453, 1436, 1328, 1151, 910, 732.

^{1}H NMR (400 MHz , $CDCl_3$) δ: 7.65 – 7.58 (m, 2H, H-22), 7.30 – 7.27 (m, 2H, H-19), 7.28 – 7.24 (m, 1H, H-20), 7.10 (d, 2H, *J* = 8.1 Hz, H-23), 7.08 – 7.05 (m, 1H, H-13), 7.06 – 7.03 (m, 2H, H-18), 7.01 – 6.96 (m, 2H, H-11, H-12), 6.94 (s, 1H, H-8), 5.18 (d, 2H, *J* = 1.9 Hz, H-16), 4.28 – 4.17 (m, 1H, H-5), 3.85 (dd, 1H, *J* = 13.5, 3.5 Hz, H-1a), 3.61 (q, 1H, *J* = 4.6 Hz, H-3), 3.41 – 3.35 (m, 1H, H-1b), 3.39 – 3.27 (m, 2H, H-6), 2.34 (s, 3H, H-25), 1.93 (ddd, 1H, *J* = 14.2, 5.5, 3.7 Hz, H-4a), 1.79 (qt, 1H, *J* = 7.3, 3.7 Hz, H-2), 1.66 (dt, 1H, *J* = 14.2, 4.7 Hz, H-4-b), 1.05 (d, 3H, *J* = 7.0 Hz, H-15).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.5 (C-24), 138.9 (C-14), 138.1 (C-21), 137.1 (C-17), 129.6 (C-8), 129.3 (C-23), 128.9 (C-19), 127.9 (C-20), 127.0 (C-22), 126.8 (C-18), 126.3 (C-10), 124.9 (C-9), 122.1 (C-12), 120.2 (C-11), 112.2 (C-7), 108.5 (C-13), 71.5 (C-3), 55.1 (C-5), 50.2 (C-16), 44.5 (C-1), 36.8 (C-2), 31.4 (C-4), 28.8 (C-6), 21.6 (C-25), 15.7 (C-15).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{29}H_{31}N_2O_3SClNa)^+$ requires 545.1636, found 545.1643.

***rac*-(*2R,5S*)-2-((1-benzyl-4-chloro-1H-indol-3-yl)methyl)-5-methyl-1-tosylpiperidin-4-one (752-Ts)**[xxvi]



[viii] Reaction was performed by Daniel Cox.

To a solution of alcohol **752-Ts** (63.0 mg, 120 μmol, 1 equiv.) in CH_2Cl_2 (1.2 mL) was added DMP (61.3 mg, 145 μmol, 1.20 equiv.) at 0 °C and the reaction mixture was stirred at room temperature for 45 min. The reaction mixture was then poured onto 1:1 mixture of saturated aq. solution of Na_2CO_3 and $Na_2S_2O_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:pentane = 20:80) afforded compound **751-Ts** as a white foam (55.3 mg, 88%).

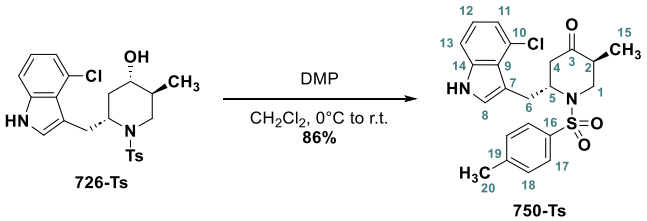
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2925, 1714, 1331, 1551, 737.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 – 7.54 (m, 2H, H-22), 7.36 – 7.30 (m, 2H, H-19), 7.32 – 7.25 (m, 1H, H-20), 7.13 – 7.09 (m, 3H, H-13, H-18), 7.09 – 7.04 (m, 2H, H-23), 7.04 – 7.01 (m, 1H, H-12), 7.01 – 6.98 (m, 1H, H-11), 6.87 (s, 1H, H-8), 5.27 – 5.14 (m, 2H, H-16), 4.76 – 4.66 (m, 1H, H-5), 3.84 (ddd, 1H, *J* = 13.5, 4.2, 1.1 Hz, H-1), 3.77 (dd, 1H, *J* = 13.5, 4.4 Hz, H-1), 3.18 (dd, 1H, *J* = 14.5, 7.3 Hz, H-6a), 3.06 (dd, 1H, *J* = 14.5, 8.6 Hz, H-6b), 2.78 (dd, 1H, *J* = 14.8, 6.4 Hz, H-4a), 2.62 (dtt, 1H, *J* = 11.1, 7.5, 3.7 Hz, H-2), 2.42 – 2.32 (m, 1H, H-4b), 2.34 (s, 3H, H-25), 1.31 (d, 3H, *J* = 7.2 Hz, H-15).

^{13}C NMR (101 MHz ,$CDCl_3$) δ: 210.9 (C-3), 143.2 (C-24), 138.1 (C-14), 136.9 (C-17), 136.8 (C-21), 129.4 (C-23), 129.2 (C-8), 129.0 (C-19), 128.0 (C-20), 127.1 (C-22), 126.9 (C-18), 126.2 (C-10), 124.6 (C-9), 122.4 (C-12), 120.4 (C-11), 110.2 (C-7), 108.7 (C-13), 56.3 (C-5), 50.3 (C-16), 46.9 (C-1), 44.6 (C-2), 41.3 (C-4), 29.6 (C-6), 21.7 (C-25), 15.9 (C-15).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{29}H_{29}N_2O_3SClNa)^+$ requires 543.1480, found 543.1473.

***rac*-(*2R,5S*)-2-((4-chloro-1*H*-indol-3-yl)methyl)-5-methyl-1-tosylpiperidin-4-one (750-Ts)**



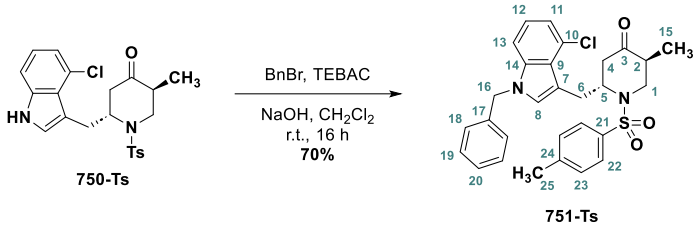
To a solution of alcohol **726-Ts** (14.0 mg, 32.3 μmol, 1 equiv.) in CH_2Cl_2 (0.5 mL) was added DMP (16.5 mg, 38.8 μmol, 1.20 equiv.) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then poured onto 1:1 mixture of saturated aq. solution of Na_2CO_3 and $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by PTLC (ethyl acetate:hexane = 60:40) afforded compound **750-Ts** as a off-white solid (12.0 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 – 8.13 (m, 1H, NH), 7.59 – 7.52 (m, 2H, H-17), 7.17 (dd, 1H, *J* = 7.7, 1.3 Hz, H-13), 7.09 – 7.05 (m, 2H, H-18), 7.03 (t, 1H, *J* = 7.7 Hz, H-12), 6.99 (dd, 1H, *J* = 7.6, 1.3

Hz, H-11), 6.88 (d, 1H, *J* = 2.5 Hz, H-8), 4.74 – 4.63 (m, 1H, H-5), 3.83 (ddd, 1H, *J* = 13.5, 4.1, 1.2 Hz, H-1a), 3.76 (dd, 1H, *J* = 13.5, 4.3 Hz, H-1b), 3.15 (dd, 1H, *J* = 14.5, 7.4 Hz, H-6a), 3.03 (dd, 1H, *J* = 14.5, 8.5 Hz, H-6b), 2.76 (dd, 1H, *J* = 14.8, 6.4 Hz, H-4a), 2.67 – 2.54 (m, 1H, H-2), 2.38 – 2.28 (m, 1H, H-4b), 2.31 (s, 3H, H-20), 1.29 (d, 3H, *J* = 7.2 Hz, H-15).

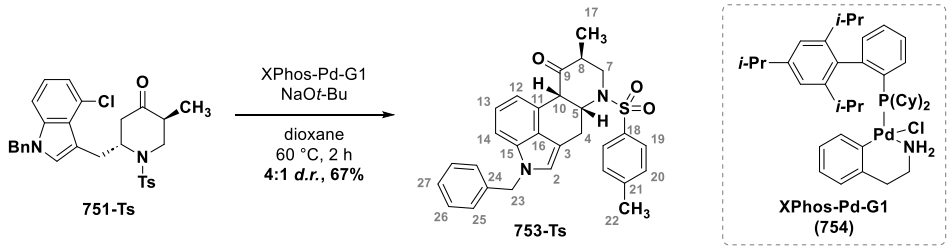
^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.1 (C-3), 143.2 (C-19), 137.8 (C-14), 136.9 (C-16), 129.5 (C-18), 127.1 (C-17), 126.0 (C-10), 125.0 (C-8), 124.0 (C-9), 122.7 (C-12), 120.7 (C-11), 111.1 (C-7), 110.1 (C-13), 56.2 (C-5), 46.8 (C-1), 44.7 (C-2), 41.3 (C-4), 29.7 (C-6), 21.6 (C-20), 15.9 (C-15).

rac-(2R,5S)-2-((1-benzyl-4-chloro-1H-indol-3-yl)methyl)-5-methyl-1-tosylpiperidin-4-one (751-Ts)



Compound **751-Ts** was prepared using ***General procedure 3.5*** from indole **750-Ts** (8.4 mg, 19.5 µmol, 1 equiv.) in reaction with benzyl bromide (7.0 µL, 58.5 µmol, 3.00 equiv.), NaOH (2.7 mg, 67.5 µmol, 3.5 equiv.) and TEBAC (2.0 mg, 8.80 µmol, 0.45 equiv.) in CH_2Cl_2 (0.3 mL). Purification by PTLC (ethyl acetate:toluene 10:90) afforded compound **751-Ts** as a white foam (7.1 mg, 70%).

rac-(*6aR,9S,10aS*)-4-benzyl-9-methyl-7-tosyl-4,6a,7,8,9,10a-hexahydroindolo[4,3-fg]quinolin-10(6H)-one (753-Ts)[ix]



An oven dried vial was charged with ketone **751-Ts** (10 mg, 19.2 µmol) and XPhos-Pd-G1 (1.5 mg, 1.9 µmol, 10 mol%). The reaction vessel was then evacuated and backfilled with argon (3 cycles). Dry dioxane (1.3 mL) was added and the reaction mixture was bubbled with argon for 20 minutes. After cooling to ≈10 °C, KHMDS (0.5 M in toluene, 41 µL, 20.1, 1.05 equiv) was added and the

[ix] Reaction was performed by Daniel Cox.

reaction mixture was stirred for another 30 min at this temperature. Cooling bath was then removed, reaction mixture warmed to room temperature and then placed to oil bath preheated to 60 °C. After stirring for 2 h, the reaction mixture was cooled to room temperature, poured onto sat. aq. solution of NH_4Cl (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed with brine (50 mL), died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by PTCL (diethyl ether:toluene = 15:85) afforded compound **753-Ts** as an off-white solid (5.6 mg, 60%).

m.p.: 80 – 82 °C.

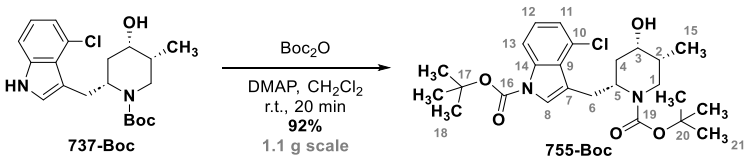
IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2918, 1720, 1341, 1455, 1162, 734.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.78 – 7.73 (m, 2H, H-19), 7.34 – 7.25 (m, 5H, H-20, H-26, H-27), 7.19 – 7.12 (m, 4H, H-13, H-14, H-25), 6.78 (d, 1H, *J* = 6.7 Hz, H-12), 6.74 (s, 1H, H-2), 5.23 (s, 2H, H-23), 4.74 (dt, 1H, *J* = 11.4, 5.3 Hz, H-5), 4.03 (d, 1H, *J* = 5.8 Hz, H-10), 3.84 (dd, 1H, *J* = 12.5, 4.6 Hz, H-7a), 3.66 (dd, 1H, *J* = 12.6, 6.3 Hz, H-7b), 3.07 (dd, 1H, *J* = 15.0, 4.9 Hz, H-4a), 2.93 – 2.85 (m, 1H, H-4b), 2.81 – 2.72 (m, 1H, H-8), 2.44 (s, 3H, H-22), 1.33 (d, 3H, *J* = 7.1 Hz, H-17).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 208.3 (C-9), 143.9 (C-21), 137.7 (C-24), 136.4 (C-18), 134.6 (C-15), 130.1 (C-20), 128.9 (C-26), 127.8 (C-27), 127.4 (C-19), 127.2 (C-25), 126.5 (C-16), 125.5 (C-11), 122.8 (C-13), 122.8 (C-2), 118.6 (C-12), 109.1 (C-3), 108.7 (C-14), 56.5 (C-5), 50.4 (C-23), 50.2 (C-10), 47.6 (C-7), 43.9 (C-8), 26.5 (C-4), 21.7 (C-22), 15.6 (C-17).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{29}H_{28}N_2O_3SNa)^+$ requires 507.1713, found 507.1715.

***rac*-tert-butyl 3-(((*2R,4S,5R*)-1-(tert-butoxycarbonyl)-4-hydroxy-5-methylpiperidin-2-yl)methyl)-4-chloro-1H-indole-1-carboxylate (755-Boc)**



To a solution of indole **737-Boc** (1.10 g, 2.90 mmol, 1 equiv.) in CH_2Cl_2 (55 mL) was added DMAP (35.5 mg, 0.290 mmol, 0.10 equiv.) and Boc_2O (760 mg, 3.48 mmol, 1.20 equiv.) and the reaction mixture was stirred at room temperature for 20 min. The reaction mixture was then dry loaded on silica gen and purified by gradient column chromatography (ethyl acetate:pentane = 10:90 to 30:70). Compound **755-Boc** was obtained as off-white foam (1.28 g, 92%).

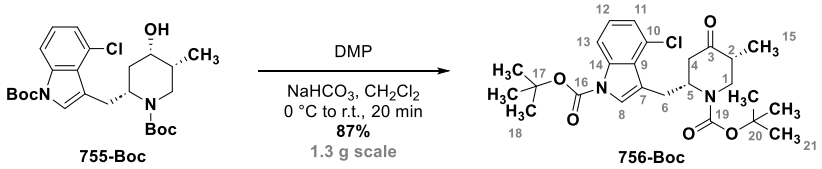
IR (neat) $\tilde{\nu}_{max}/cm^{-1}$: 3414, 2978, 1739, 1653, 1423, 1927, 1155, 1104, 878.

^{1}H NMR (500 MHz, DMSO, 373 K) δ: 8.04 (dd, 1H, *J* = 7.9, 1.4 Hz, H-13), 7.37 (s, 1H, H-8), 7.31 – 7.20 (m, 2H, H-11, H-12), 4.55 – 4.47 (m, 1H, H-5), 4.41 (d, 1H, *J* = 3.5 Hz, OH), 3.80 (p, 1H, *J* = 3.1 Hz, H-3), 3.70 (dd, 1H, *J* = 13.2, 4.4 Hz, H-1a), 3.46 (dd, 1H, *J* = 14.9, 10.7 Hz, H-6a), 3.19 (ddd, 1H, *J* = 14.9, 3.7, 1.1 Hz, H-6b), 3.00 – 2.91 (m, 1H, H-1b), 1.90 (ddd, 1H, *J* = 14.0, 3.2, 1.7 Hz, H-4a), 1.76 (ddd, 1H, *J* = 13.9, 6.5, 2.9 Hz, H-4b), 1.63 (s, 9H), 1.56 (dddd, 1H, *J* = 11.5, 7.0, 4.5, 2.7 Hz, H-2), 0.96 (s, 9H), 0.93 (d, 3H, *J* = 6.8 Hz, H-15)

^{13}C NMR (126 MHz, DMSO, 373 K) δ: 153.3 (C-19), 148.2 (C-16), 136.3 (C-14), 126.7 (C-10), 125.1 (C-9), 124.7 (C-8), 124.2 (C-12), 122.8 (C-11), 118.0 (C-7), 113.2 (C-13), 83.5 (C-17), 77.1 (C-20), 66.3 (C-3), 49.4 (C-5), 38.7 (C-1), 35.7 (C-4), 34.6 (C-2), 28.7 (C-6), 27.2 (C-18), 26.9 (C-21), 14.4 (C-15).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{25}H_{35}ClN_2O_5Na)^+$ requires 501.2127, found 501.2135.

***rac-tert*-butyl 3-(((*2R,5R*)-1-(tert-butoxycarbonyl)-5-methyl-4-oxopiperidin-2-yl)methyl)-4-chloro-1H-indole-1-carboxylate (756-Boc)**



To a solution of alcohol **755-Boc** (1.25 g, 2.61 mmol, 1 equiv.) in CH_2Cl_2 (52 mL) was added finely ground $NaHCO_3$ (1.32 g, 15.7 mmol, 6.00 equiv.) and DMP (1.33 g, 3.13 mmol, 1.20 equiv.) at 0 °C and the reaction mixture was stirred at room temperature for 20 min. The reaction mixture was then poured onto 1:1 mixture of saturated aq. solution of Na_2CO_3 and $Na_2S_2O_3$ (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:hexane = 15:85) afforded compound **756-Boc** as a white foam (1.08 g, 87%).

IR (neat) $\tilde{\nu}_{max}/cm^{-1}$: 2979, 1735, 1692, 1423, 1367, 1283, 1256, 1157, 1094, 780, 746.

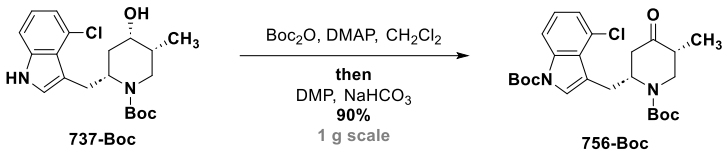
^{1}H NMR (500 MHz, DMSO, 363 K) δ: 8.05 (dd, 1H, *J* = 8.0, 1.2 Hz, H-13), 7.49 (s, 1H, H-8), 7.33 – 7.22 (m, 2H, H-11, H-12), 5.00 (s, 1H, H-5), 4.28 (dd, 1H, *J* = 13.9, 6.9 Hz, H-1a), 3.08 (ddd, 1H, *J* = 14.7, 4.3, 1.1 Hz, H-6), 3.01 (dd, 1H, *J* = 13.5, 11.7 Hz, H-1b), 2.93 (dd, 1H, *J* = 14.7, 10.8 Hz, H-6b), 2.82 (ddd, 1H, *J* = 13.9, 6.9, 1.2 Hz, H-4a), 2.59 (dddd, 1H, *J* = 14.0, 12.8, 6.9, 3.6 Hz, H-2), 2.33 (dd, 1H, *J* = 13.9, 2.2 Hz, H-4b), 1.63 (s, 9H, H-18), 1.04 (s, 9H, H-21), 0.99 (d, 3H, *J* = 6.6 Hz, H-15).

^{13}C NMR (126 MHz, DMSO, 363 K) δ: 208.1 (C-3), 153.1 (C-19), 148.1 (C-16), 136.2 (C-14), 126.4 (C-10), 125.4 (C-9), 125.2, 125.0 (C-8), 124.5 (C-12), 123.0 (C-11), 115.8 (C-7), 113.3 (C-13), 83.9 (C-17),

78.4 (C-20), 52.9 (br) (C-5), 44.4 (C-4), 44.3 (br) (C-1), 42.9 (C-2), 27.4 (br) (C-6), 27.3 (C-18), 26.9 (br) (C-21), 10.3 (C-15).

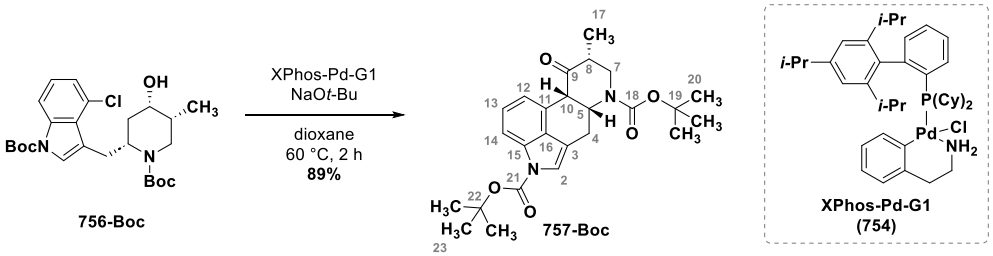
HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{25}H_{33}ClN_2O_5Na)^+$ requires 499.1976, found 499.1927.

One pot procedure for synthesis of compound 756-Boc



To a solution of indole **737-Boc** (950 mg, 2.52 mmol, 1 equiv.) in CH_2Cl_2 (31 mL) was added DMAP (31.0 mg, 0.252 mmol, 0.10 equiv.) and Boc_2O (660 mg, 3.02 mmol, 1.20 equiv.) and the reaction mixture was stirred at room temperature for 20 min. Then a finely ground $NaHCO_3$ (1.26 g, 15.0 mmol, 6.00 equiv.) and DMP (1.28 g, 3.01 mmol, 1.20 equiv.) were added and the reaction mixture was stirred for another 15 min. The reaction mixture was then poured onto 1:1 mixture of saturated aq. solution of Na_2CO_3 and $Na_2S_2O_3$ (40 mL) and extracted with CH_2Cl_2 (3x40 mL). The combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (ethyl acetate:hexane = 15:85) afforded compound **756-Boc** as a white foam (1.07 g, 90%).

***rac*-di-tert-butyl (*6aR,9R,10aS*)-9-methyl-10-oxo-6,6a,8,9,10,10a-hexahydroindolo[4,3-fg]quinoline-4,7-dicarboxylate (757-Boc)**



An oven dried vial was charged with ketone **756-Boc** (20.0 mg, 41.9 μmol, 1 equiv.), XPhos-Pd-G1 (3.1 mg, 4.19 μmol, 10 mol%) and NaO*t*-Bu (6.0 mg, 62.4 μmol, 1.50 equiv.). The reaction vessel was then evacuated and backfilled with argon (3 cycles). After cooling to ≈10 °C, dry degassed dioxane was added and the reaction mixture was bubbled with argon for 5 minutes and then stirred for another 10 min at this temperature. Cooling bath was then removed, reaction mixture warmed to room temperature and then placed to oil bath preheated to 60 °C. After stirring for 2 h, the

reaction mixture was cooled to room temperature, poured onto sat. aq. solution of NH_4Cl (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by PTCL (diethyl ether:toluene = 15:85) afforded compound **757-Boc** as a white foam (16.5 mg, 89%).

IR (thin film) $\tilde{\nu}_{max}/cm^{-1}$: 2979, 1727, 1695, 1442, 1392, 1366, 1299, 1156, 1117, 763.

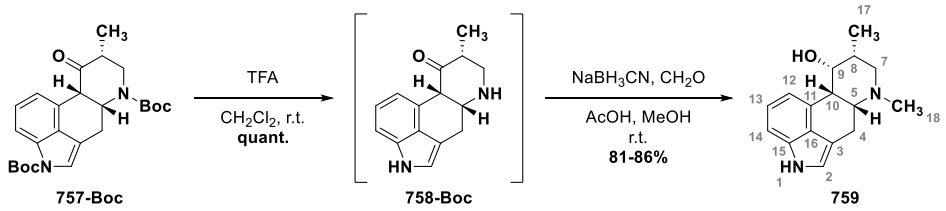
^{1}H NMR (500 MHz, DMSO, 363 K) δ: 7.77 (d, 1H, *J* = 8.2 Hz, H-14), 7.34 (d, 1H, *J* = 1.9 Hz, H-2), 7.28 (t, 1H, *J* = 7.8 Hz, H-13), 6.96 (d, 1H, *J* = 7.3 Hz, H-12), 4.92 (dt, 1H, *J* = 11.6, 5.4 Hz, H-5), 4.39 (dd, 1H, *J* = 13.5, 6.7 Hz, H-7a), 4.29 (d, 1H, *J* = 5.9 Hz, H-10), 3.07 (t, 1H, *J* = 12.6 Hz, H-7b), 2.89 (dp, 1H, *J* = 12.9, 6.5 Hz, H-8), 2.83 (dd, 1H, *J* = 15.5, 5.0 Hz, H-4a), 2.80 – 2.70 (m, 1H, H-4b), 1.64 (s, 9H, H-23), 1.47 (s, 9H, H-20), 1.48 – 1.41 (m, 1H), 0.96 (d, 3H, *J* = 6.6 Hz, H-17).

^{13}C NMR (126 MHz, DMSO, 363 K) δ: 206.8 (C-9), 153.2 (C-18), 148.9 (C-21), 132.4 (C-15), 127.7 (C-11), 127.1 (C-16), 124.4 (C-13), 121.8 (C-12), 119.4 (C-2), 114.8 (C-3), 112.7 (C-14), 83.0 (C-22), 79.5 (C-19), 54.7 (br) (C-5), 51.6 (C-10), 46.4 (br) (C-7), 42.7 (C-8), 27.6 (C-20), 27.4 (C-23), 22.2 (C-4), 10.4 (C-17).

HRMS (ES+): exact mass calculated for $[M+Na]^+$ $(C_{25}H_{32}N_2O_5Na)^+$ requires 463.2203, found 463.2214.

4.4.7 End game

***rac*-(*6aR,9R,10R,10aS*)-7,9-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-10-ol (759-Boc)**



To a solution of compound **757-Boc** (49.5 mg, 112 μmol, 1 equiv.) in CH_2Cl_2 (2.0 mL) was added TFA (2.0 mL) at 0 °C and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then concentrated under reduced pressure at room temperature.

m.p.: 104 – 106 °C.

IR (neat) $\tilde{\nu}_{max}/cm^{-1}$: 1708, 1462, 1445, 1350, 1306, 1150, 783, 704.

^{1}H NMR (500 MHz, MeOD) δ: 7.84 (d, 1H, *J* = 8.2 Hz, H-14), 7.37 (d, 1H, *J* = 1.6 Hz, H-2), 7.24 (dd, 1H, *J* = 8.2, 7.4 Hz, H-13), 6.94 (d, 1H, *J* = 7.3 Hz, H-12), 4.45 (d, 1H, *J* = 5.4 Hz, H-10), 4.40 (dt, 1H, *J* = 12.1, 4.9 Hz, H-5), 3.69 (dd, 1H, *J* = 13.1, 6.3 Hz, H-7a), 3.33 (t, 1H, *J* = 12.8 Hz, H-7b), 3.15 (dq, 1H, *J* = 13.7, 6.9 Hz, H-8), 3.10 (dd, 1H, *J* = 15.4, 4.5 Hz, H-4a), 2.99 (ddd, 1H, *J* = 15.4, 11.5, 1.9 Hz, H-4b), 1.03 (d, 3H, *J* = 6.6 Hz, H-17).

^{13}C NMR (126 MHz, MeOD) δ: 204.6 (C-9), 135.0 (C-15), 129.1 (C-11), 126.5 (C-13), 125.2 (C-16), 123.2 (C-12), 122.2 (C-2), 115.6 (C-14), 113.5 (C-3), 57.3 (C-5), 51.7 (C-10), 47.4 (C-7), 42.7 (C-8), 22.8 (C-4), 11.7 (C-17).

^{19}F NMR (MeOD, 471 MHz) δ: -77.4.

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{15}H_{17}N_2O)^+$ requires 241.1335, found 241.1339.

The obtained residue was dissolved in MeOH (6.3 mL) and acetic acid (164 μL, 2.87 mmol, 25.5 equiv.), formaldehyde (37 wt% sol. in MeOH) (92 μL, 1.24 mmol, 11.0 equiv.) and $NaBH_3CN$ (70.6 mg, 1.12 mmol, 10.0 equiv.) were added at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was poured onto sat. aq. solution of K_2CO_3 (15 mL) and was extracted with 1:3 mixture of *i*-PrOH and $CHCl_3$ (4x15 mL). The combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography ($MeOH:CH_2Cl_2:Et_3N$ = 0.5:98.5:1) afforded compound **758-Boc** as a white solid (23.4 mg, 81%).

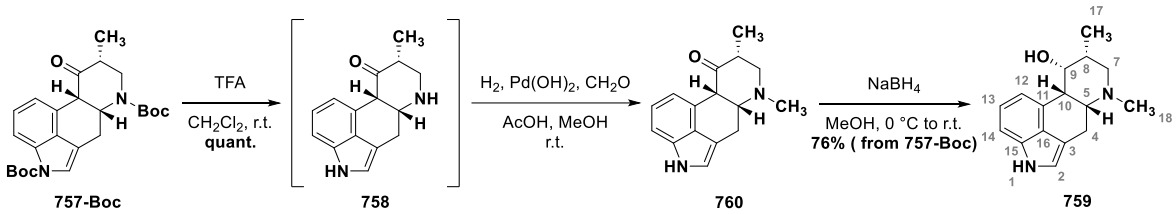
Note: product **758-Boc** is badly soluble in CH_2Cl_2 and crystallisation was observed during the attempted NMR analysis with $CDCl_3$ as a solvent.

^{1}H NMR (400 MHz, MeOD) δ: 7.20 – 7.14 (m, 1H, H-14), 7.09 (dd, 1H, *J* = 8.1, 7.0 Hz, H-13), 6.91 (d, 1H, *J* = 1.4 Hz, H-2), 6.83 (d, 1H, *J* = 7.0 Hz, H-12), 3.96 (t, 1H, *J* = 2.6 Hz, H-9), 3.39 – 3.17 (m, 3H, H-5, H-10, H-4a), 3.01 (dd, 1H, *J* = 13.1, 4.5 Hz, H-4b), 2.84 (t, 1H, *J* = 12.0 Hz, H-7a), 2.59 (s, 3H, H-18), 2.48 (dd, 1H, *J* = 12.0, 4.3 Hz, H-7b), 2.21 – 2.10 (m, 1H, H-8), 1.00 (d, 3H, *J* = 6.9 Hz, H-17).

^{13}C NMR (101 MHz, MeOD) δ: 135.4 (C-15), 132.7 (C-11), 129.3 (C-16), 123.4 (C-13), 120.0 (C-2), 116.1 (C-12), 112.0 (C-3), 109.8 (C-14), 74.6 (C-9), 60.7 (C-5), 54.8, 51.1 (C-7), 45.8 (C-10), 42.6 (C-18), 36.4 (C-8), 19.5 (C-4), 15.7 (C-17).

HRMS (ES+): exact mass calculated for $[M+H]^+$ $(C_{16}H_{20}N_2O)^+$ requires 257.1648, found 257.1646.

Alternative preparation of compound 759-Boc



To a solution of compound **757-Boc** (40.0 mg, 90.8 μmol, 1 equiv.) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL) at 0 °C and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then concentrated under reduced pressure at room temperature.

The obtained residue was dissolved in MeOH (3.0 mL) and acetic acid (40 μL, 699 μmol, 7.70 equiv.), formaldehyde (37 wt% sol. in MeOH) (40 μL, 537 μmol, 5.90 equiv.) and $Pd(OH)_2/C$ (20 wt. %) (10 mg, 14.2 μmol, 16 mol%) were added, the reaction vessel was evacuated and backfilled with hydrogen (3 cycles) and then vigorously stirred under hydrogen atmosphere (balloon) for 2.5 h. The reaction mixture was then filtered through celite and concentrated under reduced pressure (<20 °C).

The obtained residue was dissolved in MeOH (3.0 mL) and $NaBH_4$ (13.8 mg, 365 μmol, 4.00 equiv.) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured onto sat. aq. solution of K_2CO_3 (15 mL) and was extracted with 1:3 mixture of *i*-PrOH and $CHCl_3$ (4 x 15 mL). The combined organic phases were died over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by gradient column chromatography ($MeOH:CH_2Cl_2:Et_3N$ = 5:94:1 to 10:89:1) afforded compound **759** as a white solid (17.8 mg, 76%).

4.5 References for Chapter 4

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